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ABSTRACT SUPPLEMENT

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ABSTRACTS

The Liver Meeting: 2025 Abstracts

★ 0001 | CHOLESTEROL-RESPONSIVE INTERACTION OF NFE2L1-INSIG1 CONTROLS VLDL SECRETION AND ATTENUATES MASH PROGRESSION

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Background: Hepatic cholesterol overload is a central driver of metabolic dysfunction-associated steatohepatitis (MASH). While the liver exports cholesterol via very-low-density lipoprotein (VLDL) secretion to maintain homeostasis, this process is paradoxically suppressed under high cholesterol by insulin-induced gene 1 (INSIG1), which retains the sterol regulatory element-binding protein 1 (SREBP1) in the endoplasmic reticulum (ER), suppressing lipogenesis and limiting VLDL production. Despite this regulatory checkpoint, VLDL secretion persists during cholesterol overload - a critical but unresolved adaptation that prevent lipotoxicity. Here, we identify nuclear factor erythroid 2-related factor 1 (NFE2L1), an ER cholesterol sensor, as the missing link coordinating with SREBP1 activity and VLDL secretion to mitigate MASH. **Methods:** Liver-specific Nfe2l1 knockout (LKO) and wild-type (WT) mice were used to assess VLDL secretion *in vivo*. Subcellular fractionation isolated nuclear and ER compartments to quantify active (mature) SREBP1 levels. Site-directed mutagenesis generated NFE2L1 mutants, and co-immunoprecipitation (Co-IP) mapped the binding domains between NFE2L1-INSIG1. For *in vivo* rescue studies, LKO mice received hepatocyte-targeted AAV-mediated expression of NFE2L1-WT or NHB2 domain-deleted mutants (ΔNHB2). Serum and hepatic lipids were profiled via LC-MS/MS. To model human MASH, db/db mice were fed a methionine/choline-deficient (MCD) diet for 12 weeks. Liver pathology was scored blindly via immunohistochemistry (steatosis, inflammation, fibrosis). Data were analyzed by two-tailed Student's t-test or ANOVA. **Results:** NFE2L1 deficiency increased INSIG1 stability, suppressed SREBP1 activation, and impaired VLDL secretion, causing hepatic cholesterol accumulation and injury. Mechanistically, NFE2L1 binds INSIG1 via its NHB2 domain; this binding increases with free cholesterol, driving INSIG1 degradation and enabling SREBP1-driven VLDL production. In LKO mice, re-expression of NFE2L1-WT by AAV restored SREBP1 activity and VLDL secretion, while ΔNHB2 mutants failed to rescue such effects. Lipidomic profiling revealed that disrupted serum triglyceride composition in NFE2L1-LKO mice was reversed by the WT, but not by ΔNHB2 protein. Strikingly, NFE2L1 overexpression in a murine MASH model enhanced cholesterol export, and reduced liver injury, inflammation, and fibrosis via SREBP activation – without elevating atherogenic lipoproteins due to compensatory LDL receptor upregulation. **Conclusion:** We define the NFE2L1-INSIG1 axis as a cholesterol-responsive checkpoint that licenses VLDL secretion to resolve lipid toxicity and mitigate MASH. This pathway uniquely couples cholesterol sensing to lipoprotein export, offering a therapeutic strategy to combat MASH without exacerbating cardiovascular trade-offs.
Disclosures: Shijun Deng: Nothing to Disclose, Gokhan Hotamisligil: Nothing to Disclose, Isabel Graupera: Nothing to Disclose

★ 0002 | LIVER CD8 TISSUE-RESIDENT MEMORY T CELLS DRIVE INFLAMMATION IN ALCOHOL-ASSOCIATED HEPATITIS

Weizhe Zhong[1] Shawna Cooper[2] Fiona Xhafi[3] Benjamin Swartzwelter[1] Cao Sheng[2] Vijay Shah[2] Mengfei Liu[4], [1]Division of Digestive Disease, Internal Medicine, Yale University;Yale Liver Center, Yale University, [2]Mayo Clinic, Rochester, [3]Division of Digestive Disease, Internal Medicine, Yale University; Yale Liver Center,Yale University, [4]Division of Digestive Disease, Internal Medicine, Yale University;Yale Liver Cente,Yale University

Background: Alcohol-associated hepatitis (AH) is a severe liver disease marked by increased CD8 T cell infiltration. However, the role of CD8 T cells in AH pathogenesis remains unclear. We identified and

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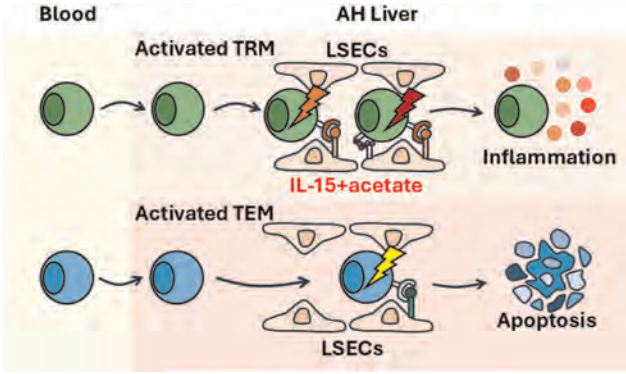
characterized liver CD8 tissue-resident memory T cells (TRM) as key drivers of inflammation in AH. **Methods:** A modified NIAAA chronic-binge alcohol model with LPS injection was used in mice. Single-cell RNA sequencing (scRNA-seq) was performed on immune cells isolated from liver and peripheral blood mononuclear cells (PBMCs). CD8 T cells were classified into naive/central memory T (TCM), effector memory T (TEM), and TRM subsets. The regulatory mechanisms underlying were analyzed via Ingenuity Pathway Analysis (IPA) and Gene Set Enrichment Analysis (GSEA). We performed *in silico* analysis of previously published human liver and PBMC scRNA-seq datasets that included data from patients with AH, alcohol-associated cirrhosis or health controls. TRM is found in liver sinusoids adherent to liver sinusoidal endothelial cells (LSECs) at homeostasis. We performed *in vitro* co-culture of human primary LSECs and CD8 T cells to assess the effects of co-culture on T cell activation and survival. To evaluate the function of IL15 signaling in liver TRM cells in AH, we administered an anti-IL-15 antibody in the AH mouse model and assessed liver injury. **Results:** In the murine AH model, we observed a marked increase in the proportion of CD8 T cells in alcohol/LPS-treated livers compared to controls. Liver TRM cells demonstrated greater cytokine release and cytotoxicity than blood-derived TEM cells. IPA identified IL15 to be an upstream regulator in liver TRM cells, with enrichment of the purinergic signaling pathway—previously shown to be essential for IL-15-induced TRM activation in metabolic dysfunction-associated steatohepatitis (MASH). GSEA further confirmed the upregulation of IL-15 signaling in liver TRM cells. Human AH data also identified a prominent population of TRM cells in AH liver, with higher cytotoxicity compared to blood TEM cells. CellChatDB analysis revealed enhanced cellular interactions between liver TRM cells and LSECs in alcohol/LPS-treated mice. *In vitro* co-culture of human primary LSECs with CD8 T cells enhanced activation in T cells stimulated by anti-CD3/CD28 beads or IL-15/acetate, but had no effect on unstimulated cells. Notably, LSEC co-culture increased T cell death after anti-CD3/CD28 stimulation but not with IL-15/acetate, suggesting IL-15 protects against activation-induced cell death. *In vivo*, blockade of IL-15 signaling with a neutralizing antibody significantly reduced liver injury in our murine AH model, suggesting that IL-15 signaling contributes to AH pathogenesis.
Conclusion: Our study highlights the critical role of liver TRM cells in driving liver inflammation in AH. IL-15 is a key regulator of these cells and represents a promising therapeutic target for the treatment of AH.



Disclosures: Weizhe Zhong: Nothing to Disclose, Shawna Cooper: Nothing to Disclose, Fiona Xhafi: Nothing to Disclose, Benjamin Swartzwelter: Nothing to Disclose, Cao Sheng: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Mengfei Liu: Nothing to Disclose

★ 0003 | RNA-BINDING PROTEIN ZFP36L1 CONTROLS HEPATOCYTE SENESCENCE AND SUSCEPTIBILITY TO ALCOHOLIC LIVER DISEASES

Kuo Du[1] Rajesh Dutta[2] David Umbaugh[2] Niansheng Ren[2] Seh Hoon Oh[2] Ullas Chembazi[3] Sushan Bangru[3] Auinash Kalsotra[3] Anna Mae Diehl[1], [1]Duke University, [2]Duke Universty, [3]University of Illinois

Background: Alcoholic liver diseases (ALD) progresses when liver regeneration is defective. Senescent cells lose their regenerative capacity and acquire a senescence-associated secretory phenotype (SASP) that promotes maladaptive responses in themselves and neighboring cells. The mechanisms that regulate senescent cell accumulation in ALD are poorly understood. ZFP36L1, an RNA-binding protein enriched in hepatocytes, is known to regulate mRNA stability via binding AU-rich elements in the 3′ UTRs of its targets, including key SASP factors. We hypothesized that ZFP36L1 plays a central role in controlling hepatocyte senescence and thereby modulates susceptibility to ALD. **Methods:** We

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analyzed four independent human ALD transcriptomic datasets comprising 28 healthy controls, 23 patients with alcohol-related cirrhosis (AC), and 35 with alcohol-related hepatitis (AH). Senescence signatures were evaluated using bulk RNA-seq and single-nucleus RNA-seq (snRNA-seq), and validated by immunostaining. Also, we generated hepatocyte-specific Zfp36l1 knockout (Zfp36l1$^{\Delta Hep}$) mice and subjected them to mouse models of AH. Liver phenotypes were assessed via histology, biochemical injury markers, and gene profiling. Mechanistic studies included mRNA stability assays and pathway analysis to examine ZFP36L1 targets. **Results:** Transcriptomic profiling showed enriched senescence signatures in AC and AH livers, with snRNA-seq confirming senescent hepatocyte accumulation and elevated SASP scores. These findings were corroborated by increased expression of direct ZFP36l1 targets including proinflammatory cytokines and p21. Mouse models of AH showed increased TNFa and accumulation of senescent hepatocytes. Zfp36l1$^{\Delta Hep}$ mice developed a pro-inflammatory, pro-senescent phenotype even under basal conditions and worse liver injury, senescence, inflammation, and fibrosis than controls after alcohol feeding. Mechanistically, ZFP36L1 deficiency stabilized TNFa and Jag1 mRNA, activating JAG1-NOTCH signaling (which reprograms hepatocyte into bipotent progenitors) and p21 (which prevents progenitor proliferation and promotes hepatocyte senescence). **Conclusion:** Our findings identify hepatocyte senescence as a critical driver of ALD and establish ZFP36L1 as a central post-transcriptional regulator of this process. By destabilizing pro-senescent transcripts (e.g., p21) and pro-inflammatory transcripts (e.g., TNF-a), ZFP36L1 safeguards against hepatocyte dysfunction and disease progression. These results highlight a novel mechanism linking RNA-binding proteins to the control of liver regeneration and suggest that therapeutic modulation of ZFP36L1 or its downstream targets may offer new strategies for treating ALD.

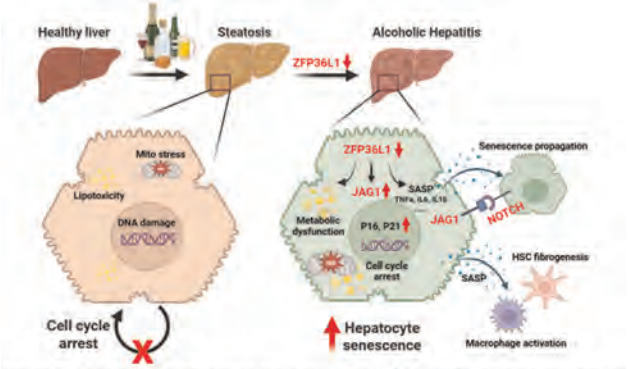

Figure 1: ZFP36L1 restricts hepatocyte senescence and fibroinflammatory crosstalk in alcoholic liver disease. Chronic alcohol exposure triggers lipotoxicity, mitochondrial stress, and DNA damage, leading to transient hepatocyte cell cycle arrest. In alcoholic hepatitis, ZFP36L1 downregulation stabilizes JAG1 mRNA and activates the JAG1–NOTCH pathway, promoting p16/p21 expression, senescence, and SASP production. This amplifies hepatocyte senescence, activates macrophages, and enhances HSC fibrogenesis, driving ALD progression.

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★ 0004 | MULTI-OMICS ANALYSES IDENTIFY A NOVEL HEPATOCELLULAR CARCINOMA SUBTYPE WITH BETTER RESPONSE TO IMMUNE CHECKPOINT INHIBITOR THERAPIES

Junjie Xu[1], [1]Zhejiang University

Background: Hepatocellular carcinoma (HCC) presents persistent therapeutic challenges due to molecular heterogeneity and unpredictable immune checkpoint inhibitor (ICI) responses. **Methods:** In this study, whole transcriptome sequencing was performed on tumor and adjacent non-tumor tissues across 242 patients with hepatocellular carcinoma (HCC) and 51 patients with intrahepatic cholangiocarcinoma (ICC) and 90 prospective ICI-treated HCC patients. Whole exome sequencing was performed in selected samples (n = 61) of each cancer subtype. Single-cell RNA sequencing was performed on fresh primary tumor samples from 15 HCC patients and 8 ICC patients. **Results:** Through integrative multi-omics analyses, we identified a novel ICI-sensitive HCC subtype (IS-HCC) characterized by a pre-dysfunctional CD8+ T cell microenvironment and distinct genomic drivers (TP53, PIK3R1, OR6P1 and CHIT1). While bulk transcriptomic profiles revealed partial similarity with intrahepatic cholangiocarcinoma (ICC), single-cell resolution uncovered unique immune dynamics in IS-HCC, marked by transitional CD8+ T cells co-expressing exhaustion (PDCD1, HAVCR2) and activation (GZMB, IFNG) markers. By validation in a prospective ICI-treated HCC cohort (n = 90), this pre-dysfunctional T cell state of IS-HCC, rather than tumor mutational burden (TMB), predicted superior ICI response (OR = 4.595, 95%CI: 1.725-12.022), challenging neoantigen-centric paradigms. Moreover, glycan biosynthesis and hypoxia related immune suppression was found in IS-HCC patients, suggesting metabolic-immune crosstalk via hypoxia and glycan pathways might be actionable targets. We developed and validated a 29-gene signature across major global HCC cohorts that stratified IS-HCC patients, who exhibited aggressive baseline features but achieved favorable response to ICI therapies. **Conclusion:** Clinically, this biomarker-driven framework transcends current selection paradigms and addresses a critical unmet need by enabling precise ICI deployment

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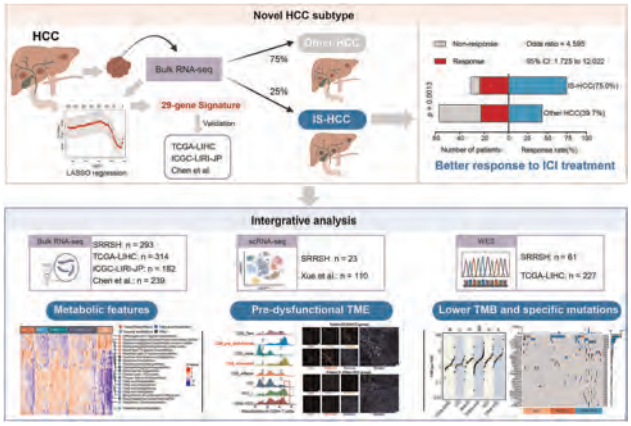
selection. Our findings redefine HCC taxonomy through immune-contextual biomarkers, offering a roadmap for biomarker-driven trials and combinatorial strategies to overcome resistance. This work bridges molecular discovery to clinical translation, with potential to double ICI efficacy rates in stratified populations and spare non-responders from futile therapies, advancing precision immuno-oncology in liver cancer.



Disclosures: Junjie Xu: Nothing to Disclose

0005 | LONG-TERM DATA OF ELAFIBRANOR IN PRIMARY SCLEROSING CHOLANGITIS: INTERIM SAFETY AND EFFICACY DATA FROM THE ONGOING OPEN-LABEL EXTENSION OF THE ELMWOOD PHASE II TRIAL

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Background: In the double-blind period (DBP) of the phase II ELMWOOD trial (NCT05627362), elafibranor (ELA) was well tolerated and improved biochemical markers of cholestasis in patients with primary sclerosing cholangitis (PSC) compared with placebo (PBO).[1] We report interim results up to 28

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weeks of the ongoing ELMWOOD open-label extension (OLE). **Methods:** Patients completing the DBP on PBO, ELA 80 mg, or ELA 120 mg were eligible to enter the OLE and receive daily ELA 120 mg. Endpoints included treatment-emergent adverse events (TEAEs) and mean changes from DBP baseline in liver biochemistry and pruritus according to the Worst-Itch Numeric Rating Scale (WI NRS) to OLE Week 28, and in non-invasive tests (NITs) of fibrosis (enhanced liver fibrosis [ELF] and PRO-C3) to OLE Week 16. **Results:** Overall, 63/64 (98.4%) patients who completed the DBP entered the OLE; 22/22 (100%) patients continued ELA 120 mg treatment, and 20/21 (95.2%) and 21/21 (100%) crossed over having received PBO and ELA 80 mg in the DBP, respectively. At data cutoff (September 2024), TEAEs have been reported by 31/60 (51.7%) patients in the OLE; the most common TEAEs were COVID-19, nausea, pruritus, and weight increase (4/60 [6.7%] for each). TEAEs that led to treatment discontinuation have occurred in 3/60 (5.0%) patients (patient 1: diarrhea, nausea, and vomiting; patient 2: hepatocellular carcinoma; patient 3: nausea, pruritus, and agitation); all three patients had crossed over from PBO. Patients crossing over from PBO have had reductions in alkaline phosphatase (ALP) at OLE Week 4 (−36.1%) and Week 28 (−40.6%); patients initially on ELA 80 mg and 120 mg maintained ALP response or achieved further reductions to Week 28 (−35.6% and −46.3%, respectively; Table). At OLE Week 28, reductions have been seen in alanine aminotransferase, aspartate aminotransferase, total bilirubin, and γ-glutamyl transferase in patients crossing over from PBO (−21.0%, −2.5%, −10.0%, −16.9%); maintained response or further reductions have been seen in patients initially on ELA 80 mg (−33.4%, −21.7%, −26.0%, −30.0%) and ELA 120 mg (−27.5%, −6.5%, −17.0%, −37.2%). Reductions in WI NRS have been observed in all groups at OLE Week 28 (crossover PBO: −0.10; crossover ELA 80 mg: −0.90; continuous ELA 120 mg: −1.28). At OLE Week 16, patients initially on ELA 80 mg or ELA 120 mg have had further reductions in NIT of fibrosis (ELF: −0.16 and −0.15; PRO-C3: −20.6% and −14.4%); these markers have stabilized or reduced in patients initially on PBO (ELF: 0.05; PRO-C3: −9.3%). **Conclusion:** ELA 120 mg has been well tolerated in patients with PSC in the ELMWOOD OLE. All groups have had reductions in biochemical markers of cholestasis and pruritus. Patients crossing over from PBO have had stabilization or reductions in NITs of fibrosis, while patients initially on ELA have seen further reductions in NITs of fibrosis with continued ELA treatment.

References: 1. Levy C, et al. *Journal of Hepatology.* 2025:[Online ahead of print]

Table. Change from DBP baseline in biochemical parameters for each treatment group

Biochemical parameter	Treatment group	Change from DBP baseline			
		DPB Week 12	OLE Week 4	OLE Week 16	OLE Week 28
ALP, n; mean % (SD)	PBO – ELA 120 mg	23, 7.3 (29.6)	18, −36.1 (15.5)	11, −31.5 (21.4)	5, −40.6 (24.8)
	ELA 80 mg – ELA 120 mg	22, −25.4 (24.2)	20, −35.0 (19.4)	11, −31.0 (25.5)	7, −35.6 (27.4)
	ELA 120 mg – ELA 120 mg	23, −45.3 (11.9)	21, −48.1 (12.1)	14, −44.0 (12.8)	8, −46.3 (11.9)
ALT, n; mean % (SD)	PBO – ELA 120 mg	23, 10.5 (35.0)	18, −0.2 (87.1)	10, −13.4 (50.5)	5, −21.0 (30.5)
	ELA 80 mg – ELA 120 mg	22, −12.8 (29.2)	20, −15.6 (22.4)	11, −17.0 (31.9)	7, −33.4 (22.2)
	ELA 120 mg – ELA 120 mg	23, −22.2 (37.8)	21, −22.1 (50.0)	14, 2.9 (107.6)	8, −27.5 (16.9)
AST, n; mean % (SD)	PBO – ELA 120 mg	23, 13.7 (42.1)	18, 10.2 (53.5)	11, 5.0 (44.5)	5, −2.5 (42.3)
	ELA 80 mg – ELA 120 mg	22, 6.9 (51.0)	20, −0.6 (23.5)	11, −3.7 (32.1)	7, −21.7 (20.5)
	ELA 120 mg – ELA 120 mg	23, −8.1 (31.8)	21, −8.6 (44.6)	14, 12.3 (72.4)	8, −6.5 (24.8)
TB, n; mean % (SD)	PBO – ELA 120 mg	23, −1.3 (31.4)	18, −10.8 (35.3)	10, −11.6 (36.1)	5, −10.0 (30.9)
	ELA 80 mg – ELA 120 mg	22, 3.1 (46.3)	20, 3.4 (60.4)	11, −18.9 (25.4)	7, −26.0 (28.5)
	ELA 120 mg – ELA 120 mg	23, −12.7 (28.7)	21, −23.1 (24.7)	14, −17.1 (27.5)	8, −17.0 (30.1)
GGT, n; mean % (SD)	PBO – ELA 120 mg	23, 14.1 (24.8)	18, −31.9 (16.0)	11, −30.1 (13.1)	5, −16.9 (39.0)
	ELA 80 mg – ELA 120 mg	22, −25.6 (19.2)	20, −31.9 (16.6)	11, −28.6 (23.3)	7, −30.0 (33.6)
	ELA 120 mg – ELA 120 mg	23, −38.8 (14.3)	21, −38.1 (15.1)	14, −32.4 (16.8)	8, −37.2 (17.4)
ELF, n; mean (SD)	PBO – ELA 120 mg	23, 0.24 (0.58)	NE	11, 0.05 (0.60)	NE
	ELA 80 mg – ELA 120 mg	22, 0.05 (0.52)	NE	12, −0.16 (0.29)	NE
	ELA 120 mg – ELA 120 mg	23, −0.01 (0.56)	NE	14, −0.15 (0.57)	NE
PRO-C3, n; mean % (SD)	PBO – ELA 120 mg	22, 1.1 (20.3)	NE	8, −9.3 (17.4)	NE
	ELA 80 mg – ELA 120 mg	21, −11.2 (13.6)	NE	9, −20.6 (20.1)	NE
	ELA 120 mg – ELA 120 mg	21, −4.9 (21.5)	NE	11, −14.4 (12.9)	NE

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DBP: double-blind period; ELA: elafibranor; ELF: enhanced liver fibrosis; GGT: γ-glutamyltransferase; NE: not evaluable; OLE: open-label extension; PBO: placebo; PRO-C3: N-terminal type III collagen propeptide; SD: standard deviation; TB: total bilirubin

Disclosures: Christopher Bowlus: Calliditas: Grant/Research Support, ChemoMab: Grant/Research Support, ChemoMab: Consultant, COUR Phamaceuticals: Grant/Research Support, Cymabay: Grant/Research Support, Cymabay: Consultant, Gilead: Grant/Research Support, GSK Pharmaceuticals: Grant/Research Support, GSK Pharmaceuticals: Consultant, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Invea Therapeutics: Consultant, Ipsen: Grant/Research Support, Ipsen: Consultant, Mirum: Grant/Research Support, NGM Bio: Consultant, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Pliant Therapeutics: Consultant, Viking Therapeutics: Grant/Research Support, Zydus Therapeutics: Grant/Research Support, Alnylam: Advisor, Amgen: Advisor, Amgen: Advisor, Amgen: Advisor, ArsenalBio: Advisor, Kezar: Advisor, Ono Pharmaceuticals: Advisor, Astra Zeneca: Advisor, AssemblyBio: Advisor, RegCell: Advisor, Esperion Therapeutics: Advisor, Gilead Biosciences: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, CymaBay Pharmaceuticals: Grant/Research Support, Takeda Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, Bristol Myers Squibb: Grant/Research Support, TARGET PharmaSolutions: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Mirum: Grant/Research Support, Ipsen: Grant/Research Support, Perspectum: Grant/Research Support, Pilant: Grant/Research Support, Sydus: Grant/Research Support, Chemomab: Consultant, CymaBay: Consultant, Therapeutics: Consultant, GSK: Consultant, Gilead: Consultant, Ipsen Bioscience: Consultant, Kezar: Consultant, NGM Bio: Consultant, Pliant Therapeutics: Consultant, Alnylam: Consultant, Amgen: Consultant, ArsenalBio: Consultant, Mirum: Consultant, Ono Pharmaceuticals: Consultant, AstraZeneca: Consultant, AssemblyBio: Consultant, RecCell: Consultant, Esperion Therapeutics: Consultant, Cynthia Levy: Cymabay: Grant/Research Support, Cymabay: Consultant, Intercept: Grant/Research Support, Intercept: Consultant, Calliditas: Grant/Research

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0006 | LEFT VENTRICULAR MASS INDEX, A KEY METRIC FOR CIRRHOTIC CARDIOMYOPATHY, IS A BETTER PREDICTOR OF MORBIDITY AND MORTALITY THAN PELD IN PEDIATRIC CIRRHOSIS

Dalia Bashir[1] Moreshwar Desai[2] Manpreet Virk[3] Curtis Kennedy[1] N. Thao Galvan[1] Tam Doan[1] Taylor Nack[2] Anna Banc-Husu[4] Divya Sabapathy[1] Noelle Gorgis[5], [1]Texas Childrens hospital/Baylor College of Medicine, [2]Baylor College of Medicine, [3]Texas Childrens hospital/Baylor College of Medicine, [4]Baylor College of Medicine, Texas Children's Hospital, [5]Childrens Hospital of Philadelphia

Background: Cirrhotic cardiomyopathy (CCM), a rapidly emerging comorbidity in both adult and pediatric cirrhosis, is associated with adverse perioperative outcomes and death. Despite its clinical relevance, the influence of CCM on the clinical trajectory and prognosis of children with cirrhosis has not been systematically studied. We aimed to examine the impact of left ventricular hypertrophy (LVH), a key echocardiographic (ECHO) metric of pediatric chronic cholestatic liver disease (CCM), on waitlist decompensation (WLD), post-transplant (LT) composite of serious adverse events (CSAE), and overall mortality, and compare its predictive value with PELD. **Methods:** We retrospectively reviewed charts of 236

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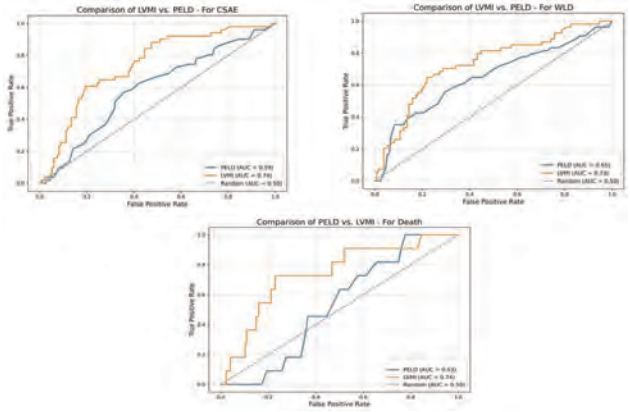
children with cirrhosis listed for liver transplantation (LT) between 2011 and 2021. LV mass (raw and indexed to height$^{2.7}$; LVMI) obtained from echo closest to LT was compared with other prognostic markers, including age at listing/LT, waitlist time, and PELD at the time of echo. Definitions: LV hypertrophy (LVH) = LVMI z score > 2; WLD = extra-hepatic organ involvement needing support pre-LT; CSAE = any post-LT life-threatening event, including graft failure; mortality = death after being listed to 1-year post-LT. Statistics: Optimal cutoff for LVMI was identified via the Youden Index. We used Fisher's exact test for categorical data and logistic regression with ROC analysis to assess the predictive ability of LVMI for WLD, CSAE, and mortality. LVMI and PELD were compared using McNemar's test ($p < 0.05$ significant). **Results:** 236 children with cirrhosis were listed for transplant, median age was 15 months [IQR: 6.6,116]; 54 females, 70 (31%) experienced WLD, 51/186 (27%) developed CSAE post-LT. Overall mortality was 11% (46% pre-LT; 54% post-LT). LVH was present in 54/236 (24%). Those with LVH had higher odds of WLD (OR 3; CI 1.6-5.7; p = 0.0012), CSAE (OR 3; CI 1.4-6; P = 0.0036), and death (OR 4.6; CI 1.9- 11; p = 0.0007). By Youden analysis, LVMI > 88 predicted WLD with 81% sensitivity and 63% specificity; LVMI > 91 predicted CSAE with 61% sensitivity and 76% specificity; and LVMI > 97 predicted mortality with 79% sensitivity and 78% specificity. LVMI performed better than PELD in predicting WLD (p = 0.02), CSAE (p = 0.044), and mortality (p = 0.02) (Figure). **Conclusion:** CCM is associated with mortality and morbidity in pediatric cirrhosis. Adding LVMI, a key metric of CCM, to PELD will vastly enhance prognostication and risk stratification in children with cirrhosis. Robust prospective multicenter studies are warranted.



Disclosures: Dalia Bashir: Nothing to Disclose, Moreshwar Desai: Nothing to Disclose, Manpreet Virk: Nothing to Disclose, Curtis Kennedy: Nothing to Disclose, N. Thao Galvan: 3D Systems: Consultant, 3DSystems: Consultant, Natera: Grant/Research Support, Tam Doan: Nothing to Disclose, Taylor Nack: Nothing to Disclose, Anna Banc-Husu: Mirum Pharmaceuticals: Site PI for industry-sponsored clinical trial, Divya Sabapathy: Nothing to Disclose, Noelle Gorgis: Nothing to Disclose

0007 | EFRUXIFERMIN WAS ASSOCIATED WITH IMPROVEMENTS IN MULTIPLE NON-INVASIVE TESTS INDICATIVE OF FIBROSIS REGRESSION IN PARTICIPANTS WITH COMPENSATED CIRRHOSIS DUE TO MASH (SYMMETRY)

Vlad Ratziu[1] Arun Sanyal[2] Guy Neff[3] Doreen Chan[4] Mark Burch[4] Erik Tillman[4] Sonja Billes[4] Arian Zari[4] Dragan Mackovic[4] Brittany De Temple[4] Reshma Shringarpure[4] Meena Jain[4] Timothy Rolph[4] Andrew Cheng[4] Kitty Yale[4] Mazen Noureddin[5], [1]Service D' Hepatogastroenterologie (FR), [2]Virginia Commonwealth University, [3]Covenant Metabolic Specialist, [4]Akero Therapeutics, [5]Houston Methodist Hospital

Background: Liver biopsy has limitations for measuring treatment effect in MASH trials and could be advantageously replaced by non-invasive tests (NITs). However, the optimal choice of NITs or combination thereof has been constrained by limited effect of interventions in patients with compensated MASH cirrhosis to date. We analyzed data from the phase 2b SYMMETRY efruxifermin trial (NCT05039450) that successfully demonstrated histological fibrosis regression in efruxifermin-treated participants with compensated cirrhosis due to MASH. **Methods:** Participants (N = 181) were randomly assigned (1:1:1) to once-weekly subcutaneous efruxifermin (28 or 50 mg) or placebo for 96 weeks. The primary outcome was ≥1-stage histological fibrosis improvement with no worsening of MASH (PMID:40341827). Here we analyzed data from individual participants (N = 137) for categorical improvements in imaging-based (liver stiffness measurement by vibration-controlled transient elastography [LSM]), serum (enhanced liver fibrosis [ELF] score), and composite (Agile 4) tests. **Results:** Baseline characteristics were: mean age 61 yrs, 67% female, mean BMI 36 kg/m^2, 80% T2D, mean LSM 24 kPa, ELF 11, platelets 183x10^9/L, ALT 40 U/L, AST 36 U/L. The proportion of participants with ≥1-stage fibrosis improvement and no worsening of MASH was 15% for placebo vs 29% for 28-mg (p = .131) and 39% for 50-mg efruxifermin (p = .009). The proportion of participants with ≥0.5 improvement (reduction) in ELF score was 14% in placebo vs 56% for 28-mg and 60% for 50-mg efruxifermin, while 6%, 27% and 38%, respectively, had an improvement in ELF of ≥1. The proportion of participants with an improvement in LSM (≥30% reduction) was 39% in placebo, vs 56% and 64% for

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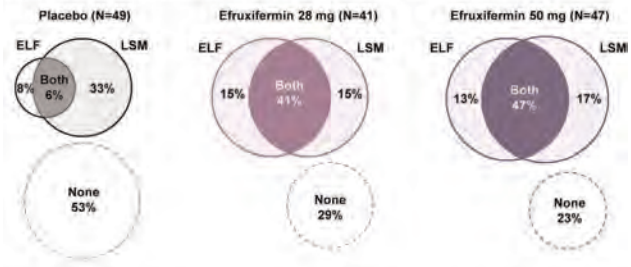
28-mg and 50-mg efruxifermin. Evaluation of participants with a response for both ELF ($\geq$0.5 reduction) and LSM ($\geq$30% reduction) resulted in a low placebo response rate (6%) and a clearly higher response rate for 28-mg (41%) and 50-mg (47%) efruxifermin (Figure). Finally, the proportion of participants who shifted from high (Agile 4 score $\geq$0.565) to low likelihood of cirrhosis (Agile 4 score $<$0.251) at Week 96, was 4% for placebo vs 9% and 30% for 28-mg and 50-mg efruxifermin. **Conclusion:** The high level of concordance between NITs, particularly for the 50-mg dose, highlights the consistent anti-fibrotic effect of efruxifermin. The combination of LSM and ELF response provided increased confidence in the ability to effectively monitor effects of efruxifermin.

Figure. Concordance of improvements in non-invasive tests in the SYMMETRY trial



Responder definitions are based on the change from baseline to week 96: ELF score ≥0.5 improvement (decrease); LSM ≥30% improvement (decrease). None indicates the proportion of participants who did not meet the above criteria for improvement in either ELF or LSM.

Disclosures: Vlad Ratziu: Novo-Nordisk: Consultant, Boehringer-Ingelheim: Consultant, Madrigal: Consultant, Akero: Consultant, 89Bio: Consultant, Sagimet: Consultant, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca ($<$5K), Terns ($<$5K), Merck ($<$5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis ($<$5K),: Consultant, Novo Nordisk: Consultant, Regeneron ($<$5K), Alnylam ($<$5K), Akero ($<$5K),: Consultant, Tern ($<$5K), Histoindex ($<$5K), Corcept ($<$5K),: Consultant, Path AI ($<$5K), Genfit ($<$5K), Mediar ($<$5K),: Consultant, Satellite Bio ($<$5K), Echosens ($<$5K), Abbott ($<$5K),: Consultant, Promed ($<$5K), Glaxo Smith Kline (~11K), Arrowhead ($<$5K): Consultant, Zydus (>60K), Boston Pharmaceutical ($<$5K), Myovent ($<$5K),: Consultant, Variant ($<$5K), Cascade ($<$5K), Northsea ($<$5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Guy Neff: Nothing to Disclose, Doreen Chan: Akero Therapeutics: Employee, Akero Therapeutics: Stock - publicly traded company, Mark Burch: Nothing to Disclose, Erik Tillman: Akero Therapeutics: Employee, Akero Therapeutics: Stock - publicly traded company, Akero Therapeutics: Employee, Akero Therapeutics: Stock - publicly traded company, Akero Therapeutics: Employee, Akero Therapeutics: Stock - publicly traded company, Akero Therapeutics: Employee, Akero Therapeutics: Stock - publicly traded company, Sonja Billes: Akero: Employee, Akero: Stock - publicly traded company, Arian Zari: Nothing to Disclose, Dragan Mackovic: Nothing to Disclose, Brittany De Temple: Nothing to Disclose, Reshma Shringarpure: Nothing to Disclose, Meena Jain: Nothing to Disclose, Timothy Rolph: Nothing to Disclose, Andrew Cheng: Nothing to Disclose, Kitty Yale: Akero Therapeutics: Employee, Mazen Noureddin: Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor: Terns,Takeda, Zydus., Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK: Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, Rivus Pharma, Cytodyn, and ChronWell: Stock – privately held company, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharmaceuticals: Consultant, Cytodyn: Consultant, GSK: Consultant, Eli Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Terns: Consultant, Takeda: Consultant, Allergan: Principal Investigator for a Drug Study, Akero: Principal Investigator for a Drug Study, BI: Principal Investigator for a Drug Study, BMS: Principal Investigator for a Drug Study, Gilead: Principal Investigator for a Drug Study, Galectin: Principal Investigator for a Drug Study, Genfit: Principal Investigator for a Drug Study, GSK: Principal Investigator for a Drug Study, Conatus: Principal Investigator for a Drug Study, Corcept: Principal Investigator for a Drug Study, Enanta: Principal Investigator for a Drug Study, Madrigal: Principal Investigator for a Drug Study, Novartis: Principal Investigator for a Drug Study, Novo Nordisk: Principal Investigator for a Drug Study, Shire: Principal Investigator for a Drug Study, Takeda: Principal Investigator for a Drug Study, Terns: Principal Investigator for a Drug Study, Viking: Principal Investigator for a Drug Study, Zydus: Principal Investigator for a Drug Study, Rivus Pharmaceuticals: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speaking and Teaching, Akero: Stock – privately held company, Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal

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0008 | ASSESSMENT OF EFFICACY AND SAFETY OUTCOMES BY LIVER FUNCTION WITH FIRST-LINE (1L) NIVOLUMAB PLUS IPILIMUMAB VS LENVATINIB OR SORAFENIB IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC): RESULTS: FROM CHECKMATE (9DW)

Peter Galle[1] Aiwu He[2] Thomas Decaens[3] Edward Gane[4] Matthias Pinter[5] David Tai[6] Armando Santoro[7] Gonzalo Pizarro[8] Michael Schenker[9] Nan Hu[10] Maria Jesus Jimenez Exposito[10] Bruno Sangro[11] Thomas Yau[12], [1]University Medical Center, Mainz, Germany, [2]MedStar Georgetown University Hospital, Washington, DC, [3]Univ. Grenoble Alpes, CHU Grenoble Alpes, Institute for Advanced Biosciences, Grenoble, France, [4]Auckland City Hospital, Auckland, New Zealand, [5]Medical University of Vienna, Vienna, Austria, [6]National Cancer Centre, Singapore, Republic of Singapore, [7]Humanitas University, Pieve Emanuele, and IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy, [8]Bradford Hill Centro de Investigacion Clinica, Recoleta, Chile, [9]Centrul de Oncologie Sf. Nectarie, Craiova, Romania, [10]Bristol Myers Squibb, Princeton, NJ, USA, [11]Clinica Universidad de Navarra and CIBEREHD, Pamplona, Spain, [12]Center of Cancer Medicine, University Department of Medicine, The University of Hong Kong, Hong Kong

Background: In an interim analysis of the phase 3 CheckMate 9DW study (median follow-up, 35.2 months [mo]), 1L NIVO + IPI demonstrated significant overall survival (OS) benefit vs LEN/SOR (median OS [mOS]: 23.7 [95% CI, 18.8–29.4] mo vs 20.6 [95% CI, 17.5–22.5] mo; HR, 0.79 [95% CI, 0.65–0.96]; $P = 0.018$). NIVO + IPI had a higher objective response rate (ORR) vs LEN/SOR (36% vs 13%; $P < 0.0001$) and durable responses per blinded independent central review (BICR) and manageable safety in pts with uHCC. We evaluated outcomes based on liver function, longitudinal changes in albumin-bilirubin (ALBI) score during treatment, and hepatic safety in CheckMate 9DW. **Methods:** Adults with uHCC without prior systemic therapy were randomized to NIVO 1 mg/kg + IPI 3 mg/kg Q3W (up to 4 cycles), followed by NIVO 480 mg Q4W, or investigator's choice of LEN 8 mg or 12 mg QD or SOR 400 mg BID (Yau T et al. *Lancet* 2025). Liver function was assessed by ALBI scores. **Results:** Among all randomized pts (N = 668), NIVO + IPI showed clinically meaningful efficacy and manageable safety vs LEN/SOR across ALBI subgroups (Figure). In all randomized pts, ALBI scores remained relatively stable throughout the treatment period in both treatment arms, with slight improvement noted with NIVO + IPI vs LEN/SOR over time (Figure). There was an 18% reduction in the risk of liver function deterioration with NIVO + IPI vs LEN/SOR (Figure). Among 332 pts treated with NIVO + IPI, any-grade immune-mediated hepatitis occurred in 63 (19%) pts, of which 51 (15%) pts had grade 3/4 events. Median time to onset of immune-mediated hepatitis was 6.0 (range, 0.9–88.9) weeks; these resolved in 47 (14%) pts with a median duration of 10.3 (range, 0.9–129.3+) weeks. Of 332 treated pts, 56 (17%) pts received high-dose steroids for immune-mediated hepatitis management. Immune-mediated hepatitis led to treatment discontinuations in 19 (6%) pts. **Conclusion:** NIVO + IPI showed a favorable benefit-risk profile vs LEN/SOR regardless of baseline ALBI grade. Pts treated with NIVO + IPI maintained their ALBI scores during the treatment period and had a longer time to liver function deterioration vs LEN/SOR. Immune-mediated hepatitis was manageable with established algorithms and most did not lead to discontinuation. These results further support 1L NIVO + IPI as a standard of care in uHCC.

A

Efficacy in all randomized pts	ALBI grade 1ª		ALBI grade 2/3ª	
	NIVO + IPI (n = 186)	LEN/SOR (n = 210)	NIVO + IPI (n = 149)	LEN/SOR (n = 123)
mOS (95% CI), mo	35.4 (23.9–NE)	23.2 (21.4–28.3)	16.9 (12.6–23.0)	14.0 (11.1–16.6)
HR (95% CI)	0.75 (0.57–0.98)		0.75 (0.57–0.99)	
OS rate (95% CI), %				
24-mo	58 (50–64)	47 (39–54)	39 (31–47)	27 (19–35)
36-mo	48 (40–56)	31 (24–38)	24 (17–32)	13 (7–21)
ORR by BICR (95% CI), %	37 (30–45)	14 (10–20)	35 (27–43)	11 (6–18)
CR, %	8	3	6	0
Safety in all treated pts, n (%)	**NIVO + IPI (n = 186)**	**LEN/SOR (n = 205)**	**NIVO + IPI (n = 146)**	**LEN/SOR (n = 120)**
Any-grade/grade 3–4 TRAEs[b]	156 (84)/78 (42)	188 (92)/87 (42)	122 (84)/59 (40)	109 (92)/51 (43)
Any-grade TRAEs[b] leading to discontinuation	37 (20)	19 (9)	22 (15)	15 (13)

[a]Baseline liver function was evaluated using ALBI score (0.66 × log10[bilirubin (μmol/L)] − 0.085 × [albumin (g/L)]); ALBI subgroups were classified by score: grade 1, ≤ −2.60; grade 2, > −2.60 to ≤ −1.39; and grade 3, > −1.39. [b]Includes events reported between first dose and 30 days after last dose of study therapy. CR, complete response; NE, not estimable; TRAE, treatment-related adverse event.

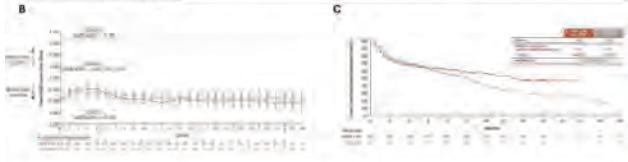

Figure legend. A. Efficacy and safety outcomes by baseline ALBI grade. B. Mean changes in ALBI score over time among all randomized patients. C. Time to liver function deterioration among all randomized patients.

Disclosures: Peter Galle: Nothing to Disclose, Aiwu He: Nothing to Disclose, Thomas Decaens: Nothing to

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0009 | BRELOVITUG (BJT-778) MONOTHERAPY ACHIEVED 100% VIROLOGIC RESPONSE IN PATIENTS WITH CHRONIC HEPATITIS D (CHD): ON TREATMENT WEEK 48 PHASE 2 STUDY RESULTS

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Background: Brelovitug (BJT-778), a fully human anti-HBsAg monoclonal antibody, is currently being evaluated in an ongoing Phase 2 study, BJT-778-001, for the treatment of chronic hepatitis delta (CHD). We report interim on treatment Week 48 safety and efficacy results of brelovitug administered subcutaneously as monotherapy in patients with CHD. **Methods:** Each treatment arm enrolled up to 20 participants with quantifiable HDV RNA, HBV DNA <100 IU/ml on nucleos(t)ides, compensated liver disease, ALT ≤ 10x ULN, and PLT ≥ 100K/ul. Participants received one of the following regimens: 1) Brelovitug 300 mg SC once weekly (QW); 2) Brelovitug 600 mg SC QW for 12 weeks followed by Q2W; and 3) Brelovitug 900 mg SC every 4 weeks with a loading dose at Week 2. Endpoints include safety/tolerability and the proportion of patients achieving (i) virologic response defined as ≥ 2 log10 IU/mL reduction in HDV RNA from BL or HDV RNA below the lower limit of quantification, target not detected ($<$LLOQ, TND); (ii) ALT normalization, and (iii) composite response defined as virologic response and ALT normalization. Additional endpoints include the proportion of subjects achieving HDV RNA $<$LLOQ, and $<$LLOQ, TND. **Results:** 47 CHD patients were enrolled: 18 into Arm 1, 11 into Arm 2, and 18 into Arm 3. Overall, median age was 44 y (20-68y), 92% white, 55% male, 28% with cirrhosis, median HDV RNA of 5.3 $\log_{10}$IU/mL, and median HBsAg of 4.2 $\log_{10}$ IU/mL. Week 48 data is available on 33 subjects. 100% of participants have achieved a virologic response with responses deepening over time. At Week 48, 64%, 75%, and 82% have achieved combined virologic response and ALT normalization with 300 mg QW, 600 mg QW/Q2W, and 900 mg Q4W with a LD at W2, respectively. Interim Week 48 on-treatment results for the efficacy endpoints are listed in the table below. Across all treatment arms, brelovitug has been safe and well tolerated with no reported serious or Grade 3/4 adverse events, and no treatment discontinuations due to adverse events. Full Week 48 results will be presented. **Conclusion:** All brelovitug regimens explored achieved 100% virologic response with a combined response rate of 64%-82% at the interim Week 48 analysis. All dosing regimens have been safe and well-tolerated. Phase 3 trials are underway.

	300 mg QW (n=18)	600 mg QW/Q2W (n=10*)	900 mg Q4W (n=18)
Virologic Response	12/12 (100%)	10/10 (100%)	11/11 (100%)
HDV RNA <LLOQ	8/12 (67%)	7/10 (70%)	9/11 (82%)
HDV RNA <LLOQ, TND	6/12 (50%)	3/10 (30%)	5/11 (45%)
ALT normalization**	7/11 (64%)	3/4 (75%)	9/11 (82%)
Virologic response + ALT normalization**	7/11 (64%)	3/4 (75%)	9/11 (82%)

*1 subject moved out of the country after Week 8
**In subjects with baseline ALT>ULN

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0010 | WEIGHT-DEPENDENT AND INDEPENDENT EFFECTS OF SEMAGLUTIDE IN PARTICIPANTS WITH MASH: SECONDARY ANALYSIS OF THE PHASE 3 ESSENCE TRIAL

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Background: In the 72-week interim analysis of the phase 3 ESSENCE trial (NCT04822181), once-weekly subcutaneous semaglutide 2.4 mg met its primary endpoint, demonstrating superiority over placebo for histological outcomes and non-invasive tests (NITs). We aimed to determine whether its therapeutic effects are fully dependent on weight loss and to quantify the magnitude of weight-dependent and weight-independent effects. **Methods:** The first 800 randomised participants were evaluated. NITs & liver biopsies were conducted at baseline and week 72. MASH-related NIT responder endpoints included $\geq$17-unit reduction in ALT and $\geq$0.22 reduction in FAST score; fibrosis-related NIT endpoints included 30% reduction in VCTE and $\geq$0.5-unit reduction in ELF score. Histological endpoints included MASH resolution and fibrosis improvement. Logistic regression assessed total, weight loss-dependent, and weight loss-independent effects (expressed as odds ratios [OR]), with percentage weight loss as the mediator and treatment as the exposure. Analyses adjusted for baseline co-variates: T2D status, fibrosis stage and body weight. Missing data were excluded. Histological and NIT responder rates were stratified by weight reduction thresholds ($\leq$2%, $\leq$5%, $\leq$7%, $>$7%). **Results:** For MASH endpoints, the total effect of semaglutide (OR [95% CI]) for ALT reduction and MASH resolution without fibrosis worsening was 4.7 (3.3–6.6) and 3.9 (2.8–5.5) respectively (Figure 1a). The corresponding weight loss-independent effects were 3.0 (2.0–4.6) and 2.0 (1.4–3.0), whilst weight loss-dependent effects were 1.5 (1.2–2.0) and 1.9 (1.6–2.4). For fibrosis endpoints, the total effect of semaglutide for VCTE and fibrosis improvement without MASH worsening was 3.0 (2.0–4.4) and 2.1 (1.5–3.1), respectively. The corresponding weight loss-independent effects were 1.7 (1.1–2.7) and 1.5 (1.0–2.4), and weight loss-dependent effects were 1.7 (1.4–2.2) and 1.4 (1.1–1.8). Histological response increased with greater weight loss on semaglutide (Figure 1b): MASH resolution rose from 48.4% to 71.5% and fibrosis improvement from 27.2% to 41.8% across the

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< 2% to > 7% weight loss range, with preservation of the estimated difference in responder proportions (EDP) versus placebo. Placebo-adjusted improvements (EDP) in ALT, FAST, VCTE and ELF with semaglutide were observed across all weight loss categories. **Conclusion:** Semaglutide confers weight-independent liver benefits, with further improvements proportionate to weight loss.

Figure 1a

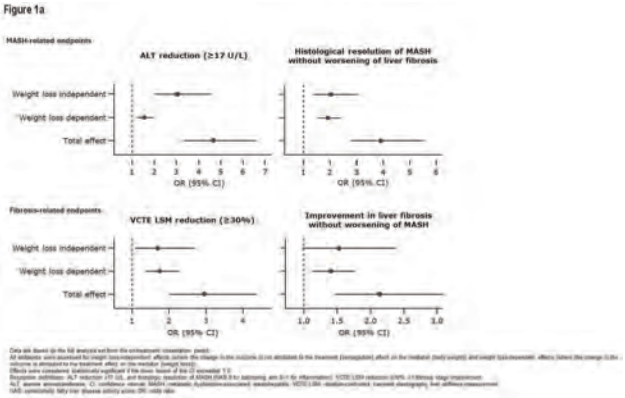
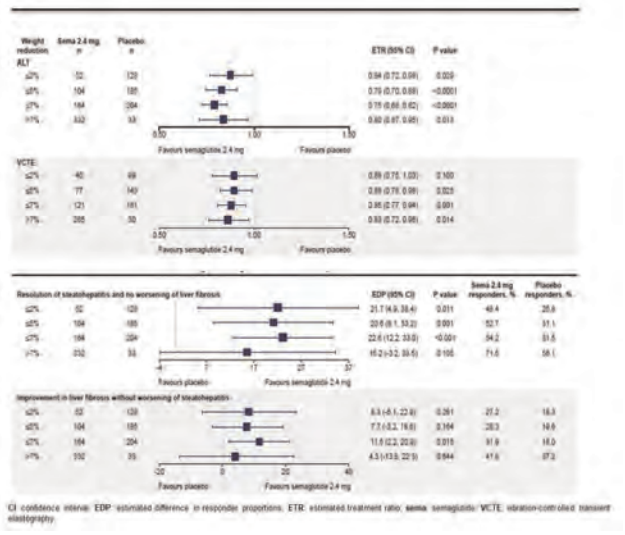


Figure 1b



CI: confidence interval; EDP: estimated difference in responder proportions; ETR: estimated treatment ratio; sema: semaglutide; VCTE: vibration-controlled transient elastography.

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★ 0011 | A PROSPECTIVE STUDY OF PHOSPHATIDYLETHANOL (PETH) AS A DIAGNOSTIC BIOMARKER FOR IDENTIFYING ALCOHOL USE DISORDER (AUD) AMONG PARTICIPANTS AT RISK OF STEATOTIC LIVER DISEASE

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Background: Alcohol intake is a leading risk factor for liver fibrosis progression in steatotic liver disease (SLD). Although alcohol use disorder (AUD) is prevalent in SLD, it has not been systematically examined. We aimed to determine the AUD prevalence in SLD and examine the performance of PEth as a biomarker of occult AUD in a large prospective cohort of participants who are at risk of steatotic liver disease in the United States. **Methods:** This prospective study included 607 (55% women) adult participants who were overweight/obese. We performed a standardized interview, physical exam, laboratory testing (including PEth), vibration-controlled transient elastography (VCTE) and magnetic resonance imaging (MRI). Hepatic steatosis was defined as MRI-proton density fat fraction (PDFF) ≥5%. Participants were classified into SLD subcategories according to the AASLD criteria. Alcohol consumption was quantified using the Lifetime Drinking History and Alcohol Use Disorders Identification Test (AUDIT). We diagnosed AUD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. We examined diagnostic test performance of PEth for the AUD diagnosis using area under the receiver operating curve (AUROC). **Results:** Study participants had a mean age (+/-sd) of 51.2 ± 13.3 years, a mean body mass index (BMI) was 32.6 (± +/- 5.9) Kg/m^2 n, and 40% were Hispanics; respectively. The prevalence of SLD was 71% including 96% MASLD, 3% for MetALD, and 1% for ALD, respectively. The prevalence of AUD in the entire cohort was 5%, with no significant difference among SLD and non-SLD participants. AUD prevalence by SLD subtype was 3.6% in MASLD, 42.9% in MetALD, and

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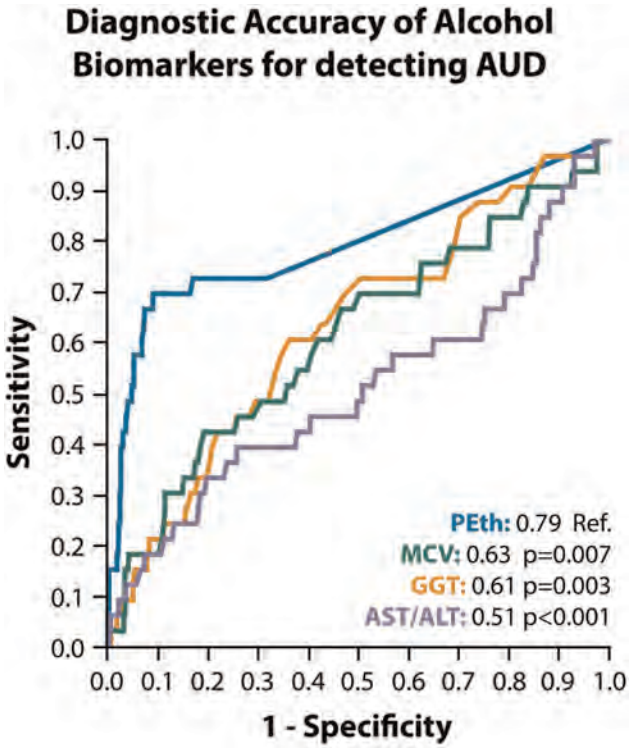
50% in ALD. PEth had a good diagnostic accuracy for AUD and yielded an AUROC of 0.80 (95% CI 0.72-0.88, p-value <0.001) with a sensitivity of 70% and specificity of 91% at the optimal cut-point of PEth $\geq$ of 43 ng/ml. We then compared Diagnostic accuracy of PEth versus other biomarkers for AUD including AST:ALT ratio, GGT and MCV and PEth remained clinically and statistically significantly superior (P-value $<$ 0.05, for all pair-wise comparisons). **Conclusion:** AUD is a common comorbidity in SLD, affecting up to half of individuals with MetALD and ALD. A PEth level $\geq$ 43 ng/mL may indicate AUD and warrant further assessment. These data have implications for changing clinical practice for which patients may benefit from AUD related interventions.



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0012 | COMPARATIVE EFFECTIVENESS OF PALLIATIVE CARE DELIVERED BY TRAINED HEPATOLOGISTS VERSUS PALLIATIVE CARE SPECIALISTS: A MULTI-CENTER CLUSTER RANDOMIZED TRIAL

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Background: Palliative care (PC) interventions improve quality of life (QoL) for patients with serious illnesses. However, there is paucity of data examining the impact of PC in patients with end-stage liver disease (ESLD). This study aims to compare the effectiveness of PC delivered by trained hepatologists to that delivered by PC specialists in improving QoL. **Methods:** We conducted a cluster randomized controlled trial involving 19 centers randomized to one of two PC models: 1) PC delivered by PC specialists (PC-led, 8 centers), or 2) PC delivered by trained hepatologists (Hep-led, 11 centers). Hepatologists in the Hep-led arm received virtual training on PC tailored for ESLD, after randomization. The enrollment period spanned from January 2019 to March 2025. Eligible ESLD patients had decompensated cirrhosis with a complication within the past 6 months and/or hepatocellular carcinoma. Both arms followed a standardized PC intervention over 4 visits (initial, 1, 2, and 3 months) that included assessment of symptoms, distress, depression, and discussion of prognosis and goals of care. The primary outcome was change in QoL, as measured by the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) instrument at 3 months. Secondary outcomes included symptom severity [ESAS], distress [DT], depression [PHQ-9], and satisfaction with care [FAMCARE-P]. Intention-to-treat analysis was performed, excluding patients who underwent transplantation or were transferred to hospice prior to month 3. To account for the cluster-based randomization, we utilized a linear mixed model with treatment arm indicator as a covariate and site (cluster) as the random effect. We adjusted for the baseline FACT-Hep total score and randomization strata. A pre-specified non-inferiority (NI) analysis of the Hep-led model with a NI margin of -4 was planned in case the superiority p-value >0.05. **Results:** A total of 935 patients were enrolled (Table). The mean age of the overall cohort was 63 years; 70% male; 14% Hispanic; and 16% African Americans. The primary etiology of liver disease was alcohol-associated in 38%, MASH in 27%, and viral hepatitis in 24%. The FACT-Hep total score improved in both arms:

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by 7.0 in the PC-led arm and 8.1 in the Hep-led arm (adjusted means, both $p < 0.01$). Pre-specified non-inferiority analyses showed that the amount of improvement in the Hep-led arm was statistically non-inferior to the PC-led arm ($p = 0.01$ for NI margin = -4). Baseline depression scores predicted change in QoL scores in the overall cohort ($p = 0.03$). Patients in both models had improvements in depression and patient satisfaction from baseline to 3 months, with better improvements in the Hep-led arm than the PC-led arm. **Conclusion:** This is the first trial demonstrating that PC intervention significantly improves QoL of patients with ESLD, with Hep-led arm as beneficial as PC-led arm. Future efforts must prioritize integration of PC into hepatology training and practice.

Table: Demographics, Clinical features and Outcomes in the Two comparative Models

Demographics	**PC Specialists led (PC-led) (N= 516)**	**Trained Hepatologists led (Hep-led) (N=419)**
Mean Age (SD) yrs	64 (10.0)	62 (10.4)
Females	24%	37%
Hispanic	12%	16%
African American	17%	14%
High School or less education	50%	48%
Charlson Comorbidity Score (mean, SD)	5.1 (2.6)	4.8 (2.1)
MELD 3.0 (mean, SD)	14.0 (4.8)	14.9 (5.5)
CTP: A/B/C	20% /62% /16%	14% /53% /33%
Hepatocellular Cancer	60%	40%
Hepatic Encephalopathy	58.7%	58.5%
***FACT-Hep subscales**	Mean raw change scores from baseline to 3-months	
Physical Well Being (PWB)	0.9 (5.4)	1.7 (5.4)
Social Well-Being (SWB)	0.5 (5.3)	0.8 (5.4)
Emotional Well-Being (EWB)	0.3 (4.6)	1.7 (4.8)
Functional Well-being (FWB)	0.8 (5.9)	1.5 (5.8)
FACT-HCS (Hepatobiliary Cancer)	2.9 (8.6)	4.1 (9.2)
FACT- G (General)	2.5 (13.8)	5.8 (14.3)
FACT-TOI (Trial Outcome Index)	4.8 (15.5)	7.3 (15.8)
FAMCARE-P (Patient Satisfaction)	1.3 (11.2)	2.8 (10.9)
***PHQ-9** (Depression)	-0.5 (5.3)	-1.5 (5.5)
***DT** (Distress Thermometer)	-0.2 (2.8)	-0.5 (3.0)
***ESAS (Edmonton Symptom Assessment Scale)**	Mean raw change scores from baseline to 3-months	
Pain	-0.2 (2.9)	-0.4 (2.7)
Tiredness	-0.5 (3.0)	-0.5 (3.0)
Well-being	-0.3 (2.8)	-0.6 (2.8)
Muscle Cramps	-0.4 (3.3)	-1.0 (3.4)
Sleep	-0.3 (3.6)	-1.1 (3.6)
Itch	-0.4 (3.4)	-1.1 (3.2)

*Decrease in ESAS, DT, and PHQ-9 is improvement in symptoms, distress and depression; while an increase in FACT-Hep scores and patient satisfaction is improvement in QoL and satisfaction with palliative care.

Disclosures: Manisha Verma: Nothing to Disclose, Victor Navarro: Nothing to Disclose, Andrzej Kosinski: Nothing to Disclose, Tamar Taddei: Nothing to Disclose, Michael Volk: Nothing to Disclose, Richard Kalman: Gilead: Speaking and Teaching, Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant, Target-RWE: Consultant, Madrigal Pharmaceuticals: Consultant, Merck (Any division): Consultant, Boehringer Ingleheim: Consultant, Sofia Jakab: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Eurofins: Grant/Research Support, Eric Orman: Sitero: Consultant, Biovie: Advisor, Maya Balakrishnan: Nothing to Disclose, Mina Rakoski: Nothing to Disclose, Don Rockey: WL Gore and Associates: Consultant, Cook Medical: Consultant, BD Medical: Consultant, AstraZeneca: Grant/Research Support, Bio89: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Durect: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Intercept: Grant/Research Support, Inventiva: Grant/Research Support, Madrigal: Grant/Research Support, Ocelot: Grant/Research Support, Salix: Grant/Research Support, Novonordisk: Grant/Research Support, Galectin: Grant/Research Support, Versantis: Grant/Research Support, Viking: Grant/Research Support, Kristel Hunt: Nothing to Disclose, Christopher Woodrell: Nothing to Disclose, Nothing to Disclose, Roniel Cabrera: Nothing to Disclose, Ayse Aytaman: Nothing to Disclose, Binu John: Exact Sciences: Grant/Research Support, Genentech: Grant/Research Support, Glycotest, Inc: Grant/Research Support, Gilead: Grant/Research Support, Exelixis: Consultant, Takeda: Grant/Research Support, GlaxoSmithKline: Consultant, Astra Zeneca: Consultant, Brendan McGuire: Alnylam pharmaceuticals: Grant/Research Support, Gyorgy Baffy: Astellas Pharma, Inc: Consultant, Novo Nordisk, Inc: Consultant, Elliot Tapper: Madrigal: Grant/Research Support, Rohit Nathan: Nothing to Disclose, Marina Roytman: Nothing to Disclose

★ 0013 | UTILITY OF CORONARY CT ANGIOGRAPHY VERSUS DOBUTAMINE STRESS IN PREDICTING OBSTRUCTIVE CORONARY ARTERY DISEASE

Hoang Anh Richardson[1] Ashley Spann[1] Samuel Nwosu[1] Donald Sengstack[1] Benjamin French[1] Jayant Bagai[1] Alexandra Shingina[2] Jeffrey Carr[1] Manhal Izzy[1], [1]Vanderbilt University Medical Center, [2]University of Michigan Health

Background: Accurate non-invasive evaluation of obstructive coronary artery disease (CAD) in liver transplant (LT) candidates is critical for risk stratification and management. Dobutamine stress echocardiography (DSE) and coronary computed tomography angiography (CCTA) are widely used diagnostic modalities; however, reports of their success rate and predictive performance in identifying obstructive CAD are variable. **Methods:** In this retrospective cohort study, we analyzed 186 adult patients with cirrhosis who underwent both CCTA and DSE prior to invasive coronary angiography (ICA) as part of pre-transplant cardiac evaluation. Patients with heart transplantation were excluded. Obstructive CAD was defined as $\geq 70\%$ stenosis on ICA. CCTA results were grouped into low-moderate risk (CAD-RADS 0, 1, 2, 3) and high risk (CAD-RADS 4, 5). Sensitivity (SN), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV) of DSE, CCTA, and CT-fractional flow reserve

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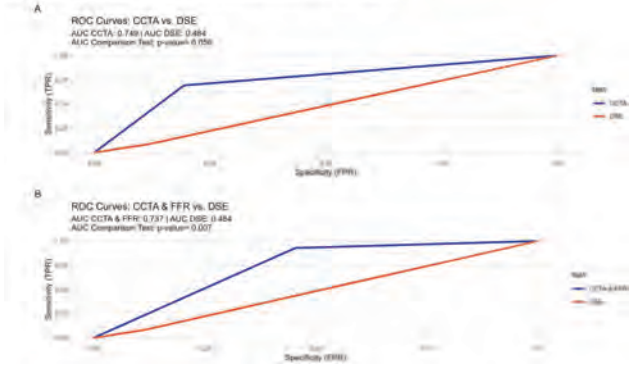
(FFR) were calculated. Receiver operating characteristic (ROC) analysis was evaluated for each testing modality with predictive performance between CCTA and DSE compared using the Delong statistical method. **Results:** Among the 61 patients who underwent ICA, preceded by CCTA and DSE, 16 had obstructive CAD confirmed by ICA. Rate of acceptable quality DSE, defined by studies with conclusive results, was 62.3% (38/61). DSE was positive for ischemia in 6.3% (1/16) of patients with obstructive CAD. 72.1% (44/61) of the obtained CCTA had definitive results. CCTA identified 56.3% (9/16) of patients with severe CAD on ICA. The SN, SP, PPV, and NPV for CCTA were 0.692 [CI 0.386, 0.909], 0.806 [95% CI 0.625, 0.925], 0.600 [95% CI 0.323, 0.837], and 0.862 [95% CI 0.683, 0.961] respectively. The SN, SP, PPV, and NPV for DSE were 0.083 [95% CI 0.002, 0.385], 0.885 [95% CI 0.698, 0.976], 0.250 [95% CI 0.006, 0.806], and 0.676 [95% CI 0.495, 0.826] respectively. 27 patients underwent FFR with CCTA. FFR was positive for a flow limiting lesion in 66.7% and negative in 33.3%. The SN, SP, PPV, and NPV for CT-FFR in diagnosing obstructive CAD were 0.636 [95% CI 0.308, 0.891], 0.267 [95% CI 0.078, 0.551], 0.389 [95% CI 0.173, 0.643], and 0.500 [95% CI 0.157, 0.843] respectively. ROC analysis demonstrated superior AUC for CCTA (AUC 0.749, $p = 0.056$) and CCTA with FFR (AUC 0.737, $p = 0.007$) compared to DSE alone (AUC 0.484) as demonstrated in Figure 1. **Conclusion:** CCTA demonstrated higher sensitivity and marginally superior predictive performance over DSE in identifying obstructive CAD in LT candidates. When combined with FFR, CCTA showed significantly improved diagnostic accuracy over DSE. These findings support the use of CCTA with FFR as a primary non-invasive modality for CAD risk stratification in transplant evaluation. Future studies are needed to validate these findings in a larger cohort.

Figure 1. ROC Analysis Comparing CCTA and CT-FFR with DSE



Disclosures: Hoang Anh Richardson: Nothing to Disclose, Ashley Spann: Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Samuel Nwosu: Nothing to Disclose, Donald Sengstack: Nothing to Disclose, Benjamin French: Nothing to Disclose, Jayant Bagai: Nothing to Disclose, Alexandra Shingina: Nothing to Disclose, Jeffrey Carr: Nothing to Disclose, Manhal Izzy: Mallinckrodt: Speaking and Teaching, Madrigal: Advisor

0014 | MELD 3.0 FAILED TO SUSTAINABLY ADDRESS SEX DISPARITIES IN US LIVER TRANSPLANT ALLOCATION

Tomohiro Tanaka[1] Dan Shane[2] Jennifer Lai[3], [1]University of Iowa School of Medicine, [2]University of Iowa College of Public Health, [3]University of California, San Francisco (UCSF)

Background: The July 2023 implementation of MELD 3.0 aimed to address longstanding sex disparities in liver transplant (LT) access. However, the causal effect of this policy change has not been formally evaluated. **Methods:** We analyzed U.S. national transplant registry data from 2/4/2020, to 9/30/2024, using a person-day structure to assess outcomes among adult ($\geq$18 years) LT candidates. Candidates with Status 1 listing or active MELD exception points were excluded. Primary outcomes included receipt of one of the top five liver organ offers and the probability of undergoing deceased donor liver transplantation. The primary exposure was the implementation of MELD 3.0. A difference-in-differences (DiD) design was used to evaluate (1) the immediate post-implementation period and (2) a secondary phase beginning three months later, capturing potential policy "burn-in" effects of the policy. DiD plot were drawn. Poisson and logistic regression models estimated offer and transplant probabilities. Mediation by height was assessed to examine residual sex disparities through a body size lens, and subgroup analyses were performed among candidates with height $<$166 cm. **Results:** We analyzed 9,952,473 person-day observations from 60,159 adult liver transplant candidates. In DiD estimates, the MELD 3.0 policy was associated with further increased organ offer rates for women at implementation (rate ratio [RR] $_{1.24}$ 1.35 $_{1.47}$) and three months later (RR $_{1.10}$ 1.15 $_{1.19}$) [Fig A]. Conversely, transplant rates for women were significantly lower than those for men before MELD 3.0 (odds ratio [OR] $_{0.84}$ 0.86 $_{0.886}$). The implimentation of MELD 3.0 conferred significantly

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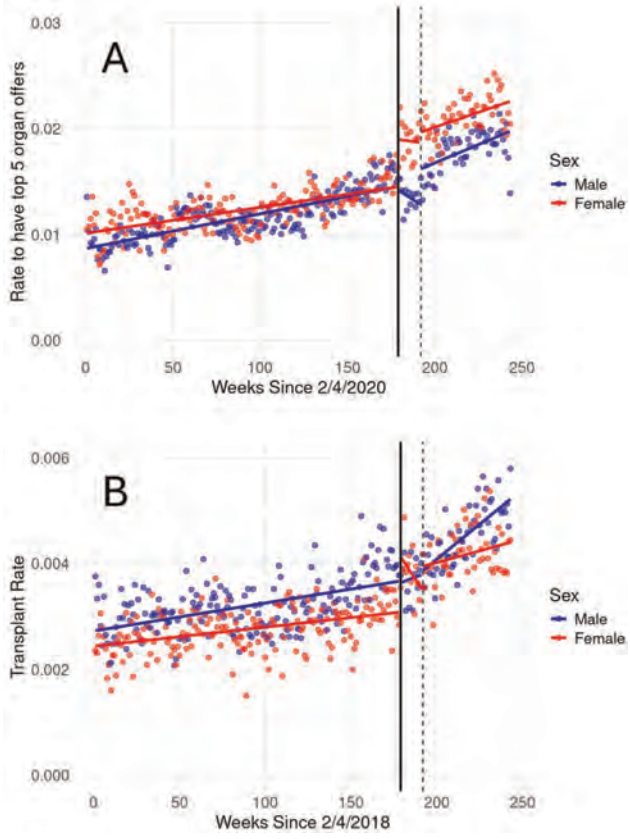
greater benefit to women than men (OR $_{1.13}$ 1.34 $_{1.59}$ immediately and $_{1.07}$ 1.17 $_{1.29}$ at three months), based on DiD estimates. However, by the end of the study period, the estimated effect of being female based on the fitted model was an OR of 0.81, suggesting a return to a level of disparity similar to the pre-MELD 3.0 era [Fig B]. Adjustment for height (OR $_{1.011}$ 1.012 $_{1.014}$ per 1 cm) eliminated the baseline female disadvantage in transplant rates ($_{0.99}$ 1.03 $_{1.07}$) while preserving the significant policy effect of MELD 3.0 ($p < 0.001$). Among taller candidates ($\geq$ 166 cm), the baseline sex disparity in transplant rates was attenuated (OR $_{0.892}$ 0.93 $_{0.970}$), whereas in the shorter group ($<$ 166 cm), rates were similar between sexes prior to the policy ($_{0.95}$ 1.01 $_{1.07}$). The policy benefit for women was similar in the taller group (OR $_{0.99}$ 1.13 $_{1.30}$), but more pronounced in the shorter group ($_{1.15}$ 1.47 $_{1.86}$); however, this sex-based advantage diminished over time, with the estimated OR converging to 0.98 by the end of the study period. **Conclusion:** MELD 3.0 temporarily improved transplant access for women, especially in the early post-implementation period. However, this effect diminished after the policy implementation, revealing persistent sex disparities linked to smaller body size even under MELD 3.0.



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0015 | LEVERAGING IMMUNOTHERAPY FOR TRANSPLANTATION IN HEPATOCELLULAR CARCINOMA (LIFT HCC): ANALYSIS OF 375 PATIENTS RECEIVING PRE-TRANSPLANT IMMUNE CHECKPOINT INHIBITORS

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Background: While immune checkpoint inhibitors (ICIs) are increasingly used in patients with hepatocellular carcinoma (HCC), data on their use in the pre–liver transplantation (LT) setting remain limited. We aimed to identify predictors of post-LT outcomes for patients receiving LT after ICIs treatment. **Methods:** A

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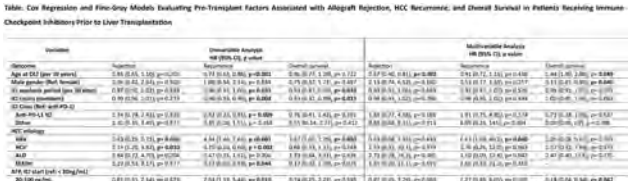
retrospective, multicenter cohort study was conducted across more than 70 centers worldwide, collecting HCC cases treated with ICIs in the context of downstaging or bridging before LT. Cox regression and Fine-Gray models were used to identify predictors of post-transplant outcomes, including recurrence-free survival (RFS), overall survival (OS), and rejection-free survival. **Results:** Among 375 patients from 12 countries, characteristics at ICI initiation were as follow: median (IQR) age: 56 (48, 62) years, 91% male, BCLC stage A in 23%, B in 36%, and C in 38%. 5.5% had metastasis and 20% had macrovascular invasion. Median tumor number and size were 3.0 (1.0, 5.0) and 4.9 cm (3.0, 7.6); 22% met Milan and 30% UCSF criteria at ICI initiation. ICI regimens included PD-1 (70%), PD-L1 (23%), PD-1/PD-L1 + CTLA-4 (3.6%), and others (2.8%). Median ICI cycles and washout were 4 (2, 10) and 72 days (37, 163), respectively. 91% received locoregional therapies. At OLT (based on pre-transplant Imaging), 38% and 43% were within Milan and UCSF criteria. Over a median follow-up of 1.6 years (95% CI 1.4-1.8), recurrence occurred in 28.0%, death in 22.2%, and rejection in 17.2% (44% mild, 54% moderate/severe; graft loss in 15% leading to retransplantation in 44% and death to 56%). One- and 4-year OS were 86% and 65%, and RFS were 73% and 55%, respectively. OS and RFS were longer among patients within Milan (vs. beyond Milan) at the time of OLT (all $p < 0.01$): 1- and 4-year OS 91% and 77%, and RFS 91% and 84% for those within Milan vs. 1- and 4-year OS 81% and 56%, and RFS 62% and 36% for those beyond Milan. AFP 100–500 vs < 20 at LT, HBV etiology, and beyond MC were associated with a higher risk of recurrence. Additionally, AFP 20–100 vs < 20 at both ICI initiation and LT, older age at LT, and female gender were associated with worse OS (Table). **Conclusion:** This represents the largest global study of pre-LT HCC patients treated with ICIs. Increased AFP and beyond MC at LT are strong predictors of HCC recurrence and shorter OS. The findings suggest that achieving Milan criteria and low AFP with ICI can lead to excellent long-term post-transplant outcomes.

Table. Cox Regression and Fine-Gray Models Evaluating Pre-Transplant Factors Associated with Allograft Rejection, HCC Recurrence, and Overall Survival in Patients Receiving Immune-Checkpoint Inhibitors Prior to Liver Transplantation



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★ 0016 | MULTIPLE LISTING ACROSS THE ACUITY CIRCLE ERAS: ARE WE DOING ENOUGH TO LIMIT DISPARITIES IN ACCESS TO TRANSPLANT?

Claire Cywes[1] Lindsay Beaman[2] Marka Ellertson[2] Leigh Meyer[2] Audrey Bankes[1] Frank Lee[3] Ali Hamandi[1] Benjamin Limburg[4] Christopher Kim[5] Tayyab Diwan[3], [1]Mayo Clinic Alix School of Medicine, [2]Mayo Clinic Rochester Biomedical Ethics Research Program,

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[3]Mayo Clinic Rochester, Department of Transplantation, [4]University of South Dakota Sanford School of Medicine, [5]Mayo Clinic Rochester Department of Bioethics

Background: Multi-listing (ML) has been shown to increase odds of transplantation compared to listing at a single center (SL). The February 2020 change of allocation process to acuity circles prioritized distance from the donor hospital in an attempt to decrease geographic disparities in access to transplant. This study aimed to assess the association between ML and transplantation across the acuity circle eras (ACE) and determine if the policy change impacted the frequency of ML as well as the percentage of ML patients transplanted at their primary center. **Methods:** UNOS data was queried for liver transplants (LT) between January 1, 2016 and November, 1 2024. ACE groups were based on the policy implemented on February 4, 2020. Multivariable logistic regressions were performed to assess ML's impact on transplant in each ACE. Primary transplant center was defined as the first center to be listed. Chi-square tests were performed to evaluate the difference in frequency of LT at primary centers. **Results:** There were 104,870 people listed for LT during the study period, 100,800 (96.1%) SL and 4,070 (3.9%) ML. The percentage of ML patients was higher in the pre-ACE compared to the post-ACE (4.5% vs 3.4%, $p < 0.001$). ML was associated with an increased likelihood of LT in the post-ACE (OR 1.113, 95% CI 1.009-1.228, $p = 0.033$) but not in the pre-ACE (OR 1.053, 95% CI 0.957-1.158, $p = 0.287$). Interestingly, there was no significant difference between those listed at 2 centers versus 3+ centers in either ACE (pre-ACE: OR 1.249, 95% CI 0.866-1.802; $p = 0.234$; post-ACE: OR 0.901, 95% CI 0.612-1.327, $p = 0.598$). There was a significantly higher percentage of patients transplanted at their primary center in the post-ACE (36.3% vs. 45.8%, $p < 0.001$). **Conclusion:** In the post-ACE, ML remains a significant factor in determining access to transplant. This is true despite the decreased proportion of ML patients and most ML patients being transplanted at their primary center. Our results show that the acuity circles policy change may have lessened geographic disparities (and potentially associated SES disparities as well), but this progress has not eliminated disparities in access to transplant overall. The question must be asked: has acuity circles gone far enough, or is there still an ethical imperative to make transplant access more equal, and should this include altering ML practices?

Disclosures: Claire Cywes: Nothing to Disclose, Lindsay Beaman: Nothing to Disclose, Marka Ellertson: Nothing to Disclose, Leigh Meyer: Nothing to Disclose, Audrey Bankes: Nothing to Disclose, Frank Lee: Nothing to Disclose, Ali Hamandi: Nothing to Disclose, Benjamin Limburg: Nothing to Disclose, Christopher Kim: Nothing to Disclose, Tayyab Diwan: Nothing to Disclose

★ 0017 | DLGAP5 PROMOTES ACUTE LIVER INJURY VIA PYROPTOTIC HEPATOCYTE INFLAMMASOME-DRIVEN MACROPHAGE METABOLIC REPROGRAMMING AND M1 POLARIZATION

Xianzhi Liu[1] Zhiyuan Chen[1], [1]Xiamen University

Background: Acute liver injury (ALI) has attracted considerable attention due to its high mortality rate and complex pathogenic mechanisms, yet current therapeutic options remain limited, with a critical need for precision interventions targeting specific cell death signaling pathways. Pyroptosis is a novel programmed cell death process exists in inflammatory diseases and Methyltransferase like 3 (METTL3) is a core N6 methyladenosine (m6A) modified methyltransferase that has been shown to regulate cell fates. However, their roles in ALI are still with little information. **Methods:** METTL3 mutant and NLRP3 knockout mouse were constructed, CCl_4-induced ALI model was established and primary cells were isolated, and cell pyroptosis and m6A modification were evaluated. MeRIP-seq analysis, molecular docking and co-immunoprecipitation assay were used to explore and validate the mechanism of METTL3 promoting pyroptosis. Co culture was used to explore cell interactions. **Results:** METTL3-mediated m6A modification was significantly upregulated in hepatocytes during ALI. Inhibition of METTL3-mediated-m6A modification alleviated hepatocyte pyroptosis and ALI. Dlgap5 was determined as the target of METTL3-mediated m6A modification, which was regulated through the IGF2BP2-dependent manner. Dlgap5 can directly bind to METTL3 and NLRP3 and thereby mediating hepatocyte pyroptosis. METTL3 mutant or AT9283-meidated Dlgap5 inhibition alleviated pyroptosis and ALI. NLRP3 inflammasome releasing by the GASMD-N-dependent membrane pores from hepatocytes activated macrophages to further exacerbate ALI. NLRP3 deficiency alleviated ALI by suppressing hepatocyte pyroptosis and blocking communication between macrophages and hepatocytes. **Conclusion:** We found METTL3-induced m6A methylation plays an important role in the process of ALI by promoting hepatocyte pyroptosis and disrupting communication between hepatocytes and macrophages. Targeted -inhibition of Dlgap5 and -blocking of NLRP3 inflammation-mediated hepatocyte-macrophage interaction provide promising strategies for ALI.

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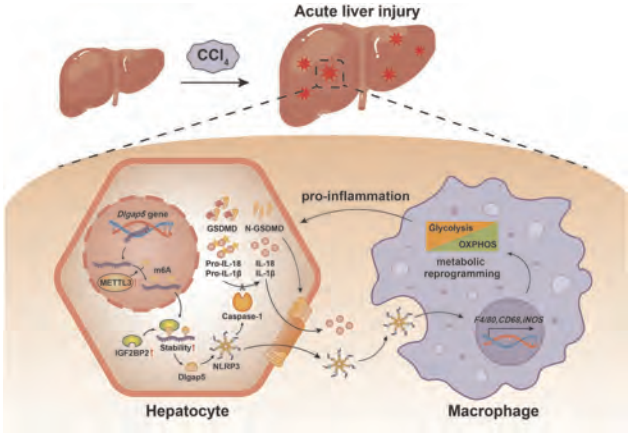
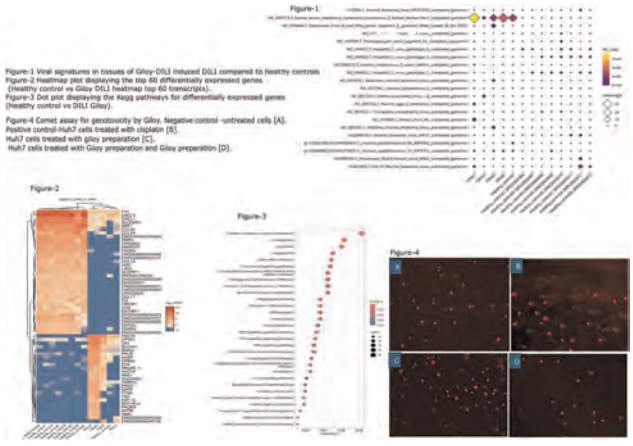


Disclosures: Xianzhi Liu: Nothing to Disclose, Zhiyuan Chen: Nothing to Disclose

0018 | DRUG-INDUCED LIVER INJURY IS MORE THAN DRUGS- THE ROLE OF METABOLIC AND VIRAL COMORBIDITIES- CASE OF TINOSPORA CORDIFOLIA (GILOY)

Sanal Madhusudana Girija[1] Sarita Gupta[1] Gulshan Kumar[2, 1]Institute of Liver and Biliary Sciences, [2]Anuvanshiki (OPC)

Background: Drug-induced liver injury (DILI) is increasingly recognized as a multifactorial syndrome. DILI frequently presents as acute-on-chronic liver failure, suggesting that underlying hepatic vulnerabilities could be key contributors to its initiation and severity. DILI from especially from herbals such as giloy, is being increasingly identified. We hypothesised that viral reactivation, particularly of latent human viruses, is a factor triggering DILI. Many viruses sense free radicals to sense host weaknesses. Phytochemicals can cause oxidative stress, which could be sensed by latent viruses, leading to their activation. Once the virus is activated, it can launch an acute immune reaction on its own. This could be relevant in the context of herbal medications like Tinospora cordifolia (Giloy), which gained popularity during the COVID-19 pandemic. The mechanisms of DILI involve both direct hepatotoxic effects (via reactive drug metabolites) and indirect immune-mediated injuries. Understanding the interplay between herbal compounds, pre-existing liver disease, and latent viral infections is critical for effective risk assessment and clinical management. **Methods:** We studied cases diagnosed as DILI and associated with Giloy in a liver specialty hospital. We performed RNASeq analysis of patient and healthy tissue samples available from the institutional biobank. We also investigated the viral signatures in patient tissue. In vitro, two liver cell lines (Huh7 and HepG2) were exposed to two Giloy preparations: P: A widely used commercial formulation not prepared according to Ayurvedic principles. K: A preparation compliant with classical Ayurvedic texts. We assessed the genotoxicity of giloy via the comet assay (cisplatin was used as a positive control) and measured Rad51 expression, a marker of oxidative DNA repair. To evaluate P450 induction, we used real-time PCR to analyse the expression of key cytochrome P450 enzymes (57 in total). **Results:** 124 DILI cases were associated with Giloy in some form. Mean age was 51 +/-14 years, 92 were men. 8 of them had liver samples stored in the institutional biobank. 87% of them had pre-existing liver disease. We found the signatures of SARS-CoV-19. Interestingly, we also found viral signatures of HCV, AAV3 (a liver-specific serotype), Thottapalayam virus (TMPV), HHV5, HHV2, and HPV, which could be pre-existing. Giloy preparations didn't cause genotoxicity. We also observed that giloy extracts could ameliorate DNA damage (although more investigations are needed to confirm these findings). However, giloy preparations had a suppressive effect on the majority of the cytochrome types. However, there were significant variations between the preparations. CYP1B was induced by the commercial preparation (P) while the authentic preparation suppressed it ($p < 0.001$). CYP2F1, CYP17A1, CYP2U1, and CYP2W1 were suppressed by both preparations. **Conclusion:** Giloy causes DILI, and pre-existing liver disease is an important determinant of DILI. It is possible that one of the giloy phytochemical metabolites caused an oxidant stress, which caused the reactivation of pre-existing virus (sleeping/latent virus), which initiated an acute immune response at least in some cases.



Disclosures: Sanal Madhusudana Girija: Nothing to Disclose, Sarita Gupta: Nothing to Disclose, Gulshan Kumar: Nothing to Disclose

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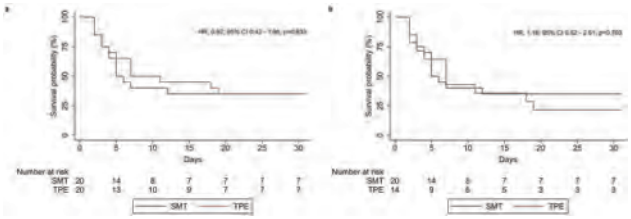
0019 | THERAPEUTIC PLASMA EXCHANGE IN PATIENTS WITH ACUTE LIVER FAILURE: A RANDOMIZED CONTROLLED TRIAL

Shekhar Swaroop[1] Sagnik Biswas[1] Arnav Aggarwal[1] Samagra Agarwal[1] Baibaswata Nayak[1] Poonam Coshic[1] . Shalimar[1], [1]All India Institute of Medical Sciences, New Delhi

Background: Acute liver failure (ALF) is a life-threatening condition with high short-term mortality without liver transplantation (LT). While therapeutic plasma exchange (TPE) has shown early promise, a recent large sample size study reported inconsistent survival benefits. In this randomized controlled trial, we evaluated the safety and efficacy of standard-volume TPE on the 30-day outcomes in ALF. **Methods:** In this single-center, open-label, randomized controlled trial, 40 adults with ALF were randomized 1:1 standard medical therapy (SMT) alone or SMT plus TPE. TPE was performed daily for up to five days or stopped as per the predefined criteria (improvement in hepatic encephalopathy or the development of shock or sepsis). A standard-volume (1-1.5 X plasma volume) centrifugation-based TPE was used with a 1:1 fresh frozen plasma and albumin replacement. The primary outcome was 30-day mortality; secondary outcomes included changes in biochemical parameters and adverse events. **Results:** Median age was 24 years (IQR 20-28); 23/40 (57.5%) were females and 57.5% viral hepatitis. Of 20 patients allocated to TPE, 14 received ≥ 1 session; 6 could not due to early hepatic encephalopathy improvement ($n = 3$) or refractory shock ($n = 3$). Among those treated with TPE- 1, 2, 3, 4 and 5 sessions were received by 5 (25%), 1 (5%), 2 (10%), 1 (5%) and 5 (25%) patients. TPE was discontinued primarily due to hemodynamic instability. The 30-day mortality was identical in both arms (65%; intention-to-treat, $p = 1.000$), with no difference on per-protocol analysis (TPE: 78.6% vs SMT: 65.0%, $p = 0.393$), Figure. TPE led to greater day 3 reductions in bilirubin (-2.8 vs +1.4 mg/dl, $p = 0.004$) and INR (-2.2 vs 0, $p = 0.013$), but ammonia reduction was not significant (-72 vs -5 μmol/L, $p = 0.340$), and no survival benefit was observed. Rates of infection and electrolyte disturbances were similar. TPE was not independently associated with survival (HR 0.92, 95% CI 0.43–1.99, $p = 0.83$). **Conclusion:** Standard-volume TPE, as used in this study, did not improve short-term survival in predominantly viral ALF and was frequently interrupted for clinical deterioration. Larger multicenter trials are needed to evaluate early initiation, optimized protocols, and integration with continuous renal replacement therapy.



Disclosures: Shekhar Swaroop: Nothing to Disclose, Sagnik Biswas: Nothing to Disclose, Arnav Aggarwal: Nothing to Disclose, Samagra Agarwal: Nothing to Disclose, Baibaswata Nayak: Nothing to Disclose, Poonam Coshic: Nothing to Disclose, Shalimar: Nothing to Disclose

0020 | USING ARTIFICIAL INTELLIGENCE/ MACHINE LEARNING FOR EARLY PREDICTION OF RESPONSE TO PLASMA EXCHANGE IN PEDIATRIC ACUTE LIVER FAILURE

Tamoghna Biswas[1] Varun Ramamohan[2] Tamal Majumder[3] Vikrant Sood[4] Rajeev Khanna[5] Seema Alam[1] Bikrant Biharilal Raghuvanshi[4], [1]Institute of Liver and Biliary Sciences, [2]Indian Institute of Technology Delhi, India, [3]Indian Institute of Technology, Delhi, India, [4]Institute of Liver and Biliary Sciences, New Delhi, India, [5]Institute of Liver and Biliary SCiences, New Delhi

Background: Therapeutic plasma exchange (TPE) improves survival in acute liver failure (ALF) but artificially lowers key prognostic markers like INR and bilirubin. Repeated TPE sessions cause significant fluctuations in these parameters, complicating decisions about proceeding with liver transplantation (LT) when a donor is available. Early prediction of response to TPE is thus critical to decide the need and timing of LT. This study aimed to develop and validate a machine learning (ML) model for early prediction of TPE response in ALF and to create a user-friendly, web-based tool to support clinical decision-making. **Methods:** All children (2-18 years) with ALF who received at least 1 session of TPE were included. TPE was offered to children with ALF who had a corrected INR $\geq$ 2.5 with an increasing INR and/or worsening grade of hepatic encephalopathy (HE) 6-12 hours thereafter. The number of sessions was guided by patients' clinical condition and 1.5 to 2 times the plasma volume was exchanged at each session. For response prediction, clinical and biochemical parameters at time points (T0 to T6) were collected (T0: Baseline; T1: 0-6 hours after 1st TPE; T2: 12-18 hours after 1st TPE; T3: 0-6 hours after 2nd TPE; T4: 12-18 hours after 4th TPE; T5: 0-6 hours after 3rd TPE; T6: 12-18 hours after 3rd TPE). Recursive feature elimination with cross-validation was used. The following classifiers were used for the ML-based prediction model:

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Random Forest Classifier, Logistic Regression, Gradient Boosting Classifier, XG Boost, and Support Vector Machine (SVM). Finally, the study's significant variables were incorporated into a web-based application. **Results:** Data of 448 patients with pediatric ALF managed at the centre till January 2025 were scanned, and 87 patients who received TPE as a therapeutic modality were included. Fourteen, 28, 35, and 10 patients received one, two, three, and more than 3 sessions of TPE, respectively. Thirty-one patients (35.6%) survived with their native liver, 13 (14.9%) received LT, and 43 (49.4%) died. On ML-based analysis, the following variables were selected after feature selection: INR at T0 and T2, ammonia at T2, jaundice-to-HE interval for time-point T2 analysis;age, use of concomitant continuous renal replacement therapy, jaundice-to-HE interval, INR at T0, T2, T4, and ammonia at T2 and T4 for time-point T4 analysis. Based on these variables, the model correctly predicted the outcomes with accuracy ranging from 0.73 (logistic regression) to 0.816 (SVM) at T2 and accuracy ranging from 0.698 (logistic regression) to 0.759 (XGBoost) at time-point T4. The models were then incorporated into an online web-based tool to be hosted after communication. **Conclusion:** ML models based on SVM, XGBoost, and Logistic Regression can reliably predict the response to TPE as early as after the first and second sessions of TPE in pediatric ALF. They can serve as an easy bedside tool to predict response to TPE and decide the need and timing of LT in pediatric ALF.

Table: Area under receiver operating characteristic curve for different machine learning algorithms, their sensitivity and positive predictive value for predicting outcomes in children with acute liver failure undergoing therapeutic plasma exchange (TPE) at different time-points (T2: 12-18 hours after first session of TPE; T4: 12-18 hours after second session of TPE)

Classifier/ Machine learning algorithm	AUROC		Positive Predictive Value		Sensitivity	
	Mean	SD	Mean	SD	Mean	SD
***Time-point T2:** Variables selected based on Recursive Feature Elimination with Cross-Validation (RFECV): 4 variables - INR T0, INR T2, Ammonia T2, Jaundice-HE interval*						
Random Forest Classifier	0.740	0.123	0.789	0.114	0.771	0.117
Logistic Regression	0.784	0.101	0.836	0.80	0.793	0.110
Gradient Boosting	0.730	0.110	0.774	0.105	0.755	0.109
XGBoost Classifier	0.765	0.114	0.800	0.102	0.783	0.107
Support Vector Machine	0.816	0.92	0.846	0.082	0.819	0.101
***Time-point T4:** Variables selected based on RFECV: 9 variables – Age, INR T0, INR T2, INR T4, Ammonia T2, Ammonia T4, Jaundice-HE interval, ALT, Concomitant use of CRRT*						
Random Forest Classifier	0.728	0.141	0.831	0.110	0.780	0.105
Logistic Regression	0.698	0.135	0.811	0.145	0.767	0.104
Gradient Boosting	0.649	0.135	0.775	0.127	0.703	0.114
XGBoost Classifier	0.759	0.144	0.855	0.103	0.797	0.108
Support Vector Machine	0.713	0.139	0.812	0.147	0.777	0.105

Disclosures: Tamoghna Biswas: Nothing to Disclose, Varun Ramamohan: Nothing to Disclose, Tamal Majumder: Nothing to Disclose, Vikrant Sood: Nothing to Disclose, Rajeev Khanna: Nothing to Disclose, Seema Alam: Nothing to Disclose, Bikrant Biharilal Raghuvanshi: Nothing to Disclose

★ 0022 | A PHASE I CLINICAL TRIAL OF THE HEPACURE BIOARTIFICIAL LIVER SYSTEM FOR ACUTE-ON-CHRONIC LIVER FAILURE

Jingyi Hu[1] Huaibin Zou[2] Hongbo Shi[2] Li Zhou[3] Pengfei Yu[2] Shaoli You[4] Hongling Liu[4] Guoyu Pan[5] Lijian Hui[6] Yu Chen[2], [1]Institute of Molecular Medicine, College of Future Technology, Peking University, Beijing, [2]Fourth Department of Liver Disease, Beijing You An Hospital, Capital Medical University, Beijing, [3]Beijing YouAn Hospital of Capital Medical University, [4]The Fifth Medical Center of Chinese People's Liberation Army General hospital, [5]Shanghai Hexaell biotech Co., Ltd. Shanghai, 201203, China, [6]School of Life Science and Technology, ShanghaiTech University

Background: Acute-on-chronic liver failure (ACLF) is one of the leading causes of mortality among patients with chronic liver disease. The HepaCure bioartificial liver system based on human induced functional hepatocytes (hiHep) was developed to provide transient liver support to restore liver function. This Phase I trial evaluated its safety and preliminary efficacy. **Methods:** This multi-center, open-label Phase I trial aimed to assess the safety of HepaCure as the primary endpoint, with secondary endpoints including treatment success rate, device performance, and changes in hepatic function. Totally 12 ACLF patients were allocated to a single arm (6h or 9h) or multiple arm (2–3 treatments) and received standard medical therapy combined with HepaCure treatment. **Results:** The study included 12 patients with ACLF: 7 with hepatitis B virus (HBV) infection, 1 with drug-induced hepatitis, 2 with alcoholic hepatitis, and 2 with fatty liver disease. Patients were equally distributed between the single-dose ($n = 6$) and multiple-dose ($n = 6$) groups. In the multiple-dose cohort, 4 patients received 2 treatments, while 2 received 3 treatments. The HepaCure was well tolerated by all patients. A total of 147 adverse events were reported by day 14, including 136 that were mild (CTCAE Grade < 3). Of these,145 were treatment-emergent adverse events with similar incidence between the 6-hour and 9-hour treatment groups; most were determined to be unrelated to the device. Three serious adverse events occurred, all assessed as unrelated to the treatment. By day 14, statistically significant improvements ($p < 0.05$) were observed in liver function parameters: AST decreased from 163.25 ± 86.76 to 97.77 ± 71.45 U/L, ALT from 99.58 ± 70.08 to 59.15 ± 49.82 U/L, total bilirubin from 323.92 ± 156.59 to 235.85 ± 118.24 μmol/L, while

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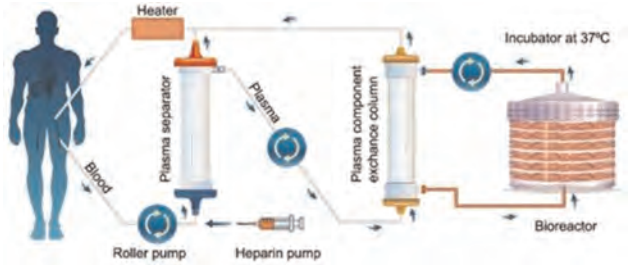
albumin increased from 29.92 ± 3.36 to 35.64 ± 4.44 g/L and PTA improved from 33.13 ± 6.47% to 39.86 ± 18.30%. Mortality was observed in one case (infection-related death at Day 36 after the first treatment), with all other patients surviving. **Conclusion:** The HepaCure system exhibited a favorable safety profile and was well tolerated, with significant improvements in hepatic function. These results suggest it is a promising treatment for ACLF, warranting further validation in large-scale Phase 2 clinical trials.



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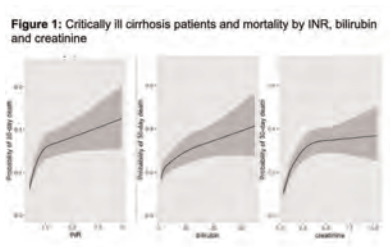
0023 | HEPATIC DYSFUNCTION AND HEPATIC FAILURE CUTOFFS IN CIRRHOSIS PATIENTS WITH ACLF

Chanyanuch Nakapakorn[1] Lauren Hall[1] Gerald Ogola[1] Jasmohan Bajaj[2] Jacqueline O'Leary[3] Patrick Kamath[4] Sumeet Asrani[5], [1]Baylor University Medical Center, [2]Virginia Commonwealth University, [3]UT Southwestern Medical Center, [4]Mayo Clinic, Rochester, [5]Liver Consultants of Texas

Background: Presence of hepatic dysfunction is central to defining acute-on-chronic liver failure (ACLF), though thresholds that define hepatic dysfunction and failure are not established. Though leading liver societies support importance of hepatic dysfunction in ACLF pathophysiology, they provide various suggested cutoffs and definitions. Recently, a global consensus (Bajaj Gastro 2025) defined hepatic dysfunction and failure based on bilirubin and INR with dysfunction (Total serum bilirubin ≥ 3 mg/dL but < 7.5 mg/dL and INR ≥ 1.3 and < 1.5) and failure (Total serum bilirubin ≥ 7.5 mg/dL and INR ≥ 1.5). However, mortality may be different given underlying kidney dysfunction as well as admission to the ICU. We sought to validate cutoffs in critically ill patients with cirrhosis and examine associated mortality in the hospital and ICU setting. **Methods:** We examined all patients with cirrhosis presenting to a large integrated healthcare system (26 hospitals, 2019-2022) with decompensation. We collected data on all hospitalized patients as well as critically ill patients with cirrhosis and followed inpatient course until inpatient mortality or death at 30 days. We created splines to assess the correlation of bilirubin, INR and creatinine after adjusting for the other two variables. We created a heatmap to assess the relations between the cutoffs. **Results:** There were 9,399 patients with cirrhosis and of these 3,913 were admitted to the ICU. Mean age was 61.2 (12.9) years, 40% females, 17.7% non-White and 21.3% Hispanic. Mortality within 30 days were 14.5% (all hospitalized) and 24.4% (ICU cohort). ICU cohort: Mortality progressively increased linearly for a given lab value, but plateaued around 2.5 (INR), 3mg/dL (creatinine) and around 7.5mg/dL (bilirubin). (Figure 1). Heatmaps assessed relationship between the three variables for relevant cutoffs with mortality range between 15-45%. (Figure 2). For an INR of 1.5, baseline mortality in the ICU was 15%, increased to 22% in presence of 7.5mg/dL and further to 33% in presence of kidney dysfunction (creatinine 2.5mg/dL). For an INR of 2.5, mortality risk increased by 10% to 23%, 33% and 45% respectively. **Conclusion:** Mortality in ACLF remains high. In critically ill patients with cirrhosis with ACLF with hepatic failure (INR 1.5 and Bilirubin 7.5), mortality within 30 days is 22%. Mortality risk is dynamic and contingent on the interaction of various factors. This data provides baseline mortality risk estimates that may be useful for further studies in ACLF using short term mortality as a relevant outcome.



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0024 | FRAILTY IS ASSOCIATED WITH THE DEVELOPMENT OF ACUTE-ON-CHRONIC LIVER FAILURE IN PATIENTS WITH END-STAGE LIVER DISEASE

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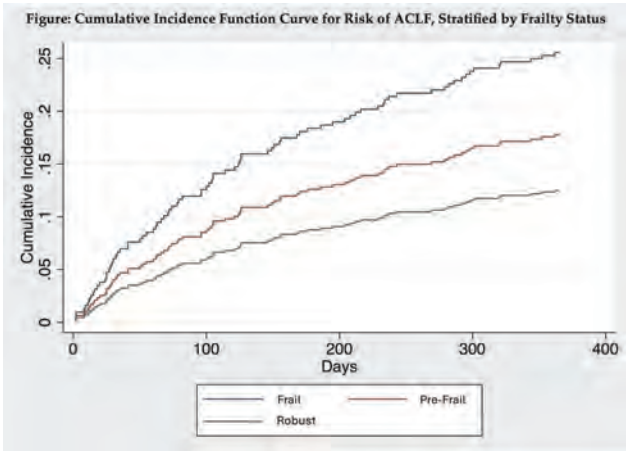
Background: Acute-on-chronic liver failure (ACLF) is associated with significant short-term mortality in patients with end-stage liver disease (ESLD). The relationship between ACLF and frailty is unclear. The purpose of this study was to investigate the association between frailty measured in an ambulatory setting and the risk of ACLF. **Methods:** We performed a retrospective chart review of adult patients enrolled in the prospective FrAILT study, who were waitlisted for liver transplantation (LT) in an ambulatory setting at five LT centers between 1/1/2019-12/31/2022. Frailty was measured with the Liver Frailty Index (LFI: grip, chair stands, balance testing). ACLF was defined using the European Association for the Study of the Liver Chronic Liver Failure Consortium (EASL-CLIF) criteria. The primary outcome was the development of ≥ grade 1 ACLF within 1 year of LFI assessment. A time-to-event analysis was performed to evaluate the association between LFI and ACLF, with death or LT as competing risks. **Results:** 460 patients were included; 62% were male and the mean age was 56.3 (± 6.9) years. Alcohol-associated liver disease (32%) and metabolic-dysfunction associated steatotic liver disease (26%) were the most common etiologies of ESLD. Mean MELD was 16.3 (± 6.4). Mean LFI was 3.90 (± 0.74), with 19% classified as frail, 64% pre-frail and 17% robust (using previously established LFI cut-offs). 87 (19%) patients developed ACLF during the 1-year follow-up period, 271 underwent LT and 13 died. On multivariable analysis adjusted for age, sex and MELD, LFI was associated with the development of ACLF (HR 1.40, 95% CI 1.06-1.86, p = 0.02, per 1.0 LFI). When categorized by frailty status, robust patients were less likely to develop ACLF compared to frail patients on univariable analysis (HR 0.45, 95% CI 0.22-0.95, p = 0.04) (Figure). However, on multivariable analysis, robust status was no longer inversely associated with the development of ACLF (HR 0.44, 95% CI 0.18-1.03, p = 0.06). **Conclusion:** In this multi-center study, frailty measured by LFI was associated with the development of ACLF by EASL-CLIF criteria. Our findings suggest that frailty's known effect on mortality in ESLD could be in part due to an increased risk of ACLF in deconditioned patients.



Disclosures: Avesh Thuluvath: Nothing to Disclose, Fawzy Barry: Nothing to Disclose, Brendan Blackburn: Nothing to Disclose, Reeti Gulati: Nothing to Disclose, Angel Wilson: Nothing to Disclose, Grace Johnson: Nothing to Disclose, Avery Longdon: Nothing to Disclose, Caroline Yu: Nothing to Disclose, Anjana Rajan: Nothing to Disclose, Yuan Zhang: Nothing to Disclose, Robert Rahimi: Nothing to Disclose, Andres Duarte-Rojo: Echosens: Grant/Research Support, Matthew Kappus: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Elizabeth Verna: Nothing to Disclose

0025 | TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT IN OLDER ADULTS: HIGHLIGHTING RISKS IN A HIGH-RISK POPULATION

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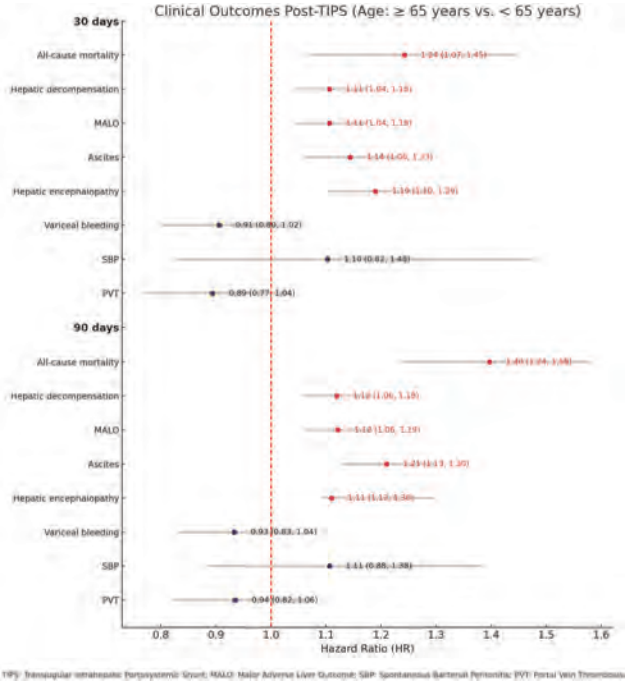
Background: Current evidence on the safety of transjugular intrahepatic portosystemic shunt (TIPS) in elderly patients is limited to retrospective observational studies, as randomized clinical trials have excluded patients with advanced age. Given the uncertainty surrounding the outcomes of TIPS in elderly patients, this study evaluates the comparative risks and outcomes following TIPS placement in elderly vs. non-elderly patients with cirrhosis. **Methods:** A retrospective cohort study was conducted using large, population-based data from TriNetX. Patients with any form of cirrhosis who underwent TIPS were identified and stratified by age into two groups: those ≥ 65 years and those < 65 years. The cohorts were matched 1:1 using propensity score matching based on gender, demographics, comorbidities, and medications. Outcomes assessed included all-cause mortality, hepatic decompensation, major adverse liver outcomes (MALO), and portal vein thrombosis (PVT). These outcomes were analyzed at 30 and 90 days following the index event. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to evaluate associations between variables. **Results:** A total of 10,258 adult patients with cirrhosis who underwent TIPS were included, of whom 4,977 were aged greater than 65 years. After matching, 3,685 elderly patients (mean age 65.0 years, 35.5% female) were compared with 3,685 non-elderly patients (mean age 49.7 years, 34.4% female). Elderly patients had significantly higher risk of 30-day all cause mortality (HR:1.24, 95%CI: 1.07-1.45), hepatic decompensation (HR:1.11, 95%CI: 1.04-1.18), MALO (HR:1.11, 95%CI: 1.04-1.18), ascites (HR:1.14, 95%CI: 1.06-1.23), hepatic encephalopathy (HR:1.19, 95%CI: 1.10-1.29). No differences were observed in variceal bleeding, SBP, and PVT. Similar Results: were observed at 90 days. **Conclusion: Discussion:** TIPS represents an innovative and life-extending procedure for patients with decompensated cirrhosis and clinically significant portal hypertension. However, this study underscores heightened risks in elderly patients compared to younger cohorts. Rather than discouraging TIPS use, this study's findings highlight the importance of increasing awareness of frequent outpatient follow-up in this vulnerable population.



Disclosures: Donghyun Ko: Nothing to Disclose, Do Han Kim: Nothing to Disclose, Christina Lee: Nothing to Disclose, Frank Lukens: Nothing to Disclose, Paul Kroner: Nothing to Disclose, Raffi Karagozian: Nothing to Disclose

0026 | TEMPORAL TRENDS IN OUTCOMES AND BURDEN OF ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) AMONG PATIENTS WITH CIRRHOSIS IN THE UNITED STATES: A NATIONWIDE ANALYSIS

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Background: Acute-on-chronic liver failure (ACLF) is a distinct clinical syndrome in individuals with chronic liver disease, marked by acute systemic inflammation, multi-organ dysfunction, and a high short-term mortality. National trends in its epidemiology and clinical outcomes remain inadequately defined. This study examines the U.S. national trends in ACLF hospitalizations, focusing on etiology, inpatient

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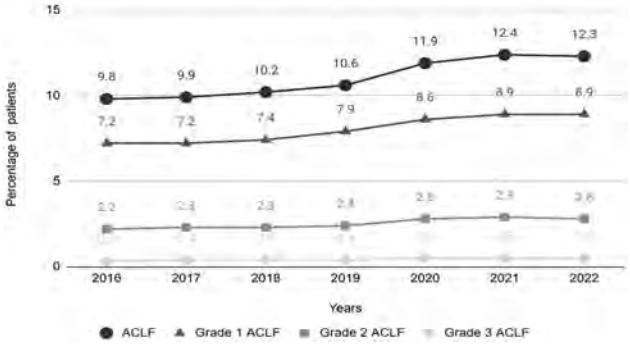
mortality, and resource utilization. **Methods:** The National Inpatient Sample (NIS) Database was used to identify adult hospitalizations with ACLF from 2016 to 2022. ACLF was defined as the presence of two organ dysfunctions (renal failure, cardiogenic shock, hepatic coma, and pulmonary dysfunction) using the NACSELD criteria. Data were collected on patient demographics, liver disease etiology, decompensations, comorbidity burden, interventions, and clinical outcomes. Outcomes assessed were in-hospital mortality, non-home discharges, and ACLF. **Results:** Out of 5.1 million hospitalizations with cirrhosis, 560,765 (11.1%) patients met the criteria for ACLF. The proportion of ACLF cases among patients with cirrhosis increased from 9.8% to 12.3% between 2016-2022 ($p < 0.001$) (Table 1)(Figure 1). The most common organ failure was renal failure (87.4%), followed by cerebellar dysfunction (56.5%) and respiratory dysfunction (48.9%). An increase in the rates of ACLF attributed to MASLD was noted between 2016 (29.5%) and 2022 (38.4%) ($p < 0.001$). The proportion of patients with alcohol-associated liver disease as an etiology decreased from 51.2% (2016) to 48% (2022) ($p < 0.001$). The rate of hepatitis C and hepatitis B declined from 22.6% (2016) to 10.5% (2022), and from 2.3% (2016) to 1.8% (2022), respectively ($p < 0.001$). Decline in rates of hepatocellular carcinoma-associated ACLF was also noted (5.3% in 2016 to 4.5% in 2022) ($p < 0.001$). The mortality among patients with ACLF remained stable between 2016 and 2022 (33.8% and 34.6%, respectively). The total hospitalization charges increased from $155,300.8 in 2016 to $195,678 in 2022 ($p < 0.001$) and the length of stay remained stable (11.14 and 11.6 days, respectively). **Conclusion:** Our findings suggest that rates of ACLF hospitalizations among patients with cirrhosis have increased. Although ALD remains the most frequent etiology rates of MASLD continue to increase progressively. Despite growing recognition and management of MASLD and cirrhosis, the rates of ACLF, as well as total hospitalization charges, have been increasing. Further interventions are needed to improve the outcomes.



Disclosures: Aalam Sohal: Nothing to Disclose, Carol Singh: Nothing to Disclose, Rahul Chikatimalla: Nothing to Disclose, Joanne Lin: Nothing to Disclose, Ruchir Paladiya: Nothing to Disclose, Bipneet Singh: Nothing to Disclose, Sunny Sandhu: Nothing to Disclose, Marina Roytman: Gilead: Speaking and Teaching, Salix: Speaking and Teaching, Madrigal: Speaking and Teaching

0027 | IMPACT OF PRE-PROCEDURAL COAGULOPATHY REVERSAL ON CLINICAL OUTCOMES FOLLOWING PARACENTESIS OR EGD IN PATIENTS WITH CIRRHOSIS AND INR > 3: A PROPENSITY SCORE-MATCHED STUDY

Fatima Elmustafa[1] Ali Osman[2] Mohammad Adam[3] Abdelhaleem Sideeg[4] Ashwani Singal[5], [1]Henry Ford Health System, [2]Washington University School of Medicine, [3]University of Missouri - Kansas City School of Medicine, [4]Virginia Mason Medical Center, [5]University of Louisville

Background: Correction of coagulopathy prior to low-risk procedures such as paracentesis and upper endoscopy remains common practice, largely driven by persistent concerns about bleeding risk—despite potential harms associated with transfusions, including volume overload, exacerbation of portal hypertension, and transfusion-related complications. Using real-world data, we aimed to investigate the clinical impact of pre-procedural coagulopathy reversal with fresh frozen plasma (FFP) or cryoprecipitate in patients with cirrhosis and INR > 3 undergoing paracentesis or esophagogastroduodenoscopy (EGD). **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network to compare outcomes in adult patients with cirrhosis and INR > 3 undergoing paracentesis or EGD, with or without pre-procedural FFP or cryoprecipitate. Propensity score matching was performed based on age, race, gender, diabetes mellitus, acute kidney injury, chronic kidney disease, esophageal varices, severe sepsis, and anticoagulant use. Primary outcomes included 30-day and 90-day mortality. Secondary outcomes were acute kidney injury (AKI), respiratory failure, need for dialysis, blood transfusion, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO), all assessed within the first 30 days. **Results:** The initial cohorts included 194,227 patients who did not receive coagulopathy reversal and 1,864 who did; 1,843 patients were successfully matched from each group for

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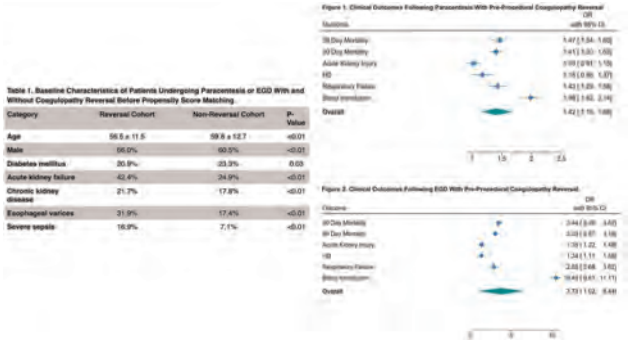
comparison. Among patients undergoing paracentesis, pre-procedural coagulopathy reversal was associated with significantly higher 30-day and 90-day mortality, as well as increased risk of respiratory failure and need for blood transfusion. There was no significant difference in the risk of AKI, TACO or TRALI (Fiqure 1). Similarly, among patients undergoing EGD, coagulopathy reversal was associated with worse outcomes, including elevated mortality at 30 and 90 days, higher risk of AKI, respiratory failure and need for blood transfusion, with no significant differences in TACO or TRALI (Fiqure 2). **Conclusion:** In patients with cirrhosis and INR > 3 undergoing paracentesis or EGD, pre-procedural reversal of coagulopathy with FFP or cryoprecipitate is associated with significantly worse clinical outcomes. These findings support existing recommendations against routine coagulation correction in this population and highlight the need for judicious use of blood products.



Disclosures: Fatima Elmustafa: Nothing to Disclose, Ali Osman: Nothing to Disclose, Mohammad Adam: Nothing to Disclose, Abdelhaleem Sideeg: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, GSK: Grant/Research Support, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, Avera Medical Group: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other

0028 | A LONGITUDINAL ANALYSIS OF CLINICAL TRAJECTORIES AND PROGNOSTIC OUTCOMES IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE (ACLF)

Wenling Wang[1] Manman Xu[1] Huaibin Zou[1] Shaoli You[2] Tao Han[3] Yu Chen[1], [1]Beijing Youan Hospital, Capital Medical University, [2]The Fifth Medical Center of Chinese PLA General Hospital, Beijing, [3]Tianjin Union Medical Center affiliated to Nankai University

Background: Acute-on-chronic liver failure (ACLF) is a clinical syndrome marked by a highly dynamic course and significant prognostic heterogeneity, necessitating ongoing assessment. This study aims to perform longitudinal monitoring of clinical indicators at multiple time points, characterize disease trajectories across distinct clinical outcomes, and identify critical intervention windows. These findings will inform new strategies for precise dynamic management of ACLF. **Methods:** Using COSSH-ACLF criteria, we prospectively recruited a nationwide multicenter cohort of ACLF patients (derivation: n = 485; validation: n = 151). Serial measurements of dynamic parameters were obtained at baseline (day 0) and key time points (days 3,7,14,21,28). Longitudinal trajectories of clinical indicators across three outcomes—death/liver transplantation, recovery, and persistent ACLF—were analyzed using mixed-effects models and generalized additive models (GAM). Differentially evolving parameters were identified for prognostic score development. **Results:** In the derivation cohort at 90 days, outcomes included death/liver transplantation (41.6%), persistent ACLF (12.6%), and recovery (45.8%). Trajectory analysis identified days 3-7 as a critical window. The death/LT group maintained sustained abnormalities (TBil > 450 μmol/L, INR > 2.5, PLT < 60×10⁹/L), while recovered patients achieved near-normalization by day 28 (TBil < 200 μmol/L, INR < 1.5, PLT > 100×10⁹/L). Persistent ACLF patients showed intermediate improvement at day 28 (TBil 200-350 μmol/L, INR 2.0-2.5, PLT 60-80×10/L. Significant heterogeneity in temporal trends was observed across all three groups (P < 0.01). Based on these parameters, we developed the simplified TIP scoring system incorporating three variables: TBil(μmol/L) scoring as ≥ 450 (3 points), 350-449 (2), 200-349 (1), or < 200 (0); INR scoring as ≥ 2.5 (3), 2.0-2.49 (2), 1.5-1.99 (1), or < 1.5 (0); and PLT(×10/L) scoring as < 60 (3), 60-79 (2), 80-99 (1), or ≥ 100 (0).Total scores (0-9) stratified patients into low- (0-2), intermediate- (3-5), and high-risk (6-9) groups. For mortality prediction, TIP achieved 28/90-day AUROCs of 0.75/0.74, performing comparably to MELD-Na (0.73/0.68), MELD (0.73/0.69), COSSH-ACLF II (0.76/0.75) and CLIF-C ACLF (0.70/0.70) (all P > 0.05) with greater simplicity. For recovery prediction, AUROCs were 0.71/0.73 - comparable to COSSH-ACLF II (P > 0.05) and superior to others (P < 0.05). External validation confirmed robustness through calibration, decision curve analysis, and risk stratification. Conclusion: This study identifies TB, INR, and PLT as critical prognostic determinants in ACLF. The 3–7 day window represents a critical intervention period. Our novel TIP scoring system—incorporating these three biomarkers—enables real-time prognostication and personalized clinical decision-making.

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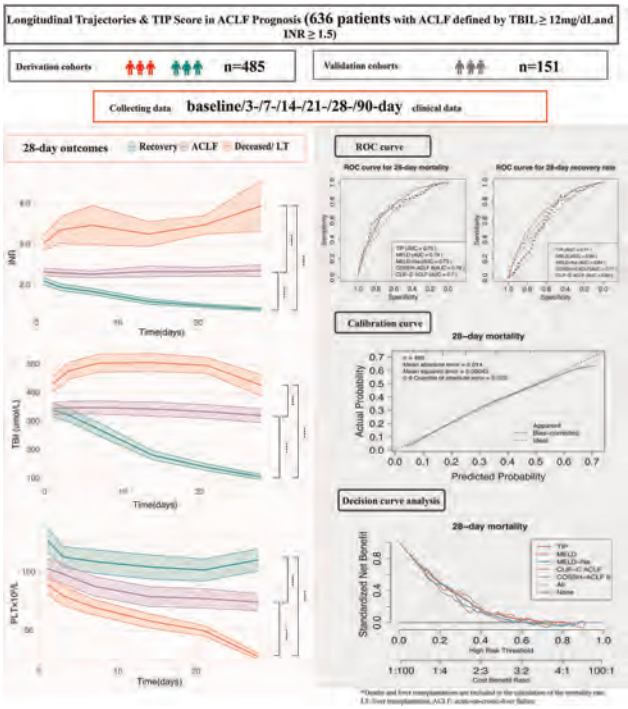

Disclosures: Wenling Wang: Nothing to Disclose, Manman Xu: Nothing to Disclose, Huaibin Zou: Nothing to Disclose, Shaoli You: Nothing to Disclose, Tao Han: Nothing to Disclose, Yu Chen: Nothing to Disclose

0029 | PRELIMINARY RESULTS: FROM THE SIMPLIFYING HEPATITIS B CARE IN PREGNANCY BY COMBINING BIRTH-DOSE VACCINE AND TENOFOVIR: THE COMBAT HBV FEASIBILITY TRIAL

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Background: Hepatitis B virus (HBV) is endemic across sub-Saharan Africa, where vertical transmission persists in resource-constrained settings such as the Democratic Republic of Congo (DRC). HBV viral load and other testing remains inaccessible in DRC, limiting implementation of evidence-based prevention. This placebo-controlled RCT aims to determine the effectiveness, safety, acceptability, and feasibility of a prophylaxis-for-all approach to prevention of vertical transmission of HBV in DRC and is among the first to evaluate this approach compared to placebo or birth-dose vaccine alone. **Methods:** Alongside existing HIV antenatal care, we introduced rapid HBV surface antigen (HBsAg) testing to screen pregnant women presenting for their first antenatal visit at three maternity centers in Kinshasa, DRC between August 2023 and January 2025. HBsAg+ women ≥ 18 years with normal creatinine (< 1.3 mg/dL) were eligible for enrollment at 28-32 weeks' gestation. Participants were randomized to receive tenofovir disoproxil fumarate or placebo upon enrollment through 4 weeks' postpartum. Infants received a birth-dose vaccine, ideally within 24 hours. Participants scored acceptability of lab draws and medication at exit visits. Safety was measured through monitoring of side effects and adverse events, and maternal alanine aminotransferase levels [ALT] through 6 months' postpartum. To determine effectiveness, infants underwent HBsAg testing at 6 months. **Results:** Of 14,027 women screened, 307(2.19%) were HBsAg-positive, and 164 eligible mothers have been enrolled and randomized to date. Most (89%) of participants deemed study activities acceptable. A third of mothers (n = 54, 32.9%) have completed follow-up through 6 months, 74 (45.4%) are being followed, 17 (10.4%) were lost to follow-up, 15 (9.2%) voluntarily withdrew, 2 (1.2%) seroconverted, and 1 (.6%) died. One quarter of participants reported mild-to-moderate side effects, 1 severe (eclampsia), and 1 death (respiratory failure). No ALT elevations (≥ 5x upper limit of normal) were observed. Of 143 infants born to date, 6 were stillborn and 4 died shortly after birth. Of live infants, 120 (83.9%) received birth-dose vaccine, 67 (55.8%) of

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which were within 24 hours. No infants have tested HBsAg-positive at 6 months. **Conclusion:** Prior to unblinding, this study preliminarily demonstrates the effectiveness, safety, acceptability, and feasibility of a prophylaxis-for-all approach to prevent vertical transmission of HBV in Kinshasa, DRC. This simplified approach strengthens overall HBV prevention, and its national adoption would be an important step toward eliminating HBV in DRC and throughout sub-Saharan Africa.

Table 1. Characteristics of mothers enrolled in the COMBAT study (blinded)

	Total (N=164)
Age, years	
Mean (SD)	30.5 (6.10)
Study facility	
Barumbu	31 (18.9%)
Binza	61 (37.2%)
Kingasani	72 (43.9%)
Gestational age at enrollment, weeks	
Mean (SD)	29.3 (1.40)
Gravidity	
Mean (SD)	3.13 (1.86)
Marital status	
Married or cohabiting	154 (93.9%)
Divorced, separated, widowed	2 (1.2%)
Never married	8 (4.9%)
Highest schooling	
Primary	7 (4.3%)
Secondary	118 (72.0%)
Higher Education	39 (23.8%)
ALT at baseline (IU/L)	
Median [Min, Max]	13.0 [5.00, 59.0]
ALT 6 weeks post-delivery (IU/L)	
Median [Min, Max]	18.0 [8.00, 99.0]
ALT 6 months post-delivery (IU/L)	
Median [Min, Max]	18.0 [9.00, 83.0]

Characteristics of infants enrolled in the COMBAT study

	Total* (N=131)
Mode of delivery	
Vaginal	112 (85.5%)
C-Section	19 (14.5%)
Gestational age at birth - in weeks	
Median [Min, Max]	39.0 [30.0, 42.0]
Birth term category**	
Full term (>=37 weeks)	86 (65.6%)
Moderate to late preterm (32-36 weeks)	44 (33.6%)
Very preterm (28-31 weeks)	1 (0.8%)
Weight - in grams	
Mean (SD)	3230 (587)
Length - in cm	
Mean (SD)	49.4 (3.05)
Head circumference - in cm	
Median [Min, Max]	34.0 [30.0, 48.0]
APGAR score at 1 min	
Median [Min, Max]	8.00 [5.00, 10.0]
APGAR score at 5 min	
Median [Min, Max]	10.0 [6.00, 10.0]
HBsAg test at 6 months	
Positive	0 (0%)
Negative	57 (43.5%)
Not tested†	21 (16.0%)
6-month visit not yet reached	53 (40.5%)

	Total* (N=131)
Birth-dose vaccine	
Yes	119 (90.8%)
0–24 hours (timely)	67 (56.3%)
25–48 hours	25 (21%)
49–72 hours	6 (5%)
>72 hours	21 (17.6%)
Never given	12 (9.2%)
Congenital abnormalities	
Yes	0 (0%)
No	131 (100%)

* Of the 143 infants born to date with complete delivery visit data, 131 were included in this table. Twelve infants were excluded: six were stillborn, four died shortly after birth, and two were voluntarily withdrawn from the study by their mothers prior to completing delivery visits.

** Preterm categorizations are based on the World Health Organization's recognized sub-categories of preterm births for gestational age. No infants were classified as extremely preterm (<28 weeks).

† Infants not tested for HBsAg at six months were either lost to follow-up, voluntarily withdrawn by their mothers, or deceased.

Abbreviations: ALT, Alanine transaminase; APGAR, Appearance, Pulse, Grimace, Activity, Respiration; HBsAg, hepatitis B surface antigen; SD, standard deviation

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0030 | THE EFFECTIVENESS OF BULEVIRTIDE MONOTHERAPY IS SIMILAR IN CHRONIC HEPATITIS DELTA PATIENTS WITH AND WITHOUT CIRRHOSIS: RESULTS: FROM THE PROSPECTIVE MULTICENTER D-SHIELD STUDY

Maria Paola Anolli[1] Elisabetta Degasperi[1] Gianpiero D'Offizi[2] Alessia Rianda[2] Alessandro Loglio[3] Mauro Viganò[3] Alessia Ciancio[4] Yulia Troshina[4] Maurizia Brunetto[5] Barbara Coco[5] Serena Zaltron[6] Anna Cambianica[6] Michele Milella[7] Elena Rosselli Del Turco[8] Laura Turco[9] Loredana Sarmati[10] Pierluigi Toniutto[11] Antonio Gasbarrini[12] Letizia Marinaro[13] Francesco Paolo Russo[14] Andrea Gori[15] Ivana Maida[16] Alessandro Federico[17] Teresa Santantonio[18] Edoardo Giovanni Giannini[19] Irene Cacciola[20] Filomena Morisco[21] Alessandra Mangia[22] Stella De Nicola[23] Antonietta Romano[24] Monia Maracci[25] Biagio Pinchera[26] Saveria Lory Crocè[27] Francesca Pileri[28] Rosa Zampino[29] Marcello Persico[30] Pietro Pozzoni[31] Sarah Dal Zoppo[32] Adriano Pellicelli[33] Nicola Coppola[34] Matteo Tonnini[35] Eleonora Grassi[36] Alessandro Soria[37] Paolo Caraceni[38] Ilaria Arena[39] Vincenzo Esposito[40] Paola Vitiello[41] Massimo Puoti[42] Pietro Lampertico[1], [1]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [2]Istituto Nazionale per le Malattie Infettive "L. Spallanzani" IRCCS, Rome Italy, [3]Gastroenterology, Hepatology and Transplantation Division, ASST Papa Giovanni XXIII, Bergamo, Italy, [4]Gastroenterology Division of Città della Salute e della Scienza of Turin, University Hospital, Turin, [5]Hepatology Unit, University Hospital of Pisa, Pisa, Italy, [6]Infectious Disease Department, Spedali Civili Brescia, Brescia, Italy, [7]Infectious Diseases Unit, Department of Biomedical Sciences and Human Oncology, University of

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Background: Bulevirtide (BLV) has been approved in Italy in May 2023 for patients with chronic hepatitis Delta (CHD), but no studies have addressed their responses to treatment and the differences in responses among patients with and without cirrhosis yet. **Methods:** CHD patients starting BLV 2 mg/day as monotherapy were included in a multicenter prospective real-life Italian study (D-SHIELD). Patients' features and treatment responses were assessed at baseline and trimonthly afterwards. The primary endpoint was the achievement of a virological response (>2 LogIU/mL HDV-RNA decline *vs.* baseline or HDV RNA undetectable) in patients with and without cirrhosis. **Results:** 459 patients from 42 centers were enrolled, 341 (74%) with cirrhosis. At baseline, ALT were 75 (49-124) *vs.* 75 (44-108) U/L ($p=0.61$), 54% *vs.* 52% men ($p=0.52$), 97% *vs.* 92% on NA therapy ($p=0.056$), 96% *vs.* 93% European origin ($p=0.20$). Conversely, baseline HDV RNA levels were 5.2 (3.9-6.0) *vs.* 5.6 (4.5-6.4) LogIU/ml ($p=0.007$), age 56 (47-62) *vs.* 51 (43-57) ($p=0.03$). Among cirrhotics, 43% had varices, 9% previous HCC, 10% previous ascites, 3% history of varices hemorrhage, 5% were decompensated. ALT declined in both groups at wk24 (35 *vs.* 35 U/L, $p=0.58$), wk48 (31 *vs.* 33 U/L, $p=0.23$) and wk72 (33 *vs.* 32 $p=0.35$). HDV RNA decline was similar in patients with and without cirrhosis at wk24 (3.5 *vs.* 3.7 LogIU/mL $p=0.29$), wk48 (3.0 *vs.* 3.3 $p=0.10$) and wk72 (3.0 *vs.* 3.3 $p=0.18$). Virological, biochemical, and combined responses were achieved by 47% *vs.* 44% ($p=0.81$), 64% *vs.* 71% ($p=0.40$), and 34% *vs.* 32% ($p=0.71$) of patients at wk24; 68% *vs.* 65% ($p=1.00$), 75% *vs.* 63% ($p=0.05$), and 59% *vs.* 45% ($p=0.047$) at wk48, and by 65% *vs.* 50% ($p=0.30$), 72% *vs.* 75% ($p=1.00$), and 55% *vs.* 33% ($p=0.13$), at wk72 in patients with and without cirrhosis, respectively. HDV RNA undetectability at wk48 and 72 was similar in patients with and without cirrhosis (27% *vs.* 23%; 29% *vs.* 17%). Among non-virological responders at wk24, a partial virological response (HDV RNA decline >1 but <2 LogIU/mL *vs.* baseline) was achieved by 18% *vs.* 29% ($p=0.48$), and 15% *vs.* 0% ($p=$ns) of patients with and without cirrhosis, at wk48 and 72, respectively, and a virological response by 21% *vs.* 24 % ($p=$ns) and 70% *vs.* 0 % ($p=$ns), respectively. **Conclusion:** D-SHIELD is the largest single country study on BLV treatment for CHD. Virological, biochemical and combined responses up to wk72 were overall similar between patients with and without cirrhosis.

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0031 | COMPARING THE EFFICACY OF BULEVERTIDE, INTERFERONS, AND NUCLEOSIDE ANALOGS IN THE MANAGEMENT OF CHRONIC HEPATITIS DELTA: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Rohan Karkra[1] Mahinaz Mohsen[1] Joshua Pagán-Busigó[1] Michael Bebawy[1] Imran Qureshi[2] Paul Gaglio[1], [1]Rutgers New Jersey Medical School, [2]RUTGERS THE STATE UNIVERSITY OF NEW JERSEY

Background: The Hepatitis D Virus (HDV) affects about 10-20 million people globally. Patients with Chronic Hepatitis Delta (CHD) are at an increased risk of hepatic fibrosis, cancer, and mortality, with an estimated 50,000 deaths every year. Several therapies such as Lamivudine, Tenofovir, Interferons, and newer drugs like Lonafarnib, Bulevirtide have been tried with variable success. This Network Meta-Analysis compares several such therapies. **Methods:** We did a comprehensive search of PubMed, Embase, and Cochrane up till March 2025, to identify all studies that investigated the efficacy of a drug for chronic Hepatitis D. The studies were reviewed for the inclusion criteria, and 3 authors extracted the data. The studied end points included complete HDV RNA suppression, ALT normalization, and combined treatment response ($\geq$2 log decrease in HDV RNA or undetectable RNA, with ALT normalization), at end of treatment ($\geq$6 months) and at follow-up ($\geq$6 months). A network meta-analysis was conducted using a random effects model, and Odds Ratios (OR) were calculated. **Results:** A total of 14 studies were included, comprising 934 patients across 10 treatment arms (Bulevirtide, interferon alpha, peginterferon alpha, Nucleos(t)ide Analogs [NAs], and their combinations). No therapy demonstrated a statistically significant biochemical response (ALT normalization) at the end of treatment compared to control. However, compared to Bulevirtide, peginterferon alpha and NAs had lower odds of normalizing ALT (OR = 0.34 and OR = 0.14, respectively; $p < 0.05$). Bulevirtide, both as monotherapy (OR = 38.63; $p < 0.05$) and in combination with NA (OR = 1.86; $p < 0.05$) or peginterferon alpha (OR = 2.29; $p < 0.05$), significantly suppressed HDV RNA to undetectable levels, compared to controls. Interferons and peginterferons also suppressed RNA, both alone and when combined with NA, whereas NA alone did not achieve this. Bulevirtide and peginterferon alpha combination demonstrated significantly greater RNA suppression (OR = 6.73; $p < 0.05$) than Bulevirtide alone. Additionally, Bulevirtide monotherapy (OR = 37.73; $p < 0.05$), Bulevirtide with NA (OR = 18.54; $p < 0.05$), and peginterferon alpha both in combination (OR = 112.69; $p < 0.05$) and alone (OR = 15.89; $p < 0.05$) had significant combined responses at the end of treatment. However, no agent was superior to Bulevirtide. Histological response was assessed infrequently, and no arm performed better than the control. At follow-up, Bulevirtide and peginterferon alpha combination was associated with higher odds of sustained biochemical (OR = 3.02; $p < 0.05$) and virological (OR = 4.12; $p < 0.05$) response. **Conclusion:** Bulevirtide in combination with Pegylated interferon alpha may be the most promising therapy for chronic Hepatitis D, while monotherapy with HBV-directed NAs are not as effective. The side effects of interferon therapy also cannot be overstated. Larger RCTs with Bulevirtide + Peginterferon alpha should be conducted.

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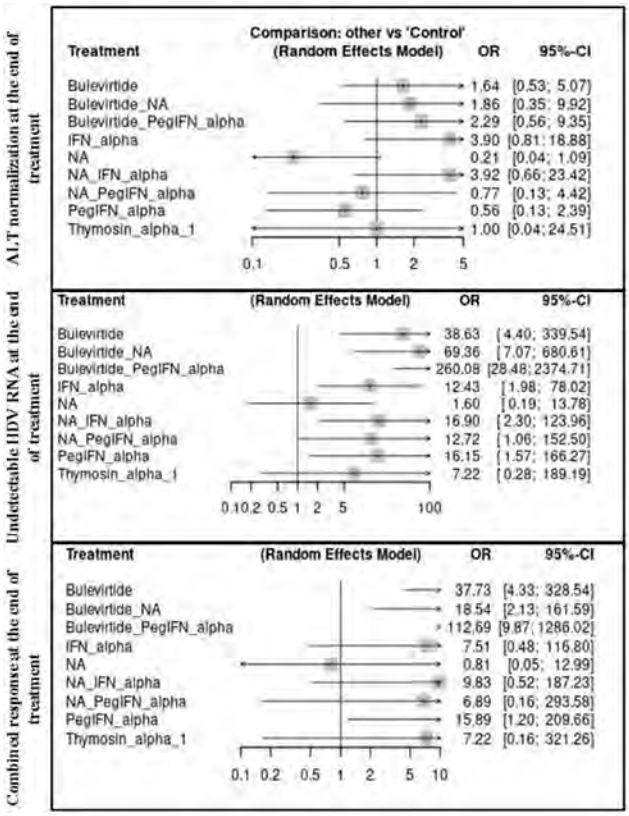

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0032 | HIGH BURDEN OF LIVER FIBROSIS IN 4,809 PEOPLE WITH HIV MONOINFECTION UNDERGOING SCREENING FOR STEATOTIC LIVER DISEASE

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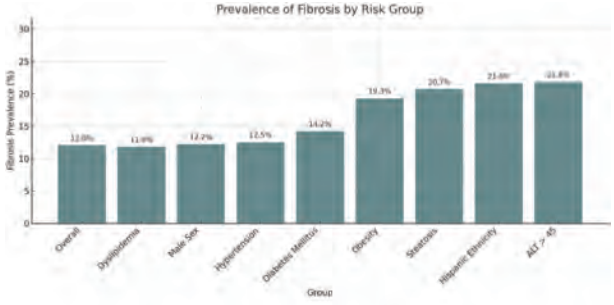
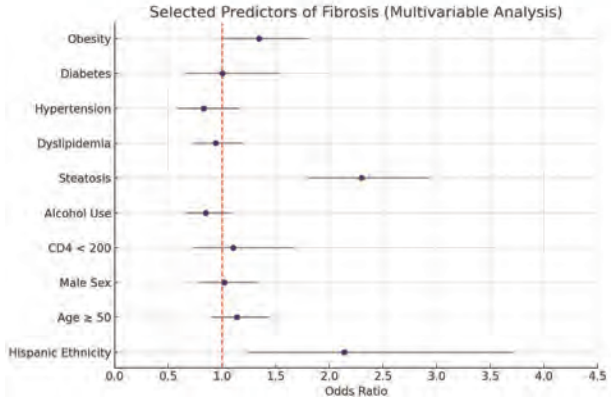
Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disease in people with HIV (PWH). Current guidelines recommend screening for liver fibrosis in the presence of metabolic comorbidities or elevated transaminases, but the true prevalence and key risk factors remain unclear. We aimed to assess the prevalence and predictors of liver fibrosis in a large, multi-national liver screening program in PWH without viral hepatitis coinfection or alcohol abuse. **Methods:** Between 2019 and 2024, we conducted a multicenter screening study of consecutive PWH from Canada and Italy. Liver fibrosis and steatosis were assessed using transient elastography. Liver fibrosis and steatosis were defined as liver stiffness measurement $\geq$8 kPa and controlled attenuation parameter $\geq$275 dB/m, respectively. The primary outcome was the overall prevalence of significant liver fibrosis. Secondary outcomes included fibrosis prevalence of fibrosis by metabolic risk profile (diabetes, obesity, metabolic syndrome), alcohol use, and steatotic liver disease, accounting for sex, ethnicity and HIV-related factors. **Results:** A total of 4,809 PWH were included (mean age 47 years, 69% men, mean BMI 25; all on antiretroviral therapy). Metabolic risk factors were common: overweight/obesity (33%/13%), dyslipidemia (39%), hypertension (15%), and diabetes (10%). Hepatic steatosis was present in 22% of patients (15% MASLD, 7% MetALD). The overall prevalence of significant fibrosis was 12%, and increased among those with diabetes, obesity, steatosis, Hispanic ethnicity or elevated ALT (Figure). Among PWH without steatosis or metabolic comorbidities, fibrosis prevalence remained notable at 9%. In multivariate analysis, independent predictors of liver fibrosis included hepatic steatosis (adjusted odds ratio [aOR] 2.66, 95% CI 2.06-3.44), Hispanic ethnicity (aOR 2.15, 95% CI 1.19-3.87) and obesity (aOR 1.39, 95% 1.01-1.90), after adjustments (Figure). Notably, 9% of patients with FIB-4 $<$ 1.30 had liver fibrosis on transient elastography, indicating that FIB-4 alone may miss at-risk PWH. **Conclusion:** This large-scale screening study reveals a high burden of liver fibrosis in PWH, largely driven by MASLD and metabolic risk factors. Fibrosis screening may need to extend beyond classical markers of dysmetabolism. Reliance on FIB-4 alone may underestimate disease burden in this population, underscoring the need for more sensitive screening approaches.





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0033 | IMPACT OF MASLD ON THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA AFTER HCV CURE IN PATIENTS WITH CHRONIC HEPATITIS C: A LARGE-SCALE, MULTICENTER COHORT STUDY

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Background: Although HCV cure can be achieved with direct-acting antiviral (DAA) therapy, advanced age and severe fibrosis remain well-established risk factors for hepatocellular carcinoma (HCC), warranting long-term surveillance. In contrast, the impact of metabolic dysfunction-associated steatotic liver disease (MASLD) on HCC development following HCV elimination is not fully elucidated. This study aimed to assess the association between MASLD and HCC incidence after HCV cure, stratified by fibrosis severity. **Methods:** We analyzed 2,689 Japanese patients with HCV cure and no prior history of HCC, enrolled in a multicenter database between 2014 and 2025. Fibrosis status was assessed using the FIB-4 index and categorized into three groups: FIB-4 <1.45, 1.45–3.25, and >3.25. Within each group, the association between MASLD and HCC development was evaluated. Cumulative HCC incidence was estimated using the Kaplan-Meier method, and independent risk factors were identified via Cox proportional hazards analysis. **Results:** In the FIB-4 <1.45 group ($n=480$), no cases of HCC were observed during follow-up. In the FIB-4 1.45–3.25 group ($n=1,132$; MASLD: 386, non-MASLD: 746), the 5- and 8-year cumulative HCC incidence rates were significantly higher in the MASLD group (4.3% and 5.9%) than in the non-MASLD group (1.4% and 2.0%) (Log-rank $P<0.001$). Multivariate analysis identified age ($P=0.026$), serum albumin level ($P<0.001$), and MASLD (hazard ratio [HR]: 3.93, $P<0.001$) as independent predictors of HCC. In the FIB-4 >3.25 group ($n=1,060$; MASLD: 395, non-MASLD: 664), the 5- and 8-year cumulative HCC incidence rates were also significantly higher in the MASLD group (14.7% and 18.6%) compared to the non-MASLD group (9.5% and 10.9%) (Log-rank $P=0.003$). Multivariate analysis similarly identified age ($P=0.040$), serum albumin level ($P=0.002$), and MASLD (HR: 1.91, $P<0.001$) as significant risk factors for HCC. **Conclusion:** MASLD was significantly associated with increased HCC incidence in patients who achieved HCV cure through DAA therapy, regardless of fibrosis stage. These findings underscore the importance of incorporating MASLD into post-cure risk stratification and highlight the need for tailored surveillance and management strategies.

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0034 | CHRONIC HEPATITIS DELTA INFECTION DISPLAYS INFLAMMATORY AND ONCOGENIC GENE SIGNATURES ALONG WITH DEFECTIVE ANTIVIRAL RESPONSE

Arshi Khanam[1] Ameer Abutaleb[2] Furkan KAYSİN[3] Cihan Yurdaydin[3] Shyam Kottilil[1], [1]Institute of Human Virology, University of Maryland School of Medicine, [2]GW School of Medicine and Health Sciences, Washington DC, USA, [3]Koc University School of Medicine, Istanbul, Turkey

Background: Background: and Aims: Hepatitis delta virus (HDV) infection causes the most severe form of

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chronic viral hepatitis due to rapid progression towards end-stage liver disease including cirrhosis and hepatocellular carcinoma (HCC) leading to high mortality. Factors driving disease acceleration need to be investigated to prevent advanced disease progression. We aimed to identify molecular signatures predicting the rapid onset of severe hepatic ailment in chronic hepatitis delta (CHD) infected patients. Methods: We investigated peripheral blood transcriptomic profiles in chronic HBV and HDV coinfected (CHB/CHD-coinfection) patients and compare them with CHB-monoinfection to recognize gene signatures associated with CHD-induced disease progression. Multiplex cytokine bead array and flow cytometry assays were performed to validate RNAseq and examine the markers of inflammation, fibrosis and immune exhaustion. Results: Transcriptomic profile revealed significant upregulation of genes related to inflammation, oncogenesis, tumor growth, invasion, metastasis and inhibition of anti-tumor response such as CXCL2, 3, 8, TNFSF9, IFITM1, IL-17, IGHA2, AREG, SEMA3F, CSF1R, TREML4, ANGPTL4 and LILRB2 in CHB/CHD-coinfection than CHB-monoinfection. Interestingly, none of the CHB/CHD-coinfected patients we analyzed had cirrhosis or HCC, yet these patients experienced significant elevation of inflammatory and oncogenic genes, indicating HDV triggers these genes much before the onset of cirrhosis or HCC that contributes to rapid disease progression/acceleration towards end-stage disease. Analysis of the top canonical pathways further proved the association of these differentially expressed genes in severe inflammatory response and oncogenic process. Results from ELISA further confirmed induction of inflammatory and fibrogenic cytokines (IL-17, CXCL2, CXCL13 and TGF-β) in the plasma of CHB/CHD-coinfection. Additionally, patients with CHB/CHD-coinfection experienced severe immune exhaustion in effector CD4 and CD8 T cell compartment by displaying higher inhibitory receptors PD-1 and TIGIT, which then resulted in poor antiviral response in terms of IFN-gamma, TNF-alpha, perforin and granzyme B secretion against HBV and HDV than CHB-monoinfection alone. Polyfunctional responses among CD4/CD8 T cells coproducing IFN-gamma, TNF-alpha, along with perforin and granzyme B were reduced in CHB/CHD-coinfection. Conclusion: HDV coinfection leads to a dichotomous immune response, whereby suppressing antiviral (HBV and HDV-specific) T cell immunity, while having exaggerated inflammatory and oncogenic responses resulting in accelerated liver disease progression, cirrhosis and HCC.

Disclosures: Arshi Khanam: Nothing to Disclose, Ameer Abutaleb: Nothing to Disclose, Furkan KAYSİN: Nothing to Disclose, Cihan Yurdaydin: Nothing to Disclose, Shyam Kottilil: Red Queen Therapeutics: Consultant, Orsobio: Stock – privately held company

★ 0035 | REAL-WORLD INSIGHTS INTO PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS: FIRST UPDATE FROM THE PROSPECTIVE TREATFIC REGISTRY

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Background: Progressive familial intrahepatic cholestasis (PFIC) is a group of rare pediatric cholestatic liver diseases, characterized by impaired bile flow. Previous retrospective analysis through the "NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion" registry allowed us to identify genotype-phenotype relationships for FIC1- and BSEP-deficiency. Recently, more PFIC subtypes have been characterized and in addition, ileal bile acid transporter inhibitors (IBATi) are increasingly used for treatment. Therefore, we initiated a prospective analysis of the treatment of PFIC, TreatFIC, in 2023. The objective of TreatFIC is to determine the natural history of all PFIC subtypes and collect real-world

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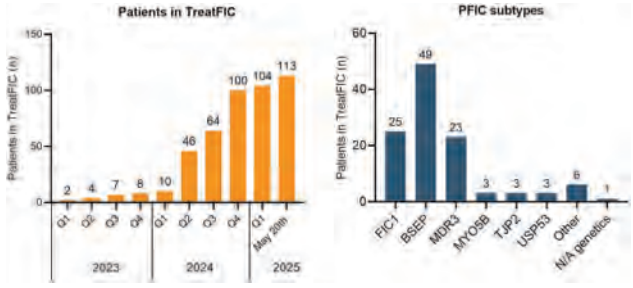
data on the efficacy and safety of current treatments, including IBATi. Here, we provide the first update on TreatFIC. **Methods:** This multicenter prospective registry includes genetic and clinical data from individuals with genetically confirmed PFIC subtypes. Demographic and clinical data were collected retrospectively and after prospectively every six months via REDCap after TreatFIC enrollment. The data cut-off was May 20, 2025. **Results:** Upon starting in January 2023, legal procedures with 50 centers worldwide have started, of which 26 centers have full IRB approval and data transfer agreements as of May 2024. We included 113 individuals from 18 centers world-wide, with different subtypes of PFIC (Figure). At data-cut off, 14 patients have a surgical biliary diversion (SBD) (median age at SBD 2.8 (0.42-9.7) years) and 27 patients had undergone liver transplantation (LtX) (median age at LtX 5.7 (0.5-30.5) years) of which 4 first had SBD before liver transplantation. Forty-six individuals are using odevixibat, 8 individuals used odevixibat in the past, 11 individuals are using maralixibat, 2 individuals used maralixibat in the past and 48 individuals are not treated with an IBATi. **Conclusion:** TreatFIC is rapidly expanding and provides prospective data on the treatments of individuals with PFIC and their efficacy. The number of included individuals has grown rapidly since its initiation in 2023. TreatFIC will allow to assess real-world data on the current treatments for PFIC diseases. To further increase the impact of the registry, centers that treat children or adults with PFIC are invited to participate (pfic@bkk.umcg.nl).



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★ 0038 | TITLE: IMPROVING ACCESS TO ALCOHOL USE DISORDER PHARMACOTHERAPY IN HEPATOLOGY: A QUALITY IMPROVEMENT INITIATIVE

Summer Collier[1], [1]*University of California, San Diego*

Background: Alcohol-associated liver disease (ALD) is the leading cause of liver-related morbidity and mortality in North America. Despite strong evidence supporting pharmacologic treatment for alcohol use disorder (AUD), pharmacotherapy remains significantly underutilized in hepatology settings. Identified barriers include provider unfamiliarity, safety concerns in cirrhosis, and system-level workflow limitations. **Aim:** To increase prescription rates of AUD pharmacotherapy in a high-volume hepatology clinic through targeted, scalable quality improvement (QI) interventions integrated into existing workflows. **Methods:** This single-center, quasi-experimental QI study compared two cohorts of adults with ALD and alcohol use seen in a hepatology clinic: pre-intervention (January–March 2023; $n = 143$) and post-intervention (January–March 2025; $n = 175$). Interventions included provider education, standardized alcohol screening, integration of decision-support tools (including a prescribing algorithm and documentation templates), and clinic access to long-acting injectable naltrexone. Outcomes were assessed via retrospective chart review. Multivariable logistic regression using backward stepwise elimination was performed to identify predictors of AUD pharmacotherapy initiation. **Results:** AUD pharmacotherapy prescribing increased from 10% pre-intervention to 43% post-intervention ($p < 0.00001$), in a high risk ALD population; 86% with cirrhosis. Documented

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discussions of pharmacotherapy rose from 33% to 80% ($p < 0.00001$), while deferral to psychiatry or primary care decreased from 7% to 1% ($p = 0.006$). Among those prescribed treatment, use of first-line agents such as oral naltrexone and acamprosate increased, and long-acting naltrexone was newly adopted. Regression analysis (AUC = 0.77) identified three independent predictors of pharmacotherapy initiation: post-intervention year (OR = 6.03, 95% CI [3.20–11.34], $p < 0.001$), recent positive PEth (phosphatidylethanol) test (OR = 2.44 vs. no PEth, 95% CI [1.28–4.64], $p = 0.007$), and a trend toward lower Child Pugh scores (OR = 0.87, 95% CI [0.75–1.00], $p = 0.057$). Model deviance R^2 was 16.2%, reflecting moderate fit likely influenced by unmeasured variables such as patient readiness to engage in behavior change. **Conclusion:** Embedded, interdisciplinary QI interventions can increase AUD pharmacotherapy rates in hepatology without requiring structural clinic overhauls. This approach enhanced provider autonomy, reduced unnecessary deferrals, and optimized the use of clinical tools such as PEth testing and a prescribing algorithm. Findings support broader implementation of pragmatic, evidence-based strategies to improve AUD care for patients with ALD in specialty settings.

Variable		2023 Cohort (N=143)	2025 Cohort (N=175)	p-value
Age (yrs), mean (SD)		54 (12)	51 (12)	0.06432
Gender, n (%)				0.015
	Male	79 (55)	120 (69)	
	Female	64 (45)	55 (31)	
Ethnicity, n (%)				0.0038
	White/non-Hispanic	88 (62)	76 (43)	
	Hispanic/Latino	43 (30)	67 (38)	
	Black/African American	3 (2)	7 (4)	
	Asian	4 (3)	3 (2)	
	Native/Pacific Islander	2 (1)	1 (<1)	
	Middle Eastern/Arabic	1 (<1)	5 (3)	
	Other	2 (1)	16 (9)	
Insurance Type, n (%)				0.0104
	Commercial	22 (15)	28 (16)	
	Medicare	41 (29)	26 (15)	
	Medicaid	80 (56)	120 (69)	
	No Insurance	0	1 (<1)	
Cirrhosis, n (%)		118 (83)	156 (89)	0.089
Na-MELD, mean (SD)		14 (6)	14 (6)	0.98404
Child-Pugh score, mean (SD)		7 (2)	7 (2)	0.98404
Hepatic Encephalopathy, n (%)				0.282
	No	83 (58)	91 (64)	
	Yes	60 (42)	84 (48)	
Ascites, n (%)				0.336
	No	69 (48)	75 (43)	
	Yes	74 (52)	100 (57)	
Esophageal Varices, n (%)				0.14
	No	110 (77)	147 (84)	
	Yes	32 (22)	28 (16)	
Serum Creatinine, mean (SD)		0.79 (0.26)	0.92 (0.92)	0.912
Total Bilirubin, mean (SD)		2.24 (3.29)	2.21 (3.33)	0.108
INR, mean (SD)		1.39 (0.42)	1.35 (0.37)	0.374
EtgS Result w/in 6 months, n (%)				0.0036
	No Result	62 (43)	46 (26)	
	Negative Result	32 (22)	42 (24)	
	Positive Result	49 (34)	87 (50)	

Disclosures: Summer Collier: Nothing to Disclose

★ 0039 | ALCOHOL, CARDIOMETABOLIC RISK FACTORS, AND CIRRHOSIS: TEN-YEAR RISK ESTIMATES FROM A NATIONWIDE DANISH COHORT

Jonas Rønn[1] Gro Askgaard[1] Lone Madsen[1] Peter Jepsen[2] Hamish Innes[3] Jessica Mellinger[4] Marie Eliasen[5], [1]Department of Hepatology and Gastroenterology, Zealand University Hospital, Køge, Denmark, [2]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark, [3]School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK, [4]Henry Ford Health- Michigan State University, [5]Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Denmark

Background: Alcohol consumption and cardiometabolic risk factors increase the risk of cirrhosis, and their combined effects have gained recognition with the introduction of the MetALD term. We estimated 10-year risks of cirrhosis according to alcohol consumption and cardiometabolic risk factors. **Methods:** We included participants from the population-based Danish National Health Surveys 2010-2017 and followed them in registries through 2022 for an incident hospital diagnosis of cirrhosis, linking data on alcohol consumption, smoking status, height and weight from questionnaires with data on diabetes and redeemed hypertension- and dyslipidemia prescriptions from health registries. A drink was defined as 12 grams of alcohol. We computed the 10-year risk of cirrhosis, accounting for death as a competing event and used inverse probability weights to adjust for the differences in age between participants across the strata of risk factors for cirrhosis. **Results:** The study included 304,023 participants with a median age of 52 years (IQR 43-61); 54 % were female, 3% consumed more than 28 drinks per week, 17% had a BMI greater than 30, and 4.5% had diabetes. During 2,905,528 person-years of follow-up, 1010 participants were diagnosed with cirrhosis. The level of alcohol consumption had a powerful influence on the 10-year risk of cirrhosis with an 11-fold higher risk for 29-41 drinks/week of 2.29% and 30-fold higher risk of 5.2% for those consuming more than 42 drinks/week compared to 0.2% for those drinking 1-14 drinks/week (Table 1). The largest number of cirrhosis cases occurred among participants consuming fewer than 29 drinks per week, where diabetes increased the 10-year risk of cirrhosis by fourfold, and other cardiometabolic risk factors (BMI over 30, hypertension, dyslipidemia, and smoking) increased the risk by two- to threefold. Among participants drinking more than 28 drinks/week, the

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influence of cardiometabolic risk factors on the 10-year cirrhosis risk weakened; however, notably, the highest 10-year risks of cirrhosis were found in participants drinking more than 28 drinks/week who also had diabetes or hypertension. A high BMI did not significantly affect the risk of cirrhosis in drinkers of 28-42 drinks/week, with 10-year risks of 1.9% vs. 1.8% for BMI of 18.5-25 vs. BMI > = 30. **Conclusion:** The level of alcohol consumption has a substantial impact on the absolute 10-year risk of cirrhosis. The impact of cardiometabolic risk factors on the 10-year risk of cirrhosis is markedly weaker than alcohol, especially among those who consume more than 28 drinks/week. However, most cases of cirrhosis develop in the large population segment who drink small or moderate amounts of alcohol, indicating that preventive efforts should not be restricted to those who consume the most alcohol.

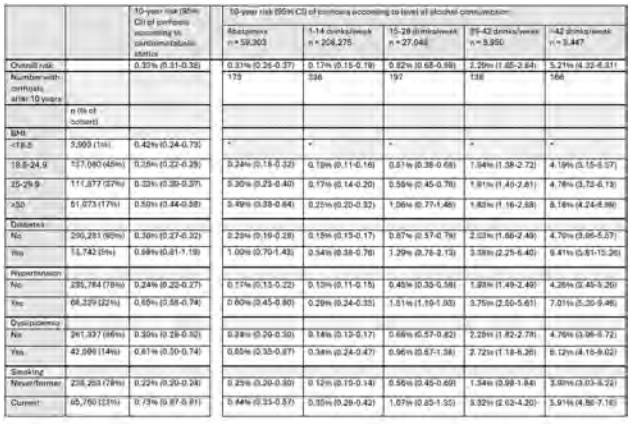

Table 1. Absolute 10-year risk with 95% confidence intervals of incident cirrhosis according to cardiometabolic risk factors for different levels of alcohol consumption for participants in the Danish National Health Surveys 2010 - 2017. A drink was defined as 12 grams of alcohol. We used inverse probability weights to adjust for the differences in age between patients with different risk factors for cirrhosis.

* Subgroup analyses on BMI <18.5 omitted due to low number of cases.

Disclosures: Jonas Rønn: Nothing to Disclose, Gro Askgaard: Nothing to Disclose, Lone Madsen: Nothing to Disclose, Peter Jepsen: Nothing to Disclose, Hamish Innes: Nothing to Disclose, Jessica Mellinger: GlaxoSmithKline: Advisor, Novo Nordisk: Consultant, Boehringer Ingelheim: Consultant, Marie Eliasen: Nothing to Disclose

0040 | INCREASED ALCOHOL USE AFTER BARIATRIC SURGERY PREDICTS FIBROSIS PROGRESSION IN MASLD: WOMEN AT HIGHEST RISK

Brittany Bromfield[1] Kathleen Corey[2] Jay Luther[2] Wei Zhang[2] Russell Goodman[2] Esperance Schaefer[1], [1]Brigham and Women's Hospital, [2]Massachusetts General Hospital

Background: Bariatric surgery improves metabolic dysfunction-associated steatotic liver disease (MASLD) through weight loss and metabolic changes but has been associated with hazardous drinking. Many patients experience sustained improvement in MASLD, but up to 20% of patients paradoxically develop progressive fibrosis. We aimed to identify independent and modifiable predictors of fibrosis progression after bariatric surgery. **Methods:** We analyzed a cohort of 455 adults with biopsy-confirmed MASLD who underwent sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB) (median 7.5-year follow-up). Fibrosis progression was defined as advancement to a higher FIB-4 risk category (<1.3 to ≥ 1.3 or ≥ 2.67). Change in alcohol use (ΔAUDIT-C) was assessed using validated screening and was analyzed as a continuous, categorical, and threshold-based variable. Cox proportional hazards regression evaluated time to progression, adjusting for age, sex, change in BMI (ΔBMI) and baseline FIB-4. **Results:** Eighty-four (18.4%) patients progressed to a higher FIB-4 category. In a multivariable analysis, three independent predictors emerged: older age increased risk (HR 1.06, 95% CI 1.03-1.09, $p<0.001$), BMI loss was protective (HR 0.95, 95% CI 0.93-0.98, $p=0.0009$), and each 1-point increase in ΔAUDIT-C conferred 19% higher risk (HR 1.19, 95% CI 1.09-1.29, $p<0.001$).The alcohol effect showed striking sex differences: women demonstrated 24% increased risk per ΔAUDIT-C point (HR 1.24, 95% CI 1.12-1.38, $p<0.001$) while men showed no significant association (HR 1.07, 95% CI 0.92-1.25, $p=0.35$). This association did not differ by surgery type (p_interaction = 0.57) or GLP-1 RA use (p_interaction = 0.39). Categorical analysis revealed dose-response patterns by sex. Among women, hazard ratios increased progressively: 1.29 for 1-point increases, 2.15 for 2-point increases, and 3.61 for ≥ 3-point increases ($p=0.005$). Men showed no elevated risk until ≥ 3-point increases (HR 2.76, $p=0.010$). Maximal rank analysis identified a ≥ 1-point increase in ΔAUDIT-C as the optimal cutoff for discriminating fibrosis risk (HR 1.95, 95% CI 1.22–3.12, p = 0.005). Female RYGB patients had the highest increase in alcohol use (ΔAUDIT-C +0.82 vs. +0.38 for SG, p = 0.02) and at-risk drinking conversion (23% vs. 8%, p = 0.01). **Conclusion:** Post-operative increases in alcohol use are an independent predictor of fibrosis progression after bariatric surgery, with effects most pronounced in women. Women show significant risk at modest alcohol increases (≥ 1-point ΔAUDIT-C), while men require larger increases (≥ 3-points) before risk emerges. A ≥ 1-point increase in AUDIT-C elevated risk, supporting its use as a clinical threshold for intervention. These findings support the need for routine longitudinal alcohol monitoring after weight loss surgery and highlight the importance of sex-specific counseling and early intervention to prevent alcohol-related liver injury.

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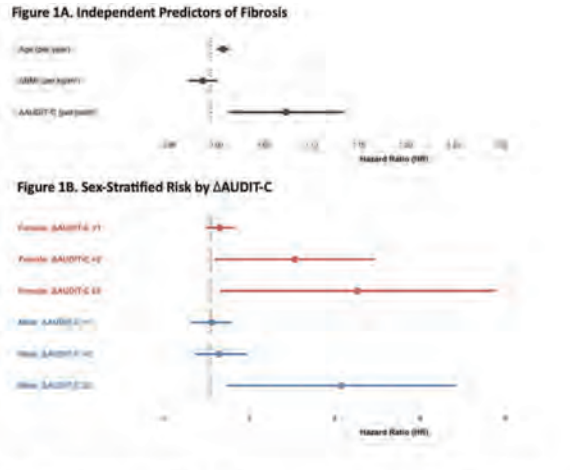


Figure 1. Independent predictors of fibrosis progression and sex-stratified risk by alcohol consumption changes. (A) Forest plot showing hazard ratios (HR) and 95% confidence intervals for independent predictors of fibrosis progression. Age per year, change in body mass index (ΔBMI) per kg/m², and change in AUDIT-C score (ΔAUDIT-C) per point were analyzed using multivariable Cox regression. The vertical dashed line represents HR = 1.0 (no effect). (B) Sex-stratified analysis of fibrosis progression risk by ΔAUDIT-C category. Hazard ratios and 95% confidence intervals are shown for males (blue) and females (red) across different levels of alcohol consumption change: +1 point, +2 points, and ≥3 points increase in AUDIT-C score. The vertical dashed line represents HR = 1.0 (no effect).

Disclosures: Brittany Bromfield: Nothing to Disclose, Kathleen Corey: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Jay Luther: Nothing to Disclose, Wei Zhang: Nothing to Disclose, Russell Goodman: Nothing to Disclose, Esperance Schaefer: Nothing to Disclose

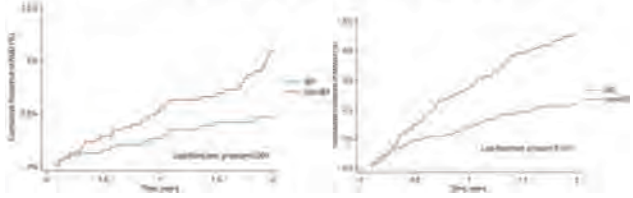
★ 0041 | INCRETIN-BASED THERAPIES AND POST-BARIATRIC ALCOHOL USE DISORDER: A PROPENSITY-MATCHED COHORT STUDY

Butros Fakhoury[1] Leandro Sierra[2] Vinay Jahagirdar[1] Luis Díaz[3] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]Cleveland Clinic Foundation, [3]University of California San Diego

Background: Post-bariatric surgery (BS) patients are at an increased risk for developing alcohol use disorder (AUD). Incretin-based therapies (IBTs) are commonly utilized as adjunctive weight loss therapy in post-BS patients with inadequate weight loss or weight regain . Emerging evidence suggests that IBTs may modulate reward pathways and reduce alcohol consumption. However, their impact on the incident AUD compared to other anti-obesity medications (AOMs) remains unclear. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network. Adults who received either an IBT (semaglutide, liraglutide, tirzepatide) or a non-IBT AOM (e.g., orlistat, phentermine) following BS between January 1, 2010, and January 1, 2024, were included. Patients with prior AUD were excluded. Propensity score matching was performed using demographics, medical and psychiatric comorbidities, and substance use. Outcomes included new-onset AUD and initiation of AUD medications between 1 month and 2 years post–AOM initiation. Incidence rates, Kaplan–Meier curves, and hazard ratios (HRs) were calculated. **Results:** After matching, 4,024 patients were included in each group with a median follow-up of 2 years. The proportion undergoing Roux-en-Y gastric bypass was comparable between groups (IBT 35.8% vs. non-IBT 36.2%). Semaglutide and phentermine were the most commonly prescribed agents in the IBT and non-IBT groups, respectively. IBT use was associated with significantly lower risk of new-onset AUD (HR 0.46; 95% CI 0.26–0.84; $P = 0.009$) and initiation of medications for AUD (HR 0.48; 95% CI 0.37–0.63; $P < 0.001$). **Conclusion:** In this large, multi-institutional cohort of post-BS patients, IBT use was associated with a significantly reduced risk of developing AUD and initiating pharmacologic treatment for AUD compared to non-IBT AOMs. These associations were consistent across multiple sensitivity analyses, highlighting a potential dual benefit of IBTs in both weight management and AUD risk mitigation in this high-risk population.

Table 1. Baseline Characteristics before and after PSM with SMD.

Variable	Before PSM					After PSM				
	IBT N=10,564		Non-IBT N=4,455		SMD	IBT N=4,024		Non-IBT N=4,024		SMD
Age at Index	51.7	11.5	46.3	10.9	**0.486**	47.1	11.0	47.3	10.6	0.015
Sex, Female	8269	78.3%	3811	85.5%	**0.190**	3392	84.3%	3406	84.6%	0.010
Race										
White	6596	62.4%	2719	61.0%	0.029	2489	61.9%	2469	61.4%	0.010
Black	2184	20.7%	934	21.0%	0.007	823	20.5%	842	20.9%	0.012
Hispanic	1163	11.0%	549	12.3%	0.041	482	12.0%	485	12.1%	0.002
Asian	141	1.3%	24	0.5%	0.083	19	0.5%	24	0.6%	0.017
Other Race	407	3.9%	188	4.2%	0.019	160	4.0%	172	4.3%	0.015
Overweight and obesity	10247	97.0%	4335	97.3%	0.018	3933	97.7%	3919	97.4%	0.023
Type 2 diabetes mellitus	5813	55.0%	1216	27.3%	**0.587**	1199	29.8%	1202	29.9%	0.002
MASLD	2669	25.3%	816	18.3%	**0.169**	759	18.9%	773	19.2%	0.009
Major depressive disorder	1880	17.8%	608	13.6%	**0.114**	583	14.5%	575	14.3%	0.006
Anxiety disorders	5387	51.0%	1897	42.6%	**0.169**	1807	44.9%	1819	45.2%	0.006
Cannabis related disorders	158	1.5%	51	1.1%	0.031	58	1.4%	48	1.2%	0.022
Nicotine dependence	1407	13.3%	552	12.4%	0.028	522	13.0%	489	12.2%	0.025
Cocaine related disorders	51	0.5%	15	0.3%	0.023	18	0.4%	15	0.4%	0.012
Opioid related disorders	267	2.5%	76	1.7%	0.057	73	1.8%	73	1.8%	<0.001



Disclosures: Butros Fakhoury: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Vinay Jahagirdar: Nothing to Disclose, Nothing to Disclose, Luis Díaz: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose

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

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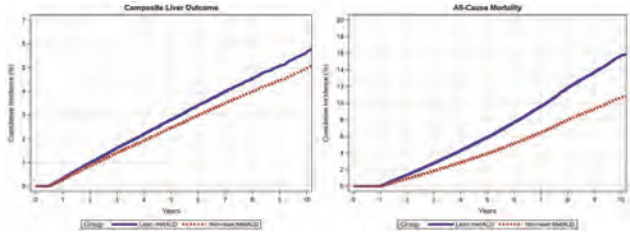
0042 | CLINICAL FEATURES AND OUTCOMES OF LEAN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE WITH INCREASED ALCOHOL INTAKE (LEAN METALD)

Binu John[1] Samuel Soon[2] Ashwani Singal[3] Suthat Liangpunsakul[4] Naim Alkhouri[5] Robert Wong[6] Ponni Perumalswami[7] Basile Njei[8] Mazen Noureddin[9] Bassam Dahman[2], [1]University of Miami and Miami VA, [2]Virginia Commonwealth university, [3]University of Louisville, [4]Indiana University School of Medicine, [5]Arizona Liver Health, [6]VA Palo Alto Healthcare System, [7]University of Michigan Medical Center, [8]Yale University, [9]Houston Methodist Hospital

Background: MetALD (Metabolic Dysfunction-Associated Steatotic Liver Disease [MASLD] with increased alcohol consumption) is a distinct subtype of steatotic liver disease characterized by hepatic steatosis, cardiometabolic risk factors (CMRF), and alcohol use. The primary objective of this study was to evaluate the incidence of major adverse liver outcomes (MALO), including hepatocellular carcinoma, hepatic decompensation, liver transplantation, liver-related death, and all-cause mortality, in patients with lean MetALD versus those with non-lean MetALD. **Methods:** This was a retrospective cohort study using data from the Veterans Health Administration between January 1, 2013, and December 31, 2022, with follow-up through May 31, 2023. Lean MetALD was defined as MetALD with a BMI <25 kg/m² (<23 kg/m² for Asians). The baseline was defined as the first documentation of steatosis. We used a multivariable time-updated Fine and Gray competing risk model, treating non–liver-related death as a competing risk. All-cause mortality was analyzed using a multivariable Cox proportional hazard model, with liver transplantation treated as a censoring event. Both models were adjusted for age, sex, race/ethnicity, baseline cirrhosis, diabetes, tobacco use, AST, ALT, and platelet count. **Results:** We identified 98,932 patients who met criteria for MetALD, including 12,802 with lean MetALD. Compared to those with non-lean MetALD, patients with lean MetALD were older (mean age 63.5 vs. 58.3 years), more likely to have cirrhosis at baseline (7.5% vs. 5.4%), to be current or former smokers (87.4% vs. 77.5%), and had slightly higher peak AUDIT-C scores over the prior five years. In contrast, patients with non-lean MetALD were more likely to have type 2 diabetes (14.1% vs. 7.1%) and each of the five CMRFs. Patients with lean MetALD had a AST:ALT ratio >1 (43.0 vs. 38.3), while the opposite was true for non-lean MetALD (38.3 vs. 49.2). Additionally, lean MetALD patients had higher MCV (93.6 vs. 91.1), and lower platelet counts (208.3 vs. 210.7 $\times 10^9$/L). Patients with lean MetALD had higher adjusted incidence rates per 1,000 person-years for decompensation (25.05 vs. 20.12, $p<0.0001$), liver-related death (2.15 vs. 1.67, $p=0.02$), MALO (27.38 vs. 22.13, $p<0.0001$), and all-cause mortality (29.78 vs. 19.04, $p<0.0001$). On multivariable analysis, lean MetALD was independently associated with a 14% increased hazard of MALO compared to non-lean MetALD (adjusted Hazard Ratio [aHR] 1.14, 1.05–1.24) and a 51% higher hazard of all-cause mortality (aHR 1.51, 1.44–1.59). Conclusion: Within the spectrum of MetALD, patients with lean MetALD tend to behave more like ALD, whereas those with non-lean MetALD exhibit clinical features similar to MASLD. Patients with lean MetALD was associated with a higher risk of liver-related outcomes and all-cause mortality compared to non-lean MetALD.



Disclosures: Binu John: Exact Sciences: Grant/Research Support, Genentech: Grant/Research Support, Glycotest, Inc: Grant/Research Support, Gilead: Grant/Research Support, Exelixis: Consultant, Takeda: Grant/Research Support, GlaxoSmithKline: Consultant, Astra Zeneca: Consultant, Samuel Soon: Nothing to Disclose, Ashwani Singal: Nothing to Disclose, Suthat Liangpunsakul: Nothing to Disclose, Naim Alkhouri: Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Boston Pharma: Grant/Research Support, Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support,

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0043 | METABOLOMIC ANALYSIS OF FEMALE AND MALE PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS

Mansoor Jalal Zai[1] Wajahat Mehal[2] Sherry McKee[1] Bubu Banini[2], [1]Yale School of Medicine, [2]Yale University

Background: Acute alcohol-associated hepatitis (AH) is clinically more severe in females, however sex differences in alcohol associated liver disease (ALD) especially AH remain poorly characterized. Metabolomic profiling may uncover novel pathways related to AH, especially in females. **Methods:** Serum metabolomic profiles from female (F) and male (M) patients with AH and heavy drinking controls (HD) were analyzed using ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS). Metabolites with Variable Importance in Projection > 1.5, log2 fold change > 2.0, and $p < 0.05$ in pairwise comparisons were considered significant. Analysis was performed by Creative Proteomics. **Results:** In total, 7,321 metabolites were detected in positive ion mode and 14,330 in negative ion mode. Enrichment analysis identified commonly affected pathways in both sexes with AH compared to their HD controls, including glycerolipid metabolism, steroid biosynthesis, arachidonic acid metabolism, linoleic acid metabolism, primary bile acid biosynthesis, glycerophospholipid metabolism, inositol phosphate metabolism, among others. In both sexes, glycine-conjugated bile acids such as glycocholate and glycochenodeoxycholate were increased. However, taurocholate was decreased only in females with AH; similarly taurine and hypotaurine metabolism were significantly enriched only in the females with AH compared to HD (enrichment ratio = 30; p = 2.29E-12), suggesting sex-specific alterations in bile acid metabolism. **Conclusion:** Comprehensive metabolomic analysis of female and male adults with AH demonstrates sex-independent perturbation in various pathways. In addition, sex-specific changes in taurocholate and taurine metabolism were seen. Further analyses are expected to reveal key insights into disease mechanisms and help explain the greater susceptibility of females to ALD.

Disclosures: Mansoor Jalal Zai: Nothing to Disclose, Wajahat Mehal: Nothing to Disclose, Nothing to Disclose, Sherry McKee: Nothing to Disclose, Bubu Banini: Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Merck: Grant/Research Support

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★ 0044 | VALIDATION OF NONINVASIVE CLINICAL PATHWAYS TO IDENTIFY ADVANCED FIBROSIS IN METALD AND ALD

Luis Antonio Diaz[1] Natalia Baeza[2] Francisco Idalsoaga[3] Ming-Hua Zheng[4] Ming-Hua Zheng[4] Fátima Higuera de la Tijera[5] Fernando Javier Barreyro[6] Rakhi Maiwall[7] Shiv Kumar Sarin[7] Anand V. Kulkarni[8] Ramagundam Ramyasri[8] Gustavo Ayares[9] Terry Cheuk-Fung Yip[10] Vincent Wai-Sun Wong[10] Grace Lai-Hung Wong[10] Jimmy Che-To Lai[10] YU JUN WONG[11] Xin En Goh[11] May Xuan Goh[11] David Marti-Aguado[12] Cristiane Villela-Nogueira[13] Nathalie Leite[13] Gil Fernando Salles[13] Claudia Regina Lopes Cardoso[13] Mohamed El-Kassas[14] Daniza Alexandra Contreras De Los Santos[15] José Antonio Velarde-Ruiz Velasco[16] Alceo Galimberti[17] Fernando Bessone[17] Francisco Javier Valentin-Cortez[18] Alejandra Mijangos-Trejo[18] Norberto C. Chavez-Tapia[18] Ezequiel Ridruejo[19] Mirta Peralta[20] Juan Pablo Roblero[21] Daniela Simian[21] Pamela Gil G[21] Sheel Patel[22] Ashwani K. Singal[22] Pedro Montes[23] Jordi Gratacós-Ginès[24] Elisa Pose[24] Katrina Pekarska[25] Richard Parker[25] Mohamad Ali Ibrahim[26] Prasun K. Jalal[26] Graciela Castro-Narro[27] Mazen Noureddin[28] Naim Alkhouri[29] Winston Dunn[30] Patrick S. Kamath[31] Arun Sanyal[32] Richard K. Sterling[32] Veeral Ajmera[1] Rohit Loomba[1] Marco Arrese[9] Ramon Bataller[33] Juan Pablo Arab[34], [1]MASLD Research Center, Division of Gastroenterology and Hepatology, University of California San Die, [2]Departamento de Gastroenterología, Escuela de Medicina, Pontificia Universidad Católica de Chile, S, [3]Department of Medicine, Division of Gastroenterology, Western University, London Health Sciences Cen, [4]MAFLD Research Center, Department of Hepatology, The First Affiliated Hospital of Wenzhou Medical Un, [5]Departamento de Gastroenterología, Hospital General de México "Dr. Eduardo Liceaga", Ciudad de Méxic, [6]Departamento de Gastroenterología, Escuela de Medicina, Universidad Nacional de Misiones, Misiones, [7]Department of Hepatology, Institute of Liver and Biliary Sciences, Delhi, India, [8]Department of Hepatology and Liver Transplantation, AIG Hospitals, Hyderabad, India, [9]Departamento de Gastroenterología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Sa, [10]Medical Data Analytics Centre, Department of Medicine and Therapeutics, The Chinese University of Ho, [11]Department of Gastroenterology & Hepatology, Changi General Hospital, Singapore; Yong Loo Lin School, [12]Digestive Disease Department, Clinic University Hospital, INCLIVA Health Research Institute, Valenci, [13]División de Hepatología, Escola de Medicina, Hospital Universitário Clementino Fraga Filho, Universi, [14]Endemic Medicine Department, Faculty of Medicine, Helwan University, Cairo, Egypt, [15]Instituto Nacional de Diabetes, Endocrinología y Nutrición (INDEN), Santo Domingo, Dominican Republi, [16]Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara, Mexico, [17]Department of Gastroenterology, Hospital Centenario de Rosario, Santa Fe, Argentina, [18]Department of Gastroenterology and Obesity, Medica Sur Hospital, Mexico City, Mexico., [19]Hepatology Section, Department of Medicine, Centro de Educación Médica e Investigaciones Clínicas No, [20]Hospital Francisco J. Muñiz, Ciudad Autónoma de Buenos Aires, Argentina, [21]Sección de Gastroenterología, Departamento de Medicina Interna, Hospital Clínico Universidad de Chil, [22]Division of Gastroenterology, Hepatology and Nutrition, University of Louisville School of Medicine, [23]Departamento de Gastroenterología, Hospital Nacional – Daniel Alcides Carrión, Bellavista, Peru, [24]Liver Unit, Hospital Clínic de Barcelona, Barcelona, Spain, [25]Leeds Liver Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [26]Department of Gastroenterology and Hepatology, Baylor College of Medicine, Houston, Texas, USA, [27]Department of Gastroenterology, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán, [28]Houston Methodist Hospital, Houston, Texas, USA, [29]Department of Hepatology, Summit Clinical Research, San Antonio, Texas, USA, [30]University of Kansas Medical Center, Kansas, USA, [31]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA, [32]Division of Gastroenterology, Hepatology, and Nutrition, Department of Internal Medicine, Virginia C, [33]University of Pittsburgh, [34]Virginia Commonwealth University

Background: Metabolic dysfunction-associated steatotic liver disease (MetALD) and alcohol-associated liver disease (ALD) progress faster to advanced fibrosis, yet data on the performance of noninvasive clinical algorithms are limited. We aimed to (1) quantify the false-negative rate of standard algorithms combining Fibrosis-4 index (FIB-4) and vibration-controlled transient elastography (VCTE) for detecting advanced fibrosis in MetALD and ALD, and (2) evaluate the diagnostic accuracy of FIB-4 for advanced fibrosis in MetALD. **Methods:** In this retrospective cohort, we included 764 well-characterized adults with MetALD (n = 334, 43.7%) or ALD (n = 430, 56.3%) from 14 countries between 2003 and 2025 according to the 2023 criteria; other concomitant liver diseases were excluded. All underwent VCTE (> 8 kPa considered elevated); 244 (31.9%) also had liver biopsy. FIB-4 was categorized using standard thresholds: low risk < 1.3, indeterminate 1.3–2.67 (2.0–2.67 if ≥ 65 years), and high risk > 2.67. The primary outcome was the

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proportion of patients with biopsy-proven ≥F3 fibrosis missed when both FIB-4 and VCTE were interpreted as low risk. In MetALD, we further assessed FIB-4 performance by area under the receiver-operating characteristic curve (AUROC) analysis. **Results:** Mean age was 49.5 years (IQR 41–59); 73.1% were male; mean BMI 28.0 kg/m² (IQR 24.1–31.6); 32.2% had diabetes. Ethnic distribution was 43.0% Asian, 38.5% Hispanic, and 17.8% non-Hispanic White. Median FIB-4 was 1.57 (IQR 0.92–3.29); median LSM 8.6 kPa (IQR 5.9–22.3). Among those biopsied (n = 244), 14.3% had F3 and 11.9% had cirrhosis (F4). Overall, 43.7% were low risk by FIB-4, 25.1% indeterminate, and 31.2% high risk. Of the low FIB-4 group, 28.1% had elevated VCTE (32.0% MetALD; 24.9% ALD). Sixteen participants classified as low-risk by both FIB-4 and LSM had ≥F3 fibrosis on biopsy—false-negative rate 6.6% overall (5.7% MetALD; 7.4% ALD)(Figure). In MetALD, FIB-4 yielded an AUROC of 0.736 (95%CI 0.610–0.863) for ≥F3 fibrosis; the optimal cut-point was ≥1.65 (sensitivity 74%, specificity 73%). Applying ≥1.65 to participants over 65 years with MetALD reduced the false-negative rate to 2.0%, while the referral rate rose only from 30.3% to 33.6%. **Conclusion:** Standard noninvasive pathways combining FIB-4 and VCTE had low false-negative rates for advanced fibrosis in MetALD and ALD. In patients with MetALD aged over 65 years, lowering the FIB-4 threshold to ≥1.65 may improve early detection of advanced fibrosis in MetALD.

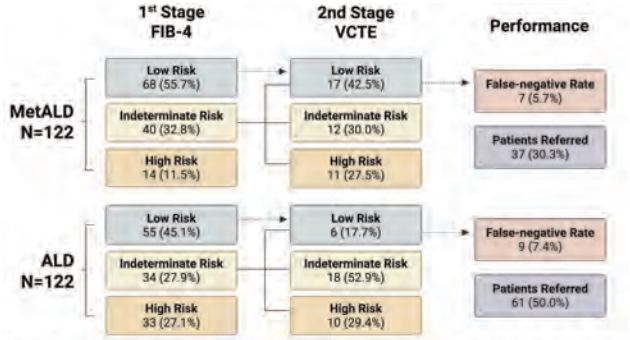

Figure: Performance of the clinical algorithms using the Fibrosis-4 index (FIB-4) and vibration-controlled transient elastography (VCTE) to detect advanced fibrosis in metabolic dysfunction–associated steatotic liver disease (MetALD) and alcohol-associated liver disease (ALD).

Disclosures: Luis Antonio Diaz: Nothing to Disclose, Natalia Baeza: Nothing to Disclose, Francisco Idalsoaga: Nothing to Disclose, Ming-Hua Zheng: Nothing to Disclose, Ming-Hua Zheng: Nothing to Disclose, Fátima Higuera de la Tijera: Nothing to Disclose, Fernando Javier Barreyro: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Anand V. Kulkarni: Nothing to Disclose, Ramagundam Ramyasri: Nothing to Disclose, Gustavo Ayares: Nothing to Disclose, Terry Cheuk-Fung Yip: Nothing to Disclose, Vincent Wai-Sun Wong: Nothing to Disclose, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Jimmy Che-To Lai: Nothing to Disclose, YU JUN WONG: Nothing to Disclose, Xin En Goh: Nothing to Disclose, May Xuan Goh: Nothing to Disclose, David Marti-Aguado: Nothing to Disclose, Cristiane Villela-Nogueira: Nothing to Disclose, Nathalie Leite: Nothing to Disclose, Gil Fernando Salles: Nothing to Disclose, Claudia Regina Lopes Cardoso: Nothing to Disclose, Mohamed El-Kassas: Nothing to Disclose, Daniza Alexandra Contreras De Los Santos: Nothing to Disclose, José Antonio Velarde-Ruiz Velasco: Nothing to Disclose, Alceo Galimberti: Nothing to Disclose, Fernando Bessone: Nothing to Disclose, Francisco Javier Valentin-Cortez: Nothing to Disclose, Alejandra Mijangos-Trejo: Nothing to Disclose, Norberto C. Chavez-Tapia: Nothing to Disclose, Ezequiel Ridruejo: Nothing to Disclose, Mirta Peralta: Nothing to Disclose, Juan Pablo Roblero: Nothing to Disclose, Daniela Simian: Nothing to Disclose, Pamela Gil G: Nothing to Disclose, Sheel Patel: Nothing to Disclose, Ashwani K. Singal: Nothing to Disclose, Pedro Montes: Nothing to Disclose, Jordi Gratacós-Ginès: Nothing to Disclose, Elisa Pose: Nothing to Disclose, Katrina Pekarska: Nothing to Disclose, Richard Parker: Orphalan: Consultant, Mohamad Ali Ibrahim: Nothing to Disclose, Prasun K. Jalal: Nothing to Disclose, Graciela Castro-Narro: Nothing to Disclose, Mazen Noureddin: Nothing to Disclose, Naim Alkhouri: Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research

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0045 | SIMILAR LONG-TERM INCIDENCE OF HEPATOCELLULAR CARCINOMA (HCC) IN CHRONIC HEPATITIS B PATIENTS WHO INITIATED ENTECAVIR (ETV) VERSUS TENOFOVIR ALAFENAMIDE (TAF): A REAL-B STUDY

Haruki Uojima[1] Rui Huang[1] Mindie Nguyen[1] Huy Trinh[2] Akito Nozaki[3] Philip Vutien[4] Hidenori Toyoda[5] Takashi Honda[6] Hiroshi Abe[7] Masanori Atsukawa[8] Tsunamasa Watanabe[9] Toru Ishikawa[10] Masaru Enomoto[11] Yasuhito Tanaka[12] Koichi Takaguchi[13] Pei-Chien Tsai[4] Mayumi Maeda[1] Ramsey Cheung[1] Takanori Ito[6] Manabu Morimoto[3] Ming-Lung Yu[14] Chung-Feng Huang[4] Wan Long Chuang[4] Chia-Yen Dai[4] Ming-Lun Yeh[4] Chao Wu[15] Tomonori Senoh[13] Jee-Fu Huang[4], [1]Stanford University Medical Center, [2]San Jose Gastroenterology, [3]Yokohama City University Medical Center, [4]Kaohsiung Medical University, [5]Ogaki Municipal Hospital, [6]Nagoya University Graduate School of Medicine, [7]Shinmatsudo Central General Hospital, [8]Nippon Medical School, [9]St. Marianna University School of Medicine, [10]Saiseikai Niigata Hospital, [11]Osaka Metropolitan University, [12]Kumamoto University, Kumamoto, [13]Kagawa Prefectural Central Hospital, [14]Kaohsiung Medical University/ Kaohsiung Medical University Hospital, [15]Nanjing University

Background: CHB remains a major global health burden, and long-term antiviral therapy can reduce HCC risk. ETV and TAF are both first-line therapies with potent viral suppression and favorable safety profiles. Previous comparisons between ETV and TDF yielded conflicting results regarding HCC prevention, with data with adequate adjustment for differences in treatment eras and patient characteristics showing no significant differences, but comparative data for ETV vs. TAF are limited. We aimed to investigate the long-term risk HCC with ETV vs. TAF in the same era following TAF approval in 2016. **Methods:** We enrolled previously treatment-naïve CHB patients from 24 centers across 7 countries from the REAL-B consortium who initiated either ETV or TAF between 2016 and 2023 who had no viral co-infections or prior malignancy. The primary study outcome was HCC incidence via Fine and Gray competing risk models. To balance patient background characteristics, we used inverse probability of treatment weighting (IPTW) and, as a sensitivity analysis, propensity score matching (PSM) with both matched for age, sex, race, alcohol use, cirrhosis, hepatic steatosis, HBsAg, HBV DNA, platelet, AST, ALT, and albumin. **Results:** The study included 1,437 patients (710 ETV, 727 TAF) with similar mean follow-up (48.5 ± 25.0 vs. 48.7 ± 22.5, respectively, P = 0.84). Prior to matching, ETV patients were significantly older, more likely male or had cirrhosis. After IPTW, the ETV and TAF groups had balanced characteristics (all standardized difference < 0.1). During follow-up, HCC occurred in 12 ETV patients and 14 TAF patients, corresponding to incidence rates of 0.10 and 0.18 per 100 person-years, respectively (P = 0.19). There was no statistically significant difference in the HCC risk of ETV vs. TAF patients (SHR: 2.17; 95% CI: 0.68–6.85; P = 0.19), with consistent findings across subgroups by age, sex, presence of cirrhosis, hepatic steatosis, HBeAg, ALT and HBV DNA levels and in sensitivity analyses using PSM. **Conclusion:** In this real-world multinational study of previously treatment-naïve CHB patients who initiated treatment during the same era, HCC incidence did not differ significantly between those who initiated ETV or TAF, with consistent findings across multiple analytic methods and patient subgroups. These results suggest that both agents provide comparable HCC prevention benefits, and therapeutic selection should be based on cost and other patient factors.

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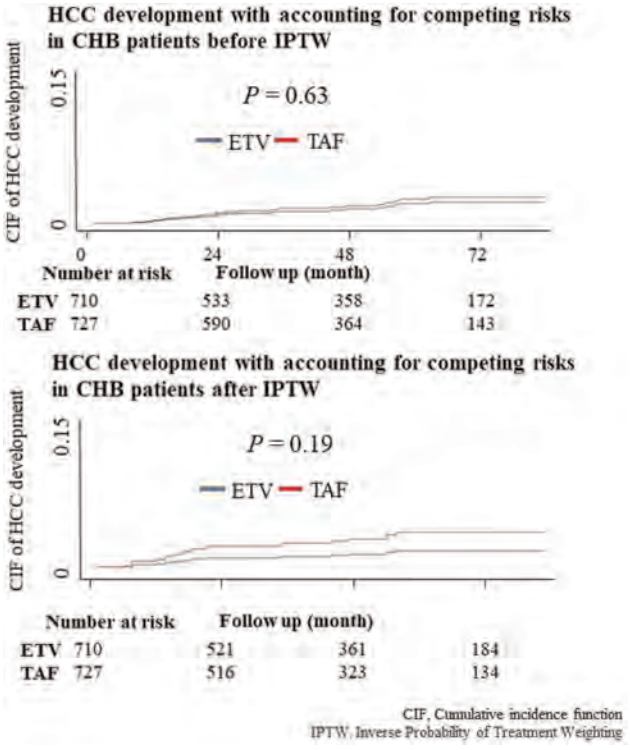

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0046 | HBV RNA AND QUANTITATIVE HBSAG DIFFERENTIATE PARTIAL CURE FROM INACTIVE CARRIERS WITH HBEAG NEGATIVE CHRONIC HEPATITIS B

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Background: Functional cure (hepatitis B surface antigen (HBsAg) loss and HBV DNA negative) is the primary therapeutic endpoint of chronic hepatitis B (CHB). HBsAg can be derived from both cccDNA and integrated HBV DNA (iDNA). Thus, there may be persons who fail to achieve functional cure due to HBsAg derived from integrated HBV DNA i.e. partial cure (PC). We hypothesize that HBV RNA, a marker of cccDNA activity, may be used to identify such subjects. This study aimed to examine virological profiles of subjects in different phases of HBeAg(-)CHB to differentiate PC patients from inactive carriers (IC) and those with HBV DNA <2000 IU/ml with elevated ALT levels (grey zone 1 (GZ1)). **Methods:** Untreated subjects with HBeAg(-)CHB were classified based on HBV DNA and ALT levels at the time of sera collection into 7 groups: HBsAg loss, partial cure (PC) (HBV DNA <10 IU/mL and normal ALT), inactive carrier (IC) (HBV DNA <2000 IU/mL and normal ALT), grey zone 1 (GZ1) (HBV DNA <2000 IU/mL with elevated ALT), grey zone 2 (GZ2) (HBV DNA >2000 IU/mL with normal ALT), grey zone 3 (GZ3) (HBV DNA >2000 IU/mL with ALT $>$ ULN-$<$ 2X ULN), and immune active (IA) (HBV DNA >2000 and ALT >2xULN). Stored sera were tested for qHBsAg (negative samples were further tested with ultrasensitive HBsAg Next assay), HBsAg isoforms (large, middle and small), HBV RNA, and phosphorylated and non-phosphorylated HBcAg (Abbott Diagnostics research use only). Multiple logistic regression identified predictors of HBV RNA negativity. **Results:** 180 samples were tested: 30 HBsAg loss, 30 PC, 30 IC, 20 GZ1, 20 GZ2, 20 GZ3, and 30 IA. Subject demographics and results of virological testing are shown in Table 1. Subjects with HBsAg loss were older compared to other groups. The proportion testing HBV RNA negative was 73% in the HBsAg loss group, 43% PC, 17% IC, 5% GZ 1, 0% GZ 2, 10% GZ 3 and 0% IA. Interestingly, 4/30 (13%) HBsAg loss subjects tested HBsAg positive by qHBsAg assay and 10/30 were positive using the HBsAg Next assay. The proportion with qHBsAg levels <100 IU/mL was 97% in the HBsAg group, 43% PC, 30% IC, 15% GZ1, 5% GZ 2, 15% GZ 3. and 0% IA. A virological profile of HBV RNA negative and qHBsAg <100 was observed in 33% PC, 10% IC, 5% GZ1, and 5% GZ3 compared to the 73% HBsAg group could differentiate the PC group from the IA and GZ1

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groups. On multiple logistic regression, low log_{10}HBV DNA ($p = 0.007$) and log_{10}qHBsAg ($p = .02$) were significantly associated with negative HBV RNA levels. **Conclusion:** Negative HBV DNA and HBV RNA results together with a qHBsAg level < 100 IU/mL are useful in differentiating PC from IA and GZ1. Up to one third of untreated subjects in the PC phase of CHB have virological profiles similar to those with HBsAg loss and may be functionally cured.

	Partial Cure (n=30)	Inactive Carrier (n=30)	Gray Zone 1 (n=20	Gray Zone 2 (n=20)	Gray Zone 3 (n=20)	Immune Active (n=30)	HBsAg Loss (n=30)
Age (SD)	44	46	46	45	46	45	55
Male Sex (%)	13 (43)	14 (47)	12 (60)	10 (50)	11 (55)	15 (50)	21 (70)
Race							
American Indian or Alaska Native	0	1	0	0	0	0	0
Asian	13	14	9	10	15	16	16
Black/African American	11	13	6	9	1	8	4
White	2	2	5	1	3	5	9
Multiracial	1	0	0	0	1	0	1
Unknown	3	0	0	0	0	1	0
BMI (SD)	27	28	28	25	25	25	28
ALT	26	21	51	21	45	167	33
Genotype							
A	0	3	2	4	3	3	8
B	0	4	3	4	9	9	3
C	4	1	4	1	3	4	4
D	2	3	0	4	2	8	1
E	2	4	3	5	1	4	0
Other	1	0	0	0	0	0	1
Log qHBsAg (mean)	2.3	3.9	4.2	4.6	4.1	4.3	5
Log Small HBsAg isoforms	6.2	6.1	6.3	6.7	6.2	6.4	–
Log Medium HBsAg	5.4	5.3	5.6	5.8	5.5	5.8	–
Log Large HBsAg	4.1	4.3	3.9	4.5	4.2	4.8	–
Log HBV DNA		2.8	3.6	4.2	6.2	7.1	1.3
Log HBV RNA	1.02	1.73	1.84	2.45	2.60	4.39	0.43
RNA negative (%)	13 (43)	5 (17)	1 (5)	0 (0)	2 (10)	0 (0)	22 (73)
RNA negative & qHBsAg <100 IU/mL (%)	10 (33)	3 (10)	1 (5)	0 (0)	1 (5)	0 (0)	22 (73)
HBcAg	0.10	0.14	0.15	0.12	2.55	250.48	0.13
P-HBcAg	0.27	0.27	0.31	0.29	12.32	999.77	0.34
P-HBcAg Negative (%)	29 (97)	29 (97)	20 (100)	19 (95)	15 (75)	11 (37)	28 (93)

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0047 | OUTCOMES FOLLOWING ANTIVIRAL THERAPY DISCONTINUATION IN HBEAG-NEGATIVE, NON-CIRRHOTIC CHRONIC HEPATITIS B PATIENTS WITH LOW BASELINE HBSAG TITERS: THE ADAPT TRIAL

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Background: The benefits and risks of antiviral therapy discontinuation, including sustained virologic response and HBsAg seroclearance, remain controversial in chronic hepatitis B (CHB) patients. **Methods:** This multicenter, single-arm discontinuation trial (ADAPT trial, NCT04782375) enrolled HBeAg-negative, non-cirrhotic CHB patients from four centers in Korea who discontinued antiviral therapy (tenofovir disoproxil fumarate [TDF], tenofovir alafenamide [TAF], entecavir [ETV], or others) between September 2021 and June 2023. Eligible patients had received antiviral treatment for at least 2 years, had undetectable HBV DNA (< 20 IU/mL), serum HBsAg titers $< 3{,}000$ IU/mL, and alanine aminotransferase (ALT) levels < 40 U/L at the time of discontinuation. Follow-up visits occurred every 4 weeks until week 24, and less frequently until week 48. The primary endpoint was viral rebound (HBV DNA $\geq 2{,}000$ IU/mL) at week 24. Secondary endpoints included HBsAg seroclearance and retreatment rates at week 48. **Results:** Of 140 patients (mean age 52.6 years, 73.6% male), the antiviral treatment at discontinuation included TDF (58.6%), TAF (7.1%), ETV (29.3%), and others (5.0%). Median baseline HBsAg titer was 439 IU/mL (IQR 100–839), mean ALT was 22 U/L. Nine patients withdrew, 131 completed 24-week follow-up. At week 24, viral rebound occurred in 84 (60.0%) patients, of whom 83 resumed antiviral therapy. Among 56 patients without viral rebound, 14 (25.0%) resumed therapy based on pre-defined criteria. Consequently, by week 24, 97 patients (69.3%) resumed antiviral therapy, while 34 patients (24.3%) remained off-treatment. By week 48, HBsAg seroclearance occurred in 7 patients (5.0%), all with baseline HBsAg titers < 300 IU/mL. At week 48, 104 patients (74.3%) resumed antiviral therapy, and 27 patients (19.3%) remained off-treatment. 3 patients experienced ALT flares (ALT ≥ 5 times the upper limit of normal) without hepatic decompensation. **Conclusion:** In this multicenter trial of 140 non-cirrhotic, HBeAg-negative CHB patients with baseline HBsAg titers $< 3{,}000$ IU/mL, 74.3% required retreatment by week 48 due primarily to viral rebound. Only 5.0% achieved HBsAg seroclearance, exclusively among patients with baseline HBsAg titers < 300 IU/mL. These findings do not support universal discontinuation of antiviral therapy for most CHB patients.

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0048 | PARTIAL CURE AFTER FINITE HBV THERAPY IS ASSOCIATED WITH EXCELLENT LONG-TERM OUTCOMES – RESULTS: FROM A POOLED ANALYSIS OF THE RETRACT-B AND CREATE DATASETS

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Background: Partial cure (HBsAg <100 IU/mL with undetectable HBV DNA at 6 months after withdrawal of antiviral therapy) has been introduced as an alternate surrogate endpoint for HBV trials. We aimed to assess long-term virological outcomes in patients with partial cure. **Methods:** Data from patients who met criteria for partial cure at 6 months after nucleos(t)ide analogue (NA) withdrawal were collected from 2 global cohorts of patients who underwent finite NA therapy (RETRACT-B and CREATE). Criteria for NA cessation were based on international guidelines (*e.g.,* HBsAg positive, HBeAg negative, and virally suppressed at end of therapy [EOT]). The primary outcome was the HBsAg loss rate at 5 years after NA withdrawal. Secondary outcome was clinical relapse (HBV DNA ≥ 2000 IU/mL and ALT ≥ 2 xULN). Outcomes in patients with partial cure were compared with patients from RETRACT-B who did not achieve partial cure, and who were HBsAg positive and free from clinical relapse or retreatment at 6 months after NA cessation. Aalen Johansen estimators with Grey's test were used for statistical comparison, considering retreatment and HBsAg loss as competing events. **Results:** We identified 100 patients with partial cure. At 6 months after EOT, median age was 54 [44-61] years, 76% were male, 70% Asian, 27% White, median HBsAg was 0.82 [0.05-1.60] log10 IU, 45% was previously treated with TDF/TAF (43% ETV) and 1% had a history of cirrhosis. Median follow up after achievement of partial cure was 3.8 [1.7-6.3] years. At 5 years after NA cessation, 62% of patients with partial cure achieved HBsAg loss compared to 7% in those without partial cure ($p < 0.001$). And only 5% of patients with partial cure developed clinical relapse (vs. 38%, $p < 0.001$). Achievement of partial cure was associated with superior 5 year HBsAg loss rates when compared to patients without partial cure, both in patients with EOT HBsAg <100 IU/mL (66% vs. 28%, $p < 0.001$) and in those with EOT HBsAg >100 IU/mL (53% vs. 4%, $p < 0.001$). Among patients with partial cure, those with HBsAg <10 IU/mL ($n = 56/100$) had higher HBsAg loss rates (81% vs. 32%, $p < 0.001$) and less clinical relapse (0% vs. 14%, $p = 0.012$) at 5 years after EOT, compared to patients with levels between 10 - 100 IU/mL. **Conclusion:** Patients with partial cure after finite NA therapy have excellent long-term outcomes, especially if HBsAg is <10 IU/mL, supporting further exploration of partial cure as a surrogate endpoint in HBV cure trials.

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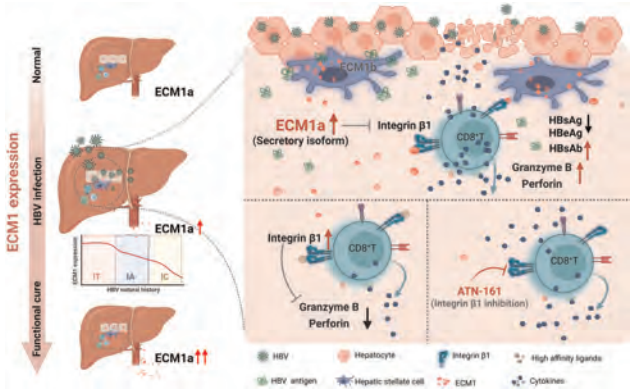
★ 0049 | SECRETORY ECM1A RESTORES HBV-SPECIFIC CD8˚ T CELL RESPONSE VIA INTEGRIN β1 BLOCKADE TO PROMOTE HBSAG LOSS IN CHRONIC HBV INFECTION

Zheyu Dong[1] Peng Chen[1] Yuxin Zhou[1] Qiuyue Ye[1] Yuqing Shao[1] Junling Chen[1] Yadong Wang[1] Libo Tang[1] Jinlin Hou[1] Bing Sun[2] yongyin li[1], [1]Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China, [2]Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences, Shanghai, China

Background: Antigen-specific CD8+T cells are crucial effectors for hepatitis B virus (HBV) clearance but become functionally impaired in chronic infection. Extracellular matrix protein 1 (ECM1), an extracellular matrix component essential for hepatic environmental homeostasis, is involved in regulating the immune response. This study aims to investigate the role of ECM1 in HBsAg clearance and its underlying mechanism in anti-HBV immune responses. **Methods:** Blood and liver samples were obtained from 147 chronic HBV-infected individuals and 76 healthy controls. Multi-omics approaches including single-cell RNA sequencing (scRNA-seq), co-immunoprecipitation (Co-IP), mass spectrometry, and *in vitro* stimulation assays were employed to assess ECM1's impact on anti-HBV CD8+T cell response. HBV mouse mode with hepatic stellate cell (HSC)-specific ECM1 knockout were established for *in vivo* validation. **Results:** Screening identified six upregulated extracellular matrix components (MMP2/7, ECM1, VCAN, COL5A1/15A1) in HBV-infected livers from GEO databases. Notably, serum ECM1 was the only component correlating with disease status in our cohort, showing significantly higher levels in patients achieving HBsAg clearance versus those with persistent infection. The assays of clinical liver specimens and HBV mouse models revealed that the elevated ECM1 originates from hepatic stellate cells (HSCs). Functionally, the secretory isoform ECM1a, but not the non-secretory isoform ECM1b, enhanced HBsAg-specific cytotoxic T cell (CTL) responses, leading to HBsAg clearance. Moreover, HSC-specific ECM1 knockdown delayed HBV clearance in mice. Mechanistically, the P300-H314 domain unique to ECM1a (deficient in ECM1b) competitively bound integrin β1, thereby neutralizing the suppression of CD8˚ T cell function of integrin 1 and restoring anti-HBV immunity. Meanwhile, scRNA-seq revealed that the reduction of integrin 1 on peripheral and intrahepatic CD8˚T cells from chronic HBV-infected patients correlated with functional cure and favorable response to pegylated interferon- therapy. Consistent with this finding, pharmacological inhibition of integrin 1 signaling with ATN-161 accelerated viral clearance in HBV mouse models. Conclusion: The secretory isoform ECM1a facilitates HBV clearance by antagonizing integrin 1-mediated CD8+T cell exhaustion, enhancing cytotoxic cytokine production and HBsAg loss. Our findings unveil a novel extracellular matrix-immunity crosstalk mechanism and identify ECM1 as a potential therapeutic target for chronic HBV infection.



Disclosures: Zheyu Dong: Nothing to Disclose, Peng Chen: Nothing to Disclose, Yuxin Zhou: Nothing to Disclose, Qiuyue Ye: Nothing to Disclose, Yuqing Shao: Nothing to Disclose, Junling Chen: Nothing to Disclose, Yadong Wang: Nothing to Disclose, Libo Tang: Nothing to Disclose, Jinlin Hou: Nothing to Disclose, Bing Sun: Nothing to Disclose, yongyin li: Nothing to Disclose

0050 | LOW HBSAG LEVELS BUT LESS HBSAG DECLINES REPRESENTS THE HIGH RISK OF HCC AND THE RARITY OF HBSAG LOSS IN NUC-TREATED PATIENTS WITH BASELINE HBEAG-POSITIVITY

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Background: Some chronic hepatitis B (CHB) patients developed hepatocellular carcinoma (HCC) despite long-term nucleos(t)ide analogue (NUC)

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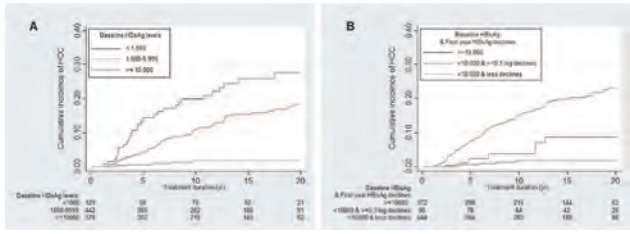
treatment. The recent paper showed that low hepatitis B surface antigen (HBsAg) associated with HCC risk in patients with hepatitis B e antigen (HBeAg) positive immune-tolerant phase. In this study, we evaluated the association between HBsAg levels and HCC development in NUC-treated patients with baseline HBeAg positivity. **Methods:** This study enrolled consecutive 947 CHB patients with baseline HBeAg-positivity who received NUC treatment for at least 1 year and whose baseline and on-treatment HBsAg levels could be measured by commercial assay. The subjects were classified into the following 3 groups based on baseline HBsAg levels: < 1,000 IU/mL, 1,000-9,999 and ≥ 10,000. Regarding on-treatment HBsAg, we evaluated the changes in HBsAg from baseline to year 1. The outcomes we evaluated were HCC incidences and HBsAg loss (< 0.05 IU/mL) according to baseline and on-treatment HBsAg kinetics. **Results:** (1) Baseline median (IQR) HBsAg levels were 5,885 (2,138-21,000) IU/mL. In the entire cohort, 129 patients (13.6%) were categorized into < 1,000 IU/mL, 442 (46.7%) into 1,000-9,999 and 376 (39.7%) into ≥ 10,000. The number of patients who achieved ≥ 0.3 log IU/mL declines (= 50% declines) in HBsAg from baseline to year 1 was 323 (34.1%). (2) Annual incidence rates of HCC were 1.3, 10.5, and 12.7 per 1,000 person-years in patients with < 1,000 IU/mL, 1,000-9,999 and ≥ 10,000 of baseline HBsAg, respectively, with higher incidences of HCC in < 1,000 IU/mL and 1,000-9,999 than those of ≥ 10,000 (P < 0.001) (Fig A). Moreover, patients who achieved ≥ 0.3 log declines in HBsAg in the first year were significantly less likely to develop HCC than those without it (P < 0.001). Multivariable Cox regression, adjusted for age, sex, cirrhotic status, platelet counts, ALT and baseline viral loads, showed that baseline low HBsAg levels were associated with high risk of HCC with their hazard ratios for HCC in < 1,000 IU/mL and 1,000-9,999 of 3.44 and 2.77, respectively. Also, the decline in HBsAg ≥ 0.3 log in the first year was associated with low risk of HCC with its hazard ratio of 0.31. Baseline higher ALT levels were associated with the decline in HBsAg ≥ 0.3 log. (3) We categorized the cohort into the following 3 groups, baseline HBsAg <10,000 & less declines in HBsAg in the first year, baseline HBsAg <10,000 & ≥ 0.3 log declines in HBsAg and baseline HBsAg ≥ 10,000. Cumulative HCC incidences were higher in patients with HBsAg <10,000 & less declines in HBsAg than those in the other two groups (P<0.001) (Fig B). However, Cumulative HBsAg seroclearance rates were lower in patients with HBsAg <10,000 & less declines in HBsAg (P = 0.003). **Conclusion:** Baseline low HBsAg levels but less HBsAg declines seem to be an unfavorable status which represents the high risk of HCC and the rarity of HBsAg loss, in NUC-treated patients with baseline HBeAg-positivity.



Disclosures: Tetsuya Hosaka: Gilead Sciences: Speaking and Teaching, Eisai: Speaking and Teaching, Fujirebio Inc.: Speaking and Teaching, Fumitaka Suzuki: Nothing to Disclose, Mariko Kobayashi: Nothing to Disclose, Yasue Takeuchi: Nothing to Disclose, Hitomi Sezaki: Nothing to Disclose, Norio Akuta: Nothing to Disclose, Yoshiyuki Suzuki: Nothing to Disclose, Satoshi Saitoh: Nothing to Disclose, Yasuji Arase: Nothing to Disclose, Kenji Ikeda: Nothing to Disclose, Hiromitsu Kumada: Nothing to Disclose

★ 0052 | HEPATIC STELLATE CELL NOTCH CONTRIBUTES TO LIVER FIBROSIS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Meng Li[1] Junjie Yu[1] Domenick Raphael[1] Brent Mayfield[1] Changyu Zhu[1] Robert Schwabe[1] Utpal Pajvani[1], [1]Columbia University Irving Medical Center

Background: Hepatic stellate cells (HSCs) are key drivers of fibrosis in metabolic dysfunction-associated steatohepatitis (MASH). Our previous research has demonstrated that inter-hepatocyte Jagged1 (Jag1)/Notch signaling is necessary for MASH-induced liver fibrosis in mice. We observed high HSC Notch activity in mice and patients with MASH and hypothesized that increased hepatocyte Jag1 exacerbates liver fibrosis through direct HSC Notch activation. **Methods:** We generated HSC-specific Notch loss-of-function (LOF) and gain-of-function (GOF) mice and fed them with a MASH-inducing diet rich in fructose, palmitate, and cholesterol (FPC) or with normal chow diet. We over-expressed hepatocyte Jag1 in the livers of HSC-specific Notch LOF mice by hydrodynamic injection of a Jag1-encoding plasmid. We knocked down hepatocyte Jag1 by injection of GalNAc–modified siJag1 in FPC-fed wildtype mice. We sorted HSCs from FPC-fed HSC-specific Notch LOF mice for RNA sequencing and analysis, and conducted tethered ligand assays to evaluate direct effects of Jag1 on HSC activity. **Results:** HSC-specific Notch LOF ameliorated FPC diet-associated liver fibrosis, likely due to reduced HSC proliferation. Conversely, HSC-specific Notch GOF exacerbated FPC-induced liver fibrosis in both male

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and female mice, but forced activation of Notch in HSCs was insufficient to induce liver fibrosis in chow diet-fed mice. Mechanistically, we observed that knockdown of hepatocyte Jag1 significantly decreased HSC Notch activity in FPC-fed mice, and conversely, forced hepatocyte Jag1 increased HSC Notch activity, which partially accounted for Jag1-induced liver fibrosis. Similarly, Jag1-induced Notch signaling drove HSC activity in primary mouse HSCs and a human HSC cell line. **Conclusion:** These data illustrate the pathological role and therapeutic potential of the HSC Notch in MASH-associated liver fibrosis. Furthermore, as these effects appear synergistic with effects of hepatocyte Notch activity to augment liver fibrosis, our findings highlight the therapeutic potential of blocking hepatocyte Jag1 to simultaneously impact multiple arms of MASH pathogenesis.

Disclosures: Meng Li: Nothing to Disclose, Junjie Yu: Nothing to Disclose, Domenick Raphael: Nothing to Disclose, Brent Mayfield: Nothing to Disclose, Changyu Zhu: Nothing to Disclose, Robert Schwabe: Nothing to Disclose, Utpal Pajvani: Nothing to Disclose

0053 | DEVELOPMENT OF A YAP PROTAC WITH ANTI-FIBROTIC POTENTIAL

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Background: The transcriptional coactivator Yes-associated protein (YAP) is a driver for hepatic stellate cell (HSC) activation and liver fibrosis, but historically challenging to target due to its intrinsically disordered nature. We have developed a YAP degrader (designated YZ-6) based on Proteolysis-Targeting Chimera (PROTAC) technology [*Zhou et al., Exploring Degradation of Intrinsically Disordered Protein Yes-Associated Protein Induced by Proteolysis TArgeting Chimeras. J Med Chem. 2024 Sep 12;67(17):15168-15198*]. This study aims to test whether YZ-6 can degrade YAP in HSC and have inhibitory effects on development of liver fibrosis in mice. **Methods:** YZ-6 was linked to a known YAP binder NSC682769 with VHL ligand 2 or pomalidomide via diverse linkers. Effects of YZ-6 on YAP degradation and transcriptional activities were examined by Western Analysis and luciferase under the control of 8xGTIIC promoter in human HSC LX2 cells. Cell cycle and apoptosis were analyzed in flow cytometry based on staining with propidium with or without Annexin V antibody. In addition, biliary fibrosis and ductular reaction were induced and analyzed after the feeding of 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) followed by intraperitoneal injection of YZ-6 (35 mg/kg body weight, twice a week for 14 days). **Results:** YZ-6 recruited the E3 ligase VHL for the rapid and sustained degradation of YAP. It also effectively inhibited its nuclear localization, curtailing YAP/TEAD-mediated transcription in LX2 and rat progenitor WB-F344 cells. Moreover, YZ-6 induced 43.2% and 40.6% apoptosis in LX2 and WB-F344 cells whereas mock controls only caused 3.4% and 2.9% apoptotic cells in Annexin V staining. Increased cells in G1 phase were also observed, indicating that YZ-6 promoted cell cycle arrest. Additionally, YZ-6 administration caused low levels of YAP content and attenuated biliary fibrosis as evidenced by reduced levels of connective tissue growth factor, alpha smooth muscle actin, and collagen type I after DDC-induced liver injury. These changes were associated with decreased proliferation of bile ductular epithelial cells based on staining with Ki67 and cytokeratin 19 antibodies. **Conclusion:** YZ-6 can inhibit HSC activation and reduce DDC-induced liver fibrosis and DR. These results underscore the potential of PROTAC-mediated YAP degradation as a strategy for treating fibrosis during chronic liver injury.

Disclosures: Liya Pi: Nothing to Disclose, tian tian: Nothing to Disclose

0054 | HOT AND COLD LIVER FIBROSIS REFLECT OPPOSING HEPATOCELLULAR CARCINOMA TRAJECTORIES IN EXPERIMENTAL METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Bruno Cogliati[1] Chittampalli Yashaswini[2] Alessandro Marins-Dos-Santos[3] Joana Almeida[1] Fanglin Ma[1] Kenneth Li[1] Li Chen[4] Dipankar Bhattacharya[1] Shuang Wang[1] Scott Friedman[2], [1]Icahn School of Medicine at Mount Sinai, [2]Icahn School of Medicine at Mount Sinai (ISMMS), [3]Icahn School of Medicine at Mount Sinai Dean's Flow Cytometry Core, [4]PharmaNest Inc.

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a rising cause of hepatocellular carcinoma (HCC) that emerges within a fibrotic niche. The composition of fibrotic tissue, classified as "hot" (immune-infiltrated) or "cold" (immune-depleted), plays a critical role in the pathogenesis of cardiac fibrosis (10.1016/j.cels.2025.101198), but it is uncertain whether these fibrosis immunophenotypes occur in liver disease and HCC. Here, we model hot versus cold fibrosis in murine MASH to investigate their links to HCC progression. **Methods:** The 'FAT-MASH' protocol (10.1016/j.jhep.2018.03.011) was administered for 40 weeks to induce advanced fibrosis and HCC. Following this 40 weeks of injury, all dietary and chemical insults were withdrawn, and mice were monitored at 2, 8, 16, and 24 weeks post-intervention

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to evaluate fibrosis remodeling and HCC progression. Serum and liver tissues were collected for biochemical, histological, immunohistochemical, flow cytometry, and transcriptomic analyses to characterize the macrophage-myofibroblast circuit and the fibrotic immune landscape. **Results:** At 40 weeks of MASH, mice exhibited marked steatosis, fibrosis, and large HCCs, along with elevated serum levels of ALT, AST, and lipids. Following cessation of injury, mice displayed distinct regression dynamics: between weeks 2-24 of regression, steatosis and tumor burden declined significantly, while fibrosis persisted. Interestingly, tumor size increased again at 24 wks. By FACS of fibrotic tissue there was an early decline in total leukocytes, macrophages, and T cells, followed by immune reconstitution by weeks 16-24. Transcriptomic profiling revealed initial upregulation of metabolic pathways and suppression of inflammatory pathways, which reversed at later time points. Macrophage infiltration decreased during weeks 2-8, whereas hepatic stellate cell (HSC) numbers peaked during injury and remained stable throughout regression. **Conclusion:** Persistent collagen deposition and sustained HSC activation indicate a "point of no return" for fibrosis regression in this model. The immune profile of persistent fibrosis critically influences HCC behavior in experimental MASH. The evolving immune landscape of fibrosis, from a transient "cold" phase (2-8 weeks) to a "hot" phase (16-24 weeks), correlates with an initial decrease and subsequent rebound of tumor size. These findings underscore the importance of fibrosis immune contexture in dictating tumor fate and suggest a new therapeutic paradigm that targets fibrotic immunophenotypes in MASH-related HCC.
Disclosures: Bruno Cogliati: Nothing to Disclose, Chittampalli Yashaswini: Nothing to Disclose, Alessandro Marins-Dos-Santos: Nothing to Disclose, Joana Almeida: Nothing to Disclose, Fanglin Ma: Nothing to Disclose, Kenneth Li: Nothing to Disclose, Li Chen: Nothing to Disclose, Dipankar Bhattacharya: Nothing to Disclose, Shuang Wang: Nothing to Disclose, Scott Friedman: Nothing to Disclose

0055 | INHIBITION OF MITOCHONDRIAL FUMARASE (FH1) RESULTS: IN RELEASE OF MITOCHONDRIAL DNA AND HSC ACTIVATION

Suyavaran Arumugam[1] Xinshou Ouyang[2] Wajahat Mehal[2], [1]Yale University, [2]Section for Digestive diseases, Yale School of Medicine

Background: Ethanol is known to activate hepatic stellate cells (HSC) but the mechanism is poorly understood. Here we examined the ability of ethanol, via acetaldehyde, to activate HSC. We further examined the mechanism underlying ethanol-induced functional changes. **Methods:** Primary human HSC were isolated by liver perfusion and optiprep-GBSS density gradient centrifugation. HSC were exposed to 50mM ethanol for 16 h and assayed for transcriptional and metabolic changes. In parallel blockers of ethanol metabolic enzymes were tested in the LX-2 HSC cell line prior to ethanol stimulus. Mitochondrial proteins from LX-2 cells were analyzed via LCMS/MS LTQ-Orbitrap technique to identify changes in phosphorylation. Inhibitors such as VBIT4 10μM (VDAC inhibitor), STING inhibitor (IFM-4490 at 20μM) were used as per experimental target. We screened the TCA cycle enzymes via siRNA to identify possible targets for ethanol induced alterations. Single amino acid mutants of target TCA cycle enzymes were screened in HSC to delineate the ethanol mediated mitochondrial DNA (mtDNA) release and STING activation. **Results:** Ethanol resulted in mtDNA release and activation of primary mouse and human HSC at 50mM, and enhanced TGF-b (2.5ng/ml) mediated activation at 10mM concentrations. Alcohol dehydrogenase 5 (ADH5) knockdown or 4 methyl pyrazole pretreatments in LX-2 blocked ethanol mediated mtDNA release ($P < 0.0001$). Exposure to acetaldehyde (200μM) induce changes undistinguishable from ethanol. Upon ethanol stimulation STING colocalized to the Golgi-complex. STING inhibitor significantly suppressed ethanol induced ACTA2 transcription. Moreover, the mitochondrial phospho-proteome data showed SLC25A6 (ANT3), VDAC1 and SAM50 as the top significant modified proteins indicating the activation of mitochondrial permeability transition pore in ethanol treated LX-2 cells. TCA cycle siRNA screening showed that fumarase (FH1) knockdown activated HSC. Ethanol was observed to significantly suppress FH1 enzyme activity, leading to elevated mitochondrial fumarate and mitochondrial DNA damage as a source for STING activation. We further confirmed ethanol suppresses FH1 activity via acetylation of lysine residues K80 and K230 in the active site and block fumarate binding. In vivo FH1 inhibition worsened fibrosis in mouse model on alcohol for 5 weeks, which was blocked by STING inhibitor. **Conclusion:** Ethanol metabolism to acetaldehyde in HSC results in inhibition of FH1, mtDNA release, with activation the c-GAS-STING-IRF3 pathway. We identified that acetaldehyde mediates lysine acetylation in mitochondrial FH1 leading to its inhibition and fumarate accumulation. Increased mitochondrial fumarate induces mtDNA damage resulting in HSC activation and fibrosis progression. These findings provide novel insights into ethanol metabolite mediated fibrogenic activation of HSCs and potential therapeutic targets for hepatic fibrosis in ALD.

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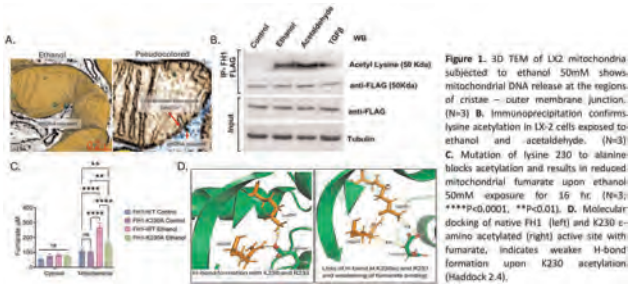

Figure 1. 3D TEM of LX2 mitochondria subjected to ethanol 50mM shows mitochondrial DNA release at the regions of cristae – outer membrane junction. (N=3) **B.** Immunoprecipitation confirms lysine acetylation in LX-2 cells exposed to ethanol and acetaldehyde. (N=3) **C.** Mutation of lysine 230 to alanine blocks acetylation and results in reduced mitochondrial fumarate upon ethanol 50mM exposure for 16 hr. (N=3; ****P<0.0001, **P<0.01). **D.** Molecular docking of native FH1 (left) and K230 ε-amino acetylated (right) active site with fumarate, indicates weaker H-bond formation upon K230 acetylation (Haddock 2.4).

Disclosures: Suyavaran Arumugam: Nothing to Disclose, Xinshou Ouyang: Nothing to Disclose, Wajahat Mehal: Nothing to Disclose, Nothing to Disclose

0056 | ACTIVATED HEPATIC STELLATE CELLS (AHSCS) ARE ESSENTIAL FOR THE PROLIFERATION OF ZONE 3 HEPATOCYTES DURING RECOVERY FROM TOXIC LIVER INJURY IN MICE

Sadatsugu Sakane[1] Hiroaki Fuji[2] Rabi Murad[3] Animesh Singh[1] Charlene Miciano[4] Hyun Young Kim[1] Mojgan Hosseini[1] Kanani Hokutan[1] Vivian Zhang[5] Raquel Weber[6] Wonseok Lee[1] Souradipta Ganguly[7] Karin Diggle[8] Xiao Liu[1] Debanjan Dhar[3] Linda Burkly[9] Allen Wang[1] David Brenner[3] Tatiana Kisseleva[1], [1]University of California, San Diego, [2]Hyogo College of Medicine, [3]Sanford Burnham Prebys Medical Discovery Institute, [4]University of California San Deigo, [5]Universtity of California, San Diego, [6]University of California San Diego, [7]Sanford Burnham Prebys, [8]University of Californania, San Diego, [9]Editas Medicine Inc.

Background: Activated Hepatic Stellate Cells (aHSCs) are the major source of fibrogenic myofibroblasts in the liver. We investigated the role of aHSCs in the development and recovery from carbon tetrachloride (CCl_4)-induced liver injury. For this purpose, human Diphtheria Toxin Receptor was overexpressed in Collagen Type I and Lrat expressing activated HSCs, so that administration of Diphtheria Toxin-α (DTA) to CCl_4-injured mice induced cellular death of $DTR^+Col1a1^+Lrat^+$ aHSCs. **Methods:** $Col1a1^{fl\text{-}stop\text{-}fl\text{-}DTR}$ mice, in which a floxP-stop-floxP-DTR cassette was knocked into the *col1a1* genetic locus, were crossed with $Lrat^{Cre}$ mice, which express Cre in HSCs in the liver, to generate $Lrat^{Col1a1\text{-}DTR}$ mice. $Lrat^{Col1a1\text{-}DTR}$ mice were subjected to CCl_4 (25 μl every other day for one week by oral gavage) liver injury. Upon cessation of liver injury, $Lrat^{Col1a1\text{-}DTR}$ mice were treated with a single dose of DTA (50ng/g) or PBS (+DTA or vehicle, n≧10 per group) to induce aHSC ablation. Mice were sacrificed at day 1, 3, 7, and 28. **Results:** CCl_4-treated vehicle and +DTA mice developed hepatocyte injury, inflammation, and mild fibrosis. Upon CCl_4 cessation, livers of vehicle mice contained areas of hepatocyte necrosis as well as marked hepatocyte proliferation at day 1, and fully recovered from injury by day 3. In turn, CCl_4-injured +DTA mice exhibited severe liver necrosis and inflammation on day 1, which remained on day 3 centered on Zone 3. At day 7, mice exhibited the loss of body weight (»20%) and liver weight (»50%). Half of CCl_4-injured +DTA mice died within 2 weeks after aHSC ablation, the surviving mice showed gradual weight gain and histological improvement. The loss of liver mass in recovering CCl_4-injured +DTA mice was attributed to the marked shrinkage of hepatocyte cytoplasm and decrease of Zone 3 due to impaired hepatocyte proliferation in the absence of HSCs. At day 28, the liver volume and architecture returned to normal due to increased hepatocyte proliferation, and this effect was associated with restoration of HSC numbers in the livers of CCl_4-injured +DTA mice. RNA-seq revealed that CCl_4-injured DTA^+ mice showed loss of metabolic function, increased Zone 1 markers and decreased Zone 3 markers on days 3 and 7, along with decreased levels of many aHSC-derived growth factors, which were normalized by day 28. **Conclusion:** Activated HSCs are essential for the proliferation of Zone 3 hepatocytes during recovery from CCl_4-induced acute liver injury. Ablation of aHSCs cannot be used for anti-fibrotic therapy.

Disclosures: Sadatsugu Sakane: Nothing to Disclose, Hiroaki Fuji: Nothing to Disclose, Rabi Murad: Nothing to Disclose, Animesh Singh: Nothing to Disclose, Charlene Miciano: Nothing to Disclose, Hyun Young Kim: Nothing to Disclose, Mojgan Hosseini: Nothing to Disclose, Kanani Hokutan: Nothing to Disclose, Vivian Zhang: Nothing to Disclose, Raquel Weber: Nothing to Disclose, Wonseok Lee: Nothing to Disclose, Souradipta Ganguly: Nothing to Disclose, Karin Diggle: Nothing to Disclose, Xiao Liu: Nothing to Disclose, Debanjan Dhar: Nothing to Disclose, Linda Burkly: Nothing to Disclose, Allen Wang: Nothing to Disclose, David Brenner: Nothing to Disclose, Tatiana Kisseleva: Nothing to Disclose

0057 | BETA-ARRESTIN-2-MEDIATED HEPATOCYTE-HSC INTERACTION PROMOTES HSC ACTIVATION AND FIBROGENESIS

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Background: Beta-arrestin-2 (ARRB2) is a regulator of the G-protein-coupled receptors, such as the profibrotic Angiotensin II type 1 receptor (AGTR1), redirecting signalling to G-protein-independent pathways. Their role in liver fibrosis is not fully understood and was investigated in this study. **Methods:** Fibrosis was induced in Arrb2-deficient and wildtype (Wt) mice using bile duct ligation (BDL) or carbon tetrachloride (CCl4). AGTR1 was stimulated either G protein-dependent by angiotensin II administration or by the modified peptide [Ser(1), Ile(4), Ile(8)]-angiotensin II to selectively activate ARRB2 downstream of AGTR1. Fibrosis and HSC activation were investigated by gene and protein expression/histological staining. Crosstalk between primary murine hepatic stellate cells (HSC) and hepatocytes was analysed in vitro. Gene array analyses identified mediators of ARRB2-dependent signalling in primary human HSC. Findings in experimental liver fibrosis were confirmed in human tissue and hepatic cells (hepatocytes, HSC). **Results:** ARRB2 is increased in liver cirrhosis, mainly in activated HSC and injured hepatocytes. In turn, ARRB2 deficiency decreases fibrosis and HSC activation in vivo. Interestingly, ARRB2-loaded extracellular vesicles (EV) released from injured Wt hepatocytes can activate ARRB2-deficient HSC, while ARRB2-deficient EV had no effect in Wt HSC. Transcriptome analysis of human primary HSC revealed that ARRB2 induces retinoic acid receptor responder 1 (RARRES1). RARRES1 correlates with profibrotic factors, such as collagen 1, alpha-smooth muscle actin and transforming growth factor beta expression. **Conclusion:** Chronic liver injury leads to the release of ARRB2-loaded EV by hepatocytes. These EVs are taken up by HSC and induce fibrosis. ARRB2 regulates RARRES1 and may induce pre-malignant transformation.

Disclosures: Robert Schierwagen: Nothing to Disclose, Peter Dietrich: Nothing to Disclose, Sabine Klein: Nothing to Disclose, Frank Uschner: Nothing to Disclose, Cristina Ortiz: Nothing to Disclose, Olaf Tyc: Nothing to Disclose, SANDRA TORRES NUNEZ: Nothing to Disclose, Richard Premont: Nothing to Disclose, Leon Grünewald: Nothing to Disclose, Johanne Poisson: Nothing to Disclose, Pierre-Emmanuel Rautou: Nothing to Disclose, Jordi Gracia-Sancho: Gilead Sciences: Independent Contractor, Novo Nordisk: Independent Contractor, Inventiva: Independent Contractor, Barcelona Liver Bioservices: Stock – privately held company, Oncomatryx: Independent Contractor, Quinton: Independent Contractor, Marko Poglitsch: Nothing to Disclose, Thomas Walther: Nothing to Disclose, Thomas Vogl: Nothing to Disclose, Christian Münch: Nothing to Disclose, Christoph Welsch: Nothing to Disclose, Mercedes Fernandez: Nothing to Disclose, Stefan Zeuzem: Nothing to Disclose, Richard Moreau: Nothing to Disclose, Claus Hellerbrand: Nothing to Disclose, Krista Rombouts: Nothing to Disclose, Wolfgang Kastenmüller: Nothing to Disclose, Anna Mae Diehl: Nothing to Disclose, Jonel Trebicka: Nothing to Disclose

0058 | TARGETING LRH-1 IN MICE PROMOTES LIVER HOMEOSTASIS AND INFLAMMATORY ATTENUATING TRANSCRIPTIONAL PROFILES TO AMELORIATE TYPEII DIABETES

Eric Ortlund

Background: Obesity is a significant global health challenge, which exacerbates metabolic dysfunction and leads to insulin resistance and liver disease. Liver receptor homolog-1 (LRH-1) is a key metabolic regulator in the liver, alleviates insulin resistance when activated, and represses inflammation in digestive tissues. However, targeting LRH-1 with synthetic ligands in vivo is challenging due to poor pharmacokinetic properties of current agonists. Moreover, mouse LRH-1 inaccurately reflects ligand binding and activation of human LRH-1 due to several variations in the ligand binding pocket. **Methods:** We use a combination of synthetic chemistry, structural biology, biochemistry, pharmacokinetic

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studies and cellular assays to develop ME610. We use CRISPR gene editing to humanize the mouse Lrh-1 gene and a range of pre-clinical studies to evaluate target engagement and efficacy in a HFD model of TypeII diabetes. **Results:** We design and synthesize an LRH-1 agonist (ME610), with improved pharmacokinetic properties and developed a novel "humanized" LRH-1 mouse model to more accurately assess human-like target engagement *in vivo*. ME610 improves glucose and insulin tolerance in diet-induced diabetic mice and drastically reduces intrahepatic fat. ME610 reduces liver weights compared to vehicle treated males but not females. Although, ME610 reduces fatty depot weights compared to vehicle treated controls for both male and female mice. Tissue slices and oil red o staining indicate ME610 reduces intrahepatic fat deposition and partially restores tissue architecture for both male and female mice. We show a significant reduction in liver di- and triglycerides by lipidomics. Using RNAseq, we observed activation of a transcriptional profile consistent with reduced free fatty acid import into the liver and enhanced β-oxidation. We also observe elevation of direct LRH-1 targets in the acute phase response, indicating resolution of ER damage, and upregulation of other liver homeostatic regulators HNF4α and TLE3 (PPARγ activator). ME610 upregulates acute phase and inflammatory genes within hours; however, prolonged treatment with ME610 in the context of HFD results in a hepatic gene expression profile that restores homeostasis and reduces inflammation. Our findings suggest that LRH-1 restores metabolic function by balancing an inflammatory response with promotion of liver homeostasis. **Conclusion:** We improved the solubility and metabolic stability of an LRH-1 modulator. We show that humanized LRH-1 (hmLRH-1) mice are phenotypically normal and develop T2DM when fed a high fat diet (HFD). Therefore, hmLRH-1 mice are suitable for studying LRH-1 agonism *in vivo*. We report that LRH-1 agonism ameliorates insulin resistance in overweight mice and significantly reduces intrahepatic fat. We define the transcriptional and lipidomics profiles associated with LRH-1 activation in healthy and T2DM mice.

Disclosures: Eric Ortlund: Nothing to Disclose

0059 | PPAR GAMMA REGULATES PNPLA3 IN A TISSUE SPECIFIC MANNER IN OBESE PEOPLE AND MICE WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

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Background: The patatin-like phospholipase domain-containing protein 3 (PNPLA3) I148M variant is associated with the development of metabolic dysfunction-associated steatotic liver disease, but its metabolic function is not fully understood yet. Hence, there is a growing interest in understanding the role of PNPLA3 in adipose tissue and the liver as key determinants of metabolic flexibility. **Methods:** We analysed white adipose tissue (WAT) from 41 obese women on pioglitazone (30 mg/day for 16 weeks) and a diabetic and hyperlipidaemic mouse model (STAM) receiving HFD supplemented with 0.01% pioglitazone for 2 weeks. We reanalysed published NGS data obtained from Gene Expression Omnibus from inducible adipocyte-specific Pparg knockout mice, hepatocyte-specific Pparg knockout mice, and human adipose stem cell-derived adipose tissues treated with rosiglitazone to validate our *in vitro* data. Mechanistically, we used *in silico* analysis, gene expression analysis, luciferase reporter, and gel shift assay systems to demonstrate the interaction between PNPLA3 and PPARG. **Results:** We observed increased *PNPLA3* mRNA transcripts in the subcutaneous femoral fat but not in the visceral fat of obese women who received pioglitazone. In the STAM mouse, pioglitazone treatment markedly increased expression of *Pnpla3* (+31%) and *Pparg2* (+50%)mRNA and its downstream target genes such as *Fabp4* and *Pgc1a* in the gonadal WAT. In the liver (with lower *PNPLA3* expression compared to WAT), however, pioglitazone treatment did not significantly increase *Pnpla3* and *Pparg* expressions. RNA-seq data analysis from the inducible adipocyte-specific Pparg knockout mice revealed that ablating Pparg reduced *Pnpla3* expression. Interestingly, the PPARG agonist did not affect *Pnpla3* expression in the liver. Mechanistically, rosiglitazone induced *PNPLA3* in human stem cell-derived adipocytes and differentiating SGBS adipocytes (+88%) and significantly increased the luciferase activity in PPARG-PNPLA3 co-transfected Cos 7 cells (+50%), demonstrating PPARG-mediated induction of *PNPLA3* promoter activity. Interestingly, two PPREs at positions -713/-707 (+92%) and -790/-780 (+93%) were bound by the PPARG nuclear protein in the differentiating adipocytes, while mutations of these reduced PPARg binding activity by sites 40% and 60%, respectively. **Conclusion:** PPARG regulates PNPLA3 and this transcriptional regulation is tissue-specific, with profound differences between white adipose tissues and

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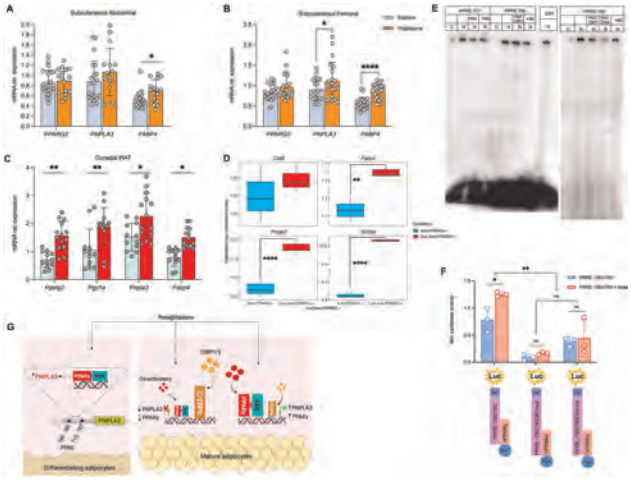
the liver. Pharmacological agonists for PPARG (glitazones) thereby modulate PNPLA3 expression in a tissue-specific manner.



Disclosures: Emmanuel Dixon: Nothing to Disclose, thierry claudel: Nothing to Disclose, Ursula White: Nothing to Disclose, Robert Zimmermann: Nothing to Disclose, Guenter Haemmerle: Nothing to Disclose, Martin Wabitsch: Nothing to Disclose, Claudia Fuchs: Nothing to Disclose, Veronica Mlitz: Nothing to Disclose, Michael Trauner: Albireo: Grant/Research Support, Alnylam: Grant/Research Support, Cymabay: Grant/Research Support, Falk: Grant/Research Support, Gilead: Grant/Research Support, Intercept: Grant/Research Support, MSD: Grant/Research Support, Takeda: Grant/Research Support, Ultragenyx: Grant/Research Support, Abbvie: Travel Grants, Falk: Travel Grants, Gilead: Travel Grants, Intercept: Travel Grants, Janssen: Travel Grants, Abbvie: Advisor, Albireo: Advisor, BiomX: Advisor, Boehringer Ingelheim: Advisor, Falk Pharma GmbH: Advisor, Genfit: Advisor, Gilead: Advisor, Hightide: Advisor, Intercept: Advisor, Ipsen: Advisor, Janssen: Advisor, MSD: Advisor, Novartis: Advisor, Phenex: Advisor, Pliant: Advisor, Regulus: Advisor, Siemens: Advisor, Shire: Advisor, BMS: Speaking and Teaching, Falk: Speaking and Teaching, Gilead: Speaking and Teaching, Intercept: Speaking and Teaching, Ipsen: Speaking and Teaching, Madrigal: Speaking and Teaching, MSD: Speaking and Teaching, Medical Universities of Graz and Vienna: Co.Inventor of patents for medical use of norUDCA filed by, Genentech: Grant/Research Support, Mirum: Advisor, Agomab: Advisor, Chemomab: Advisor, ProQR Therapeutics: Advisor, Rectify: Advisor

0060 | MULTIOMICS ANALYSIS REVEALS MYD88-DEPENDENT INHIBITION OF MITOCHONDRIAL OXIDATIVE FUNCTION DURING HYPERAMMONEMIC STRESS CAUSES SARCOPENIA OF CIRRHOSIS

Nicole Welch[1] Srinivasan Dasarathy[1] Amy Attaway[1] Saurabh Mishra[1] Annette Bellar[1] Pugazhendhi Kannan[1] Seshu Pothabathula[1] Jasmin Cunningham[1] Ramesh Rodda[1], [1]Cleveland Clinic

Background: Myeloid differentiation primary response-88 (MyD88) is an adaptor protein that activates NFκB signaling during hyperammonemic stress response (HASR) by direct interaction with the membrane ammonia transceptor, RhBG to cause sarcopenia of cirrhosis. During HASR, skeletal muscle oxidative dysfunction with impaired electron transport chain function with oxidative stress and post-mitotic senescence have been reported. The mechanism(s) of impaired mitochondrial oxidative function and upstream regulators are unknown. We dissected the mechanistic link between MYD88 and mitochondrial oxidative function during HASR and sarcopenia of cirrhosis. **Methods:** Untargeted data (RNAseq, proteomics, metabolomics) were performed in differentiated murine myotubes and muslce tissue. Differentially expressed genes/proteins (DEG/DEPs) in WT or MyD88 knock out (KO) C2C12 myotubes and in muscle from male and female mice with MyD88 muscle specific deletion (msd) or parental controls with/without HASR were determined (n = 8 in each group). MitoCarta3.0, a database containing mitochondrial-targeted proteins was compared against the list of DEG/DEPs and mitochondrial proteins identified. Volcano plots, upset plots, and hierarchical scatter plots were used to visualize DEG/DEPs. Untargeted metabolomics data were analyzed using HILIC (positive/negative modes), with pathway enrichment assessed via KEGG and BioCyc. Validation was performed via immunoblotting for critical proteins in the electron transport chain complexes (OXPHOS) and ACLY phosphorylation. TCA cycle intermediates were measured using GC-MS in myotubes. **Results:** Heatmaps of RNAseq and proteomics data revealed increased expression of OXPHOS components, especially complex I, in MyD88KO during HASR. TCA cycle enzymes (IDH2, ACLY, SHDA) were higher in MyD88KO vs WT myotubes. MyD88^{msd} skeletal muscle showed higher OXPHOS and TCA cycle components (notably ACLY,

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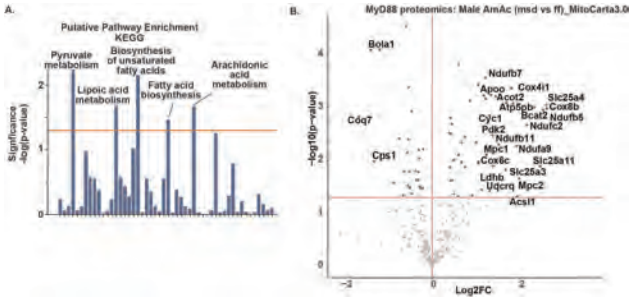
MDH2). No sex differences were observed. KEGG analysis identified pyruvate metabolism, fatty acid synthesis, and lipoic acid biosynthesis as enriched pathways (Fig 1A). Volcano plots confirmed higher expression of mitochondrial membrane and OXPHOS proteins in MyD88^{msd} compared to controls with hyperammonemia (Fig 1B). Immunoblots showed lower expression of OXPHOS and phosphorylated ACLY during HASR that were reversed by MyD88 deletion in myotubes and mouse muscle. Impaired Complex I during HASR was significantly ($p < 0.05$) reversed by MyD88 deletion. TCA intermediates (α-KG, citrate, fumarate, malate) were lower with HASR and were restored ($p < 0.05$) with MyD88 deletion. **Conclusion:** Activation of MyD88 during HASR causes mitochondrial oxidative dysfunction and contributes to sarcopenia and contractile dysfunction (frailty) in cirrhosis. Targeting MYD88 is a therapeutic option to reverse mitochondrial dysfunction during HASR and reverse sarcopenia/frailty in cirrhosis.



Disclosures: Nicole Welch: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Saurabh Mishra: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Seshu Pothabathula: Nothing to Disclose, Jasmin Cunningham: Nothing to Disclose, Ramesh Rodda: Nothing to Disclose

0061 | SPATIAL ORGANELLOMICS: A NEW WINDOW INTO HEPATOCYTE SUBTYPES, ZONAL DIVERSITY, AND DISEASE PROGRESSION

Daniel Feliciano[1] Raghabendra Adhikari[1], [1]Janelia Research Campus/HHMI

Background: Hepatocyte heterogeneity underlies the liver's capacity to perform diverse metabolic functions and adapt to nutritional and environmental challenges. While this heterogeneity is often characterized at the transcriptional level, organelle architecture—driven by both gene expression and protein-level regulation—may serve as a more direct proxy for functional cell states. However, existing tools have lacked the resolution to connect tissue organization with organelle structure. Here, we introduce Spatial Organellomics (sOrganellomics), a new pipeline combining 3D imaging of hepatic acini, deep-learning-based segmentation, and machine learning to map organelle features in hepatocytes at single-cell resolution. **Methods:** We applied sOrganellomics to mouse liver samples labeled to visualize mitochondria, peroxisomes, and lipid droplets, across three nutritional conditions: control diet, western diet, and control diet plus fasting. Using our pipeline, we segmented individual cells, organelles, and organelle-organelle contacts in 3D and extracted hundreds of organelle metrics per hepatocyte. Machine learning was used to define hepatocyte categories, analyze spatial distributions, and predict nutritional and pathophysiological states. **Results:** Our analysis revealed that hepatocytes display diverse subcellular architectures not only across classical liver zones (portal, mid-lobular, central) but also within each zone, where multiple hepatocyte categories coexist in distinct proportions—highlighting a previously underappreciated intra-zonal heterogeneity. Nutritional perturbations led to a marked reduction in this intra-zonal diversity, indicating constrained cellular plasticity under metabolic stress. Unsupervised clustering identified 11 hepatocyte subtypes based on organelle organization alone, among all three nutritional conditions. These signatures were sufficient for machine learning models to accurately classify hepatocyte categories, dietary states, and early stages of metabolic-associated steatotic liver disease (MASLD) in a mouse model. **Conclusion:** sOrganellomics reveals that organelle architecture serves as a powerful marker of hepatocyte identity and metabolic adaptation. By uncovering intra-zonal heterogeneity and its modulation by diet, our findings offer new insights into liver plasticity and disease progression. This high-resolution strategy may help establish imaging-based biomarkers for MASLD and other liver conditions.

Disclosures: Daniel Feliciano: Nothing to Disclose, Raghabendra Adhikari: Nothing to Disclose

0062 | TRANSCRIPTIONAL REGULATION OF THE HEPATIC ACETYLOME BY NRF2 IN AUTOPHAGY-IMPAIRED LIVER

Kamal Baral[1] Kapil Thapa[2] Leah Spade[1] Ramsey Rohner[1] Ghaidaa Majari[1] Yuhua Xue[1] Gang Liu[1] Krzysztof Moroz[1] Xiao-Ming Yin[1] Bilon Khambu[1], [1]Tulane University School of Medicine, [2]Tulane University School of Science and Engineering

Background: The hepatic acetylome, governed by protein acetylation, plays a critical role in regulating metabolic pathways, epigenetic modifications, signal

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transduction, cell proliferation, and apoptosis. Despite its importance, the mechanisms maintaining acetylome homeostasis in the liver remain poorly understood. This study demonstrates that autophagy is essential for preserving hepatic acetylome integrity through a non-degradative, transcriptional mechanism. **Methods:** We utilized a range of genetically engineered mouse models, including hepatocyte-specific Atg7- and Atg5-deficient mice (hepAtg7$^{-/-}$, hepAtg5$^{-/-}$), inducible Atg7 knockout mice (Atg7$^{Hep\text{-}ERT2}$), and double knockout mice lacking both Atg7 and Nrf2. Pharmacological inhibition of autophagy was achieved using chloroquine and leupeptin, while autophagy activation was induced via fasting and in Becn1$^{F121A/F121A}$ mice. Liver tissues were analyzed for global protein acetylation, acetyl-CoA levels, histone acetylation, and expression of acetyl-CoA biosynthesis enzymes. Promoter analysis was conducted using Benchling to identify Nrf2-ARE binding motifs. Rescue experiments involved intraperitoneal administration of acetyl-CoA. Human liver autopsy samples from normal and cirrhotic patients were evaluated for autophagy markers, acetylation status, and expression of acetyl-CoA biosynthesis enzymes. **Results:** Autophagy-deficient livers exhibited a marked reduction in global protein acetylation across nuclear, cytosolic, mitochondrial, and membrane compartments, despite upregulation of other post-translational modifications such as ubiquitination, SUMOylation, and phosphorylation. Conversely, autophagy activation enhanced hepatic acetylation levels. Mechanistically, autophagy maintained hepatic acetyl-CoA levels by suppressing the expression of key biosynthetic enzymes (Acly, Acss1/2, Mlycd, Pdha1). Replenishment of acetyl-CoA in autophagy-deficient mice restored acetylation levels and mitigated liver injury. Transcriptional profiling identified Nrf2 as a key regulator of these enzymes. Notably, Nrf2 deletion in autophagy-deficient mice restored acetyl-CoA biosynthesis enzyme expression and normalized the hepatic acetylome. These findings were corroborated in human cirrhotic liver samples, which showed reduced autophagy, acetyl-CoA biosynthesis enzyme expression, and protein acetylation. **Conclusion:** Autophagy sustains hepatic acetylome homeostasis through transcriptional regulation of acetyl-CoA biosynthesis enzymes, mediated by Nrf2. This non-degradative role of autophagy reveals a novel regulatory axis with implications for liver metabolism and chronic liver disease.

Disclosures: Kamal Baral: Nothing to Disclose, Kapil Thapa: Nothing to Disclose, Leah Spade: Nothing to Disclose, Ramsey Rohner: Nothing to Disclose, Ghaidaa Majari: Nothing to Disclose, Yuhua Xue: Nothing to Disclose, Gang Liu: Nothing to Disclose, Krzysztof Moroz: Nothing to Disclose, Xiao-Ming Yin: Nothing to Disclose, Bilon Khambu: Nothing to Disclose

★ 0063 | OUTCOMES OF ENDOSCOPIC ULTRASOUND-GUIDED SHUNT MODULATION FOR RECURRENT HEPATIC ENCEPHALOPATHY: PUSHING BOUNDRIES OF ENDOHEPATOLOGY

Sahaj Rathi[1] Arpit Shastri[2] Amrita Kalantri[2] Nipun Verma[2] Madhumita Premkumar[3] Sunil Taneja[2] Ajay Duseja[3], [1]Virginia Commonwealth University, [2]Post Graduate Institute of Medical Education and Research, [3]Postgraduate Institute of Medical Education & Research

Background: Spontaneous portosystemic shunts (SPSS) may lead to recurrent/refractory hepatic encephalopathy (rHE) due to shunting of gut-derived toxins from mesenteric to systemic circulation bypassing the liver. Occlusion of SPSS, usually via interventional radiology(IR) transvenous techniques, is known to improve outcomes. Endoscopic ultrasound (EUS) guided transgastric shunt obliteration (ETSO) has recently been described as an effective alternative modality, being considerably versatile and less resource intensive. In patients with rHE and poor liver reserves, shunt obliteration can increase in portal pressures and precipitate decompensation. The novel technique of EUS guided porto-splenic split (EPSS) involves occluding the splenic vein to terminate shunting without increasing portal pressure. It redirects mesenteric flow to the portal vein and splenic outflow to renal vein via the splenorenal shunt. We describe the clinical outcomes of EUS guided shunt modulation procedures, ETSO and EPSS, in rHE. **Methods:** In our retrospective review of prospectively maintained data, patients with recurrent or refractory hepatic encephalopathy despite optimal medical management were evaluated for the presence of a large SPSS($>$ 8mm). Patients who failed prior IR procedures or were not candidates for IR due to technical or financial reasons were offered EUS guided shunt modulation. The procedure was performed by cyanoacrylate glue $\pm$ coil embolization of the shunt(ETSO) or the splenic vein (EPSS) via a transgastric approach. Choice of procedure was based on liver reserves and shunt anatomy. **Results:** EUS guided shunt modulation was performed in 19 patients(ETSO, n = 15 or EPSS,n = 4) ETSO Resolution of OHE was seen in 14 of the 15 patients. Complete obliteration of shunt at index procedure was done for 10 cases. None developed overt HE over median followup of 493(range 7-906) days. Deliberate partial obliteration was performed in 5 cases to reduce risk of decompensation. Recurrence of symptoms necessitated a second session for residual shunt in 3 cases after 2, 12 and 16 months of index procedure. Four patients expired after 7, 50, 110 and 172 days, due to complications unrelated to procedure. EPSS 4

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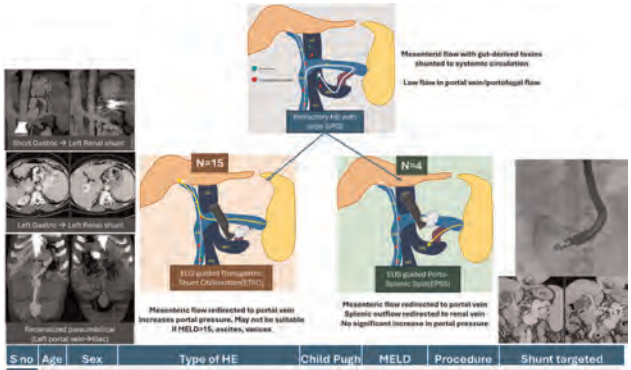
patients underwent EPSS based on poor liver reserves and suitable anatomy(shunt arising close to splenic hilum). All achieved resolution of rHE. Over a median followup of 303(range 209-624) days, only one had an episode of overt HE, precipitated by urinary tract infection, which resolved and did not recur subsequently. One patient expired after 303 days presumably due to renal failure after diarrhea. None of the patients developed procedure related serious adverse events. No significant change in MELD scores was noted at 3, 6, and 12 months of follow up. **Conclusion:** EUS-guided shunt modulation procedures can achieve effecrive and durable resolution of rHE, especially in patients poor liver reserves and who are not candidates for IR procedures.



S no	Age	Sex	Type of HE	Child Pugh	MELD	Procedure	Shunt targeted
1	74	Male	Persistent	7	10	ETSO	Splenorenal
2	47	Male	Persistent	8	10	ETSO	Splenorenal
3	74	Male	Persistent	8	13	ETSO	Splenorenal
4	57	Male	Persistent	6	11	ETSO	Paraumbilical
5	66	Male	Persistent	7	15	ETSO	Splenorenal
6	70	Female	Multifactorial, shunt being the only reversible factor	9	13	ETSO	Splenorenal
7	50	Male	Recurrent	9	13	ETSO	Splenorenal
8	45	Male	Recurrent	6	8	ETSO	Splenorenal
9	45	Male	Recurrent	11	19	ETSO	Splenorenal
10	60	Male	Persistent	8	14	ETSO	Splenorenal
11	66	Female	Recurrent	6	9	ETSO	Splenorenal
12	67	Male	Recurrent	5	10	ETSO	Splenorenal
13	57	Male	Recurrent	7	11	ETSO	Splenorenal
14	43	Female	Recurrent	6	10	ETSO	Splenorenal
15	73	Male	Recurrent	7	10	ETSO	Meso-renal
16	46	Male	Recurrent, extrapyrimidal manifestations	11	20	EPSS	Splenorenal
17	68	Male	Recurrent	7	9* Ascites, PVT	EPSS	Splenorenal
18	55	Male	Persistent	9	16	EPSS	Splenorenal
19	85	Female	Recurrent	9	19	EPSS	Splenorenal

Disclosures: Sahaj Rathi: Nothing to Disclose, Arpit Shastri: Nothing to Disclose, Amrita Kalantri: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, Sunil Taneja: Nothing to Disclose, Ajay Duseja: Nothing to Disclose

0064 | STENT DIAMETER AND MEDICATIONS ARE NOT ASSOCIATED WITH REDUCED ODDS OF HEPATIC ENCEPHALOPATHY AFTER TIPS: A CONTEMPORARY MULTICENTER COHORT STUDY FROM THE ALTA STUDY GROUP

Yael Nobel[1] Bartley Thornburg[2] Lisa VanWagner[3] Justin Boike[2] Michael Fallon[4] Pallav Kolli[5] Adnan Said[6] Carrie Frenette[7] Aparna Goel[8] Jennifer Lai[5] Sumeet Asrani[9] Giuseppe Joseph Morelli[10] Nicholas Lim[11] Arun Jesudian[12] Adam Deising[13] Sonali Paul[14] Doug Simonetto[15] Erin Spengler[16] Mehnush Hameie[2] Cynthia Padilla[2] Dyanna Gregory[3] Elizabeth Verna[1], [1]Columbia University Irving Medical Center, [2]Northwestern University, [3]UT Southwestern, [4]Banner Health, [5]UCSF, [6]University of Wisconsin, [7]Gilead, [8]Stanford University, [9]Baylor Scott & White Health, [10]Tulane University, [11]University of Rochester, [12]Cornell University Medical Center, [13]Scripps Health, [14]University of Chicago, [15]Mayo Clinic, [16]VA UT Health

Background: A feared complication after transjugular intrahepatic portosystemic shunt (TIPS) is the development of severe hepatic encephalopathy (HE). Current strategies for preventing HE include patient selection, small stent diameter, and use of prophylactic medications (lactulose or rifaximin). Contemporary incidence and predictors of severe HE after TIPS, and whether current preventive strategies are effective, are unknown. **Methods:** This is a study from the Advancing Liver Therapeutic Approaches in Portal Hypertension (ALTA), a multi-center prospective cohort study across 13 U.S. centers of adults ($\geq$18 years) who were scheduled for TIPS between 7/2019-1/2025 and completed up to 5 years of follow-up. Patients who successfully underwent TIPS and had post-TIPS hospitalization data available were included in the current study. Severe HE after TIPS was defined as either repeated ($>=2$) hospitalizations or TIPS revision for the primary indication of HE during the study period. Predictors of severe HE were evaluated using multivariable logistic regression. **Results:** 702 TIPS recipients with a median of 306 days (IQR 101-658) of follow-up were included. Overall, 201 subjects required at least one post-TIPS re-hospitalization, 97 required repeated re-hospitalizations, and 26 required TIPS revision for a primary indication of HE. Subjects who developed severe HE after TIPS ($n=105$; 15% of cohort) were older (median 61 vs. 58 years, $p<0.01$), more likely to have diagnosis of HE before TIPS (49% vs. 38%, $p=0.06$), more likely to have TIPS indication of volume overload (ascites or hepatic hydrothorax) as opposed to other indications (67% vs. 49%, $p<0.01$), and more likely to be on renal replacement therapy at time of TIPS (4% vs. 1%, $p=0.02$). Following TIPS, 52% and 39% of patients were prescribed lactulose and rifaximin, respectively. MELD-Na at TIPS, final internal stent diameter, and prescription of preventive medications did not differ significantly between subjects who did or did not develop severe HE. When adjusting for covariates, TIPS recipient-related factors (age, TIPS indication, renal failure) were significant predictors of severe HE, while stent diameter and

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medications did not reduce odds of severe HE (Table). **Conclusion:** In this contemporary, multicenter cohort with prospectively-assessed clinical and procedural factors, advanced age and clinical decompensation (volume overload, renal dysfunction) were the main drivers of severe HE after TIPS, while other factors commonly considered for HE prevention (MELD-based selection criteria, small stent diameter, and preventive medications) did not affect odds of severe HE.

Table. Multivariable logistic regression of adjusted odds of severe HE after TIPS.

	Odds Ratio (95% CI) of Severe HE after TIPS	P-value
Final TIPS stent diameter		
Stent diameter <=8mm	1.0 (Ref)	-
Larger stent diameter	0.8 (0.5-1.4)	0.54
Rifaximin or Lactulose Prescribed at TIPS	1.3 (0.8-2.3)	0.34
MELD-Na Score at TIPS		
<=10 (Lowest quartile)	1.0 (Ref)	-
10-14 (Second quartile)	0.9 (0.5-1.9)	0.86
14-17 (Third quartile)	0.8 (0.4-1.6)	0.54
>17 (Highest quartile)	1.1 (0.5-2.1)	0.88
Age (per 5-year increase)	1.2 (1.0-1.3)	**<0.01**
History of HE before TIPS	1.5 (0.9-2.6)	0.11
TIPS indication of volume overload	1.7 (1.0-2.9)	**0.04**
Renal replacement therapy at time of TIPS	5.0 (1.1-23.1)	**0.03**

Disclosures: Yael Nobel: Nothing to Disclose, Bartley Thornburg: Nothing to Disclose, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, Justin Boike: Nothing to Disclose, Michael Fallon: Nothing to Disclose, Pallav Kolli: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Advisor, Carrie Frenette: Gilead Sciences: Employee, Aparna Goel: Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Sumeet Asrani: Nothing to Disclose, Giuseppe Joseph Morelli: Nothing to Disclose, Nicholas Lim: Nothing to Disclose, Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant, Mallinckrodt Pharmaceuticals: Consultant, Mallinckrodt Pharmaceuticals: Speaking and Teaching, Adam Deising: Salix: Speaking and Teaching, Mallinckrodt: Speaking and Teaching, Sonali Paul: Nothing to Disclose, Doug Simonetto: Nothing to Disclose, Erin Spengler: Nothing to Disclose, Mehnush Hameie: Nothing to Disclose, Cynthia Padilla: Nothing to Disclose, Dyanna Gregory: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose

0065 | BEACON: AT-HOME, SELF-ADMINISTRATION OF A TEST FOR CRITICAL FLICKER FREQUENCY AS A SCREENING TEST FOR MINIMAL HEPATIC ENCEPHALOPATHY

Philip Vutien[1] Richard Li[2] Ravi Karkar[3] James Fogarty[2] Sean Munson[2] Sabrina Omer[2] Michael Yacoub[4] George Ioannou[1], [1]University of Washington Medical Center, [2]University of Washington, [3]University of Massachusetts Amherst, [4]Pacific Northwest University of Health Sciences

Background: Critical flicker frequency (CFF) is the maximum frequency at which an observer perceives a light source as flickering instead of a steady continuous light. CFF is a validated, objective screening test for hepatic encephalopathy, which causes a reduction in CFF. We previously developed "Beacon" (Figure 1), a portable device that enables self-administration of accurate CFF measurement. This study aimed to assess the feasibility and reliability of at-home, repeated CFF testing in patients with cirrhosis. **Methods:** We recruited 21 patients with cirrhosis, after excluding those with recent alcohol use, color blindness, or severe vision impairment. Each participant received a Beacon device and a smartphone with pre-installed software to measure CFF using two different protocols: 1) method of limits-descending (MOL-D) and 2) forced choice. Participants were instructed to complete ≥ 5 tests (using both MOL-D and forced choice protocols) per week for the first 2 weeks, then 1 test per week for at least 4 weeks thereafter. Outcome measures include testing protocol adherence, CFF stability over time, and duration to complete the tests. **Results:** Among the 21 patients, 76% were male and 76% were Caucasian. Most patients had alcohol-related liver disease (43%), chronic hepatitis C (19%), or metabolic dysfunction-associated steatohepatitis (19%) as the etiology for their liver disease. Mean MELD score at study enrollment was 13.5 and eight (38%) had a prior history of HE. 18 participants (86%) completed the full six-week testing schedule (Figure 2), including both daily and weekly measurements. 3 participants (ID# 9, #18, #20) dropped out after completing only daily testing. Median CFF values ranged, across all patients, from 35.7-50.6 Hz (median 42.7 Hz) for descending only and 37.5-53.3 Hz (median 43.7 Hz) for forced choice. Overall, CFF measurements were stable over time: median within-patient IQR was 1.67 Hz (MOL-D) and 2.34 Hz (forced choice). The forced choice protocol required significantly more time to complete (median 4.91 min, IQR 3.75) compared to MOL-D (median 2.73 min, IQR 1.25). **Conclusion:** Beacon is a novel, portable, self-administered device for at-home CFF testing in patients with cirrhosis. This device demonstrated high

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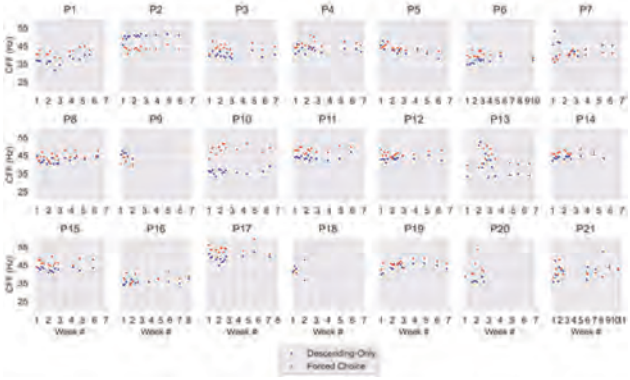
patient adherence and stable measurements over time. Future studies should assess the role of longitudinal CFF self-monitoring in predicting overt HE and related outcomes.

Figure 1: Beacon light source and paired smartphone application which controls the light source.

Figure 2: At-home testing results for patients: daily CFF testing with MOL-D and forced choice methods for 2 weeks, then weekly.



Disclosures: Philip Vutien: Nothing to Disclose, Richard Li: Nothing to Disclose, Ravi Karkar: Nothing to Disclose, James Fogarty: Nothing to Disclose, Sean Munson: Nothing to Disclose, Sabrina Omer: Nothing to Disclose, Michael Yacoub: Nothing to Disclose, George Ioannou: Nothing to Disclose

0066 | DIFFERENTIAL EFFECTS OF VASOPRESSIN AND TERLIPRESSIN AS ADJUNCT VASOPRESSORS ON HEMODYNAMIC PARAMETERS IN PATIENTS WITH CIRRHOSIS AND SEPTIC SHOCK: FINAL RESULTS: FROM THE VITEL-C RANDOMIZED CONTROLLED TRIAL [NCT05315557]

Rakhi Maiwall[1] Vishnu Girish[1] Harsh Tevethia[1] Mohit Prajapati[1] Fagun Sharma[1] Prashant Agarwal[1] Satender Pal Singh[1] Rajan Vijayaraghavan[1] sumegh talwalkar[1] Ayush Jain[1] Bindiya Arora[1] Priyanka Sharma[1] Charvi Nayyar[1] Sherin Thomas[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences (ILBS), New Delhi

Background: Critically ill patients with cirrhosis and septic shock (CIC) carry a substantial risk of multiorgan dysfunction. Although norepinephrine is first-line, adjunctive vasopressors—vasopressin (VASO) and terlipressin (TERLI)—may differentially influence hemodynamics, cardiorenal biomarkers, and endothelial function. **Methods:** In this open-label randomized trial, 120 adult CIC were assigned 1:1 to VASO (0.03 U/min; n = 60) or TERLI (1 mg/24 h; n = 60) alongside norepinephrine (NE), after they were unresponsive to NE. **Results:** One hundred and twenty CIC patients (mean age 46.8 ± 10.4 years; 97% male; 41% alcohol-related liver disease) were equally randomised to receive vasopressin (VASO; n = 60) or terlipressin (TERLI; n = 60). Baseline parameters—including mean arterial pressure (MAP; 68.24 ± 10.15 vs. 67.01 ± 9.82 mmHg), arterial lactate (3.12 ± 1.27 vs. 2.89 ± 1.31 mmol/L), MELD score (28.4 ± 5.89 vs. 29.9 ± 8.96) and KDIGO stage distribution (stage 0: 34% vs. 38%; stage 1: 34% vs. 22%; stage 2: 16% vs. 20%; stage 3: 16% vs. 20%)—were comparable (all $p > 0.05$). Shock reversal at 6 h (58% vs. 48%; $p = 0.32$) and 72 h (34% vs. 50%; $p = 0.11$) did not differ; however, at 3 h, TERLI showed significant shock reversal(23% vs 6%, $p = 0.02$). Urine output was significantly greater with TERLI at 6 h (53.1 ± 22.22 vs. 41.8 ± 21.62 mL/h; $p = 0.006$) and 12 h (48.19 ± 24.61 vs. 39.75 ± 20.15 mL/kg; $p = 0.044$), while KDIGO stage at 72 h remained similar ($p = 0.4$). Hemodynamic assessment demonstrated higher systemic vascular resistance (SVR) with VASO at 12 h (1250 ± 300 vs. 1050 ± 250 dynes/cm^5 $p < 0.05$) and 24 h (1300 ± 320 vs. 1100 ± 280 dynes/cm^5; $p < 0.05$), and greater lactate clearance with VASO at 6 h (–2.81 ± 16.5% vs. –10.65 ± 18.3%; $p = 0.02$) and 24 h (–0.07 ± 17.5% vs. –14.8 ± 21.7%; $p < 0.001$). Biomarker profiling revealed greater reductions in angiopoietin-1 (ANG-1; 239.9 ± 45.8 → 206.3 ± 35.2 pg/mL) and urinary neutrophil gelatinase-associated lipocalin (uNGAL; 1155.8 ± 170.6 → 1025.7 ± 155.7 ng/mL) with VASO versus TERLI (224.9 ± 102.2 → 218.3 ± 60.4 pg/mL; 1 134.7 ± 183.6 → 999.98 ± 107.4 ng/mL), whereas N-terminal pro–B-type natriuretic peptide (NT-proBNP) decreased with VASO (2.51 ± 3.69 → 2.21 ± 2.12 pg/mL) but increased with TERLI (1.34 ± 0.73 → 1.49 ± 0.48 pg/mL). Other secondary outcomes—including duration of mechanical ventilation and renal-replacement therapy—did not differ. Adverse events (34% vs. 8%; $p = 0.001$) and rebound hypotension (44.1% vs. 21.2%; $p = 0.046$) were significantly more frequent with TERLI. **Conclusion:** In CIC with septic shock, vasopressin is comparable to terlipressin as an adjunct to norepinephrine in reversing shock. While terlipressin led to a faster reversal of shock, it was associated with a higher incidence of adverse events and rebound hypotension. A distinct biomarker profile was noted with vasopressin conferring greater reductions in ANG-1 and NGAL, whereas terlipressin increased NT-proBNP.

Disclosures: Rakhi Maiwall: Nothing to Disclose, Vishnu Girish: Nothing to Disclose, Harsh Tevethia:

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0067 | THE USE OF TERLIPRESSIN IS ASSOCIATED WITH LOWER MORTALITY AND LIVER-RELATED COMPLICATION EVENTS COMPARED TO THE USE OF NOREPINEPHRINE IN PATIENTS WITH DECOMPENSATED CIRRHOSIS: A MULTINATIONAL ANALYSIS

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Background: Terlipressin improves and reduces hepatorenal syndrome (HRS) more than norepinephrine (NE) in patients with decompensated cirrhosis, by vasoconstricting the splanchnic circulation, lowering portal hypertension, and thus improving renal blood flow. There is also data suggesting that the use of terlipressin reduces ascites and variceal bleeding in patients with decompensated cirrhosis, but data on other complications remain contradictory. Thus, we aim to investigate the impact terlipressin has on various complications of decompensated cirrhosis when compared with NE in a global patient population setting. **Methods:** In this retrospective cohort study, a total of 958 patients with decompensated cirrhosis were investigated. The TriNetX, a global network database, was utilized for this study. A total of 479 patients on terlipressin and 479 patients on NE were matched based on the following characteristics: age, gender, race/ethnicity, comorbidities (such as, but not limited to, esophageal/gastric varices, chronic hepatic failure, HRS, hepatopulmonary syndrome, ascites, spontaneous bacterial peritonitis, liver transplant status, HTN, DMII, CKD), medications (carvedilol), MELD labs. After matching the demographics and clinical characteristics of patients with decompensated cirrhosis in the groups receiving terlipressin vs. NE, the following clinical primary outcomes were analyzed for both 30 and 90 days interval: all cause-mortality, hepatic decompensation, major adverse liver outcomes (MALO), ascites, hepatic encephalopathy (HE), variceal bleeding, spontaneous bacterial peritonitis (SBP), liver transplantation, paracentesis (Table 1). The Cox proportional hazard model was used to calculate the hazard ratio (HR) between the terlipressin and NE group. **Results:** Within both 30 and 90 days of receiving terlipressin, patients with decompensated cirrhosis had a statistically significant reduction in all-cause mortality [HR: 0.531, 0.589], HE [HR: 0.594, 0.721], and paracentesis [HR:0.527, 0.545], respectively. The use of terlipressin led to a reduction in ascites in both 30 and 90 days interval [0.920, 0.934] respectively; however, the values were not stastistically significant. **Conclusion:** Our retrospective study demonstrated improvement in complications of decompensated cirrhosis with the use of terlipressin, confirmed with the significant reduction in all cause mortality, HE, and the frequency of needed paracentesis. Additionally, the reduction in the frequency of paracentesis may correlate with the reduction in ascites. Overall, terlipressin reduced the majority of complications related to decompensated cirrhosis, favoring the use of terlipressin over norepinephrine in patients with decompensated cirrhosis.

Table 1. Clinical Outcomes of Patients With Decompensated Cirrhosis using Terlipressin vs Norepinephrine

Outcomes	Terlipressin Included	Terlipressin Events	Norepinephrine Included	Norepinephrine Events	HR (95% CI)
30 days					
All-cause mortality	400	159	416	242	**0.531 (0.434, 0.649)**
Hepatic decompensation	479	147	479	154	0.834 (0.665, 1.047)
MALO	479	189	479	180	0.945 (0.770, 1.159)
Ascites	479	86	479	83	0.920 (0.680, 1.245)
Hepatic encephalopathy	479	72	479	106	**0.594 (0.440, 0.802)**
Variceal bleeding	479	14	479	16	0.815 (0.397, 1.671)
SBP	479	17	479	15	1.058 (0.528, 2.130)
Liver transplantation	479	13	479	19	0.620 (0.306, 1.258)
Paracentesis	479	66	479	109	**0.527 (0.388, 0.717)**
90 days					
All-cause mortality	400	196	416	259	**0.589 (0.489, 0.710)**
Hepatic decompensation	479	173	479	164	0.895 (0.723, 1.109)
MALO	479	210	479	191	0.969 (0.796, 1.179)
Ascites	479	105	479	96	0.934 (0.708, 1.233)
Hepatic encephalopathy	479	96	479	111	**0.721 (0.548, 0.948)**
Variceal bleeding	479	20	479	18	0.974 (0.514, 1.844)
SBP	479	23	479	17	1.204 (0.642, 2.257)
Liver transplantation	479	17	479	24	0.598 (0.320, 1.115)
Paracentesis	479	74	479	115	**0.545 (0.406, 0.731)**

Abbreviations: HR: Hazard Ratio; CI: Confidence Interval; MALO: Major Adverse Liver Outcome; SBP: Spontaneous Bacterial Peritonitis

Disclosures: Christina Lee: Nothing to Disclose, Donghyun Ko: Nothing to Disclose, Do Han Kim: Nothing to Disclose, Paul Kroner: Nothing to Disclose, Raffi Karagozian: Nothing to Disclose

0068 | REAL-WORLD PRACTICE PATTERNS AND OUTCOMES OF TERLIPRESSIN USE FOR HEPATORENAL SYNDROME–ACUTE KIDNEY INJURY (HRS-AKI): RESULTS: FROM THE HRS-HARMONY CONSORTIUM

Andrew Allegretti[1] Jevon Robinson[1] Eric Orman[2] Giuseppe Cullaro[3] J. Pedro Teixeira[4] Javier Neyra[5] Aanchal Kapoor[6] Douglas Simonetto[7] Stevan Gonzalez[8] Sumeet Asrani[9] Hugo Vargas[10] Anjana Rajan[11] Zachary Fricker[12] Ethan Weinberg[13] Juan Carlos Velez[14] Justin Belcher[15] Hani Wadei[16] Brett Fortune[17] R. Todd Frederick[18] Omar Mehkri[6] Bridget Dolan[19] Caleigh Pickett[6] Jeremy Skvarce[19] Saloni Sachar[6] Christina

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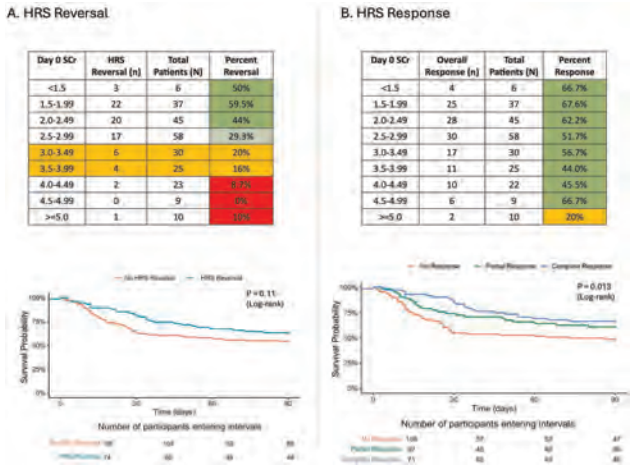
Background: Terlipressin became the first FDA-approved therapy for HRS-AKI in September 2022. We present its initial experience at 16 U.S. academic medical centers. **Methods:** Consecutive patients with HRS-AKI treated with terlipressin from approval through May 2024 were followed longitudinally for 90 days after drug initiation. Patients were categorized as meeting Standard Criteria (conforming to FDA labeling guidance) or Extended Criteria (acute on chronic liver failure [ACLF] grade 3, serum creatinine [sCr] >5 mg/dL, or hypoxia at initiation). Primary outcomes were HRS Reversal (sCr <1.5 mg/dL plus reduction ≥ 0.3 mg/dL at end of treatment) and Overall Response (Complete and Partial Response, defined by the 2015 International Club of Ascites). Fine and Gray competing risks models [with liver transplant (LT) as a competing event] were used to assess 90-day mortality. **Results:** 243 patients were analyzed: median age 58 years, 59.7% male, 55.6% alcohol-associated cirrhosis, initiation sCr 2.79 [IQR 2.27, 3.57] mg/dL, MELD 3.0 31 [26, 37]. 40.5% died and 28.4% received LT by 90 days. Patients received 200 [125, 350] g albumin prior to initiation and 62.5 [0, 125] g while on terlipressin. HRS Reversal occurred in 30.9%, Overall Response in 55.1% (29.6% Complete Response, 25.5% Partial Response). SCr at initiation was inversely associated with both HRS Reversal ($p<0.001$) and Overall Response ($p=0.03$, Figure). 49% patients met Standard Criteria while 51% met Extended Criteria, most commonly due to ACLF grade 3 (44.9%). Standard Criteria was associated with higher rates of Overall Response (62.9% vs. 47.1%; $p=0.019$), HRS Reversal (35.5% vs. 26.1%; $p=0.146$), and fewer adverse events leading to terlipressin discontinuation (12.1% vs. 22.7%; $p=0.044$), including respiratory failure/new oxygen requirement (5.6% vs. 13.4%; $p=0.063$). In adjusted analysis, HRS Reversal was not associated with reduced mortality (aHR 0.70 [95% CI 0.38, 1.28]; $p=0.25$) but Overall Response was (aHR 0.57 [0.38, 0.85]; $p=0.006$). **Conclusion:** Terlipressin was more effective and safer when adhering to FDA labeling for patient selection, which reinforces the importance of this guidance. Overall Response appears to be a relevant clinical endpoint for future studies.



Disclosures: Andrew Allegretti: Nothing to Disclose, Jevon Robinson: Nothing to Disclose, Eric Orman: Sitero: Consultant, Biovie: Advisor, Giuseppe Cullaro: Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant, J. Pedro Teixeira: Outset Medical: Consultant, Jolla Pharmaceutical Company/Innoviva: Grant/Research Support, Astute Medical/bioMérieux: Grant/Research Support, Eli Lilly and Company: Stock - publicly traded company, Novo Nordisk A/S: Stock - publicly traded company, Pfizer Inc.: Stock - publicly traded company, Javier Neyra: Nothing to Disclose, Aanchal Kapoor: Nothing to Disclose, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Stevan Gonzalez: Mallinckrodt Pharmaceuticals: Speaking and Teaching, Mallinckrodt Pharmaceuticals: Consultant, Sumeet Asrani: Nothing to Disclose, Hugo Vargas: Nothing to Disclose, Anjana Rajan: Nothing to Disclose, Zachary Fricker: River2Renal Corp: Grant/Research Support, Lipocine, Inc: Grant/Research Support, Bausch, Inc: Grant/Research Support, Pick Research: Consultant, Atheheum Partners: Consultant, Ethan Weinberg: PharmaIN: Consultant, BioVie: Consultant, Sequana: Consultant, Novo Nordisk: Advisor, Amgen: Consultant, Astra Zeneca: Consultant, Kezar: Consultant, Juan Carlos Velez: Mallinckrodt: Speaking and Teaching, Mallinckrodt: Advisor, Travere: Advisor, Vera Therapeutics: Advisor, Calliditas: Advisor, Justin Belcher: Mallinckrodt Pharmaceuticals: Advisor, Hani Wadei: Nothing to Disclose, Brett Fortune: Gilead Sciences: Consultant, Madrigal Pharma: Consultant, WL Gore and

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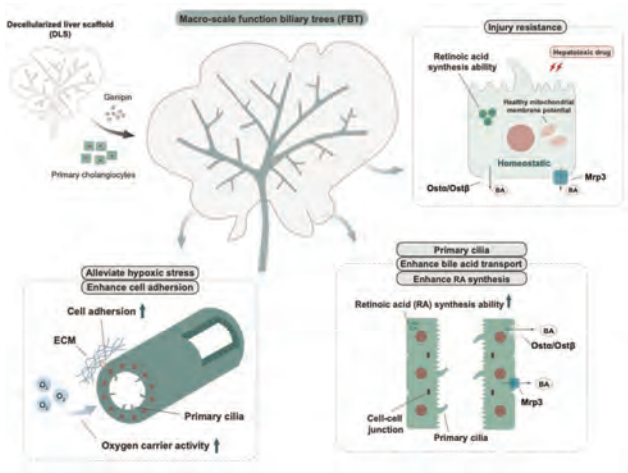
★ 0069 | GENERATION OF MACRO-SCALE FUNCTIONAL BILIARY TREES WITH PRIMARY CILIA AND ENHANCED INJURY RESISTANCE

Jun Li[1] Shiwen Ma[1] Jiaxian Chen[1] Meiqian Hu[1] Jiaojiao Xin[1] Jing Jiang[1] Dongyan Shi[1], [1]The First Affiliated Hospital, Zhejiang University School of Medicine

Background: The reconstruction of functional biliary trees (FBT) is crucial in the development of bioengineered liver. However, the decellularized liver scaffolds (DLS) as the scaffold of FBT exhibit mechanical instability that leads to luminal collapse and subsequent hypoxic stress, severely compromising FBT functions. Furthermore, existing engineered biliary structures lack sufficient injury resistance to withstand the pathological microenvironment of end-stage liver disease. **Methods:** This work aimed to construct macro-scale FBT with enhanced injury resistance using rat DLS optimized by genipin and mouse primary cholangiocytes. The newly developed FBTs were systematically evaluated through functional assays, transcriptomic analysis, and hepatotoxic drug-induced injury testing to validate their structural stability and injury resistance. **Results:** The FBT generated with genipin-crosslinked DLS demonstrated enhanced structural stability and fluid mechanical properties, which significantly improved cholangiocyte adhesion and attenuated hypoxia response as evidenced by transcriptomic profiling. Morphological evaluation revealed that the bioengineered FBT recapitulated the hierarchical branching architecture of native biliary networks, with well-organized luminal structures and proper apical-basal polarity. Scanning electron microscopy identified elongated, upright primary cilia projecting from the luminal cholangiocytes, while JC-1 staining confirmed preserved mitochondrial membrane potential—indicative of cellular health. Functionally, the FBT exhibited enhanced bile acid transport, marked by the upregulation of *Slc51a/Slc51b* (encoding OST-α/OST-β) and *Abcc3* (encoding MRP3), along with enhanced retinoic acid (RA) synthesis capacity. Notably, such FBT exhibited unique injury resistance, maintaining cellular homeostasis and bile acid transport function after hepatotoxic drug exposure. Transcriptomic analysis confirmed that the newly developed FBT maintained anti-injury signatures and RA synthesis capacity compared to non-crosslinked controls. **Conclusion:** Our macro-scale FBT, with primary ciliary architecture and enhanced injury resistance, provides a promising strategy for bioengineered liver construction and clinical translation.



Disclosures: Jun Li: Nothing to Disclose, Shiwen Ma: Nothing to Disclose, Jiaxian Chen: Nothing to Disclose, Meiqian Hu: Nothing to Disclose, Jiaojiao Xin: Nothing to Disclose, Jing Jiang: Nothing to Disclose, Dongyan Shi: Nothing to Disclose

0070 | FAZIRSIRAN IS EFFECTIVE IN EARLY AND ADVANCED FIBROSIS IN PATIENTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE

Jen-Chieh Chuang[1] Ying-Wooi Wan[1] Ruixue Hou[1] Maria Paraskevopoulou[1] Loredana Cuccia[1] Susana Gonzalez[1] Tami Nussbaum[1] Nirav Desai[1] Thomas Schluep[2] James Hamilton[2] Virginia Clark[3] Pavel Strnad[4], [1]Takeda Development Center Americas, Inc., Cambridge, MA, USA, [2]Arrowhead Pharmaceuticals, Inc., Pasadena, CA, USA, [3]University

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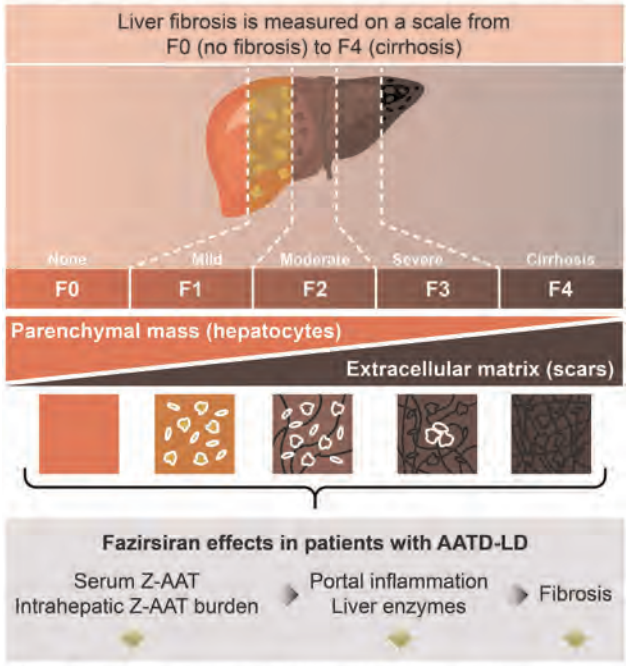
Background: Fazirsiran, a GalNAc siRNA targeting misfolded alpha-1 antitrypsin (Z-AAT; coded by *SERPINA1*) in the liver, is in phase 3 development for AAT deficiency-associated liver disease (AATD-LD). Fazirsiran selectively enters hepatocytes via the asialoglycoprotein receptor (ASGPR; coded by *ASGR1*). It is unclear whether *ASGR1* expression is altered in advanced fibrosis or if dense extracellular matrix in fibrotic tissue may restrict fazirsiran delivery to hepatocytes. Here we assessed *ASGR1* and *SERPINA1* expression across fibrosis stages and evaluated the impact of fibrosis on fazirsiran uptake and activity. **Methods:** Liver tissue bulk transcriptomics and single nuclei/cell (sn/sc) RNAseq were used to identify genes dynamically modulated in advanced fibrosis from 10 studies of several fibrotic liver diseases. Overall *ASGR1* and *SERPINA1* expression was assessed in samples from: AATD-LD with Pi*ZZ vs healthy controls with a Pi*MM genotype; PSC vs healthy controls; advanced MASH (F3/4) vs MASLD or healthy controls. *ASGR1* and *SERPINA1* expression in hepatocytes was evaluated using snRNAseq from patients with MASLD or MASH, and scRNAseq from other cirrhosis etiologies vs healthy controls. Analysis of fazirsiran phase 2 studies (AROAAT-2001/-2002 [NCT03945292, NCT03946449]) investigated whether fazirsiran's effects on silencing *SERPINA1*, reducing Z-AAT burden, improving liver function and reducing fibrosis were affected by baseline fibrosis status. **Results:** Across bulk transcriptomic datasets, *SERPINA1* expression was maintained while *ASGR1* expression was reduced in advanced fibrosis (F3/4). However, sn/sc RNAseq data demonstrated that expression of both *ASGR1* and *SERPINA1* in hepatocytes was sustained in advanced fibrosis, even in cirrhosis. In fazirsiran phase 2 studies, hepatic Z-AAT burden tended to be elevated in patients with AATD-LD and advanced fibrosis (median 62 and 33 nmol/g for F3/4 vs F0–2, respectively; Wilcoxon test, $p = 0.09$). Advanced baseline fibrosis (F3/4 [n = 23] vs F0–2 [n = 8]) did not impair fazirsiran's effects vs baseline on reducing: serum Z-AAT (–89 vs –90%; $p = 0.58$), hepatic Z-AAT burden (–94 vs –89%; $p = 0.28$), portal inflammation (–0.5 vs 0.0; $p = 0.86$), liver enzymes (ALT –54 vs –28%, $p = 0.02$; AST –32 vs –14%, $p = 0.09$; GGT –40 vs –13%, $p = 0.03$), and liver stiffness measured by FibroScan (–1.38 vs –1.12 kPa, $p = 0.44$). **Conclusion:** Hepatocellular *ASGR1* and *SERPINA1* expression is constant in patients with advanced fibrosis stages although loss of parenchymal cells (hepatocytes) may lead to reduced overall *ASGR1* expression. Analysis of fazirsiran phase 2 studies indicates that fazirsiran is effective in both advanced and early fibrosis. Collectively, these findings support further development of fazirsiran in patients with AATD-LD and advanced fibrosis, given that accumulation of the disease-causing Z-AAT protein remains high. Writing support provided by S Chambers, Oxford PharmaGenesis.

Figure. Advanced fibrosis does not affect *SERPINA1* or *ASGR1* expression in hepatocytes, even in cirrhosis, hence outcomes from fazirsiran treatment in patients with AATD-LD are not affected by baseline fibrosis status (F3/4 vs F0–2).



AATD-LD, alpha-1 antitrypsin deficiency-associated liver disease; Z-AAT, misfolded alpha-1 antitrypsin.

Disclosures: Jen-Chieh Chuang: Takeda: Employee, Ying-Wooi Wan: Nothing to Disclose, Ruixue Hou: Takeda Pharmaceuticals: Employee, Maria Paraskevopoulou: Nothing to Disclose, Loredana Cuccia: Nothing to Disclose, Susana Gonzalez: Nothing to Disclose, Tami Nussbaum: Nothing to Disclose, Nirav Desai: Nothing to Disclose, Thomas Schluep: Nothing to Disclose, James Hamilton: Nothing to Disclose, Virginia Clark: Novo Nordisk: Research support, Takeda: Research support, Vertex: Research support, Takeda: Consulting fees, Vertex: Research support, Takeda: Consulting fees, Vertex: Consulting fees, 89 Bio: Grant/Research Support, hamni pharmaceuticals: Grant/Research Support, Novo Nordisk: Research support, Takeda: Research support, Vertex: Research support, Takeda: Consulting fees, Vertex: Research support, Takeda: Consulting fees, Vertex: Consulting fees, 89 Bio: Grant/Research Support, hamni pharmaceuticals: Grant/Research Support, Pavel Strnad: Arrowhead Pharmaceuticals: Grant/Research Support, CSL Behring: Grant/Research Support, CSL Behring: Speaking and Teaching, BioMarin Pharmaceutical: Consultant, GSK: Consultant, Intellia: Consultant, Takeda Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Swedish Orphan Biovitrum: Consultant, Swedish Orphan Biovitrum: Speaking and Teaching,

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0071 | INDUCIBLE DUAL LOSS OF β- AND γ-CATENIN IN BILE DUCTS LEADS TO CHOLESTATIC INJURY AND MORTALITY OR REPAIR BASED ON THE EXTENT OF CELL JUNCTION LOSS

Vik Meadows[1] Yekaterina Krutsenko[1] Elena Provencal[1] Minakshi Poddar[1] Sucha Singh[1] Satdarshan (Paul) Monga[1], [1]University of Pittsburgh

Background: Loss of β-catenin in adherens junctions is compensated by γ-catenin, a homologous desmosomal protein. Previously, we have shown dual loss of β- and γ-catenin in liver epithelial cells leads to progressive intrahepatic cholestasis and mortality. Loss of these catenins in hepatocytes alone led to cholemia, but without notable mortality or morbidity. In this study we determine any impact of loss of both catenins from cholangiocytes on hepatic health. **Methods:** We utilized Ctnnb fl/fl; Jup fl/fl mice with Opn-iCreERT2+/- to delete both β-catenin (*Ctnnb1*) and γ-catenin (*Jup*) from cholangiocytes. Littermate control with no Opn-iCreERT2+/+ were used as controls. All mice received tamoxifen (100 mg/kg) dissolved in corn oil injected intraperitoneally. Mice were randomly assigned to two groups: DKO2 received 2 doses of tamoxifen and DKO4 received 4 doses of tamoxifen. Both male and female mice were used in this study. **Results:** DKO2 mice showed morbidity and elevated ALT, AST, and total bilirubin levels by 2 weeks but normalized by 6 weeks post-injection. In contrast, DKO4 mice exhibited severe biliary infarcts, over 20% body weight loss by 2 weeks, and 100% mortality by 5 weeks. Total bile acids increased in DKO2 (at 2 weeks) and DKO4 (all time points) compared to controls. Histological analysis indicated immune cell infiltration, stellate cell activation, and severe portal fibrosis in DKO4 mice, along with increased bile duct mass. DKO2 mice displayed trends towards increased bile duct mass, fibrosis, and inflammation that resolved at 6 weeks post-injection. Single-nucleus RNA sequencing revealed stressed hepatocytes in DKO4, suggesting mitochondrial distress and inflammation. In DKO4 cholangiocytes, RUNX3 and IL12 signaling pathways linked to fibrosis were enriched. Increased expression of myofibroblast genes in DKO4 hepatic stellate cells indicated activated fibrosis progression. DKO2 also showed an increase in Sox9-positive cells in the portal area, some being HNF4-positive, indicating biliary program activation in hepatocytes. **Conclusion:** The loss of β- and γ-catenin from cholangiocytes can cause severe intrahepatic cholestatic injury, depending on bile duct integrity and an intact cholangiocyte population. In DKO4 mice, severe bile duct loss leads to significant liver dysfunction and death, while DKO2 mice show a reparative response to cholestatic injury via increased hepatocyte-to-biliary reprogramming. Understanding the mechanisms that promote this process may help develop novel cholangiopathy therapies.

Disclosures: Vik Meadows: Nothing to Disclose, Yekaterina Krutsenko: Nothing to Disclose, Elena Provencal: Nothing to Disclose, Minakshi Poddar: Nothing to Disclose, Sucha Singh: Nothing to Disclose, Satdarshan (Paul) Monga: Mermaid Bio: Advisor, Vicero: Advisor, AntlerA: Advisor, Genentech: Speaking and Teaching, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Mermaid Bio: Consultant, Fog Pharmaceuticals: Grant/Research Support, Surrozen: Consultant, Genentech: Independent Contractor

0072 ★ NEW SUBMISSION | NEW INSIGHTS INTO PATHOGENIC MECHANISMS OF LIVER FIBROSIS IN HEMOCHROMATOSIS

Xia Xiao[1] Yongtao Wang[2] Raymond Chung[2] Jodie Babitt[1], [1]Massachusetts General Hospital/Harvard Medical School, [2]Massachusetts General Hospital

Background: Hemochromatosis is a disorder that leads to excessive iron accumulation in the liver, with ~70% of patients eventually developing liver cirrhosis through mechanisms that remain unknown. Mutations in hemochromatosis genes, HFE, TFR2, and HJV, cause reduced hepatic SMAD1/5/8 signaling, which is critical not only for systemic iron regulation but also for liver fibrosis, as we showed previously. However, the specific mechanism by which defective hepatic SMAD1/5/8 signaling contributes to liver fibrosis is poorly understood. SMAD1/5/8 and SMAD2/3 signaling pathways can counter-regulate each other through a negative feedback loop, and both pathways require SMAD4 to proceed with signal transduction. Here we investigated whether excessive hepatocyte SMAD2/3 signaling, as a consequence of hepatocyte SMAD1/5/8 signaling deficiency, contributes to liver fibrosis in the context of hemochromatosis. **Methods:** To investigate SMAD2/3 pathway activity, we measured phosphorylated (p)SMAD2/3 in isolated primary hepatocytes from *Smad1/5/8* hepatocyte conditional knockout (CKO)

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mice. We then generated mice with a combined deletion of hepatocyte *Smad4* together with *Smad1/5/8* to eliminate both SMAD 2/3 and SMAD1/5/8 signals, performed RNAseq analysis and compared iron levels and liver fibrosis between *Smad1/5/8/4* CKO mice and *Smad1/5/8* CKO mice. **Results:** pSMAD2/3 levels were increased in *Smad1/5/8* KO hepatocytes compared to Cre- controls. As previously reported, Smad1/5/8 CKO mice developed iron overload, spontaneous liver injury and fibrosis, as indicated by increased liver injury markers (serum ALT, bilirubin), enhanced collagen accumulation (Sirius Red Staining), and elevated liver fibrosis markers (*Acta2* and *Col1a1*). In contrast, although *Smad1/5/8/4* CKO mice had a similar degree of iron overload, deletion of hepatocyte *Smad4* prevented the spontaneous liver injury and fibrosis, and improved liver function observed in *Smad1/5/8* CKO mice. This is evidenced by RNAseq results and reductions in all liver injury/fibrosis markers in *Smad1/5/8/4* CKO mice, bringing them in line with those in Cre- littermates. **Conclusion:** The liver injury and fibrosis in *Smad1/5/8* CKO mice is SMAD4-dependent, suggesting a potential pathogenic role of hepatocyte SMAD2/3 signaling in SMAD1/5/8 deficient hemochromatosis. This study represents the first investigation into the molecular mechanisms underlying liver fibrosis in hemochromatosis beyond the role of iron overload, paving the way for new therapeutic advances.

Disclosures: Xia Xiao: Nothing to Disclose, Yongtao Wang: Nothing to Disclose, Raymond Chung: GSK: Grant/Research Support, Salix: Grant/Research Support, GSK: Consultant, Precision Biosciences: Consultant, Boehringer: Grant/Research Support, BMS: Grant/Research Support, Jodie Babitt: Nothing to Disclose

0073 | RAPIDLY IMPROVED CU BALANCE IN WILSON DISEASE PATIENTS ON TIOMOLYBDATE CHOLINE

Aftab Ala[1] Thomas Sandahl[2] Anna Czlonkowska[3] Chandler Robinson[4] Andrew Cittadine[4] Valentina Medici[5] Karl Heinz Weiss[6] Frederick Askari[7], [1]Kings College Hospital, [2]Aarhus University Hospital, [3]Institute of Psychiatry and Neurology, [4]Monopar Therapeutics, [5]University of California Medical Center, [6]Stadtmission Heidelberg, [7]University of Michigan Medical Center

Background: Wilson disease (WD) is a rare autosomal recessive disorder caused by copper (Cu) accumulation in the liver and brain due to mutations in the P-type ATPase Cu transporter ATP7B. Tiomolybdate choline (TMC) is an oral once daily Cu-binding agent being investigated for the treatment of WD. The current oral chelators for WD present a less than satisfactory treatment in WD patients as they can cause neurological worsening, potential debilitating side effects, and have multiple times per day dosing regimens. **Methods:** This open-label, single-arm Phase 2 trial evaluated the effect of once daily repeat-dose TMC on Cu balance, safety, and tolerability in patients with WD. To determine Cu balance, patient intake (food and drink) and output (feces and urine) were collected and analyzed for Cu content during a pre-treatment baseline period (study days -4 through -1) and two treatment periods (study days 1-8 and 25-39). In the first treatment period, patients received 15 mg/day. In the second treatment period, the dose was increased to 30 mg/day on study day 29, except in patients who experienced an elevation in alanine aminotransferase (ALT) and were reduced to 15 mg every other day. **Results:** A total of 9 WD patients were enrolled. One patient discontinued the study early on due to a protocol violation of failing to discontinue penicillamine treatment. In the 8 who completed the study, the cumulative mean daily Cu balance was statistically significantly lower compared to pre-treatment baseline during the TMC 15 mg/day period (days 1-28) and during the whole study period (days 1-39). This improvement was due to increased fecal Cu excretion with TMC treatment. No clinically significant changes were observed in laboratory parameters, vital signs, physical examinations, or ECG results. Any elevations in ALT that occurred were grade 1 or 2 and reversible with dose modulation. No serious adverse events or deaths were reported, and no treatment-emergent adverse events (TEAEs) led to TMC discontinuation. **Conclusion:** TMC treatment resulted in a rapid and persistent improvement in daily Cu balance, due to increased fecal excretions of Cu. No significant safety issues were identified, and all TEAEs were reversible. Combined with the long-term efficacy and safety data presented at EASL 2025, the results from this key Cu balance trial indicate that TMC may provide meaningful clinical benefit in WD patients and could serve as a possible future model for early-stage drug development programs in WD.

Disclosures: Aftab Ala: Nothing to Disclose, Thomas Sandahl: Arbormed: Advisor, Orphalan: Speaking and Teaching, Alexion: Grant/Research Support, Univar: Consultant, Ultragenyx: Advisor, Anna Czlonkowska: Nothing to Disclose, Chandler Robinson: Monopar Therapeutics Inc.: Employee, Andrew Cittadine: Monopar Therapeutics: Executive role, Valentina Medici: Orphalan: Advisor, Arbormed: Research Grant, Ultragenix: Research Grant, Alexion: Advisor, Vivet: Grant/Research Support, Eton Pharmaceuticals: Consultant, Mars Inc.: Advisor, Karl Heinz Weiss: Nothing to Disclose, Frederick Askari: Alexion: Advisor, Ultragenyx Pharmaceutical, Inc.: Advisor, Vivet: Advisor, Deep Genomics: Advisor, Intercept: Advisor

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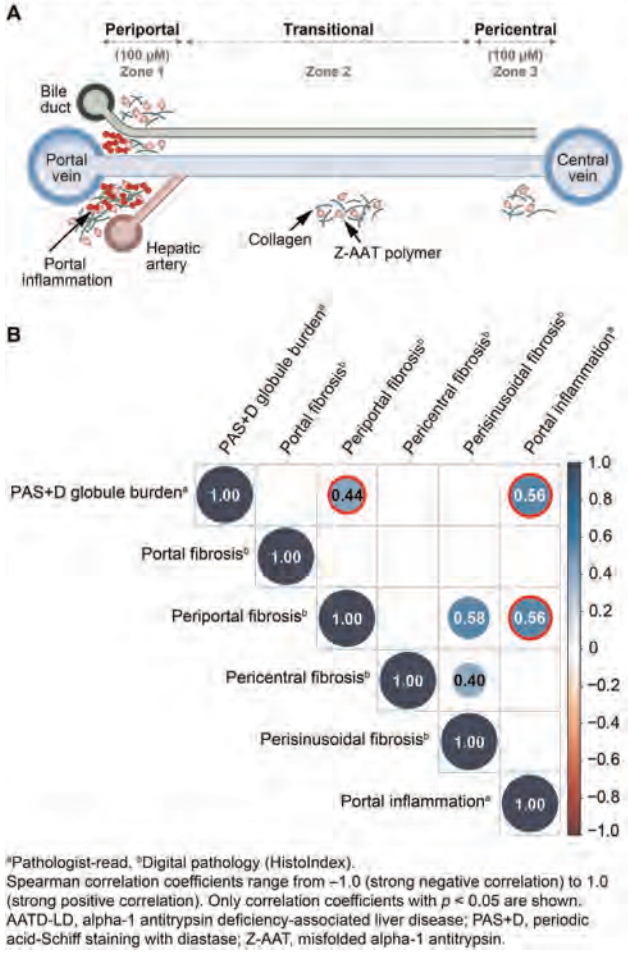
0074 | ARTIFICIAL INTELLIGENCE-BASED QFIBROSIS® ANALYSIS CORRELATES WITH CHANGES IN HISTOLOGICAL FEATURES IN ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE FOLLOWING TREATMENT WITH FAZIRSIRAN

Vandana Gupta[1] Feng Hong[1] Xinhua Hu[1] Ying-Wooi Wan[1] Jen-Chieh Chuang[1] Jie Cheng[1] William Weber[1] Natasha Darras[1] Susana Gonzalez[1] Paresh Thakker[1] Nirav Desai[1] Thomas Schluep[2] James Hamilton[2] Kutbuddin Akbary[3] Dean Tai[3] Pavel Strnad[4] Virginia Clark[5] Romil Saxena[6] Kay Washington[7] Cynthia Behling[8], [1]Takeda Development Center Americas, Inc., Cambridge, MA, USA, [2]Arrowhead Pharmaceuticals, Inc., Pasadena, CA, USA, [3]HistoIndex Pte Ltd, Singapore, Singapore, [4]University Hospital RWTH Aachen, Aachen, Germany, [5]University of Florida, Gainesville, FL, USA, [6]Emory School of Medicine, Atlanta, GA, USA, [7]Vanderbilt University Medical Center, Nashville, TN, USA, [8]Independent Pathologist Consultant, San Diego, CA, USA

Background: Change in liver fibrosis is considered a clinically meaningful endpoint for the evaluation of investigational therapies in liver disease; automated scoring methods that objectively evaluate histological changes in liver fibrosis over time are needed. qFibrosis® (qF) is an artificial intelligence (AI)-based fibrosis quantification method that incorporates collagen morphology and zonal distribution (Figure A). This study aimed to compare qF analyses with histological liver features in patients with alpha-1 antitrypsin deficiency-associated liver disease (AATD-LD) treated with fazirsiran (an investigational small interfering RNA therapy) using data from phase 2 clinical trials. **Methods:** Liver biopsy samples from fazirsiran- or placebo-treated patients with AATD-LD enrolled in AROAAT-2001/-2002 trials (NCT03945292/NCT03946449) were analyzed by qF. Previously developed models were used to quantify qF as individual composite index values for a given sample (Gupta V *et al. J Hepatol* 2025;82:S719). Correlation of qF (METAVIR) stage and continuous value with intrahepatic misfolded alpha-1 antitrypsin (Z-AAT) burden assessed by periodic acid-Schiff staining with diastase (PAS+D) and histological features (portal inflammation, interface hepatitis, hepatocyte cell death) were evaluated by Spearman correlation analysis. **Results:** Overall, data from 41 patients from AROAAT-2001 (n = 25) and AROAAT-2002 (n = 16) were analyzed. When analyzed cross-sectionally (78 pre-/post-treatment visit data points), qF (METAVIR) stage and continuous value positively correlated with PAS+D globule burden, portal inflammation, interface hepatitis and hepatocyte cell death. Longitudinal analysis demonstrated that change in qF (METAVIR) stage and continuous value post-treatment with fazirsiran (29 data points) correlated with change in PAS+D globule burden, portal inflammation and interface hepatitis. After treatment with fazirsiran, change in PAS+D globule burden positively correlated with change in portal inflammation (46 data points; $\rho = 0.56$; $p < 0.0001$), specifically periportal fibrosis (37 data points; $\rho = 0.44$; $p < 0.001$; Figure B). **Conclusion:** METAVIR fibrosis assessed by digital pathology (qF analyses) positively correlated with PAS+D globule burden, portal inflammation, interface hepatitis and hepatocyte cell death in liver biopsy samples from patients with AATD-LD. This study suggests a spatial and pathobiological relationship between change in disease-driving Z-AAT globule burden and changes in portal inflammation and liver fibrosis after fazirsiran treatment. AI-based digital pathology approaches may support therapeutic development in AATD-LD but require validation in larger cohorts with longer observation periods. Writing support provided by R Tooze, Oxford PharmaGenesis.

Figure. (A) Illustration of the zonal locations of fibrosis and (B) correlation of change in PAS+D globule burden with portal-based inflammation and periportal fibrosis in patients with AATD-LD.



[a]Pathologist-read, [b]Digital pathology (HistoIndex).
Spearman correlation coefficients range from −1.0 (strong negative correlation) to 1.0 (strong positive correlation). Only correlation coefficients with $p < 0.05$ are shown.
AATD-LD, alpha-1 antitrypsin deficiency-associated liver disease; PAS+D, periodic acid-Schiff staining with diastase; Z-AAT, misfolded alpha-1 antitrypsin.

Disclosures: Vandana Gupta: Takeda Pharmaceuticals: Employee, Feng Hong: Nothing to Disclose, Xinhua Hu: Nothing to Disclose, Ying-Wooi Wan: Nothing to Disclose, Jen-Chieh Chuang: Takeda: Employee, Jie Cheng: Nothing

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0075 | REPLACING CREATININE WITH CYSTATIN C ENHANCES MORTALITY PREDICTION IN ALL MODERN LIVER ALLOCATION SCORES

Giuseppe Cullaro[1] Manuel Rodriguez-Peralvarez[2] Ignacio Roca[3] Elizabeth Verna[4] Andrew Allegretti[5] Kavish Patidar[6] ADRIAN GADANO[7] Fernando Cairo[8] Jennifer Lai[9] Ezequiel Mauro[10], [1]Columbia University Irving Medical Center, [2]Hospital Universitario Reina Sofía, IMIBIC, [3]Hospital El Cruce de Florencio Varela, [4]Columbia University Medical Center, [5]Massachusetts General Hospital, [6]Houston Methodist Hospital, [7]Hospital Italiano de Buenos Aires, [8]HOSPITAL EL CRUCE, [9]UCSF, [10]Hospital Clinic i Provincial de Barcelona

Background: Among patients with decompensated cirrhosis, Cystatin C (CysC) more accurately captures kidney function compared to serum creatinine (sCr) and therefore should better predict mortality in liver transplant candidates. However, the impact of replacing sCr with CysC in modern liver allocation scores remains uncertain. **Methods:** We combined data from 1,301 patients with CysC measured during transplant evaluation at UCSF (USA), Hospital El Cruce, and Hospital Italiano (Argentina) between 2014-2024. CysC (mg/L) and sCr (mg/dL) were treated as interchangeable on a 1:1 scale. We compared the impact of replacing sCr with CysC in the MELD-Na, MELD 3.0, and GEMA-AI models through comparisons of AUCs and categorical net reclassification indices (NRI). Patients were stratified into 5 risk tiers (6-9, 10-19, 20-29, 30-39, 40+) to calculate NRI. We evaluated factors associated with reclassification including age, sex, hospital, Child-Pugh score (CPS), and Sarcopenia HIBA score. **Results:** We analyzed 383 patients from Hospital Italiano, 397 from Hospital El Cruce, and 521 from UCSF ($N = 1,301$). The cohort was 38.6% female, mean age 53.9 ± 11.2 years, CPS 9.0 ± 2.1, CKD-EPI eGFR 91.0 ± 28.9 mL/min/1.73m², Royal Free GFR 67.4 ± 27.7 mL/min, baseline MELD-Na 19 ± 6, MELD 3.0 15 ± 8, and GEMA-AI 18 ± 6. There were 61 90-day deaths (5.6% in Argentina, 3.3% in the US). CysC substitution increased scores by 1.9 ± 2.0 points for MELD-Na, 4.5 ± 3.1 for MELD 3.0, and 2.8 ± 2.3 for GEMA-AI. AUCs remained similar (MELD-Na: 0.78 vs 0.79, $p = 0.09$; MELD 3.0: 0.78 vs 0.79, $p = 0.58$; GEMA-AI: 0.77 vs 0.80, $p = 0.07$), but NRI analysis showed significant improvement. Overall NRI was +10.0% for MELD-Na, +13.7% for MELD 3.0, and +15.5% for GEMA-AI (all $p < 0.05$). Among 90-day deaths, 100% of reclassified patients moved to higher risk tiers: MELD-Na: 28% (18/61), MELD 3.0: 57% (35/61), GEMA-AI 39% (23/59) (Figure 1). Reclassified patients were more likely to be female (45 vs 33% for MELD 3.0, 48 vs 35% for GEMA-AI), had higher sarcopenia HIBA (-0.3 vs -0.9 for MELD-Na, -0.5 vs -1.0 for MELD 3.0, -0.1 vs -1.0 for GEMA-AI) and higher mortality (6.7% vs 4.2% for MELD-Na, 5.8% vs 3.7% for MELD 3.0, 7.3% vs 3.7% for GEMA-AI) ($p < 0.05$ for all comparisons). **Conclusion:** In a geographically diverse cohort, replacing sCr with CysC significantly improves risk stratification across MELD-Na, MELD 3.0, and GEMA-AI models, without compromising discrimination. CysC consistently identifies high-risk patients, particularly those with sarcopenia as indicated by sarcopenia HIBA score, leading to appropriate upward reclassification of all deaths. These results support incorporating CysC into liver allocation models to enhance prognostic accuracy.

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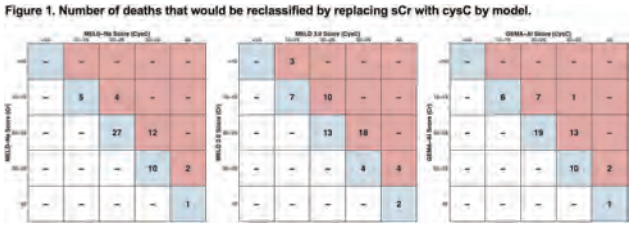

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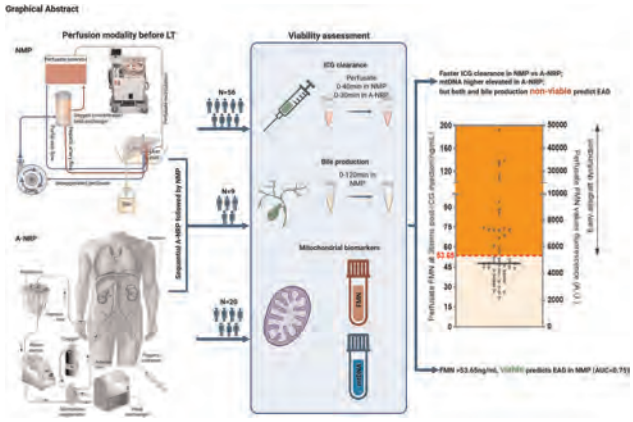
0076 | LIVER VIABILITY ASSESSMENT DURING NORMOTHERMIC MACHINE PERFUSION AND NORMOTHERMIC REGIONAL PERFUSION USING INDOCYANINE GREEN CLEARANCE AND MITOCHONDRIAL BIOMARKERS: A PROSPECTIVE STUDY

Xiaojun Cai[1] Zixin Sha[1] Dana Perry[1] Burcin Taner[1] Liu Yang[1] Kristopher Croome[1], [1]Mayo Clinic Florida

Background: Ex-vivo normothermic machine perfusion (NMP) and abdominal normothermic regional perfusion(A-NRP) are emerging strategies for reconditioning and preserving marginal donor livers. However, objective and reliable biomarkers to evaluate graft viability and predict post-transplant outcomes remain limited, with current assessments relying heavily on clinical judgment. Indocyanine green (ICG), a hepatocyte-specific fluorescent dye, has been extensively utilized in liver surgery, including liver transplantation (LT). This study aimed to evaluate the utility of ICG clearance testing (IGT) and mitochondrial biomarkers—flavin mononucleotide (FMN) and mitochondrial DNA (mtDNA)—during NMP and A-NRP to assess graft quality prior to liver transplantation (LT). **Methods:** Perfusate and bile samples from human donor livers with NMP and A-NRP experience were collected at Mayo Clinic Florida. ICG kinetics, FMN levels, and mtDNA expression were analyzed. Associations between these biomarkers and clinical outcomes, including early allograft dysfunction (EAD) and primary perfusion syndrome (PRS), were evaluated. **Results:** A total of 72 donor livers were included: 63 from donation after circulatory death (DCD) and 9 from donation after brain death (DBD). No patient deaths or graft failures occurred in this cohort. The ICG retention rate at 5 minutes (ICGR5) was significantly lower in NMP compared to A-NRP ($p < 0.001$). However, ICG clearance did not differ significantly between EAD and non-EAD groups. FMN levels in the perfusate predicted EAD with a c-statistic of 0.7465 (95% CI: 0.6019–0.8912, $p = 0.0028$), and a threshold of 53.65 ng/mL was identified as optimal. Perfusate mtDNA levels were significantly lower in NMP than in A-NRP ($p < 0.05$), but mtDNA concentrations did not differ between EAD and non-EAD groups. None of the biomarkers—including ICG retention, FMN, or mtDNA—were predictive of PRS. **Conclusion:** This first prospective study demonstrates that FMN released during NMP holds promise as a predictive biomarker for EAD, potentially enhancing pre-implantation risk stratification. In our cohort, all transplanted donor livers showed effective pre-procurement ICG clearance. While there is no statistically significant difference between the EAD and PRS groups, these findings provide a strong foundation for further research, particularly in the evaluation of marginal livers.



Disclosures: Xiaojun Cai: Nothing to Disclose, Zixin Sha: Nothing to Disclose, Dana Perry: Nothing to Disclose, Burcin Taner: Nothing to Disclose, Liu Yang: Nothing to Disclose, Kristopher Croome: Nothing to Disclose

0077 | IMPACT OF ACUITY CIRCLES POLICY ON ABO BLOOD TYPE-RELATED WAITLIST OUTCOMES IN LIVER TRANSPLANTATION

Dilara Hatipoglu[1] Anna Goebel[1] K Rajender Reddy[1] Nadim Mahmud[2], [1]University of Pennsylvania, [2]Hospital of the University of Pennsylvania

Background: We aimed to assess the impact of Acuity Circles (AC) allocation policy on ABO blood type–related disparities in liver transplant waitlist outcomes. **Methods:** This retrospective cohort study utilized data from the United Network for Organ Sharing (UNOS).

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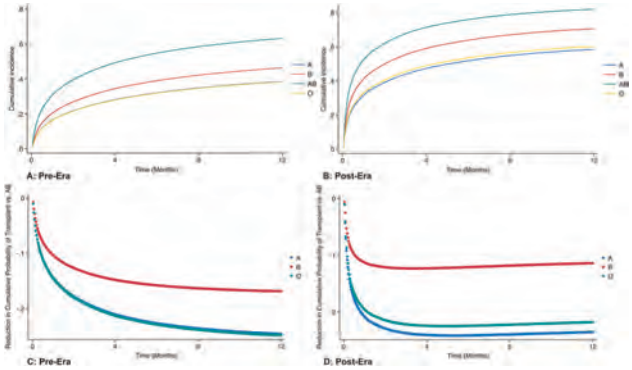
The study included adult patients listed for liver transplantation between 2/2002 and 09/2023. Patients with hepatocellular carcinoma (HCC) exceptions and those listed for multi-organ transplantation were excluded. Data were stratified by pre- and post-AC reform era based on policy initiation in 2/2020. The primary exposure was recipient ABO type and the primary outcome was time to transplant in months. Median spline plots were used to visualize time to transplant by MELD score and ABO type in each era. A Fine and Gray competing risk regression analysis was performed over a one-year time horizon, adjusting for age, race, sex, BMI, etiology of liver disease, MELD score at listing, ascites category, hepatic encephalopathy grade, and U.S. region. Competing events included mortality, living donor transplant, and delisting. Cumulative incidence probabilities of transplant for each ABO type were computed relative to AB for each era. **Results:** A total of 179, 376 patients were included, of whom 34,433 were listed for transplant following AC reform. Post-AC patients were more likely to be female (41.3% vs 38.4%, $p < 0.001$), obese (39.0% vs 36.6%, $p < 0.001$), had higher median MELD score at listing (21 vs 17, $p < 0.001$), and experienced shorter median time to transplant (0.5 vs 1.9 months, $p < 0.001$). Blood type distribution showed a statistically significant ($p < 0.036$) increase in transplant rates for patients of type A (37.9% vs 37.6%), type AB (3.9% vs 3.8%), and type O (46.6% vs 46.4%), while type B decreased group (11.6% vs 12.1%). Time to transplant, stratified by ABO type and MELD score at listing, demonstrated a notable reduction in wait time, particularly for patients with lower MELD scores following AC reform compared to the pre-policy era. In competing risk models, there was a significant interaction between ABO type and policy era ($p < 0.0001$). Relative to AB, patients with blood types B and O had less reduction in cumulative probability of transplant in the post-AC era relative to pre-AC, though absolute disparities remained (Figure 1). **Conclusion:** Acuity circle policy implementation resulted in more equitable distribution in transplant outcomes by recipient ABO type, though disparities in access remain.



Disclosures: Dilara Hatipoglu: Nothing to Disclose, Anna Goebel: Nothing to Disclose, K Rajender Reddy: Nothing to Disclose, Nadim Mahmud: Grifols: Grant/Research Support

0078 | CONTEMPORARY PATTERNS IN OUT OF SEQUENCE ALLOCATION IN LIVER TRANSPLANTATION

Jacqueline Henson[1] Xuyang Xia[1] Ryan McDevitt[1] Norine Chan[1] Andrew Barbas[1] Lindsay King[1] Andrew Muir[1] Debra Sudan[1] Stuart Knechtle[1] Lisa McElroy[1], [1]Duke University

Background: Candidates for deceased donor organ allocation are prioritized by the match run. A deviation from this rank order is termed out-of-sequence (OOS) allocation. OOS is intended as a mechanism to expedite organ placement and improve utilization in circumstances when standard allocation is not feasible. OOS has increased in recent years, though contemporary patterns of use of OOS allocation in liver transplantation (LT) are not well characterized. We aimed to describe current OOS allocation practices in LT and evaluate their association with organ utilization. **Methods:** We conducted a retrospective cohort study using the Organ Procurement and Transplantation Network Potential Transplant Recipient dataset to examine the evolution in OOS allocation from 2019 and 2023. We examined OOS prevalence, timing, and variability across Organ Procurement Organizations (OPO) and transplant centers. OPO- and center-level characteristics were obtained from the Scientific Registry of Transplant Recipients OPO- and program-specific reports. OPO-level organ utilization was assessed using the adjusted observed/expected donor yield. Center-level offer acceptance was evaluated using the adjusted observed/expected offer acceptance ratios. Chi-square testing and correlation were used to compare groups and evaluate associations. **Results:** From 2019 to 2023, the proportion of match runs with OOS allocation rose from 4% (490/11427) to 13% (1880/14885) ($p < 0.001$). This proportion increased for nearly all OPOs (median 12% from 3%), and there was broader center participation (76% vs. 52%, $p < 0.001$). In 2023, OPO-level OOS use varied and ranged from 2-45% (2019: range 0-19%). At the center level, OOS accounted for as many as 45% of accepted offers (median 8%, interquartile range 2-16%) in 2023. The geographic distribution of OPO OOS use by quartile along with the top participating centers is shown in Figure 1. OOS events occurred earlier in the match run in 2023 (median sequence number 15 vs. 31) and sooner after initiation (median 19.8 vs. 21.2 hours). In addition, a greater proportion occurred prior to donor clamp time (67% vs. 44%, $p < 0.001$). There was no

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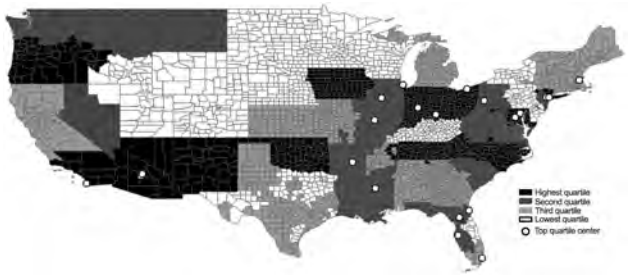
significant correlation between OPO-level OOS use and adjusted observed/expected donor yield ($r = 0.20$, $p = 0.13$), though OOS acceptance at the center level was associated with adjusted offer acceptance ratios (overall: $r = 0.37$, $p < 0.001$; hard-to-place organs: $r = 0.43$, $p < 0.001$). **Conclusion:** OOS allocation has increased significantly in LT and is being initiated earlier in the allocation process. The highest use is concentrated among a subset of OPOs and transplant centers, often in overlapping geographic areas. OPO-level OOS use was not associated with improved organ utilization. These findings highlight the need for further evaluation and potential further standardization of OOS practices in LT.



Disclosures: Jacqueline Henson: Nothing to Disclose, Xuyang Xia: Nothing to Disclose, Ryan McDevitt: Nothing to Disclose, Norine Chan: Nothing to Disclose, Andrew Barbas: Nothing to Disclose, Lindsay King: Nothing to Disclose, Andrew Muir: Gilead: Grant/Research Support, Cymabay: Grant/Research Support, Ultragenyx: Grant/Research Support, Regcell: Consultant, Debra Sudan: CareDx, Inc: Grant/Research Support, Paragonix: Grant/Research Support, Transmedics: Grant/Research Support, VectivBio: Grant/Research Support, Shire: Grant/Research Support, Stuart Knechtle: Nothing to Disclose, Lisa McElroy: CareDx: Grant/Research Support, Veloxis: Grant/Research Support, NIMHD: Grant/Research Support, NIDDK: Grant/Research Support

0079 | OUTCOMES FOR PATIENTS LISTED FOR LIVER TRANSPLANTATION WITH LOW MELD-NA SCORES: HIGH FREQUENCY OF DEATH, REMOVAL FROM WAITLIST AND LIVER TRANSPLANTATION

Hamza Dahshi[1] Ahmad Anouti[2] Thomas Cotter[3] Emaree Cobb[4] Alan Hutchison[5] Michael Charlton[6] Mary Rinella[5], [1]Case Western Reserve University School of Medicine, [2]University of Texas Southwestern, [3]UT Southwestern Medical Center, [4]University of Chicago, [5]The University of Chicago, [6]Madrigal Pharmaceuticals

Background: The MELD-based score remains the cornerstone in liver transplant (LT) organ allocation, prioritizing those with higher scores guided by the 'sickest first' principle. Organ acquisition for low-MELD LT candidates (e.g. < 15, with 15 identified as a threshold for listing for LT) remains challenging, despite this subset remaining at risk of adverse outcomes, while their disease trajectory while waitlisted remains poorly characterized. This study investigates the evolution of MELD-Na among waitlisted LT candidates, and the role of liver disease etiology and disease-modulating risk factors. **Methods:** We performed a retrospective analysis of adult LT candidates patients listed between 2016 and 2022 on the UNOS database. MELD-Na trajectories were evaluated at 3, 6, 9, and 12 months post-listing. Fine & Gray subdistribution hazard regression was used to assess predictors of MELD progression, accounting for transplant and death as competing events. Survival was assessed via Kaplan–Meier. **Results:** Among 76,205 adult first-time liver transplant candidates, 37.5% had MELD-Na scores < 15 at listing. At 6 months, 17.2% of patients with MELD-Na < 15 had a ≥ 4-point increase in MELD-Na, decreasing to 11.76% by 12 months. Patients with delta MELD ≥ 4 at 3 months had a 1-year survival rate of 85.8% (95% CI: 85.1–86.6), compared to 94.6% (95% CI: 94.4–94.8) in delta MELD < 4 ($p < 0.001$). Starting from a MELD score ≥ 11, delta MELD ≥ 4 was the first point at which survival decreased below 90% and was distinct from delta MELDs 1–2. As delta MELD increased beyond 4 points (i.e., ≥ 5), 1-year survival continued to decline progressively. At 1 year, patients with MELD < 15 had a survival rate of 95.9% (95% CI: 95.6–96.1), while those with MELD ≥ 15 had a significantly lower survival of 89.1% (95% CI: 88.8–89.4, $p < 0.001$) (Figure 1). Competing risk regression identified significant predictors of MELD increase ≥ 4. Compared to alcohol-associated cirrhosis, patients with metabolic dysfunction-associated steatotic liver disease (MASLD) (HR 1.36, 95% CI: 1.28–1.44), and those with cholestatic or autoimmune liver disease (PSC, PBC, AIH) (HR 1.51, 95% CI: 1.41–1.62) had significantly higher risk of worsening MELD. In contrast, HCC (HR 0.68, 95% CI: 0.64–0.71) and Black race (HR 0.86, 95% CI: 0.82–0.90) were associated with significantly lower risk of MELD worsening (Table 1). Among patients with missing MELD at 6 months ($n = 42{,}009$), 72% had undergone transplant, 8% had died, and 20% had been removed or were lost to follow-up. **Conclusion:** A substantial proportion of patients listed with MELD-Na < 15 experience significant deterioration, with delta MELD-Na ≥ 4 as a meaningful threshold predicting death and a transition from expected variability to clinical deterioration. MASLD and cholestatic/autoimmune liver disease are associated with greater risk. These findings underscore the need to revisit referral thresholds and monitoring intensity for low MELD-Na patients.

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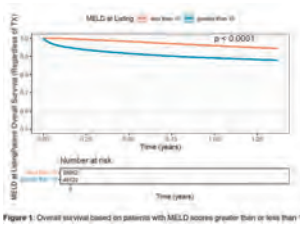

Figure 1: Overall survival based on patients with MELD scores greater than or less than 15

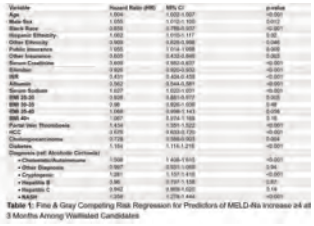

Table 1: Fine & Gray Competing Risk Regression for Predictors of MELD-Na increase ≥4 at 3 Months Among Waitlisted Candidates

Disclosures: Hamza Dahshi: Nothing to Disclose, Ahmad Anouti: Nothing to Disclose, Thomas Cotter: Nothing to Disclose, Nothing to Disclose, Emaree Cobb: Nothing to Disclose, Alan Hutchison: Nothing to Disclose, Michael Charlton: Nothing to Disclose, Mary Rinella: akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant

0080 | RISK PREDICTORS FOR RECURRENT AND DE NOVO MASLD POST LIVER TRANSPLANTATION

Drew Castleberry[1] Sai Nikhila Ghanta[1] Aakash Rana[2] Mauricio Garcia Saenz de Sicilia[1] Srikanth Vallurupalli[1] Ragesh Babu Thandassery[1], [1]University of Arkansas for Medical sciences, [2]Central Arkansas Veterans Healthcare System

Background: Risk factors for recurrent metabolic dysfunction associated steatotic liver disease (R-MASLD) and de-novo MASLD (D-MASLD) post liver transplantation (LT) are not well understood. Epicardial fat thickness (EFT) is a well-established indicator of metabolic syndrome. We studied the characteristics of R-MASLD and D-MASLD in LT and its correlation with EFT and other indicators of metabolic health. **Methods:** 173 patients who underwent LT between Jan. 2015 and June 2019 at a single center were included in the study. Vibration controlled transient elastography (Fibroscan®) was performed every year post-LT, and liver stiffness measurement (>10 kPa possible cACLD, >20kPa- definite cACLD) and continued attenuation parameter ($\geq$ 275 db/m - hepatic steatosis) were calculated. Hepatic steatosis and presence of at least one cardiometabolic risk factor defined MASLD. Epicardial fat thickness (EFT) on pre-LT trans thoracic echocardiogram (TTE) was calculated. **Results:** Mean age pre-LT was 54.6 $\pm$10.7 years (89.3% Caucasians,59.2% males) with median BMI 29 (24.6-32.8). Indications for LT included 39.8% MASLD and 60.2% non-MASLD etiologies (alcohol 24.3%, chronic hepatitis C 23.4%). 82.6% were alive at 5 years post-LT, median (IQR) follow-up of 7.5 (6.6-8.9) years. At 5 years post-LT, MASLD was identified in 57.3% (D-MASLD 38.8%, R-MASLD in 18.4%). In the non-MASLD pre-LT group, 64.5% developed D-MASLD, and in MASLD pre-LT group, 53.7% developed R-MASLD. Definite cACLD developed in 4.9% and possible cACLD in 20.4%. Higher proportion of patients with D-MASLD developed possible cACLD ($p=0.04$), Table-1. None developed clinically significant portal hypertension (as

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defined by Baveno VII criteria). Obesity at 1 year post-LT increased the risk of developing R-MASLD (hazard ratio (CI) 4.1(1.4-11.9), p = 0.007). Similar risk was not observed for D-MASLD. Type of immunosuppressants did not correlate with the risk of developing R-MASLD or D-MASLD. Increased EFT (≥5mm) correlated with D-MASLD (HR = 4.3, CI = 1.7-23.9, p = 0.04) and not R-MASLD. **Conclusion:** In this cohort with high pre-LT prevalence of obesity, significant proportion of patients developed MASLD at 5-year post-LT follow-up, with high rates of both recurrent and de novo MASLD. D-MASLD appears to progress faster to develop possible cACLD. Pre-LT EFT appears to correlate with D-MASLD and obesity at 1-year post-LT with R-MASLD. Emphasis on treatment of obesity and metabolic syndrome is crucial to improve outcomes post-LT.

Table 1

Comparison of recurrent and de novo MASLD post liver transplantation

	Recurrent MASLD	De novo MASLD	
Pre-LT characteristics			
Age pre-LT (SD), years	53.6 (±10.6)	56.1 (±8.4)	p=0.16
Gender (M/F), %	68.4/31.6	77.5/22.5	p=0.001
BMI pre-LT (IQR)	33.2(27.9-35.4)	29.23 (24.9-32.8)	p=0.01
HCC pre-LT, %	15.8	30	p=0.09
SLK, %	8.3	25.0	p=0.19
EFT pre-LT (IQR), mm	1.8(0.9-4.2)	2.0 (1.3-3.2)	p=0.03
Donor age (SD) , years	33.0 (19.4)	33.2(14.2)	p=0.09
Donor BMI (IQR)	26.5(22-28.8)	26(24.4-29.1)	p=0.24
Post-LT characteristics			
BMI at 1 year (IQR)	33.1 (29.2-35.8)	26.7 (24.1-30.3)	p=0.03
Metabolic syndrome at 1 year, %	63.2	50.0	p=0.34
Diabetes Mellitus at 1 year, %	52.6	42.5	p=0.04
FibroScan CAP at 5 years, dB/m	299 (294-327)	301(275-330)	p=0.001
FibroScan LSM at 5 years, kPa	7.1 (5.5-8.9)	5.8(4.5-8.0)	p=0.13
Possible cACLD at 5 years, %	28.6	52.4	p=0.04

MASLD- metabolic dysfunction associated steatotic liver disease, LT- liver transplantation, BMI- body mass index, HCC- hepatocellular carcinoma, SLK- simultaneous liver kidney transplantation, EFT- epicardial fat thickness, CAP- continued attenuation parameter, LSM- liver stiffness measurement, cACLD -compensated advanced chronic liver disease

Disclosures: Drew Castleberry: Nothing to Disclose, Sai Nikhila Ghanta: Nothing to Disclose, Aakash Rana: Nothing to Disclose, Mauricio Garcia Saenz de Sicilia: Nothing to Disclose, Srikanth Vallurupalli: Nothing to Disclose, Ragesh Babu Thandassery: Nothing to Disclose

0081 | COFFEE INTAKE, ADDITIVES, AND LIVER HEALTH: ASSOCIATIONS WITH CIRRHOSIS, HEPATOCELLULAR CARCINOMA, LIVER-RELATED MORTALITY, AND MRI IMAGING BIOMARKERS IN THE UK BIOBANK: A PROSPECTIVE STUDY

Hyunseok Kim[1] Abdelrahman Attia[1] Minsun Kwak[1] Walid Ayoub[1] Derin Celtik[1] Beza Mengistu[2] Kelsy Larios[2] David Kim[3] Alexander Kuo[1] Paul Martin[1] Hirsh Trivedi[1] Aarshi Vipaini[1] Yun Wang[1] Suthat Liangpunsakul[4] Debiao Li[1] Stephen Pandol[1] Shelly Lu[1] Ju Dong Yang[1], [1]Cedars-Sinai Medical Center, [2]UCLA, [3]Rutgers New Jersey Medical School, [4]Indiana University Medical Center

Background: Coffee intake has been linked to lower liver disease risk, but prior studies were mostly cross-sectional, retrospective, or based on small cohorts. Whether associations differ by coffee type (caffeinated vs. decaf), additives (sugar/sweeteners), or metabolic/genetic modifiers remains unclear. Data on coffee and imaging-derived liver biomarkers are also limited. We evaluated associations between coffee intake, type, and additives with incident cirrhosis, hepatocellular carcinoma (HCC), liver-related mortality, and MRI liver biomarkers, including potential effect modification by diabetes, alcohol use, and *PNPLA3* genotype. **Methods:** In UK Biobank (n = 354,957), participants without cirrhosis or HCC at baseline were followed for liver outcomes. Coffee intake, type, and additives were assessed by touchscreen questionnaire. Outcomes were identified through linked hospital and death records. Multivariable Cox models estimated adjusted hazard ratios (HRs). In a liver MRI subcohort (~10 years post-baseline; n = 76,114), coffee intake was reassessed, and cross-sectional associations with liver fat (PDFF), iron, and fibroinflammation (corrected T1 or cT1) were examined. cT1 was modeled as a binary trait using a clinical threshold of ≥800ms. **Results:** Over a median 13-year follow-up, ≥5 cups/day was associated with reduced risk of cirrhosis (HR 0.67 [95% CI 0.58-0.78]), HCC (0.53 [0.34-0.83]), and liver-related mortality (0.58 [0.45-0.74]) (Table). Protective associations were observed for both caffeinated and decaffeinated coffee, and were strongest for unsweetened coffee; sugar and artificial sweeteners modestly attenuated benefits. In the MRI subcohort, higher coffee intake was associated with lower PDFF (-0.83%, 95% CI -1.02 to -0.65) and liver iron (-0.018, 95% CI -0.029 to -0.007). Higher coffee intake was also associated with lower odds of elevated cT1: ORs were 0.76 (0.65-0.89) for low, 0.82 (0.69-0.98) for moderate, and 0.80 (0.64-0.99) for high intake-suggesting a potential plateau at moderate-to-high intake levels. Associations were attenuated among participants with diabetes but remained consistent across alcohol use categories and *PNPLA3* genotype. **Conclusion:** In this large, prospective cohort, higher coffee intake was associated with favorable liver outcomes and imaging biomarkers. Findings support coffee, especially when consumed without additives, as a potentially accessible and low-cost strategy for liver disease prevention in the general population.

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Table: Associations Between Coffee Intake and Liver Outcomes and MRI Biomarkers

Coffee Intake	Cirrhosis HR (95% CI)	HCC HR (95% CI)	Liver Mortality HR (95% CI)	Δ PDFF (%, 95% CI)	cT1 ≥800ms OR (95% CI)	Δ Liver Iron (mean, 95% CI)
None (ref)	1.00	1.00	1.00	0.00	0	0.000
Low (1–2 cups/day)	0.79 (0.71-0.87)	0.76 (0.57-0.99)	0.69 (0.58–0.82)	-0.28 (-0.42, -0.15)	0.76 (0.65-0.89)	-0.0014 (-0.0090, 0.0061)
Moderate (3–4 cups/day)	0.64 (0.56-0.73)	0.65 (0.47-0.92)	0.59 (0.48–0.73)	-0.37 (-0.52, -0.22)	0.82 (0.69-0.98)	-0.0077 (-0.0163, 0.0009)
High (≥5 cups/day)	0.67 (0.58-0.78)	0.53 (0.34–0.83)	0.58 (0.45–0.74)	-0.83 (-1.02, -0.65)	0.80 (0.64-0.99)	-0.0183 (-0.0291, -0.0074)

Adjusted for age, sex, race/ethnicity, household income, metabolic traits, alcohol intake, smoking, and *PNPLA3* genotype

Disclosures: Hyunseok Kim: Nothing to Disclose, Abdelrahman Attia: Nothing to Disclose, Minsun Kwak: Nothing to Disclose, Walid Ayoub: Intercept: Speaking and Teaching, Mirum: Grant/Research Support, GSK: Grant/Research Support, Madrigal: Grant/Research Support, Cymabay: Consultant, Ipsen: Grant/Research Support, Zydus: Grant/Research Support, Gilead: Grant Research Support, Derin Celtik: Nothing to Disclose, Beza Mengistu: Nothing to Disclose, Kelsy Larios: Nothing to Disclose, David Kim: Nothing to Disclose, Alexander Kuo: Nothing to Disclose, Paul Martin: Nothing to Disclose, Hirsh Trivedi: Nothing to Disclose, Aarshi Vipaini: Nothing to Disclose, Yun Wang: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Debiao Li: Nothing to Disclose, Stephen Pandol: Nothing to Disclose, Shelly Lu: Nothing to Disclose, Ju Dong Yang: Exact Sciences: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Exelixis: Consultant, Fujifilm Medical Sciences: Consultant

0082 | TEMPORAL AND DEMOGRAPHIC TRENDS IN LIVER DISEASE AND LIVER CANCER MORTALITY ATTRIBUTABLE TO SUBSTANCE USE DISORDERS IN THE UNITED STATES, 1999–2020

Raghava Rao Alluri[1] Priyasi Monga[2] Sandeep Kotnani[3] Madhu babu Adusumilli[4] Dhrumil Sakariya[5] Nivid Patel[6] Nimrat Dhillon[7] VISHRANT AMIN[8] Hardik Desai[9], [1]Prime South GME Consortium/Harlingen Medical Center Program, [2]Wellstar Spalding Regional Hospital, Griffin, Georgia, [3]Rutgers Monmouth Medical Center, [4]HCA Ocala Florida hospital -UCF, [5]Davao Medical School Foundation Poblacion District, Davao City,Philippines, [6]American university of Barbados, [7]Sri guru Ram das institute of medical sciences and research, vallah, Amritsar, Punjab, [8]HMH JFK University Medical Center, [9]Independent Clinical and Public Health Researcher

Background: Substance use disorders (SUDs) are an emerging contributor to chronic liver disease and hepatocellular carcinoma mortality in the United States. Despite growing awareness of the opioid crisis and poly-substance misuse, the epidemiological contribution of SUDs to liver-related mortality remains insufficiently quantified across sociodemographic and geographic strata. **Methods:** We conducted a retrospective analysis of mortality data from 1999 to 2020 using the CDC WONDER database, identifying deaths due to liver disease or liver cancer in which substance use disorders were listed as a contributing cause. We calculated Annual Percentage Change (APC) to quantify temporal trends, disaggregated by substance type, region, urbanization, state, race, ethnicity, gender, and age group. **Results:** From 1999 to 2020, the absolute number of deaths due to liver disease and liver cancer associated with substance use disorders increased from 3,822 to 10,547 (APC: +2.66%). Opioid-related deaths surged from 76 to 420 (APC: +8.9%), and deaths involving psychoactive drugs rose from 58 to 293 (APC: +8.2%). In contrast, alcohol-related deaths showed a slight decline from 2,718 to 2,594 (APC: –0.23%). Regionally, the South and Midwest demonstrated the highest escalation, with deaths in the South increasing from 687 to 2,718 (APC: +4.99%) and in the South from 960 to 4,098 (APC: +3.92%). By urbanization, nonmetro areas exhibited a notable increase from 253 to 1,066 deaths (APC: +4.8%), while metropolitan areas rose from 346 to 1489 deaths (APC: +4.64%). State-level trends revealed the most significant rise in Indiana, with an (APC: +9.98%), followed by Iowa (APC: +8.07%) and Arkansas (APC: +7.29%). Racial disparities were evident, with Asian or Pacific islander populations experiencing the most accelerated rise—from 36 to 169 deaths (APC: +4.21%). Among Hispanic groups, deaths in Hispanic or Latino individuals grew from 570 to 977 (APC: +0.2%), compared to a rise from 3,223 to 9,541 (APC: +3.0%) in non-Hispanic individuals. Gender-specific analysis showed a steeper increase in females (APC: +3.23%) than males (APC: +2.46%). Age-wise, the 85+ year group exhibited the highest annual rise, with deaths increasing from 39 to 201 (APC: +8.14%), followed by the 65-74 group (APC: +5.69%). **Conclusion:** Our findings reveal a sharp rise in liver-related deaths linked to opioids and psychoactive substances, especially in rural areas, older adults, females, and Asian or Pacific Islanders—emphasizing the need for targeted, population-specific interventions.

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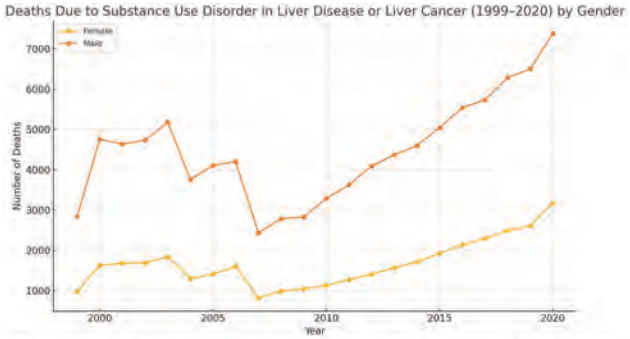

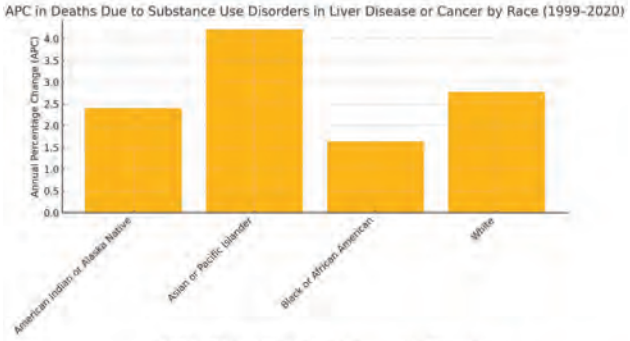

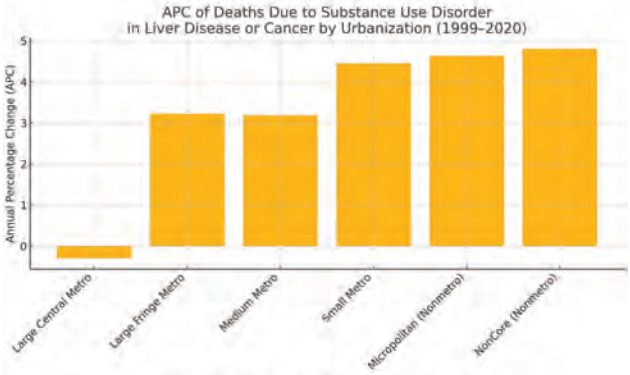

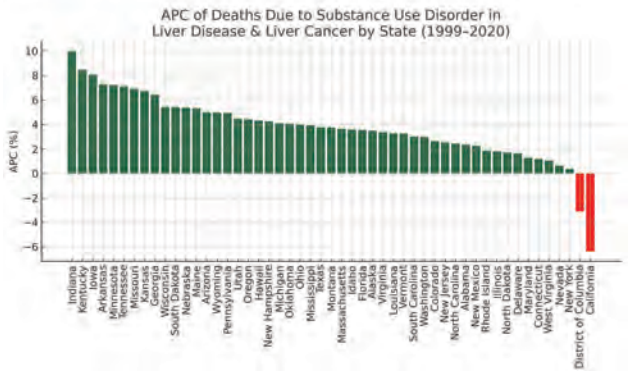

Disclosures: Raghava Rao Alluri: Nothing to Disclose, Priyasi Monga: Nothing to Disclose, Sandeep Kotnani: Nothing to Disclose, Madhu babu Adusumilli: Nothing to Disclose, Dhrumil Sakariya: Nothing to Disclose, Nivid Patel: Nothing to Disclose, Nimrat Dhillon: Nothing to Disclose, VISHRANT AMIN: Nothing to Disclose, Hardik Desai: Nothing to Disclose

0083 | ASSOCIATIONS OF PRIMARY BILIARY CHOLANGITIS AND PRIMARY SCLEROSIS CHOLANGITIS WITH ADVERSE PREGNANCY OUTCOMES: A PROPENSITY-SCORE MATCHED ANALYSIS OF A NATIONAL COHORT

Priyanka Gaur[1] *Tatyana Kushner*[1] *Kate Johnson*[1] *Emma Leipsner*[1], [1]*Weill Cornell Medicine*

Background: Primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) are rare, progressive cholestatic liver diseases with varying phenotypes characterized by pruritus and fibrosis. Understanding of how these diseases impact pregnancy course is limited with counseling often extrapolated from intrahepatic cholestasis of pregnancy (ICP). We sought to leverage a large national dataset to evaluate the independent influence of PBC and PSC on pregnancy outcomes. **Methods:** We performed a population-based retrospective study of pregnant persons ages 12-55 from 2005-2025 using the TriNetX research network with deidentified electronic health record data from 100 U.S. health care organizations. Cohorts were stratified by presence of PSC and PBC up to one year prior to pregnancy diagnosis. A PSC pregnant cohort was compared to a non-PSC pregnant cohort, and a PBC pregnant cohort was compared to a non-PBC pregnant cohort. Primary outcomes were ICP, preterm delivery, preeclampsia, gestational hypertension, postpartum hemorrhage, cesarean section, fetal growth restriction, and stillbirth. Propensity score matching (PSM) with replacement was performed on a 1:1 basis with the nearest neighbor method, and multivariable logistic regression was applied to balanced cohorts. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were reported. **Results:** We identified 5,070,078 pregnant participants of which 480 (0.009%) had PBC and 292 (0.006%) had PSC. There were more individuals in the PSC group who self-reported Black/African American race ($p = 0.02$) and more individuals in the PBC group who self-reported Hispanic/Latino ethnicity ($p = 0.01$). Those with PBC were more likely to have pregestational diabetes and hypertension compared to PSC, and PSC more likely to have inflammatory bowel disease ($p = 0.01$). On univariate analysis, those with PSC had increased odds of preterm delivery, postpartum hemorrhage, preeclampsia, fetal growth restriction, and ICP compared to those without PSC (all $p < 0.05$). After PSM, only ICP was significant (aOR 3.4, 95% CI 1.6-7.0) (Table 1). Compared to pregnant individuals without PBC, those with PBC were at increased odds of preterm delivery, preeclampsia, and ICP in univariate analysis (all $p < 0.05$). These outcomes were not significantly different after PSM. **Conclusion:** Pregnancy outcomes in this population are generally favorable. Pregnant individuals with PBC and PSC had similar risks of preterm delivery and preeclampsia compared to unaffected pregnancies, but those with PSC were more likely to experience ICP. After PSM, these risks

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were attenuated apart from individuals with PSC who were more likely to develop ICP. These findings support the use of ursodeoxycholic acid and antenatal surveillance, given that obstetric risks appear most associated with ICP.

Table 1. Unadjusted and adjusted odds ratios for obstetric outcomes among propensity-score matched cohorts with PSC and PBC compared to pregnancy cohorts without disease status.

Pregnant PSC compared to pregnant non-PSC (n = 282 pairs)				
	OR	95% CI	aOR	95% CI
Preterm delivery	2.3	1.3, 3.9	1.4	0.6, 3.3
Preeclampsia	2.0	1.3, 2.0	1.8	0.9, 3.7
Intrahepatic cholestasis of pregnancy	62.5	43.5, 90.0	3.4	1.7, 7.0
Gestational diabetes	1.3	0.8, 2.1	1.6	0.8, 3.3
Postpartum hemorrhage	2.0	1.1, 3.4	1.4	0.62, 3.3
Cesarean section	1.5	1.0, 2.2	1.2	0.7, 2.1
Fetal growth restriction	2.0	1.3, 3.0	2.0	1.0, 4.1
Stillbirth (too low to calculate)	-	-	-	-
Pregnant PBC compared to pregnant non-PBC (n = 447 pairs)				
	OR	95% CI	aOR	95% CI
Preterm delivery	2.3	1.5, 3.7	1.2	0.60, 2.43
Preeclampsia	1.9	1.3, 2.8	1.5	0.9, 2.6
Intrahepatic cholestasis of pregnancy	14.9	7.9, 27.8	1.8	0.84, 4.0
Gestational diabetes	1.31	0.9, 1.9	1.03	0.63, 1.7
Postpartum hemorrhage	0.99	0.5, 1.9	0.58	0.26, 1.28
Cesarean section	1.33	0.96, 1.9	1.08	0.69, 1.68
Fetal growth restriction	0.89	0.53, 1.5	1.2	0.59, 2.6
Stillbirth (too low to calculate)	-	-	-	-

[1] Covariates in propensity score matching model included age, race, ethnicity, chronic hypertension, pregestational diabetes, systemic lupus erythematosus, rheumatoid arthritis, tobacco use, thyroid disease, cardiac disease, chronic kidney disease, in vitro fertilization, asthma, and obesity (BMI ≥ 30).

Disclosures: Priyanka Gaur: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Kate Johnson: Nothing to Disclose, Emma Leipsner: Nothing to Disclose

0084 | SOCIAL CAPITAL AS A NOVEL POPULATION-LEVEL DETERMINANT OF LIVER-RELATED MORTALITY: A NATIONWIDE COUNTY-LEVEL ANALYSIS

Tiange Zhang[1] *Jennifer Dodge*[1] *Norah Terrault*[1], [1]*University of Southern California*

Background: Social capital - the connections enabling trust and reciprocity in communities - has emerged as an important health determinant, but its association with liver-related mortality has not been examined. **Methods:** Using county-level data for adults aged ≥25 years from CDC WONDER 2010-2019 and ICD-10 coded deaths due to chronic liver diseases (including cirrhosis, hepatocellular carcinoma), liver-related age-adjusted mortality rates (AAMR) were obtained. Social capital was assessed via a validated index of 19 county-level indicators including three subtypes: bonding capital-connections within groups (e.g. similar race, age, class, language); bridging capital-connections across groups (e.g. membership in religious organizations, charities); and linking capital-connections to authorities (e.g. political participation, voter eligibility, linkage to government). Indicators were averaged by subtype (each 0 to 1) and summed for overall social capital score. Quartiles ranked counties from low (Q1) to high (Q4) capital. Linear regression estimated mortality differences by social capital adjusted for county-level covariates. **Results:** Liver-related AAMR were available for 73.3% of US counties, covering 98.7% of all liver-related deaths. Mean social capital scores were overall 1.15 (range 0.71-1.54), bonding 0.65 (0.41-0.78), bridging 0.24 (0.09-0.58), and linking 0.25 (0.11-0.55) (Fig. 1). At county-level, social capital quartiles (Q1 to Q4) showed similar proportions of female (51.5% to 52.0%), while unemployment rates declined (5.6% to 4.8%) and rural residence increased (8.9% to 29.3%) across quartiles. Mean liver-related AAMR was 20.7 (SD 0.8) deaths per 100,000, with rates of 21.7 (SD 1.3), 20.9 (SD 0.6), 20.3 (SD 0.6), and 18.0 (SD 0.6) for counties with Q1 to Q4 social capital, respectively. After adjusting for county-level covariates related to demographics (age, sex), comorbidities (diabetes, obesity, heavy alcohol use), and structural factors (rural residence, unemployment), low overall social capital was associated with 2.7 (95% CI:1.1-4.4), 1.4 (95% CI:0.7-2.0), and 1.2 (95% CI:0.5-1.9) more deaths per 100,000 in Q1-Q3 versus Q4. Bonding and bridging, but not linking, capital were associated with liver-related mortality. **Conclusion:** Lower county-level social capital – especially bonding and bridging types – are independently associated with higher liver-related mortality in a dose-response manner. These results call for greater efforts to characterize social capital and population-level strategies to strengthen social capital as a novel approach to addressing liver disease mortality.

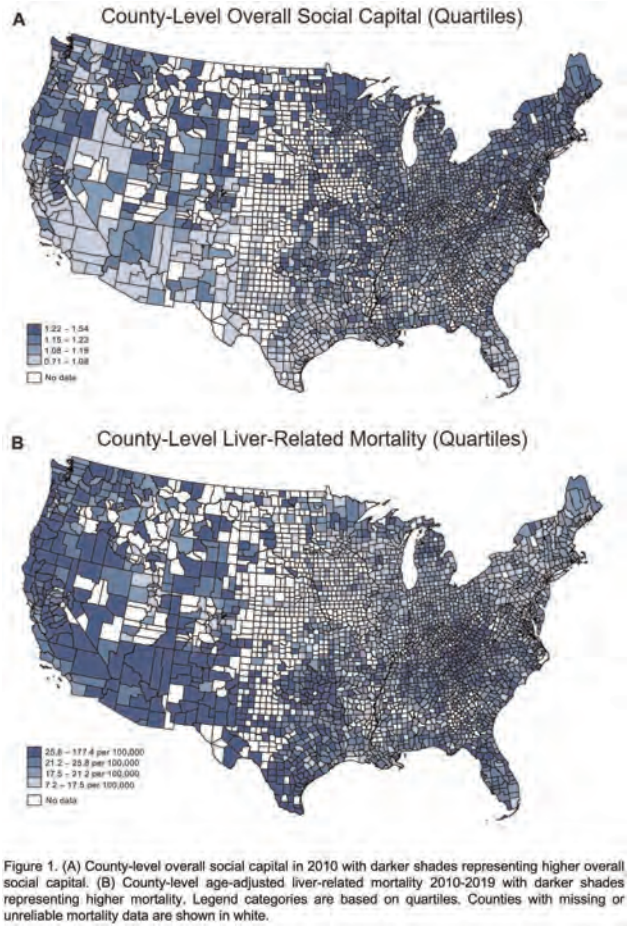

Figure 1. (A) County-level overall social capital in 2010 with darker shades representing higher overall social capital. (B) County-level age-adjusted liver-related mortality 2010-2019 with darker shades representing higher mortality. Legend categories are based on quartiles. Counties with missing or unreliable mortality data are shown in white.

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0085 | PATIENT-REPORTED SYMPTOM BURDEN AS A PREDICTOR OF HOSPITALIZATIONS IN A MULTISITE COHORT OF PATIENTS WITH ADVANCED LIVER DISEASE: RESULTS: FROM THE PACE-LT CONSORTIUM

Nneka Ufere[1] Elizabeth Aby[2] Chengbo Zeng[3] Grace Bizup[1] Enya Zhu[4] Michael Kriss[5] Jon Rice[6] Thomas Leventhal[2] Deepika Devuni[7] Anita Krishnarao[7] Brett Fortune[8] Clara Tow[9] Paola Mejia[9] Lindsay King[10] Jacqueline Henson[4] Sarah Lieber[11] Alvaro Noriega Ramirez[11] Lauren Nephew[12] Patricia Jones[13] Nathaly Cortez Bazan[13] Melanie Hundt[9] Kali Zhou[14] Hyosun Han[14] Hersh Shroff[15] Krista Hunt[15] Shari Rogal[16] Alan Noll[1] Stela Celaj[17] Areej Mazhar[18] Dempsey Hughes[18] Anushka Dalvi[1] Malia Armstrong[1] Lucinda Li[19] Maria Edelen[3] Areej El-Jawahri[1], [1]Massachusetts General Hospital, [2]University of Minnesota, [3]Brigham and Women's Hospital, [4]Duke University, [5]University of Colorado School of Medicine, [6]University of Colorado, [7]University of Massachusetts, [8]Montefiore Medical Center, [9]Montefiore, [10]Duke University School of Medicine, [11]UTSW, [12]Indiana University, [13]University of Miami, [14]USC, [15]UNC Chapel Hill, [16]University of Pittsburgh, [17]UPMC, [18]Northwestern, [19]UCLA

Background: There is a growing body of literature supporting the use of patient-reported outcomes to facilitate symptom assessment in cirrhosis care. We sought to examine the association between patient-reported symptom burden and subsequent 90-day hospitalization in a multicenter cohort of adult outpatients with advanced liver disease (AdvLD). **Methods:** Data was derived from two prospective US observational cohorts: 1) 218 adult outpatients with AdvLD recruited from a single liver transplant center between 8/2018-9/2022; 2) 433 adult outpatients with AdvLD undergoing transplant evaluation recruited from 12 transplant centers between 4/2023-4/2024. Symptom burden was assessed using the validated 10-item revised Edmonton Symptom Assessment System assessing 10 common symptoms in AdvLD: pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, poor well-being, and muscle cramps. Each individual ESAS symptom and total ESAS symptom burden (t-ESAS) was categorized as none or mild (score ranges 0-3 or 0-39, respectively), moderate (ranges 4-6 or 40-69), or severe (ranges 7-10 or 70-100). The primary outcome was a hospitalization within 90 days after completing the ESAS assessment. We calculated adjusted risk ratios of 90-day hospitalization by symptom severity using each individual ESAS symptom scores and total ESAS symptom burden scores, applying inverse-probability weighting (with death as competing risk), adjusting for age, gender, race, ethnicity, hepatic encephalopathy, ascites, and comorbidity burden. **Results:** Among the 651 patients, median age was 59 (IQR: 50-65), 57% were male, 84% were White, 17% were Hispanic, 58% had ascites, and 43% had hepatic encephalopathy. In total, 23% had a hospitalization within 90 days. In adjusted analyses, all individual ESAS symptoms were positively associated with 90-day hospitalization, with tiredness demonstrating the strongest association (aRR = 1.12 [95% CI; 1.06-1.18] per one-unit increase in the tiredness score) (Table). Compared to patients with none or mild symptom burden, those with moderate (aRR = 1.86; 95% CI: 1.38-2.50) and severe (aRR = 2.30; 95% CI: 1.40-3.77) symptom burden had a significantly higher risk of hospitalization within 90 days. **Conclusion:** We found a dose-response relationship between ESAS symptom burden scores and risk of 90-day hospitalization in a multisite cohort of outpatients with AdvLD after controlling for ascites, hepatic encephalopathy, comorbidity burden, and sociodemographic characteristics. Patient-reported symptom burden represents a modifiable risk factor and the results of our study suggest that outpatient ESAS scores may aid in risk-stratification for outpatients with AdvLD. These data provide evidence for the potential role of symptom monitoring interventions to improve healthcare utilization in cirrhosis care.

Table. Adjusted risk ratios of 90-day hospitalization by individual ESAS symptoms and total ESAS symptom burden

Individual ESAS symptom score (0-10)	aRR (95%CI)	p-value
Pain	1.06 (1.02, 1.11)	0.006
Tiredness	1.12 (1.06, 1.18)	<0.001
Drowsiness	1.09 (1.03, 1.14)	<0.001
Nausea	1.09 (1.04, 1.13)	<0.001
Lack of appetite	1.09 (1.05, 1.14)	<0.001
Shortness of breath	1.07 (1.02, 1.11)	0.002
Depression	1.05 (1.00, 1.10)	0.036
Anxiety	1.05 (1.01, 1.10)	0.023
Poor wellbeing	1.08 (1.03, 1.14)	0.002
Muscle cramps	1.06 (1.02, 1.10)	0.006
Degree of symptom burden		
Low burden (t-ESAS 0-39)	Reference	
Moderate burden (t-ESAS 40-69)	1.86 (1.38-2.50)	<0.001
Severe burden (t-ESAS 70-100)	2.30 (1.40-3.77)	<0.001

Note: We adjusted for age, gender, race, ethnicity, hepatic encephalopathy, ascites, and comorbidity burden. Results represent the risk of 90-day admission per 1-unit increase in the symptom score. t-ESAS; total ESAS symptom burden score

Disclosures: Nneka Ufere: Nothing to Disclose, Elizabeth Aby: United Health Care Group: Stock - publicly traded company, Medtronic: Stock - publicly traded company, Chengbo Zeng: Nothing to Disclose, Grace Bizup: Nothing to Disclose, Enya Zhu: Nothing to Disclose, Michael Kriss: Nothing to Disclose, Jon Rice:

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0086 | A RWE-BASED CHARACTERIZATION OF PATIENTS ADMITTED IN US HOSPITAL FOR AN EVENT OF ACUTE DECOMPENSATION HIGHLIGHTS DIFFERENCES IN THE MANAGEMENT OF INPATIENTS

Jonel Trebicka[1] Bérénice Alard[2] Thierry Artzner[3] William Bernal[4] Joan Claria[5] Lise Lotte Gluud[6] Jennifer Lai[7] Jacqueline O'Leary[8] Pierre-Emmanuel Rautou[9] Debbie Shawcross[10] Bart Staels[11] Florence Wong[12] CRISTINA SANCHEZ GARRIDO[13] Eva Usón-Raposo[13] Carol Addy[14] Maxime Anné[2] Stéphanie Ferreira[2] Dean Hum[14] Jérémy Magnanensi[2] Pierbruno Ricci[2] Katharina Staufer[15] Richard Moreau[16] Arun Sanyal[17] Jasmohan Bajaj[17] Javier Fernandez[18] Paolo Angeli[19], [1]University Hospital Münster, Münster, Germany, [2]GENFIT SA, [3]Hôpitaux Universitaires de Strasbourg, Strasbourg, France, [4]King's College Hospital, [5]Fundacio de Recerca Clinic Barcelona-IDIBAPS, [6]Hvidovre Hospital, Hvidovre, Denmark, [7]University of California, San Francisco, United States, [8]University of Texas Southwestern, Dallas, United States, [9]Université Paris-Cité, INSERM, Paris, France; Hôpital Beaujon, Clichy, France, [10]Kings College London, London, United Kingdom, [11]University Lille 2, [12]University of Toronto, [13]European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain, [14]GENFIT CORP, [15]Versantis AG (GENFIT Group), Zurich, Switzerland, [16]European Foundation for the Study of Chronic Liver Failure (EF CLIF), [17]Virginia Commonwealth University, [18]Hospital Clinic, IDIBAPS and CIBEREHD, Barcelona, Spain, [19]University of Padova

Background: Acute decompensation (AD) of liver cirrhosis is defined as the acute development or worsening of ascites, gastrointestinal bleeding (GB), hepatic encephalopathy (HE), bacterial infection (BI) or any combination thereof, requiring hospitalization, and is associated with high risk of adverse liver-related outcomes. Using real-world data, we aimed to characterize the population of patients (pts) hospitalized in the US for an AD event and explore hospital care practices according to the type of AD and medical history of pts. **Methods:** All hospitalizations of pts with chronic liver disease, recorded between January 2023 and April 2025 in the Komodo's Healthcare Map US real-world database and associated with at least one AD event recorded on the date of admission, were included. For each hospitalization, the most specialized healthcare provider recorded on the first day (d) of hospitalization as well as the one seen during the entire hospital stay were extracted. The time to the first consultation with a hepatologist and/or gastroenterologist (HG) was determined, as well as the size of the hospital (small: <100 beds, medium: 100-499 beds, large: ≥ 500 beds). Hospitalizations were grouped based on either etiology of pts or type of AD recorded on the first day of hospitalization to assess potential differences in hospital care. **Results:** In total, the data from 118,457 hospitalizations in 82,741 pts (59% male, mean age at admission 54y) were analyzed. The median duration of hospitalization was 5 d. Among all pts, 52% had only 1 admission reported, 8% had ≥ 5 and 0.1% had ≥ 20 hospitalizations. 14.6% of admissions were recorded in large hospitals, 31.9% in medium-sized and 3.4% in small hospitals. Main known etiology was alcohol-associated liver disease (ALD) (38%, n = 45,033), followed by metabolic dysfunction-associated steatohepatitis (MASH, 4%, n = 4,907), and hepatitis C (3%, n = 3,180). Among admissions of pts with ALD only (n = 43,893), the main reason for hospitalization was ascites (66%) while this event was reported in 42% of admission of pts with MASH and only 18% for pts with hepatitis C. Regardless of etiology or type of event at admission, internal medicine was the main specialty involved in care (33-41% of hospitalizations). Overall, HG were consulted in only 17% of the hospitalizations, with a mean delay of 1.17 d after admission. In case of admission of pts with ALD or MASH, HG were more frequently consulted during hospital stay (20-21%) compared with pts with Hep C (9%), with the shortest

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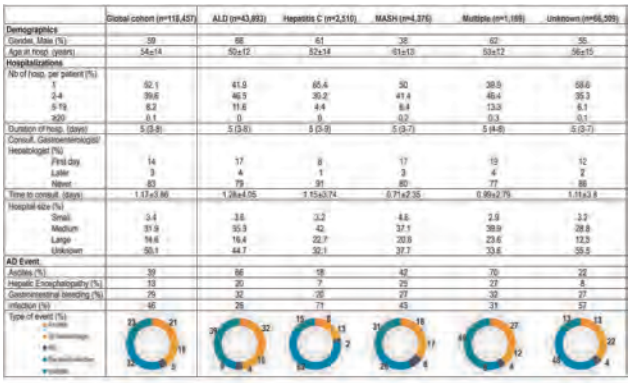
delay for MASH (mean: 0.71 d). Pts admitted with GB were the most likely to be seen by HG (27%, mean delay: 0.36 d), followed by ascites (19%), HE (14%), and BI (5%; mean delay of 2.15 d). **Conclusion:** Pts hospitalized for an AD event were managed differently depending on etiology and type of AD events. The majority were never seen by a hepatologist and/or gastroenterologist during their hospital stay, highlighting a key opportunity for healthcare improvement.



Disclosures: Jonel Trebicka: Nothing to Disclose, Bérénice Alard: GENFIT SA: Employee, Thierry Artzner: Nothing to Disclose, William Bernal: Genfit: Advisor, Flagship Pioneering: Advisor, Joan Claria: Nothing to Disclose, Lise Lotte Gluud: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Jacqueline O'Leary: Genfit: Consultant, Grifols: Advisor, CVS: Stock - publicly traded company, Mallinckrodt: Advisor, Novo Nordisk: Advisor, PharmaIn: Advisor, Grifols: Consultant, Cellion: Advisor, Mallinckrodt: Advisor, PharmaIn: Consultant, Genfit: Consultant, PharmaIn: Consultant, Genfit: Consultant, Pierre-Emmanuel Rautou: Nothing to Disclose, Debbie Shawcross: EnteroBiotix: Consultant, MRM Health: Advisor, Satellite Bio: Consultant, Norgine: Grant/Research Support, Apollo Therapeutics: Consultant, Genfit: Advisor, Alfa Sigma: Advisor, Bart Staels: Genfit SA: Consultant, Florence Wong: Mallinckrodt: Consultant, Mallinckrodt Pharmaceutical Inc: Grant/Research Support, River 2 Renal: Consultant, Sequana Medical: Consultant, sequana Medical: Grant/Research Support, Inventiva: Grant/Research Support, Inventiva: Consultant, CRISTINA SANCHEZ GARRIDO: Nothing to Disclose, Eva Usón-Raposo: Nothing to Disclose, Carol Addy: GENFIT: GENFIT stock options, Maxime Anné: Nothing to Disclose, Stéphanie Ferreira: Nothing to Disclose, Dean Hum: Nothing to Disclose, Jérémy Magnanensi: Nothing to Disclose, Pierbruno Ricci: Nothing to Disclose, Katharina Staufer: Nothing to Disclose, Richard Moreau: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Genfit: Grant/Research Support, Enterobiotix: Advisor, Boehringer Ingelheim: Advisor, Javier Fernandez: GRIFOLS: Advisor, Paolo Angeli: Nothing to Disclose

0087 | ULTRA-SHORT GLECAPREVIR/PIBRENTASVIR PLUS EZETIMIBE PREVENTS CHRONIC HCV IN HCV-INFECTED RECIPIENTS OF HCV-UNINFECTED NON-LIVER TRANSPLANTS: 6-YEAR OUTCOMES OF THE TORONTO PROTOCOL

Wesam Aleyadeh[1] Marcelo Cypel[2] Atul Humar[2] Ilona Bahinskaya[2] Jordan Feld[3], [1]Toronto Centre for Liver Disease, [2]University Health Network, [3]Toronto General Hospital

Background: The rise in hepatitis C virus (HCV)–positive organ donors due to the opioid crisis has expanded the transplant donor pool. However, optimal antiviral timing and duration in HCV-uninfected (D+/R−) recipients remain unclear. We previously reported that a 7-day course of glecaprevir/pibrentasvir (G/P) plus ezetimibe (E), the "Toronto Protocol", prevented chronic infection in a pilot study. Here, we present outcomes from the full cohort treated with this protocol since its adoption as standard of care. **Methods:** This retrospective cohort included all D+/R− recipients of non-liver solid organ transplants treated with the Toronto Protocol (G/P+E with 1 dose pre-transplant and 7 days post-transplant). Patients were followed until last available HCV RNA or death. The primary endpoint was chronic HCV infection, defined as detectable HCV RNA 12 weeks post-transplant or need

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for retreatment. Secondary outcomes included patient and graft survival, treatment-related adverse events, and HCV-related complications. **Results:** Among 113 D+/R− recipients (54 kidney, 33 lung, 16 heart, 6 kidney-pancreas, 4 pancreas), all (100%) achieved undetectable HCV RNA at 12 weeks. Mean age was 55 years (range 19–82), and 65% were male. Median follow-up was 156 weeks (range 7–324). At 6 months, patient survival was 96% (108/113) and graft survival was 99% (112/113). No patients required retreatment or had any reported viremia. No treatment-related adverse events or HCV-associated complications including fibrosing cholestatic hepatitis, cryoglobulinemia, or glomerulonephritis were observed. Anti-HCV surface antibodies developed in 27 patients (24%) and persisted despite viral clearance. **Conclusion:** A 7-day course of glecaprevir/pibrentasvir plus ezetimibe achieved 100% virologic cure across 113 D+/R− recipients with no HCV-related morbidity or treatment failure. This protocol was safe, well tolerated, and feasible for pre-discharge completion. These data support the Toronto Protocol as a scalable strategy for maximizing safe donor organ utilization from HCV-positive donors.

Variable	Overall (%) (n=113)
Sex	
Male	74 (65%)
Female	39 (35%)
Mean age (range)	55 (19-82)
Median post-transplant follow-up (weeks; range)	156 (7-322)
Transplanted organ	
Kidney	54 (48%)
Lung	33 (29%)
Heart	16 (14%)
Kidney/Pancreas	6 (5%)
Pancreas	4 (4%)
Undetectable HCV RNA at 12 weeks	113 (100%)
Patient survival at 6-months	108 (96%)
Death-censored graft survival at 6-months	112 (99%)
Adverse events related to treatment	0 (0%)
HCV-related complications*	0 (0%)

*Fibrosing cholestatic hepatitis, cryoglobulinemia, and glomerulonephritis

Table 1. Baseline characteristics and outcomes of HCV-uninfected recipients of HCV-infected solid organs treated with the Toronto Protocol (n=113)

Disclosures: Wesam Aleyadeh: Nothing to Disclose, Marcelo Cypel: Nothing to Disclose, Atul Humar: Nothing to Disclose, Ilona Bahinskaya: Nothing to Disclose, Jordan Feld: AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support, AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support

0088 | MDL-001 AS A NEXT-GENERATION HCV THUMB-1 INHIBITOR WITH CLINICAL-STAGE SAFETY

Virgil Woods[1] Tyler Umansky[1] Sean Russell[1] Adolfo Garcia-Sastre[2] Kris White[2] William Brubaker[3] Davey Smith[4], [1]Model Medicines, San Diego, CA, USA, [2]Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [3]Farmington Pharma Development, [4]School of Medicine, University of California, San Diego, La Jolla, CA, USA

Background: The Hepatitis C virus (HCV) polymerase (NS5B) harbors a Thumb-1 subdomain that was previously a target for antiviral drug development. However, many inhibitors of this domain exhibit a limited spectrum of activity, demonstrating efficacy only against specific viral genotypes or under restricted conditions. By leveraging ChemPrint™, a machine learning model for ligand binding, in conjunction with our proprietary GALILEO™ drug discovery platform, we have identified MDL-001 as a novel Thumb-1 inhibitor for HCV. This abstract presents MDL-001's potency as evaluated in a genotype 1b replicon system, a cell-based assay employing a subgenomic replicon to simulate viral RNA replication, and it summarizes Phase I safety data indicating no serious adverse events. **Methods:** ChemPrint™ was trained on extensive thumb-pocket inhibitor data and used to screen a library of well-characterized

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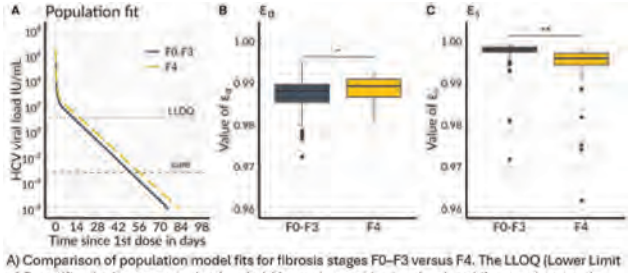
small molecules with established human safety records. MDL-001 emerged as a high-confidence candidate predicted to target the NS5B Thumb-1 subdomain. Antiviral efficacy against genotype 1b HCV (isolate Con1) was evaluated using the Huh-luc/neo-ET replicon system, measuring viral RNA reduction by standard readouts. Rodent safety studies assessed tolerability up to 1000 mg/kg, and archived Phase I data (collected for a prior indication) were re-examined for adverse events and preliminary pharmacokinetics. **Results:** In the Huh-luc/neo replicon (genotype 1b), MDL-001 achieved an EC_{50} of 3.28 µM with no detectable toxicity up to 10 µM (TC_{50} > 10 µM). Follow-up rodent studies confirmed high oral bioavailability and demonstrated no significant adverse findings at single doses as high as 1000 mg/kg. Past Phase I clinical trials (n ≈ 100 subjects) showed no serious adverse events, supporting the compound's favorable tolerability and once-daily dosing potential. Although primarily developed for HCV, preliminary screens suggest MDL-001's scaffold could be active against other RNA viruses with similar Thumb-1 architecture. **Conclusion:** By selectively targeting the HCV Thumb-1 subdomain, MDL-001 showed low-micromolar EC_{50} values in a genotype 1b replicon assay and an excellent safety margin in animal and early human studies. This next-generation approach to HCV therapy supports further clinical evaluation of MDL-001 as an orally available, well-tolerated antiviral that may also have broader applications against other single-stranded RNA viruses.

Disclosures: Virgil Woods: Nothing to Disclose, Tyler Umansky: Nothing to Disclose, Sean Russell: Nothing to Disclose, Adolfo Garcia-Sastre: Avimex: Consultant, Accurius: Consultant, Castlevax: Consultant, Amovir: Stock – privately held company, Vivaldi: Stock – privately held company, Contrafect: Stock - publicly traded company, Pagoda: Stock – privately held company, Virofend: Stock – privately held company, Kris White: Nothing to Disclose, William Brubaker: Nothing to Disclose, Davey Smith: Nothing to Disclose

0089 | MULTISCALE MODELING OF RESULTS: FROM A PHASE 2 STUDY OF AN 8-WEEK COMBINATION REGIMEN OF BEMNIFOSBUVIR AND RUZASVIR IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION

Carolin Zitzmann[1] *Ruy Ribeiro*[1] *Sergey Izmailyan*[2] *Shannan Lynch*[2] *Keith Pietropaolo*[2] *Maria Arantxa Horga*[3] *Xiao-Jian Zhou*[2] *Janet Hammond*[2] *Alan Perelson*[1], [1]*Los Alamos National Laboratory,* [2]*Atea Pharmaceuticals, Inc.,* [3]*horga.arantxa@ateapharma.com*

Background: Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent, pan-genotypic HCV polymerase and NS5A inhibitors, respectively. The novel combination BEM/RZR was assessed for safety and efficacy in a phase 2 open-label study of 275 HCV-infected individuals including those with compensated cirrhosis (NCT05904470). Previously, we developed a multiscale model of HCV infection and treatment to estimate the in vivo effectiveness of antiviral therapies in blocking HCV replication and viral assembly/secretion. Here we use that model to evaluate the efficacy of the BEM/RZR combination. **Methods:** In this single arm study, a subset of 215 treatment-naïve, study drug adherent, noncirrhotic and cirrhotic individuals with chronic HCV received 550 mg BEM once daily (QD) + 180 mg RZR (QD) for 8 wks. The previously developed multiscale model was fit to the plasma viral load (VL) measured using the Roche cobas® HCV quantitative nucleic acid test with a lower limit of quantitation (LLOQ) of 15 IU/mL and the ALT data from all subjects simultaneously via population fitting. **Results:** The 215 participants were infected with GT1 (n = 151), GT2 (n = 4), GT3 (n = 58), and GT4 (n = 2) and 16% had F4 compensated cirrhosis. After treatment initiation, the VL decreased in a triphasic manner, with a very rapid first phase lasting < 12 h, followed by a slower 2nd phase and an even slower 3rd phase. The model fit both the VL and ALT data well. The population estimate of the time to reach the LLOQ was 12 days for individuals in F0-F3 and 16 days for those in F4, while the population estimate of the time to cure (VL ≤ 6.7×10^{-4} IU/mL) was 7.2 wks for F0-F3 and 8.1 wks for F4, with some variability between individuals. The population estimate of the effectiveness of the combination in blocking viral assembly/secretion was extremely high at 0.998 for F0-F3 [95% CI 0.997, 0.999] and 0.995 for F4 [95% CI, 0.991, 0.997], while the population estimate of the effectiveness in blocking viral replication was 0.988 for F0-F4 [95% CI, 0.983, 0.991]. The estimated efficacy of therapy was similar across GT1, 2, 3, and 4. **Conclusion:** BEM/RZR for 8 weeks was highly effective in blocking both viral replication and viral assembly/secretion in HCV-infected patients independent of genotype and fibrosis score. The time to cure estimates support 8 wk treatment for non-cirrhotic patients and longer treatment duration (e.g., up to 12 wks) for those with compensated cirrhosis.



A) Comparison of population model fits for fibrosis stages F0–F3 versus F4. The LLOQ (Lower Limit of Quantification) represents the threshold for undetectable virus levels, while cure denotes the viral load threshold for cure (VL ≤ 6.67×10^{-4} IU/mL).
B) Boxplots of individual parameter estimates for the drug's effectiveness, ε_a, in blocking HCV replication across fibrosis stages F0–F3 and F4.
C) Boxplots of individual parameter estimates for the drug's effectiveness, ε_s, in blocking viral assembly and secretion across fibrosis stages F0–F3 and F4.
[Significance based on t-tests; * denotes p ≤ 0.05 and ** denotes p ≤ 0.01]

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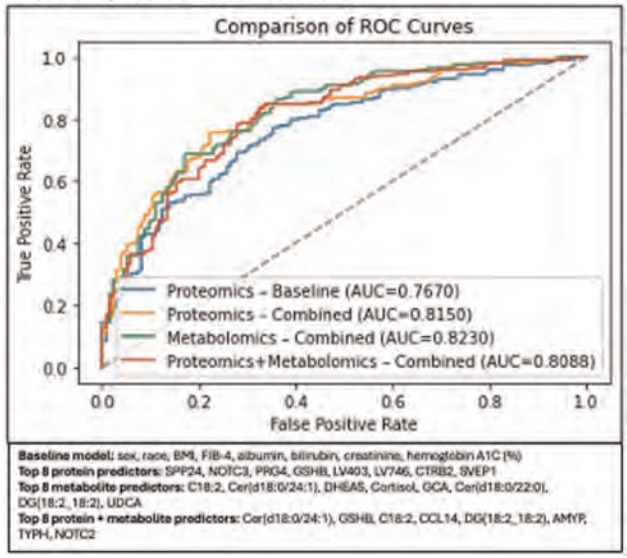
Disclosures: Carolin Zitzmann: Nothing to Disclose, Ruy Ribeiro: Atea Pharmaceuticals: I have grant support, but I am not the PI of that grant., Sergey Izmailyan: Nothing to Disclose, Shannan Lynch: Atea Pharmaceuticals: Employee, Keith Pietropaolo: Nothing to Disclose, Maria Arantxa Horga: Nothing to Disclose, Xiao-Jian Zhou: Nothing to Disclose, Janet Hammond: Nothing to Disclose, Alan Perelson: Nothing to Disclose

0090 | A MULTI-OMIC BLOOD-BASED MODEL ACCURATELY PREDICTS LIVER RELATED EVENTS IN PATIENTS WITH CIRRHOSIS AFTER HEPATITIS C VIRUS CURE WITH DIRECT ACTING ANTIVIRALS

Cynthia Moylan[1] Emrys Yan[2] Kara Wegermann[3] Marlene Violette[4] Lucas Li[4] Rebecca Mangus[3] Mehak Bajaj[5] David Hsu[3] Matthew Foster[3] Frida Abramov[6] Keyur Patel[7] Joseph Lucas[2] Susanna Naggie[8], [1]Durham Veterans Affairs Medical Center and Duke University Medical Center, [2]Vital Statistics, [3]Duke University Medical Center, [4]Duke University School of Medicine, [5]Durham Veterans Affairs Medical Center, [6]Gilead, [7]University of Toronto, [8]Durham Veterans Affairs Medical Center and Duke Clinical Research Institute

Background: Successful eradication of chronic hepatitis C virus (HCV) infection with direct acting antivirals (DAA) significantly reduces long-term liver-related morbidity and mortality. Patients with cirrhosis remain at risk of decompensation despite sustained virologic response (SVR). Currently we lack non-invasive tools able to accurately identify patients with the greatest risk of decompensation and hepatocellular carcinoma (HCC) after SVR. Our aims were to validate and optimize a predictive biosignature of hepatic decompensation and HCC developed previously in HIV/HCV coinfected patients. **Methods:** Plasma and clinical data were obtained at entry into the Gilead SVR Registry, comprising participants with cirrhosis from registered clinical trials who achieved SVR with DAA (NCT02292706). We performed a nested case control study of participants who did (case, n = 182) and did not (control, n = 138) develop incident hepatic decompensation (ascites, varices, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, and hepatic hydrothorax) or HCC during follow-up. Plasma metabolites and peptides were measured using Biocrates Q500 and Bile Acids and Quantitative Data Independent Acquisition LC-MS/MS, respectively. Logistic regression with LASSO variable selection with leave one out cross validation was used to develop the best fit model to predict liver-related events. The study was approved by the Durham Veterans Affairs Medical Center IRB and analyses were performed in Python. **Results:** Registry participants were followed for a mean of 3.7 +/- 1.5 years. The overall cohort (n = 291) was primary White race (90%) and male sex (75%). Cases were older (median 61 vs. 58.5 years), more likely to be HCV genotype 1, and had higher liver transaminases, bilirubin, FIB-4 scores, and liver stiffness than controls (all $p < 0.01$). The proteomic and metabolomic models all had a higher predictive area under the curve (AUC) compared to standard baseline clinical data alone (see Figure), with a combined model of metabolites and baseline clinical data having the greatest accuracy (AUC 0.823). Top eight proteins and metabolites are shown (see Figure) and included those involved in matrix and tissue maintenance, cell fate determination, immune regulation, and detoxification, while top metabolites included acylcarnitines, dihydroceramides, hormones and bile acids. **Conclusion:** Blood-based metabolomic and proteomic markers can predict future liver-related events in participants with cirrhosis post-SVR with higher accuracy than simple clinical parameters alone. Prospective validation in real-world cohorts is required.

Figure. Receiver operating characteristic (ROC) curves for each analyte model compared to baseline model alone.



Disclosures: Cynthia Moylan: GSK: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Exact Sciences: Grant/Research Support, Sirtex: Advisor, NovoNordisk: Consultant, Emrys Yan: Nothing to Disclose, Kara Wegermann: Mirum Pharmaceuticals: Study investigator (research funds to institution), Madrigal Pharmaceuticals: Study investigator (research funds to institution), FocusMed CME: Speaking and Teaching, Marlene Violette: Nothing to Disclose, Lucas Li: Nothing to Disclose, Rebecca Mangus: Nothing to Disclose, Mehak Bajaj: Nothing to Disclose, David Hsu: Nothing to Disclose, Matthew Foster: Nothing to Disclose, Frida Abramov: Nothing to Disclose, Keyur Patel: Novo-Nordisk: Consultant, Gilead Sciences: Consultant, Merck: Consultant, Resalis: Advisor, Boehringer Ingelheim: Advisor, Joseph Lucas: Nothing to Disclose, Susanna Naggie: Nothing to Disclose

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0091 | REVERSE-ENGINEERING STRATEGY IDENTIFIED DDR1 AS HCC CHEMOPREVENTION TARGET POST HCV CURE

Courtney Katz[1] Hiroaki Kanzaki[1] Hiroyuki Suzuki[1] Naoto Fujiwara[2] Sumit Mishra[1] Subhojit Paul[1] Soumith Paritala[1] Ece Janet Dinc[1] Jingxuan Chen[1] Jeon Lee[1] Pratibha Selvakumar[1] Indu Raman[1] Prithvi Raj[1] Hayato Nakagawa[2] Amit Singal[1] Adam Yopp[1] Raymond Chung[3] Emilie Crouchet[4] Thomas Baumert[5] Yujin Hoshida[1], [1]University of Texas Southwestern Medical Center, [2]Graduate School of Medicine, Mie University, [3]Massachusetts General Hospital, [4]Institut de Recherche sur les Maladies Virales et Hépatiques, Inserm, University of Strasbourg, [5]INSERM

Background: HCC risk persists in a subset of HCV-cured patients after antiviral therapies. We previously reported a molecular signature predictive of future development of incident HCC after HCV cure (prognostic liver signature for HCV-cured patients [PLS-HCVcure]). This signature can be utilized for "reverse-engineering" exploration of chemoprevention for post-SVR HCC. **Methods:** To identify candidate chemopreventive agents, we performed in silico screening of 3,919 compounds using PLS-HCVcure and an etiology-agnostic HCC risk signature, PLS, we previously reported. In vitro validation was conducted using collagen-stimulated HepG2 cells and a PLS-inducible cell-based (cPLS) model. In vivo testing was performed in the DEN+CCl4 mouse model. Clinical relevance of the candidate compound and its target were assessed by single-nuclei and spatial transcriptomic profiling and ex vivo treatment of precision-cut liver slices (PCLS) from six HCV-cured patients. **Results:** The in silico compound screening identified a DDR1 inhibitor, 7rh, as a top candidate. In HepG2 cells cultured on collagen-coated plates, DDR1 knockdown suppressed collagen-induced PLS-HCVcure and PLS. In the cPLS model, 7rh favorably modulated PLS in a dose-dependent manner. In the DEN+CCl4 mouse model, which was identified as one of the most suitable models via a meta-analysis of diverse rodent models, treatment with 7rh significantly reduced tumor burden and favorably modulated the HCC risk signatures. Molecular pathways involved in DNA damage repair, cell cycle, apoptosis, necroptosis, TNF-alpha signaling, and RAS/ERK signaling were suppressed. Carcinogen-related DNA mutational signatures were unchanged. In the clinical SVR liver tissue, single-nuclei transcriptome profiling identified a hepatocyte subpopulation with DDR1 activation and induction of PLS-HCVcure and PLS. Spatial transcriptome profiling is ongoing to map the subpopulation on fibrotic liver tissues and identify inter-cell type interactions contributing to hepatocarcinogenesis. Four SVR PCLS tissues (67% response rate) showed improvement of PLS in response to 7rh treatment. **Conclusion:** These findings support pharmacological DDR1 inhibition as a promising chemopreventive strategy in HCV-cured patients with advanced fibrosis.

Disclosures: Courtney Katz: Nothing to Disclose, Hiroaki Kanzaki: Nothing to Disclose, Hiroyuki Suzuki: Nothing to Disclose, Naoto Fujiwara: Nothing to Disclose, Sumit Mishra: Nothing to Disclose, Subhojit Paul: Nothing to Disclose, Soumith Paritala: Nothing to Disclose, Ece Janet Dinc: Nothing to Disclose, Jingxuan Chen: Nothing to Disclose, Jeon Lee: Nothing to Disclose, Pratibha Selvakumar: Nothing to Disclose, Indu Raman: Nothing to Disclose, Prithvi Raj: Nothing to Disclose, Hayato Nakagawa: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Adam Yopp: Nothing to Disclose, Raymond Chung: GSK: Grant/Research Support, Salix: Grant/Research Support, GSK: Consultant, Precision Biosciences: Consultant, Boehringer: Grant/Research Support, BMS: Grant/Research Support, Emilie Crouchet: Nothing to Disclose, Thomas Baumert: Nothing to Disclose, Yujin Hoshida: Helio Genomics: Advisor, Alentis Therapeutics: Stock – privately held company, Espervita Therapeutics: Stock – privately held company, Elevar Therapeutics: Advisor, Espervita Therapeutics: Advisor, Roche Diagnostics: Advisor

0092 | EIGHT VERSUS TWELVE WEEKS OF SOFOSBUVIR/VELPATASVIR FOR TREATMENT-NA&IUML;VE, NON-CIRRHOTIC CHRONIC HEPATITIS C: AN INTERIM ANALYSIS OF A MULTICENTRIC, OPEN LABEL, RANDOMIZED, NON-INFERIORITY (RESOLVE) TRIAL

Amit Goel[1] SUMIT RUNGTA[2] Vinod Kumar[3] . Shalimar[4] Ajay Kumar[5] Surender Singh[1] Harshita Katiyar[1] Ajay Mishra[1] Ashish Awasthi[6] Amar Deep[7] Vikasendu Agarwal[8] Radha Dhiman[1] Rakesh Aggarwal[9], [1]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [2]King George's Medical University, [3]Banaras Hindu University Institute of Medical Sciences, [4]All India Institute of Medical Sciences, [5]Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, [6]CSIR-Central Drug

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Background: Sofosbuvir and velpatasvir combination for 12 weeks is a standard treatment regimen for chronic hepatitis C virus (HCV) infection without cirrhosis. Since shorter treatment regimens are advantageous, we compared 8 weeks versus 12 weeks of treatment with this drug combination. **Methods:** Treatment-naïve, HCV viraemic (HCV RNA > 10,000 IU/mL), mono-infected adults (> 18 years), with no evidence of cirrhosis (liver stiffness > 12.5 Kpa (FibroScan®) or AST-platelet ratio index (APRI) > 2.0) were centrally randomized, using a computer-generated sequence, to receive sofosbuvir/velpatasvir for either 8 or 12 weeks. Primary outcome assessed was sustained virological response at 12 weeks after treatment completion (SVR12). HCV RNA was measured using COBAS 5800® (Roche). HCV genotyping was done using in-house Sanger sequencing of 5´-UTR and/or core regions of HCV genome. Estimated sample size for 5% non-inferiority margin, 90% power, 2.5% one-sided alpha error, and 10% data loss was 880. Data are presented as mean ± standard deviation, or proportion, as appropriate. **Results:** Data for the first 727 (82.6%) of the planned 880 participants (age 38.1 ± 12.7 years; male 47.5%; $\log_{10}$ HCV RNA 6.06 ± 1.08; genotype [n = 386] 1/3/4 proportions = 21%/77.7%/1.3% respectively; liver stiffness [n = 664] 6.6 ± 2.1 KPa; APRI [n = 63] 0.68 ± 0.34) were analyzed. Baseline characteristics were comparable between the participants in the 12- and 8-week arms (Table). Of the 727 participants, 65 (8.9%) dropped out for various reasons before SVR12 could be ascertained, 654 (90.0%) achieved SVR12 and 8 (1.1%) failed to achieve SVR12. In intention-to-treat (ITT) analysis, SVR12 was achieved in the overall cohort, 12-week, and 8-week arms in 654 (90.0%; 95% confidence interval 87.5-92.1), 325 (88.6%; 84.9-91.6), and 329 (91.4%; 88.0-94.1) participants, respectively. On per-protocol (PP) analysis, SVR12 was achieved in the overall cohort, 12-week, and 8-week arms in 654/662 (98.8%; 97.6-99.5), 325/329 (98.8%; 96.0-99.3), and 329/333 (98.8%; 97.0-99.7), respectively. The ITT and PP SVR12 rates in the 8-week group were lower by −2.8% (95% CI: -7.4% to 1.8%) and 0% (-1.7% to 1.7%), meeting the pre-specified criterion for non-inferiority. **Conclusion:** Sofosbuvir/velpatasvir for 8 weeks was non-inferior to standard 12-week treatment in chronic HCV infection without cirrhosis. Hence, in such patients, treatment duration can be reduced from 12 to 8 weeks, with advantages of lower cost and better compliance (Trial registration ID: CTRI/2022/03/041368).

Table: Comparison of baseline clinical and laboratory characteristics, and outcomes

Characteristics	12-week treatment (n=367)	8-week treatment (n=360)	p value
Age (years)	38.6 ± 12.7	37.6 ± 12.7	0.282
Male sex, n (%)	174 (47.4)	171 (47.5)	0.981
Diabetes mellitus, n (%)	13 (3.5)	15 (4.2)	0.662
Hypertension, n (%)	11 (3.0)	11 (3.1)	0.963
Platelet counts (x10^3/μL)	202 ± 84	201 ± 76	0.751
Total serum bilirubin (mg/dL)	0.7 ± 0.4	0.7 ± 0.4	0.315
Serum albumin (g/dL)	4.4 ± 0.4	4.4 ± 0.5	0.612
Alanine aminotransferase (IU/L)	85 ± 65	84 ± 76	0.858
Aspartate aminotransferase (IU/L)	67 ± 42	65 ± 50	0.623
Prothrombin time (INR)	1.04 ± 0.11	1.04 ± 0.12	0.939
Serum creatinine (mg/dL)	0.85 ± 0.22	0.85 ± 0.23	0.775
Liver stiffness (KPa)	6.6 ± 2.0	6.6 ± 2.2	0.959
AST-Platelet Ratio Index	0.69 ± 0.35	0.68 ± 0.33	0.969
HCV RNA ($\log_{10}$ [IU/ml])	6.04 ± 1.11	6.08 ± 1.06	0.577
HCV genotype,* n (%)			
1	35 (17.8)	46 (24.3)	0.239
3	160 (81.2)	140 (74.1)	
4	2 (1.0)	3 (1.6)	
Primary end-point, n (%)**			
SVR12 achieved	325 (88.6)	329 (91.4)	0.519
SVR12 failed	4 (1.1)	4 (1.1)	
Loss to follow-up, etc	38 (10.3)	27 (7.5)	

Categorical are shown as number (%) and continuous data as mean ± standard deviation; INR = international normalized ratio; *Data available for only a subset of participants; **Intention-to-treat analysis

Disclosures: Amit Goel: Nothing to Disclose, SUMIT RUNGTA: Nothing to Disclose, Vinod Kumar: Nothing to Disclose, . Shalimar: Nothing to Disclose, Ajay Kumar: Nothing to Disclose, Surender Singh: Nothing to Disclose, Harshita Katiyar: Nothing to Disclose, Ajay Mishra: Nothing to Disclose, Ashish Awasthi: Nothing to Disclose, Amar Deep: Nothing to Disclose, Vikasendu Agarwal: Nothing to Disclose, Radha Dhiman: Nothing to Disclose, Rakesh Aggarwal: Nothing to Disclose

★ 0093 | THE ROLE OF TRAIP IN ALCOHOL-INDUCED LIVER INJURY THROUGH REGULATING Β-CATENIN UBIQUITIN DEGRADATION VIA DIRECT INTERACTION

Zhan Wu[1] Yubing Chen[2] Stephen Tomlinson[3] Sebastian Mueller[4] Songqing He[2] Guandou Yuan[2], [1]First Affiliated Hospital of Guangxi Medical University, [2]The First Affiliated Hospital of Guangxi Medical University, [3]Medical University of South Carolina, [4]Center for Alcohol Research, University Hospital Heidelberg

Background: Oxidative stress plays a critical role in the pathogenesis of alcohol-related liver disease (ALD), although the precise mechanisms involved remain unclear. Studies indicate that tumor necrosis factor receptor associated factor interacting protein (TRAIP) plays a key role in oxidative stress. We aimed to elucidate the role of TRAIP in ALD, and its mechanism of regulating liver oxidative stress. **Methods:** Different ALD models were established using mice with liver-specific overexpression (LSO) and knockout (LKO) of TRAIP to investigate its role in ALD. Chromatin immunoprecipitation and luciferase assays confirmed

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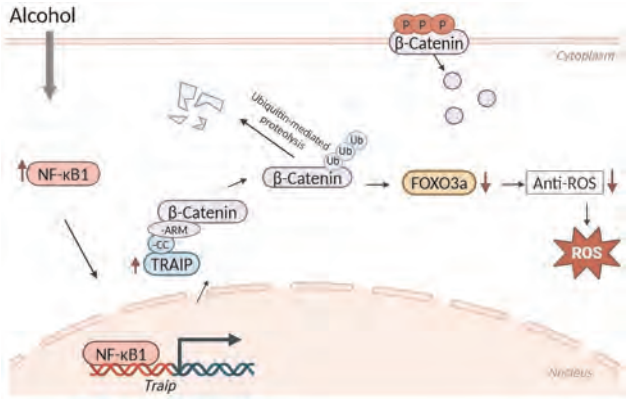
the transcription factor binding site for the transcription factors associated with TRAIP. Different structural components of TRAIP and β-catenin were constructed using cloning technology, and used to determine their sites of interaction. **Results:** The expression of TRAIP was significantly upregulated in liver tissues from both human and murine ALD. In ethanol-fed TRAIP^{LSO} mice, oxidative stress and inflammation in the liver increased markedly, while fat deposition decreased. The opposite effect was detected in TRAIP^{LKO} mice. Mechanistically, ethanol induced NF-κB1 activation, and led to the transcription of TRAIP. Up-regulated TRAIP promoted β-catenin ubiquitous degradation via a direct interaction of its coiled coil domain with the Armadillo domain of β-catenin, resulting in inhibition of the downstream target gene FOXO3, which exacerbates antioxidative stress in the liver. Stablization of β-catenin by SKL20001 effectively mitigated ethanol induced liver oxidative stress damage. **Conclusion:** This study reveals that TRAIP is a key mediator in ALD by inducing oxidative stress and inflammation via promoting β-catenin degradation and inhibiting FOXO3. SKL20001 is a promising treatment for ALD.



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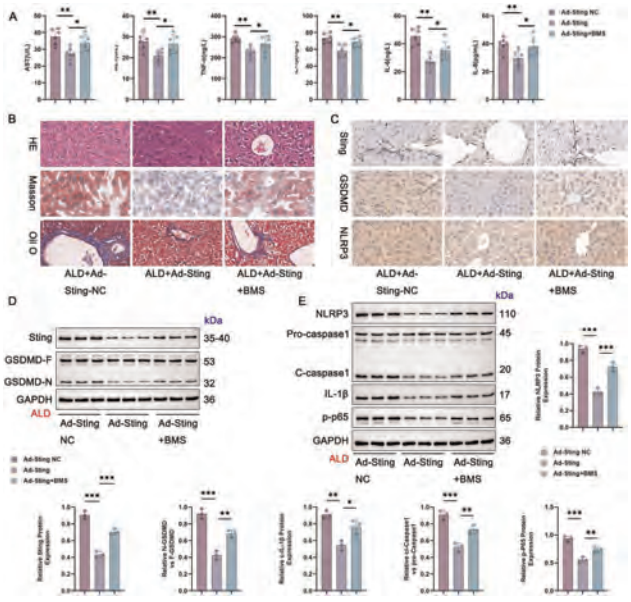
★ 0094 | STING KNOCKDOWN ATTENUATES ALCOHOLIC LIVER DISEASE PROGRESSION VIA NLRP3-MEDIATED PYROPTOSIS SUPPRESSION

Yu xuan Song[1] Mengsi Liu[1] Mingying Zhou[1] Xueyi Ren[1] Bo Feng[1] Yandi Xie[1], [1]Peking University People's Hospital, Peking University Hepatology Institute

Background: Alcoholic liver disease (ALD) is a globally prevalent condition with limited therapeutic options. The stimulator of interferon genes (STING) pathway has been implicated in inflammatory liver diseases, but its role in ALD progression remains incompletely understood. This study aimed to investigate the mechanistic link between STING and NLRP3-mediated pyroptosis in ALD pathogenesis. **Methods:** An ALD mouse model was established using a 5% alcohol Lieber-DeCarli diet. Adenovirus-mediated STING shRNA knockdown was performed to assess its effects on liver injury, inflammation, and pyroptosis. NLRP3 inhibition (MCC950) and activation (BMS-986299) were employed to evaluate the STING-NLRP3 axis. In vitro, alcohol- and LPS/ATP-induced pyroptosis models were constructed in AML12 hepatocytes to validate the findings. **Results:** STING expression was significantly upregulated in ALD mice, correlating with worsened liver function, inflammation, fibrosis, and lipid accumulation. STING knockdown ameliorated these pathological features, reduced serum pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-8, LPS), and suppressed pyroptosis markers (NLRP3, GSDMD-N, caspase-1, IL-1β, p-p65). Similar protective effects were observed with NLRP3 inhibition. Mechanistically, STING knockdown attenuated hepatocyte pyroptosis by disrupting NLRP3 inflammasome activation, as evidenced by reduced co-immunoprecipitation of NLRP3. NLRP3 agonist BMS-986299 reversed the benefits of STING knockdown, confirming NLRP3 as a downstream effector. Additionally, STING silencing alleviated oxidative stress by lowering ROS, MDA, and 4-HNE while restoring GSH and SOD levels. **Conclusion:** STING knockdown mitigates ALD progression by suppressing NLRP3-dependent pyroptosis and oxidative stress, highlighting its potential as a therapeutic target for ALD.



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0095 | ENVIRONMENTAL FOREVER CHEMICAL EXPOSURES MODIFY THE SEVERITY OF ALCOHOL-ASSOCIATED LIVER DISEASE

Frederick Ekuban[1] Tyler Gripshover[1] Matthew Smith[2] Jianzhu Luo[1] Vatsalya Vatsalya[1] Kushal Biswas[3] Dhimitter Bello[3] Jennifer Schlezinger[4] Hao Zheng[1] Maiying Kong[1] Jae Yeon Hwang[1] Juw Won Park[1] Dean Jones[2] Craig McClain[1] Matthew Cave[1], [1]University of Louisville, Louisville, KY, USA, [2]Emory University, Atlanta, GA, USA, [3]University of Massachusetts Lowell, Lowell, MA, USA, [4]Boston University, Boston, MA USA

Background: Per- and polyfluoroalkyl substances (PFAS) are forever chemicals that have been associated with metabolic dysfunction-associated steatohepatitis. Recent findings show PFAS have been detected in popular US beers above EPA limits (PMID: 40272161), highlighting potential exposure pathways for alcohol consumers. The potential role of PFAS in alcohol-associated steatohepatitis (ASH), therefore warrants investigation. We hypothesize that PFAS disrupt liver metabolism and exacerbate ASH. **Methods:** Exposomics and metabolomics (LC-MS^2 & GC-MS^2) were performed in archived plasmas from subjects with ASH (severe = 96, moderate = 28) and non-drinking controls (n = 11). Associations between biomarkers of PFAS exposure, ASH severity, and the metabolome were determined using linear regression models. Male C57BL/6J mice on chronic-binge ethanol feeding were co-exposed to PFOS (1 mg/kg) or vehicle control for 10 days. Comprehensive liver disease phenotyping and RNA-Seq were performed. **Results:** 691 environmental pollutants were present in the human plasmas, including six PFAS with detection rates exceeding 94%. 25.9% of subjects had high PFAS exposures ($\sum$PFAS > 20 ng/m), and PFOS accounted for half of total PFAS. PFOS and PFUnA were positively associated with the disease severity biomarkers, ABIC and MELD, respectively. PFOA and PFTrDA were increased in ASH *vs.* controls. PFOS, PFOA, and PFHxS were associated with 806, 3318 and 721 plasma metabolic features, respectively. In mice, 60% of the administered PFOS dose accumulated in the liver. PFOS upregulated ethanol-metabolizing enzymes in liver and lowered blood alcohol levels. PFAS worsened ethanol-induced hepatic steatosis and liver injury. PPARα was the top identified upstream transcriptional regulator. In both the mouse model and in the human subjects, PFOS was associated with enrichment in pathways related to linoleate, carnitine, and vitamin metabolism. **Conclusion:** A significant number of pollutants, some at high levels, were present in ASH subjects. PFAS forever chemicals were detected in 100% of them. PFAS were associated with metabolic disruption and ASH severity. Data from the reverse-translational mouse model suggest that the associations observed in human subjects may be causal. Hypothesis generating multi-omics experiments identified potential mechanisms, some of which were consistent across species. Associations between the remaining 691 identified pollutants and human ASH are currently being determined. Environmental exposures may modify the liver and systemic responses to alcohol consumption, and more research is required in these areas.

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★ 0096 | GLP-1 DYSREGULATION IN ALCOHOLIC LIVER DISEASE: ELUCIDATING INTESTINAL MECHANISMS AFFECTED BY CHRONIC ALCOHOL ABUSE

Yang Wang[1] Xiaoxue Yuan[1] Xi Wang[1] Song Yang[2], [1]Beijing Ditan Hospital, Capital Medical University, [2]Center of Liver Diseases Division, Beijing Ditan Hospital, Capital Medical University

Background: Chronic alcohol abuse is a well-established cause of alcoholic liver disease (ALD). Recent evidence highlights alcohol consumption as a primary etiological factor, disrupting the intestinal microenvironment and compromising intestinal epithelial barrier integrity and gut microbiota homeostasis. Intestinal hormones, including glucagon-like peptide-1 (GLP-1) produced by intestinal L cells, play pivotal roles in the gut-liver axis, regulating blood glucose and body weight. Notably, alcohol consumption elevates GLP-1 secretion, resulting in higher circulating GLP-1 levels in ALD patients. Paradoxically, GLP-1 receptor (GLP-1R) agonists have shown promise in reducing alcohol craving and intake in individuals with alcohol use disorders. However, the mechanisms driving elevated GLP-1 expression in ALD remain unclear, as does the impact of this dysregulation on the efficacy of GLP-1-based therapies. This research elucidates the causes of elevated GLP-1 expression in ALD and evaluates its implications for GLP-1 analog and agonist efficacy. **Methods:** To analyze intestinal conditions, we used two experimental models: (1) Acute

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Alcohol Exposure (single 30% ethanol gavage in C57BL/6N mice) and (2) Chronic ALD (8-week 30% ethanol gavage in C57BL/6N mice). We measured serum GLP-1 levels, quantified intestinal enteroendocrine cell (EEC) populations, and employed AlphaFold3 for de novo structural modeling of the GLP-1R-GLP-1 complex. Molecular dynamics (MD) simulations assessed the binding stability of the complex under alcohol-related conditions. Immunofluorescence staining validated in silico predictions by visualizing GLP-1 and GLP-1R co-localization in intestinal tissues. **Results:** The acute alcohol exposure model revealed a significant redistribution of endocrine cells and elevated serum GLP-1 levels. Conversely, the chronic alcohol exposure group exhibited a decline in the total population of intestinal endocrine cells and a blunted GLP-1 response. MD simulations showed that GLP-1R fluctuates more in ethanol and acetaldehyde, reducing protein structure stability. Reduced C-terminal flexibility may limit conformational adjustment of GLP-1R, decreasing its efficiency in recognizing GLP-1. Confocal results showed decreased co-localization of GLP-1 and GLP-1R in ALD mice. **Conclusion:** A single alcohol intake causes a transient increase in GLP-1 levels, while long-term excessive alcohol exposure may lead to decompensated negative feedback regulation of GLP-1. Alcohol affects the binding efficiency of GLP-1 and GLP-1R.

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0097 | TARGETING GLP-1 AND GCG RECEPTORS AS POTENTIAL THERAPEUTIC APPROACHES FOR ALCOHOL-ASSOCIATED LIVER DISEASE: FOCUSING ON THE ROLE OF THE LIVER-GUT AXIS

TUO SHAO[1] Zelin Gu[1] Xiaoyi Wang[1] Chuanlong Zhu[2] Raymond Chung[3] Weifeng Zhao[1], [1]Soochow University, [2]Nanjing Medical University, [3]Massachusetts General Hospital

Background: Alcohol-associated liver disease (ALD) is a major global cause of chronic liver disease, with limited treatment options due to its complex, multifactorial pathogenesis. Given the pivotal role of the gut-liver axis in ALD, we investigated the therapeutic potential of targeting glucagon-like peptide-1 receptor (GLP-1R) and glucagon receptor (GCGR) pathways in a murine ALD model. **Methods:** C57BL/6 mice were subjected to the NIAAA model, involving 10 days of Lieber-DeCarli ethanol liquid diet followed by a single binge ethanol dose (9 hours before sacrifice). Mice received subcutaneous injections of PBS, a GLP-1R agonist (Semaglutide), a GCGR agonist (IUB288), or a GLP-1R/GCGR dual agonist on days 1, 4, 6, and 8 (0.05 mg/kg) during ethanol feeding. We assessed serum markers, liver histology, immune cell infiltration, proinflammatory cytokines, hepatic triglyceride content, intestinal single-cell RNA sequencing, transcriptomic profiles, fecal microbiota composition, microbial metabolites, and intestinal barrier integrity. **Results:** Both GLP-1R and GCGR agonists improved liver function, reduced liver/body weight ratios, and lowered serum ALT, AST, and hepatic triglyceride levels, with the dual agonist showing the strongest effects. Mechanistically, these treatments upregulated hepatic and circulating fibroblast growth factor-21 (FGF21) via PPAR-FGF21 pathway activation, reducing hepatic steatosis. In the intestine, GLP-1R and dual agonist treatments increased $CD4^+$ T cells, enterocytes, enteroendocrine cells, and Paneth cells, while decreasing B cells, $CD8^+$ T cells, and macrophages. Notably, GLP-1R agonist therapy significantly corrected alcohol-induced gut microbiota dysbiosis in both mice and ALD patients by suppressing Enterobacteriaceae and Enterococcaceae overgrowth while enriching beneficial families. Semaglutide and dual agonist also modulated key microbial metabolites (long-chain fatty acids, bile acids, indole derivatives) that reinforce intestinal barrier integrity and stimulate GLP-1 secretion. Both agents significantly reduced bacterial translocation by enhancing tight junction expression, promoting epithelial proliferation, and dampening hepatic inflammation. **Conclusion:** Targeting GLP-1R and GCGR pathways provides an effective therapeutic strategy for ALD, with the dual agonist delivering superior efficacy by comprehensively modulating the gut-liver axis, restoring intestinal and hepatic homeostasis, and attenuating alcohol-induced injury.

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★ 0098 | ADIPOCYTE MIR-150 DEFICIENCY AMELIORATES ALCOHOL-INDUCED LIVER INJURY BY PROMOTING ADIPOSE TISSUE BROWNING

Jing Ma[1] THEMIS THOUDAM[1] Nazmul Huda[1] Hui Gao[1] Ge Zeng[1] Yanchao Jiang[1] Zhihong Yang[1] Suthat Liangpunsakul[1], [1]Indiana University school of medicine

Background: Alcohol-associated liver disease (ALD) is driven not only by hepatic injury but also by

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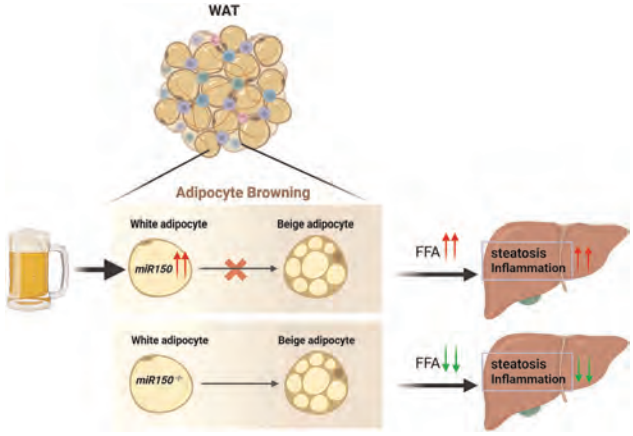
dysregulated crosstalk between adipose tissue and the liver. Adipose dysfunction contributes to hepatic steatosis and inflammation during chronic alcohol exposure. miR-150, a miRNA involved in immune and metabolic regulation, has recently emerged as a potential mediator of inter-organ communication. However, its role in adipose tissue–liver signaling in the context of ALD remains unclear. **Methods:** MiR150 levels were measured in serum (S) and liver (L) samples from healthy controls (HC, N = 15 for S, 5 for L), heavy drinkers (HD, N = 17 for S), and alcohol-associated hepatitis (AH, N = 65 for S, 5 for L) patients. Correlations between miR150 levels, MELD scores, and serum transaminases were analyzed. Global *miR150* knockout mice (*miR150*$^{-/-}$) and adipocytes cell-specific miR150 knockout mice (*miR150*-$^{Adi-/-}$) were generated to assess the function of *miR150* in a chronic plus binge alcohol feeding model. **Results:** Serum and hepatic miR-150 levels were significantly reduced in AH patients compared to healthy controls. Serum miR-150 was inversely correlated with AST levels but not with MELD scores. In ethanol-fed mice, hepatic and serum miR-150 expression was markedly decreased, while its expression in white adipose tissue (WAT) was elevated. Genetic deletion of miR-150 (miR150$^{-/-}$) attenuated ethanol-induced liver injury and steatosis, as evidenced by decreased serum ALT and hepatic triglyceride levels. miR150$^{-/-}$ mice exhibited increased hepatic expression of fatty acid β-oxidation-related proteins, including PPARα, PGC1α, UCP2, CPT1A, and hormone-sensitive lipase (HSL), along with reduced expression of fatty acid translocase (FAT), a mediator of fatty acid uptake. In WAT, miR-150 deletion led to upregulation of β-oxidation-associated genes (e.g., *Pgc1α*, *Ucp2*, *Cpt1α*) and reduced plasma free fatty acid (FFA) levels in ethanol-fed mice. Adipocyte-specific miR-150 knockout (miR150$^{Adi-/-}$) mice showed significantly reduced ethanol-induced liver injury, steatosis, and inflammation, along with decreased hepatic triglycerides, lower ALT, and reduced expression of inflammatory genes. These mice also displayed lower plasma FFA levels. Mechanistically, adipocyte-specific deletion of miR-150 promoted WAT browning, evidenced by elevated UCP1 expression, reduced adipocyte size, and increased expression of browning-related genes such as *Cycs* and *Dio2*. In vitro, miR-150-deficient adipocytes derived from preadipocytes demonstrated enhanced expression of browning-related genes (*Cpt1a*, *Cpt2*, *Cycs*, *Acadvl*, *Cox7a*, *Cox8b*, *Dio2*). **Conclusion:** Our findings identify miR-150 as a novel regulator of adipose–liver communication in ALD, linking adipocyte-derived miR-150 to the regulation of WAT browning and hepatic lipid metabolism. Targeting adipose-specific miR-150 may represent a promising therapeutic strategy to ameliorate alcohol-induced liver injury.



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★ 0099 | LIVER SPECIFIC SEXUAL FUNCTION ASSESSMENT TOOL

Yooyun Chung[1] *Deepak Joshi*[1] *Niloufar Safinia*[1] *Michael Heneghan*[1], [1]*King's College London*

Background: Patients with liver disease (LD) or liver transplantation (LT) may experience sexual dysfunction (SD). The existing tools to assess SD are not specific to LD/LT and our aim was to develop a liver specific sexual function (SF) assessment tool. **Methods:** This cross-sectional study assessed SD in 822 patients with LD/LT (472 men, 350 women) at King's College Hospital. A 24-item SF assessment tool in LD/LT (SFL) for men and women were developed through a literature search, input from a multidisciplinary panel of experts and patient group feedback. The international index of erectile function (IIEF) for men, female sexual function index (FSFI) and female sexual distress scale (FSDS) for women were used as gold standard, non-liver specific SF assessment tools. Chronic liver disease questionnaire (CLDQ) was used as a liver specific quality of life (QoL) assessment tool and clinical data was gathered from patient medical records. Factor analyses (FA) were used to assess the psychometric properties of the new SFL scale. **Results:** Exploratory FA reduced the SFL to a 13-item scale with good internal consistency reliability (α = 0.96). Spearman's coefficient showed the 13-item SFL to significantly correlate with FSFI/ FSDS in women and IIEF in men (indicating criterion validity). SFL had strong correlation with the CLDQ (construct validity). The prevalence of SD were 39-46% for women and 51% for men with 23% of men having severe symptoms. A major advantage of SFL is

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that it can be used in all gender allowing inclusivity for transgender or for whom gender identity differs from the sex assigned at birth. SFL showed that women had greater degree of SD than men (0.50 for women vs 0.23 for men, $p < 0.001$). CLDQ indicated a poorer quality of life in women compared to men ($p < 0.001$). Patients with cirrhosis had greater SD and poorer quality of life according to SFL and CLDQ respectively when compared to those without cirrhosis or following LT. For women, the FSFI and FSDS were not able to detect this difference indicating the SFL can detect disease related changes in QoL. Multiple regression analysis identified age, ALBI score, feeling anxious and depressed as predictors for SD. **Conclusion:** SD affects approximately 50% of patients with LD/LT. SFL has significant correlation with the gold standard SF assessment tools and the liver specific CLDQ. The presence of cirrhosis, ALBI score, anxiety and depression are associated with risk of SD.

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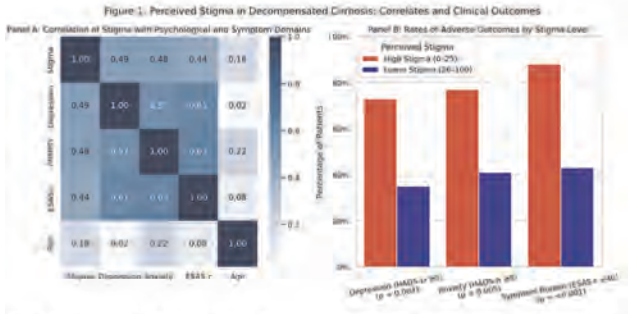
0100 | PERCEIVED STIGMA AMONG PATIENTS WITH DECOMPENSATED CIRRHOSIS AND ITS ASSOCIATION WITH PSYCHOLOGICAL DISTRESS AND SYMPTOM BURDEN

Brittany Bromfield[1] Chengbo Zeng[1] Nancy Mason[2] Michelle Diop[2] Sara Kenimer[2] Karen O'Brien[2] Kirsten Engel[2] Lucinda Li[3] John Donlan[2] Teresa Indriolo[4] Enya Zhu[5] Malia Armstrong[2] Grace Bizup[2] Anushka Dalvi[2] Cristal Brown[6] Wei Zhang[2] Nneka Ufere[2], [1]Brigham and Women's Hospital, [2]Massachusetts General Hospital, [3]UCLA, [4]Stanford University, [5]Duke University, [6]University of Texas at Austin Dell Medical School

Background: Despite its known impact in conditions like HIV and obesity, the specific burden of stigma and its association with patient-reported outcomes in decompensated cirrhosis (DC) remain under-investigated. We aimed to quantify liver-related stigma and examine its associations with psychological distress (e.g., depression and anxiety symptoms) and symptom burden in DC. **Methods:** We conducted a single-site cross-sectional study of prospectively enrolled outpatients with DC from 7/2018-9/2022. Participants completed validated instruments: the 4-item perceived stigma domain from the Short-Form Liver Disease Quality of Life questionnaire (asks the following: 1) I am embarrassed about how I look in public; 2) Some people are uncomfortable around me because of my liver disease; 3) Because of my liver disease I feel flawed and incomplete; 4) Some people avoid me because of my liver disease; score range 0–100; higher scores = lower perceived stigma), the Revised Edmonton Symptom Assessment Scale (range 0–100; scores ≥ 40: moderate-to-severe symptom burden), and the Hospital Anxiety and Depression Scale (range 0–21; scores ≥ 8: clinically significant depression/anxiety symptoms). We used multivariable linear regression adjusted for age, gender, and diagnosis of alcohol-related liver disease to examine the association of perceived stigma with psychological distress and symptom burden. **Results:** Among 218/312 (70%) patients (median age 60 [IQR 51–65]; 54% male; 89% White; 58% alcohol-related liver disease; median MELD-Na 16; 50% listed for transplant), the mean stigma score was 65.7 (SD 26.3). Stigma scores were significantly lower (i.e., greater perceived stigma) among those with more advanced liver disease (Child-Pugh A vs. B vs. C: 80.6 vs. 67.8 vs. 57.8; $p = 0.001$) and younger patients (ages 18–44: 61.4 vs. 45–64: 62.9 vs. ≥ 65: 73.8; $p = 0.019$). Patients in the highest quartile of perceived stigma (scores 0-25) were significantly more likely to report clinically significant depression (73% vs. 35%, $p = 0.004$) and anxiety (77% vs. 41%, $p = 0.005$) symptoms, and moderate-to-severe symptom burden (88% vs. 43%, $p < 0.001$) compared to those reporting lower perceived stigma (scores 26–100). In adjusted analyses, greater perceived stigma was independently associated with more severe depression symptoms (absolute $\beta = 0.08$, $p < 0.001$), anxiety symptoms (absolute $\beta = 0.08$, $p < 0.001$), and total symptom burden (absolute $\beta = 0.34$, $p < 0.001$). **Conclusion:** Stigma is a prevalent, debilitating burden in DC, particularly among younger patients and those with advanced disease, and is independently associated with psychological distress and symptom burden. Addressing stigma as a modifiable driver of distress through multilevel interventions and early psychosocial support is essential to improving health outcomes in cirrhosis care.

Figure 1. Perceived Stigma in Decompensated Cirrhosis: Correlates and Clinical Outcomes



Panel A: Heatmap displaying absolute Pearson correlation coefficients between perceived stigma and key clinical outcomes. Greater perceived stigma (lower scores on the SF-LDQOL stigma domain) was moderately correlated with depression ($r = 0.49$), anxiety ($r = 0.48$), and symptom burden (ESAS-r, $r = 0.44$), and weakly correlated with age ($r = 0.18$).

Panel B: Bar chart comparing the proportion of patients with clinically significant depression (HADS-D ≥8), anxiety (HADS-A ≥8), and symptom burden (ESAS-r ≥40) between those in the highest quartile of perceived stigma (scores 0–25) and those with lower stigma (scores 26–100). Patients with greater stigma reported substantially higher rates of depression (73% vs. 35%, $p = 0.004$), anxiety (77% vs. 41%, $p = 0.005$), and symptom burden (88% vs. 43%, $p < 0.001$).

Disclosures: Brittany Bromfield: Nothing to Disclose, Chengbo Zeng: Nothing to Disclose, Nancy Mason: Nothing to Disclose, Michelle Diop: Nothing to Disclose, Sara Kenimer: Nothing to Disclose, Karen O'Brien:

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0101 | TARGETING MENTAL HEALTH AND FATIGUE IN PBC, PSC, AND CIRRHOSIS: A SUBGROUP ANALYSIS FROM THE EMPOWER RANDOMIZED CONTROLLED TRIAL

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Background: Fatigue, anxiety, and depression are common in people with chronic liver disease, yet few scalable interventions directly target these symptoms. Mind-body approaches - including psychological strategies, movement, meditation, and breathwork show potential benefit, but large randomized trial data in liver populations remain limited. **Methods:** This liver-specific subgroup analysis was embedded in the 3-arm eMPower RCT (NCT05786482), which evaluated a 12-week online mind-body wellness program combining acceptance and commitment therapy informed strategies, breathwork, meditation, mindful-movement, and disease-specific education. Adults with PBC, PSC, or cirrhosis were randomized to waitlist control (n = 85), eMPower (n = 84), or eMPower + weekly non-clinician check-ins (n = 86), with analysis comparing the two intervention groups to control. Validated measures assessed mental health (HADS), fatigue (Modified Fatigue Impact Scale (MFIS)), frailty (online Fried Frailty Phenotype, Edmonton Frail Scale (EFS)), demoralization (Demoralization-II), and quality of life (SF-12, EQ-5D-5L), and liver-specific outcomes (Chronic Liver Disease Questionnaire (CLDQ)). Analyses used ANCOVA, adjusted for baseline values, sex, and age. The primary outcome was change in HADS total score; secondary outcomes included MFIS and SF-12 scores. A nested qualitative study explored participant perspectives on symptoms and program engagement. **Results:** Among 255 liver participants (PBC 72.2%, cirrhosis 20.0%, PSC 7.8%), the mean age was 59 years ± 11.1 and 88% were female. At 12 weeks, those in the intervention arms showed greater improvements than controls in HADS total (–3.4 points; $p < 0.001$; MCID: 1.5–2.0), MFIS total (–5.9 points; $p < 0.001$; MCID: 4–8), SF-12 Mental Component Summary Score (+3.6 points; $p < 0.001$; MCID: 3–5), and Demoralization-II (–2.3 points; $p = 0.003$; MCID: 2). Physical, cognitive, and psychosocial fatigue subdomains improved alongside frailty (Fried: –1.2 points; $p = 0.001$) and EQ-5D-5L functional domains. Qualitative interviews reinforced fatigue as "cyclical," "draining," and deeply intertwined with mental health. Participants described improved self-efficacy using the program's breathwork and movement. **Conclusion:** This is the largest randomized evaluation of a digital mind-body intervention in chronic liver disease. As a subgroup analysis of a larger trial, while not powered to detect change, the eMPower program significantly improved mental health, fatigue, and quality of life in adults with PBC, PSC, and cirrhosis. Effects exceeded established MCIDs, reinforcing the clinical relevance of these changes. Findings support the use of scalable, low-intensity digital strategies to address symptom burden in hepatology care.

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0102 | GETTING TO IMPLEMENTATION: A STEPPED WEDGE CLUSTER RANDOMIZED TRIAL OF A HOSPITAL-LEVEL INTERVENTION TO IMPROVE HEPATOCELLULAR CARCINOMA SURVEILLANCE

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Background: Adherence to HCC surveillance guidelines remains variable and low nationally. Implementation science offers strategies to address gaps between evidence and practice. We aimed to empirically identify and prescribe successful implementation strategies through Getting To Implementation (GTI), a manualized facilitation approach to increase HCC surveillance. **Methods:** This hybrid type III, stepped-wedge, cluster-randomized trial was conducted at 12 Veterans Health Administration (VA) hospitals between October 2020 and October 2022. GTI guided clinician teams in each hospital select, apply, and evaluate data-driven implementation strategies. HCC surveillance was monitored over time, and mixed effects models were used to assess the impact of the intervention on implementation reach (defined as The primary outcome of reach was defined as the receipt of HCC surveillance by at-risk Veterans) and sustainment (defined as reach over time). The a priori threshold for successful implementation was completion of the GTI steps by at least 80% of hospitals. **Results:** Facilitators supported hospital teams for an

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average of 19 ± 5 hours over a 6-month active implementation period. Ten of 12 sites (83%) completed GTI, meeting adoption threshold. Hospitals applied a median of five strategies. HCC surveillance increased from mean 32.2% to mean 40.8% from pre- to post-intervention, and further increasing to 42.1% in the sustainment period. In unadjusted and adjusted models, odds of HCC surveillance were significantly higher during intervention (adjusted odds ratio, aOR = 1.67, 95% CI:1.59, 1.75) and 6-month sustainment (aOR = 1.68, 95% CI:1.60, 1.76), compared with baseline, with no difference between active and sustainment periods, indicating sustained improvement after facilitation ended. **Conclusion:** GTI sustainably improved HCC surveillance by approximately 10%, suggesting that data-driven implementation strategies can be "prescribed" to efficiently improve hepatology care measures.

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0103 | CLINICAL OUTCOMES AND HEMIN USE OF PATIENTS WITH ACUTE HEPATIC PORPHYRIA IN THE PHASE 3 ENVISION STUDY WHO WERE NOT ATTACK-FREE AFTER 6 MONTHS OF GIVOSIRAN TREATMENT

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Background: Acute hepatic porphyria (AHP) is a group of rare disorders with acute attacks of severe abdominal pain and neurological symptoms, increased aminolevulinic acid (ALA) and porphobilinogen (PGB) levels, chronic symptoms and long-term complications. In ENVISION, givosiran, an RNA interference therapeutic approved for AHP treatment, led to sustained reductions in annualized attack rate (AAR). **Methods:** Eligible patients with AHP, ≥ 12 years old, with ≥ 2 attacks requiring hospitalization, urgent care, or hemin at home in the 6 months (M) before enrollment, entered a 6M placebo-controlled double-blind period with 30M open-label extension (OLE) in which all patients received givosiran. This *post hoc* analysis included patients who completed the OLE. Subgroups were defined by attack frequency after the first 6M of givosiran (0 attacks, attack-free; ≥ 1 attack, not attack-free). **Results:** Of 94 randomized patients, 79 completed ENVISION; 46 (58%) were attack-free after M6 of givosiran and remained so for the OLE. Among 33 (42%) patients not attack-free at M6, the mean reduction in AAR (attacks requiring hospitalization, urgent care, or hemin at home) per 6M interval was 57% after > 6-12M of treatment and 85% after > 30-36M, relative to historical AAR (mean [SD], 12.8 [9.6]). Proportions of patients who were attack-free during 6M treatment intervals increased from 9% at > 6-12M to 79% at > 30-36M; those with no hemin use increased from 36% to 76% at the same time points. Health-related quality of life (HRQoL) improved in both groups (Table): at 6M and 36M of treatment, mean SF-12 v2 Physical Component Summary scores increased from baseline by 7.3 and 8.3 points (attack-free) and 4.1 and 9.1 points (not attack-free); EQ-VAS scores increased by 6.9 and 19.9 points (attack-free) and 2.2 and 17.5 points (not attack-free). After 6M and 36M of givosiran treatment, median ALA reductions from baseline were 88% and 93% (attack-free) and 85% and 92% (not attack-free); median PGB reductions from baseline were 88% and 97% (attack-free) and 86% and 93% (not attack-free). **Conclusion:** Both groups had fewer attacks and other treatment-related improvements with the first 6M of givosiran treatment regardless of the 6M attack status. Those who were not attack-free after the first 6M had further attack reductions and HRQoL improvements with prolonged treatment. The results suggest that the response to givosiran treatment helps with chronic symptoms as well as AHP attacks and further clinical improvement is expected over time.

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Table: Clinically Meaningful Increases in Health-Related Quality of Life (HRQoL) Outcomes

HRQoL Outcome	Clinically Meaningful Increase[a]
SF-12 v2 Physical Component Summary scores	≥2-5 points
EQ-VAS scores	≥7-8 points

[a]Based on values reported as clinically meaningful in other chronic diseases

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0104 | HEPATOLOGY-LED EDUCATION ON ALCOHOL-RELATED LIVER DISEASE DURING CHEMICAL DEPENDENCY TREATMENT: IMPACT ON RETURN TO DRINKING AND CLINICAL OUTCOMES

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Background: Chemical dependency programing for alcohol use disorder (AUD) traditionally focuses on treatment of the underlying use disorder with a limited focus on medical complications of alcohol use. To address this gap, we introduced a group-based educational session led by a hepatology provider for adults undergoing inpatient alcohol treatment. This is a retrospective study looking at effect of this educational intervention on return to alcohol use and downstream healthcare utilization. **Methods:** Adult patients attending treatment were divided into cohorts before and after implementation of this program (historical control 10/2021-9/2022, educational intervention 1/2023-12/2023). Patient demographics, ICD codes for AUD/ARLD, laboratory results, and return to drinking were abstracted. **Results:** 569 patients were included (n = 275 historical control, n = 294 educational intervention). The majority were white (70.5%) males (65.0%). The mean age at the start of treatment was 40.6 years old. Follow up was longer for the historical control as expected (Table 1). Prior to the start of treatment 55.5% had a previous inpatient diagnosis code for AUD, and 17.1% and 5.8% had any coding for compensated or decompensated ARLD, respectively. There were no baseline differences in terms of liver disease severity (Table 1). Just under a third (31.8%) returned to alcohol use after treatment, which was higher in historical controls (38.2%) compared to the educational intervention (25.9%, p = 0.002). The average return to drinking was 223.1 days, which was not different between the cohorts (222.3 v. 224.3, p = 0.18). The proportion of adults returning to drinking was higher in the historical control at 90 days (12.4% v. 5.4%, p = 0.005), 180 days (22.9% v. 12.2%, p = 0.001), and 365 days (30.9% v 20.8%, p 0.007) post treatment. Outcomes were measured after completing treatment (Table 1). Fib-4 was minimally higher in historical controls, but otherwise there were no cohort differences in coding for inpatient AUD or different stages of ARLD. In people who returned to drinking, regardless of cohort, there were higher rates of coding for inpatient AUD and compensated ARLD with higher Fib-4 scores during follow up. **Conclusion:** Return to alcohol use after treatment occurs in a significant minority of patients. We found that integrating a hepatology provider into treatment to educate patients about ARLD was associated with reduced return to drinking, potentially by increasing disease awareness and motivation for abstinence. Although the intervention was not associated with a reduction in adverse outcomes, individuals who maintained abstinence exhibited less severe liver disease and lower healthcare utilization related to AUD. This highly scalable approach represents a shift toward upstream, preventive hepatology care for ARLD and holds significant potential to improve outcomes for AUD.

	All patients (n=569)	Historical Control (n=275) (10/1/2021-9/30/2022)	Educational Intervention (n=294) (1/1/2023-12/31/2023)	P-value	Return to Drinking (n=181)	No Return to Drinking (n=388)	P-value
Demographics							
Male gender	65.0% 370	67.6% 186	62.6% 184	0.22	67.4% 122	63.9% 248	0.45
White	70.5% 401	**75.3% 207**	**66.0% 194**	**0.03**	**79.6% 144**	**66.2% 257**	**0.001**
African American	14.6% 83	13.8% 38	15.3% 45	0.64	13.3% 24	15.2% 59	0.61
American Indian or Alaskan Native	3.3% 19	2.6% 7	4.1% 12	0.36	2.2% 4	3.9% 15	0.45
Asian	3.9% 22	**1.5% 4**	**6.1% 18**	**0.004**	1.7% 3	4.9% 19	0.07
Hispanic	3.0% 17	3.3% 9	2.7% 8	0.81	3.3% 6	2.8% 11	0.79
Age at the start of treatment (mean +/- S.D.)	40.6 +/- 11.6	40.4 +/- 11.9	40.8 +/- 11.3	0.45	**42.2 +/- 11.6**	**39.9 +/- 11.5**	**0.044**
ICD codes prior to treatment							
Inpatient AUD	55.5% 316	54.6% 150	56.5% 166	0.67	**80.7% 146**	**43.8% 170**	**<0.000**
Compensated ARLD	17.1% 97	15.6% 43	18.4% 54	0.44	**26.0% 47**	**12.9% 50**	**<0.000**
Decompensated ARLD	5.8% 33	4.7% 13	6.8% 20	0.37	5.52% 10	5.93% 23	1.00
Labs prior to treatment							
FIB-4 (mean +/- S.D., range)	2.2 +/-2.3 (0.15-15.2)	2.1 +/- 2.1 (0.14-14.0)	2.3 +/- 2.5 (0.2-15.1)	0.50	**2.5 +/-2.3 (0.1-14.1)**	**2.0 +/-2.3 (0.2-15.2)**	**0.0002**
% FIB-4 < 1.67	57.9% 248	57.7% 116	58.2% 132	1.00	**46.6% 76**	**64.9% 172**	**<0.000**
% FIB-4 > 2.67	27.1% 116	26.4% 53	27.8% 63	0.83	**35.0% 57**	**22.3% 59**	**0.003**
ICD codes after treatment							
Inpatient AUD	30.4% 173	35.3% 97	25.9% 76	0.32	**75.1% 136**	**0.5% 37**	**<0.000**
Compensated ARLD	9.3% 39	6.7% 16	9.9% 23	0.24	**28.2% 51**	**5.9% 23**	**<0.000**
Decompensated ARLD	5.1% 24	4.2% 10	6.0% 14	0.41	6.1% 11	3.4% 13	0.18
Labs after treatment							
FIB-4 (mean +/- S.D, range)	1.9 +/- 2.4 (0.1-25.2)	**1.9 +/- 2.8 (0.1-25.2)**	**1.9 +/-1.9 (0.3-13.4)**	**0.04**	**2.2 +/- 2.8 (0.1-25.4)**	**1.5 +/- 1.8 (0.2-13.4)**	**<0.000**
% FIB-4 < 1.67	67.0% 209	69.1% 114	64.6% 95	0.24	**57.2% 95**	**78.1% 114**	**<0.000**
% FIB-4 > 2.67	16.4% 51	13.9% 23	19.1% 28	0.14	18.7% 31	13.7% 20	0.15
Follow up period (days)	775.9 +/- 253.0	**1013.2 +/- 105.3**	**553.8 +/- 106.6**	**<0.000**	**837.4 +/- 231.9**	**747.2 +/- 257.6**	**0.0001**

Disclosures: Mary Thomson: Nothing to Disclose, Lisa Vollmer: Nothing to Disclose, Alexander Hubbell: Nothing to Disclose, Elizabeth Aby: United Health Care

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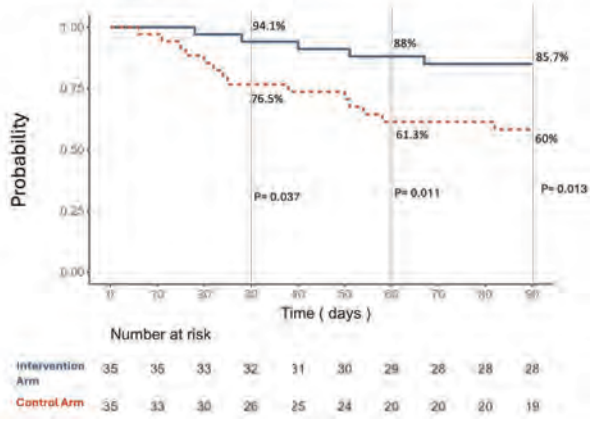
★ 0105 | COMBINATION OF RIFAXIMIN, PLASMA EXCHANGE, AND GRANULOCYTE COLONY STIMULATING FACTOR WITH STANDARD MEDICAL THERAPY VERSUS STANDARD MEDICAL THERAPY ALONE IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS: RESULTS: FROM THE GRACE-AH RANDOMIZED CONTROLLED TRIAL

Dr. Ashwin Vinod[1] Nipun Verma[1] Pratibha Garg[1] Malavika Sanal[1] Parminder Kaur[1] Jayant Agarwal[1] Sahaj Rathi[1] Arka De[1] Divjot Lamba[1] Rekha Hans[1] Ashish Kakkar[1] Abhishek Ghosh[1] Sunil Taneja[1] Ratti Ram Sharma[1] Ajay Duseja[1], [1]PGIMER Chandigarh

Background: Severe alcohol associated hepatitis (SAH) is a prototypical multi-axial disease characterized by bacterial translocation, immune dysregulation, and impaired hepatic regeneration, contributing to high short-term mortality. Monotherapies have shown limited efficacy due to this complex pathobiology. There is a pressing need for combinatorial therapies that address these interlinked mechanisms. This study evaluated the efficacy of a novel multimodal approach—targeting gut-liver axis (rifaximin), endothelial and immune modulation (therapeutic plasma exchange, TPE), and hepatic regeneration or modulation of cell death (granulocyte-colony stimulating factor, G-CSF)—in addition to standard medical therapy (SMT), compared to SMT alone in SAH non-responders. **Methods:** In this single center randomized controlled trial conducted from April 2023 to April 2024, 70 patients with SAH non-responsive to SMT were randomized to receive either combinatorial therapy (intervention arm) (n = 35) or SMT alone (control arm) (n = 35). Patients were followed for 90 days. The primary endpoint was overall survival; secondary outcomes included transplant-free survival, organ dysfunction scores, infection rates, stem cell mobilization, bacterial translocation, endothelial injury, cell death, and safety. Linear mixed effects models were used to evaluate the change over time of the biomarkers between the groups (fixed effect) after adjusting for individual patient trajectories (random effect). **Results:** Thirty, Sixty, and Ninety-day survival were significantly higher in the intervention arm (Figure 1) (90-day survival- 85.7% vs. 60%; $p = 0.013$). Hazard ratio for mortality at 90 days was 0.29 (95% CI: 0.11–0.82; $p = 0.019$). The intervention also led to reductions in MELD, CLIF-C-OF, and mDF scores, lower infection rates (40% vs. 68.6%; $p = 0.031$), and improved stem cell mobilization (CD34+; $p < 0.001$). Improvements in biomarkers of translocation (LPS) [beta (95% CI) = -32.36 (-38.8 to -25.91)], endothelial injury (vWF) [beta (95% CI) = -29.9 (-37.1 to -22.65)], and necroptosis (RIPK3) [beta (95% CI) = -4.071 (-5.125 to -3.017)] were also noted. **Conclusion:** This first-in-human proof-of-concept trial demonstrates a significant survival benefit with multi-axial modulation of bacterial translocation (rifaximin), endothelial dysfunction (TPE), and cell death (G-CSF) in SAH. Future studies should explore patient enrichment strategies to further optimize outcomes in this high-risk population.

Figure 1- Overall survival in the study population



Disclosures: Dr. Ashwin Vinod: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Pratibha Garg: Nothing to Disclose, Malavika Sanal: Nothing to Disclose, Parminder Kaur: Nothing to Disclose, Jayant Agarwal: Nothing to Disclose, Sahaj Rathi: Nothing to Disclose, Arka De: Nothing to Disclose, Divjot Lamba: Nothing to Disclose, Rekha Hans: Nothing to Disclose, Ashish Kakkar: Nothing to Disclose, Abhishek Ghosh: Nothing to Disclose, Sunil Taneja: Nothing to Disclose, Ratti Ram Sharma: Nothing to Disclose, Ajay Duseja: Nothing to Disclose

0106 | AIF-1 GENETIC UPREGULATION IS A RISK FACTOR FOR ALCOHOL-ASSOCIATED LIVER DISEASE PROGRESSION

Priscila Correa Antonello[1] Colin Hodgkinson[1] Cheryl Marietta[1] Dechun Feng[1] Baskar Mohana Krishnan[1] Maria Parra[2] Zhaoli Sun[2] Bin Gao[1] David Goldman[1] Michelle Antoine[1], [1]National Institutes of Health, [2]Johns Hopkins University School of Medicine

Background: Prolonged heavy alcohol comsumption associated with alcohol use disorder (AUD) often results in various hepatic injuries, beginning with fatty liver and potentially progressing to more serious conditions of alcohol-associated liver disease (ALD), such as hepatitis, cirrhosis, or liver cancer. Chronic inflammation, driven

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by the persistent activation of immune cells such as macrophages and neutrophils, is thought to contribute significantly to the progression of liver damage. The Allograft Inflammatory Factor 1 (*AIF-1/IBA1*) gene, encodes a calcium-binding protein critical for immune functions, including cell proliferation, migration and activation. In this work we investigated whether the rs3132451 single-nucleotide polymorphism (SNP) in the promoter region of *AIF-1* influences its expression and affects immune and liver injury profiles in chronic alcohol use. **Methods:** A total of 868 individuals were analyzed and classified by AUD status based on DSM-IV/V criteria. Using a comprehensive serum panel, we assessed liver function and immune profiles of patients with and without AUD. Participants were genotyped for the *AIF-1* SNP (rs3132451), and classified into *C/C* (control/reference), *C/G* (heterozygous), or *G/G* (homozygous/risk) genotypes. A second cohort diagnosed with alcohol-associated hepatitis was evaluated to study the SNP's relationship with more advanced liver disease. A third group of abstinent individuals with a history of AUD was included to assess whether immune changes persisted after alcohol use cessation. **Results:** Individuals with the *G/G* genotype showed higher levels of *AIF-1* expression in liver tissue and immune cells. Chronic alcohol consumption, regardless of genotype, was linked to increased numbers of monocytes and neutrophils, along with elevated liver enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT)). However, those with both the *G/G* genotype and chronic alcohol use were more likely to exceed clinical thresholds for neutrophilia and iron overload. In patients with alcohol-associated hepatitis, the *G/G* genotype was associated with increased neutrophil infiltration in liver tissue and higher Model for End-Stage Liver Disease (MELD) scores, indicating more severe liver dysfunction. In abstinent individuals with prior AUD, elevated immune cell levels—especially neutrophils and monocytes—persisted over time, with the *G/G* genotype (particularly in males) linked to prolonged immune activation. **Conclusion:** The rs3132451 *G/G* variant of the *AIF-1* gene appears to worsen alcohol-related immune and liver disturbances, particularly through its role in promoting neutrophil activity. These findings suggest that genetic variation in *AIF-1* may influence the severity and progression of alcohol-induced liver injury, and that some immune disruptions may persist even after alcohol use stops.

Disclosures: Priscila Correa Antonello: Nothing to Disclose, Colin Hodgkinson: Nothing to Disclose, Cheryl Marietta: Nothing to Disclose, Dechun Feng: Nothing to Disclose, Baskar Mohana Krishnan: Nothing to Disclose, Maria Parra: Nothing to Disclose, Zhaoli Sun: Nothing to Disclose, Bin Gao: Nothing to Disclose, David Goldman: Nothing to Disclose, Michelle Antoine: Nothing to Disclose

0107 | LONG-TERM OUTCOMES FOLLOWING HOSPITALIZATION FOR ACUTE ALCOHOL-ASSOCIATED HEPATITIS

Sara Hatoum[1] Don Rockey[2], [1]Medical University of South Carolina, [2]MUSC

Background: Alcohol-associated hepatitis (AAH) is an acute form of liver injury resulting from excessive alcohol use. Due to limited treatment options and rising rates of harmful drinking, AAH is becoming an increasingly common indication for liver transplant. Unfortunately, liver transplant is not an option for many patients due to strict eligibility criteria and limited organ availability. Here, we aimed to identify clinical predictors and examine the rates of in-hospital and long-term mortality, as well as liver transplantation, in patients hospitalized for acute AAH. **Methods:** In this cohort analysis, we examined consecutive patients with definite AAH, based on NIAAA Alcoholic Hepatitis Consortia criteria, who were admitted to an academic medical center between 2012 and 2022 and underwent transjugular liver biopsy with hepatic venous pressure gradient (HVPG) measurement. Clinical and laboratory data was obtained for each patient to determine clinical and biochemical outcomes. Baseline MELD and HVPG were calculated at the time of biopsy. Patients were considered to have resolution of their portal hypertensive complications if they had resolution of ascites (off diuretics), encephalopathy (off lactulose/rifaximin), and no variceal hemorrhage. **Results:** The cohort included 154 patients with acute AAH with a mean MELD score of 27 and HVPG of 17. 147/154 patients had ascites, 49/154 had hepatic encephalopathy, and 8/154 had variceal hemorrhage. During hospitalization, 15 patients (10%) died, 5 (3%) were discharged to hospice, and 9 (6%) underwent orthotopic liver transplantation (OLT). After discharge, 22 patients (14%) were lost to follow-up, while 103 (67%) were followed for a mean of 1.8 years. Among these 103 patients, 46 died and 5 underwent OLT. The mean baseline MELD score of patients who died during follow-up was significantly higher than those who were alive at the end of follow-up (28 ± 7 vs 24 ± 6, $p = 0.01$), but there was no significant difference in the mean baseline HVPG (17 ± 6 vs 17 ± 7, $p = 0.8$) or rate of biopsy proven cirrhosis (54% vs 53%, $p > 0.9$) between the two groups (Table 1). 68/103 patients remained abstinent, while 35/103 resumed alcohol use. Patients who remained abstinent had a significantly lower mortality rate than those who resumed alcohol (29% vs 74%, $p < 0.0001$). Additionally, 17/68 (25%) of abstinent patients had complete resolution of their portal hypertensive complications despite a mean baseline HVPG of 19. **Conclusion:** Patients hospitalized for acute AAH experience high rates of in-hospital and long-term mortality, particularly those with elevated MELD scores. Sustained alcohol abstinence following discharge was strongly

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associated with improved survival, and in some patients, resolution of portal hypertension and recompensation. Biopsy proven cirrhosis did not have a significant impact on survival rates following hospital discharge.

Table 1: Characteristics of patients followed up after hospital discharge

Indicator	Died during follow-up (n=46)	Alive at the end of follow-up (n=57)	P value
Age	45±11	44±12	0.8
Male (%)	46	51	0.7
Baseline MELD	28±7	24±6	0.01
Baseline HVPG	17±6	17±7	0.8
Biopsy proven cirrhosis (%)	54	53	>0.9
Abstinent (%)	44	84	<0.0001

Disclosures: Sara Hatoum: Nothing to Disclose, Don Rockey: WL Gore and Associates: Consultant, Cook Medical: Consultant, BD Medical: Consultant, AstraZeneca: Grant/Research Support, Bio89: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Durect: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Intercept: Grant/Research Support, Inventiva: Grant/Research Support, Madrigal: Grant/Research Support, Ocelot: Grant/Research Support, Salix: Grant/Research Support, Novonordisk: Grant/Research Support, Galectin: Grant/Research Support, Versantis: Grant/Research Support, Viking: Grant/Research Support

0108 | REVERSE TRANSCRIPTASE INHIBITORS ARE ASSOCIATED WITH REDUCED LIVER-RELATED COMPLICATIONS IN AUD: ESTABLISHING A PATHOGENIC ROLE OF ENDOGENOUS RETROVIRUSES IN AH AND ALD

Maddie Kubiliun[1] Ashutosh Shukla[1] Tomas Rodriguez[1] Musa Ali Rizvi[2] Samuel Piaker[1] Mujeeb Basit[2] Zhaoli Sun[3] Andrew Cameron[3] Mack Mitchell[1] Ronac Mamtani[4] Jay Luther[5] Suraj Patel[1], [1]University of Texas Southwestern Medical Center, [2]UT Southwestern Medical Center, [3]Johns Hopkins University, [4]University of Pennsylvania, [5]Massachusetts General Hospital

Background: Endogenous retroviruses (ERVs) make up ~8% of the human genome. Typically silenced, ERVs can be reactivated by inflammatory stimuli such as alcohol, triggering innate immune responses and worsening liver injury. Our preclinical mouse data show that blocking ERV reverse transcription with FDA-approved reverse transcriptase inhibitors (RTIs) attenuates alcohol-induced liver injury and inflammation. In two complementary studies, we aimed to (1) evaluate hepatic ERV expression in patients with alcoholic hepatitis (AH) and cirrhosis (AC), and (2) assess whether RTI use is associated with reduced liver-related complications in individuals with alcohol use disorder (AUD). **Methods:** Liver RNA-seq from 25 patients with alcoholic hepatitis (AH) or cirrhosis (AC) was analyzed using a custom pipeline to quantify full-length human ERV (hERV) expression, with a focus on the evolutionary young hERV-K family. hERV-K reverse transcriptase protein levels were measured in matched liver biopsies. To assess the clinical impact of RTIs, we performed a retrospective cohort study using the nationwide Epic Cosmos database. Patients with AUD and prior RTI exposure were matched 1:1 to unexposed AUD patients using propensity scores accounting for demographic, metabolic, and psychiatric covariates. Individuals with pre-existing liver disease or CD4 < 200 were excluded. Liver-related outcomes were identified by SNOMED CTs and ICD-10 codes, and associations with RTI exposure were evaluated using multivariable logistic regression. Landmark analyses were used to adjust for immortal time bias. **Results:** RNA-seq revealed significant upregulation of hERV expression in AH (FC 8.6, $p = 0.03$) and AC samples (FC 2.5, $p = 0.006$) compared to controls. Furthermore, hERV expression linearly correlated with AH severity. hERV-K reverse transcriptase protein levels were increased in liver biopsies from AH and AC patients. In the retrospective study, we identified 13,921 AUD patients with prior RTI exposure and 13,921 propensity-matched AUD patients without RTI exposure; both groups had similar follow-up durations. RTI-exposed AUD patients had reduced odds of cirrhosis (OR 0.77, $p = 2.1e\text{-}5$), MALOs (OR 0.81, $p = 1.2e\text{-}3$), AH (OR 0.74, $p = 5.4e\text{-}6$), HCC (OR 0.67, $p = 6.3e\text{-}3$), and all-cause mortality (OR 0.84, $p = 1.3e\text{-}3$). **Conclusion:** Hepatic hERV expression is increased in AH and AC, and correlates with disease severity. RTI exposure is associated with reduced liver-related outcomes, including AH, AC and mortality in AUD. These findings support a pathogenic role for ERVs in ALD and highlight RTIs as a potential therapeutic strategy.

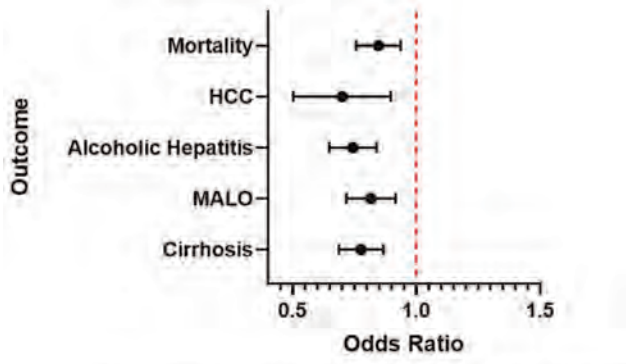

Fig 1: Odds of liver-related outcomes among RTI users vs non-RTI users with AUD

Disclosures: Maddie Kubiliun: Nothing to Disclose, Ashutosh Shukla: Nothing to Disclose, Tomas Rodriguez: Nothing to Disclose, Musa Ali Rizvi: Nothing to Disclose, Samuel Piaker: Nothing to Disclose, Mujeeb Basit: Pfizer: Advisor, Zhaoli Sun: Nothing to Disclose, Andrew Cameron: Nothing to Disclose, Mack Mitchell: Nothing to Disclose, Ronac Mamtani: Nothing to

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Disclose, Jay Luther: Nothing to Disclose, Suraj Patel: Nothing to Disclose

0109 | TEN-YEAR POST-TRANSPLANT SURVIVAL OUTCOMES AFTER EARLY LIVER TRANSPLANT FOR SEVERE ALCOHOL-ASSOCIATED HEPATITIS: AN ACCELERATE-AH STUDY

Matthew Dukewich[1] Christine Hsu[2] Neha Jakhete[3] George Therapondos[4] Sheila Eswaran[5] Ethan Weinberg[6] Mohamed Shoreibah[7] Manotri Chaubal[8] Adam Khalaf[8] Amol Rangnekar[9] Kirti Shetty[10] Cerise Kleb[3] Sevda Aghayeva[6] Ruona Ebiai[4] Sameera Shuaibi[4] Chandler Shapiro[5] John Rice[11] Jessica Musto[11] R. Mark Ghobrial[12] Ashton Connor[13] Michael Lucey[11] Norah Terrault[14] Brian Lee[15], [1]University of Southern California- Keck Medicine, [2]National Institute of Diabetes and Digestive and Kidney Diseases, [3]University of Maryland, [4]Ochsner Medical Center, [5]Rush University Medical Center, [6]University of Pennsylvania, [7]University of Alabama at Birmingham, [8]Georgetown University, [9]Georgetown University Hospital, [10]University of Maryland, Baltimore, [11]University of Wisconsin, [12]Houston Methodist JC Walter Transplant Center, [13]Houston Methodist, [14]University of Southern California, [15]Keck School of Medicine

Background: Early (<6 months of sobriety) liver transplant (LT) for severe alcohol-associated hepatitis (AH) is the fastest growing indication for LT in the US and Europe. Studies in this population have been limited to short-term (1- and 3-year) post-LT outcomes. Leveraging the ACCELERATE consortium, herein we investigate long-term (>3 year) post-LT alcohol use and survival outcomes and patient factors associated with early (<3 years) vs. late (>3 years) return to alcohol use and mortality. **Methods:** In this retrospective cohort of 9 US LT centers, we included LT recipients for clinically diagnosed severe AH between 2006-2021. Kaplan-Meier survival analysis estimated survival rates post-LT. Alcohol use was captured at first detection during post-LT follow-up by clinical interview and biomarkers (e.g. ethyl glucuronide or phosphatidylethanol) (early use < 3 years post-LT, late use > 3 years post-LT). Multinomial logistic and multivariable Cox regression were used to compare the relative risk ratios (aRRR) and hazard ratios (aHR) of pre-LT clinical, demographic, and psychosocial factors associated with early or late return to alcohol use (vs no alcohol use) and early or late mortality. **Results:** Among 316 included LT recipients (67% male, median age 43 years, median MELD-Na at LT of 37), median post-LT follow-up was 4.4 (IQR 1.5-7.0) years. Early return to any alcohol use occurred in 79 (risk 25.9% [95%CI 12.0-23.5%]) while late return to any alcohol use occurred in 19 (risk by 7 years post-LT 10.4%, [6.3-16.9%]) with an overall median of 273 days (IQR 91-730 days) to first post-LT drink. Older age (aRRR 0.97 [0.95-0.99] per year) and male sex (aRRR 0.50, 95%CI 0.32-0.80) were associated with lower risk for early return to alcohol use (vs. no return to use), while Medicaid (vs. private) insurance was associated with greater risk for late return to alcohol use (aRRR 3.74, 95%CI 1.28-11.0) in age, sex, and MELD adjusted analysis. There were a total of 66 deaths (21.0%) during post-LT follow-up, at a median of 1.9 years (IQR 0.8-8.0 years) post-LT. Post-LT survival was 80.8% (75.3-85.2%) at 5-years, 75.2% (68.3-80.7%) at 7-years, and 67.6% (58.6-75.0%) at 10-years. Demographics associated with psychosocial risk, peri-operative vascular complications, and return to alcohol use were associated with early post-LT mortality; need for dialysis at LT, biliary complications, and return to alcohol use were associated with late post-LT mortality (Table). **Conclusion:** In this first report of 10-year post-LT outcomes among early LT for severe AH recipients, long-term post-LT survival is better or on par with other indications for LT. More than 25% of ELT recipients returned to alcohol use in the first 3-years post-LT, while an additional 10% returned to alcohol use by 7-years post-LT. We identified different risk factors for early vs. late post-LT outcomes, which informs candidate selection and longitudinal post-LT interventions to improve outcomes.

Table. Association of Pre-LT Factors with Post-LT Return to Alcohol Use and Post-LT Survival

Disclosures: Matthew Dukewich: GlaxoSmithKline: Stock - publicly traded company, Christine Hsu: Nothing to Disclose, Neha Jakhete: Proctor & Gamble: Stock - publicly traded company, George Therapondos: Novo Nordisk: Consultant, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Ipsen: Speaking and Teaching, Gilead: Speaking and Teaching, Sheila Eswaran: Nothing to Disclose, Ethan Weinberg: PharmaIN: Consultant, BioVie: Consultant, Sequana: Consultant, Novo Nordisk: Advisor, Amgen: Consultant, Astra Zeneca: Consultant, Kezar: Consultant, Mohamed

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0110 | THE IMPACT OF CANNABINOIDS ON THE RISK OF ALCOHOL-ASSOCIATED LIVER DISEASE

Butros Fakhoury[1] Vinay Jahagirdar[1] Kaanthi Rama[1] David Hudson[2] Wei Wang[1] Luis Díaz[3] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]Western University & London Health Sciences Centre, [3]University of California San Diego

Background: Alcohol-associated liver disease (ALD) is a major cause of liver-related morbidity and mortality, yet effective therapeutic options remain limited. Preclinical data suggest that modulation of the hepatic endocannabinoid system, particularly via cannabidiol (CBD), may reduce alcohol-induced liver injury. Due to CBD's limited clinical use, we sought to evaluate the association between cannabis use and ALD risk among patients with alcohol use disorder (AUD). **Methods:** Using the TriNetX US Collaborative Network, we identified adult patients with AUD from 2010 to 2022, excluding those with preexisting liver disease. Patients were stratified into three cohorts: cannabis use disorder (CUD), cannabis users without CUD (CU), and non-cannabis users (non-CU). Propensity score matching was performed based on cardiometabolic risk factors, liver function, psychiatric comorbidities, and other substance use. Outcomes included ALD, hepatic decompensation, and all-cause mortality over 3 years. Kaplan–Meier curves and Cox regression were used to estimate hazard ratios (HRs). **Results:** After matching, 32,125 patients were included in each of the CUD and non-CU groups; 11,114 in each of the CUD vs. CU comparison; and 11,231 in the CU vs. non-CU comparison. Compared to non-CU, CUD was associated with reduced risks of ALD (HR 0.61; 95% CI 0.54–0.69; $p < 0.001$), hepatic decompensation (HR 0.78; 95% CI 0.68–0.89; $p < 0.001$), and all-cause mortality (HR 0.86; 95% CI 0.79–0.94; $p < 0.001$). CU was associated with reduced ALD risk (HR 0.80; $p = 0.015$), but not decompensation or mortality. Compared to CU, CUD was also associated with lower ALD risk (HR 0.75; $p = 0.007$). Sensitivity analyses excluding patients with obesity, diabetes, or other substance use disorders yielded consistent results. As a positive control, CUD was associated with increased schizophrenia risk (HR 1.20; $p < 0.001$), but not cerebrovascular disease (HR 0.94; $p = 0.122$), supporting the internal validity of the cohort. **Conclusion:** In this large, propensity-matched cohort of AUD patients, cannabis use was associated with a reduced risk of ALD, with the greatest risk reduction seen in patients with CUD compared to CU and non-CU. Given the established risks of cannabis and the emerging evidence supporting CBD's hepatoprotective potential, further clinical studies evaluating CBD's role in ALD prevention and treatment are warranted.

Table 1. Outcomes by Cannabis Use Status at 3-Year Follow-Up

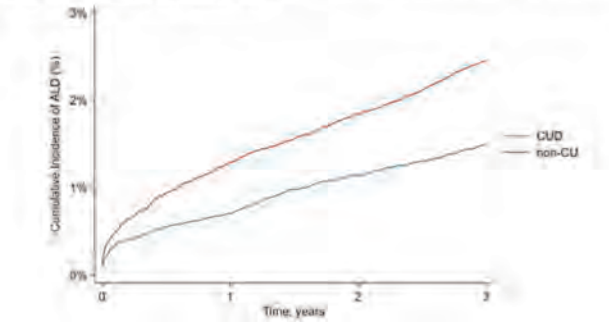
Cohort	Outcome	Incidence rate (1000PY)	HR (95% CI)	P-value
CUD vs non-CU	ALD	CUD: 3.90 vs Non-CU: 6.81	0.61 (0.54–0.69)	<0.001
	Hepatic decompensation	CUD: 4.86 vs Non-CU: 6.31	0.78 (0.68–0.89)	<0.001
	All-cause mortality	CUD: 13.39 vs Non-CU: 15.59	0.86 (0.79–0.94)	<0.001
CU vs non-CU	ALD	CU: 8.26 vs Non-CU: 10.13	0.80 (0.67–0.96)	0.015
	Hepatic decompensation	CU: 7.86 vs Non-CU: 8.44	0.92 (0.76–1.11)	0.376
	All-cause mortality	CU: 17.47 vs Non-CU: 19.36	0.89 (0.79–1.02)	0.083
CUD vs CU	ALD	CUD: 6.07 vs CU: 8.21	0.75 (0.61–0.92)	0.007
	Hepatic decompensation	CUD: 6.30 vs CU: 7.80	0.82 (0.67–1.01)	0.059
	All-cause mortality	CUD: 17.14 vs CU: 17.28	1.01 (0.88–1.15)	0.934

Abbreviations: ALD, alcohol-related liver disease; CUD, cannabis use disorder; CU, cannabis users; non-CU, non-cannabis user; PY, person-years.

Table 2. Sensitivity Analyses and Control Outcomes.

Sensitivity Analysis				
Cohort	Outcome	Incidence rate (1000PY)	HR (95% CI)	P-value
CUD vs non-CU, excluding BMI≥30 and HBA1C≥6	ALD	CUD: 6.96 vs Non-CU: 13.04	0.55 (0.42–0.67)	<0.001
	Hepatic decompensation	CUD: 7.44 vs Non-CU: 9.62	0.77 (0.61–0.98)	0.029
	All-cause mortality	CUD: 16.72 vs Non-CU: 20.31	0.82 (0.70–0.96)	0.014
CUD vs non-CU, positive control outcome	Schizophrenia	CUD: 42.94 vs Non-CU: 35.81	1.22 (1.16–1.28)	<0.001
CUD vs non-CU, negative control outcome	Cerebrovascular Diseases	CUD: 18.45 vs Non-CU: 19.63	0.94 (0.88–1.02)	0.122

Abbreviations: ALD, alcohol-related liver disease; BMI, body mass index; CUD, cannabis use disorder; HBA1C , hemoglobin A1c; non-CU, non-cannabis user; PY, person-years.



Disclosures: Butros Fakhoury: Nothing to Disclose, Vinay Jahagirdar: Nothing to Disclose, Kaanthi Rama: Nothing to Disclose, David Hudson: Nothing to Disclose, Wei Wang: Nothing to Disclose, Luis Díaz: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose

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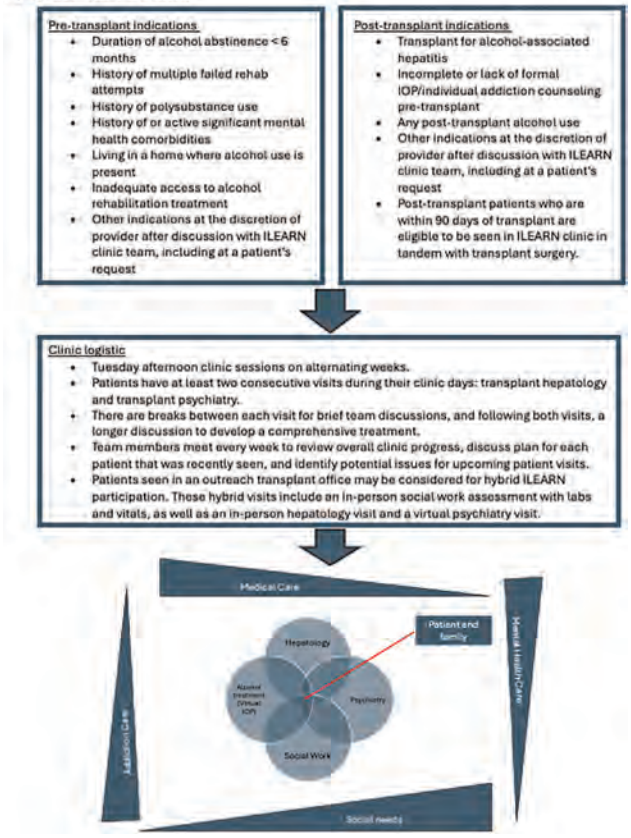
0111 | A BLUEPRINT FOR MULTIDISCIPLINARY CARE FOR ALCOHOL-ASSOCIATED LIVER DISEASE ACROSS TRANSPLANT PATHWAY: STRUCTURE, MAUD UTILIZATION, AND EARLY OUTCOMES

Jonathan Nahas[1] Bellinda Accime[1] Therese Bittermann[1] Christina Cerra[1] Arpita Goswami Banerjee[1] Kimberley Johnson[1] Renee Maggiaro[1] Emily Patrick[1] Ethan Weinberg[1] Robert Weinrieb[1] Marina Serper[1], [1]University of Pennsylvania

Background: Multidisciplinary care models to address both alcohol-associated liver disease (ALD) and alcohol use disorder (AUD) allow patients to receive coordinated care for their liver disease and substance use. Limited data exist regarding the design of these clinics and their effect on objective biomarkers of alcohol consumption among patients in the liver transplant (LT) pathway. **Methods:** We report on our center's multidisciplinary ALD/AUD clinic, ILEARN (Integrated Liver transplant Engagement And Recovery Network), from its inception in 7/2023 through 5/2025. The clinic serves patients with high-risk ALD in any phase of the transplant pathway. The clinic schedules sequential, co-located visits with hepatology and psychiatry with asynchronous integration of social work and AUD counseling. Clinic workflow and indications are shown in the Figure. **Results:** Our ILEARN cohort included 60 patients, equally distributed between pre- and post-LT at the time of their initial clinic visit (50% post-LT, 43% in evaluation, 7% listed). The cohort was 53% male, 87% White, and with mean age 50 years. At LT evaluation, mean SIPAT was 28. Among those transplanted, mean MELD 3.0 was 31. Three-quarters were enrolled in a tailored, virtual intensive outpatient program (IOP). The most recent phosphatidylethanol (PEth) was negative in 87%. Only 7% had a PEth above 200 ng/mL. Of those with a positive PEth, 25% were below 25 ng/mL, and PEth value was downtrending while receiving ILEARN care in 80%. Medications for AUD (MAUD) were prescribed in 40% of ILEARN patients, with naltrexone and gabapentin being the most common. Nearly 2/3 of the patients receiving naltrexone were newly started while in ILEARN. Only 1/60 patients had evidence of graft dysfunction attributed to alcohol. Five patients (8%) seen in the clinic died. Two were due to sepsis while in LT evaluation. Of the 3 post-LT mortalities, 2 were attributed to neurologic complications and 1 to early graft failure. No deaths were related to alcohol. **Conclusion:** Our center experience demonstrates that a multidisciplinary ALD/AUD clinic across the LT pathway is associated with a reduction in objective biomarkers of alcohol use, and our MAUD rates of 40% are well above published rates < 10%. Future studies will compare outcomes among patients with ALD that did not go through the clinic as well as provide longer term longitudinal data.

Figure. ILEARN clinic workflow



Disclosures: Jonathan Nahas: Nothing to Disclose, Bellinda Accime: Nothing to Disclose, Therese Bittermann: Nothing to Disclose, Christina Cerra: Nothing to Disclose, Arpita Goswami Banerjee: Nothing to Disclose, Kimberley Johnson: Nothing to Disclose, Renee Maggiaro: Nothing to Disclose, Emily Patrick: Nothing to Disclose, Ethan Weinberg: PharmaIN: Consultant, BioVie: Consultant, Sequana: Consultant, Novo Nordisk: Advisor, Amgen: Consultant, Astra Zeneca: Consultant, Kezar: Consultant, Robert Weinrieb: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Eurofins: Grant/Research Support

0112 | EVOLVING RISK FACTORS FOR EARLY ALLOGRAFT DYSFUNCTION IN DCD LIVER TRANSPLANTATION IN THE ERA OF MACHINE PERFUSION

ATSUSHI NISHIMAGI[1] Rikako Oki[1] Luckshi Rajendran[1] Emily Kerby[1] Adhnan Mohamed[1] Ahmed Nassar[1]

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Background: Early allograft dysfunction (EAD) remains a known risk factor for poor graft survival (GS) in LT from DCD. This study aimed to investigate how the risk factors for EAD have changed with the advent of NMP. **Methods:** Adult LT alone from DCD donor which were performed from 2015-2024 were evaluated. Patients were divided into two groups based on the use of NMP, and logistic regression analysis was performed to identify risk factors associated with the development of EAD in each group. Additionally, the impact of EAD on 1-year GS was assessed using Kaplan-Meier analysis. All NMPs were initiated at donor hospitals (on-site NMP). **Results:** This study included 201 adult DCD liver transplant patients, in which LT was performed using NMP in 100 patients and non-NMP- in 101 patients. Donor age was significantly higher in the NMP group compared to the non-NMP group (46 years vs 38 years; $p = 0.007$). There was no significant difference in recipient age between the NMP group and the non-NMP group (60 years vs 58 years; $p = 0.803$). Multivariable logistic regression model for EAD is shown in Table 1. In the non-NMP group, donor age, donor gender(male), recipient gender (male) were identified as a significant risk factor for EAD. (OR 1.074, 95% CI 1.03-1.12, $p < 0.001$, OR 3.155, 95% CI 1.15-8.63, $p = 0.03$, OR 2.72, 95% CI 1.01-7.33, $p = 0.047$) In contrast, in the NMP group, donor age and recipient gender were no longer a significant risk factor for EAD. Donor gender(male) and donor BMI were also identified as a significant risk factor for EAD. (OR 4.94, 95% CI 1.17-20.9, $p = 0.03$, OR 1.137, 95% CI 1.05-1.23, $p = 0.002$, OR 1.14). Kaplan-Meier analysis revealed no significant difference in 1-year GS between patients with and without EAD in the non-NMP group ($p = 0.423$). In the NMP group, EAD was significantly associated with poorer 1-year GS. ($p = 0.009$). **Conclusion:** With NMP use, DCD donor age became significantly older. While donor age was considered a risk factor for EAD in non-NMP DCD LT, donor age was not a risk factor for EAD in NMP DCD LT, indicating that NMP mitigates age-related risk and contributes to expanding the donor pool without compromising post-transplant outcomes. However, the donor gender (male) is a risk factor for EAD regardless of the NMP, and the donor BMI is a risk factor for EAD in NMP. Therefore, these risk factors may need to be considered in DCD donor selection.

non NMP	Univariate			Multivariate		
	OR	95%CI	p	OR	95%CI	p
Donor Age	1.06	(1.02-1.10)	0.002	1.07	(1.03-1.12)	<0.001
Donor Gender (Male)	2.27	(0.98-5.26)	0.06	3.16	(1.15-8.63)	0.03
Donor BMI	1.07	(0.998-1.14)	0.06	1.05	(0.99-1.12)	0.13
Recipient Age	1.03	(0.98-1.07)	0.24			
Recipient Gender (Male)	2.49	(1.08-5.77)	0.03	2.73	(1.01-7.33)	0.047
Recipient BMI	0.96	(0.89-1.04)	0.31			
Recipient MELD	0.96	(0.90-1.01)	0.11			
PVT	2.37	(0.45-12.3)	0.31			
Operation time (min)	1.00	(0.998-1.01)	0.24			
Transfusion amount (RBC+ Cell Saver)	0.99	(0.96-1.03)	0.61			
NMP	Univariate			Multivariate		
	OR	95%CI	p	OR	95%CI	p
Donor Age	1.01	(0.97-1.06)	0.53			
Donor Gender (Male)	1.93	(0.64-5.84)	0.24	4.95	(1.17-20.95)	0.03
Donor BMI	1.09	(1.02-1.16)	0.01	1.14	(1.05-1.23)	0.002
Recipient Age	1.03	(0.98-1.08)	0.31			
Recipient Sex	1.04	(0.39-2.77)	0.94			
Recipient BMI	1.00	(0.92-1.09)	0.95			
Recipient MELD	0.97	(0.91-1.04)	0.41			
PVT	0.85	(0.29-2.61)	0.78			
Operation time (min)	1.00	(0.99-1.003)	0.55			
Transfusion amount (RBC+ Cell Saver)	1.02	(0.989-1.04)	0.30			

Disclosures: ATSUSHI NISHIMAGI: Nothing to Disclose, Rikako Oki: Nothing to Disclose, Luckshi Rajendran: Nothing to Disclose, Emily Kerby: Nothing to Disclose, Adhnan Mohamed: Nothing to Disclose, Ahmed Nassar: Nothing to Disclose, Abbas Al-Kurd: Nothing to Disclose, Atsushi Yoshida: Nothing to Disclose, Marwan Abouljoud: Nothing to Disclose, Shunji Nagai: Nothing to Disclose

0113 | SIMILAR LONG-TERM LIVER RELATED AND MORTALITY OUTCOMES FOR LIVING LIVER DONORS COMPARED TO THE GENERAL POPULATION

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Background: Understanding the long-term outcomes after living liver donation (LLD) is important to support LLD programs and for informed consent. Data from Korea have suggested survival after LLD maybe worse compared to the general population. No long-term outcomes have been described for LLD cohorts in North America. The aim of this study was to describe health-related outcomes and mortality of LLDs compared to a matched general population. **Methods:** Individuals in Ontario, Canada who were LLDs from 2004-2022 were identified using a validated algorithm in administrative healthcare data (sensitivity 99%, specificity 100%) and followed to the end of 2023. Each LLD was matched 30-days post donation to five healthy individuals in the general population based on birth year, sex, income quintile and census division. Baseline characteristics between groups were compared and liver-related outcomes (viral hepatitis, cirrhosis/decompensation, hepatocellular carcinoma, transplant), psychiatric outcomes, and overall mortality were identified using linked databases. Overall survival was

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compared using the Kaplan-Meier method and the association between being an LLD and mortality was evaluated using Cox regression with the robust variance estimator to account for the matched design. Small cells <6 were supressed due to privacy policies. **Results:** A total of 949 LLDs were identified and matched to 4,745 from the general population (median age 35 [IQR 28-44], 57% female). After a median follow-up of 9 years (IQR 4-14), $<1\%$ of LLDs and matched controls had any liver-related event ($p=.654$). Mortality was also similar between groups with 13 (1.4%) of LLDs and 59 (1.3%) dying during the study period ($p=.846$; Figure). Using Cox regression, there was no association between LLD and mortality (HR 1.06, 95% CI 0.58-1.92; $p=.845$). LLDs did however have a higher rate of psychiatric encounters during follow-up (17% vs. 9%, $p<.001$) which were driven by a higher proportion of encounters for mood and anxiety disorders and adjustment/trauma/reaction disorders. No differences were observed in psychotic disorders or substance use disorders. **Conclusion:** Long-term liver-related and mortality outcomes are similar for LLDs compared to the general population. Psychiatric encounters for mood and adjustment disorders are more frequent for LLDs. These results can be used to support the use of LLD in North America and for informed consent for potential donors.

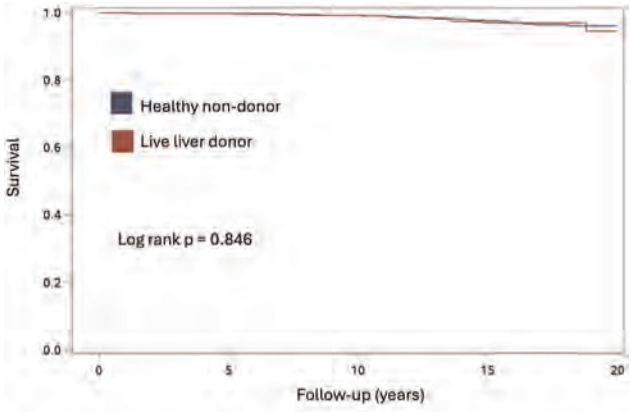

Figure: Long-term overall survival of living liver donors compared to the general population.

Disclosures: Jennifer Flemming: Nothing to Disclose, Maya Djerboua: Nothing to Disclose, Nazia Selzner: Nothing to Disclose

★ 0114 | DOSE-ESCALATION STUDIES OF MESENCHYMAL STROMAL CELL THERAPY FOR DECOMPENSATED LIVER CIRRHOSIS: PHASE IA/IB RESULTS: AND IMMUNE MODULATION INSIGHTS

Lei Shi[1] Ziying Zhang[1] Ze-Rui Wang[2] Song Mei[3] Weiqi Yao[4] Mengqi Yuan[1] Zhe Xu[1] Lei Huang[1] Yu Zhang[5] Peng Zhang[6] Yonggang Li[1] Fu-Sheng Wang[1], [1]Senior Department of Infectious Diseases, The Fifth Medical Center of Chinese PLA General Hospital, [2]Senior Department of Gastroenterology, the First Medical Center of Chinese PLA General Hospital, [3]Beijing Children's Hospital; Shanghai Jiao Tong University School of Medicine, [4]School of Life and Health Sciences, Hubei University of Technology, [5]Wuhan Optics Valley Zhongyuan Pharmaceutical Co., Ltd., [6]Rare Disease Center, Beijing Children's Hospital, Capital Medical University

Background: Decompensated liver cirrhosis (DLC) is characterized by severe liver dysfunction and immune dysregulation, posing significant treatment challenges. Mesenchymal stromal cells (MSCs) therapy has shown promise in DLC treatment, but the optimal dosing strategies and dose-dependent therapeutic mechanisms in humans remain unclear, limiting its clinical application. **Methods:** We conducted sequential Phase Ia/Ib trials using a single-arm, dose-escalation design to evaluate the safety and tolerability of MSCs therapy in DLC patients while also exploring its immunomodulatory effects and gathering preliminary therapeutic signals. In Phase Ia, four dose cohorts received a single dose of MSCs: 5.0×10^7, 1.0×10^8, 1.5×10^8, and 2.0×10^8 cells. Patients were followed up on Days 3, 7, 14, and 28. Multi-omics analyses, including single-cell RNA sequencing and cytometry by time of flight, were conducted to investigate immune cell dynamics and dose-dependent responses. Building on these findings, Phase Ib included two dose cohorts, each of whom received three doses of MSCs administered one week apart: 1.0×10^8 and 2.0×10^8 cells per dose. Patients were followed up on Days 7, 14, 21, and 28 to further evaluate the safety and feasibility of multiple-dose regimens. The trials were registered at ClinicalTrials.gov (NCT05227846 and NCT05984303). **Results:** MSCs therapy demonstrated good safety and tolerability in both Phase Ia and Phase Ib trials, with no severe adverse events, dose-limiting toxicities, or serious unexpected adverse reactions observed up to Day 28. Multi-omics analyses revealed that higher MSC doses elicited stronger immunomodulatory effects, particularly by modulating monocyte subsets. In particular, myxovirus resistance 1 positive (MX1+) monocytes, a key monocyte population, exhibited dose-dependent changes and was identified as a mediator of MSC-induced immunomodulation. These effects were sustained for up to seven days post-treatment but diminished by Day 14. Preliminary clinical signals included improvements in Child–Pugh scores, Model for End-Stage Liver Disease scores, liver function markers, and quality-of-life metrics, particularly in the higher-dose and multiple-dose groups. **Conclusion:** This study demonstrates the safety and tolerability of MSCs therapy in patients with DLC and provides the first human-based evidence on the dose-effect relationship

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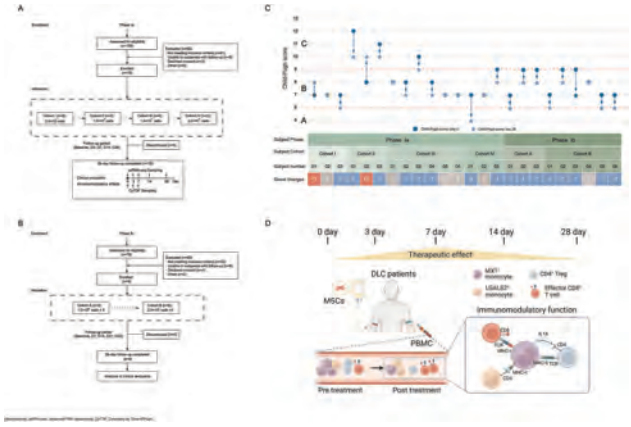
and optimal administration regimens. The identification of MX1+ monocytes as a critical mediator highlights the potential of MSCs therapy to modulate immune dysfunction in DLC. These findings offer valuable insights for optimizing MSCs therapy and inform the design of future efficacy-focused clinical trials.



Disclosures: Lei Shi: Nothing to Disclose, Ziying Zhang: Nothing to Disclose, Ze-Rui Wang: Nothing to Disclose, Song Mei: Nothing to Disclose, Weiqi Yao: Nothing to Disclose, Mengqi Yuan: Nothing to Disclose, Zhe Xu: Nothing to Disclose, Lei Huang: Nothing to Disclose, Yu Zhang: Nothing to Disclose, Peng Zhang: Nothing to Disclose, Yonggang Li: Nothing to Disclose, Fu-Sheng Wang: Nothing to Disclose

0115 | INTEGRATING PROTEOMICS AND TRANSCRIPTOMICS TO STUDY LIVER TRANSPLANT ACUTE REJECTION

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

Background: Acute rejection (AR) is a common complication that can lead to graft failure after liver transplantation. Most prior serum and liver biopsy biomarker studies have utilized gene expression-based methods, but few have examined concomitant protein expression. This investigation combines transcriptomics and proteomics approaches to uncover potential liver biomarkers for AR and to better understand its molecular pathogenesis. **Methods:** Clinically-indicated post-transplant liver biopsies (n = 27) were used for gene and protein expression analysis. Samples were classified as: (1) AR with abnormal LFT (n = 11); and (2) control with normal LFT (n = 16). RNAseq was used for transcriptomics study and mass spectrometry-based label-free quantitative proteomics was performed to assess protein expression. **Results:** Transcriptomic analysis reveals that 1179 genes are significantly upregulated and 229 genes are downregulated in the AR group compared to control (Padj < 0.05). The top 5 differentially expressed genes include *TNFRSF9*, *SERPINA12*, *CXCL10*, *DLGAP5* and *PLK1*. Pathway enrichment analysis shows that multiple metabolic process pathways including hepatic lipid and protein metabolic processes, and mitochondrial translation are downregulated in AR ($P < 0.05$). As expected, several signaling pathways related to allograft rejection and inflammatory response are upregulated in AR. Proteomics study identified a total of 3455 proteins, with 267 proteins upregulated and 67 proteins downregulated in AR compared to control ($P < 0.05$). Consistent with the results from the transcriptomics study, metabolic and biosynthetic processes are downregulated in AR, and proteins related to immune response and antigen processing and presentation are upregulated in AR. Top differentially expressed proteins include APOL3, CD74, LSP1, HIST1H1D, HLA-DRA and FABP5. Among the 334 differentially expressed proteins, 281 of them do not have significant changes in gene expression, including proteins involved in the metabolic processes, actin cytoskeleton and focal adhesion. **Conclusion:** Genes and proteins that are related to hepatic metabolic processes are downregulated in liver biopsies from patients with AR compared to control. As expected, immunologic response related pathways are upregulated in AR. Most differentially expressed proteins detected with proteomics do not have similar changes in gene expression, indicating potential post-transcription regulation and/or modulation of protein stability. These data demonstrate the importance of proteomic, and not simply transcriptomic studies in accurately identifying biomarkers for AR.

Disclosures: Xiaoying Liu: Nothing to Disclose, Connor Lantz: Nothing to Disclose, Richard Green: Mirum Pharmaceuticals: Advisor

0116 | TACROLIMUS-RESISTANT, TCR-DEFICIENT, GPC3-SPECIFIC CAR T CELLS FOR SAFE AND EFFECTIVE TREATMENT OF HEPATOCELLULAR CARCINOMA AFTER LIVER TRANSPLANTATION

Lorenz Kocheise[1] Mohamed Reda Benmebarek[1] Gabriel Bacil[1] Dan Li[1] Xiao Bin Zhu[1] Patrick Huang[1] Yuta Myojin[1] Kylynda Bauer[1] Chi Ma[1] Rajiv Trehan[1] Firouzeh Korangy[1] Mitchell Ho[1] Tim F Greten[1],
[1]National Cancer Institute

Background: Liver transplantation is a curative treatment for early-stage hepatocellular carcinoma (HCC), while immunotherapy remains the first-line therapy for advanced disease. However, managing recurrent HCC after liver transplantation poses a significant therapeutic challenge, as immune checkpoint inhibitors are contraindicated due to the high risk of allograft rejection. Tumor-specific chimeric antigen receptor (CAR) T cells

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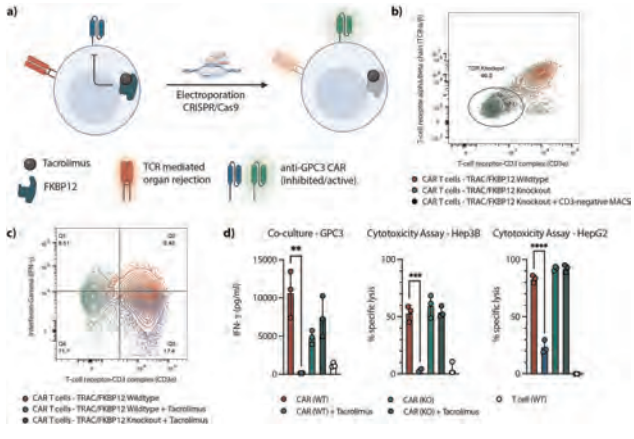
targeting glypican-3 (GPC3) offer a promising alternative strategy. Here, we describe a CAR T cell platform designed for post-transplant application, featuring CRISPR/Cas9-mediated knockout of the *FK506-binding protein 12* (*FKBP12*) locus to confer tacrolimus-resistance and maintain CAR T cell function under continuous immunosuppression. Concurrent disruption of the *TRAC* locus eliminates T cell receptor (TCR) expression, reducing the risk of allograft rejection mediated by the endogenous TCR of these tacrolimus resistant CAR T cells. **Methods:** Resting human T cells were electroporated with a ribonucleoprotein (RNP) complex composed of a 1:1 mixture of single-guide RNAs targeting *FKBP12* and *TRAC*, pre-incubated with recombinant high-fidelity Cas9 protein. Following electroporation, cells were expanded in culture with CD3/CD28 beads and supplemented with IL-2, IL-7, and IL-15 and transduced with a second-generation anti-GPC3-CAR. Engineered T cells were validated and analyzed by genomic sequencing, flow cytometry, cytotoxicity assays using HCC cell lines, and antigen-specific stimulation assays. **Results:** Knockout efficiencies for *TRAC* and *FKBP12* following electroporation ranged from 70-90%, as determined by flow cytometry and genomic sequencing, respectively. TCR-negative CAR T cells were enriched to high purity ($>$ 99%) using conventional Magnetic-Activated Cell Sorting for CD3-negative cells. Upon GPC3-specific antigen stimulation, tacrolimus significantly inhibited interferon-gamma (IFN-g) production in wildtype (WT) CAR T cells, but not in *FKBP12* knockout (KO) cells (169.6 pg/ml vs. 9903 pg/ml, $p = 0.0035$). The cytotoxic activity of WT CAR T cells co-cultured with Hep3B (1.49% vs. 54.03%, $p < 0.0001$) and HepG2 (23.35% vs. 92.30%, $p < 0.0001$) tumor cells was markedly reduced in the presence of tacrolimus, whereas KO CAR T cells maintained a robust killing capacity under the same conditions. **Conclusion:** This dual-edited CAR T cell platform offers a safe and effective approach for the development of cellular immunotherapy for recurrent HCC in the post-transplant setting while continuing tacrolimus-based immunosuppression.



Disclosures: Lorenz Kocheise: Nothing to Disclose, Mohamed Reda Benmebarek: Nothing to Disclose, Gabriel Bacil: Nothing to Disclose, Dan Li: Nothing to Disclose, Xiao Bin Zhu: Nothing to Disclose, Patrick Huang: Nothing to Disclose, Yuta Myojin: Nothing to Disclose, Kylynda Bauer: Nothing to Disclose, Chi Ma: Nothing to Disclose, Rajiv Trehan: Nothing to Disclose, Firouzeh Korangy: Nothing to Disclose, Mitchell Ho: Nothing to Disclose, Tim F Greten: Nothing to Disclose

0117 | SINGLE-NUCLEI RNA SEQUENCING OF HUMAN LIVER IDENTIFIES CELL TYPE SIGNATURES THAT DISTINGUISH AUTOIMMUNE HEPATITIS FROM DISEASE CONTROLS

Marc Sherman[1] Daniel Schafer[1] Molly Thomas[2] George Lauer[1] Alexandra-Chloe Villani[1] Wolfram Goessling[1], [1]Massachusetts General Hospital, [2]Oregon Health Sciences University

Background: Autoimmune hepatitis (AIH) is a progressive liver disease diagnosed syndromically by abnormal liver tests, characteristic autoantibody profiles, suggestive histopathology, and steroid responsiveness. Single-nucleus RNA sequencing (snRNA-Seq) offers an opportunity to uncover cellular and molecular features that discriminate AIH from other hepatic disorders and reveal underlying disease pathogenesis. **Methods:** Liver biopsies from individuals undergoing evaluation for suspected AIH were prospectively collected under an IRB-approved protocol at Massachusetts General Hospital. Control tissue was obtained from hepatic resections in patients without underlying liver disease. Nuclei were isolated and profiled via snRNA-Seq using the 10x Genomics platform, and data were processed using SCANPY. Following cell-type annotation, each sample's cell type frequency was represented as a "cell type abundance phenotype" (CTAP), and spectral and agglomerative clustering were applied to CTAPs without reference to clinical diagnosis. **Results:** We analyzed 32 liver samples from patients ultimately diagnosed—after 2+ years of clinical follow-up—with AIH (n = 6), metabolic dysfunction-associated steatohepatitis (MASH, n = 10), simple steatosis (n = 2), AIH overlap syndromes (n = 3), other hepatic conditions (n = 5), or no liver disease (n = 6). Across these samples, 487,140 nuclei passed quality control and included all major liver cell types including hepatocytes, lymphoid and myeloid lineages. Naïve clustering of CTAPs revealed four patient groups. One cluster (CTAP-1) encompassed 6 of 6 AIH, both AIH-PBC overlap cases, and an AIH-MASH case. Other clusters corresponded to MASH and disease

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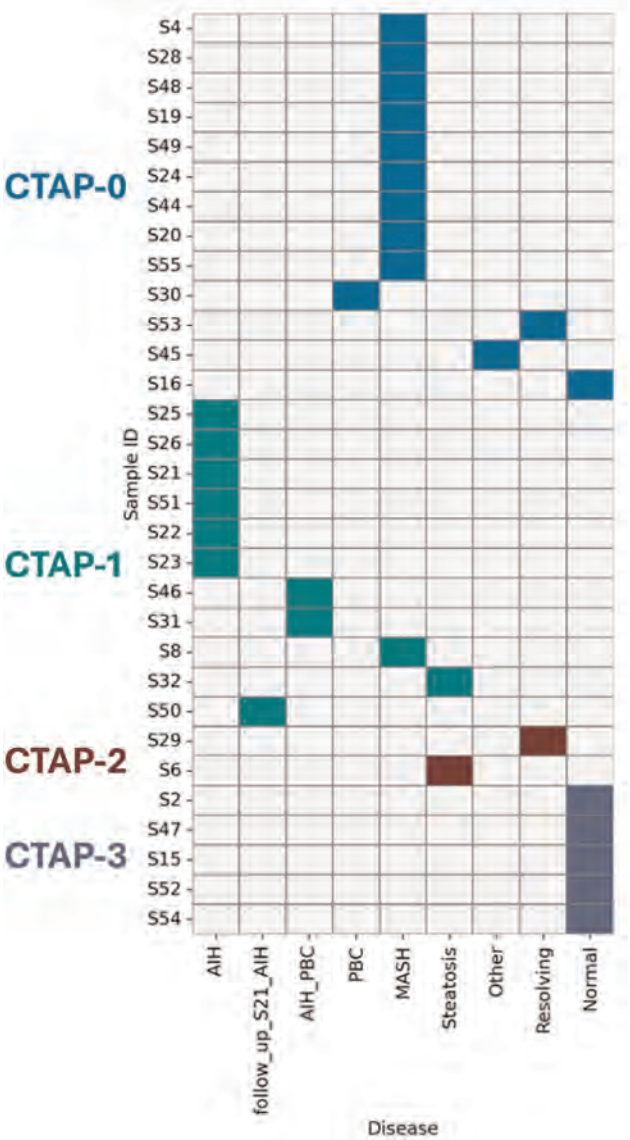
controls. T-resident memory cells and mucosal invariant T-cells (MAIT) were found to be unbiased drivers of clustering, while plasma cells were only modestly important for distinguishing AIH from disease controls, and the plasma-to-B cell ratio remained stable across conditions. **Conclusion:** Cell type composition derived from snRNA-Seq data enables disease classification in liver tissue independent of clinical labels. Unexpectedly, tissue-resident memory T-cell and MAIT cell abundances were more critical for discerning AIH than plasma cell abundance. This approach holds promise for improving our diagnosis of AIH and may facilitate stratification of AIH subtypes in future large-scale studies.



Disclosures: Marc Sherman: Nothing to Disclose, Daniel Schafer: Nothing to Disclose, Molly Thomas: Nothing to Disclose, George Lauer: Nothing to Disclose, Alexandra-Chloe Villani: Nothing to Disclose, Wolfram Goessling: Nothing to Disclose

★ 0118 | SPATIALLY RESOLVED SINGLE-CELL ANALYSIS OF PSC LIVER EXPLANTS REVEALS NICHE-SPECIFIC DISEASE EFFECTS

Jake Herb[1] Jiayu Zhang[1] Jane Stevens[1] Christopher Tastad[1] Ksenija Sabic[1] Maria Isabel Fiel[2] Alexandros Polydorides[1] Jawad Ahmad[2] Thomas Schiano[1] Joseph DiNorcia[1] Jang Moon[2] Chiara Rocha[1] Antonios Arvelakis[2] Marcelo Facciuto[1] Parissa Tabrizian[2] Sander Florman[1] Judy Cho[1], [1]Icahn School of Medicine at Mount Sinai, [2]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Primary sclerosing cholangitis (PSC) is an immune-mediated biliary disease characterized by concentric rings of fibrosis around bile ducts (periductal fibrosis). This study aims to resolve niche-specific disease effects in the PSC liver and define drivers of periductal fibrosis using spatial transcriptomics and snRNA-seq. **Methods:** Formalin-fixed, paraffin-embedded (FFPE) liver tissue was collected from 71 patients (37 PSC, 34 controls) undergoing liver transplant or resection between 2015 and 2024. The control group comprised 16 patients with MASH and 18 patients with metastatic colorectal cancer (metCRC, with tissue collected from the tumor-free margin). snRNA-seq was performed using the 10X Genomics Fixed-RNA Profiling workflow. Differential gene expression analysis (DEGA) was performed on pseudobulked data using edgeR. Spatial transcriptomics was performed on adjacent sections from 24 patients (16 PSC, 8 controls) using the Xenium Analyzer and a custom 480-gene panel. Cell segmentation and annotation were performed using Cellpose and Tangram. NOVAE, a graph-based model, was used to identify distinct spatial domains within the Xenium data and to identify spatially variable genes. **Results:** Using snRNA-seq, we measured 399,401 high-quality nuclei (257,250 nuclei from PSC patients and 142,151 nuclei from controls). We identified three distinct populations of cholangiocytes (BEC.A, BEC.B, and BEC.C) and, using spatial transcriptomics, showed that BEC.B cells are associated with the ductular reaction, while BEC.C cells are restricted to large bile ducts. DEGA revealed that BEC.B cells express high levels of TGFB1 and TGFB2, whereas BEC.C cells show enriched expression of PSC GWAS genes, including CCDC88B, GPR35, and SOCS1. We identified five unique populations of fibroblasts (FIB.A, FIB.B, FIB.C, FIB.D, and FIB.E) and, using spatial transcriptomics and DEGA, demonstrated that FIB.D cells are specific for periductal fibrotic lesions and sharply upregulate the negative Wnt regulators SFRP2 and SFRP4 ($p \leq 6.43E-39$). We identified four unique macrophage populations, including a pro-inflammatory subset that showed increased expression of NFKB2,

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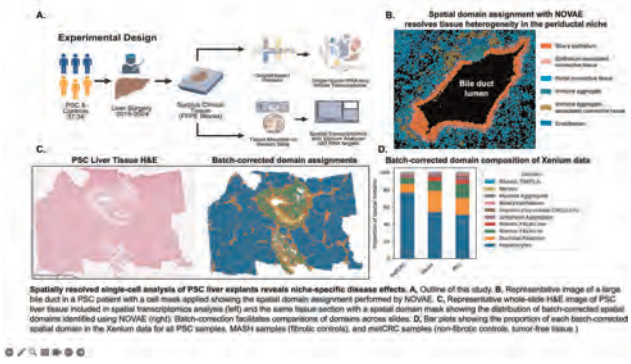
CXCL2, and ITGAX, in PSC samples. Spatial transcriptomics revealed the presence of myeloid aggregates adjacent to areas of ulceration in the biliary epithelium that showed high ITGAX expression. **Conclusion:** Using a spatially-resolved single-cell approach, we are able to map cell subsets identified using snRNA-seq to distinct niches in the PSC liver. We show that periductal fibrotic lesions are enriched for cholangiocytes expressing a module of PSC GWAS genes and fibroblasts expressing negative Wnt regulators. We show that a minority subset of pro-inflammatory macrophages displays higher level of activation in PSC and expresses marker genes found in myeloid aggregates adjacent to areas of bile duct ulceration.



Spatially resolved single-cell analysis of PSC liver explants reveals niche-specific disease effects. A, Outline of this study. **B,** Representative image of a large bile duct in a PSC patient with a cell mask applied showing the spatial domain assignment performed by NOVAE. **C,** Representative whole-slide H&E image of PSC liver tissue included in spatial transcriptomics analysis (left) and the same tissue section with a spatial domain mask showing the distribution of batch-corrected spatial domains identified using NOVAE (right). Batch-correction facilitates comparisons of domains across slides. **D,** Bar plots showing the proportion of each batch-corrected spatial domain in the Xenium data for all PSC samples. MASH samples (fibrotic controls), and metCRC samples (non-fibrotic controls, tumor-free tissue.)

Disclosures: Jake Herb: Nothing to Disclose, Jiayu Zhang: Nothing to Disclose, Jane Stevens: Nothing to Disclose, Christopher Tastad: Nothing to Disclose, Ksenija Sabic: Nothing to Disclose, Maria Isabel Fiel: Nothing to Disclose, Alexandros Polydorides: Nothing to Disclose, Jawad Ahmad: Nothing to Disclose, Thomas Schiano: Nothing to Disclose, Joseph DiNorcia: Nothing to Disclose, Jang Moon: Nothing to Disclose, Chiara Rocha: Nothing to Disclose, Antonios Arvelakis: Nothing to Disclose, Marcelo Facciuto: Nothing to Disclose, Parissa Tabrizian: AstraZeneca: Speaking and Teaching, Aztrazeneca: Speaking and Teaching, Boston Scientific: Speaking and Teaching, Sander Florman: Nothing to Disclose, Judy Cho: Nothing to Disclose

★ 0119 | ROLE OF THE AUTOPHAGY INHIBITOR RUBICON IN A PSC MOUSE MODEL

Lukas Michael Gulden[1] Leonie Katz[1] Lena Voško[1] Peter Fickert[1] Katrin Panzitt[1] Martin Wagner[1], [1]Medical University Graz

Background: Autophagy is a fundamental self-digestion process required for cell homeostasis. We have previously shown that hepatic autophagy is impaired in patients with chronic cholestasis including primary sclerosing cholangitis (PSC). On a molecular level, bile acids induce Rubicon in a FXR dependent manner. Rubicon is an inhibitor of the autophagosome to lysosome fusion and therefore the induction of Rubicon prevents proper execution of autophagic processing. Since patients which chronic cholestasis and PSC have substantially increased hepatic Rubicon levels, we hypothesized that inhibition of Rubicon in cholestasis may improve impaired autophagy and consequently reduce cholestatic liver injury in a mouse model for PSC. **Methods:** We crossbred full body Rubicon- and MDR2-knockout mice over 3 generations to yield male and female Rubicon+/+/MDR2+/+ (wildtype), Rubicon+/+/MDR2-/- (MDR2-knockout) and Rubicon-/-/MDR2-/- (double-knockout) mice. Animals of both sexes were harvested at an earlier (8-10 weeks) and an older age (25-27 weeks). Markers of liver injury, inflammation, fibrosis and ductular reaction were analyzed on histologic, serum, mRNA and protein levels. In addition, we tested the effects of Rubicon deletion on bile flow under normal and choleretic (pretreatment with UDCA) conditions. **Results:** Deletion of Rubicon does not affect bile flow. Compared to MDR2-knockout mice Rubicon-MDR2-double-knockout mice show reduced liver injury (ALT, AST, AP, serum bile acids), inflammatory markers (TNFa, Icam) and less fibrosis (col1a1, desmin, hydroxyproline). While the effect in the early age group is only significant in female mice, a significant improvement can be observed in both sexes at older age. However, ductular reaction (CK19 IHC) and onion-skin-like fibrosis (Sirius Red staining) remains almost unchanged in double-knockout mice. **Conclusion:** Rubicon-knockout alleviates hepatocellular damage in the MDR2- knockout PSC-mouse-model but does not affect bile duct injury. Thus, inhibition of Rubicon may probably not diminish the initial bile duct injury but may ameliorate the detrimental hepatocellular consequences of the ascending pathophysiology of cholestatic liver diseases. We therefore believe that Rubicon may be a future distinct molecular target for chronic cholangiopathies including PSC.

Disclosures: Lukas Michael Gulden: Nothing to Disclose, Leonie Katz: Nothing to Disclose, Lena Voško: Nothing to Disclose, Peter Fickert: Dr. Falk Pharma GmbH: Consultant, Roche Austria GmbH: Speaking and Teaching, Takeda Pharma Ges.m.b.H.: Speaking and Teaching, Dr. Falk Pharma Österreich GmbH: Speaking and Teaching, Dr. Falk Pharma Österreich GmbH: Advisor, Dr. Falk Pharma Österreich GmbH: Advisor, Gilead Sciences GesmbH: Speaking and Teaching, Roche Diagnostics GmbH: Consultant, Ipsen Pharma Austria GmbH: Advisor, Gilead Sciences GesmbH: Consultant, Gilead Sciences GesmbH: Advisor, Dr. Falk Pharma GmbH: Consultant, Katrin Panzitt: Nothing to Disclose, Martin Wagner: Nothing to Disclose

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0120 | IDENTIFICATION OF BST2, IL18R1, IL4R, AND KCNJ11 AS ASSOCIATED WITH PRURITUS RESPONSE TO ELAFIBRANOR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: PROTEOMIC RESULTS: FROM THE ELATIVE® TRIAL

Mark Swain[1] Maria del Pilar Schneider[2] Pascale Plas[2] Jacquie Maignel[2] Aurélie Martin[2] Lola Lecru[2] Nuno Antunes[3] George Harb[3] Marwan Sleiman[2] Hugo Gomes da Silva[2] Andrew Mason[4], [1]Liver Unit, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [2]Ipsen, Paris, France, [3]Ipsen, Cambridge, MA, USA, [4]CEGIIR, University of Alberta, Edmonton, AB, Canada

Background: Pruritus is a common symptom in patients (pts) with primary biliary cholangitis (PBC). Elafibranor (ELA), a peroxisome proliferator-activated receptor (PPAR) agonist exerting effects on PPARα and PPARδ, is approved for second-line treatment of PBC and has shown clinically meaningful improvements in pruritus, as assessed by pt-reported outcome (PRO) measures. Previously, proteins associated with pruritus pathways, including BST2, IL18R1, IL4R, and KCNJ11, were identified to be downregulated in pts with PBC treated with ELA; IL31 has also been associated with pruritus in PBC. We examine the relationship between the expression of these proteins and pruritus response to ELA. **Methods:** Serum samples were collected from pts in the phase III ELATIVE® trial (NCT04526665) at baseline (BL) and Week (Wk) 52, and analysed using the Olink® Explore HT proteomic panel. Spearman correlations were evaluated between PRO measures of pruritus (Worst Itch Numeric Rating Score [WI-NRS], 5-D Itch, and PBC-40 Itch) and pruritus-associated protein expression (BST2, IL18R1, IL31, IL4R, and KCNJ11). Analyses were conducted in the overall population and in pts with moderate-to-severe pruritus (WI-NRS ≥ 4) at BL. Proteins are reported by the names of their encoding genes. **Results:** Of 161 pts in ELATIVE®, serum samples were included from 119; 50 pts had moderate-to-severe pruritus at BL, 37 of whom received ELA. At BL in the overall population, BST2, IL18R1, and IL4R expression levels were significantly correlated with each other ($r \geq 0.66$; $p < 0.05$). In ELA-treated pts with moderate-to-severe pruritus at BL, expression changes from BL (CfB) to Wk 52 between these proteins were also significantly correlated ($r \geq 0.55$; $p < 0.05$). At BL in the overall population, significant correlations were observed between IL18R and IL4R expression and WI-NRS and PBC-40 Itch ($r = 0.20–0.25$; $p < 0.05$), and between BST2 expression and PBC-40 Itch ($r = 0.23$; $p < 0.05$). Similar relationships were seen in pts with moderate-to-severe pruritus at BL, although not all were significant. In ELA-treated pts with moderate-to-severe pruritus at BL, a significant correlation was observed between CfB to Wk 52 in BST2 expression and WI-NRS ($r = 0.37$; $p < 0.05$). Although not significant, correlations between CfB to Wk 52 in IL18R1 and KCNJ11 expression and pruritus were also seen in these pts ($r = 0.32$; $p = 0.06$). No significant correlations were seen between CfB to Wk 52 in IL31 expression and pruritus in these pts. **Conclusion:** Significant correlations were observed between BST2, IL18R1, and IL4R and pruritus at BL. In ELA-treated pts with moderate-to-severe pruritus at BL, CfB to Wk 52 in BST2 and pruritus were also significantly correlated. These data suggest a potential role for these proteins in the pathophysiology of pruritus in PBC, and strong correlations between BST2, IL18R1, and IL4R suggest a complex interplay associated with pruritus and treatment response.

Disclosures: Mark Swain: Nothing to Disclose, Maria del Pilar Schneider: IPSEN INNOVATION: Employee and shareholder of Ipsen, Pascale Plas: IPSEN: Employee, Jacquie Maignel: IPSEN: Employee, IPSEN: Stock – privately held company, Aurélie Martin: Nothing to Disclose, Lola Lecru: Nothing to Disclose, Nuno Antunes: Nothing to Disclose, George Harb: Nothing to Disclose, Marwan Sleiman: Nothing to Disclose, Hugo Gomes da Silva: Nothing to Disclose, Andrew Mason: Ipsen: Grant/Research Support, Ipsen: Speaking and Teaching, Ipsen: Advisor, Gilead: Advisor, Gilead: Grant/Research Support, GSK: Grant/Research Support

0121 | IDENTIFICATION OF ANTI-DOK2 ANTIBODIES IN PATIENTS WITH AUTOIMMUNE HEPATITIS VIA A HUMAN PROTEIN MICROARRAY

Kazumichi Abe[1] Jun Wada[2] Manabu Hayashi[2] Tatsuro Sugaya[2] Naoto Abe[2] Yosuke Takahata[2] Masashi Fujita[2] Hiromasa Ohira[2], [1]Fukushima Medical University School of Medicine, [2]Fukushima Medical University

Background: Autoantibodies such as antinuclear antibodies (ANAs) and anti-smooth muscle antibodies (ASMAs), which are detected in many cases of autoimmune hepatitis (AIH), are not disease-specific, so they have limited value in disease diagnosis. In this study, we aimed to identify disease-specific autoantibodies related to AIH diagnosis or pathogenesis. **Methods:** We comprehensively analysed human protein microarrays (containing more than 16,000 human proteins, including membrane, cytoplasmic, and nuclear proteins, synthesized in a wheat germ cell-free system using cDNA). To identify AIH-specific autoantibodies, we performed a cross-sectional study of AIH patients ($n = 67$) and matched healthy controls (HCs) ($n = 25$) via ELISA. An independent cohort of 123 AIH patients and 75 HCs was analysed for

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validation. All patient data were collected before corticosteroid therapy. We also evaluated the associations between candidate protein antigen expression and clinical findings in AIH patients. Candidate protein antigen expression in liver tissues was confirmed by immunohistochemistry. **Results:** According to comprehensive human protein microarray analysis, docking protein 2 (DOK2) was selected from six antigens significantly upregulated in AIH patients. The mean serum anti-DOK2 level was significantly higher in AIH patients (36.1-37.4 AU) than in those with other liver diseases (2.6-9.2) or HCs (1.0-4.5 AU) in the exploration and validation cohorts (P value/AUROC, vs HCs, <0.0001/0.87-0.90). Serum anti-DOK2 levels were positively correlated with serum IgG levels and liver histological activity. The serum IgG level was an independent factor for increasing of anti-DOK2 antibody levels in patients with AIH. Immunostaining revealed DOK2 positive cells were found in the hepatic lobules in patients with AIH. While immunohistochemical staining was performed using CD68, a surface marker for macrophages, CD68-positive cells were visually localized in the hepatic lobule in agreement with DOK2-positive cells. **Conclusion:** We demonstrated the first evidence that serum anti-DOK2 antibody levels were associated with the diagnosis and disease activity of AIH patients.

Disclosures: Kazumichi Abe: Nothing to Disclose, Jun Wada: Nothing to Disclose, Manabu Hayashi: Nothing to Disclose, Tatsuro Sugaya: Nothing to Disclose, Naoto Abe: Nothing to Disclose, Yosuke Takahata: Nothing to Disclose, Masashi Fujita: Nothing to Disclose, Hiromasa Ohira: Nothing to Disclose

0122 | CANDIDA ALBICANS CONTRIBUTES TO LIVER FIBROSIS IN PRIMARY SCLEROSING CHOLANGITIS

Burcin Ozdirik[1] Phillipp Hartmann[2] Punnag Saha[1] Eliane Münte[1] KHURANA AMIT[1] Fernanda Raya Tonetti[1] Henriette Kreimeyer[1] Cristina Llorente[2] Xinlian Zhang[1] Frank Tacke[3] Derrick Fouts[4] Bernd Schnabl[2], [1]University of California San Diego, [2]University of California, San Diego, [3]Charité - Berlin, [4]J. Craig Venter Institute

Background: Primary sclerosing cholangitis (PSC) is a rare, immune-mediated liver disease with no treatment options other than liver transplantation. Emerging evidence highlights the gut-liver axis as a key contributor to PSC pathogenesis. However, the role of intestinal fungi remains unclear. Our aim was to characterize the fecal mycobiome in patients with PSC and explore whether fungal dysbiosis and IL-17-mediated immune activation could represent a potential therapeutic target in preclinical models. **Methods:** Fecal samples from 92 patients with PSC, 94 patients with inflammatory bowel disease (IBD), and 57 healthy controls were analyzed using ITS2 sequencing to profile the gut mycobiome. Stool samples were cultured on YPD agar plates, and colonies were tested for the presence of *Candida (C.) albicans* using qPCR with specific primers. We induced fibrotic cholangiopathy in wild-type C57BL/6 mice by feeding 0.05% 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) for two weeks, along with oral gavage of *C. albicans* or PBS to assess microbial impact on disease progression. In a follow-up experiment, mice receiving *C. albicans* and DDC diet were treated with an IL-17 blocking antibody. **Results:** ITS2 sequencing analysis revealed a significant increase in the fecal abundance of *Candida* species (spp.) in patients with PSC compared with healthy controls or patients with IBD respectively ($p = 0.009$; $p = 0.026$). Notably, patients with PSC and concurrent IBD showed a higher abundance of *Candida* spp. compared with healthy controls ($p = 0.022$). Further, a higher percentage of patients with PSC demonstrated the presence of *C. albicans* in fecal samples compared with healthy controls ($p = 0.013$). Our *in vivo* models revealed significantly higher liver fibrosis in mice gavaged with *C. albicans* as quantified by Sirius Red staining (6.45% vs. 10.03%; $p = 0.043$) and fibrogenic gene expression. This increase in disease progression was significantly reduced by treatment with an IL-17 blocking antibody per Sirius Red (14.65% vs. 9.85%; $p = 0.006$) and fibrogenic gene expression. **Conclusion:** *Candida spp.,* in particular *C. albicans*, are enriched in the gut of patients with PSC. IL-17 blockade *in vivo* reduced fibrosis, implicating fungal dysbiosis-driven immune activation in PSC progression. Antifungal or IL-17-targeted therapies could be explored as therapy for patients with PSC.

Disclosures: Burcin Ozdirik: Nothing to Disclose, Phillipp Hartmann: Nothing to Disclose, Punnag Saha: Nothing to Disclose, Eliane Münte: Nothing to Disclose, KHURANA AMIT: Nothing to Disclose, Fernanda Raya Tonetti: Nothing to Disclose, Henriette Kreimeyer: Nothing to Disclose, Cristina Llorente: Nothing to Disclose, Xinlian Zhang: Nothing to Disclose, Frank Tacke: Nothing to Disclose, Derrick Fouts: Nothing to Disclose, Bernd Schnabl: Nothing to Disclose

0123 | SINGLE-CELL TRANSCRIPTIONAL PROFILING OF CHRONIC WOODCHUCK HEPATITIS-INDUCED HEPATOCELLULAR CARCINOMA (HCC) REVEALS A PROLIFERATIVE TUMOR SUBTYPE AND TUMOR-DRIVEN IMMUNE EXHAUSTION SHARED WITH HUMAN HCC

Yijia Liu[1] Jawairia Atif[2] Zoe Clarke[3] Lawrence Wood[1] Xue-Zhong Ma[2] Lewis Liu[2] Xinle Wang[2] Justin Manuel[2] Rachel Edgar[3] Sharon Hyduk[2] Thomaz Michalak[4] Gary

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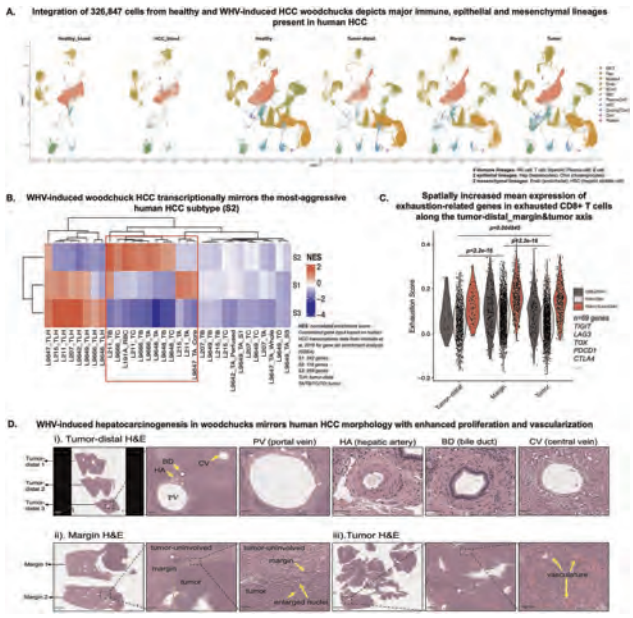
Bader[3] Ian McGilvray[2] Sonya MacParland[1], [1]University of Toronto, Toronto, ON; University Health Network, Toronto, ON, [2]University Health Network, Toronto, ON, [3]University of Toronto, Toronto, ON, [4]Memorial University of Newfoundland, St. John's, NL

Background: Despite the use of immune checkpoint inhibitors (ICI) targeting well-characterized immune exhaustion pathways, the ICI response rate in chronic hepatitis B (CHB)-induced HCC remains below 40%. This may be attributed to a limited cell level understanding of the HCC niche. To address this, we employed the woodchuck hepatitis virus (WHV)-induced HCC model to characterize the immunological niche within the HCC ecosystem to identify targetable cell-cell interactions that drive the HCC-related T cell dysfunction. **Methods:** Single-cell RNA sequencing was performed on peripheral blood mononuclear cells (PBMCs) and liver biopsies from healthy (n = 8) and WHV-induced HCC woodchucks (n = 9). Spatial sampling from 9 HCC animals included matched non-malignant liver tissue (n = 8), tumor margins (n = 20), and multiple intratumoral regions (n = 23). The transcriptomic analysis was coupled with histology to visualize changes in liver morphology. **Results:** Our map of 326,847 cells from 74 samples captured 5 major immune lineages, 2 epithelial lineages, and 2 mesenchymal lineages. Gene set enrichment analysis (GSEA) based on human HCC transcriptomic data suggested that woodchuck HCC tumors transcriptionally resemble the less differentiated, most-aggressive human HCC subtype. T cell profiling revealed an increase in the ratio of exhausted CD8+ T to effector CD8+ T cells in HCC animals compared to healthy controls (p = 8.9e-05). Quantification of the CD8+ T cell exhaustion score using 69 exhaustion-related markers (e.g., TOX, CTLA4, PDCD1) showed a higher exhaustion level in CD8+ T cells in all sites of the HCC-bearing liver (p < 2.2e-16). Notably, a spatial gradient of exhaustion in three CD8+ T cell populations (CD8LoTOX+, TOX +CD8+, TOX+CTLA4+CD8+) was observed from tumor-distal to tumor regions. Pseudotime trajectory analysis using Slingshot suggested that exhausted CD8 + T cells diverged along a developmental path distinct from that of terminally differentiated KLRG1+ effector CD8+ T cells. Hematoxylin and eosin (H&E) staining confirmed tumor morphologies similar to those seen in human HCC, including nuclei-enlarged hepatocytes, pseudoglandular structures, and enriched vascularization. **Conclusion:** Our single-cell characterization of WHV-induced woodchuck HCC demonstrated a transcriptionally and morphologically proliferative tumor subtype, and revealed an immune-exhausted tumor landscape that mirrors human HCC. Future longitudinal studies using woodchucks could track the emergence of the CD8+ T cell population that gives rise to the exhausted CD8+ T cells with hepatitis progression, as they might represent a more therapeutically targetable group.



Disclosures: Yijia Liu: Nothing to Disclose, Jawairia Atif: Nothing to Disclose, Zoe Clarke: Nothing to Disclose, Lawrence Wood: Nothing to Disclose, Xue-Zhong Ma: Nothing to Disclose, Lewis Liu: Nothing to Disclose, Xinle Wang: Nothing to Disclose, Justin Manuel: Nothing to Disclose, Rachel Edgar: Nothing to Disclose, Sharon Hyduk: Nothing to Disclose, Thomaz Michalak: Nothing to Disclose, Gary Bader: Adela Bio: Stock – privately held company, Ian McGilvray: Nothing to Disclose, Sonya MacParland: Nothing to Disclose

0124 | DEVELOPMENT OF GENE-EDITED T CELL THERAPY TARGETING TERT IN HEPATOCELLULAR CARCINOMA

Hidetoshi Nakagawa[1] Yuta Tamaru[1] Eishiro Mizukoshi[1] Taro Yamashita[1], [1]Kanazawa University Hospital

Background: Hepatocellular carcinoma (HCC) is characterized by recurrent genetic alterations, notably mutations in the promoter region of the telomerase reverse transcriptase (TERT) gene. While recent advancements in tyrosine kinase inhibitors and immune checkpoint blockade have expanded therapeutic options, TERT remains refractory to direct pharmacological targeting. Given the high frequency and early occurrence of TERT promoter mutations in HCC pathogenesis, TERT represents a compelling molecular vulnerability warranting further investigation as a therapeutic target. **Methods:** Immune reactivity against the HLA-A*24:02-restricted telomerase reverse transcriptase (TERT)-derived peptide (VYGFVRACL) was evaluated in lymphocytes from hepatocellular carcinoma (HCC) patients

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using interferon-gamma (IFN-γ) ELISpot assays. The TERT peptide vaccine was administered as an adjuvant therapy in conjunction with radiofrequency ablation (RFA). Antigen-specific T cell populations were characterized by single-cell RNA sequencing coupled with T cell receptor (TCR) repertoire analysis. Functional assessment of TCR-engineered T cells was performed through both in vitro cytotoxicity assays and in vivo tumor models. **Results:** Comprehensive genomic analysis of 59 hepatocellular carcinoma (HCC) patients revealed TERT promoter mutations in 57% (34/59) of cases. Antigen-specific immune responses to the HLA-A*24:02-restricted TERT peptide were detected in 3 of 31 (10%) HCC patients, while no reactivity was observed in healthy donors (0/11) or individuals with chronic hepatitis (0/29). In a separate cohort, the TERT peptide elicited robust immune responses in 8 of 14 cases (57%). TERT-specific T cells exhibited a memory-like phenotype characterized by expression of *IL7R* and *NOSIP* contributing to prolonged survivals. Notably, the TERT-reactive TCR clone A12.78 mediated antigen-specific recognition and cytolytic activity against TERT-expressing HepG2 cells in vitro, and significantly suppressed tumor progression in HepG2-engrafted NSG mice in vivo. **Conclusion:** TERT-directed immunotherapeutic strategies represent a promising avenue for the treatment of hepatocellular carcinoma.

Disclosures: Hidetoshi Nakagawa: Nothing to Disclose, Yuta Tamaru: Nothing to Disclose, Eishiro Mizukoshi: Nothing to Disclose, Taro Yamashita: Nothing to Disclose

0125 | LIVER ZONATION BREAKDOWN FUELS HEPATOCELLULAR CARCINOMA IN CHRONIC LIVER DISEASE

SUE YANG[1] Federico Tullio[1] Joana Almeida[1] Sai Ma[1] Bruno Cogliati[1] Guo-cheng Yuan[1] Shamsa Rohan[1] Azra Krek[1] Lida Yang[1] Charlotte Ng[2] Jan Tchorz[3] Tianliang Sun[1], [1]Icahn School of Medicine at Mount Sinai, [2]Humanitas University, [3]Novartis Institutes for BioMedical Research

Background: Hepatocytes exhibit remarkable heterogeneity and plasticity, essential for sustaining liver regeneration and zonated metabolic function. Disruption of liver metabolic zonation is a hallmark of chronic liver disease (CLD) and is increasingly linked to hepatocellular carcinoma (HCC), yet how shifts in zonation contribute to tumor initiation remains unclear. ZNRF3 and RNF43, negative regulators of WNT/β-Catenin signaling, maintain the pericentral-to-periportal zonation and constrain hepatocyte proliferation. This study investigates whether loss of ZNRF3/RNF43 induced zone-1–to–zone-3 reprogramming promotes tumorigenesis in the context of CLD. **Methods:** Single-nucleus RNA-seq, spatial transcriptomics, mRNA FISH, and histological staining were applied to human CLDs samples (HCV, HBV, MASH) and MASH mouse models to characterize zonation disruption. Spatial transcriptome comparisons between MASH mice and ZNRF3/RNF43-deficient livers under homeostasis revealed overlapping patterns of zone-3 expansion. To trace hepatocyte fate, *ZNRF3/RNF43$^{fl/fl}$; LSL-EGFP* mice subjected to low-dose AAV8-TBG-Cre for clonal tracing or high-dose for bulk RNA-seq. GFP+ hepatocytes were monitored over 1–11 months with histology (CYP2E1, Ki-67, GS), spatial transcriptomics, bulk RNA-seq, and EdU labeling to assess proliferation, metabolic reprogramming, and tumor formation. **Results:** Zone-3 signature extension into zone-1 was consistently observed across human CLDs and mouse models. This pattern strongly overlapped with spatial β-Catenin activity in ZNRF3/RNF43-deficient livers, supporting its utility as a model of zone-1 to zone-3 reprogramming. Clonal tracing revealed increased proliferation, expanded clone sizes, and tumor formation localized primarily to zone-1, as confirmed using *Axin2CreER; ZNRF3/RNF43; LSLGFP* mice. Spatial transcriptomics revealed enhanced detoxification pathways and mTOR signaling. Rapamycin treatment reduced clone expansion in zone-1, indicating mTORC1 dependency. By 9 months, dysplastic lesions and HCCs emerged, marked by a lipid metabolism–enriched signature distinct from classical β-Catenin-mutant HCCs but matching a subset of human HCCs. **Conclusion:** ZNRF3/RNF43 deletion induced zone-1–to–zone-3 hepatocyte reprogramming, clonal expansion, and metabolic rewiring, accompanied by mTORC1 activation and early HCC development. This model highlights the pivotal role of spatial identity in CLD-associated tumorigenesis and provides a platform for developing spatially targeted therapies.

Disclosures: SUE YANG: Nothing to Disclose, Federico Tullio: Nothing to Disclose, Joana Almeida: Nothing to Disclose, Sai Ma: Nothing to Disclose, Bruno Cogliati: Nothing to Disclose, Guo-cheng Yuan: Nothing to Disclose, Shamsa Rohan: Nothing to Disclose, Azra Krek: Nothing to Disclose, Lida Yang: Nothing to Disclose, Charlotte Ng: Nothing to Disclose, Jan Tchorz: Nothing to Disclose, Tianliang Sun: Nothing to Disclose

0126 | PHOTOTHERMALLY MODULATED LIPOSOME ENABLING EFFICIENT RELEASE OF 2-DEOXY-D-GLUCOSE SAFELY DISPLAYS VIGOROUS ANTITUMOR EFFECT AGAINST LIVER CANCER

Keisuke Hino[1] Satoshi Arai[2] KYO SASAKI[3] Kazuma Daikoh[3] Sohji Nishina[3], [1]Shunan Memorial Hospital, [2]Kanazawa University, [3]Kawasaki Medical School

Background: A glucose derivative, 2-deoxy-D-glucose (2DG), exerts cytotoxic effects against several cancers through suppression of Warburg effect. However, the clinical application of 2DG is not recognized because of

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adverse events due to high dose administration. We developed a novel drug delivery system (DDS) which delivers and releases 2DG efficiently into cancer cells, using thermodynamic cell engineering. The aim of this study was to assess antitumor effect and safety of this DDS against liver cancer. **Methods:** Liposomes, where 2DG was encapsulated and a photothermal agent (a near-infrared [NIR] absorbing dye) was embedded in the lipid bilayers, were engineered, with their surface modified with cancer-targeting cyclic peptide (iRGD) (iRGD-2DG-nanoheater [iRGD-2DG-NanoHT]). The antitumor effect of iRGD-2DG-NanoHT was assessed in murine HCC models. **Results:** Results:: NIR absorbing dye was more accumulated in liver tumors in mice treated with iRGD-2DG-NanoHT than those with 2DG-NanoHT (without iRGD). A fluorescent dye, calcein that was encapsulated in LNPs was more vigorously released above 37° through phase transitions after NIR irradiation. Thus, modification with iRGD and incorporation of NIR absorbing dye enabled iRGD-2DG-NanoHT to be more specifically delivered to tumor cells and to release 2DG more vigorously in tumor tissue. The body surface temperature rose above 37° in the area around liver but remained below 37° in the area apart from the liver 5 minutes after NIR irradiation in mice treated with iRGD-2DG-NanoHT or iRGD-NanoHT. Mice treated with iRGD-2DG-NanoHT showed significantly reduced tumor volume with more necrotic tumor cells and increased mononuclear cell infiltration than those treated with 2DG alone or iRGD-NanoHT. Mechanistically, treatment with iRGD-2DG-NanoHT displayed cytotoxicity based on both ER stress-induced apoptosis via AMPK phosphorylation and ferroptosis via reduction of GSH/GPX4 axis, and induced HMGB-1 (damage-associated molecular patterns, DAMPs)-mediated antitumor immunity in addition to increase in chemokine production. Finally, Mice treated with iRGD-2DG-NanoHT did not show obvious adverse effects compared to control mice. **Conclusion:** iRGD-2DG-NanoHT has potential as a new therapeutic treatment for liver cancer based on its cancer-specific DDS.

Disclosures: Keisuke Hino: Nothing to Disclose, Satoshi Arai: Nothing to Disclose, KYO SASAKI: Nothing to Disclose, Kazuma Daikoh: Nothing to Disclose, Sohji Nishina: Nothing to Disclose

0127 | PD-L1(+) MACROPHAGES ACTIVATED BY TUMOR-DERIVED GM-CSF INDUCE CD8(+) T CELL EXHAUSTION IN HEPATOCELLULAR CARCINOMA

Takuto Nosaka[1] Masahiro Ohtani[1] Junki Yamashita[1] Yosuke Murata[1] Yu Akazawa[1] Tomoko Tanaka[1] Tatsushi Naito[1] Kazuto Takahashi[1] Yasunari Nakamoto[1], [1]University of Fukui

Background: The efficacy of immune checkpoint inhibitors (ICI)-based treatment is limited in patients with hepatocellular carcinoma (HCC). In tumor microenvironment, tumor-associated macrophages (TAMs) critically influence cancer progression and ICI treatment response through immunosuppression. We have reported TAMs promote the proliferative potential of HCC cells (J Immunol. 2018, Biomed phar. 2023). Granulocyte macrophage (GM)-CSF is one of the key mediators for activation of TAMs. In this study, we aimed to clarify the spatial interactions between PD-L1 (+) TAMs activated by GM-CSF and CD8(+) T cells in resected HCC tissues. **Methods:** Multiplex immunohistochemistry (mIHC) (OPAL: CD8, CD68, CD163, CD11c, PD-L1, and DAPI) was performed on 113 resected HCC specimens. Cell distribution and spatial location in the tumor center, tumor border, non-tumor border, and non-tumor area were determined using inForm (Akoya). Intercellular distances were measured using Phenoptr, and the interaction variable (proportion of target cells within 25 μm) was calculated. The mouse HCC cell line, BNL, transfected with GM-CSF vector was intraportally injected into BALB/c mice. Anti-GM-CSF antibody and/or anti-PD-L1 were injected intraperitoneally into the mice. **Results:** Spatial analysis of HCC tissue showed that higher interaction variable of PD-L1(+) TAMs and CD8T cells in the tumor center had significantly worse in recurrence and survival rates. Multivariate analysis revealed that vascular invasion, fibrosis, and interaction variable; PD-L1(+) TAM with CD8(+) T cells (T area) were independent factors for postoperative recurrence after HCC resection. The interaction variable correlated positively with the number of GM-CSF(+) tumor cells, but not with M-CSF. *In vitro*, GM-CSF upregulated PD-L1 expression and chemokines, such as CXCL9, 10, 11, in macrophages and impaired CD8(+) T cell antitumor activity. In an HCC mouse model, GM-CSF enhanced spatial interactions of PD-L1(+) TAMs and CD8(+) T cell, promoting tumor growth through immunosuppression. Anti-GM-CSF therapy disrupted PD-L1(+) TAMs and CD8(+) T cell interaction, and its combination with anti-PD-L1 synergistically boosted antitumor immunity ($p < 0.05$). **Conclusion:** The spatial analysis of PD-L1(+) TAMs and CD8(+) T cells in resected HCC revealed that a higher interaction variable was associated with increased recurrence and elevated tumor cell-derived GM-CSF expression. Targeting GM-CSF may reprogram the TAM-driven immunosuppressive niche, enhancing antitumor immunity and offering a promising therapeutic strategy for patients with HCC.

Disclosures: Takuto Nosaka: Nothing to Disclose, Masahiro Ohtani: Nothing to Disclose, Junki Yamashita: Nothing to Disclose, Yosuke Murata: Nothing to

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0128 | SIRPA KNOCKOUT IN T CELLS INHABITS IMMUNE EVASION OF HEPATOCELLULAR CARCINOMA

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Background: Immune checkpoint inhibitors, such as anti-PD-1/PD-L1 antibodies, have shown significant antitumor activity in a subset of advanced patients, current evidence indicates that this therapeutic strategy elicits responses in only approximately 20% of advanced HCC . This limited efficacy highlights the potential involvement of alternative immune checkpoints in facilitating tumor immune evasion. A critical aspect of this process is T cell apoptosis. In this study, we discovered that SIRPα is associated with T cell apoptosis in HCC, diverging from the classical role of SIRPα as an inhibitory immune receptor on macrophages. **Methods:** By screening key genes associated with apoptosis in T cells through CRISPR libraries and identifying differentially expressed genes before and after high-concentration IL-2 culture of TILs from HCC patients, we intersected the genes identified by both methods with critical immune checkpoint-related genes. This analysis revealed that the SIRPα is correlated with T cell apoptosis in HCC tissues. In vitro studies utilized PBMCs or murine T cells to evaluate the role of SIRPα in apoptosis. In vivo experiments involved SIRPα$^{-/-}$mice to assess the impact of SIRPα on tumor growth, followed by flow cytometric analysis of T cell function. We investigated T cells in SIRPα$^{-/-}$ mice bearing subcutaneous tumors after depleting macrophage populations. We evaluated T cell functionality in mice treated with a SIRPα inhibitor. CD3^{+} T cells isolated from SIRPα$^{-/-}$ mice were adoptively transferred intravenously into tumor-bearing nude mice to determine their therapeutic effects on tumor growth. **Results:** Analyzing sequencing data, we identified a significant association between SIRPα and T cell apoptosis in HCC. In vitro, SIRPa deficiency inhibited apoptosis of T cells from PBMC and SIRPα$^{-/-}$ mice, while overexpression of SIRPα promoted T cell apoptosis. In vivo,SIRPα deficiency significantly inhibited tumor growth. SIRPα$^{-/-}$ mice exhibited markedly increased proportions of CD4^{+} and CD8+ T cells both in peripheral blood and tumor tissues, accompanied by elevated levels of GZMB. Following macrophage depletion in SIRPα$^{-/-}$ mice, WT mice displayed larger tumor volumes compared to SIRPα$^{-/-}$ mice. Importantly, even after macrophage depletion, the SIRPα$^{-/-}$ mice maintained higher proportions of CD4^{+} and CD8^{+} T cells in both peripheral blood and tumor tissues, along with sustained elevated GZMB levels and reduced PD-1 expression. In adoptive cell theropy experiment, tumors in mice receiving SIRPα$^{-/-}$ CD3^{+} T cell showed significant growth suppression. **Conclusion:** These findings demonstrate that SIRPa deficiency enhances T cell anti-apoptotic capacity and cytotoxic activity, suppressing HCC progression. The results suggest that SIRPa drives tumor immune evasion in HCC by mediating T cell apoptosis, thereby providing novel therapeutic strategies and potential targets for HCC immunotherapy.

Disclosures: Xue Zhang: Nothing to Disclose, Hongsong Chen: Nothing to Disclose, Dongbo Chen: Nothing to Disclose

0129 | METABOLIC REPROGRAMMING OF GLUTAMINE–GLUTAMATE AXIS IN FONTAN-ASSOCIATED LIVER DISEASE (FALD)

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Background: Fontan-associated liver disease (FALD) results from chronic hypoxia and hepatic congestion after the Fontan procedure and may progress to cirrhosis or hepatocellular carcinoma over time. Conventional biomarkers are insufficiently sensitive to detect disease progression. Since hepatic amino acid metabolism plays a central role in systemic homeostasis, we hypothesized that serum free amino acids (FAAs) may reflect pathophysiologic changes in FALD. **Methods:** Human experiments: Serum levels of 20 free amino acids (FAAs) were measured by HPLC in patients with FALD (n = 40; 4 cirrhosis, no HCC), healthy controls (HC; n = 17), and patients with hepatitis C virus (HCV; n = 64). Serum FAAs, AST and ALT activity, and glutamine synthetase (GS), which is expressed in pericentral hepatocytes affected by congestion, were compared among these groups and analyzed for correlation. Spatial transcriptomics (VISIUM) was performed on representative FALD liver tissue. Mice experiments: A murine FALD model (pIVCL; Hepatology 2022) was used to compare serum FAAs, AST, ALT, GS, hepatic GS, GPT, GOT2 expression at 6, 19 and 54 weeks. Liver RNA-seq profiles with those of sham mice at 6 week. Cell experiments: To investigate the effects of hypoxia observed in FALD, hepatocytes (PXB or immortalized mouse hepatocytes) were cultured in portal blood-mimicking medium (PBM; Hepatology 2021) under normoxia or hypoxia (1% O_2). FAAs in culture supernatant and oxidative stress were assessed. **Results:** FALD patients showed significantly increased serum glutamate

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(Glu) and decreased glutamine (Gln) compared to HC and HCV, while total FAA level remained unchanged. Serum GS levels positively correlated with Glu and negatively with Gln. VISIUM revealed upregulated *GLUL* (GS) in hepatocytes within congested and inflamed areas in FALD liver, but the expression of *GOT* and *GPT* showed a diffuse expression pattern. In pIVCL mice, Glu levels were elevated in both serum and liver up to 54 weeks. Consistent with these findings, serum GS levels increased, whereas hepatic GS expressions decreased; however, the expression of hepatic GOT2 and GPT remained unchanged. RNA-seq-based pathway analysis indicated involvement of amino acid metabolism and oxidative stress pathways in the liver of pIVCL. *in vitro*, hypoxia induced ROS in hepatocytes and suppressed FAAs consumption, except for Gln, and induced glycolysis, reflected in elevated glucose consumption and lactate production. Consistent with these findings, Glu level was significantly increased in the culture supernatant. **Conclusion:** Glutamine–glutamate imbalance and altered GS expression under hypoxia and congestion characterize FALD and may serve as potential metabolic biomarkers.
Disclosures: Eiji Kakazu: Nothing to Disclose, Taiji Yamazoe: Nothing to Disclose, Masaaki Mino: Nothing to Disclose, Michitaka Matsuda: Nothing to Disclose, Shinji Kondo: Nothing to Disclose, Tatsuya Kanto: Nothing to Disclose

0130 | YAP CONTRIBUTES TO LIVER FIBROSIS THROUGH MEDIATING CAPILLARIZATION OF LIVER SINUSOIDAL ENDOTHELIAL CELLS VIA GATA6/ENOS SIGNALING

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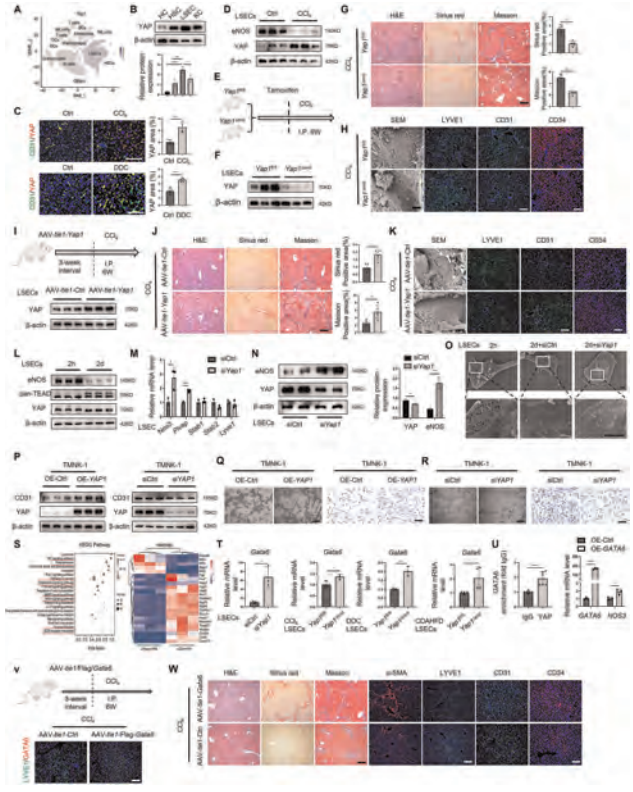
Background: Capillarization of liver sinusoidal endothelial cell (LSEC) is a central event in response to liver fibrosis. In this study, we investigated the role of YAP in LSEC capillarization and liver injury. **Methods:** YAP expression was assessed in liver samples from mice injured by CCl_4 injection and DDC diet. EC-specific *Yap1* conditional knockout mice (*Yap1*$^{\Delta end}$) were generated by breeding the *Yap1*$^{fl/fl}$ mice with the *Cdh5*-Cre^{ERT2} mice. HA-PEI/si*Yap1* nanoparticles were applied to specifically inhibit YAP expression in LSEC. **Results:** YAP was primarily expressed in LSEC and its expression was elevated during liver fibrosis. EC-specific *Yap1* deficiency significantly increased the fenestrae in LSEC and mitigated hepatocyte death and liver fibrosis. Overexpression of YAP in EC aggravated capillarization, hepatocyte death and liver fibrosis. Mechanistically, YAP inhibited *Gata6* transcription via binding to its promoter and thus resulted in LSEC capillarization. Overexpression of GATA6 in EC alleviated capillarization and liver fibrosis by activating *Nos3* transcription. Moreover, specifical delivery of HA-PEI-*siYap1* nanoparticles to LSEC alleviated liver fibrosis in mice. **Conclusion:** The YAP-GATA6/eNOS signaling is essential in LSEC capillarization and subsequent liver fibrosis. Interventions targeting YAP in LSEC offers a promising strategy for the treatment of liver fibrosis.



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0131 | ASSOCIATION BETWEEN LIVER RELATED FACTORS AND POST- CARDIAC SURGERY MORTALITY

Christina Liava[1] Juan Crestanello[2] Kevin Greason[2] Mauricio Villavicencio Theoduloz[2] Philip Spencer[2]

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Joseph Dearani[2] Hartzell Schaff[2] Patrick Kamath[2] Moira Hilscher[2], [1]MAYO CLINIC, ROCHESTER, MN, [2]MAYO CLINIC ROCHESTER

Background: We determined: 1. Impact of pre-operative cirrhosis, steatotic liver disease (SLD), and congestive hepatopathy (CH) on mortality post cardiac surgery, and 2. Post-operative predictors of 30-day and 1-year mortality. **Methods:** A total of 10,418 patients (> 18 years old) who underwent cardiac surgery from 2013 through 2023 were categorized as: controls (n = 8,820, no liver disease and normal liver biochemistry), cirrhosis (n = 244, diagnosed by imaging, histology, laboratory, or portal hypertension), CH (n = 995, diagnosed by laboratory and hepatic vein dilation with no other causes of liver disease), or SLD (n = 359, identified on imaging). Post-operative liver injury was graded according to the model for end stage liver disease (MELD) score, Food and Drug's Administration (FDA's) drug-induced liver injury severity index, and liver failure [LF: bilirubin > 7.5mg/dL and International Normalized Ratio (INR) ≥ 1.5]. Logistic and Cox regression analysis identified factors associated with 30-day and 1-year mortality. **Results:** Mortality at 30 days (controls 0.1%; CH 7.7%, cirrhosis 7%, and SLD 3.8%, $P < 0.001$) and 1-year (controls 2.3%; CH 17.2%, cirrhosis 17.6%, and SLD 6.7%, $P < 0.001$) were higher in patients with liver disease. 30-day mortality (Table 1) was associated with a) pre-operative grade 2 or 4 liver injury severity, serum albumin ≤ 3mg/dL and MELD ≥ 10, and b) post-operative grade ≥ 2, transaminases > 20X with shock, LF, and day 7 MELD ≥ 15. 1-year mortality (Table 1) was associated with a) postoperative transaminases > 20X, liver failure, day 7 MELD ≥ 10, and day 30 MELD ≥ 15. Patients with CH were at higher risk of postoperative shock and grade 4 liver injury. Day 7 predictors of very low 30-day mortality (< 3%) were no shock, transaminases < 20X and MELD < 10; high 30-day mortality (29%) were transaminases > 20X and MELD ≥ 15; and very high 30-day mortality (61.5%) were LF with hepatic encephalopathy and MELD ≥ 15. Day 7 predictors of very low 1-year mortality (< 3%) were MELD < 10; high 1-year mortality (37.5%) were transaminases > 20X with shock and MELD 10-15; and very high 1-year mortality (43.8%) were LF with infection and MELD > 20. **Conclusion:** CH and SLD are associated with increased 30-day and 1-year mortality post cardiac surgery, especially with pre-operative MELD ≥ 10. Day 7 grade 4 liver injury and MELD score ≥ 10 were associated with 30-day and 1-year mortality. These results inform risk stratification of patients with liver disease considered for cardiac surgery.

Table 1. Patterns of Pre- and Post-operative Liver Injury as well as MELD Score Categories and Mortality Risk

Pre-operative Liver parameters, n (%)	8-30-Day Mortality OR (95% CI)	P Value	1-12-Month Mortality HR (95% CI)	P Value
Severity Grading				
Normal AST/ALT	1.00 (ref.)	-	1.00 (ref.)	-
Grade 1 (AST/ALT < 3)	1.36 (0.90-2.04)	.142	**1.31 (1.01-1.71)**	**.045**
Grade 2 (AST/ALT 3-5)	**4.93 (2.60-9.35)**	**<.001**	0.84 (0.35-2.04)	.700
Grade 3 (AST/ALT 5-20)	1.00 (0.31-3.25)	.999	1.00 (0.44-2.24)	.994
Grade 4 (AST/ALT > 20)	**3.87 (1.10-13.57)**	**.035**	1.30 (0.32-5.24)	.709
Serum Albumin				
Albumin ≤ 3mg/dL	**3.17 (1.96-5.11)**	**<.001**	1.33 (0.88-2.02)	.177
Scoring System				
MELD ≥ 10	**1.66 (1.18-2.35)**	**.004**	**1.41 (1.13-1.77)**	**.002**
Post-operative Liver Parameters, n (%)	**8-30-Day Mortality OR (95% CI)**	**P Value**	**1-12-Month Mortality HR (95% CI)**	**P Value**
Patterns				
Shock + AST/ALT >20	**5.58 (4.04-7.72)**	**<.001**	**2.70 (2.01-3.63)**	**<.001**
Shock + AST/ALT <20	1.10 (0.81-1.47)	.552	1.16 (0.94-1.43)	.165
No Shock + AST/ALT >20	0.92 (0.12-7.01)	.939	0.05 (0.01-17.79)	.316
No Shock + AST/ALT <20	0.15 (0.09-0.25)	<.001	0.59 (0.47-0.75)	<.001
Isolated Bilirubin Elevation	0.49 (0.12-2.01)	.321	0.90 (0.43-1.90)	.783
Isolated ALP elevation	0.12 (0.02-0.85)	.034	**1.55 (1.02-2.34)**	**.039**
ALP + Bilirubin Elevation	N/A	.997	1.36 (0.73-2.55)	.337
Liver Failure	**12.29 (8.75-17.28)**	**<.001**	**4.40 (3.24-5.97)**	**<.001**
Recovered	0.02 (0.05-0.08)	<.001	0.08 (0.04-0.15)	<.001
Hepatic Encephalopathy	**2.95 (1.63-5.36)**	**<.001**	**2.90 (1.64-5.14)**	**<.001**
Infection	1.71 (0.96-3.04)	.070	**4.88 (2.70-8.83)**	**<.001**
Scoring System				
MELD at day 7 ≥ 16	**2.56 (1.86-3.54)**	**<.001**	**2.08 (1.65-2.63)**	**<.001**
MELD at Day 30 ≥ 14	N/A	-	**2.04 (1.60-2.59)**	**<.001**
Severity Grading				
Normal AST/ALT	1.00 (ref.)	-	1.00 (ref.)	-
Grade 1 (AST/ALT < 3)	2.25 (0.69-7.36)	.178	0.59 (0.42-0.84)	.003
Grade 2 (AST/ALT 3-5)	**4.38 (1.31-14.58)**	**.016**	0.57 (0.38-0.86)	.008
Garde 3 (AST/ALT 5-20)	**8.52 (2.64-27.54)**	**<.001**	0.89 (0.61-1.31)	.567
Garde 4 (AST/ALT > 20)	**19.04 (5.91-61.40)**	**<.001**	**1.62 (1.07-2.44)**	**.023**
MELD Score Categories	**< 10**	**10-15**	**15-20**	**> 20**
Pre-operative MELD				
30-day Mortality, %	3.9	8.4	5.5	9.2
1-year Mortality, %	13.6	14.9	16.1	18.8
Post-operative MELD at day 7				
30-day Mortality, %	2.0	2.8	9.6	12.5
1-year Mortality, %	8.9	15.7	15.8	22.5
Post-operative MELD at day 30				
1-year Mortality, %	11.7	14.7	17.0	26.9

OR: Odds Ratio; HR: Hazard Ratio; CI: Confidence Interval; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; MELD: Model for End Stage Liver Disease; INR: International Normalized Ratio

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0132 | ROLE FOR ENDOKYNE-1 IN LSEC–HSC COMMUNICATION AND ITS ASSOCIATION WITH ADVANCED CHRONIC LIVER DISEASE

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Background: Liver sinusoidal endothelial cells (LSECs) play a central role in regulating hepatic microcirculation and paracrine signaling. In chronic liver disease (CLD), LSECs undergo capillarization, losing their specialized phenotype and contributing to fibrosis and cirrhosis. Prior transcriptomic analyses identified *Endokyne-1* (EK1) as one of the most upregulated cytokines in LSECs from cirrhotic livers. This study aims to characterize the role of EK1 and its receptor EK1R in CLD progression. **Methods:** Human liver samples (healthy and cirrhotic) from internal and external cohorts were used for transcriptomic and protein analyses. EK1 expression was assessed in five independent human CLD transcriptomic datasets, as well as in serum and tissue samples (n = 61 CLD vs n = 52 healthy livers; n = 40 CLD vs n = 12 controls for serum). In vivo, EK1 was studied in a rat model of progressive liver injury induced by CCl_4 inhalation (2 weeks, 6 weeks, 12 weeks, n = 6/time-point), and in a conditional knockout mouse model lacking EK1R in hepatic stellate cells ($EK1R^{\Delta HSC}$), with CCl_4-induced fibrosis (n = 10). In vitro, primary rat LSECs and quiescent HSCs (qHSCs) were used in gain- and loss-of-function studies to examine EK1-mediated paracrine signaling. **Results:** Meta-analysis of five public human liver transcriptomic cohorts revealed consistent upregulation of *EK1* in advanced CLD. This was validated in our internal cohort at both mRNA and protein levels in liver tissue and serum. In animal models, EK1 was markedly increased in cirrhotic livers (fold change: mRNA 16.2x, protein 8x vs healthy), with LSECs identified as the primary source. EK1 was detected in LSEC-conditioned media, indicating active secretion. Functionally, recombinant EK1 activated qHSCs, increasing *ACTA2* and *COL1A1* expression. Conversely, EK1-silenced cirrhotic LSECs failed to induce HSC activation. In vivo, $EK1R^{\Delta HSC}$ mice showed improved liver function (−33% ALT), reduced fibrotic gene expression (−25% collagen) and decreased αSMA expression (−25%). **Conclusion:** LSEC-derived EK1 is a disease-induced cytokine that promotes hepatic stellate cell activation through the EK1–EK1R axis in advanced CLD. Disruption of this signaling pathway attenuates fibrogenesis and improves liver function, highlighting EK1–EK1R as a potential therapeutic target. Further studies will explore the utility of EK1 as a biomarker of advanced liver disease.

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0133 | OUTCOMES AND PATENCY OF TIPS FOR PORTAL VEIN THROMBOSIS FROM THE ALTA STUDY GROUP

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Background: TIPS creation is a recently established treatment for acute and chronic portal vein thrombosis (PVT) and related portal hypertension (pHTN) complications. Prior studies have been limited to single center experience raising questions about long-term patency of TIPS in PVT and associated complications. **Methods:** Advancing Liver Therapeutic Approaches in

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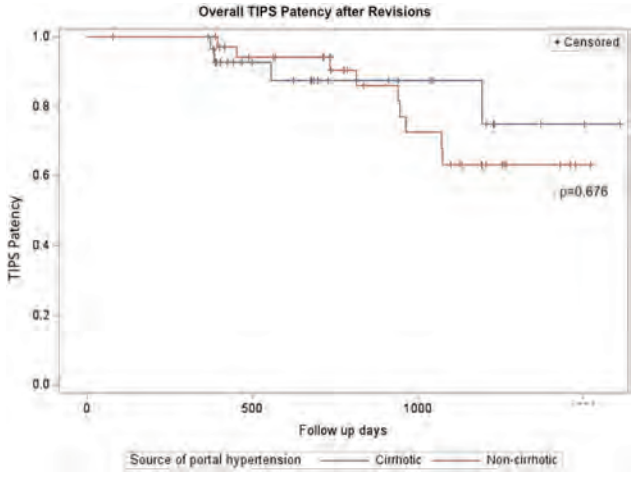
Portal Hypertension (ALTA-TIPS) is a prospective, multicenter observational cohort conducted at 13 U.S. centers, enrolling adults ($\geq$18 years) who underwent TIPS creation between 6/2019–12/2024 with $\geq$6 months follow-up. Collected data included procedural details, patency, transplant/survival status, and complications such as hepatic encephalopathy (HE).

Results: Of 852 enrolled subjects, 123 (14%) underwent TIPS creation for management of acute or chronic PVT. 71 participant (58%) were cirrhotic (cPVT) and 52 (49%) were non-cirrhotic (ncPVT). A defined hypercoagulable state was more common in non-cirrhotic PVT subjects (19 vs. 6, $p < 0.001$). TIPS creation in non-cirrhotic subjects was primarily for chronic PVT management (40, 77%), while cirrhotic PVT indications included ascites (18, 25%), bleeding (11, 16%), transplant facilitation (12, 17%), or a combination of pHTN complications (30, 42%). Revision of the TIPS either with angioplasty or restenting for complete occlusion or TIPS dysfunction was more common among ncPVT (n = 36, 70%) compared to cPVT (n = 28, 39%), $p = 0.001$. Overall patency after subsequent revisions for subjects with at least 1 year of follow up was no different in ncPVT compared to cPVT, $p = 0.676$ (Figure). The overall permanent occlusion rate for both ncPVT and cPVT was significantly higher (19% vs 5.6%, $p < 0.0001$) compared to non-PVT TIPS recipients No pre-TIPS clinical factors predicted occlusion. Post-TIPS HE hospitalizations were less frequent in the ncPVT (7, 14%) compared to cPVT group (22, 31%), $p = 0.0294$.

Conclusion: TIPS creation for management of PVT was common among all TIPS recipients in a large multicenter cohort. Non-cirrhotic PVT was associated with hypercoagulability and higher reintervention rates. Despite frequent revisions in both groups, overall patency remained acceptable.



Disclosures: Justin Boike: W. L. Gore and Associates: Grant/Research Support, Eurofins Transplant Genomics: Advisor, Echosens: Consultant, W. L. Gore and Associates, Inc.: Consultant, K. Pallav Kolli: Nothing to Disclose, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, Elizabeth Verna: Nothing to Disclose, Mike Fallon: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Advisor, Catherine Frenette: Gilead Sciences: Employee, Aparna Goel: Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Sumeet Asrani: Nothing to Disclose, Consuelo Soldevila-Pico: Nothing to Disclose, Mary Thomson: Nothing to Disclose, Brett Fortune: Gilead Sciences: Consultant, Madrigal Pharma: Consultant, WL Gore and Associates: Consultant, BD medical: Consultant, Adam Deising: Nothing to Disclose, Sonali Paul: Intercept: Grant/Research Support, Target PharmaSolutions: Grant/Research Support, Eli Lilly: Stock - publicly traded company, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Margarita German: Nothing to Disclose, Mehnush Hameie: Nothing to Disclose, Cynthia Padilla: Nothing to Disclose, Dyanna Gregory: Nothing to Disclose, Bartley Thornburg: Nothing to Disclose

0134 | CLINICAL CHARACTERISTICS AND INFLUENTIAL FACTORS OF PORTO-SINUSOIDAL VASCULAR DISEASE WITH PORTAL HYPERTENSION

Weihua Cao[1] Yao Xie[1] Minghui Li[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: Porto-sinusoidal vascular disease (PSVD) remains underdiagnosed. This study aimed to investigate the clinical characteristics, influencing factors, and clinical outcomes of PSVD. **Methods:** This was a prospective observational study. Patients diagnosed with PSVD via liver biopsy were enrolled. Demographic and clinical data were collected. Patients were stratified into portal hypertension (PH) group and non-PH group based on the presence of PH (Figure 1). Clinical and histopathological features were evaluated according to the latest PSVD diagnostic criteria. Additionally, influencing factors for PSVD with

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PH and clinical outcomes of PSVD patients were investigated. **Results:** 282 PSVD patients were enrolled, 113 with PH and 169 without PH. The most common initial presentation was abnormal liver function (69.15%) in Table 1. Additionally, 39 patients (13.83%) presented with splenomegaly detected during routine examinations, 8 (2.84%) with gastrointestinal bleeding, and 22 (7.80%) with thrombocytopenia in Table 1. Disease duration prior to biopsy ranged from 1 month to 5 years in Table 1. PSVD predominantly affected middle-aged women (56.38%), with a mean age of 44.82 ± 14.56 years. PH group patients had significantly lower white blood cell (WBC, $p = 0.020$) and platelet (PLT, $p < 0.001$) counts, reduced albumin ($p = 0.019$) and prothrombin activity (PTA, $p < 0.001$), elevated INR ($p < 0.001$), and higher liver stiffness measurement (LSM, $p < 0.001$). Non-PH group exhibited lower total bilirubin (TBIL, $p = 0.006$) and direct bilirubin (DBIL, $p < 0.001$), but higher γ-glutamyl transferase (GGT, $p = 0.019$). Histopathological analysis revealed obliterative portal venopathy (OPV, 86.17%) as the most characteristic feature, while portal tract abnormalities (93.26%) and perisinusoidal fibrosis (59.57%) were common nonspecific findings. PH group showed higher prevalence of OPV ($p = 0.048$) and incomplete septal cirrhosis (ISC, $p = 0.040$). Non-PH group had more portal tract abnormalities ($p = 0.033$), whereas architectural disturbance ($p < 0.001$) and non-zonal sinusoidal dilation ($p = 0.001$) predominated in PH group. Multivariate logistic regression identified PLT ($p = 0.001$) and LSM ($p < 0.001$) as independent risk factors for PSVD patients with PH. During a median follow-up of 18.5 months, 5.56% of patients with compensated liver experienced variceal bleeding. Non-PH patients did not progress to PH. **Conclusion:** PSVD may present as either PH or liver enzyme abnormalities, with significant differences in histopathological features among patients exhibiting distinct clinical manifestations. PLT and LSM are independent risk factors for PSVD with PH. In contrast, PSVD patients without PH exhibit slower disease progression, with elevated GGT levels being a predominant clinical feature.

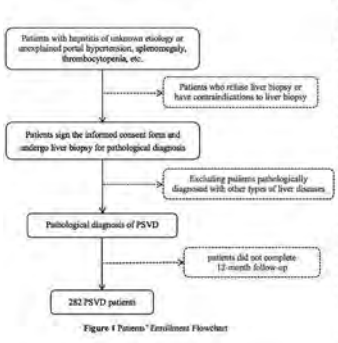
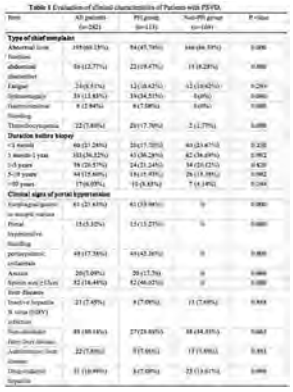


Figure 1 Patients' Enrollment Flowchart



Disclosures: Weihua Cao: Nothing to Disclose, Yao Xie: Nothing to Disclose, Minghui Li: Nothing to Disclose

★ 0135 | PATIENT REPORTED OUTCOME MEASUREMENT IS FEASIBLE DURING AMBULATORY LIVER CARE AND REQUIRES PROVIDER SUPPORT VIA CARE DELIVERY INNOVATION

Nadia Blessing[1] Miranda Stovall[1] Suhani Lodha[1] Christine Abeysekera[1] Carla Kettler[1] Marwan Ghabril[1] Naga Chalasani[2] Eric Orman[1] Archita Desai[1], [1]Indiana University, [2]Indiana University Medical Center

Background: Individuals with chronic liver disease (CLD) and cirrhosis face high symptom burden, poor health-related quality of life (HRQOL), and significant unmet health-related social needs (HRSN). However, few studies assess patient-reported outcome measurements (PROMs) in routine care or provider comfort in addressing the results. This study evaluated the feasibility of PROM collection during routine care, the burden of unmet needs in ambulatory CLD/cirrhosis patients, and provider comfort in addressing them. **Methods:** We performed a prospective study of adults seen for routine non-transplant hepatology care at an academic health center from 7/2024 to 5/2025. Participants were recruited by phone 1-2 weeks prior to their scheduled visit to complete PROMs measuring HRQOL (PROMIS-29 v2.0), HRSN (Accountable Health Communities Screening Tool, Social Network Index), and informational needs (Brief Health Literacy Scale, MyCirrhosisCoach, PROMIS Informational Support). Scores were interpreted using validated cutoffs. Hepatology providers ($n = 18$) were also surveyed to determine their comfort and training level (5-point scale) with managing each domain. Baseline characteristics and survey responses were summarized using means and compared by cirrhosis status. **Results:** From 829 adults who were approached, response rate was 31% ($n = 386$). Consent rate was 52% of those responding and 24% of all approached ($n = 202$). Lack of interest in study was low (16%, $n = 63$). The majority (78%, $n = 158$) completed study assessments and are described in the Table. Half had cirrhosis and were similar to those with CLD except lower household income and cause of liver disease. PROM score categories and needs identified were similar between those with and without cirrhosis ($p > 0.05$, Figure). Rates of poor PROs and needs by cirrhosis status are shown in the Figure alongside provider comfort in their management. Poor HRQOL was reported by 24%-71% depending on the domain measure with over 50% of providers reporting discomfort in responding to pain

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interference or social participation. The most common HRSN was financial needs (28%). Provider discomfort rates were high in all HRSNs domains (range 53-74%). Social isolation was noted by 20% and loneliness by 70%, with 80% of providers expressing discomfort in addressing these PROs. Informational needs were also common including low health literacy (27%), obstacles to medication adherence (36%) and lack of informational support (56%), with provider discomfort noted by 32-44% of providers. **Conclusion:** Routine measurement of PROs is feasible in ambulatory liver care and reveals significant burden of unmet needs, regardless of cirrhosis status. In parallel, provider discomfort in managing these domains is striking. Taken together, routine PROMs in liver care, paired with innovative care pathways to enhance providers' comfort and capability may improve patient-centered outcomes in this high-need population.

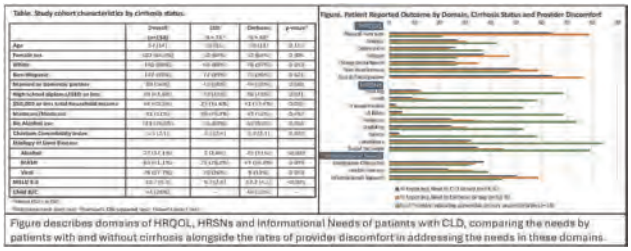

Figure describes domains of HRQOL, HRSNs and Informational Needs of patients with CLD, comparing the needs by patients with and without cirrhosis alongside the rates of provider discomfort in addressing the needs in these domains.

Disclosures: Nadia Blessing: Nothing to Disclose, Miranda Stovall: Nothing to Disclose, Suhani Lodha: Nothing to Disclose, Christine Abeysekera: Nothing to Disclose, Carla Kettler: Nothing to Disclose, Marwan Ghabril: Nothing to Disclose, Naga Chalasani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Eric Orman: Sitero: Consultant, Biovie: Advisor, Archita Desai: Nothing to Disclose

★ 0136 | PREDICTORS OF TIME TO TRANSPLANT IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: A NATIONWIDE ANALYSIS

Imran Qureshi[1] Muhammad Ali Ibrahim Kazi[2] Ritik Mahaveer Goyal[3] Muhammad Hassaan Arif Maan[4] Wajiha Khan[4] Rohan Karkra[4] Siddharth Verma[5] Ahmed Al-Khazraji[4] Paul Gaglio[4], [1]RUTGERS THE STATE UNIVERSITY OF NEW JERSEY, [2]Luminis Health Anne Arundel Medical Centre, Annapolis, Maryland, United States, [3]Rutgers New Jersey Medical School, [4]Rutgers New Jersey Medical School, Newark, New Jersey, United States, [5]Veterans Affairs Medical Center, East Orange, New Jersey, United States

Background: Hepatocellular carcinoma(HCC) is on the rise globally and is the third most common cause of cancer-related death. Liver transplant(LT) is a potentially curative treatment modality in select patients with HCC, with potentially better outcomes than alternative treatments. Herein, we evaluate factors associated with delay in LT. **Methods:** Using the National Cancer Database, we identified 16,893 patients with HCC who received LT between 2004 and 2022. We conducted multivariate linear regression using sociodemographic factors as well as neoadjuvant therapy, liver fibrosis, and AFP levels as predictors of time to LT. We reported coefficients in days to transplant from diagnosis of HCC, along with their 95% confidence intervals(CI) and p-values. **Results:** Our analysis (Figure 1) showed that compared to Whites, Blacks(20.94 days, 95% CI:7.86 to 34.03, $p < 0.01$) and Asians(49.98 days, 95% CI:34.19 to 65.76, $p < 0.01$) had longer time to LT. Hispanics experienced more delays than non-Hispanics (16.26 days, 95% CI:4.77 to 27.75, $p < 0.01$). Areas with 9.1–15.2% high school non-graduates(12.91 days, 95% CI:0.64 to 25.18, $p = 0.04$) and $\geq 15.3\%$ high school non-graduates(22.99 days, 95% CI:8.84 to 37.14, $p < 0.01$) were associated with longer delays to LT. In contrast, residing in lower-income areas were surprisingly associated with shorter time to treatment: $< \$46,277$(–30.91 days, 95% CI:–44.59 to –17.23, $p < 0.01$), \$46,277–57,856(–27.05 days, 95% CI:–38.73 to –15.37, $p < 0.01$), and \$57,857–74,062(–16.56 days, 95% CI:–26.88 to –6.24, $p < 0.01$). Patients with a Charlson-Deyo Comorbidity score of ≥ 3 had shorter time to LT(–30.82 days, 95% CI:–39.76 to –21.87, $p < 0.01$). Treatment at a community hospital vs. academic hospital was associated with increased delays(10.68 days, 95% CI:0.98 to 20.38, $p = 0.03$). Compared to the Northeast, the South(–21.78 days, 95% CI:–32.07 to –11.48, $p < 0.01$) and Midwest(–14.03 days, 95% CI:–25.57 to –2.49, $p = 0.02$) had shorter LT wait times, whereas the West had longer delays(51.32 days, 95% CI:38.62 to 64.01, $p < 0.01$). HCC before age 50 was associated with earlier LT(–40.13 days, 95% CI:–52.91 to –27.35, $p < 0.01$). Receipt of neoadjuvant therapy(164.08 days, 95% CI:152.44 to 175.72, $p < 0.01$), cirrhosis/severe fibrosis(21.54 days, 95% CI:3.18 to 39.90, $p = 0.02$) and elevated AFP(20.89 days, 95% CI:9.58 to 32.20, $p < 0.01$) were also associated with delayed LT. Sex, insurance, or setting did not significantly influence time to LT. **Conclusion:** Our study demonstrates that race, ethnicity, education, income, comorbidity burden, type of hospital, and region influence time to LT in patients with HCC. Multiple other factors, such as techniques of tumor downstaging, locoregional therapy, or receipt of immunotherapy, may influence the time to transplant. This shows that there are significant socioeconomic disparities in time to LT, raising the need for targeted public health interventions to address these.

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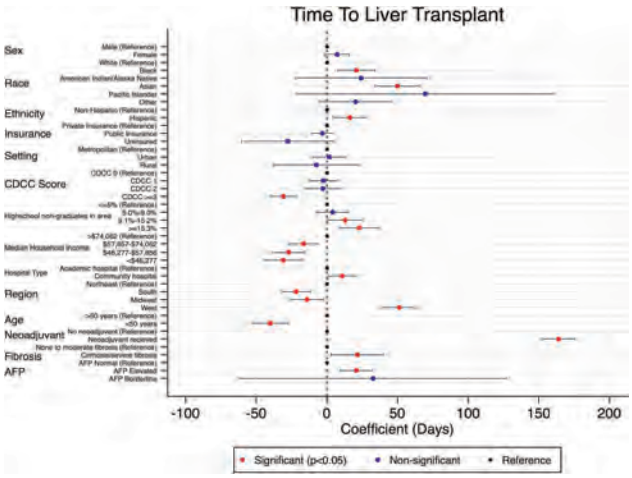

Disclosures: Imran Qureshi: Nothing to Disclose, Muhammad Ali Ibrahim Kazi: Nothing to Disclose, Ritik Mahaveer Goyal: Nothing to Disclose, Muhammad Hassaan Arif Maan: Nothing to Disclose, Wajiha Khan: Nothing to Disclose, Rohan Karkra: Nothing to Disclose, Siddharth Verma: Nothing to Disclose, Ahmed Al-Khazraji: Nothing to Disclose, Paul Gaglio: Nothing to Disclose, Nothing to Disclose

0137 | PATIENT PERSPECTIVES AND PERCEIVED BARRIERS TO LIVER TRANSPLANTATION IN A SAFETY-NET HOSPITAL SYSTEM

Andrea Amaro[1] Kali Zhou[1] Saroja Bangaru[1], [1]University of Southern California-Los Angeles General Medical Center

Background: Safety-net hospital (SNH) systems shoulder a disproportionate burden of cirrhosis, yet only a minority are referred for and successfully complete liver transplantation (LT). A previous study of SNH providers across the country found that patient-related factors, including insurance, finances, and psychosocial aspects, are frequently perceived as barriers to LT referral. There is limited investigation into and understanding of the safety-net patient perspective on LT. **Methods:** This ongoing anonymous survey study is being conducted among patients with cirrhosis at a large urban SNH hepatology clinic, starting in February 2025. The 49-item survey assesses knowledge of, perceptions about, and desired resources for care related to cirrhosis and LT. Surveys are being distributed to pre-screened patients in the waiting room in English or Spanish and completed independently or with family members. No identifying information is collected. **Results:** 147 patients have participated in the survey to date. Mean age was 56 (45-67) years. Respondents were 59% male, 82% foreign-born, and 92% Hispanic ethnicity. 56% of surveys were completed in Spanish. 40% had an annual household income of $10,000 or less, and 71% were insured by Medicaid. Most common etiologies of cirrhosis included alcohol (46%), metabolic-dysfunction associated steatotic liver disease (25%), and viral hepatitis (11%). 50% of patients had a prior paracentesis, 35% had hematemesis, and 35% had liver-related confusion. 54% reported having previously discussed LT with a physician, including 16% who had already been evaluated at an LT center. Regarding knowledge of LT, there was notable uncertainty: 37% were unsure whether cirrhosis is an indication for LT, 35% unsure if LT can cure cirrhosis symptoms, 76% unsure or did think all hospitals provide LT, and 75% unsure if insurance covers LT. Regarding potential barriers to LT, interestingly, 60-63% either agreed or strongly agreed they had adequate caregiver support, adequate transportation, and the ability to take off work to attend appointments, but 37% felt LT would be too much for their family and 51% were concerned about post-LT finances. Over two-thirds of patients felt the following resources would be extremely useful: a video about cirrhosis (70%); a video about liver transplantation (69%); a detailed explanation of costs of LT (74%); assistance with transportation to appointments (68%). **Conclusion:** Knowledge of benefits and availability of LT could be improved among SNH patients with cirrhosis. Caregiver support, transportation, and work obligations are reported barriers, though finances were the most prevalent source of concern. Educational interventions and detailed financial counseling may facilitate LT referral and completion of evaluation for low-income populations.

Disclosures: Andrea Amaro: Nothing to Disclose, Kali Zhou: Gilead Sciences Inc: Grant/Research Support, Merck: Grant/Research Support, Saroja Bangaru: Nothing to Disclose

0138 | BARRIERS BEYOND BIOLOGY: THE IMPACT OF PSYCHOSOCIAL VARIABLES ON LISTING FOR EARLY LIVER TRANSPLANTATION IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS

Olivia Blocker[1] Elina Stoffel[2] Himel Mallick[1] Jialin Gao[1] Eric Liu[1] Morgan Lozano[1] Virgina Parker[1] Robert Brown[1] Gene Im[2] Elizabeth Verna[2] Stephanie Rutledge[1], [1]Weill Cornell Medicine, [2]Columbia Medical Center

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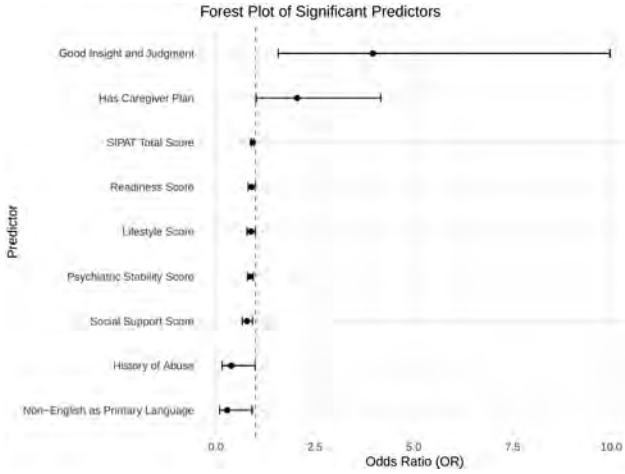
Background: Severe alcohol-associated hepatitis (AH) is an acute manifestation on the spectrum of alcohol-associated liver disease with high short-term mortality. An increasing number of transplant centers are considering patients with AH for early liver transplantation (eLT) without 6 months of abstinence. Instead of a fixed period of abstinence, the evaluation includes a detailed psychosocial assessment that could disadvantage individuals with social vulnerabilities. Our aim was to define how psychosocial variables and social determinants of health (SDOH) affect the likelihood of being listed for LT. **Methods:** We conducted a retrospective cohort study of patients > 18 years old hospitalized with probable or definite severe AH (per NIAAA criteria, MELD > 20) who underwent evaluation for eLT at two academic centers in New York City between January 2012 and May 2025. Patients were defined as "declined" if they were initially either declined or deferred for LT, as we could not account for changes in variables over time among those later accepted. Variables were manually extracted from social work documentation. A univariate logistic regression model was used to assess the association between psychosocial variables and acceptance for LT. The model was adjusted for MELD 3.0; age and sex were not associated with the outcome of interest and were not adjusted for. We did not adjust for all covariates as some covariates may function as mediators or colliders rather than true confounders, and we wanted to avoid overfitting. **Results:** Between 2012 and 2025, 133 patients with severe AH were evaluated for eLT: 82/133 (61%) were accepted, 36/133 (27%) were declined, 15/133 (11%) were deferred; of those deferred, 3/15 (20%) were later accepted. The majority (35/51, 69%) were deferred or denied for psychosocial factors. The mean age was 44 years (SD: 10) and 37% were female; 57% identified as White, 16% Black, 8% Hispanic, 5% Asian, and the remainder as other or were unknown. We analyzed 30 variables in a univariate logistic regression model. We found that having good insight/judgement – specifically regarding their diagnosis and understanding of the transplant process – had the highest odds ratio (OR) for LT acceptance (3.96, 95% CI: 1.57–9.96). Other significant variables included having a caregiver plan (OR = 2.05, 95% CI: 1.01-4.16). Speaking a non-English primary language (OR = 0.28, 95% CI: 0.09-0.91) and a history of abuse (OR = 0.38, 95% CI: 0.15-0.98) predicted lower likelihood of listing. **Conclusion:** The decision regarding early LT in severe AH is crucial, given that 6-month survival is ~30% without LT versus ~90% with LT. Many are not candidates for early LT due to psychosocial factors and relapse risk; thus, it is important to define the most influential decision-making factors. We need to be cognizant of factors that influence listing for LT but may not correlate with relapse risk or outcomes, which exacerbate healthcare inequities.



Disclosures: Olivia Blocker: Nothing to Disclose, Elina Stoffel: Nothing to Disclose, Himel Mallick: Nothing to Disclose, Jialin Gao: Nothing to Disclose, Eric Liu: Nothing to Disclose, Morgan Lozano: Nothing to Disclose, Virgina Parker: Nothing to Disclose, Robert Brown: Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant, Gene Im: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose, Stephanie Rutledge: Paige AI: Stock – privately held company, Intercept Pharmaceutical: Consultant

0140 | HEALTH LITERACY IS AN IMPORTANT DETERMINANT OF HEALTH OUTCOMES: IDENTIFYING RISK FACTORS FOR POOR HEALTH LITERACY IN CHRONIC LIVER DISEASE

Hannah Lee[1] Alana Saddic[1] Priyam Das[2] Niki Wadhwa[1] Mary Kate Lantzy[1] Grant Chin[1] Jessica Mittler[1] Deborah DiazGranados[1] Eshban Serosh[1] Richard Sterling[1], [1]Virginia Commonwealth University, [2]Virginia Commonwealth Univeresity

Background: A multidimensional concept, health literacy (HL) is defined as the ability to access, understand, appraise, and apply health information to manage one's health. HL is a central determinant of health and a priority in addressing chronic disease management. Little is known about the HL status in chronic liver disease (CLD) patients and their outcomes. **Methods:** A prospective study of CLD patients using the Health Literacy Questionnaire (HLQ) was performed. The HLQ measures the full construct of HL assessing 9 aspects to uncover mechanisms of health inequities to inform intervention development. Cohort characteristics, HLQ scores, and interaction between demographic/ clinical variables, health-related behaviors, number of admissions and their HL scores were assessed. **Results:** 84 patients were

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included (mean age: 56, MELD 12, females 57%, White 81%, Black 10%, Other 10%, ALD 31%, MASLD 49%, MetALD 7%, HCV 10%, cirrhosis 68% (CTP 66% A, 24% B, 11% C), and Education: 47% high school or less, 39% college, 14% > college. For HLQ part 1 (response scale 1-4), scores for "Feeling understood and well supported by healthcare providers" (mean,SD) (3.5,0.50) were the highest and "Appraisal of health information" (3.0,0.61) were the lowest. For part 2 of the HLQ (response scale 1-5), scores for "Ability to actively engage with health care providers" (4.15,0.65) were the highest and "Ability to find good health information" (3.82,0.64) were the lowest. Alcohol liver disease (ALD) had lower HL scores in 3 of the 9 domains (Table). High Patient Health Questionnaire (PHQ-9) had lower HL scores in 8 of the 9 domains. High General Anxiety disorder (GAD- 7) had lower HL scores in all 9 domains. High Edmonton Symptoms Assessment (ESAS) scores had lower HL scores in 7 out of the 9 domains. History of drug/ alcohol use was associated with higher PHQ/ GAD $p < .01$, ESAS $p < .01$ scores, and lower HLQ scores in 4 of the 9 domains. Higher number of admissions were associated with ALD $p < .01$, history of drug/alcohol use $p < .05$, mental health disorder $p < .01$, and high GAD $p < .01$/ ESAS $p < .001$ scores. **Conclusion:** Lower HL was associated with ALD, anxiety/ depression, history of drug/ alcohol use, and poorer QOL. History of drug/ alcohol use, ALD, mental health disorder, anxiety, and poorer QOL were associated with higher number of admissions. Our novel data provides opportunities for interventions to address poor HL to improve patient QOL and reduce health care utilization such as optimization of behavioral health and palliative/ symptom-based care.

Negative correlations between Health literacy Questionnaire and clinical, depression/ anxiety and quality of life assessments in chronic liver disease

Health Literacy Questionnaire	1: Feeling understood and supported by health care providers	2: Having sufficient information to manage my health	3: Actively managing my health	4: Social support for health	5: Appraise Health information	6: Ability to engage with health care providers	7: Ability to navigate the health care system	8: Ability to find good health information	9: Ability to understand health information to know what to do
Alcohol liver disease	p < 0.01	ns	ns	ns	ns	ns	p < 0.05	p< 0.05	ns
History of drug/ alcohol use	p < 0.001	ns	p < 0.01	ns	ns	ns	p < 0.01	p < 0.05	ns
Patient health questionnaire (PHQ-9)	ns	p < 0.01	p < 0.001	p < 0.001	p < 0.05	p < 0.01	p < 0.001	p < 0.001	p < 0.01
General anxiety disorder (GAD-7)	p < 0.05	p < 0.01	p < 0.001	p < 0.05	p < 0.001	p < 0.01	p < 0.001	p < 0.001	p < 0.001
Edmonton Symptom Assessment (ESAS)	ns	p < 0.001	p < 0.001	p < 0.05	ns	p < 0.01	p < 0.01	p < 0.01	p < 0.01

*non not significant

Disclosures: Hannah Lee: Nothing to Disclose, Alana Saddic: McKesson: Stock - publicly traded company, Eli Lilly: Stock - publicly traded company, Priyam Das: Nothing to Disclose, Niki Wadhwa: Nothing to Disclose, Mary Kate Lantzy: Nothing to Disclose, Grant Chin: Nothing to Disclose, Jessica Mittler: Nothing to Disclose, Deborah DiazGranados: Nothing to Disclose, Eshban Serosh: Nothing to Disclose, Richard Sterling: ABIM: GI Specialty Board, Abott: Grant/Research Support, AbbVie: Grant/Research Support, Roche: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/ Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research Support

0141 | DEVELOPMENT AND INTERNAL VALIDATION OF THE LABORATORY-BASED LIVER FRAILTY INDEX (LAB-LFI)&MDASH; A PREDICTION MODEL BASED ON CIRCULATING BIOMARKERS FOR FRAILTY IN PATIENTS WITH CIRRHOSIS

Michael Li[1] Nghiem Ha[1] Srilakshmi Seetharaman[1] Chiung-Yu Huang[1] Catherine Lee[1] Jennifer Lai[1], [1]University of California, San Francisco

Background: Frailty, as measured by the Liver Frailty Index (LFI), is a well-established predictor of outcomes in cirrhosis patients. However, the LFI consists of grip, chair stands, and balance testing, limiting frailty testing to in-person encounters. We sought to develop an index correlated with frailty from hypothesis-driven, biologically relevant blood-based biomarkers. **Methods:** Based on prior work screening candidate frailty biomarkers, 7 serum/plasma analytes (myostatin, IL-6, growth differentiation factor-15 [GDF-15], testosterone, leucine-rich alpha-2 glycoprotein [LRG1], fetuin-A, and IGF-1) were measured by ELISA in 520 ambulatory cirrhosis patients and log2-transformed for analyses. "Frail" was defined as LFI $\geq$ 4.4. The study cohort was split randomly in half; LASSO regression was employed to develop the prediction model in the training set and internally validated in the test set. Other machine learning methods (generalized additive model [GAM], Random Forest, and XGBOOST) were utilized to construct models to compare discrimination for frailty. **Results:** Of 520 ambulatory cirrhosis patients (median age 59, median MELD 14), 111 (21%) were frail. All 7 log2-transformed biomarkers were significantly associated with frailty on univariable testing, and all but myostatin and LRG1 remained significantly associated with frailty after using logistic regression to adjust for age, sex, liver disease etiology, and MELD (Fig A). Lab-LFI was derived from the training set using LASSO regression, with the following formula for log odds of frailty: *-1.61 - 0.24*(log2[myostatin]) + 0.35*(log2[IL-6]) + 0.23*(log2[GDF-15]) - 0.52*(log2[testosterone]) + 0.05*(log2[LRG1]) - 0.61*(log2[Fetuin-A]) – 0.27*(log2[IGF-1])*. In the test set, Lab-LFI had a c-statistic of 0.80 (95% CI 0.74-0.87) for predicting frailty. Lab-LFI also had good calibration (Hosmer-Lemeshow $p = 0.740$). The GAM, random forest, and XGBOOST approaches produced models with similar performance (c-statistics 0.79-0.82; Fig B); as such, the LASSO model was chosen for maximum interpretability. Addition of clinical variables to the LASSO model, including MELD labs, sex, and liver disease etiology, did not improve discrimination (c-statistic 0.78, 95% CI 0.72-0.85). **Conclusion:** We developed and internally validated the Lab-LFI, a frailty prediction model consisting of 7

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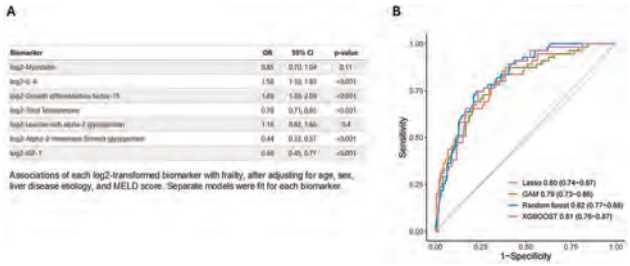
laboratory-based biomarkers with excellent discrimination. Lab-LFI enables assessment of *physical* function, as MELD does with *liver* function. Furthermore, several Lab-LFI biomarkers can be altered through supplementation (testosterone) or biologics (inhibition of IL-6 and GDF-15), raising the exciting possibility for therapeutic targets to modify frailty.



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0142 | INTEGRATING WEARABLE, RADIOLOGIC, LABORATORY, AND METABOLOMIC BIOMARKERS TO CHARACTERIZE FRAILTY IN CIRRHOSIS: INSIGHTS FROM A PROSPECTIVE OBSERVATIONAL STUDY

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Background: Frailty is an independent predictor of mortality in cirrhosis, reflecting multisystem physiological decline. Current tools such as the Liver Frailty Index (LFI) rely on clinic-based assessments and may not capture early or evolving changes. This study evaluated wearable-derived, imaging, laboratory, and metabolomic markers as objective indicators of frailty in cirrhosis. **Methods:** This single-center prospective study (CTRI/2022/09/045668) enrolled adults with cirrhosis. Frailty was assessed using the LFI at baseline. Four domains were evaluated: (1) Wearables: Patients wore Garmin Vivosmart 5 for up to two weeks to record daily step count and physiological activity; (2) Imaging: CT-derived skeletal muscle index and MRI-based psoas area were measured; (3) Laboratory: Routine clinical parameters including serum phosphorus, total protein, and lymphocyte differential were analyzed; (4) Metabolomics: Targeted LC-MS quantified plasma amino acids and acylcarnitines. Spearman correlations were used to assess associations with LFI. **Results:** Forty-eight patients were included (15 compensated, 21 decompensated, 10 ACLF 0–1, 2 ACLF 2–3); 57% were pre-frail and 43% frail by LFI. Daily step count showed a significant inverse correlation with frailty ($r = –0.472$, $p < 0.001$). Skeletal muscle area was also inversely associated with frailty ($r = –0.496$, $p < 0.001$). Lower serum phosphorus ($r = –0.508$, $p < 0.001$) and total protein ($r = –0.444$, $p < 0.001$) were significantly associated with frailty. Metabolomic analysis showed positive correlations of LFI with free carnitine ($r = 0.447$, $p = 0.002$), acetylcarnitine ($r = 0.427$, $p = 0.003$), 4-hydroxyproline ($r = 0.500$, $p < 0.001$), methionine ($r = 0.428$, $p = 0.003$), and lysine ($r = 0.407$, $p = 0.005$). **Conclusion:** Frailty in cirrhosis is associated with objective alterations across wearable, radiologic, laboratory, and metabolomic domains. Integration of wearable technology with molecular and imaging markers may enable scalable, continuous frailty monitoring and serve as a framework for evaluating targeted interventions in liver disease.

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0143 | FRAILTY, COGNITIVE IMPAIRMENT AND COMORBID CONDITIONS ADD TO CIRRHOSIS SEVERITY IN PREDICTION OF 12-MONTH HOSPITALIZATIONS IN A MULTI-CENTER OUTPATIENT CIRRHOSIS COHORT

Jasmohan Bajaj[1] Jennifer Lai[2] Puneeta Tandon[3] Jacqueline O'Leary[4] Florence Wong[5] Guadalupe Garcia-Tsao[6] Hugo Vargas[7] Philip Vutien[8] Scott Biggins[9] Kaitlyn Wethey[10] Tahira Shaikh[11] Stephanie Tsai[12] Jawaid Shaw[13] Andrew Fagan[14] Patrick Kamath[15] Leroy Thacker[13] K Rajender Reddy[16], [1]Virginia Commonwealth University, [2]UCSF, [3]University of Alberta, [4]Dallas VAMC, [5]University of Toronto, [6]Yale University, [7]Mayo Clinic Arizona, [8]University of Washington, [9]U Washington, [10]U Penn, [11]U Alberta, [12]UTSW, [13]VCU, [14]Richmond VA, [15]Mayo Rochester, [16]University of Pennsylvania

Background: Cirrhosis etiology control & changing demographics require re-evaluation of prediction models for outcomes such as hospitalizations. An integrated multi-site approach with cirrhosis-related factors, comorbidities, cognitive function, and frailty metrics is needed. Aim: To determine the integrated impact of cirrhosis-related & unrelated factors in 12-month hospitalization

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prediction in outpatients with cirrhosis. **Methods:** NAC-SELD-3 (North American Consortium for the Study of End-Stage Liver Disease) is a cohort of outpatients with compensated & decompensated cirrhosis recruited from 10 centers across North America (Fig A). We enrolled pts able to consent, those with eradicated HCV, & without HIV/illicit drug use or alcohol misuse. Demographics, cirrhosis severity/history, comorbidities using Charlson comorbidity index (CCI), & medications were recorded. Liver frailty index instruments (LFI, high = worse), EncephalApp Stroop (High time = worse), SF-36 (low = worse), Mini-mental status (MMSE) & animal naming tests (ANT) both low = worse, were administered. Patients were systematically followed for 12 months using in-person visits every 6 months and phone calls every 3 months in between. Logistic regression analyses for hospitalizations was performed using baseline variables that were significantly different at $p < 0.10$. **Results:** 981 patients (61 yrs, 70% men, 76% White, 6% Latinx) who were able to complete EncephalApp Stroop and LFI were included. Median CCI was 5 (3-6) which denotes a moderate comorbidity burden. Cirrhosis details: 39% were compensated; major etiologies were alcohol (47%), MASLD (26%), & eradicated HCV (17%). Median MELD-Na was 11, 35% had prior HE & 19% difficult to control ascites. Hospitalizations: 334 (34%) required admissions at 12M; >85% were liver related. Pts who needed hospitalization were younger, had higher CCI, cirrhosis severity/medications, worse EncephalApp Stroop, ANT, SF-36 and LFI (Fig B). Regression (Fig C): Variables associated with greater 12M hospitalizations were cirrhosis-related (baseline diuretic use, higher MELD-Na), cognitive (higher with longer EncephalApp Stroop time), frailty (worse with higher LFI) and higher CCI. Age and greater SF-36 score (better quality of life) were associated with lower 12M hospitalizations. **Conclusion:** In this multi-center experience of nearly 1000 outpatients with compensated and decompensated cirrhosis with controlled etiologies, frailty, covert HE, patient-reported outcomes and comorbidity burden add to cirrhosis-related factors for the prediction of hospitalizations at 12 months. A holistic, integrative approach to outpatients with cirrhosis is needed to improve prognostication and potentiall reduce this burden.

Fig A: Sites included in the North American Consortium for Study of End-Stage Liver Disease 3

Fig B: Clinical Comparison % (N) unless otherwise mentioned

	No Admission (n=647)	Admission (n=334)	p-value
Age mean (SD)	61.0 (10.4)	59.6 (10.6)	0.09
Female Sex	31% (201)	30% (101)	0.79
Charlson Comorbidity Index median (IQR)	5 (3, 6)	5 (4, 6)	0.008
Cirrhosis history			
Compensated status	49% (315)	21% (70)	<0.0001
MELD-Na median (IQR)	10 (8, 14)	14 (9, 18)	<0.0001
History of SBP	5.3% (34)	11.4% (38)	0.005
Medications at consent			
Non-selective β-blockers	43.7% (282)	51.5% (172)	0.02
Rifaximin	20.3% (131)	37.4% (125)	<0.0001
Lactulose	28.2% (182)	46.5% (162)	<0.0001
Proton Pump Inhibitors	42.9% (277)	54.2% (181)	<0.0001
SBP Prophylaxis	6.7% (43)	15.6% (52)	<0.0001
Diuretics	42.6% (275)	65.9% (220)	<0.0001
Statins	29.8% (192)	30.5% (102)	0.80
Patient reported outcomes(median [IQR])			
Liver Frailty Index	3.0 [2.0, 3.0]	3.00 [3.0, 4.0]	<0.0001
AUDIT-10 Score	0.0 [0.0, 2.0]	0.00 [0.0, 2.0]	0.75
Mini mental status exam	30.00 [29.0, 30.0]	30.0 [29.0, 30.0]	0.46
Animal naming test	20.0 [17.0, 23.0]	18.0 [15.0, 22.0]	0.002
Total Stroop Time	172.8 [153.7, 198.3]	188.9 [161.6, 221.2]	<0.0001
SF-36 General Health	50.0 [35.00, 65.0]	40.0 [25.0, 50.0]	<0.0001

Fig C. Multi-variable models for Admission Prediction

Variable	p-value	OR (95% CI)
Age	0.01	0.98 (0.85, 0.99)
Liver Frailty Index	<0.001	1.38 (1.12, 1.61)
Charlson Comorbidity Index	0.02	1.11 (1.01, 1.22)
Total Stroop Time	0.02	1.02 (1.01, 1.03)
SF-36 General Health Score	0.01	0.98 (0.97,0.99)
Diuretics	0.009	1.73 (1.25, 2.39)
MELD-Na	0.007	1.04 (1.01, 1.07)

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Wethey: Nothing to Disclose, Tahira Shaikh: Nothing to Disclose, Stephanie Tsai: Nothing to Disclose, Jawaid Shaw: Nothing to Disclose, Andrew Fagan: Nothing to Disclose, Patrick Kamath: Sequana: Advisor, NovoNordisk: Advisor, GSK: Advisor, GSK: Advisor, Leroy Thacker: Nothing to Disclose, K Rajender Reddy: Nothing to Disclose

0144 | PROGNOSTIC ROLE OF HVPG AND NON-INVASIVE TESTS ACROSS THE SPECTRUM OF ADVANCED STEATOTIC LIVER DISEASE

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Background: The spectrum of steatotic liver disease (SLD) includes patients with metabolic dysfunction-associated liver disease (MASLD), alcohol-related liver disease (ALD), and a mixed phenotype (MetALD). Granular data on the impact of SLD-subtypes on the natural history of compensated advanced chronic liver disease (cACLD), as well as the prognostic role of clinically significant portal hypertension (CSPH) and non-invasive tests (NITs), are needed. **Methods:** We included 696 SLD patients with cACLD from 17 European centers undergoing hepatic venous pressure gradient (HVPG) and NIT assessment until December 2023. The underlying etiology was MASLD in 58%, MetALD in 20% and ALD in 22%. The primary outcome of interest was first hepatic decompensation. **Results:** Most patients had Child-Pugh A (89%) with a median MELD of 8 [7-10]. CSPH (HVPG $\geq$ 10 mmHg) was present in 60% (MASLD: 56%/ MetALD: 57%/ ALD: 74%), with a high diagnostic accuracy of ANTICIPATE $\pm$ NASH across the SLD spectrum (AUROC in MASLD: 0.828/ MetALD: 0.882/ ALD: 0.856). The median follow-up was 45.0 months, with a 1- and 2-year cumulative incidence of first decompensation of 7.1% and 13.6%, respectively. Liver stiffness measurement (Harrell's C: 0.69), ANTICIPATE $\pm$ NASH (C: 0.73) and albumin (C: 0.72) provided good prognostic accuracy for hepatic decompensation during follow-up and were comparable to HVPG (C: 0.76) when combining ANTICIPAT E $\pm$ NASH with albumin (C: 0.77). In a multivariable model including MELD and albumin, both the presence of CSPH (hazard ratio [HR]: 3.97; $p < 0.001$) and ANTICIPATE $\pm$ NASH $\geq$ 60% (HR: 2.79; $p < 0.001$) were linked to a significantly higher risk of decompensation (see Figure). With regard to etiology-specific differences, the 1- and 2-year cumulative decompensation incidences were 5.0%/9.9% in MASLD, 6.1%/14.6% in MetALD and 13.7%23.1% in ALD. After adjusting for age, sex, MELD, albumin and HVPG, the risk of hepatic decompensation did not differ significantly across SLD subcategories. HVPG showed the highest predictive accuracy regarding the 2-year decompensation risk in MASLD (0.79, Brier-score: 0.071) and MetALD (0.80, Brier: 0.076) vs. ALD (0.69, Brier: 0.082). **Conclusion:** The higher decompensation risk in ALD and MetALD is primarily explained by more severe liver disease at presentation, as differences diminished after adjusting for these factors. NITs show excellent diagnostic performance for CSPH across the SLD spectrum and achieve similar prognostic accuracy as HVPG.

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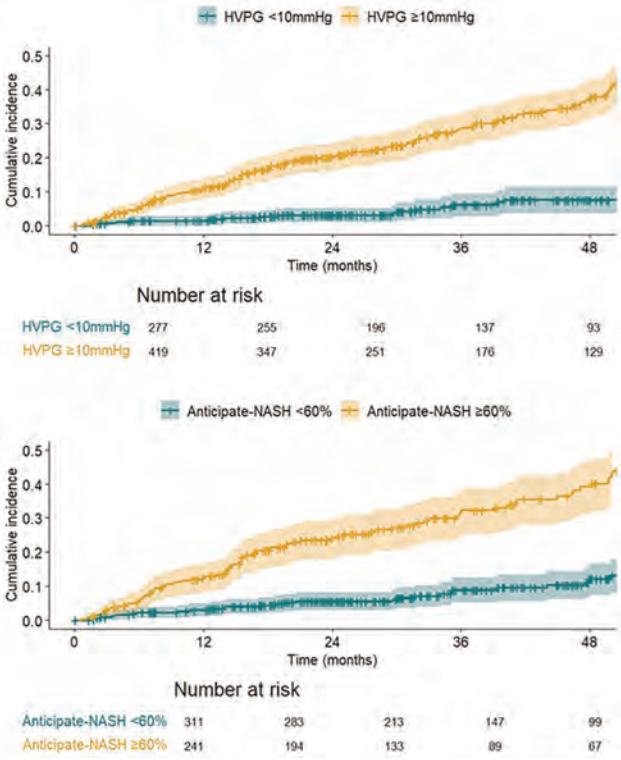

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and Teaching, Thomas Reiberger: Nothing to Disclose, Sven Francque: Nothing to Disclose, Virginia Hernandez-Gea: COOK MEDICAL: Advisor, GORE MEDICAL: Speaking and Teaching, Georg Semmler: Amgen: Travel Support

0145 | BELAPECTIN REDUCES LIVER STIFFNESS PROGRESSION AND PREVENTS VARICES AT 18 MONTHS IN MASH CIRRHOSIS: RESULTS: FROM THE NAVIGATE TRIAL

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Background: MASH cirrhosis is associated with portal hypertension, clinical decompensation, and development of esophageal varices (EV). Currently, there are no approved therapies for MASH cirrhosis. Belapectin, a galectin-3 inhibitor, is being evaluated in NAVIGATE (NCT04365868), a Phase 2b/3 randomized, placebo-controlled trial aimed at preventing variceal development in patients with compensated MASH cirrhosis and portal hypertension without baseline EV. **Methods:** NAVIGATE enrolled 355 subjects with compensated MASH cirrhosis and portal hypertension without baseline varices. Of these, 287 completed 18 months of blinded therapy, and 272 had evaluable FibroScan® data and endoscopy at both baseline and 18 months. Liver stiffness measurement (LSM) was analyzed using two predefined worsening thresholds: $\geq$30% relative increase and $\geq$10 kPa absolute increase from baseline. These thresholds were selected based on prior studies indicating clinically meaningful change. The incidence of new EV at 18 months was evaluated in relation to LSM progression. Statistical comparisons were conducted using the chi-square test. **Results:** Among 272 subjects, $\geq$30% worsening in LSM was observed in 21 of 89 subjects (23.6%) in the placebo group compared to 11 of 94 (11.7%, P = 0.03) in the belapectin 2 mg group, and 14 of 89 (15.7%) in the 4 mg group. For $\geq$10 kPa worsening, 12 of 89 subjects (13.5%) in the placebo group worsened, compared to 4 of 94 (4.3%, P = 0.02) in the 2 mg group and 9 of 89 (10.1%, P = NS) in the 4 mg group. Subjects who experienced worsening in LSM were more likely to develop new EV. Among those with a $\geq$30% LSM increase, 23.8% had EV at 18 months compared to 15.7% in those without worsening (P = 0.1951). Similarly, 14.3% of subjects with a $\geq$10 kPa increase developed EV compared to 8.3% without worsening (P = 0.2141). Although not statistically significant, likely due to sample size, these trends support the relationship between LSM progression and variceal development. **Conclusion:** Belapectin 2 mg/kg was associated with significantly less worsening of LSM at 18 months compared to placebo, using both $\geq$30% and $\geq$10 kPa thresholds. Furthermore, less worsening in LSM was linked to a lower incidence of new varices, reinforcing the clinical relevance of LSM progression as a surrogate marker. These findings suggest a potential beneficial effect of belapectin on disease progression in MASH cirrhosis and warrant further investigation in future studies.

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★ 0146 | DAPAGLIFLOZIN CAN REDUCE THE INCIDENCE OF CHRONIC KIDNEY DISEASE IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE ASSOCIATED CIRRHOSIS PATIENTS WITH MODERATE ASCITES. A RANDOMIZED CONTROLLED TRIAL (DAPA-CLD)

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Background: Non-alcoholic fatty liver disease (NAFLD)-associated cirrhosis is often complicated by renal dysfunction, yet early strategies to prevent chronic kidney disease (CKD) in these patients are limited. Dapagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, has demonstrated renoprotective effects in patients without cirrhosis, metabolic benefits, and potential to aid in resolution of ascites in patients with cirrhosis; however, its role in cirrhosis remains insufficiently studied. **Methods:** Patients with MASLD associated cirrhosis with moderate ascites on diuretics were randomized in a 1:1 open label block randomization to receive either dapagliflozin, initiated at 5mg and subsequently increased to 10mg, plus standard of care (SOC) (Group 1) or SOC alone (Group 2). The primary endpoint of the study was proportion of patients developing CKD, defined as sustained eGFR < 60 mL/min/1.73 m² over ≥ 3 months, at 1 year. The secondary endpoints included development of CKD at interim time points, incidence of acute kidney disease, ascites resolution, changes in metabolic parameters, and drug-related adverse events. Analysis was performed as intention-to-treat. **Results:** Baseline parameters including age (57.08 ± 7.79 vs 57.52 ± 7.01; $p = 0.77$), duration of cirrhosis (35.82 ± 30.5 vs 35.54 ± 31.27; $p = 0.96$), incidence of diabetes (78% vs 76%; $p = 0.48$), baseline eGFR (97.8 ± 29.73 vs 95.6 ± 28.6; $p = 0.30$), MELD score (11.1 ± 2.36 vs 10.78 ± 2.61; $p = 0.66$) were similar. At 12 months, CKD developed more frequently in group 2 [13 (26%) vs. 4 (8%); $p = 0.02$; HR of 0.31 (95% CI: 0.10–0.95). A higher proportion of patients had resolution of ascites (80% vs 68%; $p = 0.01$), with higher proportion requiring discontinuation of diuretics (60% vs 28.6%; $p = 0.0048$], with lower median dose of frusemide (2.88 ± 5.73 vs 8.78 ± 10.76; $p = 0.008$) and spironolactone (7.19 ± 12.89 vs 15.54 ± 17.34; $p = 0.02$) at 12 months in group 1. Metabolic parameters, including triglycerides (84.03 ± 20.13 vs 98 ± 31.40 mg/dL; $p = 0.41$), HDL (40.15 ± 13.11 vs 40.62 ± 9.70 mg/dL; $p = 0.92$), BMI (28.35 ± 5.53vs24.66 ± 7.39 kg/m²; $p = 0.18$), and waist circumference (101 ± 10.97 vs. 98.81 ± 12.69 cm; $p = 0.66$), were comparable. HbA1c was significantly lower in group1 ($5.21 \pm 0.81\%$ vs. $6.26 \pm 1.28\%$; $p = 0.03$) and glycemic control was similar in the two groups (79.4% vs 75%; $p = 0.23$). At 12 months, the incidence of AKD was significantly higher in group 2 (3% vs 19.5%; $p = 0.03$) and mean eGFR at 12 months was higher in group 1 (112.8 ± 32.45 vs. 86.93 ± 28.97 mL/min/1.73 m²; $p = 0.04$). Most common adverse event was genitourinary infections seen in 3(6%) patients, of which 2 required drug discontinuation while no liver related complications were seen. **Conclusion:** Dapagliflozin significantly reduced the incidence of CKD and improved ascites control in patients with MASLD-associated cirrhosis without major adverse effects.

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0147 | IMPROVEMENTS IN NON-INVASIVE BIOMARKERS AND BIOPSY RESPONSES WITH THE GLUCAGON RECEPTOR/GLUCAGON-LIKE PEPTIDE-1 RECEPTOR DUAL AGONIST SURVODUTIDE: CONCORDANCE ANALYSIS FROM A PHASE 2 TRIAL IN PEOPLE WITH METABOLIC DYSFUNCTION–ASSOCIATED STEATOHEPATITIS AND FIBROSIS

Quentin Anstee[1] Naim Alkhouri[2] Luiza Borowska[3] Corinna Schoelch[4] Mandy Fraessdorf[3] Renee Marshall[5] Daniel Mazo[3] Arun Sanyal[6] Jörn Schattenberg[7] Vincent Wong[8] Ramy Younes[3] Mazen Noureddin[9], [1]Newcastle University, UK, [2]Summit Clinical Research, [3]Boehringer Ingelheim International GmbH, [4]Boehringer Ingelheim Pharma GmbH & Co KG, [5]Boehringer Ingelheim Pharmaceuticals Inc., [6]Virginia Commonwealth University, [7]University Medical Center Homburg, [8]The Chinese University of Hong Kong, [9]Houston Methodist Hospital

Background: The combination of elastography and blood biomarker non-invasive tests (NITs) have been proposed to replace histology-based efficacy endpoints. This post-hoc analysis assessed NIT-based efficacy endpoints, and examined if the observed changes in histology were corroborated by NITs following treatment with survodutide, a GCGR/GLP-1R dual agonist, in a phase 2 trial in participants with biopsy-confirmed MASH and F1–F3 fibrosis. **Methods:** Among 295 people aged 18–80 years randomized to once-weekly s.c. survodutide 2.4, 4.8, or 6.0 mg, or placebo (PBO) for 48 weeks, 170 participants had F2–F3 fibrosis stage at baseline, and paired biopsy results were included in this analysis. We evaluated the concordance among participants of ≥0.5 absolute reduction in enhanced liver fibrosis (ELF™) score and ≥30% reduction in liver stiffness measurement (LSM; by vibration-controlled transient elastography [FibroScan®]) with histological improvement in fibrosis with no worsening of MASH, as well as ≥30% reduction in liver fat content (LFC) (magnetic resonance imaging proton density fat fraction assessed) and ≥17 U/L reduction in alanine aminotransferase (ALT) with histological resolution of MASH with no worsening of fibrosis. **Results:** A ≥0.5 reduction in ELF™ score and ≥30% reduction in LSM was observed in 38.9 vs 4.1% of participants treated with survodutide vs PBO, respectively; improvement in fibrosis with no worsening of MASH was observed in 52.8 vs 24.5%, respectively. A reduction in ELF™, LSM, and improvement in fibrosis with no worsening of MASH was observed in 18.5 vs 2.0% of participants treated with survodutide vs PBO, respectively ($p < 0.05$ for all doses). A ≥30% reduction in LFC and ≥17 U/L reduction in ALT was observed in 58.8 vs 5.6% of participants treated with survodutide vs PBO, respectively; resolution of MASH with no worsening of fibrosis was observed in 62.3 vs 13.0%, respectively. A reduction in LFC, ALT, and resolution of MASH with no worsening of fibrosis was observed in 38.6 vs 1.9% of participants treated with survodutide vs PBO, respectively ($p < 0.001$ for all doses) (Table). **Conclusion:** The concordance of multiple NITs and biopsy results provides clear evidence of a robust effect from survodutide (over and above the PBO response) in the improvement of fibrosis (reduction of ELF™ and LSM) and resolving steatohepatitis (reduction of LFC and ALT) across all doses after 48 weeks.

Table. Number of responders at Week 48

	2.4 mg survodutide	4.8 mg survodutide	6.0 mg survodutide	Total survodutide	Placebo
N	38	40	30	108	49
Improvement in fibrosis with no worsening of MASH	22 (57.9%)	16 (40.0%)	19 (63.3%)	57 (52.8%)	12 (24.5%)
≥0.5 absolute reduction in ELF™	21 (55.3%)	27 (67.5%)	17 (56.7%)	65 (60.2%)	10 (20.4%)
≥30% reduction in LSM (VCTE)	22 (57.9%)	29 (72.5%)	13 (43.3%)	64 (59.3%)	8 (16.3%)
Reduction in ELF™ + LSM	13 (34.2%)	21 (52.5%)	8 (26.7%)	42 (38.9%)	2 (4.1%)
Reduction in ELF™ + biopsy response	11 (28.9%)	9 (22.5%)	9 (30.0%)	29 (26.9%)	3 (6.1%)
Reduction in LSM + biopsy response	14 (36.8%)	12 (30.0%)	10 (33.3%)	36 (33.3%)	3 (6.1%)
Reduction in ELF™ + LSM + biopsy response	7 (18.4%)	7 (17.5%)	6 (20.0%)	20 (18.5%)	1 (2.0%)
Fisher's exact test[a]	0.019	0.02	0.011	0.004	
N[b]	40	43	31	114	54
Resolution of MASH with no worsening of fibrosis	25 (62.5%)	26 (60.5%)	20 (64.5%)	71 (62.3%)	7 (13.0%)
≥30% reduction in LFC (MRI-PDFF)	32 (80.0%)	35 (81.4%)	25 (80.6%)	92 (80.7%)	10 (18.5%)
≥17 U/L reduction in ALT	25 (62.5%)	33 (76.7%)	21 (67.7%)	79 (69.3%)	14 (25.9%)
Reduction in LFC + ALT	21 (52.5%)	27 (62.8%)	19 (61.3%)	67 (58.8%)	3 (5.6%)
Reduction in LFC + biopsy response	23 (57.5%)	23 (53.5%)	17 (54.8%)	63 (55.3%)	2 (3.7%)
Reduction in ALT + biopsy response	15 (37.5%)	20 (46.5%)	14 (45.2%)	49 (43.0%)	1 (1.9%)
Reduction in LFC + ALT + biopsy response	14 (35.0%)	17 (39.5%)	13 (41.9%)	44 (38.6%)	1 (1.9%)
Fisher's exact test[a]	<0.001	<0.001	<0.001	<0.001	

F2–F3 population with paired biopsy results

[a]Responders in all 3 categories vs complement.

[b]Based on participants with paired baseline and Week 48 MRI-PDFF measurements.

ALT, alanine aminotransferase; ELF™, enhanced liver fibrosis; LFC, liver fat content; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MRI-PDFF, magnetic resonance imaging proton density fat fraction; VCTE, vibration-controlled transient elastography.

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0148 | A RANDOMIZED, PLACEBO-CONTROLLED, PHASE 2 STUDY OF THE SAFETY AND EFFICACY OF COMBINATION TREATMENT WITH SEMAGLUTIDE, CILOFEXOR AND FIRSOCOSTAT IN PATIENTS WITH COMPENSATED CIRRHOSIS DUE TO METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (WAYFIND)

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Background: We assessed the efficacy and safety of semaglutide (SEMA; glucagon-like peptide-1 receptor agonist) alone and in fixed-dose combination with cilofexor (CILO; farnesoid X receptor agonist) and firsocostat (FIR; liver-targeted acetyl-CoA carboxylase inhibitor) in patients (pts) with compensated cirrhosis (F4C) due to metabolic dysfunction-associated steatohepatitis (MASH; NCT04971785). **Methods:** In a multicenter, double-blind, phase 2b study, adults with biopsy-proven F4C due to MASH were randomized (3:3:3:2) to receive SEMA 2.4 mg/week + CILO 30 mg/FIR 20 mg/day, SEMA 2.4 mg/week, CILO 30 mg/FIR 20 mg/day, or placebo (PBO) for 72 weeks. The primary endpoint was the proportion of pts with fibrosis improvement without MASH worsening at week 72 with SEMA +CILO/FIR vs. PBO. Secondary (with prespecified testing hierarchy; Table) and exploratory efficacy endpoints and safety were also assessed. All P values are nominal. Liver biopsies were read by central pathologists (primary endpoint) and by AIM-MASH AI Assist from PathAI (exploratory). **Results:** 457 pts were randomized; 453 had ≥ 1 study drug dose (mean age: 62 yrs; T2D: 68.2%; mean platelets: 191×10^9/L). There was no significant difference in the proportions of pts with fibrosis improvement without MASH worsening at week 72 with SEMA +CILO/FIR vs PBO (13.7% vs. 8.3%; $P = 0.2289$). However, fibrosis improvement was seen with CILO/FIR vs PBO (20.3% vs. 8.3%; $P = 0.0174$). A difference was observed with PathAI analysis with SEMA+CILO/FIR vs. PBO (21.0% vs. 6.0%; $P = 0.0011$). MASH resolution was greater with SEMA+CILO/FIR vs. CILO/FIR or PBO and with SEMA vs. PBO in both pathologist (Table) and

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PathAI analyses (data not shown). The most frequent (≥15% of pts) adverse events (AEs) occurring more often with SEMA+CILO/FIR vs. PBO were nausea (47.6% vs. 22.6%), diarrhea (27.4% vs. 17.9%), constipation (24.2% vs. 8.3%), vomiting (21.8% vs. 7.1%), and decreased appetite (15.3% vs. 6.0%). Serious AEs and AEs leading to study discontinuation were similar across all groups. One death occurred in each of the SEMA and CILO/FIR groups. **Conclusion:** SEMA+CILO/FIR did not achieve the primary endpoint of fibrosis improvement compared with PBO based on pathologist review. However, SEMA-containing regimens achieved MASH resolution and CILO/FIR achieved fibrosis improvement compared with PBO. Interestingly, PathAI showed clinical benefit with SEMA+CILO/FIR, suggesting that combination therapies should be explored for MASH.

Table. Primary (solid line), secondary (dashed line), and exploratory efficacy endpoint results (non-responder imputation) from the WAYFIND study

	SEMA+CILO/FIR (n=126)	SEMA (n=128)	CILO/FIR (n=123)	Placebo (n=60)
Proportion of patients with fibrosis improvement (≥1 stage) without MASH worsening (≥1-pt increase in hepatocellular ballooning/lobular inflammation)[a]				
n (%)	17 (13.7)	19 (15.6)	25 (20.3)	7 (8.3)
Differences in proportion, % (95% CI)				
vs Placebo	5.7 (−3.6, 14.9) P=0.2289	7.7 (−1.7, 17.1) P=0.1080	11.9 (2.1, 21.7) **P=0.0174**	–
vs CILO/FIR	−6.5 (−16.2, 3.2) P=0.1908	–	–	–
vs SEMA	−1.8 (−11.1, 7.4) P=0.6959	–	–	–
Proportion of patients with MASH resolution (lobular inflammation = 0 or 1; hepatocellular ballooning = 0) without fibrosis worsening[a]				
Evaluable patients[b], n	82	81	88	49
n (%)	47 (57.3)	40 (49.4)	28 (31.8)	11 (22.4)
Differences in proportion, % (95% CI)				
vs Placebo	35.7 (18.8, 52.6) **P<0.0001**	27.1 (10.4, 43.8) **P=0.0014**	9.2 (−6.8, 25.2) P=0.2620	–
vs CILO/FIR	26.1 (11.3, 40.9) **P=0.0006**	–	–	–
vs SEMA	9.8 (−5.8, 25.3) P=0.2190	–	–	–

A stratified Mantel–Haenszel test was used to compare the difference in proportions of patients based on baseline re-read and week 72 biopsies, with baseline diabetes status and ELF score category as stratification factors. Owing to the sequence of hierarchical testing, statistical comparisons of secondary and exploratory endpoints are considered descriptive in nature.

[a]Based on evaluation of liver biopsies by central pathologists.

[b]Evaluable patients had both hepatocellular ballooning and lobular inflammation of grades ≥1 at baseline re-read.

CILO, cilofexor; ELF, enhanced liver fibrosis; FIR, firsocostat; MASH, metabolic dysfunction-associated steatohepatitis; SEMA, semaglutide.

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0149 | SAFETY AND EFFICACY OF COTADUTIDE, A DUAL GLP-1 AND GLUCAGON RECEPTOR AGONIST IN ADULTS WITH NON-CIRRHOTIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS WITH FIBROSIS: FINAL RESULTS: FROM A PHASE IIB RANDOMIZED, PLACEBO-CONTROLLED, PROOF-OF CONCEPT STUDY

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Background: Cotadutide, a dual GLP-1 and glucagon receptor agonist has previously demonstrated improvements in non-invasive liver markers of inflammation, steatosis and fibrosis in biopsy-proven MASH with fibrosis. **Methods:** PROXYMO-ADVANCE was a Phase IIb (Part A) / III (Part B), double-blind, placebo-controlled study to evaluate the safety and efficacy of cotadutide vs. placebo, in adults with non-cirrhotic MASH with fibrosis. Due to strategic reasons, recruitment was stopped early, and only a portion of Part A was conducted as a proof-of-concept study. Primary objectives included safety, and all efficacy objectives (histology-based at week 48) were exploratory. 54 adults with biopsy-proven MASH with fibrosis stage 2/3 (on-study/historical biopsy) were randomized to receive cotadutide 300 µg or 600 µg, or matching-placebo as a daily subcutaneous injection via a multi-dose pen for 48 weeks (included a 12-week titration for 300 µg and 24-week titration for 600 µg). Analyses involved the full-analysis set (FAS) comprising those receiving at least one dose of investigational product and per-protocol subset with evaluable post-baseline biopsy after at least 36 weeks on treatment. **Results:** Mean treatment duration was similar across the groups. Adverse events (AEs) were more frequent in the cotadutide group (94.3%) vs. placebo (68.4%), with nausea (40%), vomiting (31.4%), and decreased appetite (20%) as the most common AEs. 75.9% completed the study; 66.7% underwent post-baseline biopsy. MASH resolution without worsening of liver fibrosis was observed in 35.3%, 44.4%, and 26.3%, in the cotadutide 300 µg, cotadutide 600 µg, and placebo groups, respectively. Cotadutide 600 µg showed an 18.1% treatment-response difference (95% CI -13.0, 46.4, $p = 0.257$, FAS) compared to the placebo group. Liver fibrosis improvement by at least one stage, without MASH worsening, occurred in 5.9%, 61.1%, and 21.1% for the cotadutide 300 µg, cotadutide 600 µg, and placebo groups, respectively. Cotadutide 600 µg showed a 40.1% response difference (95% CI 8.1, 64.8, $p = 0.022$, FAS) compared to the placebo group. **Conclusion:** Cotadutide 300 µg and 600 µg showed safety and tolerability consistent with its known profile in adults with non-cirrhotic MASH with fibrosis. Numerical improvements in MASH resolution were observed without worsening of liver fibrosis. Compared to placebo, a higher proportion in the Cotadutide 600 µg group experienced liver fibrosis improvement without MASH deterioration.

Disclosures: Ashwini Mallappa: AstraZeneca: Hold stock, Tom Conrad: AstraZeneca: Employee, Debra Carter: Nothing to Disclose, John Monyak: AstraZeneca: Employee, AstraZeneca: Stock - publicly traded company, Ranganatha Yadav SL: AstraZeneca: Hold Company Stocks, AstraZeneca: Hold Company Stocks, Richard Torstenson: Nothing to Disclose, Nayyar Iqbal: AstraZeneca Pharma: Employee, David Sjöström: AstraZeneca: Employee, AstraZeneca: Stock – privately held company, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor

0150 | EFRUXIFERMIN IMPROVED MARKERS OF PORTAL HYPERTENSION AS EVALUATED BY BAVENO VII CRITERIA IN COMPENSATED CIRRHOSIS DUE TO MASH: RESULTS: FROM A 96-WEEK, PLACEBO-CONTROLLED, PHASE 2B TRIAL (SYMMETRY)

Mazen Noureddin[1] Naga Chalasani[2] Mary Rinella[3] Doreen Chan[4] Mark Burch[4] Erik Tillman[4] Sonja Billes[4] Arian Zari[4] Dragan Mackovic[4] Brittany De Temple[4] Reshma Shringarpure[5] Meena Jain[4] Timothy Rolph[4] Andrew Cheng[4] Kitty Yale[4], [1]Houston Methodist Hospital, [2]Indiana University Medical Center, [3]The University of Chicago, [4]Akero Therapeutics, [5]Akero Therapeutics, Inc

Background: In the SYMMETRY trial, efruxifermin, a bivalent FGF21 analog, improved fibrosis by histology in participants with compensated cirrhosis due to MASH (NCT05039450). The presence of clinically significant portal hypertension (CSPH) in this population is associated with a high risk of hepatic decompensation. In this secondary analysis, non-invasive tests commonly deployed in clinical practice were used to assess the impact of efruxifermin treatment on presence of CSPH and risk of hepatic decompensation. **Methods:** SYMMETRY was a phase 2b, randomized, placebo-

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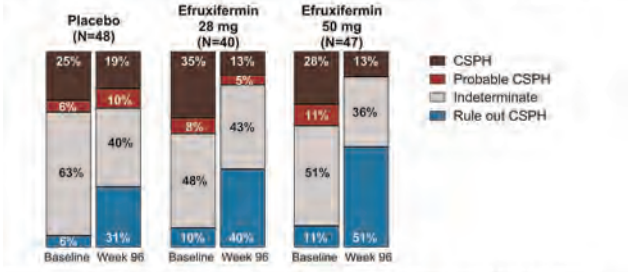
controlled, double-blind trial that enrolled 181 participants with biopsy-confirmed compensated cirrhosis (PMID:40341827). Participants were randomly assigned (1:1:1) to once-weekly efruxifermin (28 or 50 mg) or placebo for 96 weeks. Individual participants were analyzed at baseline and week 96 for: (1) presence of CSPH based on Baveno VII criteria incorporating liver stiffness measurement (LSM) by transient elastography (FibroScan) and platelet count; and (2) risk of liver-related events based on the published criterion of $>20\%$ decrease in Agile 4 (PMID:38512249). **Results:** Baseline characteristics were: 61 yrs, 67% female, BMI 36 kg/m^2, 80% T2D, LSM 24 kPa, ELF 11, platelets 183x10^9/L, ALT 40 U/L, AST 36 U/L. At baseline, 37% of participants overall had CSPH/probable CSPH, and CSPH could be ruled out in only 9%. In those with CSPH/probable CSPH, other markers were also indicative of more advanced disease. At week 96, fewer participants in the 28-mg (18%, $p=.20$) and 50-mg (13%, $p<.05$) efruxifermin groups were in the CSPH/probable CSPH category versus placebo (29%) (Figure). Compared to placebo (31%), there was a higher proportion of participants for whom CSPH could be ruled out in the 28-mg (40%, $p=.39$) and 50-mg (51%, $p<.05$) efruxifermin groups. Finally, the proportion of participants with a $>20\%$ decrease in Agile 4 score was 42% for placebo vs 58% and 64% for 28-mg and 50-mg efruxifermin. **Conclusion:** Fibrosis improvement with efruxifermin after 96 weeks of treatment was associated with reduced presence of CSPH and lower risk of hepatic decompensation. Accordingly, reversal of fibrosis by efruxifermin in patients with compensated cirrhosis may prevent progression to decompensation and liver-related outcomes. These endpoints are being evaluated in phase 3 trials.

Figure. Presence of CSPH assessed by Baveno VII criteria in the SYMMETRY trial



Data are for participants with paired baseline and week 96 data. Baveno VII criteria for CSPH: LSM ≥25; Probable CPSH: LSM ≥20 and platelet count <150 or LSM 15-20 and platelet count <110; Rule out CSPH: LSM ≤15 and platelet count ≥150. Indeterminate includes all other participants.

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0151 | SAROGLITAZAR IMPROVES HEPATIC STEATOSIS IN WOMEN WITH PCOS AND MASLD: RESULTS: OF EVIDENCES VII RANDOMIZED CONTROL STUDY

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is common in polycystic ovary syndrome (PCOS) and associated with more severe histology. Therapies specifically focusing on MASLD in PCOS patients are lacking. We therefore investigated the efficacy and safety of saroglitazar 4 mg/day in women with PCOS and MASLD. **Methods:** EVIDENCES VII (NCT03617263) is a multicenter, randomized, double-blind, placebo-controlled trial of saroglitazar 4mg/day for 24 weeks in women with PCOS and MASLD. The primary end point was a change in MRI-PDFF from baseline to 24 weeks in the per-protocol population (PPP) which included individuals who had an evaluable MRI PDFF at both baseline and at end of treatment. Prespecified secondary and exploratory efficacy, safety, and tolerability end points were evaluated. **Results:** 155 women with PCOS and suspected MASLD were assessed for eligibility. After applying eligibility criteria, 60 women were randomized to receive either 4 mg saroglitazar (n = 30) or placebo (n = 30). The PPP consisted of 25 saroglitazar and 23 placebo-controlled participants with baseline MRI-PDFF (mean ± SD) of 22.02% ± 8.24% and 22.66% ± 9.47%, respectively. Two groups were well matched except for higher HgA1c in the saroglitazar group (5.9% vs 5.5%, p = 0.035). MRI-PDFF absolute change from baseline (CFB) to 24 weeks was -3.13 ± 5.35 with saroglitazar vs -0.40 ± 4.98 with placebo (p = 0.061). The % CFB of MRI-PDFF at 24 weeks

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was -14.67 ± 27.77 with saroglitazar vs 1.89 ± 27.47 with placebo ($p = 0.041$). The effect of saroglitazar were more pronounced after adjusting for HbA1c, demonstrating significant improvement based on both absolute CFB ($p = 0.002$) and %CFB ($p < 0.001$) in MRI-PDFF. The proportion with ≥30% reduction in MRI-PDFF was significantly higher with saroglitazar than placebo (36% vs 8.7%, $p = 0.024$) and mean %CFB favored saroglitazar for ALT (-37% vs 4.8%, $p = 0.007$), AlkP (-28% vs -2.1%, $p < 0.001$), triglyceride (-16% vs 18%, $p = 0.009$), Total-Cholesterol (-13% vs -1.5%, $p < 0.001$) and sdLDL-C (-21% vs 1.4%, $p = 0.027$). There were no significant changes by treatment for HOMA-IR, sex hormone binding globulin, free androgen index, or other sex hormones. Saroglitazar was well tolerated with no differences in body weight, waist circumference or adverse events between the treatment groups. **Conclusion:** In patients with PCOS and MASLD, saroglitazar 4mg/day significantly improved hepatic steatosis and dyslipidemia.

Disclosures: Niharika Samala: Novo Nordisk: Consultant, Monika Sarkar: GSK: Grant/Research Support, Zydus Pharmaceuticals: Grant/Research Support, Gilead Sciences: Grant/Research Support, SREEMALA Murthy: Nothing to Disclose, Taufik Momin: Nothing to Disclose, Sukanya Krishnan: Nothing to Disclose, Farheen Shaikh: Nothing to Disclose, Naga Chalasani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose

0152 | IMPROVEMENT IN LIVER FAT CONTENT AND MASH BIOMARKERS WITH ONCE WEEKLY UTREGLUTIDE (GL0034), A GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST IN SUBJECTS WITH MAFLD: A PHASE 1A/2B STUDY

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Background: Utreglutide (GL0034, UTG), a novel, once weekly glucagon-like peptide-1 receptor agonist, demonstrated safety in phase 1 study along with clinically relevant reduction in body weight among healthy subjects and individuals with overweight and obesity. Improvements in lipid and metabolic biomarkers were also evident. This phase 1b/2a study evaluated the efficacy, safety, tolerability and pharmacokinetics of utreglutide in the treatment of MAFLD. **Methods:** In this randomized, double-blind, placebo-controlled, parallel group, multicenter study 48 participants, both male and females, aged 18 to 70 years with a body mass index (BMI) ≥30 kg/m^2 and liver fat content ≥10% as assessed by MRI-proton density fat fraction (PDFF) were randomized (3:1) to subcutaneous UTG doses with dose titration period (2×0.4, 4×0.8, 4×1.6 mg) of 10 weeks and fixed dose period (2.4 mg) of 3 weeks; or placebo once weekly for 13 weeks. Safety, tolerability, and key efficacy along with exploratory biomarkers were assessed at baseline and week 14. The biomarkers presented here include body weight (BW), waist circumference (WC), liver fat content by MRI-PDFF, plasma Pro-C3 (N-terminal type III collagen propeptide), controlled attenuated parameter (CAP) mean as assessed by FibroScan@, cytokeratin 18 fragment M30 (CK-18/M30) levels, liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], leptin, lipid panel [triglycerides (TG), total cholesterol (TC), and ApoB] and urate levels. **Results:** Utreglutide was well-tolerated and related adverse effects were mainly gastrointestinal including nausea and vomiting. The BW reduction at week 14 from baseline (BL) was 7.6 kg ($P < 0.001$) and accompanied by 9.3 cm reduction in WC ($P < 0.001$). The percent change in relative liver fat content as assessed by MRI-PDFF from BL to week 14 was 25.4 ($P < 0.001$). The non-invasive fibrosis marker, Pro-C3 levels significantly decreased by 13.2% ($P < 0.001$) and followed by reduction in CAP mean by 12.8% ($P < 0.001$) along with a 3.7% reduction in CK18/M30 fragment levels ($P < 0.05$). The liver enzyme reductions were also noted with 5.2% in ALT ($P < 0.05$) and 3.9% in AST. Improvement in lipid panel was observed together with significant reduction in leptin and urate levels by 14.0% ($P < 0.01$) and 9.8% ($P < 0.001$) respectively (Table). **Conclusion:** Once weekly utreglutide dosing for 13 weeks in subjects with MAFLD was well tolerated and demonstrated marked reductions of body weight, liver fat, non-invasive fibrosis markers, liver enzymes, lipids along with leptin and urate.

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Table. Biomarker levels in subjects with MAFLD at baseline and week 14 after treatment with once weekly utreglutide for 13 weeks

Sr. No.	Parameters	Week	Placebo (N=11)	Utreglutide (N=31)
1	BMI (kg/m^2)	BL	**40.6 ± 4.61**	**41.3 ± 6.28**
2	BW (kg)	BL	**119.2 ± 20.75**	**112.9 ± 19.22**
	CBL	W14	-3.5 ± 4.11* (-2.8)	-7.6 ± 3.46*** (-7.0)
3	WC (cm)	BL	**126.8 ± 13.91**	**125.6 ± 12.53**
	CBL	W14	-2.6 ± 3.99 (-2.0)	-9.3 ± 8.37*** (-7.2)
4	MRI-PDFF (%)	BL	**22.2 ± 9.78**	**20.9 ± 6.60**
	CBL	W14	-0.1 ± 2.32 (0.6)	-5.5 ± 3.76*** (-25.4)
5	Pro-C3 (ng/mL)	BL	**88.8 ± 30.30**	**98.6 ± 34.30**
		W14	91.2 ± 23.35 (6.2)	81.5 ± 21.27*** (-13.2)
6	CAP Mean (dB/m)	BL	**336.8 ± 18.38**	**342.5 ± 27.40**
		W14	319.5 ± 49.15 (-5.1)	298.0 ± 37.18*** (-12.8)
7	CK-18/M30 (U/L)	BL	**264.8 ± 212.17**	**182.4 ± 137.25**
		W14	266.4 ± 156.84 (17.5)	151.7 ± 87.70* (-3.7)
8	ALT (U/L)	BL	**44.4 ± 21.61**	**34.2 ± 15.44**
		W14	42.5 ± 24.68 (-6.6)	30.0 ± 9.50* (-5.2)
9	AST (U/L)	BL	**32.7 ± 7.79**	**30.3 ± 11.96**
		W14	30.4 ± 11.73 (-6.98)	27.3 ± 6.60 (-3.9)
10	TG (mmol/L)	BL	**1.9 ± 0.51**	**1.9 ± 0.77**
		W14	1.6 ± 0.41** (-17.3)	1.5 ± 0.51*** (-14.1)
11	TC (mmol/L)	BL	**5.5 ± 0.96**	**5.2 ± 1.08**
		W14	5.5 ± 0.95 (1.5)	4.9 ± 1.01** (-5.8)
12	ApoB (g/L)	BL	**1.1 ± 0.25 (N=8)**	**1.1 ± 0.25 (N=25)**
		W14	1.1 ± 0.26 (-3.3)	1.0 ± 0.24*** (-10.1)
13	Leptin (ng/mL)	BL	**44.5 ± 17.23**	**75.9 ± 53.88**
		W14	61.7 ± 30.25** (40.2)	61.6 ± 37.16** (-14.0)
14	Urate (mmol/L)	BL	**0.4 ± 0.06**	**0.4 ± 0.07**
		W14	0.4 ± 0.06 (1.0)	0.3 ± 0.08*** (-9.8)

All values are mean ± SD; values in parenthesis indicate mean percent changes.
*P<0.05, **P<0.01, ***P<0.001, vs respective group Day 1 levels; Paired Student's t-test.
ApoB, apolipoprotein B; AST, Aspartate aminotransferase; ALT, alanine aminotransferase; BL, Baseline, which is week 1 for all parameters except MRI-PDFF performed at screening; BMI, body mass index; BW, body weight; CAP, controlled attenuated parameters as determined by FibroScan®; CBL, change from baseline; CK-18/M30, Cytokeratin 18 fragment detected by M30 monoclonal antibody ELISA; GGT, γ-Glutamyl transferase; MRI-PDFF, Magnetic Resonance imaging-Proton Density Fat Fraction, Pro-C3, N-terminal pro-peptide of type-III collagen; TC, cholesterol; TG, triglycerides. W14, Week 14, follow-up visit after 13 weeks of treatment.
UTG doses with dose titration period (2×0.4 , 4×0.8 , 4 ×1.6mg) of 10 weeks and fixed dose period (2.4 mg) of 3 weeks; or placebo once weekly for 13 weeks. For BW and WC in treatment group N=30.

Disclosures: Rajamannar Thennati: Sun Pharmaceutical Industries Limited: Employee, Vinod Burade: Nothing to Disclose, Muthukumaran Natarajan: Nothing to Disclose, Pradeep Shahi: Nothing to Disclose, Ravishankara Nagaraja: Nothing to Disclose, Bernard Thorens: Nothing to Disclose, Tina Vilsboll: Nothing to Disclose, Richard Pratley: Nothing to Disclose, John Olynyk: Resonance Health Pty Ltd: Consultant, Rohit Loomba: Nothing to Disclose

★ 0153 | LARGE-SCALE MULTI-TRAIT GWAS LINKS OPA1 GENE TO LIVER FIBROSIS AND MASLD

Xinting Yu[1] Shisong Rong[2] Yury Popov[3], [1]University of South Florida, [2]Harvard Medical School, [3]BIDMC Harvard Medical School

Background: Liver fibrosis is highly related to the mortality of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Previous studies found mitochondrial dysfunction plays an important role in the development of liver fibrosis from MASLD. We have recently demonstrated that release of mitochondria-derived damage-associated molecular patterns (mito-DAMPs) from injured hepatocytes directly activate hepatic stellate cells and promote fibrosis independent of inflammation. However, the specific genetic and molecular mechanisms underlying relevant mitochondrial dysfunction in fibrosis remains underexplored. This study aims to broadly investigate the genetic architecture of liver fibrosis and MASLD with a specific focus on genes involved in mitochondrial turnover (e.g. mitophagy and mitochondrial fusion) in relation to liver fibrosis from MASLD. **Methods:** We integrated genome-wide association study (GWAS) summary statistics datasets focused on liver fibrosis/MASLD-related traits, exhaustively sourced from the UK Biobank (UKBB), FinnGen, GWAS Catalog, and extensive literature review. Genetic correlation analysis among these datasets was performed using linkage disequilibrium score regression (LDSC). We then employed Multi-Trait Analysis of GWAS (MTAG) on genetically aligned/integrated datasets to identify strong genome-wide association signals pertinent to fibrosis/MASLD. Validation of MTAG results was conducted through comparisons with a comprehensive meta-analysis of MASLD GWASs. We mapped genes and pathways related to mitophagy and mitochondrial fusion using MitoCarta3.0 and extensive literature review, and their associations with fibrosis/MASLD were analyzed using Multi-marker Analysis of GenoMic Annotation (MAGMA) within our MTAG GWAS framework. **Results:** Among 12 identified GWAS datasets relevant to liver fibrosis and MASLD, six of these correlated GWAS datasets, covering 6,944,270 individuals, were successfully integrated in the downstream MTAG analyses. The results from the MTAG GWAS were highly concordant with known gene loci identified previously in the meta-analysis of GWASs for MASLD ($P < 0.05$, $R^2 = 0.94$). Among 22 genes related to mitochondrial mitophagy and fusion (*BCL2L13, FKBP8, FUNDC1, NIPSNAP1, PARK7, PARL, PGAM5, PINK1, TOMM7, USP30, VPS13D, CALCOCO2, PARK2, NIPSNAP1, ARL2, MFN1, MFN2, MTCH2, OMA1, OPA1, PHB2, PLD6*), a single gene Optic Atrophy 1 (*OPA1*), with a known function in mitochondrial fusion and cristae shaping but not previously implicated in MASLD, was strongly associated with all fibrosis/MASLD MTAG GWASs ($P < 0.00208$). **Conclusion:** We identified for the first time a significant association of a mitochondrial fusion gene *OPA1* with liver fibrosis and MASLD. Further investigations are warranted to elucidate the precise biological role of *OPA1* and its variants in relation to MASLD progression and associated fibrosis.

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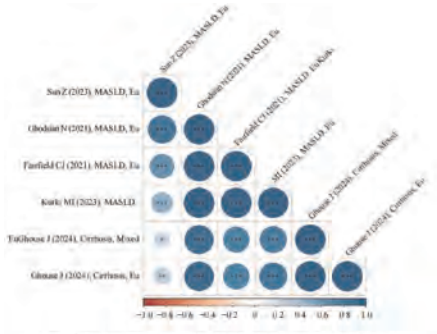

Figure 1 Genetic correlation analysis of 6 GWASs for MASLD related traits using linkage disequilibrium score regression (LDSC).

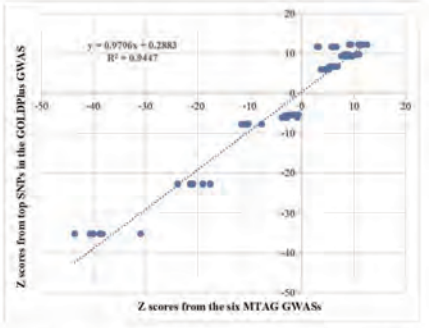

Figure 2. Significant correlation of Z-scores from the six resulting MTAG GWASs with published meta-analysis of GWASs for MASLD. The Z-scores of the top SNPs from the GOLDPlus GWAS and our MTAG GWASs were significantly correlated (P<0.001), supporting the robustness of our MTAG analysis.

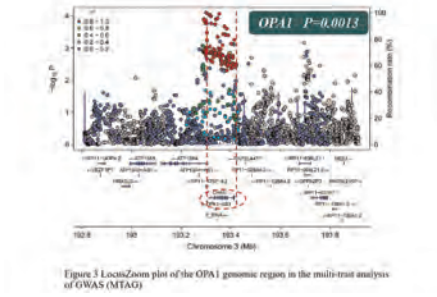

Figure 3 LocusZoom plot of the OPA1 genomic region in the multi-trait analysis of GWAS (MTAG)

Disclosures: Xinting Yu: Nothing to Disclose, Shisong Rong: Nothing to Disclose, Yury Popov: Nothing to Disclose

0154 | DIAGNOSTIC AND CLINICAL IMPLICATIONS OF HIGH SPLEEN-TO-LIVER STIFFNESS RATIO IN MASLD – A PROSPECTIVE, COMPARATIVE STUDY

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Background: Liver stiffness measurement (LSM) and spleen stiffness measurement (SSM) are established surrogate parameters for portal hypertension (PH), exhibiting strong correlation with the hepatic venous pressure gradient (HVPG). However, SSM may overcome the limitations of HVPG and LSM lacking capability of capturing presinusoidal PH. We investigated the SSM/LSM ratio and its association with HVPG, as well as splenomegaly as a PH marker across different chronic liver disease etiologies. **Methods:** In this prospective study 399 patients with compensated liver disease undergoing HVPG measurements and 2D-SWE-based LSM and SSM were enrolled. A dataset containing demographic, biochemical, and imaging-based parameters was used for correlative and multivariate analyses. **Results:** Patients with alcohol-associated liver disease (ALD; n = 200) exhibited higher LSM (median: 45.5 kPa) and HVPG (median: 15.0 mmHg) than patients with metabolic dysfunction-associated steatotic liver disease (MASLD; n = 49; LSM: 20.9 kPa; HVPG: 12.0 mmHg). Conversely, SSM did not differ significantly between the cohorts (ALD: 58.8 kPa vs. MASLD: 52.8 kPa; p = 0.868). This resulted in a higher SSM/LSM ratio in MASLD (1.66) compared to ALD (1.28). Highest SSM/LSM values were observed in patients with porto-sinusoidal vascular liver disease (PSVD; 3.19). Importantly, upon adjustment for HVPG, MASLD retained significantly larger spleen diameters. Mathematical modeling revealed consistently higher SSM in MASLD than in ALD at any given HVPG. **Conclusion:** The SSM/LSM ratio shows significant etiological differences. The SSM/LSM ratio remained higher in MASLD than in ALD after adjustment for PH severity and – together with larger spleen size - supports the hypothesis of a presinusoidal PH component in MASLD.

Disclosures: Christian Sebesta: Nothing to Disclose, Mathias Jachs: Gilead Sciences Inc.: Speaker and/or consultant, Echosens Inc.: Speaking and Teaching, Lukas Hartl: Nothing to Disclose, Michael Schwarz: Nothing to Disclose, Lorenz Balcar: Nothing to Disclose, Benedikt Hofer: Nothing to Disclose, Nina Dominik: Nothing to Disclose, Georg Kramer: Nothing to Disclose, Bernhard Scheiner: AstraZeneca: Consultant, AstraZeneca: Grant/Research Support, AstraZeneca: Travel support, Roche: Travel support, Eisai: Speaking and Teaching, Eisai: Grant/Research Support, Albert Friedrich Stattermayer: Nothing to Disclose, Benedikt Simbrunner: Nothing to Disclose, Till Schöchtner: Nothing to Disclose, Nicolas Balutsch: Nothing to Disclose, Paul Thoene: Nothing to Disclose, Friedrich Haimberger: Nothing to Disclose, Michael Trauner: Albireo: Grant/Research Support, Alnylam: Grant/

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0155 | DISTINGUISHING MASLD AND METALD/ALD USING PHOSPHATIDYLETHANOL AND NON-INVASIVE TESTS: A MULTICENTER COHORT ANALYSIS

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Background: Accurately quantifying ethanol consumption is of utmost importance for MASLD and MetALD clinical trials. Due to the potential for underreporting in alcohol use surveys, phosphatidylethanol (PEth) is increasingly utilized in clinical trials to rule in MASLD or rule out MetALD or ALD. Therefore, it is important to understand the prevalence of exclusionary PEth levels to estimate potential enrollment for these trials. The aims of the study are to examine whether PEth can accurately identify patients with more MASLD-like or MetALD/ALD-like liver disease in the clinical trial setting and to assess the performance of non-invasive tests (NITs) in those with elevated PEth. **Methods:** A multicenter database of patients enrolled in clinical trials for MASLD pharmacologic therapies was reviewed, from which patients with PEth test results were identified. Patients were further stratified by PEth results indicating high alcohol intake ($\geq$20 ng/mL). NIT performance to detect F3/F4 fibrosis on biopsy was also quantified. Statistical analysis was performed using SAS software with $p < 0.05$ considered statistically significant. **Results:** Among 1811 patients with baseline PEth data, 202 (11%) had PEth $\geq$20 (86, 40-229; median, IQR) and 154 (9%) had PEth $\geq$40 (129, 68-318). Patients with PEth $\geq$20 were more likely to be male (69% vs 40%; $p < 0.001$) and non-diabetic (66% vs 48%; $p < 0.001$; Table 1). Fibrosis stage was similar among groups ($p = 0.20$). Having PEth $\geq$20 was associated with higher AST, ALT, GGT, and FIB-4, and lower HbA1c and LSM (all $p < 0.05$). LSM had higher performance in identifying F3/F4 fibrosis in patients with PEth $\geq$20 (AUC, 95% CI; 0.76, 0.66-0.87) vs $<$20 (0.66, 0.62-0.70). Conversely, FIB-4 ($\geq$20: 0.68, 0.56-0.80; $<$20: 0.70, 0.66-0.74) and AST/ALT ratio ($\geq$20: 0.56, 0.44-0.69; $<$20: 0.61, 0.57-0.66) had superior performance in patients with PEth $<$20. **Conclusion:** In this prospective multicenter cohort of participants enrolled in MASLD clinical trials, 11% had PEth $\geq$20, indicating possible misclassification by MetALD/ALD. In this cohort, PEth $\geq$20 ng/mL identified clinical characteristics associated with excessive alcohol consumption (elevated GGT, AST, and FIB-4), suggesting an appropriate cutoff to distinguish MASLD-like vs. MetALD/ALD-like phenotypes, which lends support to utilizing this cutoff in clinical trial inclusion/exclusion criteria. LSM may be superior to FIB-4 or AST/ALT for determining the presence of F3/F4 fibrosis in the MetALD/ALD population. Our findings highlight the value of PEth and LSM to improve clinical trial design across the spectrum of steatotic liver disease.

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Table 1. Demographics and clinical characteristics of patients with metabolic dysfunction-associated steatotic liver disease (MASLD), stratified by phosphatidyl ethanol test results. Values ≥20 ng/mL imply moderate to heavy alcohol consumption consistent with MASLD with increased alcohol intake (MetALD).

	PEth <20 ng/L (N=1609)	PEth ≥20 ng/L (N=202)	p-value
Age (years), median (IQR)	58 (50-64)	58 (49-64)	0.45
Sex, n (%)			<0.001
Male	640 (39.8%)	140 (69.3%)	
Female	968 (60.2%)	62 (30.7%)	
Race, n (%)			0.36
White	1378 (86.2%)	170 (85.0%)	
Black/African American	66 (4.1%)	14 (7.0%)	
Asian	78 (4.9%)	9 (4.5%)	
American Indian/Alaska Native	14 (0.9%)	1 (0.5%)	
Native Hawaiian/Pacific Islander	6 (0.4%)	0 (0.0%)	
Multiple/other	29 (1.8%)	5 (2.5%)	
Not reported/unknown	28 (1.8%)	1 (0.5%)	
Ethnicity, n (%)			0.48
Hispanic or Latino	589 (37.4%)	78 (39.0%)	
Not Hispanic or Latino	985 (62.6%)	122 (61.0%)	
Diabetes status, n (%)			<0.001
Non-diabetic	762 (47.8%)	134 (66.3%)	
Diabetic	833 (52.2%)	68 (33.7%)	
Fibrosis score, n (%)			0.20
F0	53 (7.4%)	7 (8.1%)	
F1	61 (8.5%)	8 (9.3%)	
F2	209 (29.0%)	22 (25.6%)	
F3	331 (46.0%)	47 (54.7%)	
F4	66 (9.2%)	2 (2.3%)	
AST (U/L), median (IQR)	32 (24-47)	39 (28-54)	0.005
ALT (U/L), median (IQR)	39 (27-62)	46 (29-71)	0.03
AST:ALT ratio, median (IQR)	0.82 (0.67-1.00)	0.84 (0.68-1.02)	0.94
Platelets (G/L), median (IQR)	235 (188-280)	228 (183-273)	0.46
HbA1c (%), median (IQR)	6.3 (5.7-7.1)	6.0 (5.6-6.4)	<0.001
Total bilirubin (mg/dL), median (IQR)	0.6 (0.4-0.8)	0.6 (0.5-0.8)	0.32
GGT (U/L), median (IQR)	41 (27-68)	59 (38-103)	<0.001
FIB-4 score, median (IQR)	1.28 (0.90-1.80)	1.43 (1.00-1.91)	0.046
LSM (kPa), median (IQR)	10.9 (8.8-15.4)	10.5 (8.4-13.5)	0.002
CAP (dB/m), median (IQR)	328 (297-360)	321 (295-357)	0.54

ALT, alanine transferase; AST, aspartate transferase; CAP, controlled attenuation parameter; FIB-4, fibrosis 4; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1C; LSM, liver stiffness measurement; PEth, phosphatidyl ethanol

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0156 | SCREENING PATHWAYS USING NON-INVASIVE TESTS OF LIVER FIBROSIS IN STEATOTIC LIVER DISEASES: IS IT TIME TO UPDATE THE GUIDELINES?

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Background: Vibration-Controlled Transient Elastography (VCTE) is a reference for the non-invasive evaluation of liver fibrosis. Due to the high prevalence of liver risk factors but low prevalence of advanced liver fibrosis, patients must be accurately selected before referral for VCTE. SAFE, MAF-5, eLIFT, and Liver Risk Score (LRS) are new simple blood fibrosis tests recently developed to identify at-risk patients. We aimed to evaluate screening pathways using these new tests. **Methods:** We included all consecutive patients with suspected steatotic liver disease who were referred for a non-invasive evaluation at the Liver Screening Center of a tertiary care center between 09/2019 and 12/2024. Patients underwent complete phenotyping, including VCTE and blood sampling. Five simple blood fibrosis tests were calculated: FIB4 (published thresholds $<1.30/>2.67$), SAFE ($<0/>100$), MAF-5 ($<0/\geq 1$), eLIFT (≥ 8), and LRS ($<8/>12$); as well as two specialized blood tests: ELF (≥ 9.5) and FibroMeter^{V2G} (FM; ≥ 0.45). Ten sequential algorithms (first-line simple blood test, then second-line specialized blood test if first-line result in the grey zone) were thus evaluated. The following objectives were considered for a screening pathway: 1/ at least two-thirds of VCTE ≥ 8 kPa detected (sensitivity, Se $\geq 67\%$), 2/ more than half of patients with VCTE ≥ 8 kPa among those referred (positive predictive value, PPV $\geq 50\%$), 3/ at least 80% Se for VCTE ≥ 12 kPa, and 4/ according to objectives #1 and #2 (Se 67% and PPV 50%), an expected rate of referral at 44% in our population. **Results:** 1,457 patients were referred to the Liver Screening Center (MASLD: n = 1,183; MetALD/ALD: n = 274), of whom 481 (33%) had VCTE ≥ 8 kPa. AUROCs for VCTE ≥ 8 kPa were: FIB4: 0.718 ± 0.04, SAFE: 0.782 ± 0.013, MAF-5: 0.749 ± 0.014, eLIFT: 0.767 ± 0.013, LRS: 0.771 ± 0.013, ELF: 0.746 ± 0.014, FM: 0.779 ± 0.013. Used with the published thresholds, the recommended sequential FIB4-ELF algorithm reached the objectives: 64% Se and 57% PPV for VCTE ≥ 8 kPa, 77% Se for VCTE ≥ 12 kPa, 37% referral, 39% second-line test. Similar results were obtained with the FIB4-FM algorithm. The algorithms using SAFE or MAF-5 provided excellent sensitivity (84-88%) but high referral rate (56-69%). Conversely, the algorithms using LRS had low referral rate (22%) but poor sensitivity (48%). The thresholds of the five simple blood tests were refined to target VCTE ≥ 8 kPa (80% sensitivity/95% specificity):

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FIB4: $<1.20/>2.90$; SAFE: $<80/>220$, MAF-5: $<1.4/>5.1$, LRS: $<6.5/>10.6$, and eLIFT: $<7/>11$. With these thresholds, all the ten sequential algorithms evaluated showed similar accuracy and reached the objectives: 65-68% Se and 55-60% PPV for VCTE ≥ 8 kPa, 78-80% Se for VCTE ≥ 12 kPa, 36-39% referral rate, 39-47% second-line test. **Conclusion:** The recommended screening pathways for steatotic liver diseases should be updated and include the blood fibrosis tests recently developed for the case finding of at-risk patients. **Disclosures:** Jérôme Boursier: Novo Nordisk: Consultant, Lilly: Consultant, Madrigal: Advisor, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Sanofi: Speaking and Teaching, Echosens: Grant/Research Support, Gilead: Grant/Research Support, Intercept: Grant/Research Support, Inventiva: Grant/Research Support, Ipsen: Grant/Research Support, Siemens: Grant/Research Support, Diafir: Grant/Research Support, Jeanne Fichez: Nothing to Disclose, Odile Blanchet: Nothing to Disclose, Isabelle Fouchard: Nothing to Disclose, Adrien Iannes: Nothing to Disclose, Marine Roux: Nothing to Disclose, frederic oberti: Nothing to Disclose

0157 | UTILITY OF FIB-4, AGILE 4, AND PLATELET COUNT TO RULE OUT CIRRHOSIS ON BIOPSY IN PATIENTS WITH LSM BETWEEN 15-25 KPA: A MULTI-CENTER COHORT STUDY

Naim Alkhouri[1] Jörn Schattenberg[2] Rashmee Patil[3] Elizabeth Brombosz[1] Gražina Binkauskiene[1] Michelle Mazuranic[1] ALMA LAURA LADRON DE GUEVARA[4] Marcelo Kugelmas[5] Dimple Desai[6] Aasim Sheikh[7] John Poulos[8] Joseph Galati[9] Vlad Ratziu[10] Mazen Noureddin[11], [1]Summit Clinical Research, [2]Saarland University Medical Center, University of the Saarland, [3]Pinnacle Clinical Research, [4]CENTRO DE INVESTIGACION Y GASTROENTEROLOGIA, [5]South Denver Gastroenterology, [6]South Texas Research Institute, [7]Gastrointestinal Specialists of Georgia, [8]Coastal Research Institute, [9]Liver Specialists of Texas, [10]Service D' Hepatogastroenterologie (FR), [11]Houston Methodist Hospital

Background: Recent expert panel recommendations and AASLD guidance update recommended against the use of at-risk MASH pharmacologic treatment in patients with VCTE liver stiffness measurement (LSM) ≥ 20 kPa and consider treatment with caution in those with LSM 15-19.9 kPa due to the risk of having MASH cirrhosis. However, given known issues with the positive predictive value of LSM in MASH patients, it is of utmost importance for the field to be able to identify patients with LSM 15-25 kPa that have F2/F3 fibrosis and would possibly benefit from pharmacologic treatment. The aim of this study was to examine the performance of non-invasive tests (NITs) in identifying F2/F3 or F4 fibrosis in patients with LSM 15-25 kPa in a large multicenter database of patients with biopsy-proven MASH. **Methods:** An institutional database of patients screened for inclusion in MASH from multi-center pharmacotherapeutic trials with ≥ 2 metabolic risk factors was used for this analysis. Patients with LSM 15-20 kPa or LSM 20-25 kPa were identified for further analysis. Comparisons were made between those found to have F2/F3 on biopsy vs F4. NIT performance was compared to biopsy results. SAS software was used to perform statistical analyses with $p<0.05$ considered statistically significant. **Results:** Of 18402 patients reviewed, 4326 had baseline liver biopsy and LSM results, 882 of whom had LSM between 15 and 25. Among patients with LSM between 15-20 kPa ($n=586$, 66%; 354 F2/F3 and 232 F4) and 20-25 kPa (296, 34%; 141 F2/F3 and 155 F4), patients with F4 fibrosis were significantly older (both $p<0.001$), more likely to be White (both $p<0.001$), and had lower BMI (both $p<0.001$). In patients with LSM 15-20 kPa, model performance was highest using Agile 4 (AUC, 95% CI: 0.76, 0.69-0.83), followed by platelet count (0.71, 0.66-0.76) and FIB-4 (0.69, 0.64-0.75; Table 1). Among the LSM 20-25 kPa group, platelet count had superior performance (0.75, 0.69-0.82), followed by FIB-4 (0.73, 0.66-0.80), and Agile 4 (0.70, 0.60-0.79). Combining all tests resulted in an AUC of 0.76 (0.69-0.82) in the 15-20 kPa group and 0.75 (0.66-0.84) in the 20-25 kPa group. To reach $\geq 90\%$ sensitivity, for the Agile 4 score, a cutoff value of 0.104 was needed in the 15-20 kPa group and 0.099 in the 20-25 kPa group. **Conclusion:** This study highlights the interaction between NIT performance and liver stiffness in a large, multicenter cohort, where combined scores outperformed single NITs.

Table 1. Performance of non-invasive tests to detect MASH fibrosis (F2/F3) or cirrhosis (F4).

	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Accuracy
LSM 15-20 kPa						
Agile 4[a]	0.76 (0.69-0.83)	90%	46%	34%	94%	56%
FIB-4[b]	0.69 (0.64-0.75)	91%	37%	38%	90%	53%
Platelets[c]	0.71 (0.66-0.76)	90%	34%	38%	88%	51%
Combined[d]	0.76 (0.69-0.82)					
LSM 20-25 kPa						
Agile 4[e]	0.70 (0.60-0.79)	89%	22%	42%	76%	48%
FIB-4[f]	0.73 (0.66-0.80)	91%	37%	53%	84%	60%
Platelets[g]	0.75 (0.69-0.82)	93%	28%	53%	82%	58%
Combined[h]	0.75 (0.66-0.84)					

[a]Using cutoff of 0.104
[b]Using cutoff of 1.15
[c]Using a cutoff of 266,000 platelets/µl
[d]Combined Agile 4, FIB-4, and platelets
[e]Using cutoff of 0.099
[f]Using cutoff of 1.20
AUC, area under the curve; CI, confidence interval; FAST, FibroScan-AST; FIB-4, fibrosis 4 score; LSM, liver stiffness measurement; NPV, negative predictive value; PPV, positive predictive value

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0158 | DEVELOPMENT, VALIDATION, AND PROGNOSTIC EVALUATION OF LIVERHEALTH SCORE FOR THE PREDICTION OF LIVER FIBROSIS AND LIVER-RELATED EVENTS IN THE GENERAL POPULATION: A PROSPECTIVE, MULTICOHORT STUDY

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Background: Non-invasive tools for identifying liver fibrosis in the general population remain limited in accuracy and generalizability. This study aimed to develop and validate a novel score to predict liver fibrosis and liver-related events in the general population. **Methods:** The LiverHealth project is a large, ongoing, prospective, community-based cohort study conducted in China among individuals aged 18 years and older, in which all participants underwent liver stiffness measurement (LSM) using transient elastography (Fibroscan). Participants from the first two sites (Haizhou District and Yandu District), enrolled between September and November 2024, were included in the derivation cohort (n = 4050). Participants from subsequent sites (Maojian District, Huanghua City, Yiyang New District, and Qiantang District), enrolled between December 2024 and April 2025, formed the first external validation cohort 1 (n = 5042). The second external validation cohort (n = 6301) comprised individuals from the NHANES 2017–2020. The UK Biobank population (n = 355949) was used as the prognosis cohort, among whom 8585 individuals underwent a second assessment between 2012 and 2013 (median interval: 4.5 years), forming the dynamic cohort. Diagnostic accuracy was assessed using the AUC and compared with 12 established non-invasive scores across different liver stiffness measurement (LSM) thresholds ($\geq$6, $\geq$8, $\geq$10, $\geq$12, and $\geq$15 kPa) and at-risk MASH (FAST score > 0.35). **Results:** The LiverHealth score incorporated waist circumference, aspartate aminotransferase, gamma-glutamyltransferase, platelet count, and glycated hemoglobin. LiverHealth score showed superior performance in predicting LSM $\geq$8 kPa in the derivation cohort (AUC = 0.82 [0.79-0.85]), validation cohort 1 (AUC = 0.80 [0.76-0.83]), and validation cohort 2 (AUC = 0.82 [0.80-0.84]), outperforming existing 12 scores. LiverHealth score consistently outperformed or equaled other scores in predicting LSM $\geq$6, $\geq$10, $\geq$12, and $\geq$15 kPa and at-risk MASH across all cohorts (Figure 1A-1C). Furthermore, participants were stratified into low-, medium-, and high-risk groups using cutoffs of 2.517 and 2.830, achieving > 80% sensitivity and > 90% specificity in all cohorts. Compared with low-risk group, the medium- and high-risk groups had significantly higher incidence of liver-related events (LREs, Figure 1D). The hazard ratio in the high-risk group was 18.05 for liver-related death, 23.86 for cirrhosis, and 8.92 for liver cancer, compared with low-risk group. Furthermore, in the dynamic cohort, 60.8% of individuals remained in the high-risk group. Compared to those who consistently stayed in the low-risk group, participants who progressed to a higher risk group exhibited a significantly increased incidence of LREs (Figure 1F-1D). **Conclusion:** The LiverHealth score, based on simple parameters, accurately predicted liver fibrosis and liver-related events in the general population.

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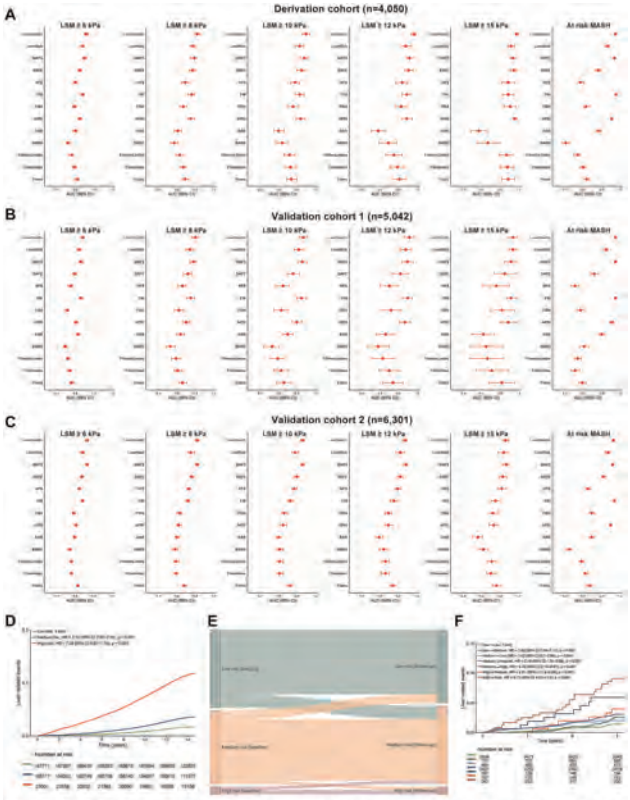

Figure 1. Discriminatory accuracy of different scores in the prediction of the degree of liver stiffness in the derivation cohort (A), validation cohort 1 (B), and validation cohort 2 (C); Cumulative incidence of liver-related events by LiverHealth score groups (D); Longitudinal changes in LiverHealth score risk groups from baseline (2006-2010) to follow-up (2012-2013) in the dynamic cohort (E); Cumulative incidence of liver-related events according to longitudinal LiverHealth score risk groups in the dynamic cohort (F).

The presence of liver fibrosis was defined as liver stiffness measurement (LSM) ≥ 6 kPa. Clinically significant liver fibrosis was defined as LSM ≥ 8 kPa. Suggestive Compensated advanced chronic liver disease (cACLD) was defined as LSM ≥ 10 kPa, advanced fibrosis as LSM ≥ 12 kPa, highly suggestive cACLD as LSM ≥ 15 kPa, and at-risk MASH (FibroScan AST [FAST] score >0.35)

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★ 0159 | A RANDOMIZED CONTROLLED TRIAL IN SILICO FOR RISK STRATIFICATION IN POPULATION SCREENING FOR FIBROTIC MASH

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Background: Coordinated efforts needed to mitigate the accelerating epidemic of MASLD include early diagnosis of fibrotic MASH and linkage to care for effective interventions. For detection of fibrotic MASH, there is consensus for a two-step process, starting with a risk stratification score followed by liver stiffness measurement (LSM). The Steatosis-Associated Fibrosis Estimator (SAFE) score was developed for this purpose, improving upon the FIB-4 score by incorporating metabolic variables known to correlate with MASH fibrosis. In this work, we applied a novel digital twin-based trial emulation framework using synthetic data and compare the outcome of stratification using SAFE versus FIB4 in MASH screening in the community. **Methods:** We trained tabular diffusion models on a US population-based data set (NHANES 2017-2020, N = 5,076) for synthetic data generation. Synthetic data fidelity was assessed using Wasserstein distance and multivariate correlation (R^2) to verify preservation of critical multivariate relationships. The sample size of 50,000 subjects, randomly assigned 1:1 to SAFE or FIB-4 arms, based on power considerations from prior NHANES analysis. Subjects 40 years or older with cardiometabolic risk factors and a high stratification score (SAFE $\geq$ 100 or FIB4 $\geq$ 1.3) underwent LSM by transient elastography (VCTE). The primary outcome was the proportion of subjects detected with fibrotic MASH (defined as LSM 8-12 kPa and CAP $\geq$ 274 dB/m or LSM $\geq$ 12 kPa regardless of CAP). Secondary end points included the number of VCTEs performed, the diagnostic yield of VCTE and the number needed to screen to detect a case of fibrotic MASH. **Results:** The synthetic data achieved satisfactory fidelity with mean Wasserstein distance 0.003 and $R^2 = 0.998$. Table 1 compares the two arms. For the primary end point in the simulated trial, SAFE detected more fibrotic MASH than FIB4 (6.0% vs 5.4%). It did so with a higher efficiency - requiring 42% fewer VCTEs (22.4% vs 38.8%) and yielding a 90% higher diagnostic rate, among those undergoing VCTE, with SAFE (26.7% vs 14.0%). SAFE required only 3.8 VCTEs per case detected compared to 7.1 for FIB4, representing 47% fewer procedures per diagnosis. Among subjects with diabetes, SAFE demonstrated an even larger difference (detection rate 16.8% vs 10.9%). **Conclusion:** This in silico analysis suggests that SAFE may outperform FIB-4

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in detecting fibrotic MASHwhile reducing resource deployment and potential harms of unnecessary diagnostic testing. This work utilizing diffusion-generated synthetic data and digital twin methodology provides a framework for informing trial designs and testing multiple scenarios, potentially accelerating the development of evidence-based screening programs.

Characteristic	Original Data	Synthetic FIB-4 Arm	Synthetic SAFE Arm
Total participants, n	5,076	25,000	25,000
Demographics			
Age, years	59.8 ± 11.7	59.8 ± 11.4	59.9 ± 11.5
Gender, n (%)			
Male	2,519 (49.6)	12,431 (49.7)	12,337 (49.3)
Female	2,557 (50.4)	12,569 (50.3)	12,663 (50.7)
Race/Ethnicity, n (%)			
1 Non-Hispanic Asian	606 (11.9)	2,936 (11.7)	3,042 (12.2)
2 Non-Hispanic White	1,868 (36.8)	9,678 (38.7)	9,824 (39.3)
3 Non-Hispanic Black	1,301 (25.6)	6,370 (25.5)	6,249 (25.0)
4 Hispanic	1,085 (21.4)	5,237 (20.9)	5,143 (20.6)
5 Other	216 (4.3)	779 (3.1)	742 (3.0)
Anthropometric Measurements			
BMI, kg/m^2	30.2 ± 7.0	30.3 ± 6.9	30.1 ± 6.9
Weight, kg	83.6 ± 21.8	83.9 ± 21.7	83.5 ± 21.4
Height, cm	166.1 ± 10.1	166.2 ± 9.9	166.1 ± 9.9
Waist circumference, cm	102.9 ± 15.8	103.1 ± 15.7	102.8 ± 15.6
Hip circumference, cm	107.7 ± 14.3	107.8 ± 14.2	107.6 ± 14.1
Comorbidities			
Diabetes, n (%)	1,395 (27.5)	6,500 (26.0)	6,478 (25.9)
Hypertension, n (%)	3,572 (70.4)	18,006 (72.0)	17,988 (72.0)
Liver Assessment			
Liver stiffness (LSM), kPa	6.3 ± 5.6	6.3 ± 5.5	6.2 ± 5.4
LSM>8, n (%)	676 (13.3)	3,428 (13.7)	3,310 (13.2)
LSM>12, n (%)	257 (5.1)	1,338 (5.4)	1,285 (5.1)
CAP score, dB/m	274 ± 61	275 ± 59	274 ± 59
CAP>274, n (%)	2,474 (48.7)	12,281 (49.1)	12,076 (48.3)
Fibrotic MASH, n (%)	571 (11.2)	2,953 (11.8)	2,850 (11.4)
Liver Enzymes			
AST, U/L	22.1 ± 15.0	21.8 ± 14.1	21.5 ± 11.7
ALT, U/L	22.1 ± 18.4	21.9 ± 17.9	21.6 ± 14.6
GGT, U/L	34.7 ± 57.3	33.1 ± 50.8	32.4 ± 47.1
Alkaline phosphatase, U/L	80.4 ± 26.0	79.8 ± 24.5	79.9 ± 24.4
Total bilirubin, mg/dL	0.46 ± 0.27	0.46 ± 0.26	0.46 ± 0.26
Albumin, g/dL	4.0 ± 0.3	4.0 ± 0.3	4.0 ± 0.3
Globulin, g/dL	3.1 ± 0.5	3.1 ± 0.4	3.1 ± 0.4
Lipid Profile			
Total cholesterol, mg/dL	190 ± 42	190 ± 40	190 ± 40
HDL cholesterol, mg/dL	54.0 ± 16.2	53.7 ± 15.5	54.0 ± 15.5
Hematologic Parameters			
Platelets, ×10^3/µL	241 ± 65	241 ± 62	240 ± 62
Ferritin, ng/mL	177 ± 203	171 ± 178	173 ± 194
Lifestyle Factors			
Alcohol consumption, g/day	6.3 ± 16.1	6.1 ± 15.3	5.9 ± 14.7
RCT In Silico Results			
Fibrotic MASH Detection, n (%)		1,359 (5.4)	1,499 (6.0)
VCTE Utilization, n (%)		9,699 (38.8)	5,607 (22.4)
Diagnostic Yield (%)		14.0	26.7
Number needed to screen, n		18.4	16.7
Number of VCTEs per case detected, n		7.1	3.8

Disclosures: Joseph Ahn: AITRICS: Consultant, Mingzhao Hu: Nothing to Disclose, Yung-Kyun Noh: Nothing to Disclose, Alina Allen: Novo Nordisk: Grant/Research Support, Novo Nordisk: Advisor, Target Pharma: Grant/Research Support, Pfizer: Grant/Research Support, Boehringer Ingelheim: Advisor, Madrigal: Advisor, GSK: Advisor, Oncoustics: Grant/Research Support, Escopics: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Madrigal: Grant/Research Support, Siemens: Grant/Research Support, W. Ray Kim: Nothing to Disclose, Nothing to Disclose

0160 | ONE-YEAR CHANGES IN ALT AND LSM, BUT NOT IN CAP, PREDICT LONG-TERM LIVER OUTCOMES IN PATIENTS WITH MASLD

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Background: The availability of new drugs for the treatment of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) underlines the need of early predictors of response to such therapies. This study evaluated the impact of 1-year changes in liver stiffness measurement by Vibration-Controlled Transient Elastography (LSM by VCTE), controlled attenuation parameters (CAP), and serum alanine aminotransferase (ALT) on liver outcomes in patients with MASLD. **Methods:** A large multicenter cohort of MASLD patients with LSM ≥ 8kPa and prospective follow-up was enrolled. Liver-related events (LRE), including hepatocellular carcinoma (HCC) and liver decompensation (LD), were evaluated during follow-up. LSM, CAP, and ALT were assessed at baseline and at 1-year follow-up. Cumulative incidence functions and cause-specific Cox regression analyses were performed to correlate 1-year reduction in LSM, CAP, and ALT with the risk of developing LRE, LD and HCC. **Results:** In 2443 patients with MASLD and LSM ≥ 8 kPa, a 1-year reduction in ALT of 17 IU/L (HR 0.62; 95% CI 0.41-0.95; p = 0.02) and a 20% reduction in LSM (HR 0.44; 95% CI 0.29-0.67; p < 0.001) were both

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independently associated with a lower risk of LRE (Figure 1). Similarly, in 1412 patients with MASLD and LSM ≥ 10kPa, a 1-year reduction in ALT of at least 17 IU/L (HR 0.62; 95% CI 0.39-0.98; p = 0.04) and a 20% reduction in LSM (HR 0.42; 95% CI 0.27-0.66; p < 0.001) were independently associated with a decreased risk of LRE (Figure 2). Comparable results were observed when considering LD separately, but not for HCC. One-year changes in CAP did not predict liver outcomes. When combining 1-year reduction in ALT of 17 IU/L and a 1-year 20% reduction in LSM, the 5-year probabilities of LRE ranged from 2.1% in the best profile to 5% in the worst profile in patients with LSM ≥ 8kPa (Figure 3), and from 3.3% to 8.1% in those with LSM ≥ 10kPa (Figure 4). **Conclusion:** One-year reductions in ALT of 17 IU/L and in LSM by 20%, but not changes in CAP, reduce long-term liver outcomes in patients with MASLD, providing suggestion on monitoring therapy effectiveness.

Figure 1

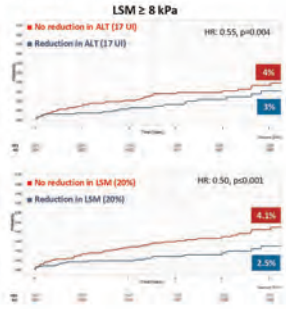


Figure 2

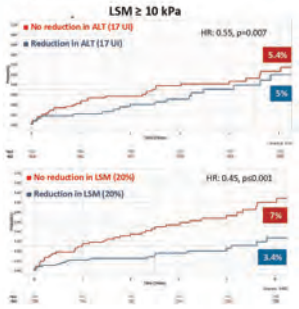


Figure 3

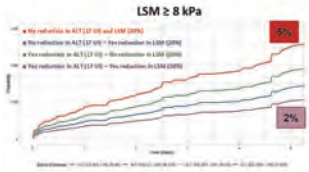
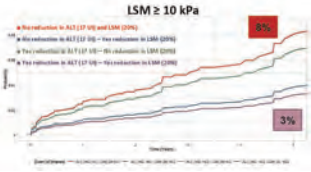


Figure 4



Disclosures: Grazia Pennisi: Nothing to Disclose, Giuseppe Infantino: Nothing to Disclose, Gabriele Di Maria: Nothing to Disclose, Emmanuel Tsochatzis: Nothing to Disclose, Elisabetta Bugianesi: Nothing to Disclose, Masado Yoneda: Nothing to Disclose, Ming-Hua Zheng: Nothing to Disclose, Hannes Hagström: Nothing to Disclose, Jerome Boursier: Nothing to Disclose, Jose Luis Calleja: Nothing to Disclose, Boon Bee George Goh: Nothing to Disclose, Wah-Kheong Chan: Abbvie: Advisor, Abbott: Speaking and Teaching, Novo Nordisk: Consultant, Roche: Advisor, Zuellig Pharma: Advisor, Boehringer Ingelheim: Consultant, Echosens: Speaking and Teaching, Hisky Medical: Speaking and Teaching, Viatris: Speaking and Teaching, Rocio Gallego-Durán: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (< 5K), Terns (< 5K), Merck (< 5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (< 5K),: Consultant, Novo Nordisk: Consultant, Regeneron (< 5K), Alnylam (< 5K), Akero (< 5K),: Consultant, Tern (< 5K), Histoindex (< 5K), Corcept (< 5K),: Consultant, Path AI (< 5K), Genfit (< 5K), Mediar (< 5K),: Consultant, Satellite Bio (< 5K), Echosens (< 5K), Abbott (< 5K),: Consultant, Promed (< 5K), Glaxo Smith Kline (~11K), Arrowhead (< 5K): Consultant, Zydus (>60K), Boston Pharmaceutical (< 5K), Myovent (< 5K),: Consultant, Variant (< 5K), Cascade (< 5K), Northsea (< 5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Victor de Ledinghen: Nothing to Disclose, Philip N Newsome: Nothing to Disclose, Jian-Gao Fan: Nothing to Disclose, Laurent Castéra: Nothing to Disclose, Michelle Lai: Nothing to Disclose, Celine Fournier: Echosens: Employee, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Angelo Armandi: Nothing to Disclose, Atsushi Nakajima: Nothing to Disclose, Wen Liu: Nothing to Disclose, Ying Shang: Nothing to Disclose, Marc De Saint Loup: Nothing to Disclose, Elba Llop: Nothing to Disclose, Kevin Kim Jun Teh: Nothing to Disclose, Carmen Lara Romero: Nothing to Disclose, Amon Asgharpour: Nothing to Disclose, Sara Mahgoub: Nothing to Disclose, Mandy Chan: Echosens: Employee, Manuel Romero-Gómez: Nothing to Disclose, Huapeng LIN: Nothing to Disclose, Seung Up Kim: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Adele Tulone: Nothing to Disclose, Jimmy Che-To Lai: Nothing to Disclose, Boyu Yang: Nothing to Disclose, Hye Won Lie: Nothing to Disclose, Abraham Aregay Desta: Nothing to Disclose, Giacinta Ciancimino: Nothing to Disclose, Marco Enea: Nothing to Disclose, Calogero Camma: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Consultant, Boehringer Ingelheim: Consultant, Echosens: Speaking and Teaching, Eli Lilly: Consultant, Gilead: Consultant, Gilead: Grant/Research Support, Intercept: Consultant, Inventiva: Consultant, Illuminatio Medical Technology: Stock – privately held company, Merck: Consultant, Novo Nordisk: Consultant, Pfizer:

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0161 | PERFORMANCE OF EXPERT PANEL CRITERIA IN PREDICTING AT-RISK AND NOT-AT-RISK MASH: DATA FROM A LARGE MULTI-CENTER COHORT

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Background: As the incidence of MASLD and MASH rises, it is increasingly important to identify patients who are at risk of liver-related morbidity from those who are not using non-invasive tests (NITs). Consequently, a 2024 expert panel summary (PMID 39038768) and an AASLD practice guidance update recommended algorithms of NITs to identify patients with at-risk MASH who might benefit from pharmacologic treatment based on liver enzymes, VCTE CAP for steatosis, and LSM for fibrosis. The purpose of this study is to investigate the efficacy of these algorithms in identifying patients with at-risk vs not-at-risk MASH. **Methods:** A large database of patients evaluated for inclusion in MASH pharmacotherapeutic trials with biopsy results available was reviewed. Patients were stratified into at-risk vs not-at-risk MASH based on biopsy results (NAS ≥ 4 and F2 or F3 fibrosis), and biopsy findings were used to determine performance of the most utilized NITs. Statistical analysis and NIT performance assessment were done with SAS software with $p < 0.05$ considered statistically significant. **Results:** Of 2647 patients identified, 1408 (53%) had at-risk MASH. Demographically, patients with at-risk MASH were more likely to be female ($p = 0.001$), non-White ($p < 0.001$), and Hispanic ($p < 0.001$). The performance of single NITs in identifying at-risk MASH ranged between sensitivity of 14-97% and specificity of 7-89% (Table 1). When multiple NITs were utilized, as recommended by expert guidelines, sensitivity was highest for CAP >280 dB/m, LSM 8-15 kPa, and AST >17 IU/L in females or >20 in males (60%). In combined models, specificity was highest for CAP, LSM 15.1-20 kPa, and AST >17 IU/L females/ >20 males (93%). Combined CAP, LSM 10-15 kPa, and high AST (>30 IU/L) yielded the highest AUC of all models considered (0.61), as well as the highest % correctly classified as at-risk (60%). The proportion of patients correctly identified as having at-risk MASH was highest (55%) using CAP alone, followed by AST alone (53%). **Conclusion:** These results suggest that the algorithms recommended by the experts can adequately identify high-risk patients via non-invasive tests, but that additional confirmatory tests (e.g., MRI-PDFF, MRE, or combination scores such as MAST) might be needed to definitively distinguish patients who will benefit from pharmacologic therapy for at-risk MASH.

Table 1. Performance of non-invasive tests in predicting at-risk MASH (F2/F3).

Test	Sensitivity	Specificity	PPV	NPV
AST[a]	97.1%	7.0%	54.3%	68.0%
LSM				
10-15 kPa	42.9%	71.0%	62.7%	52.3%
15.1-20 kPa	14.4%	88.5%	58.8%	47.7%
CAP[b]	93.8%	22.9%	57.8%	74.2%
CAP[b] + LSM 8-15 kPa + AST[a]	60.3%	57.4%	61.7%	56.0%
CAP[b] + LSM 10-15 kPa + AST[a]	38.9%	78.7%	67.5%	53.1%
CAP[b] + LSM 15.1-20 kPa + AST[a]	13.1%	93.0%	68.0%	48.5%
CAP[b] + LSM 10-15 kPa + AST >30	31.4%	90.8%	79.5%	53.8%

[a] AST: >17 IU/L if F; >20 IU/L if M
[b] CAP: >280 dB/m
AST, aspartate transferase; CAP, controlled attenuation parameter; CI, confidence interval; LSM, liver stiffness measurement; NPV; negative predictive value; PPV, positive predictive value

Disclosures: Rashmee Patil: Nothing to Disclose, Jörn Schattenberg: Apollo Endoscopy, Boehringer Ingelheim, Gilead Sciences: Consultant, Intercept Pharmaceuticals: Consultant, Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals: Consultant, MSD, Northsea Therapeutics, Novartis, Novo Nordisk: Consultant, Pfizer, Roche, Sanofi, and Siemens Healthineers: Consultant, Boehringer Ingelheim, Siemens Healthcare GmbH: Grant/Research Support, Alentis, Alexion, Altimmune, Astra Zeneca, 89Bio,Bionorica,: Consultant, Boehringer Ingelheim, Gilead Sciences, GSK, Ipsen, Inventiva: Consultant, Madrigal Pharmaceuticals, Lilly, MSD, Northsea Therapeutics,: Consultant, Novo Nordisk, Pfizer, Roche, Sanofi, and Siemens Healthineer: Consultant, AbbVie, Academic Medical Education (AME),: Speaking and Teaching, Boehringer Ingelheim, Echosens: Speaking and Teaching, Forum für Medizinische Fortbildung (FOMF), Gilead Sciences: Speaking and Teaching, MedicalTribune, MedPublico GmbH, MedScape,: Speaking and Teaching, Novo Nordisk, Madrigal Pharmaceuticals,: Speaking and Teaching, Akero, Alentis, Alexion, Altimmune, Astra Zeneca, 89Bio: Consultant, Bionorica, Boehringer Ingelheim, Gilead Sciences, GSK,: Consultant, HistoIndex, Ipsen, Inventiva Pharma, Madrigal Pharmaceutical: Consultant, Kríya Therapeutics, Lilly, MSD Sharp & Dohme GmbH: Consultant, Northsea Therapeutics, Novartis, Novo Nordisk: Consultant, Pfizer, Roche, Sanofi, Siemens Healthineers,: Consultant, Summit Clinical, and Vantage Biosciences Research: Consultant,

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0162 | MISSED LIVER FIBROSIS RISK STRATIFICATION OPPORTUNITIES IN THE ALL OF US COHORT IN THE UNITED STATES

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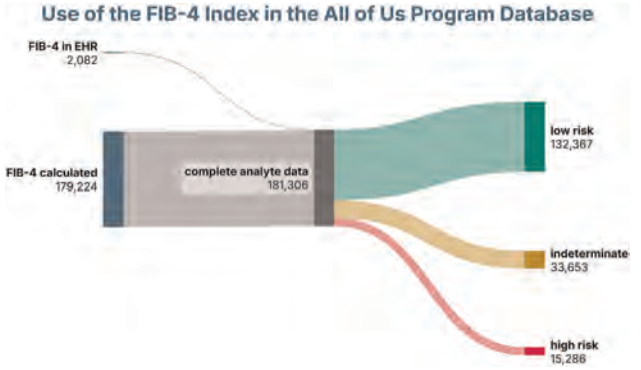
Background: Liver fibrosis is a progressive pathological condition with substantial public health implications, associated with increased liver-related and cardiovascular mortality, as well as being a major contributor to global health and economic burdens. Non-invasive tests (NITs) for fibrosis assessment, such as the Fibrosis-4 (FIB-4) Index, offer inexpensive, scalable risk stratification, though adoption remains low, and sensitivity and specificity varies across age and comorbidity groups. The study aimed to examine variation in liver fibrosis risk and to assess the utilization of FIB-4 scoring in electronic health records (EHRs) in the United States. **Methods:** This study evaluated the prevalence of liver fibrosis in the "All of Us" database (N = 623,464) using FIB-4 scores derived from laboratory data. We analyzed 181,306 participants with complete FIB-4 inputs (AST, ALT, platelet count, age). In addition to computing FIB-4 scores using available data, we also identified participants with FIB-4 scores already recorded in their EHRs. Risk groups were: low (< 1.30), indeterminate (1.30–2.67, or 2.00–2.67 for adults 65+), and high risk (> 2.67). Liver fibrosis among three risk groups are also reported. **Results:** Of the 181,306 participants with complete analyte data, 2,082 (1.2%) had a previously calculated FIB-4 score in their EHR. After calculating FIB-4 scores in the remaining 179,224 participants, 72.99% were low risk, 18.56% indeterminate, and 8.43% high risk. Of the 15,286 participants classified as high risk, 269 (1.76%) had a previously calculated FIB-4 score in their EHR (see Figure). 14,574 (28.82%) of those with type 2 diabetes and 17,287 (22.96%) with BMI ≥ 30 kg/m2 had intermediate or high-risk scores. **Conclusion:** Despite the availability of routine liver biochemistry, liver fibrosis risk using the FIB–4 index was rarely assessed among the participants, even among those later determined in our calculations to be at high risk. Integrating automated FIB-4 calculation and structured reflex testing follow-up pathways into clinical workflows could address this gap and enable timely fibrosis assessment.



Disclosures: Kyle Sellers: Nothing to Disclose, Trenton White: Nothing to Disclose, Meena Bansal: Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor, Nicolai Brachowicz: Nothing to Disclose, Hannes Hagström: Nothing to Disclose, Paul Brennan: Nothing to Disclose, Luis Antonio Diaz: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Melina Manolas: Nothing to Disclose, Xiaotao Zhang: Nothing to Disclose, Jeffrey Lazarus: Boehringer Ingelheim: Grant/Research Support, Abbvie: Grant/Research Support, Echosens: Grant/Research Support, Gilead Sciences: Grant/Research Support, Madrigal: Grant/Research Support, MSD: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pfizer: Grant/Research Support, Roche Diagnostics: Grant/Research Support, Echosens: Consultant, NovoVax: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Abbvie: Speaking and Teaching, Echosens: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Janssen: Speaking and Teaching, Moderna: Speaking and Teaching, MSD: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, Pfizer: Speaking and Teaching

0163 | FACTORS ASSOCIATED WITH BALLOONING VS. NO BALLOONING IN PATIENTS WITH F2/F3 FIBROSIS: DATA FROM MULTICENTER MASH RANDOMIZED CLINICAL TRIALS

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Background: Phase 2 and 3 clinical trials for therapies targeting MASH fibrosis require hepatocyte ballooning to be present on biopsy. Screen failures due to the absence of ballooning, despite having significant fibrosis, are relatively common, which can reduce enrollment and inflate duration and costs. Identifying patients unlikely to qualify can reduce study burden from patients ultimately ineligible for enrollment and avoid biopsy-related risks in patients unlikely to have ballooning. We assessed characteristics and non-invasive biomarkers associated with F2/F3 fibrosis and absence of ballooning on biopsy to reduce screen failures in clinical trials. **Methods:** A multicenter database of patients screened for enrollment in MASH pharmacotherapeutic studies was investigated. Patients identified as having F2 or F3 fibrosis on biopsy were further stratified by the presence of hepatocyte ballooning on biopsy. Statistical analysis was performed using SAS software with $p < 0.05$ considered statistically significant. **Results:** Of the 2833 patients with F2/F3 fibrosis, 1103 (39%) were not eligible for inclusion in clinical trials because hepatocyte ballooning was not noted on biopsy. Patients with no ballooning were more likely to be male (54% vs 38%), White (74% vs 65%), and non-Hispanic/Latino (33% vs 37%; all $p < 0.001$). They were also less likely to have diabetes (31% vs 59%), AST > 30 IU/L (46% vs 23%), and HbA1c $\geq 6.5\%$ (28% vs 39%; all $p < 0.001$). LSM and CAP measurements and FAST and FIB-4 scores were significantly lower in patients without ballooning (all $p < 0.001$). MRI-PDFF was similar between groups (17 [12-22] vs 17 [13-23]%; $p = 0.09$). Among non-invasive tests (NITs) to identify patients with F2/F3 fibrosis and NAS ≥ 4 with ballooning (Table 1), combined AST ≥ 30 IU/L + CAP ≥ 280 dB/m and AST + CAP + LSM ≥ 8.5 kPa had the highest AUC (both 0.63). CAP alone had the highest sensitivity (93.5%), negative predictive value (58.3%), and % correctly classified (61.6%). Combining all 4 NITs resulted in the highest specificity (89.0%) and positive predictive value (92.9%). LSM alone, CAP alone, and combined CAP + LSM all exceeded 80% sensitivity. **Conclusion:** The results of this study suggest AST, HbA1c, LSM, and CAP may be helpful in pre-screening patients for formal screening in MASH clinical trials. Limiting screening efforts to patients with these risk factors may reduce the proportion of screen failures and ultimately improve efficiency in these studies.

Table 1. Performance of non-invasive tests for detecting patients with F2/F3 liver fibrosis and with a NAFLD activity score (NAS) ≥4 and hepatocyte ballooning on biopsy.

Test	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Accuracy	% Correctly Classified
AST	0.62 (0.60–0.64)	76.8%	46.8%	69.1%	56.7%	65.1%	57.2%
LSM	0.54 (0.52–0.55)	87.6%	19.7%	64.3%	49.1%	62.0%	59.0%
CAP	0.54 (0.53–0.56)	93.5%	14.8%	64.3%	58.3%	63.7%	61.6%
HbA1c	0.59 (0.55–0.60)	43.8%	71.6%	81.2%	31.3%	51.1%	39.8%
AST + LSM	0.62 (0.60–0.65)	68.5%	56.5%	71.9%	52.5%	63.9%	54.0%
AST + CAP	0.63 (0.61–0.65)	71.7%	53.9%	71.5%	54.2%	64.9%	55.8%
AST + HbA1c	0.59 (0.57–0.61)	31.8%	86.5%	86.9%	31.1%	46.2%	30.4%
HbA1c + CAP	0.59 (0.56–0.63)	44.2%	74.5%	89.8%	21.0%	49.2%	42.1%
HbA1c + LSM	0.58 (0.55–0.62)	40.6%	76.1%	89.0%	21.1%	46.8%	38.7%
CAP + LSM	0.56 (0.54–0.58)	82.6%	29.6%	65.8%	51.0%	62.6%	57.8%
AST + CAP + LSM	0.63 (0.61–0.65)	64.4%	61.6%	73.0%	51.8%	63.3%	52.0%
AST + HbA1c + LSM	0.58 (0.56–0.61)	28.9%	88.0%	92.0%	20.6%	39.2%	28.2%
AST + HbA1c + CAP	0.59 (0.57–0.62)	31.2%	87.8%	92.8%	20.1%	40.5%	30.4%
HbA1c + CAP + LSM	0.59 (0.56–0.63)	40.3%	78.2%	90.3%	20.6%	46.5%	38.6%
AST + HbA1c + LSM + CAP	0.59 (0.56–0.62)	28.5%	89.0%	92.9%	19.7%	38.5%	27.9%

Cutoff values: AST ≥30 IU/L, LSM ≥8.5 kPa, CAP ≥280 dB/m, HbA1c ≥6.5%

AST, aspartate transferase; AUC, area under curve; CAP, controlled attenuation parameter; CI, confidence interval; HbA1c, hemoglobin A1c; LSM, liver stiffness measurement; NPV, negative predictive value; plt, platelet count; PPV, positive predictive value

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0164 | NEW CRITERIA FOR OBESITY IMPROVE IDENTIFICATION OF INDIVIDUALS AT RISK OF LIVER FIBROSIS: COMPARISON WITH BMI IN >6000 INDIVIDUALS

Ellen Lyngbeck Jensen[1] Nikolaj Torp[1] Georg Semmler[1] Katrine Bech[1] Stine Johansen[1] Johanne Hansen[1] Helle

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

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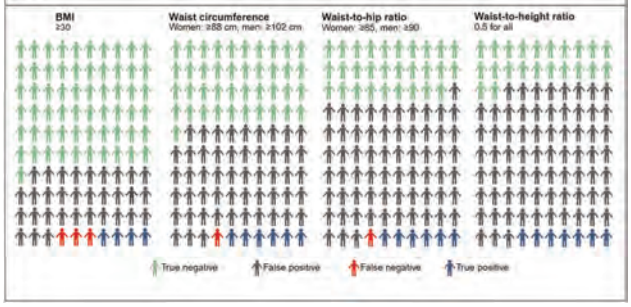
Background: AASLD and EASL recommend fibrosis screening in individuals with obesity due to its strong association with steatotic liver disease. As BMI does not directly reflect body composition or fat distribution, new clinical obesity criteria have been proposed by a Lancet Commission. We evaluated which metric best identified patients at risk for advanced fibrosis and the clinical consequences if applied as index criterion for fibrosis screening. **Methods:** We conducted a population-based fibrosis screening study evaluating obesity, defined by BMI ($\geq$30 kg/m²) and three alternative anthropometric indices: waist circumference ($\geq$102 cm for men, $\geq$88 cm for women), waist-to-hip ratio ($\geq$0.90 for men, $\geq$0.85 for women), and waist-to-height ratio ($\geq$0.50). Each was assessed as an index criterion for fibrosis screening, both alone and in combination with FIB-4 $<$1.3 as a rule-out step before liver stiffness measurement (LSM). LSM was assessed using vibration-controlled transient elastography (VCTE), with $\geq$8 kPa indicating risk of advanced fibrosis and confirmed using ELF $\geq$9.8. **Results:** We included 6,819 participants (mean age 57 years; 51% men), 7% had VCTE $\geq$8 kPa and 3% had both VCTE $\geq$8 kPa and ELF $\geq$9.8. Obesity was present in 36% as assessed by BMI, 58% by waist circumference, 70% by waist-to-hip ratio, and 78% by waist-to-height ratio. For discrimination of VCTE $\geq$8 kPa, AUCs were 0.70 (BMI), 0.76 (waist circumference), 0.74 (waist-to-hip ratio) and 0.73 (waist-to-height ratio). For the combined endpoint (VCTE $\geq$8 kPa and ELF $\geq$9.8), AUCs were 0.62 (BMI), 0.65 (waist circumference), 0.63 (waist-to-hip ratio), and 0.59 (waist-to-height ratio). Waist circumference demonstrated significantly better discriminatory ability than the other measures ($p<0.05$). Using obesity as index criterion for fibrosis screening (Figure), BMI resulted in the lowest proportion of individuals requiring further evaluation but missed 39% cases of VCTE $\geq$8 kPa. In comparison, waist circumference missed 17%; waist-to-hip ratio 10% cases, and waist-to-height ratio 6%. Finally, we applied FIB-4 $<$1.3 to rule out liver fibrosis, BMI + FIB-4 classified 10% of the cohort needing further evaluation but missed 70% cases with VCTE $\geq$8 kPa. Corresponding proportions were 18%/57% for waist circumference, 24%/52% for waist-to-hip ratio, and 26%/51% for waist-to-height ratio. **Conclusion:** Waist circumference outperforms BMI for identifying obesity-related fibrosis risk. BMI above 30 kg/m^2 is not suited for pre-test selection of patients at risk of fibrosis due to a substantial false-negative rate. Measures of waist circumference combined with FIB-4 improve the accuracy of reliably ruling out liver fibrosis.

Figure: Illustration of the consequences of using each of the four obesity measures as the index criterion for fibrosis screening in a population of 100 individuals of which 7 have TE ≥8 kPa



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0165 | COMPARATIVE EFFECTIVENESS OF BARIATRIC SURGERY, GLP-1 RA, AND SGLT2I ON COMPOSITE LIVER EVENTS IN MASLD PATIENTS: A MULTICENTER RETROSPECTIVE COHORT STUDY

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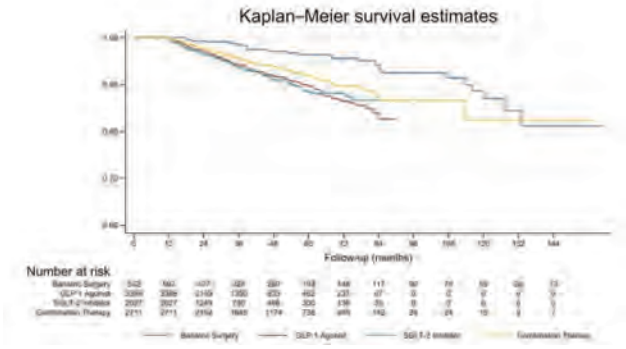
Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease globally, can progress to ascites, hepatic encephalopathy, esophageal varices, hepatocellular carcinoma (HCC), and liver transplant. While bariatric surgery, GLP-1 receptor agonists (GLP-1 RA), and SGLT2 inhibitors (SGLT2i) have shown to reduce disease progression, no studies have compared their effectiveness. This study aims to compare how different interventions effect the incidence of composite liver events in MASLD patients. **Methods:** This multicenter retrospective cohort study at Banner Health evaluated the effect of specific interventions on MASLD patients, who were identified based on ICD codes and metabolic criteria. The cohort received bariatric surgery, GLP-1 RA, SGLT2i, or combination therapy and was followed for at least 12 months. Composite liver events included: LREs (ascites, hepatic encephalopathy, or esophageal varices), liver transplant and hepatocellular carcinoma (HCC) 12 months post intervention. Medication use was verified, and bariatric procedures were confirmed via ICD codes and were only included if performed by a bariatric surgeon. Competing risk analysis was performed to assess composite liver event incidence among treatment groups with bariatric surgery as the reference group while adjusting for confounding variables. A Kaplan-Meier survival curve was generated to illustrate composite liver event free survival. **Results:** The cohort included 14,589 patients: 4.6% underwent bariatric surgery, 45.4% received GLP-1 RA, 27.2% SGLT2i and 22.8% combination therapy. Univariate and multivariate analysis show that bariatric surgery treatment group had statistically significant lower rates of composite liver events —LREs, liver transplant, and hepatocellular carcinoma — 12 months post treatment compared to the GLP1-RA and SGLT2i treatment groups. However, multivariate analysis does not show statistically significant difference compared to the combination therapy treatment group (Table 1). Kaplan-Meier survival analysis demonstrated superior liver event free survival in the bariatric surgery group (Figure 1). **Conclusion:** Bariatric surgery is more effective than GLP1-RA and SGLT2i in lowering liver events in MASLD patients 12 months post intervention even when adjusting for confounding factors. Further studies can assess comparative intervention effects on MASLD patient subgroups with and without cirrhosis at the time of intervention. Furthermore, future prospective studies are necessary to validate these findings and comprehensively evaluate the long-term impact of these interventions on liver events in MASLD patients.

Table 1

Intervention	Composite Liver Events in MASLD Patients			
	HR (95% CI)	p-value	aHR (95% CI)	p-value
Bariatric Surgery	Reference			
Glucagon-Like Peptide-1 Agonist (GLP-1 RA)	2.44 (1.60 – 3.72)	0.000	1.61 (1.04 – 2.48)	0.032
Sodium-Glucose Cotransporter 2 Inhibitor (SGLT2i)	2.53 (1.64 – 3.91)	0.000	1.67 (1.05 – 2.65)	0.031
Combination Therapy	1.89 (1.24 – 2.88)	0.003	1.34 (0.86 – 2.07)	0.198

HR: Hazard Ratio
aHR: Adjusted Hazard Ratio for tobacco use, age, BMI, sex, race, HTN, HLD, DM
CI: Confidence Interval

Figure 1



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0166 | GLP-1 RECEPTOR AGONISTS ARE SUPERIOR TO BARIATRIC SURGERY FOR PREVENTION OF ALL CAUSE MORTALITY AND MAJOR ADVERSE LIVER OUTCOMES IN TYPE 2 DIABETES MELLITUS AND OBESITY IN REAL WORLD CLINICAL PRACTICE

Ana Oliveira[1] Kavin Parmar[1] Vinay Jahagirdar[1] Arun Sanyal[1], [1]Virginia Commonwealth University

Background: Bariatric surgery (Ba) and GLP1 receptor agonists (GLP1 RA) improve multiple outcomes in type 2 diabetes mellitus (T2DM) and obesity, the key risk factors for metabolic dysfunction associated steatotic liver disease (MASLD). The real-world comparative effectiveness of GLP-1 RA vs Ba for major adverse liver- (MALO) and cardio-renal-metabolic (CRM)-outcomes in these populations are unknown. Aims: (1) To define the effectiveness of GLP-1 RA (inclusive of the GLP-1/GIP dual agonist Tirzepatide) vs Ba alone for MALO and CRM, (2) to compare the effectiveness of GLP-1 RA vs Ba on these outcomes. **Methods:** A retrospective analysis of hospitalized patients was performed using the TriNetX global collaborative network. Those with obesity+T2DM who received either GLP-1 RA or Ba with follow up to 4 years were included and compared to controls matched for age, race/ethnicity, sex, BMI, smoking status, use of statins and outcome-specific confounders. For MALO, groups were matched for AST, ALT, platelets and bilirubin in addition to the above-noted parameters. Similar matching was done for the comparison of GLP-1 RA vs Ba. Exclusion criteria included those who did not get a GLP-1 RA for 4 years or having the outcome prior to the start date. Odds ratio (O.R.) with 95% CI are reported. **Results:** A total of 16.7M individuals with obesity and T2DM were identified; of these 74361 received a GLP-1 RA and 11255 received Ba. Effectiveness of GLP-1 RA vs controls: In T2DM +obesity, the impact of GLP-1 RA (vs controls) was (O.R. 95% CI): Mortality (0.22, 0.2-0.24), MALO (0.45, 0.4-0.5), MACE (0.49, 0.46-0.52), obesity-related cancer (0.58, 0.51-0.65), chronic kidney disease (CKD) (0.7, 0.65-0.74). Effectiveness of Ba vs controls: The Odds ratio for outcomes were: Mortality (0.31, 0.26-0.38), MALO (0.99, 0.8-1.2), MACE (0.48, 0.41-0.56), obesity-related cancer (0.67, 0.5-0.9), CKD (0.37, 0.3-0.44). Comparative effectiveness of GLP-1 RA vs Ba: The distribution of BMI at the end of follow up period was left-shifted in Ba vs GLP-1 RA. The O.R. for outcomes were: Mortality (0.64, 0.49-0.83), MALO (0.41, 0.31-0.55), MACE (0.94, 0.8-1.1), obesity-related cancer (0.92, 0.67-1.3), CKD (1.5, 1.25-1.84). In those who also had MASLD, the impact of GLP-1 RA and Ba on outcomes are shown in the Table. **Conclusion:** Both Ba and GLP-1 RA improved outcomes in T2DM + obesity. GLP-1 RA were superior with respect to mortality and MALO, especially in those with MASLD, while Ba was superior for CKD prevention.

Population: MASLD + T2DM + obesity	Mortality O.R., 95% CI	MALO O.R., 95% CI	Ascites O.R., 95% CI	Encephalopathy O.R., 95% CI
GLP-1 RA vs control	0.14, 0.1-0.17	0.35, 0.3-0.42	0.27, 0.21-0.35	0.92, 0.6-1.4
Ba vs control	0.27, 0.19-0.4	0.49, 0.34-0.69	0.45, 0.28-0.69	0.99, 0.4-2.8
GLP-1 RA vs Ba	0.57, 0.3-1	0.73, 0.45-1.2	0.5, 0.24-1.14	1, 0.41-2.4

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0167 | TWO-YEAR TIME COURSE OF BIOMARKER AND IMAGING RESPONSES IN WELL-COMPENSATED MASH CIRRHOSIS PATIENTS TREATED WITH RESMETIROM

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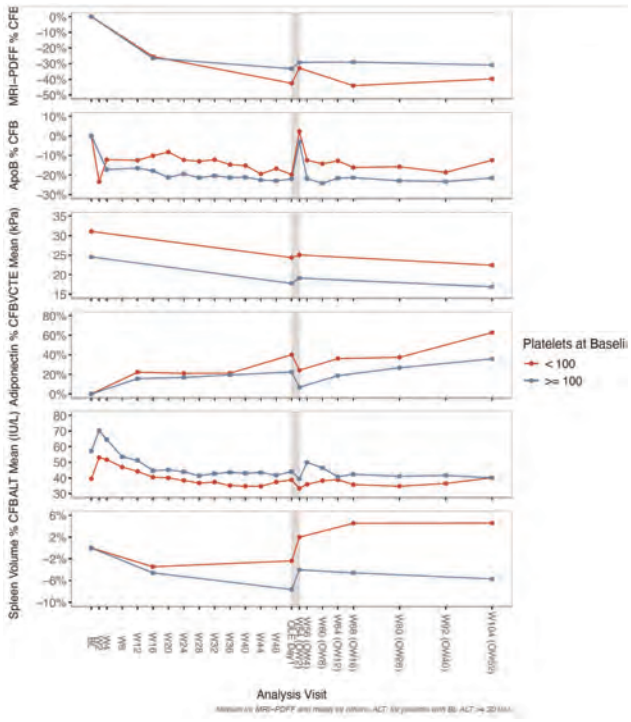
Background: Resmetirom (RES), a selective thyroid hormone receptor beta agonist, is an approved therapy for metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis based on improvement in both NASH and fibrosis. We evaluated two years data in 122 compensated MASH cirrhosis patients treated with RES to assess durability of responses, and the impact of a treatment interruption that occurred between year 1 and 2. **Methods:** A total of 122 patients with Child Pugh A MASH cirrhosis (based on MASH F4 on historic biopsy $>66\%$ or clinical diagnosis) were treated with 80 mg resmetirom for up to 2 years (MAETRO-NAFLD-1 (NCT04197479) year 1; open-label extension trial (NCT04951219) year 2. Patients experienced a mean gap of 77 (58) days in RES treatment between years 1 and 2. Non-invasive biomarkers and imaging were analysed at baseline and out to 2 years. Results are presented as mean change or % change from baseline. **Results:** Baseline characteristics included mean age 61.3 (9.1), female 56%, Hispanic 27%, BMI 35.3 (7.6)kg/m^2, T2D 70%. Median (Q1,Q3): VCTE 20.1 (17.1,31.3)kPa; ELF 10.7 (10.0,11.5); MRI-PDFF 8.6% (6.0%,11.5%). Agile3$^+$, 0.96(.89,.99); Agile 4, 0.69(0.35,0.84). CSPH or probable CSPH was predicted in 49%, 93% with platelets(PLT) <100k; 35%, PLT ≥ 100K. Spleen volume in patients with platelet (PLT) count <100k (n = 30) and ≥ 100k (n = 92) were 867 (319) and 487 (220), respectively. Treatment interruption after year 1 resulted in loss of RES biomarker effects including lipids, MRI-PDFF, VCTE, adiponectin and spleen volume (figure). Treatment with RES restored year 1 biomarker effects except in some with baseline PLT <100K. Five of total 6 decompensation events were in patients with PLT <100K and elevated spleen volume. RES effects at year 2: mean (95% CI) change from baseline in <100K, ≥ 100k, respectively: VCTE -7.9 (-14.1,-1.8), -6.4 (-8.7,-4.0) kPa; mean (95% CI) % change from baseline, ALT 6%(-11%, 23%), -25%(-32%, -19%); AST 31% (8%, 54%), -18% (-25%, -11%); GGT -19% (-39%, 0), -40% (-47%, -33%) (baseline ALT $\geq$ 30 IU/L); LDL -9% (-19%, 1%), -17% (-23%, -12%); ApoB -12% (-19%, -6%), -22% (-25%,-18%); TGs -13% (-35%, 9%), -20% (-27%, -14%); Adiponectin 63% (31%, 94%), 36% (26%, 46%); Spleen volume 5% (1%, 9%) and -6% (-9%, -2%). High Agile shifted to lower Agile (35%); CSPH shifted to a lower CSPH risk score in 65%. Discontinuation rate was 8%. Mild gastrointestinal disorders were the most common adverse events. **Conclusion:** Resmetirom treatment for 2 years showed statistically significant improvement in multiple imaging and biomarker parameters. Temporary interruption of RES treatment between year 1 and 2 led to temporary attenuation of beneficial effects that generally reversed with treatment restoration. These findings highlight the potential of resmetirom to demonstrate clinical benefit in MAESTRO-NASH OUTCOMES, an ongoing 845 MASH cirrhosis patient clinical outcome study.



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0168 | IMPACT OF GLP-1 RECEPTOR AGONIST TIMING ON LIVER OUTCOMES FOLLOWING ENDOSCOPIC SLEEVE GASTROPLASTY: A 36-MONTH PROSPECTIVE COHORT ANALYSIS

Kate Solpari[1] Dominique Gay[1] Ali Lahooti[1] Muhammad Usman Baig[1] Reem Sharaiha[1], [1]Weill Cornell Medical College

Background: Endoscopic sleeve gastroplasty (ESG) effectively treats obesity and metabolic dysfunction-associated steatotic liver disease (MASLD). While GLP-1 receptor agonists (GLP-1 RAs) are increasingly used with

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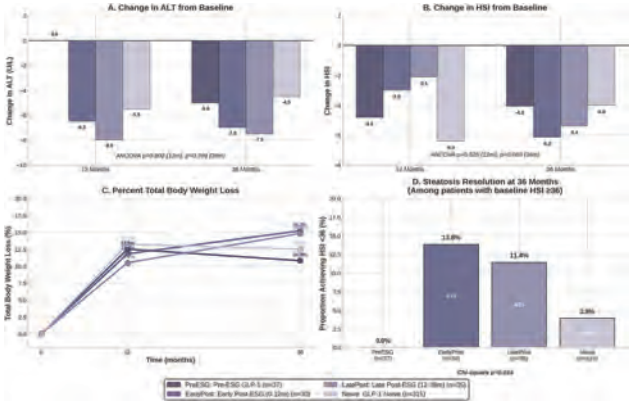
bariatric procedures, optimal timing remains unclear. We evaluated whether GLP-1 RA timing relative to ESG affects liver-related outcomes. **Methods:** We analyzed 417 ESG patients from a prospective registry, categorizing them by GLP-1 RA exposure through 36 months: PreESG (on GLP-1 RA before ESG, n = 37), EarlyPost (initiated 0-12m post-ESG, n = 30), LatePost (initiated 12-36m post-ESG, n = 35), and Naive (no GLP-1 RA through 36m, n = 315). Primary outcomes included changes in ALT, FIB-4, and Hepatic Steatosis Index (HSI) at 12 and 36 months. Secondary outcome was proportion achieving HSI <36 (steatosis resolution) at 36 months among those with baseline HSI ≥ 36. ANCOVA models adjusted for baseline values, percent total bodyweight loss (TBWL), age, BMI, and type 2 diabetes (T2DM). **Results:** Baseline characteristics differed significantly for age ($p = 0.007$) and T2DM prevalence ($p < 0.001$), with the PreESG group being older (median 51 vs 45 years) and having higher T2DM rates (32.4% vs 7.6% in the Naïve group). Baseline BMI, ALT, FIB-4, and HSI were similar across groups. Most groups demonstrated significant improvements in ALT and HSI at both timepoints. At 36 months, median ALT decreased from 26.0 to 21.0 (G1), 26.5 to 19.5 (G2), 25.0 to 17.5 (G3), and 24.0 to 19.5 (G4). HSI showed similar patterns with significant reductions in all groups except G1 at 36m ($p = 0.099$). FIB-4 remained stable across all groups. ANCOVA revealed no significant effect of GLP-1 RA timing on magnitude of change in ALT, FIB-4, or HSI at 12 or 36 months after adjusting for confounders (all $p > 0.05$). TBWL was the strongest predictor of improvement for all markers ($p < 0.001$). However, among patients with baseline HSI ≥ 36, those receiving GLP-1 RAs post-ESG showed higher rates of steatosis resolution at 36 months: 13.8% (EarlyPost) and 11.4% (LatePost) vs 3.9% (Naive) and 0% (PreESG), $p = 0.014$. **Conclusion:** ESG effectively improves liver biochemistry and steatosis regardless of GLP-1 RA use. While the magnitude of improvement in liver markers is primarily driven by weight loss rather than GLP-1 RA timing, post-ESG GLP-1 RA initiation may enhance steatosis resolution rates. These findings suggest that GLP-1 RAs started after ESG may provide additional metabolic benefits beyond weight loss alone.



Disclosures: Kate Solpari: Nothing to Disclose, Dominique Gay: Nothing to Disclose, Ali Lahooti: Nothing to Disclose, Muhammad Usman Baig: Nothing to Disclose, Reem Sharaiha: boston scientific: research support, Surgical Intuitive: Consultant

★ 0169 | EFFECT OF ALTERNATE DAY FASTING OVER STANDARD MEDICAL MANAGEMENT ALONE TO REVERSE NON-ALCOHOLIC STEATOHEPATITIS, A RANDOMIZED CONTROLLED TRIAL. FAST TRIAL

Babu Lal Meena[1] Varsha Shasthry[1] Uma Kanal[1] PRATIBHA KALE[1] Omkar Rudra[1] Deepti Sharma[1] Manoj Sharma[1] Ibrar Ahmed Khan[1] Shiv Kumar Sarin[1] Suguna Sree Aakula[1],
[1]Institute of Liver and Biliary Sciences

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a highly prevalent liver disease with limited short-term therapeutic options. Untreated MASH progresses to cirrhosis and HCC. This randomized trial evaluated the efficacy of alternate day fasting (ADF) with standard of care (SOC) vs SOC only as a lifestyle intervention in MASH. **Methods:** The study was approved by the ethics committee and registered on clinicaltrials.gov. Ninety patients with biopsy-proven MASH were randomized to ADF(n = 45) or SOC standard care (Group 2, n = 45), and followed for six months. Biochemical resolution was defined as normalization of ALT, AST, and GGT along with improvements in controlled attenuation parameter(CAP), liver stiffness measurement(LSM), and enhanced liver fibrosis(ELF) scores. Quality of life(CLDQ NASH, SF-36) and metabolic parameters were also assessed. **Results:** The groups were comparable at baseline with a mean age of 41.9 ± 9.8 years, 56% males, and a mean BMI of 31.5 ± 2.7. Baseline LSM averaged 9.26 ± 1.75kPa, ELF score was 10.05 ± 0.38, CAP was 341.39 ± 27.66dB/m. Comorbidities were similar between groups. At 6 months, biochemical resolution was achieved in 73.3% of ADF group versus 31.1% of SOC group($p < 0.001$). Mean weight loss was greater in the ADF group(10.4 kg vs. 4.6 kg; $p < 0.001$). WHR at follow-up was significantly improved in the ADF group compared to SOC (0.91 ± 0.05 vs. 0.96 ± 0.07, $p = 0.01$. ADF group showed greater improvements in liver fat and fibrosis with CAP scores of 250 ± 3.1 vs. 297 ± 39.6 dB/m, LSM of 8.46 ± 2.0 vs. 9.2 ± 1.85kPa ($p < 0.001$), and ELF scores of 8.96 ± 0.92 vs. 9.56 ± 0.82 ($p = 0.002$). Lipid profile (TG, HDL-C, LDL-C, total cholesterol) and HbA1c showed significant improvement in the ADF group compared to SOC at follow-up (TG:165 ± 50 vs.220 ± 75; HDL-C:45 ± 8

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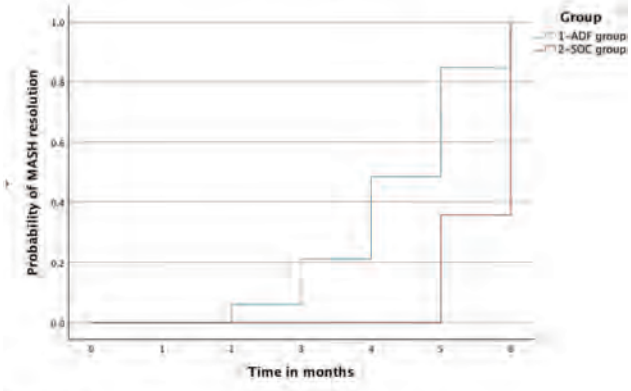
vs.38 ± 7; LDL-C:120 ± 25 vs.135 ± 30; Cholesterol:200 ± 32 vs.215 ± 41; HbA1c:6.2 ± 1.0 vs.6.9 ± 1.3; all $p \leq 0.05$). Quality of life also improved significantly in ADF group: CLDQ NASH(5.62 ± 1.0 vs. 4.07 ± 0.3), SF-36 physical component summary (PCS)(52.5 ± 9.1 vs. 43.9 ± 7.6), and mental component summary (MCS) (54.4 ± 8.5 vs. 46.2 ± 7.8); all $p < 0.001$. Bone density at the femoral neck showed no significant differences between groups at the end of the study (T score, -0.92 ± 0.52 vs. -1.01 ± 0.59; $p = 0.454$). **Conclusion:** Alternate-day fasting significantly improved liver biochemistry, fibrosis markers, weight, and quality of life in MASH patients, supporting its use as an effective lifestyle intervention.

Figure: Kaplan-Meier curve showed biochemical resolution of MASH.



Patient at risk.

	Baseline	1	2	3	4	5	6
ADF	45	45	44	42	38	28	12
SOC	45	45	45	44	43	41	36

Disclosures: Babu Lal Meena: Nothing to Disclose, Varsha Shasthry: Nothing to Disclose, Uma Kanal: Nothing to Disclose, PRATIBHA KALE: Nothing to Disclose, Omkar Rudra: Nothing to Disclose, Deepti Sharma: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Ibrar Ahmed Khan: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Suguna Sree Aakula: Nothing to Disclose

★ 0170 | IMPACT OF SEMAGLUTIDE ON CIRRHOSIS AND COMPLICATIONS IN PATIENTS WITH MASLD AND DIABETES: A RETROSPECTIVE COHORT STUDY

Ludovic Saba[1] Sarah Lieber[1] Dyanna Gregory[1] Indira Bhavsar-Burke[1] Maddie Kubiliun[2] Mark Pedersen[3] Thomas Kerr[3] Maria Rita Lepe-Suastegui[1] Lisa VanWagner[3], [1]UT Southwestern Medical Center, [2]UT Southwestern, [3]University of Texas Southwestern Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is linked to type 2 diabetes (T2DM), cirrhosis and increased mortality. Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), has demonstrated histologic benefit in a recent phase-3 trial. Whether these gains translate into improved clinical outcomes in MASLD and T2DM remains unknown. We evaluated semaglutide association with cirrhosis, decompensation, and mortality in a real-world cohort. **Methods:** We used TriNetX (2015-2025), a large-scale database comprising electronic health records from 104 U.S. healthcare organizations to compare outcomes among adults ≥ 18 years with MASLD (ICD-10 K76.0 or K75.81, excluding other liver diseases) and T2DM (E11.x) by semaglutide user status, stratified by cirrhosis status. Baseline was the first encounter with both codes, and persons with any study outcome on or before baseline were excluded. Semaglutide exposure required a first prescription ≥ 90 days after baseline without prior exposure. Propensity score matching (1:1) balancing 15 demographic/metabolic covariates was used with follow-up ascertained up to 3 years. In persons without cirrhosis, outcomes included progression to cirrhosis and incident cirrhosis complications. In cirrhosis, outcomes were composite and individual cirrhosis complications, hepatocellular carcinoma, and liver transplantation. Binary outcomes were analyzed with logistic regression, and time-to-event outcomes with Cox proportional-hazards models. **Results:** Baseline characteristics and median follow-up were well balanced after matching. Mean age was 57 (SD 13.5) and 60 (SD 13.2) years, 52.7% and 59.6% women for the non-cirrhosis and cirrhosis cohorts, respectively. In persons without cirrhosis, non-semaglutide users had roughly twice the odds of incident cirrhosis and 2.4 times higher odds of decompensation. In the cirrhosis cohort, non-semaglutide use was associated with 60% higher decompensation risk. All-cause mortality was ~4-fold higher in non-users, regardless of cirrhosis status (Table 1). **Conclusion:** In this propensity-matched, real-world cohort of > 100,000 U.S. adults with MASLD and T2DM, semaglutide use was associated with significantly lower odds of cirrhosis, fewer cirrhosis-related complications, and improved survival. These findings extend the histologic efficacy observed in recent clinical trials to clinically meaningful endpoints and support semaglutide's potential role as a disease-modifying agent in MASLD.

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Table 1 - Propensity-matched outcomes and follow up time in persons with MASLD and T2DM in semaglutide users versus non-users, stratified by cirrhosis status, TriNetX database, 2015-2025

Stratum	Outcome	No Semaglutide** N=54,704	Semaglutide** N=54,704	Effect †	95 % CI
No cirrhosis N=109,408	Median follow-up (days, Q1-Q3)	407 (65-749)	528 (195-862)	—	—
	Incident cirrhosis	1.0	0.5	OR 2.0	(1.7-2.3)*
	Composite cirrhosis complications‡	2.0	0.9	OR 2.4	(2.1-2.7)*
	Ascites	1.5	0.5	OR 2.9	(2.5-3.3)*
	Variceal bleeding	0.02	0.02	OR 1.0	(0.4-2.4)
	Jaundice	0.6	0.3	OR 1.7	(1.4-2.0)*
	Hepatic encephalopathy	0.07	0.03	OR 2.9	(1.6-5.3)*
	Hepatorenal syndrome	0.02	0.02	OR 1.1	(0.5-2.6)
	All-cause mortality	7.3	2.4	HR 4.0	(3.7-4.4)*
Stratum	**Outcome**	**No Semaglutide** N=6,998**	**Semaglutide** N=6,998**	**Effect†**	**95 % CI**
Cirrhosis N=13,996	Median follow-up (days, Q1-Q3)	335 (150-639)	489 (170-808)	—	—
	Composite cirrhosis complications‡	7.6	4.9	OR 1.6	(1.4-1.9)*
	Ascites	6.3	3.4	OR 1.9	(1.6-2.2)*
	Variceal bleeding	0.7	0.6	OR 1.2	(0.8-1.9)
	Jaundice	1.1	0.6	OR 1.8	(1.2-2.6)*
	Hepatic encephalopathy	3.7	2.6	OR 1.4	(1.2-1.8)*
	Hepatorenal syndrome	1.0	0.5	OR 2.2	(1.5-3.3)*
	Hepatocellular carcinoma	1.2	1.2	OR 1.0	(0.7-1.4)
	Liver transplantation	0.5	0.3	OR 1.5	(0.9-2.6)
	All-cause mortality	18.3	5.7	HR 4.6	(3.9-5.4)*

† Report odds ratios (OR) for binary outcomes and hazard ratios (HR) for time-to-event mortality; values > 1 indicate higher risk in non-semaglutide users (e.g., referent: semaglutide users)

‡ Defined as any variceal bleeding, ascites, jaundice, hepatic encephalopathy, or hepatorenal syndrome.

* Statistically significant

**Cohorts were matched for age, sex, race, ethnicity, BMI, HbA1c, comorbidities (chronic kidney disease, heart failure, hypertension, hyperlipidemia), smoking status, and cardio-metabolic medications (antihypertensives, oral hypoglycemics, insulin, diuretics) captured -365 to 0 days relative to index.

Disclosures: Ludovic Saba: Nothing to Disclose, Sarah Lieber: Nothing to Disclose, Dyanna Gregory: Nothing to Disclose, Indira Bhavsar-Burke: Nothing to Disclose, Maddie Kubiliun: Nothing to Disclose, Mark Pedersen: Nothing to Disclose, Thomas Kerr: Madrigal: Consultant, GSK: Grant/Research Support, Maria Rita Lepe-Suastegui: Nothing to Disclose, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support

0171 | THE IMPACT OF METABOLIC RISKS AND ALCOHOL USE ON DISEASE SEVERITY IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Background: Metabolic risks and moderate alcohol consumption can promote adverse outcomes in MASLD. Our aim was to assess the impact of components of metabolic syndrome (MS) and mild-moderate alcohol use (M/F $<60/50$ g/day) on the diagnostic performance of common non-invasive tests (NITs), (FIB-4, ELF, liver stiffness measurement (LSM) by transient elastography). **Methods:** The Global MASLD (G-MASLD) project enrolled MASLD patients with liver biopsy, clinical and NIT data. Factors associated with the presence of advanced fibrosis (F3-F4) and accuracy of common NITs for predicting advanced fibrosis were assessed. **Results:** A total of 17,643 biopsy-proven MASLD patients were included: age 51 ± 13 years, 48% male, 70% with obesity, 47% type 2 diabetes (T2D), 53% hypertension, 53% hyperlipidemia, 35% advanced fibrosis. Subjects with advanced fibrosis had more components of MS, especially T2D (Figure). In a multivariate model, only obesity and T2D were independently associated with advanced fibrosis: OR (95% CI) = 1.16 (1.07-1.26) and 2.42 (2.24-2.61), respectively (both $p < 0.01$). However, higher cumulative number of MS components was associated with a greater risk of advanced fibrosis: 23% in patients with 1 MS component, 33% with 2 MS components, 32% with 3 MS components, and 43% with 4 MS components (trend $p < 0.0001$). In a subgroup with alcohol use data ($n = 8740$, 26% advanced fibrosis), the relationship of advanced fibrosis with MS remained (trend $p < 0.0001$) and was not affected by the (self-

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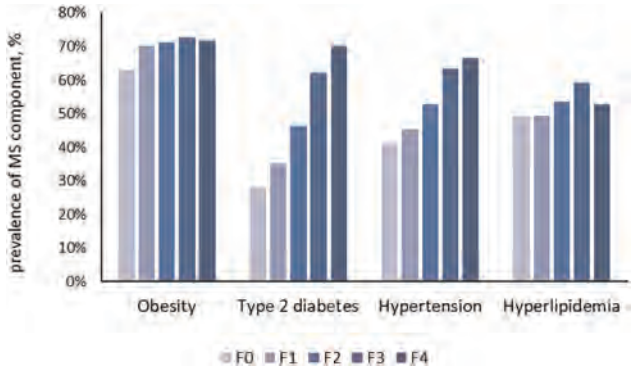
reported) amount of alcohol use beyond very low levels (25% in subjects with 0-4 g/day, 34% in 4-9 g/day, 27% in 10-20 g/day for male or 10-13 g/day for female, 36% in subjects meeting the criteria for MetALD of $\geq$21/14 g/day for male/female). The crude AUC of FIB-4 for predicting advanced fibrosis was 0.80 (0.79-0.81), significantly lower in patients with T2D (0.76 (0.75-0.77), $p < 0.01$); however, there was no significant difference by the presence of obesity or alcohol use (all $p > 0.01$). The AUC of ELF was 0.78 (0.77-0.80), not affected by obesity, alcohol use ($p > 0.05$), lower in patients with T2D (0.74 (0.72-0.76), $p < 0.01$). The AUC of LSM was 0.84 (0.83-0.85), not affected by obesity, T2D, or alcohol use (all AUC changes ≤ 0.02, all $p > 0.01$). **Conclusion:** Metabolic risks and alcohol use synergistically increase the risk of advanced fibrosis in MASLD. Except for LSM, the diagnostic accuracy of commonly used NITs for predicting advanced fibrosis may be negatively affected by T2D.



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0172 | RISK OF LIVER-RELATED EVENTS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: IMPACT OF CARDIOMETABOLIC RISK FACTOR COUNT AND ITS LONGITUDINAL CHANGES

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Background: The risk of liver-related events (LREs) varies both across individuals and over time in patients with metabolic dysfunction–associated steatotic liver disease (MASLD). This study investigated the risk of LRE in MASLD based on cardiometabolic risk factor (CMRF) count and its longitudinal changes. **Methods:** This cohort study analyzed data from a cohort of patients with MASLD who underwent vibration-controlled transient elastography (VCTE) at 16 tertiary referral centers between February 2004 and January 2023, with prospective data collection at 14 centers. Patients were stratified based on the CMRF count. Additionally, individuals who underwent follow-up examinations at 2 years after initial VCTE were categorized according to changes in their CMRF count from baseline. LRE risk was evaluated using a multivariable-adjusted Cox proportional hazards model. **Results:** Among 16,603 patients (mean [SD] age, 52.5 [13.7] years; 9600 [57.8%] were male), 316 patients (1.9%) developed LREs during a median follow-up of 51.7 months (IQR, 25.2-85.2). The risk of LREs increased gradually with a higher baseline CMRF count (1: reference; 2: HR 1.25 [95% CI: 0.78–1.98]; 3: HR 1.79 [95% CI: 1.17–2.76]; 4: HR 1.85 [95% CI: 1.19–2.86]; 5: HR 2.69 [95% CI: 1.59–4.54]; per 1-higher: HR 1.29 [95% CI: 1.15–2.90]). Among those with follow-up data, an increase in CMRF count was associated with an higher risk of LREs (per +1 change; HR 1.21 [95% CI: 1.18–1.27]), with a greater risk in those who consistently had high CMRF counts compared to those who newly developed high CMRF counts (per +1 baseline count; HR 1.23 [95% CI: 1.21–1.35]). Conversely, a reduction in CMRF count was associated with a lower risk of LREs (per -1 change; HR 0.86 [95% CI: 0.82–0.89]). **Conclusion:** Both baseline CMRF count and its longitudinal changes were significantly associated with LRE risk in MASLD.

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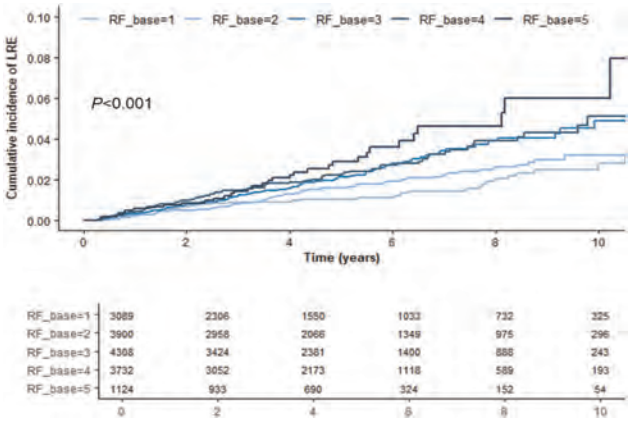

Disclosures: Hanah Lee: Nothing to Disclose, Hyung Joon Kim: Nothing to Disclose, Seung Up Kim: Nothing to Disclose

0173 | COMPARATIVE ANALYSIS OF SEMAGLUTIDE AND TIRZEPATIDE USE IN PERSONS WITH MASLD: IMPLICATIONS FOR PROGRESSION TO CIRRHOSIS AND COMPLICATIONS

Ludovic Saba[1] Sarah Lieber[1] Dyanna Gregory[1] Indira Bhavsar-Burke[1] Maddie Kubiliun[2] Thomas Kerr[1] Mark Pedersen[3] Rita Lepe[4] Lisa VanWagner[3], [1]UT Southwestern Medical Center, [2]UT Southwestern, [3]University of Texas Southwestern Medical Center, [4]UTSW Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of cirrhosis and mortality. Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), has demonstrated histologic benefit in a recent phase-3 trial. Likewise, tirzepatide, a dual gastric inhibitory peptide (GIP)/GLP-1 RA, is being investigated for MASLD, yet comparative evidence on clinical outcomes is limited. **Methods:** We used TriNetX (2015-2025), a large-scale database comprising electronic health records from 104 U.S. healthcare organizations to compare outcomes among adults ≥18 years with MASLD (ICD-10 K76.0 or K75.81). Baseline was the first MASLD encounter; persons with other liver disease or any study endpoint on/before baseline were excluded. Separate analyses were conducted for those with and without cirrhosis at baseline. We created 2 cohorts: semaglutide ≥ 90d after baseline with no exposure to tirzepatide and tirzepatide ≥ 90d after baseline with no exposure to semaglutide. Propensity score matching (1:1) balanced 12 covariates. Outcomes were ascertained for up to 3 years. In persons without cirrhosis, outcomes were progression to cirrhosis and incident composite cirrhosis complications. In cirrhosis, outcomes were composite and individual cirrhosis complications (variceal bleeding, ascites, jaundice, hepatic encephalopathy), hepatocellular carcinoma (HCC), and liver transplantation. Logistic and Cox models (HR) compared semaglutide to tirzepatide (reference), as appropriate. **Results:** Baseline characteristics and median follow-up were well balanced after matching (Table 1). The odds of developing cirrhosis did not differ between persons prescribed semaglutide (0.25%) vs. tirzepatide (0.24%) (OR 1.1, 95% CI 0.7-1.7, p = 0.74). Similarly, the odds of composite cirrhosis complications did not differ between semaglutide and tirzepatide users with (OR 1.0, 95% CI 0.8-1.3, p = 1.00) or without cirrhosis (OR 0.9, 95% CI 0.7-1.3, p = 0.72). Risks of individual complications, HCC, and liver transplantation were also similar between treatment groups. Cox regression showed no survival difference between semaglutide and tirzepatide users in those with (HR 0.55, 95% CI 0.27–1.12) and without (HR 1.04, 95% CI 0.72–1.50) cirrhosis. **Conclusion:** In this large, propensity-matched real-world cohort of persons with MASLD, semaglutide and tirzepatide users had no differences in risk of cirrhosis progression, complications, or survival, suggesting potential therapeutic equivalence for hepatic outcomes. Prospective head-to-head trials are needed to guide optimal agent selection.

Table 1. Baseline characteristics and follow-up time after propensity-score matching among persons with MASLD in semaglutide versus tirzepatide users stratified by cirrhosis status, TriNetX database, 2015-2025

Stratum	Characteristic	Semaglutide N=16,962	Tirzepatide N=16,962	Std Diff
No cirrhosis N=33,924	Median follow-up, days (Q1-Q3)	329 (159-499)	301 (151-452)	
	Age, y (mean ± SD)	54.9 ± 13.3	54.8 ± 12.8	0.007
	Female, %	61.0	60.2	0.017
	White, %	75.2	74.1	0.025
	Hispanic/Latino, %	10.2	10.5	0.012
	Black/African American, %	8.1	8.3	0.007
	Type 2 diabetes, %	51.1	51.4	0.006
	BMI, kg·m^{-2} (mean ± SD)	37.3 ± 7.7	38.0 ± 7.8	0.098
Stratum	**Characteristic**	**Semaglutide N=1,628**	**Tirzepatide N=1,628**	**Std Diff**
Cirrhosis N=3,396	Median follow-up, days (Q1-Q3)	317 (156-478)	301 (123-479)	
	Age, y (mean ± SD)	59.4 ± 12.6	58.9 ± 12.2	0.037
	Female, %	59.6	57.6	0.040
	White, %	79.7	78.2	0.036
	Hispanic/Latino, %	10.9	11.2	0.012
	Black/African American, %	4.4	4.9	0.023
	Type 2 diabetes, %	72.2	71.7	0.011
	BMI, kg·m^{-2} (mean ± SD)	36.3 ± 7.7	37.6 ± 7.8	0.171

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0174 | REAL-WORLD CLINICAL AND ECONOMIC OUTCOMES BY FIBROSIS STAGE IN PATIENTS WITH METABOLIC DYSFUNCTION–ASSOCIATED STEATOHEPATITIS (MASH)

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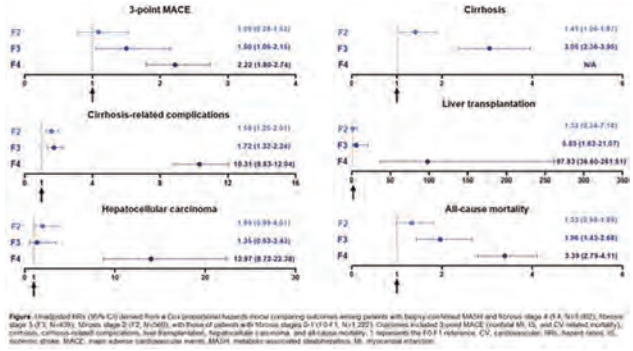
Background: Therapies for metabolic dysfunction-associated steatohepatitis (MASH) aim to improve clinically meaningful outcomes among patients with moderate to advanced fibrosis (fibrosis stages F2-F3). It is critical to better understand the real-world relationship between MASH with F2-F3 and major adverse cardiovascular events (MACE), major adverse liver outcomes (MALO), and healthcare resource utilization (HCRU). **Methods:** This retrospective cohort study used structured and unstructured data from electronic medical records of patients with biopsy-confirmed MASH at the Mayo Clinic (January 1, 2005-March 31, 2024) to compare MACE and MALO among patients stratified by histologically confirmed baseline fibrosis stages (F0-F4). A univariate Cox proportional hazards model estimated associations between fibrosis stage and time-to-event outcomes for 3-point MACE (nonfatal myocardial infarction, ischemic stroke and cardiovascular-related mortality) and MALO (cirrhosis [or related complications], hepatocellular carcinoma, liver transplant, or all-cause mortality). Per patient per month (PPPM) for HCRU categories were compared for patients stratified by F-stage. **Results:** Among 5,233 patients with biopsy-confirmed MASH (mean follow-up 7 years), 59% were female, with a mean age of 53 years. The most prevalent comorbidities were obesity (67%) and type 2 diabetes (46%). Among patients with F2, the risk (hazard ratio [HR]; 95% CI) of cirrhosis (1.41; 1.06-1.87) and related complications (1.58; 1.25-2.01) was significantly higher vs patients with F0-F1. Patients with F3 had a higher risk of 3-point MACE (1.50; 1.05-2.15) and multiple MALO, including cirrhosis (3.05; 2.36-3.96), cirrhosis-related complications (1.72; 1.32-2.24), liver transplantation (5.85; 1.62-21.07), and all-cause mortality (1.96; 1.43-2.68), vs patients with F0-F1 (Figure). HCRU did not significantly differ for patients with F2 or F3 vs patients with F0-F1. However, patients with F3 had significantly lower HCRU (PPPM) vs F4 (inpatient: 0.02 vs 0.06, $P = 0.0014$; outpatient: 0.35 vs 0.48, $P = 0.0001$; emergency room: 0.03 vs 0.06, $P = 0.0058$). **Conclusion:** Patients with F3 were at higher risk of MACE and MALO, and patients with F2 had an increased risk of MALO vs patients with F0-F1. HCRU in patients with F2 and F3 was similar to patients with F0-F1, but lower than patients with F4. Given that the risk of MACE, MALO, and HCRU increases with fibrosis severity, patients with MASH and F2-F3 may benefit from therapies targeting cardiometabolic risk factors.



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0175 | RECOMPENSATION IN MASLD AND METALD RELATED DECOMPENSATED CIRRHOSIS

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Background: Recompensation of decompensated liver disease in the spectrum of metabolic-dysfunction-associated steatotic liver disease (MASLD) and Metabolic Dysfunction-Associated Steatotic Liver Disease with Alcohol Consumption (MetALD) is largely unknown. We assessed rates of recompensation (Baveno VII criteria) and survival in such patients following one or more modifiable interventions of

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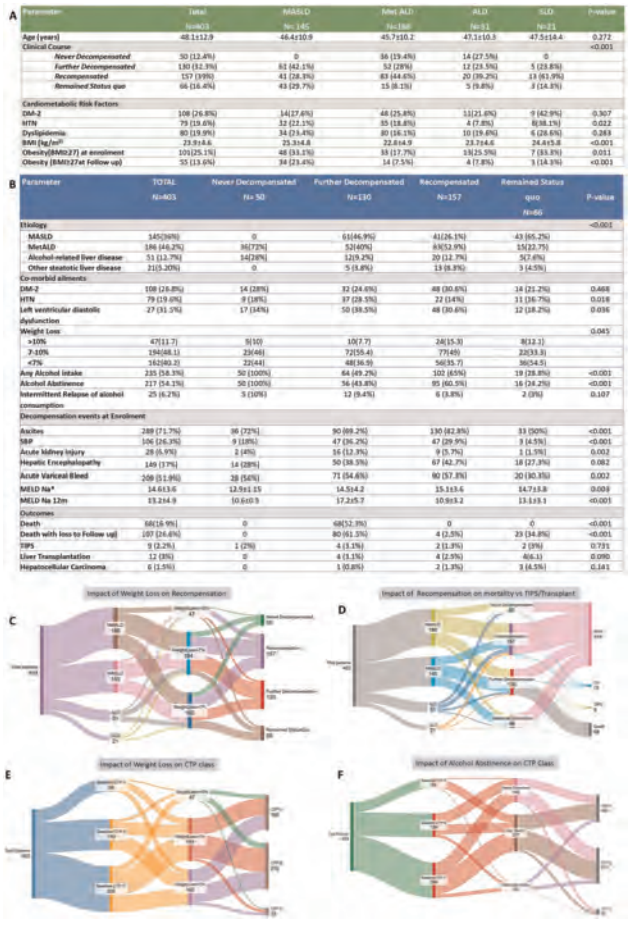
alcohol abstinence, attainment of weight loss, and amelioration of cardiometabolic risk factors. **Methods:** Between June 2021- March 2025, patients with decompensated MASLD/MetALD/ Alcohol-related cirrhosis (ALD) were evaluated with a 6-monthly follow-up for recompensation per Baveno-VII criteria, and improvement of CTP class with reduction in liver severity scores and synthetic function. Decompensation events at enrolment and at follow up were noted, with surveillance for hepatocellular carcinoma, and portal hypertension. Alcohol abstinence was confirmed by PeTH testing. **Results:** Of 403 patients with MASLD-related cirrhosis(age 53.2 ± 11.5 years,63% men, MELD-Na:16.5 ± 4.6,235 (58.3%) with any alcohol intake, 108 (26.8%) with DM-2, 79 (19.6%) with HTN, 5(1.2% with CAD, 44(10.9%) with tobacco intake. Decompensation events included ascites (294,73%), hepatic encephalopathy (138,34.2%), and variceal bleeding (182,45.2%). On follow of 30 months, 50 (12.4%) never decompensated, 130(32.3%) had further decompensation, and 66(16.4%) remained in the same CTP/MELD-Na class. *(Figure 1A-B)* Although all 235 quit alcohol consumption initially, 56(23.8%) admitted to intermittent alcohol relapse, and an additional 10(3.9%) were found to have a positive PeTH test. Recompensation occurred in 157 (39%) at a median time of 14.6(IQR-12.5-16.5) months, including 28.3%, 44.6%, 39.2% in patients with MASLD, MetALD, and ALD, respectively. ($P < 0.001$) *(Figure 1C-F)* Ascites resolved in 86% (diuretic withdrawal achieved in 39% of patients). Therapy included diet and lifestyle modification, carvedilol (307,76.2%), diuretics (347,86%), lactulose (308, 76.4%), and rifaximin (183, 45.4%). In 108 patients with DM-2, antidiabetic agents prescribed were metformin (100/108,92.6%, gliptins (47/108,43.5%), SGLT-2 inhibitors (35/108,32.4%), and insulin (22/108,20.4%). On multivariable Cox proportional hazards analysis, low bilirubin(aHR-0.8, 95% CI-0.6- 0.9,$P < 0.001$), weight loss $> 7\%$ estimated dry weight (aHR-1.6, 95% CI:1.3- 3.9, $P < 0.001$), and absence of large esophageal varices(aHR-0.4, 95% CI:0.2- 0.9, $P = 0.048$) predicted recompensation. 68(16.9%) patients died, 9(2.2%) and 12(3%) underwent liver transplant, while 6(1.5%) developed hepatocellular carcinoma. **Conclusion:** Alcohol abstinence, and sustained weight loss of $> 7\%$ estimated dry weight with supportive therapy, resulted in recompensation in 38.9% of patients over a follow-up of $>$ 2 years, with recompensation more likely in MetALD or ALD as compared with MASLD.



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0176 | VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY DYNAMICS IN THE GENERAL POPULATION: LONGITUDINAL RESULTS: FROM THE EUROPEAN LIVERSCREEN CONSORTIUM

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Chacon[3] Pere Torán[3] Sarwa Murad[1] Harry Janssen[1] Anita Arslanow[6] Aleksander Krag[7] Isabel Graupera[6] Pere Ginés[6] Maja Thiele[2] Willem Pieter Brouwer[4], *[1]Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Centre, Rotterdam, [2]Odense University Hospital, [3]Institut Universitari d'Investigació en Atenció Primària Jordi Gol, Mataró, Barcelona, Spain, [4]Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Centre, Rotterdam, [5]Centre for Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospital, [6]Liver Unit, Hospital Clínic, University of Barcelona, Barcelona, Catalonia, Spain, [7]University of Southern Denmark*

Background: Vibration-controlled transient elastography (VCTE) is widely used to screen for liver fibrosis, but the incidence and predictors of significant liver stiffness measurement (LSM) changes in the general population are unknown. **Methods:** In this prospective, multicenter cohort study from the European LiverScreen project, we analyzed longitudinal LSM data from three population-based cohorts (Barcelona, Rotterdam and Odense). Participants underwent baseline and follow-up VCTE, alongside questionnaires, anthropometric and laboratory standardized assessments. Clinically significant LSM change was defined as a $\geq$30% increase or decrease from baseline and crossing the 8 kPa threshold (incident fibrosis). Logistic regression models were adjusted for age, sex, baseline LSM, cohort, and follow-up duration. Here we report on the main longitudinal results and (dynamic) factors associated with LSM changes. **Results:** Of 7,884 participants with a valid baseline LSM, 4,536 had follow-up data (median follow-up 4.3 years, IQR 4.1–8.4 years, 24,907 person-years). The follow-up cohort had a median age of 62 years [56-68] and 52% were females. At baseline, 5.5% (251/4,536) had an LSM $\geq$8 kPa, of which 43% (110/251) experienced a clinically significant decrease during follow-up. Of those with a $<$8 kPa LSM at baseline, 2.6% (112/4,258) developed incident fibrosis with 54% (61/112) of these participants increasing to $\geq$10kPa at follow-up. Baseline obesity (aOR 2.66 95% CI: 1.38-5.12), alcohol risk consumption (aOR 1.80 95% CI: 1.07-3.03), diabetes (aOR 1.90 95% CI: 1.16-3.10), and increased ALT (aOR 2.42 95%CI: 1.50-3.89) independently predicted a clinically significant LSM increase, as did an increase in serum fasting glucose (aOR 2.94, 95% CI: 1.70-5.07) or ALT (aOR 2.49, 95% CI: 1.40-4.42) from $<$upper limit of normal (ULN) to $\geq$ULN during follow-up. Conversely, the presence diabetes was a negative predictor for significant LSM decrease (aOR 0.49, 95% CI: 1.10-1.91). **Conclusion:** In this large, prospective, population-based European study, we observed a 2.6% 4-year incidence of liver fibrosis. Baseline metabolic dysfunction and elevated ALT were independent predictors of liver stiffness progression, while type 2 diabetes significantly reduced the likelihood of improvement. These findings support targeted fibrosis screening in individuals with metabolic risk factors and alcohol overuse and suggest that a 4-year screening interval may be appropriate for the general population.

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0177 | SUBTYPING METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE USING ELECTRONIC HEALTH RECORD-LINKED GENOMIC COHORTS REVEALS DIVERSE ETIOLOGIES AND PROGRESSION

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), affecting over 25% of the global population, presents challenges for pharmacotherapy due to its heterogeneity. Stratifying MASLD into reproducible, homogeneous subgroups can advance precision medicine and elucidate mechanisms underlying differential disease progression. **Methods:** Patient cohorts were derived from two population genomics studies: the Mayo Clinic Biobank and the Tapestry Study (Cohorts A and B). Cohort A (5,544 cases) was divided into development and validation sets (75:25, A1:A2), while Cohort B (4,079 cases) served as an independent validation cohort. Subgroups were identified in Cohort A1 using model-based latent class analysis (LCA) with 13 selected clinical variables and validated across other cohorts. Three methods for assigning new patients to subgroups were applied: distance-, density-, and probability-based models. Longitudinal electronic health records (EHRs) were analyzed to assess subgroup-specific disease progression and treatment response over a 10-year follow-up. **Results:** Five MASLD subgroups were identified in the cohort A1: C1 (non-obese cardiometabolic MASLD), C2 (male-predominant cardiorenal MASLD), C3 (female-predominant obese mood-disorder MASLD), C4 (idiopathic MASLD), and C5 (polygenic MASLD with high hepatitis), each defined by unique genetic, clinical, and metabolic profiles. Subgroup C4 showed a high liver transplantation rate and was enriched for HCC risk variants. Subgroup C5, characterized by high polygenic risk scores, exhibited elevated liver enzymes and increased risks of fibrosis and cirrhosis, alongside pronounced metabolic traits like obesity, T2D, and kidney disease, distinguishing it from C4. Longitudinal EHRs revealed subgroup-specific disease progression patterns, including cardiometabolic (C2), psycho-neurological (C3), and liver-specific (C5) events, highlighting MASLD's interindividual variability and the need for tailored, subgroup-specific therapeutic strategies (Figure 1). **Conclusion:** The analysis identified five MASLD subtypes with distinct clinical and genetic signatures. New patient assignment models were applied, with the distance-based approach demonstrating the highest accuracy. Longitudinal data analysis underscored the clinical value of disease subtyping, providing mechanistic insights into phenotypic heterogeneity and highlighting the need for personalized therapeutic strategies.

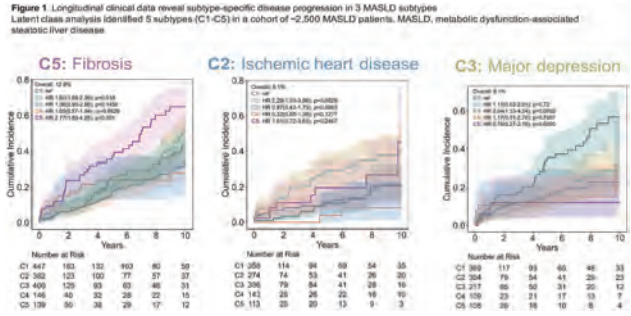

Figure 1. Longitudinal clinical data reveal subtype-specific disease progression in 3 MASLD subtypes
Latent class analysis identified 5 subtypes (C1-C5) in a cohort of ~2,500 MASLD patients. MASLD, metabolic dysfunction-associated steatotic liver disease

Disclosures: Shulan Tian: Nothing to Disclose, Tahmina Priya: Nothing to Disclose, Huihuang Yan: Nothing to Disclose, Kirk Wangensteen: Nothing to Disclose, Alina Allen: Novo Nordisk: Grant/Research Support, Novo Nordisk: Advisor, Target Pharma: Grant/Research Support, Pfizer: Grant/Research Support, Boehringer Ingelheim: Advisor, Madrigal: Advisor, GSK: Advisor, Oncoustics: Grant/Research Support, Escopics: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Madrigal: Grant/Research Support, Siemens: Grant/Research Support, Konstantinos Lazaridis: Nothing to Disclose, Danfeng Yao: Nothing to Disclose, Eric Klee: Nothing to Disclose

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0178 | HSD17B13 RS72613567 VARIANT IS ASSOCIATED WITH HISTOLOGICAL PROGRESSION AND REGRESSION IN MASLD AND IT ALSO SIGNIFICANTLY MODIFIES THE EFFECT OF BMI CHANGE ON LIVER HISTOLOGY

Eduardo Vilar-Gomez[1] Katherine Yates[2] Tiebing Liang[1] Chaowapong Jarasvaraparn[1] Laura Wilson[2] David Kleiner[3] Arun Sanyal[4] Rohit Loomba[5] Naga Chalasani[6], [1]Indiana University School of Medicine, [2]Johns Hopkins University, [3]National Cancer Institute, Bethesda, [4]Virginia Commonwealth University, [5]University of California, San Diego, [6]Indiana University Medical Center

Background: *HSD17B13* rs72613567 variant has been linked to reduced inflammation and fibrosis in MASLD, however, its association with longitudinal histology changes remains unexplored. We aimed to examine relationships between *HSD17B13* rs72613567 and long-term liver histology outcomes in MASLD. **Methods:** We evaluated 671 participants (444 adults, 227 children) with biopsy-proven MASLD and ≥2 biopsies from NASH-CRN studies with a follow-up period limited to 10 years. Liver biopsies were assessed by experienced pathologists in a blinded fashion. Histology ***progression*** was defined as MASL to MASH or ≥1-point fibrosis increase; ***regression*** as MASH to MASL without fibrosis worsening or ≥1-point fibrosis decrease without MASH worsening. Interval-censored Cox models examined *HSD17B13* associations (additive model) with histological outcomes, adjusted for race/ethnicity, sex, *PNPLA3* rs738409, *TM6SF2* rs58542926, BMI, T2DM, and study design clusters. **Results:** *HSD17B13*-A allele frequency was 16%. *HSD17B13*-A allele was associated with lower MASL (aHR: 0.46) and fibrosis (aHR: 0.69) progression, and higher MASH resolution (aHR: 1.58) and fibrosis regression (aHR: 1.42) ($P < 0.05$ for all). BMI increase from baseline was associated with higher MASL (aHR: 1.06) and fibrosis (aHR: 1.06) progression, while BMI decrease was associated with higher MASH resolution (aHR: 1.17) and fibrosis regression (aHR: 1.15) ($P < 0.05$ for all) (Figure). Relationships between *HSD17B13*, BMI, and histology changes showed the same directionality among children and adults. *HSD17B13*-A allele carriage significantly modified the relationship between BMI change from baseline and histology progression and regression. Among A allele carriers, the risk of MASL (at A-allele: 1.05 vs non-A allele: 1.09, $P < 0.05$) and fibrosis (at A-allele: 1.04 vs non-A allele: 1.06, $P < 0.05$) progression due to BMI increase was significantly attenuated compared to non-A allele carriers. Similarly, among A allele carriers, the likelihood of MASH (at A-allele: 1.25 vs non-A allele: 1.03, $P < 0.05$) and fibrosis (at A-allele: 1.13 vs non-A allele: 1.08, $P < 0.05$) regression due to BMI decrease was significantly higher. **Conclusion:** *HSD17B13* rs72613567 is associated with histological progression and regression in MASLD and it also significantly modifies the effect of BMI change on liver histology, suggesting a crucial gene-environment interaction influencing disease trajectory.

Figure. Associations between *HSD17B13* rs72613567, changes in BMI from baseline, and histology outcomes.

	Histology progression			
	MASL to MASH (N=263) [a]		Adjusted Hazard Ratio (95% CI) [e]	P value
	No (N=182)	Yes (N=81)		
HSD17B13 A allele [d]	45 (25)	18 (22)	0.46 (0.29-0.73)	<0.001 [f]
BMI (kg/m²) change [h]	1.51 ± 3.74	2.23 ± 3.38	1.06 (1.04-1.08)	<0.001 [f]
	Fibrosis ≥1 (N=585) [b]		Adjusted Hazard Ratio (95% CI) [e]	P value
	No (N=415)	Yes (N=170)		
HSD17B13 A allele [d]	133 (32)	40 (23)	0.69 (0.51-0.92)	0.014 [f]
BMI (kg/m²) change [h]	0.71 ± 3.42	1.46 ±3.39	1.06 (1.04-1.08)	<0.001 [f]
	Histology regression [c]			
	MASH to MASL (N=322) [c]		Adjusted Hazard Ratio (95% CI) [e]	P value
	No (N=205)	Yes (N=117)		
HSD17B13 A allele [d]	55 (27)	48 (41)	1.58 (1.13-2.22)	0.008 [f]
BMI (kg/m²) change [h]	0.88 ± 3.03	-1.00 ± 3.06	1.17 (1.12-1.24)	<0.001 [f]
	Fibrosis ≥1 (N=513) [d]		Adjusted Hazard Ratio (95% CI) [e]	P value
	No (N=323)	Yes (N=190)		
HSD17B13 A allele [d]	89 (28)	64 (34)	1.42 (1.09-1.85)	0.005 [f]
BMI (kg/m²) change [h]	0.99 ± 3.22	-0.70 ± 3.38	1.15 (1.12-1.18)	<0.001 [f]

[a] It includes participants with MASL at baseline. [b] It includes participants with baseline fibrosis stages from 0 to 3. [c] It includes participants with MASH at baseline. [d] It includes participants with baseline fibrosis stages from 4 to 1. [e] Interval-censored Cox models adjusted for race/ethnicity, sex, *PNPLA3*, *TM6SF2*, age, BMI, T2DM, baseline scores (fibrosis or NAFLD activity score for fibrosis or MASL/MASH outcomes, respectively) and study design clusters. [f] Benjamini-Hochberg adjusted p-values < 0.05. [g] Risk estimates calculated under additive genetic models. [h] Changes from baseline, and risk estimates represent BMI increases for histology progression and BMI decreases for histology regression.

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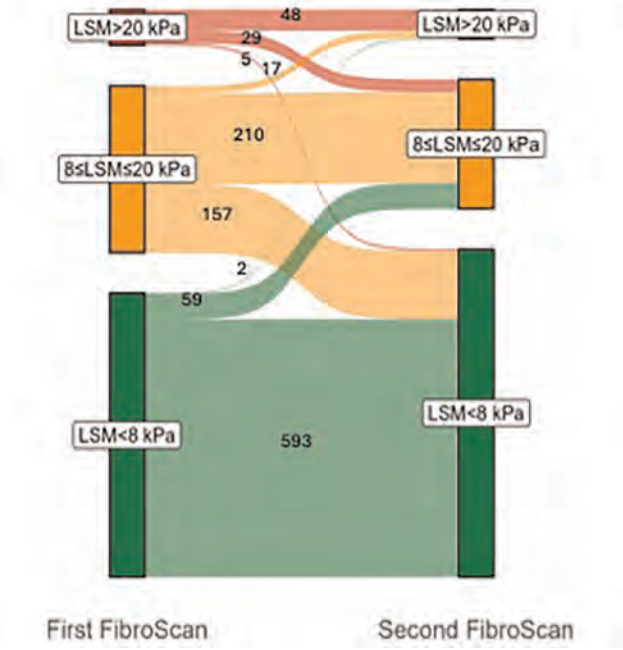
0179 | THE USEFULNESS OF REPEATING LSM BY VCTE FOR SELECTING MASLD PATIENTS FOR PHARMACOLOGICAL TREATMENT: RESULTS: IN A LARGE REAL-WORLD COHORT OF PATIENTS

Helene Fontaine[1] Tiphaine Vidal-Trécan[2] Yelena Schwartz[2] Jean-Baptitste Julla[2] Jean-Plerre Riveline[2] Vanessa Esnault[1] Dominique Valla[1] Jean-Francois Gautier[2] Laurent Castera[1], [1]Dept of Hepatology, Hopital Beaujon, AP-HP, Clichy, France, [2]Dept of Diabetology, Hopital Lariboisière, AP-HP, Paris, France

Background: Liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) is currently recommended by AASLD guidance to select patients with MASH F2F3 for pharmacological treatment when LSM is ≥8 and ≤20 kPa. However, repeating VCTE has been suggested for these patients to reduce false positives, though data on LSM variability is scarce. We examined LSM variability over one year and tested whether repeating VCTE increases the accuracy of diagnosing fibrosis stage F2F3. **Methods:** Among a large cohort of MASLD patients from two academic centers, 1,120 patients (age 59±12 years; 42.6 % female; median BMI 30.3 (7.5) kg/m2; LSM 7.1 (5.3) kPa; CAP 299.0 (75.0) dB/m) with two valid VCTEs (≥ 10 valid measurements) within one year were selected for the study of LSM variability. A subgroup of 110 patients who underwent two VCTEs followed by a. liver biopsy (LB) within one year (median (IQR) interval between the second VCTE and LB: 3.5 (56.8) days) was also evaluated. Factors associated with LSM variability were assessed. **Results:** The within-subject coefficient of variation (wCV) for LSM was 25.6% [95% CI: 23.8-27.2] among the 1,120 patients and 26.9% [22.8-30.4] among the 110 patients with LB. Most patients remained within the same LSM value category at the second VCTE (Figure). Among the 384 patients with suspected F2F3 (LSM ≥8 and ≤20 kPa) at baseline, 157 (41%) returned to an LSM <8 kPa at the second VCTE. Meanwhile, 29 of the 77 patients (38%) with an LSM >20 kPa returned to an LSM between 8 and 20 kPa. Multivariate analysis revealed that change in LSM was associated with change in CAP and BMI, and the time interval between the two VCTEs. Of the 110 patients with a LB, the highest AUC value for diagnosing F≥2 (65%) was obtained when relying on the lowest of the two LSM values: 0.84 [0.76-0.92] vs. 0.78 [0.69-0.87] for the first VCTE and 0.79 [0.70-0.88] for the second. Of the 56 patients qualified for treatment (LSM 8-20 kPa according to the lowest LSM), 36 (72%) were classified as F2-F3 with LB. However, 21 (39%) of the 54 patients not qualifying for treatment (LSM <8 kPa or >20 kPa) were F2-F3 and would have been missed. **Conclusion:** In a large, real-world cohort of 1,120 patients with MASLD and two VCTEs, LSM variability over one year was 25.6%, which was associated with change in CAP and BMI. Repeating VCTE and using the lowest LSM value enables more accurate selection of MASLD patients with F2F3 for treatment.

Figure. Changes in LSM categories (LSM 8-20 kPa: eligible for pharmacological treatment; LSM <8 or >20 kPa: not eligible) over 1 year in 1,120 MASLD patients (Sankey diagram)



Disclosures: Helene Fontaine: Gilead: employee until october 2023, Tiphaine Vidal-Trécan: Grunenthal: Speaking and Teaching, Novo Nordisk: Consultant, Eli Lilly: Consultant, Grunenthal: Consultant, Astra Zeneca: Speaking and Teaching, Yelena Schwartz: Nothing to Disclose,

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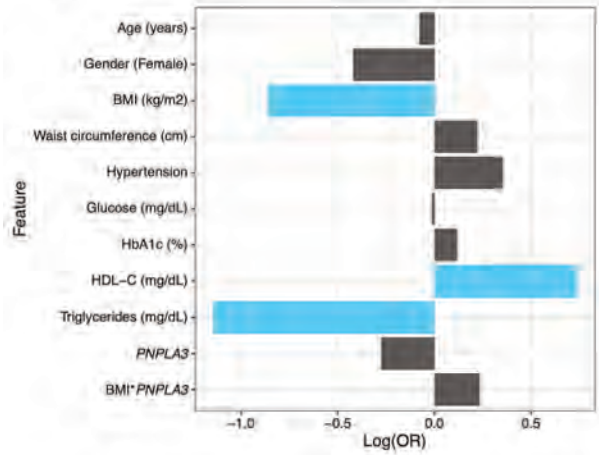
0180 | PROTECTIVE FACTORS AGAINST LIVER DISEASE DEVELOPMENT IN TYPE 2 DIABETES: A PROSPECTIVE STUDY INTEGRATING LONGITUDINAL MRI/MRE IMAGING AND STABLE ISOTOPE TRACING

Federica Tavaglione[1] Veeral Ajmera[1] Luis Díaz[2] Kelvin Li[3] Egbert Madamba[1] Ricki Bettencourt[1] Lisa Richards[1] Marc Hellerstein[3] Rohit Loomba[1], [1]University of California San Diego, [2]Pontificia Universidad Católica de Chile, [3]University of California Berkeley

Background: Type 2 diabetes is the strongest factor contributing to the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD). Approximately two-thirds of individuals with type 2 diabetes have MASLD, and about 1 in 6 show evidence of advanced fibrosis. Within this context, encountering someone with type 2 diabetes who does not have MASLD is infrequent, even more so if they remain free of liver disease over time. Herein, we aimed to identify factors associated with hepatoprotection in a prospective cohort of individuals with type 2 diabetes and longitudinal MRI/MRE imaging. **Methods:** This prospective study included 148 individuals with type 2 diabetes who underwent a standardized clinical research visit, including MRI/MRE imaging, at baseline and 2-year follow-up. Hepatoprotection was defined as individuals not having steatosis (MRI-PDFF $< 5\%$) and significant fibrosis (MRE < 3 kPa) at both time points. Factors associated with hepatoprotection were assessed using Firth's penalized logistic regression. As complementary analyses, regularized logistic regression models were fitted using Least Absolute Shrinkage and Selection Operator (LASSO), Ridge, and Elastic Net approaches. **Results:** The mean (SD) age and body mass index (BMI) were 65 (8) years and 30.4 (4.3) kg/m^2, respectively. After a median follow-up of 2 (1.5-2.4) years, 27 (18%) individuals demonstrated hepatoprotection. These individuals had lower BMI and waist circumference, lower liver enzymes, and a more favorable lipid profile ($p < 0.05$). No hepatoprotected individuals were homozygous carriers of the *PNPLA3* I148M risk allele. Across all modeling approaches, lower BMI (OR 0.82, 95% CI 0.66–0.99; $p = 0.036$), lower circulating triglycerides (OR 0.98, 95% CI 0.97–0.99; $p = 0.002$), and higher HDL cholesterol (OR 1.06, 95% CI 1.02–1.11; $p = 0.006$) consistently emerged as the strongest predictors of hepatoprotection (Figure). To explore potential biological mechanisms, an exploratory analysis was performed in 11 individuals with type 2 diabetes and de novo lipogenesis (DNL) quantified by stable isotope tracing, revealing reduced hepatic DNL in those free from liver disease ($p < 0.05$). **Conclusion:** Managing modifiable risk factors, such as body weight and lipid profile, may be critical for preventing MASLD development and progression in individuals with type 2 diabetes.

Figure: Factors associated with protection against liver disease development in individuals with type 2 diabetes.



Log odds ratios (log[OR]) were estimated using Firth logistic regression, with hepatoprotection as the dependent variable. The bar plot displays the strength and direction of the association between each trait and the dependent variable. Positive log(OR) values indicate a direct association, whereas negative values indicate an inverse association. The magnitude of the log(OR) reflects the strength of the relationship. Predictors shown in blue were statistically significant in the model ($p<0.05$). For continuous predictors, effect sizes are presented as log(OR) for standardized variables (z-scores) to allow comparison across predictors. The corresponding odds ratios and confidence intervals from the unstandardized model are reported in the abstract text. The same significant predictors were consistently selected across all other logistic regression models (LASSO, Ridge, and Elastic Net).

Disclosures: Federica Tavaglione: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Luis Díaz: Nothing to Disclose, Kelvin Li: Nothing to Disclose, Egbert Madamba: Nothing to Disclose, Ricki Bettencourt: Nothing to Disclose, Lisa Richards: Novo Nordisk: Advisor, Madrigal: Advisor, Marc Hellerstein: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM

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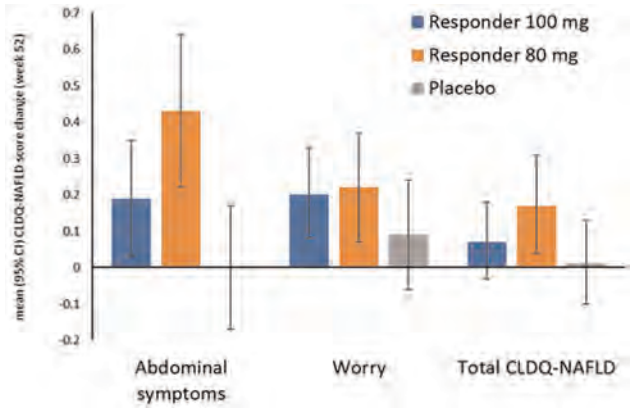
0181 | IMPROVEMENT IN HEALTH-RELATED QUALITY OF LIFE AFTER TREATMENT WITH RESMETIROM IN CIRRHOTIC AND NON-CIRRHOTIC PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: DATA FROM MAESTRO-NAFLD

Zobair Younossi[1] Fatema Nader[2] Dominic Labriola[3] Rebecca Taub[4] Andrei Racila[1] Maria Stepanova[1], [1]The Global NASH Council, [2]Center for Outcomes Research in Liver Diseases, CORLD, [3]Madrigal Pharmaceutical, [4]Madrigal Pharmaceuticals

Background: Resmetirom is approved for treatment of F2-F3 metabolic dysfunction-associated steatohepatitis (MASH) in the United States. Our aim was to assess health-related quality of life (HRQL) in metabolic dysfunction steatotic liver disease (MASLD) patients with and without cirrhosis treated with resmetirom in MAESTRO-NAFLD clinical trial. **Methods:** MASLD patients with cirrhosis (CP-A) or MASLD without cirrhosis were enrolled in a 52-week, Phase 3 double-blind placebo-controlled study of resmetirom (Period 1 of MAESTRO-NAFLD) and upon treatment completion, were offered to enroll in a 52-week open-label extension study of resmetirom (Period 2). HRQL was assessed using LDQOL, CLDQ-NAFLD and WPAI throughout treatment Period 1 (baseline, week 24, week 52) and treatment Period 2 (day 1, week 12, week 28, week 52). For non-cirrhotic MASLD, PDFF response was defined as a decrease in MRI-PDFF $\geq$30% from baseline while for cirrhotic MASLD, it was defined as $\geq$20% decrease in MRI-PDFF (if baseline MRI-PDFF $>$5%). **Results:** MAESTRO NAFLD included 1307 MASLD patients (combined double-blind placebo-controlled mITT and open-label groups). Of these, 193 with cirrhosis (23% with baseline MRI-PDFF $\leq$5%) and 1114 were without cirrhosis (baseline MRI-PDFF $\geq$8%). At baseline, HRQL scores of patients with cirrhosis were significantly lower (up to -16% of score range) for all 6 domains of CLDQNAFLD, 14/17 domains of LDQOL, Activity Impairment of WPAI ($p < 0.05$). Among patients with cirrhosis, there was no significant difference in baseline HRQL scores between those with MRI-PDFF $\leq$5% and $>$5% (all $p > 0.05$). In patients with cirrhosis, by week 24 of treatment with resmetirom during Period 1, there were improvements in Worry (CLDQ-NAFLD) and Health Distress (LDQOL) up to +4% of score range which sustained by week 52 and throughout Period 2 (day 1, week 12, week 28) ($p < 0.05$). In cirrhotic subjects with MRI-PDFF $>$5%, PDFF response by Period 1 week 52, there was an improvement in Stigma score (LDQOL): mean change (+4.0 vs. -5.7, $p = 0.011$). By weeks 24 and 52 of treatment, non-cirrhotic patients receiving placebo experienced worsening of HRQL in some physical health-related domains of LDQOL (mean decrease up to -5%; $p < 0.05$) while no decreases were observed in non-cirrhotic patients treated with resmetirom. In addition, non-cirrhotic patients receiving resmetirom experienced improvement in Abdominal and Worry domains of CLDQ-NAFLD and Health Distress of LDQOL (mean increase up to +5% of score range size); no similar improvements were observed in placebo (all $p > 0.05$). Noncirrhotic patients with PDFF response experienced improvements in Abdominal and Worry scores (up to +7%) which were greater than those seen in placebo or non-responders (Figure). **Conclusion:** Patients without or with cirrhosis due to MASLD treated with resmetirom experience sustained improvement in select disease-specific HRQL scores.



Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, Fatema Nader: Nothing to Disclose, Dominic Labriola: Nothing to Disclose, Rebecca Taub: Nothing to Disclose, Andrei Racila: Nothing to Disclose, Maria Stepanova: Nothing to Disclose

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0182 | RELATIONSHIP OF DIURNAL EATING BEHAVIORS AND INCIDENT MASLD AND CIRRHOSIS IN A POOLED ANALYSIS OF THREE LARGE PROSPECTIVE COHORTS

Robert Wilechansky[1] Kevin Casey[2] Andrew Chan[2] Tracey Simon[2], [1]Oregon Health & Science University, [2]Massachusetts General Hospital

Background: MASLD and cirrhosis have become pressing public health issues, and preventive efforts are critical. Prior studies have suggested benefit of certain diets and diurnal eating patterns for the prevention of diabetes and cardiovascular disease. It is known that the liver has an intrinsic circadian clock that regulates metabolism; less is certain about how diurnal variations in eating behaviors impact the development of MASLD and cirrhosis. **Methods:** We conducted a prospective study of participants without baseline liver disease enrolled in three large US cohorts: the Nurses' Health Study I and II and the Health Professionals Follow-Up Study. Participants completed validated questionnaires every 2-4 years assessing demographics, dietary habits, and medical diagnoses. In this study, participants were grouped into categories based on exposure status, including eating late at night, skipping breakfast, and the number of times eating per day. The primary outcome was physician-diagnosed incident cirrhosis, and the secondary outcome was incident MASLD; both were self-reported. Cox proportional hazard models with time-varying exposure data were used to estimate multivariable (MV)-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for incident MASLD and cirrhosis. Models were adjusted for age, cohort, BMI, daily caloric intake, diabetes mellitus, dyslipidemia, smoking, weekly physical activity, alcohol use, and adherence to the Alternate Healthy Eating Index (AHEI). **Results:** Among 199,155 participants, a total of 312 incident cirrhosis cases and 4,477 incident MASLD cases were reported over a median 16 years of follow-up. The full cohort comprised 78% women with median age 59 years, 22% with obesity (BMI > = 30), and 5% with diabetes mellitus. Baseline characteristics were well-balanced between exposure groups. In MV-adjusted models, late-night eating was associated with an increased risk of incident cirrhosis (aHR 1.28, 95% CI 1.02-1.62, p-trend = 0.036) and incident MASLD (aHR 1.31, 95% CI 1.24-1.39, p-trend < 0.001). In age-adjusted models, skipping breakfast (aHR 1.51, 95% CI 1.05-2.16, p-trend = 0.03) and eating 1-2 times per day (aHR 1.75, 95% CI 1.15-2.67, p-trend = 0.006) were associated with increased cirrhosis risk; these effects were not seen in MV-adjusted models. In age-adjusted models, eating five or more times per day (aHR 1.21, 95% CI 1.12-1.32, p-trend = < 0.001) was associated with increased MASLD risk; this effect was not seen in MV-adjusted models. Skipping breakfast was not associated with incident MASLD. Results were consistent across subgroups stratified by median AHEI score and BMI category. **Conclusion:** In a pooled analysis of three large, well-phenotyped prospective cohorts, eating late at night was associated with increased risk of incident MASLD and cirrhosis after accounting for multiple factors. Confirmatory studies may impact nutrition guidelines in chronic liver disease.

Table 2. Eating Behaviors and Risk of Cirrhosis

	Cases/Person-Years	Age-Adjusted HR (95% CI)	*MV-Adjusted HR (95% CI)
Late Night			
No	165/2,077,043	1.00	1.00
Yes	147/1,032,978	1.60 (1.28, 2.00)	1.28 (1.02, 1.62)
p-trend		<0.001	0.036
Skip Breakfast			
No	278/2,844,222	1.00	1.00
Yes	34/265,800	1.51 (1.05, 2.16)	1.10 (0.76, 1.59)
p-trend		0.026	0.629
Times Eating/Day			
1 to 2	30/197,571	1.75 (1.15, 2.67)	1.57 (1.03, 2.41)
3	79/923,474	1.00	1.00
4	113/1,089,460	1.03 (0.77, 1.38)	1.07 (0.80, 1.43)
5+	90/899,516	0.83 (0.61, 1.12)	0.92 (0.67, 1.26)
p-trend		0.006	0.090

*Adjusted for age, cohort, BMI, caloric intake, DM, high cholesterol, smoking, physical activity, alcohol use, AHEI

Table 3. Eating Behaviors and Risk of MASLD

	Cases/Person-Years	Age-Adjusted HR (95% CI)	*MV-Adjusted HR (95% CI)
Late Night			
No	2,331/2,074,554	1.00	1.00
Yes	2,146/1,030,805	1.57 (1.48, 1.67)	1.31 (1.24, 1.39)
p-trend		<0.001	<0.001
Skip Breakfast			
No	4,183/2,839,886	1.00	1.00
Yes	314/265,473	0.96 (0.86, 1.08)	0.98 (0.87, 1.10)
p-trend		0.505	0.723
Times Eating/Day			
1 to 2	225/197,343	1.06 (0.91, 1.22)	1.05 (0.90, 1.21)
3	852/922,582	1.00	1.00
4	1,515/1,087,886	1.11 (1.02, 1.21)	0.99 (0.91, 1.08)
5+	1,885/897,548	1.21 (1.12, 1.32)	1.06 (0.98, 1.15)
p-trend		<0.001	0.192

*Adjusted for age, cohort, BMI, caloric intake, DM, high cholesterol, smoking, physical activity, alcohol use, AHEI

Disclosures: Robert Wilechansky: Nothing to Disclose, Kevin Casey: Nothing to Disclose, Andrew Chan: Nothing to Disclose, Tracey Simon: Nothing to Disclose

★ 0183 | HEPATOCYTE-MACROPHAGE CROSSTALK REWIRES LIVER ZONATION FEATURES IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Hanyang Liu[1] Shuai Chen[2] Dabao Shang[3] Xiaogang Xiang[3] Frank Tacke[4] Adrien Guilot[4], [1]Charité – Universitätsmedizin Berlin, [2]The Third Affiliated Hospital of Nanjing Medical University, China, [3]Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, [4]Charite - Universitatsmedizin Berlin

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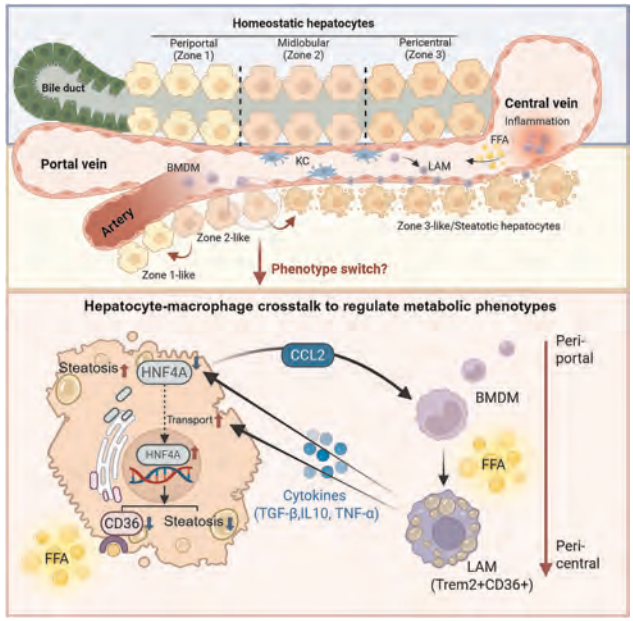
Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is among the most prevalent chronic liver diseases globally, significantly contributing to liver malignancies. As is known, hepatocytes play predominant roles in liver homeostasis and diseases. The spatial heterogeneity of hepatocytes is classified into periportal (PP), midlobular (ML), and pericentral (PC) zones, each with distinct metabolic, regenerative, and inflammatory roles, a concept known as liver zonation. Simultaneously, liver macrophages (including Kupffer cells and infiltrating macrophages) act as key but multifaceted regulators in MASLD, widely participating in metabolism, inflammation, fibrosis and regeneration. Responding to steatotic (mainly lipid) stress, macrophages acquire lipid-associated phenotypes and function as disease promoters through interactions with liver cells. However, the mechanisms of hepatic zonal regulation and hepatocyte-macrophage interactions in MASLD remain unclear. **Methods:** This study implemented the transcriptomic and metabolomic analyses on MASLD patients' livers with single-cell and spatial resolution, to decipher metabolic phenotypes and cellular interactions of hepatocytes. Mouse models with MASLD (fed with choline-deficient, L-amino acid-defined, high-fat diet) and macrophage depletion (injected with clodronate-liposome) were constructed, coupled with hepatocyte-specific genetic modification (administered by adeno-associated virus). Then, the multiplex immunofluorescent staining was employed to elucidate alterations of hepatocyte-macrophage interactions and liver zonation features. Lastly, primary mouse hepatocytes and bone marrow-derived macrophages were utilized to verify specific functions and mechanisms under the interaction. **Results:** This study revealed that PC metabolic features override PP with the progression of liver steatosis. In contrast to PP and PC, ML hepatocytes exert excessive lipid and carbohydrate metabolic capacities. Exclusively in ML hepatocytes, *HNF4A* expression was upregulated with MASLD progression but downregulated with steatosis remission. Impaired hepatic HNF4A functions led to upregulation of CD36 and CCL-2, exacerbating liver steatosis and macrophage infiltration. Lipid-associated macrophages reshaped the balance of PP-PC metabolic features by regulating HNF4A functions in hepatocytes. Furthermore, enhancing hepatic *Hnf4a* expression restored metabolic features, ameliorating steatosis and macrophage-driven inflammation in the liver. **Conclusion:** This study demonstrated a novel mechanism of hepatocyte-macrophage interaction, highlighting liver zonation as a pathological factor in MASLD progression. Hepatic HNF4A emerges as a pivotal microenvironmental regulator, providing therapeutic potential in restoring liver metabolic functions and mitigating liver inflammation of MASLD.



Disclosures: Hanyang Liu: Nothing to Disclose, Shuai Chen: Nothing to Disclose, Dabao Shang: Nothing to Disclose, Xiaogang Xiang: Nothing to Disclose, Frank Tacke: Nothing to Disclose, Adrien Guilot: Nothing to Disclose

★ 0184 | SEXUALLY DIMORPHIC PALMITOYLATION OF UTY OF LIVER SINUSOIDAL ENDOTHELIAL CELLS DRIVES ADVANCED METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) VIA PGF2Α/SPIN1 AXIS

Ruiqi Li[1] Xixuan Wang[1] Jun Guo[2] Hao Ren[1] TianHao Mao[3] Caiyun Zhang[3] Zihao Liang[4] Dawei Yang[4] Yuzheng Zhuge[5] Feng Zhang[5] Wei Chen[4] Changhua Yi[4] Qingfang Xiong[1] Shuling Chen[1] Wei Zhang[5] YongFeng Yang[1], [1]The Second Hospital of Nanjing, Medical School, Southeast University, [2]The Second Hospital of Nanjing, [3]Nanjing Key Laboratory of Hepatology, The Second Hospital of Nanjing, [4]The Second Hospital of Nanjing, Affiliated to Nanjing University of Chinese Medicine, [5]Nanjing Drum Tower Hospital, Medical School, Southeast University

Background: The pronounced male predominance in advanced metabolic dysfunction-associated steatohepatitis (MASH) remains mechanistically undefined beyond hormonal influences. Here, we identify a Y chromosome-encoded epigenetic circuit centered on UTY (ubiquitously transcribed tetratricopeptide repeat-containing protein Y-linked) that orchestrates sex-specific MASH through metabolic reprogramming of liver sinusoidal endothelial cells (LSECs). **Methods:** Utilizing endothelial-specific Uty knockout (Uty EC-CKO) male mice subjected to GAN diets for 20 weeks

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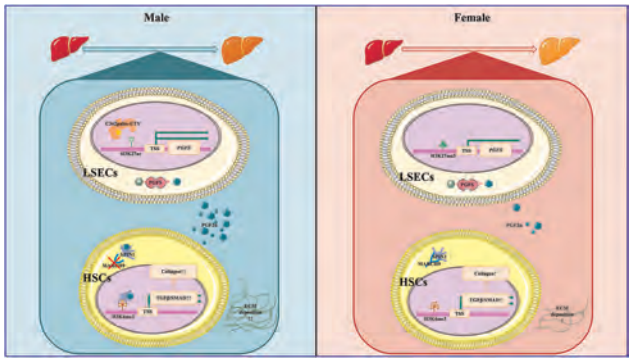
(MASH), we combined multi-omics profiling, chromatin topology analysis, and intercellular communication assays to delineate the UTY-mediated sexual dimorphism in MASH progression. **Results:** Male LSECs exhibited enhanced UTY demethylase activity through Cys379 palmitoylation, driving H3K27me3 erasure at the prostaglandin F synthase (PGFS) promoter. PGFS-derived PGF2α secretion from male LSECs was 2.5-fold higher than females, activating co-cultured hepatic stellate cells (HSCs) via SPIN1 stabilization. PGF2α binding to SPIN1 disrupted its MARCH9-mediated ubiquitination, enabling SPIN1-H3K4me3 complex formation at fibrogenic loci (TGFβ1, Wnt5a). PGF2α exacerbated proinflammatory cytokine release in M1 macrophages. Pharmacological inhibition of UTY palmitoylation (2-BP) or SPIN1-H3K4me3 interaction attenuated collagen deposition by 48-62% in male models, while female fibrogenesis remained unaffected. **Conclusion:** Our work unveils a Y chromosome-driven paradigm wherein palmitoylated UTY licenses male-dominant MASH through epigenetic-metabolic coupling in LSECs. The UTY-PGF2α-SPIN1 axis represents a precision therapeutic target for addressing sex disparities in MASH.



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★ 0185 | NEUTROPHIL EXTRACELLULAR TRAPS DRIVE B CELL–MEDIATED FIBROGENESIS IN MASH BY SILENCING HES1 AND PROMOTING PLASMA CELL DIFFERENTIATION

Songhan Pang[1] Amelia Bergeron[1] Carolyn Tsung[1] Yiyu Zhang[1] Hongji Zhang[1], [1]University of Virginia

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a severe form of metabolic dysfunction-associated steatotic liver disease (MASLD) that can progress to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Although FDA-approved Resmetirom shows promise in reversing MASLD, its efficacy in advanced fibrosis is limited and long-term safety remains unknown. MASH-Fibrosis is difficult to treat partly due to alterations in the hepatic immune microenvironment involving multiple cell types that contribute to inflammation and fibrosis. B cells have emerged as critical contributors to the immunopathogenesis of MASH-Fibrosis, yet their mechanism remains incompletely understood. In this study, we investigated how NETs modulate B cell function to promote MASH-Fibrosis. **Methods:** Male C57BL/6 mice were fed a Western diet (WD) for 40 weeks to induce MASH-Fibrosis. NETs were inhibited via neutrophil-specific PAD4 knockout ($PAD4^{fl/fl\ LysM\text{-}Cre}$) or daily DNase I treatment. Fibrosis was assessed by Sirius Red and Masson staining; cytokines and chemokines were measured by Luminex assays. Hepatic $CD45^+$ leukocytes were analyzed by scRNA-seq and flow cytometry. Plasma B cells, HES1, and differentiation markers (CD138, Prdm1, Xbp1) were evaluated by flow cytometry and in vitro NET stimulation assays. Mature B cells were depleted in vivo using muMT mice. **Results:** Fibrosis was observed with Sirius Red and Masson staining in the WD induced MASH-Fibrosis model and was significantly ameliorated by NETs inhibition. WD-induced MASH-Fibrosis increased hepatic $CD19^+CD138^+$ plasma B cells and suppressed HES1 expression, both of which were reversed by NET inhibition in vitro. NETs suppressed HES1 and promoted plasma cell differentiation, an effect abrogated by DNase I. scRNA-seq revealed significant immune landscape changes across nine hepatic immune cell types in MASH, with B cells showing a prominent transcriptomic shift. Flow cytometry confirmed this B cell subpopulation shift, which was also reversed by NET inhibition. B cell depletion or NET inhibition significantly reduced liver fibrosis, inflammation, and cytokine levels. **Conclusion:** Our data show increased neutrophil–B cell interactions and transcriptomic shifts in hepatic B cells in a WD-induced MASH-Fibrosis model. NETs drive pro-fibrogenic plasma cell differentiation by silencing HES1 in B cells during MASH-Fibrosis progression. Targeting NET-driven B cell reprogramming may offer a therapeutic strategy to limit MASH-related inflammation and fibrosis.

Disclosures: Songhan Pang: Nothing to Disclose, Amelia Bergeron: Nothing to Disclose, Carolyn Tsung: Nothing to Disclose, Yiyu Zhang: Nothing to Disclose, Hongji Zhang: Nothing to Disclose

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★ 0186 | GENERATION OF MULTILINEAGE, HIGHLY VASCULARIZED LIVER ORGANOIDS ENABLE DISEASE MODELLING AND EXHIBIT TRANSPLANTATION POTENTIAL

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Background: Human pluripotent stem-cell (iPSC) derived organoids have emerged as novel multicellular models for studying human development and disease. However, current liver organoid models lack cellular diversity, making them less physiologically relevant compared to native tissue. Additionally, current organoid protocols rely on extracellular matrix/matrigel embedding, whose xenogeneic origin limits their suitability for clinical applications. Therefore, exploring alternatives to generate multilineage vascularized liver organoids in a matrigel-free environment remains a significant area of focus. **Methods:** De-identified human iPSCs were obtained from Cellular Dynamics International-California Institute of Regenerative Medicine (CDI-CIRM). We developed a novel method to efficiently generate highly vascularized, multicellular, functional liver organoids from human iPSCs, obviating the need for matrigel embedding. Phenotypic and functional analysis were conducted using specific markers and various functional assays. To highlight the clinical relevance of the liver organoid model, we investigated its utility in steatohepatitis disease modelling, and *in-vivo* engraftment in immuno-compromised mice. **Results:** Our protocol recapitulated *in-vivo* liver development and generated complex liver organoids that exhibited major hepatic cell types, including hepatocytes, cholangiocytes, stellate cells, sinusoidal endothelial cells, and Kupffer-like cells, confirmed by phenotypic analysis and functional assays. Liver organoids displayed functional vascular networks with perfusable lumens, as confirmed by fluorescent Ulex europaeus agglutinin I (UEAI) incubation. Upon free-fatty acid treatment, liver organoids reproduced key features of steatohepatitis, including steatosis, inflammation and fibrosis. *In-vivo* engraftment showed that all hepatic cell-types were well-maintained even after 4-weeks of engraftment, and graft-derived endothelial cells developed functional anastomoses with the mouse vasculature with evident blood flow. Moreover, the engrafted organoids stably produced human-specific albumin in the recipient mice bloodstream, thus highlighting their translational potential for *in-vivo* applications. **Conclusion:** This study presents a robust method for generating vascularized, multicellular liver organoids that may provide a versatile and valuable personalized platform for disease modeling, and regenerative therapy applications.

Disclosures: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs, National Institute of Health or the United States government.

0187 | DELETION OF LYPLAL1 REDUCES CELLULAR UPTAKE OF FATTY ACIDS AND PROMOTES MITOCHONDRIAL B-OXIDATION TO PROTECT AGAINST METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Rawdat Hussain[1] Chinmay Raut[1] Prabhu Ponnandy[1] Akram Irshaid[2] Yue Chen[1] Lishi Yin[1] Tiffany Russell[1] Brian Halligan[3] Elizabeth Speliotes[3], [1]University of Michigan, [2]Michigan State University, [3]University of Michigan Medical Center

Background: Human genetics studies have linked single-nucleotide polymorphisms (SNPs) near LYPLAL1 with Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) but whether these SNPs act through LYPLAL1 to cause MASLD is unknown. To investigate the role of LYPLAL1 in MASLD, we analyzed rare loss-of-function (LOF) LYPLAL1 mutations using UK BioBank (UKBB) whole exome sequencing data and knocked out LYPLAL1 in human liver cells. **Methods:** We identified 100 rare missense or stop-gain LYPLAL1 variants that had AlphaMissense or GPN-MSA scores in the top 20% for causing protein disruption. We conducted burden testing in European males and females for effects on inverse normally transformed UKBB MRI Proton Density Fat Fraction (PDFF) (N = 30,050 males and 32,135 females) and UKBB ICD-based MASLD (N = 172,664 males and 208,795 females) with REGENIE. Results were meta-analyzed using fixed effects meta-analysis in METAL using sample size and direction of effect. We used CRISPR-Cas9 to knock out (KO) LYPLAL1 in a human liver cell line (HuH-7), measuring lipid levels biochemically and with imaging, fatty acid (FA) uptake by flow cytometry, and changes in *de novo* lipogenesis (DNL) and mitochondrial β-oxidation through RT-qPCR and Seahorse analysis. LYPLAL1 subcellular localization was determined by overexpressing LYPLAL1-HA tagged protein and using immunocytochemistry. **Results:** Rare loss-of-function variants were protective against MASLD in European individuals ($Z = -2.071$, $p = 0.03837$) across PDFF and ICD diagnoses and sexes. LYPLAL1 KO resulted in reduced lipid intensity and triglycerides when treated with oleic acid. Using the fluorescent FA analog NBD-stearate, we showed that LYPLAL1 KO cells had reduced FA import capability

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with decreased expression of transporters CD36 and FABP1. Expression of metabolic regulators PPARα, MLXIPL, and β-oxidation genes was higher in LYPLAL1 KO cells, with only minor changes in expression of DNL genes. These cells showed increased levels of FA oxidation in Seahorse analysis and treatment with mitochondrial β-oxidation inhibitor etomoxir restored lipid accumulation in the KO cells. We found that LYPLAL1-HA was abundantly present in mitochondria with oleic acid treatment. **Conclusion:** LYPLAL1 LOF variants had a protective effect against human MASLD and decreased intracellular lipid content in a human liver cell line. Increased levels of FA oxidation and decreased FA uptake likely protect against steatosis in LYPLAL1 KO cells.

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0188 | LOSS OF DNMT1 IN HEPATOCYTES PROMOTES INFLAMMATION AND FIBROSIS DURING MASLD/MASH DEVELOPMENT IN MICE

Lina Jegodzinski[1] Darko Castven[1] Juliana Marques Affonso[1] Diana Becker[2] Dina Greinert[1] Maria Robles[3] Jenny Hetzer[4] Mohammad Rahbari[4] Suchira Gallage[4] Nisar Malek[5] Mathias Heikenwälder[6] Jens Marquardt[1], [1]Department of Medicine I, University Medical Center Schleswig-Holstein, Lübeck, [2]Department of Medicine, University Medical Center of the Johannes Gutenberg University, Mainz, [3]Institute of Medical Psychology and Biomedical Center (BMC), Faculty of Medicine, LMU, Munich, [4]University Tübingen, Faculty of Medicine, M3-Research Center; German Cancer Research Center (DKFZ), [5]University Tübingen, Faculty of Medicine, M3-Research Center; Department Internal Medicine I, [6]University Tübingen, Faculty of Medicine, M3-Research Center, German Cancer Research Center (DKFZ)

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) constitutes an increasingly prevalent and clinically relevant spectrum of liver diseases. Key pathogenic drivers include lipotoxicity and mitochondrial dysfunction induced by excessive lipid accumulation in hepatocytes. Disruption of epigenetic regulation, particularly DNA methylation, is a major molecular hallmark of chronic inflammatory liver diseases. However, its role in MASLD pathogenesis remains unexplored. **Methods:** At 6-8 weeks of age, hepatocyte-specific *Dnmt1* knockout (KO; $Dnmt1^{flox/flox;Alb\text{-}Cre}$) and wild-type (WT; $Dnmt1^{flox/flox}$) control mice were exposed to a Western diet (WD) or a control diet (CD) for up to six months to induce MASLD/MASH. Comprehensive serum analyses and immunohistochemistry were performed. Liver samples were further subjected to RNA sequencing to assess transcriptomic changes. **Results:** *Dnmt1* KO mice exhibited reduced weight gain and attenuated hyperinsulinemia compared to WT controls. While levels of triglyceride accumulation were comparable in both genotypes, KO mice developed significantly higher intrahepatic cholesterol levels after six months of WD. Notably, serum alkaline phosphatase (ALP) levels were markedly increased in KO mice within three months of WD feeding. Histological analyses revealed increased hepatocellular senescence (p21) and enhanced inflammatory infiltration characterized by F4/80° macrophages and CD8° T cells. Strikingly, advanced hepatic fibrosis was observed exclusively in KO mice after six months of WD. Transcriptomic profiling of KO livers demonstrated enrichment of pathways associated with oxidative stress and mitochondrial dysfunction. **Conclusion:** Loss of *Dnmt1* in hepatocytes aggravates immune-cell infiltration and biliary injury during MASLD/MASH development, ultimately leading to increased liver damage and fibrosis. These findings emphasize the pathogenic role of epigenetic dysregulation, particularly through DNMT1 loss, in MASH progression and may offer novel targets for future therapeutic intervention.

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0189 | GLOBAL PROGRESS TOWARD THE ELIMINATION OF HEPATITIS B: COUNTRY-LEVEL PROVISIONAL ACHIEVEMENTS OF WHO TARGETS FOR PREVENTION, CARE, AND REDUCTIONS IN MORTALITY

Jana Manning[1] John Ward[1] Lindsey Hiebert[1], [1]Coalition for Global Hepatitis Elimination

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Background: In 2015, the WHO set goals for the elimination of hepatitis B virus (HBV) as a global health threat. Tracking country progress towards elimination informs national planning by revealing achievements and challenges that must be overcome to eliminate HBV. **Methods:** Provisional data were systematically collected from CGHE National Hepatitis Elimination Profiles and the WHO Global Health Observatory for 166 countries and territories. Data were assessed for the number of countries provisionally meeting the 2030 HBV mortality goal of < 4 /100,000 and progress on the WHO Path to Elimination (PTE) tiers for key interventions, including timely birth dose vaccination (BD), 3-dose vaccination (3D), diagnosis (D), and treatment (T). The tiers were defined as follows: Gold (BD,3D ≥ 90%, D ≥ 80%, T ≥ 70%), Silver (BD ≥ 50%,3D ≥90, D ≥ 70%, T ≥ 60%), and Bronze (BD policy in place, 3D ≥90%, D ≥ 60%, T ≥ 50%). Data for blood safety and infection control were not included. For each country, data for the most recent year were used. Descriptive analysis, including regional cross-tabulations and distribution measures, was conducted in IBM SPSS. **Results:** The mean HBV mortality rate was 15.2 per 100,000. A total of 46 countries (28%) reported mortality rates at or below the 2030 target. In the WHO African region, 40 (86%) countries exceeded 20 deaths per 100,000; Liberia reported the highest rate (167.4). Among 103 countries reporting data, mean BD coverage was 76.8%; 62 countries reported no data or 0% coverage. A total of 164 countries reported 3D coverage with a mean of 84.8%. Of 163 countries with data, the mean diagnosis rate was 15.2% (SD = 19.1); 77 countries (47%) had coverage <10%. Average treatment coverage among persons diagnosed was 11.8% (SD = 16.2). Progress towards Path to Elimination tiers *Vaccination*: For 3D coverage, 84 countries (51%) met Gold. For BD, 103 countries (62%) met the Bronze target, 91 (55%) met Silver, and 49 (30%) met Gold. *Diagnosis*: Nineteen countries (11%) met Bronze for diagnosis coverage, 13 (8%) met Silver, and 9 (5%) achieved the Gold tier. Only Madagascar, Japan, and Iraq met the 2030 WHO target of treating at least 80% of those diagnosed. *Treatment*: Eight countries (5%) met bronze, 7 (4%) met Silver, and 6 (4%) met Gold. Overall Path to Elimination: No countries met the combined criteria for the overall Bronze, Silver, or Gold tiers. **Conclusion:** Countries have achieved progress on certain key HBV interventions, particularly hepatitis B vaccination. However, overall progress towards the WHO PTE tiers is limited. HBV diagnosis and treatment coverage is low, especially in high-burden regions such as sub-Saharan Africa. Urgent expansion of HBV screening programs, simplified models of care, and continued improvements in HepB BD vaccination are needed to accelerate progress toward hepatitis B elimination.

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0190 | THE IMPACT OF CHRONIC HEPATITIS B AND ITS CLINICAL PHASES ON SIGNIFICANT LIVER FIBROSIS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Jie Li[1] Fajuan Rui[2] Jing Zhang[3] Yixuan Zhu[4] YongFeng Yang[5] Liang Xu[6] Ming-Hua Zheng[7] Qi Zheng[8] Haijun Huang[9] Chao Wu[1] Qing Xie[10] Junping Shi[11] Yuemin Nan[12], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, China, [2]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, China, [3]Beijing Youan Hospital, Capital Medical University, Beijing, China, [4]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University,China, [5]The Second Hospital of Nanjing, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China, [6]Tianjin Second People's Hospital, Tianjin, China, [7]The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China, [8]The First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian, China, [9]Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College,Zhejiang, China, [10]Ruijin Hospital, [11]The Affiliated Hospital and Institute of Hepatology and Metabolic Disease of Hangzhou Normal Univers, [12]Hebei Medical University Third Hospital, Shijiazhuang,Hebei, China

Background: The overlap between chronic hepatitis B (CHB) and metabolic dysfunction-associated steatotic liver disease (MASLD) has been growing. This study aimed to investigate the effect of chronic hepatitis B virus (HBV) infection on the progression of significant liver fibrosis in patients with MASLD. **Methods:** This multi-center, cross-sectional study enrolled MASLD patients who underwent liver biopsy across 16 medical centers in China between April 2004 and April 2024. Logistic regression analyses were conducted to examine the association between CHB and significant fibrosis. Propensity score matching (PSM) was used to reduce confounding factors and balance MASLD patients with and without CHB. **Results:** A total of 2,703

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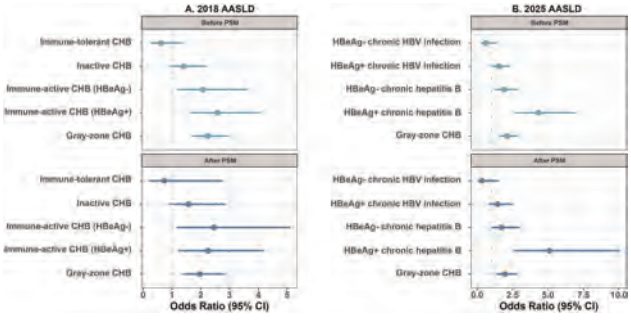
MASLD patients were included in this study (median age 40 years, 70.81% male), including 892 with MASLD only and 1,811 MASLD with CHB, among whom 930 were treatment-naïve CHB. The proportion of significant fibrosis was remarkedly higher in MASLD patients with CHB than in those with MASLD only (50.86% vs. 37.33%, $P < 0.001$). Based on the 2018 AASLD guidelines, all treatment-naïve CHB patients were categorized into five phases: immune-tolerant CHB (n = 43), inactive CHB (n = 114), HBeAg-negative immune-active CHB (n = 65), HBeAg-positive immune-active CHB (n = 127), and gray-zone CHB (n = 453). Multivariate regression analyses indicated that concurrent CHB was independently associated with higher risks of significant fibrosis (odds ratio [OR]: 2.28, 95% confidence interval [CI]: 1.81-2.89, $P < 0.001$). Both immune-active and gray-zone CHB were associated with increased risks of significant fibrosis (HBeAg-negative immune-active: OR: 2.07, 95% CI: 1.18-3.63, $P = 0.012$; HBeAg-positive immune-active: OR: 2.59, 95% CI: 1.64-4.08, $P < 0.001$; Gray-zone: OR: 2.25, 95% CI: 1.70-2.98, $P < 0.001$). After PSM, these associations remained significant, with adjusted ORs of 2.46 (95% CI: 1.18-5.11, $P = 0.016$), 2.26 (95% CI: 1.22-4.20, $P = 0.010$), and 1.97 (95% CI: 1.38–2.81, $P < 0.001$) in patients within HBeAg-negative immune-active, HBeAg-positive immune-active, and gray-zone, respectively. These findings were consistent with those when the category of CHB phases were based on the 2025 EASL guidelines. **Conclusion:** CHB independently increases the risk of fibrosis in MASLD patients, particularly in immune-active or gray-zone phases. This highlights the need for targeted screening and individualized management in high-risk groups.



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0191 | GLUCOSE-LIKE PEPTIDE-1 RECEPTOR AGONISTS AND REDUCED LIVER AND NON-LIVER COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES AND VIRAL HEPATITIS

Xinrong Zhang[1] Scott Barnet[1] Linda Henry[1] Ramsey Cheung[2], [1]Division of Gastroenterology and Hepatology, School of Medicine, Stanford University Medical Center, [2]Stanford University Medical Center

Background: Glucose-like peptide-1 receptor agonists (GLP-1RA) are a novel class of anti-diabetic drugs that can treat obesity and type 2 diabetes (T2D) and has been shown to reverse steatohepatitis and reduce cardiovascular risk. T2D and viral hepatitis frequently coexist and worsen liver and non-liver outcomes, but effective pharmacological therapies are limited. We aimed to evaluate the long-term effect of GLP-1RA on liver and non-liver complications among patients with T2D and viral hepatitis in the United States. **Methods:** Patients with T2D and viral hepatitis initiating GLP-1RA were included from 2007 to 2022 in Merative™ Marketscan® Research Databases. Primary outcomes included (1) hepatocellular carcinoma (HCC) and cirrhosis, and (2) cardiovascular disease (CVD), chronic kidney disease (CKD), and non-liver cancer. Propensity score matching (PSM) was applied to balance baseline characteristics and Cox regression models were conducted to estimate hazard ratio (HR) and 95% confidence interval (CI). **Results:** 61,164 patients with T2D and viral hepatitis were initially analyzed. Patients with and without GLP-1RA use were 1:4 matched by propensity score for their demographics, comorbidities, and background medications. A total of 9,499 patients with T2D and CHB (2,133 in GLP-1RA and 7,366 in non-GLP-1RA group; mean age 57.2 years and 41% were female at baseline) were included. Compared with non-GLP-1RA group, GLP-1RA use was associated with 34% lower risk of any liver-related outcomes (HR 0.66, 95% CI 0.53-0.81; $P < 0.001$), 50% lower risk of HCC (HR 0.50, 95% CI 0.29-0.88; $P = 0.016$), 35% lower risk of cirrhosis (HR 0.65, 95% CI 0.52-0.80; $P < 0.001$), 18% lower risk of CVD (HR 0.82, 95% CI 0.66-1.02; $P = 0.079$), 34% lower risk of CKD (HR 0.66, 95% CI 0.53-0.83; $P < 0.001$), and 28% lower risk of non-liver cancer (HR 0.72, 95% CI 0.53-0.99; $P = 0.042$) (Table 1). The association remained similar regardless of age, sex, diabetes duration, presence of diabetic complications, hypertension, hyperlipidemia, obesity and metabolic dysfunction-associated steatotic liver disease, use of antiviral treatment and background antidiabetic agents including metformin, sodium glucose co-transporter 2

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inhibitors, dipeptidyl peptidase-4 inhibitors and insulin. **Conclusion:** In a nationwide cohort, GLP-1RA use was associated with a substantially lower risk of liver and non-liver complications than non-GLP-1RA group among patients with T2D and viral hepatitis. Further randomised trials are warranted.

Table 1. Incidence rates and risk for liver and non-liver outcomes in GLP-1RA and non-GLP-1RA users after propensity score matching

Outcomes*	Total patients	Event	Person-years	Incidence per 1000 person-years (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Any liver-related outcomes							
Non-GLP-1RA	4,291	571	12,054	47.37 (43.56-51.42)	<0.001	ref	
GLP-1RA	1,284	100	3,230	30.96 (25.19-37.66)		0.66 (0.53-0.81)	<0.001
HCC							
Non-GLP-1RA	5,860	109	17,133	6.36 (5.22-7.67)	0.009	ref	
GLP-1RA	1,745	14	4,529	3.09 (1.69-5.19)		0.50 (0.29-0.88)	0.016
Cirrhosis							
Non-GLP-1RA	4,301	573	12,082	47.43 (43.62-51.47)	<0.001	ref	
GLP-1RA	1,285	99	3,235	30.60 (24.87-37.26)		0.65 (0.52-0.80)	<0.001
CVD							
Non-GLP-1RA	5,012	460	14,093	32.64 (29.73-35.76)	0.038	ref	
GLP-1RA	1,494	98	3,780	25.93 (21.05-31.60)		0.82 (0.66-1.02)	0.079
CKD							
Non-GLP-1RA	4,869	524	13,467	38.91 (35.65-42.39)	<0.001	ref	
GLP-1RA	1,429	90	3,589	25.08 (20.18-30.82)		0.66 (0.53-0.83)	<0.001
Non-liver cancer							
Non-GLP-1RA	5,421	243	15,612	15.56 (13.67-17.63)	0.031	ref	
GLP-1RA	1,626	46	4,172	11.03 (8.07-14.71)		0.72 (0.53-0.99)	0.042

*Matched for age, sex, smoking, alcohol use disorder, duration of diabetes, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, HBV treatment, HCV treatment, hyperlipidemia, hypertension, obesity/overweight, COPD, MASLD/MASH, liver cirrhosis, hepatocellular carcinoma, cardiovascular disease, chronic kidney disease, non-liver cancer, CCI, metformin, SGLT-2i, DPP-4i, sulfonylureas, thiazolidinediones, insulin, ACEI/ARB, β-blockers, CCB and statin

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blockers; CCI, Charlson Comorbidity Index; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptidase 1 receptor agonist; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; SGLT-2i, sodium-glucose cotransporter-2 inhibitor

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0192 | ASSOCIATION BETWEEN STATIN USE AND THE RISK OF HEPATOCELLULAR CARCINOMA AND HEPATIC DECOMPENSATION IN CHRONIC HEPATITIS B: A NATIONWIDE COHORT STUDY

Young Chang[1] Jeong-Ju Yoo[1] Jae Young Jang[1] Tom Ryu[1] Soung Won Jeong[1] Sae Hwan Lee[1] sang gyune kim[2] Young Seok Kim[3] Hong Soo Kim[1],
[1]Soonchunhyang University, [2]Mayo Clinic Rochester, [3]Soon Chun Hyang University

Background: Statins have been suggested to provide hepatoprotective benefits beyond their lipid-lowering effects. This study aimed to evaluate whether statin use is associated with a reduced risk of hepatocellular carcinoma (HCC) and hepatic decompensation in patients with chronic hepatitis B (CHB). **Methods:** We analyzed data from the Korean National Health Insurance Service database, identifying 1,351,240 CHB patients from 2017 to 2022. After applying washout and exclusion criteria, the final cohort included 37,297 statin users with hyperlipidemia, 2,845 non-users with hyperlipidemia, and 379,985 non-users without hyperlipidemia. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for HCC and hepatic decompensation were calculated across subgroups defined by cirrhosis and antiviral therapy status. **Results:** Statin use was significantly associated with a reduced risk of hepatocellular carcinoma in the overall population (IRR, 0.05; 95% CI, 0.04–0.06). This association remained significant in both cirrhotic (IRR, 0.06; 95% CI, 0.03–0.10) and non-cirrhotic patients (IRR, 0.04; 95% CI, 0.03–0.06), and was consistently observed regardless of antiviral therapy status. Statin use was also linked to a significantly lower risk of hepatic decompensation in the overall cohort (IRR, 0.09; 95% CI, 0.06–0.13), with particularly strong effects seen in non-cirrhotic patients (IRR, 0.09; 95% CI, 0.06–0.12). The protective association was evident in both antiviral users and non-users. In cirrhotic patients, however, the association was attenuated. **Conclusion:** Statin use was significantly associated with reduced risks of HCC and hepatic decompensation in CHB patients, independent of antiviral therapy. The effect was consistently observed across clinical subgroups, though diminished in cirrhotic patients.

Disclosures: Young Chang: Nothing to Disclose, Jeong-Ju Yoo: Nothing to Disclose, Jae Young Jang: Nothing to Disclose, Tom Ryu: Nothing to Disclose, Soung Won Jeong: Nothing to Disclose, Sae Hwan Lee: Nothing to Disclose, sang gyune kim: Nothing to Disclose, Young Seok Kim: Nothing to Disclose, Hong Soo Kim: Nothing to Disclose

0193 | HEPATOCELLULAR CARCINOMA RISK BETWEEN UNTREATED IMMUNE TOLERANT VS. TREATED IMMUNE ACTIVE CHRONIC HEPATITIS B PATIENTS: A LONGITUDINAL ANALYSIS OF NATIONAL VETERANS AFFAIRS COHORT

Robert Wong[1] Zeyuan Yang[2] Ramsey Cheung[3], [1]VA Palo Alto Healthcare System, [2]Palo Alto Veterans Institute for Research, [3]Stanford University Medical Center

Background: There have been conflicting data on the risk of hepatocellular carcinoma (HCC) between untreated immune tolerant (U-IT) vs. treated immune active (T-IA) chronic hepatitis B (CHB) patients. Some studies report significantly higher HCC risk in U-IT vs. T-IA, whereas others report no differences, but the vast majority of studies were in Asian populations. Data among predominantly non-Asian Western populations are lacking. We aim to evaluate differences in HCC risk between U-IT vs. T-IA among a large Western CHB cohort. **Methods:** Using the longitudinal national Veterans Affairs database, we identified adults with non-cirrhotic CHB that met criteria for U-IT or T-IA from 1/1/2010 to 12/31/2021 (with follow-up through 12/31/2024). Patients with concurrent HIV,

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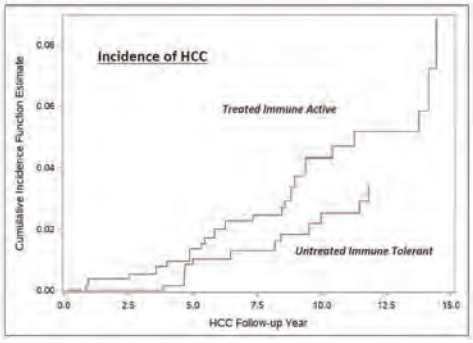
HCV, HDV, or prior cirrhosis or HCC diagnosis were excluded. Propensity score weighting (PSW) methods were applied to balance baseline factors between U-IT and T-IA patients. Patients with at minimum 1 year of follow-up were evaluated longitudinally until development of HCC, censoring event (death or 6 months after start of antiviral therapy in U-IT), or end of the study period. HCC incidence (per 100 person-years) was compared between U-IT and T-IA, and Cox proportional hazards regression models evaluated differences in HCC risk between groups. **Results:** A total of 591 U-IT and 555 T-IA CHB patients were identified. After PSW, baseline characteristics were similar between groups, with mean age 56.4-57.5 years, 45-50% non-Hispanic white, 37-40% African American, 9-10% Asian, 25-29% with concurrent diabetes, and 35-39% with FIB-4 $>$ 3.25. Over a median follow up of 6.4 years (IQR 3.0-10.4), the incidence of HCC was significantly higher in T-IA vs. U-IT patients (0.54 [95% CI 0.41-0.72] vs. 0.28 [0.19-0.42] per 100 person-years, $p < 0.01$) (Figure). On Cox proportional hazards regression, when compared to T-IA patients, U-IT chronic HBV patients had significantly lower risk of HCC (HR 0.52, 95% CI 0.32 – 0.83, $p < 0.01$). **Conclusion:** Among a national Western cohort of predominantly non-Asian Veterans with CHB, significantly higher risk of HCC was observed in T-IA vs. U-IT patients, which differs from existing studies from Asian countries. These data continue to emphasize the importance of timely identification and prompt initiation of CHB antiviral therapy in patients who have transitioned into the IA phase.

Figure. Incidence of Hepatocellular Carcinoma Between Untreated Immune Tolerant vs. Treated Immune Active Chronic Hepatitis B Patients



Disclosures: Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Zeyuan Yang: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose

0194 | SUMMIT: A NOVEL DEEP LEARNING MODEL USING SERIAL IMPUTATION-FREE CLINICAL DATA FOR HCC RISK PREDICTION IN CHRONIC HEPATITIS B

Tung-Hung Su[1] Yi-Hsien Hsieh[2] Shao-Wu Lee[3] Fen-Fang Chen[4] You-Hsiang Wang[2] Francis Poon[5] Wei-Yu Kao[6] Weichung Wang[7] Che Lin[2] Jia-Horng Kao[4], [1]National Taiwan University Hospital, [2]Graduate Institute of Communication Engineering, National Taiwan University, Taipei, Taiwan, [3]Department of Internal Medicine, Taichung Veterans Geneneral Hospital, Taichung, Taiwan, [4]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, [5]Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan, [6]Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan, [7]Institute of Applied Mathematical Sciences, National Taiwan University, Taipei, Taiwan

Background: Identifying high-risk patients for hepatocellular carcinoma (HCC) among individuals with chronic hepatitis B (CHB) is crucial for timely surveillance. Although several risk scores have been developed, they often require complete data for calculation at a specific moment. We aimed to create an HCC prediction model using serial laboratory and clinical data that accommodates missing values. **Methods:** Patients with CHB who were not receiving antiviral therapy and were followed longitudinally at a tertiary medical center in Taiwan were screened. We excluded patients with prior malignancy, hepatitis C, HIV, liver transplantation, or a follow-up duration of less than five years. Laboratory data (including complete blood count, liver function tests, renal and glucose profiles, and viral markers), abdominal ultrasonographic findings, and hospital admissions within one year before the index date were summarized at three-month intervals. We applied our Scalable nUMerical eMbeddIng Transformer (SUMMIT) model to predict five-year HCC development without requiring data imputation. The performance of the SUMMIT model was compared with traditional HBV risk scores (e.g., REACH-B). An external validation was conducted using data from another tertiary medical center. Model performance was evaluated using AUROC, AUPRC, sensitivity, specificity and the C-index, where threshold-sensitive metrics were obtained with a decision threshold maximizing the Youden index on the training set. **Results:** A total of 12,455 untreated CHB patients were included, with a median age of

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49 years; 53% were male. Of these, 7060 (HCC: 261, 3.7%) were assigned to the training set, while 4708 patients (HCC: 179, 3.8%) and another 687 patients (HCC: 46, 6.7%) who could calculate the REACH-B score were assigned as two testing sets. Compared with logistic regression, support vector machine, random forest, and XGBoost models, the SUMMIT model achieved significantly higher AUROC (0.902), AUPRC (0.317; baseline: 0.023), sensitivity (0.750), specificity (0.877), and C-index (0.898) for predicting five-year HCC development. These metrics outperformed those of traditional models such as REACH-B (AUROC: 0.794), CU-HCC (AUROC: 0.868), RWS-HCC (AUROC: 0.856), and AGED (AUROC: 0.756) scores. The sensitivity of the SUMMIT model increased as the time approached HCC development. Using the external validation dataset (n = 9038), the AUROC and AUPRC were 0.792 and 0.024 (baseline: 0.007), respectively. **Conclusion:** The SUMMIT model accurately estimates HCC risk using serial laboratory and clinical data in untreated CHB patients and accommodates missing data. It outperformed other machine learning algorithms and traditional HBV risk scores and was validated externally.

Table 1. The performance of the SUMMIT model compared to other machine learning models.

	AUROC	AUPRC	Sensitivity	Specificity	C-index
LR	0.785 (0.743, 0.830)	0.128 (0.079, 0.175)	0.732 (0.651, 0.811)	0.668 (0.655, 0.681)	0.781 (0.740, 0.826)
SVM	0.826 (0.788, 0.867)	0.156 (0.094, 0.209)	0.643 (0.553, 0.729)	0.841 (0.830, 0.852)	0.823 (0.787, 0.863)
RF	0.851 (0.812, 0.893)	0.259 (0.158, 0.312)	0.455 (0.360, 0.544)	0.967 (0.963, 0.973)	0.847 (0.808, 0.889)
XGB	0.833 (0.792, 0.878)	0.214 (0.133, 0.282)	0.643 (0.556, 0.732)	0.891 (0.882, 0.901)	0.829 (0.789, 0.873)
SUMMIT	0.902 (0.874, 0.936)	0.317 (0.223, 0.407)	0.750 (0.670, 0.832)	0.877 (0.867, 0.886)	0.898 (0.870, 0.931)

SUMMIT: Scalable nUMerical eMbedding Transformer, AUROC: area under the receiver operating characteristic curve, AUPRC: area under precision-recall curve, LR: logistic regression, SVM: support vector machine, RF: random forest, and XGB: eXtreme Gradient Boosting models

Disclosures: Tung-Hung Su: Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Merck Sharp and Dohme: Speaking and Teaching, Roche: Speaking and Teaching, Sysmex: Speaking and Teaching, Eisai: Speaking and Teaching, Yi-Hsien Hsieh: Nothing to Disclose, Shao-Wu Lee: Nothing to Disclose, Fen-Fang Chen: Nothing to Disclose, You-Hsiang Wang: Nothing to Disclose, Francis Poon: Nothing to Disclose, Wei-Yu Kao: Nothing to Disclose, Weichung Wang: Nothing to Disclose, Che Lin: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose

★ 0195 | CD4-DEPENDENT MECHANISMS DRIVE HEPLISAV-B MEDIATED HBSAG CLEARANCE AND ANTI-HBV IMMUNITY IN CHRONIC HBV CARRIER MICE

James Ahodantin[1] Jiapeng Wu[1] Masaya Funaki[2] Lydia Tang[3] Shyam Kottilil[1] Lishan Su[1], [1]University of Maryland Baltimore, [2]Kanazawa University, [3]University of Maryland, Baltimore

Background: Chronic HBV infection affects over 250 million globally, often leading to severe liver diseases. Current antiviral treatments rarely achieve functional cure, necessitating novel immunotherapeutic strategies like therapeutic vaccines to overcome immune tolerance and achieve HBV functional cure. HEPLISAV-B, an FDA-approved HBV vaccine combining HBsAg with the TLR9 agonist CpG-1018, has demonstrated superior immunogenicity clinically. This study evaluated HEPLISAV-B's therapeutic potential in a chronic HBV infection mouse model that exhibits immune tolerance to conventional HBV vaccination. **Methods:** We used an AAV-HBV carrier mouse model with chronic HBV infection and immune tolerance. Mice received two intramuscular doses of HEPLISAV-B (HBsAg/CpG: 2 ug/300 ug) four weeks apart. We monitored plasma HBV DNA, HBsAg, and HBeAg levels. Immunoblot and immunofluorescence analyses assessed liver HBsAg and HBcAg. Immune responses were evaluated by ELISA for anti-HBs IgG, ELISPOT for IFN-γ and IgG production, and flow cytometry for splenic and hepatic immune cell profiling, including CD4 and CD8 T cells, B cells, and regulatory T cells (Tregs). CD4 and CD8 T cell depletion using specific antibodies delineated their contributions. **Results:** HEPLISAV-B administration achieved HBsAg clearance and suppressed HBV production via a non-cytolytic mechanism. We observed a significant 1000-fold reduction in plasma HBV DNA and decreased HBeAg, with HBsAg becoming undetectable. Hepatic HBV DNA and RNA levels were also significantly reduced, suggesting inhibition of HBV RNA transcription and pgRNA reverse transcription. Treatment elicited robust, durable anti-HBs IgG responses ($\geq 10^4$ U/ml) and promoted Th1-biased CD4 T cell responses, characterized by enhanced IFN-g and TNF-a secretion. Immunophenotyping revealed increased splenic CD45 cells, B cells, effector memory CD8 T cells, and central memory CD4 T cells, alongside reduced Tregs and PD-1 expression on CD4 T cells. Crucially, HEPLISAV-B's therapeutic efficacy was completely abrogated by CD4 T cell depletion, while CD8 T cell depletion enhanced viral control and anti-HBs IgG responses. **Conclusion:** HEPLISAV-B effectively breaks immune tolerance in chronic HBV infection, leading to stable HBsAg clearance, suppressed viral production, and robust, durable anti-HBV humoral and cellular immunity. Our findings unequivocally demonstrate that CD4 T cells are critically essential for mediating these therapeutic effects. These results highlight HEPLISAV-B's strong potential as a promising therapeutic vaccine candidate for achieving functional cure in patients with chronic HBV infection.

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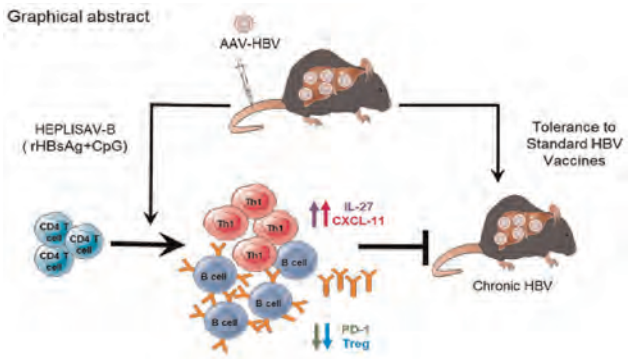


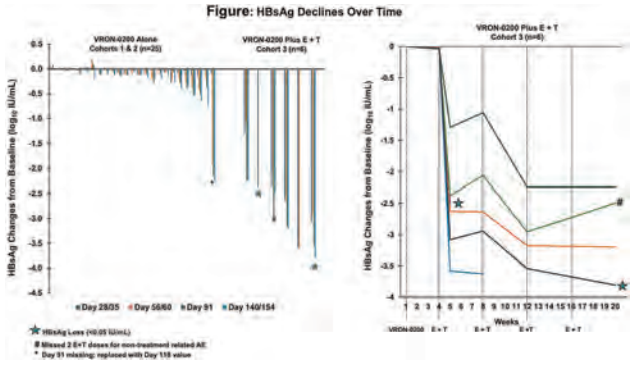
Disclosures: James Ahodantin: Nothing to Disclose, Jiapeng Wu: Nothing to Disclose, Masaya Funaki: Nothing to Disclose, Lydia Tang: Arbutus: Grant/Research Support, Gilead Sciences: Grant/Research Support, Moderna: Grant/Research Support, Shyam Kottilil: Red Queen Therapeutics: Consultant, Orsobio: Stock – privately held company, Lishan Su: Nothing to Disclose

0196 | HBSAG DECLINES OBSERVED WITH VRON-0200 ALONE ARE RAPIDLY ENHANCED WITH THE ADDITION OF COMBINATION ANTIVIRAL THERAPIES: RESULTS: FROM A PHASE 1B STUDY FOR FUNCTIONAL CURE IN CHRONICALLY HBV-INFECTED PATIENTS

Grace Lai-Hung Wong[1] Tien Huey Lim[2] Sue Currie[3] Andrew Luber[3] Marie Bonhomme[4] Edward Gane[5], [1]The Chinese University of Hong Kong, Hong Kong, Hong Kong, [2]NZ Liver Transplant Unit, Auckland, New Zealand, [3]Virion Therapeutics LLC, Philadelphia, USA, [4]PPD, Part of Thermo Fisher Scientific, Richmond, USA, [5]Auckland City Hospital, University of Auckland, Auckland, New Zealand

Background: HBsAg loss at EOT has been observed with some new therapies; however, sustained off-tx responses (Functional Cure), even with 24 to 48 weeks of PEG-IFN, have been very limited. VRON-0200 is an immune modulator that expresses a genetically encoded checkpoint modifier, fused with HBV core and pol (but not S) antigens, designed to enhance, broaden, and prolong CD8+ T cell responses. Here, we report safety, immunogenicity, HBsAg and HBsAb data from all patients(pts), including the combination cohort (the addition of Elebsiran and Tobevibart (E+T)). **Methods:** 34 CHB pts, NUC-suppressed with HBsAg <500IU/mL(Cohorts 1(C1) and 2(C2)), or $<1{,}000$IU/mL (Cohort 3(C3)), were randomized to receive i.m. VRON-0200 low(C1) or high dose (C2) prime on D1, w/wo VRON-0200 boost on D91; C3 receive VRON-0200 prime, followed by 6 mthly doses of E+T starting on D28, alone, or, with a VRON-0200 boost on D196. Safety, virologic, and immunologic assessments are performed. HBsAg (ELISA; LLOD:0.05IU/mL), HBsAb (detectable at >10mIU/mL), and T cell frequencies (IFN-γ ELISpot (core, pol, S antigen)), were measured. **Results:** As of May 20, 2025, 34 pts were included: 28 (82%) male, 29(85%) Asian, median age, 46.5yrs, and median BL HBsAg,178 IU/mL (range:10 – 842). In 9,937 pt safety days, 35 TRAEs were reported: 4-GR2, 31-GR1, with no tx-related SAEs or D/Cs. After a single VRON-0200 prime,10 pts(29%) had sum of core and pol IFN-γ responses above their pre-tx responses. In C1 and C2, VRON-0200 lowered HBsAg levels >0.4 log10IU/mL in 6/27(22%) and 7/26(27%) at D91 and D154, respectively; these HBsAg declines were observed at D28 and deepened over time (Figure). Boost dose did not enhance declines. In C3, at D35 (7 days post first E+T dose), HBsAg levels rapidly declined in all pts (100%; $n=6$): -3.6, -3.1, -2.6, -2.5, -2.4 and -1.3 $\log_{10}$IU/mL; all <10IU/mL (Figure); and all seroconverted from HBsAb negative to positive. Additional data to be reported. **Conclusion:** VRON-0200 alone, or in combination, had no observed safety concerns, and was well tolerated. Despite not targeting HBsAg, a single VRON-0200 dose was able to lower S-antigen in ~25% of pts. The combination of VRON-0200 with elebsiran and tobevibart rapidly and profoundly enhanced VRON-0200 HBsAg declines within 7 days in all pts, with further declines being observed with additional doses. These results suggest that broad immune restoration is possible and, coupled with VRON-0200's safety, tolerability, and ease of administration, support its potential use as the backbone therapy, in combination treatments, for HBV functional cure.

Figure: HBsAg Declines Over Time



Disclosures: Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline,

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0197 | SAFETY, TOLERABILITY, IMMUNOGENICITY, AND ANTIVIRAL EFFICACY OF GS-2829 AND GS-6779, A NOVEL, ARENAVIRAL-VECTORED, THERAPEUTIC HEPATITIS B VACCINE: RESULTS: FROM A PHASE 1B STUDY IN VIRALLY SUPPRESSED PATIENTS WITH CHRONIC HEPATITIS

Edward Gane[1] Chi-Yi Chen[2] Tsung-Hui Hu[3] Ching-Chu Lo[4] Pin-Nan Cheng[5] Tung-Hung Su[6] Ming-Lung Yu[7] Frida Abramov[8] Mario Cortese[8] David Pan[8] Scott Balsitis[8] Teri Chew[8] Sarah Arterburn[8] Christopher Richards[8] Anu Osinusi[8] Wen-Juei Jeng[9] Yao-Chun Hsu[10], [1]University of Auckland, Auckland, New Zealand, [2]Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi, Taiwan, [3]Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, [4]Department of Internal Medicine, St. Martin De Porres Hospital, Chiayi City, Taiwan, [5]College of Medicine, National Cheng Kung University, Tainan, Taiwan, [6]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, [7]Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [8]Gilead Sciences, Inc., Foster City, CA, USA, [9]Chang Gung Memorial Hospital, Linkou, Taiwan and Chang Gung University, Taoyuan, Taiwan, [10]E-Da Hospital, School of Medicine, I-Shou University, Kaohsiung, Taiwan

Background: Therapeutic vaccines, such as non-replicating arenaviral vectors GS-2829 and GS-6779, are a promising approach to achieve durable immune response and functional cure for chronic hepatitis B (CHB) infection. GS-2829 and GS-6779 were engineered to express hepatitis B surface antigen (HBsAg) and core antigen (HBcAg), and highly conserved polymerase (pol) reverse transcriptase and ribonuclease H domains. We evaluated the safety, tolerability, immunogenicity, and antiviral efficacy of GS-2829 and GS-6779 in virally suppressed patients (pts) with CHB. **Methods:** In this multicenter, randomized (4:1), blinded, placebo-controlled Phase 1b study, alternating intramuscular administrations of GS-2829 or GS-6779 every 4 weeks (ie, 1 cycle = GS-2829 at week 0; GS-6779 at week 4) were evaluated: cohort 5, 2 cycles of low doses; cohort 6, 2 cycles of high doses; cohort 7, 3 cycles of high doses. Safety and tolerability were monitored via treatment-emergent adverse events (AEs), serious AEs, and laboratory abnormalities. Viral efficacy included HBsAg, hepatitis B e antigen (HBeAg), and hepatitis B core-related antigen (HBcrAg). Immunogenicity was evaluated by interferon-gamma ELISpot analysis of hepatitis B virus (HBV)-specific T cells. **Results:** Thirty pts (n = 10 per cohort) were enrolled; median age was 51 years, 63% were male, 100% were Asian, 7% had prior interferon use, and genotype B was most common (43%). At baseline (BL), median (Q1, Q3) HBsAg levels for pts in cohorts 5–7 who received the vaccine were 1579 (480, 2901), 863 (521, 2584), and 401 (138, 925) IU/mL, respectively; 0/8, 7/8 (88%), and 4/8 (50%) pts were HBeAg positive. Among 11 HBeAg-positive pts at BL who received the vaccine, 5 (45%) achieved HBeAg loss. Quantitative declines in HBeAg and HBcrAg were observed in additional HBeAg-positive pts. In 25% (4/16) of pts in high-dose cohorts, HBsAg declined by ~0.5 $\log_{10}$ IU/mL with mild (Grade $\leq$1) alanine aminotransferase increases (Figure A). Pts on the vaccine showed induced HBV-specific T-cell responses (Figure B)—mainly against HBcAg and pol—and 94% of pts in high-dose cohorts had $\geq$3-fold increases from BL in T cells for $\geq$1 HBV antigen. All AEs were Grade $\leq$2 and nonserious; none led to discontinuation of study drugs. **Conclusion:** Alternating doses of GS-2829 and GS-6779 were safe and well tolerated in virally suppressed pts with CHB. These safety, virology, and immunogenicity data support further investigation of GS-2829 and GS-6779 as CHB treatment.

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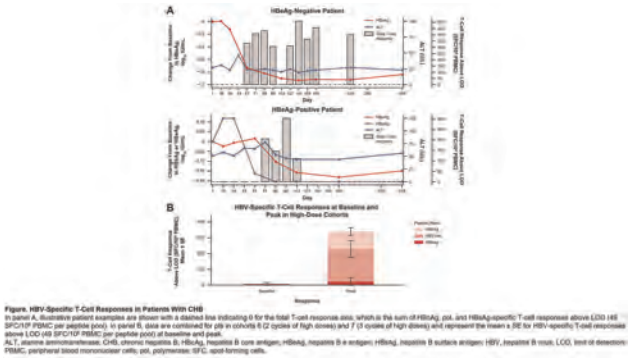

Disclosures: Edward Gane: Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Chi-Yi Chen: Nothing to Disclose, Tsung-Hui Hu: Nothing to Disclose, Ching-Chu Lo: Nothing to Disclose, Pin-Nan Cheng: Nothing to Disclose, Tung-Hung Su: Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Merck Sharp and Dohme: Speaking and Teaching, Roche: Speaking and Teaching, Sysmex: Speaking and Teaching, Eisai: Speaking and Teaching, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Frida Abramov: Nothing to Disclose, Mario Cortese: Nothing to Disclose, David Pan: Nothing to Disclose, Scott Balsitis: Nothing to Disclose, Teri Chew: Nothing to Disclose, Sarah Arterburn: Nothing to Disclose, Christopher Richards: Gilead Sciences: Employee, Anu Osinusi: Nothing to Disclose, Wen-Juei Jeng: Nothing to Disclose, Yao-Chun Hsu: Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Sysmex: Advisor, Abbvie: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Roch: Speaking and Teaching, AsuperBio: Advisor, Grifols: Speaking and Teaching, GlaxoSmithKline: Consultant, AusperBio: Consultant

0198 | ORAL ONCE-DAILY 300 MG ALG-000184, A NOVEL CAPSID ASSEMBLY MODULATOR, DEMONSTRATED PROFOUND AND SUSTAINED SUPPRESSION OF HBV DNA TO < 10 IU/ML IN ALL TREATMENT NA&IUML;VE (TN) OR CURRENTLY-NOT-TREATED (CNT) SUBJECTS WITH CHRONIC HBV INFECTIO

Man-Fung Yuen[1] Kosh Agarwal[2] Alina Jucov[3] Alexei Haceatrean[3] Min Wu[4] Kha Le[4] Jennifer Rito[4] Lawrence Blatt[4] Sushmita Chanda[4] Tse-I Lin[4] Hardean Achneck[4] Edward Gane[5], [1]Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong, China, [2]King's College Hospital, [3]ARENSIA Exploratory Medicine, Republican Clinical Hospital and Nicolae Testemitanu State University, [4]Aligos Therapeutics, [5]Faculty of Medicine, University of Auckland, Auckland, New Zealand

Background: Previous data from study ALG-000184-201 (NCT04536337) demonstrated favourable safety and potent antiviral effect with 300 mg ALG-000184 monotherapy for ≤ 96 weeks. Here, we present the complete 96-week monotherapy data. **Methods:** In the study Part 4 Cohort B, TN/CNT HBeAg+ and HBeAg- subjects received open-label 300 mg ALG-000184 monotherapy for 96 weeks, followed by 8 weeks of nucleos(t)ide analogues (NA) monotherapy. **Results:** 10 HBeAg+ and 11 HBeAg- subjects were enrolled. Mean baseline levels of HBV markers in HBeAg+ and HBeAg- subjects were HBV DNA 8.0 and 4.3 $\log_{10}$ IU/mL, HBV RNA 5.3 and 2.0 $\log_{10}$ copies/mL, HBsAg 4.3 and 3.5 $\log_{10}$ IU/mL, HBcrAg 8.3 and 3.1 $\log_{10}$ U/mL, respectively. The mean baseline HBeAg level in HBeAg+ subjects was 2.6 $\log_{10}$ PEI U/mL. During monotherapy, a profound and persistent antiviral effect on HBV DNA suppression was observed. At Week 48, 60% (6/10) of HBeAg+ subjects achieved HBV DNA levels < low limit of quantitation (LLOQ, 10 IU/mL, target detected [TD]), and none achieved < LLOQ (target not detected [TND], < 4.29 IU/mL). At Week 96, these rates increased to 100% (10/10) < LLOQ [TD or TND] and 50% (5/10) < LLOQ [TND]. The

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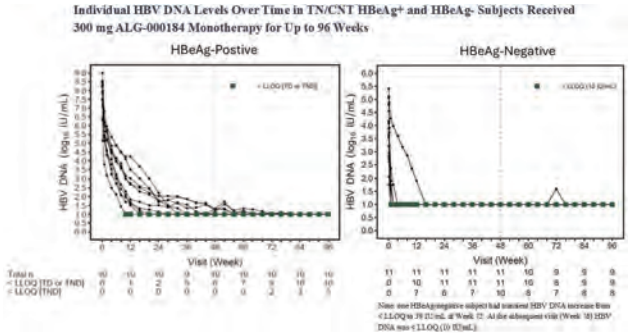
mean reductions from baseline in HBV DNA were 6.9 and 7.0 log_{10} IU/mL at Weeks 48 and 96, respectively. All 11 HBeAg- subjects achieved HBV DNA < LLOQ [TD or TND] by Week 20 with 89% (8/9) subjects achieving HBV DNA < LLOQ [TND] at Week 96. Additionally, all subjects achieved HBV RNA < LLOQ (10 copies/mL) by Week 6 in HBeAg- or by Week 52 in HBeAg+ subjects. No viral breakthrough, as assessed by HBV DNA levels, occurred in any subject. Furthermore, multi-log reductions in HBV antigens were observed in HBeAg+ subjects along with a significant decline in HBcrAg levels in HBeAg- subjects. Treatment was well tolerated with no serious adverse events (AEs) reported and no discontinuations due to treatment-emergent AEs (TEAEs). Grade 3 TEAEs included asymptomatic ALT elevations (HBeAg+: n = 3; HBeAg-: n = 1) and cholesterol/triglycerides increase (n = 1), all resolved while dosing continued. All Grade 3 TEAEs of ALT increase accompanied a significant decline in HBV DNA, with no clinical meaningful change in synthetic/excretory liver functions. **Conclusion:** Treatment with 300 mg ALG-000184 monotherapy for 96 weeks led to maintained, profound suppression of HBV DNA in TN/CNT chronic HBV infection subjects with no viral breakthrough. These findings support the continued development of ALG-000184 as a potentially improved monotherapy regimen for chronic suppression. A head-to-head comparison of ALG-000184 vs Tenofovir monotherapy has been initiated in the Phase 2 B-SUPREME study.



Disclosures: Man-Fung Yuen: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose, Alina Jucov: Nothing to Disclose, Alexei Haceatrean: Nothing to Disclose, Min Wu: Aligos Therapeutics: Employee, Kha Le: Nothing to Disclose, Jennifer Rito: Nothing to Disclose, Lawrence Blatt: Nothing to Disclose, Sushmita Chanda: Nothing to Disclose, Tse-I Lin: Nothing to Disclose, Hardean Achneck: Aligos Therapeutics: Employee, Edward Gane: Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor

0199 | EFFICACY AND SAFETY OF TOBEVIBART (VIR-3434) ALONE OR IN COMBINATION WITH ELEBSIRAN (VIR-2218) IN PARTICIPANTS WITH CHRONIC HEPATITIS DELTA VIRUS INFECTION: WEEK 48 ENDPOINT RESULTS: FROM THE PHASE 2 SOLSTICE TRIAL

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Background: Hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis with limited treatment options. The phase 2 SOLSTICE study is investigating the antiviral activity and safety of the monoclonal antibody tobevibart alone and in combination with the small interfering RNA (siRNA) elebsiran in participants with chronic HDV infection, with or without compensated cirrhosis, on NRTI therapy (NCT05461170). **Methods:** Safety and efficacy were assessed in participants receiving either tobevibart 300 mg plus elebsiran 200 mg subcutaneously (SC) every 4 weeks (tobevibart+elebsiran Q4W *de novo*) or tobevibart 300 mg SC every 2 weeks (tobevibart Q2W) for 48 weeks. The primary endpoint was a combined endpoint (CE) defined as HDV RNA < LOD (14 IU/mL) or ≥ 2 log10 decrease compared to baseline plus ALT normalization at week 24. The proportion of participants with HDV RNA < LLOQ, target not detected (TND), otherwise referred to as HDV RNA TND, is also reported by cirrhotic and non-cirrhotic status at baseline. **Results:** At 48 weeks of therapy, declines for HDV RNA and HBsAg were greatest in participants receiving tobevibart+elebsiran Q4W

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therapy. Higher rates of HDV RNA TND were observed in participants treated with tobevibart+elebsiran Q4W than in those receiving tobevibart Q2W, with this difference even more pronounced among cirrhotic participants. In participants receiving tobevibart+elebsiran Q4W, 56% of participants achieved CE and 38% achieved HDV RNA TND + ALT normalization at week 48. Participants receiving tobevibart+elebsiran Q4W maintained a multiple log reduction in HBsAg with HBsAg <10 IU/mL in ~90% at 48 weeks. Treatment-emergent adverse events were primarily Grade 1-2, transient in nature, with the most common being influenza-like syndrome, myalgia, headache, and chills in both treatment groups. No treatment-related serious adverse events occurred. **Conclusion:** At 48 weeks of therapy, higher rates of antiviral responses including HDV RNA TND and reductions in HBsAg were observed in participants receiving tobevibart+elebsiran Q4W; whereas lower antiviral rates were observed in participants receiving tobevibart Q2W. Adverse events were generally mild to moderate and transient, with no treatment-related SAEs observed. These results support further development of tobevibart+elebsiran Q4W, which is now being evaluated in a comprehensive registrational phase 3 ECLIPSE program in participants with chronic HDV infection.

	Tobevibart Q2W	Tobevibart+Elebsiran Q4W *de novo*
Week 48	N = 33[a]	N = 32[a]
HDV RNA TND, n (%)	16 (49)	21 (66)
HDV RNA TND, non-cirrhotic, n/N1[b] (%)	10/18 (56)	8/14 (57)
HDV RNA TND, cirrhotic, n/N2[b] (%)	6/15 (40)	13/18 (72)
HDV RNA <LOD or ≥ 2 $\log_{10}$ decrease from Day 1, n (%)	26 (79)	31 (97)
HDV RNA < LLOQ, n (%)	22 (67)	30 (94)
HDV RNA < LOD, n (%)	21 (64)	28 (88)
ALT normalization, n (%)	20 (61)	18 (56)
Change in ALT relative to Day 1, U/L, Median (Q1, Q3)	-22 (-74, -11)	-40 (-76, -6)
Combined Endpoint[c], n (%)	20 (61)	18 (56)
HDV RNA TND + ALT normalization, n (%)	12 (36)	12 (38)
Change in HBsAg relative to Day 1, $\log_{10}$IU/mL, Median (Q1, Q3)	-2.0 (-2.4, -1.3)	-3.5 (-3.9, -3.2)
Serious Adverse Events (SAE)	1 (3)[d]	0
TEAE by maximum severity grade, n (%)		
Grade 1	9 (27)	8 (25)
Grade 2	20 (61)	18 (56)
Grade ≥3	2 (6)[d]	0

[a] N is the number of participants who have completed the study visit or discontinued before the study visit
[b] N1 is the number of participants who were non-cirrhotic at baseline and N2 is the number of participants who were cirrhotic (CPT-A) at baseline
[c] The combined endpoint is defined as HDV RNA <LOD (14 IU/mL) or ≥ 2 log10 decrease compared to baseline plus ALT normalization.
[d] Grade 3+ TEAE reported were grade 4 neutropenia which recovered to grade 2-3 without treatment and grade 3 hepatocellular carcinoma (SAE) deemed unrelated to study drugs by the investigator.
HDV RNA assay = Roboqene 2.0 (LLOQ = 63 IU/mL; LOD = 14 IU/mL; <LLOQ, TND = target not detected)

Disclosures: Tarik Asselah: GSK: Speaker, GILEAD: Consultant, VIR Biotechnology: Speaker, Roche: consultant, ABBVIE: Speaking and Teaching, Aligos therapeutics: Consultant, Bluejay Therapeutics: Consultant, Antios therapeutics: Consultant, GSK: Consultant, Anca Streinu-Cercel: Nothing to Disclose, Alina Jucov: Nothing to Disclose, Edward Gane: Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Heiner Wedemeyer: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose, Michael Chattergoon: Nothing to Disclose, Brianna Bullard: Nothing to Disclose, Yimeng Lu: Vir Biotechnology: Employee, Cheng Huang: Nothing to Disclose, Rima Acosta: Vir Biotechnology: Employee, Cara Pilowa: Nothing to Disclose, Todd Correll: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose

0200 | HBV ENTRY INHIBITOR REVERSES RESISTANCE TO PEGYLATED INTERFERON IN HBEAG-POSITIVE CHRONIC HEPATITIS B PATIENTS: RESULTS: FROM A PHASE II MULTICENTER DOUBLE-BLIND RANDOMIZED TRIAL OF HEPALATIDE

Junliang Fu[1] Qing Mao[2] Qinglong Jin[3] Jia Shang[4] Hui Chen[5] Yongqian Cheng[1] Chenxin Meng[6] Jianxia Du[7] Guangming Li[8] Xiaoping Wu[9] Xiaoling Liu[10] Bei Zhong[11] Qin Zhang[12] Xiaolu Tang[13] Hanzhi Fang[13] Hongli Liu[13] Fusheng Wang[1], [1]The Fifth Medical Center of Chinese PLA General Hospital, [2]Southwest Hospital, Army Medical University, [3]The First Hospital of Jilin University, [4]Henan Provincial People's Hospital, [5]Jilin Hepatobiliary Disease Hospital, [6]The Sixth People's Hospital of Shenyang, [7]The Second Hospital of Nanjing, [8]Henan Provincial Infectious Disease Hospital, [9]The First Affiliated Hospital of Nanchang University, [10]Chizhou People's Hospital, [11]Qingyuan People's Hospital, [12]Shanghai Tongren Hospital, [13]Shanghai HEP Pharma Co. Ltd.

Background: Pegylated Interferon (PEG-IFN) remains the most established finite-duration therapy for chronic hepatitis B (CHB). IFN induces antiviral gene expression in hepatocytes and modulates immune cell activity to overcome HBV-associated immune tolerance. However, its limited efficacy in subgroups such as HBeAg-positive patients has prompted continued efforts to enhance interferon-based strategies. Although combinations of PEG-IFN with nucleos(t)ide analogues (NAs) have shown benefits in selected populations, their overall efficacy remains inconsistent. Enhancing IFN responsiveness through agents targeting other stages of the HBV life

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cycle may offer a synergistic benefit. This phase II trial evaluated the efficacy and safety of combining hepalatide, an HBV entry inhibitor, with PEG-IFN alpha-2a in CHB patients. **Methods:** In this multicenter, randomized, double-blind trial (NCT04426968), 96 interferon-naïve CHB patients (77 HBeAg-positive, 19 HBeAg-negative) were randomly assigned in a 1:1:1:1 ratio to receive daily subcutaneous hepalatide (2.1 mg, 4.2 mg, or 6.3 mg) or placebo for 24 weeks, each combined with weekly PEG-IFN (180 μg) for 48 weeks. Virological response, defined as a ≥ 2 $\log_{10}$ IU/mL reduction in HBV DNA or HBV DNA <20 IU/mL, as well as serum HBsAg levels, were assessed at week 24. Safety profiles were also monitored throughout the study. **Results:** The combination treatment was well tolerated, with no additional adverse events attributable to hepalatide beyond those associated with PEG-IFN alone. By week 24, 5 of 6 (83.3%) HBeAg-negative patients receiving PEG-IFN monotherapy achieved HBV DNA <20 IU/mL, whereas none of the 18 HBeAg-positive patients reached this level, indicating marked resistance to PEG-IFN. However, the addition of hepalatide (4.2 mg) significantly reversed this resistance. Virological response rates at week 24 were significantly higher in HBeAg-positive patients treated with 4.2 mg hepalatide (83.3%, 95% CI: 58.6–96.4; $p<0.025$) compared to placebo (44.4%, 95% CI: 21.5–69.2). Overall, combination therapy achieved a virological response in 74.6% (44/59) of HBeAg-positive patients and resulted in greater mean HBV DNA reductions from baseline (Fig 1A). Due to higher baseline viral loads, extended treatment might be necessary for HBeAg-positive patients to achieve HBV DNA <20 IU/mL. Importantly, the proportion of HBeAg-positive patients achieving HBsAg levels <3000 IU/mL notably increased from baseline to week 24 with PEG-IFN plus hepalatide compared to placebo (Fig 1B), potentially expanding eligibility for HBsAg mRNA-targeted therapies. **Conclusion:** The addition of hepalatide to PEG-IFN therapy effectively reversed resistance in HBeAg-positive CHB patients, leading to improved antiviral efficacy. These results support further evaluation of this combination strategy to enhance long-term interferon-based treatment outcomes.

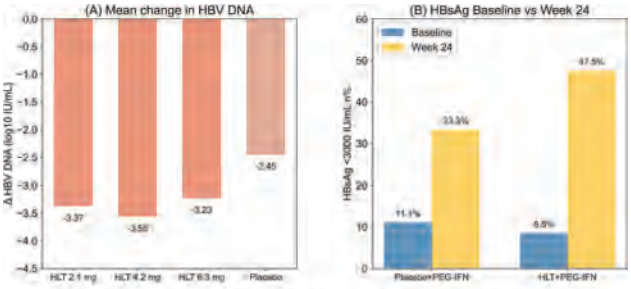

Figure 1. (A) Mean HBV DNA reduction from baseline in HBeAg-positive patients. (B) Percentage of HBeAg-positive patients with HBsAg lower than 3000 IU/mL at baseline and at 24 weeks.

Disclosures: Junliang Fu: Nothing to Disclose, Qing Mao: Nothing to Disclose, Qinglong Jin: Nothing to Disclose, Jia Shang: Nothing to Disclose, Hui Chen: Nothing to Disclose, Yongqian Cheng: Nothing to Disclose, Chenxin Meng: Nothing to Disclose, Jianxia Du: Nothing to Disclose, Guangming Li: Nothing to Disclose, Xiaoping Wu: Nothing to Disclose, Xiaoling Liu: Nothing to Disclose, Bei Zhong: Nothing to Disclose, Qin Zhang: Nothing to Disclose, Xiaolu Tang: Nothing to Disclose, Hanzhi Fang: Shanghai HEP Pharma Co., Ltd.: Employee, Hongli Liu: Nothing to Disclose, Fusheng Wang: Nothing to Disclose

0201 | HUMAN BILIARY ATRESIA EXTRAHEPATIC CHOLANGIOCYTE ORGANOIDS EXPRESS INCREASED ER AND OXIDATIVE STRESS, ALTERED DRUG METABOLISM AND CELL POLARITY CHANGES

Orith Waisbourd-Zinman[1] Adi Har-Zahav[2] Yara Hamody[2] Keren Danan[3] Ana Tobar[4] Michal Basphelchik[2] Raanan Shamir[5] Irit Gat-Viks[6], [1]Faculty of Medical and Health Sciences, Tel Aviv University, [2]Felsenstein Medical Research Center, Faculty of Medical and Health Sciences, Tel Aviv University, [3]The Shmunis School of Biomedicine and Cancer Research, George S. Wise Faculty of Life Sciences, Tel, [4]Department of Pathology, Beilenson Medical Center, Petach-Tiqva, [5]Pediatric Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center, [6]The Shmunis School of Biomedicine and Cancer Research, George S. Wise Faculty of Life Sciences

Background: Biliary atresia (BA), the leading cause of liver transplantation in children, presents in neonates with jaundice and progressive extrahepatic bile duct obstruction, yet its etiology and pathogenesis remain unknown. Here, we aimed to investigate the molecular mechanisms underlying BA and the susceptibility of cholangiocytes in the extrahepatic biliary tree using patient-derived extrahepatic cholangiocyte organoids (EHCOs). **Methods:** EHCOs were derived from common bile ducts remnants of BA patients undergoing Kasai portoenterostomy and from non-BA controls at the time of liver transplantation. Transcriptomic profiling was performed via bulk RNA sequencing, and analyzed in two ways: differentially expressed pathways and perturbation analysis to predict aberrant functions. Key findings were validated through mechanistic assays, immunofluorescence staining, qPCR and transmission electron microscopy (TEM). **Results:** Transcriptomic analysis predicted significant alteration in endoplasmic reticulum (ER) stress, dysregulations of drug metabolism, alongside pronounced alterations in cellular adhesion and polarity-related genes in BA-derived EHCOs. Cell-to-cell alterations were observed with

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various proteins including E-cadherin, RhoU, Sox17 and CFTR. BA EHCOs had an increased endoplasmic reticulum (ER) stress response, exemplified by elevated *PERK, BiP*, and *ATF4* along with abnormal ER on TEM. While *CHOP, ERO1A, WFS1*, and *SOD3* were decreased suggestive of abnormal ER stress response. BA EHCOs displayed increased toxicity to biliatresone-induced injury and inhibition of cytochrome P450 resulted in attenuation of the ER stress markers *PERK, BiP* and *ATF4*. Finally, liver hilum biopsies from BA patients undergoing Kasai portoenterostomy confirmed elevated PERK and PGR78(*BiP*) consistent with the EHCOs analysis. **Conclusion:** BA EHCOs exhibit disrupted polarity, ER stress, and increased susceptibility to drug toxicity. These findings highlight key pathogenic mechanisms in BA and suggest that targeting these pathways may help mitigate cholangiocyte injury in BA.

Disclosures: Orith Waisbourd-Zinman: Nothing to Disclose, Adi Har-Zahav: Nothing to Disclose, Yara Hamody: Nothing to Disclose, Keren Danan: Nothing to Disclose, Ana Tobar: Nothing to Disclose, Michal Basphelchik: Nothing to Disclose, Raanan Shamir: Nothing to Disclose, Irit Gat-Viks: Nothing to Disclose

0202 | DYSPLASTIC LYMPHATIC ENDOTHELIAL NICHE SIGNALS REGULATE EPITHELIAL OUTCOMES IN BILIARY ATRESIA

Leonie Schumm[1] Robert Lorenz Chua[2] Matylda Zofia Kuzinska[1] Marie Uecker[3] Rose Behncke[1] Philip Bufler[1] Christian Conrad[2] Milad Rezvani[1], [1]Charite University Medicine Berlin, [2]Berlin Institute of Health, [3]Medizinische Hochschule Hannover

Background: Biliary Atresia (BA) is the leading cause of pediatric liver transplantation. The complex inflammatory pathophysiology of BA is extensively studied. Yet, the mechanisms by which inflammatory and morphogenic dysregulations cause biliary dedifferentiation and impaired bile drainage remain unclear. **Methods:** In our multi-modal and multi-dimensional analyses of clinically stratified liver samples from BA patients and cholestatic controls, we dissected the immune and morphogenic landscapes (Fig.1). Multiplexed immunofluorescence (mpIF), whole-mount light-sheet microscopy, single-nuclei RNA sequencing (snRNA-Seq), and spatial transcriptomics were applied. Stratified BA samples aimed at understanding intrahepatic mechanisms behind biliary outcomes after hepatoportoenterostomy: infants achieving bile drainage (successful Kasai), indicated by normalized bilirubin levels at 100 days post-Kasai, versus those needing liver transplantation (failing Kasai). Intrahepatic cholangiocyte organoids (ICOs) functionally validated inferred data. **Results:** MpIF revealed the expansion of dysplastic lymphatic endothelial cells (LECs) in the portal areas of BA patients. Whole mount light-sheet microscopy enabled detailed characterization of the abnormal LEC network morphology in BA. SnRNA-Seq and mpIF captured LEC heterogeneity and a surge of T-cell and dendritic cell-engaging chemokines in failing Kasai patients, while the same set of LEC-derived chemokines inhibited ICO growth at high doses but promoted growth in a trophic milieu. These findings indicate an inflammatory rheostat of physiological biliary growth with significant contribution of the LEC network. In addition, LECs appeared defective in Notch-signaling, underscoring that dysplastic LECs in BA may not only cause autoinflammation but also biliary dedifferentiation. **Conclusion:** In summary, we demonstrate LEC-derived regulatory effects on biliary outcomes between successful and failing Kasai patients. Targeting dysfunctional LEC signaling may be relevant for future cohort-specific treatment.

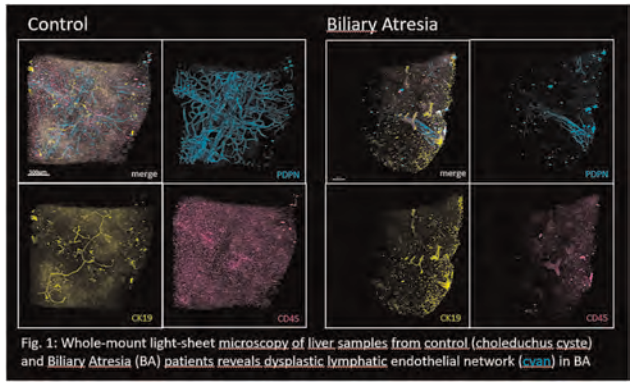

Fig. 1: Whole-mount light-sheet microscopy of liver samples from control (choledochus cyste) and Biliary Atresia (BA) patients reveals dysplastic lymphatic endothelial network (cyan) in BA

Disclosures: Leonie Schumm: Nothing to Disclose, Robert Lorenz Chua: Nothing to Disclose, Matylda Zofia Kuzinska: Nothing to Disclose, Marie Uecker: Nothing to Disclose, Rose Behncke: Nothing to Disclose, Philip Bufler: Nothing to Disclose, Christian Conrad: Nothing to Disclose, Milad Rezvani: Nothing to Disclose

★ 0203 | DEVELOPMENT AND VALIDATION OF A RISK SCORE FOR SCREENING SIGNIFICANT LIVER FIBROSIS IN THE GENERAL PEDIATRIC POPULATION: A PROSPECTIVE COHORT STUDY

xiaoguo li[1] Bicheng Ye[1] Shanghao Liu[1] Gaojun Teng[1] Xiaolong Qi[1], [1]zhongda hospital, Southeast University, Nanjing, China.

Background: Reliable and accessible screening tools are required to screen for significant liver fibrosis in the general pediatric populations. We aimed to develop and validate a novel tool for effective screening of liver fibrosis in this population. **Methods:** This prospective cohort study comprised three independent cohorts: training, validation

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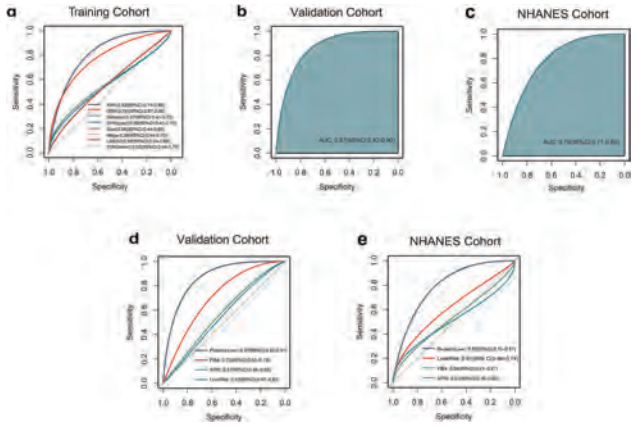
and National Health and Nutrition Examination Survey (NHANES) cohorts. Nine machine learning algorithms were assessed, and the one with the highest area under the curve (AUC) was chosen to develop the PediatricLiver score. Significant liver fibrosis was defined as a liver stiffness measurement (LSM) of ≥8.0 kPa as determined by transient elastography. **Results:** In total of 1,767 participants were included, with a mean (SD) age of 14.88 (2.16) years (43.69% male; n = 772) and a mean LSM of 5.35 (2.04) kPa. The training cohort comprised 437 participants. The PediatricLiver score, developed using the K-Nearest Neighbors algorithm, incorporated age, sex, body mass index (BMI), low-density lipoprotein cholesterol, gamma-glutamyl transferase, albumin, and globulin levels. The score showed good performance with an AUC of 0.82 (95% CI: 0.74–0.89), with a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 0.78, 0.70, 0.13, and 0.98, respectively. A PediatricLiver score <5.53 indicates a low risk of significant liver fibrosis. The score was confirmed in the validation (n = 730) and NHANES (n = 600) cohorts and showed AUCs of 0.87 (95% CI: 0.82–0.90) and 0.79 (95% CI: 0.71–0.86), sensitivity of 0.90, specificity of 0.68, PPV of 0.17, and NPV of 0.99, and sensitivity of 0.84, specificity of 0.60, PPV of 0.10, and NPV of 0.99. The score outperformed established non-invasive fibrosis scores. In the validation cohort, it achieved an AUC of 0.87, significantly outperforming Fibrosis-4 (AUC = 0.72), AST to platelet ratio index (AUC = 0.57), and LiverRisk (AUC = 0.55). And the score demonstrated good performance in BMI-defined subgroups. In the normal-weight subgroups, AUC values ranged from 0.80 to 0.85. In the overweight/obese subgroups, AUC values ranged from 0.75 to 0.83. A free, open-access web-based calculator for the PediatricLiver score (https://pediatricliverscore.shinyapps.io/child_shiny/). **Conclusion:** The PediatricLiver score is a novel machine learning-based tool for screening significant liver fibrosis in the general pediatric population.



Disclosures: xiaoguo li: Nothing to Disclose, Bicheng Ye: Nothing to Disclose, Shanghao Liu: Nothing to Disclose, Gaojun Teng: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose

0204 | FRACTURES IN PATIENTS WITH ALAGILLE SYNDROME: DATA FROM THE GALA STUDY GROUP

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Background: Alagille syndrome (ALGS) is an autosomal dominant disorder associated with cholestasis and multi-system anomalies, including skeletal involvement. This study aims to describe fracture rates and patterns in ALGS. **Methods:** The Global ALagille Alliance (GALA) is an international, multicenter, retrospective study of ALGS patients. We characterized fracture rate and locations, and other clinical data in GALA. Chi-square tests, regression analyses and Wilcoxon rank-sum tests were performed. **Results:** Of 1561 patients in GALA, 182 (11.7%) patients reported at least 1fracture. 3 patients were excluded for incomplete data. Most fractures (63.7%) occurred before the age of 6 years and 25.7% were before age 2. The majority of patients had 1 fracture (62%), and the remaining had 2 fractures (14.5%), 3 (9%), and $>=4$ (14%). The mechanism of injury differed based on whether the patient had 1-2 vs. $>=3$ fractures ($p=0.006$) (Figure 1). Most fractures were in lower extremity long bones including femur (26.4%), tibia (18.3%), and fibula (6.1%), but unusual locations including skull (6.4%) and rib (3.3%) were also reported. There was no difference in platelets between those with or without fracture ($p=0.5$) nor in those with 1 fracture compared to multiple fractures ($p=0.2$). In a multivariate regression analysis, platelets were associated with age at fracture, but not sex, mechanism of injury, or history of tibia/femur fracture. Compared to the entire GALA cohort, those with fracture were more likely to have a congenital skeletal anomaly (63% vs. 51%, $p<0.002$), renal anomaly (47% vs. 35%, $p<0.001$), and been listed for liver transplant (48.9% vs. 27.6%, $p<0.001$). **Conclusion:** Fractures are a common complication in ALGS, affecting mostly young children and lower extremity long bones. Given the young age and location of fracture, these could be falsely attributed to non-accidental trauma. Reporting these fractures is important to protect caregivers of children with ALGS and to inform child abuse specialists. Cholestatic liver disease is a known risk factor for fractures, however, given the role of Notch signaling in bone development, in ALGS, patients may have intrinsic risk factors separate from cholestasis. Our

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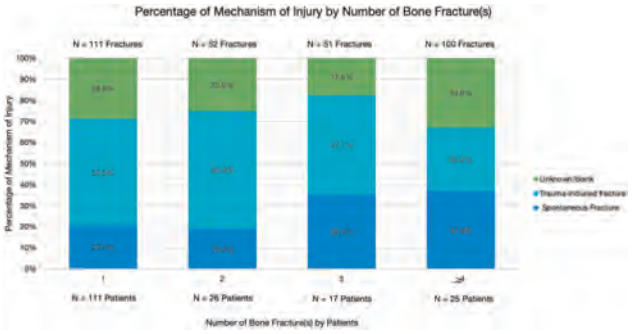
data show that fractures were more common in patients with other congenital anomalies, including skeletal and renal, and platelets did not differ based on history of fracture, suggesting that fracture risk may be impacted by more than advanced liver disease. More investigation is needed to determine if bone directed therapy may be beneficial to children with ALGS.



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0205 | NOVEL EMAPALUMAB-CONTAINING REGIMEN FOR TREATMENT OF INDETERMINATE SEVERE HEPATITIS IN THE SETTING OF T-CELL–MEDIATED IMMUNE DYSREGULATION

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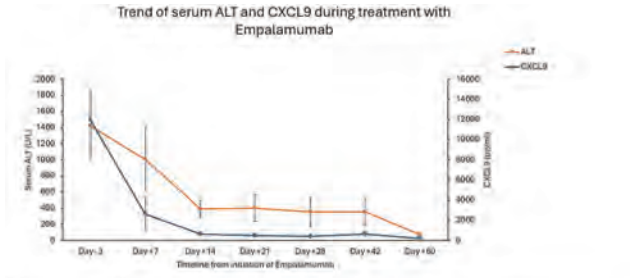
Background: Indeterminate severe hepatitis (iSH) in children is characterized by CD8˚ cytotoxic T cell infiltration and may lead to acute liver failure. Recent studies indicate that interferon-gamma (IFN-γ) plays a significant role in iSH pathogenesis. We report the largest retrospective study showing that Emapalumab (EMB), a monoclonal antibody neutralizing IFN-γ, can promote iSH resolution in a cohort of patients with steroid-refractory/dependent iSH. **Methods:** We retrospectively reviewed the medical records of 12 children diagnosed with iSH between 2019 and 2025. Liver biopsies in most patients demonstrated dense CD8˚ T-cell infiltration. Patients were classified as steroid-refractory—defined by persistent elevation or worsening of alanine transaminase (ALT) despite corticosteroid therapy, or steroid-dependent, in which ALT levels rose upon tapering steroids. Resolution of iSH was defined as normalization of ALT to <100 IU/mL. C-X-C motif chemokine ligand 9 (CXCL9), an IFN-γ chemokine, was used as a biomarker to monitor response to EMB therapy. **Results:** At presentation, patient characteristics included a median age of 56 months (22–136), ALT 2,491 U/L (1,453–4,937), total bilirubin 8.0 mg/dL (5.2–12.9), direct bilirubin 6.2 mg/dL (3.7–9.5), international normalized ratio (INR) 1.2 (1.0–1.4). Initial treatment included corticosteroids (prednisone-equivalent dose: 1–4 mg/kg/day) for a median duration of 55 days (29-78). Due to steroid refractoriness or dependence, EMB was used as a second-line agent in 8 patients and as a third- or fourth-line agent in 4 patients. EMB was initiated at a median of 37 days post-diagnosis (range: 3–104), at a starting dose ranging from 1-5 mg/kg, with a median of 11 doses (6–35). At initiation, median ALT was 1031 U/L (398-4937), total Bilirubin 3.1 mg/dl (0.4-17), direct bilirubin 2 mg/dl (0.2-10.5), INR 1.2 (0.9-1.9) and CXCL9 was 8993 pg/mL (900–33,739, normal <647 pg/mL). After four weeks of EMB therapy, CXCL9 and ALT decreased significantly, with complete normalization of ALT achieved at a median of 54 days (12-120). EMB was well tolerated, with no reported adverse events attributed to the drug. At last follow-up (median: 539 days; range: 90–1,460), all patients were alive with normal liver function, and none required liver transplantation. **Conclusion:** This study provides strong clinical evidence supporting IFN-γ blockade in iSH. EMB was associated with rapid normalization of liver function and marked reduction in CXCL9 levels, even in patients unresponsive to conventional therapies. Importantly, all patients survived without progression to liver failure or need for transplantation, and no major EMB-related adverse events were observed. These findings highlight the promising role of EMB as a targeted immunotherapy for iSH and support prospective clinical trials to define its optimal dosing, duration, and long-term efficacy in this high-risk population.



Notable reduction of ALT (levels shown on the left Y-axis in U/L, represented in the orange line) and CXCL9 (levels shown on the right Y-axis, represented in the blue line) in patients undergoing Emapalumab treatment. ALT: Alanine aminotransferase. CXCL9: Chemokine (C-X-C motif) ligand 9.

Disclosures: Urvi Kapoor: Nothing to Disclose, Kirsty Hillier: Sobi: Advisory Board, Jennifer Vittorio: Mirum Pharma: Consultant, Gloria Contreras Yametti: Nothing to Disclose, Debora Kogan-Liberman: Mirum: Consultant, Dana Goldner: Takeda: prior site PI for alpha-1 antitrypsin clinical trial, Albireo/Ipsen: Prior site PI for biliary atresia study, Taylor Fitch: Nothing to Disclose,

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★ 0206 | INDUCTION OF EXHAUSTION PATHWAYS DEFINES THE IMMUNE MICROENVIRONMENT AND PREDICTS SURVIVAL WITH NATIVE LIVER IN PEDIATRIC ACUTE LIVER FAILURE

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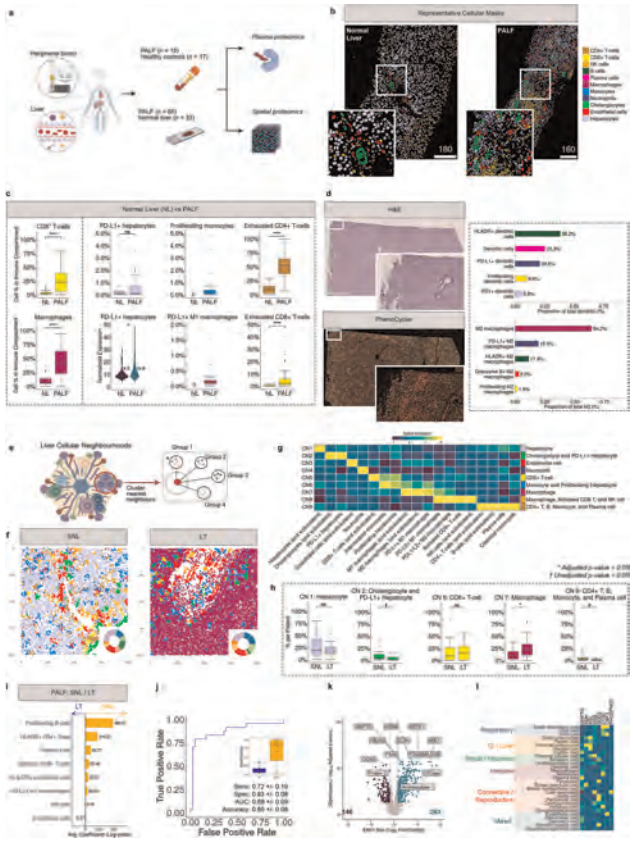
Background: Pediatric acute liver failure (PALF) is a rapidly progressive, multi-etiologic disease in otherwise healthy children. Despite its multifactorial nature, a unifying feature of PALF is a dense inflammatory infiltrate with a subset of patients distinguished by an activated T cell phenotype. Here, we look to expand our understanding of the immune microenvironment in PALF by spatial and plasma proteomics to discover features that differentiate patients who survive with native liver (SNL). **Methods:** Our single center cohort of 66 patients with PALF (24 with SNL and 34 indeterminate etiology) was compared to 33 normal liver controls (NL) (Fig. 1A). Custom immunophenotyping panels were utilized across two complementary spatial proteomic technologies to compare patients across NL vs. PALF, indeterminate vs. known cause, SNL vs. LT, and across time. Tissues results were correlated to peripheral biomarkers in a cohort of 11 PALF patients as compared to 16 healthy controls. **Results:** A total of 1.7 x 10^6 cells were identified across two spatial proteomic technologies, with enrichment of CD8+ T-cell and macrophage populations in PALF (Fig. 1B-D). Use of functional markers highlight exhaustive T cell phenotypes and damage compensatory mechanisms through parenchymal and macrophage PD-L1 upregulation and PALF exclusive proliferating monocyte subpopulations (Fig. 1C). Deep immune profiling of an indeterminate case of PALF through Phenocycler revealed significant populations of novel immunoregulatory M2 macrophage and dendritic cell populations not yet described in literature (Fig. 1D). Observation of mixed immune aggregates prompted cellular neighbourhood analysis revealing the presence of T, B, plasma, and myeloid tertiary lymphoid organs (TLO) present in PALF tissues (Fig. 1E-G). These TLOs alongside PD-L1+ hepatocyte-cholangiocyte islands associate with SNL, suggestive of spatial niches that may regulate autoimmunity (Fig. 1H). Unbiased predictive modeling of subclusters linked to outcomes reveals an enrichment of populations associated with these TLOs with robust statistical performance (Fig. 1I-J). Analysis of 1500 metabolic and immune centric peripheral plasma proteins confirms over 400 differentially expressed factors (Fig. 1K). Predictive modeling also identified 8 PALF candidate proteins that map to hepatic and immune-centric populations (Fig. 1L). **Conclusion:** Our results demonstrate that liver parenchymal and myeloid lineage subpopulations express immunoregulatory factors that reliably predict disease outcome. These subpopulations co-localize in space with adjunctive T, B, and plasma cell populations to form TLOs that may form the sites of immunoregulation to curb unmitigated hepatic damage. Furthermore, these populations can be linked to circulating proteins and can be used in conjunction as predictive biomarkers in identifying and prognosticating disease progression.



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0207 | ETIOLOGY OF PEDIATRIC ACUTE LIVER FAILURE IN PATIENTS SCREENED FOR THE TREATMENT FOR IMMUNE MEDIATED PATHOPHYSIOLOGY (TRIUMPH) TRIAL

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Background: Many cases of pediatric acute liver failure (PALF) are of unknown cause, designated indeterminate (IND-PALF). The liver injury in the majority of IND-PALF cases is characterized by hepatic CD8+ T-cell inflammation, and this phenotype has been labeled Activated T-cell PALF (TC-PALF). The Treatment for Immune Mediated Pathophysiology (TRIUMPH) trial is a multicenter double-blind, randomized, placebo-controlled trial testing the efficacy and safety of high dose methylprednisolone or antithymocyte globulin as treatment for children with PALF of unknown cause (U01DK127995). We describe the landscape of PALF during TRIUMPH enrollment to date. **Methods:** Patients aged 1-17 years admitted to a participating center hospital 2/9/2022 – 4/14/2025 who met PALF criteria were screened for TRIUMPH eligibility. Patients were not enrolled due to 1) met a study exclusion criterion, 2) improved and no longer met PALF criteria, and 3) declined to participate. TRIUMPH enrolled subjects were classified as TC-PALF if they had a liver biopsy with predominant CD8+ T-cell inflammation. **Results:** 568 PALF patients were screened by 21 study centers and 436 (77%) were ineligible for TRIUMPH. Acetaminophen toxicity (n = 189, 44%) was the most common exclusion (median age 15 years (IQR 13-16), 81% female), followed by liver injury due to ischemia (n = 83, 19%) and sepsis (n = 52, 12%). 121 patients met ≥ 2 exclusion criteria. 5 patients were excluded due to a positive adenovirus test during the outbreak in 2022 and 9 between 1/23-4/25; 15 were excluded due to SARS-CoV-2. Table 1 lists patient exclusions. 96 patients met TRIUMPH inclusion criteria but were not enrolled due to rapid improvement (n = 69) or consent decline (n = 27). Common reasons for declining to participate included risks of study medications and unknown benefits to participants. 36 subjects enrolled in TRIUMPH: median age 5 years (IQR 2-10), 50% female. 24 (67%) were classified as TC-PALF based on liver histology; the other 12 subjects remained in the IND-PALF group (n = 3 minimal CD8 staining, n = 9 no liver tissue available). **Conclusion:** In this contemporary multicenter study, acetaminophen toxicity was the most common PALF etiology identified. Among 132 eligible patients, 52% rapidly improved prior to consenting for TRIUMPH. Many IND-PALF patients can now be classified as TC-PALF and TRIUMPH trial results may shed light on optimal treatment for this group. Ongoing ancillary studies will explore more detailed characterization of patients not enrolled in TRIUMPH including those with rapid improvement.

Table 1. Reasons for exclusion for 436 patients who met at least 1 TRIUMPH exclusion criteria

Individual Reasons for Exclusion:	N	%
Acute drug- or toxin-induced liver injury	213	35.5
Acetaminophen	189	31.5
Others	24	4.0
Liver injury due to ischemia	83	13.9
Sepsis	52	8.7
Therapy with an immunosuppressive agent, including chemotherapy, within the past 6 weeks	48	8.0
History of malignant neoplasm within 5 years or current disease	32	5.3
Imminent risk of death as judged by site investigator	26	4.3
Solid organ or stem cell transplant recipient	19	3.2
History of recreational drug use within the past 4 weeks	18	3.0
Evidence of active viral infection	17	2.8
Hepatitis E	1	0.1
Herpes Simplex Virus	1	0.1
Adenovirus	14	2.3
Other/Unknown	1	0.1
Diagnosis of autoimmune hepatitis	17	2.8
Diagnosis of hemophagocytic lymphohistiocytosis	15	2.5
Positive test for SARS-CoV-2	15	2.5
Diagnosis of inborn error of metabolism	12	2.0
Other(s)	32	5.3

#Note that multiple patients met more than 1 exclusion criteria and percentages reflect contribution to 599 individual exclusion criteria entered in screening dataset

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★ 0208 | BYSTANDER ACTIVATION OF CYTOTOXIC CD8 T CELLS AS A MECHANISM FOR INDETERMINATE PEDIATRIC ACUTE LIVER FAILURE

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Background: Indeterminate Pediatric Acute Liver Failure (IPALF) is the most common etiology listed for children requiring liver transplant for PALF. IPALF is believed to be mediated by activated cytotoxic T cells and is sometimes referred to as T cell PALF (TC-PALF). A mechanistic understanding of how T cells in IPALF are activated and recruited may offer diagnostic, prognostic and/or therapeutic benefits. **Methods:** 10x Genomics 5' single-cell RNA-sequencing with VDJ sequencing, and fixed RNA profiling were used to create a single-cell RNA map of the IPALF liver. Flow cytometry, and IF staining were performed to confirm transcriptomic findings on a protein level. **Results:** Our combined 5' and fixed RNA single-cell transcriptomic map was comprised of 106,107 cells from 8 IPALF, 6 ALF, 3 Dx-PALF and 3 healthy pediatric patients. The IPALF liver map was rich in T cells, and the predominant T cell population in IPALF was cytotoxic CD8 T cells. The cytotoxic T cell population expressed markers associated with bystander activation and lacked markers associated with canonical TCR mediated activation ($NKG2D^+/CD25^-$). TCR clonality analysis indicated a polyclonal T cell population and inferred cell-ligand receptor analysis implicated CCL5:CCR5 signalling as a potential recruitment mechanism. A similar transcriptional phenotype was not seen in our three control groups. Our in-silico findings were supported by increased expression of CD8 and NKG2D in IPALF compared to healthy pediatric on IF and flow cytometry. **Conclusion:** We present an expansion of our previously reported first single-cell atlas of the liver cellular microenvironment in IPALF. We found the IPALF liver uniquely displays a transcriptional signature associated with bystander activation. These findings were supported on a protein level using IF/IHC and flow cytometry. Bystander activation of CD8 T Cells may cause IPALF in some children.

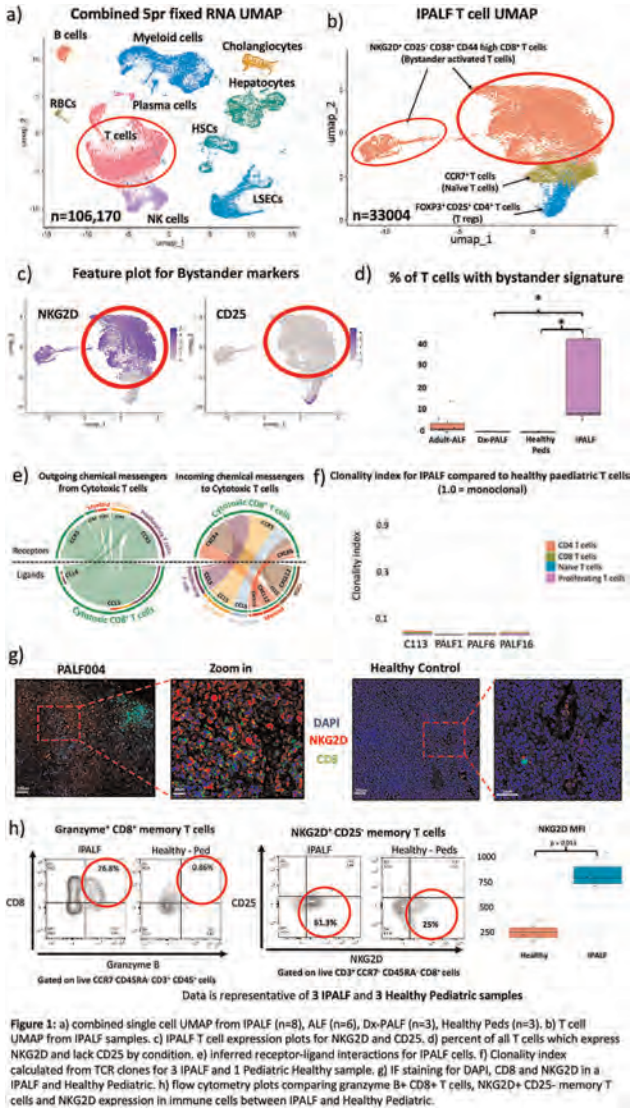

Figure 1: a) combined single cell UMAP from IPALF (n=8), ALF (n=6), Dx-PALF (n=3), Healthy Peds (n=3). b) T cell UMAP from IPALF samples. c) IPALF T cell expression plots for NKG2D and CD25. d) percent of all T cells which express NKG2D and lack CD25 by condition. e) inferred receptor-ligand interactions for IPALF cells. f) Clonality index calculated from TCR clones for 3 IPALF and 1 Pediatric Healthy sample. g) IF staining for DAPI, CD8 and NKG2D in a IPALF and Healthy Pediatric. h) flow cytometry plots comparing granzyme B+ CD8+ T cells, NKG2D+ CD25- memory T cells and NKG2D expression in immune cells between IPALF and Healthy Pediatric.

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★ 0209 | EPITOPE MISMATCH SUCCESSFULLY IDENTIFIES PEDIATRIC LIVER TRANSPLANT RECIPIENTS AT RISK FOR LATE T-CELL MEDIATED REJECTION

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Background: De novo anti-HLA donor specific antibodies (dnDSA) production is associated with higher mismatch (MM) load for T cell epitopes evaluated by PIRCHE-II and B cell epitopes evaluated by HLAMatchmaker. We have previously reported an association between development of dnDSA and an increased likelihood of T cell mediated rejection (TCMR) in pediatric liver transplant (LT) recipients.We therefore sought to determine if evaluation of T and B cell epitope differences in HLA-DR/DQ MM can offer a risk stratification strategy for follow- up and intervention. **Methods:** A retrospective chart review of 85 pediatric patients consecutively transplanted with an isolated LT at our center between 2019 and 2023 identified 85 patients with high resolution HLA typing and DSA measurement. Clinical data collected included demographics, transplant information, and tacrolimus levels. TCMR was biopsy proven. MM analysis was performed using PIRCHE-II and Matchmaker to derive PIRCHE, Snow, and Matchmaker scores. Statistical analysis: Descriptive statistics by dnDSA were summarized by dnDSA and comparisons between dnDSA groups were performed using two-sample t tests or Pearson's chi-squared tests. For the time to TCMR, multivariable Cox analyses using stepwise and *lasso* variable selection were performed. Landmark Cox regression was followed for the cohort after 1-year post LT. **Results:** Figure 1 shows patients included in analysis. 29 patients had dnDSA (43.9%) within 1-year post LT. Recipients with dnDSA had significantly higher median epitope MM scores ($p = 0.001$). 26 patients had TCMR (40.6%). Using a lasso model that included PIRCHE-II, Matchmaker, Snow scores, and mean tacrolimus level, the time to TCMR was shorter in recipients with high epitope MM scores vs. those with low scores [95%CI:718 (463, NA) days vs.1451 (722, NA) days $p = 0.051$]. Looking only at the cohort who developed TCMR after 1-year post LT, the time to TCMR was significantly shorter in recipients with high epitope MM scores vs. those with low scores (Figure 2; $p = 0.044$). **Conclusion:** Combined T and B cell MM load for HLA-DR/DQ is a useful tool to stratify pediatric LT recipients at risk for development of TCMR after 1-year post LT.

Disclosures: Deepika Reddy: Nothing to Disclose, Udeme Ekong: Nothing to Disclose

0210 | OUTCOMES AFTER PEDIATRIC FIRST VARICEAL HEMORRHAGE – RESULTS: FROM 44 CENTERS PARTICIPATING IN THE INTERNATIONAL MULTICENTER PEDIATRIC PORTAL HYPERTENSION REGISTRY (IMPPHR)

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Background: Approaches to managing varices in children are controversial in part due to a lack of high-quality evidence regarding outcomes after pediatric first variceal hemorrhage (1VH). The International Multicenter Pediatric Portal Hypertension Registry (IMPPHR), a research collaboration of 44 centers in 18 countries on 6 continents, aims to address this knowledge gap. **Methods:** Resources and potential approaches to managing portal hypertension were assessed by querying center characteristics and clinical activity undertaken between Jan 2018 and Dec 2019. Medical records were reviewed for subjects, 0–18 years, at the centers who had 1VH between July 2012 and June 2017 with follow up to June 2020 or the first of death or liver transplant. K-means clustering was employed to cluster centers *a priori* based upon parameters in Table 1. Kaplan-Meier and multivariant Cox regression modeling were employed to assess outcomes and risk factors. 95% confidence intervals are reported [i.e. (5,95)]. **Results:** The 44 centers could be segregated into 3 clusters based upon a matrix of procedural range and volume parameters (Table). 347 subjects (129-biliary atresia [BA], 118-portal vein thrombosis [PVT], 100 other diagnoses) had 1VH at a median of 37 (13, 108) months. At 3 years post 1VH, overall survival was 87.9% (84.2,91.8), while survival with native liver (SNL) was 61.3% (56.2,66.8). Three-year survival and SNL after 1VH were significantly greater in subjects with PVT (96.4 and 95.5%) or noncirrhotic diseases (100 and 95.7%) compared to BA (85.6 and 33.9%) and other cirrhotic diseases (69.2 and 41.2%). In BA SNL after 1VH was markedly reduced in subjects whose total bilirubin did not fall below 2 mg/dL within 6 months of Kasai procedure ($p < 0.001$). Diuretic use (an indirect marker of decompensated disease) (HR 2.2 [1.5,3.2]) and employment of sclerotherapy (HR 3.2 [1.9,5.5]) were associated with significantly reduced SNL, and sclerotherapy was associated with increased mortality (HR 6.8 [2.0,22.9]). Subjects undergoing sclerotherapy ($n = 111$) were younger (median age 11 months) more likely to have biliary atresia (66%), with poor bile flow (31%) and to have ascites (50%). On multivariate analysis the impact of sclerotherapy was independent of age at 1VH as either a continuous variable or with a cut-off of 24 months. Overall 6-week mortality after 1VH was 4% (PVT 0%) and after propensity matching was significantly lower in cluster 1 compared to cluster 2 centers (cluster 1 – 0%, cluster 2 -7.7%, cluster 3 - 2.2%, $p = 0.009$). 6-week mortality for subjects undergoing sclerotherapy was 10.8%. **Conclusion:** In general early mortality following 1VH in pediatrics is low, especially for children with PVT or noncirrhotic diseases. Outcomes are worse in those with decompensated disease or those receiving sclerotherapy. Sclerotherapy appears to be employed in a specific high risk group of subjects. Center characteristics may impact short-term mortality after 1VH.

Table – Cluster Characteristics

Characteristic	Cluster 1	Cluster 2	Cluster 3
# centers	5	21	18
# hospital beds	312 [268, 378][1]	152 [60, 204]	372 [296, 477]
# ICU beds	31 [20, 60]	14 [10, 20]	48 [37, 69]
# whole liver OLT	8 [7, 9]	0 [0, 5]	18 [9, 21]
# technical variants + living donor OLT	57 [44, 91]	6 [0, 20]	10 [4, 26]
# TIPS + PSS[2]	15 [7, 15]	0 [0, 2]	1 [0, 4]
# Mesorex bypass	6 [2, 8]	0 [0, 1]	0 [0, 1]
# EVL + EST[3]	164 [18, 186]	17 [15, 30]	26 [21, 40]
% EVL/(EVL + EST)	80 [60, 84]	90 [67, 100]	92 [76, 100]

[1]median [IQR], [2] transjugular intrahepatic portosystemic + portosystemic shunt. [3] endoscopic variceal ligation + endoscopic sclerotherapy

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0211 | ZETOMIPZOMIB, A FIRST-IN-CLASS SELECTIVE IMMUNOPROTEASOME INHIBITOR, DEMONSTRATES STEROID SPARING BIOCHEMICAL REMISSION IN PATIENTS WITH RELAPSED OR INSUFFICIENTLY RESPONDING AUTOIMMUNE HEPATITIS IN A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2A STUDY

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Background: Zetomipzomib (zeto), a selective immunoproteasome inhibitor, has shown anti-inflammatory activity in systemic lupus erythematosus. We report safety, tolerability, and efficacy of the PORTOLA study (NCT05569759), a Phase 2a, 24-week (W), randomized, double-blind, placebo-controlled trial of zeto in patients (pts) with autoimmune hepatitis (AIH) and ongoing hepatic inflammation despite standard treatments (txs). **Methods:** Eligible pts were $\geq$18 years of age with uncontrolled active disease or flare, ALT 1.25–10 $\times$ ULN, and modified HAI $\geq$5/18 on liver biopsy. Pts with decompensated cirrhosis were excluded. Pts (N = 24, intention-to-to-treat [ITT] population) were randomized (2:1) to zeto 60 mg or PBO s.c. weekly (QW) for 24 Ws in conjunction with 20 – 40 mg prednisone equivalent/day. Pts followed a suggested protocolized steroid taper. Primary efficacy endpoint was complete response (CR), defined as normalization of liver enzymes and IgG (if elevated at baseline). Secondary endpoints included the proportion of pts achieving CR with low corticosteroid (CS) dose ($\leq$5 mg prednisone equivalent/day) by W24. Samples were taken for exploratory biopsy and biomarkers. **Results:** A total of 16 AIH pts received zeto 60 mg s.c. QW for up to 24 Ws. The most common adverse events (AE) were grade 1 or 2 injection site reactions. Infectious treatment-emergent adverse events (TEAEs) were similar between zeto- and PBO-treated pts (Table 1). Three serious AEs were reported (2 zeto, 1 PBO), all unrelated. In the ITT population (N = 24), 50% (8/16) of zeto-treated pts vs. 37.5% (3/8) of PBO had CR. 31.3% (5/16) of zeto-

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treated pts achieved CR with low CS dose by W24 vs. 12.5% (1/8) in the PBO arm. In a prespecified group of 21 AIH pts with CS treatment at screening, the average daily CS dose at screening was 11.4 mg/day in the PBO arm (7 pts randomized, 6 pts dosed) and 23.4 mg/d in the zeto arm. By W24, 57.1% (8/14) of zeto-treated pts achieved CR vs. 28.6% (2/7) in PBO arm. Further, 35.7% (5/14) of zeto-treated pts achieved CR with low CS dose, including 3 with complete CS withdrawal by W24 vs. no PBO arm pts. No loss of CR was observed in any zeto patient achieving CR during the 24-W period. Histological improvements, including remission, were observed after 24 Ws of zeto treatment in those with CR, with 6/8 pts achieving a ≥ 2-point improvement. **Conclusion:** Zetomipzomib treatment was associated with a favorable safety profile and showed promising efficacy in achieving steroid-sparing CR in a difficult-to-treat population of pts with AIH.

Table 1. PORTOLA Safety: Favorable Safety and Tolerability Profile with Zetomipzomib Treatment (Safety Population)

Adverse Events in Double-blind Treatment Period	Placebo n=7 n (%)	Zetomipzomib n=16 n (%)
Patient with at least 1 Treatment Emergent Adverse Event (TEAE)	7 (100.0)	16 (100.0)
Most common TEAE:		
Injection Site Reaction (ISR) – All Grade 1 or 2	4 (57.1)	15 (93.8)
Systemic Injection Reaction (SIR) – All Grade 1 or 2	1 (14.3)	12 (75.0)
TEAE leading to study drug discontinuation	0 (0)	3* (18.8)
Grade 3 TEAE^ (no Grade 4 or 5 TEAEs reported)	1 (14.3)	3 (18.8)
Serious TEAE	1† (14.3)	2‡ (12.5)
Infectious TEAE	6 (85.7)	9 (56.3)
Grade ≥3 Infectious TEAE	0 (0)	1 (6.3)
Opportunistic Infections	0 (0)	0 (0)
Death	0 (0)	0 (0)

*Grade 2 unrelated AIH flare (treatment failure per protocol), Grade 2 related hives, and Grade 1 related fatigue

^Grade 3 TEAEs were deemed unrelated

†Grade 3 unrelated variceal bleeding x2, with hematemesis and atrial fibrillation

‡Grade 3 unrelated fever (post-liver biopsy) and unrelated Grade 3 influenza B infection

Disclosures: Craig Lammert: Eli Lilly: Consultant, Kezar Life Sciences: Consultant, Amgen: Consultant, Autoimmune Hepatitis Association: Consultant, RegCell: Consultant, Neel Anand: Kezar Life Sciences: Employee, Pfizer: Stock - publicly traded company, Exelixis: Stock - publicly traded company, Johnson & Johnson: Stock - publicly traded company, Celldex: Stock - publicly traded company, David Bade: Kezar Life Sciences: Employee, Theo Brandt-Sarif: Nothing to Disclose, Shraddha Desai: Kezar Life Sciences: Stocks, Diana Lam: Kezar Life Sciences: Employee, Tony Muchamuel: Kezar Life Sciences: Employee, Kiruthi Palaniswamy: Kezar Life Sciences: Employee, Rachel Peterson: Nothing to Disclose, Kathryn Ray: Kezar Life Sciences: Employee, Zung To: Nothing to Disclose, Jennifer Whang: Kezar Life Sciences: Employee, Aparna Goel: Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant

★ 0212 | MACHINE LEARNING PROGNOSTIC MODEL PREDICTS ALL-CAUSE MORTALITY OR LIVER TRANSPLANT IN PATIENTS WITH AUTOIMMUNE HEPATITIS

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Background: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease requiring long-term immunosuppressive therapy. Despite treatment, 50–87% relapse after withdrawal, increasing cirrhosis risk to 38% with multiple relapses. Currently, there is only one prognostic model developed, but it is trained on a small dataset and it does not include important predictors. It's built based on age, cirrhosis at diagnosis, and ethnicity. As such, it does not include labs that would reflect therapy response; a reported significant survival predictor. **Aim:** To develop a machine learning (ML)-based prognostic model for AIH. **Methods:** Data: We used the Canadian Network for Autoimmune Liver disease (CaNAL) dataset, a comprehensive multicenter longitudinal registry from 13 Canadian tertiary centers including adults (≥18 years). *Inclusion:* simplified IAIHG score. *Exclusion:* acute severe AIH, cirrhosis or transplant at baseline, death or transplant within 1 year, follow-up < 1 year, or missing key data. Outcome: A binary endpoint of all-cause mortality and/or liver transplant. Predictors: Simple blood tests including AST, ALT, ALP, GGT, IgG, total bilirubin, neutrophils, lymphocytes, platelets, albumin, INR, and hemoglobin. Model: We developed a data pipeline in Python in two stages: imputation and classification. The data was split 60/20/20 for training, validation, and testing. *a) Imputation:* We imputed the labs using machine learning. A

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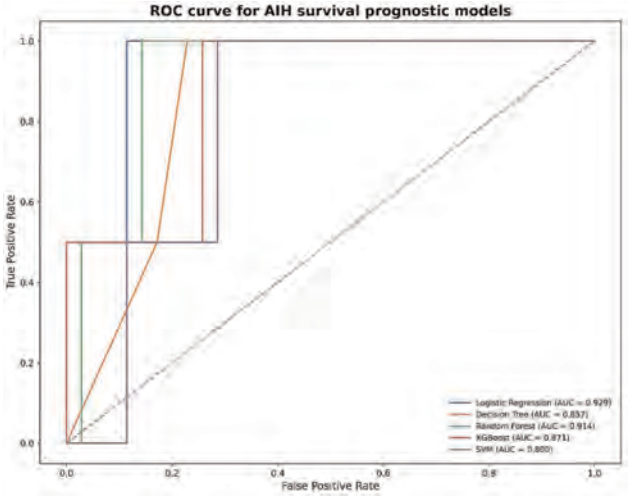
patient must have at least one lab in the first six months post-diagnosis to have imputation. *b) Classification:* Lab predictors were selected using univariate logistic regression ($p < 0.05$) before being fed to the ML models. We then evaluated commonly used ML models including logistic regression (LR), decision tree, random forest (RF), extreme gradient boosting (XGBoost), and support vector machine (SVM). Metrics included AUC, sensitivity, and specificity. **Results:** Out of 1799 patients (1965–2024), 323 were excluded. The mean age at diagnosis was 47.6 ± 16 years. 192 patients reached the outcome. We selected labs at a 3-month time point because it was the only time point at which AST and ALT significantly correlated with event in the univariate analysis. Significant predictors in the univariate logistic regression included ALP, INR, GGT, IgG, albumin, platelets, AST, and ALT. AUCs for LR, RF, XGBoost, decision tree, and SVM were 0.93, 0.91, 0.87, 0.86, and 0.80, respectively. **Conclusion:** ML models using standard labs at 3 months post-diagnosis can accurately predict survival in AIH. This supports early risk stratification. Moreover, both logistic regression and random forest are the best-performing models of prediction, with AUCs > 90%. Ongoing data collection aims to further improve model accuracy and build even more complex models for more robust predictions.



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0213 | SELADELPAR IS ASSOCIATED WITH A SUSTAINED REDUCTION IN CHOLESTATIC MARKERS AND A CONSISTENT SAFETY PROFILE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED UP TO 48 MONTHS IN THE ONGOING, OPEN-LABEL ASSURE STUDY

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Background: Seladelpar (SEL) is a first-in-class delpar (selective PPAR-delta agonist) indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients (pts) intolerant to UDCA. Here, we report the latest interim, long-term biochemical efficacy and safety data in a pooled population of pts treated with SEL in ASSURE. **Methods:** The ASSURE study (NCT03301506) is an ongoing, open-label, long-term, Phase 3 trial of SEL in pts with PBC rolling over from the placebo-controlled, Phase 3 RESPONSE trial (NCT04620733) or with prior participation in legacy SEL trials. The Phase 2 and 3 parent studies for ASSURE required an inadequate response or

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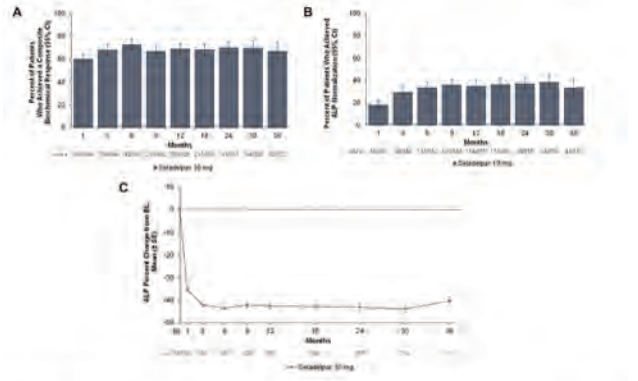
intolerance to UDCA. Using a data cutoff of 1/31/2025, pts were pooled starting with their initiation of SEL (at entry into RESPONSE for those randomized to SEL, and at entry into ASSURE for all other pts). Pts received blinded, daily oral SEL 10 mg in RESPONSE and open-label, daily oral SEL 10 mg in ASSURE. Efficacy endpoints included a composite biochemical response (CBR; ALP $< 1.67 \times$ the upper limit of normal [ULN], ALP decrease $\geq 15\%$ from baseline [BL], and total bilirubin $\leq$ ULN), ALP normalization, ALP percent change from BL, and other laboratory parameters summarized through 36 months (M). Safety was assessed by exposure-adjusted adverse events (AEs) per 100 pt-yrs of exposure through 48M. **Results:** Among 337 pts treated with open-label SEL 10 mg, 258 were treated for ≥ 2 yrs and 117 were treated for ≥ 3 yrs, with 122 pts reaching their 36M visit as of the data cutoff. At all time points, the majority of pts achieved a CBR: 69% (225/325) at 12M, 70% (181/258) at 24M, and 67% (82/122) at 36M (Figure A). ALP normalized in 35% of pts (114/325) who reached their 12M visit, with similar percentages of 37% (96/258) at 24M and 34% (41/122) at 36M (Figure B). Treatment with SEL resulted in sustained reductions in ALP, with mean percent changes from BL of −43% at 12M, −43% at 24M, and −40% at 36M (Figure C). Sustained reductions were also observed in ALT and GGT through 36M. SEL was well tolerated, with overall AEs reported in 83.2 pts per 100 pt-yrs in yr 1 and 62.3 in yr 4. **Conclusion:** SEL led to sustained reductions in biochemical markers of cholestasis with up to 36M of open-label treatment. SEL also appeared to be safe and well tolerated; no new safety signals were identified with up to 48M of follow up.

Figure. Composite Biochemical Response (A), ALP Normalization (B), and ALP Percent Change From BL (C) Through 36 Months of Open-Label Seladelpar Treatment



n/N = number of responders at each time point/total number of evaluable patients at each time point.

n = number of evaluable patients at each time point.

ALP, alkaline phosphatase; BL, baseline.

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0214 | IMPACT OF LINERIXIBAT ON PHARMACODYNAMIC BIOMARKERS AND MEDIATORS OF CHOLESTATIC PRURITUS IN PRIMARY BILIARY CHOLANGITIS (PBC) IN THE PHASE 3 GLISTEN STUDY

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Background: Cholestatic pruritus is common in PBC, affecting up to 89% of patients (pts) throughout the course of their disease. GLISTEN (NCT04950127), the largest investigational study for pruritus in PBC, investigated the efficacy and safety of linerixibat, a targeted ileal bile acid transporter inhibitor. This analysis evaluated the effects of linerixibat on pharmacodynamic biomarkers of bile acid synthesis and reabsorption (serum complement component 4 [C4] and fibroblast growth factor-19 [FGF-19]), as well as potential mediators of pruritus (total serum bile acids [TSBA], autotaxin [ATX] and interleukin [IL]-31). This study examined changes in biomarkers and pruritus mediators over 32 weeks, and correlations between biomarker levels, pruritus mediators and pruritus severity in pts receiving linerixibat over 24 weeks. **Methods:** GLISTEN was a Phase 3, randomized, double-blind, placebo-controlled study of 238 pts with PBC and moderate-to-severe pruritus at baseline. In the primary intervention period, pts received linerixibat 40 mg twice daily or placebo for 24 weeks; in the crossover period, pts either switched or maintained treatment for a further 8 weeks. Biomarkers were quantified at baseline and every 4 weeks through Week 32. Correlations between change from baseline (CFB) in biomarker levels versus CFB in weekly itch score (measured using a 0–10 worst itch numerical rating scale) were assessed post hoc. **Results:** Serum C4 significantly increased ($p < 0.001$), and FGF-19 significantly decreased ($p < 0.001$), with linerixibat versus placebo over 24 weeks (Table). These changes align with the pharmacology of linerixibat. Pruritus mediators were significantly reduced with linerixibat versus placebo over 24 weeks (Table: all $p < 0.001$). These reductions (TSBA, ATX, IL-31) were observed at Week 4 and maintained throughout the treatment period. Over the crossover period, pts who switched from linerixibat to placebo had decreases in C4 and increases in FGF-19, TSBA, ATX and IL-31. In the post hoc analysis, reductions in TSBA and IL-31 in linerixibat-treated pts weakly correlated with reductions in pruritus at Week 4 (TSBA: $r = 0.20$, $p = 0.04$; IL-31: $r = 0.24$, $p = 0.05$). Significant weak correlations were observed between changes in C4, FGF-19 and ATX in linerixibat-treated pts, and reductions in pruritus over time (C4: $r = -0.289$, $p < 0.0001$; FGF-19: $r = 0.205$, $p < 0.0001$; ATX: $r = 0.093$, $p = 0.028$). **Conclusion:** In pts with PBC and moderate-to-severe pruritus, linerixibat modulated C4 and FGF-19 levels, consistent with its mechanism of action. Linerixibat significantly reduced potential pruritus mediators versus placebo, which correlated with reductions in pruritus. These data support that linerixibat reduces TSBA and other potential mediators of cholestatic pruritus, supporting the biologic plausibility of its action. Furthermore, these effects were reversible upon linerixibat treatment discontinuation. Funding: GSK (212620)

Table. Summary of change from baseline in biomarkers in linerixibat versus placebo (reporting here over 24 weeks)

Biomarker	Ratio linerixibat to placebo			Sample size	
	LS mean ratio	95% CI	P-value	Linerixibat patient count	Placebo patient count
C4	2.55	(2.22, 2.93)	<0.001	119	116
FGF-19	0.58	(0.51, 0.65)	<0.001	118	116
TSBA	0.75	(0.66, 0.85)	<0.001	119	116
ATX	0.68	(0.52, 0.95)	<0.001	118	116
IL-31	0.53	(0.44, 0.65)	<0.001	65	70

ATX, autotaxin (measured as a surrogate of lysophosphatidic acid [LPA]); C4, serum complement component 4; CI, confidence interval; FGF-19, fibroblast growth factor-19; IL-31, interleukin 31; LS, least squares; TSBA, total serum bile acids.

Disclosures: Andreas Kremer: Abbvie: Advisor, Abbvie: Consultant, Advanz: Advisor, Advanz: Consultant, Alentis: Advisor, AlphaSigma: Consultant, AlphaSigma: Speaking and Teaching, AstraZeneca: Advisor, Avior: Advisor, Bayer: Advisor, CymaBay: Advisor, Escient: Advisor, Falk: Consultant, Falk: Speaker, Gilead: Consultant, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GSK: Consultant, GSK: Speaking and Teaching, GSK: Advisor, Intercept: Consultant, Intercept: Grant/Research Support,

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0215 | VOLIXIBAT LEADS TO IMPROVEMENTS IN FATIGUE AND SLEEP FOR ADULTS WITH PRIMARY BILIARY CHOLANGITIS: DATA FROM VANTAGE

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Background: Primary biliary cholangitis (PBC) is a rare, autoimmune, cholestatic liver disease which greatly impacts overall health-related quality of life (HRQoL). Pruritus, fatigue, and sleep disturbance are frequent complaints in PBC. The burden of fatigue and sleep disturbances in patients with PBC is severe and has been difficult to adequately treat. Volixibat (VLX) is a minimally absorbed ileal bile acid transporter inhibitor which blocks the enterohepatic recirculation of bile acids. Treatment with VLX in the completed Part 1 (dose selection) of the VANTAGE study showed statistically significant and clinically relevant improvements in pruritus. Here, we explore the impact of VLX on fatigue and sleep in PBC. **Methods:** VANTAGE is a 28-week randomized, multicenter, double-blind, placebo (PBO)-controlled Phase 2b study in adults with PBC and cholestatic pruritus. The study has an adaptive design: a completed Part 1 period (1:1:1 randomization, VLX 20mg, 80mg or PBO BID) and an ongoing Part 2 confirmatory period (1:1 randomization, VLX 20mg BID or PBO BID). The primary efficacy endpoint of change in pruritus (Adult ItchRO) score from Baseline (BL) to Week 28 has been previously reported. Here we report data from Part 1 on fatigue and sleep to Week 28, assessed via two validated HRQoL tools (PBC-40 and PROMIS). VLX 20mg and 80mg arms were pooled for this analysis (VLX). Results are shown utilizing MMRM and descriptive statistics. **Results:** Thirty-one participants with moderate-to-severe pruritus were randomized (VLX = 20; PBO = 11). After VLX treatment, there was a trend towards greater improvements (LS mean [SE]) in fatigue (PBC-40: VLX -4.2 [1.7], PBO: -2.4 [2.8]; PROMIS Fatigue: VLX: -3.8 [1.9], PBO: -0.9 [3.2]) and sleep (PROMIS Sleep Disturbance: VLX: -4.3 [1.8], PBO: -0.9 [3.3]). A higher percentage of VLX-treated participants had a meaningful reduction on PROMIS-Fatigue scores (≥ 3 point reduction) compared to PBO (VLX: 47.1%; PBO: 16.7%). A higher proportion of VLX-treated participants reported normal/mild fatigue and sleep disturbances after 28 weeks of treatment compared to BL (Fatigue: BL: 8/14, W 28: 10/14; Sleep: BL: 10/14, W28: 13/14), with minimal changes in PBO-treated participants. **Conclusion:** VANTAGE Part 1 results support the hypothesis that efficacious pruritus treatment with VLX may result in improvements in sleep and fatigue in PBC. Improvements in fatigue and sleep will be further evaluated in the ongoing Part 2 period of the VANTAGE study.

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0216 | VALIDATING LIVER STIFFNESS MEASUREMENT IN PREDICTING OUTCOMES IN PRIMARY SCLEROSING CHOLANGITIS: AN INTERNATIONAL CROSS-CENTRE STUDY OF MORE THAN 1000 PATIENTS

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Background: Liver stiffness measurements (LSM) by transient elastography is associated with advanced fibrosis and adverse clinical outcomes in PSC. We externally validated multivariable regression models using LSM to predict major clinical endpoints. **Methods:** In a retrospective PSC cohort from Toronto, we assessed the association between LSM and a composite outcome of decompensation (ascites, variceal hemorrhage, HE), liver transplant, or death. LSM was modeled as a time-dependent continuous (log-transformed) or categorical variable (<9.6, 9.6–14.4, >14.4 kPa) in multivariable Cox models adjusted for age, sex, PSC and IBD duration, and other time-dependent covariates (ALP, Tbili, plts, albumin). Final models were externally validated in 3 retrospective PSC cohorts: CALiD (13 U.S. centers), Edmonton (Canada), and Hamburg (Germany). Sensitivity analysis involved independent derivation of the logLSM model at each site, with pooled adjusted hazard ratios (aHR) via random-effects meta-analysis. **Results:** Amongst the Toronto derivation cohort, 1321 valid LSM from 2012-2023 from n = 403 (median age 34 y.o., 92% large-duct PSC, 61% male, 75% concurrent IBD, 9.5% overlap, 84 events) were evaluated. The final models incorporated LSM, age, sex, ALP and Tbili; other variables did not influence or worsened model performance (by AIC/BIC). There were 2,997 valid LSM amongst 3 external validation cohorts (CALiD: 1563 from n = 375, 64 events; Edmonton: 894 from n = 294, 95 events; Hamburg: 540 from n = 160, 37 events). LogLSM was independently associated with the composite outcome (pooled aHR 3.55, 95% CI: 2.96-4.27, Figure). Discrimination (by c-statistic) for the Toronto-derived multivariable logLSM model was 0.89, 0.84, and 0.89, with calibration slope of 1.00 (95% CI: 0.64-1.36), 0.98 (95% CI: 0.81-1.15), and 0.85 (95% CI: 0.66-1.04) for CALiD, Edmonton, and Hamburg, respectively. In the categorical LSM multivariable model, an LSM of 9.6-14.4 kPa was not significant (aHR 1.93, 95% CI: 0.86-4.32), while LSM >14.4 kPa remained prognostic (aHR 6.40, 95% CI: 3.48-11.8). Discrimination was 0.89, 0.84 and 0.86 with calibration slope of 1.00 (95% CI: 0.59-1.41), 0.98 (95% CI: 0.81-1.15), and 1.00

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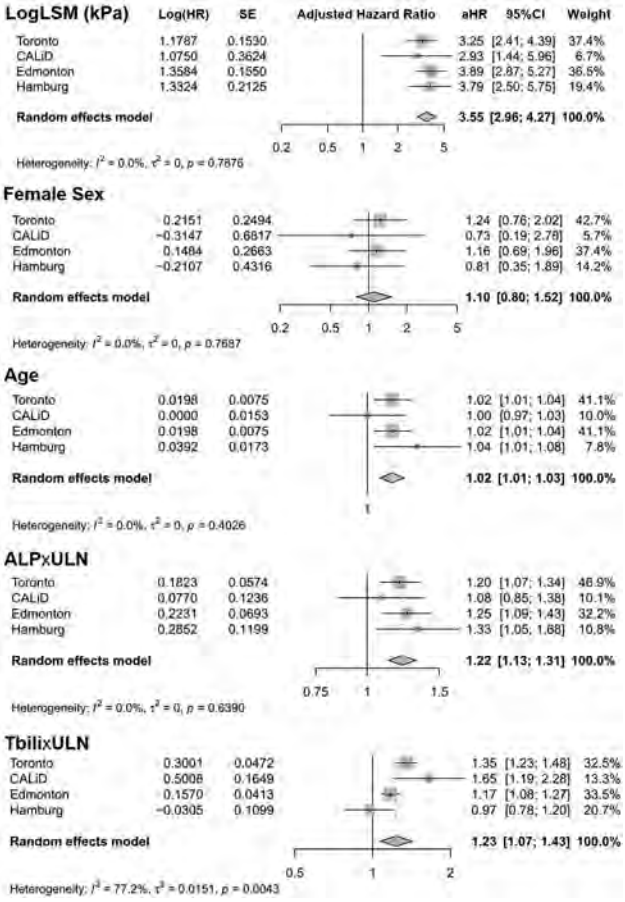
(95% CI: 0.77-1.24) for the CALiD, Edmonton, and Hamburg cohorts, respectively. **Conclusion:** Using data from four real-world cohorts, we externally validated multivariable models demonstrating liver stiffness measurement (LSM) as a predictor of decompensation, liver transplant, and/or death in PSC, supporting its use for longitudinal risk stratification and trial design.



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★ 0217 | INTEGRATION ACROSS PRIMARY LIVER TUMORS IDENTIFIES CLINICALLY RELEVANT MOLECULAR SUBTYPES OF HCC

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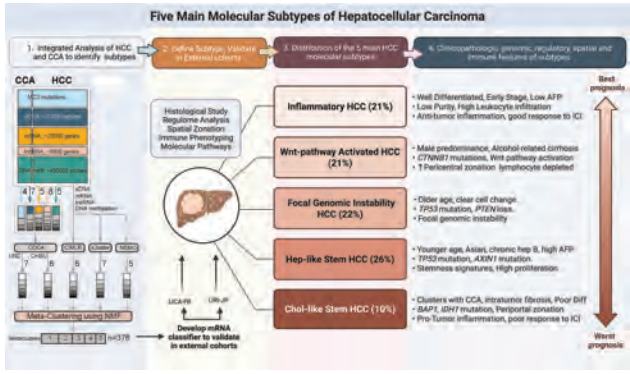
Background: Hepatocellular carcinoma (HCC) is a heterogeneous disease with variable outcomes, yet existing molecular classifications lack clinical adoption. To overcome limitations in reproducibility and to account for mixed HCC/cholangiocarcinoma (CCA) tumors, we conducted a cross-lineage analysis of HCC and CCA. **Methods:** We analyzed 378 tumors from TCGA (HCC n = 345 and CCA n = 33) using multi-omic data (mutations, CNAs, mRNA/lncRNA expression, DNA methylation) and applied 4 clustering algorithms (COCA, CIMLR, iCluster, NEMO). A consensus 5-subtype classification was defined using NMF and translated into an mRNA-based classifier, which was validated in two external cohorts (ICGC-Japan, n = 240; ICGC-France, n = 161). Subtype features were compared to regulons for known transcription factors, zonation spatial signatures, immunotherapy response markers and previous HCC subtype classification. **Results:** We identified 5 distinct HCC subtypes: (1) cholangiocyte-like stem HCC (enriched in BAP1/IDH1 mutations, clustered with CCA- n = 36); (2) hepatocyte-like stem HCC (high AFP, stemness signatures, n = 78); (3) Wnt-pathway HCC (CTNNB1 mutations, n = 74); (4) focal genomic instability HCC (FIST, amplifications, TP53 mutations- n = 76); and (5) inflammatory HCC (low purity, immune infiltration- n = 70). Comparison with 6 existing classifications revealed the chol-like stem-HCC to be a distinct and aggressive subtype that was previously obscured in HCC-only analyses. Regulatory network analysis revealed proliferation-linked regulons enriched in both cholo-like and hep-like stem-like subtypes and metabolic regulons in Wnt-pathway and FIST HCCs (all $p < 0.01$). Immune profiling showed that inflammatory HCC exhibited strong anti-tumor immunity and association with signatures of ICI responsiveness, whereas chol-like stem HCC showed higher immunosuppressive infiltration, and Wnt-pathway HCC displayed T cell exclusion (all $p < 0.01$). Single-cell zonation analysis revealed a pericentral identity for Wnt-pathway HCC and periportal identity for chol-like stem HCC. Lastly, a 5-subtype ranscriptional classifier was validated it in 2 external cohorts, where it faithfully reproduced subtype distributions, molecular features (eg. CTNNB1/TP53 mut), clinical associations (eg. survival, vascular invasion) and immune signatures seen in TCGA, confirming the biological relevance of our subtypes. **Conclusion:** We present a new and refined molecular classification of HCC. By incorporating features from both HCC and CCA, we uncover an aggressive CCA-like stem HCC subtype. Immune profiling reveals striking subtype-specific differences, ranging from "cold" Wnt-pathway tumors to highly inflamed but immunosuppressive CCA-like HCC, and immunotherapy-responsive inflammatory HCCs. Lastly, we have developed a validated transcriptional classifier that provides a scalable tool for classifying tumors across diverse datasets.



Disclosures: Renumathy Dhanasekaran: Nothing to Disclose, Mauro Castro: Nothing to Disclose, Bahar Tercan: Nothing to Disclose, Jordan Lee: Nothing to Disclose, Christopher Wong: Nothing to Disclose, Guangrong Qin: Nothing to Disclose, A. Gordon Robertson: Nothing to Disclose, Kyle Ellrott: Nothing to Disclose, Michael Torbenson: Nothing to Disclose,

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★ 0218 | PER- AND POLYFLUOROALKYL SUBSTANCES, GENETIC SUSCEPTIBILITY, AND HEPATOCELLULAR CARCINOMA: A NESTED CASE CONTROL STUDY IN THE MULTIETHNIC COHORT

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Background: Per- and polyfluoroalkyl substances (PFAS) are a broad class of synthetic persistent organic pollutants with long biological half-lives that may increase the risk of Hepatocellular carcinoma (HCC), potentially by interacting with hepatic lipid metabolism associated genes. Since exposure to PFAS via food and water is ubiquitous, understanding whether PFAS exposure increases HCC risk may help identify interventions to reduce HCC incidence. We aimed to examine the associations between prediagnostic blood PFAS levels and risk of HCC, and to explore whether genetic factors associated with hepatic lipid metabolism modify these relationships. **Methods:** We analyzed 235 HCC cases and 235 controls matched on birth year, date of blood collection, sex, race/ethnicity, fasting status, and study area from the Multiethnic Cohort (MEC). Blood levels of 12 PFAS were measured from samples collected prior to diagnosis, and incident HCC cases were identified using the SEER registry. Associations between PFAS and HCC risk were evaluated using conditional logistic regression. To identify single nucleotide polymorphisms (SNPs) that may modify associations of PFAS and HCC, we used a candidate gene approach by identifying 21 SNPs from a validated polygenic risk score (PRS) on metabolic associated fatty liver disease (MASLD). Interactions between PFAS and these 21 SNPs, along with the interaction between PFAS and the MASLD PRS, were tested using conditional logistic regression. All models were adjusted for smoking, diabetes, dietary factors, weighted MASLD PRS, and genetic ancestry scores. **Results:** Two PFAS were associated with HCC risk. PFHpA was associated with 1.34 times higher odds of HCC (95% CI: 1.01-1.77; $p = 0.04$) and PFNA was associated with 1.32 times higher odds of HCC (95% CI: 1.01-1.73; $p = 0.045$). Further, the association between PFNA and HCC was modified by rs5117, an intron variant on the *APOC1* gene. In those with no risk alleles, PFNA was associated with 0.031 times lower risk of HCC (95% CI: 0.15-0.66), but in those with two risk alleles, PFNA was associated with 1.52 times higher risk of HCC (95% CI: 1.22-1.90; adjusted $p_{int} = 0.004$). No other PFAS were associated with HCC risk. **Conclusion:** PFHpA and PFNA were associated with higher risk of HCC, and the associations between PFNA and HCC appeared to be modified by genetic factors. Public health interventions to decrease exposure to these PFAS may help decrease incidence of HCC.

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0219 | LONG - CHAIN ACYL - COA SYNTHETASE 4 (ACSL4): A NEWLY - IDENTIFIED DRIVER AT THE HEPATOCELLULAR CARCINOMA INVASIVE FRONT GOVERNING TUMOR INVASION, METASTASIS AND PATIENT PROGNOSIS

Yusufukadier Maimaitinijiati[1] Yuan Meng[1] Shizhong Yang[2] Zhiyu Chen[3] Jiahong Dong[2] Xiong Chen[1], [1]Hepatopancreatobiliary Center, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China, [2]Hepatobiliary Pancreatic Center, Beijing Tsinghua Chang Gung Hospital, Beijing, China, [3]Department of Hepatobiliary Surgery, The First Hospital Affiliated to Army Medical University

Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide, posing a significant global health challenge. The tumor invasive front (TIF), as the most active site for tumor cell invasion, plays a pivotal role in cancer progression and metastasis. Identifying biomarkers at the TIF is crucial for

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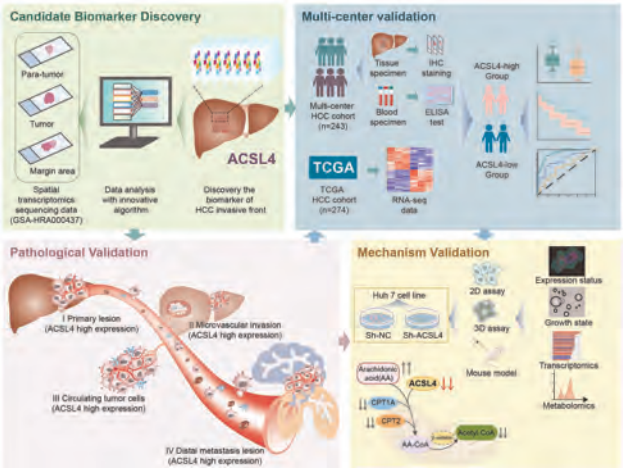
developing targeted therapies to disrupt HCC's invasive and metastatic potential. This study leverages spatial transcriptomic sequencing data from HCC clinical specimens and innovative gene screening algorithms to identify acyl-CoA synthetase long-chain family member 4 (ACSL4) as a novel TIF marker closely associated with HCC invasion, metastasis, and prognosis. **Methods:** We first applied an innovative gene screening algorithm to identify ACSL4 as a molecular biomarker of the HCC invasive front using spatial transcriptomic sequencing data. We then confirmed ACSL4's expression characteristics across various stages of HCC invasion and metastasis, including primary lesions, circulating tumor cells (CTCs), microvascular invasion (MVI), intrahepatic metastatic lesions, and extrahepatic distant metastases. The clinical value of ACSL4 was further demonstrated through a multi-center cohort study. Finally, we elucidated the functional mechanisms of ACSL4 using in vivo, in vitro experiments, and multi-omics joint analyses. **Results:** ACSL4 is specifically overexpressed in the TIF region of HCC and is involved in the entire metastatic process, from primary lesions to distant metastatic sites. The multi-center cohort study revealed that high ACSL4 expression was significantly associated with poorer overall survival and recurrence-free survival compared to low ACSL4 expression ($P < 0.05$). Furthermore, higher ACSL4 expression was more prevalent among patients who experienced recurrence than those without recurrence in both the multi-center cohort (37.19% vs. 25.62%) and the TCGA cohort (57.66% vs. 46.72%). ACSL4 expression levels were also significantly higher in tissue samples from patients with microvascular invasion (MVI) compared to those without MVI. In vivo and in vitro experiments indicated that ACSL4 promotes HCC invasion and metastasis by regulating arachidonic acid β-oxidation.
Conclusion: ACSL4 is a novel TIF biomarker that governs HCC invasion, metastasis, and patient prognosis. Our findings highlight its potential as a therapeutic target for HCC management.



Disclosures: Yusufukadier Maimaitinijiati: Nothing to Disclose, Yuan Meng: Nothing to Disclose, Shizhong Yang: Nothing to Disclose, Zhiyu Chen: Nothing to Disclose, Jiahong Dong: Nothing to Disclose, Xiong Chen: Nothing to Disclose

0220 | SELECTED GENETIC VARIANTS RELATED TO ALTERED CHOLINE METABOLISM ARE ASSOCIATED WITH HISTOLOGICAL SEVERITY IN PATIENTS WITH MASLD

Callie Zaborenko[1] Tae-Hwi Schwantes-An[1] Marco Abreu[1] Jie Yao[2] Jingyi Tan[2] Xiuqing Guo[2] Jerome Rotter[2] Naga Chalasani[3] Brent Neuschwander-Tetri[4], [1]Indiana University School of Medicine, [2]The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, [3]Indiana University Medical Center, [4]Saint Louis University

Background: Choline deficiency has been shown to be associated with steatotic liver disease and its severity. We investigated the association between genetic variants which may contribute to altered choline availability and metabolism and histological severity in patients with well characterized MASLD. **Methods:** Using 3,358 participants from the NASH CRN studies, we estimate logistic regressions predicting advanced fibrosis (≥ F3) and steatohepatitis (NAFLD Activity Score ≥ 4) from 23 SNPs in 11 candidate genes (*MTHFR, FMO3, MTR, CHDH, MTRR, BHMT, SLC44A1, CHKA, MTHFD1, PEMT, and RFC1*) which play role in choline metabolism. Sub-group analyses were conducted based on age, ancestry, BMI, and *PNPLA3* rs738409. Rare variant analysis was conducted among European (EUR) and Admixed American (AMR) adults. **Results:** The study cohort was 53% female, with mean age 40 years, mean BMI 34 kg/m2, 25% with advanced fibrosis, and 66% had steatohepatitis. SNPs in 4 genes, *CHDH*, *CHKA*, *FMO3*, and *PEMT,* showed strong and consistent relationships with advanced fibrosis and steatohepatitis (Table). *CHDH* rs12676 was related to higher odds of advanced fibrosis across full sample and all subgroups (full sample: OR = 1.19; 95% CI 1.04-1.36; p = 0.01). *CHKA* rs10791957 was protective against advanced fibrosis in males (OR = 0.82; 95% CI 0.68-0.99; p = 0.036). *FMO3* rs2266782 was also protective, especially in adults with two copies of *PNPLA3* rs738409, against advanced fibrosis (OR = 0.79; 95% CI 0.65-0.96; p = 0.016) and steatohepatitis (OR = 0.72; 95% CI 0.56-0.94; p = 0.018). *PEMT* rs12325817 was related to lower odds of advanced fibrosis across full sample and all subgroups (full sample: OR = 0.82; 95% CI 0.74-0.93; p = 0.001). In the rare variant analysis two genes, *MTHFD1* (Burden p = 0.03147) and *SLC44A1* (Burden p = 0.0490), were related to advanced fibrosis in EUR adults, but not AMR adults. No rare variants were associated with steatohepatitis. **Conclusion:** Both common and rare

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variants related to choline metabolism are associated with advanced fibrosis in MASLD. However, the relationship with steatohepatitis is less robust. Across both outcomes, common variants in *CHDH* were consistently deleterious, whereas *CHKA*, *FMO3*, and *PEMT* were protective. Variants in these genes may provide insights into the heterogeneity of MASH pathogenesis and treatment targets.

Table: Summary of variants in four genes showing associations with advanced fibrosis and/or steatohepatitis in MASLD

Outcome	Gene	SNP	Groups	Direction	Sig count*
Advanced fibrosis (AF)	CHDH	rs12676	Everyone (full, females, not Obese, PNPLA3=1, PNPLA3=2); adults (full, males, not Obese, PNPLA3=1&2); EUR adults (full, not Obese)	Deleterious	12
AF	CHDH	rs9001	Everyone (full, females, PNPLA3=1, PNA3=2)	Deleterious	4
AF	CHKA	rs10791957	Everyone (full, males); adults (males); EUR adults (males, not Obese)	Protective	5
AF	CHKA	rs2512612	Everyone (full, males); adults (males); EUR adults (full, males, not Obese)	Protective	6
AF	CHKA	rs6591331	EUR adults (males)	Protective	1
AF	CHKA	rs7928739	EUR adults (males)	Protective	1
AF	FMO3	rs2266782	Adults (full, males)	Protective	2
AF	PEMT	rs12325817	Everyone (full, males, Obese, PNPLA3=0, PNPLA3=1); adults (full, PNPLA3=0)	Protective	7
AF	PEMT	rs3760188	Everyone (full, males, Obese, PNPLA3=0, PNPLA3=1); adults (full, PNPLA3=0)	Protective	7
AF	PEMT	rs4646343	Everyone (full, males, Obese, PNPLA3=0, PNPLA3=2)	Protective	5
NAS>4	CHDH	rs12676	Adults (PNPLA3=2)	Protective	1
NAS>4	CHDH	rs9001	Everyone (not Obese)	Deleterious	1
NAS>4	FMO3	rs2266782	Everyone (Obese, PNPLA3=2,); adults (full, males, PNPLA3=0&2); EUR adults (full, males, obese, PNPLA3=0&2)	Protective	11
NAS>4	PEMT	rs12325817	EUR adults (PNPLA3=0)	Protective	1
NAS>4	PEMT	rs3760188	EUR adults (PNPLA3=0)	Protective	1
NAS>4	PEMT	rs4646343	EUR adults (PNPLA3=0)	Protective	1

*Sig count – the number of groups which had a significant relationship between the SNP and outcome of interest. The twenty-four groups: everyone, all females, all males, obese participants, not obese participants, PNPLA3=1 participants, PNPLA3=2 participants, PNPLA3=3 participants, all adults, all adult females, all adult males, obese adults, not obese adults, PNPLA3=1 adults, PNPLA3=2 adults, PNPLA3=3 adults, EUR adults, EUR adult females, EUR adult males, obese EUR adults, not obese EUR adults, PNPLA3=1 EUR adults, PNPLA3=2 EUR adults, and PNPLA3=3 EUR adults.

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★ 0221 | GENOME-WIDE CRISPR SCREEN IDENTIFIES LOSS OF FUNCTION OF DNAJC22 PROTECTS AGAINST STEATOTIC LIVER DISEASE

Aaron Hakim[1] Gavin Schnitzler[2] Michael Cho[3] Cindy Zheng[2] John Doench[2] Rajat Gupta[2], [1]Beth Israel Deaconess Medical Center, [2]Broad Institute of Harvard and MIT, [3]Channing Division of Network Medicine

Background: The accumulation of lipid droplets within hepatocytes is a causal mechanism for driving progressive liver disease. Identifying the genes which regulate lipid accumulation in hepatocytes and are associated with protection from liver disease across human biobanks may identify novel therapeutic targets. **Methods:** We performed a pooled genome-wide CRISPR-Cas9 knockout screen to systematically identify genes which regulate fatty-acid triggered neutral lipid accumulation in human hepatocytes. We integrated our CRISPR screen hits with human genome-wide association studies (GWAS) to prioritize a gene of previously unknown function, *DNAJC22*, for functional validation as a genetic mediator of steatotic liver disease. **Results:** Our CRISPR screen identified 829 hits (FDR < 0.05), including canonical lipogenesis/lipolysis genes, Mendelian lipid storage disorder genes, and multiple drug targets currently in clinical trials for steatotic liver disease. Knockout of *DNAJC22* by CRISPR-Cas9 or silencing by RNA interference dramatically decreased lipid accumulation in hepatocytes. We show that *DNAJC22* is a liver-enriched, hepatocyte-specific chaperone that interacts with VCP/p97, an inhibitor of adipose triglyceride lipase (ATGL). A rare (minor allele frequency 0.014), predicted pathogenic variant in *DNAJC22* (rs146774114, p.Ala163Thr) demonstrated significant protection against chronic liver disease across multiple human biobanks. The minor allele associated with reduced risk of cirrhosis in a multi-ancestry GWAS (n = 15,225 cases, n = 1,564,786 controls, odds ratio [OR] = 0.85, p = $7.8x10^{-03}$); reduced risk of all-cause liver disease in FinnGen (n = 15,135 cases, n = 485,213 controls, OR = 0.69, p = $1.6x10^{-04}$); reduced risk of steatotic liver disease in Million Veteran Program (n = 90,408 cases, n = 128,187 controls, OR = 0.85, p = $2.8x10^{-08}$); and reduced liver injury in UK Biobank (n = 312,672, alanine aminotransferase [ALT] p = $4.2x10^{-07}$, aspartate aminotransferase [AST] p = $4.0x10^{-05}$). We identified significant gene-environment interactions in UK Biobank between *DNAJC22* rs146774114 and body mass index in association with ALT and AST (p-interaction $1.8x10^{-06}$ and $1.5x10^{-03}$, respectively). **Conclusion:** Utilizing high-throughput genetic screens and integrating with human genetic association studies, we identified and validated *DNAJC22* as a novel therapeutic target for steatotic liver disease. Imbalances in ATGL-mediated triglyceride hydrolysis may reflect a central mechanism of steatotic liver disease.

Disclosures: Aaron Hakim: Olix Pharmaceuticals: Advisor, Deep Track Capital, LP: Consultant, Gavin Schnitzler: Nothing to Disclose, Michael Cho: Nothing to Disclose, Cindy Zheng: Nothing to Disclose, John Doench: Nothing to Disclose, Rajat Gupta: Nothing to Disclose

0222 | AN EPIGENETIC ATLAS OF MASH: ULTRA-DEEP PAIRED LIVER TISSUE AND PLASMA CFDNA METHYLATION SEQUENCING ENABLES NON-INVASIVE MEASUREMENT OF PATHWAY ACTIVITY

Soheil Damangir[1] Manal Abdelmalek[2] Georgia Sofia Karachaliou[3] Cynthia Guy[3] Leila Bazargan[1] Chong Lu[1]

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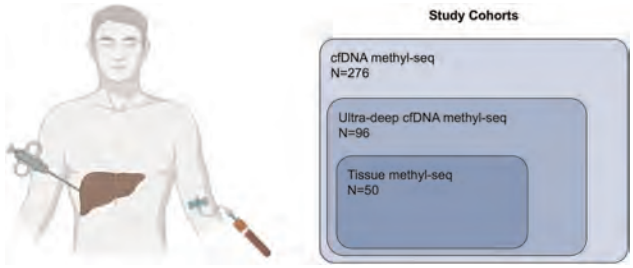
Background: Noninvasive profiling of pathways involved in MASH pathogenesis remains a challenge, hindering identification of diagnostic and therapeutic targets. Therefore, a technology that enables interrogation of liver methylome, and resultant changes in activity of pathways driving MASLD, from a simple blood draw would be transformational. The aim of this study is to present a novel technology and related data for such measurement. Using methylation sequencing of paired liver tissue and circulating cell free DNA (cfDNA) for the first time we 1) define tissue-specific differentially methylated regions (DMRs) related to MASH, 2) demonstrate their direct detectability in blood, and 3) quantify the relevant pathways that are differentially methylated. **Methods:** Plasma samples from 276 Duke MASLD Biobank subjects were analyzed with deep methylation sequencing (methyl-seq); a subset (n = 96) underwent further ultra-deep methyl-seq; and deep methyl-seq was done on paired liver tissue on a further subset (n = 50). Those 50 subjects serve as the discovery cohort; the rest as validation. High-confidence DMRs between clinically significant fibrosis (F2/3/4) vs. low fibrosis (F0/1) groups were extracted using a probabilistic model. Pathway enrichment analysis was used to identify relevant hyper- and hypomethylated pathways in tissue, i.e. discovery, and in the paired ultra-deep plasma samples, further verified in the independent validation cohort. We used the validated method on the plasma samples to discover pathways involved in MASH on a large scale. **Results:** We identified 1765 loci that were differentially methylated in liver tissue (FDR < 0.05). In the significant fibrosis group several pathways were hypermethylated (FDR < 0.05) including those related to WNT and VEGF signaling, while loci enriched in several pathways were hypomethylated (FDR < 0.05) including those associated with TGF-beta and immune cell activation. Functional analysis of tissue-specific signatures revealed enrichment of hypermethylated loci (FDR < 0.05) in distinct hepatocyte populations, while hypomethylated loci were enriched in stromal cells. DMRs in liver were differentially methylated in paired plasma cfDNA samples ($p < 0.01$) and in the validation cohort ($p < 0.05$), showing the utility of cfDNA as a measure of epigenetic changes in liver. Importantly, this enabled larger scale functional analysis using all 276 plasma samples which in addition to the abovementioned, revealed differential methylation (FDR < 0.05) in pathways implicated in MOAs of MASH therapies currently under investigation. **Conclusion:** This technology captures MASH-related changes in the liver methylome from a blood sample. This enables noninvasive measurement of differential activation of signaling pathways implicated in MASH pathogenesis, providing a novel approach to personalize diagnosis and treatment of MASH as well as monitoring changes related to the MOA of the treatment.



Disclosures: Soheil Damangir: Nothing to Disclose, Manal Abdelmalek: 89Bio, Akero, Madrigal, Inventiva, Novo Nordisk, Intercept, Merck,: Advisor, Hanmi, Novo Nordisk: Consultant, Madrigal, Gilead, Inventiva, 89Bio, Akero, Hanmi: Research paid to my institution, Pfizer, Merck: Stock – privately held company, Medscape; Clinical Care Options; Fishawack Inc, LLC; CLDF: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Georgia Sofia Karachaliou: Nothing to Disclose, Cynthia Guy: Sagimet: Consultant, Madrigal: Consultant, HistoIndex: Consultant, Leila Bazargan: Nothing to Disclose, Chong Lu: Nothing to Disclose, Pourya Naderi: Hepta Bio Inc.: Consultant, Hamed Amini: Hepta Bio, Inc.: Executive role, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Anna Mae Diehl: Nothing to Disclose

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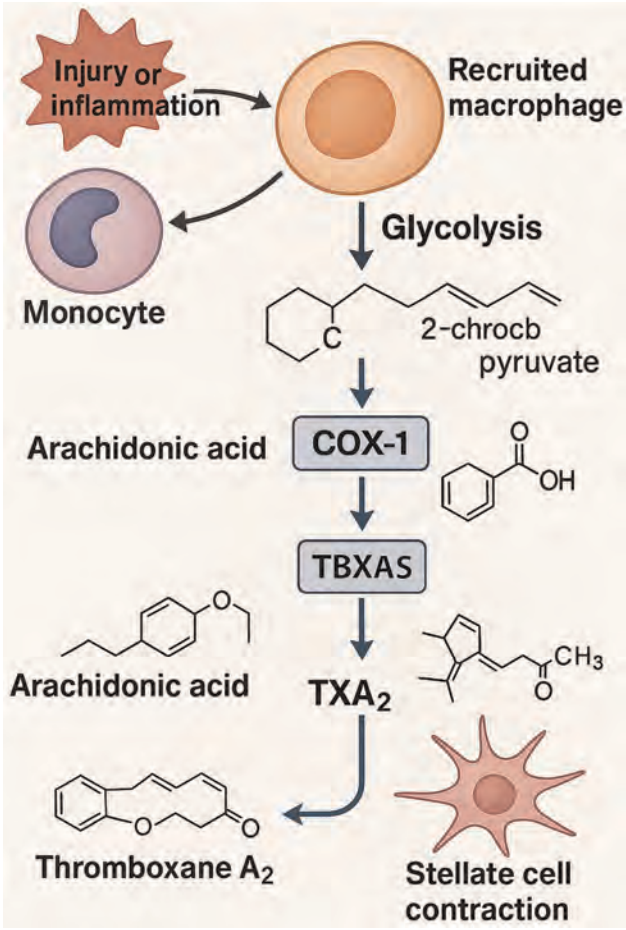
★ 0223 | CXCR3+ MONOCYTE-DERIVED MACROPHAGES CONTRIBUTE TO CONGESTIVE PORTAL HYPERTENSION THROUGH THE GLYCOLYSIS-DEPENDENT SYNTHESIS OF VASOACTIVE MOLECULES: INSIGHTS FROM MULTIOMICS

Papawee Sutthirat[1] Nidhi Jalan-Sakrikar[1] Sofia Jerez Ortega[1] Vijay Shah[1] Moira Hilscher[1], [1]Mayo Clinic Rochester

Background: Congestive hepatopathy (CH) and Fontan associated liver disease (FALD) can lead to portal hypertension (PHTN) which is associated with morbidity and mortality. Our prior studies show that peri-central (zone 3) liver sinusoidal endothelial cells (LSECs) express CXCL9 in CH. Treatment with an inhibitor of CXCR3, the cognate receptor for CXCL9, significantly decreases portal pressure and macrophage recruitment in a murine model of CH (partial ligation of the inferior vena cava, pIVCL). We hypothesize that CXCR3+ monocyte-derived macrophages (MoMF) drive congestive PHTN through the synthesis of vasoactive molecules. **Methods:** Integration of single-nucleus RNA sequencing (snRNA-seq) data, CosMx Spatial Molecular Imager (SMI), and imaging mass cytometry (IMC) was performed to analyze zone-specific changes in gene expression and cell-cell interactions in liver samples from patients with Fontan-associated liver disease (FALD) and healthy controls. Intra-hepatic leukocytes (IHLs) were isolated from wild-type (WT) mice 6 weeks after pIVCL or sham procedures for cytometry by time of flight (CyTOF). MoMFs were isolated from WT mice and treated with 2-deoxy-D-glucose (2-DG), an inhibitor of the rate-limiting glycolysis enzyme hexokinase-2 (HK2), or transfected with siRNA targeting HK2 (siHK2) to inhibit glycolysis. Mechanistic studies utilized RT-PCR to analyze mRNA expression and ELISA to quantify vasoactive molecule, thromboxane-A2 (TXA2). **Results:** CosMx SMI and IMC analyses revealed spatial changes in immune cell populations and gene expression patterns in FALD. While most immune cell populations were unchanged, intra-hepatic macrophages (IHMs) were significantly increased in FALD compared to controls. CyTOF performed on IHLs isolated after pIVCL identified a unique subpopulation of CXCR3+/CCR2+/CXCL4+ MoMFs recruited in CH. Spatial mapping identified enrichment of CXCR3+ [MH1] IHMs in zone 3. Pathway analysis of CosMx SMI data identified upregulation of glycolysis and arachidonic acid metabolism pathways in CXCR3+ MoMFs localized to zone 3, including the enzyme *COX-1* (log2FC 411.66, *p*-value < 0.05), which generates vasoconstrictive TXA2. We hypothesized that glycolysis fuels the COX-1-mediated synthesis of TXA2 in MoMFs in FALD. Treatment of WT MoMFs with 2-DG led to a significant decrease in COX-1 expression and TXA2 production (*p*-value < 0.05). WT MoMFs transfected with siHK2 secrete less TXA2 than siControl MoMFs (*p*-value < 0.0001). Notably, thromboxane receptor (*TBXA2R*) expression was significantly upregulated in hepatic stellate cells (HSCs) in FALD (log2FC 1.66, *p*-value < 0.03), suggesting that TXA2 signaling modifies HSC contraction. **Conclusion:** CXCR3+ MoMFs recruited to zone 3 in FALD demonstrate enhanced glycolysis and TXA2 production. We propose that TXA2 generated by MoMFs promote contraction of HSCs, leading to sinusoidal constriction and PHTN.



Disclosures: Papawee Sutthirat: Nothing to Disclose, Nidhi Jalan-Sakrikar: Nothing to Disclose, Sofia Jerez Ortega: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Moira Hilscher: Orphalan: Consultant

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0224 | PRESSURE-INDUCED ENDOTHELIAL FIBULIN-7 MODULATES HSC PHENOTYPE AND LOWERS PORTAL PRESSURE IN EXPERIMENTAL CIRRHOSIS

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Background: Portal hypertension (PH) is a frequent and life-threatening complication of chronic liver disease (CLD). Beyond being a consequence of liver microvascular dysfunction and fibrosis, elevated porto-sinusoidal pressure directly alters liver sinusoidal endothelial cells (LSEC). This study aimed to identify and characterize PH-induced effectors that contribute to CLD pathophysiology. **Methods:** RNAseq was performed in primary LSEC cultured under physiological or pathological pressure using a microfluidic liver-on-a-chip device. Genes dysregulated by pressure were compared to genes dysregulated in 3 preclinical models of cirrhosis (CCl_4, TAA and BDL rats). The expression of the most promising effector, fibulin-7 (FBLN7), was validated in CCl_4-induced cirrhotic rats (qPCR and IF), and characterized in liver biopsies (WB) and in blood plasma (ELISA) from healthy and cirrhotic patients with PH ($n = 13$ CLD vs $n = 8$ controls and $n = 49$ CLD vs $n = 11$ controls, respectively). Functional studies used siRNA/adenovirus to knockdown/overexpress FBLN7 and assess its effects on LSEC phenotype and paracrine interactions. Finally, AdFBLN7 (or AdGFP control) was administered *in vivo* to cirrhotic rats and hepatic and systemic hemodynamics were measured 6 days later ($n = 9$/group). **Results:** Thirty-one genes were commonly dysregulated by pressure *in vitro* and by cirrhosis *in vivo*, being FBLN7 the most consistently upregulated. Molecular analysis confirmed a +92% protein increase in cirrhotic rats, predominantly in LSEC. FBLN7 upregulation in CLD was validated in human samples ($fc = 3$ in liver tissue and +38% in plasma). *In vitro* silencing of FBLN7 in primary LSEC mainly dysregulated cell surface and extracellular proteins, suggesting a possible paracrine effect. Interestingly, the supernatant of human endothelial cells overexpressing FBLN7 ameliorated the phenotype of primary human hepatic stellate cells (HSC), reducing *ACTA2* (-38%) and *PDGFRB* (-33%). All $p < 0.05$. *In vivo* overexpression of FBLN7 significantly improved PH (portal pressure: 10.46 +/- 0.59 mmHg in AdGFP vs 8.88 +/- 0.19 mmHg in AdFBLN7; -15%), whilst no effects in mean arterial pressure and portal blood flow were observed. Hemodynamic benefits were associated with a reduction in liver fibrosis (-26%, $p = 0.1$). **Conclusion:** FBLN7 is a pressure-induced endothelial effector that is upregulated in experimental and human CLD, modulates LSEC-HSC paracrine signaling, and improves hepatic hemodynamics when overexpressed *in vivo*. These findings identify FBLN7 as a promising therapeutic target for the management of PH.

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0225 | DIRECT FXA-INHIBITOR EDOXABAN IMPROVES PORTAL HYPERTENSION IN EXPERIMENTAL TOXIC AND METABOLIC FIBROSIS MODELS

Katharina Bonitz[1] Thomas Sorz-Nechay[2] Henriette Horstmeier[2] Vlad Taru[2] Georg Kramer[2] Oleksandr Petrenko[2] Katja Sommer[2] Benedikt Simbrunner[2] Kerstin Zinober[2] Hubert Scharnagl[3] Michael Trauner[2] Philipp Schwabl[2] Thomas Reiberger[2] Benedikt Hofer[2], [1]Medical University Vienna, [2]Medical University of Vienna, [3]University Hospital Graz

Background: Protease-activated receptors (PARs) mediate activation of hepatic stellate cells and increase inflammatory cell recruitment. In this study we investigate the effects of the direct FXa (PAR agonist) inhibitor Edoxaban in experimental liver cirrhosis. **Methods:** Liver fibrosis was induced in male C57BL/6 mice by either oral gavage of carbon tetrachloride (CCl_4, 2mL/kg, 3x/week) for 12 weeks (Peak-CCl4), or choline-deficient L-Amino acid defined high fat diet (Peak-CDAHFD). Healthy controls received either olive oil or standard CHOW. Edoxaban (EDOX, 2x/day, 10mg/kg) was administered concomitantly during the last two weeks of disease induction (EDOX-CCl4 and EDOX-CDAHFD) ($n = 8$-12). To assess disease severity, we quantified portal pressure (PP), collagen proportionate area (CPA) and serum transaminases. For mechanistic understanding we performed FACS, immunohistochemistry (IHC) and whole liver transcriptomics, which was analyzed using DESeq2. **Results:** At peak disease severity, both models showed significant fibrosis and elevated PP. EDOX treatment led to a significant reduction in PP in both models (Peak-CCl4: 9.06 ± 0.89 vs. EDOX-CCl4: 7.22 ± 1.23 mmHg; Peak-CDAHFD: 7.40 ± 1.03 vs. EDOX-CDAHFD: 6.11 ± 1.11 mmHg) and liver injury markers were reduced in the CCl4 model (AST: Peak-CCl4: 5362 ± 4168 vs. EDOX-CCl4: 1374 ± 1646 U/L; ALT: Peak-CCl4: 7529 ± 5726

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vs. EDOX-CCl4: 2547 ± 2636 U/L). Histologically, CPA was not affected by EDOX, yet IHC showed a reduction in aSMA with EDOX in the CDAHFD model, indicating reduced HSC activation. Furthermore, EDOX significantly reduced hepatic macrophage infiltration on F4/80 IHC in both models. This was confirmed by FACS profiling in the CDAHFD model, showing less hepatic macrophages and neutrophils with EDOX treatment. On a transcriptomic level Gene set enrichment analysis (GSEA) and transcription factor inference revealed that EDOX reduced proinflammatory gene expression in both models, with a particularly pronounced decrease of NFkB activity in the CCl4 model. EDOX also led to a restoration of metabolic activity in both models, including pathways related to fatty acid, bile acid and xenobiotic metabolism. **Conclusion:** Edoxaban treatment induced significant improvements in portal hypertension in two mouse models of liver disease progression. Mechanistically, Edoxaban acted by ameliorating the proinflammatory hepatic environment, as shown by reduced macrophage infiltration and suppressed NFkB-modulated proinflammatory pathways.

Disclosures: Katharina Bonitz: Nothing to Disclose, Thomas Sorz-Nechay: Nothing to Disclose, Henriette Horstmeier: Nothing to Disclose, Vlad Taru: Nothing to Disclose, Georg Kramer: Nothing to Disclose, Oleksandr Petrenko: Nothing to Disclose, Katja Sommer: Nothing to Disclose, Benedikt Simbrunner: Nothing to Disclose, Kerstin Zinober: Nothing to Disclose, Hubert Scharnagl: Nothing to Disclose, Michael Trauner: Albireo: Grant/Research Support, Alnylam: Grant/Research Support, Cymabay: Grant/Research Support, Falk: Grant/Research Support, Gilead: Grant/Research Support, Intercept: Grant/Research Support, MSD: Grant/Research Support, Takeda: Grant/Research Support, Ultragenyx: Grant/Research Support, Abbvie: Travel Grants, Falk: Travel Grants, Gilead: Travel Grants, Intercept: Travel Grants, Janssen: Travel Grants, Abbvie: Advisor, Albireo: Advisor, BiomX: Advisor, Boehringer Ingelheim: Advisor, Falk Pharma GmbH: Advisor, Genfit: Advisor, Gilead: Advisor, Hightide: Advisor, Intercept: Advisor, Ipsen: Advisor, Janssen: Advisor, MSD: Advisor, Novartis: Advisor, Phenex: Advisor, Pliant: Advisor, Regulus: Advisor, Siemens: Advisor, Shire: Advisor, BMS: Speaking and Teaching, Falk: Speaking and Teaching, Gilead: Speaking and Teaching, Intercept: Speaking and Teaching, Ipsen: Speaking and Teaching, Madrigal: Speaking and Teaching, MSD: Speaking and Teaching, Medical Universities of Graz and Vienna: Co.Inventor of patents for medical use of norUDCA filed by, Genentech: Grant/Research Support, Mirum: Advisor, Agomab: Advisor, Chemomab: Advisor, ProQR Therapeutics: Advisor, Rectify: Advisor, Philipp Schwabl: Nothing to Disclose, Thomas Reiberger: Nothing to Disclose, Benedikt Hofer: IPSEN: Travel support, FALK: Travel support

0226 | INHIBITION OF H2S PRODUCTION REDUCES PORTAL PRESSURE BY DECREASING INTRAHEPATIC RESISTANCE IN RATS WITH CIRRHOSIS

Raffaele Buono[1] Marika Crescenzi[1] Massimo Bolognesi[1] Marco Di Pascoli[1], [1]Padua University

Background: Hydrogen sulfide (H2S) is a gasotransmitter known for its vasodilatatory properties, and it is also involved in regulating oxidative stress, inflammation and fibrosis in the liver. However, its role in the development of portal hypertension and complications of cirrhosis is not clear. **Methods:** We evaluated the hemodynamic effects of *in vivo* inhibition of H2S production in a rat model of experimental cirrhosis. Eight control rats and sixteen rats with bile duct ligation-induced cirrhosis were studied. Eight cirrhotic rats were treated with propargylglycine (PAG; 30 mg/kg via intragastric gavage), a specific inhibitor of cystathionine γ-lyase (CSE), the main source of H2S in the cardiovascular system and liver. Portal and systemic pressures were measured via polyethylene-50 catheters. Small resistance mesenteric arteries were mounted on a wire myograph system, and dose-response curves to acetylcholine (ACh) and sodium hydrosulphide (NaHS), an H2S donor, were evaluated. Plasma levels of ALT, creatinine and bilirubine were assessed in cirrhotic rats. Moreover, hepatic mRNA expression of inducible nitric oxide synthase (iNOS), endotelial nitric oxide synthase (eNOS), IL-6, TGF-β, collagen I, CSE, cystathionine-β-synthase (CBS), and glutathione synthetase (GSS) was evaluated by Taqman assays Real Time PCR in cirrhotic rats. **Results:** In cirrhotic rats, PAG treatment significantly reduced portal pressure (10.4 ± 2.7 mmHg versus 16.0 ± 3.9 mmHg, $P = < 0.05$) without affecting systemic pressure. No differences were observed in mesenteric artery responses to ACh or NaHS between treated and untreated cirrhotic rats. Treated cirrhotic rats had significantly lower creatinine (24.9 ± 7.0 μmol/L versus 34.6 ± 7.9 μmol/L; $P = 0.026$) and ALT levels (23.7 ± 19.0 U/L vs 99.7 ± 21.7 U/L; $P = < 0.001$), with no significant differences in bilirubin levels. In the liver, PAG reduced the expression of CBS ($P = 0.032$) and eNOS ($P = 0.016$), and increased the expression of iNOS ($P = 0.03$), with no effect on CSE. In the liver, PAG also reduced IL-6 ($P = 0.008$), TGFβ ($P = 0.008$), and collagen I ($P = 0.008$), while increasing GSS ($P = 0.016$). **Conclusion:** In vivo inhibition of H2S synthesis in cirrhotic rats reduces portal pressure and the expression of markers of hepatic inflammation and fibrosis, without no effects on mesenteric vasodilation. These findings suggest that targeting H2S may represent an intriguing therapeutic strategy to impact on portal hypertension by acting on intrahepatic resistance.

Disclosures: Raffaele Buono: Nothing to Disclose, Marika Crescenzi: Nothing to Disclose, Massimo Bolognesi: Nothing to Disclose, Marco Di Pascoli: Nothing to Disclose

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0227 | DYSFUNCTIONAL KYNURENINE METABOLISM PROMOTES NEUROINFLAMMATION DURING HEPATIC ENCEPHALOPATHY DEVELOPMENT

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Background: Hepatic encephalopathy (HE) is a severe neurologic complication in patients with liver disease. While metabolic dysfunction and neuroinflammation underlie HE pathogenesis, what and how metabolites contribute to HE pathogenesis has not been specified. The study aims to identify the metabolites developing HE and elucidate the underlying mechanisms. **Methods:** Bile duct ligation (BDL) was conducted on C57BL/6 mice to make the HE model. The Open field test evaluated the neurobehavioral change of the mise. The Visium spatial transcriptome and CyTOF single-cell immune profiling were used to analyze the cellular dynamics in the brain during HE development. The mouse brain, liver, and blood were used for metabolomics to identify HE-associated metabolites. HE-associated metabolites, including Kynurenine, were measured in the serum of the patients with liver diseases. **Results:** The mice revealed decreased locomorbidity and anxiety-like behavior by OFT from 6 days after BDL induction. The brain spatial transcriptomics revealed that specific brain regions (e.g. cortex, striatum) upregulated neuroinflammation-associated genes, such as IL1b and Icam1. Brain immune profiling revealed an increased pro-inflammatory macrophage subpopulation that was distinguished from resident microglia, indicating the involvement of neuroinflammation in HE development. Importantly, no hyperammonemia was observed at this early stage, suggesting the contribution of non-ammonia factors to HE development. Metabolomics defined Kynurenine, which was commonly observed in the HE model mice's blood, liver, and brain and patients' serum with decompensated cirrhosis. Systemic administration of Kynurenine upregulated IL1b and Icam1 in the brain and induced abnormal behavior in the mice. IDO, which metabolizes Tryptophan into Kynurenine, was upregulated in the liver of HE model mice and cirrhosis patients. Oral administration of 1-MT, an IDO inhibitor, suppressed IL1b and Icam1 in the BDL mice. **Conclusion:** The brain immune and metabolomic profiling of the mouse model and patients delineated Kynurenine as a novel immunometabolic factor increased early in HE development. Kynurenine could be a novel biomarker and therapeutic target of HE.

Disclosures: Michitaka Matsuda: Nothing to Disclose, Eiji Kakazu: Nothing to Disclose, Tatsuya Kanto: Nothing to Disclose

0228 | CRUCIAL ROLE FOR ALBUMIN TO RESCUE IMPAIRED B CELL FUNCTION AND VIABILITY IN PATIENTS WITH ACUTELY DECOMPENSATED CIRRHOSIS

Berta Romero-Grimaldo[1] Mireia Casulleras[2] Bryan Contreras[1] Marta Duran-Güell[2] María Belén Sánchez-Rodríguez[2] Carlos Rojano Alfonso[2] Giuliana Magri[3] Javier Fernández[4] Richard Moreau[3] Cristina López-Vicario[1] Joan Claria[1], [1]Biochemistry and Molecular Genetics Service, FCRB-IDIBAPS, CIBERehd, EF CLIF, [2]Biochemistry and Molecular Genetics Service, FCRB-IDIBAPS, EF CLIF, [3]European Foundation for the Study of Chronic Liver Failure (EF CLIF), [4]Liver Unit, FCRB-IDIBAPS, CIBERehd, EF CLIF

Background: Lymphopenia is a risk factor for mortality in patients with liver cirrhosis. In this study we investigated the functional status of B lymphocytes in patients with acutely decompensated (AD) cirrhosis. In addition, since recent studies have shown that AD patients receiving albumin infusions had lower mortality and incidence of infections, we also explored the direct effects of albumin on B cells. **Methods:** B cell immunophenotyping was performed by flow cytometry in peripheral blood from 36 patients with AD cirrhosis and 18 healthy subjects. In vitro studies were performed in peripheral blood mononuclear cells (PBMCs) isolated by Ficoll and B cells isolated by magnetic-activated cell sorting. Cells were incubated with human serum albumin (15 mg/mL) or vehicle for increasing periods of time (24-72 hours) with and without T-dependent or T-independent stimuli. Gene expression was determined by qPCR and Fluidigm and cell proliferation and viability by flow cytometry. Immunoglobulin and cytokine/chemokine levels in cell supernatants were measured by ELISA and in a Milliplex magnetic bead panel, respectively. **Results:** Compared to healthy subjects, PBMCs and B cells from patients with AD cirrhosis showed reduced viability and lower capacity to produce immunoglobulins under both resting conditions and following T-dependent and T-independent stimulation. Incubation of PBMCs and B cells with albumin upregulated immunoglobulin gene expression and increased the production of IgG, specially of the IgG subclass 2, which responds to bacterial capsular polysaccharide antigens. Again, responses to albumin were observed under both resting conditions and following T-dependent and T-independent stimulation. Under resting conditions, albumin also increased the release of B cell-activating cytokines/chemokines like IL-6, IL-4 and CXCL10. Furthermore, albumin enhanced B cell viability and induced the expression of the gene coding for activation-induced cytidine deaminase (AID), an essential enzyme for the humoral adaptive immune response. **Conclusion:** These data provide evidence of the ability of albumin to boost B cell function and to expand

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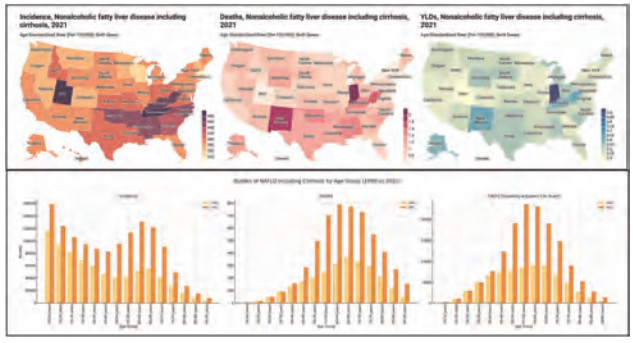
their viability, which are seriously compromised in patients with AD cirrhosis. **Disclosures:** Berta Romero-Grimaldo: Nothing to Disclose, Mireia Casulleras: Nothing to Disclose, Bryan Contreras: Nothing to Disclose, Marta Duran-Güell: Nothing to Disclose, María Belén Sánchez-Rodríguez: Nothing to Disclose, Carlos Rojano Alfonso: Nothing to Disclose, Giuliana Magri: Nothing to Disclose, Javier Fernández: Nothing to Disclose, Richard Moreau: Nothing to Disclose, Cristina López-Vicario: Nothing to Disclose, Joan Claria: Nothing to Disclose

★ 0229 | TEMPORAL TRENDS AND GEOGRAPHIC DISPARITIES IN NAFLD INCLUDING CIRRHOSIS ACROSS THE UNITED STATES, 1990–2021

Yashkumar Kamani[1] Mahendra Kumar[2] Sandeep Kotnani[3] Raghava Rao Alluri[4] Mahir Modi[5] Madhu babu Adusumilli[6] Jainil Parikh[7] VISHRANT AMIN[8] Hardik Desai[9], [1]BronxCare Health System, [2]Sardar Patel Medical College, Bikaner, India, [3]Rutgers Monmouth Medical Center, [4]Prime South GME Consortium/Harlingen Medical Center Program, [5]GCS Medical College Hospital and Research Centre, [6]HCA Ocala Florida hospital -UCF, [7]GMERS MEDICAL COLLEGE, GOTRI, VADODARA, [8]HMH JFK University Medical Center, [9]Independent Clinical and Public Health Researcher

Background: Nonalcoholic fatty liver disease (NAFLD), including cirrhosis, has emerged as a leading cause of chronic liver disease globally, driven by rising rates of obesity, metabolic syndrome, and sedentary lifestyles. Despite its increasing clinical and public health significance, age- and sex-specific trends in the burden of NAFLD across the United States remain under characterized, especially over long-term periods. **Methods:** We estimated the burden of NAFLD, including cirrhosis, in the United States from 1990 to 2021 utilizing standardized global burden of disease study 2021. Outcomes assessed included total prevalence, deaths, and disability-adjusted life years (DALYs), years lived with disability (YLDs) stratified by age group, sex, and state-level geography. Annual percentage change (APC) in age-standardized incidence rate (ASIR), mortality rate (ASMR), and DALY rate (ASDALR) was calculated using Joinpoint regression to quantify temporal trends over the study period. **Results:** Between 1990 and 2021, the total prevalence of NAFLD rose from 23.2 million (95% UI: 21.3–25.4) to 44.6 million (40.7–48.6), deaths increased from 2,607 (1,826–3,516) to 5,520 (3,799–7,563), and DALYs doubled from 73,608 (52,004–100,811) to 147,584 (101,373–206,069). ASIR, ASMR, and ASDALR showed APC of +0.64%, +0.58%, and +0.54%, respectively. At the subnational level, the highest APC in ASIR was observed in Tennessee (+0.81%), followed by Kentucky (+0.76%) and North Dakota (+0.70%). For ASMR, the greatest increases occurred in West Virginia (+2.11%), Oklahoma (+1.89%), Kentucky (+1.82%), and Tennessee (+1.79%). Age-specific analysis revealed the highest APC in incidence among individuals under 20 years (+0.83%), followed by those aged 20–54 years (+0.70%) and 55 years and above (+0.52%). Sex-specific trends showed a disproportionately higher burden among females, with APCs in ASIR of 0.56% (female) versus 0.70% (male), in ASMR of 0.79% (female) versus 0.32% (male), and in ASDALR where females experienced a slight increase (+0.14%) while males showed a decline (–0.3%). **Conclusion:** From 1990 to 2021, NAFLD burden in the U.S. more than doubled, with the steepest rises among youth, females, and southern states—signaling the need for early, targeted, and region-specific interventions. The shifting epidemiology toward younger age groups highlights a critical window for prevention before progression to advanced liver disease.



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★ 0230 | EXPLANATORY MODELS OF WEIGHT AND LIVER DISEASE AMONG PATIENTS WITH MASLD: A QUALITATIVE STUDY

Megan Pham[1] Sriya Kakarla[1] Myriam Ibarra[1] Yarian Garcia-Alayon[1] Crystal Arguelles[1] Alexis Moreleon[1] Maya Balakrishnan[2], [1]Baylor College of Medicine, [2]Ben Taub General Hospital

Background: Effective counseling for patients with metabolic dysfunction-associated steatotic liver disease (MASLD) requires understanding how they conceptualize their weight and liver disease. Patients' beliefs about the causes of weight gain and weight loss strategies influence their motivation and engagement in behavior change. This qualitative study explored explanatory models of body

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weight, liver disease, and weight loss among Hispanic adults with MASLD- a high-risk population in the United States. **Methods:** We conducted in-depth interviews with 51 patients with BMI $\geq$ 25 kg/m^2 and MASLD, purposively sampled and stratified by gender and acculturation status. Using framework analysis, we assessed how they conceptualized their body weight and MASLD diagnosis. **Results:** Three major themes emerged. First, there were gender differences in how patients conceptualized their weight. Men tended to attribute their weight to long-term lifestyle behaviors, while women contextualized weight in relation to life transitions, emotional stress, hormonal/medical factors, and social roles. Secondly, while men generally described a linear causal link between health behaviors, their weight, and MASLD, women more frequently offered complex explanations incorporating genetics, stress, or medication side effects into their understanding of liver disease. Third, across genders, patients perceived their excess weight as the root cause of barriers hindering their ability to lose weight. They described physical (e.g., pain, fatigue) and psychosocial (e.g., depression, fear of failure) challenges from being overweight that made it hard to initiate or sustain weight loss behaviors. **Conclusion:** To provide effective counseling that supports meaningful weight loss in patients with MASLD, it is essential to understand how patients perceive their weight and liver disease, as these beliefs strongly shape their motivation and capacity for behavior change. Our study highlights that patients often viewed their weight as a physical and psychological barrier impeding their ability to adopt and sustain lifestyle changes. These perceptions were deeply rooted in personal and social contexts shaped by gender, stress, and life experiences. Recognizing and addressing these explanatory models is key to providing culturally sensitive, gender-informed, and patient-centered care that supports long-term change.
Disclosures: Megan Pham: Nothing to Disclose, Sriya Kakarla: Nothing to Disclose, Myriam Ibarra: Nothing to Disclose, Yarian Garcia-Alayon: Nothing to Disclose, Crystal Arguelles: Nothing to Disclose, Alexis Moreleon: Nothing to Disclose, Maya Balakrishnan: Nothing to Disclose

★ 0231 | DOUBLE TROUBLE: A 25-YEAR NATIONWIDE ANALYSIS OF CHRONIC LIVER DISEASE IN THE ERA OF METABOLIC SYNDROME

Simran Joshi[1] Muhammad Ali[2] Husnain Ahmad[3] Corinne Caissie[1] Muhammad Khan[4] Sushrut Ingawale[5] Muhammad Rahim[3] Salman Attari[6] Rishi Chowdhary[7] Susan Feldman[8] Mohammad Islam[1] Marquise Soto[9] Cheng-Hung Tai[1], [1]Yale New Haven Health/Yale University School of Medicine, [2]Jinnah Postgraduate Medical Center, [3]Shalamar Medical and Dental College, [4]Bacha Khan Medical College, [5]Quinnipiac University - Frank H Netter MD School of Medicine, [6]Asian Institue of Medical Sciences, [7]Metrohealth Medical Center, [8]Susanfeldm@gmail.com, [9]Massachusetts General Hospital/Harvard Medical School

Background: Chronic liver disease (CLD) and metabolic syndrome (MetS) frequently coexist, sharing pathophysiologic mechanisms that compound morbidity and mortality. Despite their growing burden, national data on long-term mortality trends in comorbid CLD and MetS remain scarce. This study aims to evaluate 25-year mortality trends among U.S. adults with comorbid CLD and MetS, highlighting regional and demographic disparities to inform targeted public health strategies. **Methods:** Mortality data from the CDC WONDER database (1999–2023) were analyzed using Joinpoint regression to assess CLD and MetS-related deaths among U.S. adults aged 25 and older. Age-adjusted mortality rates (AAMRs) per million were calculated, along with the average annual percent change (AAPC) and corresponding 95% confidence intervals (CI). **Results:** Over the 25-year period, MetS among individuals with CLD accounted for 291,154 deaths in the United States. The overall AAMR rose markedly from 2.79 per 100,000 in 1999 to 8.59 in 2023, with a striking average annual percent change (AAPC) of 4.49% (95% CI: 4.25–4.71; $p < 0.000001$). Males consistently exhibited higher mortality than females (6.36 vs. 3.64 per 100,000), with a steeper upward trend (AAPC: 4.53% [95% CI: 4.30–4.77] vs. 4.37% [95% CI: 4.02–4.71]; both $p < 0.000001$). Among racial/ethnic groups, American Indian or Alaska Native (AI/AN) individuals had the highest AAMR (15.46), followed by Hispanic or Latino (8.25), Non-Hispanic (NH) White (4.68), NH Black (4.48), and Asian individuals (2.70). The sharpest increase in mortality was observed in AI/AN populations (AAPC: 5.31%; 95% CI: 4.66–6.02), followed by NH Whites (5.17%), NH Blacks (2.60%), Hispanics (2.30%), and Asians (1.75%), all with $p < 0.000001$ except Asians ($p = 0.0208$). Regionally, the South experienced the most pronounced rise (AAPC: 5.19%; 95% CI: 4.86–5.53), followed by the Midwest (4.56%), West (4.03%), and Northeast (2.90%). States with the highest AAMRs included New Mexico (7.99), South Dakota (7.54), and Kentucky (6.85). Rural areas had slightly higher AAMRs than urban areas (4.96 vs. 4.28) and a steeper increase over time (AAPC: 6.25% vs. 4.24%; both $p < 0.000001$). Age-stratified analysis revealed the highest mortality in adults aged 75 and older (AAMR: 14.36), followed by middle-aged (AAMR: 7.21) and younger adults (AAMR: 0.79). The greatest increase was also among the elderly (AAPC: 5.08%), followed by younger (4.74%) and middle-aged adults (4.30%), all with $p < 0.000001$. **Conclusion:** CLD and MetS-related mortality has increased substantially over the past 25 years, with the most notable increases seen in females, AI/AN, NH Whites, rural areas, the South region and individuals aged 75 and older. These

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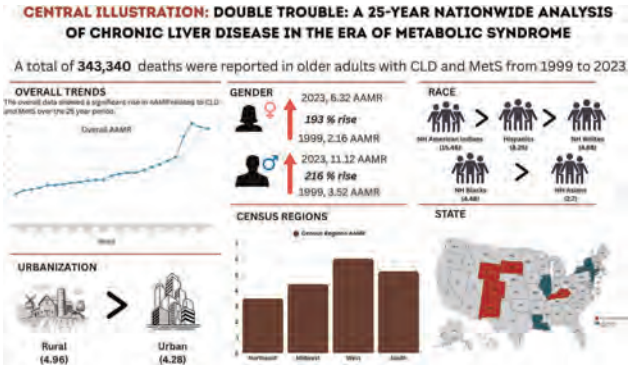
disparities highlight the urgent need for targeted intervention to address the growing mortality in vulnerable population.



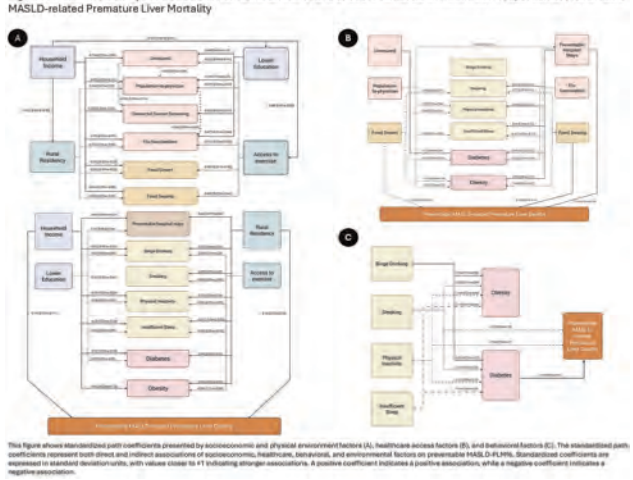
Disclosures: Simran Joshi: Nothing to Disclose, Muhammad Ali: Nothing to Disclose, Husnain Ahmad: Nothing to Disclose, Corinne Caissie: Nothing to Disclose, Muhammad Khan: Nothing to Disclose, Sushrut Ingawale: Nothing to Disclose, Muhammad Rahim: Nothing to Disclose, Salman Attari: Nothing to Disclose, Nothing to Disclose, Rishi Chowdhary: Nothing to Disclose, Susan Feldman: Nothing to Disclose, Mohammad Islam: Nothing to Disclose, Marquise Soto: Nothing to Disclose, Cheng-Hung Tai: Nothing to Disclose

0232 | STRUCTURAL DETERMINANTS OF PREVENTABLE MASLD-RELATED PREMATURE LIVER MORTALITY ACROSS U.S. COUNTIES: A NATIONWIDE ECOLOGICAL ANALYSIS (2010–2020)

James Paik[1] Shira Zelber-Sagi[2] Annette Paik[3] Linda Henry[4] Yusuf Yilmaz[5] Mohamed El-Kassas[6] Saleh Alqahtani[7] Zobair Younossi[4], [1]Beatty Liver and Obesity Research Program, Inova Health System, Falls Church, VA, [2]Tel-Aviv Sourasky Medical Center, [3]Beatty Liver and Obesity Program, Inova Health System, Falls Church, VA, [4]The Global NASH Council, [5]Recep Tayyip Erdoğan University, [6]Helwan University, [7]Liver, Digestive, and Lifestyle Health Research Section, and Organ Transplant Center of Excellenc

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver mortality in the U.S., yet a substantial proportion of MASLD-related premature liver mortality (MASLD-PLM) may be preventable. Understanding structural and geographic drivers is critical for targeted public health interventions. **Methods:** This cross-sectional ecological study analyzed county-level data from the National Vital Statistics System and County Health Rankings & Roadmaps (2010-2020) across 3,143 U.S. counties. Preventable MASLD-PLM was defined as deaths before age 80 exceeding expected rates based on the three states with the lowest MASLD-PLM. County-level exposures encompassed socioeconomic status, rurality, food and physical environments, healthcare access, and chronic disease burden. Structural equation modeling (SEM) quantified direct and indirect pathways to proportion of preventable MASLD-PLM. **Results:** From 2010–2020, MASLD-PLM averaged 17,977 deaths annually, of which 56.1% (~10,078 deaths/year) were deemed preventable. Proportion of Preventable MASLD-PLM varied significantly by geography, with a clear rural gradient (39.2% in large central metros vs. 74.7% in noncore counties). Counties with higher proportion of preventable MASLD-PLM had lower median income, limited healthcare access, more adverse food environments, and higher rural residency. SEM revealed that higher household income was associated with lower preventable MALSD-PLM both directly (standardized $\beta = -0.14$) and indirectly ($\beta = -0.49$), largely mediated through improved education, healthcare access, and healthier environments. Rural residency ($\beta = +0.16$), food desert exposure ($\beta = +0.15$), and food swamp density ($\beta = +0.10$) had direct associations with higher preventable MASLD-PLM. Access to exercise ($\beta = -0.19$ indirect) was protective, while preventable hospitalizations ($\beta = +0.10$ indirect) and population-to-physician ratios ($\beta = +0.03$ indirect) contributed via healthcare barriers. Behavioral and metabolic risks, including smoking ($\beta = +0.10$), physical inactivity ($\beta = +0.18$), and diabetes prevalence ($\beta = +0.13$), were also directly associated with higher preventable MASLD-PLM. Figure. **Conclusion:** Over half of MASLD-related premature liver deaths in the U.S. appear preventable, with disproportionate burdens in rural and socioeconomically disadvantaged counties. Structural determinants-including income, rurality, healthcare access, and food environments-play a central role.

Figure. Mediation Pathways of Social, Economic, Healthcare, and Environmental Determinants on Proportion of Preventable MASLD-related Premature Liver Mortality



Disclosures: James Paik: Nothing to Disclose, Shira Zelber-Sagi: Nothing to Disclose, Nothing to Disclose, Annette Paik: Nothing to Disclose, Linda Henry: Nothing to

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Disclose, Yusuf Yilmaz: Nothing to Disclose, Mohamed El-Kassas: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant

0233 | RACIAL/ETHNIC AND SOCIOECONOMIC DISPARITIES IN STEATOTIC LIVER DISEASE: THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

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Background: Steatotic liver disease (SLD) is a major contributor to the increasing liver-related morbidity and mortality. It has been reported that Hispanics are disproportionately affected by SLD. However, few studies have examined the racial/ethnic disparities beyond genetic susceptibility and socioeconomic disparities in SLD. **Methods:** We conducted a cross-sectional analysis of 4968 participants (1178 non-Hispanic Black, 594 Chinese, 1174 Hispanic, and 2022 non-Hispanic White) in the Multi-Ethnic Study of Atherosclerosis study, aged 44-84 years and free of viral hepatitis and cirrhosis. Hepatic steatosis was assessed by hepatic attenuation values using computed tomography. We used standard and multilevel linear regression models, to examine the differences in hepatic steatosis associated with race/ethnicity (accounting for genetic susceptibility using a polygenic risk score [PRS]), individual-level socioeconomic status (SES) measures (education and poverty-to-income ratio), and neighborhood-level SES measure (neighborhood deprivation score). **Results:** Overall hepatic attenuation was 60 $\pm$ 11 HU among all participants. After adjusting for age, gender, and PRS, Hispanic participants showed significantly higher levels of hepatic steatosis (lower hepatic attenuation values, β = -3.00 [95% CI: -3.9, -2.2]) compared to White participants. For individual-level SES, after adjusting for age and gender, we found significant inverse associations of both income and education with hepatic steatosis. At the neighborhood level, a higher deprivation score was associated with increased hepatic steatosis levels, adjusting for age, gender, and race/ethnicity, with minimal change in estimates after additional adjustment for individual SES. (Table). **Conclusion:** This population-based study documents higher SLD burden among Hispanic participants beyond genetic susceptibility. Lower income and lower education levels are associated with higher hepatic steatosis. Residential socioeconomic environment is associated with hepatic steatosis, independent of individual-level SES. These findings highlight that SLD-related disparities exist across disadvantaged populations and call for liver-related prevention efforts focused on upstream determinants of health.

Table. Adjusted associations between individual and contextual levels of SES and hepatic steatosis (HU, lower values indicate higher hepatic steatosis)

	Beta (95% CI) *
Income-to-Poverty Ratio	
< 1	-1.43 (-2.56, -0.31)
1-1.99	-0.50 (-1.39, 0.39)
2-3.99	-0.49 (-1.22, 0.26)
≥ 4	Ref
Education	
Less than high school	-2.04 (-2.98, -1.10)
High school or some college	-1.14 (-1.82, -0.45)
College and above	Ref
Neighborhood deprivation score	**-0.53 (-0.86, -0.19)**

*adjusting for age and gender for income-to-poverty ratio and education models; adjusting for additional race/ethnicity for neighborhood deprivation score model.

Disclosures: Heli Xu: Nothing to Disclose, Ana Diez-Roux: Nothing to Disclose, Usama Bilal: Nothing to Disclose, Brisa Sanchez: Nothing to Disclose, Kari Moore: Nothing to Disclose, Jana Hirsch: Nothing to Disclose, Matthew Budoff: Nothing to Disclose, Steven Solga: Nothing to Disclose, Xiuqing Guo: Nothing to Disclose, Jie Yao: Nothing to Disclose, Jerome Rotter: Nothing to Disclose, Stephen Dickinson: Nothing to Disclose, MARIANA LAZO: Nothing to Disclose

0234 | OLDER PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) HAVE HIGHER RATES OF LEAN MASLD AND MORE ADVANCED FIBROSIS BUT BETTER HEALTH RELATED QUALITY OF LIFE (HRQL)

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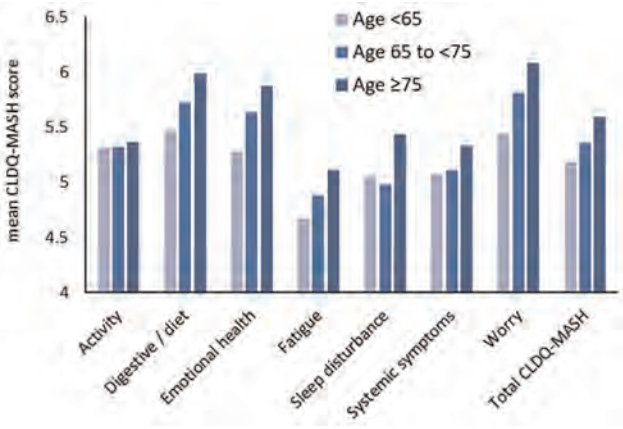
Background: The Impact of age on MASLD outcomes has not been fully assessed. Our aim was to assess the clinical and patient reported outcomes (PROs) of MASLD patients based on age groups. **Methods:** Patients with MASLD were prospectively enrolled into our Global NAFLD/MASLD Registry™ (GNR). Clinical and PROs (FACIT-F, CLDQ-MASH, and WPAI) data were analyzed in MASLD patients of <65 years vs. 65-74 years vs. ≥ 75 years. **Results:** 8441 MASLD patients from 18 countries were included: mean (SD) age 52 (13) years, 46% male, 65% obese, 38% type 2 diabetes (T2D), 49% hypertension, 47% hyperlipidemia, 14% with advanced fibrosis, 19% depression, 39% clinically overt fatigue and 24% sleep apnea. Of these, 83% were <65 years, 14.5% were 65-74 years, and 2.3% were ≥ 75 years old. The proportion of lean MASLD (by BMI) rose from 5% in the <65 group to 9% in the 65-74 group to 17% in the ≥ 75 group, while the prevalence of T2D was 35% in <65 vs. 50% in 65-74 vs. 49% in ≥ 75; the rates of hypertension and hyperlipidemia also increased with age (all $p < 0.0001$). In a subgroup of patients with waist circumference (63%), the proportion of lean MASLD remained higher in older patients: 10% in <65 vs. 12% in 65-74 vs. 18% in ≥ 75 ($p = 0.01$). The prevalence of advanced fibrosis (by FIB-4 or imaging or biopsy) was higher in older patients: 12% in the <65 group, 24% in the 65-74 group, and 28% in the ≥ 75 group. In multivariate logistic regression analysis, older age was independently associated with a higher risk of advanced fibrosis in MASLD (OR (95% CI) = 2.05 (1.73-2.43) for age 65-74 years, 2.83 (1.99-4.02) for age ≥ 75 years vs. reference age <65 years, $p < 0.0001$), along with obesity and T2D ($p < 0.05$); the association of fibrosis with older age was similar in lean and non-lean MASLD patients (all $p > 0.05$ for interaction). In patients of ≥ 65 years, only T2D was a predictor of advanced fibrosis (OR = 2.56 (1.94-3.38), $p < .0001$). The HRQL scores by CLDQ-MASH and FACIT-F were higher in older patients with MASLD (Figure). In multivariate analysis adjusted for confounders, older age was independently associated with higher PRO scores in emotional well-being-related domains (Emotional Health and Worry of CLDQ-MASH, Emotional well-being of FACIT-F) and lower scores in the Activity/Energy domain of CLDQ-MASH (all $p < 0.05$). In patients of ≥ 65 years, independent predictors of lower PRO scores included female sex, the presence of obesity and T2D, history of psychiatric comorbidities, clinically overt fatigue, abdominal pain, sleep apnea, and the lack of regular exercise ($p < 0.05$). **Conclusion:** Older patients with MASLD seen in tertiary care hepatology clinics have higher PRO scores despite more advanced fibrosis but lower rate of overweight/obesity.



Disclosures: Yusuf Yilmaz: Nothing to Disclose, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Mohamed El-Kassas: Nothing to Disclose, Vasily Isakov: Nothing to Disclose, Marlen Ivon Fernandez: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company, Eli Lilly: Consultant, Merck: Consultant, Yuichiro Eguchi: Nothing to Disclose, Manuel Romero-Gómez: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, Elisabetta Bugianesi: Nothing to Disclose, Wah Kheong Chan: Abbott: Consultant and Speaking, Abbvie: Advisor, Abbott: Research Grant, Advisor, and Speaking, Boehringer Ingelheim: Consultant and Advisor, Novo Nordisk: Advisor and Speaking, Roche: Advisor, Zuellig Pharma: Advisor, Echosens: Speaking, Hisky Medical: Speaking, Viatris: Speaking, Khalid Alswat: Nothing to Disclose, Saeed Hamid: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, GSK: Grant/Research Support, CLD Foundation:

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★ 0235 | EFFICACY OF A LACTOCOCCUS LACTIS-BASED SYNBIOTIC DEVELOPED FROM A HUMAN MICROBIOTA-ASSOCIATED MICE MODEL FOR PREVENTING METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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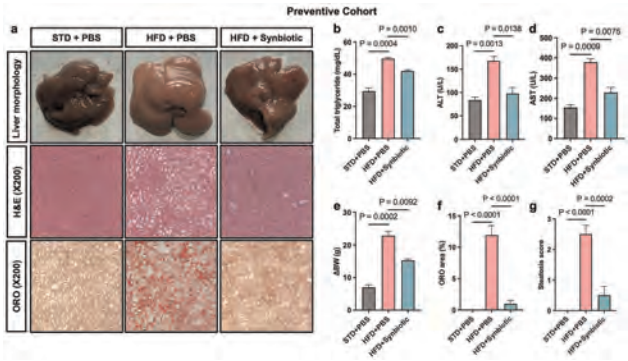
Background: The gut microbiome plays a critical role in metabolic dysfunction-associated steatotic liver disease (MASLD). Specific *Lactococcus lactis* strains and microbial metabolites demonstrate therapeutic potential. A rationally designed microbial formulation may offer synergistic benefits, but its efficacy in MASLD remains unproven. **Methods:** *L. lactis* strains were isolated from feces of healthy human donors and recipient mice in a human microbiota-associated model. Species- and strain-level identification and functional analysis were performed using MALDI-TOF and PacBio whole-genome sequencing. After developing a proprietary synbiotic containing *L. lactis* strains and microbial metabolites (under patent consideration), eight-week-old male C57BL/6J mice were assigned to two experimental cohorts: (1) preventive cohort - mice were simultaneously fed a high-fat diet (HFD) and synbiotic for 12 weeks to evaluate preventive efficacy; (2) therapeutic cohort - mice were fed an HFD for 8 weeks to establish MASLD, followed by a longer, 16-week oral synbiotic treatment to assess reversal potential. **Results:** Five distinct *L. lactis* strains were identified, functionally enriched in MASLD-related pathways, with minimal antimicrobial resistance, biocide/metal tolerance, or genomic virulence. In the preventive cohort, synbiotic-treated mice, when compared to HFD-fed controls, achieved significant reductions in body weight gain (15.23 ± 0.44 g vs. 22.84 ± 1.29 g), serum triglycerides (41.95 ± 0.67 mg/dL vs. 49.67 ± 0.70 mg/dL), ALT (97.91 ± 12.15 U/L vs. 168.00 ± 9.31 U/L), AST (228.70 ± 25.01 U/L vs. 379.30 ± 16.35 U/L), liver weight (1.17 ± 0.42 g vs. 1.62 ± 0.10 g), and hepatic cholesterol (3.20 ± 0.53mg/g vs. 7.96 ± 0.61 mg/g) (all $p < 0.05$). Histological examination showed reduced NAS (steatosis grade: 0.50 ± 0.29 vs. 2.50 ± 0.29) and Oil Red O area (0.99 ± 0.50% vs. 11.95 ± 1.50%) (all $p < 0.05$). Gut barrier integrity, assessed by the FITC-dextran permeability assay, was restored (0.99 ± 0.01 vs. 1.35 ± 0.05, $p = 0.0104$). In the therapeutic cohort, synbiotic treatment led to modest, non-significant reductions in weight gain and hepatic triglycerides, but significantly improved intestinal permeability (0.97 ± 0.08 vs. 1.79 ± 0.21, $p = 0.0270$). **Conclusion:** A novel *L. lactis*-based synbiotic prevents MASLD development in mice, demonstrating the clinical potential of microbial interventions in managing MASLD. *Supported by Innovation and Technology Fund-Midstream Research Programme for Universities (ITS/046/22MS).*



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0236 | MICROBIOME ROLES IN ESTROGEN HOMEOSTASIS AS REVEALED BY ESTROGEN CHALLENGE

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Background: Increased estrogen circulation is a known consequence of cirrhosis, but little is known about the effects of an estrogen burden on the liver. The liver plays a central role in estrogen homeostasis, which requires a balance between host- and microbiome-mediated processing. In the host, the liver uses estrogen receptors to sense circulating estrogen levels and facilitates excretion via several conjugation pathways, including glucuronidation. The gut microbiome reverses host estrogen conjugation via β-glucuronidases and other enzymes, which restore the modified estrogens to active forms. These estrogens preferentially are absorbed across the intestinal wall and return to the bloodstream through the enterohepatic (portal vein) circulation, which contributes to the central role of the liver in estrogen metabolism. **Methods:** We explored the hepatic handling of estrogen by exposing 84 eight-week-old C57BL/6J mice (43 females, 41 males) to either a subcutaneous estradiol pellet (0.25mg/day for 21 days), placebo pellet, or no pellet. Hepatic tissues were harvested after sacrifice and analyzed for expression of the estrogen receptor gene *Esr1* and the estrogen conjugation genes *Ugt1a1* and *Ugt1a9*. The same analyses were then repeated in 24 formerly germ-free female C57BL/6J mice who were conventionalized in early adulthood (at seven weeks) using the cecal contents of either control (CMT-C) or estradiol-exposed (CMT-E) females from the conventional study, followed by three weeks of exposure to an estradiol pellet or not. **Results:** At the peak of estradiol treatment, there was no treatment effect on *Esr1*, *Ugt1a1*, or *Ugt1a9* expression in conventional females. However, in conventionalized ex-germ-free females, all three genes were expressed at reduced levels (Figure 1 for *Ugt1a9* as an example). Within the ex-germ-free females, transfer of the CMT-E microbiome led to a further decrease in *Esr1*, *Ugt1a1*, and *Ugt1a9* expression, while the primary estrogen exposure itself had no effect (Figure 1). **Conclusion:** These findings demonstrate that the intestinal microbiome contributes mechanistic links to hepatic estrogen metabolism, distinct from direct estrogen-mediated effects. The gut microbiome-hepatic axis thus represents a promising avenue for interventions to regulate both estrogen metabolism and the expression of hepatic genes critical to estrogen homeostasis.

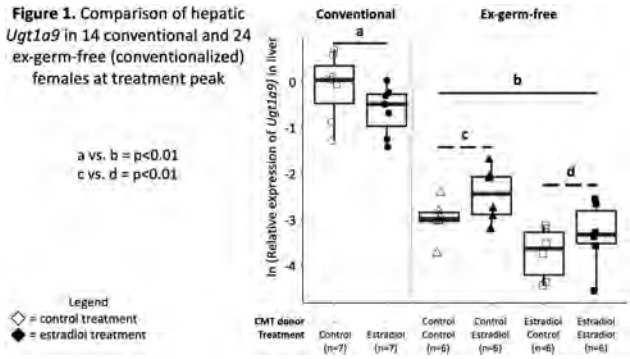

Figure 1. Comparison of hepatic *Ugt1a9* in 14 conventional and 24 ex-germ-free (conventionalized) females at treatment peak

Disclosures: Anushka Subrahmanian: Nothing to Disclose, Liisa Veerus: Nothing to Disclose, Anjali Patel: Nothing to Disclose, Xingnan Li: Nothing to Disclose, Adrian Franke: Nothing to Disclose, Martin Blaser: Nothing to Disclose

0237 | SALIVARY MICROBIOME AND SERUM METABOLOMICS ADD TO CLINICAL BIOMARKERS TO PREDICT 6-MONTH HOSPITALIZATIONS IN A MULTI-CENTER CIRRHOSIS OUTPATIENT COHORT

Jasmohan Bajaj[1] K Rajender Reddy[2] Jennifer Lai[3] Jacqueline O'Leary[4] Puneeta Tandon[5] Florence Wong[6] Guadalupe Garcia-Tsao[7] Hugo Vargas[8] Patrick Kamath[9] Scott Biggins[10] Philip Vutien[11] Ana Limon-Moro[12] Jawaid Shaw[13] Masoumeh Sikaroodi[14] Brian Bush[15] Leroy Thacker[15] Patrick Gillevet[14], [1]Virginia Commonwealth University, [2]University of Pennsylvania, [3]UCSF, [4]Dallas VA, [5]University of Alberta, [6]University of Toronto, [7]Yale University, [8]Mayo Clinic Arizona, [9]Mayo Rochester, [10]UPMC, [11]UW Seattle, [12]U Alberta, [13]Richmond VA, [14]GMU, [15]VCU

Background: Prognosticating outcomes such as hospitalizations in cirrhosis outpatients is challenging, especially with changing etiologies and demographics. Aim: Determine impact of multi-omic strategies on outcome prediction. **Methods:** NACSELD3 (North American Consortium for the Study of End-Stage Liver Disease 3) enrolls cirrhosis outpatients with controlled and eradicated etiologies from 10 centers and follows them

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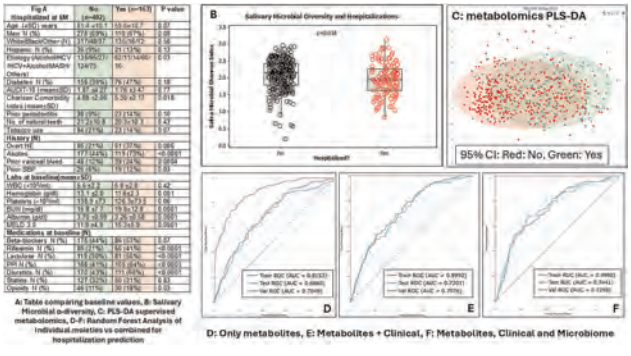
systematically. At baseline, clinical/demographic and cirrhosis details were recorded and saliva and serum samples were collected for microbiome and metabolome analysis respectively. Multi-omic bioinformatic studies to determine interaction of microbiota and metabolites with clinical prediction of 6-month hospitalizations were performed; microbiome was analyzed using 16SrRNA sequencing with diversity & LEfSe, metabolome using LC/MS & then PLS-DA supervised. Combined: Random forest using individual & combined modalities with AUC and latent factor analysis to determine which factors were most significant were performed. **Results:** 565 patients (60.2 years, 68% men, 35% alcohol, 33% MASH, 21%, eradicated HCV with MELD3.0 12) were enrolled. 163 (29%) required 6-month hospitalizations; most (75%) were liver-related. Those hospitalized had worse cirrhosis severity, co-morbidity indices, but similar demographics and oral health variables (Fig A). Microbiome: Salivary microbiome alpha-diversity was lower (1.96 ± 0.48 versus 2.09 ± 0.45, $p = 0.018$) with greater pathobionts (*Streptococcus*, *Treponema, Enterococcaceae)* and lower commensal genera (*Veillonella, Prevotella, Haemophilus*, *Lachnospiraceae* spp) at baseline (Fig B). Serum metabolomics: showed 1729 metabolites, of which 1420 were named. Supervised analysis using PLS-DA shows major separation at the 95% CI between those who were ultimately hospitalized or not showed significant separation at baseline between hospitalized/not patients using supervised analyses with microbial-origin (phenyllactate, secondary bile acids, indoles), choline moieties, and polyamine/GABA (3-ureidopropionate/spermidine) metabolites being most prominent (Fig C). Combined: Area-under-the curve using random forest for clinical, microbial, and metabolomic variables were higher than that of these individually (Fig D-F). Latent factor analysis showed clinical variables (MELD3.0, hemoglobin and albumin) with the greatest impact followed by salivary microbiota and then serum microbiome for hospitalization prediction. **Conclusion:** In a multi-center North American outpatient cirrhosis cohort with controlled etiologies, serum metabolomics focused on microbial products and salivary microbiome add to clinical variables to prognosticate 6-month hospitalization.



A: Table comparing baseline values, B: Salivary Microbial α-diversity, C: PLS-DA supervised metabolomics, D–F: Random Forest Analysis of individual modalities vs combined for hospitalization prediction

D: Only metabolites, E: Metabolites + Clinical, F: Metabolites, Clinical and Microbiome

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Nothing to Disclose, Brian Bush: Nothing to Disclose, Leroy Thacker: Nothing to Disclose, Patrick Gillevet: Nothing to Disclose

0238 | HEPATOCYTE-DERIVED EXOSOMAL MIR-122 MEDIATES LIVER-TO-BRAIN CROSSTALK IN ALCOHOL-EXPOSED ALZHEIMER'S DISEASE MICE AND EXACERBATES NEUROINFLAMMATION

Veronika Brezani[1] Radhika Joshi[1] Marti Ortega-Ribera[1] Viliam Brezani[1] Mrigya Babuta[1] Bruna Santos[1] Adam Zivny[1] Gyongyi Szabo[2], [1]BIDMC & Harvard Medical School, [2]Beth Israel Deaconess Medical Center

Background: Alcohol consumption triggers inflammation in the liver and in the brain. We have previously demonstrated that alcohol increases circulating levels of exosomes enriched in miR-122, a hepatocyte-specific microRNA, in both humans and mice. Given that hepatic encephalopathy involves liver inflammation that activates microglia in the brain, we hypothesized that alcohol-induced hepatocyte-derived exosomes mediate liver-to-brain communication in Alzheimer's disease (AD) by transferring miR-122, thereby promoting neuroinflammation. **Methods:** Wild-type (WT) and APP/PS1 transgenic (AD) mice received alcohol binges (3.5 g/kg) every alternate day for a period of one month. Exosomes were isolated from serum or the supernatants of mouse hepatocytes treated with ethanol. Mouse BV-2 microglia were exposed to hepatocyte-derived exosomes prior to lipopolysaccharide (LPS) stimulation, and cytokine expression was analyzed after 24 hours. Liver and brain tissues were analyzed at mRNA and protein levels. **Results:** Alcohol significantly increased exosome biogenesis in vivo and release from primary hepatocytes in vitro. Ethanol-induced hepatocyte-derived exosomes were enriched in mature miR-122 compared to controls. Microglial uptake of hepatocyte-derived exosomes was confirmed by PKH26 staining. Exosomes from alcohol-treated hepatocytes sensitized microglia to LPS stimulation to produce significantly increased inflammatory chemokines MCP-1 and CCL3. Transfection of microglia with a miR-122 mimic recapitulated this pro-inflammatory sensitization, which was reversed after miR-122 inhibitor delivery. This supports our hypothesis that the transfer of miR-122 from ethanol-treated hepatocytes to microglia increases the pro-inflammatory responses in microglia. In APP/PS1 (AD) mice, chronic alcohol significantly increased circulating exosome numbers and miR-122 levels in the brain. Alcohol-treated AD mice showed elevated ALT, indicating liver damage, and increased inflammatory markers in the liver and inflammasome activation in the brain compared to WT mice. Importantly, ethanol-treated AD mice showed elevated amyloid β deposition in the hippocampus. This correlated with changes in ADAM10, a miR-122 target and important enzyme for cleaving amyloid precursor protein. **Conclusion:** Our findings reveal a novel alcohol-induced liver-brain crosstalk mediated by hepatocyte-derived exosomal miR-122 in AD. Alcohol-induced exosomes enhance neuroinflammatory responses via microglial sensitization and thereby exacerbate AD-related pathology. These results underscore the importance of hepatocyte-microglia communication in alcohol-associated neuroinflammation.

Disclosures: Veronika Brezani: Nothing to Disclose, Radhika Joshi: Nothing to Disclose, Marti Ortega-Ribera: Nothing to Disclose, Viliam Brezani: Nothing to Disclose, Mrigya Babuta: Nothing to Disclose, Bruna Santos: Nothing to Disclose, Adam Zivny: Nothing to Disclose, Gyongyi Szabo: CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpTo-Date Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpTo-Date Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, CYTA Therapeutics: Consultant, Durect Corporation: Consultant,

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0239 | TARGETING NEUTROPHIL RECRUITMENT/SIGNALING ATTENUATES BILIARY DISEASE IN A MOUSE MODEL OF CAROLI DISEASE

Romina Fiorotto[1] Santo Diprima[2] Anna Palmiotti[2] syeda zehra[2] Lauren Malouin[2] Mario Strazzabosco[1], [1]Yale University, [2]Yale School of Medicine

Background: Caroli Syndrome (CS) is characterized by biliary malformations, cholangiocyte dysfunction, and portal fibrosis and recurrent bacterial cholangitis. *PKHD1*, the mutated gene, encodes fibropolycystin, a protein involved in cell polarity, matrix interaction, and differentiation. The *Pkhd1*$^{del4/del4}$ (Pkhd1-KO) mouse, an orthologous model of CS, exhibits biliary cysts, peribiliary inflammation, fibrosis, and portal hypertension. This study aimed to assess the role of the inflammatory microenvironment in disease progression in Pkhd1-KO mice. **Methods:** Liver tissues from 3-month-old Pkhd1-KO mice and wild-type littermates were analyzed. Bacteria in livers were identified by Gram staining and liver lysate cultures. Cystic area, inflammatory infiltrates, and fibrosis were quantified by immunohistochemistry (CK19, CD45, Sirius Red). The inflammatory infiltrate and cholangiocyte-immune crosstalk was profiled by single-cell RNA sequencing (scRNA-seq). Infiltrate composition was confirmed by immune mass cytometry (IMC). Pkhd1-KO mice were treated with sulfamethoxazole/trimethoprim (SMZ/TMP) or a Cxcr2 inhibitor. **Results:** Pkhd1-KO mice showed biliary infection with *Enterococcus* spp. inside the cysts. Treatment with SMZ/TMP diet significantly reduced inflammation, fibrosis, and partially cystic area in Pkhd1-KO mice. scRNA-seq and IMC revealed enrichment of neutrophils and T cells in the infiltrate. Gene expression of recruiting chemokines for neutrophils and T cells (*Cxcl1, Cxcl5, Mif, Cxcl20, Il23, Cxcl16) along with* activation of NF-κB and bacterial defense pathways were upregulated in Pkhd1 cholangiocytes and downregulated following treatment with antibiotics. Connectome analysis confirmed cholangiocyte-immune cell interactions. Immunostaining (NIMP-R14, MMP9) showed activated neutrophils in and around cysts that were reduced after antibiotics. T cell sub-clustering revealed IL-17A producing γδ T cells in Pkhd1-KO livers that were markedly reduced after antibiotics. Inhibition of Cxcr2, the receptor of Cxcl1,5 in neutrophils,significantly decreased cystic area, inflammation, and fibrosis. **Conclusion:** Biliary infection with Enterococcus spp. drives neutrophil recruitment and inflammation in Pkhd1-KO mice. Targeting neutrophil signaling, by Cxcr2 inhibition, reduces cyst growth, T-cell infiltration and fibrosis, indicating a major role of neutrophils in orchestrating the inflammatory response to biliary pathobionts.

Disclosures: Romina Fiorotto: Nothing to Disclose, Santo Diprima: Nothing to Disclose, Anna Palmiotti: Nothing to Disclose, syeda zehra: Nothing to Disclose, Lauren Malouin: Nothing to Disclose, Mario Strazzabosco: Nothing to Disclose

★ 0240 | DECIPHERING HOT AND COLD FIBROTIC NICHES IN HUMAN CHRONIC LIVER DISEASE USING SPATIAL MULTIOMICS

Jacky Tam[1] Fabio Colella[1] Kexin Kong[1] Pak Kwan Qiu[2] Juliet Luft[1] George Finney[3] Ginevra Pistocchi[3] Laura Pallett[3] Prakash Ramachandran[1], [1]Institute for Regeneration and Repair, University of Edinburgh, [2]Cambridge Institute of Therapeutic Immunology and Infectious Disease, University of Cambridge, [3]Institute of Immunity and Transplantation, University College London

Background: Irrespective of etiology, the degree of fibrosis predicts worse prognosis in chronic liver diseases (CLD). However, CLD progression and responses to therapies in are highly variable, suggesting that fibrosis itself maybe heterogeneous. Recently the idea of distinct “hot” and “cold” fibrotic niches has been proposed, with different cellular compositions and treatment targets. Whilst conceptually appealing, this paradigm has not been validated in the liver. Here, we aimed to use novel spatial techniques to dissect heterogeneity in the human

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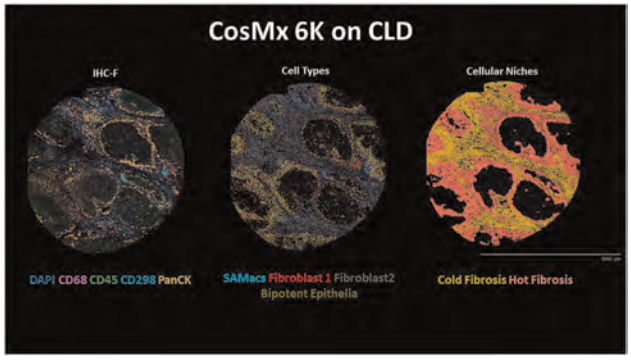
liver fibrotic niche and define the nature of hot and cold fibrosis. **Methods:** We applied spatial transcriptomics (ST; Stereo-seq, n = 12 and CosMx 6K, n = 22) and proteomics (69 antibody panel on Phenocycler-Fusion [PCF], n = 60) to healthy, MASLD, PSC and ALD liver samples, encompassing biopsies and explants of differing fibrosis stages. Stereo-seq data (225μm²/spot) underwent clustering, differential abundance testing, pseudospatial trajectory inference, deconvolution and ligand-receptor analyses. CosMx and PCF data underwent cell segmentation, cell-type identification, spatial mapping and cellular neighbourhood analysis. **Results:** Unbiased ST using Stereo-seq identified transcriptional heterogeneity in the liver fibrotic niche with two distinct clusters, FN1 and FN2, mapping to the scar-edge and scar-core respectively. Differential expression and pseudospatial trajectory analyses demonstrated that FN1 was most enriched for fibrogenic gene expression (e.g. *COL1A1*, *COL3A1*). Cellular deconvolution highlighted accumulation of scar-associated macrophages (SAMacs) and myofibroblasts in FN1 indicative of hot fibrosis, whilst FN2 was more akin to cold fibrosis. The hot FN1 niche expanded in both intermediate and advanced fibrosis, while the cold FN2 niche was more prevalent in advanced disease. We confirmed these findings using single-cell resolution CosMx and PCF data, defining a hot fibrosis cellular neighbourhood containing activated hepatic stellate cells, SAMacs and bipotential epithelial cells (Fig). Hot fibrosis was enriched for CD44 interactions, suggesting this may be a means to modulate this niche. **Conclusion:** We present a new paradigm for studying liver fibrosis, using spatial multiomics to decipher the cellular and molecular features of hot and cold fibrotic niches in human liver. These findings indicate that a more nuanced approach to antifibrotic drugs is needed, individualising therapy according to the type of fibrosis present in different patients.



Disclosures: Jacky Tam: Nothing to Disclose, Fabio Colella: Nothing to Disclose, Kexin Kong: Nothing to Disclose, Pak Kwan Qiu: Nothing to Disclose, Juliet Luft: Nothing to Disclose, George Finney: Nothing to Disclose, Ginevra Pistocchi: Nothing to Disclose, Laura Pallett: Nothing to Disclose, Prakash Ramachandran: Nothing to Disclose

★ 0241 | ABSTRACT WITHDRAWN

★ 0242 | ACUTE ETHANOL-INDUCED MITOCHONDRIAL DEPOLARIZATION (MTDEPO) ENHANCES OXYGEN CONSUMPTION AND TRIGGERS PERICENTRAL MITOPHAGY IN MOUSE HEPATOCYTES

Matthew Savoca[1] Kenji Takemoto[2] Zhi Zhong[1] John Lemasters[1], [1]Medical University of South Carolina, [2]Yamaguchi University

Background: Acute and chronic ethanol (EtOH) cause hepatic mtDepo, an adaptive response that enhances overall EtOH and acetaldehyde metabolism. Here, our AIM was to characterize hepatic mtDepo relative to mitochondrial respiratory function after acute *in vivo* EtOH-treatment of mice, the subsequent activation and zonation of mitophagy. **Methods:** Male C57BL/6J and GFP-LC3 mice were gavaged with 6 g/kg EtOH or vehicle. To assess mitochondrial membrane potential ($\Delta\Psi$) in hepatocytes *in vivo*, 0.05 μmol of Mitotracker Red (MTR) was administered 1h prior to liver fixation or hepatocyte isolation at 6h after EtOH or vehicle treatment. Oxygen consumption rates (OCRs) of hepatocytes were measured with a Seahorse XFe96 Analyzer. To evaluate $\Delta\Psi$ in isolated hepatocytes, cells were loaded with 500 nM Rhodamine 123 (Rh123). For analysis of $\Delta\Psi$ and GFP-LC3 puncta forming *in vivo* in hepatocytes within the liver lobule, slices of fixed liver were prepared from GFP-LC3 mice treated with MTR for observation by confocal microscopy. **Results:** After vehicle, intracellular MTR fluorescence was mitochondrial in all liver zones, signifying mitochondrial polarization. OCRs (ATP-linked, proton leak-linked, and maximal) of sorted periportal (PP) hepatocytes were ~4 times that of pericentral (PC). After EtOH, intracellular MTR fluorescence became non-mitochondrial in the central half but not the portal half of liver lobules, signifying mtDepo. Mitophagy indicated by GFP-LC3 puncta was also only increased in the central half. After EtOH, OCRs of both PP and PC hepatocytes were ~2-times that of vehicle, but PC hepatocytes displayed greater proportional increases compared to PP. In PC hepatocytes isolated from EtOH-treated mice, basal OCR was

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inhibited by oligomycin and stimulated by uncoupler, suggesting reversal of mtDepo after isolation, which Rh123 uptake confirmed. **Conclusion:** After EtOH, mtDepo is restricted to the central half of liver lobules with a sharp midzonal demarcation from the portal half. In sorted hepatocytes without EtOH treatment, OCRs of PP hepatocytes are substantially greater than PC, but both PP and PC OCRs increase after EtOH with PC increasing proportionally more. However, mtDepo in PC hepatocytes after *in vivo* EtOH treatment reverses during isolation. Increased mitochondrial respiratory capacity in all sublobular zones likely promotes adaptive detoxifying EtOH metabolism. These findings document sharp zonal differences in hepatic metabolic responses to EtOH exposure that may help shed light on the progression to alcoholic liver disease.

Disclosures: Matthew Savoca: Nothing to Disclose, Kenji Takemoto: Nothing to Disclose, Zhi Zhong: Nothing to Disclose, John Lemasters: Nothing to Disclose

0243 | THE NOVEL NON-ANTICOAGULANT SYNTHETIC HEPARAN SULFATE 18-MER REDUCES HEPATIC NON-PARENCHYMAL CELL TISSUE FACTOR INDUCTION AND INHIBITS COAGULATION ACTIVATION IN STERILE LIVER INJURY

Amish Patel[1] Katelyn Arnold[2] Gina Capece[1] James Luyendyk[3] Nigel Mackman[2] Jian Liu[2] Lauren Poole[1], [1]Rutgers Robert Wood Johnson Medical School, [2]University of North Carolina at Chapel Hill, [3]Michigan State University

Background: Strong evidence links blood coagulation to the progression of liver disease. Direct anticoagulants could be effective therapies for liver disease, but the safety and efficacy of this strategy remains unclear due to the tenuous hemostatic balance in these patients. An ideal therapy would inhibit pathological coagulation without compromising hemostasis, but the mechanisms triggering coagulation in liver disease are not known. This study tests the hypothesis that the extrinsic coagulation pathway, initiated by binding of the ligand factor VIIa to its receptor tissue factor (TF), activates the coagulation cascade in acute sterile liver injury and tests a novel pharmacologic approach to safely disable this pathway. **Methods:** Mice with whole-body TF deficiency (LowTF) or hepatocyte-selective TF deficiency ($HPC^{\Delta TF}$) and respective littermate controls were challenged with carbon tetrachloride (CCl_4, 1 ml/kg i.p.) or vehicle (corn oil). Plasma and liver tissues were collected after 24 h. In separate studies, wild-type mice were administered a novel non-anticoagulant synthetic heparan sulfate (HS 18-mer, 5 mg/kg, s.c.) or vehicle (saline) 2 h and 8 h after CCl_4. **Results:** CCl_4 challenge caused robust activation of the blood coagulation cascade, measured by plasma thrombin-antithrombin (TAT) complexes, alongside hepatic injury. Coagulation was completely blocked in CCl_4-challenged LowTF mice. Surprisingly, coagulation was not affected in $HPC^{\Delta TF}$ mice, implying that coagulation activation is not directly driven by TF activation in necrotic hepatocytes. Rather, *in situ* hybridization identified that TF (*F3*) gene expression was induced in hepatic non-parenchymal cells (NPCs) in the necrotic region of the CCl_4-challenged liver. TF gene expression can be induced in multiple cell types, e.g., leukocytes, by inflammatory stimuli. Synthetic HS 18-mer, which lacks anti-coagulant activity, has been previously shown to have anti-inflammatory activity in acetaminophen-induced acute liver injury. Interestingly, 18-mer inhibited CCl_4-induced coagulation and reduced TF expression in hepatic NPCs. **Conclusion:** These results indicate that coagulation activation in sterile liver injury is associated with induction of TF in hepatic NPCs. Hepatic NPC TF induction and coagulation activation are both blocked by anti-inflammatory 18-mer. These results point to a novel strategy to block coagulation in acute liver injury through a mechanism fully distinct from controlling hemostasis.

Disclosures: Amish Patel: Nothing to Disclose, Katelyn Arnold: Nothing to Disclose, Gina Capece: Nothing to Disclose, James Luyendyk: Nothing to Disclose, Nigel Mackman: Nothing to Disclose, Jian Liu: Nothing to Disclose, Lauren Poole: Nothing to Disclose

0244 | INTEGRIN $\alpha_4\beta_7$ PROMOTES REPAIR AND REGENERATION IN ACETAMINOPHEN-INDUCED LIVER INJURY BY RECRUITING MONOCYTES AND DRIVING THEIR PRO-REPARATIVE PROGRAMMING

Reben Raeman[1] Ravi Rai[1] PABITRA PAL[1] Daniel Rossmiller[1] Smita Iyer[1] Michael Oertel[1], [1]University of Pittsburgh

Background: Acetaminophen overdose is the leading cause of drug-induced acute liver failure (ALF) worldwide, yet effective therapies remain limited beyond the earliest stages of injury. Monocytes recruited to the liver during the early phase of APAP-induced liver injury (AILI) promote inflammation, but during the reparative phase, they adopt pro-resolving and regenerative states that support injury resolution and regeneration. Despite this recognized functional plasticity, the molecular cues driving monocyte recruitment and their transition from pathogenic to reparative states remain poorly defined. Here, we investigated how the integrin receptor $\alpha_4\beta_7$ and its ligand mucosal addressin cell adhesion

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molecule 1(MAdCAM-1) drive monocyte recruitment to the liver and license their differentiation into reparative monocyte derived macrophages (MoMs). **Methods:** AILI was induced in 10-week-old wild-type (WT) mice by a single intraperitoneal injection of acetaminophen (APAP; 300 mg/kg). Mice were randomized to receive either an isotype IgG control or an $\alpha_4\beta_7$-blocking monoclonal antibody (mAb) 4 hours later. Liver injury, regeneration, and immune responses were assessed using histology, immunohistochemistry, qPCR, flow cytometry, and transcriptomic profiling. **Results:** During the resolution phase, 48 hours post-APAP, $\alpha_4\beta_7^{\circ}$ MoMs were selectively enriched in the liver, while $\alpha_4\beta_7^{\circ}$ T, B, and NK cells declined. A similar pattern was observed in the spleen, where $\alpha_4\beta_7^{\circ}$ monocytes and macrophages increased, but $\alpha_4\beta_7^{\circ}$ neutrophils and lymphocytes remained unchanged. These findings suggest that $\alpha_4\beta_7^{\circ}$ monocytes, but not adaptive lymphocytes, are selectively licensed for hepatic recruitment during AILI resolution. Blockade of $\alpha_4\beta_7$ impaired monocyte recruitment, disrupted hepatic immune landscape, delayed liver regeneration, and led to 40% mortality within 48 hours. Transcriptomic profiling of hepatic MoMs from $\alpha_4\beta_7$-blocked mice showed reduced expression of genes associated with tissue repair and regeneration compared to IgG controls, indicating that $\alpha_4\beta_7$/MAdCAM-1 signaling is required to program MoMs toward a reparative phenotype during the resolution phase of AILI. **Conclusion:** These findings suggest that unlike metabolic and fibrotic liver disease where $\alpha_4\beta_7$/MAdCAM-1 axis promotes inflammation and fibrosis, this axis plays a pro-reparative and pro-regenerative role in AILI. These findings redefine $\alpha_4\beta_7$ as a potential therapeutic target to enhance recovery following AILI.
Disclosures: Reben Raeman: Nothing to Disclose, Ravi Rai: Nothing to Disclose, PABITRA PAL: Nothing to Disclose, Daniel Rossmiller: Nothing to Disclose, Smita Iyer: Nothing to Disclose, Michael Oertel: Nothing to Disclose

0245 | HIGH-DIMENSIONAL CYTOMETRY FOR SINGLE-CELL IMMUNE PROFILING UNCOVERS IMMUNOPATHOLOGICAL MECHANISMS IN IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY (DILI)

M Lucena[1] Daniel Di Zeo-Sánchez[2] Marina Villanueva[3] Irene Díaz Alberola[3] Gonzalo Matilla Cabello[3] Angela Remesal Doblado[3] Antonio Segovia Zafra[3] José María Pinazo Bandera[4] MIREN GARCIA CORTES[4] Francisco Ruiz-Cabello[5] Mercedes Robles-Diaz[6] Raul Andrade[6] Camilla Stephens[6], [1]Universidad de Malaga, [2]IBIMA-plataforma Bionand, UMA, [3]IBIMA-Bionand Platform, [4]UGC Aparato Digestivo, Servicio de Farmacología Clínica, IBIMA, [5]Instituto de Investigación Biosanitaria IBS Granada, [6]Universidad de Málaga

Background: Idiosyncratic drug-induced liver injury (DILI) involves an individual-specific adaptive immune response. However, the exact immunopathogenic mechanisms behind DILI are still not well understood. This study aimed to analyze the systemic immune response associated with DILI using high-dimensional single-cell cytometry, capturing both inflammatory and regulatory dynamics during the acute episode and recovery phase. **Methods:** Peripheral blood samples were collected from 23 DILI patients (recruited from the Spanish DILI Registry) at detection (visit 1) and during recovery (>30 days, visit 2) and from 32 healthy controls (HC). Samples were analyzed using mass cytometry (CyTOF) with a custom-designed 40-marker panel. Unsupervised clustering (FlowSOM, PhenoGraph) and dimensionality reduction (FitSNE, t-SNE-CUDA) identified different immune cell subsets within peripheral blood mononuclear cells (PBMC) and granulocytes. Differential abundance and marker expression were evaluated using Wilcoxon and Kruskal-Wallis tests with BH correction. **Results:** A total of 38 PBMC and 17 granulocyte metaclusters were identified. At DILI detection, patients exhibited increased frequencies of CD8° effector memory T cells (HLA-DR$^{\circ}$ CD38°), Th1/Th17-polarized CD4° cells, activated $\gamma\delta$ T cells, and MAIT cells compared to HC. Simultaneously, elevated expression of CD25, CD38, and TIGIT in Tregs, NK, and dendritic cells reflected a concurrent regulatory and exhaustion signature. Markers of immune migration to the liver, including gut-lymphocyte homing, were increased ($\alpha4\beta7$, CCR6, CXCR3). During recovery, most inflammatory features partially normalized, including CD38 expression in cytotoxic and non-conventional T cell subsets, such as $\gamma\delta$ and MAIT cells. However, regulatory signatures such as TIGIT$^{\circ}$ Tregs and pDC activation persisted or increased. **Conclusion:** DILI exhibits a distinct immunophenotypic profile characterized by concurrent activation of cytotoxic and unconventional T cell subsets, along with early regulatory responses. A robust inflammatory response marks the early phase of DILI and diminishes during recovery, while regulatory and exhaustion signatures remain elevated. These findings enhance the understanding of the immune-mediated mechanisms of DILI, highlighting immunophenotyping as a valuable tool for monitoring disease progression. Funding: CIBERehd-ISCIII, FEDER, PI19/00883, PI21/01248, PID2022-140169OB-C21, PI24/0125.

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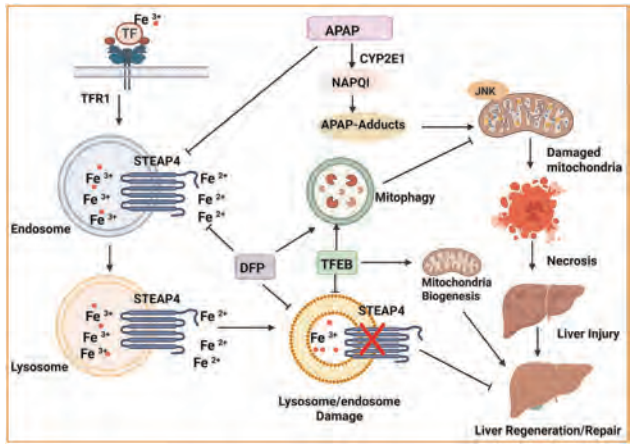
0246 | LACK OF HEPATIC STEAP4 IMPAIRS LIVER REGENERATION DUE TO INCREASED LYSOSOMAL IRON ACCUMULATION AND DYSFUNCTION IN ACETAMINOPHEN-INDUCED LIVER INJURY IN MICE

Peng Cao[1] Mengwei Niu[2] Hong-Min Ni[3,] [1]University of Kansas Medical center, KS, USA, and Tongji Medical College, China, [2]University of Kansas Medical Center, [3]The University of Kansas Medical Center

Background: Understanding the mechanisms behind liver repair in acetaminophen (APAP)-induced liver injury (AILI) is crucial for developing therapeutic approaches. Six-transmembrane epithelial antigen of the prostate 4 (STEAP4) is a metalloreductase involved in iron homeostasis. It is not yet known how APAP affects hepatic STEAP4 and endolysosomal iron homeostasis in regulating liver regeneration during AILI. **Methods:** Wild-type (Alb Cre- STEAP4flox/flox) and liver-specific STEAP4 knockout (Alb Cre+ STEAP4flox/flox, KO) mice were administered APAP for various durations. In some experiments, deferiprone (DFP), an iron chelator, was given either with or after APAP administration. Biochemical and histological analyses were conducted to evaluate serum, hepatic, and endolysosomal iron homeostasis, as well as liver injury and regeneration. **Results:** The expression of *STEAP4* decreased in human AILI livers. APAP treatment reduced hepatic STEAP4 expression in a time-dependent manner in mouse livers. Liver-specific STEAP4 KO mice exhibited similar hepatic necrosis and serum ALT levels during the early phase of liver injury (6–24 hours) but displayed delayed liver recovery and regeneration at 48 hours post-APAP treatment compared to APAP-treated wild-type mice. Confocal microscopy analysis indicated that STEAP4 is primarily localized on the endolysosomal membrane in hepatocytes. The loss of STEAP4 led to the accumulation of iron in endolysosomal compartments, disrupting lysosomal membrane integrity and causing the release of cathepsin B following APAP treatment. This endolysosome disruption coincided with decreased hepatic mTOR activity, mitophagy and hepatocyte proliferation 48 hours after APAP treatment. Post-treatment with the iron chelator DFP corrected mitochondrial and lysosomal dysfunction, thereby protecting against AILI. Moreover, overexpression of STEAP4 or TFEB (a master transcription factor of lysosomal biogenesis) restored lysosomal membrane integrity and promoted liver regeneration and repair in liver-specific STEAP4 KO mice. **Conclusion:** STEAP4 is not essential during the early injury phase but is crucial for liver regeneration by maintaining lysosomal iron homeostasis and lysosomal functions following APAP overdose. Targeting STEAP4 or addressing endolysosomal iron overload may offer therapeutic benefits that extend beyond the limited window of N-acetylcysteine efficacy in AILI.



Disclosures: Peng Cao: Nothing to Disclose, Mengwei Niu: Nothing to Disclose, Hong-Min Ni: Nothing to Disclose

0247 | REFERRALS TO TERTIARY CANCER CENTER SHOW SIGNIFICANT DIAGNOSTIC DISCREPANCIES IN HEPATOCELLULAR CARCINOMA DIAGNOSIS BY LI-RADS CRITERIA IN PATIENTS WITH CIRRHOSIS

Gabriel Lupu[1] Parsa Pazooki[2] Lauren Burke[1] A. Sidney Barritt[1] Sasha Deutsch-Link[3] Oren Fix[1] Neil Shah[1] Hersh Shroff[3] Andrew Moon[4], [1]University of North Carolina at Chapel Hill, [2]University of North Carolina at Chapel Hill School of Medicine, [3]UNC Chapel Hill, [4]University of North Carolina

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Background: The diagnosis of hepatocellular carcinoma (HCC) relies primarily on CT or MRI imaging using the LI-RADS classification system, introduced in 2011 and included in AASLD guidelines in 2018. The Organ Procurement and Transplantation Network (OPTN) and AASLD recommend that imaging be reviewed by a multidisciplinary tumor board and interpreted by an expert radiologist at a transplant center. With evolving liver disease etiologies and growing LI-RADS use, this study aimed to identify discrepancies in LI-RADS application between external imaging and expert reinterpretation of suspicious liver nodules. **Methods:** We performed a single-center, retrospective cohort study of adults with cirrhosis referred to an HCC clinic for liver nodules (9/30/2016–12/6/2024). Primary outcomes included the presence of LI-RADS classification and the number of LR-4/5 nodules on external reports versus transplant center reinterpretation. We collected data on demographics, liver disease etiology and severity, HCC staging, and transplant evaluation. We performed a descriptive summary of LI-RADS use and baseline patient characteristics. Wilcoxon signed-rank test was used to assess patient-level changes in LR-4/5 nodule counts. **Results:** We identified 89 patients; 76 had abdominal CT/MRI imaging and cirrhosis. Of these, 27.6% of patients were female, 35.5% lived rurally, and the most common liver disease was MASLD (40.8%; Table 1). LI-RADS was fully reported in 61.8% of external reports. Among nodules lacking LI-RADS classification on referral, 85.7% were found to be LR-4/5 on reinterpretation. Of the 62 LR-4/5 nodules present on referral, 55 retained LR-4/5 classification on reinterpretation. 26 (37.7%) patients had an increased LR-4/5 count, 6 (8.7%) had a decreased count, and 37 (53.6%) remained unchanged ($P < 0.001$). 29 (38.1%) patients were newly classified as having an LR-5 lesion. Among 15 patients eligible for United Network for Organ Sharing (UNOS) downstaging on reinterpretation, 8 had absent or incomplete LI-RADS on external imaging. **Conclusion:** LI-RADS was correctly reported in only 61.8% of external reports compared to transplant center reinterpretation. This reinforces OPTN/AASLD recommendations for expert imaging review and underscores the risk of missed referral opportunities for HCC treatment and transplantation. Accurate LI-RADS use in external imaging can improve referrals, expedite patient care, and increase access to liver transplantation and locoregional therapies.

Table 1. Baseline characteristics of patients with cirrhosis referred to a multidisciplinary HCC clinic stratified by presence or absence of LI-RADS classification on referral imaging

	LI-RADS Present on Referral Imaging	
	No	Yes
N = 76 (Patients)	29 (38.2%)	47 (61.8%)
Age (SD)	69.83 (7.81)	66.23 (9.52)
Urban/Rural		
Urban	17 (58.6%)	32 (68.1%)
Rural	12 (41.4%)	15 (31.9%)
Sex		
Male	23 (79.3%)	32 (68.1%)
Female	6 (20.7%)	15 (31.9%)
Liver Disease Etiology		
Viremic HCV	4 (13.8%)	4 (8.5%)
HCV post SVR	8 (27.6%)	5 (10.6%)
HBV-Related	0 (0.0%)	1 (2.1%)
Alcohol-Associated	4 (13.8%)	15 (31.9%)
MASLD	12 (41.4%)	19 (40.4%)
Other*	1 (3.4%)	3 (6.4%)
Referral Setting		
External GI or Other Subspecialty	28 (96.6%)	40 (85.1%)
Primary Care or Urgent Care	1 (3.4%)	5 (10.6%)
Emergency Room or Admission	0 (0.0%)	2 (4.3%)
Referral Imaging Type		
CT Abdomen	6 (20.7%)	1 (2.1%)
MRI Abdomen	23 (79.3%)	46 (97.9%)
UNOS Downstaging Criteria Met		
No	21 (72.4%)	40 (85.1%)
Yes	8 (27.6%)	7 (14.9%)
Transplant Evaluation		
No	25 (86.2%)	35 (74.5%)
Yes	4 (13.8%)	12 (25.5%)
Total Nodules on Referral**	35 (30%)	88 (70%)
LR-4/5 Nodules on Referral	0 (0%)	62 (70.5%)
LR-4/5 Nodules on Reinterpretation	30 (85.7%)	55 (62.5%)

* Other liver disease etiologies included autoimmune hepatitis, 1; hereditary hemochromatosis, 2; unknown, 1
**4 patients had innumerable nodules and were unable to be discretely quantified
Body Mass Index (BMI); Hepatitis C Virus (HCV); Sustained Virologic Response (SVR); Hepatitis B Virus (HBV); Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD); Model for End Stage Liver Disease (MELD); Alpha-fetoprotein (AFP); United Network for Organ Sharing (UNOS)

Disclosures: Gabriel Lupu: Nothing to Disclose, Parsa Pazooki: Nothing to Disclose, Lauren Burke: Nothing to Disclose, A. Sidney Barritt: Nothing to Disclose, Sasha Deutsch-Link: Nothing to Disclose, Oren Fix: Nothing to Disclose, Neil Shah: GSK: Advisor, Ipsen: Advisor, GSK: Consultant, Ipsen: Consultant, Hersh Shroff: Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant

0248 | ADVANCING HCC HISTOLOGICAL DIFFERENTIATION GRADING THROUGH MULTIPLE INSTANCE LEARNING ON DIGITIZED WHOLE SLIDE IMAGE

Yan Miao[1] Philip Yu[2] Tak-Siu Wong[3] Regina Lo[1] Ho-Ming Cheng[1] Lequan Yu[1] Lung Yi (Loey) MAK[1] Man-Fung Yuen[1] Wai-Kay Seto[1], [1]The University of Hong Kong, [2]The Education University of Hong Kong, [3]Pamela Youde Nethersole Eastern Hospital

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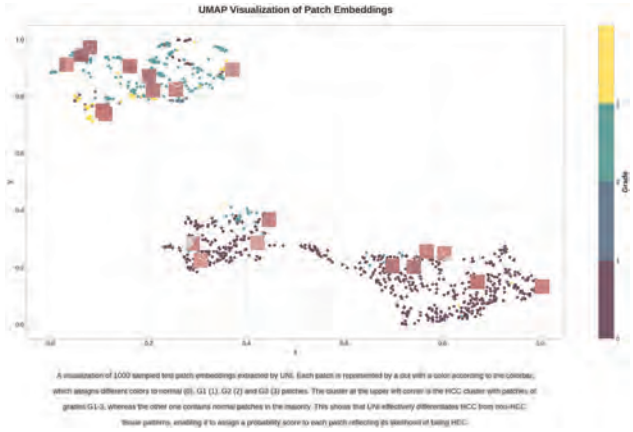
Background: Hepatocellular carcinoma (HCC), a leading cause of cancer-related mortality, necessitates precise interpretation of histological differentiation to guide clinical management. While artificial intelligence (AI) has shown promise in computational pathology, systematic comparisons of AI frameworks for HCC grading remain underexplored. This study evaluates multiple instance learning (MIL) strategies for aggregating patch-level features from whole slide images (WSIs) to optimize slide-level tumor grading. **Methods:** WSIs from 54 surgically resected HCC patients (n = 392 slides: 139 normal, 253 tumors [G1/well-differentiated = 9, G2/moderately-differentiated = 185, G3/poorly-differentiated = 59]) were annotated by pathologists per AJCC 8th edition criteria. Tumor differentiation was reported by a board-certified liver histopathologist with more than 10 years of experience. WSIs were segmented into 1024×1024-pixel patches, labeled by tumor differentiation if containing tumor tissue. A pretrained UNI foundation model (a large vision transformer) was fine-tuned as a patch feature extractor. Three aggregation models were compared: 1) Logistic Regression (traditional machine learning model, probability-based), 2) Attention-based MIL (the fundamental building block for most of the latest AI models), and 3) Transformer-based MIL (state-of-the-art model). The dataset was split into training (70%), validation (15%), and test (15%) sets. **Results:** UMAP visualization of UNI embeddings revealed distinct clustering between sampled normal (class 0) and tumor (grades G1–3) test patches. At the slide level, Logistic Regression achieved an AUC of 0.808 (0.660-0.920), a sensitivity of 0.600 (0.452-0.806), a specificity of 0.907 (0.852-0.950), a PPV of 0.658 (0.423-0.910), and an NPV of 0.922 (0.871-0.961). The attention MIL achieved an AUC of 0.886 (0.705-0.994), a sensitivity of 0.850 (0.725-0.951), a specificity of 0.939 (0.887-0.977), a PPV of 0.864 (0.741-0.959), and an NPV of 0.941 (0.892-0.979). The transformer MIL achieved an AUC of 0.888 (0.706-0.998), a sensitivity of 0.892 (0.784-0.976), a specificity of 0.957 (0.913-0.988), a PPV of 0.891 (0.780-0.974), and an NPV of 0.957 (0.915-0.987). All metrics were macro-averaged across multiclass predictions. The transformer's capacity to process long patch sequences enhanced diagnostic accuracy, while MIL frameworks surpassed traditional probability aggregation. **Conclusion:** Integrating MIL with pretrained foundation models significantly improves slide-level HCC differentiation grading by effectively leveraging histological patterns across WSIs. The transformer's contextual reasoning underscores its potential for complex computational pathology tasks.



Disclosures: Yan Miao: Nothing to Disclose, Philip Yu: Nothing to Disclose, Tak-Siu Wong: Nothing to Disclose, Regina Lo: Nothing to Disclose, Ho-Ming Cheng: Nothing to Disclose, Lequan Yu: Nothing to Disclose, Lung Yi (Loey) MAK: Nothing to Disclose, Man-Fung Yuen: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose

0249 | APPLYING THE LI-RADS ULTRASOUND SURVEILLANCE PROTOCOL FOR HCC: EFFECTS ON DOWNSTREAM IMAGING UTILIZATION

Christopher Hernandez[1] Kexin Dong[2] Julian McDonald[1] Ali Siddiqui[1] Patrick Sullivan[1] Marcel Yibirin Wakim[1] Yamini Adusumelli[2] Soobin Song[2] Christina LeBedis[1] Arpan Mohanty[1], [1]Boston Medical Center, [2]Boston University School of Medicine

Background: The Liver Imaging Reporting and Data System (LI-RADS) Ultrasound (US) Surveillance protocol provides standardized terminology, technique, interpretation, and reporting for hepatocellular carcinoma (HCC) surveillance in at-risk patients. Despite its structured approach, it is not widely adopted in clinical practice. A key feature is the US category (US-1: negative, US-2: subthreshold, US-3: positive), which guides follow-up imaging recommendations. US-2 exams warrant repeat ultrasound in 3 to 6 months, while US-3 findings prompt further diagnostic imaging. However, the impact of implementing the LI-RADS US surveillance protocol on subsequent imaging utilization patterns remains understudied. **Methods:** In this retrospective study, we assessed how follow-up imaging patterns might differ if LI-RADS US surveillance had been applied. We reviewed 3,159 consecutive outpatient ultrasounds performed for

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HCC surveillance between January 1, 2020, and December 21, 2022, at an urban academic safety-net hospital where LI-RADS US surveillance protocol was not utilized in routine reporting. Exams not conducted for HCC surveillance or performed in patients without cirrhosis or hepatitis B were excluded. All ultrasounds were retrospectively assigned LI-RADS US categories and visualization scores. Clinical characteristics and follow-up imaging data were abstracted from medical records. **Results:** During the study period, 1,634 patients (mean age 55 years; 62% male) underwent between one and six ultrasounds for HCC surveillance. The indication for screening was cirrhosis in 1,664 (53%) exams and hepatitis B in 1,495 (47%). Visualization scores were A (no limitations) in 2,933 (92.8%) studies, B (moderate limitations) in 209 (6.6%), and C (severe limitations) in 17 (0.5%). Among the 3,142 studies with visualization scores of A or B, 3,011 (96%) were classified as US-1, 49 (1.6%) as US-2, and 82 (2.6%) as US-3. Follow-up cross-sectional imaging was ordered in 2/3,011 (0.07%) of US-1 studies (both completed), 39/49 (79.6%) of US-2 studies (completed in 32/39), and 73/82 (89.0%) of US-3 studies (completed in 64/73). HCC was diagnosed in 1 patient in the US-1 group, none in the US-2 group, and 14 in the US-3 group. The US-1 patient had an elevated AFP, which would have triggered cross-sectional imaging independent of LI-RADS classification. **Conclusion:** Adoption of the LI-RADS Ultrasound Surveillance protocol may reduce non-indicated imaging, particularly among studies categorized as US-2.

Disclosures: Christopher Hernandez: Nothing to Disclose, Kexin Dong: Nothing to Disclose, Julian McDonald: Nothing to Disclose, Ali Siddiqui: Nothing to Disclose, Patrick Sullivan: Nothing to Disclose, Marcel Yibirin Wakim: Nothing to Disclose, Yamini Adusumelli: Nothing to Disclose, Soobin Song: Nothing to Disclose, Christina LeBedis: Nothing to Disclose, Nothing to Disclose, Arpan Mohanty: Nothing to Disclose

0250 | LIVER STIFFNESS AND CANCER RISK STRATIFICATION USING MR ELASTOGRAPHY

Shohei Kimura[1] Nobuharu Tamaki[1] Takuya Shima[1] Mina Taguchi[1] Yudai Yamazaki[1] Naoki Uchihara[1] Risa Seike[1] Yuki Tanaka[1] Junko Yagita[1] Ryohei Kobayashi[1] Yuka Kasano[1] Yasuyuki Komiyama[1] Kenta Takaura[1] Shohei Tanaka[1] Hitomi Takada[1] Chiaki Maeyashiki[1] Yutaka Yasui[1] Hiroyuki Nakanishi[1] KAORU TSUCHIYA[1] Namiki Izumi[1] Masayuki Kurosaki[1],
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Background: Magnetic resonance elastography (MRE) enables non-invasive assessment of liver stiffness and provides high diagnostic accuracy for liver fibrosis. However, the association between MRE-derived liver stiffness and the development of hepatocellular carcinoma (HCC) remains unclear. This study aimed to evaluate the association between liver stiffness measured by MRE and the risk of HCC development. **Methods:** We retrospectively analyzed 2,037 patients who underwent MRE between April 2015 and August 2024. Patients were regularly screened for HCC every 3–6 months using ultrasound or contrast-enhanced CT/MRI. HCC was diagnosed based on characteristic imaging findings or histology. Laboratory data within 30 days of each MRE were reviewed. **Results:** The median age was 66 years, and 46.2% were male. The median liver stiffness was 3.40 kPa; 956 patients (46.9%) had values $\geq$3.62 kPa, indicative of advanced fibrosis ($\geq$F3). During a median follow-up of 2.8 years, the overall cumulative incidences of HCC were 1.8% at 1 year and 5.3% at 3 years. The 3-year cumulative incidence of HCC was significantly higher in patients with liver stiffness $\geq$3.62 kPa than in those with lower values (8.3% vs. 2.3%, $p < 0.001$). Multivariate analysis identified age (HR: 1.06, 95% CI: 1.04–1.08, $p < 0.001$), male sex (HR: 2.69, 95% CI: 1.53–3.26, $p < 0.001$), liver stiffness by MRE (HR: 1.23 per 1kPa, 95% CI: 1.16–1.30, $p < 0.001$), platelet count (HR: 0.998 per 10^4/μL, 95% CI: 0.99–1.00, $p < 0.001$), and hypertension (HR: 1.54, 95% CI: 1.06–2.24, $p = 0.02$) as independent predictors of HCC development. **Conclusion:** Liver stiffness measured by MRE is independently associated with the development of HCC. MRE-based risk stratification may be useful for optimizing HCC surveillance strategies in patients with chronic liver disease.

Disclosures: Shohei Kimura: Nothing to Disclose, Nobuharu Tamaki: Nothing to Disclose, Takuya Shima: Nothing to Disclose, Mina Taguchi: Nothing to Disclose, Yudai Yamazaki: Nothing to Disclose, Naoki Uchihara: Nothing to Disclose, Risa Seike: Nothing to Disclose, Yuki Tanaka: Nothing to Disclose, Junko Yagita: Nothing to Disclose, Ryohei Kobayashi: Nothing to Disclose, Yuka Kasano: Nothing to Disclose, Yasuyuki Komiyama: Nothing to Disclose, Kenta Takaura: Nothing to Disclose, Shohei Tanaka: Nothing to Disclose, Hitomi Takada: Nothing to Disclose, Chiaki Maeyashiki: Nothing to Disclose, Yutaka Yasui: Nothing to Disclose, Hiroyuki Nakanishi: Nothing to Disclose, KAORU TSUCHIYA: Chugai: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Eisai: Speaking and Teaching, Takeda: Speaking and

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Teaching, Namiki Izumi: Nothing to Disclose, Masayuki Kurosaki: Nothing to Disclose

0251 | CLINICAL SIGNIFICANCE OF PREOPERATIVE MRI FEATURES IN PREDICTING PROGNOSIS FOR HEPATOCELLULAR CARCINOMA TREATED WITH TACE COMBINED WITH TARGETED THERAPY AND IMMUNOTHERAPY

Xue-Gang Lu[1] Zhi-Cheng Jin[1] Fang Nie[1] Gao-Jun Teng[1], [1]Southeast University

Background: This study investigates the predictive value of preoperative MRI mosaic patterns in patients with HCC for OS following TACE combined with targeted immunotherapy. By integrating imaging features based on LI-RADS and definitions from previous literature, the study aims to identify imaging biomarkers with independent prognostic significance and validate their application value in clinical prognosis evaluation. **Methods:** A retrospective cohort of 444 HCC patients treated with TACE and targeted immunotherapy between January 2018 and December 2022 was analyzed. Enhanced three-phase MRI sequences, focusing on mosaic architecture in T2WI and arterial phase sequences, were used to assess imaging features. Univariate and multivariate Cox regression identified independent prognostic factors, and PSM balanced baseline differences. Kaplan-Meier survival curves and Log-rank tests compared survival differences before and after matching. Subgroup and sensitivity analyses were conducted to assess the robustness of results. **Results:** Univariate Cox regression identified 22 variables significantly associated with OS, with T2WI signal heterogeneity being notable (HR = 2.01, 95% CI: 1.40–2.87, $P < 0.001$). Multivariate analysis confirmed T2WI signal heterogeneity as an independent risk factor (HR = 1.84, 95% CI: 1.09–3.09, $P = 0.021$). Propensity score matching (1:1, caliper 0.05) balanced baseline characteristics and showed significant OS differences between heterogeneous and homogeneous T2WI signal groups ($P = 0.004$). Post-matching univariate Cox analysis confirmed T2WI heterogeneity as a significant OS predictor (HR = 1.90, 95% CI: 1.22–2.95, $P = 0.004$). Subgroup analyses revealed its prognostic value in males ($P = 0.012$), patients aged ≤60 years ($P = 0.009$), BCLC stage A/B ($P = 0.004$), hepatitis B ($P = 0.026$), cirrhosis ($P < 0.001$), and portal hypertension ($P = 0.006$). Sensitivity analysis confirmed stability of the results ($P < 0.05$). **Conclusion:** T2WI signal homogeneity has been identified as an independent prognostic factor for OS in patients with HCC undergoing TACE combined with systemic therapy. Heterogeneous T2WI signals are associated with poorer prognosis, highlighting their potential value as imaging biomarkers to support personalized treatment planning. Further exploration of the prognostic implications of mosaic patterns across different imaging phases may provide additional insights into their clinical utility.

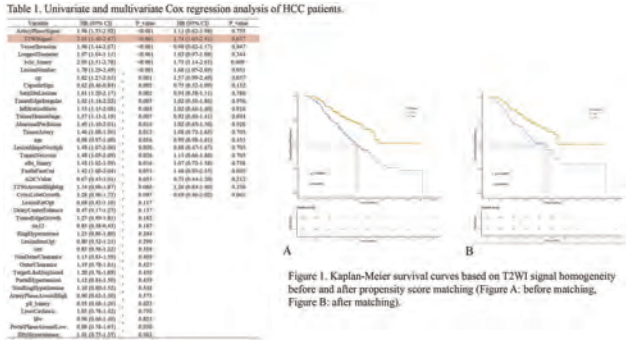
Table 1. Univariate and multivariate Cox regression analysis of HCC patients.

Figure 1. Kaplan-Meier survival curves based on T2WI signal homogeneity before and after propensity score matching (Figure A: before matching, Figure B: after matching).

Disclosures: Xue-Gang Lu: Nothing to Disclose, Zhi-Cheng Jin: Nothing to Disclose, Fang Nie: Nothing to Disclose, Gao-Jun Teng: Nothing to Disclose

0252 | ENHANCING HEPATOCELLULAR CARCINOMA SURVEILLANCE: COMPARATIVE EVALUATION OF AFP, AFP-L3, DCP, AND COMPOSITE SCORING MODELS IN A BIOBANK-BASED CASE-CONTROL STUDY

Coskun Demirtas[1] Sehnaz Akin[2] Demet Yilmaz Karadag[1] Tuba Yilmaz[3] Ugur Ciftci[3] Cavid Huseyinov[3] Tugba Tolu[3] Yasemin Kaldirim Armutcuoglu[3] Osman Cavit Ozdogan[3] Fatih Eren[1], [1]Marmara University School of Medicine, Institute of Gastroenterology, [2]Marmara University School of Medicine, Department of Internal Medicine, [3]Marmara University School of Medicine, Division of Gastroenterology and Hepatology

Background: Early detection of hepatocellular carcinoma (HCC) is critical but restricted by limiations in current surveillance tools. Biomarkers such as AFP-L3 and DCP, as well as biomarker and/or clinical parameter derived composite models (GALAD, GAAP, ASAP, aMAP, Doylestown), may improve detection in addition to AFP, yet comparative data across diverse populations remain limited. **Methods:** In this biobank-based case-control study, we evaluated 442 adults (165 HCC, 277 chronic liver disease [CLD] controls) from January 2019 to 2024. Serum AFP, AFP-L3, and

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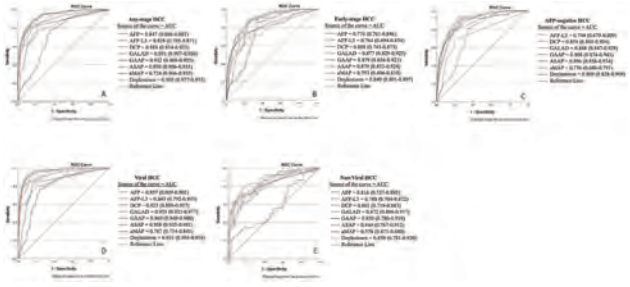
DCP levels were measured using the μTASWako i30 system. Scoring models were calculated using validated formulas. Diagnostic performance for any-stage and early-stage HCC was assessed across three thresholds: Youden-index derived optimal cut-offs, literature-established cut-offs, and cut-offs ensuring 90% specificity. ROC analysis was performed. Subgroup analyses were stratified by etiology and AFP status. **Results:** DCP was the most sensitive individual biomarker at optimal (85.5%) and 90% specificity (74.6%) cut-offs, while AFP-L3 was the most sensitive individual biomarker (61.2%) at the established cut-off. At optimal cut-offs, GALAD showed the highest sensitivity for any-stage (90.3%) and early-stage (89.1%) HCC, with 70-80% specificity. Using established cut-offs, GALAD retained the highest sensitivity for any-stage (75.8%) and early-stage (57.8%) with 93.5% specificity. At 90% specificity, GALAD exhibited the highest sensitivity for any-stage (81.2%) and early-stage (68.8%), followed by ASAP (80.0% and 66.7%, respectively). In ROC analysis, GALAD, ASAP, and GAAP achieved the highest similar AUCs for any-stage (0.931–0.932), early-stage (0.877–0.879), while GAAP showed a slightly higher AUC in AFP-negative HCCs (0.908). GALAD demonstrated the best performance in non-viral HCCs (AUC 0.872), whereas GAAP and ASAP showed similarly high AUC values in viral etiology (AUC 0.955-960). **Conclusion:** In our study, GALAD, ASAP, and GAAP significantly outperformed individual biomarkers for detecting HCC across all disease stages, AFP profiles and etiology status. GALAD offered the most consistent diagnostic accuracy across different cut-off strategies, particularly in non-viral and early-stage HCCs. These findings support the integration of composite biomarker models into tailored HCC surveillance strategies, especially in diverse global populations.



Disclosures: Coskun Demirtas: Nothing to Disclose, Sehnaz Akin: Nothing to Disclose, Demet Yilmaz Karadag: Nothing to Disclose, Tuba Yilmaz: Nothing to Disclose, Ugur Ciftci: Nothing to Disclose, Cavid Huseyinov: Nothing to Disclose, Tugba Tolu: Nothing to Disclose, Yasemin Kaldirim Armutcuoglu: Nothing to Disclose, Osman Cavit Ozdogan: Nothing to Disclose, Fatih Eren: Nothing to Disclose

★ 0253 | ABSTRACT WITHDRAWN

0254 | IMPACT OF HEPATIC STEATOSIS AND METABOLIC DYSFUNCTION ON DISEASE SEVERITY AND TREATMENT OUTCOMES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Ajay Duseja[1] Muhammad Uwais Ashraf[2] Priya Singh[2] Sweta Rose[2] Suvradeep Mitra[2] Arka De[2] Nipun Verma[2] Madhumita Premkumar[1] SUNIL TANEJA[2] Harish Bhujade[2] Naveen Kalra[2], [1]Postgraduate Institute of Medical Education & Research, [2]Postgraduate Institute of Medical Education and Research, Chandigarh, India

Background: Severity and response in hepatocellular carcinoma (HCC) are dependent on various risk factors. This study aimed to assess the influence of hepatic steatosis and metabolic dysfunction on HCC severity and treatment response to locoregional therapy (LRT). **Methods:** In this prospective cohort study, 209 HCC patients (July 2023-December 2024), comprehensive assessment of hepatic steatosis was performed using magnetic resonance proton density fat fraction (MR-PDFF), controlled attenuation parameter (CAP), and liver biopsy (where feasible). Cardiometabolic risk factors (CMRF) were evaluated and treatment responses was assessed using LI-RADS and mRECIST criteria. **Results:** Patients were predominantly male (86.6%) with a mean age of 59.9 ± 10.4 years. Alcohol related liver disease was

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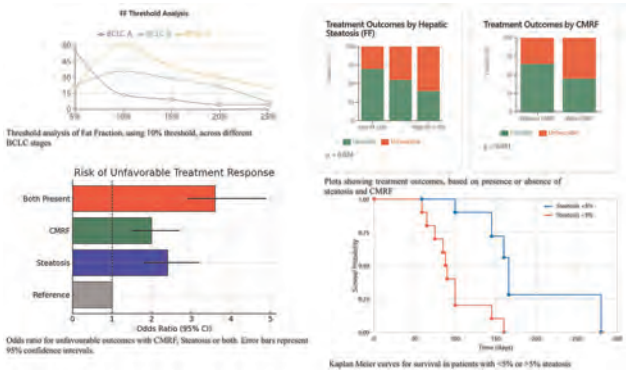
the predominant etiology (32.2%), followed by metabolic dysfunction-associated steatotic liver disease (MASLD, 22.6%). CMRF prevalence was strikingly high (51.6%), with diabetes (42%), obesity (40%) and hypertension (33%) being the most common. Hepatic steatosis was present in 41.15% of all HCC patients, significantly higher than the general population prevalence ($p = 0.0378$). Using a 10% fat fraction threshold, a significant correlation between steatosis and advanced BCLC stages was observed ($p < 0.001$), with high fat fraction ($\geq 10\%$) being present in 13.6% of BCLC A, 35.7% of BCLC B, and 60.0% of BCLC C cases. Among patients undergoing locoregional therapy ($n = 58$), those with CMRF showed significantly less favorable response rates (45% vs. 65%, $p = 0.031$). In multivariate analysis, fat fraction remained an independent predictor of poor treatment response (aOR 1.06, 95% CI: 1.00-1.12, $p = 0.048$). The novel CRAFPIT score, incorporating CRP, AFP, fat fraction, PIVKA-II, insulin, and tumor size, demonstrated excellent predictive accuracy for treatment response (AUC 0.92). **Conclusion:** Hepatic steatosis and metabolic dysfunction significantly influence HCC severity and treatment outcomes across etiologies with higher risk for advanced disease at presentation and poorer treatment response. The CRAFPIT score offers potential for improved risk stratification and treatment planning.



Disclosures: Ajay Duseja: Nothing to Disclose, Muhammad Uwais Ashraf: Nothing to Disclose, Priya Singh: Nothing to Disclose, Sweta Rose: Nothing to Disclose, Suvradeep Mitra: Nothing to Disclose, Arka De: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, SUNIL TANEJA: Nothing to Disclose, Harish Bhujade: Nothing to Disclose, Naveen Kalra: Nothing to Disclose

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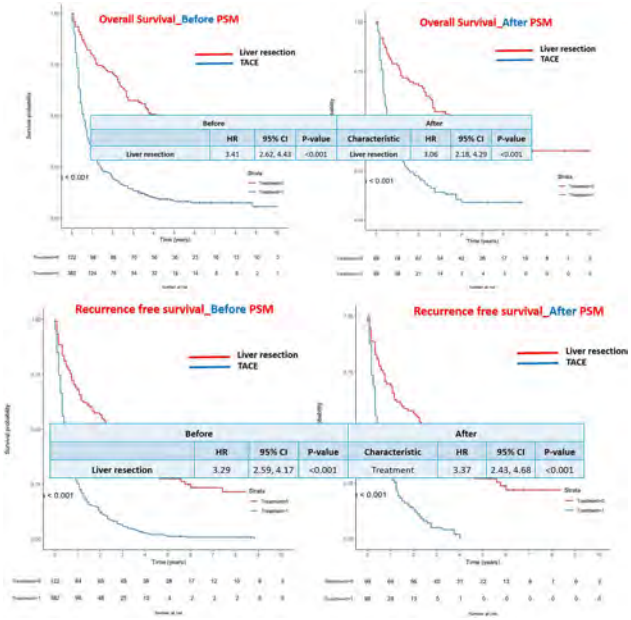
0256 | LIVER RESECTION VERSUS TRANS-ARTERIAL CHEMOEMBOLIZATION FOR HUGE HEPATOCELLULAR CARCINOMA (>10CM): A NATIONWIDE PROPENSITY SCORE ADJUSTED ANALYSIS

Jai Young Cho[1] Boram Lee[1] Hae Won Lee[1], [1]Seoul National University Bundang Hospital

Background: The treatment of hepatocellular carcinoma (HCC) > 10 cm remains controversial. The ongoing debate regarding the treatment of patients with HCC > 10 cm is partly due to the necessity of tailoring treatment to individual patient conditions. This study aims to address the important controversy regarding the management of large HCC, focusing on providing insights into the comparative effectiveness of liver resection (LR) and Transarterial Chemoembolization (TACE). **Methods:** Patients registered in the Korean Primary Liver Cancer Registry (KPLCR) were selected. The KPLCR is a random sample consisting of approximately 15% of patients newly diagnosed with primary liver cancer registered in the Korean Central Cancer Registry (KCCR), which is a nationwide cancer registry and includes more than 95% of all cancer cases in Korea. The study design utilizes data from the KPLCR covering the years 2008 to 2017 to investigate the treatment outcomes for HCC larger than 10 cm. Starting with 15,307 cases, the study identified 9,310 HCC patients with follow-up data, excluding those with missing initial treatment data (n = 5,863) and follow-up loss (n = 132). From these, 7,662 patients with single HCC were selected, further excluding cases with multiple HCC (n = 1,394) and distant metastasis (n = 254). This refined the cohort to 504 patients with HCC tumors larger than 10 cm, who were then divided into two treatment groups: 122 patients underwent liver resection (LR), and 382 patients received TACE. **Results:** After PSM, the baseline characteristics showed no significant differences between the LR group (n = 99) and the TACE group (n = 99). Before propensity score matching (PSM), the hazard ratio (HR) for LR was 3.41 (95% CI: 2.62-4.43, $p < 0.001$), indicating a significantly better survival probability for the LR group compared to the TACE group. After PSM, the HR for LR was slightly reduced to 3.06 (95% CI: 2.18-4.29, $p < 0.001$), but the survival advantage of LR over TACE remained highly significant. Before PSM, the HR for LR was 3.29 (95% CI: 2.59-4.17, $p < 0.001$), indicating a markedly better recurrence-free survival (RFS) for the LR group compared to the TACE group. After PSM, the HR for LR increased slightly to 3.37 (95% CI: 2.43-4.68, $p < 0.001$), maintaining the significant survival advantage of LR over TACE. **Conclusion:** This study provides a comprehensive analysis of treatment outcomes for HCC > 10 cm, comparing LR and TACE using data from the KPLCR. The results indicate that LR is associated with significantly better OS and RFS compared to TACE, both before and after PSM.



Disclosures: Jai Young Cho: Nothing to Disclose, Boram Lee: Nothing to Disclose, Hae Won Lee: Nothing to Disclose

0257 | LIVING DONOR LIVER TRANSPLANTATION REMAINS UNDERUTILIZED FOR CHOLANGIOCARCINOMA DESPITE COMPARABLE SURVIVAL

Farinaz Ghodrati[1] Samir Abu-Gazala[1] Nadim Mahmud[1], [1]Hospital of the University of Pennsylvania

Background: Cholangiocarcinoma (CCA) is an aggressive disease with a 5-year overall survival of less than 10%. While liver transplantation offers curative potential for select patients with CCA, it remains an uncommon and understudied indication. Limited data exist on national trends in liver transplantation for CCA and on whether post-transplant outcomes differ between deceased donor and living donor grafts. Clarifying these differences may help guide clinical decision-making and expand access to transplant options in appropriately selected patients. **Methods:** This was a retrospective cohort study using data from the United Network for Organ Sharing from 2002 to 2022. Adult patients who were waitlisted with known CCA were identified. Candidate and transplantation data were ascertained,

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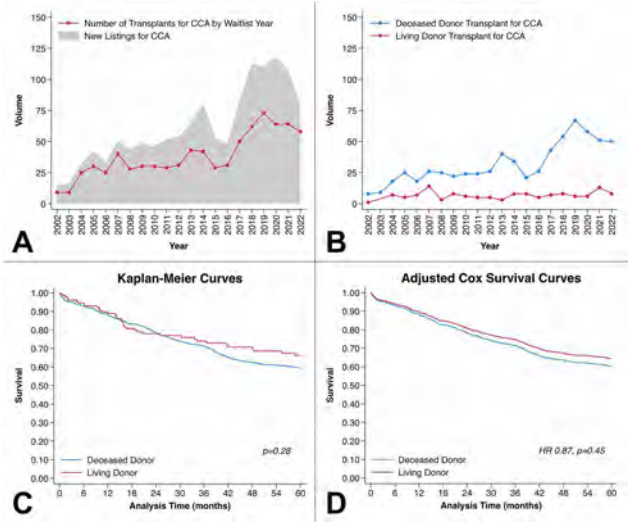
including receipt of deceased donor liver transplant (DDLT) or living donor liver transplant (LDLT). Linear regression was used to evaluate trends in CCA listings and transplants were evaluated over time, which were further stratified by donor type. Among patients who received transplant, survival analysis was then performed to evaluate the association between donor type and post-transplant mortality through 5 years. Unadjusted Kaplan-Meier and multivariable Cox regression analyses (adjusted for age, sex, race/ethnicity, and BMI, MELD, ascites, and encephalopathy at transplant) were performed. **Results:** A total 1,291 waitlisted patients were included; the cohort had median age 54 years, 68.6% male, 87.7% white, with median MELD-Na at listing of 8. Over time there were significant increases in new listings for CCA (beta 4.39, 95% CI 3.29-5.50, $p < 0.001$) and absolute number of transplants for CCA (beta 2.49, 95% CI 1.81-3.17, $p < 0.001$; Figure panel A). There was an increase over time in DDLT (beta 2.27, 95% CI 1.64-2.90, $p < 0.001$) but not in LDLT ($p = 0.18$; Figure panel B). In survival analysis, there was no significant difference in post-transplant mortality through 5 years between DDLT and LDLT for CCA in either Kaplan-Meier ($p = 0.28$) or Cox regression models (HR 0.87, 0.61-1.25, $p = 0.45$; Figure panels C/D). **Conclusion:** Liver transplantation for CCA has increased over the past two decades, driven primarily by growth in deceased donor transplants. Despite stable LDLT rates, post-transplant survival was comparable between DDLT and LDLT. These findings suggest that living donor liver transplantation may be underutilized for CCA and highlight the need to optimize patient and provider awareness regarding outcomes by donor type.



Disclosures: Farinaz Ghodrati: Nothing to Disclose, Samir Abu-Gazala: Nothing to Disclose, Nadim Mahmud: Grifols: Grant/Research Support

0258 | MOLECULAR-BASED THERAPIES FOR PRIMARY LIVER CANCERS: REAL-WORLD DATA FROM 120 PATIENTS OF THE 2025 FRENCH GENOMIC MEDICINE INITIATIVE

Claudia Campani[1] Pierre Laurent Puig[2] Francois Villeret[3] Yasmina Benmerabet[4] Jeanne Netter[5] Yasmina Chouik[3] Eleonore Spitzer[6] Philippe Merle[3] Marianne Ziol[7] Amna Laidin[8] Laetitia Marisa[9] Marie Lequoy[10] Mohamed Bouattour[4] Camille Tlemsani[11] Massih Ningarhahi[12] Manon Allaire[6] Jessica Zucman-Rossi[8] jean charles nault[13]

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Background: Advanced primary liver cancers (PLCs) — hepatocellular carcinoma (HCC), combined hepatocellular–cholangiocarcinoma (cHCC-CCA), cholangiocarcinoma (CCA), fibrolamellar carcinoma (FLC), hepatic sarcoma, and hepatic epithelioid haemangioendothelioma (HHE)—are hard to treat after first-line therapy fails. The 2025 French Genomic Medicine Initiative aimed to find actionable targets for personalized treatment based on Whole Exome/Whole Genome/RNA sequencing of the tumor. **Methods:** Patients with PLC progressing under first-line systemic therapy were enrolled across eight centers in the French Medicine Genomic Program. Tumor and blood samples were analyzed using WGS/WES/RNASeq to identify targetable genetic alterations classified using the ESCAT scale. The results of the genomic analyses and potential targeted therapies were discussed in molecular tumor board. Clinical and pathological data, radiological responses and outcomes were recorded. **Results:** 120 patients were enrolled: 80 HCC, 25 CCA,

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9 cHCC-CCA, 4 FLC, 1 hepatic angiosarcoma, and 1 HHE. Recurrent alterations included *TP53* (46%), *TERT* (44%), *CTNNB1* (20%) and *RB1* (16%) in HCC; and *TP53* (55%), *ARID1A* (20%), *BAP1* (20%) and *PIK3CA* (15%) in CCA and in cHCC-CCA, *TP53* (66.6%), *PIK3CA* (22.2%) and ARID2 (11%) In cHCC-CCA. All FLC cases harbored the *DNAJB1/PRKACA* fusion but without associated targetable alterations. Among the 103 analyzable genomic analysis, 66 patients (64%) harbored had at least one actionable alteration (59% in HCC, 80% in CCA, 78% in cHCC-CCA). Among the 66 patients with targetable genomic alterations and taking into account the highest ESCAT scale, 3 patients (4.5%) harbored ESCAT II, 49 patients (74%) ESCAT III, and 14 patients ESCAT IV (21%) genomic alterations. Thirty-one patients (22 patients with HCC, 4 with CCA, 3 with cHCC-CCA, 1 with HEE and 1 with angiosarcoma) received matched therapy (47% of patients with targetable alterations) after one line of previous systemic treatments in 10 patients, 2 lines in 9 patients and 3 lines or more in 12 patients. Two of these patients have ESCAT II mutations, 22 tiers III mutations and 7 tiers IV mutations (*ERBB2/ERBB3* amplification, *PTEN* deletion, high HRD, *TSC1/TSC2* inactivation, *CD4/CDK6* amplification, *FGFR1* amplification, *FGF19* amplification, *MET* overexpression…). Among these 31 patients, disease control (stable disease/radiological response) was achieved in 29% of these patients (23% in HCC, 50% in CCA, 67% in cHCC-CCA). Patients with disease control had a longer median PFS compared to patients without disease control (7.07 months versus 2.33 months, $P = 0.016$, Figure 1). Finally, disease control rate was observed in 38% of ESCAT II/III versus 0% of ESCAT IV alterations. **Conclusion:** Comprehensive genomic profiling of advanced primary liver cancers is feasible and was associated with disease control in a subset of heavily pretreated patients with ESCAT II/III genetic alterations.

Disclosures: Claudia Campani: Nothing to Disclose, Pierre Laurent Puig: Nothing to Disclose, Francois Villeret: Nothing to Disclose, Yasmina Benmerabet: Nothing to Disclose, Jeanne Netter: Nothing to Disclose, Yasmina Chouik: Nothing to Disclose, Eleonore Spitzer: Nothing to Disclose, Philippe Merle: Nothing to Disclose, Marianne Ziol: Nothing to Disclose, Amna Laidin: Nothing to Disclose, Laetitia Marisa: Nothing to Disclose, Marie Lequoy: Nothing to Disclose, Mohamed Bouattour: Nothing to Disclose, Camille Tlemsani: Nothing to Disclose, Massih Ningarhahi: Nothing to Disclose, Manon Allaire: Nothing to Disclose, Jessica Zucman-Rossi: Nothing to Disclose, jean charles nault: BAyer: Research grants, Ipsen: Research grants

0259 | HOW COLLABORATIVE WORKING WILL ACHIEVE THE WHO TARGET -TO ELIMINATE HEPATITIS C VIRUS (HCV) IN CHILDREN AND YOUNG PEOPLE BY 2030

Carla Lloyd[1] Tayebah Abbasi[2] Palaniswamy Karthikeyan[3] Sanjay Bansal[4] William Irving[5] Paddy McMaster[6] Alasdair Bamford[7] Caroline Foster[8] Anna Turkova[9] Dhamyanthi Thangarajah[10] Siske Struik[11] Mark Gillyon-Powell[12] Ashley Brown[8] Chayarani Kelgeri[2] Joanne Crook[13] Sarah Tizzard[14] Monica Mitcham[15] Penny North-Lewis[3] Rachel Cockayne[16] Hayley Allen[2] Stephen Corcoran[2] Clare Rayner[2] Deirdre Kelly[17]

[1]Birmingham Women's and Children's Hospital NHS FT, [2]Birmingham Women's and Children's NHS FT, [3]Leeds General Hospital, [4]King's College Hospital, [5]Nottingham University, [6]Manchester Hospital, [7]Great Ormond Street Hospital, [8]Imperial College London, [9]University College London, [10]Chelsea and Westminster Hospital, [11]Cardiff and Vale University Hospital, [12]NHS England, [13]KIng's College Hospital London, [14]St George's Hospital, London, [15]Birmingham Women's and Children's NHSFT, [16]Birmingham Women's and Children's, [17]Birmingham Women's and Children's NHFT and University of Birmingham

Background: HCV infection is a major global health problem in adults & children. Direct Acting Anti-viral therapy (DAA) with cure rates of 99% was licensed for children 3–12 years in 2020. To ensure equitable access, safe, effective & convenient supply of these medications during the Covid-19 Pandemic, we established a virtual, national treatment pathway for children & young people (CYP) aged 3-18yrs with HCV in England & evaluated its feasibility, efficacy & treatment outcomes. **Methods:** A virtual, paediatric Multidisciplinary Team Operational Delivery Network (pODN), funded by NHS England (NHSE), was established in 04/21 with relevant paediatric specialists (hepatologists, virologists, infectious disease and pharmacists) providing a single point of contact for referrals & support. A national pathway for referral & treatment protocols were agreed for DAA HCV therapy funded by NHSE at no cost to referring centres. On referral the pODN discuss & agree the most appropriate DAA therapy based on clinical presentation &patient preferences, including ability to swallow tablets. Treatment was prescribed in association with the local hepatologist, paediatrician & pharmacist, without the need for the children & families to travel to national centres. Data collected: Demographic; clinical; social; treatment; treatment outcomes; End of Treatment (EoT) Sustained Viral Response (SVR) at 12weeks & 12months in patients where reached. Feedback on feasibility & satisfaction on the pathway was sought from referrers & families. **Results:**

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155 CYP referred by 14 centres, were discussed & approved for treatment, 04/21–05/25. Median (range) age yrs 8(3-17); 78F; Vertical Transmission (146/155) was the main route of transmission. Genotype 1 &3 were the most common infection; Harvoni was prescribed in 77 (48 tablets;29 granules): Epclusa in 60 (39 tablets;21granules); & Maviret in 18 (10 tablets;8 granules). 133 reached EoT; 1 child failed treatment showing an increase in viral load of EoT; treatment resistance results awaited; 132/133 cleared virus at EoT (>99% clearance); 100% 12mSVR (95/95). Referring teams found the referral process simple & clear; ODN meetings very informative: highly satisfied with overall service. Families reported DAA treatment was fully explained; staff were attentive, thoughtful providing an excellent service, with treatment closer to home(Table1). **Conclusion:** The UK National paediatric virtual network is safe, cost effective & popular with both families & referrers. Treatment success rate was >99% (132/133) in those who completed treatment with 100% confirmed SVR12m. It has enhanced access to anti-viral therapy for CYP who are treated closer to home, reducing travel time to specialist centres preventing long-term liver disease & spread of HCV & made a fundamental contribution to achieving NHSE target to eliminate HCV in children & adolescents ahead of the WHO 2030 target Acknowledgements: Referring teams; BWC; NHS England

Median (range) age in years	8.4 (3.0 – 17.8)
Genotype	
• 1	74
• 2	6
• 3	70
• 4	5
Gender	78F;77M
Ethnicity	
• African	4
• Arabic	1
• Asian	28
• Caucasian	93
• Eastern European	7
• Mixed	8
• Unknown	14
Route of transmission	
• Horizontal	3
• Vertical	146
• Unknown	6
Treatments prescribed:	
• Epclusa: Tablets/Granules	39/21
• Harvoni: Tablets/Granules	48/29
• Maviret: Tablets/Grants	10/8
Treatment outcomes:	
• Awaiting to start treatment	19/155
• Treatment in Progress	3
• Reached EoT and cleared virus	132/133
• Treatment failure – awaiting resistance testing	1/133
• Reached and achieved 12mSVR	95/95
Referrer feedback comments	
• Referral process is simple and clear	
• ODN meetings are informative	
• Overall satisfaction	
• Direct contact and links provided to support local teams	
• Great idea to direct, guide and support local teams to avoid delays and pressure on specialist units.	
• Excellent initiative, patient oriented and definitely improves the quality of care provided	
• Support from Chairperson ensuring referrers felt at ease and reassured	
Patient and parent feedback	
• Aware of treatment for HCV before referral to ODN	
• Confidentiality maintained	
• Adequate information provided	
• Treatment managed by local team	
• Treatment closer to home	
• Thoughtful providing an excellent service	

Disclosures: Carla Lloyd: Nothing to Disclose, Tayebah Abbasi: Nothing to Disclose, Palaniswamy Karthikeyan: Nothing to Disclose, Sanjay Bansal: Nothing to Disclose, William Irving: Nothing to Disclose, Paddy McMaster: Nothing to Disclose, Alasdair Bamford: Nothing to Disclose, Caroline Foster: Nothing to Disclose, Anna Turkova: Nothing to Disclose, Dhamyanthi Thangarajah: Nothing to Disclose, Siske Struik: Nothing to Disclose, Mark Gillyon-Powell: Nothing to Disclose, Ashley Brown: Nothing to Disclose, Chayarani Kelgeri: Nothing to Disclose, Joanne Crook: Nothing to Disclose, Sarah Tizzard: Nothing to Disclose, Monica Mitcham: Nothing to Disclose, Penny North-Lewis: Nothing to Disclose, Rachel Cockayne: Gilead Sciences: Grant/Research Support, Hayley Allen: Gilead: Gilead Sciences fellowship grant, Stephen Corcoran: Nothing to Disclose, Clare Rayner: Nothing to Disclose, Deirdre Kelly: Mirum: Advisor, Intercept: Advisor, Astra Zeneca: Advisor, Takeda: Advisor

0260 | IMPACT OF REAL-WORLD HEPATITIS C VIRUS ANTIBODY TESTING MODALITIES ACROSS DIFFERENT COMMUNITY AND CLINICAL SETTINGS ON EFFECTIVE LINKAGE TO CARE

Grishma Hirode[1] Camelia Capraru[1] Aaron Vanderhoff[1] Andrew Mendlowitz[1] Brett Wolfson-Stofko[1] Joel Karkada[1] David Smookler[1] Mediongo-Abasi Usoro[1] Steven Friedman[2] Kathy Bates[3] Tony Mazzulli[4] Joshua Juan[5] Hemant Shah[1] Bettina Hansen[6] Harry Janssen[7] Mia Biondi[1] Jordan Feld[8], [1]Toronto Centre for Liver Disease/Viral Hepatitis Care Network (VIRCAN), University Health Network, [2]Department of Emergency Medicine, University Health Network, [3]Emergency Department, Toronto Western Hospital, University Health Network, [4]Department of Microbiology, University Health Network/Sinai Health System, [5]Toronto Western Hospital Liver Center, [6]Erasmus MC Rotterdam, [7]Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, [8]Toronto General Hospital

Background: Optimal hepatitis C virus (HCV) screening and treatment is required to prevent transmission, and progression to advanced liver disease. Existing strategies largely focus on risk-based or population-based screening. This is a large real-world analysis comparing the effectiveness of HCV antibody (Ab) screening modalities across different community and clinical settings to understand barriers to progress through the care cascade. **Methods:** Cross-sectional study of individuals who completed HCV Ab testing at multiple centres in Ontario, Canada May 2010-June 2023. Ab testing occurred by phlebotomy-based

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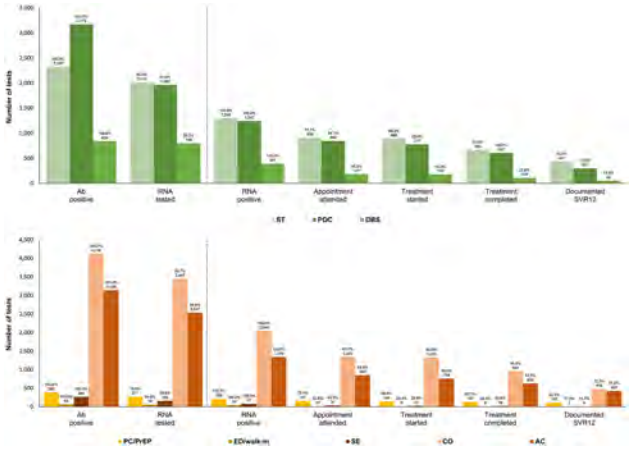
serological testing (ST), point-of-care (POC) testing, or a dried blood spot (DBS) collection card. HCV RNA testing was setting-specific and used DBS for POC and DBS Ab, and phlebotomy-based tests for ST (no reflex testing). Turnaround time was 1-2 weeks for Ab and RNA for all modalities except POC. Ab test settings included primary care/HIV pre-exposure prophylaxis clinics (PC/PrEP), emergency department/walk-in clinics (ED/walk-in), one-time screening events (SE), community outreach programs (CO), and addiction clinics (AC). **Results:** Among 61,605 tests (mean age 47 years, 51% women, 50% ST, 42% POC, 5% DBS), HCV Ab+ prevalence was 14% (n = 8,352; 50% newly identified, 32% aged 35-44 years, 63% men) and highest at AC (41%) and among DBS (26%). Overall, among HCV Ab+, 80% completed RNA testing of whom 57% were RNA+. Among RNA+, 65% attended a follow-up appointment. Among those who attended the appointment, 94% started treatment, 77% of those who started had documented treatment completion, and 60% of those who completed treatment had documented SVR12. PC/PrEP used ST (97%), ED/walk-in used both POC (38%) and DBS (62%), and SE, CO, and AC largely used POC (≥ 75%). Ab testing modality was closely related to test setting, and PC/PrEP was most effective at linkage to care (figure). After an HCV RNA+ result, treatment initiation was better in those tested by POC than DBS. **Conclusion:** Our data highlight strategies to improve progression through the cascade and linkage to care. Identifying the most effective setting-specific testing modality based on the population, staff, and available resources is crucial during the development of an HCV screening program. Receipt of an immediate response with POC likely increased patient engagement by setting up an appointment to receive the RNA result and initiate treatment if positive.



Disclosures: Grishma Hirode: Nothing to Disclose, Camelia Capraru: Nothing to Disclose, Aaron Vanderhoff: Nothing to Disclose, Andrew Mendlowitz: Nothing to Disclose, Brett Wolfson-Stofko: Nothing to Disclose, Joel Karkada: Nothing to Disclose, David Smookler: Nothing to Disclose, Mediongo-Abasi Usoro: Nothing to Disclose, Steven Friedman: Nothing to Disclose, Kathy Bates: Nothing to Disclose, Tony Mazzulli: Nothing to Disclose, Joshua Juan: Nothing to Disclose, Hemant Shah: Nothing to Disclose, Bettina Hansen: Nothing to Disclose, Harry Janssen: Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Academic Medical Education: Consultant, H.C. Wainwright & Co: Consultant, Mia Biondi: Gilead Sciences: Grant/Research Support, Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, AbbVie: Grant/Research Support, Cepheid: Grant/Research Support, Jordan Feld: AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support, AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support

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0261 | POINT-OF-CARE HCV RNA TESTING IN STREET MEDICINE: ADVANCING PATIENT ENGAGEMENT AND MEDICAID POLICY IN KENTUCKY, USA

Philip Graham[1] Morgan Cole[2] Lisa Yarber-Cambron[2] Laura Guy[2], [1]Northern Kentucky Health, [2]Solutions Health

Background: Kentucky ranks among the top 3 US states in prevalence of acute hepatitis C virus (HCV) infection. In June 2024, the FDA authorized the Cepheid Xpert® HCV VL Fingerstick (CXHVF), the first FDA-approved point-of-care (POC) HCV RNA test. Previously validated in diverse global settings, this assay offers the potential to streamline diagnosis and linkage to care. In the US, efficient diagnosis and linkage to care is a critical strategy for Medicaid beneficiaries diagnosed with HCV, among whom significant barriers persist and treatment uptake remains low. Among these barriers are KY Medicaid prior authorization (PA) requirements for quantitative HCV RNA results, limiting the utility of qualitative POC testing like CXHVF. We implemented CXHVF testing pilot in 2 organizations serving people who use drugs and assessed the acceptability, feasibility, and impact on completion of 1st appointment where AASLD pretreatment labs are drawn. **Methods:** In February 2025, the KY Department for Public Health Viral Hepatitis Program (VHP), in collaboration with the Gilead FOCUS Program, selected two partner organizations serving people who use and/or inject drugs to pilot the CXHVF. Each site implemented the system in community-based settings and systematically tracked clinical implementation challenges, patient demographics, test results, co-administered tests, completion of 1st appointment, ect. Biweekly, partner sites, VHP, and FOCUS convened to review clinical/ implementation findings. Separately, VHP regularly met with Department of Medicaid Services (DMS) to share findings. **Results:** Between February and May, 143 individuals were screened for HCV using the CXHVF. Of these, 88 (61.5%) were under age 46, 88 (61.5%) were male, 120 (83.9%) were White, and 87 (60.8%) reported IDU. Overall RNA positivity rate was 32.9%. Patient engagement was high; of those with HCV RNA-positive results, 55.3% completed their first appointment between 1 and 51 days with an average time of 8 days, and $>95\%$ screened for HCV agreed to concurrent HIV and syphilis screening. Furthermore, through VHP's sharing of patient engagement pilot findings, DMS updated the PA to accept qualitative RNA results. **Conclusion:** This real-world pilot demonstrated that the CXHVF is acceptable and feasible in community-based settings serving high-risk populations. High patient willingness to test, coupled with significant uptake of co-administered STI screening, and meaningful follow-through to the completion of the 1st appointment underscores the clinical utility of this POC platform. The pilot findings also contributed to a significant policy shift that reduces barriers Medicaid beneficiaries to treatment. These findings illustrate how implementation of innovative diagnostics can improve engagement and catalyze policy change in support of HCV elimination goals.

Disclosures: Philip Graham: Nothing to Disclose, Morgan Cole: Nothing to Disclose, Lisa Yarber-Cambron: Nothing to Disclose, Laura Guy: Nothing to Disclose

0262 | MOBILE HCV RNA TESTING IN ACTION: POINT-OF-CARE ENABLED DIAGNOSIS AND SVR CONFIRMATION TO DRIVE FIELD-BASED HCV ELIMINATION

Dylan Moore[1] Ann Moore[2], [1]Arizona Liver Health and Viral ElimiNation (VEN) Centers, [2]Arizona Liver Health

Background: Timely confirmation of active hepatitis C virus (HCV) infection is critical for initiating treatment, avoiding unnecessary lab draws, and conserving outreach resources. In field-based models, delays between antibody screening and RNA confirmation frequently lead to loss to follow-up, especially among individuals experiencing homelessness, substance use, or incarceration. To address this gap, VEN Centers integrated the Cepheid GeneXpert HCV RNA point-of-care (POC) platform into its mobile outreach model, enabling same-day diagnosis, treatment planning, and sustained virologic response (SVR) confirmation. This real-time strategy aims to enhance engagement, improve efficiency, and strengthen HCV elimination efforts in the field. **Methods:** Between April 1 and May 22, 2025, HCV antibody-positive individuals encountered during VEN outreach were tested using Cepheid POC RNA at the point of contact. Testing occurred in diverse non-clinical environments including home visits ($n=30$), recovery centers ($n=13$), guerrilla street outreach ($n=10$), mobile units ($n=8$), homeless services ($n=5$), syringe service programs ($n=3$), and jail ($n=1$), using units deployed in mobile vans or vehicles. Venous samples were also submitted for standard lab confirmation. Patients were categorized by HCV history and testing purpose (initial diagnosis or SVR verification). **Results:** Among 70 HCV antibody-positive individuals tested: • 32 (45.7%) were RNA positive and eligible for treatment • 26 (37.1%) were RNA negative post-treatment, confirming SVR • 8 self-reported active HCV but were RNA negative, avoiding unnecessary labs • 4 newly screened were RNA negative, indicating spontaneous clearance. Cepheid

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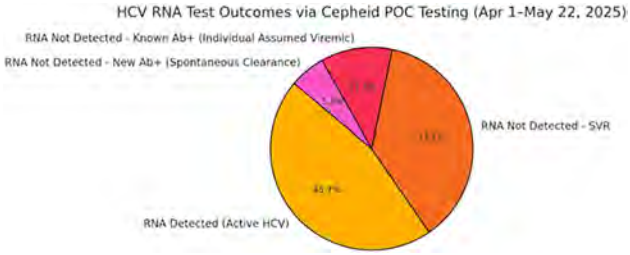
results were 100% concordant with lab-based quantification. The platform provided real-time infection status, facilitated immediate treatment planning, allowed for SVR verification, and supported patient education, streamlining resources and minimizing re-engagement efforts. **Conclusion:** VEN Centers effectively implemented Cepheid GeneXpert RNA testing in a mobile, field-based HCV model, demonstrating clinical utility and operational feasibility. By embedding rapid RNA diagnostics into outreach across homes, shelters, and the streets, the approach enabled same-day clinical decisions, reduced lab burden, and improved engagement. This model offers a scalable blueprint for RNA confirmation within outreach-driven HCV elimination strategies. Additional treatment and outcome data will be presented at the conference.

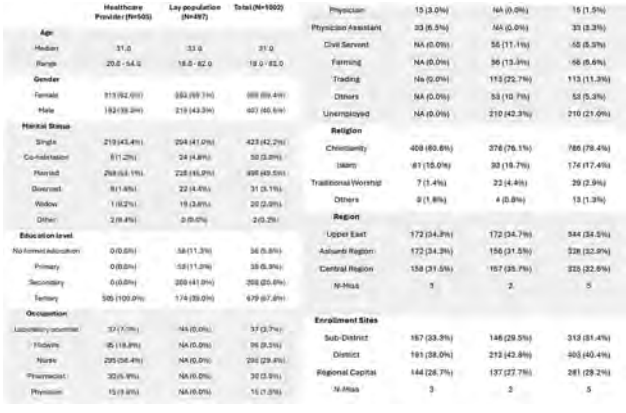


Disclosures: Dylan Moore: Nothing to Disclose, Ann Moore: Nothing to Disclose, Nothing to Disclose

0263 | ILLUMINATING GAPS, IGNITING CHANGE: A DATA-POWERED APPROACH TO HCV EDUCATION IN GHANA

Zamzam Ismail Artan Ali[1] Lewis Roberts[2] Yvonne Nartey[3] Charles Adjei[4] Amoako Duah[5] Peter Fosu[6], [1]Mayo Clinic, [2]Mayo Clinic Rochester, [3]University of Cape Coast School of Medical Sciences, Ghana, [4]University of Ghana, [5]University of Ghana medical center, [6]Hepatitis Alliance of Ghana

Background: Hepatitis C virus (HCV) is one of the leading causes of liver cirrhosis and hepatocellular cancer globally. Despite existence of curative therapy, HCV-related deaths and complications remain a public health concern, especially in low- and middle-income countries. In Ghana, the national HCV seroprevalence is approximately 2.6%. However, the burden is higher in northern Ghana, ranging from 8% to 14%. Led by its National Viral Hepatitis Control Programme (NVHCP), Ghana launched the Screening and Treatment Opportunity Project for Hepatitis C (STOP HepC) in March 2023 which aims to link 50,000 Ghanaians to free HCV treatment. To increase enrolment, a nationwide education and awareness campaign on HCV was developed. This knowledge, attitude and practice survey is part of Ghana's national HCV campaign. **Methods:** A cross-sectional study in Ghana's Upper East, Central, and Ashanti regions, enrolled 1002 participants (n = 497 lay population and n = 505 healthcare workers). A questionnaire, informed by a literature review of HCV literacy and attitudes, was designed to collect sociodemographic data, HCV testing history, knowledge, attitudes, and practices using yes/no and Likert-scale formats. The instrument was piloted in the Greater Accra Region among 30 healthcare workers and lay population prior to the main study. Data collection for the main study took place from 13th June to 27th July 2024. We excluded those unable to consent, and healthcare workers in mandatory service/internship. Trained research personnel administered questionnaires in English or local languages (Buli, Fante, Twi) where relevant. Descriptive analysis of participants responses was performed, and logistic regression examined the association between factors such as hearing about HCV, knowing someone with HCV and prior HCV testing. **Results:** Demographic characteristics of study participants are shown in table 1. The mean knowledge score for the lay population is 0.294 and for healthcare providers is approximately 0.672. Despite 94% of healthcare providers hearing about HCV, only 40.8% were tested, vs 29% of the 51% of the lay population who had heard about it. Lack of awareness correlated with not testing, Individuals who had heard about HCV were 10 times more likely to have been tested for HCV compared to those who had not heard about it [OD = 10, 95% CI 5.38-21.82, $p < 0.005$] after adjusting for confounders. Furthermore, the odds of HCV testing were 7 times higher among persons who knew someone with HCV compared to those who did not [OD = 7, 95% CI 5-10.6 $p < 0.005$].We will build a predictive model to help inform the focus of the education campaign. **Conclusion:** The study revealed a significant gap in HCV knowledge. Hearing about HCV and knowing someone with the condition were strong predictors of testing. There is a need for targeted and context specific educational campaign, informed by predictive models developed from this data to enhance HCV testing and awareness in Ghana.



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0264 | GLOBAL PROGRESS TOWARD HEPATITIS C ELIMINATION: MONITORING ACHIEVEMENTS OF WHO GOALS AND TARGETS FOR HEPATITIS C PREVENTION AND CARE

Zoe Ching[1] Lindsey Hiebert[2] John Ward[1], [1]Coalition for Global Hepatitis Elimination, [2]Coalition of Global Hepatitis Elimination

Background: In 2015, WHO established global goals to eliminate Hepatitis C virus (HCV) as a global health threat, defined by reductions in HCV incidence and mortality by 2030. To monitor progress toward achievement of elimination goals, WHO created the Path to Elimination (PTE) tiers (bronze, silver, gold) of coverage targets for HCV prevention, diagnosis, and treatment. **Methods:** Provisional data from WHO Global Health Observatory, Georgetown HIV Policy, UN population data, peer-reviewed literature, and CGHE National Hepatitis Elimination Profiles were analyzed for 167 countries and territories to assess progress toward the 2030 elimination goals for HCV incidence (< 5 new infections/100,000) and mortality (< 2/100,000). Three coverage targets were examined from the PTE criteria: % of HCV infected persons diagnosed (D); % of HCV diagnosed persons treated (T); and number of needle/syringes (NS) distributed per person who inject drugs per year. The tiers are defined as: Bronze ($D \geq 60\%$, $T \geq 50\%$, NS present), Silver ($D \geq 70\%$, $T \geq 60\%$, NS + opioid agonist therapy (OAT) present), Gold ($D \geq 80\%$, $T \geq 70\%$, > 150 NS). Data are presented for the most recent year available. **Results:** Progress Towards WHO Mortality and Incidence Goals A total of 25 (15%) and 24 (14%) countries are at or below the 2030 targets for HCV mortality and incidence, respectively. 10 countries (6%) meet both targets, with 6 of those countries in the Americas (Bolivia, Brazil, Chile, Ecuador, Paraguay, and Peru). Progress Towards PTE tiers For NS Coverage, 66 (39%) met Bronze, 53 (32%) met Silver, and 12 (7%) met Gold. For diagnosis coverage, 20 (12%) meet Bronze, 13 (8%) meet Silver, and 10 (6%) meet Gold. No countries in the South East Asia Region (SEARO) reached Bronze. The US diagnosis coverage (68%) meets Bronze. For treatment coverage, 29 (17%) meet Bronze, 19 (11%) meet Silver, and 10 (6%) meet Gold. Rwanda is the only African country that reached Gold. The US has 43% in HCV treatment coverage. Two other countries (Egypt and Norway) meet Gold, while three countries meet Silver (Australia, Georgia, Spain). **Conclusion:** Although achievement of PTE tiers requires validation by WHO, provisional data reveal the countries on the PTE for the 2030 targets and WHO 2030 Elimination Goals. Challenges remain for most countries. The US and other countries need to commit the resources for expanding NS services, access to HCV treatment, and policies to scale-up HCV screening to accelerate progress toward HCV elimination.

Disclosures: Zoe Ching: Nothing to Disclose, Lindsey Hiebert: Nothing to Disclose, John Ward: Abb Vie, Abbott, Gilead, Siemens, Roche, Pharco, Virion,: Grant/Research Support, Dynavax, Merck, Cepheid,: Grant/Research Support

◆ 1001 | ACTIVATION OF HEPATIC USP5 AMELIORATES MASLD VIA DEUBIQUITINATING CPT-1A

Qinmei Sun[1] Jiamei Chen[2] Siting Gao[3] Xin Xin[2] Yidan Shang[2] Yaoshan Zhou[2] Ru-Tao Lin[2] Yiyang Hu[2] Ping Liu[2] qin feng[2], [1]shanghai university of traditional chinese medicine, [2]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, [3]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicin

Background: The pathogenesis of Metabolic dysfunction-associated steatotic liver disease (MASLD) is complex. Deubiquitinating enzymes (DUBs) are crucial for liver pathophysiology by precisely controlling protein function, localization and degradation. This study evaluated the potential role and therapeutic value of Ubiquitin specific protease 5 (USP5) in MASLD.

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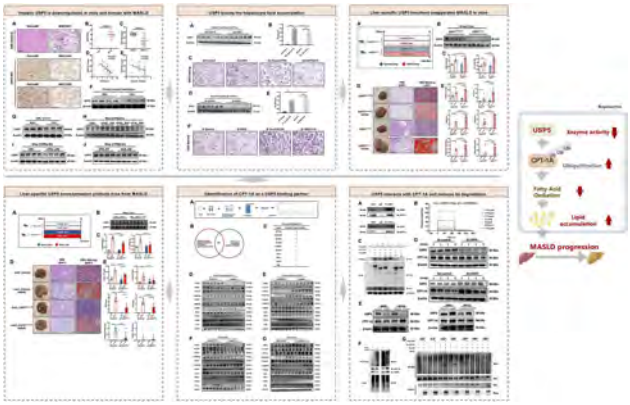
Methods: Firstly, the role of USP5 in MASLD was evaluated through liver tissues of MASLD patients, mice, and steatosis hepatocytes. Then, the hepatocyte specific USP5 knockout mice and the liver-specific USP5 overexpression mouse was constructed and feeding with a high-fat and high-sugar diet to establish MASLD. Further, chromatography-tandem mass spectrometry (CoIP-MS) analysis, co-immunoprecipitation (CoIP), and Surface Plasmon Resonance (SPR) was used to identified the interacting protein of USP5. Then, CHX, MG132 and ubiquitination assays were used to reveal the deubiquitination of USP5. Finally, a series of USP5 truncation plasmids and ubiquitin chain plasmids were constructed to clarify the mechanism of USP5 regulating downstream protein. **Results:** Both clinical samples and experimental models consistently demonstrated significantly downregulated USP5 protein expression in MASLD. Whether *in vitro* or *in vivo*, knockdown or knockout of USP5 could markedly aggravated hepatic steatosis and inflammation, whereas USP5 overexpression significantly alleviated these characteristic lesions. Subsequently, CoIP-MS identified CPT-1A, a rate-limiting enzyme in fatty acid oxidation, as a novel USP5-interacting protein. This interaction was further confirmed by endogenous co-IP and SPR, demonstrating direct binding between USP5 and CPT-1A ($Ka = 3.995E \pm 4(1/Ms)$, $Kd = 0.005009$ (1/s)). Mechanistically, the protein truncation test revealed that the 749-835 amino acid domain of USP5 could mediate this interaction. Further, CHX and MG132 treatment demonstrated that USP5 binding could stabilize CPT-1A by extending its protein half-life. And, ubiquitination assays found that USP5 deficiency enhanced CPT-1A polyubiquitination, while USP5 overexpression reduced this modification. Most importantly, the ubiquitin chain linkage mapping identified K6-linked polyubiquitination as a specific mechanism through USP5 regulating CPT-1A. **Conclusion:** This study indicates the mechanism whereby USP5 inhibits MASLD through deubiquitination-mediated stabilization of CPT-1A, suggesting that targeting USP5 is a potential therapeutic strategy for MASLD.



Disclosures: Qinmei Sun: Nothing to Disclose, Jiamei Chen: Nothing to Disclose, Siting Gao: Nothing to Disclose, Xin Xin: Nothing to Disclose, Yidan Shang: Nothing to Disclose, Yaoshan Zhou: Nothing to Disclose, Ru-Tao Lin: Nothing to Disclose, Yiyang Hu: Nothing to Disclose, Ping Liu: Nothing to Disclose, qin feng: Nothing to Disclose

◆ 1002 | GENIPOSIDE ALLEVIATES MASH BY TARGETING USP15 TO ENHANCE PLIN2 UBIQUITINATION AND PROMOTE HEPATIC LIPOPHAGY

Chen Zou[1] Xin Xin[2] Xiao Xu[1] Qinmei Sun[1] Zhuoyuan Wang[1] Sheng Lyu[1] Ru-Tao Lin[1] Ziming An[1] Yiyang Hu[1] qin feng[1], [1]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, [2]Shanghai University of Traditional Chinese Medicine

Background: Geniposide (GE), a natural iridoid glycoside, is known for its anti-inflammatory, antioxidant, and glucolipid metabolic regulatory effects, particularly in reducing hepatic lipid deposition and inflammation, which suggests its potential in treating metabolic dysfunction-associated steatohepatitis (MASH). This study aims to explore the therapeutic targets of GE in MASH and clarify its pharmacological mechanisms. **Methods:** In this study, MASH mouse model induced by high trans-fatty acid and high-sugar diet (HFHC) and FFAs (Free Fatty Acids)-induced AML12 cells and primary hepatocytes models were used to investigate the anti-MASH effect of GE. The potential GE-binding proteins were screened by HuProt protein chip and pull-down mass spectrometry (MS). The interaction between GE and the target protein was verified by cellular thermal shift assay (CETSA) and Drug Affinity Responsive Target Stability (DARTS). AML12 cell models with USP15 overexpression or knockout via stable transfection confirmed that USP15 is crucial for GE - regulated lipid deposition in MASH. Co-immunoprecipitation (Co-IP) MS was used to screen the downstream substrates of the binding protein. **Results:** In both in vivo and in vitro MASH models, GE treatment significantly improved MASH pathogenesis, with a notable reduction in hepatic lipid deposition. Proteomic analysis demonstrated that USP15 is a potential direct binding target of GE, which was further validated by CETSA and DARTS assays. Genetic knockout of USP15 in AML12 cells not only alleviated intracellular lipid accumulation but also attenuated the therapeutic efficacy of GE, highlighting USP15 dependency in GE-mediated lipid regulation. Mechanistically, Co-IP MS identified PLIN2, a key lipophagy regulatory protein, as a physical interactor of USP15, with their subcellular co-localization confirmed by immunofluorescence and Co-IP. GE

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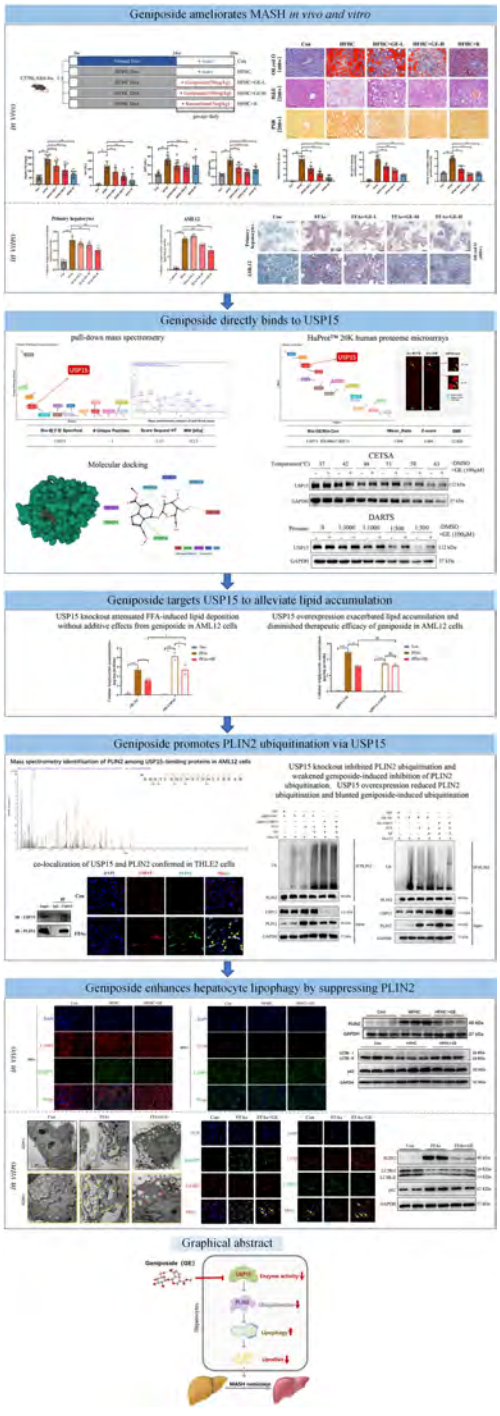
treatment significantly promoted PLIN2 ubiquitination, an effect reversed by USP15 overexpression. Critically, in both in vivo and in vitro, GE administration was associated with decreased PLIN2 protein expression in hepatocytes, which correlated with significantly enhanced lipophagic activity as assessed by LC3B puncta formation and autophagic flux analyses. **Conclusion:** Our research clearly demonstrated that GE can enhance hepatocyte lipophagy and reduce MASH-related hepatic lipid deposition by targeting hepatic USP15 and then up-regulating PLIN2 ubiquitination.



Disclosures: Chen Zou: Nothing to Disclose, Xin Xin: Nothing to Disclose, Xiao Xu: Nothing to Disclose, Qinmei Sun: Nothing to Disclose, Zhuoyuan Wang: Nothing to Disclose, Sheng Lyu: Nothing to Disclose, Ru-Tao Lin: Nothing to Disclose, Ziming An: Nothing to Disclose, Yiyang Hu: Nothing to Disclose, qin feng: Nothing to Disclose

◆ 1004 | GENIPIN 1-GENTIOBIOSIDE TARGETING IRAK4 TO INHIBIT NLRP3 INFLAMMASOME ACTIVITY IN LIVER MACROPHAGES TO ALLEVIATE METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS INFLAMMATION

Zhuoyuan Wang[1] Beiyu Cai[2] Xin Xin[1] Qinmei Sun[3] Ziming An[1] Qian Huang[1] Sheng Lyu[1] Xiaojun Gou[4] Yiyang Hu[1] Fu-rong Qiu[1] qin feng[1], [1]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, [2]Shuguang Hospital Afflicated to Shanghai University of Traditional Chinese Medicine, [3]Shanghai University of Traditional Chinese Medicine, [4]Baoshan District Hospital of Integrated Traditional Chinese and Western Medicine of Shanghai

Background: Genipin 1-gentiobioside (GG), a major active component isolated from Gardenia jasminoides, a traditional Chinese medicine for liver-related diseases, lacks defined efficacy and mechanisms against Metabolic Dysfunction-Associated Steatohepatitis (MASH). This study aims to uncover the therapeutic effects of GG on MASH and its underlying mechanisms. **Methods:** Mice were fed a high-fat high-carbohydrate diet with sugar water (HFHC) for 18 weeks to establish MASH. At the last 6 weeks, mice in the GG group received GG (50/100 mg/kg/day) by oral gavage. In vitro, free fatty acid induced primary hepatocytes and AML-12 cells were employed. Histopathological examination, biochemical examination and other methods were used to evaluate the effect of GG on MASH. Transcriptomic analysis reveals the regulatory effect of GG on hepatic inflammation in MASH mice. Dynamic molecular docking simulation, cell thermal migration analysis (CETSA) and drug affinity reaction target stability (DARTs) were used for prediction and identification. Subsequently, we evaluated the effects of GG on IRAK4 activity, NF-κB transcription, and NLRP3 inflammasome activation in both in vivo and in vitro models. The in vitro model utilized LPS+ATP to induce NLRP3 inflammasome activation in bone marrow-derived macrophages. Systemic IRAK4 knockout mice were established with wild-type mice as controls, and both in vitro and in vivo approaches were employed to investigate the impact of GG on the IRAK4/NF-κB/NLRP3 signaling pathway. **Results:** GG significantly

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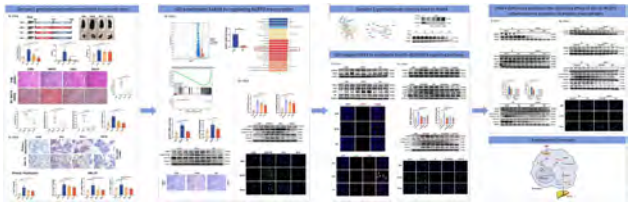
ameliorates MASH in both in vivo and in vitro models, through NLRP3 transcriptional regulation. In line with the suggestion of dynamic molecular docking, CETSA and DARTS assays demonstrated that GG binds to IRAK4 and stabilizes its protein structure. Critically, integrated in vivo and in vitro evidence demonstrates that GG potently suppresses IRAK4 activity in macrophages, thereby inhibiting NF-κB transcriptional activity, blunting NLRP3 inflammasome activation, and ultimately reducing pro-inflammatory mediator expression. However, when IRAK4 was knocked out, this inhibitory effect was significantly attenuated both in vivo and in vitro. **Conclusion:** GG ameliorates MASH by targeting IRAK4 to inhibit NF-κB transcriptional activity, thereby blunting NLRP3 inflammasome activation in hepatic macrophages. This mechanistic insight provides a foundation for its therapeutic translation.



Disclosures: Zhuoyuan Wang: Nothing to Disclose, Beiyu Cai: Nothing to Disclose, Xin Xin: Nothing to Disclose, Qinmei Sun: Nothing to Disclose, Ziming An: Nothing to Disclose, Qian Huang: Nothing to Disclose, Sheng Lyu: Nothing to Disclose, Xiaojun Gou: Nothing to Disclose, Yiyang Hu: Nothing to Disclose, Fu-rong Qiu: Nothing to Disclose, qin feng: Nothing to Disclose

◆ 1005 | LIVER SINUSOIDAL ENDOTHELIAL CELL INTERCELLULAR ADHESION MOLECULE 1 (ICAM1) PROMOTES LIVER INFLAMMATION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Qianqian Guo[1] Nantawat Satthawiwat[1] Akitoshi Sano[1] Xin Dai[1] Chady Meroueh[1] Khaled Warasnhe[1] Alexander Washinton[1] Alex Krivonos[1] Sheng Cao[2] Enis Kostallari[2] Johan Jonker[3] Bart van de Sluis[3] Feda Hamdan[1] Samar Ibrahim[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester, [3]University Medical Center Groningen

Background: During metabolic dysfunction associated steatohepatitis (MASH), liver sinusoidal endothelial cells (LSEC) acquire a pro-inflammatory phenotype characterized by increased adhesion molecules expression and myeloid cells associated liver inflammation. We aim to uncover the pathogenic role and the transcriptional regulation of ICAM1, an upregulated LSEC adhesion molecule in MASH and lipotoxicity. **Methods:** Models of lipotoxicity and MASH employed include an in *vitro* model of primary human LSEC treated with palmitate (PA), an *ex vivo* model of cultured precision cut MASH mouse liver slices, and *in vivo* models of high fat fructose and cholesterol (FFC) diet and choline deficient high fat diet (CDHFD) induced MASH. Mice with diet-induced MASH received ICAM1 neutralizing antibody (ICAM1 Ab) or isotype control. **Results:** Analysis of GeoMx digital spatial profiling on human liver tissue (Figure1) showed enhanced outgoing extracellular matrix (ECM)-receptor signaling from endothelial cells to myeloid cells in MASH patients. The ECM- receptor signaling constitutes of profibrogenic genes contributes to the majority of communication patterns between LSECs and Myeloid cells. While cell-cell contact signaling including adhesion molecules, and secreted signaling including proinflammatory cytokines contributes mainly to the communication patterns in patients with steatosis. Differentially expressed proinflammatory and profibrogenic related genes from Von Willebrand factor (vwf)+ LSECs as well as CD68+ macrophages and (elastase) ELA2+ neutrophils showed distinct zonal distribution signatures. Furthermore, ICAM1 immunostaining is increased in human MASH and correlates with disease severity. Assay for Transposase-Accessible Chromatin with sequencing (ATAC-seq) on primary mouse LSEC revealed abundant open chromatin region at *Icam1* promoter in MASH. Chromatin immunoprecipitation (ChIP) showed enrichment for the active epigenetic mark H3K27ac and Bromodomain and Extra-Terminal motif (BET) protein member 4 (BRD4) at the *ICAM1* promoter region in PA-treated primary human LSEC. Furthermore, BET protein pan inhibitor iBET151 suppressed PA-induced upregulation of LSEC ICAM1 and proinflammatory chemokines *in vitro* and *ex vivo* models of lipotoxicity and MASH. Using loss of function paradigm, we show that GSK3β/c-Jun signaling acts as upstream regulator of lipotoxicity-induced ICAM1 upregulation. Flow-based adhesion assay shows reduced neutrophils and monocytes adhesion to PA treated LSEC in the presence of ICAM1 neutralizing antibody. ICAM1Ab-treated mice in 2 diet-induced MASH mouse models had reduced liver injury inflammation and fibrosis. **Conclusion:** LSEC ICAM1 is epigenetically upregulated during lipotoxicity via a GSK3β/c-Jun/BRD4 dependent mechanism and enhances myeloid cells adhesion. ICAM1 inhibition is salutary in murine MASH and might serve as a potential therapeutic target in human MASH.

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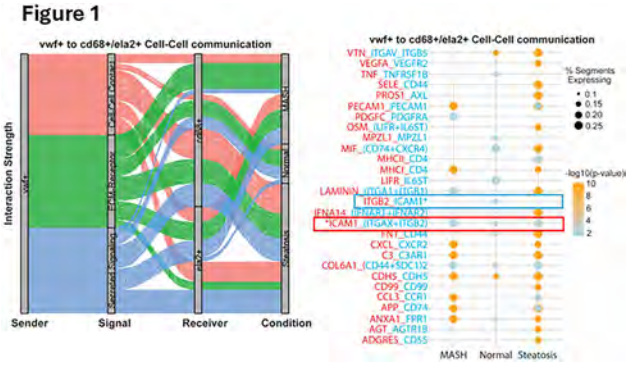

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◆ 1006 | ENDOTHELIAL GLYCOGEN SYNTHASE KINASE 3β DELETION ATTENUATES MITOCHONDRIAL DYSFUNCTION, FERROPTOSIS, AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS IN MURINE MASH

Akitoshi Sano[1] Qianqian Guo[1] Khaled Warasnhe[1] Nantawat Satthawiwat[1] Petra Hirsova[1] Davide Povero[1] Samar Ibrahim[1], [1]Mayo Clinic Rochester

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is characterized by lipotoxicity and liver inflammation. During MASH, liver sinusoidal endothelial cells (LSECs) develop a proinflammatory phenotype known as lipotoxic endotheliopathy, leading to increased pathogenic myeloid cell hepatic infiltration. We have reported that LSEC glycogen synthase kinase 3 (GSK3β) acts as a major kinase hub in MASH. However, the molecular mechanisms and functional outcome of lipotoxicity-induced GSK3β activation in LSEC remain to be elucidated. **Methods:** Endothelial cell-specific *Gsk3β* knockout ($Gsk3\beta^{\triangle End}$) mice were generated by crossing $Gsk3\beta^{fl/fl}$ mice with mice expressing tamoxifen-inducible Cre recombinase under the regulation of the vascular endothelial cadherin promoter. Mice were fed a choline-deficient high-fat diet (CDHFD) or high fat, fructose, and cholesterol (FFC) to induce MASH. Palmitate and/or linoleate-treated primary human LSECs (hLSECs) were employed as an *in vitro* model of lipotoxicity. **Results:** The expression of Intercellular adhesion molecule-1 (ICAM1) (a marker of lipotoxic endotheliopathy), liver inflammation and injury markers were significantly reduced in the CDHFD-fed $Gsk3\beta^{\triangle End}$ mice. Immunophenotyping by flow cytometry on intrahepatic leukocytes showed reduced infiltrating monocytes and conventional type 1 dendritic cellsin CDHFD-fed $Gsk3\beta^{\triangle End}$. Similar results were replicated in mice fed the FFC diet and treated with the GSK3 inhibitor elraglusib, suggesting that LSEC GSK3β modulate dendritic cell maturation. This was further confirmed by transcriptome analysis on LSECs from chow and CDHFD-fed $Gsk3\beta^{\triangle End}$ and $Gsk3\beta^{fl/fl}$ mice showing downregulation of several pro-inflammatory and pro-fibrogenic pathways in the CDHFD-fed $Gsk3\beta^{\triangle End}$ when compared to $Gsk3\beta^{fl/fl}$. Moreover, liver fibrosis and portal pressure were reduced in CDHFD-fed $Gsk3\beta^{\triangle End}$ mice. Pathway analysis on hLSECs transcriptomic identified ferroptosis as a major pathway in LSECs under toxic lipid treatment, which was suppressed with pharamcological GSK3 inhibition. Bodipy C11 and cell viability assays showed that GSK3 inhibition rescued lipotoxicity-induced ferroptosis sensitivity in hLSECs. Moreover, GSK3 inhibition in vitro restored hLSECs mitochondrial respiration, biogenesis and improved the morphological changes induced by lipotoxicity via activation of the AMPK pathway. **Conclusion:** GSK3β inhibition in LSEC attenuates lipotoxic endotheliopathy via inhibiting ferroptosis and restoring mitochondrial function. Moreover, LSEC GSK3 inhibition attenuates proinflammatory myeloid cells hepatic infiltration likely by modulating dendritic cell maturation and reducing ICAM-1 expression. Hence, GSK3 inhibition could serve as a potential therapeutic strategy in human MASH.

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◆ 1007 | ACETYLATION OF RETINOID X RECEPTOR A (RXRA) PRESERVES ANTI-FERROPTOTIC CAPACITY AND MITIGATES MASH PROGRESSION

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Background: Liver fibrosis remains a key driver of morbidity in metabolic dysfunction-associated steatohepatitis (MASH), the progressive form of MASLD. Although highly prevalent, only a subset of patients with MASLD progress to advanced fibrosis, suggesting a loss of intrinsic hepatic resilience. Recent evidence implicates ferroptosis —a regulated form of lipid peroxidation-induced cell death —as a critical contributor to hepatocyte injury and fibrogenesis. However, upstream molecular regulators of hepatocellular ferroptosis remain largely undefined. To identify potential regulators of this loss in resilience to MASH, we reanalyzed published snRNA-seq data (GSE189600) comparing MASLD and MASH patients. Given that many genes contribute to ferroptosis, we developed a custom algorithm (FerroEnrich)[24] to calculate the ferroptosis index and identify key regulatory genes involved in the pathogenesis of metabolic liver diseases. Our analysis revealed enrichment of the ferroptosis pathway and identified GTP cyclohydrolase 1 (GCH1) as a predominant ferroptosis regulator, particularly in diseased livers. To test the hypothesis that GCH1-dependent antiferroptotic capacity acts as a resilience factor mitigating MASH progression, we investigated the molecular mechanism underlying GCH1 downregulation in MASH and demonstrated the feasibility of restoring this protective pathway. We hypothesize that inflammatory signals (e.g., TNFα) reduce RXRα acetylation, impair GCH1 transcription, and predispose hepatocytes to ferroptosis and fibrosis. We aim to define the novel RXRα-GCH1 regulatory mechanism and test whether restoring RXRα acetylation or GCH1 expression enhances hepatocellular resilience and attenuates liver injury in experimental MASH. **Methods:** We employed a multi-tiered approach combining in-silico analyses of ATAC-seq datasets (GSE162870) to assess GCH1 expression patterns in MASH liver. This revealed decreased chromatin accessibility at the RXRα/PPARα binding region within the promoter of GCH1. ChIP-qPCR further confirmed reduced binding of RXRα and PPARα to the GCH1 promoter. To elucidate why RXRα deficiency selectively impairs PPARα signaling and GCH1 expression, we revisited the role of RXRα post-translational modification in regulating its interaction with nuclear receptor partners. Using affinity purification–mass spectrometry, we identified a previously unreported acetylation site on RXRα (Ac-RXRα). To determine the physiological relevance of RXRα acetylation, we generated hepatocyte-specific RXRα knockout mice ($RXR\alpha^{hepKO}$) using Albumin-Cre and challenged them with high-fat, Western, or MASH diet. RXRα acetylation was manipulated via intravenous AAV8-TBG vectors expressing wild-type RXRα, a KQ mutant (acetylation mimic), or a KR mutant (acetylation mutant). Ferroptosis-dependent functional changes were evaluated following AAV8-mediated restoration of GCH1 expression. Liver histology (H&E, Sirius Red), fibrosis scoring, and qPCR analysis of fibrotic and inflammatory markers (Col1a1, Tnfα, Tgfβ1) were performed. Ferroptosis was assessed using LiperFluo staining, 4-HNE quantification, MDA assays, and transmission electron microscopy. RXRα acetylation was measured by IHC and western blot analysis. Data were analyzed by ANOVA or unpaired t-test ($p < 0.05$). **Results:** GCH1 expression was significantly reduced in hepatocytes from fibrotic human MASH livers. Concurrently, ATAC-seq and ChIP-qPCR results revealed decreased RXRα/PPARα binding and chromatin accessibility at the GCH1 promoter, implicating transcriptional deregulation. In $RXR\alpha^{hepKO}$ mice fed Western and MASH diets, we observed exacerbated steatosis, lobular inflammation, and fibrosis. These mice also exhibited increased expression of pro-fibrotic and ferroptosis-related genes, along with elevated levels of hepatic and circulating PCSK9, a marker of dyslipidemia and cardiovascular risk. RXRα acetylation was reduced in TNFα-treated hepatocytes and MASH mouse livers. AAV8-mediated expression of the acetylation mimic RXRα-KQ restored GCH1 transcription, suppressed lipid peroxidation (MDA, 4-HNE), and improved mitochondrial integrity, whereas the KR deacetylation mutant failed to confer these protective effects. AAV8-mediated GCH1 overexpression rescued hepatocyte ferroptosis and oxidative injury in $RXR\alpha^{hepKO}$ livers, with reduced fibrosis and improved hepatic histology, supporting GCH1 as a critical effector of RXRα-mediated protection. **Conclusion:** Our study identifies RXRα acetylation as a key regulator of hepatocellular resilience through the transcriptional activation of GCH1, a ferroptosis suppressor. Inflammatory signaling impairs RXRα acetylation, resulting in GCH1 downregulation, lipid peroxidation, mitochondrial dysfunction, and fibrogenesis. Restoration of RXRα acetylation or GCH1 expression reverses ferroptotic injury and fibrosis, establishing the RXRα–GCH1 axis as a potential dual-action therapeutic target for MASH.

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◆ 1008 | HYDROXYNONENAL INDUCES INTRACELLULAR ORGANELLE CHANGES IN HEPATOCYTES SIMILAR TO THOSE OBSERVED IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

Hidenori Kido[1] Masahiro Yanagi[2] Eishiro Mizukoshi[2] Taro Yamashita[2], [1]Kanazawa University Hospital, Gastroenterology, [2]Kanazawa University

Background: We previously reported the ultrastructural changes in intracellular organelles characteristic of Metabolic dysfunction-associated steatotic liver

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disease (MASLD) using transmission electron microscopy (Journal of Gastroenterology 2025, in press). We have also demonstrated that hydroxynonenal (HNE), derived from diets rich in unsaturated fatty acids and from cellular membranes, plays a role in the progression of MASLD (Cellular and Molecular Gastroenterology and Hepatology 2022). In the present study, we report the discovery that HNE-induced damage to intracellular organelles in hepatocytes shares key morphological features with the characteristic changes observed in MASLD. **Methods:** (1) Analysis in the HNE administration model We examined optical microscopy, HNE immunostaining, and electron microscopy findings using: HepG2 human hepatocellular carcinoma cells, Liver tissue from mice administered intraperitoneal HNE three times per week for 24 weeks, Liver biopsy specimens from Japanese macaques administered intramuscular HNE once per week for 24 weeks. (2) Analysis in the MASLD model We analyzed liver tissue from: Mice fed a choline-deficient, methionine-lowered, amino acid-defined high-fat diet (CDAA) for 8 weeks, Liver biopsies from 40 patients at our institution (11 non-MASLD, 29 MASLD). All samples were evaluated using light microscopy, HNE immunostaining, and electron microscopy. **Results:** (1) In the HNE administration model, we observed mitochondrial abnormalities including loss of double membrane clarity, disrupted cristae, and the presence of highly degenerated spherical mitochondria. Glycogen granules were diminished, and the rough endoplasmic reticulum (rER) exhibited spherical expansion. These findings were consistent across HepG2 cells, HNE-treated mice, and HNE-treated macaques. (2) In CDAA-fed mice, mitochondrial double membrane blurring and cristae disruption appeared as early as week 4. By week 8, spherical degeneration of mitochondria, reduced glycogen granules, and dilated rER were observed. Similar abnormalities were noted in liver biopsies from MASLD patients. Based on previously established criteria, MASLD patients showed significantly more severe ultrastructural abnormalities compared to non-MASLD patients. The extent of these changes correlated with the NAFLD activity score and with the degree of HNE accumulation assessed via immunohistochemistry. **Conclusion:** Using transmission electron microscopy, we observed HNE-induced structural damage to intracellular organelles in hepatocytes. These findings support the involvement of HNE in the pathogenesis of MASLD and offer insights into the mechanisms underlying hepatocellular injury in this condition.

Disclosures: Hidenori Kido: Nothing to Disclose, Masahiro Yanagi: Nothing to Disclose, Eishiro Mizukoshi: Nothing to Disclose, Taro Yamashita: Nothing to Disclose

◆ 1009 | ALCOHOL RESHAPES LIVER ZONAL PLASTICITY AND IMMUNE-METABOLIC REPROGRAMMING IN METABOLIC-SYNDROME ASSOCIATED HEPATOCELLULAR CARCINOMA

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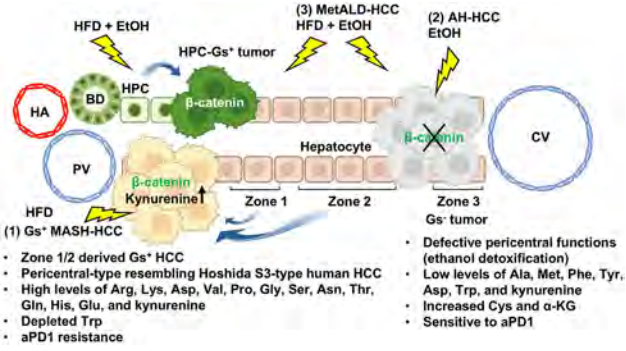
Background: Hepatocellular carcinoma (HCC) arising from metabolic dysfunction- or alcohol-associated steatohepatitis (MASH or AH) is an escalating health challenge complicated by overlapping pathologies of metabolic dysfunction-associated alcohol-related liver disease (MetALD). β-catenin governs hepatic zonation and is mutated in 27% of human HCC; however, the tumor origin and immuno-metabolic rewiring remain elusive. **Methods:** Male mice were subcutaneously injected with 200 μg STZ at 2 days after birth (P2) in combination with the feeding of HFD starting at P30. For MetALD-tumor induction, the STAM mice were exposed to 20% alcohol in drinking water at P60. MASH and MetALD mice were euthanized at P150 by CO_2 inhalation. For the AH-HCC model, male mice were subcutaneously injected with 200 μg STZ at P2 and received ethanol containing Lieber-DeCarli diet at P60 and euthanized at P210. **Results:** Herein, we modeled MASH-associated HCC resembling the Hoshida S3-type cancer in the STAM model. These β-catenin-activated tumors originated in periportal/midlobular zones, showed defects in amino acid breakdown, and induced immunosuppressive kynurenine. Conversely, ethanol consumption triggered AH-HCC with low canonical β-catenin signaling. Unexpectedly, ethanol also mediated massive steatosis, senescence, ductular reaction, and β-catenin$^+$ MetALD-HCC of biliary/progenitor origin while decreasing kynurenine production. Compared to immune-excluded MASH-HCC, ethanol enhanced tumor sensitivity to anti-programmed-death-1 (aPD1) *immunotherapy in MetALD-HCC.* **Conclusion:** These findings reveal novel effects of ethanol on β-catenin-driven zonal plasticity and immuno-metabolic reprogramming with therapeutic implications on targeting subtype-specific HCC of steatotic liver diseases (SLD).



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◆ 1010 | STARD1-DEPENDENT MITOCHONDRIAL CHOLESTEROL TRAFFICKING ACTIVATES THE NLRP3 INFLAMMASOME COMPLEX IN MASH

Hala Jaara[1] Mariana Acevedo Roldan[2] Laura Fàbrega[1] Susana Núñez[3] Vicent Ribas[3] Carmen Garcia-Ruiz[4] Jose Fernandez-Checa[4] SANDRA TORRES NUNEZ[3], [1]IIBB-CSIC-IDIBAPS-CIBEREHD-UB, [2]IIBB-CSIC-VHIR, [3]IIBB-CSIC-IDIBAPS-CIBEREHD, [4]IIBB-CSIC-IDIBAPS-CIBEREHD-USC

Background: Despite significant advances in understanding the pathogenesis of metabolic dysfunction-associated steatohepatitis (MASH), effective pharmacological treatments for its prevention or management remain unavailable. Recent evidence suggests that the accumulation of cholesterol within mitochondria stimulates reactive oxygen species (ROS) generation, leading to mitochondrial dysfunction, inflammation, and cell death that culminate in the progression of MASH to hepatocellular carcinoma (HCC). The NLRP3 inflammasome, a protein complex activated by cellular stress, is activated by ROS, operates predominantly in macrophages, thereby linking mitochondrial damage to inflammatory liver disease. STARD1, a protein responsible for transporting cholesterol into mitochondria, is upregulated in MASH and contributes to HCC development. We hypothesize that STARD1-mediated mitochondrial ROS generation activates the NLRP3 inflammasome, likely through interactions between liver macrophages and hepatocytes. The overall goal was to explore the consequences of STARD1 induction and its impact on NLRP3 inflammasome activation and the interplay between macrophages and hepatocytes in a murine MASH dietary model. **Methods:** We generated mice with hepatocyte-specific (StARD1$^{\Delta Hep}$) and macrophage-specific (StARD1$^{\Delta Mac}$) deletion of StARD1 and were fed either a standard or a high-cholesterol/sodium cholate diet (2% cholesterol + 0.5% sodium cholate). In some groups, macrophages were depleted by intraperitoneal injection of clodronate liposomes (0.1 ml per 10 g of mouse weight). The study assessed liver injury, inflammation, steatosis, and the expression of inflammatory markers. **Results:** The findings revealed that deleting StARD1 specifically in hepatocytes led to a 50% reduction in mitochondrial cholesterol accumulation and significantly lower expression of inflammasome-associated genes (*Nlrp3, Asc, Casp1*), providing protection against diet-induced liver inflammation. Macrophage depletion in StARD1$^{f/f}$ further reduced liver inflammation with lower expression of *F4/80, Cd68* and inflammasome-associated genes, but did not provide additional benefit beyond StARD1 deletion in StARD1$^{\Delta Hep}$ mice. Similarly, deletion of StARD1 in macrophages alone also resulted in reduced inflammation, demonstrated by decreased expression of *F4/80* and inflammasome-associated genes), as well as a 50% reduction in liver damage assessed by H&E and ALT release. **Conclusion:** Overall, these results identify STARD1 as a molecular trigger of NLRP3 activation and highlight a cross-talk between hepatocytes and macrophages in cholesterol-driven liver injury and inflammation, highlighting its potential as a therapeutic target in MASLD.

Disclosures: Hala Jaara: Nothing to Disclose, Mariana Acevedo Roldan: Nothing to Disclose, Nothing to Disclose, Laura Fàbrega: Nothing to Disclose, Susana Núñez: Nothing to Disclose, Vicent Ribas: Nothing to Disclose, Carmen Garcia-Ruiz: Nothing to Disclose, Jose Fernandez-Checa: Nothing to Disclose, SANDRA TORRES NUNEZ: Nothing to Disclose

◆ 1011 | HECTD3 UBIQUITINATES AND STABILIZES PRDX4 TO AMELIORATE METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Rui Jin[1] Nan Geng[1] Fajuan Rui[1] Wenjing Ni[1] Yixuan Zhu[1] Guangqi Zhu[1] Xiangyu Wu[1] Huan Zhang[1] Shengxia Yin[1] Qianwen Zhao[1] Jie Li[1], [1]Department of Infectious Disease, Nanjing Drum Tower Hospital

Background: Metabolic dysfunction-associated steatohepatitis (MASH) poses a significant global public health challenge. The pathological process of MASH is a tangled progression associated with metabolic syndrome and systemic inflammatory response syndrome. HECTD3, as an E3 ubiquitin ligase, is implicated in the regulation of multiple inflammation and fibrosis associated signaling pathways. However, its role in MASH remains inadequately clarified. This study aimed to investigate the function of HECTD3 driving the development of MASH and explore its potential downstream mechanisms. **Methods:** Hepatocellular HECTD3 were over-expressed in mice via the AAV8 system, and male C57BL/6J mice (six weeks old) were fed either a Choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) for 10 weeks,or a high-fat, high-fructose diet (HFHFD) diet for 16 weeks to induce MASH. THLE-2 and AML12 cells were utilized for in vitro studies. **Results:** HECTD3 protein abundance was markedly downregulated in the livers of mice fed a CDAHFD or HFHFD and hepatocytes stimulated by PA. Hepatocyte-specific overexpression of HECTD3 alleviated the progression of MASH. Consistently, lipid accumulation were observed in HECTD3-overexpressed hepatocytes after PA stimulation. The results of co-immunoprecipitation combined with multi-dimensional mass spectrometry analysis revealed that PRDX4 is a potential binding partner of HECTD3. Further endogenous and exogenous co-IP experiments confirmed the interaction between the E3 ubiquitin ligase HECTD3 and PRDX4. Both immunofluorescence and western blot results demonstrated that hepatocyte-

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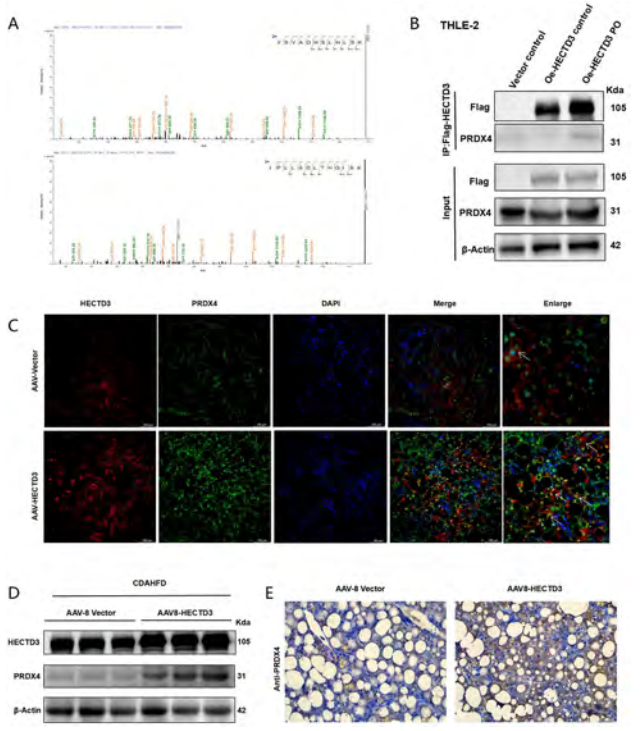
specific overexpression of HECTD3 in MASH mice increased the protein expression level of PRDX4 in the liver, consistent with *in vivo* observations. *In vitro* experiments further confirmed that PRDX4 protein levels were elevated in HECTD3-overexpressed hepatocytes, accompanied by enhanced total ubiquitination of PRDX4. **Conclusion:** HECTD3 interacts with PRDX4 and stabilizes its protein expression by mediating PRDX4 ubiquitination. HECTD3 serves as a key positive regulator of PRDX4 and may represent a promising novel therapeutic target for MASH treatment.



Disclosures: Rui Jin: Nothing to Disclose, Nan Geng: Nothing to Disclose, Fajuan Rui: Nothing to Disclose, Wenjing Ni: Nothing to Disclose, Yixuan Zhu: Nothing to Disclose, Guangqi Zhu: Nothing to Disclose, Xiangyu Wu: Nothing to Disclose, Huan Zhang: Nothing to Disclose, Shengxia Yin: Nothing to Disclose, Qianwen Zhao: Nothing to Disclose, Jie Li: Nothing to Disclose

◆ 1012 | ATRACTYLENOLIDE III CAN INHIBIT THE ACTIVATION OF NLRP3 INFLAMMASOME IN LIVER MACROPHAGES BY TARGETING RIPK3 TO TREAT METABOLIC-ASSOCIATED STEATOHEPATITIS

Ziming An[1] Xin Xin[1] Wuxing Cai[1] Zuoyuan Wang[1] Qinmei Sun[1] Yiyang Hu[1] qin feng[1], [1]Shanghai shuguang hospital

Background: Metabolic dysfunction-associated steatohepatitis (MASH) represents a critical progressive stage in metabolic dysfunction-associated steatotic liver disease (MASLD) development. Atractylenolide III (ATL III), a bioactive sesquiterpene lactone derived from Atractylodes macrocephala Koidz, demonstrates diverse pharmacological properties, including antioxidant and anti-inflammatory activities. However, its therapeutic potential and molecular mechanisms in MASH remain unexplored. **Methods:** Three experimental MASH models were employed: (1)a 26-week high-fat high-cholesterol (HFHC) diet-induced model, (2) a 24-week adeno-associated virus 9 -mediated NLRP3 knockdown MASH model, and (3) a 26-week receptor-interacting protein kinase 3 (RIPK3) knockout MASH model. Histopathological features (H&E, Oil Red O staining) and hepatic triglyceride (TG) content were analyzed. For in vitro studies, bone marrow-derived macrophages (BMDMs) isolated from wild-type and NLRP3 or RIPK3-knockout mice were stimulated with LPS+ATP. Direct binding targets of ATL III were identified using drug affinity responsive target stability (DARTS), cellular thermal shift assay (CETSA), and surface plasmon resonance (SPR). **Results:** ATL III significantly ameliorated MASH in mice, as evidenced by reduced hepatic TG accumulation, improved histopathology, and suppressed NLRP3 inflammasome activation through downregulation of NLRP3 mRNA and protein levels. NLRP3 knockdown in vivo impaired ATL III's therapeutic efficacy despite alleviating MASH phenotypes. In vivo and in vitro studies demonstrated that NLRP3 deficiency abrogated ATL III's ability to suppress inflammasome activation, confirming NLRP3 as a critical mediator of its anti-inflammatory action. DARTS/CETSA/SPR assays identified RIPK3 as a direct binding target of ATL III, with SPR confirming high-affinity interaction (KD $= 3.797 \times 10^{-7}$ M). ATL III inhibited RIPK3 phosphorylation and subsequent NF-κB activation, leading to reduced NLRP3 transcription. RIPK3 knockout mice exhibited improved liver histopathology but failed to respond to ATL III treatment. Consistently, both in vivo and vitro models revealed no suppression of NF-κB phosphorylation, NLRP3 expression, or inflammasome activation upon ATL III treatment, underscoring RIPK3's indispensable role in its mechanism. **Conclusion:** ATL III exerts robust therapeutic effects in experimental MASH by targeting RIPK3 to inhibit NF-κB-driven NLRP3 transcription and inflammasome activation in macrophages. These findings establish RIPK3 as a pivotal regulatory node and identify ATL III as a promising candidate for MASH intervention.

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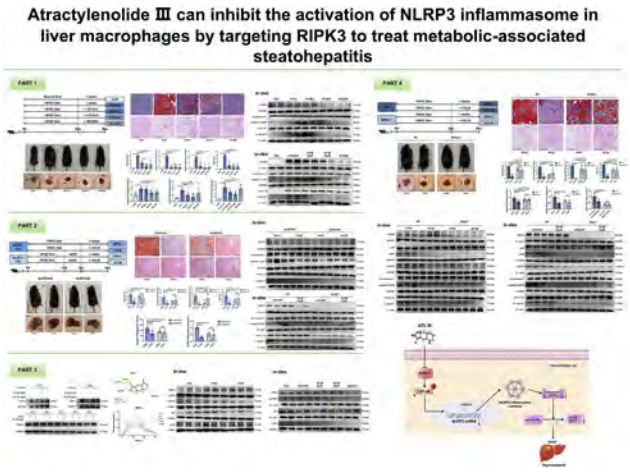

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◆ 1013 | LIPOTOXIC ER STRESS EPIGENETICALLY UPREGULATES ALARMIN S100A11 VIA A LIPID INDUCED ENHANCER IN MASH

Hanna Erickson[1] P. Vineeth Daniel[1] Feda Hamdan[2] Amy Mauer[2] Yasuhiko Nakao[2] Daheui Choi[2] Gyanendra Puri[2] Yeriel Yoon[2] Alexander Revzin[2] Harmeet Malhi[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a multifactorial liver disease that is characterized by abnormal lipid accumulation in the liver and subsequent inflammation and fibrosis. Its incidence and progression are influenced by both genetic and environmental factors. Abnormal lipid accumulation in the liver leads to lipotoxic endoplasmic reticulum (ER) stress in hepatocytes leading to release of proinflammatory stress signals in the form of extracellular vesicles (EVs). However, whether this process is epigenetically regulated is unknown. **Methods:** We performed an unbiased proteomic screen of EVs released in response to lipotoxic ER stress. We subsequently assessed gene expression in palmitate (PA)-treated hepatocytes in the absence or presence of pharmacologic inhibitors for each of the three ER stress pathways. Using publicly available ChIP-seq data, we identified an H3K27 acetylation site near a regulated gene. To block this open chromatin region, we designed a targeting sgRNA that was introduced to dCas9-KRAB-expressing cell lines and mice. The mice were subsequently treated with 6 weeks of high fat, high fructose, high cholesterol (FFC) diet, which recapitulates human MASH, or 3 weeks of choline-deficient, L-amino acid-defined, high fat (CDAHF) diet, which is a rapid disease model of MASH. **Results:** We found increased levels of S100A11 protein, a known alarmin, in PA-induced hepatocyte-derived EVs and in serum of human MASH patients. S100A11 mRNA and protein levels were also enriched in PA-treated hepatocytes. Pharmacologic inhibition of IRE1α and not the PERK or ATF6a pathways blocked PA-induced S100A11 upregulation. We identified an H3K27 acetylation site upstream of S100A11 that was enhanced in response to PA treatment, which we named a Lipotoxic Induced Enhancer (LIE). Blocking this site with dCas9-KRAB blunted S100A11 upregulation in response to lipotoxic ER stress in the livers of mice fed FFC or CDAHF diets. This also resulted in reduced hepatic injury, steatosis, and inflammatory loci in the liver of these mice. **Conclusion:** Our study shows that lipotoxic signaling through IRE1α increases the expression of pro-inflammatory alarmin S100A11 in hepatocytes and in hepatocyte-derived EVs through H3K27 acetylation at an upstream LIE domain and that blocking this signaling results in improved inflammation and liver injury in MASH mouse models. This suggests that S100A11 may be a therapeutic target for MASH.

Disclosures: Hanna Erickson: Nothing to Disclose, P. Vineeth Daniel: Nothing to Disclose, Feda Hamdan: Nothing to Disclose, Amy Mauer: Nothing to Disclose, Yasuhiko Nakao: Nothing to Disclose, Daheui Choi: Nothing to Disclose, Gyanendra Puri: Nothing to Disclose, Yeriel Yoon: Nothing to Disclose, Alexander Revzin: Nothing to Disclose, Harmeet Malhi: MERCK: Consultant, Takeda: Consultant

◆ 1014 | HEPATIC METHYLTRANSFERASE LIKE 7B PROMOTES FATTY LIVER DISEASE THROUGH MRNA STABILITY CONTROL OF LIPOGENESIS

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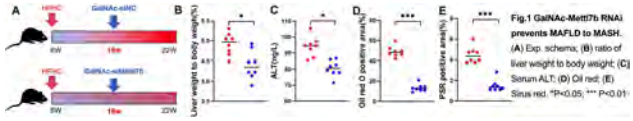
Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) encompasses a continuum from simple steatosis (MAFL) to metabolic dysfunction-associated steatohepatitis (MASH), a more advanced form marked by necroinflammation and fibrosis. Yet, the underlying molecular mechanisms remain incompletely understood. We aim to investigate the role of methyltransferase like 7B (METTL7B), a member of the mammalian methyltransferase-like (METTL) family, in MAFLD/MASH and explore potential mechanisms. **Methods:** We analyzed public liver transcriptome/proteome datasets to profile METTL genes in MAFLD and MASH. *Mettl7b* liver-specific knockout (*HKO*) mice on a high-fat diet and primary hepatocytes were used for functional studies. Techniques included lipid analysis, RNA-seq, qRT-PCR, IP-proteomics, IP-Western blot, and assessments of mRNA stability, protein ubiquitination, truncation mutants, and molecular docking to identify METTL7B partners and mechanisms. **Results:** METTL7B is elevated in both steatosis and steatohepatitis, with increased expression in MASH patients exhibiting fibrosis at stages F3-F4. *HKO* mice show significantly reduced liver weight compared to WT controls (liver, 1.5 $\pm$0.03 vs.1.78$\pm$0.03 g), decreased liver lipid accumulation (TC, 10$\pm$0.7 vs. 19.9$\pm$1.5 mg/g, $P<0.01$), improved liver injury (ALT, 75$\pm$1.9 vs. 88$\pm$0.5 ng/L), and improved metabolic dysfunction (fasting insulin and glucose, $P<0.01$, GTT, $P<0.01$) in western HFD induced MAFLD/MASH. Inflammation (CD11b-positive area, 1.0%$\pm$0.1 vs. 3.1%$\pm$0.18, $P<0.01$) and fibrosis (Sirus red-positive area, 1.7%$\pm$0.3 vs. 4.6%$\pm$0.5, $P<0.01$). Additionally, HKO mice exhibit specific downregulation of genes involved in the de novo lipogenesis (DNL) pathway, including *Srebf1* (*Srebf1* mRNA 39% $\pm$0.1 vs. 100% in WT). In contrast, gain-of-function studies show that METTL7B exacerbates lipid accumulation and inflammation in hepatocytes. Furthermore, GalNAc-siRNA-mediated hepatocyte-specific *Mettl7b* RNA interreference alleviates the transition from MAFL to MASH in mice (Fig.1). Mechanistically, METTL7B interacts with a group of RNA-binding proteins (RBPs) with top hit of poly(A) binding protein cytoplasmic 1 (PABPC1). Molecular docking and IP analyses identified that the RNA recognition motif 4 (RRM4) domain specifically interacts with METTL7B. Interestingly, the canonical methyltransferase domain of METTL7B does not participate in this interaction, rather, strong binding occurs through the C-terminal regions comprising amino acids 1-74 and 172-244 of METTL7B. Additionally, PABPC1 binds to *SREBF1* mRNA, protecting it from degradation, with the RRM1 domain exhibiting high affinity. **Conclusion:** METTL7B promotes MAFLD by stabilizing PABPC1, preventing SREBF1 mRNA degradation and sustaining DNL genes, establishing a pathogenic METTL7B-PABPC1-SREBF1 axis and potential therapeutic target in MASH.



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◆ 1015 | HEPATIC STELLATE CELL-DERIVED WNTS CONTROL LIVER HOMEOSTASIS AND METABOLISM

Nicholas Khoo[1] Tyler Yasaka[1] Minakshi Poddar[1] Sucha Singh[1] Aaron Bell[1] Ravi Rai[1] Ian Sipula[1] Amber Vandevender[1] Xiachao Ma[1] Reben Raeman[1] Silvia Liu[1] Michael Jurczak[1] Satdarshan (Paul) Monga[1],
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Background: Hepatocytes perform essential metabolic tasks and have a remarkable capacity for regeneration following injury. These functions are spatially organized across liver lobules in a phenomenon known as liver zonation (LZ). While Wnt signaling from endothelial cells (ECs) is an established mediator of LZ, the role of hepatic stellate cells (HSCs) in this process remains largely unexplored. **Methods:** To determine the role of HSC-derived Wnts, we generated HSC-Wls-KO mice by conditionally deleting Wntless (Wls), which is essential for all Wnt secretion, through breeding Wls-floxed- with Lrat-Cre- mice. Based on baseline observations, we also fed a Western Diet (WD) to HSC-Wls-KO mice and littermate controls (Con). **Results:** HSC-Wls-KO mice exhibited decreased body weight and fat mass, increased energy expenditure, and enhanced lipid metabolism, suggesting systemic metabolic changes. Single-nucleus RNA sequencing revealed changes in hepatocyte LZ in HSC-Wls-KO livers, including a loss of periportal and expansion of pericentral gene expression programs linked to bile acid synthesis and fatty acid oxidation. These findings were confirmed by single-cell spatial transcriptomics. Immunohistochemistry validated these results, showing increased expression of pericentral markers (CYP2E1, CYP1A2) and decreased expression of periportal (CYP2F2) and even midzonal (HAMP1, HAMP2)

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markers. Functionally, HSC-Wls-KO livers displayed a twofold increase in hepatic bile acid pools, shifts in bile acid composition, and increased mitochondrial respiration with a preference for lipid substrates. HSC-Wls-KO mice fed WD were resistant to weight gain and steatosis, although histological analysis revealed notable sinusoidal dilatation. Spatially resolved CellChat analysis in Con livers showed that HSC-derived Wnts appear to control Wnt2 expression in sinusoidal ECs, with HSC-Wls-KO livers showing expanded Wnt2 expression in ECs towards the periportal zone. **Conclusion:** We reveal a previously underappreciated role for HSC-derived Wnts as regulators of liver metabolism via the HSC-EC-hepatocyte signaling axis. Additional studies are ongoing to further understand the mechanistic basis of these novel observations.

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◆ 1016 | LOSS OF ENDOSOMAL MICROAUTOPHAGY LEADS TO DEVELOPMENT OF HEPATIC FIBROSIS

Debajyoti Das[1] Mridul Sharma[1] Jihane Benhammou[2] Rajat Singh[1], [1]University of California Los Angeles, [2]University of California, Los Angeles

Background: Macroautophagy is a quality control (QC) pathway wherein double membrane autophagic vesicles engulf cytoplasmic organelles and proteins, which are delivered to lysosomes for degradation. Macroautophagy maintains hepatocellular QC by turning-over damaged organelles, such as mitochondria (via mitophagy) or lipid droplets (via lipophagy) in lysosomes. A large body of literature shows that loss of macroautophagy leads to development and progression of the metabolic dysfunction-associated steatotic liver disease (MASLD) spectrum. In addition to macroautophagy, a second poorly-studied form of autophagy called endosomal microautophagy (eMI) has recently been shown to also turnover organelles, e.g., mitochondria and ER, although the relationship of eMI with metabolic liver disease remains unknown. In this study, we determined the effect of liver-specific loss of eMI on the development and progression of the MASLD spectrum in mice and tested for the correlation of loss of eMI with human MASLD spectrum. **Methods:** We used C57BL6/J mice (injected with hepatocyte-specific AAV8 vectors) to selectively silence *VPS4B* (of the ESCRT pathway) that encodes for AAA-ATPase, which plays a critical role in multivesicular body (MVB) formation and late endosomal turnover of engulfed cargo. We assessed the onset and progression of MASLD to MASH and fibrosis through assessments of livers triglycerides (TGs), serum ALT/ASTs, liver H/E and Sirius Red staining. We also analyzed archived human datasets of MASLD subjects to draw correlations between loss of eMI and severity of human MASLD spectrum. **Results:** We found that loss of *VPS4B* in GAN diet-fed mice led to rapid onset of MASLD and its accelerated progression to MASH/fibrosis when compared to diet-matched controls, indicated by increased expression of inflammatory genes, elevated liver TGs, Sirius Red-positivity, and high NAS scores. Electron microscopy revealed defects in the late endosomal compartment, including the failure to form MVBs, and marked accumulation of damaged organelles. Consistently, human MASH/fibrotic livers showed significantly downregulation of *VPS4B* gene as well as other genes critically involved in the ESCRT/EMI pathway. **Conclusion:** Our study reveals the undefined role of the eMI pathway in development of MASLD and its acceleration to MASH and fibrosis, revealing a novel pathway that could be targeted to prevent the development or progression of the MASLD spectrum.

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◆ 1017 | ELUCIDATING THE ROLES OF COMPLEMENT C3 IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing threat to

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global public health, affecting approximately 30% of adults and becoming the leading reason for liver transplantation. Nevertheless, very limited approved specific treatment is currently available for MASLD. Accumulating evidence suggests an important role of the complement system in causation of MASLD. As the axial component of the complement system, C3 is predominantly produced in the liver, the metabolic 'engine' of the body; however, its role in metabolism remains little known. **Methods:** In this study, we have carried out a comprehensive characterisation of C3 spatial expression in normal and MASLD human liver using single cell RNA sequencing and bulk RNA sequencing data. Data were validated in free fatty acid-induced steatotic human hepatocytes and a high fat diet-induced mouse MASLD model. **Results:** We found that C3 was expressed in a zonal manner, with abundant expression in both periportal and pericentral hepatocytes. Cellular deconvolution of MASLD liver showed a disruption of hepatic zonal structure, with a depletion of pericentral hepatocytes while periportal hepatocytes were expanded. This alteration of hepatic zonal distribution was disease severity dependent with involvement of liver progenitor activation. RNA sequencing data from 408 liver biopsies confirmed significant alterations of complement C3 expression in response to MASLD development. C3 was upregulated in all forms of MASLD and positively correlated with liver fat load in patients with steatohepatitis. C3 expression was increased in steatotic human hepatocytes and hepatic C3 expression was higher in a mouse MASLD model. C3 knockout protected against high fat diet induced hepatic lipid droplet accumulation. In the hepatic response to a high fat diet, C3 knockout repressed hepatic *de novo* lipogenesis and triglyceride synthesis through downregulating liver lipogenic regulators. **Conclusion:** We demonstrate the impact of lipid accumulation on C3 expression in hepatocytes and show that C3 knockout impacts hepatic lipid handling. Overall, our study provides new insights into the role of C3 in MASLD pathogenesis and suggests its potential as a therapeutic target for the treatment of MASLD.

Disclosures: Van-Dien Nguyen: Nothing to Disclose, Timothy Hughes: Nothing to Disclose, Birong Zhang: Nothing to Disclose, B. Paul Morgan: Nothing to Disclose, You Zhou: Nothing to Disclose

◆ 1018 | SUPPRESSED GPCR-DEPENDENT CALCIUM SIGNALING PROMOTES HEPATIC STEATOSIS

Paula Bartlett[1], [1]*Rutgers University - New Jersey Medical School*

Background: Hormones and catecholamines acting through G-protein coupled receptors (GPCRs) linked to inositol triphospate (IP_3) production and increases in calcium (Ca^{2+}) regulate many hepatic functions. In the liver hormones such as glucagon, catecholamines and vasopressin integrate and synergize to regulate the frequency and extent to which intracellular Ca^{2+} waves propagate across hepatic lobules to regulate metabolism. These signals oppose the anabolic effect of insulin, control blood glucose levels and regulate hepatic carbohydrate and lipid metabolism. Healthy liver is divided into functional lobules supplied by blood from the hepatic artery and portal vein which drain to the central vein. The metabolic functions of the liver are stratified into zones depending on their location on the porto-central axis, with periportal hepatocytes specialized in gluconeogenesis whereas, pericentral hepatocytes prioritize lipogensis. Dysregulation of hepatic Ca^{2+} homeostasis has been implicated in the development of MASLD, but changes in GPCR-dependent Ca^{2+} regulation of metabolism specifically in different metabolic zones has not been explored. **Methods:** We established liver specific GCaMP6f (calcium sensor) and IP_3R (calcium release channel) knockout mouse strains. Mice were fed a 45% high-fat diet (HFD) or control diet (10% fat), and the effects of HFD on GPCR-dependent Ca^{2+} signaling determined using single cell and intravital fluroscence microscopy. **Results:** We show that GPCR-dependent Ca^{2+} signals in hepatocytes are suppressed by HFD due to a decrease in IP_3. Intravital imaging revealed HFD imparied Ca^{2+} signal propagation across liver lobules. GPCRs sensitive to negative PKC regulation are impaired by HFD, indicating diet-dependent increases in DAG and PKC activity may perturb Ca^{2+} signalling. A comparison of GPCR-dependent Ca^{2+} signals in isolated periportal and pericentral hepatocytes revealed that periportal hepatoctes were most sensitive to the effects of HFD. This loss of sensitivity in periporal hepatocytes may explain why the propagation of Ca^{2+} signals across liver lobules is suppressed by HFD. Finally, IP_3R1 knockout attenuated the amplitude of hormone induced Ca^{2+} transients and lobular wave propagation rates and increased hepatic triglyceride accumulation compared to littermate controls in HFD fed mice. **Conclusion:** Propagation of GPCR-dependent Ca^{2+} signals across liver lobules regulates hepatic meabolism promoting glucnoeogenesis and glucgenolysis in the periporal zone, and inhibting lipogenesis in the pericental zone. HFD suppresses Ca^{2+} signaling and knockout of IP_3R1 increases lipid accumulation, together these results indicate that full strength Ca^{2+} signals in hepatocytes are an important inhibitor of lipogenic pathways. Suppression of hepatic Ca^{2+} signalling affects the regulation of hepatic metabolism and contributes to the etiology of MASLD.

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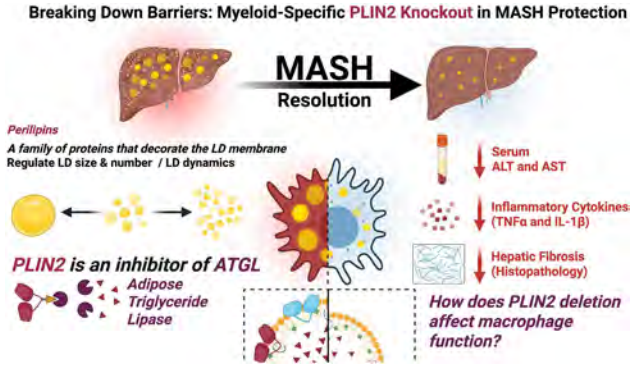
◆ 1019 | MACROPHAGE PERILIPIN 2 ACCELERATES LIVER INFLAMMATION AND FIBROSIS IN MASH

Andrew Hakeem[1] Gavin Fredrickson[1] Patrick Fehrenbach[1] Fanta Barrow[1] Preethy Parthiban[1] Haiguang Wang[1] Xavier Revelo[1], [1]University of Minnesota

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease marked by hepatic lipid overload, persistent inflammation, and fibrotic remodeling. Macrophages are key regulators of disease progression, but the metabolic programs governing their inflammatory activity remain incompletely understood. Perilipin 2 (PLIN2) is a lipid droplet-coating protein highly expressed in macrophages that reside in lipid-rich microenvironments, but its immunometabolic role in MASH is undefined. Previous studies have shown that systemic PLIN2 deficiency reduces hepatic steatosis and inflammation, implicating PLIN2 as a pathological mediator of metabolic liver disease. Thus, we hypothesized that macrophage-intrinsic PLIN2 drives hepatic inflammation and fibrosis by constraining lipid catabolism and promoting pro-inflammatory signaling in macrophages. **Methods:** We generated CX3CR1-Cre PLIN2$^{fl/fl}$ (PLIN2$^{M\Phi\text{-}KO}$) and littermate wildtype mice and subjected them to a high-fat, high-carbohydrate (HFHC) diet for 16 weeks to induce MASH. Disease severity was assessed by histology, hepatic lipid quantification, and qPCR to assess inflammatory gene expression. Bone marrow-derived macrophages (BMDMs) from PLIN2$^{M\Phi\text{-}KO}$ and littermate controls were isolated for *in vitro* cytokine analysis following LPS exposure. **Results:** Compared with littermate controls, PLIN2$^{M\Phi\text{-}KO}$ mice exhibited reduced hepatic triglyceride accumulation, diminished lobular inflammation, and attenuated collagen deposition. Hepatic expression of pro-inflammatory genes, including *Mcp1*, *Il1b*, and *Tnfa* was significantly suppressed in PLIN2-deficient livers. In vitro, BMDMs from PLIN2$^{M\Phi\text{-}KO}$ mice secreted lower levels of tumor necrosis factor α in response to LPS, suggesting that PLIN2 promotes inflammatory cytokine production in macrophages. **Conclusion:** Here, we identified PLIN2 as a key immunometabolic regulator of hepatic macrophages, linking lipid droplet stability to inflammatory activation in MASH. These findings suggest that PLIN2 modulates macrophage function by coupling lipid storage to cytokine production. Targeting macrophage lipid droplet homeostasis may represent a novel therapeutic strategy to ameliorate inflammation and fibrosis in MASH.



Disclosures: Andrew Hakeem: Nothing to Disclose, Gavin Fredrickson: Nothing to Disclose, Patrick Fehrenbach: Nothing to Disclose, Fanta Barrow: Nothing to Disclose, Preethy Parthiban: Nothing to Disclose, Haiguang Wang: Nothing to Disclose, Xavier Revelo: Nothing to Disclose

◆ 1020 | MITOCHONDRIAL CHAPERONE DNAJA3 AND 3D GENOMIC INFLUENCES: INSIGHTS INTO MASH TO HCC TRANSITION

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Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is emerging as a major contributor to hepatocellular carcinoma (HCC). While MAFLD often progresses to metabolic dysfunction-associated steatohepatitis (MASH) and eventually HCC, the genetic mechanisms driving this transition remain unclear. **Methods:** We performed a genome-wide association study (GWAS) on variants related to body fat distribution in 344,369 individuals, followed by analysis of MASH and HCC associations in 1,009 NCI-UMD participants. Expression quantitative trait loci (eQTL) analyses, 3D chromatin interaction mapping, luciferase reporter assays, and RBFOX2 knockdown experiments were conducted to evaluate the regulatory impact of variant rs3747579 on DNAJA3 expression. **Results:** GWAS identified the rs3747579-TT variant as significantly associated with MASH-driven HCC. eQTL and chromatin conformation analyses revealed that this variant resides in an enhancer region with physical interaction to the mitochondrial chaperone gene DNAJA3, which showed reduced expression in TT carriers. Furthermore, only individuals with the protective CC genotype exhibited a positive

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correlation between DNAJA3 and RAD21 expression, implicating allele-specific enhancer looping. Chromatin immunoprecipitation and knockdown experiments identified RBFOX2, a splicing regulator with chromatin-binding activity, as a key modulator. Loss of RBFOX2 led to reduced DNAJA3 expression. Luciferase assays demonstrated higher enhancer activity for the rs3747579-CC allele compared to the TT allele. **Conclusion:** Our data identify rs3747579-TT as a potential oncogenic variant that disrupts DNAJA3 expression via altered 3D enhancer interactions, contributing to the MASH to HCC transition. These findings emphasize the role of 3D genome architecture in gene regulation and suggest DNAJA3 as a novel therapeutic target for MASH-associated HCC.
Disclosures: Yuto Shiode: Nothing to Disclose, Xin Wei Wang: Nothing to Disclose, Ching-Wen Chang: Nothing to Disclose

◆ 1021 | GENOME-WIDE CRISPR SCREENING IDENTIFIES ACSL3 AS A KEY MEDIATOR OF LIPOTOXICITY AND ER STRESS IN MASH

Yuta Myojin[1] Takahiro Kodama[1] Hideharu Nagasawa[1] Ryo Takahashi[2] Kazuhiro Murai[1] Kosuke Yusa[3] Tomomi Hashidate-Yoshida[4] Hideo Shindou[4] Yoshinobu Saito[1] Hayato Hikita[1] Tetsuo Takehara[5], [1]Department of Gastroenterology and Hepatology, the University of Osaka, Graduate School of Medicine, [2]1Department of Gastroenterology and Hepatology, the University of Osaka, Graduate School of Medicine, [3]Stem Cell Genetics, Institute for Life and Medical Sciences, Kyoto University, [4]Department of Lipid Life Science, National Institute of Global Health and Medicine, Japan Institute, [5]Kansai Rosai Hospital

Background: The landscape of hepatocellular carcinoma (HCC) is shifting, with metabolic-associated steatohepatitis (MASH) emerging as a leading cause globally, replacing viral hepatitis. This shift parallels rising rates of obesity and metabolic syndrome. While a thyroid hormone receptor-β (THR-β) agonist was recently approved as a therapy for MASH, novel molecular targets—particularly those mediating lipotoxic hepatocyte death—are still required to address MASH progression and HCC risk. **Methods:** To identify novel regulators of lipotoxicity, we performed a genome-wide CRISPR-Cas9 knockout (KO) screen in Cas9-expressing HLF hepatocyte cells transduced with a lentiviral sgRNA library. Cells were cultured for 4 weeks under either (1) 200 μM palmitic acid (PA) to induce lipotoxic stress or (2) control medium. sgRNA representation was quantified by targeted sequencing, and gene enrichment was analyzed using MAGeCK. Top candidates were validated through gene knockout in HLF and primary human hepatocytes. Functional characterization included IncuCyte-based proliferation assays, real-time PCR, targeted lipidomics, RNA-seq, spatial transcriptomics (Visium), and analysis of public single-cell RNA-seq datasets. **Results:** The genome-wide screen identified ACSL3, INSIG1, and NF2 as significantly enriched in the PA-treated group. Among these, only ACSL3 KO conferred resistance to PA-induced cell death in both HLF cells and primary human hepatocytes. ACSL3 KO cells maintained proliferation under PA exposure, as visualized by real-time IncuCyte imaging, and exhibited minimal apoptosis, as assessed by flow cytometry. ACSL3 KO suppressed the PA-induced upregulation of GRP78, suggesting attenuation of endoplasmic reticulum (ER) stress. Targeted lipidomic profiling revealed reduced intracellular accumulation of saturated fatty acids, particularly palmitate, in ACSL3 KO cells. In parallel, quantitative PCR showed downregulation of genes involved in de novo lipogenesis. Together, these results indicate that ACSL3 promotes lipotoxic ER stress by enhancing intracellular saturated lipid accumulation. In human liver samples, bulk RNA-seq analysis demonstrated elevated ACSL3 expression in MASH livers compared to those with viral hepatitis. Visium spatial transcriptomics confirmed ACSL3 enrichment specifically in steatotic hepatocytes. Furthermore, public single-cell RNA-seq datasets revealed marked upregulation of ACSL3 in hepatocytes from patients with end-stage MASH, supporting its pathological relevance in human disease. **Conclusion:** ACSL3 drives saturated fatty acid–induced ER stress and hepatocyte death. Its consistent upregulation in advanced human MASH highlights ACSL3 as a promising therapeutic target to alleviate lipotoxicity and potentially prevent MASH-associated HCC.
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◆ 1022 | NUCLEAR TRANSLOCATION OF D-2-HYDROXYGLUTARATE DEHYDROGENASE (D2HGDH) DRIVES PROGRESSION OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

Xixuan Wang[1] Shuling Chen[2] Jing Fan[3] Hao Ren[4] Ruiqi Li[4] Jun Guo[2] Zihao Liang[2] Dandan Yin[2] TianHao Mao[3] Hongli Liu[4] Caiyun Zhang[3] Yuzheng Zhuge[5] Feng Zhang[5] Wei Chen[2] Changhua Yi[2] Qingfang Xiong[4] Jiangao Fan[6] Dawei Yang[2] Wei Zhang[5] YongFeng

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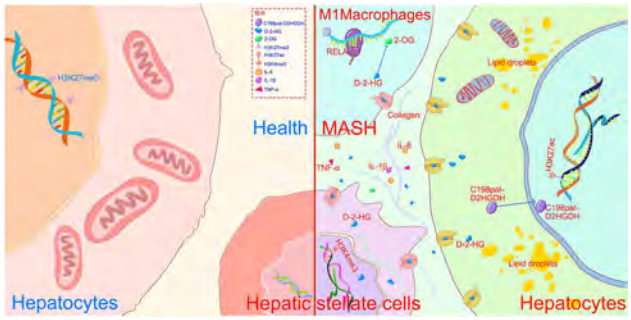
Background: Metabolic dysfunction-associated steatohepatitis (MASH) represents an advanced stage of metabolic dysfunction-associated steatotic liver disease (MASLD) characterized by hepatic steatosis, inflammation, and progressive fibrosis. **Methods:** Male C57BL/6J mice were fed a Gubra-Amylin NASH (GAN) diet (40% fat, 2% cholesterol, 20% fructose) for 12–32 weeks to model MASH progression. Liquid chromatography–mass spectrometry (LC-MS) and chiral-resolved LC-MS quantified D-2-hydroxyglutarate (D-2-HG) and 2-oxoglutarate (2-OG) levels in serum, urine, liver tissues, and conditioned media, validated via isotopic tracing with 13C-labeled glutamine/glucose. D2HGDH nuclear translocation was investigated via subcellular fractionation, acyl-biotin exchange (ABE) assays for palmitoylation, truncation/mutant constructs, and HDAC1 interaction analyses using co-immunoprecipitation (Co-IP) and AlphaFold-predicted structural modeling. Chromatin accessibility (ATAC-seq), histone modifications (CUT&Tag for H3K27ac/H3K4me3), and RNA m6A methylation assays were performed to assess nuclear D2HGDH-driven epigenetic reprogramming in hepatocytes and macrophages. Data were analyzed using GraphPad Prism (v9.0) with ANOVA, Tukey's post-hoc tests, and nonparametric alternatives where appropriate, ensuring reproducibility across biological replicates and clinical cohorts. **Results:** D-2-HG levels significantly increased in MASH patients and murine models, correlating with fibrosis severity and serving as a diagnostic biomarker for liver stiffness. Under lipotoxic stress, D2HGDH translocates to the nucleus via C198 palmitoylation, accumulates 2-OG, binds HDAC1, and shifts histone H3K27 modifications from methylation (H3K27me3) to acetylation (H3K27ac), activating lipogenic genes like ACC1. Hepatocyte-derived D-2-HG activates HSCs by inhibiting KDM2B-mediated H3K4me3 demethylation. D-2-HG polarizes macrophages toward a proinflammatory M1 phenotype via FTO-dependent m6A demethylation of RELA mRNA, stabilizing NF-κB transcripts and amplifying cytokine release. Pharmacological inhibition of D2HGDH palmitoylation or 2-OG supplementation reversed nuclear D2HGDH localization, suppressed lipid accumulation, and attenuated inflammation/fibrosis in vitro and in vivo. **Conclusion:** Nuclear D2HGDH and cytosolic D-2-HG create a feedforward loop—nuclear 2-OG drives epigenetic lipogenesis, while secreted D-2-HG exacerbates intercellular fibrosis and inflammation, defining a metabolite-centric mechanism in MASH pathogenesis.



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◆ 1023 | HEPATOCYTE-DERIVED ARGINASE-2 PROTECTS FROM METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Jeongowoo Park[1] Hui Han[1] Xiaodong Ge[1] Sai Santosh Babu Komakula[1] Nithyananthan Subramaniyam[1] Sukanta Das[1] Chao Wang[1] Wei Chen[1] Dipti Athavale[1] Abid Anwar[1] Dan Lantvit[1] Grace Guzman[1] Natalia Nieto[1], [1]University of Illinois at Chicago

Background: Arginase-2 (ARG2), the mitochondrial isoform of arginase, primarily catalyzes the hydrolysis of L-arginine. Emerging evidence suggests it also plays a role in mitochondrial bioenergetics. We previously reported that ARG2 induction in hepatocytes mediates the protective effects of SPP1^{high} macrophages in metabolic dysfunction-associated steatohepatitis (MASH). However, the contribution of hepatocyte-specific ARG2 loss to MASH progression and its underlying mechanisms remain unclear. **Methods:** To generate hepatocyte-specific *Arg2* knockout mice, we crossed *Arg2*$^{fl/fl}$ with *Albumin*-Cre mice. Male and female mice were fed a high-fat, high-fructose, high-cholesterol (HFHC) diet for six months to induce MASH. Control mice received an isocaloric diet with calories balanced through carbohydrates. **Results:** Bone marrow transplants revealed that *Spp1*$^{KI\ Mye}$ → *Alb*.Cre mice exhibited reduced steatosis, inflammation, and hepatocyte

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ballooning degeneration. However, no differences in MASH severity were observed between *Spp1*$^{KI\ Mye}$ → *Arg2*$^{\Delta Hep}$ and *Lyz2*.Cre → *Arg2*$^{\Delta Hep}$ mice. MASH progression was exacerbated in *Arg2*$^{\Delta Hep}$ mice, as indicated by increased hepatic steatosis, elevated liver triglycerides, serum cholesterol, and ALT levels, as well as enhanced monocyte infiltration. These mice also exhibited greater fibrosis, characterized by increased collagen type-I deposition and higher expression of *Col1a1* and *Acta2* mRNA. Metabolic dysregulation was further supported by the downregulation of key genes involved in fatty acid oxidation, including *Cpt1a*, *Cpt2*, and *Crat*. Mitochondrial dysfunction was evident, with reduced basal respiration and ATP production, accompanied by decreased expression of respiratory chain complex subunits: complex I (NADH:ubiquinone oxidoreductase), complex II (succinate dehydrogenase), and complex V (ATP synthase). Additionally, mitochondrial DNA copy number, as indicated by *Atp6*, *CoxII*, *Nd1*, and *Nd5*, was reduced. Mass spectrometry analysis revealed decreased hepatic acetyl-CoA levels and reduced concentrations of medium- to long-chain acyl-carnitines, including decanoyl-L-carnitine and oleoyl-L-carnitine. **Conclusion:** Loss of hepatocyte-specific ARG2 aggravates MASH by promoting lipid accumulation, monocyte infiltration, and fibrosis, in association with impaired mitochondrial fatty acid transport and reduced β-oxidation.

Disclosures: Jeongowoo Park: Nothing to Disclose, Hui Han: Nothing to Disclose, Xiaodong Ge: Nothing to Disclose, Sai Santosh Babu Komakula: Nothing to Disclose, Nithyananthan Subramaniyam: Nothing to Disclose, Sukanta Das: Nothing to Disclose, Chao Wang: Nothing to Disclose, Wei Chen: Nothing to Disclose, Dipti Athavale: Nothing to Disclose, Abid Anwar: Nothing to Disclose, Dan Lantvit: Nothing to Disclose, Grace Guzman: Nothing to Disclose, Natalia Nieto: Nothing to Disclose

◆ 1024 | SESTRIN 3 SUPPRESSES HEPATIC STELLATE CELL ACTIVATION AND LIVER FIBROSIS

Menghao Huang[1] X Charlie Dong[2], [1]Indiana University School of Medicine, [2]Indiana University

Background: Sestrin 3 (Sesn3) is a member of a conserved protein family characterized by three unique domain structures not found in other proteins across the proteome. Despite its known involvement in metabolic regulation, the role of Sesn3 in the pathogenesis of metabolic dysfunction-associated steatohepatitis (MASH) remains undefined. Hepatic fibrosis, a key pathological feature of MASH, arises from aberrant wound-healing responses and excessive extracellular matrix (ECM) deposition. Among the various liver cell types involved, hepatic stellate cells (HSCs) are the primary contributors to ECM accumulation. **Methods:** To investigate the role of Sesn3 in hepatic fibrosis, we generated HSC-specific Sesn3 knockout and transgenic mice and subjected them to a diet-induced MASH model. Liver phenotypes were assessed histologically and molecularly. Transcriptomic and proteomic analyses were conducted to identify pathways regulated by Sesn3. Fluorescence imaging was used to evaluate fibrogenic activity in primary HSCs and human HSC cell line LX-2 with Sesn3 deletion or overexpression. Co-immunoprecipitation assays were performed to identify Sesn3-interacting proteins. **Results:** HSC-specific deletion of Sesn3 significantly exacerbated hepatic fibrosis in response to the MASH diet, while transgenic overexpression of Sesn3 in HSCs conferred protection against fibrosis. Transcriptomic profiling revealed upregulation of ECM-related pathways, including the Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (Wwtr1/TAZ) pathway. Biochemical and cell biological analyses demonstrated that Sesn3 directly modulates YAP/Wwtr1 activity through protein-protein interactions, thereby influencing fibrogenic gene expression and ECM deposition. **Conclusion:** Sesn3 serves as a critical negative regulator of hepatic fibrosis by modulating the YAP/Wwtr1 signaling pathway in HSCs. These findings suggest Sesn3 as a potential therapeutic target for preventing or treating fibrosis in MASH.

Disclosures: Menghao Huang: Nothing to Disclose, X Charlie Dong: Nothing to Disclose

◆ 1025 | MULTI-ORGAN CROSSTALK VIA EXOSOMAL TCA CYCLE ENZYMES UNDERLIES METABOLIC BENEFITS OF EXERCISE AND DAYTIME TIME-RESTRICTED FEEDING IN MURINE MASH RESOLUTION

Xixuan Wang[1] Shuling Chen[2] Ruiqi Li[3] TianHao Mao[4] Jun Guo[2] Yang Wang[2] Zihao Liang[2] Caiyun Zhang[4] Hao Ren[1] Wei Chen[2] Changhua Yi[2] Qingfang Xiong[1] Dandan Yin[2] Dawei Yang[2] YongFeng Yang[1], [1]The Second Hospital of Nanjing, Medical School, Southeast University, [2]The Second Hospital of Nanjing, Affiliated to Nanjing University of Chinese Medicine, [3]The Second Hospital of Nanjing, Medical School, Southeast University, [4]Nanjing Key Laboratory of Hepatology, The Second Hospital of Nanjing

Background: Emerging evidence highlights the interplay between peripheral organs and hepatic metabolism in metabolic dysfunction-associated steatohepatitis (MASH), yet systemic mechanisms linking behavioral interventions to tissue repair remain unclear. **Methods:** We established a murine MASH model via 24-week GAN diet followed by 8-week

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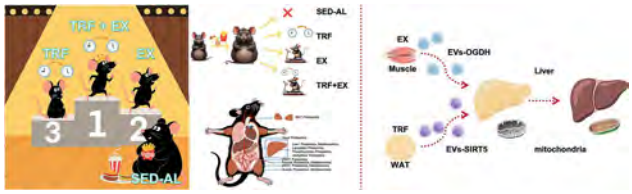
normal chow realimentation, with four intervention groups: sedentary ad libitum (SED-AL), exercise (EX), daytime time-restricted feeding (TRF), and EX +TRF. Body weight, insulin resistance, pathological staining of different organs, ultrastructure under electron microscope of different organs, and multi-omics of different organs were detected. **Results:** While both TRF and EX+TRF demonstrated superior weight loss, all active interventions ameliorated insulin resistance and hepatic steatosis. Strikingly, EX induced skeletal muscle damage and reduced adipocyte lipid droplet size, whereas TRF preferentially restored adipose morphology without myofiber injury. Ultrastructurally, EX uniquely rescued hepatic mitochondrial cristae disruption in MASH. Multi-omics integration revealed profound TCA cycle rewiring across liver, muscle, and adipose tissues, with phospho-/acetyl-/lactyl-proteomics implicating post-translational regulation of metabolic enzymes. Mechanistically, exercise triggered skeletal muscle secretion of citrate synthase (CS), IDH3, and OGDH via exosomes, which restored hepatic mitochondrial energetics and attenuated lipid peroxidation. Conversely, TRF stimulated adipose-derived exosomes enriched with phosphorylated/acylated TCA modifiers, synergistically enhancing hepatic metabolic flexibility. **Conclusion:** Our findings establish a novel paradigm of inter-organ communication through exosomal enzyme trafficking, positioning combined chrono-exercise therapy as a systems-level strategy for MASH resolution.



Disclosures: Xixuan Wang: Nothing to Disclose, Shuling Chen: Nothing to Disclose, Ruiqi Li: Nothing to Disclose, TianHao Mao: Nothing to Disclose, Jun Guo: Nothing to Disclose, Yang Wang: Nothing to Disclose, Zihao Liang: Nothing to Disclose, Caiyun Zhang: Nothing to Disclose, Hao Ren: Nothing to Disclose, Wei Chen: Nothing to Disclose, Changhua Yi: Nothing to Disclose, Qingfang Xiong: Nothing to Disclose, Dandan Yin: Nothing to Disclose, Dawei Yang: Nothing to Disclose, YongFeng Yang: Nothing to Disclose

1026 | URIDINE HOMEOSTASIS IS IMPAIRED IN OBESITY AND MASLD AND AFFECTS FATTY ACID METABOLISM

Ozzy Ayebo[1] Montana Bilger[2] Michael Boerrigter[2] Yongbin Chen[3] Peyton Classon[3] Guillermo Delgado Aparicio[2] Rondell Graham[3] Davide Povero[3], [1]Mayo Clinic, [2]DeepSpace Biology, [3]Mayo Clinic Rochester

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common chronic liver disease. Disruption of uridine level are associated with obesity and MASLD. However, how uridine regulates fatty acid metabolism remains largely unknown. Our goal is to elucidate how uridine influences fatty acid flux during obesity and MASLD development. **Methods:** Human and murine hepatocytes were treated with fatty acid mix with or without uridine. Fatty acid metabolism was assessed by lipidTOX, Seahorse Mito Stress test and immunoblotting. Male C57BL/6 mice were fed a chow or obesogenic high fat, fructose and cholesterol (FFC) diet for 8 weeks and received uridine (50 mg/kg) or vehicle for 3 weeks. Liver, adipose tissue, plasma and muscle were harvested for further analysis. Metabolic and molecular profiling were assessed by multi-omics analysis, histological, and molecular assays. **Results:** Liver uridine levels decreased with disease progression in murine MASLD ($p < 0.03$). Uridine synthesis enzyme UMPS was significantly depleted in human MASLD as compared to normal livers ($p < 0.002$). In vitro, UMPS knockdown in HepG2 cells reduced cellular uridine levels, increased accumulation of lipid droplets, and impaired mitochondrial respiration which was restored by exogenous uridine treatment. In vivo, uridine-treated FFC-fed mice (FFC +uridine) significantly increased energy expenditure, ambulatory activity, respiratory exchange and metabolic rate without affecting food and water intake, as compared to control mice. In FFC-fed mice, uridine reduced body, liver and adipose tissue weight. This was associated with a marked reduction of liver and muscle steatosis in FFC+uridine mice. Liver phospho-proteomics analysis identified large abundance of proteins involved in fatty acid catabolism and storage in FFC +uridine mice. Conditioned media of mouse adipose tissue from FFC mice with or without uridine treatment, cultured ex vivo for 24 hours, identified differential enrichment of bioactive mediators involved in adipose tissue lipolysis and obesity, such as resistin and GDF15. Lastly, treatment of mouse hepatocytes with FFC-vehicle adipose tissue conditioned media significantly impaired mitochondrial metabolism, which was restored by exposure to FFC+uridine adipose tissue conditioned media. **Conclusion:** Uridine directly or indirectly regulates anorexigenic response, energy metabolism and fatty acid storage, thus identifying novel targets for MASLD and obesity treatment.

Disclosures: Ozzy Ayebo: Nothing to Disclose, Montana Bilger: Nothing to Disclose, Michael Boerrigter: Nothing to Disclose, Yongbin Chen: Nothing to Disclose, Peyton Classon: Nothing to Disclose, Guillermo Delgado Aparicio: Nothing to Disclose, Rondell Graham: Astellas Pharma: Reseach - funds to institution,

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BioNTech: Advisory board, Daiichi Sankyo: Advisory board, Davide Povero: Nothing to Disclose

1027 | INHIBITION OF BRUTON'S TYROSINE KINASE IN MACROPHAGE ALLEVIATES METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE BY SUPPRESSING IL-6/JAK2/STAT3/SOCS3 PATHWAY

Shiwei Chen[1] Jingkang Zhang[2] Baode Chen[1] Cheng Zhou[2] Min Zheng[3], [1]The first Affiliated Hospital, College of Medicine, Zhejiang University, [2]Zhejiang University, [3]The First Affiliated Hospital,College of Medicine, Zhejiang University

Background: Metabolic dysfunction associated steatotic liver disease (MASLD) is the most prevalent liver disease currently characterized by hepatic steatosis and metabolic inflammation. Bruton's tyrosine kinase (BTK) is a crucial immune target for various inflammatory diseases and metabolic disorders. However, the role of BTK in MASLD still deserves further study. **Methods:** MASLD mouse model was induced by high-fat-diet (HFD). The expression and activation of BTK in the liver were compared between MASLD mouse and the control. BTK inhibitor, BTK knockout and myeloid-conditional BTK knockout mice were ultilized to observe the effect of BTK on mouse MASLD. Further, the molecular mechanism was investigated in the co-culture system composed of macrophage and hepatocyte in vitro. Flow cytometry, western blot, ELISA, qPCR, energy metabolism monitoring system were used in this research. **Results:** BTK was significantly activated (phosphorylated) in MASLD mouse liver. Both pharmacological inhibitor and gene knockout of BTK could markedly attenuate the hepatic steatosis and inflammation, increase oxygen consumption and energy consumption in MASLD mouse. Among various immune cell subsets in mouse liver, BTK in macrophage was enhanced most significantly after HFD-feeding, suggesting that BTK in macrophages plays a major role in the pathogenesis of MASLD. Thus, mouse with BTK depletion in macrophage was established and showed less hepatic steatosis and inflammation compared to the control after HFD-feeding. Mechanically, inhibition of BTK reduced the recruitment of macrophage in MASLD mouse liver, as well as skewed the polarization of macrophage toward M2 phenotype, and inhibited the release of proinflammatory cytokines (especially IL-6). In the co-culture system composed of macrophage and hepatocyte in vitro, inhibition of BTK inhibitor significantly reduced the secretion of IL-6 from macrophage, further suppressed the phosphorylation of JAK2/STAT3 and decreased the expression of SOCS3 in hepatocyte, resulting in the reduction of the lipid deposition and triglyceride (TG) content in hepatocyte. **Conclusion:** Inhibition of BTK in macrophage alleviated MASLD via reducing IL-6 secretion from macrophage and further suppressing JAK2/STAT3/SOCS3 signaling pathway in hepatocyte. Therefore, BTK in macrophage might be a valuable therapeutic target for MASLD.

Disclosures: Shiwei Chen: Nothing to Disclose, Jingkang Zhang: Nothing to Disclose, Baode Chen: Nothing to Disclose, Cheng Zhou: Nothing to Disclose, Min Zheng: Nothing to Disclose

1028 | HEPATIC DELETION OF THE WNT MODULATORS ZNRF3/RNF43 REVERSES METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Tianliang Sun[1] Federico Di Tullio[1] SUE YANG[2] Shamsa Roshan[2] Joana Almeida[2] Abigail Glezer[2] Jonathan Conrad[2] Siddarth Vinod Kumar[2] Shahina Saeed[2] Marina Barcena-Varela[2] Anthony Lozano[2] Lianyong Su[3] Derrick Zhao[3] Emily Bramel[2] Amaia Lujambio[2] Huiping Zhou[3] Sai Ma[2] Lida Yang[2] Bruno Cogliati[2] Scott Friedman[4], [1]Icahn School of Medicine at Mount Sanai, [2]Icahn School of Medicine at Mount Sinai, [3]Virginia Commonwealth University, [4]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Metabolic-associated steatohepatitis (MASH) is a leading cause of liver failure and hepatocellular carcinoma (HCC), yet effective therapies remain limited. MASH is marked by steatosis, inflammation, fibrosis, and impaired regeneration. The liver's remarkable regenerative capacity is compromised in MASH. Enhancing regeneration without triggering tumorigenesis could represent a novel therapeutic strategy. ZNRF3 and RNF43 are negative regulators of β-Catenin, a key mediator of liver regeneration, metabolism, inflammation, and fibrosis. However, their role in MASH regression remains unknown. **Methods:** MASH was induced using two models: the fibrosis and tumor (FAT)-MASH model (Western diet combined with low-dose CCl_4) or the Gubra Amylin (GAN) MASH diet. Hepatocyte-specific deletion of ZNRF3/RNF43 was achieved via AAV8-TBG-Cre; AAV8-TBG-GFP served as control. Phenotypic regression was assessed through histological analyses (Oil Red O, H&E, Sirius Red), immunostaining (GS, Ki-67, CYP2E1), and serum ALT. RNA-seq, qPCR, and LC-MS/MS were used to identified metabolic drivers of regression. **Results:** Short-term deletion of ZNRF3/RNF43 in hepatocytes robustly reversed key features of established MASH, including steatosis, inflammation, and fibrosis. The improved liver regeneration occurred without altering liver-to-body weight ratios, without redistributing lipid to other tissues, and were not

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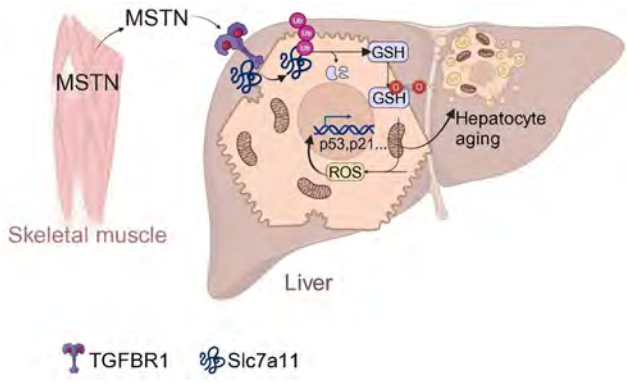
associated with increased incidence of HCC during the study period. Mechanistically, MASH regression was dependent on β-catenin activation. This activation selectively drove upregulation of the alternative bile acid synthesis pathway, specifically increasing expression of *Cyp27a1* and *Cyp7b1*, and expanding the chenodeoxycholic acid (CDCA)-derived bile acid pool. These changes were accompanied by improved bile acid and lipid transport and metabolic handling. Importantly, ZNRF3/RNF43 deletion did not increase tumor burden when compared to β-catenin gain-of-function mutants co-expressing c-Myc via hydrodynamic tail vein injection (HDTVI), nor did it promote HCC progression in the FAT-MASH-HCC model. **Conclusion:** Transient, hepatocyte-specific deletion of ZNRF3/RNF43 reverses MASH via β-catenin-dependent activation of the alternative bile acid synthesis pathway. This regenerative approach effectively reduces MASH pathology without promoting HCC, representing a promising and safe therapeutic strategy.
Disclosures: Tianliang Sun: Nothing to Disclose, Federico Di Tullio: Nothing to Disclose, SUE YANG: Nothing to Disclose, Shamsa Roshan: Nothing to Disclose, Joana Almeida: Nothing to Disclose, Abigail Glezer: Nothing to Disclose, Jonathan Conrad: Nothing to Disclose, Siddarth Vinod Kumar: Nothing to Disclose, Shahina Saeed: Nothing to Disclose, Marina Barcena-Varela: Nothing to Disclose, Anthony Lozano: Nothing to Disclose, Lianyong Su: Nothing to Disclose, Derrick Zhao: Nothing to Disclose, Emily Bramel: Nothing to Disclose, Amaia Lujambio: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Huiping Zhou: Nothing to Disclose, Sai Ma: Nothing to Disclose, Lida Yang: Nothing to Disclose, Bruno Cogliati: Nothing to Disclose, Scott Friedman: Nothing to Disclose

1029 | MUSCLE DRIVEN MSTN CONTRIBUTES TO MASLD PROGRESSION VIA HEPATOCYTE SENESCENCE

Jie Li[1], [1]*Department of Infectious Diseases, Nanjing Drum Tower Hospit*

Background: Recent studies suggest that the alterations in skeletal muscle may contribute to the pathogenesis of metabolic dysfunction-associated steatohepatitis (MASH). Myokines, a type of bioactive peptides released by skeletal muscle, play a pivotal role in regulating peripheral tissues, especially the liver. Among them, myostatin (MSTN) has emerged as a critical regulator of muscle mass and hepatic metabolism. However, its specific role and underlying mechanisms in MASH development remain unclear. **Methods:** MASH was induced in mice using high-fat, high-fructose diet (HFHFD) and choline-deficient, amino acid-restricted, high-fat diet (CDAHFD). Muscle-specific MSTN knockdown was achieved using an adeno-associated virus 8 (AAV8) system. MSTN expression in the serum of MASH patients was assessed via Elisa. The role of MSTN in MASH progression was investigated using recombinant MSTN protein and co-cultures of C2C12 muscle cells and primary mouse hepatocytes. Additionally, RNA sequencing was employed to analyze the impact of MSTN on the hepatocyte transcriptome. **Results:** The expression of MSTN was significantly elevated in both the muscle tissue and serum of MASH patients, but showed no notable changes in the liver. Further analysis demonstrated a positive correlation between circulating MSTN levels and both hepatic inflammation and alanine aminotransferase. Skeletal muscle-specific knockdown of MSTN significantly inhibited the progression of HFHFD- and CDAHFD-induced MASH. RNA-sequencing suggested that recombinant MSTN protein may accelerate hepatocyte senescence and promote MASH progression by regulating solute carrier family 7 member 11 (SLC7A11)-mediated glutathione metabolism. Recombinant MSTN protein induced ubiquitination-dependent degradation of SLC7A11 in a dose-dependent manner. Conversely, SLC7A11 overexpression significantly alleviated MSTN-induced hepatocyte steatosis, inflammation, and senescence, accompanied by reduced reactive oxygen species (ROS) accumulation, elevated glutathione levels, and restored mitochondrial maximal respiration rate. **Conclusion:** The crosstalk between muscle and liver indicated that reducing muscular MSTN expression alleviated the severity of liver damage under the context of MASH. MSTN secreted from muscular may represent a promising therapeutic strategy for treating MASH.



Disclosures: Jie Li: Nothing to Disclose

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1030 | BILE ACID DYSREGULATION AND LOSS OF HEPATIC POLARITY AT EARLY STAGES DRIVES MASLD PROGRESSION

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Background: Bile acid metabolism dysregulation and subtle micro-cholestatic features are often observed in patients with Metabolism dysfunction associated steatotic liver disease (MASLD). The mechanistic role of bile acid metabolism dysregulation in MASLD pathogenesis remains unclear. **Methods:** We performed a comprehensive RNA transcriptomic and lipidomic analysis on spectrum of MASLD patients (n = 140) to identify key bile acid metabolism and hepatocyte function genes that are differentially regulated across the disease spectrum. Then we leverage on bio-engineered iPSC derived 2.5D hepatic tri-culture model – HepaSin, comprising of hepatocytes (iHeps), stellate cells (iHSCs), and Kupffer cells (iKCs) to dissect the functional role of key genes in disease progression. Further, we explore strategies reinforcing hepatocellular polarity and bile acid homeostasis to ameliorate MASLD progression before irreversible liver damage occurs. **Results:** Clinical RNA transcriptomic and lipidomic analysis on MASLD patients (n = 140) revealed that bile acid dysregulation is associated with loss of hepatic polarity and function at early stages of MASLD. We show that lipid accumulation at early stages reduces the cortical tension and disrupts the tight junction E-cadherin/β-catenin complex. Failing to re-establish cortical tension and loss of E-cadherin/β-catenin complex impairs hepatocyte polarity and bile canaliculi integrity causing dysregulated bile acid transport and intracellular accumulation of bile acids (↑CYP7A1). Accumulation of 12α-hydroxylated bile acids, especially deoxycholic acid (DCA), further exacerbates MASLD progression through impaired FXR activation and increased lipoptoxicity. Restoring hepatocyte polarity at early stages improved hepatocyte function and rescued from MASLD progression in vitro. **Conclusion:** Lipid accumulation induced disruption of cortical tension causes bile metabolism dysregulation causing micro-cholestasis condition at early stages of MASLD. Elevated intracellular accumulation of bile acids and Impaired bile metabolism exacerbates MASLD progression. Restoring hepatic polarity rescues bile acid toxicity and improves MASLD progression. Thus stratergies reinforcing hepatic polarity can be explored as therapeutic stratergy to treat MASLD.

Disclosures: Kartik Mitra: Nothing to Disclose, Mark Muthiah: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Yu Hanry: Nothing to Disclose, Zixuan Zhang: Nothing to Disclose, Farah Tasnim: Nothing to Disclose, Peter Low: Nothing to Disclose

1031 | CHRONIC NANOPLASTIC EXPOSURE PROMOTES METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE PROGRESSION VIA HEDGEHOG SIGNALING

Jinsol Han[1] Hayeong Jeong[1] Youngmi Jung[1], [1]Pusan National University

Background: Nanoplastics (NPs), plastic particles less than 1 μm, are a global pollution problem. Chronically exposed NPs accumulate in various organs including kidney, adipose tissue and liver. Recently studies have reported that deposited NPs adversely affect lipid metabolism in the liver. Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common metabolic disorder featured by abnormal fat accumulation in the liver. Despite rising concerns about chronic NP exposure and MASLD, the mechanisms by which NPs contribute to the development and progression of MASLD remain poorly understood. Herein, we investigated the pathophysiological effects of NPs in MASLD and elucidated the underlying mechanism. **Methods:** To assess the effect of hepetocytes injured by NP and lipotoxicity on hepatic stellate cells (HSCs), primary HEPs (pHEPs) isolated from healthy male mice were treated with 100 μg/mL of 100nm sized-NPs and 50 μM palmitic acid (PA). Conditioned media (CM) from pHEP treated with both NPs and PA ted pHEPs was subsequently given to quiescent pHSCs. To evaluate in vivo impact of NPs in MASLD progression, mice were administered either vehicle or NPs via drinking water while being fed a choline-deficient, L-amino acid-defined high-fat diet (CDAHFD) for 12 weeks. At the end of the treatment period, mice were sacrificed to collect blood and liver samples. **Results:** NPs exacerbated PA-induced hepatocyte damage and significantly elevated the production of Sonic Hedgehog (SHH), a ligand in the Hh pathway. pHSCs cultured in CM from NPs+PA-treated pHEPs showed increased proliferation compared to those cultured in CM from PA-treated pHEPs. In pHSCs exposed to CM from NPs+PA-given pHEPs, levels of

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Smoothened (SMO), a receptor in the Hh pathway, and GLI2, a transcriptional activator, were remarkably upregulated, along with increased expression of fibrotic markers, compared to the PA group. In mice fed CDAHFD, chronic NP exposure markedly upregulated SHH and GLI2 expression in liver tissues. GLI2-positive cells were more apparent in the livers of mice treated with NPs+CDAHFD than in other groups. pHEPs from the NPs+CDAHFD group also showed significantly increased SHH expression, and pHSCs from these mice had upregulated SMO and GLI amount relative to other groups. **Conclusion:** These findings demonstrate that chronic NP exposure increases vulnerability to MASLD progression by promoting Hh signaling, suggesting that NPs are a deleterious factor contributing to the development and progression of MASLD.

Disclosures: Jinsol Han: Nothing to Disclose, Hayeong Jeong: Nothing to Disclose, Youngmi Jung: Nothing to Disclose

1032 | REGULATORY T (TREG) CELL DEPLETION AMELIORATES HCC PROGRESSION IN MASH BY RESTORING ANTI-TUMOR INNATE AND ADAPTIVE IMMUNE RESPONSES

Joanna Picó[1] Amalia Tzoumpa[2] Yin Huang[2] Beatriz Lozano-Ruiz[2] Pedro Zapater[2] Jose Antonio Gomez-Sanchez[3] José Manuel González-Navajas[2], [1]University of Miguel Hernández (ISABIAL-IDIBE), [2]CIBER, ISABIAL, [3]ISABIAL

Background: Regulatory T cells (Tregs) promote immune tolerance and support tumor immune evasion. Despite being studied in many tumors, their role in metabolic dysfunction-associated steatohepatitis (MASH)-associated HCC remains poorly understood. With the rising incidence of MASH-HCC and limited efficacy of immune checkpoint inhibitors (ICIs) in this context, likely due to heightened immunosuppression, identifying new therapeutic targets is critical. Understanding Tregs interactions with immune cells may uncover resistance mechanisms and guide novel interventions. **Methods:** An orthotopic HCC model with underlying MASH (MASH-HCC) was established in male DTR-Foxp3 mice. To induce MASH, mice were fed a Western Diet (WD; high in fat, cholesterol, and sucrose) for 24 weeks, or maintained on a standard chow diet (CD; CD-HCC). At week 22, Hep53.4 murine cells were orthotopically injected. One week later, Tregs were selectively depleted via intraperitoneal administration of diphtheria toxin (DT; 6.25μg/Kg, twice weekly for 2 weeks), while control mice received vehicle. At week 25, tumor burden was measured, and tumor and blood samples were collected for flow cytometry and histological analysis. Treg depletion was confirmed by flow cytometry. **Results:** Treg depletion led to a significant reduction in tumor volume ($p = 0.04$) and weight ($p = 0.02$) in mice with MASH-HCC (WD+DT), but not in CD-HCC mice (CD+DT). In the tumor microenvironment, NK cells increased significantly only in WD+DT mice ($p = 0.03$), as did IFNγ expression by NK ($p = 0.02$), $CD4^+$ ($p = 0.03$), and $CD8^+$ T cells ($p = 0.001$), with no changes in CD-fed mice. Similarly, blood NK and NKT cell frequencies rose after Treg depletion in WD-fed mice ($p = 0.01$; $p = 0.004$), suggesting a stronger Treg-mediated suppression in the MASH-HCC setting. In contrast, CD-HCC tumors showed higher levels of macrophages ($p = 0.03$) and M1-like tumor-associated macrophages (TAMs) ($p = 0.03$) in the absence of Tregs, which were unaffected in the WD group. CD+DT mice also showed an increase in monocytic myeloid-derived suppressor cells (M-MDSCs) ($p = 0.047$), pointing to a potential compensatory suppressive mechanism. Finally, although total dendritic cells (DCs) remained unchanged, WD+DT mice displayed a selective rise in cDC1 ($p = 0.01$) and a reduction in cDC2 ($p = 0.02$), not observed in CD-fed counterparts. **Conclusion:** Our findings emphasize the immunosuppressive role of Tregs in MASH-HCC, impairing both innate and adaptive anti-tumor responses. These results highlight Tregs as a promising therapeutic target. Further experiments are underway to dissect their suppressive mechanisms and assess the effect of their depletion in combination with ICIs in MASH-HCC.

Disclosures: Joanna Picó: Nothing to Disclose, Amalia Tzoumpa: Nothing to Disclose, Yin Huang: Nothing to Disclose, Beatriz Lozano-Ruiz: Nothing to Disclose, Pedro Zapater: Nothing to Disclose, Jose Antonio Gomez-Sanchez: Nothing to Disclose, José Manuel González-Navajas: Nothing to Disclose

1033 | LACTYLATION OF FATP2 EXACERBATES THE PROGRESSION OF MASH BY INHIBITING THE PGC1A/PPAR SIGNALING PATHWAY

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), defined as ectopic lipid accumulation in hepatocytes without excessive alcohol consumption and viral infections, is the most prevalent liver disease worldwide, yet few effective therapies are available. Recently, intracellular lactate is reported to drive a novel type of posttranslational modification,

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lysine lactylation (Kla); however, whether lactylation is involved in MASLD development remains unknown. **Methods:** Lactate modification proteomics is used to identify differentially expressed proteins with lactate modification sites in the MASH model mice. To validate the role of lactylation-modified FATP2 in the progression of MASH by constructing hepatocyte-specific knockout FATP2 mice. Immunoprecipitation and Western blotting were used to validate the lactylation modification site and downstream targets of FATP2 in vitro. **Results:** In this study, by using lactylation modification proteomics, we identified 128 proteins and 199 lactylation modification sites. Among these lactylation sites, we verified that lactylation at K572 in fatty acid transport protein 2 (FATP2) facilitated lipogenesis and reduced fatty acid beta-oxidation in hepatocytes. Interestingly, compared with littermate controls (*Slc27a2$^{f/f}$, Slc27a2* gene encodes FATP2), hepatocyte-specific *Slc27a2* deficient mice (*Slc27a2$^{\triangle hep}$*) mice were more resistance to metabolic dysfunction-associated steatohepatitis (MASH) diet-induced steatosis and fibrosis. Mechanistically, lactylation of FATP2 inhibited the expression of PPAR downstream target genes by downregulating PGC1α expression, thereby reducing fatty acid beta-oxidation and promoting lipid accumulation. **Conclusion:** Overall, our study reveals lactylation plays an important role in the development and progression of MASLD. Targeting FATP2 lactylation may provide a novel therapeutic target for MASH.
Disclosures: Jiaxin Tan: Nothing to Disclose, man Li: Nothing to Disclose, Yong He: Nothing to Disclose

1034 | COMMON REGULATORY MECHANISMS FOR HEPATOCYTE STATE TRANSITIONS ARE DEFECTIVE IN ALCOHOL-RELATED AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Alcohol-related liver disease (ALD) and MASLD, top causes of steatotic liver disease (SLD), are progressive conditions marked by hepatocyte (Hep) lipotoxicity, inflammation and impaired regeneration, often leading to liver failure. As SLDs advance, mature Heps decline, immature Heps accumulate and liver functions deteriorate. This suggests that SLDs progress when mechanisms orchestrating state transitions in Heps are dysregulated. The Hedgehog pathway (Hh) controls Hep fate and regenerative responses. We reported that depleting Smo (an essential Hh component) in mature Heps induced iron-dependent lipid peroxidation (ferroptotic stress) that triggered Hep senescence, stalled regeneration and sensitized mice to MASLD. Here, we investigated the role of Hep Hh activity in ALD. **Methods:** We analyzed liver single nucleus RNA sequencing data from controls and patients with advanced ALD (alcohol cirrhosis, AC, or hepatitis, AH) for SMO expression, senescence, and ferroptosis signatures. Senescent Heps (ScHeps) were quantified across disease states and stratified by SMO status. Pathway analysis was done on SMO(−) Heps. Liver steatosis, injury, inflammation, and markers of immature Heps were compared in Hep-specific Smo-KO and control mice fed Lieber-DeCarli ethanol diets. **Results:** SMO-expressing Heps decreased in advanced human ALD. ScHeps increased accordingly (2.8% in controls, 34.9% in AC and 62.2% in AH). Notably, only 2.4% of ScHeps expressed SMO, while 97.6% were SMO(−). The ferroptosis marker score was also enriched in SMO(−) Heps, confirming the strong association between decreased SMO, senescence and ferroptotic stress. ScHeps promote maladaptive repair. Pathway enrichment analysis of SMO(−) Heps revealed activation of pro-inflammatory and stress response pathways; pathways involved in mitochondrial function, oxidative phosphorylation, and bile acid metabolism were downregulated. Smo-KO mice were more sensitive to ALD, exhibiting worse hepatic triglyceride accumulation, enhanced Oil Red O staining, increased Tnfα/Il1β expression, more F4/80(+) macrophages and greater accumulation of cells with immature Hep markers. **Conclusion:** Hep Hh signaling inhibits lipotoxicity and inflammatory stress responses that restrict Hep maturation and proliferative capacity. This enables regeneration during ALD. Coupled with prior MASLD data, these results indicate that SLDs progress when conserved mechanisms that control state transitions in Heps are dysregulated.
Disclosures: Rajesh Dutta: Nothing to Disclose, Seh-Hoon Oh: Nothing to Disclose, Kuo Du: Nothing to Disclose, David Umbaugh: Nothing to Disclose, Auinash Kalsotra: Nothing to Disclose, Anna Mae Diehl: Nothing to Disclose

1035 | TM6SF2-DRIVEN MASH RESISTANCE TO RESMETIROM; SNP REVERSION RESTORES EFFICACY

Chih Ling Chung[1] Shahrbanoo Keshavarz-Aziziraftar[1] Mohammad Mehraban[1] Luis Jasper[1] Yuanyuan Qin[2] Elizabeth Theusch[1] Marisa Medina[2], [1]University of California San Francisco, [2]University of California, San Francisco

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), are rising in global prevalence, posing a

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growing public health challenge. The 2024 FDA approval of resmetirom, a selective thyroid hormone receptor-β (THR-β) agonist, represents the first pharmacological advance for MASH. However, clinical data reveal suboptimal responses in a large majority of patients, suggesting a role for genetic variability in therapeutic outcomes. **Methods:** We established MASH models using human patient-derived induced pluripotent stem cells (iPSCs) and iPSC-derived hepatocytes (iPSC-Heps). iPSCs were differentiated to iPSC-Heps over 23 days using our published protocol. In vitro assays using oleate challenge were established and cells were stained with Nile Red, imaged and quantified. Data were analyzed by Prism with statistical analysis. **Results:** Resmetirom reduced oleic acid–induced steatosis in non-carrier iPSC-iHeps but showed dramatically diminished efficacy in TM6SF2 rs58542926 (E167K) carrier MASH-derived iPSC-Heps. TM6SF2 rs58542926 (E167K) SNP reversion restored resmetirom's intracellular lipid-lowering activity, with similar effects in double-reverted iHeps (TM6SF2 rs58542926 and SUGP1 rs10401069 both reverted to non-carrier). **Conclusion:** Our findings highlight the influence of genetic background on resmetirom response and underscore the potential for precision medicine or combinatorial therapies to optimize treatment in MASH. Our data also suggests that genotyping patients may play a strong role in therapy selection. Furthermore, carriers of TM6SF2 rs58542926 may require different theraapeutic approaches.

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1036 | MIR-432-MEDIATED REGULATION OF TM6SF2 IN MASLD: A TARGETED MIR-MASK STRATEGY FOR RESTORING HEPATIC LIPID HOMEOSTASIS

Mohammad Mehraban[1] Shahrbanoo Keshavarz-Aziziraftar[1], [1]University of California San Francisco

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects ~25% of the global population and increasingly burdens healthcare systems. The TM6SF2 rs58542926 (E167K) SNP is a known genetic driver of MASLD progression to steatohepatitis (MASH), impairing TM6SF2 function and promoting hepatic lipid accumulation, inflammation, and fibrosis. Our recent findings reveal that this SNP introduces a novel binding site for miR-432, enabling miRNA-mediated degradation of TM6SF2 mRNA and reducing protein expression. **Methods:** To test novel therapeutic approaches we tested backbone stabilized oligonucleotides to either directly inhibit miR-432 or miR-mask oligonucleotides designed to interfere with microRNA recognition of the TM6SF2 rs58542926 site by miR-432 specifically. Using patient-derived iPSC-derived hepatocytes we tested the efficacy of our oligonucleotides to block binding, restore TM6SF2 RNA and protein levels. We further tested functional restoration of activity by reducing intrahepatic steatosis in unchallenged and oleate challenged iHeps. **Results:** We designed a miR-mask—an oligonucleotide that blocks the miR-432 binding site on TM6SF2 mRNA without interfering with endogenous miR-432 function. Using iPSC-derived hepatocytes (iHeps), we observed a dose-dependent increase in TM6SF2 mRNA expression, with up to a 22-fold rise upon miR-mask treatment. We also confirmed TM6SF2 protein level restoration via western-blot analysis. Functionally, miR-mask application reduced lipid accumulation in oleate-treated iHeps, indicating restored TM6SF2 activity. Importantly, overall miR-432 levels remained unchanged, preserving its effects on other targets. **Conclusion:** Unlike traditional antisense oligonucleotides (ASOs) that suppress miRNAs broadly, miR-masks offer allele-specific precision by selectively protecting target mRNAs. This minimizes off-target effects and maintains cellular homeostasis. These findings present a novel therapeutic strategy for SNP carriers by stabilizing TM6SF2 expression and improving hepatic lipid metabolism without disrupting native miRNA networks.

Disclosures: Mohammad Mehraban: Nothing to Disclose, Shahrbanoo Keshavarz-Aziziraftar: Nothing to Disclose

1037 | HETEROZYGOUS FADS2 DELETION EXACERBATES HFHC DIET–INDUCED STEATOHEPATITIS VIA ALTERATIONS IN PHOSPHOLIPID AND CERAMIDE METABOLISM

Kazuyoshi Kon[1] Heyon-Cheol Lee-Okada[2] Kumiko Arai[1] Shunsuke Ikejima[1] Kyoko Fukuhara[1] Reiko Yaginuma[1] Kei Ishizuka[1] Hiroo Fukada[1] Akira Uchiyama[1] Shunhei Yamashina[1] Takehiko Yokomizo[2] Kenichi Ikejima[1], [1]Juntendo University Graduate School of Medicine, [2]Juntendo University School of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) develops due to both genetic predisposition and acquired factors such as aging, overeating, and obesity; however, the underlying mechanisms remain incompletely understood. We previously demonstrated that aged mice exhibit more severe diet-induced steatohepatitis due to decreased expression of fatty acid

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desaturase 2 (FADS2) (Ishizuka et al., J Gastroenterol Hepatol, 2020). Here, we aimed to investigate how FADS2 downregulation affects steatohepatitis using FADS2 heterozygous knockout (FADS2$^{+/-}$) mice. **Methods:** Male FADS2$^{+/-}$ and wild-type C57BL/6 (BL6) mice were fed either a high-fat, high-cholesterol (HFHC) or control diet for 8 weeks. Hepatic mRNA/protein expression was analyzed by RT-PCR and Western blotting. Liver fibrosis was assessed via Sirius Red staining. Lipidomics was performed using LC-MS. **Results:** Under control diet, liver histology in FADS2$^{+/-}$ mice was comparable to that in BL6 mice. In contrast, HFHC-fed FADS2$^{+/-}$ mice showed marked macrovesicular steatosis and pericellular fibrosis, with serum ALT levels significantly increased to 151 $\pm$ 30 IU/L vs. 71 $\pm$ 15 IU/L in BL6 mice. Hepatic TNFα, CCL2, and CXCL10 were over 2–3-fold higher in FADS2$^{+/-}$ mice. HO-1 expression also doubled. Fibrosis markers (PDGFβ, TGFβ1, type I collagen, TIMP1) were significantly elevated in FADS2$^{+/-}$ mice. Lipidomics revealed reduced levels of PUFA-containing phospholipids (PE 16:0/20:4, 16:0/22:6, 18:0/20:4, 20:4/16:1) and lysophospholipids (LPC sn-2 20:4, sn-2 20:3). In contrast, DAGs containing 16:0, 18:1 and TAGs containing 16:0, 16:1, 18:1 were significantly increased. Ceramide d18:1/24:1 and lactosylceramide d18:1/24:1 were upregulated, whereas sphingomyelins d18:1/20:0, 22:0–24:0 were decreased. These findings indicate a shift in ceramide metabolism from sphingomyelin toward the glycosphingolipid pathway. **Conclusion:** In FADS2$^{+/-}$ mice fed an HFHC diet, reduced PUFA-containing phospholipids and elevated SFA/MUFA-rich DAGs and TAGs likely enhanced lipotoxicity. In addition, altered ceramide metabolism appears to promote macrophage and stellate cell activation. FADS2 downregulation drives hepatic lipid profiles, promoting inflammation and fibrosis in HFHC diet–induced steatohepatitis.

Disclosures: Kazuyoshi Kon: Nothing to Disclose, Heyon-Cheol Lee-Okada: Nothing to Disclose, Kumiko Arai: Nothing to Disclose, Shunsuke Ikejima: Nothing to Disclose, Kyoko Fukuhara: Nothing to Disclose, Reiko Yaginuma: Nothing to Disclose, Kei Ishizuka: Nothing to Disclose, Hiroo Fukada: Nothing to Disclose, Akira Uchiyama: Nothing to Disclose, Shunhei Yamashina: Nothing to Disclose, Takehiko Yokomizo: Nothing to Disclose, Kenichi Ikejima: Nothing to Disclose

1038 | REGULATION OF IN VITRO FIBROGENIC PATHWAYS THROUGH CHOLECYSTOKININ RECEPTOR INHIBITION

Martha Gay[1], [1]Georgetown University

Background: Cholecystokinin (CCK) receptors, which are G-protein-coupled receptors, play crucial roles in gastrointestinal physiology; however, their overexpression in cancer and fibrosis is implicated in disease progression and therapeutic resistance. Recent evidence suggests that activation of cholecystokinin (CCK) receptors in hepatic stellate cells (HSCs) induces fibrosis-associated gene expression, contributing to liver pathology in conditions such as metabolic dysfunction-associated steatohepatitis (MASH) and hepatocellular carcinoma (HCC). We have demonstrated that a diet high in saturated fat stimulates the expression of hepatic CCK-B receptors in a murine model of non-alcoholic steatohepatitis. The CCK receptor antagonist, proglumide, reversed inflammation, fibrosis, and steatosis, thereby preventing the development of HCC in the murine Metabolic dysfunction-associated steatohepatitis (MASH) model. **Methods:** Methods/murine cells: Using C57BL/6 mice, we will follow the standard protocol for the isolation of murine hematopoietic stem cells (HSC). Stellate cells will be isolated and cultured then stimulated with CCK *in vitro* (1-100nM). Another group of stellate cells will be treated with CCK and proglumide to determine if proglumide can prevent activation of fibrosis genes. Stellate cellular protein will also be extracted and subjected to Western blot analysis for fibrosis- and collagen-associated proteins. Macrophages release cytokines and chemokines that activate stellate cells. For our co-culture experiments, we will culture murine RAW264.7 macrophages with mouse HSCs to activate fibrosis genes and proteins by cytokine/chemokine activation of stellate cells. Methods/ human cells: We will use the immortalized LX-2 human HSC line to evaluate the activation of the fibrosis genes with the addition of CCK to the growth media and examine if proglumide prevents the activation of the LX-2 cells and perform independently CCK-B or CCK-A receptor CRISPR to determine if CCK-induced fibrosis activation is mediated by the CCK-B or CCK-A receptor. Clonal CRISPR CCK-receptor KO stellate cells will also be activated by co-culture and /or with spent media from our human U937 macrophages. Anticipated outcomes: When stellate cells are grown on plastic *in vitro*, they become activated. We know that the cytokines and chemokines released from macrophages will stimulate stellate cells; however, the stimulation and collagen synthesis may not be as pronounced if the stellate cells are not already in an activated state. **Results:** Cholecystokinin (CCK) receptors, particularly CCK-B receptors, have been identified in tissue fibroblasts and are implicated in the production of collagen-associated proteins that promote fibrosis and potentially impede therapeutic interventions in malignancies. However, the role of CCK receptors in liver fibrosis and hepatocellular carcinoma (HCC) remains underexplored. We hypothesize that HCC may originate from liver progenitor or stem cells, and the expression of CCK-B receptors plays a significant role in this process under inflammatory conditions. In a previous study, we evaluated the effects of CCK-B receptor expression in a liver injury model induced by a 0.1% diet of 3,5-

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diethoxycarbonyl-1,4-dihydrocollidine (DDC). Cytokine expression was assessed to measure the inflammatory response and its correlation with fibrosis and hepatocellular carcinoma (HCC) progression. Cytokines, small signaling proteins secreted by immune cells, play a crucial role in immune responses and cell signaling. Dysregulation of cytokine expression has been linked to various inflammatory and immunological diseases. Our results suggest that CCK-B receptor expression in liver cells plays a pivotal role in mediating fibrosis and may contribute to the development of HCC under sustained inflammatory pressure. **Conclusion:** This investigation aims to clarify the molecular mechanisms by which CCK receptor signaling drives hepatic fibrosis and explore the therapeutic potential of proglumide in reversing fibrosis-related gene expression in liver disease
Disclosures: Martha Gay: Nothing to Disclose

1039 | TWO PRE-CLINICAL SHORT INTERFERING RNA MOLECULES TARGETING HUMAN HSD17BETA13 FOR THE TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Jieun Song[1] Xuan Luong[1] Dieudonne Buh Kum[1] Lillian Adame[1] Peter Althoff[1] Sarah Stevens[1] Saul Martinez Montero[1] Christopher Novotny[2] Jerome Deval[1] Ruchika Jaisinghani[1] Erin Coyne[2] Aneerban Bhattacharya[1] Antitsa Stoycheva[1] Tilani De Costa[1] Seetha Krishnamoorthy[1] Dana Cho[1] John Cortez[1] Jacquelyn Sousa[1] Kellan Passow[1] Vivek Rajwanshi[1] Craig Parish[2] Salman Jabri[2] Shane Daguison[1] Vikrant Gohil[1] Qingling Zhang[1] Toni Williamson[2] Sushmita Chanda[1] Dinah Misner[1] Saswata Talukdar[2] David Smith[1] Julian Symons[1] Leonid Beigelman[1], [1]Aligos Therapeutics, [2]Merck

Background: The liver-enriched, hepatocyte-specific, lipid droplet-associated protein 17-beta hydroxysteroid dehydrogenase isoform 13 (HSD17beta13 or HSD) is a strong genetic risk factor for the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD) into the more severe metabolic dysfunction-associated steatohepatitis (MASH). A loss-of-function splice variant rs72613567: TA is associated with decreased inflammation and liver injury in patients with fatty liver, indicating that HSD17beta13 is an attractive therapeutic target. The aim of our studies was to characterize short interfering RNA (siRNA) molecules that effectively silence the expression of HSD17beta13 and could be used as potential therapies for MASLD/MASH. **Methods:** An on-/off-target luciferase reporter assay in COS-7 cells and RT-qPCR assay in primary human hepatocytes (PHH) were used to screen proprietary human HSD-targeting siRNAs in vitro for effective silencing of target gene expression. Select compounds were then tested in vivo in PK/PD studies using human AAV-HSD mice, human knock-in (KI)-HSD mice, or wild type non-human primates (NHP). Endpoints included target quantification via RT-qPCR and Western blot analysis. RNA-Seq analysis of treated PHH was conducted to monitor siRNA selectivity and repeat-dose studies were conducted in rats to assess safety. **Results:** We report here two promising pre-clinical siRNAs targeting HSD17beta13, ALG-HSD #1 and ALG-HSD #2, that outperformed competitor controls in cell-based assays and in vivo studies in multiple preclinical species, providing potent target knockdown and high selectivity. The lead sequences demonstrated favorable in-vitro activity with EC_{50} values as low as 5 pM and maximal target RNA reductions of $>$ 90% and with minimal off-target activity in the luciferase reporter, PHH RT-qPCR, and PHH RNA-Seq assays. In both AAV-HSD and KI-HSD mice, selected lead siRNAs exhibited effective target gene silencing (79-92% target RNA reduction); similar robust activity that was durable up to 42 days post-single dose was observed in NHP ($>$ 90% target RNA reduction, $>$ 80% target protein reduction; Figure 1). Furthermore, the two compounds exhibited favorable safety profiles in rats with similarly strong on-target activity ($>$ 95% target RNA reduction). **Conclusion:** We discovered several potent siRNA molecules that selectively and effectively silence human *HSD17beta13* gene expression in vitro and in vivo. We implemented novel chemical modifications that worked to either increase potency without compromising selectivity or improving selectivity with conserved potency. The data generated in these studies allowed for the progression of select liver targeted GalNAc-conjugated siRNAs ALG-HSD #1 and ALG-HSD #2 into later-stage preclinical studies.
Disclosures: Jieun Song: Nothing to Disclose, Xuan Luong: Aligos Therapeutics: Employee, Dieudonne Buh Kum: Nothing to Disclose, Lillian Adame: Nothing to Disclose, Peter Althoff: Nothing to Disclose, Sarah Stevens: Nothing to Disclose, Saul Martinez Montero: Nothing to Disclose, Christopher Novotny: Nothing to Disclose, Jerome Deval: Nothing to Disclose, Ruchika Jaisinghani: Nothing to Disclose, Erin Coyne: Nothing to Disclose, Aneerban Bhattacharya: Nothing to Disclose, Antitsa Stoycheva: Nothing to Disclose, Tilani De Costa: Nothing to Disclose, Seetha Krishnamoorthy: Nothing to Disclose, Dana Cho: Nothing to Disclose, John Cortez: Nothing to Disclose, Jacquelyn Sousa: Nothing to Disclose, Kellan Passow: Nothing to Disclose, Vivek Rajwanshi: Nothing to Disclose, Craig Parish: Nothing to Disclose, Salman Jabri: Nothing to Disclose, Shane Daguison: Nothing to Disclose, Vikrant Gohil: Nothing to Disclose, Qingling Zhang: Nothing to Disclose, Toni Williamson: Merck & Co. Inc.: Employee, Sushmita Chanda: Nothing to Disclose, Dinah Misner:

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Nothing to Disclose, Saswata Talukdar: Nothing to Disclose, David Smith: Nothing to Disclose, Julian Symons: Nothing to Disclose, Leonid Beigelman: Nothing to Disclose

1040 | MACROPHAGE LCP1 DEFICIENCY PROMOTES LIVER FIBROSIS IN MASH

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease posing a major global health concern. The infiltration and dysregulation of immune cells, especially macrophages, play a crucial role in the pathogenesis of MASH, contributing to inflammation, fibrosis, and potentially the progression to HCC. Lymphocyte cytosolic protein 1 (LCP1) is an actin-bundling protein that regulates actin assembly, cell adhesion, and immune cell infiltration. However, the role of LCP1 in MASH progression remain unclear. Thus, the aim of this study is to unravel the role and mechanism of LCP1 in MASH progression. **Methods:** LCP1 expression was evaluated in liver samples from MASH patients and various experimental mouse models using qPCR, western blot, and immunofluorescence (IF). *In vivo* experiments were performed using myeloid-specific LCP1 knockout (KO) mice (LysM-Cre $LCP1^{fl/fl}$) and their littermate controls in two MASH models (FAT-MASH and CDAHFD). Then, scRNA-seq, qPCR (for pro-fibrotic markers Col1a1, Col3a1, αSMA, Tgfβ, Mertk, and the macrophage marker F4/80), Sirius Red staining, and immunofluorescence (IF) staining (Col1a1, αSMA, F4/80, Mertk, Galectin-3, and Fabp5) were conducted. **Results:** LCP1 expression was increased in the liver of MASH patients compared to those of control, as assessed by western blot and qPCR. These findings were also observed in various mouse models (FAT-MASH and CDAHFD). IF staining results showed that LCP1 was mainly expressed in $F4/80^+$ macrophages in normal liver, and that $F4/80^+$ $LCP1^+$ macrophages expand in human and experimental MASH liver. Moreover, we found that myeloid-specific LCP1 KO promotes liver fibrosis in both the FAT-MASH model and CDAHFD model, as confirmed via qPCR (pro-fibrotic markers), Sirius Red staining, and IF staining (αSMA and Col1a1). In addition, the mRNA expression levels of macrophage marker F4/80 and the pro-fibrotic gene Mertk were increased in the liver of myeloid-specific LCP1 KO mice compared with their littermate controls in the FAT-MASH model. scRNA-seq data also confirmed that hepatic macrophages were increased in the myeloid-specific LCP1 KO group. Notably, our IF staining results showed that macrophages (marked by F4/80), especially pro-fibrotic $MerTK^+$ macrophages, $Galectin3^+$ macrophages, and $Fabp5^+$ macrophages, were expanded in scar areas (marked by Col1a1 or αSMA). **Conclusion:** LCP1 is highly expressed in human and experimental MASH liver. Myeloid-specific LCP1 knockout leads to an expansion of macrophages, particularly pro-fibrotic ones, within scar areas rich in activated hepatic stellate cells, thereby driving fibrosis progression in MASH. Ongoing research will focus on elucidating the mechanisms behind macrophage expansion (infiltration, proliferation, or migration from other areas) and how LCP1 regulates these processes. Additionally, the GAN diet will be used to validate the results in FAT-MASH and CDHFD models.

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1041 | INOSITOL HEXAPHOSPHATE AND INOSITOL AMELIORATE METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS IN WD/CCL4 TREATMENT MICE

Zhao Chen[1] Feng Liu[1] Huiying Rao[1], [1]Peking University Hepatology Institute

Background: Inositol Hexaphosphate (IP6) and inositol (INS), primarily extracted from plants, possess antioxidative and anti-tumor effects. However, whether they can alleviate metabolic dysfunction-associated steatohepatitis (MASH)remains unclear. This study aimed to assess and compare the effects of IP6 and INS on MASH, as well as the underlying mechanisms. **Methods:** A western diet combined with low doses of CCl4 (WD/CCl4) was used to induce MASH in mice and evaluate the protective effects of IP6 and INS. Assessments of transcriptomics, metabolomics, and lipidomics analyses were conducted to explore potential molecular mechanisms. Additionally, the effects of IP6 and INS in vitro using free fatty acid (FFA)-treated HepG2 cells and activated hepatic stellate cells were investigated. **Results:** Treatment with IP6 or INS significantly reduced obesity, fibrosis and lipid accumulation, improved insulin sensitivity and glucose homeostasis, and prevented hyperglycemia in NASH mice. However, IP6 exerted more beneficial effects against inflammation and oxidative stress. IP6 and INS also alleviated FFA-induced lipid accumulation in HepG2 cells. Liver transcriptomics revealed the deleterious effects of WD/CCl4 on gene expression and their reversal by IP6 and INS. Metabolomics and lipidomics analyses indicated that IP6 and INS can effectively improve disorders in glycerophospholipid metabolism by regulating the

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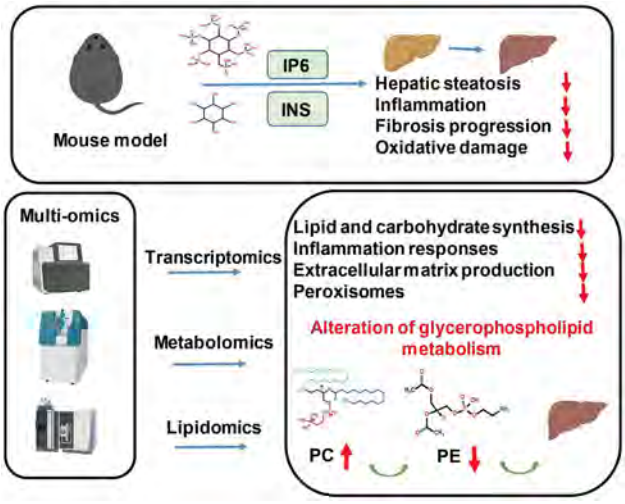
expression of related genes and metabolites. Especially in the aspect of oxidative phosphorylation metabolism, IP6 is more effective than INS. **Conclusion:** Both IP6 and INS effectively improve MASH primarily by ameliorating disorders in glycerophospholipid metabolism. This finding provides a theoretical basis for the prevention and treatment of MASH in patients through the rational intake of foods containing IP6 and INS.



Disclosures: Zhao Chen: Nothing to Disclose, Feng Liu: Nothing to Disclose, Huiying Rao: Nothing to Disclose

1042 | ESTROGEN DEFICIENCY ENHANCES AHR-DRIVEN PATHWAYS IN METABOLIC LIVER DISEASE

Jessica Cassavaugh[1] Sarah Kispert[1] Eva Csizmadia[1] Maria Serena Longhi[1] Simon Robson[1], [1]Beth Israel Deaconess Medical Center

Background: Metabolic-associated Fatty Liver Disease (MASLD) is highly associated with increased cardiovascular morbidity and mortality. Declining estrogen levels during menopause elevate the risk of MASLD and other metabolic disorders. We hypothesize that estrogen protects against MASLD by modulating aryl hydrocarbon receptor (AhR) activity. We therefore investigated mechanisms whereby estrogen lack disorders AhR transcriptional activity to exacerbate experimental MASLD. **Methods:** Liver tissue from ovariectomized (OVX) C57BL/6 mice were assessed for fat burden and reactive oxygen species (ROS), and serum cytokines. Expression of CYP1A1 and other AhR targets were measured using western blotting and q-RT-PCR. In hepatocytes, fatty acid ROS were measured along with q-RT-PCR to measure CYP1A1 and other AhR associated targets. A gene-expression profile in fatty acid treated hepatocytes was identified by means of a targeted PCR array. **Results:** A high-fat diet (HFD) combined with OVX leads to increased fatty acid deposition and reactive oxygen species (ROS), contributing to oxidative stress. Both HFD and OVX resulted in higher serum levels of proinflammatory cytokines, including TNF-α and IL-6. Protein expression of AhR and TNFa as well as gene expression of CYP1A1, a transcriptional target of AhR, was elevated in liver tissue from OVX mice. In hepatocytes, estradiol and endogenous AhR activation by unconjugated bilirubin was protective from fatty acid-induced ROS production. Conversely, exogenous AhR activation with benzo[a]pyrene and estrogen inhibition exacerbate ROS production. Gene expression of CYP1A1 was markedly increased with estrogen inhibition or exogenous activation of AhR. PCR array analysis reveals significant gene expression changes related to the AMPK, insulin resistance, and PPAR signaling pathways with exogenous AhR activation. Notably, highly regulated genes exhibit an amplified cluster of estrogen receptor alpha binding motifs, suggesting estrogen's role in modulating these pathways. **Conclusion:** Estrogen deficiency accelerates the progression of metabolic-associated fatty liver disease (MASLD) by increasing fat accumulation and inflammation, particularly when combined with a high-fat Western diet. These results may be driven by AhR-associated transcriptional changes of CYP1A1 and increases in proinflammatory signaling pathways. These findings underscore the complex interplay between diet, estrogen signaling, and liver health, highlighting potential therapeutic targets for conditions like MASLD.

Disclosures: Jessica Cassavaugh: Nothing to Disclose, Sarah Kispert: Nothing to Disclose, Eva Csizmadia: Nothing to Disclose, Maria Serena Longhi: Nothing to Disclose, Simon Robson: Nothing to Disclose

1043 | MALNUTRITION-INDUCED METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IMPAIRS PHOSPHOLIPID BIOSYNTHESIS AND TRIGLYCERIDE SECRETION IN EARLY LIFE MOUSE MODEL

Larissa Neves[1] Krishnakant Soni[1] Margaret Conner[2] Geoffrey Preidis[1], [1]Baylor College of Medicine and Texas Children's Hospital, [2]Baylor College of Medicine

Background: Globally, malnutrition is responsible for 45% of deaths of children under the age of five. Malnutrition impairs gastrointestinal and metabolic functions including dyslipidemia, nutrient

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malabsorption, and slow gut motility. In severe malnutrition, hepatic lipid accumulation results in steatotic liver disease. Steatosis is the most prevalent form of liver disease worldwide, with nearly 10% of children affected. Currently, there is no FDA-approved drug to treat steatosis and the mechanisms by which malnutrition causes steatosis are poorly understood. Models of liver steatosis suggest that impaired phospholipid metabolism alters lipid homeostasis and secretion. Rodents fed a methionine-choline-deficient diet exhibit steatosis and altered quantities and ratios of phosphatidylcholine (PC) and phosphatidylethanolamine (PE). Disrupting PC and PE homeostasis impairs hepatic lipid secretion by very low-density lipoproteins (VLDL). Whether altered phospholipid homeostasis contributes to steatosis in protein malnutrition is unknown. Therefore, I hypothesize that protein malnutrition causes hepatic lipid accumulation by altering phospholipid biosynthesis and impairing VLDL secretion. **Methods:** Our lab models malnutrition by feeding weanling male and female C57BL/6J mice a low-protein, low-fat diet (LPLFD) until 8 weeks of life. Previously, we reported that LPLFD reduces body weight and length in male and female mice with a poorer outcome in males. To examine lipid accumulation from LPLFD and control mice, I stained flash-frozen liver sections with oil red O and quantified liver triglycerides via thin-layer chromatography. I used western blot to quantify the expression of key phospholipid biosynthesis enzymes, including phosphatidylethanolamine N-methyltransferase (PEMT), phosphatidylserine decarboxylase (PSD), choline dehydrogenase (CHDH), and betaine-homocysteine S-methyltransferase (BHMT). Additionally, I evaluated VLDL secretion via lipoprotein profiling of serum samples using high-performance liquid chromatography (HPLC). **Results:** Hepatic lipid accumulation and triglycerides were dramatically increased, and PEMT expression was markedly decreased, in malnourished male and female mice compared to controls. In contrast, expression of hepatic PSD, CHDH, and BHMT was sexually dimorphic; these proteins were reduced in malnourished males but not females. Lipoprotein profiling with HPLC revealed that LPLFD reduced serum VLDL, suggesting that impaired triglyceride secretion leads to hepatic lipid accumulation in protein malnutrition. **Conclusion:** Together, these results suggest that malnutrition induces liver steatosis by altering phospholipid biosynthesis and impairing VLDL secretion. Understanding the role that phospholipids play in LPLFD-induced steatosis allows for further exploration of therapies to ameliorate or prevent steatosis in malnourished children.

Disclosures: Larissa Neves: Nothing to Disclose, Krishnakant Soni: Nothing to Disclose, Margaret Conner: Nothing to Disclose, Geoffrey Preidis: Nothing to Disclose

1044 | SINGLE-CELL ATLAS OF HUMAN LIVER AND BLOOD IMMUNE CELLS ACROSS FATTY LIVER DISEASE STAGES REVEALS DISTINCT SIGNATURES LINKED TO LIVER DYSFUNCTION AND FIBROGENESIS

Owen Martin[1] Michael Wallace[2] Christopher Oetheimer[2] Hailey Patel[2] Michael Butler[2] Lai Ping Wong[2] Joshua Elbaz[2] Charlotte COSTENTIN LAURENT[3] Shadi Salloum[4] Zoe Reinus[2] Adaeze Obinelo[2] Ulandt Kim[4] Stuti Shroff[2] Kathleen Corey[4] Edgar Charles[5] Ruslan Sadreyev[2] Raymond Chung[4] Nadia Alatrakchi[2], [1]Massachusetts General Hospital & Harvard Medical School, [2]Massachusetts General Hospital and Harvard Medical School, [3]Grenoble Alpes University, [4]Massachusetts General Hospital, [5]Bristol Myers Squibb

Background: Immune cells play a central yet poorly understood role in metabolic dysfunction-associated steatotic liver disease and steatohepatitis (MASLD/MASH), a global cause of liver disease with limited treatment. Limited access to human livers and lack of studies across MASLD/MASH stages thwart identification of stage-specific immunological targets. **Methods:** We studied 25 patients spanning the full MASLD/MASH spectrum (without other causes of chronic liver disease) who underwent clinical liver biopsy for diagnosis at Massachusetts General Hospital upon detection of hepatic fatty inclusions by ultrasound/CT-scan/MRI. Immune cells from paired liver fine needle aspirates and peripheral blood samples were subjected to single-cell RNA-sequencing (scRNA-seq) via the 10X Genomics platform and investigated for changes in frequency and computationally-resolved function with clinical measurements of MASLD/MASH. **Results:** Transcriptomic analysis delineated distinct immune cell signatures linked to liver dysfunction. Findings included heightened immunoregulatory programs with MASH progression, such as enriched hepatic regulatory T cells, monocytic myeloid-derived suppressor cells, *TREM2*$^{+}$*S100A9*$^{+}$ macrophages, and mature regulatory dendritic cells. Hepatic cytotoxic T-cell functions increased with inflammation but decreased with fibrosis (acquiring an exhausted signature) while natural killer cell-driven toxicity intensified. **Conclusion:** We created a human cross-compartment scRNA-seq atlas of immune cells spanning the MASLD/MASH spectrum. We uncovered contributions of immune cells to the hepatic inflammatory and profibrotic milieu and multiple types of immune regulation leading to T-cell exhaustion that can contribute to increased vulnerability to liver cancer and infections in patients with MASH. Our dataset is a valuable resource that provides a basis for a deeper understanding of immunological plasticity

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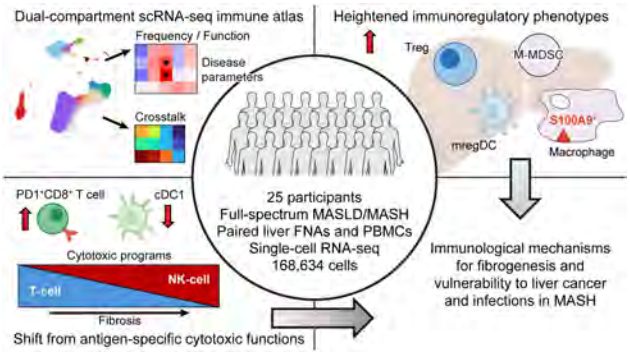
and dysfunction in chronic liver disease in humans and provides a roadmap to new targeted antifibrotic therapies.



Disclosures: Owen Martin: Nothing to Disclose, Michael Wallace: Nothing to Disclose, Christopher Oetheimer: Nothing to Disclose, Hailey Patel: Nothing to Disclose, Michael Butler: Nothing to Disclose, Lai Ping Wong: Nothing to Disclose, Joshua Elbaz: Nothing to Disclose, Charlotte COSTENTIN LAURENT: Nothing to Disclose, Shadi Salloum: Nothing to Disclose, Zoe Reinus: Nothing to Disclose, Adaeze Obinelo: Nothing to Disclose, Ulandt Kim: Nothing to Disclose, Stuti Shroff: Nothing to Disclose, Kathleen Corey: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Edgar Charles: Nothing to Disclose, Ruslan Sadreyev: Nothing to Disclose, Raymond Chung: GSK: Grant/Research Support, Salix: Grant/Research Support, GSK: Consultant, Precision Biosciences: Consultant, Boehringer: Grant/Research Support, BMS: Grant/Research Support, Nadia Alatrakchi: Nothing to Disclose

1045 | GENETIC OR PHARMACOLOGICAL INHIBITION OF HEPATIC TMEM141 ATTENUATES MASH AND FIBROSIS VIA THE ROS-HNF4α SIGNALING PATHWAYNEW SUBMISSION

Jiayou Wang[1] Chwen-Lih W Chen[2] Raja Gopoju[1] Shuwei Hu[1] Yang Wang[1] Hui Wang[1] Zaid Batayneh[2] Xiaoli Pan[2] Yeong-Renn Chen[2] Jeffrey Mellott[2] Patrick Kang[2] Liya Yin[1] Yanqiao Zhang[3], [1]University of Arizona College of Medicine – Phoenix, [2]Northeast Ohio Medical University, [3]University of Arizona College of Medicine - Phoenix

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and its advanced form, metabolic dysfunction-associated steatohepatitis (MASH), have become a global epidemic due to obesity and genetic susceptibility. **Methods:** Here, we report transmembrane protein 141 (TMEM141), a protein with a largely unknown function, as a key regulator of MASH and MASH-associated fibrosis. **Results:** Hepatic TMEM141 is reduced in MASLD/MASH patients and mouse models of MASLD/MASH due to increased microRNA-149. Unexpectedly, genetic inactivation of hepatocyte TMEM141 protects against MASLD/MASH induced by a high fat/cholesterol/fructose (HFCF) diet, whereas hepatic overexpression of human TMEM141 exacerbates MASLD/MASH. We further show that TMEM141 localizes within mitochondria and interacts with mitochondrial complex I to regulate ROS production. Inactivation of TMEM141 reduces ROS production, induces hepatocyte nuclear factor 4α (HNF4α), and fails to protect against HFCF diet-induced MASH or fibrosis in the absence of hepatocyte HNF4α. Finally, pharmacological inhibition of hepatic TMEM141 by N-acetylgalactosamine (GalNAc)-siTmem141 significantly promotes the reversal of HFCF diet-induced MASH and fibrosis. **Conclusion:** These findings underscore a critical role of TMEM141 in MASH development and suggest that targeting hepatic TMEM141 may represent a novel and promising strategy for treating MASH and MASH-associated fibrosis.

Disclosures: Jiayou Wang: Nothing to Disclose, Chwen-Lih W Chen: Nothing to Disclose, Raja Gopoju: Nothing to Disclose, Shuwei Hu: Nothing to Disclose, Yang Wang: Nothing to Disclose, Hui Wang: Nothing to Disclose, Zaid Batayneh: Nothing to Disclose, Xiaoli Pan: Nothing to Disclose, Yeong-Renn Chen: Nothing to Disclose, Jeffrey Mellott: Nothing to Disclose, Patrick Kang: Nothing to Disclose, Liya Yin: Nothing to Disclose, Yanqiao Zhang: Nothing to Disclose

1046 | ROLE OF LY6D IN HEPATIC LIPID METABOLISM AND ITS THERAPEUTIC POTENTIAL IN MASLD

Soyeon Shin[1] Yeongmin Kim[1] Moon-young Park[1] Chang-Myung Oh[1], [1]GIST

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent cause of chronic liver disease worldwide. Despite its high prevalence, the underlying mechanisms driving its progression and effective treatment options remain poorly understood. Ly6D, a membrane protein anchored to the cell surface via glycosylphosphatidylinositol and expressed in immune cells such as B-cells and T-cells, has been investigated in various diseases, including certain cancers, although its role in hepatic lipid metabolism and inflammation remains to be elucidated. This study investigates the role of Ly6D in MASLD progression and evaluates its potential as a therapeutic target for MASH, a severe progression of MASLD. **Methods:** Ly6D hepatocyte-specific knockout

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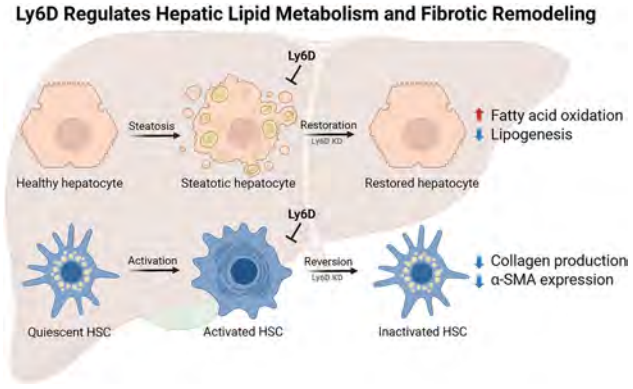
(KO) mice were generated using Alb-cre transgenic mice. Both KO and control mice were fed a high-fat diet (HFD) for 8 weeks to induce MASLD. Ly6D expression was quantified by qPCR and Western blot. Liver lipid accumulation was assessed by H&E and Oil Red O staining. To study Ly6D's role in MASH, human hepatic stellate LX-2 cells were used in vitro. Additionally, hepatic stellate cell-specific analyses were performed using Lrat-cre transgenic mice, which enable selective genetic targeting of hepatic stellate cells. **Results:** In mice fed a standard chow diet (SCD) and an HFD, liver tissues were separated into parenchymal cells (hepatocytes) and non-parenchymal cells (NPCs) for analysis. Ly6D RNA levels were significantly elevated in both cell types in the HFD group compared to SCD controls, with a notably higher upregulation observed in NPCs ($p < 0.05$). Hepatocyte-specific Ly6D KO mice generated using Alb-cre transgenic mice exhibited a significant reduction in MASLD progression compared to controls after 8 weeks of HFD feeding. Histological analysis showed significant reduction of liver steatosis in Ly6D KO mice. To further investigate Ly6D's role in MASH, Ly6D expression was silenced in human hepatic stellate LX-2 cells using siRNA. Ly6D silencing significantly attenuated the expression of activation markers such as α-SMA upon TGF-β1 stimulation ($p < 0.05$), indicating suppression of hepatic stellate cell activation. Additionally, hepatic stellate cell-specific studies were conducted in vivo using Lrat-cre transgenic mice. These findings demonstrate that Ly6D plays a critical role in both hepatic lipid metabolism and stellate cell activation, suggesting that targeting Ly6D may mitigate MASLD progression. **Conclusion:** Our findings highlight Ly6D as a significant contributor to MASLD pathogenesis, suggesting it as a potential therapeutic target. While initial results are promising, especially in reducing liver steatosis and stellate cell activation, further studies are essential to validate its role in MASH. Future research should explore the long-term effects and feasibility of Ly6D-targeted therapies to better understand their clinical application.



Disclosures: Soyeon Shin: Nothing to Disclose, Yeongmin Kim: Nothing to Disclose, Moon-young Park: Nothing to Disclose, Chang-Myung Oh: Nothing to Disclose

1047 | EXTRACELLULAR VESICLES FROM THE IPSC-DERIVED MESENCHYMAL STEM CELLS AMELIORATED LIVER FIBROSIS IN MASH-RELATED CIRRHOTIC MICE

Tsuyoshi Fujioka[1] Toshihiko Matsumoto[1], [1]Yamaguchi University Graduate School of Medicine

Background: In recent years, extracellular vesicles (EVs) derived from mesenchymal stem cells (MSCs) have shown promise in treating liver cirrhosis. However, limitations in cell proliferation make continuous use of EVs from the same donor's MSCs difficult. Therefore, we developed iPSC-derived MSCs (iMSCs) and examined the therapeutic effects of iMSC-EVs on MASH-related liver fibrosis. **Methods:** We characterized iMSCs by comparing their EV production and microRNA expression profiles in EVs to those of bone marrow-derived MSCs (BMSCs), as measured by nanoparticle tracking analysis and microRNA arrays, respectively. Next, human hepatic stellate cells (hHSCs) were activated with TGFβ and then treated with iMSC-EVs and their fibrosis-related gene expression was determined. To evaluate the effects of iMSC-EVs in vivo, a mouse model of MASH-related liver fibrosis was established by feeding Gubra-Amylin-NASH (GAN) diet and a single intraperitoneal injection of carbon tetrachloride. The mice were divided into control group and iMSC-EV group. The iMSC-EV group received intravenous injection of iMSC-EVs once a week for 4 weeks. Blood and liver samples were analyzed using biochemical tests and histological examinations. We also compared the gene expression profiles of the livers of both groups by performing a comprehensive analysis of mRNA expression profiles and using Ingenuity Pathway Analysis. **Results:** iMSCs produced more EVs than BMSCs. Thirty-nine microRNAs were extracted from the microarray data that exhibited a normalized intensity of greater than 1,000 in both iMSC- and BMSC-EVs. Five of these microRNAs had anti-fibrotic effects on hHSCs. As expected, iMSC-EVs inhibited the expression of fibrosis-related genes (COL1A1, COL1A2 and ELN) in activated hHSCs. In a murine model of MASH-related fibrosis, the iMSC-EV group showed improved liver function, reduced dyslipidemia, and elevated albumin levels compared to the control group. Histological examination revealed a significant reduction in the fibrotic areas, accompanied by a decrease in CD11c-positive M1 macrophages (Mφ) and an increase in CD163-positive M2 Mφ in the livers of iMSC-EV group. Gene expression analysis revealed suppression of extracellular matrix organization pathway and Rho

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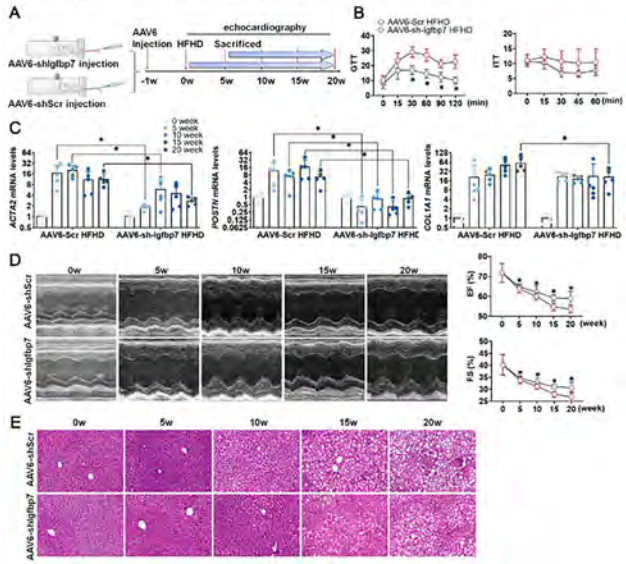
GTPase cycle pathway in the iMSC-EV group. **Conclusion:** iMSC-EVs suppress HSC activation and induce M2 Mφ, thereby exhibiting anti-fibrotic effects. Our iMSC-EVs will be a new treatment option for cirrhotic patients.
Disclosures: Tsuyoshi Fujioka: Nothing to Disclose, Toshihiko Matsumoto: Nothing to Disclose

1048 | INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 7: A PROMISING BIOMARKER FOR HEPATIC FIBROSIS AND CARDIAC DYSFUNCTION IN METABOLIC DYSFUNCTION-ASSOCIATED STEOTOTIC LIVER DISEASE

Jie Li[1] Wenjing Ni[1] Qianqian Chen[1] Yixuan Zhu[1] Fajuan Rui[1] Zhiwen Fan[1] Shengxia Yin[1] Qianwen Zhao[1], [1]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University

Background: Individuals with metabolic dysfunction-associated steatotic liver disease (MASLD) face an elevated risk of liver-related complications and cardiovascular diseases. We have found that insulin-like growth factor binding protein 7 (Igfbp7) is a promising marker for the cross-disease communication between liver and heart. This study aimed to investigate the role of Igfbp7 in the process of liver fibrosis and its impact on cardiac dysfunction under the context of MASLD. **Methods:** Circulating Igfbp7 levels and liver tissue expression were examined in patients with liver fibrosis. Male C57BL/6J mice were fed a high-fat, high-fructose diet (HFHD) for 20 weeks to induce MASLD-associated liver fibrosis. Igfbp7 knockdown in mature myofibroblasts was achieved using Igfbp7-targeting shRNA under the Postn promoter, packaged into AAV6 (AAV-shIgfbp7). Echocardiography was performed to assess cardiac function. Liver histology was analyzed with hematoxylin-eosin (HE) staining. In vitro studies utilized TGF-β-activated human hepatic stellate cells (LX-2) to explore Igfbp7-associated mechanisms. **Results:** Reanalysis of single-cell sequencing data identified Igfbp7 as a significantly deferentially expressed gene implicated in liver fibrosis and heart failure under the context of MASLD. Circulating IGFBP7 levels correlated positively with liver stiffness measurements (LSM) in patients with liver fibrosis concurrent with heart failure. IGFBP7 expression was proportionally associated with liver fibrosis severity verified in liver samples among patients with liver fibrosis. HFHD-fed MASLD mice exhibited increased liver fibrosis and reduced cardiac function, which were alleviated by Igfbp7 knockdown. *Igfbp7* mRNA levels were elevated alongside myofibroblast markers (*Acta2, Postn, Col1a1*) in MASLD mice but decreased following Igfbp7 knockdown. Glucose tolerance test and insulin tolerance test showed an improved performance in mice with Igfbp7 knockdown (Figure 1). Consistent findings were observed in primary hepatic stellate cells (HSCs) from wild-type mice, where Igfbp7 expression increased during spontaneous activation. TGF-β-activated LX-2 cells displayed enhanced Igfbp7 expression, migration, proliferation, and contraction, and these effects were mitigated by Igfbp7 knockdown. **Conclusion:** IGFBP7 serves as a promising biomarker for assessing liver fibrosis severity and cardiac dysfunction in MASLD. Targeting IGFBP7 could offer therapeutic potential for managing liver and cardiovascular complications in MASLD patients.

Figure 1. IGFBP7 aggravated liver fibrosis and cardiac dysfunction in MASLD.
(A) Protocol of establishment of Igfbp7 knockdown mouse model; (B) Glucose tolerance test and insulin tolerance test; (C) The mRNA levels of *Igfbp7* and myofibroblast markers in mice subjected with HFHD; (D) Echocardiography and analysis of left ventricular ejection fraction and fractional shortening in mice subjected with HFHD; (E) Hematoxylin-eosin staining of mice subjected with HFHD. Abbreviations: Igfbp7: insulin-like growth factor binding protein 7; HFHD: high-fat, high-fructose diet; MASLD: metabolic dysfunction-associated steatotic liver disease.



Disclosures: Jie Li: Nothing to Disclose, Wenjing Ni: Nothing to Disclose, Qianqian Chen: Nothing to Disclose, Yixuan Zhu: Nothing to Disclose, Fajuan Rui: Nothing to Disclose, Zhiwen Fan: Nothing to Disclose, Shengxia Yin: Nothing to Disclose, Qianwen Zhao: Nothing to Disclose

1049 | INHIBITION OF HEPATOCYTE FERROPTOSIS IN THE TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE BY QUSHI HUAYU DECOCTION

Yuqing Pan[1] Aojie Mao[1] Chuchu Yu[1] Huajie Tian[1] Yiyang Hu[1] Yu Zhao[1], [1]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine

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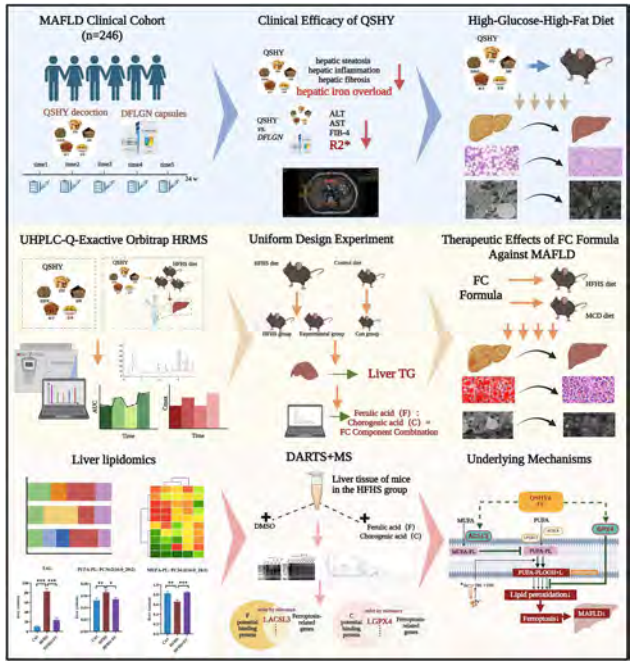
Background: Hepatocyte ferroptosis plays a critical role in the progression of metabolic dysfunction-associated steatotic liver disease (MASLD). Qushi Huayu Decoction (QSHY), a traditional Chinese medicine composing five herbs, has demonstrated therapeutic potential in MASLD patients in our previous clinical trial. Hepatic R2* magnetic resonance imaging (R2*-MRI) was significant decreased in patients post-QSHY intervention. This study aimed to evaluate the anti-ferroptotic effects of QSHY in MASLD and further identify an optimized active component combination that retains the original formula's efficacy. **Methods:** A MASLD mouse model was established using a high-fat diet and high-sugar drinking water (HFHS). The chemical constituents of QSHY and its blood-incorporated components were analyzed via ultra-high-performance liquid tandem quadrupole-Q-Electrostatic Field Orbitrap High Resolution Mass Spectrometry (UHPLC-Q-Exactive Orbitrap HRMS). Mice were treated with QSHY decoction (1.733 g/kg) or a combination of ferulic acid (F) and chlorogenic acid (C) (80 mg/kg + 60 mg/kg). Mitochondrial morphology was assessed by transmission electron microscopy (TEM). Liver lipid profiles were analyzed using lipidomics, and potential drug-binding proteins were screened via drug affinity responsive target stability combined with mass spectrometry (DARTS+MS). **Results:** QSHY dose-dependently alleviated hepatocyte ferroptosis in MASLD mice. UPLC-MS identified 36 chemical components in QSHY, 22 of which were detected in the bloodstream of MASLD mice. A homogeneous design study prioritized six top-ranking liver Cmax components, leading to the identification of an optimized ferulic acid-chlorogenic acid combination (FC). Both QSHY and FC significantly decreased liver TG, serum ALT and AST levels. TEM revealed improved mitochondrial ultrastructure in treated mice. Mechanistically, QSHY and FC decreased serum and hepatic iron levels, downregulated transferrin receptor (TFR), and upregulated ferritin heavy chain 1 (FTH1), mitigating iron overload. Furthermore, they reduced malondialdehyde content, upregulated glutathione peroxidase 4 (GPX4), and downregulated key lipid peroxidation enzymes (ACSL4, LPCAT3). Hepatic lipidomics revealed that QSHY and FC reduced triglyceride and polyunsaturated fatty acid-containing phospholipids while increasing monounsaturated fatty acid-containing phospholipids. DARTS+MS analysis suggested that ferulic acid and chlorogenic acid may exert anti-ferroptotic effects by binding to ACSL3 and GPX4, respectively. **Conclusion:** QSHY and its optimized FC combination attenuate MASLD and inhibit hepatocyte ferroptosis, ferulic acid and chlorogenic acid may exert anti-ferroptotic effects by binding to ACSL3 and GPX4, respectively.



Disclosures: Yuqing Pan: Nothing to Disclose, Aojie Mao: Nothing to Disclose, Chuchu Yu: Nothing to Disclose, Huajie Tian: Nothing to Disclose, Yiyang Hu: Nothing to Disclose, Yu Zhao: Nothing to Disclose

1050 | HEPATOCYTE-SPECIFIC HAF DEFICIENCY PROMOTES LIPID DYSREGULATION THROUGH MAPK PATHWAY ACTIVATION IN A MURINE MODEL OF MASH-HCC

Karen Acuna-Pilarte[1] Po-An Hu[1] Kimberley Evason[2] Ethan Reichert[1] Mei Yee Koh[1], [1]University of Utah, [2]University of California, San Francisco

Background: Progression of Metabolic dysfunction-associated steatotic liver disease (MASLD) to metabolic dysfunction-associated steatohepatitis (MASH) is marked by disruption of lipid metabolism and inflammatory pathways that can drive liver cancer development. We previously showed that conditional deletion of the hypoxia-associated factor (HAF) in mouse hepatocytes triggers NF-κB downregulation and increased apoptosis, resulting in MASH at 6 months and HCC at 18 months. HAF is downregulated in steatotic human livers, showing that loss of HAF might be key in the development of human MASH. Intriguingly, despite profound MASH, the HAF-deficient mice showed reduced overall body mass and increased lean mass, resembling human lean MASH, which is associated with a lower index of detection, resulting in later disease diagnosis. This study aims to elucidate the molecular

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mechanisms by which HAF deficiency drives MASLD/MASH and to explore potential pathways underlying lean-MASH. **Methods:** We isolated hepatocytes from a conditional HAF knockout mouse model and assessed two major pathways within the MAPK signaling cascade: p38 mitogen-activated protein kinase (p38) and c-Jun NH2-terminal kinase (JNK). Phosphorylation of p38 and JNK, along with downstream targets and autophagy markers, was evaluated via western blotting following TNF-α stimulation. Cytokine profiling was performed on hepatocyte-conditioned media. Levels of hepatokines of interest were validated and quantified by ELISA. To assess the involvement of NF-κB in these signaling events, hepatocytes were treated with the inhibitor BAY11-7082, and subsequent p38/JNK activation was analyzed. **Results:** HAF-deficient hepatocytes exhibited elevated basal phosphorylation of p38 and JNK, independent of TNF-α stimulation. Surprisingly, upstream kinases ASK1 and MKK6 were downregulated, indicating activation of p38/JNK via a non-canonical mechanism. NF-κB inhibition did not further enhance p38/JNK activation, suggesting that JNK/p38 upregulation occurs independently of NF-κB suppression in HAF-deficient cells. Cytokine profiling revealed increased FGF21 secretion, a known p38/JNK target and autophagy regulator. Moreover, autophagy was impaired in HAF-deficient hepatocytes, as evidenced by reduced LC3A/B and elevated p62 levels. Additionally, LDLR expression was diminished, implying disrupted cholesterol homeostasis. **Conclusion:** Our findings reveal that hepatocyte-specific HAF deficiency induces non-canonical activation of p38 and JNK, contributing to lipid dysregulation through FGF21 resistance, impaired autophagy, and LDLR suppression. These mechanisms may play a role in lean-MASH pathogenesis.

Disclosures: Karen Acuna-Pilarte: Nothing to Disclose, Po-An Hu: Nothing to Disclose, Kimberley Evason: Nothing to Disclose, Ethan Reichert: Nothing to Disclose, Mei Yee Koh: Nothing to Disclose

1051 | ALTERNATIVELY SPLICED TISSUE FACTOR: A NOVEL CONTRIBUTOR TO MASLD PROGRESSION

Clayton Lewis[1] Kateryna Stone[1] Sabahat Ahsan[1] Josepha Sedzro[2] Lanuza Faccioli[3] Zhiping Hu[3] Rodrigo Florentino[3] Alejandro Soto-Gutierrez[3] Jiang Wang[1] James Luyendyk[4], [1]University of Cincinnati, [2]University of Michigan, [3]University of Pittsburgh, [4]Michigan State University

Background: Nearly one in three people in the United States have some degree of metabolic dysfunction associated steatotic liver disease (MASLD). 18% of these people develop a more fibrotic and severe form of disease termed metabolic dysfunction-associated steatohepatitis (MASH). Alternatively spliced tissue factor (asTF) is a soluble isoform of tissue factor (TF). In contrast to the full-length isoform of TF, which initiates the extrinsic pathway of coagulation, asTF does not trigger coagulation. Instead, asTF activates integrin-associated signaling cascades that elicit angiogenesis from endothelial cells. We have shown that patients with fibrotic liver diseases, including MASH, have significantly higher levels of circulating asTF than healthy individuals, and that these levels correlate with disease severity. Here we sought to identify the subcellular localization of asTF in normal and diseased livers, determine drivers of its expression, and examine the functional consequences of asTF signaling on non-parenchymal cells. We hypothesize that paracrine asTF signaling drives endothelial capillarization and enhanced extracellular matrix deposition by non-parenchymal cells, hallmark features of MASH. **Methods:** Immunohistochemistry was used to identify the localization of asTF in 30 human liver tissue specimens. Hepatocyte-like cell line HepaRG and primary hepatocytes were assessed for their responivness to hypoxia and nutrient deprivation, key environmental features imposed by fibrotic disease, via qPCR and western blotting. Non-parenchymal human cell lines TMNK1 and LX-2 were assessed for responsiveness to exogenous recombinant asTF via extracellular matrix (ECM) deposition and tubule formation assays. **Results:** In normal liver tissue, asTF localized to exocysts adjacent to apical membranes of pericentral hepatocytes. Polarized expression was progressively lost with increasing fibrosis; instead, high asTF levels were observed across the liver. Hypoxia stimulated asTF and flTF expression by cell line HepaRG. MASH patient hepatocytes had high asTF protein expression and minimal flTF expression. When primary hepatocytes were cultured *ex vivo*, flTF expression increased while asTF was suppressed. Hypoxia stimulated expression of both TF isoforms *in vitro*. Recombinant asTF stimulated activation of Akt in TMNK1 cells and Erk in LX-2 cells, simultaneously promoting ICAM1 and COL3A1 expression, respectively. In an ECM deposition assay, asTF promoted a 36% increase in COL3A1 deposition by LX2 cells and a 36% increase in COL1A1 by TMNK1 cells. asTF enhanced tubule formation by TMNK1 by 55%. **Conclusion:** Hypoxia and nutrient deprivation drive aberrant asTF expression by hepatocytes, and non-parenchymal cells display profibrogenic phenotypes when stimulated by asTF. Thus, asTF is likely a novel contributor to the pathological remodeling of the liver in the progression from MASLD to MASH.

Disclosures: Clayton Lewis: Nothing to Disclose, Kateryna Stone: Nothing to Disclose, Sabahat Ahsan: Nothing to Disclose, Josepha Sedzro: Nothing to Disclose, Lanuza Faccioli: Nothing to Disclose, Zhiping Hu: Nothing to Disclose, Rodrigo Florentino: Nothing to Disclose,

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Alejandro Soto-Gutierrez: Nothing to Disclose, Jiang Wang: Nothing to Disclose, James Luyendyk: Nothing to Disclose

1052 | INHIBITION OF OX40 IN CD4+ T CELLS ATTENUATES HEPATIC INFLAMMATION IN A HUMAN EX VIVO MODEL OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Lucia Valenzuela Perez[1] Hyun Se Kim Lee[1] Alexander Washington[1] Shravan Mishra[1] Patrick Starlinger[2] Samar Ibrahim[1] Adebowale Bamidele[1] Enis Kostallari[1] Petra Hirsova[1], [1]Mayo Clinic Rochester, [2]Mayo Clinic

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is characterized by chronic liver inflammation and fibrosis, with effector CD4+ T cells contributing to its pathogenesis. Our single-cell transcriptomics revealed a striking increase in CD4+ T cells expressing the co-stimulatory receptor OX40 in murine MASH livers. In turn, inhibition of the OX40L-OX40 axis reduced MASH severity in mice with established MASH. Here, we aimed to evaluate OX40 and OX40L protein expression and the therapeutic potential for human MASH. **Methods:** C57BL/6J mice were fed chow or a high-fat, fructose, and cholesterol (FFC) diet for 26 weeks. OX40 and OX40L protein expression was assessed in hepatic leukocytes, peripheral blood mononuclear cells (PBMCs), spleen, lamina propria (LP), and mesenteric lymph nodes (MLN) by flow cytometry. Human precision-cut liver slices (PCLS) were incubated in a MASH-inducing media (GFIPO: glucose, fructose, insulin, oleate, palmitate ± TNFα) and treated with Rocatinlimab, an antagonistic anti-OX40 monoclonal antibody. Markers of steatosis and inflammation were assessed by qPCR. **Results:** Within the murine CD45+ intrahepatic leukocytes, OX40 expression was predominantly detected in CD4+ T cells, with a significantly higher percentage in MASH livers, but was barely present in CD8+ T cells or other leukocytes. OX40+ CD4+ T cells were also increased in the spleen and PBMC, but not in MLN or LP. OX40L expression was low in normal liver leukocytes but significantly elevated in MASH livers, mainly due to increased OX40L+ monocyte-derived macrophages and a slight increase in OX40L+ dendritic cells. No changes in OX40L+ leukocytes were found in the spleen, MLN, LP, or PBMCs, indicating that OX40L upregulation is a liver-specific phenomenon. Human precision-cut liver slices incubated in GFIPO media developed steatosis alongside upregulation of genes linked to lipogenesis (e.g., FASN, DGAT2, SCD1) and inflammation, including CCL2 and OX40. Treatment of PCLS with Rocatinlimab decreased the mRNA expression of key CD4+ T cell-associated inflammatory markers, including IFNγ and CXCL10, indicating a role for OX40 signaling in MASH pathogenesis. **Conclusion:** In murine MASH, OX40 and OX40L were upregulated specifically in hepatic CD4+ T cells and monocyte-derived macrophages, respectively. Blocking OX40 in the human ex vivo MASH model reduced markers of inflammation, highlighting OX40 as a promising immunotherapeutic target to alleviate MASH.

Disclosures: Lucia Valenzuela Perez: Nothing to Disclose, Hyun Se Kim Lee: Nothing to Disclose, Alexander Washington: Nothing to Disclose, Shravan Mishra: Nothing to Disclose, Patrick Starlinger: Nothing to Disclose, Samar Ibrahim: Mirum pharmaceutical: Advisor, Albeiro pharma: Advisor, Adebowale Bamidele: Nothing to Disclose, Enis Kostallari: Nothing to Disclose, Petra Hirsova: Nothing to Disclose

1053 | INVESTIGATING THE ROLE OF MTARC1 RS2642438 (A165T) IN THE DEVELOPMENT AND PROGRESSION OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) USING HUMAN LIVER ORGANOIDS

Amel Ben Saad[1] Arden Weilheimer[1] Alan Mullen[1], [1]University of Massachusetts Chan Medical School

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent cause of chronic liver disease. MASLD is a progressive and multifactorial disease, starting with steatosis, which can progress to steatohepatitis, then fibrosis and can result in cirrhosis and/or liver cancer. Therapeutic options for patients with MASLD are limited. A better understanding of the pathogenesis and progression of MASLD is needed to identify more effective treatments. Different factors can regulate development, progression, and complications in MASLD, including environmental and genetic factors. Genome-wide association studies (GWAS) have identified susceptibility loci or SNPs (single nucleotide polymorphism) associated with an altered risk in developing liver disease, including the mitochondrial amidoxime reducing component 1 (*MTARC1*) *rs2642438 (A165T*) variant. In MASLD, there are strong data supporting the protective effect of the *MTARC1 rs2642438* variant in patients compared to those with the reference sequence, but little is known about the role of MTARC1 and the molecular pathways it regulates in the liver. The aim of this work is to investigate how *MTARC1 rs2642438* protects against MASLD progression using human liver organoids. **Methods:** We first edited human pluripotent stem cells (hPSCs) using prime editing to create the *MTARC1 rs2642438* variant. We then differentiated hPSCs with the *MTARC1* variant and those with the reference sequence into liver organoids and studied their phenotype and response to conditions that recapitulate MASLD in culture. **Results:** We find that liver organoids with the *MTARC1 rs2642438* variant recapitulate the protective phenotype observed in patients carrying the variant, with a reduction in steatosis and fibrosis. **Conclusion:** Understanding how MTARC1

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regulates the evolution of MASLD and resulting liver injury in a human model system will help us develop new therapeutic approaches to disrupt the progression of disease.

Disclosures: Amel Ben Saad: Nothing to Disclose, Arden Weilheimer: Nothing to Disclose, Alan Mullen: Nothing to Disclose

1054 | MASLD AND PNPLA3^{I148M} ASSOCIATE WITH SKELETAL FRAGILITY VIA DELETERIOUS LIVER-BONE CROSSTALK

Galen Goldscheitter[1] Mulugeta Seneshaw[1] Faridoddin Mirshahi[1] Ronnie Li[1] Damian Genetos[2] Henry Donahue[1] Arun Sanyal[1], [1]Virginia Commonwealth University, [2]University of California - Davis

Background: MASLD associates with increased risk of fracture and greater morbidity and mortality post-fracture. The PNPLA3 I148M variant (PNPLA3^{I148M}) accounts for most MASLD heritability and accelerates steatohepatitis development in MASLD. We have previously established that MASLD, and PNPLA3^{I148M}, are independent risk factors for bone disease, but mechanisms underlying this process are unexamined. **Methods:** 8-week-old DIAMOND (S129/C57BL6) isogenic cross mice (n = 40), a validated model of MASH, were injected with AAV containing human WT PNPLA3 (PNPLA3^{WT}) or PNPLA3^{I148M}. Groups were randomized to chow diet and normal water (CDNW) or high-fat diet and sugar water (WDSW) for 36 weeks. Only mice fed WDSW develop MASH. Bone geometry was analyzed by microcomputed tomography, strength in 3-point bending, and marrow adiposity via IHC against perilipin-1. *Pnpla3* expression was measured via RT-qPCR. Liver and bone RNA were sequenced in bulk on the Illumina NovaSeq XPlus platform. RNASeq analysis yielded differential gene expression, gene set enrichment, and ligand-target inference. **Results:** (1) Compared to CDNW, PNPLA3^{WT} mice fed WDSW developed diet-induced obesity and moderate steatohepatitis with stage 2 or 3 fibrosis; and PNPLA3^{I148M} mice developed more severe steatohepatitis and stage 3 or early stage 4 fibrosis. Only PNPLA3^{WT} WDSW mice lose bone volume and strength compared to CDNW, while PNPLA3^{I148M} sensitized mice to lose bone mass independent of diet. Bone marrow adiposity is markedly higher among mice fed WDSW than CDNW especially among PNPLA3^{I148M} (*Fig. A*). *Pnpla3* was expressed in both liver and bone. (2) Inflammatory interleukin signaling and TLR4 signaling pathways are upregulated in bone, suggesting a pro-resorptive inflammatory phenotype among mice fed WDSW, exacerbated by PNPLA3^{I148M}, while down-regulation of metabolic genes and calcium channels indicates a bone formation deficit (*Fig. B*). (3) NicheNet identified *Il1rn, Ccl12, Tnf, Il1b*, *Cd209, Ihh, Rarres1, Pdgfb,* and *Areg* as hepatic ligands dysregulating skeletal transcripts (*Fig. D*). These include induction of *Tnf, Il6, Il10, Il12b, Pparg,* and *Nfkbiz* and suppression of *Tgfb2, Tnfrsf11b, Pthlh, Vegfd,* and *Mmp3* in bone (*Fig. C*). **Conclusion:** Diet-induced obesity and MASLD associate with multiple markers of bone disease which are exacerbated by PNPLA3^{I148M}. Further, these hepatic features associate with a bone inflammatory phenotype accelerating skeletal catabolism while preventing osteoanabolism. These data firmly establish deleterious liver-bone crosstalk in MASLD with PNPLA3^{I148M}, driven by inflammatory cytokines upregulated in MASLD.

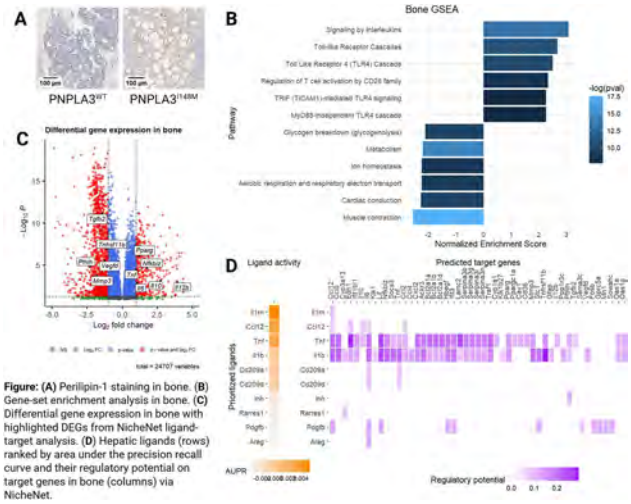

Figure: **(A)** Perilipin-1 staining in bone. **(B)** Gene-set enrichment analysis in bone. **(C)** Differential gene expression in bone with highlighted DEGs from NicheNet ligand-target analysis. **(D)** Hepatic ligands (rows) ranked by area under the precision recall curve and their regulatory potential on target genes in bone (columns) via NicheNet.

Disclosures: Galen Goldscheitter: Nothing to Disclose, Mulugeta Seneshaw: Nothing to Disclose, Faridoddin Mirshahi: Nothing to Disclose, Ronnie Li: Nothing to Disclose, Damian Genetos: Nothing to Disclose, Henry Donahue: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (< 5K), Terns (< 5K), Merck (< 5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (< 5K),: Consultant, Novo Nordisk: Consultant, Regeneron (< 5K), Alnylam (< 5K), Akero (< 5K),: Consultant, Tern (< 5K), Histoindex (< 5K), Corcept (< 5K),: Consultant, Path AI (< 5K), Genfit (< 5K), Mediar (< 5K),: Consultant, Satellite Bio (< 5K), Echosens (< 5K), Abbott (< 5K),: Consultant, Promed (< 5K), Glaxo Smith Kline (~11K), Arrowhead (< 5K): Consultant, Zydus (>60K), Boston Pharmaceutical (< 5K), Myovent (< 5K),: Consultant, Variant (< 5K), Cascade (< 5K), Northsea (< 5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda:

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Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor

1055 | THE INNER NUCLEAR MEMBRANE PROTEIN SUN1 REGULATES CULLIN-3 NEDDYLATION TO MAINTAIN INSULIN SENSITIVITY

Kapil Upadhyay[1] Yunshu Yang[1] Aren Shah[1] Venkatesha Basrur[1] Alexey Nesvizhskii[1] Graham Brady[1], [1]University of Michigan, Ann Arbor, Michigan, USA

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease and a growing cause of morbidity and mortality, with strong epidemiologic links to obesity and insulin resistance. We previously reported an association between the common nuclear envelope variant rs6461378 (g.842031C > T; *SUN1* H118Y) and hepatic steatosis, histologic MASLD, and related metabolic traits including insulin resistance. Here we report identification of a novel variant-specific SUN1-cullin-3 association, providing a potential mechanistic basis by which wild-type (WT) SUN1 protects against MASLD, while H118Y SUN1 drives insulin resistance and MASLD. **Methods:** To discover SUN1-interacting proteins and elucidate how H118Y SUN1 contributes to MASLD, we performed affinity purification-mass spectrometry (AP-MS) in Huh7 cells stably expressing mCherry-tagged WT or H118Y SUN1 and control Huh7 cells (n = 3 replicates each). Differential protein-protein interactions identified by AP-MS were validated by co-immunoprecipitation (co-IP) and immunoblotting. Confirmatory functional studies included siRNA-mediated gene silencing, pharmacologic blockade of protein neddylation (MLN4924), and insulin treatment followed by cell lysis, SDS-PAGE, and immunoblot. **Results:** Unbiased AP-MS revealed a novel regulatory SUN1-cullin-3 interaction, with comparative analysis showing that WT SUN1 interacted robustly with cullin-3, while cullin-3 interaction was markedly diminished with H118Y SUN1 (abundance ratio 0.01 relative to WT SUN1; $P < 10^{-15}$), which was confirmed via co-IP and immunoblot (see Figure). Silencing of endogenous *SUN1* via siRNA in Huh7 cells increased cullin-3 neddylation – a modification essential for cullin RING ligase (CRL)-mediated ubiquitination of target proteins, including insulin receptor substrate (IRS) proteins. Furthermore, H118Y SUN1-expressing Huh7 cells exhibited elevated levels of neddylated cullin-3 and reduced IRS-1 levels compared to WT SUN1-expressing cells. Finally, pharmacologic inhibition of cullin neddylation restored IRS-1 levels and insulin sensitivity in H118Y SUN1-expressing cells. **Conclusion:** Our findings support a model in which the H118Y variant of SUN1 disrupts its regulation of cullin-3, leading to enhanced cullin-3 neddylation and impaired insulin signaling. These findings provide both a potential mechanism of H118Y SUN1-driven insulin resistance and a viable therapeutic approach for its reversal.

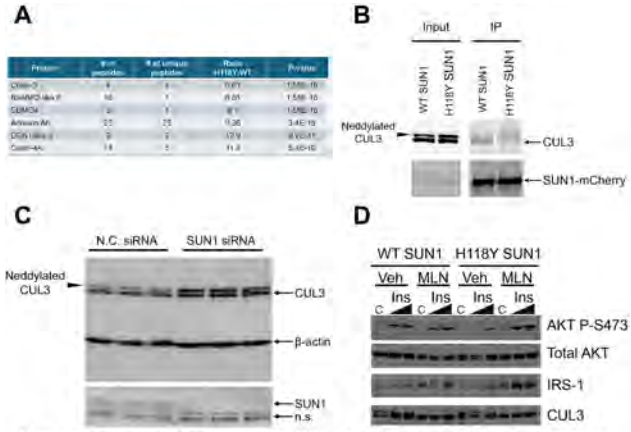

Figure Legend: Unbiased AP-MS reveals a novel SUN1-cullin-3 interaction that regulates insulin signaling. *A*, several of the top unique or preferential WT or H118Y SUN1-interacting proteins identified via AP-MS are shown. *B*, stably expressed WT SUN1 co-precipitates endogenous CUL3 (cullin-3) to a greater degree than H118Y SUN1 in Huh7 cells. Native cullin-3 is indicated by an arrow, while neddylated cullin-3 (higher band) is indicated via arrowhead. *C*, *SUN1* silencing increased cullin-3 neddylation in Huh7 cells. Cells were treated with siSUN1 oligos or a negative control (N.C.) oligo in triplicate, followed by lysis, SDS-PAGE, and immunoblot. n.s., non-specific bands present due to incomplete stripping of the membrane. *D*, a cullin neddylation inhibitor (MLN4924; MLN) restores insulin (Ins) sensitivity in H118Y SUN1-expressing Huh7 cells. Cells were treated with 1 or 10 nM human insulin for 20 min, with or without MLN4924 pre-treatment (1 μM, 16h), followed by lysis, SDS-PAGE, and immunoblot. C, control medium; Veh, vehicle (DMSO).

Disclosures: Kapil Upadhyay: Nothing to Disclose, Yunshu Yang: Nothing to Disclose, Aren Shah: Nothing to Disclose, Venkatesha Basrur: Nothing to Disclose, Alexey Nesvizhskii: Nothing to Disclose, Graham Brady: Orphalan: (note I am a co-I, not a PI), Ultragenyx: (note I am a co-I, not a PI), Vivet Therapeutics: (note I am a co-I, not a PI), Bausch Health US, LLC: Grant/Research Support, Bausch Health US, LLC: (note that I am a co-I, not a PI)

1056 | INTEGRATIVE FUNCTIONAL DISSECTION OF NONCODING GENETIC VARIANTS ASSOCIATED WITH METABOLIC LIVER DISEASE

Yang Xiao[1] Biying Zhu[2] Na He[2] Bin Chen[3] Chen Li[2] Yifan Liu[4] Jiayu Zhang[4] Xiao Chang[5] Fulong Yu[2] Marijana Vujkovic[4] Julie Lynch[6] Kyong-Mi Chang[4] Daniel Rader[4] Mitchell Lazar[4] Wenxiang Hu[2], [1]UNIVERSITY OF PENNSYLVANIA, [2]Department of Basic Research, Guangzhou National Laboratory, Guangzhou 510005, China, [3]Zhongshan School of Medicine, Sun Yat-Sen University, Guangdong 510080, China, [4]Institute for Diabetes, Obesity, and Metabolism, Department of Medicine, University of Pennsylvania, [5]College of Medical Information and Artificial Intelligence for Medical Sciences, Shandong, China, [6]Salt Lake City Veterans Affairs Medical Center, Salt Lake City, UT, 84112, USA

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent and clinically heterogeneous, highlighting the needs to identify individuals at high risk. Genetic predisposition is a major contributor to MASLD. While genome-wide association studies (GWAS) have identified numerous genetic variants

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associated with MASLD, their causality and functional roles, especially in non-coding regions, remain largely unexplored. **Methods:** To systematically investigate MASLD-associated noncoding variants from GWAS, we used a massively parallel reporter assay (MPRA) to screen for cis-regulatory activity *in vitro*. We also performed single-nucleus ATAC-seq (snATAC-seq) on human livers to map active regulatory regions *in vivo*. By integrating these two datasets, we prioritized functional variants in the form of single nucleotide polymorphisms (SNPs) likely involved in MASLD. We determined their target genes using CRISPR perturbation and base editing, and assessed clinical relevance via polygenic risk score in the Million Veteran Program (MVP) cohort. **Results:** Roughly half of MASLD-associated noncoding SNPs showed cis-regulatory activity, with 365 demonstrating allele-specific effects *in vitro*. Integrating with snATAC-seq data prioritized 87 functional variants (FrVar) in a cell type-specific context. We linked FrVar to their target genes, including rs474513, which regulates the transcription of cation transporter OCT3 and OCT3-associated lipid metabolism. The polygenic risk score built from FrVar performed comparably to the one built from 9 well-known MASLD risk variants, including PNPLA3 I148M. **Conclusion:** Our integrative approach reveals the regulatory functions of noncoding SNPs in MASLD, which were largely unknown. These variants influence key gene expression and MASLD-associated pathology, and serve as strong predictors of disease risk, offering insights into MASLD patient management and risk stratification.

Disclosures: Yang Xiao: Nothing to Disclose, Biying Zhu: Nothing to Disclose, Na He: Nothing to Disclose, Bin Chen: Nothing to Disclose, Chen Li: Nothing to Disclose, Yifan Liu: Nothing to Disclose, Jiayu Zhang: Nothing to Disclose, Xiao Chang: Nothing to Disclose, Fulong Yu: Nothing to Disclose, Marijana Vujkovic: Nothing to Disclose, Julie Lynch: Nothing to Disclose, Kyong-Mi Chang: Virion Therapeutics: Data Monitoring Committee member, GSK: Advisor, Daniel Rader: Nothing to Disclose, Mitchell Lazar: Pfizer: Advisor, Flare Therapeutics: Advisor, Eccogene: Advisor, Wenxiang Hu: Nothing to Disclose

1057 | THE DUAL ROLE OF APOLIPOPROTEIN C3 IN THE DEVELOPMENT OF MAFLD

Wei Zhang[1] Xiawen Yang[2] Mingming Gao[3] Xiangsha Kong[4] Lin Zhang[5] Zhengxi Wang[6] Haizhao Yan[7], [1]Peking University People's Hospital, Beijing, China, [2]Wuyi University, Jiangmen, Guangdong, China, [3]Hebei Medical University, Shijiazhuang, Hebei, China, [4]Peking University People's Hospital, Beijing, China, [5]Peking University People's Hospital, Beijing, China, [6]Capital Medical University, Beijing, China, [7]Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China

Background: Apolipoprotein C3 (APOC3) plays a pivotal role in mediating plasma triglyceride (TG) homeostasis. However, it remains controversial whether APOC3 is related to metabolic dysfunction-associated steatotic liver disease (MASLD) and its potential mechanism in the progression. The aims of our study were to clarify the histological features of the liver in APOC3-transgenic animal models, to explore its potential mechanisms and to assess the correlation of APOC3 levels to hepatic steatosis degree in MAFLD patients. **Methods:** APOC3 knockout (KO) rabbits and human APOC3 overexpressing mice with a background of Leptin deficiency (ob/ob-C3Tg) were used in the experiment. The plasma lipids, glucose and insulin were measured, and the insulin (ITT) and glucose tolerance test (GTT) were performed. The clinical data were collected and analyzed in MAFLD patients whose steatosis degree (CAP) and fibrosis stages (SLM) were evaluated using FibroScan. **Results:** After 22 weeks of the high fructose and fat diet feeding, liver histological analysis in APOC3 KO rabbits exhibited macrovesicular steatosis, but no hepatocellular ballooning (Fig1). They also showed constantly and significantly lower levels of plasma TG, TC and FFA compared with wild-type rabbits. However, higher insulin levels and no change of glucose levels were found. These results suggested that APOC3 deficiency could increase excess lipid accumulation in the hepatocytes and its role be associated with insulin resistance (IR). After 16 weeks of chow diet feeding, liver histological assessment in ob/ob- C3Tg mice indicated macrovesicular and microvesicular steatosis, inflammatory cell infiltration and hepatocellular ballooning (Fig1). They had significantly higher levels of plasma TG, TC and FFA compared with ob/ob mice. And no significant differences in results of ITT, GTT and glucose evaluation between two groups were found. As we all know, ob/ob mice do not spontaneously progress from steatosis to steatohepatitis. These results suggested that the APOC3 overexpressing could induce the incidence of steatohepatitis, and its role might not be associated with IR. In the patient cohort, no significant correlations were found between plasma APOC3 and CAP or LSM values. **Conclusion:** In this study, our findings provide new insight into the roles of APOC3 in MAFLD. APOC3 plays dual roles as an inhibition in the progress from normal to steatosis, and a promotion in the process from steatosis to steatohepatitis. The deficient and overexpression of APOC3 are paradoxically associated with insulin resistance, and further experiments are ongoing.

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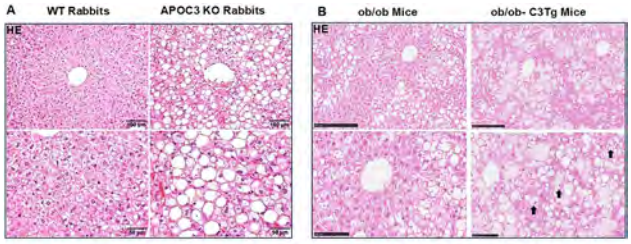

Figure 1. Representative images of liver cross-sections stained with hematoxylin and eosin (H&E) (**A**) APOC3 KO rabbits exhibited macrovesicular steatosis without hepatocellular ballooning and inflammation. (**B**) ob/ob- C3Tg mice exhibited macrovesicular and microvesicular steatosis, and hepatocellular ballooning (Black arrow).

Disclosures: Wei Zhang: Nothing to Disclose, Xiawen Yang: Nothing to Disclose, Mingming Gao: Nothing to Disclose, Xiangsha Kong: Nothing to Disclose, Lin Zhang: Nothing to Disclose, Zhengxi Wang: Nothing to Disclose, Haizhao Yan: Nothing to Disclose

1058 | ERBB3 IS A NOVEL THERAPEUTIC TARGET FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Shehnaz Bano[1] Bharat Bhushan[1] George Michalopoulos[1] Anne Orr[1] John Stoops[1] Shirish Paranjpe[1] Joseph Locker[1] Alejandro Soto-Gutierrez[1] Rodrigo Florentino[1], [1]University of Pittsburgh

Background: MASLD is the most common chronic liver disorder worldwide, yet effective targeted therapies remain elusive. In our previous study, pan-ErbB inhibition showed promising efficacy in reversing steatosis and fibrosis in a preclinical MASLD model. However, the specific ErbB receptor responsible for these therapeutic effects remains undefined. Our prior work also demonstrated that hepatocyte-specific deletion of ErbB1 (EGFR) does not prevent MASLD, implicating other ErbB family members. This study investigates for the first time the role of ErbB3 (HER3), the only other ErbB receptor expressed in hepatocytes, in MASLD pathogenesis using a hepatocyte-specific knockout model. **Methods:** Hepatocyte-specific ErbB3 knockout (ErbB3-HepKO) mice were generated by administering AAV8-TBG-CRE to ErbB3$^{flox/flox}$ mice and were fed fast-food diet for up to 5 months. Complementary studies were conducted in steatotic primary human hepatocytes to validate translational relevance. **Results:** ErbB3-HepKO attenuated MASLD progression in mice, evidenced by marked reductions in hepatic steatosis and fibrosis markers along with improved insulin sensitivity. ErbB3 deletion decreased expression of major lipogenic genes while upregulating lipolytic genes. Mechanistically, ErbB3 regulated critical MASLD driving transcription factors like PPARγ and HNF4α, with increased nuclear HNF4α expression in KO livers. Further, ErbB3 deletion downregulated several pro-inflammatory and fibrotic pathways including TNFα and TGFβ. Notably, NRG1, the ErbB3 ligand, and ErbB3 signaling were elevated in both murine and human MASLD/MASH, correlating with disease severity. The protective effects of ErbB3 deletion paralleled those observed with pharmacological pan-ErbB inhibition in our previous studies. Importantly, both a clinically approved pan-ErbB inhibitor and specific ErbB3 knockdown reduced lipid accumulation in primary cultures of steatotic human hepatocytes from MASH patients, as well as in healthy hepatocytes exposed to fatty acids, further supporting the clinical relevance of targeting ErbB3. **Conclusion:** Our findings identify ErbB3 in hepatocytes as a pivotal regulator of MASLD progression, distinct from EGFR, and demonstrate that its deletion recapitulates the therapeutic benefits of pan-ErbB inhibition. This work highlights ErbB3 as a novel and promising therapeutic target for MASLD, with conserved NRG1/ErbB3 signaling pathways in human disease, paving the way for targeted interventions.

Disclosures: Shehnaz Bano: Nothing to Disclose, Bharat Bhushan: Nothing to Disclose, George Michalopoulos: Nothing to Disclose, Anne Orr: Nothing to Disclose, John Stoops: Nothing to Disclose, Shirish Paranjpe: Nothing to Disclose, Joseph Locker: Nothing to Disclose, Alejandro Soto-Gutierrez: Nothing to Disclose, Rodrigo Florentino: Nothing to Disclose

1059 | DEVELOPMENTAL EXPLORATION OF FERMENTED AMOMUM XANTHIOIDES DERIVATIVES AS NOVEL THERAPEUTIC AGENTS FOR MASLD AND METABOLIC SYNDROME

Seung-Ju Hwang[1], [1]Daejeon University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), alongside metabolic syndrome (MS), represents a growing global health burden due to its increasing prevalence and limited pharmacological treatment options. This research series was designed to evaluate the therapeutic efficacy of Amomum xanthioides (AX) and its bioenhanced forms—specifically the ethyl acetate fraction (EFAX) and fermented AX using Bacillus subtilis (BAX) or Lactobacillus casei (LAX)—in high-fat diet (HFD)-induced murine models. **Methods:** Two separate preclinical experiments were conducted using male C57BL/6J mice, fed a 60% HFD for 10 weeks. From week 4 to 10, AX-based formulations (AX, EFAX, BAX, LAX) and metformin (200 mg/kg/day) were administered orally. Experimental groups included (1) control vs. AX vs. LAX and (2) control vs. AX vs. BAX). Primary outcomes focused on hepatic steatosis (hepatic triglyceride

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and cholesterol levels) and insulin resistance (fasting glucose and serum insulin), while secondary parameters included changes in body composition, food intake, and hepatic inflammatory status. **Results:** AX and its processed forms significantly alleviated HFD-induced weight gain, adiposity, and hepatic lipid buildup. LAX, in particular, notably improved insulin resistance markers, including fasting glucose, insulin, and HOMA-IR, via enhanced expression of GLUT2/GLUT4 and insulin receptors. Both BAX and LAX exerted potent anti-inflammatory effects by lowering systemic IL-6 and downregulating hepatic pro-inflammatory mediators (TNF-α, IL-1β) and oxidative stress markers (ROS and MDA). Furthermore, LAX promoted lipid homeostasis through suppression of lipogenesis (SREBP-1 and GPAM) and activation of lipolysis-related proteins (PPAR-α and AMPK-α). Improvements in circulating lipid profiles further supported the metabolic benefits of BAX and LAX. **Conclusion:** These findings indicate that microbial fermentation significantly enhances the pharmacological actions of AX. Fermented AX products, particularly LAX and BAX, exhibit promising therapeutic potential for MASLD and MS through multifaceted metabolic and anti-inflammatory mechanisms.

Disclosures: Seung-Ju Hwang: Nothing to Disclose

1060 | HSD17B13 REGULATES HEPATIC LIPID DROPLET DYNAMICS IN A MOUSE MODEL OF MASLD

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by hepatic lipid droplet (LD) accumulation. Genetic studies in MASLD identified multiple hepatic LD proteins that modulate disease severity, suggesting LD as a key organelle in disease pathogenesis. 17-beta hydroxysteroid dehydrogenase-13 (HSD17B13) is an LD-associated liver enzyme in which genetic loss-of-function variants confer protection from MASLD-associated liver injury in humans. Although anti-HSD17B13 therapies are in clinical trials, HSD17B13 function is unknown. We aimed to determine the effects of HSD17B13 on hepatic LD properties and dynamics. **Methods:** *Hsd17b13* knock-out (KO) and wildtype (WT) mice were fed high-fat diet for 8 weeks. Liver LDs were isolated by sucrose gradient and ultracentrifugation and analyzed by LC/MS/MS (lipidomics) and western blot (protein). Primary hepatocytes (PH) from WT and *Hsd17b13*-KO mice were treated with oleate:palmitate (2:1) with LD size measured by microscopy and LD fusion via live-cell imaging. **Results:** *Hsd17b13*-KO did not affect body weight, liver weight, or liver triglyceride content, as we previously published. However, *Hsd17b13*-KO livers and *Hsd17b13*-KO PH showed larger LDs. LD fusion was more frequent in *Hsd17b13*-KO PH, and CIDEC, which mediates LD fusion, was upregulated in livers from *Hsd17b13*-KO, with no change in proteins related to LD consumption (lipolysis or autophagy). Moreover, in WT PH, HSD17B13 was only found on small LDs, with no droplet >6 μm diameter showing HSD17B13. *Hsd17b13*-KO LDs had higher phosphatidylinositol (PI) concentration compared to WT. Interestingly, protein levels of two enzymes involved in the PI cycle, phosphatidylinositol 3-kinase and phosphatidylinositol 4-kinase, were increased in *Hsd17b13*-KO LDs. In a protein-lipid overlay assay, HSD17B13 directly interacted with PI and two phosphoinositides (PIPs) species. Through molecular docking, we identified regions rich in lysine and arginine residues in HSD17B13 interacting with PI/PIPs. **Conclusion:** In conclusion, HSD17B13 inhibits LD fusion and the formation of large LDs, possibly through its PI/PIPs interaction. Further experiments are needed to determine if this role underlies the protective effect of HSD17B13 loss-of-function variants.

Disclosures: Lila Gonzalez Hodar: Nothing to Disclose, David Kleiner: Nothing to Disclose, Lalith Perera: Nothing to Disclose, Yaron Rotman: Astra Zeneca: My spouse is an employee

1061 | MINCLE—THE IMMUNE ALARM AMPLIFYING METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

Farhin Patel[1] Colin Varnet[1] Adam Kim[1], [1]UConn Health

Background: In the U.S., the prevalence of MASH has increased radically, currently affecting 5% of the adult population. MASH is a progressive liver disease that is linked to obesity and metabolic syndrome, where excessive accumulation of fat in the liver leads to inflammation and fibrosis. Patients with MASH have an increased risk for severe infections, likely due to dysfunctional immune responses. Mincle is a pattern recognition receptor in the C-type lectin receptor family that is involved in MASH through recognition of damage-associated molecular patterns (DAMPs), which leads to infiltrating immune cells and increased injury in liver and adipose tissue. Mincle knockout (MKO) mice are protected from liver injury caused by a high-fat diet, making Mincle a potential therapeutic target. But our group has found that MKO mice have worse adipose tissue inflammation in response to acute stimulation with bacterial lipopolysaccharides (LPS). We hypothesize that Mincle is an essential immune regulator in the liver and adipose tissue during MASH and in response to infection.

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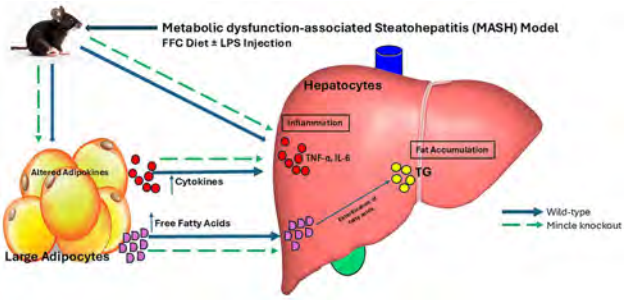
Methods: To model MASH, 5-week-old C57BL/6 and MKO mice were fed with a fat-, fructose, and cholesterol-rich (FFC) diet or standard rodent chow for 12 weeks. Mice were administered LPS (0.7 mg/kg) or saline intraperitoneally 24 hr before euthanizing as a model of acute bacterial infection during MASH. At the end of the experiment, the animals were monitored in the Comprehensive Lab Animal Monitoring System (CLAMS) for total metabolic activity. **Results:** MKO-FFC-LPS mice depicted reduced liver weight, liver-to-body weight ratio, and triglyceride levels compared to the WT-FFC-LPS group. Both liver and adipose tissue had reduced inflammatory markers in the MKO FFC-LPS group compared to the WT-FFC-LPS. In adipose tissue, the MKO-FFC-LPS fed group markedly inhibited the Ly6G levels compared to the WT-FFC-LPS fed group. Similarly, adipokines like leptin and resistin transcript levels were down-regulated, while adiponectin was up-regulated in the MKO-FFC-LPS fed group compared to the WT-FFC-LPS fed group. CLAMS data show that MKO mice ate less FFC diet than WT mice, but similar levels of energy expenditure. In response to LPS, MKO-FFC-LPS mice ate much more food than WT-FFC-LPS mice, suggesting a better overall response to infection. **Conclusion:** Targeting Mincle could be a strategic preventative approach for attenuating inflammation in MASH.



Disclosures: Farhin Patel: Nothing to Disclose, Colin Varnet: Nothing to Disclose, Adam Kim: Nothing to Disclose

1062 | XIAYUXUE DECOCTION ALLEVIATES MASH BY RESHAPING GUT MICROBIOTA AND REGULATING ARACHIDONIC ACID AND BILE ACID METABOLISM VIA ACTIVATING FXR-SHP1/2 PATHWAY AND AFFECTING M6A TRANSCRIPTIONAL MODIFICATIONON

Yang Cheng[1], [1]Shuguang Hospital affiliated to Shanghai University of TCM

Background: Metabolic dysfunction-associated steatohepatitis (MASH) has emerged as a major global health challenge. Xiayuxue decoction, composed of Rheum palmatum L., Prunus persica (L.) Batsch, and Eupolyphaga sinensis Walker, is widely utilized in managing MASH in China. However, its precise therapeutic mechanisms remain elusive. This study aimed to elucidate the therapeutic mechanisms of Xiayuxue decoction in MASH by investigating its roles in gut microbiota remodeling, bile acid and arachidonic acid metabolism regulation, and m6A transcriptional modification. **Methods:** The chemical composition of Xiayuxue decoction was characterized using UHPLC-Exactive Orbitrap HRMS. A methionine-choline-deficient (MCD) diet-induced MASH model was established in male C57BL/6J mice for 5 weeks. Serum samples were collected for biochemical analysis of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and total bile acids (TBA). Hepatic histopathology was assessed through hematoxylin-eosin (H&E) and Sirius red staining, while intrahepatic lipid accumulation was quantified via triglyceride (TG) assay kit and Oil Red O staining. Gut microbiota composition was analyzed by 16S rRNA gene sequencing. Liver, serum, and fecal metabolites, particularly arachidonic acid derivatives, were profiled using LC-MS/MS system. Real-time quantitative PCR, Western blotting, and dot blot analyses were performed to evaluate mRNA and protein expression patterns associated with bile acid metabolism, lipid homeostasis, inflammatory response, and m6A modification machinery. In vitro, RAW264.7 macrophages were treated with deoxycholic acid (DCA) or Xiayuxue decoction to assess their effects on inflammatory cytokine production and m6A dynamics. **Results:** 16S rRNA sequencing revealed that Xiayuxue decoction ameliorated intestinal dysbiosis in MASH mice. Compared with the MCD group, the decoction significantly restored α diversity and β diversity ($P < 0.01$). **Conclusion:** Xiayuxue decoction alleviates MASH by reshaping gut microbiota and regulating arachidonic acid and bile acid metabolism via activating FXR-SHP1/2 pathway and affecting m6A transcriptional modification.

Disclosures: Yang Cheng: Nothing to Disclose

1063 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS SENSITIZES TO ACETAMINOPHEN HEPATOTOXICITY

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Background: Obesity is a global epidemic and a major driver of Metabolic Dysfunction-Associated Steatotic Liver

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Disease (MASLD), which is characterized by hepatic steatosis, liver injury, inflammation, and fibrosis. These changes exacerbate liver injury and alter drug metabolism. Acetaminophen (APAP) overdose remains the leading cause of drug-induced liver injury (DILI), and sex differences are known to influence susceptibility and severity. However, the interplay between obesity-driven MASLD and APAP hepatotoxicity, particularly regarding sex disparities, is not well understood. **Methods:** Male and female C57BL/6J mice were fed either a standard or high-fat high-cholesterol (60% calories from fat and 0,5% added cholesterol; HFHC) diet for 3 months. Male and female mice were administered a single APAP dose (300 mg/kg) and sacrificed 4 hours later. Biochemical, histological, and molecular responses were assessed to evaluate the synergistic damage between diet and APAP. **Results:** Feeding HFHC diet robustly increased body weight, liver mass, and hepatic lipid accumulation in both sexes, with males exhibiting more pronounced macrosteatosis and higher cholesterol, triglycerides, and free cholesterol levels than females. Histology analyses confirmed severe macrosteatosis in males and relative protection in females. HFHC feeding downregulated fatty acid oxidation genes (*Cpt1*, *Vlcad*, *Pgc1a*, *Pparα*) and upregulated lipogenic genes (*Srebf1*, *Pparγ*), with changes being more predominant in male than female mice. APAP further impaired these pathways, especially when combined with HFHC.

Markers of liver injury (ALT, AST) and autophagy impairment (p62 accumulation) increased with HFHC and APAP, being male mice more affected than female mice. HFHC diet and APAP treatment induced Inflammatory infiltration (F4/80 macrophages, MPO+ neutrophils), with males showing a pro-inflammatory profile (increased expression of *Il-1β, Il-6* and *Spp1*) and females an anti-inflammatory response (*Il-10, TGF-β, Arg1*), linked to higher estrogen receptor α expression and miRNA34a levels in females. HFHC and APAP induced stress markers, including Stard1, Sab, and p-JNK, particularly in males, indicating greater mitochondrial and ER stress. Gene expression analyses revealed sex-specific differences in ER stress (Ddit3, Xbp1s/u, Hspa5) and cytochrome P450 enzymes (Cyp7a1, Cyp27a1), with males more susceptible to stress and lipid dysregulation. **Conclusion:** Male mice exhibit greater vulnerability to diet- and APAP-induced hepatic steatosis, oxidative and ER stress, inflammation, and injury, driven by heightened metabolic and inflammatory pathway activation, suggesting that females are protected due to estrogen pathway activation. These findings highlight a sex-dependent MASH sensitization to APAP hepatotoxicity and underscore the need for sex-tailored interventions in MASLD and DILI.

Disclosures: Laura Fàbrega: Nothing to Disclose, Paula Segales: Nothing to Disclose, Susana Núñez: Nothing to Disclose, Manuel Romero-Gómez: Nothing to Disclose, Carmen Garcia-Ruiz: Nothing to Disclose, Jose Fernandez-Checa: Nothing to Disclose

1064 | SYNERGISTIC EFFECTS OF ECC4703, A LIVER-TARGETING THRB FULL AGONIST, IN COMBINATION WITH ECC0509, A SELECTIVE SSAO INHIBITOR, OR SEMAGLUTIDE IN A MASH ANIMAL MODEL

Jianfeng Xu[1] Xuefeng Sun[1] Jingye Zhou[2], [1]Eccogene (Shanghai) Co., Ltd., [2]Eccogene Inc.

Background: Metabolic dysfunction-associated steatohepatitis (MASH, previously known as nonalcoholic steatohepatitis [NASH]) is a chronic, serious, life-threatening, inflammatory liver disease characterized by increased liver fat content, hepatocellular injury, inflammation, and progressive fibrosis. In view of the complexity of manifestation and serious nature of the disease, employing a combination of orthogonal mechanisms may be necessary to achieve optimal efficacy for the treatment of MASH. Eccogene is developing ECC4703, a selective THRβ full agonist, and ECC0509, a mechanism-based inhibitor of semicarbazide sensitive amine oxidase (SSAO). Both molecules have demonstrated favorable safety and tolerability profiles, PK and PD profiles supporting once daily dose, and clear target engagement in phase I clinical trials. Additionally, GLP-1 analogues are being widely used for the treatment of diabetes and obesity which are common co-morbidities of MASH. **Methods:** The mouse MASH model was established by high fat diet feeding and CCL4 induction, followed by 28-days treatment of Vehicle (G1), Semaglutide 10 nmol/kg (G2), ECC4703 3 mg/kg (G3), ECC0509 20 mg/kg (G4), ECC4703 3mg/kg and Semaglutide 10 nmol/kg (G5) and ECC4703 3 mg/kg and ECC0509 20 mg/kg (G6), respectively. At the end of the study, the liver tissue was dissected for histology evaluation of NAFLD Activity Score (NAS) and fibrosis. Liver enzymes, liver cholesterol and triglyceride (TG), plasma cholesterol and TG, fasting glucose and insulin were also measured. **Results:** THRβ agonist ECC4703 is effective to decrease liver NAS and fibrosis along with other metabolic benefits in this MASH model. The combination of ECC4703 with other mechanisms, i.e., Semaglutide or ECC0509, resulted in greater improvement compared to mono-agent treatment in fibrosis score and other metabolic and liver related endpoints. **Conclusion:** ECC4703 has the potential to be the corner stone for combination with other mechanisms to treat MASH in humans.

Disclosures: Jianfeng Xu: Eccogene (Shanghai) Co., Ltd.: Executive role, Xuefeng Sun: Nothing to Disclose, Jingye Zhou: Nothing to Disclose

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1065 | TOX3 PROMOTES MASH PROGRESSION BY REGULATING HEPATIC A-LINOLENIC ACID METABOLISM VIA THE PI3K/AKT SIGNALING PATHWAY

Shaoping She[1] Liying Ren[1] Xue Zhang[1] Dongbo Chen[1] Ran Fei[1] Feng Liu[1] Huiying Rao[1] Hongsong Chen[1], [1]Peking University People's Hospital, Peking University Hepatology Institute

Background: The escalating global burden of metabolic dysfunction-associated steatohepatitis (MASH), now a predominant etiology of chronic liver disease, underscores an urgent need for mechanistically informed therapies. Thymocyte selection-associated high mobility group box factor 3 (TOX3) is a member of an evolutionarily conserved DNA-binding protein family. While our prior work identified TOX3 as a driver of hepatocellular carcinoma (HCC) through lipid metabolic reprogramming, its functional role in MASH pathogenesis remains unexplored. This study aims to delineate the mechanistic contributions of TOX3 to MASH progression and evaluate its therapeutic potential. **Methods:** TOX3 expression was profiled in liver biopsies from MASH patients and validated in two mechanistically distinct murine MASH models: Western diet with carbon tetrachloride injection (WD + CCl_4) and high-fat methionine-choline deficient diet (HFMCD). The role of TOX3 was evaluated in systemic Tox3 gene knockout (*Tox3*$^{-/-}$) mice and hepatocyte-specific Tox3 knockout (*Tox3*^{Hep}) mice in vivo. In vitro studies involved treating THLE-2 (normal hepatocytes) and HepG2 cells with free fatty acids (FFA) and lipopolysaccharide (LPS), as well as manipulating TOX3 expression via small interfering RNA (siRNA) and overexpression plasmids. Multi-omics integration of single-cell RNA sequencing and serum metabolomics were used to explore the molecular mechanism of TOX3 regulation of MASH progression. **Results:** In this study, we found that TOX3 expression was significantly downregulated in both MASH patients and WD+CCl_4 or HFMCD-induced mouse MASH models. TOX3 deficiency resulted in a marked amelioration of MASH pathological phenotypes in mice, including hepatic steatosis, inflammation, and fibrosis. In vitro studies demonstrated that TOX3 overexpression significantly promoted lipid droplet formation and upregulated pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) expression in THLE-2 cells under combined FFA/LPS stimulation, whereas TOX3 silencing in HepG2 cells reversed these phenotypes. Mechanistically, our multi-omics analyses revealed that TOX3 activates the PI3K/Akt signaling pathway to drive α-linolenic acid (ALA) metabolic reprogramming in hepatocytes. This process synergistically enhances lipogenesis (via the SREBP-1c/FASN axis) and secretion of pro-inflammatory cytokines (e.g., TNF-α and IL-6), ultimately accelerating the pathological progression of MASH. **Conclusion:** Collectively, our findings established TOX3 as a critical regulator of MASH pathogenesis through PI3K/Akt-mediated coupling of lipid metabolism and inflammatory cascades. Targeting TOX3-mediated crosstalk between metabolic and inflammatory pathways may offer novel therapeutic strategies for MASH and its complications.

Disclosures: Shaoping She: Nothing to Disclose, Liying Ren: Nothing to Disclose, Xue Zhang: Nothing to Disclose, Dongbo Chen: Nothing to Disclose, Ran Fei: Nothing to Disclose, Feng Liu: Nothing to Disclose, Huiying Rao: Nothing to Disclose, Hongsong Chen: Nothing to Disclose

1066 | LEVERAGING MULTI-OMIC APPROACHES TO INTERROGATE DYSREGULATION IN MASH LIVER DISEASE

APOORVA MOHAN[1] Divya Ravichandar[1] Anjali Rao[1] Edith Vaquero[1] SANGEETHA MAHADEVAN[2] David Lopez[1] GRANT BUDAS[2] Anna Zagorska[1] Lauri Diehl[1] Hsiu-Chun Chuang[1], [1]GILEAD SCIENCES, [2]GILEAD SCIENCES, INC.

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a chronic liver disease marked by involvement of different cell types and widespread dysregulation of key cellular pathways. Single cell RNAseq approaches provide insight into transcriptionally altered cellular populations and, when combined with spatial transcriptomic (ST) approaches, enable the dissection and localization of these aberrant populations in disease specific niches. The experimental execution and analyses of these large datasets are currently poorly standardized. In this study, we have streamlined the experimental and analytical steps to generate a high-quality, robust multi-omic dataset and to facilitate an unbiased characterization of parenchymal and fibrotic niches in MASH. **Methods:** Formalin fixed paraffin embedded (FFPE) liver surgical resection samples from 6 healthy, 6 MASH F3 and 7 MASH F4 patients were processed through the 10X Genomics Visium ST workflow using semi-automated workflows to improve the staining differentiation of histological features. Matched snRNASeq datasets were generated using the 10X genomics Chromium FLEX workflow for FFPE samples. We performed Transmission Electron Microscopy on the snRNAseq-FFPE preparations to verify the sample type recovered from the FFPE-FLEX workflow. A systematic quality control and filtering process, including ambient RNA correction, was implemented to eliminate contaminant populations and generate a high-quality single-nuclei atlas for MASH. **Results:** Transmission electron

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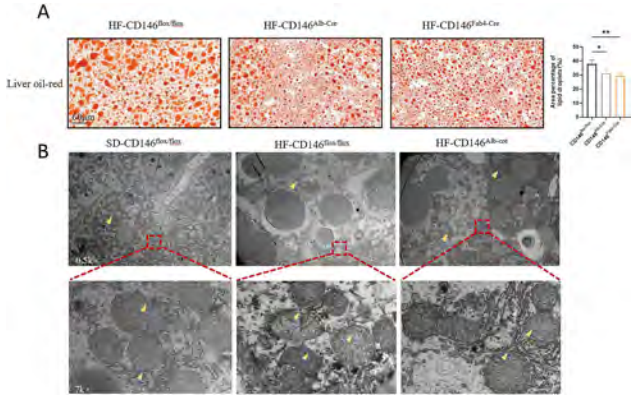
microscopy confirmed the presence of intact nuclei in the dissociations performed through the 10x Chromium FLEX workflow from MASH liver FFPE samples. We generated a single nuclei atlas from Healthy and MASH F3, F4 FFPE samples containing 42,901 nuclei after performing ambient RNA correction and removal of contaminant nuclei populations. We observed robust recovery of expected cell types as well as cell types such as neutrophils and certain fibroblast subtypes which are frequently underrepresented in standard single cell data sets from frozen samples. The use of semi-automated approaches for tissue staining in Visium ST reduced the staining variability between samples. This enabled accurate annotation of distinct histological features for downstream analysis. Integrated clustering of spots from the MASH F4 samples enabled spatial mapping of transcriptional identities onto histologically distinct regions driving unbiased characterization of these features for downstream analytical approaches. **Conclusion:** This study streamlined and standardized experimental and analytical workflows to generate a robust multi-omic dataset for characterizing parenchymal and fibrotic niches in MASH. The high-quality single nuclei atlas obtained from paired samples is best suited for deconvolution of the spatial transcriptomic data and to examine the perturbations in the disease-relevant niches. **Disclosures:** APOORVA MOHAN: Gilead Sciences: Employee, Divya Ravichandar: Nothing to Disclose, Anjali Rao: Nothing to Disclose, Edith Vaquero: Nothing to Disclose, SANGEETHA MAHADEVAN: Nothing to Disclose, David Lopez: Nothing to Disclose, GRANT BUDAS: Nothing to Disclose, Anna Zagorska: Nothing to Disclose, Lauri Diehl: Nothing to Disclose, Hsiu-Chun Chuang: Nothing to Disclose

1067 | THE ROLE AND MECHANISM OF CD146 IN REGULATING MITOCHONDRIAL FUNCTION IN MASLD

Yixue Shu[1] Yulin Yan[1] Ruirui Li[1] Bingqing Yang[2] Quan Sun[1] Qi Wang[2], [1]Capital Medical University, Beijing, China., [2]Beijing Ditan Hospital, Capital Medical University, Beijing, China.

Background: The incidence of metabolic dysfunction-associated steatohepatitis (MASLD) has surged due to changes in lifestyle and diet, becoming the most common chronic liver disease globally. Its pathogenesis is primarily based on the "multiple-hit" hypothesis, in which mitochondrial dysfunction is a core influencing factor. CD146, a multifunctional cell adhesion molecule, shows increased expression in the liver with the worsening of chronic liver disease, this suggests that CD146 plays an important role in the occurrence and development of MASLD, but whether this role is related to mitochondrial dysfunction remains unclear. **Methods:** This study generated hepatocyte-specific ($CD146^{Alb\text{-}Cre}$) and adipocyte-specific ($CD146^{Fabp4\text{-}Cre}$) CD146 knockout mouse models, with $CD146^{flox/flox}$ mice serving as controls. The mice were subjected to a high-fat, high-fructose diet for 25 weeks to induce MASLD. The pathological and physiological effects of CD146 deficiency were systematically evaluated using histopathological examination, flow cytometry, transmission electron microscopy (TEM) ultrastructural assessment, and omics characterization, as well as in vitro experiments. **Results:** In the HFHF-induced MASLD mouse model, CD146 expression was significantly upregulated in the liver. CD146-deficient (CD146-CKO) mice exhibited attenuated body weight gain, reduced serum ALT levels, and marked improvement in hepatic steatosis and adipose tissue accumulation. Immunophenotypic analysis revealed significantly reduced infiltration of pro-inflammatory immune cells in the livers of CD146-CKO mice, along with increased polarization of macrophages towards the anti-inflammatory M2 phenotype. TEM observations showed increased mitochondrial number and improved structure in hepatocytes of CD146-CKO mice. Proteomics and lipidomics analyses indicated upregulated expression of key molecules in pyruvate metabolism, downregulated lipogenic genes (Srebp1 and Acacb), increased membrane phospholipid content, and reduced pro-inflammatory triglyceride subspecies in CD146-CKO mice. In vitro experiments confirmed that CD146 knockdown in the AML12 hepatocyte cell line significantly decreased lipid accumulation and reactive oxygen species (ROS) production induced by oleic acid and palmitic acid. **Conclusion:** CD146 likely plays a crucial role in the pathophysiology of MASLD by modulating mitochondrial function. Its deficiency improves hepatic lipid deposition and systemic metabolic disorders, offering a new potential therapeutic target for MASLD treatment.



Disclosures: Yixue Shu: Nothing to Disclose, Yulin Yan: Nothing to Disclose, Ruirui Li: Nothing to Disclose, Bingqing Yang: Nothing to Disclose, Quan Sun: Nothing to Disclose, Qi Wang: Nothing to Disclose, Nothing to Disclose

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1068 | DIFFERENTIAL EFFECTS OF HEPATOCYTE ADENOSINE KINASE OVEREXPRESSION AND AGING ON ADIPOSITY AND DIET-INDUCED MASH ASPECTS IN MICE

HONGGUI LI[1], XIAOXIAO WANG[1], XIAOJING LI[1], AND CHAODONG WU[1], Honggui Li[1] Xiaoxiao Wang[1] Xiaojing Li[1], [1]Texas A&M University

Background: Adenosine kinase (ADK), an enzyme expressed at its highest levels in hepatocytes, was recently shown to promote excessive fat deposition and stimulate liver inflammation. However, how ADK influences metabolic dysfunction-associated steatohepatitis (MASH) with consideration of aging as a biological variable remains unknown. **Methods:** The present study aimed to determine the effect of hepatocyte ADK overexpression (Hep-ADK^{Tg}), along with aging, on altering adiposity and MASH aspects in mice on a fat-enriched methionine- and choline-deficient diet (fMCD). **Results:** When at young adulthood, both fMCD-fed Hep-ADK^{Tg} mice and fMCD-fed Hep-ADK^{WT} mice displayed overt MASH phenotype while the severity of fMCD-induced MASH in Hep-ADK^{Tg} was greater. In an *in vitro* system, ADK overexpression brought about an increase in palmitate-induced fat deposition in hepatocytes incubated with MCD-mimicking media. In response to aging, Hep-ADK^{WT} mice displayed significantly increased severities of fMCD-induced hepatic steatosis and liver inflammation and showed slight decreases in body weight adiposity whereas Hep-ADK^{Tg} mice revealed increased severity of fMCD-induced hepatic steatosis and marginal changes in liver inflammation, as well as body weight and adiposity. At the level of liver RNA transcriptome, the effect of aging on promoting fMCD-induced liver inflammation in Hep-ADK^{WT} mice was attributable to activation of various proinflammatory signaling events (e.g., STING1 and NFkB) that were indicated by aging-driven up-regulation of differentially expressed genes (DEGs). Consistent with increased hepatic steatosis that was largely due to decreased fatty oxidation, down-regulation of liver DEGs indicated inhibition of liver AMPK signaling and PPARa/RXRa activation, as well as PPARd in aged Hep-ADK^{WT} mice relative to young Hep-ADK^{WT} mice. However, under aged conditions, Hep-ADK^{Tg} mice sustained body weight and adiposity whereas Hep-ADKWT revealed a significant weight loss in response to fMCD. Moreover, in response to fMCD feeding for 8 weeks, aged Hep-ADK^{Tg} mice did not reveal a significant increase in liver inflammation although showing an increase in the severity of hepatic steatosis relative to Hep-ADK^{WT} mice. In addition, liver RNA transcriptomes only revealed a small number of DEGs, three of which were increased and might be associated with MASH. **Conclusion:** Collectively, these results demonstrate that ADK overexpression in hepatocytes and aging differentially influenced the outcomes of adiposity and fMCD-induced MASH aspects. As such, there is a need to consider aging as a biological variable while ADK is a viable target for managing MASH.

Disclosures: Honggui Li: Nothing to Disclose, Xiaoxiao Wang: Nothing to Disclose, Xiaojing Li: Nothing to Disclose

1069 | ENVIRONMENTAL EXPOSURE TO BISPHENOL A MODULATES TRAINED IMMUNITY-RELATED PATHWAYS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD), CONTRIBUTING TO DISEASE PROGRESSION. A PRELIMINARY ANALYSIS

Mario Romeo[1] Fiammetta Di Nardo[1] Annachiara Coppola[1] Alessia Silvestrin[1] Giusy Senese[1] Carmine Napolitano[1] Paolo Vaia[1] Marco Niosi[1] Marcello Dallio[1] Alessandro Federico[1], [1]University of Campania Luigi Vanvitelli

Background: Trained Immunity (TI) represents a novel concept of the immunological response involving the innate immune cells, triggered by a second antigenic contact, gaining a long-term, reversible pro-inflammatory phenotype. Dysregulation of innate immunity, leading to low-grade chronic inflammation, promotes the progression of Metabolic dysfunction-associated steatohepatitis (MASH). Bisphenol A (BPA) is a well-known endocrine-disrupting compound (EDC), widely produced worldwide and potentially accumulable in human tissues, including the liver. Our group recently identified BPA as an alternative antigen capable of activating TI in healthy individuals, suggesting potential implications in immunometabolic shifts and altered immune reactivity. However, the impact of EDC exposure on TI pathways in MASH patients remains unexplored. **Methods:** We recruited 26 healthy individuals and 30 patients with histological confirmation of MASH. A 10 mL serum sample was collected to extract and quantify BPA and isolate and stimulate monocytes following a predefined TI protocol. Specifically, BPA was extracted from serum using a liquid-liquid extraction with methanol (1:1, v/v), followed by solid-phase extraction for purification and concentration. BPA quantification was performed using a high-performance liquid chromatography (HPLC) system coupled with a triple quadrupole mass spectrometer. Monocytes from healthy individuals and MASH patients were isolated via density gradient centrifugation and then stimulated with BPA for 24 hours (at concentrations of 1 nM, 10 nM, and

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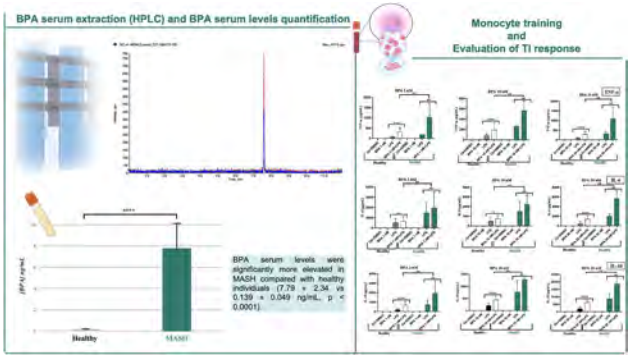
20 nM) and lipopolysaccharide (LPS) (10 ng/mL) for 24 hours (on days 0 and 6, respectively). **Results:** Serum BPA levels were significantly higher in MASH patients compared to healthy individuals (7.79 ± 2.34 vs 0.139 ± 0.049 ng/mL, $p < 0.0001$). BPA-induced TI (1 nM, 10 nM, and 20 nM) was more pronounced in MASH patients than in healthy individuals, with increased levels of pro-inflammatory cytokines (TNF-alpha and IL-6) observed for each BPA concentration tested (all $p < 0.05$). Furthermore, MASH patients exhibited elevated IL-10 levels in response to BPA exposure ($p < 0.05$), possibly as a compensatory mechanism (Figure). **Conclusion:** BPA acts as a potent stimulator of innate immune training in MASH patients, fueling a pro-inflammatory phenotype that may contribute to the initiation, progression, and persistence of the disease.



Disclosures: Mario Romeo: Nothing to Disclose, Fiammetta Di Nardo: Nothing to Disclose, Annachiara Coppola: Nothing to Disclose, Alessia Silvestrin: Nothing to Disclose, Giusy Senese: Nothing to Disclose, Carmine Napolitano: Nothing to Disclose, Paolo Vaia: Nothing to Disclose, Marco Niosi: Nothing to Disclose, Marcello Dallio: Nothing to Disclose, Alessandro Federico: Nothing to Disclose

1070 | WESTERN DIET EXACERBATES C–MYC–INDUCED HEPATOCARCINOGENESIS IN DIAMOND MICE

Yun-Ling Tai[1] NAN WU[2] Derrick Zhao[2] Grayson Way[2] Meiyi Song[2] Hui Li[2] Sareh Bayatpour[2] Lianyong Su[2] Xuan Wang[2] Emily Gurley[2] Phillip Hylemon[3] Arun Sanyal[2] Huiping Zhou[2], [1], Virginia Commonwealth University, [2]Virginia Commonwealth University, [3]Virginia Commonwealth University and Richmond Veterans Affairs Medical Center

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. Increasing evidence implicates metabolic risk factors—particularly dietary influences—as critical drivers of HCC pathogenesis. The Western diet supplemented with sugar water (WDSW) promotes hepatic steatosis, inflammation, and tumorigenesis, yet the mechanistic crosstalk between diet-induced metabolic stress and hepatocarcinogenesis remains incompletely defined. In this study, we employed a hydrodynamic tail vein injection (HTVI)-based murine model of HCC to investigate the impact of WDSW on tumor development and molecular signaling. **Methods:** Both male and female mice with a mixed background of C57Bl/6J and 129S1/SvImJ (B6/129) were subjected to HTVI with a Sleeping Beauty (SB) transposon system encoding the oncogene, c-Myc, to induce HCC. Following injection, mice were randomized to receive either a WDSW or a normal chow diet (ND) for six weeks. Tumor burden and liver pathology were assessed by hematoxylin and eosin (H&E) staining. *c-Myc* expression was confirmed via Western blotting and qPCR. Gene expression profiling was performed using the NanoString nCounter Mouse PanCancer Pathways Panel. **Results:** HTVI effectively delivered *c-Myc* to the liver, as confirmed by Western blot and qPCR. WDSW feeding significantly enhanced *c-Myc*-driven tumorigenesis compared to ND. Serum chemistry revealed elevated ALT, AST, and ALP in *c-Myc*-injected mice, with further increases observed in the WDSW group. Metabolic profiling showed increased levels of total bilirubin, cholesterol, triglycerides, and VLDL, alongside reduced glucose levels—indicating a dysmetabolic state induced by WDSW. NanoString profiling identified significant upregulation of pathways related to growth factor signaling (e.g., *FGF1, FGF21, VEGFA, HGF, IGF1, ERBB3*), Wnt/β-catenin signaling (*Wnt2, Wnt5a, Wnt5b, Axin1, Fzd8*), inflammation (*STAT1, IL1α, NF-κB, SOCS2, JAK1*), cell cycle and DNA damage response (*Ccnd1, Ccnd2, Bcl2l1, Casp7, Casp8*), and metabolic stress. Notably, *Hspa8* and *Gpc3* expression were markedly elevated in the WDSW + *c-Myc* group. **Conclusion:** Our findings demonstrate that WDSW significantly exacerbates *c-Myc*-driven hepatocarcinogenesis. The combination of *c-Myc* overexpression and diet-induced lipotoxicity accelerates metabolic dysfunction, inflammation, and tumor-promoting molecular changes, providing mechanistic insights into the diet-oncogene interplay in MASH-associated HCC.

Disclosures: Yun-Ling Tai: Nothing to Disclose, NAN WU: Nothing to Disclose, Derrick Zhao: Nothing to Disclose, Grayson Way: Nothing to Disclose, Meiyi Song: Nothing to Disclose, Hui Li: Nothing to Disclose, Sareh Bayatpour: Nothing to Disclose, Lianyong Su: Nothing to Disclose, Xuan Wang: Nothing to Disclose, Emily Gurley: Nothing to Disclose, Phillip Hylemon: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix,

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1071 | HEPATIC LIPIDOMIC PROFILING ASSOCIATED WITH HEPATOCYTE PPARG EXPRESSION AND ACTIVATION IN MICE WITH DIET-INDUCED MASH

Sara Osorio-Valencia[1] Samuel Lee[1] Izabela Hawro[1] Gregory Norris[1], [1]University of Illinois at Chicago

Background: Hepatocyte peroxisome proliferator-activated receptor gamma (*Pparg*) contributes to the progression of metabolic dysfunction-associated steatohepatitis (MASH). Specifically, we have reported that hepatocyte-specific *Pparg* knockout ($Pparg^{\Delta Hep}$) male mice have reduced MASH progression when they are fed a high-fat, cholesterol, and fructose diet (HFCF). However, the hepatic benefits mediated by $Pparg^{\Delta Hep}$ are not only explained by reduced level of steatosis. Here, we have profiled hepatic lipid species in two groups of control and $Pparg^{\Delta Hep}$ male mice that were fed a HFCF for 24 or 34 weeks. **Methods:** Previously, we generated control or $Pparg^{\Delta Hep}$ mice by injecting *Pparg* floxed male mice with AAV8-TBG-Null or AAV8-TBG-Cre, respectively, before feeding them a HFCF diet for 24 weeks (Group 1), or after feeding male *Pparg* floxed mice a HFCF diet for 24 weeks (Group 2). In the group 2, a subset of control or $Pparg^{\Delta Hep}$ mice were then treated with Rosiglitazone (PPARg agonist) for 8 weeks. In this study, we used LC/MS to identify glycerophospholipids, sphingolipids, and neutral lipids, or GC/MS to quantify the total amount of fatty acids in livers. **Results:** The LC/MS workflow identified up to 316 lipid species. The HFCF diet significantly reduced 106 and 57 lipid species in Groups 1 and 2, respectively. Of note, 45 lipid species were commonly reduced in both groups—primarily glycerophospholipids containing polyunsaturated fatty acids (PUFAs) and free PUFAs. Moreover, the activation of hepatocyte PPARg with Rosiglitazone in control mice, but not in $Pparg^{\Delta Hep}$ mice, reduced the levels of 33 lipids, including phosphatidylcholine PC(38:4, 40:6, and 42:10), phosphatidylethanolamine PE(38:6), Lyso-PC and Lyso-PE(20:4, 22:6), cardiolipin CL(74:9), and FA(24:4, 22:6). These were also reduced by HFCF diet. Furthermore, using GC/MS we confirmed a Pparg-dependent negative effect of HFCF diet on total PUFA levels, particularly FA(20:4) and FA(22:4). Surprisingly, in group 1 and 2, $Pparg^{\Delta Hep}$ increased the levels of 31 and 10 lipid species, respectively. Of note, $Pparg^{\Delta Hep}$ increased the levels of PC(40:6) and PC (42:10) in both HFCF-fed groups. Supporting the hepatocyte *Pparg*-dependent effect on the hepatic lipid profile, our publicly available RNA-seq datasets of group 1 and 2 (GSE162249 and GSE162276) revealed that key genes involved in hepatic PC and PE biosynthesis (*Pemt*, *Etnk2*), as well as fatty acid elongation (*Elovl2*), were downregulated by HFCF diet and rosiglitazone in control mice, but this effect was reversed in $Pparg^{\Delta Hep}$ mice. **Conclusion:** Our comprehensive lipidomic analysis in a diet-induced MASH model reveals a hepatocyte *Pparg*-dependent negative regulation of specific PUFA-containing PC species. Reduced expression of hepatic *Elovl2*, *Etnk2*, and *Pemt* might account for the reduced levels of these lipid species, and contribute to the progression of MASH.

Disclosures: Sara Osorio-Valencia: Nothing to Disclose, Samuel Lee: Nothing to Disclose, Izabela Hawro: Nothing to Disclose, Gregory Norris: Nothing to Disclose

1072 | ROLE OF EXTRACELLULAR ATP (ATPE) AND ASSOCIATED PATHWAYS IN INFLAMMATION RELATED TO METABOLIC DYSFUNCTION – ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) PROGRESSION

Vanessa Garcia-Fernandez[1] Antonio Gil-Gómez[1] Rocío Muñoz Hernández[2] Sheila Gato-Zambrano[1] Angela Rojas[1] Isabel Fernandez[1] RAQUEL MILLÁN DOMÍNGUEZ[1] Rocio Gallego-Duran[3] Douglas Maya-Miles[1] Paloma Carrillo-Fernandez[1] Javier Ampuero Herrojo[1] Manuel Romero-Gómez[1], [1]SeLiver Group. Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocí, [2]Centro de Investigación Biomédica en Red, [3]Ibis- Biomedicine Institute of Sevilla

Background: Extracellular ATP (eATP) is a damage-associated molecule that triggers the inflammatory response, inducing immune cell infiltration and cytokine release. ENTPD1 is an ectonucleotidase that hydrolyzes ATP, reducing eATP levels and modulating inflammation. P2RX7 is an ATP receptor which triggers de NLRP3 inflammasome pathway. The aim of this study was to determine the role of eATP and its associated pathways in the progression of MASLD. **Methods:** Preliminary studies involved of thirty-six male C57BL/6J mice with High Fat High Carbohydrate and Cholesterol (HFHCC) diet (n = 29) or chow (n = 7) for 52 weeks and thirty male C5BL/6J mice were fed a CDACHFD diet (n = 20) or chow (n = 10) diet for 8 weeks. A new study with forty male C57BL/6J mice fed a HFHCC diet (n = 20) or chow (n = 20) was performed. *Entpd1, P2rx7* and *Nlrp3* genes and Entpd1

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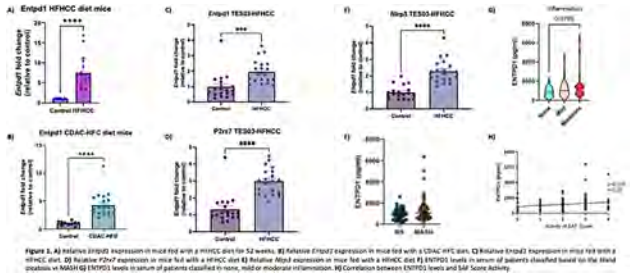
and P2rx7 protein expression were assessed by PCR and IHC assays. Moreover, serum ENTPD1 levels were measured by ELISA in one-hundred three biopsy proven MASLD patients classified as bland steatosis (n = 42) or MASH (n = 61) using SAF and NAS Score. **Results:** In mice fed HFHCC for 52 weeks, Entpd1 gene expression was 5 times higher than controls ($p < 0.0001$), while CDACHFD-fed mice showed a 4-fold increase. In the recent study, *Entpd1* was increased in the diet group (fold change 1 ± 0.83 vs 1.97 ± 0.75; $p = 0.0005$). *P2rx7* (fold change 1 ± 0.62 vs 2.24 ± 0.58; $p < 0.0001$) and *Nlrp3* (fold change 1 ± 0.41 vs 2.28 ± 0.71; $p < 0.0001$) were increased in the mice fed with HFHCC diet. The IHC assay showed an Entpd1 protein expression around the central vein in the control group, while no expression around the portal vein. However, in both HFHCC and CDACHFD diet mice, the expression showed a shift towards the portal vein, with a heightened expression in that region and a decline in the central vein region. Regarding P2rx7 expression, there is an elevated number of positive cells per area in mice fed HFHCC diet (272.4 ± 79.82 *vs.* 391.8 ± 121.8; $p = 0.0035$). Patients with MASH (1368 ± 1094pg/ml) had increased ENTPD1 levels compared to bland steatosis patients (925 ± 474pg/ml) ($p = 0.006$). Based on inflammation, an increase in ENTPD1 serum levels were observed as inflammation increased [none (n = 19), 879 ± 484 pg/ml; mild (n = 56), 1164 ± 757 pg/ml; moderate (n = 28), 1444 ± 1312 pg/ml; $p = 0.112$]. A correlation between ENTPD1 levels and SAF Score's activity was found ($p = 0.03$). **Conclusion:** The gene expression of *Entpd1*, *P2rx7* and *Nlrp3* and protein levels of Entpd1 and P2rx7 were increased along with the progression of the disease, suggesting that eATP related pathways play an important role in the progression of MASLD.



Disclosures: Vanessa Garcia-Fernandez: Nothing to Disclose, Antonio Gil-Gómez: Nothing to Disclose, Rocío Muñoz Hernández: Nothing to Disclose, Sheila Gato-Zambrano: Nothing to Disclose, Angela Rojas: Nothing to Disclose, Isabel Fernandez: Nothing to Disclose, RAQUEL MILLÁN DOMÍNGUEZ: Nothing to Disclose, Rocio Gallego-Duran: Nothing to Disclose, Douglas Maya-Miles: Nothing to Disclose, Paloma Carrillo-Fernandez: Nothing to Disclose, Javier Ampuero Herrojo: Nothing to Disclose, Manuel Romero-Gómez: Nothing to Disclose

1073 | TSG-6 IMPROVES HYPERLIPIDEMIA BY SUPPRESSING ASGR1–PCSK9 AXIS BUT AGGRAVATES HEPATIC STEATOSIS IN DIET-INDUCED HYPERLIPIDEMIA

Hayeong Jeong[1] Jinsol Han[1] Youngmi Jung[1], [1]Pusan National University

Background: The liver plays a central role in lipid metabolism by regulating lipid uptake, synthesis, storage, and export. Dysregulation of hepatic lipid metabolism not only contributes to the development of hepatic steatosis but also leads to systemic hyperlipidemia. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an essential regulator controlling LDL cholesterol levels by degrading hepatic lipid transporters such as low-density lipoprotein receptor (LDLR) and cluster of differentiation 36 (CD36), on hepatocytes, which ultimately lowers the clearance of LDL cholesterol. Hence, inhibiting PCSK9 has emerged as a promising therapeutic approach treating hyperlipidemia. However, given the strong association between hyperlipidemia and fatty liver, PCSK9 suppression may inadvertently promote hepatic lipid accumulation by enhancing lipid uptake into hepatocytes. Therefore, it is necessary to clarify the effect of impact of PCSK9-targeted interventions on hepatic lipid metabolism and liver function. Tumor necrosis factor-α-stimulated gene 6 protein (TSG-6), an anti-inflammatory cytokine secreted by mesenchymal stem cells, has recently been reported to influence hepatic lipid metabolism. Therefore, we investigated the effects of TSG-6 on hyperlipidemia and liver function, with a particular focus on its regulatory role in PCSK9 expression. **Methods:** Mice were fed a chow diet or a high-fat, high-fructose, high-cholesterol diet (HFHFrHC) for 12 weeks. TSG-6 (1.5 μg/kg, every other day) or PBS (vehicle) was injected intraperitoneally with feeding diet for 4 additional weeks. **Results:** Mice in the HFHFrHC groups developed enlarged, pale livers with increased lipid accumulation and severe liver damage compared to chow-fed controls. TSG-6 did not have any effects in chow-fed mice. However, in the HFHFrHC-fed groups, TSG-6-treated mice exhibited larger hepatic lipid droplets compared to vehicle-treated mice. The liver-to-body weight ratio also tended to be higher in TSG-6–treated mice than in vehicle-treated controls. Immunoprecipitation of TSG-6 followed by LC-MS/MS analysis identified asialoglycoprotein receptor 1 (ASGR1)- a receptor known to interact with PCSK9- as a binding partner of TSG-6 in hepatocytes. TSG-6 treatment down-regulated hepatic ASGR1 and PCSK9 levels while upregulating CD36 and LDLR expression. These changes were associated with a reduction in serum triglyceride (TG) levels, but an increase in hepatic TG accumulation in the HFHFrHC groups. **Conclusion:** These findings demonstrate that ASGR1 suppression by TSG-6 blocks PCSK9, and enhances hepatic lipid thereby facilitating clearance of circulating lipids. These results indicate that although TSG-

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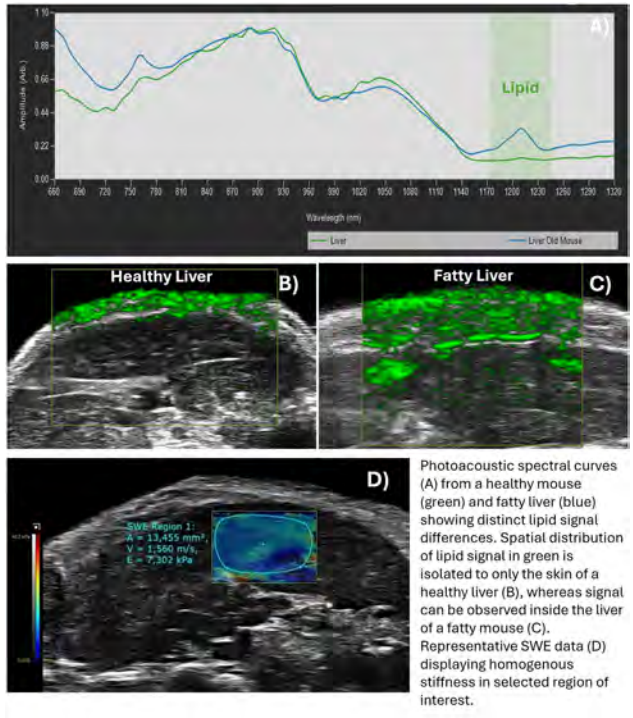
6 shows promise as a treatment for hyperlipidemia, it may contribute to the progression of hepatic steatosis.
Disclosures: Hayeong Jeong: Nothing to Disclose, Jinsol Han: Nothing to Disclose, Youngmi Jung: Nothing to Disclose

1074 | HIGH RESOLUTION MULTIMODAL APPROACH FOR COMPREHENSIVE NON-INVASIVE PRECLINICAL ASSESSMENT OF THE LIVER

Melissa Yin[1] Kristiina Aasa[1] Cassidy Rose[1] Ross Williams[1] Peter Kesa[1] Caroline O'Riordan[1] Philippe Trochet[1] Dieter Fuchs[1], [1]FUJIFILM VisualSonics Inc

Background: Early diagnosis is paramount in the treatment and management of liver disease in the clinical setting. This also translates to preclinical research, where proper staging of liver damage plays an instrumental role in the development and evaluation of novel treatments. Here, we present a multimodal approach for non-invasive assessment of the liver, combining high-frequency ultrasound with photoacoustic imaging (HFUS-PA). This approach provides anatomical, functional, and mechanical (stiffness changes relating to fibrosis development via shear wave elastography) information. As well as molecular details in the form of lipid detection relating to steatosis development. Combined, this multi-faceted approach supports the characterization of dynamic changes related to liver disease progression. **Methods:** Multi-modal liver assessments were performed in healthy and diet-induced MASLD C57Bl/6J mice using the Vevo® F2 LAZR-X20 HFUS-PA imaging system (FUJIFILM VisualSonics). Liver capillary function was assessed by injecting 50 μL of MicroMarker® contrast agents. Liver oxygenation was evaluated via an oxygen challenge assay where isoflurane anesthetized animals were subjected to varying concentrations of O_2—98% O_2, 5% O_2, 98% O_2. Shear wave elastography (SWE) stiffness measurements were obtained both in vivo and on phantoms for validation. **Results:** On liver fibrosis phantoms, all SWE measurements were within 1-2 standard deviations, or less than a 10% difference from the supplier-certified values. In vivo characterization of healthy mouse liver revealed reproducible values for stiffness (6.986 ± 1.263 kPa) and capillary perfusion (time-to-peak of 3.2 ± 0.4 sec) in the median lobe. The average liver oxygenation showed an sO_2 of 79.6 ± 11.5% which dropped to 34.7 ± 2.6% at 5% O_2, then swiftly recovered to baseline after returning to 98% O_2. In MASLD mice, increased stiffness ($p < 0.05$) was seen as early as 4 weeks after diet-commencement. Furthermore, when comparing lipid-specific PA signal in normal vs fatty liver, increased lipid signal intensity was observed in the fatty liver. **Conclusion:** Multimodal imaging using a HFUS-PA system allowed for detailed liver characterization in mice, offering novel means to detect and investigate liver disease. Using high resolution SWE, we report clinically relevant measurements of stiffness related to fibrosis development. Molecular imaging using PA showed differences in lipid accumulation in the liver—a potential method for detecting steatosis development prior to fibrosis formation. This, along with additional anatomical and functional measurements, will provide a comprehensive assessment of liver changes related to disease progression, all on one platform.



Photoacoustic spectral curves (A) from a healthy mouse (green) and fatty liver (blue) showing distinct lipid signal differences. Spatial distribution of lipid signal in green is isolated to only the skin of a healthy liver (B), whereas signal can be observed inside the liver of a fatty mouse (C). Representative SWE data (D) displaying homogenous stiffness in selected region of interest.

Disclosures: Melissa Yin: Nothing to Disclose, Kristiina Aasa: Nothing to Disclose, Cassidy Rose: Nothing to Disclose, Ross Williams: Nothing to Disclose, Peter Kesa: Nothing to Disclose, Caroline O'Riordan: Nothing to Disclose, Philippe Trochet: Nothing to Disclose, Dieter Fuchs: Nothing to Disclose

1075 | HISTONE DEACETYLASE 3 CONTROLS HEPATIC LIPID METABOLISM VIA NON-ENZYMATIC MECHANISMS

Nischay Rege[1] Amy Hauck[2] Mohit Midha[1] Kristina Heliodoro[1] Kun Zhu[1] Mitchell Lazar[1], [1]University of Pennsylvania, [2]University of Minnesota

Background: Nuclear receptors (NRs) are transcription factors that can activate or repress the transcription of target genes. Ligands affect the transcriptional activity of many NRs making them attractive candidates for pharmacological therapy. In fact, therapeutic agents targeting NRs have cleared phase 2 clinical trials for the treatment of liver diseases including the FDA-approved resmetirom, which targets thyroid hormone receptor β, elafibranor, which targets

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PPARα/δ, and seladelpar, which targets PPARδ. NRs canonically repress gene transcription through the activity of histone deacetylase 3 (HDAC3), an enzyme that deacetylates histones at gene enhancers. HDAC3 is a class I histone deacetylase that uniquely requires complexation with the deacetylase-activation domain (DAD) of Nuclear Receptor Corepressors 1 and 2 (respectively NCOR-1 and NCOR-2, also known as SMRT) to achieve deacetylase activity. Knockout of HDAC3 in the murine liver causes steatosis through derepression of lipogenic genes. The canonical view of HDAC3-mediated transcriptional repression was challenged by the rescue of hepatic steatosis by the introduction of an enzymatically inactive HDAC3 mutant (termed Y298F) into HDAC3 knockout livers. We hypothesize HDAC3 acts as a scaffolding protein at NR-associated genomic binding sites, recruiting key transcription factors that are responsible for repressing rescued genes. **Methods:** We have developed a chimeric molecule comprising HDAC1 with two helices substituted by analogous motifs from HDAC3 termed HDAC1-D3. This molecule is expected to bind NCOR upon transduction into an HDAC3-depleted mouse liver but fail to rescue hepatosteatosis because of its inability to recruit the putative transcription factor responsible for repressing lipogenic genes due to its variant surface topography. We have utilized RNA-seq to characterize the transcriptional effects of epitope-tagged HDAC molecules transduced into HDAC3-depleted mouse livers and assessed their genomic occupancy using ChIP-seq. IP-mass spectrometry was used to characterize the interactomes of HDAC3 and mutant proteins. characterize the interactomes of HDAC3 and mutant proteins. **Results:** Whereas the catalytically inert Y298F mutant displayed native-like genomic occupancy and repressed a subset of genes that were upregulated in hepatic HDAC3 knockout, leading to a near-complete rescue of the hepatosteatosis, HDAC1-D3 failed to rescue hepatic steatosis and to repress lipogenic HDAC3 target genes despite engaging NCOR. **Conclusion:** The failure of HDAC1-D3 to rescue the HDAC3 knockout phenotype despite its similar three-dimensional structure suggests surface residues of HDAC3 that are not present in the chimeric molecule are critical to the non-enzymatic function of HDAC3. We are now comparing the interactomes of HDAC3 and HDAC1-D3 to identify transcription factors that interact with these residues and repress target genes.

Disclosures: Nischay Rege: Nothing to Disclose, Amy Hauck: Nothing to Disclose, Mohit Midha: Nothing to Disclose, Kristina Heliodoro: Nothing to Disclose, Kun Zhu: Nothing to Disclose, Mitchell Lazar: Pfizer: Advisor, Flare Therapeutics: Advisor, Eccogene: Advisor

1076 | REDUCED ZMPSTE24 EXPRESSION LEADS TO PRELAMIN ACCUMULATION AND DEVELOPMENT OF STEATOSIS IN MASLD PATIENTS

Joseph Schinderle[1] Irina Bochkis[1], [1]University of Pittsburgh

Background: Metabolic-associated steatotic liver disease (MASLD, formerly NAFLD) is highly prevalent in type 2 diabetes mellitus (T2D) and its incidence has increased rapidly with the obesity epidemic. Mutations of nuclear lamina-associated genes including *LMNA* have been associated with fatty liver. We previously described a mechanism relating changes at the nuclear lamina that lead to opening of previously repressed chromatin and upregulation of lipid synthesis and storage pathways to development of steatosis in MASLD. **Methods:** We performed RNA-Seq, Foxa2 and Lamin B1 ChIP-Seq and protein analysis for expression of ZMPSTE24 in livers of MASLD patients with varying degrees of steatosis. **Results:** Here we report that the changes at the nuclear envelope in MASLD patients are caused by downregulation of ZMPSTE24, an enzyme that processes prelamin to mature lamin A, leading to accumulation of prelamin. In addition, Zmpste24 mutant mice develop hepatic steatosis and Zmpste24 deficiency is linked to upregulation of p53 target genes. Functional analysis determined p53 as a regulator in genes differentially expressed and bound by FOXA2 in both male and female MASLD patients, corresponding to observations in Zmpste24 knockout animals. ZMPSTE24 expression is repressed by mir-141-3p in male MASLD patients. **Conclusion:** Downregulation of ZMPSTE24 leads to the nuclear lamina changes responsible to development of MASLD we had previously reported. Hence, MASLD should be considered as a type of laminopathy and approaches to restore ZMPSTE24 expression and nuclear lamina function should be tested for treatment of the disease.

Disclosures: Joseph Schinderle: Nothing to Disclose, Irina Bochkis: Nothing to Disclose

1077 | PROTEOMIC PROFILING OF A STEATOTIC MONKEY LIVER ORGANOID MODEL FOR MASLD

Bowen Gao[1] Li Wang[2] Yun Ma[1] Wayel Jassem[3], [1]King's College London, [2]Suzhou Jiyan Biopharmaceutical Technology, [3]King's College London/King's College Hospital

Background: Although several methods for inducing liver steatosis have been well demonstrated in

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rodents, the variability between species limits the extrapolation of these results to humans. Human liver studies are constrained by limited samples availability and strict ethical regulations. Liver organoids derived from monkey tissue offer a genetic background closer to humans, making them a promising compromise for modelling Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD). This research aims to establish and characterize a reliable monkey-derived model for future drugs evaluation in MASLD. **Methods:** Liver organoids were constructed from monkey liver tissue. After 5 days differentiation, 250μM palmitic acid (PA) and oleic acid (OA) were added into the culture system for 24 hours to induce steatosis in the organoids. Lipid accumulation was evaluated by Oil Red O staining and total cholesterol (TC) quantification. Organoids were harvested before and after treatment with free fatty acid for DIA based LC-MS/MS proteomics profiling. Statistical significance was defined as $q < 0.05$ (Benjamini-Hochberg FDR correction) for enrichment analysis and $p < 0.05$ for individual proteins. **Results:** Oil Red O staining and TC detection confirmed lipid accumulation and secretion in the liver organoids ($p < 0.05$). Proteomic profiling identified 8643 proteins with 834 proteins showing differential expression between steatotic and control group, 634 upregulated and 200 downregulated. GO enrichment analysis revealed a downregulation of DNA replication initiation (enrichment ratio = 45.05, $q = 0.026$), suggesting a suppression in cell proliferation and DNA repair induced by oxidative stress from lipotoxic conditions, rather than a developmental immaturity. Conversely, pathways related to collagen trimer complex formation were upregulated (enrichment ratio = 23.15, $q = 0.0018$), indicating a remodeling of extracellular matrix (ECM) and increased risk for fibrosis. Additionally, triglyceride lipase activity was upregulated (enrichment ratio = 14.9, $q = 0.023$), involving key lipases such as hepatic lipase (LIPC) and phospholipase A1 member A (PLA1A), which might reflect an adaptive response and metabolic reprogramming. Noteworthy, TGF-β1 was upregulated significantly (Fold change = 16.37104, $p = 6.26 \times 10^{-167}$), indicating a robust activation. **Conclusion:** Free fatty acid-treated monkey liver organoids showed significant features of cell cycle abnormalities, inflammation, metabolic disorders and ECM remodeling. Preliminary findings suggest that monkey liver organoids are a promising and reliable model for MASLD research and have the potential to recapitulate liver fibrosis. This model will be used in future studies to evaluate anti-steatosis compounds as part of preclinical testing.

Disclosures: Bowen Gao: Nothing to Disclose, Li Wang: Nothing to Disclose, Yun Ma: Nothing to Disclose, Wayel Jassem: Nothing to Disclose

1078 | INTESTINAL LIPASE INHIBITION PREVENTS OBESITY BUT EXACERBATES MASH

Alvin Chan[1] Tomek Czernuszewicz[2] Kelsey Jarrett[1] Rochelle Lai[1] Andrew Lau[1] Angela Cheng[1] Zeinab Mamouei[2] Jessica Pesner[2] Christopher Hamad[1] Samuel French[1] Clara Magyar[1] Kevin Francis[1] Elizabeth Tarling[1] Thomas Vallim[3], [1]UCLA, [2]Revvity, inc., [3]University of California, Los Angeles

Background: Excessive dietary fat intake contributes to the development of metabolic dysfunction-associated steatohepatitis (MASH), but emerging evidence suggests that the type of fat (saturated vs unsaturated fat) plays a critical role in shaping disease progression. Our previous work demonstrates that polyunsaturated fatty acids (PUFAs) are preferentially absorbed over saturated fats to maintain metabolic homeostasis. However, orlistat, a lipase inhibitor used for weight loss, disrupts this selective uptake on a Western-style diet, leading to hepatic PUFA depletion. **Methods:** Here, we examined orlistat's effects in a MASH model using the Gubra-Amylin NASH (GAN) diet—a high-fat diet rich in palmitic acid (C16:0) and linoleic acid (C18:2, n-6)—to determine how dietary fat composition influences orlistat's impact on MASH. Mice were fed the GAN diet with or without orlistat for 32 weeks to induce MASH. Disease progression was monitored longitudinally using whole-body MRI and *in vivo* 3D shear wave elastography with the Vega® imager (Revvity) to assess liver size, stiffness, and echogenicity. These noninvasive imaging measures correlated with lipidomic and histologic assessments of steatosis and fibrosis. **Results:** Orlistat-treated mice were protected from obesity but not MASH, with comparable levels of steatosis and fibrosis to untreated controls. Notably, orlistat exacerbated liver transaminases and inflammatory cell infiltration, indicating increased hepatic inflammation. Mechanistically, orlistat non-selectively inhibits lipases and broadly blocks the absorption of all fatty acids. Given the abundance of linoleic acid in the GAN diet, essential PUFAs were disproportionately reduced. Since PUFAs are known to suppress *de novo* lipogenesis, their depletion likely promotes hepatic lipid accumulation and inflammatory signaling, accelerating MASH progression. Ongoing studies will elucidate the mechanisms by which impaired fatty acid absorption by orlistat triggers liver inflammation. **Conclusion:** Overall, these findings suggest that orlistat, despite its anti-obesity effects, aggravates liver injury in the context of MASH. Importantly, its therapeutic potential and risk appear to depend on the fat content of the diet, underscoring the significance of dietary fat composition in strategies that target lipid absorption.

Disclosures: Alvin Chan: Nothing to Disclose, Tomek Czernuszewicz: Nothing to Disclose, Kelsey Jarrett:

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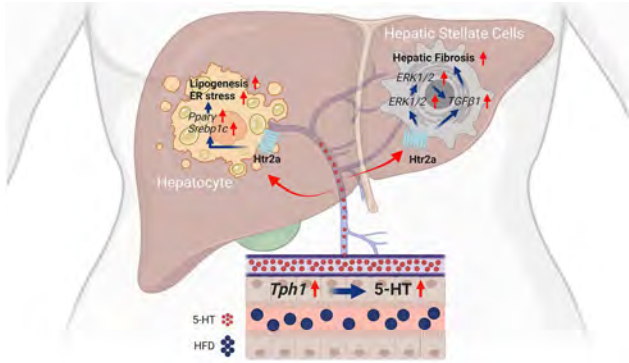
Nothing to Disclose, Rochelle Lai: Nothing to Disclose, Andrew Lau: Nothing to Disclose, Angela Cheng: Nothing to Disclose, Zeinab Mamouei: Nothing to Disclose, Jessica Pesner: Nothing to Disclose, Christopher Hamad: Nothing to Disclose, Samuel French: Nothing to Disclose, Clara Magyar: Nothing to Disclose, Kevin Francis: Nothing to Disclose, Elizabeth Tarling: Nothing to Disclose, Thomas Vallim: Nothing to Disclose

1079 | INHIBITION OF SEROTONIN SIGNALING THROUGH HTR2A MITIGATES MASLD AND LIVER FIBROSIS

WON-IL CHOI[1] Won Hee Lee[2] Jung Eun Nam[2] Yerim Seong[2] Byung-Kwan Jeong[2] Jun Yong Park[3] Jin Hee Ahn[4] Hail Kim[2], [1]Jeonbuk National University Medical School, [2]Korea Advanced Institute of Science and Technology, [3]Yonsei University College of Medicine, [4]Gwangju Institute of Science and Technology

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease, characterized by hepatic steatosis (MASL), inflammation (MASH), fibrosis, and hepatocellular carcinoma (HCC). We previously demonstrated that gut-derived serotonin promotes hepatic lipid accumulation via the gut–liver axis, and that hepatocyte-specific knockout (KO) of the serotonin receptor HTR2A protects against MASLD development. However, a major limitation in studying the full spectrum of MASLD pathophysiology has been the lack of a preclinical model that faithfully recapitulates its progression. In this study, we established a novel MASLD mouse model and investigated the impact of HTR2A inhibition on disease progression. **Methods:** MASLD was induced using a combination of low-dose streptozotocin and high-fat diet (STZHFD), which successfully reproduced the full MASLD spectrum. Hepatic fibrosis was further modeled using chronic carbon tetrachloride (CCl_4) administration or bile duct ligation (BDL). To investigate the role of serotonin signaling in MASLD progression, we employed gut-specific *Tph1* KO, hepatocyte-specific *Htr2a* KO, and hepatic stellate cell (HSC)-specific *Htr2a* KO mice. **Results:** STZHFD mice progressively developed steatosis (MASL), steatohepatitis (MASH), fibrosis, and HCC within the context of metabolic dysfunction. Both gut-specific *Tph1* KO and hepatocyte-specific *Htr2a* KO mice exhibited significant improvements in MASL, MASH, and fibrosis. In contrast, HSC-specific *Htr2a* KO mice showed reduced hepatic fibrosis without improvements in MASL or MASH, indicating a direct profibrogenic role of HTR2A in HSCs. In vitro, *Htr2a* expression was upregulated during HSC activation, and Htr2a-deficient HSCs failed to activate in response to profibrotic stimuli. **Conclusion:** These findings underscore the pivotal role of serotonin–HTR2A signaling in MASLD progression. Targeted genetic or pharmacologic inhibition of HTR2A effectively ameliorates MASL, MASH, and fibrosis, identifying HTR2A as a promising intrahepatic therapeutic target for MASLD.



Disclosures: WON-IL CHOI: Nothing to Disclose, Won Hee Lee: Nothing to Disclose, Jung Eun Nam: Nothing to Disclose, Yerim Seong: Nothing to Disclose, Byung-Kwan Jeong: Nothing to Disclose, Jun Yong Park: Nothing to Disclose, Jin Hee Ahn: Nothing to Disclose, Hail Kim: Nothing to Disclose

1080 | DOMINANT-INHIBITION OF RXRA PREVENTS HIGH-FAT DIET-INDUCED OBESITY AND LIVER STEATOSIS IN MICE BY REGULATING FOOD INTAKE AND ENERGY EXPENDITURE

Hiroyasu Sakai[1] Yohei Shirakami[2] Masahito Shimizu[2], [1]Gifu University Graduate School of Medicine, [2]Gifu University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by liver steatosis linked to obesity and metabolic disorders, and its prevalence is rising in tandem with the increasing number of obesity cases. Retinoid X Receptor-α (RXRα) is a retinoid nuclear receptor that forms heterodimers with other nuclear receptors, thereby regulating downstream gene expression and influencing various physiological functions. While some studies have explored the relationship between RXRα and MASLD, its specific role in the disease remains unclear. Therefore, we investigated the role of RXRα in MASLD development using RXRα transgenic (RXRα-TG) mice, in which a dominant-negative form of RXRα can be induced through doxycycline administration. **Methods:** Male RXRα-TG and their control counterparts, aged nine to ten weeks, were administered either a normal diet (ND) or a 60% high-

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fat diet (HFD) that induces obesity and hyperinsulinemia resembling MASLD, along with 0.2% doxycycline, and were sacrificed ten weeks after the experiment begun. **Results:** RXRα-TG mice exhibited significantly lower body weight at the time of sacrifice across both dietary conditions compared to control mice. These mice also showed a significant reduction in food intake. Specifically, in HFD-treated RXRα-TG mice, the weight of epididymal adipose tissue was significantly lower compared to their control counterparts. Serum analyses revealed that while triglyceride levels were significantly elevated in HFD-treated RXRα-TG mice, total cholesterol, free fatty acids, and insulin levels were markedly decreased. Interestingly, while the administration of HFD led to liver steatosis in control mice, this condition was ameliorated in HFD-treated RXRα-TG mice, where fat droplet accumulation was reduced. Correspondingly, liver triglyceride and total cholesterol levels were significantly lower in HFD-treated RXRα-TG mice. Furthermore, adipocyte size was significantly smaller in these mice compared to controls. Additionally, the expression levels of thermogenesis-related genes, *Ucp2* and *Adrb3*, were significantly higher in the livers of HFD-treated RXRα-TG mice when compared to control mice. In the epididymal adipose tissue, the expression of *Ucp1* (thermogenesis), *Acox1*, *Ehhadh*, and *Pparα* (fatty acid oxidation) genes was also significantly increased in HFD-treated RXRα-TG mice. This enhanced expression correlates with a significant rise in rectal temperature in those mice, indicating an increased energy expenditure. **Conclusion:** Dominant-inhibition of RXRα prevents high-fat diet-induced obesity and liver steatosis in mice by reducing food intake and increasing energy expenditure. These results suggest that RXRα could be a possible therapeutic target for obesity and MASLD.
Disclosures: Hiroyasu Sakai: Nothing to Disclose, Yohei Shirakami: Nothing to Disclose, Masahito Shimizu: Nothing to Disclose

1082 | THE EFFECT OF HYDROXYNONENAL ON HEPATIC MACROPHAGES IN THE PATHOGENESIS OF MASH

Masahiro Yanagi[1] Eishiro Mizukoshi[1] Hidenori Kido[1] Taro Yamashita[1], [1]Kanazawa University

Background: Oxidative stress is an important factor in the pathogenesis of MASH, and we have previously reported the effect of hydroxynonenal (HNE), a lipid peroxide, on hepatocytes in the pathogenesis of MASH. On the other hand, hepatic macrophages have been reported to play an important role in the development of liver fibrosis in MASH by producing inflammatory cytokines and fibrosis-promoting factors. In this study, we analyzed the effects of HNE on hepatic macrophages in the development of MASH. **Methods:** (1) We evaluated CD68, F4/80, and HNE staining of liver tissues from MASH patients and MASH model mice fed choline-deficient methionine-lowered, L-amino acid-defined (CDAA) diet and atherogenic high fat (AHF) diet. (2) HNE and CD68 staining were performed in 60 MAFLD patients, and the association between the degree of HNE deposition (scored in 3 levels: HNE0-2) and the number of hepatic macrophage aggregates (HMA) was analyzed. (3) Normally fed mice were divided into HNE-treated and non-treated groups, and HNE (10 mg/kg body weight) was administered intraperitoneally daily to the treated group. F4/80 and Sirius red staining of liver tissue at 8 weeks was performed to evaluate the presence of HMA and the degree of liver fibrosis. (4) CDAA mice were divided into Alda-1 (ALDH2 agonist) treated and non-treated groups, and Alda-1 (20 mg/kg body weight) was administered to the treated group three times a week. F4/80 and Sirius red staining of liver tissue from both groups of mice at 8 weeks was performed to analyze the effects of HNE detoxification on HMA formation and liver fibrosis. **Results:** (1) Numerous HMAs were observed in the liver tissues of MASH patients and CDAA and AHF mice, and strong HNE deposition was observed on the HMAs. (2) Liver tissues with higher HNE scores showed significantly more HMA (HNE0/HNE1/HNE2: 0.22/0.92/1.99 /mm2, $p < 0.0001$) and significantly more advanced liver fibrosis. (3) The liver tissues of the HNE-treated group showed the formation of HMAs, and the degree of liver fibrosis was significantly higher than that of the non-treated group. (4) The liver tissues of the Alda-1-treated group showed a significant reduction in HMA counts (treated/non-treated group: 191/119 /field, $p = 0.0159$) and a significant improvement in liver fibrosis compared to the non-treated group. **Conclusion:** In the pathogenesis of MASH, HNE may be involved in the formation of HMA and the development of liver fibrosis.
Disclosures: Masahiro Yanagi: Nothing to Disclose, Eishiro Mizukoshi: Nothing to Disclose, Hidenori Kido: Nothing to Disclose, Taro Yamashita: Nothing to Disclose

1083 | HEPATIC HOMEOSTASIS OF INTERLEUKIN-10 VIA REGULATION OF LIPOTOXICITY CONTRIBUTES TO THE IMPROVEMENT OF METABOLISM-ASSOCIATED STEATOTIC LIVER DISEASE PROGRESSION

Akira Kado[1] Kazuya Okushin[1] Takeya Tsutsumi[1] Toshiyuki Kishida[1] Kazuhiko Ikeuchi[1] Kyoji Moriya[2] Hiroshi Yotsuyanagi[3] Kazuhiko Koike[4] Mitsuhiro Fujishiro[1], [1]The University of Tokyo, [2]Tokyo Health Care

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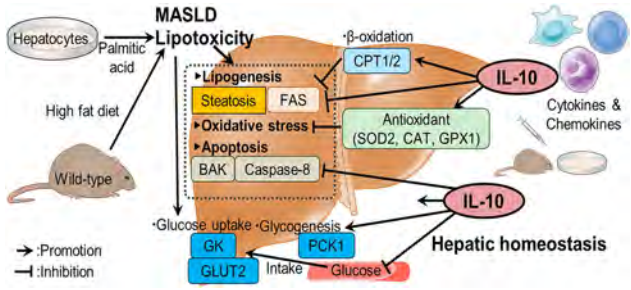
University, [3]The Institute of Medical Science, The University of Tokyo, [4]Kanto central hospital

Background: Metabolism-associated steatotic liver disease (MASLD) is characterized by hepatic lipotoxicity, which disrupts fatty acid and glucose metabolism and induces oxidative stress (OS) and apoptosis. Effective regulation of hepatic lipotoxicity is clinically needed. Interleukin (IL)-10, an endogenous anti-inflammatory cytokine, has been reported to be upregulated in liver tissue and immune cells of MASLD patients (*J Gastroenterol.* 2019), suggesting a potential compensatory role in maintaining intracellular homeostasis. This study aimed to investigate the homeostatic effects of IL-10 against lipotoxicity using *in vitro* and *in vivo* models that recapitulate MASLD pathology. **Methods:** Normal human hepatocytes were treated with palmitic acid (PA) and various concentrations of IL-10. Gene expression related to fatty acid and glucose metabolism, OS, and apoptosis was assessed, with partial validation in HepG2 cells. In vivo, six-week-old male C57BL/6J mice were fed a high-fat diet (HFD) for 12 weeks and treated with or without IL-10 (50 μg/kg) every other day for the final 6 weeks. Biochemical, histological, and gene expression analyses were performed. **Results:** In PA-treated hepatocytes, IL-10 significantly reduced intracellular lipid accumulation by downregulating fatty acid synthase (FAS) and enhancing β-oxidation (CPT1/2). IL-10 also promoted hepatic glucose storage by upregulating genes involved in glucose metabolism (GLUT2, GK, GS, PCK1). Additionally, IL-10 suppressed OS by increasing antioxidant gene expression (SOD1, CAT, GPX1) and reduced apoptosis by downregulating caspase8 and caspase3/7 activity. In HFD-fed mice, IL-10 treatment mirrored these effects: hepatic lipid droplet-containing cells were significantly reduced ($11.9 \pm 2.5\%$ vs. $32.8 \pm 3.7\%$, $p < 0.01$), and glucose uptake/glycolysis (GLUT2, GK) and gluconeogenesis (PCK1) were enhanced, resulting in lower fasting blood glucose levels (98.3 ± 5.7 vs. 178.3 ± 31.6 mg/dL, $p < 0.01$). Similar changes were observed in the antioxidant system, with a significant suppression of OS (2.4 ± 0.3 vs. $34.0 \pm 0.6\%$, $p < 0.01$), and apoptosis was significantly suppressed (0.5 ± 0.1 vs. $11.1 \pm 0.6\%$, $p < 0.01$). **Conclusion:** IL-10 exerts a protective, homeostatic effect in MASLD by attenuating lipotoxicity-induced hepatic dysfunction. It reduces lipid accumulation, OS, and apoptosis while enhancing glucose storage and glycolysis (energy metabolic activity). These findings, which bridge immunology, metabolism, and hepatology, indicate that enhancing endogenous IL-10 activity may offer a novel therapeutic strategy for MASLD.



Disclosures: Akira Kado: Nothing to Disclose, Kazuya Okushin: Nothing to Disclose, Takeya Tsutsumi: Nothing to Disclose, Toshiyuki Kishida: Nothing to Disclose, Kazuhiko Ikeuchi: Nothing to Disclose, Kyoji Moriya: Nothing to Disclose, Hiroshi Yotsuyanagi: Nothing to Disclose, Kazuhiko Koike: Nothing to Disclose, Mitsuhiro Fujishiro: Nothing to Disclose

1084 | NOVEL HAF-DRIVEN MECHANISMS CONTRIBUTING TO METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE AND HEPATOCELLULAR CARCINOMA

Po-An Hu[1] Karen Acuna-Pilarte[1], [1]University of Utah

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), which affects over 30% of the U.S. population, can advance to metabolic dysfunction-associated steatohepatitis (MASH) and hepatocellular carcinoma (HCC). Hypoxia-associated factor (HAF, SART1) has been known to be involved in NF-κB pathway regulation and apoptosis inhibition, and is significantly increased in human HCC, where it is associated with poor prognosis. Thus, identifying the potential mechanisms by which HAF contributes to MASH-HCC development will provide new insights and therapeutic targets for the early detection and treatment of MASH-HCC. **Methods:** To determine whether HAF promotes tumorigenesis in vivo, we used hydrodynamic tail-vein injection (HDTVi) of EV/SART1 into C57BL6 mice to induce hepatocyte-specific HAF overexpression. These mice were fed the GAN diet to simulate MASLD. To investigate the effect of HAF on tumor growth in vivo, we used HAF overexpressing HEPG2 xenografts grown in nude mice. Additionally, primary hepatocytes from HDTVi EV/SART1 mice were isolated three weeks after HDTVi and subjected to Seahorse metabolic analysis, mRNA sequencing, and western blotting after BSA/palmitate treatment. To complement these studies, the

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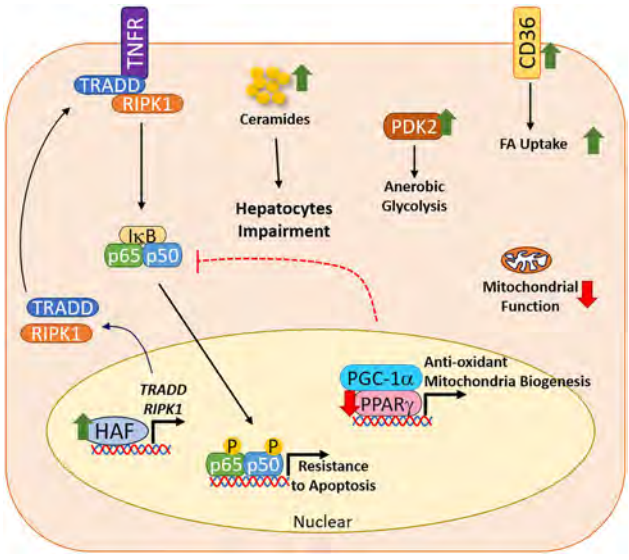
human HCC cell lines HEPG2 or PLC/PRF/5 were transfected with EV/SART1 to generate HAF-overexpressing cells. HEPG2 cells were subjected to 13C-palmitate tracing to investigate the impact of HAF on FA metabolism in vitro, whereas the impact of HAF on levels of proteins involved in mitochondrial function or metabolic regulation was determined using PLC/PRF/5 cells as well as the isolated HDTVi-HAF hepatocytes. **Results:** We observed a trend of improved glucose tolerance in the HDTVi-HAF mice, whereas HAF overexpression was associated with significantly increased xenograft growth. The mRNA sequencing of HDTVi-HAF hepatocytes showed increased levels of genes involved in fatty acid metabolism and glycolysis. However, western blotting revealed that levels of PPARγ and COX-IV were downregulated, whereas levels of CD36, CPT-I/II, GLUT4, and PDK2 were upregulated, suggesting reduced mitochondrial biogenesis and increased FA uptake, β-oxidation, and anerobic glycolysis, which may increase oxidative stress and promote a tumor-permissive environment. Indeed, Seahorse analysis studies confirmed that HAF-overexpressing hepatocytes have impaired mitochondrial function, including defective β-oxidation. Palmitate tracing experiments revealed elevated levels of lipotoxic ceramides and acylcarnitines in HAF-overexpressing HEPG2 cells. **Conclusion:** Our data suggest that increasing HAF levels may promote tumor progression, in part by promoting a metabolic shift from mitochondrial β-oxidation to increased anerobic glycolysis and lipotoxic lipid accumulation. This may promote hepatocyte stress and generate a tumor-permissive environment that could potentiate progression to HCC.



Disclosures: Po-An Hu: Nothing to Disclose, Karen Acuna-Pilarte: Nothing to Disclose

1085 | INCREASED SEVERITY OF DIET-INDUCED MASLD IN MALE MICE WAS ACCOMPANIED BY LIVER TRANSCRIPTOME INDICATING DECREASED SIGNALING EVENTS OF FATTY ACID OXIDATION AND INCREASED STING1 SIGNALING

XIAOJING LI[1], HONGGUI LI[1], XIAOXIAO WANG[1], AND CHAODONG WU[1], Xiaojing Li[1] Honggui Li[1] Xiaoxiao Wang[1], [1]Texas A&M University

Background: Sex-specific differences in the progression of metabolic dysfunction-associated steatotic liver disease (MASLD) have been widely reported, with males exhibiting more severe disease phenotypes than females in both animal models and clinical studies. Although the hepatic transcriptome in diet-induced MASLD has been studied, the findings remain inconsistent and highly variable. Further investigation is needed to elucidate how transcriptomic data can enhance our understanding of sex-specific mechanisms underlying MASLD pathogenesis. **Methods:** In the present study, male and female C57BL/6J mice were fed a low-fat diet (LFD) or a high-fat diet (HFD). General phenotypic parameters, including hepatic histopathology, glucose metabolism, and liver inflammation, and liver transcriptomic profiling were assessed. **Results:** After 12 weeks of HFD feeding, both male and female mice developed MASLD phenotype compared to their respective LFD controls. However, male-HFD mice exhibited a greater increase in body weight gain and severer hepatic pathology, characterized by extensive ballooning degeneration. Hepatic inflammation levels were also significantly higher in male-HFD mice compared to female-HFD mice, indicated by increased macrophage filtration and phosphorylation states of p65 and p46. Furthermore, male-HFD mice displayed more pronounced glucose intolerance and insulin resistance. Transcriptomic analysis revealed a total of 756 significantly differentially expressed genes (DEGs), with 337 upregulated and 428 downregulated in male-HFD mice compared to female-HFD. Pathway enrichment analysis based on all DEGs indicated a significant downregulation of AMP-activated protein kinase (AMPK) signaling. Further analysis revealed that the upregulated DEGs were predominantly enriched in inflammatory pathways, particularly cGAS–STING signaling and interleukin-1 family signaling. Notably, upstream regulator analysis based on Ingenuity Pathway Analysis identified *Sting1* as a central upstream regulator, suggesting its pivotal role in driving inflammatory gene expression. In contrast, the downregulated DEGs were mainly associated with suppressed fatty acid oxidation pathways, such as PPARα/RXRα activation, along with decreased expression of key metabolic regulators including *Ppara* and *Ppargc1b*. **Conclusion:** These findings highlight

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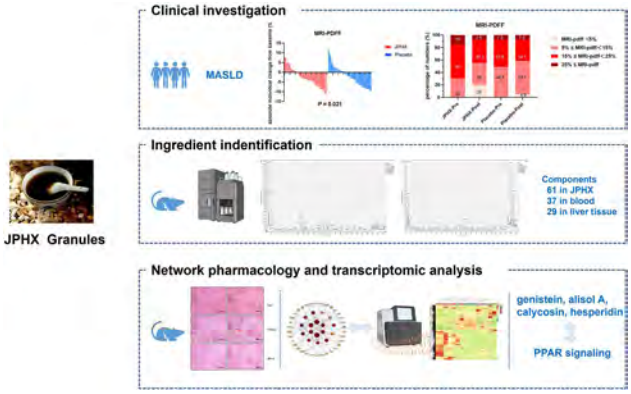
an increased severity of diet-induced MASLD in male mice, associated with distinct transcriptomic alterations characterized by increased STING1 signaling and decreased signaling events of fatty acid oxidation. The identification of *Sting1* as a central regulatory node suggests it may serve as a potential therapeutic target for sex-specific interventions in MASLD.

Disclosures: Xiaojing Li: Nothing to Disclose, Honggui Li: Nothing to Disclose, Xiaoxiao Wang: Nothing to Disclose

1086 | THERAPEUTIC EFFICACY AND PHARMACOLOGICAL MECHANISMS OF JIANPI HUOXUE FORMULA IN TREATING METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Pingping Yao[1] Zhen Tu[1] Yuqing Pan[1] Aojie Mao[1] Yiyang Hu[1] Yu Zhao[1], [1]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a global health concern. Traditional Chinese medicine (TCM) has shown broad clinical application, but evidence-based efficacy evaluations remain limited. Jianpi Huoxue Formula (JPHX), an empirically validated TCM prescription for MASLD, lacks clear mechanistic understanding. This study aimed to assess its clinical efficacy for MASLD and explore its therapeutic mechanisms to support broader clinical application. **Methods:** MASLD patients were randomized into an intervention group (n = 41, JPHX granules) or a placebo control group (n = 41). The primary efficacy endpoint was the change in liver fat content measured by MRI-proton density fat fraction (MRI-PDFF) after 24 weeks, with secondary endpoints including liver function, blood lipids, and glucose metabolism. Safety was also evaluated. LC-Q-TOF/MS was used to qualitatively analyze JPHX's chemical components and their blood/liver distribution. A MASLD mouse model was established using a high-fat diet and sugar water (55% fructose + 45% sucrose, 42 g/L) for 12 weeks. Mice were treated with JPHX (2.1 g/kg, clinically equivalent dose) for 4 weeks, alongside normal-diet controls. Liver and serum biomarkers were assessed, and liver transcriptome sequencing was performed. Network pharmacology was employed to identify JPHX component targets and disease-associated pathways, followed by functional enrichment analysis and cross-validation with KEGG enrichment results from transcriptomic data to predict therapeutic mechanisms. **Results:** Among 102 screened MASLD patients, 82 were enrolled, with 81 included in the full analysis set (FAS). After 24 weeks, the JPHX group showed a significant reduction in MRI-PDFF (LSmean: 3.11%, SE: 1.31, P = 0.021) compared to placebo. Notably, 20% of JPHX-treated patients (vs. 4.9% in placebo) achieved MRI-PDFF < 5% (P = 0.021). In the per-protocol set (PPS), JPHX significantly lowered serum AST (LSmean: -8.59 U/L, P = 0.04). Safety profiles were comparable (P > 0.05), with no severe adverse events. LC-Q-TOF/MS identified 61 components in JPHX, 37 in blood, and 29 in liver tissue. In mice, JPHX alleviated hepatic steatosis, reduced NAS scores, and decreased liver TG, serum ALT, AST, and fasting glucose. It also improved glucose/insulin tolerance and increased energy expenditure/oxygen consumption. Transcriptomics and network pharmacology jointly highlighted the PPAR and MAPK signaling pathways. Key bioactive compounds (genistein, alisol A, calycosin, hesperidin) were predicted to modulate PPAR signaling, warranting further validation. **Conclusion:** JPHX significantly reduces liver fat content and improves liver injury in MASLD patients over 24 weeks, demonstrating good safety. Components like genistein, alisol A, calycosin, and hesperidin may mediate therapeutic effects via PPAR signaling pathway regulation.



Disclosures: Pingping Yao: Nothing to Disclose, Zhen Tu: Nothing to Disclose, Yuqing Pan: Nothing to Disclose, Aojie Mao: Nothing to Disclose, Yiyang Hu: Nothing to Disclose, Yu Zhao: Nothing to Disclose

1087 | AI IN THE HISTOPATHOLOGY WORKFLOW: DETECTING HEPATOCELLULAR BALLOONING TO SUPPORT SCORING OF STEATOTIC LIVER DISEASE

Jack Breen[1] Dylan Windell[1] Philip Wakefield[1] Reema Kainth[1] Paul Aljabar[1] Caitlin Langford[1] Kenneth Fleming[2] Eve Fryer[3] Timothy Kendall[4] Rob Goldin[5], [1]Perspectum Ltd, [2]University of Oxford, [3]John Radcliffe Hospital, [4]University of Edinburgh, [5]Imperial College London

Background: Hepatocyte Ballooning (HB) is a key pathological feature used to diagnose metabolic dysfunction-associated steatohepatitis, but manual scoring is

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inconsistent, with low agreement on which cells are ballooned and on the overall severity of ballooning across a biopsy. The molecular and cellular mechanisms of ballooning are unknown, however, identifying progressive disease markers (such as non-classic HB) may allow the detection of changes in clinical trials. Artificial intelligence (AI) models can objectively detect and quantify ballooning and improve diagnostic consistency. In this study, we present a ballooning detection model and demonstrate its application in scoring liver biopsy whole slide images (WSIs) as a decision support tool for pathologists. **Methods:** Ballooning scores (0-2) were determined by a pathologist in 601 haematoxylin and eosin (H&E)-stained WSIs from three mixed liver disease cohorts. HB was annotated in 40 WSIs from two trials for model training, using human-in-the-loop relabelling after the first WSI. The third trial was reserved for external validation. Several WSI-level features were derived from the sizes and densities of AI detections. Associations between automated metrics and manual labels were assessed using Kendall's Tau correlation. Agreement between three pathologists was measured based on classifying AI outputs as classic HB, non-classic HB, or false positives in a random sample of 216 detections across 54 WSIs. **Results:** Automated metrics were found to be significantly associated (p-value < 0.05) with manual scores, including the density of large detections (Tau 0.39-0.58, Figure 1), the largest detection size (Tau 0.38-0.55), and the average size (Tau 0.37-0.49). When classifying AI outputs, pathologists exhibited only 31%, 46% and 49% pairwise agreement, consistent with previous studies. Overall, 82% of detections were labelled as HB by at least one pathologist. However, each individual pathologist labelled 31-67% of detections as HB, of which 16-71% were labelled as classic balloons. **Conclusion:** Our findings indicate that automated approaches can detect both classic and non-classic ballooned hepatocytes, and derived features correlate with manual scoring. Inter-rater agreement on ballooning severity remains low in clinical trials, however, these automated models may be used as an assistive tool for pathologists to improve the consistency of reader alignment and efficiency of liver disease diagnosis.

A)

	Trial 1 (n = 279)	Trial 2 (n = 130)	Trial 3 (n = 152)
Ballooning Score (0) detections	0.18 (n = 20)	0.00 (n = 49)	0.07 (n = 57)
Ballooning Score (1) detections	0.70 (n = 153)	0.08 (n = 64)	0.05 (n = 23)
Ballooning Score (2) detections	1.63 (n = 106)	0.56 (n = 17)	0.29 (n = 72)
Kendall's Tau	0.42	0.58	0.39
P – Value	< 0.0001	< 0.0001	< 0.0001

B)

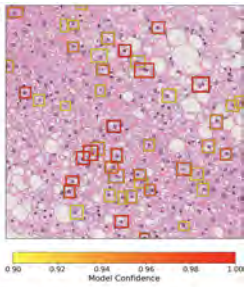

Figure 1: Hepatocyte Ballooning detection model overview. (A) Model performance with mean AI detections >1800 μm² per mm² compared with manual histological scores in unseen WSIs from 3 individual clinical trials, where Trial 3 was exclusively used for external validation. (B) Bounding boxes indicating model confidence levels (>90%) of detected ballooned hepatocytes.

Disclosures: Jack Breen: Perspectum Ltd: Employee, Dylan Windell: Perspectum: Employee, Philip Wakefield: Perspectum ltd: Employee, Reema Kainth: Perspectum: Employee, Paul Aljabar: Nothing to Disclose, Caitlin Langford: Perspectum Ltd: Employee, Kenneth Fleming: Nothing to Disclose, Eve Fryer: Nothing to Disclose, Timothy Kendall: Resolution Therapeutics: Consultant, Clinnovate Health: Consultant, HistoIndex: Consultant, Servier Laboratories: Speaking and Teaching, Fibrofind: Consultant, Kynos Therapeutics: Consultant, Perspectum Diagnostics: Consultant, Concept Life Sciences: Consultant, Incyte Corporation: Speaking and Teaching, Rob Goldin: Nothing to Disclose

1088 | ESTABLISHMENT OF A MURINE MODEL OF MICROVESICULAR STEATOSIS ASSOCIATED WITH ANOREXIA NERVOSA AND ITS PATHOPHYSIOLOGICAL CHARACTERIZATION

Michiko Ishii[1] Kyoko Hoshikawa[2] Yuiko Takeda[1] Fumiya Suzuki[1] Keita Maki[1] Tomohiro Katsumi[1] Taketo Nishina[1] Hiroaki Haga[1] Yoshiyuki Ueno[1], [1]Yamagata University Faculty of Medicine, [2]Yamagata University

Background: Anorexia nervosa (AN), a condition frequently affecting young women, is often associated with microvesicular hepatic steatosis. Although it is hypothesized that hypoalbuminemia and impaired synthesis of lipid-transporting proteins underlie lipid accumulation in the liver, the precise molecular mechanisms remain elusive. Furthermore, the distinction between hepatic lipid metabolism in AN and that observed in simple starvation has not been clearly defined. This study aimed to establish a murine model of AN-associated microvesicular steatosis and to compare it with models of simple caloric restriction and diet-induced obesity, thereby elucidating the unique pathogenesis of fatty liver in AN. **Methods:** Female C57BL/6 mice (5 weeks old) were divided into four groups ($n = 8$ each): (1) food-restricted (FR), (2) anorexia nervosa-like (AN), (3) high-fat diet (HFD), and (4) control (Ctr). After 7 days of acclimatization, FR and AN mice underwent progressive time-restricted feeding (6 h/day on Day 6 to 3 h/day from Day 9 onward). HFD and Ctr groups received ad libitum feeding from Day 6. On Day 17, animals were euthanized; serum and liver tissues were collected. Serum was analyzed for ALT, total cholesterol (T-CHO), and triglycerides (TG). Liver pathology was assessed by H&E and EM staining, Oil Red O staining, and immunohistochemistry for Adipophilin (Perilipin 2). Transcriptomic profiling was conducted by RNA sequencing (RNA-seq). **Results:** Two mice in the HFD group died during the protocol. Significant weight

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loss was observed in FR (71.3%) and AN (68.5%) groups compared to controls ($p < 0.01$). Histologically, HFD mice exhibited macrovesicular steatosis, whereas no overt lipid droplets were observed in FR and AN groups by H&E. However, Oil Red O staining revealed microvesicular lipid accumulation in 37.5% of AN mice ($p = 0.054$ vs. FR). Adipophilin immunostaining demonstrated a significantly increased positive area in both AN and HFD groups compared to controls ($p < 0.05$). Serum TG levels were significantly lower in FR and AN groups ($p < 0.05$). No single biochemical marker predicted the histological accumulation of fat droplets alone. Interestingly, within the AN group, mice exhibiting hepatic steatosis had significantly less weight loss than those without steatosis (75% vs. 64%). RNA-seq clustering showed that AN and FR mice grouped similarly, with distinct gene expression profiles from both HFD and Ctr groups. **Conclusion:** We successfully established a murine model of AN-associated microvesicular steatosis. Our findings suggest that conventional serum biochemical markers are insufficient to evaluate the degree of hepatic lipid accumulation in AN. Future studies are warranted to explore the involvement of hepatic autonomic signaling in the unique pathogenesis of fatty liver in AN.

Disclosures: Michiko Ishii: Nothing to Disclose, Kyoko Hoshikawa: Nothing to Disclose, Yuiko Takeda: Nothing to Disclose, Fumiya Suzuki: Nothing to Disclose, Keita Maki: Nothing to Disclose, Tomohiro Katsumi: Nothing to Disclose, Taketo Nishina: Nothing to Disclose, Hiroaki Haga: Nothing to Disclose, Yoshiyuki Ueno: Abbvie Inc: Speaking and Teaching, Eisai Inc: Speaking and Teaching, Chugai Pharmatheutical: Speaking and Teaching

1089 | FUNCTION AND REGULATION OF NONSENSE-MEDIATED MRNA DECAY IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Marcos Jaso Vera[1] Shohei Takaoka[1] Xiangbo Ruan[1], *[1]Johns Hopkins University School of Medicine*

Background: MASH is a severe liver disease that affects 6% of the US adults. There is currently only one FDA-approved medicine for treating MASH with limited effectiveness, indicating a critical need for further understanding of MASH pathology. Nonsense-Mediated mRNA Decay (NMD) plays a crucial role in mammalian development and physiology. In addition to degrading mRNAs with premature termination codons, NMD targets ~10% of physiological mRNAs to promote an appropriate cellular response to environmental changes. Previous studies showed that liver-specific knockout of Upf2, a core component of NMD, leads to disrupted hepatic metabolism and liver damage. However, it is still unknown if and how NMD deficiency contributes to MASH. By analyzing previously existing RNA-seq databases, our lab reported an association between a loss of NMD and changes in mRNA levels during mild fatty liver disease in mice. Additionally, we analyzed a published RNA-seq dataset of human liver patients and found that established NMD targets, including ATF4, PDRG1, and DDIT3, were upregulated in MASH patients. We hypothesize that NMD plays a significant role in the development of fatty liver disease. **Methods:** UPF2 was knocked down in human hepatic stellate cells by using siRNA and lipofectamine as indicated by the supplier. Upf2 fl/fl mice were used for *in vivo* studies by getting hepatocyte-specific knock-outs using a specific adenovirus carrying the Cre gene under the control of a human thyroxine binding globulin (TBG) promoter. RNA-seq databases were analyzed by using an in-house pipeline. qPCR and Western Blot was performed using SYBR-Green and IR dyes, respectively. **Results:** The depletion of UPF2 resulted in upregulation of fibrosis marker genes, including an increase in α-SMA expression. By overlapping genes that are simultaneously upregulated in Upf2Hep-KO mice, MASH diet-fed humanized-liver mice, and MASH patients, we identified a group of hepatic NMD targets, including TNFRSF12A, CXCL10, and PDGFA, that may promote liver damage due to a failure in NMD. Furthermore, we found an increase in RIP3K expression in Upf2Hep-KO mice liver, suggesting a potential pathway for cell death. As we know that protein levels of RIP3K are low in hepatocytes, this mechanism could involve non-parenchymal cells stimulated by the Upf2 absence in the hepatocyte. We aim to find how NMD deficiency contributes to MASH development. Additionally, we will test the therapeutic potential of restoring NMD in mouse and human MASH models. **Conclusion:** NMD is showing to be an essential player in MASH development by tightly regulating the transcript levels of important genes involved in liver fibrosis, like TNFRSF12A, CXCL10 and PDGFA.

Disclosures: Marcos Jaso Vera: Nothing to Disclose, Shohei Takaoka: Nothing to Disclose, Xiangbo Ruan: Nothing to Disclose

1090 | LIVER REGENERATION AND ASSOCIATED METABOLIC BENEFITS FOLLOWING VERTICAL SLEEVE GASTRECTOMY/PARTIAL HEPATECTOMY IN DIET-INDUCED OBESE MICE

Andriy Myronovych[1] Alfor Lewis[1] Mouhamadoul Toure[1] Sabrina Morrison[1] Jacob Abbott[1] Nadejda Bozadjieva-Kramer[1] Randy Seeley[1], *[1]University of Michigan*

Background: Obesity has reached epidemic levels and is associated with severe comorbidities, such as

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MAFLD and its manifestation MASH. Fatty liver regeneration is impaired in obese mice and humans, and while bariatric surgery is effective in treating severe obesity and its comorbidities (including MASH) its impact on liver regeneration remains unclear. Therefore, we evaluated the effect of vertical sleeve gastrectomy (VSG) on hepatic regeneration and associated metabolic parameters in obese mice. **Methods:** Diet-induced obese mice underwent concomitant VSG and 70% partial hepatectomy (VSG-PH) – a single-event, novel murine surgical model. Other mice underwent Sham, 70% PH or VSG surgeries as stand-alone procedures. Survival rate, body weight and composition dynamics, food intake and glucose regulation were monitored. Plasma samples were collected at 2-week intervals after surgery. Mice were euthanized at 48 hours post-surgery to assess liver regeneration and at 2 months to evaluate metabolic effects. Hepatic steatosis, triglyceride and cholesterol content, and liver regeneration were evaluated after sacrifice. **Results:** VSG-PH mice exhibited a satisfactory survival rate after surgery with comparable metabolic benefits to the VSG group. They consumed less food, lost a significant amount of body weight, reduced body fat mass and improved glucose metabolism compared to Sham and PH groups. Plasma triglyceride levels were improved in the early post-surgery period, while plasma cholesterol levels were consistently low in the VSG-PH group throughout the study (changes not observed in the PH group). Liver injury was significantly reduced in VSG-PH mice compared to Sham and PH mice (as evidenced by the liver injury markers ALT and AST) at early and late post-surgery time points. Hepatic steatosis (NAS Score), liver cholesterol and triglyceride contents were greatly decreased in VSG-PH mice, being similar to VSG but not PH mice. Conversely, successful liver regeneration in the VSG-PH group was comparable with the PH group, as evidenced by liver weight/body weight ratios. However, PH mice did not exhibit any metabolic benefits and regenerated livers with the signs of steatosis. **Conclusion:** Experimental surgery of VSG-PH leads to significantly improved metabolic parameters and culminates in regeneration of a fully functional and healthy residual liver. Overall, our data suggest that weight management therapy is essential for proper morphology and function of regenerated livers in the setting of obesity.

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1091 | HEPATOCYTE HEDGEHOG SIGNALING CONTROLS FERROPTOSIS TO PREVENT AGING-RELATED MULTI-ORGAN DYSFUNCTION

Ji Hye Jun[1] Soon-Woo Cho[2] Alan Yao[2] Rajesh Dutta[2] Seh-Hoon Oh[2] Zhi Li[3] Kuo Du[2] David Umbaugh[2] Nanchao Wang3[2] Yirui Xu[2] Jingting Li[2] Lingyan Shi[3] Jen-Tsan Ashley Chi[2] Junjie Yao[2] Anna Mae Diehl[2], [1]Gyeongsang National University 52828, 501 Jinjudaero, Jinju-si, Gyeongnam, Republic of Korea, [2]Duke University, [3]Shu Chien-Gene Lay Department of Bioengineering, University of California, San Diego, California,

Background: Aging increases vulnerability to metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic kidney disease (CKD), yet mechanisms linking liver aging to multi-organ decline are unclear. Hedgehog (Hh) signaling regulates hepatic regenerative capacity and metabolic flexibility. Previously, we reported that aging suppresses the Hh pathway in hepatocytes (Heps). By deleting Smo (a critical Hh pathway component), we proved that disrupting Hh signaling in Heps induced Hep senescence and MASLD. Importantly, in human livers with MASLD, Hep Smo expression decreased as the liver burden of senescent Heps and MASLD severity increased, justifying further research to determine how Smo controls liver aging. **Methods:** We used multi-omics profiling (bulk/single-cell RNA-seq), lipid peroxidation assays, and histopathology to evaluate livers and kidneys of Hep-specific Smo knockout (Smo-KO) mice under chow or choline-deficient high-fat diet (CDAHFD) conditions. Liver perfusion was measured using non-invasive ultrasound localization microscopy (ULM), and lipid unsaturation ratio was quantified using stimulated Raman Scattering (SRS) ratiometric imaging. Iron-dependent lipid peroxidation (ferroptosis) was inhibited using ferrostatin-1 (Fer-1). Findings in mice were validated by analysis of liver RNA seq and plasma O-link proteomic data from MASLD patients. **Results:** Hep-specific Smo deletion induced ferroptotic stress, lipid peroxidation and senescence in young mouse livers. It also disrupted liver and systemic iron homeostasis. More specifically, zone 2 Hep expression of iron regulatory genes was altered and zone 2 Hep expression of the potent vasoconstrictor and renin substrate, angiotensinogen, was increased while Lyve1, a fenestrated liver sinusoidal marker, was decreased in zone 2 liver. These zonally-localized changes were accompanied by decreased liver and renal perfusion and induction of fibrotic steatohepatitis and kidney damage/dysfunction. Treating Smo-KO mice with Fer1 reversed all of this pathology. Analysis of human MASLD cohort data confirmed dysregulation of iron regulatory genes/proteins and revealed increased plasma renin levels in MASLD patients with F3-4 fibrosis. **Conclusion:** Our study reveals a previously unrecognized inter-

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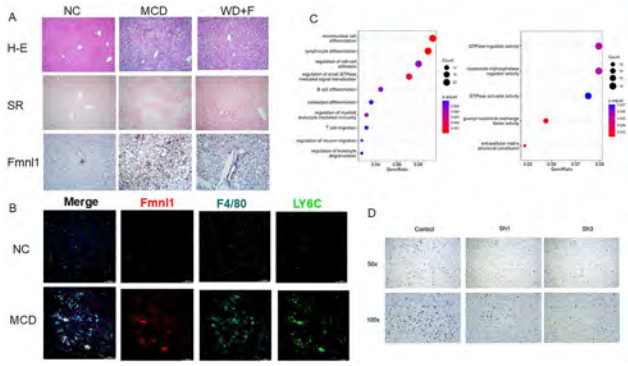
organ aging axis and identifies Hedgehog-ferroptosis signaling as a tractable target for preventing or treating MASLD and associated aging-related metabolic diseases.
Disclosures: Ji Hye Jun: Nothing to Disclose, Soon-Woo Cho: Nothing to Disclose, Alan Yao: Nothing to Disclose, Rajesh Dutta: Nothing to Disclose, Seh-Hoon Oh: Nothing to Disclose, Zhi Li: Nothing to Disclose, Kuo Du: Nothing to Disclose, David Umbaugh: Nothing to Disclose, Nanchao Wang3: Nothing to Disclose, Yirui Xu: Nothing to Disclose, Jingting Li: Nothing to Disclose, Lingyan Shi: Nothing to Disclose, Jen-Tsan Ashley Chi: Nothing to Disclose, Junjie Yao: Nothing to Disclose, Anna Mae Diehl: Nothing to Disclose

1092 | THE EXPRESSION OF FMNL1 IN MONOCYTE-DERIVED MACROPHAGES PROMOTES HEPATIC INFLAMMATION IN MASLD

Zilong Wang[1] Xiaoxiao Wang[1] Huiying Rao[1] Rui Huang[1] Feng Liu[1] Xin AI[1] Ran Fei[1], [1]Peking University Hepatology Institute

Background: Metabolic dysfunction - associated steatotic liver disease (MASLD) is characterized by hepatic steatosis and inflammation, involving the activation of immune cells, particularly macrophages. Fmnl1, a member of the Formin protein family, is implicated in cytoskeletal remodeling and cell migration. This study aimed to explore the role of Fmnl1 in the pathogenesis of MASLD, focusing on its expression in macrophages and its potential regulatory mechanisms. **Methods:** We utilized immunohistochemistry to assess Fmnl1 expression in liver tissues from MASLD patients and a mouse model induced by a methionine-choline deficient (MCD) diet. Multi-color fluorescence immunostaining was employed to identify FMNL1 localization in livers. THP-1 and RAW 264.7 cell lines were treated with oleic acid (OA)/ palmitic acid (PA) and lipopolysaccharide (LPS) to simulate a fatty inflammatory environment. Fmnl1 expression was manipulated using lentiviral-mediated gene knockdown, and F-actin staining with phalloidin was performed to evaluate changes in the cytoskeleton. Transwell assays assessed cell migration capabilities. RNA sequencing and pathway enrichment analysis were conducted on FMNL1 knockdown cells. Additionally, mass spectrometry and co-immunoprecipitation (Co-IP) were performed to explore interactions involving Fmnl1 and Cdc42. A GTP-bound Cdc42 pulldown assay was performed to determine Cdc42 activity by measuring GTP- Cdc42. **Results:** Immunohistochemical analysis revealed increased Fmnl1 expression in MASLD patient liver tissues and MCD mouse models, primarily localized in monocyte-derived macrophages. In THP-1 and RAW 264.7 cells, OA/PA and LPS treatment significantly upregulated Fmnl1 expression. Knockdown of Fmnl1 resulted in decreased actin polymerization, as evidenced by reduced F-actin staining. Transwell assays demonstrated impaired migratory capacity of Fmnl1-deficient macrophages. RNA sequencing revealed enriched pathways related to GTPase activity, and subsequent analysis identified Cdc42 as a regulator of Fmnl1 expression. Cdc42 activity increased in a time-dependent manner following OA/PA and LPS stimulation, correlating with enhanced migratory capabilities in macrophages upon Cdc42 activation. **Conclusion:** Our findings indicate that Fmnl1 plays a crucial role in the pathogenesis of MASLD by promoting the migration of monocyte-derived macrophages into the liver, thereby enhancing inflammation. This process is regulated by Cdc42, linking GTPase activity to FMNL1 expression in response to inflammatory stimulation. Therefore, it is possible that the Fmnl1 signaling pathway is a potential therapeutic target for MASLD.



Disclosures: Zilong Wang: Nothing to Disclose, Xiaoxiao Wang: Nothing to Disclose, Huiying Rao: Nothing to Disclose, Rui Huang: Nothing to Disclose, Feng Liu: Nothing to Disclose, Xin AI: Nothing to Disclose, Ran Fei: Nothing to Disclose

1093 | ZONAL DYNAMICS OF FIBROSIS PROGRESSION AND REGRESSION IN A MURINE MASLD-HCC MODEL USING AI-BASED COLLAGEN AND STEATOSIS ANALYSIS

Yuyun Song[1] Ke Yin[1] Cong Xu[1] Fei Ran[1] Baiyi Liu[1] Zilong Wang[1] Xin AI[1] Minjun Liao[1] Yayun Ren[2] Kutbuddin Akbary[2] Xiao Teng[2] Wei Wang[3] Qiang Yang[3] Huiying Rao[1] Xiaoxiao Wang[1] Feng Liu[1], [1]Peking University People's Hospital, [2]HistoIndex Pte Ltd., Singapore 117674, Singapore, [3]Hangzhou Choutu Technology Co., Ltd., HangZhou 310052, China

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), including its inflammatory form MASH, can progress to cirrhosis and hepatocellular carcinoma (HCC). Rodent models, particularly those induced by Western diets (WD), are widely used for

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studying MASLD, yet detailed characterization of fibrosis dynamics remains limited. This study leverages Second Harmonic Generation/Two Photon Excitation (SHG/TPE) imaging and artificial intelligence (AI)-based analysis to characterize regional fibrosis progression and regression in a murine MASLD-HCC model. **Methods:** MASLD-associated HCC was induced in mice using a combination of Western diet with fructose (WDF) and intraperitoneal CCl_4 (WD-CCl_4) over 28 weeks, followed by a diet switch to normal diet for 12 weeks. Liver tissues were collected at weeks 0, 8, 16, 28, and 40. Histological evaluation (H&E and picrosirius red staining) and SHG/TPE imaging (Genesis, HistoIndex Pte Ltd, Singapore) were performed. AI-based image analysis quantified steatosis and fibrosis. Statistical comparisons were conducted using one-way ANOVA with Dunnett's post hoc tests, with $p < 0.05$ considered statistically significant. **Results:** By week 28, tumor formation was observed, with 49.59% steatosis area as early as week 8 and remaining at 54.72% in non-tumor tissue at week 28. Collagen deposition progressively increased during induction. Upon diet withdrawal, steatosis rapidly regressed to 13.27% by week 40. However, overall collagen content did not decline significantly; instead, selective regression was observed in fibrous septa and in collagen co-localized to macrosteatotic regions, particularly within lobular and portal areas, suggesting early fibrosis regression occurs preferentially around resolving steatosis. **Conclusion:** SHG/TPE imaging with AI-analysis enables detailed zonal analysis of fibrosis and steatosis dynamics in MASLD murine models. This approach reveals spatial patterns of fibrosis regression and supports optimized selection of in vivo models for preclinical drug development.

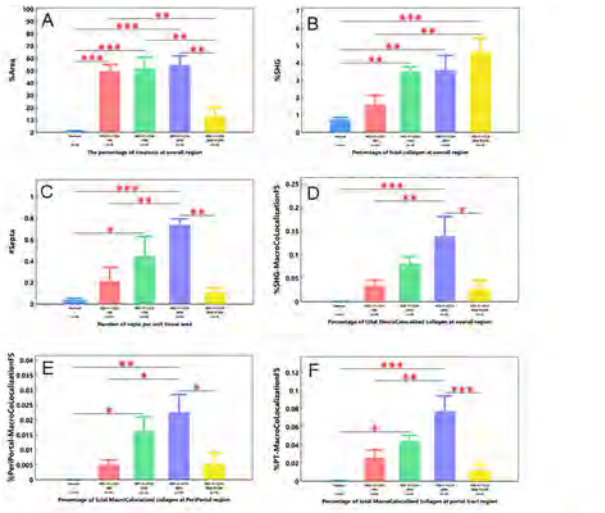

Figure 1: Temporal changes in steatosis and fibrosis in non-tumor regions of the WD-CCl_4 mouse model. Steatosis(A) peaks by week 8 and regresses after diet switch, while overall collagen(B) remains elevated. Notably, fibrosis in septa(C) and areas surrounding macrosteatosis(D,E,F) shows selective regression.

Disclosures: Yuyun Song: Nothing to Disclose, Ke Yin: Nothing to Disclose, Cong Xu: Nothing to Disclose, Fei Ran: Nothing to Disclose, Baiyi Liu: Nothing to Disclose, Zilong Wang: Nothing to Disclose, Xin Al: Nothing to Disclose, Minjun Liao: Nothing to Disclose, Yayun Ren: HistoIndex Pte Ltd: Employee, Kutbuddin Akbary: HistoIndex Pte Ltd: Employee, Xiao Teng: Nothing to Disclose, Wei Wang: Nothing to Disclose, Qiang Yang: Nothing to Disclose, Huiying Rao: Nothing to Disclose, Xiaoxiao Wang: Nothing to Disclose, Feng Liu: Nothing to Disclose

1094 | MESENCHYMAL-DERIVED EXTRACELLULAR VESICLES AS AN EMERGING TOOL FOR THE TREATMENT OF METABOLIC-ASSOCIATED FATTY LIVER DISEASE (MASLD)

Rocío Muñoz Hernández[1] Antonio Gil-Gómez[2] Vanessa Garcia-Fernandez[1] Sheila Gato[1] Angela Rojas[1] Javier De la Peña[3] Patricia Bernal[1] José Borrero de Acuña[3] Rocio Gallego-Duran[1] Isabel Fernandez[1] Douglas Maya-Miles[1] Paloma Carrillo[1] Sara Romero-Otero[1] Javier Ampuero[1] Manuel Romero-Gómez[1], [1]Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universi, [2]nstituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad, [3]Department of Microbiology, University of Seville, Seville, Spain

Background: The burden of MASLD is increasing worldwide and represents a major health concern due to its high prevalence, complexity, heterogeneity, and dynamics, requiring a multitarget therapy apporach. MASLD is characterized by progression to liver cirrhosis, end-stage liver disease, and acute-on-chronic liver failure, with liver transplantation remaining the gold standard of care. We aimed to investigate the therapeutic potential of Mesenchymal-derived extracellular vesicles (MSC-EVs) in MASLD. **Methods:** The MSC-derived EVs were obtained from the supernatant of bone marrow-derived MSC cultures and concentrated using a peristaltic pump and a specialized cassette for extracellular vesicle separation (Pellicon XL Cassette, Biomax 100 kDa). Thereafter, the concentrated sample was subjected to size exclusion chromatography using a column (qEV2, IZON), allowing for the separation of unwanted proteins from the extracellular vesicles, thereby yielding a significantly purer sample. Nano particle tracking analysis (NTA) was used to quantify and determine the EVs diameter. We have conducted a pilot study in an animal model of MASLD (n = 4) (High fat, high carbohydrates, and cholesterol (HFHCC-42% fat, high sucrose, 1.25% cholesterol + glucose/fructose in the drinking water) for 16 weeks and treated with 10^8 EVs in 100µl PBS injected thorough the tail vein, twice a week for 4 weeks. Five animals were included in the control treated with HFHCC for 16 weeks and a control group with chow diet was also included.

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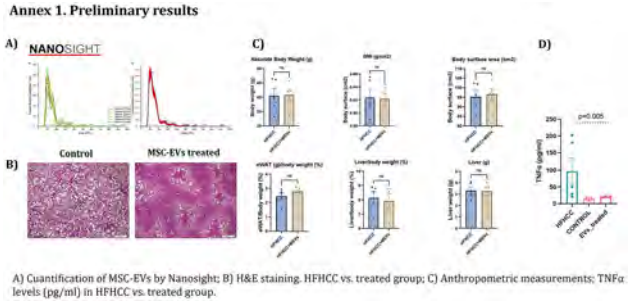
Results: As shown in figure A, after MSC-cells culture EVs were extracted and quantify with NTA, $4x10^9$ particles/ml with an average size of 154nm were obtained. Anthropometric data are shown in figure B; no significant changes were observed in absolute body weight, BMI and neither in liver weight, thus demonstrating that the beneficial effects of EVs- treatment could be independent of changes in anthropometric data. After 4 weeks treatment with MSC-EVs, we demonstrated a decrease in fat liver tissue compared to HFHCC mice (Fig 3C). Finally, a significant decrease in TNF-α levels after treatment with EVs was observed after comparing HFHCC group and control group (D). **Conclusion:** EV therapy appears to target hepatic inflammation as its primary mechanism of action, as evidenced by improvements in liver tissue and reductions in systemic inflammation, without significant changes in anthropometric measures.



Disclosures: Rocío Muñoz Hernández: Nothing to Disclose, Antonio Gil-Gómez: Nothing to Disclose, Vanessa Garcia-Fernandez: Nothing to Disclose, Sheila Gato: Nothing to Disclose, Angela Rojas: Nothing to Disclose, Javier De la Peña: Nothing to Disclose, Patricia Bernal: Nothing to Disclose, José Borrero de Acuña: Nothing to Disclose, Rocio Gallego-Duran: Nothing to Disclose, Isabel Fernandez: Nothing to Disclose, Douglas Maya-Miles: Nothing to Disclose, Paloma Carrillo: Nothing to Disclose, Sara Romero-Otero: Nothing to Disclose, Javier Ampuero: Nothing to Disclose, Manuel Romero-Gómez: Nothing to Disclose

1095 | HUMAN-SPECIFIC SUPPRESSION OF HEPATIC FATTY ACID CATABOLISM BY RNA-BINDING PROTEIN HUR

Shohei Takaoka[1] Marcos Jaso Vera[1] Xiangbo Ruan[1], [1]Institute for Fundamental Biomedical Research, Johns Hopkins All Children's Hospital

Background: RNA-binding proteins (RBPs) play essential roles in all major steps of RNA processing. Genetic studies in humans and mouse models support that many RBPs are crucial for maintaining homeostasis in key tissues/organs. However, the extent to which the function of RBPs is conserved between humans and mice remains unclear, as RBPs typically bind to non-coding regions of RNA, which are less conserved than coding regions. HuR, an RBP, was recently found to regulate fatty acid catabolism genes in a species-specific manner. **Methods:** We re-analyzed our RNA-seq data from the HuR-knockdown humanized liver mouse model. We performed GO term analysis to assess the impact on gene expression, particularly those involved in fatty acid catabolism. To explore the potential mechanism of species-specific HuR-mediated suppression of fatty acid catabolism-related genes, co-overexpression of HuR and PPARα was performed in cultured human and mouse cells. HMGCS2 was used as a model gene to study mechanisms of regulation. To understand the pathophysiological significance of our findings, published RNA-seq data from human patients with fatty liver disease and diet-induced obesity (DIO) mouse models were re-analyzed. We applied the intron-exon combined RNA-seq analysis pipeline to draw coverage plots of the HMGCS2 gene body and inspect pre-mRNA expression and mature mRNA expression. **Results:** Knockdown of human HuR in human hepatocytes led to broad upregulation of fatty acid catabolism genes, an effect not seen with mouse HuR. HuR suppressed PPARα-induced expression of fatty acid catabolism genes in human cells but not in mouse cells. This suppression was independent of PPARα's expression or localization and unrelated to mRNA stability or promoter activity. Instead, HuR inhibited pre-mRNA processing of genes like HMGCS2, leading to intron accumulation. Overexpression of HuR blocked, while knockdown sensitized, the response to PPARα agonists. Analysis of RNA-seq data revealed impaired HMGCS2 pre-mRNA processing in human patients with fatty liver disease, but not in DIO mouse models. **Conclusion:** HuR suppresses fatty acid catabolism gene expression in a human-specific manner by inhibiting pre-mRNA processing. This may help explain the reduced efficacy of PPARα agonists in treating human fatty liver disease compared to mouse models, highlighting the importance of considering species-specific regulatory mechanisms in translational research.

Disclosures: Shohei Takaoka: Nothing to Disclose, Marcos Jaso Vera: Nothing to Disclose, Xiangbo Ruan: Nothing to Disclose

1096 | MECHANISTIC ROLE OF LATERAL HABENULAR NUCLEUS 5-HT_7 RECEPTORS IN LIVER–BRAIN CROSSTALK UNDERLYING NAFLD-ASSOCIATED DEPRESSION

Yuming Zhang[1] Jinyao Su[1] SongYan Guo[1], [1]Shaanxi Provincial People's Hospital

Background: Depression is increasingly recognized as a common yet underexplored comorbidity in individuals with non-alcoholic fatty liver disease (NAFLD). While the liver–brain axis has been implicated, the precise neurocircuitry

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remains poorly defined. The lateral habenular nucleus (LHb), an epithalamic structure critical for processing aversive and reward-related signals, is hyperactive in depression and densely innervated by serotonergic projections. Among serotonin receptors, 5-HT_7 plays a pivotal role in mood regulation. Building on our previous work in Parkinsonian models implicating LHb 5-HT_7 receptors signaling in emotional dysregulation, we examined its involvement in NAFLD-associated depressive phenotypes. **Methods:** A NAFLD model was induced in male Sprague–Dawley rats through an 8-week high-fat diet (60% fat, 25.9% carbohydrate, 14.1% protein). Animals underwent behavioral testing (sucrose preference and forced swim tests), followed by targeted intra-LHb microinjection of the 5-HT_7 receptors agonist AS19 or antagonist SB269970. In vivo electrophysiological recordings, monoamine assays across key limbic regions (medial prefrontal cortex, amygdala, habenula, ventral hippocampus), and immunofluorescence imaging were used to dissect underlying mechanisms. **Results:** NAFLD rats showed clear anhedonia and behavioral despair. Activation of LHb 5-HT_7 receptors by AS19 aggravated depressive-like behaviors, whereas blockade with SB269970 produced robust antidepressant effects in both NAFLD and control rats. Neurochemical analyses revealed significant alterations in dopamine and noradrenaline levels across limbic circuits, in a drug- and disease-dependent manner. Electrophysiological recordings demonstrated that AS19 enhanced the firing rate of LHb glutamatergic neurons, while SB269970 suppressed neuronal activity. Notably, both effects were more sustained in NAFLD rats. Interestingly, 5-HT_7 receptor expression and colocalization with LHb glutamatergic neurons remained unchanged. **Conclusion:** Our findings identify a novel mechanism by which NAFLD sensitizes LHb 5-HT_7 receptors signaling, enhancing glutamatergic excitability and disrupting monoaminergic tone in mood-related brain regions. These results underscore the LHb 5-HT_7 receptors as a promising therapeutic target for metabolic syndrome–associated depression, bridging hepatic dysfunction and central affective regulation.

Disclosures: Yuming Zhang: Nothing to Disclose, Jinyao Su: Nothing to Disclose, SongYan Guo: Nothing to Disclose

1097 | HEPATIC EXTRACELLULAR VESICLES SUPPRESS MACROPHAGE IMMUNE RESPONSE IN AN OLEATE- AND CERS6-DEPENDENT MANNER

Joseph Dempsey[1] Carole Smith[1] Julia Harkin[1] Samira Abdirahim[1] Rotonya Carr[2], [1]University of Washington, [2]University of Washington Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) can progress from steatosis to metabolic dysfunction-associated steatohepatitis (MASH)—the more lipotoxic, inflammatory phenotype. The drivers of this transition remain incompletely understood. Ceramide synthase 6 (CERS6) is a ceramide synthetic enzyme that produces long-chain ceramides (primarily C16:0) which we and others have linked to lipotoxicity and inflammation. C16:0 ceramides are increased in MASLD patients and are present in hepatocyte-derived extracellular vesicles (EVs) in murine and human MASLD. We hypothesize that hepatocellular accumulation of CERS6-derived C16:0 ceramides promotes the steatosis to MASH transition through C16:0-endowed hepatocyte EVs and subsequent activation of hepatic macrophages. **Methods:** Wild-type (WT) and CERS6 knockout (KO) HepG2 cells were exposed to EV-free media with oleate (0 or 1 mM) for 48 hours (WT-control, WT-oleate, KO-control, and KO-oleate). Lipid droplets were quantified by in-cell western using immunofluorescent LipidSpot488. HepG2-derived EVs were isolated using the ExoQuick-TC kit, and EV particle concentration and size was evaluated by NanoSight. For EV-induced immune response, PMA-differentiated THP-1 cells were exposed to EVs for 6 hours. THP-1 and HepG2 cells were isolated in Qiazol for RNA expression by RT-qPCR and protein expression by western blot. **Results:** WT and CERS6-KO cells exposed to oleate had more lipid droplets and higher perilipin 2 protein expression versus normal media. The mean number of EV particles isolated from the media of oleate-exposed WT and KO cells increased 1.8 and 1.5 times, respectively, versus controls. Mean particle size of KO-control EVs increased from 134.5 nm to 148 nm compared to WT-control EVs. Particle size distribution was right-skewed in an oleate- and CERS6-dependent manner, with KO-oleate EVs having a mean size of 170.5 nm. Differentiated THP-1 cells exposed to EVs from WT-oleate, KO-control, or KO-oleate showed decreased RNA expression of the macrophage inflammatory markers CXCL1, IL6, IL1β, and IL2β compared to cells exposed to WT-control EVs. **Conclusion:** EVs from CERS6-deficient cells and WT cells incubated in oleate elicited a reduced inflammatory response in macrophages, highlighting a potential therapeutic target in MASLD progression. This study suggests that CERS6 contributes to the progression from steatosis to MASH by modulating the size and inflammatory potential of hepatocyte-derived EVs.

Disclosures: Joseph Dempsey: Nothing to Disclose, Carole Smith: Nothing to Disclose, Julia Harkin: Nothing to Disclose, Samira Abdirahim: Nothing to Disclose, Rotonya Carr: Nothing to Disclose

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1098 | NOVEL HUMANIZED IMMUNE SYSTEM MOUSE MODELS FOR LIVER FIBROSIS AND MASH

Dan Georgess[1] Clothilde Philouze[1] Omayra Martin-Rodriguez[1] Anaïs Meynet-Cordonnier[1] Sebastien Tabruyn[1], [1]Transcure Bioservices

Background: The development of predictive preclinical models that recapitulate human-relevant, targetable biology is critical to accelerating drug discovery. Here, we present two distinct humanized mouse models for liver fibrosis and MASH, designed to evaluate therapeutics targeting the human immune drivers of liver fibrosis, inflammation, and steatosis. **Methods:** CD34+ HSC-humanized NCG mice (HIS-NCG) were subjected to one of two disease induction protocols: (1) a 23-day course of carbon tetrachloride (CCl_4) treatment, or (2) a 14-day high-fat methionine- and choline-deficient (HFMCD) diet. **Results:** Both protocols induced rapid (within 2 weeks) health deterioration and significant liver injury, evidenced by elevated ALT levels compared to controls. However, the resultant liver phenotypes differed substantially. CCl_4 treatment induced severe fibrosis (88% of mice with either bridging F3 fibrosis or cirrhosis) without accompanying steatosis or notable macrophage infiltration. In contrast, the HFMCD diet led to a more comprehensive MASH phenotype, including a NAFLD activity score (NAS) of 6, advanced steatosis, F1 fibrosis, marked infiltration of human $CD68^+$ macrophages, and elevated circulating LGALS3BP further confirming liver injury, fibrosis, and inflammation. **Conclusion:** In summary, we describe two robust and reproducible humanized mouse models tailored for the rapid evaluation of human immune-targeting or cross-reactive therapeutic candidates: the HFMCD HIS-NCG model for MASH and the CCl_4 HIS-NCG model for advanced fibrosis. Furthermore, dual-humanized models (human immune system and liver) are also available to support studies of combination therapies targeting both immunity and metabolism. These next-generation mouse models hold significant promise for transforming the therapeutic landscape in MASH and infectious hepatitis.
Disclosures: Dan Georgess: Nothing to Disclose, Clothilde Philouze: Nothing to Disclose, Omayra Martin-Rodriguez: Nothing to Disclose, Anaïs Meynet-Cordonnier: Nothing to Disclose, Sebastien Tabruyn: Nothing to Disclose

1099 | SALIDROSIDE ALLEVIATES MASH THROUGH PPARΓ-MEDIATED INFLAMMATORY SIGNALING PATHWAY

Jun Zhang[1], [1]Ningbo No.2 Hospital

Background: Metabolic dysfunction-associated steatohepatitis (MASH), a progressive stage of metabolic associated fatty liver disease (MAFLD), lacks effective therapies. Salidroside, a bioactive compound from Rhodiola rosea, exhibits anti-inflammatory and metabolic regulatory properties, but its mechanism in MASH remains unclear. **Methods:** A choline-deficient L-amino acid-defined high-fat diet (CDAHFD)-induced MASH mouse model was used. Mice received salidroside (25 or 50 mg/kg) or pioglitazone (10 mg/kg) for four weeks. PPARγ inhibitor GW9662 was co-administered to validate pathway specificity. Multi-omics analyses (transcriptomics, metabolomics) identified key pathways. Network pharmacology, molecular docking, and Western blotting were employed to explore targets and mechanisms. **Results:** Salidroside reduced hepatic lipid deposition, serum ALT/AST levels, and inflammatory cytokines (IL-1β, IL-6, TNFα) in MASH mice. Transcriptomics and metabolomics revealed PPAR signaling as the most enriched pathway. Salidroside activated PPARγ, suppressed NF-κB phosphorylation, and downregulated pro-inflammatory factors. Co-treatment with GW9662 abolished these effects, confirming PPARγ dependency. Molecular docking showed strong binding affinity between salidroside and PPARγ. **Conclusion:** Salidroside ameliorates MASH by activating PPARγ, thereby inhibiting NF-κB-mediated inflammation and hepatic lipid accumulation. This study highlights PPARγ/NF-κB signaling as a critical target for salidroside, offering a foundation for developing natural therapies against MASH.
Disclosures: Jun Zhang: Nothing to Disclose

1100 | COMBINED EFFECT OF ATORVASTATIN AND AMBRISENTAN ON THE HEMODYNAMIC ALTERATIONS AND LIVER FIBROSIS IN A TRANSLATIONAL RAT MODEL OF MASLD WITH ADVANCED FIBROSIS

Maria de la Serra Cusidó Sabidó[1] Imma Raurell[2] Núria Juan Benítez[1] María Martínez Gómez[3] Sophia Christina Parks[4] Juan M Pericàs[5] Maria Martell[5] Joan Genescà[5], [1]Liver Disease Group, VHIR; UAB, [2]Liver Disease Group, VHIR; Liver Unit, VHUH; CIBERehd, [3]Liver Disease Group, VHIR; UAB; CIBERehd, [4]Liver Disease Group, VHIR, [5]Liver Disease Group, VHIR; Liver Unit, VHUH; CIBERehd; UAB

Background: Metabolic-dysfunction Associated Steatotic Liver Disease (MASLD) is characterized by hepatic steatosis, which can progress to inflammation, fibrosis, and portal hypertension (PH). Despite its increasing clinical burden, therapeutic options remain limited due to the lack of translational animal models that fully recapitulate the human disease spectrum. Previous work from our group developed a non-fibrotic NASH model, which, when

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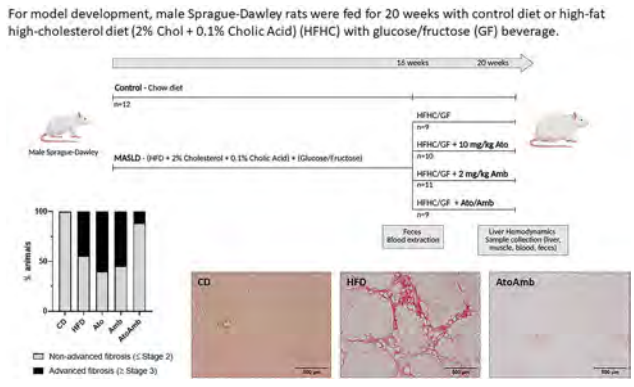
treated with Atorvastatin (Ato) and Ambrisentan (Amb) reduced steatohepatitis and PH. Considering the results in the NASH model, in this study we evaluate the combined effect of Ato and Amb on liver fibrosis, endothelial dysfunction, and hemodynamic alterations in a recently developed translational model of MASLD with advanced fibrosis. **Methods:** At the end of the model, liver hemodynamic was assessed. The samples were used for histological evaluation (H&E and Sirius Red), and gene and protein analysis for fibrosis, insulin signaling and endothelial function (Fig. 1). **Results:** MASLD rats exhibited increased AST/ALT, PH, insulin resistance, steatohepatitis and advanced fibrosis, corresponding to our known model features. Neither Ato nor Amb alone or combined reduced body weight or reverted insulin resistance. Endothelial dysfunction was partially reversed by AtoAmb, P-Enos and KLF2 were restored, yet P-AKT remained suppressed, indicating limited sinusoidal recovery. Markedly, AtoAmb led to fibrosis regression, evidenced by 1) decreased histological fibrosis stage, 2) reduced collagen deposition (Fig. 1), 3) downregulation of Col1a1, αSMA to near-control levels, and 4) lower levels of metalloprotease inhibitor TIMP1. However, severe steatosis and PH remained largely unaffected. Correlation analyses showed poor association between portal pressure and fibrosis, but a stronger correlation between portal pressure and steatosis severity, suggesting steatosis as the main driver to sinusoidal compression and so PH. **Conclusion:** The combination of Ato and Amb demonstrated a synergistic effect reversing liver fibrosis in a translational rat model of MASLD but failed to reduce PH, likely due to persistent severe steatosis and sinusoidal compression. These findings highlight the dissociation between fibrosis and portal pressure in advanced MASLD and emphasize the need for multi-targeted strategies addressing both lipid accumulation and fibrosis for effective PH management.



Disclosures: Maria de la Serra Cusidó Sabidó: Nothing to Disclose, Imma Raurell: Nothing to Disclose, Núria Juan Benítez: Nothing to Disclose, María Martínez Gómez: Nothing to Disclose, Sophia Christina Parks: Nothing to Disclose, Juan M Pericàs: Nothing to Disclose, Maria Martell: Nothing to Disclose, Joan Genescà: Nothing to Disclose

1101 | EFFECTS OF DIETARY PATTERNS ON METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A STUDY IN MORBIDLY OBESE RATS UNDERGOING BARIATRIC SURGERY

Wei-Yu Kao[1] Chin-Ying Wu[2] Chen-Yu Liao[3] Weu Wang[4] Ching-Wen Chang[3] Chi-Long Chen[5] Chun-Chao Chang[6] Shih-Yi Huang[3], [1]Taipei Medical University Hospital, [2]School of Nutrition and Health Sciences, Taipei Medical University, Taipei, Taiwan, [3]Graduate Institute of Metabolism and Obesity Sciences, Taipei Medical University, Taipei, Taiwan, [4]Division of Digestive Surgery, Department of Surgery, Taipei Medical University Hospital, Taipei, [5]Department of Pathology, Taipei Medical University Hospital, Taipei, Taiwan, [6]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei Medical Univ

Background: The global rise in metabolic syndrome, obesity, and diabetes has contributed to the increased prevalence of non-alcoholic fatty liver disease (NAFLD). Obesity, characterized by excessive fat accumulation, significantly contributes to NAFLD, posing a major public health concern due to its adverse effects on overall health. Treatment strategies for obesity include lifestyle modification of diets and exercise, pharmacotherapy, and bariatric surgery, with surgery being particularly effective for long-term weight control in morbidly obese patients. This study aims to model NAFLD in morbidly obese rats and evaluate the effects of bariatric surgery, dietary changes, and exercise on liver pathology and lipid metabolism. **Methods:** A total of 102 male Wistar rats (8 weeks old) with morbid obesity and fatty liver were used. After 14 weeks of diet induction, the rats underwent sleeve gastrectomy. Following surgery, they were subjected to 18 weeks of calorie-restricted diets (CRD), non-ketogenic low-carbohydrate diets (LCD). Blood and liver samples were collected every 6 week period for analysis, including biochemical values and inflammation-related blood factors. **Results:** At 18 weeks post-surgery, body weight in the high-fat diet (HFD) group continued to increase and remained significantly higher than in all other groups. The CRD group showed significantly lower body weight compared to the LCD group. After a 14-week diet induction for morbid obesity and fatty liver, liver weight, perirenal fat weight, and epididymal fat weight were significantly higher in the HFD group compared to the control group ($p < 0.05$ for all). At

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18 weeks post-gastrectomy, no significant differences in liver weight were observed between the groups. In terms of blood biochemistry, after 14 weeks of diet induction, serum SGOT and SGPT levels were significantly higher in the HFD group compared to the control group ($p < 0.05$ for both). At 18 weeks post-surgery, SGOT, SGPT, and triglyceride (TG) levels in the HFD group were significantly lower than those at week 0 post-surgery ($p < 0.05$ for all). Histopathological liver analysis revealed that the HFD induced hepatic lipid accumulation and resulted in a significantly higher NAFLD score than the control group. Sleeve gastrectomy and dietary interventions reduced both lipid accumulation and NAFLD scores. **Conclusion:** Sleeve gastrectomy improved liver fat and NAFLD-related biochemical markers in rat models. Among the dietary interventions, the calorie-restricted diet was more effective in reducing body weight and visceral fat compared to the non-ketogenic low-carbohydrate diet.
Disclosures: Wei-Yu Kao: Nothing to Disclose, Chin-Ying Wu: Nothing to Disclose, Chen-Yu Liao: Nothing to Disclose, Weu Wang: Nothing to Disclose, Ching-Wen Chang: Nothing to Disclose, Chi-Long Chen: Nothing to Disclose, Chun-Chao Chang: Nothing to Disclose, Shih-Yi Huang: Nothing to Disclose

1102 | MACROPHAGE RECEPTOR LRP1 MEDIATES NECROPTOTIC HEPATOCYTE ENGULFMENT AND SUPPRESSES A PRO-FIBROTIC PATHWAY INVOLVING HEPATOCYTE TAZ DOWNREGULATION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Hongxue Shi[1] Ira Tabas[2] Xiaobo Wang[1] Eui Jung Jung[1] Saheli Chowdhury[1], [1]Columbia University Irving Medical Center, [2]Columbia University

Background: MASH is an advanced stage of fatty liver disease and the leading cause of human chronic liver disease. Necroptosis in hepatocytes is a key feature during MASH progression, and improving necroptotic hepatocyte (necHC) engulfment by liver macrophage dampens MASH progression. However, the receptor in liver macrophage for recognizing and binding necHCs and the mechanism underlying the suppressed hepatic stellate cell activation by efferocytic macrophage is unknown. This study is focused on investigating the crucial role of the liver macrophage receptor LRP1 in the clearance of necHCs-mediated lowering hepatocyte TAZ expression during MASH progression. **Methods:** LRP1 expression was assayed in liver tissue sections obtained from humans and mice with normal and MASH. The necHC uptake by using siRNA-LRP1 in liver macrophage was assayed. For mouse MASH experimental mode, male C57BL/6J mice were fed either a high-fat choline-deficient L-amino-defined (HF-CDAA) diet for 8 weeks or a fructose-palmitate-cholesterol (FPC) diet for 16 weeks. For all mouse models, causation was tested by liver macrophage-Lrp1knockout mice, and hepatocyte TAZ knockout mice, followed by assessment of necHC uptake by liver macrophages, TAZ expression, and MASH fibrosis. For ex vivo studies, the engulfment of mouse necHCs by mouse liver macrophages and hepatic stellate cell activation from conditioned media transfer experiment were assayed. **Results:** We have shown improved necHC clearance by deleting macrophage Sirpα expression, associated with decreased liver pro-fibrotic factor TAZ expression in the HF-CDAA diet-fed MASH mice. Furthermore, down-regulation of liver TAZ expression was found in anti-CD47 or anti-SIRPα neutralization antibody-treated FPC diet-fed MASH mice. The conditioned media from necHCs efferoytotic macrophages decreased TAZ expression in AML12 cells ex vivo. Most importantly, liver hepatocyte TAZ deficiency did not further lower TAZ expression and hepatic fibrosis when administration of anti-SIRPα neutralization antibody in the HF-CDAA diet-fed MASH mice. Increased liver macrophage LRP1 expression was shown in human and mouse MASH liver. Treated with scramble RNA did not affect necHC uptake, while siRNA-Lrp1 treatment decreased necHC engulfment in the presence of anti- SIRPα by liver macrophage ex vivo. The improved necHC engulfment by liver macrophage was reversed in anti-SIRPα treated HF-CDAA diet-fed MASH mice, associated with increased liver fibrosis. **Conclusion:** Increased liver macrophage LRP1 expression is a compensatory mechanism for facilitating necHC engulfment when do-not-eat-me molecules exist. Down-regulation of hepatocyte TAZ expression contributes to the lower liver fibrosis effects when improving necHC clearance by liver macrophage in MASH diet-fed mice. These findings define a new mechanism contributing to MASH progression with potential therapeutic implications.
Disclosures: Hongxue Shi: Nothing to Disclose, Ira Tabas: Nothing to Disclose, Xiaobo Wang: Nothing to Disclose, Eui Jung Jung: Nothing to Disclose, Saheli Chowdhury: Nothing to Disclose

1103 | FORMATION AND REGULATION OF A HEPATIC LIPOGENIC METABOLON

Xiaotong Zhu[1] Chaiwan Kim[1] Jay Horton[1], [1]UT Southwestern Medical Center

Background: Elevated rates of *de novo* hepatic lipogenesis (DNL), which converts acetyl-CoA into fatty acids (FAs), significantly contributes to hepatic

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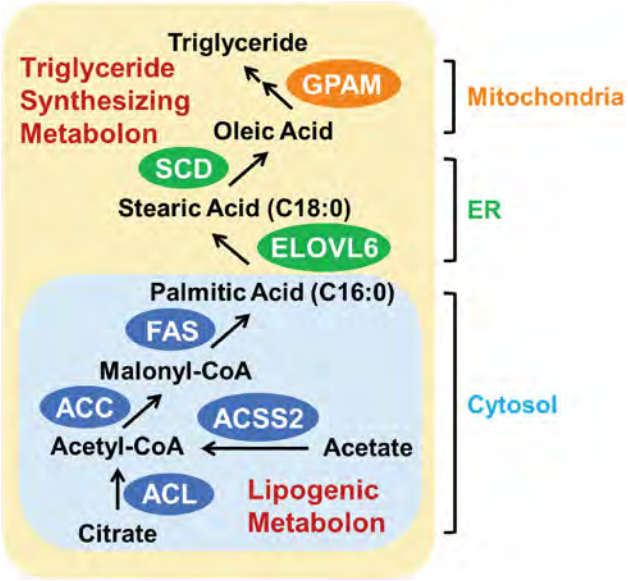
triglyceride (TG) accumulation in metabolic dysfunction-associated fatty liver disease (MAFLD). Inhibitors of FA synthesis are in various stages of clinical development for the treatment of MAFLD. Here, we further investigate a post-transcriptional mechanism that regulates FA synthesis and that might contribute to the development of MASLD. **Methods:** Immunofluorescence, electron microscopy (EM), and cellular fractionation were used to localize proteins that synthesize FAs and TGs: ATP-citrate lyase (ACL), acyl-CoA synthetase short-chain family member 2 (ACSS2), (acetyl-CoA carboxylase 1) ACC1, fatty acid synthase (FAS), MIG12, Spot 14 (S14), and glycerol-3-phosphate acyltransferase 1 (GPAM). Protein–protein interactions were assessed via ACC1 immunoprecipitation (IP) and sucrose gradient ultracentrifugation. Blue native PAGE evaluated ACC1 polymerization of primary hepatocytes. Enzymatic assays using liver lysates and recombinant proteins were used to measure lipid synthesis under different metabolic states. **Results:** Under anabolic conditions, such as refeeding or insulin treatment, immunoprecipitation of ACC1 co-immunoprecipitates the additional key enzymes to synthesize FAs and TGs (ACL, ACSS2, FAS, MIG12, S14, and GPAM). The individual enzymatic activities of these lipogenic proteins are also enhanced under these conditions as is overall FA and TG synthesis. Immunofluorescence and electron microscopy reveal that this metabolon localizes around lipid droplets (LDs) and at the mitochondria-LD interface in the anabolic state, facilitating efficient substrate channeling through the lipid synthesis pathway. **Conclusion:** Our findings support the existence of a lipogenic metabolon that assembles under anabolic states to coordinate FA and TG synthesis. This spatially organized, post-translational mechanism enhances metabolic efficiency and may serve as a novel therapeutic target in MAFLD.



Disclosures: Xiaotong Zhu: Nothing to Disclose, Chaiwan Kim: Nothing to Disclose, Jay Horton: Pfizer: Consultant, Merck: Consultant, Regeneron: Consultant, AbbVie: Consultant

1104 | NEUTROPHIL EXTRACELLULAR TRAPS DRIVE KUPFFER CELL-MEDIATED FIBROGENESIS IN MASH BY REPRESSING IRG1

Yiyu Zhang[1] Songhan Pang[1] Amelia Bergeron[1] Hongji Zhang[1] Allan Tsung[1], [1]University of Virginia

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a severe form of metabolic dysfunction-associated steatotic liver disease (MASLD) marked by immune activation and fibrosis, with the potential to progress to cirrhosis and hepatocellular carcinoma. While Resmetirom was recently approved for MASLD, its efficacy in patients with liver fibrosis remains limited and perioperative risks often delay surgical interventions in MASH-fibrosis, underscoring the need for new therapeutic strategies. Neutrophil extracellular traps (NETs)—web-like chromatin structures released by neutrophils—exacerbate liver inflammation and fibrosis, while we have shown that NETs regulate the inflammatory microenvironment to drive MASH-fibrosis, the underlying mechanism remains unclear. Kupffer cells (KCs), as liver-resident macrophages, are central to immune responses and fibrogenesis in MASH, yet their mechanism remains incompletely understood. This study investigates how NETs modulate KC function to drive fibrosis in MASH. **Methods:** MASH was induced in C57BL/6 mice by Western diet (WD) feeding for 40 weeks. NET was inhibited using neutrophil-specific Pad4 knockout (Pad4$^{fl/fl}$ MRP8-Cre) or DNase I treatment (10 mg/kg I.P. 5x/week). Liver fibrosis was assessed via Sirius Red and Masson's trichrome staining. Hepatic CD45+ leukocytes were analyzed by single-cell RNA sequencing (scRNA-seq). KC-specific IRG1 expression was validated via western blot. **Results:** WD-fed mice developed significant hepatic fibrosis, which was markedly reduced by NET inhibition. scRNA-seq revealed broad immune remodeling in MASH liver, with KC displaying one of the most prominent transcriptional changes, characterized by pro-inflammatory and pro-fibrogenic gene expression. Neutrophil-Kupffer cell interactions were significantly elevated compared to other immune cell types. Expression of immune-responsive gene 1 protein (IRG1), a key regulator of KC metabolic reprogramming, was suppressed in KCs during MASH-fibrosis but restored upon NET inhibition. **Conclusion:** NETs promote pro-fibrogenic reprogramming of Kupffer cells in MASH by downregulating IRG1 expression. Targeting NET-KC interactions may represent a

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promising therapeutic strategy to attenuate liver inflammation and fibrosis in MASH.

Disclosures: Yiyu Zhang: Nothing to Disclose, Songhan Pang: Nothing to Disclose, Amelia Bergeron: Nothing to Disclose, Hongji Zhang: Nothing to Disclose, Allan Tsung: Nothing to Disclose

1105 | KAHWEOL ATTENUATES WESTERN DIET-INDUCED HEPATIC STEATOSIS BY SUPPRESSING FATTY ACID SYNTHASE

Byoung Kuk Jang[1] Hye Young Seo[1] Ji Yeon Park[1] Jaeseok Hwang[2] Mi Kyung Kim[1], [1]Keimyung University School of Medicine, [2]Keimyung university

Background: Hepatic steatosis is a key feature of metabolic dysfunction-associated steatotic liver disease (MASLD) and is exacerbated by a Western diet (WD), leading to metabolic dysregulation, inflammation, and fibrosis. Our previous research demonstrated that kahweol, a diterpene found in unfiltered coffee, exhibits protective effects against liver inflammation, fibrosis, and hepatocellular carcinoma (HCC). This study investigates the potential role of kahweol in attenuating WD-induced hepatic steatosis and its underlying mechanisms. **Methods:** C57BL/6 mice were fed a chow diet, WD, or WD supplemented with kahweol (40 mg/kg) for 16 weeks. Metabolic parameters, including body weight, liver function markers, lipid profile, and glucose metabolism, were assessed. Hepatic steatosis, inflammation and fibrosis were evaluated using histological and molecular analyses, including real-time RT-PCR and Western blotting. RNA sequencing was performed to identify differentially expressed genes and enriched signaling pathways in response to kahweol treatment. **Results:** WD significantly increased body weight, impaired glucose tolerance, and elevated serum AST and ALT levels, indicating liver damage. Kahweol treatment ameliorated these effects by improving glucose tolerance and reducing liver enzyme levels. In addition, WD upregulated the expression of lipogenic genes (FASN, SREBP-1c, PPARγ), inflammatory markers (F4/80, TNFα, IL-1β, and IL-6), and fibrosis markers (collagen, α-SMA, and PAI-1) in the liver, whereas Kahweol treatment significantly downregulated these genes. These results were consistent with the RNA-seq analysis, which further confirmed that Kahweol inhibited lipogenesis by suppressing the expression of key lipogenic genes, including FASN and PPARγ. **Conclusion:** These results suggest that Kahweol alleviates WD-induced hepatic lipid accumulation, inflammation, and fibrosis by suppressing adipogenic genes such as FASN and modulating PPAR signaling. This study provides new insights into the potential use of Kahweol as a therapeutic candidate for MASLD.

Disclosures: Byoung Kuk Jang: Nothing to Disclose, Hye Young Seo: Nothing to Disclose, Ji Yeon Park: Nothing to Disclose, Jaeseok Hwang: Nothing to Disclose, Mi Kyung Kim: Nothing to Disclose

1106 | MODELING METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS IN HUMAN LIVER MICROPHYSIOGICAL SYSTEMS FOR CLINICAL PREDICTION

Rachelle Baun[1] Nathan Sorensen[1] Dennis McDuffie[1] Crystal Yuri Oh[1] Dan Sazer[1] Hani Jouihan[2] Damien Demozay[2] Emma Henriksson Kraft[2] Helena Lykkegaard[2] Sara Toftegaard Hjuler[2], [1]Novo Nordisk, [2]Novo Nordisk, Inc.

Background: Metabolic Dysfunction-Associated Steatohepatitis (MASH) is an advanced form of Metabolic dysfunction-Associated steatotic Liver Disease (MASLD) and is strongly linked to obesity and the metabolic syndrome [Dufour et al., 2022]. There are currently no approved treatments for MASH due to the lack of efficacy in the clinical trials which can be attributed to the complexity of disease, which involves lipo-toxicity, insulin resistance, inflammation, and fibrosis. Furthermore, the lack of relevant non-invasive biomarkers makes the approval path difficult. Animal models of MASH, such as high-fat diet and ob/ob mouse models, develop metabolic syndrome and steatosis but lack certain human inflammatory hallmarks as well as advanced fibrosis progression characteristic of MASH in the human. Thus, the aim of this research is to recreate a human MASH model using a liver micro physiological system for clinical prediction of compound efficacy and biomarker discovery and validation. **Methods:** Using the CN Bio Liver Chip platform [Kostrzewski et al., 2017], we are able to create a human, 3D model of MASH, incorporating human hepatocytes, Kupffer and stellate cells from healthy donors. Culture conditions for healthy and MASH (elevated glucose, insulin, fatty acids, and +/- TGFb) were identified for culture medium, stellate cell propagation, and seeding methods. Endpoints consisted of general liver function (albumin production, CYP3A activity, glucose output, intracellular triglyceride formation and secretion), cytokine expression (pro-inflammatory markers associated with liver fibrosis), and collagen secretion (indicative of fibrosis). Tool compounds, such as Activin receptor-like kinase 5 inhibitor (ALK5i), were used to test against MASH culture conditions. Transcriptomics analysis was performed to understand pathways affected by MASH culture conditions and effects of tool compound perturbations. **Results:** Liver

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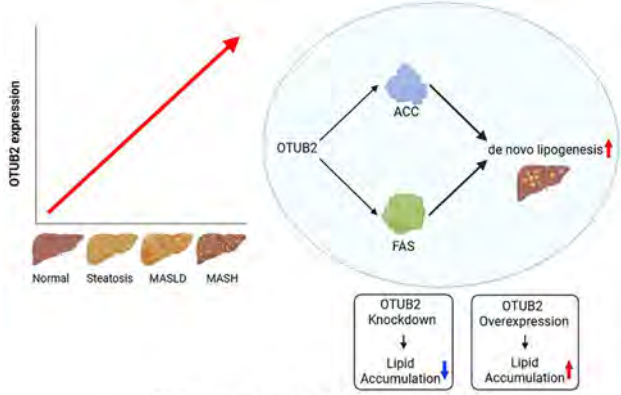
Chips cultured in MASH medium had 2-3 fold lower CYP3A activity compared to those treated with ALK5i. Evaluation of mRNA expression revealed that fibrotic makers, aSMA and collagen 1 were significantly down regulated with ALK5i treatment; and more so in the TGFß treated MASH conditions. It was confirmed via western that ALK5i treatment significantly decreased aSMA. Alk5i was able to inhibit pro-collagen 1 secretion in both +/- TGFß MASH conditions. For recapitulation of inflammatory cytokine release, Kupffer cell response was indicated by high expression of IL-6, IL-1ß, and IL-10 at earlier culture times. **Conclusion:** MASH can be modelled in vitro with relevant liver cell types to help us recapitulate the disease progression over time and to understand the roles of the different cell types in this disease progression.

Disclosures: Rachelle Baun: Novo Nordisk: Employee, Nathan Sorensen: Nothing to Disclose, Dennis McDuffie: Nothing to Disclose, Crystal Yuri Oh: Nothing to Disclose, Dan Sazer: Nothing to Disclose, Hani Jouihan: Nothing to Disclose, Damien Demozay: Nothing to Disclose, Emma Henriksson Kraft: Novo Nordisk: Employee, Novo Nordisk: Minor stock holder, Helena Lykkegaard: Nothing to Disclose, Sara Toftegaard Hjuler: Nothing to Disclose

1107 | ROLE OF OTUB2 IN REGULATING HEPATIC LIPID METABOLISM DURING METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) PROGRESSION

Yeongmin Kim[1] Soyeon Shin[1] Chahyeon Yun[1] Chang-Myung Oh[1], [1]Gwangju Institute of Science and Technology(GIST)

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is an advanced chronic liver disease characterized by excessive hepatic lipid accumulation and metabolic imbalance. Increasing evidence suggests that disruptions in proteostasis, particularly involving deubiquitinase activity, play a critical role in the progression of metabolic liver diseases. Among deubiquitinases, Otub2 has emerged as a key regulator of cellular processes including protein stability, signal transduction, and metabolic regulation. Although Otub2's functions have been studied in cancer and immune responses, its role in hepatic lipid metabolism and MASLD progression remains largely unknown. Elucidating Otub2's involvement could provide valuable insights into molecular mechanisms driving MASLD and reveal new therapeutic targets. **Methods:** Published RNA-seq datasets from MASLD patients were analyzed to evaluate changes in Otub2 expression during disease progression. The association between Otub2 expression and liver steatosis was examined using H&E-stained human liver histology from the GTEx project. To explore cell-type–specific changes in Otub2, mice were fed a high-fat diet for 16 weeks, after which hepatic parenchymal and non-parenchymal cells were isolated for expression analysis. Functional studies in hepatocytes involved siRNA-mediated knockdown and overexpression of Otub2. Lipid accumulation and expression of enzymes related to de novo lipogenesis (FAS, ACC) were assessed by Oil Red O staining and Western blot analysis. **Results:** Otub2 expression showed a progressive and significant increase correlating closely with MASLD stages. Histological examination of liver tissues from GTEx patients with elevated Otub2 revealed pronounced hepatic steatosis characterized by extensive lipid droplet accumulation in H&E-stained sections. In a murine high-fat diet model, Otub2 was broadly upregulated in both hepatic parenchymal and non-parenchymal cells. Functional experiments showed that siRNA-mediated knockdown of Otub2 in hepatocytes substantially attenuated palmitic acid–induced lipid accumulation, accompanied by marked downregulation of key lipogenic enzymes, fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC). Concurrently, genes involved in fatty acid oxidation (FAO) pathways were significantly upregulated, suggesting a metabolic shift favoring lipid catabolism. In contrast, overexpression of Otub2 led to enhanced lipid accumulation, increased expression of lipogenic enzymes, and decreased expression of FAO-related genes. **Conclusion:** Otub2 is pivotal in maintaining hepatic lipid homeostasis during MASLD by coordinately regulating lipid synthesis and oxidation. Targeting Otub2 may offer a promising therapeutic approach for MASLD, and further investigation of its regulatory network could advance understanding of metabolic liver disease pathogenesis.



OTUB2 promotes hepatic lipid accumulation by upregulating ACC and FAS during MASLD progression

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1108 | BENEFICIAL EFFECTS OF MILK-DERIVED EXTRACELLULAR VESICLES ON LIVER FIBROSIS PROGRESSION BY RESTORING INTESTINAL BARRIER INTEGRITY

Shinya Sato[1] NORIHISA NISHIMURA[1] Kosuke Kaji[1] Tadashi Namisaki[1] Hitoshi Yoshiji[1], [1]Nara Medical University

Background: Metabolic dysfunction associated steatotic liver disease (MASLD) has emerged as the most prevalent chronic liver disease, leading to metabolic dysfunction associated steatohepatitis (MASH), cirrhosis, and hepatocellular carcinoma (HCC). However, no treatment for MASH-related fibrosis is available for clinical use. Extracellular vehicles (EVs) are bilayer membrane vesicles released from various cells into the extracellular space, participating in multiple life processes. Recent studies have indicated that bovine milk-derived EVs (B-mEVs) suppress inflammation, have anti-tumor effects, and protect the intestinal barrier in an *in vivo* model. Whether EVs from bovine milk exert a beneficial effect against MASH is worth investigating. We explored the effect of B-mEVs on MASH-related liver fibrosis by modulating the gut barrier function. **Methods:** MASH-related liver fibrosis was induced in female C57BL/6J mice by feeding them a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) for eight weeks. B-mEVs (1.2 mg/kg) were orally administered every two days for four weeks. Seven-week-old female C57BL/6J mice were randomly divided into four groups and treated for 12 weeks as follows, n = 5 for each; i)normal chow with vehicle; ii) normal chow with B-mEVs; iii)CDAHFD diet with vehicle; iv) CDAHFD diet with B-mEVs. The mice were then sacrificed for histological analyses to assess the effect of B-mEVs on steatohepatitis and fibrosis. Intestinal barrier integrity was also evaluated by the intestinal permeability using FITC-dextran and immunohistochemistry of tight junction proteins (TJPs). The effect of B-mEVs on the Caco-2 cell line barrier function was similarly evaluated *in vitro* using the permeability assay. **Results:** B-mEVs significantly suppressed macrophage expansion, proinflammatory responses, and liver fibrosis in CDAHFD-fed mice by blocking hepatic translocation of lipopolysaccharide (LPS) and activating toll-like receptor (TLR) 4 signaling. Moreover, B-mEVs improved intestinal permeability by restoring TJPs like ZO-1, Occludin, and Claudin-2. B-mEVs also directly suppressed LPS-induced barrier dysfunction and TJP depletion in Caco-2 cells. **Conclusion:** B-mEVs reduced MASH-related fibrosis by inhibiting lipid accumulation and macrophage expansion and suppressing LPS/TLR4/NF-κB-mediated inflammatory responses by restoring intestinal barrier function.

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1109 | LOBEGLITAZONE COMBINED WITH HGF ALLEVIATES FFAS-INDUCED INTRACELLULAR LIPID ACCUMULATION BY MODULATING MITOCHONDRIAL METABOLISM IN HEPG2 CELLS

Jeayeon Park[1] Yun Bin Lee[1], [1]Seoul National University Hospital

Background: Lobeglitazone, a thiazolidinedione antidiabetic agent, predominantly activates peroxisome proliferator-activated receptor gamma (PPARγ) and has shown efficacy in improving insulin resistance and hepatic steatosis. Hepatocyte growth factor (HGF) plays roles in liver regeneration and inflammation; however, its involvement in hepatic steatosis is not well understood. In this study, we investigated the effects of lobeglitazone and HGF on free fatty acids (FFAs)-induced hepatic steatosis in HepG2 cells and explored the underlying mechanisms. **Methods:** HepG2 cells were treated with FFAs to induce intracellular lipid accumulation, followed by treatment with lobeglitazone, HGF, or their combination. Intracellular lipid accumulation was assessed by Oil Red O (ORO) staining. Mitochondrial function was evaluated using MitoTracker fluorescence staining, while the expression of mitochondrial function-related genes and proteins was analyzed by real-time reverse transcription quantitative polymerase chain reaction (RT-qPCR) and Western blotting. Oxidative stress markers were quantified by enzyme-linked immunosorbent assay (ELISA). **Results:** Lobeglitazone alone reduced intracellular lipid accumulation in FFAs-treated HepG2 cells, and this effect was further enhanced by co-treatment with HGF, as demonstrated by ORO staining (Figure 1A). Co-treatment markedly restored mitochondrial function impaired by FFAs, indicated by elevated MitoTracker signal (Figure 1B). RT-qPCR and Western blotting showed that PPARα expression, which had been suppressed by FFAs treatment, was partially restored by lobeglitazone and more effectively restored by the combination with HGF. PPARγ expression, which had been upregulated under the same conditions, was more completely normalized by co-treatment compared to lobeglitazone alone. In addition, the co-treatment of lobeglitazone and HGF more strongly upregulated mitochondrial metabolism-related proteins, including peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) and carnitine palmitoyltransferase 1A (CPT1A) (Figure 1C, 1D). By reducing

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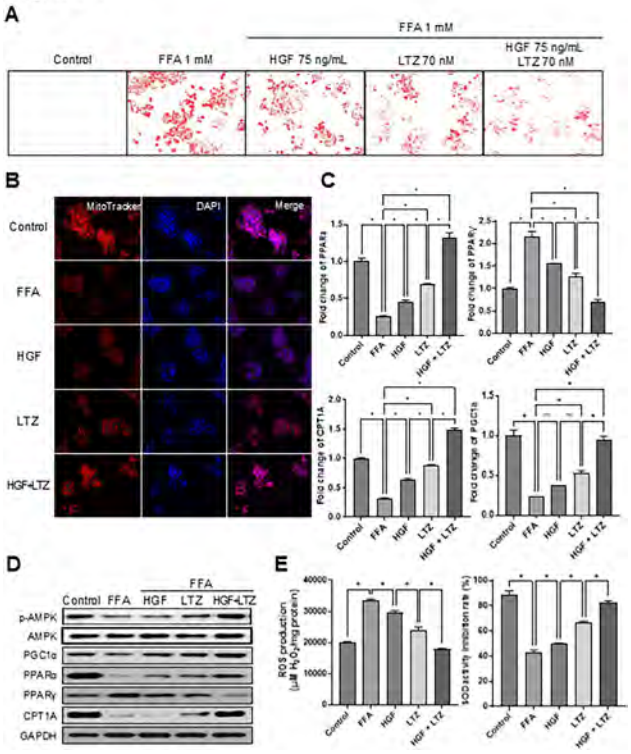
reactive oxygen species (ROS) production and restoring superoxide dismutase (SOD) activity, the co-treatment effectively mitigated FFAs-induced oxidative stress, as demonstrated by ELISA (Figure 1E). **Conclusion:** Lobeglitazone alone attenuated FFAs-induced intracellular lipid accumulation and favorably modulated PPARα/γ expression and mitochondrial metabolism-related markers, while co-treatment with HGF led to more pronounced effects across these parameters.

Figure 1



Disclosures: Jeayeon Park: Nothing to Disclose, Yun Bin Lee: Eisai: Consultant, Gilead Sciences: Consultant, Roche: Consultant, Chong Kun Dang Pharmaceutical Corporation: Grant/Research Support, Samil Pharmaceutical: Grant/Research Support

1110 | DIETARY FRUCTOSE-INDUCED METABOLIC REPROGRAMMING DETERMINES INTESTINAL STEM CELL FATE AND PROMOTES MASLD DEVELOPMENT THROUGH ENHANCED LIPID ABSORPTIO

Madison Taylor[1] Bradford Hill[1] Robert Mitchell[1] Elizabeth Hudson[1] Craig McClain[1] Ming Song[1], [1]University of Louisville

Background: Dietary fructose is primarily metabolized by Ketohexokinase (KHK) in the small intestine and plays a critical role in facilitating lipid absorption. Given that dietary fructose is an important risk factor in MASLD, the aim of this study is to determine the metabolic effect of fructose on small intestine stem cells (ISCs) and the implications in lipid absorption and the pathogenesis of MASLD. **Methods:** Small intestinal organoids were derived from crypts isolated from the proximal small intestine of adult male *Khk*$^{-/-}$ mice and WT littermates and were cultured and passaged with IntestiCult™ organoid growth medium. Mitochondrial stress tests were performed in organoids by Seahorse XF96 Analyzer. Lipid absorption test was performed in *Khk*$^{-/-}$ mice and their WT littermates. Male *Khk*$^{-/-}$ mice and WT littermates were subjected to STAM/MASH model and the metabolic phenotypes were profiled. **Results:** Fructose inhibits ISC self-renewal and proliferation compared to glucose. Conversely, KHK deficiency promotes ISC self-renewal and proliferation, suggesting the metabolic effect of fructose promotes ISC differentiation to enterocytes. Mitochondrial stress test showed that fructose markedly increases mitochondrial respiration compared to glucose as shown by oxygen consumption rate (OCR), and that was inhibited by inhibitors of glutaminolysis pathway (compound 968, AOA and R162) but not by mitochondrial pyruvate carrier (MPC) inhibitor UK-5099, suggesting fructose induced oxidative phosphorylation is glutamine-dependent and pyruvate-independent. Mechanistically, fructose aberrantly stabilizes HIF-1 through fructose 1-phosphate (F1P)/pyruvate kinase M2 (PKM2) axis, and that inhibits pyruvate dehydrogenase (PDH) via activation of pyruvate dehydrogenase kinase 1 (PDK1), therefore preventing pyruvate from entering TCA cycle. In support of this, KHK deficiency significantly reduces lipid absorption. Additionally, fecal fatty acids (NEFA) levels were significantly increased in *Khk*$^{-/-}$ mice compared to WT littermates in a chronic high-fat high-fructose (HFHFr) feeding model. Moreover, *Khk*$^{-/-}$ mice are protected from hepatic steatosis in a STAM/MASH model. **Conclusion:** Our data provide evidence that fructose-induced metabolic reprograming toward oxidative phosphorylation inhibits ISC proliferation and promotes differentiation to enterocytes, and that in turn, facilitates lipid absorption and contributes to MASLD development.

Disclosures: Madison Taylor: Nothing to Disclose, Bradford Hill: Nothing to Disclose, Robert Mitchell: Nothing to Disclose, Elizabeth Hudson: Nothing to Disclose, Craig McClain: Nothing to Disclose, Ming Song: Nothing to Disclose

1111 | BROAD ASSESSMENT OF PRIMARY HEPATOCYTE DONORS FOR USE IN MICROPHYSIOLOGICAL SYSTEMS AND IN VITRO ASSAYS TO MODEL HUMAN LIVER DISEASE

Oliver Culley[1] James Christophi[1] Gareth Guenigault[1] Rachelle Prantil Baun[2] Phil Keegan[2] Yassen Abbas[1] Dennis McDuffie[2] Dan Sazer[2] Kien Lim[2] Sara

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Toftegaard Hjuler[2] *Tomasz Kostrzewski*[1], [1]*CN Bio,* [2]*Novo Nordisk*

Background: Primary human hepatocytes (PHHs) remain the gold standard for *in vitro* liver research and drug development, with widespread use across the industry. One key benefit of PHH use in research is the ability to explore the role of patient variability. However, differences in tissue quality and PHH isolation can contribute to data variance and a lack of reproducibility. In this study we aimed to characterise a broad range of PHH donors in both 2D and 3D platforms to identify high quality PHH sources, for use in translational microphysiological systems (MPS). This research would explore whether 2D cell culture can predict PHH performance in MPS, with a particular focus on insulin sensitivity, a key feature for metabolic disease modelling. **Methods:** PHHs isolated from 23 human donors (from four commercial vendors) were assessed for ability to culture in both 2D, and in a 3D liver MPS platform. Two key parameters were assessed: hepatocyte functionality, through biomarkers albumin and cytochrome P450; and hepatocyte insulin sensitivity, a key marker for metabolic disease modelling. PHHs were assayed after 4 days in 2D culture, and 8 days in Liver MPS for their response to 3 nM insulin challenge, with the production of glucose and phospho-Akt measured. **Results:** Of the 23 donors tested, 44% were found to successfully culture in the liver MPS platform with >10 μg/day/million cells of albumin at Day 8; and high levels (>0.5 pmol/min/million cells) of CYP3A4 activity at Day 8. 48% of PHH donors showed insulin sensitivity in the 3D Liver MPS, but importantly the same donors that were insulin sensitive in 2D were not sensitive in the liver MPS, with 2 donors found to be non-responsive to insulin challenge in 2D but significantly responsive in the 3D MPS platform. Additionally, the dynamic range of responses to insulin challenge was significantly greater between the donors in the MPS compared with the cells in 2D. **Conclusion:** This work demonstrates that detailed qualification and testing of primary cells is critical in understanding how *in vitro* studies will perform, allowing establishment of robust disease models such as MASLD/MASH or viral hepatitis. Given the observed differences in results, with regards to PHH donor validation, between 2D culture and 3D Liver MPS, it is important to assay key cellular functions in the context in which they will be used, as PHH that perform well in 2D may not always perform equivalently in 3D.

Disclosures: Oliver Culley: Nothing to Disclose, James Christophi: Nothing to Disclose, Gareth Guenigault: Nothing to Disclose, Rachelle Prantil Baun: Nothing to Disclose, Phil Keegan: Nothing to Disclose, Yassen Abbas: Nothing to Disclose, Dennis McDuffie: Nothing to Disclose, Dan Sazer: Nothing to Disclose, Kien Lim: Novo Nordisk: Employee, Sara Toftegaard Hjuler: Nothing to Disclose, Tomasz Kostrzewski: CN Bio: Employee

1112 | KISSPEPTIN RECEPTOR SIGNALING ALLEVIATES HEPATIC DE NOVO LIPOGENESIS (DNL) AND FIBROSIS: NEW THERAPEUTIC TARGET TO TREAT MASLD

Moshmi Bhattacharya[1] *Kimberly Izarraras*[1], [1]*Rutgers Robert Wood Johnson Medical School*

Background: Kisspeptin (KP) is a circulating peptide hormone that signals via the G protein-coupled receptor, KISS1R. The central roles of KP/KISS1R signaling in regulation of energy balance and metabolism are well known. Peripherally, the liver produces kisspeptin; however, the role of KP/KISS1R signaling in the liver is largely undefined. Our previous work demonstrated that administration of KP in mouse models of MASLD decreases hepatic steatosis by activating the master energy sensor, AMPK, and increasing the b-oxidation of hepatic fats. However, whether KP directly regulates hepatic de novo lipogenesis (DNL), and fibrogenesis is not known. The objective of this study is to determine 1) whether KP attenuates hepatic DNL and 2) the impact of kisspeptin on fibrogenesis. We hypothesize that KP treatment decreases hepatic DNL and fibrogenesis. **Methods:** DNL was assessed using metabolic tracing with ^2H_2O-enriched water followed by mass spectrometry, using DIAMOND mice (a mouse model of MASLD), upon administration of KP. In another cohort of DIAMOND mice, hepatic *Kiss1r* was overexpressed using AAV8-TBG-viruses, and the effect of hepatic steatosis was evaluated. To evaluate a role for KP in regulating fibrogenesis, human precision cut liver slices (hPCLS) from fibrotic livers and human hepatic stellate cells (LX-2) were treated with KP and the expression of fibrogeneic and inflammatory markers were evaluated. **Results:** Metabolic tracing of KP-treated steatotic livers demonstrated a decrease in DNL. Transcriptomic profiling of KP-treated livers identified disruption of key metabolic pathways, the most prominent being a decrease in fatty acid metabolism, and the downregulation of *Cidea,* a key regulator of lipid droplet formation. Mechanistically, we found that KP decreased levels of transcription factor SREBP-1c, a crucial regulator of genes involved in DNL, including *Cidea*. To evaluate a role of KP in regulating fibrogenesis, hPCLS and LX-2 cells were treated with KP resulting in a decrease in fibrogenic and inflammatory markers. Mechanistically, KISS1R signaling downregulated TGFβ signaling and SNAIL expression, via activation of protein-phosphatases PP2A, a binding partner of KISS1R. **Conclusion:** Enhancement of KISS1R

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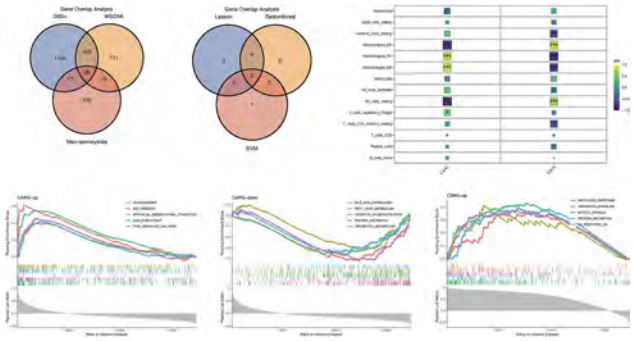
signaling alleviates hepatic *DNL* and fibrogenesis, identifying KP/KISS1R as a therapeutic target in MASLD.

Disclosures: Moshmi Bhattacharya: Nothing to Disclose, Kimberly Izarraras: Nothing to Disclose

1113 | INTEGRATED ANALYSIS OF WGCNA AND MACHINE LEARNING REVEALS MACROPINOCYTOSIS-RELATED BIOMARKERS IN METABOLIC-ASSOCIATED STEATOHEPATITIS

Xin Wang[1] Feng Liu[1] Huiying Rao[1], [1]Peking University People's Hospital

Background: Metabolic-associated steatohepatitis (MASH), the progressive stage of metabolic-associated fatty liver disease (MAFLD), has emerged as a major public health concern due to its strong association with liver cirrhosis, hepatic failure, and rising global prevalence linked to metabolic syndrome and obesity epidemics, while current therapeutic strategies remain limited. Macropinocytosis, a large-scale fluid-phase endocytosis process dependent on actin cytoskeleton reorganization, represents a critical adaptive mechanism through which cells respond to metabolic stress. This process maintains energy homeostasis by internalizing extracellular proteins and lipids. This study aims to explore the potential role of macropinocytosis-related genes in the pathogenesis of MASH. **Methods:** Gene expression profiles were obtained from MASH-related bulk RNA-seq datasets (GSE126848 and GSE89632) and a single-cell RNA sequencing (scRNA-seq) dataset (GSE216836). Key candidate genes were first identified using the limma R package and the WGCNA algorithm, followed by an intersection with macropinocytosis-related genes retrieved from GeneCards, yielding 26 overlapping genes. Three distinct machine learning algorithms were employed to screen two hub genes. Subsequent analyses included immune cell infiltration profiling, Gene Set Enrichment Analysis (GSEA), nomogram construction, ROC curve evaluation, and scRNA-seq trajectory analysis to investigate the associations of hub genes with co-expressed networks, specific cell subpopulations, and MASH progression. Finally, functional validation of CDH5 and CAPG in MASH pathogenesis was performed using *in vitro* cell models and *in vivo* models. **Results:** Through bioinformatics analysis, we identified 26 macropinocytosis-associated genes in MASH. Subsequent integration of machine learning, external validation, and experimental assays selected CAPG and CDH5 as hub genes, demonstrating their robust association with macropinocytosis dysregulation in MASH pathogenesis. **Conclusion:** This study identified potential hub genes that may serve as diagnostic and therapeutic targets for MASH, offering novel perspectives for the clinical management of MASH patients.



Disclosures: Xin Wang: Nothing to Disclose, Feng Liu: Nothing to Disclose, Huiying Rao: Nothing to Disclose

1114 | DIRECT EFFECTS OF GLP-1/GLUCAGON DUAL AGONIST SURVODUTIDE ON HEPATIC STELLATE CELLS AND LIVER CANCER CELL LINES

Toru Nakamura[1] Yasuko Imamura[1] Atsutaka Masuda[1] Hironori Koga[1] Takumi Kawaguchi[1], [1]Kurume University School of Medicine

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is associated with a high risk of progression to liver fibrosis and hepatocellular carcinoma (HCC), and elucidating the disease-modifying effects of new agents is an urgent need. Survodutide, a dual GLP-1/glucagon receptor agonist, has shown promising effects on weight loss and hepatic steatosis in clinical studies. However, its direct effects on hepatic stellate cells (HSCs) and HCC cells remain unclear. This study aimed to evaluate the direct impact of survodutide on cell proliferation and fibrogenic gene expression in human hepatic stellate and liver cancer cell lines. **Methods:** Seven liver cancer cell lines (HepG2, Hep3B, HuH7, HAK1A, HAK1B, HLF, HAK5), one normal hepatocyte cell line (OUMS29), and an HSC line (LX-2) were analyzed for GLP1R and GCGR expression by RT-PCR and Western blotting. Cell proliferation was assessed using an MTT assays with or without palmitic acid (PA) treatment. LX-2 cells were treated with survodutide under TGF-β-stimulated and unstimulated conditions, and mRNA expression of fibrogenic genes (TGFβ1, COL1a1, Acta2, Timp1) was quantified by qPCR. **Results:** GLP1R expression was undetectable in all cell lines, whereas GCGR was consistently expressed, with HuH7 showing the highest mRNA levels. Survodutide modestly promoted the proliferation in Hep3B and HuH7 cells at select concentrations under PA-free conditions but significantly inhibited the proliferation in all liver cancer cell lines at 1000 nM under PA-loaded conditions ($p < 0.05$). In LX-2 cells, survodutide enhanced the proliferation at low concentrations (10 nM)

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without TGF-β, but suppressed it in a dose-dependent manner under TGF-β stimulation, with significant inhibition at ≥100 nM ($p < 0.05$). Survodutide did not alter the expression of fibrogenic genes regardless of TGF-β stimulation. **Conclusion:** Survodutide directly suppressed the proliferation of human HCC cells under lipotoxic stress. Survodutide also inhibited activated human HSC proliferation under profibrotic conditions, without affecting fibrogenic gene expression. These findings suggest a potential direct anti-tumor and anti-fibrotic effect of survodutide in the context of MASH progression.

Disclosures: Toru Nakamura: Nothing to Disclose, Yasuko Imamura: Nothing to Disclose, Atsutaka Masuda: Nothing to Disclose, Hironori Koga: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching

1115 | EFFECTS OF THE FGF21 ANALOGUE EFRUXIFERMIN ON CELL PROLIFERATION AND FIBROGENIC GENE EXPRESSION IN HEPATIC STELLATE CELLS AND LIVER CANCER CELL LINES

Toru Nakamura[1] Yasuko Imamura[2] Atsutaka Masuda[2] Hironori Koga[2] Takumi Kawaguchi[2], [1]Kurume University, [2]Kurume University School of Medicine

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease that leads to fibrosis and hepatocarcinogenesis. Efruxifermin, an FGF21 analogue, is known to improve lipid and glucose metabolism, but its direct effects on hepatic stellate cells (HSCs) and hepatocellular carcinoma (HCC) cells remain unclear. This study aimed to evaluate the effects of efruxifermin on cell proliferation and fibrogenic gene expression in human HSC and liver cancer cell lines. **Methods:** Seven liver cancer cell lines (HepG2, Hep3B, HuH7, HAK1A, HAK1B, HLF, HAK5), one normal hepatocyte cell line (OUMS29), and an HSC line (LX-2) were analyzed for FGFR1 and βKlotho expression using RT-PCR and Western blotting. Cell proliferation was assessed using an MTT assays with or without palmitic acid (PA) treatment. LX-2 cells were treated with efruxifermin under TGF-β-stimulated and unstimulated conditions, and mRNA expression of fibrogenic genes (TGFβ1, COL1a1, Acta2, Timp1) was quantified by qPCR. Smad signaling (Smad2/3/4 phosphorylation) was evaluated by Western blotting. **Results:** FGFR1 was expressed in all cell lines and was highly expressed in HepG2, HAK5, and LX-2. βKlotho was highly expressed in HepG2, Hep3B, and HuH7, but undetectable in LX-2 and some liver cancer cell lines. Under PA-free conditions, efruxifermin promoted the proliferation in HuH7, HAK1B, and HAK5, while inhibiting HLF cell growth at concentrations ≥10 nM ($p < 0.05$). Under PA treatment, HuH7, Hep3B, HAK1B, and HAK5 showed dose-dependent growth inhibition from 1 nM ($p < 0.05$). In LX-2 cells, efruxifermin promoted the proliferation at low doses under TGF-β-free conditions, but significantly inhibited the proliferation at 100 nM under TGF-β stimulation ($p < 0.05$). Fibrogenic gene expression remained unchanged following efruxifermin treatment, regardless of TGF-β stimulation. However, phosphorylation of Smad2 (p-Smad2) was decreased, while the levels of p-Smad3 and Smad4 were unaffected. **Conclusion:** Efruxifermin directly suppressed the proliferation of human HCC cells under lipotoxic conditions. Efruxifermin also directly inhibited growth of human HSCs under profibrotic stimulation, suggesting a context-dependent antiproliferative effect. Although fibrogenic gene expression was not significantly altered, selective suppression of p-Smad2 suggests partial modulation of TGF-β signaling. These findings offer mechanistic insights into the potential of efruxifermin to modulate fibrosis progression and hepatocarcinogenesis in MASH.

Disclosures: Toru Nakamura: Nothing to Disclose, Yasuko Imamura: Nothing to Disclose, Atsutaka Masuda: Nothing to Disclose, Hironori Koga: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching

1116 | REGULATION OF AMINO ACID CATABOLISM BY A HUMAN-SPECIFIC INCRNA IN NONALCOHOLIC FATTY LIVER DISEASE

Xiangbo Ruan[1], [1]Johns Hopkins All Children's Hospital

Background: Impaired amino acid (AA) metabolism in the liver has recently emerged as a hallmark of NAFLD in humans. Decreased expression of genes in the AA catabolism and urea cycle pathways can result in the accumulation of AAs and of ammonia, which in turn may lead to increased oxidative stress, hepatocyte death, and activation of hepatic stellate cells. These key

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events may drive a range of presentations of NAFLD, from simple steatosis to the advanced form of NAFLD, steatohepatitis (NASH). While clinical and experimental observations support a potential causal role of impaired AA catabolism in NAFLD, we do not yet know which molecular mechanisms drive these dysregulated processes. **Methods:** Recent studies in animal models support the hypothesis that long non-coding RNA (lncRNA) genes regulate vital metabolic pathways. As most human lncRNAs are non-conserved, we recently employed a novel *humanized liver mouse model* to study lncRNAs expressed in human livers. We identified a human hepatocyte-specific lncRNA, hLMR1 (human lncRNA metabolic regulator 1), that promotes hepatic cholesterol synthesis. Our promising follow-up studies demonstrated that hLMR1 represses an array of genes in the AA catabolism and ureagenesis pathways, suggesting hLMR1 could be a key factor contributing to impaired hepatic AA catabolism and ureagenesis in NAFLD patients. **Results:** We found that: (1) hLMR1 is upregulated in NAFLD patients; (2) knocking down of hLMR1 in a humanized liver mouse model results in robust upregulation of genes in the AA catabolism and ureagenesis pathways; (3) hLMR1 overexpression in primary human hepatocytes suppresses AA catabolism and ureagenesis; (4) hLMR1 is nuclear-enriched and extensively interacts with pre-mRNAs of amino acid catabolism genes to suppress their expression. **Conclusion:** Upregulation of hLMR1, leading to suppressed AA catabolism and ureagenesis in the liver and, ultimately, progression of NAFLD.
Disclosures: Xiangbo Ruan: Nothing to Disclose

1117 | VISCERAL ADIPOSE TISSUE FROM MORBID OBESITY PATIENTS PROMOTES THE PROLIFERATION OF HEPATOCELLULAR CARCINOMA CELLS

Byoung Kuk Jang[1] Ji Yeon Park[1] Hye-Young Seo[1] Jae Seok Hwang[1] Mi Kyung Kim[1], [1]Keimyung University School of Medicine

Background: Obesity is a major risk factor for metabolic dysfunction-associated steatotic liver disease (MASLD) and hepatocellular carcinoma (HCC). Recent studies suggest that visceral adipose tissue (VAT) plays a more significant role than subcutaneous adipose tissue (SAT) in cancer progression. However, although VAT is involved in cancer progression, its specific role and underlying molecular mechanisms in HCC remain poorly understood. **Methods:** To investigate the role of VAT in HCC, RNA sequencing (RNA-seq) was performed on VAT and SAT samples obtained from male and female obese patients. KEGG pathway analysis was conducted to identify differentially activated signaling pathways. In addition, conditioned media (CM) from VAT (VAT-CM) and SAT (SAT-CM) from male obese patients were applied to Hep3B (hepatocellular carcinoma cell line), and cell proliferation was assessed using the CCK-8 assay. Furthermore, RNA-seq analysis was conducted on Hep3B cells treated with VAT-CM and SAT-CM to identify transcriptional changes related to HCC progression. **Results:** KEGG pathway analysis revealed that multiple oncogenic pathways, including WNT signaling, IGF signaling, and inflammatory response pathways, were significantly upregulated in VAT compared to SAT. These pathways are known to be strongly associated with HCC development and progression. Furthermore, Hep3B cells treated with VAT-CM exhibited significantly enhanced proliferation compared to those treated with SAT-CM, suggesting that VAT-derived factors may contribute to HCC growth. Furthermore, RNA-seq analysis of Hep3B cells treated with VAT-CM showed activation of oncogenic and inflammatory signaling pathways, suggesting that VAT-derived inflammatory factors may play an important role in promoting hepatocellular carcinoma (HCC) progression. **Conclusion:** These findings suggest that VAT, particularly in male obese patients, promotes hepatocellular carcinoma (HCC) progression by enhancing cancer cell proliferation and activating tumor-promoting pathways. This study highlights the importance of VAT-derived factors in obesity-associated HCC and suggests that targeting VAT-related inflammatory and metabolic pathways may provide potential therapeutic strategies.
Disclosures: Byoung Kuk Jang: Nothing to Disclose, Ji Yeon Park: Nothing to Disclose, Hye-Young Seo: Nothing to Disclose, Jae Seok Hwang: Nothing to Disclose, Mi Kyung Kim: Nothing to Disclose

◆ 1118 | PRECLINICAL PHARMACOLOGY AND SAFETY OF CRMA-1001, A NOVEL EPIGENETIC EDITOR FOR CHRONIC HEPATITIS B THAT DEMONSTRATES HBV SURFACE ANTIGEN LOSS IN ANIMAL MODELS VIA PRECISE HBV DNA METHYLATION

Sarah Voytek[1] Yesseinia Anglero-Rodriguez[1] John Xiong[1] Glen Acosta[1] Rayman Choo-Wing[1] Ricardo Ramirez[1] Erica Hildebrand[1] Amber DiPiazza[1] Sameer Abraham[1] Ava Zhai[1] Lenka Hoffman[1] Arogya Khadka[1] Jhon Medina[1] Caroline Mugambwa[1] Chloe Pantano[1] Yasaman Rezvani[1] Kayla Hudson[1] Shefal Parikh[1] Padma Malyala[1] Melissa Bonner[1] Jennifer Marlowe[1], [1]nChroma Bio

Background: A major challenge in achieving functional cure for chronic hepatitis B virus (HBV) infection is the ability to permanently silence the production of viral antigens from both covalently closed circular DNA (cccDNA) and integrated HBV DNA (intDNA) and

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preventing viral replication. Genomic medicines for HBV aim to overcome these challenges. CRMA-1001 is an investigational epigenetic editor consisting of an mRNA and guide RNA packaged in a lipid nanoparticle. CRMA-1001 methylates both forms of HBV DNA, without creating cuts or nicks, resulting in HBV DNA suppression and induction of HBV surface antigen (HBsAg) loss. **Methods:** The pharmacologic effect of a single or repeat administration of CRMA-1001 was evaluated for up to 6 months in AAV-HBV (episomal DNA) and transgenic (Tg)-HBV (intDNA) mouse models. To evaluate specificity and on-target methylation, host gene expression and host and HBV DNA methylation were analyzed in multiple cell types using RNA-seq and methylation sequencing. To evaluate potency in non-human primates (NHPs), CRMA-1001's effector construct was assessed using the endogenous *PCSK9* target gene. The safety and biodistribution profile of CRMA-1001 was also assessed in NHPs. **Results:** A single dose of CRMA-1001 resulted in durable, dose-dependent decreases in circulating HBsAg, with 70% of AAV-HBV mice achieving loss of HBsAg and 90% achieving loss of HBV DNA at the highest dose tested. Repeat dosing improved the reduction of circulating HBsAg versus a single dose. In vitro, on-target methylation of cccDNA and intDNA was observed. No clinically meaningful unintended effects on human genes, defined as increased methylation associated with altered expression, were seen in primary human hepatocytes. The pharmacokinetic, biodistribution, and toxicology profile of CRMA-1001 in NHPs supported further development. Assessment of the same epigenetic editing construct directed at *PCSK9* in NHPs demonstrated saturating silencing of circulating PCSK9 protein for >1 year with a single dose and suggested best-in-class potency. **Conclusion:** CRMA-1001 demonstrated robust silencing of HBsAg expression from both cccDNA and intDNA in mouse models that persisted through the follow-up period, with the same construct silencing PCSK9 expression for >1 year in NHPs. CRMA-1001 achieved HBsAg loss with an acceptable safety and specificity profile. These results support the initiation of clinical trials with CRMA-1001 with the goal of functional cure with a single course of treatment.

Disclosures: Sarah Voytek: nChroma Bio: Employee, nChroma Bio: Stock – privately held company, Yesseinia Anglero-Rodriguez: Nothing to Disclose, John Xiong: Nothing to Disclose, Glen Acosta: nChroma Bio: Stock – privately held company, nChroma Bio: Employee, Rayman Choo-Wing: Nothing to Disclose, Ricardo Ramirez: Nothing to Disclose, Erica Hildebrand: nChroma Bio: Employee, nChroma Bio: Stock – privately held company, Chroma Medicine: Employee, Chroma Medicine: Stock – privately held company, Amber DiPiazza: Nothing to Disclose, Sameer Abraham: Nothing to Disclose, Ava Zhai: Nothing to Disclose, Lenka Hoffman: Nothing to Disclose, Arogya Khadka: Nothing to Disclose, Jhon Medina: nChroma Bio: Employee, Caroline Mugambwa: Nothing to Disclose, Chloe Pantano: Nothing to Disclose, Yasaman Rezvani: Nothing to Disclose, Kayla Hudson: Nothing to Disclose, Shefal Parikh: Nothing to Disclose, Padma Malyala: Nothing to Disclose, Melissa Bonner: Nothing to Disclose, Jennifer Marlowe: nChroma Bio: Executive role, Solid Biosciences: Executive role

◆ 1119 | TRIPLE-TARGETING IMMUNOMODULATOR C3 TREATMENT PROMOTES HBV CLEARANCE THROUGH FUNCTIONAL RECONSTITUTION OF HOST IMMUNITY IN HBV-CARRIER MOUSE MODELS

Yu Wu[1] Xin Liu[1] Ting Zhang[1] Xiangmei Chen[1] Fengmin Lu[1], [1]Peking University Health Science Center

Background: Chronic hepatitis B (CHB) is still a major global health problem. Although achieving functional cure could substantially improve clinical outcomes, current first-line therapies demonstrate suboptimal efficacy in attaining this goal. Restoration of HBV specific immune responses is fundamental for achieving functional cure but immunomodulator monotherapy often yields unsatisfactory outcomes. Consequently, the development of multi-target immunotherapies has become a hot topic in the pursuit of CHB functional cure. **Methods:** In this study, a novel aptamer-based triple-targeting immunomodulator C3 was used to explore its potential for CHB functional cure *in vitro* and *in vivo*. Dually humanized mice engrafted with human liver and immune system, rAAV8-1.3X HBV mice, and hydrodynamic injection mice were employed to validate the therapeutic efficacy and safety of C3 against CHB through intravenous injection. Virological clearance was assessed through Southern blot, ELISA and immunohistochemistry. Single-cell RNA sequencing (scRNA-seq) and flow cytometry were employed to delineate C3-induced immune activation profiles. Besides, the combinatorial antiviral efficacy and response maintenance after withdraw of bepirovirsen or siRNA (si1260/1848) with C3 was systematically evaluated in rAAV8-1.3X HBV mouse models. **Results:** Across multiple HBV-carrier mouse models, C3 treatment demonstrated rapid clearance of serum HBV DNA, HBsAg, and HBeAg, with a subset of animals achieving undetectable HBV DNA levels and HBsAg seroconversion, accompanied by significantly reduced intrahepatic HBV DNA and RNA. Consistantly, few HBcAg- and HBsAg-positive hepatocytes in murine liver tissues were observed. Additionally, no significant adverse effects or toxicities were observed in C3 treatment groups. Notably, combination therapies demonstrated that C3 significantly accelarate the seroclearance of HBsAg and ameliorated the viral rebound, which was typically observed after RNAi therapy cessation. Mechanistically, C3 promotes immune cell infiltration into

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the liver, and significantly enhances the function of antigen-presenting cells (APCs) and T cells. **Conclusion:** The triple-targeting immunomodulator C3 could eliminate HBV infection and ameliorate the viral rebound via host immune system activation, representing C3 a promising CHB therapeutic candidate.

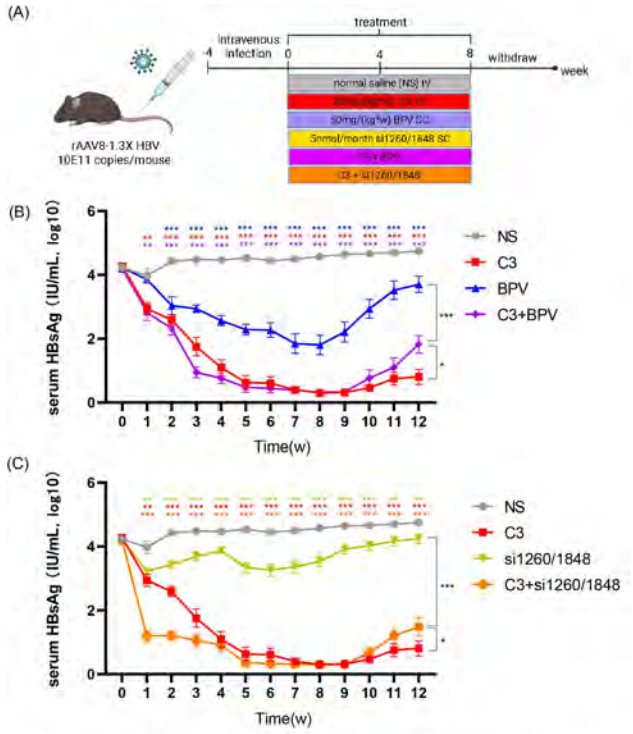

Fig. 1 C3 accelarate the seroclearance of HBsAg and ameliorated the viral rebound. (A)Flowchart of combination therapies. (B) Serum HBsAg levels in mice following C3, BPV, or combination therapy (n = 9-10 per group);(C) Serum HBsAg levels in mice following C3, BPV, or combination therapy (n =10 per group); Statistical analyses between the treated groups and the untreated group were done by one-way ANOVA. *p<0.05; **p<0.01; ***p<0.001. IV: intravenous injection; SC: subcutaneous injection.

Disclosures: Yu Wu: Nothing to Disclose, Xin Liu: Nothing to Disclose, Ting Zhang: Nothing to Disclose, Xiangmei Chen: Nothing to Disclose, Fengmin Lu: Nothing to Disclose

◆ 1120 | TREATMENT OF TENOFOVIR AMIBUFENAMIDE VERSUS TENOFOVIR ALAFENAMIDE IN PATIENTS WITH CHRONIC HEPATITIS B-RELATED CIRRHOSIS: EVIDENCE FROM A MULTICENTER REAL-WORLD STUDY

Jun Chen[1] Zebing Huang[2] Yan Huang[2], [1]Xiangya Hospital Central South University, [2]Xiangya Hospital, Central South University

Background: Chronic hepatitis B (CHB)-related cirrhosis remains a significant global health challenge, and effective antiviral therapies are essential for long-term management. Tenofovir amibufenamide (TMF) has shown potent antiviral efficacy in randomized clinical studies for patients with CHB. However, Real-world data on TMF in cirrhotic population remain scarce. This study aimed to assess the effectiveness and safety of TMF in the real world and compared its outcomes with those of tenofovir alafenamide (TAF). **Methods:** In this multicenter, real-world cohort study, 606 patients with CHB-related cirrhosis were recruited from 11 hospitals. After adjusting for confounding factors using the propensity score matching method, patients were divided intoa TMF treatment group (TMF 25 mg, n = 304) and a TAF treatment group (TAF 25 mg, n = 302). Additionally, TMF-treated patients with hepatitis B cirrhosis were divided into treatment-naive (TN) and treatment experienced (TE) groups with low-level viremia. Safety and efficacy were thoroughly evaluated, with a focus on the virologic response (VR) rate, alanine transaminase (ALT) normalization rate, liver stiffness measurement (LSM), renal function, and changes in the lipid profile after 48 weeks of treatment. The fibrosis 4 score was also calculated in both groups. **Results:** In all subgroups (overall population, low-level viremia, HBeAg-positive, and HBeAg-negative), the primary efficacy endpoint (HBV DNA **Conclusion:** TMF was non-inferior to TAF in terms of anti-HBV efficacy and showed blood lipid and renal safety in compensated chronic hepatitis B related cirrhosis in 48 weeks.

Disclosures: Jun Chen: Nothing to Disclose, Zebing Huang: Nothing to Disclose, Yan Huang: Nothing to Disclose

◆ 1121 | PHASE 3 TRIAL OF HYDRONIDONE FOR LIVER FIBROSIS IN CHRONIC HEPATITIS B

Xiaobo Cai[1] Yin Qu[1] Yanbin Wang[2] Wen Xie[2] Mengyu Zhao[3] Ling Zhang[3] Ying Luo[3] Ping Yin[4] Jun Cheng[2] Lungen Lu[1], [1]Shanghai General Hospital, Shanghai Jiaotong University School of Medicine, [2]Beijing Ditan Hospital, Capital Medical University, [3]Continent Pharmaceuticals, [4]Tongji Medical College, Huazhong University of Science and Technology

Background: Currently, no potential direct anti-fibrotic drugs are available for patients with chronic hepatitis B (CHB). Hydronidone is a novel anti-fibrotic agent that inhibits TGF-β,hepatic stellate cellactivation and promotes HSC apoptosis. Our previous phase 2 trial demonstrated that hydronidone significantly improved liver fibrosis regression in CHB patients. To further evaluate its efficacy and safety, we conducted this phase 3 multicenter trial in CHB patients with liver fibrosis, administering hydronidone at a dose of 270 mg/day. **Methods:** In this 52-week, randomized, double-blind, placebo-controlled phase 3 trial, CHB patients with biopsy-confirmed significant liver fibrosis (Ishak score ≥3) were assigned (1:1) to receive either hydronidone (270 mg/day) or placebo, both combined with

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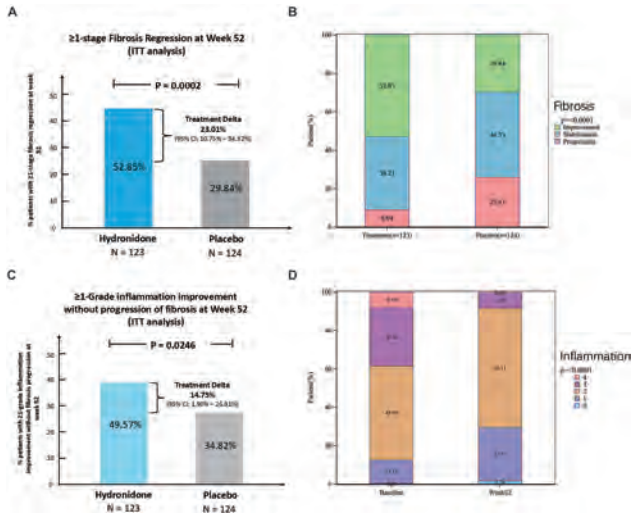
entecavir as the basic antiviral treatment. The primary endpoint was fibrosis reversal, defined as a ≥1-point reduction in Ishak stage after 52 weeks of treatment compared to baseline. **Results:** Between January 16, 2022, and October 22, 2024, a total of 453 participants were screened for eligibility, and 247 randomized participants (hydronidone: n = 123; placebo: n = 124) were eventually included across 39 hospitals in China. The demographic and clinical characteristics of the participants at baseline were well balanced between the trial and placebo groups. For the primary end point, hydronidone demonstrated significantly greater efficacy in achieving fibrosis reversal. The fibrosis reversal was achieved in 65 (52.85%) participants in the hydronidone group versus 37 (29.84%) participants in the placebo group, with an absolute difference of 23.01% (P = 0.0002). Despite antiviral therapy with entecavir, 25.81% of placebo-treated patients experienced fibrosis progression, compared to only 8.94% in the hydronidone group. A key secondary endpoint of improvement in liver inflammation (≥1-grade reduction) without fibrosis progression was met by 49.57% of hydronidone-treated patients versus 34.82% in the placebo group (P = 0.0246). Both groups showed comparable rates of HBV DNA undetectability (81.74% vs. 85.47%) and ALT normalization (80% vs. 88.89%). Adverse event profiles were similar between groups. Serious adverse events occurred in 4.88% with hydronidone and 6.45% with placebo of participants and no discontinuations due to adverse events. **Conclusion:** Hydronidone was superior to placebo in promoting fibrosis regression and demonstrated a favorable safety profile in CHB patients. (NCT05115942)



Disclosures: Xiaobo Cai: Nothing to Disclose, Yin Qu: Nothing to Disclose, Yanbin Wang: Nothing to Disclose, Wen Xie: Nothing to Disclose, Mengyu Zhao: Nothing to Disclose, Ling Zhang: Nothing to Disclose, Ying Luo: Nothing to Disclose, Ping Yin: Nothing to Disclose, Jun Cheng: Nothing to Disclose, Lungen Lu: Nothing to Disclose

◆ 1122 | GLOBAL, REGIONAL, AND AGE-STRATIFIED TEMPORAL TREND OF CHRONIC HEPATITIS B AND LIVER CANCER BURDEN: A SECONDARY ANALYSIS BASED ON THE GLOBAL BURDEN OF DISEASE STUDY

Kimberly Ho[1] Yunhao Li[2] Wai Keung Leung[2], [1]Brown University, [2]University of Hong Kong

Background: Despite global advances in hepatitis B (HBV) vaccination and antiviral therapy, the impact of declining HBV incidence on hepatocellular carcinoma (HCC) trends remains unclear. Given HCC's long latency period, its relationship with HBV likely varies by age, geography, and sociodemographic index (SDI). Prior studies examined HBV and HCC trends, but few have assessed their correlation globally with age stratification. We conducted an age-stratified analysis to examine the global trends between chronic HBV (CHB) infection and HCC incidence. **Methods:** We extracted cross-sectional data from the Global Burden of Diseases to analyze acute hepatitis B (AHB), CHB, and HCC burden from 1990–2021 globally, nationally, and by age group (<50 vs ≥50 years). Joinpoint regression showed significant temporal shifts. Linear regression assessed correlations between the Average Annual Percentage Change (AAPC) in CHB and HCC incidence by age group. **Results:** CHB incidence declined globally and steeply in China (middle SDI; AAPC -4.32), followed by the US (high SDI; AAPC -3.62) and India (low-middle SDI; AAPC -2.30) from 1990 to 2021 (all $p < 0.001$). AHB incidence also declined globally, particularly in China (AAPC -2.88) and the US (AAPC -2.38), with sharpest reductions in 2019–2021. India had modest decline in 1990-2021 (AAPC -1.16; all $p < 0.001$). Trends between CHB and HCC also showed age-specific patterns (Figure 1). There was a weak but significant negative correlation in the group <50 years ($r = -0.18$, $p = 0.0109$). China and the US did not show a negative change in HCC despite decline in CHB. India had lower CHB decline without corresponding reduction in HCC. No significant correlation between CHB and HCC was seen in those ≥50 years ($r = -0.12$, $p = 0.0849$). China had strong, significant negative correlation between CHB and HCC with a decline in both. India was an outlier with rising HCC despite CHB decline. The US showed no clear association between trends in CHB and HCC. **Conclusion:** Younger individuals showed significant inverse correlation between CHB and HCC, likely reflecting benefits of vaccination efforts such as China's 1992 neonatal program. Countries with lower SDI like India may lag due to a high HBV burden and limited public health infrastructure. Other HCC drivers like HCV and MASLD may predominate in other regions. This age-stratified analysis highlights greater overall global decline in HCC in younger populations and persistent disparities in prevention and HBV control.

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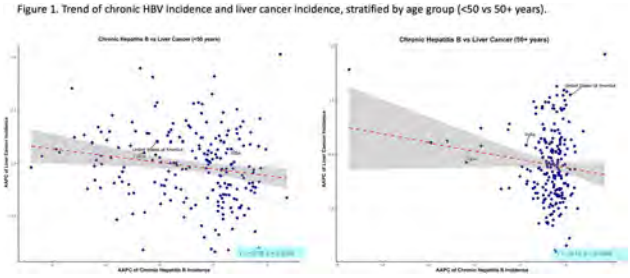

Disclosures: Kimberly Ho: Nothing to Disclose, Yunhao Li: Nothing to Disclose, Wai Keung Leung: AbbVie: Speaking and Teaching, Johnson and Johnson: Speaking and Teaching, Takeda: Grant/Research Support, Ferring: Speaking and Teaching

◆ 1123 | SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF MULTIPLE DOSES OF AB-101, A SMALL-MOLECULE PD-L1 INHIBITOR, IN CHRONIC HEPATITIS B PATIENTS

Edward Gane[1] Man-Fung Yuen[2] Oana Sandulescu[3] Rajneesh Kumar[4] Alina Jucov[5] Pietro Lampertico[6] Stefano Fagiuoli[7] Grace Lai-Hung Wong[8] Marta Dobrayanska[9] Emily Thi[10] Timothy Eley[10] Sharie Ganchua[10] Christine Espiritu[10] Varun Sharma[10] Joanne Brown[10] Ganapati Reddy Pamulapati[10] Karen Sims[10] Tilly Varughese[10], [1]University of Auckland and New Zealand Clinical Research, [2]The University of Hong Kong, [3]National Institute for Infectious Diseases "Prof. Dr. Matei Bals", Carol Davila University of Medici, [4]Department of Gastroenterology and Hepatology, Singapore General Hospital, [5]Arensia Exploratory Medicine GmbH, [6]University of Milan, [7]Gastroenterology, Hepatology and Transplantation, ASST Papa Giovanni XXIII, [8]The Chinese University of Hong Kong, Prince of Wales Hospital, [9]Arensia Exploratory Medicine, Ukraine, [10]Arbutus Biopharma

Background: Programmed death 1 (PD-1)/ programmed death-ligand 1 (PD-L1) inhibition using immune checkpoint inhibitor antibodies has been associated with HBsAg loss and seroconversion in some patients with chronic hepatitis B (CHB). AB-101 is an investigational oral small-molecule PD-L1 inhibitor being developed for the treatment of CHB in combination with other agents. A Phase 1a/1b study is ongoing to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of AB-101 in healthy subjects (HS) and patients with CHB suppressed on nucleos(t)ide analogue (NA) therapy. Preliminary results from HS and the first CHB cohort have been reported previously. Here we report follow-up data from the first CHB cohort and data from the second, higher dose CHB cohort. **Methods:** AB-101-001 is an ongoing randomized, double-blind, placebo-controlled 3-part study evaluating the safety, tolerability, PK and PD of AB-101 in HS and NA-suppressed CHB patients. In Part 3, patients with CHB were randomized 10:2 and administered AB-101 at 10 mg (Cohort 3A) or 30 mg (Cohort 3B) or placebo daily (QD) for 28 days. Safety was monitored via adverse event (AE) and immune related AE (irAE) reporting, vital signs, physical examination, ECGs, and laboratory assessments up to 6 months after dosing. Blood samples for single and repeat dose PK and PD were collected. PD was assessed via measurement of PD-L1 levels from peripheral cells (receptor occupancy [RO]). **Results:** AB-101 was well tolerated in CHB patients with no related serious adverse events, irAEs, or related Grade 3 or 4 treatment emergent adverse events (TEAEs). Cohorts 3A and 3B were predominantly male (92%, 75%) with mean ages of 42.8 and 45 years, respectively. Follow-up is complete for Cohort 3A. A total of 6 TEAEs (3 related to AB-101) and no irAEs were observed through follow-up. Dosing and follow-up are ongoing for Cohort 3B. No clinically significant laboratory, vital sign, or ECG abnormalities were reported in either cohort. Concentrations of AB-101 were largely comparable to healthy subjects. Mean maximal RO was 39% and 83% for 10 mg (N = 6) and 30 mg (N = 6) QD respectively, through 7-28 days of dosing. **Conclusion:** Oral doses of AB-101 up to 30 mg QD for 28 days were generally well tolerated in NA-suppressed CHB patients. Preliminary interim PD data indicate dose-related increases in RO, with 83% mean maximal RO at the 30 mg dose. Cohort 3B is ongoing and all available data, including safety, PK, RO and HBV biomarkers, will be presented.

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◆ 1124 | SEX DISPARITIES IN VIRAL HEPATITIS: CLINICAL AND EPIDEMIOLOGICAL EVIDENCE FROM THE ITALIAN PITER COHORTS

Loreta Kondili[1] Samantha Hall[2] Maria Giovanna Quaranta[3] Luigina Ferrigno[3] Homie Razavi[4], [1]Istituto Superior Di Sanita (ISS), [2]Center for Disease Analysis, [3]Istituto Superiore Di Sanita (ISS), [4]Center for Disease Analysis Foundation

Background: The influence of sex on long-term disease progression, treatment adherence, and therapeutic response remains underexplored in chronic viral hepatitis, particularly in hepatitis B and D virus (HBV and HDV) infections. To address this gap, we analyzed sex-based clinical and epidemiological differences in HBV and HDV populations enrolled in the national PITER cohorts. **Methods:** We analyzed baseline clinical and virological data from the PITER HBV and HDV cohorts. Sex-based associations with antiviral treatment status, treatment duration, disease severity (as measured by FIB-4), and virological response were evaluated using chi-square tests and multivariate regression models. **Results:** Epidemiological and clinical data on chronic HBV and HDV infection by gender are summarized in Table 1. In the HBV cohort, females were more frequently PCR-positive and had a higher median viral load at enrollment. Nevertheless, males were significantly more likely to receive treatment (odds ratio: 1.79; $p < 0.001$), independent of age and place of birth. Overall, HBV treatment coverage was high, with 73.1% of HBsAg-positive males and 60.3% of females undergoing antiviral therapy. The median treatment duration was 6.1 years and did not significantly differ between sexes, except in the 60–79 age group, where males had a longer duration. Liver fibrosis at treatment initiation, measured by the FIB-4 score, increased with age and was consistently higher in males, suggesting more advanced liver disease at baseline. In the HDV cohort, no significant sex-based differences were observed. The median age was 60 years, and 33% of infections occurred in migrants. HDV viremia rates ranged from 71% to 74.8%, with first-year treatment uptake nearly identical between sexes:62.9% in males and 62.8% in females. The proportion of individuals initiating HDV treatment increased with age in both groups. **Conclusion:** The clinical and virological profiles of HBV differ by sex, with treatment initiation appearing to be influenced more by disease severity than by HBV DNA positivity alone. In contrast, HDV infection shows minimal sex-based differences in clinical characteristics and treatment uptake. These baseline, real-world data on HBV and HDV, stratified by sex, provide a valuable foundation for future studies aiming to forecast the burden of chronic liver disease and to explore potential sex-related differences in the long-term impact of treatment on disease progression. The young age of non-Italian females affected by chronic HBV and HDV infections in our cohorts highlights the importance of sex-sensitive approaches in the clinical management of viral hepatitis. Even in countries with successful HBV vaccination programs, additional public health measures remain necessary to curb the burden of viral hepatitis,particularly among unvaccinated migrant populations.

				HBV		HDV		
Variable	Country of Birth	Male	Female	Adjusted Odds Ratio (Male vs Female)	p-value	Male	Female	p-value
Total (HBsAg+ for HBV & anti-HDV+ for HDV)		3,870	2,395			402	258	
	Italian Native	3,112	1,688			298	141	
	Migrant	756	706			104	117	
Median Age		64	61			60	60	
PCR Status								
PCR Negative at Enrolment		2,461	1,226			100	58	
PCR Positive at Enrolment		1,213	1,020			245	172	
PCR Not Conducted at Enrolment		196	149			58	28	
Viremic Rate		33.0%	45.4%	0.59 (0.53-0.66)	< 0.001	71.0%	74.8%	> 0.05
Median Viral Load (IU/ml) at Enrolment		602	790			66,456	54,200	
Treatment								
Treated		2,823	1,443			154	108	
Untreated		1,038	951			91	64	
% Treated		73.1%	60.3%	1.79 (1.60-1.99)	< 0.001	62.9%	62.8%	> 0.05
Treatment by Age Group								
20 - 39		142	79	1.91 (1.34-2.74)	< 0.001	11	8	> 0.05
40 - 59		834	460	1.83 (1.53-2.19)	< 0.001	73	49	> 0.05
60 - 79		1,573	763	1.74 (1.48-2.04)	< 0.001	69	50	> 0.05
80+		274	141	0.92 (0.56-1.50)	0.75	1	1	> 0.05
Treatment by Age Group & Country of Birth								
20 - 39	Italian Native	28	14	1.52 (0.64-3.70)	0.34	0	1	> 0.05
	Migrant	114	65	1.98 (1.34-2.95)	< 0.001	11	7	> 0.05
40 - 59	Italian Native	561	261	1.80 (1.42-2.29)	< 0.001	40	13	> 0.05
	Migrant	272	199	1.77 (1.33-2.35)	< 0.001	33	36	> 0.05
60 - 79	Italian Native	1,501	689	1.75 (1.47-2.07)	< 0.001	63	33	> 0.05
	Migrant	71	74	1.36 (0.78-2.40)	0.28	6	17	> 0.05
80+	Italian Native	270	139		> 0.05	1	1	> 0.05
	Migrant	4	2		> 0.05	0	0	> 0.05
Treatment Duration (in Years) by Age Group								
20 - 39		3.51	4.34		0.098	-	-	
40 - 59		5.92	5.32		0.017	-	-	
60 - 79		7.16	6.25		< 0.001	-	-	
80+		7.2	6.57		0.3	-	-	
Treatment Duration (in Years) by Age Group & Country of Birth								
20 - 39	Italian Native	4.12	4.36		0.86	-	-	
	Migrant	3.38	4.33		0.07	-	-	
40 - 59	Italian Native	6.25	5.52		0.03	-	-	
	Migrant	5.24	5.05		0.61	-	-	
60 - 79	Italian Native	7.17	6.35		< 0.001	-	-	
	Migrant	6.74	5.29		0.05	-	-	
80+	Italian Native	7.23	5.52		0.24	-	-	
	Migrant	4.33	10		0.15	-	-	
Liver Staging								
Average FIB-4 Score at Initiation								
20 - 39		0.92	0.85		0.38	-	-	
40 - 59		1.65	1.43		< 0.01	-	-	
60 - 79		2.43	2.22		0.03	-	-	
80+		3.1	2.91		0.53	-	-	
Average Last FIB-4 Score								
20 - 39		0.83	0.92		0.45	-	-	
40 - 59		1.64	1.46		0.15	-	-	
60 - 79		2.26	2.23		0.84	-	-	
80+		2.95	2.71		0.38	-	-	
Average FIB-4 Score at Initiation by Age and Country of Birth								
20 - 39	Italian Native	1.01	1.07		0.85	-	-	
	Migrant	0.91	0.62		0.27	-	-	
40 - 59	Italian Native	1.59	1.39		< 0.01	-	-	
	Migrant	1.58	1.48		0.42	-	-	
60 - 79	Italian Native	2.45	2.14		< 0.01	-	-	
	Migrant	2.06	2.91		0.02	-	-	
80+	Italian Native	3.09	2.91		0.55	-	-	
	Migrant	3.55	2.92		0.44	-	-	
Average Last FIB-4 Score by Age and Country of Birth								
20 - 39	Italian Native	0.68	0.71		0.79	-	-	
	Migrant	0.85	0.95		0.5	-	-	
40 - 59	Italian Native	1.64	1.37		0.03	-	-	
	Migrant	1.83	1.55		0.72	-	-	
60 - 79	Italian Native	2.22	2.19		0.81	-	-	
	Migrant	2.86	2.56		0.68	-	-	
80+	Italian Native	-	-					
	Migrant	-	-					

Disclosures: Loreta Kondili: Gilead Science: Grant/Research Support, Samantha Hall: Nothing to Disclose,

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◆ 1125 | TRACKING A DECADE OF HEPATITIS B OUTCOMES IN THE UK: INSIGHTS FROM NATURAL LANGUAGE PROCESSING DRIVEN EHR ANALYSIS

Mahd Siddiqi[1] Saima Ajaz[1] Mohammad Al-Agil[1] Kosh Agarwal[1], [1]Kings College Hospital, London, United Kingdom

Background: Hepatitis B virus (HBV) infection is a persistent global health issue, with over 296 million people chronically infected worldwide. Individuals are at risk of adverse complications such as hepatocellular carcinoma (HCC) and cirrhosis. In the UK, recent public health strategies have emphasised early detection, long-term monitoring, and expanded access to antivirals. However, real-world evidence on the impact of these efforts on HBV-related outcomes is limited. This study aimed to evaluate trends in HBV diagnoses, treatment uptake, and complications over the past decade using natural language processing (NLP) of electronic health records (EHRs). **Methods:** Our study retrospectively analysed the past decade (2013 to 2023) of HBsAg-positive patients' EHRs at King's College Hospital, London. Data were extracted and collated using CogStack, an NLP platform to process clinical text. Key variables included yearly HBsAg-positive diagnoses, antiviral therapy (tenofovir, entecavir), liver-related complications (HCC, cirrhosis, liver transplantation), and all-cause mortality. Demographic information was assessed, and trends were examined across diagnoses and major clinical endpoints. **Results:** A total of 7,158 HBsAg-positive patients were identified through CogStack. The cohort had a male predominance (55.7% male and 44.4% female) and was ethnically diverse: Black (35.8%), Unknown (25.7%), White (19.0%), Asian (13.9%), Other (5.5%), and Mixed (0.3%). Across the cohort, 1,501 patients (21.2%) had cirrhosis, 2,224 (31.4%) had HCC, and 106 (1.5%) underwent liver transplantation. Between 2013 and 2023, annual HBsAg-positive diagnoses significantly decreased from 2,382 to 394, representing an 83.5% reduction (compound annual decline: 16.5%). Over the same period, cirrhosis cases decreased from 283 to 209 (-26.1%; -3.0% annually) and HCC diagnoses dropped from 395 to 195 (-50.6%; -6.8% annually). Liver transplant numbers fluctuated annually (range: 7 to 17), returning to 9 in 2023, the same level as 2013. Statistical analysis (Mann-Kendall test) confirmed a significant monotonic decline in new diagnoses (τ = -0.67, p = 0.003). However, trends for cirrhosis (τ = 0.27, p = 0.283), HCC (τ = 0.20, p = 0.445), and liver transplantation (τ = 0.06, p = 0.813) were not statistically significant. **Conclusion:** The integration of advanced NLP tools shows potential for improvement in the identification of HBV patients and assessing the effectiveness of screening and treatment initiatives. To build on this progress, we must enhance our digital-health infrastructure, deepen targeted outreach, and streamline linkage to care and adherence support.

Disclosures: Mahd Siddiqi: Nothing to Disclose, Saima Ajaz: Nothing to Disclose, Mohammad Al-Agil: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose

◆ 1126 | DIVERGENT EFFECTS OF GLYCEMIC BURDEN ON HBEAG SEROCLEARANCE AND HCC RISKS IN HBEAG-POSITIVE CHB: A LARGE MULTICENTER COHORT STUDY

Shang-Chin Huang[1] Rex Wan-Hin Hui[2] Tai-Chung Tseng[1] Karen Cheuk Ying Ho[2] Lung Yi Mak[2] Chun-Jen Liu[1] Wai-Kay Seto[2] Tung-Hung Su[1] Man-Fung Yuen[2] Jia-Horng Kao[1], [1]National Taiwan University Hospital, [2]The University of Hong Kong

Background: HBeAg seroclearance marks a critical milestone in the natural course of chronic hepatitis B (CHB). With the rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic comorbidities, their impact on HBeAg-positive CHB remains poorly understood, particularly regarding viral clearance and long-term oncologic outcomes. **Methods:** HBeAg-positive CHB patients with serial HBeAg measurements were consecutively enrolled from the National Taiwan University Hospital (NTUH, internal cohort). Steatotic liver disease (SLD) and cardiometabolic risk factors were defined per international guidelines. Cumulative incidences of HBeAg seroclearance and hepatocellular carcinoma (HCC) were compared after adjustment for confounding factors. External validation was conducted in an independent cohort from The University of Hong Kong (HKU, external cohort). **Results:** This study included 2,531 HBeAg-positive patients in the internal cohort and 866 in the external cohort, with a median follow-up of 8.2 and 14.4 years, respectively. At baseline, the median age was 38.8 and 39.2 years, and the proportion of males was 57.8% and 61.0%, respectively. Nucleos(t)ide analogue therapy had been initiated in 30.6% and 36.6% of patients, while diabetes mellitus (DM) was present in 5.3% and 4.5%. In both cohorts, SLD was not associated with HBeAg seroclearance. Conversely, DM significantly increased the likelihood of HBeAg seroclearance (internal cohort: adjusted hazard ratio [aHR]: 1.38, 95% confidence interval [CI]: 1.07 – 1.77; external cohort: aHR 1.61, 95% CI 1.02 – 2.55; both $p < 0.05$). The glycemic burden consistently demonstrated a dose-dependent association with HBeAg seroclearance (aHR: 1.41 and 1.17 for HbA1c $\geq$6.5% and

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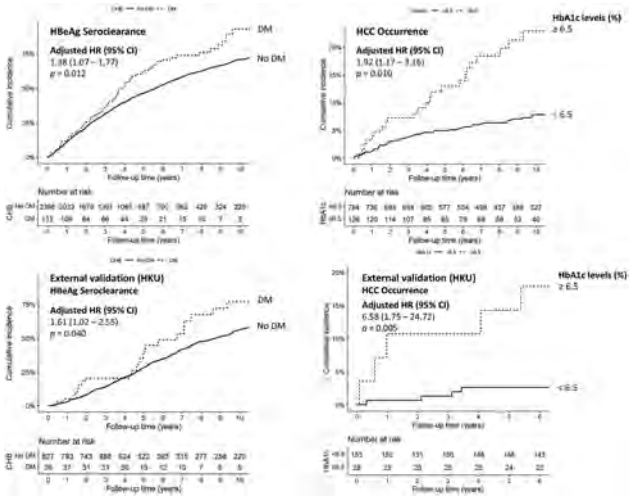
5.9 – 6.4% vs. ≤5.8%; p for trend = 0.006). HbA1c ≥ 6.5% was also independently associated with an increased HCC risk (internal cohort: aHR: 1.92, 95% CI: 1.17 – 3.16; external cohort: aHR 6.58, 95% CI 1.75 – 27.42; both $p < 0.05$). The sensitivity analyses, including propensity score matching, multiple imputation for missing data, and time-dependent covariate analysis for antiviral therapy, confirmed the robustness of results. **Conclusion:** The glycemic burden exerts a diverse and paradoxical impact on HBeAg-positive CHB, enhancing HBeAg seroclearance while increasing HCC risks. These findings underscore the importance of routine glycemic monitoring and metabolic control in this special population. The mechanisms behind the virus-host metabolic interplay represent a novel area for future research.



Disclosures: Shang-Chin Huang: Gilead Sciences: Speaking and Teaching, Rex Wan-Hin Hui: Nothing to Disclose, Tai-Chung Tseng: Nothing to Disclose, Karen Cheuk Ying Ho: Nothing to Disclose, Lung Yi Mak: Nothing to Disclose, Chun-Jen Liu: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose, Tung-Hung Su: Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Merck Sharp and Dohme: Speaking and Teaching, Roche: Speaking and Teaching, Sysmex: Speaking and Teaching, Eisai: Speaking and Teaching, Man-Fung Yuen: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose

◆ 1127 | FACTORS ASSOCIATED WITH HEPATITIS B INFECTION IN SUB-SAHARAN AFRICA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Nkengeh Tazinkeng[1] Sonia Yonta Kenne[2] Jan René Nkeck[3] Monela Ntonifor[4] Fatima Elmustafa[5] Ryan Tanjoh[6] Ephesians Anutebeh[1] Yasmin Osman Ali[7] Adedeji Adenusi[8] David Makanga[1] Lydia Lantum Dzeenyuy[9] Cameg-Brenda Meriki[10] Emmanuel Agyemang[1] Noon Altijani[11] Valirie Ndip Agbor[12], [1]Rutgers/Newark Beth Israel Medical Center, New Jersey, USA, [2]Centre Hospitalier de l'Estran, Pontorson, France, [3]Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon, [4]North Carolina Agricultural and Technical State University, North Carolina, USA, [5]Henry Ford Hospital System, Michigan, USA, [6]South Liverpool & Birkenhead GP training program, Mersey and West Lancashire Hospitals NHS Trust, UK, [7]Hennepin Healthcare, Minnesota, USA, [8]One Brooklyn Health-Interfaith Medical Center, New York, USA, [9]Faculty of Health Sciences, University of Buea, Cameroon, [10]Faculty of Health Sciences, University of Bamenda, Cameroon, [11]Postgraduate Team, Education Centre, Liverpool University Hospitals NHS Foundation Trust, UK, [12]Department of Clinical Sciences, Global Health Trials Unit, Liverpool School of Tropical Medicine,UK

Background: Hepatitis B virus (HBV) is the main cause of liver disease in the WHO Africa region, where despite the availability of effective vaccines, the burden of new infections surpasses that of all other regions combined. Progress towards HBV elimination is hampered by insufficient domestic funding. Previous evidence on the determinants of HBV in sub-Saharan Africa (SSA) has been limited by small sample sizes. This systematic review and meta-analysis investigated the factors associated with HBV infection in SSA. **Methods:** Following the PRISMA guidelines, we conducted a comprehensive search on MEDLINE, Embase, Global Health Library, and Africa-specific databases (AFROLIB, African Index Medicus, and African Journals Online) for articles published from inception of the databases to 27 October 2024. Random-effects meta-analytic models were used to calculate pooled log-transformed odds ratios (ORs) and their variances to evaluate the determinants of HBV infection. Heterogeneity across studies was assessed using the I² statistic and Cochran's Q test. **Results:** We screened 3838 studies for eligibility and included 137, comprising 1,784,317 participants. Most were cross-sectional studies (126/137), published between 2011 and 2020 (85/137). East (n = 66) and West Africa (47) had the most publications, with Ethiopia (n = 41), Nigeria (13), and Ghana (12) contributing the most publications. The following factors were significantly associated with higher rates of HBV infection: Male gender (OR 1.4, 95% confidence interval: 1.2–1.6), being unemployed (1.6, 1.2–1.9), living with a person infected with HBV (2.9, 2.1–4.0), sharing razors (2.6, 1.3–5.0), history of blood transfusion (2.1, 1.4–3.1), history of surgery (1.8, 1.3–2.4), dental procedures (1.6, 1.1–2.4), tattoos (2.1, 1.6–2.8), history of traditional operation and scarification (1.5, 1.3–1.8), history of abortion (2.2, 1.4–3.4), history of STI (2.4, 1.7–3.5), HIV infection (1.4, 1.2–1.7), and multiple sexual partners (3.0, 2.1–4.4). **Conclusion:** This study

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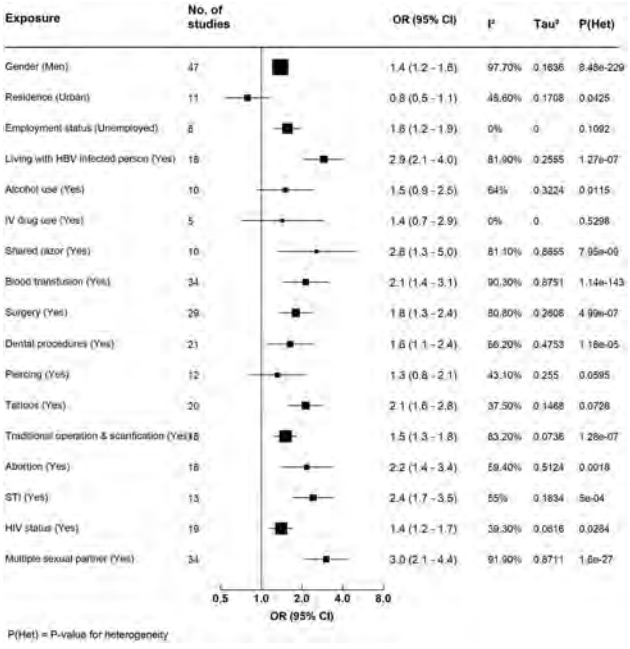
suggests that household and healthcare exposures, and sexual behavior are the most emerging drivers of HBV transmission in SSA. These insights can guide targeted public health interventions such as education, improved infection control policies, and vaccination programs.

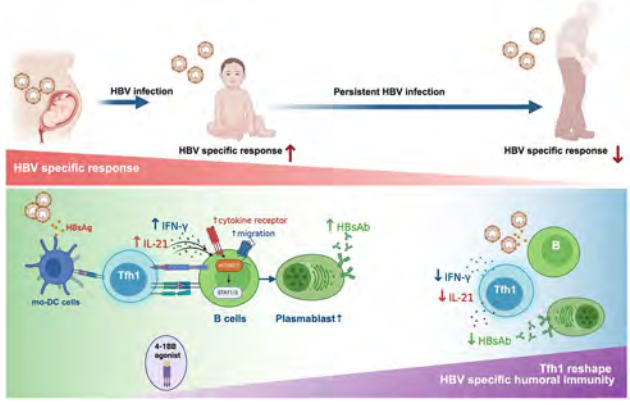


Disclosures: Nkengeh Tazinkeng: Nothing to Disclose, Sonia Yonta Kenne: Nothing to Disclose, Jan René Nkeck: Nothing to Disclose, Monela Ntonifor: Nothing to Disclose, Fatima Elmustafa: Nothing to Disclose, Ryan Tanjoh: Nothing to Disclose, Ephesians Anutebeh: Nothing to Disclose, Yasmin Osman Ali: Nothing to Disclose, Adedeji Adenusi: Nothing to Disclose, David Makanga: Nothing to Disclose, Lydia Lantum Dzeenyuy: Nothing to Disclose, Cameg-Brenda Meriki: Nothing to Disclose, Emmanuel Agyemang: Nothing to Disclose, Noon Altijani: Nothing to Disclose, Valirie Ndip Agbor: Nothing to Disclose

◆ 1128 | 4-1BB COSTIMULATION RESTORE TFH1 FUNCTION TO AUGMENT HBV-SPECIFIC HUMORAL IMMUNITY IN CHRONIC INFECTION

yongyin li[1] Yanchen Ma[1] Xiaoyi Liu[1] Haonan Lou[1] Hui Zhang[1] Jinyan Jiang[1] Weiying He[1] Libo Tang[1] Yunfei Gao[1] Jinlin Hou[2] ZHIHUA LIU[2], [1]NanFang Hospital, Southern Medical University, [2]Nanfang Hospital, Southern Medical University

Background: Chronic HBV infection is closely associated with dysregulated humoral immunity. Although our study demonstrated that Mother-to-child transmission (MTCT) could be dramatically reduced by the comprehensive interventions among HBV-infected pregnant women (Nature Medicine,2024), how intrauterine HBV antigen exposure shapes host humoral immunity remains incompletely understood. Here, we investigated the humoral immune profile in cord blood from neonates born to HBV-infected mothers to identify potential therapeutic targets and validate whether targeting these pathways could restore HBV-specific humoral immunity through clinical cohorts with persistent chronic infection. **Methods:** We analyzed cord blood samples from 73 neonates born to HBsAg-positive mothers and 24 counterpart controls (HBsAg-negative mothers) within our previously reported clinical cohort (NCT05172453). B cell and CD4$^+$ T cell phenotypes and transcriptomes were analyzed by flow cytometry and RNA-seq. HBV-specific B cells were quantified via ELISPOT and ELISA. Additionally, peripheral blood from 85 untreated chronic HBV patients (aged 1–65 years) were evaluated by full-spectrum flow cytometry to determine Tfh1-cell functional dominance and age-related distribution. **Results:** Cord blood from HBV antigen-exposed neonates exhibited enhanced HBV-specific B cell responses along with significantly elevated frequencies of type 1 follicular T helper cells (Tfh1) compared to controls. HBsAg could induced naïve CD4$^+$ T cells to differentiate into Tfh1 cells, but not the other T helper cells (Th1/Th2/Th17) or alternative follicular T helper cells (Tfh2/Tfh17) subsets. These Tfh1 cells secrete both IFN-γ and IL-21, which synergistically enhanced HBsAb production by B cells via the activation of mTORC1-STAT1/STAT3 pathway. These data demonstrate that primary HBV antigen exposure preferentially induces a Tfh1-polarized immune response that initiates HBV-specific humoral immunity. To assess Tfh1 dynamics in chronic infection, we performed full-spectrum flow cytometry on a clinical HBV cohort, revealing an age-dependent decline in both Tfh1 frequency and 4-1BB expression, which positively correlated with HBsAb-secreting B cell counts. Strikingly, 4-1BB stimulation in vitro restored Tfh1 function, rescuing IFN-γ and IL-21 production and enhancing B cell help. **Conclusion:** Tfh1-derived IFN-γ and IL-21 potentiate HBsAb production by activating mTORC1-STAT1/STAT3 signaling in B cells. The age-dependent decline in Tfh1 frequency and 4-1BB expression suggests progressive immune dysfunction in chronic HBV infection. Targeting 4-1BB may rejuvenate Tfh1 activity, offering a novel strategy to restore HBV-specific humoral immunity.



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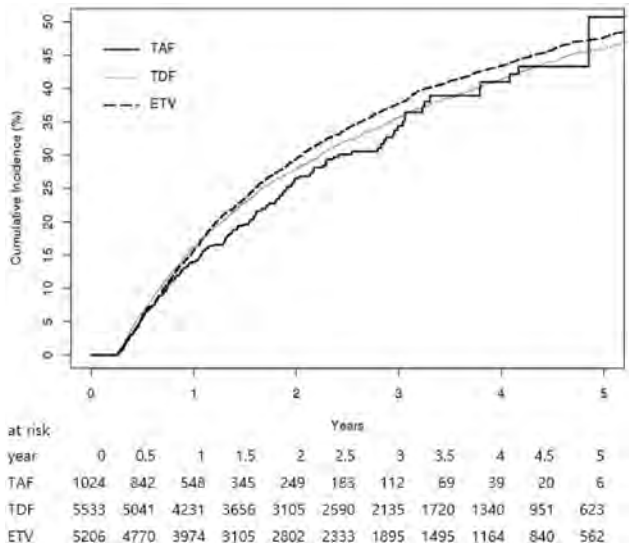
◆ ★ 1129 | TENOFOVIR ALAFENAMIDE, TENOFOVIR DISOPROXIL FUMARATE, AND ENTECAVIR ON HCC RECURRENCE AND DEATH AFTER CURATIVE TREATMENT: A KOREAN NATIONWIDE REAL-WORLD STUDY

Ji Eun Han[1] Gi Hyeon Seo[2] Yoon Je Cho[1] Hyo Jung Cho[1] jaeyoun cheong[1] Soon Sun Kim[1], [1]Ajou University School of Medicine, [2]VUNO Inc. Seoul, Korea

Background: Chronic hepatitis B (CHB) can lead to hepatocellular carcinoma (HCC) due to persistent covalently closed circular DNA and integrated HBV DNA, even after curative HCC treatment. Hepatitis B viral load is a prognostic factor for HCC recurrence, underscoring the importance of effective antiviral therapy. Entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) are first-line nucleot(s)ide analogs for CHB. TAF, approved in Korea in 2017, has shown favorable safety, but long-term real-world data on HCC recurrence and mortality remain limited. This study aimed to compare the effects of ETV, TDF, and TAF on HCC recurrence or death after curative treatment in Korea. **Methods:** This retrospective cohort study used data from the Korean Health Insurance Review and Assessment Service and included 11,763 CHB patients (aged 19–99) who received ETV, TDF, or TAF for $\geq$3months and underwent curative HCC treatment (surgical resection or local ablation, including radiofrequency ablation, percutaneous ethanol injection therapy, cryoablation, or microwave ablation) between November 1, 2017, and July 31, 2023. Patients who switched to TAF for $\geq$90 days were assigned to the TAF group. The primary outcome was HCC recurrence or death. Inverse probability of treatment weighting (IPTW) was applied to adjust for age, sex, comorbidities, and treatment modality. Kaplan-Meier survival curves and Cox proportional hazards regression were used to compare outcomes among the groups. **Results:** A total of 11,763 patients (TAF: 1,024, TDF: 5,533, ETV: 5,206) were analyzed, with a median follow-up of 29.4 months. The incidence rates of HCC recurrence or death per 100 person-years were 16.66 in the TAF group, 15.20 in the TDF group, and 16.57 in the ETV group. In IPTW-adjusted analysis, TAF was not associated with a significantly different risk of recurrence or death compared to ETV (HR: 0.88, 95% CI: 0.76–1.02, p = 0.098) or TDF (HR: 0.93, 95% CI: 0.80–1.07, p = 0.307). Multivariate Cox regression analysis identified male sex, older age, diabetes, liver cirrhosis, and local ablation therapy as independent risk factors for HCC recurrence or death (all $p < 0.05$). Kaplan-Meier analysis showed no significant difference among the groups. **Conclusion:** In patients with CHB-related HCC who received curative treatment, the risk of HCC recurrence or death did not differ significantly among patients treated with TAF, TDF, or ETV.



at risk											
year	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
TAF	1024	842	548	345	249	183	112	69	39	20	6
TDF	5533	5041	4231	3656	3105	2590	2135	1720	1340	951	623
ETV	5206	4770	3974	3105	2802	2333	1895	1495	1164	840	562

Disclosures: Ji Eun Han: Nothing to Disclose, Gi Hyeon Seo: Nothing to Disclose, Yoon Je Cho: Nothing to Disclose, Hyo Jung Cho: Nothing to Disclose, jaeyoun cheong: Nothing to Disclose, Soon Sun Kim: Nothing to Disclose

◆ 1130 | A NOVEL MRNA-BASED IMMUNOTHERAPY INDUCES STRONG HBV-SPECIFIC CD8+ T CELL RESPONSES IN VITRO AND IN VIVO

Yuchun Nie[1] Gongxin He[2] Ren Zhu[2] (Zoe) Jia Meng[2] Wenyuan Fan[2] Jialin Chen[2] Xiaowu Chen[2], [1]Shanghai CureGene Pharmaceutical, [2]Shanghai CureGene Pharmaceutical Co.

Background: Chronic hepatitis B (CHB) virus infection is a major health burden. Currently long-term treatment with nucleoside drugs suppresses HBV replication, but rarely results in functional cure (HBV DNA and HBsAg level undetectable for $>$6 months). Recent researches indicate that reactivation of HBV-specific immunity is the key for functional cure of CHB. We discovered novel mRNA-based immunomodulators (IMs) encoding various HBV RNA fragments, capable of eliciting strong HBV-specific immune

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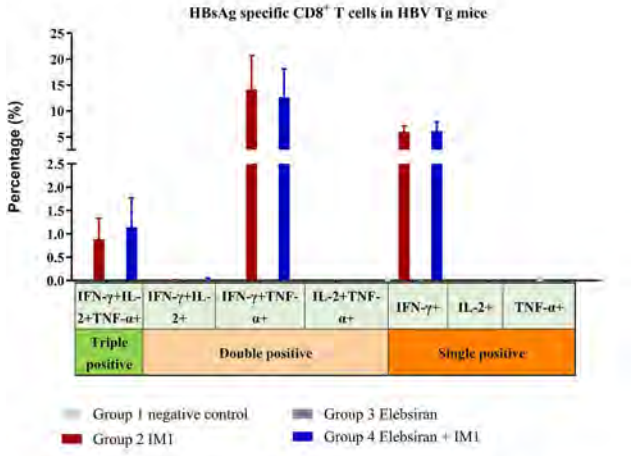
responses in vitro and in vivo and complete eliminating HBV from mouse model. **Methods:** IMs were injected at 1~10 μg/mouse in wild-type and HBV mice models, including AAV-HBV or HBV transgenic (tg) mice. Mice sera were collected for biochemical and viral biomarker analysis. The splenocytes were harvested for cellular immune responses analysis. To further test immune activation of IMs in human immune cells, an in vitro immune stimulation system was assembled with human PBMCs. **Results:** Here we report the results of IM1 which induced strong HBV-specific immune response. After three dosages, extreme high anti-HBsAb (> 100,000 IU/mL) was elicited in Balb/c mice. Meanwhile, a significant amount of HBV-specific IFN-γ+ T cells were induced. Next, we accessed their ability to induce both anti-viral & immune responses in AAV-HBV mice. The IM1 monotherapy resulted in 1.4 log IU/mL reduction of HBsAg, which maintained at a low level for at least 60 days post treatment. Strikingly, the combination of siRNA and IM1 lead to a reduction of HBsAg to undetectable level (> 3 log IU/mL) without relapse. At the same time, we observed extensive HBV-specific CD8+ T cell populations in those IM1 treated mice; the HBV-specific CD8 + T cell responses were more pronounced when IM1 was combined with siRNA. In addition, HBV tg mice were treated with IM1 and siRNA, their HBsAg level was sustained at undetectable level 70 days post treatment. Simultaneously, vigorous HBV specific polyfunctional CD8+ T cells were induced (Figure 1). In order to understand whether IM1 could stimulate human CD8+ T cells, the primary human T cells were cocultured with IM1 transfected mDC. Significant high amount of HBV specific CD8+ T cells were induced successfully. **Conclusion:** We developed a novel mRNA-based immunotherapy, which can clear HBV in various mice models (see another poster from CureGene), likely through eliciting strong, polyfunctional and long-lasting HBV-specific immune responses.

Figure 1



HBV-specific T cells were evaluated by intracellular cytokines staining in spleen from HBV tg mice 70 days post-treatment.

Disclosures: Yuchun Nie: Nothing to Disclose, Gongxin He: Nothing to Disclose, Ren Zhu: Nothing to Disclose, (Zoe) Jia Meng: Nothing to Disclose, Wenyuan Fan: Nothing to Disclose, Jialin Chen: Nothing to Disclose, Xiaowu Chen: Shanghai CureGene Pharmaceutical Co: Employee

◆ 1131 | A FUNCTIONAL CURE AFTER NUCLEOS(T)IDE ANALOGUE DISCONTINUATION IN NON-CIRRHOTIC PATIENTS WITH HBEAG-NEGATIVE CHRONIC HEPATITIS B

Zeynep Melekoglu Ellik[1] Özge Koç[1] Fatma Tuğçe Şah Ünal[1] Emin Bodakci[2] Mesut Gumussoy[1] Abdullah Mubin Ozercan[3] Volkan YILMAZ[1] ramazan erdem er[1] Hale Gokcan[1] Atilla Halil Elhan[1] Ramazan Idilman[1], [1]Ankara University School of Medicine, [2]Gaziantep City Hospital, [3]Fırat University School of Medicine

Background: Discontinuation of long-term nucleos(t)ide analog (NA) treatment can induce functional cure in patients with chronic hepatitis B (CHB); however, data are scarce. This study aimed to evaluate HBsAg loss after NA treatment discontinuation in non-cirrhotic patients with HBeAg-negative CHB and to determine virological outcomes after NA discontinuation. **Methods:** This single-center cohort study included 146 non-cirrhotic, HBeAg-negative CHB patients who achieved long-term viral suppression under NAs treatment. Seventy-three patients discontinued NA therapy after more than 5 years of treatment and at least the last 3 years of virological suppression (consolidation period). The historical age- and sex-matched control group comprised 73 patients who continued NA therapy for a 60-month observational period. HBV reactivation was defined as HBV DNA > 2000 IU/mL with serum ALT levels exceeding two times the upper limit of normal. The primary endpoint was sustained HBsAg loss for at least 6 months, while the secondary outcome was virological and biochemical response at month 60 after NA cessation. **Results:** Patients' characteristics were similar in both groups. HBsAg loss occurred in eight patients (11%) in the discontinuation group, while none were observed in the treatment-continued group (p = 0.004). The cumulative probability of HBsAg loss was 13% at month 120. Multivariate Cox regression analysis revealed that a younger age at NA cessation (< 50 years), (Odds ratio [OR]: 6.71, 95%CI: 1.166-38.603, p = 0.033) and abnormal baseline serum AST level (≥ 40 U/L) (OR: 7.394, 95%CI: 1.249-43.783, p = 0.027) were independent predictors of HBsAg loss. Anti-HBs seroconversion was observed in six patients with HBsAg loss. Forty-four patients (60%) experienced sustained remission. HBV reactivation occurred in 29 patients, primarily (72%) within the first three months

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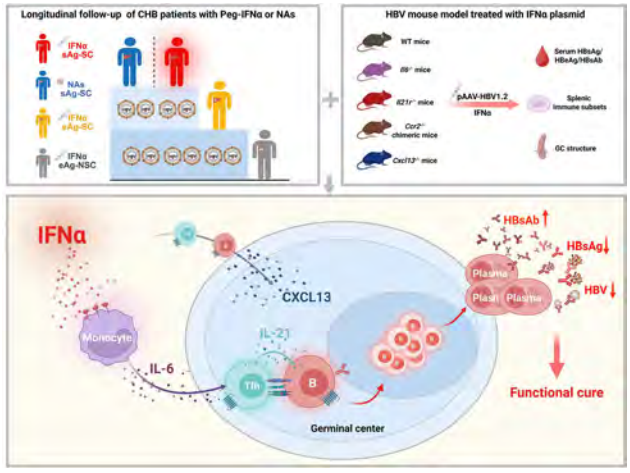
after treatment discontinuation. Patients' characteristics were not associated with HBV reactivation. However, HBV reactivation was slightly higher in patients with HBsAg titer of > 1000 IU/mL at NA discontinuation than in those patients with < 1000 IU/mL (p = 0.097). NA retreatment was initiated in all relapsed patients, resulting in a virological and biochemical response upon re-initiation of therapy. No serious adverse events or hepatic decompensation were observed. **Conclusion:** NA discontinuation in non-cirrhotic patients with HBeAg-negative CHB was associated with a functional cure. Younger age and abnormal aminotransferase levels at baseline may predict a higher likelihood of achieving this outcome. NA discontinuation is safe and tolerable in selected patients with CHB.

Disclosures: Zeynep Melekoglu Ellik: Nothing to Disclose, Özge Koç: Nothing to Disclose, Fatma Tuğçe Şah Ünal: Nothing to Disclose, Emin Bodakci: Nothing to Disclose, Mesut Gumussoy: Nothing to Disclose, Abdullah Mubin Ozercan: Nothing to Disclose, Volkan YILMAZ: Nothing to Disclose, ramazan erdem er: Nothing to Disclose, Hale Gokcan: Nothing to Disclose, Atilla Halil Elhan: Nothing to Disclose, Ramazan Idilman: Nothing to Disclose

◆ 1132 | INTERFERON-α ENHANCES HBSAG-SPECIFIC B CELL RESPONSES VIA MONOCYTE-TFH-B CELL AXIS TO FACILITATE FUNCTIONAL CURE OF HEPATITIS B

yongyin li[1] Shihong Zhong[1] Yang Zhou[1] Libo Tang[1] Xiaofang Li[2] Jinlin Hou[1] Jianhua Li[2] Xiaoyong Zhang[1], [1]Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China, [2]Key Laboratory of Medical Molecular Virology (MOE/NHC/CAMS), Department of Pathogen Biology, School

Background: Achieving a functional cure for chronic HBV infection remains an unmet challenge. Our recent clinical trial demonstrated the combination of siRNA with peg-IFNα resulted in a higher rate of functional cure compared to siRNA monotherapy (New Engl J Med. 2024). This finding substantiates an important role of IFNα in mediating functional cure, however, its underlying immune mechanisms remain poorly defined, particularly in how IFNα shaping antiviral humoral immunity. Herein, we aimed to elucidate how IFNα regulates B cell immunity to facilitate functional cure. **Methods:** We longitudinally followed CHB patients receiving Peg-IFNα therapy and stratified them based on virological outcomes at week 72: HBeAg-non-seroconversion (eAg-NSC, n = 11), HBeAg-seroconversion (eAg-SC, n = 7), and HBsAg seroconversion (sAg-SC, n = 6). In addition, 3 CHB patients who achieved HBsAg seroconversion after five years of nucleos(t)ide analogues therapy (NAs-sAg-SC) were enrolled for comparison. Peripheral blood was collected at baseline and week 12 for scRNA-seq and flow cytometry. The effects of IFNα on immune subsets and HBV-specific B cell responses were further examined through in vitro cytokine stimulation assays and in vivo validation using *Il6*$^{-/-}$, *Il21r*$^{-/-}$, *Ccr2*$^{-/-}$ chimeric, and *Cxcl13*$^{-/-}$ HBV mouse models treated with IFNα plasmid. **Results:** scRNA-seq and flow cytometry revealed that Peg-IFNα selectively expanded Tfh and plasma cells specifically in sAg-SC patients. However, in vitro stimulation of purified CD19^{+}B cells with IFNα showed minimal effects indicating the involvement of intermediary cells. Given the robust upregulation of IL6–related gene programs in monocytes, we further investigated IFNα's effects on these cells and confirmed that IFNα enhanced humoral immunity by augmenting monocyte-derived IL6 secretion. Intriguingly, while IL-6 failed to directly activate B cells, subsequent analyses revealed that IFNα enhanced IL6–mediated Tfh cell interactions and promoted IL6ST-high Tfh subsets with elevated IL21 expression in sAg-SC patients. In vitro IL6 stimulation increased IL21 production in CXCR5^{+}CD4^{+} T cells, whereas IL21 induction was abolished in *Il6−/−* or monocyte-deficient mice. Transcriptomic profiling of IL21–stimulated B cells showed significant enrichment of humoral response. scRNA-seq further revealed elevated IL21–IL21R signaling between Tfh and GC-like/plasma B cells exclusively in IFNα–treated sAg-SC patients. Finally, spatial analysis demonstrated that IFNα promoted GC formation via CXCL13-CXCR5 signaling. Notably, GC development was abrogated in *Il6*$^{-/-}$, *Ccr2*$^{-/-}$ chimeric, and *Cxcl13*$^{-/-}$ mice. **Conclusion:** IFNα promotes anti-HBV humoral immunity via a monocyte-Tfh-B cell axis, strategically bridging innate and adaptive immunity to facilitate HBV cure. These findings provide mechanistic insights and identify potential targets to optimize IFNα-based therapeutic strategies.



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Disclosures: yongyin li: Nothing to Disclose, Shihong Zhong: Nothing to Disclose, Yang Zhou: Nothing to Disclose, Libo Tang: Nothing to Disclose, Xiaofang Li: Nothing to Disclose, Jinlin Hou: Nothing to Disclose, Jianhua Li: Nothing to Disclose, Xiaoyong Zhang: Nothing to Disclose

◆ 1133 | REAL-WORLD IMPACT OF EVOLVING CHINESE CHRONIC HEPATITIS B GUIDELINES ON ANTIVIRAL TREATMENT UPTAKE: A 5-YEAR LONGITUDINAL ANALYSIS

Wei Ye[1], [1]Nanjing Second Hospital

Background: The Chinese Society of Hepatology has progressively refined chronic hepatitis B (CHB) management guidelines, expanding treatment eligibility criteria. This study evaluates the temporal association between guideline updates and real-world antiviral treatment rates in a large clinical cohort. **Methods:** We conducted a retrospective analysis of HBV DNA-positive adults at Nanjing Second Hospital (2019-2024). Annual treatment rates were calculated as the proportion of eligible patients receiving nucleos(t)ide analogs or interferon. Three guideline epochs were examined: 2015 version, 2019 version, and 2022 version. **Results:** The Chinese guidelines for CHB management have undergone three major revisions: the 3rd edition in December 2015, the 4th edition in December 2019, and the 5th edition in December 2022. Our data demonstrate the following treatment patterns according to respective guideline versions. In 2019, when following the 2015 guideline criteria, 2,430 of 4,489 HBV DNA-positive patients (54%) received antiviral therapy. After implementation of the 2019 guidelines, treatment rates increased to 59% (2,239/3,782) in 2020, 57.9% (2,268/3,913) in 2021, and 61.6% (2,246/3,645) in 2022. Following adoption of the 2022 guidelines, the treatment rate rose to 65% (2,204/3,343) in 2023. Current data through 2024 show further improvement to 74% (1,374/1,878), demonstrating a consistent upward trend. **Conclusion:** This longitudinal analysis demonstrates the significant clinical impact of Chinese CHB guideline evolution, with each iteration contributing to progressive improvements in treatment rates. These findings underscore the importance of regular, evidence-based guideline updates and systematic implementation strategies in optimizing CHB management.

Disclosures: Wei Ye: Nothing to Disclose

◆ 1134 | LONGITUDINAL PATTERNS OF QUANTITATIVE HBSAG DECLINE IN A LARGE REAL-WORLD COHORT OF TREATED CHRONIC HEPATITIS B PATIENTS

Sanam Tabataba Vakili[1] Leila Amiri[1] Aaron Vanderhoff[2] Andrew Mendlowitz[1] Grishma Hirode[1] Harry Janssen[3] Adam Gehring[4] Scott Fung[4] Jordan Feld[5], [1]Toronto Centre for Liver Disease, University Health Network, Toronto, Ontario, Canada, [2]Toronto Centre for Liver Disease; Viral Hepatitis Care Network (VIRCAN), University Health Network, [3]Toronto Centre for Liver Disease, University Health Network; Erasmus University Medical Centre, Rott, [4]University Health Network, [5]Toronto General Hospital

Background: Quantitative hepatitis B surface antigen (qHBsAg) levels reflect virologic activity and host immune control in chronic hepatitis B (CHB). Characterizing the kinetics of qHBsAg over time can inform prognosis and response prediction to emerging cure-directed therapies. **Methods:** We conducted a retrospective analysis of adult CHB patients with ≥ 1 qHBsAg measurement and ≥ 1 year of follow-up from April 2010 to May 2022 at a tertiary liver center in Canada. qHBsAg values were log-transformed and changes in qHBsAg (ΔqHBsAg) were standardized by subtracting each patient's baseline level, anchoring all trajectories at 0. Individual linear regression models estimated the slope of Δ(qHBsAg) over time for each patient. Slope distributions were analyzed overall and stratified by baseline qHBsAg levels. Model-predicted and observed group trends were compared to validate fit. **Results:** Among 7,677 CHB patients (56.6% male; mean age 49.8 years), median follow-up was 5.04 years. The median baseline qHBsAg level was 1,110 IU/mL, ranging from 0.05 to 124,925 IU/mL. Overall, 69.6% had qHBsAg <3000 IU/mL, including 84.1% of those over age 50. The mean slope of Δlog(qHBsAg) was –0.210 log IU/mL/year, indicating an overall decline. Patients with low baseline levels (0.05–10 IU/mL) showed the most consistent trajectories, while those $>10{,}000$ IU/mL had steeper declines (–0.437 log/year) but with greater variability. LOESS-smoothed plots revealed uniform reductions in lower qHBsAg categories and erratic trends in those with higher values. Factors associated with rapid qHBsAg decline (>0.25 log IU/mL/year) were identified using multivariable logistic regression; this threshold was selected because it is above the median slope, providing greater sensitivity for detecting covariate associations. Lower baseline qHBsAg (OR = 0.96 per log increase), higher ALT (OR = 1.32), treatment (OR = 1.23), and cirrhosis (OR = 1.23) were independently associated with greater odds of qHBsAg decline >0.25 logIU/year. Age was not a significant predictor in the overall model and sex had a modest effect (Male sex OR = 1.17). In models stratified by baseline qHBsAg level, treatment and baseline

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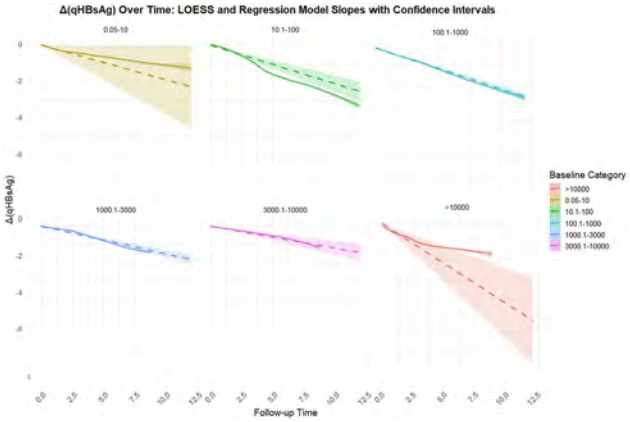
ALT remained strong predictors of more rapid qHBsAg decline in those with baseline levels > 3,000 IU/mL but were also associated with Δlog(qHBsAg) in those with lower baseline qHBsAg levels. **Conclusion:** In this large real-world cohort, qHBsAg levels declined over time in most CHB patients. The rate and consistency of decline were influenced by baseline qHBsAg levels, ALT, treatment, and cirrhosis. Lower baseline levels showed consistent trajectories, while higher levels exhibited variable but deeper declines. These patterns may help guide individualized monitoring and treatment strategies.



Disclosures: Sanam Tabataba Vakili: Nothing to Disclose, Leila Amiri: Nothing to Disclose, Aaron Vanderhoff: Nothing to Disclose, Andrew Mendlowitz: Nothing to Disclose, Grishma Hirode: Nothing to Disclose, Harry Janssen: Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Academic Medical Education: Consultant, H.C. Wainwright & Co: Consultant, Adam Gehring: Aligos Therapeutics: Grant/Research Support, Bluejay Therapeutics: Grant/Research Support, GSK: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology: Grant/Research Support, EVOQ Therapeutics: Grant/Research Support, Arbutus Biopharma: Advisor, Assembly Biosciences: Advisor, Gilead Sciences: Advisor, Virion Therapeutics: Advisor, Aligos Therapeutics: Consultant, Arbutus Biopharma: Consultant, Barinthus Biotherapeutics: Consultant, Bluejay Therapeutics: Consultant, Gilead Sciences: Consultant, GSK: Consultant, Immunocore: Consultant, Roche: Consultant, Vir Biotechnology: Consultant, Virion Therapeutics: Consultant, Scott Fung: Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Abbvie: Advisor, Novo Nordisk: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Grant/Research Support, GSK: Advisor, GSK: Speaking and Teaching, Lupin: Speaking and Teaching, AstraZeneca: Speaking and Teaching, AstraZeneca: Advisor, Jordan Feld: AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support, AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support

◆ 1135 | PROTEOMIC CHARACTERISTICS AND DIAGNOSTIC BIOMARKER IDENTIFICATION IN THE PROGRESSION OF HBV-RELATED LIVER DISEASE

Mengqi Li[1] Wenhao Shi[2] Yiying Zhu[2] Wen Xie[1], [1]Center of Liver Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China, [2]Analysis Center, Chemistry Department, Tsinghua University, Beijing, China

Background: Hepatitis B virus (HBV) infection is a major global public health challenge. HBV-related liver diseases progress through multiple stages, from chronic hepatitis B to cirrhosis and hepatocellular carcinoma (HCC). The changes in plasma protein expression across different disease stages have not been fully explored. This study aims to identify the proteomic characteristics of plasma proteins at different stages of HBV-related liver diseases and explore potential biomarkers for HCC. **Methods:** This study employed data-independent acquisition mass spectrometry, combined with trend clustering and enrichment analysis, to explore changes in plasma protein levels across different disease stages and their biological

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significance. The Least Absolute Shrinkage and Selection Operator regression was used for variable selection, and three machine learning algorithms, including Random Forest (RF), Decision Tree, and Extreme Gradient Boosting, were employed to develop a diagnostic model for HCC. **Results:** Proteomic analysis was conducted on plasma samples from 30 healthy controls, 30 chronic hepatitis B patients, 30 HBV-related cirrhosis patients, and 30 HBV-related HCC patients. The analysis identified four major protein clusters: Cluster I, elevated in chronic hepatitis B, enriched in hemostasis and immune response pathways; Cluster II, elevated in both HBV-related cirrhosis and HCC, enriched in extracellular matrix pathways; Cluster III, showing decreased expression from chronic hepatitis B to cirrhosis and HCC, enriched in hemostasis, metabolism, and immune response pathways; and Cluster IV, upregulated in HCC, enriched in cellular stress response, cell cycle regulation, immune response, and extracellular matrix pathways. The study identified five potential biomarkers for HCC: Transketolase (TKT), Polyadenylate-binding protein 1 (PABPC1), Alpha-1-antichymotrypsin (SERPINA3), Chitinase-3-like protein 1 (CHI3L1), and Papilin (PAPLN). The RF-based diagnostic model (P5) demonstrated optimal performance (AUROC = 0.983, Figure 1), outperforming traditional alpha-fetoprotein testing (AUROC = 0.839). **Conclusion:** This study revealed the proteomic characteristics of plasma proteins at different stages of HBV-related liver disease and developed a diagnostic model for HCC with high diagnostic performance. The identified plasma proteins offer new insights into the mechanisms of disease progression and provide new biomarkers for HCC diagnosis.

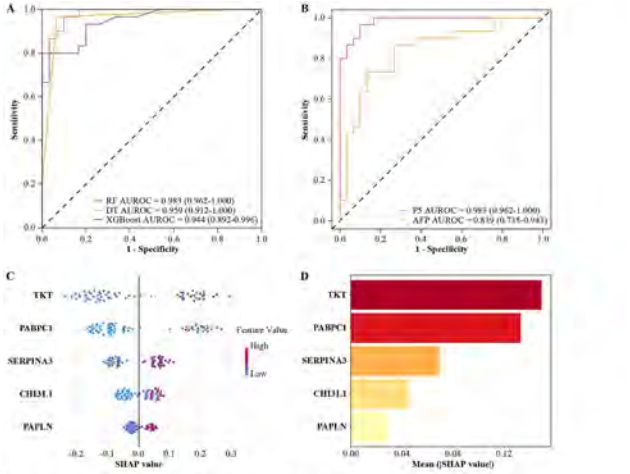

Figure 1 Machine Learning Model Diagnostic Performance and Feature Importance Analysis
AUROC: Area under the receiver operating characteristic curve; RF: Random forest; DT: Decision tree; XGBoost: Extreme gradient boosting; AFP: Alpha-Fetoprotein; TKT: Transketolase; PABPC1: Polyadenylate-binding protein 1; SERPINA3: Alpha-1-antichymotrypsin; CHI3L1: Chitinase-3-like protein 1; PAPLN: Papilin; SHAP: SHapley Additive exPlanations.

Disclosures: Mengqi Li: Nothing to Disclose, Wenhao Shi: Nothing to Disclose, Yiying Zhu: Nothing to Disclose, Wen Xie: Nothing to Disclose

◆ 1136 | SPATIAL COMPARTMENTALIZATION OF HBV AND HDV IN COINFECTED LIVER TISSUE MEDIATED BY HDV-INDUCED SUPPRESSION OF HBSAG NEW SUBMISSION

Soichi Takeda[1] Anirudh Krishnan[1] Davide De Battista[1] Neelam Redekar[2] Hanh Nguyen[1] Sandra Kendra[1] Quan Yu[1] Rana Eltahan[3] David McGivern[3], [1]Hepatic Pathogenesis Section, Laboratory of Infectious Diseases, NIAID, NIH, Bethesda, USA, [2]Integrated Data Science Section, Research Technologies Branch, NIAID, NIH, Bethesda, USA, [3]Office of Blood Research and Review, Center for Biologics Evaluation and Research, FDA

Background: As HDV is a defective virus, which requires HBsAg for virion assembly and propagation, it remains unclear whether hepatocellular carcinoma (HCC) arises from the underlying cirrhosis, direct oncogenic effects of HDV, or a combined effect of HBV and HDV. We investigated the spatial distribution of viral antigens and transcriptional differences in HDV/HBV coinfected vs. HBV-monoinfected patients with HCC. **Methods:** RNAsequencing was performed on paired tumor and nontumorous liver tissues from patients with HDV-associated HCC (n = 4), non-HCC HDV cirrhosis (n = 7), and HBV-associated HCC (n = 11). All HBV HCC patients received nucleos(t)ide analogue antiviral therapy prior to surgery or liver transplantation. *In vivo* molecular findings were complemented by *in vitro* studies. Immunohistochemistry was used to localize viral markers (HDAg, HBsAg, HBcAg, and HDV RNA by *in situ* hybridization). Triple immunostaining with anti-HBsAg and two in-house antibodies generated against HDAg and large HDAg (L-HDAg) was conducted on 46 HDV liver specimens, including 10 HDV HCC (paired tumor and nontumorous tissue) and 26 specimens from the right and left lobes of 8 non-HCC HDV cirrhosis obtained at the time of liver transplantation. **Results:** Confocal microscopy showed variable HDAg expression across patients and tissues, with a predominance of small HDAg (S-HDAg) both within and outside tumors. HBcAg was absent in all tumor and nontumorous tissues from HDV-infected livers, except in one patient with HDV cirrhosis. Among HBV-related HCC cases, HBcAg was detected in a few cells in only one nontumorous sample. *In situ* HDV RNA correlated with the expression of HDAg. Contrary to expectations, HDAg and HBsAg rarely colocalized, suggesting compartmentalization of HDV and HBV within the hepatic microenvironment. Transcriptomic analysis showed distinct molecular signatures with upregulation of genes involved in cell cycle and DNA repair in HDV HCC and metabolism switch-off in HBV HCC. Notably, HDV HCC was characterized by

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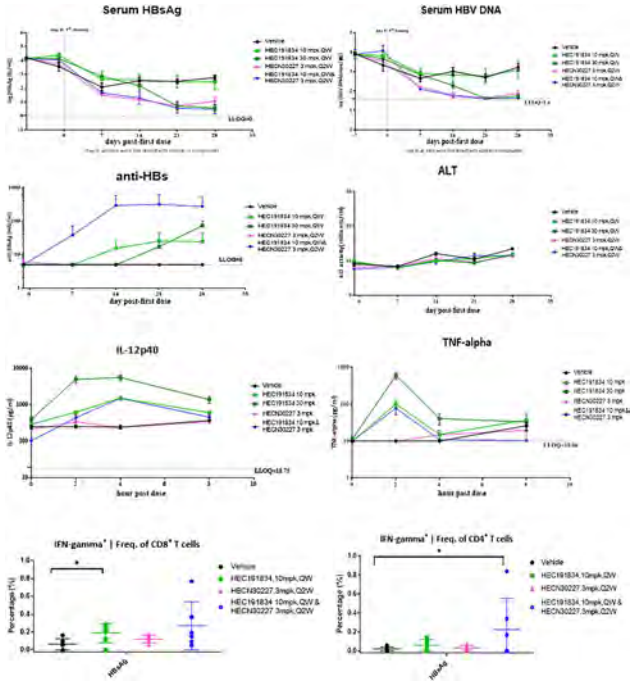
upregulation of host genes previously reported to inhibit HBsAg expression (Hyrina et al.2019) in both tumor and nontumor tissue, compared to HBV HCC. To elucidate the molecular basis for HBsAg suppression in HDAg-infected cells, we interrogated *in vitro* transcriptomic data and found that transfection with an HDV plasmid [pSVL(D3)], in the absence of HBV, into Huh7 cells induced upregulation of host genes involved in HBsAg suppression. **Conclusion:** Our study demonstrates spatial compartmentalization of HDV and HBV within coinfected livers, with minimal colocalization of HDAg and HBsAg at the single-cell level. *In vivo* and *in vitro* analyses reveal that HDV suppresses HBsAg expression through host gene modulation. These findings uncover a mechanism underlying the mutual exclusion of HDV and HBV antigen expression in coinfected hepatocytes and provide new insights into HDV biology and pathogenesis.

Disclosures: Soichi Takeda: Nothing to Disclose, Anirudh Krishnan: Nothing to Disclose, Davide De Battista: Nothing to Disclose, Neelam Redekar: Nothing to Disclose, Hanh Nguyen: Nothing to Disclose, Sandra Kendra: Nothing to Disclose, Quan Yu: Nothing to Disclose, Rana Eltahan: Nothing to Disclose, David McGivern: Nothing to Disclose

◆ 1137 | HEC191834, A HIGHLY SELECTIVE AND POTENT HTLR8 AGONIST, EXHIBITS SYNERGISTIC ANTIVIRAL ACTIVITY WITH SIRNA IN AN AAV-HBV MOUSE MODEL

Pu Wang[1] Guanghua Yan[2] YingLin Zuo[2] Baohua Gu[2] Jing Li[2] Yunfu Chen[2], [1]Sunshine Lake Pharma Co., Ltd., Dongguan 523871, PR China, [2]Sunshine Lake Pharma Co., Ltd., Dongguan

Background: Achieving a functional cure for chronic hepatitis B (CHB) requires reducing hepatitis B surface antigen (HBsAg) and restoring immune responses. HBsAg rebound after small interfering RNA (siRNA) or antisense oligonucleotide therapy highlights the need for immune stimulators. HEC191834, a novel human Toll-like receptor 8 (hTLR8) agonist, was evaluated for its selectivity, immune-modulatory effects, and synergistic antiviral activity with siRNA in preclinical models. **Methods:** HEC191834 selectivity was assessed in hTLR7 and hTLR8 reporter cells. Immune-stimulatory effects were evaluated in hPBMCs and cynomolgus monkeys, and antiviral activity was tested in primary human hepatocytes (PHH) and an AAV-HBV-transduced, hTLR8-humanized mouse model. Mice received 4-week treatments: 1) HEC191834 orally (10 or 30 mg/kg weekly), 2) HECN30227 (HBV-X-targeting siRNA) subcutaneously (3 mg/kg biweekly), or 3) their combination. Viral parameters, ALT, IL-12p40, and TNF-α were measured. IFN-γ^+ T cells were analyzed by intracellular cytokine staining post-HBsAg peptide stimulation. Liver RNA sequencing (RNAseq) assessed gene expression. **Results:** HEC191834 exhibited potent hTLR8 agonism (EC_{50} = 16 nM) with >6250-fold selectivity over hTLR7. It induced IL-12p40, IFN-γ, IL-8 and TNFα in hPBMCs, and the conditioned medium showed inhibitory activity against HBV in PHH. The EC_{50} of HBV DNA, HBV RNA, and HBsAg were 10.6 nM, 8.8 nM, and 127.6 nM, respectively. In cynomolgus monkeys, HEC191834 dose-dependently increased IL-12p40 (0.3–10 mg/kg). In the AAV-HBV mouse model, HEC191834, but not HECN30227, induced IL-12p40, TNF-α, anti-HBs antibodies, and HBV-specific IFN-γ^+ $CD4^+$/$CD8^+$ T cells. Both 30 mg/kg HEC191834 and 3 mg/kg HECN30227 significantly reduced serum HBV DNA and HBsAg compared to controls. Notably, the combination synergistically enhanced anti-HBs and HBV-specific IFN-γ^+ T cells. Serum ALT levels remained unchanged across groups. RNAseq analysis of liver tissue revealed comprehensive effects of HBV infection and drug treatment on antiviral and immune-regulatory pathways. **Conclusion:** HEC191834 is a novel, potent, and selective hTLR8 agonist with synergistic antiviral activity when combined with an HBV-targeting siRNA. These findings support further clinical studies to evaluate its potential for achieving a functional HBV cure.



Disclosures: Pu Wang: Nothing to Disclose, Guanghua Yan: Nothing to Disclose, YingLin Zuo: Nothing to Disclose, Baohua Gu: Nothing to Disclose, Jing Li: Nothing to Disclose, Yunfu Chen: Nothing to Disclose

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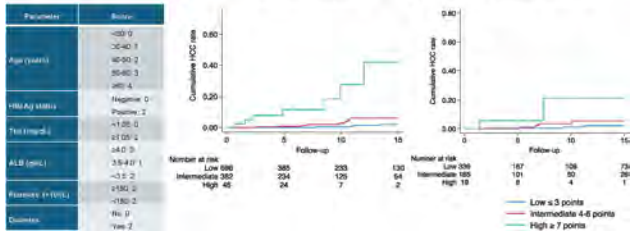
◆ 1138 | IREAL-B AS A SIMPLE RISK SCORE FOR THE PREDICTION OF HEPATOCELLULAR CARCINOMA IN UNTREATED CHRONIC HEPATITIS B PATIENTS WITH INDETERMINATE PHASE: A PRACTICE IMPLICATION

Rui Huang[1] Huy N. Trinh[2] Satoshi Yasuda[3] Angela Chau[1] Mayumi Maeda[1] Ai Thien Do[1] Daniel Q. Huang[4] Takanori Ito[5] Takashi Honda[5] Masatoshi Ishigami[5] Ritsuzo Kozuka[6] Masanori Atsukawa[7] Tsunamasa Watanabe[8] Carmen Monica Preda[9] Cheng-Hao Tseng[10] Sebastián Marciano[11] Pei-Chien Tsai[12] Dong-Hyun Lee[13] Son Do[14] Keigo Kawashima[15] Jian Zhang[16] Haruki Uojima[17] Raluca Ioana Marin[9] Irina Sandra[9] Kaori Inoue[18] Hirokazu Takahashi[18] Jiayi Li[19] Eiichi Ogawa[20] Ramsey Cheung[1] Jie Li[21] Ming-Lung Yu[12] Adrián Gadano[11] Yasuhito Tanaka[22] Yao-Chun Hsu[23] Maria Buti[24] Masaru Enomoto[6] Chao Wu[21] Seng Gee Lim[25] Hidenori Toyoda[3] Mindie Nguyen[1], [1]Stanford University Medical Center, Palo Alto, CA, USA, [2]San Jose Gastroenterology, San Jose, CA, USA, [3]Ogaki Municipal Hospital, Ogaki, Japan, [4]National University Hospital, Singapore, [5]Nagoya University Graduate School of Medicine, Nagoya, Japan, [6]Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan, [7]Nippon Medical School, Tokyo, Japan, [8]St. Marianna University School of Medicine, Kawasaki, Japan, [9]Clinic Fundeni Institute, Romania, [10]E-Da Cancer Hospital/I-Shou University, Kaohsiung, Taiwan, [11]Liver Unit Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [12]Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [13]Good Gang-An Hospital, Busan, South Korea, [14]Digestive Health Associates of Texas, Dallas, Texas, USA, [15]National Institute of Infectious Diseases, Tokyo, Japan, [16]Chinese Hospital, San Francisco, CA, USA, [17]Kitasato University School of Medicine, Sagamihara, Japan, [18]Saga University Hospital, Saga, Japan, [19]Palo Alto Medical Foundation, Mountain View Division, Mountain View, CA, USA, [20]Kyushu University Hospital, Fukuoka, Japan, [21]Nanjing Drum Tower Hospital, Nanjing University, Nanjing, China, [22]Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, [23]E-Da Hospital/I-Shou University, Kaohsiung, Taiwan, [24]Hospital Universitari Valle d'Hebron and Universitat Autònoma de Barcelona, Barcelona, Spain, [25]National University Health System, Singapore

Background: Close to half of patients with chronic hepatitis B (CHB) fall into the indeterminate phase with a higher risk of hepatocellular carcinoma (HCC) than the untreated patients with inactive phase as well as the treated patients with active phase. However, the HCC risk varied significantly among diverse subgroups of indeterminate CHB patients. We developed and validated the risk score to stratify the HCC risk in a large consortium of untreated CHB with indeterminate phase to help inform treatment decision of indeterminate patients. **Methods:** We conducted a retrospective multinational REAL-B cohort study which included 2,075 adult CHB patients with indeterminate phase based on the AASLD guidance from 23 sites of 9 countries/regions. Patients were randomly divided into a derivation dataset (n = 1,384) and a validation dataset (n = 691) with a ratio of 2:1. An HCC risk score was developed based on multivariable Cox regression models and scores system for simplification. Harrell's c-index was used as discrimination. **Results:** A total of 38 (1.8%) patients developed HCC during a median follow-up of 6.54 (IQR: 2.6-12.5) years. The 15-year cumulative HCC incidence rates were 3.58% (95% CI: 2.28%-5.61%) and 3.67% (95%CI: 2.02%-6.63%) in the derivation dataset and validation dataset, respectively. In the derivation dataset, age, platelets, HBeAg status, albumin, total bilirubin and the presence of diabetes were independently associated with HCC development. The indeterminate REAL-B (iREAL-B) score was developed for the prediction of HCC based on those six predictors with good predictability of HCC (Harrell's C-index = 0.84) in the derivation dataset. The predictability of iREAL-B score was similar (Harrell's C-index = 0.77) in the validation dataset. Patients with low (0-3), intermediate (4-6) and high (≥ 7) iREAL-B scores had 15-year cumulative HCC incidence rates of 1.91% (95%CI: 0.07%-5.11%), 6.07% (95%CI: 3.10%-11.7%), 41.94% (95%CI: 18.42%-76.59%) in the derivation dataset and 2.23% (95%CI: 0.67%-7.31%), 5.44% (2.01%-14.30%), 21.3% (4.88%-68.22%) in the validation dataset, respectively (Figure). **Conclusion:** iREAL-B, which is based on 6 simple readily available clinical parameters (age, platelets, HBeAg status, albumin, total bilirubin and the presence of diabetes) can help risk stratify indeterminate patients to inform shared decision making between patients and care providers regarding antiviral treatment.

Figure. Construction and predictive performance of iREAL-B score for prediction of HCC development.



Disclosures: Rui Huang: Nothing to Disclose, Huy N. Trinh: Nothing to Disclose, Satoshi Yasuda: Nothing to Disclose, Angela Chau: Nothing to Disclose, Mayumi Maeda: Nothing to Disclose, Ai Thien Do: Nothing to Disclose, Daniel Q. Huang: Nothing to Disclose, Takanori Ito: Nothing to Disclose, Takashi Honda: Nothing to Disclose, Masatoshi Ishigami: Nothing to Disclose, Ritsuzo Kozuka: Nothing to Disclose, Masanori Atsukawa: Nothing to Disclose, Tsunamasa Watanabe: Nothing to Disclose, Carmen Monica Preda: Nothing to Disclose, Cheng-Hao Tseng: Nothing to

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Disclose, Sebastián Marciano: Nothing to Disclose, Pei-Chien Tsai: Nothing to Disclose, Dong-Hyun Lee: Nothing to Disclose, Son Do: Nothing to Disclose, Keigo Kawashima: Nothing to Disclose, Jian Zhang: Nothing to Disclose, Haruki Uojima: Nothing to Disclose, Raluca Ioana Marin: Nothing to Disclose, Irina Sandra: Nothing to Disclose, Kaori Inoue: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Jiayi Li: Nothing to Disclose, Eiichi Ogawa: Gilead Sciences: Grant/Research Support, Ramsey Cheung: Nothing to Disclose, Jie Li: Nothing to Disclose, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Adrián Gadano: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose, Yao-Chun Hsu: Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Sysmex: Advisor, Abbvie: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Roch: Speaking and Teaching, AsuperBio: Advisor, Grifols: Speaking and Teaching, GlaxoSmithKline: Consultant, AusperBio: Consultant, Maria Buti: Nothing to Disclose, Masaru Enomoto: Nothing to Disclose, Chao Wu: Nothing to Disclose, Seng Gee Lim: Nothing to Disclose, Hidenori Toyoda: AbbVie: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Takeda: Speaking and Teaching, Eisai: Speaking and Teaching, Kowa: Speaking and Teaching, Terumo: Speaking and Teaching, Fujifilm WAKO: Speaking and Teaching, Chugai: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Bayer: Speaking and Teaching, Mindie Nguyen: Nothing to Disclose

◆ 1139 | PROTEOMIC PROFILING IN PREFILLED SYRINGE STUDY DEMONSTRATES BEPIROVIRSEN'S IMMUNE STIMULATORY EFFECT

Jennifer Singh[1] Scott Van Buren[1] Cheng Zhu[2] Johannes Freudenberg[1] Kristen Consalvo[1] Luca Pagliaroli[1] Sohil Joshi[1] Puneet Dhawan[1] Amir Youssef[1] Poonam Shah[3] Jill Walker[4], [1]GSK, Collegeville, PA, USA, [2]GSK, Waltham, MA, USA, [3]GSK, Stevenage, UK, [4]GSK, San Francisco, CA, USA

Background: Bepirovirsen is an investigational antisense oligonucleotide that impacts hepatitis B virus (HBV) infection in three ways by: (1) reducing hepatitis B surface antigen, (2) suppressing viral DNA, and (3) stimulating immune activity. A Phase 1 randomized trial evaluated the relative bioavailability of subcutaneous bepirovirsen when delivered from a vial or a ready-to-use prefilled syringe (PFS) fitted with a safety syringe device (SSD) in healthy participants. Here, serum protein changes at early time points following bepirovirsen administration were evaluated to further elucidate the mechanism of action of bepirovirsen and its role in immune stimulation. **Methods:** This Phase 1, open-label, parallel group study (NCT06058390) randomized (3:3:2:2) 160 healthy adult participants to receive a single 300 mg dose of bepirovirsen from a vial administered by a healthcare professional (HCP; Arm 1), from the PFS SSD administered by an HCP (Arm 2), self-administered using the PFS SSD with training from an HCP (Arm 3), or self-administered using the PFS SSD without training (Arm 4). Proteomics data were generated from participants' serum samples (collected at baseline, 2, 4, 8, 12, 24, and 48 hours post-treatment) using the Olink Explore 1536 Panel (consisting of cardiometabolic, inflammation, neurology, and oncology 384 panels). Linear modeling using the Limma method was applied to investigate immune protein changes across different subgroups. Comparisons were made between each time point versus baseline and across treatment arms, sex, and injection sites (upper arm, abdomen, or thigh [Arm 1, 2] and abdomen or thigh [Arm 3, 4]). Results from this study were then compared with those from an earlier Phase 2a study in patients with chronic HBV infection (NCT02981602). **Results:** Across multiple immune pathways, the majority of proteins downstream of Toll-like receptors (TLR) and select immune protein signatures showed significant induction, with peak induction observed at 24–48 hours post-treatment (Table). Profiling of selected proteins downstream of TLRs showed strong innate immune responses as early as 2 hours post-dose. No systematic differences were observed across treatment arms, but some immune protein profiles differed by sex or injection site. Activated immune proteins identified from the Phase 2a study showed similar stimulation patterns to those identified in this study. **Conclusion:** These data demonstrate that bepirovirsen mediates a strong innate immune response, with the highest activity observed at 24–48 hours, suggesting a sustained immune response that lasts at least 48 hours. The similar immune protein profile changes observed in patients with chronic HBV infection and in healthy volunteers in this study suggests that this immune response is stimulated by bepirovirsen treatment regardless of the presence of HBV. Funding: GSK (219239)

Table. Number of differentially expressed innate immune proteins in serum compared to baseline

Time point, hours	Number of upregulated proteins	Number of downregulated proteins	Total number of differentially expressed proteins
2	5	0	5
4	10	0	10
8	15	0	15
12	19	0	19
24	22	1	23
48	15	1	16

Disclosures: Jennifer Singh: GSK: Employee, GSK: Stock - publicly traded company, Holds two US patents #11,021,502 and #11,873,312: Royalties or patent

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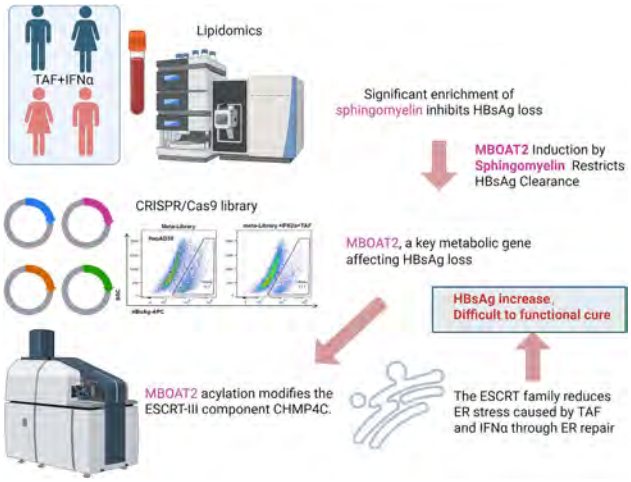
beneficiary, Scott Van Buren: GlaxoSmithKline: Employee, Cheng Zhu: Nothing to Disclose, Johannes Freudenberg: Nothing to Disclose, Kristen Consalvo: GSK: Employee, Luca Pagliaroli: Nothing to Disclose, Sohil Joshi: Nothing to Disclose, Puneet Dhawan: GSK: Employee, Amir Youssef: Nothing to Disclose, Poonam Shah: Nothing to Disclose, Jill Walker: GSK: Employee

◆ 1140 | MBOAT2–ESCRT AXIS LIMITS THE ANTIVIRAL EFFECT OF TENOFOVIR ALAFENAMIDE PLUS INTERFERON-A IN CHRONIC HEPATITIS B

Bei Jiang[1] Zhiqaing Liu[2] Yixuan Wang[2] Mu Qiao[2] Yue Hu[3], [1]Tianjin Second People's Hospital, [2]Shandong Cancer Hospital and Institute, Shandong First Medical University, [3]Tianjin Second People's Hospital Department of Gastroenterology

Background: Pegylated interferon-α (PEG-IFNα) combined with nucleos(t)ide analogues (NAs) such as tenofovir alafenamide (TAF) is widely used to treat chronic hepatitis B virus (HBV) infection, yet ≥70 % of patients fail to achieve functional cure, defined as hepatitis B surface antigen (HBsAg) seroclearance. The contribution of host metabolic genes to this limited response remains poorly understood. **Methods:** A genome-scale CRISPR/Cas9 single-guide RNA library targeting 2,981 human metabolic genes was applied to HBV-infected hepatocytes exposed to tenofovir alafenamide (TAF) plus IFNα to identify regulators of HBsAg clearance. Findings were validated through: (i) time-course mRNA/protein analyses in cell lines and HBV mouse models; (ii) targeted and untargeted lipidomics; (iii) pharmacological or siRNA manipulation of sphingolipid synthesis and MBOAT2 expression; (iv) co-immunoprecipitation and mutagenesis to map MBOAT2 interactions with ESCRT components; and (v) histological and biochemical assessment of liver biopsies from chronically infected patients before and after TAF + PEG-IFNα therapy. **Results:** Treatment with TAF + IFNα progressively elevated intracellular sphingomyelin, which in turn up-regulated MBOAT2 expression in vitro, in AAV mouse models, and in CHB patient biopsies. MBOAT2 emerged as the top hit whose deletion enhanced HBsAg loss under antiviral pressure. MBOAT2 levels remained high even when serum HBsAg declined clinically. Sphingomyelin-driven MBOAT2 bound ESCRT proteins CHMP4C promoted itsacylation-dependent activation, attenuated TAF + IFNα–induced endoplasmic-reticulum stress (diminished IRE1α phosphorylation, reduced BiP, and less ER vacuolization). This process facilitated endoplasmic reticulum membrane repair and fluidity, thereby sustaining HBV-DNA replication and HBsAg secretion. Pharmacologic blockade of sphingomyelin synthesis or genetic silencing of MBOAT2 restored ER-stress signaling and markedly potentiated the antiviral efficacy of TAF + IFNα. **Conclusion:** We delineate a previously unrecognized sphingomyelin–MBOAT2–ESCRT axis that shields HBV from TAF + PEG-IFNα-mediated suppression by dampening ER stress and sustaining HBsAg production. Targeting MBOAT2 or sphingomyelin biosynthesis offers a promising strategy to enhance functional cure rates in chronic HBV infection.



Disclosures: Bei Jiang: Nothing to Disclose, Zhiqaing Liu: Nothing to Disclose, Yixuan Wang: Nothing to Disclose, Mu Qiao: Nothing to Disclose, Yue Hu: Nothing to Disclose

◆ 1141 | THE PROFILE OF HEPATITIS D VIRUS (HDV)-INFECTED PATIENTS RECEIVING A LIVER TRANSPLANT IN THE UNITED STATES AND EUROPE OVER THE PAST TWO DECADES

Zobair Younossi[1] Giacomo Germani[2] Robert Wong[3] Maria Stepanova[1] Fatema Nader[4] Vincent Karam[5] Maria Buti[6] George Papatheodoridis[7] Pietro Lampertico[8] Saleh Alqahtani[9] Linda Henry[1] Patrizia Burra[10], [1]The Global NASH Council, [2]Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy, [3]VA Palo Alto Healthcare System, [4]Center for Outcomes Research in Liver Diseases, CORLD, [5]The European Society for Organ Transplantation, Amsterdam, the Netherlands, [6]Hospital Valle Hebron, [7]First Academic Department of Gastroenterology, Medical School of National and Kapodistrian Univer, [8]University of Milan, [9]Liver, Digestive, and Lifestyle Research Section, and Organ Transplant Center of Excellence, King, [10]3. Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy

Background: Hepatitis D virus (HDV) coinfection with hepatitis B virus (HBV) is a relatively uncommon but an important indication for liver transplantation. The aim was to

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compare clinical presentation and outcomes between patients transplanted with HDV and those who were transplanted for HBV only. **Methods:** Adult liver transplant recipients with HBV from the European Liver Transplant Registry (ELTR) and the U.S. Scientific Registry of Transplant Recipients (SRTR) were included (years 2000-2022). Common clinical parameters and post-transplant mortality were collected and summarized by the presence of HDV coinfection (as determined by the respective listing diagnosis). **Results:** Of 13,093 HBV-infected patients, 2,327 (18%) had HDV coinfection (HDV group) and 10,766 (82%) had HBV mono-infection (HBV group). Overall, a significantly higher number of HDV transplants were reported from European centers than US (24% of all HBV-infected patients from ELTR had HDV vs. 2.6% of all HBV-infected patients from SRTR). In both registries, the proportions of HDV patients among LT recipients with HBV infection remained stable over time in the last 20 years (both trend $p > 0.05$). As compared to the HBV group, HDV liver transplant recipients were significantly younger (mean ± SD age: 48 ± 10 years vs. 54 ± 10 years), had lower BMI (25.4 ± 4.0 vs. 26.3 ± 4.7), and less likely to be male (68% vs. 83%) (all $p < 0.0001$). In addition, fewer HDV patients were listed for liver transplantation with a secondary diagnosis of HCC (27% vs. 44%, $p < 0.0001$), and their MELD scores at the time of transplantation were higher (17.6 ± 7.4 vs. 17.0 ± 9.3, $p < 0.0001$). In this context, ascites was more frequent in HDV (66% vs. 55%, $p < 0.0001$) while the rates of hepatic encephalopathy were similar ($p > 0.05$). Post-transplant mortality was lower in HDV patients: cumulative 15% vs. 27% over median (IQR) of 5.2 (1.3-11.7) years, 1-year 8% vs. 12%, 3-year 14% vs. 20%, 5-year 19% vs. 26%, 10-year 32% vs. 39% (all $p < 0.01$). Similar trends were also observed in the subpopulation of HDV vs. HBV patients without HCC (1-year mortality 8% vs. 14%, 3-year 13% vs. 21%, 5-year 17% vs. 25%, 10-year 29% vs. 38%; all $p < 0.01$) while mortality rates in patients with HCC were similar between HDV and HBV groups (1-year 10% vs. 10%, 3-year 19% vs. 20%, 5-year 25% vs. 28%, 10-year 40% vs. 41%; all $p > 0.05$). **Conclusion:** Compared to HBV mono-infection patients, HDV patients were more often listed for decompensated liver disease and at younger age suggesting the need of effective therapies to suppress HDV replication. Nevertheless, the HDV group appears to have similar or more favorable post-transplant outcomes in comparison to patients transplanted with HBV alone.

Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, Giacomo Germani: Nothing to Disclose, Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Maria Stepanova: Nothing to Disclose, Fatema Nader: Nothing to Disclose, Vincent Karam: Nothing to Disclose, Maria Buti: Nothing to Disclose, George Papatheodoridis: Abbvie: Advisor, Abbvie: Grant/Research Support, Abbvie: Speaking and Teaching, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Genesis: Advisor, Genesis: Speaking and Teaching, Gilead: Advisor, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GlaxoSmithKline: Advisor, Ipsen: Advisor, Ipsen: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Roche: Advisor, Roche: Speaking and Teaching, Takeda: Advisor, Albireo: Advisor, Amgen: Advisor, BioArs: Advisor, Elpen: Advisor, Janssen: Advisor, Merck Sharp & Dohme: Advisor, Vir Biotechnology: Advisor, Gilead: Grant/Research Support, Takeda: Grant/Research Support, Vianex: Grant/Research Support, Pietro Lampertico: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Linda Henry: Nothing to Disclose, Patrizia Burra: Nothing to Disclose

◆ 1142 | A NOVEL MRNA-BASED IMMUNOTHERAPY ACHIEVES COMPLETE ELIMINATION OF HUMAN HEPATITIS B VIRUS IN CHRONIC HBV MOUSE MODELS

Gongxin He[1] Zoe Jia Meng[1] Wenyuan Fan[1] Jialin Chen[1] Xiaowu Chen[2] Ren Zhu[1] Yuchun Nie[1],
[1]Shanghai CureGene Pharmaceutical Co, Ltd,
[2]Shanghai CureGene Pharmaceutical Co

Background: Chronic hepatitis B (CHB) remains a formidable global public health challenge, with ~250 million patients and more than 1.2 million new infections each year. Despite recent advances in antiviral treatments-including siRNA and antisense oligonucleotide (ASO) therapies in clinical trials, achieving functional cure remains elusive. Current consensus underscores the necessity of combining immunomodulatory strategies with direct-acting antivirals to substantially improve functional cure rates. **Methods:** We developed two mRNA-based immunomodulators (IMs) and evaluated their therapeutic potential in combination with entecavir and either a siRNA (Elebsiran) or an ASO (Bepirovirsen) in two distinct chronic HBV mouse models for elimination of HBV both in the periphery and intrahepatic compartment. **Results:** Combination therapies containing one of the IMs led to a rapid and profound decline in HBsAg and HBV DNA, whereas prophylactic HBV vaccine (Engerix) had minimum impact on these viral markers. Remarkably, these antiviral effects persisted for at least 10 weeks after treatment discontinuation, with no viral rebound observed (Figure 1). Further, HBcAg immunostaining in the liver sections at two timepoints (post last dosing and 10 weeks later) clearly demonstrated durable intrahepatic viral control. Consistent antiviral effects were demonstrated in both AAV-HBV and transgenic mouse models. Combinations with either siRNA or ASO yielded similar results. Treatments with siRNA or

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ASO alone showed rapid viral rebound after treatment discontinuation. Notably, seroconversion was also observed in animals receiving combination therapies. **Conclusion:** Our study demonstrated that either novel IMs, when used in combination with direct antivirals, achieved a rapid, robust, and sustained suppression of HBV infection in chronic mouse models. We observed rapid and sustained declines in HBsAg and HBV DNA in plasma and HBcAg in the liver. Unlike treatments lacking the IMs, which only induced a rapid yet transient HBsAg and HBV DNA decline followed by a rapid rebound of these viral markers once the treatments were discontinued, our approach clearly promotes durable viral control and clearance of HBV from the mouse models mediated by HBV-specific immune responses (see the other poster from CureGene). These findings highlight the transformative potential of mRNA-based immunotherapy to significantly improve functional cure rates in chronic hepatitis B patients.

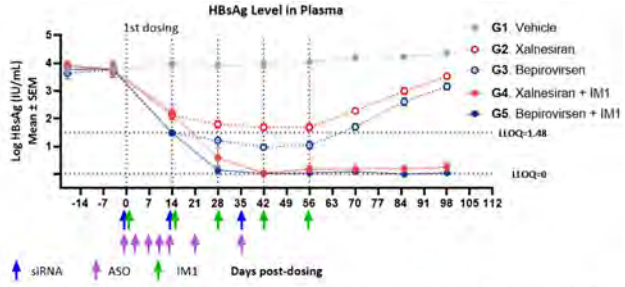

Fig 1. HBsAg levels in the AAV-HBV mouse model after treatment with G1 (vehicle), G2 (Xalnesiran), G3 (Bepirovirsen), G4 (Xalnesiran and IM1) or G5 (Bepirovirsen and IM1). Arrows indicate days of dosing with either siRNA/ASO (blue) or IM1 (green). LLOQ, lower limit of quantification.

Disclosures: Gongxin He: Nothing to Disclose, Zoe Jia Meng: Nothing to Disclose, Wenyuan Fan: Nothing to Disclose, Jialin Chen: Nothing to Disclose, Xiaowu Chen: Shanghai CureGene Pharmaceutical Co: Employee, Ren Zhu: Nothing to Disclose, Yuchun Nie: Nothing to Disclose

◆ 1143 | THE SAFETY AND EFFICACY PROFILE OF CANOCAPAVIR IN A PHASE 2 TRIAL: A CAPSID ASSEMBLY MODULATOR FOR LOW-LEVEL VIREMIA TREATMENT

Yanhang Gao[1] Ge Yu[1] Baini Li[2] Bin He[2] Fei Kong[1] Zhihong Lu[2] Huanming Chen[2] Man-Fung Yuen[3] Junqi Niu[1], [1]The First Hospital of Jilin Uiversity, [2]Shanghai Zhimeng Biopharma Inc., [3]The University of Hong Kong

Background: Canocapavir is a hepatitis B virus (HBV) capsid assembly modulator with a novel pyrazole chemical structure. It showed a desired pharmacokinetics and safety profile in Phase 1 studies. The Phase 2 study of Canocapavir (NCT05484466) was conducted to evaluate its safety, tolerability, and efficacy in low-level viremia (LLV) patients with Entecavir (ETV)-treated chronic hepatitis B (CHB) patients. **Methods:** Non-cirrhotic, ETV-treated CHB patients with HBV DNA levels $< 2{,}000$ IU/mL but ≥ 50 IU/mL were randomized to 50 mg or 100 mg Canocapavir once daily or matching placebo. Treatment was stratified by hepatitis B e antigen (HBeAg) status. After 48 weeks of treatment, all subjects are set to continue taking ETV as monotherapy for a 12-week follow-up. The efficacy endpoints included the percentage of subjects who achieved a complete virologic response (CVR), as defined by a serum HBV DNA level of ≤ 10 IU/mL, at the end of the 24/48-week, and the time to achieve CVR in each group. **Results:** A total of 83 subjects were randomized, with one subject excluded from full analysis set (FAS) due to the absence of valid post-dose efficacy data. The demographic characteristics of 82 subjects (FAS) were mean age 40.6 years; male 64.6 %; HBeAg positive 79.3%. The percentage of subjects reported at least one TEAEs was similar among three treatment groups and the majority of TEAEs were mild or moderate (CTAE 5.0 Grade 1 or 2) in severity. There were 6 SAEs, 2 from the 100 mg cohort and 4 from the placebo, and all SAEs were considered to be not related or unlikely related. No case of ALT flare was observed. At week 24, the percentages of patients who achieved CVR were 14.3%, 46.2%, and 82.1% in the placebo, 50 mg, and 100 mg cohorts, respectively. At week 48, the percentages were 10.7%, 53.8%, and 78.6%, respectively. The 100 mg cohort exhibited the most rapid decline in HBV DNA, attaining CVR with a median of 3.07 weeks. **Conclusion:** Current results indicate that adjunctive treatment of Canocapavir with ETV was generally well tolerated and effective for LLV patients with reduced HBV DNA to less than 10 IU/mL and maintained. Canocapavir enhanced viral suppression when combined with ETV. These findings support the further development of Canocapavir for the treatment of CHB.

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◆ 1144 | HEPATITIS B SURFACE ANTIGEN LOSS IS ASSOCIATED WITH REVERSAL OF SYSTEMIC AND INTRAHEPATIC B-CELL DYSREGULATION IN CHRONIC HEPATITIS B

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Background: Hepatitis B virus (HBV) infection remains a major global health issue and can lead to chronic hepatitis B (CHB). Hepatitis B surface antigen (HBsAg) seroclearance is associated with improved clinical outcomes and is considered a functional cure. This study investigates B-cell phenotype, function, and dynamics in patients with CHB, focusing on their potential contribution to HBsAg loss. **Methods:** Patients and Methods: In this prospective and longitudinal study, 114 individuals were included: 21 patients who achieved HBsAg loss (HBsAg-), 50 untreated CHB patients, 20 nucleos(t)ide analogs-treated CHB patients, and 23 healthy controls. Plasma cytokines and markers of B-cell exhaustion were quantified using ELISA and Meso Scale Discovery assays. B-cell subsets were assessed using flow cytometry. Additionally, immunohistochemistry staining and digital image analysis was performed on liver tissue to examine the hepatic immune microenvironment. **Results:** Untreated CHB patients displayed elevated plasma levels of TNFα, IL-10, soluble BAFF, and G-CSF, which normalized in HBsAg- individuals. Phenotypically, CHB patients had reduced frequencies of $CD19^+$ $CD27^+CD38$^hi plasma B cells and increased $CD19^+$ $CD10^+$ $CD27^-$ $CD21^-$ atypical memory B cells compared to both controls and HBsAg- individuals. HBsAg-specific B-cell analyses further confirmed a higher frequency of atypical B cells in CHB patients relative to treated and healthy individuals. Longitudinal analyses revealed a progressive increase in atypical B cells in untreated CHB patients, while HBsAg- individuals showed a reduction in atypical B cells alongside with an increase in plasma B cells. In liver tissue, CHB patients exhibited increased infiltration of B cells and formation of tertiary lymphoid structures all of which were normalized in HBsAg-. **Conclusion:** These findings indicate systemic and intrahepatic B-cell dysregulation in CHB, with functional and phenotypic restoration in patients who cleared HBsAg. These insights may support future therapies aiming to enhance immune control of HBV.

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1145 | GAPS IN HEPATITIS B TREATMENT AMONG U.S. VETERANS: A RETROSPECTIVE ANALYSIS WITHIN THE VETERANS HEALTH ADMINISTRATION

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Background: Chronic hepatitis B (HBV) continues to be a leading cause of liver disease morbidity and mortality. Despite effective antiviral therapies, linkage to care and treatment adherence continues to be suboptimal nationally. Veterans are a unique cohort with access to integrated care through the Veterans Health Association (VHA). Treatment gaps of the VHA in accordance to societal guidelines remain unclear. **Methods:** Veterans with HBsAg positivity, elevated ALT, and HBV viremia were identified. Patients were stratified based on cirrhosis status via ICD 10 codes or calculated Fibrosis-4 scores, and other comorbidities. Treatment eligibility was assessed per AASLD guidelines. Subgroup analyses examined disparities by race/ethnicity, mental health comorbidities, and rural vs. urban residence. **Results:** Of 57,403 veterans with a positive HBV sAg, 3,366 had both an elevated ALT and HBV PCR level (5.8%), and 7,867 had Hepatocellular Carcinoma (HCC) or Cirrhosis (13.7%). In total, there were 9,715 veterans treatment eligible (16.92%) per AASLD guidelines. Among these, 4,017 were treated (41%). Veterans with cirrhosis were less likely to be treated (35%, $P < 0.001$). Non-hispanic white veterans (65%) and Hispanic or Latino veterans (65%) were less likely to be treated ($P < 0.0001$) compared to Asian veterans (67%). Veterans residing in rural areas as indicated by geospatial codes were less likely to be treated (67%) compared to urban (55%) residing veterans ($P < 0.0001$). Patients with AUD as identified by AUDIT-C were less likely to be treated (62%, $P < 0.0001$). And when comparing AUD with other mental health related comorbidities (i.e. depression, anxiety, and etc) or substance use disorder, veterans with AUD was also less likely to be treated for HBV (39%, $P < 0.0001$). Patients with HIV were more likely to be treated (44%, $P < .0001$), whereas veterans who were treated for HCV were less likely to be treated for HBV (28%, $P < .0001$). There was no detectable association between treatment for those with comorbid metabolic associated steatitic liver disease ($P = 0.69$). **Conclusion:** Despite centralized care within the VHA, major treatment gaps persist for HBV-infected veterans. Racial, geographic, and psychosocial disparities potentially impact treatment uptake. Targeted strategies are needed to address these inequities and improve HBV outcomes within the VHA.

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Table 1: Demographics of HBV Treatment Eligible Veterans per AASLD guidelines

				N = 9715		
		No HBV Rx	Yes HBV Rx	Total		
Gender	Female	232 (63%)	137 (37%)	369	4%	
	Male	5466 (58.5%)	3880 (41.5%)	9346	96%	P = 0.09
Ethnicity	Non-Hispanic White	3172 (65%)	1702 (35%)	4874	50%	
	Non-Hispanic Black	1849 (54%)	1579 (46%)	3428	35%	
	Hispanic or Latino	239 (65%)	129 (35%)	368	4%	
	Asian	158 (32%)	333 (67%)	491	5%	
	Other	280 (51%)	274 (49%)	554	6%	P <0.0001
Rurality vs. Urban	Rural	1746 (67%)	850 (33%)	2596	27%	
	Urban	3673 (55%)	2957 (45%)	6630	68%	P <.0001
Cirrhosis	No	587 (32%)	1261 (68%)	1848	19%	
	Yes	5111 (65%)	2756 (35%)	7867	81%	P <.0001
HIV	No	2282 (63%)	1327 (37%)	3609	37%	
	Yes	3416 (56%)	2690 (44%)	6106	63%	P <.0001
Treatment of HCV	No	4027 (55%)	3342 (45%)	7369	76%	
	Yes	1671 (71%)	675 (28%)	2346	24%	P<.0001
MASH/MASLD	No	2501 (59%)	1747 (41%)	4248	44%	
	Yes	3197 (58%)	2270 (42%)	5467	56%	P = 0.6937
Alcohol Use Disorder (AUD)	No	1774 (53%)	1580 (47%)	3364	35%	
	Yes	3924 (62%)	2427 (38%)	6351	65%	P<0.0001
No Mental Health Comorbidity		569 (53%)	502 (47%)	1071	11%	P<.0001
Non-AUD/Substance Use Disorder		288 (53%)	251 (47%)	539	6%	
AUD/SUD Only		814 (61%)	510 (39%)	1324	14%	
Any Mental Health Comorbidity		4027 (59%)	2754 (41%)	6781	70%	

Disclosures: Phillip Chen: Nothing to Disclose, Steven-Huy Han: Madrigal: Speaking and Teaching

1146 | MITOCHONDRIAL RESPIRATORY CHAIN REGULATES HBV AUTOPHAGIC DEGRADATION THROUGH DUAL MODULATION OF LYSOSOMAL ACIDIFICATION

Zhiqiang Wei[1] Xueyu Wang[1] Yanying Yan[1] Minwei Li[1] Zhengyun Xiao[1] Guohua Lou[1] Zhenggang Yang[1] Min Zheng[1], [1]Zhejiang University

Background: Mitochondria are crucial organelle involved in cellular homeostasis in both health and a wide range of diseases. Mitochondrial abnormalities have been observed in the hepatocytes of CHB patients. Given that mitochondria serve as the central hub of cellular signaling pathways, mitochondrial dysfunction inevitably results in significant alterations. However, the role of mitochondrial dysfunction in the persistence of viral replication remains unclear. **Methods:** We tested the role of mitochondrial dysfunction in viral replication in vivo and in vitro. **Results:** Both mitochondria and lysosomes were dysfunctional in HBV-replicating cells. Moreover, HBV replication inhibited mitochondrial respiratory chain both *in vitro* and *in vivo*. Inhibition of mitochondrial respiratory complex I activity using rotenone (Rot) increased HBV replication and decreased autophagic degradation capacity *in vitro* and *in vivo*. Mechanistically, elevated mitochondrial reactive oxygen species (mtROS) levels by Rot treatment or SOD2 knockdown led to deteriorated lysosomal membrane permeabilization, which elevated lysosomal pH and promoted HBV replication. While scavenging mtROS with mitoquinone (mitoQ) and mitoTEMPO (mitoT) had the opposite effect. Additionally, mitochondrial dysfunction reduced mitochondrial ATP production and diminished mitochondria-lysosome contacts. Obstructing mitochondrial ATP synthesis with Oligomycin A treatment or disruption of mitochondria-lysosome contacts with vacuolar protein sorting 13 A (VPS13A) knockdown resulted in lysosomal alkalinization and increased HBV replication by inhibiting vacuolar (H+)-adenosine triphosphatase (v-ATPase) assembly in an mtROS-independent manner. Ultimately, inhibition of mitochondrial complex I facilitated HBV secretion by promoting endosomal trafficking of HBV components. **Conclusion:** Mitochondrial function plays a crucial role in HBV autophagic degradation. HBV impairs mitochondrial function, leading to a reduction in the lysosomal degradation capacity, which may hinder effective clearance of the virus.

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1147 | INTEGRATED CARE PATHWAYS FOR HEPATITIS B: A HOLISTIC CO-DESIGNED SERVICE FOR PEOPLE LIVING WITH HEPATITIS B IN ENGLAND

Stuart Flanagan[1] Daniel Forton[2] Doug Macdonald[3] Binta Sultan[1] Jessica Carter[4] David Leeman[5] Ruth Simmons[5] Kosh Agarwal[6] Bo Wang[7] Patrick Kennedy[8] Ashley Brown[9] Douglas Thorburn[3] Sital Shah[6] Helen Boothman[10] Julian Surey[11] Kabir Sandhu[12] Nina Van Syl[13] Alice Ward[7] Amy Bowkett[14] Katherine McNaughton[15] Gary Dark[14] Stephen Hindle[16] Carrie Gardner[16] Ian Jackson[16] Rachel Hill-Tout[16] Simon Barton[16] Denis Onyango[17] Rachel Halford[18] Vanessa Hebditch[19] Supa Chantschool[20] Claire Martin[20] Joy Ko[1], [1]Central & North West London NHS Foundation Trust, [2]St George's Hospital, [3]Royal Free Hospital NHS Trust, [4]Clerkenwell Medical Practice, London, [5]UK Health Security Agency, [6]Kings' College Hospital NHS Trust, [7]Guys & St Thomas' NHS Trust, [8]Barts and The London

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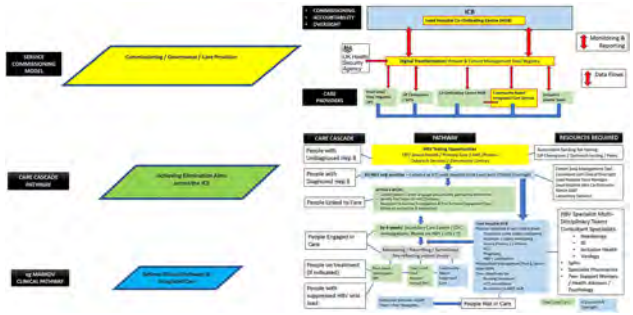
Background: The success of the Emergency Department opt-out Blood Borne Virus testing programme in England has led to >4800 people being newly diagnosed with Hepatitis B Virus (HBV), and >1100 identified as 'not in care'. This represents merely one facet of the undiagnosed HBV population. Currently viral hepatitis services are significantly challenged with increasing HBV diagnoses. There is an urgent need to develop a service specification for specialised adult outpatient HBV services providing a template clinical pathway as well as supporting individuals to stay well, remain engaged in care whilst ensuring equitable access. **Methods:** In 2024, NHS London established the HBV Pathway Development Task & Finish Group to develop holistic pathways and services for people living with this disease. More than 50 stakeholders were consulted, including people with lived experience, British Liver Trust, World Hepatitis Alliance, clinicians, allied healthcare professionals, General Practitioners, UKHSA and Integrated Care Board members. Representatives from each stakeholder group contributed to the Task & Finish outputs. Six areas were identified as being under resourced: 1. Presence of the patient voice in decision making. 2. Placement of specialised HBV care within Integrated Care Systems. 3. Agreed Standards of Equitable Care. 4. Data Management & Cohort Management Tools. 5. Engagement Support. 6. Role of Primary care and community-based care. **Results:** The Task & Finish Group developed: 1. A co-designed HBV template service model to provide care for patients from diagnosis to assessment, treatment, monitoring, community based integrated care and the vaccination of contacts. 2. A template digital solution for a patient cohort management tool and patient registry to provide oversight of all individuals identified as HBV SAg positive within the ICS, to ensure engagement can be supported and case cascade outcomes collated from a plurality of providers. 3. A workforce solution to include specialist expertise, people with lived experience, and administrative support. **Conclusion:** The NHS London Pathways group co-designed a care model (figure 1) to ensure quality of life and wellbeing outcomes for people living with HBV are maximised and that negative outcomes (cirrhosis, hepatocellular carcinoma, transplantation, death) are minimised. This model enshrines that people with HBV are central to decisions about their health and social care and that information must be culturally and language competent (in recognition of the diverse backgrounds of those living with HBV). To achieve WHO HBV elimination targets, co-designed models of care must be priority for Integrated Care Systems and resourced appropriately.



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1148 | ESTIMATING POSTPARTUM TREATMENT-ELIGIBLE POPULATION IN HIGHLY VIREMIC HBV-INFECTED WOMEN UNDER UPDATED GUIDELINES

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Background: Short-term antiviral therapy during pregnancy is now a standard strategy to prevent mother-to-child transmission among highly viremic hepatitis B virus (HBV)-infected women. Postpartum alanine aminotransferase (ALT) elevations or flares are commonly observed in these women, regardless of whether they received antiviral therapy during pregnancy. Recently updated guidelines have lowered the HBV DNA and ALT thresholds for initiating treatment. This study aims to estimate the postpartum treatment-eligible population under the expanded treatment eligibility criteria. **Methods:** A cohort of 351 HBV-infected mothers with high viral loads was followed for up to one year postpartum. Of these, 248 received tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) from 30-32 gestational weeks until 2-4 weeks postpartum. The remaining 103 women did not receive any antiviral therapy during pregnancy. Serum ALT levels and HBV viral loads were measured at 6 and 12 months postpartum. During postpartum follow-up, these women received standard care for chronic hepatitis B and antiviral treatment was initiated or re-initiated according to Taiwan's National Health Insurance treatment criteria, which largely aligns with the APASL guidelines. The proportion of women meeting treatment eligibility was estimated based on the AASLD guidelines and the expanded criteria introduced in the 2024 WHO guidelines. **Results:** At six months postpartum, 12.3% (43/351) of women met the AASLD treatment criteria, while 69.2% (243/351) met the WHO criteria. There were no significant differences in eligibility rates between women who received antiviral therapy during pregnancy and those who did not. At 12 months postpartum, 9.1% met the AASLD criteria and 51.5% met the WHO criteria. Among women who received antiviral therapy during pregnancy, the proportions meeting either criterion did not differ between those treated with TDF and those treated with TAF. At one year postpartum, 11.9% of women were receiving antiviral treatment under standard care, closely aligning with the proportion meeting the AASLD criteria. **Conclusion:** Under the expanded treatment eligibility criteria, the proportion of highly viremic mothers eligible for postpartum antiviral treatment increased from 9-12% to 51-69% at 6-12 months postpartum. Enhanced monitoring and increased awareness among both patients and healthcare providers are essential for optimizing postpartum care in women with chronic hepatitis B and advancing global HBV elimination efforts.

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1149 | SERIAL INCREASES OF ALPHA-FETOPROTEIN LEVELS PREDICT THE RISK OF CHRONIC HEPATITIS B-RELATED HEPATOCELLULAR CARCINOMA

Tung-Hung Su[1] Yun-Chun Wu[2] Shang-Chin Huang[3] Chun-Ming Hong[3] Shih-Jer Hsu[4] Tai-Chung Tseng[1] Chen-Hua Liu[4] Hung-Chih Yang[4] Chun Jen Liu[4] Pei-Jer Chen[1] Jia-Horng Kao[4], [1]National Taiwan University Hospital, [2]Roche Products Ltd, Taipei, Taiwan, [3]National Taiwan University, [4]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

Background: Alpha-fetoprotein (AFP) has been used as a diagnostic and prognostic marker for hepatocellular carcinoma (HCC). However, the low sensitivity limits its usefulness for HCC surveillance. In this study, we aimed to evaluate the serial changes of AFP as a predictive marker for HCC and whether it could perform better than a single AFP measurement. **Methods:** We conducted a retrospective cohort study to screen eligible patients with chronic hepatitis B followed in a tertiary medical center in Taiwan from 2006 to 2021. They received regular HCC surveillance with abdominal ultrasonography and AFP biannually. Those with prior liver malignancies, follow-up less than 1 year, and pregnant women were excluded. Several time-varying AFP parameters were generated from longitudinal AFP measurements. These include the last recorded values, average values, and slope of change over various time windows. The slope would be assigned as zero if there is only a single AFP measurement. A Cox proportional hazards model with time-dependent AFP parameter was built to identify the risk predictors of HCC incidence. Statistical analysis was performed using the R statistical software. **Results:** Overall, 42,552 patients with chronic hepatitis B were screened, after a 10% random sampling and excluding ineligible patients, and finally, 3258 patients were included for further analyses. The median age was 50 years, and 56% were men. In this cohort, 5.7% had cirrhosis, 4.9% had HCV-coinfection, and 29.9% received anti-HBV therapy. After a median follow-up of 7.8 years, 125 patients developed HCC. Older age, male sex, cirrhosis, diabetes, a 6-month AFP increase rate, and HBV antiviral therapy were factors predictive of HCC. After adjustment for confounding factors, the 6-month AFP increase rate (HR: 1.02, $P = 0.003$) was predictive for the development of HCC with an AUROC of 0.845. It was also confirmed in a subgroup of patients with two or more AFP measurements as a sensitivity analysis. Before HCC development, the last 6-month AFP increase rate was 0.41 vs. 0.01 ng/mL in the HCC and non-HCC patients, respectively. **Conclusion:** A 6-month AFP increase rate is a significant predictor for the development of HCC in patients with chronic hepatitis B. AFP should be serially monitored and judged to improve HCC surveillance.

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Table 1. The risks for the development of HCC among HBV patients

Variable	Univariate Model		Multivariable Model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Cirrhosis	8.68 (5.94, 12.68)	<0.001	4.51 (2.99, 6.80)	<0.001
Age at HBV diagnosis (years)	1.05 (1.04, 1.07)	<0.001	1.05 (1.03, 1.06)	<0.001
Male	3.46 (2.20, 5.44)	<0.001	2.98 (1.89, 4.72)	<0.001
Diabetes	3.35 (2.22, 5.06)	<0.001	1.80 (1.17, 2.76)	0.007
The slope of AFP within 6 months before the event with a 3-month latent period (ng/ml per month)	1.02 (1.00, 1.03)	0.047	1.02 (1.00, 1.04)	0.03
The slope of ALT within 6 months before the event with 3-month latent period (ng/ml per month)	1.00 (1.00, 1.00)	0.734	1.00 (1.00, 1.00)	0.70
HBV drug	2.90 (2.04, 4.13)	<0.001	2.05 (1.39, 3.01)	<0.001
AUC (Concordance)			0.845	

Disclosures: Tung-Hung Su: Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Merck Sharp and Dohme: Speaking and Teaching, Roche: Speaking and Teaching, Sysmex: Speaking and Teaching, Eisai: Speaking and Teaching, Yun-Chun Wu: Nothing to Disclose, Shang-Chin Huang: Gilead Sciences: Speaking and Teaching, Chun-Ming Hong: Nothing to Disclose, Shih-Jer Hsu: Nothing to Disclose, Tai-Chung Tseng: Nothing to Disclose, Chen-Hua Liu: Nothing to Disclose, Hung-Chih Yang: Nothing to Disclose, Chun Jen Liu: Nothing to Disclose, Pei-Jer Chen: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose

1150 | TEMPORAL ATTENUATION OF THE PARABOLIC ASSOCIATION BETWEEN BASELINE HBV DNA AND HCC RISK FOLLOWING ANTIVIRAL THERAPY IN CHRONIC HEPATITIS

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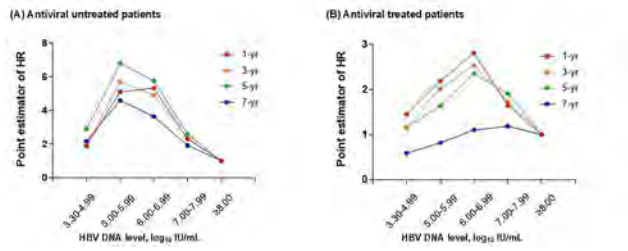
Background: A non-linear parabolic association between baseline HBV DNA levels and hepatocellular carcinoma (HCC) risk has been reported, regardless of antiviral treatment. However, it remains unclear whether this association persists over time after initiating antiviral therapy. This study aimed to evaluate the temporal evolution of the relationship between baseline HBV DNA levels and HCC risk at various landmark time points in patients with chronic hepatitis B (CHB). **Methods:** In this multicenter retrospective cohort study of 9,904 non-cirrhotic CHB patients with baseline HBV DNA levels $\geq$2,000 IU/mL (4,888 antiviral-treated and 5,016 untreated), we performed time-dependent landmark analyses at 1, 3, 5, and 7 years after cohort entry. Multivariable Cox regression was used to evaluate the association between baseline HBV DNA levels, categorized into discrete groups, and subsequent HCC risk at each time point, stratified by antiviral treatment status. **Results:** During a median follow-up of 7.4 and 8.6 years, 202 antiviral-treated (4.1%) patients and 322 untreated (6.4%) patients developed HCC, respectively. Among untreated patients, the parabolic association between baseline HBV DNA and HCC risk persisted across all landmark time points, with the highest risk observed at moderate viral loads (6.00–6.99 $\log_{10}$ IU/mL: hazard ratio [HR], 5.32; $p < 0.001$ at 1-year, HR, 5.70; $p < 0.001$ at 3-year, HR, 6.81; $p < 0.001$ at 5-year, and HR, 4.59; $p < 0.001$ at 7-year landmark), compared with HBV DNA levels $\geq$8.00 $\log_{10}$ IU/mL. In contrast, among antiviral-treated patients, the parabolic association progressively attenuated over time (HBV DNA 6.00–6.99 $\log_{10}$ IU/mL: hazard ratio [HR], 2.81; $p < 0.001$ at 1-year, HR, 2.54; $p = 0.001$ at 3-year, HR, 2.36; $p = 0.02$ at 5-year, and HR, 1.10; $p = 0.83$ at 7-year landmark). At the 7-year landmark, the relationship between baseline HBV DNA and HCC risk had flattened, indicating no significant difference in HCC risk across baseline viral load categories. **Conclusion:** The parabolic association between baseline HBV DNA levels and HCC risk persists in untreated patients but progressively flattens over time with antiviral therapy. These findings suggest that antiviral treatment mitigates HBV DNA–driven hepatocarcinogenesis, supporting earlier initiation of therapy in CHB patients.

Figure. Temporal association between baseline HBV DNA levels and HCC risk. (A) Antiviral untreated patients and (B) antiviral treated patients. HBV, hepatitis B virus; HCC, hepatocellular carcinoma.



Disclosures: Hyeyeon Hong: Nothing to Disclose, Won-Mook Choi: Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, Roche: Consultant, Gi-Ae Kim: Nothing to Disclose, Jonggi Choi: GILEAD SCIENCE: Grant/Research Support, Gwang Hyeon Choi: Nothing to Disclose, Yun Bin Lee: Eisai: Consultant, Gilead Sciences: Consultant, Roche: Consultant, Chong Kun Dang Pharmaceutical Corporation: Grant/Research Support, Samil Pharmaceutical: Grant/Research Support, Dong Hyun Sinn: Nothing to Disclose, YOUNG-SUK LIM: Nothing to Disclose

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1151 | HEPATITIS B SURFACE ANTIGEN LEVEL IDENTIFIES INACTIVE CHRONIC HEPATITIS B PATIENTS WITH HCC RISK BELOW SURVEILLANCE THRESHOLD

Tai-Chung Tseng[1] Shang-Chin Huang[1] Mei-Hung Pan[2] Chun Jen Liu[1] Chien-Jen Chen[2] Tung-Hung Su[1] Hung-Chih Yang[1] Chen-Hua Liu[1] Pei-Jer Chen[1] Hwai-I Yang[2] Jia-Horng Kao[1], [1]National Taiwan University Hospital, [2]Academia Sinica, Taipei, Taiwan

Background: Chronic hepatitis B (CHB) is a major global health concern, primarily due to hepatocellular carcinoma (HCC) development. This study aimed to identify inactive CHB patients with negligible HCC risk using hepatitis B surface antigen (HBsAg) levels, which is the key to define partial HBV cure. **Methods:** Data from 2674 inactive CHB patients (non-cirrhotic, HBeAg-negative, normal ALT, HBV DNA <2000 IU/mL) in the ERADICATE-B and REVEAL-HBV cohorts were analyzed. The primary endpoint was HCC development, with HBsAg levels used to identify patients with annual HCC risk $<0.2\%$. **Results:** Over a median follow-up of 26.3 years, 76 patients developed HCC. Among 989 inactive CHB patients with HBsAg <100 IU/mL, the annual HCC incidence was 0.08% (95% CI: 0.05%-0.13%), lower than those with HBsAg ≥ 100 IU/mL (adjusted HR: 0.35, 95% CI: 0.21-0.61). Their HCC risk was lower than the recommended threshold for HCC surveillance. Notably, even for older patients recommended for HCC surveillance, those with HBsAg levels <100 IU/mL were associated with HCC risk lower than the surveillance threshold. After 1:4 propensity-score matching, the risks of HCC and liver-related mortality were comparable to those of the NonB/NonC population. Moreover, inactive CHB patients with negligible HCC risk could be identified by combining HBsAg <100 IU/mL and normal ALT levels, without the need for HBV DNA testing, as validated in the NTUH-iMD cohort. **Conclusion:** Serum HBsAg levels <100 IU/mL effectively identify inactive CHB patients with negligible HCC risk and limited viral activity, which is important in optimizing surveillance strategies and defining partial HBV cure.

Disclosures: Tai-Chung Tseng: Nothing to Disclose, Shang-Chin Huang: Gilead Sciences: Speaking and Teaching, Mei-Hung Pan: Nothing to Disclose, Chun Jen Liu: Nothing to Disclose, Chien-Jen Chen: Nothing to Disclose, Tung-Hung Su: Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Merck Sharp and Dohme: Speaking and Teaching, Roche: Speaking and Teaching, Sysmex: Speaking and Teaching, Eisai: Speaking and Teaching, Hung-Chih Yang: Nothing to Disclose, Chen-Hua Liu: Nothing to Disclose, Pei-Jer Chen: Nothing to Disclose, Hwai-I Yang: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose

1152 | CHRONIC HEPATITIS B SURFACE ANTIGEN SEROCONVERSION IN THE COVID-19 VACCINATION ERA

Allison Carroll[1] Michael Butler[1] Vy Nguyen[1] Xuan Zhang[2] Raymond Chung[1], [1]Massachusetts General Hospital, [2]Newton Wellesley Hospital

Background: Chronic hepatitis B virus (HBV) infection affects over 250 million people despite widespread prevention efforts. Annual hepatitis B surface antigen (HBsAg) seroconversion rates in chronic HBV infection have historically been low (~1%). Coronavirus disease 2019 (COVID-19) vaccines are mRNA and protein subunit vaccines that first became available in the United States in December 2020. Receipt of COVID-19 vaccine has been associated with nonspecific immune stimulation. There has been limited data on seroconversion after COVID-19 vaccination without validation in a larger healthcare system. Here we evaluated rates of HBV seroconversion across a large, US-based academic health center before and after the COVID-19 vaccine became available. **Methods:** A large electronic health record database for the MGB healthcare system (Research Patient Data Registry) was queried for patients with at least one positive HBsAg (1979-2024), resulting in 3,025 unique patients. Chronic HBV was defined as at least two positive HBsAg at least six months apart ($n = 2,274$). We defined two study windows to evaluate HBV conversion rates before and after the introduction of COVID-19 vaccine (12/13/2016 – 12/12/2020 and 12/13/2020- 12/13/2024 respectively). Patients were included in each window if they had a positive HBsAg test before or during the window and at least one HBsAg test (positive or negative) during the window, indicating ongoing follow-up. Conversion was defined as a first negative HBsAg result within the window, and conversion rates were compared between windows using a two-proportion test. **Results:** Among patients with chronic HBV and active follow-up, the annualized clearance rate was significantly higher in the 2020-2024 window compared to the 2016-2020 window. From 2016–2020, 45 of 1,247 patients (3.6%) cleared HBsAg, corresponding to an

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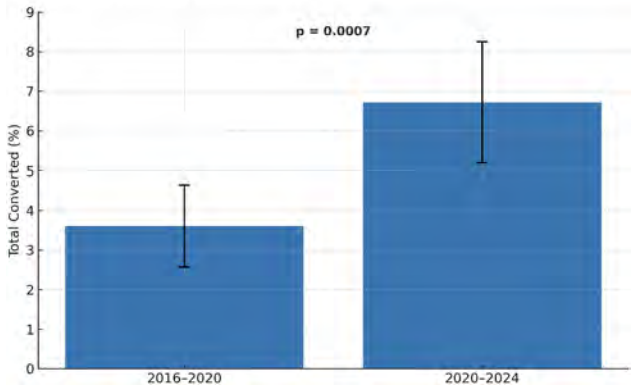
annual conversion rate of 0.72%. In the 2020–2024 window, 69 of 1,027 patients (6.7%) converted, with an annual rate of 1.34%. This difference in conversion rates was statistically significant (p = 0.0007; 95% CI, 1.26% to 4.96%; Figure 1). There was no significant difference in distribution of age, sex or number of HBsAg tests performed between groups (p = 0.48, 0.32, 0.78 respectively). **Conclusion:** HBV clearance rates were significantly higher following the introduction of the COVID-19 vaccine, suggesting a potential association between COVID-19 vaccination and increased likelihood of HBsAg seroclearance. Further study evaluating the precise relationship between HBsAg loss with receipt of COVID-19 vaccine is warranted.

Figure 1. Annualized rate of HBsAg clearance before and after COVID-19 vaccination availability



Disclosures: Allison Carroll: Nothing to Disclose, Michael Butler: Nothing to Disclose, Vy Nguyen: Nothing to Disclose, Xuan Zhang: Nothing to Disclose, Raymond Chung: GSK: Grant/Research Support, Salix: Grant/Research Support, GSK: Consultant, Precision Biosciences: Consultant, Boehringer: Grant/Research Support, BMS: Grant/Research Support

1153 | IB-001 IS A PARTIAL AGONIST OF THE TYPE I INTERFERON PATHWAY THAT EXHIBITS POTENT ANTI-HBV ACTIVITY WITH THE POTENTIAL FOR AN IMPROVED SAFETY PROFILE

Cheyne Kurokawa[1] Nathanael Sallada[1] Ruipeng Wang[1] Qingxiang Liu[1] Lynn Chen[1] Marcus Bolton[1] Eunice Cho[1] Aracely Romero[1] Madison Mann[1] Andrew Mercer[1] Yueh-Ming Loo[1] Wade Blair[1], [1]INTEGERBIO, INC.

Background: The type I interferon (IFN) system is a potent innate immune defense mechanism against viral pathogens. While IFNs have been utilized in patients as antiviral drugs, toxicity has limited widespread therapeutic use. Our goal is to develop synthetic interferons, SYNFERON™ molecules, that maintain the antiviral properties of type I IFN while reducing the inflammatory properties for an improved safety profile. SYNFERON molecules (SYN) are comprised of bispecific antibody-derived domains that bind IFN alpha receptors 1 and 2 (IFNAR1/2) and activate the IFN pathway with novel biological outcomes. **Methods:** STAT1 phosphorylation in human PBMCs was monitored by flow cytometry. Primary human hepatocytes (PHH) were infected with HBV or co-infected with HBV and hepatitis delta virus (HDV) and HBV DNA or HDV RNA was measured. FRG liver-humanized mice were infected with HBV and serum HBV DNA levels were measured. Human IFNAR1/2 knock-in mice were infected with respiratory syncytial virus (RSV) and viral load was measured in lungs 5 days after infection. Neutrophil count was also measured. **Results:** IB-001 represents a development candidate comprised of SYN1 expressed as a fusion to human serum albumin to extend half-life. We show that the IB-001 parental molecule, SYN1, activates IFNAR1/2 signaling as demonstrated by monitoring the phosphorylation of STAT transcription factors in primary cells. IB-001 exhibited antiviral activity against multiple virus families, including HBV and HDV in PHH, that was more potent than that measured for IFNα. In addition, IB-001 potently inhibited HBV replication in a mouse model of HBV infection and was more potent than Pegasys® at clinically relevant doses. IB-001 showed reduced induction of pro-inflammatory cytokines/chemokines in primary human cells and in vivo as well as reduced antiproliferative activity against bone marrow progenitor cells compared to IFNα, indicating the potential for improved safety. Furthermore, IB-001 inhibited RSV infection of mice without toxicity, while the antiviral efficacy of Peg-IFNa was linked to toxicity. Finally, our results show that IB-001 retains immune modulatory properties associated with the type I IFN pathway. **Conclusion:** Our data demonstrate that IB-001 confers potent antiviral activity against HBV and HDV in vitro and HBV in vivo with reduced inflammatory properties resulting in the potential for an improved tolerability and safety profile in the clinic.

Disclosures: Cheyne Kurokawa: IntegerBio: Employee, Nathanael Sallada: Nothing to Disclose, Ruipeng Wang: Nothing to Disclose, Qingxiang Liu: Nothing to Disclose, Lynn Chen: Nothing to Disclose, Marcus Bolton: Nothing to Disclose, Eunice Cho: Nothing to Disclose, Aracely Romero: Nothing to Disclose, Madison Mann: Nothing to Disclose, Andrew Mercer: IntegerBio: Employee, Yueh-Ming Loo: AstraZeneca: Employee, IntegerBio Inc.: Employee, Wade Blair: Nothing to Disclose

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1154 | TREATMENT ADHERENCE PATTERNS AND FOLLOW-UP CHALLENGES IN CHB PATIENTS: A COMPREHENSIVE SINGLE-CENTER ANALYSIS

Ziqun Qu[1] Wei Ye[1], [1]Nanjing Second Hospital

Background: The management of chronic hepatitis B virus (HBV) infection presents significant challenges in maintaining treatment adherence and minimizing loss to follow-up (LTFU), particularly among high-risk populations. This study aimed to comprehensively evaluate treatment initiation rates, regimen selection patterns, and LTFU dynamics among HBV DNA-positive patients, with special emphasis on clinically vulnerable subgroups including those with low-level viremia (LLV) or renal impairment. **Methods:** We conducted a retrospective analysis of data from January 1 to August 20, 2024, at Nanjing Second Hospital. The study population comprised 1,878 consecutive HBV DNA-positive patients. Primary endpoints included: (1) treatment initiation rates stratified by treatment status, (2) antiviral regimen selection in renal impairment (creatinine >104 μmol/L), (3) treatment modification rates in LLV patients, and (4) LTFU rates at 3- and 6-month intervals. Secondary analyses examined LTFU patterns in key clinical subgroups. **Results:** The overall treatment initiation rate was 73% (1,374/1,878). Among treatment-naïve patients with renal impairment ($n=113$), first-line regimen selection showed: ETV/TAF 72% (81/113), TMF 24.7% (28/113), and TDF 3.5% (4/113). Only half (50%, 138/278) of LLV patients on prior therapy received guideline-recommended regimen modifications. The cohort demonstrated alarmingly high LTFU rates: 79% (984/1,245) at 3 months declining to 10% (125/1,245) by 6 months. Subgroup analyses revealed particularly concerning 3-month LTFU rates: 72% (102/141) in LLV patients undergoing treatment modification, 56% (45/80) in treatment-naïve renal impairment patients receiving ETV/TAF, and 69% (20/29) in renal-impaired experienced patients transitioning to ETV/TAF. **Conclusion:** This study reveals a critical gap in HBV management with high early attrition at 3 months and partial re-engagement at 6 months, particularly among high-risk populations. These findings support prioritizing high genetic barrier agents to prevent resistance, enhancing early retention strategies, and selecting renal-safe regimens for prolonged unsupervised treatment.

Disclosures: Ziqun Qu: Nothing to Disclose, Wei Ye: Nothing to Disclose

1155 | LEAD OPTIMIZATION AND SELECTION OF A POTENTIAL BEST-IN-CLASS HBV ASO

Jin Hong[1] Vivek Rajwanshi[1] Dinah Misner[1] JIMMY LU[2] Kusum Gupta[1] Antitsa Stoycheva[1] Dana Cho[1] John Cortez[1] Min Luo[1] Hyunsoon Kang[1] Kellan Passow[1] Jacquelyn Sousa[1] Shane Daguison[1] Jieun Song[1] Lillian Adame[1] Cheng Liu[1] Sarah Stevens[1] Aneerban Bhattacharya[1] Rostom Ahmed-Belkacem[3] Susan Luong[1] Lawrence Blatt[1] Li Sun[2] David Smith[1] Leonid Beigelman[3] Julian Symons[1], [1]Aligos Therapeutics, [2]Amoytop Biotech., [3]Previously Aligos Therapeutics

Background: To achieve functional cure in chronic hepatitis B, the future treatment regimen will likely include direct antiviral and immunomodulatory drugs. Current clinical stage HBV ASOs, bepirovirsen (GSK-836) and AHB-137, are unique in their dual RNase H-mediated direct antiviral and immunomodulatory (e.g. TLR8 agonist) activities. GSK-836 as a single agent achieved a moderate functional cure rate of ~10% in a phase 2b trial, this was superior to many other modalities such as siRNA, but still suboptimal. Our aim is to develop a best-in-class HBV ASO with an improved overall therapeutic index over both clinical stage HBV ASOs. **Methods:** RNase H-mediated activity was analyzed with an HBsAg ELISA in HepG2.2.15 cells and AAV-HBV mice. To validate ASO hTLR8 activity in vivo, hTLR8 knock-in mice were dosed with ASO subcutaneously and mouse cytokine induction was monitored. Toxicity derived from ASO off-target effects was measured in a HepG2 Caspase3/7 assay and an ATP assay in InSphero 3-D liver microtissues. PXB mice with humanized livers were tested to assess the potential hepatotoxic effect of the ASOs. **Results:** Over 1300 ASOs were designed, synthesized and screened. Three optimized leads ALG-170675, ALG-171036 and ALG-171191 were selected for further investigation to identify a lead candidate. The three leads incorporated a novel ASO platform technology that reduced caspase activity in vitro when compared to clinical stage ASOs. In the HepG2.2.15 assay, ALG-171036, ALG-171191 showed enhanced in vitro RNase H-mediated activities compared to GSK-836 with EC_{50} values of 2.4, 2.8 and 8.6 nM respectively. ALG-170675 demonstrated comparable activity to GSK-836 with an EC_{50} value of 9.2 nM. In AAV-HBV mice, ALG-171191 exhibited deeper HBsAg knockdown in mouse plasma than clinical stage ASOs. ALG-171036 and ALG-170675 demonstrated superior HBsAg knockdown to GSK-836. Enhanced liver drug exposures over clinical benchmarks were

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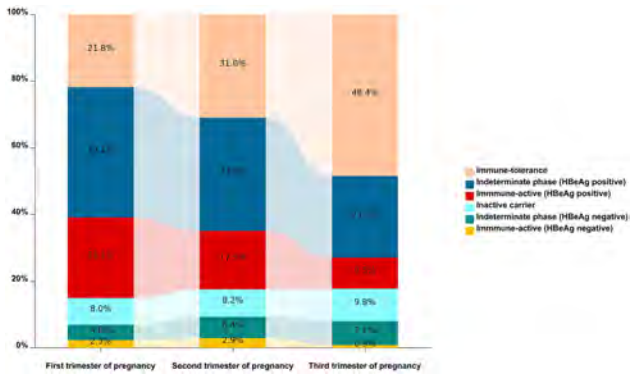
found for all three lead ASOs. Comparable hTLR8 agonist activities in vitro and in vivo were observed for all lead ASOs and clinical benchmarks. In vitro toxicology studies showed CC_{50} values >500 μM in a 3-D human liver microtissue assay for all three leads and no human ALT elevation when dosed at 7 x 50 mg/kg in uninfected PXB mice with humanized livers. **Conclusion:** Optimized HBV ASO leads ALG-170675, ALG-171036 and ALG-171191 showed significant potential to be best-in-class HBV ASOs. Further investigations are underway.

Disclosures: Jin Hong: Nothing to Disclose, Vivek Rajwanshi: Nothing to Disclose, Dinah Misner: Nothing to Disclose, JIMMY LU: Nothing to Disclose, Kusum Gupta: Nothing to Disclose, Antitsa Stoycheva: Nothing to Disclose, Dana Cho: Nothing to Disclose, John Cortez: Nothing to Disclose, Min Luo: Nothing to Disclose, Hyunsoon Kang: Nothing to Disclose, Kellan Passow: Nothing to Disclose, Jacquelyn Sousa: Nothing to Disclose, Shane Daguison: Nothing to Disclose, Jieun Song: Nothing to Disclose, Lillian Adame: Nothing to Disclose, Cheng Liu: Nothing to Disclose, Sarah Stevens: Nothing to Disclose, Aneerban Bhattacharya: Nothing to Disclose, Rostom Ahmed-Belkacem: Nothing to Disclose, Susan Luong: Nothing to Disclose, Lawrence Blatt: Nothing to Disclose, Li Sun: Nothing to Disclose, David Smith: Nothing to Disclose, Leonid Beigelman: Nothing to Disclose, Julian Symons: Nothing to Disclose

1156 | HIGHER RISK OF POSTPARTUM PHASE TRANSITION TO IMMUNE-ACTIVE AMONG HBEAG-POSITIVE PREGNANT WOMEN WITH INDETERMINATE PHASE

Qiao Tang[1] Peng Hu[0], [1]The second affiliated hospital of Chongqing medical uni., [0] The First Affiliated Hospital of Chongqing Medical University

Background: Investigation on natural history of hepatitis B infection helps to guide the timing of initiating antiviral therapy, and which was primarily performed in non-pregnant patients. The natural history dynamics in pregnant women with chronic hepatitis B (CHB) remain unknown. **Methods:** We performed a retrospective-prospective real-world study including 352 pregnant women with CHB. Dynamics of natural history during pregnancy (including 248 HBeAg-positive and 48 HBeAg-negative participants) and the postpartum period (including 108 HBeAg-positive who received short-term antiviral intervention and 21 HBeAg-negative participants), and liver disease progression of different phases were investigated. **Results:** The proportion of immune-tolerance (IT) gradually increased, whereas the proportion of HBeAg-positive indeterminate phase (IP) and HBeAg-positive immune-active (IA) gradually decreased during pregnancy. In the third trimester of pregnancy, IT was dominant (48.7%), followed by HBeAg-positive IP (24.6%), HBeAg-positive IA (9.4%), inactive carrier (9.4%), HBeAg-negative IP (7.1%) and HBeAg-negative IA (0.9%). A numerical higher cumulative incidence of postpartum maintenance the phase and a significantly lower cumulative incidence of transition to HBeAg-positive IA in pregnant women with IT compared with pregnant women with HBeAg-negative IP. The cumulative incidence of postpartum maintenance the phase and transition to HBeAg-negative IA were comparable between pregnant women with IC and HBeAg-negative IP ($p > 0.05$). Pregnant women with different phases had similar low risk of postpartum liver disease progression. **Conclusion:** Pregnancy, short-term antiviral therapy, and delivery may have an impact on natural history of HBV infection in HBeAg-positive pregnant women, especially in those with indeterminate phase at 24-28 weeks of gestation.



Disclosures: Qiao Tang: Nothing to Disclose, Peng Hu: Nothing to Disclose

1157 | A NOVEL POST-TRANSCRIPTIONAL MECHANISM OF HBSAG SUPPRESSION BY HOST FACTORS

YAN ZHAOYU[1] Takehisa Watanabe[1] Sanae Kimura Hayashi[1] Chang Wu[1] Katsuya Nagaoka[1] Yasuhito Tanaka[1], [1]Kumamoto University

Background: SAG-524 is a small-molecule compound that we previously reported to suppress HBsAg expression, at least in part by destabilizing HBV RNAs through PAPD5. However, the full post-transcriptional regulatory network downstream of SAG remains undefined. Given the importance of RNA-binding proteins (RBPs) in viral RNA fate, we sought to identify novel RBPs involved in HBsAg regulation, with the aim of uncovering alternative effector pathways mediating host-driven antiviral responses. **Methods:** Luciferase

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assays were performed to identify 3′ untranslated regions (UTR) required for SAG-mediated suppression of HBsAg. Predicted RBPs were retrieved from "RBPDB" and subjected to siRNA knockdown in HepG2.2.15 cells, followed by quantification of HBsAg in culture supernatants. Protein–protein interaction data from "BioGRID" and the published CRISPR-Cas9 screening datasets related to HBsAg expression were used for overlap analysis. RNA-seq was conducted after the knockdown, and HBV RNA and HBsAg were quantified by qPCR and CLEIA, respectively. **Results:** Initial screening identified MARP1, an m6A reader acting in concert with other cofactors, as a protein binding to the SAG-responsive 3′UTR of HBV-RNA. "BioGRID" and the CRISPR screening datasets were used to prioritize associated RBPs, among which RBP3 was selected and followed by functional analysis. Knockdown of RBP3 in HepG2.2.15 cells significantly reduced HBsAg in the medium without altering total HBV RNA, indicating a post-transcriptional effect. RNA-seq was conducted in the RBP3 depleted HepG2.2.15 cells, and the top differentially expressed genes were compared with the CRISPR screening datasets related to HBsAg downregulation. PRG1 was identified as a common hit. Western blotting confirmed the upregulation of PRG1 protein in the RBP3 depleted cells. Further knockdown of PRG1 did not affect HBV RNA but led to a marked increase in extracellular HBsAg. **Conclusion:** This study identified a host regulatory module of HBsAg expression initiated by MARP1. RBP3 was identified as a functional cofactor of MARP1 that regulated HBsAg levels through PRG1. These findings support further investigation into host-mediated antigen control. This study suggests that the MARP1/RBP3/PRG1 pathway represents a novel molecular mechanism involved in HBsAg regulation.

Disclosures: YAN ZHAOYU: Nothing to Disclose, Takehisa Watanabe: Nothing to Disclose, Sanae Kimura Hayashi: Nothing to Disclose, Chang Wu: Nothing to Disclose, Katsuya Nagaoka: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

1158 | SAFE BUT NOT SILENT: HBV REACTIVATION IN NON-LIVER ORGAN TRANSPLANTATION

Imran Hasanoglu[1] Melike Hallemoglu Topcu[2] Tansu Yamazhan[3] Ayse Ozlem Mete[4] Muammer Celik[5] Esra Tanyel[6] Tugba Arslan Gulen[7] Bengu Tatar[8] Elif Ates[9] Ayse Yasemin Tezer[2] Sibel Altunisik Toplu[10] Selda Sayin Kutlu[11] Erkan Olcucuoglu[2] Oguzhan Acet[3] Yelda Deligoz Bildaci[5] Melda Dilek[12] Edip Akpinar[7] Adam Uslu[8] Adem Safak[9] Fatmanur Celik Basaran[2] Turgut Piskin[10] Belda Dursun[11] Vildan Avkan Oguz[5] Hande Arslan[9], [1]Ankara Yildirim Beyazit University Bilkent City Hospital, [2]Ankara Bilkent City Hospital, [3]Ege University Faculty of Medicine, [4]Gaziantep University Faculty of Medicine, [5]Dokuz Eylul University Faculty of Medicine, [6]Ondokuz Mayıs University Faculty of Medicine, [7]Adana City Training and Research Hospital, [8]Izmir City Hospital, [9]Baskent University Faculty of Medicine, [10]Inonu University Faculty of Medicine, [11]Pamukkale University Faculty of Medicine, [12]Ondokuz Mayis University Faculty of Medicine

Background: Hepatitis B virus (HBV) reactivation remains a clinically significant but under-recognized complication in non-liver solid organ transplant recipients (SOTR). By analyzing real-world data from multiple centers, this study evaluated the risk and clinical trajectory of HBV reactivation in non-liver SOTR. **Methods:** This retrospective study, conducted across 12 transplant centers, included non-liver SOTRs with a minimum of one year of post-transplant follow-up. Patients were considered at risk for HBV reactivation if either the donor or recipient tested positive for HBsAg and/or anti-HBc IgG prior to transplantation. Data were collected on patient demographics, type of transplanted organ, immunosuppressive regimens, and the use of antiviral prophylaxis. **Results:** The study included 309 patients from 12 transplant centers, among whom 95.8% were kidney recipients, followed by lung (3.5%) and heart (0.6%) transplant recipients. The mean age was 51.4 years, and 71.5% were male. About one-third received organs from deceased donors (32.6%). Induction therapy mainly involved anti-thymocyte globulin (65.3%), while maintenance commonly included calcineurin inhibitors (97.4%), antimetabolites (94.8%), and prednisone (84.1%). HBV prophylaxis was given to 43% of patients, using tenofovir alafenamide (33.0%), lamivudine (29.3%), entecavir (27.8%), and tenofovir disoproxil fumarate (2.2%). HBV reactivation was observed in 11 patients, yielding an overall reactivation rate of 3.5% during a median follow-up period of 68.5 months (2-252 months). Patients who received antiviral prophylaxis experienced significantly fewer HBV reactivation. No HBV-related mortality was observed. Among the six seronegative recipients who received HBsAg-positive donors, none developed HBV reactivation during follow-up. Clinical characteristics and outcomes of the patients are presented in Figure 1. **Conclusion:** Although relatively uncommon, HBV reactivation in non-liver solid organ transplant recipients remains a clinically significant concern. These findings underscore the importance of thorough pre-transplant screening and individualized antiviral prevention strategies. Although the number of patients is limited, the data supports the cautious use of HBsAg-positive donors under strict prophylactic protocols, offering a potential avenue to expand the donor pool without compromising recipient safety.

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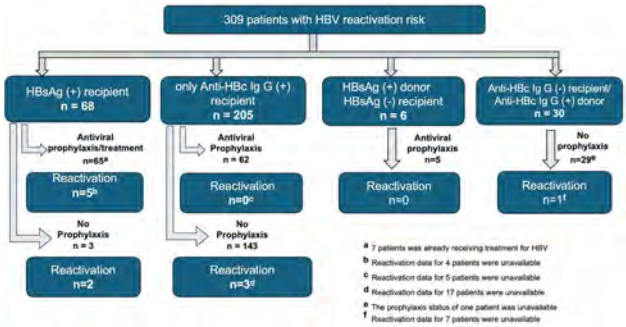

Disclosures: Imran Hasanoglu: Nothing to Disclose, Melike Hallemoglu Topcu: Nothing to Disclose, Tansu Yamazhan: Nothing to Disclose, Ayse Ozlem Mete: Nothing to Disclose, Muammer Celik: Nothing to Disclose, Esra Tanyel: Nothing to Disclose, Tugba Arslan Gulen: Nothing to Disclose, Bengu Tatar: Nothing to Disclose, Elif Ates: Nothing to Disclose, Ayse Yasemin Tezer: Nothing to Disclose, Sibel Altunisik Toplu: Nothing to Disclose, Selda Sayin Kutlu: Nothing to Disclose, Erkan Olcucuoglu: Nothing to Disclose, Oguzhan Acet: Nothing to Disclose, Yelda Deligoz Bildaci: Nothing to Disclose, Melda Dilek: Nothing to Disclose, Edip Akpinar: Nothing to Disclose, Adam Uslu: Nothing to Disclose, Adem Safak: Nothing to Disclose, Fatmanur Celik Basaran: Nothing to Disclose, Turgut Piskin: Nothing to Disclose, Belda Dursun: Nothing to Disclose, Vildan Avkan Oguz: Nothing to Disclose, Hande Arslan: Nothing to Disclose

1159 | MEETING HEPATITIS B ELIMINATION GOALS IN THE ALASKA NATIVE POPULATION

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Background: In the United States, hepatitis B was only endemic in western Alaska primarily among Alaska Native (AN) Peoples; Prior to 1980, the annual incidence of hepatocellular carcinoma (HCC) in children was among the highest in the world peaking at almost 3/100,000 (Figure 1). In the 1980s the Alaska Native Tribal Health Organizations screened 53,860 AN peoples for hepatitis B virus (HBV) infection, administered HBV vaccine to 43,618 HBV seronegative persons, and initiated universal newborn vaccination. Between 1962 and 1999, 1658 AN peoples were identified with chronic hepatitis B (CHB) and entered into a registry and are followed on a regular basis. In this study we examine the impact of this effort 40 years later comparing to the 2030 WHO global HBV elimination goals. **Methods:** This is a population-based outcome study. We used vaccine and electronic and State of Alaska Department of Health records to assess progress towards HBV elimination goals in the AN population by examining rates of newborn and childhood vaccination between 2015-2019. We used records from the National Cancer Institiure funeded Alaska Native Tumor Board from 1969 through 2019 to identify persons with HBV-related HCC. We also examined changes in HBV incidence rates of new hepatitis B antigen positive (HBsAg) infection in this region from 1990 through 2019, using both electronic and State of Alaska records. Finally, we calculated the incidence of HBV associated HCC in persons under 20 years of age.as well as the number of new cases of HBsAg. **Results:** In HBV endemic regions in Alaska between 2015 and 2019, approximately 90% of newborns received an HBV vaccine birth dose and over 80% of infants received a complete HBV vaccine series by 18 months of age. Over 99% of AN peoples diagnosed with CHB are in a computerized registry and labs and radiographic studies are reviewed yearly. Since 1998, annual incidence of new HBsAg-positive tests among AN peoples ranged from 1.4 to 2.6 per 100,000, down from 6.2 per 100,000 ststewide between 1993 and 1997. There have been no HBsAg-positive or HBV-related HCC cases identified in AN peoples under age 20 since 1993. **Conclusion:** Mass population-based screening for HBV seromarkers and vaccination of those seronegative coupled with continuing universal newborn immunization instituted four-decades ago have halted transmission of HBV in an endenic area in Western Alaska. The greatest impact has been on children under 20 years of age where both new cases of HBsAg-positive HBV infection which can lead to chronic HBV as well as new cases of HCC have been eliminated. This approach has sucessfully shown that the 2030 elimiation goals. HBV eliminaion goals can be successfully achieved.

Disclosures: Brian McMahon: Nothing to Disclose, Lesleigh Kowalski Frank .: Nothing to Disclose, Lisa Townshend-Bulson: Gilead Sciences: Grant/Research Support, mary snowball: Nothing to Disclose

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1160 | IMDUSIRAN (AB-729) IS SAFE AND WELL-TOLERATED AFTER REPEAT DOSING IN CHRONIC HEPATITIS B PATIENTS: AN INTEGRATED SAFETY ANALYSIS OF PHASE 1 AND 2 IMDUSIRAN CLINICAL TRIALS

Tilly Varughese[1] Man-Fung Yuen[2] Grace Lai-Hung Wong[3] Kosh Agarwal[4] Kevin Gray[1] Deana Antoniello[1] Varun Sharma[1] Joanne Brown[1] Elina Medvedeva[1] Gaston Picchio[1] Karen Sims[1], [1]Arbutus Biopharma, [2]The University of Hong Kong, [3]The Chinese University of Hong Kong, Prince of Wales Hospital, [4]Institute of Liver Studies, Kings College Hospital

Background: Imdusiran (IDR) is a N-Acetylgalactosamine–conjugated, pan-genotypic small interfering RNA that blocks all HBV RNA transcripts, resulting in suppression of viral replication and all viral antigens. The safety and tolerability of repeat subcutaneous dosing of 60 mg or 90 mg of IDR when added to background nucleos(t)ide analogue (NA) therapy were evaluated in an integrated analysis of clinical trial results from over 150 subjects with chronic hepatitis B (CHB). **Methods:** Safety data including clinical and laboratory results was pooled (n = 151) and evaluated from a Phase 1 trial (AB-729-001; ACTRN12620000295943) and three Phase 2 combination treatment trials of IDR with immunotherapies (AB-729-201; NCT04980482, AB-729-202; ACTRN12622000317796) or a capsid assembly modulator (ABI-H0731-204; NCT04820686). Patients were divided into 4 groups by treatment regimen for the safety analysis as follows: Group 1 was IDR 60 mg x 4 doses [24 weeks (W)]+NA with 48 weeks follow up after IDR dosing from AB-729-202 Group B (n = 20); Group 2 was IDR 60 mg x 4 doses (24W)+NA lead-in from AB-729-202 Groups A and C through W26 and AB-729-201 lead-in period in all cohorts through W28 prior to the addition of immunotherapies (n = 85); Group 3 was IDR 60 mg x 6 doses (48W)+NA with 48 weeks follow up after IDR dosing from AB-729-001 Cohort F and ABI-H0731-204 Group 3 (n = 24); and Group 4 was IDR 90 mg x 6 doses (48W)+NA with 48 weeks follow up after IDR dosing from AB-729-001 Cohorts G, I and K (n = 22). **Results:** The majority of treatment emergent adverse events (TEAEs) in all 4 groups were Grades 1-2, with only 5 (3.3%) TEAEs reported as Grade 3 (only two Grade 3 TEAEs of alanine aminotransferase (ALT) elevations were deemed related to IDR). Related TEAEs that occurred most frequently among all groups were injection related events (13.9%) and ALT elevations (6.0%). The most frequent lab abnormalities observed were ALT and aspartate aminotransferase (AST) elevations (50% and 29% of subjects in all groups, respectively) with >95% of elevations being Grade 1 or 2. The only Grade 4 lab abnormalities observed were creatine kinase elevations in one patient each in Groups 1-3 that were unrelated to IDR and likely related to physical exercise. The safety profile from Group 4 (IDR 90 mg x 6 doses) was similar to the other groups. There were no deaths, Grade 4 TEAEs or SAEs related to IDR, or signs/symptoms of hepatic decompensation in any of the trial subjects. **Conclusion:** IDR therapy in patients with CHB was safe and well tolerated when administered at both 60 mg and 90 mg dose levels every 8 weeks for 4 – 6 doses (24 – 48 weeks) and through up to 48 weeks of follow up after IDR dosing.

Table 1: Treatment Emergent Adverse Events with Repeat Imdusiran Dosing Across Phase 1 and Phase 2 Clinical Trials

Number (%) [Events] of Subjects with Any	Group 1 (n=20)	Group 2 (n=85)	Group 3 (n=24)	Group 4 (n=22)	Total (N=151)
TEAE	17 (85.0) [68]	42 (49.4) [103]	17 (70.8) [83]	18 (81.8) [76]	94 (62.3) [330]
TEAE related to IDR	2 (10.0) [5]	15 (17.6) [27]	9 (37.5) [26]	9 (40.9) [12]	35 (23.2) [71]
Grade 3 TEAEs	0	3 (3.5) [3]	0	2 (9.1) [2]	5 (3.3) [5]
Grade 3 TEAEs Related to IDR	0	2 (2.4) [2]*	0	0	2 (1.3) [2]*
Grade 4 TEAEs or SAEs related to IDR	0	0	0	0	0
TEAEs Related to IDR in 2 or more subjects					
Injection related reactions	2 (10.0) [4]	5 (5.9) [12]	7 (29.2) [18]	7 (31.8) [7]	21 (13.9) [41]
ALT elevation	1 (5.0) [2]	5 (5.9) [6]	2 (8.3) [3]	1 (4.5) [1]	9 (6.0) [12]
Dizziness	0	1 (1.2) [1]	1 (4.2) [1]	0	2 (1.3) [2]
Pruritus	0	1 (1.2) [1]	1 (4.2) [1]	0	2 (1.3) [2]
Headache	0	1 (1.2) [1]	1 (4.2) [1]	0	2 (1.3) [2]
Nausea	0	1 (1.2) [1]	0	1 (4.5) [1]	2 (1.3) [2]

ALT=alanine transaminase; IDR=imdusiran; N=number; TEAE=treatment emergent adverse event; W=weeks
*The only two Grade 3 TEAEs reported related to IDR were 2 subjects with ALT elevations.
Group 1: IDR 60 mg q8W x 4 doses [24 W] + NA with follow-up up to 48 weeks after the last dose – AB-729-202 Group B
Group 2: IDR 60 mg q8W x 4 doses [24 W] + NA – AB-729-202 Groups A and C with follow up until Week 26 (2 weeks after the last dose); AB-729-201 all lead-in cohorts with follow up until Week 28 (4 weeks after the last dose)
Group 3: IDR 60 mg q8W x 6 doses [48 W] + NA with up to 48 weeks post dosing follow-up - AB-729-001 Cohort F and ABI-H0731-204 Group 3
Group 4: IDR 90 mg q8W x 6 doses [48 W] + NA with up to 48 weeks post dosing follow-up - AB-729-001 Cohorts G, I and K

Disclosures: Tilly Varughese: Arbutus Biopharma: Employee, Man-Fung Yuen: Nothing to Disclose, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Kosh Agarwal: Nothing to Disclose, Kevin Gray: Nothing to Disclose, Deana Antoniello: Nothing to Disclose, Varun Sharma: Nothing to Disclose, Joanne Brown: Nothing to Disclose, Elina Medvedeva: Nothing to Disclose, Gaston Picchio: Arbutus Biopharma: Employee, Karen Sims: Nothing to Disclose

1161 | HEPATITIS B CORE-RELATED ANTIGEN (HBCRAG) MEASUREMENTS CAN PREDICT THE RISK OF ALT FLARE IN PATIENTS WITH HBEAG-NEGATIVE CHRONIC HEPATITIS B INFECTION IN INACTIVE PHASE

Tetsuya Hosaka[1] Fumitaka Suzuki[1] Mariko Kobayashi[1] Hitomi Sezaki[1] Norio Akuta[1] Yoshiyuki Suzuki[1] Satoshi Saitoh[1] Yasuji Arase[1] Yasue Takeuchi[1] Kenji Ikeda[1] Hiromitsu Kumada[1], [1]Toranomon Hospital

Background: Serum hepatitis B core-related antigen (HBcrAg) has been known as surrogate markers of intrahepatic covalently closed circular DNA (cccDNA) and transcriptional activity. However, its clinical usefulness is still unclear in inactive chronic hepatitis B infection (CHB). In this study, we evaluated the risk of ALT flare in HBeAg-negative CHB using HBcrAg measurements. **Methods:** This study

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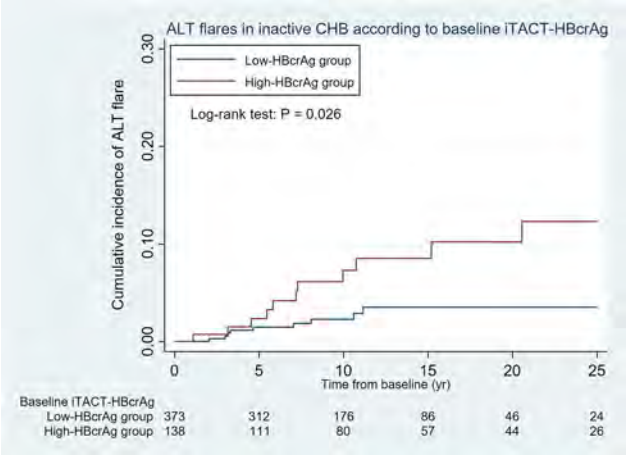
enrolled 511 HBeAg-negative non-cirrhotic patients without antiviral therapy who had been followed up for at least 1 year and whose baseline HBcrAg levels could be measured by highly-sensitive HBcrAg assay (iTACT-HBcrAg). The lower limit of quantification of iTACT-HBcrAg assay is 2.1 Log U/mL. Normal ALT was defined as 35 IU/L in male and 25 in female. According to baseline HBcrAg, the entire cohort was categorized into two groups; HBcrAg $<$ 3.0 log U/mL as the low-HBcrAg group and $\geq$ 3.0 as the high-HBcrAg group. Inactive phase was defined as persistently normal ALT and low viral loads ($<$ 2,000 IU/mL) from baseline to year 1. ALT flare was defined as $>$ twice upper limit of normal (ULN). We also evaluated severe ALT flares over 100 IU/L and hepatocellular carcinoma (HCC) incidences according to baseline HBcrAg levels. We excluded the events of elevated ALT by obvious metabolic factors. **Results:** (1) In the entire cohort, median HBcrAg level was 2.2 log U/mL. 373 patients (73%) were categorized into the low-HBcrAg, and 138 (27%) into the high-HBcrAg groups. Patients in the high-HBcrAg group were significantly younger and had higher HBsAg levels than those in the low-HBcrAg group. (2) During follow-up of median 10 years, ALT flares occurred in 22 patients in the entire cohort. Annual incidence rates of ALT flares were 2.3 and 5.8 per 1,000 person-years in the low-HBcrAg and high-HBcrAg groups, respectively, with a lower incidence of ALT flares in the low-HBcrAg (P = 0.026) (Fig A). In the low-HBcrAg group, cumulative incidences of ALT flares in patients with HBcrAg $<$ 2.1 were marginally lower than those with HBcrAg 2.1-2.9 (P = 0.096). However, there were no significant differences in severe ALT flare and HCC incidences between the low-HBcrAg and high-HBcrAg groups. **Conclusion:** Patients with HBcrAg over 3.0 log U/mL in inactive HBeAg-negative CHB had the higher risk of ALT flares than those without it. HBcrAg can be a useful tool for predicting phase transition in inactive CHB.



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1162 | APPLYING AASLD, EASL, AND WHO HEPATITIS B TREATMENT GUIDELINES TO A COMMUNITY-BASED HEPATITIS B REGISTRY

Zinnia Dong[1] Amy Tang[2], [1]North East Medical Services, [2]North East Medical Servies

Background: Community health centers (CHCs) are high-impact settings for hepatitis B virus (HBV) screening and retention in care. An estimated 1.6 to 2.4 million people have chronic HBV in the United States, and in 2022, Federally Qualified Health Centers (FQHCs) cared for almost 45,000 people with chronic HBV. North East Medical Services (NEMS) is an FQHC in the San Francisco Bay Area serving over 70,000 patients annually with a large HBV registry-based care management program, of which over one-third of HBV registry patients have been prescribed HBV antiviral treatment. We aimed to describe the cohort of HBV treatment-naïve NEMS patients indicated for HBV antiviral treatment based on the American Association for the Study of Liver Diseases' (AASLD) 2015 guidelines and 2018 guidance and the recently updated 2024 World Health Organization (WHO) and 2025 European Association for the Study of the Liver (EASL) guidelines. **Methods:** We performed a retrospective analysis of treatment-naïve HBV registry patients with at least one primary care medical visit at the FQHC from 10/2/23 to 5/19/25. HBV registry patients had a positive HBV surface antigen (HBsAg) or HBV DNA in the last 3 years or a chronic HBV ICD-code on their problems list. Demographic and clinical data were extracted from the FQHC's electronic health records and used for determining treatment indications. **Results:** Of the 1,850 treatment-naïve chronic HBV patients, we identified 920 (50%) patients using WHO guidelines, 270 (15%) patients using EASL guidelines, and 45 (2%) patients using AASLD guidelines who were indicated for treatment. WHO's guidelines had the lowest threshold for HBV antiviral treatment initiation with metabolic dysfunction-associated steatotic liver disease (MASLD) (63%) and diabetes mellitus (34%) contributing the largest treatment indication. Using EASL's guidelines, HBV DNA $\geq$2,000 IU/mL with a hepatocellular carcinoma (HCC) risk factor had the largest impact; and of

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these HCC risk factors, age (77%) contributed the most. AASLD's guidance was the strictest, which was influenced by higher ALT criteria and reliance on HBV "e" antigen (HBeAg) for determining treatment eligibility, as 14% of the treatment-naïve population did not have a documented HBeAg status. **Conclusion:** CHCs are crucial in the nation's viral hepatitis elimination plan as they provide longitudinal care to low-income immigrant populations. Utilizing an HBV registry, we identified 2% to 50% of treatment-naïve chronic HBV patients indicated for HBV antiviral treatment using recommendations and guidelines from AASLD, EASL, and WHO. A simplified HBV treatment guidance that distills the complexities of the various HBV antiviral treatment thresholds and is tailored to primary care providers would greatly impact and improve HBV care delivery in this primary care setting.

Table 1. Applying AASLD, WHO, and EASL HBV treatment guidelines to treatment-naive HBV registry patients (N = 1,850)

	AASLD 2015/18 n (%[1])	WHO 2024 n (%[1])	EASL 2025 n (%[1])
Total unique treatment-indicated patients[2]	45 (2%)	920 (50%)	270 (15%)
Cirrhosis	5 (11%)	5 (1%)	-
Detectable HBV DNA	-	-	3 (1%)
Fibrosis threshold[3]	26 (58%)	63 (7%)	18 (7%)
Elevated HBV DNA[4] & ALT[5]	14 (31%)	210 (23%)	55 (20%)
MASLD[6]	-	581 (63%)	88 (33%)
Diabetes mellitus[6]	-	314 (34%)	30 (11%)
Viral coinfection[6]	-	2 (<1%)	0
Immunosuppresion[6]	-	0	0
Extrahepatic manifestations[6]	-	0	0
Current smoker[6]	-	-	44 (16%)
Age[6, 7]	0	-	209 (77%)
HBeAg + & Age >30 years[6]	-	-	17 (6%)
BMI ≥30[6]	-	-	23 (9%)
Place of birth in Africa[6]	-	-	0

AASLD: American Association for the Study of Liver Diseases; BMI: body mass index; EASL: European Association for the Study of the Liver; HBeAg: hepatitis B "e" antigen; HBV: hepatitis B virus; MASLD: metabolic dysfunction-associated steatotic liver disease; WHO: World Health Organization

[1] Proportions are out of total unique treatment-indicated patients by guideline
[2] Proportions are out of total treatment-naive HBV registry patients
[3] **AASLD:** ≥F2 (gray zone) ; **WHO:** ≥F2 ; **EASL:** ≥F3 & HBV DNA detectable, ≥F2 & HBV DNA ≥2,000 IU/mL
[4] **AASLD:** ≥2,000 IU/mL (HBeAg -), ≥20,000 IU/mL (HBeAg +) ; **WHO & EASL:** ≥2,000 IU/mL
[5] **AASLD:** >70 U/L (men), > 50 U/L (women) ; **WHO:** >30 U/L (men), > 19 U/L (women) ; **EASL:** >40 U/L
[6] **EASL:** No advanced fibrosis or cirrhosis & HBV DNA ≥2,000 IU/mL
[7] **AASLD:** >40 years & persistent elevated ALT > ULN ; **EASL:** >40 years (men), >50 years (women)

Disclosures: Zinnia Dong: Nothing to Disclose, Amy Tang: Nothing to Disclose

1163 | IN SILICO ANALYSIS OF INTRAHEPATIC NEUTROPHILS IN ON-TREATMENT CHRONIC HEPATITIS B PATIENTS WITH LIVER FIBROSIS

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Background: The dynamics of intrahepatic neutrophils and their functional heterogeneity in chronic hepatitis B (CHB) patients with liver fibrosis undergoing antiviral therapy (AVT) remain poorly defined. This study aimed to elucidate the characteristics of intrahepatic neutrophils in on-treatment CHB-associated liver fibrosis using in silico analyses based on liver transcriptomics. **Methods:** Transcriptomics of 54 serial liver biopsies obtained from 28 CHB liver fibrosis patients at baseline (0W), 78 weeks (78W), and 260 weeks (260W) post-AVT were analyzed to characterize intrahepatic neutrophil dynamics. Publicly available transcriptomics (GSE84044) from 82 AVT-naïve CHB patients with liver fibrosis were enrolled to verify intrahepatic neutrophil profiles at baseline. Additionally, publicly available single-cell RNA sequencing data (scRNA-seq; GSE186343) from 5 CHB liver fibrosis patients were utilized to map the heterogeneity of intrahepatic neutrophils. **Results:** Deconvolution analyses revealed that the fraction of neutrophils exhibited an upward trend at 78W ($P = 0.2770$), and increased significantly at 260W ($P < 0.001$) of AVT, accompanied by sustained reductions in the number of T cells, $CD8^+$ T cells, and NK cells. Additionally, patients were stratified into Neu-Low and Neu-High groups based on average neutrophil fractions. The Neu-Low group showed higher Ishak scores and elevated expression of liver fibrosis-specific matrisome genes, regardless of treatment status. Moreover, Gene Set Enrichment Analysis indicated that the KEGG pathways involved in extracellular matrix remodeling, immune response, and cell cycle regulation were significantly activated in the Neu-Low group, while metabolic pathways, including carbohydrate, lipid, and amino acid-related metabolism pathways were evidently downregulated. These baseline characteristics of intrahepatic neutrophils were validated in the AVT-naïve GSE84044 cohort. Furthermore, scRNA-seq analysis based on GSE186343 identified three distinct intrahepatic neutrophil subpopulations: NEU1 ($FCGR3B^+CXCR2^+CMTM2^+$), NEU2 ($LGALS1^+CST3^+GSTP1^+$) and NEU3 ($CCL5^+IL32^+GZMA^+$), among which the fraction of NEU2 progressively increased post-AVT by deconvolution analysis. NEU2 exhibited upregulated gene profiles associated with antigen presentation and immunosuppression, suggesting a role in maintaining immune homeostasis and preventing excessive inflammatory responses during AVT. **Conclusion:** Intrahepatic neutrophil fractions increased during antiviral therapy for HBV-related fibrosis. Lower neutrophil levels were associated with more severe fibrosis and metabolic dysfunction. Neutrophils exhibited heterogeneity, with NEU2 expanding during therapy and potentially contributing to immune homeostasis.

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1164 | ASSOCIATION OF BASELINE SERUM HBV RNA AND ANTIVIRAL RESPONSE IN CHRONIC HEPATITIS B PATIENTS WITH NUCLEOS(T)IDE ANALOGUE TREATMENT

Jian Wang[1] Rui Huang[1] Chao Wu[1], [1]Nanjing Drum Tower Hospital

Background: Hepatitis B virus (HBV) RNA is a novel serological marker which can reflect the intrahepatic HBV covalently closed circular DNA (cccDNA) transcriptional activity. We investigated the association between serum HBV RNA levels and antiviral response in patients with chronic hepatitis B (CHB). **Methods:** A total of 685 CHB patients who received nucleos(t)ide analogues (NAs) treatment were included. HBV RNA was measured by cobas HBV RNA quantitative assay (RUO, Roche Molecular Systems, CA, USA), with a lower limit of detection of 10 copies/mL. Biochemical response (BR), virological response (VR), and serological response (SR) were defined as normal ALT (<40 U/L), undetectable HBV DNA levels (<20 IU/mL), and HBeAg clearance (for HBeAg positive patients), respectively. **Results:** At baseline, the median age of patients was 41.0 years with 52.7% of HBeAg-positive. The median levels of ALT, HBV RNA, HBV DNA, and HBsAg were 68.2 U/L, 4.7 Log_{10} copies/mL, 6.2 Log_{10} IU/mL, and 3.6 Log_{10} IU/mL, respectively. HBeAg-positive patients had a higher median HBV RNA level (6.3 Log_{10} copies/mL vs. 2.4 Log_{10} copies/mL, $P<0.001$) than HBeAg-negative patients. Serum HBV RNA levels were positively associated with serum HBV DNA ($r=0.82$, $P<0.001$) and HBsAg levels ($r=0.69$, $P<0.001$). After 48 weeks of NAs treatment, 73.9%, 72.5%, and 9.4% of patients achieved BR, VR, and SR, respectively. Patients with baseline HBV RNA <5 Log_{10} copies/mL had significantly higher rates of VR (92.0% vs. 50.0%, $P<0.001$) and SR (20.0% vs. 6.6%, $P<0.001$) than those with baseline HBV RNA ≥ 5 Log_{10} copies/mL. However, the BR rates (75.4% vs. 72.7%, $P=0.505$) were comparable between patients with different HBV RNA levels. Baseline HBV RNA <5 Log_{10} copies/mL was associated with higher chance of achieving VR (OR 4.0, 95% CI: 2.3-6.9, $P<0.001$) after adjusted for age, sex, ALT levels, and HBeAg status, as well as SR (OR 4.4, 95% CI: 2.0-9.6, $P<0.001$) after adjusted for age, sex, and ALT levels. **Conclusion:** Baseline HBV RNA <5 Log_{10} copies/mL was associated with higher rates of VR and SR in CHB with NAs treatment. Serum HBV RNA may serve as a promising marker for predicting treatment response in CHB patients with NA therapy.

Disclosures: Jian Wang: Nothing to Disclose, Rui Huang: Nothing to Disclose, Chao Wu: Nothing to Disclose

1165 | TWO-YEAR HISTOLOGICAL EFFICACY OF TENOFOVIR ALAFENAMIDE ON LIVER FIBROSIS IN TREATMENT-NAÏVE PATIENTS WITH CHRONIC HEPATITIS B

Jialing Zhou[1] Xiaoning Wu[1] Chuanwu Zhu[2] Jiming Zhang[3] Ping Li[4] Tao Han[5] HUIGUO DING[6] Chenghai Liu[7] Wen Xie[8] Qing Xie[9] Yali Zong[10] Yameng Sun[1] Chen Shao[6] Hui Liu[6] Tongtong Meng[1] Hong You[1] Jidong Jia[1], [1]Beijing Friendship Hospital, Capital Medical University, [2]The Fifth People's Hospital of Suzhou, [3]Huashan Hospital, Shanghai Medical College, Fudan University, [4]Tianjin Second People's Hospital, [5]Tianjin Third Central Hospital, China, [6]Beijing Youan Hospital, Capital Medical University, [7]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, [8]Beijing Ditan Hospital, Capital Medical University, [9]Ruijin Hospital, Shanghai Jiaotong University School of Medicine, [10]The Ninth Hospital of Nanchang

Background: The antiviral efficacy of tenofovir alafenamide (TAF) has been well confirmed in patients with chronic hepatitis B (CHB) in both controlled trials and real-world studies. However, the histological effect of TAF on liver fibrosis remains unclear. **Methods:** This prospective study recruited treatment-naïve patients with CHB and biopsy-proven liver fibrosis or cirrhosis from 10 tertiary hospitals in China (NCT04939441). After receiving TAF monotherapy for 96 weeks, all participants received a second liver biopsy. Fibrosis regression was defined as a ≥ 1 stage decrease in fibrosis assessed by Ishak score or predominant regression as assessed by P-I-R criteria. Virological response (VR: HBV DNA <20 IU/mL) and biochemical response (ALT ≤ 40 IU/L), liver stiffness measurement (LSM) by VCTE, aspartate aminotransferase-to-platelet ratio index (APRI), and Fibrosis 4 Score (FIB-4), were also employed every 24 weeks during treatment. The Wilcoxon signed-rank test was used for non-parametric paired sample analysis. **Results:** A total of 100 treatment-naïve patients with CHB (61% HBeAg positive) were enrolled, with 82 patients completing a second liver biopsy and 80 of them provided assessable liver sections. At baseline, 10%, 39%, 30% and 21% of the participants had Ishak score 1/2, 3, 4, and 5/6, respectively; 34%, 34%,14% and 19% of them had necroinflammation activity grade (HAI) 1, 2, 3, and 4, respectively. After 96 weeks of TAF treatment, 70% (56/80) of the participants showed fibrosis regression, whereas 29% (23/80) showed no change in Ishak score. Among the 17 patients with cirrhosis at baseline, 15 achieved Ishak score decrease by ≥ 1 and 2 became predominant regression, resulting in a significantly higher regression rate than that in non-cirrhotic participants (17/17 vs 39/63, $p < 0.009$). Similarly, 52% of

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the participants showed a reduction of at least one grade of necroinflammation (HAI). The median HBV DNA level declined from 5.73 log IU/ml at baseline to 0 log IU/ml at week 96, achieving VR rates of 73% at week 48 and 86% at week 96. The ALT normalization rate was 78% at week 48 and 74% at week 96. The LSM decreased from 9.7 at baseline to 6.5 kPa at week 96 ($p < 0.001$), with 51% of the participants experiencing a $>30\%$ decline. APRI and FIB-4 scores also decreased significantly from 0.55 and 1.14 at baseline to 0.31 and 0.99 at week 96, respectively (both $p < 0.001$). **Conclusion:** After 96 weeks of TAF treatment, liver fibrosis was significantly regressed, as evidenced by improvements in both histological and non-invasive measurements.

Disclosures: Jialing Zhou: Nothing to Disclose, Xiaoning Wu: Nothing to Disclose, Chuanwu Zhu: Nothing to Disclose, Jiming Zhang: Nothing to Disclose, Ping Li: Nothing to Disclose, Tao Han: Nothing to Disclose, HUIGUO DING: Nothing to Disclose, Chenghai Liu: Nothing to Disclose, Wen Xie: Nothing to Disclose, Qing Xie: Nothing to Disclose, Yali Zong: Nothing to Disclose, Yameng Sun: Nothing to Disclose, Chen Shao: Nothing to Disclose, Hui Liu: Nothing to Disclose, Tongtong Meng: Nothing to Disclose, Hong You: Nothing to Disclose, Jidong Jia: Nothing to Disclose

1166 | HEPATOTOXIC-LIKE CD38$^+$HLADR$^+$PD1$^+$CD8$^+$ T CELLS DEFINE A FUNCTIONALLY DISTINCT SUBSET ASSOCIATED WITH HBSAG REDUCTION AND HBV-SPECIFIC IMMUNITY IN CHB

Hsiang-Wei Huang[1] Rachel Wen-Juei Jeng[2] Chia-Wei Lin[1] Yen-Chun Liu[3] Jian He Fan[1] Thi Kim Duyen Nguyen[1] Wei-Ting Ku[1] Cheng-Heng Wu[1] Chun-Yen Lin[1], [1]Chang Gung University, [2]Chang Gung Memorial Hospital, Linkou Medical Center, [3]Chang Gung Memorial Hospital, Linkou main branch

Background: Chronic hepatitis B (CHB) is characterized dysfunctional HBV-specific CD8$^+$ T cell responses. Recent studies suggest CD38$^+$HLADR$^+$CD8$^+$ T cells with hepatotoxic, innate-like features may contribute to liver inflammation in chronic hepatitis C. However, their relationship with HBV-specific immunity remains unclear. This study aimed to characterize these T cell subsets and evaluate their association with HBV-specific immune response in CHB patients. **Methods:** A total of 43 CHB patients with ALT $\geq 2\times$ the upper limit of normal (ULN) were prospectively enrolled at a treatment-free timepoint. Peripheral CD8$^+$ T cells were analyzed using a single-cell RNA sequencing (scRNAseq) approach. Flow cytometry was subsequently performed to validate cell phenotypes . HBV-specific T cell responses (Core, polymerase, X, and S peptides) were evaluated by IFN-γ ELISPOT. Associations between T cell subsets, HBV-specific immunity, and on-treatment HBsAg reduction velocity were analyzed by linear regression analysis. **Results:** A cluster of peripheral CD8$^+$ T cells, recognized as CD38$^+$HLADR$^+$CD8$^+$ T cells with a hepatotoxic transcriptome profile (Gehring et al., J Clin Invest, 2023) was identified by a scRNAseq approach using unsupervised clustering. This cluster showed a distinct transcriptional signature enriched in NK receptor pathways and cytokine-responsive modules, and exhibited significantly higher innate-like scores compared to the other CD8$^+$ T cell clusters. This CD38$^+$HLADR$^+$CD8$^+$ T cell cluster was further subclustered into PD1$^+$ and PD1$^-$ subsets. In CHB patients with active hepatitis before treatment, the frequency of PD1$^+$CD38$^+$HLADR$^+$CD8$^+$ T cells was significantly associated with the velocity of on-treatment HBsAg reduction (estimate: 0.626, $p < 0.01$). Furthermore, this subset was significantly correlated with HBV Core- and S-specific T cell responses as measured by ELISPOT (estimates: 7.511, $p < 0.01$; 3.812, $p < 0.05$, respectively). These associations were not observed in the PD1$^-$CD38$^+$HLADR$^+$CD8$^+$ T cell subset, suggesting functional heterogeneity within this hepatotoxic CD8$^+$ T cell cluster and a potential link to the rejuvenation of HBV-specific CD8$^+$T cells. **Conclusion:** PD1$^+$CD38$^+$HLADR$^+$CD8$^+$ T cells display hepatotoxic transcriptomic features. The frequency of this subset is significantly associated with HBV Core- and S-specific T cell responses and subsequent on-treatment HBsAg reduction. Therefore, this subset may be closely related to the recovery of HBV-specific CD8$^+$ T cell responses and contribute to HBsAg seroclearance.

Disclosures: Hsiang-Wei Huang: Nothing to Disclose, Rachel Wen-Juei Jeng: GSK: Advisor, Gilead: Advisor, Chia-Wei Lin: Nothing to Disclose, Yen-Chun Liu: Nothing to Disclose, Jian He Fan: Nothing to Disclose, Thi Kim Duyen Nguyen: Nothing to Disclose, Wei-Ting Ku: Nothing to Disclose, Cheng-Heng Wu: Nothing to Disclose, Chun-Yen Lin: Nothing to Disclose

1167 | CORE PROTEIN MUTATIONS IN HBSAG/HBV DNA DOUBLE-NEGATIVE OCCULT HEPATITIS B INFECTION AND THEIR BIDIRECTIONAL REGULATION ON VIRAL REPLICATION

Minghui Zeng[1] Liang Xu[1] Yuqiang Mi[1] Wentao Kuai[1], [1]Tianjin City Second People's Hospital

Background: Patients with occult hepatitis B virus infection (OBI) can transmit HBV through blood transfusion or vertical mother-to-child transmission. but the formation mechanism of OBI has not been fully clarified. HBV gene mutation is considered to be one of the key factors. Previous studies have mostly focused on the

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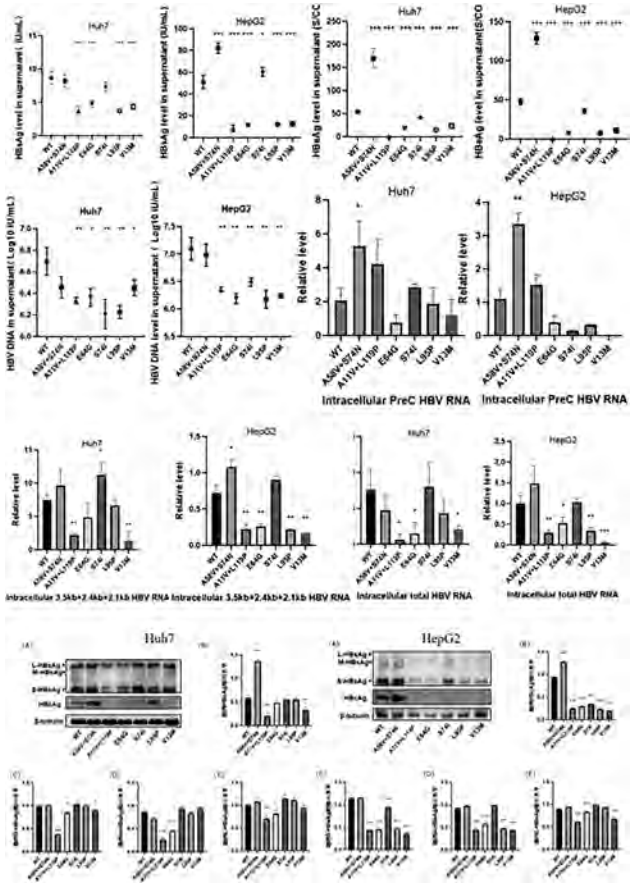
mutation characteristics of S region and X region in HBV DNA positive patients, while the exploration of core protein (CP) encoded by C region in HBsAg/HBV DNA double negative OBI population remains a blank. **Methods:** HBV DNA was extracted from the patient's serum by phenol-chloroform method, and the CP gene fragment of HBV DNA was amplified by nested PCR. The target fragment was purified and cloned into dPMD-18T vector and transformed into DH5α competent cells. Plasmid was extracted after plate coating and Sanger sequencing was used to confirm the amplified fragment sequence. Bioinformatics tools were used to predict mutant protein, and the dynamic changes of the mutant HBcAg were analyzed by molecular dynamics simulation. WT and mutant plasmids were transfected into Huh7 and HepG2 cell. Chemiluminescence microparticle immunoassay was used to detect HBsAg and HBeAg in supernatant, PCR- immunofluorescence probe method was used to quantify HBVDNA, the expression of intracellular HBcAg and HBsAg subtype (L/M/S) were analyzed by Western blot, and the levels of HBV RNA were detected by qPCR to systematically evaluate the effect of CP region mutation on HBV expression. **Results:** 1. All patients showed nucleotide mutations in CP region, with 100% mutation rates at G2137A/T and G2152T/A sites. 46.2%(6/13) of the patients had missense mutations, including A11V, V13M, A58V, E64G, S74N, S74I, L95P and L119P. Among them, two patients had double mutations, A58V +S74N and A11V+L119P respectively. 2. A58V+S74N mutation can increase the distribution area of CP in cytoplasm; E64G mutation can increase the isoelectric point of protein; The mutations of A58V+S74N, A11V +L119P and L95P cause the long helix of the protein to bend. 3. A58V+S74N mutation significantly promoted HBcAg synthesis and HBeAg expression, as well as the levels of HBV preC RNA and 3.5kb HBV RNA. 4. A11V +L119P and V13M mutations inhibited the synthesis of HBcAg, the expression of HBsAg, HBeAg and HBV DNA, and simultaneously reduce the level of 2.4 kb+2.1 kb HBV RNA. 5. E64G mutation inhibited the secretion of HBsAg, HBeAg and HBV DNA,accompanied by a decrease in the expression of 0.7 kb HBV RNA. 6. A11V +L119P and E64G Mutations significantly inhibited intracellular S/M/L-HBsAg synthesis, while V13M mainly showed the decrease of S-HBsAg synthesis. **Conclusion:** A58V+S74N mutation can promote virus transcription and protein expression, while other mutations suppress virus replication to varying degrees. Among them, A11V+L119P and V13M mutations may destroy the capsid assembly interaction between HBsAg and HBcAg, and E64G mutation may be related to X gene regulation.



Disclosures: Minghui Zeng: Nothing to Disclose, Liang Xu: Nothing to Disclose, Yuqiang Mi: Nothing to Disclose, Wentao Kuai: Nothing to Disclose

1168 | SERUM HEPATITIS B CORE-RELATED ANTIGEN LEVEL STRATIFIES RISK OF IMMUNE-ACTIVE TRANSITION IN INACTIVE CHRONIC HEPATITIS B PATIENTS

Kuan-Hui Hsin[1] Tai-Chung Tseng[1] Chun-Jen Liu[1] Chun-Ming Hong[1] Tung-Hung Su[1] Hung-Chih Yang[1] Chen-Hua Liu[1] Pei-Jer Chen[1] Jia-Horng Kao[1], [1]National Taiwan University Hospital

Background: Chronic hepatitis B (CHB) affects millions of people globally, with one-third classified as inactive CHB. However, 20-30% of them progress to immune-active CHB. We aimed to explore whether hepatitis B core-related antigen (HBcrAg), reflecting the size and transcriptional activity of covalently closed circular DNA (cccDNA), predicts immune-active transition, HBV-

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associated hepatitis and HCC, with the goal of refining risk stratification in this special population. **Methods:** Among 2666 treatment-naïve CHB patients from the ERADICATE-B cohort, 540 fulfilled the criteria of inactive CHB (non-cirrhotic, HBeAg-negative, persistently normal ALT at 1 year, HBV DNA < 2,000 IU/mL). Three viral biomarkers were determined retrospectively using stored serum samples. The endpoints were immune-active transition (ALT ≥ 2-fold the upper limit of normal (ULN) and HBV DNA ≥ 2,000 IU/mL), HBV-associated hepatitis (ALT ≥ 100 IU/L and HBV DNA ≥ 2,000 IU/mL) and HCC. Kaplan–Meier curves and Cox proportional hazard models were used to evaluate the long-term prognostic utility of HBcrAg. **Results:** Among the 540 inactive CHB patients, a total of 8,016.9 person-years of follow-up were accumulated (mean ± SD: 13.98 ± 5.91 years). During this period, 158 (1.97 %/y) progressed to immune-active CHB, 82 (0.96 %/y) experienced HBV-associated hepatitis, and 8 (0.09 %/y) developed HCC. Among three HBV biomarkers, HBcrAg outperformed HBsAg and HBV DNA in predicting immune-active transition, with an AUROC of 0.59 (95% CI: 0.54–0.64). Patients with HBcrAg levels ≥ 10 KU/mL (N = 172) had a higher risk of developing immune-active transition than those with levels < 10 KU/mL (N = 368), with a hazard ratio (HR) of 1.74 (95% CI: 1.27–2.39) (Table 1). In multivariable analysis including age, sex, HBcrAg, HBsAg, and HBV DNA, HBcrAg ≥ 10 KU/mL remained the only independent viral risk factor (Table 1). In addition, HBcrAg levels ≥ 10 KU/mL were also associated with increased risks of developing HBV-associated hepatitis (HR: 2.40, 95% CI: 1.55–3.71), and HCC (HR: 13.97, 95% CI: 1.72–113.54). **Conclusion:** Inactive CHB patients constitute a clinically heterogeneous population, and reliable viral markers are essential to guide clinical decision-making. Previous studies have demonstrated that serum HBsAg levels < 1000 IU/mL can effectively identify patients with low viral activity and minimal risk of HCC. In our study on 540 inactive CHB patients, baseline HBcrAg levels ≥ 10 KU/mL emerged as an independent predictor of immune-active transition, HBV-associated hepatitis and HCC. These findings underscore the clinical utility of HBcrAg, thereby supporting refinements to current management strategies.

	Patient Number	P-yrs of Follow-up	Events Number	Annual Incidence rate (per 100 P-yrs)	Crude HR (95% CI)	Adjusted HR (95% CI)
Gender						
Female	249	3703.34	73	1.97 (1.57-2.48)	1.0	1.0
Male	291	4313.54	85	1.97 (1.59-2.44)	0.98 (0.71-1.34)	0.99 (0.72-1.36)
Age (Per 1y)					0.99 (0.97-1.01)	1.00 (0.98-1.02)
HBV DNA (IU/ml)					1.23 (0.96-1.59)	1.18 (0.91-1.52)
HBsAg (IU/ml)						
< 1000	290	4310.49	74	1.72 (1.37-2.16)	1.0	1.0
≥ 1000	250	3706.39	84	2.27 (1.83-2.81)	1.30 (0.95-1.77)	1.09 (0.78-1.52)
HBcrAg (KU/ml)						
< 10	368	5564.27	89	1.60 (1.30-1.97)	1.0	1.0
≥ 10	172	2452.61	69	2.81 (2.22-3.56)	1.74 (1.27-2.39)	1.64 (1.17-2.29)

Table 1. Factors associated with transition to immune active chronic hepatitis B (CHB) in 540 inactive CHB patients by Cox proportional hazards regression model
P-yrs: person-years, HR: hazard ratio

Disclosures: Kuan-Hui Hsin: Nothing to Disclose, Tai-Chung Tseng: Nothing to Disclose, Chun-Jen Liu: Nothing to Disclose, Chun-Ming Hong: Nothing to Disclose, Tung-Hung Su: Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Merck Sharp and Dohme: Speaking and Teaching, Roche: Speaking and Teaching, Sysmex: Speaking and Teaching, Eisai: Speaking and Teaching, Hung-Chih Yang: Nothing to Disclose, Chen-Hua Liu: Nothing to Disclose, Pei-Jer Chen: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose

1169 | HEPATITIS B VIRUS CCCDNA FORMATION REGULATED BY DOCK11 VIA PARP1

Hideo Takayama[1] Kouki Nio[1] Taro Yamashita[1], *[1]Kanazawa University*

Background: Hepatitis B virus (HBV) infection is one of the most important infectious diseases worldwide. Although nucleos(t)ide analogues have enabled effective suppression of HBV replication in clinical settings, eliminating covalently closed circular DNA (cccDNA) formed in the nucleus of hepatocytes remains a major challenge. Consequently, the risk of HBV reactivation and carcinogenesis persists. We recently identified Dedicator of Cytokinesis 11 (DOCK11) as a molecule involved in HBV maintenance. In this study, we aimed to investigate the role of DOCK11 in HBV cccDNA formation. **Methods:** First, we established an in vitro system for HBV cccDNA formation by incubating nuclear extracts (NEs) with HBV relaxed circular DNA (rcDNA) isolated from the supernatant of HepAD38 cells, a liver-derived cell line that inducibly expresses the HBV genome. We then prepared NEs from DOCK11-overexpressing HepG2 cells and DOCK11-knockout Huh7 cells to evaluate the effect of DOCK11 in this in vitro system. Additionally, we performed immunoprecipitation of DOCK11 from the overexpression samples, followed by liquid chromatography-mass spectrometry (LC/MS) to identify key components of the DOCK11-HBV complex. Finally, we used super-resolution microscopy to observe DOCK11-overexpressing HepG2 cells and UV-irradiated DOCK11-knockdown Huh7 cells, in order to examine the interaction between DOCK11 and the identified component. **Results:** In vitro cccDNA formation system revealed that DOCK11 overexpression promotes HBV cccDNA formation by 42% ($p < 0.005$), while DOCK11 knockout suppresses HBV cccDNA formation by 85% ($p = 0.0001$). These results suggest that DOCK11 plays a regulatory role in HBV cccDNA formation. Immunoprecipitation experiments further indicated that DOCK11 forms a complex with HBV DNA. LC/MS analysis of the DOCK11-HBV

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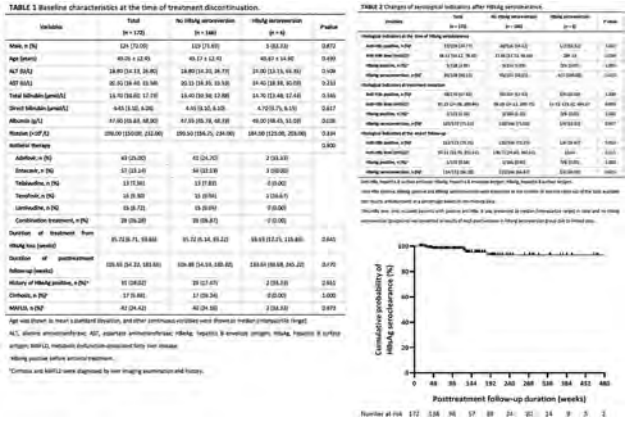
DNA complex identified poly [ADP-ribose] polymerase 1 (PARP1), a key molecule involved in DNA repair, as a major component of the complex. Moreover, super resolution microscopy demonstrated nuclear colocalization of DOCK11 and PARP1, and revealed that the recruitment of PARP1 to DNA damage sites is abolished in DOCK11-knockout cells. These results suggest that DOCK11 is essential for the recruitment of PARP1 to DNA damage sites. **Conclusion:** This study demonstrates that DOCK11 plays a crucial role in HBV cccDNA formation by forming a complex with HBV DNA and PARP1. These findings indicate that DOCK11 may serve as promising therapeutic target for preventing HBV cccDNA formation.

Disclosures: Hideo Takayama: Nothing to Disclose, Kouki Nio: Nothing to Disclose, Taro Yamashita: Nothing to Disclose

1170 | DURABILITY AND OUTCOMES OF HBSAG LOSS IN CHRONIC HEPATITIS B PATIENTS TREATED BY NUCLEOS(T)IDE ANALOGUE

Minghui Li[1] Si Xie[2] Weihua Cao[1] Xinxin Li[1] Ziyu Zhang[1], [1]Beijing Ditan Hospital, Capital Medical University, [2]Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University

Background: Hepatitis B surface antigen (HBsAg) seroclearance, is associated with improved outcomes for chronic hepatitis B (CHB) patients. Only few patients can achieve HBsAg loss through nucleos(t)ide analogue (NA) therapy, and little is known about it. So our study investigated the durability and outcomes of HBsAg loss achieved by NA therapy, and the predictive factors of HBsAg reversion in CHB patients. **Methods:** CHB patients who achieved confirmed HBsAg loss after NA therapy were retrospectively enrolled and followed up every 3-6 months. The sustained HBsAg loss rate was evaluated. The rate and the predictive factors of HBsAg reversion, the rate of hepatitis B virus (HBV) desoxyribose nucleic acid (DNA) relapse, and the incidence of hepatitis recurrence, decompensated cirrhosis, hepatocellular carcinoma (HCC) were also investigated. **Results:** Of the 172 patients included, sustained HBsAg seroclearance was found in 96.51% patients after 105.65 (54.22, 181.65) weeks post-treatment follow-up. Six patients occurred HBsAg reversion. Only one patient developed HBV DNA relapse following HBsAg seroreversion, which was accompanied by hepatitis recurrence. One patient experienced liver decompensation and another patient developed HCC. Hepatitis B surface antibody (anti-HBs) and consolidation treatment were not associated with HBsAg seroreversion. We did not find any predictive factors of HBsAg seroreversion in this study. **Conclusion:** The HBsAg loss induced by NA is stable in most of patients after discontinuation of treatment. Anti-HBs seroconversion is not a prerequisite for discontinuation of NA. Patients with CHB exhibit improved clinical outcomes after HBsAg seroclearance.



Disclosures: Minghui Li: Nothing to Disclose, Si Xie: Nothing to Disclose, Weihua Cao: Nothing to Disclose, Xinxin Li: Nothing to Disclose, Ziyu Zhang: Nothing to Disclose

1171 | LG2M AND AFP, WHEN COMBINED WITH PAGE-B, EFFECTIVELY RISK-STRATIFY CHB PATIENTS FOR EARLY AND LATE STAGE HCC REGARDLESS OF SLD STATUS

Michael Stec[1] Mark Anderson[1] Ming-Lung Yu[2] Chung-Feng Huang[2] Gavin Cloherty[1], [1]Abbott Laboratories, [2]Kaohsiung Medical University/ Kaohsiung Medical University Hospital

Background: Hepatocellular Carcinoma (HCC) causes both EpCAM and CD90 expressing cancer stem cells (CSCs) to form, and evidence of these CSCs can be found through the serological presence of AFP and LG2m, respectively. We highlight a risk-stratification method, PAGE-CSC, which combines PAGE-B with both LG2m and AFP immunoassays to effectively identify chronic hepatitis B (CHB) patients at risk for developing HCC within 5 years, regardless of Steatotic Liver Disease (SLD) comorbidities or HCC stage at time of diagnosis. **Methods:** AFP and research use only (RUO) LG2m immunoassays were run on the Alinity i platform (Abbott Laboratories) to analyze baseline (BL) serum collected from 1,016 CHB patients, 332 of which had SLD comorbidities. Patients were put on first-line NUC therapy and regularly monitored for over 10 years. GraphPad Prism 9 was then used to run Kaplan-Meier analyses from BL data to determine the effectiveness of

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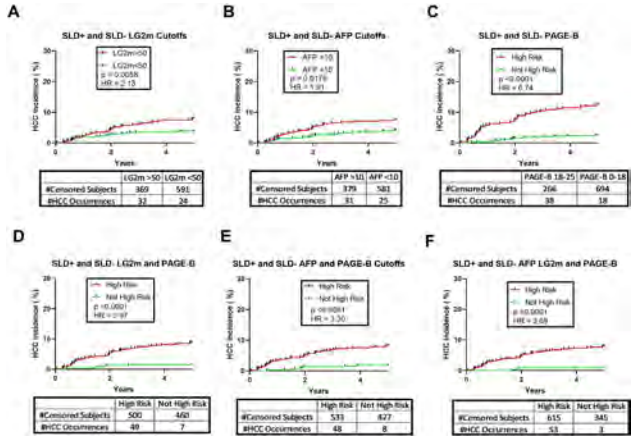
various HCC risk-stratification methods within the cohorts. **Results:** Kaplan-Meier analyses were run on BL PAGE-B for the SLD$^+$ and SLD$^-$ cohorts to identify those who would develop HCC within 5 years, both showed significance ($p < 0.0001$, and $p = 0.0003$, respectively). Additional Kaplan-Meier Analyses were run combining PAGE-B with a 10 ng/mL AFP cutoff, PAGE-B with a novel 50 pg/mL LG2m cutoff, and PAGE-B with both LG2m and AFP cutoffs between the cohorts, all of which showed significance ($p < 0.0001$, $p = 0.0007$, and $p = 0.0003$, respectively, for the SLD$^-$ cohort and $p = 0.0037$, $p = 0.0094$, and $p = 0.0092$ respectively for the SLD$^+$ cohort). While PAGE-B was effective in identifying 68.2% of patients in the SLD- cohort and 66.7% of patients in the SLD$^+$ cohort that developed HCC within 5 years, the risk-stratification model incorporating PAGE-B, AFP, and LG2m (PAGE-CSC) had the greatest sensitivity with 95% identification in the SLD$^-$ cohort and 91.7% identification in the SLD$^+$ cohort. Unsurprisingly when this same assessment was run on the combined cohort, this combined model of PAGE-CSC had the greatest sensitivity at 94.6% with a p-value of < 0.0001. By the Barcelona Clinic Liver Cancer (BCLC) staging system PAGE-CSC also improved upon PAGE-B by 17.6%, 25.0%, 50.0%, and 44.1% for stages 0, A, B, and C, respectively. **Conclusion:** The PAGE-CSC risk stratification system that combines the PAGE-B model with indicators of both EpCAM and CD90 expressing CSCs, through serological AFP and LG2m, respectively, better accounts for the heterogeneous nature of HCC than current proposed methods. This was proven in the SLD$^+$ cohort, the SLD$^-$ cohort, and the combined SLD$^{+/-}$ cohort and regardless of the HCC stage at time of diagnosis.



Disclosures: Michael Stec: Nothing to Disclose, Mark Anderson: Nothing to Disclose, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Chung-Feng Huang: Nothing to Disclose, Gavin Cloherty: Nothing to Disclose

1172 | ESTIMATING THE ECONOMIC BURDEN OF CHRONIC HEPATITIS B IN FRANCE USING THE FRENCH NATIONAL HEALTH DATA SYSTEM

Samuel Nilusmas[1] Clotilde Lepers[2] Paul Burgat[1] Jonathan Bellet[1] Clovis Lusivika Nzinga[1] Sylvie Deuffic-Burban[3] Fabrice Carrat[4], [1]Sorbonne Université, Inserm, iPLesp, Paris, France, [2]Université Paris Cité, Inserm, IAME, Hôpital Bichat, AP-HP Nord, Paris, France, [3]Université Paris Cité and Université Sorbonne Paris Nord, Inserm, IAME, Paris, France, [4]Sorbonne Université, Inserm, iPLesp, Hôpital Saint-Antoine, AP-HP, Paris, France

Background: Chronic hepatitis B (CHB) causes a wide spectrum of liver disease, from early-stage forms to life-threatening conditions such as decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC). Disease progression places a substantial burden on healthcare systems. We conducted a national observational study to estimate monthly healthcare costs by health state (pre-cirrhosis, cirrhosis, DC, HCC, liver transplantation [LT], death) using the French National Health Data System (SNDS). **Methods:** The SNDS covers over 99% of the French population. It includes information on reimbursed outpatient care, hospital discharge diagnoses, interventions, and death. We identified all individuals with CHB residing in France between 01/01/2012, and 31/12/2022. Health states were defined using ICD-10 codes. For each health state, and separately for nucleosit(d)ic analogues (NA) treated and untreated pre-cirrhotic patients, monthly costs per patient were estimated using descriptive statistics. Additional costs for LT and death were assessed separately. Disease state classification was clinically validated in a subset of ANRS CO22 HEPATHER patients individually linked to SNDS to assess the robustness of cost estimates. **Results:** A total of 114,662 patients with CHB were identified in the SNDS. Of these, 102,756 were in a pre-cirrhotic state, 10,273 in cirrhosis, 416 in DC, 372 in HCC, and 1,972 underwent LT. In the HEPATHER-linked cohort (n = 4,627), 3,985 were in a pre-cirrhotic state, 363 in cirrhosis, 203 in DC, 186 in HCC, and 122 underwent LT. In the SNDS, median monthly costs increased with disease severity: €107 for untreated pre-cirrhosis (Q1-Q3: 44-373), €314 (132–686) for treated pre-cirrhosis (€144 (55-764) excluding NA cost), €954 (403–2,111) for cirrhosis, €1,254 (480–2,898) for DC, €1,233 (558–2,561) for HCC and €1,520 (1,045–2,304) post-LT. Additional cost for LT was €55,538 (31,555–72,823) and those for death ranged from €4,713 (221-12,955) to €11,356 (289-19,762). In the HEPATHER-linked SNDS subset, costs were slightly lower but remained within similar ranges, supporting the consistency of the estimates across sources. **Conclusion:** This study provides robust

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stage-specific cost estimates for CHB using national administrative data. The consistency observed in the HEPATHER-linked subset supports the reliability of disease state identification and associated cost estimations in the SNDS. These estimates can inform cost-effectiveness analyses and lifetime projections using Markov models.

Disclosures: Samuel Nilusmas: Nothing to Disclose, Clotilde Lepers: Nothing to Disclose, Paul Burgat: Nothing to Disclose, Jonathan Bellet: Nothing to Disclose, Clovis Lusivika Nzinga: Nothing to Disclose, Sylvie Deuffic-Burban: Nothing to Disclose, Fabrice Carrat: Nothing to Disclose

1173 | THE RELATIONSHIP BETWEEN THE DURABILITY OF RESPONSE TO INTERFERON THERAPY FOR HEPATITIS B VIRUS INFECTION AND THE PROPORTION/FUNCTION OF HLA-DR+CD38+CD8+ T LYMPHOCYTES

Minghui Li[1] Yao Xie[1] Yanjie Lin[2] weihua cao[1], [1]Beijing Ditan Hospital, Capital Medical University, [2]Peking University First Hospital

Background: Interferon (IFN) exerts dual roles in anti-hepatitis B virus (HBV) therapy, including direct antiviral effects and immune modulation. Some patients exhibit an early hepatitis B surface antigen (HBsAg) response during the initial phase of IFN therapy, but HBsAg decline stagnates in later stages, and antiviral efficacy diminishes even with continued IFN treatment. The immunological mechanisms underlying this phenomenon remain unclear. Activated CD8+ T lymphocytes play a pivotal role in viral clearance, and the co-expression of CD38 and HLA-DR serves as a key marker of T cell activation. Therefore, we aimed to investigate the phenotypic and functional changes of HLA-DR+CD38+CD8+ T lymphocytes in chronic hepatitis B (CHB) patients receiving IFN therapy and their association with sustained IFN treatment response. **Methods:** CHB patients were divided into three groups: treatment-naive, nucleos(t)ide analog (NAs)-experienced, and IFN-experienced plateau groups. After baseline assessments, treatment-naive and some NAs-experienced patients received Peg-IFNα therapy. Patients in the IFN-experienced plateau group (showing stagnant HBsAg decline) discontinued IFN and resumed it after a treatment-free interval. Peripheral blood samples were collected at specified timepoints to assess clinical indicators and analyze HLA-DR+CD38+CD8+ T cell phenotypes/function via flow cytometry. **Results:** A total of 151 patients were enrolled: 53 treatment-naive, 51 NAs-experienced, and 47 IFN-experienced plateau patients. HLA-DR+CD38+CD8+ T cells were further stratified into HLA-DR+CD38dim and HLA-DR+CD38hi subsets. During IFN therapy, both treatment-naive and NAs-experienced groups showed an initial surge in HLA-DR+CD38dim subsets (all $P < 0.0001$), followed by a significant decline (all $P < 0.0001$), while HLA-DR+CD38hi subsets increased markedly (all $P < 0.0001$) (Figure 1A-B). In IFN-experienced plateau patients, after 12–24 weeks of discontinuation, HLA-DR+CD38dim subsets rebounded ($P < 0.0001$), whereas HLA-DR+CD38hi subsets decreased ($P < 0.0001$). Upon IFN retreatment for 12–24 weeks, HLA-DR+CD38dim subsets declined again ($P < 0.0001$), while HLA-DR+CD38hi subsets increased ($P < 0.001$), accompanied by significant HBsAg reduction compared to baseline ($P < 0.05$). Notably, only HLA-DR+CD38hi subsets showed sustained reduction post-retreatment ($P < 0.05$) (Figure 1C). Compared to HLA-DR+CD38dim subsets, HLA-DR+CD38hi cells exhibited lower co-stimulatory molecule expression and impaired cytotoxic effector function (Figure 2). **Conclusion:** During IFN therapy, the transition of HLA-DR+CD38dim (activated) to HLA-DR+CD38hi (cytotoxic-impaired) subsets in CD8+ T cells may explain the loss of sustained antiviral efficacy. Intermittent IFN therapy reverses this trend, overcoming the IFN plateau phase and restoring antiviral activity.

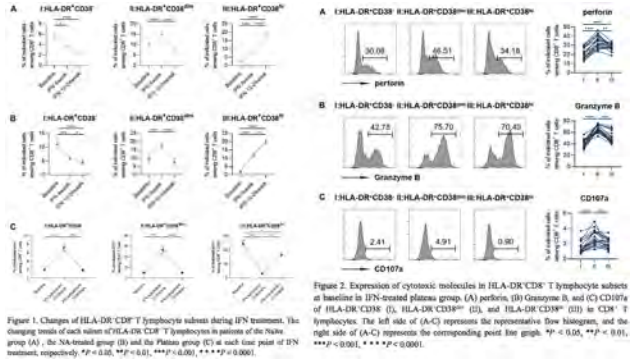

Figure 1. Changes of HLA-DR⁺CD8⁺ T lymphocyte subsets during IFN treatment. The changing trends of each subset of HLA-DR⁺CD8⁺ T lymphocytes in patients of the Naïve group (A) , the NA-treated group (B) and the Plateau group (C) at each time point of IFN treatment, respectively. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, * * * *$P < 0.0001$.

Figure 2. Expression of cytotoxic molecules in HLA-DR⁺CD8⁺ T lymphocyte subsets at baseline in IFN-treated plateau group. (A) perforin, (B) Granzyme B, and (C) CD107a of HLA-DR⁺CD38⁻ (I), HLA-DR⁺CD38^{dim} (II), and HLA-DR⁺CD38^{hi} (III) in CD8⁺ T lymphocytes. The left side of (A-C) represents the representative flow histogram, and the right side of (A-C) represents the corresponding point line graph. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, * * * *$P < 0.0001$.

Disclosures: Minghui Li: Nothing to Disclose, Yao Xie: Nothing to Disclose, Yanjie Lin: Nothing to Disclose, weihua cao: Nothing to Disclose

1174 | LACTATE TRIGGERS HBV-SPECIFIC CD8⁺ T CELL EXHAUSTION THROUGH MITOPHAGY SUPPRESSION-MEDIATED MITOCHONDRIAL DYSFUNCTION

yongyin li[1] Zhipeng liu[1] yuhao Wang[1] Shihong Zhong[1] Linnan Song[1] Ziqian Yu[1] chen wang[1] Xiaoyi Liu[1] Libo Tang[1], [1]NanFang Hospital,Southern Medical University

Background: Hepatitis B virus (HBV) -specific T cells exhibit an exhausted phenotype associated with glycolytic metabolic disruption and perturbation of

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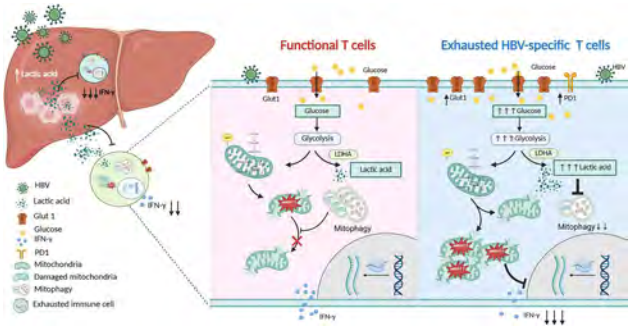
mitochondrial homeostasis. However, their relationship and underlying mechanisms remain elusive. Since lactate, a key glycolytic metabolite that can modulate immune response, we investigated its role in HBV-specific T cell dysfunction during chronic HBV infection. **Methods:** We recruited 242 patients with chronic HBV infection and 78 health controls. The metabolic characteristics of peripheral blood mononuclear cells (PBMC) were comprehensively analyzed using RNA-seq, metabonomics and scRNA-seq. Additionally, we systematically evaluated the glucose uptake, mitochondrial function, autophagy flux, and mitophagy activity of HBV-specific $CD8^+$ T cells using flow cytometry from both PBMC and liver mononuclear cells (LMC). To investigate lactate-mediated T cell exhaustion, we performed exogenous stimulations with Bay-876, lactate, Oligomycin, and Midivi-1, and assessed through multiparametric cytokine profiling and functional assays. **Results:** The glucose metabolic status in PBMC was significantly activated during HBV infection, accompanied by the accumulation of lactate. Specifically, HBV-specific $CD8^+$ T cells exhibited more dramatically increased Glut1 expression and 2-NBDG uptake than global T cells, especially in intrahepatic HBV-specific $CD8^+$ T cells. Restraining glucose uptake *via* Bay-876 improved HBV-specific T cell function, while lactate accelerated their dysfunction. Mechanistically, lactate elicited aberrant mtROS production and mitochondrial membrane potential *via* suppressing mitophagy dysfunction. Meanwhile, reversing mitochondrial dysfunction by MitoQ and MitoTempo restored the HBV-specific T cells function. However, aggravating mitophagy impairment by Midivi-1blunted the production of IFN-γ and TNF-α in HBV-specific T cell. Concurrently, dysfunctional autophagy also significantly contributed to HBV-specific T cells dysfunction, but this effect was independent of the lactate-mediated exhaustion pathway. **Conclusion:** Lactate drives HBV-specific T cell exhaustion by disrupting mitochondrial function *via* restraining mitophagy. These results highlight lactate metabolism as a potential therapeutic target for chronic HBV infection.



Disclosures: yongyin li: Nothing to Disclose, Zhipeng liu: Nothing to Disclose, yuhao Wang: Nothing to Disclose, Shihong Zhong: Nothing to Disclose, Linnan Song: Nothing to Disclose, Ziqian Yu: Nothing to Disclose, chen wang: Nothing to Disclose, Xiaoyi Liu: Nothing to Disclose, Libo Tang: Nothing to Disclose

1175 | ELEVATED HBCRAG LEVELS ARE ASSOCIATED WITH YOUNG-ONSET HEPATOCELLULAR CARCINOMA IN HBV INFECTION

YOSHIAKI KOBAYASHI[1] Taiki Okumura[1], [1]Shinshu University School of Medicine

Background: Young-onset hepatocellular carcinoma (HCC) in patients with hepatitis B virus (HBV) infection poses a significant clinical challenge. Hepatitis B core-related antigen (HBcrAg) can reflect intrahepatic covalently closed circular DNA activity in HBV patients; however, its significance in young-onset HCC remains underexplored. The present study examined the age-dependent distribution patterns of HBcrAg and other disease markers along with their association with young-onset HCC. **Methods:** This retrospective cross-sectional investigation analyzed two cohorts from Shinshu University Hospital. Cohort 1 included 101 elderly ($\geq$65 years) HBV-infected patients without a history of HCC recruited between April 2018 and February 2022. Cohort 2 comprised 43 patients with newly diagnosed HBV-related HCC who were seen between May 2005 and June 2023 and categorized as either young-onset ($<$65 years) or elderly-onset ($\geq$65 years). HBcrAg was measured using an ultrasensitive immunoassay (iTACT technology, Fujirebio Inc., Tokyo, Japan). **Results:** In Cohort 1, 13.9% (14/101) of cases were HBcrAg positive using conventional sensitivity testing (3.0 log U/mL), suggesting an association between lower HBcrAg and decreased young-onset HCC risk. In Cohort 2, young-onset HCC patients had significantly higher alanine aminotransferase (median 39 vs. 21 U/L, $p=0.006$), HBV DNA (3.3 vs. 1.8 log IU/mL, $p=0.031$), and iTACT-HBcrAg (4.9 vs. 2.5 log U/mL, $p<0.001$) levels compared with elderly-onset patients. Hepatitis B e antigen positivity was also significantly more frequent in the young-onset group (29.4% vs. 7.7%, $p=0.049$). Multivariable analysis revealed iTACT-HBcrAg level as significantly associated with young-onset HCC (odds ratio 1.78; 95% confidence interval 1.20–2.63; $p=0.004$). Moreover, HBcrAg demonstrated superior predictive performance (area under the receiver operating characteristic curve [AUROC] 0.80) versus both hepatitis B surface antigen (AUROC 0.67) and fibrosis-4 index (AUROC 0.50) for young-onset HCC, with a calculated optimal cut-off value of 3.0 log U/mL. At this threshold, young-onset HCC patients had a significantly higher HBcrAg positivity rate compared with elderly-onset patients (88.2% vs. 34.6%, $p<0.001$).

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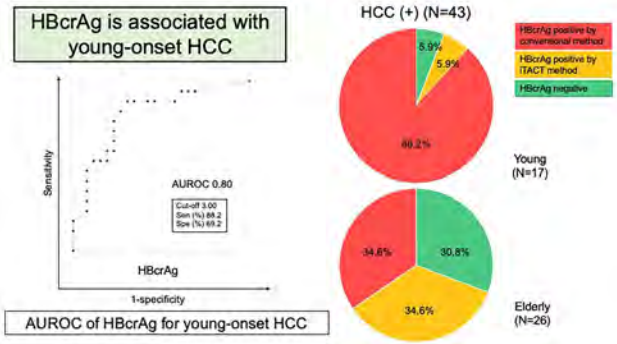
Conclusion: HBcrAg may represent a useful biomarker to identify younger HBV patients at increased risk of HCC for closer follow-up.



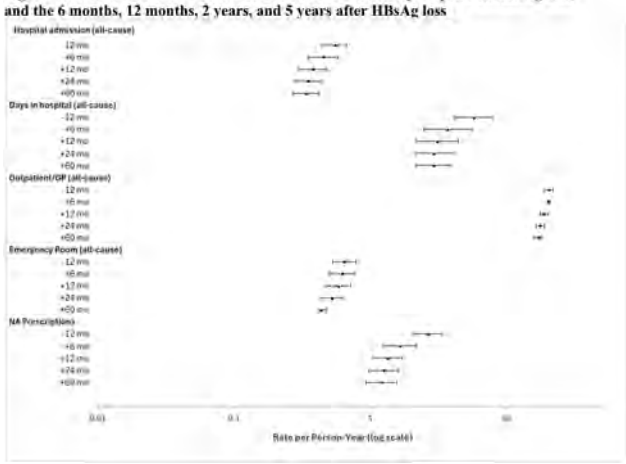
Disclosures: YOSHIAKI KOBAYASHI: Nothing to Disclose, Taiki Okumura: Nothing to Disclose

1176 | CHARACTERISTICS AND HEALTHCARE RESOURCE UTILIZATION FOR PATIENTS EXPERIENCING HEPATITIS B SURFACE ANTIGEN LOSS AND LIVING WITH CHRONIC HEPATITIS B VIRUS IN THE UNITED STATES

Myriam Drysdale[1] Rose Chang[2] Megan Pinaire[2] Manasi Mohan[2] Rui Song[2] Shuang Wang[2] Theo Man[2] Anna Coutinho[3] Mei Sheng Duh[2] Dickens Theodore[4] Iain Gillespie[5], [1]GSK, London, UK, [2]Analysis Group, Inc., Boston, MA, USA, [3]GSK, Collegeville, PA, USA, [4]GSK, Durham, NC, USA, [5]GSK, Stevenage, UK

Background: Chronic hepatitis B virus (cHBV) infection represents a critical public health issue worldwide and in the United States (US). The loss of hepatitis B surface antigen (HBsAg) is regarded as an indicator of functional cure in cHBV infection; however, its influence on healthcare resource utilization (HCRU) within the US population is not well understood. **Methods:** A retrospective cohort study was conducted using data from the Optum® electronic health records database for patients with cHBV infection between 1 Jan 2012 and 31 Dec 2019. Exposure was HBsAg loss, defined as ≥2 consecutive negative HBsAg tests ≥6 months apart, with the second marking date of loss. Time to seroreversion up to 5 years was also evaluated using Kaplan-Meier analysis. HCRU outcomes such as hospital admissions, emergency room (ER) visits, outpatient visits, and anti-HBV prescriptions were evaluated among patients with HBsAg loss and reported as rates per person-year (PPY) in the 12 months prior to HBsAg loss and 6, 12, 24, and 60 months post-HBsAg loss. **Results:** A total of 24,694 patients were included (~11% on stable nucleos(t)ide analogue [NA] treatment), among whom 776 (3%) experienced HBsAg loss. Nine patients (1%) seroreverted within 5 years of follow-up; median time to seroreversion was not reached. Hospital admissions, days in hospital and NA prescriptions were numerically lower in the 12 months after than in the 12 months before HBsAg loss (0.4 vs 0.6 PPY; 3.1 vs 5.7 PPY; 1.3 vs 2.6 PPY, respectively). Rate of ER visits was 0.7 PPY in the 12 months before HBsAg loss, 0.6 PPY in the 12 months after loss, and 0.4 PPY in the 60 months after loss. Rate of outpatient visits was 20.4 PPY in the 12 months before HBsAg loss, 18.9 in the 12 months after loss and 17.0 in the 60 months after loss. **Conclusion:** Rates of all-cause HCRU and NA prescriptions were numerically lower after HBsAg loss than before HBsAg loss. HBsAg loss, although rare, was found to be durable, with a very small proportion of patients experiencing seroreversion within 5 years. Funding: GSK Study 217281.

Figure: All-cause and cHBV-related HCRU rates PPY in the year prior to HBsAg loss, and the 6 months, 12 months, 2 years, and 5 years after HBsAg loss



Disclosures: Myriam Drysdale: Nothing to Disclose, Rose Chang: Nothing to Disclose, Megan Pinaire: Nothing to Disclose, Manasi Mohan: Nothing to Disclose, Rui Song: Nothing to Disclose, Shuang Wang: Nothing to Disclose, Theo Man: Nothing to Disclose, Anna Coutinho: GSK: Employee, Mei Sheng Duh: GSK: Grant/Research Support, Abbvie Inc.: Grant/Research Support, Acadia Pharmaceuticals Inc.: Grant/Research Support, Alexion Pharmaceuticals, Inc.: Grant/Research Support, Abbvie Inc.: Grant/Research Support, Acadia Pharmaceuticals Inc.: Grant/Research Support, Acadia Pharmaceuticals Inc.: Grant/Research Support, Alexion Pharmaceuticals, Inc.: Grant/Research Support, Apellis Pharmaceuticals Inc.: Grant/Research Support, Astrazeneca: Grant/Research Support, Biomarin Pharma-

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1177 | CONSTRUCTION OF A COMBINED PREDICTIVE MODEL FOR LIVER FIBROSIS STAGING IN CHRONIC HEPATITIS B PATIENTS BASED ON CAPSID-ANTIBODY-COMPLEXES

Jin Li[1] Li Zhu[2] Tingting Li[2], [1]The Affiliated Infectious Diseases Hospital of Soochow Unive, [2]The Affiliated Infectious Diseases Hospital of Soochow University

Background: Hepatitis B virus infection represents a significant public health challenge globally, as it can lead to the progressive development of liver fibrosis. There exists a significant lack of effective noninvasive predictive models for liver fibrosis staging assessment in chronic hepatitis B (CHB) patients. Our previous studies identified that circulating CACs display significant positive correlation with liver fibrosis staging. This paper aims to establish a combined predictive model for liver fibrosis staging of chronic hepatitis B patients based on circulating capsid-antibody-complexes (CACs) and to facilitate clinical implementation. **Methods:** A total of 161 treatment-native CHB patients who underwent liver biopsy were enrolled and divided into two groups: 64 individuals with no or mild fibrosis (S < 2) and 97 individuals with advanced fibrosis (S ≥ 2). The expression levels of circulating CACs were determined by enzyme-linked immunosorbent assay (ELISA) techniques. Univariate and multivariate logistic regression analysis was used to screen the key factors for liver fibrosis staging of CHB patients. Receiver operating characteristic curve (ROC) was used to evaluate the diagnostic efficiency of the combined prediction model. **Results:** The expression levels of CACs ($P = 6.19E-11$), M30 ($P = 1.60E-13$), M65 ($P = 6.79E-11$), ALT ($P = 2.20E-5$), AST ($P = 6.16E-8$), GGT ($P = 0.0009$), ALB ($P = 0.0120$), PLT ($P = 9.62E-7$), APRI ($P = 1.54E-11$) and FIB-4 ($P = 6.19E-8$) scores displayed statistically differences between the S < 2 group and the S ≥ 2 group. Importantly, circulating CACs exhibited the most significant positive correlation with liver fibrosis staging (r = 0.5253, $P = 3.3E-3$). Through univariate and multivariate logistic regression analysis, circulating CACs, M30 and PLT were identified as independent key factors for liver fibrosis staging of CHB patients. Furthermore, a combined prediction model was constructed as follows: logistic(p) = -1.976 + 3.701*CACs + 0.036*M30 - 0.014*PLT, with an area under the ROC curve (AUC) of 0.923, a sensitivity of 93.8% and a specificity of 81.2%. The performance of our combined model was superior to APRI (AUC = 0.814) and FIB-4 score (AUC = 0.752), and the differences were statistically significant between the ROC curves (P < 0.05). **Conclusion:** In our study,it was identified that circulating CACs, M30, and PLT serve as independent predictors for liver fibrosis staging of CHB patients. Based on these key biomarkers, a promising combined model for liver fibrosis staging was constructed and evaluated. This combined model based on circulaing CACs demonstrated high predictive diagnostic efficiency for liver fibrosis staging. It may contribute to achieving more accurate liver fibrosis staging assessment in clinical, thereby facilitating precise treatment and functional cure for CHB patients.

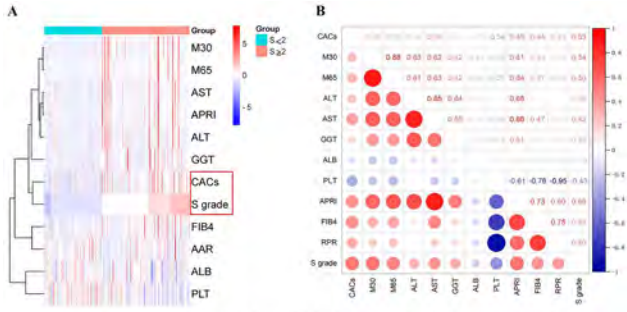

Figure 1. Cluster and correlation analysis revealed that the CACs level positively correlated with S grade.

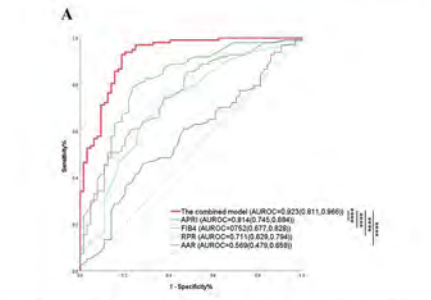

Figure 2. The area under the ROC curve of the combined model (Logit(p) = -1.908 + 3.647*CACs + 0.035*M30 - 0.014*PLT) was 0.923.

Disclosures: Jin Li: Nothing to Disclose, Li Zhu: Nothing to Disclose, Tingting Li: Nothing to Disclose

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1178 | A PHASE 1 STUDY OF THE SIRNA HRS-5635 IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC HEPATITIS B

Zhaoyi Yang[1] Yongyi Zeng[2] Xian Yu[3] Shuang Li[4] Guang-Ming Li[4] Xuebing Yan[5] Xuejia Zhai[6] Lingling Xu[7] Ying Wang[7] Huilan Zhu[7] Aizong Shen[1], [1]The First Affiliated Hospital of University of Science and Technology of China, [2]Mengchao Hepatobiliary Hospital of Fujian Medical University, [3]The Second Affiliated Hospital of Chongqing Medical University, [4]Zhengzhou Sixth People's Hospital, [5]The Affiliated Hospital of Xuzhou Medical University, [6]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, [7]Jiangsu Hengrui Pharmaceuticals

Background: HRS-5635 is a novel N-acetyl-D-galactosamine–conjugated siRNA that targets the HBV X gene, suppressing the expression of viral proteins, and thereby exerting antiviral effects. This first-in-human study aimed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of HRS-5635 in healthy volunteers and patients with chronic hepatitis B (CHB). **Methods:** This was a multicenter, randomized, double-blind, placebo-controlled phase 1 study (ClinicalTrials.gov: NCT05808374). In the single ascending dose (SAD) part, healthy volunteers received subcutaneous HRS-5635 at 50, 100, 200, 400, and 600 mg (n = 3 for 50 mg; n = 6 each for other dose levels) or placebo (n = 10). In the multiple ascending dose (MAD) part, nucleoside analog-treated CHB patients were given 3 subcutaneous HRS-5635 at 100 mg, 200 mg, or 400 mg every 4 weeks (n = 6 per dose level) or placebo (n = 6). **Results:** HRS-5635 was safe and well tolerated in healthy and CHB participants. In the MAD, the most common treatment-emergent adverse events (TEAEs) occurring more frequently with HRS-5635 than placebo were upper respiratory tract infection, increased blood creatine phosphokinase (CK), hypercalcemia, and increased blood CK MB. No TEAEs led to treatment discontinuation. No serious TEAEs or TEAEs leading to death occurred. After single dose of HRS-5635, absorption was rapid, with a median T_{max} of 3.00 to 6.00 h; the geometric mean $t_{1/2}$ was 3.97 to 5.12 h; HRS-5635 was essentially cleared from plasma within 48 h post-dose; and its exposure increased in an approximately dose-proportional manner from 50 to 200 mg, but increased more than dose proportionally at 200 to 600 mg. No obvious differences in plasma exposure were found between healthy and CHB participants. HRS-5635 showed no apparent accumulation upon 3 doses administered every 4 weeks. The maximum reduction in hepatitis B surface antigen (HBsAg) from baseline was 1.615 to 1.886 $\log_{10}$ IU/mL after 3 doses of HRS-5635 administered every 4 weeks, compared with 0.009 $\log_{10}$ IU/mL with placebo. **Conclusion:** HRS-5635 at the tested doses were tolerated, showed favorable safety and pharmacokinetic profiles, and demonstrated preliminary evidence of antiviral activity through HBsAg reduction, supporting further clinical development of HRS-5635 for treating CHB.

Disclosures: Zhaoyi Yang: Nothing to Disclose, Yongyi Zeng: Nothing to Disclose, Xian Yu: Nothing to Disclose, Shuang Li: Nothing to Disclose, Guang-Ming Li: Nothing to Disclose, Xuebing Yan: Nothing to Disclose, Xuejia Zhai: Nothing to Disclose, Lingling Xu: Nothing to Disclose, Ying Wang: Nothing to Disclose, Huilan Zhu: Nothing to Disclose, Aizong Shen: Nothing to Disclose

1179 | HEPATIC STEATOSIS INHIBITS HEPATITIS B VIRUS REPLICATION BY PROMOTING MIR-122-5P-SOX4

Guanghui Ren[1] Sitong Yi[1] Shi Yin[1] Guiqun Huang[1] Ying Zhu[1], [1]Department of Infectious Disease, The First Affiliated Hospital of Dalian Medical University, Dalian, China

Background: Chronic hepatitis B (CHB) and metabolic dysfunction-associated fatty liver disease (MAFLD) are prevalent chronic liver diseases. The rising incidence of CHB-MAFLD comorbidity necessitates exploration of their interplay. MiR-122, a liver-specific miRNA, modulates chronic liver diseases, but its role in CHB-MAFLD remains unclear. **Methods:** Serum miR-122 levels in CHB patients with or without MAFLD were assessed via qPCR. Bioinformatics identified miR-122-5p targets linked to comorbidity. An HBV-infected steatotic cell model was used to evaluate miR-122-5p's effects on viral replication and targets. Gene knockdown/overexpression and molecular assays (qPCR, Western blot, ELISA) elucidated the roles of miR-122/SOX4 in HBV regulation. **Results:** A total of 360 patients with CHB were included, of which 66.1% received antiviral therapy. The antiviral regimens included nucleoside analogue (NAs) monotherapy as well as polyethylene glycol interferon α-2b in combination/sequence with NAs. Interferon therapy accounted for 27.8% of the cases and NAs accounted for 72.2% of the cases. CHB-MAFLD patients showed reduced HBV DNA, pgRNA, HBsAg (all $P < 0.05$), and elevated miR-122 versus CHB-only on baseline. The downstream target gene of miR-122-5p was SOX4. The comorbidity model exhibited suppressed HBV replication markers (DNA, pgRNA, HBsAg, HBcrAg) and upregulated miR-122-5p/SOX4. MiR-122-5p knockdown increased HBV replication, while overexpression suppressed it. Similarly, SOX4 knockdown enhanced HBV activity, whereas SOX4 overexpression inhibited it.

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Conclusion: CHB-MAFLD comorbidity may suppress HBV replication via miR-122/SOX4 upregulation, suggesting a novel regulatory axis. This highlights miR-122 as a potential therapeutic target in dual-pathology management.

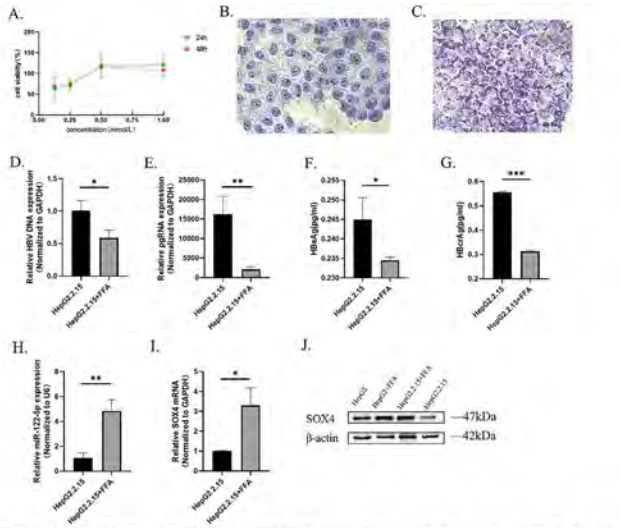


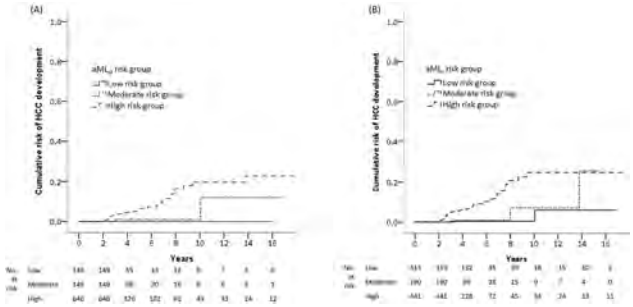
Figure 1. Establishment of Steatotic HBV-Infected Cell model and expression levels of hepatitis B virus, miR-122-5p and SOX4. A. CCK8 method to screen the optimal stimulation concentration and time of FFA; B. 200× magnification images of BSA group; C. 200× magnification images of FFA group; D. HBV DNA expression level; E. pgRNA expression level; F. HBsAg expression level; G. HBcrAg expression level; H. miR-122-5p expression level; I. SOX4mRNA expression level; J. SOX4 protein expression level. * indicates $p < 0.05$, ** indicates $p < 0.01$, *** indicates $p < 0.001$.

Disclosures: Guanghui Ren: Nothing to Disclose, Sitong Yi: Nothing to Disclose, Shi Yin: Nothing to Disclose, Guiqun Huang: Nothing to Disclose, Ying Zhu: Nothing to Disclose

1180 | ENHANCED PREDICTION OF HBV-RELATED HCC USING AMAP AND LIVER STIFFNESS ASSESSED BY VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY

Hye Yeon Chon[1] Hyung Joon Yim[2] Su Jong Yu[3] JA KYUNG KIM[1] Sang Hoon Ahn[4] Yeon Seok Seo[5] Seung Up Kim[4] sang gyune kim[6], [1]Yongin Severance Hospital, Yonsei University College of Medicine, [2]Korea University Ansan Hospital, Korea University College of Medicine, [3]Seoul National University College of Medicine, [4]Yonsei University College of Medicine, [5]Korea University College of Medicine, [6]Soonchunhyang University Bucheon Hospital

Background: While the age-male-albumin-bilirubin-platelet (aMAP) score combined with liver stiffness (LS) measurement has shown promise in assessing liver fibrosis, its utility in predicting hepatocellular carcinoma (HCC) risk remains unexplored. This study evaluated the feasibility and predictive performance of combining the aMAP score with LS measurements for HCC in patients with chronic hepatitis B (CHB). **Methods:** We analyzed 944 CHB patients who initiated antiviral therapy (AVT) between May 2005 and July 2021 at five tertiary hospitals in Korea. All patients underwent baseline and 2- year vibration-controlled transient elastography (VCTE) assessments. The predictive accuracy of aMAP alone, and aMAP combined with LS for advanced fibrosis (aML_{af}), and aMAP combined with LS for cirrhosis (aML_c) was assessed using receiver operating characteristic (ROC) curve analysis, calibration plots, and decision curve analysis. **Results:** During a median follow-up of 47.7 months, 44 patients developed HCC, whose aMAP was significantly higher than that of the patients who did not develop HCC. The aML_{af} and aML_c models demonstrated superior predictive performance compared to conventional models, with AUROCs at 3 years of 0.843 and 0.839, respectively (both $P < 0.05$ versus PAGE-B and modified PAGE-B). In multivariate analysis, elevated aMAP (hazard ratio [HR] = 1.125, 95% confidence interval [CI] = 1.033-1.225), aML_{af} (HR = 1.049, 95% CI = 1.005-1.095), and aML_c (HR = 1.039, 95% CI = 1.008-1.071) were independent predictors for HCC development. Notably, no HCC cases occurred in the aML_{af} low-risk group during follow-up. **Conclusion:** The integration of aMAP score with LS measurements significantly improves HCC risk prediction in CHB patients receiving antiviral therapy. This combined model may enable more precise risk stratification and personalized surveillance strategies.



Disclosures: Hye Yeon Chon: Nothing to Disclose, Hyung Joon Yim: Nothing to Disclose, Su Jong Yu: Nothing to Disclose, JA KYUNG KIM: Nothing to Disclose, Sang Hoon Ahn: Nothing to Disclose, Yeon Seok Seo: Nothing to Disclose, Seung Up Kim: Nothing to Disclose, sang gyune kim: Nothing to Disclose

1181 | SINGLE-CELL ATLAS REVEALED METABOLICALLY ACTIVE T CELLS AND MONOCYTES AS DRIVERS OF HBSAG SEROCONVERSION IN HBV REACTIVATION PATIENTS

Jayesh Kumar Sevak[1] MOJAHIDUL ISLAM[1] Gayantika Verma[1] Manoj Kumar[1] Ankur Jindal[1] Varsha Shasthry[1]

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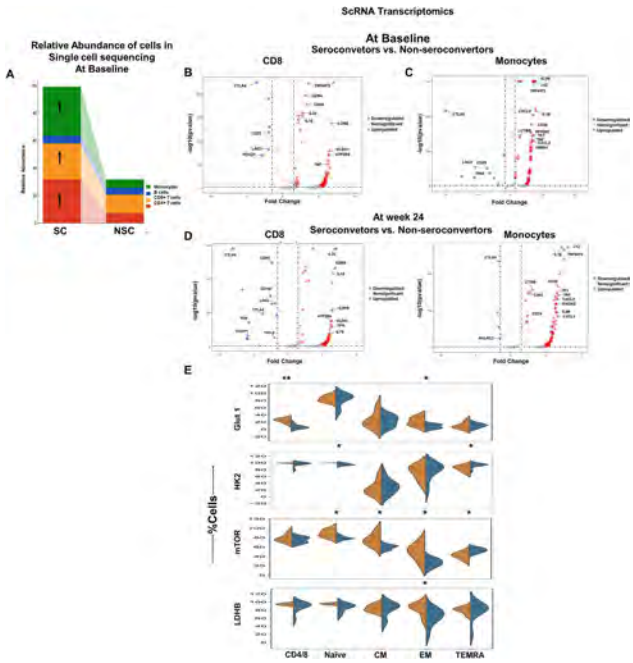
Syed Naqui Kazim[2] Shiv Kumar Sarin[1] Nirupma Trehanpati[1], [1]Institute of Liver and Biliary Sciences, [2]. Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, New Delhi, India

Background: HBsAg seroconversion is very low (5-6%) in hepatitis B virus (HBV) reactivation patients on anti-viral treatment. Underlying immune-metabolic mechanisms in seroconverters (SC) and non-seroconverters (NSC) remains poorly understood. We aimed to characterize the immune and metabolic landscape in SC and NSC at baseline and week 24 using single-cell RNA sequencing and validation by flowcytometry. **Methods:** Out of sixty seven hepatitis B reactivation (rHBV) patients (age 39 ± 13, ALT > 5XULN, HBV DNAlog10$^{4-8}$), twelve patients on anti-viral treatment were seroconverted after 24 weeks (anti-HBs > 10IU/ml). Single cell sequencing using BD rhapsody platform was performed in three seroconvertors (SC) and three non-seroconvertors (NSC) at baseline and 24 wks. Sequencing data was further validated by flow Immune-metabolic panel in five SC and sixteen NSC patients. **Results:** At baseline, there was no difference in HBV DNA and HBsAg levels in SC and NSC. Single-cell transcriptomic profiling revealed that at baseline CD8$^+$ T cell and monocyte compartment was increased (Fig1 A). T cell showed upregulation of CD69, IL32, TNF, GZMA, IL2RB, ATP2B4and KLRG1 indicating activated, cytolytic and metabolically functional T cells in SCs compared to NSCs (Fig1 B). In contrast, NSCs had elevated expression of CTLA4, PDCD1, LAG3, CD25 exhaustion markers (Fig1 A). At baseline, SC monocytes displayed a pro-inflammatory, M1-like profile characterized by increased TNFAIP3, IL1β, CXCL8, TNF, and TREM1, whereas NSC monocytes exhibited a suppressive phenotype with high TIM3 and CTLA4 expression (Fig1 C). By week 24, SCs maintained earlier gene expression and emerged with raised TPR, CD74, CXCL3 immune-metabolic genes. But NSCs had continuous exhaustion state with upregulated TOX and FOXP1 (Fig1 D). Further, immune metabolic profiling by flow cytometry in validation cohort showed higher Glut1, HK2, mTOR, and LDHB expressing naïve, central memory, and effector memory CD4$^+$ and CD8$^+$ T cell subsets in SCs (Fig1 E). **Conclusion:** Despite no diiference in HBV DNA and HBsAg levels, few reactivation patients clear the virus by host mediated immunity. Seroconversion is orchestrated by robust activated, cytolytic, metabolic T cells and M1 macrophage polarization. This data emphasised that exhausted phenotype of non-seroconverters can be restored by inducing metabolically active activated T cells.



Disclosures: Jayesh Kumar Sevak: Nothing to Disclose, MOJAHIDUL ISLAM: Nothing to Disclose, Gayantika Verma: Nothing to Disclose, Manoj Kumar: Nothing to Disclose, Ankur Jindal: Nothing to Disclose, Varsha Shasthry: Nothing to Disclose, Syed Naqui Kazim: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose

1182 | EFFECT OF TOBEVIBART (VIR-3434) AND ELEBSIRAN (VIR-2218) MONOTHERAPY ON HEPATITIS B SURFACE ANTIGEN COMPOSITION IN PATIENTS WITH CHRONIC HEPATITIS B

Gregory Camus[1] Andrea Cathcart[1] Jonathan Seltmann[2] Thomas Berg[2] Hasan Imam[1] Andre Arizpe[1] Madlen Matz-Soja[2] Florian van Bömmel[3], [1]Vir Biotechnology, Inc., San Francisco, CA, USA, [2]Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Germany, [3]Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germa

Background: Tobevibart (VIR-3434) is an Fc-engineered monoclonal antibody targeting the conserved antigenic loop of HBsAg. Elebsiran (VIR-2218) is a small interfering RNA targeting the HBx region. Reductions in large (LHBs) and medium (MHBs) HBsAg during nucleos(t)ide analogue (NA) therapy have been linked to functional cure, likely reflecting covalently closed circular DNA (cccDNA) transcriptional activity. We investigated the effect of tobevibart and elebsiran, two agents with distinct modes of action, on

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serum HBsAg isoforms in participants with predominantly HBeAg-negative chronic hepatitis B (CHB). **Methods:** Sera from the VIR-3434-1002 and VIR-2218-1001 trials were retrospectively analyzed. VIR-3434-1002 included three patient cohorts: Part B (n = 30; NA ≥ 2 months, baseline [BL] HBsAg < 3000 IU/mL), Part C (n = 23; NA ≥ 2 months, BL HBsAg ≥ 3000 IU/mL), and Part D (n = 16; no NA, BL HBV DNA ≥ 1000 IU/mL). Patients received a single subcutaneous dose of 6–300 mg tobevibart. VIR-2218-1001, cohort 1d (n = 15) received six doses of elebsiran over 20 weeks. HBsAg isoforms (LHBs, MHBs, HBsAg) were quantified via DiaSorin platform with specific monoclonal antibodies on days 1, 8, and 57 (VIR-3434-1002) or weeks 0, 24, and 44 (VIR-2218-1001). **Results:** In VIR-3434-1002, tobevibart significantly reduced LHBs and MHBs levels and MHBs proportions (%) in a dose-dependent manner, particularly in Part B. At day 8, LHBs and MHBs declined across all doses; MHBs proportions dropped from 3.8% to 0% ($p < 0.001$) in Part B and slightly rebounded to 0.7% by day 57. The strongest suppression was observed with the 300 mg dose. However, effects in patients with BL HBsAg > 3000 IU/mL were limited. In VIR-2218-1001, elebsiran led to a significant reduction in total HBsAg, LHBs, and MHBs levels (all $p < 0.001$) by week 24, with sustained suppression at week 44. MHBs proportions declined from 1.6% to 0% at end of treatment (EOT, $p < 0.001$) and to 0.2% at follow-up ($p = 0.007$). Patients with BL HBsAg < 3000 IU/mL showed sustained undetectable MHBs. **Conclusion:** Tobevibart led to significant reductions in LHBs and MHBs levels, and MHBs proportions in patients with BL HBsAg < 3000 IU/mL. Elebsiran, in contrast, effectively suppressed LHBs and MHBs with sustained undetectable MHBs regardless of HBsAg baseline levels. Our findings suggest differential effects of the two agents on cccDNA-related HBsAg expression and support further evaluation of LHBs and MHBs as predictors of functional cure.

Disclosures: Gregory Camus: Gilead: Stock - publicly traded company, Vir Biotechnology: Employee, Andrea Cathcart: VIR Biotechnology: Employee, Jonathan Seltmann: Nothing to Disclose, Thomas Berg: Nothing to Disclose, Hasan Imam: Nothing to Disclose, Andre Arizpe: Vir Biotechnology: Stock - publicly traded company, Biogen: Employee, Madlen Matz-Soja: Nothing to Disclose, Florian van Bömmel: Nothing to Disclose

1183 | SAFETY AND EFFECTIVENESS OF PEGINTERFERON ALFA-2B COMBINED WITH TENOFOVIR AMIBUFENAMIDE IN PATIENTS WITH CHRONIC HEPATITIS B

Ru-Yue Chen[1] Sheng-li Ma[2] Yu-Meng Zhu[3] Ya-jie Pan[1] Xue-Yan lv[1] Yue-Hang Wang[1] Zhuang-Zhuang Zhai[1] Xue-Jing Xue[1] Qing-Lei Zeng[1], [1]The First Affiliated Hospital of Zhengzhou University,Zhengzhou,China, [2]The People's Hospital of Yongcheng City,Henan, China, [3]The Luoyang Central Hospital,Henan,China

Background: Data on the combination of Peg-IFN α-2b and tenofovir amibufenamide (TMF) remain limited. This study aims to evaluate the safety and effectiveness of Peg-IFN α-2b combined with TMF in patients with CHB. **Methods:** Patients treated with TMF (25 mg/day) and Peg-IFN α-2b (180 μg/week) from January 2022 to May 2025 were retrospectively enrolled from three hospitals in Henan, China. This study included two groups: the switch combination group, consisting of patients who transitioned from nucleos(t)ide analog (NA) monotherapy to a combination of TMF and Peg-IFN α-2b; and the treatment-naive combination group, comprising patients who received TMF plus Peg-IFN α-2b as initial therapy. The primary endpoint of this study was the rate of hepatitis B surface antigen (HBsAg) loss at 48 weeks of treatment, the secondary endpoints were the rate HBV DNA undetectable (< 25 IU/mL) and safety profiles during treatment. **Results:** A total of 180 patients were enrolled, with 120 patients in the switch combination group and 60 patients in the treatment-naive combination group. The treatment period of NA monotherapy in switch group was 67.45 ± 35.36 months. At baseline, the age, HBV DNA, hepatitis B e antigen (HBeAg), HBsAg, alanine aminotransferase (ALT) levels of the patients in the switch combination group and treatment-naive combination group were 38.48 ± 0.89 vs. 37.20 ± 1.28 years ($p = 0.413$), 4.1 (2.6, 6.5) vs. 4.9 (3.1, 7.8) $\log_{10}$ IU/mL ($p = 0.169$), 255.0 (11.0, 406.6) vs. 304.9 (12.1, 459.7) PEIU/mL ($p = 0.536$), 2.63 ± 1.14 vs. 2.79+1.18 $\log_{10}$ IU/mL ($p = 0.370$), 34.10 ± 4.31 vs. 50.14 ± 6.62 U/L ($p = 0.037$), respectively; At 48 weeks of treatment (Figure 1), the HBV DNA undetectable rates were 99.17% (119/120) vs. 96.67% (58/60) ($p = 0.537$), the HBeAg clearance rates were 76.67% (23/30) vs. 42.86% (6/14) ($p = 0.026$), the HBsAg loss rates were 44.16% (53/120) vs 28.33% (17/60) ($p = 0.040$), in the switch combination group and treatment-naive combination group, respectively. Regarding laboratory abnormalities, the main adverse events during treatment were the ALT elevation (57.50% [69/120] vs. 33.33% [20/60], $p = 0.002$), leukopenia(46.67% [56/120] vs. 31.67% [19/60], $p = 0.054$), neutropenia(45.83% [55/120] vs. 28.33% [17/60], $p = 0.024$), thrombocytopenia (65.83% [79/120] vs. 40.00% [24/60], $p = 0.001$), in the switch combination group and treatment-naive combination group, respectively. Only one patient presented with elevated total bilirubin (39.2 μmol/L). No serious adverse events occurred. **Conclusion:** At week 48 of treatment, the switch combination group exhibited significantly higher rates of HBsAg loss and HBeAg seroconversion compared to the treatment-naïve combination group.

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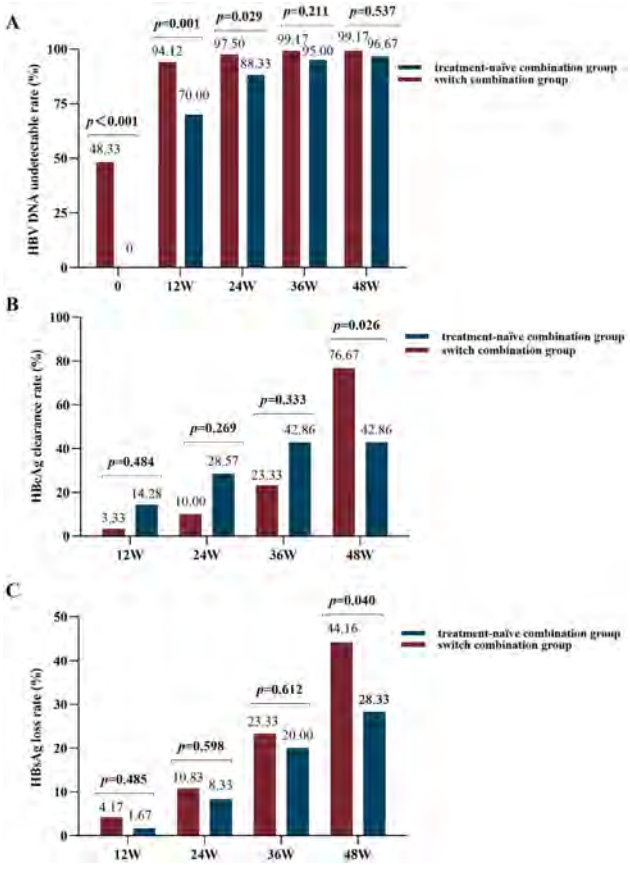
Both groups maintained a favorable overall safety profile throughout the treatment period. These findings suggest that initiating therapy with nucleos(t)ide analogs followed by combination with Peg-IFN α may be a reasonable and promising strategy to promote HBsAg loss.



Disclosures: Ru-Yue Chen: Nothing to Disclose, Sheng-li Ma: Nothing to Disclose, Yu-Meng Zhu: Nothing to Disclose, Ya-jie Pan: Nothing to Disclose, Xue-Yan Iv: Nothing to Disclose, Yue-Hang Wang: Nothing to Disclose, Zhuang-Zhuang Zhai: Nothing to Disclose, Xue-Jing Xue: Nothing to Disclose, Qing-Lei Zeng: Nothing to Disclose

1184 | ELEVATED SOLUBLE IMMUNE BIOMARKERS IN SUBJECTS WITH HBSAG LOSS AFTER TREATMENT WITH IMDUSIRAN AND IMMUNOTHERAPEUTIC AGENTS IN THE IM-PROVE I AND IM-PROVE II STUDIES

Sharie Ganchua[1] Christine Espiritu[1] Kevin Gray[1] Deana Antoniello[1] Man-Fung Yuen[2] Grace Lai-Hung Wong[3] Kosh Agarwal[4] Leonard Hooftman[5] Bethan Jones[5] Vicky Wheeler[5] Tilly Varughese[1] Karen Sims[1] Emily Thi[1], [1]Arbutus Biopharma, Warminster, PA, USA, [2]The University of Hong Kong, Queen Mary Hospital, Hong Kong, China, [3]The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China, [4]King's College Hospital, London, UK, [5]Barinthus Biotherapeutics, Harwell, UK

Background: Functional cure of chronic hepatitis B (CHB) requires suppression of viral replication, reduction of HBV antigens and induction of anti-HBV immune responses. Imdusiran (IDR) is an *N*-Acetylgalactosamine–conjugated, pan-genotypic small interfering RNA that blocks all HBV RNA transcripts, resulting in suppression of viral replication and all viral antigens. IM-PROVE I and IM-PROVE II are Phase 2a studies assessing combination treatment of IDR with an immunotherapeutic in nucleots(t)ide analogue (NA) treated CHB subjects. IM-PROVE I assessed 24 weeks (W) of IDR lead-in followed by 12W or 24W of pegylated interferon alfa-2a (IFN) with or without additional IDR doses. IM-PROVE II assessed 24W of IDR lead-in followed by the immunotherapeutic VTP-300, VTP-300 + low dose nivolumab (LDN), or placebo. On-treatment comparison of soluble immune biomarker profiles of subjects from the IM-PROVE I and II studies is presented. **Methods:** Longitudinal plasma samples were collected from 105 subjects (n = 43 IM-PROVE I; n = 62 IM-PROVE II) through W48/end of treatment. Soluble immune biomarkers were assessed using Luminex multiplex panels (58 analytes). **Results:** Transient increases ($\geq$3 to 130-fold from baseline) in soluble immune biomarkers associated with immune activation, Th1 cell-mediated response, inflammation regulation and immune checkpoint proteins occurred during IDR lead-in in subjects in both IM-PROVE I and IM-PROVE II. Elevations of the same immune biomarkers were observed in all subjects who lost HBsAg ($\leq$LLOQ, $\leq$0.05 IU/mL) by W48 in IM-PROVE I and in 1 of 4 subjects in IM-PROVE II, with higher elevations in IM-PROVE I subjects. In subjects who had anti-HBs antibodies by W48, a greater breadth of elevated immune biomarkers occurred in IM-PROVE I compared to IM-PROVE II. For both IM-PROVE I and II studies, 63-76% of the subjects who experienced increases in soluble immune biomarkers on-treatment met the criteria for NA discontinuation and had baseline HBsAg levels of $\leq$1000 IU/mL. **Conclusion:** IDR treatment is associated with increases in soluble immune biomarkers in both IM-PROVE I and IM-PROVE II studies. In subjects who lost HBsAg and had anti-HBs antibodies, a greater breadth and magnitude of immune biomarker increases were observed in IM-PROVE I subjects compared to IM-PROVE II. In both studies, subjects who showed increases in soluble immune biomarkers on-treatment met NA discontinuation criteria

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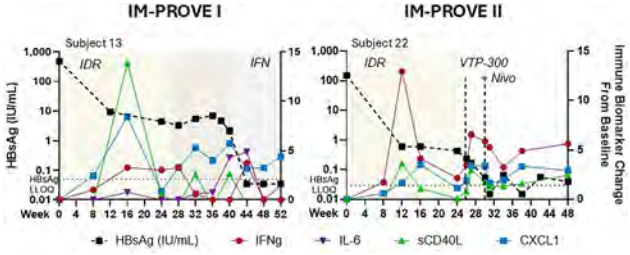
and had baseline HBsAg ≤1000 IU/mL.



Disclosures: Sharie Ganchua: Arbutus Biopharma Inc.: Employee, Christine Espiritu: Arbutus Biopharma Corp: Employee, Kevin Gray: Nothing to Disclose, Deana Antoniello: Nothing to Disclose, Man-Fung Yuen: Nothing to Disclose, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Kosh Agarwal: Nothing to Disclose, Leonard Hooftman: Nothing to Disclose, Bethan Jones: Barinthus Biotherapeutics: Employee, Vicky Wheeler: Nothing to Disclose, Tilly Varughese: Arbutus Biopharma: Employee, Karen Sims: Nothing to Disclose, Emily Thi: Arbutus Biopharma: Employee and holds shares in Arbutus Biopharma

1185 | IMC-I109V, A SOLUBLE T CELL RECEPTOR (TCR) BISPECIFIC TARGETING HBSAG (ENVXCD3), IS TOLERABLE AND ACTIVE AGAINST HEPATITIS B IN A FIRST-IN-HUMAN (FIH) SINGLE ASCENDING DOSE (SAD) STUDY

Jeong Heo[1] Anca Streinu-Cercel[2] Mark Nelson[3] Stefan Bourgeois[4] YOUNG-SUK LIM[5] Paola Cicconi[6] Santiago Moreno-Guillen[7] Stephen Ryder[8] Jordi Navarro Mercade[9] Hyun Woong Lee[10] Jason Wustner[11] Adel Benlahrech[12] Kehmia Titanji[13] Lucy Dorrell[12] Man-Fung Yuen[14], [1]Pusan National University Hospital, Busan, Republic of Korea, [2]National Institute of Infectious Diseases "Prof. Dr. Matei Bals", Bucharest, Romania, [3]Chelsea and Westminster NHS Foundation Trust, UK, [4]ZAS Cadix, Antwerp, Belgium, [5]Asan Medical Center, Seoul, Republic of Korea, [6]Nuffield Department of Medicine, University of Oxford, Oxford, UK, [7]Hospital Universitario Ramón y Cajal, Madrid, Spain, [8]NIHR Biomedical Research Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK, [9]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [10]Gangnam Severance Hospital, Seoul, Republic of Korea, [11]Immunocore LLC, Conshohocken, PA, USA, [12]Immunocore Ltd, Abingdon, UK, [13]Immunocore LLC, Gaithersburg, MD, USA, [14]Queen Mary Hospital, The University of Hong Kong, Hong Kong

Background: HBsAg seroclearance, a key biomarker of resolved chronic HBV (CHB), is rarely achieved with standard of care. IMC-I109V is a soluble high-affinity HBV-specific TCR anti-CD3 bispecific molecule that redirects non-exhausted T cells to kill HBV-infected hepatocytes presenting HLA-A*02:01-HBsAg peptide complexes. We conducted a FIH SAD study to assess the safety, tolerability, pharmacokinetic and pharmacodynamic (PD) activity of IMC-I109V in CHB. **Methods:** HLA-A*02:01-positive adults aged 18-65 with non-cirrhotic HBeAg-negative CHB on nucleos(t)ide analogue therapy and serum HBsAg <3000 IU/mL were enrolled in sequential ascending dose cohorts evaluating a single dose of IMC-I109V, given as an IV infusion on day 1. Tolerability and liver function tests were monitored over 24h post end of infusion (EOI) and through day 29. PD activity was determined from post-dose changes in serum ALT, HBsAg and IL-6. **Results:** Twenty participants (17 males, 3 females) were allocated to IMC-I109V at doses of 0.8 (n = 4), 2.4 (n = 2), 7 (n = 6) and 20 (n = 8) μg. In the 7-20 μg dose groups, 4 participants experienced transient systemic symptoms (Grade 1-2) with onset <24h post-EOI, which were followed by ALT elevations on day 2-3 (n = 3, Grade 1-2; n = 1, Grade 3) without alterations in bilirubin or prothrombin time. ALT changes resolved to Grade ≤1 within 14 days. One participant in the 20 μg group developed Grade 2 cytokine release syndrome that responded promptly to dexamethasone, resolving within 4 hours. Although this event did not meet dose-limiting toxicity criteria, it was classified as an SAE due to an extended hospital stay (<1 day). The observed AEs were consistent with the expected mechanism of action (MoA) of IMC-I109V, and their short duration with its rapid clearance (serum half-life ~14 hours). Small decreases in HBsAg were seen at lower doses, while at 7-20 μg doses, HBsAg reductions exceeding a pre-specified threshold of -0.2 $\log_{10}$ IU/mL were seen in 4 participants (maximum -0.85 $\log_{10}$, Figure), 3 of whom maintained reduced levels through day 29. Transient, dose-dependent elevations in serum IL-6 (median 6.5-fold at 7-20 μg doses), indicative of immune cell activation, accompanied the changes in ALT and HBsAg. **Conclusion:** IMC-I109V was associated with rapidly reversible MoA-related AEs in people with HBeAg-negative CHB. The FIH evidence for dose-

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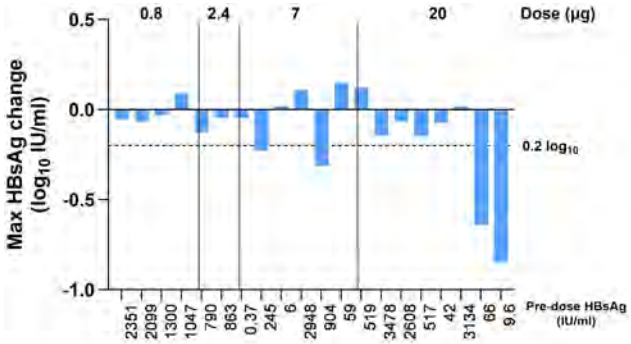
dependent reductions in HBsAg via this novel mechanism supports further evaluation of IMC-I109V in multiple dose regimens aimed at achieving sustained HBsAg loss.



Change in serum HBsAg after single IMC-I109V dose
Data shows maximum change during 28 days of follow-up. Bars represent individual participants; day 1 pre-dose HBsAg values are indicated on x axis.

Disclosures: Jeong Heo: Gilead: Grant/Research Support, Roche: Speaking and Teaching, Yuhan: Speaking and Teaching, Abbvie: Speaking and Teaching, AstraZeneca: Advisor, Oncolys Japan: Grant/Research Support, Surrozen: Advisor, MedVir: Advisor, Anca Streinu-Cercel: Nothing to Disclose, Mark Nelson: Nothing to Disclose, Stefan Bourgeois: Nothing to Disclose, YOUNG-SUK LIM: Nothing to Disclose, Paola Cicconi: Nothing to Disclose, Santiago Moreno-Guillen: Nothing to Disclose, Stephen Ryder: Nothing to Disclose, Jordi Navarro Mercade: Nothing to Disclose, Hyun Woong Lee: Nothing to Disclose, Jason Wustner: Nothing to Disclose, Adel Benlahrech: Nothing to Disclose, Kehmia Titanji: Immunocore Ltd: Employee, Lucy Dorrell: Immunocore Ltd: Employee, Man-Fung Yuen: Nothing to Disclose

1186 | CHARACTERIZATION OF HIV/HBV CO-INFECTED PATIENTS ACHIEVING HIGH RATES OF HEPATITIS B SURFACE ANTIGEN LOSS IN THE ALLIANCE PHASE 3 CLINICAL STUDY

Caleb Marceau[1] Pamela Odorizzi[1] Nikita Kolhatkar[1] Thomas Aeschbacher[1] David Pan[1] June Wai Man Mung[1] Sophia Rahman[1] Michelle D' Antoni[1] Ross Martin[1] Scott Balsitis[1] Sharline Madera[1] Frida Ambramov[1] Jason Hindman[1] Hongmei Mo[1] Anchalee Avihingsanon[2], [1]Gilead Sciences, [2]Thai Red Cross AIDS Research Centre

Background: Sustained Hepatitis B virus S-Antigen (HBsAg) loss is a marker of Chronic Hepatitis B virus (CHB) functional cure but occurs in only ~1% of HBV monoinfected patients per year on nucleos(t)ide therapy. We sought to characterize patients achieving HBsAg loss after initiating tenofovir containing antiretroviral treatment for HIV/HBV co-infected participants on the ALLIANCE trial. **Methods:** A total of 241 treatment naïve HIV/HBV co-infected participants with HBV DNA (COBAS 6800) of $\geq$2000IU/ml were enrolled in the ALLIANCE trial from study start (May 2018) to study completion (March 2024). Longitudinal quantitative HBsAg and HBeAg levels were measured for participants achieving HBsAg-loss. HBsAg loss was indicated by a negative HBsAg test result as determined by immunochemiluminometric assay (ICMA $<$0.05 IU/ml). **Results:** Of the 241 participants enrolled 54 (22.4%) were HBeAg(-) and 187 (77.6%) were HBeAg (+) at baseline. 55 (22.8%) participants achieved HBsAg loss of which 6 (11%) and 49 (26%) participants were HBeAg(-) and HBeAg(+) respectively at baseline. Baseline quantitative HBsAg levels were measured for 38 participants achieving HBsAg loss on study (5 and 33 for HBeAg(-) and HBeAg(+) groups respectively). For the HBeAg(-) group, 3 participants had baseline HBsAg levels of less than 2 IU/mL, and 2 participants had baseline HBsAg levels of 52,438 IU/mL and 4,669 IU/mL. For the HBeAg(+) group, 3 participants had baseline HBsAg levels of less than 3,000IU/mL, and 30 participants had median baseline HBsAg levels of 83,859 IU/mL with a range of 4,642 IU/mL to $>$249,750 IU/mL. Kinetics from treatment initiation to HBsAg loss was fast with 23 participants (5 and 18 for HBeAg(-) and HBeAg(+) groups respectively) achieving HBsAg loss within 48 weeks. HBsAg loss rates by genotype (GT) were 9/26 (34.6%) for GT-A, 4/45 (8.9%) GT-B, 28/111 (25.2%) GT-C, 8/29 (27.6%) GT-D, 2/4 (50%) GT-F with the remaining 4/26 (15.4%) having undetermined GT. Additionally, HBsAg loss was associated with higher levels of ALT ($>$ULN) and CD4+ T-cell counts ($>$200 cells/µL) at baseline. **Conclusion:** TAF/TDF treatment in HIV/HBV co-infected participants on the ALLIANCE trial resulted in high rates and rapid HBsAg loss even with high baseline HBsAg levels in many participants. HBsAg loss was associated with higher baseline ALT and CD4+ T-cell counts and was more frequent in participants with HBV GT-A and HBV GT-F. These suggest a role for viral and immune factors in HBsAg loss which can inform CHB functional cure therapeutic strategies.

Disclosures: Caleb Marceau: Gilead Sciences: Employee, Pamela Odorizzi: Nothing to Disclose, Nikita Kolhatkar: Gilead Sciences: Employee, Thomas Aeschbacher: Nothing to Disclose, David Pan: Nothing to Disclose, June Wai Man Mung: Gilead Sciences:

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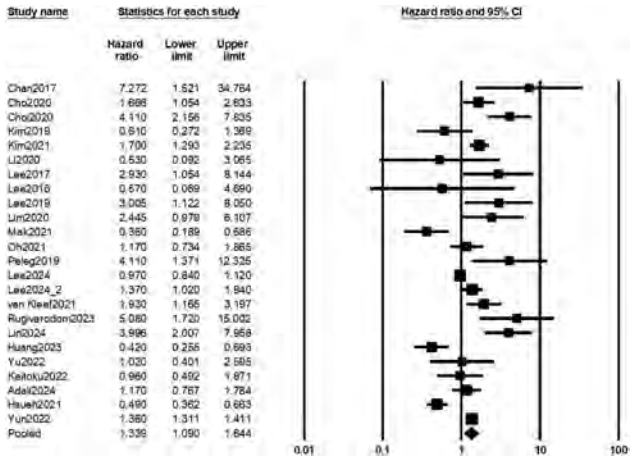
1187 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE INCREASES HEPATOCELLULAR CARCINOMA RISK IN CHRONIC HEPATITIS B: A SYSTEMATIC REVIEW AND META-ANALYSIS

Hanah Lee[1] Eunju Kim[1] Jong-In Chang[1] Hyung Joon Kim[1], [1]Chung-Ang University

Background: The recent introduction of the nomenclature "metabolic dysfunction-associated steatotic liver disease (MASLD)" highlights the importance of cardiometabolic risk factors in liver disease. While MASLD is acknowledged as a significant contributor to liver-related morbidity, its impact on hepatocellular carcinoma (HCC) risk in chronic hepatitis B (CHB) remains controversial. This systematic review and meta-analysis aimed to evaluate the association between MASLD and HCC risk in CHB. **Methods:** Data from observational studies were collected through PubMed, EMBASE, and the Cochrane Library from inception to March 1, 2025. The primary outcome was the association between MASLD and HCC. **Results:** A total of 27 studies involving 329,798 patients with CHB were included. SLD including non-alcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), and MASLD, was associated with an increased risk of HCC (OR 1.99, 95% CI 1.40–2.59, $I^2 = 76\%$). When stratified by disease classification, all SLD subtypes remained associated with an increased HCC risk (MASLD OR 1.85, 95% CI 0.49–3.20; MAFLD OR 1.92, 95% CI 0.38–3.46; NAFLD OR 2.04, 95% CI 1.27-2.82). In subgroup analyses, the association remained consistent in both Asian (OR, 1.90; 95% CI 1.19–2.60; $I^2 = 78\%$), and non-Asian regions (OR, 2.29; 95% CI 1.16–3.43; $I^2 = 81\%$), as well as in studies with a median follow-up duration of ≥ 5 years (OR, 2.32; 95% CI, 1.51–3.13), those excluding alcohol use (OR, 2.57; 95% CI, 1.36–3.78), and those using biopsy-proven steatosis (OR, 3.28; 95% CI, 1.66–4.90). Similar associations were observed in hospital-based (OR 2.0, 95% CI 1.32–2.69) and nationwide datasets (OR 1.22; 95% CI 0.96–1.49). When stratified by antiviral therapy (AVT) use, there was no association between SLD and HCC risk in the non-AVT group (OR 0.95, 95% CI 0.58-1.32), whereas a positive association was observed in the AVT group (OR 1.32, 95% CI 0.93-1.71). Finally, studies that included only steatohepatitis showed the strongest association with an increased HCC risk (OR 3.66, 95% CI 1.83-5.49). **Conclusion:** MASLD is associated with an increased risk of HCC in patients with CHB, particularly in those with steatohepatitis, highlighting the importance of identifying concomitant steatosis in CHB.



Disclosures: Hanah Lee: Nothing to Disclose, Eunju Kim: Nothing to Disclose, Jong-In Chang: Nothing to Disclose, Hyung Joon Kim: Nothing to Disclose

1188 | HBCRAG AND HBSAG KINETICS AFTER TREATMENT CESSATION: IMPLICATIONS FOR FUNCTIONAL CURE AND HEPATITIS FLARES

Yao-Chun Hsu[1] Ying-Nan Tsai[2] Jia-Ling Wu[3] Cheng-Hao Tseng[4] Tzu-Haw Chen[4] Mindie Nguyen[5] Jaw-Town Lin[4] Katsuya Nagaoka[6] Yasuhito Tanaka[6], [1]E-Da Hospital, I-Shou University, [2]E-Da Hospital, [3]National Cheng Kung University, [4]E-Da Hospital/I-Shou University, [5]Stanford University Medical Center, [6]Kumamoto University

Background: Circulatory levels of hepatitis B core-related antigen (HBcrAg) and hepatitis B surface antigen (HBsAg) are emerging biomarkers for managing chronic hepatitis B (CHB). Prior studies have

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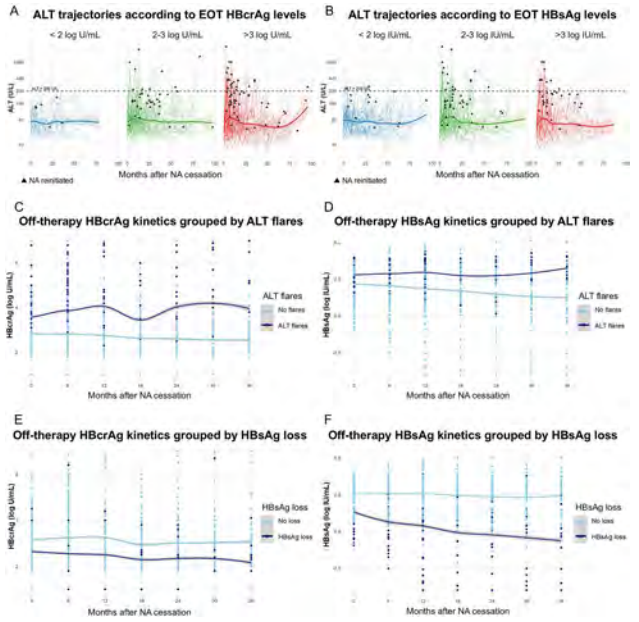
demonstrated end-of-treatment (EOT) levels of HBcrAg and HBsAg are associated with clinical outcomes after cessation of nucleos(t)ide analogue (NAs). However, the post-treatment cessation kinetics of these biomarkers remain unclear, and their associations with hepatitis flares and functional cure have not been elucidated. **Methods:** This is a multicenter center cohort study that prospectively enrolled adults with non-cirrhotic CHB who received first-line NAs for at least 2 years, and were HBeAg-negative with undetectable HBV DNA in serum before stopping the treatment. Highly sensitive iTACT assays were used to measure HBcrAg and HBsAg at treatment cessation and then every 6 months for up to 3 years. Functional cure was defined as HBsAg loss with undetectable HBV DNA, while hepatitis flares were defined as alanine aminotransferase (ALT) elevation above 5 times the upper limit of normal. The kinetics of HBcrAg and HBsAg were analyzed, and their associations with functional cure and hepatitis flares were evaluated using time-dependent models. **Results:** A total of 206 patients were enrolled, with a median age of 50.0 years (interquartile range [IQR], 42.1–58.7) and predominantly male (78.6%, n = 162). After a median treatment duration of 37.6 months (IQR, 36.7–47.8), the median EOT HBcrAg and HBsAg levels were 3.0 log U/mL (IQR, 2.3–3.9) and 2.7 log IU/mL (IQR, 1.5–3.1), respectively. During a median follow-up of 70.3 months (IQR, 41.8–103.5), 30 patients achieved functional cure, corresponding to a cumulative incidence of 16.0% (95% CI, 10.3–22.7%) at 8 years, and 68 patients developed hepatitis flares, with a 8-year cumulative incidence of 33.9% (95% CI, 26.9–41.0%). As illustrated in Figure 1, the ALT trajectories significantly differed according to EOT HBcrAg and HBsAg levels. Both HBcrAg and HBsAg significantly decreased over 3 years in patients without hepatitis flares. In contrast, patients who experienced flares showed no significant changes over time. Similarly, patients who achieved functional cure exhibited significant reductions in HBcrAg and HBsAg, whereas the levels remained unchanged in those without functional cure. In multivariable analyses, the time-varying HBcrAg level was more accurate than the HBsAg level in predicting ALT flares, while time-varying HBsAg was superior in forecasting functional cure. **Conclusion:** Dynamic reductions in HBcrAg and HBsAg levels were observed in patients with favorable outcomes following NA cessation. Comparative analyses revealed that HBcrAg was more effective in predicting hepatitis flares, whereas HBsAg better predicted functional cure. Monitoring both biomarkers may provide complementary information to tailor management strategies for the practice of finite NA therapy.



Disclosures: Yao-Chun Hsu: Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Sysmex: Advisor, Abbvie: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Roch: Speaking and Teaching, AsuperBio: Advisor, Grifols: Speaking and Teaching, GlaxoSmithKline: Consultant, AusperBio: Consultant, Ying-Nan Tsai: Nothing to Disclose, Jia-Ling Wu: Nothing to Disclose, Cheng-Hao Tseng: Nothing to Disclose, Tzu-Haw Chen: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose, Jaw-Town Lin: Nothing to Disclose, Katsuya Nagaoka: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

1189 | HIBIT-TAG ENABLES THE TRACKING OF POLYMERASE ACTIVITY IN HBV LIFE CYCLE

Wan Yu[1] Xinyu Du[2] Qiqin Lei[3] Tianhao Mao[4] Fengmin Lu[5] Ting Zhang[5] Xiangmei Chen[5] Huan Wang[3], [1]Zunyi Medical University, Guizhou, China., [2]Zhengzhou University, Zhengzhou, China., [3]Zunyi Medical University, Zunyi, Guizhou, China., [4]The Second Hospital of Nanjing, Affiliated to Nanjing University of Chinese Medicine, China., [5]School of Basic Medical Sciences, Peking University Health Science Center, China.

Background: Chronic hepatitis B (CHB) is still a major global health problem. As a critical rate-limiting enzyme in HBV replication, polymerase (Pol) plays an important role in HBV life cycle. However, the biological characteristics of Pol remain poorly understood due to technological limitations. Here in this study, we engineered

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novel systems to achieve visual tracking and quantitative analysis of Pol using the unique features of HiBiT peptide tag. **Methods:** First, the 11-amino acid of HiBiT tag was inserted into the region between Spacer and TP regions of Pol protein to establish two different HBV Pol tracking systems, which called HBVcircle-HiBiT-Pol and prcccDNA/Cre-HiBiT-Pol, resepctively. Next, bioluminescence assay was employed to evaluate intra- and extracellular expression of HiBiT-Pol in HepG2 cells transfected with the above systems. Chemiluminescence assay was used to quantify HBeAg and HBsAg while qPCR was performed to measure HBV DNA levels in culture supernatants. Recombinant viral particles were collected from cell culture supernatant and purified by iodixanol density gradient centrifugation for compositional analysis. Finally, the infectivity of recombinant viral particles was validated using the HepG2-NTCP cell infection model. **Results:** HiBiT-tag was successfully expressed without compromising HBV replication efficiency in both the HBVcircle-HiBiT-Pol and prcccDNA/Cre-HiBiT-Pol. No significant differences were observed in HBsAg, HBeAg levels or HBV DNA replication efficiency between HiBiT-tagged and wild-type constructs. Consistent with these findings, intracellular core protein expression level and the ratios of L/M/S-HBs isoforms remained unaltered. Importantly, HiBiT-tag was specifically detected in viral particles likely included naked capsids, Dane particles, and pgRNA-containing virus-like particles. As expected, the tagged virions maintained infectivity in HepG2-NTCP cells with persistent HiBiT signals detected in subsequent viral progeny. **Conclusion:** A system for real-time visualization and quantitation of HBV polymerase was established, which enabled us to detect the dynamics of Pol protein in HBV life cycle.

Disclosures: Wan Yu: Nothing to Disclose, Xinyu Du: Nothing to Disclose, Qiqin Lei: Nothing to Disclose, Tianhao Mao: Nothing to Disclose, Fengmin Lu: Nothing to Disclose, Ting Zhang: Nothing to Disclose, Xiangmei Chen: Nothing to Disclose, Huan Wang: Nothing to Disclose

1190 | THE ROLE OF ALIX AND VPS4A IN AUTOPHAGY AND ENDOSOMAL PATHWAYS AND THEIR RELATION TO HBV REPLICATION

Mengji Lu Jia Li[1], [1]University Hospital Essen, Essen, Germany

Background: Background & Aims: Autophagic and endosomal pathways coordinately contribute to hepatitis B virus (HBV) production. Alix and VPS4A are two important endosomal sorting complex required for transport (ESCRT) components involved in membrane scission. Previous studies showed that Alix and VPS4A participate in HBV replication and modulate the release of HBV particles. Yet, the mechanisms remain elusive. In the present study, we investigated the role of Alix and VPS4A in HBV biogenesis in the context of endosomal membrane trafficking and autophagy. **Methods:** Methods: We examined the production, trafficking, and release of HBV particles by using gene silencing and overexpression of wild-type (WT) and dominant-negative (DN) mutants of Alix and VPS4A in HBV replication cell models. **Results:** Results: Alix silencing increased the levels of intracellular HBV DNA and subviral particles (SVPs/HBsAg), extracellular HBsAg, and virions, while decreasing the secreted naked capsids. Alix silencing promotes HBsAg secretion along the early endosomes while it reduces HBsAg transported to late endosomes and autophagosomes. Alix silencing impairs autophagosome formation by activating the AKT/MTOR pathway and increasing autophagosome degradation in lysosomes. VPS4A silencing has minimal effects on HBV production, while DN VPS4A significantly blocks HBV secretion. DN VPS4A disrupts endosomal trafficking and HBsAg colocalization within early endosomes and late endosomes, while promoting autophagosome formation and lysosome activity, resulting in HBV degradation. **Conclusion:** Conclusion: Our findings demonstrate that the endosomal pathway plays a critical role in HBV progeny secretion, particularly when lysosomal activity is suppressed. Conversely, increased lysosomal function drives HBV degradation through the autophagosome-lysosome pathway.

Disclosures: Mengji Lu: Nothing to Disclose, Jia Li: Nothing to Disclose

1191 | INCREASED POSTOPERATIVE RISK IN CIRRHOTIC WOMEN WITH CHRONIC HEPATITIS B UNDERGOING HYSTEROSCOPIC SURGERY

Calvin Pan[1] Xiulan Li[2] Fuqiang Xu[2] Nan Wang[2] Yanmei Li[2] Yifan Wang[2] Yuxiang Zhou[2] Huadong Tang[2] Xin Liu[2] Ying Hou[2] Meina Bian[2] Qing Liu[2], [1]NYU Langone Health, NYU School of Medicine, [2]Beijing You'an Hospital, Capital Medical University, Beijing, China

Background: Patients with chronic hepatitis B (CHB) and cirrhosis face increased postoperative risks, especially those with decompensated disease due to impaired hemostasis, immune dysfunction, portal hypertension, and reduced liver synthetic function. However, limited data exist on outcomes following hysteroscopic surgery in this population. This study aimed to evaluate perioperative complications in CHB-related cirrhotic women undergoing hysteroscopic procedures, to guide preoperative assessment and

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perioperative management. **Methods:** This retrospective cohort study was conducted at a tertiary hospital between March 2012 and June 2024. It included consecutive women with mono-HBV infection who underwent hysteroscopic surgery. Cirrhotic and non-cirrhotic patients were matched 1:1 using propensity scores. The primary outcomes were perioperative and 30-day postoperative complications, including their frequency and severity, classified according to the Clavien-Dindo classification. Secondary outcomes included the identification of independent predictors of complications in cirrhotic patients using multivariate logistic regression based on preoperative variables. **Results:** A total of 196 patients were included after propensity score matching (98 with cirrhosis and 98 without). The mean age was 53.5 years, and 51.52% were postmenopausal. Preoperative characteristics, including age, BMI, and frequency of diabetes, were comparable between the two groups, though laboratory abnormalities were more prevalent in the cirrhosis group (Table 1). Among cirrhotic patients, the mean Child-Pugh score was 5.89 ± 1.59, with 55.1% (54/98) classified as decompensated. The most frequent complications were fever (5/196, 2.6%), abdominal pain (4/196, 2.0%), nausea or vomiting (4/196, 2.0%), and abdominal distension (4/196, 2.0%). Compared to the non-cirrhotic group, cirrhotic patients had a significantly higher overall complication rate (15.3% [15/98] vs. 9.2% [4/98], P = 0.008). Based on the Clavien-Dindo classification, cirrhotic patients had a significantly higher rate of Grade I complications (13.27% vs. 5.2%, P = 0.035), while Grade II (1.02% vs. 0%, P = 0.37) and Grade III (1.02% vs. 0%, P = 0.36) complication rates were not significantly different. No Grade IV or V complications occurred in the entire cohort. Notably, all complications were non-hepatic. Multivariate analysis did not identify significant preoperative predictors of postoperative complications in cirrhotic patients. **Conclusion:** Women with CHB-related cirrhosis undergoing hysteroscopic surgery have a significantly higher risk of mild, non-hepatic postoperative complications compared to non-cirrhotic women. Despite this elevated risk, no liver-related mortality was observed, suggesting that hysteroscopic surgery can be safely performed with appropriate perioperative monitoring in this population.

Table 1. Clinical characteristics of the participants and liver cirrhosis status

Variables, mean ±SD or (pecified	Entire cohort (n=196)	Group A Cirrhosis (n=98)	Group B Non-cirrhotic (n=98)	*P*-value between groups A vs B
Age, years	53.5±8.4	54.4±9.1	52.7±7.6	0.16
BMI ≥24 kg/m², n (%)	26.43±19.56	24.99±4.22	26.61±21.14	0.48
Post-menopause, n (%)	102 (53.1)	59 (46.2)	43 (43.9)	0.07
Hypertension, n (%)	26 (13.3)	19 (19.4)	7 (7.2)	0.01
Diabetes mellitus, n (%)	31 (15.8)	18 (18.4)	13 (13.3)	0.33
Prothrombin time, second	12.55±2.16	13.23±2.77	11.86±0.84	<0.001
Prothrombin activity, %	84.71±16.06	77.06±17.13	92.41±10.26	<0.001
Platelets, x1,000 µL	179.58±99.95	110.63±71.68	249.25±72.23	<0.001
Alanine aminotransferase, U/L	24.32±18.50	20.49±18.55	22.10±18.20	0.16
Aspartate aminotransferase, U/L	30.92±20.46	38.11±23.29	23.56±15.56	<0.001
Total bilirubin, mg/dL	17.74±20.48	32.76±22.92	12.61±5.52	<0.001
Albumin, g/L	39.10±6.05	37.16±5.67	41.06±5.93	<0.001
Globulin, g/L	29.21±15.13	29.32±6.74	29.09±20.46	0.92
Gamma-glutamyl transferase, U/L	24.59±22.97	32.1±24.99	16.99±17.87	<0.001
Creatinine, µmol/L	52.54±21.69	54.6±29.52	50.44±7.59	0.18
Child-Pugh scores	–	5.89±1.59	–	–
Decompensation of cirrhosis, n (%)	54 (27.6)	54 (55.1)	–	–

Disclosures: Calvin Pan: Gilead Science, Inc.: Grant/Research Support, Wuxi Hisky Medical Technologies Co., Ltd.: Grant/Research Support, Xiulan Li: Nothing to Disclose, Fuqiang Xu: Nothing to Disclose, Nan Wang: Nothing to Disclose, Yanmei Li: Nothing to Disclose, Yifan Wang: Nothing to Disclose, Yuxiang Zhou: Nothing to Disclose, Huadong Tang: Nothing to Disclose, Xin Liu: Nothing to Disclose, Ying Hou: Nothing to Disclose, Meina Bian: Nothing to Disclose, Qing Liu: Nothing to Disclose

1192 | SINGLE-CELL SEQUENCING REVEALS THE MECHANISM OF HBSAG CLEARANCE MEDIATED BY PD-1 INHIBITOR COMBINED WITH PEG-IFNA

Chenrui Liu[1] Yaping Li[1] Liu Yang[1] Meng Zhang[1] Shuangsuo Dang[1], [1]The Second Affiliated Hospital of Xi'an Jiaotong University

Background: While pegylated interferon-alpha (Peg-IFNα) remains a cornerstone for chronic hepatitis B (CHB) functional cure, more than 60% of patients fail to achieve HBsAg seroclearance after 48-week therapy. Although PD-1 blockade has shown promise in reversing immune dysfunction, its synergistic potential with Peg-IFNα remains underexplored. **Methods:** In this prospective cohort study (ChiCTR2400091948), 64 HBeAg-negative CHB patients without HBsAg clearance (<0.05 IU/mL) after 48-week Peg-IFNα therapy were stratified into two groups according to treatment preference : Treatment group (n = 33): Subcutaneous PD-1 mAb (1mg/kg Q12W) + ongoing Peg-IFNα + Nucleos(t)ide Analogues (NAs); Control group (n = 31): Continued Peg-IFNα therapy + NAs. Paired PBMC samples from 3 treatment group patients at baseline and Week 12 (post-PD-1 initiation) were collected for single-cell sequencing. ELISA quantification of 9 IFN-related proteins (IFIT1, MX1, IFI6, ISG15, OAS1, EIF2AK2, STAT1, IRF7, IFITM3) in all 64 patients at baseline, Week 12 and Week 24. **Results:** ELISA validation demonstrated no significant differences in baseline levels of nine interferon-related proteins between the treatment group and control group (P > 0.05 for all). At Week 24, the treatment group showed pronounced increases in ISG15 (45.38 ± 4.33 pg/mL vs. 36.50 ± 6.30 pg/mL, P < 0.001) and IRF7 (1481.90 ± 217.93 pg/mL vs. 1113.70 ± 401.35 pg/mL, P = 0.001). However, there was no significant change in the levels of the aforementioned proteins in the serum of the control group. Single-cell sequencing yielded 19 clusters, which were identified as 10 distinct cell types. Differential gene expression analysis across cell types before and after treatment

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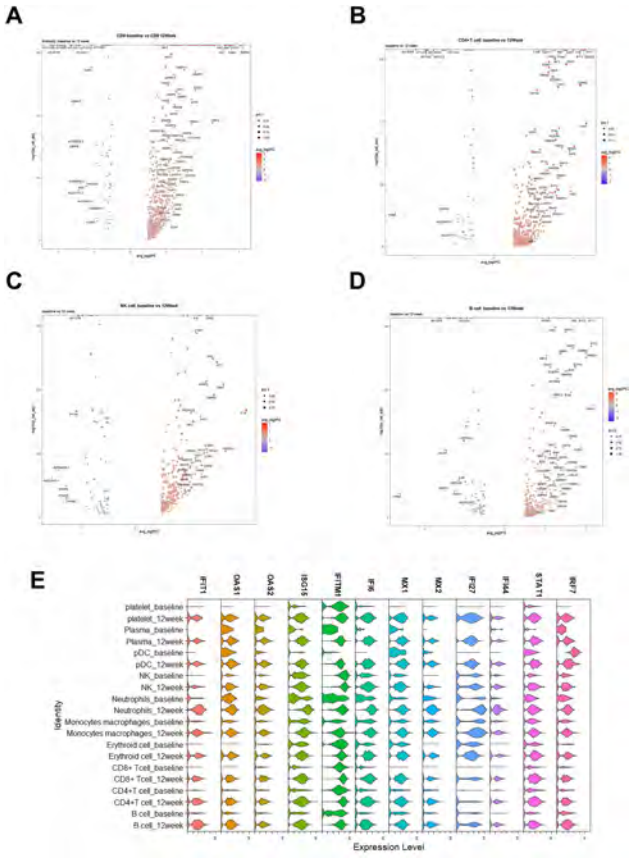
revealed that in three interferon non-responders treated with PD-1 inhibitors for 12 weeks, CD4+ T cells, CD8+ T cells, NK cells, and B lymphocytes exhibited significant upregulation of interferon signaling pathway-related genes (STAT1, IRF7, IRF9) and effector protein-coding genes induced by interferon (IFIT1, IFIT2, IFIT3, OAS1, OAS2, OAS3, MX1, MX2, ISG15, etc.). After enrichment analysis of up-regulated genes in various cell groups, it was found that the up-regulated genes were mainly related to antiviral immunity. **Conclusion:** CHB patients undergoing long-term Peg-IFNα therapy may exhibit insufficient activation of the interferon signaling pathway, which is a critical factor contributing to their low HBsAg clearance efficiency. However, the addition of PD-1 inhibitors can significantly enhance the biological efficacy of Peg-IFNα in these HBsAg-persistent patients by promoting the restoration of interferon pathway functionality and activating downstream effector genes. The combination therapy markedly elevated peripheral blood levels of ISG15 and IRF7.



Disclosures: Chenrui Liu: Nothing to Disclose, Yaping Li: Nothing to Disclose, Liu Yang: Nothing to Disclose, Meng Zhang: Nothing to Disclose, Shuangsuo Dang: Nothing to Disclose

1193 | HEPATITIS B VIRUS SP1CIRCLE DNA GENERATED FROM SP1 DOUBLE-STRAND LINEARIZED DNA COULD PROMOTE HBV REPLICATION

Liang Wang[1] Qianqian Jiang[2] Wan Yu[3] Ting Zhang[4] Xiaoping Wu[1] Xiangmei Chen[4] Fengmin Lu[4], [1]The First Affiliated Hospital, Jiangxi Medical College, Nangchang University, [2]Peking University People's Hospital, Peking University Hepatology Institute, [3]Zunyi Medical University, [4]School of Basic Medical Sciences, Peking University

Background: Spliced RNA 1 (SP1) is the most abundant spliced variant of the viral pregenomic RNA. The lack of hM region (nt2806-2994) of the HBV cis-acting sequence would prevent rcDNA formation and instead, lead to the generation of SP1 double-stranded linear DNA (SP1-derived dslDNA, SP1-dslDNA). It remains unknown whether SP1-dslDNA can undergo circularization through non-homologous end joining (NHEJ) to generate SP1circle DNA, a proceed similar to the NHEJ-mediated formation of cccDNA from wild-type HBV dslDNA. **Methods:** The SP1 variant (pcDNA3.1-SP1) was constructed using a plasmid containing integrated HBV DNA that mimics dslDNA, with nucleotides 2447-489 removed from the dslDNA. The purified SP1-dslDNA fragments (nt1818-3215/0-1827 with nt2447 to 489 removed) amplified by PCR were transfected into HepG2 cells. Subsequently, the extracted Hirt DNA was used for amplicon sequencing with primers targeting the head-to-tail junction region of SP1-dslDNA, if circulization occured. To further investigate its impact, SP1circle DNA was constructed by modifying an established HBV circle plasmid (a cccDNA mimic) through deletion of nucleotides 2447–489. In addition, its impact on HBV replication was investigated through co-transfection of SP1circle with HBVcircle plasmids (with the Pol protein tagged by a Hibit-tag) into HepG2 cells. **Results:** Via NHEJ, SP1-dslDNA could circularize to produce a series of indels sequence within the head-to-tail junction region in HepG2 cells. Notably, since a subset (~9.09%) of SP1circle DNAs retained functional BCP/CP promoters and partially intact preC/C ORF, both HBeAg and core proteins were detected without HBsAg or HBV DNA detected. Next, co-transfection of SP1circle and HBVcircle increased extracellular HBV DNA levels in the supernatant compared to co-transfection of HBVcircle with an empty vector. Luciferase reporter assays revealed that co-transfection with SP1circle enhanced polymerase (Pol) protein levels in both cellular lysates and supernatant. Western blot analysis showed that SP1 co-transfection significantly increased total and cytoplasmic TIAR protein levels, suggesting that SP1circle may promote HBV replication by upregulating TIAR expression which

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inturn enhanced polymerase translation. **Conclusion:** SP1-dsIDNA could circularize through NHEJ to produce SP1circle which could express core protein, potentially enhancing HBV replication through TIAR mediated Pol protein translation.
Disclosures: Liang Wang: Nothing to Disclose, Qianqian Jiang: Nothing to Disclose, Wan Yu: Nothing to Disclose, Ting Zhang: Nothing to Disclose, Xiaoping Wu: Nothing to Disclose, Xiangmei Chen: Nothing to Disclose, Fengmin Lu: Nothing to Disclose

1194 | PREDICTING HBSAG SEROCLEARANCE AFTER 48 WEEKS OF PEGYLATED INTERFERON THERAPY IN INACTIVE CARRIERS: A MACHINE LEARNING APPROACH

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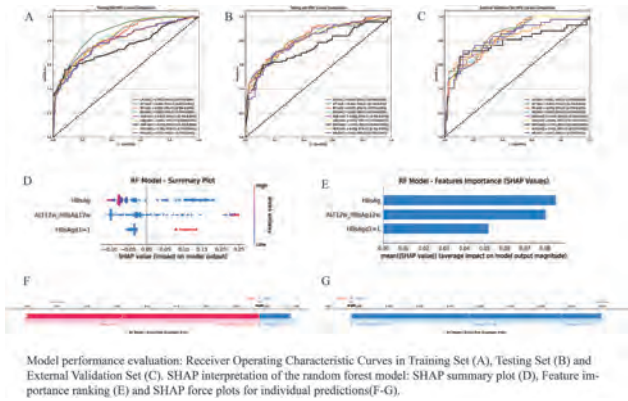
Background: To investigate the predictors of hepatitis B surface antigen (HBsAg) seroclearance after 48 weeks of pegylated interferon (Peg-IFN) therapy in inactive HBsAg carriers (IHCs), and to develop a machine learning model to optimize clinical decision-making. **Methods:** A total of 777 IHC patients who received at least 48 weeks of Peg-IFN therapy were retrospectively enrolled from the multicenter "Hepatitis B Clinical Cure—Starlight Project" (STARHB) cohort in China. Least absolute shrinkage and selection operator (LASSO) regression and the Boruta algorithm were used to select predictive variables. Nine machine learning models were constructed, including logistic regression (LR), decision tree (DT), and random forest (RF). Model performance was evaluated using 10-fold cross-validation and externally validated in an independent cohort (n = 167) from three medical centers in Beijing. Shapley additive explanations (SHAP) were applied to interpret variable contributions. **Results:** The HBsAg seroclearance rate at week 48 was 29.9% (232/777). Key predictive factors included baseline HBsAg level, HBsAg decline at week 12, and the ratio of alanine aminotransferase (ALT) to HBsAg at week 12. The RF model demonstrated the best performance, with an area under the receiver operating characteristic curve (AUC) of 0.829 (95% confidence interval [CI]: 0.784–0.874) and specificity of 0.774 in the training set. In the external validation cohort, the AUC was 0.838 (95% CI: 0.759–0.917) with a specificity of 0.968. SHAP analysis indicated that baseline HBsAg level was the most important predictor. **Conclusion:** The RF model developed in this study accurately predicts HBsAg seroclearance in IHC patients receiving Peg-IFN therapy, offering a novel strategy for early identification of candidates with favorable response and for personalized treatment planning.



Model performance evaluation: Receiver Operating Characteristic Curves in Training Set (A), Testing Set (B) and External Validation Set (C). SHAP interpretation of the random forest model: SHAP summary plot (D), Feature importance ranking (E) and SHAP force plots for individual predictions(F-G).

Disclosures: Jianxia Dong: Nothing to Disclose, Shan Ren: Nothing to Disclose, Jing Zhao: Nothing to Disclose, Pengxuan Wu: Nothing to Disclose, Haitian Yu: Nothing to Disclose, Xinyue Chen: Nothing to Disclose, Sujun Zheng: Nothing to Disclose

1195 | CIRCULAR RNA SETD2 (CIRCSETD2) INCREASES DDX3 EXPRESSION TO INHIBIT AUTOPHAGY BY SPONGING MIR-181A-5P IN HEPATITIS B VIRUS INFECTION

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Background: Circular RNA (circRNA) is a covalently closed non-coding RNA produced by back-splicing mechanism. They act as competing endogenous RNA to modulate various cell functions and infections. Hepatitis B virus (HBV) utilizes cellular recycling mechanism autophagy for its proliferation. It modulates the expression of various host factors, such as non-coding RNAs and several host restriction factors to induce autophagy. Circular RNA SET domain containing 2 (circSETD2) was reported to inhibit hepatocellular carcinoma progression. However, its role in HBV infection is not yet established. A recent study showed that miR-181a-5p, upregulated in HBV, was sponged by circSETD2 in trophoblasts. Dead Box RNA helicase 3 (DDX3), a host restriction factor of HBV infection, was targeted by miR-181a-5p in HIV infection. In this study, we explored the role of circSETD2 in the modulation of miR-181a-5p and DDX3 in HBV infection. **Methods:**

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CircSETD2 were cloned into pcDNA3.1(+) circRNA mini vector. $pHBV_{3.1}$, HBx plasmids were transfected into HepG2 or pCircSETD2 was transfected to HepG2.2.15 cells using Lipofectamine-2000 reagent. miR-181a-5p mimics and inhibitors were transfected in HepG2.2.15 cells using SiPORT NeoFX transfection reagent. After 48 hours, cells were collected for RNA and protein isolation. CircSETD2, HBx and miR-181a-5p expression were analysed by qPCR. DDX3 and autophagy markers ATG5, Beclin1 and LC3 II expression were analysed by Western blot. **Results:** The expression of circSETD2 was lower in HepG2.2.15 cells compared to HepG2 cells ($p \leq 0.005$). HBV and HBx transfection in HepG2 cells downregulated circSETD2 expression ($p \leq 0.05$). CircSETD2 transfection in HepG2.2.15 cells downregulated the expression of miR-181a ($p \leq 0.05$), whereas HBV and HBx transfection in HepG2 cells upregulated the expression of miR-181a-5p. miR-181a-5p mimics transfection in HepG2.2.15 cells resulted in downregulation of DDX3 and upregulation of ATG5, Beclin1 and LC3 II ($p \leq 0.05$). Conversely, miR-181a-5p inhibitor induced the expression of DDX3 and reduced the levels of ATG5, Beclin1 and LC3 II. Further, circSETD2 transfection in HepG2.2.15 cells led to the upregulation of DDX3 and downregulation of ATG5, Beclin1 and LC3 II ($p \leq 0.05$). **Conclusion:** The data suggested that HBV inhibits circSETD2 expression to enhance miR-181a-5p, which in turn inhibits DDX3, and the decreased DDX3 results in enhanced autophagy.

Disclosures: MD ISMAIL: Nothing to Disclose, Teja Naveen Sata: Nothing to Disclose, Runa Nasrin Sheuly: Nothing to Disclose, Amrendra Kumar Sah: Nothing to Disclose, Srijita Paul: Nothing to Disclose, Gopal Sharma: Nothing to Disclose, Senthil Kumar Venugopal: Nothing to Disclose

1196 | PROTEOMIC ANALYSIS OF SERUM EXTRACELLULAR VESICLES IDENTIFIES FIBULIN-3 AS A NOVEL PREDICTOR OF HCC IN CHB PATIENTS

Emi Sometani[1] Kazuhiro Murai[1] Takao Kitanaka[1] Takayuki Miyake[1] Shinji Kuriki[1] Jihyun Sung[1] Kazuki Maesaka[1] Satoshi Shigeno[1] Yuta Myojin[1] Kumiko Shirai[1] Yuki Tahata[1] Yoshinobu Saito[1] Takahiro Kodama[1] Hayato Hikita[1], [1]The University of Osaka

Background: Although nucleos(t)ide analog (NUC) therapy reduces the incidence of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB), HCC can still develop even when HBV DNA is suppressed. Identifying predictive markers for HCC during NUC therapy is of significant clinical importance. In this study, we performed proteomic analysis of serum extracellular vesicle (EV) proteins and aimed to identify novel biomarkers predictive of HCC development. **Methods:** A total of 242 CHB patients were included in the study. All had stored serum samples available, had been treated with NUCs for at least one year at the time of sample collection, had serum HBV DNA levels below 3.0 log IU/mL, and had no prior history of HCC. We performed proteomic analysis of serum EV proteins using stored sera and identified candidate proteins predictive of HCC development. The serum levels of the identified candidate proteins were then measured using ELISA to evaluate their potential as predictive biomarkers. **Results:** The median age of the patient cohort was 55 years, and 144 patients were male. During the observation period, 44 patients (18.2%) developed primary HCC. Proteomic analysis identified five candidate EV proteins; EGF-containing fibulin-like extracellular matrix protein 1 (fibulin-3), vascular cell adhesion protein 1 (VCAM-1), Fibronectin, von Willebrand factor (vWF), Fibroblast growth factor-binding protein 2 (FGFBP2). The serum levels of all five candidate proteins were subsequently quantified by ELISA. Among these, fibulin-3 and VCAM-1 levels were extracted as significant factors in univariate analysis of the COX proportion hazards model. In multivariate analysis, gender (HR: 2.70 [1.21-6.05]), γ-GTP (HR: 1.01 per 1 U/L increase [1.004-1.011]), AFP (HR: 1.05 per 1ng/mL increase [1.01-1.08]), fibulin-3 (HR: 1.06 per 1μg/mL increase [1.02-1.11]), and FIB-4 index (HR: 1. 24 per 1-point increase [1.05-1.42]) were identified independent factors, while VCAM-1 was not. Serum Fibulin-3 levels had a median of 10.1 μg/mL. Using the Youden index, a cutoff value of 10.8 μg/mL was determined. The cumulative incidence of HCC was significantly higher among patients with fibulin-3 $\geq$ 10.8 μg/mL, AFP $\geq$ 3.0 ng/mL, γ-GTP $\geq$ 22 U/L, FIB-4 index $\geq$ 1.93, and male gender. Among patients with none or more than three of these five risk factors, the 10-year HCC cumulative incidence rates were 0% and 37.2%, respectively. **Conclusion:** Serum Fibulin-3 was identified as a biomarker for predicting HCC in CHB patients under NUC treatment.

Disclosures: Emi Sometani: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Takao Kitanaka: Nothing to Disclose, Takayuki Miyake: Nothing to Disclose, Shinji Kuriki: Nothing to Disclose, Jihyun Sung: Nothing to Disclose, Kazuki Maesaka: Nothing to Disclose, Satoshi Shigeno: Nothing to Disclose, Yuta Myojin: Nothing to Disclose, Kumiko Shirai: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Takahiro Kodama: Nothing to Disclose, Hayato Hikita: Nothing to Disclose

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1197 | IL-1B FROM PERIPHERAL BLOOD CD14+ MONOCYTES PREDICTS SERUM HBSAG DECLINE IN PATIENTS WITH CHRONIC HEPATITIS B

Satoshi Shigeno[1] Takahiro Kodama[1] Kazuhiro Murai[1] Hayato Hikita[1] Tomohide Tatsumi[1] Tetsuo Takehara[1], [1]Department of Gastroenterology and Hepatology, The University of Osaka, Graduate School of Medicine

Background: Although nucleotide analogs (NAs) suppress viral replication in patients with chronic hepatitis B (CHB), they rarely achieve HBsAg seroclearance. While a reduction in HBsAg levels is associated with seroclearance, the factors regulating HBsAg levels remain poorly understood. To advance toward a "functional cure," we investigated the host immune dynamics involved in the reduction of HBsAg levels. **Methods:** Peripheral blood mononuclear cells (PBMCs) were collected from CHB patients who showed a decrease in serum HBsAg from $>1{,}000$ IU/mL to <100 IU/mL after over two years of NA therapy (declining group), and from those with persistently high levels ($>1{,}000$ IU/mL, persistent group). Single-cell RNA sequencing (scRNA-seq), targeting 397 immune-related genes, was performed to investigate immune cell dynamics. The findings were validated in an independent cohort of 32 patients and further extended to a long-term follow-up cohort of 45 patients, in whom cytokine levels were measured one year after initiation of NA therapy. In vitro analysis was performed with HBV-expressing cell line HepG2/2.2.15. **Results:** scRNAseq revealed ten distinct immune cell populations, with the monocyte cluster in the declining group exhibiting higher antigen presentation and phagocyte gene scores. Differential gene expression analysis revealed that IL-1β expression in the $CD14^+$ monocyte cluster was significantly higher in the declining group than in the persistent group. In the validation cohort, IL-1β expression level of isolated circulating $CD14^+$ classical monocytes was also significantly higher in the declining group. In vitro, treatment with recombinant IL-1β reduced the HBsAg levels in the supernatant of HepG2/2.2.15 in a dose-dependent manner. In ex vivo studies, stimulating $CD14^+$ monocytes with HBs antigen significantly increased IL-1β expression in the declining group. Finally, in the long-term follow-up cohort, serum IL-1β levels measured one year after initiation of NA therapy were significantly higher in the declining group, and multivariate analysis identified high serum IL-1β as independent predictors of HBs antigen decline. **Conclusion:** In CHB patients, differences in the IL-1β production capacity of peripheral blood classical monocytes might contribute to the decline of serum HBsAg levels during NA treatment.

Disclosures: Satoshi Shigeno: Nothing to Disclose, Takahiro Kodama: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Tomohide Tatsumi: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

1198 | HEPATOCELLULAR CARCINOMA SCREENING RATES AMONG INDIVIDUALS WITH CHRONIC HEPATITIS B IN A LARGE URBAN ACADEMIC CENTER

Cameron Adams[1] Terry Li[1] Feng Su[2], [1]New York University, [2]NYU

Background: Routine hepatocellular carcinoma (HCC) screening facilitates early cancer detection and improves survival among patients with chronic hepatitis B (HBV). However, screening adherence remains suboptimal due to patient, provider, and system-level barriers. The primary objective of this study was to identify barriers to screening by determining the proportion of ordered screening tests that were successfully completed among patients with chronic HBV at a large urban academic hospital. Our secondary objective was to determine the overall screening rate in the cohort and identify variables that differed between those who underwent screening and those who did not. **Methods:** Inclusion criteria were age ≥ 18 years, a diagnosis of chronic HBV, and established follow up with either primary care or gastroenterology/hepatology during the study period. Patients were excluded if they had a prior HCC diagnosis or a history of liver transplantation. Overall screening rate was determined by identifying the proportion of patients undergoing abdominal ultrasound, CT abdomen, or MRI ordered for screening purposes during a 1-year period from 10/01/2022 to 10/01/2023. Screening completion was defined as completion of the first ordered screening test during the study period. **Results:** A total of 330 individuals met inclusion criteria. Of 226 screening tests that were ordered, 204 (90%) were completed. The overall screening rate during the study period was 62%. The screening rate was significantly higher in individuals with cirrhosis compared to those without cirrhosis (83% vs 60%, $p = 0.024$). No significant difference was observed based on marital status, gender, insurance type, English fluency and type of imaging ordered. Patients under the care of a gastroenterologist or hepatologist had significantly higher screening rates compared to those not under specialist care (73% vs 26%, $p < 0.00001$). **Conclusion:** HCC screening rates among individuals with chronic HBV remain suboptimal. The vast majority of patients for whom a screening test is ordered proceed to completion of the test, suggesting that the barrier to screening may be at the level of providers ordering screening tests and/or linkage to care rather than lack of patient adherence to

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recommended screening. Engagement with specialty care is strongly associated with improved adherence to screening, highlighting the importance of early referral and coordinated care in this high-risk population.

Table 1. Demographic Information.

Variable	All Subjects (n=330)	Completed Screening (n =204)	Did Not Complete Screening (n =126)	p-value (chi-squared)
Age, median (years)	56	56	57	0.95
BMI, median (kg/m^2)	25.1	25	25.7	0.12
Gender				0.13
Male (%)	153 (46)	88 (43)	65 (52)	
Female (%)	177 (54)	116 (57)	61 (48)	
Marital Status				0.2
Married (%)	206 (62)	134 (66)	72 (57)	
Single (%)	85 (26)	51 (25)	34 (27)	
Divorced (%)	29 (9)	13 (6)	16 (13)	
Widowed (%)	10 (3)	6 (3)	4 (3)	
Insurance Type				0.08
Private (%)	205 (62)	137 (67)	68 (54)	
Medicare (%)	91 (28)	51 (25)	40 (32)	
Medicaid (%)	31 (9)	14 (7)	17 (13)	
None (%)	3 (1)	2 (1)	1 (1)	
English Fluency				0.14
Yes (%)	265 (80)	169 (83)	96 (76)	
No (%)	65 (20)	35 (17)	30 (24)	
Screening Ordered				
Yes (%)	226 (68)	204 (100)	22 (17)	
No (%)	104 (32)	0	104 (83)	
Type of Screening Ordered				0.39
US (%)	167 (74)	149 (73)	18 (82)	
CT (%)	1 (0.4)	1 (0.4)	0	
MRI (%)	58 (26)	54 (26)	4 (18)	
Cirrhosis				0.024*
Yes (%)	24 (7)	20 (10)	4 (3)	
No (%)	306 (93)	184 (90)	122 (97)	
Specialist Care				<.00001*
Yes (%)	249 (75)	183 (90)	66 (52)	
No (%)	81 (25)	21 (10)	60 (48)	

Disclosures: Cameron Adams: Nothing to Disclose, Terry Li: Nothing to Disclose, Feng Su: Nothing to Disclose

1199 | NOVEL FIBROGENIC MACROPHAGE SUBPOPULATION DRIVES HBV-RELATED LIVER FIBROSIS AND OFFERS A TARGET FOR ANTIBODY THERAPY

Masaya Sugiyama[1] Aiko Sakai[2], [1]Japan Institue for Health Security, [2]Japan Institute for Health Security

Background: Chronic hepatitis B virus (HBV) infection has been demonstrated to lead to rapid progression of liver fibrosis and hepatocellular carcinoma (HCC), thus bypassing the traditional multistep carcinogenesis model. Despite its clinical significance, no effective antifibrotic therapies are currently available, making hepatic fibrosis a major unmet medical need. In the previous study, we utilized chimeric mice with human hepatocytes infected with HBV (HBV-chimeric mice) as a model of HBV-associated liver fibrosis. The aim of this study was to identify novel fibrogenic cell populations using single-cell RNA sequencing (scRNA-seq) of liver tissues from both HBV-chimeric mice and HBV-infected patients, and to explore potential therapeutic targets for fibrosis suppression. **Methods:** scRNA-seq was performed on liver tissues obtained from HBV-chimeric mice and human patients with chronic HBV infection. The resulting datasets were analyzed to identify cell populations associated with fibrosis progression and to characterize their gene expression profiles. The presence of these cell populations was validated through immunohistochemistry and fluorescence-activated cell sorting (FACS). To assess therapeutic efficacy, HBV-chimeric mice were treated with an anti-GPNMB monoclonal antibody, and hepatic fibrosis was evaluated after three months. **Results:** scRNA-seq analysis of HBV-chimeric mouse livers revealed a distinct macrophage subpopulation enriched in fibrotic regions. This macrophage subtype, characterized by $C1Q^+$/$GPNMB^+$/$CD68^+$ expression, was also identified in resected liver specimens from HBV-infected patients. The frequency of this subpopulation positively correlated with fibrosis stage in HBV cases but not in HCV-related liver disease. Functional inhibition of GPNMB with monoclonal antibodies in HBV-chimeric mice significantly reduced both fibrosis grade and the expression of fibrosis-associated genes after three months of treatment ($p < 0.05$). **Conclusion:** GPNMB-positive macrophages played a critical role in HBV-associated liver fibrosis. Targeting these cells with anti-GPNMB antibodies effectively suppressed fibrosis progression, underscoring their potential as a novel therapeutic target. These findings could provide a rationale for the development of antibody-based therapies for fibrotic liver diseases in patients with chronic HBV infection.

Disclosures: Masaya Sugiyama: Nothing to Disclose, Aiko Sakai: Nothing to Disclose

1200 | THE GLOBAL BURDEN OF ACUTE AND CHRONIC HEPATITIS B IN YOUNG AND MIDDLE-AGED ADULTS FROM 1990 TO 2021

Mohammed Youssef[1] MOHAMED A ELNAGGAR[2] Mohamed Eldesouki[3] Mona Ali[4] HESHAM ELGOUHARI[5] Sherif Elhanafi[6], [1]Hunt Regional Medical Center, [2]University of Connecticut, [3]New York Medical College at Saint Michael Medical Center, [4]Mansoura University Egypt, [5]texoma liver center, [6]Division of Gastroenterology, Texas Tech University Health Sciences Center El Paso

Background: Viral hepatitis B (Hep. B) is a significant health concern; it is one of the leading causes of chronic liver diseases and liver cancer worldwide. According to the WHO it is estimated that 254 million individuals worldwide are affected with chronic Hep B. In this study we aim to investigate the global incidence, mortality and disability-adjusted life years (DALYs) related to acute and chronic Hep B among Young and middle-aged adults. **Methods:** Global data were extracted from the GBD database for the age group between 15-49 years from 1990 to 2021. The total burden of hepatitis B includes acute Hep. B, chronic Hep. B including cirrhosis, and liver cancer due to hepatitis B. The primary outcome was the total Hep B related, mortality rate, and incidence rate. global trends were visualized using GBD derived mortality figures and graphs, with data further stratified by sex and by Socio-demographic

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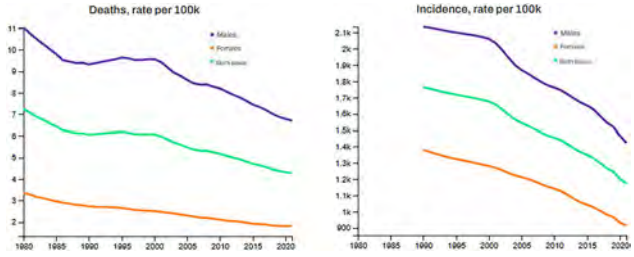
Index (SDI). **Results:** The total mortality rate of Hepatitis B in 1990 was 127.909 death vs 168,802.07 in 2021. The mortality rate decreased from 6.06 CI (5.34-6.98) per 100,000 in 1990 to 4.28 CI (3.65-4.91) per 100,000 in 2021. Gender specific data showed that males had a mortality rate of 9.32 CI (8.15-10.77) and 6.69 CI (5.70-7.75) per 100,000 in 1990 and 2021 respectively. Females had a lower mortality rate of 2.72 CI (2.29-3.22) and 1.80 CI (1.51-2.11) per 100,000 in 1990 and 2021 respectively. The incidence rate of Hep B in 1990 was 1,763.66 CI (1,307-2,259) per 100,000 and 1,171 CI (878.05- 1,530.09) per 100,000 in 2021. The DALYs decreased from 316.57 CI (278.22-362.66) in 1990 to 220.14 CI (190.66-250.97) in 2021 in this age group. The prevalence rate decreased from 6,470.26 CI (5,889- 7,178) per 100,000 in 1990 to 4,451 CI (4,058-4,912) per 100,000 in 2021. Low SDI countries had the highest Hep B mortality rate in 1990 and 2021 with rates of 8.52 CI (6.97-10.34) and 5.61 CI (4.61-6.71) respectively. High SDI countries had the lowest mortality rate in 1990 and 2021 with rates of 2.39 CI (2.05-2.73) and 1.28 CI (1.06-1.48) respectively. **Conclusion:** This study highlights a global decline in Hep B related burden among individuals aged between 15-49 from 1990-2021. This decline can be explained by improved prevention and treatment strategies. Despite this progress and the wide availability Hep B vaccine, males and low SDI countried suffered more for Hep B complications. Targeted public health efforts are needed to close these gaps and accelerate progress toward HBV elimination goals.



Disclosures: Mohammed Youssef: Nothing to Disclose, MOHAMED A ELNAGGAR: Nothing to Disclose, Mohamed Eldesouki: Nothing to Disclose, Mona Ali: Nothing to Disclose, HESHAM ELGOUHARI: Nothing to Disclose, Sherif Elhanafi: Nothing to Disclose

1201 | IMMUNE DYSREGULATION IN PREGNANT WOMEN WITH CHRONIC HEPATITIS B: IMPAIRED MDSC FUNCTION AND ENHANCED T CELL ACTIVATION

Xingfei Pan[1] Panpan Zhai[1] Li Pan[1] Xueting Ou[1] Liyang Zhou[1] Jun Huang[2] Calvin Pan[3,] [1]The Third Affiliated Hospital, Guangzhou Medical University, Guangzhou, China, [2]China Sino-French Hoffmann Institute, Guangzhou Medical University, [3]Guangzhou Medical University, Guangzhou, China; NYU Langone Health, NYU School of Medicine

Background: Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells with potent immunosuppressive activity, particularly in chronic inflammatory conditions. However, limited data are available regarding MDSC activity in pregnant women with chronic hepatitis B (CHB). We aimed to compare the status of MDSCs in pregnant women with CHB versus healthy controls, focusing on their abundance and the expression of molecules and immune cells commonly associated with MDSC function. **Methods:** We prospectively enrolled mothers at a tertiary care hospital in China between May 6, 2024, and April 8, 2025, including both CHB-infected mothers and healthy controls. Clinical data, along with peripheral blood, umbilical cord blood, and placental samples, were collected at delivery. MDSC counts and subsets were analyzed by flow cytometry. We also measured molecules and immune cells commonly associated with MDSC function, including $CD4^+$ T cells, CD80, CD163, reactive oxygen species (ROS), arginase-1 (Arg-1), transforming growth factor-β (TGF-β), programmed death-ligand 1 (PD-L1), and interleukin-10 (IL-10). **Results:** Among 160 participants (CHB: n = 69; healthy: n = 91), the mean age was 33 years. In the CHB group, the median (IQR) HBV DNA level was 52.98 (29.00, 827.20) IU/mL; 18.84% were HBeAg-positive, and 30.43% received antiviral therapy. Compared to healthy mothers, those with CHB had significantly lower counts of neutrophils (11.57 vs. 10.22, $p = 0.01$) and monocytes (1.02 vs. 0.86, $p = 0.0007$). MDSC analyses revealed a significant reduction in the proportion of total MDSCs (54.2% vs. 38.4%, $p = 0.0002$), granulocytic MDSCs (51.5% vs. 25.8%, $p < 0.0001$), and expression of MDSC-associated markers (Figure 1), including CD163 (69.9% vs. 46.1%, $p < 0.0001$), ROS (52.43×10^4 vs. 36.24×10^4, $p = 0.006$), Arg-1 (7.370×10^4 vs. 4.45×10^4, $p < 0.0001$), TGF-β (78.4% vs. 65.9%, $p = 0.0005$), PD-L1 (48.9% vs. 39.0%, $p = 0.0019$), and IL-10 (53.8% vs. 33.5%, $p < 0.0001$). In contrast, $CD4^+$ T cell counts and CD80 expression were significantly elevated in the CHB group compared to controls. **Conclusion:** Compared to healthy pregnant women, those with CHB exhibited a marked reduction in MDSC abundance and immune-regulating function, as reflected by decreased expression of CD163, ROS, Arg-1, TGF-β, PD-L1, and IL-10. Conversely, $CD4^+$ T cell numbers and CD80 expression were increased. These immunologic shifts may influence the regulation of maternal-fetal immune tolerance in the context of chronic HBV infection.

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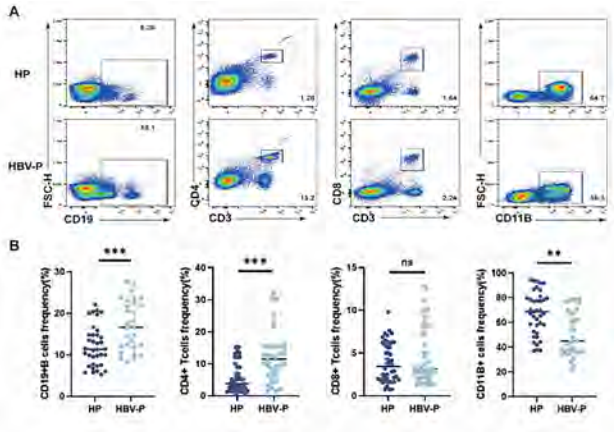

Figure 1. Changes in peripheral blood immune cell composition in pregnant women with chronic hepatitis B.
PBMCs were isolated from pregnant women with chronic hepatitis B (CHB, n = 69) and healthy pregnant women (n = 91). The composition of $CD19^+$ B cells, $CD3^+CD4^+$ T cells, $CD3^+CD8^+$ T cells, and $CD11b^+$ myeloid cells was analyzed by the fluorescence activated cell sorter
(A) Representative histograms of B cells, $CD4^+$ T cells, $CD8^+$ T cells, and myeloid cells.
(B) Proportions of immune cell subsets in peripheral blood. Data are shown as mean ± SD. $^{**}p < 0.01$, $^{*}p < 0.05$.

HP, healthy pregnant women; HBV-P, pregnant women with CHB.

Disclosures: Xingfei Pan: Nothing to Disclose, Panpan Zhai: Nothing to Disclose, Li Pan: Nothing to Disclose, Xueting Ou: Nothing to Disclose, Liyang Zhou: Nothing to Disclose, Jun Huang: Nothing to Disclose, Calvin Pan: Gilead Science, Inc.: Grant/Research Support, Wuxi Hisky Medical Technologies Co., Ltd.: Grant/Research Support

1202 | INVESTIGATION OF CORE I97L MUTATION AND HOST IMMUNE RESPONSE INVOLVED IN FUNCTIONAL CURE OF CHRONIC HEPATITIS B

Takashi Honda[1] Kena Yamamoto[1] Kazuyuki Mizuno[1] Hisanori Muto[1] Shinya Yokoyama[1] Takanori Ito[1] Norihiro Imai[1] yoji ishizu[1] Yoshiki Murakami[2] Sachiyo Yoshio[3] Tatsuya Kanto[4] Hiroki Kawashima[1] Tetsuya Ishikawa[1], [1]Nagoya University Graduate School of Medicine, [2]Tokyo Medical Univesity/Asahi University, [3]National Institute of Global Health and Medicine, [4]National Center for Global Health and Medicine

Background: Functional cure (FC) is a treatment goal for chronic hepatitis B (CHB). We previously reported that the I97L mutation in the HBV core region reduces cccDNA production and is associated with FC. This study aimed to evaluate whether the core I97L mutation can predict FC in CHB and how it relates to host immune responses for viral clearance. **Methods:** Study 1: In 129 CHB patients, clinical and viral factors associated with FC were analyzed using the Cox proportional hazards model. Study 2: Peripheral blood mononuclear cells (PBMC) were obtained from 10 FC and 9 non-FC patients matched for clinical background, using the patients from Study 1. PBMCs were stimulated with peptides containing the amino acid sequence of the core region I97 (wild-type peptide) and core region I97L (mutant peptide), and the IFNγ-producing cell ratio was compared using Enzyme-Linked ImmunoSpot (ELISpot) assay (R&D Systems). HLA typing was also performed. Study 3: Serum cytokines were measured at baseline (Pre, from Study 1) and at the time of PBMC collection (Post, from Study 2). **Results:** In Study 1, both univariate and multivariate analyses identified HBsAg levels and I97L mutation as significant predictors of FC ($P < 0.001$, $P = 0.004$). In Study 2, PBMC in non-FC patients exhibited significantly higher IFN-γ responses to the wild-type peptide compared to the mutant peptide. While no significant HLA differences were observed between FC and non-FC groups, HLA-A*24:02 positivity rate was more frequent in I97L carriers (75.0%) as compared in wild-type (14.3%) ($P < 0.05$). In Study 3, the expression level of cytokine was not different at Pre. However, at the Post levels of CXCL9, CCL22, and TNF-α, were significantly lower in FC patients ($P < 0.05$). From pre- to post, significant changes were observed in CXCL9, CXCL11, CXCL13, CCL2, CCL15, and IL-4. Notably, CXCL9 levels decreased significantly in FC patients and correlated with the reduction in ALT. HLA-A*24:02 was enriched among patients with I97L mutation compared to the general Japanese population. IFNγ production in response to wild-type peptide correlated with elevated post-CXCL9 levels, especially in non-FC patients. **Conclusion:** The elimination of wild strains by the host's acquired immune response may have acted as a selective pressure leading to the emergence of the I97L mutation. This suggested core I97L mutation may be a valuable predictor for FC in addition to low HBs antigen levels.

Disclosures: Takashi Honda: Nothing to Disclose, Kena Yamamoto: Nothing to Disclose, Kazuyuki Mizuno: Nothing to Disclose, Hisanori Muto: Nothing to Disclose, Shinya Yokoyama: Nothing to Disclose, Takanori Ito: Nothing to Disclose, Norihiro Imai: Nothing to Disclose, yoji ishizu: Nothing to Disclose, Yoshiki Murakami: Nothing to Disclose, Sachiyo Yoshio: Nothing to Disclose, Tatsuya Kanto: Nothing to Disclose, Hiroki Kawashima: Nothing to Disclose, Tetsuya Ishikawa: Nothing to Disclose

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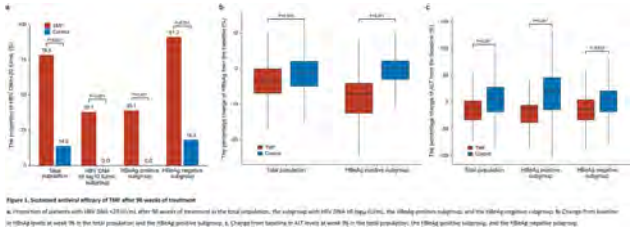
1203 | UPDATE OF 96 WEEKS TENOFOVIR AMIBUFENAMIDE TREATMENT IN CHRONIC HBV-INFECTED PATIENTS WITH NORMAL ALANINE AMINOTRANSFERASE (THE PROMOTE STUDY)

Honglian Gui[1] Yingqiu Shen[2] Lin Tan[3] Qing Xie[1] Lihong Qu[2] Piao Hu[4] Feng Qian[5] Xiaoping Wu[6] Yuanwang Qiu[7] Sujun Zheng[8] Jiaojian Lv[9] Yunzhen Shi[10] Jun Li[11] Yongfang Jiang[12] Zhizhen Hu[13] Yan Huo[13] Fanru Nie[13] Weijian Huang[13], [1]Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, [2]East Hospital Affiliated To Tongji University, [3]The Second People's Hospital of Fuyang, [4]Hangzhou Xiaoshan First People's Hospital, [5]The Fifth People's Hospital of Suzhou, Hospital of Infectious Diseases Affiliated to Soochow Univers, [6]The First Affiliated Hospital of Nanchang University, [7]Wuxi Fifth People's Hospital, [8]Beijing You 'an Hospital, Capital Medical University, [9]Lishui People's Hospital, [10]Dongyang People's Hospital, [11]Jiangsu Provincial People's Hospital, [12]The Second Xiangya Hospital of Central South University, [13]Jiangsu Hansoh Pharmaceutical Group Co., Ltd.

Background: The primary analysis of the PROMOTE study showed significant efficacy in chronic HBV-infected patients at 48 weeks with normal alanine aminotransferase (ALT) levels with favorable bone, renal and blood lipid safety profiles. Here we report a prespecified updated analysis after 96 weeks follow-up. **Methods:** Participants aged 18-65 diagnosed as chronic hepatitis B virus infection, with serum HBV DNA > 20IU/mL and normal ALT ($\leq$1×ULN [40 IU/L]) were randomly assigned to the TMF (25 mg/day) group or blank control group. Blood samples were analyzed for HBV DNA, HBsAg, HBeAg, and ALT levels, with the proportion of participants with serum HBV DNA levels < 20 IU/mL at week 96. **Results:** This analysis included 193 participants (93 TMF, 100 control). At 96 weeks, TMF treatment demonstrated significantly higher rates of HBV DNA suppression to < 20 IU/mL compared to control (78.49% vs 14.0%, $p < 0.001$). In patients with high baseline viral load (HBV DNA $\geq$8 log10 IU/mL), TMF treatment achieved HBV DNA < 2,000 IU/mL in 95.24% of patients (including 38.1% with HBV DNA < 20 IU/mL), compared with 5.56% (0 < 20 IU/mL) in controls. Among HBeAg-negative patients, TMF treatment demonstrated significantly higher rates of HBV DNA suppression to < 20 IU/mL (91.3% vs 18.31%; $p < 0.001$). Compared with the control group, TMF treatment resulted in a significant reduction in HBsAg levels from baseline (-0.29 vs -0.07 log10 IU/mL, $p < 0.001$), with this trend being similarly significant in the HBeAg-positive subgroup (-0.30 vs 0 log10 IU/mL, $p < 0.001$). Participants receiving TMF demonstrated significantly greater reductions in ALT levels compared with controls (-12.25% vs 6.25%, $p < 0.001$). This treatment effect was consistently observed in both HBeAg-positive (-10.81% vs 21.43%, $p = 0.007$) and HBeAg-negative (-13.01% vs 5.0%, $p = 0.008$) subgroups. Notably, one case of acute hepatitis with ALT flare (ALT > 5×ULN) unrelated to other causes occurred in the control group, while none were observed in the TMF group. No between-group differences were observed in creatinine levels, glomerular filtration rates, or lipid profiles. **Conclusion:** TMF demonstrated sustained potent antiviral efficacy, while maintaining favorable safety profiles and tolerability. TMF treatment appears to reduce the incidence of virus replication associated ALT flare. Long-term follow up are required to observe the benefit of outcome improvement after antiviral treatment in such population. Clinical trial Registry: NCT05797714.



Disclosures: Honglian Gui: Nothing to Disclose, Yingqiu Shen: Nothing to Disclose, Lin Tan: Nothing to Disclose, Qing Xie: Nothing to Disclose, Lihong Qu: Nothing to Disclose, Piao Hu: Nothing to Disclose, Feng Qian: Nothing to Disclose, Xiaoping Wu: Nothing to Disclose, Yuanwang Qiu: Nothing to Disclose, Sujun Zheng: Nothing to Disclose, Jiaojian Lv: Nothing to Disclose, Yunzhen Shi: Nothing to Disclose, Jun Li: Nothing to Disclose, Yongfang Jiang: Nothing to Disclose, Zhizhen Hu: Nothing to Disclose, Yan Huo: Nothing to Disclose, Fanru Nie: Nothing to Disclose, Weijian Huang: Nothing to Disclose

1204 | THE ROLE AND MECHANISM OF THE HOST RESTRICTION FACTOR SLFN5 IN HEPATITIS B VIRUS TRANSCRIPTION AND REPLICATION

Ning Han[1], [1]Sichuan University

Background: Hepatitis B virus (HBV) infection remains a global health challenge, with current treatments unable to fully eradicate it. Host restriction factors (HRFs), especially those induced by interferons, play a key role in antiviral defense. Schlafen family member 5 (SLFN5), an interferon-α-inducible HRF, has shown antiviral activity against viruses like HIV-1 and herpes simplex virus. However, its role in HBV infection is unclear. This study aims to investigate SLFN5's function

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in regulating HBV transcription and replication, offering potential for HRF-based antiviral therapies against HBV. **Methods:** Differentially expressed genes in HBV-infected dHepRG cells with or without interferon-α (IFN-α) treatment were analyzed by RNA sequencing and Interferome database integration. SLFN5 was identified as an IFN-α-inducible HRF, validated by qRT-PCR and western blotting. Its effect on HBV replication was evaluated in cell models through gain- and loss-of-function experiments, measuring HBV RNA, DNA, and antigens. *In vivo*, SLFN5 modulation was assessed using an AAV8-HBV mouse model. Mechanistic studies included promoter activity assays and pathway validation. **Results:** Transcriptomic analysis and the Interferome database identified SLFN5 as an interferon-α-inducible host restriction factor, upregulated in interferon-α-induced HBV-infected dHepRG cells, validated by qPCR and western blotting. SLFN5 overexpression suppressed HBV RNA, DNA, and antigens in multiple HBV models, while knockdown enhanced viral replication. *In vivo*, SLFN5 overexpression in an AAV8-HBV mouse model reduced HBV intermediates, serum HBsAg, and HBV DNA, whereas knockdown promoted replication. Mechanistically, SLFN5's antiviral effect was dependent on its C-terminal domain and the ATR/CHK1 pathway. SLFN5 knockdown increased ATR phosphorylation, and this effect was reversed by the ATR inhibitor AZD6738. **Conclusion:** This study shows that SLFN5 is significantly upregulated in HBV-infected cells following interferon treatment, potentially acting as a host restriction factor to inhibit HBV replication. SLFN5 overexpression suppresses HBV transcriptional replication. Specifically, SLFN5 restricts HBV replication through its C-terminal domain and by regulating the ATR/CHK1 signaling pathway.

Disclosures: Ning Han: Nothing to Disclose

1205 | ANTIVIRAL THERAPY FAILS TO RESOLVE IMMUNE DYSFUNCTION AND INFLAMMATORY SIGNALLING IN INNATE-LIKE CD8$^+$ T CELLS IN CHRONIC HEPATITIS B

Lung Yi Mak[1] Shue Xiong[2] Sebastian Deschler[3] Corrina Pade[2] Chanelle Fernandes[2] Tizong Miao[2] Gerard Hernandez-Mir[2] Yu Lei[2] Anna Riddell[4] Apostolos Koffas[2] Katrin Boettcher[3] Patrick Kennedy[2], [1]The University of Hong Kong, [2]Queen Mary University of London, [3]University of Tubingen, [4]Barts Health NHS Trust

Background: CD56+ CD8 T cells straddle the boundary between innate and adaptive immunity and are distinguished from other CD8 T cell subpopulations, exhibiting high NK receptor (NKR's) expression and exerting effector functions in a TCR-independent manner, associated with 'bystander' activation. Previous studies have recognised the role of bystander T cells correlating with liver inflammation. Evaluating this cell population may provide insights into reasons for immunological failure of novel therapies for chronic hepatitis B (CHB) cure. **Methods:** We studied blood-circulating CD8 T cells from treated and untreated (treatment-naïve) CHB patients compared to healthy controls (HC). The proportion of activated CD8 T cells, expression of NKRs, impact of free fatty acids (FFA's) and functional profile of these cells was analysed by multi-parameter flow cytometry. Transcriptomic analysis of CD8 T cells was also performed. **Results:** Activated (CD38+HLA-DR+) CD8 T cells expressing CD56 were significantly greater in CHB vs HC's, with a higher expression of NKRs (NKG2A, NKp30) on innate-like T cells (CD56+ CD8+). The percentage of CD56+ CD8 T cells expressing NKRs were greater in subjects with 'immune active' vs 'immune control' disease. Contrarily, CHB subjects undergoing antiviral therapy (AVT), exhibited a reduced percentage of CD56+ CD8 T cells, however their NKR expression remained significantly higher than in treatment-naïve patients. Undertaking transcriptomic analysis on sorted CD8 T cells, we noted mRNA expression of innate-like markers (KLRK1, NCR3) was higher in treated vs. untreated immune control patients indicating innate-like immune defects are not recovered by AVT.To determine cellular effector function, stimulation was undertaken with anti-CD3/CD28 (TCR-dependent) and IL-15 (TCR-independent). We noted IFNg production was similar on CD56+ CD8 T cells with either stimulation method, but TNFa production was greater following IL-15 stimulation, indicating a differential functional profile in a TCR-independent manner. Functional CD56+ CD8 T cells were more susceptible to FFA's as inflammatory mediators. **Conclusion:** We demonstrate the increased expression of CD56+ CD8 T cells expressing NKR's in CHB, signalling with TCR-independence, causing bystander activity with greater susceptiblity to inflammatory mediators. Further work analysing the impact of AVT in CHB and CHB-MASLD patients is underway, to guide the development of therapeutic targets in the functional cure program.

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1206 | UTILIZING IMMUNOLOGIC AND METABOLIC MARKERS IN ASSESSMENT OF LOW-LEVEL VIREMIA IN PATIENTS WITH CHRONIC HEPATITIS B RECEIVING NUCLEOS(T)IDE ANALOGS

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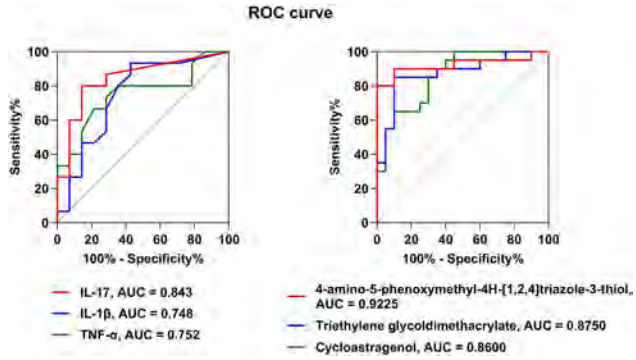
Background: Low-level viremia (LLV) is associated with disease progression and unfavorable clinical outcomes of chronic hepatitis B (CHB), including liver fibrosis, cirrhosis, and hepatocellular carcinoma. This study aims to analyze the clinical characteristics of CHB patients with LLV and evaluate the immunological status and metabolic differences between patients with maintained virologic response (MVR) and patients with LLV. **Methods:** We conducted a single-center retrospective study and analyzed clinical data from 270 patients with CHB after first-line nucleos(t)ide analogs (NAs) therapy over 48 weeks. Patients were divided into two groups: 90 MVR patients with HBV DNA < 10 IU/mL and 180 LLV patients with HBV DNA between 10 IU/mL and 2000 IU/mL. Demographic and clinical characteristics, serum cytokines levels and results of baseline serum non-targeted metabolomics were comprehensively compared. **Results:** Patients with LLV demonstrated significantly higher levels of ALT, AST, qHBsAg and percentage of HBeAg positivity compared to those with MVR after NAs therapy over 48 weeks ($p < 0.05$ for all). Dynamic cytokines levels were analyzed in 14 MVR patients and 15 LLV patients. LLV patients showed higher levels of serum IL-17 and TNF-α compared to those who achieved MVR, from baseline through the 96-week follow-up period ($p < 0.05$ for all). Serum IL-1β levels were significantly higher in LLV patients at baseline and 48 weeks post-NA therapy. ROC analysis indicated baseline serum IL-1β,IL-17 and TNF-α could predict the occurrence of LLV. The cut-off value for IL-1β was 12.45 pg/mL, with an AUC of 0.748, a sensitivity of 0.933 and a specificity of 0.571. The cut-off value for IL-17 was 3.85 pg/mL, with an AUC of 0.843, a sensitivity of 0.8 and a specificity of 0.857. The cut-off value for TNF-α was 10.9 pg/mL, with an AUC of 0.752, a sensitivity of 0.667 and a specificity of 0.786. Analysis of baseline serum non-targeted metabolomics were conducted in 20 MVR patients and 20 LLV patients. 101 different metabolites were detected in patients with MVR compared to those with LLV. The top three metabolites with significant differences were 4-amino-5-phenoxymethyl-4H-[1,2,4]triazole-3-thiol, triethylene glycoldimethacrylate and cycloastragenol. ROC analysis indicated potential predicative value for LLV of baseline 4-amino-5-phenoxymethyl-4H-[1,2,4]triazole-3-thiol (AUC 0.9225), triethylene glycoldimethacrylate (AUC 0.8750) and cycloastragenol (0.8600). **Conclusion:** Baseline serum IL-1β,IL-17 and TNF-α have potential value of LLV prediction. Baseline serum 4-amino-5-phenoxymethyl-4H-[1,2,4]triazole-3-thiol, cycloastragenol and triethylene glycoldimethacrylate are potential metabolic markers for prediction of LLV. This study indicates potential clinical application and further exploration of immunologic and metabolic markers in both prediction and disease management evaluation of LLV.



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1207 | BRELOVITUG (BJT-778) BINDS A CONFORMATIONAL EPITOPE HIGHLY CONSERVED ACROSS HBV GENOTYPES

Craig Pace[1] Hilario Ramos[1] Jerome Deval[1] Nancy Shulman[1] Hassan Javanbakht[1], [1]Bluejay Therapeutics

Background: Brelovitug is a fully human highly potent, pan-genotypic IgG1 neutralizing monoclonal antibody that targets the HBsAg antigenic loop on the surface of both HBV and HDV virions. In this study, we mapped the brelovitug epitope and assessed the conservation of its epitope residues among global HBsAg sequences. **Methods:** The brelovitug epitope was mapped by evaluating its binding to a panel of HBsAg variants, including 60 variants bearing single alanine substitutions in the antigenic loop, and 44 naturally occurring HBsAg escape variants found in CHB patients. Plasmids encoding these HBsAg variants were transfected into Huh-7 cells, and brelovitug binding was quantified by ELISA, measuring the area under the curve (AUC) after capturing HBsAg from supernatants with a

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polyclonal anti-HBsAg antibody. To control for differences in HBsAg expression, brelovitug binding to each variant was normalized to both polyclonal antibody binding and brelovitug binding to wild type HBsAg. Conservation of brelovitug epitope residues was determined from 29,987 HBsAg sequences spanning HBV genotypes A - H obtained from the HBV Database. **Results:** Brelovitug binding was substantially reduced for HBsAg alanine-scan variants I110A, G119A, Q129A, P142A, T143A, D144A, G145A, I150A, P151A and I152A. While brelovitug had substantially reduced binding when HBsAg residues I110, Q129, P142, T143 and D144 were substituted with alanine, it maintained wild type binding to the naturally occurring escape variants at these positions (I110L, Q129H, P142S, T143L and D144E). The only naturally occurring variants that displayed reduced brelovitug binding were those containing substitutions at G145A/E/R, P142/G145R, D144E/G145R and T132N/T143S substitutions. Across 29,987 global HBsAg sequences, conservation of the brelovitug epitope residues ranged from 98.2% at position G145 to 99.9% at positions I150, P151 and I152. **Conclusion:** HBsAg residues I/L110, G119, Q/H129, S/A132, P142, T/L/S143, D/E144, G145, I150, P151 and I152 are critical for brelovitug binding. These amino acids are highly conserved ($\geq$98.2%) among HBsAg from HBV genotypes A – H consistent with brelovitug's pan-genotypic neutralization activity in vitro. Therefore, brelovitug binds to a highly conserved epitope comprised of these residues, reinforcing its potential as a broadly effective therapeutic for chronic hepatitis B and D.

Disclosures: Craig Pace: Bluejay Therapeutics: Employee, Johnson and Johnson Innovative Medicine: Employee, Hilario Ramos: Bluejay Therapeutics: Employee, Bluejay Therapeutics: Stock – privately held company, Jerome Deval: Nothing to Disclose, Nancy Shulman: Bluejay Therapeutics, INC: Salary and equity, Hassan Javanbakht: Nothing to Disclose

1208 | SUSTAINED REDUCTION OF HBV ANTIGEN LEVELS DURING THE 8-WEEK FOLLOW-UP PERIOD IN TREATMENT NA&IUML;VE (TN) OR CURRENTLY-NOT-TREATED (CNT) HBEAG-POSITIVE SUBJECTS WITH CHRONIC HEPATITIS B VIRUS INFECTION AFTER 96-WEEK 300 MG ALG-000184, WITH OR WITHOUT ENTECAVIR (ETV)

Man-Fung Yuen[1] Edward Gane[2] Kosh Agarwal[3] Hong Ren[4] Yanhua Ding[5] Alina Jucov[6] XieEr LIANG[7] Jia Xu[5] Alexei Haceatrean[6] Kha Le[8] Jennifer Rito[8] Lawrence Blatt[8] Sushmita Chanda[8] Tse-I Lin[8] Hardean E. Achneck[8] Jinlin Hou[7], [1]Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong, China, [2]Faculty of Medicine, University of Auckland, Auckland, New Zealand, [3]King's College Hospital, Institute of Liver Studies, London, United Kingdom, [4]The Second Affiliated Hospital of ChongQing Medical University, Chongqing, China, [5]The First Hospital of Jilin University, Changchun, China, [6]ARENSIA Exploratory Medicine, Republican Clinical Hospital and Nicolae Testemitanu State University, [7]Nanfang Hospital, Southern Medical University, Guangzhou, China, [8]Aligos Therapeutics, Inc.

Background: ALG-000184-201 (NCT04536337) is a multi-centre phase 1 clinical trial conducted in healthy volunteers and TN/CNT subjects with chronic Hepatitis B virus infection. Previous data demonstrated favourable safety and potent antiviral effects with ALG-000184 $\pm$ ETV for $\leq$ 96 weeks. Here, we present HBV antigen data during treatment and the 8 weeks follow up (FU). **Methods:** TN or CNT HBeAg+ subjects received either 100 mg ALG-000184 + ETV for $\leq$ 24 weeks or 300mg ALG-000184 $\pm$ ETV for $\leq$ 96 weeks. Following completion of ALG-000184 dosing, subjects entered an 8-week follow-up period, during which only nucleos(t)ide analogues (NA) was administered. **Results:** Mean baseline levels were comparable in 100 mg ALG-000184 + ETV ($\leq$ 24 weeks, N = 8) and 300 mg ALG-000184 $\pm$ ETV ($\leq$ 96 weeks, N = 21), with HBsAg at 4.7 vs. 4.4 $\log_{10}$ IU/mL; HBeAg at 2.6 vs. 2.5 $\log_{10}$ PEI U/mL; and HBcrAg at 8.5 vs 8.3 $\log_{10}$ U/mL, respectively. At Week 24, a dose-dependent HBV antigen reduction was observed with mean reductions of HBsAg, HBeAg and HBcrAg of 0.5 vs 0.6 $\log_{10}$ IU/mL, 0.2 vs 0.6 $\log_{10}$ PEI U/mL and 0.6 vs 1.2 $\log_{10}$ U/mL in 100 mg ALG-000184 + ETV (n = 4) and 300 mg ALG-000184 $\pm$ ETV (n = 19), respectively. In the 16 subjects receiving 300 mg ALG-000184 $\pm$ ETV for 96 weeks, continuous mean reductions were observed in HBsAg, HBeAg and HBcrAg levels (0.9 $\log_{10}$ IU/mL, 1.5 $\log_{10}$ PEI U/mL, 2.2 $\log_{10}$ U/mL at Week 96, respectively). Notably, of these 16 subjects, HBV antigens changed minimally during the 8 weeks FU with mean reductions at FU Week 8 of 0.8 $\log_{10}$ IU/mL for HBsAg, 1.2 $\log_{10}$ PEI U/mL for HBeAg and 1.9 $\log_{10}$ U/mL for HBcrAg. **Conclusion:** 100 or 300 mg ALG-000184 $\pm$ ETV for $\leq$ 24 weeks or $\leq$ 96 weeks resulted in dose- and duration-dependent multi-log reductions in HBV antigens in TN/CNT HBeAg+ subjects. Additionally, sustained reductions in HBV antigens were observed during the 8-week post-ALG-000184 follow-up period after longer treatment with higher dose of 300 mg ALG-000184. This may indicate cccDNA depletion, associated with the CAM-E secondary mechanism of action.

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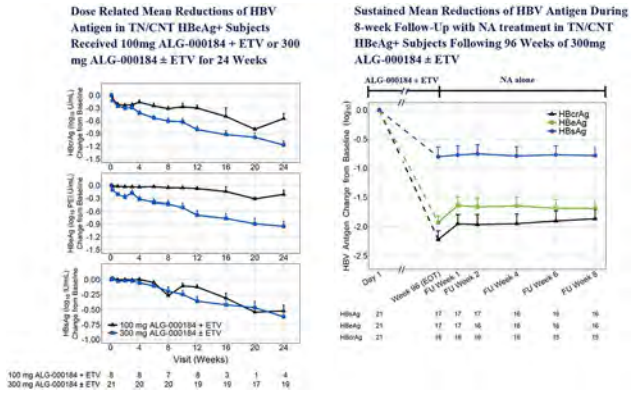

Disclosures: Man-Fung Yuen: Nothing to Disclose, Edward Gane: Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Kosh Agarwal: Nothing to Disclose, Hong Ren: Nothing to Disclose, Yanhua Ding: Nothing to Disclose, Alina Jucov: Nothing to Disclose, XieEr LIANG: Nothing to Disclose, Jia Xu: Nothing to Disclose, Alexei Haceatrean: Nothing to Disclose, Kha Le: Nothing to Disclose, Jennifer Rito: Nothing to Disclose, Lawrence Blatt: Nothing to Disclose, Sushmita Chanda: Nothing to Disclose, Tse-I Lin: Nothing to Disclose, Hardean E. Achneck: Aligos Therapeutics: Employee, Jinlin Hou: Nothing to Disclose

1209 | INHIBITION OF HSPG2 EXPRESSION IMPAIRS HBV ENTRY AND REPLICATION THROUGH THE C-MET SIGNALING PATHWAY

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Background: Hepatitis B virus (HBV) entry into hepatocytes depends on heparan sulfate proteoglycans (HSPGs) and the sodium taurocholate co-transporting polypeptide (NTCP), a bile acid transporter (BAT). Among HSPGs, we focused on HSPG2, which contributes to the binding of cMET and NK4, which is competitive antagonist against HGF. We examined the impact of HSPG2 suppression on HBV infection and explored the underlying mechanisms. **Methods:** Primary human hepatocytes isolated from humanized liver chimeric TK-NOG mice (HepaSH cells) were inoculated with HBV (500 genome equivalent (GEq)/cell) prepared by concentrating the culture supernatant of HBV genome-integrated cells (HepAD38.7). **Results:** Silencing HSPG2 expression with siRNA 3 days prior to HBV inoculation significantly reduced covalently closed circular DNA (cccDNA). The suppression of HSPG2 expression significantly increased cMET expression and decreased NTCP expression. The downregulation of NTCP expression induced by HSPG2 suppression was reversed by silencing c-MET. On the other hand, the suppression of NTCP expression did not alter the mRNA expression levels of HSPG2. Silencing NTCP expression with siRNA 3 days prior to HBV inoculation significantly reduced cccDNA. Suppression of both HSPG2 and NTCP expression had no additional effect on cccDNA reduction compared to the suppression of NTCP alone. Suppression of HSPG2 may inhibit HBV entry by downregulating NTCP expression via upregulation of c-MET. Suppression of NTCP expression 20 days after HBV inoculation did not reduce the expression levels of cccDNA, but the suppression of HSPG2 expression did. Given the possibility that HSPG2 suppression may influence HBV replication through mechanisms beyond entry inhibition, we investigated PPARγ, a host transcription factor known to activate HBV transcription. Suppression of HSPG2 upregulated cMET and pMET, and downregulated PPARγ. Suppression of PPARγ led to downregulation of NTCP, NR5A2 (a regulator of bile acid transporter expression), and CTNNB1, an upstream activator of NR5A2. Suppression of CTNNB1 downregulated NR5A2 and NTCP. The suppression of NR5A2 downregulated NTCP. It was suggested that cMET regulated NTCP expression via PPARγ, CTNNB1 and NR5A2. **Conclusion:** Suppression of HSPG2 expression was suggested to have an effect that suppress both HBV entry and replication via cMET signaling pathway.

Disclosures: Kazuhiro Murai: Nothing to Disclose, Tasuku Nakabori: Nothing to Disclose, Takao Kitanaka: Nothing to Disclose, Takayuki Miyake: Nothing to Disclose, Shinji Kuriki: Nothing to Disclose, Emi Sometani: Nothing to Disclose, Jihyun Sung: Nothing to

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Disclose, Satoshi Shigeno: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Takahiro Kodama: Nothing to Disclose, Hayato Hikita: Nothing to Disclose

1210 | UP TO 12 MONTHS' DURABILITY OF FUNCTIONAL CURE WITH BEPIROVIRSEN PLUS PEG-IFN SEQUENTIAL THERAPY IN B-TOGETHER RESPONDERS: B-SURE STUDY

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Background: Bepirovirsen, an unconjugated antisense oligonucleotide that targets all hepatitis B virus (HBV) RNAs, is in Phase 3 development for chronic HBV infection. Data from B-Together (NCT04676724) indicated that a subset of participants on nucleos(t)ide analogs (NAs) achieved either a complete response (CR) or a partial response (PR) following 12 or 24 weeks of bepirovirsen and 24 weeks of pegylated interferon α-2a (Peg-IFN) sequential therapy. This response was sustained for 24 weeks following the end of Peg-IFN treatment. Participants with a CR or PR at the end of B-Together were eligible for the B-Sure long-term durability study (NCT04954859; ongoing). Here we present up to 2-year follow-up data on the durability of response for B-Together complete responders (CRs) and partial responders (PRs) who enrolled in B-Sure. **Methods:** CR was defined as both hepatitis B surface antigen (HBsAg) $<$ lower limit of quantification (LLOQ) andHBV DNA $<$ LLOQ (20 IU/mL), and PR as detectable HBsAg (LLOQ $<$ HBsAg $<$ 100 IU/mL) and HBV DNA $<$ LLOQ, at the end of B-Together. If eligible, participants discontinued NA 3 months into B-Sure ($\geq$ 9months from the end of bepirovirsen plus Peg-IFN sequential therapy) and were followed to determinethe achievement and durability of functional cure (HBsAg and HBV DNA $<$ LLOQ for a minimum of 24weeks off all HBV treatment). Adverse events (AEs) were recorded at each visit. **Results:** In total, 23 On-NA participants (13 CRs, 8 PRs and 2 non-responders) from B-Together were enrolled into B-Sure (Figure); mean age was 51.3 years. At entry into B-Together, 19 participants (83%) were hepatitis B e-antigen (HBeAg) negative, 16 (70%) had documented HBV infection $\geq$ 10 years, and 17 (74%) had HBsAg $\leq$ 1000 IU/mL. Three months after entry into B-Sure, 12/13 CRs discontinued NAs; 9/12 maintained CR to 6 months post NA cessation, thus achieving functional cure; the three losses in CR (3/12) were due to HBsAg reversion or study withdrawal. Additionally, 7/8 participants who had data up to 12 months post NA cessation maintained functional cure at the 12 month visit (i.e. functional cure for 6 months), and 2/2 participants who had data up to 18 months post NA cessation maintained functional cure at the 18 month visit (i.e. functional cure for 12 months; Figure). No CRs restarted NAs during B-Sure. Overall, 3/8 PRs discontinued NAs 3 months after B-Sure entry. None achieved functional cure, 2/3 participants maintained PR at 6 and 12 months post NA cessation; the one loss of PR was due to virological relapse (Figure). Among the 3 PRs who discontinued NAs, 1 restarted NA therapy by 9 months post NA cessation. No CRs/PRs who discontinued NAs had alanine aminotransferase (ALT) $\geq$ 2x upper limit of normal; 1 participant had HBV DNA $>$ 2000 IU/mL with no ALT increase. There were no new safety signals. **Conclusion:** These data provide evidence of the durability of functional cure for up to 1 year in CRs to sequential bepirovirsen plus Peg-IFN therapy. Funding: GSK (206882)

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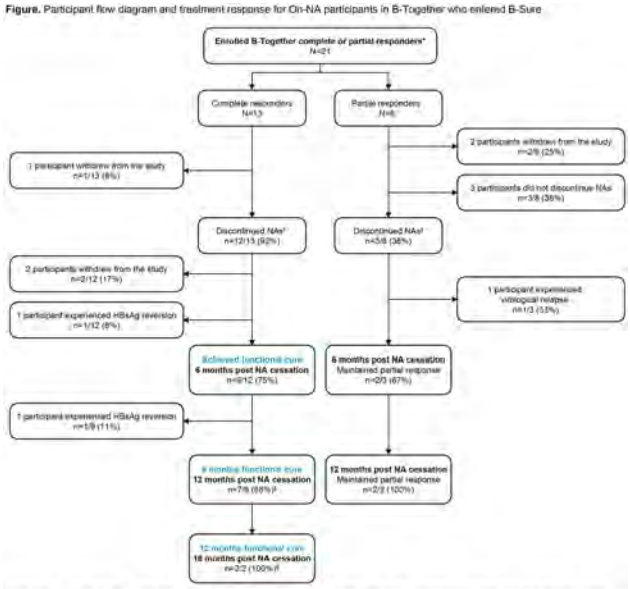

*2 non-responders from B-Together were enrolled into B-Sure but were excluded from the flow diagram, these non-responders were included in the demographic results; †for complete responders to be eligible for NA discontinuation they must; achieve the B-Together primary outcome and maintain a complete response without reversion (HBsAg ≥LLOQ or HBV DNA ≥LLOQ confirmed by 2 consecutive visits) in the absence of rescue medication up to 3 months into B-Sure (excluding blips), have stable NA treatment for 3 months into B-Sure and have ALT<1.25xULN at 2.5 months into B-Sure. †for partial responders to be eligible for NA discontinuation they must: maintain HBsAg reduction ≥1.0 log_{10} IU/mL from the baseline of B-Together with HBsAg levels <100 IU/mL and HBV DNA <LLOQ for 24 weeks after the actual end of treatment in the absence of rescue medication and maintained until their end of study visit in the B-Together and up to 3 months into B-Sure (excluding blips), have stable NA treatment for 3 months into B-Sure and have ALT<1.25xULN at 2.5 months into B-Sure; †1 participant had not reached the 12 months post NA cessation visit at the time of the data cutoff. ‡6 participants had not reached the 18 months post NA cessation visit at the time of the data cutoff. ALT, alanine aminotransferase; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification; NAs nucleos(t)ide analogs; ULN, upper limit of normal

Disclosures: Carla Coffin: Gilead: Grant/Research Support, Janssen Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, Altimmune Pharmacueticals: Fund paid to the University of Calgary, Riche Pharmaceuticals: Grant/Research Support, GSK: Funds paid to the University of Calgary, GSK: unknown, Gilead Sciences: Funds Paid to the University of Calgary, Janssen: Grant/Research Support, Gilead: Consultant, GSK: Consultant, Gilead: Sponsored lecturer (national or International), GSK: Sponsored lecturer (national or International), Roche: Consultant, Gilead (paid to the University of Calgary): Consultant, Roche (paid to the University of Calgary): Consultant, GSK (paid to the University of Calgary): Consultant, Gilead (paid to the University of Calgary): Speaking and Teaching, GSK (paid to the University of Calgary): Speaking and Teaching, Pietro Andreone: Nothing to Disclose, Joaquin Cabezas: Nothing to Disclose, Natalya Gankina: Nothing to Disclose, Stuart Gordon: Nothing to Disclose, Jeong Heo: Gilead: Grant/Research Support, Roche: Speaking and Teaching, Yuhan: Speaking and Teaching, Abbvie: Speaking and Teaching, AstraZeneca: Advisor, Oncolys Japan: Grant/Research Support, Surrozen: Advisor, MedVir: Advisor, Pietro Lampertico: Nothing to Disclose, Vyacheslav Morozov: Nothing to Disclose, Svetlana Romanova: Nothing to Disclose, Pablo Ryan: Nothing to Disclose, Guoping Sheng: Nothing to Disclose, Tatiana Stepanova: Nothing to Disclose, Krzysztof Tomasiewicz: Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, GSK: Speaking and Teaching, Bausch Healthcare: Advisor, Pfizer: Speaking and Teaching, Takeda: Advisor, Natalya Voloshina: Nothing to Disclose, Hyung Joon Yim: Nothing to Disclose, Alexandra Walker: Nothing to Disclose, Jane Dong: Nothing to Disclose, Geoff Quinn: Nothing to Disclose, Isabelle Santhiapillai: Nothing to Disclose, Helene Plein: Nothing to Disclose, Yi Cui: Nothing to Disclose, Raju Gowda: Nothing to Disclose, Matthijs Broer: GlaxoSmithKline: Employee, Melanie Paff: Nothing to Disclose, Dickens Theodore: GSK: Employee, GSK: Stock - publicly traded company, Rob Elston: Nothing to Disclose, Marjan Hezareh: Nothing to Disclose

1211 | PREDICTING HBSAG SEROCLEARANCE IN PEG-IFNα TREATED CHRONIC HEPATITIS B PATIENTS PRESENTING WITH HIGH HBV DNA OR HBSAG LEVELS:A NOVE NOMOGRAM

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Background: Chronic hepatitis B (CHB) patients with unfavorable baseline markers(HBV DNA > 20 IU/mL and/or HBsAg > 1500 IU/mL) typically exhibit suboptimal responses to pegylated interferon-α (Peg-IFNα) therapy. However, a clinically relevant subset still achieves functional cure (HBsAg seroclearance). We developed and validated a dynamic, parameter-incorporated nomogram to predict 6-month, 12-month and 18-month HBsAg seroclearance in this challenging population, facilitating personalized treatment decisions. **Methods:** A prospective training cohort of 178 treatment-naïve CHB patients (HBV DNA > 20 IU/mL and/or HBsAg > 1500 IU/mL) was enrolled from Tianjin Second People's Hospital (July 2020–June 2024), randomly split into training (n = 124) and internal validation (n = 54) sets (7:3 ratio). An independent external cohort (n = 182) from Tianjin Third Central Hospital was used for geographical validation. LASSO-regularized Cox regression identified key predictors, and the final model was rigorously evaluated for discrimination (time-dependent AUC, C-index), calibration (Brier score), and clinical utility (decision curve analysis). Follow-up extended 3–6 months post-treatment to confirm seroclearance. **Results:** The derivation (n = 124), internal validation (n = 54), and external validation (n = 182) cohorts showed well-balanced baseline characteristics (all P > 0.05). LASSO-selected predictors included: Baseline HBsAg (log10 IU/mL; HR 0.741, 95%CI 0.62-0.89), 3-month HBsAg decline (log10 IU/mL; HR 0.256, 0.18-0.36), HBeAg seroconversion by month 3 (HR 0.469, 0.32-0.69), ALT flares

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(1-2×ULN: HR 2.449, 1.8-3.3; >2×ULN: HR 2.306, 1.7-3.1). The nomogram achieved exceptional discrimination: Training cohort: C-index 0.929 (95%CI 0.90-0.95), time-dependent AUCs 0.981/0.913/0.946 at 6/12/18 months; Internal validation: C-index 0.886 (0.85-0.92), AUCs 0.947/0.940/0.839; External validation: C-index 0.946 (0.92-0.97), AUCs 0.958/0.932/0.961. Calibration curves demonstrated excellent agreement between predicted and observed probabilities. Kaplan-Meier analysis confirmed significantly faster HBsAg seroclearance in low-risk vs high-risk groups ($P < 0.001$). **Conclusion:** This dynamic nomogram represents the first validated tool integrating on-treatment virological responses to predict HBsAg seroclearance in CHB patients with unfavorable baseline markers. With superior accuracy and clinical applicability, it enables: Early identification of Peg-IFNα responders at month 3. The model's implementation could optimize therapeutic strategies and improve functional cure rates in this challenging patient population.

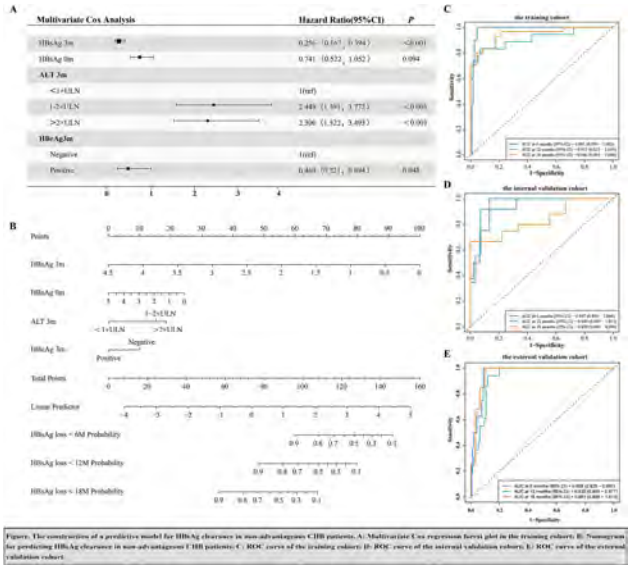

Figure. The construction of a predictive model for HBsAg clearance in non-advantageous CHB patients. A: Multivariate Cox regression forest plot in the training cohort; B: Nomogram for predicting HBsAg clearance in non-advantageous CHB patients; C: ROC curve of the training cohort; D: ROC curve of the internal validation cohort; E: ROC curve of the external validation cohort.

Disclosures: Wentao Kuai: Nothing to Disclose, Liang Xu: Nothing to Disclose, Jiaxin Han: Nothing to Disclose

1212 | A VIRAL LOAD-BASED MODEL TO PREDICT HEPATOCELLULAR CARCINOMA AND ANTIVIRAL TREATMENT BENEFIT IN CHRONIC HEPATITIS B

Won-Mook Choi[1] Gi-Ae Kim[2] Jonggi Choi[1] Gwang Hyeon Choi[3] Yun Bin Lee[4] Dong Hyunn Sinn[5] Nae-Yun Heo[6] Sehee Kim[1] YOUNG-SUK LIM[1], [1]Asan Medical Center, University of Ulsan College of Medicine, [2]Kyung Hee University School of Medicine, [3]Seoul National University Bundang Hospital, Seoul National University College of Medicine, [4]Seoul National University, [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, [6]Inje University Haeundae Paik Hospital, Inje University College of Medicine

Background: Chronic hepatitis B (CHB) remains a leading cause of hepatocellular carcinoma (HCC) worldwide. Early identification of high-risk individuals could enhance prevention strategies through timely initiation of antiviral therapy. However, current HCC risk prediction models do not simultaneously consider both untreated and treated CHB patients. This study aimed to develop and externally validate a risk score for non-cirrhotic CHB patients, incorporating the non-linear association between HBV DNA levels and HCC risk. **Methods:** A multivariable Cox regression analysis was performed using data from 5,865 treatment-naïve, non-cirrhotic CHB patients with baseline HBV DNA >2,000 IU/mL at Asan Medical Center in Korea. External validation was conducted in an independent cohort of 8,664 patients from 10 centers across Korea, Hong Kong, and Taiwan. **Results:** Over a median follow-up of 8.0 years, 398 patients (6.8%) in the derivation cohort developed HCC. Independent risk factors included male sex, older age, absence of antiviral therapy, lower platelet count, and moderate HBV DNA levels. A distinct parabolic relationship was observed between HBV DNA and HCC risk, with the highest risk at 6.0–7.0 $\log_{10}$ IU/mL (HR 4.99 compared to >8.0 $\log_{10}$ IU/mL; $p < 0.001$). Based on these five predictors, a 15-point risk model—the ASAN ALT-independent HBV-related HCC (ABC) score—was constructed, demonstrating strong discriminatory ability (c-index 0.83). In the external cohort, the ABC score outperformed existing models (PAGE-B, modified PAGE-B, and REACH-B) in both discrimination and calibration, effectively identifying high-risk patients who may benefit most from antiviral treatment. **Conclusion:** The ABC score offers an accurate and practical tool for assessing HCC risk in both untreated and treated CHB patients, reflecting the non-linear effect of viral load. This model supports personalized clinical decision-making regarding antiviral therapy initiation.

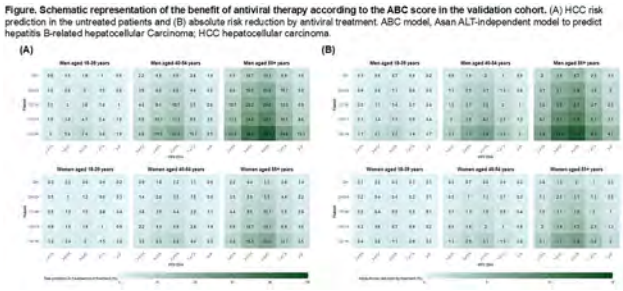

Figure. Schematic representation of the benefit of antiviral therapy according to the ABC score in the validation cohort. (A) HCC risk prediction in the untreated patients and (B) absolute risk reduction by antiviral treatment. ABC model, Asan ALT-independent model to predict hepatitis B-related hepatocellular Carcinoma; HCC hepatocellular carcinoma.

Disclosures: Won-Mook Choi: Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, Roche: Consultant, Gi-Ae Kim: Nothing to Disclose, Jonggi Choi: GILEAD SCIENCE: Grant/Research Support, Gwang Hyeon Choi: Nothing to Disclose, Yun Bin

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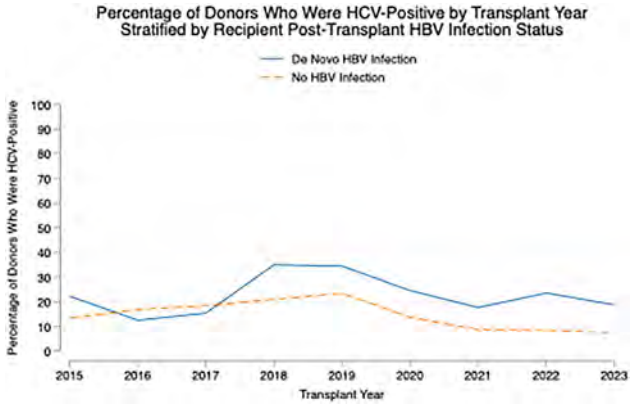
Lee: Eisai: Consultant, Gilead Sciences: Consultant, Roche: Consultant, Chong Kun Dang Pharmaceutical Corporation: Grant/Research Support, Samil Pharmaceutical: Grant/Research Support, Dong Hyunn Sinn: Nothing to Disclose, Nae-Yun Heo: Nothing to Disclose, Sehee Kim: Nothing to Disclose, YOUNG-SUK LIM: Nothing to Disclose

1213 | TRENDS IN DONOR-DERIVED HBV INFECTION IN LIVER TRANSPLANT PATIENTS

Dilara Hatipoglu[1] Emily Blumberg[1] Maarouf Hoteit[1] Ingi Lee[1] Therese Bittermann[2], [1]University of Pennsylvania, [2]Perelman School of Medicine

Background: Unexpected donor-derived hepatitis B virus (HBV) infection in liver transplant recipients is a clinically significant and incompletely understood complication. Identifying risk factors for de novo HBV is important, particularly in an era where maximizing organ utilization is critical to addressing organ shortage. **Methods:** We conducted a retrospective cohort study using United Network for Organ Sharing (UNOS) liver transplant registry data. We included adult ($\geq$ 18 years) liver transplant recipients between 2015 - 2024. To ensure an HBV-naïve population, recipients were excluded if they had HBV diagnosis or positive pre-transplant hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), or nucleic acid testing (NAT). We also excluded recipients missing pre-transplant HBsAg or anti-HBc, and those without HBV follow-up data in the first year. Donors with positive or missing HBV markers were also excluded. The primary outcome was de novo HBV infection, defined as a new positive HBsAg or NAT within one year post-transplant in previously confirmed HBV-negative recipients. Multivariable logistic regression was performed with a priori selected variable based on clinical judgement and literature review. **Results:** A total 29,707 liver transplant recipients met inclusion criteria. We identified 238 (0.8%) cases of de novo HBV infection. Compared to uninfected patients, those with infection were more likely to receive grafts from younger donors (median age 35 vs 39, $p = 0.025$) and donors with a history of IV drug use (34.5% vs 18.8%, $p < 0.001$). In adjusted analysis, donor HCV NAT positivity (OR 1.84, 95% CI 1.24 – 2.73, $p = 0.002$) and HCV Ab +/NAT- status (OR 2.11, 95% CI 1.33 – 3.33, $p = 0.001$) were associated with higher odds of infection (Figure 1). Recipients transplanted after 2021, when universal donor HBV screening was implemented, had lower odds (OR 0.45, 95% CI 0.33 – 0.62, $p < 0.001$). **Conclusion:** We identified 238 cases of de novo HBV infection despite negative pre-transplant testing. Donor HCV exposure was strongly associated with recipient infection. These results suggest that a proportion of post-transplant patients develop donor derived infection despite negative serologies. Possible mechanisms include window period HBV exposure or possible HBV-HCV viral interference. These results support close post-transplant surveillance in increased risk organ recipients and inform risk-benefit discussions regarding HCV-exposed donor organ



Disclosures: Dilara Hatipoglu: Nothing to Disclose, Emily Blumberg: Takeda: Grant/Research Support, Scynexis: Grant/Research Support, Maarouf Hoteit: HepQuant, LLC: Advisor, Cook Medical: Consultant, Ingi Lee: Moderna: Clinical adjudication committee for norovirus vaccine trial, Therese Bittermann: Nothing to Disclose

1214 | INTRAHEPATIC IMMUNOPHENOTYPING OF PARTICIPANTS WITH CHRONIC HEPATITIS B RECEIVING BEPIROVIRSEN IN THE B-FINE STUDY REVEALS DIVERSE CHANGES IN IMMUNOLOGICAL STATUS

Adam Gehring[1] Yanal Ghosheh[1] Andre Boonstra[2] Nadia Alatrakchi[3] Upkar Gill[4] Boris Beudeker[2] Raymond Chung[3] Jordan Feld[1] Harry Janssen[2] Patrick Kennedy[4] Robert De Knegt[2] Leigh Felton[5] Lin-Ming Shen[6] Robert Elston[5] Dickens Theodore[7] Melanie Paff[7] Maria Agostini[8] Johannes Freudenberg[7] Yvonne Teo[7] Sorcha O'Byrne[5] Jenn Singh[7] Jill Walker[8], [1]Toronto Centre for Liver Disease, University Health Network, Toronto, ON, Canada, [2]Erasmus Medical Center, Rotterdam, The Netherlands, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Queen Mary University of London, London, United Kingdom, [5]GSK, Stevenage, UK, [6]GSK, Waltham, MA, USA, [7]GSK, Collegeville, PA, USA, [8]GSK, San Francisco, CA, USA

Background: Bepirovirsen is an unconjugated antisense oligonucleotide under development for chronic hepatitis B virus (HBV) infection. Previous analyses have shown that bepirovirsen can stimulate the immune system; however, no studies to date have examined the

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intrahepatic immune response. In the open-label Phase 2a B-Fine study (NCT04544956), we analyzed longitudinal liver fine needle aspirates (FNA) from participants (pts) with chronic HBV infection treated with bepirovirsen. **Methods:** Pts with chronic HBV infection on stable nucleos(t)ide analogs, with hepatitis B surface antigen (HBsAg) levels >100 IU/mL, received bepirovirsen 300 mg once weekly for 12 weeks (with loading doses on Days 4 and 11), then were followed for 24 weeks (until Week 36). This translational study focused primarily on assessing the effect of bepirovirsen on immunological and disease biomarkers in the liver and periphery, which was evaluated as an exploratory endpoint. RNA sequencing was performed on single cells (scRNA-seq) recovered from the liver by FNA (collected at baseline and up to 4 additional timepoints). Differential expression (DE) analysis was used to compare FNA from baseline and (a) timepoints proximal to the HBsAg nadir or (b) timepoints coinciding with HBsAg decline (i.e. HBsAg slope) to investigate putative immune drivers of HBsAg decline. The primary endpoint evaluated treatment efficacy, i.e. serum HBsAg loss (HBsAg concentration below the lower limit of quantification [LLOQ; 0.05 IU/mL]) at any time up to and including Week 12. **Results:** Overall, 11 pts completed the study. All major immune lineages (T, B, natural killer [NK], macrophages, monocytes, dendritic cells) were identified by scRNA-seq of liver FNA. Subclustering of major lineages included 12 T cell, 5 macrophage and 3 NK cell subclusters. DE analysis found pt-specific differences in immune gene expression between baseline and HBsAg nadir, and baseline and HBsAg slope, irrespective of response. Changes in the $CD56^{dim}$ and tissue-resident NK cell clusters indicated altered cell signaling (e.g. *FOS, CD247*) in some pts, although the impact on NK cell function was unclear. In total, 3 pts achieved the primary endpoint (including 1 sustained responder with HBsAg and HBV DNA 10 IU/mL and $1.5–<3\log_{10}$ IU/mL were obtained by 2 and 3 pts, respectively. Alanine aminotransferase increases >3 times the upper limit of normal were observed in 2 of 3 responders; these increases occurred in conjunction with HBsAg decline. **Conclusion:** Variable clinical, virological and immunological responses to bepirovirsen treatment were observed among pts with chronic HBV infection in this study. Overall, repeat FNA sampling captured activation of the immune compartment in the liver, regardless of response. Three pts achieved HBsAg loss following bepirovirsen treatment. Funding: GSK (212602).

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1215 | INTRAHEPATIC AND PERIPHERAL IMMUNOPHENOTYPING OF PARTICIPANTS WITH CHRONIC HEPATITIS B RECEIVING BEPIROVIRSEN IN THE B-FINE STUDY STRONGLY SUGGESTS THAT BEPIROVIRSEN MAY TRIGGER A HUMORAL RESPONSE

Andre Boonstra[1] Adam Gehring[2] Yanal Ghosheh[2] Nadia Alatrakchi[3] Upkar Gill[4] Boris Beudeker[1] Raymond Chung[3] Jordan Feld[2] Harry Janssen[1] Patrick Kennedy[4] Robert de Knegt[1] Leigh Felton[5] Lin-Ming Shen[6] Robert Elston[5] Dickens Theodore[7] Melanie Paff[7] Naveen Prasad[5] Johannes Freudenberg[7] Yvonne Teo[7] Sorcha O'Byrne[5] Jenn Singh[7] Jill Walker[8], [1]Erasmus Medical Center, Rotterdam, The Netherlands, [2]Toronto Centre for Liver Disease, University Health Network, Toronto, ON, Canada, [3]Massachusetts General Hospital, Boston, MA, USA, [4]Queen Mary University of London, London, United Kingdom, [5]GSK, Stevenage, UK, [6]GSK, Waltham, MA, USA, [7]GSK, Collegeville, PA, USA, [8]GSK, San Francisco, CA, USA

Background: Recent evidence suggests a role for B cells in the immune response to hepatitis B virus (HBV) infection and bepirovirsen, an unconjugated antisense oligonucleotide. Here, we investigated how B cell and humoral responses are impacted by bepirovirsen, currently under development for chronic HBV infection. In the open-label Phase 2a B-Fine study (NCT04544956), we analyzed matched liver fine needle aspirates (FNA) and peripheral blood from participants (pts) with chronic hepatitis B infection treated with bepirovirsen. **Methods:** Pts with chronic HBV infection on stable nucleos(t)ide analogs, with hepatitis B surface antigen (HBsAg) levels >100 IU/mL, received bepirovirsen 300 mg once weekly for 12 weeks (with loading doses on Days 4 and 11), then were followed for 24 weeks (until Week 36). This translational study focused primarily on assessing the effect of bepirovirsen on immunological and disease biomarkers in the liver and periphery, which was evaluated as an exploratory endpoint. Biomarker analyses included RNA sequencing (RNA-seq) of whole blood and single cells recovered from the liver by FNA (collected at baseline and up to 4 additional timepoints thereafter), serum proteomics and flow cytometry on peripheral blood mononuclear cells (PBMCs). Differential expression analysis was used to (a) identify transcriptomic and proteomic changes in gene or protein expression in the periphery and (b) investigate putative immune mechanisms of HBsAg decline in the liver. The primary endpoint evaluated treatment efficacy, i.e. serum HBsAg loss (HBsAg concentration below the lower limit of quantification [LLOQ; 0.05 IU/mL]) at any time up to and including Week 12. **Results:** Overall, 11 pts completed the study. Single cell RNA-seq identified all major immune lineages, including 4 B cell and 3 plasma lineage subclusters; differential expression analysis suggested B cell activation in the liver, irrespective of response. Differential analysis of whole blood RNA-seq indicated immune activation (e.g. *CD80, CXCR6, MS4A1*) and immunoglobulin transcription (e.g. *IGHM*, *IGLC3*), consistent with a humoral response. Differential analysis of serum proteomics also indicated B cell activation (e.g. *CD22*, *FCRL2*). Flow cytometry of PBMCs showed an increase in frequency of $Ki67^+$ B cells, but no overall expansion in the $CD19^+$ compartment. Three pts achieved the primary endpoint, including 1 sustained responder with HBsAg and HBV DNA 3 times the upper limit of normal were observed in 2 of the 3 responders; these increases occurred in conjunction with HBsAg decline. **Conclusion:** The proteomic, transcriptomic (liver and peripheral) and flow cytometry data obtained from the B-Fine study strongly suggest that bepirovirsen triggers a humoral immune response in treated pts. Three pts achieved HBsAg loss following bepirovirsen treatment. Funding: GSK (212602)

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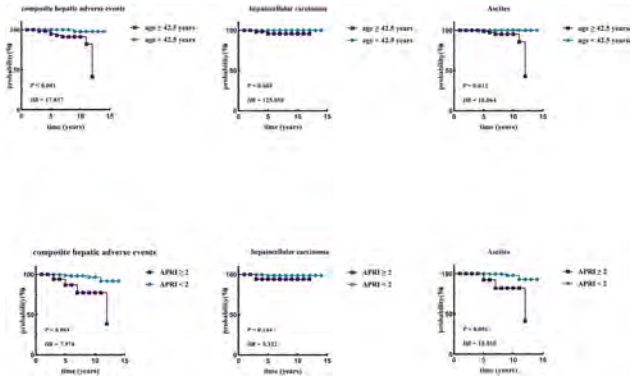
1216 | A STUDY ON THE LONG-TERM CLINICAL OUTCOMES OF HBSAG DISAPPEARANCE IN CHB PATIENTS TREATED WITH INTERFERON

Wen Deng[1] Minghui Li[1] Yao Xie[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: To investigate the risk and influencing factors of long-term liver clinical outcomes in patients with hepatitis B surface antigen (HBsAg) conversion to negative after treatment with Pegylated interferon α (Peg-IFN α). **Methods:** A retrospective analysis was conducted on patients who achieved HBsAg disappearance and discontinued Peg-IFN α treatment at Beijing Ditan Hospital from October 2008 to December 2023. The baseline time was considered as the point of HBsAg conversion to negative and medication discontinuation, with the endpoint time being the first occurrence of liver adverse events (hepatocellular carcinoma (HCC) or ascites) or the last follow-up. The primary evaluation indicators included the incidence and influencing factors of long-term liver adverse events. The secondary evaluation indicators encompassed liver fibrosis, cirrhosis, and improvements in liver function indicators. **Results:** A total of 456 eligible patients were included for analysis. During the follow-up period of 70 (11-173) months, the incidence of liver adverse events, HCC, and ascites were 2.30%, 1.76%, and 0.55%, respectively. Advanced age and cirrhosis were significant influencing factors for liver adverse events after HBsAg disappearance and discontinuation (*HR* = 1.075, *95%CI* 1.028-1.125, *P* = 0.002; *HR* = 41.393, *95%CI* 4.773-358.958, *P* < 0.001). Compared with the time of HBsAg disappearance and discontinuation, the Aspartate Aminotransferase to Platelet Ratio Index (APRI) score significantly improved at the follow-up endpoint [0.53 (0.37, 0.86) *vs.* 0.25 (0.19, 0.35), *Z* = -15.765, *P* < 0.001]. Additionally, the percentage of patients with cirrhosis significantly decreased (5.62% *vs.* 0.86%, *P* < 0.001). **Conclusion:** Patients with HBsAg disappearance and discontinuation of medication have a lower risk of developing liver adverse events, with cirrhosis and advanced age identified as significant risk factors for these adverse events.



Disclosures: Wen Deng: Nothing to Disclose, Minghui Li: Nothing to Disclose, Yao Xie: Nothing to Disclose

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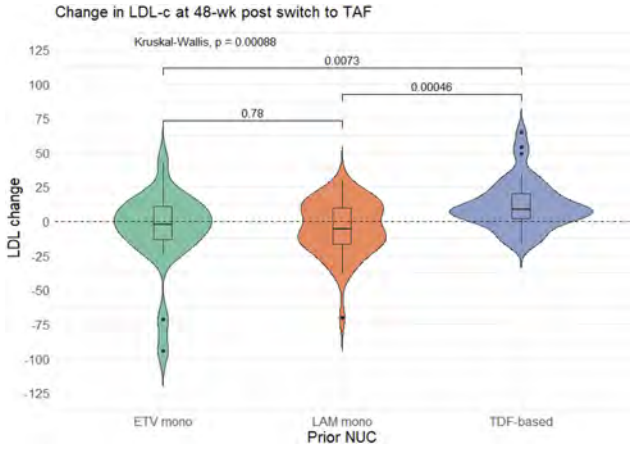
1217 | ★ EFFECT OF SWITCHING FROM PRIOR NUCLEOS(T)IDE ANALOGUE(S) TO TENOFOVIR ALAFENAMIDE ON LIPID PROFILE AND CARDIOVASCULAR RISK IN PATIENTS WITH CHRONIC HEPATITIS B

Witchayaporn Praguylertluck[1] Pimsiri Sripongpun[1] Apichat Kaewdech[1] Naichaya Chamroonkul[1], [1]Prince of Songkla University

Background: Tenofovir alafenamide (TAF) is recommended as the 1st line treatment of chronic hepatitis B (CHB). However, increased LDL-c in those who were switched from Tenofovir disoproxil fumarate (TDF) to TAF was observed. Whereas data regarding switching from other antiviral agents to TAF are limited. We investigated how switching to TAF affected lipid and cardiovascular outcomes in CHB patients. **Methods:** We conducted a prospective observational study including CHB patients who had to switch from their prior NUC to TAF according to the Thai national reimbursement policy in late 2022. All enrolled patients had lipid tests and transient elastography (TE) done at 0 and 48- week post-switch to TAF. Demographic data, prior NUC, liver biochemistry, controlled attenuated parameter (CAP) and liver stiffness (elastic modulus; E) data measured by TE were collected. The changes in lipid, Thai cardiovascular (CV) risk score, and TE results between 0 and 48-week were compared. **Results:** A total of 110 patients who were switched to TAF and completed 48-week follow-up were analyzed. The prior NUCs were as follows: 47 Lamivudine (LAM), 2 Entecavir (ETV), and 41 TDF-based. Baseline characteristics were similar between the three groups except for underlying disease of hypertension was more frequent and baseline total cholesterol levels were lower in the TDF-based group. At 48-week post-switch, the median LDL-c changes were -2.45, -5.9 and +8.8 mg/dL ($p < 0.001$), total cholesterol changes were -4.5, -4 and +17 mg/dL ($p < 0.001$), and weight changes were 0, 0, and +1 kg ($p = 0.010$) in the ETV, LAM, and TDF-based group, respectively. Whereas the changes in hepatic steatosis (measured by CAP), and liver stiffness (measured by E) as well as Thai CV risk score were not significantly different. No cardiovascular events occurred during follow-up. Results from the multivariable logistic regression analysis confirmed that TDF-based regimen at baseline, prior to the switch to TAF, was significantly associated with worsening LDL-c (defined by increase of LDL-c level or increase dose/intensity of lipid lowering agent) with an adjusted odds ratio of 3.84 (95%CI 1.55-10.22, $p = 0.005$), after adjusted with change in BMI, age, sex, and baseline coexisting hypertension. **Conclusion:** Significant increase in LDL-c and total cholesterol after switching to TAF were observed only in patients with prior TDF, but not in those with prior ETV or LAM. Careful monitoring of lipids after the switch may not universally needed. Data regarding long-term cardiovascular outcomes are warrant.



Disclosures: Witchayaporn Praguylertluck: Nothing to Disclose, Pimsiri Sripongpun: Nothing to Disclose, Apichat Kaewdech: Nothing to Disclose, Naichaya Chamroonkul: Nothing to Disclose

1218 | ASSESSMENT OF HCC RISK STRATIFICATION AND THE ROLE OF PRES1/2 DELETIONS DURING NUCLEOS(T)IDE ANALOGUE THERAPY IN CHRONIC HEPATITIS B

KOTARO DOI[1] Jun Inoue[2] Masashi Ninomiya[2] Akitoshi Sano[3] Mio Tsuruoka[2] Kosuke Sato[2] Kieshi Ouchi[2] KENGO WATANABE[2] Atsushi Masamune[2], [1]Division of Gastroenterology, Tohoku University Graduate School of Medicine, [2]Tohoku University Hospital, [3]Mayo Clinic, Rochester

Background: Hepatocellular carcinoma (HCC) remains a major concern in chronic hepatitis B (CHB) patients despite nucleos(t)ide analogue (NA) treatment. We previously reported that abnormal ALT levels (≥ 31 U/L) after 1 year of NA treatment were associated with HCC development. We also developed a FAL-1 score, based on the FIB-4 index and ALT at 1 year of NA treatment, to estimate HCC risk. However, the cause of persistent ALT abnormalities during NA treatment despite undetectable serum HBV DNA is unclear. Previous studies have suggested that deletions in the preS1/2 region of the HBV genome are associated with progression of liver fibrosis and HCC development, possibly through mitochondrial dysfunction and ER stress. The aim of this study was to validate the FAL-1 score compared to established HCC risk scores and to explore the association between preS1/2 deletion and ALT abnormalities during NA treatment. **Methods:** A cohort of 725 CHB patients from 23 centers was analyzed to compare the FAL-1 score with established

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HCC risk scores (PAGE-B, mPAGE-B, APA-B, and aMAP). Additionally, 38 patients who received ETV, TDF, or TAF as first-line therapy and had preserved serum samples collected before NA treatment were evaluated. Total DNA was extracted from the samples and subjected to nested PCR targeting the preS1/2 region to detect deletions. Patients with deletion signals ≥40% of the total amplified signal were classified as the high-del group; others were classified as the low-del group. **Results:** In the 725-patient cohort, the 5-year HCC incidence was 11.3%, 7.2%, 11.9%, 10.1%, and 18.3% in the high-risk groups for PAGE-B, mPAGE-B, APA-B, aMAP, and FAL-1, and 1.0%, 0.8%, 5.0%, 2.5%, and 0.5% in the low-risk groups for each score. At 10 years, the HCC incidence was 22.1%, 15.3%, 35.4%, 15.9%, and 22.2%, in the high-risk groups, and 1.0%, 2.5%, 6.4%, 2.5%, and 0.5% in the low-risk groups. The FAL-1 low-risk group (n = 259, 35.9%) showed a low incidence of HCC over 10 years, whereas the high-risk group (n = 113, 15.7%) showed a relatively early occurrence of HCC within 5 years. In the preS1/2 deletion analysis, the preS1/2 region was successfully amplified in 37/38 patients (97.4%), and deletions were found in 18/37 (48.6%) patients. The ALT level after 1 year of NA treatment was significantly higher in the high-del group than in the low-del group (35 vs. 26 U/L, P = 0.021). The cumulative incidence of HCC was also significantly higher in the high-del group than in the low-del group (25% vs. 7% at 2 years, P = 0.027). The proportion of patients with a high FAL-1 score was significantly higher in the high-del group (P = 0.045). **Conclusion:** The FAL-1 score effectively identified CHB patients with a low long-term risk of HCC. PreS1/2 deletions are associated with persistent ALT abnormalities during NA treatment and elevated FAL-1 scores. Persistent ALT abnormalities despite virological suppression may reflect underlying viral factors and contribute to hepatocarcinogenesis.

Disclosures: KOTARO DOI: Nothing to Disclose, Jun Inoue: Nothing to Disclose, Masashi Ninomiya: Nothing to Disclose, Akitoshi Sano: Nothing to Disclose, Mio Tsuruoka: Nothing to Disclose, Kosuke Sato: Nothing to Disclose, Kieshi Ouchi: Nothing to Disclose, KENGO WATANABE: Nothing to Disclose, Atsushi Masamune: Nothing to Disclose

1219 | CHARACTERIZATION OF THE FUNCTION AND PHENOTYPE OF NK CELLS IN PATIENTS WITH CHRONIC HEPATITIS B WHO ACHIEVED FUNCTIONAL CURE

Yuki Nakaya[1] Goki Suda[2] Kazumi Yamasaki[3] Kouichi Miura[4] Norie Yamada[5] Hirayuki Enomoto[6] Jun Inoue[7] Takashi Honda[8] Yosuke Osawa[9] Satoru Joshita[10] Daichi Onomura[1] Yuji Hoshi[1] Chunfeng Li[11] Evguenia Maiorova[11] Hongmei Mo[11] Kazumoto Murata[1], [1]Division of Virology, Department of Infection and Immunity, Jichi Medical University, [2]Department of Gastroenterology and Hepatology, Graduate School of Medicine, Hokkaido University, [3]Clinical Research Center, NHO Nagasaki Medical Center, [4]Division of Gastroenterology, Department of Medicine, Jichi Medical University, [5]Department of Internal Medicine, Center of Liver Diseases, Seizankai Kiyokawa Hospital, [6]Department of Gastroenterology, Hyogo Medical University, [7]Division of Gastroenterology, Tohoku University Graduate School of Medicine, [8]Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, [9]Department of Gastroenterology, International University of Health and Welfare Hospital, [10]Department of Medicine, Yodakubo Hospital, [11]Gilead Sciences Inc

Background: Hepatitis B virus (HBV) is a global health concern as the causes of cirrhosis and liver cancer. HBV semi-permanently exists in the hepatocytes by generating covalently closed circular DNA (cccDNA) in the nuclei, hence the complete cure is currently impossible. The goal of therapies for chronic hepatitis B (CHB) has recently shifted toward the achievement of a functional cure (FC), which is defined as a dual state of sustained undetectable serum HBV DNA and hepatitis B surface antigen (HBsAg). Although it is reported that innate immunity may play a major role in anti-HBV effects, its detailed features in patients who achieved FC have not been clarified. Here, we characterized natural killer (NK) cells, a major component of innate immunity, in patients with FC. **Methods:** We studied NK cell receptor expression, cytotoxic activity, and IFN-γ production in peripheral blood mononuclear cells (PBMCs) from 41 patients who lost HBsAg within 1 year before this study (32 with FC and 9 with HBV DNA), 42 CHB patients (13 treatment-naïve and 29 with nucleos(t)ide analogs (NUC)), 17 inactive carriers (IC), and 15 healthy volunteers (HV). PBMCs were treated with or without interleukin (IL)-12 and IL-18 for 18 h, following stimulation with K562 cells with monensin for 5 h. NK cells defined as a subset of $CD3^-$ $CD56^+$ in the lymphocytes were analyzed by a multicolor fluorescence-activated cell sorting (FACS) LSRFortessa X-20. Median values of each group were compared, and statistical differences were determined by Mann-Whiteney U test. **Results:** The proportion of NK cells in PBMCs were significantly lower in CHB patients and IC than HV as well as FC (Figure 1A). Phenotypically, NK cells in patients with FC are related to lower expression of PD-1, an immune suppressive mediator, and higher expression of activation markers such as CD69, NKG2c, and NKp46 when compared with those of CHB patients, especially in the population of FcεRIγ-positive NK cells (conventional NK cells). The

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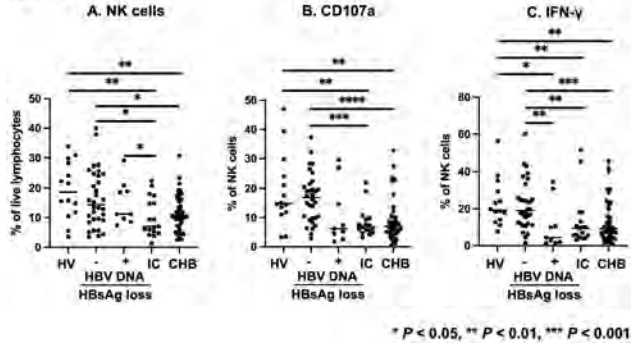
frequency of functionally active NK cells characterized by expression of CD107a and IFN-γ in patients with FC was comparable to HV, and statistically higher than those of CHB patients and IC (Figure 1B, 1C). Of note, these trends were observed in patients with FC, but not in patients who lost HBsAg but had detectable HBV DNA. Interestingly, the cytotoxic activity and IFN-γ production in NK cells in CHB patients under treatment with NUC were not affected by the presence or absence of serum HBV DNA. In addition, NK cells were phenotypically and functionally similar between CHB patients and IC. **Conclusion:** NK cells are phenotypically and functionally impaired in CHB patients and IC but recovered only when CHB patients achieved both undetectable serum HBV DNA and HBsAg, suggesting that some of the products from cccDNA, other than serum HBsAg or HBV DNA, may affect the function of NK cells.

Figure 1



Disclosures: Yuki Nakaya: Nothing to Disclose, Goki Suda: Nothing to Disclose, Kazumi Yamasaki: Nothing to Disclose, Kouichi Miura: Nothing to Disclose, Norie Yamada: Nothing to Disclose, Hirayuki Enomoto: Nothing to Disclose, Jun Inoue: Nothing to Disclose, Takashi Honda: Nothing to Disclose, Yosuke Osawa: Nothing to Disclose, Satoru Joshita: Nothing to Disclose, Daichi Onomura: Nothing to Disclose, Yuji Hoshi: Nothing to Disclose, Chunfeng Li: Nothing to Disclose, Evguenia Maiorova: Nothing to Disclose, Hongmei Mo: Nothing to Disclose, Kazumoto Murata: Nothing to Disclose

1220 | LONG-TERM HCC RISK AFTER NA WITHDRAWAL IN PATIENTS WITH CHRONIC HEPATITIS B – RESULTS: OF A GLOBAL COHORT STUDY (RETRACT-B)

Edo Dongelmans[1] Grishma Hirode[2] Florian van Bömmel[3] Rachel Wen-Juei Jeng[4] Rong-Nan Chien[5] Chien Hung Chen[6] Mai Kilany[2] Tung-Hung Su[7] Jia-Horng Kao[7] Wai-Kay Seto[8] Lilian Yan Liang[9] Dag Henrik Reikvam[10] Marte Holmberg[11] Arno Furquim d'Almeida[12] Margarita Papatheodoridi[13] Benjamin Maasoumy[14] Bettina Hansen[1] Anna Pocurull[15] Norah Terrault[16] Marc Ghany[17] Asgeir Johannessen[11] Anna Lok[18] Thomas Vanwolleghem[12] Sabela Lens[15] Markus Cornberg[14] Man-Fung Yuen[8] Grace Lai-Hung Wong[9] Milan Sonneveld[1] George Papatheodoridis[13] Thomas Berg[3] Yao-Chun Hsu[19] Jordan Feld[2] Harry Janssen[1], [1]Erasmus University Medical Center, [2]Toronto General Hospital/University of Toronto, [3]Leipzig University Medical Center, [4]Chang Gung Memorial Hospital, Linkou Medical Center, [5]Chang Gung Memorial Hospital Linkou Medical Center, [6]Kaohsiung Chang Gung Memorial Hospital, [7]National Taiwan University Hospital, [8]The University of Hong Kong, [9]The Chinese University of Hong Kong, [10]Oslo University Hospital, [11]University of Oslo, [12]Antwerp University Hospital, [13]Medical School of National and Kapodistrian University of Athens, [14]Hannover Medical School, [15]Hospital Clinic Barcelona, IDIBAPS and CIBEREHD, [16]Keck Medicine of University of Southern California, [17]NIH/NIDDK, [18]University of Michigan Medical Center, [19]E-Da Hospital/I-Shou University

Background: Continuous nucleos(t)ide analogue (NA) therapy is proven to reduce HCC risk in patients with chronic hepatitis B (CHB). However, the effect of stopping NA therapy on subsequent HCC risk is unknown. Therefore, our aim was to assess the long-term HCC risk after NA cessation in a large cohort. **Methods:** Data from patients enrolled in the RETRACT-B cohort study, a large global cohort including long-term follow up after NA withdrawal, were used. Patients with CHB were included if virally suppressed on NA-therapy, HBeAg negative and ALT < 5xULN at end of therapy (EOT). Patients with a co-infection, HCC diagnosed in the past or within 6 months after EOT and/or prior IFN-therapy within 1 year before NA cessation were excluded. The primary end-point was the overall cumulative HCC incidence after NA withdrawal, including HCC cases after resuming NA. Next, we assessed predictors for HCC using Cox regression, and assessed the performance of the PAGE-B score (age, sex and platelets < 1 year before EOT) for risk stratification (low/intermediate/high-risk: ≤9/10-17/≥18). **Results:** In total 2,027 patients were included. Mean (SD) age at EOT was 52 (±11) years, 72% were male, 81% was Asian,15% White, 4% Black, mean HBsAg at EOT was 2.7 (±0.8) log10 IU/mL, and 10% had a history of cirrhosis. Mean PAGE-B score at EOT (n = 1,279) was 12 (±5), low/intermediate/high-risk: 25%/54%/21%. In total, 41 patients (17 with a history of cirrhosis) developed HCC. The 10 year cumulative HCC incidence was 3.8%, being 10.7% in patients with a history of cirrhosis at EOT compared to 2.7% in patients without cirrhosis, p < 0.001. In patients with HCC, 85% was male, median age was 59 [53-67] years at EOT and

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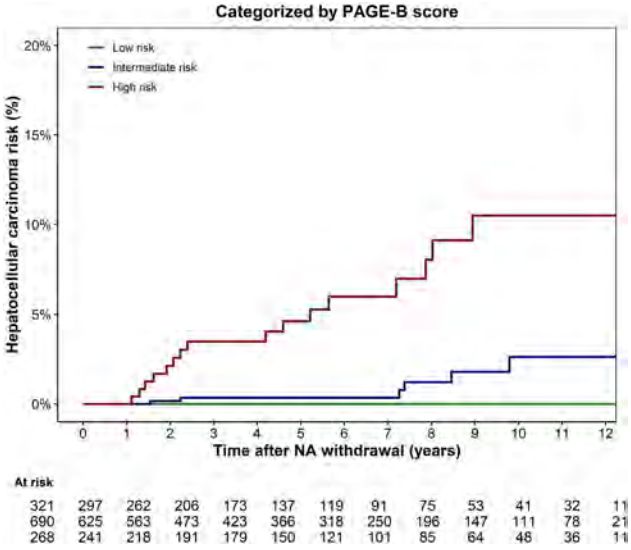
median time until HCC diagnosis was 40 [17-86] months. Among HCC cases without cirrhosis at EOT (n = 24), 16 (67%) patients had known metabolic risk factors or steatotic liver disease at NA cessation. In multi-variate Cox Regression model, older age (aHR 1.08,p < 0.001), male sex (aHR 4.46,p = 0.019), lower platelets (aHR 0.99,p = 0.034) and history of cirrhosis (aHR 4.28,p = 0.001) were associated with increased HCC risks. Ethnicity, type of NA and HBsAg at EOT were not associated with HCC risk in univariate models (all p > 0.05). PAGE-B was highly effective in risk stratification, with a 10 year HCC risk of 0%/2.6%/10.5% for a low/intermediate/high-risk score (p < 0.001). **Conclusion:** Patients with CHB remain at risk of HCC after NA withdrawal (4% at 10yrs). Patients with a high PAGE-B score at EOT have the highest HCC risk (11% at 10yrs), while those with a low PAGE-B score had negligible HCC risks, and may not need HCC surveillance.



Disclosures: Edo Dongelmans: Roche: Speaking and Teaching, Grishma Hirode: Nothing to Disclose, Florian van Bömmel: Nothing to Disclose, Rachel Wen-Juei Jeng: GSK: Advisor, Gilead: Advisor, Rong-Nan Chien: Nothing to Disclose, Chien Hung Chen: Nothing to Disclose, Mai Kilany: Nothing to Disclose, Tung-Hung Su: Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Merck Sharp and Dohme: Speaking and Teaching, Roche: Speaking and Teaching, Sysmex: Speaking and Teaching, Eisai: Speaking and Teaching, Jia-Horng Kao: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose, Lilian Yan Liang: Nothing to Disclose, Dag Henrik Reikvam: Gilead: Independent Contractor, Marte Holmberg: Nothing to Disclose, Arno Furquim d'Almeida: Nothing to Disclose, Margarita Papatheodoridi: Nothing to Disclose, Benjamin Maasoumy: Nothing to Disclose, Bettina Hansen: Nothing to Disclose, Anna Pocurull: Nothing to Disclose, Norah Terrault: Nothing to Disclose, Marc Ghany: Vir Bio: Grant is to NIDDK, NIH not to Investigator, Asgeir Johannessen: Nothing to Disclose, Anna Lok: Abbott Diagnostics: Consultant, Chroma: Consultant, Grifols: Consultant, GlaxoSmithKline: Consultant, Novo Nordisk: Advisor, Pfizer: Consultant, Precision Biosciences: Consultant, Roche Diagnostics: Consultant, Virion: Consultant, Zenasbio: Consultant, Brii Biosciences: Advisor, Moderna: Advisor, Pioneering: Advisor, Thomas Vanwolleghem: Johnson and Johnson: Advisor, Johnson and Johnson: Advisor, Johnson and Johnson: Advisor, GSK: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Fujirebio: Grant/Research Support, Fujirebio: Grant/Research Support, Fujirebio: Grant/Research Support, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Abbvie: Speaking and Teaching, Abbvie: Speaking and Teaching, Johnson and Johnson: Advisor, Johnson and Johnson: Advisor, Johnson and Johnson: Advisor, GSK: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Fujirebio: Grant/Research Support, Fujirebio: Grant/Research Support, Fujirebio: Grant/Research Support, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Abbvie: Speaking and Teaching, Abbvie: Speaking and Teaching, Johnson and Johnson: Advisor, Johnson and Johnson: Advisor, Johnson and Johnson: Advisor, GSK: Grant/Research Support, GSK: Grant/Research Support, GSK: Grant/Research Support, Fujirebio: Grant/Research Support, Fujirebio: Grant/Research Support, Fujirebio: Grant/Research Support, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Abbvie: Speaking and Teaching, Abbvie: Speaking and Teaching, Sabela Lens: Nothing to Disclose, Markus Cornberg: Nothing to Disclose, Man-Fung Yuen: Nothing to Disclose, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Milan Sonneveld: Roche: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Consultant, ViR: Advisor, GSK: Grant/Research Support, Fujirebio: Grant/Research Support, George Papatheodoridis: Abbvie: Advisor, Abbvie: Grant/Research Support, Abbvie: Speaking and Teaching, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Genesis: Advisor, Genesis: Speaking and

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1221 | NEW SUBMISSIONA LONG-ACTING AQUEOUS NANOSUSPENSION OF VONAFEXOR PRODRUG ATTENUATES LIVER FIBROSIS DEVELOPMENT IN CCL_4 MOUSE FIBROSIS MODEL

Natalia Osna[1] Asrafi Sultana[1] Anup Pathania[1] Weimin Wang[1] Grace Bybee[1] Haritha Chava[1] Deanna Mosley[1] Christopher Bauer[1] Todd Wyatt[1] Larisa Poluektova[1] Benson Edagwa[1], [1]University of Nebraska Medical Center

Background: Chronic hepatitis B (CHB) leads to the development of end-stage liver disease. However, therapeutic targets are not well-characterized. A synthetic non-steroid, non-bile acid farnesoid X receptor agonist, Vonafexor (Von) is a promising candidate for liver fibrosis prevention. However, its short half-life requires daily administration. To address this limitation and enhance drug delivery into the liver, we modified Von into a lipophilic prodrug and then nanoformulated it into an aqueous nanosuspension stabilized by surfactants presented in other parenteral products (NM2Von). The prodrug formulation was designed to improve the therapeutic index and half-life of Von through slow nanoparticle dissolution, prodrug release, and hydrolysis mechanisms in addition to sustaining therapeutic drug levels in the liver. **Methods:** In vivo experiments were performed on HBV-replicating transgenic mice injected with carbon tetrachloride (CCl_4), 1 mg/g of body weight twice a week for 3 months. Mice were also administered intramuscular injections of 200 mg/kg NM2Von at weeks 1, 5, and 10, and then euthanized 24h after the last CCl_4 injection to collect blood and liver tissues. The drug efficacy was evaluated by pro-fibrotic genes (αSMA, *TIMP, Col1aA1,* $TGF\beta$) expression, immunohistology, and Sirius Red staining in liver tissue. The effectiveness of a long-acting formulation was also evaluated in vitro on hepatocytes, macrophages, and hepatic stellate cells (HSC, LX-2 cells). LX-2 cells were preactivated with TGFβ and then exposed to NM2Von to measure pro-fibrotic gene activation. **Results:** In vitro, NM2Von significantly attenuated pro-fibrotic gene activation in HSC. Monthly in vivo administration of NM2Von reduced liver fibrosis development in livers from HBV-replicating mice, as demonstrated by decreased activation of pro-fibrotic markers and collagen deposition in the liver. Additionally, while exposure to CCL4 increased PKC activity in liver tissue to induce TGFβ, NM2Von efficiently reversed it in male and female mice. **Conclusion:** Administered monthly, NM2Von reduced liver fibrosis development, presumably due to decreased activation of HSC. This indicates its potential efficacy in preventing/attenuating liver fibrosis, a frequent outcome of HBV infection. These promising preclinical data support the potential clinical

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translation of this novel long-acting NM2Von formulation.

Disclosures: Natalia Osna: Nothing to Disclose, Asrafi Sultana: Nothing to Disclose, Anup Pathania: Nothing to Disclose, Weimin Wang: Nothing to Disclose, Grace Bybee: Nothing to Disclose, Haritha Chava: Nothing to Disclose, Deanna Mosley: Nothing to Disclose, Christopher Bauer: Nothing to Disclose, Todd Wyatt: Nothing to Disclose, Larisa Poluektova: Nothing to Disclose, Benson Edagwa: Nothing to Disclose

1222 | LOW RISK OF FIBROSIS PROGRESSION DURING THE IMMUNE TOLERANT PHASE IN CHRONIC HEPATITIS B PATIENTS

Lisa van Velsen[1] Mai Kilany[2] Norah Terrault[3] Terry Cheuk-Fung Yip[4] Karen Ho[5] Gabriele Ricco[6] Sabela Lens[7] Marc Ghany[8] Elena Vargas-Accarino[9] Stéphanie Narguet[10] Bettina Hansen[11] Tarik Asselah[10] Maria Buti[12] Yao-Chun Hsu[13] Xavier Forns[7] Maurizia Brunetto[14] Wai-Kay Seto[5] Man-Fung Yuen[5] Grace Lai-Hung Wong[4] Jordan Feld[2] Milan Sonneveld[1] Harry Janssen[1], [1]Erasmus University Medical Center, [2]Toronto General Hospital, [3]University of Southern California, [4]The Chinese University of Hong Kong, [5]The University of Hong Kong, [6]University Hospital of Pisa, [7]Hospital Clinic Barcelona, [8]NIH/NIDDK, [9]Hospital Universitari Vall d'Hebron, [10]Hôpital Beaujon, [11]Erasmus MC Rotterdam, [12]Hospital Valle Hebron, [13]I-Shou University, [14]University of Pisa

Background: Immune tolerant (IT) chronic hepatitis B patients (CHB) are considered to have a high viral load, and minimal inflammation and fibrosis. However, it remains unclear whether these patients continue to have minimal fibrosis over time. Therefore, we studied the risk of fibrosis progression in IT patients with CHB. **Methods:** This is a multicenter international cohort study containing data from a large cohort of mono-infected CHB patients from 12 sites in North America, Europe and Asia from the RADICAL-consortium. Baseline refers to the first clinic visit at the investigational site. Patients were strictly defined as IT if they persistently had 1) HBeAg-positivity, 2) ALT $\leq$40 U/L, 3) HBV DNA $\geq$5 logIU/ml and 4) METAVIR F0-1 during the first year after baseline (based on liver stiffness measurement [LSM] $<$8 kPa or biopsy). Fibrosis progression was defined as an increase to F2-4 in 2 consecutive fibrosis measurements or the last measurement based on LSM or biopsy. Cumulative incidences were obtained through Kaplan Meier method, censored for start of antiviral therapy (AVT). A sensitivity analysis was performed restricted to fibrosis progression during the IT phase (also censored for transition out of the IT phase which was defined as: HBeAg loss, ALT $>$40 U/L or HBV DNA $<$5 log IU/ml). Predictive factors were obtained through univariable Cox regression. **Results:** In total, 416 IT patients were included with a median age of 31 (IQR 24-40) years, 34% were male, 96% had an Asian ethnicity and 42% had a metabolic comorbidity. Median ALT and HBV DNA at baseline were 26 (20-30) U/L and 8.3 (8.0-8.7) log IU/mL. In total, patients were followed for a median of 131 (89-187) months, during which 61% patients started on AVT after a median of 57 (29-97) months. The median time to last fibrosis measurement was 70 (33-122) months. Overall, 11 patients progressed to F2-4 during follow-up. The cumulative 3-, 5-, 7- and 10-year incidences of fibrosis progression were 0.4%, 1.4%, 3.2% and 4.2%. Fibrosis progression was more likely in patients with a metabolic comorbidity (HR: 4.13, $p=0.036$) or an age $>$30 (HR: 9.60, $p=0.031$) years at baseline. Of the 11 patients with fibrosis progression prior to start of AVT, 7 patients progressed after transitioning out of the IT phase, and 4 patients progressed to F2-4 while persistently in the IT phase. The cumulative 3-, 5-, and 7-year incidences of fibrosis progression during the IT phase were 0.3%, 1.9% and 2.9%. One patient developed hepatocellular carcinoma (HCC). The cumulative 10-year incidence of HCC was 0.3%. **Conclusion:** IT patients exhibit a 4.2% risk of fibrosis progression and a 0.3% risk of HCC after 10 years of follow-up. The majority of fibrosis progression (64%) occurred after transitioning out of the IT phase. Thus, fibrosis progression and HCC are uncommon in patients who remain to have a strictly defined IT phenotype.

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1223 | INVERTED U-SHAPED ASSOCIATION BETWEEN HEPATITIS B CORE-RELATED ANTIGEN AND HEPATOCELLULAR CARCINOMA INCIDENCE IN PATIENTS WITH CHRONIC HEPATITIS B

Ji Eun Han[1] Yoon Je Cho[1] Hyelynn Jeon[2] Hye Young Chang[3] Hyo Jung Cho[1] jaeyoun cheong[1] Hyun Woong Lee[3] Soon Sun Kim[1] Min Ji Son[1], [1]Ajou University School of Medicine, [2]Ajou University Medical Center, [3]Yonsei University College of Medicine, Gangnam Severance Hospital

Background: Despite advancements in antiviral therapy, chronic hepatitis B (CHB) remains a major global cause of hepatocellular carcinoma (HCC). Persistent high viral load drives disease progression, highlighting the need for a sensitive biomarker to assess viral activity. While antiviral therapy suppresses HBV DNA replication, it does not eliminate intrahepatic cccDNA, allowing residual transcriptional activity to persist. Hepatitis B core-related antigen (HBcrAg) reflects cccDNA transcription and may serve as a biomarker. This study aimed to investigate whether baseline HBcrAg levels can predict HCC development. **Methods:** This retrospective study included 204 CHB patients who initiated antiviral therapy between September 2015 and February 2023 at a tertiary center in Korea. Patients were followed for HCC development until October 2023, with a median follow-up duration of 5.5 years. HBcrAg levels were measured using a chemiluminescence immunoassay on the LUMIPULSE G12000 automated analyzer (Fujirebio, Tokyo, Japan). Baseline HBcrAg levels were categorized into tertiles: low (<5.17 log U/mL), moderate (5.17–6.87 log U/mL), and high (≥ 6.87 log U/mL). Kaplan-Meier and Cox regression analyses were performed. **Results:** HCC was diagnosed in 24 out of 204 patients. Kaplan-Meier analysis and the log-rank test revealed that patients in the moderate HBcrAg group (5.17–6.87 log U/mL) had the highest cumulative incidence of HCC during follow-up. The 5-year cumulative incidence of HCC was 8.4% (95% CI: 1.0–15.2) in the low HBcrAg group, 20.2% (8.6–30.3) in the moderate group, and 3.2% (0.0–7.5) in the high group (log-rank $P = 0.001$). Multivariable Cox regression analysis included the following covariates: age, sex, liver cirrhosis (LC), platelet count, total bilirubin, albumin, creatinine, FIB-4, HBeAg positivity, HBsAg, and HBcrAg. Higher total bilirubin (HR 1.90; 95% CI, 1.06–3.43, $P = 0.031$) and moderate HBcrAg levels (HR 5.29; 95% CI, 1.60–17.58, $P = 0.006$) were associated with an increased risk of HCC development. In contrast, a higher HBsAg level (HR 0.03; 95% CI, 0.00–0.53, $P = 0.016$) was associated with a lower risk of HCC development. **Conclusion:** These findings indicate that patients with pre-treatment moderate

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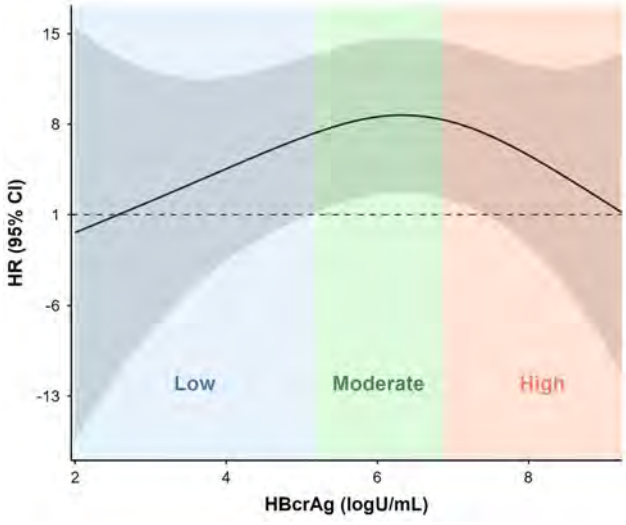
HBcrAg levels exhibited the highest incidence of HCC during the follow-up period despite receiving antiviral treatment. Based on this trend, pre-treatment HBcrAg levels may serve as a potential biomarker for predicting the long-term risk of HCC.



Disclosures: Ji Eun Han: Nothing to Disclose, Yoon Je Cho: Nothing to Disclose, Hyelynn Jeon: Nothing to Disclose, Hye Young Chang: Nothing to Disclose, Hyo Jung Cho: Nothing to Disclose, jaeyoun cheong: Nothing to Disclose, Hyun Woong Lee: Nothing to Disclose, Soon Sun Kim: Nothing to Disclose, Min Ji Son: Nothing to Disclose

1224 | PERSISTENT DISPARITIES AND DIVERGING TRENDS: STATE-LEVEL AND REGIONAL HEPATITIS B BURDEN IN THE UNITED STATES, 1990-2021

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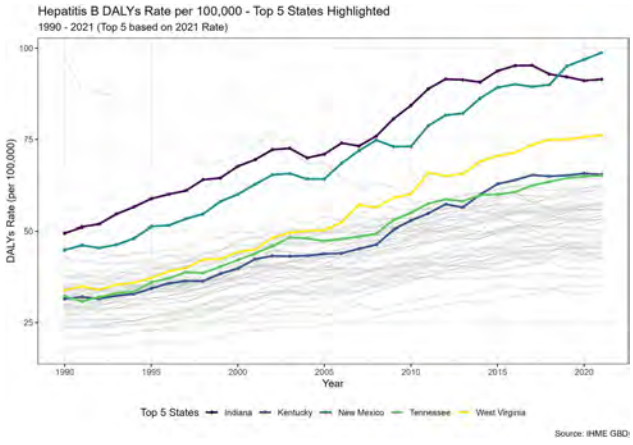
Background: Hepatitis B virus (HBV) infection remains a significant cause of morbidity and mortality in the United States. While national progress in prevention has occurred, understanding state-level and regional variations over time is crucial for effective public health strategies. We aimed to characterize the trends in HBV prevalence, incidence, mortality, and disability-adjusted life years (DALYs) across US states and Census Divisions from 1990 to 2021. **Methods:** We analyzed state-level data for the United States and the District of Columbia from 1990-2021 using estimates from the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease (GBD) study. We extracted all-ages rates per 100,000 population for HBV Prevalence, Incidence, Deaths, and DALYs. Trends were visualized for each state and aggregated by US Census Division (using unweighted state averages). States ranking in the top 5 for each metric based on 2021 rates were identified and highlighted. Analyses were performed using R statistical software. **Results:** From 1990 to 2021, HBV prevalence and incidence rates generally declined across most US states, although substantial state-level heterogeneity persists. States including New Mexico, West Virginia, Kentucky, Alaska and Indiana frequently appeared in the top 5 for highest prevalence and/or incidence rates in 2021. In stark contrast, HBV death and DALY rates demonstrated concerning *increasing* trends in numerous states over the same period. States consistently ranking highest for mortality and DALYs in 2021 included West Virginia, New Mexico, Kentucky, Indiana, and Tennessee. Regional analysis revealed significant disparities; Pacific, West South Central, and East South-Central divisions generally exhibited higher average death and DALY rates compared to New England and North Central divisions throughout the study period, with particularly steep increases noted in the East South Central and West South-Central divisions for mortality and morbidity metrics. **Conclusion:** Despite decades of prevention efforts reflected in declining HBV incidence and prevalence, significant geographic disparities in HBV burden persist across the US. The alarming divergence, with rising HBV-related mortality and DALY rates in several states and regions, underscores an urgent need for targeted, state-specific interventions focused on improving linkage to care, management of chronic HBV infection, and addressing the drivers of HBV-related liver disease progression and mortality.



Disclosures: Thanathip Suenghataiphorn: Nothing to Disclose, Kanachai Boonpiraks: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Narathorn Kulthamrongsri: Nothing to Disclose

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1225 | DUAL ORAL THERAPY TARGETING FUNCTIONAL CURE OF CHRONIC HEPATITIS B: SYNERGISTIC EFFECTS OF SAG-524 AND A NOVEL CAPSID ASSEMBLY MODULATOR

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Background: The SAG-524, which we are developing, acts as an HBV RNA destabilizer by inhibiting PAPD5, a noncanonical poly(A) polymerase stabilizing HBV RNA. Inhibition of PAPD5 disrupts protective RNA tailing, promoting HBV RNA degradation and reducing HBsAg and HBcrAg production. This study aimed to evaluate the combined effects of SAG-524 and a novel capsid assembly modulator (CAM: CBT-209) and explore the potential for clinical application by testing anti-HBV effects *in vitro* and *in vivo*. **Methods:** *In vitro*, we first conducted preliminary studies in HepAD38 cells to assess the combination effects of SAG-524 and CAM. Next, we treated HBV-infected PXB cells with SAG-524 (1 μM), CBT-209 (10 μM), or ETV (0.1 nM), either alone or combined with SAG-524, for 15 days and compared their anti-HBV activities. *In vivo*, we administered SAG-524 (20 mg/kg/day, BID) and CBT-209 (20 mg/kg/day, BID) either alone or together to HBV-infected human liver chimeric mice (PXB mice) by oral administration for four weeks, then evaluated serum HBV markers and intrahepatic HBV-cccDNA. **Results:** *In vitro*, SAG-524 and CAM combination strongly suppressed HBV RNA in HepAD38 cells. In PXB cells, SAG-524 alone reduced extracellular HBV DNA by over 1 log copies/mL, and combining with CBT-209 or ETV resulted in an additional 1 log copies/mL reduction. Monotherapy with CBT-209 or ETV resulted in only slight reduction of extracellular HBsAg and HBcrAg. Northern blot showed decreased HBV RNA with SAG-524 alone and further reduction when combined with CBT-209 or ETV. Southern blot showed HBV replication was suppressed by SAG-524 alone and reduced below detection with combination therapy. *In vivo*, the combination therapy with SAG-524 and CBT-209 resulted in the most potent suppression of HBV markers. Serum HBV DNA was decreased by 4.4 log IU/mL in both the CBT-209 monotherapy group and the combination group; notably, one animal in the combination group achieved undetectable levels. Serum HBsAg was reduced by more than 2.5 IU/mL with SAG-524 or CBT-209 alone, but in the combination group, all animals showed levels below 0.5 IU/mL, demonstrating the strongest HBsAg suppression. Furthermore, the combination group exhibited a 3.2 log U/mL reduction in serum HBcrAg, and the greatest suppression of intrahepatic cccDNA levels was also seen with combination therapy. **Conclusion:** This study demonstrates that combination therapy with SAG-524 and CBT-209 exhibits potent anti-HBV activity, leading to marked reductions in HBV DNA, HBsAg, and HBcrAg levels. These findings suggest that dual oral therapy with SAG-524 and CBT-209 holds promise as a strategy to achieve a functional cure for chronic hepatitis B.

Disclosures: Takehisa Watanabe: Nothing to Disclose, Sanae Hayashi: Nothing to Disclose, Yutaka Furutani: Nothing to Disclose, YAN ZHAOYU: Nothing to Disclose, Shintaro Ogawa: Nothing to Disclose, Chang Wu: Nothing to Disclose, Hiroki Inada: Nothing to Disclose, Satoshi Narahara: Nothing to Disclose, Katsuya Nagaoka: Nothing to Disclose, Hiroko Setoyama: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

1226 | UNDERSTANDING QUALITY-OF-LIFE IMPACTS OF HEPATITIS DELTA VIRUS

Beatrice Zovich[1] Shreya Koirala[1] Chari Cohen[1], [1]Hepatitis B Foundation

Background: Hepatitis delta virus (HDV) is the most severe form of viral hepatitis and can cause rapid progression to serious liver disease. It is estimated that 5% of people living with chronic hepatitis B globally also have HDV. Despite potential disease severity, little has been documented about the effects of HDV on quality of life. This mixed-methods study attempted to capture the ways in which HDV shapes daily life for those living with the virus around the world. **Methods:** A survey was created using Qualtrics, with questions developed *a priori* through literature review. The survey was disseminated through social media, newsletters, Google ads, and website postings. Qualitative in-depth interviews were conducted virtually with those who indicated interest in participating from the survey. Interview data were analyzed via Dedoose using grounded theory to describe QoL impacts. **Results:** Seventy-two respondents from 25 countries completed the survey, with the largest representation from Pakistan, the United States, and the Philippines. A third of respondents (31%) were between 35 and 44 years of age, and 27% were between 45 and 54 years of age. Just under three quarters (71%) were male. 70% experienced symptoms, most commonly fatigue (69%), abdominal pain (41%), muscle or joint pain (38%), and loss of appetite (38%). 27% ranked their symptoms as a 7 on a severity scale from 1-10. Around half had been prescribed treatment for hepatitis B and 65% for HDV. A total of 13 individuals participated in

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qualitative interviews. Most were male with an average age of 42 years, and half were from the U.S. and Pakistan. Interview participants described difficulty concentrating, impacts on job performance, frequent anxiety, depression and despair, fear, hope for a cure, and concerns about stigma. Strained communication with providers, issues with access to treatment and care, and financial struggles due to the disease were also expressed. **Conclusion:** A hepatitis delta diagnosis can reverberate across all areas of an individual's life. As approved HDV treatments become available and testing becomes more widespread, it is important to raise awareness of these numerous physical and psychosocial impacts, especially in terms of how they differ from hepatitis B mono-infection. This will help us holistically address patient health and improve quality of life for those diagnosed with HDV.

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1227 | IMPACT OF HDV COINFECTION ON LIVER OUTCOMES AND MORTALITY IN CHRONIC HBV: INSIGHTS FROM THE ANRS CO22 HEPATHER COHORT

Lucia Parlati[1] Samuel Nilusmas[2] Jérôme Nicol[2] Clovis Lusivika-Nzinga[2] Laurent Alric[3] Fabien Zoulim[4] Jerome Boursier[5] Tarik Asselah[6] Juliette Foucher[7] Dominique Thabut Damais[8] Damien LABARRIERE[9] Nathalie Ganne Carrie[10] Caroline JEZEQUEL[11] Francois Habersetzer[12] Jean Pierre Bronowicki[13] Georges-Philippe Pageaux[14] Sophie Métiver[15] Thomas Decaens[16] Ghassan Riachi[17] Vincent Leroy[18] Violaine OZENNE[19] Jean Charles Duclos Vallée[20] Isabelle Rosa[21] Paul Carrier[22] Philippe Mathurin[23] Jerome Gournay[24] Moana Gelu-Simeon[25] Fabrice Carrat[26] Marc Bourliere[27], [1]Cochin Hospital, Hepatology Departement, [2]Sorbonne Université, Inserm, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, [3]Toulouse III University-Paul Sabatier, Toulouse, France, [4]Universite Claude Bernard Lyon 1, [5]Angers University, [6]Hôpital Beaujon, [7]Centre Hospitalier Bordeaux, [8]AP-HP Sorbonne Université, Hôpital Universitaire Pitié-Salpêtrière, APHP, France, [9]Centre Hospitalier Régional, Orléans, France., [10]AP-HP, Hepatology Department, Avicenne Hospital, Bobigny F-93000, France, [11]CHU Rennes, Department of Hepatology, Rennes, France, [12]Service d'hépato-gastroentérologie, Institut Hospitalo-Universitaire de Strasburg, France, [13]Department of Hepatology and Gastroenterology, University Hospital of Nancy, Nancy, France., [14]Service d'Hépato-Gastroentérologie et transplantation,CHU de Montpellier, Université de Montpellier, [15]Department of Gastroenterology and Hepatology, University of Toulouse, France, [16]Université Grenoble Alpes, Inserm U 1209, CNRS UMR 5309, Grenoble, France, [17]Service d'Hépato-gastroentérologie, Centre Hospitalo-Universitaire Charles-Nicolle, Rouen, France, [18]Assistance publique-Hopitaux de Paris, [19]Department of Hepatology and Gastroenterology, Hôpital Saint Antoine, Paris, France, [20]AP-HP Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif, France, [21]Centre Hospitalier Intercommunal de Créteil, Créteil, France., [22]Hépato-gastro-entérologie, Hospital Dupuytren, Limoges, France, [23]CHRU de Lille, Hôpital Claude Huriez, Rue M. Polonovski CS 70001, 59 037 Lille Cedex, France, [24]Gastroenterology Department, University Hospital of Nantes, Nantes, France, [25]Service d'Hépato-Gastroentérologie, CHU de la Guadeloupe, F-97159 Pointe-à-Pitre Cedex, France, [26]Unité de Santé Publique, Hôpital Saint-Antoine, Assistance Publique-Hôpitaux de Paris, [27]Hopital Saint Joseph

Background: Accurate data on liver-related complications and mortality in HDV-HBV patients versus HBV patients remain scarce. This study explores the prognosis of HDV-HBV patients within the ANRS CO22 HEPATHER French cohort. **Methods:** We conducted a multicenter, nationwide, prospective observational cohort study from August 2012 to April 2023. The incidence of hepatic events (cirrhosis decompensation and HCC), liver transplantation and mortality was assessed based on HDV status, HDV RNA detectability and liver fibrosis. HBV-HDV patients were compared to a matched population of HBV patients, with matching performed based on sex, age, and center of care (1:5 matching ratio applied). **Results:** Our cohort included 185 HDV patients, matched to 925 HBV patients. The median age was 43 years (Q1-Q3: 34-51), with a majority (66%) being male. Compared to HBV patients, those with HBV-HDV were more often of African origin (56% vs. 41%, $p < 0.0001$) and had a higher prevalence of advanced fibrosis at inclusion (45% vs. 14.2%, $p < 0.0001$), particularly those with detectable HDV RNA ($n = 100$) (54.4% vs. 38.9%, $p = 0.0009$). HDV patients had a poorer prognosis. The incidence rates (per 1,000 person-years) of death, HCC, cirrhosis decompensation, and liver transplantation were significantly higher in HBV-HDV patients compared to HBV patients: 15 (9–25) vs 5 (3–7) ($p = 0.0003$), 16 (9–26)

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vs 3 (1.75–5) ($p < 0.0001$), 14.8 (8–24) vs 1.4 (0.6–3) ($p < 0.0001$), and 10.8 (5–19) vs 0.8 (0.2–1.9) ($p < 0.0001$), respectively. Patients with detectable HDV RNA had a significantly higher incidence of hepatic decompensation compared to those with undetectable HDV RNA: 27.4 (15–45) vs 0 (0–8) per 1,000 person-years ($p = 0.0002$) and a lower survival rate free from hepatic complications. A mediation analysis shows that approximately 50% of the effect of HDV coinfection on HCC or mortality is mediated by fibrosis (indirect effect), meaning that HDV leads to increased fibrosis, which in turn elevates the risk of HCC or death. The remaining 50% of the effect of HDV co-infection appears to be independent of fibrosis (direct effect) (Table1). **Conclusion:** HDV coinfection increases the risk of hepatic events and death in HBV patients. Controlling HDV infection may have a dual benefit: an immediate reduction in risk through the direct effect, and a longer-term benefit through the reduction of fibrosis and its associated risks.

Table 1. Estimated direct (NDE) and indirect (NIE) effects of HDV co-infection on liver outcomes: mediation by fibrosis

Outcome	NDE (HR) [95% CI]	NIE (HR) [95% CI]	Total Effect (HR) [95%CI]	Proportion Mediated	P value (NDE)	P value (NIE)
Death	1.66 [0.8 – 3.43]	1.685 [1.3 – 2.19]	2.797 [1.29 – 6.05]	50.7% [24.1 – 177.1%]	0.171	<0.001
HCC	2.361 [1.11 – 5.04]	2.31 [1.74 – 3.06]	5.453 [2.43 – 12.24]	49.4% [31.6 – 86.3%]	0.026	<0.001
Decompensated cirrhosis	4.159 [1.44 – 12]	2.171 [1.58 – 2.99]	9.027 [2.98 – 27.31]	35.2% [23.1 – 52.8%]	0.008	<0.001
Liver transplantation	4.761 [1.47 – 15.37]	2.845 [1.92 – 4.22]	13.542 [3.93 – 46.62]	40.1% [29.1 – 55.9%]	0.009	<0.001

Disclosures: Lucia Parlati: Nothing to Disclose, Samuel Nilusmas: Nothing to Disclose, Jérôme Nicol: Nothing to Disclose, Clovis Lusivika-Nzinga: Nothing to Disclose, Laurent Alric: MSD, Abbvie, Sanofi: Speaking and Teaching, Fabien Zoulim: Ausperbio: Grant/Research Support, Ausperbio: Consultant, Blue Jay: Grant/Research Support, Blue Jay: Consultant, Aligos: Grant/Research Support, Aligos: Consultant, Gilead: Consultant, GSK: Consultant, nChroma: Consultant, Precision: Consultant, Jerome Boursier: Nothing to Disclose, Tarik Asselah: GSK: Speaker, GILEAD: Consultant, VIR Biotechnology: Speaker, Roche: consultant, ABBVIE: Speaking and Teaching, Aligos therapeutics: Consultant, Bluejay Therapeutics: Consultant, Antios therapeutics: Consultant, GSK: Consultant, Juliette Foucher: abbvie: Speaking and Teaching, GSK: Consultant, gilead: Speaking and Teaching, Dominique Thabut Damais: Nothing to Disclose, Damien LABARRIERE: Nothing to Disclose, Nathalie Ganne Carrie: Nothing to Disclose, Caroline JEZEQUEL: Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Francois Habersetzer: Nothing to Disclose, Jean Pierre Bronowicki: Nothing to Disclose, Georges-Philippe Pageaux: Nothing to Disclose, Sophie Métiver: Nothing to Disclose, Thomas Decaens: Nothing to Disclose, Ghassan Riachi: Nothing to Disclose, Vincent Leroy: Nothing to Disclose, Violaine OZENNE: GILEAD: Consultant, Jean Charles Duclos Vallée: Nothing to Disclose, Isabelle Rosa: Nothing to Disclose, Paul Carrier: GILEAD: Congress invitation, Philippe Mathurin: Nothing to Disclose, Jerome Gournay: Nothing to Disclose, Moana Gelu-Simeon: Nothing to Disclose, Fabrice Carrat: Nothing to Disclose, Marc Bourliere: Gilead: consultant, AbbVie: speaker, GSK: advisor

1228 | SAFETY AND PHARMACOKINETICS OF BJT-628, AN ORALLY AVAILABLE LIVER-TARGETED HBV TRANSCRIPT INHIBITOR FOR THE TREATMENT OF CHRONIC HEPATITIS B IN HEALTHY VOLUNTEERS

Edward Gane[1] Christian Schwabe[2] Jeff Zablocki[3] Nancy Shulman[3] Raj Bhardwaj[4] Joelle Batonga[4] Hassan Javanbakht[3] Susanna Tan[3], [1]University of Auckland, Auckland, New Zealand, [2]New Zealand Clinical Research, Auckland, New Zealand, [3]Bluejay Therapeutics, Inc., California, USA, [4]Certara, Inc., New Jersey, USA

Background: BJT-628 is a liver-targeted small molecule inhibitor that targets the noncanonical poly(A) polymerases, PAPD5, and 7. These host enzymes are thought to support the hepatitis B virus by stabilizing HBsAg viral mRNA transcripts through polyadenylation. BJT-628 is a pro-drug that undergoes enzymatic hydrolysis upon absorption into systemic circulation and generates the active metabolite BJT-338. Its liver-targeted design enhances drug concentrations in the liver while minimizing systemic exposure and therefore may improve therapeutic specificity and reduce potential off-target effects. In pre-clinical studies, BJT-628 led to a significant reduction in HBsAg levels in an HBV infection mouse model. **Methods:** In the single ascending dose (SAD) part, a single dose of BJT-628 was evaluated in 3 cohorts (35, 105, and 315 mg), as well as food effect with a high-fat diet. In the multiple ascending dose (MAD) part, 14 days of daily dosing with BJT-628 were evaluated in 2 cohorts (35 mg and105 mg). Each cohort contained 8 healthy volunteers randomized 3:1 to oral BJT-628 or matching placebo. Safety evaluation included the incidence of treatment emergent adverse events (TEAEs), laboratory assessments, vital signs, ECGs, and physical examinations. Plasma pharmacokinetics (PK) of BJT-628 and active metabolite BJT-338 are summarized using non-compartmental analysis. Blinded data are presented. **Results:** In both the SAD and MAD portions of the study, TEAEs were observed in 24/48 (50.0%) participants. All TEAEs were Grade 1 or 2 severity. The most common TEAEs were headache

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(6/48, 12.5%) and dyspepsia (4/28, 8.3%). No serious adverse events, clinically significant vital signs, physical and neurological exam, ECGs, or laboratory abnormalities were observed. PK was characterized by rapid absorption of both BJT-628 prodrug and BJT-338 active metabolite. Under single and multiple dose fasted PK conditions, pro-drug and metabolite AUC and Cmax increased dose proportionally. Peak and overall exposure increased by 30-44% under fed conditions. After 14 days of dosing, minimal accumulation was observed for pro-drug and active metabolite. Half-life was short for pro-drug and active metabolite, not impacted by dose, and were comparable between single and multiple dosing (approximately 0.9-1 and 1.4-1.6 hours, respectively). **Conclusion:** Single and multiple doses of BJT-628 in healthy volunteers were safe and well tolerated. BJT-628 dosing in CHB patients is anticipated.

Disclosures: Edward Gane: Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Christian Schwabe: Nothing to Disclose, Jeff Zablocki: Nothing to Disclose, Nancy Shulman: Bluejay Therapeutics, INC: Salary and equity, Raj Bhardwaj: Nothing to Disclose, Joelle Batonga: Nothing to Disclose, Hassan Javanbakht: Nothing to Disclose, Susanna Tan: Bluejay Therapeutics: Employee

1229 | ALCOHOL SUPPRESSES TYPE I IFN RESPONSES IN HBV INFECTION VIA RIG-I AND STING PATHWAY INHIBITION

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Background: Chronic hepatitis B virus (HBV) infection can progress to severe liver diseases, including cirrhosis and hepatocellular carcinoma, with alcohol consumption further exacerbating disease progression. Despite this clinical association, the mechanisms by which alcohol influences HBV pathogenesis and impairs host antiviral immunity remain poorly understood. In this study, we investigated the effects of ethanol and its metabolites on HBV replication and innate immune responses, focusing on the nucleic acid sensing pathways RIG-I/MAVS and cGAS/STING. **Methods:** We used hepatocyte-based models (HepAD38, HepG2.2.15) and HBV-infected primary human hepatocytes (PHHs) to study ethanol effects. Ethanol metabolism was simulated using an acetaldehyde-generating system (AGS), comprising yeast alcohol dehydrogenase (ADH), NAD^+, and 50 mM ethanol. HBV replication was measured via viral RNA, DNA, covalently closed circular DNA (cccDNA), HBsAg, and HBcAg levels. Innate immune responses were assessed by analyzing RIG-I/MAVS and cGAS/STING signaling, STAT1 phosphorylation, type I IFN production, and ISG expression (e.g., APOBEC3B, 3G). **Results:** Exposure to ethanol or AGS significantly increased HBV RNA, DNA, cccDNA, HBsAg, and HBcAg levels in hepatocytes. In HBV-infected PHHs, similar elevations in viral markers were noted following ethanol treatment. Mechanistically, ethanol and HBV co-treatment suppressed the expression of RIG-I, MAVS, and cGAS in PHHs and AGS-treated HepAD38 and HepG2.2.15 cells. Phosphorylation of IRF3, induced by poly(I:C) stimulation, was diminished in HBV+ cells exposed to ethanol, leading to impaired production of IFN-β and type I IFNs. Type I IFNs are crucial for STAT1 phosphorylation, which subsequently induces the activation of antiviral ISGs. We observed that ethanol also inhibited STAT1 phosphorylation and downregulated the expression of APOBEC3B and APOBEC3G. Furthermore, ethanol exposure in IFNα-stimulated HepAD38 and PHH cells increased the expression of ZBP1, a key innate immune sensor and regulator of inflammatory cell death. **Conclusion:** Ethanol exposure enhances HBV replication and disrupts antiviral immunity by suppressing RIG-I/MAVS and cGAS/STING pathways and downstream IRF3 and STAT1 signaling, impairing ISG induction. Concurrently, ethanol enhances ZBP1 expression, potentially priming infected hepatocytes for inflammatory cell death, thereby contributing to HBV persistence and liver disease progression.

Disclosures: Anup Pathania: Nothing to Disclose, Larisa Poluektova: Nothing to Disclose, Natalia Osna: Nothing to Disclose

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1230 | EFFICACY OF PEGINTERFERON α-2B TREATMENT IN HBV-INFECTED CHILDREN AGED &LE;5 YEARS: SUBGROUP ANALYSIS FROM A LARGE-SCALE, PROSPECTIVE STUDY (SPROUT PROJECT)

Hongfei Zhang[1] Qing He[2] Wenxian Ouyang[3] Shuangjie Li[3] Yilan Zeng[4] Hong Zhang[4] Jia Shang[5] Fang Wang[2] Lijuan Ouyang[6] Yujing Tang[6] Xiaogua Liu[7] Pengfei Xu[7] Hongxia Zhou[8] Hui Lv[9] Xiaorong Mao[10] Hong Wan[11] Rendong Wei[12] Shuangsuo Dang[13] Chen Pan[14] Riying Lv[15] Zhenkun He[16] Yahui Liu[17], [1]Beijing Chen Jumei Foundation, China, [2]Shenzhen Third People's Hospital, China, [3]Hunan Children's Hospital, China, [4]Public Health Clinical Center of Chengdu, China, [5]Henan Provincial People's Hospital, China, [6]Xiamen Hospital of Traditional Chinese Medicine, China, [7]Xi'an Children's Hospital, China, [8]The Infectious Diseases Hospital of Handan City, China, [9]Shandong Public Health Clinical Center, China, [10]The first hospital of lanzhou university, China, [11]Lanzhou Second People's Hospital, China, [12]Qingdao Sixth People's Hospital, China, [13]The Second Affiliated Hospital of Xi'an Jiaotong University, China, [14]Mengchao Hepatobiliary Hospital of Fujian Medical University, China, [15]Guigang City People's Hospital, China, [16]Huaihe Hospital of Henan University, China, [17]Kuitun Hospital of Yili Kazakh Autonomous Prefecture, China

Background: Current evidence regarding antiviral therapy for pediatric HBV infection remains limited. We aimed to explore the efficacy and safety of different antiviral strategies for HBV-infected children, and a stratified analysis was conducted on children in the lower age group (3-5 years old). **Methods:** This was a prospective, multicenter real-world study (NCT05792761) that enrolled three types of HBV-infected children aged 3-18 years, including treatment-naïve, NA-experienced and normal ALT level populations. All patients received NA monotherapy or combined with peginterferon α-2b (PegIFNα-2b, Pegbing®, Xiamen Amoytop Biotech Co., Ltd.) for 96 weeks. Data from 158 children aged 3-5 years treated with PegIFNα-2b for 48 weeks were analysed. **Results:** Among the 158 pediatric patients, 57.0% were male, 86.7% were HBeAg positive and 89.5% were HBV DNA positive. Patients were divided into an ALT normal group (n = 86) and an ALT abnormal group (n = 72). The mean baseline HBsAg levels were 4.0 and 3.8 $\log_{10}$ IU/mL, HBeAg were 2.7 and 2.3 $\log_{10}$ COI, and HBV DNA were 6.2 and 5.8 $\log_{10}$ IU/mL in the two groups, respectively. 71.5% of patients were treatment-naïve patients. Both in total population and treatment-naïve patients, the ALT abnormal group obtained greater HBsAg declines, reaching 2.64 and 2.45 $\log_{10}$ IU/mL at week 48, respectively, compared with 1.74 and 1.88 $\log_{10}$ IU/mL in the ALT normal group. In the total population, HBsAg loss rates in the ALT abnormal and normal groups at week 48 were 37.5% and 11.6%, respectively ($p = 0$), and HBeAg loss rates were 31.7% and 11.7%, respectively ($p = 0.004$). 29.2% and 23.0% of patients in the ALT abnormal group achieved HBsAg seroconversion and HBeAg seroconversion by week 48, significantly higher than 9.3% and 7.8% in the ALT normal group ($p = 0.001$ and 0.012). The HBsAg response in the ALT abnormal group was also significantly better than in the ALT normal group among the treatment-naïve patients, with HBsAg loss rates of 32.2% and 11.1% ($p = 0.007$) and HBsAg seroconversion rates of 27.1% and 9.3% at week 48, respectively. HBeAg loss (27.85 vs. 14.0%, $p = 0.086$) and seroconversion (18.5% vs. 8.0%, $p = 0.116$) rates were not statistically different between the two groups. An increase in ALT levels was also observed in the ALT normal group during the treatment. **Conclusion:** HBV-infected children aged 3-5 years treated with PegIFNα-2b achieved high HBsAg and HBeAg loss rates, especially those with abnormal ALT, with both rates exceeding 30% after 48 weeks. Younger children with abnormal ALT can better pursue functional cure based on PegIFNα therapy.

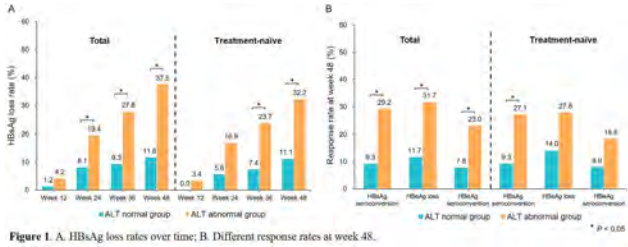

Figure 1. A. HBsAg loss rates over time; B. Different response rates at week 48.

Disclosures: Hongfei Zhang: Nothing to Disclose, Qing He: Nothing to Disclose, Wenxian Ouyang: Nothing to Disclose, Shuangjie Li: Nothing to Disclose, Yilan Zeng: Nothing to Disclose, Hong Zhang: Nothing to Disclose, Jia Shang: Nothing to Disclose, Fang Wang: Nothing to Disclose, Lijuan Ouyang: Nothing to Disclose, Yujing Tang: Nothing to Disclose, Xiaogua Liu: Nothing to Disclose, Pengfei Xu: Nothing to Disclose, Hongxia Zhou: Nothing to Disclose, Hui Lv: Nothing to Disclose, Xiaorong Mao: Nothing to Disclose, Hong Wan: Nothing to Disclose, Rendong Wei: Nothing to Disclose, Shuangsuo Dang: Nothing to Disclose, Chen Pan: Nothing to Disclose, Riying Lv: Nothing to Disclose, Zhenkun He: Nothing to Disclose, Yahui Liu: Nothing to Disclose

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1231 | GLS4 INHIBITS HEPATITIS B VIRUS INFECTION BY ACTIVATING THE INTERFERON SIGNALING PATHWAY

lingzhu zhao[1] SIDUO XU[2] Zhiqiang Wei[3] Xueyu Wang[3] Zhenggang Yang[3] Min Zheng[3], [1]The First Affiliated Hospital, College of Medicine, Zhejiang, [2]the first affiliated hospital, college of medicine,zhejiang university, [3]the first affiliated hospital, college of medicine, zhejiang university

Background: Nearly 300 million people worldwide still have chronic hepatitis B virus (HBV) infection despite preventive vaccinations. Current treatment can control HBV replication but do not lead to functional cure. The formation of normal HBV nucleocapsid is a critical step in sustaining the HBV life cycle. GLS4, a novel heteroaryldihydropyrimidine (HAP) compound, can induce aberrant non-capsid polymers of HBV, resulting in pgRNA encapsulated abnormally for reverse transcription, thereby inhibiting the secretion of HBV virions. However, it is unknown whether exposure to the cytoplasm of pgRNA activates innate immunity in hepatocytes. Thus, the effects of GLS4 on innate immune were investigated in human hepatoma cell lines. **Methods:** RNAseq of normal and GLS4 treatment group was performed on Hep G2.2.15 to detect related changes in gene expression. Western blotting, qRT-PCR and immunofluorescence were used to investigate the effects of GLS4 treatment on the innate immune of HBV-infection hepatoma cell line HepG2 and HBV-replicating cell line HepG2.2.15. **Results:** KEGG analysis of RNAseq data showed that HBV-related pathway was enriched, and the expression of interferon receptors were significantly up-regulated. In two human hepatoma cell lines, GLS4 increased RNA receptor RIG-I expression and caused phosphorylation of interferon regulatory factor 3 (IRF3), which promoted the transcription of interferon, thereby activating the JAK-STAT signaling pathway and increasing expression of antiviral proteins such as OAS1. In addition, knockdown of OAS1 significantly reversed the inhibitory effect of GLS4 on HBV replication. **Conclusion:** This study suggests that GLS4 inhibits HBV replication by not only disrupting the correct assembly of the nucleocapsid, but also activating the interferon signaling pathway.

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1232 | PHARMACOLOGICAL ACTIVATION OF LUBAC SYNERGIZES WITH IFNα TO INHIBIT HBV REPLICATION VIA IRF9 M1-LINKED UBIQUITINATION

peng chen[1] Yuxin Zhou[1] Zheyu Dong[1] Yuqing Shao[1] Qiuyue Ye[2] Yadong Wang[1] Libo Tang[3] yongyin li[1], [1]Nanfang Hospital, Southern Medical University, [2]Afiliated Hospital of Guizhou Medical University, [3]Nanfang Hospital, Southern Medical Univerisity

Background: Combination therapy with interferon-alpha (IFNα) is a promising strategy for chronic hepatitis B virus (HBV) infection; however, the underlying mechanisms remain largely unclear. The linear ubiquitin assembly complex (LUBAC), composed of HOIP, HOIL-1, and SHARPIN, is the only E3 ligase that generates linear (M1-linked) ubiquitination and plays a critical role in antiviral response. This study aims to elucidate LUBAC's regulatory function in IFNα responsiveness and explore pharmacological strategies that enhance IFNα-based combination therapy. **Methods:** We systematically evaluated IFNα's effects on LUBAC activity by liver tissues from the patients with chronic HBV infection, HBV mouse models and HBV-infected cell lines. The role of LUBAC in IFNα treatment efficacy and HBV suppression was evaluated both *in vitro* and *in vivo*. Mechanistic studies were conducted using chromatin immunoprecipitation-quantitative PCR (ChIP-qPCR), RNA sequencing, and Western blot. The synergistic antiviral effect of pharmacological LUBAC activation combined with IFNα was tested in cell lines and multiple HBV mouse models. **Results:** IFNα treatment specifically upregulated M1-linked ubiquitination in hepatocytes, with minimal effects on other ubiquitin linkages. HOIL-1 knockdown, which impaired LUBAC function, enhanced HBV replication, as evidenced by increased levels of HBV DNA, HBeAg, HBsAg in HBV-replicating cell lines and in a mouse model established by hydrodynamic injection (HDI) of the 1.2×HBV plasmid. Notably, HOIL-1 knockdown substantially diminished the antiviral efficacy of IFNα both *in vitro* and *in vivo*. In contrast, HOIL-1 overexpression not only inhibited HBV replication but also synergized with IFNα to enhance antiviral responses. Mechanistically, ChIP-qPCR revealed that IFNα promoted IRF9 binding to the *HOIL-1* and *HOIP* promoters, thereby upregulating the expression of *HOIL-1*, *HOIP* and M1-linked ubiquitin. In turn, HOIL-1 interacted with IRF9 to mediate its M1-linked ubiquitination, facilitating IRF9 nuclear translocation and subsequent induction of interferon-stimulated genes. Importantly,

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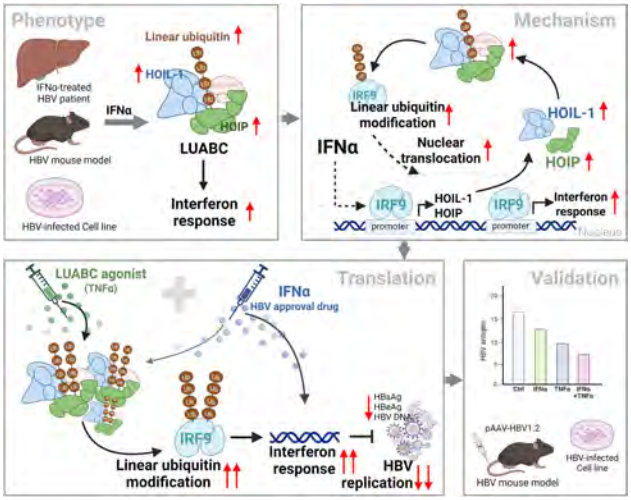
pharmacological activation of LUBAC by TNFα promoted IRF9 M1-linked ubiquitination and nuclear translocation, synergizing with IFNα to amplify antiviral efficacy. **Conclusion:** Our findings establish LUBAC as a critical amplifier of IFNα antiviral responses by promoting IRF9 M1-linked ubiquitination and nuclear translocation. These results propose LUBAC-targeted pharmacologic activation as a novel strategy to boost IFNα efficacy, especially in IFNα-nonresponsive HBV patients.



Disclosures: peng chen: Nothing to Disclose, Yuxin Zhou: Nothing to Disclose, Zheyu Dong: Nothing to Disclose, Yuqing Shao: Nothing to Disclose, Qiuyue Ye: Nothing to Disclose, Yadong Wang: Nothing to Disclose, Libo Tang: Nothing to Disclose, yongyin li: Nothing to Disclose

1233 | DE NOVO DIAGNOSIS OF HBV AND HDV INFECTIONS IN HARM REDUCTION AND MIGRANT SUPPORT CENTERS IN SPAIN: PROSPECTIVE RESULTS: FROM THE DESCRIBE STUDY

Pablo Ryan[1] Antonio Madejon[2] Jorge Valencia[1] Sabela Lens[3] Xavier Forns[3] Javier García-Samaniego[4], [1]Hospital Universitario infanta Leonor, Ciber de Enfermedades Infecciosas (CIBERINFEC), Madrid, Spain, [2]Unidad de Hepatología, Hospital Universitario La Paz., [3]Hepatology Department, Hospital Clínic, Universidad de Barcelona, IDIBAPS, CIBEREHD, Barcelona, Spai, [4]Hepatology Unit. Hospital Universitario La Paz. IdiPaz. Madrid, Spain

Background: Epidemiological surveillance of HBV and HDV infections is particularly important in populations with limited engagement with healthcare systems. Identifying the prevalence of HDV coinfection is clinically relevant, as persistent HDV replication is associated with increased liver-related mortality. DESCRIBE is a retrospective/prospective program to analyze the prevalence of HDV infection in two major urban settings in Spain. We previously describe the serologic and active HDV infection (retrospective, AASLD 2023). This prospective phase focused on individuals without a prior diagnosis of HBV or HDV, attending a harm reduction centers: a mobile harm reduction unit operating in informal settlements and migrant centers in Madrid, and a fixed-site harm reduction center in Barcelona. **Methods:** Between 2023 and 2024, individuals without known HBV or HDV infection were recruited from two locations: (1) a mobile harm reduction program in Madrid covering "Cañada Real" shantytown and centers serving undocumented migrants (n = 439), and (2) the fixed-site harm reduction center "La Mina" in Barcelona (n = 276) HBsAg was assessed using rapid diagnostic tests followed by confirmatory assays. In HBsAg-positive individuals, anti-HDV and HDV-RNA were tested to determine HDV exposure. **Results:** Fifty-nine individuals tested positive for HBsAg via rapid testing. Twelve of them (20%) were considered false positives based on confirmatory assays, resulting in an HBsAg prevalence of 47/715 (6.6%). Most HBsAg-positive individuals were male (42/47; 91%) with a mean age of 31.4 years, 66% were from sub-Saharan Africa, 23% from Europe, 4% from Asia, and 4% from Latin AmericaEight (17%) reported intravenous drug use; 2 were coinfected with HIV and 5 with HCV. The vast majority of HBsAg-positive cases were were identified in Madrid, in the migrant centers (46/47). Only 1/47 (2%) patients tested positive for anti-HDV, but HDV RNA was undetectable (no active HDV infection). **Conclusion:** In this cohort of high-risk individuals without prior serological testing or regular contact with healthcare services, chronic HBV infection prevalence was 6.6%. Surveillance and preventive efforts should prioritize populations from African origin. HDV seroprevalence was very low (2% of HBsAg-positive), and no active HDV infection was found.

Disclosures: Pablo Ryan: Nothing to Disclose, Antonio Madejon: Nothing to Disclose, Jorge Valencia: Nothing to Disclose, Sabela Lens: Nothing to Disclose, Xavier Forns: Nothing to Disclose, Javier García-Samaniego: Nothing to Disclose

1234 | METABOLIC COMORBIDITIES AND THE RISK OF LIVER-RELATED EVENTS IN INDIVIDUALS WITH HEPATITIS B VIRUS INFECTION

Laura Telep[1] Lesley Patmore[2] Lai San Hong[3] AMANDA SINGER[1] Leland Yee[1] Catherine Frenette[1] Harry

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Janssen[4] Milan Sonneveld[2], [1]Gilead Sciences, Inc., Foster City, CA, USA, [2]Erasmus University Medical Center, Rotterdam, The Netherlands, [3]Gilead Sciences, Inc., Foster City, CA, USA; Redsen Limited, Tring, UK, [4]Erasmus University Medical Center, The Netherlands; Toronto Centre for Liver Disease, Canada

Background: Individuals with hepatitis B virus (HBV) infection have an increased risk of hepatocellular carcinoma (HCC) and other liver-related complications. HBV coupled with metabolic comorbidities (MCs) may further increase the risk of liver-related events (LREs). Here, we investigate the impact of MCs on the risk of developing LREs in US patients with chronic HBV infection. **Methods:** This observational cohort study used closed US medical claims data (HealthVerity Marketplace™; Oct 2015–Dec 2024) from individuals aged ≥18 with chronic HBV infection (index date set to first inpatient or first of two outpatient claims). LREs included cirrhosis, liver decompensation, HCC, and liver transplant. Patients were excluded if there was evidence of LREs or other forms of chronic liver disease, or human immunodeficiency virus, prior to index. The earliest record of each MC (diabetes mellitus [DM], hypertension, hyperlipidemia, and overweight/obesity) was identified using all available data. Incidence of any LRE during follow-up (composite outcome) was examined among individuals with individual MCs. Adjusted hazard ratios (aHRs) are presented using overlap weights to balance demographics, comorbidities, and prescriptions (including nucleos[t]ide analogs) in the 6 months prior to index. Individuals who developed an MC during follow-up prior to experiencing an LRE were censored (primary analysis) or switched to the MC cohort (sensitivity analysis; not shown). **Results:** Out of 292,349,478 individuals, 259,305 had chronic HBV infection; 147,987 had evidence of an MC. In the primary analysis, some individual MCs were associated with an increased risk of LREs (aHR [95% confidence interval]; DM: 1.34 [1.15–1.55]; hypertension: 1.32 [1.12–1.55]), while others demonstrated no association (hyperlipidemia: 0.88 [0.77–1.01]; overweight/obesity: 0.92 [0.80–1.05]; Table 1). Findings were similar for the cirrhosis and liver decompensation outcomes (not shown). No exposures were associated with significantly increased risk of HCC or liver transplant. Findings were similar in the sensitivity analysis. **Conclusion:** Among individuals with HBV, those with evidence of DM or hypertension had an increased risk of LREs. Future studies are needed to understand the underlying mechanisms of these combined exposures and the impact of treatment on improving HBV outcomes.

Table 1. Liver-related events among individuals with HBV infection and metabolic comorbidities compared to those with HBV infection alone

Metabolic comorbidities	Population (unweighted)	Population (weighted)	Number of events	Per 100 PY	IR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
No diabetes mellitus	47,809	7,295	1,756	1,360.72	1.29 (1.23–1.35)	1.00	1.00
Diabetes mellitus	12,006	7,293	726	309.29	2.35 (2.18–2.53)	1.78 (1.63–1.94)	1.34 (1.15–1.55)
No hypertension	38,013	7,295	1,140	1,052.80	1.08 (1.02–1.15)	1.00	1.00
Hypertension	21,248	7,290	1,267	573.51	2.21 (2.09–2.34)	2.03 (1.87–2.20)	1.32 (1.12–1.55)
No hyperlipidemia	31,013	10,634	1,022	784.48	1.30 (1.22–1.39)	1.00	1.00
Hyperlipidemia	26,702	10,626	1,284	730.99	1.76 (1.66–1.88)	1.38 (1.27–1.50)	0.88 (0.77–1.01)
No overweight/obesity	42,805	10,308	1,658	1,154.09	1.44 (1.37–1.51)	1.00	1.00
Overweight/obesity	16,296	10,302	713	415.46	1.72 (1.59–1.85)	1.17 (1.07–1.27)	0.92 (0.80–1.05)

Liver-related events is a composite outcome, comprising cirrhosis, liver decompensation, HCC, and liver transplant outcomes. Outcomes are only included if they were recorded after ≥185 days (~6 months) of follow-up. Individuals who developed a metabolic comorbidity during follow-up, prior to having an outcome, were censored. (a) Adjusted hazard ratios are presented using overlap weights to balance demographics, comorbidities, and prescriptions (including nucleos[t]ide analogs) in the 6 months prior to index. CI: confidence interval; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HR: hazard ratio; IR: incidence rate; PY: patient-years.

Disclosures: Laura Telep: Gilead Sciences, LLC: Employee, Gilead Sciences, LLC: Stock - publicly traded company, Lesley Patmore: Nothing to Disclose, Lai San Hong: Gilead: Independent Contractor, Astra Zeneca: Independent Contractor, AMANDA SINGER: Gilead Sciences: Employee and own stock, Leland Yee: Nothing to Disclose, Catherine Frenette: Nothing to Disclose, Harry Janssen: Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Academic Medical Education: Consultant, H.C. Wainwright & Co: Consultant, Milan Sonneveld: Roche: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Consultant, ViR: Advisor, GSK: Grant/Research Support, Fujirebio: Grant/Research Support

1235 | ASSESSMENT OF TRADITIONAL AND NOVEL VIROLOGIC MARKERS AS PREDICTORS OF FUNCTIONAL CURE AND HBEAG LOSS WITH PEGYLATED INTERFERON IN CHRONIC HEPATITIS B: A SYSTEMATIC REVIEW AND META-ANALYSIS

Ying Zhang[1] Longfei Wang[1] Jing Chen[1] Mindie Nguyen[2] Qi Zheng[1], [1]The First Affiliated Hospital of Fujian Medical University, [2]Stanford University Medical Center

Background: Functional cure (loss of HBsAg) rates remain unsatisfactory after pegylated interferon (PEG-IFN) therapy for chronic hepatitis B. To guide PEG-IFN therapy, this study evaluates the role of virological markers

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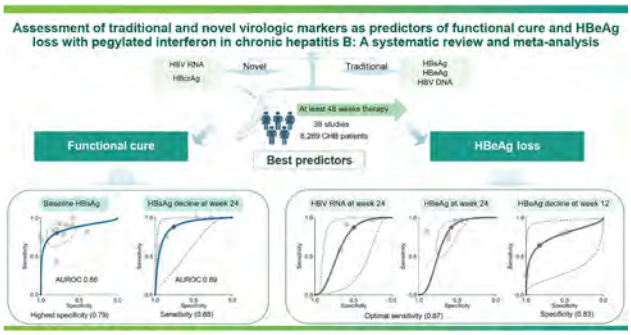
to identify patients with higher likelihood of functional cure and/or hepatitis B e antigen (HBeAg) loss or seroconversion. **Methods:** A systematic search of PubMed, Embase, Cochrane Library, and Web of Science up to November 2023 identified studies on virological markers predicting functional cure and HBeAg loss after PEG-IFN therapy. Predictive effectiveness was assessed using the summary receiver operating characteristic curve (SROC). **Results:** We analyzed 38 studies (8,289 patients). HBsAg decline at week 24 had the highest area under receiver operating characteristic curve (AUROC) (0.89) and sensitivity (0.88) for predicting functional cure, while baseline HBsAg had a comparable AUROC (0.86) and highest specificity (0.79), with both being significantly better than baseline hepatitis B core-related antigen and hepatitis B virus (HBV) RNA (all $P < 0.001$). For HBeAg loss or seroconversion, HBV DNA, HBV RNA, HBeAg, and HBeAg decline at week 12, as well as HBV DNA and HBeAg decline at week 24, all exhibit comparable predictive value (AUROC = 0.75–0.78). HBV RNA and HBeAg at week 24 showed optimal sensitivity (0.87), and HBeAg decline at week 12 had the highest specificity (0.83). **Conclusion:** HBsAg decline at week 24 and baseline HBsAg levels are better predictors of functional cure than novel virologic markers, while on-treatment HBV RNA and HBeAg levels and dynamic changes are the most reliable indicators for HBeAg loss.



Disclosures: Ying Zhang: Nothing to Disclose, Longfei Wang: Nothing to Disclose, Jing Chen: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose, Qi Zheng: Nothing to Disclose

1236 | KINETIC CHARACTERIZATION OF HBV ACUTE INFECTION AND HEPLISAV-B TREATMENT IN RAAV-HBV MOUSE MODEL

Aarim Khan[1] James Ahodantin[2] Louis Shekhtman[1] Jiapeng Wu[2] Lydia Tang[3] Shyam Kottilil[2] Harel Dahari[1] Lishan Su[2], [1]Loyola University Chicago, [2]University of Maryland School of Medicine, [3]University of Maryland, Baltimore

Background: Heplisav-B (Dynavax Technologies Corporation) is a new FDA approved 2-dose hepatitis B vaccine with a CpG adjuvant with higher rates of seroprotection. Here, we sought to characterize the kinetics of serum hepatitis B viral genome (HBV DNA), hepatitis B surface antigen (HBsAg), hepatitis B e-antigen (HBeAg), anti-HBs antigen IgG (IgG), and alanine aminotransferase (ALT) in rAAV-HBV infected mice with and without Heplisav-B, for 25 weeks. **Methods:** Ten rAAV-HBV infected mice were included. Heplisav-B was administered in 6 mice at weeks 4 and 8 post infection (p.i.). Blood samples were collected every 2 weeks until 25 weeks p.i. Kinetic phases were identified by linear regression. For simplicity we present mice per group as an agglomerate mouse. A plateau is defined as not different than slope 0 ($p > 0.05$). **Results:** In the unvaccinated agglomerate mouse (Fig. 1A), HBV DNA and HBsAg had a multiphasic increase consisting of a rapid first phase increase during the first 2 weeks p.i. (median doubling time, $t_2 = 0.64$ days), followed by a slower increase phase ($t_2 = 13$ days) until 16 weeks p.i., after which HBV-DNA levels plateaued at 8.90 log(ge/ml) until end of the experiment (EOE). HBsAg paralleled HBV DNA increase kinetic phases reaching a plateau at 0.11 log(ng/ml). IgG remained close to the assay detection level until 16 weeks p.i., after which it increased ($t_2 = 4.8$ days) to 2.46 log(U/ml) by EOE. ALT remained at pre-infection levels until EOE. In the vaccinated agglomerate mouse (Fig. 1B), a first phase increase ($t_2 = 0.64$ days) in HBV DNA was seen, that was followed by a second phase decline (half-life, $t_{1/2} = 3.5$ days) after the 1st dose of Heplisav-B was administered at 4 weeks p.i. and until the 2nd dose at week 8 p.i. This was followed by a third phase increase ($t_2 = 19$ days) starting from 8 weeks p.i. until EOE. HBsAg decreased (median $t_{1/2} = 3.2$ days) beginning at 4 weeks p.i. until 8 weeks p.i. to below detection, where it remained until EOE. IgG saw a steady increase ($t_2 = 6.4$ days) after 4 weeks p.i., then plateaued after 12 weeks p.i. HBeAg increased up to vaccination at week 4 and then declined slowly until week 12 and remained unchanged until EOE. Notably, at the end of the experiments vaccinated mice had a median 1.96 log lower HBV-DNA ($p = 0.034$), 3.76 log lower HBsAg ($p = 0.02$), 0.51 log lower HBeAg ($p = 0.04$) and 1.18 log higher IgG ($p = 0.04$) than unvaccinated mice, demonstrating vaccine effectiveness. **Conclusion:** HBV infection in rAAV-HBV infected mice is highly dynamic despite the absence of HBV spread. Minimum serum HBV DNA t1/2 in mice was estimated to be 3.5 days. Heplisav-B demonstrated effective therapeutic potential to suppress HBsAg in the rAAV-HBV infected mouse model. The infection kinetics presented here is an important step in characterizing this experimental model system so that it can be effectively used to elucidate the dynamics of the HBV life cycle and thus possibly reveal effective therapeutic vaccine effects.

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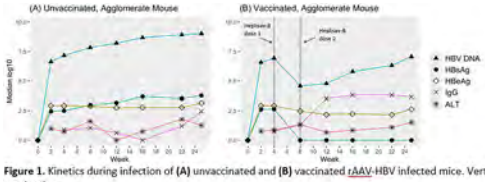

Figure 1. Kinetics during infection of (A) unvaccinated and (B) vaccinated rAAV-HBV infected mice. Vertical gray lines indicate time of vaccination.

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1237 | THE IMPACT OF METABOLIC-ASSOCIATED FATTY LIVER DISEASE ON THE TREATMENT EFFICACY OF PEGYLATED INTERFERON-BASED THERAPY IN PATIENTS WITH CHRONIC HEPATITIS B

Jiaxin Han[1] Wentao Kuai[1] Minghui Zeng[1] Yuqin Li[1] Lianxin Xu[1] Huiling Xiang[2] Liang Xu[1], [1]Tianjin Second People's Hospital, [2]Tianjin Third Central Hospital

Background: To investigate the impact of metabolic-associated fatty liver disease (MAFLD) on therapeutic efficacy, lipid metabolism, and clinical outcomes in chronic hepatitis B (CHB) patients with HBV DNA > 20IU/mL receiving pegylated interferon (Peg-IFN) antiviral therapy. **Methods:** A retrospective cohort study was conducted, enrolling 620 CHB patients with HBV DNA > 20IU/ml treated with Peg-IFN at the Department of Hepatology, Tianjin Second People's Hospital and Tianjin Third Central Hospital from December 2020 to December 2024. Participants were categorized into a CHB-only group (n = 373) and an MAFLD-CHB comorbid group (n = 247). Propensity score matching (1:1) was applied to balance baseline characteristics. LASSO-COX regression identified independent predictors of CVR and HBsAg clearance. Flow cytometry was employed to monitor immune cell subsets and cytokine profiles. **Results:** After propensity score matching, 247 patients were included in each group. The CHB group demonstrated significantly higher cumulative CVR rates at multiple timepoints (3 months: 36.84% vs 24.54%,P = 0.041; 12 months:77.19% vs 62.72%,P = 0.013; end of treatment:78.94% vs 65.45%,P = 0.019; end of follow-up: 80.7% vs 68.18%,P = 0.026) and a shorter median time to first CVR (4.5 vs. 5.8 months, P = 0.025). LASSO-COX regression identified HBV DNA levels (HR:0.486,95%CI:0.297-0.793,P = 0.004), MAFLD comorbidity (HR:0.736,95%CI:0.550-0.986,P = 0.040), HBsAg levels (HR:0.808,95%CI:0.706-0.926,P = 0.002), triglycerides (HR:0.793,95%CI:0.661-0.951,P = 0.012), and HBeAg positivity (HR:0.611,95%CI:0.433-0.862,P = 0.005) as independent predictors of CVR. Although HBsAg clearance rates increased over time in both groups, no significant intergroup differences were observed (16.6% vs. 15.4% at follow-up, P > 0.05). Kaplan-Meier analysis revealed no difference in median time to HBsAg clearance (Log-rank P = 0.2). Notably, six independent predictors of HBsAg clearance were identified: baseline HBV DNA levels (adjusted HR = 0.651, 95% CI 0.507–0.835; P < 0.001), HBsAg titers at 3-month follow-up (adjusted HR = 0.368, 95% CI 0.305–0.443; P < 0.001), baseline LDL-C concentrations (adjusted HR = 0.609, 95% CI 0.460–0.807; P < 0.001), baseline fasting glucose levels (adjusted HR = 0.409, 95% CI 0.254–0.660; P < 0.001), 3-month γ-GGT activity (adjusted HR = 1.004, 95% CI 1.002–1.007; P < 0.001), and baseline HDL-C levels (adjusted HR = 4.320, 95% CI 2.185–5.933; P < 0.001). Immunological profiling demonstrated significantly lower CD4+/CD8+ T lymphocyte ratios (1.1% vs. 1.4%, P < 0.05) and elevated IL-10 levels (3.1 vs. 2.2, P < 0.05) in the MAFLD-CHB group. **Conclusion:** MAFLD comorbidity may delay virological response, prolong time to first CVR, and promote liver fibrosis progression in CHB patients undergoing Peg-IFN therapy, potentially mediated through decreased CD4+/CD8+ T lymphocyte ratios and elevated IL-10 levels.

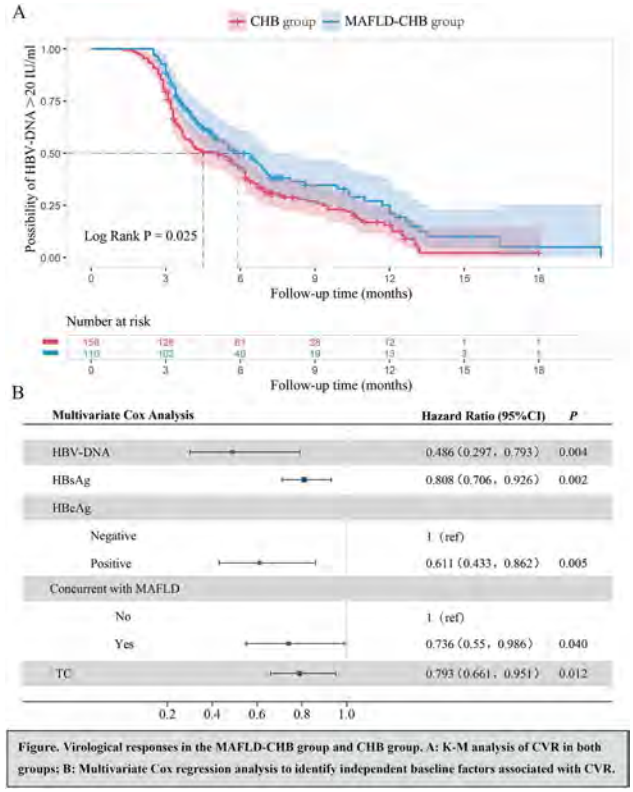

Figure. Virological responses in the MAFLD-CHB group and CHB group. A: K-M analysis of CVR in both groups; B: Multivariate Cox regression analysis to identify independent baseline factors associated with CVR.

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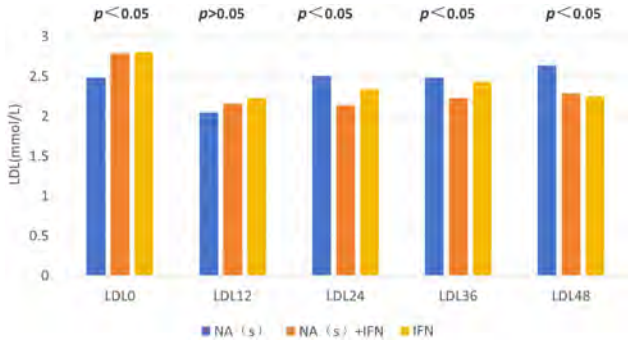
Disclosures: Jiaxin Han: Nothing to Disclose, Wentao Kuai: Nothing to Disclose, Minghui Zeng: Nothing to Disclose, Yuqin Li: Nothing to Disclose, Lianxin Xu: Nothing to Disclose, Huiling Xiang: Nothing to Disclose, Liang Xu: Nothing to Disclose

1238 | THE EFFECT OF PEG-IFNA2B ON THE METABOLIC STATUS OF CHB COMBINED WITH MASLD

Baiguo Xu[1] Aili Fan[2] Jiawen Feng[2] Lei Liu[1] Jia Lian[1] Huiling Xiang[1] Qing Ye[1], [1]Department of Hepatology of The Third Central Hospital of Tianjin, China, [2]The Third Central Clinical College of Naikai University, China

Background: The proportion of chronic hepatitis B patients with MASLD is increasing. Peg-IFNα2b is one of the core drugs for CHB antiviral therapy, and its mechanism of action involves not only direct inhibition of virus replication, but also immune regulation and inflammation regulation. However, previous studies have mostly focused on the antiviral efficacy of interferon, with limited attention paid to its impact on improving host metabolic status. This study aims to reveal the potential regulatory effect of interferon on metabolic syndrome in patients with CHB through long-term follow-up observation of the dynamic changes in metabolic parameters such as blood lipids, blood glucose, uric acid, BMI, and waist circumference treated with interferon. **Methods:** This is a prospective observational study. The patients with CHB who met the indications of antiviral treatment of the Guidelines were collected as the research objects, and were followed up for at least 48 weeks. The therapeutic effect and impact on metabolic related indicators of Peg-IFNα2b and nucleotide analogs (NA), as well as the combination therapy group were analyzed. **Results:** There are 585 CHB patients who meet the inclusion criteria, including 322 patients combined with MASLD. The group with MASLD had higher BMI, CAP, TG, LDL and serum uric acid values at baseline ($p < 0.05$). Compared with NA group, patients treated with Peg-IFNα2b showed a significant decrease in waist circumference, BMI, CAP and LDL at the 48 weeks ($p < 0.05$). There is not much difference in blood sugar and uric acid between the two groups. In the Peg-IFNα2b based treatment process, there was no significant statistical difference in virological indicators, including HBsAg and HBVDNA, between CHB without MASLD and CHB with MASLD group at 48 weeks. No difference was found in the clinical cure rate between the two groups. 45 patients achieved clinical cure, including 20 cases combined with MASLD. All cured patients were treated with Peg-IFNα2b based therapy (Peg-IFNα2b alone or combined with NA). **Conclusion:** There was no doubt that Peg-IFNα2b treatment plays an important role in the clinical cure of CHB, and it also significantly improves waist circumference, BMI, CAP, LDL and metabolic disorder of chronic hepatitis B combined with MASLD.



Disclosures: Baiguo Xu: Nothing to Disclose, Aili Fan: Nothing to Disclose, Jiawen Feng: Nothing to Disclose, Lei Liu: Nothing to Disclose, Jia Lian: Nothing to Disclose, Huiling Xiang: Nothing to Disclose, Qing Ye: Nothing to Disclose

1239 | MATHEMATICAL MODELING QUALITATIVELY RECAPITULATES HBV DNA AND HBV RNA RESPONSE UNDER NUCLEOS(T)IDE ANALOGUE OR NUCLEIC ACID POLYMERS MONOTHERAPY

Ashish Goyal[1] Scott Cotler[2] Yuji Ishida[3] Chise Tateno[3] Kazuaki Chayama[4] Alexander Ploss[5] Andrew Vaillant[6] Harel Dahari[1], [1]Loyola University Chicago, [2]Loyola University Health System, [3]PhoenixBio Co., Ltd., [4]Hiroshima Institute of Life Sciences, [5]Princeton University, [6]Replicor Inc.

Background: We (Hershkovich et al. Antiviral Res. 2025;234:106061) and others reported that while serum HBV DNA dramatically declined from pre-treatment levels in chronic HBV-infected patients treated with nucleos(t)ide analogue (NA), HBV RNA largely remained unchanged. In contrast, we observed a decline in both HBV DNA and HBV RNA during nucleic acid polymers (NAPs) monotherapy (Jansen et al. J Hepatology;2015(62):S250). Here, we aimed to develop a mathematical model that can explain the difference in these kinetic pictures. **Methods:** The modeling approach taken here was inspired by our previous work that successfully recapitulated HBV DNA kinetics during acute infection in humanized mice (Goyal et al. Hepatology;2023:78(S1):S530-S531). This previous model included accumulation of intracellular covalently closed circular DNA (cccDNA; accumulation up to 5 cccDNA per infected cell), production of encapsidated pregenomic RNA (pgRNA) from cccDNA in a saturated manner (i.e., Michaelis–Menten equation) and production of relaxed circular DNA (rcDNA) from pgRNA in a linear fashion. The model also included secretion of encapsidated

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pgRNA and rcDNA as serum HBV RNA and serum HBV DNA, respectively. We assumed that steady state serum HBV RNA levels are approximately ~2log lower than HBV DNA levels as was observed in patients treated with ETV (Fig. 1A) or NAPs (Fig. 1B). Treatment effects were further simulated by assuming that NAs block reverse transcriptase (RT) with 95% efficacy whereas NAPs block the secretion of both serum HBV RNA and HBV DNA with an efficacy of 95%. **Results:** Our model simulations qualitatively recapitulate HBV DNA and HBV RNA response under ETV monotherapy (Fig. 1A) by assuming that ETV mainly acts as a RT inhibitor which drives a steep serum HBV DNA decline. Moreover, serum HBV RNA remains unchanged due to slower conversion of pgRNA to rcDNA, which results in excess intracellular HBV RNA compared to HBV DNA. We assumed that NAPs block secretion of both HBV DNA and HBV RNA (in addition to subviral particles – to be included in more comprehensive models) from infected cells to explain in part the decline in both HBV DNA and HBV RNA under NAPs monotherapy treatment (Fig. 1B). **Conclusion:** Modeling results suggest that serum HBV RNA remains largely unchanged during treatment with NAs due to excess intracellular HBV RNA in comparison to intracellular HBV DNA.

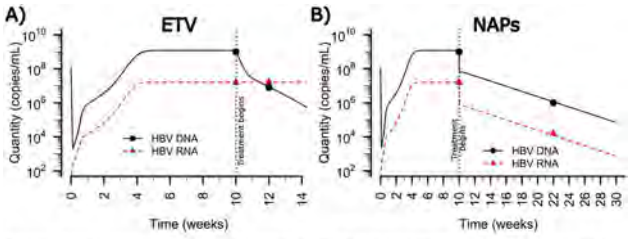

Figure 1: Model simulations (lines) of serum HBV DNA and HBV RNA during acute infection and post-treatment initiation indicated by vertical dotted lines. Modeling HBV kinetics during monotherapy with **(A)** entecavir (ETV) or **(B)** REP2139-Ca (NAP) treatment. Circles represent measured HBV DNA and HBV RNA data as reported by Jansen et al. J Hepatology;2015(62):S250.

Disclosures: Ashish Goyal: Nothing to Disclose, Scott Cotler: Nothing to Disclose, Yuji Ishida: Nothing to Disclose, Chise Tateno: Nothing to Disclose, Kazuaki Chayama: Nothing to Disclose, Alexander Ploss: Nothing to Disclose, Andrew Vaillant: Replicor Inc.: Employee, Replicor Inc.: Stock – privately held company, Harel Dahari: Nothing to Disclose

1240 | PEGINTERFERON ALPHA-2B AND NUCLEOS(T)IDE ANALOGS COMBINATION THERAPY FOR CHRONIC HEPATITIS B PATIENTS WITH HIGH HBSAG LEVEL AT THE END OF TREATMENT (52 WEEKS) FROM ONGOING CREATED EXCELLENT STUDY

Wenhua Zhang[1] Haitao Tang[1] Qinghua Lu[2] Haifang Cao[2] Tingxia Chao[1] Fengmei Wang[1] Wenling Jia[1] Chunhui Liang[1] Feng Ren[3] Hongfei Zhang[4], [1]Gansu Wuwei Tumour Hospital, Wuwei, China, [2]The 4th People's Hospital of Qinghai Province, Xining, China, [3]Beijing Youan Hospital, Capital Medical University, Beijing, China, [4]Jumei Doctor Group Medical (Shenzhen) Co., Ltd, Shenzhen, China

Background: Chronic hepatitis B (CHB) patients with HBV DNA 1500 IU/mL (Non-preferred population for clinical cure, NPPCC). **Methods:** The CREATED EXCELLENT study (ChiCTR2400081073) is a multicenter, prospective, positive-controlled study. CHB patients with NAs treated for ≥3 months and HBsAg >1500 IU/mL were enrolled and divided into two groups. The NAs monotherapy group continued to receive their original NAs (ETV/TDF/TAF/TMF) treatment, while the PegIFNα-2b+NAs group received PegIFNα-2b (180 μg/week) in addition to NAs. The total treatment period was 52 weeks, and all participants were followed up for 24 weeks after the end of treatment (EOT). **Results:** A total of 682 patients (NAs monotherapy group, n=330; PegIFNα-2b+NAs group, n=352) were included. At baseline, there were 170 patients with HBsAg between 1500 and 3000 IU/mL (NAs group: 21.81%, PegIFNα-2b +NAs group: 27.84%), 133 patients with HBsAg between 3000 and 6000 IU/mL (NAs group: 18.23%, PegIFNα-2b +NAs group: 20.68%), 90 patients with HBsAg between 6000 and 9000 IU/mL (NAs group: 12.11%, PegIFNα-2b +NAs group: 14.24%); and 289 patients with HBsAg greater than 9000 IU/mL (NAs group: 47.91%, PegIFNα-2b+NAs group: 37.23%). The baseline average HBsAg level in the NAs group was 18767.23 ± 5623.33 IU/mL and in the PegIFNα-2b+NAs group was 17346.91IU/mL ($P > 0.05$). After 52 weeks of treatment, the average HBsAg level of the NAs group was 16963.92 ± 5127.89 IU/mL and the PegIFNα-2b+NAs group was 3589.40 ± 1223.47 IU/mL($P <$ HBsAg < HBsAg < HBsAg **Conclusion:** Compared with NAs monotherapy, PegIFNα-2b combined with NAs therapy for the treatment of NPPCC (HBsAg >1500 IU/mL) rapidly reduced HBsAg levels, and increased the number of PPCC (HBsAg <1500 IU/mL), thereby providing a new treatment strategy for CHB patients with high-level HBsAg to achieve clinical cure.

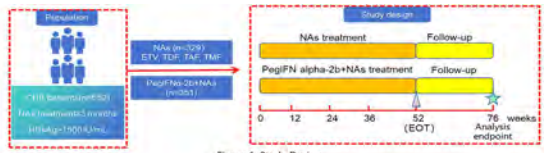

Figure 1. Study Design

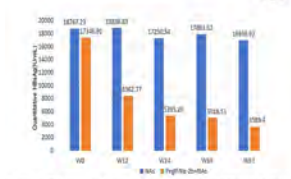

Figure 2.The average level of serum HBsAg at different times

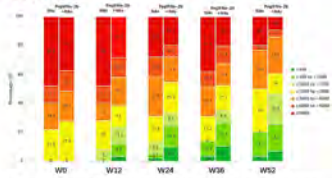

Figure 3. The stratification ratio of serum HBsAg in different times

Disclosures: Wenhua Zhang: Nothing to Disclose, Haitao Tang: Nothing to Disclose, Qinghua Lu: Nothing

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to Disclose, Haifang Cao: Nothing to Disclose, Tingxia Chao: Nothing to Disclose, Fengmei Wang: Nothing to Disclose, Wenling Jia: Nothing to Disclose, Chunhui Liang: Nothing to Disclose, Feng Ren: Nothing to Disclose, Hongfei Zhang: Nothing to Disclose

1241 | EFFECT OF FINITE DURATION PEGINTERFERON ALPHA-2B WITH OR WITHOUT NUCLEOS(T)IDE ANALOGUES ON LONG-TERM PROGNOSIS IN CHRONIC HEPATITIS B: PRELIMINARY 24-WEEK RESULTS: FROM THE MULTICENTER REAL-WORLD &LDQUO;VISION&RDQUO; STUDY IN CHINA

Qing-Lei Zeng[1] Hongyu Zhang[1] Yaqing Liu[2] Guoqiang Zhang[3] Haiyan Chen[4] Chuanwen Chen[5] Yuzhong Wang[6] Guifu Shi[7] Zujiang Yu[1] hongxia liang[1], [1]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China, [2]The First People's Hospital of Shangqiu, Shangqiu, Henan, China, [3]Luoyang Central Hospital, Luoyang, Henan, China, [4]Xinyang Central Hospital, Xinyang, Henan, China, [5]Shangcheng County People's Hospital, Xinyang, Henan, China, [6]The Fifth People's Hospital of Anyang, Anyang, Henan, China, [7]Zhumadian Central Hospital, Zhumadian, Henan, China

Background: Optimizing antiviral strategies and achieving a functional cure remain major challenges in the management of chronic hepatitis B (CHB). Loss of hepatitis B surface antigen (HBsAg) and achievement of a functional cure are associated with reduced risks of cirrhosis and hepatocellular carcinoma. This study aimed to evaluate the long-term effects of a finite duration of peginterferon alpha-2b (Peg-IFN α-2b) with or without nucleos(t)ide analogues (NAs) in patients with CHB (The Vision Study). **Methods:** This was a multicenter, prospective, observational real-world study. Eligible patients received either NA monotherapy or a combination of Peg-IFN α-2b (PegBing®) plus NA. All patients who completed treatment in accordance with Chinese CHB Guidelines were followed for at least five years to compare long-term outcomes between the two regimens. This analysis focuses on patients who had completed 24 weeks of treatment. **Results:** A total of 23 patients in the NA monotherapy group and 186 patients in the Peg-IFN α-2b + NA group were included. The mean ages were 40.2 ± 8.20 and 40.9 ± 9.70 years ($p = 0.7330$), and the proportion of males was similar between groups: 60.9% (14/23) vs. 60.8% (113/186) ($p = 0.991$). In the NA monotherapy group, 2, 14, 3, and 4 patients received entecavir (ETV), tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF), and tenofovir amibufenamide (TMF), respectively. In the Peg-IFN α-2b + NA group, 64, 56, 43, and 23 patients received Peg-IFN α-2b plus ETV, TAF, TDF, and TMF, respectively. At baseline, 39.1% (9/23) and 31.2% (58/186) of patients were HBeAg-positive ($p = 0.2451$). Mean levels of HBV DNA, HBsAg, and alanine aminotransferase (ALT) were 3.216 ± 2.066 vs. 3.264 ± 2.201 $\log_{10}$ IU/mL ($p = 0.9444$), 2.981 ± 1.101 vs. 2.743 ± 1.289 $\log_{10}$ IU/mL ($p = 0.3971$), and 27.92 ± 19.74 vs. 38.30 ± 42.04 U/L ($p = 0.2451$) in the NA and Peg-IFN α-2b + NA groups, respectively. After 24 weeks of treatment, HBeAg loss was observed in 0% (0/9) vs. 31.2% (15/58) of patients ($p = 0.193$). Mean HBV DNA, HBsAg, and ALT levels were 1.917 ± 0.725 vs. 1.829 ± 0.779 $\log_{10}$ IU/mL ($p = 0.7690$), 2.840 ± 1.270 vs. 2.032 ± 1.668 $\log_{10}$ IU/mL ($p = 0.0294$), and 26.74 ± 13.06 vs. 57.20 ± 44.99 U/L ($p = 0.0015$), respectively. Additionally, after 24 weeks of treatment, a >1 $\log_{10}$ IU/mL reduction in HBsAg levels was observed in 4.3% (1/23) of patients in the NA monotherapy group, compared to 30.1% (56/186) in the Peg-IFN α-2b + NA group ($p = 0.009$), and the HBsAg loss was achieved in 4.3% (1/23) vs. 6.5% (12/186) of patients ($p = 1.000$). The treatment was well tolerated, with no severe adverse events reported. **Conclusion:** These findings suggest that a HBsAg loss may be attainable with currently approved antiviral agents, even following a fixed 24-week treatment course, warranting further long-term investigation.

Disclosures: Qing-Lei Zeng: Nothing to Disclose, Hongyu Zhang: Nothing to Disclose, Yaqing Liu: Nothing to Disclose, Guoqiang Zhang: Nothing to Disclose, Haiyan Chen: Nothing to Disclose, Chuanwen Chen: Nothing to Disclose, Yuzhong Wang: Nothing to Disclose, Guifu Shi: Nothing to Disclose, Zujiang Yu: Nothing to Disclose, hongxia liang: Nothing to Disclose

1242 | MATHEMATICAL MODELING SUGGESTS THAT 2 MG/DAY BULEVIRTIDE MONOTHERAPY EFFICACY IS SUBOPTIMAL IN MOST HDV-INFECTED PATIENTS WITH COMPENSATED CIRRHOSIS AND CSPH

Adquate Mhlanga[1] Louis Shekhtman[1] Ori Wasserman[1] Ashish Goyal[1] Elisabetta Degasperi[2] Maria Paola Anolli[3] Sara Colonia Uceda Renteria[2] Dana Sambarino[2] Marta Borghi[2] Riccardo Perbellini[2] Floriana Facchetti[2] Annapaola Callegaro[2] Scott Cotler[1] Harel Dahari[1] Pietro Lampertico[4], [1]Loyola University Chicago, [2]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, [3]Department of Pathophysiology and Transplantation, University of Milan, [4]University of Milan

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Background: We recently identified HDV kinetic patterns in 18 patients with compensated cirrhosis and clinically significant portal hypertension (CSPH) treated with the entry inhibitor bulevirtide (BLV) for 48 weeks and found that a biphasic decline was most prevalent (JHEP Rep. 2023;6(2):100966). We aim to further characterize HDV, HBsAg and ALT kinetics under 96 weeks of BLV (2 mg/day) monotherapy in these patients and 20 additional patients to provide insights into HDV-host dynamics and evaluate BLV efficacy in blocking infection (η) via mathematical modeling. **Methods:** 38 patients were included. All patients received nucleos(t)ide analogues for HBV. Blood samples were collected at weeks 0, 4, 8, 16, 24, 32, 40, 48 and every 12 weeks thereafter. We developed a mathematical model that includes HDV-free and HDV-infected HBsAg-producing hepatocyte dynamics to explain observed HDV, ALT and HBsAg kinetics using a nonlinear mixed-effects approach. Kinetic patterns were characterized and the critical drug efficacy (CDE) was estimated for each patient, such that for $\eta >$ CDE, HDV is ultimately cleared (i.e., cure), while $\eta <$ CDE results in a new lower viral plateau or viral breakthrough. **Results:** 6 patients were non-responders (less than 1.6 log HDV decline from baseline). After an initial decline, the 32 responder patients exhibited 4 different kinetic patterns (Fig. 1): a flat partial response (Fig. 1A), where the viral kinetics reached a new lower plateau (FPR, n = 18); a biphasic response (Fig. 1B) with a second slower phase of HDV decline (BP, n = 2); a viral breakthrough (Fig. 1C) marked by a 1.6 log HDV kinetic increase from nadir (VB, n = 6); and a triphasic kinetic pattern (Fig. 1D) marked by a plateau or slight increase followed by a 2nd decline in viral kinetics reaching LLD (TP, n = 6). ALT normalization was reached in 29 patients (76%) at a mean 11.9 (95% CI: 5.9 – 17.9) weeks. HBsAg remained at pre-treatment levels (Fig. 1). The model reproduced the observed HDV, ALT and HBsAg kinetic patterns well in all responders (Fig. 1A, B and C), excluding the 6 TP patients (Fig. 1D). Modeling indicated that BLV inhibited infection of hepatocytes with overall efficacy 82% (95% CI: 65 – 92%) and estimated a HDV-infected cell $t_{1/2}$ of 6.93 (95% CI: 3.94 – 9.92) days. BLV efficacy (η) was $<$ CDE in 16 FPR and all VB cases. Modeling explained VB by an increase of susceptible cells (i.e., HDV-free hepatocytes), ALT normalization by a decline in HDV-infected cells, and stable HBsAg by an overall constant number of HBsAg-producing hepatocytes during treatment. **Conclusion:** The HDV FPR and VB observed in patients during 96 weeks of BLV is consistent with the modeling prediction that the efficacy of BLV 2 mg/day is $<$ CDE to achieve HDV cure in many patients with compensated cirrhosis and CSPH. Higher BLV doses or its combination with other anti-HDV drugs might potentially raise treatment efficacy to $>$ CDE to achieve cure. Explaining the HDV triphasic pattern requires further study.

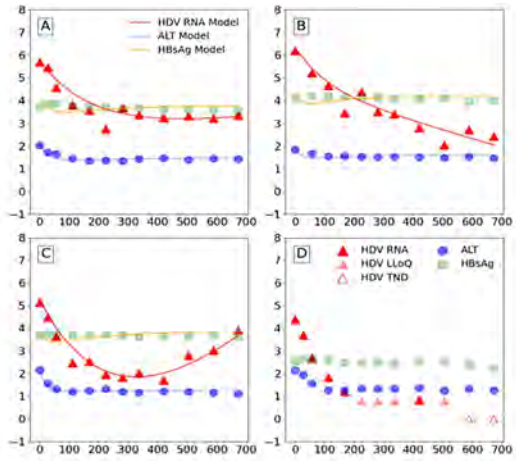

Figure 1. Measured kinetics (symbols) and modeling best curve fits (lines) in representative responder patients with a flat partial viral response (**A**), biphasic viral decline (**B**), viral breakthrough (**C**), and triphasic viral response (**D**). Estimated BLV efficacy in blocking infection (η) and death/loss of HDV-infected cells (δ) in A, B and C were (η = 90%, δ = 0.045 day^{-1}), (η = 96%, δ = 0.05 day^{-1}), and (η = 75%, δ = 0.08 day^{-1}), respectively. Modeling was not performed in triphasic (D). HDV RNA was measured using Robogene 2.0 (lower limit of detection, LLD = 6 IU/mL). ALT normalization was defined as 41 and 59 U/L for women and men, respectively.

Disclosures: Adquate Mhlanga: Nothing to Disclose, Louis Shekhtman: Nothing to Disclose, Ori Wasserman: Nothing to Disclose, Ashish Goyal: Nothing to Disclose, Elisabetta Degasperi: Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, IPSEN: Speaking and Teaching, Maria Paola Anolli: Nothing to Disclose, Sara Colonia Uceda Renteria: Nothing to Disclose, Dana Sambarino: Nothing to Disclose, Marta Borghi: Nothing to Disclose, Riccardo Perbellini: Nothing to Disclose, Floriana Facchetti: Nothing to Disclose, Annapaola Callegaro: Nothing to Disclose, Scott Cotler: Nothing to Disclose, Harel Dahari: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose

1243 | EFFICIENT HBV DNA INFECTION LAUNCH IN HEPATOCYTE CHIMERIC MICE IDENTIFIES ANTI-HBS NEUTRALIZING ANTIBODY RESISTANT VARIANTS

Yingpu Yu[1] Eleftherios Michailidis[2] Leon Seifert[1] Mengyin Zhang[1] Chenhui Zou[3] Catherine Freije[1] Georgios Dangas[2] Andreas Puschnik[4] Audrey Hanson[4] Evelyn Rocha[4] Xupeng Hong[5] Corrine Quirk[1] Yichen Zhou[3] Florian Lempp[4] Charles Rice[1] William Schneider[1] Ype de Jong[3], [1]Rockefeller University, [2]Emory University, [3]Weill Cornell Medicine, [4]Vir Biotechnology, [5]The Rockefeller University

Background: Efficiently initiating HBV infection in human hepatocyte chimeric mice from DNA has

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historically been challenging. We developed methods to launch HBV infection in chimeric huFNRG mice from recombinant (r)cccDNA. We here aimed to quantify the launch efficiencies and use the most efficient method for deep mutational scanning (DMS) of the HBsAg antigenic loop to identify anti-HBs antibody resistant variants. **Methods:** To quantitatively compare launch methods, we engineered the viral genome to contain silent mutant barcodes. We created DNA pools containing silent mutants that were spiked into wildtype (WT) DNA at 1:2 ratios ranging from 1:1000 to ~1:500,000. We measured the efficiency of various launch methods, including direct intrahepatic injection (IHI), by deep sequencing viral DNA from serum and quantifying the barcodes. We then synthesized a rcccDNA library containing >4000 codon variants within the antigenic loop open reading frame (ORF) to screen for resistance to a neutralizing antibody. **Results:** The IHI method was the most efficient method, launching 8,000 rcccDNA molecules in all mice tested and 64,000 in most mice. The antigenic loop DMS library, or WT control rcccDNA, was launched by IHI, and once viremia was established, huFNRG mice were injected with anti-HBs or control antibodies. In the presence of control antibody, many variants were enriched consistently between mice, illustrating that variants other than WT can spread more efficiently in the absence of an adaptive immune system. Treatment with anti-HBs suppressed WT viremia for the duration of the experiment, whereas viremia continued to rise in 3 out of 5 mice infected with the variant library. In animals with breakthrough viremia, many G145 variants could propagate in the presence of anti-HBs, with G145Q, G145S and G145R encoding variants being the most prevalent. Interestingly, 4 of 6 arginine codons were present, while the 2 arginine codons that create a stop codon in the overlapping polymerase ORF were not detected. These results highlight that the DMS library enables more efficient discovery of mutants compared to WT virus and illustrate restraints imposed by the overlapping ORFs. **Conclusion:** The IHI technique efficiently initiates HBV infection from thousands of rcccDNA molecules in parallel, enabling high-throughput characterization of HBV variant fitness and direct-acting antiviral resistance *in vivo*.

Disclosures: Yingpu Yu: Nothing to Disclose, Eleftherios Michailidis: Nothing to Disclose, Leon Seifert: Nothing to Disclose, Mengyin Zhang: Nothing to Disclose, Chenhui Zou: Nothing to Disclose, Catherine Freije: Nothing to Disclose, Georgios Dangas: Nothing to Disclose, Andreas Puschnik: Vir Biotechnology: Employee, Audrey Hanson: Nothing to Disclose, Evelyn Rocha: Nothing to Disclose, Xupeng Hong: Nothing to Disclose, Corrine Quirk: Nothing to Disclose, Yichen Zhou: Nothing to Disclose, Florian Lempp: Nothing to Disclose, Charles Rice: Nothing to Disclose, William Schneider: Nothing to Disclose, Ype de Jong: Pfizer: Consultant

1244 | IM-PROVE I: HBV GENOTYPE RESPONSIVENESS TO PEGYLATED INTERFERON ALFA-2A MAY BE ENHANCED WITH IMDUSIRAN COMBINATION TREATMENT

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Background: Functional cure of chronic hepatitis B (CHB) requires suppression of HBV replication, antigens and induction of anti-HBV immune responses. Imdusiran (IDR) is an *N*-Acetylgalactosamine–conjugated, pan-genotypic small interfering RNA that blocks all HBV RNA, resulting in suppression of viral replication and all antigens. IM-PROVE I is a Phase 2a study assessing combination treatment of IDR with pegylated interferon alfa-2a (IFN) in HBeAg-negative nucleots(t)ide analogue (NA) treated CHB subjects. After a 24-week (W) IDR-lead-in, subjects received 12 or 24W of IFN with or without additional IDR doses. HBV genotypes (GT) are known to influence response to IFN, with the greatest HBsAg declines in GT A and the lowest response for GT C in HBeAg-negative patients. The association of GT with HBsAg response during IFN treatment with IDR dosing and clinical outcomes for subjects in IM-PROVE I is presented. **Methods:** Baseline plasma samples from 43 subjects were used to determine HBV GT by ultra-deep sequencing or serology (IMMUNIS® HBV GT EIA by Institute of Immunology Co). Data on percentages of patients achieving HBsAg decline during IFN treatment (defined as HBsAg decrease from W28 through W40 for 12W IFN cohorts or W52 for 24W IFN cohorts), functional cure and NA discontinuation criteria (DC) are presented

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with respect to subjects with different HBV GTs. **Results:** The mean (SD) age across subjects was 45.3 (6.4) and 28% were female. The overall GT distribution across subjects was GT A 9.3%, GT B 32.6%, GT C 44.2%, GT D 11.6% and GT E 2.3%. 53.4% of subjects had baseline HBsAg <1000 IU/mL and 4.3% were GT A, 43.5% GT B, 30.4% GT C, 17.4% GT D and 4.3% GT E. During IFN treatment, 10 subjects experienced HBsAg declines: 10% were GT A, 50% GT B, and 30% GT C. Of the 10 IFN responsive subjects, 5 went on to achieve functional cure off all treatment following NA DC. Of these 5 subjects, 4 were GT B or C. 10 additional subjects met NA DC criteria for HBsAg response and achieved HBsAg <100 IU/mL: 40% were GT B, 40% GT D and 20% GT C; these subjects NA DC but did not achieve functional cure by end of study. **Conclusion:** In this limited dataset, the majority of subjects who achieved HBsAg response during IFN treatment with or following IDR dosing were GT B or C. These findings contrast with historical data from IFN therapy and suggest that IDR may enhance IFN responsiveness in CHB patients with specific HBV GTs. Further studies in larger cohorts are warranted to confirm these observations.

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1245 | SUSTAINED FUNCTIONAL CURE IN CHRONIC HEPATITIS B PATIENTS TREATED WITH PEGINTERFERON ALPHA-2B COMBINED WITH TDF: UPDATE RESULTS: OF 104 WEEKS EXTENDED FOLLOW-UP AFTER A PHASE 3 TRIAL

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Background: Although previous studies have shown good durability of HBsAg loss, the durability of functional cure remains to be investigated. We aimed to assess the long-term durability of functional cure in patients who achieved by peginterferon alpha-2b (PegIFNα-2b). **Methods:** Patients who achieved functional cure (maintain HBsAg loss and HBV DNA undetectable for 24 weeks follow-up after all drugs discontinuation) at the end of a phase 3 trial (NCT04846491) were enrolled in cohort 1 of this long-term follow-up study (NCT06707922) and observed for 5 years. In the preliminary phase 3 trial, nucleos(t)ide analogue (NA)-experienced patients were randomized to receive tenofovir disoproxil fumarate (TDF) monotherapy (group 1), TDF combined with PegIFNα-2b (Pegbing®, Xiamen Amoytop Biotech Co., Ltd.) 180 μg/week (group 2) or 90 μg/week (group 3); after 48 weeks of TDF treatment, patients in group 1 either continue TDF monotherapy (group 1a) or add PegIFNα-2b 180 μg/week (group 1b). Treatment-naïve patients were also included to receive TDF combined with PegIFNα-2b 180 μg/week (group 4). The treatment period was 144 weeks and the follow-up was 24 weeks. PegIFNα-2b were given intermittently in cycles. **Results:** A total of 88 patients who achieved functional cure were enrolled in cohort 1 of this follow-up study, including 32, 23, 29 and 4 patients from groups 2, 1b, 3 and 4 of the preliminary phase 3 trial, respectively, and no patients from group 1a. The mean age of NA-experienced patients in groups 2, 1b and 3 ranged from 36.1 to 41.5 years, with 58.6% to 82.6% being male. For treatment-naïve patients in group 4, the mean age was 30.5 years and 25% were male. By 104 weeks of follow-up, 90.6% (29/32), 87.0% (20/23), 89.7% (26/29) and 100% (4/4) of patients maintained functional cure in groups 2, 1b, 3 and 4, respectively (Figure 1). All patients who relapsed had HBsAg reversion while maintaining HBV DNA negativity. Only one patient in group 3 experienced HBV DNA reactivation (≥ 20 IU/mL) at 52 weeks of follow-up but returned undetectable by 104 weeks of follow-up. **Conclusion:** PegIFNα-2b combination therapy induced durable functional cure, with maintenance rates of approximately 90% in NA-experienced patients and 100% in treatment-naïve patients at 104 weeks of extended follow-up. Only one transient HBV DNA relapse was observed in the low-dose PegIFNα-2b group. PegIFNα-based therapy enables sustained functional cure and safe discontinuation of all drugs.

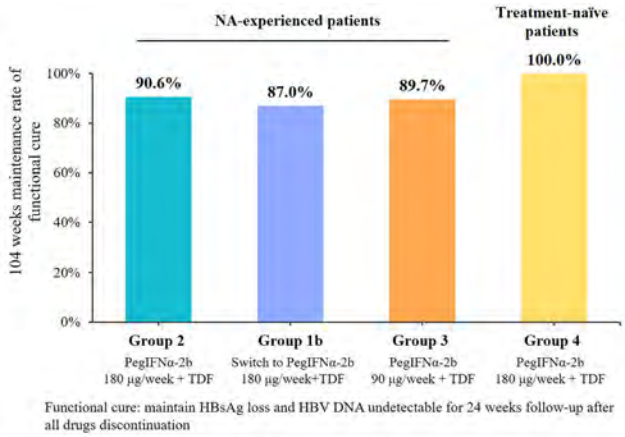

Figure 1. 104 weeks maintenance rate of functional cure in each group.

Disclosures: Fengqin Hou: Nothing to Disclose, Jia Shang: Nothing to Disclose, Qing Xie: Nothing to Disclose, Chunliang Lei: Nothing to Disclose, Jianmei Lin: Nothing to Disclose, Guoxin Hu: Nothing to Disclose, Zhiliang Gao: Nothing to Disclose, Yilan Zeng: Nothing to Disclose, Jiabin Li: Nothing to Disclose, Qianguo Mao: Nothing to Disclose, Liying Zhu: Nothing to Disclose, Jun Chen: Nothing to Disclose, Xiaozhong Wang: Nothing to Disclose, Zuxiong Huang: Nothing to Disclose, Jiming Zhang: Nothing to Disclose, Ping An: Nothing to Disclose, Xiulan Xue: Nothing to Disclose, Yan Huang: Nothing to Disclose, Tianyan Chen: Nothing to Disclose, Jianqi Lian: Nothing to Disclose, Yueyong Zhu: Nothing to Disclose, Huiling Xiang: Nothing to Disclose, Xinyue Chen: Nothing to Disclose, Hui Guo: Nothing to Disclose, Ruoyi He: Nothing to Disclose, Yalin Yin: Nothing to Disclose, Li Sun: Nothing to Disclose, Guiqiang Wang: Nothing to Disclose

1246 | EFFICACY AND SAFETY OF PEG-IFN-A-2B PLUS NUCLEOS(T) IDE ANALOG THERAPY IN PATIENTS WITH COMPENSATED HEPATITIS B VIRUS-RELATED CIRRHOSIS: RESULTS: FROM THE CHESS2306 COHORT

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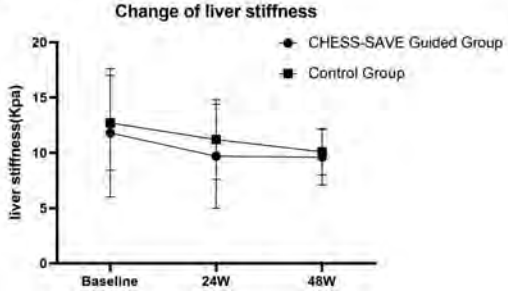
Background: Chronic hepatitis B (CHB) is a major public health concern, and patients with compensated cirrhosis are at risk for significant liver complications. Pegylated interferon alpha-2b (Peg-IFN-α-2b) combined with nucleos(t)ide analogs (NAs) has shown promise in enhancing antiviral efficacy and improving liver fibrosis. The CHESS-SAVE score is a noninvasive approach to assess decompensated event risk: (CHESS-SAVE score = 0.036*stiffness-0.152*albumin-0.011*platelets +1.177*[Varices: 0 if absent, 1 if present], where stiffness is in kPa, albumin in g/L, and platelets in$\times 10^5$/L. Score $<$-1.5 = low risk, <0 = medium risk, ≥ 0 = high risk). This study compared liver stiffness, virological response, and safety between patients (low/medium CHESS-SAVE risk) receiving Peg-IFN-α-2b + NAs vs. NAs alone. **Methods:** This prospective, non-randomized observational study included 201 patients in the CHESS-SAVE guided group (Peg-IFN-α-2b + NAs) and 238 patients in the control group (NAs alone). Patients were followed for 48 weeks, with liver stiffness assessed via transient elastography and adverse drug reactions monitored. **Results:** Baseline characteristics were comparable (Table 1). Liver stiffness in the CHESS-SAVE group decreased from 11.8 kPa to 9.7 kPa at week 24 (change: -2.1 kPa, $p < 0.05$), while the control group decreased from 12.7 kPa to 11.2 kPa (change: -1.5 kPa, $p < 0.05$). No significant difference in reduction between groups ($p > 0.05$, Figure 1). By week 48, CHESS-SAVE group stiffness decreased to 9.6 kPa (-2.2 kPa), and the control group to 10.1 kPa (-2.6 kPa), with no significant difference. HBsAg clearance occurred in 5 patients in the CHESS-SAVE group vs. 0 in the control group($p < 0.05$). HBV-DNA was fully suppressed in both groups. One patient in the treatment group withdrew due to mental symptoms. Adverse events: CHESS-SAVE group: 7 (3.5%) neutropenia, 1(0.5%) granulocytosis,30(14.9%) mild thrombocytopenia,4(2.0%)severe thrombocytopenia.21(10.4%)bilirubin increase $\leq$ 2ULN,1(0.5%) $>$ 2ULN. Control group:1(4.2%) neutropenia,20(8.4%) mild thrombocytopenia, 6(2.5%) severe thrombocytopenia.40 (16.8%)bilirubin increase $\leq$ 2ULN,7(2.9%) $>$ 2ULN.Neutropenia was significantly higher in the CHESS-SAVE group ($p < 0.05$), but other cytopenias showed no significant differences. Bilirubin elevation incidence was not higher in the CHESS-SAVE group. **Conclusion:** The addition of Peg-IFN-α-2b to NAs therapy demonstrated a higher HBsAg clearance rate, and liver stiffness can also be decreased after treatment. Serious adverse reactions were rare in patients with compensated hepatitis B virus-related cirrhosis whose CHESS-SAVE scores were low and medium risk.

Table 1. Baseline data

	CHESS-SAVE Guided Group (n=201)	Control (n=238)	P value
Age(yr)	50.9±16.8	50.5±10.9	>0.05
Male	165(82.1%)	177(74.4%)	>0.05
BMI(m^2/kg)	24.3(22.4, 26.4)	24.0(22.7, 25.8)	>0.05
HBsAg(IU/ml)	283.3(0.1, 13497.5)	680.0(0.1, 50000.0)	>0.05
HBeAg(+)	30(14.9%)	83(34.7%)	<0.01
HBV-DNA(IU/ml)	0(0,65.2)	0(0, 1947)	<0.05
WBC($\times 10^9$/L)	4.05±1.77	4.74±1.49	>0.05
NEUT($\times 10^9$/L)	2.95±1.43	2.74±1.09	>0.05
PLT($\times 10^9$/L)	141±53	135±61	>0.05
ALT(U/L)	32.0(21.9, 49.8)	37.0(24.0, 59.0)	>0.05
AST(U/L)	28.0(22.0, 36.9)	29.0(23.0, 41.8)	>0.05
ALB(g/L)	44.9±4.5	42.2±5.3	>0.05
TBil(μmol/L)	18.4±9.0	20.2±10.2	>0.05
PT(s)	13.0±8.4	13.1±10.2	>0.05
FBG(mmol/L)	5.3(4.7, 5.9)	5.1(4.7, 5.8)	>0.05
LDL	2.6±0.9	2.3±0.9	>0.05
Cr	68.9±12.6	65.6±14.3	>0.05
LSM	11.8±5.8	12.7±4.3	>0.05

BMI: body mass index; HBeAg: hepatitis B e antigen; WBC: white blood cell; NEUT: neutrophil; PLT: platelet; ALT: alanine transaminase; AST: aspartate transaminase; ALB: albumin; TBil: total bilirubin; PT: prothrombin time; FBG: fasting blood glucose; LDL: low density lipoprotein cholesterol; Cr: creatinine; LSM: liver stiffness measurement;

Figure 1



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1247 | HEPATITIS D SEROPOSITIVITY IS ASSOCIATED WITH HIGHER PREMATURE MORTALITY AMONG HEPATITIS B SURFACE ANTIGEN CARRIERS IN THE UNITED STATES: DATA FROM NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) 2011-2018

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Background: Hepatitis D virus (HDV), a satellite virus of hepatitis B virus (HBV), can be associated with a severe disease course. The outcomes of HDV patients in the U.S. is not well understood. We aimed to assess the clinical outcome of HDV positive subjects among adults with HBV using a nationally representative data from the U.S. **Methods:** We analyzed data from adults ($\geq$18 years) in NHANES 2011–2018, linked to the National Death Index through 2019. According to CDC, we defined current or past HBV infection as Anti-HBc Antibody positive (HBcAb-positive). We also considered HBsAg carriers as a separate group. HDV was determined by anti-HDV antibody assessed among HBsAg and Anti HBcAb positive individuals. Premature mortality was defined as death ($<$75/80 years for men/women). Age-standardized mortality rates (per 1,000 person-years [PY]) were calculated using the 2000 U.S. standard population. **Results:** Among 23,825 adults (mean age 46.8 years, 48.2% male, 64.2% non-Hispanic White, 11.5% non-Hispanic Black, 8.9% Mexican American, 6.4% other Hispanic, 5.6% Asian, 18.2% foreign-born), the prevalence of HBcAb-positive was 4.4% (95% CI: 3.92%-4.88%) while HBsAg carrier was 0.32% (95% CI: 0.25%–0.38%). Among those with positive Anti-HBc, 2.7% (95% CI: 1.67%-3.67%) were positive for anti-HDV. In multivariable logistic regression, HBsAg carrier state was associated with being Asian (OR: 10.44, 95% CI: 6.05–18.02), black (OR: 5.81, 95% CI: 3.23–10.47), foreign-born (OR: 4.68, 95% CI: 2.48–8.82), and those with a history of injection drug use (OR: 9.81, 95% CI: 3.18–30.24). Compared to HBsAg carriers without HDV, those with anti-HDV were more likely to be older ($\geq$65 years: 29.3% vs. 11.0%), female (56.9% vs. 40.0%), white (29.1% vs. 9.5%), and college degree (43.8% vs. 19.3%) ($p<0.05$). Over 736 PY of follow-up, age-standardized premature mortality rates for HBsAg carrier were 5.19 per 1,000 PY. Compared to HBsAg carriers without HDV, those with anti-HDV had significantly higher premature mortality rates (14.57vs. 2.89 per 1,000 PY, $p=0.04$). Repeating this analysis for HBcAb-positive with anti-HDV vs. without anti-HDV, indicated that premature mortality was 14.57 vs. 3.98 per 1000 PY ($p=0.172$). **Conclusion:** In the U.S., HDV co-infection is associated with higher premature mortality in HBsAg carriers. Identification of HDV infected individuals will be important to better manage these patients in clinical practice.

Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, James Paik: Nothing to Disclose, George Papatheodoridis: Abbvie: Advisor, Abbvie: Grant/Research Support, Abbvie: Speaking and Teaching, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Genesis: Advisor, Genesis: Speaking and Teaching, Gilead: Advisor, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GlaxoSmithKline: Advisor, Ipsen: Advisor, Ipsen: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Roche: Advisor, Roche: Speaking and Teaching, Takeda: Advisor, Albireo: Advisor, Amgen: Advisor, BioArs: Advisor, Elpen: Advisor, Janssen: Advisor, Merck Sharp & Dohme: Advisor, Vir Biotechnology: Advisor, Gilead: Grant/Research Support, Takeda: Grant/Research Support, Vianex: Grant/Research Support, Veronica Nguyen: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose, Rafael Esteban-Mur: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Zohal Zekrya: Nothing to Disclose, Linda Henry: Nothing to Disclose, Maria Buti: Nothing to Disclose

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1248 | DIFFERENTIATION OF HBV CAPSID ASSEMBLY MODULATORS BASED ON STABILIZATION OF CORE PROTEIN OLIGOMERIZATION AND RESIDENCE TIME

Cheng Liu[1] Yannick Debing[2] Dieudonné Buh Kum[1] Hannah Vanrusselt[2] Andreas Jekle[1] Hyunsoon Kang[1] Hua Tan[1] Qingling Zhang[1] Abel Acosta Sanchez[3] Pierre Raboisson[2] Julian Symons[1] Lawrence Blatt[1] Leonid Beigelman[1] David Smith[1] Sandrine Vendeville[2] Jerome Deval[1], [1]Aligos Therapeutics, [2]Aligos Belgium BV, [3]Novalix

Background: Despite the availability of vaccines against hepatitis B virus (HBV), no curative therapies are available for the estimated 300 million people worldwide who are chronically infected. Capsid assembly modulators (CAMs) are a promising new class of potential HBV antivirals. ALG-000184 is a prodrug of ALG-001075, a novel capsid assembly modulator leading to the formation of empty capsids (CAM-E). ALG-000184 has demonstrated best-in-class reductions of HBV DNA, RNA, HBsAg, HBeAg and HBcrAg in CHB patients. However, the lack of quantitative and predictive biochemical assays limits the characterization of novel and potent CAM-E compounds. Therefore, a novel jump dilution assay was designed to assess the capsid disassembly and the residence time of CAM compounds. **Methods:** Cellular antiviral activity was assessed in HepG2.117 and HepAD38 cells using intracellular HBV DNA as a readout. Cellular core immunostaining (spotting) assay, quenching assay, negative-staining electron microcopy and a thermal shift assay were used to measure and classify capsid assembly. Capsid disassembly and residence time of compounds were assessed in jump dilution assays. Compound pharmacokinetics were studied in AAV-HBV-transduced C57Bl/6 mice. **Results:** We determined that a subset of CAMs was able to trigger HBV core protein (Cp) oligomerization under denaturing conditions, leading to the hypothesis that CAMs might have heterogenous stabilizing effects on capsid assembly. We designed a novel jump dilution assay to measure the effect of CAMs on the intrinsic stability of pre-assembled capsids over time. While less potent first-generation CAMs did not significantly impede capsid disassembly, capsid stability increased up to 4 days with the most potent compounds, including ALG-001075, the parent of ALG-000184. We found that target residence time measured with the jump dilution assay correlated with cell-based antiviral potency for CAM-Es. In AAV-HBV mice expressing HBV Cp to high levels in the liver, CAMs with long residence times demonstrated excellent liver exposures. **Conclusion:** We developed a novel jump dilution assay to assess the biochemical potency/residence time of CAM compounds. Our results demonstrate that the stability of Cp oligomerization and target residence time are important parameters for the characterization of next-generation CAMs.

Disclosures: Cheng Liu: Aligos Therapeutics: Employee, Aligos Therapeutics: Stock - publicly traded company, Yannick Debing: Aligos Therapeutics, Inc.: Employee, Aligos Therapeutics, Inc.: Stock - publicly traded company, Dieudonné Buh Kum: Nothing to Disclose, Hannah Vanrusselt: Aligos Belgium: Employee, Andreas Jekle: Nothing to Disclose, Hyunsoon Kang: Nothing to Disclose, Hua Tan: Nothing to Disclose, Qingling Zhang: Nothing to Disclose, Abel Acosta Sanchez: Nothing to Disclose, Pierre Raboisson: Nothing to Disclose, Julian Symons: Nothing to Disclose, Lawrence Blatt: Nothing to Disclose, Leonid Beigelman: Nothing to Disclose, David Smith: Nothing to Disclose, Sandrine Vendeville: Nothing to Disclose, Jerome Deval: Nothing to Disclose

1249 | INFLUENCING FACTORS OF BONE MINERAL DENSITY DECLINE IN CHRONIC HEPATITIS B PATIENTS TREATED WITH TENOFOVIR AMIBUFENAMIDE OVER 5 YEARS

Zhihong Liu[1] Jinlin Hou[1] Junqi Niu[2] Min Zhang[3] Guicheng Wu[4] Lihua Sun[5] Daokun Yang[6] Lvfeng Yao[7] Yan Huang[8] Enqiang Chen[9] Yawen Luo[10] Shufang Yuan[11] Jia Shang[12] Xiaoqing Fu[13] Liang Chen[14] Peng Hu[15] Lihua Zhong[16] Fengmei Wang[17] Yao Xie[18] Xuebing Yan[19] Wenhong Zhang[20] Huazhong Chen[21] Minghua Su[22] Min Xie[23] Jidong Jia[24] Xiaorong Mao[25] Jie Li[26] Mingqin Lu[27] Qin Zhang[28] Qing Xie[29] Desheng Xie[30] Xingxiang Yang[31] Caiyan Zhao[32] Zhizhen Hu[33] Fanru Nie[33] Yan Huo[33], [1]Nanfang Hospital, Southern Medical University, [2]The First Hospital of Jilin University, [3]The Second Xiangya Hospital of Central South University, [4]Chongqing University Affiliated Three Gorges Hospital, [5]The First Affiliated Hospital of Xinjiang Medical University, [6]The First Affiliated Hospital Of Xinxiang Medical University, [7]Mengchao Hepatopiliary Hospital of Fujian Medical University, [8]Xiangya Hospital, Central South University, [9]West China Hospital, Sichuan University, [10]Affiliated Hospital of Zunyi Medical University, [11]Liuzhou People's Hospital, [12]Henan Provincial People's Hospital, [13]HangZhou XiXi hospital, [14]Shanghai Public Health Clinical Center, [15]The Second Affiliated Hospital of Chongqing Medical University, [16]The Fourth Affiliated Hospital of Harbin Medical University, [17]Tianjin Third Central Hospital, [18]Beijing Ditan Hospital Capital Medical University, [19]The Affiliated Hospital Of Xuzhou Medical University, [20]Huashan Hospital affiliated to Fudan University, [21]Taizhou Hospital Of Zhejiang Province, [22]The First Affiliated Hospital of Guangxi Medical University, [23]Guangzhou Eighth People's

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Background: Tenofovir amibufenamide (TMF) is widely utilized in the Chinese mainland for the treatment of chronic hepatitis B (CHB). In a phase III, double-blind, randomized controlled trial, TMF demonstrated non-inferior antiviral efficacy compared to tenofovir disoproxil fumarate (TDF), along with superior bone and renal safety profiles. Subsequent phase IV extension studies further revealed sustained therapeutic benefits over five years. This study aimed to evaluate the impact of 5-year treatment on bone mineral density (BMD) and to identify potential risk factors associated with BMD decline. **Methods:** All participants continued to receive oral TMF (25 mg, daily), including those who had previously switched from two years of TDF treatment during the phase III study. BMD at the lumbar spine (L1-L4), as assessed by dual energy X-ray absorptiometry, was analyzed over five years of treatment ([144+] 96 weeks). The Z-score (adjusted by age, sex and race) has been adopted in BMD evaluation as it can reflect non-physiological and non-age-related bone loss. BMD decline was defined as a decrease in Z-score of $\geq$ 0.5 from baseline at week (144+) 96. Odds ratio (OR) was calculated by multivariate logistic regression. **Results:** At week (144+) 96, 584 patients had available BMD data, and 315 (53.9%) patients showed an increase in lumbar spine Z-score. Although BMD in the TDF group was significantly lower than in the TMF group at week 96, this reduction in BMD associated with TDF treatment had recovered after switching to TMF treatment up to week (144+) 96. BMD decline was observed in 114 (19.5%) patients, including 75 (12.8%), 35 (6.0%), and 4 (0.7%) with decrease in Z-score of 0.5-1, 1-2 and $\geq$2, respectively. The distribution in decrease levels of Z-score was comparable in TMF group and TDF-to-TMF group. Notably, baseline HBV DNA $\geq$8 log10 IU/mL was found to be an independent risk factor for BMD decline (OR = 1.850, 95% CI: 1.103-3.103, p = 0.020). The following were also risk factors: serum calcium (OR = 46.133, 95% CI: 4.246-501.265, p = 0.002), parathyroid hormone (OR = 1.010, 95% CI: 1.002-1.018, p = 0.014), C-terminal telopeptide of type 1 collagen (OR = 5.103, 95% CI:1.319-19.735, p = 0.018) and baseline Z-score (OR = 1.575, 95% CI: 1.249-1.986, p < 0.001). **Conclusion:** After five years of treatment, half of the patients had an increased BMD Z score and the other decreases may be related to risk factors such as baseline high viral load and high serum calcium.

Disclosures: Zhihong Liu: Nothing to Disclose, Jinlin Hou: Nothing to Disclose, Junqi Niu: Nothing to Disclose, Min Zhang: Nothing to Disclose, Guicheng Wu: Nothing to Disclose, Lihua Sun: Nothing to Disclose, Daokun Yang: Nothing to Disclose, Lvfeng Yao: Nothing to Disclose, Yan Huang: Nothing to Disclose, Enqiang Chen: Nothing to Disclose, Yawen Luo: Nothing to Disclose, Shufang Yuan: Nothing to Disclose, Jia Shang: Nothing to Disclose, Xiaoqing Fu: Nothing to Disclose, Liang Chen: Nothing to Disclose, Peng Hu: Nothing to Disclose, Lihua Zhong: Nothing to Disclose, Fengmei Wang: Nothing to Disclose, Yao Xie: Nothing to Disclose, Xuebing Yan: Nothing to Disclose, Wenhong Zhang: Nothing to Disclose, Huazhong Chen: Nothing to Disclose, Minghua Su: Nothing to Disclose, Min Xie: Nothing to Disclose, Jidong Jia: Nothing to Disclose, Xiaorong Mao: Nothing to Disclose, Jie Li: Nothing to Disclose, Mingqin Lu: Nothing to Disclose, Qin Zhang: Nothing to Disclose, Qing Xie: Nothing to Disclose, Desheng Xie: Nothing to Disclose, Xingxiang Yang: Nothing to Disclose, Caiyan Zhao: Nothing to Disclose, Zhizhen Hu: Nothing to Disclose, Fanru Nie: Nothing to Disclose, Yan Huo: Nothing to Disclose

1250 | CHANGES OF ALBUMIN FUNCTION IN HBV-RELATED LIVER DISEASES

Mengqi Li[1] Wenyu Li[2] Qi Wang[1] Hong Zhao[1] Yidi Ge[1] Jingjing Wang[1] Haijun Yang[2] Wen Xie[1], [1]Center of Liver Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China, [2]Department of Chemistry, Tsinghua University, Beijing, China

Background: Hepatitis B virus (HBV) infection is a major global public health challenge that can lead to liver fibrosis, cirrhosis, and hepatocellular carcinoma. In cirrhotic patients, not only are albumin levels decreased, but its functionality may also undergo significant changes. Currently, there is no universally accepted method for testing albumin function. Electron paramagnetic resonance (EPR) technology has gained widespread attention for its ability to assess albumin binding capacity in various diseases. However, the application of EPR technology in HBV-related diseases remains limited, particularly in the Chinese population. Therefore, this study aims to investigate the changes in albumin function at different disease stages and the relationship between albumin function and clinical indicators in HBV-related liver diseases. **Methods:** This study utilized EPR technology with 16-doxyl stearic acid (16-DSA) as a spin probe to test plasma samples from age- and gender-matched healthy controls, chronic

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hepatitis B patients, HBV-related cirrhosis patients, and hepatocellular carcinoma patients. The results were analyzed using both spectral fitting and direct measurement methods. **Results:** This study tested 120 plasma samples from four age- and gender-matched groups: 30 healthy controls, 30 chronic hepatitis B patients, 30 hepatitis B-related cirrhosis patients, and 30 hepatocellular carcinoma patients. The results showed a significant reduction in albumin binding function in the HBV-related cirrhosis and hepatocellular carcinoma groups, particularly in the Child-Pugh C group (Figure 1). Additionally, a significant positive correlation was confirmed between the h_{-1}/h_0 ratio obtained through direct measurement and the proportion of free components derived from spectral fitting, supporting h_{-1}/h_0 ratio potential as a simple and reliable alternative indicator for assessing albumin function. The h_{-1}/h_0 ratio also correlated with several clinical indicators reflecting liver function, coagulation function, and inflammation, suggesting its potential value in evaluating disease severity. **Conclusion:** This study found a significant decline in albumin binding function in the HBV-related cirrhosis and hepatocellular carcinoma groups and confirmed that the h_{-1}/h_0 ratio effectively reflects albumin's binding ability, potentially serving as an important supplementary indicator for clinical evaluation.

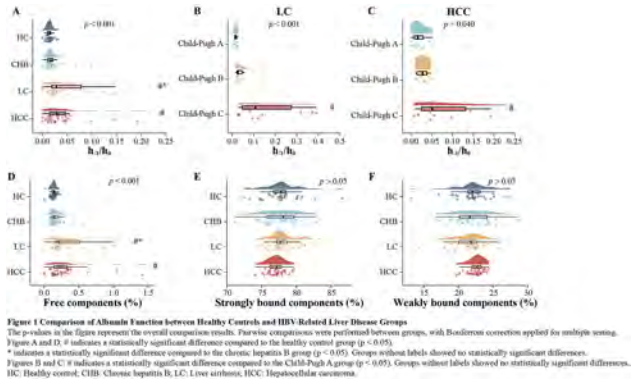

Figure 1 Comparison of Albumin Function between Healthy Controls and HBV-Related Liver Disease Groups
The p-values in the figure represent the overall comparison results. Pairwise comparisons were performed between groups, with Bonferroni correction applied for multiple testing.
Figure A and D: # indicates a statistically significant difference compared to the healthy control group ($p < 0.05$).
* indicates a statistically significant difference compared to the chronic hepatitis B group ($p < 0.05$). Groups without labels showed no statistically significant differences.
Figures B and C: # indicates a statistically significant difference compared to the Child-Pugh A group ($p < 0.05$). Groups without labels showed no statistically significant differences.
HC: Healthy control; CHB: Chronic hepatitis B; LC: Liver cirrhosis; HCC: Hepatocellular carcinoma.

Disclosures: Mengqi Li: Nothing to Disclose, Wenyu Li: Nothing to Disclose, Qi Wang: Nothing to Disclose, Hong Zhao: Nothing to Disclose, Yidi Ge: Nothing to Disclose, Jingjing Wang: Nothing to Disclose, Haijun Yang: Nothing to Disclose, Wen Xie: Nothing to Disclose

1251 | CAPSID ASSEMBLY MODULATOR ALG-001075 PREVENTS CCCDNA FORMATION AND HBV DNA INTEGRATION IN VITRO

Jordi Verheyen[1] Hannah Vanrusselt[1] Tse-I Lin[1] Zhili Wang[2] Selena Lin[2] Ying-Hsiu Su[2] Stéphane Plaisance[3] Jin Hong[4] Julian Symons[5] Lawrence Blatt[4] Andreas Jekle[4] Yannick Debing[1], [1]Aligos Belgium BV, [2]JBS Science, [3]VIB Nucleomics Core, [4]Aligos Therapeutics, Inc., [5]Aligos Therapeutics

Background: The hepatitis B virus (HBV) capsid assembly process has emerged as a key target for the treatment of chronic hepatitis B (CHB). ALG-000184 is a prodrug of ALG-001075, a novel capsid assembly modulator leading to the formation of empty capsids (CAM-E). ALG-000184 has demonstrated best-in-class reductions of HBV DNA, RNA, HBsAg, HBeAg and HBcrAg in CHB patients. Here, we investigated the effects of ALG-001075 on HBV cccDNA formation and HBV DNA integration in vitro. **Methods:** HBV cccDNA was quantified in HBV-infected HepG2-NTCP cells using Southern blot and digital PCR (dPCR). Production of double-stranded linear DNA (dslDNA), which can lead to HBV DNA integration, and relaxed circular DNA (rcDNA) from HBV-expressing HepG2.117 cells was investigated using Southern blot and PNA clamp-based qPCR. The level of HBV DNA integration after HBV infection of HepG2-NTCP cells was quantified using genomic DNA isolation, HBV sequence enrichment, next-generation sequencing and subsequent identification of HBV-host junctions. **Results:** ALG-001075 substantially reduced cccDNA formation when added together with the viral inoculum in a dose-dependent fashion, as confirmed by Southern blot, dPCR and antigen quantification, through its secondary mechanism of action. This was not the case for nucleos(t)ide analogs entecavir and tenofovir. ALG-001075 also potently and dose-dependently inhibited production of both rcDNA and dslDNA through its primary mechanism, thereby reducing the precursor pool available for HBV DNA integration. Direct quantification of HBV DNA integrations in HBV-infected cells over a relatively short period of time (14 days) showed pronounced reductions in the number of detected host-viral junctions, with superior reductions observed for ALG-001075 compared to nucleos(t)ide analogs. **Conclusion:** ALG-001075 demonstrated potent prevention of HBV cccDNA formation and HBV DNA integration, further confirming its best-in-class properties and superiority over commonly used nucleos(t)ide analogs.

Disclosures: Jordi Verheyen: Aligos Therapeutics: Employee, Hannah Vanrusselt: Aligos Belgium: Employee, Tse-I Lin: Nothing to Disclose, Zhili Wang: Nothing to Disclose, Selena Lin: Nothing to Disclose, Ying-Hsiu Su: Nothing to Disclose, Stéphane Plaisance: Nothing to Disclose, Jin Hong: Nothing to Disclose, Julian Symons: Nothing to Disclose, Lawrence Blatt: Nothing to Disclose, Andreas Jekle: Nothing to Disclose, Yannick Debing: Aligos Therapeutics, Inc.: Employee, Aligos Therapeutics, Inc.: Stock - publicly traded company

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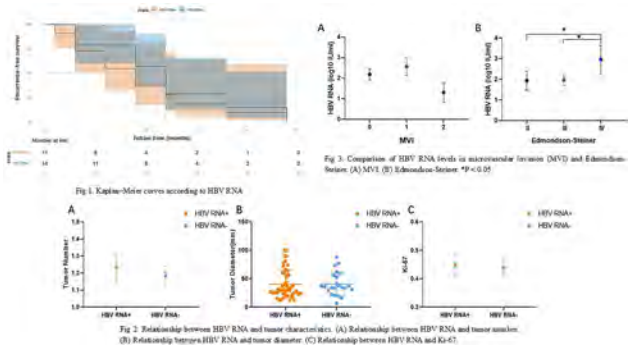
1252 | SIGNIFICANCE OF HBV RNA IN PATIENTS WITH HEPATITIS B HEPATOCELLULAR CARCINOMA

Ning Lin[1] Guangming Li[2] Zhan Zeng[3] Yifan Han[4] Huiying Rao[5] Gongming Zhang[2] yanyan yu[1] Xiaoyuan Xu[4], [1]Department of Infectious Diseases, Peking University First Hospital, Beijing, China, [2]Department of General Surgery Center, Beijing Youan Hospital, Capital Medical University, China, [3]Department of Infectious Diseases, Peking University First Hospital, Beijing, China, [4]Department of Gastroenterology, Peking University First Hospital, Beijing, China, [5]Peking University People's Hospital, Peking University Hepatology Institute, Beijing, China

Background: According to the Chinese expert consensus, serum hepatitis B virus (HBV) RNA levels can reflect hepatic cccDNA transcriptional activity and correlate with patients' virological response and prognosis. HBV RNA is recommended to be used for clinical testing. However, the significance of HBV RNA in patients with HBV-related hepatocellular carcinoma (HCC) is not clear. In this study, we investigated the significance of HBV RNA levels in tumor development and recurrence in HBV-related HCC patients. **Methods:** HBV- related HCC patients who underwent hepatectomy were retrospectively enrolled from June 2020 to April 2023 in Beijing Youan Hospital (LL-2024-127-K). Detection of HBV RNA in serum was defined as positive. Patients were divided into HBV RNA positive and negative groups. Patients' gender, age, antiviral treatment, preoperative serologic and virologic markers, and tumor characteristics were collected. The observation endpoint was 2-year recurrence after hepatectomy in patients with hepatocellular carcinoma. Kaplan–Meier curves was used to analyze the relationship between HBV RNA and recurrence. Statistical significance was set at $p < 0.05$. **Results:** The study included 80 patients with HBV- related HCC. The mean age was 55.8 years old and 38.7% patients was HBV RNA positive. In HBV RNA-positive patients, the recurrence rate at 24 months was 42.3% and the median recurrence-free survival (RFS) time was 9 months. In HBV RNA-negative patients, the recurrence rate at 24 months was 42.1% and the median RFS time was 12 months. 25.0% HBV-positive patients have multiple tumors, more than HBV-negative patients. No significant difference in tumor diameter and Ki-67 between HBV RNA-positive and negative patients. Patients with microvascular invasion (MVI) 1 and with Edmondson-Steiner IV (II vs IV,III vs IV,P **Conclusion:** HBV- related HCC patients with HBV RNA positive are prone to multiple tumors and faster recurrence. Patients with microvascular invasion and poorly differentiated tumors have higher HBV RNA levels. HBV RNA monitoring is relevant in tumorigenesis and recurrence in patients with HCC to some extent.



Disclosures: Ning Lin: Nothing to Disclose, Guangming Li: Nothing to Disclose, Zhan Zeng: Nothing to Disclose, Yifan Han: Nothing to Disclose, Huiying Rao: Nothing to Disclose, Gongming Zhang: Nothing to Disclose, yanyan yu: Nothing to Disclose, Xiaoyuan Xu: Nothing to Disclose

1253 | HEPATITIS B VACCINATION AWARENESS AND IMMUNITY IN THE UNITED STATES: GAPS BETWEEN PERCEPTION AND PROTECTION

Giovanni Roldan[1] Prowpanga Udompap[2] Jesse Fletcher[1] Timothy Davie[1], [1]University of Minnesota, [2]Minneapolis VA Medical Center

Background: Hepatitis B virus (HBV) remains a public health concern and HBV vaccination is fundamental to the WHO's HBV elimination targets. However, population awareness of immune protection and adherence to vaccination remain poorly characterized. We aimed to evaluate self-reported HBV vaccination status and discordance with serologic immunity in a nationally representative U.S. sample. **Methods:** We analyzed adults aged $\geq$20 years from NHANES 2017–2020 with available HBV vaccination history and serologic data on HBV surface antibody (HBsAb), core antibody (HBcAb), and surface antigen (HBsAg). Serologic immunity was defined as HBsAb-positive with HBcAb-negative and HBsAg-negative. Self-reported vaccination status was classified as complete, partial, unvaccinated, or unknown. Discordance was defined as a mismatch between reported vaccination and serologic immunity. National estimates were calculated using survey weights. **Results:** Among 216.9 million U.S. adults (mean age 48.0 years, 52.2% female, 64.5% non-Hispanic White), 66.1 million reported complete vaccination (30.5%), yet only 48.1% of those demonstrated serologic immunity. Conversely, 10.2% of the 112.3 million adults who denied HBV vaccination were immune, approximately 11.5 million people. Discordance affected 45.8 million people (21.1%). Rates were

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highest among adults aged 20–39 (32.4%, 95% CI: 29.3–35.6%), followed by 40–59 (18.5%) and ≥60 years (9.8%). Asian adults had the highest discordance (25.8%, 95% CI: 22.5–29.2%), while multi-racial individuals had the lowest (15.9%, 95% CI: 11.8–20.2%), the only statistically significant difference across racial groups. Although point estimates suggested higher discordance among adults below the poverty line (25.1%) compared to those with high income (20.0%), and among U.S.-born (21.6%) versus foreign-born individuals (19.0%), these differences were not statistically significant. Importantly, regardless of etiology, only 23.7% of adults with liver stiffness ≥15 kPa and 10.8% of those with FIB-4 > 2.67 reported complete HBV vaccination, with serologic immunity similarly low at 13.8% and 12.8%, respectively **Conclusion:** In this nationally representative cohort, over half of the adults who reported complete HBV vaccination lacked serologic immunity, while 1 in 10 unvaccinated adults were unknowingly HBV protected. Discordance between perceived vaccination and actual immunity affected over one in five adults, with the highest rates observed among younger adults and Asian populations. These gaps in awareness and protection highlight critical opportunities for targeted education, catch-up vaccination, and targeted outreach in national HBV elimination efforts.

Variable	N	Immune N = 55,001,131[1]	Not Immune N = 161,888,620[1]	p-value[2]
Age, years	216,889,750	39 (14)	51 (17)	
Sex	216,889,750			0.004
Male		23,235,218 (22%)	80,537,628 (78%)	
Female		31,765,912 (28%)	81,350,992 (72%)	
Race/ethnicity	216,889,750			<0.001
Mexican American		4,237,971 (22%)	14,703,015 (78%)	
Non-Hispanic Asian		4,010,526 (38%)	6,485,856 (62%)	
Non-Hispanic Black		6,275,814 (28%)	16,126,332 (72%)	
Non-Hispanic White		34,043,090 (24%)	105,799,207 (76%)	
Other Hispanic		4,064,266 (25%)	12,414,243 (75%)	
Other/Multi-Racial		2,369,464 (27%)	6,359,967 (73%)	
Foreign-born	216,889,750			0.6
Foreigner		9,632,396 (25%)	29,396,956 (75%)	
U.S. Born		45,368,735 (26%)	132,491,663 (74%)	
Household income group	192,840,206			0.5
<1 (Below poverty)		5,673,116 (25%)	17,380,093 (75%)	
≥4 (High income)		21,302,563 (27%)	57,041,471 (73%)	
1–1.99 (Low income)		8,904,989 (25%)	26,850,945 (75%)	
2–3.99 (Middle income)		13,415,463 (24%)	42,271,566 (76%)	

Disclosures: Giovanni Roldan: Nothing to Disclose, Prowpanga Udompap: Nothing to Disclose, Jesse Fletcher: Nothing to Disclose, Timothy Davie: Nothing to Disclose

1254 | REAL-WORLD TREATMENT RATES WITH NUCLEOS(T)IDE ANALOGS (NA) IN PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC) AND HEPATITIS B VIRUS (HBV) INFECTION: A POPULATION-BASED U.S. STUDY

Taotao Yan[1] Sally Tran[1] Guillermo Daniel Molina[1] Xinrong Zhang[1] Tyler Wong[1] Ramsey Cheung[1] Mindie Nguyen[1], [1]Stanford University Medical Center

Background: NA therapy is a key strategy for preventing the development of HCC in patients with chronic HBV infection. NA treatment is also associated with reduced recurrence rates and improved overall survival in HBV patients with established HCC (HBV-HCC). However, unlike HBsAg+ patients with cirrhosis which by itself a criteria for antiviral treatment independent on HBV DNA or liver enzyme levels, HCC by itself is not a criteria for antiviral treatment in most major guidelines leading to undertreatment. We aimed to quantify NA treatment rate among HBV-HCC to identify potential factors associated with no treatment. **Methods:** We conducted a study of adult patients with HCC using the Truven Health MarketScan Research Database, a database comprised of approximately 250 million U.S. residents with private health insurance (2007-2022). The primary outcome was the proportion of HBV-HCC patients who received NA treatment at any time. **Results:** We analyzed 3208 HBV-HCC patients (mean age 58 years, 81.2% male, and 68.7% cirrhosis, 69.8% with at least one gastroenterology or infectious disease [GI/ID] specialty visit, and 69.8% with receipt of HCC therapy). Only one-third (34.5%) of patients received NA in total (21.4% initiating treatment prior to HCC diagnosis, 8.9% at the time of HCC diagnosis, and 4.2% after diagnosis). NA treatment rate has increased from about 30% in 2013 or earlier to 53.1% in 2017 then remained at about 50% thereafter (Figure 1). NA treatment rates were significantly lower in females (30.5 vs. 35.5%, $P = 0.02$), patients aged >60 years (28.6 vs. 39.2%, $P < 0.001$), and those with compensated or decompensated cirrhosis compare to noncirrhosis (36.0 vs. 22.5 vs. 45.5%, $P < 0.001$). Patients without NA treatment were more likely to have preferred provider organization (PPO) insurance, a history of alcohol use, or viral hepatitis C co-infection. Patients who had GI/ID specialty visit after HCC diagnosis were more likely to receive NA treatment compared to those who had specialty visit prior to HCC diagnosis or no specialty visit at any time (40.3 vs. 34.6 vs. 30.2%, $P < 0.001$). **Conclusion:** The rate of antiviral treatment in patients with HBV-HCC was markedly suboptimal even among this cohort of HCC patients with

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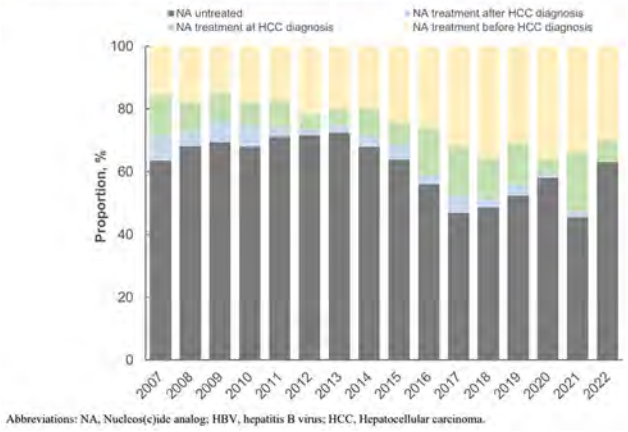
private health insurance in the U.S., with only about 30% receiving NA therapy overall and 50% in the more recent era 2015 and after. As effective and well tolerated NAs are now available in low cost generics, much more efforts are needed to increase patient and provider awareness of the potential benefits of NA which may help increase treatment rates and improve patient survival. Inclusion of HCC as an antiviral treatment criteria would also help increase treatment rates.

Figure 1. Temporal trends in the receipt of NA treatment among patients with HBV-related HCC.



Abbreviations: NA, Nucleos(t)ide analog; HBV, hepatitis B virus; HCC, Hepatocellular carcinoma.

Disclosures: Taotao Yan: Nothing to Disclose, Sally Tran: Nothing to Disclose, Guillermo Daniel Molina: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Tyler Wong: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

1255 | INCIDENCE AND DETERMINANTS OF ACHIEVING HBSAG < 100 IU/ML IN HBEAG-NEGATIVE CHB PATIENTS WITH NUCLEOS(T)IDE ANALOGUE TREATMENT

Jian Wang[1] Chao Wu[1] Rui Huang[1], [1]Nanjing Drum Tower Hospital

Background: Hepatitis B serum antigen (HBsAg) < 100 IU/mL is a key criterion of partial cure and an important threshold of stopping nucleos(t)ide analogues (NAs) therapy with a finite therapeutic strategy for chronic hepatitis B (CHB). We aimed to investigate the incidence and associated factors of achieving HBsAg < 100 IU/mL in hepatitis B e antigen (HBeAg)-negative CHB patients with NAs treatment. **Methods:** This study retrospectively included 996 HBeAg-negative CHB patients who received first-line NAs treatment with baseline HBsAg levels > 100 IU/mL from five sites in China. The cumulative incidence of achieving HBsAg < 100 IU/mL was evaluated using Kaplan-Meier and the associated factors was identified by the Cox regression analysis. **Results:** A total of 69 patients (6.9%) achieved HBsAg < 100 IU/mL during a median follow-up of 28.8 months. The 5-year cumulative incidence of HBsAg < 100 IU/mL was 13.97% (95%CI: 10.42%-17.38%). Among these, 94.2% (65/69) of the patients who achieved HBsAg < 100 IU/mL also had undetectable HBV DNA, representing a 5-year incidence of 13.15% (95% CI: 9.66-16.50%). Baseline HBsAg < 3 Log_{10}IU/mL (HR = 19.66, 95% CI: 8.84-43.71; P < 0.001) and HBV DNA < 4 Log_{10}IU/mL (HR = 2.47, 95% CI: 1.48-4.13; P = 0.001) were independently associated with a significantly higher likelihood of achieving HBsAg < 100 IU/mL. Patients with both baseline HBsAg < 3 Log_{10}IU/mL and HBV DNA < 4 Log_{10}IU/mL exhibited a 5-year incidence of HBsAg < 100 IU/mL of 58.73%, compared to 3.91% in those with HBsAg ≥ 3 Log_{10}IU/mL and HBV DNA ≥ 4 Log_{10}IU/mL. **Conclusion:** Few HBeAg-negative CHB patients achieved HBsAg < 100 IU/mL with first-line NAs therapy. The combination of baseline HBsAg and HBV DNA levels enables identification of patients with higher probability of achieving HBsAg < 100 IU/mL during NAs treatment and may benefit from a finite-duration therapeutic strategy.

Disclosures: Jian Wang: Nothing to Disclose, Chao Wu: Nothing to Disclose, Rui Huang: Nothing to Disclose

1256 | CONCOMITANT MASLD INCREASES HBSAG SEROCLEARANCE IN CHRONIC HEPATITIS B PATIENTS ON ANTIVIRAL THERAPY

Yan Dai[1] Ke Jin[1] Xinhe Sun[2] Jun Li[1], [1]First Affiliated Hospital of Nanjing Medical University, [2]Xiamen Amoytop Biotech Co., Ltd.

Background: The impact of metabolic dysfunction-associated steatotic liver disease (MASLD) comorbidity on the cure rate of chronic hepatitis B (CHB) remains unclear. This study aimed to investigate the effect of MASLD on the therapeutic outcomes of CHB. **Methods:** A total of 262 CHB patients without significant liver fibrosis receiving nucleos(t)ide analogues (NAs) and/or pegylated interferon alpha (PEG-IFNα) antiviral therapy were enrolled. They were divided into a CHB+MASLD group (n = 152) and a CHB group (n = 110). The impact of MASLD on antiviral response in CHB patients was evaluated by comparing the HBsAg seroclearance rates, using Kaplan-Meier survival analysis and logistic regression analysis between the two groups. **Results:** Compared to the CHB group, the CHB+MASLD group demonstrated a significantly increased HBsAg seroclearance rate (21.7% vs 10.9%, P = 0.03). The median time to HBsAg seroclearance was 41.1 (34.0 - 48.0) weeks in the CHB group and 29.6 (26.4 - 48.8) weeks in the CHB+MASLD group. Although seroclearance time was shorter in the CHB+MASLD group, the

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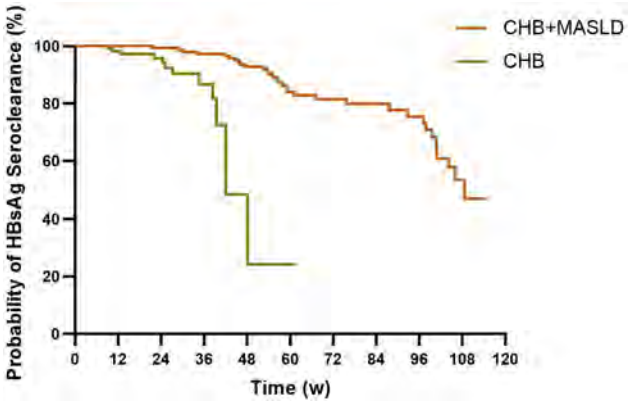
difference was not statistically significant (P = 0.39). Within the CHB+MASLD group, patients with baseline HBsAg levels ≤100 IU/ml achieved seroclearance at a significantly higher rate than those with levels >100 IU/ml (41.1% vs. 12.3%, P < 0.001). The CHB+MASLD group also exhibited a higher HBsAb seroconversion rate compared to the CHB group (7.2% vs. 3.6%), although this difference lacked statistical significance (P = 0.28), which might be attributed to the small number of cases. Kaplan-Meier survival analysis indicated significantly higher likelihood of HBsAg seroclearance in CHB+MASLD group (Log Rank P = 0.047). Logistic regression analysis revealed that the CHB+MASLD group had 2.3-fold higher odds of achieving HBsAg seroclearance compared to the CHB group (95% CI: 1.11–4.62, P = 0.025). **Conclusion:** Concomitant MASLD increases HBsAg seroclearance in CHB patients undergoing antiviral therapy, particularly with baseline HBsAg ≤100 IU/ml. Large-scale multicenter studies are warranted to explore metabolic influences on HBsAg clearance and to elucidate the underlying mechanisms.



Disclosures: Yan Dai: Nothing to Disclose, Ke Jin: Nothing to Disclose, Xinhe Sun: Nothing to Disclose, Jun Li: Nothing to Disclose

1257 | CYTOKINE PROFILING DISTINGUISHES CLINICAL FORMS OF ACUTE HBV INFECTION: INSIGHTS INTO ALF PATHOGENESIS

NEW SUBMISSION, *Davide De Battista[1] Ronald Engle[1] Jody Rule[2] Eric Chu[3] Sandra Kendra[1] Soichi Takeda[1] Hanh Nguyen[1] Zhaochun Chen[1] Dean Follmann[3] William Lee[2] [1]Hepatic Pathogenesis Section, Laboratory of Infectious Diseases, NIAID, NIH, [2]Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center at Dallas, [3]Biostatistics Research Branch, Division of Clinical Research, NIAID, NIH*

Background: Acute liver failure (ALF) caused by HBV is one of the most dramatic clinical syndromes, occurring in ~1% of patients with acute hepatitis B (AVHB). The mechanism underlying the development of ALF, and how it relates to milder forms remain unclear. Access to serum samples from the US Acute Liver Failure Study Group and Hepatitis B Research Network allowed us to investigate virus-elicited immune responses by analyzing the longitudinal cytokine profile in serial serum samples from patients with different outcomes of acute HBV infection, including ALF subtypes. **Methods:** We analyzed 231 serial serum samples from 49 well-characterized HBV patients: 7 with early- onset ALF (<10d onset of encephalopathy, HE), 11 late-onset ALF (>10d HE), 7 acute liver injury (no HE, ALI), 11 with ALF secondary to acute flare of chronic hepatitis B (reactivation–CHBALF), and 13 with AVHB. Longitudinal clinical and virological data were obtained for each patient. Genotype A predominated across all groups. Serum concentration of 19 cytokines was measured using high-multiplexing quantitative CodePlex proteomic assay. **Results:** Cytokines were classified as type 1 (IP-10, MIP-1ß, IL-8, IFN-gamma, TNF-alpha, MIP-1alpha, granzyme B, IL-1ß, IL-15), type 2 (MCP-1, IL-4, sCD137, IL-7, IL-6, IL-10), and growth factors (EGF, GM-CSF, PDGF-BB, VEGF). Distinct cytokine patterns correlated with disease severity and clinical outcome. At admission, within the ALF group, early ALF cases showed the highest expression of both type 1 (TNF-alpha, MIP-1alpha, IFN-gamma) and type 2 cytokines (IL-4, IL-7, sCD137) compared to late ALF and CHBALF. AVHB showed the highest levels of type 1 cytokines, especially IP-10, but the lowest type 2 cytokines. ALI showed an intermediate cytokine pattern between AVHB and early ALF. Notably, the restricted cytokine profile seen in late ALF and CHBALF correlated with the highest rates of mortality (82% and 88%, respectively) with IL-8 uniquely elevated in CHBALF. Over time, type 1 cytokines (IP-10, MIP-1ß, and IFN-gamma) declined in AVHB, whereas no changes were seen in ALF subtypes. Growth factor levels did not differ significantly among groups. **Conclusion:** This study reveals distinct cytokine signatures across the three major forms of HBV-associated ALF, consistent with the hypothesized different pathogenic mechanisms. Notably, a restricted cytokine profile in late ALF and CHBALF was associated with poor prognosis, raising the possibility of a direct cytopathic role of HBV in these cases.

Disclosures: Davide De Battista: Nothing to Disclose, Ronald Engle: Nothing to Disclose, Jody Rule: Nothing to Disclose, Eric Chu: Nothing to Disclose, Sandra Kendra: Nothing to Disclose, Soichi Takeda: Nothing to Disclose, Hanh Nguyen: Nothing to Disclose, Zhaochun Chen: Nothing to Disclose, Dean Follmann: Nothing to Disclose, William Lee: Nothing to Disclose

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1258 | COMPARATIVE LONG-TERM OFF-TREATMENT OUTCOMES IN HBEAG-NEGATIVE CHRONIC HEPATITIS B: PROPHYLACTIC THERAPY IN CANCER PATIENTS VS. FINITE THERAPY IN NON-CANCER PATIENTS

Hsin-Che Lin[1] Yen-Chun Liu[2] Wei Teng[3] Chao-Wei Hsu[1] Rachel Wen-Juei Jeng[4] Rong-Nan Chien[1,]
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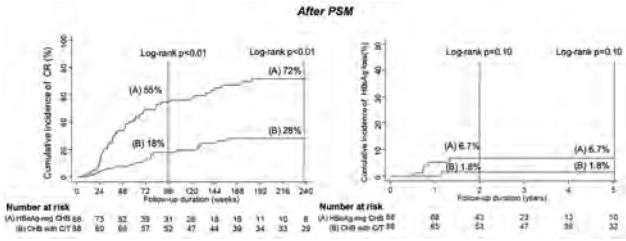
Background: Guidelines recommend finite prophylactic nucleos(t)ide analogue (NUC) therapy for cancer patients with chronic hepatitis B (CHB) receiving chemotherapy. However, the long-term outcomes after stopping Nuc therapy, such as clinical relapse or changes in HBsAg kinetics, and their relationship with immunosuppressive agents or cytotoxic drugs, remain unclear. We aim to investigate the off-NUC clinical course focusing on relapse and HBsAg loss between prophylactic (cancer) and non-cancer CHB patients after NUC therapy. **Methods:** Non-cirrhotic, HBeAg-negative CHB patients with cancer who discontinued prophylactic NUC 6 months after the end of chemotherapy (C/T-CHB cohort) were compared to non-cancer HBeAg-negative CHB patients treated with finite Nuc per APASL guidelines (CGMH off-Nuc cohort). Clinical relapse (CR) was defined as HBV DNA $\geq$2000 IU/mL with ALT $>$ 2 times the upper limit of normal (ULN). Hepatic decompensation (HD) was defined as total bilirubin $\geq$2 mg/dL and INR $\geq$1.5, with or without ascites or encephalopathy. Multivariate Cox regression was performed to evaluate the hazard of off-Nuc CR in the C/T-CHB cohort. One to one propensity score matching (PSM) was performed based on age, sex, NUC agent, pretherapy HBV DNA, and ALT and HBsAg at end of treatment (EOT). Kaplan-Meier and log-rank tests were used to compare outcomes. **Results:** Among 126 C/T CHB and 1815 CGMH off-Nuc patients, the C/T-CHB group had fewer males (46% vs. 79%; $P < 0.001$), and lower pretreatment HBV DNA (3.1 vs. 6.2 $\log_{10}$ IU/mL; $P < 0.001$), lower ALT (25 vs. 160 U/L; $P < 0.001$), and shorter treatment duration (42 vs. 156 weeks, $P < 0.001$). Multivariate Cox regression showed a lower risk of CR in the C/T CHB group [adjusted HR: 0.38; 95% CI: 0.22-0.66, $P < 0.001$], after adjusting for age, sex, prior treatment, Nuc agent, pretherapy HBV DNA, treatment duration and EOT HBsAg. In the matched cohort (n = 99 per group, median follow-up: 3.7 years), the 5-year cumulative CR incidence was lower in the C/T-CHB group (29% vs. 71%, $p < 0.01$). Relapse severity was also lower (ALT $\geq$10x ULN: 5% vs. 23%, $P < 0.01$; ALT $\geq$1000 IU/mL: 0 vs. 8%, $p = 0.01$). HD incidence was low in both groups (5-year: 3.3% vs.4.7%, $P = 0.71$). HBsAg loss was four times more frequent in the C/T-CHB group (5 years: 6.7% vs. 1.8%, $p = 0.097$), though not statistically significant. **Conclusion:** HBeAg-negative non-cirrhotic CHB patients with cancer had a lower incidence and severity of clinical relapse after stopping NUC therapy than non-cancer patients. A trend toward higher HBsAg loss in the cancer group warrants further immunological investigation.



Disclosures: Hsin-Che Lin: Nothing to Disclose, Yen-Chun Liu: Nothing to Disclose, Wei Teng: Nothing to Disclose, Chao-Wei Hsu: Nothing to Disclose, Rachel Wen-Juei Jeng: GSK: Advisor, Gilead: Advisor, Rong-Nan Chien: Nothing to Disclose

1259 | MACHINE LEARNING MODEL INTEGRATING BIOMARKERS FOR PREDICTING HBSAG SEROCLEARANCE IN PEGYLATED INTERFERON-A (PEG IFN-A)-TREATED CHB PATIENTS

Jie Li[1] Sisi Zhou[2] Shengxia Yin[1] Chao Wu[1] Xin Tong[1],
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Background: Hepatitis B virus (HBV), affecting an estimated 292 million chronic carriers globally, remains a significant public health challenge. Standard treatments for chronic HBV, including pegylated interferon-α (PEG IFN-α) and nucleos(t)ide analogues (NUCs), have distinct merits and drawbacks. While PEG IFN-α yields higher HBeAg and HBsAg seroconversion rates, its clinical utility is hampered by inconsistent patient responses. Thus, the aim of this study was to identify significant proteins as pre-treatment predictors for assessing PEG IFN-α efficacy and develop a predictive model based on machine learning for chronic hepatitis B (CHB) patients treated with PEG IFN-α. **Methods:** This retrospective cohort included 49 CHB patients who received PEG IFN-α either as monotherapy or in combination with NUCs. Serum protein expression profiles at baseline were comprehensively analyzed by mass spectrometry, integrated with machine learning algorithms including random forest, gradient-boosted decision trees, extreme gradient boosting, and support

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vector machines. A predictive model for HBsAg seroclearance was developed using Lasso feature selection followed by logistic regression modeling. Model performance was evaluated by the Receiver Operating Characteristic (ROC) curve. **Results:** A total of 49 CHB patients treated with PEG IFN-α for 48 weeks were enrolled for analysis, of whom 14 patients achieved HBsAg seroclearance. Forproteomic analysis, age-matched male patients with (n = 12) and without (n = 12) HBsAg seroclearance were selected. These 24 patients were randomly split into training and internal validation sets in a 1:1 ratio. The logistic regression model incorporating three significant proteins, including suprabasin (SBSN), mesoderm development protein (MESD), and EZRI, was established for HBsAg seroclearance prediction. These three proteins indicated that neutrophil-related immune mechanisms are pivotal for HBsAg seroclearance for CHB patients undergoing PEG IFN-α therapy. The model demonstrated achieved an ROC of 0.984 in the training set and 0.964 in the internal validation set, showing good predictive performance. **Conclusion:** This study identifies blood-derived proteomic biomarkers that predict early HBsAg seroclearance in CHB patients before initiating interferon therapy. These findings offer clinically actionable prognostic indicators, potentially enabling personalized interferon-based strategies.

Figure Predictive performance of the logistic regression model based on key proteins for HBsAg seroclearance in CHB patients treated with PEG IFN - α.

Note: CHB, chronic hepatitis B; PEG IFN - α, pegylated interferon-α.

A. Protein expression heatmap

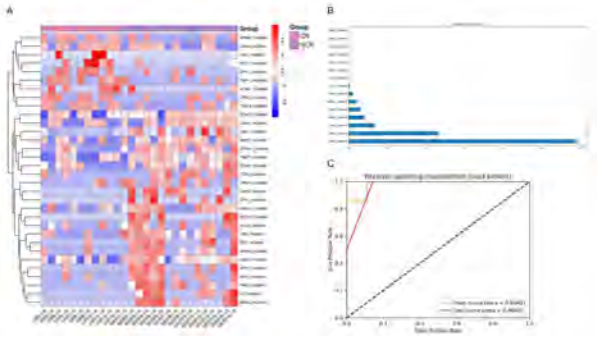
The expression patterns of proteins are shown in 24 age-matched male CHB patients (12 with and 12 without HBsAg seroclearance) after 48-week PEG IFN - α treatment. Different colors represent varying expression levels, with red indicating up - regulation and blue indicating down - regulation.

B. Protein relative importance bar plot

The relative importance of different proteins are displayed. Suprabasin (SBSN), mesoderm development protein (MESD), and EZRI are key proteins with relatively high importance scores.

C. Receiver operating characteristic (ROC) curve

The performance of the logistic regression model was constructed based on SBSN, MESD, and EZRI. The orange and red line represents the ROC of 0.984 and 0.964 in the the training and internal validation sets, respectively.



Disclosures: Jie Li: Nothing to Disclose, Sisi Zhou: Nothing to Disclose, Shengxia Yin: Nothing to Disclose, Chao Wu: Nothing to Disclose, Xin Tong: Nothing to Disclose

1260 | CHARACTERISTICS AND HEALTHCARE RESOURCE USE OF PATIENTS RECEIVING CARE FOR CHRONIC HEPATITIS B VIRUS INFECTION IN THE US: A CROSS-SECTIONAL SURVEY

Anna Coutinho[1] Chris Bell[1] Fritha Hennessy[2] Tia Pennant[2] Daniel Graham[2] Fraser Barrable[2], [1]GSK, [2]Adelphi Real World

Background: Limited data exist on patients actively seeking care for chronic hepatitis B virus [cHBV] infection, which impacts an estimated 1.6mn people in the United States [US]. Characteristics and healthcare resource use [HRU] of patients receiving care for cHBV in real-world practices are described. **Methods:** Data were drawn from the Adelphi Hepatitis Disease Specific Programme™, a cross-sectional survey with retrospective data collection of a convenience sample of physicians and their patients with cHBV in the US from Jun 2024 – Feb 2025. Specialists and primary care physicians provided patient characteristics, treatment, diagnostic tests, and HRU for up to 6 adult patients with cHBV infection. Data were analyzed descriptively and stratified by treatment status (naïve vs. treated — nucleos[t]ide analogue [NA] and/or pegylated interferon [Peg-IFN]), payer type, and race/ethnicity. **Results:** Overall, 69 physicians reported on 461 patients with cHBV infection: mean, standard deviation [SD] age: 47.0 (13.5) years; 58% male; 45% White, 28% Black or African American, 20% Asian; 50% Commercial, 27% Medicaid, 10% Medicare. Although physicians judged most patients (86%) to have mild liver disease, a high proportion (70%) received antiviral treatments, of which 94% had NAs and 8% Peg-IFN. cHBV biomarkers were tested in approximately half (HBV viral load, ALT and AST) to a third (hepatitis surface or e-antigen) of the sample, with an average of 2 tests conducted among those tested in the year prior to the survey date (Table). Antiviral-treated patients had a higher proportion tested (35%–60% vs. 21%–47%) and had a higher number of tests (Table). Testing rates were higher for Commercial (32%-56%) and Medicaid (35%-64%) but lower for Medicare patients (20%-51%). Except for HBV viral load, Asian patients had lower testing rates in general vs White or Black patients (Table). Treated patients had a higher mean (SD) number of physician visits than treatment-naïve patients, particularly with hepatologists (2.7 [1.5] vs 1.8 [0.4]) and infectious disease specialists (3.8 [2.4] vs 2.0 [1.3]). Differences were also noted by

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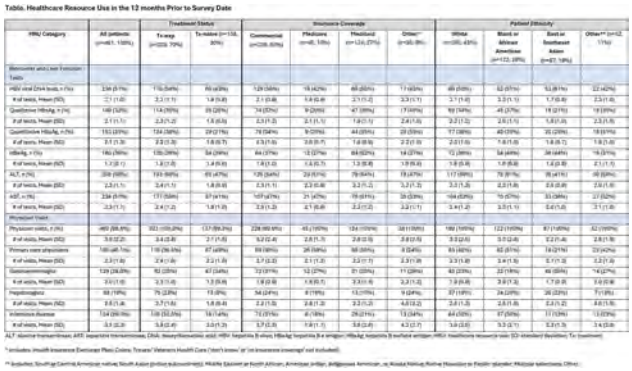
payer type and race/ethnicity in HRU rates (Table). **Conclusion:** Patients with cHBV infection managed in real-world US practices are most likely to be those currently receiving treatment. Less than half are receiving biomarker or liver function tests regardless of treatment status, payer type, or race/ethnicity, highlighting gaps in the current standard of care.



Disclosures: Anna Coutinho: GSK: Employee, Chris Bell: Nothing to Disclose, Fritha Hennessy: Nothing to Disclose, Tia Pennant: Nothing to Disclose, Daniel Graham: GSK: Independent Contractor, Fraser Barrable: Nothing to Disclose

1261 | ASSOCIATION OF HBV VIRAL MARKERS AND HCC RISK IN HBV-RELATED CIRRHOSIS PATIENTS UNDER LONG-TERM ENTECAVIR THERAPY

Tung-Hung Su[1] Hung-Hsuan Pan[1] Tsung-Hui Hu[2] Wan Long Chuang[3] Wei-Wen Su[4] Chun-Che Lin[5] Cheng Yuan Peng[6] Chia-Chi Wang[7] Yao-Chun Hsu[8] Yi-Wen Huang[9] Kuo-Chih Tseng[10] Chih-Lin Lin[11] Sheng-Shun Yang[12] Fat-Moon Suk[13] Shih-Jer Hsu[1] Tsung-Ming Chen[14] Ming-Jong Bair[15] Cheng-Kuan Lin[16] Tai-Chung Tseng[17] Jia-Horng Kao[1], [1]National Taiwan University Hospital, Taipei, Taiwan, [2]Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [3]Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [4]Changhua Christian Hospital, Changhua, Taiwan, [5]Chung Shan Medical University Hospital, Taichung, Taiwan, [6]China Medical University Hospital, Taichung, Taiwan, [7]Taipei Tzuchi Hospital, the Buddhist Tzuchi Medical Foundation, Taipei Taiwan, [8]E-Da Hospital, Kaohsiung, Taiwan, [9]Cathay General Hospital Medical Center, Taipei, Taiwan, [10]Buddhist Tzu Chi General Hospital, Da-Lin Branch, Chiayi, Taiwan, [11]Ren-Ai Branch, Taipei City Hospital, Taipei, Taiwan, [12]Taichung Veterans General Hospital, Taichung, Taiwan, [13]Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, [14]Tungs' Taichung MetroHarbor Hospital, Taichung, Taiwan, [15]Mackay Memorial Hospital, Taitung, Taiwan, [16]Far Eastern Memorial Hospital, Taipei, Taiwan, [17]National Taiwan University Hospital

Background: The risk of hepatocellular carcinoma (HCC) is reduced but not eliminated after nucleos(t)ide analogue (NA) therapy in chronic hepatitis B (CHB) patients. We aimed to investigate the role of HBV RNA, hepatitis B core-related antigen (HBcrAg), and quantitative hepatitis B surface antigen (qHBsAg) in predicting HCC in cirrhotic CHB patients receiving long-term entecavir therapy. **Methods:** This retrospective cohort study included patients with CHB-related cirrhosis who had been under entecavir for a median duration of 6.2 years from medical centers in Taiwan. Serum levels of HBV RNA, HBcrAg, and qHBsAg were quantified by automated assays. Correlation among viral markers was assessed using Pearson correlation coefficients. Multivariable Cox proportional hazards regression models were used to identify predictors for HCC development and sustained detectability of HBV RNA. **Results:** Overall, 451 CHB-related cirrhosis patients were included. The mean age was 60, the median HBV RNA level was 0.7 (log_{10} copies/ml), the median HBcrAg level was 3.2 (log_{10} U/ml), and the median qHBsAg level was 2.4 (log_{10} IU/mL). After a median follow-up of 3.3 years, 55 patients developed HCC. There was a positive correlation between HBV RNA and HBcrAg (r = 0.4515). Among patients with undetectable HBV DNA, 55.3% still had detectable HBV RNA. After adjustment for confounding factors, higher gamma-glutamyl transferase (γ-GT) levels (hazard ratio [HR], 1.01; 95% confidence interval [CI], 1.00–1.01), positive HBeAg (HR, 2.29; 95% CI,1.16-4.54), detectable HBV DNA (HR, 2.41; 95% CI, 1.11–5.21), HBcrAg > 3.23 log_{10} U/ml (HR, 1.75; 95% CI, 1.10–2.77) and shorter ETV treatment duration (HR, 0.88; 95% CI, 0.79–0.97) significantly predicted sustained HBV RNA detectability. In multivariate analysis, age (HR: 1.04, 95%CI: 1.01-1.07), FIB-4 (HR: 1.11, 95%CI: 1.02-1.22) and AFP levels (HR: 1.01, 95% CI: 1.00-1.01) were predictive of the development of HCC, while serum HBV RNA, HBcrAg, and qHBsAg were not. **Conclusion:** Among CHB-related cirrhotic patients receiving 6-year entecavir therapy, higher γ-GT and HBcrAg levels, positive HBeAg, detectable HBV DNA, and shorter duration of ETV treatment were associated with sustained HBV RNA detectability. Older age, higher FIB-4 index, and elevated AFP levels were associated with increased risk of HCC development, while serum levels of HBV RNA, HBcrAg, and qHBsAg were not predictive of HCC.

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Table 1. Multivariate Cox proportional hazards regression analysis for the risk of HCC development.

Variables	adjusted HR (95%CI)	P-value
age, year	1.04 (1.01-1.07)	0.010
male (vs. female)	1.79 (0.83-3.85)	0.136
HBeAg positivity	3.07 (0.94-10.03)	0.064
FIB-4 index	1.11 (1.02-1.22)	0.022
AFP, ng/ml	1.01 (1.00-1.01)	<0.001
HBV RNA, $\log_{10}$ copies/ml	0.90 (0.65-1.25)	0.540
HBcrAg, $\log_{10}$ U/ml	1.02 (0.60-1.74)	0.944
qHBsAg, $\log_{10}$ IU/ml	0.98 (0.63-1.51)	0.914

Disclosures: Tung-Hung Su: Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Merck Sharp and Dohme: Speaking and Teaching, Roche: Speaking and Teaching, Sysmex: Speaking and Teaching, Eisai: Speaking and Teaching, Hung-Hsuan Pan: Nothing to Disclose, Tsung-Hui Hu: Nothing to Disclose, Wan Long Chuang: Nothing to Disclose, Wei-Wen Su: Nothing to Disclose, Chun-Che Lin: Nothing to Disclose, Cheng Yuan Peng: Nothing to Disclose, Chia-Chi Wang: Nothing to Disclose, Yao-Chun Hsu: Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Sysmex: Advisor, Abbvie: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Roch: Speaking and Teaching, AsuperBio: Advisor, Grifols: Speaking and Teaching, GlaxoSmithKline: Consultant, AusperBio: Consultant, Yi-Wen Huang: Nothing to Disclose, Kuo-Chih Tseng: Nothing to Disclose, Chih-Lin Lin: Nothing to Disclose, Sheng-Shun Yang: Nothing to Disclose, Fat-Moon Suk: Nothing to Disclose, Shih-Jer Hsu: Nothing to Disclose, Tsung-Ming Chen: Nothing to Disclose, Ming-Jong Bair: Nothing to Disclose, Cheng-Kuan Lin: Nothing to Disclose, Tai-Chung Tseng: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose

1262 | EPIGENETIC EDITORS TARGETING CHRONIC HEPATITIS B ACHIEVE HBV SURFACE ANTIGEN LOSS WITH A SINGLE COURSE OF TREATMENT IN MULTIPLE HBV MOUSE MODELS

Glen Acosta[1] Rayman Choo-Wing[1] Arogya Khadka[1] Lenka Hoffman[1] Christina Blinn[1] Christine Waters[1] Jeremy Zeitler[1] Taesun Eom[1] Shefal Parikh[1] Padma Malyala[1] Yesseinia Anglero-Rodriguez[1] Sarah Voytek[1] Jenny Marlowe[1] John Xiong[1], [1]nChroma Bio

Background: Current treatments for chronic hepatitis B rarely achieve functional cure due to persistent viral expression from covalently closed circular DNA (cccDNA) and integrated HBV DNA (intDNA) in infected hepatocytes. nChroma Bio is developing epigenetic editors, a novel therapeutic modality that leverages DNA methylation to silence target genes at the level of transcription without cutting or nicking the DNA, aimed at permanently silencing both cccDNA and intDNA to improve the rate of functional cure for HBV patients. **Methods:** To demonstrate the therapeutic potential of epigenetic editors for HBV, a prototype HBV-targeting editor was tested in two HBV mouse models, a transgenic model (Genotype A) and the AAV-HBV model (Genotype D), with 6-months of follow up. Further optimization of the editor construct, LNP formulation, and mRNA/gRNA ratios resulted in nomination of a development candidate, CRMA-1001, for further testing in the HBV mouse models. **Results:** A single dose of the prototype epigenetic editor targeting HBV demonstrated >2 $\log_{10}$ reduction in hepatitis B surface antigen (HBsAg) and circulating HBV DNA in both Tg- and AAV-HBV mouse models for $>$ 6 months post dose. At the same dose level, CRMA-1001 showed ~10-fold greater HBV antigen suppression than the prototype editor in both models, demonstrating greatly enhanced in vivo potency. In AAV-HBV mice, a single dose of CRMA-1001 produced dose-dependent, durable (at least 6 months), and substantial suppression of HBV biomarkers (up to a 3.5 $\log_{10}$ reduction in HBsAg) without tolerability issues at doses up to 2 mg/kg. Notably, a significant portion of animals receiving ≥ 0.5 mg/kg achieved undetectable HBsAg (10–70% for 0.5 to 2 mg/kg) and HBV DNA (20–90% for 0.5 to 2 mg/kg). A three-dose regimen at 1 mg/kg further improved outcomes, with 90% of mice achieving no detectable HBsAg, HBeAg or HBV DNA. CRMA-1001 was also shown to be compatible with Entecavir, and combination therapy led to deeper, more durable HBV DNA suppression. **Conclusion:** In vivo pharmacology studies in clinically relevant HBV mouse models demonstrate the therapeutic potential of epigenetic editing to effectively and durably silencing viral expression from both episomal and integrated forms of HBV DNA.

Disclosures: Glen Acosta: nChroma Bio: Stock – privately held company, nChroma Bio: Employee, Rayman Choo-Wing: Nothing to Disclose, Arogya Khadka: Nothing to Disclose, Lenka Hoffman: Nothing to Disclose, Christina Blinn: Nothing to Disclose, Christine Waters: Nothing to Disclose, Jeremy Zeitler: Nothing to Disclose, Taesun Eom: Nothing to Disclose, Shefal Parikh: Nothing to Disclose, Padma Malyala: Nothing to Disclose, Yesseinia Anglero-Rodriguez: Nothing to Disclose, Sarah Voytek: nChroma Bio:

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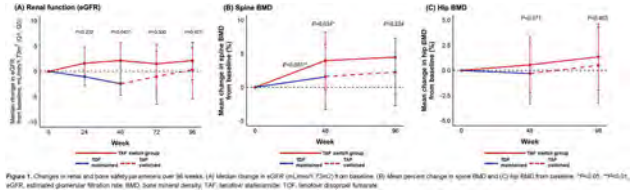
Employee, nChroma Bio: Stock – privately held company, Jenny Marlowe: nChroma Bio: Executive role, Solid Biosciences: Executive role, John Xiong: Nothing to Disclose

1263 | EFFICACY AND SAFETY OF SWITCHING TENOFOVIR DISOPROXIL FUMARATE TO TENOFOVIR ALAFENAMIDE IN CHRONIC HEPATITIS B PATIENTS WITH MULTIDRUG RESISTANCE

Jaehong Jeong[1] Jae Seung Lee[1] Dong Yun Kim[1] Sang Hoon Ahn[1] Jun Yong Park[1], [1]Yonsei University College of Medicine

Background: Tenofovir disoproxil fumarate (TDF) monotherapy effectively suppresses viral replication in patients with multidrug-resistant chronic hepatitis B (CHB). However, TDF use is associated with risks of kidney dysfunction and osteopenia. We conducted this prospective, randomized, open-label study to compare the efficacy and safety of switching from TDF to tenofovir alafenamide (TAF) in these patients. **Methods:** TDF-treated patients with CHB and multidrug resistance (e.g., resistance to more than two non-potent nucleos(t)ide analogs or to entecavir) were enrolled between 2021 and 2023. During the 96-week follow-up, patients in TAF-switch group changed from TDF to TAF at baseline, while those in the TDF-maintained/TAF-switched group continued TDF for 48 weeks before switching to TAF. **Results:** Baseline characteristics—including age, body mass index, HBeAg positivity, estimated glomerular filtration rate (eGFR), and bone mineral density (BMD) of spine and hip—did not significantly differ between the TDF-maintained/TAF-switched group (n = 13) and the TAF-switch (n = 30) group. Virologic responses were maintained in all patients. At 48 weeks, the TAF-switch group exhibited an increasing trend in eGFR, while the TDF-maintained/TAF-switched group showed a decreasing trend, yielding a statistically significant between-group difference (2.17 vs. -2.42 mL/min/1.73m^2, P = 0.045). However, at week 96, the difference was no longer significant due to recovery of eGFR in the TDF-maintained/TAF-switched group (0.34 vs. 2.15 mL/min/1.73m^2, P = 0.927). Spine BMD significantly increased from baseline in the TAF-switch group at week 48 (0.972 vs. 0.936 g/cm^2, P < 0.001), with a statistically significant between-group difference in percentage change (3.97% vs. 1.54%, P = 0.034). Hip BMD showed an increasing trend over 96 weeks in the TAF-switch group, whereas in the TDF-maintained/TAF-switched group, it initially declined but improved after switching to TAF. Between-group differences in hip BMD at weeks 48 and 96 were not statistically significant (P = 0.371 and 0.463, respectively). **Conclusion:** Switching from TDF to TAF in patients with multidrug-resistant CHB maintained virologic suppression and mitigated declines in renal function and bone mineral density.



Disclosures: Jaehong Jeong: Nothing to Disclose, Jae Seung Lee: Nothing to Disclose, Dong Yun Kim: Nothing to Disclose, Sang Hoon Ahn: Nothing to Disclose, Jun Yong Park: Nothing to Disclose

1264 | FUNCTIONAL ANALYSIS OF FUMARYLACETOACETATE HYDROLASE IN MEDIATING ANTI-HBV AND ANTI-TUMOR EFFECTS

Shouichi Namikawa[1] Takuto Nosaka[1] Yosuke Murata[1] Yu Akazawa[1] Tomoko Tanaka[1] Kazuto Takahashi[1] Tatsushi Naito[1] Masahiro Ohtani[1] Yasunari Nakamoto[1], [1]University of Fukui

Background: Chronic hepatitis B (CHB), caused by the hepatitis B virus (HBV), is a leading cause of hepatocellular carcinoma (HCC) worldwide. We established a hepatitis B virus (HBV) infection assay system using primary human hepatocytes and extracted fumarylacetoacetate hydrolase (FAH) as a host factor gene that regulates viral life cycle by RNA microarray analysis (PLoS ONE 2025). In this study, we functionally investigated the anti-HBV and anti-tumor effects of FAH using resected hepatocellular carcinoma (HCC) tissues and HBV-stably transfected HCC cell lines. **Methods:** In 111 resected HCC specimens, immunohistological staining intensities of FAH and ki67 in tumor and non-tumor areas were determined by H-score using inform (akoya), and the correlation between FAH and ki67 was investigated. FAH index was calculated by H-score of tumor/non-tumor areas, and analyzed for correlation with recurrence and prognosis. In vitro, the 1.3 mer HBV genomes of genotype C2 with basic core promoter and/or pre-core mutations (wt/wt; Low transcription, mu/mu; High t.) were stably transfected into HepG2 cells, HepG2.1-E10 (Low t.) and HepG2.D11 (High t.) were established. FAH vector and siRNA were transfected, and HBsAg, HBV-DNA, HBV-RNA measurements, proliferation assay, apoptosis assay, and sphere formation assay were performed. RNA expression was analyzed for 205 anti-tumor and anti-viral related genes using TaqMan custom array plates.

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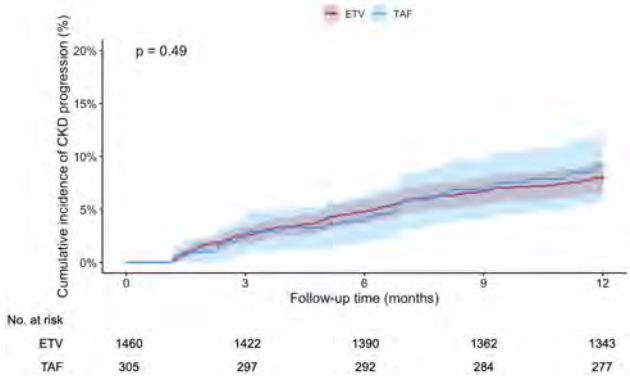
Results: The H-score of FAH in resected HCC specimens was significantly lower in tumor areas than in non-tumor areas (ΔH-score = -10.99, $p < 0.05$). The expression intensities of FAH and ki67 were inversely correlated ($p < 0.05$). Recurrence and survival rates were better in the patient group with higher FAH index ($p < 0.05$). In HepG2.D11 and HepG2.1-E10, HBsAg was increased with FAH knockdown and decreased with FAH overexpression compared to controls. Furthermore, FAH knockdown decreased cell proliferative activity, apoptosis, and increased spheres, while FAH overexpression inhibited cell proliferation, induced apoptosis, and decreased spheres. FAH overexpression increased the expression of CDKN2B, CHECK1, and CCND1 (cell cycle regulation), increased the expression of SMAD3, FAS, and BAX (apoptosis induction), and decreased the expression of NANOG and SALL4 (stem cell function). **Conclusion:** Evaluation of FAH and ki67 expression in HCC tissues and functional analysis in HBV-stably transfected HepG2 cells suggested that the FAH gene may contribute to HBV reduction, cell proliferation inhibition, apoptosis induction and stem cell function inhibition. The hepatocyte host factor FAH may be a candidate for a new therapeutic strategy for viral carcinogenesis that exhibits both anti-tumor and anti-HBV effects.

Disclosures: Shouichi Namikawa: Nothing to Disclose, Takuto Nosaka: Nothing to Disclose, Yosuke Murata: Nothing to Disclose, Yu Akazawa: Nothing to Disclose, Tomoko Tanaka: Nothing to Disclose, Kazuto Takahashi: Nothing to Disclose, Tatsushi Naito: Nothing to Disclose, Masahiro Ohtani: Nothing to Disclose, Yasunari Nakamoto: Nothing to Disclose

1265 | CHRONIC KIDNEY DISEASE PROGRESSION IN PATIENTS WITH CHRONIC HEPATITIS B ON TENOFOVIR ALAFENAMIDE VERSUS ENTECAVIR

Lilian Yan Liang[1] Terry Cheuk-Fung Yip[1] Jimmy Che-To Lai[1] Vincent Wong[1] Grace Lai-Hung Wong[1], [1]the Chinese University of Hong Kong

Background: Tenofovir alafenamide (TAF) is a prodrug of tenofovir. Tenofovir has been associated with a slightly increased risk of renal impairment. We aimed to evaluate the progression of chronic kidney disease (CKD) over 12 months in patients with chronic hepatitis B (CHB) receiving TAF and entecavir (ETV). **Methods:** This is a retrospective cohort study in Hong Kong. CHB patients who were initially treated with TAF or ETV were included. The baseline was defined as the start date of treatment. CKD progression was defined as an increase in CKD stage of at least one stage for at least three consecutive months. **Results:** After propensity score matching, 305 TAF-treated and 1460 ETV-treated CHB patients were included in the analysis. Their baseline estimated glomerular filtration rate were 84.4 $\pm$ 21.5 and 85.2 $\pm$ 21.6 mL/min/1.73 m2, respectively. During the 12-month follow-up duration, 28 TAF-treated and 116 ETV-treated patients developed CKD progression. The corresponding 12-month cumulative incidence (95% confidence interval) of CKD progression were 9.2% (5.9% - 12.4%) in TAF-treated and 8.0% (6.6% - 9.3%) in ETV-treated patients ($p = 0.492$). In the Kaplan-Meier curve, the cumulative incidence of CKD progression in TAF-treated patients was comparable with that of ETV-treated patients ($p = 0.49$). **Conclusion:** CHB patients treated with TAF had a comparable risk of renal impairment to that of ETV-treated patients.



Disclosures: Lilian Yan Liang: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Jimmy Che-To Lai: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Consultant, Boehringer Ingelheim: Consultant, Echosens: Speaking and Teaching, Eli Lilly: Consultant, Gilead: Consultant, Gilead: Grant/Research Support, Intercept: Consultant, Inventiva: Consultant, Illuminatio Medical Technology: Stock – privately held company, Merck: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet: Consultant, TARGET PharmaSolutions: Consultant, Unilab: Speaking and Teaching, Visirna: Consultant, AstraZeneca: Consultant, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support

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1266 | SINGLE-ARM META-ANALYSIS AND SYSTEMATIC REVIEW ON CLINICAL CURE OF CHRONIC HEPATITIS B AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION: IMMUNOREGULATORY MECHANISMS AND CLINICAL TRANSLATIONAL INSIGHTS

He Ma[1] Bo Feng[1], [1]Peking University People's Hospital

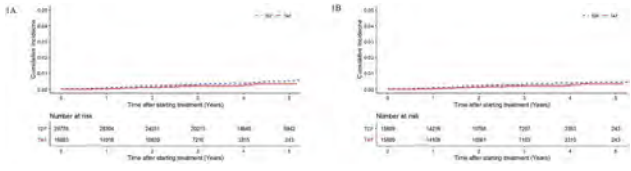
Background: The quest for a functional cure for chronic hepatitis B (CHB) remains an elusive objective. Hematopoietic stem cell transplantation (HSCT) may elicit viral clearance by immunological remodelling in recipients with positive-HBsAg; however, the factors that determine its effectiveness are yet unknown. **Methods:** Nine trials (308 patients) were subjected to single-arm meta-analysis (R4.2.2 "meta" package) in accordance with PRISMA/Cochrane criteria. Heterogeneity was addressed via random-effects models (I2 = 87.1%). Subgroup analysis accounted for donor HBsAb/recipient HBeAg impacts. **Results:** The total HBsAg clearance rate was 26% (95% CI:14% to 39%), greater than that of standard therapies. Notably, HBsAb-positive donors had significantly enhanced clearance (55% vs. 8%, p < 0.01). HBeAg-negative recipients fared better (29% vs. 2%). In patients who achieved HBsAg loss, HBsAb-positive donors and HBeAg-negative recipients are the most prevalent types (10/11). Sensitivity analysis confirmed robustness; publication bias was nonsignificant (Egger' s p = 0.271). **Conclusion:** Depending on the recipient' s HBeAg and the donor' s HBsAb status, HSCT shows promise as a treatment for CHB. HBsAb-positive donors and HBeAg-negative recipients should be given priority in order to maximize results, which may also provide new immunological therapeutic strategy for functional cure of CHB.

Disclosures: He Ma: Nothing to Disclose, Bo Feng: Nothing to Disclose

1267 | COMPARATIVE RENAL SAFETY OF TENOFOVIR ALAFENAMIDE VS TENOFOVIR DISOPROXIL FUMARATE IN CHRONIC HEPATITIS B: A KOREAN NATIONWIDE STUDY

JIHYE LIM[1] Ji won Yang[2] Ye-Jee Kim[3] Hwa Jung Kim[3] Jonggi Choi[4], [1]Yeouido St. Mary's Hospital, [2]Department of Gastroenterology, Liver Centre, Asan Medical Centre, University of Ulsan College of Me, [3]Department of Clinical Epidemiology and Biostatistics, Asan Medical Centre, University of Ulsan Coll, [4]University of Ulsan, Asan Medical Center

Background: The long-term renal safety of tenofovir-based therapy in patients with chronic hepatitis B virus (HBV) infection remains uncertain, particularly regarding end-stage kidney disease requiring renal replacement therapy (RRT). We investigated the comparative risk of renal dysfunction between tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF). **Methods:** We identified treatment-naïve adult patients with chronic HBV infection who initiated TAF or TDF between 2017 and 2020 from the Korean National Health Insurance Service. After 1:1 propensity score (PS) matching, we compared the incidence of RRT and chronic kidney disease (CKD) between the two groups. **Results:** Among 46,663 eligible patients (TAF: n = 16,885; TDF: n = 29,778), the median follow-up duration was 2.61 years (interquartile range, 1.52–3.75). During this period, 25 patients in the TAF group underwent RRT, with an incidence rate of 0.56 per 1,000 person-years (PYs), compared to 108 patients in the TDF group, with an incidence of 0.96 per 1,000 PYs. Although the cumulative risk of RRT was lower in the TAF group, the difference was not statistically significant (crude hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.47–1.16; Figure 1a). In the propensity score–matched cohort (n = 31,218), the adjusted HR for RRT in the TAF group compared to the TDF group was 0.67 (95% CI, 0.40–1.10; Figure 1b). Male sex, older age, hypertension, cirrhosis, and current smoking were associated with an increased risk of RRT. Regarding CKD, the TAF group showed a higher crude incidence (HR, 1.26; 95% CI, 1.01–1.57), which was attenuated after adjustment (HR, 1.20; 95% CI, 0.93–1.56). **Conclusion:** In conclusion, our study suggests that the type of tenofovir used did not significantly affect the risk of RRT or CKD, while the overall incidence of RRT in patients with tenofovir remained higher than that of the general population. Male patients, older patients, and those with hypertension or cirrhosis are at elevated risk of renal complications, requiring careful renal function monitoring to improve long-term outcomes.



Disclosures: JIHYE LIM: Nothing to Disclose, Ji won Yang: Nothing to Disclose, Ye-Jee Kim: Nothing to Disclose, Hwa Jung Kim: Nothing to Disclose, Jonggi Choi: GILEAD SCIENCE: Grant/Research Support

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1268 | QUANTIFICATION AND EVALUATION OF INTRAHEPATIC HBV DNA AND CCCDNA IN HBV ASSOCIATED HEPATOCELLULAR CARCINOMA

Jin Li[1] Yuanlang Ji[2], [1]The Affiliated Infectious Diseases Hospital of Soochow Unive, [2]Suzhou Medical College, Soochow University

Background: In 2022, hepatitis B resulted in an estimated 1.1 million deaths, mostly from cirrhosis and hepatocellular carcinoma (HCC). Almost 50% of all cases of HCC are associated with chronic infection with HBV. HBV cccDNA binds to histones to form the viral mini-chromosome and serves as the template for the transcription of all HBV mRNAs, which is a key factor in viral persistence infection. Several studies have investigated the HBV cccDNA level in HCC and matched non-cancerous tissues but the results are still inconclusive. Given that HBV virological factors have been linked to HCC development, the expression levels and clinical significance of HBV DNA and cccDNA in liver tissues require further investigation. **Methods:** This study collected 40 HBV-HCC patients, including serum samples, liver carcinoma tissues and matched peritumoral tissues. Quantitative PCR was used to measure HBV DNA and cccDNA levels in liver carcinoma tissues and matched peritumoral tissues, and their correlations with tumor markers and disease progression were assessed. According to TNM staging, 16 HBV-HCC patients were assigned into TNM 0 group and 24 HBV-HCC patients were assigned into TNM 2-4 group. Additionally, 31 HBV-HCC patients without lymphovascular invasion (LVI) belonged to LVI 0 group, and 9 patients with LVI enrolled into LVI 1 group. **Results:** Significant correlations were observed between HBV DNA levels in carcinoma tissues (HBV DNA-ca) and cccDNA-ca ($r = 0.38$, $p = 0.0155$), HBV DNA in peritumoral tissues (HBV DNA-pa) ($r = 0.57$, $p = 1.32E-04$) and cccDNA-pa ($r = 0.34$, $p = 0.0311$). The cccDNA-ca levels demonstrated positive associations with HBV DNA-pa ($r = 0.55$, $p = 2.70E-04$) and cccDNA-pa ($r = 0.51$, $p = 8.83E-04$), while cccDNA-pa was significantly correlated with HBV DNA-pa ($r = 0.60$, $p = 3.85E-05$). Notably, all viral markers (HBV DNA-ca, cccDNA-ca, HBV DNA-pa, cccDNA-pa) exhibited strong positive correlations with TNM staging ($r > 0.4$, $p < 0.01$). Furthermore, cccDNA-ca, HBV DNA-ca, and cccDNA-pa showed significant associations with LVI and alpha-fetoprotein (AFP) levels ($r > 0.35$, $p < 0.05$) (Figure 1). Comparative analysis revealed higher HBV DNA-ca, cccDNA-ca, HBV DNA-pa, and cccDNA-pa levels in TNM stages II–IV group compared to TNM stage 0 group (Figure 2). Similarly, cccDNA-ca, HBV DNA-pa, and cccDNA-pa levels were elevated in LVI-positive (LVI 1) than in LVI-negative (LVI 0) group (Figure 3). **Conclusion:** This study highlights significant correlations between HBV DNA and cccDNA levels in liver carcinoma tissues and matched peritumoral tissues of HBV-HCC patients. These levels were closely associated with TNM staging and tumor progression. Monitoring HBV DNA and cccDNA in liver tissues may provide valuable insights for evaluating disease progression and prognosis of HBV-HCC patients.

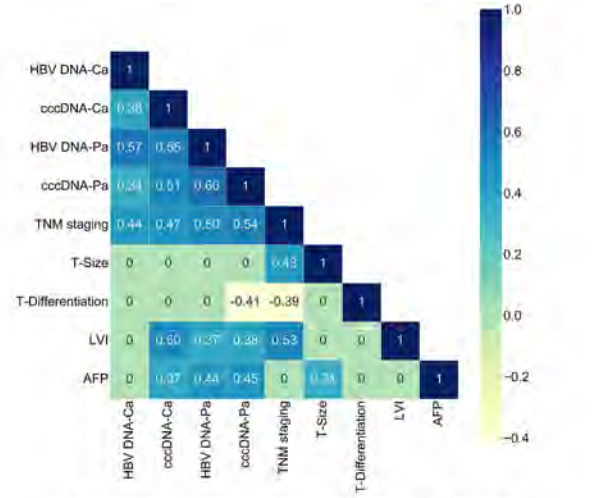

Figure 1. Correlation matrix heatmap among HBV DNA, cccDNA and clinical indicators.

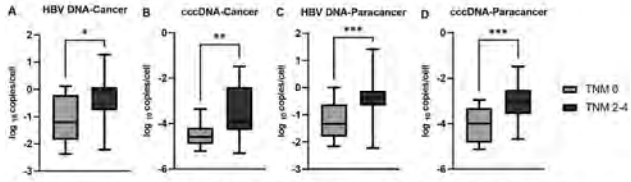

Figure 2. The comparison of HBV DNA and cccDNA between TNM 0 vs 2-4 groups.

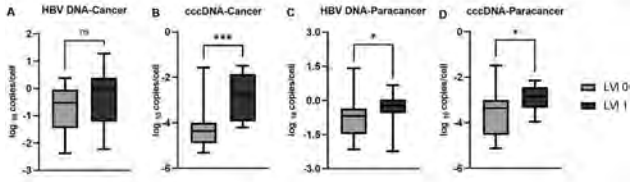

Figure 3. The comparison of HBV DNA and cccDNA between LVI 0 vs 1 groups.

Disclosures: Jin Li: Nothing to Disclose, Yuanlang Ji: Nothing to Disclose

1269 | AN EGCG-LOADED FERRITIN NANODRUG INDUCING HBSAG CLEARANCE FOR HBV THERAPY

Yixin Dong[1] Xizhi Yin[1] Xiangru Shan[2] Chuanlong Zhu[1], [1]The First Affiliated Hospital of Nanjing Medical University, [2]China Pharmaceutical University

Background: Hepatitis B virus (HBV) infection remains a serious threat to global health. Current antiviral therapies are often associated with systemic side effects or drug resistance, highlighting the need for developing more effective HBV treatment strategies. As the most abundant viral antigen in the bloodstream, hepatitis B surface antigen (HBsAg) serves as a key therapeutic

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target. The elimination of HBsAg might substantially enhance HBV treatment efficacy. In this study, we designed a novel ferritin-based nanodrug to induce HBsAg clearance through ferritinophagy, and evaluated its antiviral activity. **Methods:** HBsAg-affinity peptides were modified on the outer surface of the human H chain ferritin nanocage, named HA, to enable its ability to bind HBsAg in the cytoplasm. And encapsulated EGCG molecules within the ferritin cage (HE) to enhance complete autophagy. The interaction of HA and HBsAg was verified by surface plasma resonance (SPR) analysis. And the effects of HE on HBsAg were characterized by Western blot (WB). We then evaluated the antiviral efficacy of these ferritin-based nanodrugs by determining levels of HBsAg, HBeAg, and HBV DNA. **Results:** Structural characterization confirmed the successful preparation of functionalized ferritin nanocages (HA), which maintained the characteristic 12-nm spherical morphology as verified by DLS and TEM. SPR analysis demonstrated special binding between HA and HBsAg, with an equilibrium association constant (KD) of 37.8 nM. WB analysis indicated significant LC3-II accumulation (1.6-fold increase) and NCOA4 down-regulation (26% reduction) after treatment with HA, indicating that HBsAg clearance was relied on the ferritinophagy of HA, and this process could be effectively promoted by EGCG. Importantly, the EGCG-loaded nanodrug (HE) exhibited strongest antiviral efficacy compared to individual HA or EGCG treatments, reducing extracellular HBeAg levels by 20%, HBsAg levels by 40%, and HBV DNA by 37% in HepAD38 cell lines. **Conclusion:** The results demonstrate the great potential of our ferritin-based nanodrug as a novel HBV treatment agent. This nanodrug was confirmed to directly bind HBsAg and effectively induce HBsAg clearance through the ferritin-mediated ferritinophagy process under the promotion of EGCG, suggesting a promising new therapeutic strategy for HBV infection.

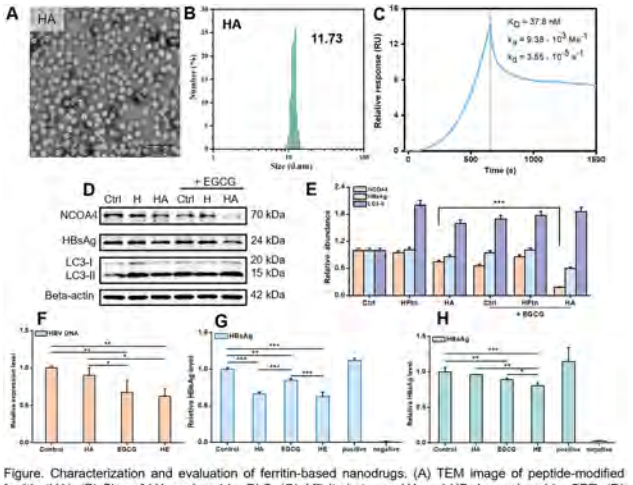

Figure. Characterization and evaluation of ferritin-based nanodrugs. (A) TEM image of peptide-modified ferritin (HA), (B) Size of HA analyzed by DLS, (C) Affinity between HA and HBsAg analyzed by SPR, (D) WB analysis of cellular HBsAg and ferritinophagy-related proteins levels, (E) Gray scale analysis summary of WB, (F) qPCR analysis of HBV DNA, ELISA analysis of HBsAg (G) and HBeAg (H). *p < 0.05, **p < 0.01, ***p < 0.001.

Disclosures: Yixin Dong: Nothing to Disclose, Xizhi Yin: Nothing to Disclose, Xiangru Shan: Nothing to Disclose, Chuanlong Zhu: Nothing to Disclose

1270 | OPTIMIZING HBV COMBINATION THERAPY: DUAL TARGETING OF INTRACELLULAR REPLICATION AND EXTRACELLULAR VIRIONS WITH ENTECAVIR AND HBVZ10

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Background: Current combination therapies for chronic hepatitis B (CHB) focus on intracellular inhibitors, such as NAs, RNAi, or capsid modulators, but these regimens, like NA monotherapy, fail to fully suppress HBV replication. Consequently, low levels of virions are continuously released, initiating new rounds of infection and replenishing cccDNA pool. However, these virions can be neutralized by extracellular blockers like anti-HBs Ab. Durable blockade of virion spread requires sustained high levels of anti-HBs Ab. In CHB, a lack of detectable anti-HBs Ab stems from the immune system's limited capacity to produce enough Ab to match the large circulating HBsAg pool. To overcome this, we developed HBVZ10, a novel HBV therapy candidate that employs an optimized AAV8 vector to deliver human anti-HBs Ab genes to muscle cells, enabling sustained and high-level Ab production beyond B cells. This study evaluated whether pairing entecavir (ETV) with HBVZ10 enhances HBsAg seroclearance. **Methods:** HBV infected chimeric mice received either ETV monotherapy (18 weeks, starting day 42 pi, baseline viremia ~7.5 log) or combination therapy with a single HBVZ10 dose (2.5×10^{10} genome copies) plus ETV. Mice were monitored for 9 more weeks after stopping ETV. Endpoints included kinetic serum HBsAg levels and average hepatic rcDNA and cccDNA levels at termination (day 231 pi), assessed by sampling each liver 20 times. **Results:** A single 2.5×10^{10} dose of HBVZ10 achieved anti-HBs Ab titers $\geq$100,000 mIU/mL, sustained for at least 200 days. Eight of 9 mice in the combination group achieved progressive HBsAg clearance to undetectable levels, compared to only 1 of 10 in the monotherapy group ($p = 0.033$). HBV relapse occurred after ETV withdrawal in the ETV only group but was largely prevented in the

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combination group, resulting in approximately 10-fold and 100-fold reductions in hepatic rcDNA and cccDNA levels, respectively. **Conclusion:** Sustained high-level anti-HBs Ab expression from HBVZ10 complements ETV by durably blocking new rounds of infection including HBV relapse with released virions. Meanwhile, ETV inhibits virion production, thus enhancing the efficiency of HBVZ10-mediated neutralization. This synergistic mechanism improves efficiency for both cccDNA elimination and HBsAg seroclearance. Thus, combining an intracellular replication inhibitor (ETV) with a durable extracellular virion blocker (HBVZ10) may offer a superior regimen compared to all intracellular inhibitors-based combinations.

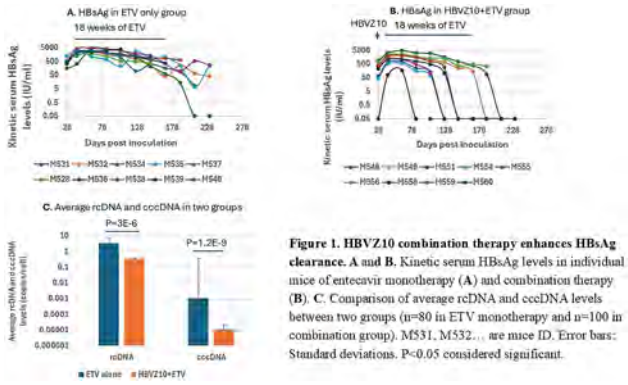

Figure 1. HBVZ10 combination therapy enhances HBsAg clearance. A and B. Kinetic serum HBsAg levels in individual mice of entecavir monotherapy (**A**) and combination therapy (**B**). **C.** Comparison of average rcDNA and cccDNA levels between two groups (n=80 in ETV monotherapy and n=100 in combination group). M531, M532… are mice ID. Error bars: Standard deviations. P<0.05 considered significant.

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1271 | INVESTIGATING HBSAG-SPECIFIC MEMORY T CELL RESPONSES IN VACCINE-INDUCED LONG-TERM IMMUNE PROTECTION AGAINST HBV

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Background: Hepatitis B virus (HBV) remains a significant global health burden, despite the availability of a highly effective prophylactic vaccine. The mechanisms underlying vaccine-induced long-term immune protection, particularly the role of memory T cells, remain incompletely understood. Here, we investigate the presence and phenotype of HBsAg-specific memory T cells in individuals with a history of HBV vaccination to elucidate their contribution to durable immunity. **Methods:** We analyzed peripheral blood samples from twenty HLA-A*02-positive healthy donors with history of HBV vaccination. Spectral flow cytometry combined with unsupervised bioinformatics analysis was used to characterize HBsAg-specific $CD8^+$ T cells. These were identified using HLA-A*02:01-restricted MHC class I multimers targeting immunodominant HBsAg peptides, as well as through Intracellular Cytokine Staining (ICS) and Activation-Induced Marker (AIM) assays following stimulation with HBsAg peptide pools. Influenza A virus (IAV)-specific multimers and peptide pools served as comparative controls. **Results:** HBsAg-specific $CD8^+$ T cells were detected in 11 out of 20 donors (55%), indicating that a substantial proportion of vaccinated individuals retain detectable antigen-specific memory T cells long after immunization. Phenotypic analysis revealed that, in contrast to influenza-specific memory $CD8^+$ T cells —which exhibited a mixed effector-memory and EMRA profile ($CCR7^-CD45RA^{+/-}$)— HBsAg-specific T cells predominantly displayed a "naïve-like" memory phenotype ($CD45RA^+CCR7^+CD62L^+KLRG1^-$). This phenotype is characteristic of long-lived memory T cells capable of maintaining homeostatic quiescence while preserving the ability to mount robust responses. Functional assays confirmed that upon antigen re-exposure, these cells could expand and secrete pro-inflammatory cytokines, including TNF-α and IFN-γ, supporting their role in effective recall responses. **Conclusion:** Our findings demonstrate that HBsAg-specific $CD8^+$ T cells with a distinct naïve-like memory phenotype persist long-term following HBV vaccination. These cells retain proliferative and functional capacity, suggesting a role in durable vaccine-induced immunity, identifying a potential correlate of long-term protection and providing insight to guide future HBV-targeted immunotherapies.

Disclosures: Margaux Bossis: Nothing to Disclose, Diane Biron: Nothing to Disclose, Phuong-Ha Le: Nothing to Disclose, Nour Nasser: Nothing to Disclose, Fanny Onodi: Nothing to Disclose, Emilie Artru: Nothing to Disclose, Abdellah Mansouri: Nothing to Disclose, Georg Lauer: Nothing to Disclose, Tarik Asselah: GSK: Speaker, GILEAD: Consultant, VIR Biotechnology: Speaker, Roche: consultant, ABBVIE: Speaking and Teaching, Aligos therapeutics: Consultant, Bluejay

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Therapeutics: Consultant, Antios therapeutics: Consultant, GSK: Consultant, Pierre Tonnerre: Nothing to Disclose

1272 | STUDY ON THE ROLE OF NK CELLS IN INTERMITTENT INTERFERON THERAPY

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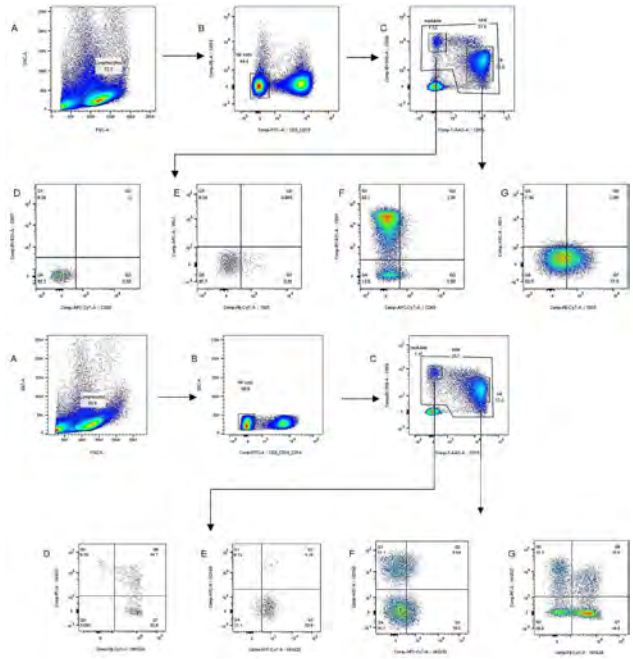
Background: To investigate changes in the phenotype and frequency of natural killer (NK) cells during intermittent interferon (IFN) therapy in patients with chronic hepatitis B (CHB) and explore their relationship with clinical outcomes. **Methods:** CHB patients were categorized into three groups based on antiviral treatment status: a treatment-naïve group, an IFN-treated plateau group, and an oral nucleos(t)ide analog antiviral therapy group. The treatment-naïve group received IFN therapy. Patients in the plateau group (experiencing stalled HBsAg decline during IFNα therapy) discontinued IFNα and resumed it after a 12–24-week IFN-free interval. The oral therapy group continued their original regimen. Viral and serological data were collected from the treatment-naïve group at baseline, 4 weeks, and 12–24 weeks of IFN therapy. For the plateau group, data were collected at IFN discontinuation, after the 12–24-week interval, and after 12–24 weeks of IFN retreatment. Peripheral blood mononuclear cells (PBMCs) were isolated at follow-up timepoints, and NK cell phenotypes/frequencies were analyzed via multicolor flow cytometry. **Results:** A total of 207 CHB patients were enrolled: 68 in the treatment-naïve group, 50 in the HBsAg plateau group, and 89 in the oral therapy group. At baseline, the plateau group exhibited significantly lower CD56dim and higher CD56bright NK cell frequencies compared to the treatment-naïve group (all $P < 0.001$), with both subsets showing functional suppression. During IFN therapy, the treatment-naïve group showed declining HBsAg levels. CD56dim frequencies decreased significantly at 4 and 12–24 weeks ($P = 0.024$ and $P < 0.001$, respectively), alongside reduced activating receptors NKG2D (at 4 weeks, $P = 0.021$) and NKG2C (at 12–24 weeks, $P < 0.001$), and increased inhibitory receptor NKG2A ($P < 0.001$). CD56bright frequencies rose, with elevated NKG2A and NKG2D ($P < 0.01$). In the plateau group, CD56bright frequencies decreased during the 12–24-week IFN-free interval ($P = 0.008$) but increased after IFN retreatment ($P = 0.001$). The activating marker CD69 rose during the interval ($P = 0.018$) and declined post-retreatment ($P = 0.006$). CD56dim frequencies showed nonsignificant fluctuations, but inhibitory NKG2A increased significantly post-retreatment ($P = 0.001$). **Conclusion:** IFN therapy reduces the cytotoxic CD56dim subset and enhances the cytokine-secreting CD56bright subset, with activity modulated by multiple factors. The plateau phase may be associated with this shift, reflecting NK cells' dual role in immune regulation and inflammatory control.



Disclosures: Minghui Li: Nothing to Disclose, Yao Xie: Nothing to Disclose, Xiaoyue Bi: Nothing to Disclose, Weihua Cao: Nothing to Disclose

1273 | HEPATOCELLULAR CARCINOMA RISK IN HISPANICS WITH CHRONIC HEPATITIS B: A NATIONAL MULTI-CENTER STUDY

Ariel Lee[1] Phillip Chung[1] Christopher Wong[1] Scarlet Yang[2] Tatyana Kushner[2] Mohammed Al-Hasan[3] Lisa Quirk[4] Amit Singal[4] Hasmik Adetyan[5] Naomy Kim[5] Ju Dong Yang[5] Nicole Kim[6] James Kashima[6] Sachin Shah[7] Isaac Avila-Vargas[7] Neil Mehta[7] Jonathan Lim[8] Christine Hsu[8] Kali Zhou[9], [1]Department of Medicine, Keck School of Medicine, University of Southern California, [2]Division of Gastroenterology and Hepatology, Department of Medicine, Weill Cornell Medicine, [3]Department of Internal Medicine, UT Southwestern Medical Center, Dallas, [4]Department of Internal Medicine, UT Southwestern Medical Center, [5]Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, [6]Division of Gastroenterology, University of Washington, [7]Department of Medicine, University of California, San

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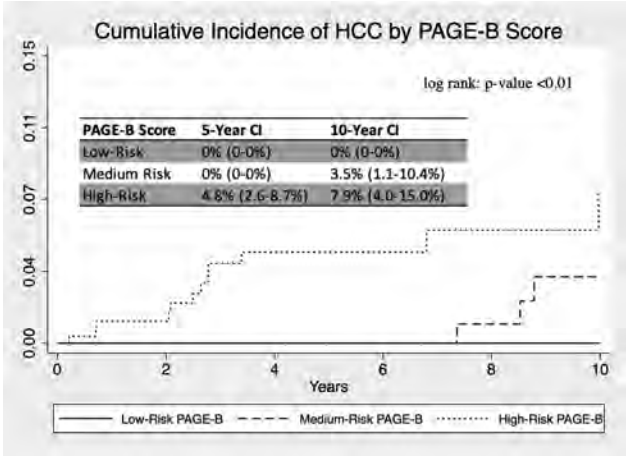
Background: Hispanic individuals with chronic hepatitis B (HBV) in the United States (US) represent an understudied population with respect to hepatocellular carcinoma (HCC) risk. To address this paucity of data, we established a multi-center national cohort to characterize US Hispanics living with chronic HBV and estimate the incidence of HCC. **Methods:** We conducted a retrospective cohort study of Hispanic adults with chronic HBV from eight US sites, identified by positive hepatitis B surface antigen (HBsAg) and EMR-reported Hispanic ethnicity. Clinical, demographic, and laboratory data were abstracted from EMR. Cohort entry was date of HBsAg testing. We used Kaplan-Meier analysis to evaluate our primary outcome, i.e., the cumulative incidence (CI) of HCC, per AASLD criteria, overall and stratified by cirrhosis status and PAGE-B score; we excluded those diagnosed with HCC within 3 months of positive HBsAg as prevalent HCC in incidence analysis. **Results:** 784 patients were included, including 55% foreign-born (30% Mexico, 18% Central America, and 4% South America), 12% US-born and 33% unknown. Median age was 50 years (IQR 39–59); 62% were male, and among those with known status, 76% were HBeAg-negative, 57% inactive carriers, with median HBV DNA of 357 IU/mL (IQR 0-17,686). 46% received antiviral therapy and 22% had cirrhosis. Co-morbid conditions included 26% with MASLD, 12% AUD, 11% HCV, and 26% HIV. Over median follow-up of 4.7 years (IQR 1.6-9.1), 32 patients developed HCC, 15 of which prevalent. HCC cases were older (56 vs 49 years), more male (81% vs 62%), and cirrhotic (93% vs 19%), with higher median liver enzymes and lower platelets and albumin (all $p < 0.05$). 4%, 21%, and 75% of cases were in the low-, medium-, and high-risk PAGE-B groups, respectively. The 1-, 5-, and 10-year CI of HCC was 0.5%, 1.8%, and 4.4%, respectively, increasing to 2.2%, 7.5%, and 16.8% among those with cirrhosis. The overall incidence rate of HCC was 4.3 per 1000 person-years (2.8-6.5). CI differed by PAGE-B score, with a 1-, 5-, 10-year CI for those with high-risk PAGE B score of 1.1%, 4.8%, and 7.9% (See Figure). **Conclusion:** In this multi-center cohort of US Hispanics with chronic HBV, incidence of HCC was low overall, but significantly higher in those with cirrhosis or high-risk PAGE-B group. Nearly half of HCCs were prevalent, suggesting delayed HBV screening or possibly referral bias. These findings are critical to informing HCC surveillance strategies for this group.



Disclosures: Ariel Lee: Nothing to Disclose, Phillip Chung: Nothing to Disclose, Christopher Wong: Nothing to Disclose, Scarlet Yang: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Mohammed Al-Hasan: Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Hasmik Adetyan: Nothing to Disclose, Naomy Kim: Nothing to Disclose, Ju Dong Yang: Exact Sciences: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Exelixis: Consultant, Fujifilm Medical Sciences: Consultant, Nicole Kim: Madrigal: Grant/Research Support, Madrigal Pharmaceuticals: Clinical trial (to institution), Madrigal: Grant/Research Support, James Kashima: Nothing to Disclose, Sachin Shah: Nothing to Disclose, Isaac Avila-Vargas: Nothing to Disclose, Neil Mehta: Merck: Consultant, FujiFilm WAKO: Consultant, Jonathan Lim: Nothing to Disclose, Christine Hsu: Nothing to Disclose, Kali Zhou: Gilead Sciences Inc: Grant/Research Support, Merck: Grant/Research Support

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1274 | INDUCTION OF STRONG ANTI-HBV IMMUNE RESPONSES IN IMMUNOSUPPRESSED MICE BY NASAL ADMINISTRATION OF HBS/HBC CONTAINING ANTIGEN

Toyoki Shimamoto[1] Osamu Yoshida[1] Ryo Yano[1] Yuki Okazaki[1] Atsushi Yukimoto[1] Yoshiko Nakamura[1] Takao Watanabe[1] Masashi Hirooka[1] Yoshio Tokumoto[1] Masanori Abe[1] Yoichi Hiasa[1], [1]Ehime University

Background: Liver transplanted patients due to HBV related diseases require a lifelong nucleos(t)ide analogue medication and HBIG administration to prevent HBV recurrence. We have developed a nasal administrative vaccine containing HBs/HBc antigen, named CVP-NASVAC. CVP-NASVAC demonstrated stronger immunogenicities compared with conventional HB vaccine, because CVP-NASVAC induced anti-HBs and HBcAg specific CTL in HBV carriers who are regarded as immune-tolerogenic status against HBV. In this study, we hypothesized that CVP-NASVAC might induce anti-HBV immune responses in immune-suppressed condition and protect liver transplanted patients from HBV recurrence. **Methods:** Immunosuppressed mice (IS) and immunocompetent mice (IC) were developed by injecting either tacrolimus (2mg/kg/day) or PBS (PBS) intraperitoneally into 8-10 week old C57BL6 male mice 1 week before start vaccination (-1 week). CVP-NASVAC (HBsAg 1mg, HBcAg 1mg, intranasally) or conventional HB vaccine (conv HB, HBsAg 1mg, subcutaneously) were administrated into IS or IC for total 3 times (0, 2, 4 week). 4th dose of CVP-NASVAC was added at 9 week in IS with CVP-NASVAC group. Then mice were sacrificed at 10 weeks for evaluating anti-HBV immune responses such as, IgG-type-anti-HBs (CLEIA), IgG-type-anti-HBc (ELISA), HBcAg specific CTL (ELISPOT). **Results:** CVP-NASVAC induced similar levels of IgG-type-anti-HBs in IC compared with conv HB vac. Although there was no significant difference in IgG-type-anti-HBs titers between CVP-NASVAC and conv HB after 3 doses in IS, 4th dose of CVP-NASVAC in IS significantly raised IgG-type-anti-HBs titers and positivity. CVP-NASVAC, but not conv HB, induced IgG-type-anti-HBc and IFN-γ producing HBcAg specific CTL in both IC and IS. **Conclusion:** CVP-NASVAC induced anti-HBV immune responses in immunosuppressed condition and could be a treatment option for preventing HBV recurrence after liver transplantation due to HBV related diseases.

Disclosures: Toyoki Shimamoto: Nothing to Disclose, Osamu Yoshida: Nothing to Disclose, Ryo Yano: Nothing to Disclose, Yuki Okazaki: Nothing to Disclose, Atsushi Yukimoto: Nothing to Disclose, Yoshiko Nakamura: Nothing to Disclose, Takao Watanabe: Nothing to Disclose, Masashi Hirooka: Nothing to Disclose, Yoshio Tokumoto: Nothing to Disclose, Masanori Abe: Nothing to Disclose, Yoichi Hiasa: Nothing to Disclose

1275 | IDENTIFICATION OF SERUM MIRNAS CHARACTERISTIC OF CASES OF CHRONIC HEPATITIS B THAT ACHIEVE FUNCTIONAL CURE

Yoshiki Murakami[1] Takashi Honda[2] Yuichirou Harada[3] Shinya Yokoyama[2] Kenta Yamamoto[2] Takanori Ito[4] Norihiro Imai[2] yoji ishizu[2] Masahiko Kuroda[3] Hiroki Kawashima[2], [1]Tokyo Medical Univesity/Asahi University, [2]Nagoya University Graduate School of Medicine, [3]Tokyo Medical University, [4]Nagoya University

Background: The current treatment goal for chronic hepatitis B (CH) is functional cure (FC) through the disappearance of HBsAg. We analyzed the expression patterns of serum miRNAs in CH and FC and attempted to develop a method to predict cases that will improve from CH to FC. **Methods:** Analysis 1: Total RNA was extracted from serum of 11 FC cases, 13 CH cases, and 3 CH cases with HBV DNA less than 3 log/IU among CH cases (hereafter CHL), and miRNA expression analysis was performed by small RNA-sequencing. Support vector machines (SVM) were used to determine a function that would enable classification between CH, and FC. Analysis 2: Six cases of CH undergoing follow-up were analyzed. Three cases improved from CH to FC, and three cases remained in CH. miRNA expression analysis and amino acid analysis of the core region were performed. **Results:** Analysis 1: Expression level of 17 miRNAs with False Discovery Rate (FDR) < 0.05 in the comparison among FC, CHL, and CH, was identified. Three miRNAs with FDR < 0.05 were also identified in the comparison between the FC and CH groups. Correlated with the amount of HBV DNA, the expression of three miRNAs, miR-455-5p, 192-5p, and 125b-5p, was increased, while the expression of miR-125a-5p was decreased. Three miRNAs (miR-455-5p, 192-5p, and 125b-5p) whose expression showed a positive correlation with HBV DNA quantity were obtained, while miR-125a-5p showed a negative correlation. Two decision trees for miR-99a-5p and miR-342-3p were able to efficiently distinguish between FC and CH based on SVM. Analysis 2: As CH improved to FC, the expression of miR-454-3p and 590-3p increased in all three cases, and the expression of four miRNAs (miR-574-5p, 361-3p, 483-5p, 194-5p) decreased. Expression of miR-485-3p was decreased in cases that improved from CH to FC, and expression increased in cases that remained CH. In all cases of FC improvement, the 97th amino acid sequence in the core region was initially wild type, but mutated from I to L upon improvement to FC. **Conclusion:** Patients with chronic HBV infection showed specific miRNA expression patterns according to disease type (CH, CHL, FC), and disease differentiation was possible using SVM based on miRNA

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expression patterns. It was shown that miRNAs that show different expression patterns according to the clinical course can be used to predict clinical course (FC improvement prediction).

Disclosures: Yoshiki Murakami: Nothing to Disclose, Takashi Honda: Nothing to Disclose, Yuichirou Harada: Nothing to Disclose, Shinya Yokoyama: Nothing to Disclose, Kenta Yamamoto: Nothing to Disclose, Takanori Ito: Nothing to Disclose, Norihiro Imai: Nothing to Disclose, yoji ishizu: Nothing to Disclose, Masahiko Kuroda: Nothing to Disclose, Hiroki Kawashima: Nothing to Disclose

1276 | BASELINE RATES OF PERINATAL HEPATITIS B SCREENING AND VACCINATION IN PHILADELPHIA OBSTETRIC CLINICS PRIOR TO THE UNIVERSAL TRIPLE SCREENING ERA

M. Elle Saine[1] Julia Szymczak[2] William Short[1] Celeste Durnwald[1] Robert Gross[1] Vincent Lo Re III[1] Jessie Torgersen[3], [1]Hospital of the University of Pennsylvania, [2]University of Utah School of Medicine, [3]University of Pennsylvania Perelman School of Medicine

Background: Prenatal care is a key opportunity to screen patients for hepatitis B virus (HBV), link them to care or vaccination, and prevent perinatal transmission. In 2023, the US Centers for Disease Control and Prevention recommended all adults receive a one-time HBV triple panel screening to identify those in need of vaccination. Baseline metrics of HBV screening and vaccination are needed among pregnant patients to understand how to optimize implementation of these interventions. **Methods:** We conducted a retrospective cohort study using electronic health records among all pregnant patients with a first prenatal visit at two outpatient obstetrics clinics in Philadelphia between January 2018 and December 2022, with 12 months of follow-up post-delivery. Only the first eligible pregnancy during this period was included. Outcomes were: 1) completion of HBV surface antigen (HBsAg) screening during pregnancy, 2) completion of one-time HBV triple panel screening (HBsAg, core antibody [anti-HBc], surface antibody [anti-HBs]), and 3) receipt of ≥1 dose of HBV vaccine (among patients without laboratory evidence of HBV immunity) within the follow-up period. Univariate logistic regression analyses evaluated factors associated with HBV vaccination. **Results:** Among 11,853 pregnant patients, 9,782 (82.5%) completed HBsAg screening during pregnancy; 6,227 (63.6%) during the first trimester. Overall, only 82 (0.69%) patients underwent triple screen prior to delivery; 30 (36.6%) were nonimmune. Additionally, 663 patients had a history of anti-HBs testing prior to delivery, of whom, 245 (36.9%) had a negative (229 [34.5%]) or indeterminant (16 [2.4%]) test. Among 11,802 patients without laboratory evidence of immunity, 51 (0.4%) received ≥1 dose of HBV vaccine during pregnancy or post-partum follow-up, and 13 (25.5%) completed the HBV vaccine series within the follow-up period. Receipt of HBV vaccination did not differ by age, race, clinic, provider type, or Medicaid status (Table 1). **Conclusion:** Prior to universal HBV screening recommendations, fewer than 1% of pregnant patients had documented HBV triple panel screening before delivery. HBsAg screening rates in the two outpatient practices were high, suggesting feasibility of triple panel implementation within existing clinical workflows. Among patients without demonstrated HBV immunity, vaccination rates were very low. Future research is needed to evaluate uptake of universal HBV triple panel screening and optimize vaccination during pregnancy and post-partum care.

Table 1. Univariate logistic regression predicting receipt of at least one dose of hepatitis B vaccine during pregnancy or within 12 months post-partum.

	Total (%) (N=11,853)	Not Vaccinated* (N=11,802)	≥1 HBV Vaccine† (N=51)	Odds Ratio (95% CI)	P value
Age (mean [SD])	29.08 (6.05)	29.08 (6.05)	29.14 (6.51)	1.00 (0.96 - 1.05)	0.96
Race					
White	2,641 (22.28%)	2,634 (22.32%)	7 (13.73%)	Ref	Ref
Black/African American	7,183 (60.43%)	7,127 (60.39%)	36 (70.59%)	1.80 (0.84 – 4.28)	0.12
Asian	914 (7.71%)	909 (7.70%)	5 (9.80%)	2.07 (0.66 – 6.54)	0.22
Hispanic/Latinx	575 (4.85%)	574 (4.86%)	1 (1.96%)	0.66 (0.08 – 5.34)	0.69
Other	560 (4.72%)	558 (4.73%)	2 (3.92%)	1.35 (0.28 – 6.51)	0.71
Clinic					
Non-teaching	4,964 (41.88%)	4,942 (41.87%)	22 (43.14%)	Ref	Ref
Teaching	6,889 (58.12%)	6,860 (58.13%)	29 (56.86%)	0.95 (0.54 – 1.65)	0.86
Provider Type					
Attending	4,353 (36.72%)	4,336 (36.74%)	17 (33.33%)	Ref	Ref
Resident	612 (5.16%)	611 (5.18%)	1 (1.96%)	0.42 (0.05 – 3.14)	0.39
Nurse Practitioner	5,248 (44.28%)	5,223 (44.26%)	25 (49.02%)	1.22 (0.66 – 2.26)	0.53
Insurance					
Non-Medicaid	5,693 (48.03%)	5,662 (47.97%)	31 (60.78%)	Ref	Ref
Medicaid	6,160 (51.97%)	6,140 (52.03%)	20 (39.22%)	0.59 (0.34 – 1.04)	0.07

Abbreviations: HBV, hepatitis B virus; CI=confidence interval; SD=standard deviation.
Not vaccinated patients did not have documented laboratory evidence of HBV immunity and did not receive the HBV vaccine during pregnancy or within 12 months post-partum.
†Vaccinated patients did not have documented laboratory evidence of HBV immunity and received the HBV vaccine during pregnancy or within 12 months post-partum.

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1277 | RISK FACTORS AND CONSEQUENCES OF PRE- AND ON-TREATMENT ALANINE AMINOTRANSFERASE (ALT) FLARES IN PATIENTS WITH CHRONIC HEPATITIS B VIRUS (CHBV) INFECTION: A UNITED STATES (US) COHORT STUDY

Myriam Drysdale[1] Rose Chang[2] Shuang Wang[2] Megan Pinaire[2] Manasi Mohan[2] Rui Song[2] Mei Sheng Duh[2] Grace Dolman[3] Dickens Theodore[4] Iain Gillespie[3], [1]GSK, London, UK, [2]Analysis Group, Inc., Boston, MA, USA, [3]GSK, Stevenage, UK, [4]GSK, Durham, NC, USA

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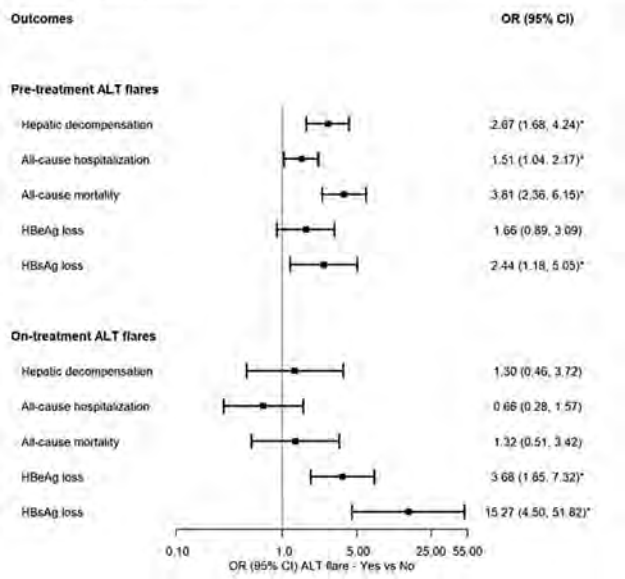
Background: Patients with cHBV infection may experience ALT flares spontaneously, or due to treatment initiation or discontinuation, likely caused by stimulation of the immune system against infected hepatocytes. We assessed 1) the association between pre-/on-treatment ALT flares and both HBsAg loss and clinical outcomes among a diverse US population; 2) potential risk factors for these flares. **Methods:** Retrospective study conducted using the Optum® de-identified electronic health record dataset (2012–2019) among patients with cHBV infection in the US. Marginal structural models estimated the association between ALT flares and clinical outcomes accounting for time-varying confounding; adjusted odds ratios (aOR) and 95% confidence intervals (CI) were reported. A Cox proportional hazards regression model was used to assess risk factors for ALT flares. **Results:** Among 14,328 cHBV patients (pre-treatment) with no co-infection, 2,298 initiated treatment (on-treatment cohort; 46% Asian, 59% men, 29% HBeAg-positive, mean age 48 years). 364 (2.5%) patients experienced ≥ 1 pre-treatment ALT flare and 84 (3.7%) ≥ 1 on-treatment flare. On-treatment ALT flares were associated with HBsAg loss and HBeAg loss (aOR [95% CI]: 15.3 [4.5, 51.8] and 3.7 [1.9, 7.3], respectively), but not with clinical outcomes (hepatic decompensation, aOR: 1.3 [0.5, 3.7]; hospitalization, aOR: 0.7 [0.3, 1.6]); death, aOR: 1.3 [0.5, 3.4]). Pre-treatment ALT flares were associated with spontaneous HBsAg loss (aOR: 2.4 [1.2, 5.1] and also associated with an increased risk of hepatic decompensation (aOR: 2.7 [1.7, 4.2]), hospitalization (OR: 1.5 [1.04, 2.2]), and death (OR: 3.8 [2.4, 6.2]), likely due to disease progression among untreated patients. Risk factors for pre-treatment ALT flare included male sex, history of flares, metabolic syndrome, liver fibrosis, compensated cirrhosis (CC) and decompensated liver disease (DLD). Risk factors for on-treatment flare included younger age, white race, history of flares, liver fibrosis, CC and DLD. **Conclusion:** Understanding the risk factors and consequences of ALT flares in patients with cHBV infection is critical for providing optimal care. In line with literature, on-treatment flares were associated with HBsAg and HBeAg loss. Flares occurring before treatment initiation were associated with long-term clinical outcomes, while no association with adverse clinical outcomes was observed for flares occurring during treatment. Funding: GSK Study 217283.

Figure. Forest plot of adjusted associations between clinical/virological outcomes and pre-treatment and on-treatment ALT flares among patients with cHBV infection in the US



ALT, alanine aminotransferase; CI, confidence interval; cHBV, chronic hepatitis B virus; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; OR, odds ratio

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Healthcare: Grant/Research Support, Grace Dolman: GSK: Employee, Dickens Theodore: GSK: Employee, GSK: Stock - publicly traded company, Iain Gillespie: GSK: Employee & holds stock (publically traded company)

1278 | EXPOSURE TO TENOFOVIR ALAFENAMIDE AND TENOFOVIR DISOPROXIL FUMARATE AND THE RISK OF HEPATOCELLULAR CARCINOMA

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Background: Nucleos(t)ide analogs have been associated with reduced risk of hepatocellular carcinoma (HCC) in patients with hepatitis B virus (HBV) infection. Many, though not all, studies have suggested that tenofovir-based therapies are more effective than entecavir in reducing HCC risk. Here, we examine HCC risk based on exposure to tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF) in patients with chronic hepatitis B. **Methods:** Data from four pivotal phase 3 trials were pooled to examine the association between TAF/TDF exposure and HCC occurrence. These included Studies 102 and 103, in which patients were randomized (2:1) to TDF vs adefovir dipivoxil (ADV) for 48 weeks, followed by open-label TDF (up to 8 years' total treatment [384 weeks]), and Studies 108 and 110, in which patients were randomized (2:1) to TAF vs TDF for up to 144 weeks, followed by open-label TAF (up to 8 years' total treatment). HCC occurrence was classified as an adverse event and assessed as part of routine care (hepatic ultrasonography conducted in Studies 108 and 110). The outcome variable in the uni- and multi-variate Cox proportional hazards analyses was HCCs occurring after 48 weeks of treatment initiation or switching (ADV to TDF), as HCCs occurring within the timeframe may be considered to have pre-existed. This design allows consideration of predictor variables at baseline and up to 48 weeks without a concern for immortal time bias. Exposure to TAF vs TDF was the main predictor variable and was captured by the total TAF exposure time/(total TAF exposure time + total TDF exposure time), with values ranging between 0 (TDF only) and 1 (TAF only). **Results:** In total, 2,273 patients (Studies 102/103: n = 641; Studies 108/110: n = 1,632) were included in the pooled analysis. By Year 8, 46 (2.0%) patients had developed HCC (9 cases occurred within the first 48 weeks and were excluded). Table 1 presents the results of the univariate and multivariate Cox proportional hazards analyses. In the univariate model, sex, age, cirrhosis, normalization of alanine aminotransferase (ALT) levels at Week 24, and exposure to TAF vs TDF were significantly associated with decreased HCC risk. In the final multivariate analysis, exposure to TAF vs TDF was significantly associated with a 70.0% reduction in HCC risk compared to TDF (hazard ratio = 0.30). Independently, ALT normalization at Week 24 was also significantly associated with decreased HCC risk. **Conclusion:** Long-term TAF treatment was associated with a greater reduction in HCC risk than TDF treatment. Differences in study design, population, and timing should be considered, and real-world data may help to confirm these findings.

Table 1. Factors associated with HCC development (Cox regression analysis)

Parameter	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Sex, male vs female	2.93 (1.14–7.51)	0.0255	4.14 (1.57–10.93)	0.0041
Age, years	1.08 (1.05–1.11)	<0.0001	1.09 (1.05–1.13)	<0.0001
Asian, yes vs no	1.72 (0.79–3.77)	0.1727	3.19 (1.32–7.72)	0.0102
Cirrhosis, yes vs no	4.32 (2.24–8.33)	<0.0001	-	-
Baseline HBeAg, positive vs negative	0.59 (0.31–1.14)	0.1166	-	-
Baseline HBV DNA level				
6–8 $\log_{10}$ IU/mL vs <6 $\log_{10}$ IU/mL	1.31 (0.63–2.69)	0.4704	-	-
>8 $\log_{10}$ IU/mL vs <6 $\log_{10}$ IU/mL	0.51 (0.19–1.36)	0.1775	-	-
ALT normalization at Week 24,† yes vs no	0.29 (0.13–0.67)	0.0037	0.29 (0.13–0.68)	0.0041
Exposure, time on TAF vs TDF	0.41 (0.20–0.83)	0.0136	0.30 (0.13–0.71)	0.0061

p values were determined using Chi-squared tests. An initial multivariate analysis was conducted using all parameters, then was re-run using only parameters found to be significant predictors of HCC (in the multivariate model); therefore, parameters without data were not found to be significant. †At AASLD criteria were used for defining ULN: 25 U/L for females and 35 U/L for males. AASLD: American Association for the Study of Liver Diseases; ALT: alanine aminotransferase; DNA: deoxyribonucleic acid; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; HR: hazard ratio; IU: International Unit; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; ULN: upper limit of normal.

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Consultant, H.C. Wainwright & Co: Consultant, Sang Hoon Ahn: Nothing to Disclose, Ira Jacobson: Nothing to Disclose, Masashi Mizokami: Nothing to Disclose, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Frida Abramov: Nothing to Disclose, Leland Yee: Nothing to Disclose, Hongyuan Wang: Gilead Sciences: Employee, Catherine Frenette: Nothing to Disclose, Scott Fung: Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Abbvie: Advisor, Novo Nordisk: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Grant/Research Support, GSK: Advisor, GSK: Speaking and Teaching, Lupin: Speaking and Teaching, AstraZeneca: Speaking and Teaching, AstraZeneca: Advisor, Patrick Marcellin: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose, Jinlin Hou: Nothing to Disclose, Seng Gee Lim: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose, Maria Buti: Nothing to Disclose

1279 | SEX AND AGE-BASED CLINICAL HETEROGENEITY IN HIGH HBV DNA PATIENTS

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Background: High HBV DNA level is a crucial predictor of adverse long-term outcomes in chronic hepatitis B (CHB). Despite similarly high viral loads, patients may differ significantly in liver inflammation (ALT), fibrosis progression, and clinical outcomes. This heterogeneity's relationship to age and sex, particularly in females, and its implications for mother-to-child transmission (MTCT) remain unclear. Understanding these nuances is vital for accurate risk stratification and tailored antiviral treatment. **Methods:** We retrospectively analyzed 420 CHB patients with HBV DNA $>$ 10^7 IU/mL. Demographics, education, marital status, residence, occupation, reproductive history, and MTCT prevention practices were recorded. Patients were stratified by sex and age group to identify clinical variations and their potential causes. Special focus was given to female patients' MTCT characteristics. **Results:** The cohort (217 males, 203 females) showed a similar age distribution between sexes, with a mean age of 38.14 $\pm$ 9.50 years for males and 38.32 $\pm$ 9.75 years for females (P = 0.870). Overall ALT abnormality was significantly higher in males compared to females. Specifically, males had higher median ALT (71 vs. 49 U/L, $P < 0.001$), CAP (231 vs. 211 dB/m, $P = 0.005$), and LSM (6.5 vs. 6.1 kPa, $P = 0.040$). Stratified by age, females aged 50-60 exhibited higher LSM and CAP values, whereas HBsAg and HBeAg levels declined with age. Conversely, younger males displayed higher ALT levels that decreased with age; similarly, viral markers decreased progressively. Among females, higher educational attainment (college level and above) correlated significantly with lower child HBV infection rates ($P = 0.010$). Younger mothers (< 30 years) had higher child infection rates compared to older mothers (mean age 27 vs. 31, $P = 0.024$). **Conclusion:** Significant heterogeneity exists among high-HBV DNA CHB patients, with pronounced sex and age-related differences. Elevated ALT in older females correlates with fatty liver, coinciding with increased fibrosis. Higher maternal education and younger maternal age are associated with reduced and increased MTCT, respectively. Personalized clinical management strategies considering sex, age, and social determinants are essential to optimize patient outcomes and prevent vertical transmission.

Table 1. Baseline characteristics of chronic HBV patients with high viral load, stratified by sex.

	Total (n=420)	Male (n=217)	Female (n=203)	*P*
Age (years)	38.23 ± 9.60	38.14 ± 9.50	38.32 ± 9.75	0.870
HBV DNA (lg) (IU/mL)	7.60 (7.30, 7.80)	7.70 (7.30, 7.80)	7.60 (7.40, 7.70)	0.760
HBsAg (IU/mL)	30,109.00 (9,902.00, 55,855.00)	32,063.00 (9,902.00, 55,855.00)	27,844.00 (9,902.00, 55,855.00)	0.740
HBeAg (S/CO)	1,320.00 (887.00, 1,597.00)	1,411.00 (887.00, 1,597.00)	1,392.00 (887.00, 1,597.00)	0.560
ALT (U/L)	59.00 (30.00, 123.00)	71.00 (30.00, 123.00)	49.00 (25.00, 71.00)	<0.001
AST (U/L)	41.00 (25.00, 71.00)	43.00 (25.00, 71.00)	36.00 (25.00, 71.00)	0.080
CAP (dB/m)	223.00 (195.00, 257.00)	231.00 (195.00, 257.00)	211.00 (195.00, 257.00)	0.005
LSM (kPa)	6.40 (5.10, 9.20)	6.50 (5.10, 9.20)	6.10 (5.10, 9.20)	0.040

Note. Data are presented as mean ± standard deviation (age) or median (interquartile range, IQR) for non-normally distributed variables. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid (log₁₀ IU/mL); LSM, liver stiffness measurement; S/CO, signal-to-cutoff ratio. Statistical comparisons were performed using the Mann–Whitney U test.Statistical comparisons were performed using the Mann–Whitney U test for continuous variables or chi-square test for categorical variables. *P*-values <0.05 were considered statistically significant.

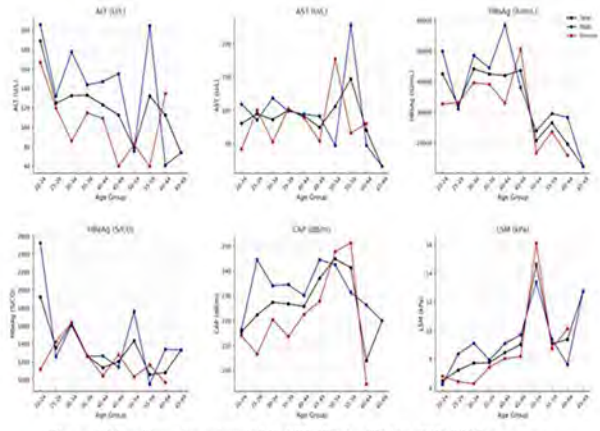

Figure 1. Mean biomarker values (ALT, AST, HBsAg, HBeAg, CAP, LSM) across age groups, stratified by sex.

Disclosures: Jie Liu: Nothing to Disclose, Jia Li: Nothing to Disclose, Guifeng Li: Nothing to Disclose

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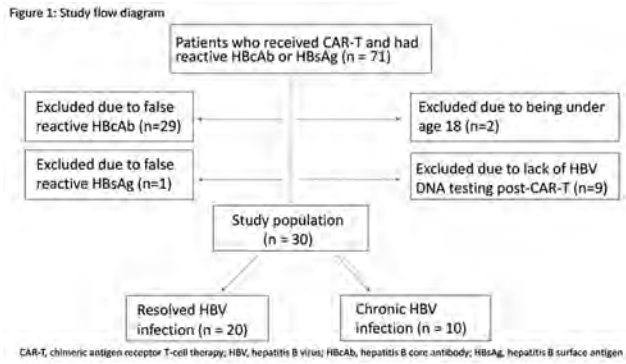
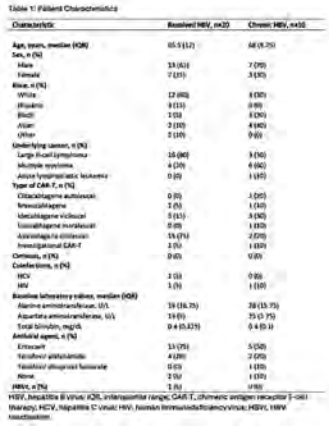
1280 | HEPATITIS B VIRUS REACTIVATION IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES RECEIVING CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY

Abdullah Shaikh[1] Khalis Mustafayev[1] Filippos Koutroumpakis[1] Joanne arvelaez Pascucci[1] Hao Chi Zhang[1] Krina Patel[1] Sairah Ahmed[1] Harrys Torres[1], [1]The University of Texas MD Anderson Cancer Center

Background: Chimeric antigen receptor T-cell therapy (CAR-T) targeting CD19 or B-cell maturation antigen has been associated with hepatitis B virus reactivation (HBVr), but there are limited data on HBVr after CAR-T in patients with hematological malignancies. We studied the incidence, characteristics, and management of HBVr in this patient population. **Methods:** We retrospectively identified adult lymphoma and myeloma patients with a history of resolved or chronic HBV who received CAR-T between 1/1/2015 and 8/31/2024. Patients with false reactive HBV core antibody (HBcAb), false reactive HBV surface antigen (HBsAg), or incomplete HBV DNA data were excluded. Resolved HBV was defined as negative HBsAg with positive HBcAb; chronic HBV, as positive HBsAg for $\geq$6 months with positive HBcAb; and occult HBV, as negative HBsAg with detectable HBV DNA. HBVr was defined per the 2018 AASLD guidelines. The risk of HBVr was categorized as low ($<$1%), moderate (1-10%), or high ($>$10%). **Results:** Of the 71 HBV-infected patients who received CAR-T during the study period, 30 were included in the analysis (Figure 1). The patients' characteristics are given in Table 1. Most patients were men (20 [67%]), were over age 65 (17 [57%]), had large B-cell lymphoma (19 [63%]), received axicabtagene ciloleucel (axi-cel; 17 [57%]), had resolved HBV (20 [67%]), and were evaluated by HBV specialists (22 [73%]). The median follow-up time after CAR-T was 30 months (interquartile range, 45 months). Most patients with resolved HBV (19/20 [95%]) or chronic HBV (9/10 [90%]) were on HBV prophylaxis; the most common antivirals were entecavir (75%) and tenofovir alafenamide (21%). Only 1 patient (3%), who had resolved HBV, developed HBVr. This patient received rituximab-based therapy followed 1 month later by axi-cel. Approximately 1 week after completing CAR-T, he developed HBVr with low-grade viremia ($<$10 IU/mL) while receiving entecavir, which was continued with no further episodes of HBVr. Two patients (1 with resolved HBV, and 1 with occult HBV with intermittent low-grade viremia), who were closely monitored by HBV specialists, did not receive HBV prophylaxis after CAR-T; neither developed HBVr. **Conclusion:** CAR-T poses a low to moderate risk of HBVr in infected patients with hematologic malignancies. HBV prophylaxis can prevent HBVr in this patient population. However, a select group of patients with HBV can be closely monitored without HBVr prophylaxis.





Disclosures: Abdullah Shaikh: Nothing to Disclose, Khalis Mustafayev: Nothing to Disclose, Filippos Koutroumpakis: Nothing to Disclose, Joanne arvelaez Pascucci: Nothing to Disclose, Hao Chi Zhang: Nothing to Disclose, Krina Patel: Nothing to Disclose, Sairah Ahmed: Nothing to Disclose, Harrys Torres: Gilead: Principal Investigator, Merck: Principal Investigator

1281 | METABOLIC EFFECTS AND CARDIOVASCULAR DISEASE RISKS OF TDF OR TAF IN PATIENTS WITH CHRONIC HEPATITIS B:A SYSTEMATIC REVIEW AND META-ANALYSIS

Peng Hu[0] Yuan-hai Zhou[0], [0] The First Affiliated Hospital of Chongqing Medical University

Background: The effects of Tenofovir Disoproxil Fumarate (TDF) or Tenofovir Alafenamide (TAF) on lipid profiles have been observed in chronic hepatitis B (CHB) treatment. However, the metabolic features and their impact on cardiovascular risk remain unclear. We conducted a systematic review and meta-analysis to evaluate these effects. **Methods:** We searched for studies from four major databases (PubMed, Web of

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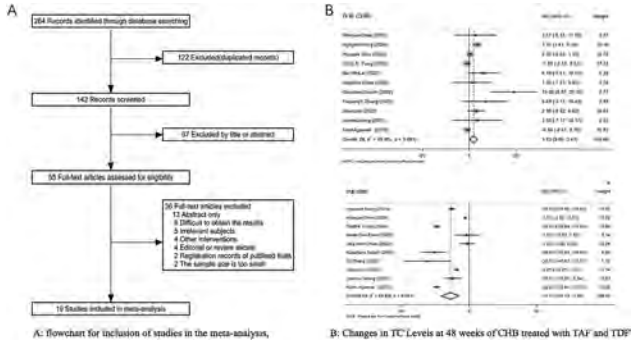
Science, EMBASE, and the Cochrane Library) that reported the effects of TDF or TAF on metabolism and cardiovascular disease risk. The changes in metabolic parameters and 10-year atherosclerotic cardiovascular disease (ASCVD) risk were compared with baseline in the TDF and TAF treatment groups. Extracted data were analyzed with the random-effects model or the fixed-effects model. Potential sources of heterogeneity were investigated using sensitivity and subgroup analyses. **Results:** A total of 19 studies including 19,396 CHB patients (12,067 in TDF-only group, 5423 in TAF-only group, and 1906 in TDF-switched group) were included in this meta-analysis. We found that both TAF and TDF treatment mildly increase the 10-year ASCVD risk. The TAF treatment showed significant increases in body weight, with no significant effects were observed on lipid levels or blood glucose. While TDF treatment has a lipid-lowering effect and caused weight loss. Subanalyses emphasized the impact of changing antiviral treatment strategies on metabolism. We found an increased risk of dyslipidemia and body weight gain after switching from TDF to TAF treatment. **Conclusion:** Although TAF and TDF treatments exhibit different metabolic characteristics, both mildly increase the risk of cardiovascular disease.



A: flowchart for inclusion of studies in the meta-analysis, B: Changes in TC Levels at 48 weeks of CHB treated with TAF and TDF

Disclosures: Peng Hu: Nothing to Disclose, Yuan-hai Zhou: Nothing to Disclose

1282 | UBIQUITINATION OF NTCP AT RESIDUE K340 IS A CRITICAL DETERMINANT FOR NTCP ENDOCYTOSIS AND HEPATITIS B VIRUS (HBV) INFECTIO

Monique Appelman[1] Anh Nguyen[2] Andreas Oswald[3] Aaron Lucko[3] Coen Paulusma[4] Ulrike Protzer[3] Stan van de Graaf[5], [1]UMC Utrecht, [2]Amsterdam UMC, [3]Institute of Virology, Technical University of Munich / Helmholtz Munich, [4]Tytgat Institute for Liver and Intestinal Research, [5]Amsterdam UMC, Tytgat Institute for Liver and Intestinal Research

Background: The sodium taurocholate co-transporting polypeptide (NTCP), the main hepatic uptake transporter of conjugated bile salts, has been identified as the docking receptor required for the hepatitis B and D virus (HBV/HDV) entry. The mechanism of NTCP-dependent internalization of HBV/HDV into hepatocytes is, however, poorly understood. We investigated the contribution of posttranslational modification of NTCP on transporter endocytosis as well as HBV docking and infection. **Methods:** NTCP ubiquitination was determined by immunoprecipitation of wild-type NTCP ($NTCP^{WT}$). To identify amino acids involved in NTCP ubiquitination, lysine residues (K) in the C-terminus of NTCP were substituted by arginine (R). HepG2 cells overexpressing NTCP mutants were assessed for protein levels, bile salt uptake activity, NTCP endocytosis and HBV infectivity. TAK-243 was used to assess global ubiquitination effects on uptake activity and HBV infection in $NTCP^{WT}$ HepG2 and HepaRG cells. **Results:** NTCP is ubiquitinated. Compared to $NTCP^{WT}$, the $NTCP^{K340R}$ mutant showed reduced ubiquitination, suggesting that this is the main ubiquitination target within NTCP. Furthermore, $NTCP^{K340R}$ had increased NTCP membrane abundance, coinciding with enhanced bile salt uptake. Notably, $NTCP^{K340R}$ endocytosis was strongly impaired. HBV-derived myr-preS1 peptide binding to $NTCP^{K340R}$ -expressing cells remained intact, increasing the total cellular binding of preS1 peptides-$NTCP^{K340R}$ plasma membrane abundance. Nevertheless, HBV infection of $NTCP^{K340R}$-expressing HepG2 was strongly reduced compared to $NTCP^{WT}$. In line with this, TAK-243 treatment reduced cellular ubiquitination levels and increased the bile salt uptake while reducing the HBV infection. **Conclusion:** The lysine residue at position 340 plays a crucial role in NTCP ubiquitination. Interfering with NTCP ubiquitination resulted in impaired NTCP endocytosis and a concomitant reduction in HBV infection. Our study directly shows that NTCP-mediated endocytosis is critical for HBV entry into the liver.

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1283 | HBV INDUCES LIVER FIBROSIS THROUGH THE ROS AND PYRUVATE-PPARα-DEPENDENT PATHWAY

Xiaoqiong Duan[1] Shasha Li[2] Qingyuan Li[1] Wenxian Wen[1] Olivia Mezzetti[3] Charlotte Warner[3] Min Xu[3] Andre Jeyarajan[3] Yujia Li[1] Yaoqiong Shi[1] Ning Jiang[4] Wenting

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Background: Chronic hepatitis B (CHB) is a major etiology of liver cirrhosis. We previously found that pyruvate, a key intermediate in many metabolic pathways, increases HBV replication. However, the mechanism by which pyruvate mediates HBV-induced liver fibrosis is not well characterized. We hypothesize that HBV induces liver fibrosis through a pyruvate-peroxisome proliferator-activated receptor α (PPARα) - reactive oxygen species (ROS) pathway. **Methods:** We evaluated HBV-induced fibrogenesis in HBV HepAD38, HBV-infected NTCP-HepG2 cells, and hepatic stellate cell lines (HSC, LX2) in mono- and co-culture models, as well as in sera from CHB patients, HBV carrier mouse, HBV-Transgenic mouse (HBV-Tg), humanized liver mouse, and human precision-cut liver slice (PCLS) models. Cells were cultured in medium without pyruvate. Infectious HBV viral particles (HBVvp) were purified from HepAD38 supernatant (HBVsup). We evaluated the effects of the PPARα agonist fenofibrate, the PPARα antagonist GW6471, PPARa RNAi knockdown, and the ROS inhibitor diphenyliodonium chloride (DPI) on HBV-induced liver fibrosis. HBV replication and the expression of pyruvate, PPARα, TGF-β1, and liver fibrosis-related genes were monitored by qRT-PCR, Western blot, or ELISA. **Results:** We found that HBV increased pyruvate levels and fibrosis-related gene expression in both HBV-infected hepatocytes and patient sera. Supernatants from HBV-infected cells (HBVsup) and pyruvate supplementation independently and additively increased expression of profibrotic genes (TGF-β1, TIMP-1, COL1A1, and α-SMA), activated ROS production, and inhibited PPARα expression. Notably, PPARα inhibition and siRNA knockdown increased ROS production and profibrogenic gene expression, while activation of PPARα blocked HBVsup- and pyruvate-induced ROS generation and fibrogenesis. ROS was confirmed to be downstream of PPARα-related fibrogenesis, as ROS inhibition abrogated HBVsup-, pyruvate supplementation-, or PPARα inhibition-induced liver fibrosis. **Conclusion:** HBV infection induces pyruvate production and decreases PPARα expression, leading to increased ROS generation and liver fibrosis. Pyruvate and PPARα represent novel targets for antifibrotic therapeutic development in CHBV.

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1284 | PEGINTERFERON ALPHA-2B RETREATMENT PROMOTES HBSAG LOSS IN CHRONIC HEPATITIS B PATIENTS WITH LOW HBSAG LEVELS: UPDATE RESULTS: OF 60-WEEK FOLLOW-UP AFTER A PHASE 3 TRIAL

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Background: Peginterferon alpha (PegIFNα)-based therapy has been proven to promote HBsAg loss and enable functional cure in patients with chronic hepatitis B. However, the efficacy of PegIFNα retreatment remains to be explored. Our study specifically evaluated the efficacy of PegIFNα-2b retreatment in patients who initially responded well in a phase 3 trial. **Methods:** This is a long-term follow-up study (NCT06707922) of a randomized controlled phase 3 trial (NCT04846491). At the end of the phase 3 trial, nucleos(t)ide analogue (NA)-experienced patients with HBsAg decline ≥ 1 $\log_{10}$ IU/mL and HBsAg level < 100 IU/mL, as well as treatment-naïve patients with HBsAg decline ≥ 1.5 $\log_{10}$ IU/mL and HBsAg level < 1500 IU/mL were enrolled in cohort 2. All patients initially received treatment with PegIFNα-2b (Pegbing®, Xiamen Amoytop Biotech Co., Ltd.)180 μg/week combined with tenofovir alafenamide fumarate (TAF) for 72 weeks, after which all drugs were discontinued and patients were followed up to 5 years. PegIFNα-2b was given intermittently in cycles (8 weeks of treatment + 4 weeks of interval, repeating every 12 weeks). Here, we report the results of the 60-week analysis in cohort 2. **Results:** A total of 47 NA-experienced patients and 15 treatment-naïve patients were included in cohort 2. The average ages of the two populations were 42.5 and 34.5 years, and 85.1% and 66.7% were male. The mean baseline HBsAg level of NA-experienced patients was 13.04 IU/mL, and HBeAg and HBV DNA were negative in all patients. Treatment-naïve patients had mean baseline HBsAg and HBeAg levels of 269.56 IU/mL and 2.24 COI, respectively, with 73.3% were HBeAg negative and 100% were HBV DNA undetectable. HBsAg levels significantly declined in both patients as treatment progressed. By week 60, the mean reduction in HBsAg from baseline amounted to 1.29 and 1.10 $\log_{10}$ IU/mL in NA-experienced and treatment-naïve patients, respectively (Figure 1a). 48.9% (23/47) of NA-experienced patients and 33.3% (5/15) of treatment-naïve patients achieved HBsAg loss at week 60 (Figure 1b), while the HBsAg seroconversion rates were 32.5% (13/40) and 23.1% (3/13), respectively. Among four treatment-naïve patients with HBeAg positive, one achieved HBeAg loss and seroconversion. **Conclusion:** Nearly 50% of NA-experienced patients and over 30% of treatment-naïve patients still achieved HBsAg loss after retreatment with PegIFNα-2b. Patients with good initial responses to PegIFNα have great chance to pursure functional cure by retreatment with PegIFNα.

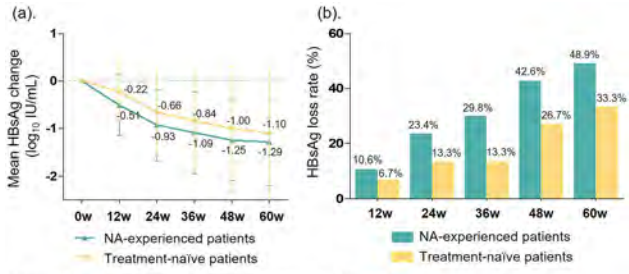

Figure 1. (a) Mean HBsAg change over time; (b) HBsAg loss rate over time.

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1285 | ASSESSMENT OF THE USE AND IMPLEMENTATION OF QHBSAG IN CLINICAL MICROBIOLOGY LABORATORIES IN SPAIN: RESULTS: FROM A NATIONAL SURVEY

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Background: The quantification of hepatitis B surface antigen (qHBsAg) provides essential information on disease phase and residual viral activity. Its relevance is even greater in the context of new therapeutic agents aimed at achieving a functional cure for HBV. Despite its clinical value, the implementation of qHBsAg in Clinical Microbiology (CM) laboratories, as well as awareness of its practical applications, remains limited. This study aims to assess the level of implementation and awareness of the use of qHBsAg in CM labs in Spain, in order to identify barriers and opportunities for its standardization and optimal integration into the management of chronic HBV infection. **Methods:** A cross-sectional, observational, and descriptive study was conducted between March and April 2025 through a survey distributed to CM labs in Spain. The questionnaire collected information on the implementation of qHBsAg, the methodologies used, the number of HBsAg-positive patients, and the main barriers to its application. In centers where the test was available, additional data on quantitative results were requested, categorized into predefined ranges. **Results:** A total of 91 responses were received from 118 CM labs invited. Only 37.4% of centers reported performing qHBsAg. Among non-quantifying centers, 86% did not refer samples to external laboratories, and the most frequently reported reason was a lack of clinical demand (46.4%). Other barriers included lack of equipment and resources, often in combination. Hospital number of beds were significantly associated with implementation ($p = 0.041$): no hospital with < 200, 23.3% with 200-500, 44.9% with 500-1000, and 62.5% with ≥ 1000 beds performed quantification. Regarding geographical distribution, quantification rates varied between autonomous communities but showed no statistically significant differences, possibly due to uneven representation across regions. Among centers that perform qHBsAg, 57.6% do so only after a positive result from a qualitative screening result, 27.3% upon specific request, and 15.2% use the quantitative assay as the initial test. Notably, 69.7% of these centers report the result proactively to the requesting physician, and 81.8% dilute samples above the upper quantification limit to obtain the exact value. In the past year, 40.7% of quantified determinations were below 100 IU/mL, while 27.1% exceeded 3000 IU/mL. **Conclusion:** The survey results show that HBsAg quantification remains underutilized in CM labs in Spain, with limited implementation and heterogeneous practices among centers. The findings help identify specific barriers—such as perceived low demand and lack of integration within clinical care pathways—and provide a solid foundation for designing educational and organizational interventions to support the effective implementation of qHBsAg in routine clinical practice.

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1286 | HIV CO-INFECTION WORSENS INPATIENT OUTCOMES IN HEPATITIS B: A NATIONWIDE ANALYSIS WITH SOCIODEMOGRAPHIC INSIGHTS

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Background: Chronic hepatitis B virus (HBV) infection affects millions worldwide and is a leading cause of cirrhosis and hepatocellular carcinoma. When co-infection with human immunodeficiency virus (HIV) occurs, the clinical course of HBV can worsen due to impaired immune control, accelerated liver disease progression, and complex treatment interactions. Despite these known risks, the inpatient impact of HIV co-infection in HBV-positive patients remains underexplored in large-scale datasets. Moreover, HIV and HBV disproportionately affect populations already facing structural disadvantages, including racial minorities, individuals with low income, and those reliant on public insurance. Understanding how both clinical and social factors shape hospitalization outcomes in this co-infected population is essential to guiding equitable and evidence-based care. **Methods:** We conducted a retrospective cross-sectional analysis using the Nationwide Inpatient Sample (2018–2022). Adult hospitalizations with HBV and HIV infection were identified using ICD-10-CM codes. The primary exposure was HIV co-infection among HBV-positive patients. Outcomes included in-hospital mortality, sepsis, ICU-level care (defined by procedure codes for mechanical ventilation or vasopressor use), length of stay (LOS), and total hospital charges. Multivariable survey-weighted logistic and linear regression models were used to assess associations between HIV co-infection and outcomes, adjusting for age, sex, race, insurance status, income quartile by ZIP code, comorbidities, and hospital characteristics. **Results:** Among an estimated 204,705 hepatitis B–related hospitalizations in the United States from 2018 to 2022, approximately 12,130 (5.9%) involved documented HIV co-infection. Compared to HBV-only patients, those with HIV were younger, more likely to be male, Black, Medicaid-insured, and reside in lower-income ZIP code quartiles. After adjusting for demographic, clinical, and hospital-level factors, HIV co-infection was independently associated with significantly worse outcomes. Co-infected patients had higher odds of in-hospital mortality (adjusted odds ratio [aOR] 1.48; 95% CI: 1.22–1.80; $p < 0.001$), sepsis (aOR 1.88; 95% CI: 1.68–2.09; $p < 0.001$), and ICU-level care (aOR 1.28; 95% CI: 1.08–1.51; $p = 0.003$). Additionally, co-infection was associated with longer hospital stays (+1.7 days; $p < 0.001$) and 28% higher total hospital charges ($p < 0.001$). **Conclusion:** HIV co-infection is associated with significantly worse inpatient outcomes among hepatitis B patients, including higher mortality, sepsis, ICU use, and healthcare costs. These findings highlight the need for integrated clinical management and attention to social risk factors in this high-risk population.

Variable	HBV only (n = 204,705)	HBV + HIV (n = 12,130)	p-value
Age, mean (95% CI)	55.3 (55.1–55.5)	51.3 (50.8–51.8)	<0.001
Female (%)	43.5	19.4	<0.001
Black (%)	22.3	56.0	<0.001
Medicaid as primary payer (%)	29.4	39.1	<0.001
Diabetes (%)	28.7	16.5	<0.001
Hypertension (%)	51.4	47.7	0.0009
Congestive Heart Failure (%)	17.6	19.3	0.059
Lowest-income ZIP quartile (%)	30.6	46.9	<0.001
Large hospital bed size (%)	57.8	65.8	<0.001
South hospital region (%)	28.1	17.7	<0.001
In-hospital mortality (%)	4.4	5.5	0.0126
Sepsis (%)	14.1	22.4	<0.001
ICU proxy (vent/pressor) (%)	6.4	8.7	<0.001
Length of stay, mean (days)	5.4 (5.3–5.4)	7.1 (6.9–7.3)	<0.001
Total charges, mean (USD)	$95,482.00	$109,048.00	<0.001

Table 1. Baseline Demographic, Clinical, and Hospital Characteristics of Hospitalized Patients with Hepatitis B, Stratified by HIV Co-Infection Status (NIS 2018–2022).

Disclosures: Iqra Qazi: Nothing to Disclose, Fnu Versha: Nothing to Disclose, Sunita Devi: Nothing to Disclose, Harika Chintalapalli Patta: Nothing to Disclose, Nigil Thaimuriyil: Nothing to Disclose

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1287 | TOWARDS THE ELIMINATION OF MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS B VIRUS IN HONG KONG: INSIGHTS FROM A POST-VACCINATION SEROLOGIC TESTING PROGRAM

Vivien Tsui[1] Chin Man Poon[2] Zenith Hin Yam Wu[2] Bonnie Chun Kwan Wong[2] Jeffrey Cing Hon Lai[1], [1]Hospital Authority, Hong Kong, China, [2]Special Preventive Programme, Centre for Health Protection, Department of Health, Hong Kong, China

Background: Hong Kong has implemented comprehensive measures to prevent mother-to-child transmission (MTCT) of hepatitis B virus (HBV), including universal antenatal HBsAg screening, universal neonatal hepatitis B vaccination, and hepatitis B immunoglobulin administration for at-risk newborns, all with a coverage of >98%. In Aug 2020, antiviral prophylaxis for pregnant women with high viral load (HBV DNA >200000 IU/mL) was introduced in public hospitals. In 2022, a post-vaccination serologic testing (PVST) program was launched to identify infants with immunoprophylaxis failure (IF) or inadequate immune response. This study explores potential factors contributing to residual MTCT, which might inform gaps in current prevention strategies. **Methods:** The PVST program covered infants born to HBV-infected women from Oct 2020 onwards, who received tests for HBsAg and anti-HBs at 9-12 months of age after completing the primary hepatitis B vaccination series. HBsAg-positive infants were referred to pediatricians, where clinical review on maternal factors, including HBV status awareness, viral load, antiviral prophylaxis eligibility, and treatment adherence, was conducted to identify possible factors associated with IF. **Results:** From Jan 2022 to Dec 2024, 2806 infants were enrolled in the PVST program. Nine (0.3%) tested positive for HBsAg, including one set of twins. All eight mothers were aware of their HBV status during antenatal care. Three (37.5%) mothers were unaware of their eligibility for antiviral prophylaxis, as they received antenatal care either before the implementation of the prophylaxis program or outside the program's coverage. One (12.5%) mother had an HBV DNA of 162000 IU/mL, below the prophylaxis threshold. One (12.5%) mother who was on long-term tenofovir treatment self-discontinued treatment during pregnancy. Three (37.5%) mothers eligible for antiviral prophylaxis either refused or did not adhere to the regimen. **Conclusion:** The absence of completed maternal antiviral prophylaxis in all MTCT cases underscores its critical role in minimizing residual HBV transmission risk in Hong Kong. Achieving the vision of a hepatitis B-free generation necessitates strengthening territory-wide healthcare provider training in HBV management and targeted public education to improve prophylaxis uptake and adherence. Furthermore, the IF in an infant born to a mother with HBV DNA below the current treatment threshold warrants a critical review and evaluation of the prophylaxis initiation criteria.

Disclosures: Vivien Tsui: Nothing to Disclose, Chin Man Poon: Nothing to Disclose, Zenith Hin Yam Wu: Nothing to Disclose, Bonnie Chun Kwan Wong: Nothing to Disclose, Jeffrey Cing Hon Lai: Nothing to Disclose

1288 | HISTOLOGICAL CHARACTERISTICS AND CLINICAL OUTCOMES OF HBEAG-NEGATIVE CHRONIC HBV INFECTION PATIENTS WITH UNDETECTABLE HBV DNA

Lin Weijia[1] Rongrong Ding[1] Shuangshuang Sun[1] Liang Chen[1], [1]Shanghai Public Health Clinical Center

Background: The research on the histological characteristics and clinical outcomes of the liver in patients with chronic hepatitis B virus (HBV) infection who are negative for HBeAg-negative and whose HBV DNA cannot be detected is still insufficient. This study aims to explore the histological characteristics and clinical outcomes of the liver of this type of patients. **Methods:** A total of 275 treatment-naive HBeAg-negative patients with chronic HBV infection who underwent liver biopsy in Shanghai Public Health Clinical Center from January 2010 to July 2022. Patients were categorized into two groups based on HBV DNA status: HBV DNA-negative (n = 168) and HBV DNA-positive (n = 107). The lower limit of HBVDNA detection was 500 IU/mL. The clinical characteristics and liver histological distribution of the two groups of patients were compared. This study defines pathological grade ≥ G2 or/and stage ≥ S2 as significant liver histological changes (SLHC), G0-1 and S0-1 as mild liver histological changes. Longitudinal follow-up was conducted for 100 patients with mild liver histological changes. APRI ≥ 1.5, FIB-4 ≥ 3.25, or liver stiffness measurement (LSM) ≥ 8.0 kPa were defined as the presence of significant liver fibrosis. The Kaplan-Meier curve was used to analyze the cumulative occurrence risk of significant liver fibrosis and HBsAg clearance. **Results:** There was no significant difference between HBVDNA-negative and positive patients in Age, Male, ALT, AST, GGT, TBIL, ALB, PT, WBC, PLT, APRI, and FIB-4 ($P > 0.05$). The serum HBsAg level in the HBV DNA negative group was significantly lower than that in the positive group (2.87 vs. 3.11 $\log_{10}$ IU/ml, $P = 0.031$). Among the overall population, significant liver histological changes accounted for 27.3%, and there was no significant difference between the two groups (26.2% in the HBV DNA negative group vs. 29.0% in the positive group, $P > 0.05$). The cumulative

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incidence of significant liver fibrosis showed no statistically significant difference between the two groups (Log-rank $P = 0.362$, HR = 0.490, 95%CI = 0.102-2.369). The HBsAg clearance rate was slightly higher in the HBV DNA negative group, but there was no significant difference between the two groups (Log-rank $P = 0.075$). **Conclusion:** In HBeAg-negative chronic HBV infection patients, there was no significant difference in the significant liver histological changes, the cumulative risk of significant liver fibrosis, and HBsAg clearance between patients with undetectable and positive HBV DNA. Compared with patients with positive HBV DNA, patients with undetectable HBV DNA had lower serum HBsAg levels and slightly higher serum HBsAg clearance rates.

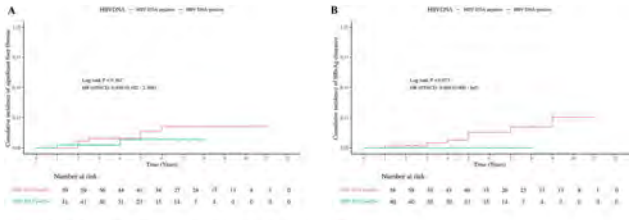

Figure 2 Cumulative incidence of significant liver fibrosis (A), HBsAg clearance (B).

Disclosures: Lin Weijia: Nothing to Disclose, Rongrong Ding: Nothing to Disclose, Shuangshuang Sun: Nothing to Disclose, Liang Chen: Nothing to Disclose

1289 | BRIDGING THE GAP BETWEEN ACIP GUIDELINES AND PRACTICE: IMPROVING HEPATITIS B VACCINATION RATES IN INTERNAL MEDICINE RESIDENT CLINICS

Mohammad Adam[1] Ehsan Sha'ban[2] Ameen Awad[2] Abdelsabour Hassan[2] Himil Mahadevia[2] Julie Banderas[2] David Wooldridge[2], [1]University of Missouri - Kansas City School of Medicine, [2]University of Missouri-Kansas City

Background: Chronic hepatitis B virus (HBV) infection remains a major public health concern in the United States, contributing to cirrhosis, hepatocellular carcinoma, and liver-related mortality. Despite a highly effective vaccine, only 30% of adults aged ≥19 years had completed the hepatitis B vaccination series by 2018. In response to rising incidence, the Advisory Committee on Immunization Practices (ACIP) updated its guidelines to recommend universal adult vaccination for individuals aged 19–59. Yet, vaccination rates remain suboptimal. At our institution, baseline data from 2020 showed hepatitis B vaccine utilization among eligible outpatients was <1%, underscoring a critical gap in preventive care. We aimed to increase vaccine ordering rates among eligible patients in two internal medicine resident clinics by 30%. **Methods:** A QI intervention was conducted from September 2024 to March 2025 in two university-affiliated outpatient clinics. Strategies included interactive lectures, weekly educational emails, meme-based messages via Telegram, and visual workstation reminders. Vaccine utilization rate (orders among eligible patients) was the primary outcome. Hepatitis B surface antigen (HBsAg) screening orders were tracked as a process measure reflecting HBV status assessment. A balancing measure assessed inappropriate vaccine orders (e.g., for previously vaccinated or infected patients). Resident knowledge was evaluated via pre- and post-intervention surveys, which also explored perceived barriers to vaccination. **Results:** Hepatitis B vaccine utilization increased tenfold from 0.4% in November to 4.1% in February. Monthly vaccine orders rose from 1 to 11. HBsAg screening improved from 0.7% (2/289) to 3.8% (10/264). No inappropriate vaccine orders were recorded. Survey participation remained stable (24 pre vs. 27 post), with correct knowledge responses increasing from 38% to 76%, and incorrect responses dropping from 74 to 32. Residents identified competing clinical priorities (53%), patient hesitancy (32%), uncertainty about prior vaccination (9%), and insurance issues (6%) as major barriers. **Conclusion:** Following updated ACIP guidelines, our targeted QI strategy improved hepatitis B vaccine uptake in resident-run outpatient clinics. Educational outreach, reminder systems, and workflow optimization enhanced provider knowledge and vaccination behavior. Sustained improvement will require continued focus on guideline awareness, patient engagement, and efficient vaccination record review.

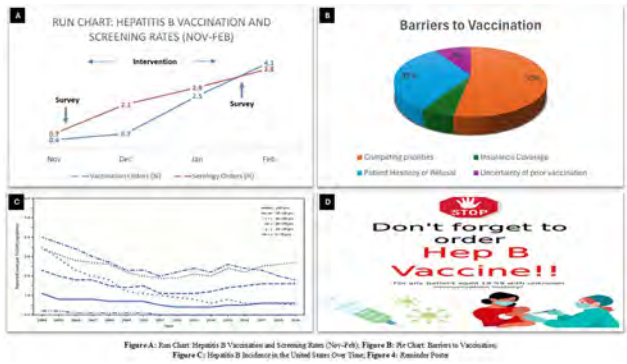

Figure A: Run Chart: Hepatitis B Vaccination and Screening Rates (Nov-Feb); Figure B: Pie Chart: Barriers to Vaccination; Figure C: Hepatitis B Incidence in the United States Over Time; Figure 4: Reminder Poster

Disclosures: Mohammad Adam: Nothing to Disclose, Ehsan Sha'ban: Nothing to Disclose, Ameen Awad: Nothing to Disclose, Abdelsabour Hassan: Nothing to Disclose, Himil Mahadevia: Nothing to Disclose, Julie Banderas: Nothing to Disclose, David Wooldridge: Nothing to Disclose

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1290 | ECONOMIC BURDEN OF NON-CIRRHOTIC PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION IN THE UNITED STATES

Anna Coutinho[1] Kiran Rai[2] Amisha Patel[2] Thomas Jennison[2] Rosie Hulme[2] Vera Gielen[3] Seth Anderson[3] Christopher Bell[1], [1]GSK, [2]Adelphi Real World, [3]GSK (at time of study)

Background: While the long-term complications of chronic hepatitis B virus [cHBV] infection are well-recognized, the disease is considered as manageable with limited data on the economic burden of non-cirrhotic patients. This study described the costs and healthcare resource utilization [HRU] of patients with non-cirrhotic cHBV infection in the US. **Methods:** This retrospective cohort study used administrative claims data from the Merative™ MarketScan® Database. Patients were indexed on the chronologically first cHBV diagnosis occurring between Jan 2017–Jun 2022. Included patients were aged ≥18 years, had continuous eligibility ≥12 months prior to (baseline) and ≥3 months after index, and without liver disease progression or co-infection (HIV, HCV or HDV) at baseline. All-cause HRU per year and costs per patient per year [PPPY] (2022 USD) were evaluated from the index date until the earliest date of liver disease progression or the end of follow-up. Data were analyzed descriptively overall, by treatment status with nucleos(t)ide analogues [Nas]/Peg-interferon [IFN] and newly- or previously- diagnosed status. **Results:** A total of 7,466 patients were included: mean (standard deviation [SD]) age 47.1 (12.1) years; 53.2% female; mean (SD) follow-up of 2.6 (1.8) years; 37.8% newly diagnosed. Overall, 31.3% of patients were treated with NAs/IFN during follow-up, higher in previously vs newly diagnosed patients (42.5% vs. 12.8%). Total mean (SD) costs were $24,230 (88,409) PPPY with treated patients having higher costs versus untreated patients ($32,240 vs $20,115). Hospitalization ($11,922 untreated vs $10,105 treated) and ER visit costs ($487 untreated vs $414 treated) did not differ by treatment status; however, untreated patients had a higher proportion with hospitalizations and ER visits whereas treated patients had more lab and imaging tests (Table). Newly diagnosed patients had higher total mean costs PPPY ($29,798 vs $20,845) and had a higher proportion with hospitalizations and ER visits and lower proportion with lab or imaging tests than previously diagnosed patients (Table). **Conclusion:** Despite the uncomplicated nature of non-cirrhotic cHBV infection, economic burden is high. Results demonstrate a disparity in cHBV infection management with potential opportunities for improving care among those untreated and newly diagnosed.

Table. All-cause Healthcare Resource Use and Costs of Non-Cirrhotic Patients with cHBV

	Overall (n=7,466)	NA/IFN Treated (n=2,534)	Not Treated with NA/IFN (n=4,932)	Newly diagnosed (n=2,823)	Previously diagnosed (n=4,643)
All-cause healthcare costs PPPY (2022 USD), mean (SD)					
Total	$24,230 (88,409)	$32,240 (99,096)	$20,115 (82,088)	$29,798 (114,846)	$20,845 (67,237)
Medical	$18,955 (83,983)	$21,571 (92,687)	$17,612 (79,115)	$25,667 (110,342)	$14,875 (62,423)
Pharmacy	$5,274 (16,214)	$10,669 (17,950)	$2,503 (14,487)	$4,130 (19,231)	$5,970 (14,025)
All-cause HRU					
Inpatient, n (%)	2,558 (34.3%)	576 (22.8%)	1,980 (40.1%)	1,419 (50.3%)	1,139 (24.5%)
# of visits per year (95% CI)	0.26 (0.25, 0.26)	0.18 (0.17, 0.19)	0.30 (0.29, 0.31)	0.47 (0.45, 0.48)	0.14 (0.14, 0.15)
Emergency Room, n (%)	3,014 (40.4%)	868 (34.3%)	2,146 (43.5%)	1,526 (54.1%)	1,488 (32.0%)
# of visits per year (95% CI)	0.64 (0.63, 0.65)	0.39 (0.38, 0.41)	0.77 (0.76, 0.79)	1.17 (1.15, 1.20)	0.35 (0.34, 0.36)
Physician visits, n (%)	1,735 (23.2%)	616 (24.3%)	1,119 (22.7%)	783 (27.7%)	952 (20.5%)
# of visits per year (95% CI)	0.47 (0.46, 0.48)	0.48 (0.47, 0.50)	0.47 (0.46, 0.48)	0.69 (0.67, 0.71)	0.35 (0.34, 0.37)
Outpatient hospital, n (%)	2,582 (34.6%)	887 (35.0%)	1,695 (34.4%)	1,144 (40.5%)	1,438 (31.0%)
# of visits per year (95% CI)	0.78 (0.77, 0.79)	0.91 (0.89, 0.94)	0.71 (0.70, 0.73)	1.03 (1.01, 1.05)	0.65 (0.63, 0.66)
Other, n (%)	6,811 (91.2%)	2,407 (95.0%)	4,404 (89.3%)	2,478 (87.8%)	4,333 (93.3%)
# of visits per year (95% CI)	4.48 (4.45, 4.51)	4.52 (4.47, 4.57)	4.46 (4.42, 4.50)	5.35 (5.30, 5.41)	4.01 (3.97, 4.04)
Lab tests, n (%)	6,529 (87.4%)	2,348 (92.7%)	4,181 (84.8%)	2,340 (82.9%)	4,189 (90.2%)
# of tests per year (95% CI)	4.58 (4.55, 4.61)	6.27 (6.22, 6.33)	3.66 (3.62, 3.69)	4.07 (4.02, 4.12)	4.86 (4.82, 4.89)
Imaging tests, n (%)	5,691 (76.2%)	2,215 (87.4%)	3,476 (70.5%)	1,831 (64.9%)	3,860 (83.1%)
# of tests per year (95% CI)	1.63 (1.61, 1.65)	2.13 (2.09, 2.16)	1.36 (1.34, 1.38)	1.22 (1.20, 1.25)	1.85 (1.83, 1.88)

CI: confidence interval; HRU: healthcare resource utilization; IFN: peg-interferon; NA: nucleos(t)ide analogue; PPPY: per patient per year; SD: standard deviation.

Disclosures: Anna Coutinho: GSK: Employee, Kiran Rai: Nothing to Disclose, Amisha Patel: Nothing to Disclose, Thomas Jennison: Nothing to Disclose, Rosie Hulme: Nothing to Disclose, Vera Gielen: Nothing to Disclose, Seth Anderson: Nothing to Disclose, Christopher Bell: Nothing to Disclose

1291 | ISOGENIC STUDIES OF BASAL CORE PROMOTER AND PRECORE MUTANT VARIANTS ACROSS HEPATITIS B VIRUS GENOTYPES

Leon Seifert[1] Georgios Dangas[2] Yingpu Yu[1] Chenhui Zou[1] Catherine Freije[1] Xupeng Hong[1] Mengyin Zhang[1] Corrine Quirk[1] Yichen Zhou[3] Kosuke Ogata[4] Charles Rice[1] William Schneider[1] Eleftherios Michailidis[5] Ype De Jong[3], [1]The Rockefeller University, New York, NY, USA, [2]Department of Pediatrics, Emory University, Atlanta, [3]Weill Cornell Medicine, New York, NY, USA, [4]Kyoto University, Kyoto, Japan, [5]Department of Pediatrics, Emory University, Atlanta, GA, USA

Background: Studying isogenic hepatitis B virus (HBV) mutants in human hepatocyte chimeric mice remains a major challenge. Infection efficiency using cell culture-derived virus is limited, and patient serum samples

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typically contain heterogeneous viral populations. To overcome these limitations, we developed a method to initiate HBV infection via intrahepatic injection of recombinant HBV cccDNA into human hepatocyte chimeric mice (*HBV rcccDNA launch*), enabling the study of viral variants with isogenic controls. We applied this method to investigate basal core promoter (BCP; A1762T/G1764A) and precore (PC; G1896A) mutants in HBV genotypes A, C and D. **Methods:** We generated isogenic, infectious viral stocks of wild-type (WT), BCP-, and PC-mutant variants in HBV-A, HBV-C and HBV-D using the HBV rcccDNA launch method. These stocks were used to infect human hepatocyte chimeric mice, and key viral parameters (HBV DNA, HBsAg, HBeAg) were monitored over time. Liver samples were collected and human hepatocytes were isolated at peak serum viremia. These HBV-infected, mouse-passaged primary human hepatocytes (mpPHHs) were then cultured to assess interferon (IFN) responses using pulse-SILAC proteomics. **Results:** Using HBV rcccDNA launch, we generated viral stocks with defined viral sequences corresponding to either WT or isogenic mutant variants, allowing for direct comparisons of HBV mutant variant in a controlled genetic background. These isogenic variants remained genetically stable, showing neither reversion back to WT nor acquisition of additional mutations. Consistent with clinical observations, no HBeAg secretion was observed in PC-mutant infection, while BCP-mutant infection led to an ~90% reduction of HBeAg serum levels compared to WT. The WT, BCP- and PC-mutant variants showed distinct viral kinetics that were genotype-dependent: in HBV-A and HBV-D, BCP-mutant infection showed a more rapid increase in serum viremia compared to WT and PC-mutant infection. In contrast, in HBV-C an accelerated increase in serum viremia was observed only in the presence of both mutations (PC/BCP double-mutant). Transcriptomic and proteomic studies uncovered unique, variant-specific profiles both in harvested liver tissue and in the pre-infected, IFN-stimulated mpPHHs. **Conclusion:** The BCP mutation, alone or in combination with the PC mutation, accelerates viral infection kinetics in human hepatocyte chimeric mice, and primary human hepatocytes display distinct responses to BCP- and PC-mutant infection. These findings promise to enhance our understanding of how these HBeAg lowering variants may contribute to liver disease progression in chronic HBV infection.

Disclosures: Leon Seifert: Nothing to Disclose, Georgios Dangas: Nothing to Disclose, Yingpu Yu: Nothing to Disclose, Chenhui Zou: Nothing to Disclose, Catherine Freije: Nothing to Disclose, Xupeng Hong: Nothing to Disclose, Mengyin Zhang: Nothing to Disclose, Corrine Quirk: Nothing to Disclose, Yichen Zhou: Nothing to Disclose, Kosuke Ogata: Nothing to Disclose, Charles Rice: Nothing to Disclose, William Schneider: Nothing to Disclose, Eleftherios Michailidis: Nothing to Disclose, Ype De Jong: Nothing to Disclose

1292 | ADHERENCE PATTERNS TO ANTIVIRAL THERAPY IN OLDER ADULTS WITH HEPATITIS B: INSIGHTS FROM GROUP-BASED TRAJECTORY MODELING

Javeria Khalid[1] *Jieni Li*[1] *Rajender R Aparasu*[1],
[1]*University of Houston*

Background: Over one million people in the U.S. live with chronic hepatitis B (CHB), with a considerable percentage being older adults. The effectiveness of first-line nucleoside analogs (NAs) is significantly influenced by treatment adherence; however, evidence on longitudinal adherence patterns is limited. Therefore, we aim to examine adherence trajectories of NAs and identify predictors of non-adherence among older adults with CHB. **Methods:** This retrospective cohort study included continuously enrolled Medicare enrollees aged 65 years and older with CHB from 2014-2019. We included incident users of first-line NAs (including entecavir [ETV], tenofovir disproxil fumarate [TDF] and tenofovir alafenamide [TAF]) for CHB. Monthly adherence was evaluated using the proportion of days covered (PDC). Longitudinal patterns of adherence were discerned by group-based trajectory modeling (GBTM) over a 12-month follow-up period. The predictors of adherence trajectories were analyzed by a multinomial logistic regression model, accounting for sociodemographic and clinical factors as per the Andersen Behavioral Model. **Results:** Among 3,317 incident users of NAs, the mean age was 72.6 years, and 57.85% were male. GBTM identified three distinct adherence patterns: consistently adherent (57.1%), gradual decline in adherence (25%), and rapid decline in adherence (17.9%). The consistently adherent patients varied across the individual NAs (54.13% of ETV, 58.32% of TDF, and 71.91% of TAF). In the multinomial logistic regression model, using consistently adherent group as reference, compared to patients initiated on ETV, those prescribed with TAF had lower odds of being in the gradual decline (OR = 0.59; 95% CI: 0.43–0.81) and rapid decline groups (OR = 0.49; 95% CI: 0.34–0.72). African American patients had higher likelihood of belonging to the gradual (OR = 1.38; 95% CI: 1.05–1.82) and slow decline groups (OR = 1.52; 95% CI: 1.11–2.09), while Asian patients had lower odds for gradual decrease in adherence decline (OR = 0.70; 95% CI: 0.54–0.90). Lower likelihood of gradual decline was also observed among patients with HIV (OR = 0.62; 95% CI: 0.42–0.92), hepatocellular carcinoma (OR = 0.61; 95% CI: 0.38–0.98), and compensated cirrhosis (OR = 0.75; 95% CI: 0.58–0.98). **Conclusion:** Approximately two-thirds of older adults with CHB consistently adhered to NAs, and both clinical and demographic factors were associated with rapid and slow decline of adherence.

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Findings from this study can inform the development of targeted interventions to improve NAs adherence among older adults.
Disclosures: Javeria Khalid: Nothing to Disclose, Jieni Li: Nothing to Disclose, Rajender R Aparasu: Nothing to Disclose

1293 | HBSAG SCREENING AND RISK FACTORS IN A NATIONWIDE PRIVATE LABORATORY PROGRAM

Liliana-Simona Gheorghe[1] Irma Csiki[1] Mihaela Ghioca[1] Mirela Chitul[1] Razvan Cerban[1] Carmen Ester[1] Roxana Saizu[1] Speranta Iacob[1], [1]Fundeni Clinical Institute

Background: Chronic viral hepatitis continues to exert a significant burden on public health in Romania. The RE-LINK project explores the potential of private laboratory networks to contribute to the national hepatitis elimination strategy through structured screening and reflex testing. This abstract presents the results of the prospective phase, focused on HBsAg testing and associated comorbidities in 8,188 adults from predefined risk groups. **Methods:** From January to March 2025, 8,188 individuals were tested for HBsAg, anti-HCV and anti-HDV antibodies in a national private laboratory chain. All HBsAg-positive patients underwent reflex testing for anti-HDV antibodies and HBV DNA, and a standardized questionnaire collected information on risk factors, comorbidities and socioeconomic status. **Results:** The overall HBsAg positivity rate was 3.03%, with detectable HBV viremia in 77% of cases. Anti-HDV antibodies were positive in 1.6% of HBsAg-positive patients. Only 5.4% of tested persons were vaccinated against HBV. HBsAg was more prevalent in men (3.84%) than women (2.62%) ($p = 0.014$). The median age was significantly higher in HBsAg-positive vs. negative individuals (57 vs. 54 years; $p = 0.002$). The key factors associated with HBsAg positivity ($p < 0.05$) included: knowledge of elevated transaminases ($p < 0.0001$), low platelet count ($p < 0.0001$), diabetes mellitus ($p = 0.03$), cardiovascular disease ($p = 0.0016$), neurological/psychiatric disorders ($p = 0.036$), frequent hospitalizations (≥ 2/year) ($p = 0.0042$), history of blood transfusions ($p = 0.017$), incarceration history ($p = 0.032$), known STIs ($p = 0.033$), HIV infection ($p = 0.038$), family history of hepatitis B/C/D ($p < 0.0001$), previous residence in orphanages/institutions ($p = 0.024$), abortion history ($p < 0.0001$), alcohol consumption above risk thresholds ($p = 0.012$). **Conclusion:** The RE-LINK prospective screening study confirms that private laboratory networks can serve as scalable platforms for viral hepatitis detection and linkage to care. This dataset provides the most extensive evidence to date of clinical and demographic risk associations for HBsAg positivity in Romania. Integration of such structured screening with reflex testing in national policy frameworks could accelerate HBV and HDV micro-elimination and reduce complications through earlier identification of high-risk individuals.
Disclosures: Liliana-Simona Gheorghe: Nothing to Disclose, Irma Csiki: Nothing to Disclose, Mihaela Ghioca: Nothing to Disclose, Mirela Chitul: Nothing to Disclose, Razvan Cerban: Nothing to Disclose, Carmen Ester: Nothing to Disclose, Roxana Saizu: Nothing to Disclose, Speranta Iacob: Nothing to Disclose

1294 | MITOCHONDRIAL STRESS IN PATIENTS WITH CHRONIC HEPATITIS B-RELATED HEPATOCELLULAR CARCINOMA

Abdellah Mansouri[1] Luis Correa[1] Manon Van den heede[1] Dorothy Tonui[2] Margaux BOSSIS[3] Stéphanie Narguet[4] Adel HAMMOUTENE[1] Nathalie BOYER[5] Pierre Tonnerre[3] Valerie PAradis[2] Tarik Asselah[6], [1]INSERM U1149, Centre de Recherche sur l'Inflammation, Université de Paris Cité, Paris, France., [2]INSERM U1149, Centre de Recherche sur l'Inflammation, Université de Paris Cité, Paris, France, [3]Institut de Recherche Saint-Louis, Université Paris-Cité, Inserm U1342, Paris, France., [4]Assistance Publique Hôpitaux de Paris, Hôpital Beaujon, Clichy-92110, France, [5]Assistance Publique Hôpitaux de Paris, Hôpital Beaujon, Service d'Hépatologie, Clichy, France, [6]Hôpital Beaujon

Background: Hepatitis B virus (HBV) interacts with hepatic mitochondria and increases liver oxidative stress. We hypothesized that HBV-induced mitochondrial stress might account for the pathophysiology of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). **Methods:** Fifty (50) mono-infected patients with CHB and HCC and 25 healthy controls were included in the study. Liver mitochondrial DNA (mtDNA) damage was screened by long PCR, Southern blot and Slot blot analysis. The expression of the mtDNA-encoded cytochrome *c* oxidase subunits 1 (MT-CO1), Parkinson-juvenile disease protein 2 (PRKN), Phosphatase and Tensin-Induced Putative Kinase-1 (PINK1), Lon Peptidase 1 (LONP1), mitochondrial chaperonins HSPD1 and HSPA9, as well as liver pro-inflammatory cytokines TNF-alpha and IL6 mRNA was investigated by Western-blotting and/or Reverse Transcriptase-quantitative PCR. In vitro, the HBV antigen HBx was expressed in hepatocarcinoma HepG2 cells, treated or not with cisplatin (CDDP), and mitochondrial parameters, Jun-c NH2 terminal Kinase 1 (JNK1) activation as well as apoptosis features were investigated. **Results:** Whereas 100% of patients with HCC exhibited multiple

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mtDNA deletions, only 11% of the controls of comparable age ($kc^2 = 6.4$; $p < 0.01$) carried a single common mtDNA deletion. Significant decreases were observed in patients with HCC as compared to controls for the mtDNA-encoded MT-CO1 (0.69 ± 0.28 and 1.33 ± 0.85, *p < 0.001*), nuclear DNA-encoded HSPA9 (0.44 ± 0.21 and 1.13 ± 0.21, *p < 0.001*), HSPD1 (0.82 ± 0.25 and 1.80 ± 0.66, *p < 0.05*), LONP1 (0.80 ± 0.17 and 1.09 ± 0.32, *p < 0.05*), PRKN (0.44 ± 0.28 and 1.11 ± 0.38, *p < 0.0001*), and PINK1 (0.52 ± 0.06 and 1.16 ± 0.28, *p < 0.0001*). Liver TNFalpha mRNA was 1.53 ± 0.2 and 0.79 ± 0.14 (*p < 0.05*) and IL6 mRNA was 6.98 ± 0.88 and 1.36 ± 0.19 (*p < 0.05*) in patients with HCC and controls, respectively. Protein levels of MT-CO1, LONP1, PRKN, and PINK1 significantly decreased in patients HCC compared to the healthy controls. In vitro, HBx confers resistance to CDDP-induced JNK1 activation and to hepatocarcinoma HepG2 cells apoptosis. **Conclusion:** Diverse mtDNA damages were associated with alterations in mitochondrial function, mitochondrial unfolded protein response, mitophagy and liver inflammation in patients with CHB and HCC. Hbx antigen seems to confer chemo-resistance to CDDP in HepG2 cells.

Disclosures: Abdellah Mansouri: Nothing to Disclose, Luis Correa: Nothing to Disclose, Manon Van den heede: Nothing to Disclose, Dorothy Tonui: Nothing to Disclose, Margaux BOSSIS: Nothing to Disclose, Stéphanie Narguet: Nothing to Disclose, Adel HAMMO UTENE: Nothing to Disclose, Nathalie BOYER: Nothing to Disclose, Pierre Tonnerre: Nothing to Disclose, Valerie PAradis: Nothing to Disclose, Tarik Asselah: GSK: Speaker, GILEAD: Consultant, VIR Biotechnology: Speaker, Roche: consultant, ABBVIE: Speaking and Teaching, Aligos therapeutics: Consultant, Bluejay Therapeutics: Consultant, Antios therapeutics: Consultant, GSK: Consultant

1295 | EXPANSION OF DYSFUNCTIONAL MEMORY B CELLS IS ASSOCIATED WITH HEPATITIS FLARES AND DISEASE ACTIVITY IN CHRONIC HEPATITIS B

Thi Kim Duyen Nguyen[1] Yen-Chun Liu[2] Hsiang-Wei Huang[2] Chia-Wei Lin[2] Jian He Fan[2] Wei-Ting Ku[1] Cheng-Heng Wu[2] Rachel Wen-Juei Jeng[2] Chun-Yen Lin[2], [1]Chang Gung University, [2]Chang Gung Memorial Hospital, Linkou Medical Center

Background: Atypical memory B cells (atMBC) are a functionally impaired subset of B cells with enhanced pro-inflammatory cytokine profile that expand in chronic immune activation, including chronic hepatitis B (CHB). However, the clinical significance of atMBCs in CHB remains poorly understood. This study aims to elucidate the role of atMBCs in CHB by examining their relationship with hepatitis flare and virological parameters. **Methods:** A total of 42 patients with CHB were prospectively enrolled, including NA-treated (n = 30) and treatment-naïve (n = 12) subjects. Patients represented a spectrum of disease activity and ALT levels. Hepatitis flare was defined as ALT > 5 times the upper limit of normal (ULN). Six subsets of B cells in peripheral blood mononuclear cells were analyzed by flow cytometry. Clinical parameters, including ALT, HBV DNA, and quantitative HBsAg levels were collected at the time of sampling. Linear regression and Spearman correlation analysis were applied when necessary with statistical significance defined as $p < 0.05$. **Results:** The frequencies of atMBCs and activated memory B cells (actMBC) were significantly increased in CHB patients who were experiencing hepatitis flares compared to normal ALT CHB patients ($p = 0.003$ and $p = 0.0104$, respectively). The frequency of atMBCs was not associated with age and gender. AtMBCs and actMBCs were highly correlated with each other ($r = 0.7639$, $p < 0.0001$). atMBCs were positively associated with HBV DNA levels ($p = 0.0392$), but not with HBsAg levels ($p = 0.1806$). In contrast, actMBCs demonstrated a significant positive correlation with HBsAg levels ($p = 0.0182$). Classical memory B cells (cMBC) and naïve B cells were reduced in patients with hepatitis flare, although the differences were not statistically significant ($p = 0.342$ and $p = 0.1952$, respectively). Interestingly, the ratio of atMBC/actMBC was numerically significantly higher in patients with ALT > 5x ULN than patients with normal ALT (median: 4.112 vs. 2.547, $p = 0.0811$). This observation suggests that a higher grade of inflammation is associated with a stronger tendency toward the development of atMBC. **Conclusion:** Hepatitis flare in CHB is associated with an increase in both atypical and activated memory B cells. Moreover, a higher grade of liver inflammation correlates with a stronger tendency toward the development of atypical memory B cells. This implies that functionally exhausted atypical memory B cells might play an important role in patients with high grade of inflammation.

Disclosures: Thi Kim Duyen Nguyen: Nothing to Disclose, Yen-Chun Liu: Nothing to Disclose, Hsiang-Wei Huang: Nothing to Disclose, Chia-Wei Lin: Nothing to Disclose, Jian He Fan: Nothing to Disclose, Wei-Ting Ku: Nothing to Disclose, Cheng-Heng Wu: Nothing to Disclose, Rachel Wen-Juei Jeng: GSK: Advisor, Gilead: Advisor, Chun-Yen Lin: Nothing to Disclose

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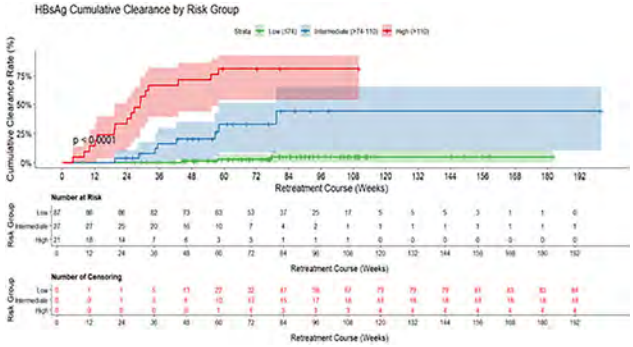
1296 | IMPACT OF INTERFERON RETREATMENT ON ACHIEVING HBSAG CLEARANCE IN PREVIOUSLY TREATED CHRONIC HEPATITIS B PATIENTS: IDENTIFICATION OF PREDICTIVE FACTORS AND CONSTRUCTION OF A PREDICTION MODEL

Huiling Xiang[1] Jun Li[2] Yanchao Fu[1] fei yan[2] Jing Chen[2] Qin Du[3] Qing Ye[1] Jing Liang[1] Chao Yang[1] Jiayin Wang[1], [1]Department of Gastroenterology and Hepatology, Tianjin University Central Hospital, [2]The Third Central Clinical College of Tianjin Medical University, Tianjin University Central Hospita, [3]Nankai University Affiliated Third Central Hospital, Tianjin University Central Hospital

Background: To explore predictive indicators for achieving HBsAg clearance in chronic hepatitis B (CHB) patients undergoing retreatment with interferon after initial non-response, providing evidence for clinical selection of responder populations. **Methods:** This single-center retrospective cohort study enrolled CHB patients and those with compensated cirrhosis who failed to achieve HBsAg clearance after first-line interferon therapy between January 2017 and April 2025. All participants received retreatment with pegylated interferon α-2b (Peg-IFNα-2b) monotherapy or combination therapy with nucleos(t)ide analogs (NAs), with a median follow-up of 48 weeks. The primary endpoint was HBsAg clearance (defined as HBsAg <0.05 IU/mL). Candidate variables were screened via univariate Cox proportional hazards regression analysis, optimized using least absolute shrinkage and selection operator (LASSO) regression, and core variables were identified through multivariate Cox regression analysis. A prediction model was constructed, and its discriminative ability was evaluated using Kaplan-Meier survival curves. **Results:** A total of 135 patients (median age 40.0 years, 74.1% male) with prior interferon non-response were included. Among them, 28 (20.74%) achieved HBsAg clearance after retreatment. Univariate, LASSO, and multivariate Cox regression analyses identified three independent predictors: HBsAg decline during initial interferon therapy (hazard ratio [HR] = 2.050), baseline HBsAg level at retreatment initiation (HR = 0.518), and treatment-free interval duration (HR = 1.015). The prediction model incorporating these variables demonstrated strong discriminative performance (area under the curve [AUC] = 0.930), with sensitivity of 92.6% and specificity of 80.5%. The Harrell's C-index was 0.904 (95% CI: 0.865–0.944). Stratification by nomogram scores revealed significantly higher cumulative HBsAg clearance rates at 48 weeks in high-score groups (≥ 74 points) compared to low-score groups (71.4% vs. 20.3% vs. 1.3%, log-rank $P < 0.001$) **Conclusion:** Retreatment with interferon can achieve HBsAg clearance in 20.74% of CHB patients who previously failed interferon therapy. Baseline factors including greater HBsAg reduction during initial therapy, lower HBsAg levels at retreatment initiation, and longer treatment-free intervals are associated with favorable outcomes. The proposed scoring system effectively identifies optimal candidates for interferon retreatment.



Disclosures: Huiling Xiang: Nothing to Disclose, Jun Li: Nothing to Disclose, Yanchao Fu: Nothing to Disclose, fei yan: Nothing to Disclose, Jing Chen: Nothing to Disclose, Qin Du: Nothing to Disclose, Qing Ye: Nothing to Disclose, Jing Liang: Nothing to Disclose, Chao Yang: Nothing to Disclose, Jiayin Wang: Nothing to Disclose

1297 | ATEZOLIZUMAB/BEVACIZUMAB (A-B) IS A WIDELY USED IMMUNOTHERAPY FOR ADVANCED HEPATOCELLULAR CARCINOMA (HCC), WITH ITS EFFICACY FURTHER ENHANCED WHEN COMBINED WITH RADIOTHERAPY (RT). HOWEVER, THE PRECISE MECHANISMS UNDERLYING RT'S IMMUNOMODULATORY EFFECTS REMAIN INCOMPLETELY UNDERSTOOD. IN THIS MULTICENTER, REAL-WORLD COHORT STUDY, WE AIMED TO ASSESS THE CLINICAL BENEFITS OF A-B IN PATIENTS WITH HBV-RELATED HCC AND ELUCIDATE THE IMMUNE-MODULATING EFFECTS OF RT THROUGH SINGLE-CELL RNA SEQUENCING (SCRNA-SEQ) ANALYSIS

Kwon Yong Tak[1] Jeong Won Jang[1] Hee Chul Nam[1] Pil Soo Sung[1] Hyun Yang[1] SI HYUN BAE[1] Seung Kew Yoon[1] Ahlim Lee[1] Ji Won Han[1] Soon Kyu Lee[1] Myeong

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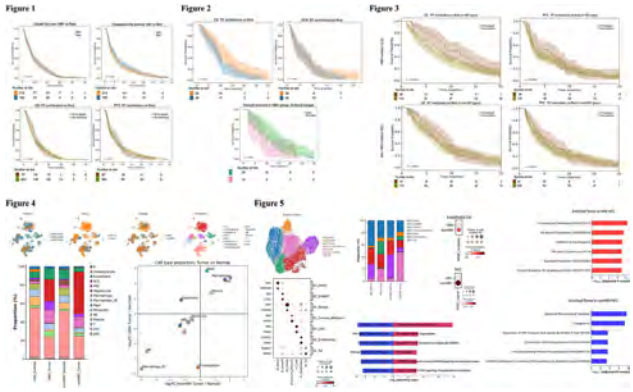
Jun Song[2] Hae Lim Lee[1] Chang Wook Kim[3] Jung Hyun Kwon[2], [1]The Catholic University of Korea, College of Medicine, [2]The Catholic University of Korea, [3]Uijeongbu St. Mary's Hospital

Background: Between September 2020 and January 2025, a total of 519 hepatocellular carcinoma (HCC) patients who met the eligibility criteria and received A-B treatment were included in the study. Among them, 260 patients (50.1%) had underlying hepatitis B virus (HBV) infection, and 85 patients (32.7%) received combination therapy with RT. The primary endpoints evaluated were progression-free survival (PFS) and overall survival (OS). scRNA-seq datasets from GSE156625, GSE149614, and GSE151530 were obtained with metadata extracted from the corresponding publications. **Methods:** Between September 2020 and January 2025, a total of 519 HCC patients who met the eligibility criteria and received A-B treatment were included in the study. Among them, 260 patients (50.1%) had underlying HBV, and 85 patients (32.7%) received RT combination therapy. The primary endpoints evaluated were progression-free survival (PFS) and overall survival (OS). scRNA-seq datasets from GSE156625, GSE149614, and GSE151530 were obtained with metadata extracted from the corresponding publications. **Results:** The median follow-up duration was 7.6 months. In A-B monotherapy, no significant differences were observed in PFS and OS between those with HBV-related HCC and others (7.56 vs. 7.19 months, $P = 0.7410$ and 4.04 vs. 4.93 months, $P = 0.5369$, respectively). However, in RT combination group, HBV-related HCC group demonstrated a trend toward improved OS (9.03 vs. 8.02 months, $P = 0.0300$). Among HBV patients, antiviral therapy was associated with a prolonged OS (11.90 vs. 7.23 months, $P = 0.0890$). scRNA-seq data from three datasets, comprising 43 patients and 88,572 cells, were collected and analyzed. Single-cell transcriptomic analysis revealed an increase in SPP1+ endothelial cells (ECs), suggesting enhanced non-VEGF-mediated angiogenesis in the HBV group. Consistently, pathway analysis indicated a downregulation of VEGF receptor expression in HBV-associated HCC. In cancer cells, HBV-related HCC had increase in inflammatory signatures with downregulation of VEGF ligand expression. **Conclusion:** The efficacy of A-B in HCC may be influenced by underlying etiology and treatment combination. While no significant differences in survival outcomes were observed between HBV-related and non-HBV-related HCC patients receiving monotherapy, HBV-related HCC exhibited improved OS when combined with RT. Additionally, antiviral therapy was associated with a trend toward prolonged survival in HBV patients. Mechanistic analysis using scRNA-seq revealed an increase in VEGF-independent endothelial cells, suggesting a shift toward non-VEGF-mediated angiogenesis in HBV-related HCC, accompanied by downregulation of VEGF receptor expression. These findings highlight potential differences in angiogenic pathways between HBV and non-HBV HCC, which may influence responses to VEGF-targeted therapy and provide insights for optimizing treatment strategies.



Disclosures: Kwon Yong Tak: Nothing to Disclose, Jeong Won Jang: Nothing to Disclose, Hee Chul Nam: Nothing to Disclose, Pil Soo Sung: Nothing to Disclose, Hyun Yang: Nothing to Disclose, SI HYUN BAE: Nothing to Disclose, Seung Kew Yoon: Nothing to Disclose, Ahlim Lee: Nothing to Disclose, Ji Won Han: Nothing to Disclose, Soon Kyu Lee: Nothing to Disclose, Myeong Jun Song: Nothing to Disclose, Hae Lim Lee: Nothing to Disclose, Chang Wook Kim: Nothing to Disclose, Jung Hyun Kwon: Nothing to Disclose

1298 | A NUCLEOSOME SWITCH PRIMES HEPATITIS B VIRUS INFECTION

Robert Schwartz[1], [1]Weill Cornell Medicine

Background: Chronic hepatitis B virus (HBV) infection is a global health problem causing significant liver disease and hepatocellular carcinoma. After viral entry, the HBV genome is shuttled into the nucleus and repaired from a partially double-stranded, relaxed circular DNA into a fully double-stranded, covalently closed circular DNA (cccDNA). The cccDNA rapidly becomes populated with host histone octamers and serves as the primary template for viral transcription. The viral protein HBx has a paradoxical relationship to cccDNA transcription during the earliest stages of infection. HBx induces the degradation of the host Smc5/6 complex, which otherwise would transcriptionally silence cccDNA, but is absent from the mature virion and must be expressed *de novo* in freshly infected hepatocytes. HBx is thought to be the earliest-expressed viral gene, with its transcript most abundant in the first 24 hours after HBV infection.

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Moreover, the interplay between cccDNA chromatin state and viral transcription kinetics remains poorly understood despite its potential importance to the establishment of active chronic infection. **Methods:** Traditional genetic and cell biology approaches lack the temporal and biochemical resolution necessary to characterize this critical intermediate in HBV infection establishment. To surmount these difficulties, we developed a method to generate recombinant cccDNA minichromosomes in a chemically defined system, allowing us to characterize its biophysical properties and map nucleosome occupancy on the chromosome. **Results:** We apply biochemical techniques to demonstrate that chromatin assembly on cccDNA is spatially defined and critical for HBx mRNA expression, but not other viral transcripts. This is further confirmed in native HBV infection using transcriptomic and MNase-seq analysis. Finally, we demonstrate that small molecule-mediated disruption of nucleosome integrity is sufficient to inhibit HBx transcription, cccDNA content, and viral infection in hepatocytes. **Conclusion:** In summary, we show that cccDNA chromatin structure specifically regulates HBV RNA transcription and how when disrupted inhibits and alters HBV infection.

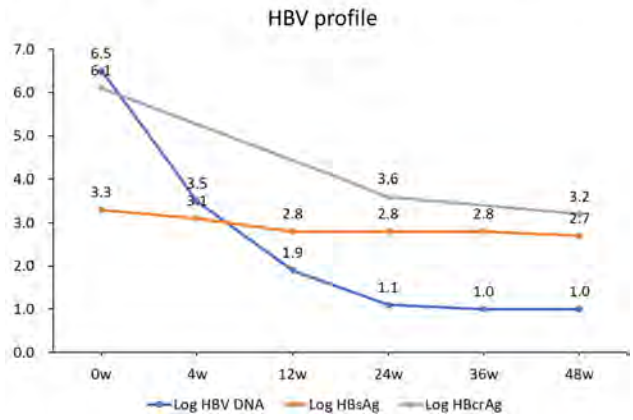
Disclosures: Robert Schwartz: Miromatrix Inc: Advisor, Lime Therapeutics: Advisor, Otsuka Inc.: Grant/Research Support, Alnylam Pharmaceuticals: Speaking and Teaching, Alnylam Pharmaceuticals: Consultant

1299 | THE CLINICAL EFFICACY OF TENOFOVIR ALAFENAMIDE RE-TREATMENT IN CHRONIC HEPATITIS B PATIENTS WITH CLINICAL RELAPSE AFTER DISCONTINUATION OF ORAL ANTIVIRAL THERAPY

Tung-Hung Su[1] Yao-Chun Hsu[2] Yu-Jen Fang[3] Chih-Lin Lin[4] Chia-Chi Wang[5] Kuo-Chih Tseng[6] Chi-Yi Chen[7] Jia-Horng Kao[8], [1]National Taiwan University Hospital, [2]I-Shou University, [3]National Taiwan University Hospital, Yun-Lin Branch, Yun-Lin, Taiwan, [4]Department of Gastroenterology, Ren-Ai Branch, Taipei City Hospital, Taipei, Taiwan, [5]Taipei Tzuchi Hospital, the Buddhist Tzuchi Medical Foundation, Taipei, Taiwan, [6]Buddhist Tzu Chi General Hospital, Da-Lin Branch, Chiayi, Taiwan, [7]Chia-Yi Christian Hospital, [8]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

Background: Retreatment is frequent in patients with chronic hepatitis B (CHB) who developed clinical relapse after cessation of oral antiviral therapy. Whether retreatment using the original regimen or switching to tenofovir alafenamide (TAF) would be beneficial remains unclear. We aimed to investigate the clinical effectiveness of switching to TAF after clinical relapse. **Methods:** This multicenter study enrolled CHB patients who experienced clinical relapse after discontinuing entecavir or tenofovir disoproxil fumarate [TDF] and switched the regimen to TAF for 48 weeks of retreatment. The primary endpoint was the rate of virological remission (HBV DNA <20 IU/mL), and the secondary endpoints were the rate of ALT normalization (<41 U/L), the change of HBsAg level, renal function, body weight, and lipid profiles. **Results:** The CHANGE (Chronic Hepatitis b patients switch to tAf after discontinuation of Nucleoside analoGuE) study (NCT04496882) included 48 patients previously treated with entecavir ($n=27$) or TDF ($n=21$) for a median duration of 3.2 years. At TAF retreatment, the median age was 48 years, 12.5% was HBeAg positive and HBV DNA was 6.5 $\log_{10}$ IU/mL. The virological remission rate was 58%, 77%, and 77% at 24, 36, and 48 weeks of therapy. The ALT normalization rate was 77%, 90%, and 85%, respectively. After 48-week TAF therapy, both their median HBsAg (3.3 to 2.7 $\log_{10}$ IU/mL, $P<0.001$) and HBcrAg (6.1 to 3.2 $\log_{10}$ IU/mL, $P<0.001$) declined significantly. Four of 6 (67%) HBeAg-positive patients cleared their HBeAg. There was a significant reduction of liver fibrosis by M2BPGi level (0.88 to 0.63 C.O.I., $P<0.001$). There was a significantly increase of serum creatinine (0.85 to 0.89 mg/dL, $P=0.022$), T-CHO (179 to 187 mg/dL, $P=0.019$), TG (81 to 94 mg/dL, $P=0.016$), and LDL (105 to 118 mg/dL, $P<0.001$), and a significantly reduction of HDL (59 to 55 mg/dL, $P=0.049$), while their body weight remained stable. The change of T-CHO, TG, and HDL after 48-week TAF therapy were insignificant if patients switched from TDF to TAF. The compliance was $>90\%$ and no significant adverse events were reported. **Conclusion:** TAF re-treatment after off-therapy relapse is safe and effective in viral suppression, ALT normalization, and liver fibrosis improvement. The renal function and lipid profiles should continue to be monitored.

Figure 1. The serial HBV serological and virological markers after retreatment of TAF in patients who experienced off-therapy flare of chronic hepatitis B.



Disclosures: Tung-Hung Su: Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers

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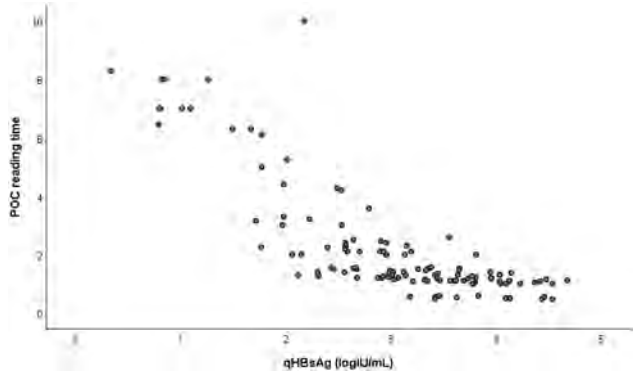
1300 | REDUCING READ TIME OF POINT-OF-CARE TEST DOES NOT AFFECT DETECTION OF HEPATITIS B AND CORRELATES WITH HBSAG LEVELS

Judit Romero[1] ARIADNA RANDO-SEGURA[2] amanda beatriz Cohn[1] Xavier Major[3] Elena Vargas-Accarino[1] Adriana Palom[1] Juan Carlos Ruiz Cobo[4] Mar Riveiro-Barciela[4] Maria Buti[4], [1]Vall Hebron Research Institute, [2]Liver Pathology Laboratory, Microbiology and Biochemistry Department, Vall d'Hebron Clinical Laborat, [3]Programme on Addictions, HIV, Sexually Transmitted Infections and Viral Hepatitis, Public Health Ag, [4]Hospital Universitari Vall d'Hebron

Background: Global elimination of hepatitis B virus (HBV) requires improved diagnosis, particularly in resource-limited settings. Point-of-care (POC) HBsAg test are valuable for identification of HBV infection in community settings, particularly in areas with limited access to healthcare services. We investigated whether individuals with high levels of HBsAg could be identified using a shorter reading time (standard: 15–20 minutes), and potentially avoiding the need for HBV DNA testing where unavailable. **Methods:** Patients with past or current HBV infection and healthy controls were included between January and May 2025. Quantitative HBsAg was measure by a commercial assay (Elecsys HBsAg II, Roche) and qualitative HBsAg by rapid point-of-care (POC) test (Determine HBsAg 2, Abbott; LOD: 0.1 IU/mL). HBV-DNA was quantified by real-time PCR with the COBAS 6800 system (LOD: 10 IU/mL). Whole blood from finger-prick samples was tested immediately, and time to positive result was recorded. **Results:** Overali,133 patients were tested: 117 HBsAg-positive, 4 with past HBV infection and 12 healthy controls. Among HBsAg-positive subjects, 55 presented HBsAg $\leq$1,000 and 62 subjects $>$1,000 IU/mL. All HBsAg-positive patients had a positive POC result at a mean time of 2.27 $\pm$ 2.04 minutes. Test reading time was strongly negatively correlated with HBsAg levels (Pearson's r = –0.808, $p < 0.001$) (figure 1). Patients with HBsAg $\leq$1,000 IU/mL had a longer reading time than those with $>$1,000 IU/mL (3.5 $\pm$ 2.4 vs 1.16 $\pm$ 0.43 minutes, $p < 0.001$). HBV-DNA was detected in 59 cases, but no significant difference was found in POC reading times between those with detectable and undetectable HBV-DNA (N = 58) (1.37 vs 1.5, $p = 0.085$). However, inactive carriers (n = 20), defined as HBsAg $\leq$1,000 IU/mL and HBV-DNA $<$2,000 IU/mL, showed longer reading times compared to chronic hepatitis B (CHB, n = 10) (2.82 vs 1.09, $p = 0.005$). Using a 90-second cut-off, the test identified CHB (HBsAg $>$1000 IU/mL and $>$2000 IU/mL HBV DNA) with 80% sensitivity and 88% specificity (PPV 95.6% and NPV 57%) and at 60 seconds the sensitivity was 30%, specificity 100% (87.7% PPV and 100% NPV). All 4 patients with past infection and 12 healthy carriers tested negative on the capillary POC test. **Conclusion:** The wait time for the HBsAg rapid POC blood test can be reduced from 15-20 min to 5 min and continue to reliably identify patients with HBV infection. Shortening the test time could increase high-throughput screening, and reduce loss to follow-up.



Disclosures: Judit Romero: Nothing to Disclose, ARIADNA RANDO-SEGURA: Nothing to Disclose, amanda beatriz Cohn: Nothing to Disclose, Xavier Major: Nothing to Disclose, Elena Vargas-Accarino: Nothing to Disclose, Adriana Palom: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Juan Carlos Ruiz Cobo: Nothing to Disclose, Mar Riveiro-Barciela: Nothing to Disclose, Maria Buti: Nothing to Disclose

1301 | EARLIER AND MORE SEVERE RELAPSE AFTER NUCLEOS(T)IDE ANALOGUE DISCONTINUATION IN HBEAG-POSITIVE CHRONIC HEPATITIS B PATIENTS

Yen-Chun Liu[1] CHIEN-WEI PENG[1] Rachel Wen-Juei Jeng[1] Rong-Nan Chien[1], [1]Chang Gung Memorial Hospital, Linkou Medical Center

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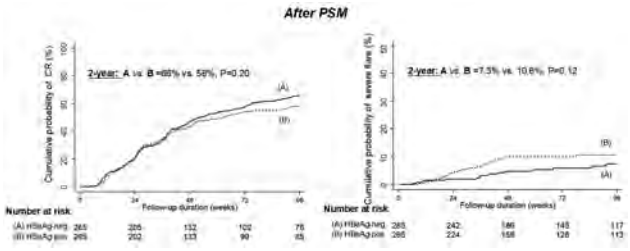
Background: HBeAg-positive and -negative chronic hepatitis B (CHB) represent distinct immunovirological phenotypes. However, many studies of finite nucleos(t)ide analogue (Nuc) therapy have analyzed them together, potentially obscuring the impact of baseline HBeAg status on off-Nuc outcomes. This study aimed to compare the incidence, timing, and severity of relapses after finite Nuc therapy between pretherapy HBeAg-positive and -negative patients. **Methods:** CHB patients who stopped Nuc therapy per APASL criteria (HBV DNA undetectable $\geq$1 year; HBeAg loss for $\geq$1 year) were analyzed. Clinical relapse (CR) was defined as ALT $\geq$2 times upper limit of normal (xULN) and HBV DNA $\geq$2000 IU/mL. Severe flare was defined as ALT $\geq$1000 U/L, total bilirubin $\geq$3.5 mg/dL or CR with hepatic decompensation (HD: total bilirubin $>$ 2mg/dL and INR $\geq$1.5). CR incidence, timing, and severity were compared between HBeAg-positive and -negative patients before and after propensity score matching (PSM) by age, sex, pretherapy ALT, HBV DNA, and end-of-treatment (EOT) HBsAg. Cox regression was used to identify predictors of severe flare. **Results:** A total of 286 HBeAg-positive and 2355 HBeAg-negative patients were analyzed (median follow-up: 4.6 years). CR occurred in 60% vs. 67%, respectively. HBeAg-positive patients had higher ALT at CR (345 vs. 244 U/L, $p<0.01$), more ALT $\geq$10$\times$ ULN (48% vs. 37%, $p<0.01$), higher HBV DNA at CR (7.3 vs. 5.7 $\log_{10}$ IU/mL), earlier relapse (34 vs. 39 weeks, $P<0.01$), and higher CR-related mortality (2% vs. 0.3%, $p=0.04$). After PSM ($n=265$/group), baseline characteristics were balanced. HBeAg-positive patients still had higher peak ALT, (345 vs. 269 U/L), HBV DNA at CR (7.3 vs. 6.4 $\log_{10}$IU/mL), and HD incidence (3% vs. 0%) (all $p<0.05$). The 2-year cumulative incidence of severe flare was higher in HBeAg-positive patients before and after PSM (pre: 11% vs. 8%, $p=0.02$; post: 11% vs. 7%, $p=0.12$), while CR rates post PSM were comparable (58% vs. 66%, $p=0.20$). In multivariate analysis, pretherapy HBeAg positivity (aHR: 1.6), cirrhosis (aHR: 1.8), ALT $\geq$5$\times$ ULN (aHR: 1.8), and non-entecavir use (aHR: 1.7) independently predicted severe flare among off-Nuc CR patients. **Conclusion:** HBeAg-positive CHB patients experience earlier and more severe relapses after finite NUC therapy. Off-therapy outcomes should be stratified by baseline HBeAg status, with intensified monitoring recommended for those with cirrhosis, pretherapy flare, or non-entecavir use.



Disclosures: Yen-Chun Liu: Nothing to Disclose, CHIEN-WEI PENG: Nothing to Disclose, Rachel Wen-Juei Jeng: GSK: Advisor, Gilead: Advisor, Rong-Nan Chien: Nothing to Disclose

1302 | IDENTIFICATION OF FDA-APPROVED COMPOUNDS THAT SUPPRESS HBS ANTIGEN THROUGH LIBRARY SCREENING

Kazuhiro Murai[1] Akiyoshi Shimoda[1] Takao Kitanaka[1] Takayuki Miyake[1] Shinji Kuriki[1] Emi Sometani[1] Jihyun Sung[1] Satoshi Shigeno[1] Kumiko Shirai[1] Yuki Tahata[1] Yoshinobu Saito[1] Takahiro Kodama[1] Hayato Hikita[1],
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Background: Hepatitis B surface antigen (HBsAg), a structural protein of the hepatitis B virus (HBV), plays a role in the development of hepatocellular carcinoma and immune exhaustion, thereby facilitating chronic infection. Current anti-HBV therapy, nucleos(t)ide analogue (NUC) have little effect on HBsAg. We aim to discover novel agents that reduce HBsAg using an FDA-approved compound library and to define the mechanisms responsible for their efficacy. **Methods:** A library of 1134 FDA-approved drugs was screened on HepG2.2.15.7 cells, HBV genome integrated cells, at 9.9 μM for 7 days. After incubation, HBsAg levels in the supernatant and cell viability were measured. Compounds reducing viability by more than 1 standard deviation (SD) were excluded; those reducing HBsAg by more than 1.5 SD were selected as candidates. These were retested at 5 and 0.5 μM. Compounds reducing HBsAg at both doses were selected as final candidates. To explore the mechanism, final candidates were tested on HepG2.2.15.7 and HBV-inoculated (1000 genome equivalent/cell) primary human hepatocytes from TK-NOG mice (HepaSH cells). **Results:** A total of 126 compounds were excluded from further analysis due to their cytotoxic effects. Six compounds were identified as candidate compounds with HBsAg levels decreased. Among them, only ethacridine and auranofin significantly reduced HBsAg levels at both 5 μM and 0.5 μM concentrations. Using HepaSH cells, while ethacridine did not decrease HBsAg, auranofin decreased HBsAg. Auranofin did not reduce the levels of hepatitis B e antigen (HBeAg), HBV DNA in the supernatant, or pregenomic RNA (pgRNA). In addition, Western blotting did not show a change in intracellular HBsAg by auranofin. Transmission electron microscopy revealed more vesicles within the endosomes of auranofin-treated HepaSH cells than those of untreated HepaSH cells. Western blotting showed that auranofin treatment enhanced protein expression of Galectin-3, a marker of damaged lysosomes. Immunofluorescence staining demonstrated co-localization of HBsAg with

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Galectin-3. It is suggested that auranofin-induced lysosomal damage led to the accumulation of Galectin-3, which co-localized with HBsAg, resulting in the suppression of extracellular HBsAg secretion. **Conclusion:** FDA approved drug library screening identified auranofin which suppresses HBsAg levels.

Disclosures: Kazuhiro Murai: Nothing to Disclose, Akiyoshi Shimoda: Nothing to Disclose, Takao Kitanaka: Nothing to Disclose, Takayuki Miyake: Nothing to Disclose, Shinji Kuriki: Nothing to Disclose, Emi Sometani: Nothing to Disclose, Jihyun Sung: Nothing to Disclose, Satoshi Shigeno: Nothing to Disclose, Kumiko Shirai: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Takahiro Kodama: Nothing to Disclose, Hayato Hikita: Nothing to Disclose

1303 | IMPACT OF BASELINE HBEAG STATUS ON HBV OUTCOMES IN THE ALLIANCE STUDY

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Background: Baseline (BL) hepatitis B e-antigen (HBeAg) status has been associated with differential hepatitis B virus (HBV) treatment responses in individuals with HBV monoinfection. In treatment-naïve adults with HIV-1 and HBV co-infection, the ALLIANCE study demonstrated that bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) achieved superior HBV DNA suppression compared to dolutegravir plus emtricitabine/tenofovir disoproxil fumarate (DTG+F/TDF) at Week (W) 48, with sustained improvements through W144. This subanalysis assessed HBV virologic outcomes by BL HBeAg status. **Methods:** ALLIANCE (NCT03547908) was a randomized, double-blind, active-controlled Phase 3 clinical study. Here we present data from participants who received B/F/TAF through W144 ($\geq$96 weeks of blinded treatment + 48-week optional open-label extension [OLE]), and in participants who switched to B/F/TAF after $\geq$96 weeks of DTG+F/TDF through OLE W48. BL demographics, HBV DNA $<$29 IU/mL, ALT normalization (2018 AASLD criteria), HBeAg loss/seroconversion and surface antigen (HBsAg) loss/seroconversion at W96 and OL W48, were assessed by BL HBeAg status using Missing = Excluded (M = E) approach. **Results:** Among 241 participants, 54 (22.4%) enrolled with BL HBeAg-, median age 38, 89% male; 187 (77.6%) enrolled with BL HBeAg+, median age 31, 98% male. BL HBeAg status was comparable across treatment groups. At W96, all participants with BL HBeAg- achieved HBV DNA $<$29 IU/mL regardless of treatment group while 74.7% and 70.3% of those with BL HBeAg+ achieved the same on B/F/TAF and DTG+F/TDF, respectively. In BL HBeAg+, W96 HBeAg loss/seroconversion were 41%/34.9% on B/F/TAF and 20.9%/16.5% on DTG+F/TDF; and HBsAg loss/seroconversion for BL HBeAg- and HBeAg+ were 18.5%/11.1% and 27.2%/9.9% and 4.5%/4.5% and 17.8%/7.8%, respectively. ALT normalization was 93.3% (BL HBeAg-) and 72.5% (BL HBeAg+) on B/F/TAF, and 50.0% and 64.7% on DTG+F/TDF, respectively. At OLE W48, BL HBeAg- participants exhibited higher HBV DNA suppression rates across treatment groups compared to HBeAg+, with continued HBe/sAg loss/seroconversion and ALT normalization observed through OLE W48. **Conclusion:** In HIV/HBV co-infected individuals who started tenofovir-containing combination ART, BL HBeAg- correlated with greater HBV suppression when compared to BL HBeAg+ through 144 weeks. Continued improvements in HBe/sAg loss/seroconversion and/or ALT normalization persisted through 144 weeks of tenofovir-containing combination ART in both BL HBeAg- and BL HBeAg+.

Virologic and Immunologic Outcomes Through W144 (M=E)

Randomized Phase: W96				
	B/F/TAF		**DTG+F/TDF**	
HBeAg status at baseline[a] n/N (%)	+ **N=90**	- **N=29**	+ **N=97**	- **N=25**
HBV DNA < 29 IU/mL	62/83 (74.7)	27/27 (100.0)	64/91 (70.3)	22/22 (100.0)
HBeAg loss	34/83 (41.0)	NA	19/91 (20.9)	NA
HBeAb seroconversion	29/83 (34.9)	NA	15/91 (16.5)	NA
HBsAg loss	22/81 (27.2)	5/27 (18.5)	16/90 (17.8)	1/22 (4.5)
HBsAb seroconversion	8/81 (9.9)	3/27 (11.1)	7/90 (7.8)	1/22 (4.5)
ALT normalization (2018 AASLD)[b]	29/40 (72.5)	14/15 (93.3)	22/34 (64.7)	5/10 (50.0)
W144 (W48 Open-Label Extension Phase)[c]				
	B/F/TAF		**Switch From DTG+F/TDF to B/F/TAF**	
HBeAg status at baseline[a] n/N (%)	+ **N=90**	- **N=29**	+ **N=72**	- **N=17**
HBV DNA < 29 IU/mL	60/81 (74.1)	25/25 (100)	55/66 (83.3)	16/16 (100)
HBeAg loss	26/58 (44.8)	NA	8/47 (17.0)	NA
HBeAb seroconversion	17/58 (29.3)	NA	6/47 (12.8)	NA
HBsAg loss	13/58 (22.4)	3/13 (23.1)	3/55 (5.5)	0/15 (0)
HBsAb seroconversion	8/58 (13.8)	3/13 (23.1)	0/55 (0)	0/15 (0)
ALT normalization (2018 AASLD)[b]	28/38 (73.7)	13/14 (92.9)	11/18 (61.1)	2/7 (28.6)

[a]Baseline in randomized phase is defined as the first dose date of randomized study drug (ie, B/F/TAF, DTG+F/TDF). Baseline in open-label extension phase is defined as the first dose date of B/F/TAF in the randomized phase for B/F/TAF group, the first dose date of B/F/TAF in the extension phase for switch from DTG+F/TDF to B/F/TAF group. [b]Reduction in ALT to ≤ ULN for participants with ALT > ULN at baseline, based on American Association for the Study of Liver Diseases 2018 criteria, where ULN is 25 U/L for females and 35 U/L for males. [c]OLE W48 corresponds to W144 for B/F/TAF group and W48 for DTG+F/TDF to B/F/TAF group.

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Hung: Nothing to Disclose, Sasisopin Kiertiburanakul: Nothing to Disclose, Man-Po Lee: Nothing to Disclose, Hui Liu: Gilead Science, Inc.: stock - privately held company (individual stocks), Sharline Madera: Nothing to Disclose, Jason Hindman: Gilead Sciences: Employee, Taisheng Li: Nothing to Disclose

1304 | LONG-READ TRANSCRIPTOMIC LANDSCAPE OF LIVER BIOPSIES FROM PATIENTS FUNCTIONALLY CURED OF CHB

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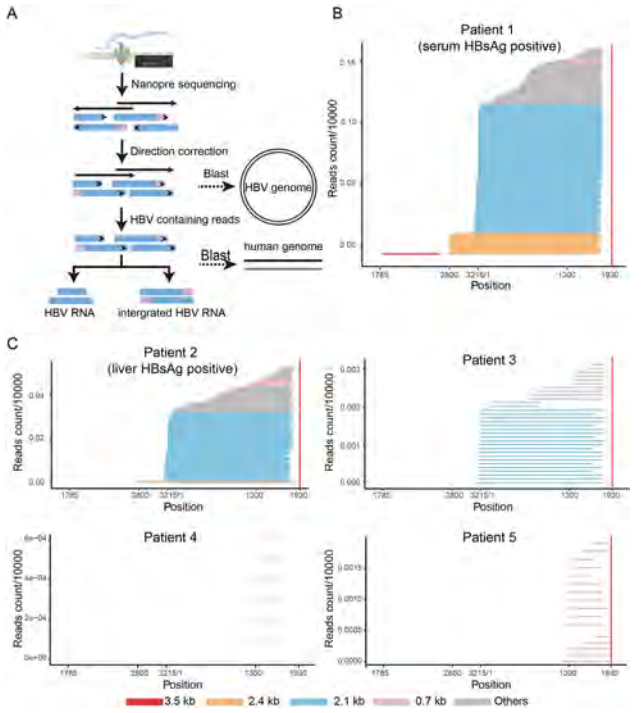
Background: HBsAg seroclearance is considered the hallmark of hepatitis B virus infection resolution. Nonetheless, about 5-10% of patients who achieved functional cure with pegylated interferon–based regimens subsequently experience HBsAg seroreversion. Therefore, an in-depth characterization of the HBV transcriptomic landscape in liver tissue would improve our understanding on the virological charateristics for sustant HBsAg seroclearance in patients with functional cure of chronic hepatitis B. **Methods:** HBV transcripts in the liver tissue from four patients(patient2-5)who have achieved HBsAg seroclearance following NA/Peg-IFNα combination therapy were analyzed via long-read transcriptome sequencing through Nanopore sequencing. In parallel, an interferon treatment naïve patient was recruited as control (patient1). The sequencing reads were subjected to quality control, and then aligned to the HBV ayw genotype using minimap2. The alignment results were visualized using R. **Results:** Analysis of polyadenylation status revealed the entirely lack of classical polyadenylation (0%) in both the untreated patient (P1) and the cured patient (P2) with intrahepatic HBsAg-positive staining, which suggested the viral transcripts were originated from the integrated HBV DNA. In contrast, the cured, hepatic HBsAg-negative group (P3-P5) showed a small fraction (1.2%) of classically polyadenylated HBV RNA, indicating a minor contribution from cccDNA, though transcripts from integrated HBV DNA still predominated. Further analysis revealed that the 2.1kb HBsAg RNA in the untreated control (P1) was the most abundant species (61%), followed by the 2.4kb HBsAg RNA (9%), while the 0.7kb RNA constituted a minor fraction (0.4%). A same pattern of 2.4/2.1kb HBsAg RNA was observed in patient (P2) with liver HBsAg-positive with 0.7kb RNA abundancy at 2%. For the cured group (P3-P5), the 0.7kb RNA species was notably more abundant, representing 33% of the HBV RNA reads, though the 2.1kb HBsAg RNA accounted for 37% of transcripts and undetectable (0%) 2.4kb HBsAg RNA. **Conclusion:** Long-read sequencing demonstrated that low-level HBV transcripts, predominantly transcribed from integrated viral DNA, persist in hepatic tissue despite serologic HBsAg clearance. Accordingly, vigilant surveillance for virologic relapse is especially critical when immunosuppressive therapy is anticipated or underway in those functional cured CHB patients.



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1305 | NOVEL, HIGH-SENSITIVE IMMUNOASSAYS FOR PHOSPHORYLATED AND NON-PHOSPHORYLATED HBCAG DETECTION

Rene Geissler[1] Megha Patel[1] Michael Berg[1] Gavin Cloherty[1], [1]Abbott

Background: Current HBV guidelines for treatment eligibility are based on HBV DNA viral load levels. Specifically, for HBV infected patients with DNA levels ≥2,000 IU/ml (HBeAg-) or ≥20,000 IU/ml (HBeAg+), antiviral therapies are recommended. However, HBV molecular assays to monitor HBV DNA levels are often unavailable or unaffordable in low- and middle-income countries (LMIC). We previously developed two novel HBcAg immunoassays to specifically detect non-phosphorylated HBcAg as surrogate marker for HBV DNA-containing particles (referred as HBcAg) and phosphorylated HBcAg (referred as P-HBcAg), which represents

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non-HBV DNA-containing particles. HBcAg and P-HBcAg correlate best with HBV DNA as compared to HBV core-related antigen (HBcrAg). Here, we describe improved P-HBcAg/HBcAg assays with superior performance and higher sensitivity that should enable decisions to put patients on antiviral therapy. **Methods:** The improved P-HBcAg and HBcAg assays use specific monoclonal antibodies to capture and detect either non-phosphorylated or phosphorylated HBcAg that are secreted from HBV infected hepatocytes into the blood stream. P-HBcAg and HBcAg signals are measured as relative light units (RLUs). We analyzed single timepoint specimens from HBV infected patients with viral loads ranging from 10^2 to 10^8 HBV DNA IU/ml. **Results:** Several factors were optimized, including new monoclonal antibodies, to increase the limit of quantification (LOQ) for P-HBcAg and HBcAg, respectively. Serial dilutions of specimens from HBV infected patients revealed that P-HBcAg could be detected at HBV DNA levels as low as 60 IU/ml. HBcAg, which represents infectious HBV DNA-containing particles and is the least abundant antigen, is still detectable at HBV DNA levels as low as 1,000 IU/ml. **Conclusion:** The ability to specifically detect low abundant P-HBcAg/HBcAg levels at the lower limit of HBV DNA levels that qualify for treatment eligibility provides additional insights for disease staging. The assays have the potential to be made available at lower cost compared to molecular assays and are more easily deployable in low- and middle-income countries where HBV diagnosis and verification of response to therapies are most needed.

Disclosures: Rene Geissler: Abbott: Employee, Abbott: Stock – privately held company, Megha Patel: Nothing to Disclose, Michael Berg: Nothing to Disclose, Gavin Cloherty: Nothing to Disclose

1306 | DYNAMICS OF GENE EXPRESSION IN THE HUMANIZED LIVER INFECTED WITH PRECORE AND BASAL CORE PROMOTER MUTATED HBV

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Background: Mutations within the precore (PC) and basal core promoter (BCP) regions of the HBV genome are associated with fulminant hepatitis and HBV reactivation. We previously reported that PC and BCP mutations were associated with enhanced viral replication and cell death induced by ER stress using HBV infection models, indicating these mutations might be associated with liver damage in patients with fulminant hepatitis or HBV reactivation (Uchida et al, *Hepatology*, 2023). In previous study, RNAseq revealed the molecular characteristics in PC/BCP mutant HBV infection. Herein, we assessed dynamics of the expression of the genes which is up- or down-regulated in PC/BCP mutated HBV infection. **Methods:** Mice with humanized livers were infected with either wild-type (HBV-wt) or mutant-type PC/BCP HBV (HBV-mt/mt) and sacrificed at various phase of HBV replication. Three HBV-infected mice were assigned for each time points. The top 10 genes extracted from RNAseq in humanized liver infected with PC/BCP mutated HBV were investigated. As a control, uninfected mice were prepared. **Results:** HBV-mt/mt-infected mice without human albumin reduction (indicating human hepatocyte loss) were sacrificed at the four time points (average serum HBV DNA levels were 6.36, 7.71, 9.9, and 10.7 log copies/ml, respectively). HBV-mt/mt-infected mice with human hepatocyte loss were also sacrificed (HBV DNA levels was 10.6 log copies/ml). For HBV-wt infection, the mice were sacrificed at the time that serum HBV DNA level was 6.09, 7.33, 7.56, and 9.3log copies/ml, respectively. HBV-mt/mt infected mice showed higher replication compared with HBV-wt infection. The expression of FST, DDB2, PHLDA3, and GDF15 was stable in HBV replication phase and excessively increased at and after peak of viremia. CES and FAM111B expression was down-regulated only in HBV-mt/mt mice at and after the peak of viremia. GPC3 expression was down-regulated in mice infected with both HBV-wt and HBV-mt/mt with higher viremia over 9 log copies of HBV DNA levels. **Conclusion:** HBV infection induce the change of gene expression in HBV-infected hepatocytes, and the dynamics of gene expression was different between HBV-mt/mt infection and HBV-wt infection. This difference might be affected the phenotype for liver diseases. Further study is needed to clarify the pathophysiology of hepatitis B.

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1307 | LONG-TERM EFFECTS OF PEGINTERFERON-BASED THERAPY VERSUS NUCLEOS(T)IDE ANALOGUE MONOTHERAPY IN NON-CIRRHOTIC HBEAG-POSITIVE CHRONIC HEPATITIS B PATIENTS

Qiankun Hu[1] Xueyun Zhang[2] Yuxian Huang[1], [1]Shanghai Public Health Clinical Center, Fudan University, [2]Huashan Hospital, Fudan University

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Background: The long-term clinical benefits of interferon (IFN)-based therapy compared to nucleos(t)ide analogue (NA) monotherapy in HBeAg-positive chronic hepatitis B (CHB) have not been well defined. This study aimed to evaluate the cumulative incidence of new-onset cirrhosis, serological responses, and hepatocellular carcinoma (HCC) development between these treatment strategies. **Methods:** Two independent cohorts of non-cirrhotic, HBeAg-positive CHB patients were analyzed: a treatment-naïve cohort (n = 686) and an NA-experienced cohort (n = 531). Patients received either IFN-based therapy or NA monotherapy. Propensity score matching (PSM) was employed to minimize intergroup heterogeneity. The primary endpoint was the cumulative incidence of new-onset cirrhosis. **Results:** After PSM, the 10-year cumulative incidence of new-onset cirrhosis was significantly lower in the IFN-based therapy group compared to the NA monotherapy group in both the treatment-naïve (3.3% vs 20.0%, $p = 0.005$) and NA-experienced (4.9% vs 20.9%, $p = 0.034$) cohorts. IFN-based therapy also resulted in significantly higher serological response rates across both cohorts, including HBeAg loss (treatment-naïve: 84.7% vs 55.6%; NA-experienced: 60.4% vs 43.6%, both $p < 0.001$) and HBsAg loss (treatment-naïve: 14.3% vs 5.7%, $p = 0.006$; NA-experienced: 10.2% vs 1.3%, $p < 0.001$). Subgroup analysis showed that patients receiving IFN-based therapy who achieved HBeAg loss within 96 weeks had the greatest long-term benefits, with lower cirrhosis incidence and higher HBsAg loss rates. Although the incidence of HCC was lower in the IFN-based group, the difference did not reach statistical significance (both $p > 0.05$). **Conclusion:** IFN-based therapy provides superior long-term benefits over NA monotherapy in reducing cirrhosis risk and enhancing serological responses in HBeAg-positive CHB patients.

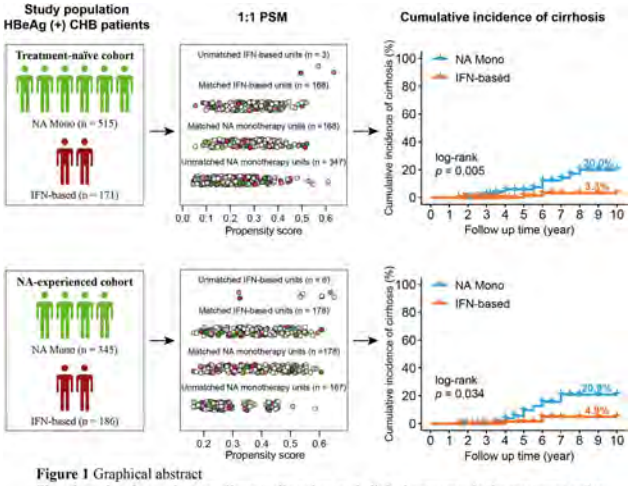

Figure 1 Graphical abstract
Flowchart showing patient enrollment, allocation, and clinical outcomes in the treatment-naïve and NA-experienced cohorts.
Abbreviations: CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; IFN, interferon; NA, nucleos(t)ide analogue; PSM, propensity score matching.

Disclosures: Qiankun Hu: Nothing to Disclose, Xueyun Zhang: Nothing to Disclose, Yuxian Huang: Nothing to Disclose

1308 | RETROSPECTIVE ANALYSIS OF B-CLEAR STUDY HBSAG LEVELS WITH THE ULTRASENSITIVE LUMIPULSE HBSAG ITACT ASSAY AND ASSOCIATION WITH RESPONSE AND RELAPSE

Scott Speer[1] Yasuhito Tanaka[2] Jerome Bouquet[3] Jennifer Cremer[4] Gift Nyamundanda[5] Lauren Maynard[5] Maria Agostini[3] Dickens Theodore[4] Rob Elston[5] Jill Walker[3], [1]GSK, Collegeville, PA, USA, [2]Department of Gastroenterology and Hepatology, Kumamoto University, Kumamoto, Japan, [3]GSK, South San Francisco, CA, USA, [4]GSK, Durham, NC, USA, [5]GSK, Stevenage, Hertfordshire, UK

Background: Bepirovirsen is an unconjugated antisense oligonucleotide in development for chronic hepatitis B virus (HBV) infection that has been shown to reduce hepatitis B surface antigen (HBsAg). The B-Clear Phase 2b study used the CE marked Roche Elecsys HBsAg II quant II (clinical trial test [CTT]) assay to measure HBsAg reductions. In this post hoc analysis, we explored whether the in-development Fujirebio Lumipulse iTACT HBsAg (iTACT) assay could support modeling of response or relapse in participants (pts) with chronic HBV infection receiving bepirovirsen. **Methods:** B-Clear randomized pts with chronic HBV infection on or not on nucleos(t)ide analogs to receive up to 300 mg bepirovirsen weekly for 12 or 24 weeks with or without loading doses.[1] Responders were pts who achieved HBsAg < limit of detection (LOD; 0.05 IU/mL) and HBV DNA < lower limit of quantification (LLOQ; 20 IU/mL) for 24 weeks after planned bepirovirsen treatment end in the absence of rescue medication. Non-responders did not achieve this endpoint, and a subset of those were relapsers who achieved HBsAg < LOD and HBV DNA < LLOQ at any time point but did not maintain HBsAg or HBV DNA loss. Samples from responders, non-responders, and relapsers at Weeks 9, 17, 23, and off-treatment Weeks 4, 12, and 24 (N = 50 pts, N = 300 samples) were analyzed using the iTACT HBsAg assay (LLOQ = 0.0005 IU/mL). For both assays, a linear mixed effects model evaluated the association of HBsAg with response. Logistic and/or multinomial regression models evaluated the association of HBsAg with response or relapse. **Results:** Both assays showed a strong association between HBsAg and response over time; the overall p value for all time points was the same (0.0011; Table). The iTACT assay provided quantitative

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values for 165/183 (90%) of samples that were < LLOQ with the CTT. The relative associations with response and relapse for the iTACT and CTT assays (area under the receiver operating characteristic curves; higher percentages indicate better discrimination) were 75% vs 62% [Week 17 response], 74% vs 64% [Week 17 relapse], 72% vs 58% [Week 23 response], and 80% vs 64% [Week 23 relapse], respectively. **Conclusion:** The iTACT HBsAg assay provides additional data with improved resolution to support pharmacokinetic/pharmacodynamic modeling. However, further studies with larger sample sizes and additional time points are needed to confirm the findings.

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1. Yuen MF, et al. N Engl J Med 2022;387:1957–68

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Table. Association of HBsAg values over time with response

Assay	Contrast	Visit	Fold change (95% CI)	p-value	Overall p-value
CTT quantitative HBsAg assay	Responder vs non-responder	Week 9	0.12 (0.0295, 0.5101)	0.0049	0.0011
		Week 17	0.32 (0.0763, 1.3042)	0.1065	
		Week 23	0.77 (0.1851, 3.1620)	0.7056	
		OT Week 4	0.41 (0.0995, 1.7000)	0.2137	
		OT Week 12	0.11 (0.0254, 0.4556)	0.0033	
		OT Week 24	0.02 (0.0060, 0.1020)	<0.0001	
iTACT quantitative HBsAg assay	Responder vs non-responder	Week 9	0.20 (0.0294, 1.3570)	0.0973	0.0011
		Week 17	0.07 (0.0097, 0.4551)	0.0068	
		Week 23	0.11 (0.0160, 0.7238)	0.0229	
		OT Week 4	0.09 (0.0135, 0.6151)	0.0151	
		OT Week 12	0.02 (0.0025, 0.1185)	0.0001	
		OT Week 24	0.01 (0.0014, 0.0658)	<0.0001	

CI, confidence interval; CTT, clinical trial test; HBsAg, hepatitis B surface antigen; OT, off-treatment

Disclosures: Scott Speer: GSK: Employee, GSK: Stock - publicly traded company, Astrazeneca: Employee, Yasuhito Tanaka: Nothing to Disclose, Jerome Bouquet: GSK: Employee, GSK: Stock - publicly traded company, Jennifer Cremer: Nothing to Disclose, Gift Nyamundanda: Nothing to Disclose, Lauren Maynard: Nothing to Disclose, Nothing to Disclose, Maria Agostini: Nothing to Disclose, Dickens Theodore: GSK: Employee, GSK: Stock - publicly traded company, Rob Elston: Nothing to Disclose, Jill Walker: GSK: Employee

1309 | THE RATE OF OCCULT HEPATITIS B VIRUS INFECTION IN HIGH ENDEMIC AREAS - VALUE IN EVALUATING LIVER FIBROSIS AND THE ROLE OF HBCRAG

Thuy Pham[1] Dat Ho[1] Toan Nguyen[1,] [1]Medic Medical Center

Background: Aim: Vietnam is a high epidemiological area of hepatitis B virus with high rates of cirrhosis and liver cancer. Among those, occult hepatitis B virus infection (OBI) plays an important but it is easily neglected. Therefore, the purpose of the study is to invests: -OBI rate in HBsAg negative, and AntiHBc positive subjects. -To evaluate the degree of liver fibrosis in these patients. -The role of HbcrAg. **Methods:** Research subjects and methods: Cross-sectional retrospective, random screening of 1492 subjects, HBsAg negative, AntiHBc positive subjects were tested for HBV DNA using polymerase chain reaction (PCR) amplification technique to determine the OBI rate. These subjects were also evaluated for liver fibrosis and tested for HBcrAg. **Results:** Results: Among 1492 subjects, there were 537 (35.99%) cases of HBsAg negative and AntiHBc positive. These patients were tested for HBV DNA to determine the OBI rate, accounting for 7.26% (39/537), average age was 49 ± 12, female was 49.72% (267/537). In the OBI group, F1 fibrosis was 7.69% (3/39), F2 was 15.38% (6/39), F3 was 30.76% (12/39), and F4 was 47.36% (18/39). There were 2 HCC patients with F4 fibrosis, accounting for 5.12% (2/39). When quantifying HBcrAg, 53.84% were greater than 2 log U/mL and less than or equal to 3 log U/ml, 46.15 % (18/39) were greater than 3 log U/mL, 2 HCC patients had HBcrAg greater than 3 log U/mL. All patients in the group of HBsAg negative, AntiHBc positive with non-OBI had F1 liver fibrosis and only 7.22% (36/498) patients had HBcrAg greater than 2 log U/mL. **Conclusion:** It is necessary to screen for OBI in the group of patients with HBsAg negative, AntiHBc positive, pay attention to patients with higher liver fibrosis score (F3, F4), HBcrAg greater than 2 log U/mL, and patients with clinical manifestations of HCC. **Disclosures:** Thuy Pham: Nothing to Disclose, Dat Ho: Nothing to Disclose, Toan Nguyen: Nothing to Disclose

1310 | FREQUENCY, AGE, CHARACTERISTICS, AND OUTCOMES OF SEROLOGICAL STATUS TRANSITION IN HBEAG-NEGATIVE CHB PATIENTS: INSIGHTS FROM THE HEPCARE LONG-TERM LONGITUDINAL COHORT

Ci Song[1] Jie Jiang[2] Siyu Wang[1] Chengxiao Yu[3] Wentao Yao[1] Jiao Qian[2], [1]Nanjing Medical University, [2]Jiangsu Provincial Center for Disease Control and Prevention, [3]The First Affiliated Hospital of Nanjing Medical University

Background: Serological transitions toward functional or partial cures in HBeAg-negative chronic hepatitis B (ENCHB) patients are crucial for understanding the natural history of HBV, evaluating antiviral treatment efficacy, and assessing the long-term risks of adverse outcomes. This study analyzed serological transition patterns, the incidence and characteristics of functional and partial cures, and their impact on long-term

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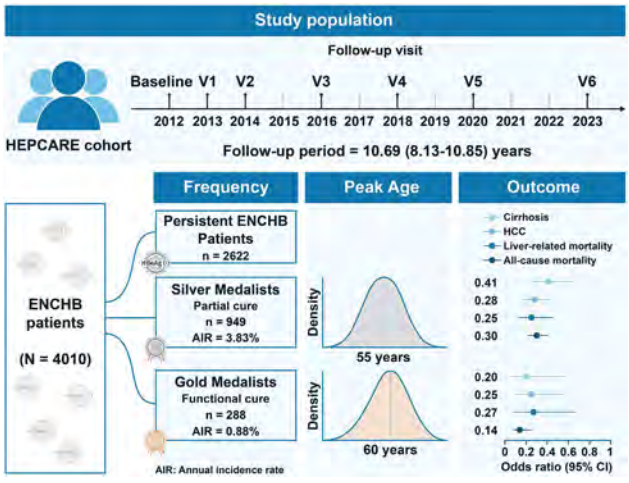
outcomes in ENCHB patients. **Methods:** In this multicenter, long-term prospective HEPCARE cohort, 4,010 ENCHB patients were followed from 2012 to 2023. Functional cure was defined as sustained HBsAg loss and undetectable HBV DNA during follow-up, which were categorized as "gold medalists". Partial cure was defined as sustained undetectable HBV DNA, categorized as "silver medalists". Patients with unchanged serological status were classified as persistent ENCHB. **Results:** After a median follow-up of 10.69 years, 288 and 949 patients were classified as gold and silver medalists respectively, with annual incidence rates of 0.88% for functional cure and 3.83% for partial cure. Most gold medalists (67.7%, 195 patients) first experienced HBV DNA seroclearance, followed by HBsAg loss. Among the patients who achieved partial cure, 112 experienced HBV DNA reactivation. Regardless of baseline HBV DNA levels, antiviral therapy significantly increased the incidence of partial cure by age 50 ($P < 0.001$), but had no significant effect on functional cure. The gold and silver groups showed statistically lower HBV DNA levels compared to the persistent ENCHB group at baseline, while serum ALT and AST levels exhibited a significant decline from 2016. Furthermore, the long-term risk of adverse outcomes (i.e. all-cause and liver-related mortality, cirrhosis, and hepatocellular carcinoma) was similar between the gold and silver groups, both of which showed significantly reduced risks compared to the persistent ENCHB group. **Conclusion:** Functional and partial cures are key milestones in the management of ENCHB, significantly reducing disease progression and mortality. Dynamic monitoring of serological markers can help improve both short- and long-term outcomes.



Disclosures: Ci Song: Nothing to Disclose, Jie Jiang: Nothing to Disclose, Siyu Wang: Nothing to Disclose, Chengxiao Yu: Nothing to Disclose, Wentao Yao: Nothing to Disclose, Jiao Qian: Nothing to Disclose

1311 | SYSTEMATIC REVIEW AND META ANALYSIS OF HEPATOCELLULAR CARCINOMA RISK IN HISPANIC AND LATIN AMERICAN PATIENTS WITH CHRONIC HEPATITIS B

Jonathan Lim[1] Ariel Lee[2] Gisela Butera[3] Sungyoung Auh[1] Kali Zhou[2] Christine Hsu[1], [1]National Institute of Diabetes and Digestive and Kidney Diseases, [2]Keck Medicine of USC, [3]National Institutes of Health Library

Background: Hepatocellular carcinoma (HCC) incidence in chronic hepatitis B (CHB) varies by race. Current AASLD guidelines recommend HCC screening in African or African American individuals at earlier ages and in males and females with CHB aged > 40 years and > 50 years, respectively, from endemic regions. HCC incidence in Hispanic and Latin American CHB is not well studied, and surveillance in this group is not specifically addressed. This systematic review evaluates overall HCC incidence in Hispanics and Latin Americans with CHB. **Methods:** A systematic review was conducted using PubMed, Embase, CENTRAL, Web of Science, and LILACS to search for eligible observational cohort studies and randomized-control trials prior to February 4, 2025. Eligible studies included Hispanic and/or Latin American adults (greater than or equal to 18 years old) with CHB. Outcomes evaluated include HCC and mortality incidence. Two reviewers (AL and JL) independently extracted data and performed risk of bias assessments using a tool developed and validated by Hoy et al. 2012, with discrepancies resolved by CH. Statistical analysis was performed using the R package “metarate”. Heterogeneity was assessed using Cochrane’s Q-test and quantified by I^2. **Results:** 2395 studies were screened, with 84 studies eligible for full-text review. 75 studies were excluded due to wrong outcomes, study populations, study designs, and duplication. 9 observational studies were included in the meta-analysis: 5 from the US, 3 from Brazil, and 1 across multiple countries. The overall pooled HCC incidence rate for Hispanic/Latin American CHB patients was 1.08 (95% CI 0.51-1.66) per 100 patient-years (pt-yrs). The I^2 was 80%, suggestive of a large amount of heterogeneity. After excluding a study conducted among only CHB patients with cirrhosis, the HCC incidence rate decreased to 0.87 (95% CI 0.43-1.31) per 100 pt-yrs. Influential analyses showed that when removing one study with 100% co-infected HIV (human immunodeficiency virus), the overall pooled incidence rate was similar (1.25 [95% CI 0.59-1.91] per 100 pt-yrs). When removing one study with 100% co-infected hepatitis D, effect estimates also remained similar (1.01 [95% CI 0.40-1.63] per 100 pt-yrs). The incidence of all-cause mortality using 4 studies was 1.98 (95% CI 0.92-3.05) per 100 pt-yrs. **Conclusion:**

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The calculated HCC incidence rate in Hispanic/Latin American CHB patients is similar than other at-risk populations and above the threshold of $>0.2\%$ per year where screening for HCC becomes recommended for CHB patients from endemic areas. This suggests the need for screening in this population, and further prospective studies are needed to confirm the observed rate.

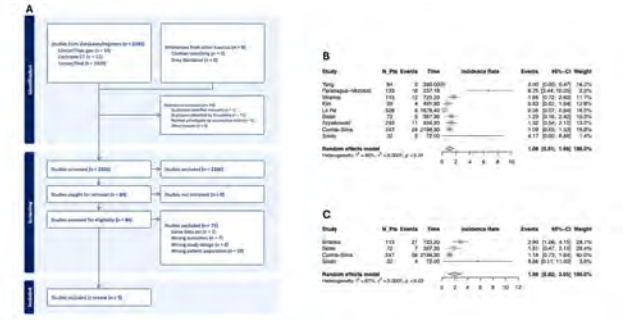

Figure 1: A) PRISMA Diagram Depicting Studies Reviewed in Full Text, Excluded, and Reasons for Excluding, Forest Plots Visualizing B) Pooled HCC Incidence and C) All-Cause Mortality in Hispanic/Latin American CHB Patients

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1312 | IMMUNE COMPLEXES OF BJT-778 ENHANCE CROSS-PRESENTATION OF HBSAG AND ACTIVATION OF CD8+ T CELLS

Adam Gehring[1] Loghman Salimzadeh[2] Stuti Shah[2] Danie La[2] Hilario Ramos[3] Leesun Kim[3] Nancy Shulman[3] Hassan Javanbakht[3], [1]Toronto Centre for Liver Disease, Schwartz-Reisman Liver Research Centre, Toronto, Canada, [2]Toronto Centre for Liver Disease, University Health Network, Toronto, Canada, [3]Bluejay Therapeutics, Inc., Redwood City, United States

Background: Chronic hepatitis B (CHB) is characterized by persistently high levels of hepatitis B surface antigen (HBsAg), which contribute to the dysfunction of HBV-specific T cells. BJT-778 is a fully humanized IgG1 monoclonal antibody that targets the antigenic loop of HBsAg and is currently in Phase 1/2 clinical development for chronic hepatitis B and D. We previously demonstrated that BJT-778 enhances the uptake of HBsAg by professional antigen-presenting cells (APCs) through the formation of immune complexes (ICs), leading to improved activation of CD4+ T cell responses. However, its capacity to promote cross-presentation and activation of CD8+ T cells has not yet been investigated. **Methods:** CD14+ monocytes isolated from healthy HLA-A02+ donors were loaded with either recombinant HBsAg or CHB serum-derived HBsAg in the presence or absence of BJT-778 to form ICs. Cells were differentiated into monocyte-derived dendritic cells (moDCs) and matured with R848, sCD40L, and IFNγ. Mature DCs were co-cultured with an HLA-A02-restricted HBsAg-specific CD8+ T cell clone. Antigen-specific responses were measured via IFN-γ ELISpot. **Results:** Formation of HBsAg ICs using BJT-778 significantly enhanced activation of CD8+ T cells compared to antigen alone. This enhancement was observed with both recombinant and serum-derived HBsAg, demonstrating the capacity of BJT-778 ICs to drive cross-presentation of diverse antigen sources. Across multiple CHB patient sera tested, BJT-778 ICs consistently increased the magnitude of IFN-γ production by CD8+ T cells, indicating improved cross-priming efficiency. In contrast, antigen alone or healthy control sera showed minimal CD8 T cell activation. **Conclusion:** BJT-778 not only enhances the uptake of HBsAg by antigen-presenting cells but also facilitates efficient cross-presentation to CD8+ T cells. These findings expand the mechanistic understanding of BJT-778 beyond CD4+ T cell activation, demonstrating its ability to boost HBV-specific CD8+ T cell responses. Together, the data support combining BJT-778 with immunomodulators to enhance both HBV-specific CD4 and CD8 T cell immunity.

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1313 | HIGHER UNGLYCOSYLATED HBSAG PROPORTION MAY PREDICT FASTER DECLINE KINETICS OF HBSAG IN CHRONIC HEPATITIS B

Chunfeng Li[1] ANDREW LOPEZ[2] Nadine Peinovich[1] Savrina Manhas[1] Yu Hu[1] Jiani Li[1] Christopher Richards[1] Caleb Marceau[1] Ross Martin[1] Jeong Heo[3] Edward Gane[4] Frida Abramov[1] Hongmei Mo[1] Evguenia Maiorova[1], [1]Gilead science Inc, [2]GILEAD SCIENCES,

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Background: A functional cure for Chronic Hepatitis B (CHB), defined as sustained loss of HBsAg, is a key treatment goal. N-linked glycosylation modification at N146 of HBsAg resulted in two forms of HBsAg: glycosylated (GpS) or unglycosylated (pS). In most CHB patients, the ratio of serum pS to GpS is 1:1 since glycosylation site N146 is not fully utilized. Host-dependent glycosylation of HBsAg may affect immune recognition, protein folding, and viral secretion. However, the relationship between HBsAg decline and HBsAg glycosylation levels is poorly understood in CHB patients. In this study, the association between GpS levels and HBsAg decline in CHB patients was investigated. **Methods:** Baseline (BL) serum samples were randomly selected from CHB patients in two similarly designed phase 3 studies of tenofovir alafenamide and/or tenofovir disoproxil fumarate: GS-US-320-0108 (HBeAg-negative) and GS-US-320-0110 (HBeAg-positive). Western blot analysis was used to quantify GpS and pS band intensities, from which pS/GpS ratios were calculated. Quantitative HBsAg levels were measured every 12 weeks through week 144, and every 24 weeks until week 384. HBsAg decline was analyzed from BL to week 384. BL sequences were analyzed to detect mutations at N146 glycosylation site. Pearson correlation was used to calculate P value if not stated. **Results:** A total of 66 patients, including 48 HBeAg+ and 18 HBeAg-, with HBV genotypes (GTs) distributed as follows: GTA (N = 11), GTB (N = 24), GTC (N = 30), and GTF (N = 1) were analyzed. BL pS/GpS ratios ranged from 0.23 to 4.03. HBsAg decline at week 48 varied from 0 to 6.19 log. An average pS/GpS ratio for HBeAg+ CHBs (1.99) was higher than that for HBeAg- CHBs (1.07, $P < 0.0001$, Student t test). A significant positive correlation was found between BL pS/GpS ratio and HBsAg decline at week 48 ($r = 0.57$, $p < 0.0001$), in HBeAg+ ($r = 0.52$, $p = 0.0002$) but not in HBeAg- patients ($r = -0.13$, $p = 0.6$). Similar correlations persisted from weeks 96 to 196 ($r > 0.5$, $p < 0.001$). For example, the largest HBsAg decline from baseline (6.19 log) was observed at week 48 in a patient with BL pS/GpS as 2.95. GT-specific correlations were checked for GTA ($r = 0.59$, $p = 0.056$), GTB ($r = 0.60$, $p = 0.002$), and GTC ($r = 0.51$, $p = 0.0045$). Patients who achieved HBsAg loss ($N = 12$) had higher pS/GpS ratios compared to those who did not ($N = 54$, $P = 0.0103$, Student t test) (Figure 1A). Among those who achieved HBsAg loss, faster S loss kinetics were associated with higher pS/GpS ratios (Figure 1B). No mutations at N146 glycosylation site were found in any samples at BL. **Conclusion:** The higher proportion of unglycosylated HBsAg correlated with faster HBsAg decline in HBeAg+ patients suggesting BL pS/GpS ratio could serve as a potential biomarker for predicting treatment response in HBeAg+ CHB patients. Further studies are warranted to elucidate the underlying mechanism of this correlation. **Disclosures:** Chunfeng Li: Nothing to Disclose, ANDREW LOPEZ: Nothing to Disclose, Nadine Peinovich: Nothing to Disclose, Savrina Manhas: Nothing to Disclose, Yu Hu: Nothing to Disclose, Jiani Li: Nothing to Disclose, Christopher Richards: Gilead Sciences: Employee, Caleb Marceau: Gilead Sciences: Employee, Ross Martin: Gilead Sciences: Employee, Jeong Heo: Gilead: Grant/Research Support, Roche: Speaking and Teaching, Yuhan: Speaking and Teaching, Abbvie: Speaking and Teaching, AstraZeneca: Advisor, Oncolys Japan: Grant/Research Support, Surrozen: Advisor, MedVir: Advisor, Edward Gane: Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Frida Abramov: Nothing to Disclose, Hongmei Mo: Nothing to Disclose, Evguenia Maiorova: Nothing to Disclose

1314 | IDENTIFICATION OF HOST FACTORS INVOLVED IN INDUCING FUNCTIONAL CURE

Takashi Honda[1] Yuichirou Harada[2] Shinya Yokoyama[1] Kena Yamamoto[1] Takanori Ito[1] Norihiro Imai[1] yoji ishizu[1] Masahiko Kuroda[2] Hiroki Kawashima[1] Yoshiki Murakami[3], [1]Nagoya University Graduate School of Medicine, [2]Tokyo Medical University, [3]Tokyo Medical Univesity/Asahi University

Background: The primary objective of existing therapies for chronic hepatitis B (CH) is to achieve hepatitis B surface antigen (HBsAg) clearance, indicative of a functional cure (FC). We have reported that the 97th amino acid mutation in the core region is associated with FC, but the cellular factors involved remain unclear. This study aimed to identify cellular factors associated

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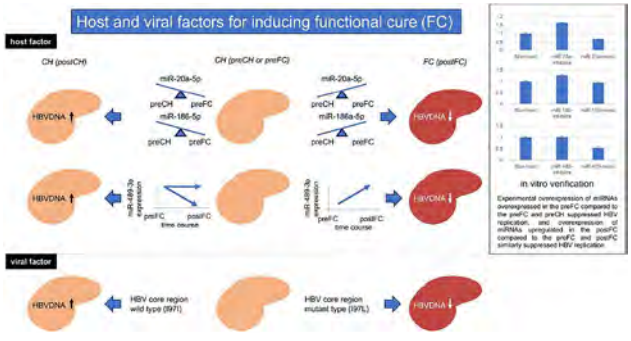
with FC induction. **Methods:** Serum samples from six patients with CH—three who achieved FC and three who remained in CH—were prepared. For cases in which CH progressed to FC during follow-up, the specimen taken at the first visit was defined as preFC, and the specimen taken after FC was defined as postFC. For cases in which CH remained CH during follow-up, the specimen taken at the first visit was defined as preCH, and the specimen taken most recently was defined as postCH. These sera were co-cultured with primary human hepatocytes (PHHs) for 12 days. After cell culture, we analyzed the expression of miRNA, mRNA, and protein in PHHs, bioinformatically identified miRNAs and target genes and also analyzed miRNA expression derived from cell supernatants. **Results:** In patients who improved from CH to FC, expression of miR-489-3p significantly increased after the transition. Expression of genetic suppressor element 1 (GSE1), a target gene of miR-489-3p, was suppressed. Overexpression of miR-489-3p suppressed HBV replication. Comparison of preCH and preFC, expression of miR-20a-5p and miR-186-5p in preFC was significantly higher than preCH. miR-20a-5p and miR-186-5p targeted Rho GTPase-activating protein 12 (ARHGAP12) and RELA proto-oncogene, NF-kB subunit (RELA), respectively. Overexpression of these miRNAs or silencing of the corresponding target genes with siRNA suppressed HBV replication. Analysis of culture supernatants revealed that four miRNAs (miR-6747-3p, 3193, 101-5p, and let-7e-3p) were differentially expressed depending on whether cases improved to FC or remained in CH, and six additional miRNAs (miR-4504, 128-1-5p, 660-3p, 501-5p, 449a, and 4526) were expressed only in either FC or CH. **Conclusion:** This study established an in vitro experimental model to improve the transition of CHB to FC using patient serum, and identified the cellular factors involved in FC induction. The miRNAs and target genes obtained herein may provide useful therapeutic targets to induce FC. Cell supernatant miRNAs may serve as potential diagnostic markers for FC.



Disclosures: Takashi Honda: Nothing to Disclose, Yuichirou Harada: Nothing to Disclose, Shinya Yokoyama: Nothing to Disclose, Kena Yamamoto: Nothing to Disclose, Takanori Ito: Nothing to Disclose, Norihiro Imai: Nothing to Disclose, yoji ishizu: Nothing to Disclose, Masahiko Kuroda: Nothing to Disclose, Hiroki Kawashima: Nothing to Disclose, Yoshiki Murakami: Nothing to Disclose

1315 | EFFICACY COMPARISON OF NUCLEOS(T)IDE ANALOGUES MONOTHERAPY VERSUS COMBINATION THERAPY WITH PEG-IFNA AT 48 WEEKS IN PATIENTS WITH CHRONIC HEPATITIS B AND LOW-LEVEL VIREMIA: A PROSPECTIVE STUDY

Shiyu Wang[1] Minghui Li[1] Ziyu Zhang[1] Xinxin Li[1] Wen Deng[1] Xin Wei[1] Linmei Yao[1] Zixuan Gao[1] Shuojie Wang[1], [1]Department of Hepatology Division 2, Beijing Ditan Hospital, Capital Medical University

Background: Low-level viremia patients with chronic hepatitis B is closely associated with the progression of liver fibrosis, development of decompensated cirrhosis, hepatocellular carcinoma (HCC) risk, and reduced long-term survival rates. Through a 48-week prospective cohort study, we compared the efficacy of nucleos(t)ide analogues (NAs) monotherapy versus combination therapy with pegylated interferon-alpha (Peg-IFNα) in CHB patients with low-level viremia. **Methods:** Patients with chronic hepatitis B (CHB) and low-level viremia (HBV DNA: 20–2000 IU/mL) who had persistently positive HBV DNA after 48 weeks of nucleos(t)ide analogue (NAs) therapy at Beijing Ditan Hospital (January 2022 to December 2024) were enrolled. Clinical data from two groups—those receiving NAs + Peg-IFNα(n = 272) and NAs (n = 90)—were prospectively analyzed to evaluate antiviral efficacy at 48 weeks and compare therapeutic outcomes. **Results:** At 48 weeks of treatment, the HBeAg seroclearance rates in the NAs + Peg-IFNα group and NAs group were 44.97% (76/169) and 50.00% (30/60), respectively ($P = 0.746$). The complete virologic response rates were 26.84% (73/272) versus 15.56% (14/90) ($P = 0.03$), and the HBsAg loss rates were 15.44% (42/272) compared to 2.22% (2/90) ($P = 0.004$). The median baseline ALT levels were 27.00 (18.15, 38.85) U/L in the NAs + Peg-IFNα group and 28.30 (20.00, 43.00) U/L in the NAs group. ALT levels in the NAs + Peg-IFNα group were significantly higher than those in the NAs group at 12, 24, 36, and 48 weeks, peaking at 12 weeks. Additionally, AST levels in the NAs + Peg-IFNα group remained consistently higher than those in the NAs group at all time points (12, 24, 36, and 48 weeks) ($P < 0.05$). The median baseline HBsAg levels were 3.36 (2.49, 3.78) $\log_{10}$ IU/mL in the NAs + Peg-IFNα group and 3.28 (2.52, 3.81) $\log_{10}$ IU/mL in the NAs monotherapy group. At baseline, the NAs + Peg-IFNα group showed

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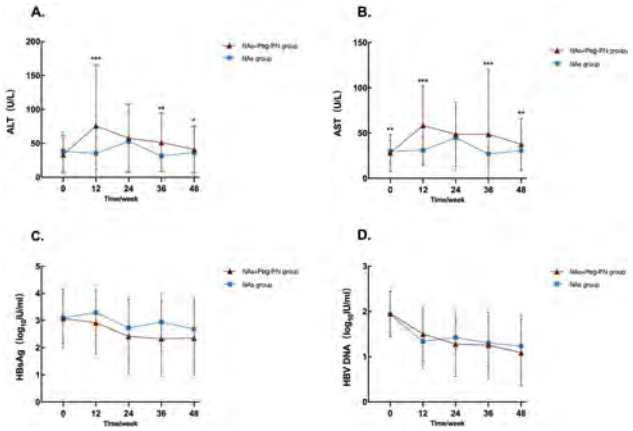
numerically higher HBsAg levels compared to the NAs group, though this difference was not statistically significant (Z = -0.24, P = 0.814). At subsequent time points, the median HBsAg levels in the NAs + Peg-IFNα group remained lower than those in the NAs group, but these differences also lacked statistical significance (P > 0.05). By week 48, both HBsAg and HBV DNA levels were significantly reduced compared to baseline in both treatment groups. At baseline, the median HBV DNA level in the NAs + Peg-IFNα group was 1.81 $\log_{10}$ IU/mL compared to 1.75 $\log_{10}$ IU/mL in the NAs group (P > 0.05). By week 24 of treatment, the median HBV DNA level in the NAs + Peg-IFNα group was numerically lower than that in the NAs group, though this difference also did not reach statistical significance(1.38 $\log_{10}$ IU/mL vs. 1.43 $\log_{10}$ IU/mL)(P > 0.05). **Conclusion:** In the optimized treatment of patients with low-level viremia (LLV), the NAs + Peg-IFNα regimen demonstrated significantly higher rates of complete virologic response and HBsAg loss compared to NA monotherapy optimization strategies.



Disclosures: Shiyu Wang: Nothing to Disclose, Minghui Li: Nothing to Disclose, Ziyu Zhang: Nothing to Disclose, Xinxin Li: Nothing to Disclose, Wen Deng: Nothing to Disclose, Xin Wei: Nothing to Disclose, Linmei Yao: Nothing to Disclose, Zixuan Gao: Nothing to Disclose, Shuojie Wang: Nothing to Disclose

1316 | STUDY ON THE EFFECTIVENESS AND SAFETY OF TAF IN THE TREATMENT OF ELDERLY CHB PATIENTS IN CHINA

Jie Tan[1] Huiling Fu[2] Lizhen Chen[1] Xinjie Hao[2] Tao Liu[2] Yuhong Dong[2] Jun Yu[2] Jianping Duan[2] Jinjin Li[2] Haifeng Zhang[2] Qingxi Wang[2] Zhaohui Wang[2] Yuwen Song[1] Bing Qiao[2] He Wang[2] Weili Cui[2] Shijing Gao[2] Jingjing Guo[2] Wei Zhao[2] Yong Zhou[2] Yongning Xin[3], [1]Qingdao Hospital, University of Health and Rehabilitation Sciences (Qingdao Municipal Hospital), [2]Qingdao Public Health Clinical Center, [3]Qingdao Hospital, University of Health and Rehabilitation Sciences (Qingdao Municipal Hospital)

Background: Tenofovir alafenamide fumarate (TAF) has significant antiviral effects and favorable safety in patients with chronic hepatitis B (CHB). This study aimed to investigate the effectiveness and safety of TAF in elderly (60 years and older) CHB patients and to clarify the impact of TAF on bone and renal health. **Methods:** A total of 201 CHB patients aged 60 years and older who received TAF antiviral treatment in multiple hospitals in Qingdao, China from June 2021 to December 2023 were included. The indicators at baseline, 24 weeks, 48 weeks, 72 weeks and 96 weeks were collected and analyzed. **Results:** A total of 187, 175, 162, and 54 elderly CHB patients completed the 24, 48, 72 and 96-week follow-ups, respectively. Compared with the baseline period, significant improvements in bone mineral density (BMD) was observed in both the lumbar spine (-0.91SD vs. -0.73SD, P = 0.011) and femoral neck (-1.03SD vs. -0.91SD, P = 0.017) at week 96. Compared with the baseline level, at week 96, there were no significant changes in BUN (5.60mmol/L vs. 5.24mmol/L, P = 0.642), creatinine (70.21umol/L vs. 68.32umol/L, P = 0.151), and eGFR (85.28mL/min/1.73m² vs. 85.56mL/min/1.73m², P = 0.873). At any time, there were no significant changes in urinary protein, α1-MG, β2-MG, or URBP. The HBV DNA undetectable (lower limit of detection is 20IU/ml) rate was 83.58% at baseline, and with the prolonged use of TAF, HBV DNA undetectable rate increased to 87.70%, 93.75%, 96.82%, and 98.15% at weeks 24, 48, 72, and 96, respectively. Compared with baseline, HBsAg levels significantly decreased at week 48 (1045.68IU/ml vs. 856.15IU/ml, PP < 0.01). **Conclusion:** After 2 years of TAF treatment in CHB patients aged 60 years and older, the BMD of the lumbar spine and femoral neck significantly improved, and the renal function was stable. The HBV DNA undetectable rate gradually increased, and the HBsAg levels significantly decreased.

Disclosures: Jie Tan: Nothing to Disclose, Huiling Fu: Nothing to Disclose, Lizhen Chen: Nothing to Disclose, Xinjie Hao: Nothing to Disclose, Tao Liu: Nothing to Disclose, Yuhong Dong: Nothing to Disclose, Jun Yu: Nothing to Disclose, Jianping Duan: Nothing to Disclose, Jinjin Li: Nothing to Disclose, Haifeng Zhang: Nothing to Disclose, Qingxi Wang: Nothing to Disclose, Zhaohui Wang: Nothing to Disclose, Yuwen Song: Nothing to Disclose, Bing Qiao: Nothing to Disclose, He Wang: Nothing to Disclose, Weili Cui: Nothing to Disclose, Shijing Gao: Nothing to Disclose, Jingjing Guo: Nothing to Disclose, Wei Zhao: Nothing to Disclose, Yong Zhou: Nothing to Disclose, Yongning Xin: Nothing to Disclose

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1317 | EFFICACY OF NAS IN COMBINATION WITH PEG-IFN FOR FUNCTIONAL CURE IN PATIENTS WITH CHB: A META-ANALYSIS OF RCTS

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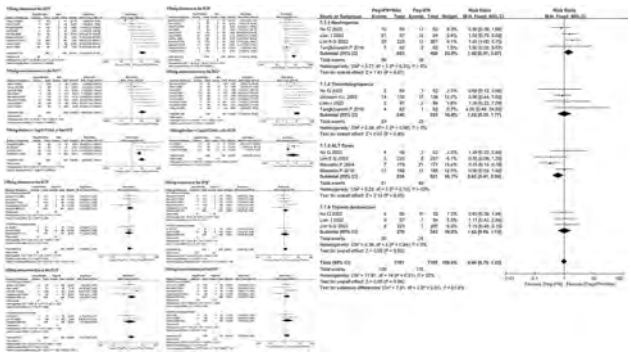
Background: The goal of treating chronic hepatitis B (CHB) is to achieve functional cure. We aimed to evaluate the efficacy of the combination of nucleoside (acid) analogues (NAs) and pegylated interferon (Peg-IFN) on the functional cure of CHB patients at the EOT and at the EOF. **Methods:** PubMed, Embase, and Web of Science were searched systematically up to March 15, 2025. Sixteen RCTs on CHB patients receiving combination or monotherapy were included. **Results:** Compared with NAs treatment, the NAs combined with Peg-IFN treatment group significantly improved HBsAg clearance rate (RR: 14.05, 95% CI 6.13-32.20) and HBsAg seroconversion rate (RR: 12.82, 95% CI 5.08-32.33) at the EOT. Moreover, compared with NAs treatment, the NAs combined with Peg-IFN treatment group significantly improved HBsAg clearance rate (RR: 7.70, 95% CI 4.24-13.98), HBsAg seroconversion rate (RR: 11.93, 95% CI 5.14-27.67) at the EOF. However, compared with Peg-IFN monotherapy, the combination therapy group did not show any improvement in HBsAg clearance rate, HBsAg seroconversion rate, and the rate of qHBsAg decrease >1 log10 IU/mL at the EOT and the EOF. Moreover, in terms of safety, the Peg-IFN monotherapy group showed more ALT flares (ALT $> 5 \times$ ULN) during the treatment process. **Conclusion:** Compared with NAs therapy, Peg-IFN combined with NAs therapy significantly improves functional cure rate. However, combination therapy shows no additional advantage over Peg-IFN monotherapy in achieving functional cure. The Peg-IFN monotherapy group has a higher incidence of ALT flares than the combination therapy group.



Disclosures: Yaqin Zhang: Nothing to Disclose, Yao Xie: Nothing to Disclose, Minghui Li: Nothing to Disclose

1318 | MULTIMODAL SPATIAL PROFILING OF LIVER BIOPSIES FROM INDIVIDUALS WITH CHRONIC HBV INFECTION REVEALS A PREVIOUSLY UNDESCRIBED POPULATION OF HBV-INTEGRATED HEPATOCYTES

SANGEETHA MAHADEVAN[1] Ricardo Ramirez[1] Hatef Mehrabian[1] CHRISTINA MOON[1] APOORVA MOHAN[1] Edith Vaquero[1] Rosanna Win[1] Subhra Chaudhuri[1] Hsiu-Chun Chuang[1] Kai-Hui Sun[1] Abhishek Aggarwal[1] Anjali Rao[1] Scott Balsitis[1] Simon Fletcher[1] Meghan Holdorf[1] Li Li[1] Lauri Diehl[1], [1]Gilead Sciences, Inc.

Background: HBV cccDNA+ and HBV-integrated (iHBV) hepatocytes are both present in the livers of individuals with chronic hepatitis B (CHB), and recent studies have indicated that elimination of both HBV+ cell populations is required for functional cure. To better understand these cell populations, we combined Spatial Transcriptomics (ST), single-nucleus RNA-Seq (snRNA-Seq), chromogenic in situ hybridization (CISH), and multiplex immunofluorescence (mIF) with machine learning methods to profile archival liver biopsy samples from CHB patients. Six commercially-procured liver tissue sections ($n=2$ healthy, $n=4$ CHB) and 6 core-needle biopsies from study GS-US-174-0149 ($n=4$ CHB baseline, $n=2$ CHB Tenofovir Disoproxil Fumarate-treated) were profiled by 10X Visium CytAssist using the Human Transcriptome panel with the addition of custom-designed probes targeting HBV. Serial FFPE sections were analyzed by CISH (viral RNA) and mIF (HBsAg, HBV core), which were used to train machine learning classifiers. In addition, snRNA-Seq was performed on $n=1$ healthy and $n=3$ CHB samples. **Methods:** Six commercially-procured liver tissue sections ($n=2$ healthy, $n=4$ CHB) and 6 core-needle biopsies from study GS-US-174-0149 ($n=4$ CHB baseline, $n=2$ CHB Tenofovir Disoproxil Fumarate-treated) were profiled by 10X Visium CytAssist using the Human Transcriptome panel with the addition of custom-designed probes targeting HBV. Serial FFPE sections were analyzed by CISH (viral RNA) and mIF (HBsAg, HBV core), which were used to train machine learning classifiers. In addition, snRNA-Seq was performed on $n=1$ healthy and $n=3$ CHB samples. **Results:** HBV RNA and DNA were successfully co-detected alongside human transcripts using custom spike-in of HBV-specific probes into a ST panel. Spots containing cccDNA+ hepatocytes (HBs+, HBc+, HBx+, rcDNA+ RNA by ST) had increased immune cell (e.g., T cell, B cell) and type II interferon transcriptional signatures compared to iHBV (HBs+, HBx+, HBc-, and rcDNA- RNA by ST) or uninfected hepatocytes. Integrated analysis identified a population of iHBV hepatocytes which were HBcAg- and HBsAg- by mIF but HBs RNA+ by ST and CISH. These iHBV cells produced similar levels of HBs RNA as iHBV cells which were HBsAg+ by mIF, but were

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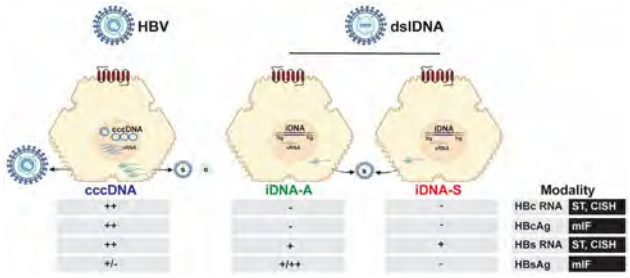
spatially distinct and exhibited a peri-portal zonal bias in the liver. At the individual cell level, a higher percentage of HBV + cells was also detected by snRNA-seq than by mIF. **Conclusion:** Our findings indicate the presence of a previously undescribed population of HBV-integrated hepatocytes which may suggest higher intrahepatic viral burden than previously described.

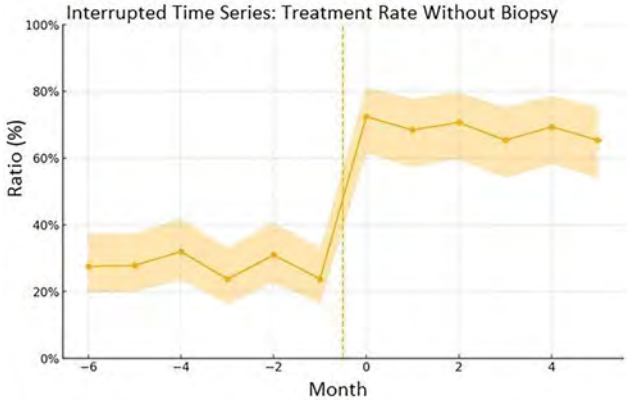


Disclosures: SANGEETHA MAHADEVAN: Nothing to Disclose, Ricardo Ramirez: Gilead Sciences, INc.: Employee, Hatef Mehrabian: Gilead Sciences Inc: Employee, CHRISTINA MOON: Nothing to Disclose, APOORVA MOHAN: Gilead Sciences: Employee, Edith Vaquero: Nothing to Disclose, Rosanna Win: Nothing to Disclose, Subhra Chaudhuri: Nothing to Disclose, Hsiu-Chun Chuang: Nothing to Disclose, Kai-Hui Sun: Nothing to Disclose, Abhishek Aggarwal: Nothing to Disclose, Anjali Rao: Nothing to Disclose, Scott Balsitis: Nothing to Disclose, Simon Fletcher: Gilead Sciences, Inc.: Employee, Meghan Holdorf: Gilead: Employee, Li Li: Nothing to Disclose, Lauri Diehl: Nothing to Disclose

1319 | POLICY MATTERS: A SUCCESS STORY IN HEPATITIS B TREATMENT ACCESS FOLLOWING REIMBURSEMENT POLICY CHANGE

Rahmet Guner[1] Imran Hasanoglu[1] Nazlim Demir[2] Ozlem Altuntas Aydin[3] Derya Ari[4] Oguz Karabay[5] Esra Zerdali[6] Yusuf Hayran[2] SILA AKHAN[7] Birsen Asena Emre[3] Meral Akdoğan Kayhan[4] Sibel Yildiz Kaya[8] Asli Vatan[5] Deniz Kakalicoglu Ozden[9] Tugba Arslan Gulen[10] Asli Haykir Solay[11] Bilger Cavus[12] Dilek Yıldız Sevgi[13], [1]Ankara Yildirim Beyazit University Bilkent City Hospital, [2]Selcuk University Faculty of Medicine, [3]University of Health Sciences Basaksehir Cam and Sakura City Hospital, [4]Ankara Bilkent City Hospital, [5]Sakarya University Faculty of Medicine, [6]Istanbul Haseki Education and Research Hospital, [7]Kocaeli University Faculty of Medicine, [8]Istanbul University Cerrahpasa Faculty of Medicine, [9]University of Health Sciences Haseki Sultangazi Education and Research Hospital, [10]Adana City Hospital, [11]Ankara Etlik City Hospital, [12]Istanbul University Istanbul Faculty of Medicine, [13]Hamidiye Etfal Education and Research Hospital

Background: On November 2, 2024, a revised reimbursement policy in Türkiye partially removed the requirement for liver biopsy in the treatment of chronic hepatitis B (CHB), aiming to improve access to antiviral therapy. This study aimed to evaluate the policy's comprehensive impact on treatment initiation rates, antiviral drug choices, age-specific effects, and projected economic benefits in the context of hepatitis B elimination goals. **Methods:** We retrospectively analyzed data from 1,035 CHB patients across 18 tertiary centers. Patients were categorized into two periods: pre-policy change (Nov 2, 2023 – Nov 1, 2024; n = 583) and post-policy change (Nov 2, 2024 – May 1, 2025; n = 452). The primary outcome was the proportion of patients initiating therapy without biopsy. Interrupted time series (ITS) analysis assessed changes in trend and level post-policy and multilevel logistic regression examined center-level variability and interaction by age <40 years, ALT, AST, and FIB-4. Economic projections assumed a biopsy cost of $250. **Results:** The proportion of patients initiating treatment without biopsy increased from 27.6% pre-policy change to 68.6% post-policy change (RR = 2.48; p < 0.0001). ITS confirmed a significant immediate increase of +41.3 percentage points (p < 0.001) (Fig. 1). In multivariable analysis, the post-policy change period was independently associated with higher odds of initiating treatment without biopsy (aOR = 6.90; 95% CI 5.05–9.43), with a significant interaction for patients under 40 years (aOR = 0.33; p = 0.002). No significant changes were observed in antiviral preferences (entecavir, TDF, TAF; all p > 0.30). FIB-4 had limited discriminatory power for biopsy decisions (AUC = 0.42). Avoidance of 189 biopsies in the study cohort resulted in projected savings of $47,250, with an estimated national annual cost benefit between $6 million and $30 million. **Conclusion:** The recent reimbursement policy change in Türkiye has substantially improved access to antiviral therapy for CHB by reducing dependency on invasive liver biopsies. This shift has led to a simplified clinical workflow, reduced procedural burden on patients, and yielded considerable cost savings. The marked increase in treatment initiation, especially among patients previously deterred by biopsy requirements, highlights the real-world impact of policy-driven interventions.



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1320 RELINK: GETTING HEPATITIS B AND C PATIENTS BACK INTO CARE IN MARYLAND AND VIRGINIA | A COMMUNITY-ROOTED OUTREACH STRATEGY BUILT ON CULTURAL TRUST, REAL RELATIONSHIPS, AND LESSONS LEARNED THE HARD WAY

Yanhong Zou[1] Sandra Marrero-Ashford[1], [1]Hepatitis B Initiative of Washington, D.C. Inc.

Background: Too many people are diagnosed with Hepatitis B or C and never make it to treatment. They fall through the cracks—because of a disconnected phone, stigma, addiction, or simply because no one followed up. The ReLink Project was created to find them again—and bring them back. We focused on: 1. Immigrant communities with a high Hepatitis B and Hepatitis C burden. 2. People who use drugs and those who are unstably housed are at the highest risk for untreated HCV. **Methods:** 1. 470 individuals with HBV and 410 with HCV were identified in Maryland and Virginia. 2. Outreach by trained CHWs from the same communities. 3. Contact via phone, clinic, email, message, letter, rehab centers, shelters. 4. Data tracked: contact success, current care status, and new linkage. **Results:** Key Rusult: Population-based insights. 1.Vietnamese Clients(HBV & HCV). 1)Highest care retention. 2)Tested with trusted provider (Dr. Tran). 3)CHW (Jennifer) was there at testing and follow-up. 2. Mongolian Clients(HBV & HCV). 1)Language alignment, but fewer stayed in care. 2)Tested through HBI, but no ongoing provider relationship. 3)Many had moved or become unreachable. 3.African Immigrant Clients (HBV). 1)Higher rate of declined care. 2) Barriers: stigma, mistrust, spiritual beliefs. 4.U.S.-Born Clients (HCV). 1)Least reachable. 2)Most from harm reduction or recovery centers. 3)Many lost phones or relapsed, but all who were reached accepted care. Lesson Learned. 1. Main barrier: Disconnected numbers, no response, missing contact information, and relocated. 2. Key win: 100% of reachable HCV clients who needed care accepted linkage. 1)Referrals don't work without relationships. 2)CHWs must be assigned at diagnosis, especially in rehab and shelter settings. 3) Clients need someone to walk them into care, not just give them the address. 4)Contact info decays quickly—we need faster follow-up and better systems. What We are Building Next. 1. CHW-led in-person outreach is now active. 2. AI-powered follow-up system (launching 2026) to help track disconnected clients. 3. Deep partnerships with community clinics and rehab programs. 4. Continued investment in relationship-first engagement. **Conclusion:** The Relink Project's findings emphasize the need for a systems-level approach to hepatitis care that focuses on swift engagement, continued support, and removing barriers to healthcare access. As the project progresses, efforts will focus on refining the CHW model and exploring technological solutions to streamline follow-up. Ultimately, the project illustrates that overcoming obstacles in healthcare requires persistence, cultural humility, and coordinated support. By diligently following up and reconnecting every patient to care, regardless of time passed or challenges faced, we can improve our lives and make meaningful progress in the fight against viral hepatitis. These lessons broadly apply to linkage-to-care efforts for other diseases, especially in underserved populations.

	HBV	HCV
Total Patients	470	410
Succsfully Contacted	75%(349)	43%(172)
Already in Care/Treated	85% (298 of 439 contacted)	94% (162 of 172 contacted)
Newly Linked to Care	20(8.9%)	10(0%)

Disclosures: Yanhong Zou: Nothing to Disclose, Sandra Marrero-Ashford: Nothing to Disclose

1321 | END-OF-THERAPY HBSAG, HBCRAG, AND HBV RNA PREDICT 8-YEAR OUTCOMES AFTER NUCLEOS(T)IDE ANALOGUE CESSATION IN CHRONIC HEPATITIS B

Meng-Ju Lin[1] Tung-Hung Su[1] Chun-Jen Liu[1] Hung-Chih Yang[1] Jyh-Ming Liou[1] Tai-Chung Tseng[1] Chen-Hua Liu[1] Chun-Ming Hong[1] Pei-Jer Chen[1] Jia-Horng Kao[1], [1]National Taiwan University Hospital

Background: Nucleos(t)ide analogues (NA) are the cornerstone for the treatment of hepatitis B virus (HBV)

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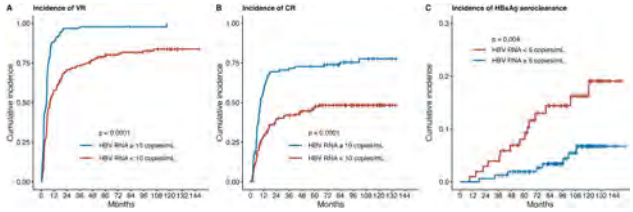
infection. Finite NA therapy has been proposed to facilitate hepatitis B surface antigen (HBsAg) clearance; however, virological relapse (VR, HBV DNA > 2000 IU/mL) and clinical relapse (CR, VR and ALT > 2-fold upper limit of normal) are common. The role of quantitative HBsAg, hepatitis B core-related antigen (HBcrAg), and HBV RNA to predict outcomes after NA cessation remained undetermined. **Methods:** Non-cirrhotic chronic hepatitis B (CHB) patients who discontinued NA therapies in a tertiary medical center were prospectively enrolled. The serum at the end-of-therapy (EOT) was collected to quantify HBsAg, HBcrAg, and HBV RNA. The patients were monitored prospectively at the 1st, 3rd, and every 3 months after treatment cessation to monitor HBV DNA and alanine aminotransferase (ALT) levels. HBsAg, HBcrAg, and HBV RNA levels were logarithmically transformed or categorized for univariate and multivariable analyses to predict VR, CR, and HBsAg seroclearance. **Results:** Overall, 260 patients (39.6% initially HBeAg-positive) were included, and 194 (74.6%) fulfilled the Asian Pacific Association for the Study of the Liver (APASL) guidance for stopping NAs. Before NA cessation, 156 (60.0%) patients received entecavir, 81 (31.1%) received tenofovir-based therapies, and the rest received other NAs or combination therapies. The median treatment and follow-up duration were 37 months and 7.9 years. At EOT, HBV RNA levels were <5, 5–10, and ≥ 10 copies/mL in 39.2%, 25.0%, and 35.8% of patients, respectively. At the end of follow-up, 229 (88.1%) and 148 (56.9%) patients developed VR and CR, respectively, and 23 (8.8%) patients developed HBsAg seroclearance. Multivariable Cox regression analysis showed age (adjusted HR [aHR]: 1.02, 95% CI: 1.00-1.03, P = 0.024), tenofovir use (aHR: 1.61, 95% CI: 1.21-2.14, P = 0.001), HBsAg (aHR: 1.26, 95% CI: 1.04-1.53, P = 0.018), and HBV RNA (aHR: 1.69, 95% CI: 1.46-1.95, P < 0.0001) significantly predicted VR. Age (aHR: 1.02, 95% CI: 1.00-1.04, P = 0.012), HBcrAg (aHR: 1.26, 95% CI: 1.05-1.50, P = 0.012), and HBV RNA (aHR: 1.34, 95% CI: 1.14-1.57, P = 0.0003) predicted CR. EOT HBV RNA $\geq$ 10 copies/mL conferred higher risk of VR (2.16-fold) and CR (1.57-fold) than HBV RNA $\leq$ 10 copies/mL. EOT HBV RNA detectability ($\geq$ 5 or < 5 copies/mL) stratifies the risk of HBsAg seroclearance; however, HBsAg level (aHR: 0.23, 95% CI: 0.14-0.36, P < 0.0001) was the only factor strongly associated with HBsAg seroclearance in multivariable analysis. EOT HBV RNA remained predictive of VR and CR in patients who met the APASL criteria. **Conclusion:** VR and CR are frequent after NA cessation. In a cohort including both HBeAg-positive and -negative patients, whether or not they met the APASL stopping criteria, EOT HBsAg, HBcrAg, and HBV RNA predicted subsequent relapses. A low HBsAg level at EOT was the strongest predictor of subsequent HBsAg seroclearance.



Disclosures: Meng-Ju Lin: Nothing to Disclose, Tung-Hung Su: Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Merck Sharp and Dohme: Speaking and Teaching, Roche: Speaking and Teaching, Sysmex: Speaking and Teaching, Eisai: Speaking and Teaching, Chun-Jen Liu: Nothing to Disclose, Hung-Chih Yang: Nothing to Disclose, Jyh-Ming Liou: Nothing to Disclose, Tai-Chung Tseng: Nothing to Disclose, Chen-Hua Liu: Nothing to Disclose, Chun-Ming Hong: Nothing to Disclose, Pei-Jer Chen: Nothing to Disclose, Jia-Horng Kao: Nothing to Disclose

1322 | ANALYSIS OF IMMUNE RESPONSES IN HIV/HBV CO-INFECTED PATIENTS EXPERIENCE HBSAG LOSS AFTER TDF/TAF-BASED ANTIVIRAL THERAPY IN THE ALLIANCE CLINICAL STUDY

David Pan[1] Nikita Kolhatkar[1] Pamela Odorizzi[1] Caleb Marceau[1] Rod Dunbar[2] Daniel Verdon[2] Scott Balsitis[1] Sharline Madera[1] Frida Abramov[3] Jason Hindman[1], [1]Gilead Sciences, [2]University of Auckland, [3]Gilead Sciences, Inc.

Background: A functional cure for chronic hepatitis B (CHB), defined by hepatitis B s antigen (HBsAg) loss and sustained HBV DNA suppression, is rarely achieved, even with long-term antiviral therapy. In the phase 3, randomized, double-blind ALLIANCE trial, treatment-naïve adults co-infected with HIV-1/HBV received either bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) or dolutegravir (DTG) + emtricitabine/tenofovir disoproxil fumarate (F/TDF). HBsAg loss/seroconversion rates were significantly higher, particularly with B/F/TAF, than those reported in TDF or TAF HBV monoinfection studies. This analysis aimed to further characterize immune responses in participants who achieved HBsAg loss through at least 144 weeks of follow-up. **Methods:** A sub-study analysis of the ALLIANCE trial evaluated plasma collected from 48 participants (HBsAg loss (n = 25), non-HBsAg loss (HBsAg +, n = 23)). The two cohorts were balanced based on treatment, demographic, and viral parameters. Plasma samples were collected longitudinally from baseline, pre- and post HBsAg loss, pre- and post- HBsAg antibody seroconversion (if detected), end of treatment, open-label

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extension (OLE), and ALT flare (if detected). Chemokine and cytokine levels were quantified using multiplex ELISA (O-link). Peripheral blood mononuclear cells (PBMCs) were collected from 31 participants during the OLE phase (HBsAg loss (n = 16), non-HBsAg loss (n = 15)) and were used to characterize HBV-specific T cell responses using a 2-color Fluorospot (IFNg/granzyme B). **Results:** Peripheral inflammatory cytokines and chemokines decreased after initiation of antiviral treatment in all participants regardless of HBsAg loss when compared to their baseline cytokine profile. While not statistically significant, tissue-homing cytokines, CXCL9, CXCL10 and CXCL11 trended higher at the time of HBsAg loss when compared to those who remained HBsAg+. HBV-specific T cell responses trended higher in HIV/HBV co-infected participants with HBsAg loss and were skewed towards hepatitis B core antigen specificity. **Conclusion:** This sub-analysis of HIV/HBV coinfected participants treated with B/F/TAF suggests that antiviral treatment results in an overall reduction in systemic inflammation irrespective of HBsAg loss. However, modest increases in HBV-specific T-cell responses and increases in tissue homing chemokines were observed in those who achieved HBsAg loss, indicating a potential role for immune activation in promoting functional cure.

Disclosures: David Pan: Nothing to Disclose, Nikita Kolhatkar: Gilead Sciences: Employee, Pamela Odorizzi: Nothing to Disclose, Caleb Marceau: Gilead Sciences: Employee, Rod Dunbar: Nothing to Disclose, Daniel Verdon: Nothing to Disclose, Scott Balsitis: Nothing to Disclose, Sharline Madera: Nothing to Disclose, Frida Abramov: Nothing to Disclose, Jason Hindman: Gilead Sciences: Employee

1323 | DOSE-DEPENDENT BUT ATTENUATED RISK OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY WITH INCREASING HBV DNA LOAD IN MOTHERS WITH CHRONIC HEPATITIS B

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Background: Chronic hepatitis B virus (HBV) infection remains prevalent among women of childbearing age in China. Intrahepatic cholestasis of pregnancy (ICP), a liver disorder occurring in late pregnancy, is linked to adverse perinatal outcomes. Although HBV has been proposed as a risk factor for ICP, the association between HBV DNA levels and ICP remains unclear. **Methods:** We conducted a retrospective case-control study of 71,342 pregnant women who delivered at Guangzhou Women and Children's Medical Center between January 2019 and November 2021. Intrahepatic cholestasis of pregnancy (ICP) was diagnosed based on elevated total bile acid levels (> 10 μmol/L), with or without pruritus or abnormal liver function tests. Women with ICP were compared to those without (controls) to assess potential risk factors. HBV infection status and, for those infected, HBV DNA levels, along with other clinical characteristics, were extracted from medical records. Multivariate logistic regression was performed to assess the association between HBV infection or HBV DNA levels and ICP, adjusting for maternal age, gallbladder disease, pancreatic disorders, hepatitis C, cirrhosis, and the use of assisted reproductive technology. **Results:** Among 1,075/71,342 women diagnosed with ICP, HBV prevalence was significantly higher than in women without ICP (12.3% vs. 4.1%, P < 0.01). After adjusting for potential confounders, HBV infection was associated with increased ICP risk (adjusted odds ratio [aOR] 3.14; 95% CI: 2.60–3.80). To examine the relationship between HBV DNA levels and ICP risk, mothers were categorized into five groups based on their hepatitis B surface antigen (HBsAg) status and HBV DNA load. Group 0 included 18,429 women without HBV infection and served as the reference group. Group 1 comprised 130 women with HBV DNA levels less than 10^3 IU/mL, group 2 included 404 women with HBV DNA levels between 10^3 and $< 10^5$ IU/mL, group 3 included 471 women with HBV DNA levels between 10^5 and 10^7 IU/mL, and group 4 included 356 women with HBV DNA levels of 10^7 IU/mL or higher. The risk of ICP increased in a dose-dependent manner with rising HBV DNA levels, peaking in group 3 (aOR 9.44; 95% CI: 5.97–14.90). However, this elevated risk was not observed in group 4 (Table 1), where HBV DNA levels were $\geq 10^7$ IU/mL (aOR 1.55; 95% CI: 0.82–2.92). **Conclusion:** HBV infection is an independent risk factor for ICP. The relationship between HBV DNA levels and ICP is nonlinear, with peak risk at intermediate viral loads (10^5–10^7 IU/mL), possibly reflecting immune activity during the immune-clearance phase. Pregnant women with moderate HBV DNA levels may benefit from closer monitoring for ICP and related complications.

Table 1. Odds Ratios and 95% Confidence Intervals for Developing ICP in HBV-Infected Women and Subgroup Analyses

Variables	Crude OR (95% CI)	Adjusted OR (95% CI) [‡]
Hepatitis B infection		
No	1(reference)	1(reference)
Yes	3.24 (2.69,3.90)	3.14 (2.60-3.80)
HBV DNA levels		
Non-HBV infected cases	1 (reference)	1 (reference)
Hepatitis B infected cases		
- HBV DNA ≤1,000 IU/mL	3.03 (2.40,3.83)	2.96 (2.34,3.76)
- HBV DNA >3log10 to ≤ 5log10 IU/mL	3.30 (2.12,5.14)	3.22 (2.06,5.03)
- HBV DNA >5log10 to ≤ 7log10 IU/mL	9.82 (6.26,15.41)	9.44 (5.97,14.90)
- HBV DNA >7log10 IU/mL	1.64 (0.87,3.08)	1.55 (0.82,2.92)

Abbreviations: OR = odds ratio; CI = confidence interval.

[‡] Adjusted for maternal age, pancreatic disease, hepatitis C, gallbladder disorders, and use of assisted reproductive technology

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1324 | CLINICAL TRIALS FOR CURING CHRONIC HEPATITIS B: A COMPREHENSIVE ANALYSIS OF DESIGN PRINCIPLES AND THEIR IMPACT ON TRIAL PERFORMANCE

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Background: The development of novel agents for chronic hepatitis B (CHB) has rapidly evolved, but only with a few candidates progressing to phase III trials. This study aimed to systematically analyze the key elements of clinical trial design for curing CHB and evaluate their impact on the trial performance. **Methods:** We conducted a systematic review of clinical trial registries (ClinicalTrials.gov, WHO Clinical Trials Registry Platform, and Chinese Clinical Trial Registry) and publications (PubMed, Embase, and the Cochrane Library) for CHB cure trials. The relationship of the design characteristics and the performance of the trials were analyzed with Cox regression and meta-analysis. **Results:** A total of 244 trials and 23 publications involving 1,798 patients were included. Phase I clinical trials had a completion rate of 65.5%, with 38.7% advancing to phase II. For phase II trials, the completion rate was 48.9%, only with 4.3% advancing to phase III. Novel trial designs were adopted by 30.3% of the CHB clinical trials. Smaller sample size significantly was associated with higher completion rates in both phase I (HR: 0.980, 95% CI: 0.966–0.994) and phase II trials (HR: 0.994, 95% CI: 0.988–0.999). Shorter treatment duration was associated with higher completion rates only in phase I trials (HR: 0.992, 95% CI: 0.986–0.998). Meta-analysis of early-phase trials showed that direct-acting antivirals (SMD: 5.43, 95% CI: 0.22–10.64) were superior to control groups in achieving HBV cure. **Conclusion:** This study demonstrates that smaller sample sizes and shorter treatment durations are significantly associated with higher completion rates in early-phase trials. These findings highlight the importance of optimizing trial design to facilitate the development of cure therapy for CHB.

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1325 | EVALUATION OF FIBROSIS STATUS IN TREATMENT-NAIVE HEPATITIS B PATIENTS WITH LOW LEVEL VIREMIA USING MR ELASTOGRAPHY AND NONINVASIVE FIBROSIS SCORES: FIB-4 AND APRI HAVE INSUFFICIENT EFFICACY IN DETECTING EARLY-STAGE FIBROSIS

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Background: This study aimed to evaluate the fibrosis status of hepatitis B virus (HBV) carriers with low viral load using MR elastography and noninvasive fibrosis scores. **Methods:** Treatment-naive HBV patients with HBV DNA levels <2000 IU/ml, normal liver function tests and abdominal ultrasonography findings were included in the study. Retrospectively, patients were classified into two groups: Those with persistently low HBV DNA levels (<2000 IU/mL) over the past two years were defined as the "true inactive carrier group", while those with at least two HBV-DNA values between 2000-20000 IU/mL were classified as the "gray zone group". Non-invasive liver fibrosis scores including FIB-4, NFS, APRI, GUCI, HUI, BARD, FORNS, CDS, LOK index were calculated for all patients. The presence or absence of liver fibrosis was determined according to the kPA levels, which is the liver stiffness measurement obtained from MR elastography (MRE). **Results:** The study included 79 treatment-naive HBV patients (mean age: 54.06 $\pm$10.8; 42 M/ 37 F) who met the inclusion criteria. Based on liver stiffness measurements (LSM) obtained by MRE, 55 patients (68%) had normal stiffness values (<2.5 kPa) 16 patients (20%) showed mildly increased stiffness (2.5-3.0 kPa), and 8 patients (9%) had LSM values between 3.0-3.5 kPa,consistent with stage 1-2 fibrosis. No cases of advanced fibrosis or cirrhosis were identified. The mean liver stiffness in the gray zone group was significantly higher than in the true inactive carrier group (2.75 ± 0.81 vs. 2.31 ± 0.39 kPa; p:0.007). Among the commonly used noninvasive fibrosis scores, weak but statistically significant correlations were observed between the BARD score, NFS, HUI and the liver stiffness value (kPA) obtained by MRE (r: 0.24; $p<0.01$, 0.33; $p<0.01$ and 0.37; $p<0.01$, respectively). In contrast, APRI and FIB-4 scores did not correlate with liver stiffness values measured by MRE (p:0.20 and p:0.14, respectively).The FIB-4 score was able to detect only 5 of 24 patients with fibrosis and/or inflammation based on MRE findings, failing to detect

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early- stage fibrosis in the remaining 19 patients. In 9 of 55 patients in whom fibrosis was not detected by MRE, the FIB-4 score was found to be compatible with moderate fibrosis (sensitivity 70.7%, specificity 35%, positive predictive value 83% and negative predictive value 20.3%). Sensitivity of the APRI score in detecting the absence of fibrosis was 70%, specificity was 50%, with a positive predictive value 98% and a negative predictive value 4%. **Conclusion:** Noninvasive fibrosis scores have limited effectiveness in detecting early-stage fibrosis in HBV patients with low viral load. Imaging methods should be considered for the evaluation of liver fibrosis in this patient population.

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1326 | ENHANCING CHRONIC HEPATITIS B CARE THROUGH HOSPITAL-BASED MANAGEMENT INTERVENTIONS: THE "HOT WAVE PROJECT" EXPERIENCE

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Background: Hepatitis B virus (HBV) infection remains a significant global health challenge, with effective management being crucial to prevent severe liver complications. This study evaluates the impact of the "Hot Wave Project," a series of process-oriented interventions implemented at The Third Affiliated Hospital of Sun Yat-sen University in China, on improving key management metrics for HBV patients. **Methods:** Starting in 2022, the "Hot Wave Project" was initiated, which included: education on HBV-related knowledge for doctors in non-infectious disease departments, laboratory report reminders for HBsAg-positive patients to be referred to the infectious disease clinic, various forms of patient education, dedicated personnel for patient follow-up, and big data monitoring of HBV infection data within the hospital. Data on HBsAg screening rates, antiviral treatment rates among HBsAg-positive patients, regular follow-up rates, and referral rates from non-infectious disease departments were collected and compared between 2021 and 2024. **Results:** From 2021 to 2024, the total number of HBsAg screenings at the hospital increased from 129,655 (screening rate 11.75%) to 154,989 (screening rate 15.25%). The overall antiviral treatment rate for HBsAg-positive patients improved from 71.00% in 2021 to 80.25% in 2024 ($P < 0.0001$). The regular follow-up rate for these patients rose from 59.96% to 61.50% ($P < 0.0001$). In non-infectious disease departments, the referral rate of HBsAg-positive patients to the infectious disease clinic increased from 9.26% in 2021 to 17.87% in 2024 ($P < 0.0001$). This increase contributed to an overall improvement in the antiviral treatment rate for these patients, which rose from 34.47% in 2021 to 59.63% in 2024. Specifically, in 2021, the antiviral treatment rate was 31.42% for patients who were not referred and 64.37% for those who were referred. By 2024, these rates had increased to 56.86% and 72.39%, respectively. **Conclusion:** The implementation of the "Hot Wave Project" significantly enhanced the treatment accessibility and management of HBV patients at The Third Affiliated Hospital of Sun Yat-sen University in China. Continued efforts and further studies are essential to maintain these improvements and assess their long-term impact.

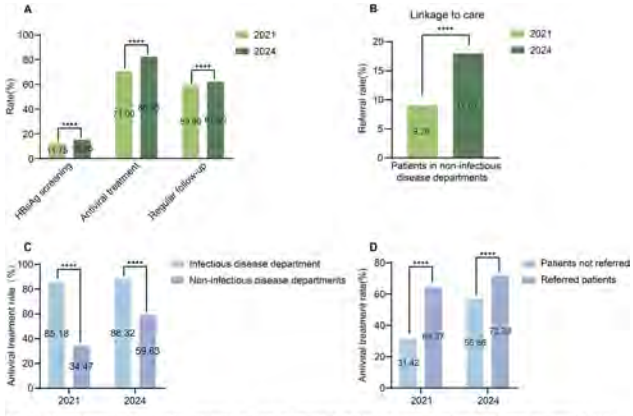

Figure 1. (A) The hospitalwide HBsAg screening rate, antiviral treatment rate, and regular follow-up rate for HBsAg-positive patients in 2021 and 2024. (B) The referral rate ofHBsAg-positive patients from non-infectious disease departments in 2021 and 2024. (C) The antiviral treatment rates in infectious disease and non-infectious disease departments in 2021 and 2024. (D) The differences in antiviral treatment between referedand non-referred patients in non-infectious disease departments in 2021. ****, Chi-square test $p < 0.0001$.

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1327 | EFFECTIVENESS AND SAFETY OF TENOFOVIR ALAFENAMIDE FOR CHRONIC HEPATITIS B PATIENTS WITH DECOMPENSATED CIRRHOSIS: A REAL-WORLD STUDY IN CHINA

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Background: Tenofovir alafenamide fumarate (TAF) has shown excellent efficacy and safety in the treatment of chronic hepatitis B (CHB), but research data in patients with decompensated cirrhosis remain limited. This study aims to investigate the efficacy and safety of TAF in CHB patients with decompensated cirrhosis. **Methods:** This is a retrospective-prospective, multicenter, real-world clinical study enrolling patients with decompensated hepatitis B cirrhosis who receive daily TAF 25 mg treatment, with a planned follow-up period of at least 48 weeks. The primary endpoint is the HBV DNA negativity rate (< 20 IU/ml) at 48 weeks, while the secondary endpoint is the ALT normalization rate at 48 weeks. Other endpoints include changes from baseline in HBsAg, Child-Pugh (CTP) score, and Model for End-Stage Liver Disease (MELD) score. Safety is also analyzed, including drug-related adverse events (AEs) / serious adverse events (SAEs), and clinical outcomes such as liver transplantation, hepatocellular carcinoma (HCC), mortality, renal function, and lipid abnormalities. **Results:** By May 12, 2025, a total of 106 patients (72 males, 34 females; mean age: 53.5 ± 9.26 years) were enrolled from 6 medical centers, among whom 46 completed 48-week follow-up. After 48 weeks of TAF treatment, the HBV DNA negativity rate increased from 57.55% at baseline to 96.65% (*P < 0.001*), while HBsAg, ALT, and AST levels significantly decreased compared with baseline (all *P < 0.05*). For ALT normalization rate, when using gender-specific criteria (" < 30 U/L for males, < 19 U/L for females"), no significant change was observed compared with baseline (*P > 0.05*); however, when using the uniform criterion " < 40 U/L for both genders", the normalization rate increased significantly (*P < 0.01*). The proportion of patients with Child-Pugh (CTP) score B/C significantly decreased from 60.38% (64/106) at baseline to 30.43% (14/46) at week 48 (*P = 0.004*). Renal function indicators (serum creatinine [Scr], β2-microglobulin [β2-MG], eGFR) and lipid profiles were not significantly affected during treatment. During follow-up, 3 patients developed HCC, while no drug-related adverse events (AEs) / serious adverse events (SAEs), liver transplantation, or mortality were observed. **Conclusion:** TAF demonstrated favorable efficacy and safety in the treatment of CHB patients with decompensated cirrhosis.

Characteristics	Baseline (n=106)	24Weeks (n=33)	48Weeks (n=46)	Statistical value	P
HBV DNA undetectable (%)	37.55 (61/106)	81.82 (27/33)	95.65 (44/46)	χ^2=24.929	<0.001
HBsAg [M (Q$_{25}$, Q$_{75}$), IU/mL]	676.40 (176.23, 1933.00)	259.90 (28.03, 770.20)	329.80 (50.73, 837.20)	H=8.687	0.013
ALT [M (Q$_{25}$, Q$_{75}$), U/L]	26.77 (18.10, 46.36)	21.20 (15.15, 32.21)	22.20 (16.25, 30.35)	H=7.511	0.023
ALT normal rate (%)*					
male < 30IU/L, female < 19IU/L	47.17 (30/106)	60.61 (20/33)	65.22 (30/46)	χ^2=4.901	0.086
both male and female < 40IU/L	67.92 (72/106)	87.88 (29/33)	89.13 (41/46)	χ^2=10.871	0.004
AST [M (Q$_{25}$, Q$_{75}$), U/L]	36.72 (24.80, 60.80)	30.80 (23.16, 39.20)	26.70 (20.47, 37.57)	H=8.403	0.015
ALP [M (Q$_{25}$, Q$_{75}$), U/L]	87.50 (72.11, 122.23)	83.65 (70.67, 96.75)	77.80 (68.58, 95.07)	H=4.570	0.112
GGT [M (Q$_{25}$, Q$_{75}$), U/L]	30.04 (19.21, 59.70)	22.00 (15.25, 40.75)	25.21 (19.16, 47.37)	H=3.317	0.190
TBIL [M (Q$_{25}$, Q$_{75}$), μmol/L]	24.06 (16.88, 44.70)	28.70 (17.45, 44.40)	21.95 (17.35, 34.84)	H=0.787	0.675
ALB [M (Q$_{25}$, Q$_{75}$), g/L]	34.30 (29.15, 39.26)	33.80 (26.75, 37.50)	38.80 (33.07, 41.58)	H=10.388	0.005
CTP score				H=11.186	0.004
CTP A (%)	39.62 (42/106)	42.42 (14/33)	69.57 (32/46)		
CTP B (%)	46.23 (49/106)	39.39 (13/33)	23.91 (11/46)		
CTP C (%)	14.15 (15/106)	18.19 (6/33)	6.52 (3/46)		
MELD score				H=0.076	0.962
< 15 (%)	89.62 (95/106)	87.88 (29/33)	89.13 (41/46)		
≥ 15-20 (%)	7.55 (8/106)	9.09 (3/33)	8.70 (4/46)		
≥ 20-30 (%)	2.83 (3/106)	3.03 (1/33)	2.17 (1/46)		
≥ 30-40 (%)	0 (0/106)	0 (0/33)	0 (0/46)		
≥ 40 (%)	0 (0/106)	0 (0/33)	0 (0/46)		
BUN [M (Q$_{25}$, Q$_{75}$), mmol/L]	5.40 (4.53, 6.50)	5.50 (4.70, 6.89)	5.85 (5.02, 7.15)	H=3.727	0.155
SCr [M (Q$_{25}$, Q$_{75}$), μmol/L]	69.74 (58.08, 80.56)	71.54 (57.00, 85.47)	74.23 (66.89, 93.80)	H=4.934	0.085
β2-MG [M (Q$_{25}$, Q$_{75}$), mg/L]	2.32 (1.90, 3.02)	2.39 (2.04, 3.22)	2.01 (1.56, 2.96)	H=2.151	0.341
Na [M (Q$_{25}$, Q$_{75}$), mmol/L]	139.23 (137.08, 140.92)	139.10 (132.96, 141.55)	139.96 (138.66, 141.43)	H=1.606	0.448
eGFR [M (Q$_{25}$, Q$_{75}$), ml/min/1.73m^2]	99.71 (85.76, 117.91)	94.46 (79.44, 110.03)	90.71 (76.69, 112.01)	H=3.553	0.169
TG [M (Q$_{25}$, Q$_{75}$), mmol/L]	0.83 (0.61, 1.32)	0.94 (0.68, 1.43)	0.81 (0.68, 1.32)	H=1.054	0.590
TC ($\bar{x}$ ± s, mmol/L)	3.34 ± 0.85	3.40 ± 0.86	3.55 ± 0.88	F=0.591	0.555
HDL ($\bar{x}$ ± s, mmol/L)	1.13 ± 0.36	1.09 ± 0.40	1.16 ± 0.44	F=0.201	0.818
LDL [M (Q$_{25}$, Q$_{75}$), mmol/L]	1.81 (1.28, 2.36)	1.80 (1.22, 2.72)	2.09 (1.56, 2.47)	H=2.277	0.320

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1328 | ENTRY INHIBITION COMBINED WITH IFN IMMUNOTHERAPY ACHIEVED UNDETECTABLE INTRAHEPATIC HBV CCCDNA: RESULTS: FROM A PHASE II RANDOMIZED DOUBLE-BLIND CLINICAL TRIAL

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Background: Current clinical practice can hardly eliminate HBV from the host completely because of the persistent reservoir of covalently closed circular DNA (cccDNA) in hepatocyte nucleus. It remains a major challenge in achieving a sterilizing cure for chronic hepatitis B (CHB). Although Pegylated interferon (PEG-IFN) may promote cccDNA degradation via immune modulation, its clinical effect is insufficient to terminate chronic HBV infection. Targeting cccDNA replenishment through inhibition of viral entry offers a complementary mechanism and may have synergistic effects if combined with PEG-IFN. This phase II trial evaluated the efficacy and safety of combining the HBV entry inhibitor hepalatide with PEG-IFN alpha-2a in CHB patients. **Methods:** In this multicenter, randomized, double-blind study (NCT04426968), 96 treatment-naïve CHB patients received daily subcutaneous hepalatide (2.1 mg, 4.2 mg, 6.3 mg) or placebo, in combination with weekly PEG-IFN (180 μg) for 24 weeks. Virological response was defined as a ≥ 2 $\log_{10}$ IU/mL reduction in HBV DNA or HBV DNA < 20 IU/mL. Virological parameters, including serum HBV DNA, HBsAg, HBV pgRNA, and intrahepatic cccDNA quantification in liver biopsies, were assessed at baseline and week 24. Safety and tolerability were closely monitored. **Results:** At week 24, virological response rates were significantly higher in the 4.2 mg hepalatide group (87.5%, 95%CI: 67.64–90.34, $p = 0.0248$) compared to placebo (58.3%, 36.64–77.89). Notably, cccDNA became undetectable in 33.3% (1/3) and 40.0% (2/5) of patients receiving 4.2 mg and 6.3 mg hepalatide, respectively, while remaining detectable in all placebo-treated patients. Despite persistent HBsAg expression, which may derive from integrated HBV DNA rather than cccDNA, this reduction was accompanied by a notable decline in serum pgRNA. At week 24, mean (SD) change in pgRNA from baseline in the 4.2 mg group reached -3.15 (1.93) $\log_{10}$ copies/mL, compared to -2.52 (1.79) in the placebo group. Hepalatide demonstrated a favorable safety profile with only mild injection-site reactions. **Conclusion:** PEG-IFN may promote cccDNA degradation via immune activation, while entry inhibitors block its replenishment by preventing new HBV infection. The combination of hepalatide and PEG-IFN demonstrated measurable intrahepatic cccDNA reduction, supporting a potential strategy for depleting the HBV reservoir. These findings warrant validation in larger studies to further explore their potential contribution to achieving a sterilizing cure for CHB.

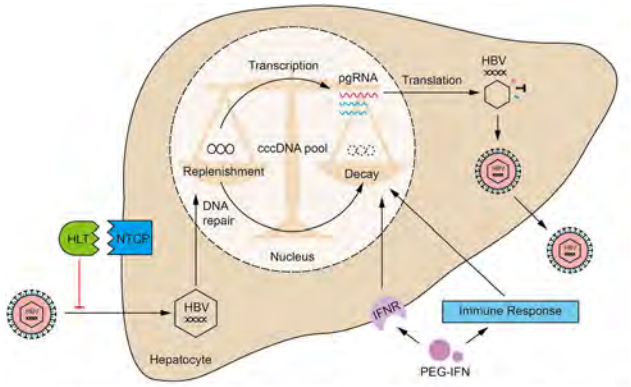

Figure 1. Mechanism of Hepalatide (HLT) and the equillibrium of cccDNA pool. HLT blocks HBV entry, halting cccDNA replenishment, while PEG-IFN accelerates cccDNA decay—shifting the cccDNA balance toward eventual pool exhaustion.

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1329 | HERACLIS_BLV_D: PERSISTENCY AND ADHERENCE TO REAL-LIFE THERAPY WITH BULEVIRTIDE (BLV) IN CHRONIC HEPATITIS D (CHD)

Dimitra Lakiotaki[1] Margarita Papatheodoridi[1] Vasilios Sevastianos[2] Kalliopi Zachou[3] Dimitrios Christodoulou[4] John Koskinas[5] Melanie Deutsch[5] Alexandra Alexopoulou[5] Ioannis Elefsiniotis[6] Christos Triantos[7] Elena Gigi[8] Theodoros Androutsakos[1] Dimitrios Karagiannakis[1] Iliana Mani[5] Dimitrios Dimitropoulos[9] Maria Mela[10] Emmanouil Sinakos[8] Spyros Michopoulos[11] Konstantinos Mimidis[12] Nikolaos Papadopoulos[13] Athanasios Kontos[9] Christos Veteranos[10] Dimitrios Lymperopoulos[10] George Giannoulis[3] Vasilios papadimitropoulos[5] Evdoxia Avramopoulou[7] Alkistis Papatheodoridi[11] Spyridon Pantzios[14] Larisa Vasilieva[5] Hariklia Kranidioti[5] Emmanouil Koullias[5] Nikolaos Psichos[4] Paraskevi Fytili[1] John Vlachogiannakos[1] Evangelos Cholongitas[1] Spilios Manolakopoulos[5] Ioannis Goulis[8] George Dalekos[3] George Papatheodoridis[1], [1]General Hospital of Athens "Laiko", Medical School of National &

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Background: BLV has been approved for the treatment of CHD, but real-world data on persistency/adherence is lacking. We aimed to assess the rates and predictors of persistency/adherence to long-term BLV therapy as well as the effects on response rates in CHD. **Methods:** HERACLIS_BLV_D study (NCT05928000) included adult CHD patients who started BLV 2 mg/day and were followed according to standard clinical practice. HDV RNA was assessed by PCR at central lab (sensitivity <100 IU/ml). Virological response (VR) was defined as HDV RNA undetectable (complete VR) or decline >2 log and biochemical response (BR) as normal ALT (≤ 40 IU/L). Persistency was defined by absence of BLV discontinuation considered as no executed BLV prescription for >3 months at the end of follow-up. Adherence was determined by the rates of monthly prescriptions of BLV boxes of 30 vials (percentage of executed prescriptions over certain months divided by the number of months). **Results:** In total, 76 patients were included [age 50 ± 12 years, males 49%, migrants 72%, PWIDs 7%, BMI 25 ± 4 kg/m², liver stiffness 15.9 ± 9.5 kPa, cirrhosis 59%). VR/BR rates were 73%/71% at 12 and 93%/74% at 24 months. Thirteen (17%) patients discontinued BLV (none for adverse events); 5/76 (7%) in the 1st, 5/71 (7%) in the 2nd and 3/54 (6%) in the 3rd year. Of the 13 patients who discontinued BLV (migrants 77%, cirrhosis 54%), 4 died of liver disease (decompensated cirrhosis:3, cholangiocarcinoma:1), 1 died of lung cancer and 8 were lost to follow-up. VR was achieved in 7 and BR in 5 of 10 patients who discontinued BLV and were tested at ≥ 6 months. In patients on therapy, mean adherence was 97 ± 7% in 1st year declining to 93 ± 13% in 2nd and 91 ± 17% in 3rd year ($P \leq 0.010$). No patient characteristic was associated with poor (<90%) or good (≥ 90%) adherence to BLV therapy. Patients with poor vs good adherence had lower relevant response rates (1st year – VR: 40% vs 77%, $P = 0.108$; complete VR: 40% vs 61%, $P = 0.392$ & 2nd year – VR: 60% vs 97%, $P = 0.033$; complete VR: 40% vs 87%, $P = 0.040$; BR: 40% vs 78%, $P = 0.103$). **Conclusion:** In real-life, 6-7% of CHD patients may discontinue BLV therapy annually for several reasons including death, often despite satisfactory responses and good tolerability. Adherence to BLV therapy is excellent in the 1st year, but its mean rate declines in the 2nd and 3rd year remaining however >90%. Poor (<90%) adherence cannot be predicted, but it negatively affects the VR rates emphasizing the need for interventions to improve long-term treatment retention.

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1330 | CAM-E AND CAM-A COMPOUNDS DIFFERENTIALLY AFFECT PHOSPHORYLATED AND NON-PHOSPHORYLATED HEPATITIS B CORE PROTEIN IN VITRO

Rene Geissler[1] Hannah Vanrusselt[2] Jordi Verheyen[2] Tse-I Lin[2] Lawrence Blatt[3] Julian Symons[4] Andreas Jekle[3] Megha Patel[5] Gavin Cloherty[1] Yannick Debing[2], [1]Abbott, [2]Aligos Belgium BV, [3]Aligos Therapeutics, Inc., [4]Aligos Therapeutics, [5]Abbott Laboratories

Background: Phosphorylation of hepatitis B core protein (HBc) plays a key role in HBV capsid formation. Empty particles have hyperphosphorylated HBc and DNA-containing particles contain very low levels of phosphorylated HBc. Capsid assembly modulators (CAMs) bind to HBc and modulate the assembly of viral capsids. This study explored the nuanced roles of CAM-E and CAM-A compounds in modulating the dynamics of HBc phosphorylation states, by specifically quantifying both phosphorylated (P-HBcAg) and non-phosphorylated core (HBcAg) proteins, emphasizing the differential impacts of the CAM classes on viral particle formation. **Methods:** A combination of in vitro assays and quantitative analyses was employed to evaluate the effects of CAM-E and CAM-A compounds on HBc phosphorylation states. HepAD38 cells and HBV-infected primary human hepatocytes were treated with different CAMs and nucleoside analogs. Medium and cell lysates were collected after 7 days of culture and used for the P-HBcAg and HBcAg chemiluminescent microparticle immunoassays (CMIA). Specific chemotypes were tested to compare their efficacy and to identify potential mechanistic variations among CAM compounds. **Results:** CAM-Es significantly reduced HBcAg levels, affecting DNA-containing particles both intra- and extracellularly. P-HBcAg levels, representing empty particles, increased correspondingly. CAM-A treatment also reduces HBcAg levels similarly to CAM-E. However, at high CAM-A concentrations, P-HBcAg levels decreased; while at lower concentrations, they increased. Similar patterns were observed across different CAM chemotypes with minor variations. Nucleos(t)ide analogs showed no effect on HBcAg and P-HBcAg over the time course of these experiments. **Conclusion:** These findings confirm that the distinct mechanisms of action of CAM-E and CAM-A compounds are reflected in HBc phosphorylation states and their subsequent effects on viral particle dynamics. The observed concentration-dependent effects of CAM-A compounds on P-HBcAg levels suggest a nuanced interaction that may involve capturing P-HBcAg in intracellular aggregates at higher concentrations. The lack of direct impact by nucleos(t)ide analogs on HBcAg and P-HBcAg levels is in line with their known mechanism of action and underscores the specificity of CAMs in targeting HBc.

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1331 | COMBINED MUTATIONS OF HEPATITIS B VIRUS BASAL CORE PROMOTER AND PRECORE REGION CORRELATE WITH IMMUNE-MEDIATED VIRAL CONTROL AND LIVER DAMAGE

Zhao Zhou[1] Guangxin Yu[1] Guiwen Guan[1] Danli Yang[2] Xiangmei Chen[1] Fengmin Lu[1], [1]Peking University, [2]Peking Univeristy

Background: It has been known that basal core promoter (BCP) and/or precore (PC) region mutations favor persistent hepatitis B virus (HBV) infection via facilitating viral immune evasion and viral replication during the disease progression of chronic hepatitis B (CHB). **Methods:** Serum samples were extracted from 153 CHB patients to detect mutations in HBV BCP and PC region by targeting amplicon sequencing. Mutation rates of single sites and combined mutations were calculated by self-written scripts. **Results:** Among the 129 identified mutation sites, the prevalence of 84 sites and the mean mutation rates of 103 sites were found decreased in HBeAg negative patients when compared to HBeAg positive ones. Among the 14 high-rate ($\geq$ 10%) mutation sites, most of them existed in combined mutations which were much more common in HBeAg negative patients. Further analysis showed that mutation rate of some high-rate mutation sites and their combined mutations were closely associated with

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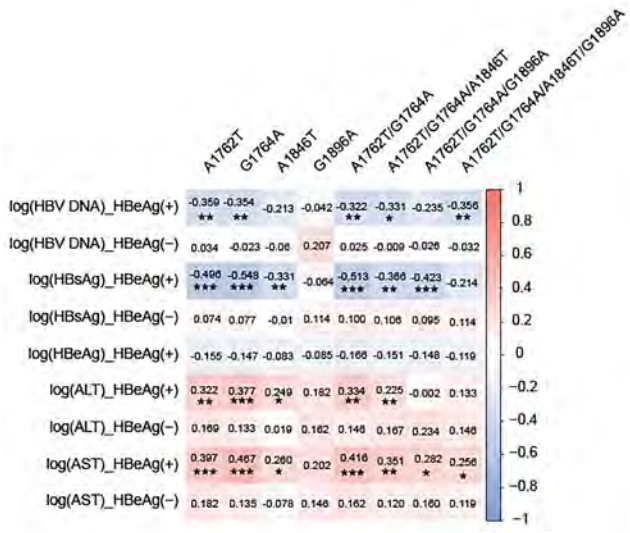
patients' clinical indicators. In HBeAg-positive patients, HBV DNA level was correlated negatively with the rate of A1762T, G1764A, A1846T and G1896A but were positively correlated with inflammation markers, including ALT and AST. Mutation rates of some combined mutations constructed by the aforementioned four sites were also correlated negatively with HBV DNA levels but positively with inflammation markers (Figure1). These correlations weakened or disappeared in HBeAg-negative patients. **Conclusion:** This study helps for better understanding the role of mutations and combined mutations in BCP/PC region and their interaction with host immune in disease progression. It suggested that it was the selection of host immune, as reflected by the active hepatic inflammatory damage, that leaded to the accumulation of single site mutations and combined mutations with characteristics of facilitating immune evasion and viral replication.



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1332 | APOLIPOPROTEIN C3 ELEVATION IN ISOLATED MAFLD VERSUS HBV CO-INFECTION: DISTINCT METABOLIC PHENOTYPES AND CLINICAL IMPLICATIONS

Kong Xiangsha[1] Lin Zhang[1] Danli Ma[1] Wei Zhang[1], *[1]Peking University People's Hospital*

Background: Metabolic-associated fatty liver disease (MAFLD) and Chronic Hepatitis B virus (HBV) infection are prevalent global chronic liver diseases. Altered immune homeostasis in both diseases may contribute to hepatocellular carcinoma (HCC) progression. Understanding mechanisms of HBV-MAFLD coexistence is crucial for targeted therapies, particularly given HBV's potential impact on MAFLD lipid metabolism and steatosis. This study investigates the HBV co-infection effects on lipid profiles, hepatic steatosis, and metabolic impairments in MAFLD patient. **Methods:** Study Population Retrospective analysis of patients diagnosed with MAFLD (based on predefined criteria) between January 2021 - 2023. Data collection Demographics/anthropometrics (age, gender, weight, BMI, waist/hip circumference); lipid profile (TC, TG, HDL-C, LDL-C); glucose; liver enzymes (ALT, AST, GGT); apolipoproteins (ApoA1, ApoB, ApoC3); HBV serology were collected. Hepatic steatosis/fibrosis assessed via ultrasound and FibroScan. Statistical analysis Continuous variables were compared using one-way ANOVA, categorical variables with χ^2 tests. Statistical significance was defined as $p < 0.05$. **Results:** Clinical characteristics MAFLD with HBV cohort ($n = 72$) was older than isolated MAFLD group ($n = 110$) (median 47 vs. 43.5 years, $p = 0.039$), with more patients aged ≥ 50 years (44.44% vs. 36.36%). Isolated MAFLD patients had higher BMI (27.56 vs. 25.09 kg/m², $p = 0.01$), greater prevalence of class I obesity (25.45% vs. 6.94%), and higher rates of central obesity (males: 45.8% vs. 28.8%; females: 60.5% vs. 25.0%). Metabolic and Hepatic Parameters Isolated MAFLD group showed elevated ApoB (0.813 vs. 0.761 g/L, $p = 0.025$) and ApoC3 (11.77 vs. 10.39 mg/dL, $p = 0.040$). Hepatocellular injury was more severe: ALT (64 vs. 29 U/L), AST (39 vs. 26.5 U/L), and γ-GGT (52 vs. 32 U/L) were more higher in isolated MAFLD group ($p < 0.001$). Median CAP showed no significant difference between the two groups (Isolated MAFLD group: 314.5 dB/m vs. MAFLD with HBV group: 305 dB/m, $p = 0.359$). The proportion of patients with moderate/severe steatosis (CAP ≥ 300 dB/m) was higher in the NAFL group (37.3% vs. 22.2%), but this difference did not reach statistical significance ($p = 0.910$). **Conclusion:** Isolated MAFLD presents a metabolically driven phenotype (younger age, severe obesity, central obesity) characterized by ApoC3-driven dyslipidemia (promoting hepatic lipogenesis) and elevated ApoB, correlating with significant liver injury consistent with metabolic steatohepatitis (MASH). In contrast, MAFLD-HBV patients are older with milder obesity and attenuated metabolic dysregulation, suggesting HBV influences progression via non-metabolic pathways.

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1333 | IMPROVEMENT OF HEPATIC STEATOSIS AND ITS ASSOCIATION WITH HBSAG CLEARANCE IN CHRONIC HEPATITIS B PATIENTS RECEIVING PEGYLATED INTERFERON-ALPHA THERAPY

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Background: Hepatic steatosis is frequently observed in chronic hepatitis B (CHB) patients and has been implicated in modulating host immune responses and antiviral efficacy. Pegylated interferon-alpha (PegIFNα) is a finite-duration therapy capable of inducing functional cure. However, the interaction between hepatic steatosis and treatment response to PegIFNα remains inadequately characterized. This study aimed to evaluate longitudinal changes in hepatic fat content during PegIFNα treatment and investigate its association with HBsAg clearance. **Methods:** We conducted a retrospective cohort study of 162 CHB patients treated with PegIFNα (180 μg/week) for ≥48 weeks between April 2020 and April 2021. All patients had prior nucleos(t)ide analog therapy for ≥3 months. Hepatic steatosis was quantified using controlled attenuation parameter (CAP) by transient elastography and stratified as follows: S0 (CAP <248 dB/m, n=91), S1 (248–267 dB/m, n=40), S2 (268–279 dB/m, n=11), S3 (≥280 dB/m, n=20). HBsAg levels, CAP, and BMI were assessed at baseline and every 12 weeks. The primary outcomes were HBsAg seroclearance at week 48 and change in CAP. Correlation between CAP reduction and HBsAg loss was assessed using Pearson's correlation. **Results:** At baseline, increasing steatosis severity was significantly associated with older age, male sex, and higher BMI (all $p<0.001$). After 48 weeks of PegIFNα therapy, the overall HBsAg clearance rate was 40.6% (66/162). Group-specific clearance rates were 46.2% (42/91) in S0, 32.5% (13/40) in S1, 27.3% (3/11) in S2, and 50.0% (10/20) in S3. Despite greater hepatic fat burden, S3 patients exhibited the highest clearance rate, comparable to the non-steatotic S0 group. CAP levels significantly decreased in all steatosis groups, with the greatest absolute reduction in S3 (−32.7 dB/m, $p<0.0001$), followed by S2 (−31.1 dB/m, $p=0.006$), and S1 (−22.5 dB/m, $p<0.0001$). S0 showed no significant change in CAP ($p=0.68$). BMI decreased across all groups (mean Δ−1.0 kg/m², $p<0.001$). A moderate positive correlation was observed between CAP reduction and HBsAg clearance rate across the four groups (Pearson's $r=0.46$), though this did not reach statistical significance ($p=0.11$), possibly due to small subgroup sizes. Baseline BMI was not predictive of CAP improvement ($r=0.12$, $p=0.14$) or HBsAg loss ($r=0.08$, $p=0.31$). **Conclusion:** PegIFNα therapy in CHB patients results in not only significant serological responses but also measurable metabolic benefits, particularly reduction in hepatic steatosis. Importantly, patients with severe baseline steatosis achieved comparable or even superior HBsAg clearance rates to those without steatosis, challenging assumptions about steatosis-related treatment resistance. These findings suggest that improvements in liver fat content may support immune-mediated HBsAg clearance and highlight the potential dual benefit of PegIFNα in serological and metabolic domains.

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1334 | SURVEY ON THE AWARENESS AND CLINICAL APPLICATION OF THE " GUIDELINES FOR THE PREVENTION AND TREATMENT OF CHRONIC HEPATITIS B (CHINESE VERSION 2022)" AMONG CHINESE CLINICIANS

Yuanyuan Kong[1] Yujie Guo[2] Yujuan Guan[3] Xuan Liang[4] Zhongjie Hu[5] Xiaobo Lu[6] Mingqin Lu[7] Yongfeng Yang[8] Meifang Han[9] Hong You[1] Zhiyun Yang[2] Jidong Jia[1], [1]Beijing Friendship Hospital, Capital Medical University, [2]Beijing Ditan Hospital, Capital Medical University, [3]Guangzhou Eighth People's Hospital, Guangzhou Medical University, [4]The Sixth People's Hospital of Shenyang, [5]Beijing YouAn Hospital, Capital Medical University, [6]The First Affiliated Hospital of Xinjiang Medical University, [7]The First Affiliated Hospital of Wenzhou Medical University, [8]The Second Hospital of Nanjing, Nanjing, [9]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Background: To evaluate clinicians' awareness and current status of clinical practice regarding the HBV guidelines set by the Chinese Society of Hepatology and Chinese Society of Infectious Diseases (CSH/CSID, 2022 version). **Methods:** From July 19 to December 31, 2024, a self-developed electronic questionnaire was distributed via the WeChat mini-program to collect data from Chinese 1,588 clinical physicians nationwide on their knowledge and practices regarding 18 questions across three domains: testing and referral, diagnosis and treatment, and follow-up. **Results:** Among all respondents, only 350 clinicians correctly understood all the updated key points of antiviral indications and treatment for special populations in the Chinese HBV Guidelines (2022 version), with an overall awareness rate of just 22.0%. The actual proportion of

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patients with HBV DNA positivity and age >30 years receiving antiviral treatment ranged from 20% to 40%. For patients with HBV DNA positivity and either liver cirrhosis or a family history of hepatocellular carcinoma (HCC), the proportion receiving antiviral treatment ranged from 80% to 100%. Follow-up rates for patients at 1 year, 3 years, and 5 years gradually declined, ranging from 70% to 90%, 25% to 45%, and 25% to 45%, respectively. These declines were associated with factors such as insufficient time for follow-up management by clinicians, patients' lack of awareness about the disease, and poor adherence to follow-up. **Conclusion:** There is a gap between clinicians' awareness and practice of the Chinese HBV Guidelines (2022 version). It is recommended to further strengthen the standardized management and training of the entire process of "detection, diagnosis, treatment, and management" for patients with chronic hepatitis B in healthcare institutions to promote the implementation of the guidelines.

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1335 | HEPATITIS B SCREENING IN AN URBAN SAFETY-NET HEALTH SYSTEM BEFORE AND AFTER CHANGES TO CDC GUIDELINES

Karlyn Tunnell[1] *Kathryn Thompson*[1] *Lesley Miller*[1], [1]*Emory University School of Medicine*

Background: Before 2023, the Centers for Disease Control and Prevention (CDC) recommended screening for hepatitis B (HBV) only in individuals at increased risk. In 2023, these guidelines were updated to recommend screening all adults at least once in their lifetime and more frequently for those at increased risk. The recommended screening tests include three serologic tests: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis B surface antibody (HBsAb). There is a gap in the literature regarding how these recommendations have impacted clinical practice. Our study examined screening rates at primary care centers across a single health system before and after the changes in CDC guidelines. **Methods:** We conducted a retrospective analysis of patients across 10 primary care centers within Grady Health System in Atlanta, Georgia two years preceding the changes in CDC guidelines (March 10, 2021-March 10, 2023) and two years following the changes in CDC guidelines (March 11, 2023-March 10, 2025). We examined screening rates, demographic data, and various HBV risk factors as defined by the CDC. Descriptive statistics and independent two-sample t-tests were used to identify differences in screening rates before and after the guideline change. **Results:** There was a statistically significant increase in HBV screening rates among all patients seen in primary care clinics after the change in guidelines. Screening with any component of the three-part serologic test increased from 14.13% to 19.55% (p-value <0.001), and screening with all three components increased from 7.59% vs 12.01% (p-value <0.001). However, there was no statistically significant change in screening rates among patients with identified HBV risk factors. Notably, patients with liver disease were screened at a statistically significantly lower rate after the CDC guidelines changed (13.57% vs 10.13%, p-value 0.024). In contrast, patients without any documented risk factors were screened at a statistically significantly higher rate after the CDC guidelines changed (66.42% vs. 71.33%, p-value <0.001). **Conclusion:** Our study demonstrated an overall increase in HBV screening rates after the updated CDC guidelines. Notably, the increase was almost exclusive to groups without any identified risk factors. This study highlights the need for targeted interventions to enhance routine screening, especially in patient populations at highest risk for HBV.

	Patients screened for HBV before CDC guidelines changed (03/10/2021-03/09/2023) n=6057 (number of patients screened for HBV with all three HBV tests)	Patients screened for HBV after CDC guidelines changed (03/10/2023-03/09/2025) n=10120 (number of patients screened for HBV with all three HBV tests)	Mean difference between groups	P-value
Number of patients screened for HBV with all three HBV tests** / Total number of patients seen in primary care clinics	$\frac{6057}{79770} = 7.59\%$	$\frac{10120}{84242} = 12.01\%$	4.42%	<0.001*
Female sex	48.60%	52.8%	4.19%	<0.001*
Male sex	51.40%	47.17%	4.22%	<0.001*
Ages 18-29	9.38%	10.51%	1.14%	0.462
Ages 30-39	15.78%	16.92%	1.13%	0.446
Ages 40-49	19.93%	21.78%	1.85%	0.201
Ages 50-59	27.06%	26.69%	0.37%	0.790
Ages 60-69	25.62%	23.60%	2.03%	0.150
Ages 70+	11.16%	9.67%	1.49%	0.333
Cirrhosis	3.40%	2.42%	0.98%	0.540
Other liver disease	13.57%	10.13%	3.44%	0.024*
Elevated liver function tests	4.08%	2.90%	1.18%	0.459
HCV	7.88%	5.24%	2.64%	0.093
HIV	3.02%	2.34%	0.68%	0.672
High-risk sexual behavior	0.83%	1.04%	0.21%	0.896
End-stage renal disease on dialysis	9.39%	6.74%	2.65%	0.088
Exposure to hepatitis	0.10%	0.07%	0.03%	0.986
Intravenous drug use	2.72%	3.01%	0.29%	0.857
None of the above risk factors	66.42%	71.33%	4.91%	<0.001*
HBV screening test	Patients screened for HBV before CDC guidelines changed (03/10/2021-03/09/2023) n= 79770 (total number of patients seen in primary care clinics)	Patients screened for HBV after CDC guidelines changed (03/10/2023-03/09/2025) n=84242 (total number of patients seen in primary care clinics)	Mean difference between groups	P-value
Any HBV screening test	14.13%	19.55%	5.42%	<0.001*
HBsAg	13.31%	18.27%	4.95%	<0.001*
HBsAb	9.12%	14.63%	5.51%	<0.001*
HBcAb	8.09%	12.66%	4.57%	<0.001*

Table 1: Descriptive statistics and independent two-sample t-tests of patients that were screened for HBV before and after updated CDC guidelines

*Indicates statistically significant difference (p-value < 0.05)

**Three screening tests include HBV surface Ab, HBV core Ab, and HBV surface Ag

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1336 | COMBINED ASSESSMENT OF PRES1 AND HBV RNA FOR PREDICTING HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS B PATIENTS RECEIVING ENTECAVIR THERAPY

Hatsue Fujino[1] Masataka Tsuge[1] Yusuke Johira[1] Ryoichi Miura[1] Yasutoshi Fujii[1] Atsushi Ono[1] Eisuke Murakami[1] Tomokazu Kawaoka[1] Daiki Miki[1] Shiro Oka[1], [1]Hiroshima University

Background: Prediction of hepatocellular carcinoma (HCC) risk in patients with chronic hepatitis B (CHB) is important for determining appropriate treatment strategies. PreS1 is involved in viral infectivity and replication, while HBV RNA reflects viral transcriptional activity. However, the relationship between these markers and their respective impacts on HCC risk remain unclear. This study aimed to evaluate the clinical utility of PreS1 and HBV RNA levels for predicting HCC risk after initiation of entecavir (ETV) therapy. **Methods:** A total of 87 treatment-naïve CHB patients who started ETV therapy were enrolled (median age: 49 years; median observation period: 8.7 years). Serum PreS1 antigen levels were quantified by ELISA using a PreS1-specific antibody, and HBV RNA levels were measured using the Roche cobas 6800 HBV RNA Investigational Assay. **Results:** A significant correlation was observed between baseline PreS1 and HBV RNA levels ($r = 0.610$, $P < 0.001$). However, no correlation was found between the reductions in these markers after ETV initiation. At 1 year, patients with lower PreS1 or HBV RNA levels showed significantly higher rates of HBV DNA suppression compared to those with higher levels ($P = 0.001$ and $P < 0.001$, respectively). Notably, the group with both low PreS1 and low HBV RNA levels achieved HBV DNA suppression most rapidly. Interestingly, a significant reduction in HBsAg levels was observed in patients with high HBV RNA levels ($P = 0.003$). Based on baseline PreS1 and HBV RNA levels, patients were stratified into four groups. The group with low PreS1 and high HBV RNA showed the highest incidence of HCC, followed by the group with high PreS1 and low HBV RNA. **Conclusion:** The combined assessment of PreS1 and HBV RNA levels may allow for more accurate stratification of antiviral response and HCC risk in CHB patients. In particular, patients with low PreS1 and high HBV RNA levels are at the highest risk of developing HCC and may require intensive monitoring and early therapeutic intervention.

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1337 | CROSS-SECTIONAL ASSOCIATION BETWEEN AWARENESS OF HEPATITIS B INFECTION STATUS AND HEALTH-RELATED BEHAVIORS: NHANES 2013 TO 2020

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Background: In the United States, hepatitis B virus (HBV) infection prevalence is higher among individuals born outside the U.S. (1.28% vs. 0.15%), with the highest burden observed among non-Hispanic Asians (3.85%). The national HBV elimination plan aims to increase awareness of the infection status from 50% to 90% by 2030. Awareness of HBV infection may be associated with health-related behaviors, including asymptomatic screening and symptomatic testing. Using nationally representative data, we aimed to: (a) examine associations between socio-demographic factors (race/ethnicity and immigration status) and HBV infection status and awareness categories; and (b) evaluate whether health-related behaviors differ across these categories independent of other factors. **Methods:** In this cross-sectional analysis of 18,250 participants aged >20 years in the National Health and Nutrition Examination Survey cycles 2013 – 2020, we categorized participants based on serology and awareness of HBV infection status: current HBV and aware, current HBV and unaware, past HBV infection, and negative for HBV. We generated a health-related behavior score (0-8) using eight variables capturing health care service utilization, self-motivated, and self-directed health behaviors. We estimated the prevalence ratio (PR) of a favorable health-related behavior score ($>=6$ considered favorable) and 95% confidence intervals (CI) comparing HBV infection status and awareness categories to those negative for HBV using Poisson regression. **Results:** Current HBV infection, irrespective of awareness, was more prevalent among non-Hispanic Asians and immigrants ($p < 0.001$). The only socio-demographic and health-related behaviors that were not associated with HBV status and awareness categories were healthcare utilization, diet, sleep,

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and supplement use. The prevalence of favorable health-related behavior scores differed by HBV status and awareness categories in unadjusted analyses ($p < 0.001$). However, after adjusting for socio-demographic and other covariates, no statistically significant differences were observed when comparing individuals with current HBV infection (aware: PR = 0.60; 95% CI: 0.29–1.22; unaware: PR = 1.22; 95% CI: 0.90–1.65) or past infection (PR = 0.90; 95% CI: 0.82–1.00) to uninfected individuals (Table 1). **Conclusion:** After adjusting for confounding variables, engagement in favorable health-related behaviors did not differ significantly by HBV infection or awareness status. Although current infections were more prevalent among non-Hispanic Asians and immigrants, awareness status was not associated with a higher likelihood of favorable health-related behaviors. These findings underscore challenges to achieving 90% awareness and the need for targeted interventions in high-risk groups. We suggest further evaluating the underlying assumptions in the HBV elimination strategy to ensure its feasibility.

Table 1: *Multivariable-adjusted association of HBV infection status and awareness of infection categories with a favorable health-related behavior score*, NHANES 2013-2020 (pre-pandemic).*

Variable	Level	Exponentiated Beta**	Lower CI	Upper CI
HBV Infection and Awareness Category	Negative for HBV Infection	1.00		
	Current HBV Infection and Aware	0.60	0.29	1.22
	Current HBV Infection and Unaware	1.22	0.90	1.65
	Past or Present HBV Infection	0.90	0.82	1.00
Biological Sex	Male	1.00		
	Female	1.31	1.23	1.39
Race/Ethnicity	Non-Hispanic White	1.00		
	Non-Hispanic Black	1.08	1.00	1.18
	Mexican American	0.93	0.85	1.02
	Other Hispanic	1.03	0.87	1.21
	Non-Hispanic Asian	1.04	0.93	1.16
	Other Race - Including Multi-Racial	1.13	1.03	1.23
Number of Years in the U.S.	U.S. Born	1.00		
	<5	0.97	0.85	1.11
	5-15	1.06	0.96	1.17
	15-30	1.12	1.03	1.22
	>30	1.04	0.95	1.14
	Missing	0.85	0.62	1.16
Level of Education	Less than High School	1.00		
	High School and Some College	1.47	1.34	1.61
	College and Above	1.99	1.84	2.16
Relationship Status	Married/Living with Partner	1.00		
	Never Married	0.96	0.90	1.02
	Widowed/Divorced/Separated	0.89	0.84	0.94
Pregnancy Status	Not Pregnant	1.00		
	Pregnant	1.24	1.11	1.39
	Not Applicable	0.93	0.86	1.01
Age Category	20 to <35	1.00		
	35 to <50 Years	0.88	0.83	0.94
	50 to <65 Years	0.98	0.90	1.07
	65 Years and Over	1.18	1.07	1.29
BMI Category	BMI Less Than 18.5	1.00		
	BMI Between 18.5 - 24.9	1.18	0.97	1.43
	BMI Between 25 - 30	1.18	0.97	1.43
	BMI Above 30	1.06	0.87	1.30
	Missing	0.89	0.62	1.30
Federal Poverty Level	Level 1	1.00		
	Level 2	1.16	1.06	1.27
	Level 3 or Above	1.37	1.25	1.49
	Missing	1.25	1.16	1.41
Insurance Coverage	No	1.00		
	Yes	1.65	1.50	1.81
Comorbidity Category	No Comorbidity	1.00		
	Single Comorbidity	1.03	0.97	1.09
	Multimorbidity	1.01	0.95	1.07

**Score is the sum of 8 health-related behaviors (smoking status, hepatitis B vaccination status, dietary supplement use, healthcare utilization, alcohol consumption, physical activity level, quantity of sleep, quality of diet). For each behavior, the "healthy" category was assigned a value of 1, and the "unhealthy" category was assigned a value of 0. The score has a range of 0 to 8. A favorable score value is defined as >=6 points, which is based on a sensitivity analysis.*

***Prevalence ratios were estimated from Poisson regression models and is adjusted for biological sex, age category, ethnicity, level of education, level of poverty, insurance coverage, number of years living in the U.S., relationship status, BMI category, pregnancy status, and comorbidity.*

Disclosures: Samandika Saparamadu: Nothing to Disclose, Elizabeth A. Platz: Nothing to Disclose, Oshozimhede E Iyalomhe: Nothing to Disclose

1338 | CAPSID ASSEMBLY MODULATOR ALG-001075 BINDS AND DIRECTLY TARGETS HBEAG

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Background: The hepatitis B virus (HBV) capsid assembly process has emerged as a key target for the treatment of chronic hepatitis B (CHB). ALG-000184 is a prodrug of ALG-001075, a novel capsid assembly modulator leading to the formation of empty capsids (CAM-E). ALG-000184 has demonstrated best-in-class reductions of HBV DNA, RNA, HBsAg, HBcrAg and HBeAg in CHB patients. ALG-000184 induced an immediate 0.4 $\log_{10}$ PEI U/mL reduction in the first two weeks of treatment of HBeAg-positive patients, suggesting a potential direct effect of ALG-001075 on HBeAg. **Methods:** The impact of ALG-001075 and other CAMs on the HBeAg biogenesis was studied using transient HBeAg expression in Huh7 cells and stably transfected HepG2 cells, with plasmids encoding either wild-type or T33N-mutated HBeAg. The effect on HBeAg secretion was assessed utilizing a Chemiluminescent Immunoassay (CLIA) to determine EC_{50} values, while a Western blot analysis was conducted to characterize the impact of ALG-001075 on HBeAg and its precursors. Interactions between CAMs and purified, fluorescently labeled HBeAg were further investigated using a biophysical spectral shift assay. **Results:** ALG-001075 and other CAMs strongly reduced the levels of secreted HBeAg in the absence of other HBV proteins, suggesting a direct effect on HBeAg. EC_{50} values for HBeAg inhibition were considerably higher than for HBV DNA inhibition but strongly increased upon introduction of the T33N mutation into HBeAg, indicating a similar binding site to the HBV core protein. Western blot analysis showed CAMs also impacted the HBeAg precursor (p22), contributing to HBeAg secretion inhibition. Finally, biophysical analysis through spectral shift confirmed direct binding of ALG-001075 and other CAMs to wild-type HBeAg but not to the HBeAg T33N mutant. **Conclusion:** ALG-001075 demonstrated direct binding to HBeAg and pronounced in vitro reductions in secreted HBeAg levels, in line with clinical observations for its prodrug ALG-000184, suggesting direct inhibition of HBeAg as a third mechanism of action for ALG-001075. Although the direct HBeAg effect requires higher compound concentrations than the primary and secondary effects of CAMs, the high pharmacokinetic exposure achieved with prodrug ALG-000184 and relative HBeAg-targeting potency of parent ALG-001075 likely enable the clinical observation of this effect.

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Disclosures: Jordi Verheyen: Aligos Therapeutics: Employee, Hannah Vanrusselt: Aligos Belgium: Employee, Thomas Klein: Nothing to Disclose, Tse-I Lin: Nothing to Disclose, Cheng Liu: Aligos Therapeutics: Employee, Aligos Therapeutics: Stock - publicly traded company, Julian Symons: Nothing to Disclose, Lawrence Blatt: Nothing to Disclose, Andreas Jekle: Nothing to Disclose, Yannick Debing: Aligos Therapeutics, Inc.: Employee, Aligos Therapeutics, Inc.: Stock - publicly traded company

1339 ASSESSING THE FREQUENCY OF HEPATITIS DELTA VIRUS SCREENING IN PATIENTS WITH CHRONIC HEPATITIS B | RESULTS FROM AN INTERACTIVE DECISION SUPPORT TOOL APP IN ALIGNMENT WITH AASLD GUIDANCE

Carley Yawn[1] Zachary Schwartz[1] Paul Kwo[2,] [1]Clinical Education Alliance, [2]Stanford University Medical Center

Background: The 2018 American Association for the Study of Liver Diseases (AASLD) guidance recommends risk-based screening for hepatitis delta virus (HDV) in patients with chronic hepatitis B (CHB). Key risk indicators include (1) coinfection with hepatitis C virus (HCV) and/or HIV and (2) low HBV DNA levels plus elevated alanine aminotransferase (ALT) levels, among other clinical factors. However, these criteria can be complex to apply in real-world settings, potentially contributing to under-screening. Amid a growing trend toward universal HDV screening, tools that simplify guideline interpretation may be helpful. To support healthcare professionals (HCPs) in identifying patients who meet screening criteria, the Hep B Consult point-of-care app was developed to provide patient-specific recommendations based on user-entered clinical data. **Methods:** We analyzed real-world data from the Hep B Consult app from March 3, 2023, to May 13, 2025. The evaluation focused on CHB cases where HCPs had selected AASLD as their preferred guideline. Cases were deemed eligible for HDV screening if they met the criteria established by AASLD: • Scenario 1: HCV and/or HIV coinfection. • Scenario 2a: low or unknown HBV DNA level AND ALT > ULN or unknown. • Scenario 2b: low or unknown HBV DNA level AND healthcare workers at elevated risk (no ALT level required). Patient cases were then categorized by whether HDV screening was completed (HDV antibody listed as positive or negative) or incomplete (HDV antibody status unknown). **Results:** Among 2170 patient cases entered by HCP learners selecting AASLD as their preferred guideline, 430 cases met criteria for HDV screening, but 48 (34.4%) of these had no HDV screening information. Among these 430 cases where HDV screening was indicated, 158 cases had positive HDV antibody. Among these, 21 (13.3%) lacked follow-up HDV RNA testing. These cases suggest missed opportunities for early detection and intervention in a high-risk population. **Conclusion:** This analysis highlights a significant care gap: More than one third of CHB patient cases meeting AASLD guidance–based criteria for HDV screening were not screened, and follow-up HDV RNA testing was often missed. These findings may highlight the difficulty HCPs face in identifying whom to screen based on complex risk-based criteria. As the field considers a shift toward universal HDV screening, our data suggest current practices fall short. Broader integration of tools like Hep B Consult may support improved guideline adherence and enhance patient outcomes.
Disclosures: Carley Yawn: Nothing to Disclose, Zachary Schwartz: Nothing to Disclose, Paul Kwo: Nothing to Disclose

1340 | DIFFERENT IMPACT OF HBV GENOTYPE ON HBSAG DECLINE KINETICS DURING AND AFTER NUCLEOS(T)IDE ANALOGUE THERAPY IN HBEAG-NEGATIVE CHRONIC HEPATITIS B

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Background: In HBeAg-negative chronic hepatitis B (CHB), serum HBsAg kinetics serve as a surrogate marker for functional cure. While host and viral factors influencing HBsAg decline during nucleos(t)ide analogue (Nuc) therapy have been identified, genotype-specific differences in HBsAg kinetics across treatment phases remain unclear. We investigated whether HBV genotype (GT) differentially modulates HBsAg reduction during active Nuc treatment and after treatment cessation. **Methods:** A total of 614 non-cirrhotic HBeAg-negative CHB patients [GT-B: 535 (87.1%), GT-C: 79 (12.9%)] treated with finite-course Entecavir (ETV) or Tenofovir Disoproxil Fumarate (TDF) according to APASL stopping criteria at Chang Gung Memorial Hospital (CGMH)-Linkou, Taiwan, were included. HBsAg levels were assessed at the start of treatment (SOT), end-of-treatment (EOT), and last follow-up. Two propensity score–matched (PSM) cohorts were constructed: PSM-cohort 1 (n = 158) for on-treatment analysis (matched by age, sex, treatment-naïve status, Nuc agent, and SOT ALT, HBV DNA, and HBsAg levels); and PSM-cohort 2 (n = 132) for off-treatment analysis (matched by

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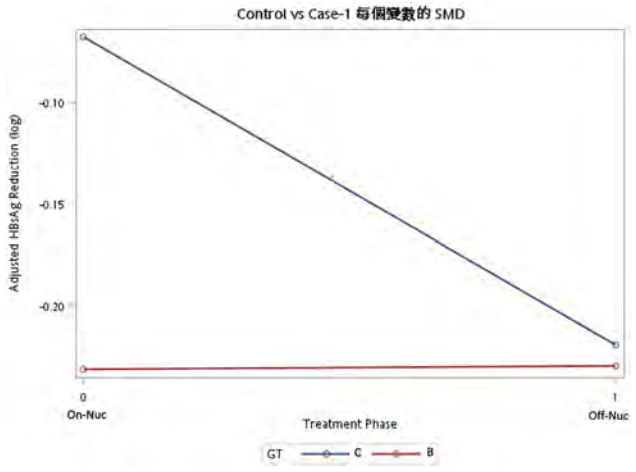
EOT age, sex, Nuc agent, and baseline laboratory parameters). Generalized linear regression was used to identify predictors of HBsAg reduction. A multivariable linear mixed model (LMM) was employed to evaluate genotype-by-phase interaction. External validation was conducted in an independent cohort of 701 patients [GT-B: 541 (77.2%), GT-C: 160 (22.8%)] from CGMH-Kaohsiung. **Results:** In PSM-cohort 1, patients with GT-B exhibited significantly greater on-treatment HBsAg reduction compared to those with GT-C (–0.21 vs. –0.05 $\log_{10}$ IU/mL/year, $p < 0.001$). In PSM-cohort 2, GT-C patients demonstrated a significantly faster off-treatment decline (–0.22 vs. –0.08 $\log_{10}$ IU/mL/year, $p = 0.001$) and a higher HBsAg loss rate (15.2% vs. 0%, $p = 0.001$). Similar trends were observed in the external validation cohort. In the full cohort, GT-B ($\beta = 0.194$, $p < 0.0001$), older age at SOT, and higher SOT ALT, HBV DNA, and HBsAg levels were independently associated with a greater on-treatment HBsAg decline. For off-treatment decline, GT-C ($\beta = -0.1669$, $p = 0.0057$), younger EOT age, and lower HBsAg at EOT were independent predictors. A LMM confirmed a significant genotype-by- phase interaction ($p = 0.0144$), indicating that HBV genotype differently modulates HBsAg reduction kinetics across treatment phases (Figure). Following Nuc cessation, GT-C patients exhibited accelerated HBsAg decline, whereas GT-B patients showed stable HBsAg levels. **Conclusion:** HBV genotype modulates HBsAg reduction kinetics in a phase-specific manner. GT-B is associated with a greater decline during Nuc therapy, whereas GT-C shows enhanced off-Nuc HBsAg reduction and subsequent HBsAg loss. These findings underscore the need for genotype-specific immunologic studies to elucidate underlying mechanisms.



Disclosures: Rachel Wen-Juei Jeng: GSK: Advisor, Gilead: Advisor, Chien-Hung Chen: Nothing to Disclose, Yen-Chun Liu: Nothing to Disclose, Rong-Nan Chien: Nothing to Disclose

1341 | INTEGRATED PLASMA PROTEOMICS AND METABOLOMICS IDENTIFY FIBROSIS-LINKED SIGNATURES IN HBEAG-NEGATIVE NAIVE CHB PATIENTS WITH LOW HBSAG

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Background: HBsAg levels indicate viral activity and immune control in HBeAg-negative, treatment-naive chronic hepatitis B patients, but associated molecular changes remain unclear. This study integrates plasma proteomics and metabolomics to identify distinct molecular signatures linked to HBsAg levels, revealing disease heterogeneity and potential biomarkers. **Methods:** We recruited thirty-treatment-naive HBeAg-negative chronic hepatitis B (nCHBV) patients were stratified into Group I ($HBsAg^{low}$, $n = 10$; HBsAg < 2000 IU/mL) and Group II ($HBsAg^{high}$, $n = 20$; HBsAg > 2000 IU/mL, HBV DNA > 2000 IU/mL, ALT $> 1.2\times$ULN) and healthy control (HC, $n = 10$). Liver histopathological scoring, plasma cytokine profiling, proteomic and metabolomic analyses were performed. **Results:** Total nCHBV patients compared to HC, plasma proteomics pathway enrichment analysis showed significant activation of immune and fibrosis-related pathways, including complement cascade (C3/C5), $\alpha4\beta7$ integrin, TLR signaling, and fibrin clot formation compared to healthy controls. Key discriminatory proteins APCS, HBD, SAA2, and S100A8 were markedly elevated ($FC > 4$, $p < 0.05$). Metabolomic analysis revealed increased levels of S-adenosylmethionine, glutamic acid, and indolepyruvate, linked to arginine and tryptophan metabolism ($FC > 1.5$, $p < 0.05$). Further, nCHBV $HBsAg^{low}$ compared to $HBsAg^{high}$ subgroups, pathway enrichment analysis showed upregulation of IL-4 signaling, platelet activation/degranulation, PTP1B signaling, ECM interactions, and fibrin clot formation ($FC > 2$, $p < 0.05$). $HBsAg^{low}$ specific proteins included ARG1, S100A9, S100A8, and PLEK ($FC > 10$, $p < 0.05$). Metabolomic profiling showed elevated dihydrofolic acid and 5-methoxyindoleacetate in HBsAglow, indicating altered folate and tryptophan metabolism ($FC > 1.5$, $p < 0.05$). Integrated proteomic-metabolomic data in $HBsAg^{low}$ indicated coordinated TLR4 signaling activation, enhanced fibrin clot formation, and disrupted tryptophan metabolism, correlating with plasma cytokines CXCL8, CXCL11, CXCL12 levels and liver fibrosis severity. The ARG1, S100A9, S100A8, and PLEK panel

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demonstrated highest diagnostic accuracy for identifying HBV patients at risk of subclinical inflammation and fibrosis (FC > 10, p < 0.05). **Conclusion:** Integrated multiomics and cytokine analysis identified inflammation- and fibrosis-associated proteins and metabolites specific to nCHBV-HBsAg^{low} patients, which should be closely monitored for disease progression using a proteomics panel including ARG1, S100A9, S100A8, and PLEK.

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1342 | MMP-9 SUPPRESSES THE ANTI-HBSAG B CELL RESPONSE DURING CHRONIC HBV INFECTION

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Background: Our previous research indicated that Matrix Metalloproteinase (MMP)-9, together with MMP-2, are involved in the regulation of intrahepatic anti-HBV effector T cell responses in acute self-limiting HBV infection. However, it remains unclear if MMP-9 also plays a role in regulating anti-HBV immune responses and mediating HBV clearance in the scenario of chronic HBV infection. **Methods:** We employed MMP-9 gene knockout (KO) and RNA interference techniques in chronic HBV replication mouse models. **Results:** The absence of MMP-9 in FVB mice led to significantly accelerated clearance of Hepatitis B surface antigen (HBsAg) in peripheral blood and increased production of Hepatitis B surface antibody (HBsAb) in pAAV-HBV1.2 or BPS plasmids hydrodynamic injection (HDI) mouse models. Adoptive transfer of spleen immune cells from MMP-9 KO mice to wild-type mice could also accelerate serum HBsAg clearance and enhance HBsAb production in the pAAV-HBV1.2 HDI mouse model, suggesting that the anti-HBV effect of MMP-9 KO is mainly mediated by immune cells. RNA-seq analysis showed that MMP-9 KO significantly induced enrichment of genes related to the B-cell receptor signaling pathway in the splenocytes of mice post pAAV-HBV1.2 HDI compared to wild-type mice. MMP-9 KO mice also showed significantly enhanced B cell activation, as well as increased numbers of germinal B cells and follicular helper CD4+ T cells infiltration in the liver post pAAV-HBV1.2 HDI compared to wild-type mice. In vivo knockdown of MMP-9 expression by RNAi also resulted in significantly accelerated serum HBsAg clearance in wild-type FVB and C57BL/6 mice post pAAV-HBV1.2 HDI. **Conclusion:** MMP-9 may play a role in negatively regulating anti-HBV B cell responses during chronic HBV infection. Targeting MMP-9 could serve as a novel strategy for the treatment of chronic HBV infection.

Disclosures: Dongliang Yang: Nothing to Disclose, Dilhumare Ablikim: Nothing to Disclose, Yuhan Chen: Nothing to Disclose, Mengxiao Zhao: Nothing to Disclose, Yanqin Du: Nothing to Disclose, Xuecheng Yang: Nothing to Disclose, Mengji Lu: Nothing to Disclose, Xin Zheng: Nothing to Disclose, Jia Liu: Nothing to Disclose

1343 | CHARACTERISTICS ASSOCIATED WITH SUBSPECIALTY CARE WITHIN A HEPATITIS B VIRUS (HBV) COHORT AT A TERTIARY CARE URBAN HOSPITAL

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Background: Hepatitis B virus (HBV) has a prevalence in the US around 0.4%. Those with chronic infection remain at risk for complications including cirrhosis and hepatocellular carcinoma (HCC), and require subspecialty care due to complexities with management and cancer screening. We aim to evaluate the roughly 1,300 patients within our hospital system with HBV to determine patient characteristics that are associated with subspecialist follow-up. **Methods:** Patients 18 years and older with a positive hepatitis B surface antigen (HBsAg) from January 2011-November 2022 were included. We obtained demographic data, medical and social history, laboratory and imaging data. We compared the medical and social characteristics between the cohorts who followed with subspecialty care, primary care, and those without any follow up care to determine characteristics associated with subspecialty care and examined hepatocellular carcinoma screening rates. **Results:** Our cohort includes 1,314 patients with a positive HBsAg. Of those, 666 (50.7%) had any follow-up (PCP or subspeciality), and 450 (34%) had subspecialty follow-up (1+ visit with gastroenterology, hepatology, or infectious disease). Among the 450 with any follow-up, those who engaged in subspecialty care were older (50 vs 45 years, $p = 0.019$), and had higher rates of end-stage liver disease (30.7% vs 9.6%, $p < 0.001$) and elevated FIB4 (18.9% vs 7.0%, $p < 0.001$). There were similar rates of drug use (26.9% vs 29.8%, $p = 0.45$), housing insecurity (2.2% vs 2.5%, $p = 0.78$), and HIV (11.1% vs 13.6%, $p = 0.36$).

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Although there were similar rates of obtaining hepatitis C antibody (83.9% vs 74.3%, p = 0.22), those in subspecialty care were more likely to have had at least one alphafetoprotein AFP (79.3% vs 20.8%, p < 0.001). **Conclusion:** Subspecialty care in chronic HBV is associated with improved screening and identification of severe liver disease but likely reflects referral bias. Importantly, patients facing social barriers, including drug use and housing insecurity, can and do access subspecialty care when connected. Primary care, emergency, and inpatient settings are crucial referral points and should be leveraged to promote specialist engagement. Interventions such as electronic consults or proactive referrals from primary care may improve HBV care delivery in underserved populations.

	PCP follow up only	Subspecialty follow up	p-value	No Followup	Any Followup (PCP or subspecialty)	p-value2
	N=216	N=450		N=648	N=666	
Age	45 (34-58)	50 (38-58)	0.019	49 (38-61)	49 (37-58)	0.052
Sex			<0.001			0.31
Female	106 (49.1%)	157 (34.9%)		238 (36.7%)	263 (39.5%)	
Male	110 (50.9%)	293 (65.1%)		410 (63.3%)	403 (60.5%)	
HCV Ab obtained	26 (74.3%)	104 (83.9%)	0.22	179 (82.1%)	130 (81.8%)	1.00
Drug use	59 (29.8%)	121 (26.9%)	0.45	108 (30.7%)	180 (27.8%)	0.34
ESLD	19 (9.6%)	138 (30.7%)	<0.001	70 (19.9%)	157 (24.2%)	0.13
Housing insecurity	5 (2.5%)	10 (2.2%)	0.78	30 (8.5%)	15 (2.3%)	<0.001
HIV	27 (13.6%)	50 (11.1%)	0.36	39 (11.1%)	77 (11.9%)	0.76
Any AFP obtained	45 (20.8%)	357 (79.3%)	<0.001	175 (27.0%)	402 (60.4%)	<0.001
Low FIB4	97 (68.3%)	197 (53.1%)	0.002	198 (54.2%)	294 (57.3%)	0.37
High FIB4	10 (7.0%)	70 (18.9%)	<0.001	64 (17.5%)	80 (15.6%)	0.46

Disclosures: Lindsay Matthews: Nothing to Disclose, Yedidya Saiman: Nothing to Disclose

1344 | LONGITUDINAL CHANGES IN FIB-4 INDEX AND RISK FACTORS FOR FIBROSIS PROGRESSION IN UNTREATED HEPATITIS B VIRUS CARRIERS: A MULTICENTER STUDY

KENGO WATANABE[1] Jun Inoue[1] Takehiro Akahane[2] Hiroaki Haga[3] Tomoo Kobayashi[4] Satoshi Takai[5] Shinichiro Minami[6] Kojiro Kataoka[7] Mami Kida[8] Toshihiro Sato[9] Noriyuki Obara[10] Masashi Ninomiya[1] Mio Tsuruoka[11] Kosuke Sato[1] Keishi Ouchi[1] KOTARO DOI[1] Tomoya Sasazaki[1] Hirofumi Niitsuma[1] Yoshiyuki Ueno[3] Atsushi Masamune[1], [1]Tohoku University Graduate School of Medicine, [2]Japanese Red Cross Ishinomaki Hospital, [3]Faculty of Medicine, Yamagata University, [4]Tohoku Rosai Hospital, [5]Iwaki City Medical Center, [6]Akita University Graduate School of Medicine, [7]Japanese Red Cross Sendai Hospital, [8]Kurihara Central Hospital, [9]LC Clinic Sendai, [10]JCHO Sendai Hospital, [11]Tohoku University Hospital

Background: According to the guideline of the Japan Society of Hepatology, antiviral therapy is recommended for patients with chronic hepatitis B who have both HBV DNA ≥ 3.3 log IU/mL and ALT ≥ 31 U/L. However, patients who do not meet these criteria may still develop fibrosis and have an increased risk of hepatocellular carcinoma over time. The objective of this multicenter study was to evaluate fibrosis progression using longitudinal changes in the FIB-4 index in nucleos(t)ide analogue (NA)-untreated HBV carriers and to identify associated clinical risk factors. **Methods:** We retrospectively enrolled HBsAg-positive patients who were first seen in 2019 and had not received prior NA therapy. Annual FIB-4 index values were calculated, and follow-up was terminated if treatment was initiated. The slope of FIB-4 change (S1) was divided by the age-related physiological slope (S2), and the ratio of S1 to S2 (S1/S2) was defined as a fibrosis progression grade. Cases with S1/S2 ≥ 2.0 were considered as fibrosis progressors. Patients with baseline FIB-4 ≥ 4.0, other diseases causing thrombocytopenia, or follow-up < 3 years were excluded. **Results:** Of the 584 cases from 10 institutions, 452 patients were included in the study (median age: 58 years; 48% male; median ALT: 21 U/L; platelet count: 21.1×10^4/μL; HBV DNA: 2.9 log IU/mL; baseline FIB-4: 1.34; median follow-up: 7 years). Fibrosis progression occurred in 25.4% of patietns. Patients were stratified into four groups based on HBV DNA (cutoff: 3.3 log IU/mL) and ALT (cutoff: 31 U/L): Group a: high DNA/high ALT (n = 48); Group b: high DNA/low ALT (n = 121); Group c: low DNA/high ALT (n = 68); Group d: low DNA/low ALT (n = 215). The median fibrosis progression grades were 0.77, 0.95, 0.61, and 1.15, respectively; group d had the highest grade. In a multivariate analysis, high HbA1c levels were significantly associated with progression in group d (odds ratio [OR] 2.67, P = 0.045), while a higher platelet count predicted progression in group b (OR 1.10, P = 0.006). Interestingly, steatosis was associated with increased progression in patients with HBV DNA ≥ 4.0 log IU/mL (2.80 vs. 0.64, P = 0.007), whereas it was associated with reduced progression in those with DNA < 4.0, (0.52 vs. 1.08, P = 0.004). **Conclusion:** Fibrosis can progress in patients with HBV infection, even when ALT and HBV DNA levels were low, particularly when HbA1c is elevated. In patients with high HBV DNA levels and low ALT levels, fibrosis may still progress despite normal platelet counts. Furthermore, the impact of fatty liver varies by HBV DNA level, suggesting a need to revisit treatment strategies and consider proactive interventions for high-risk subgroups.

Disclosures: KENGO WATANABE: Nothing to Disclose, Jun Inoue: Nothing to Disclose, Takehiro Akahane: Nothing to Disclose, Hiroaki Haga: Nothing to Disclose, Tomoo Kobayashi: Nothing to Disclose, Satoshi Takai: Nothing to Disclose, Shinichiro Minami: Nothing to Disclose, Kojiro Kataoka: Nothing to Disclose, Mami Kida: Nothing to Disclose, Toshihiro Sato: Nothing to Disclose, Noriyuki Obara: Nothing to Disclose, Masashi Ninomiya: Nothing to Disclose, Mio Tsuruoka: Nothing to Disclose, Kosuke Sato: Nothing to Disclose, Keishi Ouchi: Nothing to Disclose, KOTARO

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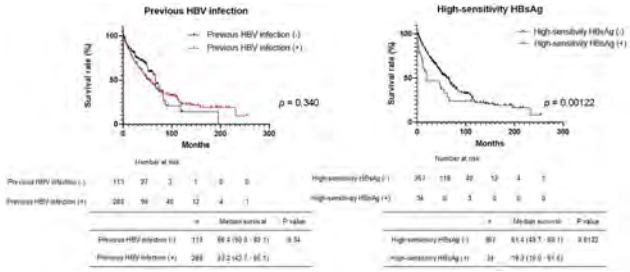
DOI: Nothing to Disclose, Tomoya Sasazaki: Nothing to Disclose, Hirofumi Niitsuma: Nothing to Disclose, Yoshiyuki Ueno: Abbvie Inc: Speaking and Teaching, Eisai Inc: Speaking and Teaching, Chugai Pharmaceutical: Speaking and Teaching, Atsushi Masamune: Nothing to Disclose

1345 | POSITIVITY OF HIGH-SENSITIVITY HBSAG TEST, NOT PREVIOUS HBV INFECTION, INDICATES POOR PROGNOSIS IN PATIENTS WITH NON-HBV-RELATED HCC

Naohiro Yasuura[1] Goki Suda[1] Masatsugu Ohara[1] Daisuke Yokoyama[1] Shoichi Kitano[1] Takatsugu Tanaka[1] Akimitsu Meno[1] Takashi Kitagataya[1] Masato Nakai[1] Takuya Sho[1] Naoya Sakamoto[1], [1]Hokkaido University Faculty of Medicine and Graduate School of Medicine

Background: The prognostic impact of previous-HBV-infection (pHBV) in non-HBV-related hepatocellular carcinoma (non-HBV HCC) remains unclear. Recently a high-sensitivity HBs antigen test has been developed. The prevalence and significance of high-sensitivity HBs antigen positivity (hHBsAg+) in non-HBV HCC patients with pHBV have not been fully clarified. **Methods:** We retrospectively screened patients with newly diagnosed non-HBV HCC (standard HBsAg-test negative) from April 2000 to March 2023. Patients with insufficient clinical information or positive HBV-DNA were excluded. We evaluated the prevalence, characteristics and prognostic impact of pHBV and hHBsAg+ in non-HBV HCC. We compared three groups as follows: Group 1 – without pHBV, Group 2 - with pHBV and without hHBsAg+, and Group 3 – with pHBV and hHBsAg+. **Results:** A total of 401 non-HBV HCC patients were included (288 with pHBV/113 without pHBV). pHBV did not affect overall survival (OS). Among non-HBV HCC patients with pHBV, 11.8% (34/288) were hHBsAg+ and had more advanced stages of HCC, higher AFP levels, higher vascular invasion rates. Comparison of OS among 3 groups revealed significantly shorter OS in Group 3 (66.4, 56.6, and 19.3 months in Groups 1, 2, and 3, respectively ; $p = 0.036$). Multivariate Cox regression indicated that only Group 3 was significantly and independently associated with shorter OS (HR: 2.044, $p = 0.011$) in addition to BCLC stage, Child-Pugh grade, platelet counts, AST, and AFP. Subgroup analysis in patients with non-B-non-C aetiology HCC revealed that Group 3 had significantly shorter OS than the other groups (OS: 66.4 months vs 44.6 months vs 11.4 months, $p = 0.035$) and, multivariate Cox regression indicated that only Group 3 was significantly and independently associated with shorter OS (HR: 2.954, $p = 0.005$). Subgroup analysis in patients with non-B-non-C aetiology and BCLC stage B/C/D HCC revealed that Group 3 had significantly shorter OS than the other groups (OS: 44.5 months vs 20.9 months vs 5.9 months, $p < 0.001$) and, multivariate Cox regression indicated that only Group 3 was significantly and independently associated with shorter OS (HR: 7.426, $p < 0.001$). **Conclusion:** In patients with non-HBV-related HCC, hHBsAg+ is significantly and independently associated with poor prognosis. This association is particularly evident in HCC patients with NBNC aetiology and advanced HCC. These findings have potential utility in the clinical management of and therapeutic strategies for patients with non-HBV-related HCC.



Disclosures: Naohiro Yasuura: Nothing to Disclose, Goki Suda: Nothing to Disclose, Masatsugu Ohara: Nothing to Disclose, Daisuke Yokoyama: Nothing to Disclose, Shoichi Kitano: Nothing to Disclose, Takatsugu Tanaka: Nothing to Disclose, Akimitsu Meno: Nothing to Disclose, Takashi Kitagataya: Nothing to Disclose, Masato Nakai: Nothing to Disclose, Takuya Sho: Nothing to Disclose, Naoya Sakamoto: Gilead Sciences, Eisai, AbbVie, Chugai: Speaking and Teaching

1346 | IDENTIFICATION OF HBV CURE PATIENTS BY HBV RNA AND HBV GENOME COVERAGE MAP IN PLASMA

Daryl Lau[1] Selena Lin[2] Hsin-Ni Liu[3] Zach Heimer[2] Rohullah Rasikh[1] Mati Ullah[1] Khawaja Hassam[4] Mansoor Rahman[1] Zhili Wang[2] Ying-Hsiu Su[5], [1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States, [2]JBS Science, Inc., Doylestown, PA, United States, [3]The Baruch S Blumberg Institute, Doylestown, PA, United States, [4]Lahey Hospital and Medical Center, [5]Baruch S. Blumberg Institute

Background: Despite prolonged NUC therapy, the rate of functional cure, defined as HBsAg loss and transcriptionally silent cccDNA, remains low. In HBeAg (-) CHB, most of the HBsAg is derived from integrated HBV DNA (iDNA). Some may have achieved either non-replicative cccDNA or cccDNA depletion but still have HBsAg from iDNA. We applied our liquid biopsy biomarker that estimates intrahepatic HBV DNA genome coverage and serum HBV RNA as cccDNA surrogate markers to determine potential cure among

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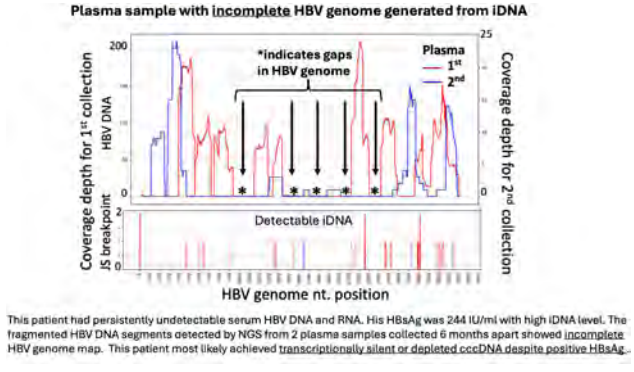
HBeAg(-) CHB patients with various HBsAg levels. **Methods:** We utilized the HBV-targeted Next Generation Sequencing (NGS) platform and *ChimericSeq* bioinformatics to quantify iDNA and construct genome map with fragmented HBV (fHBV) DNA on plasma samples from 83 HBeAg(-) CHB patients. Samples with incomplete HBV DNA genome coverage likely had cccDNA depletion as illustrated in Figure. Second-generation HBV RNA assay (LOD 0.49 U/ml) was by Abbott Diagnostics. 73 patients on continuous NUC for at least 3 years with undetectable or <10 IU/ml serum HBV DNA were selected. Among them, 5 achieved HBsAg loss (<0.05 IU/ml) and 69 had HBsAg levels between 0.4 and $>25{,}000$IU/ml. In addition, 10 patients with spontaneous HBsAg clearance were included. **Results:** 78 (94%) of this cohort were Asians and 51 (61%) were male. The mean age was 53 (range: 27 to 79) years. All the subjects had detectable plasma iDNA. HBsAg was positively correlated with iDNA ($r=0.23$, $p=0.016$) and fHBV DNA ($r=0.27$, $p=0.003$). This finding suggested that most of the HBsAg was derived from iDNA. There was no significant correlation between HBV RNA and HBsAg ($p=0.24$). 11 (73%) subjectswith HBsAg <0.05 IU/ml had undetectable HBV RNA and partial HBV DNA genome coverage. In addition, 5 subjects with HBsAg ranged from 1.5 to 244 IU/ml also had undetectable HBV RNA and partial HBV coverage. By using the criteria of both undetectable serum HBV RNA and partial HBV genome coverage, 16 (19%) of this cohort most likely achieved transcriptionally silent cccDNA or cccDNA depletion. Their detectable fHBVDNA would have been derived from iDNA. **Conclusion:** HBsAg can be derived from cccDNA and iDNA; currently, there is no diagnostic test to distinguish the sources of HBsAg. By applying undetectable HBV RNA and partial HBV DNA genome coverage criteria, we were able to identify patients who had potentially achieved HBV cure regardless of their HBsAg levels. This encouraging surrogate liquid biopsy for "HBV cure" need to be further validated.



This patient had persistently undetectable serum HBV DNA and RNA. His HBsAg was 244 IU/ml with high iDNA level. The fragmented HBV DNA segments detected by NGS from 2 plasma samples collected 6 months apart showed incomplete HBV genome map. This patient most likely achieved transcriptionally silent or depleted cccDNA despite positive HBsAg.

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1347 | INTEGRATIVE CLINICAL AND MOLECULAR RISK SCORE FOR PREVENTION OF HBV-RELATED HCC

Hiroyuki Suzuki[1] Hiroaki Kanzaki[1] Naoto Fujiwara[2] Jingxuan Chen[1] Courtney Katz[1] Soumith Paritala[1] Ece Janet Dinc[1] Subhojit Paul[1] Sumit Mishra[1] Jeon Lee[1] Hsiao-Ling Huang[3] Ming-Chin Yu[4] Tsung-Han Wu[3] Vera Kim[5] Venancio Alves[5] Flair Jose Carrilho[5] Suzane Ono[5] Adam Yopp[1] Amit Singal[1] Emilie Crouchet[6] Thomas Baumert[6] Sen-Yung Hsieh[3] Yujin Hoshida[1], [1]University of Texas Southwestern Medical Center, [2]Mie University, [3]Chang Gung Memorial Hospital, [4]New Taipei Municipal TuCheng Hospital, [5]University of São Paulo School of Medicine, [6]University of Strasbourg

Background: Patients with HBV-related chronic liver disease remain at risk even with the use of antiviral therapies. Clinical variable-based scores such as PAGE-B score have been proposed for HCC risk precision in patients with HBV-related chronic liver disease. However, there is still room for improvement to refine risk stratification and early detection of HBV-related HCC. **Methods:** We defined and validated multi-omic molecular signatures (transcriptome including viral-host fusion transcripts, single nucleotide polymorphisms [SNPs] in coding regions, somatic DNA mutational signature, and somatic DNA mutations with predicted functional consequence) associated with time to incident HCC development and validated their outcome association in total of 111 patients with HBV-related cirrhosis (median follow-up 9.3 years; IQR 3.4–12.3 years). These candidate molecular signatures were integrated with PAGE-B. The HBV-specific transcriptomic signature was used for *in silico* screening of compounds that favorably modulated the HBV HCC risk signatures. Candidate compounds were tested in two models: an *in vitro* cell-based model (cPLS), inducible for the prognostic liver signature (PLS) we previously reported, and an *ex vivo* organotypic culture of precision-cut liver slice (PCLS) derived from HBV-infected patients. **Results:** In the derivation set including 39 HBV cirrhosis patients, we defined a 95-gene transcriptomic signature, which was associated with fibrogenic molecular pathways among several others. In addition, DNA mutational signatures related to reactive oxygen species-induced DNA damage were associated with HCC risk. Spatial mapping of these signatures on liver tissue samples is currently underway. No ~ marginal association was observed for SNPs previously reported for HCC risk association. These HCC risk-associated molecular signatures were integrated with PAGE-B score, and evaluated

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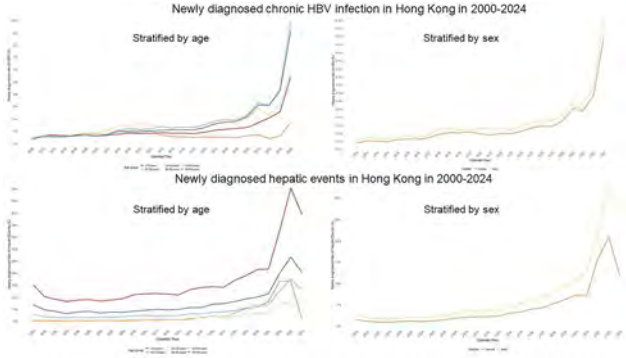
in independent validation sets, including a longitudinal cohort (n = 42) and a case-control series (n = 30). The integrative score was associated with HCC risk on the longitudinal cohort (Firth-adjusted HR, 16.2; 95% CI, 1.9-135.7) and the case-control series (Firth-adjusted OR, 12.3; 95% CI, 1.1-1705.8). Two candidate compounds were identified as potential chemopreventive agents to improve high-risk pattern of the molecular signatures. Their assessment in the cPLS and PCLS models are currently ongoing. **Conclusion:** An integrative clinical and molecular risk score for HBV-related HCC showed promising performance in our preliminary validation studies, which warrants further validation. The score may also serve as a companion biomarker for the candidate chemoprevention agents.

Disclosures: Hiroyuki Suzuki: Nothing to Disclose, Hiroaki Kanzaki: Nothing to Disclose, Naoto Fujiwara: Nothing to Disclose, Jingxuan Chen: Nothing to Disclose, Courtney Katz: Nothing to Disclose, Soumith Paritala: Nothing to Disclose, Ece Janet Dinc: Nothing to Disclose, Subhojit Paul: Nothing to Disclose, Sumit Mishra: Nothing to Disclose, Jeon Lee: Nothing to Disclose, Hsiao-Ling Huang: Nothing to Disclose, Ming-Chin Yu: Nothing to Disclose, Tsung-Han Wu: Nothing to Disclose, Vera Kim: Nothing to Disclose, Venancio Alves: Nothing to Disclose, Flair Jose Carrilho: Nothing to Disclose, Suzane Ono: Nothing to Disclose, Adam Yopp: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Emilie Crouchet: Nothing to Disclose, Thomas Baumert: Nothing to Disclose, Sen-Yung Hsieh: Nothing to Disclose, Yujin Hoshida: Helio Genomics: Advisor, Alentis Therapeutics: Stock – privately held company, Espervita Therapeutics: Stock – privately held company, Elevar Therapeutics: Advisor, Espervita Therapeutics: Advisor, Roche Diagnostics: Advisor

1348 | COVID-19 PANDEMIC INTENSIFIED AGE AND SEX DISPARITIES IN DIAGNOSTIC AND HEPATIC EVENT INCIDENCES IN INDIVIDUALS WITH CHRONIC HEPATITIS B

Grace Lai-Hung Wong[1] Vicki Hui[1] Mandy Lai[1] Jimmy Che-To Lai[2] Vincent Wong[2] Terry Cheuk-Fung Yip[2], [1]Medical Data Analytics Centre, State Key Laboratory of Digestive Disease, The Chinese University of, [2]The Chinese University of Hong Kong

Background: Age and sex significantly influence the diagnosis and outcomes of chronic hepatitis B (CHB). Lockdowns amid the COVID-19 pandemic might have further exacerbated the impact. This study evaluated the secular trends in diagnostic rates of chronic hepatitis B virus (HBV) infection and the incidences of hepatic events, focusing on disparities by age and sex region over two decades before, during, and after the COVID-19 pandemic. **Methods:** Individuals with CHB were identified from a territory-wide database from year 2000 to 2024. Age- (18-30, 30-40, 50-60, 60-70, 70-80, >80 years) and sex-stratified diagnostic rates of HBV in 2000-2024 were calculated based on the number of individuals tested annually, Incidences of hepatic events, including hepatocellular carcinoma, decompensating events, and liver transplantation, were calculated among HBV-infected individuals. **Results:** A total of 276394 individuals were diagnosed with HBV. Newly diagnosed HBV rates increased over time across all age groups, with the most dramatic increase observed in patients of 50-59 years old, from 0.36% [0.34%–0.39%] in 2000 to 3.31% [3.31%–3.42%] in 2021, dropped to 3.11% [2.98%–3.25%] in 2022, then bounced back to 9.82% [9.44%–10.19%] in 2024. Men had consistently higher diagnostic rates for HBV than women: it peaked in 2021 for both sexes – 2.84% [2.77%–2.91%] in men and 2.56% [2.50%–2.62%] in women; dropped to 2.83% [2.75%–2.91%] in men and 2.56% [2.50%–2.62%] in women in 2022, then bounced back to 8.19% [7.97%–8.41%] in men and 6.90% [6.71%–7.09%] in women in 2024. Incidence of hepatic event increased significantly with age over time; it was highest in patients of 70 years or older, rising from 15.00% [14.30%–15.71%] in 2000 to 55.32% [53.76%–56.89%] in 2023 dropped to 44.32% [42.21%–46.44%] in 2024. Men had consistently more hepatic events than women; it peaked in 2022 for both sexes – 22.06% [21.37%–22.74%] in men and 15.76% [15.14%–16.37%] in women (Figure). **Conclusion:** Newly diagnosed HBV rates showed substantial increases, particularly among middle-aged males. Hepatic event rates rose with age, especially in older males. Such disparities have been intensified amid COVID-19 pandemic, and mostly relieved toward the end of the pandemic.



Disclosures: Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking

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1349 | A MARKOV MODEL COST THRESHOLD ANALYSIS OF POTENTIAL HEPATITIS B VIRUS CURE REGIMENS IN THE U.S

Grace Lai-Hung Wong[1] Boyu Yang[2] Jimmy Che-To Lai[1] Vincent Wong[1] Robert Wong[3] Anna Lok[4] Terry Cheuk-Fung Yip[1], [1]The Chinese University of Hong Kong, [2]Medical Data Analytics Centre, State Key Laboratory of Digestive Disease, The Chinese University of, [3]VA Palo Alto Healthcare System, [4]University of Michigan Medical Center

Background: Various hepatitis B virus (HBV) cure regimens are actively undergoing clinical development and will soon be available for regulatory approval. Patients without liver cirrhosis who fulfill the current treatment criteria may further benefit from functional cure of HBV. We aimed to evaluate the treatment cost-effective thresholds with different anticipated success rates of functional cure for a potential HBV cure regimen in the U.S. using a Markov model, with long-term oral nucleos(t)ide analogue (NUC) treatment as a reference. **Methods:** The base case is a 50-year-old man with non-cirrhotic hepatitis B e antigen-negative hepatitis with serum HBV DNA suppressed for at least one year with oral NUC treatment. We used a Markov model to simulate patients' progression through a discrete series of health states, comparing a functional cure to current practice with long-term NUC treatment. Outcomes from the model included lifetime costs of treatment, monitoring and medical management; quality-adjusted life-years (QALYs); and risk of clinical endpoints (compensated and decompensated cirrhosis, hepatocellular carcinoma [HCC], liver transplantation and death). The threshold incremental cost-effectiveness ratio (ICER) was set at USD100,000. **Results:** Compared with current long-term NUC treatment, a functional cure regimen with a 30% success rate in the base case patient would yield 18.69 QALYs (0.38 QALY gained compared with long-term NUC) per patient. Cost-effectiveness analyses suggest that a functional cure regimen could be cost-effective at a one-time treatment cost under US$66,708. Corresponding one time treatment costs and QALYs gained (vs. long-term NUC) are estimated at US$44,205 and 0.25 QALYs, US$89,210 and 0.51 QLAYs, US$111,712 and 0.64 QALYs for a potential HBV treatment with functional cure rates of 20%, 40%, and 50%, respectively (Table). **Conclusion:** A Markov model-based cost-effectiveness analysis demonstrates that a hypothetical HBV cure regimen with a 30% functional cure in aforementioned base case could be cost-effective if less than US$66,708. Cost-effectiveness thresholds and QALYs gained would vary depending on patient characteristics, liver disease severity, and actual treatment success rates.

Table. Life-long per person quality-adjusted life-years (QALYs) gained and threshold costs of a functional cure regimen with different anticipated success rates of functional cure compared with current long-term antiviral treatment.

	Cure rate 20%	Cure rate 30%	Cure rate 40%	Cure rate 50%
Long-term antiviral treatment				
QALYs (years)		18.31		
Drug cost with current antivirals (US$)		5,891		
Medical Management cost (US$)		108,508		
Functional cure				
QALYs (years)	18.56	18.69	18.82	18.95
QALYs gained (years)	0.25	0.38	0.51	0.64
Drug cost with current antivirals (US$)	4,539	4,013	3,487	2,961
Medical Management cost (US$)	90,701	81,570	72,438	63,307
Treatment cost-effective threshold (US$)	44,205	66,708	89,210	111,712

Base case: A 50-years-old man with non-cirrhotic hepatitis B e antigen-negative hepatitis with serum HBV DNA suppressed for at least one year with oral nucleos(t)ide analogue (NUC) treatment.

Disclosures: Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Boyu Yang: Nothing to Disclose, Jimmy Che-To Lai: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company, Eli Lilly: Consultant, Merck: Consultant, Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/

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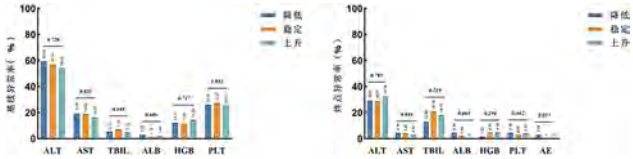
1350 | ASSOCIATION OF HBSAB LEVEL CHANGES WITH HEPATIC OUTCOMES IN NON-CIRRHOTIC CHB PATIENTS FOLLOWING HBSAG LOSS

Wen Deng[1] Yao Xie[1] Minghui Li[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: The relationship between changes in hepatitis B surface antibody (HBsAb) levels and liver-related adverse events following hepatitis B surface antigen (HBsAg) clearance remains unclear. This study aimed to investigate the association between HBsAb level dynamics and hepatic adverse outcomes in non-cirrhotic patients after HBsAg loss. **Methods:** Patients achieving HBsAg seroclearance after pegylated interferon-alpha (Peg-IFNα) therapy at Beijing Ditan Hospital, Capital Medical University from October 2008 to December 2023 were retrospectively analyzed. Patients were stratified into four groups according to baseline HBsAb levels: negative (<10 mIU/mL), low (10-100 mIU/mL), moderate (100-1000 mIU/mL), and high (≥ 1000 mIU/mL) groups. During follow-up, they were further categorized into declining, stable, and increasing groups based on HBsAb titer dynamics. The primary endpoint was the incidence of liver-related adverse events following HBsAg seroclearance. **Results:** A total of 390 patients were included, with a median age of 38.00 years (32.00-44.00) and a median follow-up duration of 53.50 months (11.00-173.00). Liver-related adverse events were observed in 4 cases (1.03%), all occurring in the HBsAb-declining group (4/131, 3.05%), while no events were detected in either the HBsAb-stable (0/120) or HBsAb-increasing (0/139) groups ($P=0.017$). A significant inverse correlation was found between HBsAb level dynamics and the incidence of hepatic adverse events ($rs=-0.125$, $P=0.014$). **Conclusion:** Declining HBsAb levels following HBsAg seroclearance may be associated with an increased risk of liver-related adverse events.



Disclosures: Wen Deng: Nothing to Disclose, Yao Xie: Nothing to Disclose, Minghui Li: Nothing to Disclose

1351 | NEW SUBMISSION: A LONG-ACTING LIPOPHILIC TFV PHOSPHONATE PRODRUG SUSTAINS SUPPRESSION OF HBV REPLICATION

Natalia Osna[1] Samiksha Raut[1] Grace Bybee[1] Haritha Chava[1] Mojisola Ogunnaike[1] Weimin Wang[1] Anup Pathania[1] Howard Gendelman[1] Larisa Poluektova[1] Benson Edagwa[1], [1]University of Nebraska Medical Center

Background: Chronic hepatitis B (CHB) treatment requires daily oral therapy with Tenofovir (TFV) prodrugs, TFV disoproxil/TFV alafenamide- fumarates (TDF/TAF), or entecavir. Treatment cessation leads to HBV reactivation, underscoring the significance of adherence to therapy. Since long-acting formulations improve treatment outcomes, we developed an amino acid-free hydrophobic and lipophilic crystalline phosphonate TFV prodrug named M5TFV. M5TFV is scalable, cost-effective, and as efficacious as M1TFV, another injectable long-acting TFV prodrug that we previously reported (Sci Adv, 2023). Now, we address the mechanisms by which M5TFV nanosuspension (NM5TFV) sustains suppression of HBV replication in hepatocytes. **Methods:** M5TFV was synthesized and nanoformulated as an aqueous nanosuspension using Tween 20 and PEG 3350 as the stabilizing surfactants. In vivo, experiments were performed on HBV transgenic (TG05) mice administered a single intramuscular injection of NM5TFV at 200 and 400 mg/kg TFV equivalents. HBV viral load in blood was tested weekly until the HBV DNA rebound occurred. For in vitro studies, HepAD38 cells were treated with NM5TFV, 25 μM, 8h, followed by incubation in a medium for 48h. HBV DNA and cccDNA were determined by qPCR. After IFNα signaling induction (400 IU, 6h), interferon-stimulated genes (ISGs), ISG15, OAS1, and APOBEC3G were measured by RT-PCR. **Results:** At the two doses evaluated in mice, NM5TFV exhibited >2.5 log 10 reduction in HBV DNA, lasting over two months after a single injection, with a rebound at 12 weeks, similar to NM1TFV. Exposure of HepAD38 cells to NM5TFV reduced HBV DNA and cccDNA levels 2-fold.

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HepAD38 cells co-cultured with human monocyte-derived macrophages (MDMs) did not potentiate NM5TFV's suppression of HBV DNA/cccDNA, suggesting that intracellular M5TFV prodrug is efficiently activated in infected HepAD38 cells, independent of MDM active drug transfer. Also, in HepAD38 cells and precision-cut liver slices from Tg05 mice, the suppression magnitude of HBV DNA by NM5TFV was the same. NM5TFV (unlike NM1TFV) did not increase the induction of ISGs by IFNα. **Conclusion:** NM5TFV exhibited significant anti-viral activity by directly suppressing HBV DNA and cccDNA in infected hepatocytes, with no ISG activation. Notably, a single intramuscular well-tolerated injection of NM5TFV sustained HBV DNA suppression in HBV-replicating mice for at least ten weeks. Thus, NM5TFV is a perfect long-acting candidate for CHB treatment.
Disclosures: Natalia Osna: Nothing to Disclose, Samiksha Raut: Nothing to Disclose, Grace Bybee: Nothing to Disclose, Haritha Chava: Nothing to Disclose, Mojisola Ogunnaike: Nothing to Disclose, Weimin Wang: Nothing to Disclose, Anup Pathania: Nothing to Disclose, Howard Gendelman: Nothing to Disclose, Larisa Poluektova: Nothing to Disclose, Benson Edagwa: Nothing to Disclose

1352 | SINGLE-CELL DISSECTION OF THE IMMUNE LANDSCAPE IN HBV-ASSOCIATED HEPATOCELLULAR CARCINOMA REVEALS VIRAL-DRIVEN IMMUNE DYSFUNCTION

PeiChing Chang[1], [1]National Yang Ming Chiao Tung University

Background: Chronic HBV infection creates a unique tumor microenvironment (TME) in hepatocellular carcinoma (HCC), yet the mechanisms linking viral persistence to immune suppression remain unclear. **Methods:** To dissect this complexity, we performed single-cell RNA sequencing (scRNA-seq) on HBV-associated HCC specimens and uncovered a cellular ecosystem shaped by chronic viral exposure and immune exhaustion. Analysis of over 20,000 single-cell transcriptomes revealed heterogeneous immune and tumor compartments, including diverse $CD8^+$ T-cell states and transcriptionally distinct HBV-infected HCC subpopulations. **Results:** Notably, we identified an unexpected trajectory of $CD8^+$ T-cell states spanning naïve-like, memory, and exhausted phenotypes, ending with progenitor-exhausted T cells. A stem-like precursor population, previously thought to precede terminal exhaustion, was instead positioned at the terminal end of the differentiation axis, suggesting alternative exhaustion pathways shaped by chronic viral exposure. Moreover, cell-cell interaction analysis uncovered selective immunoregulatory interactions between HBV-enriched tumor subsets and dysfunctional T-cell populations, implicating temporally regulated mechanisms of immune evasion. **Conclusion:** Together, these findings reveal the intricate interplay between HBV-infected HCC cells and T cells, highlighting virus-associated immunosuppressive dynamics that may inform future immunotherapeutic strategies in virally driven cancers.
Disclosures: PeiChing Chang: Nothing to Disclose

1353 | EFFICACY AND RISK FACTORS OF PEGINTERFERON ALFA-2B MONOTHERAPY IN INITIAL TREATMENT OF PATIENTS WITH HBEAG NEGATIVE CHRONIC HEPATITIS B

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Background: To evaluate the efficacy of initial treatment with peginterferon alfa-2b (peg-IFN alfa-2b) monotherapy in patients with HBeAg negative chronic hepatitis B (CHB), and explore the factors affecting the clearance of hepatitis B surface antigen. **Methods:** This study included 47 HBeAg negative CHB patients from December 2019 to December 2024, who were treatment-naïve with a serum HBsAg < 100IU/ml. These patients had a willingness to receive interferon treatment, and after thorough examination to rule out relevant contraindications and sufficient communication, they received peg-IFN alfa-2b monotherapy. Serum HBsAg, HBV DNA, biochemical changes and adverse reactions during treatment were monitored every 3 months. These patients had treated for at least 24 weeks, of which 32 patients had completed 48 weeks of treatment. **Results:** The average age of these patients was 40.6 years, with 34 males accounting for 72.3%. After 24 weeks of treatment, average HBsAg level decreased from a baseline level of 30.4 ± 31.5 IU/ml to 6.0 ± 13.9 IU/ml, and 26 patients (55.3%) achieved surface antigen clearance. Univariate analysis suggested that lower HBsAg levels at baseline and 4 weeks, baseline HBV DNA < 100IU/ml, and HBsAg seroconversion at 12 weeks were associated with HBsAg clearance at 24 weeks. However, multivariate analysis indicated that lower HBsAg levels at baseline and 4 weeks were independent predictors of HBsAg clearance at 24 weeks. Among patients who completed 48 weeks of treatment, 81.3% achieved HBsAg clearance. Overall, the treatment was well tolerated. **Conclusion:** The lower the baseline HBsAg level, the greater the probability of HBsAg clearance in patients receiving initial interferon monotherapy.

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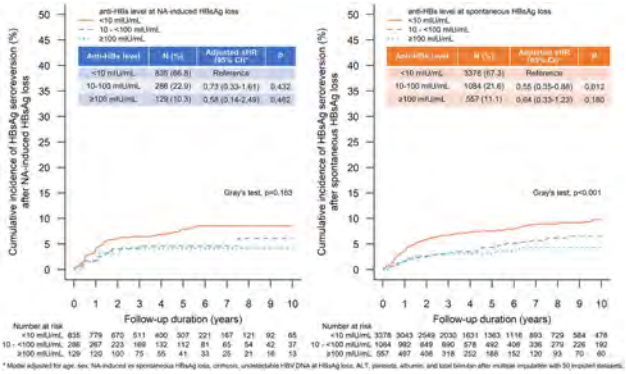
Disclosures: Jing Chen: Nothing to Disclose, Lin Jianmei: Nothing to Disclose

1354 | IMPACT OF HEPATITIS B SURFACE ANTIBODY (ANTI-HBS) LEVEL AT HEPATITIS B SURFACE ANTIGEN (HBSAG) SEROCLEARANCE ON LONG-TERM RISK OF HBSAG SEROREVERSION

Terry Cheuk-Fung Yip[1] Jimmy Che-To Lai[1] Mandy Lai[1] Vincent Wong[1] Henry Lik-Yuen Chan[2] Grace Lai-Hung Wong[1], [1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, [2]Department of Internal Medicine, Union Hospital, Hong Kong

Background: The impact of anti-HBs seroconversion and anti-HBs level at the time of HBsAg loss on the durability of nucleos(t)ide analogues (NA)-induced HBsAg loss remains unclear. We examined the role of anti-HBs status and level on the risk of HBsAg seroreversion in patients with chronic hepatitis B who achieved NA-induced HBsAg loss, with spontaneous HBsAg loss as a reference. **Methods:** A retrospective territory-wide cohort of adult patients with chronic hepatitis B virus monoinfection who achieved NA-induced or spontaneous HBsAg loss from 2000-2022 was identified from an electronic health database in Hong Kong. Patients with HBsAg loss after liver transplantation, no HBsAg test results after HBsAg loss, malignancies, and immunosuppressant use were excluded. Patients were followed from HBsAg loss to HBsAg seroreversion, 6 months after the last HBsAg test, death, last follow-up (Dec 31, 2024), or 10 years, whichever earlier, with death as a competing event. **Results:** Of 6,269 patients, 1,250 had NA-induced HBsAg loss (mean age 55 ± 13 years, 29% women, 8.4% cirrhosis, 33.2% positive anti-HBs); and 5,019 had spontaneous HBsAg loss (mean age 57 ± 13 years, 43% women, 1.8% cirrhosis, 32.7% positive anti-HBs). In 1,250 patients with NA-induced HBsAg loss, 891 continued to receive NA therapy for a median of 12.3 (IQR 5.9-24.6) months after HBsAg loss. At a median follow-up of 3.9 (2.1-7.1) years after HBsAg loss, 78 (6.2%) and 318 (6.3%) developed HBsAg seroreversion after NA-induced and spontaneous HBsAg loss, respectively. Positive anti-HBs at HBsAg loss was not associated with a lower risk of HBsAg seroreversion after NA-induced HBsAg loss (adjusted subdistribution hazard ratio [asHR] 0.71, 95% CI 0.37-1.35, $p = 0.291$) but was protective against HBsAg seroreversion after spontaneous HBsAg loss (asHR 0.58, 95% CI 0.40-0.86, $p = 0.006$). Compared to low-detectable anti-HBs level (10-100 mIU/mL), an anti-HBs level ≥ 100 mIU/mL was not associated with a further reduced risk of HBsAg seroreversion in patients with NA-induced HBsAg loss (asHR 0.80, 95% CI 0.15-4.31, $p = 0.791$) or spontaneous HBsAg loss (asHR 1.16, 95% CI 0.53-2.53, $p = 0.707$) (Figure). In patients with NA-induced HBsAg loss, undetectable HBV DNA at HBsAg loss (asHR 0.28, 95% CI 0.21-0.36) was associated with a lower risk of HBsAg seroreversion. **Conclusion:** Anti-HBs seroconversion does not add to the durability of NA-induced HBsAg loss. A higher anti-HBs level may not confer additional protection against HBsAg seroreversion.



Disclosures: Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Jimmy Che-To Lai: Nothing to Disclose, Mandy Lai: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company, Eli Lilly: Consultant, Merck: Consultant, Henry Lik-Yuen Chan: Aligos: Advisor, Arbutus: Advisor, Roche: Advisor, Virion: Advisor, Vaccitech: Advisor, Gilead: Speaking and Teaching, GSK: Advisor, Precision BioSciences: Advisor, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support

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1355 | QUANTITATIVE HBSAG LEVELS REMAINED ELEVATED WITH PROLONGED NUCLEOS(T)IDE ANALOGUE THERAPY OVER 10 YEARS

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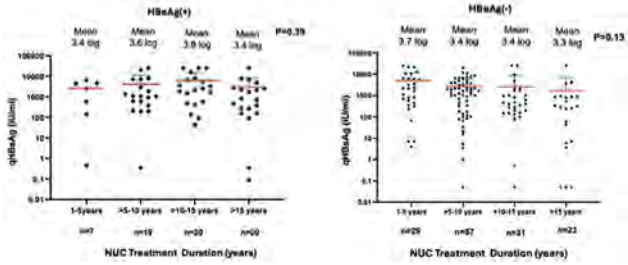
Background: The current treatment goal for chronic hepatitis B (CHB) is functional cure with HBsAg loss but it is seldom achieved with current nucleos(t)ide analogue (NUC) therapy. some patients on prolonged NUC may benefit from alternative treatment strategies. In this study, we evaluated the levels of quantitative HBsAg (qHBsAg) in both HBeAg (+) and (-) CHB patients with long-term NUC therapy. **Methods:** This is a retrospective study conducted at a single tertiary liver center. Patients who received NUC therapy for >1 year and achieved persistently undetectable (UD) or <10 IU/ml HBV DNA were selected. They must have qHBsAg by Quest Diagnostics at their last clinic visit. Most patients started therapy >5 years ago before qHBsAg was available in our center. Statistical analysis was by GraphPad Prism. **Results:** 206 [66 HBeAg (+), 140 HBeAg (-)] CHB patients with predominantly (91%) Asians were included. [Table 1] HBeAg (+) patients were younger, had higher pretreatment HBV DNA levels (6.8 vs 4.6 log IU/ml, $p<0.0001$), and longer treatment duration (11.9 vs. 9.1years, $p=0.0005$). Cirrhosis was present in 5 HBeAg(-) and none of the HBeAg(+) patients. 2 HBeAg(-) patients without cirrhosis had HCC after 2 and 8 years on NUC therapy respectively. There was a weak negative correlation ($r = -0.17$, $p=0.03$) between qHBsAg levels and treatment duration in the HBeAg (-) group but not in the HBeAg (+) group ($r = -0.06$, $p=0.62$). At last follow-up visit, 7 (5%) HBeAg(-) and 1 (1.5%) HBeAg(+) patients had qHBsAg <0.05 IU/ml but only 4 had UD qualitative HBsAg. Those had therapy for >15 years, the mean qHBsAg levels were 3.3 and 3.4 log IU/ml for HBeAg(-) and (+) patients respectively. [Figure] The mean and median qHBsAg values were similar for shorter treatment durations in both groups. HBsAg remained >1000 IU/ml after 1-5, >5-10, and >10 years of NUC therapy in 59%, 32%, and 32% of HBeAg(-); 57%, 58%, and 58% of HBeAg(+) patients respectively. Among the HBeAg(+) patients, 38 (58%) had HBeAg loss. The pretreatment HBV DNA levels were similar between those with (6.77 log) and without (6.99 log) HBeAg loss ($p=0.6$). The last follow up qHBsAg titers were also similar (3.45 log vs.3.7 log, $p=0.15$). **Conclusion:** After long-term continuous NUC therapy for greater than 10 years, qHBsAg remained >1000 IU/ml in over 30% and 50% of the HBeAg(-) and HBeAg(+) CHB patients despite optimal HBV DNA suppression. Only 8 (3.9%) patients achieved qHBsAg <0.05 IU/ml. These findings could inform patient selection for alternative treatment options as new therapeutic agents become available for definitive HBV control.

Table. Demographic and Clinical features

	HBsAg(-) (n=140)	HBeAg (+) (n=66)	P value
Male (n,%)	67 (47.9%)	30 (45.5%)	NS
Asian (n,%)	122 (87%)	65 (98%)	NS
Age (year; mean, range)	56.8 (33.7-80.9)	47.6 (32.4-70.3)	<0.0001
Pretreatment HBV DNA (log IU/ml; mean, range)	4.6 (1.5-8)	6.8 (3-9)	<0.0001
Pretreatment HBV DNA (log IU/ml) 1-5 years NUC >5-10 years NUC >10-15 years NUC >15 years NUC	(p=0.54) 4.4 4.5 5.1 4.1	(p=0.56) 6.8 7.2 7.3 5.9	
NUC treatment duration (year; mean, range)	9.1 (1.1-24.8)	11.9 (1.4-23.9)	0.0005
Pretreatment cirrhosis (n,%)	5 (3.6%)	0 (0%)	

Figure. qHBsAg levels by years on NUC therapy



Disclosures: Syed Bilal Shah: Nothing to Disclose, Saeed Ahmad: Nothing to Disclose, Ashraf Ullah: Nothing to Disclose, Nicole Lue: Nothing to Disclose, Umar Iqbal Javid Choudhary: Nothing to Disclose, NAEEM KHAN: Nothing to Disclose, Mati Ullah Dad Ullah: Nothing to Disclose, Daryl Lau: Gilead: Grant/Research Support, GSK: Consultant, Abbott Laboratories: Consultant

1356 | CHANGES IN CX3CR1 EXPRESSION IN DENDRITIC CELLS DURING INTERFERON INTERMITTENT THERAPY IN CHB PATIENTS

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Background: The emergence of a plateau phase characterized by slow decline in hepatitis B surface

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antigen (HBsAg) during Interferon (IFN) therapy represents a critical challenge contributing to suboptimal treatment outcomes. As central antigen-presenting cells initiating antiviral immunity, the functional status of dendritic cells (DCs) directly impacts the effectiveness of IFN therapy. The chemokine receptor CX3CR1 plays a pivotal role in DC migration to inflamed tissues and co-localization with T cells. This study aimed to investigate the association between the onset of the HBsAg decline plateau phase and the expression of CX3CR1 on peripheral blood DCs in patients with CHB receiving IFN therapy. **Methods:** Patients included were divided into CHB group (CHB without any antiviral treatment before), NAs group (treated with NAs) and P group (IFN treated and plateau arriving). After perfecting the baseline related examination, the patients in the P group were retreated with IFN after 12-24W of IFN intermission. For patients in the CHB group and NAs group at baseline; patients in P group at baseline when IFN was stopped, 12-24W of IFN intermission and 12-24W of IFN retreatment, the percentage of $CX3CR1^+$ DCs and the CX3CR1 MFI of $CX3CR1^+$ DCs were collected. **Results:** 49 patients in CHB group, 47 patients in NA group and 47 patients in the P group were included. At baseline, the percentage of $CX3CR1^+$ cells in pDC, the percentage of $CX3CR1^+$ cells in mDC and the CX3CR1 MFI of $CX3CR1^+$ mDC, the CX3CR1 MFI of $CX3CR1^+$ mDC2, the percentage of $CX3CR1^+$ cells in DN mDC and the CX3CR1 MFI of $CX3CR1^+$ DN mDC in the P group were significantly lower than those in the NA group and CHB group. 35 patients in P group were followed up for 12-24W of IFN intermission. The $CX3CR1^+$ cells in DN mDC and CX3CR1 MFI of $CX3CR1^+$ DN mDC increased significantly; 11 patients in the P group were followed up until 12-24W of IFN retreatment, and the data of three follow-up points were obtained. It was found that the percentage of $CX3CR1^+$ cells in DN mDC and CX3CR1 MFI of $CX3CR1^+$ DN mDC all showed a trend of increasing first and then decreasing. **Conclusion:** The plateau phase of slow HBsAg decline during IFN therapy in CHB patients may be associated with insufficient expression of CX3CR1 on peripheral blood DCs, particularly on CD141/CD1c double negative myeloid dendritic cells (DN mDCs).

Comparison between CHB group, NA group and P group

	CHB Group(n=49)	NA Group(n=47)	P Group(n=47)	Three Groups H	Three Groups P	CHB Group vs P Group P	CHB Group vs NA Group P	P Group vs NA Group P
mDC/Single cells(%)	0.347 (0.250, 0.540)	0.445(0.278, 0.629)	0.153 (0.097, 0.427)	18.316	0.000***	0.027*	0.401	0.000***
CX3CR1+mDC%	97.1(78.5,98.97.1)	91(73.25,99.65)	69.3(56.66,74.93)	36.106	0.000***	0.000***	0.356	0.000***
CX3CR1+mFI/DCMFI	13505.5(8430.20165.5)	12159(9962.15027)	4053(2908.3,4353)	84.143	0.000***	0.000***	1.000	0.000***
mDC1/Single cells(%)	0.00245 (0.0018025, 0.00569)	0.002185(0.001305, 0.0089215)	0.00275(0.00122,0.00433)	1.13	0.568	/	/	/
mDC2/Single cells(%)	0.127(0.048,0.141)	0.144(0.101,0.233)	0.114(0.084,0.212)	15.461	0.001***	0.042*	0.001***	0.343
CX3CR1+mDC2%	83.05(69.1,90.15)	80(69.9,92.75)	74.3(58.83,83.4)	4.788	0.091	/	/	/
CX3CR1+mFI/DC2MFI	8173.5(5376.5,9642.2)	8419(6124.5,362.5)	3781.5(2949.4,4177.8)	12.686	0.002**	0.002**	1.000	0.026*
DNmDC/Single cells(%)	0.270(0.133,0.429)	0.278(0.147,0.429)	0.055(0.017,0.157)	42.757	0.000***	0.000***	1.000	0.000***
CX3CR1+DNmDC%	90.45(79.33,95.78)	88.2(80.35,93.1)	21.55(13.63,36.38)	84.880	0.000***	0.000***	0.649	0.000***
CX3CR1+DNmDCMFI	17839(11199,24371)	10568(11680,23474)	4234(3262,5999)	82.426	0.000***	0.000***	1.000	0.000***
pDC/Single cells(%)	0.06(0.028,0.107)	0.144(0.068,0.237)	0.078(0.030,0.163)	21.563	0.000***	0.312	0.000***	0.001**
CX3CR1+pDC%	3.03(1.86,6.43)	1.96(0.79,4.06)	1.35(1.35,5.33)	5.788	0.034*	0.21	1.000	
CX3CR1+pDCMFI	3967(2754,4893)	3575(2796,4787)	3157(3604.25,3661.5)	5.866	0.053	/	/	/

*P < 0.05, **P < 0.01, ***P < 0.001

Disclosures: Minghui Li: Nothing to Disclose, Yao Xie: Nothing to Disclose, Liu Yang: Nothing to Disclose, weihua cao: Nothing to Disclose, Wen Deng: Nothing to Disclose

1357 | HEPATITIS B VIRUS REACTIVATION IN INFLAMMATORY BOWEL DISEASE PATIENTS ON BIOLOGICS: A SYSTEMATIC REVIEW OF RISK AND PREVENTION

Yu An Lin[1] Lan Nguyen[2] Mohammed Ayyad[1] Paul Gaglio[1], [1]Rutgers NJMS, [2]University at Buffalo

Background: Biologic therapies are widely used in inflammatory bowel disease (IBD), but hepatitis B virus (HBV) reactivation remains a concern, particularly in patients with chronic or resolved infection. While this risk is better characterized in other autoimmune conditions, data specific to IBD are limited. This systematic review therefore evaluates HBV reactivation risk in IBD patients on biologics, stratified by HBV serostatus, prophylaxis use, and biologic agent. **Methods:** We searched PubMed, Embase, and Scopus (1996–2024) for studies describing HBV reactivation in IBD patients receiving biologics. Of 1,489 screened articles, nine studies (seven full-text articles, two abstracts) were included, encompassing retrospective and prospective designs across diverse geographic regions. Extracted data included HBV serologic status, antiviral prophylaxis use, biologic agents, and reactivation outcomes. **Results:** Among patients with chronic HBV, reactivation was more frequent in the absence of prophylaxis (20/121, 16.5%). In resolved HBV cases, reactivation was rare (2/242, 0.8%) and occurred only without prophylaxis. Prophylaxis was associated with a lower incidence of reactivation: 80% (16/20) of reactivations occurred without it, while 20% (4/20) occurred despite it. All reported reactivations involved anti-TNF agents. Specifically, reactivations occurred in 11.1% (7/63) patients on infliximab and 7.7% (2/26) patients on adalimumab. Meanwhile, certolizumab (n = 6) and golimumab (n = 2) were less frequently used and not implicated in any reactivation. No reactivation was observed among the 17 patients treated with ustekinumab. Only two studies reported HBV screening prior to biologic initiation, with baseline testing applied in just 44.3% (5,425/12,244) of patients. Across four studies, prophylaxis was also underused, prescribed in only 45.1% (69/153) of chronic HBV patients despite elevated risk. **Conclusion:** IBD patients with chronic HBV infection face a measurable risk of reactivation during biologic therapy, especially without prophylaxis. Reactivation in resolved HBV is rare but possible. While anti-TNF agents were linked to all reactivation cases, data are insufficient to compare risk across biologic classes. Therefore, larger prospective studies are needed to clarify these risks and guide

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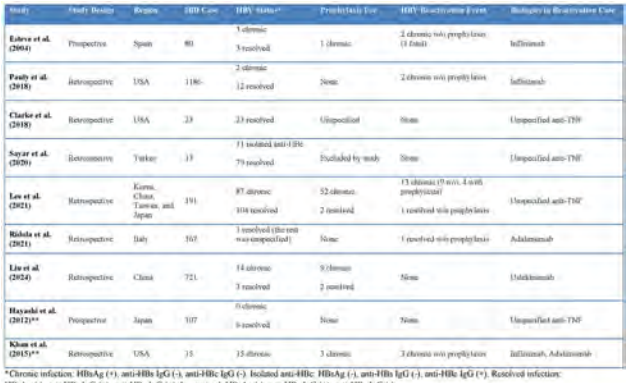
prevention strategies. Routine HBV screening and risk-based prophylaxis were underutilized, although they remain essential for safe biologic use in IBD, along with multidisciplinary coordination.



Study	Study Design	Region	IBD Case	HBV Status*	Prophylactic Use	HBV Reactivation Event	Biologics in Reactivation Case
Esteve et al. (2004)	Prospective	Spain	80	5 chronic 3 resolved	1 chronic	2 chronic w/o prophylaxis (1 fatal)	Infliximab
Pauly et al. (2018)	Retrospective	USA	1186	2 chronic 12 resolved	None	2 chronic w/o prophylaxis	Infliximab
Clarke et al. (2018)	Retrospective	USA	23	23 resolved	Unspecified	None	Unspecified anti-TNF
Sayar et al. (2020)	Retrospective	Turkey	13	71 isolated anti-HBc 79 resolved	Excluded by study	None	Unspecified anti-TNF
Lee et al. (2021)	Retrospective	Korea, China, Taiwan, and Japan	191	87 chronic 104 resolved	52 chronic 2 resolved	13 chronic (9 w/o, 4 with prophylaxis) 1 resolved w/o prophylaxis	Unspecified anti-TNF
Ribola et al. (2021)	Retrospective	Italy	167	3 resolved (the rest was unspecified)	None	1 resolved w/o prophylaxis	Adalimumab
Liu et al. (2024)	Retrospective	China	721	14 chronic 3 resolved	9 chronic 2 resolved	None	Ustekinumab
Hayashi et al. (2012)**	Prospective	Japan	107	0 chronic 6 resolved	None	None	Unspecified anti-TNF
Khan et al. (2015)**	Retrospective	USA	35	35 chronic	3 chronic	2 chronic w/o prophylaxis	Infliximab, Adalimumab

*Chronic infection: HBsAg (+), anti-HBs IgG (-), anti-HBc IgG (-). Isolated anti-HBc: HBsAg (-), anti-HBs IgG (-), anti-HBc IgG (+). Resolved infection: HBsAg (-), anti-HBs IgG (+), anti-HBc IgG (+). Immunized: HBsAg (-), anti-HBs IgG (+), anti-HBc IgG (-)
**Conference abstract only. Full text not available for data extraction

Table 1. Overview of included studies evaluating HBV reactivation risk in IBD patients on biologics

Disclosures: Yu An Lin: Nothing to Disclose, Lan Nguyen: Nothing to Disclose, Mohammed Ayyad: Nothing to Disclose, Paul Gaglio: Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Mallinkrodt: Speaking and Teaching

1358 | COMPARISON OF THE IMPACT OF TENOFOVIR ALAFENAMIDE AND ENTECAVIR ON HEPATITIS B SURFACE ANTIGEN DECLINE AND FACTORS INFLUENCING PARTIAL HBSAG RESPONSE AFTER 96 WEEKS OF CONTINUED THERAPY

shanfei ge[1] Yuliang Zhang[1] Shipeng Ma[1] Liang Wang[1] Xin Wan[1] Yulun Tang[1] Qian Liu[1], [1]The First Affiliated Hospital of Nanchang University

Background: Hepatitis B surface antigen (HBsAg) serological clearance is a critical therapeutic goal in the treatment of chronic hepatitis B (CHB). Although nucleos(t)ide analogues (NAs) suppress viral replication effectively, their impact on HBsAg loss remains suboptimal. Tenofovir alafenamide (TAF), a novel prodrug of tenofovir with improved hepatocyte delivery and one of the recommended first-line treatment for CHB has demonstrated favorable efficacy and safety profile. However, the comparative data on HBsAg levels between TAF and entecavir (ETV) remains limited. This study aimed to evaluate HBsAg decline and identify predictors of partial serological response after 96 weeks of ETV or TAF treatment in treatment-naïve CHB patients. **Methods:** This was a single-center retrospective study that enrolled treatment-naïve CHB patients initiated on ETV or TAF for at least 48 weeks from September 2019 to March 2025. Propensity score matching (PSM) was applied to balance baseline characteristics. HBsAg partial serological response was defined as a $\geq$ 1 log IU/mL decline from baseline. The precentage decline of HBsAg was calculated using the formula: (post-treatment HBsAg concentration - baseline HBsAg concentration) / baseline HBsAg concentration*100%. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of HBsAg partial serological response after 96 weeks. The area under the receiver operating characteristic curve (AUC) was used to evaluate the predictive value of these factors for HBsAg partial serological response. **Results:** After PSM, yielding 105 matched pairs in ETV and TAF treatment group. The baseline characteristics were well balanced between ETV and TAF groups ($P > 0.05$). At 48 weeks, the median percent decline of HBsAg was significantly higher in the TAF group compared to the ETV group [-2.53% (-10.13%, 0.24%) vs -4.92% (-14.23%, -1.78%), $Z = -2.55$, $P = 0.011$]. At 96 weeks, 17 out of 89 patients (19.10%) who continued ETV or TAF treatment achieved HBsAg partial serological response. Multivariate logistic regression showed that baseline HBsAg levels (OR = 278.70, 95% CI: 2.82–27552.73, $P = 0.016$) and the percent decline of HBsAg at 48 weeks (OR = 0.79, 95% CI: 0.64–0.96, $P = 0.021$) were independent predictors of achieving HBsAg partial serological response after 96 weeks of treatment. ROC analysis demonstrated that both baseline HBsAg levels (AUC = 0.913, 95% CI: 0.850–0.975, $P < 0.001$) and the percent decline of HBsAg at 48 weeks (AUC = 0.908, 95% CI: 0.814–1.000, $P < 0.001$) were strong predictors of HBsAg partial serological response at 96 weeks. **Conclusion:** Compared to ETV, TAF significantly reduced HBsAg levels. Baseline HBsAg levels and the percent decline of HBsAg at 48 weeks are independent and effective predictors of HBsAg partial serological response after 96 weeks treatment, supporting their role in guiding individualized CHB treatment strategies.
Disclosures: shanfei ge: Nothing to Disclose, Yuliang Zhang: Nothing to Disclose, Shipeng Ma: Nothing to Disclose, Liang Wang: Nothing to Disclose, Xin Wan: Nothing to Disclose, Yulun Tang: Nothing to Disclose, Qian Liu: Nothing to Disclose

1359 | OPTIMIZATION OF THE PREPARING PROTOCOL IMPROVES HUMAN HEPATOCYTE ENGRAFTMENT IN HUMANIZED MICE THAT SUPPORT HIGH INFECTION OF HBV

Junhao Liu[1] Zhenchuan Miao[1] Boyao Nie[1] Tianyu Zhang[1] Ziqian Yu[1] Binbin Yu[1] Yijuan Nie[1] Ming Yin[1] [1]Beijing Vitalstar Biotechnology Co., Ltd

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Background: Humanized liver mouse models are of significant value in studying human hepatocyte-specific functions and liver diseases. URG mice, which are highly immunodeficient mice with a TetOn-regulated uPA transgene, can be induced liver damage by expressing uPA gene specifically in the liver upon Doxycycline administration, allowing the engraftment of exogenous hepatocytes including human's. Although URG mice have the advantages of easy breeding, good health status, early experiments showed that the human hepatocyte replacement rate was rarely more than 50%, or the human serum albumin (HSA) content rarely exceeded 6 mg/mL. Despite continuous induction with Dox, the chimeric rate tended to decline after 8 weeks transplantation. Here reports that optimizing the protocol for preparing Hu-URG (URG mice transplanted primary human hepatocytes) significantly increased the chimerism that supports high infection of HBV. **Methods:** The Dox induction scheme after the transplantations in URG mice was changed from a fixed concentration of Dox in drinking water, intending to cause a chronic liver damage. The diet for URG mice was changed from breeding feed to a low-fat feed with $<4\%$ crude fat content. HSA content measurement and immunohistochemical staining were employed to exhibit the chimerism of human hepatocytes. Liver tissues were collected from five Hu-URG mice approximately 10 weeks post-PHH transplantation for RNA-seq analysis alongside PHHs. HuURG mice then were inoculated with different sources of HBV and detected for viral indicators in the serum and livers. **Results:** After optimization, the HSA contents in Hu-URG significantly increased, the highest up to 15 mg/mL. IHC analysis showed that the positive staining areas of human albumin, CK-18, CYP3A4, etc., in the liver sections could occupy up to 95%, and uniformly distributed in every lobe. In Hu-URG mice that did not change to low-fat diet, human hepatocytes usually accumulated a large amount of fat as showed in the sections, and became steatotic after 8 weeks of transplantation. The low-fat feed significantly reduced lipid droplet liver sections, and enable the HSA level stable nearly 12 months. HuURG mice were easily infected with HBV isolates either from clinical hepatitis B patient serum, HBV transgenic mouse serum, or HepAD38 cell culture supernatant, producing long-term high viremia. RNA-seq results indicate that in the livers of Hu-URG, the genes related to human drug-metabolizing enzymes, glucose metabolism, lipid metabolism, and coagulation factors are highly similar to those in PHHs in terms of both types and expression levels. **Conclusion:** The use of low-fat feed can improve the steatosis of engrafted human hepatocytes, increase chimerism and extend the stable period. The optimized Hu-URG mouse model supports long-term stable infection of various genotypes of HBV, providing an ideal in vivo model for HBV biological research and evaluation of anti-hepatitis B drugs.

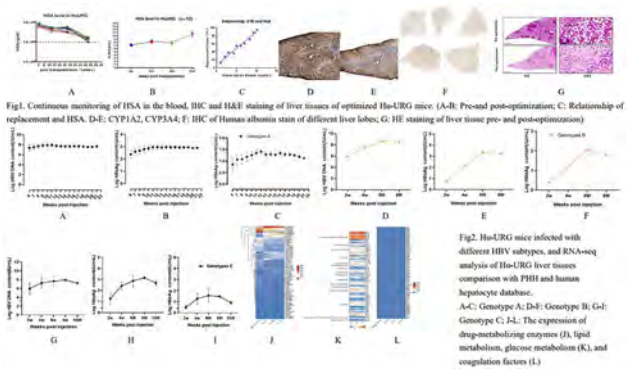

Fig1. Continuous monitoring of HSA in the blood, IHC and H&E staining of liver tissues of optimized Hu-URG mice. (A-B: Pre-and post-optimization; C: Relationship of replacement and HSA. D-E: CYP1A2, CYP3A4; F: IHC of Human albumin stain of different liver lobes; G: HE staining of liver tissue pre- and post-optimization)

Fig2. Hu-URG mice infected with different HBV subtypes, and RNA-seq analysis of Hu-URG liver tissues comparison with PHH and human hepatocyte database.
A-C: Genotype A; D-F: Genotype B; G-I: Genotype C; J-L: The expression of drug-metabolizing enzymes (J), lipid metabolism, glucose metabolism (K), and coagulation factors (L)

Disclosures: Junhao Liu: Nothing to Disclose, Zhenchuan Miao: Nothing to Disclose, Boyao Nie: Nothing to Disclose, Tianyu Zhang: Nothing to Disclose, Ziqian Yu: Nothing to Disclose, Binbin Yu: Nothing to Disclose, Yijuan Nie: Nothing to Disclose, Ming Yin: Nothing to Disclose

1360 | UNCOVERING THE OVERUSE: A HOSPITAL-WIDE ANALYSIS OF UNNECESSARY HBSAG RETESTING

Rahmet Guner[1] Ebrar GÜNEY[1] Imran Hasanoglu[1] Ahmet Sertçelik[1] Ayşe Kaya[1] Fatma Eser[1] Muge Ayhan[1] Bedia Dinç[1] Bircan Kayaaslan[1], [1]Ankara Bilkent City Hospital

Background: Achieving the global goal of viral hepatitis elimination requires not only effective screening strategies but also the rational use of healthcare resources. Despite clear diagnostic guidelines, repeated hepatitis B surface antigen (HBsAg) testing without clinical indication is frequently observed in hospital settings, potentially leading to increased laboratory burden, unnecessary costs, and misallocation of resources. **Methods:** This retrospective descriptive study analyzed all adult patients who underwent HBsAg testing at a tertiary care hospital between January 1, 2022, and December 31, 2023. Demographic characteristics and the number of test requests per patient were evaluated. In patients who had more than one HBsAg test, the time interval between repeat tests was calculated and stratified by the requesting clinical department. An interval of 14 days or less was considered potentially inappropriate based on clinical guidelines. Categorical data were reported as frequency, percentage, and odds ratio (OR) with 95% confidence intervals (CI); continuous variables were expressed as median and interquartile range (IQR). **Results:** Of the 558,730 patients tested for HBsAg, 45% were male. The median age was 45.0 years (IQR: 29.0–74.0). While the overall median number of HBsAg tests per patient was 1.0, 32.6% of patients underwent repeat testing, with one patient receiving as many as 40 tests. In this subgroup, a total of 331,386 HBsAg tests were ordered. Significant variation was observed in the frequency

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and timing of repeat testing across departments. Intensive care units had the highest proportion of early repeat tests (≤14 days) at 79.9% (OR: 10.59, 95% CI: 9.89–11.34), followed by neurology (70.5%, OR: 6.38), and pulmonology (65.3%, OR: 5.01). In contrast, departments such as ophthalmology (9.7%, OR: 0.29), ENT (12.3%, OR: 0.37), and microbiology (27.3%, reference group) had significantly lower early repeat testing rates. **Conclusion:** Our findings demonstrate a high rate of potentially unnecessary repeat HBsAg testing in several clinical departments, particularly in acute care settings. These practices contribute to inefficient resource utilization and may undermine efforts to streamline viral hepatitis screening. Interventions focused on clinician education, electronic test ordering restrictions, and audit-feedback mechanisms are needed to promote more judicious test use, reduce redundancy, and align with public health goals for hepatitis elimination.

Table 1. The distribution of time intervals between repeated HBsAg tests according to the requesting clinic in patients with more than one HBsAg test ordered

	n	Median interval(days)	Q1	Q3	≤14 days %*	>14 days %*	OR (%95 CI)
Intensive care units	20388	1,0	1,0	8,0	79,9	20,1	10,59 (9,89 – 11,34)
Neurology	3513	2,0	1,0	23,0	70,5	29,5	6,38 (5,82 – 6,99)
Pulmonary Diseases	3644	3,0	1,0	31,0	65,3	34,7	5,01 (4,58 – 5,48)
Psychiatry	587	7,0	1,0	99,0	56,2	43,8	3,42 (2,86 – 4,07)
Cardiovascular Surgery	3901	29,0	7,0	106,5	35,4	64,6	1,46 (1,33 – 1,61)
Physical Medicine and Rehabilitation	4112	33,0	3,0	145,0	38,0	62,0	1,64 (1,50 – 1,78)
Thoracic Surgery	885	35,0	17,0	76,0	20,9	79,1	0,70 (0,59 – 0,84)
Child and Adolescent Psychiatry	62	36,5	3,0	173,8	33,9	66,1	1,36 (0,80 – 2,32)
Emergency Medicine	91969	44,0	8,0	148,0	30,1	69,9	1,15 (1,08 – 1,22)
Pediatrics	7760	44,0	11,0	153,0	27,3	72,7	1,00 (0,93 – 1,08)
Neurosurgery	4084	48,0	24,0	146,0	16,2	83,8	0,51 (0,46 – 0,57)
Urology	15222	50,0	28,0	112,0	11,5	88,5	0,35 (0,32 – 0,37)
Pediatric Surgery	1374	52,0	21,0	141,0	18,9	81,1	0,62 (0,54 – 0,72)
Internal Medicine	77942	53,0	7,0	147,0	29,4	70,6	1,11 (1,04 – 1,18)
Cardiology	5052	58,0	14,0	181,0	24,3	75,7	0,86 (0,79 – 0,93)
General Surgery	24264	65,0	28,0	158,0	13,6	86,4	0,42 (0,39 – 0,45)
Radiation Oncology	303	68,0	34,0	154,0	9,6	90,4	0,28 (0,19 – 0,42)
Orthopedics and Traumatology	8231	75,0	35,0	169,0	11,8	88,2	0,36 (0,33 – 0,39)
Obstetrics and Gynecology	32651	78,0	26,0	180,0	15,3	84,7	0,48 (0,45 – 0,52)
Plastic, Reconstructive and Aesthetic Surgery	3032	79,0	26,0	210,8	15,5	84,5	0,49 (0,44 – 0,55)
Infectious Dis and Clinical Microbiology (ref.)	5569	83,0	10,0	172,0	27,3	72,7	1,00
Otorhinolaryngology	3064	83,0	35,0	196,0	12,3	87,7	0,37 (0,33 – 0,42)
Ophthalmology	8013	95,0	42,0	210,0	9,7	90,3	0,29 (0,26 – 0,31)
Anesthesiology	698	104,0	14,0	249,0	24,2	75,8	0,85 (0,71 – 1,02)
Dermatology	2960	113,0	56,0	208,8	9,8	90,2	0,29 (0,25 – 0,33)
Radiology	45	119,0	33,0	209,5	8,9	91,1	0,26 (0,09 – 0,73)
Family Medicine	1405	201,0	90,0	398,5	5,1	94,9	0,14 (0,11 – 0,18)
Occupational Medicine	782	247,0	129,8	385,3	3,6	70,8	<0,01
AVERAGE	331366	49,0	9,0	147,0	**28,4**	**71,6**	–

*Row percentage

Disclosures: Rahmet Guner: Nothing to Disclose, Ebrar GÜNEY: Nothing to Disclose, Imran Hasanoglu: Nothing to Disclose, Ahmet Sertçelik: Nothing to Disclose, Ayşe Kaya: Nothing to Disclose, Fatma Eser: Nothing to Disclose, Muge Ayhan: Nothing to Disclose, Bedia Dinç: Nothing to Disclose, Bircan Kayaaslan: Nothing to Disclose

1361 | RISK FACTORS FOR LOW VIRAL LOAD IN CHB PATIENTS RECEIVING NAS

Ziyi Zhang[1] Xijie Zhao[1] Rong Mu[1] Rongjiong Zheng[1] Xiaobo Lu[1], [1]The First Affiliated Hospital of Xinjiang Medical University

Background: Low viral load (LLV) refers to a situation where HBV DNA remains persistently or intermittently at a level of 20-2000 IU/mL in patients with chronic hepatitis B (CHB) after receiving first-line nucleoside (acid) analogues (NAs) treatment for at least 48 weeks. Studies have shown that LLV is associated with the progression of liver fibrosis and an increased risk of liver cancer, but the prevalence and risk factors of LLV in the real world remain unclear. This study aims to analyze the prevalence of LLV and its risk factors among CHB patients receiving NAs treatment. **Methods:** A total of 1,582 patients with chronic hepatitis B (CHB) who received standard first-line nucleos(t)ide analogues (NAs) (entecavir/tenofovir disoproxil fumarate/tonofovir alafenamide fumarate) for more than 48 weeks were retrospectively included. The patients were divided into the low-level viremia (LLV) group (HBV DNA 20 - 2000 IU/mL), the complete virological response (CVR) group (HBV DNA < 20 IU/mL), and the virological non-response group (HBV DNA ≥ 2000 IU/mL) based on the virological response at 48 weeks of treatment. Baseline clinical data were collected, and multivariate Logistic regression analysis was used to identify the risk factors for LLV. According to the research purpose, only the LLV group and the CVR group were included for comparative analysis. **Results:** A total of 1582 patients completed the follow-up. The mean age was (47.6 ± 11.6) years, with 61.3% being male. The mean hepatitis B virus DNA level was 5.3 Log10 IU/ml. The incidence of LLV was 19.72% (312/1582). The baseline HBV DNA level in the LLV group was significantly higher than that in the CVR group (6.61 ± 0.9 vs 5.12 ± 1.1 Log10 IU/mL, p < 0.001), but there were no statistical differences in gender, platelets, ALT, ALB, TBIL, AFP, etc. (p > 0.05 for all). Multivariate analysis showed that age > 50 years (OR = 1.53, 95% CI: 1.30-1.80, p = 0.001), baseline HBeAg positive (OR = 2.87, 95% CI: 1.80-4.57, p < 0.001), HBsAg ≥ 8000 IU/mL (OR = 2.73, 95% CI: 2.15-3.49, p < 0.001), and HBV DNA ≥ 6 Log10 IU/mL (OR = 1.41, 95% CI: 1.06-1.88, p=0.019) were independent risk factors for LLV. **Conclusion:** Patients over 50 years old, with high HBsAg/HBV DNA levels and HBeAg positivity significantly increase the risk of LLV after NAs treatment for CHB. It is necessary to strengthen virological monitoring for high-risk groups and explore optimized treatment strategies.

Disclosures: Ziyi Zhang: Nothing to Disclose, Xijie Zhao: Nothing to Disclose, Rong Mu: Nothing to Disclose, Rongjiong Zheng: Nothing to Disclose, Xiaobo Lu: Nothing to Disclose

1362 | THE BIDIRECTIONAL REGULATION BETWEEN USP20 AND HBSAG AND ITS POTENTIAL IMPACT ON HEPATITIS B VIRUS IMMUNE EVASION

Anxing Niu[1] Jin Liu[1] Wenhui Tu[2] Feng Qian[1] Li Zhu[1] Chuanwu Zhu[1], [1]The Affiliated Infectious Diseases Hospital of Soochow University, [2]Taizhou Municipal Hospital

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Background: The persistent expression of hepatitis B surface antigen (HBsAg) is a hallmark of chronic HBV infection and a major barrier to achieving functional cure. Research indicates that the host ubiquitination system regulates HBsAg stability, with ubiquitination promoting its proteasomal degradation, while the virus may counteract this by utilizing deubiquitinating enzymes (DUBs). However, the specific regulatory molecules (such as E3 ubiquitin ligases/DUBs), mechanisms of viral-host interactions, and epigenetic regulatory networks remain unclear. Understanding these mechanisms will provide a theoretical foundation for therapeutic strategies aimed at HBsAg degradation. This study aimed to identify key DUBs regulating HBsAg stability and elucidate the regulatory relationship between USP20 and HBsAg as well as its potential impact on HBV infection. **Methods:** A DUB overexpression library was screened in HepG2.2.15 cells. USP20-HBsAg interaction was validated via co-immunoprecipitation (Co-IP). USP20's regulatory effects on HBsAg stability were assessed through cycloheximide (CHX) chase experiments and ubiquitination assays. HBsAg-mediated USP20 degradation was examined using proteasome/lysosome inhibitors. NF-κB pathway activity was evaluated by measuring phosphorylated p65 (p-p65) levels in HMC3 cells. **Results:** USP20 was firstly identified as a specific DUB regulating HBsAg, and their interaction between USP20 and HBsAg was confirmed by Co-IP. USP20 upregulated endogenous (pHBV1.3-induced) and exogenous (Myc-HBsAg) HBsAg in a dose-dependent manner, while USP20 knockdown remarkably Inhibited HBsAg expression. USP20 overexpression prolonged the half-life of HBsAg, whereas USP20 knockdown accelerated its degradation, indicating that USP20 can stabilize HBsAg via deubiquitination pathway. Ubiquitination assays indicated that USP20 significantly inhibited polyubiquitination modification of HBsAg, and the effect could be reversed by knockdown of USP20 or the inhibitor GSK2643943A. HBsAg gradient transfection specifically downregulated USP20 (but not USP33, a member of the homologous family), and the regulation was independent of ubiquitin-proteasome or the autophagy-lysosome pathways. Functional experiments of NF-κB pathway showed that USP20 overexpression significantly enhanced the LPS-induced p-p65 levels, while HBsAg co-expression could inhibit this pathway activation by degrading USP20. **Conclusion:** This study reveals a bidirectional USP20-HBsAg regulatory axis: USP20 stabilizes HBsAg to promote viral persistence, while HBsAg degrades USP20 to inhibit NF-κB-driven antiviral immunity. Targeting this dynamic equilibrium may offer novel strategies for HBV functional cure.

Disclosures: Anxing Niu: Nothing to Disclose, Jin Liu: Nothing to Disclose, Wenhui Tu: Nothing to Disclose, Feng Qian: Nothing to Disclose, Li Zhu: Nothing to Disclose, Chuanwu Zhu: Nothing to Disclose

1363 | CHARACTERIZATION OF VARIOUS GENOTYPE HBV CARRIER MOUSE MODELS GENERATED BY AAV VECTOR DELIVERY

Zhenchuan Miao[1] Ming Yin[1], [1]Beijing Vitalstar Biotechnology Co., Ltd

Background: Functional cure (also known as clinical cure) is the ideal treatment goal recognized by the prevention and treatment guidelines for chronic hepatitis B (CHB). Hepatitis B virus (HBV) includes at least 8 genotypes and more variants, which cause different symptoms in infected individuals with different genetic backgrounds. To develop new effect drugs and realize personalized treatment for this disease, it is necessary to establish clinically relevant animal models of HBV infection. AAV-HBV mouse model prepared by injection of rAAV viral vectors carried the entire HBV genome demonstrate a good HBV carrier and useful in anti-HBV drug evaluation in vivo. According to previous studies, especially with genotype B, it's particularly difficult to maintain long-term stable virological indicators when constructing AAV-HBV.This study aims to compare the virological indicators, hepatic damage, and immune tolerance characteristics of models established by injecting different doses of AAV-HBV constructed with 1.3 fold length of HBV genome sequences of different genotypes into mice (especially with genotype B), in order to explore the implications of the models for hepatitis B research and new therapy development. **Methods:** Different doses of genotypes B, C, and D AAV-HBV were injected into C57BL/6 and immunodeficient NPG mice, and the levels of HBV DNA, HBsAg, HBeAg in serum of the mice were measured. **Results:** The levels of viremia indicators in the mouse models established by each type of AAV-HBV were dose-dependent. Genotype D AAV-HBV could establish a stable HBV carrier state at an injection dose even as low as 1E8 vg/mouse, while genotype C AAV-HBV could only maintain HBV viremia in immunocompetent mice at an injection dose more than 2E9 vg/mouse. Lower dose C-type AAV-HBV deliveries only sustained viremia for a few weeks in the mice, while in immunodeficient mice, HBV viremia remained stable. It was found difficult for Type-B AAV-HBV to establish a stable HBV infection state in immunocompetent mice even at dose of 1E11 vg/mouse, except for using a mutant Type-B HBV sequence. Interestingly, the highly immunodeficient mice (NPG) injected with 1E11 vgs of AAV-HBV of subtypes B/C/D, genotypes B and D easily maintained stable virological indicators, while genotype C was relatively difficult to sustain. **Conclusion:** The efficiency of establishing AAV-HBV mouse models varies with HBV genomes of different genotypes, and the levels of HBV viremia are related to the capacity of HBV antigens to induce immune tolerance, in addition

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to the viral replication efficiency. The decline in HBV virological indicators in the model is due to immune clearance. The ability of each genotype of HBV to induce immune tolerance in mice is in an order of D > C > B. The results suggest that the polymorphism of HBV antigens is related to the different clinical characteristics of hepatitis B.

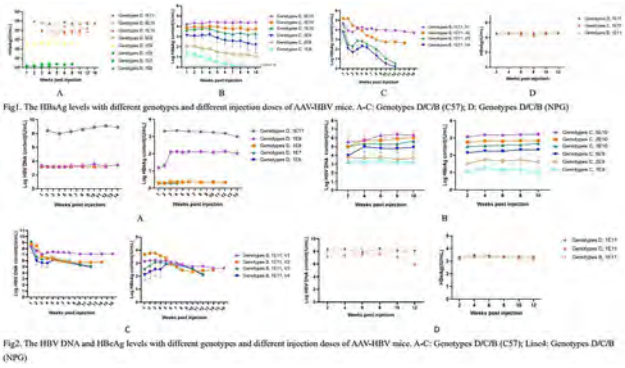


Fig1. The HBsAg levels with different genotypes and different injection doses of AAV-HBV mice. A-C: Genotypes D/C/B (C57); D: Genotypes D/C/B (NPG)

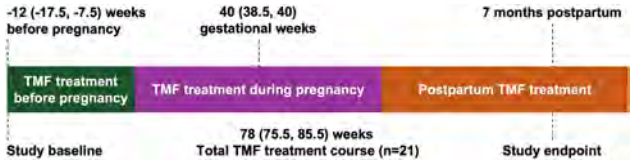
Fig2. The HBV DNA and HBeAg levels with different genotypes and different injection doses of AAV-HBV mice. A-C: Genotypes D/C/B (C57); Line4: Genotypes D/C/B (NPG)

Disclosures: Zhenchuan Miao: Nothing to Disclose, Ming Yin: Nothing to Disclose

1364 | SAFETY AND EFFECTIVENESS OF TENOFOVIR AMIBUFENAMIDE FOR PREGNANT WOMEN WITH CHRONIC HEPATITIS B

Ru-Yue Chen[1] Yan-Qin Ai[2] Ya-Jie Pan[1] Xue-Yan Lv[1] Yue-Hang Wang[1] Zhuang-Zhuang Zhai[1] Xue-Jing Yu[1] Qing-Lei Zeng[1], [1]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [2]Xuchang Central Hospital, Xuchang, Henan, China

Background: There are currently no studies on the safety and effectiveness of tenofovir amibufenamide (TMF) in pregnant women with chronic hepatitis B (CHB). This study aims to investigate the safety and efficacy of TMF in this population. **Methods:** The clinical data of women of childbearing age who took TMF tablet (25mg per day, orally after meals) and became pregnant were retrospectively collected from January 2022 to February 2025. The changes of hepatitis B virus (HBV) markers, biochemistry, blood routine and other parameters and adverse events were analyzed at baseline, during pregnancy, and within 7 months after delivery, and the infants' growth indexes at birth and 7 months of age and the effect of hepatitis B immunization were also analyzed. **Results:** This study included a total of 21 women of reproductive age and the 21 infants they gave birth to (Figure). (1) At baseline (pregnancy -12 [-17.5, -7.5] weeks), the median age, HBV DNA, and alanine aminotransferase (ALT) levels were 30 (25.5, 33) years, 6.9 (1.4, 7.9) $\log_{10}$ IU/mL, and 120 (53, 200) U/L, respectively. Among them, 17 cases were hepatitis B e antigen (HBeAg) positive. Routine blood tests, renal function, and other indicators were all normal. (2) During pregnancy, maternal HBV DNA and ALT levels gradually decreased, with median values at delivery of 0 (0, 0) $\log_{10}$ IU/mL and 17 (15, 27.5) U/L, respectively. Additionally, hemoglobin and serum creatinine levels showed a gradual decline, while the estimated glomerular filtration rate (eGFR) showed an increasing trend. (3) At 7 months postpartum, HBeAg seroconversion occurred in 3 cases (17.6% [3/17]), all patients had HBV DNA levels below the lower limit of detection (< 25 IU/mL), the median ALT level was 16 (13.5, 19) U/L, and hemoglobin, serum creatinine, and eGFR levels returned to baseline. (4) The main adverse events during maternal treatment were nausea (85.7% [18/21]), anorexia (61.9% [13/21]), and fatigue (42.9% [9/21]). The main complication was premature rupture of membranes (14.2% [3/21]). (5) At birth, the infants had a median gestational age of 38.5 (38.5, 40) weeks, with 12 males. There were no cases of preterm or post-term birth, no birth defects or malformations. The Apgar score at 1 minute after birth was 9 (9, 10). Growth indicators (height, weight, and head circumference) were all normal. All newborns received standard HBV immunoprophylaxis, and 11 (52.4%) were breastfed. (6) At 7 months of age, all infants had normal growth indicators, and all were hepatitis B surface antigen negative. The median level of hepatitis B surface antibody was 490 (222, 675) mIU/mL. **Conclusion:** This study preliminarily suggests that TMF treatment for pregnant women with chronic hepatitis B has favorable maternal and infant safety and effectiveness profiles. Combined with the hepatitis B immunization, it can successfully prevent HBV mother-to-child transmission. Future studies with larger sample sizes are needed to validate this conclusion.



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1365 | PERIOPERATIVE RISKS AND PREDICTORS OF COMPLICATIONS IN HBV-RELATED CIRRHOSIS PATIENTS UNDERGOING GYNECOLOGIC LAPAROSCOPY

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Background: Liver cirrhosis is a well-established risk factor for postoperative complications and liver-related mortality. However, data on the safety of gynecological laparoscopic surgery in cirrhotic patients remain limited, particularly in those with chronic hepatitis B (CHB). This study aimed to evaluate perioperative risks and complications in CHB-related cirrhotic patients undergoing gynecological laparoscopic surgery to inform clinical decision-making. **Methods:** This retrospective cohort study was conducted at a tertiary care university center in China between March 2012 and June 2024. CHB patients who underwent gynecological laparoscopic surgery during this period were included, excluding those with HIV or HCV coinfections. Cirrhotic and non-cirrhotic patients were matched 1:1 using propensity scores. Primary outcomes were perioperative and 30-day postoperative complications, including frequency and severity (Clavien-Dindo classification). Secondary outcomes included the identification of independent predictors of complications in cirrhotic patients through multivariate logistic regression of preoperative variables **Results:** A total of 94 patients were included, with a mean age of 52.5 years; 45.7% were postmenopausal. Baseline characteristics were comparable between groups, except for laboratory abnormalities, which were more frequent in the cirrhotic group (Table 1). The mean (SD) Child-Pugh score of cirrhotic patients was 6 ± 1 (43% classified as decompensated). The most common complications were pyrexia (12/94, 12.8%), abdominal distension (7/94, 7.4%), and external genital swelling (4/94, 4.3%). Postoperative complications occurred significantly more often in cirrhotic patients than in non-cirrhotic patients (40.4% [19/47] vs. 8.5% [4/47], $p < 0.01$). However, the rates of moderate to severe complications (Clavien-Dindo Grades II–IV) did not differ significantly between groups: Grade I (21.3% vs. 4.3%, $p = 0.01$), Grade II (14.9% vs. 2.1%, $p = 0.06$), and Grades IV–V (4.3% vs. 2.1%, $p > 0.99$). Notably, no complications were liver-specific. Elevated bilirubin levels and older age were independently associated with a higher frequency and severity of complications. **Conclusion:** Gynecological laparoscopic surgery in patients with HBV-related cirrhosis carries a higher risk of mild postoperative complications, particularly in patients with older age or elevated bilirubin. No liver-related mortality was observed. While the procedure appears generally safe, vigilant postoperative monitoring is warranted in this population.

Table 1. Clinical characteristics of the participants and liver cirrhosis status

Variables, mean ±SD or specified	Entire cohort (n=94)	Group A Cirrhosis (n=47)	Group B Non-cirrhotic (n=47)	*P*-value between groups A vs B
Age, years	52±8	52±8	53±8	0.91
BMI(≥24 kg/m²), n (%)	51 (54.3)	30 (63.8)	21 (44.7)	0.06
Post-menopause, n (%)	43 (45.7)	23 (48.9)	20 (42.6)	0.53
Hypertension, n (%)	23 (24.5)	11 (23.4)	12 (25.5)	0.81
Diabetes mellitus, n (%)	15 (16.0)	6 (12.8)	9 (19.1)	0.40
History of abdominal surgery, n (%)	40 (42.6)	23 (48.9)	17 (36.2)	0.25
Prothrombin time, second	13.4±2.0	12.4±2.3	10.8±1.3	<0.001
Prothrombin activity, %	88.6±15.3	80.5±15.3	96.8±10.1	<0.001
Platelets, x1 .000 µL	179.2±77.5	130.4±66.2	228.1±83.5	<0.001
Alanine aminotransferase, U/L	22±12	24±12	19±8	0.06
Aspartate aminotransferase, U/L	27±11	31±12	22±7	<0.001
Total bilirubin, mg/dl	17.5±10.0	22.1±12.4	12.8±5.5	<0.001
Albumin, g/L	40.4±4.7	38.7±5.2	42.1±3.3	<0.001
Globulin, g/L	28.5±4.6	29.6±4.9	27.4±4.0	0.02
Gamma-glutamyl transferase, U/L	37±25	34±31	20±12	0.094
Creatinine, µmol/L	51±8	49±7	52±8	0.07
Child-Pugh score	–	6±1	–	–
Decompensation of cirrhosis, n (%)	20 (21.3)	20 (42.6)	–	–
Type of surgery				0.94
Benign adnexal surgery of the uterus, n (%)	31 (33.0)	15 (31.9)	16 (34.0)	
Total hysterectomy ± adnexectomy, n (%)	55 (58.5)	28 (59.6)	27 (57.5)	
Lymph node dissection ± additional procedures, n (%)	8 (8.5)	4 (8.5)	4 (8.5)	

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1366 | HBSAG DECREASES IN A BIPHASIC MANNER AFTER LIVER TRANSPLANTATION AND HBIG MAINLY ENHANCES THE FIRST PHASE DECLINE

Leeor Hershkovich[1] Sara Battistella[2] Louis Shekhtman[1] Anna Pocurull[2] Thais Leonel[2] Sergio Rodriguez-Tajes[2] Yilliam Fundora[2] Sabela Lens[2] Sofía Pérez-Del-Pulgar[2] Scott Cotler[3] Harel Dahari[1] Xavier Forns[2], [1]Loyola University Chicago, [2]Liver Unit, Hospital Clínic, IDIBAPS, University of Barcelona, [3]Loyola University Health System

Background: Differences in HBsAg kinetics following liver transplantation (LT) between patients receiving nucleos(t)ide analogues (NUC) plus hepatitis B immunoglobulin (HBIG) and NUC alone have not been well characterized. Here we aim to mathematically model very frequent HBsAg kinetics during and after LT in patients treated with NUC with or without HBIG and assess the impact of HBIG on HBsAg kinetics. **Methods:** Between 2020 and 2023, 7 HBV LT recipients were prospectively enrolled. All patients were being treated with NUC preceding and after LT, of whom 3 patients additionally received HBIG during surgery and subsequently every 24 hours for 1 week

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after LT (Fig. 1). We developed a mathematical model to explain HBsAg clearance, and to explore the impact of HBIG on HBsAg clearance during graft reperfusion. The model includes an initial rate constant (c_0), an extended decline rate constant (c_{RP}), and a constant *k* controlling the transition from c_0 to c_{RP}. We further incorporated blood transfusion into our model to account for dilution of circulating HBsAg. **Results:** At the beginning of the anhepatic phase, the median HBsAg level was 1.32 log IU/mL (IQR 1.08-1.94). All four NUC alone patients had an insignificant change in HBsAg during the anhepatic phase (Fig 1A). One out of 3 HBIG patients had sufficient data during the anhepatic phase (Fig. 1B) and showed a significant decline (~1.2 log). Baseline HBsAg at the beginning of reperfusion was 1.11 log IU/mL (IQR 0.90-1.42). Six of the 7 participants experienced a decline in a biphasic manner, consisting of an initial rapid decline followed by a slower and continuous decline until reaching negativity (Fig. 1 C-D). Modeling indicated a shorter HBsAg $t_{1/2}$ in HBIG participants (median 0.8 [IQR 0.5-2.0] hours vs. 2.0 hours [IQR 1.2-5.4]), however the decline rate of the slower phase was not different, with a median $t_{1/2}$ of 96.5 hours. **Conclusion:** Participants receiving HBIG achieved HBsAg negativity quicker than those who did not (median 5 days vs 6 months). Our model suggests that HBIG has an impact at the beginning of reperfusion, increasing the slope and duration of the initial phase of HBsAg decline, allowing patients to reach negativity faster, although HBsAg became undetectable in all patients over time. The observed initial rapid HBsAg decrease immediately post-reperfusion can at least in part due to HBsAg removal from circulation by hepatocytes, whereas the 2nd slower decrease phase likely represents a more physiological clearance rate of HBsAg from circulation as estimated during drug perturbation (Fig. 1C-D, gray area).

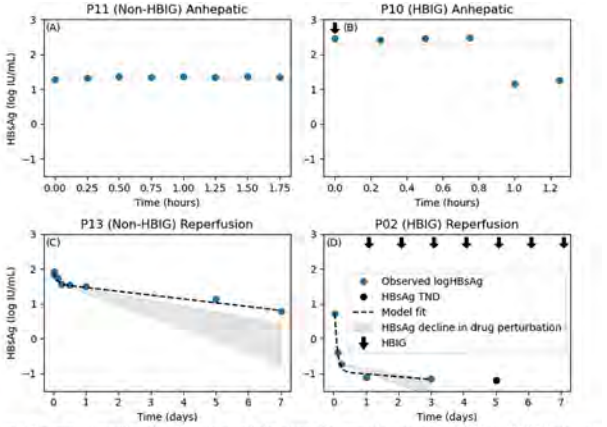

Figure 1: Representative patients for anhepatic/reperfusion phase of treatment (rows) and non-HBIG and HBIG (columns). Black arrows indicate timing of HBIG dosing, dashed line is the line of best fit in our mathematical model, and the gray area is the IQR of HBsAg estimated $t_{1/2}$ from a previous study (under anti-HBsAg drug perturbation of chronic infected patients) [PMID 32398799]. All participants were negative for or had very low levels of HBV DNA at the start of therapy (not shown).

Disclosures: Leeor Hershkovich: Nothing to Disclose, Sara Battistella: Nothing to Disclose, Louis Shekhtman: Nothing to Disclose, Anna Pocurull: Nothing to Disclose, Thais Leonel: Nothing to Disclose, Sergio Rodriguez-Tajes: Nothing to Disclose, Yilliam Fundora: Nothing to Disclose, Sabela Lens: Nothing to Disclose, Sofía Pérez-Del-Pulgar: Nothing to Disclose, Scott Cotler: Nothing to Disclose, Harel Dahari: Nothing to Disclose, Xavier Forns: Nothing to Disclose

1367 | EFFICACY OF NAS COMBINED WITH PEGIFNA-2B IN CHRONIC HEPATITIS B PATIENTS WITH / WITHOUT METABOLIC-RELATED FATTY LIVER DISEASE: A MULTICENTER, PROSPECTIVE REAL-WORLD STUDY

Guo Feng[1] Huxi baiheti[1] Dou Jing[1] Zeng Shengtao[2] Da Xin[3] Lu Xiaobo[4] Wu Yanqin[5] Maimaitiaili ·Tuerxun[6] Zhang Yongping[7] Wang Zhuanguo[1] Maimaitijiang ·Wubuliaishan[8] Wang Jun[9] Yue Yonghong[1] Wang Xiaobo[1] Chen Min[10] Ma Yan[1] Sayilaxi ·Jieensinue[1] Ning Zhonghui[1] Xu Qiang[1] Wang Hongfeng[1] Ni Ka[1] Ailifeire ·Abulajiang[1] Zhang Rong[1] WU Xu[11] Wang Xiaozhong[1], [1]Traditional Chinese Medical Hospital Affiliated to Xinjiang Medical University, [2]Yili Prefecture Xinhua Hospital, [3]Kelamayi Center Hospital, [4]The First Affiliated Hospital of Xinjiang Medical University, [5]Bazhou People's Hospital, [6]The First People's Hospital of Kashgar, [7]People's Hospital of Xinjiang Uygur Autonomous Region, [8]Hotan Infectious Diseases Hospital, [9]The First People's Hospital of Aksu Prefecture, [10]Changji Branch Hospital, First Affiliated Hospital of Xinjiang Medical University, [11]The Fourth Clinical Medical College of Xinjiang Medical University

Background: Functional cure is now an achievable and ideal goal of hepatitis B virus (HBV) treatment. However, the antiviral efficacy in chronic hepatitis B (CHB) patients with and without metabolic-related fatty liver disease (MAFLD) remains controversial. The purpose of this study was to evaluate the difference in hepatitis B surface antigen (HBsAg) clearance rate between CHB patients with and without MAFLD treated with PegIFNα-2b combined with NAs, and to provide a reference for clinical treatment. **Methods:** This is a prospective, multicenter, real-world clinical study. CHB patients with or without MAFLD treated with NAs for more than 6 months, HBeAg negative, HBsAg $\leq$ 1500 IU/mL, HBV DNA positive or negative, ALT $< 5 \times$ ULN were included. All patients were treated with PegIFNα-2b combined with NAs for 48 weeks. The primary outcome was the difference in HBsAg clearance rate between CHB patients with and without MAFLD at 48 weeks. Secondary outcome was the proportion of

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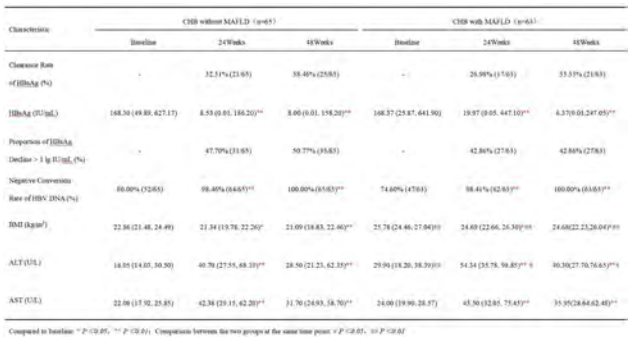
participants with HBsAg decline > 1 lg IU/mL. Other outcomes included the proportion of participants with HBV DNA undetectable, changes in body mass index (BMI), liver function biomarkers and blood routine. Safety was also assessed. **Results:** A total of 528 CHB patients with or without MAFLD from 10 centers were included in this study from December 1, 2022 to May 15, 2025. Of these, 128 patients (63 with MAFLD and 65 without MAFLD) had completed 48 weeks of treatment. The HBsAg clearance rates at 24 and 48 weeks were 26.98% (17/63) and 33.33% (21/63) in CHB patients with MAFLD, and 32.31% (21/65) and 38.46% (25/65) in CHB patients without MAFLD. The differences between the two groups were not statistically significant (all P values > 0.05). Both groups showed significant reductions in HBsAg levels from baseline to 24 and 48 weeks (all P values P values > 0.05). By week 48, the proportions of CHB patients with MAFLD and without MAFLD achieving an HBsAg decline > 1 lg IU/mL were 42.86% and 50.77%, respectively (P > 0.05). After 48 weeks of treatment, the proportion of patients with HBV DNA undetectable reached 100% in both groups. CHB patients with MAFLD had a higher baseline BMI and ALT compared to those without MAFLD, and BMI decreased significantly with prolonged treatment in both groups. ALT and AST in the two groups were significantly higher than baseline at 24 weeks (P > 0.05), and decreased at 48 weeks. **Conclusion:** MAFLD has no impact on HBsAg clearance in CHB patients treated with NAs combined with PegIFNα-2b.



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◆ 1368 | LINKING PERSONS WITH A HISTORY OF EXPERIENCING HOMELESSNESS TO HEPATITIS C VIRUS (HCV) TREATMENT BY ESTABLISHING DATA EXCHANGE BETWEEN A PUBLIC HEALTH HCV REGISTRY AND A HOMELESS SERVICES AGENCY — LOS ANGELES COUNTY, JANUARY–MAY, 2025

Prabhu Gounder[1] Jennifer Paul[2] Sophie Varma[1] Mirna Ponce Jewell[1] Heidi Behforouz[2], [1]Los Angeles County Department of Public Health, [2]Los Angeles County Department of Health Services

Background: In 2024, there were an estimated 75,312 persons experiencing homelessness (PEH) in Los Angeles (LA) County. One study estimated that 27% of PEH in the Skid Row area of LA had hepatitis C virus (HCV) infection. Although HCV is curable, it can be challenging to treat PEH until food and housing insecurity are addressed. Housing for Health (HFH) is a County program that provides supportive housing for PEH. We describe a pilot data exchange collaboration between LA County Department of Public Health (DPH) and HFH to identify and link PEH to HCV care. **Methods:** Clinical laboratories in LA are required to report positive anti-HCV antibody and all HCV polymerase chain reaction results to DPH; data management is conducted to relate all test results to unique persons to create a HCV registry. Persons with a positive anti-HCV antibody or PCR test and no corresponding negative PCR result classified as having potentially untreated HCV. We cross-referenced the DPH Countywide HCV registry with the HFH client list to identify persons with potentially untreated HCV. We worked with the assigned HFH case managers (CM) to reach out to clients interested in HCV treatment and make an appointment with their clinical provider. **Results:** In January 2025, we cross-referenced 26,073 HFH clients against the DPH HCV registry and identified 1,463 (6%) persons with potentially untreated HCV (1123 HCV PCR positive, 340 anti-HCV positive). Of the 104 HFH clients with untreated HCV who we targeted for initial outreach, 45 (43%) were unreachable because they were discharged from HFH before linkage with a provider or did not have an assigned CM. Of the 60 clients assessed by a CM, 18 (30%) declined treatment; 34 (81%) of 42 clients interested in treatment were linked to their provider, 8 (24%) of 34 clients linked to provider had a subsequent negative HCV PCR while 14

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(41%) initiated HCV treatment, and 6 (42%) of 14 clients initiating HCV treatment completed it as of May 2025. **Conclusion:** It is challenging to conduct phlebotomy in the street and treat HCV in unhoused persons. This pilot program demonstrated the potential for identifying PEH with HCV through data exchange with a Public Health HCV registry that eliminated the need for repeat testing for HCV screening/confirmation. Partnering with a County homeless services agency allowed for treating HCV by leveraging existing resources. This data-to-action model for partnering with Public Health to support linkage to HCV care can be adapted for other high prevalence populations who are disconnected from the health system, such as local jails or harm reduction clinics.

Disclosures: Prabhu Gounder: Nothing to Disclose, Jennifer Paul: Nothing to Disclose, Sophie Varma: Nothing to Disclose, Mirna Ponce Jewell: Nothing to Disclose, Heidi Behforouz: Nothing to Disclose

◆ 1369 | GLOBAL TREATMENT RATES AND IMPACT OF DIRECT-ACTING ANTIVIRALS (DAA) ON SURVIVAL AND CANCER RECURRENCE IN PATIENTS WITH HEPATITIS C VIRUS-RELATED HEPATOCELLULAR CARCINOMA (HCV-HCC): A SYSTEMIC REVIEW AND META-ANALYSIS OF 81 STUDIES AND 22,474 PATIENTS

Taotao Yan[1] Takanori Ito[2] Tsukasa Yasuda[2] Takaya Suzuki[2] Michael Le[1] Rui Huang[3] Yu Shi[4] Haruki Uojima[1] Vy Nguyen[1] Xiangrong Gao[1] Zhiwen Fan[1] Ramsey Cheung[1] Mindie Nguyen[1], [1]Stanford University Medical Center, [2]Department of Gastroenterology & Hepatology, Nagoya University Hospital, Nagoya, Japan, [3]Nanjing Drum Tower Hospital, [4]1Division of Gastroenterology and Hepatology, Stanford University Medical Center

Background: Direct-acting antivirals (DAAs) is recommended for all patients with viremic HCV infection except those with limited life expectancy. Data on DAA treatment rate and its impact on long-term clinical outcomes remains under-characterized. We aimed to estimate DAA treatment rates among HCV-HCC patients and compare the incidence of overall mortality and HCC recurrence in DAA-treated and untreated HCV-HCC patients using a systematic review and meta-analytic approach. **Methods:** We searched PubMed, Embase, and the Cochrane library for eligible studies from inception until Jan 15, 2025. Primary outcomes were the pooled proportion of HCV-HCC patients who received DAA at or after HCC diagnosis and the pooled incidence of overall mortality and HCC recurrence per 100 person-years by DAA treatment status in patients with HCV- HCC using random effect models. **Results:** We initially identified 3784 potential articles and included a total of 81 eligible studies (19 reporting on DAA treatment rate, 49 on overall survival, and 60 on HCC recurrence) involving 22,474 patients from 13 countries/regions. The pooled DAA treatment rate was 36.2% overall (95% CI 36.7-46.3%, $I^2 = 98.5\%$) among 12,771 HCV-HCC patients from 19 studies, with no significant difference by geographic region: 32.4% in America, 40.2% in Europe, 40.4% in Asia, and 35.7% in Africa ($P = 0.90$) (Table 1). In meta-regression adjusting for study year and study setting, HCC cure (vs. active HCC) was significantly associated with higher DAA treatment rate ($P = 0.04$). The pooled incidence of overall mortality was 5.2 (95% CI: 3.4–7.0; $I^2 = 94.3\%$) in 10,074 DAA-treated patients compared to 23.8 (95% CI: 13.4–34.1; $I^2 = 99.3\%$) in 7,468 untreated patients, $P < 0.001$; with similar trends in subgroup analyses among those with cirrhosis (2.8 vs. 16.7, $P = 0.003$), curative HCC (3.3 vs. 12.2, $P < 0.001$), and active HCC (20.9 vs. 57.5, $P = 0.09$). The pooled incidence of HCC recurrence based on data from both comparative and noncomparative studies was 17.9 (95% CI: 15.1-20.7; $I^2 = 96.4\%$) in 6,983 DAA-treated patients as compared to 20.8 (95% CI: 14.9-26.7; $I^2 = 99.3\%$) in 2,051 untreated patients, $P = 0.36$. However, the incidence of HCC recurrence was significantly lower in DAA-treated patients among 4,191 patients from 23 comparative studies (13.5 vs. 20.8, $P = 0.03$) and in 497 treated vs. 633 untreated propensity score matched patients from 6 of these studies (11.8 vs. 20.9, $P < 0.001$). DAA treatment was significantly associated with reduced overall mortality (pooled adjusted hazard ratio [aHR] 0.39) and reduced HCC recurrence (pooled aHR 0.47), both $P < 0.001$. **Conclusion:** DAA-treated HCV-HCC patients had 4 times lower overall mortality and about half HCC recurrence rates but only one-third across major world regions received this beneficial therapy, highlighting the need for better access to DAA prescription and treaters as well as increased patient and provider awareness.

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Table 1. Pooled DAA treatment rates in patients with HCV-related HCC, overall and in subgroups by study characteristics.

Population	Studies, n	Total participants, n	Treatment rate (95% CI), %	*P* value
Overall	19	12771	36.2 (26.7-46.3)	-
DAA initiation time				
Before HCC treatment	1	174	41.4 (34.2-48.8)	-
After HCC treatment	14	5753	34.0 (22.3-46.8)	-
After HCC cure	4	1512	41.6 (34.3-48.9)	-
Before LT	3	258	53.6 (36.6-70.1)	-
WHO region				0.90
America	6	9001	32.4 (15.0-52.8)	
Europe	3	576	40.2 (29.6-51.4)	
Africa	3	453	40.4 (16.7-66.8)	
Asia	7	2741	35.7 (18.3-55.4)	
Country/region				0.32
US	5	8204	29.5 (10.5-53.1)	
Italy	2	537	40.0 (24.4-56.6)	
Egypt	3	453	40.4 (16.7-66.8)	
Japan	4	832	48.0 (30.7-65.6)	
Taiwan	3	1909	20.7 (1.4-53.2)	
Other	2	836	47.8 (44.4-51.3)	
Country income level				0.73
High	16	12318	35.5 (25.0-46.7)	
Lower middle	3	453	40.4 (16.7-66.8)	
Sex				0.73
Female	12	3209	38.1 (24.4-52.9)	
Male	12	8561	34.9 (22.8-48.1)	
Cirrhosis				0.31
No	5	1777	24.7 (10.0-43.1)	
Yes	12	9060	36.1 (23.6-49.8)	
CTP grade				0.30
A	5	1094	46.5 (36.9-56.3)	
B/C	5	505	37.9 (25.7-50.8)	
HCC status				0.03
Curative	11	3080	44.1 (35.9-52.5)	
Active	4	1755	23.6 (2.0-55.4)	
Unknown	5	7237	20.5 (7.9-36.6)	
HCC therapy				<0.001*
No treatment	1	1419	18.5 (16.6-20.6)	
Palliative therapy	8	3706	36.4 (10.9-66.7)	
TACE/Y90	4	451	50.1 (2.9-97.4)	
Systemic therapy/Other	4	1835	22.0 (3.3-49.8)	
Curative therapy	15	3537	46.8 (39.6-54.1)	
Liver transplantation	5	1189	43.6 (27.4-60.4)	
Resection/Ablation	10	1980	49.6 (43.3-55.9)	

*P value for compare treatment rate by HCC therapy (no treatment vs. palliative therapy vs. curative therapy).

Abbreviations: DAA, Direct-acting antivirals; HCV, Hepatitis C virus; HCC, Hepatocellular carcinoma; LT, liver transplantation; CTP, Child-Turcotte-Pugh; TACE, Transcatheter arterial chemoembolization; Y90, Yttrium-90 radiation therapy.

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◆ 1370 | NATIONAL POPULATION-BASED HEPATITIS C SCREENING AND ELIMINATION PROGRAMME IN LITHUANIA: WHAT RESULTS: HAVE WE ACHIEVED?

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Background: In Lithuania National HCV screening program started in May, 2022. General practitioners (GPs) received special promoting fee for serological HCV antibody testing: 1. For people born between 1945 and 1994 (once in a lifetime) and 2. For people who inject drugs (PWID) or HIV-positive people (annual testing). This initiative is the first in Central and Eastern Europe. The aim of this study was to assess the results of the first 34 months of the programme and evaluate the different scenarios for achieving the WHO 2030 targets. **Methods:** GPs invited people to perform a serum blood test for HCV antibodies. Anti-HCV+ patients were referred to a gastroenterologist or infectologist for HCV RNA testing, and if result was positive, direct-acting antiviral (DAA) therapy was prescribed. Information about patients was obtained from the National Health Insurance Fund. The Markov disease progression model elaborated by the CDA Foundation was used to assess HCV elimination progress. The data from the 2022-2023 screening were used as inputs. Three scenarios were developed: the 'Base' scenario - return to pre-screening program level in 2023 and 2 scenarios with different extents of treatment. **Results:** At the beginning of 2022, about 1.8 million people born in 1945-1994 lived in Lithuania. Between May 5, 2022 and February 28, 2025, from this population 1362472 people (75.7%) were tested for HCV antibodies. Anti-HCV+ were found in 1.28% of cases. In the risk group, 8396 PWID and/or HIV+ people were screened, of whom 28.9 % were seropositive. Among anti-HCV+ persons 83.8% was from population and 16.2 % from risk groups. Specialists consulted 58% anti-HCV+ persons and viremia was detected in 53,1 %. Among anti-HCV+ persons from population specialist consulted 63%, but only 29% from risk group ($p < 0.001$). During 34-month (May 2022- February 2025) period 3 times more HCV patients were treated with DAA than during the same period before starting of the program (7577 vs 2470). The Markov disease progression model to assess HCV elimination progress showed the following scenarios: Scenario 1: if the same number of patients are treated as before the screening, the WHO targets will not be reached. Scenario 2: treating 70% of infected patients will meet most but not all WHO targets. Scenario 3: by treating all infected patients by 2030, the WHO target will be met by saving 150 lives and preventing 90 new cases of decompensated cirrhosis and 120 cases of hepatocellular carcinoma. **Conclusion:** In a European country with a moderate HCV seroprevalence, a population-based screening program is feasible and the number of patients treated has increased more than 3-fold in the first 34 months. Current status of the program predict that till 2030 country will meet most but not all WHO targets (the second scenario). Special measures to increase motivation and compliance of risk group patients to

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program logistic are necessary to achieve all WHO 2030 targets in Lithuania.

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◆ 1371 | THE IMPACT OF VIRAL CLEARANCE BY DIRECT-ACTING ANTIVIRAL ON PROGNOSIS AND LIVER-RELATED EVENTS IN HEPATITIS C VIRUS-RELATED DECOMPENSATED CIRRHOSIS

Yuki Tahata[1] Hayato Hikita[1] Yoshihito Uchida[2] Atsunori Tsuchiya[3] Seiichi Mawatari[4] Hidekatsu Kuroda[5] Daiki Miki[6] Nobuharu Tamaki[7] Yoichi Hiasa[8] Masaru Enomoto[9] Goki Suda[10] Taro Yamashita[11] Hiroshi Yatsuhashi[12] Hitoshi Yoshiji[13] Masato Nakamura[14] Taro Takami[15] Hisamitsu Miyaaki[16] Yasuhiro Asahina[17] Kanji Yamaguchi[18] Kentaro Matsuura[19] Ryosuke Tateishi[20] Yasunari Nakamoto[21] Eiji Kakazu[22] Shuji Terai[23] Masahito Shimizu[24] Yoshiyuki Ueno[25] Norio Akuta[26] Takahiro Kodama[1] Tomomi Yamada[27] Tetsuo Takehara[28], [1]Osaka University Graduate School of Medicine, [2]Saitama Medical University, [3]Faculty of Medicine, University of Yamanashi, [4]Kagoshima University Graduate School of Medicine and Dental Sciences, [5]Iwate Medical University, [6]Graduate School of Biomedical and Health Sciences, Hiroshima University, [7]Musashino Red Cross Hospital, [8]Ehime University Graduate School of Medicine, [9]Osaka Metropolitan University, [10]Graduate School of Medicine, Hokkaido University, [11]Kanazawa University, [12]National Hospital Organization Nagasaki Medical Center, [13]Nara Medical University, [14]Graduate School of Medicine, Chiba University, [15]Yamaguchi University Graduate School of Medicine, [16]Nagasaki University of Graduate School of Biomedical Sciences, [17]Institute of Science Tokyo, [18]Graduate School of Medical Science, Kyoto Prefectural University of Medicine, [19]Nagoya City University Graduate School of Medical Sciences, [20]The University of Tokyo, [21]Faculty of Medical Sciences, University of Fukui, [22]National Center for Global Health and Medicine, [23]Niigata University, [24]Gifu University, [25]Yamagata University, [26]Toranomon Hospital, [27]Osaka University Hospital, [28]Kansai Rosai Hospital

Background: Sustained virologic response (SVR) can be achieved by direct-acting antiviral (DAA) therapy in approximately 90% of patients with hepatitis C virus (HCV)-related decompensated cirrhosis. However, the impact of SVR on prognosis and liver-related events in this population remains unclear. **Methods:** A total of 206 patients with HCV-related decompensated cirrhosis who initiated 12-week sofosbuvir and velpatasvir (SOF/VEL) therapy between February 2019 and December 2021 at 31 Japanese institutions were included. Decompensated cirrhosis was defined as Child-Pugh class B (CP-B) or CP-C, or CP-A with a history of decompensating events. The observation period began at the initiation of SOF/VEL. We evaluated liver transplantation (LT)-free survival, cumulative incidence of decompensating events requiring hospitalization, and de novo hepatocellular carcinoma (HCC). Decompensating events were defined as ascites, encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, sepsis and acute kidney injury. SVR was defined as undetectable serum HCV-RNA at 12 or 24 weeks after the end of therapy (EOT). **Results:** The median age was 68 years; 9.7%, 75.7%, and 14.6% of patients were CP-A, CP-B and CP-C, respectively. The SVR rate was 91.3%. During a median follow-up of 43.7 months from the start of SOF/VEL, 44 patients died (19 liver failure, 10 HCC, 2 variceal bleeding, 13 non-liver-related causes), and 4 underwent LT. The 3- and 5-year LT-free survival rates were 82.9% and 69.0%, respectively. Multivariate Cox proportional hazard analysis identified virologic response and CP class at 12 weeks after the EOT as significant factors. The 3-year LT-free survival rates were 86.2% and 50.0% in patients with SVR and virologic failure, respectively ($p = 0.001$). Decompensating events occurred in 51 patients (ascites was the most common event), with 3- and 5-year incidence rates of 21.8% and 32.0%. In multivariate Cox proportional hazard, virologic response, baseline variceal status, and CP class were significant predictors; the 3-year incidence rates were 19.7% and 68.7% in patients with SVR and virologic failure, respectively ($p = 0.008$). Among 117 patients without prior HCC, 26 developed de novo HCC, with a 3-year cumulative incidence of 17.4%. In multivariate Cox proportional hazard analysis, baseline AFP level was significant, while virologic response was not. The 3-year HCC incidence rates were 17.0% and 25.0% in patients with SVR and virologic failure, respectively ($p = 0.292$). **Conclusion:** In patients with HCV-related decompensated cirrhosis, viral clearance through DAA therapy was associated with improved LT-free survival and a reduced incidence of decompensating events. However, the development of HCC may still occur in SVR patients, and careful surveillance is required.

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Hiasa: Nothing to Disclose, Masaru Enomoto: Nothing to Disclose, Goki Suda: Nothing to Disclose, Taro Yamashita: Nothing to Disclose, Hiroshi Yatsuhashi: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose, Masato Nakamura: Abbvie: Speaking and Teaching, Kowa company: Speaking and Teaching, Astellas Pharma: Speaking and Teaching, Taro Takami: Nothing to Disclose, Hisamitsu Miyaaki: Nothing to Disclose, Yasuhiro Asahina: Nothing to Disclose, Kanji Yamaguchi: Nothing to Disclose, Kentaro Matsuura: Nothing to Disclose, Ryosuke Tateishi: EA Pharma: Speaking and Teaching, MSD: Speaking and Teaching, Aska Pharma: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Abbvie: Speaking and Teaching, Eisai: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Covidien: Speaking and Teaching, Bayer: Speaking and Teaching, Century Medical: Speaking and Teaching, Canon Medical: Speaking and Teaching, Asahikasei Pharma: Speaking and Teaching, Terumo: Speaking and Teaching, TechsoMed: Speaking and Teaching, Sumitomo Pharma: Speaking and Teaching, Taisho Pharmaceutical: Speaking and Teaching, Daiichi-Sankyo: Speaking and Teaching, Chugai: Speaking and Teaching, Fujifilm: Speaking and Teaching, Yasunari Nakamoto: Nothing to Disclose, Eiji Kakazu: Nothing to Disclose, Shuji Terai: Nothing to Disclose, Masahito Shimizu: Nothing to Disclose, Yoshiyuki Ueno: Abbvie Inc: Speaking and Teaching, Eisai Inc: Speaking and Teaching, Chugai Pharmatheutical: Speaking and Teaching, Norio Akuta: Nothing to Disclose, Takahiro Kodama: Nothing to Disclose, Tomomi Yamada: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

◆ 1372 | MOLECULAR CONVERGENCE OF POST-SVR HEPATOCELLULAR CARCINOMA WITH MASLD/MASH- AND ALD-ASSOCIATED HCC

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Background: In hepatitis C patients, the contribution of metabolic factors—linked to MASLD/MASH—to hepatocarcinogenesis remains poorly understood, particularly after viral eradication. We compared gene profiles of hepatocellular carcinoma (HCC) between HCV-SVR, steatotic liver disease (SLD), and HCV-non-SVR patients. **Methods:** This study analyzed 126 resected HCCs from patients with HCV and SLD, classifying them as HCV-SVR (n = 22), HCV-non-SVR (n = 56), and SLD (n = 48). Deep sequencing of 2910 hotspots in 55 cancer-related genes was conducted to examine mutations and copy number variations in both cancerous and background liver tissues. **Results:** The HCV-SVR group comprised more patients who consumed alcohol (45.5% vs. 15.7%, p = 0.008); were obese (54.5% vs. 17.9%, p = 0.002); and had dyslipidemia (18.2% vs. 3.6%, p = 0. 029) and hyperuricemia (18.2% vs. 3.6%, p = 0.029) than HCV-non-SVR group. Mutational profiling of the HCV-SVR HCC showed significantly lower alteration rates of *AXIN1* (13.6% vs. 42.9%, p = 0.016), *ARID2* (9.1% vs. 39.3%, p = 0.013), and *TP53* (9.1% vs. 32.1%, p = 0.030) than HCV-non-SVR patients. Compared with HCV-non-SVR-HCC, SLD-HCCs exhibited significantly lower rates of *TERT* promoter mutations (62.5% vs. 85.7%, p = 0.004); *ARID2* alterations (12.5% vs. 39.3%, p = 0.003); and *AXIN1* alterations (12.5% vs. 42.9%, p = 0.002). HCV-SVR/MASH/MASLD/ALD-HCC had significantly lower alteration rates of the Wnt/β-catenin (41.4% vs. 60.7%, p = 0.048) and chromatin remodeling pathways (27.1% vs. 48.2%, p = 0.026) than HCV-non-SVR-HCC. Furthermore, shorter disease free survival was significantly associated with *AXIN1* alteration (HR 0.43, p = 0.003); Wnt/β-catenin pathway alteration (HR 0.49, p = 0.005); tumor number ≥ 2 (HR 0.44, p = 0.004); TMN stage (p = 0.014); vascular invasion (HR 0.43, p = 0.001); differentiation (p = 0.014); and serum DCP level (HR 1.00, p < 0.001) in 102 patients who underwent hepatectomy as the initial curative treatment for primary HCC. **Conclusion:** HCC that develops ≥ 5 years after SVR was associated with features of metabolic disease and SLD in the nontumorous liver. Furthermore, our comprehensive genetic analysis revealed that the genetic features of HCV-SVR HCC were similar to those of MASH/MASLD-HCC and ALD-HCC. These findings suggested that these diseases share molecular subtypes and that the treatment response may be strongly associated with hepatic steatosis and cardiometabolic factors.

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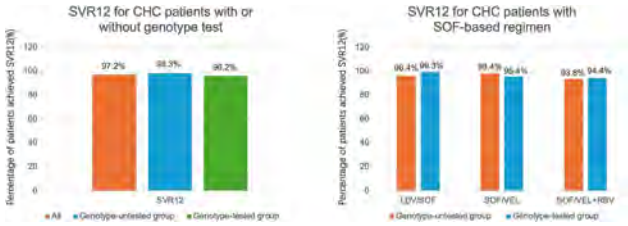
◆ 1373 | SOFOSBUVIR-BASED REGIMEN ACHIEVED HIGH VIROLOGICAL RESPONSE IN NON-GENOTYPED HCV PATIENTS FROM A GENOTYPE 3 HIGH-PREVALENCE REGION OF SOUTHWEST CHINA: A RETROSPECTIVE COHORT STUDY (SAIN-C)

Liu Li[1] Mei Li[2] Rui-Ling Liu[3] Fu-Zhen Xie[4] Ming Fang[2] Xing-Qiang Gao[5] Li-Hua Li[6] Chun-Xia Dao[7] Rui-Ling Hui[8] Chang-Xian Lu[9], [1]Kunming Third People's Hospital, Yunnan Province, China, [2]Fuyuan County People's Hospital, Yunnan Province, China, [3]Xuanwei People's Hospital, Yunnan Province, China, [4]Gengma County People's Hospital, Yunnan Province,China, [5]Luoping County People's Hospital, Yunnan Province, China, [6]Xishuangbanna People's Hospital, Yunnan Province, China, [7]Menglian County People's Hospital, Yunnan Province, China, [8]Qujing First People's Hospital, Yunnan Province, China, [9]Lincang People's Hospital, Yunnan Province, China

Background: To leverage a simplified strategy without genotype test in high-prevalence regions of hepatitis C virus (HCV) genotype 3 (GT3) infection, and explore the efficacy of sofosbuvir(SOF)-based regimen for chronic hepatitis C (CHC) patients with unknown genotypes. **Methods:** CHC patients who visited hospitals including Kunming Third People's Hospital in Yunnan province were retrospectively included. Patients were treated with Sofosbuvir/Velpatasvir (SOF/VEL) or Ledipasvir/Sofosbuvir (LDV/SOF) ± Ribavirin(RBV) for 12 weeks. The sustained virological response after 12 weeks of follow-up after the end of treatment(SVR12) between genotype-tested and the untested group were compared. **Results:** From January 2022 to December 2024, a total of 2445 cases were enrolled from 9 hospitals including 4 county-level primary hospitals and 5 city-level hospitals. Baseline characteristics: average age of 52.6 ± 15.4 years, with 1295 males (53.0%) and 2066 farmers (84.5%). 1208 cases (49.4%) were in the untested genotype group. Mean level of HCV RNA was 6.08 ± 1.09 IU/mL. 64 cases (2.6%) already had cirrhosis before treatment initiation. After 12 weeks off-treatment, totally 2377 cases achieved SVR12 (97.2%), with 1187 cases in genotype-untested group (98.3%) and 1190 cases in genotype-tested group(96.2%). No significant difference could be found between two groups. For patients with SOF/VEL, 97.1%(1941/1998) achieved SVR12, including 98.4%(1145/1164) in genotype-untested group and 95.4% (796/834) in genotype-tested group . For SOF/VEL+RBV regimen, 97.1% achieved SVR12, with 98.4% (1145/1164) in genotype-untested group and 95.4%(796/834) in genotype-tested group. For patients treated with LDV/SOF, SVR12 rate was 99% (304/307), with 96.4% (27/28) in genotype-untested group and 99.3%(277/279) in genotype-tested group . **Conclusion:** SOF-based regimen could achieve high SVR regardless of genotype testing, even in high-prevalence regions of HCV GT3 infection. We believe this simplified strategy could be considered for genotype testing unavailable areas.



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◆ 1374 | OUTCOMES OF DIRECT ACTING ANTIVIRAL AGENTS IN CHRONIC HEPATITIS C PATIENTS WITH PRE-EXISTING HEPATOCELLULAR CARCINOMA

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Background: Chronic hepatitis C (CHC) is a significant global health issue and a well-known risk factor for hepatocellular carcinoma (HCC). The advent of direct-acting antivirals (DAAs) has revolutionized hepatitis C treatment by achieving high rates of viral clearance and improving liver function. However, the benefits of DAAs for patients with pre-existing HCC—particularly regarding recurrence, progression, and overall survival—remain controversial. The aim of our study was to assess the outcome of various direct acting antiviral agents for CHC patients with pre-existing HCC. **Methods:** In this real-world observational study, we recruited chronic hepatitis C patients with pre-existing HCC who was treated with DAAs after diagnosis of HCC. Patients were administered various DAAs; daclatasvir+asunaprevir, sofosvubir+ribavirin, sofosbuvir+daclatasvir, ledipasvir/Sofosbuvir ± ribavirin, ombitasvir/Paritaprevir/Ritonavir and Dasabuvir ± Ribavirin, glecaprevir/pibrentasvir, velpatasvir/Sofobuvir ± ribavirin. The primary efficacy endpoint was sustained virological response at post-treatment week 12 (SVR12). Adverse events (AEs) during treatment, overall survival, HCC recurrence after HCV treatment was also evaluated. **Results:** This study included 105 patients (mean age, 67 ± 9.87, male, n = 67) with HCV

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genotypes 1b (n = 64), 2 (n = 41). 17.1% (n = 18) had a Child-Pugh score of B. BCLC HCC stage is A in 68, B in 28 and C in 9 patients and 41 (39%) patients have viable HCC at the start of HCV treatment. Thirty-one patients had prior HCV treatment experience, including 25 with interferon based treatment, 5 with DAAs. SVR12 rates were 92.3% (ITT, 97/105) and 93% (mITT, 94/101). SVR12 for each DAAs was shown Table 1. AEs occurred in four patients but improved with symptomatic treatment. HCC was recurred or progressed during or after DAAs treatment in 80 patients and median time to progression was 10.8 months (95% CI, 3.01-18.59) months). Overall survival after DAAs treatment was 66.7% and median survival was 81.2 months (95% CI 62.41-99.99). In multivariate analysis, viable HCC at the start of HCV treatment (p = 0.003), BCLC HCC stage (p = 0.015) and ribavirin use (p = 0.001) are significantly associated with overall survival. **Conclusion:** This study demonstrated that the DAAs achieved favorable treatment outcomes and was well tolerated in CHC patients with pre-existing HCC. HCC tumor stage, presence of viable HCC and ribavirin use was significantly associated with survival.

Table 1. SVR12 in each direct acting antiviral agents

	SVR12, % (N)	SVR12, % (N)
daclatasvir+asunaprevir	91.7 (22/24)	91.7 (22/24)
sofosvubir+ribavirin	78.9 (15/19)	78.9 (15/19)
ledipasvir/Sofosbuvir ±ribavirin	75 (6/8)	100 (6/6)
sofosbuvir+daclatasvir	87.7 (7/9)	88.9 (7/8)
ombitasvir/Paritaprevir/Ritonavir and Dasabuvir ± Ribavirin	100 (10/10)	100 (10/10)
glecaprevir/pibrentasvir	100 (13/13)	100 (13/13)
velpatasvir/Sofobuvir ± ribavirin	100 (20/20)	100 (20/20)

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◆ 1375 | OCCULT HEPATITIS C VIRUS INFECTION ACCELERATES NON-HEPATOCELLULAR CANCER DEVELOPMENT BY AUGMENTING REGULATORY B CELLS: A 15-YEAR PROSPECTIVE COHORT STUDY

Ming-Ling Chang[1], [1]Department of Gastroenterology and Gastroenterology

Background: How occult hepatitis C virus (HCV) infection (OCI) affects the prognosis of chronic hepatitis C patients with sustained virological responses (SVRs) following anti-HCV therapy remains elusive. **Methods:** A 15-year prospective study of 509 SVR patints who had been assessed for OCI, defined as HCV RNA detectable in peripheral blood mononuclear cells (PBMCs) but undetectable in serum, was conducted. **Results:** Of 509 SVR patients, 139 (27.3%) had OCI. Two (1.4%) male OCI patients developed relapse of HCV infection with a duration of 4 years (direct-acting antiviral-treated SVR) and 10 years (interferon-based therapy-treated SVR), respectively. A higher non-hepatocellular (non-HCC) cancer cumulative incidence was noted in patients with than those without OCI (23.07% vs. 11.74%, $p = 0.002$); most non-HCC cancers occurred before SVR [before SVR (18% vs. 10.5%, $p = 0.004$); after SVR (5.9% vs. 2.2%, $p = 0.032$)], while the HCC cumulative incidences were comparable between patients with and without OCI (6.15% vs. 5.1%, $p = 0.405$). OCI was independently associated with non-HCC cancer development (95%CI hazard ratio: 1.042~ 3.268). Of OCI patients, most HCV RNAs existed in the B cells of PBMC. Higher rates of interleukin-10 (IL10)-regulatory B cell (Breg) (CD19+ CD24hi CD27+ cells) (17.39+/-8.00 % vs. 11.55+/-5.63 %, $p = 0.013$) and naive regulatory T cell (Treg) (CD4 +Foxp3+CD45RA+ cells)(11.21 +/- 7.24 vs. 4.76 +/-2.24%, $p = 0.012$) but lower rates of B cells (3.45 +/-1.16 % vs. 4.72 +/-1.63%, $p = 0.01$) and memory Treg (CD4+Foxp3+CD45RA- cells) (88.56+/-7.23 vs. 95.24+/-2.25%, $p = 0.011$) were noted in SVR patients with than those without OCI. While tumor immune cell proportion and cancer cell proliferation activities were comparable between the patients with and without OCI. **Conclusion:** During a 15-year follow-up, about one third of the SVR patients harbored OCI, in which HCV parasitizes B-cells to downregulate B-cells but upregulate Bregs, this scenario might accelerate non-hepatic oncogensis, as early as before SVR.

Disclosures: Ming-Ling Chang: Nothing to Disclose

◆ 1376 | PREDICTION OF LIVER-RELATED EVENTS AFTER SUSTAINED VIROLOGICAL RESPONSE IN PATIENTS WITH DECOMPENSATED HCV CIRRHOSIS

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Background: Direct acting antiviral (DAA) therapy results in high rates of sustained virological response (SVR) even in patients with decompensated hepatitis C virus (HCV) cirrhosis. However, these patients remain at risk for liver-related events (LREs). We aimed to assess the incidence and risk factors for LREs in patients with decompensated HCV cirrhosis who have achieved SVR. **Methods:** We conducted an international multicenter retrospective cohort study including patients with decompensated HCV cirrhosis (Child-Turcotte-Pugh (CTP) ≥ 7 and/or history of decompensation) treated with DAAs. Patients aged ≥ 65, and those that developed HCC or underwent liver transplantation (LT) before SVR were excluded from analyses. LREs were defined as the first of a composite of HCC, LT or death. Predictive factors were assessed by multivariable Cox regression (MVA) adjusting for age, sex, diabetes mellitus (DM), current or history of alcohol use disorder (AUD), creatinine, bilirubin, albumin, platelets and INR at moment of SVR. A risk score was constructed by adding the obtained hazards through MVA. **Results:** We included 612 patients with a median age of 54 (IQR 49-59) years, 70% was male, 49% had AUD, 22% had DM, and the median MELD score at the time of SVR was 11.0 (8.9-13.0). Median follow-up time after SVR was 21 (8-33) months. In total, 235 LREs were recorded in 193 (32%) patients (59 HCC, 57 LT and 119 deaths). The 1-, and 3-year cumulative incidence of LREs were 18% and 44% in the overall cohort. The presence of DM (aHR: 1.5, $p = 0.020$), AUD (aHR: 1.5, $p = 0.011$), higher bilirubin (aHR for bilirubin 20-40 umol/L: 1.4, aHR for > 40 umol/L: 1.8, $p = 0.026$) and lower albumin (aHR for albumin 28-35g/L: 2.0, aHR for albumin < 28g/L: 3.4, $p < 0.001$) levels were independently associated with an increased risk of LREs. Patients were subsequently allocated to a low-risk group (no risk factors), intermediate risk (risk points > 0 & < 4) and high risk (≥ 4 risk points). In the overall cohort, 12% of patients had a predicted low risk, 61% a predicted intermediate risk and 27% a predicted high risk of LREs. Amongst patients with no risk factors, the cumulative 1-year incidence of LREs was 2%, compared to 17% and 25% in those at intermediate and high risk ($p < 0.001$). The cumulative 3-year incidence of LREs was 21/39/61% in patients at low/intermediate/high predicted risk (Figure 1). Similar findings were observed when further decompensation was added as an outcome. When applying the score on HCC, the cumulative 1-, and 3-year incidences were 0/6/10% and 12/16/23% in patients at low/intermediate/high predicted risk ($p = 0.145$). **Conclusion:** Patients with decompensated HCV cirrhosis remain at high risk of HCC, liver transplant and death despite SVR. A simple risk score based on the presence of DM, AUD, elevated bilirubin and lower albumin can be used to identify patients at highest risk, who could potentially benefit from stringent surveillance and evaluation for LT.

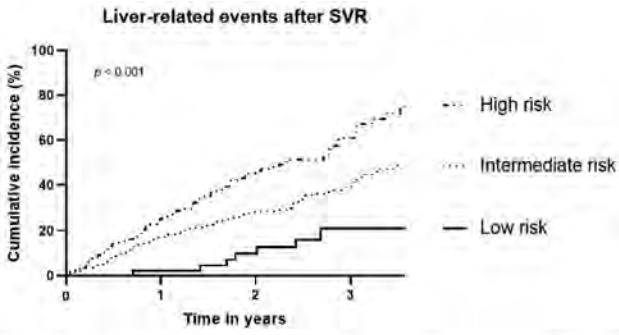

Figure 1. Cumulative incidence of liver-related events in patients with decompensated cirrhosis who achieved SVR stratified for a predicted high, intermediate and low-risk.

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◆ 1377 | INCIDENCE AND RISK FACTORS FOR HEPATOCELLULAR CARCINOMA AFTER SUSTAINED VIROLOGIC RESPONSE CHANGE OVER TIME IN PATIENTS WITH HEPATITIS C VIRUS TREATED WITH DIRECT-ACTING ANTIVIRAL

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Background: We previously reported that the incidence and risk factors for hepatocellular carcinoma (HCC) after sustained virologic response (SVR) change over time in hepatitis C virus (HCV) patients treated with interferon-based therapy. However, whether these patterns also apply to patients treated with direct-acting antiviral (DAA) remains unclear. **Methods:** This study included 3,049 HCV-infected patients without a history of HCC who initiated DAA therapy between September 2014 and December 2022 and achieved SVR at 26 Japanese hospitals. SVR was defined as undetectable serum HCV-RNA at 24 weeks after the end of therapy. FIB-4 index of 3.25 or more was defined as patients with advanced liver fibrosis. The observation period began at SVR confirmation. Annual HCC incidence rate was evaluated separately for patients with and without advanced liver fibrosis. Segmented regression analysis was performed to identify a change point in the trend of HCC occurrence. Risk factors associated with HCC occurrence after SVR were examined by Cox proportional hazard analysis before and after the identified joinpoint. **Results:** The median age was 69 years, and 1,240 patients (41%) were diagnosed as having advanced liver fibrosis. During a median follow-up of 51.6 months from SVR, 118 and 32 patients developed de novo HCC occurrence in patients with and without advanced liver fibrosis, respectively. The 7-year cumulative HCC incidence rates after SVR were 13.4% in patients with advanced liver fibrosis and 2.5% in those without ($p < 0.001$). Among patients with advanced liver fibrosis, annual HCC incidence rates at 1, 2, 3, 4, 5, and 6 years after SVR were 2.7%, 3.1%, 1.8%, 1.5%, 0.9%, and 2.4%, respectively, suggesting a possible decline followed by a rise in incidence. In contrast, annual HCC incidence rates remained below 0.5% throughout the observation period in patients without advanced liver fibrosis. Segmented regression analysis identified a joinpoint at 4.5 years after SVR in patients with advanced liver fibrosis. Risk factors for HCC occurrence were therefore analyzed separately for the early phase (≤ 4 years) and the late phase (> 4 years) after SVR. In multivariate analysis, male sex ($p = 0.027$), higher gamma-glutamyl transpeptidase (GGT) level at SVR ($p < 0.001$), lower albumin level at SVR ($p = 0.013$), and higher AFP level at SVR ($p < 0.001$) were significantly associated with HCC occurrence in the early phase. In the late phase, only higher GGT level at SVR ($p = 0.021$) was significantly associated with HCC

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occurrence in univariate analysis. **Conclusion:** In patients with advanced liver fibrosis, HCC incidence decreases for up to 4 years following SVR but may increase thereafter. Risk factors for HCC occurrence appear to differ between the early and late phase after SVR.

Disclosures: Yuki Tahata: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Yasutoshi Nozaki: Nothing to Disclose, Hisashi Ishida: Nothing to Disclose, Atsushi Hosui: Nothing to Disclose, Masanori Miyazaki: Nothing to Disclose, Ryotaro Sakamori: Gilead Sciences, Inc.: Speaking and Teaching, AbbVie Inc.: Speaking and Teaching, Kazuyoshi Ohkawa: Nothing to Disclose, Nobuyuki Tatsumi: Nothing to Disclose, Fumihiko Nakanishi: Nothing to Disclose, Yoshinori Doi: Nothing to Disclose, Takayuki Yakushijin: Nothing to Disclose, Mitsuru Sakakibara: Nothing to Disclose, Kazuho Imanaka: Nothing to Disclose, Naruyasu Kakita: Nothing to Disclose, Sadaharu Iio: Nothing to Disclose, Yuichi Yoshida: Nothing to Disclose, Kumiko Shirai: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Yuki Makino: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Nothing to Disclose, Takahiro Kodama: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

◆ 1378 | SAFETY AND EFFICACY OF 8-WEEKS GLECAPREVIR/PIBRENTASVIR IN PERSONS WITH ACUTE HEPATITIS C IN GERMANY AND AUSTRIA

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Background: Although recommended by international guidelines current direct-acting antivirals (DAAs) for chronic hepatitis C are not approved for the treatment of acute HCV infection. In high-risk populations, initiating HCV treatment immediately after diagnosis is critical to prevent onward transmission. Previously, safety and efficacy of 8-weeks Glecaprevir/Pibrentasvir (G/P) was presented in 286 participants with acute hepatitis C (AASLD 2024 abstract #5031). This exploratory analysis aims to confirm the efficacy and safety of G/P in persons with acute hepatitis C enrolled in Germany and Austria. **Methods:** A post-hoc analysis of safety and efficacy of 8-weeks G/P was carried out in a subset of participants enrolled in Germany and Austria from a single-arm, prospective phase 3b study (NCT04903626) in adults with acute/recent HCV infection (Table 1) who had not previously been treated for current infection. **Results:** 79 participants were enrolled and treated in Austria (N = 7) and Germany (N = 72) between September 7, 2021, and August 26, 2024. 96.2% of participants were male with a median age of 44.0 years (IQR: 37.0 - 54.0 years) and baseline HCV RNA of 5.65 $\log_{10}$ IU/mL (IQR: 4.09 - 6.53 $\log_{10}$ IU/mL). Genotype 1, 3 and 4 infections were present in 66.2%, 10.8% and 23.0% of participants, respectively. 59.9% of participants had current alcohol use, 62.0% had a history of illicit drug use within 12 months prior to treatment (illicit injection drug use, 20.3%), and 62.0% had HIV co-infection (HIV-1 RNA < 20 copies/mL, 89.8%). The main risk behaviors for current acute HCV infection were unprotected sexual activity with other male(s) (78.5%) or multiple partners (58.2%), shared non-injection drug use equipment (20.3%) or drug-injection equipment (19.0%). Sustained virologic response at 12-weeks post-treatment (SVR12) rates were 94.9% in ITT and 100% in mITT analysis, without virologic failures, relapses or reinfections. During treatment none of the 79 participants experienced an adverse event (TEAE) leading to G/P discontinuation or serious TEAE related to G/P. 97.6% (41/42) of participants who had baseline ALT > 3× ULN showed normal ALT at final treatment visit. **Conclusion:** In this high-risk, sexually very active population with acute hepatitis C in Germany and Austria 8-weeks G/P was safe and highly effective, regardless of HIV co-infection and drug/alcohol use supporting its implementation as a key strategy toward achieving the WHO HCV elimination goal.

Table 1. Study Protocol Eligibility Criteria for Acute/Recent HCV Infection

Physician diagnosis of acute HCV infection	
AND	
Quantifiable HCV RNA at screening	
AND	
At least one of	Negative anti-HCV antibody, HCV RNA, and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 8-month period prior to screening
	Negative anti-HCV antibody, HCV RNA, and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 11-month period prior to screening AND Risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen
	Clinical signs and symptoms compatible with acute hepatitis (ALT >5×ULN and/or jaundice) in the absence of a history of chronic liver disease or other cause of acute hepatitis and positive HCV RNA or HCV core antigen all within an 8-month period prior to screening AND Risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen
	Negative anti-HCV antibody with a positive HCV RNA or HCV core antigen within a 5-month period prior to screening

ALT, alanine aminotransferase; HCV, hepatitis C virus; RNA, ribonucleic acid; ULN, upper limit of normal.

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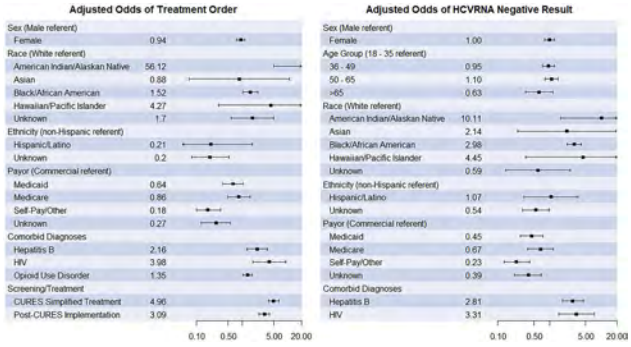
◆ 1379 | GENDER AND SOCIOECONOMIC-BASED DISPARITIES IN HEPATITIS C TREATMENT AND CURE RATES IN AN EMERGENCY DEPARTMENT-BASED SCREENING AND TREATMENT PROGRAM

Christian Rhudy[1] Daniel Moore[1] Lindsey Sheehan[2] Afomia Gelan[1] Morgan Stacey[3], [1]University of Kentucky HealthCare, [2]UK HealthCare, [3]University of Kentucky Medical Center

Background: Hepatitis C (HCV) remains a public health issue, with particularly high prevalence and mortality rates in Kentucky. To address this, University of Kentucky HealthCare (UKHC) implemented an emergency department (ED)-based screening and treatment program, UK-CURES (Cascade Utilizing Routinized screening through treatment to Eliminate Syndemics), which improved diagnosis and treatment attachment rates at the institution. However, the extent to which UK-CURES addressed sociodemographic-based disparities in HCV outcomes, particularly gender-based disparities, has not been fully investigated. **Methods:** This was a retrospective, cross-sectional study including patients screening HCVRNA positive at a UKHC ED between July 2018 and December 2023. Patients missing gender data were excluded, and only the patient's first HCV RNA positive screening (index date) at UKHC was considered. Demographic data including age group, gender, ethnicity/race, payor type as well as HIV and hepatitis B lab values, and diagnoses of opioid use (ICD-10-CM F 11*) were collected. Outcomes of interest included HCV treatment orders or negative HCVRNA results within the one-year post-index period. Association of sociodemographic attributes with outcomes was assessed using univariable logistic regression. Significant univariable predictors were included in adjusted multivariable models for each outcome. **Results:** 97,386 patients were screened for HCV, of which 4,723 (4.9%) were HCV RNA positive (female n = 1,636, 34.6%; male n = 3,087, 65.4%). Adjusted odds of treatment orders (male referent, OR 0.94, 95%CI 0.76-1.17) and negative HCVRNA results (OR 1, 95%CI 0.73-1.24) within one year did not differ significantly between male and female patients. Patients with self-pay or other insurance were significantly less likely to attach to treatment (commercial referent, OR 0.18, 95%CI 0.1-0.34) or have a negative HCVRNA result at one year (OR 0.25, 95%CI 0.13-0.41). Notably, patients receiving treatment through the UK-CURES program had significantly higher odds of receiving treatment orders (OR 4.96, 95%CI 3.84-6.4). **Conclusion:** No notable gender disparities were observed in HCV treatment ordering or cure rates, suggesting that UK-CURES ED-based screening and treatment may address any existing disparities. Lower odds of treatment and cure were observed in self-pay patients, suggesting disparities attributable to financial barriers to care exist and need to be addressed.



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◆ 1380 | CUMULATIVE REVIEW OF SOFOSBUVIR/VELPATASVIR EXPOSURE IN PREGNANT WOMEN WITH HEPATITIS C VIRUS FROM A PHARMACOVIGILANCE SAFETY DATABASE

Stacey Scherbakovsky[1] Catherine Chappell[2] Chelsea Elwood[3] Yachna Sahi[4] Frederick Pitts[4] Lauren Liu[4] Catherine Frenette[5] Tatyana Kushner[6], [1]Gilead Sciences, Inc, [2]University of Pittsburgh; Magee-Womens Research Institute, [3]Medical Lead Oak Tree Clinic and Antimicrobial Stewardship BC Women's Hospital and Health Centre, [4]Gilead Sciences, [5]Gilead Sciences, Inc., [6]Weill Cornell Medicine

Background: The prevalence and incidence of hepatitis C virus (HCV) in women of childbearing age and pregnant individuals has increased nearly tenfold over the last 20 years, paralleling rising infection rates among young adults. While no direct-acting antiviral (DAA) therapies are approved for use in pregnancy, animal studies provide encouraging safety data. Clinical studies, including the Phase 4 Safety, Tolerability, and Outcomes of Velpatasvir/SofosbuviR in Treatment of Chronic Hepatitis C Virus during Pregnancy (STORC) study, are ongoing to validate safety data for the routine use of DAAs in pregnancy. **Methods:** The cumulative review included safety data reported from Feb 2016 to June 2024 to the Gilead Pharmacovigilance database. Data included pregnancy exposures and outcomes from clinical trials, spontaneous post-marketing reports,

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solicited sources and the literature. These data were analyzed for timing of treatment initiation/discontinuation, whether SOF/VEL treatment was completed, if sustained virologic response (SVR) was achieved, pregnancy outcomes, congenital anomalies and vertical transmission. **Results:** A total of 335 pregnancy cases (337 pregnancies [2 sets of twins]) associated with SOF/VEL use were reported from spontaneous sources (216), clinical studies (66), solicited sources (46) and the literature (7). Case distribution included the USA (62%), Europe, Canada, Asia, and Australia. The median age was 30.5 years (range: 19-52), with ethnicity data available for 83 of 335 cases. Of 123 pregnancies with documented outcomes, 74 (60.2%) resulted in live births, 28 (22.8%) experienced spontaneous abortions and 21 (17.1%) underwent elective or induced abortions. Of the 74 live births, 62 (82.6%) had normal outcomes (caesarean and full-term deliveries), while 10 (13.5%) involved congenital anomalies and two (2.7%) were premature births at 30 and 33 weeks without anomaly. Congenital anomalies ranged from specific physical abnormalities to renal malformations, melanocytosis and intrauterine growth restrictions, spontaneous abortions were confounded with illicit drug use, concomitant medications not recommended in pregnancy, or other concurrent illnesses, both lacking sufficient data to link them to SOF/VEL use. **Conclusion:** The high rate of congenital anomalies is notable in the reported live births, but spontaneous reporting systems inherently risk under-reporting (63.5% with unknown or pending outcomes) and reporting bias. These cumulative data add to the body of evidence of the use of SOF/VEL in pregnancy and underscore the importance of further safety data.

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◆ 1381 | NO IMPACT OF RASS ON THE HIGH EFFICACY OF BEM AND RZR IN COMBINATION: RESISTANCE ANALYSIS FROM A PH 2 STUDY IN HCV-INFECTED PATIENTS

Qi Huang[1] Dawei Cai[1] Shannan Lynch[1] Keith Pietropaolo[1] Xiao-Jian Zhou[1] Sergey Izmailyan[1] Maria Arantxa Horga[1] Janet Hammond[1] Nancy Agrawal[1] Jean-Pierre Sommadossi[1], [1]Atea Pharmaceuticals, Inc.

Background: Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent pan-genotypic inhibitors of HCV NS5B and NS5A, respectively. A Phase 2 open-label study evaluated the efficacy/safety of BEM+RZR for 8 weeks in 275 HCV-infected patients (NCT05904470). SVR12 was 98% (99% in non-cirrhotics; 88% in compensated cirrhotics [CC]) in the primary Per-Protocol Treatment-Adherent Population (study-drug adherent). Detailed analyses were conducted of Next-Generation Sequencing (NGS) results for 14 patients in the overall population who experienced virological failure (VF), and *in vitro* phenotyping results, to establish clinical resistance profiles. **Methods:** NGS was performed at baseline and at failure for the 14 VF patients. For phenotypic analyses of potential HCV NS5A and NS5B RASs observed in baseline and on/post-treatment, single or linked RASs were engineered back to specific (sub)genotype replicons and EC_{50} fold shifts were determined in transient replicon assays. **Results:** Analysis of viral kinetics and plasma drug exposures across the whole study population indicated that the majority of VFs were due to treatment adherence issues, especially in NC. 6/7 of the NC subjects with VF were not study-drug adherent, and 4/6 developed high resistance to RZR. For the NS5A gene, 7/14 patients had pre-existing primary NS5A RASs and 5 of these 7 carried baseline NS5A RASs that were further enriched at VF, often acquiring additional RASs. Phenotyping results showed these linked NS5A RASs confer high resistance to RZR. The other 2 of these 7 carried low resistance NS5A at baseline, with additional NS5A substitutions emerging at VF, which did not confer RZR resistance alone or linked with NS5A RASs. 3/14 patients with no known NS5A RASs at baseline had high resistance RASs emerging at VF. The other 4/14 patients with no baseline NS5A RASs did not have new substitutions at VF. For the NS5B region, no primary BEM C223 substitutions or SOF S282T were detected at baseline or VF. Some NS5B substitutions emerged or were enriched, but the impact on BEM or SOF activities was minimal in transient replicon assays. Results indicate BEM viral resistance is not developing rapidly, consistent with earlier studies. **Conclusion:** The combination of BEM/RZR in this phase 2 study showed strong antiviral activity against all tested HCV genotypes (GT 1-4). VK and PK data indicated most VFs were due to poor adherence and resulted from NS5A resistance to RZR. BEM/RZR is currently in phase 3 development.

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Table 1: Summary of Virologic Failure and Associated RASs

GT	VF Type	Time	PK/PC-PP*	NS5A RAS Baseline	NS5A RAS at Fx	NS5B RAS Baseline	NS5B RAS at Fx
Subjects with Cirrhosis							
1a	Relapse	SVR4	Yes	Q30H (8%) Y93H/N (20/22%)	M28T (100%) Q30H (100%) Y93H/N (2/98%)	None	None
1a	Relapse	SVR4	Yes	None	S38Y (1%) H58N (3%)	None	None
1b	Relapse	SVR4	Yes	L31M (35%)	L31M (99%)	None	N206K (44%)
1b	Relapse	SVR12	No	P58S (99%) Y93H (1%)	P58S (99%)	N206D (48%)	N206D (100%)
3a	Relapse	SVR4	Yes	None	Y93H (100%)	K206E (1%)	None
3a	BK	W8	No	S62I/M/F/V/T (90/2/3/3/12%) Y93H (42%)	S62I/M/V/T (89/2/7/2%) Y93H (100%)	K206N (99%)	K206Q/N (1/98%)
3a	BK	W2	No	A30K (53%) S62T (99%)	A30K (67%) L31V/I (2/4%) H62A/T (2/97%) Y93H (91%)	S15R (100%) K206E (99%)	Failed amplification
Subjects without Cirrhosis							
1a	BK	W8	No	H58P (99%)	M28T (100%) Q30H (100%) H58P (100%)	Failed amplification	Failed amplification
1a	Relapse	SVR4	Yes	None	None	None	None
1a	Relapse	SVR12	No	None	L31V (100%) Y93H (100%)	None	None
1a	BK	W4	No	None	M28T (5%) Q30K/R (5/51%) L31V (56%) Y93H (55%)	Q206K (20%)	Q206K (41%)
1b	Relapse	SVR12	No	None	None	V321I (100%)	V321I (97%)
2b	Relapse	SVR4	No	None	None	None	None
3a	BK	W4	No	P58A (6%) S62T (10%) Y93H (1%)	L31I (5%) P58A (27%) Y93H (93%)	K206Q (100%)	K206Q (100%)

PK/PC-PP*: Included in the Per-Protocol Treatment Adherent

NS5A RASs monitored: 24, 28, 30, 31, 32, 58, 58, 92, 93 and 62 (GT-3 only) positions; NS5B RASs monitored: 15, 142, 159, 206, 223, 237, 282, 289, 314, 321 positions; GT, genotype; VF Type, Viral Failure Type; PK/PC-PP, Pharmacokinetic and pill- compliant per protocol; Fx, Failure; BK, Breakthrough on-treatment; SVR, Sustained virologic response; W, week

Disclosures: Qi Huang: Nothing to Disclose, Dawei Cai: Atea Pharmaceuticals, Inc.: Employee, Atea Pharmaceuticals, Inc.: Stock - publicly traded company, Shannan Lynch: Atea Pharmaceuticals: Employee, Keith Pietropaolo: Nothing to Disclose, Xiao-Jian Zhou: Nothing to Disclose, Sergey Izmailyan: Nothing to Disclose, Maria Arantxa Horga: Nothing to Disclose, Janet Hammond: Nothing to Disclose, Nancy Agrawal: Nothing to Disclose, Jean-Pierre Sommadossi: Nothing to Disclose

1382 | HEPATITIS C CARE CASCADE USING DIRECT ACTING ANTIVIRAL MEDICATIONS IN RURAL NEW YORK STATE FROM 2013-2023; A RETROSPECTIVE STUDY

Zoi Papalamprakopoulou[1] Melissa Scribani[2] Nicole Krupa[2] Paul Jenkins[2] Jennifer Victory[2] Wendy Brunner[2] Michael Cain[1] Arpan Dharia[1] Daniel Freilich[3] Andrew Talal[1], [1]Division of Gastroenterology, Hepatology, and Nutrition, University at Buffalo, NY 14203 USA, [2]Bassett Research Institute, Bassett Medical Center, 1 Atwell Road, Cooperstown, NY 13326 USA, [3]Department of Internal Medicine, Division of Infectious Diseases, Bassett Medical Center, 1 Atwell

Background: Hepatitis C virus (HCV) infection is higher in rural areas, yet access to HCV care remains more limited. We evaluated the HCV care cascade during the first decade of direct-acting antiviral (DAA) use in the primary care setting at Bassett Healthcare Network in rural New York State (NYS). **Methods:** We used retrospective electronic health record data to construct eleven annual testing cohorts (2013-2023) based upon HCV antibody testing date. Eligible patients were primary care patients aged 18-79 years. We summarized the annualized average HCV care cascade using frequencies and weighted percentages. We conducted subgroup analyses of people with opioid use disorder (OUD) versus those without OUD using chi-square. Using ANOVA, we compared changes in the HCV care cascade before and after reflex HCV RNA testing implementation in 2017 and universal HCV screening recommendations for all adults introduced in 2020. **Results:** The primary care population was 72,615 individuals, 96.4% white, 44.6% male, and 4.2% had OUD. We illustrate the annualized average HCV care cascade from 2013-2023 for both the total primary care population and the subgroup with OUD (Fig). Of the total and OUD populations, 5.0% and 8.2%, respectively, had HCV serostatus assessed. Among those tested, HCV seropositivity occurred in 2.8% and 17.5% of the total and OUD populations, respectively. Among the total population, we observed the highest HCV seropositivity (4.65%) among individuals aged 20-39 years. Among 96 HCV-seropositive individuals in the total population, 95.8% (92/96) underwent HCV RNA testing. Of those tested, 40.2% (37/92) were HCV RNA-positive. Among them, 45.9% (17/37) initiated DAAs, and 81.3% (13/16) achieved HCV cure. People with OUD had higher HCV RNA-positivity compared to those without OUD (51.3% vs. 35.7%, respectively) ($p < 0.0001$), suggesting more active disease and infectivity, and lower DAA initiation rates (35.7% vs. 57.7%, respectively) (Fig). RNA testing rates increased following implementation of RNA reflex testing in 2017 ($p = 0.0333$); HCV antibody testing increased following implementation of universal HCV screening in 2020 ($p < 0.0001$). **Conclusion:** While HCV case identification improved following the implementation of RNA reflex testing and universal screening policies, opportunities exist to improve HCV detection and DAA treatment initiation in rural NYS. Expanding DAA access for people with OUD is critical to improving rural HCV care and public health.

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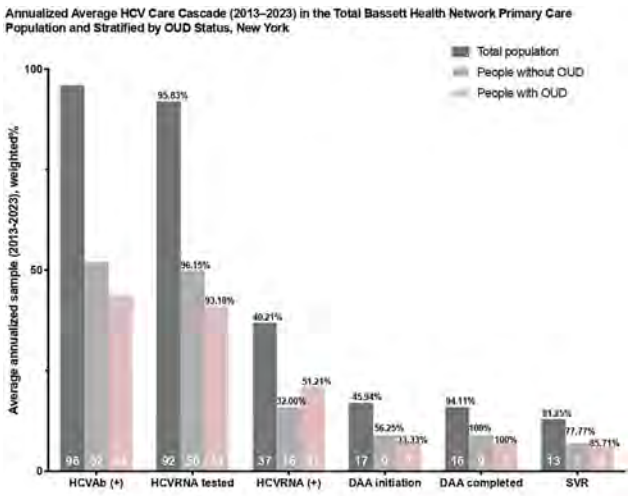

Comparison of the HCV care cascade between people with and without OUD, pooled 2013-2023.

	People with OUD (N†=3,058)		People without OUD (N=69,362)		p-value
	N	Weighted %	N	Weighted %	
HCV serologic testing (%)	254	8.3	1425	1.9	<0.0001
HCV seropositive (%)	44	17.4	32	1.5	<0.0001
HCV RNA test obtained (%)	41	94.0	30	96.0	0.1432
HCV RNA positive (%)	21	51.3	16	52.1	<0.0001
DAA initiation	7	35.65	9	57.71	<0.0001
DAA completion	7	98.77	9	99.00	0.8751
SVR (%)	6	78.5	7	84.5	0.3002

†Sample sizes shown are the average annualized sample over the study period 2013-2023. Percentages are weighted percentages over the study period.

HCV, Hepatitis C virus; DAA, direct-acting antiviral; SVR, sustained viral response; OUD, Opioid use disorder

Disclosures: Zoi Papalamprakopoulou: Nothing to Disclose, Melissa Scribani: Nothing to Disclose, Nicole Krupa: Nothing to Disclose, Paul Jenkins: Nothing to Disclose, Jennifer Victory: Nothing to Disclose, Wendy Brunner: Nothing to Disclose, Michael Cain: Nothing to Disclose, Arpan Dharia: Nothing to Disclose, Daniel Freilich: Nothing to Disclose, Andrew Talal: Gilead Sciences: Grant/Research Support, AbbVie: Consultant, Abbott Laboratories: Grant/Research Support, Novo Nordisk: Advisor, Astra Zeneca: Grant/Research Support, Novo Nordisk: Grant/Research Support, Empath Medical: Medical Director

1383 | DECENTRALIZATION IN ACTION: T&UUML;RKIYE&RSQUO;S POLICY-DRIVEN EXPANSION OF HEPATITIS C TREATMENT TO SECONDARY CARE

Imran Hasanoglu[1] Rahmet Guner[1] Mehmet Cabalak[2] Burak Kizilcay[3] Mustafa Muhammed Gulhan[4] Ummu Sena Sari[5] Islim Tuba Ozkaya[6] Meral Bayar[7] Unal Cagir[8] Cigdem Toruner Ineli[9] Armagan Toy[10] Ragip Sariismailoglu[11] Gozde Akkiraz Bac[12] Imran Icel Yildirim[13] Fidan Dogan[14] Tansu Yamazhan[15], [1]Ankara Yildirim Beyazit University Bilkent City Hospital, [2]Mustafa Kemal University Hospital, [3]Arnavutkoy State Hospital, [4]Duzce Ataturk State Hospital, [5]Ankara 29 Mayis State Hospital, [6]Mersin Toros State Hospital, [7]Silivri State Hospital, [8]Nevsehir State Hospital, [9]Kepez State Hospital, [10]Seyhan State Hospital, [11]Sivas Numune Hospital, [12]Menemen State Hospital, [13]Sultanbeyli State Hospital, [14]Ceyhan State Hospital, [15]Ege University Faculty of Medicine

Background: The primary challenge in hepatitis C elimination now lies in identifying and engaging individuals who remain undiagnosed or untreated. In response to a recent policy change in Turkiye allowing hepatitis C treatment prescriptions by secondary care physicians, a national meeting was held to promote region-specific action plans for screening, diagnosis, and treatment, contributing to national hepatitis C elimination goals. This initiative aimed to address that critical gap by empowering frontline healthcare providers and expanding access to care. **Methods:** A total of 45 physicians from 41 hospitals across 23 provinces participated. Each physician was tasked with implementing locally tailored interventions. Post-meeting, 27 physicians from 27 unique centers submitted data on their activities, including community outreach, prison-based screening, addiction center screening, and retrospective hospital records reviews. A standardized form collected data on the number of patients screened, diagnosed, and treated. **Results:** Among the 45 physicians who attended the national hepatitis C elimination meeting, 27 provided data from their local efforts. Across all efforts, 296,404 individuals were screened. The overall anti-HCV positivity rate was 1.4%, with HCV RNA testing performed in 64.3% of anti-HCV positive individuals. Among those tested, 27.8% were HCV RNA positive. In total, 734 patients were found to be HCV RNA positive, and 544 (74.1%) began treatment. Of the HCV RNA positive individuals, 257 (35.0%) were identified through prison screenings and 473 (64.4%) through retrospective hospital data. Similarly, of the patients treated, 256 (47.1%) came from prison screenings and 284 (52.2%) from hospital records screenings, highlighting the challenges of engaging retrospectively identified patients in care. These outcomes are presented in detail in Figure 1, which illustrates the distribution of HCV RNA positive cases and treatment initiation according to screening type. **Conclusion:** This decentralized national initiative has shown early success in identifying and treating hepatitis C cases in both high-risk populations and individuals identified through hospital-based screening efforts. The involvement of secondary care hospitals has played a key role in broadening access to diagnosis

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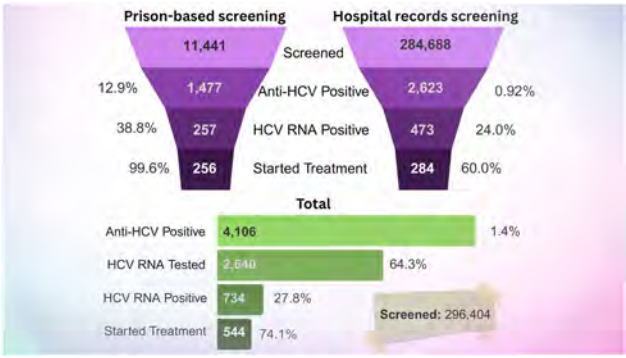
and therapy, demonstrating the positive impact of recent policy changes. However, suboptimal HCV RNA testing rates among anti-HCV positive individuals, particularly in retrospective screenings, and challenges in linking diagnosed patients to timely treatment reveal persistent gaps in the care cascade.

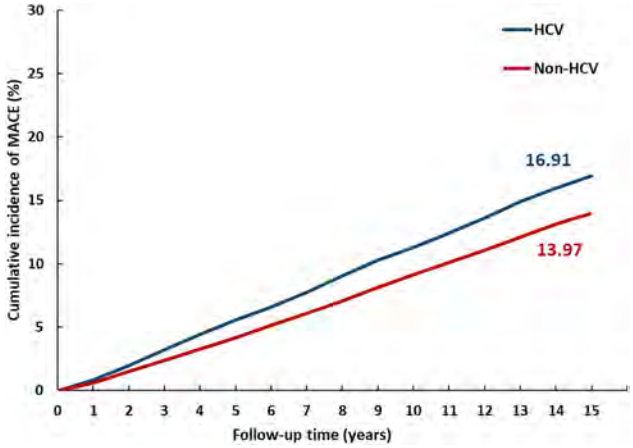


Disclosures: Imran Hasanoglu: Nothing to Disclose, Rahmet Guner: Nothing to Disclose, Mehmet Cabalak: Nothing to Disclose, Burak Kizilcay: Nothing to Disclose, Mustafa Muhammed Gulhan: Nothing to Disclose, Ummu Sena Sari: Nothing to Disclose, Islim Tuba Ozkaya: Nothing to Disclose, Meral Bayar: Nothing to Disclose, Unal Cagir: Nothing to Disclose, Cigdem Toruner Ineli: Nothing to Disclose, Armagan Toy: Nothing to Disclose, Ragip Sariismailoglu: Nothing to Disclose, Gozde Akkiraz Bac: Nothing to Disclose, Imran Icel Yildirim: Nothing to Disclose, Fidan Dogan: Nothing to Disclose, Tansu Yamazhan: Nothing to Disclose

1384 | ASSOCIATION BETWEEN HEPATITIS C VIRUS INFECTION AND CARDIOVASCULAR DISEASE: A NATIONWIDE, POPULATION-BASED COHORT STUDY IN SOUTH KOREA

Juneyoung Lim[1] Min Kyung Park[2] Eun Sun Jang[3] seungteak Lee[1], [1]Seoul national university Bundang hospital, [2]Seoul National University Hospital, [3]Seoul National University College of Medicine

Background: Chronic hepatitis C virus (HCV) infection has been increasingly associated with cardiovascular disease, but population-based evidence remains limited. This study aimed to evaluate the independent association between HCV infection and cardiovascular outcomes using a nationwide, population-based cohort in South Korea, with general population-matched controls. **Methods:** Using the National Health Insurance Service (NHIS) database of South Korea, we identified patients newly diagnosed with HCV between 2009 and 2022 who were ≥20 years old. Each HCV patient was matched with six non-HCV individuals from the general population using 1:6 matching based on age and sex. The primary outcome was the incidence of major adverse cardiovascular events (MACE), including ischemic heart disease, stroke, and peripheral arterial disease. Cox proportional hazards models were used to estimate hazard ratios, adjusting for age, sex, medication use, and comorbidities. A competing risk model additionally accounted for death and liver transplantation. **Results:** The final cohort included 30,467 HCV patients and 182,802 age- and sex-matched controls. Baseline characteristics were well balanced (mean age: 48.8 years; male proportion: 53.9% in both groups). Over the follow-up period, MACE occurred in 6,594 HCV patients and 23,258 controls. During the follow-up period, 19,265 patients developed MACE (incidence rate: 10.0 per 1,000 person-years). Before adjustment for covariates, HCV infection was associated with a 25% increased risk of MACE compared to the matched control group (hazard ratio [HR] 1.25, 95% confidence interval [CI]: 1.20–1.30, $P < 0.001$). In the adjusted model—including income, comorbidities, medication use, BMI, alcohol consumption, and smoking—HCV infection was independently associated with increased MACE risk (adjusted HR 1.21, 95% CI: 1.16–1.25, $P < 0.001$). This association remained significant in the competing risk model (adjusted HR 1.18, 95% CI: 1.14–1.23). **Conclusion:** This nationwide, general population-matched cohort study provides strong evidence that HCV infection is an independent risk factor for cardiovascular disease. These findings highlight the need for cardiovascular risk monitoring in HCV patients and further research on potential prevention strategies.



Disclosures: Juneyoung Lim: Nothing to Disclose, Min Kyung Park: Nothing to Disclose, Eun Sun Jang: Nothing to Disclose, seungteak Lee: Nothing to Disclose

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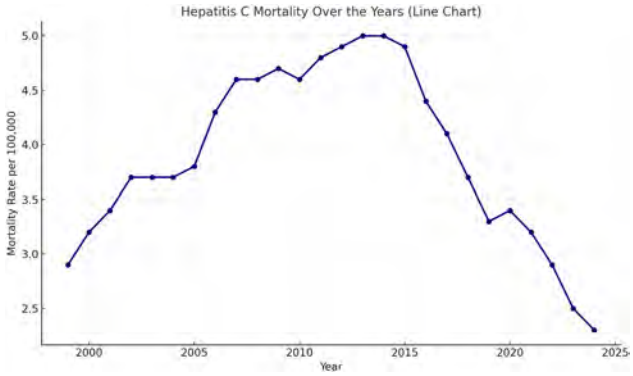
1385 | FROM DISCOVERY TO CURE — WHERE ARE WE NOW? MORTALITY TRENDS IN CHRONIC HEPATITIS C: AN ANALYSIS OF THE CDC WONDER DATABASE (1999–2024)

Ashraf Ullah[1] Mati Ullah Dad Ullah[2] Syed Bilal Shah[3] Naveed Ali[4] Rohullah Rasikh[5] Umar Iqbal Javid Choudhary[6] Hamnah Tayyab[7], [1]Guthrie Robert Packer Hospital, Pennsylvania, [2]University of Oklahoma Health Sciences Center, [3]Beth Israel Deaconess Medical Center, [4]Khyber Teaching Hospital, Pakistan, [5]Landmark Medical Center, Rhode Island, [6]The Good Samaritan Medical Center, [7]Guthrie Robert Packer

Background: Hepatitis C virus (HCV)-related cirrhosis was the leading cause of liver-related mortality, morbidity, and liver transplantation before the introduction of direct-acting antiviral (DAA) therapies. Since their introduction in 2014, DAAs have revolutionized the management of HCV by making it a curable disease. Despite these breakthroughs, hepatitis C remains a significant public health burden in the United States, particularly among historically underserved populations. Understanding mortality trends over time can provide critical insight into the effectiveness of public health interventions and identify persistent healthcare disparities **Methods:** We analyzed mortality data for the U.S from the CDC WONDER database, focusing on cirrhosis as the underlying cause of death and HCV as a contributing cause. Age-adjusted mortality rates (AAMRs) per 100,000 were calculated, and trends were analyzed using Joinpoint regression, focusing on annual percentage changes (APCs) from 1999 to 2023. **Results:** Between 1999 and 2024, there were 175,712 deaths from HCV cirrhosis. AAMRs increased from 2.92 in 1999 to 3.79 in 2013; however, after the introduction of DAA, a significant decline occurred, with AAMRs decreasing from 3.77 in 2014 to 2.3 in 2024, representing an 8.2% annual decrease. Males consistently had higher AAMRs than females. Among males, AAMRs rose by 1.5% annually from 1999 to 2014, but declined by 9.0% annually from 2014 to 2021. For females, AAMRs rose by 1.4% annually until 2013, followed by a decline of 8.8% annually from 2014 to 2019. Racial disparities persisted: non-Hispanic American Indian/Alaska Native populations had the highest mortality rate in 2022 (5.12 per 100,000), followed by Hispanics (2.45), non-Hispanic Black (2.40), non-Hispanic White (1.74), and non-Hispanic Asian populations (0.82). After 2013, mortality rates began to decline across all racial groups, with the steepest decline seen in non-Hispanic Black populations (APC: -11.0%). Geographically, metropolitan areas saw the most significant reductions in mortality rates, especially large metro areas (APC: -10.2%). Mortality rates for HCV were found to be highest for the male gender, age group 55-74 years, American Indians or Alaskan Natives, the West US Census Region, and Medium to small metropolitan areas. Geographically, states in the top 90th percentile for HCV-associated mortality included the District of Columbia, Oklahoma, Oregon, California, New Mexico, and Washington. **Conclusion:** The introduction of DAA therapies has led to a significant decline in mortality from HCV-related cirrhosis. However, racial minorities, particularly non-Hispanic American Indian/Alaska Native and Black populations, continue to experience disproportionately high mortality rates. Addressing healthcare access disparities remains crucial.



Disclosures: Ashraf Ullah: Nothing to Disclose, Mati Ullah Dad Ullah: Nothing to Disclose, Syed Bilal Shah: Nothing to Disclose, Naveed Ali: Nothing to Disclose, Rohullah Rasikh: Nothing to Disclose, Umar Iqbal Javid Choudhary: Nothing to Disclose, Hamnah Tayyab: Nothing to Disclose

1386 | RE-LINKING HEPATITIS C PATIENTS TO CARE: A QUALITY ASSURANCE INITIATIVE FROM THE CALGARY LIVER UNIT

Ofodile Joe-Uzuegbu[1] Mayur Brahmania[1] Stephen Congly[1] Yashasavi Sachar[2] Morgan Koczkur[1] Carla Coffin[1] Mark Swain[3] Henry Nguyen[3] Abdel-Aziz Shaheen[1], [1]University of Calgary Cumming School of Medicine, Calgary, AB, [2]Western University, [3]University of Calgary

Background: Despite the availability of curative treatment for the hepatitis C virus (HCV), gaps in post-treatment follow-up limit progress toward elimination. At the Calgary Liver Unit (CLU)—a tertiary referral center serving over 1.5 million people in Alberta, Canada—patients with chronic HCV receive multidisciplinary care and treatment plans that include confirmatory sustained virologic response (SVR) testing. This quality assurance (QA) project aims to systematically identify and relink these patients to confirm SVR and reduce long-

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term liver disease risk. **Methods:** A retrospective chart review was conducted for patients seen at the CLU between 2015 and 2024 who tested HCV antibody-positive. Using Alberta's integrated clinical information systems, patients were categorized by treatment status. Individuals who had no record of SVR testing or never initiated treatment, and were not known to be deceased or ineligible, were flagged for follow-up. Patients were contacted via telephone, email, or letter to offer re-engagement in care and confirmatory RNA testing. Responses were recorded using a secure platform. Summary statistics were compiled for QA monitoring. **Results:** Among 2,923 HCV Ab-positive patients, 329 were deceased and 104 were ineligible, leaving 2,490 eligible for follow-up. Of these, 2,099 (95.8%) had documented SVR and outreach was attempted in 91 (4.2%) without known SVR. In total, 29 (31.8%) were successfully contacted, 17 (58.6%) agreed to re-engage in care through scheduled clinical consultations or HCV RNA testing to confirm SVR. Of the 17 re-engaged, 10 were male, and the mean age was 56.6 years. The mean ALT and bilirubin were 43.4 U/L (IQR 18-46) and 10.9 µmol/L (IQR 6-10), respectively. In contrast, the 12 contacted patients who declined re-engagement had a higher mean age of 62.4 years, with a mean ALT of 78.2 U/L (IQR 30-97.5) and bilirubin of 11.4 µmol/L (IQR 5.8-15.3). Reported reasons for not achieving SVR among the 29 contacted included being unaware of diagnosis (n = 2), personal choice to defer care (n = 5), incarceration (n = 1), health-care access barriers (n = 2), and incomplete treatment (n = 3), while several patients declined to provide a reason. **Conclusion:** This QA initiative demonstrates a structured relinkage strategy's feasibility and early impact for HCV patients lost to follow-up. Successful re-linkage was feasible in > 50% of those contacted, with older age and higher ALT noted in those who declined follow-up. Future interventions will extend this approach to community-based primary care settings, advancing scalable models for HCV elimination across Alberta by 2030.

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1387 | PREVALENCE OF ANTI-HCV ANTIBODIES IN AT-RISK PATIENTS IN HOSPITAL SETTINGS IN COLOMBIA: A MULTICENTER STUDY

Javier Hernandez-Blanco[1] Juan Ignacio Marin Zuluaga[2] Ismael Yepes[3] Diana Chávez Bejarano[4] Alfredo Spath[5] Yanette Suarez[6] Monica Tapias[7] Patricia Reyes Pabón[8] DianaD Escobar[9] Oscar Beltran[10], [1]Colombian Hepatology Association, University of Magdalena., [2]Colombian Hepatology Association, University of Antioquia, [3]Colombian Hepatology Association, University of Cartagena, [4]Clinical Epidemiology Program, University Foundation of Health Sciences – FUCS., [5]Gilead Medical Department, [6]Colombian Hepatology Association, San Ignacio University Hospital, [7]Colombian Hepatology Association, Santafé de Bogotá Foundation, [8]Colombia Clinic, [9]Colombian Hepatology Association, Valle de Lili Foundation, [10]Colombian Hepatology Association, Universidad del Rosario

Background: Hepatitis C virus (HCV) remains a global health burden, with millions chronically infected and at risk of cirrhosis, hepatocellular carcinoma, and death. Despite the availability of curative direct-acting antivirals (DAAs), diagnosis and treatment coverage remain low, particularly in low- and middle-income countries. In Colombia, less than 1% of estimated HCV cases receive treatment. Micro- elimination strategies, including opportunistic screening in hospital settings, may help close diagnostic gaps, especially among at-risk populations. This study aimed to estimate the prevalence of HCV infection through targeted rapid antibody testing in Colombian hospitals and to evaluate the feasibility of linkage to care for positive cases. Keywords: Hepatitis C, Opportunistic Screening, Prevalence, Risk Factors, Hospitals. **Methods:** We conducted a multicenter, cross-sectional study in six hospitals across Colombia, targeting adults (≥ 18 years) attending inpatient, emergency, outpatient, and laboratory services. Participants with risk factors for HCV were screened using the Bioline™ anti-HCV rapid test at the point of care, after

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informed consent. Reactive cases were referred to as specialist evaluation and HCV RNA confirmation (PCR). The study included pre- and post-test counseling and structured pathways to support treatment linkage. Data was collected using an electronic case report form (CRF) and analyzed with R software using descriptive statistics and chi-square tests. Data were collected from December 2023 to April 2025. **Results:** Among 18,480 screened individuals, 18 tested positives for anti-HCV antibodies, yielding a prevalence of 0.097% (95% CI: 0.058%–0.154%). The median age was 51 years (IQR: 37.7–63.3), and 68.9% were female. Most were covered by the contributory health regime (56%), and outpatient care was the most frequent recruitment setting (31.1%). The highest positivity rate occurred in the Magdalena region (66.7%). Significant associations were found with intravenous (16.7%, $p = 0.0022$) and intranasal drug use (16.7%, $p = 0.0429$). Orthopedic (38.9%) and gynecological surgeries (22.2%) showed higher positivity but lacked statistical significance. No significant links were found with comorbidities. **Conclusion:** Opportunistic hospital-based screening for HCV in Colombia is feasible and can identify undiagnosed cases, particularly among people with drug use history. Despite low overall prevalence, significant associations with behavioral risk factors underscore the need to maintain focused screening approaches. This strategy also proved effective in initiating linkage to care, supporting national efforts toward HCV micro-elimination. Expansion of similar models may accelerate progress toward WHO's 2030 elimination goals in low-prevalence settings.

Disclosures: Javier Hernandez-Blanco: Nothing to Disclose, Juan Ignacio Marin Zuluaga: Nothing to Disclose, Ismael Yepes: Nothing to Disclose, Diana Chávez Bejarano: Nothing to Disclose, Alfredo Spath: GILEAD SCIENCES: Assoc Medical Director, receiving salary and other benefits, Yanette Suarez: Nothing to Disclose, Monica Tapias: Nothing to Disclose, Patricia Reyes Pabón: Nothing to Disclose, DianaD Escobar: Nothing to Disclose, Oscar Beltran: Nothing to Disclose

1388 | PROLINK-C: LEVERAGING LABORATORY INFORMATION SYSTEMS TO RECAPTURE HCV PATIENTS LOST TO FOLLOW-UP &MDASH; A MULTICENTER STUDY FROM SOUTHERN SPAIN

Federico Garcia[1] Alberto Vázquez Blanquiño[1] Ana Fuentes[1] Clara de Asís Morales Domínguez[2] Ana Belén Pérez[2] Francisco Franco Álvarez de Luna[3] Lucía Chaves Blanco[1] Lucía Pérez Rodríguez[1] Marta Illescas[1] Jaime Borrego-Jiménez[4] Teresa Cabezas[5] ISABEL VICIANA[6] José Manuel Azcona[7] Antonio Sampedro[8] Jesús Machuca[9] Inmaculada López[10] Carmen Lozano[11] Natalia Montiel Quezel-Guerraz[12] Carolina Freyre[13] Francisco Javier Casas-Ciria[14] Cesar del Prado[15], [1]Hospital Universitario Clínico San Cecilio, [2]Hospital Universitario Reina Sofía, [3]Hospital Universitario Juan Ramón Jiménez, [4]Hospital Universitario de Poniente, [5]Hospital Universitario Torrecárdenas, [6]Hospital Universitario Virgen de la Victoria, [7]Hospital Universitario Santa Ana, [8]Hospital Universitario Virgen de las Nieves, [9]Hospital Universitario Infanta Elena, [10]Hospital Universitario Costa del Sol, [11]Hospital Universitario Virgen del Rocío, [12]Hospital Universitario Puerta del Mar, [13]Hospital Universitario de Puerto Real, [14]Hospital Universitario de La Línea, [15]Hospital Universitario Punta de Europa

Background: Hepatitis C remains a major global health concern, and the World Health Organization has prioritized its elimination. In Spain, locating individuals lost to follow-up (LTFU) after a positive HCV antibody result is essential for elimination strategies. However, conventional retrieval methods have shown limited success. We present the results of an innovative "opportunistic" retrieval strategy integrated into routine healthcare workflows. **Methods:** This multicenter pilot study was conducted across several hospitals in southern Spain. It evaluated the performance of an automated "opportunistic" retrieval strategy embedded in each hospital's Laboratory Information System (LIS). A daily process generated lists of patients with previous positive anti-HCV antibody results and a currently available serum sample collected for any clinical purpose. Medical records were systematically reviewed to confirm evidence of sustained virologic response (SVR) or prior antiviral therapy. In cases without documented SVR, HCV RNA testing was performed using the available serum sample, avoiding the need for new sample collection or direct patient contact. Follow-up and linkage to care outcomes were subsequently monitored through electronic health record (EHR) review. **Results:** From May 22, 2023, to April 31, 2025, 3,222 anti-HCV-positive patients were identified. Of these, 2,859 (88.7%) had documented SVR and no reinfection risk. Among the remaining 363, HCV RNA testing was feasible in 359, identifying 124 active infections (34.5%), representing 3.8% of the total screened cohort. The majority of viremic individuals were male (71%) with a median age of 59 years (IQR 54–65). Among viremic cases, 62% had previously disengaged from care prior to achieving SVR, and 38% lacked any confirmatory RNA testing. Referrals originated from Primary Care (65%), Hospital Services (19%), and Emergency Departments (16%). All viremic cases were flagged to referring clinicians. Of the 124 patients, 66% (82) attended follow-up appointments; among them, 62% (51/82) initiated antiviral therapy, 14 declined treatment, and 17 missed their appointments. **Conclusion:** This study supports the feasibility and

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clinical utility of a LIS-based "opportunistic" strategy to recapture HCV patients lost to follow-up. By leveraging existing laboratory data and clinical encounters, this model facilitates reintegration into the HCV care cascade without requiring proactive patient outreach, thereby strengthening real-world elimination efforts.

Disclosures: Federico Garcia: Gilead: Speaking and Teaching, ViiV: Speaking and Teaching, Alberto Vázquez Blanquiño: Nothing to Disclose, Ana Fuentes: Nothing to Disclose, Clara de Asís Morales Domínguez: Nothing to Disclose, Ana Belén Pérez: Nothing to Disclose, Francisco Franco Álvarez de Luna: Nothing to Disclose, Lucía Chaves Blanco: Nothing to Disclose, Lucía Pérez Rodríguez: Nothing to Disclose, Marta Illescas: Nothing to Disclose, Jaime Borrego-Jiménez: Nothing to Disclose, Teresa Cabezas: Nothing to Disclose, ISABEL VICIANA: Nothing to Disclose, José Manuel Azcona: Nothing to Disclose, Antonio Sampedro: Nothing to Disclose, Jesús Machuca: Nothing to Disclose, Inmaculada López: Nothing to Disclose, Carmen Lozano: Nothing to Disclose, Natalia Montiel Quezel-Guerraz: Nothing to Disclose, Carolina Freyre: Nothing to Disclose, Francisco Javier Casas-Ciria: Nothing to Disclose, Cesar del Prado: Nothing to Disclose

1389 | HEPATITIS C VIRUS TESTING AND FOLLOW-UP FOR PERINATALLY EXPOSED INFANTS IN NORTH CAROLINA: FINDINGS FROM THE UNIVERSITY OF NORTH CAROLINA RELINK PROGRAM

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Background: Hepatitis C Virus (HCV) infections are increasing among reproductive-aged persons in the United States. It is estimated that 6-7% of perinatally exposed infants acquire an HCV infection, yet, as many as 70% of perinatally exposed infants are not tested or linked to appropriate care. As a part of the University of North Carolina (UNC) Relink Program, we identified, followed, and linked to care infants perinatally exposed to HCV in North Carolina. **Methods:** We searched UNC Health records (15 hospitals, 15.6% of statewide births) for infants perinatally exposed to HCV from the period May 2023-June 2024. After confirming exposure status, we reviewed infant medical records to collect demographic information and assess whether exposure status and appropriate testing recommendations were documented in hospital discharge summaries. HCV-exposed infants were then followed over time to monitor testing completion, and the families of infants untested at an age >6 months old were contacted via phone or MyChart for linkage to testing and care. Data were collected in REDCap, and summary statistics were computed in R. **Results:** We identified 79 HCV-exposed infants across North Carolina from May 2023-June 2024, 75 of whom had full medical records available. Most exposed infants were born in central North Carolina (54.7%; n = 41), 86.7% (n = 65) were born to Medicaid-insured persons, and 52% (n = 39) were born to persons with a diagnosed opioid use disorder. HCV exposure was documented in the infant's hospital discharge summary and added to the infant's problem list in 93.3% (n = 70) and 64% (n = 48) of cases, respectively. Recommendations for HCV testing were made in the infant's discharge summary in 64% (n = 48) of cases. Midway through the study period (in November 2023), the CDC published updated guidance recommending that all perinatally exposed infants be tested for HCV RNA at 2-6 months old. Among the 51 exposed births occurring after this date, recommendations for follow-up testing were made in 66.7% (n = 34) of infant discharge summaries, and 91.2% (n = 31) of these recommendations referenced the updated testing guidelines. Less than half (41.3%; n = 31) of all exposed infants completed HCV RNA testing without intervention from the program's relinkage activities. Twenty-one of these infants had a known testing date, and the majority (80.9%, n = 17) of tests were completed within the recommended timeframe of 2-6 months. Two infants (6.4% of those tested) were HCV-infected. Relink contact efforts have resulted in 11 additional infants being linked to care, of whom none have tested positive for HCV to date. **Conclusion:** Infants perinatally exposed to HCV are lost to follow-up at high rates in North Carolina. While exposure status is typically well-documented in infant discharge summaries, follow-up testing guidelines are less consistently noted and carried out. Findings suggest the need for further interventions to ensure appropriate testing and care.

Disclosures: Cory Spencer: Nothing to Disclose, Lauryn Ursery: Nothing to Disclose, Carl Seashore: Couplet Care, LLC: Scientific Advisor, Peyton Thompson: Nothing to Disclose

1390 | PREVALENCE AND RISK OF HCV INFECTION AMONG PSYCHIATRIC PATIENTS IN POLAND

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Background: HCV undiagnosed infection is particularly critical among populations of special interests, including patients hospitalized for mental disorders. They are more likely to engage in hazardous behaviours that are risk factors for communicable diseases. These factors include a high prevalence of intravenous drug use, homelessness, incarceration, and limited access to routine medical care. Additionally, the psychiatric symptoms themselves, such as reduced awareness, impaired judgment and possible less care for somatic health, may contribute to high-risk behaviours that facilitate HCV transmission. The epidemiology of HCV among patients with mental disorders seems to by insufficiently characterized, partly due to the lack of routine HCV screening in psychiatric settings. **Methods:** The Polish HCV initiative was a comprehensive cross-sectional research study conducted in Poland from 2021 to 2023, focusing on individuals hospitalized for mental health in 24 facilities. It is estimated that the study population covered over 7% of patients hospitalized due to the mental diseases. The main objective was to conduct HCV screening and collect data on prevalence and risk factors associated with HCV infection. Diagnosis of HCV infection was confirmed through positive HCV antibody screening and subsequent nucleic acid testing (NAT). Participants were interviewed by healthcare professionals, who administered a detailed questionnaire to collect the necessary data. All patients diagnosed with HCV infection were offered on-site treatment or were referred to the outpatient clinic. **Results:** The multivariate analysis identified intravenous drug use as the primary factor contributing to a positive HCV RNA test, with an odds ratio of 9.36 (95% CI: 6.09–14.39; $p < 0.001$). The presence of diagnosed and treated liver disease was also identified as a significant risk factor, with an odds ratio of 6.25 (95% CI: 4.16–9.38; $p < 0.001$).The odds ratio for blood transfusions prior to 1992 was 2.62 (95% CI: 1.30–5.29; $p = 0.007$). A recorded diagnosis of mental and behavioural disorders due to psychoactive substance abuse (ICD-10 F10-F19) had an OR of 1.802 (95% CI: 1.23–2.63; $p = 0.002$). This finding indicates that the most frequently reported group in the analysed population is also the group with the substantially increased high-risk of HCV. Those who had ever been in prison exhibited a diminished yet still markedly elevated risk of HCV infection, with an OR of 1.61 (95% CI: 1.08–2.41, $p = 0.020$). This finding reflects the heightened risk of HCV infection associated with incarceration. **Conclusion:** The prevalence of anti-HCV and HCV RNA in 1.8% and 1.3% of psychiatric patients respectively is about three times higher than in the general population in Poland. Systematic, integrated, and destigmatized approaches can facilitate better health outcomes for this vulnerable group, aligning with the goal of HCV elimination by 2030.

Disclosures: Krzysztof Tomasiewicz: Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Pfizer: Speaking and Teaching, GSK: Speaking and Teaching, Bausch Healtcare: Advisor, Takeda: Advisor, Piotr Galecki: Nothing to Disclose, Jerzy Jaroszewicz: AbbVie: Advisor, Roche: Grant/Research Support, Gilead Sciences: Advisor, Grifols: Speaking and Teaching, GSK: Advisor, MSD: Advisor, Novo Nordisk: Advisor, Novartis: Consultant, Malgorzata Pawlowska: Nothing to Disclose, Anna Piekarska: Nothing to Disclose, Krzysztof Simon: Nothing to Disclose, Dorota Zarebska-Michaluk: Gilead, Abbvie: Speaking and Teaching, Robert Flisiak: AbbVie: Advisor, Gilead: Advisor, Pfizer: Advisor

1391 | SERUM GROWTH DIFFERENTIATION FACTOR 15 PREDICTS THE PROGNOSIS OF PATIENTS WITH HEPATITIS C VIRUS-RELATED CIRRHOSIS AFTER VIRUS ELIMINATION

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Background: HCV-related cirrhosis is a major cause of hepatocellular carcinoma (HCC), and liver-related mortality. The advent of DAAs has dramatically improved treatment outcomes, with high SVR rates. However, despite viral eradication, the post-treatment prognosis remains heterogeneous. Reliable biomarkers are urgently needed to identify patients at high risk for adverse liver-related outcomes. We previously demonstrated that serum GDF15 levels are associated with the development of HCC and decompensated events in patients with metabolic dysfunction-associated steatotic liver disease. In the present study, we aimed to evaluate whether serum GDF15 levels could serve as a prognostic biomarker for liver-related events in patients with HCV-related cirrhosis after viral clearance. **Methods:** Patients with HCV-related cirrhosis were treated with DAAs at 38 institutions in Japan between February 2019 and December 2021. Data were prospectively collected and retrospectively analyzed. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards of participating centers (IRB No. 18431). Liver-related events—defined as the occurrence of HCC, hepatic decompensation, or liver-related death—were used as endpoints. Sera from registered patients were stored at –80°C at each institution, and GDF15 concentrations were measured using an enzyme-linked immunosorbent assay (ELISA) specific for human GDF15. **Results:** A total of 478 patients achieved SVR following DAA therapy. Among them, serum samples from 256 patients were available for GDF15 measurement. Of these, 162 patients without a prior history of HCC (HCC-naïve) were included in the final analysis. Median observation periods were 36.1 months (IQR: 16.6-52.7) and liver-related events were occurred in 36 patients. Patients who developed liver-related events during follow-up had significantly higher GDF15 levels at the time of end of treatment (EOT) (3.68 vs. 2.54 ng/mL) compared to those without events. In multivariable Cox proportional hazards analysis, the GDF15 level at EOT was identified as an independent risk factor for event occurrence from age and serum AFP level at baseline (hazard ratio: 1.15, $p < 0.05$). Applying a previously established cutoff of 1.75 ng/mL at EOT, patients with higher GDF15 levels had significantly lower event-free survival. While the cumulative event rate at two years was 17.9 % in the high-GDF15 group, no events occurred in the low-GDF15 group during the first two years of follow-up. **Conclusion:** Serum GDF15 levels are associated with liver-related events in patients with HCV-related cirrhosis who achieve SVR. GDF15 may serve as a valuable prognostic biomarker for identifying high-risk individuals in this population, thereby facilitating improved post-treatment surveillance and management strategies.

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1392 | PROSPECTIVE PAIRED LIVER BIOPSY STUDY OF HISTOLOGICAL CHANGES POST-DIRECT ACTING ANTIVIRAL-RELATED CURE IN CHRONIC HEPATITIS C INFECTION

Mohammed Rifat Shaik[1] Asif Hitawala[2] Elizabeth Wright[3] Alaina Magnani[4] David Kleiner[5] Marc Ghany[2],

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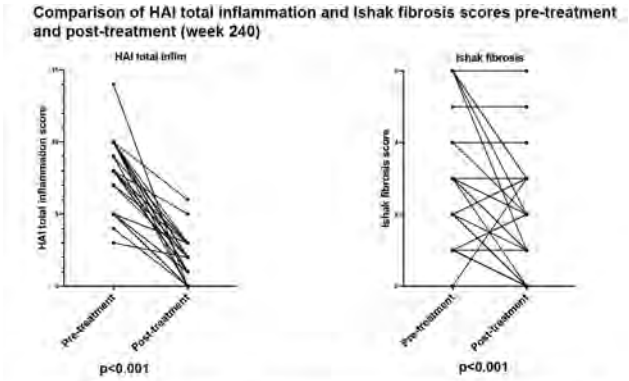
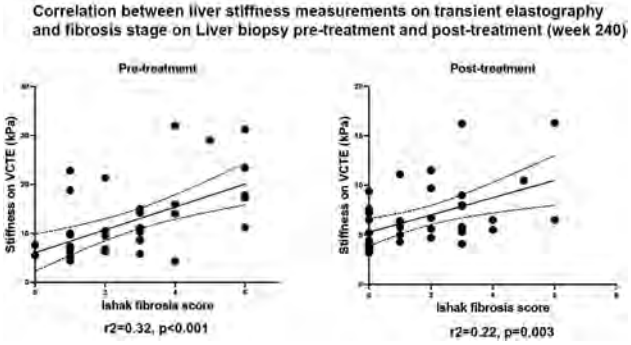
Background: Almost all persons with chronic hepatitis C (CHC) can be cured with direct acting antiviral (DAA) agents. Previous studies have demonstrated regression of hepatic fibrosis following sustained virologic response (SVR) using interferon-based regimens. However, data on histological outcomes with DAA therapy are limited. **Methods:** Adult persons cured of CHC with a DAA regimen with a pre-treatment liver biopsy were prospectively enrolled in a longitudinal follow-up study for 480 weeks. Participants are followed every 24 weeks, undergo annual HCC screening if non-cirrhotic at baseline or every 24 weeks if cirrhotic, annual transient elastography and a follow-up biopsy at week 240 (Wk240). Biopsies were reviewed by one hepatopathologist using the modified histology activity index (HAI) for inflammation, the Ishak fibrosis score for fibrosis, and a 0–4 steatosis scale based on the percentage of hepatocytes with fat. Histological improvement was defined as a ≥ 2 point decrease in HAI score with no worsening of fibrosis. Paired t-test was used to compare histologic scores and liver stiffness measurements (LSM) between baseline and Wk240. **Results:** A total of 121 subjects were enrolled of whom 46 reached Wk240. This is an interim analysis of 41/46 subjects who completed the Wk240 follow-up biopsy (5 subjects declined liver biopsy). Liver tissue was insufficient for scoring in 3 subjects. Mean age at baseline was 59 ± 9 years, 26 were male, 27 White, 2 Asian, 9 Black, 3 other. HCV genotype 1 accounted for 75% of infections, and 75% received sofosbuvir/velpatasvir. Mean baseline ALT was 95 ± 52 U/L, and mean LSM was 12.5 ± 7.5 kPa. Median duration between biopsies was 8.5 years. Pre-therapy mean total HAI and Ishak fibrosis scores were 8 ± 2 and 3 ± 2, respectively and at Wk240 2 ± 1 and 2 ± 2. SVR was durable, with undetectable HCV RNA confirmed a median of 23 times in follow-up. At Wk240, 32 (84%) showed histologic improvement (of whom 13 (34%) had HAI ≤ 3 and Ishak 0), 1 (3%) remained stable, and 5 (13%) worsened (in all cases inflammation improved by ≥ 3 points but fibrosis increased by 1 stage likely representing sampling error). LSM correlated weakly with fibrosis stage on liver biopsy at both baseline ($r^2 = 0.32$, $p < 0.001$) and post-treatment ($r^2 = 0.22$, $p = 0.003$). **Conclusion:** A majority of patients with CHC showed histologic improvement with substantial (mean 6-point) reduction in inflammation and 37% with complete resolution of fibrosis over 8.5 years after achieving SVR with DAA therapy.





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1393 | EFFECTIVE RE-ENGAGEMENT OF HEPATITIS C PATIENTS: A MULTICENTER STUDY BASED ON LABORATORY RECORDS IN ARGENTINA

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Background: Hepatitis C virus (HCV) remains a significant cause of global morbidity despite the availability of highly effective direct-acting antivirals (DAAs). In Argentina, fragmented healthcare access and a high prevalence of advanced liver disease

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underscore the need for re-engagement strategies to achieve HCV elimination. This study aimed to assess the effectiveness of a multicenter re-engagement program for HCV patients lost to follow-up in high-complexity healthcare settings. **Methods:** A multicenter prospective study (March–November 2024) analyzed blood samples from five hospitals to identify HCV antibody-positive patients. Positive cases were contacted to confirm viremia, undergo clinical evaluation, and initiate treatment. Data collected included re-engagement rates, fibrosis staging (FibroScan), genotype distribution, treatment regimens, and sustained virologic response (SVR) rates. Statistical analyses were performed using chi-square tests to compare positivity rates, genotypes, and treatments. **Results:** Among 206,053 samples, 3,334 (1.62%) tested positive for HCV antibodies, and 2,149 (64.5%) were potentially eligible for re-engagement. Non-re-engagement causes included deaths (419), previous cure (741), and liver transplants (25). Positive cases were 54.16% male ($p = 0.03$). A total of 422 patients (19.6%) were successfully re-engaged, of whom 311 (73.8%) exhibited advanced fibrosis ($\geq$F2). Genotype distribution was as follows: 1a (22.00%), 1b (18.99%), 2 (8.24%), 3 (18.72%), 4 (8.13%), and data not obtained (24.92%). No significant difference was found between genotype 3 and others ($p = 0.3$). Among re-engaged patients, 167 initiated treatment with Sofosbuvir/Velpatasvir (70.08%) or Glecaprevir/Pibrentasvir (29.92%) ($p = 0.12$). The overall SVR12 rate was 97.98% among treated patients. SVR4 was assessed in 112 patients, showing a 100% correlation with SVR12. Among re-engaged patients, 15% were unaware of their positive result, 10% were unaware of the existence of effective treatments, and 64% were unaware of disease progression. **Conclusion:** This program successfully re-engaged HCV patients lost to follow-up, achieving high SVR12 rates and demonstrating the utility of SVR4 as an early predictor of treatment success. A significant proportion of patients were unaware of their diagnosis, available treatments, or disease progression. The majority of treated patients had advanced fibrosis, highlighting the need for proactive strategies targeting high-risk populations. These findings underscore the necessity of establishing elimination programs in countries with complex healthcare systems like Argentina.

Disclosures: Fernando Cairo: Nothing to Disclose, MANUEL BARBERO: Nothing to Disclose, IGNACIO ROCA: Nothing to Disclose, LUCIA NAVARRO: Nothing to Disclose, Nicolas Dominguez: Nothing to Disclose, OMAR GALDAME: Nothing to Disclose, AYELEN TRILLO: Nothing to Disclose, Esteban Gonzalez Ballerga: Nothing to Disclose, DANIEL CALFUNAO: Nothing to Disclose, RODRIGO BELLONI: Nothing to Disclose, ADRIAN BOLOGNA: Nothing to Disclose, ANDREA CURIA: Nothing to Disclose, MELINA SUSANA: Nothing to Disclose, SILVIA BORZI: Nothing to Disclose, STEFANIA BURGOS: Nothing to Disclose

1394 | LONG-TERM BENEFITS FOLLOWING HEPATITIS C VIRUS TREATMENT THROUGH FACILITATED TELEMEDICINE; EXPERIENCES OF PEOPLE WHO USE DRUGS FIVE YEARS AFTER ACHIEVING A SUSTAINED VIROLOGICAL RESPONSE

Zoi Papalamprakopoulou[1] Tin Dang[2] Christopher Gonzalez[2] Colin Tedesco[3] Paul Updike[3] Christina Corl[3] Arpan Dharia[1] Noelia Hernandez[2] Martin Shapiro[2] Elaine Wethington[4] Andrew Talal[1], *[1]University at Buffalo, [2]Weill Cornell Medicine, [3]Catholic Health, [4]Cornell University*

Background: Facilitated telemedicine hepatitis C virus (HCV) treatment integrated into opioid treatment programs (OTPs) has shown high effectiveness and patient satisfaction among people with opioid use disorder (OUD). However, the long-term impact of a sustained virological response (SVR) obtained through facilitated telemedicine remains unexplored. We examined people with OUD perspectives on an SVR obtained through facilitated telemedicine. **Methods:** We conducted two focus group discussions (FGDs) with nine participants at least five years after achieving an SVR through facilitated telemedicine in OTPs (New York State, 2018–2020). Eligibility criteria included individuals aged at least 18 years who had previously achieved SVR through this model, remained actively enrolled in an OTP, and were able to provide informed consent. We identified a list of potential FGD participants from those who had participated in a randomized clinical trial of facilitated telemedicine. We used a semi-structured interview guide and thematically analyzed transcripts. **Results:** Participants had a mean age of 52.6 years (standard deviation = 13.7), 66.6% (6/9) were male, and 88.8% (8/9) identified as White. We identified three FGD themes each corresponding to pre-, during, or post-intervention (see Figure): (1) attitudes toward HCV and barriers to treatment among people with OUD, (2) embracing telemedicine HCV care integrated into OTPs, and (3) experiencing long-term benefits from facilitated telemedicine across all aspects of HCV care and overall well-being. Participants described feeling shame and fearful disclosing their HCV status prior to seeking care. Barriers to care included competing priorities, perceiving HCV as low-priority medical comorbidity, and third-party payer coverage restrictions (Theme 1). Participants valued telemedicine for its convenience and ability to overcome transportation barriers. Many preferred the empathetic telemedicine

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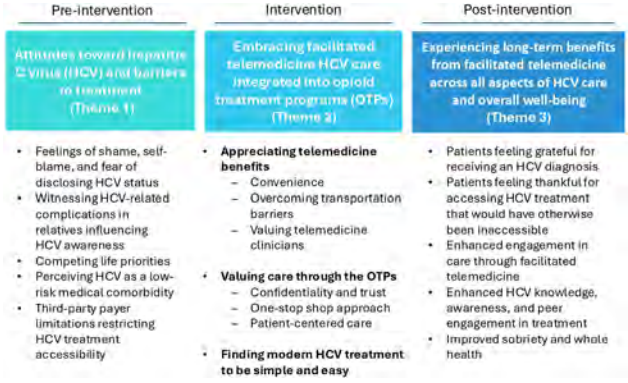
clinicians and appreciated the one-stop shop approach (Theme 2). At least five years post intervention, participants reported lasting benefits of achieving an SVR, including enhanced HCV knowledge, improved sobriety, and improvement in whole health (Theme 3). **Conclusion:** At least five years post achieving an SVR, people with OUD reported improved sobriety, overall well-being, and sustained satisfaction with telemedicine-based HCV care. These findings highlight the sustained impact of both an SVR and the care delivery model.



Disclosures: Zoi Papalamprakopoulou: Nothing to Disclose, Tin Dang: Nothing to Disclose, Christopher Gonzalez: Nothing to Disclose, Colin Tedesco: Nothing to Disclose, Paul Updike: Nothing to Disclose, Christina Corl: Nothing to Disclose, Arpan Dharia: Nothing to Disclose, Noelia Hernandez: Nothing to Disclose, Martin Shapiro: Nothing to Disclose, Elaine Wethington: Nothing to Disclose, Andrew Talal: Gilead Sciences: Grant/Research Support, AbbVie: Consultant, Abbott Laboratories: Grant/Research Support, Novo Nordisk: Advisor, Astra Zeneca: Grant/Research Support, Novo Nordisk: Grant/Research Support, Empath Medical: Medical Director

1395 | PROVIDER EDUCATION AND TRENDS IN ANTEPARTUM HEPATITIS C VIRUS SCREENING FROM 2021 – 2025 AT AN ACADEMIC MEDICAL CENTER IN CHICAGO

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Background: Perinatal hepatitis C virus (HCV) transmission presents a public health concern that threatens HCV elimination efforts. The American College of Obstetricians and Gynecologists (ACOG) updated its clinical practice guidelines for antepartum HCV screening in 2021 and 2023; they recommend universal screening for each pregnancy. Our study aims to evaluate antepartum HCV screening trends at an academic medical center in Chicago from 2021 – 2025 after the provision of maternal health provider education in 2024 – 2025. **Methods:** We conducted a retrospective cohort study of antepartum HCV screening rates at our institution from 2021 – 2025. Patients were included if they were 18 years or older with a pregnancy end date in March or April of each year. Data collected from the electronic health record included infectious diseases screening, age, race/ethnicity, insurance, and gravida. We compared the HCV screening rate difference between subsequent years using a z-test to analyze difference in proportions. We used logistic regression to assess relationships among patient characteristics and HCV screening in 2025. Pharmacists delivered antepartum HCV screening education to clinicians with in-person slide presentations at two maternal health department meetings and via an emailed link to the slides in 2024 – 2025. **Results:** From 2021 – 2025, most antepartum patients were 20 – 29 years old, Black, non-Hispanic, and had Medicaid as their payor. The antepartum HCV screening rate was 38.8% prior to the 2021 ACOG HCV screening practice advisory, and 71.0% in 2025 post-provider education. HCV screening rates increased from 38.8% to 49.5% between 2021-2022 ($p = 0.015$), from 49.5% to 49.6% between 2022-2023 ($p = 0.975$), from 49.6% to 55.5% between 2023-2024 ($p = 0.068$), and from 55.5% to 71% between 2024-2025 ($p = 0.008$). See Table 1 for additional 2025 patient characteristics. In 2025, patients who had HBV surface antigen screening had higher odds of HCV screening than those without HBV screening [OR = 55.02 (95% CI 26.03–112.81); $p < 0.001$], and patients with commercial insurance were more likely to be screened for HCV than those with Medicaid coverage [OR = 3.40 (95% CI 1.07–5.40); $p = 0.034$] (Table 2). Thirty-nine physicians of the 71 total maternal health providers attended one of two live education sessions on antepartum HCV screening. As of 5/29/2025, 28 of the 71 clinicians had opened the link to the education slides. **Conclusion:** The highest numeric and percent increases in antepartum HCV screening occurred from 2024 to 2025, in the same year that pharmacists offered HCV screening education to the maternal health clinicians. The second highest increase in HCV screening was from 2021 to 2022, after the 2021 ACOG HCV advisory. Despite improvements from 2021 – 2025, a gap remains between our institution's antepartum HCV screening rate and the guideline-advised universal screening; this necessitates further quality improvement research and education.

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Table 1. Antepartum Patient Characteristics, 2025

Patient Characteristics	2025 (N = 449)
Mean Age, in years ± SD	28.9 ± 5.8
Age at Delivery, in years, n (%)	
18-19	17 (3.8)
20-29	222 (49.4)
30-39	191 (42.5)
40-49	19 (4.2)
Ethnicity, n (%)	
Non-Hispanic	296 (65.9)
Hispanic	153 (34.1)
Race, n (%)	
Black / African American	238 (53.0)
White / Caucasian	160 (35.6)
Asian / Pacific Islander	38 (8.5)
American Indian / Alaska Native	2 (0.4)
Unknown	11 (2.4)
Insurance, n (%)	
Medicaid	319 (71.0)
Commercial	95 (21.2)
Uninsured / Self-Pay	35 (7.8)
Medicare	0 (0.0)
Multiple Payors	0 (0.0)
Gravida, n (%)	
1	90 (20.0)
2-4	235 (52.3)
≥5	124 (27.6)
Infectious Disease Screening, n (%)	
Primary Outcome: Hepatitis C Virus	319 (71.0)
Hepatitis B Virus Surface Antigen	344 (76.6)
HIV	373 (83.1)
Gonorrhea / Chlamydia	363 (80.8)
Syphilis	383 (85.3)

Table 2. Odd Ratios of Hepatitis C Virus Screening by Patient Characteristic, 2025

	2025 (N = 436)	
Patient Characteristics	OR (95% CI)	P-value
Age at Delivery, in years (reference = 20-29)		
18-19	3.55 (0.46, 27.28)	0.224
30-39	0.87 (0.47, 1.61)	0.660
40-49	0.91 (0.21, 3.95)	0.904
Ethnicity (reference = Non-Hispanic)		
Hispanic	0.81 (0.28, 2.30)	0.690
Race* (reference = Black / African American)		
White / Caucasian	1.50 (0.45, 5.03)	0.511
Asian / Pacific Islander	1.28 (0.43, 3.74)	0.655
Insurance* (reference = Medicaid)		
Commercial	2.40 (1.07, 5.40)	0.034
Uninsured / Self Pay	0.96 (0.33, 2.79)	0.932
Gravida (reference = 1)		
2-4	0.75 (0.34, 1.65)	0.472
≥5	1.28 (0.48, 3.24)	0.617
Hepatitis B Virus (HBV) Surface Antigen Screened (reference = Not Screened for HBV)		
Screened for HBV	55.02 (26.83, 112.81)	<0.001

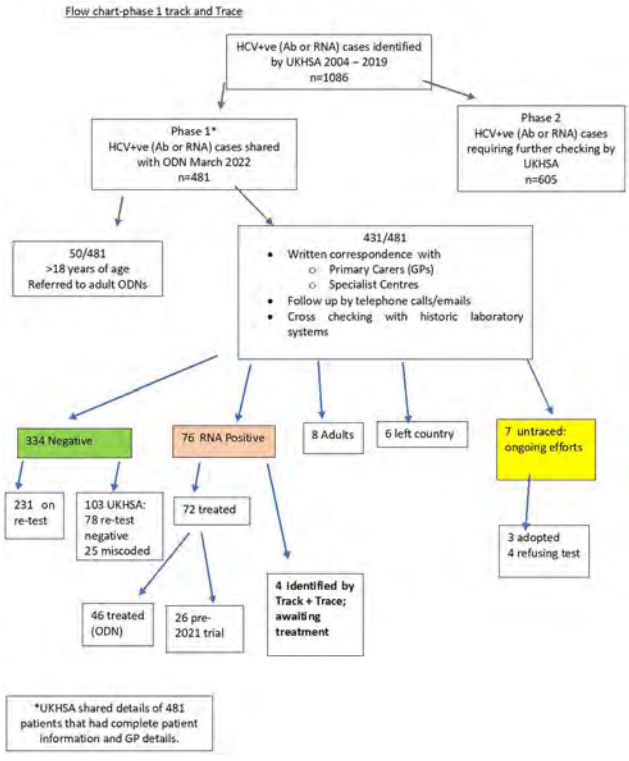
*Categories with low numbers were not included in the logistic regression model (Race: American Indian / Alaska Native and Unknown; and Insurance: Medicare and Multiple Payors)

Disclosures: Michelle Martin: Nothing to Disclose, Evan Brownsberger: Nothing to Disclose, Christin Jogan: Nothing to Disclose, Nina Mai: Nothing to Disclose, Amal Al-Bayati: Nothing to Disclose, Katie Kaczmarski: Nothing to Disclose

1396 | TRACING CHILDREN WITH SILENT HEPATITIS C IN THE UK

Clare Rayner[1] Rachel Cockayne[2] Carla Lloyd[3] Stephen Corcoran[3] Monica Mitcham[3] William Irving[1] Ruth Simmons[4] Annabel Powell[4] Deirdre Kelly[3],
[1]Birmingham Chidlren's Hospital, [2]Birmingham Women's and Children's, [3]Birmingham Children's Hospital, [4]UKHSA (United Kingdom Health Security Agency)

Background: Hepatitis C (HCV) infection is asymptomatic in children & young people (CYP) but carries long term risks of chornic liver disease, and therefore, these CYP need to be identified. Direct-acting antiviral (DAAs) drugs (licensed 2020 for CYP) provide effective cure making the World Health Organisation's (WHO) 2030 elimination target achievable. In the United Kingdom (UK), an HCV+ve test is legally 'notifiable' with cases reported to a government agency (UKHSA). Since 2022 the national paediatric Multi-Disciplinary Team Operational Delivery Network (pMDT ODN) has worked with UKHSA to Track & Trace CYP with HCV to ensure they are appropriately treated & managed. **Methods:** 1086 CYP (<18 yrs) HCV+ve between 2004 to 2019 were identified by UKHSA. Initially 481/1086 were shared with ODN in March 2022. Outcomes were determined via written & telephone communications with primary care providers (PCP); laboratory cross-checks; working with hospital specialists; & re-testing. **Results:** Of 481/1086 cases, 50 were adults leaving 431 CYP to trace. Current HCV status was ascertained in 418 (97%). Seventy-six (17.9%) had been RNA+ve & treated. In 13 cases the outcome is unknown (left UK, adopted or refused tests) (See Flow Chart-image 1). Challenges in case-finding were tracking patients, obtaining test results, & refusals to re-test. In view of the long-term health consequences of HCV, & available treatment it is essential to overcome these challenges. Obtaining re-test results was achieved by repeated cross-checking with laboratory systems, PCP & treating specialists, proving time intensive. For CYP requiring new tests, PCP & family education was provided by a specialist nurse who engaged with families to reduce stigma & support testing. A 'GP Champion' identified those who had changed GP, emigrated or been adopted. Adopted CYP in UK receive a new identity that cannot be shared at present. **Conclusion:** Tracing and treating children with HCV is essential but complex. We have successfully traced & treated 97% of CYP with a reported HCV+ve test despite significant barriers. Recommendations include dedicated track & trace staff (coordinator, GP Champion, specialist nurse), systems for transfer of neonatal HCV test records to PCPs, education for PCPs on the importance of retesting & robust laboratory systems which ensure that positive neonatal tests are followed-up until negative. Discussions are ongoing with adoption agencies to act as intermediaries to trace those CYP who have been adopted with a new identity. Our cohort provides valuable lessons for systems change to assist WHO's 2030 elimination plan.



Disclosures: Clare Rayner: Nothing to Disclose, Rachel Cockayne: Gilead Sciences: Grant/Research

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Support, Carla Lloyd: Nothing to Disclose, Stephen Corcoran: Nothing to Disclose, Monica Mitcham: Nothing to Disclose, William Irving: Nothing to Disclose, Ruth Simmons: Nothing to Disclose, Annabel Powell: Nothing to Disclose, Deirdre Kelly: Mirum: Advisor, Intercept: Advisor, Astra Zeneca: Advisor, Takeda: Advisor

1397 | NAKED-EYE DETECTION OF UNAMPLIFIED HCV RNA IN CLINICAL SPECIMENS USING A DUAL-PROBE MAGNETIC NANOPARTICLE SYSTEM WITH ENZYME-MEDIATED SIGNAL AMPLIFICATION

Wei Hou[1], [1]Translational Medicine Research Center, School of Clinical Medicine, Qilu Medical University, CHINA

Background: Hepatitis C virus (HCV) infection continues to pose a significant global health challenge, with chronic cases potentially advancing to cirrhosis and hepatocellular carcinoma. Although nucleic acid amplification tests (NAATs) are regarded as the gold standard for HCV RNA detection in the current era of direct-acting antiviral (DAA) therapies, their dependence on sophisticated instrumentation and high operational costs limits accessibility, particularly in resource-limited regions. In response to this need, we present an innovative nanoparticle-based biosensing platform that enables visual detection of unamplified HCV RNA through a combination of magnetic separation and enzyme-amplified colorimetric readout. **Methods:** Our developed biosensor integrates several key innovations, utilizing a dual-probe magnetic nanoparticle system that employs genotype-independent oligonucleotides targeting both the 5'UTR and NS3 regions of the HCV genome. This ensures specific viral RNA capture from serum samples. The methodology consists of three critical components: (1) A dual-probe magnetic nanoparticle system that captures HCV RNA with high specificity; (2) An alkaline phosphatase (ALP)-activated click chemistry cascade that generates colorimetric signals through copper-mediated aggregation of gold nanoparticles (AuNPs); (3) Target-dependent AuNP aggregation produces a visible color transition (from red to blue) that correlates with viral load, allowing for naked-eye detection. **Results:** Validation with 120 clinical specimens demonstrated an impressive 99.2% concordance with RT-qPCR results, alongside 100% specificity and complete genotype inclusivity. This establishes our platform as a viable alternative for point-of-care HCV screening. **Conclusion:** The cost-effective design and stability at ambient temperatures make this biosensor particularly suitable for use in low-resource settings. Furthermore, the modular architecture allows for rapid adaptation to detect other bloodborne pathogens (e.g., Dengue, Zika) through simple modifications of probe sequences, positioning this technology as a versatile diagnostic platform for global infectious disease surveillance.
Disclosures: Wei Hou: Nothing to Disclose

1398 | BEMNIFOSBUVIR AND RUZASVIR PROVIDED AS A FIXED-DOSE-COMBINATION DEMONSTRATES HIGH RELATIVE BIOAVAILABILITY TO THEIR INDIVIDUAL FORMULATIONS AND CAN BE DOSED WITH NO REGARD TO FOOD

Xiao-Jian Zhou[1] Brett Smith[2] Maureen Montrond[3] Keith Pietropaolo[3] Bruce Belanger[3] Shannan Lynch[3] Dayle James[3] Maria Arantxa Horga[3] Janet Hammond[3], [1]Atea Pharmaceuticals, Inc, [2]Altasciences, [3]Atea Pharmaceuticals, Inc.

Background: Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent pan-genotypic inhibitors of the HCV NS5B polymerase and NS5A protein, respectively. BEM/RZR is in phase 3 development for the treatment of chronic HCV using a fixed-dose-combination (FDC) of the two investigational drugs, each containing 275 mg BEM and 90 mg RZR. We report results from a phase 1 study evaluating the relative bioavailability (rBA) of the FDC to the individual formulations of BEM and RZR in healthy participants. The study also determined the effect of a high-fat/high-calories (HFHC) meal or famotidine on the pharmacokinetics (PK) of BEM/RZR FDC (NCT06204679). **Methods:** This adaptive study evaluated the rBA of FDC prototypes to BEM/RZR formulations and the effect of food or famotidine. The study initially enrolled 24 participants who received a single dose of 550 mg BEM (2x275 mg tablets) and 180 mg RZR (2x90 mg capsules) on an empty stomach as reference. The study continued with 24 participants who received a single dose of 550 mg BEM /180 mg RZR as 2xFDC tablets on an empty stomach and after a HFHC meal according to a randomized design. Participants further received two doses of 20 mg famotidine approximately 12h apart, with 2xFDC tablets dosed on an empty stomach together or 2h after the second dose of famotidine. Intensive PK sampling was performed over 144h and plasma concentrations of BEM and metabolites and RZR were quantitated using validated bioanalytical methodologies. **Results:** Treatment-emergent adverse events were infrequent and generally mild. Based on total plasma exposure (AUCinf), the FDC showed high rBA of 86.8, 89.0 and 113% respectively for BEM, its nucleoside metabolite AT-273 (plasma surrogate for the active intracellular triphosphate metabolite AT-9010) and RZR, respectively. An HFHC

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meal increased the AUCinf of BEM, AT-273 and RZR by 8.6, 11.1 and 38.5%, respectively. When dosed simultaneously, famotidine did not affect the total plasma exposure of BEM, AT-273 or RZR with geometric mean ratios ranging from 95.8%-103%. **Conclusion:** The BEM/RZR FDC was safe and well-tolerated when dosed without or with food or with famotidine. BEM/RZR FDC demonstrated a high rBA to the BEM and RZR individual reference formulations. A HFHC meal or simultaneously co-administered famotidine had no meaningful effect on plasma exposure of the FDC. Study results support use of the BEM/RZR FDC in the ongoing and future clinical trials. **Disclosures:** Xiao-Jian Zhou: Nothing to Disclose, Brett Smith: Nothing to Disclose, Maureen Montrond: Nothing to Disclose, Keith Pietropaolo: Nothing to Disclose, Bruce Belanger: ATEA Pharmaceuticals: Employee, Shannan Lynch: Atea Pharmaceuticals: Employee, Dayle James: Nothing to Disclose, Maria Arantxa Horga: Nothing to Disclose, Janet Hammond: Nothing to Disclose

1399 | MICRO-ELIMINATION OF HEPATITIS C (HCV) IN A LARGE AND RISKY POPULATION OF DIABETIC PATIENTS BY COLLABORATIVE CARE SYSTEM

Tsung-Hui Hu[1] Yung-Hsiang Lin[2] Rong-Nan Chien[3] Lay San Lim[4] Chia-Yu Chang[2] Te-Sheng Chang[5] Yu-Ling Lu[6] Ming-Ling Chang[7] Soh-Ching Ng[8] Chih-Lang Lin[9], [1]Division of Hepato-Gastroenterology,Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [2]Division of Endocrinology and Metabolism,Chiayi Chang Gung Memorial Hospital, Chiayi, Taiwan., [3]Taiwan National Hepatitis C Program Office, Ministry of Health and Welfare, Taipei, Taiwan, [4]Division of Endocrinology and Metabolism,Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan., [5]Division of Hepato-Gastroenterology,Chiayi Chang Gung Memorial Hospital, Chiayi, Taiwan., [6]Division of Endocrinology and Metabolism, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan., [7]Liver Research Unit, Linkou Chang Gung Memorial Hospital and University, Taoyuan, Taiwan, [8]Division of Endocrinology and Metabolism,Keelung Chang Gung Memorial Hospital, Keelung, Taiwan., [9]Division of Hepato-Gastroenterology,Keelung Chang Gung Memorial Hospital, Keelung, Taiwan.

Background: Previous studies have indicated a higher prevalence of type 2 diabetes mellitus among populations that are seropositive for the hepatitis C virus (HCV) infection and vice versa, particularly in individuals with cirrhosis. Various mechanisms have been suggested to explain the link between HCV and diabetes, primarily through the development of insulin resistance. However, there is a lack of reliable data on the prevalence of HCV in diabetic populations and outcomes after HCV treatment. HCV micro-elimination approach, which focuses treatment on DM population was also rarely reported. We aim to conduct HCV elimination for a large population with diabetes mellitus and follow up outcomes after HCV treatment. **Methods:** We conducted a study at four medical centers in Chang Gung Memorial Hospital of Taiwan (Linkou, Keelung, Chiayi, and Kaohsiung). Taking the diabetic cases in the shared care system from 2021 to 2023 as the tracking generation. Several meetings were held among hepatologists and endocrinologists from the four medical centers to improve the HCV screening process and to establish a strong linkage for diagnosis and treatment of HCV. The achievement rate of HCV care cascade, the coverage of treatment, and outcome after treatment rate were analyzed. Data on sugar and lipid profiles, renal and liver function panels, HCV antibody (HCV-Ab), HCV RNA, and urine albumin creatinine ratio (UACR) were retrieved retrospectively from these patients' electronic medical records. **Results:** Among 46,601 patients with diabetes in the shared care system, 37,159 had been screened for HCV antibodies, and 2,974 were found to be HCV seropositive, resulting in an HCV screening rate of 79.74% and a prevalence of hepatitis C virus seropositivity of 8.74%. 2697 of 2974 (90.68%) patients were linked to HCV RNA testing, with a positive HCV RNA of 62.88% and viremic (1696 patients). Overall, 1601 of 1696 have received anti-viral therapies (either IFN based or DAA treatment). The coverage of treatment was high as 94.39%. For patients treated and achieved a sustained viral response, significant improvements in HbA1C levels (7.4$\pm$1.5 to 7.1$\pm$1.3; $P < 0.001$), liver biochemical tests ($P < 0.001$), and the APRI and FIB-4 indices ($P < 0.001$) were observed after treatment. However, there was no improvement of serum creatinine, eGFR, as well as urine albumin creatinine ratio (UACR) before and after HCV treatment. **Conclusion:** In the present study, the prevalence of hepatitis C virus seropositivity in the diabetic population is 8.74%, which is about two to three times of general population in Taiwan. HCV is a significant issue in the diabetic population that we recommend an elimination program of HCV is mandatory to get the benefits following HCV treatment and to facilitate global HCV elimination.

Disclosures: Tsung-Hui Hu: Nothing to Disclose, Yung-Hsiang Lin: Nothing to Disclose, Rong-Nan Chien: Nothing to Disclose, Lay San Lim: Nothing to Disclose, Chia-Yu Chang: Nothing to Disclose, Te-Sheng Chang: Nothing to Disclose, Yu-Ling Lu: Nothing to Disclose, Ming-Ling Chang: Nothing to Disclose, Soh-Ching Ng: Nothing to Disclose, Chih-Lang Lin: Nothing to Disclose

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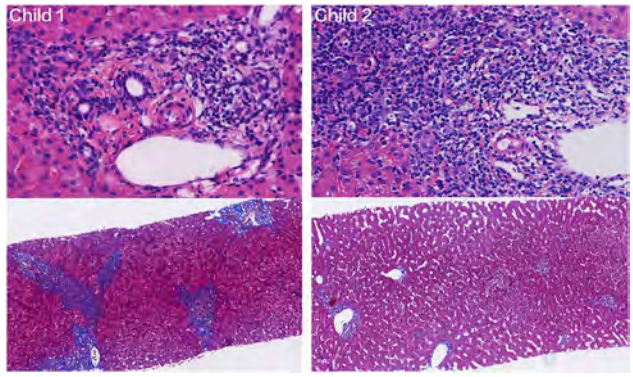
1400 | HISTOPATHOLOGICAL FEATURES AND EIGHT-WEEK TABLET-SPLIT SOFOSBUVIR/VELPATASVIR TREATMENT FOR YOUNG CHILDREN WITH ACUTE HEPATITIS C: A CASE SERIES STUDY

Ru-Yue Chen[1] Ya-Jie Pan[1] Yan-Qin Ai[2] Xue-Yan Lv[1] Yue-hang Wang[1] Zhuang-zhuang Zhai[1] Xue-Jing Yu[1] Qing-Lei Zeng[1], [1]Department of Infectious Diseases, The First Affiliated Hospital of Zhengzhou University, China, [2]Department of Infectious Diseases, Xuchang Central Hospital, Xuchang, Henan Province, China

Background: The clinical and therapeutic research on acute hepatitis C (AHC) in children under 5 remains scarce. **Methods:** Two 4-year-old children (Nos. 1 and 2) acquired hepatitis C virus (HCV) infection through unsafe injections and were diagnosed with AHC. Both children displayed no clinical symptoms and signs. Liver biopsies were performed prior to initiating an 8-week regimen of half-dose sofosbuvir/velpatasvir (200/50mg [1/2 tablet, tablet-split], a total of one bottle of Epclusa® for each child) once daily. The adverse events, HCV RNA levels, liver function, complete blood counts, renal function, lipid profiles, and other relevant parameters were monitored through week 12 post-treatment. The primary endpoint was sustained virologic response at 12 weeks (SVR12) post-treatment, and the secondary endpoint was the safety profiles. **Results:** Child No. 1 had an HCV RNA level of 1500 IU/mL and an alanine aminotransferase (ALT) level of 316 U/L, abdominal ultrosound showed splenomegaly, and the liver biopsy indicated mild hepatitis and moderate fibrosis (G1S2, Figure). Child No. 2 had an HCV RNA level of 2300 IU/mL and an ALT level of 15 U/L, and the liver biopsy indicated moderate hepatitis and mild fibrosis (G2S1, Figure). HCV genotyping revealed that both children were infected with genotype 1b. After 1 week of treatment, Child No. 1's HCV RNA level decreased to 49.2 IU/mL, with ALT normalization; and Child No. 2 had undetectable HCV RNA and ALT normalization. By week 2, Child No. 1 had undetectable HCV RNA. Finally, both children achieved SVR12, and no specific adverse events were observed during treatment or follow-up period; additionally, blood counts, renal function, lipid profiles, and electrolyte levels maintained normal. At SVR 24, child No. 1's spleen had returned to normal size. **Conclusion:** In conclusion, young children with AHC may exhibit significant liver injury, and eight-week sofosbuvir/velpatasvir appears safe and effective. Future larger sample size studies are needed to confirm the safety and efficacy of this approach.



Disclosures: Ru-Yue Chen: Nothing to Disclose, Ya-Jie Pan: Nothing to Disclose, Yan-Qin Ai: Nothing to Disclose, Xue-Yan Lv: Nothing to Disclose, Yue-hang Wang: Nothing to Disclose, Zhuang-zhuang Zhai: Nothing to Disclose, Xue-Jing Yu: Nothing to Disclose, Qing-Lei Zeng: Nothing to Disclose

1401 | THE CLINICAL EPIDEMIOLOGY AND TREATMENT OF ACUTE HEPATITIS C CAUSED BY UNSAFE CLINICAL PRACTICES

Ru-Yue Chen[1] Yan-Qin Ai[2] Ya-Jie Pan[1] Xue-Yan Lv[1] Yue-Hang Wang[1] Xue-Jing Yu[1] Zhuang-Zhuang Zhai[1] Qing-Lei Zeng[1], [1]The First Affiliated Hospital of Zhengzhou University,Zhengzhou,China, [2]Xuchang Central Hospital, Xuchang,Henan,China

Background: Compared to chronic hepatitis C, acute hepatitis C (AHC) is more difficult to detect and therefore less likely to be treated in a timely manner. This study reports the clinical epidemiological characteristics, treatment, and outcomes of AHC caused by unsafe clinical practices. **Methods:** From 2023 to 2024, an outbreak of hepatitis C caused by unsafe clinical practices occurred at a clinic in Xuchang City, Henan Province, China. The local government and Center for Disease Control and Prevention screened 630 individuals. Through comprehensive epidemiological and virological assessments, 72 adolescents and adults aged 5 years and older were identified as having AHC. Among them, 47 AHC patients agreed to receive a 12-week course of direct-acting antiviral (DAA) therapy. The criterion for evaluating treatment efficacy was sustained virological response (SVR) 12, defined as undetectable hepatitis C virus (HCV) RNA 12 weeks after completion of therapy, meanwhile, the safety profiles were closely monitored. **Results:** Among the 72 patients with detectable HCV RNA, 38 (52.8%) patients were male, 71 (98.6%) patients tested positive for HCV antibodies. The mean age was 62.5 (54.0, 72.0) years, with 4 (5.6%) patients aged 5-12 years, 4 (5.6%) patients aged 13-18 years, and 64 (88.8%) patients aged over 18 years. The mean HCV RNA level was 5.60 $\pm$ 1.64 $\log_{10}$ IU/mL, genotype 1b accounted for 87.5% (63/72), 2.8% (2/72) of patients with genotype 2a,

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and 9.7% (7/72) of patients were not tested for genotype. Among the 37 patients with alanine aminotransferase (ALT) results, the mean ALT level was 143.0 (61.8, 378.7) U/L, and 31 (83.8%) had elevated ALT levels. Only 8 (11.1%) patients presented with significant clinical symptoms (Table 1). Among the 47 patients who received DAA therapy, the regimens used were as follows: sofosbuvir/velpatasvir in 24 patients (33.3%), emitasvir/sofosbuvir in 20 patients (27.8%), ledipasvir/sofosbuvir in 2 patients (2.8%), and coblopasvir/sofosbuvir in 1 patient (1.4%). Notably, 100% (47/47) of DAA-treated patients achieved SVR 12. For the 25 untreated patients, reasons for non-treatment included financial constraints, advanced age with impaired mobility, and unspecified refusal. A standardized recall and follow-up program was subsequently initiated for these untreated patients, among 7 patients who were successfully recalled to date, with 2 patients achieved spontaneous clearance, 4 patients maintaining stable or slightly elevated HCV RNA levels, and 1 patient showing a decrease in HCV RNA levels from 5.26 to 3.41 $\log_{10}$ IU/mL. **Conclusion:** This outbreak highlights the risks of unsafe clinical practices and the importance of early detection and treatment of AHC. DAA therapy was highly effective, with all treated patients achieving SVR12. Strengthened infection control and timely intervention are crucial to preventing similar events.

Table 1 Baseline demographics and characteristics

Parameters	n=72
Age, years	62.5(54.0, 72.0)
5-12 years, n (%)	4 (5.6)
13-18 years, n (%)	4 (5.6)
>18 years, n (%)	64 (88.8)
Male, n (%)	38 (52.8)
HCV Ab (+), n (%)	71 (98.6)
HCV RNA, (Log_{10} IU/mL)	5.60±1.64
Receiving antiretroviral therapy, n (%)	47 (65.3%)
HCV genotype, n (%)	
1b	64 (88.9)
2a	2 (2.8)
unchecked	6 (8.3)
Alanine aminotransferase, U/L	143.0 (61.8, 378.7)
≤40	6 (8.3)
41-80	7 (9.7)
81-200	10 (13.9)
>200	14 (19.4)
missing value	35 (48.6)
Clinical symptoms (fatigue, nausea, jaundice etc.), n (%)	8 (11.1)
Treatment regimen, n (%)	
Sofosbuvir/Velpatasvir, n (%)	24 (33.3)
Emitasvir/Sofosbuvir, n (%)	20 (27.8)
Ledipasvir/Sofosbuvir, n (%)	2 (2.8)
Coblopasvir/Sofosbuvir, n (%)	1 (1.4)
Untreated, n (%)	25 (34.72)

Disclosures: Ru-Yue Chen: Nothing to Disclose, Yan-Qin Ai: Nothing to Disclose, Ya-Jie Pan: Nothing to Disclose, Xue-Yan Lv: Nothing to Disclose, Yue-Hang Wang: Nothing to Disclose, Xue-Jing Yu: Nothing to Disclose, Zhuang-Zhuang Zhai: Nothing to Disclose, Qing-Lei Zeng: Nothing to Disclose

1402 | HEPATITIS C IN PREGNANCY: EVALUATING SCREENING AND MANAGEMENT PRACTICES IN A RURAL POPULATION

Aleena Moin[1] Benyam Addissie[2] Lifang Zhang[3] Sara Gaines[1] Alberto Unzueta[1], [1]Geisinger Medical Center, [2]University of Rochester, [3]Department of Population Health Sciences, Geisinger Medical Center, Danville PA

Background: Hepatitis C (HCV) is now one of the most prevalent blood-borne infections, with 65% percent of infections impacting persons 20-39 years old. Rates of HCV amongst women giving live birth doubled during 2009-2014. Current guidelines now recommend hepatitis C (HCV) testing for every pregnancy, a shift from the previously recommended risk-based testing. We sought to investigate the current HCV screening practices amongst all pregnant women in our rural health system in order to identify gaps in screening practice and evaluate success of treatment. **Methods:** This was a retrospective study utilizing electronic health records from the Geisinger Health system. We evaluated all pregnancy encounters for women > 18 years between 2019 to 2023 to investigate the following AIMS: 1) Assess the health system's compliance of HCV screening guidelines by reviewing every pregnancy encounter during the study window for HCV antibody testing 2) Report the incidence of new HCV infection as delineated by positive HCV antibody and HCV RNA tests 3) Determine the rate of hepatology referral for all known positive pregnancy encounters and 4) Quantify success of treatment. **Results:** From 2019 to 2023, 23,253 pregnancies encounters were documented within our rural health system. 20,747 (89.22%) of these encounters were screened for HCV per guidelines, whereas 2506 (10.78%) of encounters had no testing. There were 478 positive HCV antibody tests and 280 positive RNA tests. 150 (53.57%) of HCV viremic patients were referred to Hepatology to be treated after their pregnancy, but only 69 (46%) initiated an appointment. In total, 91 out of 280 (32.5%) of all known positive HCV RNA cases successfully initiated HCV treatment with sustained viral response in all treated patients. Three were lost to follow up. **Conclusion:** Our retrospective study showed opportunities for improvement in both screening and linking to treatment of HCV infection for pregnant women. This was the first

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phase of initiatives and will now serve as the basis for future intervention. Our rural health system has demonstrated adequate success (89.22%) in screening for HCV with every pregnancy, as recommended per guidelines, but referral to and initiation of HCV treatment in the postpartum period as well as success in treatment, are identified as areas of future improvement. We intend to evaluate how initiation of HCV treatment is impacted by subsequent pregnancies, breastfeeding, active drug use, incarceration and other social determinants of health.

	Yes	No	Total
Hep-C antibody test in any trimester, n (%)	20,747 (89.22%)	2,506 (10.78%)	23,253
Hep-C antibody positive in any trimester, n (%)	478 (2.30%)	20,269 (97.70%)	20,747
Hep-C RNA test positive, n (%)	280 (40.46%)	412 (59.54%)	692
Hep-C RNA positive referral, n (%)	150 (53.57%)	130 (46.43%)	280
Initiate Hep-C doctor visit after referral, n (%)	69 (46.0%)	81 (54.0%)	150
HCV Treated, n (%)	91 (32.38%)	189 (67.5%)	280

Disclosures: Aleena Moin: Nothing to Disclose, Benyam Addissie: Nothing to Disclose, Lifang Zhang: Nothing to Disclose, Sara Gaines: Nothing to Disclose, Alberto Unzueta: Nothing to Disclose

1403 | DEVELOPMENT OF B-CELL LYMPHOMA AFTER TREATMENT OF HEPATITIS C WITH DIRECT-ACTING ANTIVIRAL AGENTS

Omar Zuhdi[1] Amanda Rigdon[1] Paola Campillo[1] Muhammad Ghabra[1], [1]Lakeland Regional Health Medical Center

Background: According to reports from the World Health Organization, more than 170 million people are infected with chronic hepatitis C worldwide, leading to complications including chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Remarkable advances in hepatitis C treatment have been made in recent years with the introduction of direct-acting antiviral agents (DAA's) allowing for viral eradication in greater than 98% of patients with hepatitis C. While DAA's have provided significant benefit for patients with HCV, development of B-cell lymphoma following HCV clearance with DAAs have rarely been reported in the literature. **Methods:** A systematic literature search was conducted using PubMed, Scopus, and ScienceDirect to retrieve studies from inception up to May 2025. Studies describing late-onset B-cell lymphoma after hepatitis C clearance with direct-acting antiviral agents, and no previous history of B-cell lymphoma were extracted. According to PRISMA guidelines, two reviewers completed the initial title and abstract screening, full text review, and data extraction. **Results:** Three case series and five case reports, describing 12 patients treated for hepatitis C with direct-acting antiviral agents, who subsequently developed B-cell lymphoma, were found in the current literature. The average age of the included patients was 66 years, ranging from 52-81 years of age. Sofosbuvir-based HCV therapy was used in 81% of patients, including sofosbuvir-ribavirin and sofosbuvir-ledipasvir regimens. Diffuse large B-cell lymphoma was the most common type of B-cell lymphoma among patients following hepatitis C treatment with direct-acting antiviral agents at 58.3% of patients, followed by mantle cell lymphoma (16.7%), and marginal zone lymphoma (16.7%). 42% of patients developed lymphoma within three months of HCV clearance with direct-acting antiviral agents, 33% within 3-12 months, and 25% of patients after more than 12 months. Most cases responded well to rituximab-based chemotherapy, composed of R-CHOP or similar chemotherapy regimens with complete lymphoma regression in 25% of patients, and partial lymphoma response in 41.7% of patients, and the rest of patients without fully reported responses. **Conclusion:** While direct-acting antiviral agents have provided significant benefit for patients with hepatitis C, such as prevention of liver cirrhosis and hepatocellular carcinoma, reports in recent years have described development of B-cell lymphoma after HCV clearance with direct-acting antiviral agents. Increased monitoring of patients for B-cell lymphoma following direct-acting antiviral agents treatment for HCV can allow for earlier diagnosis resulting in earlier initiation of treatment and improvement in patient outcomes.

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1404 | HIGH SVR RATES ACHIEVED WITH SIMPLIFIED MONITORING IN JAPANESE PATIENTS WITH HCV INFECTION TREATED WITH SOFOSBUVIR/VELPATASVIR: A PROSPECTIVE MULTICENTER STUDY

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Background: The advent of DAAs targeting viral proteins has revolutionized the treatment of HCV infection, making nearly all infected individuals eligible for therapy and achieving SVR rates exceeding 95%. Despite this, some patients with confirmed HCV infection defer regular outpatient visits. Given the excellent safety and efficacy profile of DAAs, simplified monitoring with reduced visit frequency may offer a practical alternative, as has been reported overseas. However, in Japan, where elderly patients and those receiving polypharmacy are common, real-world evidence on the safety and efficacy of minimal monitoring remains scarce. Sofosbuvir/velpatasvir, a pan-genotypic DAA regimen, has demonstrated high efficacy and safety and was recently approved for use in patients with chronic hepatitis C and compensated cirrhosis in Japan. Nevertheless, domestic real-world data are still limited. In a previous clinical trial involving 37 patients, visits were scheduled at treatment initiation and at weeks 2, 4, 8, and 12, leaving the utility of simplified monitoring unclarified. This prospective multicenter study aimed to evaluate treatment efficacy and safety under simplified monitoring conditions, specifically focusing on the impact of having fewer than two outpatient visits from treatment initiation to SVR12. **Methods:** This prospective multicenter study included patients who initiated treatment after January 2023 and completed at least 24 weeks of follow-up by May 2025. Primary endpoints were SVR12, safety, and the relationship between the number of outpatient visits and treatment outcomes. **Results:** As of May 2025, 51 patients had reached 12 weeks post-treatment. The median age was 67.0 years; 31 were male and 20 female. HCV genotypes included genotype 1 (n = 18), genotype 2 (n = 32), and one indeterminate case. One patient discontinued treatment at week 9 due to suspected pregnancy, but still achievedwhile achieving SVR12[1] . One otherThe another onepatients was lost to follow-up. Among the remaining 49 patients, all achieved SVR12. Thus, the SVR rate was 98% (50/51) in the intention-to-treat (ITT) analysis and 100% (49/49) in the per-protocol analysis. The number of outpatient visits from treatment initiation to SVR12 ranged from 1 to 7, with a median of 3.0. Notably, in 30 patients who had three or fewer visits, SVR rates were 100% in both ITT and per-protocol analyses. **Conclusion:** This prospective, real-world study suggests that treatment with sofosbuvir/velpatasvir in Japanese patients with chronic hepatitis C—predominantly elderly individuals—can achieve high SVR rates even under minimal monitoring. These findings support the feasibility of simplified monitoring strategies in clinical practice

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1405 | CHARACTERISTICS OF 930 PATIENTS WITH CHRONIC HEPATITIS C: A 7-YEAR REAL-WORLD COHORT FROM A TERTIARY CENTER IN GREECE

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Background: The advent of direct-acting antivirals (DAAs) has made the elimination of hepatitis C a realistic public health objective. While people who inject drugs (PWID) represent the highest-risk group, a substantial proportion of HCV-infected individuals in Greece appear to originate from the general population with no prior history of substance use (non-PWID). Aim of this study was to identify differences in the demographic and clinical profiles of PWID and non-PWID with chronic hepatitis C in a real-world Greek large cohort. **Methods:** All patients with chronic HCV infection considered eligible for DAA therapy between 2015–2022 at a tertiary liver center were retrospectively identified. Demographic, clinical, and laboratory data were retrieved from medical records. Liver stiffness measurements (LSM) by elastography were performed prior to treatment initiation. Cirrhosis was defined based on clinical, laboratory, and/or LSM values >12 kPa. **Results:** A total of 930 patients were included; 69.8% were male, with a median age of 52 years. At baseline, 9.2% had decompensated liver disease. PWID represented 56.8% of the cohort (n = 528). PWID were younger (47.1 ± 9.8 vs. 56.9 ± 13.1 years, $p < 0.001$) and had lower BMI (24.4 ± 4.4 vs. 26.4 ± 4.7 kg/m², $p < 0.001$) compared to non-PWID. Non-PWID had higher rates of diabetes (13.6% vs. 2.7%), hypertension

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(14.8% vs. 7.6%), decompensated liver disease (13.5% vs. 6.1%), and higher liver stiffness (13.9 ± 10.9 vs. 10.9 ± 7.7 kPa, p = 0.001). LSM > 9 kPa was observed in 57.4% of non-PWID versus 40% of PWID. Genotype 3 infection was more common in PWID (64% vs. 30%, p < 0.001). Treatment and outcome data were available for 853 patients. Sofosbuvir/velpatasvir (39%), glecaprevir/pibrentasvir (19.5%), and elbasvir/grazoprevir (13.2%) were the most used regimens. Sustained virologic response (SVR) rates were similar in both groups (PWID: 92%, non-PWID: 94%). All reinfection cases (n = 8) occurred in PWID during the 7-year follow-up. **Conclusion:** PWID and non-PWID with HCV infection in Greece display distinct clinical profiles that do not affect SVR rates but may influence long-term management. Non-PWID are older, have more features of metabolic syndrome, and demonstrate more advanced liver fibrosis at baseline. The number of patients with advanced liver disease and metabolic syndrome raise the importance of surveillance for hepatocellular carcinoma during next years.

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1406 | 'REACHING IN, REACHING OUT': TRACING CHILDREN OF HEPATITIS C POSITIVE WOMEN PRISONERS

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Background: Hepatitis C virus (HCV) infection is a major global health problem in adults & children which may cause serious & life-threatening damage to the liver. HCV Global Elimination by 2030 remains a target for the World Health Organisation & NHS England. Vertical transmission is the main cause of HCV infection in children. It is vital that there is an effective pathway to trace, test and treat children of mothers living with HCV (LWHCV). Identification of people in prisons LWHCV is an integral part of the HCV elimination agenda given the disproportionate burden of infection amongst residents. The aim of the 'Reaching In, Reaching Out'(RIRO) prison project is to develop & pilot pathways to trace and test children of HCV +ve women prisoners as they may be at risk of HCV. **Methods:** The pilot project was launched in 3 English female prisons with mother & baby units. The team worked with The Hepatitis C Trust & Healthcare teams to identify & counsel mothers LWHCV. Identification of women prisoners LWHCV was via prison database & arrival reports. Inclusion criteria: All women tested on entry to prison who are HCV+ve (RNA and/or Ab) & have children. Women who. * were pregnant/ breastfeeding. * do/ do not have parental responsibility (PR). Exclusion criteria: Women who. * declined to engage in the project. * were medically unfit to approach (mental health concerns). Consent forms were developed, information governance cleared & ethics achieved. Demographic details, dependents & family contacts were collected directly from women. **Results:** (See table 1). Jan-April 2025. 1642 women were incarcerated in 3 pilot sites: 1244 tested; 242 were Ab+ve, 34 RNA+ve. 30 women engaged with the RIRO team. 13 continue to be followed up. Preliminary challenges and lessons learnt: * Women prisoners may be vulnerable, so reassurance & building trust is imperative to working with them. * Accessing women may be difficult in a secure setting as lockdowns are common. * Discussing family is emotive & complex, requiring confidential private communication. * The high turnover of individuals at prison sites necessitates community follow up. * Effective partnership working is key **Conclusion:** A significant proportion of females in prison are HCV Ab +ve. It is vital to trace their children & offer testing. Pathways have been drafted, tested & adapted. Challenges have been highlighted & learning from the pilot will support the ongoing tracing of children & the roll out of RIRO into the remaining 9 English women's prisons.

Table 1: HCV status of women in 3 prison pilot sites & outcome of engagement with RIRO project (Jan-April 2025) (n=1643)

n	Status
1643	Women incarcerated at 3 pilot sites
1244/1643	Women HCV tested • 242 Ab +ve • 34 RNA +ve
198/ 1244	Women approached/ spoken to about RIRO project

30/198	Women engaged with RIRO
	• 8 Released from prison
	• 3 Didn't have children
	• 2 Declined to be part of RIRO
	• 3 Children not at risk/ low risk (i.e. HCV after children born)
	• 12 For further follow up
	  • 8 Have children: more details required
	  • 4 Dependents unknown, details required
	• 1 Child's details obtained, follow up in progress
	• 1 deemed medically unsuitable

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1407 | A NOVEL SCORE FOR PREDICTING RETURN TO DRINKING AFTER ALCOHOLIC HEPATITIS

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Background: Alcohol-associated hepatitis (AH) carries significant morbidity and mortality, with longer-term outcomes depending on alcohol cessation. The High-Risk Alcohol Relapse (HRAR) scale has been used to predict return to drinking (RTD) following liver transplantation (LT), but its use in patients with AH not undergoing LT is untested. We evaluated the performance of HRAR and developed a new model for improved predictive accuracy. **Methods:** Using data from a prospective observational cohort of patients hospitalized for AH, we calculated HRAR scores based on duration of heavy drinking, number of drinking days, and number of prior inpatient admissions for alcohol treatment. We constructed a new score to quantify the probability of RTD within 200 days after hospitalization using a generalized additive model (GAM) to capture nonlinear and interacting influences of the predictors for improved performance. In addition to the HRAR score components, the new model also included MELD, Ethnicity, Race, Age, Gender, and Education (MERAGE). In GAM, two key components of the HRAR score, the typical numbers of daily drinks and drinking days in the past 30 days, were included as a bivariate function to accommodate their nonlinear and interactive effects. Data were split 70% vs 30% for training and validation of the MERAGE score. **Results:** The study cohort included 347 patients with AH, of whom 98 (28%) had RTD within 200 days of follow-up. The mean age was 44.6 years, 43.2% were female, and 84.3% were non-Hispanic Whites. The mean baseline MELD score was 24.5. Compared to those stayed abstinent, the RTD group had greater numbers of daily drinks (12.7 vs. 9.7; $p = 0.01$) and more drinking days (21.3 vs. 13.6; $p < 0.001$), greater total number of drinks in the past 30 days (242.4 vs. 133.6; $p < 0.001$), and slightly lower baseline MELD (23.3 vs. 24.9; $p = 0.06$). GAM analysis showed RTD risk was higher in those with more than 20 drinking days, especially for those with greater daily intake. Youden Index was used to select a threshold value for the MERAGE score (optimal threshold = 0.242). The MERAGE score outperformed HRAR in the training and validation datasets (Table). In the validation set, the MERAGE had an area under the ROC curve of 0.69 vs 0.54 in the HRAR score (optimal threshold = 1.5). Compared to HRAR, the MERAGE score also had improved sensitivity, positive & negative predictive values, as well as the overall predictive accuracy. **Conclusion:** RTD results from multiple clinical and behavioral factors whose nonlinear and interacting influences may determine the level of risk. The novel MERAGE score, expanded upon the HRAR score, shows potential for improved accuracy in predicting return to drinking. Independent validation in a broad patient population is needed to establish its practical utility.

Table. Performance of the HRAR and MERAGE scores in predicting return to drinking by 200 days after hospitalization for alcohol-associated hepatitis

Score	Sensitivity	Specificity	PPV	NPV	Accuracy	AUROC
Training sample (70%)						
HRAR	0.48	0.64	0.36	0.75	0.60	0.55
MERAGE	0.83	0.64	0.49	0.90	0.69	0.78
Validation sample (30%)						
HRAR	0.38	0.65	0.24	0.78	0.59	0.54
MERAGE	0.71	0.60	0.34	0.88	0.62	0.69

Notes: PPV -positive predictive values; NPV – negative predictive values; AUROC – area under the receiver characteristic curve.

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Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, Craig McClain: Nothing to Disclose, Ramon Bataller: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Thomas Cotter: Nothing to Disclose, Nothing to Disclose, Mack Mitchell: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, Richard Sterling: ABIM: GI Specialty Board, Abott: Grant/Research Support, AbbVie: Grant/Research Support, Roche: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research Support

1408 | HCV MEDICATION TURNAROUND TIME USING SPECIALTY MAIL ODER PHARMACY VS. LOCAL PHARMACY

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Background: Despite the removal of the prior authorization (PA) requirement for hepatitis C virus (HCV) treatment for New Mexico (NM) Medicaid, insurances often restrict directly acting antivirals (DAAs) dispensing to their own or contracted mail order specialty pharmacy. The purpose of this analysis was to determine DAA turnaround time before removal of the PA in July 2024? and after for patients with Medicaid insurance prescribed DAAs by the University of NM's Truman Health Services (THS), comparing mail order pharmacy to THS's in-house pharmacy turnaround time. **Methods:** Adults >18 years of age with NM Medicaid insurance seen >1 time at THS for confirmed HCV and prescribed DAAs were included. Time to DAA receipt from initial prescription was assessed through a retrospective analysis of DAA prescription data from the electronic health record, THS pharmacy's fill records, and clinic medication room logs for meds shipped from mail order pharmacy. Turnaround time for mail order pharmacies was determined by calculating the number of days from the date of prescribing DAA to the date received at THS. Turnaround time for THS's on-site pharmacy was determined by calculating the number of days from date prescribed to date ready for pick up. Turnaround time calculations excluded weekends and holidays. DAAs sent directly to the patient or those never picked up were excluded from the turnaround time calculation. **Results:** Preliminary data between Jan. 1, 2023 and Dec. 31, 2024 indicate 138 patients at THS initiated DAA therapy. The use of external mail order pharmacy was required for 53 patients but 6 (11%) never returned to THS to start treatment. The average time to DAA receipt was 8.5 days (range 5-17). THS pharmacy was able to fill 85 prescriptions, with 49 prescriptions filled in the 18 months prior to PA removal (average of 2.7 fills/month) and 36 in the first 6-months after removal of the PA (average of 6 fills/month). When allowed to fill on-site the average time to DAA at THS was 1.67 days pre-PA removal and decreased to <1 day after removal of the PA. In contrast, time from prescription to DAA receipt with specialty mail order pharmacy averaged

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13.58 days (range 5-14 days) before the PA removal and after PA removal was 11.36 days (range 4-25 days). **Conclusion:** Requiring the use of specialty mail-order pharmacy delays access to HCV treatment, even after removing the PA requirement.

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1409 | VERTICAL TRANSMISSION OF HEPATITIS C VIRUS RUNS IN FAMILIES: HAVING A CHILD INFECTED INCREASES THE RISK OF FUTURE VERTICAL TRANSMISSION

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Background: While vertical transmission is the predominant route of pediatric hepatitis C virus (HCV) acquisition, few studies have examined how having an infected child may affect the risk of future vertical transmission. **Methods:** We conducted a population-based retrospective cohort study linking infants born from 2007 to 2021 to individuals with chronic HCV infection in Ontario, Canada. Families were defined as those in which two or more infants were born to the same individual, with at least one infant tested for HCV during a follow-up period of at least two years. HCV testing was defined as a record of an antibody (Ab) test after 18 months of age and/or an RNA test at any time. Transmission was defined as a record of Ab-positivity or RNA testing after 18 months of age, or RNA-positivity at any time. We quantified and compared the association between vertical HCV transmission and the presence or absence of an infected sibling. Factors associated with transmission were identified using mixed-effects logistic regression, adjusting for within-family clustering, family size, and relevant covariates. **Results:** A total of 1,101 infants were included from 432 families (median of 2 infants per family, IQR: 2–3). Among these, vertical transmission occurred in 85 (7.7%) children, from 72 families (16.7% with at least one child affected). The maximum number of children who acquired HCV within a single family was 2. The incidence of vertical transmission was 22.2% (95% CI: 15.1%–30.8%) in children with an HCV infected sibling compared to 6.0% (95% CI: 4.6%–7.7%) among those without ($p < 0.0001$). After adjustment, having an infected sibling (adjusted odds ratio (aOR) = 4.30; 95% CI: 2.53–7.33) and a record of substance use prior to the pregnancy (aOR = 1.92; 95% CI: 1.15–3.21) were associated with a higher likelihood of vertical transmission. Additionally, increasing age of the birthing parent (per year) (aOR = 1.06; 95% CI: 1.02–1.11) was modestly associated with a higher likelihood. **Conclusion:** The data show that vertical HCV transmission was markedly more frequent to those with an infected sibling. Increased transmission rates to siblings may relate to higher parental viral load or possibly anatomical factors. The recognition that once vertical transmission occurs there is a higher risk of it recurring in future pregnancies is important for parents and providers, and may support treatment in pregnancy to prevent additional transmission.

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1410 | LONG-TERM RESTORATION OF HCV-SPECIFIC CD4+ T CELL IMMUNITY FOLLOWING DAA-MEDIATED CLEARANCE OF CHRONIC HCV INFECTION

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Background: The advent of direct-acting antivirals (DAAs) has revolutionized the treatment of chronic hepatitis C virus (HCV) infection, leading to sustained virologic response (SVR) in over 95% of cases. Despite this success, the long-term effects of HCV clearance on T cell-mediated antiviral immunity remain unclear, particularly concerning the restoration of immune function and protection against reinfection. **Methods:** We conducted a longitudinal study using 14 PBMC samples from participants enrolled in the CHROME study (NCT03823911) with chronic HCV infection who achieved SVR following DAA treatment. Peripheral blood mononuclear cells (PBMCs) were collected at baseline and more 60 weeks post-treatment (>SVR60). We assessed serum proinflammatory markers (IP-10, MIP-1B, TNFα, IL-1B, GRO) and evaluated HCV-specific inflammatory cytokine responses in CD4+ and CD8+ T cells after HCV-specific peptides stimulation. Additionally, we analyzed activation (CD38, HLADR) and inhibitory (PD1, TIGIT, 2B4) marker expression and mitochondrial function in T cell subsets (mitoSOX, JCR/JCG). **Results:** At >SVR60, significant reductions were observed in serum IP-10, MIP-1B, and TNFα levels, indicating decreased systemic inflammation. CD4+ T cells exhibited enhanced HCV-specific cytokine production, particularly within activated CD38+ and CD38+HLADR+ subsets, with increased frequencies of TNFα+, IFNγ+TNFα+, IL-2+, and IL-21+ cells. Notably, these subsets also demonstrated reduced expression of inhibitory receptors PD1 and TIGIT and a significant increase in the mitochondrial membrane potential (JCR/JCG) in a CD4+CD38+ T cells, indicating improved mitochondrial function. There were no significant changes in the level of ROS. In contrast, CD8+ T cells showed no significant changes in cytokine production or phenotypic markers at >SVR60 compared to baseline. **Conclusion:** One-year post-DAA therapy, patients exhibited restoration of HCV-specific CD4+ T cell responses, characterized by enhanced cytokine production, decreased inhibitory receptor expression in activated T-helper cells and improved mitochondrial function of CD4+ T cell. However, CD8+ T cell responses remained unchanged, suggesting a different timeline for immune recovery. Recovery of HCV specific CD4+ T cell function may prevent of reinfection in high-risk individuals after SVR.

Disclosures: Tetiana Pozniak: Nothing to Disclose, Arshi Khanam: Nothing to Disclose, Shyam Kottilil: Red Queen Therapeutics: Consultant, Orsobio: Stock – privately held company, Poonam Mathur: Nothing to Disclose, Alip Ghosh: Nothing to Disclose

1411 | PREVALENCE AND CLINICAL SIGNIFICANCE OF LOW HCV RNA LEVELS IN KOREAN PATIENTS WITH CHRONIC HEPATITIS C INFECTION: A MULTICENTER PROSPECTIVE COHORT STUD

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Background: The clinical significance of low HCV RNA levels in chronic hepatitis C infection remains unclear, particularly in relation to treatment response and long-term outcomes. This study aimed to estimate the proportion of low viral titer patients, and to evaluate the sustained virologic response (SVR) and clinical outcomes, including hepatocellular carcinoma (HCC) incidence and composite liver-related events, in patients with low (<3000 IU/mL) versus high (≥3000 IU/mL) HCV RNA levels. **Methods:** We analyzed data from a multicenter prospective cohort collected from nine tertiary centers in Korea between 2007 and 2024. Patients with chronic HCV infection were classified into low RNA titer (HCV RNA <3000 IU/mL) and high RNA titer (HCV RNA ≥3000 IU/mL) groups. Baseline cirrhosis status and SVR rates after interferon (IFN) or direct-acting antiviral (DAA) treatment were compared. Clinical outcomes were assessed by analyzing HCC incidence and composite liver-related events, which included decompensated liver cirrhosis, liver transplantation, HCC, and death. Statistical analyses included odds ratios (ORs) for baseline characteristics, while Kaplan-Meier survival analysis and Cox proportional hazards regression were used to evaluate clinical outcomes. **Results:** A total of 2,297 patients were included. The median age was 60.0 years (IQR: 51.0–69.0), and 48.9% were male. Among them, 105 (4.6%) were in the low RNA titer group, while 2,192 (95.4%) were in the high RNA titer group. Baseline characteristics, including age ($p = 0.79$) and sex distribution ($p = 0.82$), did not significantly differ between groups. Cirrhosis prevalence was also similar (OR: 0.80, 95% CI: 0.53–1.20, $p = 0.28$). SVR rates among IFN-treated patients were 62.5% (5/8) in the low RNA titer group and 70.2% (193/275) in the high RNA titer group ($p = 0.70$). In the DAA-treated group, SVR rates were 93.5% (29/31) and 95.2% (1075/1129), respectively ($p = 0.66$). For the composite event analysis, 1,799 patients were analyzed over a median follow-up of

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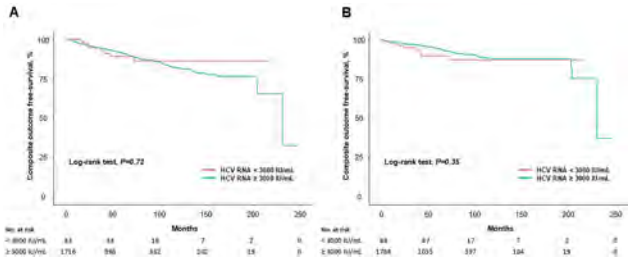
60 months (IQR: 31–95), with 191 events occurring. The high RNA titer group had an HR of 1.14 (95% CI: 0.56–2.31, p = 0.72), showing no significant difference between the groups (Figure 1A). For HCC incidence, 1,876 patients were analyzed over a median follow-up of 60 months (IQR: 31.75–95), during which 124 patients developed HCC. The high RNA titer group showed a hazard ratio (HR) of 0.71 (95% CI: 0.35–1.45, p = 0.35) compared to the low RNA titer group (Figure 1B) **Conclusion:** In Korean HCV patients, the proportion of low HCV RNA levels was less than 5%, and they had comparable SVR rates and clinical outcomes to those with high RNA levels following IFN or DAA treatment. Although these patients are minor, they include cases with decompensated cirrhosis and HCC, underscoring the need for careful clinical assessment and active treatment.

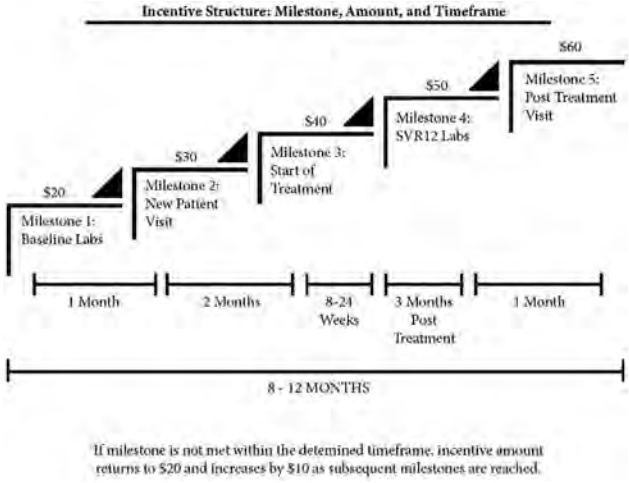


Disclosures: Juneyoung Lim: Nothing to Disclose, seungteak Lee: Nothing to Disclose, Min Kyung Park: Nothing to Disclose, Eun Sun Jang: Nothing to Disclose

1412 | MILESTONE-BASED INCENTIVES IMPROVE HEPATITIS C TREATMENT COMPLETION IN AN UNDERSERVED POPULATION: A PILOT STUDY

Aaron Skiles[1], [1]University of New Mexico

Background: Chronic hepatitis C virus (HCV) infection remains a significant public health concern, particularly among underserved populations. While highly effective antiviral therapies are available, completion rates remain suboptimal due to various barriers, including social determinants of health and limited access to care. Behavioral economics research suggests that small, structured incentives can motivate health-related behaviors. This pilot study explores whether milestone-based incentives can improve treatment adherence and achievement of sustained virologic response (SVR) in patients undergoing HCV treatment within a safety-net healthcare system. **Methods:** A prospective cohort study was conducted at the University of New Mexico Truman Health Services HCV clinic. Approximately 50 patients initiating HCV treatment were enrolled. Participants received up to $200 in merchandise card incentives for completing five treatment milestones: (1) New Patient Visit, (2) Baseline Labs, (3) Start of Treatment, (4) Post-Treatment Visit, and (5) SVR12 Labs (12 weeks post-treatment). Surveys administered during clinic visits collected demographic and social data, including access to transportation, housing, phone, insurance, and medication for opioid use disorder (MOUD). Clinical data, such as fibrosis scores and genotype, were also collected. Data were securely stored in compliance with HIPAA regulations and IRB-approved protocols. **Results:** Patients completing all five milestones and three surveys demonstrated higher SVR rates compared to baseline comparisons at the clinical site for year prior. Commonly reported barriers included transportation difficulties (60%), phone/housing instability (50%), and reliance on government assistance (70%). The majority of participants rated the gift card incentives as "Important" or "Very Important" motivators for treatment adherence. Notably, SVR rates were achieved even among participants with multiple social risk factors. **Conclusion:** Structured, milestone-based incentives are feasible and in certain patient groups are effective in improving HCV treatment adherence and SVR rates among underserved populations. Early identification of social determinants of health and integration of support services are critical to enhancing treatment outcomes. This model is low-cost, scalable, and holds promise for reducing disparities in HCV care. Further research with larger sample sizes and longitudinal follow-up is recommended. Study was completed when SVR-4 was not a recommendation and same-day start of treatment with removal of state Medicaid prior authorization allows for start-of-treatment same-day in many cases, so outcomes may be different now with current treatment protocols.



Disclosures: Aaron Skiles: Nothing to Disclose

1413 | IN VITRO MODEL OF AURKB EXPRESSION LEVELS REGULATION MEDIATED BY SOFOSBUVIR TREATMENT

Marina Camblor Murube[1] Antonio Madejon[2] Ana López López[1] Irene Francisco Recuero[1] Celia Perales[3] Araceli García Sánchez[4] Jaime Feliú[5] Aurora Sánchez-

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Background: Previous studies in cell models show that treatment with sofosbuvir (SOF) induces cell cycle modifications mediated by increased levels of epidermal growth factor receptor (EGFR) (Bojkova, 2020), vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor beta (PDGFRB) (Atif, 2022), DUSP1 or MET. The aims of thos work was to analyse the effect of sofosbuvir treatment on the levels and activity of Aurora kinase B (AURKB), an enzyme involved in cell cycle control, and its relationship with changes in cell proliferation, viability and migration, in an in vitro cell model. **Methods:** Cultures of Huh7 and Huh7.5 hepatoma cell lines were treated with SOF (C22H29N3FO9P) or daclatasvir (DCV) (BMS-790052) at different doses. AURKB expression levels of each culture were analysed by qPCR and Western-Blot. For cell proliferation assays, trypan-blue stained cells were counted using the Cell-dropTM (DeNovix). Cell viability was analysed by metabolic activity-MTT assays. Finally, cell migration capability was measured by wound assays. Results from SOF- or DCVtreated cultures were expressed in all cases as percentage induction with respect to untreated cells. **Results:** Protein and mRNA expression assays in SOF-treated Huh7 and Huh7.5 hepatocarcinoma cells showed significant increases of more than 25% in AURKB expression over untreated cells. Proliferation analysis of both cell lines showed that treatment with 5 mM doses of SOF for 72 hours induced increases in cell proliferation, which became statistically significant after 336 hours of treatment. Metabolic activity-MTT assays showed that cell viability of cultures treated with 5 mM SOF for 336 hours was higher. Finally, in Huh7 cells treated with 5 μM SOF, cell migration was observed to increase by 36% after 72h of treatment. All SOF-induced effects were reversed in the presence of AZD1152, an inhibitor of AURKB activity, confirming that they were exerted through the AURKB pathway. Finally, no differences were observed in any of the parameters studied between untreated control cells and cells treated with DCV at different doses. **Conclusion:** These results suggest that SOF can induce cell cycle modifications through AURKB activation in in vitro cell models. The effect of these changes in vivo (hepatitis C patients treated with SOF) should be analysed, taking into account that HCV eradication may induce an increase in AURKB per se, due to the inhibitory effect that the viral core protein exerts on AURKB activity.

Disclosures: Marina Camblor Murube: Nothing to Disclose, Antonio Madejon: Nothing to Disclose, Ana López López: Nothing to Disclose, Irene Francisco Recuero: Nothing to Disclose, Celia Perales: Nothing to Disclose, Araceli García Sánchez: Nothing to Disclose, Jaime Feliú: Nothing to Disclose, Aurora Sánchez-Pacheco: Nothing to Disclose, Javier García-Samaniego: Nothing to Disclose

1414 | MODELING SUGGESTS THAT UNDETECTABLE HCV RNA AT WEEKS 1 OR 2 OF DAA THERAPY COULD IDENTIFY ADULTS WITH RECENT HCV FOR SHORTER TREATMENT DURATION

Ashish Goyal[1] Tatyana Kushner[2] Kimberly Page[3] Ohad Etzion[4] Scott Cotler[1] Gail Matthews[5] Harel Dahari[1] Marianne Martinello[5], [1]Loyola University Chicago, [2]Weill Cornell Medicine, [3]University of New Mexico, [4]Soroka University Medical Center, [5]The Kirby Institute

Background: Identifying individuals with recent hepatitis C virus (HCV) infection (duration <12 months) who could be cured with short duration direct-acting antiviral (DAA) therapy would support efforts to reach World Health Organization (WHO) HCV elimination goals. Shorter treatment could improve adherence, decrease loss to follow-up, and reduce cost in key populations such as people who inject drugs (PWID) and pregnant women. Using a computational modeling approach, we previously demonstrated that undetectable HCV by day 14 among people with chronic HCV may shorten duration of DAA therapy by 4-5 weeks while achieving $>90\%$ cure (J Hepatol 2024 vol. 80(S1):S832). The efficacy of a similar approach among people with acute and recent HCV receiving glecaprevir-pibrentasvir (GLE-PIB) is unknown. **Methods:** In the TARGET3D study which evaluated HCV treatment in recently acquired HCV, 23 and 30 participants received 4 and 6 weeks of GLE-PIB, respectively (PMID: 31652357 and 37771545). Characterization of viral-host parameters, DAA efficacy in blocking HCV production, and treatment outcomes were available from previous modeling based on ~300 patients receiving DAA (Math Biosci 2022,343:108756). 100,000 parameter combinations of viral-host and treatment parameters were generated and viral kinetic profiles under GLE-PIB 300-120mg daily were simulated using a multiscale model. Each simulation represented an *in silico* patient with recent HCV receiving GLE-PIB. The time to cure (TTC) for each *in silico* patient with recent HCV, defined as time to reach <1 HCV viral copy in 15L of extracellular body fluid (i.e. $V = 7\text{x}10^{-5}$ IU/ml) was then estimated using mathematical modeling simulations. TTC of <8 weeks (56 days) of GLE-PIB indicates the potential for reduction in treatment duration. **Results:**

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The *in silico* recent HCV population closely matched HCV kinetics of the 53 trial participants; 74% of the *in silico* population had undetectable HCV RNA (< 10 IU/ml) at week 2, similar to 68% among TARGET3D participants. Modeling suggested that if HCV RNA was undetectable on or before day 14, 95% of people with recent HCV infection could be cured with GLE-PIB for 6 weeks (Fig.1A). The median predicted TTC was 24 days (IQR = 19-29 days), with 71% reaching TTC at ≤ 4 weeks (Fig.1B). Among the *in silico* population, 32% had undetectable HCV RNA at day 7, of whom 89% were predicted to achieve cure with GLE-PIB for 4 weeks (Fig.1C); the median predicted TTC was 19 days (IQR = 16-22 days) (Fig.1D). **Conclusion:** Mathematical modeling suggested that most people with recent HCV treated with GLE-PIB will have undetectable HCV RNA by week 1 or 2 and could have their treatment duration reduced by 2-4 weeks. This could improve treatment access, facilitate HCV elimination, and reduce cost, particularly in key populations most affected by HCV, such as PWID.

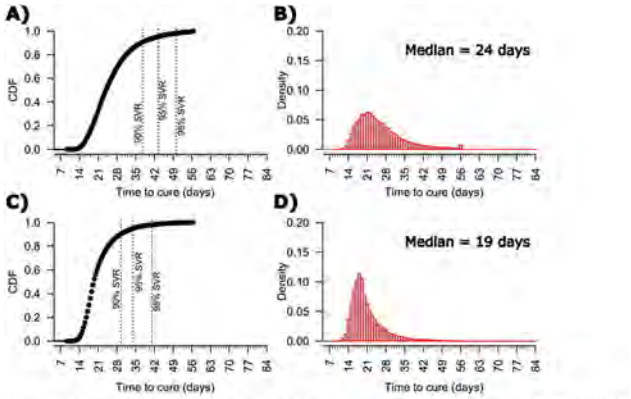

Figure 1: (A) Cumulative Distribution Function (CDF) and (B) frequency distributions of the time to cure (TTC) for ~40,000 *in silico* acute patients with undetectable HCV RNA (<10 IU/mL) at week 2. (C) Cumulative Distribution Function (CDF) and (D) frequency distributions of the time to cure (TTC) for ~32,000 *in silico* acute patients with undetectable HCV RNA (<10 IU/mL) at week 1.

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1415 | THE USE OF DIRECT-ACTING ANTIVIRALS TO ENHANCE ACCESS TO CANCER CLINICAL TRIALS FOR PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION AND CANCER

Khalis Mustafayev[1] Joanne arvelaez Pascucci[1] Aung Naing[1] Sheeba Thomas[1] Krina Patel[1] Naveen Pemmaraju[1] Naval Daver[1] Ying Jiang[1] Eduardo Yepez Guevara[1] Harrys Torres[2], [1]The University of Texas MD Anderson Cancer Center, Houston, Texas., [2]The University of Texas MD Anderson Cancer Center

Background: Most cancer patients with chronic hepatitis C virus (HCV) infection are excluded from cancer clinical trials because of their active infection. The use of direct-acting antivirals (DAAs) to eradicate HCV and allow access to cancer clinical trials has not been studied. We aimed to evaluate the safety and efficacy of using DAAs to increase access to cancer clinical trials in patients with chronic HCV infection and advanced cancer. **Methods:** HCV-infected cancer patients seen at MD Anderson Cancer Center from January 1, 2016, through February 28, 2025, were enrolled in a prospective observational study. Patients initially excluded from cancer clinical trials but ultimately enrolled after DAA treatment were defined as cases. Patients treated with DAAs but never enrolled in cancer clinical trials were defined as controls. A 1:1 matching between cases and controls was performed, with matching based on the cancer type and stage, history of > 3 lines of chemotherapy, and presence of cirrhosis. Predictors of overall survival (OS) and progression-free survival (PFS) were evaluated using multivariable Cox regression analysis. The primary outcomes were the safety and efficacy (sustained virologic response [SVR]) of DAAs. The secondary outcomes were OS and PFS. **Results:** We studied 150 consecutive HCV-infected patients with any type of cancer, including 75 cases and 75 matched controls. In both groups, most patients were men, were White, were non-cirrhotic, and had HCV genotype 1 (Table). Adverse events occurred in 36 of 150 patients (24%), including 17 of 75 cases (23%) and 19 of 75 controls (25%). Five patients (3%), 1 case, and 4 controls, had grade 3-4 adverse events, none of them related to DAAs. The SVR rate was 92% (138/150) overall, 96% (72/75) in cases, and 88% (66/75) in controls. Median OS was 61 months in cases and 59 months in controls, and median PFS was 30 months in cases and 42 months in controls. Among patients with long-term follow-up, cases had better OS than controls (hazard ratio 0.20; 95% CI 0.07–0.56; p = 0.002). Achieving an SVR was significantly associated with better PFS (hazard ratio 0.46; 95% CI 0.24–0.89; p = 0.02). The rate of cancer-related deaths was significantly lower among cases (53% [40/75] vs. 69% (52/75); p = 0.04). **Conclusion:** Participating in a cancer clinical trial after DAA treatment enhances survival for patients with cancer and chronic HCV infection.

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Table. Baseline characteristics and outcomes of HCV-infected cancer patients with and without access to cancer clinical trials after receiving DAAs *

Characteristic	Enrolled in CCT (cases) (n=75)	Unable to enroll in CCT (controls) (n=75)	p-value
Age, mean ± SD, y	61 ± 8.42	60 ± 8.26	0.412
Sex, male	53 (71)	50 (67)	0.597
Race			0.087
White	52 (69)	50 (67)	
Black	18 (24)	16 (21)	
Hispanic	4 (5)	1 (1)	
Asian	1 (1)	3 (4)	
Other	0 (0)	5 (7)	
Cancer type			> .99
Hematological malignancy	15 (20)	15 (20)	
Solid tumor	60 (80)	60 (80)	
Stage of cancer for solid tumors			0.282
2	3/60 (5)	5/60 (8)	
3	18/60 (30)	11/60 (18)	
4	39/60 (65)	44/60 (73)	
More than 3 lines of chemotherapy	74 (99)	67 (89)	0.034
HCV genotype †			
1	55 (73)	61 (81)	0.242
2	15 (20)	8 (11)	0.113
Other	7 (9)	8 (11)	0.786
Cirrhosis	29 (39)	29 (39)	>0.99
SVR	72 (96)	66 (88)	0.130
Duration of follow-up, median (IQR), days	1051 (573-1948)	1518 (878-1998)	0.209
Cancer progression during follow-up	41 (55)	29 (39)	0.072
Time from DAA treatment initiation to cancer recurrence, median (IQR), days	467 (273-1485)	770 (307-1438)	0.449
Progression-free survival, median (months)			
Hematological malignancy	61	42	0.012
Solid tumor	20	38	0.012
Overall survival, median (months)			
Hematological malignancy	104	57	<0.001
Solid tumor	41	66	0.564
Death	40 (53)	52 (69)	0.044

* Data in the table are number of patients (percentage) unless otherwise indicated.
† A patient could have more than 1 infecting genotype

Disclosures: Khalis Mustafayev: Nothing to Disclose, Joanne arvelaez Pascucci: Nothing to Disclose, Aung Naing: Nothing to Disclose, Sheeba Thomas: Sanofi: Grant/Research Support, Acerta Pharma: Grant/Research Support, Ascentage Pharma: Grant/Research Support, Cellectar Biosciences: Grant/Research Support, Cellectar Biosciences: Advisor, Bristol Myers Squibb: Grant/Research Support, Abbvie: Grant/Research Support, Genentech: Grant/Research Support, Krina Patel: Nothing to Disclose, Naveen Pemmaraju: Nothing to Disclose, Naval Daver: Nothing to Disclose, Ying Jiang: Nothing to Disclose, Eduardo Yepez Guevara: Nothing to Disclose, Harrys Torres: Gilead: Principal Investigator, Merck: Principal Investigator

1416 | RE-ENGAGEMENT TO RESCUE THERAPY WITH SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR IN HEPATITIS C AFTER DIRECT-ACTING ANTIVIRAL FAILURE

Wonseok Kang[1] Ki Tae Yoon[2] sang gyune kim[3] Moon Young Kim[4] Jae Yoon Jeong[5] Hyung Joon Yim[6] Byoung Kuk Jang[7] Soo Young Park[8] Tae Hee Lee[9] Seung Up Kim[10], [1]Samsung Medical Center, [2]Pusan National University Yangsan Hospital, [3]Soonchunhyang University Bucheon Hospital, [4]Yonsei University Wonju College of Medicine, [5]Ewha Womans University Mokdong Hospital, [6]Korea University Ansan Hospital, [7]Keimyung University School of Medicine, [8]Kyungpook National University Hospital, [9]Konyang University College of Medicine, [10]Yonsei University College of Medicine

Background: Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) became available in South Korea in late 2022, enabling rescue therapy for patients with chronic hepatitis C who had failed previous direct-acting antiviral (DAA) treatment. This study aimed to re-engage patients who were lost to follow-up after DAA failure. **Methods:** A prospective observational study was conducted at 10 tertiary medical centers in South Korea. Investigators identified patients who had previously received DAA therapy at each center and screened them for eligibility for SOF/VEL/VOX. Eligible patients were reached through phone outreach by investigators for re-engagement. SOF/VEL/VOX was administered to patients who provided written informed consent, and treatment response was assessed. **Results:** Among 4,439 patients who had received DAAs, 58 (1.3%) were lost to follow-up after treatment failure. Of these, 45 patients (77.6%) were eligible for SOF/VEL/VOX. Nineteen patients (42.2%) were successfully reached, and 8 (42.1%) returned for an in-person visit. Written informed consent was declined or withdrawn by 3 patients due to financial concerns or advanced age. Ultimately, 5 patients (62.5%) initiated SOF/VEL/VOX treatment, and all achieved a sustained virologic response at 12 weeks post-treatment. **Conclusion:** The introduction of SOF/VEL/VOX in Korea enabled the re-engagement of patients lost to follow-up after DAA failure and facilitated successful rescue therapy.

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1417 | EFFECT OF DIRECT ACTING ANTIVIRAL TREATMENT ON HEPATIC STEATOSIS IN PATIENTS WITH CHRONIC HEPATITIS C

WonKyung Cho[1] Tom Ryu[2] Jae Young Jang[2] Young Chang[3] Soung Won Jeong[2] Young Deok Cho[2], [1]Long Island Jewish Forest Hills Hospital, Northwell Health, [2]Digestive Disease Center, College of Medicine, Soonchunhyang Univesity, [3]Soonchunhyang University

Background: Hepatic steatosis is a common comorbidity in chronic hepatitis C virus (HCV) infection, linked

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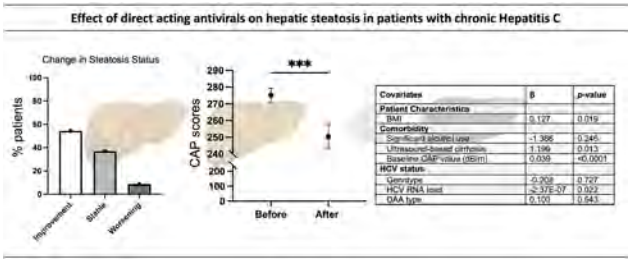
to accelerated liver disease progression and increased risk of hepatocellular carcinoma. With the advent of direct acting antivirals, HCV cure rate has exceeded 90%, and prognosis has improved drastically. However, the effect of direct acting antivirals on pre-existing liver pathologies, in particular hepatic steatosis is not well elcuidated. This study investigates steatosis evolution following DAA therapy and identifies associated clinical factors. **Methods:** We conducted a retrospective cohort study of 212 HCV-infected patients treated with DAAs between January 11, 2015, and December 31, 2022 at a tertiary medical center in South Korea. Steatosis was evaluated using controlled attenuation parameter (CAP) scores from FibroScan at baseline and 6 months post-treatment (SVR-24). Improvement was defined as ≥ 1 grade decrease in steatosis; worsening as ≥ 1 grade increase. Hepatic Steatosis Index (HSI) and laboratory profiles were also assessed. Adjusted odds ratio was calculated using multivariable logistic regression to identify predictors of steatosis improvement. **Results:** At baseline, 26.9% of patients exhibited hepatic steatosis (S1: 11.8%, S2: 8.5%, S3: 6.6%). Following SVR-24, 54.3% of patients with baseline steatosis showed improvement, 36.9% remained stable, and 8.7% worsened. Median CAP scores significantly decreased post-treatment ($p < 0.001$), while HSI slightly declined but remained above fatty liver threshold. Baseline liver function parameters and lipid panel tests were not associated with steatosis improvement. Lipid profiles showed increased total cholesterol and LDL levels post-SVR. Multivariable analysis revealed that advanced baseline steatosis (S2 OR 2.48, $p = 0.021$; S3 OR 2.20, $p = 0.028$) and high baseline HCV RNA load ($> 800{,}000$ IU/mL; OR 2.40) were independent predictors of steatosis improvement. **Conclusion:** DAA-induced HCV eradication led to hepatic steatosis improvement in over half of patients with baseline steatosis, especially among those with high viral load and advanced steatosis. These findings suggest that viral and burden may influence steatosis regression. Despite normalization of liver enzymes, metabolic parameters such as HSI and LDL remained elevated, underscoring the need for continued metabolic risk management post-SVR. Prospective studies with longer follow-up and histologic validation are warranted to confirm these findings and assess long-term impact on liver outcomes.



Disclosures: WonKyung Cho: Nothing to Disclose, Tom Ryu: Nothing to Disclose, Jae Young Jang: Nothing to Disclose, Young Chang: Nothing to Disclose, Soung Won Jeong: Nothing to Disclose, Young Deok Cho: Nothing to Disclose

1418 | SOFOSBUVIR BASED REGIMENS ARE EFFECTIVE FOR HEPATITIS C TREATMENT IN PATIENTS WITH END-STAGE RENAL DISEASE IN REAL-LIFE SETTING

Radha Dhiman[1] Ajay Kumar Mishra[2] Dharmendra Bhadauria[2] Surender Singh[2] Anupma Kaul[2] SUMIT RUNGTA[3] Harshita Katiyar[2] Manas Behera[2] Monika Yachha[2] Narayan Prasad[2] Amit Goel[2], [1]Sanjay Gandhi Postgraduate Institute of Medical Sciences, [2]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [3]King George's Medical University, Lucknow, India

Background: Sofosbuvir is a major drug in directly acting antiviral (DAA) drug regimens for HCV treatment. In patients with chronic kidney disease (CKD) and estimated glomerular filtration rate (eGFR) < 30 mL/min, the experience of sofosbuvir (SOF) based regimens is limited. We report real-life experience of treating a cohort of CKD patients with eGFR < 30 mL/min using sofosbuvir based regimens. **Methods:** Adults CKD patients who had eGFR < 30 ml/min and detectable HCV RNA were included in the study ($n = 262$). They were treated with full dose SOF (400 mg) in combination with either Velpatasvir (VEL) 100 mg or Daclatasvir (DAC) 60 mg. Regardless of DAA combination, those without cirrhosis or decompensated cirrhosis were treated for 12 and 24 weeks respectively. Those with compensated cirrhosis were treated for 12 (SOF/VEL) or 24 (SOF/DAC) weeks. Primary outcome measure was proportion of participants who could achieve sustained virological response after 12 weeks (SVR12) of treatment completion. **Results:** 271 infection episodes (262 new- or 9 re-infections) in 262 participants (men 74.1%; age 42 [32-52] years; on hemodialysis 231/262 [88.2%]; dialysis duration 15 [9-25] months; no-cirrhosis 221, 84.4%; HCV RNA(log10) 7.4 [3.6-9.1]) were treated with either SOF/DAC (201; 74.2%) or SOF/VEL (70; 25.8%). SVR12 could be tested for 226 (SOF/DAC 171, SOF/VEL 55) of 271 episodes (83.4%). Overall, SVR12 was achieved for 215 treatment episodes (intention-to-treat [ITT] analysis 215/271, 79.3%; per-protocol [PP] analysis 215/226, 95.1%). SVR12 was not affected by presence of cirrhosis (ITT no-cirrhosis 79.9% vs cirrhosis 76.2%, $p = 0.144$; PP cirrhosis 88.9% vs no-cirrhosis 96.3%, $p = 0.058$), DAA combination used for treatment (ITT SOF/DAC 94.7% vs SOF/VEL 96.4%, $p = 0.626$; PP

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SOF/DAC 80.6% vs SOF/VEL 75.7%%, p = 0.404), or hemodialysis status (ITT dialysis 79.7% vs no-dialysis 77.5%, p = 0.234; PP dialysis 94.4% vs no-dialysis 100%, p = 0.175). Eleven patients (9 SOF/DAC, 2 SOF/VEL; 7 non-cirrhosis, 4 cirrhosis) failed to achieve SVR (4.9%). Six of the nine retreatment episodes (8 second episode and 1 third episode after 8[4-13.5] and 6 months after SVR12) were tested for SVR12 and five achieved SVR12. **Conclusion:** Sofosbuvir in combination with daclatasvir or velpatasvir are highly and equally effective against HCV in CKD patients with eGFR below 30 mL/min.

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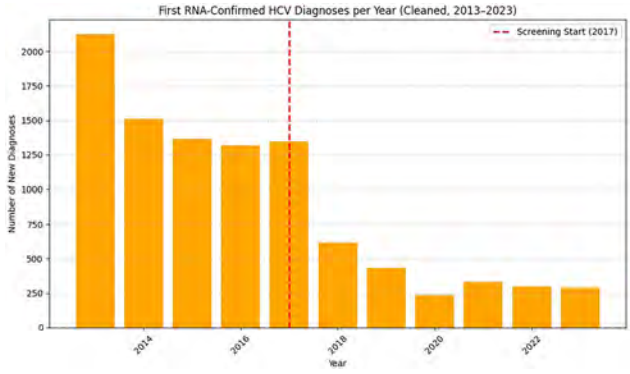
1419 | EVALUATING PROGRESS TOWARD HEPATITIS C ELIMINATION IN THE UNITED KINGDOM: A REAL-WORLD ANALYSIS USING NATURAL LANGUAGE PROCESSING

Mahd Siddiqi[1] Saima Ajaz[1] Mohammad Al-Agil[1] Kosh Agarwal[1], [1]Kings College Hospital, London, United Kingdom

Background: The UK has made significant strides in hepatitis C virus (HCV) control through national screening initiatives and the broad rollout of direct-acting antivirals (DAAs). These efforts support the WHO's goal to eliminate HCV as a public health threat by 2030. However, most countries remain off track, with only 12 countries globally, including the UK, projected to meet elimination targets. Our aim was to provide a real-world overview of HCV diagnoses, treatment patterns, and clinical outcomes before and after national screening and treatment initiatives were introduced. We assessed the impact of these programmes on key clinical endpoints, including cirrhosis, hepatocellular carcinoma (HCC), liver transplantation, and all-cause mortality. **Methods:** This study involved the retrospective analysis of electronic health records (EHRs) from patients with HCV RNA-positive at King's College Hospital, London, between the years 2013 and 2023. Structured and unstructured clinical data were extracted using CogStack, a natural language processing (NLP) platform. Variables included yearly new diagnoses, demographics, fibrosis level (LSM), liver function tests, cirrhosis status, DAAs treatment initiation, and clinical outcomes (mortality, HCC, liver transplant). Statistical analysis identified trends and factors influencing HCV incidence and clinical outcomes over the decade, coinciding with broader public health screening and elimination efforts. **Results:** Using CogStack, we identified 10,171 HCV RNA-positive patients. The cohort had a male predominance (62% male, 38% female). Ethnicity distribution was: White (58.6%), Unknown (20.1%), Black (12.6%), Other (5.3%), Asian (3.7%), and Mixed (0.3%). Evidence of cirrhosis was found in 2,696 patients (27.3%), 1,256 (12.7%) had documented HCC, and 226 (2.3%) underwent liver transplantation. Annual HCV RNA-positive diagnoses declined significantly, from 2,123 in 2013 to 291 in 2023, an 86.3% reduction, with a compound annual decline of 18.0%. Similarly, cirrhosis fell from 321 to 72 (–77.6%; –14.0% annually), HCC from 195 to 63 (–67.7%; –10.7%), and transplants from 35 to 15 (–57.1%; –8.1%). The Mann–Kendall test confirmed significant monotonic declines for all outcomes (RNA $\tau = -0.85$, $p < 0.001$; cirrhosis $\tau = -0.56$, $p = 0.020$; HCC $\tau = -0.53$, $p = 0.029$; transplant $\tau = -0.56$, $p = 0.020$). **Conclusion:** The marked downward trends in HCV diagnoses and related liver complications over the past decade highlight the success of the UK's coordinated screening and DAA treatment programmes in moving toward WHO elimination goals. Importantly, the use of CogStack's proved critical in rapidly harnessing both structured and narrative clinical data, offering a scalable model for ongoing surveillance and optimisation of public health strategies.



Disclosures: Mahd Siddiqi: Nothing to Disclose, Saima Ajaz: Nothing to Disclose, Mohammad Al-Agil: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose

1420 | REAL-WORLD OUTCOMES OF SOFOSBUVIR/VELPATASVIR IN A VARIETY OF HEPATITIS C PATIENT POPULATIONS: A RETROSPECTIVE COHORT STUDY

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Background: Sofosbuvir/velpatasvir (SOF/VEL) has revolutionized the treatment of hepatitis C virus (HCV) by providing a promising option for virus elimination across various patient groups. However, there is a need for more comprehensive real-world studies to assess its efficacy and safety specifically in the Korean population with chronic hepatitis C (CHC), where diverse clinical scenarios and patient characteristics may influence treatment outcomes. The aim of our study was to assess the effectiveness and safety of SOF/VEL-based treatment for CHC patients in Korea. **Methods:** In this real-world observational study, we recruited patients at tertiary hospital in South Korea. Patients were administered SOF/VEL (400/100mg) ± ribavirin (RBV) once daily for 12 weeks or 24 weeks. The primary efficacy endpoint was sustained virological response at post-treatment week 12 (SVR12). Adverse events (AEs) were evaluated during treatment. **Results:** This study included 87 patients (median age, 65, male, n = 50) with HCV genotypes 1 (1a+1b, n = 52), 2 (2, 2b, 2a/2c, n = 34) and 1b&2b (n = 1), as well as two cases of HBV coinfection and two cases of HIV coinfection. 46% (n = 40) of the patients included in this study had cirrhosis, 8.0% (n = 7) had a Child-Pugh score of B, and 25.3% (n = 22) were diagnosed with hepatocellular carcinoma (HCC). BCLC HCC stage is A in 4, B in 11 and C in 7 patients and 18 patients have viable HCC at the start of HCV treatment. Thirty-one patients had prior HCV treatment experience, including three with interferon (IFN) based treatment, 20 with direct acting antivirals (DAA) treatment, and eight with DAA treatment after failing IFN therapy. Among them, 98.6% [86/87, intention to treat (ITT)] and 100% [86/86, modified ITT (mITT)] received SOF/VEL. At the end of treatment, 95.4% (ITT, 83/87) and 100% (mITT, 83/83) of patients had undetectable HCV RNA. SVR12 rates were 90.8% (ITT, 79/87) and 98.7% (mITT, 79/80). In the mITT analysis, SVR12 for patients with cirrhosis and HCC was 100% and 100%. AEs occurred in eight patients but improved with symptomatic treatment. Twenty-eight patients received SOF/VEL + RBV, and among them, eight had their RBV dose reduced; however, all achieved a 100% SVR12. **Conclusion:** This study demonstrated that the SOF/VEL ± RBV achieved excellent treatment outcomes and was well tolerated in Korean patients with CHC, despite a significant proportion of patients having cirrhosis or HCC

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1421 | WOMEN OF CHILDBEARING AGE WITH UNTREATED OR INCOMPLETELY DIAGNOSED HEPATITIS C VIRUS: INTERIM RESULTS: OF A PROSPECTIVE COHORT AND LINKAGE-TO-CARE PROGRAM

Mai Sedki[1] Matthew Caliz[2] Jeff McKinney[2] Jennifer Price[2] Katrina Alcantara[2] Tasha Toliver[2] Michael Helle[2] Rena Fox[3], [1]University of California San Francisco, Stanford University, [2]University of California San Francisco, [3]University of California, San Francisco

Background: Women of childbearing age living with hepatitis C virus (HCV) are a population for whom timely diagnosis and pre-pregnancy antiviral treatment is important to reduce vertical transmission and improve long-term maternal outcomes. Two studies found younger women were less likely to progress through the HCV care cascade than the general HCV population. We identified a prospective cohort of adult women age 18-50 with HCV viremia or incompletely diagnosed HCV and implemented a targeted intervention to improve linkage to care among these patients. **Methods:** Using the electronic medical record (EMR), we identified adult women of childbearing age, defined as age 18–50, seen between 2020–2024 at a large urban health system, with either 1) a quantified or detected HCV RNA at most recent testing, or 2) a reactive HCV antibody without HCV RNA testing. Cirrhosis was identified by ICD-9/10 code followed by chart review of clinical notes. Two trained navigators reviewed any non-searchable EMR data from external systems and excluded patients with more recent negative HCV RNA results. Navigators placed ≥3 phone calls to contact patients to offer updated HCV testing and linkage with HCV specialists. No study incentives were provided. Interim results are presented. **Results:** The initial query identified n = 138 patients. After manual review of external laboratory data, the cohort consisted of 72 of whom 56% were White and 62% had Medi-cal insurance. Only 5 had a primary care provider, 60 (85%) were viremic, 11 (15%) were Ab+ without RNA testing, and 5 had cirrhosis. To date, 33 (46%) have been successfully contacted; among these, 22 agreed to a video visit, 19 visits have been scheduled, 13 visits have been completed, and 4 have started DAA treatment. Reasons for no-shows/cancelled appointments (n = 6) included evictions, accidents, drug use, lack of phone service, homelessness, and other stressors. **Conclusion:** Finding and treating women with untreated and incompletely diagnosed HCV is achievable. Our EMR algorithm identified those with HCV RNA+ or HCV Ab+ without RNA testing and we increased accuracy with outside RNA results. Our outreach successfully contacted almost half of the cohort by phone and to date, 30% of the patients who linked to care have initiated DAA therapy. Major psychosocial stressors were the primary

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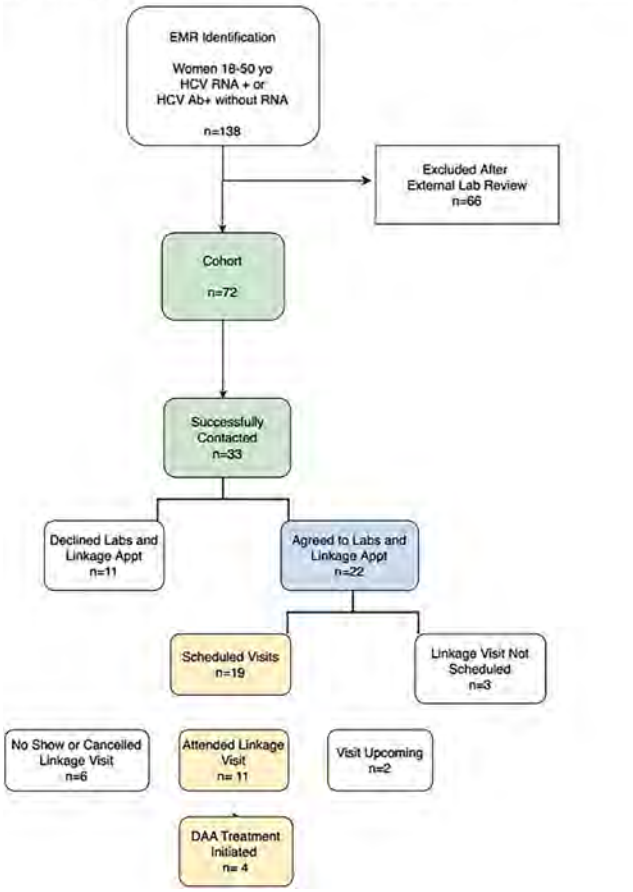
reasons patients did not attend their linkage visits. Dedicated efforts to provide HCV care to these vulnerable women who are of childbearing age should be high priority for private and public healthcare systems.

Figure 1. Linkage to care outreach to women of childbearing age with untreated HCV: Interim results



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1422 | METABOLIC IMPLICATIONS OF HDL-C/APOA1 RATIO IN HCV-INFECTED PATIENTS: A COMPARATIVE ANALYSIS OF DIABETIC AND NON-DIABETIC PATIENTS FOLLOWING SUSTAINED VIROLOGICAL RESPONSE

Irina Duport-Dodot[1] Mihai Dodot[2] Irina Sirbulescu[3] Isabela Staicu[1] anca negru[4] Anca Saran[4] Smaranda Gata[5] Laurentiu Stratan[6] Catalin Tiliscan[7] Adrian Gabriel MARINESCU[8] Sorin Arama[9] Victoria Arama[10], [1]INBI "Prof. Dr. Matei Bals, [2]UMF, I.C Fundeni, [3]INBI Prof. Dr. Matei Bals, [4]UMF "Carol Davila", INBI "PRof. Dr. Matei Bals", [5]INBI "PRof. Dr. Matei Bals", [6]UMF "Carol Davila", INBI Prof. Dr. Matei Bals, [7]UMF "Carol Davila", INBI "PRof. Dr. Matei Bals, [8]UMF "Carol Davila", INBI "Prof Dr. Matei Bals, [9]UMF "Carol Davila", INB I "PRof. Dr. Matei Bals", [10]UMF "Carol Davila, INBI "Prof. Dr. Matei Bals"

Background: The HDL-Cholesterol (HDL-C) to apolipoprotein A1 (ApoA1) ratio reflects both HDL-C levels and its functional quality. A decreased ratio indicates dysfunctional HDL, which is linked to higher cardiovascular and metabolic risks, particularly in the context of chronic inflammation and type 2 diabetes (T2DM). This ratio is considered to offer greater prognostic value compared to HDL-C levels alone, underscoring its importance in the field of hepatology and overall metabolic health. **Methods:** This study assessed HDL-C and ApoA1 ratio changes in chronic hepatitis C (HCV) infected patients with and without T2DM one year after sustained virological response (SVR). Statistical analysis used SPSS 22, with Chi-squared and t-tests, considering $p < 0.05$ as significant. **Results:** We conducted a retrospective study on 100 HCV-infected patients treated with direct-acting antivirals (DAAs), which were administered according to the national protocols, at the National Institute for Infectious Diseases, Prof. Dr. Matei Bals, Bucharest, between September 2016 and August 2019. The study group was divided into two subgroups according to the presence of T2DM. We evaluated the kinetics of HDL-C and the ApoA1 ratio across the two groups as a marker of lipid metabolism evolution. The study group consisted of 57 females and 43 males. The mean age at treatment initiation was 63 years $\pm$ 9.1 years. All patients were assessed at the initiation of treatment and one year after. At the initiation of the IFN-free treatment, the mean HDL-ApoA1 ratio in the study population was 33.06 $\pm$ 6.86. The diabetic group had a lower ratio than the non-diabetic group (29.6 vs 35.1, $p = 0.124$). One year after treatment completion, the mean HDL-C and ApoA1 ratio was 36.07 $\pm$ 7.25, with an overall increase of 3.22 $\pm$ 7.63. One year after treatment completion, the T2DM patients maintained a significantly lower mean ratio than the non-diabetic patients (33.2 versus 39.04, $p = 0.01$). The increase in HDL-C–ApoA1 ratio was higher in the nondiabetic group compared to the diabetic group (6.36 versus 0.5, $p = 0.14$). **Conclusion:** This study found that the ratio of HDL-C to ApoA1 increased one year following HCV treatment, with non-diabetic patients exhibiting a more significant improvement compared to those with T2DM. This indicates that diabetes might impede lipid recovery even after eradicating HCV infection, highlighting the importance

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of continued metabolic management. Monitoring HDL-C and ApoA1 ratio kinetics after antiviral therapy can provide more accurate insights into metabolic risk stratification in these populations.

Disclosures: Irina Duport-Dodot: Nothing to Disclose, Mihai Dodot: Nothing to Disclose, Irina Sirbulescu: Nothing to Disclose, Isabela Staicu: Nothing to Disclose, anca negru: Nothing to Disclose, Anca Saran: Nothing to Disclose, Smaranda Gata: Nothing to Disclose, Laurentiu Stratan: Nothing to Disclose, Catalin Tiliscan: Nothing to Disclose, Adrian Gabriel MARINESCU: Nothing to Disclose, Sorin Arama: Nothing to Disclose, Victoria Arama: Nothing to Disclose

1423 | PREDICTION RISK SCORE FOR DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN COMPENSATED ADVANCED CHRONIC HEPATITIS C AFTER SUSTAINED VIROLOGICAL RESPONSE

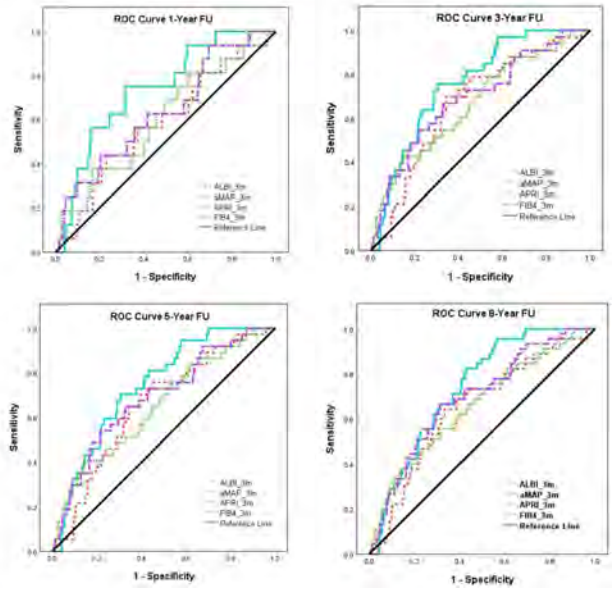
Sirajuk Khongviwatsathien[1] Tawesak Tanwandee[2], [1]Siriraj Hospital, [2]Siriraj Hospital/Mahidol University

Background: Hepatocellular carcinoma (HCC) remains a major cause of cancer-related mortality in patients with chronic hepatitis C virus (HCV) infection, even after achieving sustained virological response (SVR). Current guidelines recommend lifelong HCC surveillance in individuals with compensated advanced chronic liver disease (cACLD) following SVR. However, this approach imposes a considerable burden on healthcare systems. Stratifying HCC risk using simple, noninvasive tools may enhance the efficiency of surveillance, particularly by identifying low-risk patients who may not require routine screening. **Methods:** We conducted a retrospective study of patients with cACLD due to chronic HCV infection who achieved SVR following treatment with direct-acting antivirals (DAAs) at Siriraj Hospital between 2013 and 2023. Patients with a history of HCC or a follow-up duration of less than 12 months were excluded. Four noninvasive scoring systems—FIB-4, APRI, ALBI, and aMAP—were calculated at 12 weeks post-treatment. Predictive performance for HCC development at 1, 3, 5, and 8 years was assessed using ROC curve analysis (AUC), and Cox regression was used to identify associations with HCC development. Optimal aMAP score cutoffs were determined using Youden's J-statistic. **Results:** Out of 2,971 patients screened, 571 met the inclusion criteria. During a median follow-up of 4.59 years, 78 patients (13.7%) developed HCC, with an annual incidence of 3.12% (95% CI: 2.50–3.80). Among all models, aMAP demonstrated the highest predictive performance (AUC = 0.74; 95% CI: 0.67–0.80). Patients were stratified into three risk categories based on aMAP scores: low risk (< 55) with no HCC cases observed, intermediate risk (55–60) with an annual incidence of 0.01–2.42%, and high risk (> 60) with an annual incidence of 2.43–6.42%. Our study suggests that an aMAP score < 55 effectively excludes patients from the need for routine HCC surveillance. This threshold aligns with previous findings that identified a cutoff of < 50 as low risk across various cACLD etiologies (Fan et al., J Hepatol, 2020). The slightly higher cutoff in our cohort may reflect improvements in liver status after SVR specific to HCV-related cACLD. **Conclusion:** Our findings demonstrate that the aMAP score provides the strongest predictive performance (AUC = 0.74) compared to FIB-4, APRI, and ALBI. An aMAP cutoff of < 55 can reliably exclude cACLD HCV patients from post-SVR HCC surveillance. Adoption of this threshold may safely reduce the number of patients requiring routine surveillance, easing the strain on healthcare resources. If validated in other HCV-specific cohorts, this revised cutoff could inform future surveillance guidelines.

Diagnostic accuracies for the detection of de novo HCC at 1-, 3-, 5-, and 8-year follow-up, and the predictive performance of the four noninvasive scoring systems (NSS).

NSS* (3 months after EOT)	1-Year FU AUC (95% CI)	3-Year FU AUC (95% CI)	5-Year FU AUC (95% CI)	Overall HCC, 8-Year FU AUC (95% CI)
FIB-4	0.64 (0.49-0.78)	0.69 (0.59-0.79)	0.69 (0.60-0.78)	0.69 (0.61-0.78)
APRI	0.61 (0.46-0.75)	0.67 (0.57-0.77)	0.65 (0.56-0.75)	0.66 (0.57-0.75)
ALBI	0.59 (0.44-0.73)	0.67 (0.58-0.76)	0.66 (0.57-0.74)	0.65 (0.56-0.74)
aMAP	0.74 (0.62-0.85)	0.76 (0.68-0.83)	0.74 (0.67-0.82)	0.74 (0.67-0.80)

* Noninvasive scoring system calculated at 3 months after end of treatment



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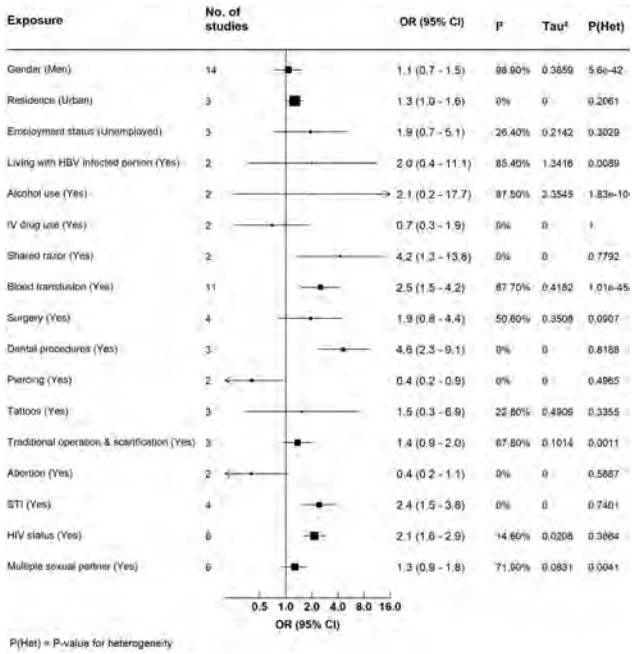
1424 | FACTORS ASSOCIATED WITH HEPATITIS C INFECTION IN SUB-SAHARAN AFRICA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Nkengeh Tazinkeng[1] Sonia Yonta Kenne[2] Jan René Nkeck[3] Monela Ntonifor[4] Fatima Elmustafa[5] Ryan Tanjoh[6] Ephesians Anutebeh[7] Yasmin Osman Ali[8] Adedeji Adenusi[9] David Makanga[7] Lydia Lantum Dzeenyuy[10] Cameg-Brenda Meriki[11] Emmanuel Agyemang[7] Noon Altijani[12] Valirie Ndip Agbor[13], [1]Rutgers/Newark Beth Israel Medical Center, [2]Centre Hospitalier de l'Estran, Pontorson, France, [3]Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Cameroon, [4]North Carolina Agricultural and Technical State University, North Carolina, USA, [5]Henry Ford Hospital System, Michigan, USA, [6]South Liverpool & Birkenhead GP training program, Mersey and West Lancashire Hospitals NHS Trust, UK, [7]Rutgers/Newark Beth Israel Medical Center, New Jersey, USA, [8]Hennepin Healthcare, Minnesota, USA, [9]One Brooklyn Health-Interfaith Medical Center, New York, USA, [10]Faculty of Health Sciences, University of Buea, Cameroon, [11]Faculty of Health Sciences, University of Bamenda, Cameroon, [12]Postgraduate Team, Education Centre, Liverpool University Hospitals NHS Foundation Trust, UK, [13]Department of Clinical Sciences,Global Health Trials Unit, Liverpool School of Tropical Medicine,UK

Background: Despite the advances in diagnosis and treatment of Hepatitis C virus (HCV) infection, there is still a growing trend in incidence in low-middle income countries where universal screening programs and linkage to care still face severe financial and logistical complexities. With lack or insufficient domestic funding, there is a need for targeted screening programs among high-risk groups. Previous evidence on the determinants of HCV in sub-Saharan Africa (SSA) has been limited by small sample sizes. This systematic review and meta-analysis investigated the factors associated with HCV infection in SSA. **Methods:** Following the PRISMA guidelines, we conducted a comprehensive search on MEDLINE, Embase, Global Health Library, and Africa-specific databases (AFROLIB, African Index Medicus and African Journals Online) for articles published in English from inception of the databases to 27 October 2024. Random-effects meta-analytic models were used to calculate pooled log-transformed odds ratios (ORs) and their variances to evaluate the determinants of HCV infection. Heterogeneity across studies was assessed using the I^2 statistic and Cochran's Q test. **Results:** We included 72 studies with a total sample of 1,094,104 participants. Most included studies were cross-sectional studies (65/72) and were published between 2011 and 2020 (45/72). East (n = 30) and West Africa (n = 24) had the most publications, with Ethiopia (n = 19), Nigeria (n = 6) and Ghana (n = 9) contributing the most publications.The following factors were associated with significantly higher odds of HCV infection: sharing razors (pooled OR 4.2, 95% confidence interval: 1.3–13.8), history of blood transfusion (2.5, 1.5–4.2), History of dental procedures (4.6, 2.3–9.1), history of STI (2.4,1.5–3.8), and HIV infection (2.1, 1.6–2.9). **Conclusion:** This study suggests that HCV transmission in SSA is multifactorial and driven by household and health-care related exposures. These insights highlight the importance of strengthening infection prevention practices in healthcare and community settings and the need for targeted public health interventions such as education, screening and access to treatment for high risk individuals.



Disclosures: Nkengeh Tazinkeng: Nothing to Disclose, Sonia Yonta Kenne: Nothing to Disclose, Jan René Nkeck: Nothing to Disclose, Monela Ntonifor: Nothing to Disclose, Fatima Elmustafa: Nothing to Disclose, Ryan Tanjoh: Nothing to Disclose, Ephesians Anutebeh: Nothing to Disclose, Yasmin Osman Ali: Nothing to Disclose, Adedeji Adenusi: Nothing to Disclose, David Makanga: Nothing to Disclose, Lydia Lantum Dzeenyuy: Nothing to Disclose, Cameg-Brenda Meriki: Nothing to Disclose, Emmanuel Agyemang: Nothing to Disclose, Noon Altijani: Nothing to Disclose, Valirie Ndip Agbor: Nothing to Disclose

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1425 | PREDICTORS OF REINFECTION AMONG PARTICIPANTS IN A HEPATITIS C TREATMENT TRIAL IN RURAL KENTUCKY

Jennifer Havens[1] Takako Schaninger[2] Michelle Lofwall[1] Sharon Walsh[1], [1]University of Kentucky College of Medicine, [2]University of Kentucky Medical Center

Background: Direct acting antivirals (DAAs) have revolutionized treatment for hepatitis C virus (HCV) infections. However, treatment delivery is disjointed in the United State (U.S.), especially among marginalized groups in under resourced areas. The purpose of the current analysis was to examine the factors associated with HCV reinfection among participants in an HCV treatment trial. **Methods:** Patients (n = 380) consented to participate in the Kentucky Viral Hepatitis Treatment (KeY Treat) trial, a test and treat model of care in a rural Appalachian county in the U.S. Most consenting participants (n = 368) initiated sofosbuvir/velpatasvir and 22.3% were lost-to-follow-up (LTFU) during the treatment phase. Sustained Virologic Response (SVR-12) was achieved by 306 participants, who represent the sample for the current analysis. Participants were tested using the Xpert HCV VL fingerstick assay at 6- and 12-months post-SVR to determine reinfection and Cox proportional hazards models were used to model reinfection. **Results:** Fourteen reinfections were detected corresponding to a reinfection rate of 4.3 per 100 person years (95% Confidence Interval: 2.5, 7.3). Most (85%) reinfections were detected within a year of SVR. Males were nine times more likely to be reinfected than females ($p < 0.001$). Injecting drugs during the period between SVR and follow-up was predictive of reinfection (adjusted Hazard Ratio [aHR]: 7.35, 95% Confidence Interval [CI]: 2.46, 21.9), as was being incarcerated prior to or at the time of reinfection. Enrollment in a medication for opioid use disorder (MOUD) program was protective against reinfection (aHR: 0.24, 95% CI: 0.07, 0.67). **Conclusion:** The low overall HCV reinfection rates observed in this study support engaging people who inject drugs in DAA treatment. Consistent with the literature, a significant risk factor for reinfection was ongoing injection drug use after cure. Given that MOUD decreases injection opioid use and MOUD engagement was protective against reinfection herein, we call for increasing access to DAA treatment within MOUD treatment programs, including MOUD programs in carceral settings. The recently updated U.S. recommendations for establishing cure at four weeks post-treatment (SVR4) versus 12 (SVR12) will encourage earlier counsel around safe injection practices and engagement in MOUD to prevent reinfection.

Disclosures: Jennifer Havens: Gilead Sciences, Inc.: Consultant, AbbVie: Advisor, Cepheid: Consultant, Takako Schaninger: Nothing to Disclose, Michelle Lofwall: Braeburn Pharmaceuticals: Research advisor, Journey Colab: research advisor, Berkshire Biomedical: research advisor, Sharon Walsh: Nothing to Disclose

1426 | UNCOVERING THE URBAN-RURAL HIDDEN BURDEN OF HEPATITIS C: A POPULATION-BASED STUDY IN SOUTHERN ITALY

Torre Pietro[1] Silvana Mirella Aliberti[1] Tommaso Sarcina[1] Mariano Festa[1] Chiara D'Amore[1] Giuseppe D'Adamo[2] Michele Gambardella[3] Antonella Santonicola[1] Gaetano Manzi[1] Mario Masarone[1] Mario Capunzo[1] Marcello Persico[1], [1]University of Salerno, Italy, [2]Internal Medicine, Umberto I Hospital, ASL SA, [3]Infectious Disease Unit, San Luca Hospital, ASL SA

Background: Although major advances in treatment have made it possible to cure HCV infection today, this disease still represents a significant global challenge, as WHO hepatitis C elimination targets are not achievable in most countries, mainly due to the high number of undiagnosed people. The primary objective of this study was to estimate the hidden burden of chronic HCV infection across the vast territory of the province of Salerno (Campania region), in Southern Italy. **Methods:** Records of patients with confirmed diagnosis of chronic HCV infection between 2015 and 2022, limited to residents of the province of Salerno, were retrieved from the prescribing centers active in that area. Age, sex, municipality of residence, HCV genotype, and liver fibrosis stage were considered in the analysis. The estimate of the hidden burden was achieved by considering observed and expected prevalence of active infection, derived from regional and national benchmarks. Municipalities were classified as urban or rural based on the resident population. **Results:** Between 2015 and 2022, a total of 3528 confirmed cases of chronic HCV infection were identified across 138 municipalities in the Province of Salerno. Patient characteristics showed a marked predominance of older individuals (mean age of 63 years), a slight male predominance (54%), about 50% of patients diagnosed with advanced liver disease (F3–F4), and genotype 1b as the most prevalent. The hidden burden of active HCV cases increased with age, except for the younger age group, and was greater in rural areas than in urban ones. Multivariable logistic regression showed that older age, urban residence, and genotype 1b were significant predictors of F3–F4 fibrosis at the time of diagnosis. **Conclusion:** To reach HCV elimination goals, targeted interventions in underdiagnosed areas are crucial. Addressing the hidden

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burden of HCV, however, requires more than just expanded screening coverage; it necessitates a deep knowledge of the complex interplay between health system accessibility, past exposure risks, and the sociocultural contexts that shape hepatitis C diagnosis, linkage-to-care, and treatment. Our municipal-level classification system, coupled with the estimate of hidden cases, could offer a replicable model for supporting precision public health strategies.

Disclosures: Torre Pietro: Nothing to Disclose, Silvana Mirella Aliberti: Nothing to Disclose, Tommaso Sarcina: Nothing to Disclose, Mariano Festa: Nothing to Disclose, Chiara D'Amore: Nothing to Disclose, Giuseppe D'Adamo: Nothing to Disclose, Michele Gambardella: Nothing to Disclose, Antonella Santonicola: Nothing to Disclose, Gaetano Manzi: Nothing to Disclose, Mario Masarone: Nothing to Disclose, Mario Capunzo: Nothing to Disclose, Marcello Persico: Nothing to Disclose

1427 | ★ HCV DAA PRESCRIBING PATTERNS AMONG SPECIALISTS AND NON-SPECIALISTS IN ONTARIO, CANADA, FROM 2017-2024

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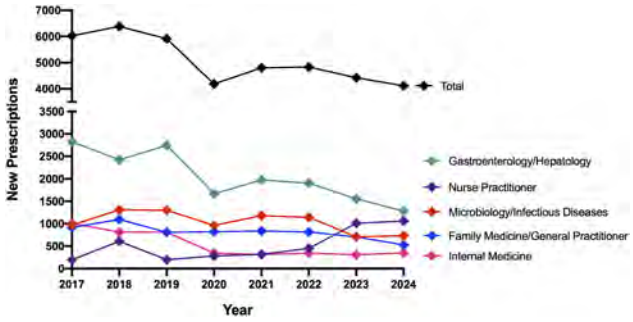
Background: As of 2018 in Canada, fibrosis eligibility restrictions for HCV direct acting antivirals (DAAs) were removed. While there was a large uptake in treatment among patients awaiting alternatives to interferon-based therapy, prescribing in Canada has continued to decrease each year since. While efforts to expand treatment to non-specialists have intensified; it is unclear whether this has occurred. We evaluated prescribing patterns of DAAs by specialty provider type in Ontario from 2017-2024, the largest province in Canada. **Methods:** The IQVIA database was used to assess DAA dispending from 2017-2024. Year, molecule, prescriber type, and first three digits of the pharmacy postal code were available. Specialties were collapsed into: Gastroenterology/Hepatology (G/H), Microbiology/Infectious Diseases (M/ID), Internal Medicine (IM), Family Medicine/General Practitioner (FM/GP), Nurse Practitioner (NP), Pediatrics, and other. We used linear regression to assess prescribing trends. **Results:** Total DAA prescriptions in Ontario in 2017 were 6027, which decreased to 4185 in 2020, had a slight rebound in 2021 and 2022, and went down to 4116 in 2024. Most specialties had decreased prescribing in 2020, with peak years in 2017-2018 and have gone down each year since, apart from NPs (Figure 1). After adjusting for specialty, prescribing volume showed a significant year-to-year decline of 63.2 (95%CI: 18.9 to 107.6; $p < 0.05$). Specialty-specific trends showed G/H volumes with the highest decline of 206.5 (95%CI: 104.2 to 308.7; $p < 0.05$) per year, followed by IM with 101.9 (95% CI: 42.7 to 161.2; $p < 0.05$) per year. In contrast, NP volumes increased over time, by 105.6 (95%CI: 9.8 to 201.4; $p < 0.05$) per year; for over a quarter of all prescriptions in the province by 2024. From 2017-2024, there were a total of only 31 prescriptions by pediatricians, despite estimates ~200-1000 children living in Ontario with HCV. **Conclusion:** In Ontario, all specialities have been able to prescribe since the public funding of DAAs. Despite efforts to engage FM/GPs in programmatic approaches to screen and treat HCV, prescribing continues to decrease; concerning as FMs/GPs largely lead OAT and methadone programs. Prescribing amongst NPs has increased, likely due to NP-led outreach, virtual care, and prescribing in community health centres. While this demonstrates the value of engaging NPs, sustained and expansion of prescribing is required by other types of providers to reach elimination.



Disclosures: Mia Biondi: Gilead Sciences: Grant/Research Support, Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, AbbVie: Grant/Research Support, Cepheid: Grant/Research Support, Andrew Mendlowitz: Nothing to Disclose, Camelia Capraru: Nothing to Disclose, Jordan Feld: AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support, AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio:

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1428 | THE MAJORITY OF PATIENTS WITH HEPATITIS C NOT ACHIEVING SVR CAN BE SUCCESSFULLY RETREATED WITH FIRST-LINE REGIMENS: RESULTS: FROM A MULTIDISCIPLINARY TEAM APPROACH TO GUIDE TREATMENT DECISIONS

Stephen Barclay[1] Alison Boyle[1] Fiona Marra[1] Erica Peters[1] Emma Thomson[1] Samantha Shepherd[1] Janice McAvennie[1] Elaine Reilly[1], [1]NHS Greater Glasgow and Clyde

Background: Amongst people who inject drugs, sustained viral response (SVR) bloods following HCV treament may not always be available. Subsequent positive RNA tests may represent treatment failure, or reinfection. We discuss such cases in a Multidisciplinary Team (MDT) setting, using assessment of reinfection risk factors and compliance, testing for NS5A resistance (RAVs), and (where available) comparison of pre and post treatment viral sequences, to judge the likelihood of reinfection vs treatment failure, and hence the necessity for first or second-line antiviral regimens. We report treatment outcomes from this approach. **Methods:** From an HCV database, patients not achieving SVR with an initial DAA regimen, who received one or more subsequent DAA regimens were identified. Patients with a genotype switch (confirming reinfection) were excluded. Treatment completion, reinfection risk factors, NS5A resistance testing, nature of subsequent treatments (1st vs 2nd line) were recorded, along with the outcome of each retreatment. **Results:** 243 patients were identified. 12/243 (4.9%) were excluded due to genotype switch. 65/231 (28.1%) had incomplete initial treatment. 139 (60.2%) had end of treatment response (EOTR) with subsequent positive RNA, 20 (8.65%) were positive at end of treatment, with the remainder positive at first test beyond end of treatment (SVR timepoint or later). A total of 263 retreatments were given, 176 (66.9%) 1st line (103 glecaprevir/pibrentasvir, 28 sofosbuvir/velpatasvir, 20 grazoprevir/elbasvir, 18 sofosbuvir/ledipasvir, 7 others) and 87 (33.1%) 2nd line (76 sofosbuvir/velpatasvir/voxilaprevir, 11 others).98 (37.2%) had documented risk factors for reinfection. 183 (69.6%) had RAV testing prior to treatment, 64 (34.9%) of which were positive. Intention to treat SVR rate was 199/263 (75.7%); 129/176 (73.3%) 1st line vs 70/87 (80.4%), $p = 0.20$. Excluding 19 with incomplete treatment, 7 reinfections and 21 with missing SVR data, per protocol SVR rate was 199/216 (92.1%); 129/141 (91.5%) 1st line vs 70/75 (93.3%) 2nd line, $p = 0.22$. **Conclusion:** An MDT approach to treatment failure, combined with resistance testing where available, allows for the majority of patients to be retreated with 1st line DAA regimen, with comparable rates of SVR to those treated with 2nd line regimens.

Disclosures: Stephen Barclay: Gilead: Speaking and Teaching, Ipsen: Travel support to attend conference, Falk: Speaking and Teaching, Falk: Advisor, Chemomab: Speaking and Teaching, Alison Boyle: Nothing to Disclose, Fiona Marra: Gilead: Speaking and Teaching, Viiv: Speaking and Teaching, Erica Peters: Nothing to Disclose, Emma Thomson: Moderna: Clinical trial PI (no personal financial benefit), Samantha Shepherd: Nothing to Disclose, Janice McAvennie: Nothing to Disclose, Elaine Reilly: Nothing to Disclose

1429 | CLINICAL CHARACTERISTICS AND RISK FACTORS OF HCV GT3 PATIENTS IN QINGHAI PROVINCE

Faying Li[1] Guoying Yu[1], [1]Infectious Disease Specialized Hospital of Qinghai Province

Background: Qinghai is a province in China with a high incidence of hepatitis C virus (HCV). The epidemiological characteristics of HCV genotype 3 (GT3) have not been clearly defined. The purpose of this study is to investigate the clinical characteristics of patients with HCV GT3 in Qinghai, and to lay the groundwork for developing appropriate prevention and treatment measures in the furture. **Methods:** A total of 755 HCV patients who tested positive for HCV antibodies and HCV RNA and had successful polymerase chain reaction (PCR) gene sequencing were prospectively enrolled at the Infectious Disease Specialized Hospital of Qinghai Province between January 2023 and December 2024. The clinical characteristics of patients with HCV GT3 were analyzed and independent risk factors for cirrhosis were identified using multifactorial regression modeling. **Results:** The prevalence of HCV GT3 in Qinghai Province showed an increasing trend (33.1%, 250/755), with HCV GT 3b being the most common subtype (71.6%, 179/250). Most HCV GT3 patients were significantly male (78.8%, 595/755), aged 40-60 years (89.6%, 677/755), and unemployed farmers (87.6%, 662/755). The main route of transmission was intravenous drug addiction (49.6%, 375/755). Compared with non-HCV GT3 patients, HCV GT3

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patients had a higher incidence of cirrhosis (39.6% [99/250] vs. 16.4% [83/505], p **Conclusion:** In recent years, the infection rate of HCV GT3 patients in Qinghai has increased, predominantly of subtype 3b and it has been significantly associated with cirrhosis. It is recommended that high-risk populations be screened and that early treatment with pan-genotypic direct antiviral agents be used to improve prognosis.
Disclosures: Faying Li: Nothing to Disclose, Guoying Yu: Nothing to Disclose

1430 | IS SVR4 TESTING AN ACCEPTABLE ALTERNATIVE MEASURE OF HCV CURE IN RE-TREATED PATIENTS FOLLOWING DAA FAILURE? A SVR4/12 CONCORDANCE EVALUATION FROM THE POLARIS CLINICAL TRIALS

Stacey Scherbakovsky[1] Marc Bourliere[2] Stephen Shafran[3] Meena Bansal[4] Stuart Gordon[5] Stefan Zeuzem[6] Candido Hernandez[1] Renee-Claude Mercier[1] Kyle Hammond[7] Liyun Ni[1] Ira Jacobson[8], [1]Gilead Sciences, Inc, [2]Hopital Saint Joseph, [3]University of Alberta, [4]Icahn School of Medicine at Mount Sinai (ISMMS), [5]Henry Ford Health System, [6]University Hospital Goethe-University, [7]Gilead Sciences, Inc., [8]NYU Hepatology Associates

Background: Guidance from AASLD/IDSA and EASL have endorsed treatment simplification as part of a global call to action for HCV elimination. Within this simplification strategy, AASLD/IDSA has recently developed a New Algorithm for Hepatitis C Point of Care Testing and Treatment, in which SVR4 is an acceptable alternative measure of HCV cure for people without cirrhosis or prior DAA exposure. However, we hypothesize that SVR4 could also apply to vulnerable patients with prior DAA exposure, to help reduce the risk of patients being lost to follow-up (LTFU). For this reason, we evaluate the SVR4/12 concordance of sofosbuvir/velpatasvir/voxilaprevir (S/V/V) in randomized clinical trials (RCTs). The POLARIS studies included patients who had previously been treated with a DAA and failed.[1,2]. **Methods:** HCV RNA data from patients in the registrational POLARIS-1, -2, -3 and -4 RCTs evaluating treatment with S/V/V for 8 and 12 weeks were evaluated. SVR was defined as patients with HCV RNA less than the lower limit of quantification (15 IU/mL) using the COBAS TaqMan HCV Test v2.0. Only patients with both SVR4 and SVR12 data were included in the concordance analysis. **Results:** 1,056 patients were evaluated for concordance from the POLARIS (1-4) trials: 611 treated with 8 weeks of S/V/V (POLARIS 2,3) and 445 with 12 weeks of S/V/V (POLARIS 1,4). In the 8-week group, 583 (95.4%) patients achieved both SVR4 and SVR12 (True Positive), giving a 100% sensitivity and 98.8% positive predictive value (PPV) [7 patients achieved SVR4 but failed SVR12]. In the 8-week group, 21 patients failed to achieve both SVR4 and SVR12 (True Negative), showing a 75% specificity and 100% negative predictive value (NPV). In the 12-week group, 431 patients achieved both SVR4 and SVR12, showing 100% sensitivity and 98.9% PPV [5 patients achieved SVR4 but failed SVR12]. In the 12-week group, 9 patients failed both SVR4 and SVR12, showing a 64.3% specificity and 100% NPV. **Conclusion:** HCV treatment with S/V/V can be infrequent in the real world and achieving SVR4 is highly predictive of HCV cure. This earlier time point to confirm HCV cure may be particularly important in persons at high-risk to be LTFU.
Disclosures: Stacey Scherbakovsky: Nothing to Disclose, Marc Bourliere: Gilead: consultant, AbbVie: speaker, GSK: advisor, Stephen Shafran: Nothing to Disclose, Meena Bansal: Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boehringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor, Stuart Gordon: Nothing to Disclose, Stefan Zeuzem: Nothing to Disclose, Candido Hernandez: Gilead Sciences: Employee, Renee-Claude Mercier: Nothing to Disclose, Kyle Hammond: Nothing to Disclose, Liyun Ni: Nothing to Disclose, Ira Jacobson: Nothing to Disclose

1431 | PREVALENCE AND TRENDS OF HEPATITIS C VIRUS INFECTION AMONG PREGNANT WOMEN IN XI'AN, CHINA: AN 11-YEAR RETROSPECTIVE STUDY

Yingli He[1] gengwen liu[2] Wenjuan Shi[3] Qiao Zhang[1], [1]The First Affiliated Hospital of Xi'an Jiaotong University, [2]Xi'an People's Hospital (Xi'an Fourth Hospital), [3]Lanzhou Second People's Hospital

Background: Understanding the prevalence and temporal trends of hepatitis C virus (HCV) infection in pregnant women is critical for guiding prevention and elimination strategies. This study aimed to assess the seroprevalence and viremia rate of HCV among pregnant women in Xi'an, China, over an 11-years period. **Methods:** We conducted a retrospective analysis of pregnant women who admitted to the Obstetrics and Gynecology Specialized Hospital of Xi'an between January 2014 to December 2024. All patients underwent either quantitative or qualitative anti-HCV detection, and HCV RNA detection was performed for those who were anti-HCV positive. Trends in anti-HCV positivity and HCV RNA positivity were analyzed across two time periods: the first five years (2014.1.1-2019.6.30) and the second five years (2019.7.1-2024.12.31). **Results:** A total of 133,765 pregnant women were screened, of which 693 (0.518%) tested positive for anti-HCV, with a median age of 30 years (IQR: 28-33). The anti-HCV seroprevalence increased significantly increased from 0.46% (279 cases) in the first five years to 0.56% (414

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cases) in the second five years (P = 0.006). Among the anti-HCV positive women, 478 (68.98%) underwent HCV RNA testing,of whom 73 (15.27%) were HCV RNA positive, with a median age of 29 years (IQR: 27-32). Notably, the HCV RNA positive rate declined significantly from 23.08% (45/195) in the first five years to 9.89% (28/283) in the second five years (P = 0.000).However, a substantial proportion (31.03%, 215 cases) of anti-HCV positive women did not receive confirmatory HCV RNA testing, highlighting a critical gap in the diagnostic cascade. **Conclusion:** The findings of this study demonstrate a rising trend in anti-HCV seroprevalence while a declining trend in HCV viremia, possibly reflecting the improvements in awareness,screening and access to treatment for hepatitis C patients in China. However there remains significant gap for improvement in the diagnostic cascade. To support the action plan of HCV elimination in Shaanxi Province, a recall program targeting both anti-HCV positive and HCV RNA-positive individuals is currently being implemented to increase HCV RNA testing uptake and facilitate timely linkage to treatment with Direct-Acting Antivirals (DAAs), supporting the ongoing efforts to eliminate HCV in Shaanxi province.

Disclosures: Yingli He: Nothing to Disclose, gengwen liu: Nothing to Disclose, Wenjuan Shi: Nothing to Disclose, Qiao Zhang: Nothing to Disclose

1432 | HCV REINFECTION AFTER DAA THERAPY AMONG HIV/HCV-COINFECTED INDIVIDUALS IN THE COUNTRY OF GEORGIA: A NATIONAL COHORT STUDY, 2015-2024

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Background: Although direct-acting antivirals (DAAs) are highly effective in curing HCV infection in nearly all HIV/HCV-coinfected individuals, high rates of reinfection may impede efforts to eliminate HCV in this population. In 2015, with technical support of US CDC and commitment from Gilead Sciences to donate DAAs, Georgia launched the world's first hepatitis C elimination program, providing free access to DAAs to all patients, including HIV/HCV co-infected persons. We aimed to study rates of HCV reinfection among after sustained virological response (SVR) among HIV patients in the country of Georgia. **Methods:** A retrospective cohort study included HIV-positive adult patients treated with DAAs during 2015-2024 and who achieved SVR, defined as undetectable HCV RNA 12 weeks post-treatment. Patients were followed until their last HCV RNA measurement performed through December 31, 2024. Reinfection was defined as detectable HCV RNA after SVR. Data were extracted from Georgia's National HIV/AIDS Health Information System, a real-time, countrywide registry of HIV care and treatment. Rate of Reinfection was calculated per 100 person-years (PY) of follow-up. **Results:** During the study period 1,046 HIV/HCV co-infected patients achieved SVR. 764 (73.0%) were screed for HCV reinfection. Among them 679 (88.9%) were men and 531 (69.5%) had a history of injecting drug use (IDU). The median age was 51 (IQR:11) years. Patients were followed for median 3.3 (IQR: 6.2) years, contributing to 3,567 PY of follow-up. 43 (5.6%) patients had HCV reinfection with an overall incidence rate of 1.2 per 100 PY. The median time to reinfection was 4.3 years (IQR: 2.7). 40 out of 43 patients with reinfection had history of IDU. Three reinfections occurred among men who have sex with men (MSM). **Conclusion:** HIV positive IDUs are at high risk of HCV reinfection following successful DAA therapy, reinforcing the critical need for targeted prevention strategies. Greater engagement of patients in harm reduction services is crucial to prevent reinfection risks, particularly in this vulnerable population and achieve HCV elimination targets.

Disclosures: Otar Chokoshvili: Nothing to Disclose, Lali Sharvadze: Nothing to Disclose, Natia Dvali: Nothing to Disclose, Pati Gabunia: Nothing to Disclose, Marine Karchava: Nothing to Disclose, Vladimer Getia: Nothing to Disclose, Lana Gatserelia: Nothing to Disclose, Revaz Metchurtchlishvili: Nothing to Disclose, Marine Ezugbaia: Nothing to Disclose, Akaki Abutidze: Nothing to Disclose

1433 | DEVELOPMENT OF NESTED-RPA BASED DIAGNOSTIC PLATFORM FOR THE IDENTIFICATION OF HCV RNA USING CRISPR/CAS13A SYSTEM

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Background: Chronic hepatitis C virus (HCV) is the second major hepatic viral burden after HBV. Screening tests are not widely accessible among high-risk populations worldwide. CRISPR-based detection platforms employing isothermal amplification methods have emerged as novel low-cost technology with high specificity and sensitivity. Cas13a, a class 2 type VI RNA targeting Cas protein, majorly employs collateral cleavage against single-stranded RNA. Cas13a detects the target RNA through its cis-cleavage, which is further activated to trans-cleave the fluorophore quencher

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(FQ)-labelled ssRNA reporter and illuminate detectable fluorescent signals. **Methods:** Leptotrichia wadei (Lwa) cas13a was expressed and purified. Nested-Recombinase Polymerase Amplification (Nested-RPA) was implemented to produce T7 RNA polymerase appended amplicons of conserved HCV regions at 42°C and 37°C. Corresponding crRNAs have been designed against amplified regions and produced using In-Vitro Transcription (IVT). With T7 RNA polymerase, the Nested-RPA-amplified HCV templates are transcribed into ssRNAs, which are further used in detection assay containing expressed Cas13a protein, crRNA, and fluorescent probes. This detection was performed in the kinetic format of the microplate reader. **Results:** LwaCas13a was expressed in Rosetta2(DE3)pLysS strain and was purified using the strep tag. Conserved regions among Indian HCV genomes are selected as targets of detection. Nested RPA was performed using primers against the HCV RNA-dependent RNA polymerase (RdRp) region. CRISPR RNAs were produced using T7 RNA polymerase. The detection assay was optimized with HCV 3a genotype RNA. This system can detect HCV RNA as low as 1000 copies [1.65 femtomolar (fM)]. This system also successfully detected the HCV RNA as low as 1000 copies from the human serum samples. **Conclusion:** This approach can be utilized as an alternative in rural areas. At the same time, with high sensitivity for rapid detection of HCV, it could be used as a novel, low-cost diagnostics platform for identifying HCV RNA.

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1434 | HEPATITIS C VIRUS (HCV) RNA POINT-OF-CARE TESTING IN A TRIBAL HEALTH SETTING: IMPLEMENTATION, CHALLENGES, AND LESSONS LEARNED

Jorge Mera[1] Kendra Lewis[1] Savana Christy[1] Andrea Blair[1] Ashley Comiford[1], [1]Cherokee Nation Health Services

Background: American Indian/Alaska Native populations have disproportionately high hepatitis C (HCV) rates and mortality. In 2015, Cherokee Nation Health Services launched an HCV elimination program that cured 99% of treated patients but achieved treatment initiation in under 60% of diagnoses. A 2023 expansion added community point-of-care (PoC) antibody screening, improving detection but requiring clinic visits for HCV RNA confirmation. To address delays and follow-up loss, CNHS was and early adopter of the FDA-approved PoC HCV RNA testing in fall 2024. The purpose of this study was to assess the effectiveness of using the PoC HCV RNA test to increase linkage to care and treatment initiation among a high-risk population, both in clinical and community settings. **Methods:** Using the Cepheid® Xpert HCV RNA platform, CNHS implemented PoC testing in tribal clinics and three community sites: a harm reduction program, a substance use recovery center, and a tribal specialty clinic. Adults (18+) visiting these sites who consented were eligible. Participants received incentives for screening and treatment initiation, and peer recovery support was available at community sites. Those testing positive were offered treatment at the tribal clinic if AI/AN or referred to external providers if non-AI/AN. Data from CNHS electronic health records and program reports were analyzed using descriptive statistics to assess test uptake, result validity, and treatment initiation. **Results:** From October 30, 2024, to May 23, 2025, overall 416 individuals were offered testing; 349 (83.9%) accepted, and 327 samples were adequate for analysis. Of those, 277 (84.7%) yielded valid results, with 26 testing HCV RNA-positive (9.4%). Twelve individuals were AI/AN, of whom nine initiated HCV direct acting antiviral agents (DAAs) treatment. Among 14 non-AI/AN positives, only one initiated HCV DAAs treatment. Sample collection challenges caused 15.3% invalid results, which improved over time with deeper-gauge lancets, hydration, and warming techniques. Incentives and peer support increased testing and linkage, but HCV treatment access for non-AI/AN individuals remained a barrier. **Conclusion:** PoC HCV RNA testing successfully identified undiagnosed infections and enabled same-day referrals, as well as HCV DAAs treatment initiation, addressing a critical gap in the HCV care continuum. As the first high-risk, community-based implementation program of its kind in this population, the findings offer valuable insights for scaling up HCV elimination strategies.

PoC HCV RNA by Location (October 30, 2024 - May 23, 2025)

Location	Test Offered	Accepted/ Collected	Tested	Test Valid	RNA Not-Detected	RNA Detected	Test Invalid
HRP*	168	137	130	109	93	16	21
Specialty Clinic	240	204	189	162	152	10	27
SURP**	8	8	8	6	6	0	2
Total	**416**	**349**	**327**	**277**	**251**	**26**	**50**

*HRP: Harm Reduction Program, **SURP: Substance Use Recovery Program

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1435 | HCV TESTING AND LINKAGE-TO-CARE PRACTICES IN A TERTIARY HOSPITAL IN SOUTHERN ITALY UNDERSCORE THE NEED FOR ROUTINE SCREENING AND TREATMENT PROGRAMS

Torre Pietro[1] Enrica Serretiello[1] Giuseppe Di Siervi[1] Emilia Vaccaro[1] Mariano Festa[1] Tommaso Sarcina[1] Luigi Gallo[1] Mario Masarone[1] Pasquale Pagliano[1] Gianluigi Franci[1] Marcello Persico[1], [1]University of Salerno, Italy

Background: Direct-acting antivirals (DAAs) have had an extraordinary impact on curing and limiting the spread of HCV infection. According to that, screening programs have been established worldwide to achieve ambitious goals, including an 80% reduction in HCV incidence and a 65% reduction in HCV-related mortality by 2030. This study aimed to assess, within a large community tertiary hospital in Southern Italy, the proportion of HCV testing among inpatients and, subsequently, the proportion of positive patients referred for treatment. This analysis was also performed to identify any differences over the years and to provide evidence to support the need for more targeted and extensive future screening initiatives. **Methods:** This retrospective analysis was conducted at the University Hospital of Salerno in the Campania region, Italy, covering the period from 2016 to 2023. Hospital admissions data and the numbers of patients tested for anti-HCV antibodies (anti-HCV) and HCV-RNA were extracted from hospital information systems. The proportion of patients with active infection who received DAA therapy was also considered. **Results:** Within the specified time frame, about 320000 patients were admitted to the Hospital for various medical conditions. Among these, 116478 (36.4%) were tested for anti-HCV, and out of these, 4214 (3.6%) were found positive. This value showed an overall decreasing trend over the years (2016: 4.0%, 2017: 4.3%, 2018: 4.1%, 2019: 4.1%, 2020: 4.1%, 2021: 3.0%, 2022: 2.8%, 2023: 3.1%). Stratification by age showed that the highest anti-HCV positivity was found in the 71-80 age group. Among anti-HCV positive patients, 2120 (50.3%) underwent HCV-RNA testing (which means that a high percentage, 49.7%, were not tested for active infection). 1450 out of 2120 (68.4%) tested positive for HCV-RNA, with a decreasing trend over time (70.8% in 2016 vs. 60.0% in 2023). The percentage of patients with active infection who underwent DAA therapy was approximately 60%, though this value varied annually. **Conclusion:** HCV testing and linkage-to-care should be reinforced also in the hospital setting, where a routine screening program might be suggested for all hospitalized patients. In addition, a specific program of testing for active HCV infection and its treatment, under the guidance of an expert liver specialist, should be suggested to promote an appropriate and aware approach to find and cure as many HCV-infected individuals as possible.

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1436 | RELINK HCV PATIENTS WITH LIMITED HEALTH CARE RESOURCE TO CARE

Tsung-Hui Hu[1] Chih-Chao Yang[2] Wei-Wen Su[3] Yen-Po Yeh[4], [1]Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [2]Changhua Hospital, Ministry of Health and Welfare, Changhua, Taiwan, [3]Changhua Christian Hospital, Changhua, Taiwan, [4]Changhua Public Health Bureau, Changhua, Taiwan

Background: Taiwan is reported to have one of the highest prevalence rates of HCV in North-East Asia, around 3%. Changhua is among one of the higher HCV prevalent counties in Taiwan, around 3.25% in 2018. Nine townships located in the remote area of Changhua have highest average HCV prevalence ($>8\%$) but with limited health care resources and frequently have no access to GI/hepatologists to care for their HCV. This is evidenced by 30% of anti HCV positive population was not linked to HCV RNA diagnosis for subsequent management. We aim to conduct a novel approach to relink this vulnerable group with positive anti-HCV is of pressing need in order to achieve WHO's goal of diagnosis and treatment. **Methods:** Changhua Public Health Bureau (CHPHB) officials has established a comprehensive population level data on HCV screening rate, diagnosis rate and treatment rate with the following steps: 1. CHPHB will coordinate efforts to perform call back through phone call, mail and physical visit. 2. CHPHB will set up telemedicine facility/station at health centers 3. Called back patients will have telemedicine visit (at health centers on site) with GI/hepatologists at station set by CHPHB. 4. Primary care physicians at health centers will be advised on decision making by GI/hepatologists with telemedicine. 5. HCV treatment decision will be driven at the physician's discretion and patients will be treated onsite. **Results:** The date of enrollment of first subject was on Dec 1, 2023. The follow up was analyzed at the end of Nov 30, 2024. The total target of 3112 patients with previous positive anti-HCV patients. Among them, 213 people have received HCV RNA test (68.2%). 870 people were found to be with detectable HCV RNA (41.0%). 751 people have received and completed direct antiviral agents (DAA) treatment (86.3%). Furthermore, we also target 457 patients who were with detectable HCV RNA, but have

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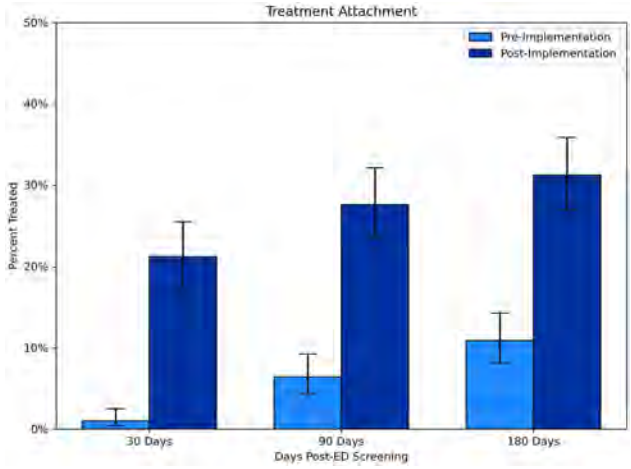
not received any treatment in the past. Under this program, 341 patients (74.6%) have received DAA treatment during the program. The causes of failure to re-link were mostly due to refuse from patients (32.6%), and unreachable communication (15.9%). **Conclusion:** For patients living in limited health care resource to car, the re-ling program (by telemedicine) provided an effective and successful methods for further cascade of care of HCV patients.

Disclosures: Tsung-Hui Hu: Nothing to Disclose, Chih-Chao Yang: Nothing to Disclose, Wei-Wen Su: Nothing to Disclose, Yen-Po Yeh: Nothing to Disclose

1437 | EVALUATING HEPATITIS C TREATMENT ATTACHMENT RATE FOLLOWING IMPLEMENTATION OF AN EMERGENCY DEPARTMENT-BASED PHARMACIST-LED TREATMENT PROGRAM

Benjamin Coy[1] Timothy Tatchell[1] Christian Rhudy[1] Jacob Johnson[1] Matthew Zeltner[1] Lindsey Sheehan[2], [1]University of Kentucky Healthcare, [2]UK HealthCare

Background: Emergency department (ED) screenings have identified high hepatitis C (HCV) prevalence in Kentucky. However, many patients are not ultimately linked to care due to high rates of loss to follow up with traditional specialist referral models. UK-CURES (University of Kentucky - Cascade Utilizing Routinized screenings to Eliminate Syndemics) was implemented as a novel pharmacist-led model to treat HCV patients through simplified treatment guidelines . The goal of UK-CURES is to improve direct acting antiviral (DAA) initiation in ED patients with HCV. **Methods:** This was a single center, retrospective cohort review of patients who screened HCV RNA positive at one of two ED sites from 10/1/2022 - 4/1/2024. Patients ineligible for HCV treatment per AASLD guidelines were excluded. Patients were grouped as pre- or post-implementation based upon an initial screening date before or after 7/1/2023. Patient demographics and dates of service, including screening and first DAA dispense date were collected. The primary outcome was treatment attachment at 30 days, defined as a dispense of a DAA within 30 days of the ED screening. Secondary outcomes included attachment within 90 and 180 days, as well as days to treatment initiation. Significant differences in pre- and post-implementation cohorts were assessed by Pearson's chi square or Fischer's exact test (categorical) and the Mann Whitney U test (numeric) as appropriate. **Results:** 814 patients met inclusion criteria (pre-implementation n = 404; post-implementation n = 410). There were no significant differences in age, sex, race, and payor type between pre- and post-implementation cohorts. Treatment attachment at 30 days was significantly higher in the post-implementation period (pre 1%, n = 1; post 21.2%, n = 87; $p < 0.0001$). Significant differences were also observed in attachment at 90 days (pre 6.4%, n = 26; post 27.6%, n = 113; $p < 0.0001$) and 180 days (pre 10.9%, n = 44; post 31.2%, n = 128; $p < 0.0001$). The median days to treatment was 105 days sooner in the post-implementation group (25 days; pre 130 days; $p < 0.0001$). **Conclusion:** Implementing a pharmacist-led ED program to engage and workup patients with HCV greatly improves treatment attachment rate. Proactive resolution of clinical and logistical barriers at point-of-care can reduce loss to follow-up in patients with HCV.



Disclosures: Benjamin Coy: Nothing to Disclose, Timothy Tatchell: Nothing to Disclose, Christian Rhudy: Amgen, Inc.: Grant/Research Support, Gilead Sciences: Grant/Research Support, Madrigral Pharmaceuticals: Grant/Research Support, Jacob Johnson: Nothing to Disclose, Matthew Zeltner: Nothing to Disclose, Lindsey Sheehan: Nothing to Disclose

1438 | CLINICAL OUTCOME OF HCV INFECTION IN CHILDREN: AN ANALYSIS BASED ON SIX CASES OF HCV INFECTED CHILDREN

Guoying Yu[1] Faying Li[1] Jie Ma[2], [1]Infectious Disease Specialized Hospital of Qinghai Province, [2]Infectious Disease Specialized Hospital of Qinghai Province.

Background: Previous studies have reported that HCV direct-acting antiviral(DAA) drugs can be used to treat pediatric and adolescent patients with HCV infection, including those aged 3-12 years and those aged 12 years and older, with favorable efficacy and safety. In this study, we analyzed the clinical data of six pediatric patients with HCV infection to investigate their clinical characteristics, disease prognosis, and management strategies. **Methods:** Data were collected from six pediatric patients with HCV patients who received screening, diagnosis, treatment and follow-up at the Infectious Disease Specialized Hospital of

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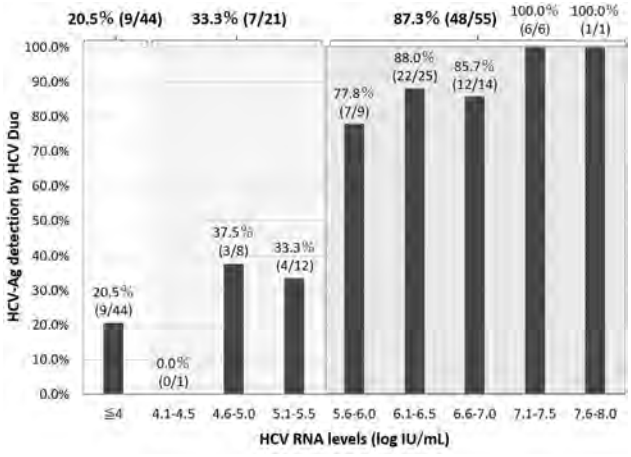
Qinghai Province between January 2022 and December 2024. The patients had completed follow-up for at least six months. Their clinical characteristics, diagnoses, and treatment outcomes were analyzed. **Results:** Six pediatric patients were retrospectively enrolled. The male to female ratio was 1:1 (three males and three females). The median age was 11.5 years. Two patients (33.33%) were attributed to vertical mother-to-child transmission. The diagnosis was confirmed by abnormal ALT levels in four patients (66.67%). All were treatment-naïve patients, with a mean HCV RNA of 6.35×10^5IU/mL at baseline. Genotype 2a was predominant (83.33%, five out of six cases), and one case had an undetectable genotype. The median ALT and AST at baseline were 58U/L and 41U/L, respectively, and there were no cirrhotic patients. The time from HCV diagnosis to treatment initiation was 6-18 months. Four patients received sofosbuvir and velpatasvir for 12 weeks, while the other two received ledipasvir and sofosbuvir for the same duration. All achieved 100% SVR12. No adverse events were reported during treatment. **Conclusion:** This small, single-center clinical study confirms the need for early treatment of pediatric patients with HCV infection to prevent serious liver-related complications caused by long-term infection. There is an urgent need to establish an integrated pathway of screening, diagnostic, and treatment pathway for pediatric patients with HCV infection.

Disclosures: Guoying Yu: Nothing to Disclose, Faying Li: Nothing to Disclose, Jie Ma: Nothing to Disclose

1439 | CLINICAL PERFORMANCE OF A NOVEL DUAL ANTIGEN-ANTIBODY ASSAY FOR HCV SCREENING: A STEP TOWARD SIMPLIFYING THE DIAGNOSTIC CASCADE

Takako Inoue[1] Hiroko Setoyama[2] Takehisa Watanabe[2] Takanori Suzuki[3] Katsuya Nagaoka[2] Etsuko Iio[2] kentaro matsuura[3] Yasuhito Tanaka[3], [1]Nagoya City University Hospital, [2]Kumamoto University, [3]Nagoya City University Graduate School of Medical Sciences

Background: A timely diagnosis is critical for HCV elimination; however, delays in confirmatory testing continue to be a major barrier to effective patient care. Elecsys HCV Duo (HCV Duo) is a novel one-step immunoassay that simultaneously detects anti-HCV antibodies (anti-HCV) and HCV core antigen (HCV-Ag) in under 30 minutes. This study evaluated the clinical utility of HCV Duo in identifying active HCV infection in Japan and assessed its potential to streamline the diagnostic workflow. **Methods:** (1) A total of 373 serum samples from chronic hepatitis C (CHC) patients were analyzed (120 HCV RNA-positive, 253 HCV RNA-negative). The sensitivity of Duo/anti-HCV was evaluated in comparison with conventional anti-HCV assays to determine its diagnostic accuracy. The sensitivity and specificity of Duo/HCV-Ag were assessed using HCV RNA as the reference standard. (2) HCV RNA distributions were assessed in 153 untreated CHC patients diagnosed between 2019 and 2023. (3) Trends in HCV RNA testing and detection rates over 5 years were examined (n = 3,213). **Results:** Duo/anti-HCV demonstrated 100% sensitivity. Duo/HCV-Ag showed 99.2% specificity and 55.0% overall sensitivity, increasing with viral load: 20.5% ($\leq$4.0 log IU/mL), 33.3% (4.1–5.5), and 87.3% ($\geq$5.6). Among untreated CHC patients (n = 153), HCV RNA levels were distributed as follows: 2.6% $\leq$4.0, 26.1% between 4.1–5.5, and 71.2% $\geq$5.6 log IU/mL—indicating that most cases fall within the Duo/HCV-Ag detectable range (Figure). Over the past 5 years, a total of 3,213 quantitative HCV RNA tests were submitted, showing a decreasing trend (1,246 in 2019 to 328 in 2023) and a cumulative detection rate of 9.4%. **Conclusion:** HCV Duo enables rapid, point-of-care identification of active HCV infection with high specificity and strong sensitivity at clinically relevant viral loads. It serves as a frontline screening tool, particularly valuable in emergency care, preoperative evaluations, and short-stay admissions, where rapid diagnosis is critical. This assay may help overcome key barriers in the HCV cascade of care, particularly in non-specialist settings. By combining antibody and antigen detection in a single step, HCV Duo eliminates the need for separate confirmatory testing, potentially increasing diagnostic follow-up and treatment initiation. By streamlining the diagnostic process, HCV Duo can minimize delays, reduce patient burden, and enhance early linkage to care, improving overall treatment outcomes. Integrating this assay into broader screening programs could play a pivotal role in accelerating national HCV elimination efforts.



Disclosures: Takako Inoue: Nothing to Disclose, Nothing to Disclose, Hiroko Setoyama: Nothing to Disclose, Takehisa Watanabe: Nothing to Disclose, Takanori Suzuki: Nothing to Disclose, Katsuya Nagaoka: Nothing to Disclose, Etsuko Iio: Nothing to Disclose, kentaro matsuura: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

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1440 | UNIQUE HCV AND HBV/HDV RE-LINKING PROGRAM IN ITALY

Alessandra Mangia[1] Valeria Piazzolla[1] Luca L'Erario[2] Mattia Lopez[3] Laura Solito[4] Daniela De Biasi[5] Gianluca Carone[6] Giovanni Manica[7] Antonio Camodeca[8] Antonio Napolitano[1] Maria Maddalena Squillante[1] Angelo L'erario[9], [1]Fondazione Casa Sollievo della Sofferenza IRCCS, [2]Laboratorio Dell'Olio Trani, [3]Laboratorio di Analisi Cliniche Palazzo s.r.l., [4]Laboratorio analisi dott. Francesco Solito S.r.l, [5]C.M.D. Analisi s.r.l., [6]Laboratorio Analisi Rosanna Santoro S.r.l., [7]Laboratorio d'analisi Paolo VI s.r.l., [8]Laboratorio di Analisi San Giorgio, [9]Sapienza University

Background: Despite the advances in HCV therapy, HCV continues to lead to approximately 400.000 deaths annually and HBV was associated with 550.000 deaths, in 2019. After diagnosis, not all patients are treated. Re-linking to care represents one of the main focusses to achieve HCV and HBV elimination. In Italy, re-linkage is hampered by Data Privacy rules which we overcome by designing our project to be conducted in collaboration with private laboratories. The aims is to explore the efficiency of a dedicated re-linking program conducted in collaboration with hub private laboratories managing in their turn spoke laboratories and covering an area of 7500 Km2 in Puglia. **Methods:** From 06/2024 to the present, our centre coordinated 10 hub laboratories with the help of Telehealth across the 6 provinces of our region. Recall activities, promoted by private laboratories, focused on patients aged 50-85 years who have been tested during the last 10 years and found to be HCVAb or HBsAg positive. Only the results on HCV infection will be reported here. The project will be completed at the end of 2025. When HCVAb positive, patients were offered counselling, DAA prescription and monitoring by Telehealth. The primary endpoint is the number of patients re-linked, out of patients HCVAb positive. The secondary endpoint, SVR after 12 weeks of SOF/VEL. **Results:** Overall, of 1582 possible candidates, only 398 were eligible for contact. Of them 95 (23.8%) had died. Overall 303 HCVAb positive individuals were identified, 66 could not be reached, 22 were not interested in treatment. With the remaining 215 HCVAb positive responding to the call, the study retrieval rate was 54%. These patients were 59% male and had a mean age of 68.6+/-12.9 yrs. Fifty five (18.1%) were HCV RNA positive. Differences between HCV RNA +or- in the Table. Overall, 51 patients, representing 23.7% of the seropositive patients reached out at the different laboratories, have been re-linked to treatment with 100% SVR so far. **Conclusion:** Our study shows that re-linkage in Italy is possible. The 54% retrieval rate of HCVAb patients, among subjects 50-85 years old, was higher than that of other EU countries. Education and information programs are needed to increase this rate. Re-linkage to care was 23.7%. Among HCV RNA+ve patients identified, 16% had low PLT counts. Efficient programs are required to allow patients with past HCV diagnosis to complete the HCV care cascade. Acknowledgments: This study was partially founded by Gilead Sciences.

	AntiHCV+ve HCV RNA negative (n=160)	AntiHCV+ve HCV RNA positive (n=55)	P value
Mean age, yrs	68.8 +/-12.3	62 +/-11.1	<0.01
Male Gender	112 (70.0%)	39 (70.9%)	>0.05
PLT<140.000 ul	11 (6.8%)	9 (16.3%)	<0.05

Disclosures: Alessandra Mangia: Gilead: Grant/Research Support, Madrigal: Consultant, Valeria Piazzolla: Nothing to Disclose, Luca L'Erario: Nothing to Disclose, Mattia Lopez: Nothing to Disclose, Laura Solito: Nothing to Disclose, Daniela De Biasi: Nothing to Disclose, Gianluca Carone: Nothing to Disclose, Giovanni Manica: Nothing to Disclose, Antonio Camodeca: Nothing to Disclose, Antonio Napolitano: Nothing to Disclose, Maria Maddalena Squillante: Nothing to Disclose, Angelo L'erario: Nothing to Disclose

1441 | FIB-4 PREDICTS LONG-TERM OUTCOMES AFTER SVR IN HCV PATIENTS WITH CIRRHOSIS: GONE BUT NOT TO BE FORGOTTEN

Anas Aljabi[1] Husam Mikati[1] Reena Cherian[1] Shawn Lewis[1] Leah Blatzer[1] Richard Sterling[1], [1]Virginia Commonwealth University

Background: While the use of direct-acting antivirals (DAA) for chronic hepatitis C virus (HCV) has high sustained virologic response (SVR) in patients with cirrhosis, they remain at risk for developing hepatic decompensation or hepatocellular carcinoma (HCC). This analysis aimed to assess the engagement in care and development of decompensation or HCC after SVR in those with cirrhosis among our HCV treatment cohorts: Department of Corrections (DOC) vs non-DOC (University) HCV treatment clinics. **Methods:** All subjects treated with DAA since 2014 across the clinics were prospectively followed in our HCV treatment registry. Demographic and clinical data were recorded. Cirrhosis was defined by transient elastography, imaging, or clinical criteria. Outcomes (decompensation or HCC) were extracted from the electronic health record. The proportion who remained in care, underwent post-treatment HCC surveillance imaging, or developed decompensation (ascites, hepatic encephalopathy (HE), portal hypertensive bleeding, or jaundice) was compared between DOC and non-DOC groups. **Results:** 2240 patients with cirrhosis were included in this analysis: baseline mean age 54 yrs, ALT 72 U/L, FIB-4 3.9, 76%

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male, 58% White/40% Black, 4% HIV, 81% genotype 1, and 51% treated in the DOC via Telemedicine. Those treated in the DOC vs non-DOC had lower FIB-4 (2.8 vs 5.1; $p < .0001$) and lower SVR (89% vs 94%; $p < .0001$) due to increased lost to follow-up prior to SVR-12 visit (9% vs 1%; $p < .0001$). Among the cohort, follow-up data were available in 1477 (65%). Of these, HCC surveillance was higher in non-DOC vs DOC clinic (81% vs 63%; $p < .0001$). HCC developed in 7.8% and decompensation in 13% of which 85% developed ascites, 61% HE, 30% bleeding, and 25% jaundice (bilirubin > 1.5 mg/dL). Patients followed in the non-DOC clinic had higher HCC (9.6% vs 1.8%; $p < .0001$) and decompensation (11.8% vs 3.6%; $p < .0001$). After adjusting for age, SVR, and treatment setting (DOC vs non-DOC), FIB-4 was highly predictive of HCC ($p < .0001$) or decompensation ($p < .0001$). The optimal pre-DAA FIB-4 that predicted post-SVR HCC or decompensation was 3.7 (AUROC 0.78). **Conclusion:** While SVR is high in patients with cirrhosis, development of HCC and decompensation can happen and are associated with higher pre-treatment FIB-4. Therefore, adherence to AASLD guidelines on continued follow-up of patients with high FIB-4 is needed to monitor for the development of HCC or decompensation after SVR in those with elevated FIB-4.

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1442 | HEPATITIS C IN PRISONS: MAINTAINING VIGILANCE IS ESSENTIAL

Veronica Patiño[1] Jose Dominguez[2] Carolina Broco[3] Andrea Robredo[3] Sofia Cid[2] Yolanda Mendez[3] Luis Tulleuda[2] María Gonzalez[2] Rubén Diez[3] Francisco Jorquera[3], [1]Complejo Asistencial Universitario de León, [2]León Penitentiary Center, [3]Complejo asistencial universitario de Leon

Background: The World Health Organization (WHO) has set a goal to eliminate hepatitis C as a public health threat by 2030. Spain, through the implementation of its National Strategic Plan for the Management of Hepatitis C, has emerged as a global leader in the treatment of HCV, with the highest number of patients treated per million inhabitants. Prisons historically exhibit a high prevalence of HCV (15-30%), have experienced a dramatic reduction in infection rates, similar to those observed in the general population ($< 0.3\%$) after interventions. One such initiative, the Jailfree project at El Dueso prison, demonstrated the efficacy of comprehensive screening and treatment strategies. However, recent difficulties in healthcare staffing in prisons, the impact of the COVID-19 pandemic have limited current epidemiological surveillance. In this context, updated data on HCV prevalence among inmates are crucial. **Methods:** This study aimed to evaluate the current prevalence of HCV at the León Penitentiary Center. An observational, cross-sectional study was conducted in May 2024. Following an educational session provided by the Gastroenterology Department of the University Hospital of León, inmates were invited to participate in voluntary screening for HBV, HCV, and HIV using a rapid diagnostic test. Individuals with positive serology underwent confirmatory viral load testing and, if viremic, were referred for specialist care and offered direct-acting antiviral (DAA) therapy. Data were analyzed using IBM SPSS Statistics, with results expressed as mean $\pm$ standard deviation; statistical significance was defined as $p < 0.05$. **Results:** Of 854 inmates, 274 (32.1%) participated. The average age was 41.53 $\pm$ 11.29 years; 86.5% were male. Anti-HCV antibodies were identified in 25 participants (9.12%), with no significant sex difference. HCV-seropositive individuals were significantly older than seronegatives (50.6 $\pm$ 6.62 vs. 40.6 $\pm$ 11.2 years, $p < 0.001$). Among the seropositive group, 7 male individuals (mean age 52.7 years) had detectable HCV RNA, indicating active infection. These cases represented 28% of seropositives and 2.55% of the total study sample. All viremic participants received DAA treatment. The prevalence of active HCV infection among inmates in León remains significantly higher than in the general population. While overall trends reflect progress, these findings underscore the ongoing need for systematic test-and-treat strategies in correctional settings. Structural challenges—particularly healthcare staffing shortages and reduced surveillance post-pandemic—must be addressed to prevent setbacks and support sustained elimination efforts. **Conclusion:** The current HCV prevalence among inmates at the León Penitentiary Center exceeds that of the general population. Maintaining systematic screening and immediate antiviral treatment within prisons is essential for achieving HCV elimination goals.

Disclosures: Veronica Patiño: Nothing to Disclose, Jose Dominguez: Nothing to Disclose, Carolina Broco: Nothing to Disclose, Andrea Robredo: Nothing to Disclose, Sofia Cid: Nothing to Disclose, Yolanda Mendez: Nothing to Disclose, Luis Tulleuda: Nothing to Disclose, María Gonzalez: Nothing to Disclose, Rubén Diez: Nothing to Disclose, Francisco Jorquera: Abbvie: Speaking and Teaching, Roche: Speaking and Teaching, Astra: Speaking and Teaching

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◆ 1443 | HEPATIC STIFFNESS, NEUROVASCULAR COUPLING, AND WORKING MEMORY: AN MRE-DRIVEN EXPLORATION OF LIVER-BRAIN CROSSTALK

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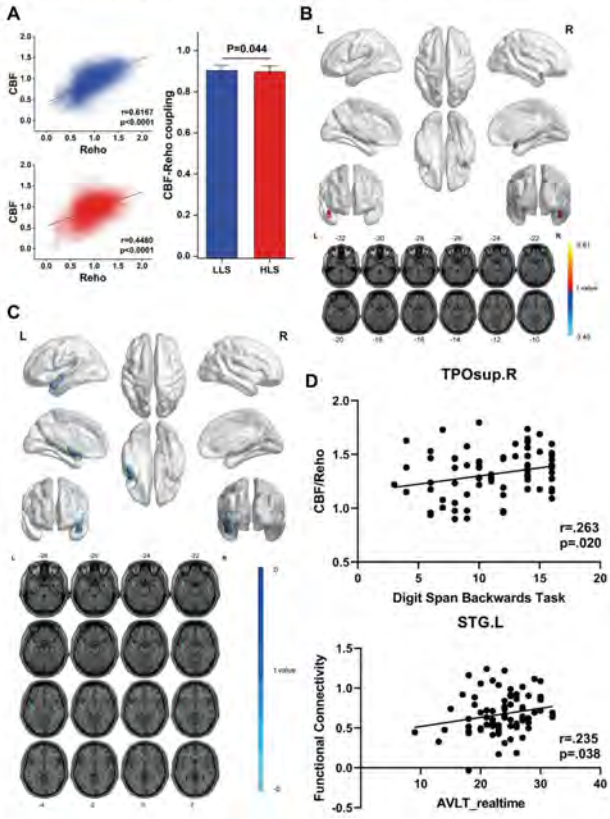
Background: Metabolic dysfunction associated steatotic liver disease (MASLD) has become the primary cause of chronic liver disease in younger adults. Alarmingly, MASLD may disrupt brain function even without cirrhosis. Magnetic resonance elastography (MRE) quantifies liver stiffness, yet its neurological implications in non-cirrhotic younger patients with MASLD remain unclear. This study aimed to demonstrate that higher liver stiffness affects brain health in young patients with non-cirrhotic MASLD. **Methods:** This was a prospective cohort involving 78 MASLD outpatients without cirrhosis [median age 26 years, (18-33)]. Using the Mayo criteria defining 2.5 kPa as the threshold for normal liver or inflammation, patients were stratified by MRE into low liver stiffness (LLS, MRE < 2.5 kPa, n = 38) and high liver stiffness (HLS, MRE ≥ 2.5 kPa, n = 40) groups. Participants underwent neuropsychological assessments, hepatic MRE, and multimodal brain magnetic resonance imaging (MRI), including resting-state fMRI and arterial spin labeling (ASL) for cerebral blood flow (CBF) and regional homogeneity (ReHo) analyses. Neuro-imaging data were processed using SPM12, with voxel-wise comparisons and global CBF-ReHo coupling analyses. T-tests and non-parametric methods were used for statistical analyses, adjusted for age and education. **Results:** HLS patients exhibited reduced global CBF-ReHo coupling ($p = 0.044$) and increased CBF/ReHo ratio in the right temporal pole (TPOsup) (voxel $p < 0.001$, cluster-level FWE-corrected, Figure 1A-B), suggesting that compensatory hyperperfusion maintains neural efficiency under metabolic stress. Functional connectivity decreased in the left superior temporal gyrus (STG) in HLS (cluster $p < 0.05$, Figure 1C). The CBF/ReHo ratio in the right temporal pole was correlated with digit span backward performance (r = 0.263, $p = 0.020$), while STG connectivity was correlated with auditory verbal learning (AVLT) (r = 0.235, $p = 0.038$, Figure 1D). No significant CBF or ReHo differences were found at the voxel level. **Conclusion:** Elevated liver stiffness in non-cirrhotic MASLD is associated with disrupted neurovascular coupling and functional connectivity in young patients, highlighting the extrahepatic manifestations of metabolic liver disease.

Figure 1. (A) Reduced global CBF-ReHo coupling in patients with high liver stiffness. (B) Differences in CBF/ReHo ratio between the two groups. (C) Brain regions showed significant differences in functional connectivity between the two groups (voxel $p<0.001$, cluster $p<0.05$, cluster-level FWE corrected). (D) Correlations between clinical indexes and CBF/Reho and functional connectivity values in the two groups. CBF, cerebral blood flow; Reho, regional homogeneity; FC, functional connectivity; HLS, high liver stiffness; TPOsup.R, right temporal pole; STG.L, left superior temporal gyrus; AVLT, auditory verbal learning.



Disclosures: Jie Li: Nothing to Disclose, Zhuoru Jiang: Nothing to Disclose, Futao Chen: Nothing to Disclose, Wenjing Ni: Nothing to Disclose, Bing Zhang: Nothing to Disclose, Jun Chen: Nothing to Disclose

◆ 1444 | HEPATOCYTE AGING SIGNATURE FROM RNASEQ IS SIGNIFICANTLY ASSOCIATED WITH HISTOLOGIC SEVERITY IN HUMAN MASLD, INDEPENDENT OF CHRONOLOGIC AGE

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Background: Aging is a risk factor for progressive metabolic dysfunction-associated steatotic liver disease (MASLD) and thus aging signatures might be used as tools to identify mechanisms that drive MASLD progression. Previously, we developed an Aging Hepatocyte Gene Signature (AHGS) by comparing transcriptomic profiles of hepatocytes from healthy young and old male mice and found that AHGS was enriched in human MASLD livers in parallel with disease severity. However, that analysis did not control for potential confounding factors, including age itself. **Methods:** We applied AHGS to bulk RNA-seq data from a demographically balanced cohort of 502 patients enrolled in the NASH Clinical Research Network (NASH-CRN). This cohort was nearly twice the size of our previous cohort and our analysis adjusted for age, sex, race, and ethnicity to evaluate the independent associations between AHGS and MASLD histological severity. AHGS scores were calculated using gene set variation analysis (GSVA) on bulk RNA-seq data. Logistic regression models, adjusted for demographic variables, assessed associations between AHGS and fibrosis (≥ 3 vs. < 3), NAS (≥ 4 vs. < 4), lobular and portal inflammation, steatosis, hepatocellular ballooning, and Mallory's hyaline. **Results:** Higher AHGS scores were significantly associated with multiple histologic features indicative of more severe MASLD. Patients with higher AHGS scores had over twice the odds of having advanced fibrosis (OR = 2.36, p = 3.95E-14) compared to those with lower scores, even after adjusting for age and other demographic factors. Similarly, the likelihood of NAS ≥ 4, reflecting more severe disease activity was nearly doubled (OR = 1.90, p = 7.19E-10). Higher AHGS was also associated with increased lobular inflammation (OR = 1.71), portal inflammation (OR = 1.93), and hepatocellular ballooning (OR = 1.61), all features of progressive hepatic damage. While the association with steatosis was more modest (OR = 1.29, p = 6.11E-03), it remained statistically significant. Biopsies of patients with higher AHGS were nearly twice as likely to show Mallory's hyaline (OR = 1.99), which reflects proteostasis, a hallmark of aging. **Conclusion:** Hepatocyte aging-associated transcriptional programs are strongly linked to MASLD histological severity, independent of chronological age and other co-variates. Progressive MASLD involves degenerative processes driven by aging-sensitive mechanisms.

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◆ 1445 | TREATMENT-INDUCED LIVER FAT REDUCTION ASSESSED BY MRI-PDFF IS STRONGLY ASSOCIATED WITH HISTOLOGICAL ENDPOINTS IN NON-CIRRHOTIC MASH CLINICAL TRIALS: A META-ANALYSIS

Kusha Mohammadi[1] Quang Nguyen[1] Tejasv Bedi[1] Selin Somersan-Karakaya[1] Stefanie Hectors[1] Gavin Imperato[1] Ifeanyichukuw Anidi[1] Emily Labriola-Tompkins[1] Muhammad Effendi[1] Katie Tuckwell[1] Sonya Aziz-Zaman[1] Jutta Miller[1] Aris Baras[1] Gary Herman[1] Dinko Gonzalez-Trotter[1] Rong liu[1] Thomas Norton[1] David Lederer[1], [1]Regeneron Pharmaceuticals, Inc.

Background: Several clinical trials have evaluated the effect of therapeutics on both liver fat and histological response in metabolic dysfunction–associated steatohepatitis (MASH). Magnetic resonance imaging–derived proton density fat fraction (MRI-PDFF) offers a feasible and non-invasive method to assess the efficacy of MASH therapeutics if a strong correlation exists between liver fat change and histological response. This systematic meta-analysis of randomized clinical trials describes the association between treatment-induced change in liver

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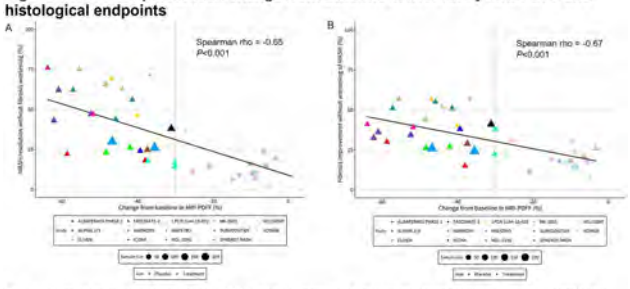
fat by MRI-PDFF and histological responses in participants with MASH and fibrosis. **Methods:** Following PRISMA guidelines, we conducted a search in Cochrane, EMBASE, and clinicaltrials.gov for all non-cirrhotic MASH trials up to April 10, 2025. Key inclusion criteria were phase 2 or 3 trials in adults ($\geq$18 years old) with change from baseline in MRI-PDFF data and $\geq$1 histology endpoint reported in a peer-reviewed journal or conference abstract. Histology endpoints included MASH resolution without fibrosis worsening, and fibrosis improvement without MASH worsening. We assessed the strength of the relationship between treatment-induced changes in MRI-PDFF and histological responses using Spearman correlation coefficients and linear regression. **Results:** Fourteen studies were included, comprising ~2600 participants. The analyses showed that the treatment-related reduction from baseline in liver fat by MRI-PDFF was strongly associated with a higher rate of MASH resolution without fibrosis worsening (Spearman rho = -0.65, $P<0.001$; Figure). In addition, treatment-related changes in liver fat by MRI-PDFF were also associated with fibrosis improvement without MASH worsening (Spearman rho = -0.67; $P<0.001$). A 30% reduction from baseline in liver fat by MRI-PDFF resulted in an estimated response rate of 31.1% (95% CI: 26.5–35.7%) for MASH resolution without worsening fibrosis and 30.3% (95% CI: 27.1–33.5%) for fibrosis improvement without MASH worsening. **Conclusion:** Treatment-related reductions in liver fat assessed by MRI-PDFF are strongly associated with both MASH resolution without fibrosis worsening as well as fibrosis improvement without MASH worsening in patients with non-cirrhotic MASH with fibrosis. These findings support change from baseline in liver fat by MRI-PDFF as a meaningful endpoint in non-cirrhotic MASH.

Figure. Relationships between change from baseline in liver fat by MRI-PDFF and histological endpoints



The mean percent change from baseline in MRI-PDFF and the percentage of patients with a histological response are reported in the figures. Each point represents a separate intervention where multiple doses or dose regimens were tested within a study. The size of the point reflects the approximate number of participants in the treatment arm. For scenarios in which the number of participants was different for individual endpoints, the larger number was chosen as the sample size. The color depicts an individual study eligible for the meta-analysis. The triangles represent active treatment arms, and the circles represent placebo arms. The black line is a simple linear regression through the studies.

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◆ 1446 | A TCF21-MIMETIC SMALL MOLECULE SERVES AS A NOVEL DRUG CANDIDATE FOR STEATOHEPATITIS AND FIBROSIS BY ALTERING THE FUNCTIONAL FEATURES AND CELLULAR CROSSTALK OF HEPATIC STELLATE CELL

Takayo Yanagawa[1] Noriaki Hirayama[2] Harumi Ogawa[2] Sachie Nakao[2] Mayumi Watanabe[2] Hideaki Sumiyoshi[2] Hiromi Miura[1] Masato Ohtsuka[1] Masayuki Tanaka[1] Yumi Iida[1] Misaki Higashiseto[1] Shigeyuki Shichino[3] Kouji Matsushima[3] Kota Tsuruya[4] Yoshitaka Arase[1] Yusuke Mishima[1] Tatehiro Kagawa[4] Yutaka Inagaki[1], [1]Tokai University School of Medicine, [2]Graduate School of MedicineTokai University, [3]Tokyo University of Science, [4]Tokai University

Background: Despite the recent approval of the first drug and the ongoing clinical trials for metabolic dysfunction-associated steatohepatitis (MASH), no drug is available that directly suppresses liver fibrosis in MASH. We previously identified Tcf21 as a deactivation factor of activated hepatic stellate cells (HSCs). Subsequently, we identified several Tcf21-mimetic small molecules that act as Tcf21 agonists to suppress progression of liver fibrosis. Adeno-associated virus-mediated *Tcf21* transfer not only suppressed progression of liver fibrosis, but also restored the hepatic lobular structure and function. However, it was unknown whether and how Tcf21-induced HSC deactivation *per se* exerts such antifibrotic and tissue repair actions. In the present study, we examined the effect of the hit Tcf21-mimetic molecule (YT0300) on progression of experimental steatohepatitis and explored the molecular mechanisms by which Tcf21 mimetic-induced HSC deactivation accelerates tissue repair of the fibrotic liver. **Methods:** The effect of YT0300 treatment was examined using the streptozotocin and high fat diet-induced murine MASH model. The fate of YT0300-induced deactivated HSCs was monitored using the type I collagen gene-driven mTFP1 reporter mice induced by tamoxifen administration. Single cell RNA sequencing was performed using cells obtained from the tracing mice that were repeatedly injected with carbon tetrachloride with or without YT0300 treatment.

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Cellular crosstalk was examined by CellChat analysis. **Results:** Administration of YT0300 suppressed both the activity of steatohepatitis and the extent of liver fibrosis in the MASH model mice. Expression of steatohepatitis signature genes such as *Adamtsl2*, *Thbs2*, and *Igfbp7* was down-regulated in the mTFP1-positive deactivated HSCs from YT0300-treated mice. YT0300 treatment also suppressed gene expression of neurotrophin 3, an autocrine fibrogenic signal, and increased expression of midkine that accelerates liver regeneration, in the HSC population. Furthermore, YT0300 administration induced a unique subset of macrophages expressing tissue repair- (*Arg1*, *Sdc1*) and angiogenesis-related genes (*Vegfa*), and enhanced crosstalk between the VEGF-expressing macrophages/HSCs and liver sinusoidal endothelial cell (LSEC) expressing VEGF receptors. Consistently, some of the mTFP1-positive deactivated HSCs in YT0300-treated mice formed a network with LSEC present in liver parenchyma. There were no differences in the peripheral blood cell counts or biochemical parameters such as alanine aminotransferase, albumin, and creatinine between the control and YT0300 groups. **Conclusion:** YT0300 treatment not only suppressed steatohepatitis and fibrosis, but also accelerated tissue repair of the fibrotic liver. Tcf21 mimetic-induced deactivation of HSCs may provide a novel option for treating MASH fibrosis by orchestrating cellular crosstalk in the fibrotic liver.

Disclosures: Takayo Yanagawa: Nothing to Disclose, Noriaki Hirayama: Nothing to Disclose, Harumi Ogawa: Kyowa kirin: Stock - publicly traded company, Sachie Nakao: Nothing to Disclose, Mayumi Watanabe: Nothing to Disclose, Hideaki Sumiyoshi: Nothing to Disclose, Hiromi Miura: Nothing to Disclose, Masato Ohtsuka: Nothing to Disclose, Masayuki Tanaka: Nothing to Disclose, Yumi Iida: Nothing to Disclose, Misaki Higashiseto: Nothing to Disclose, Shigeyuki Shichino: ImmunoGeneTeqs: Exective role, ImmunoGeneTeqs: Stock – privately held company, Kouji Matsushima: Nothing to Disclose, Kota Tsuruya: Eisai Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, Chugai Pharmaceutical Co., Ltd.: Speaking and Teaching, Chugai Pharmaceutical Co., Ltd.: Speaking and Teaching, Yoshitaka Arase: Nothing to Disclose, Yusuke Mishima: Nothing to Disclose, Tatehiro Kagawa: Nothing to Disclose, Yutaka Inagaki: AbbVie Inc.: Speaking and Teaching

1447 | MORTALITY AND LIVER-RELATED OUTCOMES OF SGLT2 INHIBITORS IN PATIENTS WITH MASLD, OBESITY, AND DIABETES: A 3-YEAR COHORT STUDY

Mohamad-Noor Abu-Hammour[1] Barish Eren[1] Walid Hazem[2] Mohamad Mahdi Osman[1] Mohammad Alabbas[1] Leandro Sierra[1] Hussam Kawas[1] Omar Sims[1] Dian Chiang[3], [1]Cleveland Clinic Foundation, [2]University Hospitals, [3]Cleveland Clinic

Background: Metabolic-associated steatotic liver disease (MASLD) patients are at elevated risk for cardiovascular and hepatic complications. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have shown benefits beyond glycemic control, with recent studies revealing potential hepatic benefits. This study aimed to evaluate the 3-year outcomes of SGLT2i treatment in patients with MASLD/MASH and T2DM. **Methods:** Using the TriNetX global research network, we conducted a retrospective cohort analysis involving adult patients diagnosed with MASLD/MASH, obesity (BMI ≥ 30 kg/m²), and T2DM receiving SGLT2i ($n = 73,811$) and compared to a control cohort not on SGLT2i ($n = 73,811$). Using propensity score matching, we balanced cohorts for demographics, comorbidities, medications, and laboratory values. Outcomes evaluated over three years included cirrhosis development, hepatocellular carcinoma (HCC), all-cause mortality (ACM), and all-cause hospitalizations (ACH). **Results:** Compared to the non-SGLT2i group, the SGLT2i cohort were associated with significantly lower risks of ACM (3.7% vs. 6.2%; HR 0.537, 95% CI 0.512-0.563, $p < 0.001$) and ACH (24.2% vs. 25.5%; HR 0.872, 95% CI 0.854-0.890, $p < 0.001$). However, patients on SGLT2i were associated with a slightly higher risk of cirrhosis development (10.0% vs. 8.9%; HR 1.063, 95% CI 1.028-1.099, $p < 0.001$). No significant differences in HCC risk were noted between the two cohorts (HR 1.079, 95% CI 0.965-1.207, $p = 0.183$) **Conclusion:** In patients with MASLD/MASH, T2DM, and obesity, treatment with SGLT2 inhibitors were associated with significantly reduced mortality and hospitalizations compared to non-users. Increased risks of cirrhosis warrant continued vigilance and further investigation to fully elucidate the hepatic safety profile of SGLT2 inhibitors.

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1448 | EARLY ONSET MASLD IN OBESE, PREPUBERTAL HISPANIC/LATINO CHILDREN: IMPLICATIONS FOR SCREENING GUIDELINES

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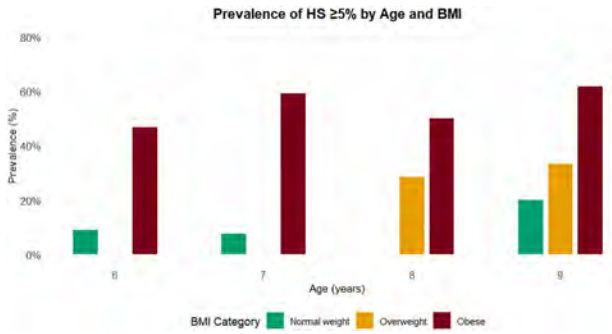
Background: Current guidelines recommend screening for MASLD beginning at age 10 years. Hispanic youth are known to be at increased risk and severity of MASLD, but few studies have included children under the age of 10 years, despite this increased risk. The aim of this study was to test for MASLD and risk factors in prepubertal Hispanic children. **Methods:** This was a prospective cohort of Hispanic/Latino children aged 6–9 years recruited from the community (NCT05292352). Children were of Hispanic/Latino heritage and without known chronic diseases as reported by their parent. Consented participants underwent MRI-PDFF for hepatic steatosis, comprehensive anthropometrics and phlebotomy for clinical labs and DNA for genotyping. Genotyping for *PNPLA3* rs738409 was performed. **Results:** Of 170 participants (mean age 7.9 years SD 1.1, 57% male), 27% were categorized as normal weight, 18% were overweight, and 55% were in the obese category for BMI. The frequency of the *PNPLA3* genotype was 15.6% CC, 51.4% CG and 31.9% GG. Overall, 34.6% of children had hepatic steatosis (HS) defined as an intrahepatic fat content ≥5% and 22% had elevated ALT. HS was most prevalent among those with a *PNPLA3* GG polymorphism (56.5%), elevated ALT (78.8%), obesity (55.3%), and in boys (41.4%). Controlling for age and sex, children with obesity were 11 times more likely to have HS (OR 11.31, CI 4.0–40.7). Those with *PNPLA3* GG were 9.2 times more likely to have HS compared to CC (OR 9.24, CI 2.42–42.8). **Conclusion:** MASLD onset may occur earlier than previously thought and delays in screening until age 10 years may miss important opportunities to interrupt the progression. The presence of obesity and *PNPLA3* risk genotype are strong predictors for MASLD, even in children as young as 6 years old. This evidence supports lowering the age of screening in Hispanic/Latino children and particularly for those who have obesity.



Disclosures: Cristian Sanchez Torres: Nothing to Disclose, Ana Ramirez Tovar: Nothing to Disclose, Scott Gillespie: Nothing to Disclose, Helaina Huneault: Nothing to Disclose, Claudia Yaranga: Nothing to Disclose, Karla DeSantos: Nothing to Disclose, Christina Carapio-Chaparro: Nothing to Disclose, Brittany James: Nothing to Disclose, Ermena Refugjati: Nothing to Disclose, Gloria Kang: Nothing to Disclose, Geetika Khanna: Nothing to Disclose, Jack Knight-Scott: Nothing to Disclose, Adina Alazraki: Nothing to Disclose, Liliana Aguayo: Nothing to Disclose, Nicola Santoro: Nothing to Disclose, Shasha Bai: Nothing to Disclose, Jean Welsh: Nothing to Disclose, Miriam Vos: Boehringer Ingelheim: Consultant, Madrigal: Consultant, Eli Lilly: Consultant, Inventiva: Consultant, Alberio: Consultant, Target Real World Evidence: Advisor, Thiogenesis: Advisor, Tern Pharmaceuticals: Stock - publicly traded company, Dexcom: Grant/Research Support, Sonic Incytes Medical Corp: Grant/Research Support, Prosciento: Advisor

1449 | AN ASSOCIATION OF COVERT HEPATIC ENCEPHALOPATHY WITH NON-ELDERLY AND MASLD IN PATIENTS WITH LIVER CIRRHOSIS AND HEPATOCELLULAR CARCINOMA: DATA-MINING ANALYSES

Dan Nakano[1] Takumi Kawaguchi[1] Tsubasa Tsutsumi[1] Ryuki Hashida[1] Keisuke Amano[1], [1]Kurume University School of Medicine

Background: Covert hepatic encephalopathy (CHE) is a complication of liver cirrhosis that contributes to impaired quality of life, increased risk of falls, and traffic accidents. While hyperammonemia and decreased hepatic reserve are established risk factors, recent attention has turned to additional variables such as age and metabolic dysfunction-associated steatotic liver disease (MASLD). This study aimed to characterize the clinical profiles associated with CHE in patients with liver cirrhosis. **Methods:** This was a retrospective observational study. We enrolled 195 patients with chronic liver disease (female/male 60/135, mean age 68.0 years, ALBI Grade 1/2/3 76/105/12) without overt hepatic encephalopathy and under 80 years of age. CHE was diagnosed using the Stroop test. SLD was diagnosed with abdominal ultrasound. Factors associated with CHE, including age, sex, BMI, serum albumin, glucose metabolism, SLD, and ammonia, were investigated using logistic regression analysis and decision-tree analysis. **Results:** CHE was observed in 36.4% (71/195) of all patients. The CHE group, compared to the non-CHE group, was younger, had a higher BMI, a higher prevalence of SLD, and lower serum albumin. Multivariate logistic regression analysis identified age (<65 years old: Odds Ratio [OR] 4.57, 95% Confidence Interval [CI] 2.29–9.13, $p < 0.001$), MASLD (OR 1.95, 95%CI 1.01–53.76, $p = 0.0456$), and the presence of hepatocellular carcinoma (HCC) (OR 0.245, 95%CI 0.08–0.71, $p = 0.0096$) as independent factors for CHE. In the decision-tree analysis, age was the initial classifier. For patients <65 years old, the second classifier was MASLD; 90.5% of those with MASLD had CHE. For patients ≥65 years old, the second classifier was the presence of HCC. Among those with HCC, the third classifier was serum ammonia level; 31.6% of patients with serum ammonia ≥80 μg/dL had CHE. **Conclusion:** The pathophysiological profiles associated with CHE differ by age. In patients

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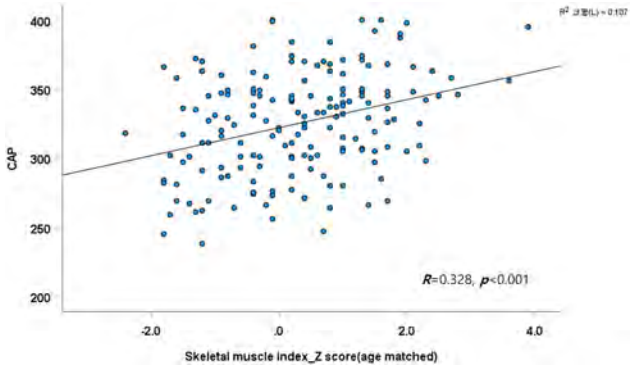
<65 years, MASLD was a dominant factor, whereas in those ≥65 years, HCC status and ammonia levels were more relevant. These findings suggest that age-specific factors contribute to the development of CHE and underscore the importance of MASLD as an emerging risk factor in non-elderly cirrhotic patients.

Disclosures: Dan Nakano: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching, Tsubasa Tsutsumi: Nothing to Disclose, Ryuki Hashida: Nothing to Disclose, Keisuke Amano: Nothing to Disclose

1450 | IMPACT OF AGE-ADJUSTED SKELETAL MUSCLE INDEX AND MODEST ALCOHOL USE ON LIVER STEATOSIS AND FIBROSIS IN MALE MASLD

Jung Hee Kim[1] JangHan Jung[1], [1]Hallym university

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a highly prevalent condition closely linked to obesity and metabolic risk factors, with a disease spectrum ranging from simple steatosis to advanced fibrosis. This study aimed to investigate the clinical, body composition, and biochemical factors associated with hepatic steatosis and advanced fibrosis severity, with particular emphasis on the role of skeletal muscle index (SMI), visceral fat area (VFA), and light alcohol consumption. **Methods:** A total of 174 male participants diagnosed with MASLD were evaluated. Hepatic steatosis and fibrosis were assessed using controlled attenuation parameter (CAP) and liver stiffness measurement (LSM, kPa), respectively. Body composition was assessed via bioelectrical impedance analysis. Univariate and multivariate regression analyses were performed to identify factors independently associated with steatosis and fibrosis severity. Subgroup analyses were conducted according to alcohol consumption. **Results:** The mean age of participants was 40.0 ± 10.4 years, and the median BMI was 28.8 kg/m². Severe hepatic steatosis was independently associated with alcohol intake (<30 g/day; OR 1.22, 95% CI 1.03–1.44, p = 0.020), higher age-adjusted SMI (z score) (OR 1.82, 95% CI 1.23–2.70, p = 0.003), and elevated triglyceride levels (OR 1.01, 95% CI 1.00–1.02, p = 0.009). Among non-drinkers, SMI remained a significant predictor of severe steatosis. A positive correlation was observed between SMI (z score) and CAP values (R = 0.328, p < 0.001).For advanced hepatic fibrosis, multivariate analysis identified elevated SMI (z score) (OR 1.84, 95% CI 1.14–2.96, p = 0.013) and increased aspartate aminotransferase (AST) levels (OR 1.04, 95% CI 1.02–1.05, p < 0.001) as independent risk factors, whereas light alcohol consumption (OR 0.068, 95% CI 0.01–0.71, p = 0.025) and higher platelet count (OR 0.99, 95% CI 0.97–1.00, p = 0.016) were associated with lower odds of advanced fibrosis. A significant positive correlation was also found between SMI and fibrosis severity (p = 0.001). Additionally, participants reporting light alcohol intake had significantly higher CAP scores (p = 0.018) but lower LSM values (p = 0.007) compared to non-drinkers. **Conclusion:** In men with MASLD, higher age adjusted SMI (z score) was independently associated with both severe steatosis and advanced fibrosis. Light alcohol intake increased steatosis but was linked to lower fibrosis severity.Notably, the consistent association of higher SMI with both steatosis and fibrosis severity suggests a potential role of muscle mass quality or myosteatosis in MASLD pathogenesis, warranting further investigation for tailored risk stratification and management.



Disclosures: Jung Hee Kim: Nothing to Disclose, JangHan Jung: Nothing to Disclose

1451 | PNPLA3 MRNA SILENCING WITH ALN-PNP REDUCES LIVER FAT IN PATIENTS WITH MASLD HOMOZYGOUS FOR PNPLA3 P.I148M

Selin Somersan-Karakaya[1] Stefanie Hectors[1] George Kalliolias[1] Emily Labriola-Tompkins[1] Tejasv Bedi[1] Kusha Mohammadi[1] Zaira Yunus[1] Jenna Octavio[1] David Workman[1] SeungHwan Lee[2] Simona Podgrabinska[1] Eriks Smagris[1] Viktoria Gusarova[1] Thomas Norton[1] Rong liu[3] Dinko Gonzalez Trotter[1] David Lederer[1] Gary Herman[1] Aris Baras[1], [1]Regeneron Pharmaceuticals, Inc., [2]Seoul National University Hospital, [3]regeneron

Background: Homozygote carriers for the patatin-like phospholipase domain-containing protein 3 (PNPLA3) p.I148M variant have increased liver fat and a higher risk of liver-related disease and mortality compared to wild type. We hypothesized that silencing PNPLA3 messenger RNA

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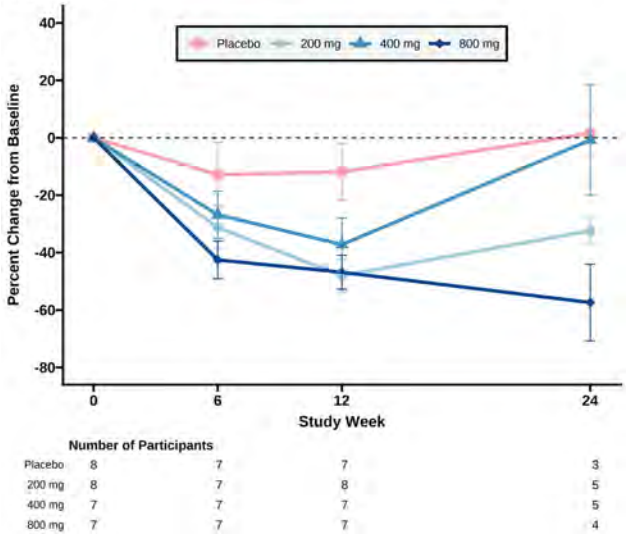
(mRNA) with ALN-PNP, an investigational N-acetylgalactosamine-conjugated RNA interference therapeutic targeting PNPLA3 mRNA, would be well tolerated, and reduce liver fat in patients who are PNPLA3 p.I148M homozygotes with metabolic dysfunction–associated steatotic liver disease (MASLD). **Methods:** In a pooled interim analysis of 2 phase 1 studies conducted in the USA and South Korea, we analyzed 30 adult PNPLA3 p.I148M homozygotes with baseline liver fat $\geq$ 8.5% by magnetic resonance imaging–derived proton density fat fraction (MRI-PDFF) who had received study drug and had $\geq$1 evaluable post-baseline MRI-PDFF assessment. Participants were randomized 1:1:1:1 to receive a single dose of ALN-PNP 200 mg, 400 mg, or 800 mg, or placebo. The primary endpoint was the incidence and severity of treatment-emergent adverse events (TEAEs). Liver fat was assessed by MRI-PDFF at Weeks 6, 12, 24, and 36 post-single dose treatment. **Results:** At baseline, mean liver fat by MRI-PDFF was 18.3%, 16.9%, 18.2%, and 17.1% in the 200 mg (n = 8), 400 mg (n = 7), and 800 mg (n = 7), and placebo (n = 8) groups, respectively. ALN-PNP reduced liver fat from baseline by 48.0%, 37.2%, and 46.8% by Week 12 in the 200 mg, 400 mg, and 800 mg groups, respectively, compared to 11.9% for placebo (Figure). In the 800 mg group, the reduction in liver fat was sustained to Week 24. There were no serious adverse events, TEAEs leading to study discontinuation, or deaths. **Conclusion:** In this single-dose study, ALN-PNP was well tolerated at all dose levels tested and reduced liver fat in PNPLA3 p.I148M homozygotes with MASLD by up to 48%.

Figure. Single doses of ALN-PNP or placebo were administered to homozygous PNPLA3 p.I148M carriers with MASLD. Liver fat changes were evaluated by MRI-PDFF at multiple timepoints. At Week 12, ALN-PNP reduced liver fat by 48.0%, 37.2%, and 46.8% in the 200 mg, 400 mg, and 800 mg groups, respectively, compared to baseline. The analysis was based on the natural log-transformed MRI-PDFF values then exponentially back-transformed onto the original scale to give geometric percent changes in MRI-PDFF from baseline. Mean ±SE are shown.



Disclosures: Selin Somersan-Karakaya: Regeneron Pharmaceuticals, Inc.: Employee, Regeneron Pharmaceuticals, Inc.: Stock - publicly traded company, Stefanie Hectors: Regeneron Pharmaceuticals: Employee, Regeneron Pharmaceuticals: Stock - publicly traded company, George Kalliolias: Nothing to Disclose, Emily Labriola-Tompkins: Regeneron: Employee, Tejasv Bedi: Nothing to Disclose, Kusha Mohammadi: Nothing to Disclose, Nothing to Disclose, Zaira Yunus: Nothing to Disclose, Jenna Octavio: Nothing to Disclose, David Workman: Nothing to Disclose, SeungHwan Lee: Nothing to Disclose, Simona Podgrabinska: Nothing to Disclose, Eriks Smagris: Regeneron Pharmaceuticals: Employee, Regeneron Pharmaceuticals: Stock – privately held company, Viktoria Gusarova: Nothing to Disclose, Thomas Norton: Nothing to Disclose, Rong liu: Nothing to Disclose, Dinko Gonzalez Trotter: Nothing to Disclose, David Lederer: Regeneron Pharmaceuticals: Employee, Regeneron Pharmaceuticals: Stock - publicly traded company, Gary Herman: Nothing to Disclose, Aris Baras: Nothing to Disclose

1452 | THE RELEVANCE OF DATA-DRIVEN MASLD CLUSTERS AND THEIR RELATIONSHIP WITH MASH AND ADVANCED FIBROSIS IN PATIENTS WITH TYPE 2 DIABETES FROM THE QUID-NASH COHORT

Laurent Castera[1] Tiphaine Vida-Trecan[2] Pauline Manchon[3] Anais Vallet-Pichard[4] Sebastien Czernichow[5] Dominique Roulot[6] Valerie Paradis[7] Catherine Postic[8] Jean-Baptitste Julla[2] Etienne Larger[4] Bernard van Beers[9] Helene Fontaine[1] Thierry Poynard[10] Pierre Bedossa[11] Stanislas Pol[12] Dominique Valla[1] Cedric Laouenan[13] Francois Pattou[14] Jean-Francois Gautier[2], [1]Dept of Hepatology, Hopital Beaujon, AP-HP, Clichy, France, [2]Dept of Diabetology, Hopital Lariboisière, AP-HP, Paris, France, [3](DEBRC), Hôpital Bichat, AP-HP, Paris, France, [4]Dept of Diabetology, Hopital Cochin, AP-HP, Paris, France, [5]Dept of nutrition and obesity, Hôpital Européen Georges Pompidou, AP-HP, Paris, France, [6]Unit of Hepatology, Hopital Avicenne, AP-HP, Bobigny, France, [7]Dept of Pathology, Hopital Beaujon, AP-HP, Clichy, France, [8]Université Paris Cité, Institut Cochin, CNRS, Inserm, Paris, France., [9]Dept of Radiology, Hopital Beaujon, AP-HP, Clichy, France, [10]Pitié-Salpêtrière Hospital, Paris, France, [11]Liverpath, Paris, France, [12]Dept of Hepatology, Hopital Cochin, AP-HP, Paris, France, [13]DEBRC, Hôpital Bichat, AP-HP, Paris, France, [14]Dept of General and Endocrine Surgery, CHU de Lille, Lille, France

Background: MASLD exhibits considerable variability in clinical outcomes. Recently, two distinct types of clinically relevant data-driven MASLD clusters were identified: liver-specific and cardiometabolic (Raverdy et al., Nat Med, 2024 / PMID: 39653777). Despite having similar liver phenotypes at baseline, these clusters have different underlying biological profiles and clinical trajectories. Currently, there is a lack of data on patients with type 2 diabetes (T2D), who are at high risk of MASLD/MASH cirrhosis and its

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complications. The present study aimed to explore the distribution of MASLD clusters and their relationship with MASH and advanced fibrosis (F3F4) in patients with T2D from the multicenter prospective Quid-NASH cohort (NCT03634098). **Methods:** Cluster analysis was performed using the partitioning around medoids method based on six clinical variables: age, BMI, HbA1c, ALT, LDL-cholesterol, and triglycerides. The cohort included 415 patients with T2D and MASLD (ALT >20/30 IU/L in females & males, respectively) attending diabetes clinics. Liver biopsies were centrally reviewed by a single expert pathologist (PB). **Results:** Clusters were determined in 383 patients (median age 60 years; male 51%; BMI 32 kg/m^2; HbA1c 7.4%; ALT 48 IU/L; LDL-cholesterol 0.8 g/l; triglycerides 1.66 g/l; MASH 55%; F3F4 36%). Figure 1A shows that three clusters were identified. Cluster 1 (Control) included 31% of patients. Cluster 2 (Cardiometabolic, CM) included 64% of patients (vs. 11% in the original study) and had the highest levels of HbA1c and triglycerides. Cluster 3 (Liver-specific, LS) included 5% of patients (vs. 7%) and had the highest ALT levels and the youngest age. Despite the marked differences between the clusters, CM and LS clusters had a higher prevalence of MASH than Control cluster (66.7% and 65.3% vs. 30.8%, respectively; $p < 0.01$) and CM had a higher prevalence of F3F4 (41.2% vs. 26.7%; $p = 0.02$) than Control cluster (Figure 1B). These findings are consistent with those reported in the original study. **Conclusion:** In this large, homogeneous cohort of patients with T2D and MASLD, our findings show that the cardiometabolic cluster accounted for two-thirds of cases, whereas the liver-specific cluster was minimal. Both clusters were associated with a higher prevalence of MASH and advanced fibrosis in the cardiometabolic cluster. These findings may be important for the future stratification of T2D patients in MASH therapeutic trials.

Figure 1A. Distribution of clusters in the Quid-NASH cohort (n=383)

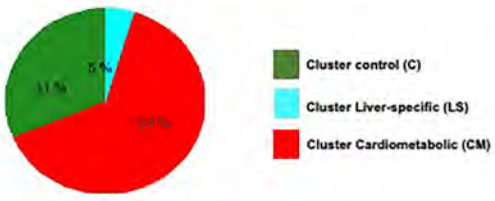
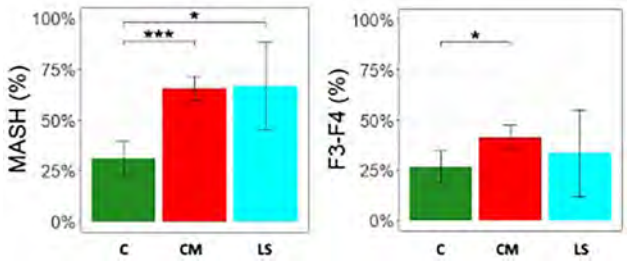


Figure 1B. Prevalence of MASH and F3F4 according to the clusters



Disclosures: Laurent Castera: Boerhinger Ingelheim: Consultant, AstraZeneca: Speaking and Teaching, Boston Pharmaceutical: Consultant, Echosens: Speaking and Teaching, Gilead: Consultant, Inventiva: Speaking and Teaching, GSK: Consultant, Madrigal: Consultant, Madrigal: Speaking and Teaching, MSD: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Speaking and Teaching, Pfizer: Consultant, Sagimet: Consultant, Siemens Healthineers: Consultant, Boerhinger Ingelheim: Speaking and Teaching, Siemens Healthineers: Speaking and Teaching, Tiphaine Vida-Trecan: Nothing to Disclose, Pauline Manchon: Nothing to Disclose, Anais Vallet-Pichard: Nothing to Disclose, Sebastien Czernichow: Nothing to Disclose, Dominique Roulot: Gilead: Consultant, Valerie Paradis: Nothing to Disclose, Catherine Postic: Nothing to Disclose, Jean-Baptitste Julla: Nothing to Disclose, Etienne Larger: Nothing to Disclose, Bernard van Beers: Nothing to Disclose, Helene Fontaine: Gilead: employee until october 2023, Thierry Poynard: Nothing to Disclose, Pierre Bedossa: Nothing to Disclose, Stanislas Pol: Nothing to Disclose, Dominique Valla: Nothing to Disclose, Cedric Laouenan: Nothing to Disclose, Francois Pattou: Nothing to Disclose, Jean-Francois Gautier: Sanofi: talks, Novo Nordisk: Talks

1453 | RATIONALE AND DESIGN OF THE FIBROLITE STUDY EVALUATING SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF AFIMKIBART IN PATIENTS WITH ADVANCED LIVER FIBROSIS

Mazen Noureddin[1] Daniel Dugger[2] Steven Levitte[2] Valentina D'Arienzo[3] Sarah Williams[4] Vaibhavi Patel[4] KT Park[2] Jorge Ross Terres[2], [1]Houston Research Institute and Houston Methodist Hospital, Houston, Texas, USA, [2]Genentech, Inc., a member of the Roche Group, South San Francisco, CA, USA, [3]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [4]Roche Products Ltd, Welwyn Garden City, Hertfordshire, UK

Background: Cirrhosis due to metabolic dysfunction-associated steatohepatitis (MASH) is increasingly a cause of liver transplantation and hepatocellular carcinoma (HCC). While resmetirom is approved for the treatment of MASH with moderate to advanced fibrosis (F2–F3), a significant unmet need remains for patients with compensated cirrhosis (F4) for reversal of cirrhosis, prevention of liver decompensation, HCC, and transplantation. Afimkibart (RO7790121/RG6631) is a fully human monoclonal antibody against tumor necrosis factor-like ligand 1A (TL1A), which acts as a key amplifier of inflammatory and fibrotic signaling pathways activated in disease states, through its receptor death receptor 3. **Methods:** The FIBROLITE

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study (NCT06903065) is a single-arm, open-label study to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity and activity of afimkibart in 50 participants with advanced MASH fibrosis (F3–F4) in the USA and Mexico. Participants will be administered afimkibart via 10-week intravenous induction regimen followed by subcutaneous administration for a total of 52 weeks. Key inclusion criteria include a body mass index of 25–45 kg/m², and MASH fibrosis (F3–F4) confirmed by transient elastography ($\geq$12.0 kPa to $\leq$25.0 kPa) and biopsy staging within 12 months of baseline or Enhanced Liver Fibrosis (ELF) score of $\geq$9.8 to $\leq$11.3 at screening. Key exclusion criteria include decompensated liver disease, non-MASH causes of liver disease, and significant alcohol consumption. **Results:** The study population is expected to represent MASH patients with F3–F4 advanced fibrosis/compensated cirrhosis. The primary outcome is the safety of afimkibart in advanced liver disease. Secondary outcomes are the PK profile and activity of afimkibart in patients with MASH fibrosis (F3–F4). The PK profile will be investigated by measuring circulating concentrations of afimkibart at specified timepoints. FIBROLITE will leverage the utility of non-invasive tests (NITs) to evaluate the antifibrotic activity of afimkibart in F3–F4 MASH by measuring change from baseline to week 52 in liver stiffness by transient elastography, serum levels of propeptide of type III collagen, serum ELF test, and fibroinflammation by iron-corrected T1 magnetic resonance imaging mapping. **Conclusion:** If an acceptable safety and PK/PD profile for afimkibart is demonstrated, a larger, placebo-controlled follow-up study in people with MASH and advanced fibrosis may be undertaken. The data obtained from NITs could elucidate the anti-fibrotic potential of afimkibart as well as the potential for composite NIT assessments in MASH therapy development.

Disclosures: Mazen Noureddin: Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor: Terns, Takeda, Zydus., Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK: Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, Rivus Pharma, Cytodyn, and ChronWell: Stock – privately held company, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharmaceuticals: Consultant, Cytodyn: Consultant, GSK: Consultant, Eli Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Terns: Consultant, Takeda: Consultant, Allergan: Principal Investigator for a Drug Study, Akero: Principal Investigator for a Drug Study, BI: Principal Investigator for a Drug Study, BMS: Principal Investigator for a Drug Study, Gilead: Principal Investigator for a Drug Study, Galectin: Principal Investigator for a Drug Study, Genfit: Principal Investigator for a Drug Study, GSK: Principal Investigator for a Drug Study, Conatus: Principal Investigator for a Drug Study, Corcept: Principal Investigator for a Drug Study, Enanta: Principal Investigator for a Drug Study, Madrigal: Principal Investigator for a Drug Study, Novartis: Principal Investigator for a Drug Study, Novo Nordisk: Principal Investigator for a Drug Study, Shire: Principal Investigator for a Drug Study, Takeda: Principal Investigator for a Drug Study, Terns: Principal Investigator for a Drug Study, Viking: Principal Investigator for a Drug Study, Zydus: Principal Investigator for a Drug Study, Rivus Pharmaceuticals: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speaking and Teaching, Akero: Stock – privately held company, Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, Akero: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Conatus: Principal Investigator, Gilead Sciences: Principal Investigator, Daniel Dugger: Genentech: Employee, Steven Levitte: Nothing to Disclose, Valentina D'Arienzo: Nothing to Disclose, Sarah Williams: Nothing to Disclose, Vaibhavi Patel: Roche Products Ltd: Employee, KT Park: Genentech: Employee, Jorge Ross Terres: Nothing to Disclose

1454 | METALD EXHIBITS AN INTERMEDIATE HEPATIC LIPIDOMIC PROFILE: OVERALL SIMILAR TO MASLD WITH ALD-LINKED CERAMIDE FEATURES

Kazuyoshi Kon[1] Hyeon-Cheol Lee-Okada[2] Shuko Nojiri[3] Kumiko Arai[1] Shunsuke Ikejima[1] Kyoko Fukuhara[1] Reiko Yaginuma[1] Kei Ishizuka[1] Hiroo Fukada[1] Akira Uchiyama[1] Shunhei Yamashina[1] Takehiko Yokomizo[2] Kenichi Ikejima[1], [1]Juntendo University Graduate School of Medicine, [2]Juntendo University School of Medicine, [3]Juntendo University

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Background: Metabolic dysfunction and alcohol-related liver disease (MetALD) is a phenotype of steatotic liver disease characterized by moderate alcohol consumption coexisting with cardiometabolic risk factors. The pathogenesis of MetALD remains incompletely understood. Lipotoxicity, driven not only by lipid quantity but also specific lipid composition changes, is central to the pathology of steatotic liver disease. To clarify the role of lipotoxicity in pathogenesis of MetALD, we conducted a lipidomics analysis on liver tissues and serum samples from patients with MetALD and compared these lipid profiles with those from metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD). **Methods:** Thirty-two biopsy-proven patients were classified according to Delphi consensus criteria into MASLD ($n = 24$), MetALD ($n = 4$), and ALD ($n = 4$). Lipidomics profiling was performed using liquid chromatography-mass spectrometry. Lipid species differing significantly ($p < 0.05$) between MASLD and ALD groups were selected via one-way ANOVA, resulting in 59 lipid species. Principal component analysis, K-means clustering, and Euclidean distance analysis within the principal component space were applied to determine whether MetALD lipid profiles were more similar to MASLD or ALD. **Results:** No significant differences were observed among groups regarding age, sex, body mass index, skeletal muscle index, blood biochemistry, controlled attenuation parameter, liver stiffness, or NAFLD activity score. Principal component plots indicated that MetALD lipid profiles occupied an intermediate position between MASLD and ALD groups in both liver tissues and serum. However, K-means clustering placed MetALD profiles predominantly within the MASLD cluster. MetALD liver lipids such as lysophosphatidylserines, non-dihydrosphingomyelins, phosphatidylcholines, phosphatidylglycerols, and sphingomyelins were more similar to MASLD profiles. Conversely, multiple bis(monoacylglycero) phosphates, specific alpha-hydroxy ceramides, lactosylceramides, and triacylglycerols exhibited profiles closely resembling those of ALD. Although clustering and distance analyses indicated a general clustering proximity of MetALD to MASLD, several individual lipid species exhibited profiles that closely resembled those observed in ALD, particularly in pathways implicated in ceramide metabolism and hepatocellular injury. **Conclusion:** MetALD exhibits an intermediate lipidomic profile between MASLD and ALD, with an overall resemblance to MASLD. However, certain lipid species implicated in pathways such as ceramide metabolism, which are considered important in alcohol-associated liver injury, appear to align more closely with ALD, suggesting a pathophysiological overlap that contributes to disease development of MetALD.

Disclosures: Kazuyoshi Kon: Nothing to Disclose, Hyeon-Cheol Lee-Okada: Nothing to Disclose, Shuko Nojiri: Nothing to Disclose, Kumiko Arai: Nothing to Disclose, Shunsuke Ikejima: Nothing to Disclose, Kyoko Fukuhara: Nothing to Disclose, Reiko Yaginuma: Nothing to Disclose, Kei Ishizuka: Nothing to Disclose, Hiroo Fukada: Nothing to Disclose, Akira Uchiyama: Nothing to Disclose, Shunhei Yamashina: Nothing to Disclose, Takehiko Yokomizo: Nothing to Disclose, Kenichi Ikejima: Nothing to Disclose

1455 | GM60106: A NOVEL CLINICAL TREATMENT FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

WON-IL CHOI[1] Sungmin Song[2] Peter Goughnour[2] Won Hee Lee[3] Hee Jong Lee[2] Byung-Kwan Jeong[3] Wonsuk Choi[3] Jun Yong Park[4] Hail Kim[3] Jin Hee Ahn[5], [1]Jeonbuk National University Medical School, [2]JD Bioscience Inc., [3]Korea Advanced Institute of Science and Technology, [4]Yonsei University College of Medicine, [5]Gwangju Institute of Science and Technology

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), represent a growing global health burden with a high unmet need for improved therapies. 5-Hydroxytryptamine receptor 2A (5HT2A) has emerged as a potential target for modulating lipid metabolism and fibrogenesis in the liver. Here, we characterize a peripherally restricted 5HT2A antagonist called GM-60106, and report Phase 1 safety and tolerability data (ClinicalTrials.gov: NCT05517564). **Methods:** The efficacy of GM-60106 on MASLD/MASH and liver fibrosis was evaluated in multiple murine models, including STZHFD model, CCL4-induced fibrosis model, and bile duct ligation (BDL) model. Histological analysis included steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis. Phase 1 trial design of GM-60106 is a randomized, double-blind, placebo-controlled study to evaluate single and multiple ascending doses in healthy adults and individuals with elevated MASLD/MASH markers. The trial comprises three parts: • Part A (single ascending dose, SAD): 64 participants across 8 cohorts. • Part B (multiple ascending dose, MAD): 24 participants across 3 cohorts, once-daily doses for 14 days. • Part C (MAD): 8 participants with elevated disease markers, once-daily dosing for 28 days. **Results:** The expression of 5HT2A increased in hepatocytes upon high-fat diet feeding and in hepatic stellate cells during their activation. GM-60106 reduced lipid accumulation, inflammation, and hepatic fibrosis in STZHFD mouse model. GM-60106 also reduced hepatic fibrosis in both

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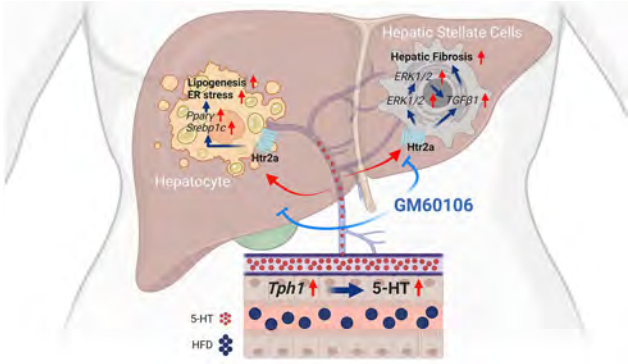
CCL4-induced fibrosis model and BDL model. In a comparative study, GM-60106 showed superior efficacy in reducing MASLD/MASH progression and hepatic fibrosis compared to Resmetirom. In the Phase 1 trial, GM60106 was well-tolerated with no dose-limiting toxicities observed. Among participants with baseline liver fat content $>12\%$ (MRI-PDFF), liver fat reductions of up to 76% were observed after 28 days of treatment. Notably, the participant with a 76% reduction in liver fat showed no accompanying weight loss, indicating a direct hepatic effect of GM-60106 independent of systemic weight changes. **Conclusion:** GM-60106 demonstrated significant efficacy in preclinical models by mitigating lipid accumulation, inflammation, and fibrosis, outperforming current alternatives like Resmetirom. The Phase 1 clinical study further validated its safety and tolerability, highlighting GM-60106 as a promising candidate for long-term treatment strategies aimed at addressing the unmet needs of patients with MASLD. These findings support the continued clinical development of GM-60106 as a potentially first-in-class therapeutic candidate for the treatment of MASLD/MASH.



Disclosures: WON-IL CHOI: Nothing to Disclose, Sungmin Song: Nothing to Disclose, Peter Goughnour: Nothing to Disclose, Won Hee Lee: Nothing to Disclose, Hee Jong Lee: Nothing to Disclose, Byung-Kwan Jeong: Nothing to Disclose, Wonsuk Choi: Nothing to Disclose, Jun Yong Park: Nothing to Disclose, Hail Kim: Nothing to Disclose, Jin Hee Ahn: Nothing to Disclose

1456 | ACCURACY OF NONINVASIVE TESTS IN ASSESSING LIVER FIBROSIS IN THE GENERAL POPULATION: A LARGE-SCALE PROSPECTIVE MULTICENTER STUDY

Jing Zhao[1] Shanghao Liu[2] Jianxiang Song[1] Hui Shi[3] Xibin Liu[4] Yijun Tang[5] Puqiang Liu[6] Xiao Liang[7] Huizhen Fan[8] Qing He[9] Yilin Zhang[2] Yong Pan[10] JianSong Ji[11] Manguo Zhao[12] Hui Yang[13] Yang Bo[14] Shuli Hao[15] Tongqin Han[16] Yongyi Zeng[17] Guo Zhang[18] Qiang Yan[19] Rong Hu[3] Haiying Feng[4] Pinglei Pan[1] Zhongji Meng[5] Jianping Zhang[6] Yongfen Zhu[7] Jianwen Sheng[8] Fengjuan Chen[9] Ruyu Liu[10] Yanru Xie[11] Lingxiao Wang[12] Junhong Yang[12] Yan Yang[12] Yajuan Zhao[13] Jing Wang[14] Youfang Gao[15] Yuxia Qi[16] Wenjuan Wang[18] Zhaowei Tong[19] Gao-Jun Teng[2] Zhenyu Dai[1] Xiaolong Qi[2], [1]Affiliated Yancheng Hospital, School of Medicine, Southeast University, [2]Zhongda Hospital, Medical School, Southeast University, [3]The First People's Hospital of Lian yungang, [4]Huanghua People's Hospital, [5]Taihe Hospital, Hubei University of Medicine, [6]Puxian People's Hospital, [7]Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, [8]Yichun People's Hospital, [9]Shenzhen third People's Hospital, [10]Beijing Ditan Hospital, Xuzhou Hospital, Capital Medical University, [11]Lishui Central Hospital, The Fifth Affiliated Hospital of Wenzhou Medical University, [12]Baiyin Central Hospital, [13]The Second Affiliated Hospital of Guangzhou Medical University, [14]General Hospital of Ningxia Medical University, [15]Bozhou People's Hospital, [16]Qingdao Public Health Clinical Center, [17]Mengchao Hepatobiliary Hospital of Fujian Medical University, [18]Guangxi Hospital Division of The First Affiliated Hospital, Sun Yat-sen University, [19]Huzhou Central Hospital

Background: Reliable and broadly applicable non-invasive tests (NITs) are essential for the early identification of liver fibrosis in the general population. This study aimed to evaluate the diagnostic performance of established NITs in predicting liver fibrosis among the general population. **Methods:** The LiverHealth project is a large, ongoing, prospective, community-based cohort study conducted in China among individuals aged 18 years and older, in which all participants underwent liver stiffness measurement (LSM) using transient elastography (Fibroscan). A total of 10,893 participants from seven regions in China—Haizhou District, Yandu District, Maojian District, Huanghua City, Yiyang New District, Qiantang District, and Puxian County—were enrolled between September 2024 and April 2025. Baseline demographic, anthropometric, and biochemical data were collected to compute multiple NIT scores, including LiverRisk, MAF-5, FIB-4, APRI, NFS, BARD, SAFE, Forns, Fibrosis Index, FibroIndex, and AAR. Liver fibrosis stages were defined based on LSM thresholds: ≥ 8.0 kPa for clinically significant liver fibrosis, ≥ 10.0 kPa for suggestive compensated advanced chronic liver disease (cACLD), ≥ 12.0 kPa for advanced fibrosis, and ≥ 15.0 kPa for highly suggestive cACLD. Diagnostic accuracy was assessed using the area under the receiver operating characteristic curve (AUC), with comparisons conducted using the DeLong test. **Results:** MAF-5 and

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LiverRisk scores demonstrated the highest diagnostic accuracy across all fibrosis thresholds. For clinically significant liver fibrosis, MAF-5 showed an AUC of 0.76 (95% CI: 0.74-0.79) and LiverRisk 0.75 (95% CI: 0.73-0.77), with no significant difference ($p = 0.122$). For suggestive cACLD (LSM $\geq$ 10.0 kPa), AUCs were 0.83 (95% CI: 0.80-0.87) for MAF-5 and 0.81 (95% CI: 0.78-0.85) for LiverRisk ($p = 0.109$). In detecting advanced fibrosis, both scores performed similarly: MAF-5 had an AUC of 0.86 (95% CI: 0.82-0.91) and LiverRisk 0.85 (95% CI: 0.80-0.90; $p = 0.478$). For highly suggestive cACLD, the AUCs were 0.87 (95% CI: 0.81-0.93) for MAF-5 and 0.88 (95% CI: 0.82-0.94; $p = 0.676$). Furthermore, MAF-5 demonstrated significantly superior performance in predicting clinically significant liver fibrosis and suggestive cACLD compared to the other nine non-invasive scores, with the exception of LiverRisk (all $p < 0.05$). **Conclusion:** Simple noninvasive tests can effectively identify individuals in the general population who are at risk of liver fibrosis. In this large-scale prospective community-based cohort in China, we found that MAF-5 and LiverRisk scores demonstrated the highest overall diagnostic accuracy.

Models	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	p value
Clinically significant liver fibrosis						
MAF-5	0.76 (0.74-0.79)	67.1	74.3	10.6	98.0	1 (reference)
LiverRisk	0.75 (0.73-0.77)	68.4	72	10	98.0	0.122
SAFE	0.73 (0.71-0.76)	62	75.9	10.5	97.8	0.003
NFS	0.67 (0.64-0.70)	51.9	74.3	8.4	97.1	<0.001
FIB4	0.65 (0.62-0.68)	46.4	76.8	8.4	96.9	<0.001
APRI	0.73 (0.7-0.75)	62.7	73	9.5	97.7	<0.001
AAR	0.63 (0.6-0.65)	58.6	62.8	6.7	97.1	<0.001
BARD	0.54 (0.51-0.57)	33.5	83.8	8.6	96.5	<0.001
Fibrosis index	0.62 (0.59-0.65)	54.4	65.3	6.7	96.9	<0.001
FibroIndex	0.65 (0.62-0.68)	47.5	74.5	7.8	96.9	<0.001
Frons	0.68 (0.65-0.71)	52.1	76.2	9.1	97.2	<0.001
Suggestive cACLD						
MAF-5	0.83 (0.8-0.87)	75.3	78.3	5.4	99.5	1 (reference)
LiverRisk	0.81 (0.78-0.85)	74.7	75.2	4.8	99.4	0.109
SAFE	0.78 (0.74-0.82)	66.9	80.7	5.4	99.3	<0.001
NFS	0.7 (0.66-0.74)	51.7	80.1	4.1	99.0	<0.001
FIB4	0.69 (0.65-0.74)	56.7	76.4	3.8	99.1	<0.001
APRI	0.8 (0.77-0.84)	68.5	79.8	5.3	99.3	0.022
AAR	0.66 (0.62-0.69)	65.7	62.4	2.8	99.1	<0.001
BARD	0.57 (0.52-0.62)	38.2	83.4	3.7	98.8	<0.001
Fibrosis index	0.66 (0.61-0.7)	61.2	64.3	2.8	99.0	<0.001
FibroIndex	0.69 (0.64-0.73)	50	78.6	3.7	99.0	<0.001
Frons	0.71 (0.67-0.75)	52.2	82.5	4.7	99.0	<0.001
Advanced fibrosis						
MAF-5	0.86 (0.82-0.91)	68.2	91.4	6.1	99.7	1 (reference)
LiverRisk	0.85 (0.8-0.9)	79.5	76.8	2.7	99.8	0.478
SAFE	0.82 (0.76-0.87)	73.9	79.2	2.8	99.7	0.0137
NFS	0.74 (0.68-0.8)	60.2	79.9	2.4	99.6	<0.001
FIB4	0.75 (0.69-0.81)	69.3	76.5	2.4	99.7	<0.001
APRI	0.85 (0.8-0.9)	77.3	79.7	3	99.8	0.473
AAR	0.64 (0.58-0.69)	73.9	48.6	1.2	99.6	<0.001
BARD	0.59 (0.52-0.66)	40.9	83.3	2	99.4	<0.001
Fibrosis index	0.69 (0.62-0.75)	46.6	86.4	2.7	99.5	<0.001
FibroIndex	0.74 (0.68-0.8)	55.7	82.9	2.6	99.6	<0.001
Frons	0.77 (0.71-0.82)	60.2	86.5	3.5	99.6	<0.001
Highly suggestive cACLD						
MAF-5	0.87 (0.81-0.93)	71.7	91.4	3.4	99.9	1 (reference)
LiverRisk	0.88 (0.82-0.94)	76.1	90.9	3.4	99.9	0.676
SAFE	0.85 (0.77-0.92)	73.9	86.1	2.2	99.9	0.316
NFS	0.78 (0.7-0.86)	69.6	82	1.6	99.8	0.013
FIB4	0.82 (0.74-0.9)	80.4	78.6	1.6	99.9	0.144
APRI	0.88 (0.81-0.94)	71.7	95.3	6.1	99.9	0.761
AAR	0.61 (0.54-0.68)	76.1	45.3	0.6	99.8	<0.001
BARD	0.62 (0.52-0.71)	45.7	83.2	1.1	99.7	<0.001
Fibrosis index	0.74 (0.64-0.83)	56.5	88.2	2	99.8	0.004
FibroIndex	0.77 (0.68-0.86)	58.7	92.7	3.3	99.8	0.021
Frons	0.82 (0.74-0.9)	76.1	82.6	1.8	99.9	0.192

Figure 1. Diagnostic accuracy of non-invasive scores.
Clinically significant liver fibrosis was defined as LSM ≥ 8 kPa. Suggestive Compensated advanced chronic liver disease (cACLD) was defined as LSM ≥ 10 kPa, advanced fibrosis as LSM ≥ 12 kPa, and highly suggestive cACLD as LSM ≥ 15 kPa.

Disclosures: Jing Zhao: Nothing to Disclose, Shanghao Liu: Nothing to Disclose, Jianxiang Song: Nothing to Disclose, Hui Shi: Nothing to Disclose, Xibin Liu: Nothing to Disclose, Yijun Tang: Nothing to Disclose, Puqiang Liu: Nothing to Disclose, Xiao Liang: Nothing to Disclose, Huizhen Fan: Nothing to Disclose, Qing He: Nothing to Disclose, Yilin Zhang: Nothing to Disclose, Yong Pan: Nothing to Disclose, JianSong Ji: Nothing to Disclose, Manguo Zhao: Nothing to Disclose, Hui Yang: Nothing to Disclose, Yang Bo: Nothing to Disclose, Shuli Hao: Nothing to Disclose, Tongqin Han: Nothing to Disclose, Yongyi Zeng: Nothing to Disclose, Guo Zhang: Nothing to Disclose, Qiang Yan: Nothing to Disclose, Rong Hu: Nothing to Disclose, Haiying Feng: Nothing to Disclose, Pinglei Pan: Nothing to Disclose, Zhongji Meng: Nothing to Disclose, Jianping Zhang: Nothing to Disclose, Yongfen Zhu: Nothing to Disclose, Jianwen Sheng: Nothing to Disclose, Fengjuan Chen: Nothing to Disclose, Ruyu Liu: Nothing to Disclose, Yanru Xie: Nothing to Disclose, Lingxiao Wang: Nothing to Disclose, Junhong Yang: Nothing to Disclose, Yan Yang: Nothing to Disclose, Yajuan Zhao: Nothing to Disclose, Jing Wang: Nothing to Disclose, Youfang Gao: Nothing to Disclose, Yuxia Qi: Nothing to Disclose, Wenjuan Wang: Nothing to Disclose, Zhaowei Tong: Nothing to Disclose, Gao-Jun Teng: Nothing to Disclose, Zhenyu Dai: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose

1457 | MIRICORILANT, A SELECTIVE GLUCOCORTICOID RECEPTOR MODULATOR, REPROGRAMS HEPATIC GENE NETWORKS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Rafael Mayoral Monibas[1] Jan Kroon[1] Hazel Hunt[1] Aprille Espinueva[1] William Guyer[1] Kavita Juneja[1], [1]Corcept Therapeutics

Background: The hormone cortisol, which regulates metabolism and stress, has been implicated in the development and progression of metabolic dysfunction-associated steatohepatitis (MASH). Miricorilant (MIRI) is an orally delivered, nonsteroidal selective glucocorticoid receptor modulator (SGRM). In a phase 1b study, patients with presumed MASH treated with MIRI 100 mg twice weekly had a 28.2% mean reduction in liver fat content, with improvements in hepatic, lipid, and glycemic markers (Alkhouri et al. *Hepatology* 2024). This study aims to explore MIRI's mechanism of action by determining its effects on gene expression in human cells in vitro. **Methods:** Transcriptomic profiling was conducted in HepaRG cells, a human bipotent progenitor cell line that can differentiate into hepatocyte-like cells. Steatosis was induced by culturing cells in an oleic acid-rich medium for 7 days. Short-term treatment (8 hours) and sub-chronic treatment (5 days) with MIRI 400 nM (171.36 ng/mL) or vehicle

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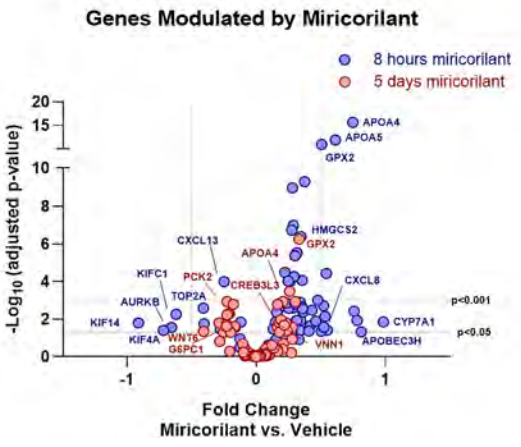
was performed, and RNA-sequencing was used to assess gene expression changes induced by MIRI. **Results:** MIRI induced a dual regulatory signature with distinct temporal dynamics. At the early time point (8 hours), MIRI treatment led to the upregulation of genes involved in lipid transport (APOA4, APOA5, CREB3L3), ketogenesis (HMGCS2), bile acid synthesis (CYP7A1), and antioxidant defense (GPX2). Balanced chemokine regulation (increased CXCL8/decreased CXCL13) indicates modulation of hepatocyte pathways for immune cell recruitment, while reducing chronic inflammatory signals. Genes associated with cell cycle and proliferation (AURKB, TOP2A, KIFC1, KIF4A, KIF14) were downregulated. Following sub-chronic treatment with MIRI for 5 days, prolonged upregulation of APOA4, CREB3L3, GPX2, and VNN1 suggested continued enhancement of lipid handling and antioxidant defense. Downregulation of CYP51A1 and gluconeogenic G6PC1 and PCK2 genes suggested longer-term reduction in steatosis and improved glucose metabolism. Downregulation of WNT6 supported reduced fibrogenesis. **Conclusion:** MIRI selectively modulated key genes in pathways that regulate hepatic steatosis, metabolism, oxidative stress, inflammation, and fibrosis. These findings provide insights into MIRI's molecular mechanism of action, potentially informing future therapeutic strategies. The ongoing phase 2b MONARCH trial (NCT06108219) is further evaluating MIRI in patients with biopsy-confirmed or presumed noncirrhotic MASH.

Figure. Miricorilant induced significant transcriptional changes in human hepatocyte-like cells under steatotic conditions



Disclosures: Rafael Mayoral Monibas: Corcept Therapeutics: Employee, Corcept Therapeutics: Stock - publicly traded company, Jan Kroon: Nothing to Disclose, Hazel Hunt: Corcept Therapeutics: Employee, Aprille Espinueva: Nothing to Disclose, William Guyer: Nothing to Disclose, Kavita Juneja: Corcept Therapeutics Incorporated: Employee, Corcept Therapeutics Incorporated: Stock - publicly traded company

1458 | PREDICTION OF STEATOTIC LIVER DISEASE: MACHINE LEARNING-BASED STUDY IN TAIWAN

Chia-Yen Dai[1] Tzu-Chun Lin[2] Hon-Yi Shi[3] Pei-Chien Tsai[4] Ming-Lun Yeh[5] Chung-Feng Huang[5] Jee-Fu Huang[5] Ming-Lung Yu[2], [1]Kaohsiung Medical University Hispital, Kaohsiung Medical University, Kaohsiung, Taiwan, [2]Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [3]Kaohsiung Medical University, [4]Kaohsiung Medical University Hospital, Medical University, Kaohsiung, Taiwan, [5]Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Kaohsiung

Background: In Taiwan, NAFLD affects approximately one-third of the population. Closely associated with metabolic disorders, non-alcoholic steatotic liver disease (SLD) have been a major disorder of liver diseases which may induce severe liver complications and substantially increase the risk of hepatocellular carcinoma. The integration of artificial intelligence (AI) into medical research has facilitated the extensive application of machine learning (ML) in predicting liver disease risk and treatment outcomes. This study aimed to apply ML algorithms to a community-based cohort in southern Taiwan to identify key risk factors for SLD and to develop predictive models with clinical applicability. **Methods:** Data were derived from community health examinations, and we colleced demographic features and clinical parameters including height, weight, waist circumference, systolic blood pressure (SBP), and diastolic blood pressure (DBP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels. Five ML algorithms were evaluated: logistic regression (LR), random forest (RF), K-nearest neighbors (KNN), adaptive boosting (AdaBoost), and extreme gradient boosting (XGBoost). Model performance was assessed using accuracy, precision, recall, F1 score, and the area under the receiver operating characteristic curve (AUROC). **Results:** A total of 7,700 participants were included (39.2% male; mean age 50.9 $\pm$ 14.9 years). The Synthetic Minority Over-sampling Technique (SMOTE) was employed to balance SLD and non-SLD groups (n = 3,850 each). The dataset was randomly divided into training (80%) and testing (20%) subsets, with no significant differences observed between groups. Among all models, XGBoost achieved the highest performance, with an accuracy of 91.66%, precision of 91.78%, recall of 91.54%, F1 score of 91.65%, and AUROC of 96.92%. Feature importance analysis identified LDL-C, body mass index (BMI), triglycerides (TG), age, and waist circumference as the most

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influential predictors of SLD. **Conclusion:** ML algorithms, particularly XGBoost, demonstrated high accuracy in predicting SLD and effectively identified key clinical predictors. These findings may enhance early diagnosis and facilitate the development of targeted intervention strategies in the management of SLD.

TABLE 1 Comparison of the machine learning (ML) model performance metrics following bootstrapping (N=7,700)

Training dataset (n=6,160)					
Model	Accuracy (95% CI)	Precision (95% CI)	Recall (95% CI)	F1 score (95% CI)	AUROC (95% CI)
LR	70.17% (70.14%-70.19%)	69.35% (69.31%-69.38%)	72.32% (72.24%-72.40%)	70.79% (70.76%-70.82%)	75.59% (75.50%-75.53%)
RF	80.61% (80.58%-80.64%)	82.37% (82.33%-82.42%)	77.89% (77.82%-77.97%)	80.06% (80.03%-80.10%)	88.68% (88.66%-88.69%)
KNN	80.86% (80.84%-80.88%)	88.19% (88.16%-88.23%)	71.27% (71.22%-71.32%)	78.83% (78.80%-78.86%)	86.80% (86.78%-86.82%)
AdaBoost	82.36% (82.33%-82.38%)	82.45% (82.42%-82.49%)	82.22% (82.17%-82.27%)	82.33% (82.31%-82.36%)	90.08% (90.07%-90.09%)
XGBoost	93.45% (93.43%-93.47%)	93.47% (93.44%-93.50%)	93.43% (93.40%-93.46%)	93.45% (93.43%-93.46%)	97.74% (97.73%-97.75%)
P value	<0.001	<0.001	<0.001	<0.001	<0.001
Testing dataset (n=1,540)					
Model	Accuracy (95% CI)	Precision (95% CI)	Recall (95% CI)	F1 score (95% CI)	AUROC (95% CI)
LR	70.84% (70.60%-70.69%)	70.00% (69.93%-70.09%)	72.30% (72.24%-72.47%)	71.13% (71.09%-71.18%)	76.84% (76.82%-76.87%)
RF	81.74% (81.69%-81.78%)	82.17% (82.09%-82.26%)	81.12% (81.00%-81.24%)	81.62% (81.57%-81.67%)	90.24% (90.21%-90.27%)
KNN	79.78% (79.73%-79.82%)	87.68% (87.61%-87.76%)	69.31% (69.20%-69.42%)	77.40% (77.34%-77.47%)	86.13% (86.09%-86.18%)
AdaBoost	81.97% (81.93%-82.01%)	82.25% (82.18%-82.32%)	81.57% (81.47%-81.66%)	81.89% (81.85%-81.94%)	90.43% (90.40%-90.46%)
XGBoost	91.60% (91.63%-91.70%)	91.78% (91.72%-91.85%)	91.54% (91.47%-91.61%)	91.65% (91.62%-91.69%)	96.92% (96.90%-96.94%)
P value	<0.001	<0.001	<0.001	<0.001	<0.001

Abbreviation: AUROC, area under the receiver operating characteristic curve; LR, logistic regression; RF, random forest; KNN, K-nearest neighbors; AdaBoost, adaptive boosting; XGBoost, eXtreme gradient boosting.

Disclosures: Chia-Yen Dai: Nothing to Disclose, Tzu-Chun Lin: Nothing to Disclose, Hon-Yi Shi: Nothing to Disclose, Pei-Chien Tsai: Nothing to Disclose, Ming-Lun Yeh: Nothing to Disclose, Chung-Feng Huang: Nothing to Disclose, Jee-Fu Huang: Roche: Consultant, Gilead: Consultant, Sysmex: Consultant, Aligos: Consultant, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Merck: Speaking and Teaching, Sysmex: Speaking and Teaching, Novo Nordisk: Consultant, Berlinger-Ingelheim: Consultant, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching

1459 | QUTAN HUOXUE FORMULA INHIBITS MASH PROGRESSION BY REGULATING CYP1B1-MEDIATED ARACHIDONIC ACID METABOLISM

Jing Zhou[1], [1]Ning bo NO.2 hospital, Zhejiang, China

Background: The incidence of metabolic dysfunction-associated steatohepatitis (MASH) is rising annually, posing a significant threat to global health. However, effective therapeutic agents remain lacking. Qutan Huoxue Formula (QTHXF), an empirically developed traditional Chinese medicine formula, has demonstrated efficacy in reducing hepatic lipid deposition and inhibiting MASH progression. **Methods:** An MASH model was established in C57BL/6 mice via 16 weeks of high-fat diet (HFD) feeding. QTHXF was administered for 6 weeks as an intervention. Changes in body weight, liver weight, hepatic lipid deposition, and biochemical indices were monitored. Hepatic alterations at the gene and metabolic levels were assessed using transcriptomics and metabolomics analyses. In vitro, palmitate was used to induce steatosis in hepatocytes, and siRNA-mediated knockdown was employed to validate the mechanism of drug action. **Results:** QTHXF significantly reduced body weight, liver weight, hepatic steatosis, serum levels of alanine aminotransferase, triglycerides, and total cholesterol, as well as NASH scores and reactive oxygen species (ROS) levels in MASH mice. Transcriptomic sequencing revealed that differentially expressed genes regulated by QTHXF were significantly enriched in ROS-related pathways, with CYP1B1 identified as a key gene. QTHXF directly targeted CYP1B1 and markedly suppressed its expression in hepatocytes. Metabolomic analysis indicated that QTHXF suppressed the activation of hepatic arachidonic acid metabolism pathways. In vitro experiments further validated the mechanism involving QTHXF regulation of CYP1B1-mediated arachidonic acid metabolism. **Conclusion:** Qutan Huoxue Formula inhibits MASH progression by attenuating hepatic oxidative stress through the regulation of CYP1B1-mediated arachidonic acid metabolism. Our findings provide a novel strategy for the clinical treatment of MASH.

Disclosures: Jing Zhou: Nothing to Disclose

1460 | INCREASED HEPATIC MICROARTERIES AND COLLAGEN DEPOSITION IN ACINAR ZONE 1 ARE ASSOCIATED WITH CLINICALLY SIGNIFICANT PORTAL HYPERTENSION CAUSED BY METABOLIC ASSOCIATED STEATOTIC LIVER DISEASE

Zhengxin Li[1] Yayun Ren[2] Xiao Teng[3] Dean Tai[3] Jörn Schattenberg[4] Chenghai Liu[5], [1]Gongli Hospital of Shanghai Pudong New Area, [2]Hangzhou Choutu Tech. Co., Ltd [3]HistoIndex, [4]Department of Internal Medicine II, Saarland University Medical Center, [5]Shuguang Hospital, Shanghai University of Traditional Chinese Medicine

Background: Metabolic-associated steatotic liver disease (MASLD) is one of the common causes of clinically significant portal hypertension (CSPH). The occurrence of CSPH is often accompanied by severe complications such as bleeding and ascites. Early identification of CSPH remains challenging. This study aims to investigate histological correlates of CSPH in MASLD to develop pathological markers for early risk stratification. **Methods:** Eighty-five needle biopsy samples with MASLD were collected from Shuguang

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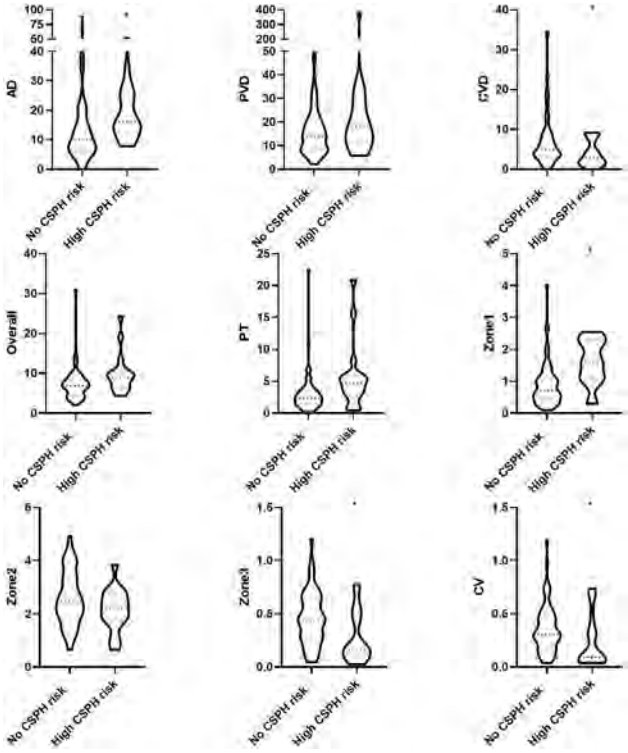
Hospital and Medical Center of the Johannes Gutenberg-University. The risk of CSPH was based on Baveno VII consensus. According to liver stiffness measurement(LSM) and platelet(PLT) count, patients were divided into two groups: no CSPH risk(LSM **Results:** Fibrosis stages (NASH-CRN) in the high CSPH risk group included F1 (n = 2), F2 (n = 3), F3 (n = 8), and F4 (n = 5); the no CSPH risk group showed F1 (n = 21), F2 (n = 37), and F3 (n = 9) (no F4 cases). Compared to the no CSPH risk group, the high CSPH risk group had higher levels of arterial density (19.73 ± 10.98 vs. 13.12 ± 12.71, P < 0.05) and CPA in acinar zone 1(1.59 ± 0.70 vs. 0.90 ± 0.68, P **Conclusion:** Arterial proliferation, collagen deposition in acinar zone 1 and loss of central veins were associated with CSPH in MASLD, suggesting potential utility as pathological markers for early CSPH screening.



Disclosures: Zhengxin Li: Nothing to Disclose, Yayun Ren: HistoIndex Pte Ltd: Employee, Xiao Teng: Nothing to Disclose, Dean Tai: Nothing to Disclose, Jörn Schattenberg: Apollo Endoscopy, Boehringer Ingelheim, Gilead Sciences: Consultant, Intercept Pharmaceuticals: Consultant, Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals: Consultant, MSD, Northsea Therapeutics, Novartis, Novo Nordisk: Consultant, Pfizer, Roche, Sanofi, and Siemens Healthineers: Consultant, Boehringer Ingelheim, Siemens Healthcare GmbH: Grant/Research Support, Alentis, Alexion, Altimmune, Astra Zeneca, 89Bio,Bionorica,: Consultant, Boehringer Ingelheim, Gilead Sciences, GSK, Ipsen, Inventiva: Consultant, Madrigal Pharmaceuticals, Lilly, MSD, Northsea Therapeutics,: Consultant, Novo Nordisk, Pfizer, Roche, Sanofi, and Siemens Healthineer: Consultant, AbbVie, Academic Medical Education (AME),: Speaking and Teaching, Boehringer Ingelheim, Echosens: Speaking and Teaching, Forum für Medizinische Fortbildung (FOMF), Gilead Sciences: Speaking and Teaching, MedicalTribune, MedPublico GmbH, MedScape,: Speaking and Teaching, Novo Nordisk, Madrigal Pharmaceuticals,: Speaking and Teaching, Akero, Alentis, Alexion, Altimmune, Astra Zeneca, 89Bio: Consultant, Bionorica, Boehringer Ingelheim, Gilead Sciences, GSK,: Consultant, HistoIndex, Ipsen, Inventiva Pharma, Madrigal Pharmaceutical: Consultant, Kríya Therapeutics, Lilly, MSD Sharp & Dohme GmbH: Consultant, Northsea Therapeutics, Novartis, Novo Nordisk: Consultant, Pfizer, Roche, Sanofi, Siemens Healthineers,: Consultant, Summit Clinical, and Vantage Biosciences Research: Consultant, AbbVie, Boehringer Ingelheim, Gilead Sciences,: Speaking and Teaching, Ipsen Novo Nordisk,: Speaking and Teaching, Madrigal Pharmaceuticals, Worldwide Clinical Trials: Speaking and Teaching, Hepta Bio.: Stock – privately held company, Akero: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Ipsen: Consultant, Inventiva Pharma: Consultant, Madrigal: Consultant, Northsea Therapeutics: Consultant, Novo Nordisk: Consultant, Roche: Consultant, Siemens Healthineers: Consultant, Boehringer Ingelheim: Grant/Research Support, AGED diagnostics: Stock – privately held company, Hepta Bio: Stock – privately held company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock – privately held company, MedPublico GmbH: Speaking and Teaching, Chenghai Liu: Nothing to Disclose

1461 | EFFECT OF MODERATE AND SEVERE HEPATIC IMPAIRMENT ON PHARMACOKINETICS, SAFETY AND TOLERABILITY OF PEGOZAFERMIN AFTER SUBCUTANEOUS ADMINISTRATION

Eric Lawitz[1] Leo Tseng[2] Kemal Balic[2] Hank Mansbach[2] Mildred Gottwald[2] Madhavi Rudraraju[3], [1]Texas Liver Institute, [2]89bio, Inc., [3]Pinnacle Clinical Research

Background: Hepatic impairment may alter the pharmacokinetics (PK) of therapeutic agents, potentially impacting safety and necessitating dose adjustments. This study assessed the PK, safety and tolerability of pegozafermin, a long-acting glycoPEGylated analog of fibroblast growth factor 21 (FGF21), in subjects with moderate and severe hepatic impairment (HI) from any etiology, including those with metabolic dysfunction-associated steatohepatitis (MASH). PK data will enable dosing recommendations in patients with varying degrees of HI. **Methods:** This multicenter, open-label,

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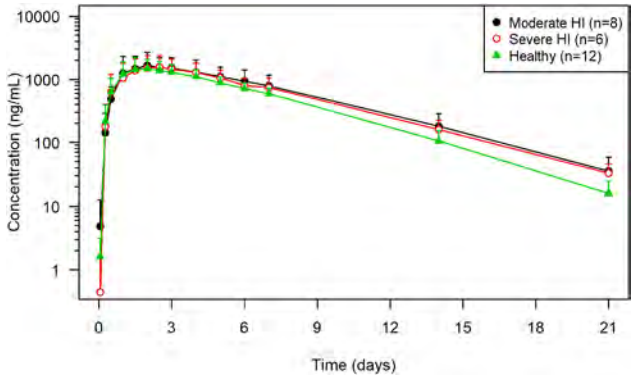
parallel-group, single-dose, PK study enrolled subjects with moderate (n = 8) and severe (n = 6) hepatic impairment (including 2 MASH subjects in each category), according to the Child-Pugh classification, and 12 healthy control subjects matched by age, sex, and body weight. All subjects received a single SC dose of pegozafermin (30 mg) via prefilled syringe. Blood samples for PK analysis were collected at predetermined intervals over 3 weeks. PK parameters, including AUC and Cmax, were determined using non-compartmental methods and compared across groups. Log-transformed PK parameters were analyzed using a statistical model, analysis of covariance (ANCOVA). The geometric least-square (LS) means and mean ratios for each group were calculated to evaluate the effect of HI on pegozafermin exposure. As part of the exploratory objectives, pharmacodynamic (PD) endpoints, including lipid panel and adiponectin levels, were evaluated as changes from baseline to Day 8. Safety and tolerability profile was also assessed. **Results:** Overall, PK profiles were similar between subjects with HI and healthy controls (Figure 1). The geometric LS mean ratios for AUC and Cmax remained within the standard bioequivalence range (80 – 125%), indicating that systemic exposure to pegozafermin is not substantially altered in subjects with moderate or severe HI. Furthermore, compared to other etiologies of cirrhosis, the presence of MASH did not appear to alter PK parameters in a meaningful way. PD biomarkers showed favorable changes at Day 8. The SC administration of pegozafermin was well tolerated across all degrees of hepatic impairment, with no new or unexpected safety signals observed. Mild to moderate gastrointestinal disorders were the most common treatment-emergent adverse events, occurring in 6 of the 26 subjects (23.1%). **Conclusion:** Pegozafermin was safe and well tolerated across subjects with HI. Moderate and severe HI, including the presence of MASH, had no clinically meaningful effect on PK profile or parameters of pegozafermin. Based on these findings, no dose adjustment is warranted in patients with HI.



Disclosures: Eric Lawitz: 89Bio: Grant/Research Support, Akero Therapeutics: Grant/Research Support, Astrazeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, Cour Pharmaceuticals: Grant/Research Support, Cymabay Therapeutics: Grant/Research Support, Eli Lilly and Company: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Hanmi Pharmaceuticals: Grant/Research Support, Hightide Biopharma: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Inventiva: Grant/Research Support, Ipsen: Grant/Research Support, Madrigal Pharmaceuticals: Grant/Research Support, Merck & Co: Grant/Research Support, NGM Biopharmaceuticals: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk Inc: Grant/Research Support, Regeneron: Grant/Research Support, Sagimet Biosciences: Grant/Research Support, Takeda: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Viking Therapeutics: Grant/Research Support, Viking Therapeutics: Grant/Research Support, Zydus Pharmaceuticals: Grant/Research Support, Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Merck & Co: Consultant, Novo Nordisk Inc: Consultant, Organovo: Consultant, Regeneron: Grant/Research Support, Regeneron: Grant/Research Support, Sagimet Biosciences: Consultant, Corcept Therapeutics: Consultant, Corcept Therapeutics: Grant/Research Support, Corcept Therapeutics: Grant/Research Support, Astrazeneca: Consultant, inventiva: Consultant, Leo Tseng: Nothing to Disclose, Kemal Balic: Nothing to Disclose, Hank Mansbach: Nothing to Disclose, Mildred Gottwald: 89bio: Employee, 89bio: Stock - publicly traded company, Madhavi Rudraraju: Nothing to Disclose

1462 | STEATOTIC LIVER DISEASE IS AN UNFAVORABLE PROGNOSTIC FACTOR OF THE RECURRENCE FOLLOWING RESECTION IN EARLY-STAGE ORAL SQUAMOUS CELL CARCINOMA

Hidetoshi Nomura[1] Reiichiro Kondo[1] Jingo Kusukawa[1] Jun Akiba[1], [1]Kurume University School of Medicine

Background: Steatotic liver disease (SLD), especially metabolic dysfunction-associated steatotic liver disease (MASLD), is getting a lot of interest in the association with the prognosis of extrahepatic diseases. It has been reported that MASLD as a risk

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factor for recurrence after resection in early esophageal cancer and early gastric cancer. However, the relationship between SLD/ MASLD and prognosis for oral squamous cell carcinoma (OSCC) is uninvestigated. The aim of this study is to investigate the association of SLD and MASLD with the risk of recurrence after resection in early-stage OSCC. **Methods:** We retrospectively analyzed 93 patients who underwent resection for Tis (carcinoma in situ) or T1 (maximum diameter < 2 cm, depth of invasion < 5 mm) OSCC between 2017 and 2024. There were 24 of Tis and 69 of T1. The mean age was 68.3 years, with a male-to-female ratio of 49:44. Smoking history and alcohol consumption history were present in 21 patients and 20 patients, respectively. SLD was assessed using the preoperative Hepatic Steatosis Index (HSI), with HSI $\geq$ 30 defined as SLD. MASLD was defined based on the presence of SLD (HSI ≥ 30) and concomitant metabolic factors. Data on metabolic factors (body mass index [BMI] $>$ 23 kg/m^2, impaired glucose tolerance, hypertension, dyslipidemia) and blood laboratory results were extracted from preoperative records. Impaired glucose tolerance, hypertension, and dyslipidemia were present in 59 patients, 51 patients, and 31 patients, respectively. The median follow-up period was 1219 days. **Results:** 50 patients were classified into the SLD group (HSI $\geq$ 30), and 43 into the non-SLD group (HSI $<$ 30). The SLD group had a significantly higher BMI than the non-SLD group (24.54 ± 2.57 vs. 20.71 ± 3.15, $p < 0.01$). MASLD was identified in 32 cases. In univariate analysis for recurrence after resection, HSI $\geq$ 30 (Hazard Ratio [HR] 2.79, $p < 0.04$), MASLD (HR 3.14, $p < 0.01$), and positive surgical margin (HR 4.19, $p < 0.01$) had a statistically significant impact. Kaplan-Meier curves confirmed that the SLD group showed significantly worse recurrence-free survival (RFS) compared to the non-SLD group (log-rank test $P < 0.03$). Similarly, patients with MASLD exhibited significantly worse RFS than those without MASLD ($p < 0.01$). Neutrophil-to-lymphocyte (N/L) ratio ($R = 0.36$, $p < 0.01$) and CRP ($R = 0.36$, $p = 0.02$) were decreased along with increase of HSI. There were no significant differences between the SLD and non-SLD groups regarding age, sex, smoking history, alcohol consumption history, T classification, or positive surgical margin status, eGFR, and γGTP. **Conclusion:** SLD/ MASLD is a significant risk factor for recurrence following resection in Tis and T1 oral squamous cell carcinoma. These findings highlight a potential link between liver health, metabolic dysfunction, and oral cancer prognosis. SLD may be associated with immunoinflammatory responses and involved in patient prognosis.

Disclosures: Hidetoshi Nomura: Nothing to Disclose, Reiichiro Kondo: Nothing to Disclose, Jingo Kusukawa: Nothing to Disclose, Jun Akiba: Nothing to Disclose

1463 | BEYOND THE AIRWAY: THE POSSIBLE HEPATIC COST OF CPAP IN OBSTRUCTIVE SLEEP APNEA

Muhammad Ali Ibrahim Kazi Hasan Kamal[1] Akshay Sharma[1] Nirav Agrawal[1] Adrien Mazer[1] Sanmeet Singh[1], [1]Anne Arundel Medical Center

Background: Obstructive sleep apnea (OSA) is a prevalent disorder marked by repeated upper airway obstruction, leading to intermittent hypoxia and systemic inflammation, which contribute to metabolic, cardiovascular, and liver-related complications. While continuous positive airway pressure (CPAP) therapy improves oxygenation and has proven cardiovascular benefits, its effect on hepatic outcomes such as NASH and cirrhosis remains unclear. Given the shared pathophysiology between OSA and metabolic liver disease, this study aimed to evaluate the incidence of NASH and liver complications in CPAP users versus non-users using a propensity-matched cohort design. **Methods:** We conducted a retrospective cohort study utilizing data from patients who underwent sleep testing and were diagnosed with OSA. Two cohorts were established: one group that initiated CPAP therapy and one that did not. Patients were matched 1:1 using propensity score matching for age, sex, ethnicity, race, and Charleston Comorbidity Index (CCI). Outcomes assessed included the development of NASH, varices, hepatic encephalopathy, ascites, and cirrhosis. Risk differences and risk ratios (RR) with 95% confidence intervals (CI) were calculated for each outcome. **Results:** A total of 204,616 patients were included in the analysis, with 102,308 patients in each matched cohort. Patients with OSA who used CPAP had a significantly higher risk of developing the following outcomes compared to those who did not use CPAP • NASH: CPAP 2.2% vs. No CPAP 1.7%. • RR: 1.288 (95% CI: 1.211–1.370), $p < 0.001$. • Varices: CPAP 0.8% vs. No CPAP 0.6%. • RR: 1.211 (95% CI: 1.093–1.342), $p < 0.001$. • Hepatic Encephalopathy: CPAP 0.5% vs. No CPAP 0.3%. • RR: 1.623 (95% CI: 1.408–1.871), $p < 0.001$. • Ascites: CPAP 3.0% vs. No CPAP 2.1%. • RR: 1.441 (95% CI: 1.364–1.522), $p < 0.001$. • Cirrhosis: CPAP 3.0% vs. No CPAP 2.5%. • RR: 1.212 (95% CI: 1.150–1.276), $p < 0.001$ **Conclusion:** In this large-scale propensity-matched cohort study, CPAP use in patients with OSA was associated with an increased risk of developing nonalcoholic steatohepatitis (NASH) and liver-related complications, including varices, hepatic encephalopathy, ascites, and cirrhosis. While CPAP therapy is well established for improving cardiovascular and respiratory outcomes, these findings suggest that CPAP alone may not adequately mitigate the hepatic risks linked to OSA. The observed associations could reflect underlying disease severity, lifestyle factors, or limitations in CPAP adherence. Given the rising prevalence of OSA and its association with systemic inflammation, oxidative stress, and metabolic dysfunction, further

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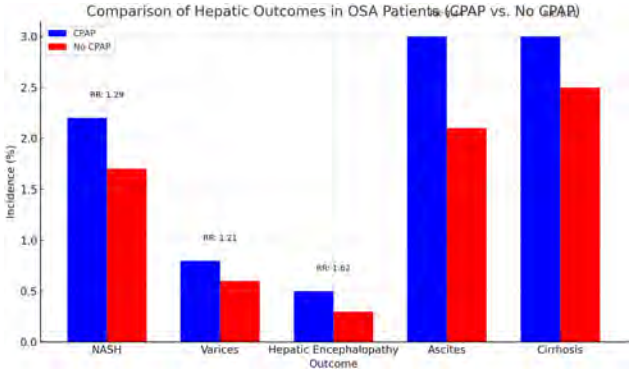
research is needed to explore the interplay between CPAP adherence, OSA severity, and lifestyle modifications to optimize hepatic outcomes in this high-risk population.

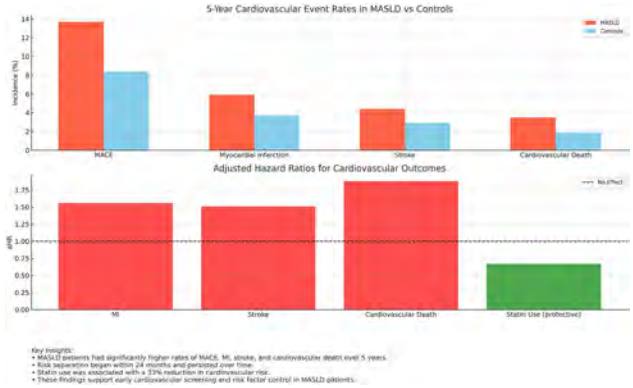


Disclosures: Muhammad Ali Ibrahim Kazi: Nothing to Disclose, Hasan Kamal: Nothing to Disclose, Akshay Sharma: Nothing to Disclose, Nirav Agrawal: Nothing to Disclose, Adrien Mazer: Nothing to Disclose, Sanmeet Singh: Nothing to Disclose

1464 | CARDIOVASCULAR DISEASE RISK IN METABOLIC ASSOCIATED FATTY LIVER DISEASE: A MULTICENTER PROPENSITY-MATCHED LONGITUDINAL ANALYSIS

Ahmed Salem[1] Sarah Meribout[1] Mohammed Abusuliman[2] Mohamed Eldesouki[3] Avleen Kaur[4] Hazem Abosheaishaa[5] Sherif Elhanafi[6] Aaron Tokayer[1], [1]Maimonides Medical Center, [2]Henry Ford Hospital, [3]New York Medical College at Saint Michael Medical Center, [4]Sunny Upstate University Medical Center, [5]Mount Sinai Queens, [6]Texas Tech University Health Science Center El Paso

Background: Metabolic associated fatty liver disease (MAFLD) is increasingly recognized as a systemic metabolic condition. While it has been associated with cardiovascular disease (CVD), the long-term real-world magnitude of this risk remains underexplored. Aim: To assess the incidence and predictors of major adverse cardiovascular events (MACE) in patients with MAFLD compared to matched non-MAFLD controls. **Methods:** We conducted a retrospective multicenter cohort study using TriNetX, a U.S.-based network of longitudinal electronic health records. Adults ($\geq$18 years) diagnosed with MAFLD (ICD-10: K76.0) from Jan 1, 2010, to Dec 31, 2023, were included. Exclusion criteria: prior MI, stroke, cardiovascular procedures, alcohol-related liver disease, viral hepatitis, or cirrhosis at baseline. Controls were matched 1:1 for age, sex, BMI, diabetes, hypertension, dyslipidemia, tobacco use, and use of statins or antiplatelets. The primary outcome was 5-year incidence of MACE: MI, stroke (ischemic or hemorrhagic), and cardiovascular death. Adjusted hazard ratios (aHR) were estimated via Cox models controlling for metabolic syndrome, HbA1c, and medications. Kaplan-Meier analysis illustrated cumulative risk. **Results:** After matching, 48,552 patients (24,276 per group) were included. Mean age: 57.4 years; 52.8% female. Median follow-up: 5.2 years. MAFLD patients had significantly higher 5-year MACE incidence: • MACE: 13.7% vs 8.4% ($p < 0.001$). • MI: 5.9% vs 3.7%; aHR 1.56 (95% CI: 1.39–1.74). • Stroke: 4.4% vs 2.9%; aHR 1.51 (95% CI: 1.32–1.73). • CV death: 3.5% vs 1.9%; aHR 1.88 (95% CI: 1.55–2.29). Statin use was protective in both groups (aHR 0.67; 95% CI: 0.56–0.80). Sensitivity analyses confirmed findings across subgroups by diabetes, sex, LDL, and BMI. Kaplan-Meier curves showed divergence by 24 months, with sustained separation over 5 years. **Conclusion:** MAFLD is independently linked to increased long-term risk of MI, stroke, and cardiovascular death. These real-world findings support classifying MAFLD as a systemic disease and underscore the need for early cardiovascular screening, aggressive risk management, and statin therapy.



Disclosures: Ahmed Salem: Nothing to Disclose, Sarah Meribout: Nothing to Disclose, Mohammed Abusuliman: Nothing to Disclose, Mohamed Eldesouki: Nothing to Disclose, Avleen Kaur: Nothing to Disclose, Hazem Abosheaishaa: Nothing to Disclose, Sherif Elhanafi: Nothing to Disclose, Aaron Tokayer: Nothing to Disclose

1465 | PREVALENCE OF STEATOTIC LIVER DISEASE AND LIVER FIBROSIS IN THE GENERAL POPULATION IN CHINA: A LARGE-SCALE PROSPECTIVE MULTICENTER STUDY

Yilin Zhang[1] Shanghao Liu[1] Hui Shi[2] Xibin Liu[3] Zhenyu Dai[4] Yijun Tang[5] Puqiang Liu[6] Xiao Liang[7] Huizhen Fan[8] Qing He[9] Yong Pan[10] JianSong Ji[11] Manguo Zhao[12] Hui Yang[13] Yang Bo[14] Shuli Hao[15] Tongqin Han[16] Yongyi Zeng[17] Guo Zhang[18] Qiang Yan[19] Rong

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Hu[2] Haiying Feng[3] Pinglei Pan[4] Zhongji Meng[5] Jianping Zhang[6] Yongfen Zhu[7] Jianwen Sheng[8] Fengjuan Chen[9] Ruyu Liu[10] Yanru Xie[11] Lingxiao Wang[12] Junhong Yang[12] Yan Yang[12] Yajuan Zhao[13] Jing Wang[14] Youfang Gao[15] Yuxia Qi[16] Wenjuan Wang[18] Zhaowei Tong[19] Gao-Jun Teng[1] Xiaolong Qi[1], [1]Zhongda Hospital, Medical School, Southeast University, [2]The First People's Hospital of Lian yungang, [3]Huanghua People's Hospital, [4]Affiliated Yancheng Hospital, School of Medicine, Southeast University, [5]Taihe Hospital, Hubei University of Medicine, [6]Puxian People's Hospital, [7]Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, [8]Yichun People's Hospital, [9]Shenzhen third People's Hospital, [10]Beijing Ditan Hospital, Xuzhou Hospital, Capital Medical University, [11]Lishui Central Hospital, The Fifth Affiliated Hospital of Wenzhou Medical University, [12]Baiyin Central Hospital, [13]The Second Affiliated Hospital of Guangzhou Medical University, [14]General Hospital of Ningxia Medical University, [15]Bozhou People's Hospital, [16]Qingdao Public Health Clinical Center, [17]Mengchao Hepatobiliary Hospital of Fujian Medical University, [18]Guangxi Hospital Division of The First Affiliated Hospital, Sun Yat-sen University, [19]Huzhou Central Hospital

Background: Comprehensive understanding of the prevalence of steatotic liver disease (SLD) and liver fibrosis in the general population is essential for shaping effective public health policies aimed at reducing the future burden of cirrhosis and liver cancer. China bears the world's highest burden of chronic liver disease, yet population-level epidemiological data remain limited. This study aimed to determine the prevalence of SLD and liver fibrosis in the general Chinese population. **Methods:** The LiverHealth project is a large, ongoing, prospective, community-based cohort study conducted in China among individuals aged 18 years and older, in which all participants underwent controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) assessment using transient elastography (Fibroscan). Between September 2024 and April 2025, participants were enrolled from seven sites across China: Haizhou District, Yandu District, Maojian District, Huanghua City, Yiyang New District, Qiantang District, and Puxian County. Comprehensive data collection included standardized questionnaires, anthropometric measurements, and laboratory tests. Logistic regression analysis was performed to identify risk factors associated with SLD and liver fibrosis. SLD was graded by CAP values: ≥248 dB/m (≥S1, mild or above), ≥268 dB/m (≥S2, moderate or above), and ≥280 dB/m (S3, severe). Fibrosis stages were defined by LSM thresholds: ≥6.0 kPa (≥F1, mild or above), ≥8.0 kPa (≥F2, moderate or above), and ≥10.0 kPa (≥F3, advanced fibrosis or above). **Results:** A total of 11,721 participants were included, with a median age of 49 years (IQR: 36.0–59.0), and 48.5% (n = 5,687) were male. The prevalence of ≥S1, ≥S2, and S3 was 43.06%, 30.35%, and 24.07%, respectively. The prevalence of ≥F1, ≥F2, and ≥F3 was 19.23%, 4.37%, and 1.65%, respectively. Additionally, 24.90% of individuals were identified with metabolic dysfunction-associated steatotic liver disease (MASLD) and 1.66% met criteria for metabolic and alcohol-related liver disease (MetALD). The prevalence of SLD and fibrosis varied significantly by sex and age groups (Figure 1A–1D). Individuals who were male, or had obesity, diabetes, hypertension, dyslipidemia, ≥2 metabolic risk factors, or elevated liver enzymes, or decreased platelet counts showed significantly higher prevalence of all grades of steatosis and fibrosis. Multivariate analysis further identified obesity, male, hypertension, diabetes, and elevated alanine aminotransferase or aspartate aminotransferase as independent risk factors associated with both SLD and fibrosis. **Conclusion:** High prevalence of SLD and liver fibrosis was identified in the general adult population in China. These findings underscore the urgent need for effective population-based screening and prevention strategies to mitigate the future burden of cirrhosis and liver cancer.

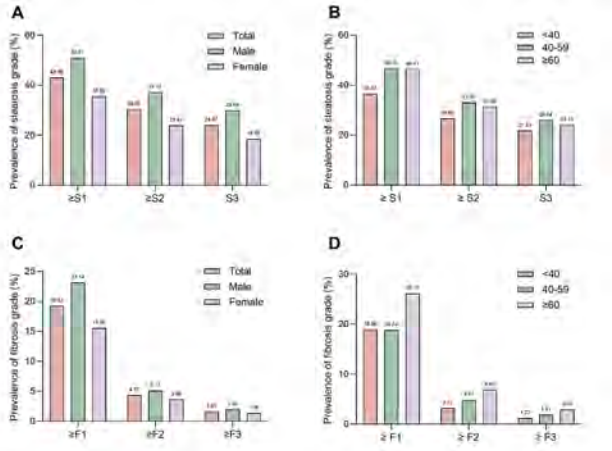

Figure 1. Prevalence of steatotic liver disease (SLD) and fibrosis by sex and age groups.

(A) SLD prevalence (≥S1, ≥S2, S3) in the overall population and by sex.

(B) SLD prevalence across age groups (<40, 40–59, ≥60 years).

(C) Fibrosis prevalence (≥F1, ≥F2, ≥F3) in the overall population and by sex.

(D) Fibrosis prevalence across age groups (<40, 40–59, ≥60 years).

Disclosures: Yilin Zhang: Nothing to Disclose, Shanghao Liu: Nothing to Disclose, Hui Shi: Nothing to Disclose, Xibin Liu: Nothing to Disclose, Zhenyu Dai: Nothing to Disclose, Yijun Tang: Nothing to Disclose, Puqiang Liu: Nothing to Disclose, Xiao Liang: Nothing to Disclose, Huizhen Fan: Nothing to Disclose, Qing He: Nothing to Disclose, Yong Pan: Nothing to Disclose, JianSong Ji: Nothing to Disclose, Manguo Zhao: Nothing to Disclose, Hui Yang: Nothing to Disclose, Yang Bo: Nothing to Disclose, Shuli Hao: Nothing to

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1466 | UNIQUE SEX-SPECIFIC ASSOCIATIONS OF METABOLIC AND HORMONAL FACTORS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

Norah Terrault[1] Jennifer Dodge[1] Laura Wilson[2] Ayako Suzuki[3], [1]university of Southern California, [2]Johns Hopkins University, [3]Duke University

Background: Biologic sex is known to influence disease onset, progression, and treatment response in many diseases. Understanding risk factors for MASH from non-MASH in persons with MASLD is essential, as MASH is associated with higher risk of fibrosis progression and need for targeted therapeutic interventions. Here, we sought to examine sex-specific clinical, metabolic and hormonal related factors associated with disease severity in MASLD. **Methods:** Cross-sectional study of participants (N = 1595 women, 1002 men; randomly split 80:20 into derivation and test sets) with biopsy-proven MASLD. The key outcome was borderline/definite MASH. Explanatory variables included laboratory parameters, metabolic and clinical comorbidities, and menopausal status/synthetic estrogen use. Numeric variables were treated as continuous or categorical depending on their relationship with the outcome. Sex-stratified multivariable models were developed in the derivation sets using two statistical approaches, logistic and elastic net regression. Optimal models were selected for men and women based on clinical utility and performance in the test sets assessed via area under the receiver operating curve (AUC) and the interaction of sex with model-identified variables assessed. **Results:** Among participants (median age 52 yrs, 72.4% White, 33.5 median BMI, 39.5% and 31.5% with prediabetes/diabetes, 51.3% low alcohol use), 49.9% had significant fibrosis and 57.1% met criteria for MASH. Women were 65.8% postmenopausal; 10.9% reported estrogen use. Model discrimination was strong across sexes: women 0.803–0.804, men 0.794-0.825. For MASH, elevated AST and HbA1c were consistently associated with increased odds in both sexes (TABLE). In women, additional associations were lower platelets, higher GGT, and absence of estrogen therapy at menopause, whereas in men, higher BMI, elevated triglycerides, and low alcohol consumption were additional associations. Interaction testing identified statistically significant interactions for sex with age (p = 0.02), alcohol use (p = 0.005), BMI (p = 0.02), with ALT approaching significant (p = 0.06). **Conclusion:** Unique sex-specific associations with MASH severity were identified, highlighting the importance of studying MASLD through a sex-specific lens inclusive of hormonal influences, both to advance knowledge regarding the pathogenic underpinnings of disease severity as well as developing more effective, personalized approaches to MASH diagnosis and management.

	MASH		
	WOMEN (N=1159)	MEN (N=776)	
	AUC (Derv): 0.803 (0.778-0.827)	AUC (Derv): 0.794 (0.764-0.825)	
	AUC (Test): 0.804 (0.757-0.852)	AUC (Test): 0.825 (0.768-0.882)	
Variable	Odds Ratios*	Odds Ratios*	Sig. sex interaction
HbA1C >6.4% vs ≤6.4%	3.61	2.23	-
HbA1C (5.6-6.4%= prediabetes) vs. not	-	1.47	-
AST [ln (IU/L)], per 1-unit increase	9.30	6.15	-
Age (yrs) , per 1-yr increase	-	1.04	0.02
Alcohol Use Low (≤7/14 drinks/wk) vs. none**	-	0.57	0.005
Triglycerides ≥150 vs. <150 mg/dl	-	1.45	-
HOMA-IR, per 1-unit increase	-	1.03	-
BMI [ln (kg/m^2)], per 1-unit increase	-	6.30	0.02
Platelets [ln (x10^9/mm^3)], per 1-unit increase	0.46	-	-
ALT [ln (IU/L)], per 1-unit increase	0.62	-	0.06
GGT [ln (IU/L)], per 1-unit increase	1.93	-	-
Estrogen use yes vs. no in pre-Menopausal women	1.64	-	-
Estrogen use yes vs. no in postmenopausal women	0.98	-	-

*As elastic net regression is a modeling approach focused on model selection and prediction, rather than inferences, 95% confidence intervals were not produced. **Alcohol use >7/14 drinks/week in women and men were excluded for being outside limits for MASLD.

Disclosures: Norah Terrault: Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, ImmunoCore: Grant/Research Support, HBV Foundation: Board member, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Jennifer Dodge: Nothing to Disclose, Laura Wilson: Nothing to Disclose, Ayako Suzuki: Nothing to Disclose

1467 | IMPACT OF FASTING GLUCOSE CONTROL ON CLINICAL OUTCOMES IN HOSPITALIZED PATIENTS WITH METABOLIC DYSFUNCTION AND ALCOHOL-RELATED LIVER DISEASE (METALD) AND DIABETES MELLITUS

Nariman Hossein-Javaheri[1] Alexander Zhu[1] Meghan Cloutier[1] Anthony Martinez[1], [1]University of Buffalo

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Background: Patients with metabolic dysfunction and alcohol-related liver disease (MetALD) and coexisting diabetes mellitus (DM) are at increased risk of morbidity and mortality, particularly with poorly controlled glycemia. However, optimal inpatient glucose management in this population remains unclear. Current guidelines generally recommend a liberalized glucose target of <180 mg/dL, but whether stricter control improves clinical outcomes has not been studied. **Methods:** In this study, 107 hospitalized patients with MetALD and DM were stratified based on fasting glucose levels ranging from 100–180 mg/dL in 10 mg/dL increments. Baseline characteristics and rates of inpatient complications—including ascites, hepatic encephalopathy, esophageal variceal bleeding (EVB), acute kidney injury (AKI), and infection—were analyzed in relation to fasting glucose levels. Significance was assessed via analysis of variance (ANOVA), with $p<0.05$ considered significant. Data are reported as mean $\pm$ SEM. **Results:** The average patient age was 53 $\pm$ 11.5 years of age, with a mean BMI of 30.3 $\pm$ 8.6 kg/m², daily alcohol use of 302 $\pm$ 39 grams, and a median MELD score of 14 (IQR 8.5–20.5). Patients with glucose levels <140 mg/dL had lower—but not statistically significant—rates of ascites (26.2% vs 41%, $p=0.13$), encephalopathy (35.3% vs 47.6%, $p=0.2$), AKI (26.1% vs 35.7%, $p=0.3$), and infections (26.1% vs 19%, $p=0.4$), though this difference was small and not statistically significant. However, EVB was significantly lower in those with glucose <140 mg/dL compared to higher levels (13.8% vs 33.3%, $p=0.02$). Above 150 mg/dL, the incidence of EVB remained lower but did not reach statistical significance (16.9% vs 30.5%, $p=0.13$). **Conclusion:** Our findings demonstrated that in hospitalized persons with MetALD and DM, a fasting glucose level <140mg/dl was associated with a lower rate of ascites, encephalopathy, and AKI and a significantly lower rate of EVB. Our study suggests maintaining glucose levels <140mg/dl in this patient population may minimize complications. Considering that diabetic patients with advanced liver disease are known to have a propensity toward hypoglycemia due to low glycogen stores and poor ability to liberate stored glucose, maintaining a stricter glycemic control while avoiding hypoglycemia might benefit patients and improve clinical outcomes.

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1468 | RISK OF PYOGENIC LIVER ABSCESS AND ITS CLINICAL COMPLICATIONS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A NATIONWIDE COHORT STUDY

Na Ryung Choi[1] Hanah Lee[2] Hyungmi An[3] Jae Yoon Jeong[4] Hwi Young Kim[5], [1]Ewha Womans University Mokdong Hospital, [2]Department of Internal Medicine, Chung-Ang University Hospital, [3]Department of Statistics and Data Science, Korea National Open University, [4]Department of Internal Medicine, Ewha Womans University Mokdong Hospital, [5]Division of Gastroenterology and Hepatology, University of Nebraska Medical Center

Background: Pyogenic liver abscess (PLA) is a severe infectious disease with significant morbidity and mortality and the incidence of pyogenic liver abscess (PLA) is rising in South Korea. This study investigated the association between metabolic dysfunction-associated liver disease (MASLD) and PLA incidence, as well as the risk of PLA complications. **Methods:** We analyzed data from 2,951,003 adults aged 40–64 years who underwent health examinations between 2009 and 2010, as recorded in the Korean National Health Insurance Service database. Hepatic steatosis was defined as a fatty liver index ≥ 30, and MASLD was identified based on established criteria. Participants were categorized into five mutually exclusive groups: (1) MASLD, (2) MASLD with increased alcohol intake (MetALD), (3) MASLD with other combined etiology, (4) alcohol-associated liver disease with cardiometabolic risk factors (ALD with CMRF), and (5) non-steatotic liver disease (non-SLD). Cox proportional hazards models were used to assess the risk of PLA and its complications. Additionally, changes in MASLD status over a four-year follow-up period were evaluated for their impact on PLA risk. **Results:** Over a median follow-up of 13 years (IQR 13–14), PLA occurred in 3,152 individuals with MASLD (N = 881,466) and 3,169 individuals without any SLD (N = 1,797,978). The incidence rate of PLA was 27.2 vs. 13.3 per 100,000 person-years in the MASLD and non-SLD group, respectively. MASLD was significantly associated with an increased risk of PLA (HR: 1.53, 95% CI: 1.45–1.61) and its complications (HR: 1.72, 95% CI: 1.27–2.33) compared to non-SLD. In the 4-year follow-up analysis, individuals with persistent MASLD had the highest risk of PLA (HR: 1.61, 95% CI: 1.39–1.74), followed by those who MASLD regressed to non-SLD (HR: 1.38, 95% CI: 1.23–1.53) and who developed MASLD during follow-up (HR: 1.27, 95% CI: 1.13–1.43) compared to individuals without any SLD at both baseline and follow-up. Other SLD categories, including MetALD, MASLD with other combined etiologies, and the ALD group, also showed a higher risk of PLA compared to the non-SLD group. **Conclusion:** MASLD was significantly

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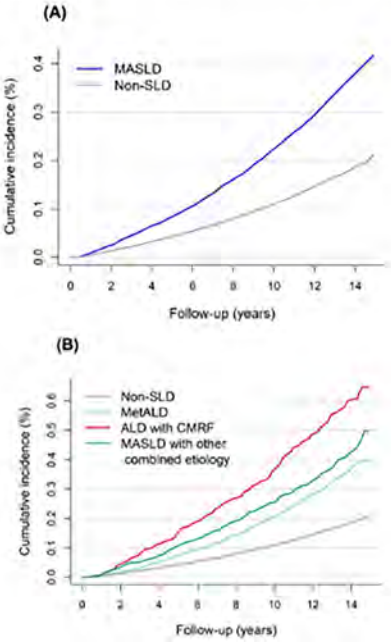
associated with an increased risk of PLA and its complications, with the highest risk observed in individuals with persistent MASLD in a large-scale cohort study using South Korea's National Health Insurance data. Given the global increase in MASLD prevalence, pyogenic liver abscess could be considered as a differential diagnosis in patients presenting with suspected infection.

Cumulative incidence of liver abscess according to the (A) MASLD and (B) SLD stauts.



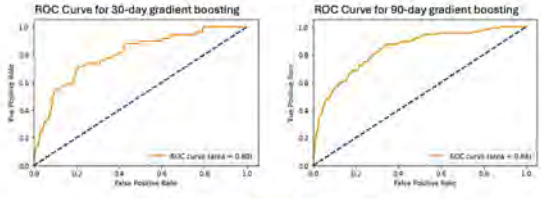
Disclosures: Na Ryung Choi: Nothing to Disclose, Hanah Lee: Nothing to Disclose, Hyungmi An: Nothing to Disclose, Jae Yoon Jeong: Nothing to Disclose, Hwi Young Kim: Nothing to Disclose

1469 | PATIENTS WITH DIABETES AT HIGH RISK OF UNDIAGNOSED ADVANCED LIVER FIBROSIS ARE AT INCREASED RISK OF POSTOPERATIVE MORTALITY AFTER ELECTIVE SURGERY

Christen Ong[1] Chloe Yitian Guo[1] Daniel Yan Zheng Lim[2] Yiying Pei[2] Bochao Jiang[2] Chanda Ho[2] Kevin Kim Jun Teh[2] Yong Mong Bee[3] Hairil Rizal[4] Chee-Kiat Tan[2] George Boon Bee Goh[2], [1]Yong Loo Lin School of Medicine, National University of Singapore, [2]Dept of Gastroenterology and Hepatology, Singapore General Hospital, [3]Dept of Endocrinology, Singapore General Hospital, [4]Dept of Anaesthesiology, Singapore General Hospital

Background: Diabetes mellitus is a common comorbidity in patients undergoing elective surgery and they may have MASLD with advanced fibrosis. It is unknown whether the preoperative FIB-4 score relates to postoperative mortality risk, and whether this risk is well estimated by existing risk models for cirrhotic patients (MELD-Na, VOCAL-Penn). Hence, we evaluated whether a high-risk preoperative FIB-4 score of >2.67 predicts postoperative mortality in diabetic patients without known advanced fibrosis or cirrhosis undergoing elective surgery. In addition, using machine learning (ML) methods, we developed new risk models incorporating FIB-4 score and evaluated them against current mortality risk prediction models. **Methods:** We analyzed 8,437 diabetic patients with FIB-4 scores from the PASAR database, a large perioperative database from a major Asian academic medical center. Median age was 65.00 (IQR 57.00 – 72.00) and 57.67% were males. Logistic regression models evaluated association between high FIB-4 scores and postoperative mortality at 30 and 90 days. Other variables included patient demographics, comorbidities, hepatic steatosis index, organ system undergoing surgery, and operative risk. Further predictive modelling was done using ML models (random forests, gradient boosting, multilayer perceptron). All models were evaluated alongside MELD-Na and VOCAL-Penn scores using the overall cohort, as well as the subgroup of patients with high-risk FIB-4 scores. SHAP analysis was used to identify key predictors in ML models. **Results:** A high-risk FIB-4 score was significantly associated with both 30-day (OR 2.46, 95%CI 1.73–3.48, $p<0.001$) and 90-day postoperative mortality (OR 2.15, 95%CI: 1.65–2.79, $p<0.001$). In the overall cohort, gradient boosting model had the best performance (30-day AUROC: 0.80, 95%CI 0.74–0.86), outperforming MELD-Na (30-day AUROC 0.66, 95%CI 0.56–0.75) and VOCAL-Penn (30-day AUROC 0.59, 95%CI 0.55–0.61). Key independent predictors included FIB-4 score category, hepatic steatosis index and preoperative white blood cell count. In the high FIB-4 subgroup, novel ML models also surpassed MELD-Na and VOCAL-Penn in overall performance. **Conclusion:** A high-risk FIB-4 score is associated with increased 30- and 90-day postoperative mortality in diabetic patients undergoing elective surgery. These patients may benefit from specialist referral for preoperative optimization. As existing risk scores do not perform well in such patients, we propose using novel ML-based risk scores instead.

Figure 1. Comparison and visualization of model performance



Model AUROC for 30-day postoperative mortality

	Logistic Regression	Random Forest	Gradient Boosting	Multilayer Perceptron	MELD-Na	VOCAL-Penn
AUROC	0.72	0.79	0.80	0.76	0.66	0.59

Model AUROC for 90-day postoperative mortality

	Logistic Regression	Random Forest	Gradient Boosting	Multilayer Perceptron	MELD-Na	VOCAL-Penn
AUROC	0.78	0.79	0.84	0.72	0.69	0.64

Highest scoring model for each metric is marked in green.

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1470 | TRANSCRIPTOMIC REGULATION OF E2F1 IN MASLD PROGRESSION IN AFRICAN AMERICANS

Tanmoy Mondal[1] Coleman Smith[2] Christopher Loffredo[3] Ruth Quartey[1] Charles Howell[4] Brent Korba[3] Zaki Sherif[1] Gail Nunlee-Bland[1] Leanna Rucker[5] Gemeyel Moses[1] Somiranjan Ghosh[1], [1]Howard University, [2]Georgetown University Hospital, [3]Georgetown University, [4]Howard University Hospital, [5]MedStar Georgetown University Hospital

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a chronic liver condition characterized by hepatic fat accumulation that can progress to advanced stages of liver disease. The prevalence of MASLD in the US has risen to 30% as of 2023. However, African Americans (AAs) paradoxically exhibit a significantly lower MASLD prevalence (13%) despite higher rates of obesity, Type 2 Diabetes, and hyperlipidemia. This unsolved trend underscores the need to investigate ethnic-specific mechanisms in the underlying susceptibility, heterogeneity, and progression of MASLD. *E2F1*, a key metabolic regulator and fibrogenic marker, modulates fatty acid oxidation and plays a critical role in lipid biosynthesis, including hepatic steatosis. Our preliminary research revealed the dysregulation of *E2F1* pathways in blood samples in AA MASLD patients, suggesting a link to their unique metabolic phenotype. Relying on these findings, our pilot study aims to elucidate the role of *E2F1* in MASLD progression among AAs through transcriptomic and clinical analyses. **Methods:** We collected whole blood from clinically identified MASLD patients and healthy AA cohorts (total n = 24, MASLD n = 16, Control n = 8 with matched age, gender). Participants' sociodemographic and medical histories were recorded. RNA sequencing was performed, followed by Ingenuity Pathway Analysis (IPA) to identify significant pathways and the biofunctions. *E2F1* expression and its regulatory up- and downstream genes, and their expression, were validated by custom TaqMan qRT-PCR Arrays (*E2F* and *TGFB* signaling pathways). **Results:** Transcriptomic analysis in AAs MASLD patients revealed significant (p value < 0.05) downregulation of key *E2F1*-regulated genes, including *CCNA1*, *CDK2*, and multiple HDACs (*HDAC1, HDAC4, HDAC5, and HDAC7*), which are involved in *hepatocyte proliferation*, *chromatin remodeling*, and *fibrogenesis.* Network analysis also indicated the activation of *TP53*, *CDKN2A*, *cyclin E*, and RB complex, suggesting a transcriptional profile that may suppress hepatic fibrosis, hence reflecting a protective regulatory mechanism. **Conclusion:** Our pilot study suggests a unique, possibly protective, E2F1-associated signature in AAs that may contribute to their lower MASLD prevalence despite metabolic risk. These preliminary findings highlight distinct *E2F1*-driven networks that may underlie ethnic differences in MASLD progression, emphasizing the need for further large-scale studies for validation.

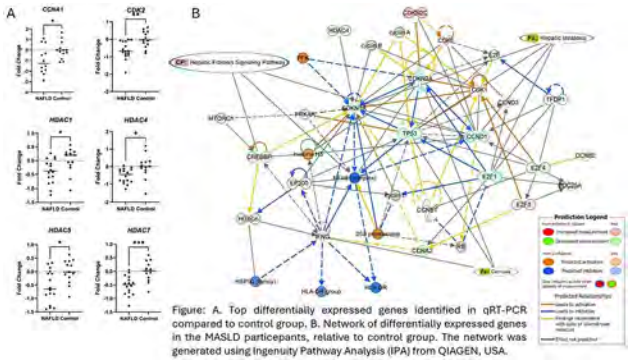

Figure: A. Top differentially expressed genes identified in qRT-PCR compared to control group. B. Network of differentially expressed genes in the MASLD particepants, relative to control group. The network was generated using Ingenuity Pathway Analysis (IPA) from QIAGEN, USA.

Disclosures: Tanmoy Mondal: Nothing to Disclose, Coleman Smith: Nothing to Disclose, Christopher Loffredo: Nothing to Disclose, Ruth Quartey: Nothing to Disclose, Charles Howell: Nothing to Disclose, Brent Korba: Nothing to Disclose, Zaki Sherif: Nothing to Disclose, Gail Nunlee-Bland: Nothing to Disclose, Leanna Rucker: Nothing to Disclose, Gemeyel Moses: Nothing to Disclose, Somiranjan Ghosh: Nothing to Disclose

1471 | CLINICAL, HISTOLOGICAL AND BILE ACIDS PROFILE FEATURES OF LEAN METABOLIC-ASSOCIATED FATTY LIVER DISEASE

Jie Liu[1] Lili Zhao[1] Jia Li[1], [1]Department of Hepatology, Tianjin Second People's Hospital

Background: The incidence rate of (metabolic-associated fatty liver disease) MAFLD is increasingly significant, along with lean MAFLD. Lean MAFLD can also lead to cirrhosis and liver cancer. However, little is known about the clinical, histological and metabolomic features of lean MAFLD patients. **Methods:** Current study enrolled consecutive MAFLD patients and available liver biopsy results. Patients were stratified by body mass index(BMI) into two groups for the comparison of their clinical and histological variables, which included

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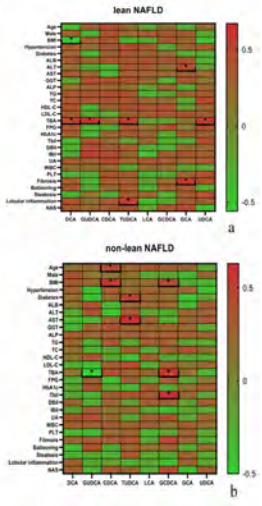
the lean MAFLD group (BMI **Results:** The prevalence rate of lean MAFLD (n = 25) in all MAFLD patients (n = 155) was 16.13%. Patients in the lean group had a significantly lower level of alanine transaminase (ALT), aspartate transaminase (AST), fasting plasma glucose (FPG), Glycosylated Hemoglobin(HbA1c%), uric acid (UA), (non-alcoholic steatohepatitis) NAS as well as pathological fibrosis and lower prevalence of diabetes(P **Conclusion:** Lean MAFLD patients had favorable metabolic and histological profile but higher levels of TBA . The specific bile acids(BAs) distribution of lean MAFLD may be associate with lobular inflammation and mild fibrosis of liver pathology.

	lean-MAFLD(n=25)	non-lean MAFLD (n=130)	P
Fibrosis,n(%)			
F0-1	18 (72%)	57 (43.8%)	
F2-4	7 (28%)	73 (56.2%)	0.01
Ballooning,n(%)			
No	10 (40%)	35 (27%)	0.187
any	15 (60%)	95 (73%)	
Steatosis，n(%)			
S1-2	20 (80%)	98 (75.4%)	0.62
S3	5 (20%)	32 (24.6%)	
Lobular inflammation ,n(%)			
0-1	22 (88%)	96 (73.8%)	
≥2	3 (12%)	34 (26.2%)	0.128
NAS	3±2	4±2	0.002
NAS＞4	7 (28%)	43 (33%)	0.505
LSM	10.4 (6.2, 17.4)	14.6 (7.7, 19.3)	0.024
CAP	296.4±24.3	312.5±30.6	0.285



Disclosures: Jie Liu: Nothing to Disclose, Lili Zhao: Nothing to Disclose, Jia Li: Nothing to Disclose

1472 | THE FADS2 RS174583 RISK ALLELE ALTERS THE HEPATIC PHOSPHOLIPID PROFILE AND CONTRIBUTES TO FIBROSIS PROGRESSION IN MASLD

Shunsuke Ikejima[1] Kazuyoshi Kon[1] Hyeon-Cheol Lee-Okada[2] Kumiko Arai[1] Kyoko Fukuhara[1] Reiko Yaginuma[1] Kei Ishizuka[1] Hiroo Fukada[1] Akira Uchiyama[1] Shunhei Yamashina[1] Takehiko Yokomizo[3] Kenichi Ikejima[1], [1]Juntendo University Graduate School of Medicine, [2]Juntendo University School of Medicne, [3]Juntendo University School of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) develops from a combination of genetic predisposition and acquired factors such as overeating, aging, and physical inactivity. While PNPLA3 single nucleotide polymorphisms (SNPs) are widely known to be associated with MASLD onset, their impact on disease progression remains insufficiently understood. We have previously suggested that SNPs in fatty acid desaturase (FADS) genes may influence the progression of steatohepatitis. In this study, we investigated the association between the risk allele of FADS2 and both intrahepatic lipid composition and fibrosis progression in MASLD. **Methods:** We analyzed 48 patients with biopsy-proven MASLD between January 2021 and September 2024. Patients were divided into two groups: those with non-progressive fibrosis (stage 0–2, n = 32) and those with advanced fibrosis (stage 3–4, n = 16). Genotyping for PNPLA3 (rs738409), MBOAT7 (rs641738), TM6SF2 (rs58542926), FADS1 (rs174556), and FADS2 (rs174583) was performed using TaqMan PCR. Lipidomic analysis of liver tissues from 24 MASLD patients was conducted using LC/MS. **Results:** A higher frequency of PNPLA3 GG and FADS2 TT genotypes—both known as risk alleles—was observed in the progressive group. The combined PNPLA3-GG/FADS2-TT genotype was significantly more frequent in the progressive group than in the non-progressive group (43.8% vs. 12%). Multivariate logistic regression adjusting for age and sex demonstrated that the PNPLA3-GG/FADS2-TT genotype was an independent risk factor for fibrosis progression (odds ratio 7.2). Lipidomic profiling revealed that patients with the FADS2-TT genotype had significantly decreased levels of phosphatidylcholine species containing 16:0/20:3n-9 and 18:0/18:3n-6, as well as lysophosphatidylcholine with sn-2_20:4, compared with those with CC or CT genotypes. Conversely, LPE_sn-1_16:1 was increased in FADS2-TT carriers. Diacylglycerol and triacylglycerol species were unaffected by the FADS2 genotype. Notably, LPE_04_sn-1_16:1 showed a positive correlation with both age and fibrosis stage (r = 0.42 and 0.34, respectively), whereas PC 16:0/20:3n-9 and 18:0/18:3n-6 levels were negatively correlated with the serum branched-chain amino acid to tyrosine ratio (r = –0.32 and –0.31, respectively), a marker of metabolic disturbance in advanced liver disease. **Conclusion:** The FADS2 risk allele promotes MASLD progression via altered hepatic phospholipid composition, characterized by reduced polyunsaturated PC and LPC and increased monounsaturated LPE. These shifts impair membrane function, enhance inflammation, and progress fibrosis. Co-inheritance of FADS2-TT and PNPLA3-GG further increases fibrosis risk, suggesting a synergistic genetic effect. FADS2 polymorphisms contribute to MASLD severity by modulating hepatic lipid profiles, particularly in the presence of PNPLA3 risk alleles.

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1473 | WHERE IS THE MASLD?: THE DIFFICULTY OF IDENTIFYING PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE WITHIN A GLOBAL DATABASE

Taylor Seacor[1] Garrick Gu[1] Anita Krishnarao[2], [1]University of Massachusetts Chan Medical School, [2]UMass Memorial Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most common etiologies of cirrhosis and leading indications for liver transplantation worldwide. The prevalence of MASLD is estimated to be 30-40%, and early diagnosis is necessary to prevent liver disease progression and decompensation. The multi-step diagnostic criteria and the various labels for MASLD have created complexity in identifying these patients within a large clinical database. The purpose of this study is therefore to highlight the innate difficulty of capturing patients with MASLD via database query which hinders our ability to study this patient population and offer therapeutic interventions on a larger scale. **Methods:** We identified adult patients with MASLD using a global de-identified database, TriNetX, consisting of 158 million patients originating from 167 healthcare organizations and 21 countries. ICD-10 coding was then used to evaluate the overall prevalence of MASLD which included ICD codes for fatty liver, hepatic steatosis, MASH, NASH, and NAFLD. We then applied the ICD-10 coding to high risk populations which included patients with type II diabetes mellitus or obesity as defined by a BMI $\geq$ 30. **Results:** Less than 2% of patients had a diagnosis of MASLD when applying ICD-10 coding to the overall database. There was also a lack of MASLD diagnoses among high risk subgroups who had concomitant type 2 diabetes or obesity. Only 7% of patients with underlying type 2 diabetes and only 4% of patients with a BMI $\geq$ 30 were diagnosed with MASLD via ICD-10 coding within the database. We found similar Results: when querying the electronic health record for our multicenter hospital system which revealed a diagnosis of MASLD in less than 1% of the population which includes a liver transplantation center. We were able to identify up to 23% of patients with MASLD in those with concomitant type 2 diabetes and 16% of patients with MASLD in those with BMI $\geq$ 30. **Conclusion:** This study confirms the difficulty of identifying patients with MASLD in a large clinical database. Even when targeting high risk cohorts with a diagnosis of type 2 diabetes or obesity, the prevalence of MASLD diagnoses based on ICD-10 coding remains incredibly low compared to estimates of global disease burden. This issue likely stems from the multi-step diagnostic criteria for MASLD and recently updated terminology. This review emphasizes the need for greater screening and diagnostic efforts, particularly in high risk subgroups, as well as an adoption of consistent ICD coding for MASLD. This would not only promote our ability to perform retrospective studies in this population but would also allow for more effective identification of patients who could benefit from emerging therapies and clinical trial enrollment.

Disclosures: Taylor Seacor: Nothing to Disclose, Garrick Gu: Nothing to Disclose, Anita Krishnarao: Nothing to Disclose

1474 | EXPLORING OPTIMAL GLYCEMIC CONTROL IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND DIABETES: A RETROSPECTIVE PROPENSITY-MATCHED COHORT ANALYSIS

Saad Ahmed[1], [1]Northwell Health NS-LIJ

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is now recognized as the most prevalent liver disease globally, paralleling rising rates of obesity, hypertension, and diabetes. Despite hemoglobin A1c (A1c) being a key diagnostic and predictive marker in MASLD, the optimal A1c target remains unclear. Previous studies in other chronic diseases suggest tighter glycemic control may not always confer survival benefit. This study investigates the association of different A1c targets with liver-related outcomes and mortality in MASLD patients with diabetes. **Methods:** We conducted a retrospective cohort study using the TriNetX U.S. Collaborative Network. Adults $\geq$18 years with a diagnosis of both MASLD and diabetes (2004–2024) were identified (n = 523,912). Two A1c-based cohorts were created: Cohort 1 (A1c $<$6%) and Cohort 2 (A1c 6–7%). After one-to-one propensity score matching on age, sex, race, BMI, hypertension, and hyperlipidemia, 101,678 patients remained in each cohort. Outcomes assessed over five years included new-onset cirrhosis, hepatocellular carcinoma (HCC), and all-cause mortality. Kaplan-Meier survival analyses and risk metrics were calculated. All outcomes were measured over a 5-year follow-up period. Patients with prior diagnosis of the outcome were excluded from each respective analysis. **Results:** After matching, baseline characteristics were well-balanced between Cohort 1 and Cohort 2. Compared to Cohort 2 (HbA1c 6.0-7.0%), Cohort 1 (HbA1c $<$6.0%) had significantly higher risks of developing cirrhosis (5.8% vs 3.6%; RR 1.61, 95% CI 1.55-1.68; HR 1.69, 95% CI 1.62-1.76), HCC (0.8% vs 0.5%; RR 1.58, 95% CI 1.42-1.77; HR 1.67, 95% CI 1.50-1.87), and all-cause mortality (11.9% vs 7.5%; RR 1.58, 95% CI 1.53-1.63; HR 1.67, 95% CI 1.62-1.72). All p-values $<$0.0001. **Conclusion:** In patients with MASLD and diabetes, targeting an A1c of 6–7% was associated with significantly lower rates of cirrhosis, HCC, and all-cause mortality compared to tighter glycemic control (A1c

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< 6%). These findings challenge conventional assumptions favoring stricter glucose targets in this population. Potential explanations include reduced hypoglycemia risk, polypharmacy burden, and the unique metabolic stressors in MASLD. Future prospective studies are warranted to refine glycemic targets and identify optimal therapeutic strategies in MASLD management.

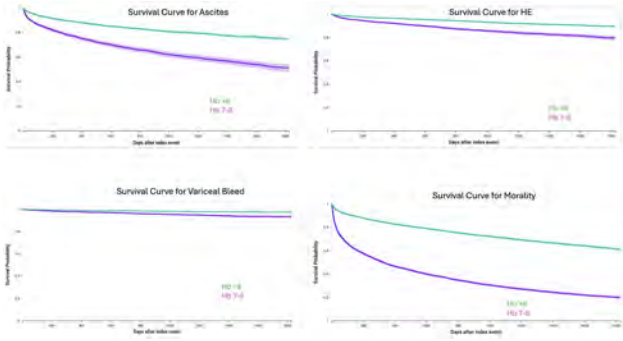
Outcome	Cohort 1 (A1c <6%)	Cohort 2 (A1c 6–7%)	Risk Difference	Risk Ratio (95% CI)	P-value
Cirrhosis	5,377 / 92,540 (5.8%)	3,497 / 96,940 (3.6%)	2.2%	1.611 (1.545–1.679)	<0.0001
Hepatocellular Carcinoma (HCC)	818 / 100,946 (0.8%)	518 / 101,250 (0.5%)	0.3%	1.584 (1.419–1.768)	<0.001
All-Cause Mortality	12,068 / 101,383 (11.9%)	7,642 / 101,444 (7.5%)	4.4%	1.365 (1.295–1.437)	<0.0001

Disclosures: Saad Ahmed: Nothing to Disclose

1475 | HIGHER HEMOGLOBIN TARGETS LINKED TO REDUCED DECOMPENSATION IN PATIENTS WITH CIRRHOSIS AND CORONARY ARTERY DISEASE

Saad Ahmed[1], [1]Northwell Health NS-LIJ

Background: A hemoglobin goal of 8 has been recommended for patients with an acute GI bleed and a history of CAD. Further, numerous studies have explored transfusion goals for patients that are critically ill or have ACS. However, the literature is sparse for hemoglobin goals for patients with a diagnosis of cirrhosis and CAD. This is of interest as patients with cirrhosis are prone to anemia, which can exacerbate disease. Likewise, 30% of patients have both CAD and cirrhosis. Thus, the goal of this project is to compare transfusion goals (7 vs 8) for patients with CAD and cirrhosis in 5 year progression to decompensating events and mortality. **Methods:** This was a retrospective cohort study conducted using the TriNetX database and the US Collaborative Network, which includes healthcare information records from 60 healthcare organizations. Two cohorts were generated for patients with both CAD and cirrhosis: group 1 with hemoglobin goal between 7-8 and group 2 with hemoglobin goal greater than 8. These cohorts were propensity matched to age of diagnosis, sex and race. This generated two cohorts each with 10,977 patients and were examined for risk and Kaplan-Meier analysis. **Results:** At the end of the 5 year period, 1,073 patients in cohort 1 (22.3%) developed ascites compared to 1,170 patients in cohort 2 (15.8%) This corresponded to a risk difference of 0.065% (P = 0.00) and a risk ratio of 1.408 (95% CI 1.307, 1.517). Next, 238 patients in cohort 1 (2.3%) and 189 patients in cohort 2 (1.8%) developed variceal bleeding. The risk difference was 0.05% (p = 0.009) with a risk ratio of 1.285 (95% CI 1.064, 1.553). 686 patients in cohort 1 (7.3%) developed HE compared to 616 in cohort 2 (6%). The risk difference was 1.3% (p = 0.00) and risk ratio was 1.216 (95% CI 1.094, 1.351). Lastly, 6,067 patients in cohort 1 (57.1%) and 2,782 in cohort 2 (25.6%) experienced mortality. Here, the risk difference was 31.5% (p = 0) and a risk ratio of 2.232 (95% CI 0.302, 0.327). **Conclusion:** We found a hemoglobin goal of at least 8 was associated with a lower rate of decompensating events and mortality. This likely is due to improved oxygen carrying capacity and organ perfusion when compared to restrictive transfusions. Greater hemoglobin can mitigate the harmful effects of hyperdynamic circulation, such as increased portal pressures, and improve hepatic decompensation. This is vital for patients with cirrhosis who are prone to hypotension and poor perfusion due to the vasodilatory effects of the disease. Our findings are consistent with the literature as anemia has been noted to be associated with hepatic decompensation. Further, iron supplementation has shown to be beneficial in mitigating the progression of cirrhosis. Ultimately, our study is unique as there have been numerous trials to study transfusion thresholds, but none have included patients with cirrhosis. Further investigation should also be conducted to reveal the mechanism of these results and the effects of different types of anemia.



Disclosures: Saad Ahmed: Nothing to Disclose

1476 | DOACS AND ANTIPLATELETS IN MASLD: ARE WE TARGETING FIBROSIS BY ACCIDENT?

Syeda Najwa Hussain[1] Pinelopi Manousou[1] Maria Kalafateli[1] Michael Yee[1] Mark Thursz[1] Tanya Jayakar[1] Atputhan Kuralarasu[1] Mary Olayiwola[1] Ali Abdul Hussein[1] Azeem Hassan[1], [1]Imperial College London

Background: Emerging evidence suggests anticoagulation therapy, including direct oral anticoagulants (DOACs) and antiplatelet agents, may exert antifibrotic effects in chronic liver disease through inhibition of hepatic stellate cell activation and profibrotic signalling

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pathways. However, data in metabolic dysfunction-associated steatotic liver disease (MASLD) remain limited. Our aim was to explore whether DOAC or antiplatelet therapy influences liver fibrosis severity in patients with MASLD, as a surrogate for potential antifibrotic effects. **Methods:** In a retrospective cross-sectional study of 314 MASLD patients from a single tertiary centre, fibrosis severity was assessed using transient elastography (TE, liver stiffness measurement (LSM) $\geq$ 8 kPa for advanced fibrosis). Patients were stratified by DOAC or antiplatelet use at the time of TE. Patients on DOACs or antiplatelet therapy were compared with a diabetes- and BMI-matched cohort. The proportion of patients with advanced fibrosis and differences in LSM were compared across groups. **Results:** Among 314 patients, 83 (26.4%) received DOACs and 101 (32.2%) received antiplatelet therapy. The proportion of advanced fibrosis was lower in the DOAC group (47.0%) than in the non-DOAC group (58.9%), though not statistically significant ($p = 0.061$). Similarly, the median LSM in DOAC users (7.6 kPa) was lower than in non-DOAC users (9.0 kPa). For antiplatelet users, the proportion of advanced fibrosis (56.4%) was comparable to non-antiplatelet users (55.4%), with no significant difference in median LSM values ($p = 0.882$). Notably, FIB-4 scores were significantly higher in both DOAC ($p = 0.048$) and antiplatelet ($p = 0.017$) groups compared to respective controls, though these differences were likely driven by age, rather than platelet counts. **Conclusion:** This study suggests a potential trend towards reduced fibrosis severity in MASLD patients receiving DOAC therapy, aligning with preclinical data on anticoagulation's antifibrotic effects. Antiplatelet therapy did not demonstrate a similar trend. Randomised clinical trials are needed to clarify the antifibrotic potential of anticoagulation in MASLD and to disentangle the confounding effects of comorbidities.
Disclosures: Syeda Najwa Hussain: Nothing to Disclose, Pinelopi Manousou: Nothing to Disclose, Maria Kalafateli: Nothing to Disclose, Michael Yee: Nothing to Disclose, Mark Thursz: Nothing to Disclose, Tanya Jayakar: Nothing to Disclose, Atputhan Kuralarasu: Nothing to Disclose, Mary Olayiwola: Nothing to Disclose, Ali Abdul Hussein: Nothing to Disclose, Azeem Hassan: Nothing to Disclose

1477 | FATTY LIVER INDEX AS A LONG-TERM PREDICTOR OF METABOLIC DYSFUNCTION: A 10-YEAR FOLLOW-UP IN A JAPANESE POPULATION

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Background: Steatotic liver disease encompasses hepatic fat accumulation and highlights the contribution of coexisting metabolic dysfunction. Fatty liver index (FLI), which is calculated using waist circumference, body mass index, and levels of γ-glutamyl transferase and triglycerides, is a simple surrogate marker for hepatic steatosis. This study aimed to evaluate whether baseline FLI can predict the development of metabolic dysfunctions including diabetes mellitus, dyslipidemia, and hypertension over a 10-year period. **Methods:** We analyzed data from 6,381 Japanese individuals (median age: 54 years [range: 23–83]; 58.1% men) who underwent annual health checkups at our center in both 2008 and 2018. Participants were stratified into FLI quartiles: T1 (0.39–6.09), T2 (6.10–14.41), T3 (14.42–32.30), and T4 (32.31–98.63). Age-adjusted logistic regression was used to calculate odds ratios (ORs) for incident metabolic dysfunction, using T1 as the reference. Receiver operating characteristic analysis was performed to identify optimal FLI cut-off values for predicting each outcome. The incidence of new events was determined based on both electronic medical records and a self-reported questionnaire survey. **Results:** Baseline FLI was significantly higher in men than women (22.7 vs. 7.1, $P < 0.01$). FLI values positively correlated with the number of cardiometabolic risk factors ($P < 0.01$). Over the 10-year follow-up, incident cases included 260 of diabetes mellitus (186 men), 1,181 of dyslipidemia (631 men), and 1,657 of hypertension (1,039 men). Compared with the T1 group, the ORs (95% CI) for incident diabetes mellitus were 1.57 (0.90–2.75) in T2, 3.05 (1.83–5.07) in T3, and 7.30 (4.53–11.80) in T4 group ($P < 0.01$). For dyslipidemia, ORs were 1.50 (1.22–1.83), 1.63 (1.33–1.99), and 2.62 (2.17–3.18); for hypertension, 1.47 (1.21–1.78), 2.13 (1.75–2.60), and 3.74 (3.03–4.63) (all $P < 0.01$). Optimal FLI cut-off values varied by sex: for diabetes mellitus, 23.8 (area under the curve: 0.683) in men and 16.5 (0.738) in women; for dyslipidemia, 25.1 (0.626) in men and 5.15 (0.652) in women; and for hypertension, 16.9 (0.621) in men and 4.43 (0.622) in women. **Conclusion:** Elevated FLI was significantly associated with increased risk of developing metabolic dysfunction over a 10-year period. FLI may serve as a practical and accessible predictor, and sex-specific cut-off values could help tailor screening and prevention strategies for cardiometabolic diseases.
Disclosures: Yoshitaka Arase: Nothing to Disclose, Yusuke Mishima: Nothing to Disclose, Kota Tsuruya: Eisai Co., Ltd.: Speaking and Teaching, Takeda Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, Chugai Pharmaceutical Co., Ltd.: Speaking and Teaching, ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, AbbVie GK: Speaking and Teaching, Tatehiro Kagawa: Nothing to Disclose

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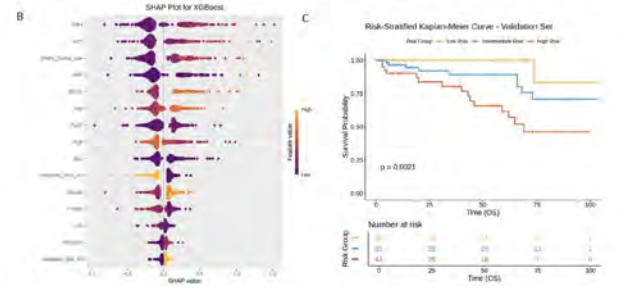
1478 | MACHINE LEARNING-BASED SURVIVAL ANALYSIS AND RISK STRATIFICATION FOR HEPATOCELLULAR CARCINOMA PATIENTS WITH CONCURRENT MASLD UNDERGOING SURGICAL RESECTION

Henry Sheng[1] Chun-Ting Ho[2] Chia-Jung Ho[3] Wei-Yu Kao[4] Yi-Hsiang Huang[3] Teh-la Huo[3] Ming-Chih Hou[3] Jaw-Ching Wu[5] Chien-Wei Su[3], [1]School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, [2]Taipei Veterans General Hospital/NYCU, [3]Taipei Veterans General Hospital, [4]Taipei Medical University Hospital, [5]National Yang Ming Chiao Tung University

Background: To identify prognostic factors for hepatocellular carcinoma (HCC) patients with concurrent metabolic dysfunction-associated steatotic liver disease (MASLD) and to assess the performance of novel machine learning (ML)-based survival analysis models in predicting outcomes and stratifying risk. **Methods:** A total of 478 treatment-naïve HCC patients with MASLD diagnosed at Taipei Veterans General Hospital between 2016 and 2023 were retrospectively analyzed. Patients were randomly divided into a training cohort (n = 336) and a validation cohort (n = 142). Baseline characteristics did not differ significantly between cohorts. The primary endpoint was overall survival (OS). Non-invasive biomarkers and pathological features obtained at diagnosis were involved in a Cox proportional-hazards (COX PH) model as appropriate categorical or continuous covariates to identify independent prognostic factors. Prognostic models were developed in the training cohort using Extreme Gradient Boosting (XGBoost), Random Survival Forest (RSF), Decision Tree (DT), and Logistic Regression (LR). Hyper-parameters were optimized via 5-fold cross-validation by maximizing Harrell's concordance index (C-index) in the training set. Model performance was validated in the validation cohort and compared based on C-index, time-dependent AUROC (td-AUROC), and endpoint-specific predictive accuracy. Shapley Additive Explanations (SHAP) were used to identify key predictors in the ML-based models. Kaplan-Meier (KM) survival analysis was performed to validate the ability of the models to stratify patient risk groups. **Results:** After a median follow-up of 38.0 months (interquartile range 10.0–68.0 months), 50 patients had died, and the 5-year OS rate was 76.9%. Independent risk factors for OS included serum aspartate transaminase (AST), alanine transaminase (ALT), and steatohepatitis status. Among the ML-based models, XGBoost demonstrated the best performance in C-Index = 0.736, td-AUROC : year 1 = 0.811, year 2 = 0.660, year 3 = 0.668, year 4 = 0.765, year 5 = 0.764, predicting OS (AUROC 0.740, 95% CI: 0.636-0.844), outperforming RSF, DT, and LR. SHAP analysis highlighted pathological tumor size, FIB-4 grade, Barcelona Clinic Liver Cancer classification (BCLC), serum AST, and alpha-fetoprotein (AFP) level, as the five most influential variables in the XGBoost model. KM survival analysis confirmed the XGBoost model's robust ability to stratify patients into distinct risk groups in both training and validation cohort (log-rank p = 0.0021). **Conclusion:** ML-based survival analysis, particularly XGBoost, provided accurate prognostic predictions and risk stratification for HCC patients with concurrent MASLD. These tools could support individualized treatment planning and optimize disease management strategies.

A

Model	AUC (95% CI)	C-Index	Accuracy	Precision	Recall	F1-score	P-value
Training dataset							
Random Survival Forest	0.720 (0.648–0.792)	0.718	0.708	0.328	0.655	0.437	<0.001
XGBoost	0.853 (0.801–0.905)	0.845	0.851	0.567	0.586	0.576	0.001
Decision tree	0.695 (0.622–0.768)	0.684	0.782	0.394	0.448	0.419	0.001
Linear regression	0.560 (0.473–0.646)	0.641	0.652	0.252	0.500	0.335	0.16
Validation dataset							
Random Survival Forest	0.726 (0.613–0.838)	0.716	0.669	0.317	0.760	0.447	0.001
XGBoost	0.740 (0.636–0.844)	0.736	0.789	0.419	0.520	0.464	0.001
Decision tree	0.648 (0.531–0.765)	0.608	0.780	0.375	0.360	0.367	0.006
Linear regression	0.431 (0.305–0.557)	0.508	0.312	0.184	0.840	0.302	0.286



Disclosures: Henry Sheng: Nothing to Disclose, Chun-Ting Ho: Nothing to Disclose, Chia-Jung Ho: Nothing to Disclose, Wei-Yu Kao: Nothing to Disclose, Yi-Hsiang Huang: Nothing to Disclose, Teh-la Huo: Nothing to Disclose, Ming-Chih Hou: Nothing to Disclose, Jaw-Ching Wu: Nothing to Disclose, Chien-Wei Su: Nothing to Disclose

1479 | LIPID-RELATED INSULIN RESISTANCE INDICES FOR THE DIAGNOSIS OF NON-ALCOHOLIC FATTY LIVER DISEASE IN CHINESE ADULTS

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Background: The non-invasive evaluation indicators for diagnosing and screening non alcoholic fatty liver disease (NAFLD) remain limited. We aim to analyze the diagnostic efficacy of lipid related insulin resistance markers in NAFLD patients with metabolic abnormalities. **Methods:** A retrospective cohort study was conducted, including NAFLD patients with metabolic abnormalities (NAFLD-MA group), non-NAFLD patients with metabolic abnormalities (Non-NAFLD-MA group), and NAFLD patients without metabolic abnormalities (NAFLD-nonMA group) all underwent liver biopsy. Five indices, namely homeostasis model assessment of

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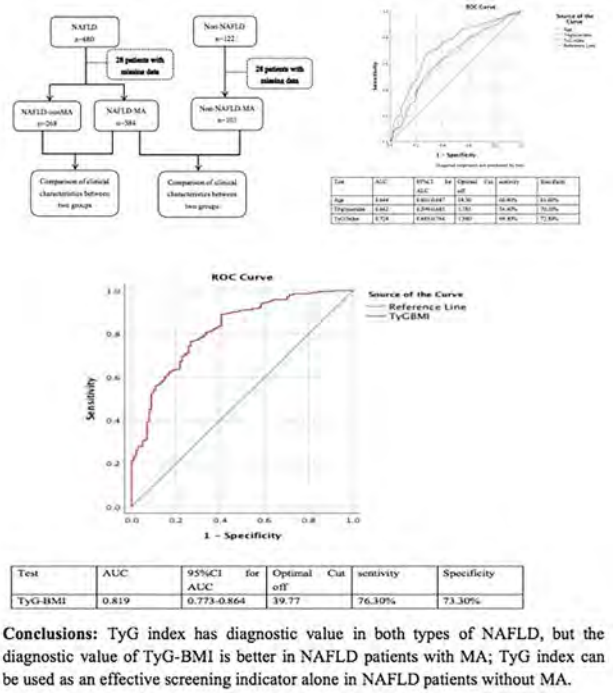
insulin resistance (HOMA-IR), lipid accumulation product (LAP), triglyceride glucose index (TyG), visceral obesity index (VAI), and triglyceride/high-density lipoprotein cholesterol (TG/HDL-C), were analyzed and compared for their relationships with NAFLD based on logistic regression. The area under the curve (AUC) of receiver-operating characteristic (ROC) curve was used to evaluate the diagnostic capability of these indicators for NAFLD. **Results:** In total, 384 NAFLD-MA cases, 101 Non-NAFLD-MA cases, 268 NAFLD-nonMA cases were enrolled. In NAFLD-MA group, BMI, obesity rate, metabolic syndrome rate, glycaemia, triglycerides, ALT, AST, GGT, HOMA-IR, LAP, VAI, TyG index and TG/HDL-C were higher than those in Non-NAFLD-MA group; Logistic regression showed that BMI and TyG index are independent risk factors for NAFLD. ROC curves analysis showed that the AUC was calculated for TyG-BMI 0.819 (95% CI 0.773–0.864), and the optimal cut-off for NAFLD detection was TyG-BMI 39.77 (sensitivity 76.30%; specificity 73.30%). For NAFLD patients with or without metabolic abnormalities, logistic regression analysis showed that Age, Triglycerides, and TyG index were independent risk factors, ROC curves analysis results showed that the AUC was calculated for TyG index 0.724 (95% CI 0.685–0.764) . The optimal cut-off for NAFLD with detection was TyG index 1.580 (sensitivity 69.30%; specificity 72.30%). **Conclusion:** TyG index has diagnostic value in both types of NAFLD, but the diagnostic value of TyG-BMI is better in NAFLD patients with metabolic abnormalities; TyG index can be used as an effective screening indicator alone in NAFLD patients without metabolic abnormalities.



Test	AUC	95%CI for AUC	Optimal Cut off	sentivity	Specificity
TyG-BMI	0.819	0.773-0.864	39.77	76.30%	73.30%

Conclusions: TyG index has diagnostic value in both types of NAFLD, but the diagnostic value of TyG-BMI is better in NAFLD patients with MA; TyG index can be used as an effective screening indicator alone in NAFLD patients without MA.

Disclosures: Weihua Cao: Nothing to Disclose, Yao Xie: Nothing to Disclose, Minghui Li: Nothing to Disclose

1480 | A HEAD-TO-HEAD COMPARISON OF MASLD WITH MAFLD DIAGNOSTIC CRITERIA IN LONGITUDINALLY ESTIMATING THE RISK OF ACUTE CARDIOVASCULAR EVENTS IN STEATOTIC LIVER DISEASE PATIENTS: A REAL-LIFE PRELIMINARY OBSERVATION

Mario Romeo[1] Fiammetta Di Nardo[1] Annachiara Coppola[1] Giuseppina Martinelli[1] Claudio Basile[1] Carmine Napolitano[1] Paolo Vaia[1] Luigi Maria Vitale[1] Alessandro Federico[1] Marcello Dallio[1], [1]University of Campania Luigi Vanvitelli

Background: Two years after the Delphi consensus-proposed revolution in the nomenclature and diagnosis of Steatotic Liver Disease (SLD), the benefits of adopting Metabolic dysfunction-associated steatotic liver disease (MASLD) rather than Metabolic dysfunction-associated fatty liver disease (MAFLD) diagnostic criteria in defining the cardiovascular risk of SLD patients have never been longitudinally evaluated in real-life. We aimed to compare MASLD and MAFLD criteria in estimating the 3-year risk of Acute Cardiovascular Event (ACE) occurrence in not-lean (NL) and lean (L) SLD patients. **Methods:** We retrospectively analyzed the anthropometrical, biochemical, clinical, Liver Stiffness Measurement (LSM), and controlled attenuation parameter (CAP) data stored in the University Hospital (UH)-official Health Documents Digitization Archive of 2136 SLD patients admitted to UH "Luigi Vanvitelli" (period: January 2015- May 2022), and followed up for 3 years. After excluding individuals with incomplete data/other causes justifying SLD, based on baseline Body Mass Index (BMI), patients were subdivided into "L" (BMI <25 kg/m2) (n:224) and "NL" (n:797) and, subsequently, by applying MAFLD and MASLD criteria, in NL-MASLD (n:206), NL-MASLD/MAFLD (n:481), NL-MAFLD (n:110), and L-MASLD (n:69), L-MASLD/MAFLD (n:98), L-MAFLD (n:57) (Figure). The collected ACEs were: Acute Myocardial Infarction, Acute Coronary Syndrome, Ictus cerebri, and Transient Ischemic Attack. **Results:** At baseline, NL- and L-patients with relative groups substantially presented similar features, except for higher Homeostatic-Model-Assessment-for-Insulin-Resistance (HOMA-IR) (p: 0.04) and high-sensitivity-C-reactive protein (hs-CRP) (p: 0.03) in L-SLD. CAP-assessed steatosis severity and LSM-determined fibrosis severity prevalence were not significantly different across the groups, both in NL and L-patients. Longitudinally, compared to MASLD, MAFLD diagnostic criteria better estimated the 3-year risk of ACEs occurrence in NL [HR: 1.316, C.I. 95%: 1.024-

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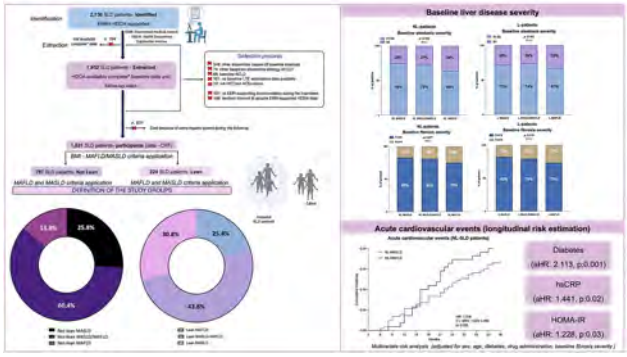
1.495, p:0.025], and not in L [p: 0.071] patients. Multivariate competing risk analysis (adjusted for sex, age, diabetes, drug administration, baseline fibrosis severity) revealed diabetes (aHR: 2.113, C.I. 95%: 1.981-2.434, p: 0.001), hsCRP (aHR: 1.441; C.I. 95%: 1.232-1.775; p: 0.02), and HOMA-IR (aHR: 1.228; C.I. 95%: 1.152-1.893; p: 0.03) as associated with ACE occurrence in NL-MAFLD (Figure). **Conclusion:** MAFLD criteria better estimate the 3-year ACE occurrence risk in NL-SLD patients.



Disclosures: Mario Romeo: Nothing to Disclose, Fiammetta Di Nardo: Nothing to Disclose, Annachiara Coppola: Nothing to Disclose, Giuseppina Martinelli: Nothing to Disclose, Claudio Basile: Nothing to Disclose, Carmine Napolitano: Nothing to Disclose, Paolo Vaia: Nothing to Disclose, Luigi Maria Vitale: Nothing to Disclose, Alessandro Federico: Nothing to Disclose, Marcello Dallio: Nothing to Disclose

◆ 1481 | HOTSPOT MUTATIONS IN TGF-β/SMAD3/4 AND SPTBN1 REVEAL NEW ROLES IN ALCOHOL AND OBESITY INDUCED HCC

Lopa Mishra[1] Puja Ghosh[1] Krishanu Bhowmick[1] Mathew Brandon[1] Bibhuti Mishra[1] Kazufumi Oshiro[2] Lopa Mishra[1], [1]Feinstein Institutes for Medical Research & Cold Spring Harbor Laboratory, [2]Feinstein Institutes for Medical Research

Background: Hepatocellular carcinoma (HCC) continues to rise at an alarming rate in the US and globally. Analyses of human cancers The Cancer Genome Atlas, reveals TGF-β pathway alterations in nearly 40% of HCC and GI cancers (Korkut Cell Systems 2016). Recurrent TGF-β pathway hotspot mutations occur in SMAD3 (R268C), SMAD4 (R360H, G385S, E174fs), and the Smad adaptor SPTBN1 (D1089Y, N32Y). Recently we observed that endogenous toxins such as lipids can modulate TGF-β to generate cancers, and these can be blocked (Cell Reports 2024). We hypothesized that the mutations could provide new insight into how toxins such as alcohol modulate protumorigenic switches in TGF-β signaling. **Methods:** SMAD3 (R268C), SMAD4 (R360H, G385S, E174fs) and SPTBN1 (D1089Y, N32Y) point mutations were introduced using CRISPR/Cas9 gene editing (Phenogenomics), to generate viable mouse models for these. Mice were placed on a normal diet vs a western diet with binge alcohol (GAN diet + 10% glucose + binge alcohol at 4.5 g/kg) for ≥24 weeks. Phenotypic characterization included immunohistochemistry, RNA-seq, co-immunoprecipitation, and metabolomic profiling. **Results:** SMAD3-R268C mice showed resistance to GAN/ethanol-induced obesity and diabetes, SMAD4-R360H mice develop a large liver and colon cancer. SPTBN1-D1089Y mice developed multiple HCCs. Metabolomic profiling showed the following (Supplementary Table 1): Reduced triglyceride levels in SPTBN1 mutant mice. In contrast, SMAD3 models had hypertriglyceridemia, visceral adiposity, and insulin resistance. Enhanced lipolysis was observed in epididymal white adipose tissue (eWAT) from SMAD4 and SPTBN1 mutants, in crosstalk lipolysis. Mechanistic studies confirmed that SPTBN1 mutations impair SMAD3 binding, and SMAD3/4 mutations disrupt oligomerization, leading to altered TGF-β transcriptional outputs, including suppression of key targets such as PAI-1, COL1A1, SNAIL1, P21, and P15—fostering metabolic dysregulation, fibrosis, and oncogenesis. **Conclusion:** Our approach reveals that pathogenic variants of SMAD3, SMAD4, and SPTBN1 differentially impact TGF-β signaling, metabolic homeostasis, and liver tumorigenesis. These findings provide mechanistic insight into the pathogenesis of alcohol induced MASH and HCC and may inform future therapeutic strategies targeting the SPTBN1-SMAD3/4 axis in liver disease.

Table 1: Metabolomic profiling of Phenogenomic mice

	WT	SMAD3$^{R268C/+}$	SMAD4$^{R360H/+}$	SPTBN1$^{D1089Y/+}$	SPTBN1$^{N32Y/+}$
Body Weight	44g	45g	51g	38 g	42g
Glucose Level	264 mg/dL	117mg/dL	283mg/dL	246 mg/dL	200mg/dL
Cholesterol	241 mg/dL	193 mg/dL	242 mg/dL	173 mg/dL	251 mg/dL
HDL	>120 mg/dL	>120 mg/dL	>120 mg/dL	>120 mg/dL	>120 mg/dL
Triglycerides	68 mg/dL	76mg/dL	78mg/dL	68 mg/dL	61mg/dL
Liver	3.1g (7%)	3.38g (7.5%)	3.88g (7.4%)	2.64g (6.94%)	2.77g (6.6%)
WAT	2.73g (6.2%)	1.28g (2.8%)	2.94g (5.7%)	2.74 g (7.2%)	2.73g (6.5%)

Disclosures: Lopa Mishra: Nothing to Disclose, Nothing to Disclose, Puja Ghosh: Nothing to Disclose, Krishanu Bhowmick: Nothing to Disclose, Mathew Brandon: Nothing to Disclose, Bibhuti Mishra: Nothing to Disclose, Kazufumi Oshiro: Nothing to Disclose, Lopa Mishra: Nothing to Disclose, Nothing to Disclose

◆ 1482 | UNDERSTANDING ICU STAYS IN ALCOHOL-ASSOCIATED LIVER DISEASE: BRIDGING DISEASE-SPECIFIC MODELING AND CLINICAL KNOWLEDGE

Sue Hyon Kim[1] Jiyoun Song[1] Sang Bin You[1] Se Hee Min[1] Marina Serper[2], [1]University of Pennsylvania, [2]University of Pennsylvania Health System

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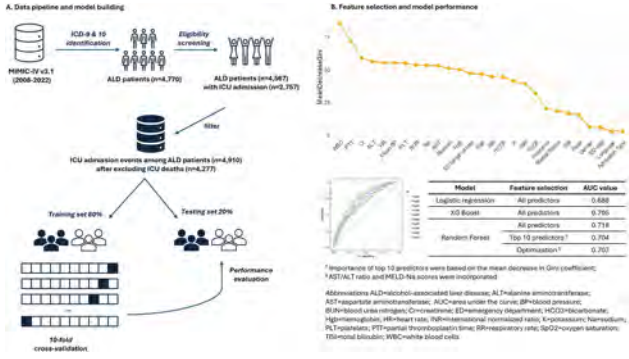
Background: Decompensated alcohol-associated liver disease (ALD) is marked by severe systemic manifestations often requiring critical care. Prior machine learning (ML) studies predicting ICU length of stay (LOS) have overlooked sociodemographic and ALD-specific factors, leaving a gap in understanding the full scope of ICU stays for patients with ALD. We compared different ML algorithms to determine the optimal model for predicting ICU LOS among this population, emphasizing disease-specific features for model optimization and interpretation. **Methods:** We used the MIMIC-IV database of 4,277 ICU admissions for ALD patients after excluding ICU deaths. To simplify patient deterioration predictions and resource management decisions, we defined a binary outcome of an extended ICU stay ($\geq$4 days) based on clinical and financial benchmarks. Per our intended use case, we included readily available features for prompt care planning and resource allocation following ICU admission. Three ML algorithms—logistic regression, Random Forest (RF), and Extreme Gradient Boosting—underwent cross-validation and testing. Feature importance analysis and model optimization were performed to achieve optimal balance between accuracy and practical utility. **Results:** Mean LOS was 3.4 ± 5.6days, with 24.9% exceeding 4 days. More than 70% of ALD patients were White males in their 50s. RF demonstrated the best performance for predicting extended ICU stays (AUC = 0.718). Reducing features to top 10 key predictors enhanced model interpretability but compromised performance (AUC = 0.704). Subsequent optimization using disease-specific features, such as MELD-Na scores and AST/ALT ratios, slightly improved performance (AUC = 0.707). While mean blood pressure and heart rate were key predictors consistent with other patient populations, our model underscored ALD-specific variables, such as liver enzymes (ALT, AST), ascites-related infection and electrolyte imbalances (WBC, sodium), coagulation dysfunction (PTT, PLT), and hepatorenal syndrome measures (Cr, BUN). **Conclusion:** Our model successfully classified extended ICU stays by integrating ALD-specific features. The development process of our model lays a foundation for creating predictive models tailored to ALD, which can support proactive planning, reduce caregiver uncertainty, and optimize resource allocation in the early stages of ICU admission. Future studies should expand on our approach to incorporate additional subtle features and test them in a demographically diverse sample of ALD patients.



Disclosures: Sue Hyon Kim: Nothing to Disclose, Jiyoun Song: Nothing to Disclose, Sang Bin You: Nothing to Disclose, Se Hee Min: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Eurofins: Grant/Research Support

1483 | ◆ ALCOHOL-INDUCED PHENOTYPIC CHANGES IN LYMPHATIC ENDOTHELIAL CELLS DRIVE TH17-MEDIATED LIVER INFLAMMATION

Young-Ri Shim[1] Yilin Yang[1] Jain Jeong[1] Matthew McConnell[1] Teruo Utsumi[1] Yasuko Iwakiri[1], [1]Yale University

Background: Alcohol-associated hepatitis (AH) involves severe inflammation and immune dysregulation. The lymphatic system modulates immune cell activity and resolves inflammation by regulating immune cell trafficking via lymphatic endothelial cells (LyECs), which secrete chemokines and cytokines. However, how ethanol affects LyEC-immune cell crosstalk remains unknown. We hypothesize that ethanol reprograms LyECs toward a dysfunctional, pro-inflammatory phenotype, enhancing immune cell recruitment and Th17 differentiation, thereby exacerbating AH. **Methods:** Mice were fed a 5% ethanol-containing Lieber-DeCarli diet for 10 days, followed by a single ethanol binge (5 g/kg; NIAAA model). Human primary hepatic and dermal LyECs were treated with 100 mM ethanol and co-cultured with peripheral blood mononuclear cells (PBMCs) from healthy donors to assess immune cell profiles by flow cytometry. To validate these findings in human disease, we analyzed a single-cell RNA-seq (scRNA-seq) dataset (GSE136103 **Results:** In ethanol-fed mice, $CD3^+$ T cells were enriched around LyECs and increased 1.43-fold ($p < 0.05$), showing

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a significant correlation with lymphatic vessel density ($r^2 = 0.61$, $p < 0.0001$), suggesting enhanced LyEC-T cell interactions. Ethanol exposure also upregulated several chemokines in LyECs ($p < 0.05$), including CXCL10 (3.7-fold), CCL2 (2.4-fold), and CCL21 (4-fold), all of which are known to attract immune cells. In co-culture assays, ethanol-treated LyECs increased the migration of $CD4^+$ T cells and monocytes expressing CXCR3 and CCR7 (1.42- and 1.38-fold, respectively; $p < 0.01$), but not neutrophils, $CD8^+$ T cells, or B cells, indicating selective recruitment. Recruited $CD4^+$ T cells also exhibited higher CXCR3 expression compared to controls ($p < 0.05$), highlighting an enhanced CXCL10–CXCR3 axis. Furthermore, ethanol-treated LyECs promoted Th17 differentiation with a 31% increase ($p < 0.05$), accompanied by elevated expression of Th17-polarizing cytokines, including IL6, TGFB1, IL1B, and IL23A (1.9–2.1-fold; $p < 0.05$). These findings further suggest that ethanol reprograms LyECs to promote inflammatory T cell responses. Consistently, scRNA-seq analysis of liver tissue from alcoholic cirrhosis patients confirmed an expanded population of Th17 cells ($IL17A^+CXCR3^+CD4^+$). Mechanistically, ethanol activated PI3K/Akt signaling, increasing phospho-Akt 3-fold ($p < 0.01$). PI3K inhibition with wortmannin suppressed chemokine expression by >50% and reduced T-cell CXCR3 by 20% (both $p < 0.01$). **Conclusion:** Ethanol drives LyEC reprogramming through PI3K/Akt activation, enhancing the expression of chemokines and Th17-promoting cytokines. This leads to increased $CD4^+$ T cell recruitment and Th17 differentiation, thereby exacerbating AH. These findings uncover a previously unrecognized role for LyECs in promoting immune dysregulation in alcohol-associated liver disease.

Disclosures: Young-Ri Shim: Nothing to Disclose, Yilin Yang: Nothing to Disclose, Jain Jeong: Nothing to Disclose, Matthew McConnell: Nothing to Disclose, Teruo Utsumi: Nothing to Disclose, Yasuko Iwakiri: Nothing to Disclose

1484 | ◆ PHOSPHATIDYLETHANOL TESTING: REAL-WORLD PATTERNS, DEMOGRAPHIC AND CLINICAL CORRELATES

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Background: Phosphatidylethanol (PEth) is a widely used biomarker for alcohol use, but interpretation may vary by patient factors and the clinical relevance of current cutoffs is uncertain. We examined the distribution of PEth values across a large healthcare network and the associations between PEth and demographics, lab markers, clinical outcomes, and self-reported alcohol use. **Methods:** We conducted a retrospective cohort study of 4,892 adults with ³1 PEth 16:0/18:1 result from January 2022-August 2024 within the Mass General Brigham system. Linear regression assessed associations between PEth and demographic characteristics, AST, LDL, A1c, hospital encounters, length of stay, and self-reported alcohol use. **Results:** 60% of patients had negative PEth (<20 ng/mL). Among positives, the median was 251 ng/mL. Among those, 18% had moderate (20–200 ng/mL) and 22% heavy (>200 ng/mL) alcohol use (Figure 1A). PEth was directly associated with AST ($\beta = 2.75$, $p < .001$) and inversely with age ($\beta = -5.98$, $p < .001$), BMI ($\beta = -5.58$, $p = .019$), and income ($\beta = -0.0009$, $p = .010$). Black patients had higher PEth than White patients ($\beta = 286.23$, $p < .001$). No differences by gender were observed (Figure 1B). Compared to those with a negative PEth result, those in PEth quartiles 1 or 2 had a similar number of encounters ($\beta = 0.30$, $p = .25$), while those in quartiles 3 or 4 had significantly more hospital encounters ($\beta = 2.21$, $p < .001$). Compared to patients with negative PEth, those in PEth quartiles 2 ($\beta = -2.02$, $p = .023$), 3 ($\beta = -3.41$, $p < .001$), and 4 ($\beta = -5.12$, $p < .001$) had shorter average lengths of stay. PEth did not correlate well with self-reported alcohol intake, and 31% of patients with positive PEth reported no alcohol use. In each quartile, the mean self-reported drinks per week were 5.6, 6.3, 7.8, 13.0 and 20.8, for negative, Q1 (20-79ng/mL), Q2 (80-251ng/mL), Q3 (252-710ng/mL), and Q4 (>710ng/mL), respectively (Figure 1C). Less than 3% of the variation in PEth was explained by self-reported drinks per week ($R = .15$, $p < .001$). When we included an interaction term for sex, we found that the relationship between PEth and self-reported alcohol use was weaker for females compared to males ($p = .018$) (Figure 1D). **Conclusion:** In a real-world population, PEth values were substantively higher than has previously been reported. We identified several key demographic associations, notably a decline with increasing age, and, concordant with current epidemiology, we found that PEth values in women were similar to men. Self-reported alcohol use poorly predicted PEth values in all groups, with a weaker correlation in women, suggesting that women are even less likely to accurately self-report alcohol intake. Taken together, the demographic disparities and limited agreement with self-report suggest PEth may better detect unhealthy alcohol use and reveal unmet care needs.

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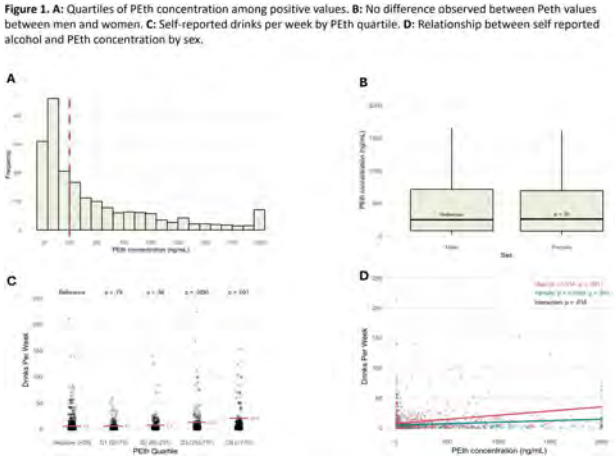

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◆ 1485 | OPTIMAL CORTICOSTEROID USE TO MITIGATE MORTALITY AND INFECTION IN PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS: LESS IS MORE

Abdelhaleem Sideeg[1] Mahima Tyagi[2] Fatima Elmustafa[3] Nimish Thakral[4] Mangesh Pagadala[5] Mohamed Elfeki[6] Winston Dunn[7] Ashwani Singal[2], [1]Virginia Mason Medical Center, [2]University of Louisville, [3]Henry Ford Hospital System, [4]University of Kentucky Medical Center, [5]Liver Institute -Methodist Dallas Medical Center, [6]University of South Dakota Sanford School of Medicine, [7]University of Kansas Medical Center

Background: Lille score is a validated tool to assess response to treatment and guide corticosteroid (aCS) use in severe alcohol-associated hepatitis (AH). However, its use in clinical trials has been inconsistent. We conducted a meta-analysis to compare mortality and infection outcomes in trials using Lille-guided CS therapy vs. those not guided by Lille score. **Methods:** Randomized controlled trials (RCTs) since the introduction of Lille score in 2007 and using CS in at least one arm were analyzed. Pooled data on mortality and infection (at 28, 90, and 180 d) are reported as odds ratios (OR) with 95% confidence intervals (CI). **Results:** A total of 21 steroid-treated arms from 12 trials (n = 2077) were included in this analysis. Of these, 2 studies used Lille score to guide treatment (n = 327), of which one study compared fixed vs. tapered CS regimen. Compared to patients receiving CS guided by Lille score, the mortality was higher in CS exposed group not guided by Lille score by about 5.2, 1.8, and 2.0 folds at 28, 90, and 180 d respectively (Table 1). However, the infection rates were similar at all the time points. 90-d infection rate was lower when comparing a) responders vs. non-responders with Lille guided CS use (23.3 vs. 40%), OR (95% CI): 0.46 (0.25-0.82), P = 0.009; b) non-Lille guided CS use vs. non-responders with Lille guided use (17.3 vs. 40%), 0.52 (0.31-0.87), P = 0.013; and c) tapered (10 mg per week) vs. fixed dose for 3 weeks in responders with Lille guided CS use (19.7 vs. 33.3%), 0.50 (0.28-0.88), P < 0.001. **Conclusion:** Lille-guided corticosteroid use in severe alcohol-associated hepatitis is associated with lower 28-day, 90-day, and 180-day mortality as compared to fixed 28-d of treatment. After one week of treatment in clinical care and trials, corticosteroids should be stopped in non-responders and tapered over 3 weeks (10 mg per week) in responders to mitigate the infection risk.

Table 1 Mortality and infection rate at 28, 90, and 180-d comparing two studies with Lille guided use of corticosteroids (CS) with 10 studies using CS not guided by Lille score.

	Lille guided CS use Event rate (95% CI)	Not guided by Lille Event rate (95% CI)	OR (95% CI)
28-d death	2.7 (0.7-10.3)	17.1 (14.4-20.1)	5.17 (1.26-21.26). P<0.001
90-d death	16 (13-19.6)	39.5 (27.4-53.1)	1.75 (1.26-2.44), P<0.001
180-d death	27 (21.5-33.3)	40.9 (34.0-48.3)	1.96 (1.09-3.50), P=0.023
28-d infection	12.6 (9.0-17.3)	18.1 (11.8-26.7)	0.88 (0.55-1.23), P=0.339
90-d infection	26.4 (21.3-32.1) [N=1]	22.1 (18.9-25.8) [N=1]	0.84 (0.60-1.17), P=0.308
180-d infection	18.1 (13.6-23.9) [N=1]	34.3 (24.4-45.8) [N=5]	1.16 (0.69-1.97), P=0.574

Disclosures: Abdelhaleem Sideeg: Nothing to Disclose, Mahima Tyagi: Nothing to Disclose, Fatima Elmustafa: Nothing to Disclose, Nimish Thakral: Nothing to Disclose, Mangesh Pagadala: Nothing to Disclose, Mohamed Elfeki: Nothing to Disclose, Winston Dunn: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, GSK: Grant/Research Support, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, Avera Medical Group: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other

◆ 1486 | NATURAL HISTORY OF HISTOLOGIC ALCOHOL-ASSOCIATED HEPATITIS: A MULTI-CENTER ANALYSIS OF 128 EXPLANTS FROM EARLY LIVER TRANSPLANTATION

Brian Lee[1] Dana Balitzer[2] David Kleiner[3] Jennifer Dodge[4] John Rice[5] George Therapondos[6] Neha Jakhete[7] Hyosun Han[4] R. Mark Ghobrial[8] Christine

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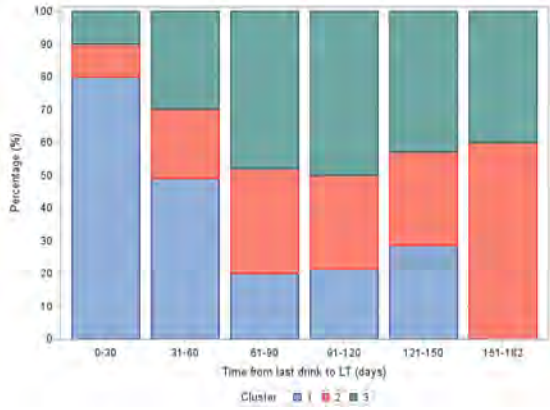
Hsu[9] Sheila Eswaran[10] Haripriya Maddur[11] Kirti Shetty[12] Neil Mehta[13] Michael Lucey[5] Ryan Gill[13] Norah Terrault[4], [1]Keck School of Medicine, [2]UCSF, [3]National Cancer Institute, Bethesda, [4]University of Southern California, [5]University of Wisconsin, [6]Ochsner Clinic, [7]University of Maryland, [8]Houston Methodist JC Walter Transplant Center, [9]National Institute of Diabetes, Digestive, [10]Rush University Medical Center, [11]College of Medicine Tucson, [12]University of Maryland, Baltimore, [13]University of California, San Francisco

Background: The natural history of alcohol-associated hepatitis (AH) by histopathology is not well-understood, due to the impracticality of repeat liver biopsies in this patient population. Using liver explants from patients undergoing early (i.e. less than 6 months from last alcohol consumption) liver transplantation for AH, combined with drinking history, we sought to identify novel histologic subgroups and assess their association with time from last alcohol consumption. **Methods:** Adults who underwent liver transplantation for AH between 2007-2019 among 9 ACCELERATE-AH sites were included. Histologic features from representative liver explant slides were assessed for consensus by 3 expert pathologists. Hierarchical cluster analysis (Gower's distance with partitioning around medoids) was used to identify histologic subgroups based on histologic features only: steatohepatitis (macrosteatosis grade, neutrophilic infiltration, Mallory-denk bodies, ballooned hepatocytes), fibrosis (Laennec stage, extent of pericellular fibrosis, presence of evolving fibrosis), bilirubinostasis, ductular reaction (CK7), and regeneration (EpCAM). Missing histology data were imputed by chained random forests. After histologic features were identified, the association of time from last alcohol consumption for each cluster was then assessed by linear regression. **Results:** Among 128 patients (70% male, median MELD at transplant of 39, median time from last alcohol consumption of 51 days), we identified 3 distinct histologic clusters (Cluster 1: n = 54; Cluster 2: n = 31; Cluster: n = 43). All clusters had similar demographic and clinical characteristics (e.g. age, sex, MELD score, pre-transplant steroid treatment). Cluster 1 had the most dominant features of steatohepatitis (26 vs. 13 vs. 12% for grade 3 macrosteatosis; 68 vs. 19 vs. 16% marked neutrophil infiltration), and least for fibrosis (6 vs. 32 vs. 33% with stage 4C fibrosis), bilirubinostasis (22 vs. 60 vs. 61% with extensive bilirubinostasis), and regeneration vs. Clusters 2 and 3. Cluster 2 (vs. Cluster 3) had predominance of ballooned hepatocytes (100 vs. 0%) and Mallory-Denk bodies (97 vs. 51%), but otherwise had similar features of macrosteatosis, bilirubinostasis, fibrosis and regeneration. All clusters had a similar degree of ductular reaction. Cluster 1 (mean of 47 [95%CI 37-56] days) was associated with the shortest interval from last alcohol consumption vs. Cluster 2 (mean of 76 [95%CI 63-89] days) and Cluster 3 (75 [95%CI 64-85] days) (Figure). **Conclusion:** Time from last alcohol consumption was associated with distinct clustering of histologic features, providing a view of the natural history of histologic AH. These results suggest that steatohepatitis may resolve and fibrosis evolve faster than previously thought for patients with severe AH. These results can inform clinical practice and trial design.

FIGURE. Percentage of patients (y-axis) vs. time from last alcohol consumption (x-axis) among 3 histologic clusters



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◆ 1487 | INCREASING RATES OF PHARMACOTHERAPY PRESCRIPTIONS FOR ALCOHOL USE DISORDER AFTER LIVER TRANSPLANTATION: AN ANALYSIS OF EPIC COSMOS DATA

Oren Fix[1] Hersh Shroff[2] Sasha Deutsch-Link[2], [1]University of North Carolina at Chapel Hill, [2]UNC Chapel Hill

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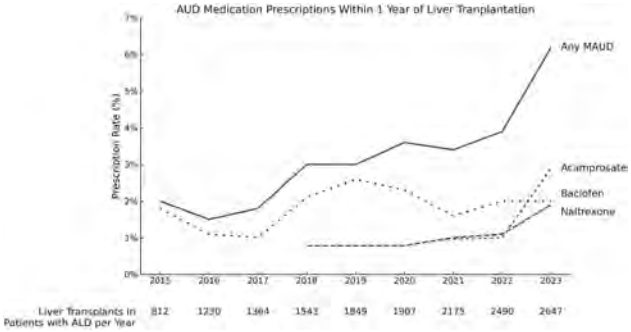
Background: Pharmacotherapy for patients with alcohol use disorder (AUD) has been shown to increase abstinence and complement psychosocial treatments for relapse prevention; however, most gastroenterologists and hepatologists are uncomfortable prescribing medications for AUD (MAUD) in patients with alcohol-associated liver disease (ALD). Data on MAUD after liver transplantation (LT) are extremely limited. **Methods:** We conducted a retrospective study using deidentified patient data from Epic Cosmos, a dataset created in collaboration with a community of Epic health systems representing 300 million patient records from over 1700 hospitals and 40,000 clinics. Inclusion criteria were LT recipients 18 years or older transplanted in the US between 1/1/2015 and 12/31/2023 with a diagnosis of ALD (ICD-10-CM K70.xx). The primary indication for LT is not available in Cosmos, which limited our ability to confirm that ALD was the primary indication for LT. We included results of ethanol biomarkers (phosphatidylethanol, urine ethyl glucuronide, serum ethanol) any time after LT and MAUD prescriptions (baclofen, naltrexone, acamprosate) within 1 year after LT. Linear regression was used to assess trends in MAUD prescriptions over time. **Results:** 17,975 patients were included in the study cohort (representing 56% of all US liver transplants during the period). Average age was 54 $\pm$11 years at the time of LT and 31% were female. 72% had a documented concomitant diagnosis of an alcohol-related disorder (ICD-10-CM F10.xx). Of 6,168 (34%) patients with an available ethanol biomarker test, 913 (15% of available tests) were positive for an ethanol metabolite. During the study period, 3.4% of patients were prescribed a MAUD within 1 year after LT (1.9% baclofen, 0.84% naltrexone, 0.85% acamprosate). MAUD prescriptions increased significantly during the study period, from 16 (2.0% of LT recipients) in 2015 to 164 (6.2%) in 2023 ($P = .001$) (see Figure). Baclofen prescriptions increased from 1.8% in 2015 to 2.0% in 2023 ($P = .255$). Naltrexone increased from 0.8% in 2018 to 1.9% in 2023 ($P = .093$). Acamprosate increased from 1.0% in 2021 to 2.9% in 2023 ($P = .324$). Data for naltrexone before 2018 and acamprosate before 2021 are unavailable because of small numbers. **Conclusion:** Despite proven efficacy, rates of MAUD prescriptions in LT recipients with a history of ALD remain low. However, overall MAUD prescriptions increased significantly during the study period. Statistically significant trends in individual medications were not observed, likely due to low numbers of prescriptions. The increasing rates of MAUD prescriptions may reflect increased provider awareness and comfort with AUD pharmacotherapy in LT recipients.



Disclosures: Oren Fix: Nothing to Disclose, Hersh Shroff: Nothing to Disclose, Sasha Deutsch-Link: Nothing to Disclose

◆ 1488 | SEX-SPECIFIC RISK THRESHOLDS OF BINGE DRINKING FREQUENCY FOR ADVANCED FIBROSIS IN THE UNITED STATES

Winston Dunn[1] Juan Pablo Arab[2] Luis Antonio Diaz[3] Ashwani Singal[4] Marco Arrese[5] Naim Alkhouri[6], [1]University of Kansas Medical Center, [2]Virginia Commonwealth University, [3]University of California San Diego, [4]University of Louisville, [5]Pontificia Universidad Catolica de Chile School of Medicine in Santiago, [6]Summit Clinical Research

Background: The 2023 steatotic liver disease (SLD) nomenclature has defined metabolic dysfunction-associated alcohol-related liver disease (MetALD) and alcohol-associated liver disease (ALD) based on average daily alcohol intake. However, binge drinking patterns have not yet been incorporated into these definitions. We aimed to assess the relationships between the frequency of binge drinking and advanced fibrosis using nationally representative data. **Methods:** We included adults ($\geq$18 years) from the NHANES 1999–2020 cohort, excluding individuals with viral hepatitis. Alcohol intake was assessed through standardized questionnaires, capturing both average daily drinking and the frequency of binge drinking in the past year (defined as $\geq$4 drinks for women and $\geq$5 drinks for men on a single occasion). Advanced fibrosis was defined as FIB-4 $\geq$2.67. We first quantified the association between MetALD and ALD-level average daily drinking and advanced fibrosis, adjusting for demographic and metabolic risk factors. We then scanned the full range of binge drinking frequency to identify cutpoints that produced comparable adjusted odds ratios for advanced fibrosis. **Results:** Among 43447 eligible participants, 770 men (2.4%) and 559 women (1.8%) had advanced fibrosis. The adjusted odds ratio of MetALD-level daily drinking (2.50, 95% CI:

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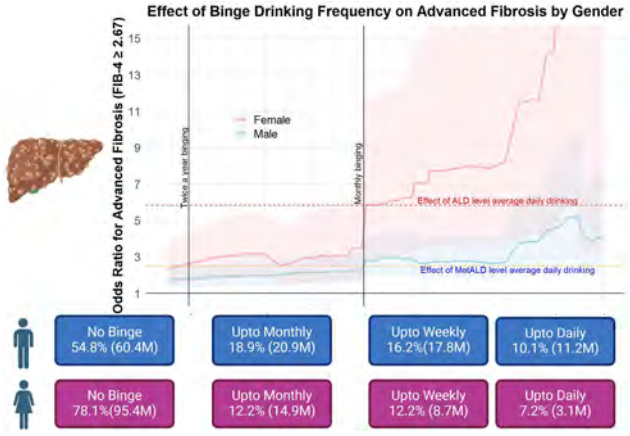
1.76–3.50) and ALD-level daily drinking for advanced fibrosis (5.82, 95% CI: 3.27–10.3) were used as reference. A total of 8,486 men (45.4%, representing 50.3 million U.S. adults) and 4,471 women (22.0%, representing 26.8 million) reported some level of binge drinking (Figure). Among women binge drinking as infrequently as twice per year conferred a risk equivalent to MetALD-level daily drinking, while monthly bingeing matched the risk of ALD-level daily drinking (Figure). Beyond monthly frequency, the risk increased exponentially. Men exhibited a higher threshold for harm: monthly bingeing approximated the risk of MetALD-level daily drinking, while daily bingeing approached the risk seen with ALD-level daily drinking (Figure). **Conclusion:** The risk of advanced fibrosis due to binge drinking differs substantially between sexes. Women face elevated risk even at low binge frequencies—comparable to the risk from MetALD-level daily drinking—whereas men require more frequent binge patterns to reach comparable risk. These findings support a sex-specific approach to MetALD and ALD definitions and highlight the need to incorporate binge drinking frequency into clinical risk stratification and public health messaging.



Disclosures: Winston Dunn: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Luis Antonio Diaz: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, GSK: Grant/Research Support, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, Avera Medical Group: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other, Marco Arrese: Nothing to Disclose, Naim Alkhouri: Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Boston Pharma: Grant/Research Support

◆ 1489 | THE GUT MICROBIOTA FINGERPRINT OF SEVERE ALCOHOLIC LIVER DISEASE: FROM SPECIES-LEVEL CHARACTERISTICS TO A DIAGNOSTIC MODEL FOR SAH

Yifan Xu[1] Song Yang[1] HUICHUN XING[1], [1]Beijing Ditan Hospital,Capital Medical University

Background: Patients with alcohol-related liver diseases exhibit intestinal microbiota dysbiosis, which becomes progressively more pronounced as the severity of the disease escalates. In the present study, patients with alcohol-related liver diseases at varying stages of disease progression were recruited. Additionally, potential species associated with the disease were further explored, and specific parameters reflecting intestinal microbiota dysbiosis in alcohol-related liver diseases were established, thereby providing novel insights for clinical diagnosis and therapeutic strategies. **Methods:** This study adopted a case-control design, enrolling healthy individuals (Healthy control, HC) as the control group. The intestinal microbiota profiles of patients with alcohol-related liver cirrhosis (ALC) were systematically analyzed. Furthermore, ALC patients were categorized into two subgroups: non-severe alcoholic hepatitis (NSAH) and severe alcoholic hepatitis (SAH), based on the severity of their alcoholic hepatitis. The differences in microbiota composition between the NSAH and SAH groups, as well as their associations with clinical parameters, were comprehensively evaluated. **Results:** Significant alterations in the intestinal microbiota are observed in patients with ALC. At the genus level, the abundance of *Streptococcus*, *Lactobacillus*, *Veillonella*, and *Enterococcus* was elevated in patients with ALC. Further analysis revealed

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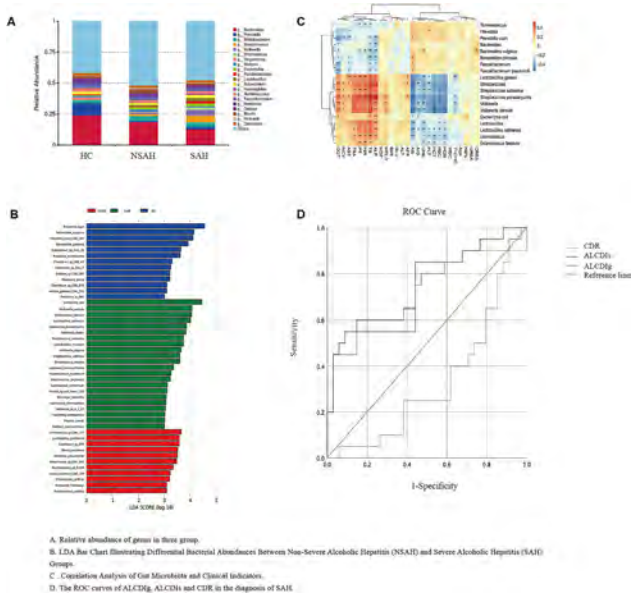
that the species *Enterococcus faecium*, *Streptococcus salivarius*, *Lactobacillus salivarius*, and *Veillonella parvula* were enriched in both ALC and SAH patients, while *Bacteroides vulgatus* and *Prevotella copri* were depleted. Based on these findings and their clinical relevance, combined with the enterotype characteristics of healthy individuals, two dysbiosis indicators were established: the genus-level alcohol-related liver cirrhosis dysbiosis index (ALCDIg) [(*Enterococcus* + *Streptococcus* + *Lactobacillus* + *Veillonella*) absolute abundance / (*Prevotella* + *Bacteroides*) absolute abundance] and the species-level ALCDIs [(*Enterococcus faecium* + *Streptococcus salivarius* + *Lactobacillus salivarius* + *Veillonella parvula*) absolute abundance / (*Prevotella copri* + *Bacteroides vulgatus*) absolute abundance]. The area under the curve (AUC) for ALCDIg was 70.9% (95% confidence interval: 55.6%-86.2%), with a sensitivity of 60% and specificity of 86%. For ALCDIs, the AUC in severe alcoholic hepatitis was 75.4% (95% confidence interval: 61.4%-89.5%), with a sensitivity of 85% and specificity of 53%. Higher ALCDIs values indicate more severe dysbiosis, making this parameter useful for evaluating dysbiosis in patients with ALC. **Conclusion:** Changes in intestinal microbiota are closely related to the progression of Alcohol-related liver disease,liver cirrhosis dysbiosis indicator (ALCDIg) can be used to evaluate the intestinal dysbiosis in patients with ALD.



A. Relative abundance of genus in three group.
B. LDA Bar Chart Illustrating Differential Bacterial Abundances Between Non-Severe Alcoholic Hepatitis (NSAH) and Severe Alcoholic Hepatitis (SAH) Groups.
C. Correlation Analysis of Gut Microbiota and Clinical Indicators.
D. The ROC curves of ALCDIg, ALCDIs and CDR in the diagnosis of SAH.

Disclosures: Yifan Xu: Nothing to Disclose, Song Yang: Nothing to Disclose, HUICHUN XING: Nothing to Disclose

◆ 1490 | ALCOHOL-ASSOCIATED LIVER DISEASE EXHIBITS HIGHER CUT-POINTS OF LIVER STIFFNESS MEASUREMENT TO STAGE ADVANCED FIBROSIS COMPARED TO METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Wei Wang[1] Stephen Hoang[2] Luis Díaz[3] Juan Pablo Arab[2], [1]Saint Mary's Hospital, Trinity Health of New England, [2]Virginia Commonwealth University School of Medicine, [3]University of California San Diego

Background: Vibration-controlled transient elastography (VCTE) is a non-invasive technique for assessing liver fibrosis, yet the optimal cut-points to stage fibrosis differ among chronic liver diseases (CLDs). Although steatotic liver disease (SLD)—comprising alcohol-associated liver disease (ALD) and metabolic dysfunction-associated steatotic liver disease (MASLD)—is the most common CLD, evidence directly comparing disease-specific VCTE thresholds is scarce. Therefore, this study aimed to quantify the differences in VCTE cut-offs required to detect each fibrosis stage in ALD versus MASLD. **Methods:** We conducted a systematic review and meta-analysis, including studies that used liver stiffness measurements (LSMs) by VCTE to define cut-points for all fibrosis stages in adults with MASLD or ALD. We searched PubMed and the Cochrane Library from January 2008 to March 2025. Between-group comparisons of threshold values for each fibrosis stage were performed using Student's t-tests. Optimal numeric cut-points were identified by maximizing Youden's J. All statistical analyses were conducted in R. **Results:** A total of 79 studies were included in our study. The reference standard was liver biopsy and/or magnetic resonance elastography. Studies of ALD patients demonstrated significantly higher median LSMs for advanced stages: F3 (ALD 14.1 kPa vs MASLD 9.65 kPa, $p = 0.0012$) and F4 (ALD 20.8 kPa vs MASLD 12.6 kPa; $p = 3.5\times10^{-5}$) (Figure 1A). However, no significant differences were observed for F0–1 or F2. The boundary separating F2 vs F3 was 11.8 kPa in ALD vs 9.2 kPa in MASLD, while it was 16.6 kPa vs 10.0 kPa for F3 vs F4, respectively (Figure 1B). **Conclusion:** Our findings demonstrate that patients with ALD may require substantially higher VCTE cut-offs to accurately diagnose advanced fibrosis (F3-F4) compared to those with MASLD. This disease-specific variation underscores the risk of misclassification if uniform thresholds are applied across SLD subtypes.

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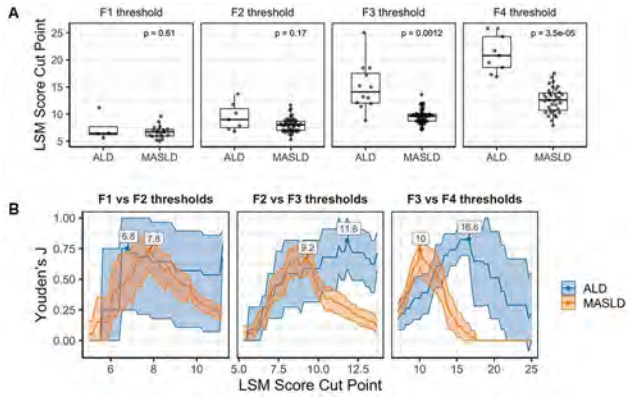

Disclosures: Wei Wang: Nothing to Disclose, Stephen Hoang: Nothing to Disclose, Luis Díaz: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose

◆ 1491 | IMPACT OF ACUTE KIDNEY INJURY ON 28- AND 90-DAY MORTALITY IN PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS: A META-ANALYSIS

frhaan zahrawi[1] Omar Alwan[2] Mohamed Alharami[3] Fawzy Naga[4] Basile Njei[5] Wajahat Mehal[5] Bubu Banini[5], [1]Franciscan Health, Olympia Fields, IL, USA, [2]Hamilton Medical Center, Dalton, GA, USA, [3]Henry Ford Warren, Warren, MI, USA, [4]Faculty of Medicine, Alexandria University, Alexandria, Egypt, [5]Yale University

Background: Acute kidney injury (AKI) is a common and serious complication in patients with alcohol-associated hepatitis (AH). AKI is associated with increased short term mortality in patients with AH. We aimed to quantify the pooled impact of AKI on 28-day and 90-day all-cause mortality in patients with AH. **Methods:** We performed meta-analyses to determine 28-day and 90-day mortality in patients with AH with versus without AKI. Data from four studies (n = 1,937) were pooled. Odds ratios (ORs) were estimated using common-effect and random-effect models. Heterogeneity was assessed using Cochran's Q, I^2, and τ^2 statistics. For 90-day mortality, a sensitivity analysis was conducted by excluding one outlier study to evaluate the robustness of the findings and reduce heterogeneity. **Results:** At 28 days (k = 4; n = 1,937; AKI = 782; non-AKI = 1,155), the common-effect model showed an OR of 3.19 (95% CI: 2.55; 4.00; p = < 0.0001) and the random-effects model showed an OR of 3.33 (95% CI: 2.28–4.88; p < 0.0001), indicating a more than threefold increased mortality risk, with sabstantial heterogeneity (I^2 = 73.3%) (Figure 1A). For 90-day mortality (k = 4; n = 1,937; AKI = 782; non-AKI = 1,155), the common-effect model OR was 2.49 (95% CI: 2.03; 3.05; p = < 0.0001) and the random-effects OR was 3.94 (95% CI: 1.40–11.09; p = 0.0093) with high heterogeneity (I^2 = 85.7%) primarily driven by one outlier study (OR = 26.22) (Figure 1B). After excluding this outlier (k = 3; n = 1,834), the random-effects OR was 2.39 (95% CI: 1.70–3.36; p < 0.0001) with reduced heterogeneity (I^2 = 62.7%) (Figure 1C). **Conclusion:** AKI significantly increases 28- and 90-day mortality in patients with AH. The mortality risk is stronger at 28 days compared to 90 days, suggesting a potential attenuation of the effect over time. Sensitivity analyses excluding an outlier study confirmed the 90-day mortality estimates and reduced heterogeneity. These findings highlight the critical prognostic impact of AKI and emphasize the need for early detection and targeted management strategies to improve patient outcomes.

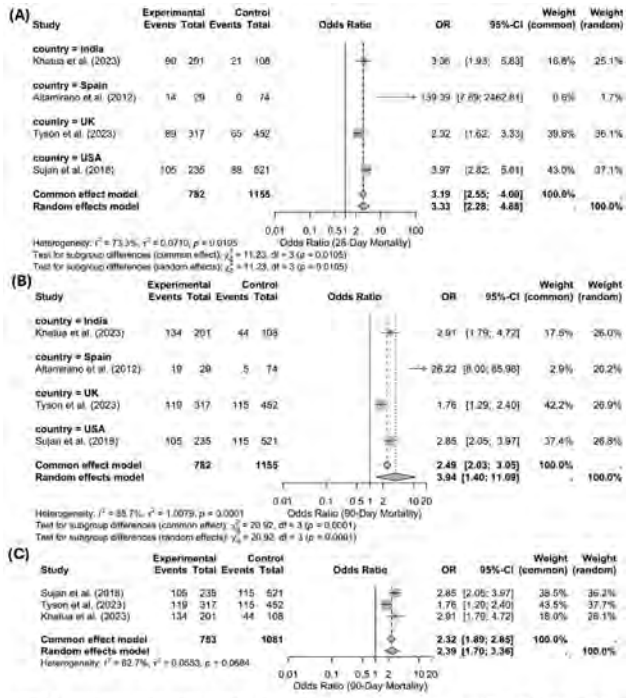

Figure 1. Odds ratios of all-cause mortality for patients with alcohol associated hepatitis with versus without acute kidney injury. (A) 28-day mortality risk (OR = 3.33; I^2 = 73.3%), (B) 90-day mortality risk (OR = 3.94; I^2 = 85.7%), (C) 90-day mortality risk after exclusion of one outlier to reduce heterogeneity (OR = 2.39; I^2 = 62.7%)

Disclosures: frhaan zahrawi: Nothing to Disclose, Omar Alwan: Nothing to Disclose, Mohamed Alharami: Nothing to Disclose, Fawzy Naga: Nothing to Disclose, Basile Njei: Nothing to Disclose, Wajahat Mehal: Nothing to Disclose, Nothing to Disclose, Bubu Banini: Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Merck: Grant/Research Support

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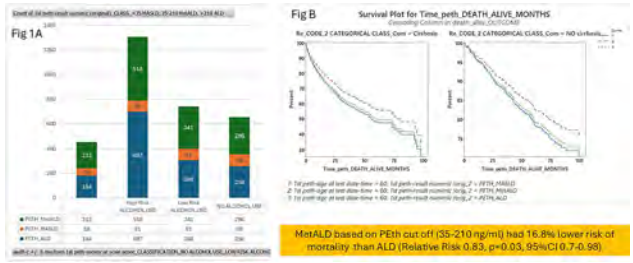
◆ 1492 | WHEN PETH GETS AN AUDIT-C - IMPLICATIONS ON CLASSIFICATION, MISCLASSIFICATION AND OUTCOMES IN STEATOTIC LIVER DISEASE

Puneet Puri[1] Thuy-duyen Vu[2] Vinod Aggarwal[3] HoChong Gilles[4] Michael Fuchs[5], [1]Virginia Commonwealth University, Richmond VA Medical Center, [2]Central Virginia VA Health Care System, [3]MedAugment, [4]McGuire Veterans Affairs Medical Center, [5]Central Virginia VA Healthcare System

Background: Integration of alcohol use in steatotic liver disease (SLD) is a critical step to understand the role and impact of alcohol on liver health and conical outcomes. We therefore investigated the concordance of currently used approaches Alcohol Use Disorders Identification Test (AUDIT-C) and Phosphatidylethanol (PEth) testing, and their impact on mortality. **Methods:** This cross-sectional study on a large national cohort of US Veterans with data from Veterans Affairs Corporate Data Warehouse was used for patients that had PEth test (11/2014 to 6/2022), and mortality outcome through 1/2024. Using ICD-9/10 codes we identified patients with and without cirrhosis, and alcohol use disorder. AUDIT-C cutoffs of 0 (no alcohol use); 1–3 for men/1–2 for women (low-risk drinking); $>=4$ for men / $>=3$ for women (high-risk drinking) were used. PEth (ng/ml) levels <35 (PEth_MASLD), 35-210 (PEth_MetALD) and >210 (PEth_ALD) classified SLD spectrum. Primary outcome of PEth and AUDIT-C concordance was evaluated, and its impact on death was examined using survival Cox-regression Fit Cox Model with Fixed Predictors only, and relative risk analyses. **Results:** Among 3153 patients with PEth test, 652 had AUDIT-C = 0 (No alcohol use). Of these, 85% had PEth level $>=35$, and 40% >210 (ALD range). Significant discordance in cutoffs for AUDIT-C and PEth risk classification for MASLD, MetALD and ALD was noted (Fig 1A). On Cox-regression analysis, PEth_MetALD had 16.8% lower risk of death compared to PEth_ALD ($p=0.03$, 95% CI 0.7-0.98, Fig 1B). No significant differences between PEth-MASLD compared to PEth_-MetALD and PEth_ALD cohorts, both in patients with and without cirrhosis. Surprisingly, among high-risk alcohol group based on AUDIT-C, PEth_MetALD cohort (35-210 ng/ml) had 38% lower risk of death compared to PEth_MASLD (<35 ng/ml, $p=0.03$, RR 0.61, 95% CI 0.4-0.94). In contrast to the published literature for AUDIT-C and PEth based mortality risk, no increased death rates were observed in our cohort likely due to discordant risk classification. **Conclusion:** Vast discrepancy between PEth test and AUDIT-C scores exists with significant risk of misclassifying new steatotic liver disease groups. These can have potential impact on natural history, outcomes and wasted resources in diagnostics and therapeutic development. Future carefully planned prospective studies with great attention to accurate measures and classification are warranted.



Disclosures: Puneet Puri: Nothing to Disclose, Thuy-duyen Vu: Nothing to Disclose, Vinod Aggarwal: Nothing to Disclose, HoChong Gilles: Madrigal: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, Mallinckrodt: Advisor, Michael Fuchs: Nothing to Disclose

◆ 1493 | SEMAGLUTIDE REDUCES HEPATIC CYP2E1 LEVELS IN MICE INDEPENDENT OF ETHANOL INTAKE AND INCREASES BLOOD ETHANOL CONCENTRATIONS

frhaan zahrawi[1] Suyavaran Arumugam[1] Bubu Banini[1] Wajahat Mehal[1], [1]Yale University

Background: The glucagon-like peptide 1 receptor (GLP-1R) agonist semaglutide acts centrally in the brain and modulates ethanol intake and ethanol-induced transcriptional and metabolic changes in the liver. GLP-1R agonism reduces key ethanol metabolizing enzymes, including Cyp2e1. Our goal was to establish if semaglutide can reduce ethanol metabolizing enzymes independent of the reduction in ethanol intake, and if this affects blood ethanol concentrations. **Methods:** We examined the effect of GLP-1R agonism in the absence of food and ethanol intake. C57BL/6N mice ($n = 25$) were separated as follows: Group 1 ($n=4$) – chow diet; Group 2 ($n=5$) – chow diet with semaglutide; Group 3 ($n=8$) control followed by 16-hour fast ; Group 4 ($n=8$) semaglutide followed by16-hour fast. In groups 2 and 4 mice received a single subcutaneous dose of 30 nmol/kg of semaglutide. At 16 h mice were euthanized, and liver tissues were collected and mRNA and protein levels of Cyp2e1 assayed. To test if GLP-1R agonism affects blood ethanol levels, a second experiment with a single fixed dose of ethanol (2.5 g/kg) was administered by gavage or intraperitoneally, and serum ethanol concentrations were measured at 30min, 90 min, 150min, 270min and 330min. **Results:** Hepatic *Cyp2e1* gene expression and protein levels were significantly reduced in mice treated with GLP-1R agonist compared to control mice. In the ethanol gavage experiment, male

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mice showed a significant P <0.001 difference in ethanol levels between the groups at times 30, 90, 150 min p $=$ 0.002 with a mean difference of -36mg/dl (SE 8.5) (Fig. 1 A). This was repeated in female mice which also showed a significant P <0.01 difference in ethanol levels between the groups at times 30, 90, 150 min with a mean difference of -29mg/dl (SE 7.8) (Fig. 1 B). Similarly GLP-1RA showed a significant P <0.001 difference in ethanol levels between the groups at times 30, 90, 150 min with a mean difference of -70mg/dl (SE 13.4) after intraperitoneal administration of ethanol (Fig. 1 C). **Conclusion:** GLP-1R agonism results in a reduction in hepatic Cyp2e1, independent of changes in ethanol intake. This would be predicted to reduce ethanol metabolism and result in elevated plasma ethanol levels, and this was seen after oral and intraperitoneal ethanol. If confirmed in humans, this may have important clinical implications.

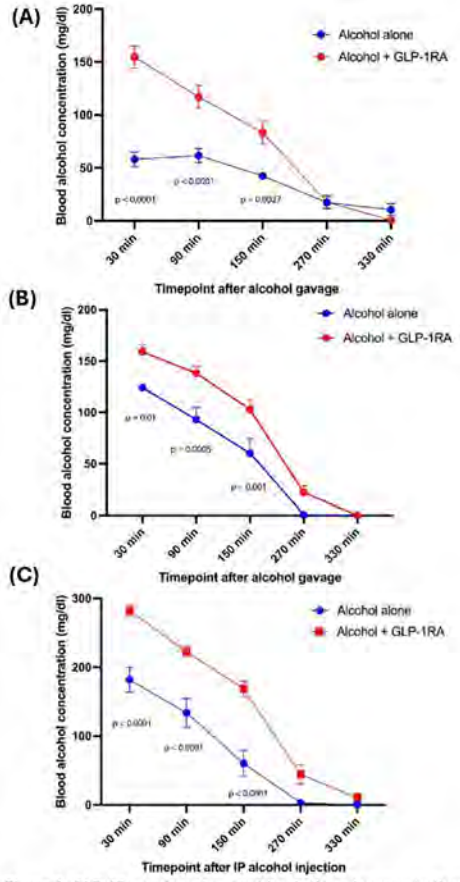

Figure 1. GLP-1R agonism elevates blood ethanol concentrations.
(A) Blood ethanol levels (BAC) were significantly higher at 30, 90, and 150 minutes after ethanol gavage in GLP-1RA vs. control in male mice.
(B) Similar increase in BAC were significant in female mice with GLP-1RA vs. control.
(C) Similar increase in BAC was significant after Intraperitoneal ethanol administration.

Disclosures: frhaan zahrawi: Nothing to Disclose, Suyavaran Arumugam: Nothing to Disclose, Bubu Banini: Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Merck: Grant/Research Support, Wajahat Mehal: Nothing to Disclose, Nothing to Disclose

◆ 1494 | METABOLIC SIGNATURES OF BILE ACID AND SPHINGOLIPID DYSREGULATION IN ALCOHOL-ASSOCIATED HEPATITIS AND CIRRHOSIS

Grayson Way[1] Lianyong Su[1] Derrick Zhao[1] Yun-Ling Tai[1] NAN WU[1] Zhihong Yang[2] Jing Ma[2] THEMIS THOUDAM[2] Kristina Chandler[2] Suthat Liangpunsakul[2] Arun Sanyal[1] Phillip Hylemon[1] Hongkun Lu[1] Huiping Zhou[1], [1]Virginia Commonwealth University, [2]Indiana University

Background: Alcohol-associated liver disease (ALD) comprises a spectrum from heavy drinking (HD) without liver injury to alcohol-associated hepatitis (AH) and alcohol-associated cirrhosis (AC). The metabolic factors driving progression from HD to AH or AC remain incompletely understood. Bile acids (BAs) and sphingolipids are critical signaling molecules that regulate hepatic metabolism and immune responses, yet their potential interplay in ALD pathogenesis remains largely unexplored. **Methods:** Patients with AH and AC were recruited from the hepatology clinic at Indiana University. The study was approved by the Indiana University Institutional Review Board. Serum samples from 11 healthy controls (HC), 11 HD, 12 AC, and 9 AH patients were analyzed by LC-MS/MS to quantify 44 BAs and 28 major sphingolipid species. Hepatic gene expression data from the public dataset GSE143318 were reanalyzed to assess genes involved in BA and sphingolipid metabolism. **Results:** Total serum BA levels were significantly elevated in AC and AH patients, particularly glycine- and taurine-conjugated BAs ($p < 0.01$). Taurine conjugation was markedly increased in AC and AH compared to HC and HD (total taurine/total BA, all $p < 0.01$), especially in primary BAs such as TCDCA and TCA. In contrast, HD patients had a higher glycine/total BA ratio than HC and AH ($p < 0.05$). Deoxycholic acid (DCA) levels were significantly reduced in AC and AH, though lithocholic acid (LCA) was unaffected. All alcohol-consuming groups had a lower DCA percentage of total BA compared to HC. Only AC and AH patients exhibited decreased DCA/cholic acid (CA) ratios ($p < 0.05$). While total sphingolipid levels were similar across groups, serum sphingosine-1-phosphate (S1P) and C24:0 ceramide were significantly reduced in AH and AC. Gene expression analysis revealed downregulation of *CERS2* and *CERS4*, key enzymes for very-long-chain ceramide biosynthesis, and dysregulation of BA transporters, including downregulation of NTCP (*SCL10A1*) and BSEP (*ABCB11*). **Conclusion:** Patients with AC and AH exhibit distinct alterations in BA conjugation and sphingolipid metabolism. HD patients exhibit significantly higher glycine conjugation ratios of bile acids, which may indicate either an early step in disease progression or a protective finding. These findings suggest a mechanistic link between disrupted bile acid and sphingolipid homeostasis in the progression of ALD.

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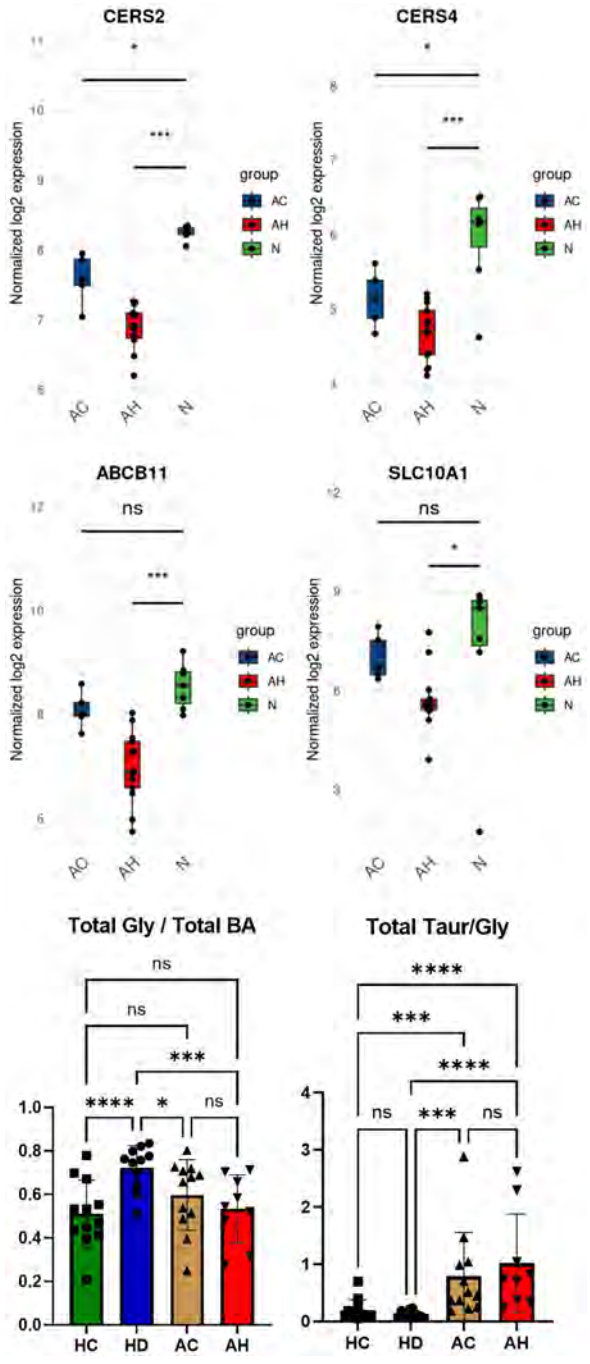

Disclosures: Grayson Way: Nothing to Disclose, Lianyong Su: Nothing to Disclose, Derrick Zhao: Nothing to Disclose, Yun-Ling Tai: Nothing to Disclose, NAN WU: Nothing to Disclose, Zhihong Yang: Nothing to Disclose, Jing Ma: Nothing to Disclose, THEMIS THOUDAM: Nothing to Disclose, Kristina Chandler: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Phillip Hylemon: Nothing to Disclose, Hongkun Lu: Nothing to Disclose, Huiping Zhou: Nothing to Disclose

◆ 1495 | HSD17B13 EXPRESSION IS INCREASED IN BALLOONED HEPATOCYTES FROM PATIENTS WITH STEATOTIC LIVER DISEASE (SLD) AND CAN BE THERAPEUTICALLY TARGETED BY GSK4532990 IN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE (ALD)

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Background: Ballooned hepatocytes are pathognomonic of steatohepatitis and are prominent in ALD. Loss-of-function *HSD17B13* variants are associated with lower amino-transferase levels and reduced progression of SLD. Histopathology studies indicate that these variants may

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protect against hepatocyte ballooning. We enabled spatial transcriptomics of ballooned hepatocytes using machine learning-guided morphological identification. We also show the potential for therapeutic silencing of *HSD17B13* using GSK4532990, a GalNAc-conjugated siRNA, with preliminary open-label safety data from the ongoing STARLIGHT P2 study in ALD (NCT06613698). **Methods:** Liver biopsies from 9 patients with SLD underwent spatial transcriptomics (Xenium, 10X Genomics) followed by H&E staining and Liver Explore deployment (for research use only; not for diagnostic use). Differential gene expression between Liver Explore predicted "ballooned hepatocytes" and "normal hepatocytes" was used to generate a ballooning gene expression signature. Three independent cohorts profiled by either single-nucleus or bulk transcriptomics with matched histopathology ballooning scores were used to validate the transcriptomic signature. In STARLIGHT, 11 ALD participants (8 Child-Pugh [C-P] A; 3 C-P B cirrhosis) received a single dose of GSK4532990 and were followed to week 8 (W8) for safety. **Results:** Ballooned vs morphologically normal hepatocytes showed increased *HSD17B13* expression (Log_2 fold change: 0.56, adj.p-value <0.03). A 6-gene ballooning signature, including *HSD17B13*, correlated with ballooning scores in a snRNAseq ($p=0.0568$) and two bulk RNAseq (both $p<0.001$) datasets. In STARLIGHT, all 11 participants completed all visits. Two participants experienced liver-related events, both with C-P A liver impairment at baseline. Events were adjudicated unlikely to be related to GSK4532990 and were conservatively managed to resolution. C-P A participants had ALT 55 (35–117) vs 39 (13–53) IU/L and AST 120 (180–73) vs 80 (144–53) IU/L, despite consistent alcohol consumption during follow-up (PEth 758 [427-1273] vs 796 [417–1169] μg/L) at baseline vs W8, (median [IQR]; Fig. 1). **Conclusion:** *HSD17B13* expression is increased in ballooned hepatocytes. Preliminary data from the ongoing STARLIGHT ALD study have not identified safety concerns from a single dose of GSK4532990. There was a trend toward reduced aminotransferases, despite ongoing alcohol consumption, that may correspond to improvements in hepatocyte ballooning.

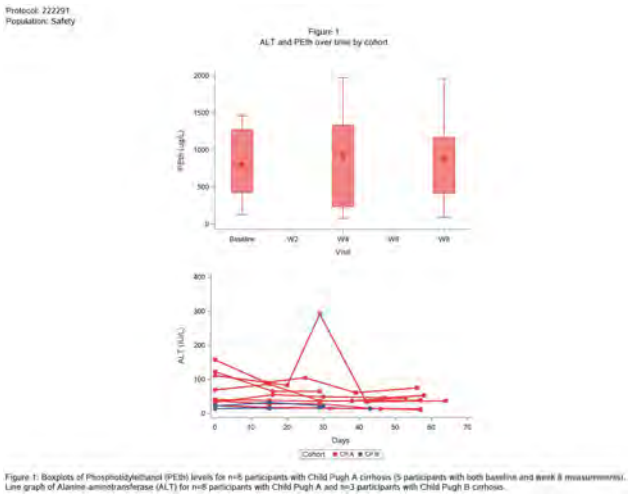

Figure 1: Boxplots of Phosphatidylethanol (PEth) levels for n=8 participants with Child Pugh A cirrhosis (5 participants with both baseline and week 8 measurements). Line graph of Alanine aminotransferase (ALT) for n=8 participants with Child Pugh A and n=3 participants with Child Pugh B cirrhosis.

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◆ 1496 | IMPACT OF ABSTINENCE ON LIVER STIFFNESS MEASUREMENT IN ALCOHOL-ASSOCIATED LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Alcohol-associated liver disease (ALD) has become a leading cause of liver failure, hepatocellular carcinoma, and liver-related mortality. While clinical guidelines emphasize cessation, the short-term impact on liver fibrosis remains poorly defined. In this study, we aimed to assess changes in liver stiffness measurement (LSM) using vibration controlled transient elastography (VCTE) following abstinence in patients with alcohol use disorder (AUD). **Methods:** A systematic review and meta-analysis was conducted using observational studies from MEDLINE, EMBASE, and Cochrane through November 2024. We included adults with AUD who underwent detoxification and had paired baseline and follow-up LSM. Pooled effect sizes and changes in LSM were calculated while stratified by alcohol abstinence and relapse. Subgroup analyses examined associations with BMI >25 kg/m^2 and baseline LSM >12.1 kPa. Studies reporting liver biopsy data were qualitatively reviewed. **Results:** A total of 1,557 AUD patients who initiated abstinence and completed paired VCTE were identified across 11 observational studies after screening 6,620 articles. Pooled LSM decreased in 12/13 follow-up cohorts but

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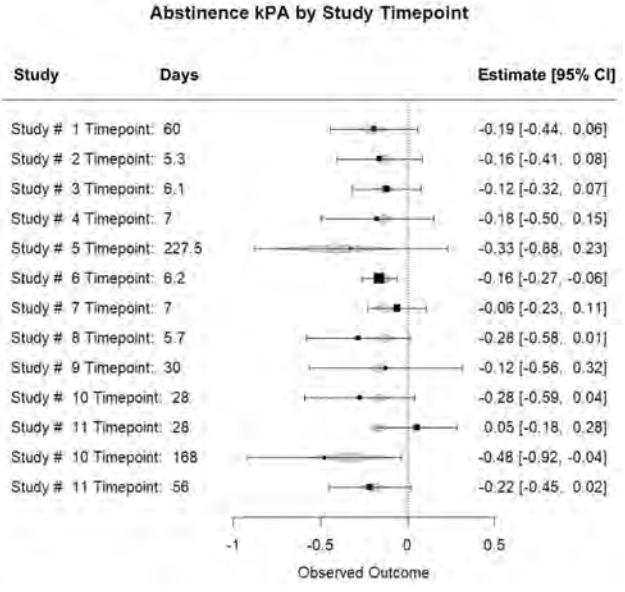
contained large pooled standard deviations. The estimated pooled effect size LSM was –0.0013 kPa/day (95% CI: –0.0030 to 0.0005; p = 0.153). Estimated mean LSM difference was -1.95 kPa at 7 days, -2.30 kPa at 28 days, and -2.76 kPa after 56 days of continued abstinence. Alcohol relapse occurred in 114/267 patients at 30 days, 82/160 patients at 56 days, and 29/64 patients after 56 days follow up. Amongst alcohol relapse patients, 3/6 studies noted an increased kPa from baseline with mean changes of +0.086 kPa at 28 days and +0.40 kPa after 56 days. In the BMI-based subgroup model, LSM declined by -0.0027 kPa/day (SE = 0.0014; p = 0.0505; 95% CI: -0.0053 to 0.0000). In studies with a baseline BMI > 25, LSM declined by -0.1159 kPa (SE = 0.0765; p = 0.1298; 95% CI: -0.2658 to 0.0340). In the baseline liver stiffness subgroup model, LSM declined by -0.0017 kPa/day (SE 0.0009; 95% CI -0.0035 to 0.0002; p = 0.075). In studies with a baseline LSM > 12.1 kPa, LSM declined by -0.0838 kPa (SE 0.0681; 95% CI -0.2172 to 0.0497; p = 0.22). Four studies provided variably reported liver biopsy data. **Conclusion:** This systematic review and meta-analysis determined LSM declined following alcohol cessation, but pooled estimates were not statistically significant due to high inter-study variability. No similar trend was observed in the relapse group. The high BMI subgroup demonstrated a marginal reduction in LSM which did not reach statistical significance. The studies reporting liver biopsy results were inconsistent and prevented pooled analysis. These findings suggest early changes in inflammation and fibrosis after alcohol cessation may be detectable by VCTE; however, further studies are needed to clarify the trajectory and reliability of regression.



Disclosures: Wesley Chow: Nothing to Disclose, Derek Wong: Nothing to Disclose, Ganeev Singh: Nothing to Disclose, Garrett Teskey: Nothing to Disclose, Lee Luniewski: Nothing to Disclose, Leah Puglisi: Nothing to Disclose, Samantha Bagsic: Nothing to Disclose, Paul Pockros: Gilead: Consultant, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, ChemoMab: Grant/Research Support, Intercept: Grant/Research Support, Up To Date: Royalties or patent beneficiary, Orphalan: Advisor, Akero: Independent Contractor, Altimmune: Independent Contractor, Boston Pharmaceuticals: Independent Contractor, Ipsen: Speaking and Teaching, Gilead: Speaking and Teaching, Prometheus: Consultant, Hamni: Independent Contractor, Madrigal: Independent Contractor, atea: Independent Contractor, Julio Gutierrez: Nothing to Disclose

◆ 1497 | PREMATURE MORTALITY ACROSS THE STEATOTIC LIVER DISEASE (SLD) SPECTRUM IS DRIVEN BY BINGE DRINKING AND METABOLIC CONDITIONS

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Background: Outcomes across SLD spectrum [metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic and alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD)] are influenced by both alcohol use and metabolic conditions (MCs). We assessed the association of MCs and alcohol use patterns with premature mortality across SLD subtypes. **Methods:** Using NHANES data (1988–2014) linked to mortality (follow-up 2019), we identified SLD by ultrasound or a validated U.S. Fatty Liver Index and classified participants as MASLD, MetALD, or ALD per the 2023 consensus. Alcohol intake was corrected to match U.S. per capita consumption.Participants were categorized as abstainers (< 12 drinks lifetime), former drinkers (≥ 12 drinks lifetime but < 12 drinks in past year), low (> 0 but < 20/30 g/day for women/men [W/M]), moderate (20–49.9/30–59.9 g/day), or heavy (≥ 50/60 g/day)

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drinkers. Active binge drinking was defined as ≥5 drinks/day in prior year. History of binge drinking was defined as ever consuming ≥5 alcoholic drinks/day. Premature mortality (death ≤80/75 years W/M), age-standardized to the 2000 U.S. population (per 1,000 person-years), was evaluated across SLD subtypes, accounting for sociodemographic factors, alcohol use (including binge drinking), and MCs (type 2 diabetes [T2D], hypertension [HTN], hyperlipidemia, and obesity), with non-SLD abstainers as reference group. **Results:** Of 27,091 participants, 79.8% had ≥1 MC; 7.8% were non-SLD abstainers, while 27.1%, 3.4% and 3.6% had MASLD, MetALD, and ALD. History of binge drinking was reported by 10.4% of SLD [ALD (26.3%), MetALD (11.9%), and MASLD (10.8%)]. Age-standardized premature mortality rates were highest in ALD (13.3), followed by MetALD (8.6), and MASLD (7.3), and lowest in non-SLD abstainers (2.7). In sociodemographic-adjusted models, all SLD subtypes had a higher risk of premature mortality while after adjusting for MCs, only ALD remained significant. In fully adjusted models, binge drinking was independently associated with an increased risk of premature mortality (Table 1). Other predictors included obesity, T2D, HTN, smoking, older age, male sex, and low education/income. **Conclusion:** Premature mortality risk varies across SLD spectrum. In MASLD and MetALD, MCs (T2D, HTN) and history of binge drinking are key drivers. In ALD, binge drinking amplifies mortality risk beyond the impact of MCs alone. These findings underscore the need to target both alcohol use and MCs in managing SLD.

Table 1. Hazard Ratios for Premature Mortality by SLD Subclassification

	Sociodemographic-adjusted Model		Fully Adjusted Model		Fully Adjusted M Active Smok
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)
Non-SLD					
Abstainers (< 12 drinks over lifetime)	Reference		Reference		Reference
SLD					
MASLD-abstainers (<12 drinks over lifetime)	**2.35 (1.18 -4.66)**	**0.0157**	1.67 (0.81 -3.44)	0.1640	1.63 (0.79 -3.35)
MASLD-former drinkers without previous binge (<12 drinks last year)	**2.38 (1.35 -4.19)**	**0.0029**	1.55 (0.83 -2.84)	0.1697	1.41 (0.76 -2.60)
MASLD-former drinkers with previous binge (<12 drinks last year but with a history of binge drinking)	**3.67 (1.63 -8.15)**	**0.0016**	**2.41 (1.00 -5.76)**	**0.0488**	2.21 (0.91 -5.40)
MASLD-low drinkers without active binge (>0 but <20 or 30 gram/day (F/M) without any active binge drinking)	1.72 (0.93 -3.19)	0.0856	1.20 (0.61 -2.34)	0.5992	1.00 (0.52 -1.93)
MASLD-low drinkers with active binge (>0 but <20 or 30 gram/day (F/M) with active binge drinking)	**2.31 (1.11 -4.83)**	**0.0260**	1.86 (0.84 -4.11)	0.1261	1.50 (0.68 -3.31)
MetALD without active binge (>20 or 30 but <50 or 60 gram/day (F/M) without any active binge drinking)	2.31 (0.77 -6.96)	0.1350	1.64 (0.53 -5.09)	0.3854	1.35 (0.43 -4.26)
MetALD with active binge (>20 or 30 but <50 or 60 gram/day (F/M) with active binge drinking)	**3.08 (1.25 -7.59)**	**0.0148**	**2.51 (1.02 -6.10)**	**0.0431**	2.01 (0.81 -4.95)
ALD (>50 or 60 gram/day (F/M) with active binge drinking)	**3.87 (2.05 -7.28)**	**<.0001**	**3.14 (1.56 -6.34)**	**0.0016**	**2.29 (1.17 -4.47)**
Age					
Aged 18-39 years	Reference		Reference		Reference
Aged 40-59 years	**3.32 (2.32 -4.76)**	**<.0001**	**2.95 (2.00 -4.34)**	**<.0001**	**2.96 (2.01 -4.36)**
Aged ≥60 years	**6.85 (4.74 -9.89)**	**<.0001**	**5.09 (3.38 -7.70)**	**<.0001**	**5.43 (3.59 -8.22)**
Male	**2.03 (1.53 -2.70)**	**<.0001**	**2.14 (1.62 -2.82)**	**<.0001**	**2.12 (1.62 -2.76)**
Non-Hispanic White	0.81 (0.64 -1.06)	0.1706	0.94 (0.72 -1.22)	0.6172	0.96 (0.75 -1.23)
College degree	**0.52 (0.37 -0.71)**	**<.0001**	**0.53 (0.38 -0.74)**	**0.0003**	**0.61 (0.44 -0.86)**

Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, James Paik: Nothing to Disclose, Shira Zelber-Sagi: Nothing to Disclose, Nothing to Disclose, Fatema Nader: Nothing to Disclose, Ariana Nader: Nothing to Disclose, Rand Jamal Alkalbani: Nothing to Disclose, Amolika Gupta: Nothing to Disclose, Manuel Reyes: Nothing to Disclose, Kathryn Hobbs: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Linda Henry: Nothing to Disclose

◆ 1498 | CHARACTERIZING SEX DIFFERENCES IN LIVER-RELATED COMPLICATIONS AMONG PATIENTS HOSPITALIZED FOR ALCOHOL-RELATED CONDITIONS

Elina Stoffel[1] Elizabeth Verna[1] Caroline Rutherford[1] Katherine Keyes[1], [1]Columbia University Medical Center

Background: Women with alcohol use disorder (AUD) are at increased risk of medical complications compared with men at comparable levels of consumption. Alcohol consumption, high-risk drinking and alcohol-related liver disease (ALD) have also increased more rapidly among woman than men. However, sex-specific patterns in AUD-related hospitalizations and liver-related outcomes remains understudied. **Methods:** We conducted a retrospective study of 1,138 patients >18 years admitted to Columbia University Medical Center from 1/2020 to 9/2024 with alcohol-related diagnoses. Eligible patients were those with their first inpatient admission with an alcohol related ICD code after 1/2020. Patient characteristics, test results and outcomes were extracted from the electronic medical record. Statistical analyses included Fisher's exact test, Pearson's Chi-squared test, Wilcoxon rank sum test. Statistical analyses were performed using R. **Results:** 1,138 patients were analyzed, 237 (21%) were female and 900 (79%) male. Baseline demographics and comorbidities were similar between men and woman except men were more likely to be Hispanic (46% vs 24%, $p < 0.001$), had higher rates of diabetes (10% vs. 5.5%, $p = 0.003$) and lower rates of CKD. At index presentation, most patients (60%) were admitted with alcohol intoxication or AUD-related diagnoses. Women were more likely than men to present with ALD (35% vs. 26%, $p = 0.003$), while non-liver alcohol-related diagnoses (such as pancreatitis or gastritis) were similarly distributed between sexes (13% vs. 11%). Cirrhosis at initial presentation (33% vs 26%; $p = 0.04$), markers of liver decompensation including ascites (30% vs 20%; $p < 0.001$) and hepatic encephalopathy (11% vs. 5%; $p = 0.014$), rates of inpatient liver transplant consult (33% vs. 20%; $p < 0.001$) and referral at discharge (61% vs. 48%; $p = 0.024$). rates of liver transplant (13% vs 8.2%, $p = 0.021$) and all-cause mortality (12% vs 7.1%, $p = 0.018$) were all significantly higher among women than men. **Conclusion:** Women are more likely to present with severe liver-related complications of alcohol use and experienced higher rates of advanced liver disease, need for liver transplantation, and mortality on their index hospitalization. These findings suggest potential disparities in disease recognition and care, highlighting the need for earlier identification and tailored management of alcohol-related liver disease in women.

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Table 1: Baseline characteristics and alcohol-related outcomes at index visit, by sex

Demographics	Overall N = 1,119[1]	Female N = 230[1]	Male N = 889[1]	p-value[2]
Age at Index Visit (N=1,119)				0.5
18-25	23 (2.1%)	5 (2.2%)	18 (2.0%)	
25-35	169 (15%)	27 (12%)	142 (16%)	
35-45	257 (23%)	57 (25%)	200 (22%)	
45-55	264 (24%)	57 (25%)	207 (23%)	
55-65	272 (24%)	52 (23%)	220 (25%)	
65-80	134 (12%)	32 (14%)	102 (11%)	
Race/Ethnicity (N=1,029)				<0.001
White	366 (36%)	93 (44%)	273 (33%)	
Hispanic	426 (41%)	53 (25%)	373 (46%)	
Black	164 (16%)	54 (25%)	110 (14%)	
AAPI	24 (2.3%)	4 (19%)	20 (2.4%)	
Other	49 (4.8%)	8 (3.8%)	41 (5.0%)	
Primary Language (N=1,112)				0.004
English	824 (74%)	205 (89%)	619 (70%)	
Spanish	250 (22%)	18 (7.8%)	232 (26%)	
Other	38 (3.4%)	7 (3.0%)	31 (3.5%)	
Alcohol-related ICD-10 category at index Visit (N=1,360)				0.003
Alcohol use/intoxication	822 (60%)	146 (52%)	676 (63%)	
Alcohol-associated liver disease	378 (28%)	98 (35%)	280 (26%)	
Other alcohol-related disease	160 (12%)	37 (13%)	123 (11%)	
Clinical characteristics (N=1,136)				
NAFLD	64 (5.6%)	18 (7.6%)	46 (5.1%)	0.14
Hepatitis B	10 (0.9%)	2 (0.8%)	8 (0.9%)	>0.9
Hepatitis C	21 (1.8%)	8 (3.4%)	13 (1.4%)	0.059
Autoimmune Liver Diseases	9 (0.8%)	4 (1.7%)	5 (0.6%)	0.10
MELD 3.0 (N=194)	17 (7)	18 (7)	17 (7)	0.3
FIB-4 (N=1,095)	6.0 (7.8)	5.7 (7.3)	6.1 (7.9)	0.8
Liver-Related Referrals				
Consult to liver transplant team (N=661)	151 (23%)	52 (33%)	99 (20%)	<0.001
Referral to liver transplant team (N=365)	187 (51%)	63 (61%)	124 (46%)	0.024
Liver-Related Outcomes (N=1,138)				
Cirrhosis	315 (28%)	78 (33%)	237 (26%)	0.043
Ascites	254 (22%)	72 (30%)	182 (20%)	<0.001
Hepatic Encephalopathy	79 (6.9%)	25 (11%)	54 (6.0%)	0.014
Varices	57 (5.0%)	7 (3.0%)	50 (5.5%)	0.10
Jaundice	42 (3.7%)	12 (5.1%)	30 (3.3%)	0.2
Alcohol-associated Hepatitis	124 (11%)	32 (14%)	92 (10%)	0.15
Hepatocellular carcinoma	16 (1.4%)	3 (1.3%)	13 (1.4%)	>0.9
Liver Transplant	105 (9.2%)	31 (13%)	74 (8.2%)	0.021
Mortality	92 (8.1%)	28 (12%)	64 (7.1%)	0.018

[1] n (%); Mean (SD)
[2] Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test

Disclosures: Elina Stoffel: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose, Caroline Rutherford: Nothing to Disclose, Katherine Keyes: Nothing to Disclose

◆ 1499 | LONG-TERM IMPACT OF ALCOHOL CONSUMPTION PATTERNS ON LIVER FIBROSIS PROGRESSION

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Background: Limited data are available regarding the long-term effects of alcohol consumption on liver fibrosis. Understanding how variations in alcohol use may impact liver health can guide clinical counseling and public health messaging. Our study quantifies the associations between different alcohol consumption patterns and the progression of liver fibrosis over a 14-year period. **Methods:** Our data came from the ALIVE Study, a community-based prospective cohort of people with a history of injection drug use. We included study participants from 2006 to 2020 who completed at least two annual visits. Group-based trajectory modeling of longitudinal AUDIT-C (Alcohol Use Disorders Identification Test - Consumption) scores classified participants into distinct patterns of alcohol consumption. We utilized a gamma-distributed generalized linear mixed model to compare longitudinal changes in liver fibrosis, measured as liver stiffness (LS) through transient elastography, across the alcohol consumption groups. Our model specified the alcohol consumption group, follow-up time, and their interaction as fixed effects, along with subject-specific random intercepts and random time slopes. We adjusted the model for age, sex, race, HIV serostatus, HBsAg, anti-HCV, comorbidities, and substance and tobacco use. **Results:** We analyzed 1790 participants (33% women, 82% Black, median age 42.1 years) with a median follow-up of 7.1 years (IQR: 2.5, 12.1). Six alcohol consumption patterns emerged: consistent minimal use (group 1), consistent low-risk use (group 2), gradual decline from low/moderate-risk use (group 3), consistent moderate-risk use (group 4), gradual decline from high-risk use (group 5), and consistent high-risk use (group 6) (Figure A). The overall predicted mean LS were highest in group 6 (10.90 kPa; 95% CI: 9.81, 11.99) and group 4 (9.02 kPa; 95% CI: 8.51, 9.53). Compared to group 6, the predicted mean LS was 20%, 21%, 25%, and 24% lower in groups 1, 2, 3, and 5, respectively (all $P < 0.05$). Additionally, LS increased significantly over time in group 6 (0.42 kPa/year; 95% CI: 0.24, 0.59) and group 4 (0.11 kPa/year; 95% CI: 0.03, 0.19), but not in the other groups. Model-predicted trajectories of mean LS depicted increasing separation between groups over time (Figure B). Group 6 showed a continuous increase and maintained the highest LS throughout, followed by group 4. The remaining four groups had minimal changes over time. **Conclusion:** Participants who consistently engaged in high-risk alcohol use had the highest levels of LS, which continued to rise over time. Conversely, those who gradually decreased their alcohol consumption, as well as those who consistently maintained minimal or low-risk use, showed little to no change in LS. Our findings highlight the importance of promoting alcohol cessation or reduction to support long-term liver health.

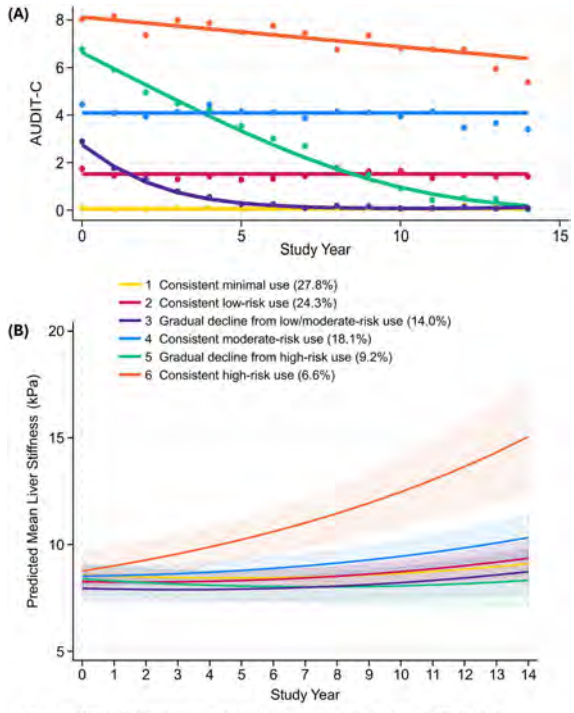

Figure. (A) Alcohol consumption trajectories and prevalences, **(B)** Model-predicted mean liver stiffness over study years, stratified by trajectory groups

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◆ 1500 | GUT-BRAIN AXIS: EMERGING THERAPEUTIC TARGET FOR ALCOHOL USE DISORDER IN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: Gut-brain axis dysfunction contributing to systemic inflammation and alcohol-related behaviors is an emerging therapeutic target for alcohol use disorder (AUD) and for alcohol-associated liver disease (ALD). **Methods:** We systematically reviewed randomized clinical trials (RCTs) on gut-brain modulation in individuals with AUD with or without liver disease. Therapies targeted a) gut dysbiosis using Fecal Microbiota Transplant (FMT), prebiotics (inulin), and probiotics, and b) neurohormonal agents like Glucagon-Like Peptide-1 (GLP-1) receptor agonists, and ghrelin receptor. Studies were identified through PubMed, Google Scholar, Web of Science, and Embase up to 2025. **Results:** Of the nine included RCTs, five (n = 16 to 50) targeted gut dysbiosis. Of these, three studies included subjects with ALD (cirrhosis, moderate AH, and severe AH in one each) while two studies included AUD subjects without liver disease. These interventions showed benefits on behavioral (alcohol craving, consumption, relapse), psychological (anxiety, sociability), biochemical (MELD score and liver enzymes), and systemic inflammation. However, the magnitude and consistency of benefits varied across studies. Four RCTs targeting GI hormones included AUD subjects without liver disease, three using GLP-1 receptor agonists and one using ghrelin. Of the three studies using GLP-1 receptor agonists (n = 48-151) two showed a reduction in alcohol use while the decrease in alcohol use did not reach statistical significance in one study. RCT using intravenous ghrelin (n = 18) showed reduction in inflammatory markers, suggesting its potential anti-inflammatory effect. However, blocking the ghrelin receptor in the presence of alcohol did not produce significant changes in systemic inflammation. **Conclusion:** The current evidence supports gut-brain axis as a potential dual therapeutic target with benefits for both AUD and ALD. Large multicenter randomized controlled studies are needed to examine therapies targeting gut-brain axis in patients with AUD and ALD.

S.N	Study	Intervention	Sample Size	Study Duration	Primary Outcomes Measured and Key Findings
A	**Therapeutics targeting Gut Dysbiosis in AUD**				
1	Bajaj et al. (2020)	Fecal Microbiota Transplant (FMT)	20 patients with alcohol cirrhosis	6 months	↓alcohol craving/consumption (p=0.02) and improvement in cognition & quality of life
2	Amadieu et al. (2021)	Inulin Supplementation	50 participants with AUD	17 days	Improved sociability and ↑BDNF (Brain derived neurotrophic factor) (p=0.04) which has negative correlation with alcohol craving score (r=-0.67, p<0.001).
3	Vatsalya et al. (2023)	Probiotics (Lactobacillus rhamnosus GG)	46 patients with moderate AAH	6 months	Significant ↓in drinking levels to social or abstinence level (p<0.001) and liver injury (MELD and AST/ALT ratio)
4	Mennig et al. (2023)	Probiotic Supplement (Seed DS-01® Daily Synbiotic)	16 non-treatment -seeking heavy drinkers	30 days + 1 month washout	No significant change in plasma biomarker levels from probiotic use. Higher alcohol use was associated with ↑ IL-6, IL-8, and MCP-1.
6	Philips et al. (2022)	FMT vs. corticosteroids	35 patients with severe AAH	3 years	FMT↓ ascites, HE, infections (p<0.05), relapse (28.6%); longer abstinence (p=0.04); ↑ 3-yr survival (65.7%) (p=0.052), ↑ Bifidobacterium, ↓ Acinetobacter
B	**Therapeutics targeting Gut derived hormones in AUD**				
1	Farokhnia et al. (2020)	IV ghrelin vs. placebo	18 participants with AUD	2 lab sessions, 1 week apart	Ghrelin↑alcohol self-administration (+25%, p = 0.04), earlier initiation (p = 0.01), and enhanced brain activation in amygdala and reward regions.
2	Klausen (2022)	Exenatide	127 AUD patients	6 months	↓ heavy drinking days (p= 0.37)
3	Probst (2023)	Dulaglutide	151 participants with A	12 weeks	↓alcohol consumption by 29% (p=0.04)
4	Handershot (2025)	Semaglutide	48 AUD patients	10 weeks	↓alcohol self-administration (p=0.01), Significantly ↓ drinks per drinking day (p=0.04), and weekly alcohol craving (p=0.01)

Disclosures: Prabha Bhandari: Nothing to Disclose, Abdelhaleem Sideeg: Nothing to Disclose, Sheel Patel: Nothing to Disclose, Hanna Blaney: Nothing to Disclose, Mohamed Elfeki: Nothing to Disclose, Chencheng Xie: Nothing to Disclose, Talal Bhatti: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, GSK: Grant/Research Support, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, Avera Medical Group: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other

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◆ 1501 | EPIGENETIC CHANGES IN ALCOHOL EXPOSED HEPATOCYTES DRIVE PATHOGENIC HEPATOCYTE-MACROPHAGE FEEDBACK LOOP LEADING TO LOSS OF LIVER FUNCTION

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Background: Alcohol-associated liver disease (ALD) is a major cause of alcohol related mortality. Previously we identified KDM5B as a key driver of alcohol induced epigenetic changes involved in ALD development, however, the mechanism behind KDM5B-induced pathological changes is not established. **Methods:** *Kdm5b* flox/flox female mice were fed a Western diet and 20% alcohol in the drinking water for 8-16 weeks (WDA). To induce KDM5B knockout, mice received $2x10^{11}$ genome copies of AAV8-CMV-Cre, AAV8-TBG-Cre or AAV8-control. Liver fibrosis was evaluated by Sirius Red and COL1A1 staining and hydroxyproline measurement. Gene expression changes were assessed with RNA-seq analysis. To test the role of myeloid C/EBPβ, Cebpb fl/fl or Cebpb fl/fl Lyz2-Cre mice were fed WDA for 16 weeks. To test the role of recruited monocyte-derived macrophages we used *Ccr2* KO mice. **Results:** We found that *Kdm5b* knockout prevented alcohol-induced liver fibrosis, inflammation and alcohol-induced loss of liver syntetic function in female mice. These changes were in part mediated by hepatocyte to non-parenchymal cell communication changes. KDM5B in hepatocytes promoted CCL-2 and CCL-5 expression in hepatocytes, resulting in a shift in liver macrophage composition. KDM5B promoted an increase in monocyte-derived macrophages infiltration and a loss of mature Kupffer cell phenotype. Moreover, we found that the loss of liver function was dependent on hepatocyte to macrophage communication feedback loop. KDM5B in hepatocytes inhibited macrophage C/EBPβ expression which in turn resulted in loss of mature Kupffer cells phenotype and prevented Kupffer cells' ability to support hepatocyte differentiation, ultimately leading to loss of liver synthetic function. CCL-2/CCR2 mediated monocyte infiltration further exacerbated liver inflammation and hepatocyte de-differentiation. **Conclusion:** KDM5B-dependent alcohol-induced epigenetic changes in hepatocytes drive pathogenic cell-cell communication leading to alcohol-induced loss of liver function in ALD. **Disclosures:** Kruti Nataraj: Nothing to Disclose, Michael Schonfeld: Nothing to Disclose, Samson Mah: Nothing to Disclose, Steven Weinman: Nothing to Disclose, Irina Tikhanovich: Nothing to Disclose, Nothing to Disclose

1502 | DIVERGING TRENDS IN INCIDENCE OF ALCOHOL USE DISORDER AND ALCOHOL-ASSSOCIATED LIVER DISEASE: A 28-YEAR POPULATION-BASED COHORT STUDY

Kamalpreet Hara[1] Alberto Calleri[1] TIFFANY WU[1] Blake Kassmeyer[1] Patrick Kamath[1] Vijay Shah[1] Douglas Simonetto[1], [1]Mayo Clinic Rochester

Background: Alcohol use disorder (AUD) and alcohol-associated liver disease (ALD) are major public health burdens. ALD encompasses conditions such as alcohol-associated hepatitis (AAH) and cirrhosis and is the leading cause of liver-related morbidity and mortality. This study examines the incidence trends of AUD and ALD over a 28-year period in Olmsted County, Minnesota. **Methods:** We conducted a retrospective population-based cohort study using data derived from the Rochester Epidemiology Project. From 1995-2023, incident cases of AUD and ALD were identified using ICD codes and only the first-ever diagnosis was included. Incidence rates were calculated in 5-year intervals and age- and sex-adjusted to the 2020 US census population, expressed as cases per 100,000 person-years to evaluate the temporal trends. **Results:** We identified 22,754 individuals with AUD and 1,895 with ALD. The median age at diagnosis was 37.5 years (IQR, 25.5, 51.8) for the AUD cohort and 52.5 years (IQR, 42.9,61.6) for the ALD cohort. Women comprised 34.9% of the AUD and 28.5% of the ALD cohort. Among ALD cases, 963 (50.8%) had AAH, 1,003 (53%) had cirrhosis. Age- and sex-adjusted AUD incidence rates showed a notable overall decline, peaking during 1995–1999 at 631.2 per 100,000 (95% CI, 610.2–652.3) and declining to 399.5 per 100,000 (95% CI, 384.3–414.6) in 2020–2023. Sex-stratified analyses revealed a 31% reduction in women (from 389.1 to 269.8) and a 40% reduction in men (from 882.8 to 531.7), though rates remained higher in men throughout. In contrast, ALD incidence increased steadily, rising from 41.9 (1995-1999) to 65.5 (2020-2023) per 100,000 over the study period. This rise was especially pronounced among women, whose incidence nearly doubled (88% increase), from 19.2 to 36.3 per 100,000. Among men, incidence increased by 45%, from 66.0 to 95.9 per 100,000. While AUD incidence declined among younger adults (20-39) after 2015, ALD incidence rose in this age group during the same time-period. **Conclusion:** This 28-year population-based cohort study reveals contrasting trends, with a decline in AUD diagnosis in recent years, while ALD cases have continued to rise, particularly among women and younger adults. These opposing trajectories may reflect a shift toward more hazardous patterns

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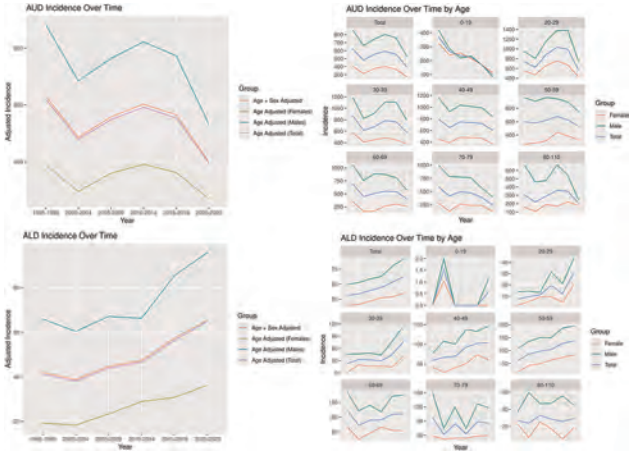
of alcohol consumption concentrated among fewer individuals and/or delayed or under recognized AUD diagnosis. Further research is needed to better understand the factors driving these trends.

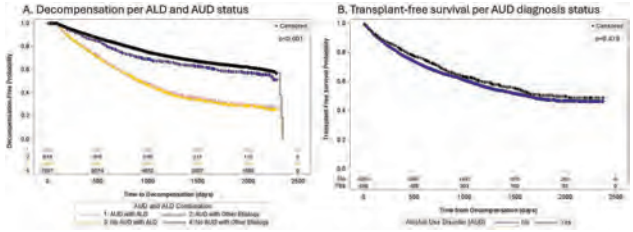


Disclosures: Kamalpreet Hara: Nothing to Disclose, Alberto Calleri: Nothing to Disclose, TIFFANY WU: Nothing to Disclose, Blake Kassmeyer: Nothing to Disclose, Patrick Kamath: Sequana: Advisor, NovoNordisk: Advisor, GSK: Advisor, GSK: Advisor, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant

1503 | ALCOHOL USE DISORDER, LIVER DECOMPENSATION, AND MORTALITY RISK ACROSS CIRRHOSIS ETIOLOGIES: A POPULATION-BASED STUDY.

Samer Gawrieh[1] Wanzhu Tu[1] Maaz Arif[1] Lauren Nephew[2] LaKeisha Boyd[1] Yang Li[1] Naga Chalasani[3] Eric Orman[2] Archita Desai[1], [1]Indiana University School of Medicine, [2]Indiana University, [3]Indiana University Medical Center

Background: The impact of alcohol use disorder (AUD) on cirrhosis outcomes across different etiologies remains unclear. Using contemporary real-world data, we evaluated the impact of AUD diagnosis on the risk of decompensation and mortality in patients with cirrhosis due to different etiologies including alcohol-associated liver disease (ALD). **Methods:** The Indiana Cirrhosis Cohort is a population-based longitudinal cohort which includes 13,264 adults diagnosed with cirrhosis between 2018 and 2020, followed from initial diagnosis to death, liver transplant (LT), or last follow up. Baseline demographics, comorbidities, and cirrhosis characteristics were collected. AUD diagnosis was made based on ICD10 F10.x. Outcomes included decompensation (ascites, encephalopathy, variceal bleeding), LT, and death. Kaplan–Meier and log-rank tests assessed transplant free survival (TFS); Multivariable Cox regression was used to examine time from diagnosis to decompensation and from decompensation to LT, death or last follow-up, by AUD status. **Results:** The cohort had mean (SD) age of 59 (12) years, 53% men, 87% White, and median follow-up 1,506 (IQR 894–2071) days. AUD diagnosis was observed in 30% of the cohort, 67% of ALD cirrhosis, and 16% of non-ALD cirrhosis. Patients with AUD diagnosis were younger (54 vs 62 years), more frequently men (67% vs 48%), Black (12 vs 7%), had Medicaid (61% vs 38%), not married (69% vs 52%), had higher baseline rates of ascites (18% vs 12%), encephalopathy (26% vs 9%), variceal bleeding (3% vs 1%), and had more frequently in the preceding year at least one emergency room visit (57% vs 40%) and hospitalization (51% vs 32%) vs those without AUD diagnosis ($P < 0.01$ for all). Among those without decompensation at entry ($N = 10,398$), AUD diagnosis had no impact on the decompensation risk in patients with ALD cirrhosis ($P = 0.5$). In those with non-ALD cirrhosis, AUD was associated with higher decompensation risk (HR 1.19, 95% CI 1.03, 1.38, $P = 0.016$, Fig 1A). During follow-up, patients with AUD diagnosis had lower LT rates (4% vs 8%) but similar mortality (36% vs 35%) vs those without AUD. TFS did not differ by AUD diagnosis ($P = 0.48$, Fig 1B); and these findings remained consistent after adjusting for cirrhosis etiology (ALD vs non-ALD). **Conclusion:** AUD diagnosis is associated with higher risk of decompensation in non-ALD cirrhosis. However, once decompensation occurred, AUD diagnosis was not independently associated with TFS regardless of liver disease etiology.



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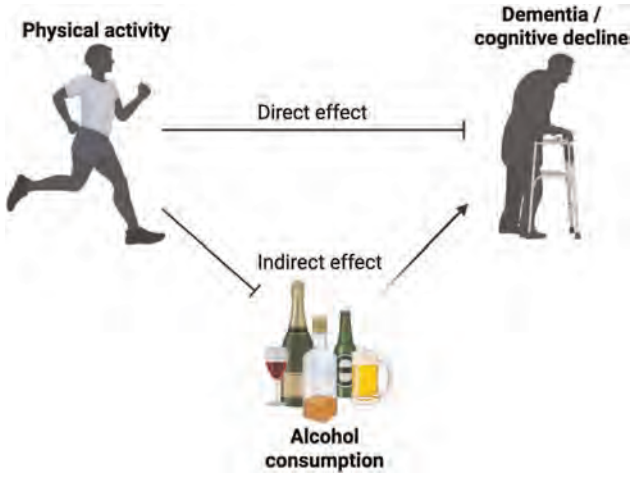
1504 | PHYSICAL ACTIVITY REDUCES THE RISK FOR DEMENTIA WITH REDUCED ALCOHOL CONSUMPTION IN ALCOHOL RELATED LIVER DISEASE (ALD): A LARGE POPULATION BASED ANALYSIS

Amy Attaway[1] Nicole Welch[1] Annette Bellar[1] Muaz Alsabbagh Alchirazi[1] fnu Shashi Kant[1] Peter Bazeley[1] Dan Rotroff[1] Takhar Kasumov[2] Srinivasan Dasarathy[1], [1]Cleveland Clinic, [2]NEOMED

Background: Alcohol consumption and ALD are contributors to brain histomorphometric changes,neurodegenration, and cognitive decline with limited therapies. Physical activity reduces the risk for dementia while simultaneously decreasing alcohol cravings/consumption. We hypothesized that physical activity mediates a reduction in alcohol consumption to cognitive decline in a large community based population analysis. **Methods:** Using a cross-sectional design of the UK Biobank (n = 393,223), we conducted a Mendelian randomization to determine the causal effect of alcohol use on physical activity and cognitive decline. Alcohol consumption data per week was obtained by self-report. Summed metabolic minutes of physical activity per week were determined based on metabolic equivalent of tasks (METs). Cognitive decline (dementia) was determined by self-report or ICD10 codes. We used a single nucleotide polymorphism (SNP) associated with alcohol risk (rs1260326, Glucokinase Regulator, GCKR) as the instrumental variable to assess the effect of alcohol consumption on physical activity. We then performed a mediation analysis to determine whether summed minutes of activity per week (treatment) influences alcohol consumption per week (mediator) to impact the risk of dementia (outcome). Statistical analyses were performed using Mendelian-Randomization and mediation R packages (4.5.0). **Results:** Our analysis included 47.8% male participants, with an overall average age (SD) of 59.2 (8.1) years. Within the cohort, 92.6% were current drinkers, 3.4% were former drinkers, and 4% were never drinkers. For current drinkers, the average (SD) alcohol consumed was 8.4 (10.2) drinks per week. To determine whether alcohol use influenced physical activity, we performed a Mendelian randomization to predict alcohol use adjusted for age and sex. We determined a statistically significant inverse effect where higher genetically predicted alcohol use was associated with lower physical activity (β coefficient -2.13, std. error 2.01, $p = 0.036$). Mediation analysis was used to determine the direct and indirect effects of physical activity on dementia risk using models adjusted for age, sex, and BMI and showed that physical activity significantly reduced dementia risk directly (ADE or Average Direct Effect: β coefficient -6.40e-08, 95% CI: -1.15e-07-0.00, $p < 0.001$), and indirectly (ACME or Average Causal Mediation Effect: β coefficient -8.75e-06, 95% CI: -1.29e-05-0.00, $p < 0.001$) by mediating a reduction in alcohol consumption. **Conclusion:** We show that physical activity is associated with reductions in dementia both directly and indirectly (by mediating alcohol consumption). Our data lay the foundation for prospective studies to determine whether targeted exercise interventions to reduce alcohol consumption can also decrease the risk for cognitive decline/dementia in patients with ALD and alcohol use disorder.



Disclosures: Amy Attaway: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Muaz Alsabbagh Alchirazi: Nothing to Disclose, fnu Shashi Kant: Nothing to Disclose, Peter Bazeley: Nothing to Disclose, Dan Rotroff: Nothing to Disclose, Takhar Kasumov: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

1505 | FAS-ASSOCIATED FACTOR FAMILY MEMBER 2 EXPRESSION IN THE LIVER MITIGATES ALCOHOL-ASSOCIATED LIVER DISEASE IN MICE

Jingjing ZHANG[1] Norihiro Imai[2] Dongming Liu[3] Shinya Yokoyama[2] Kenta Yamamoto[2] Takanori Ito[2] yoji ishizu[2]

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Takashi Honda[2] Hiroki Kawashima[2], [1]Nagoya University, [2]Nagoya University Graduate School of Medicine, [3]Tianjin Medical University Cancer Institute and Hospital

Background: Fas-associated factor family member 2 (Faf2), a lipid droplet- and endoplasmic reticulum-associated protein, regulates the post-translational degradation of apolipoprotein B in hepatocytes. A recent genome-wide association study linked Faf2 variants to alcohol-associated liver disease (ALD), yet its functional role in ALD pathogenesis remains undefined. Aim: To delineate the hepatocyte-specific role of Faf2 in the development of ALD using a murine model. **Methods:** Hepatocyte-specific Faf2 knockout (Faf2-LKO) mice were generated by crossing *Faf2$^{flox/flox}$* mice with *Albumin-Cre* transgenic mice. Faf2-LKO and littermate controls were subjected to a chronic ethanol feeding plus single binge gavage protocol. Tissues and blood were collected nine hours post-gavage. Liver histology was assessed by hematoxylin and eosin (H&E) and Sirius Red staining; serum transaminases and lipid profiles were measured. RNA sequencing of liver tissues was performed to uncover Faf2-regulated transcriptional networks. Given prior observations of sexual dimorphism, both sexes were analyzed. **Results:** Ethanol exposure in Faf2-LKO male mice resulted in significantly increased liver-to-body weight ratios and elevated serum free fatty acid and free cholesterol levels compared to controls, while Faf2-LKO females showed no differences in tissue weights or serum lipids. Aspartate transaminase and alanine transaminase levels were comparable between genotypes in both sexes. Histological analysis using H&E staining revealed prominent Zone 2 steatosis in Faf2-LKO males and widespread azonal steatosis in Faf2-LKO females compared with respective controls. Fibrosis quantification by Sirius Red staining showed no significant differences. Transcriptomic profiling identified 828 and 1,215 differentially expressed genes in Faf2-LKO males and females, respectively. Gene set enrichment analysis revealed downregulation of steroid and alcohol metabolism pathways in males, whereas IL-1 and cytokine signaling pathways were upregulated in females. **Conclusion:** Hepatocyte-specific deletion of Faf2 promotes sex-dependent hepatic steatosis and distinct transcriptional responses to ethanol exposure. These findings establish Faf2 as a novel modulator of ALD pathogenesis.

Disclosures: Jingjing ZHANG: Nothing to Disclose, Norihiro Imai: Nothing to Disclose, Dongming Liu: Nothing to Disclose, Shinya Yokoyama: Nothing to Disclose, Kenta Yamamoto: Nothing to Disclose, Takanori Ito: Nothing to Disclose, yoji ishizu: Nothing to Disclose, Takashi Honda: Nothing to Disclose, Hiroki Kawashima: Nothing to Disclose

1506 | EXPLANT HISTOLOGY OF METALD RESEMBLES AC MORE THAN MASLD

Priyanka Singh[1] Smruti Rath[1] Thomas Schiano[1] Gene Im[2], [1]Mount Sinai Hospital, [2]Columbia University Irving Medical Center

Background: Steatotic liver disease (SLD) includes alcohol-associated cirrhosis (AC), alcohol-associated hepatitis (AH), metabolic dysfunction-associated liver disease (MASLD), and the newly created metabolic and alcohol-associated liver disease (MetALD). Data regarding histological findings for MetALD are lacking. This study aims to assess histological differences among SLD subgroups and determine whether histological findings in MetALD more closely resemble AC or MASLD. **Methods:** A retrospective cohort study was performed on patients who underwent liver transplant (LT) for SLD at Mount Sinai Hospital from 1/1/2012-1/1/2023. MetALD cases were reclassified from prior AC or MASLD designations based on current consensus. Explant histology reports from each liver transplant case were reviewed for key terms reflecting defining histologic features of MASLD and AC. Chi square analyses were used to compare MetALD to the SLD subgroups. **Results:** Over the 11-year study period, 405 LT for SLD were performed at our center, with MetALD being the least common with 28 (7%), followed by AH 114 (28%), AC 126 (31%), and MASLD 137 (34%). Patients with co-morbid liver diseases or diagnoses of HCC were excluded. Of the LT for MetALD recipients, 22 (79%) and 6 (21%) were originally classified as AC and MASLD, respectively. 14% of MASLD, 12% of AC, and 18% of MetALD histology reports mentioned hepatocellular carcinoma (HCC). Mallory-Denk bodies were mentioned in 51%, 37% and 54% of MASLD, AC, and MetALD cases respectively. Although not significant, MetALD (50%) had more findings of ductular reaction compared to MASLD (34%) and AC (32%) (MASLD/MetALD: 2.46, $p = 0.17$; AC/MetALD: 3.35, $p = 0.07$). MetALD (61%) had a significantly higher rate of fibrous septa compared to MASLD (4%) (61.50, $p < 0.001$) and AC (4%) (60.25, $p < 0.001$). MetALD (29%) also had the highest rate of mention of iron deposition compared to AC (25%) and MASLD (12%), with a significant difference compared to MASLD (5.34, $p = 0.02$). Neutrophil-rich inflammation was mentioned at significantly higher rates in MetALD (7%) than MASLD (0.73%) (5.36, $p = 0.02$). There was no significant difference between MetALD (11%) and MASLD (27%), or AC (21%) for mention of burnt-out steatohepatitis. **Conclusion:** MetALD histology showed greater frequency of features typical of AC, including iron deposition, neutrophilic infiltration, and fibrous septa, compared to MASLD. Trends toward increased HCC, Mallory-Denk bodies, and ductular reaction suggest that

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both metabolic and alcohol-related injury in MetALD may lead to more severe hepatic insult. Larger studies are needed to further explore these findings.

Table 1. Histologic findings in the steatotic liver diseases

	MASLD (n= 137)	MetALD (n=28)	AC (n = 126)	AH (n = 114)	MetALD vs MASLD Chi-Square Statistic	MetALD vs MASLD P-value	MetALD vs AC Chi-Square Statistic	MetALD vs AC P-value
Hepatocellular Carcinoma	14%	18%	12%	1%	0.30	0.59	0.72	0.40
Dysplastic Nodules	21%	29%	21%	4%	0.73	0.39	0.67	0.41
Burnt-Out Steatohepatitis	27%	11%	21%	4%	3.36	0.07	1.68	0.20
Mallory Denk Hyaline	51%	54%	37%	86%	0.08	0.81	2.79	0.09
Ductular Reaction	34%	50%	32%	68%	2.46	0.12	3.35	0.07
Bridging Fibrous Septa	4%	61%	4%	6%	61.50	**<0.01**	60.25	**<0.01**
Iron Deposition	12%	29%	25%	4%	5.34	**0.02**	0.19	0.66
Lymphocytic Infiltrate	15%	18%	19%	19%	0.11	0.74	0.02	0.88
Neutrophilic Infiltrate	1%	7%	2%	34%	5.36	**0.02**	1.65	0.20

Disclosures: Priyanka Singh: Nothing to Disclose, Smruti Rath: Nothing to Disclose, Thomas Schiano: Nothing to Disclose, Gene Im: Nothing to Disclose

1507 | UNCOVERING THE DIVERSE ROLES OF LIVER MACROPHAGES IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS

Yang Wang[1] Yukun Guan[1] Dechun Feng[1] Luca Maccioni[1] Maria A Parra[2] Brandon Peiffer[2] Bryan Mackowiak[1] Takashige Kuwabara[3] Kiyoshi Mori[4] Masashi Mukoyama[3] Ramon Bataller[5] Zhaoli Sun[2] Bin Gao[1], [1]NIH/NIAAA, [2]Johns Hopkins University School of Medicine, Baltimore, [3]Kumamoto University Graduate School of Medical Sciences, [4]Shizuoka General Hospital, [5]Hospital Clinic, Barcelona, Spain

Background: Patients with alcohol-associated cirrhosis (AC) may develop severe alcohol-associated hepatitis (sAH), a disease with high short-term mortality. Our previous studies have demonstrated that sAH, but not AC livers, are infiltrated with high number of self-sustaining IL-8$^+$ neutrophils that likely drives the transition from AC to sAH. Monocyte-derived macrophages (MoMFs) also infiltrate the liver in sAH, but their roles remain largely obscure. **Methods:** In this study,we employed scRNA-seq, bulk RNA-seq, and multiplex immunofluorescence analyses to characterize liver macrophages in AC and sAH patients. Several experimental models of alcohol-induced liver injury were used to examine the roles of several population macrophages in mice. **Results:** In the current study, we characterized liver macrophages in sAH and AC. Our data revealed a marked reduction of Kupffer cells, while MoMFs were increased in sAH and AC. Single-cell RNA Seq analyses identified several populations in both AC and sAH including *C1Q*$^+$, *S100A8*$^+$, *APOE*$^+$, *TNF*$^+$ and *VSIG4*$^+$ macrophages, with sAH containing unique *C1Q*$^+$ macrophages potentially playing a role in removing apoptotic neutrophils in sAH. *C1Q*$^+$ macrophages also express a large number of genes involved in phagocytosis, pro-inflammatory, anti-inflammatory functions, suggesting that *C1Q*$^+$ macrophages have diverse functions in sAH. The roles of *C1Q*, *S100A8,* and *APOE* were further examined in experimental models of alcohol-induced liver injury. Our data revealed that *C1q* KO mice and macrophage-specific *S100a8* KO mice had similar alcohol-induced liver injury and hepatic neutrophil infiltration, while *Apoe* KO mice developed much more severe liver injury than WT mice following chronic-plus-binge ethanol challenge. **Conclusion:** Taken together, sAH and AC are infiltrated with multiple populations of macrophages playing diverse functions to drive chronic disease progression. Unique *C1Q*$^+$ macrophages in sAH play a compensatory role in removing dead cells but may also promote inflammation in sAH.

Disclosures: Yang Wang: Nothing to Disclose, Yukun Guan: Nothing to Disclose, Dechun Feng: Nothing to Disclose, Luca Maccioni: Nothing to Disclose, Maria A Parra: Nothing to Disclose, Brandon Peiffer: Nothing to Disclose, Bryan Mackowiak: Nothing to Disclose, Takashige Kuwabara: Nothing to Disclose, Kiyoshi Mori: Nothing to Disclose, Masashi Mukoyama: Nothing to Disclose, Ramon Bataller: Nothing to Disclose, Zhaoli Sun: Nothing to Disclose, Bin Gao: Nothing to Disclose

1508 | NON-ABSORBABLE ANTIBIOTICS WORSEN ALCOHOL-ASSOCIATED LIVER DISEASE IN GASTRIC ACID–SUPPRESSED MICE

Fernanda Raya Tonetti[1] Hui Han[1] Mitchell Schubert[2] Masoumeh Sikaroodi[3] Patrick Gillevet[3] Sonja Lang[4] Münevver Demir[5] Wilfred van der Donk[6] Jasmohan Bajaj[7] InTeam Consortium[8] Cynthia Hsu[1] Cristina Llorente[9], [1]Department of Medicine, University of California San Diego, La Jolla, CA, [2]Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA, [3]Microbiome Analysis Center, George Mason University, Manassas, VA, [4]Faculty of Medicine, University of Cologne, Cologne, Germany, [5]Campus Virchow Clinic, Charité University Medicine, Berlin, Germany, [6]University of Illinois at Urbana-Champaign, Urbana, IL, USA, [7]Virginia Commonwealth University, [8]InTeam Consortium, [9]University of California, San Diego

Background: Proton pump inhibitors (PPIs), which suppress gastric acid secretion, promote intestinal dysbiosis and liver disease progression in mice and humans by facilitating the expansion of intestinal *Enterococcus faecalis* and its translocation to the liver. *E. faecalis* produces cytolysin, a two-subunit exotoxin, that causes hepatocyte death. Fecal cytolysin in

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patients with alcohol-associated hepatitis (AH) predicts mortality, while targeted bacteriophage therapy reduces liver damage in humanized mice colonized with AH patient-derived microbiota. This study investigated whether gastric acid suppression-related dysbiosis and treatment with non-absorbable antibiotics targeting Gram-positive bacteria could modulate alcohol-associated liver disease (ALD) progression. **Methods:** Female *Atp4a*$^{SI/SI}$ mice, with inhibited gastric acid secretion, and WT littermates received the Lieber DeCarli diet for 9 weeks. Fecal DNA was extracted for 16S rRNA sequencing. A subset of *Atp4a*$^{SI/SI}$ mice received daily oral gavage of vancomycin (100 mg/kg) and bacitracin (273 mg/kg) during the last 4 weeks. Fecal 16S rRNA sequencing on AH patients (n = 44) with and without PPI use was analyzed from the multicenter InTeam cohort. **Results:** Alcohol-fed *Atp4a*$^{SI/SI}$ mice had increased Gram-positive taxa (*Aerococcus*, *Lactobacillus*, *Enterococcus*, and *Streptococcus*). *E. faecalis*-derived cytolysin was present and functional in *Atp4a*$^{SI/SI}$ and PPI-treated mice. Intriguingly, non-absorbable antibiotics targeting Gram-positive bacteria worsened ethanol-induced steatohepatitis, with elevated transaminases, steatosis, and increased expression of *Cxcl1*, *Cxcl2*, *Tnfa*, *Ccl5*, and *Tgfb1*. Although bacterial overgrowth declined to WT levels, with reductions in *A. viridans*, *Enterococcus*, and *Lactobacillus*, increases in *Streptococcus*, *Enterobacteriaceae*, *Parasutterella*, and *Helicobacter* were observed. Antibiotic-treated *Atp4a*$^{SI/SI}$ mice exhibited increased bacterial translocation to the liver. Similarly, PPI use in patients with AH correlated with increased *Enterococcus* and *Streptococcus* and higher 30-day mortality. Testing *in vitro* therapeutic strategies, we found that dipalmitoylphosphatidylcholine reduced cytolysin hemolysis, and caspase-1/11 inhibitors reduced cytolysin activity in primary mouse hepatocytes. **Conclusion:** Gastric acid suppression combined with non-absorbable antibiotics worsens ALD by disrupting gut microbiota and promoting bacterial translocation, underscoring the need for cautious use.

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1509 | ETHANOL DECREASES CPT2-MEDIATED CARNITINE CATABOLISM TO PROMOTE STEMNESS IN ALCOHOLIC HEPATOCELLULAR CARCINOMA

Ronghua Jin[1] *Xiaoxue Yuan*[1] *Yang Wang*[1] *Song Yang*[1] *Wenqian Geng*[1] *Xi Wang*[1], [1]*Beijing Ditan Hospital, Capital Medical University*

Background: Alcoholic Liver Cancer (ALC) is a liver disease resulting from prolonged excessive alcohol consumption. Chronic alcohol abuse can lead to pathological changes such as fatty liver, alcoholic hepatitis, and cirrhosis, which may eventually progress to Hepatocellular Carcinoma (HCC). Globally, liver cancer is one of the leading causes of cancer-related deaths, and alcoholic liver cancer, as a specific type, is particularly prevalent in regions with high alcohol consumption. The incidence of alcoholic liver disease is notably high in certain Asia-Pacific countries (such as China, Japan, and South Korea) and Eastern Europe, where the burden of liver cancer is also significant. Early diagnosis of alcoholic liver cancer remains challenging, and effective treatment methods are still lacking. Therefore, early diagnosis and further research into the molecular mechanisms of alcoholic liver cancer are crucial for improving survival rates. This not only helps to elucidate the pathogenesis of liver cancer but also provides a theoretical foundation for developing new treatment strategies. **Methods:**
CPT2 expression levels were analyzed using the TCGA database. Immunofluorescence staining was conducted on liver tissue sections from patients with alcoholic liver disease. RNA and protein were extracted from the liver tissues of patients with alcoholic liver cancer (ALC), and CPT2 expression levels were evaluated. HepG2 cells were treated with 200 mM ethanol, followed by the detection of mRNA and protein levels, as well as transcriptome sequencing. **Results:** Analysis of the TCGA database reveals a significant reduction in CPT2 expression in liver cancer patients. Immunofluorescence staining demonstrates that the progression of alcoholic liver disease is associated with a marked decrease in CPT2 expression. In comparison to adjacent normal tissues, both mRNA and protein levels of CPT2 are considerably lower in alcoholic liver cancer tissues. At the cellular level, ethanol exposure significantly diminishes CPT2 expression. Transcriptome sequencing indicates that post-ethanol treatment, genes are predominantly enriched in the Hippo pathway and cancer stem cell regulatory pathways. **Conclusion:** The high incidence and low cure rate of alcoholic liver cancer present a substantial challenge to global public health. This study reveals that ethanol reduces CPT2 expression and subsequently decreases CPT2-mediated carnitine catabolism, thereby promoting stemness

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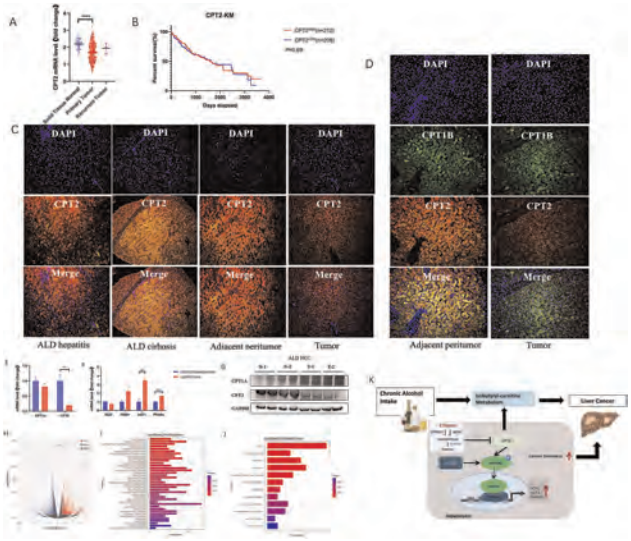
in alcoholic hepatocellular carcinoma. These findings offer a crucial theoretical basis for strategies aimed at reducing the incidence and mortality of alcoholic liver cancer.



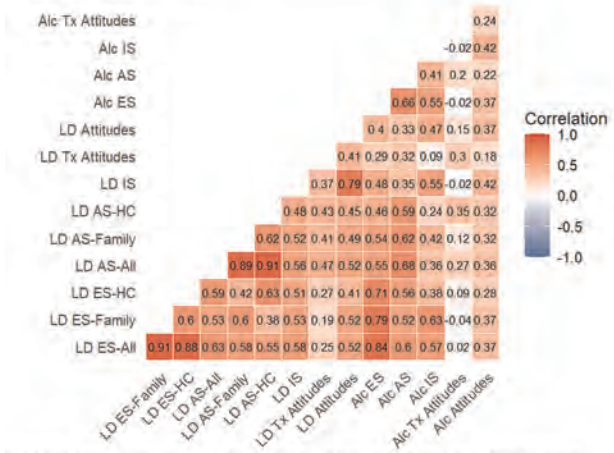
Disclosures: Ronghua Jin: Nothing to Disclose, Xiaoxue Yuan: Nothing to Disclose, Yang Wang: Nothing to Disclose, Song Yang: Nothing to Disclose, Wenqian Geng: Nothing to Disclose, Xi Wang: Nothing to Disclose

1510 | DEVELOPMENT AND VALIDATION OF THE LIVER DISEASE STIGMA SCALE (LDSS)

Wei Zhang[1] Kelly Hsu[2] Edward Wu[1] Ellen Zhen[1] Ana Ivkovic[1] Heidi Yeh[1] Emily Bethea[1] Sarah Wakeman[1] Russell Goodman[1] Esperance Schaefer[3] Jay Luther[1] Nneka Ufere[1] Raymond Chung[1] Annie Fox-Galalis[4], [1]Massachusetts General Hospital, [2]Tufts University School Of Medicine, [3]Brigham and Women's Hospital, [4]MGH Institute of Health Professions

Background: Liver disease stigma is an underrecognized barrier to equitable care. Patients with liver disease, particularly those with alcohol-associated liver disease (ALD), may experience stigma from both family and healthcare providers. Patients with ALD may internalize (apply negative stereotypes to the self) or anticipate stigma (worry about being the target of discrimination), contributing to delayed treatment, poor engagement and limited access to transplant. Despite growing attention to this issue, no validated instrument currently exists to measure liver disease–specific stigma across key stigma domains. We developed and validated the Liver Disease Stigma Scale (LDSS) to address this gap. **Methods:** Guided by stigma theory (Earnshaw & Chaudoir; Link & Phelan) and prior qualitative findings, we adapted the Substance Use Stigma Mechanisms Scale (SU-SMS) to measure stigma in the context of liver disease. The LDSS includes items assessing internalized, anticipated, and experienced stigma in both family and healthcare providers. Ten additional items were developed to capture liver disease–specific experiences. The survey was completed by 221 adults with liver disease, including 133 (60%) with ALD and 88 (40%) with non-alcohol-related etiologies. The sample was 55.5% male, with 56.0% diagnosed with cirrhosis. Exploratory factor analysis with oblimin rotation was used to confirm factor structure, and internal consistency was assessed using Cronbach's alpha. Convergent validity was assessed by examining associations between LDSS subscale scores and external measures of alcohol-related stigma (SU-SMS), as well as measures of attitudes toward AUD, ALD, and their respective treatments. **Results:** Each stigma domain (internalized, anticipated, and experienced) of the LDSS demonstrated strong internal consistency (Cronbach's alpha $>$ 0.85 in pilot testing), and an exploratory factor analysis confirmed the presence of theoretically consistent constructs (e.g., internalized liver stigma, anticipated stigma from healthcare providers, experienced stigma from family). LDSS subscale scores showed strong convergent validity, with moderate to strong positive correlations with stigma related to alcohol use and negative attitudes towards their AUD, ALD and respective treatments, supporting the scale's potential to identify patients at risk for care disengagement. (Figure). **Conclusion:** The LDSS is the first multidimensional instrument designed to assess liver disease–specific stigma. Its strong psychometric properties and theoretical grounding support its utility for stigma research and intervention development in hepatology, particularly for identifying stigma-related barriers and tailoring care for patients with alcohol-associated liver disease.

Figure: Correlation heatmap showing associations between liver disease stigma (LDSS) subscales, alcohol-related stigma (SU-SMS), and treatment-related attitudes. Diagonal self-correlations (e.g., a scale correlated with itself) are 1.0 but are not shown here due to the lower-triangular format.



LD: Liver disease, Alc: Alcohol, Tx: treatment, AS; anticipated stigma, IS: Internalized stigma, ES; Experienced stigma, HC: healthcare providers

Disclosures: Wei Zhang: Nothing to Disclose, Kelly Hsu: Nothing to Disclose, Edward Wu: Nothing to

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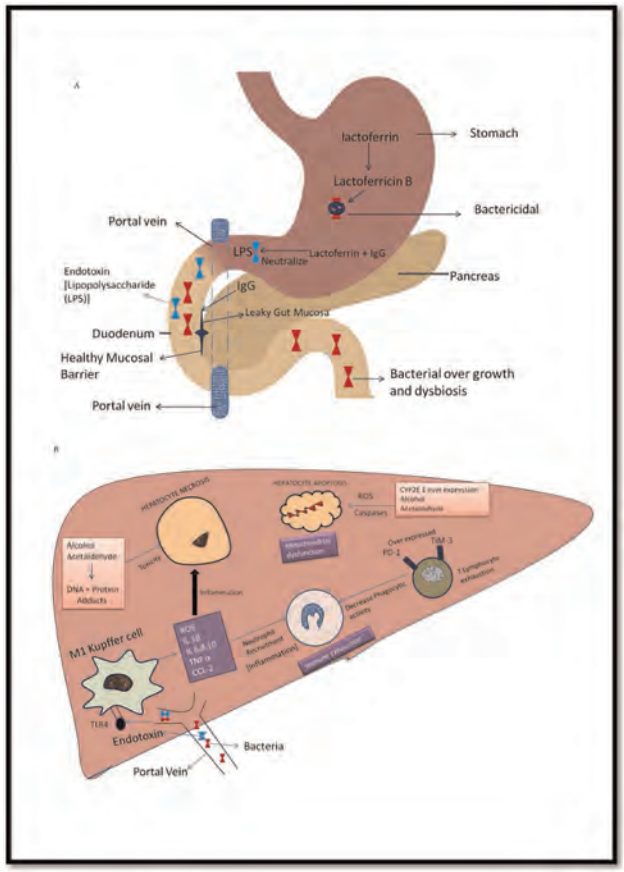
Disclose, Ellen Zhen: Nothing to Disclose, Ana Ivkovic: Nothing to Disclose, Heidi Yeh: Nothing to Disclose, Emily Bethea: Nothing to Disclose, Sarah Wakeman: Nothing to Disclose, Russell Goodman: Nothing to Disclose, Esperance Schaefer: Nothing to Disclose, Jay Luther: Nothing to Disclose, Nneka Ufere: Nothing to Disclose, Raymond Chung: Nothing to Disclose, Annie Fox-Galalis: Nothing to Disclose

1511 | EFFICACY AND SAFETY OF BOVINE COLOSTRUM IN THE TREATMENT OF SEVERE ALCOHOL-ASSOCIATED HEPATITIS: A MULTICENTER DOUBLE-BLIND, PLACEBO-CONTROLLED RANDOMIZED TRIAL

Sandeep Sidhu[1] Omesh Goyal[2] Ajay Duseja[3] Shalimar Shalimar[4] Sandeep Nijhawan[5] Dharmesh Kapoor[6] Harsh Kashyap[7] Prasanna Samuel[8] Saravanaraj Karuppasamy[9], [1]Christian Medical College & Hospital. Ludhiana, [2]Dayanand Medical College & Hospita, [3]Post Graduate Institute of Medical Education & Research, Chandigarh, [4]All India Institute of Medical Sciences, New Delhi, [5]Sawai Man Singh Medical College, Jaipur, [6]Global Hospital, Hyderabad, [7]Dayanand Medical College & Hospital, Ludhiana, [8]Christian Medical College, Vellore, [9]Christian Medical College, Vellore

Background: Severe alcohol-associated hepatitis is associated with hepatocyte necrosis, inflammation, paradoxical immune exhaustion and leaky gut,. The leading cause of mortality is bacterial infection with multi-organ failure. Corticosteroids provide only a short-term survival benefit in this disease. Bovine colostrum, rich in immunoglobulins and lactoferrin, neutralizes endotoxin and repairs the leaky intestinal mucosal barrier. We aimed to study the efficacy and safety of bovine colostrum in severe alcohol-associated hepatitis. **Methods:** This multicenter, double-blind study included patients with "probable" severe alcohol-associated hepatitis. Patients were registered with the "Trans European Network for Clinical Trials Services" They received 20 grams of freeze-dried bovine colostrum (n = 89) or placebo (Pasteurized milk powder) (n = 85) three times daily for four weeks. The primary outcome was survival at 90 days. Secondary outcomes included survival at 30 days, changes in liver pathobiology, serum cytokines, and episodes of sepsis over one month from baseline. Sensitivity Analysis: Relative Risk (RR) of mortality - Unadjusted and Adjusted (For Centre, Acute Kidney Injury, and Ascites grade) was performed for Actual Observed Outcomes, Best-case scenario and Worst-case scenario assumptions. Grades of Severity of the Adverse Events were as per the Common Terminology Criteria for Adverse Events, Version 5.0. Statistical analysis was done using IBM SPSS v.22.0 and R (version 4.3.1) **Results:** Survival at 90 days was significantly higher - 89.9% (80/89) in the colostrum arm [Model of End Stage Liver Disease score - 30.2 (Interquartile Range: 27.9-33.4)] compared to 57.6% (49/85) in the placebo arm [Model of End-Stage Liver Disease score - 31.5 (Interquartile Range: 27.9-34.2)] ($p < 0.0001$) - Hazard Ratio 0.18, 95% Confidence Interval: 0.09 - 0.38, ($p < 0.001$). Restricted mean survival time was 26.8 days longer in the colostrum arm ($p < 0.001$). The experimental arm had significantly higher survival ($p < 0.0001$), a decrease in serum endotoxin ($p < 0.001$), tumor necrosis factor-alpha levels ($p = 0.01$), and sepsis episodes ($p = 0.04$) at one month. Unadjusted RR for mortality was 0.24, $p < 0.001$; Adjusted RR was 0.22, $p < 0.001$- normal outcomes, unadjusted RR was 0.17, $p < 0.001$; the adjusted RR was 0.22, $p < 0.001$ - best case scenario, RR risk was 0.37 $p < 0.001$, adjusted RR was 0.42 $p < 0.01$ - worst-case scenario. The Relative Risk of mortality was lower in Colostrum arm. Serious adverse events were equivalent in both groups. **Conclusion:** Bovine colostrum significantly improved 90- and 30-day survival in patients with very severe alcohol-associated hepatitis by reducing serum endotoxin levels and tumor necrosis factor-alpha, as well as decreasing the frequency of sepsis episodes and improving gut integrity (decreased endotoxemia). Most deaths occurred in the first month in our study as in all Indian studies due to sepsis with few deaths later.



Disclosures: Sandeep Sidhu: Nothing to Disclose, Omesh Goyal: Nothing to Disclose, Ajay Duseja:

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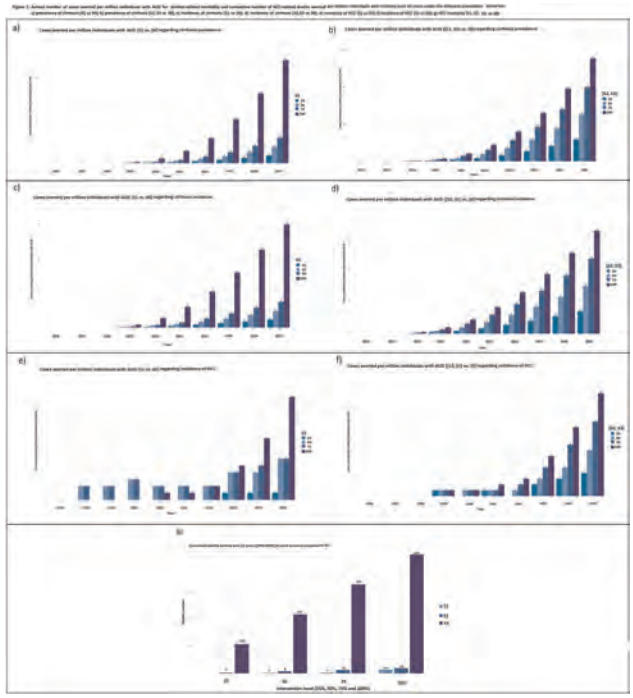
Nothing to Disclose, Shalimar Shalimar: Nothing to Disclose, Sandeep Nijhawan: Nothing to Disclose, Dharmesh Kapoor: Nothing to Disclose, Harsh Kashyap: Nothing to Disclose, Prasanna Samuel: Nothing to Disclose, Saravanaraj Karuppasamy: Nothing to Disclose

1512 | IMPACT OF PREVENTION STRATEGIES ON MORBIDITY AND MORTALITY AMONG PEOPLE WITH ALCOHOL USE DISORDERS IN FRANCE: A MODELLING STUDY (MOENA PROJECT)

Abbas MOURAD[1] Maria Patrizia Carrieri[1] Fabienne Marcellin[1] Marc Bourliere[2] Julien Mancini[1] Camelia Protopopescu[1], [1]Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Économiques & Sociales de la Santé, [2]Département d'hépatologie et Gastroentérologie, Hôpital Saint Joseph, Marseille, France

Background: Harmful alcohol use is a major cause of cirrhosis and hepatocellular carcinoma (HCC). This study uses mathematical modelling to assess the impact of different combinations of prevention strategies on changes in the prevalence and incidence of alcohol-related cirrhosis, HCC and mortality among people with alcohol use disorders (AUD) in France. **Methods:** A Markov model was developed to simulate disease progression to alcohol-related cirrhosis, HCC, and death between 2026 and 2035 among adult people with AUD in France. At each annual cycle, individuals can move between different health states depending on their clinical status and the prevention or care interventions received. The model was first parameterized during the 2000-2025 period using multiple data sources, and its outputs were validated against existing data on AUD prevalence in 2021, as well as cirrhosis prevalence/incidence and HCC incidence in 2017–2018. The model estimates the prevalence/incidence of alcohol-related cirrhosis, HCC, and mortality under 4 scenarios: S0: baseline scenario (no intervention); S1: S0+ a relative increase in the screening rate of harmful alcohol use and brief interventions in primary care varying from 25% to 100% (baseline rate: 16.8%); S2: S1 + a relative increase in access to AUD treatments of 25% to 100% (baseline rate: 48%); S3: S2 + a relative increase of 25% to 100% in the HCC screening rate (baseline rate: 20.7%). **Results:** Figure1 presents the model results on the number of cases averted for the alcohol-related cirrhosis prevalence, incidence, and HCC per million individuals with AUD, and of HCC-related deaths per million individuals with cirrhosis over the period 2026-2035. Application of S1 (vs S0) would avoid 35 to 478 cases of prevalent cirrhosis, 11 to 149 new cases of cirrhosis, as well as 1 to 10 new HCC cases in 2035. Application of S2/S3 (vs S0) would avoid 117 to 554 cases of prevalent cirrhosis, 35 to 160 new cases of cirrhosis, and 3 to 12 new HCC cases in 2035. The application of these scenarios also makes it possible to avoid a cumulative number of HCC deaths over 10 years of 0 to 14 cases for S1, 3 to 19 cases for S2 and 108 to 437 cases for S3 (vs S0). **Conclusion:** The combined implementation of prevention strategies, including early screening of AUD and HCC, and improving access to AUD treatments, could significantly reduce the prevalence and incidence of alcohol-related morbidity and mortality among people with AUD in France over a relatively short period.



Disclosures: Abbas MOURAD: Nothing to Disclose, Maria Patrizia Carrieri: Nothing to Disclose, Fabienne Marcellin: Nothing to Disclose, Marc Bourliere: Gilead: consultant, AbbVie: speaker, GSK: advisor, Julien Mancini: Nothing to Disclose, Camelia Protopopescu: Nothing to Disclose

1513 | DIGITAL PHENOTYPING CAPTURES REGRESSION OF LIVER FIBROSIS IN ALCOHOLIC CIRRHOSIS IN PARALLEL WITH ABSTINENCE-INDUCED CLINICAL IMPROVEMENT

Adelina Horhat[1] Adi Lightstone[2] Li Chen[3] Horia Stefanescu[4] ioana Rusu[4] Vincent Leroy[5] Marika Rudler[6] Leila Kara[7] Vlad Ratziu[8] Mathieu Petitjean[3], [1]Hopital Henri Mondor, Créteil, France, [2]PharmaNest,

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Background: Conventional pathology (CP) has limited ability to document fibrosis regression in cirrhosis. AI-assisted digital pathology (DP) detects changes in fibrotic matrix not captured by CP, offering enhanced sensitivity for tracking fibrosis dynamics. In pts with alcoholic cirrhosis prolonged abstinence induces clinical improvement which may reflect partial fibrosis regression. We applied the automated FibroNest™ single-fiber DP (PharmaNest, Princeton, USA) to assess fibrosis phenotype changes after alcohol abstinence in patients with severe alcoholic hepatitis (SAH). **Methods:** Paired liver biopsies from 9 pts (7 men) with histologically confirmed SAH (Maddrey ≥ 32) and a control liver biopsy after alcohol abstinence (6-15 months) were included. Tissue sections stained with Masson's Trichrome were processed using an AI-powered FibroNest™ DP platform. Composite scores of collagen quantity, morphometry (fiber shape and size) and fibrosis architecture (structural organization) were integrated into a Phenotypic Fibrosis Composite Score (Ph-FCS) to assess overall fibrosis severity and describe fibrosis temporal changes. **Results:** Median age was 47 yrs, bilirubin 5.2 mg/dL, INR 1.84, Maddrey DF 67, MELD 20. 8 pts had confirmed cirrhosis, 7 had ascites, 6 esophageal varices, median HVPG 16 mmHg (range 12-19). 7 patients were treated with corticosteroids. After confirmed abstinence the clinical condition improved: Child (A5/B7, 8/1 pts), no clinical ascites, median reduction in MELD 10, Bilirubin 3.6 mg/dl, INR 0.6, HVPG 5 mmHg. Despite unchanged cirrhosis stage in all pts at follow-up biopsy, there was measurable fibrosis regression with the mean Ph-FCS decreasing from 4.8 (se 0.27) at baseline to 3.6 (se 0.39) at follow-up ($p = 0.01$). Most pronounced improvements were observed in collagen deposition (5.83 to 3.42, $p < 0.01$) and fiber morphometry (2.36 to 1.2, $p = 0.001$). Mean PhFCS decrease was larger with longer duration between biopsies: -1.72 ($>$1yr, $N = 5$) vs -0.53 ($<$1yr). In contrast, architecture scores showed greater variability and smaller changes, suggesting that architectural remodeling may lag behind matrix regression. **Conclusion:** DP overcomes limitations of CP by showing fibrosis regression after alcohol abstinence, in parallel with clinical improvement. These results confirm the reversibility of fibrosis at the cirrhotic stage and highlight the value of AI-powered sensitive quantification of fibrosis regression for monitoring and therapeutic evaluation.

Disclosures: Adelina Horhat: Nothing to Disclose, Adi Lightstone: Nothing to Disclose, Li Chen: Nothing to Disclose, Horia Stefanescu: Nothing to Disclose, ioana Rusu: Nothing to Disclose, Vincent Leroy: Nothing to Disclose, Marika Rudler: Nothing to Disclose, Leila Kara: Nothing to Disclose, Vlad Ratziu: Novo-Nordisk: Consultant, Boehringer-Ingelheim: Consultant, Madrigal: Consultant, Akero: Consultant, 89Bio: Consultant, Sagimet: Consultant, Mathieu Petitjean: PHARMANEST INC: Employee, PHARMANEST INC: Stock – privately held company

1514 | EXTRACELLULAR VESICLES (EVS) FROM INFLAMED LIVER SINUSOIDAL ENDOTHELIAL CELLS (LSECS) PROMOTE ALCOHOL-ASSOCIATED HEPATITIS THROUGH ACTIVATING FIBROGENIC AND LIPOGENIC PATHWAYS

Young-Ri Shim[1] Yasuko Iwakiri[1], [1]Yale University

Background: Liver sinusoidal endothelial cells (LSECs) are essential for maintaining the hepatic microenvironment through their barrier, signaling, and scavenging functions. In alcohol-associated hepatitis (AH), LSECs undergo pathological changes, characterized by dysfunction and inflammatory activation, which may impact cellular crosstalk and promote liver injury. We hypothesized that in severe AH, dysfunctional and inflammatory LSECs release extracellular vesicles (EVs) that reprogram hepatocytes and hepatic stellate cells (HSCs) toward proinflammatory, lipogenic, and fibrogenic phenotypes, thereby amplifying disease progression. **Methods:** LSECs and their EVs from control and AH mice were provided by the University of Southern California's Integrative Liver Cell Core (R24AA012885). These AH mice were fed chow (control) or a hybrid high-fat diet (HCFD) for 2 weeks, followed by 8 weeks of intragastric ethanol infusion (~27 g/kg/day) with weekly binge doses (3.5–5 g/kg), and developed elevated ALT levels (274 ± 36 U/L) and histological features of PMN infiltration, ductular reaction, and fibrosis. We examined LSECs and EVs by RNA-seq and small RNA-seq analyses, respectively. The effects of LSEC-derived EVs on hepatocytes (GSE259058) and HSCs (GSE176042) were evaluated. **Results:** LSECs from AH mice exhibited inflammatory signature, with significant upregulation of *Il1b* (3.52-fold), *Il15* (5.38-fold), *Ccl3* (10.14-fold), *Ccl4* (5.02-fold), and *Ccl5* (3.19-fold) (all $p < 0.01$). Markers of capillarization were also elevated, including Vwa1 (2.28-fold), Vwf (1.4-fold), CD34 (4.09-fold), and Fabp5 (2.53-fold) (all $p < 0.05$). Genes associated with membrane trafficking and EV biogenesis, such as Anxa1, Anxa2, and Anxa6, were significantly upregulated (1.99–2.58-fold; all $p < 0.01$). EVs isolated from AH-LSECs were

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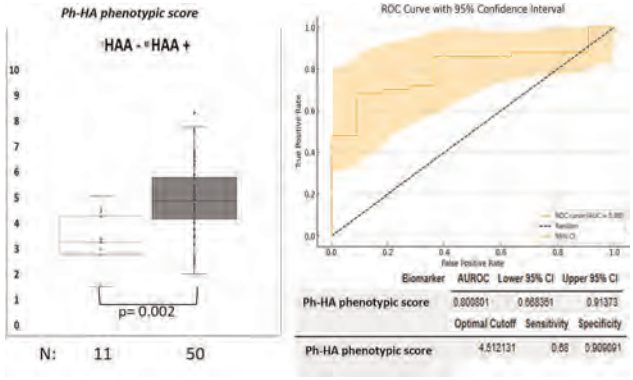
enriched in miR-320-5p (1.54-fold) ($p < 0.05$) and miR-155-5p (1.52-fold) ($p < 0.05$). Target gene analysis revealed that predicted miR-155-5p targets were upregulated in HSCs and hepatocytes, including ATCA1 in HSCs (2.49-fold; $p < 0.05$) and MET and FOS in hepatocytes (1.75- and 8.83-fold, respectively; $p < 0.01$). Predicted targets of miR-320-5p involved in lipid metabolism, such as LEPR and SCD1, were also markedly increased (17.46- and 17.74-fold; $p < 0.05$), consistent with a lipogenic shift. **Conclusion:** In severe AH, LSECs acquire a capillarized and inflammatory phenotype accompanied by increased release of EVs. These EVs, enriched in miR-155-5p and miR-320-5p, promote fibrogenic activation of HSCs and lipogenic/oncogenic reprogramming of hepatocytes. These findings highlight LSEC-derived EVs as active mediators of disease progression and suggest they may represent a novel therapeutic target in alcohol-associated hepatitis. **Disclosures:** Young-Ri Shim: Nothing to Disclose, Yasuko Iwakiri: Nothing to Disclose

1515 | ALCOHOLIC HEPATITIS IS ASSOCIATED WITH DISTINCT PHENOTYPIC CHANGES OF THE HEPATIC FIBROTIC MATRIX AS EVIDENCED BY QUANTITATIVE DIGITAL PATHOLOGY: IMPLICATIONS FOR DIAGNOSIS AND PROGNOSIS

Marika Rudler[1] Adi Lightstone[2] Li Chen[2] Charlotte Bouzbib[1] Leila Kara[3] Dominique Thabut Damais[4] Frederic Charlotte[1] Vlad Ratziu[5] Mathieu Petitjean[2], [1]Hospital Pitié Salpêtrière, [2]PHARMANEST, [3]ICAN, [4]Hospital Pitié Salpetriere, [5]Service D' Hepatogastroenterologie (FR)

Background: Alcoholic hepatitis (AH) is a severe form of alcohol-related liver injury which is defined histologically by non-specific findings and occurs often in patients (pts) with cirrhosis. We investigated whether the extracellular matrix presents distinct phenotypic changes in pts with AH that could substantiate the diagnosis and derive specific diagnostic or prognostic biomarkers. **Methods:** Pts with clinical suspicion of severe AH, Maddrey discriminant function (MDF) ≥ 32 underwent transjugular liver biopsy for histological confirmation. Biopsies stained with Masson's Trichrome were analyzed using FibroNest^{TM}, a high-resolution single-fiber digital pathology platform, to quantify fibrosis traits grouped into three sub-phenotypes: collagen quantity, fiber morphometry, and architectural complexity. These traits were aggregated into Ph-FCS, a continuous fibrosis severity biomarker. Divergent fibrosis traits between pts with (AH+) and without (AH-) histologically confirmed AH were also calibrated into a Ph-AHS specific AH biomarker. **Results:** 61 pts (45 men) were included, mean age 52 yrs (sd 12.4), MELD 26 (sd 5.7), Bilirubin 14.9 mg/dl (sd 10), MDF 73 (range 34-177). All pts had cirrhosis and 50 had histologically confirmed AH. The Ph-AHS was higher in the 50 AH+ pts than in the 11 AH- (median 4.86 vs 3.24, $p = 0.002$) indicating a distinct fibrosis phenotype in AH. The most discriminative fibrosis traits were related to collagen deposition and fiber morphometry. Ph-AHS had a AUROC of 0.80 (95% CI:0.66–0.91) for the diagnosis of AH with 68% sensitivity, and 91% specificity at an optimal cutoff of 4.51. In contrast the overall fibrosis Ph-FCS biomarker was lower but not significantly different between AH+ and AH- pts: (mean 5.3 vs. 5.9 in HAA+, $p = 0.053$), with an AUROC of 0.69 (95% CI:0.53–0.84), suggesting comparable overall fibrosis burden despite underlying phenotypic differences. Pts with AH who survived free of liver transplantation at 3 months ($N = 30$) had a marginally lower median Ph-FCS (3.2 vs 4.0, $p = 0.04$), suggesting a more severe fibrotic phenotype in non-survivors. **Conclusion:** In pts with alcohol-related liver disease, the occurrence of AH coexists with distinct phenotypic remodeling of the fibrotic matrix. DP can identify these changes and quantify them with a new digital biomarker score, Ph-AHS which could improve the diagnosis of AH. In these patients with advanced disease the fibrosis amount is only a weak predictor of survival.



Disclosures: Marika Rudler: Nothing to Disclose, Adi Lightstone: Nothing to Disclose, Li Chen: Nothing to Disclose, Charlotte Bouzbib: Nothing to Disclose, Leila Kara: Nothing to Disclose, Dominique Thabut Damais: Nothing to Disclose, Frederic Charlotte: Nothing to Disclose, Vlad Ratziu: Novo-Nordisk: Consultant, Boehringer-Ingelheim: Consultant, Madrigal: Consultant, Akero: Consultant, 89Bio: Consultant, Sagimet: Consultant, Mathieu Petitjean: PHARMANEST INC: Employee, PHARMANEST INC: Stock – privately held company

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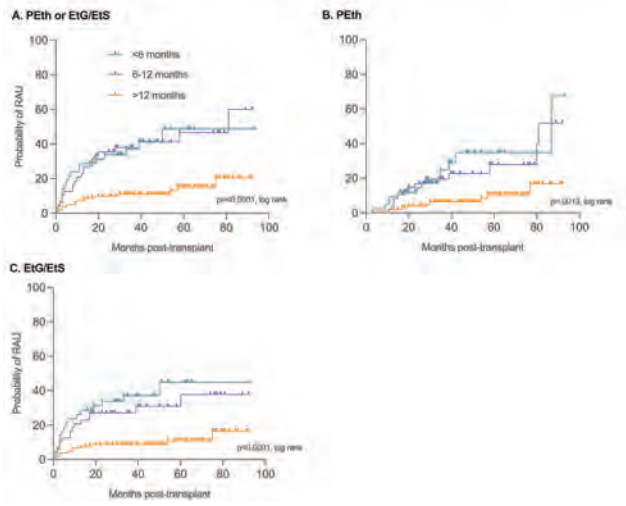
1516 | PRE-TRANSPLANT SOBRIETY PREDICTS WHEN, NOT IF, PATIENTS RETURN TO ALCOHOL USE AFTER LIVER TRANSPLANT

Sienna Li[1] Kelly Hsu[2] Sophie Van Tulder[3] Maria Diaz Soto[4] Maria Cote[3] Natalia Payan[3] Sofia Baptista[3] Eric Przybyszewski[3] Ana Ivkovic[3] Mladen Nisavic[3] Wei Zhang[3] Heidi Yeh[3] Emily Bethea[3], [1]University of Washington, [2]Tufts University School of Medicine, [3]Massachusetts General Hospital, [4]Beth Israel Medical Center

Background: Alcohol-associated liver disease (ALD) remains the leading indication for liver transplantation (LT). Biomarker-based testing offers greater reliability than self-reported data in detecting return to alcohol use (RAU) and plays a critical role in informing clinical decisions. However, further research is warranted to assess pre-transplant sobriety as a predictor of RAU and post-transplant survival. **Methods:** We conducted a single center, retrospective, cohort study of all adult (>18 years) patients with ALD who received a LT between 2016-2022. Medical records were queried for demographics, psychosocial variables, pre-transplant sobriety duration and one-year post transplant mortality. Logistic regression was used to correlate these factors with post-transplant RAU, defined as a positive urine ethyl glucuronide (EtG), urine ethyl sulfate (EtS), or serum phosphatidylethanol (PEth). **Results:** 194 LT recipients, with median age 59 years, were majority white (91%), male (72%), unemployed (61%), with English as their preferred language (97%). 125 (64%) patients were tested for biomarkers during the post-transplant period, and 52 (27% of all patients, 42% of those tested) tested positive for one or more alcohol biomarkers at least once. Median follow-up time from date of transplant was 43 months (IQR 29-63). Median time to RAU was 24 months by PEth (IQR 13-40), 7.5 months by EtG/EtS (IQR 3-17), and 9.5 months by either test (IQR 3-20). A multivariable regression analysis showed no significant association between pre-LT sobriety duration and post-LT RAU. However, survival analysis identified a shorter time to RAU for patients with <6 months ($p < .0001$) and 6-12 months ($p < .0001$) of pre-LT sobriety, compared to those with >12 months sobriety. There was no difference in one-year post-LT mortality between patients with <6 months and those with >6-month pre-LT sobriety. **Conclusion:** We observed that one-year mortality and RAU outcomes were not impacted by pre-transplant sobriety duration, supporting evolving standards that favor individualized risk assessment over fixed abstinence periods. However, shorter pre-LT sobriety (<6 months) was associated with shorter time to RAU and thus a useful factor in identifying candidates who may benefit from increased psychosocial and addiction support during the early peri-transplant period.

Figure 1. Probability of return to alcohol use (RAU) by pre-transplant sobriety duration, Kaplan-Meier analysis



Disclosures: Sienna Li: Nothing to Disclose, Kelly Hsu: Nothing to Disclose, Sophie Van Tulder: Nothing to Disclose, Maria Diaz Soto: Nothing to Disclose, Maria Cote: Nothing to Disclose, Natalia Payan: Nothing to Disclose, Sofia Baptista: Nothing to Disclose, Eric Przybyszewski: Nothing to Disclose, Ana Ivkovic: Nothing to Disclose, Mladen Nisavic: Nothing to Disclose, Wei Zhang: Nothing to Disclose, Heidi Yeh: Nothing to Disclose, Emily Bethea: Nothing to Disclose

1517 | THE INTRACELLULAR COMPLOSOME: C5-MEDIATED MACROPHAGE REPROGRAMMING IN ALD

Shannon Twardy[1] Laura Saba[2] Rebecca McCullough[3], [1]Univeristy of Colorado, Anschutz Medical Campus, [2]University of Colorado Anschutz Medical Campus, [3]University of Colorado - Anschutz

Background: Complement activation and hepatic macrophages play critical roles in the pathogenesis of alcohol-associated liver disease (ALD). Complement activation has been observed in ALD patients and ALD preclinical models, resulting in C5a-mediated immune activation via C5aR1. While traditionally described as a serum-operative system, evidence supports a cell-autonomous, intracellular complement system (complosome). Here, we characterize the C5 complosome in hepatic macrophages and determine if phenotypic responses observed in ALD occur in a C5 complosome dependent manner. It is our working hypothesis that ethanol increases mitochondrial C5aR1 (mtC5aR1) localization and intracellular C5a binding to mtC5aR1 contributes to inflammatory phenotypes including

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macrophage polarization, cytokine production, and impaired phagocytosis in hepatic macrophages that contribute to hepatocellular damage. **Methods:** Liver explants from patients with Alcohol-associated hepatitis (AH) and healthy donors were profiled for complosome expression using VSIG4 and CD68 as markers of hepatic macrophages for multispectral imaging. In a preclinical model of ethanol accelerated fibrosis, CD45+ enriched hepatic cells were subjected to single cell sequencing. Immortalized mouse Kupffer Cells (ImKCs) were cultured with 50mM ethanol and challenged with ethanol and/or 10ng/mL lipopolysaccharide (LPS) for up to 24 hours. To determine if responses to ethanol and/or LPS were C5 complosome dependent, C5 and C5aR1 KO ImKCs were generated. Mouse hepatocytes (AML12 cells) were cultured with and without ethanol and conditioned media (CM) from ethanol- and LPS-treated ImKCs and Nile Red staining was used to assess neutral lipid accumulation. **Results:** Expression of C5aR1 was increased in CD68+ cells in AH explant tissue. *In vivo*, expression of c5ar1 was enriched by ethanol feeding in all identified macrophage clusters. C5 complosome component expression was increased after EtOH and LPS exposure in ImKCs. Ethanol increased mtC5aR1 localization in a time-dependent manner. Ethanol and LPS exposure enhanced pro-inflammatory markers and secretion of pro-inflammatory mediators and suppressed anti-inflammatory markers and phagocytosis. C5 or C5aR1 KO ImKCs suppressed pro-inflammatory polarization and cytokine production and restored anti-inflammatory marker and phagocytosis. Hepatocytes cultured with ethanol and CM from stimulated WT ImKCs had enhanced lipid accumulation, that was completely suppressed in hepatocytes cultured with CM from C5 or C5aR1 KO ImKCs. **Conclusion:** Macrophage expression of C5aR1 is conserved among AH patients and in preclinical models of ALD. These data highlight a novel function of complement as a mediator of macrophage effector function and contributor to hepatocellular injury. This may suggest a feasible mechanism by which macrophages are more responsive to pathogens following alcohol exposure.

Disclosures: Shannon Twardy: Nothing to Disclose, Laura Saba: Nothing to Disclose, Rebecca McCullough: Nothing to Disclose

1518 | WHEN IS LIVER TRANSPLANT FOR ALCOHOL-ASSOCIATED HEPATITIS TOO EARLY?

Claire Durkin[1] Therese Bittermann[2], [1]University of Pennsylvania, [2]Perelman School of Medicine

Background: Early liver transplant (LT) for severe alcohol-associated hepatitis (AAH) has been increasing in prevalence over the past decade. Although AAH is associated with high mortality, 10-28% of patients evaluated for LT for AAH experience hepatic recompensation. The goal of this study was to characterize the clinical outcomes of patients awaiting LT and patient factors associated with waitlist mortality in AAH. **Methods:** This was a retrospective cohort study of the United Network for Organ Sharing database of adults ($\geq$ 18 years) waitlisted for first time, single organ LTs for AAH from 1/1/2018 to 12/31/2024. AAH was identified based on primary and secondary diagnoses codes on initial LT application. Transplantation and waitlist drop-out were identified using registration removal codes. Demographic and clinical characteristics were compared by reason for waitlist removal (i.e., death, transplantation, clinical improvement, or other reason) using chi-squared tests for categorical and Kruskal-Wallis tests for continuous variables. Logistic regression was used to evaluate risk factors for mortality within 28-days of LT waitlisting, adjusting for patient characteristics on initial transplant application. **Results:** Of the 2,704 patients waitlisted for AAH during the study period, 2,111 (83.4%) underwent LT and 206 (8.1%), 119 (4.7%), and 95 (3.8%) were removed from the waitlist due to death/deterioration, clinical improvement, or other reasons, respectively. By comparison, waitlist mortality of acute liver failure patients was 19.7% and of other non-AAH patients was 16.9%. Patients transplanted for AAH had short wait times with a median duration from listing-to-LT of 5 (interquartile range [IQR] 3-10) days. Approximately half (46.3%) of transplanted patients had no or mild ascites and no or grade 1-2 encephalopathy and half (45.2%) had intact renal function (i.e., eGFR $\geq$ 60 and not on dialysis) at listing. Patients who died/deteriorated awaiting LT experienced longer wait times with a median wait of 12 (IQR 5-32) days. Patients delisted due to clinical improvement tended to be younger and with lower initial MELD scores (both $p < 0.001$), remaining on the waitlist for an average of 270 (IQR 146-461) days. No difference in waitlist mortality rates were observed across MELD scores < 40 ($p = 0.624$, Figure 1A). On multivariable analysis, 28-day waitlist mortality was not different for listing MELD scores 25-34 and 40+ vs 35-39 as reference (all $p > 0.05$, Figure 1B). **Conclusion:** Patients with AAH undergo LT with significantly higher frequency and lower waitlist mortality compared to national averages. The prolonged waiting time prior to removal due to clinical improvement may suggest that a subset of patients are transplanted too early and not offered the opportunity to recover. MELD-based waitlisted prioritization may not be appropriate in AAH as it does not accurately stratify risk of waitlist mortality for many patients.

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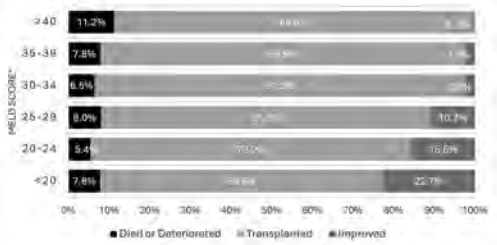
Figure 1A: Liver transplant waitlist outcomes of patients with alcohol-associated hepatitis by initial MELD score



*Number of patients per MELD score group: 759 patients with MELD≥40, 902 patients with MELD 35-39, 465 patients with MELD= 30-34, 289 patients with MELD=25-29, 187 patients with MELD=20-24, 154 patients with MELD<20

Figure 1B: Multivariable model for 28-day liver transplant waitlist mortality among patients with alcohol-associated hepatitis

	Odds Ratio	95% Confidence Interval	p-value
Age	1.03	(1.01-1.05)	<0.001
Sex (Male)	0.86	(0.59-1.27)	0.453
Race/Ethnicity			
White	Reference	Reference	Reference
Black	0.64	(0.27-1.55)	0.324
Hispanic/Latino	1.23	(0.74-2.05)	0.426
Asian	0.54	(0.13-2.29)	0.404
American Indian/Alaska Native	1.78	(0.60-5.32)	0.302
Multiracial	-	-	-
BMI (kg/m2)			
Underweight (<18)	1.07	(0.14-8.38)	0.951
Normal Weight (18.5-24.9)	Reference	Reference	Reference
Overweight (25-29.9)	1.16	(0.69-1.96)	0.581
Obesity Class I (30-34.9)	1.10	(0.63-1.91)	0.730
Obesity Class II (35-39.9)	1.38	(0.73-2.64)	0.324
Obesity Class III (>40)	1.85	(0.93-3.66)	0.079
Year of Listing	0.99	(0.90-1.10)	0.913
MELD Score			
<20*	-	-	-
20-24	0.19	(0.01-0.73)	0.023
25-29	0.65	(0.31-1.37)	0.260
30-34	1.03	(0.60-1.78)	0.906
35-39 (Median MELD Score)	Reference	Reference	Reference
≥40	1.53	(0.98-2.39)	0.063
Ascites			
None	Reference	Reference	Reference
Slight	0.91	(0.42-1.97)	0.807
Moderate	1.22	(0.57-2.58)	0.609
Encephalopathy			
None	Reference	Reference	Reference
Grade 1-2	1.22	(0.80-2.17)	0.469
Grade 3-4	3.08	(1.71-5.56)	<0.001

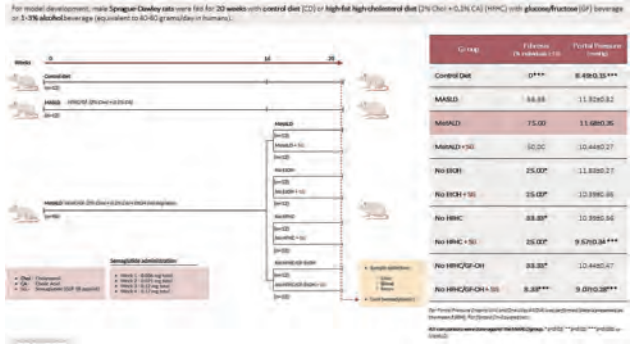
*All patients with a MELD score<20 were without 28-day mortality
Abbreviations: BMI=Body Mass Index, MELD=Model for End-Stage Liver Disease

Disclosures: Claire Durkin: Nothing to Disclose, Therese Bittermann: Nothing to Disclose

1519 | EVALUATING SEMAGLUTIDE AND LIFESTYLE INTERVENTIONS IN A NOVEL DIETARY RAT MODEL OF METABOLIC AND ALCOHOL-RELATED LIVER DISEASE WITH ADVANCED FIBROSIS

María Martínez Gómez[1] Imma Raurell[2] Maria de la Serra Cusidó Sabidó[3] Sophia Christina Parks[4] Joan Genescà[5] María Martell[6] Meritxell Ventura-Cots[7] Juan M Pericàs[5], [1]Liver Disease Group, VHIR; UAB; CIBERehd, [2]Liver Disease Group, VHIR; Liver Unit, VHUH; CIBERehd, [3]Liver Disease Group; VHIR; UAB, [4]Liver Disease Group; VHIR, [5]Liver Disease Group, VHIR; Liver Unit, VHUH; UAB; CIBERehd, [6]Liver Disease Group; VHIR; Liver Unit, VHUH; UAB; CIBERehd, [7]Liver Disease Group, VHIR; Liver Unit, VHUH; UAB

Background: Metabolic and alcohol-associated liver disease (MetALD) was recently proposed as a distinct entity however its natural history and therapy remain largely unknown. GLP-1 receptor agonists, approved for type 2 diabetes and obesity - major MetALD risk factors - have been evaluated for both metabolically and alcohol induced liver injury (MASLD and ArLD, respectively). Our aim was to develop a translational dietary rat model of MetALD with advanced fibrosis and portal hypertension (PH) to test therapeutic interventions and compare MetALD features to those of MASLD. **Methods:** The model was 20-week long, with interventions starting at week 16 (Fig.1). At the end of the study, liver hemodynamics, histology (fibrosis, ductular reaction, macrophage infiltration), biochemical markers, gene/protein expression, and immune profiling by multiplex assay were assessed. **Results:** Compared to CD, MASLD and MetALD showed an increase in body weight, dyslipidemia, AST, ALT, intrahepatic insulin resistance, steatosis, fibrosis, portal pressure (PP), ductular reaction, and macrophage infiltration, along with pro-inflammatory cytokines. Advanced fibrosis rates were higher in MetALD than MASLD (75% vs. 58.3%), but the difference was not statistically significant. Regarding interventions, semaglutide treatment induced significant weight loss in all groups (2-25%), regardless of dietary intervention or alcohol cessation. Gene analyses revealed restored insulin sensitivity after dietary intervention, independent of alcohol or semaglutide. Steatosis regressed from S3 to S1 in 50% of individuals when the diet was removed. All interventions reduced advanced fibrosis ratios showing a greater reduction in the group combining diet and alcohol removal with semaglutide ($p < 0.001$). PP and IHVR were significantly reduced in groups receiving semaglutide, whereas diet withdrawal, reaching values comparable to controls. Semaglutide alone did not significantly improve fibrosis or PP (Fig 1). **Conclusion:** Our MetALD model replicates key features of metabolic and alcohol-induced liver injury, including advanced fibrosis and PH. Adding semaglutide to diet and alcohol cessation significantly improved steatohepatitis, fibrosis, and PH. No major histopathological differences between MetALD and MASLD were found. Further research is needed to identify biomarkers distinguishing these conditions.



Disclosures: María Martínez Gómez: Nothing to Disclose, Imma Raurell: Nothing to Disclose, Maria de

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la Serra Cusidó Sabidó: Nothing to Disclose, Sophia Christina Parks: Nothing to Disclose, Joan Genescà: Nothing to Disclose, María Martell: Nothing to Disclose, Meritxell Ventura-Cots: Nothing to Disclose, Juan M Pericàs: Nothing to Disclose

1520 | START DOMAIN-CONTAINING PROTEIN 10 MODULATES RECEPTOR TYROSINE-PROTEIN KINASE ERBB-2 -MEDIATED LIPOGENESIS IN ALCOHOL-ASSOCIATED LIVER DISEASE

Manisha Dagar[1] Youngyi Lim[2] Swati Chandla[2] Monica Justo[2] Sion Lee[2] Maria Lauda Tomasi[2], [1]Cedars Sinai Medical Center, [2]CEDARS-SINAI MEDICAL CENTER

Background: In developed countries, alcoholic steatohepatitis (ASH) is major risk factor for liver cirrhosis and hepatocellular carcinoma (HCC). Recently, receptor tyrosine-protein kinase erbb-2 (ErbB2) (transmembrane receptors with tyrosine kinase activity) has been described in ASH and correlated with severity of inflammation and signs of longstanding liver injury. StAR-related lipid transfer domain containing 10 (StarD10), a phospho protein that positively regulates ErBb2 signalling pathway. We recently reported that ethanol administration lowers StarD10 phosphorylation leading to increased plasma membrane fluidity and induced ErbB2 activity in alcohol-induced breast cancer. This study aims to investigate whether phosphorylation of StarD10 regulates lipogenesis via ErbB2 in alcohol-associated liver disease (AALD). **Methods:** NIAAA mice livers and primary mouse hepatocytes. Western blot and immunoprecipitation. Duolink proximity Ligation assay (PLA) and immunofluorescence. Lipids binding and membrane fluidity assays, Phospho-peptide mapping, CRISPR-Cas9 gene editing, triglyceride and cholesterol assay. **Results:** Alcohol increased StarD10 and ErbB2 expression in NIAAA livers as well as in ethanol-treated hepatocytes. Surprisingly, alcohol also promoted StarD10 and ErbB2 physical interaction in vitro and in vivo at the plasma membrane. StarD10 was found to bind all phosphatidylinositides species (PIPs), specifically PIP(3,4)2, PIP (4,5)2 and PIP(3,4,5)3, and ethanol treatment increased it further. Ethanol-induced ErbB2 transactivation leads to PIP2 to PIP3 phosphorylation by phosphoinositide 3-Kinase (PI3K) that correlates with increased mTOR pathway in ALD. StarD10 overexpression induced SrebF1 level as well as its downstream lipogenic target genes such as FASN and ACC1. Additionally, phospho-peptide mapping revealed an overall decrease in StarD10 phosphorylation, except for one unique hyperphosphorylation residue, serine 7 (S7). CRISPR gene editing of S7 led to significant reduction in lipid accumulation, even in the presence of ethanol. These findings suggest that StarD10 binds to and may transport or stabilize PIPs leading to de novo lipogenesis. **Conclusion:** This study suggests a potential role for StarD10-induced mTOR pathway via PIPs to cause liver steatosis upon alcohol treatment. It also opens a wide field of research about functional implications of StarD10 and ErbB2 cross-talk deducing possible therapeutic strategies in ALD.

Disclosures: Manisha Dagar: Nothing to Disclose, Youngyi Lim: Nothing to Disclose, Swati Chandla: Nothing to Disclose, Monica Justo: Nothing to Disclose, Sion Lee: Nothing to Disclose, Maria Lauda Tomasi: Nothing to Disclose

1521 | IMPACT OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS ON ALCOHOL CONSUMPTION AND LIVER-RELATED OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Bernardo Moraes[1] Igor Boechat Silveira[2] Gabriel Leite[1] Gustavo Leite[1] Nathalia Lana[1] Guilherme Cançado[3], [1]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil., [2]Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil., [3]Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown promising results in reducing alcohol intake and impacting liver-related outcomes, mostly in patients with alcohol use disorder (AUD). However, their clinical benefit in this setting is debated and no prior meta-analysis has addressed the significance of these recent findings. **Methods:** We conducted a systematic review and meta-analysis to evaluate whether GLP-1RAs use is associated with reduced alcohol intake, alcohol-related events and liver-related outcomes, compared to non-use. Alcohol-related events included incident or recurrent AUD diagnosis, hospitalization or treatment due to AUD. Liver-related outcomes included progression to alcohol-related liver disease, hepatic decompensation, hepatocellular carcinoma, liver transplant or portal hypertension. A comprehensive search of PubMed, Embase, and CENTRAL was performed in May 2025. We included randomized controlled trials (RCTs) and observational studies comparing GLP-1RAs use versus non-use. Two reviewers independently screened studies, extracted data, and assessed risk of bias using RoB 2 tool for RCTs and ROBINS-I for cohort studies. A random-effects meta-analysis was conducted using

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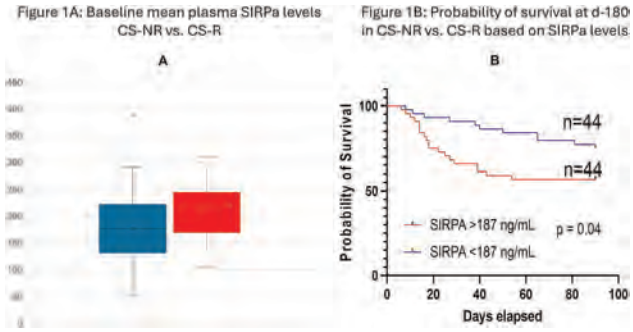
restricted maximum-likelihood estimation. Standardized mean differences (SMDs), incidence rate ratio (IRRs) or hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for primary and secondary outcomes. **Results:** Eight studies (3 RCTs, 5 observational) including 101,770 patients on GLP-1RAs and 114,335 controls were included. The primary outcome of daily alcohol intake was reported in 3 RCTs with 162 patients on GLP-1RAs and 164 controls. In the pooled analysis, GLP-1RAs use was not associated with reduced alcohol intake (SMD -0.17; 95% CI: -0.39, 0.04; I^2 = 0.0%). However, this negative finding was not sustained in subsequent analyses. Eight observational studies including 101,608 patients on GLP-1RAs provided data for the secondary outcomes. GLP-1 RAs use was associated with reduced alcohol-related events (HR 0.56; 95% CI: 0.48, 0.65; I^2 = 63.6%) and reduced liver-related outcomes (IRR 0.65; 95% CI: 0.50, 0.85; I^2 = 0.0%). **Conclusion:** This pioneering meta-analysis outlines the impact of GLP-1RAs use on reducing alcohol-related events and liver-related outcomes, despite no observed change in daily alcohol intake. Alongside ongoing trials, further RCTs are needed to evaluate the role of GLP-1RAs in modulating alcohol use and its impact on liver function.

Disclosures: Bernardo Moraes: Nothing to Disclose, Igor Boechat Silveira: Nothing to Disclose, Gabriel Leite: Nothing to Disclose, Gustavo Leite: Nothing to Disclose, Nathalia Lana: Nothing to Disclose, Guilherme Cançado: Nothing to Disclose

1522 | PLASMA SIGNAL REGULATORY PROTEIN-A, A POTENTIAL BIOMARKER TO PREDICT CORTICOSTEROID RESPONSE AND PROGNOSIS IN PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS.

Ethan Steele[1] David Malicote[1] Josiah Hardesty[1] Craig McClain[1] Samer Gawrieh[2] Srinivasan Dasarathy[3] Wanzhu Tu[2] Ramon Bataller[4] Gyongyi Szabo[5] Vijay Shah[6] Arun Sanyal[7] Suthat Liangpunsakul[2] Mack Mitchell[8] Ashwani Singal[1], [1]University of Louisville, [2]Indiana University, [3]Cleveland Clinic, [4]Barcelona Clinic, [5]Beth Israel Deaconess Medical Center, [6]Mayo Clinic Rochester, [7]Virginia Commonwealth University, [8]University of Texas Southwestern Medical Center

Background: Alcohol-associated hepatitis (AH) has a high short-term mortality in patients with severe episode (sAH) with a MELD score > 20. Corticosteroids (CS), the only available drug for patients with sAH is a suboptimal treatment, as 40-50% of patients are ineligible and a response (CS-R) rate of 50-60% in those who are eligible to receive CS. Further, response can only be determined after using CS for at least 7-d (Lille Score < 0.45), with a risk of bacterial and fungal infections especially in non-responders to CS (CS-NR). Signal regulatory protein alpha (SIRPA) is an immune cell receptor that regulates efferocytosis and inflammatory responses. Cleavage of SIRPA from its ADAM10 depends upon macrophage polarization, with its cleavage and release into the plasma in pro-inflammatory or M1 macrophage. The role of SIRPAa has not been studied in patients with AH. **Methods:** In a prospective cohort of sAH patients (2019-2024) enrolled in the Alchep Network study and treated with CS, plasma samples before CS exposure were analyzed by ELISA for cytokines and SIRPA levels (ng/mL). Patients were followed for up to 180 days from the time of CS treatment. **Results:** Of 134 sAH patients treated with CS, 88 (mean age 46.4 yrs., 39% females, 86% NH White, mean MELD 23.7, mean CTP score 10.4, mean albumin 2.56, mean WBC 9.7) with available Lille score at d-7 were analyzed. CS-R (n = 52) vs. NR (n = 36) were younger with lower MELD (22.6 vs. 25.4), BUN (11.9 vs. 18.8), and WBC (8.6 vs. 11.3). Baseline mean plasma SIRPa levels were higher in CS-NR vs. CS-R (216.6 vs. 176.2, Fig. 1A). Controlling for WBC and MELD score, SIRPA level predicted CS-R with OR (95% CI): 0.9 (0.98-1.00), P = 0.048. A total of 18 (20.5%), 29 (33%), and 32 (36.4%) died by 28, 90, and 180-d respectively. Stratifying the data at a median SIRPA level of 187, probability of survival at d-180 was higher in 44 patients with SIRPA levels < 187 vs. ≥ 187 ng/mL (Fig. 1B). In a Cox regression model controlled for MELD score, WBC, SIRPA, and Lille score, strongest predictor of death at d-180 was Lille score at d-7, with HR (95% CI) of 16.6 (2.8-99.7), p = 0.002. **Conclusion:** Plasma SIRPA is a potential biomarker to predict CS-R, and can personalize CS use in patients with sAH. Future pre-clinical studies are suggested to examine how loss of SIRPA expression or its cleavage contributes to AH pathogenesis. Prospective clinical studies are suggested to validate SIRPA as a biomarker in use of CS in patients with sAH.



Disclosures: * Ethan Steele: Nothing to Disclose, David Malicote: Nothing to Disclose, Josiah Hardesty: Nothing to Disclose, Craig McClain: Nothing to Disclose, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant,

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1523 | LONGITUDINAL TRANSITIONS BETWEEN ALCOHOL CONSUMPTION LEVELS IN US ADULTS: INSIGHTS FROM THE PATH STUDY

Olajide Adekunle[1] Andrew Brouwer[2] Ha Tran[1] Yihua Yue[1] Michael Rothberg[1] Phuc Le[1], [1]Cleveland Clinic, [2]University of Michigan

Background: Changes in alcohol consumption over time may reveal important opportunities for early intervention, yet little is known about the frequency and direction of these transitions among adults (≥ 18 years) in the United States. **Methods:** Using Waves 1-7 (2013–2023) of the Population Assessment of Tobacco and Health study, we developed a Markov multistate transition model and estimated transition rates between alcohol use states for adults, accounting

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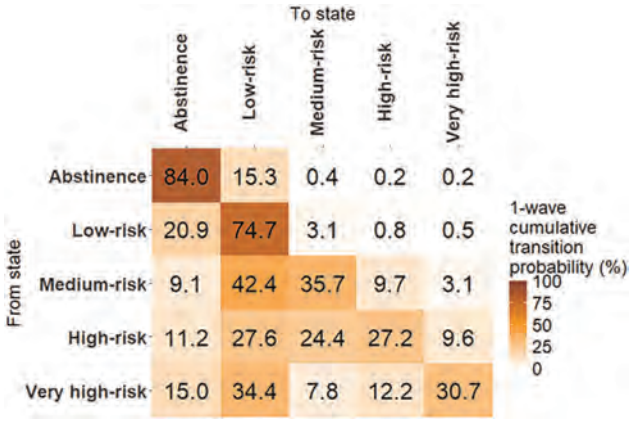
for survey weights. We excluded pregnant women and participants with one observation for alcohol use or missing data. We defined drinking states based on WHO risk levels depending on grams of alcohol consumed per day: abstinent (<1 g/day), low (male, 1-40 g/day; female, 1-20 g/day), medium (male, >40-60 g/day; female, >20-40 g/day), high (male, >60-100 g/day; female, >40-60 g/day), and very high risk (male, >100 g/day; female, >60 g/day). Transition rates were used to estimate annual transition probabilities overall and by age, sex, and race/ethnicity. **Results:** We included 19,323 participants with 110,164 observations of alcohol use. Among the participants, 63.5% and 22.0% belonged to 18-34 and 35-54 age groups, respectively, 53.2% were female, 54.9% were non-Hispanic White, 21.7% Hispanic and 15.2% non-Hispanic Black. Among abstainers, 84.0% remained abstinent after one year, while 15.3% transitioned to low-risk drinking. Most people in the low-risk state either remained in low risk (74.7%) or became abstinent (20.9%). In contrast, participants in higher-risk categories were less likely to remain at the same use level. More than 50% of medium-risk and 63% of high-risk alcohol drinkers reduced their consumption. Among people in the very high-risk state, many decreased their drinking, with the most common transition (34%) being to the low-risk category. Transitions among abstinent and low-risk individuals showed minimal variation by demographic characteristics. However, in medium- or other higher risk groups, men, White participants, and those aged 35–54 were more likely to maintain or increase use compared to women, non-White participants, and other age groups. **Conclusion:** While abstinent and low-risk individuals largely maintained their low-risk status, those in higher-risk categories tended to reduce consumption over time. However, demographic differences in transitions were more pronounced among higher-risk groups. Targeted interventions are needed to support sustained reduction in alcohol use.



Disclosures: Olajide Adekunle: Nothing to Disclose, Andrew Brouwer: Nothing to Disclose, Ha Tran: Nothing to Disclose, Yihua Yue: Nothing to Disclose, Michael Rothberg: Nothing to Disclose, Phuc Le: Nothing to Disclose

1524 | CHARACTERIZATION OF PLASMA PEPTIDOMIC SIGNATURES INVOLVED IN THE GUT-IMMUNE-LIVER AXIS OF THE EARLY-STAGE ALCOHOL-ASSOCIATED LIVER DISEASE

Anjali Kumari[1] Mukesh Kumar Sriwastva[1] Christine Dolin[1] Michael Merchant[1] Gavin Arteel[2] Maiying Kong[1] Melanie Schwandt[3] Joris Verster[1] Venkatakrishna Jala[1] Ashwani Singal[1] Craig McClain[1] Vatsalya Vatsalya[1], [1]University of Louisville, [2]University of Pittsburgh, [3]NIAAA

Background: The clinical presentation of early-stage alcohol-associated liver disease (eALD) has recently been described. However, the pathological biomarkers involved in the gut-immune-liver (GIL) axis and corresponding peptidomic changes have not yet been described. This study characterizes the role of liver pathology in the GIL axis, the corresponding novel biomarker response, and the identification of signature peptidomic. **Methods:** Forty-two adult male and female subjects were classified as healthy controls (HC, n = 6), alcohol use disorder (AUD, Gr.1, n = 10), or eALD (Gr.2, n = 26). Comprehensive metabolic panel (CMP), complete blood count (CBC), coagulation (PT+INR). Plasma samples collected were used for the detection of biomarkers for gut dysfunction, proinflammatory cytokines, and liver cell death markers (keratin 18, K18), and for peptide extraction for LC-MS/MS analysis. Differentially expressed peptides were identified and correlated. Pathway and protein-protein interaction analyses were performed to elucidate underlying biological processes. **Results:** Liver injury in Gr.2. was marked by clinical and statistically significant elevations in liver injury markers, AST (aspartate transaminase, 3~fold, $p = 0.013$), ALT (alanine transaminase, $p < 0.01$) values compared to Gr.1. Novel biomarkers of eALD (LPS [lipopolysaccharide], +sCD14 [soluble cells of differentiation 14], TNF-α [tumor necrosis factor-alpha], IL1-β [interleukin 1-beta], and K18 ratio [M65/M30]) were significantly dysregulated (Fig. 1a). Key peptides associated with gut permeability, immune activation, and liver cell death and injury (fibrinogen, collagen fragments) were statistically significantly and uniquely different between groups (Fig. 1b). Compartment-specific GIL axis analysis showed corresponding significant changes ($p < 0.05$) between the two groups: FIB-A (gut), COLA1, THRB, and FIB-B (immune), and FIB-B (liver) (Fig. 1b). **Conclusion:** We found that the characteristic feature of eALD that

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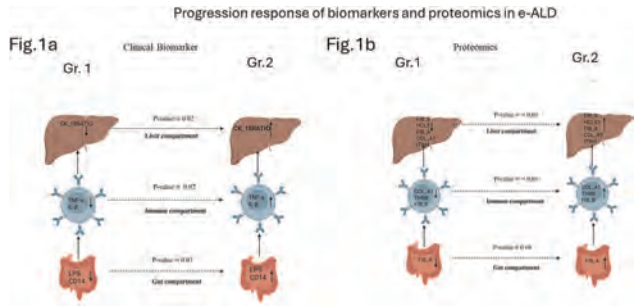
distinguishes it from AUD is the progression of liver injury. The specific changes identified by the gut alterations and proinflammatory cytokine response could be consequential in the higher necrosis, contributing to the unique GIL axis alterations in eALD. Differentiation in the biomarkers' activity was supported by the subtle, albeit significant, changes in the representative proteomic changes. Plasma peptidomic signatures effectively distinguish eALD from AUD.



Disclosures: Anjali Kumari: Nothing to Disclose, Mukesh Kumar Sriwastva: Nothing to Disclose, Christine Dolin: Nothing to Disclose, Michael Merchant: Nothing to Disclose, Gavin Arteel: Nothing to Disclose, Maiying Kong: Nothing to Disclose, Melanie Schwandt: Nothing to Disclose, Joris Verster: KNMP: Consultancy fee, Red Bull: Consultancy fee, Med Solutions: Consultancy fee, Mozand: Consultancy fee, Toast!: Consultancy fee, Sen-Jam Pharmaceutical: Stock, Venkatakrishna Jala: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, GSK: Grant/Research Support, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, Avera Medical Group: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other, Craig McClain: Nothing to Disclose, Vatsalya Vatsalya: Nothing to Disclose

1525 | SERUM FERRITIN AND ADVERSE LIVER OUTCOMES IN PATIENTS WITH METALD: AN NHANES-BASED ANALYSIS

Sheena Bhushan *Kris Kowdley*[1], [1]*Liver Institute Northwest*

Background: Metabolic Dysfunction-associated Alcohol-related Liver Disease (MetALD) is a newly defined subgroup of patients with Metabolic Dysfunction-associated Steatotic Liver Disease (MASLD) who also consume moderate amounts of alcohol which is defined as 20-50 g/day for women and 30-60 g/day for men. It has been shown in experimental studies that even moderate amount of alcohol can suppress hepcidin synthesis in the liver, leading to dysregulation of iron homeostasis, and subsequent hepatocellular injury and fibrosis. However, the clinical significance of iron biomarkers in metALD has never been evaluated at a population level. The aim of this study is to evaluate the association between elevated serum ferritin (SF) and transferrin saturation (TSAT) and clinical outcomes in individuals with metALD. **Methods:** Data were obtained from the 2017-2018 National Health and Nutrition Examination Survey (NHANES), comprising of 4,438 participants. A total of 67 individuals met the diagnostic criteria for metALD defined as a CAP $\geq$ 288 dB/m and moderate alcohol intake (20-50 g/day in women and 30-60 g/day in men). Elevated SF was defined using gender-specific thresholds of $>$450 ng/mL for men and $>$300 ng/mL for women. Primary outcomes included advanced fibrosis (kPa $\geq$ 11.7), elevated ALT, mortality, hepatocelluar carcinoma (HCC) and cirrhosis (kPa $\geq$ 12.5). Statistical Analyses were conducted using Mann-Whitney U and chi-square tests. Logistic regression was used to adjust for age, sex, BMI, diabetes, triglycerides and HDL. **Results:** An elevated SF level was present in 22.2% of metALD patients and was associated with significantly higher liver stiffness (+2.03 kPa, $p=0.001$) and a trend toward advanced fibrosis (OR 2.20, $p=0.108$), cirrhosis (OR$=$2.20, $p=0.108$) and elevated ALT (OR 2.68, 95% CI 0.47-4.62, $p=0{,}007$). Elevated TSAT ($>$45%) also showed a trend toward higher rates of advanced fibrosis (20.0% vs. 6.5%) and ALT elevation (80% and 37.1%). **Conclusion:** Elevated SF levels are associated with increased liver stiffness and a trend toward advanced fibrosis and cirrhosis. These findings support the potential utility of iron biomarkers as non-invasive indicators of disease progression in patients with metALD.

Disclosures: Sheena Bhushan: Nothing to Disclose, Kris Kowdley: Nothing to Disclose

1526 | EFFICACY OF BACLOFEN VS NALTREXONE IN ACHIEVING AND MAINTAINING ABSTINENCE IN ALCOHOL USE DISORDER IN CIRRHOSIS: BANALC NON-INFERIORITY TRIAL ALCOHOL USE DISORDER IN CIRRHOSIS

Ravi Nishad[1] *Ravinder Singh*[1] *Mohit Varshney*[1] *Shasthry SM*[1] *Shiv Kumar Sarin*[1,] [1]*Institute of Liver and Biliary Sciences*

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Background: Current published research establishes Baclofen as the gold standard of AUD treatment in patients with cirrhosis. Increasingly Naltrexone is being found to be safe and effective in this population. This study compares an emerging therapy Naltrexone against the gold standard in early cirrhotic (CTP $\leq$ 9) patients. **Methods:** Sixty-four patients with alcohol dependence and cirrhosis were enrolled and randomly assigned (1:1) to receive either Baclofen (10 mg TDS; n = 32) or Naltrexone (50 mg OD; n = 32) using block randomisation (block size: 10), with allocation and blinding managed by the trial coordinator. Medications were administered for 12 weeks and entrusted to a family member to ensure adherence and monitor side effects. Post-treatment assessments included AUDIT scores, obsessive-compulsive behaviours, cravings, binge drinking episodes, abstinence rates, and liver-related clinical and biochemical parameters. **Results:** After 12 weeks, both Baclofen and Naltrexone reduced AUDIT-12 scores in alcohol-dependent cirrhotic patients (12.61 $\pm$ 3.43 vs. 11.63 $\pm$ 3.86; $p = 0.288$). Baclofen more effectively reduced obsessive thoughts (OCD-O: 8.31 $\pm$ 1.10 vs. 10.25 $\pm$ 1.16; $p < 0.001$), while Naltrexone better reduced compulsive behaviour (OCD-C: 6.97 $\pm$ 1.12 vs. 9.66 $\pm$ 0.83; $p < 0.001$) and binge episodes (0.44 $\pm$ 0.87 vs. 2.06 $\pm$ 2.27; $p = 0.001$). Abstinence was higher with Naltrexone (65.6% vs. 43.8%; $p = 0.131$). Liver function was comparable (CTP: 6.44 $\pm$ 1.39 vs. 6.59 $\pm$ 1.45; MELD: 10.97 $\pm$ 3.60 vs. 11.84 $\pm$ 2.79; $p > 0.05$). Both drugs were effective and safe, with Baclofen favouring reduction in obsession and Naltrexone showing better outcomes in abstinence and binge control. **Conclusion:** Baclofen is more effective for obsessive thoughts, while Naltrexone is better for compulsive behaviours and binge drinking. No significant difference in abstinence rates was found, suggesting both treatments are viable options for managing alcohol dependence in early cirrhotic patients. Further studies with larger sample sizes are needed.

Disclosures: Ravi Nishad: Nothing to Disclose, Ravinder Singh: Nothing to Disclose, Mohit Varshney: Nothing to Disclose, Shasthry SM: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

1527 | LONG-TERM BENEFITS OF MENTAL HEALTH FOLLOW-UP IN PATIENTS HOSPITALIZED FOR ALCOHOLIC HEPATITIS

Ahmed Ibrahim[1] Don Rockey[1] Mohamed Eldesouki[2],
[1]Medical University of South Carolina,
[2]New York Medical College at Saint Michael Medical Center

Background: Mental health disorders, including depression, anxiety, and PTSD, are common in patients with alcohol-associated liver disease and may influence recovery after alcoholic hepatitis (AH). However, the impact of post-discharge mental health (MH) follow-up on long-term outcomes in this population requires further investigation. **Methods:** We used the TriNetX Research Network to examine adult patients ($\geq$ 18 years) hospitalized with a first episode of AH between 2010 and 2024. Patients were stratified based on whether or not they had MH follow-up within 90–180 days post-discharge, defined as $\geq$ 1 of the following: (1) outpatient psychiatry or psychology visit, (2) initiation of psychotropic medication (e.g., SSRIs, antipsychotics), or (3) enrollment in alcohol/substance use counseling. The primary outcome was all-cause mortality. Secondary outcomes included liver-related decompensation (ascites, hepatic encephalopathy, variceal bleeding), and 1-year hospital readmission. Propensity score matching (PSM) was used to balance baseline characteristics. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). **Results:** A total of 70,397 patients hospitalized with a first episode of alcoholic hepatitis were identified; 17,201 had documented post-discharge MH follow-up, and 53,196 did not. The majority of patients were White males, with similar age distributions. At baseline, those in the MH follow-up group had higher aminotransferases and bilirubin, and lower platelet counts. After matching, each cohort had 14,613 patients (mean [SD] age, 49 [12] years; 35% women), and were evenly matched in baseline characteristics and laboratory parameters. Patients with MH follow-up had significantly lower rates of all-cause mortality (11% vs 18%; HR, 0.52; 95% CI, 0.49–0.53; $p < 0.001$), hospital readmissions (50% vs 65%; HR, 0.59; 95% CI, 0.54–0.63), and liver-related decompensation events including ascites (7% vs 12%; HR, 0.54; 95% CI, 0.50–0.60), hepatic encephalopathy (13% vs 20%; HR, 0.54; 95% CI, 0.50–0.58), and variceal hemorrhage (2% vs 3%; HR, 0.81; 95% CI, 0.69–0.94). Rates of esophageal and gastric varices were also significantly lower in the MH follow-up group. **Conclusion:** Post-discharge MH follow-up after hospitalization for AH is associated with improved long-term outcomes, including lower mortality, reduced relapse, and fewer liver-related complications. These findings highlight the importance of integrating psychiatric care into the routine management of patients recovering from AH.

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Table 1. Demographic and clinical features

Baseline characteristics	No MH follow-up N=14,613	MH Follow-up N= 14,613	Std. diff.
Age (yrs, mean, ±SD)	49±12	49±12	0.06
Women, n (%)	5,093 (35%)	5,133 (35%)	0.006
White, n (%)	10,843 (74%)	10,751 (74%)	0.007
Black, n (%)	1,791 (12%)	1,837 (13%)	0.01
Hispanic/Latino, n (%)	1,338 (9%)	1,411 (10%)	0.02
Asian, n (%)	194 (1%)	195 (1%)	<0.001
Ascites	3,129 (21%)	3,102 (21%)	0.005
Hepatic encephalopathy	894 (6%)	972 (7%)	0.02
Laboratory parameters			
Albumin (g/dL, mean, ±SD)	3.5±0.8	3.3±0.8	0.02
Bilirubin (mg/dL, mean, ±SD)	4.3±6.8	2.3±4.1	0.02
INR (mean, ±SD)	1.4±0.6	1.3±0.5	0.01
Creatinine (mg/dL, mean, ±SD)	1.0±1.5	0.9±0.7	0.02
Platelets (x10^3/ mm^3, mean, SD)	171±105	193±111	0.02

Abbreviations- MH: mental health; BMI: body mass index; CKD: chronic kidney disease; INR: international normalized ratio

Table 2. Clinical outcomes

Outcomes	No MH follow-up N=14,613	MH Follow-up N= 14,613	HR (95% CI)	P value
Esophageal varices, n (%)	889/11,756 (8%)	706/12,109 (6%)	0.67 (0.60-0.74)	<0.001
Gastric varices, n (%)	205/14,155 (1%)	185/14,224 (1%)	0.78 (0.64-0.95)	0.01
Hepatic decompensation				
Ascites, n (%)	1,161/ 10,057 (12%)	786/ 10,847 (7%)	0.54 (0.50-0.60)	<0.001
Hepatic encephalopathy, n (%)	1,996/ 9,826 (20%)	1,174/ 9,337 (13%)	0.54 (0.50-0.58)	<0.001
Variceal hemorrhage, n (%)	342/13,652 (3%)	319/13,796 (2%)	0.81 (0.69-0.94)	0.006
Hospital readmission, (%)	2,138/ 3,302 (65%)	857/ 1,708 (50%)	0.59 (0.54-0.63)	<0.001
All-cause mortality, (%)	2,672/ 14,613 (18%)	1,597/ 14,613 (11%)	0.52 (0.49-0.53)	<0.001

Disclosures: Ahmed Ibrahim: Nothing to Disclose, Don Rockey: WL Gore and Associates: Consultant, Cook Medical: Consultant, BD Medical: Consultant, AstraZeneca: Grant/Research Support, Bio89: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Durect: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Intercept: Grant/Research Support, Inventiva: Grant/Research Support, Madrigal: Grant/Research Support, Ocelot: Grant/Research Support, Salix: Grant/Research Support, Novonordisk: Grant/Research Support, Galectin: Grant/Research Support, Versantis: Grant/Research Support, Viking: Grant/Research Support, Mohamed Eldesouki: Nothing to Disclose

1528 | MLCK REGULATED PLATELET CYTOSKELETAL DYNAMICS ENHANCE NEUTROPHIL CROSSTALK TO FACILITATE LIVER INFLAMMATION AND INJURE

Li Zuo[1] Juan Wang[2] Hua Wang[1], [1]Anhui Medical University, [2]the First Affiliated Hospital of Anhui Medical University

Background: Alcohol-related liver disease (ALD) is a major global cause of liver-related mortality, but its underlying pathogenic mechanisms remain incompletely understood. Emerging evidence suggests platelet activation may play a critical role in ALD progression, yet the molecular drivers and cellular consequences of this process are undefined. **Methods:** We employed electron microscopy, flow cytometry, and intravital two-photon microscopy to assess platelet activation and intrahepatic aggregation in ALD mouse models. Antiplatelet therapy (aspirin/clopidogrel) and platelet-specific Mylk knockout mice were used to evaluate functional consequences. Single-cell RNA sequencing characterized alcohol- and myosin light-chain kinase (MLCK)-dependent shifts in hepatic cell populations. In vivo dynamic imaging quantified platelet-neutrophil interactions, while mechanistic studies defined roles for CXCL7-CXCR2 signaling, mitochondrial transfer, and Piezo1-mediated Ca^{2+}/calmodulin activation of MLCK. **Results:** We demonstrate that platelet activation and intrahepatic aggregation are markedly elevated in ALD mice, correlating with cytoskeletal reorganization, pseudopod formation, and granule release. Antiplatelet therapy (aspirin/clopidogrel) attenuates hepatic inflammation and lipid accumulation, impeding disease progression. Mechanistically, myosin light-chain kinase (MLCK) emerges as a key regulator: its gene-knockout reduces platelet activation and aggregation, ameliorating ALD pathology. Single-cell sequencing reveals alcohol- and MLCK-dependent shifts in hepatocyte, platelet, and neutrophil subpopulations. Crucially, in vivo dynamic imaging identifies enhanced platelet-neutrophil interactions in portal regions, mediated by CXCL7-CXCR2 ligand-receptor binding and cytoskeleton-driven mitochondrial transfer. Activated platelets release functional mitochondria to neutrophils, triggering neutrophil extracellular traps (NETs) formation and inflammatory mediator release, processes disrupted in platelet-specific Mylk knockout mice. MLCK activation is driven by Piezo1-mediated Ca2+ influx and calmodulin signaling, linking mechanical cues to platelet hyperactivation. **Conclusion:** This work establishes MLCK as a central hub coordinating platelet-neutrophil crosstalk and cytoskeletal dynamics in ALD. Platelets emerge as active instigators of hepatic inflammation via mitochondrial transfer and NETosis, with MLCK integrating mechanical (Piezo1) and chemical (CXCL7) signals. Targeted inhibition of MLCK or platelet-neutrophil interactions represents a novel therapeutic strategy. Our findings redefine platelets as dynamic contributors to ALD pathogenesis, opening new avenues for mechanistic and translational research.

Disclosures: Li Zuo: Nothing to Disclose, Juan Wang: Nothing to Disclose, Hua Wang: Nothing to Disclose

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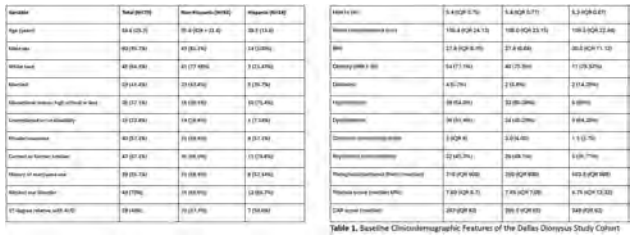
1529 | AN INTERIM UPDATE FROM THE DALLAS DIONYSUS STUDY - AN ONGOING PROSPECTIVE OBSERVATIONAL COHORT OF EARLY-STAGE METABOLIC AND ALCOHOL-ASSOCIATED LIVER DISEASE (METALD) AND ALD PATIENTS

Elias Rady[1] Hamza Dahshi[2] Ahmad Anouti[1] Bill Zhang[1] Courtney Roberts[3] Thomas Kerr[1] Amit Singal[1] Mack Mitchell[1] Thomas Cotter[1], [1]University of Texas Southwestern Medical Center, [2]Case Western Reserve University School of Medicine, Medical Scientist Training Program, [3]University of Texas Southwestern Medical School

Background: A significant proportion of patients constantly shift between steatotic liver disease (SLD) entities (MASLD, metALD, ALD) revealing a limitation of the cross-sectional nature of the 2023 AASLD nomenclature. Considering current and lifetime alcohol use as a cofactor, while accounting for the important modulating effect of metabolic co-morbidities and genetic predisposition, can help address this. Focusing on early-stage metALD/ALD is also critical, as most are diagnosed at advanced disease stages at a time when limited treatment options are available. We present our interim baseline findings from the Dallas Dionysus Study - a prospective early-stage metALD/ALD observational cohort study. **Methods:** From September 2024 to date, 70 adults with early-stage metALD/ALD and current/recent alcohol use were enrolled at UT Southwestern Medical Center and Parkland Health. Baseline surveys on demographics, co-morbidities, alcohol history, psychosocial constructs, and SDOH were administered by trained staff. Clinical assessments included anthropometrics, transient elastography, phosphatidylethanol (PEth), HbA1c, lipids, and genotyping for SLD-associated variants. A chi-square test assessed concordance between self-report alcohol use (via Timeline Follow Back (TLFB)) and PEth levels, categorized using established clinical cutoffs. **Results:** Of the 70 patients, 60 (85.7%) were male with a median age of 54.6 years (IQR 25.3) [Table1]. Alcohol use disorder, diagnosed by SCID, was present in 49 (70%). Median PEth was 318 ng/mL (IQR 909). Metabolic comorbidities were prevalent, with 92.9% of patients having at least one. Median liver fibrosis was 7.8 kPa (IQR 8.7) and median CAP scores 263 dB/m (IQR 83). Out of 11 patient who reported abstinence, 9 had a positive PEth ($\geq$ 20). There was significant discordance between TLFB and PEth ($p < 0.01$), with 21 of 42 patients (50%) underreporting their alcohol consumption. Several patients were below the metALD alcohol threshold at the time of enrollment. **Conclusion:** While self-report alcohol use remains a cornerstone in metALD/ALD management, it is important to integrate objective biomarkers such as PEth to improve classification accuracy. This is of particular importance for study candidate selection for SLD clinical trials. Upon healthcare engagement, many patients reduce alcohol consumption, highlighting that community engagement strategies may be critical to enhance metALD/ALD clinical trial recruitment.



Disclosures: Elias Rady: Nothing to Disclose, Hamza Dahshi: Nothing to Disclose, Ahmad Anouti: Nothing to Disclose, Bill Zhang: Nothing to Disclose, Courtney Roberts: Nothing to Disclose, Thomas Kerr: Madrigal: Consultant, GSK: Grant/Research Support, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Mack Mitchell: Nothing to Disclose, Thomas Cotter: Nothing to Disclose, Nothing to Disclose

1530 | NEIGHBORHOOD SOCIOECONOMIC DISADVANTAGE (AREA DEPRIVATION INDEX) AND REFERRAL TO LIVER TRANSPLANT IN PATIENTS WITH ALCOHOL RELATED LIVER DISEASE

Islam Mohamed[1] Mohamad Ali Ibrahim[2] Nagham Ramadan[2] Sherry Fares[2] Caroline Ankoma-Sey[2] Mazen Elsheikh[2] Megha Bhongade[2] Manal Hassan[3] Kumar Jalal[2], [1]The Cleveland Clinic Foundation-Fairview hospital, [2]Baylor College of Medicine, [3]The University of Texas MD Anderson Cancer Center

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Background: Alcohol- associated liver disease (ALD) has become the leading indication for liver transplantation in the USA. The Area Deprivation Index (ADI) is a validated metric of neighborhood-level socioeconomic disadvantage, incorporating income, education, employment, and housing. These factors were independently described as barriers to access to liver transplant. The aim of this study is to identify the factors associated with access to listing in each ADI category. **Methods:** In this retrospective cohort we included patients with alcohol related liver disease (ALD) referred for evaluation for liver transplantation in 2022-2024 at Baylor College of Medicine. We included patients (> 18 y.o.) with referred ALD candidates. Excluded patients with other liver cirrhosis, incomplete records and who lost follow-up. ADI was assigned based on ZIP code and categorized into tertiles based on national percentiles. Univariable and Multivariable logistic regressions were used to evaluate the association between ADI categories, demographic, and clinical factors with access to liver transplant waitlist. **Results:** Of 192 included in the study; 30 (15.6%) patients in Low ADI, 93(48.4%) in Moderate ADI and 69(35.9%) patients in High ADI referred to our center for evaluation of liver transplantation. Mean age hovered around 52 years, p = 0.627. Higher alcohol gm/ in high ADI (mean 907 g/ week) vs. low (710 g/week), p = 0.097. In univariate analysis, among patients from low ADI areas, alcohol-related legal issues (HR: 3.52; 95% CI: 1.25–9.94; p = 0.018) and smoking (p = 0.041) were significantly associated with denial of listing. In the multivariate model, MELD-Na remained an independent predictor of listing, p = 0.001. In the moderate ADI group, univariate analysis identified male gender (p < 0.001), lower hemoglobin (p = 0.005), BMI (p = 0.039), and smoking (p = 0.030) as significant predictors. Multivariable analysis confirmed female gender (p = 0.022), lower hemoglobin (p = 0.005), and insurance status (p = 0.014) as independent predictors of listing, in addition to MELD-Na (p = 0.001). For patients from high ADI areas, family history of alcohol use disorder (AUD) was the only significant univariate and multivariable predictor (HR: 2.88; 95% CI: 1.13–7.35; p = 0.026), along with platelet count (HR: 0.99; 95% CI: 0.985–0.999; p = 0.025) and MELD-Na (HR: 1.05; 95% CI: 1.00–1.10; p = 0.050) (Figure 1). **Conclusion:** Neighborhood socioeconomic disadvantage is associated with distinct and context-specific barriers to liver transplant waitlist access among patients with ALD. While MELD-Na was a consistent predictor across all groups, factors such as alcohol-related legal issues, female gender, anemia, and family history of AUD significantly influenced listing decisions in certain ADI strata. These findings highlight the importance of incorporating social determinants of health into the evaluation of liver transplants to promote equitable access.

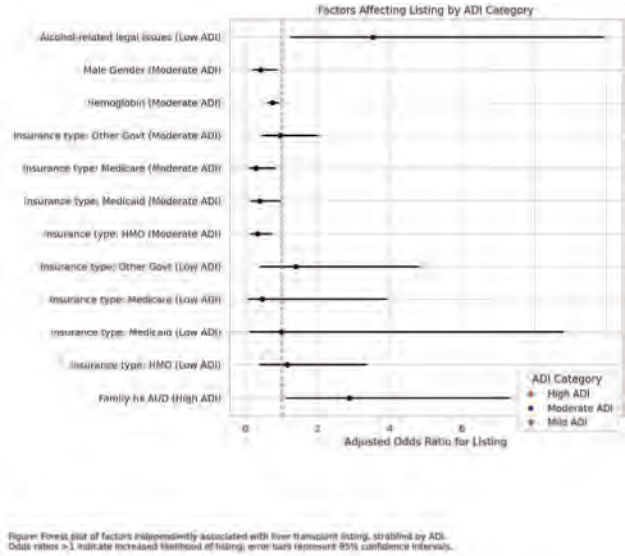

Figure: Forest plot of factors independently associated with liver transplant listing, stratified by ADI. Odds ratios >1 indicate increased likelihood of listing; error bars represent 95% confidence intervals.

Figure Legend:
Figure 1: Forest plot illustrating factors independently associated with liver transplant listing stratified by Area Deprivation Index (ADI) categories (Low, Moderate, High). The outcome is listing for liver transplantation. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) are shown for variables that remained significant in multivariate analysis for each ADI group. Notably, Insurance type was a significant predictor in the moderate ADI group, while family history of alcohol use disorder (AUD) was predictive in the high ADI group. Female gender and lower hemoglobin levels were associated with reduced likelihood of listing in the moderate ADI group.

Disclosures: Islam Mohamed: Nothing to Disclose, Mohamad Ali Ibrahim: Nothing to Disclose, Nagham Ramadan: Nothing to Disclose, Sherry Fares: Nothing to Disclose, Caroline Ankoma-Sey: Nothing to Disclose, Mazen Elsheikh: Nothing to Disclose, Megha Bhongade: Nothing to Disclose, Manal Hassan: Nothing to Disclose, Kumar Jalal: Mallinckrodt Pharmaceuticals: Advisor

1531 | IMPACT OF A SUBSTANCE USE NAVIGATION PROGRAM ON CLINICAL OUTCOMES IN PATIENTS WITH ALCOHOLIC HEPATITIS

James Vu[1] Robert Pecha[1] Jordan Holliday[1] Gregory Maynard[1] Connor Reilly[1] Daniel Colby[1] Aimee Moulin[1] Lydia Aye[1] Vikrant Rachakonda[2], [1]University of California Davis Medical Center, [2]University of California Davis

Background: Only alcohol abstinence has been shown to improve long-term survival in alcohol-associated hepatitis (AH). In February 2020, our institution implemented an inpatient Substance Use Navigation (SUN) program to support abstinence through motivational interviewing, pharmacotherapy, and linkage to ambulatory rehabilitation programs. The aim of the current study was to assess the effect of SUN consultation on clinical outcomes in AH. **Methods:** This was a

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retrospective cohort study of patients admitted with AH from July 2017 to September 2024, stratified into pre-SUN (N = 152), SUN consulted (SUN+, N = 180), and SUN non-consulted (SUN-, N = 250) groups. Primary outcomes included 90-day transplant-free survival and 30-day readmission rates. Secondary analyses examined demographic and clinical predictors of non-SUN referral. **Results:** Patients who received SUN consultation were significantly younger [40 (IQR 34 – 52) years vs. 47 (39 – 57) years pre-SUN vs. 45 (37 – 54) years SUN-, $p < 0.001$], with higher MELD 3.0 than pre-SUN but lower MELD 3.0 than non-consulted patients [25 (20-30) vs. 23 (17-29) pre-SUN vs. 29 (24 – 34) SUN-, $p < 0.001$]. Intensive care unit (ICU) admission, ascites, hepatic encephalopathy, and gastrointestinal bleeding were more common in SUN non-consulted patients; however, multivariable logistic regression models demonstrated that only ascites [OR 0.396 (95% CI 0.250 – 0.626), $p < 0.001$] and ICU admission [OR 0.417 (95% CI 0.250 – 0.698), $p = 0.001$] were associated with reduced likelihood of SUN consultation. Kaplan Meier analysis demonstrated significantly longer 90-day transplant-free survival in SUN consulted patients compared to SUN non-consulted and pre-SUN groups [86 (IQR 84 – 88) vs. 69 (65 – 73) vs 79 (75 – 83) days, respectively; $p < 0.001$ by log-rank test]. Multivariable Cox models showed that SUN consultation was associated with reduced 90-day mortality independent of MELD 3.0 [HR 0.309 (95% CI 0.172 – 0.556), $p < 0.001$]. No difference in 30-day readmission rates was observed across cohorts. **Conclusion:** Implementation of a structured SUN program was associated with improved 90-day transplant-free survival in patients hospitalized with AH, independent of liver disease severity. Those with more severe presentation were less likely to receive a SUN consultation. These findings support the role of early substance use intervention in AH.

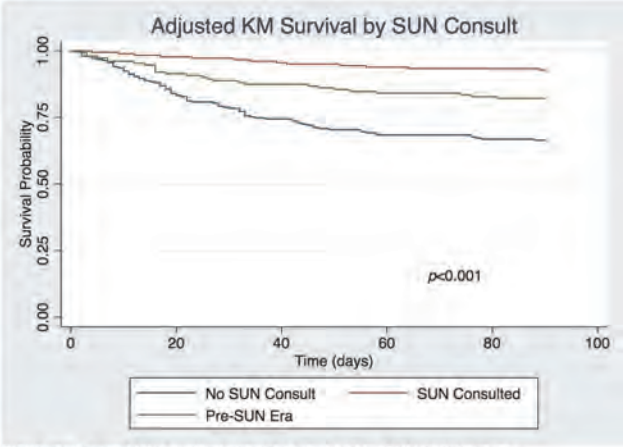

Figure 1: Kaplan Meier survival estimates stratified by SUN consult status.

Disclosures: James Vu: Nothing to Disclose, Robert Pecha: Nothing to Disclose, Jordan Holliday: Nothing to Disclose, Gregory Maynard: Nothing to Disclose, Connor Reilly: Nothing to Disclose, Daniel Colby: Nothing to Disclose, Aimee Moulin: Nothing to Disclose, Lydia Aye: Nothing to Disclose, Vikrant Rachakonda: Nothing to Disclose

1532 | CLINICAL CHARACTERISTICS AND INFLUENCING FACTORS OF RECOMPENSATION IN DECOMPENSATED ALCOHOLIC LIVER CIRRHOSIS

jingyuan zhou[1] Jia Zhou[1] Hongqin Xu[1] Yanhang Gao[1],
[1]The First Hospital of Jilin University

Background: Cirrhosis is a severe global liver disease, with alcoholic cirrhosis accounting for a significant proportion and the number of patients showing an upward trend. Traditionally, decompensated cirrhosis was considered irreversible, but the recent concept of recompensation has brought hope to patients. Currently, research on recompensation in decompensated alcoholic cirrhosis is relatively scarce, especially regarding the analysis of influencing factors and construction of prediction models. Therefore, this study aims to explore its clinical characteristics and establish a recompensation prediction model to provide evidence for clinical decision-making, thereby improving patients' prognosis and quality of life. **Methods:** A retrospective analysis was performed on 226 patients with alcoholic cirrhosis who experienced their first acute decompensatory event and initiated etiological treatment. Clinical data, laboratory indices, and imaging findings were comprehensively collected. Multiple evaluation indicators were used, and statistical analyses were conducted via SPSS 26.0, R software, etc., to screen relevant influencing factors and construct a recompensation prediction model. **Results:** 1、Abstinence significantly influenced the disease progression of patients with decompensated alcoholic cirrhosis. Whether patients abstained from alcohol ($P = 0.028 < 0.05$) was an important risk factor for recurrent acute decompensatory events. Strict abstinence promoted recompensation. 2、Among 206 patients with strict abstinence, the recompensation rate was 34.0%. Ascites occurred in over 90% of patients during the first acute decompensatory event of alcoholic cirrhosis. Patients with multiple acute decompensatory events ($\chi^2 = 18.486$, $P < 0.001$) or combined infections ($\chi^2 = 14.099$, $P < 0.001$) were less likely to achieve recompensation, and the more infection sites, the more unfavorable the outcome. 3、In laboratory tests, the recompensation group outperformed the persistent decompensation group in multiple aspects, including blood routine, coagulation function, and biochemical

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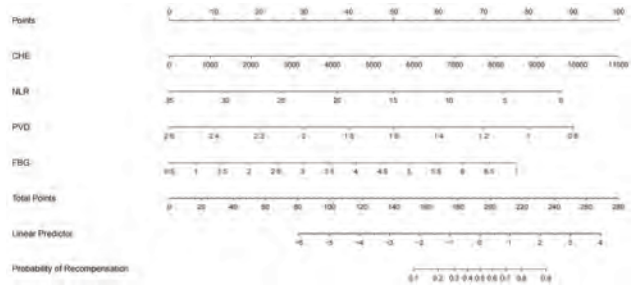
indices. For portal hypertension analysis, the portal vein diameter (PVD) and the proportion of portal hypertension collateral circulation in the recompensation group were significantly lower than those in the persistent decompensation group ($P < 0.05$). Six scoring systems—Model for End-Stage Liver Disease (MELD), MELD 3.0, Child-Pugh score, neutrophil-to-lymphocyte ratio (NLR), red blood cell distribution width-to-platelet count ratio (RPR), and albumin-bilirubin score (ALBI)—showed differences between the two groups ($P < 0.05$). 4、Univariate Logistic regression identified multiple factors associated with recompensation. After excluding collinearity via multivariate analysis, multivariate Logistic regression showed that CHE ($P = 0.003$), PVD ($P < 0.001$), and NLR ($P = 0.016$) were predictive factors for recompensation in decompensated alcoholic cirrhosis. FBG ($P = 0.065$) showed a P-value close to statistical significance, indicating potential influence. 5、The Nomogram prediction model based on cholinesterase (CHE), PVD, NLR, and fibrinogen (FBG) exhibited high accuracy, with an AUC of 0.849, sensitivity of 75.7%, and specificity of 86.0%. The Hosmer-Lemeshow test ($P = 0.1197 > 0.05$) confirmed good goodness-of-fit and accuracy. **Conclusion:** 1、Abstinence is the core factor for controlling disease progression and promoting recompensation in decompensated alcoholic cirrhosis. Patients with strict abstinence had a significantly lower recurrence rate of acute decompensatory events than relapsing drinkers. 2、The recompensation rate among strictly abstinent patients was 34.0%. Ascites occurred in $>90\%$ of patients during the first acute decompensation. Multiple decompensatory events, combined infections, and more infection sites were detrimental to recompensation. 3、Cholinesterase (CHE), portal vein diameter (PVD), and neutrophil-to-lymphocyte ratio (NLR) are key predictive factors for recompensation, with fibrinogen (FBG) showing potential influence. Patients with CHE >3113.50 U/L, fibrinogen >2.58 g/L, NLR. 4、The Nomogram model based on CHE, PVD, NLR, and FBG demonstrates excellent accuracy and discriminative ability, serving as a valuable tool for predicting recompensation probability with promising clinical application prospects.



Disclosures: jingyuan zhou: Nothing to Disclose, Jia Zhou: Nothing to Disclose, Hongqin Xu: Nothing to Disclose, Yanhang Gao: Nothing to Disclose

1533 | DYNAMIC CHANGES OF HEPATIC MACROPHAGES UPON CESSATION OF ALCOHOL CONSUMPTION IN MICE

Isabel Aranzazu Pulido Ruiz[1] Kyle Yuquimpo[1] Ayobami Dare[1] Ann Wozniak[1] Irina Tikhanovich[1] Steven Weinman[1], [1]University of Kansas Medical Center

Background: Alcohol cessation improves the prognosis of alcohol associated liver disease (ALD), but even after abstinence, recovery is slow and incomplete. A better understanding of the mechanisms of recovery could lead to new therapies. Kupffer cells (KC) and liver infiltrating macrophages (IM) change during ALD development, but how they change in after alcohol cessation has not been determined. The aim of this study was to determine the change of liver macrophages after alcohol cessation and how these might contribute to disease recovery. **Methods:** C57BL/6J and *Ms4a3*-Cre x CAG-TdT mice were fed high-fat western diet with 10%-20% alcohol in drinking water for 16 weeks (WDA diet). They were transitioned to a chow/water diet for 3, 7, or 28 days. Liver and blood were collected for histology, qPCR, western blot, and flow cytometry. **Results:** At the end of WDA feeding, liver macrophages consisted of an equal mixture of KCs and IMs. Transition forms, both KC and IM, with intermediate properties, were present. They expressed genes characteristic of lipid associated macrophages (LAMs) such as *Gpnmb*, *Trem2*, and *Cd9*) and localized primarily in crown-like structures (CLS). Following alcohol cessation, there was a rapid change in liver macrophage populations. Within 3 days there was a 78% decrease in KC *Clec4f* expression and by 7 days there was a 5-10-fold increase in IM genes such as *Cx3cr1* and *Lyz2*. Lineage tracing with *Ms4a3*-TdT mice that express TdT only in bone marrow derived cells confirmed that by 7 days, embryonic emKCs had been replaced by new moKCs. Alcohol cessation also resulted in about a 2-fold increase in CLS number and by 7 days the cells composing the CLS changed from GPNMB+VSIG4- LAMs to GPNMB+ VSIG4+ LAM-like KCs. In situ zymography showed that post alcohol cessation, the CLS became sites of high collagenase activity, and this was associated with an increase in *Mmp12* expression. **Conclusion:** Just like the situation when alcohol is started, sudden alcohol withdrawal induces an immediate change in liver macrophage populations with replacement of emKCs by new moKCs, changes in the cellular composition of crown-like structures, and an increase in MMP expression in a CLS-associated population of LAM-like KCs. These KC-like CLS cells may be involved in fibrosis remodeling. Further studies are needed to define the role that these novel resolution macrophages play in disease resolution or lack thereof.

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Disclosures: Isabel Aranzazu Pulido Ruiz: Nothing to Disclose, Kyle Yuquimpo: Nothing to Disclose, Ayobami Dare: Nothing to Disclose, Ann Wozniak: Nothing to Disclose, Irina Tikhanovich: Nothing to Disclose, Steven Weinman: Nothing to Disclose

1534 | MYOSTEATOSIS IS CLOSELY ASSOCIATED WITH SARCOPENIA AND WORSE SHORT-TERM OUTCOMES IN MALE PATIENTS WITH ARLD IN CHINA

Yu Zhang[1] Song Yang[1], [1]Beijing Ditan Hospital of Capital Medical University

Background: The burden of alcohol-related liver disease (ARLD) is increasing in China. Patients with ARLD are more likely to have comorbid muscle damage, such as myosteatosis and sarcopenia, which may impair their survival. This study aimed to evaluate the relationship between the prognoses of patients with ARLD and myosteatosis, identified using the mean muscle attenuation. **Methods:** We conducted a prospective multicenter study involving 308 hospitalized patients with ARLD. Sarcopenia and myosteatosis were evaluated using computed tomography scans. The 6-month cumulative incidence of relevant events was assessed by competing risk analysis. We used Cox proportional hazards regression models to evaluate the impact of sarcopenia and myosteatosis on mortality. **Results:** At enrolment, 116 (37.66%) patients presented with isolated myosteatosis, 21 (6.82%) with isolated sarcopenia, 99 (32.14%) with combined sarcopenia and myosteatosis and 72 (23.38%) patients showed no muscle changes. The 6-month cumulative incidence of death in patients with either sarcopenia and myosteatosis (13.13%) was over twice that of patients without muscle changes (4.16%), or with isolated myosteatosis (5.17%), and was significantly higher than that of patients with isolated sarcopenia (9.5%). Multiple Cox regression analysis showed that visceral adipose tissue area、subcutaneous adipose tissue area、VA-TI (visceral adipose tissue index)、SA-TI (subcutaneous adipose tissue index) and TBiL (total bilirubin) were independent prognostic factors of 6-month survival with hazard ratios (95% confidence intervals) of 0.923 (0.876-0.972), 1.075 (1.015-1.139), 1.277 (1.101-1.481), 0.801 (0.684-0.937), and 1.016 (1.003–1.029), respectively. **Conclusion:** Myosteatosis, whether alone or combined with sarcopenia, is highly prevalent in patients with ARLD and is associated with significantly worse short-term outcomes. Early diagnosis and intervention of myosteatosis, are important for optimizing the management of patients with ARLD.

Figure 1. Cumulative incidence of death in 2 groups

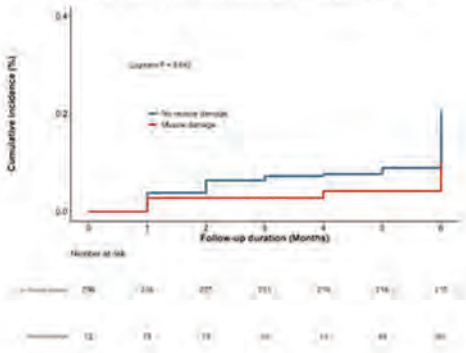
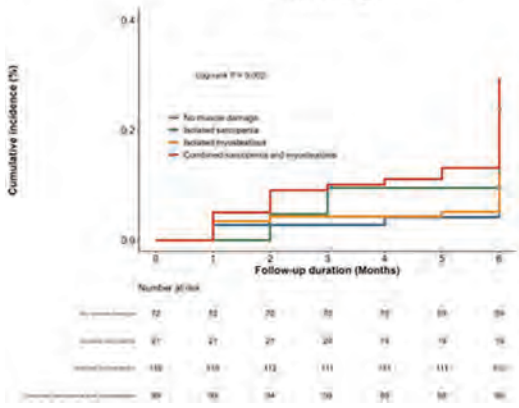


Figure 2. Cumulative incidence of death in 4 patient subgroups according to the type of muscle damage.



Disclosures: Yu Zhang: Nothing to Disclose, Song Yang: Nothing to Disclose

1535 | ROLE OF KUPFFER CELL SPP1 IN ALCOHOL-ASSOCIATED LIVER DISEASE

Nithyananthan Subramaniyam[1] Hui Han[1] Xiaodong Ge[1] Sai Santosh Babu Komakula[1] Jeongwoo Park[1] Dan Lantvit[1] Grace Guzman[1] Natalia Nieto[1], [1]University of Illinois at Chicago

Background: Alcohol-associated liver disease (AALD) is a leading cause of chronic liver disease worldwide, with rising incidence and limited treatment options beyond alcohol cessation and liver transplantation. Secreted phosphoprotein-1 (SPP1) is a glycoprotein involved in immune regulation and tissue repair. Since Kupffer cells express high levels of SPP1, the aim of this work was to investigate the role of Kupffer cell-derived SPP1 in AALD. **Methods:** We analyzed publicly available human alcoholic hepatitis datasets for *SPP1* expression. To induce early AALD, 12-week-old male and female *Clec4f.Cre* (control), *Spp1* Knock-in in Kupffer cells ($Spp1^{KI\ KC}$), *Alb.Cre* (control), and arginase 2 knock-out in hepatocytes ($Arg2^{\Delta Hep}$) were fed a

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control or ethanol Lieber-DeCarli diet for six weeks. Histopathological scores and parameters of liver injury were analyzed. **Results:** Transcriptomics analysis showed increased expression of *SPP1* mRNA in hepatic macrophages from ASH patients, which was validated by co-localization studies ($SPP1^{+}CD68^{+}$) in liver biopsies, compared to healthy individuals. Ethanol increased hepatic steatosis, liver-to-body weight, ALT activity, and triglycerides in *Clec4f.Cre* mice, but they were all reduced in $Spp1^{KI\ KC}$ mice. Moreover, qPCR analysis demonstrated that multiple genes involved in lipid metabolism were downregulated by ethanol in $Spp1^{KI\ KC}$ mice. Notably, minimal changes were found in adipocyte size in all ethanol-fed mice. We previously showed that $SPP1^{High}$ macrophages protect against MASH by increasing oncostatin M (OSM), which signals hepatocytes through its receptor (OSMR) to activate arginase-2 (ARG2) and enhance mitochondrial fatty acid oxidation. Therefore, we evaluated their expression and found a significant increase in OSM, OSMR, and ARG2 in $Spp1^{KI\ KC}$ compared to *Clec4f.Cre* mice. To test the involvement of ARG2 in AALD, *Alb.Cre* and $Arg2^{\Delta Hep}$ mice were fed the Lieber-DeCarli diets. Ethanol induced hepatic steatosis, inflammation, ALT activity, and triglycerides in $Arg2^{\Delta Hep}$ mice, but they were all reduced in *Alb.Cre* mice. $Arg2^{\Delta Hep}$ mice also showed reduced mitochondrial copy number and lower complex I expression. **Conclusion:** Kupffer cell-derived SPP1 protects against ALD by enhancing hepatocyte lipid metabolism via the OSM–OSMR–ARG2 axis.

Disclosures: Nithyananthan Subramaniyam: Nothing to Disclose, Hui Han: Nothing to Disclose, Xiaodong Ge: Nothing to Disclose, Sai Santosh Babu Komakula: Nothing to Disclose, Jeongwoo Park: Nothing to Disclose, Dan Lantvit: Nothing to Disclose, Grace Guzman: Nothing to Disclose, Natalia Nieto: Nothing to Disclose

1536 | GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST IS A PROMISING DUAL TARGET FOR METABOLIC LIVER DISEASE AND ALCOHOL USE

Sheel Patel[1] Fatima Elmustafa[2] Sara Nassar[3] Hanna Blaney[4] Harpreet Kaur[5] Winston Dunn[6] Ashwani Singal[1], [1]University of Louisville, [2]Henry Ford Health System, [3]Mansoura University Hospital, [4]Georgetown University, [5]Allegheny Health Network, [6]University of Kansas Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-associated liver disease (MetALD), and alcohol-associated liver disease (ALD) are major contributors to chronic liver disease worldwide, with overlapping pathophysiology. Combined metabolic dysfunction and alcohol use disorder (AUD) accelerate liver injury, with a higher risk for cirrhosis and complications. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) improve cardiometabolic risk profile and have also shown potential in reducing alcohol consumption. This systematic review aims to evaluate the influence of GLP-1 RAs on both alcohol use and liver-related outcomes. **Methods:** A systematic search using Web of Science, PubMed, and Embase identified 1,085 studies using terms related to GLP-1 RAs, liver disease, and alcohol use. Randomized control trials (RCTs) and observational studies assessing the effects of GLP-1 RAs on alcohol use and liver outcomes were screened, with inclusion limited to studies with >10 participants. **Results:** Of 22 studies reviewed, nine using different GLP-1RAs for variable treatment duration and follow-up were analyzed (Table 1). Of three RCTs ($n=48$ to 151) in subjects with AUD, semaglutide reduced self-reported alcohol use, dulaglutide lowered alcohol intake in current drinkers, while exenatide had no significant effect on heavy drinking days. Observational data from four studies ($n=58$ to 1470) in patients with liver disease (MetALD in 3 and MASLD in 1) showed semaglutide or tirzepatide to reduce decompensation in one study and reduce alcohol use in the other three studies. The remaining two observational studies using large databases showed GLP-1 RAs in AUD subjects reduced the risk of hospitalization in one and alcohol intoxication in the other study. **Conclusion:** GLP-1 receptor agonists are a promising therapy for liver diseases driven by metabolic dysfunction, including those with MetALD. Large scale RCTs are needed to substantiate their role in reducing alcohol use and in treating alcohol use disorders.

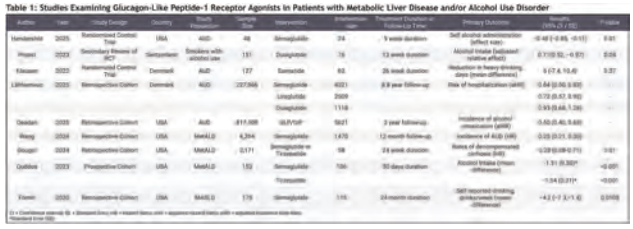
Table 1: Studies Examining Glucagon-Like Peptide-1 Receptor Agonists in Patients with Metabolic Liver Disease and/or Alcohol Use Disorder

Disclosures: Sheel Patel: Nothing to Disclose, Fatima Elmustafa: Nothing to Disclose, Sara Nassar: Nothing to Disclose, Hanna Blaney: Nothing to Disclose, Harpreet Kaur: Nothing to Disclose, Winston Dunn: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, GSK: Grant/Research Support, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, Avera Medical Group: Employee, NIAAA: Grant/Research Support, Gastro

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Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other

1537 | INCREASED FGF21 MEDIATES ALCOHOL-INDUCED METABOLIC ALTERATIONS IN TGR5-DEFICIENT MICE

SHIFAT-E FERDOUS[1] TITILAYO OLOTU[1] SHannon Boehme[1] Matthew Dilts[1] Jessica Ferrell[1], [1]Northeast Ohio Medical University

Background: Takeda G-protein coupled receptor 5 (TGR5), a bile acid activated receptor, exhibits organ-specific differential effects on metabolism, proliferation and inflammation. We recently reported that *TGR5*$^{-/-}$ mice were protected from alcohol-induced liver injury via upregulation of fibroblast growth factor 21 (FGF21). FGF21, a liver-derived hormone, plays a crucial role in lipid and glucose metabolism. FGF21 is upregulated in response to alcohol intake and suppresses alcohol consumption in a negative feedback mechanism involving liver, adipose tissue and brain. Here, we tested the hypothesis that *TGR5*$^{-/-}$ mice would voluntarily drink less ethanol, and we investigated the molecular mechanisms involved. **Methods:** Male and female *TGR5*$^{-/-}$ mice and their respective wild-type control (WT) mice were subjected to a two-bottle choice protocol with 10% ethanol and water, along with standard chow-diet for 2 weeks. Upon termination, we assessed metabolic, inflammatory and thermogenic pathways in liver, adipose tissue and brain. **Results:** Both male and female *TGR5*$^{-/-}$ mice exhibited reduced preference for ethanol compared to WT controls, which was accompanied by significantly increased circulating FGF21. Body weight and ethanol metabolizing enzymes (ADH, ALDH2) were unaltered, though female mice drank more ethanol than male mice. Interestingly, liver triglycerides were only reduced in male *TGR5*$^{-/-}$ mice, while liver cholesterol was increased in female *TGR5*$^{-/-}$ mice, possibly due to the overall increased ethanol consumption in female mice. Expression of browning, thermogenesis, and lipolysis genes (*Prdm16, Pparg, Pgc1a, Leptin, Atgl*), in white adipose tissue was increased in male *TGR5*$^{-/-}$ mice. In the hypothalamus expression of genes mediating satiety and glucose uptake (*Npy, Agrp, Glut2, Insr*) were also increased only in male *TGR5*$^{-/-}$ mice. As food intake between genotypes was not altered, these data may indicate sexual dimorphism in hypothalamic regulation of caloric intake and energy use in the context of ethanol consumption. Mechanistically, the source of hepatic FGF21 upregulation in *TGR5*$^{-/-}$ mice may be due to increased STAT5 protein expression, which will be further investigated. **Conclusion:** *TGR5*$^{-/-}$ mice have endogenously increased FGF21 levels that suppress voluntary drinking. The sex-specific differences in liver, adipose, and hypothalamic metabolism, as well as the molecular mechanism directing FGF21 expression in *TGR5*$^{-/-}$ mice, are under investigation.

Disclosures: SHIFAT-E FERDOUS: Nothing to Disclose, TITILAYO OLOTU: Nothing to Disclose, SHannon Boehme: Nothing to Disclose, Matthew Dilts: Nothing to Disclose, Jessica Ferrell: Nothing to Disclose

1538 | PREVENTING NUCLEAR PROHIBITIN 1 DEPLETION PROTECTS AGAINST ALCOHOL-ASSOCIATED LIVER INJURY AND SENSITIZATION TO COLORECTAL LIVER METASTASIS

Jyoti Chhimwal[1] Lucia Barbier Torres[2] Sonal Sinha[1] Maria Lauda Tomasi[1] Shelly Lu[1], [1]Cedars Sinai Medical Centre, [2]Cedars-Sinai Medical Center

Background: Prohibitin 1 (PHB1) is a multifunctional protein with roles in mitochondrial function, gene regulation, and stress responses largely determined by its subcellular localization. We reported hepatic PHB1 is downregulated in cholestatic liver injury and liver cancer and reduced hepatic PHB1 expression sensitizes the liver to colorectal liver metastasis (CRLM) via matrix metalloproteinase 7 (MMP-7) induction. Whether PHB1 is dysregulated in alcohol-associated liver disease (ALD) is unknown. Here, we investigated whether ethanol disrupts PHB1 localization and examined the implications of these changes. **Methods:** We employed both in vitro and in vivo ALD models and confirmed the key finding using liver samples from alcoholic hepatitis (AH) patients. Primary mouse hepatocytes were treated with 100 mM ethanol for 24 hours, and mice were subjected to the NIAAA protocol. To examine how ethanol impacts CRLM, we used a modified NIAAA protocol (18 days of ethanol feeding without the terminal binge) and pair-fed controls that had intrasplenic injection of MC38 cells on day 4 of feeding and imaged up to day 14. PHB1's nuclear export signal (NES) peptide was used to inhibit PHB1 nuclear export. PHB1 content was measured in subcellular fractions by immunoblotting and immunohistochemistry (IHC), while liver injury, inflammatory and oxidative stress responses were evaluated using enzyme assays, qRT-PCR, IHC, and immunoblotting. **Results:** We found a marked depletion of cytosolic and nuclear PHB1, but mitochondrial PHB1 was protected in

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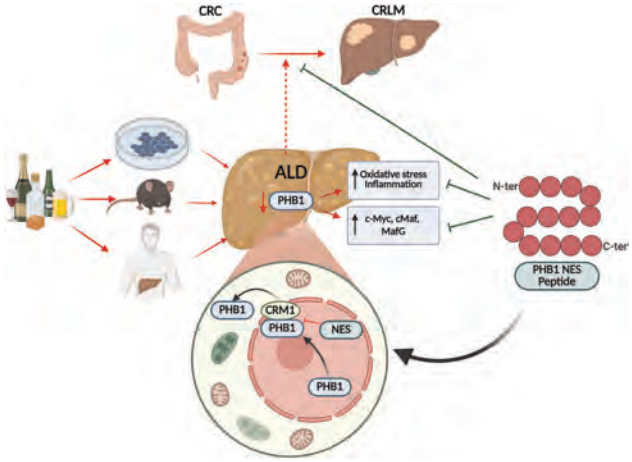
murine ALD, ALD-CRLM, and human AH. Ethanol treatment increased the interaction of PHB1 with CRM1 (aka Exportin 1) and PHB1-NES lowered their interaction and prevented ethanol-mediated nuclear PHB1 depletion. This resulted in protection from ethanol-mediated lowering of GSH level and expression of its rate-limiting enzyme. PHB1-NES also protected from induction of oncogenes known to be suppressed by PHB1, including c-MYC, MAFG, c-MAF, and MMP-7. Further, PHB1-NES protected from increased serum ALT/AST levels, inflammatory cytokines and oxidative stress in NIAAA mice. Lastly, ethanol feeding markedly sensitized to CRLM and this was completely blocked by PHB1-NES co-treatment. **Conclusion:** Ethanol consumption increased the interaction of PHB1 with CRM1, resulting in PHB1 nuclear depletion. Preventing nuclear PHB1 depletion by the PHB-NES peptide protected against ALD and ethanol-mediated sensitization to CRLM.



Disclosures: Jyoti Chhimwal: Nothing to Disclose, Lucia Barbier Torres: Nothing to Disclose, Sonal Sinha: Nothing to Disclose, Maria Lauda Tomasi: Nothing to Disclose, Shelly Lu: Nothing to Disclose

1539 | NALTREXONE VS ACAMPROSATE IN ALCOHOL USE DISORDER WITH ALCOHOL-ASSOCIATED CIRRHOSIS: A PROPENSITY-MATCHED REAL-WORLD ANALYSIS OF MORTALITY AND MORBIDITY

Ali Shaat Karim Osman[1] Raza Malik[1], [1]Lahey Hospital & Medical Center

Background: Alcohol use disorder (AUD) in individuals with alcohol-associated cirrhosis (AC) is commonly treated with medications such as naltrexone and acamprosate; however, data on their safety and effectiveness in this population remain limited. This study aimed to compare the risks of all-cause mortality, hospital admissions, hepatic encephalopathy (HE), acute kidney injury (AKI), and gastrointestinal bleeding (GIB) among patients with AUD and AC treated with naltrexone versus acamprosate. **Methods:** A retrospective cohort analysis was conducted using the TriNetX Global Collaborative Network on 04/23/2025, comprising 147 healthcare organizations. Patients ≥ 18 years old with AC and concurrent AUD were included and stratified by the following: Cohort 1 (N = 6,258) were prescribed naltrexone, and Cohort 2 (N = 4,719) were prescribed acamprosate. Individuals < 18 years old and those on disulfiram or topiramate were excluded from the study. Patients were matched 1:1 using propensity score matching based on demographics and MELD-related laboratory values, resulting in 4,508 matched pairs (Figure). The index event was defined as the first occurrence of naltrexone in Cohort 1 and the first occurrence of acamprosate in Cohort 2. Outcomes, identified via International Classification of Diseases (ICD) codes, assessed the incidence of GIB, HE, hospital admissions and death over a 5-year period. Risk analyses and Kaplan-Meier survival estimates were employed. **Results:** Following matching, treatment with naltrexone was associated with a significantly lower incidence of HE (20.3% vs. 24.3%; RR 0.84; 95% CI 0.76–0.93; $p = 0.001$), AKI (19.7% vs. 22.1%; RR 0.89; 95% CI 0.81–0.98; $p = 0.02$), and all-cause mortality (19.3% vs. 22.8%; RR 0.85; 95% CI 0.78–0.92; $p < 0.001$) compared to acamprosate. The hazard ratio for mortality was 0.794 (95% CI 0.726–0.869; $p < 0.001$), indicating a 20.6% reduction in the hazard of death with naltrexone (Figure). The proportional hazards assumption was satisfied ($p = 0.766$), confirming the stability of this effect over time. Median survival was longer and the 5-year survival probability was higher in the naltrexone group (64.2% vs. 57.5%; $p < 0.001$). There were no statistically significant differences in the incidence of GIB (11.6% vs. 13.0%; RR: 0.89; 95% CI 0.78–1.01; $p = 0.065$) or hospital admissions (7.5% vs. 8.1%; RR: 0.93; 95% CI 0.79–1.09; $p = 0.372$). **Conclusion:** Among patients with AUD and AC, treatment with naltrexone was associated with lower rates of all-cause mortality, HE, and AKI compared to acamprosate over a 5-year period. Limitations of the study include reliance on ICD codes, inability to differentiate liver-related from non-liver-related mortality, and inability to ascertain medication adherence. Nonetheless, the results support naltrexone as a potentially safer pharmacologic option in this high-risk population. Further prospective studies are warranted to validate these findings.

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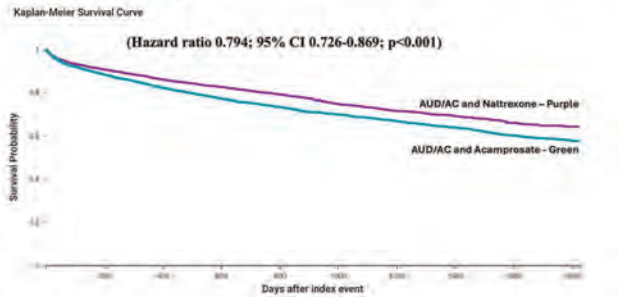
	Unmatched Data			After Propensity Score Matching		
	AUD/AC and Naltrexone (N=6,258)	AUD/AC and Acamprosate (N=4,719)	Standard Mean Difference	AUD/AC and Naltrexone (N=4,508)	AUD/AC and Acamprosate (N=4,508)	Standard Mean Difference
Demographics						
Age at index	52.7±11.3	49.4±11.2	0.289	50.1±11.0	50.0±10.9	0.004
Male	4,129	3,305	0.018	2,941	2,896	0.007
Female	1,953	1,583	0.05	1,445	1,500	0.026
White	4,428	3,305	0.018	3,209	3,194	0.007
Black or African America	697	437	0.06	429	431	0.002
Hispanic or Latino	723	532	0.01	504	523	0.013
Not Hispanic or Latino	4,166	3,015	0.058	2,930	2,914	0.007
American Indian or Alaskan Native	216	188	0.028	167	176	0.01
Asian	101	103	0.042	92	91	0.002
Native Hawaiian or Other Pacific Islander	24	12	0.023	12	12	<0.0001
MELD-Related Laboratory Values (Mean)						
Serum Sodium (mEq/L)	137±4.24	136±4.51	0.176	137±4.23	136±4.51	0.003
Serum Total Bilirubin (mg/dL)	2.47±4.38	4.69±6.36	0.41	2.71±4.8	4.62±6.31	<0.0001
Serum Creatinine (mg/dL)	0.92±2.1	0.83±1.59	0.045	0.89±1.21	0.84±1.61	0.001
Serum Albumin (g/dL)	3.45±0.78	3.16±0.79	0.381	3.43±0.79	3.16±0.79	0.001
Plasma INR	1.3±0.4	1.5±0.6	0.39	1.3±0.4	1.5±0.6	0.019

Kaplan-Meier Survival Curve Depicting 5-Year Mortality for Both Cohorts.



Disclosures: Ali Shaat: Nothing to Disclose, Karim Osman: Nothing to Disclose, Raza Malik: Nothing to Disclose

1540 | THE FIBROSIS NON-INVASIVE TEST PANEL (FIB-NIT): A NOVEL PANEL OF THREE NON-INVASIVE BIOMARKERS FOR EVALUATING FIBROSIS DYNAMICS THROUGH INDIVIDUAL COMPONENTS OF FIBROGENESIS (PRO-C3), FIBROLYSIS (CTX-III), AND CLINICAL OUTCOMES (PRO-C6) IN PATIENTS WITH VARYING SEVERITY OF ALCOHOL-RELATED LIVER DISEASE

Andressa de Zawadzki[1] Maja Thiele[2] Stine Johansen[2] Ida Villesen[2] Peter Andersen[2] Ida Spedtsberg[2] Morten Karsdal[1] Aleksander Krag[3] Diana Leeming[1], [1]Nordic Bioscience, [2]Odense University Hospital, [3]University of Southern Denmark

Background: Persistent and excessive alcohol intake induces damage to the liver, impairing its ability to properly regenerate, potentially leading to alcohol-related liver disease (ALD). Non-invasive tests (NITs) quantifying the dynamics of the extracellular matrix (ECM) remodeling and disease activity may be important for patient prognosis. We aimed to investigate the above-mentioned utility of the serologically assessed FIBrosis Non-Invasive Test panel (FIB-NIT) consisting of three single markers that can describe fibrogenesis (PRO-C3), patientoutcomes (PRO-C6) and fibrolysis (CTX-III). All, previously shown to be modulated by interventions in MASH clinical trials. **Methods:** Serum biomarkers of fibrogenesis nordicPRO-C3™ (N-terminal pro-peptide of type III collagen) and for patient outcome nordicPRO-C6™ (endotrophin; type VI collagen formation) aa well as fibrosis resolution nordicCTX-III™ (MMP degraded fragment of cross-linked type III collagen) were measured in a cross-sectional cohort of 450 biopsy-proven F0-F4 ALD patients. The biomarkers were investigated as single markers to understand disease mechanisms in relation to disease severity and prognosis of outcomes (mortality, liver related events and non-liver related outcomes) over a median 5-yr follow-up. **Results:** ALD patients with advanced fibrosis (F3-F4) and cirrhosis exhibited increased fibrogenesis as observed from higher serum PRO-C3 and PRO-C6 ($p < 0.001$) as well as higher fibrolysis as shown by higher serum levels of CTX-III ($p < 0.001$) in comparison to patients with mild-moderate fibrosis (F0-F2). Kaplan-Meier curves showed that all three biomarkers provided good prognostic value to stratify ALD patients at risk of all-cause mortality and decompensation (PRO-C3 cut off 12.6, hazard ratio for mortality (HRm) of 4.7 and decompensation (HRd) of 10.6; CTX-III cutoff 15.6, HRm of 2.2 and HRd of 2.4; PRO-C6 cut off 11.0, HRm of 3.4 and HRd of 4.8). **Conclusion:** The "FIB-NIT" biomarker panel may be utilized for evaluating fibrosis remodelling and risk of patient outcomes in ALD. This panel may offer insights into the underlying mechanisms of fibrosis progression and help understanding the mode of action of novel therapies in ALD as well as other chronic liver diseases.

Disclosures: Andressa de Zawadzki: Nothing to Disclose, Maja Thiele: Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, GSK: Advisor, GSK: Advisor, GSK: Advisor, Novo Nordisk: Speaking and Teaching, GSK: Grant/Research Support, Evido: Co-founder, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, Astra

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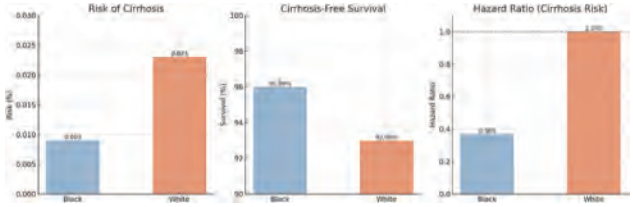
1541 | RACIAL DISPARITIES IN CIRRHOSIS RISK AND CLINICAL OUTCOMES AMONG PATIENTS WITH ALCOHOL USE: A PROPENSITY-MATCHED COHORT STUDY

sabtain saroya[1] mathew deleary[1] Noah Wheaton[1] soha mohammed[1] Marek Harris[1] Armando Ugarte[1] mudasir rashid[2] miriam michael[3], [1]howard university college of medicine, [2]Howard University Hospital Cancer Center, [3]Howard University Hospital

Background: Alcohol use is a leading cause of cirrhosis; however, the risk and progression of cirrhosis may differ across racial groups. Prior studies suggest that racial disparities may influence liver disease outcomes, but large-scale comparative analyses remain limited. This study evaluates cirrhosis incidence and time-to-event outcomes among Black and White patients with alcohol use, matched by age and sex. **Methods:** We conducted a retrospective cohort analysis of 205,450 patients (102,725 Black and 102,725 White) with documented alcohol use. Patients were propensity-matched 1:1 by age and sex. We calculated cirrhosis risk, odds ratios (OR), risk ratios (RR), and hazard ratios (HR). Cirrhosis-free survival was assessed using Kaplan-Meier curves and log-rank testing. **Results:** Cirrhosis developed in 0.9% of Black patients and 2.3% of White patients (Risk Difference: -1.4%; 95% CI: -1.5% to -1.3%; $p < 0.001$). The risk ratio was 0.39, and the odds ratio was 0.39, both indicating a significantly lower risk in Black patients. Kaplan-Meier analysis demonstrated higher cirrhosis-free survival in Black patients (95.99%) compared to White patients (92.98%), with a significant log-rank result ($\chi^2 = 728.4$; $p < 0.001$). The hazard ratio for cirrhosis in Black versus White patients was 0.37 (95% CI: 0.34–0.40; $p < 0.001$). **Conclusion:** Among patients with documented alcohol use, Black individuals demonstrated significantly lower risk and slower progression to cirrhosis compared to White individuals in an age- and sex-matched cohort. These findings underscore the presence of racial disparities in alcohol-associated liver disease outcomes and highlight the need for further investigation into underlying biological, behavioral, and systemic determinants. Understanding these differences is essential to developing targeted, equitable approaches to liver disease screening, prevention, and management.



Disclosures: sabtain saroya: Nothing to Disclose, mathew deleary: Nothing to Disclose, Noah Wheaton: Nothing to Disclose, soha mohammed: Nothing to Disclose, Marek Harris: Nothing to Disclose, Armando Ugarte: Nothing to Disclose, mudasir rashid: Nothing to Disclose, miriam michael: Nothing to Disclose

1542 | IMPACT OF ALCOHOL CONSUMPTION ON FIBROSIS PROGRESSION AND CARDIOVASCULAR EVENTS IN PATIENTS WITH MASLD AND METALD: A RETROSPECTIVE COHORT STUDY

Ares Villagrasa[1] Anna Aguilar[2] Alba Jimenez[3] Juan Manuel Pericàs[3] Meritxell Cots[3], [1]Hospital Universitari Vall Hebron, [2]Liver Unit, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Spain, [3]Liver Unit, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

Background: Alcohol-related liver disease (ArLD) is a major public health issue, where abstinence is essential to prevent progression. The combination of metabolic dysfunction and alcohol intake worsens prognosis, leading to the classification of steatotic liver disease (SLD) into MASLD and MetALD. MetALD involves at least one cardiometabolic risk factor and moderate alcohol use (20–50 g/day for women, 30–60 g/day for men), with a prevalence of 2.2–2.7% in SLD populations. Recent studies show that even low to moderate alcohol use increases fibrosis risk in MASLD, particularly with

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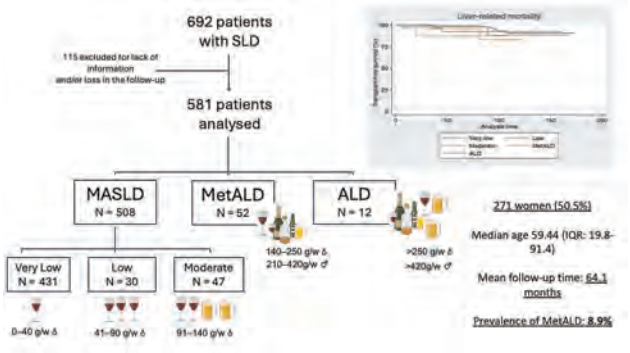
cardiometabolic comorbidities, and that MetALD is linked to higher mortality, especially in advanced fibrosis. This study aims to assess the prevalence of MetALD in a cohort of outpatients and to investigate the influence of alcohol consumption and abstinence at the end of follow-up on fibrosis progression and cardiovascular events in patients with MASLD and MetALD. **Methods:** A retrospective cohort study was conducted in outpatients with steatotic liver disease (SLD), diagnosed via imaging or CAP $\geq$275 dB/m. Patients were classified by alcohol intake (VLD, LD, MD) and reclassified as MetALD or ALD. Liver fibrosis was assessed non-invasively, and data on abstinence and cardiovascular events were collected during follow-up **Results:** Of 692 patients reviewed, 574 were analysed: 74.2% were very low-risk drinkers (VLD), 6.7% low-risk (LD), 8.1% moderate (MD), 8.9% MetALD, and 2.1% ALD. Median follow-up was 64.1 months. Women represented 50.6% of the cohort (mean age 59.4 years). Significant sex differences were observed between groups ($p < 0.0001$), while cardiometabolic risk factors were similar at baseline. Liver stiffness (LSF) differed significantly at baseline ($p = 0.0001$) and at follow-up ($p = 0.004$), with MD showing the highest LSF at follow-up (39.1 kPa; $p = 0.023$ vs VLD). Despite differences in alcohol abstinence, only age (OR = 1.00006, $p = 0.005$) and male sex (OR = 0.65, $p = 0.017$) were independently associated with fibrosis progression (> 2 kPa). No differences in overall survival or cardiovascular events were observed. Baseline LSF was borderline associated with CV risk (HR = 1.03, $p = 0.057$). Liver-related event risk differed by group ($p = 0.009$), with MetALD showing the highest estimated mortality. Only fibrosis progression was independently associated with liver-related mortality (HR = 9.53, $p = 0.040$). **Conclusion:** MetALD prevalence in our cohort is consistent with recent studies. Although MetALD patients showed greater fibrosis, only age and sex independently predicted its progression. Fibrosis change, not baseline stiffness, was the sole independent predictor of liver-related events. Monitoring fibrosis and promoting abstinence remain key to improving outcomes in patients with metabolic dysfunction and moderate alcohol use



Disclosures: Ares Villagrasa: Nothing to Disclose, Anna Aguilar: Nothing to Disclose, Alba Jimenez: Nothing to Disclose, Juan Manuel Pericàs: Nothing to Disclose, Meritxell Cots: Nothing to Disclose

1543 | NATIONWIDE TRENDS OF SIX MEDICATIONS FOR ALCOHOL USE DISORDER PRESCRIPTIONS POST-DISCHARGE IN PATIENTS HOSPITALIZED WITH ALCOHOL-ASSOCIATED LIVER DISEASE BETWEEN 2015 TO 2024

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Background: Alcohol-associated liver disease (ALD) has high hospitalization and relapse risk, yet post-discharge medications for alcohol use disorder (MAUD) are not uniformly prescribed. MAUD prescriptions have been associated with reduced recidivism and hepatic decompensations. However, real-world data on trends and percentage of MAUD use in patients with ALD are limited. We examined ten-year national trends in six MAUD prescriptions, both FDA approved and off label, after hospitalization for ALD. **Methods:** This population-level cohort study analyzed de-identified longitudinal electronic health records from TriNetX to identify insured and uninsured patients aged $\geq$ 21 hospitalized for ALD (including hepatitis and cirrhosis) between 1/1/2015 and 12/31/2024, via ICD-10 codes. Primary outcomes were prevalence (%), incidence rate (cases per 1,000 person-years) and incidence proportion (%) of post-discharge MAUD for FDA-approved medications (disulfiram, acamprosate, naltrexone) and off-label medications (topiramate, baclofen, gabapentin). Subgroup analyses were stratified by cirrhosis status and sex. Ten-year incidence trends were examined using piecewise log-linear Joinpoint regression (version 5.2.0.0), calculating annual percentage change (APC) and average annual percentage change (AAPC) with 95% confidence intervals. Advanced analyses of non-parallel AAPC comparisons between subgroups employed permutation tests and parametric methods. **Results:** Among 113 million patients in this database, ALD-related hospitalizations rose 2.4-fold from 14,616 in 2015 to 36,294 in 2024. The prevalence of patients with ALD receiving FDA

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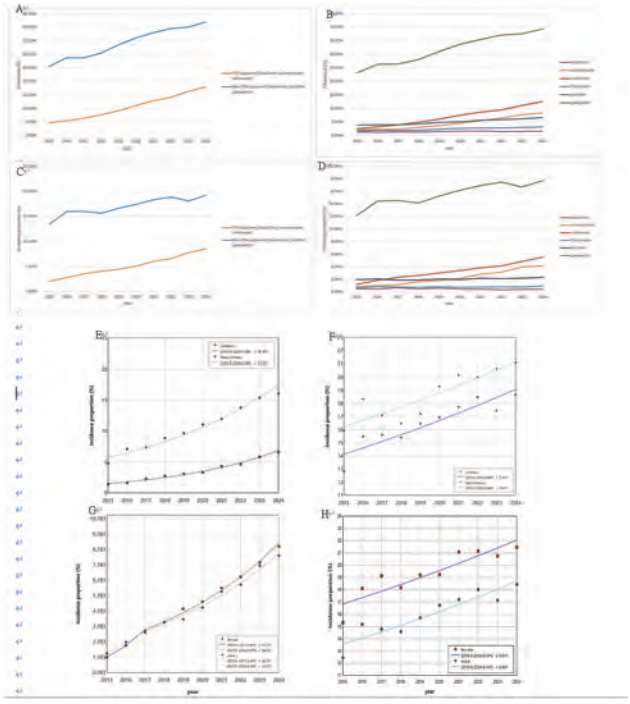
approved MAUD at discharge increased from 4.7% in 2015 to 18.0 % in 2024, with a greater increase between 2015 and 2021 (APC: 18.5%) than from 2021 to 2025 (APC: 11.9%). Use of off label MAUD rose to 42.0 % by 2024 and grew at AAPC of 5.7 %, a significantly slower pace than that of FDA approved agents (AAPC difference: 10.6%, $p < 0.001$). In 2024, gabapentin (38.8%) and naltrexone (23.1%) were most prescribed. New prescriptions of disulfiram declined from 6.6 to 5.5 cases per 1000 person years, while the other five medications rose significantly for the past decade. Acamprosate showed the largest increase (AAPC: 20.4%; 95%CI:18.5-22.2), followed by naltrexone (AAPC: 17.8%; 95%CI:16.2-19.5). Subgroup analysis revealed that patients with cirrhosis had lower baseline prescription rates but had greater relative increases in FDA approved MAUD compared to off-label MAUD (AAPC difference: 5.1%, $p < 0.001$). **Conclusion:** In our study, FDA-approved and off-label post-discharge MAUD prescriptions for hospitalized ALD patients increased significantly over the past decade. Yet by 2024, under 20% of ALD patients received FDA-approved abstinence medications. Targeted interventions are urgently needed to expand access and improve long-term alcohol cessation in this high-risk population.



Disclosures: Emily Shu-Yen Chan: Nothing to Disclose, Yee Hui Yeo: Ardelyx: Consultant, Bausch Health: Consultant, Ardelyx: pending intellectual property related to use of tenapanor, Natchaya Polpichai: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Peng-Sheng Ting: Nothing to Disclose

1544 | HOUSING STATUS AND ITS ASSOCIATION WITH COMPLICATIONS AND HOSPITAL OUTCOMES IN ALCOHOL-ASSOCIATED LIVER DISEASE

Ki Jung Lee[1] Gregory Fan[1] Anderson Huang[1] Raffi Karagozian[1] Mohammad Almeqdadi[1], [1]Tufts Medical Center

Background: Amongst unhoused individuals, alcohol use significantly contributes to the burden of liver disease. This study examines the effects of being unhoused on hospital outcomes and associated psychiatric conditions with alcohol-associated liver disease (ALD). **Methods:** Patients hospitalized with ALD from 2020 to 2024 at a tertiary care center were retrospectively reviewed. The cohort was stratified into housed (reference) and unhoused (exposure) cohorts. Exposure and reference cohorts were 1:1 propensity-score matched. Primary endpoints were length of stay (LOS), number of hospital admissions, and hepatic complications. Multivariate logistic regression and negative binomial regression models were used to evaluate categorical and discrete outcomes, respectively. **Results:** The analysis included 3,523 patients: 330 unhoused and 3,193 housed. Unhoused patients were younger, more likely to be male, and had lower BMI ($p < 0.001$). Over the 4 years of the study, Unhoused patients experienced a greater number of hospital visits (3.65 $\pm$ 0.23 vs 2.46 $\pm$ 0.06, aIRR 1.62 95% CI 1.46-1.79, $p < 0.001$), total days spent in hospital (22.35 $\pm$ 1.62 vs 15.91 $\pm$ 0.51, aIRR 1.60, 95% CI 1.42-1.82, $p < 0.001$), and higher numbers of emergency room visits (10.11 $\pm$ 0.70 vs 2.21 $\pm$ 0.07, aIRR 4.89, 95%CI 4.18-5.74, $p < 0.001$) and ICU visits (0.23 $\pm$ 0.03 vs 0.13 $\pm$ 0.01, aIRR 1.62, 95%CI 1.22-2.12, $p < 0.001$). The matched analysis showed unhoused patients having a greater number of hospital visits (aIRR 1.80, 95% CI 1.53-2.13, $p < 0.001$), longer total length of stays (aIRR 1.58, 95% CI 1.32-1.88, $p < 0.001$), more frequent emergency visits (aIRR 6.28, 95% CI 5.11-7.74, $p < 0.001$) and ICU visits (aIRR 2.04, 95% CI 1.34-3.15, $p = 0.001$). Both the unmatched and matched analyses showed that unhoused patients have an increased prevalence of substance abuse disorders, including opioid, cocaine, and fentanyl abuse, as well as psychiatric comorbidities, including anxiety, depression, and post-traumatic stress disorder. **Conclusion:** Unhoused patients with ALD experienced longer hospital lengths of stay, more frequent hospitalizations, and higher rates of hepatic complications, compounded by substance use and psychiatric comorbidities. These findings highlight the need for comprehensive care approaches to address the multifaceted challenges faced by this vulnerable population.

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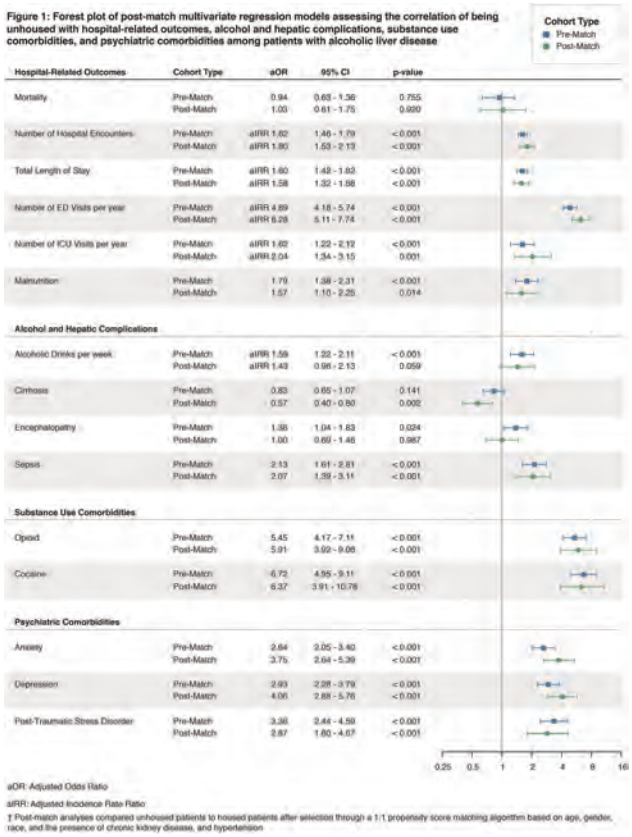

Disclosures: Ki Jung Lee: Nothing to Disclose, Gregory Fan: Nothing to Disclose, Anderson Huang: Nothing to Disclose, Raffi Karagozian: Nothing to Disclose, Mohammad Almeqdadi: Nothing to Disclose

1545 | INCIDENCE AND CLINICAL IMPLICATIONS OF ABSTINENCE-INDUCED HEPATIC RECOMPENSATION IN DECOMPENSATED ALCOHOL-RELATED CIRRHOSIS: A BAVENO MULTICENTRE STUDY

Benedikt Hofer[1] Marta Tonon[2] Laura Buttler[3] Joana Camões Neves[4] Queralt Herms[5] Enrico Pompili[6] Mina Ignat[7] Sophie Métivier[8] Susana Gomes Rodrigues[9] Daniel Gutmann[10] Jesús Donate[11] Jimmy Lai[12] Ana Clemente-Sánchez[13] Aina Marti Carretero[14] Josune Cabello[15] Charlotte Bouzbib[16] Henrik Karbannek[17] Jan Embacher[1] Lukas Parandian[1] Antonio Accetta[2] Roberta Gagliardi[2] Marie Griemsmann[3] Jordi Gratacós-Ginès[5] Mattias Mandorfer[1] Guadalupe Garcia-Tsao[18] Georg Semmler[1] Alexander Zipprich[17] Marika Rudler[16] Jonel Trebicka[15] Joan Genescà[14] Rafael Bañares[13] Terry Yip[12] Luis Téllez[11] Emmanouil Tsochatzis[10] Annalisa Berzigotti[9] Hélène Larrue[8] Horia Stefanescu[7] Paolo Caraceni[6] Elisa Pose[5] Dalila Costa[4] Benjamin Maasoumy[3] Salvatore Piano[2] Thomas Reiberger[1], [1]Department of Medicine III, Medical University of Vienna, Vienna, Austria, [2]Department of Medicine, University of Padova, Padova, Italy, [3]Hannover Medical School, Hannover, Germany, [4]Gastroenterology Department, Braga Hospital, Sete Fontes - São Victor, Braga, Portugal, [5]Liver Unit, Hospital Clínic de Barcelona, Barcelona, Spain, [6]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, [7]Hepatology Unit, Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania, [8]Department of Hepatology, University Hospital and Toulouse III - Paul Sabatier University, France, [9]Inselspital, Bern University Hospital, Bern, Switzerland, [10]Royal Free London NHS Foundation Trust, London, United Kingdom, [11]Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Madrid, Spain, [12]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, [13]University Gregorio Marañón Hospital, IiSGM, CIBERehd. Facultad de Medicina, UCM, Madrid, Spain, [14]Hospital Universitari Vall d'Hebrón, Universitat Autònoma de Barcelona, Barcelona, Spain, [15]Department of Internal Medicine B, University of Münster, Munster, Germany, [16]Sorbonne University, UPMC University Paris 06, AP-HP, Pitié-Salpêtrière Hospital, Paris, France, [17]Jena University Hospital, Friedrich Schiller University, Jena, Germany, [18]Yale University, New Haven, USA; VA-CT Healthcare System, West Haven, USA

Background: Alcohol abstinence can facilitate hepatic recompensation in decompensated alcohol-related cirrhosis (ALD). This study aimed to investigate the incidence, predictors, and clinical impact of abstinence-induced recompensation in ALD. **Methods:** In this multicentre Baveno-endorsed study, patients with decompensated ALD were included at time of abstinence until December 2022. Recompensation was defined per Baveno VII as (i) resolution of ascites and encephalopathy without ongoing treatment, (ii) absence of variceal bleeding for 12 months, and (iii) restoration of hepatic function (Child-Pugh A or MELD <10). Alcohol relapse led to censoring. **Results:** 633 patients from 17 centres were included (71.7% male; median age: 55 years; median MELD: 19 [IQR: 13-24]). The median interval between index decompensation and abstinence was 0.2 (IQR: 0.0-7.6) months. Alcohol-associated hepatitis (AH) on top of cirrhosis was present in 40.8% of patients and 47.2% had progressed to further decompensation (excluding jaundice). Over a median follow-up of 36.3 (IQR: 19.2-63.2) months, 197 patients achieved recompensation, with a cumulative incidence of 12.3% at 1 year, 23.4% at 2 years and 33.8% at 5 years. Early abstinence within 1 month of decompensation doubled the likelihood of recompensation (adjusted subdistribution hazard ratio [aSHR]:

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2.042, $p < 0.001$), while being further decompensated at abstinence significantly reduced it (aSHR: 0.650, $p = 0.013$) (see Table). During the study, 123 patients died, including 69 (56.1%) liver-related deaths. None of the recompensated patients who remained abstinent died of liver-related causes during a median observation period of 24.2 (IQR: 11.2-53.0) months after recompensation. In contrast, the incidence of liver-related death in non-recompensated patients was 9.0% at 1 year, 12.8% at 2 years and 16.9% at 5 years. Recompensation (included as time-varying covariate) was also independently associated with a lower risk of all-cause mortality (5.1% vs. 25.9% in non-recompensated; aHR: 0.255 [95%CI: 0.111-0.583], $p = 0.001$). Hepatocellular carcinoma (HCC) was diagnosed in 16 patients, yet did not occur in any of the recompensated patients. **Conclusion:** Recompensation is achieved in a relevant proportion of patients with decompensated ALD, particularly with early abstinence and in the absence of further decompensation. Achieving recompensation confers a favourable prognosis, with a negligible residual risk of liver-related death or HCC.

	Univariable analysis			Multivariable analysis		
Covariables	SHR	95% CI	p-value	aSHR	95% CI	p-value
Age (per year)	0.987	0.974-0.999	**0.045**	0.990	0.974-1.007	0.255
Male sex (vs. female sex)	0.731	0.521-1.025	0.070	0.730	0.495-1.078	0.113
Any CMRF	1.073	0.744-1.547	0.707	0.994	0.685-1.465	0.976
Abstinence achieved within 1 month of decompensation	2.398	1.568-3.667	**<0.001**	2.042	1.448-2.878	**<0.001**
Further decompensation (vs. single decompensation)	0.518	0.332-0.809	**0.004**	0.650	0.462-0.914	**0.013**
AH presentation	2.022	1.104-3.703	**0.023**	1.675	0.894-3.137	0.107
MELD (per point)	0.994	0.986-1.023	0.689	0.977	0.952-1.004	0.094
Albumin (per g/L)	0.978	0.951-1.005	0.107	0.990	0.955-1.025	0.560
Platelets (per 10 G/L)	1.019	1.003-1.035	**0.021**	1.003	0.982-1.023	0.805

Multivariable Fine and Gray competing risk regression model including centre as random effect. All-cause mortality, liver transplantation, alcohol relapse, HCC and TIPS were included as competing events. Analysis conducted on complete cases (n=472). Further decompensation excluded jaundice due to collinearity with AH. Abbreviations: aSHR, adjusted subdistribution hazard ratio; CMRF, cardiometabolic risk factor; AH, alcohol-associated hepatitis; MELD, model for end-stage liver disease. P-values in bold indicate statistical significance.

Disclosures: Benedikt Hofer: IPSEN: Travel support, FALK: Travel support, Marta Tonon: Nothing to Disclose, Laura Buttler: Nothing to Disclose, Joana Camões Neves: Nothing to Disclose, Queralt Herms: Nothing to Disclose, Enrico Pompili: Nothing to Disclose, Mina Ignat: Nothing to Disclose, Sophie Métivier: Nothing to Disclose, Susana Gomes Rodrigues: Nothing to Disclose, Daniel Gutmann: Nothing to Disclose, Jesús Donate: Nothing to Disclose, Jimmy Lai: Nothing to Disclose, Ana Clemente-Sánchez: Nothing to Disclose, Aina Marti Carretero: Nothing to Disclose, Josune Cabello: Nothing to Disclose, Charlotte Bouzbib: Nothing to Disclose, Henrik Karbannek: Nothing to Disclose, Jan Embacher: Nothing to Disclose, Lukas Parandian: Nothing to Disclose, Antonio Accetta: Nothing to Disclose, Roberta Gagliardi: Nothing to Disclose, Marie Griemsmann: Nothing to Disclose, Jordi Gratacós-Ginès: Nothing to Disclose, Mattias Mandorfer: Echosens: Speaking and Teaching, Echosens: Grant/Research Support, Ipsen: Consultant, Takeda: Consultant, Takeda: Speaking and Teaching, W.L. Gore & Associates: Speaking and Teaching, Eli Lilly: Consultant, Eli Lilly: Speaking and Teaching, Guadalupe Garcia-Tsao: Nothing to Disclose, Georg Semmler: Amgen: Travel Support, Alexander Zipprich: Nothing to Disclose, Marika Rudler: Nothing to Disclose, Jonel Trebicka: Nothing to Disclose, Joan Genescà: Nothing to Disclose, Rafael Bañares: Nothing to Disclose, Terry Yip: Nothing to Disclose, Luis Téllez: Nothing to Disclose, Emmanouil Tsochatzis: Nothing to Disclose, Annalisa Berzigotti: Nothing to Disclose, Hélène Larrue: Nothing to Disclose, Horia Stefanescu: Nothing to Disclose, Paolo Caraceni: Nothing to Disclose, Elisa Pose: Nothing to Disclose, Dalila Costa: Nothing to Disclose, Benjamin Maasoumy: Nothing to Disclose, Salvatore Piano: Nothing to Disclose, Thomas Reiberger: Nothing to Disclose

1546 | CHARACTERISTICS OF PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS RECORDED IN A CLAIMS DATABASE FROM 2016 TO 2024

Jayashri Desai[1] Scott Bunner[2] Marty Masek[2] Dannielle Lebovitch[2] Thomas Capozza[1] Amon Asgharpour[3], [1]Intercept Pharmaceuticals, Inc., Morristown, New Jersey, USA, [2]Genesis Research Group, Hoboken, New Jersey, USA, [3]Virginia Commonwealth University, Richmond, Virginia, USA

Background: Alcohol-associated hepatitis (AAH) is a rapidly progressive and life-threatening form of alcohol-associated liver disease (ALD) that is associated with high morbidity and mortality. Despite its clinical severity, real-world data quantifying the clinical burden of AAH remains limited. This study aimed to characterize the demographics, clinical characteristics, pharmacological treatments, procedures, and mortality of patients with AAH. **Methods:** This retrospective cohort study assessed claims data using the Optum Clinformatics® Data Mart Database and included adult patients with ≥ 2 inpatient claims for alcoholic hepatitis (AH; ICD-10-CM codes K70.10 and K70.11) identified between January 1, 2017, and October 30, 2024. Patients were required to have continuous medical and pharmacy enrollment for ≥ 12 months pre-index and ≥ 1 day post-index, with the index date defined as the date of first claim with an AH diagnosis. Patients with a diagnosis of AH, liver transplantation, metastatic disease, or pregnancy during the baseline (pre-index) period were excluded. Patients were followed until the end of the study period, disenrollment, or death, whichever came first. Demographics, clinical characteristics, pharmacological treatments, procedures, and mortality were assessed descriptively. **Results:** Of the 5382 patients identified, 2415 met study criteria. Most (64.8%) patients were men, with a mean (SD) age of 53.9

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(12.9) years (Table 1). The median (IQR) follow-up time was 13.2 (4.7–29.5) months. Evidence of hepatic and systemic complications representative of AAH increased substantially from baseline to follow-up (ascites, 13.2% to 62.0%; cirrhosis, 20.3% to 68.7%; hepatic failure, 7.7% to 56.7%; and acute kidney failure, 10.7% to 59.9%). Use of pharmacological treatments for alcohol use disorder (AUD) during follow-up was generally low. Key follow-up procedures included paracentesis (38.1%), hemodialysis (15.6%), liver biopsy (5.9%), and liver transplantation (5.9%). Overall, 780 (32.3%) patients died during follow-up. **Conclusion:** This large, claims-based study highlights the substantial hepatic and systemic disease burden among patients with AAH. The high prevalence of liver and renal complications, low rates of pharmacological treatments for AUD, and a mortality rate $>30\%$ during follow-up underscore the urgent, unmet need for earlier diagnosis and targeted therapies. Real-world data are critical in quantifying the disease burden and informing future research and policy decisions in AAH/ALD.

Table 1. Demographics, clinical characteristics, pharmacological treatments, procedures, and mortality in patients with alcohol-associated hepatitis (n=2415)

	Baseline	Follow-up
Age at index, mean (SD), years	53.9 (12.9)	N/A
Sex, n (%)		N/A
Male	1564 (64.8)	
Female	851 (35.2)	
Race, n (%)		N/A
White	1501 (62.2)	
African American/Black	168 (7.0)	
Asian	22 (0.9)	
Unknown/Missing	724 (30.0)	
Insurance, n (%)		N/A
Commercial	1358 (56.2)	
Medicare	1059 (43.9)	
Commercial/Medicare	<5	
Charlson Comorbidity Index score, mean (SD)	1.7 (2.0)	N/A
Follow-up time, median (IQR), months	N/A	13.2 (4.7–29.5)
Clinical characteristics, n (%)		
Ascites	319 (13.2)	1498 (62.0)
Cirrhosis	490 (20.3)	1659 (68.7)
Hepatic failure	185 (7.7)	1369 (56.7)
Acute kidney failure	259 (10.7)	1446 (59.9)
Pharmacological treatments, n (%)	N/A	
Alcohol use treatments		566 (23.4)
Constipation treatments		1300 (53.8)
Diarrhea treatments		128 (5.3)
Gluconeogenesis		843 (34.9)
Pentoxifylline		56 (2.3)
Procedures, n (%)	N/A	
Paracentesis		921 (38.1)
Hemodialysis		376 (15.6)
Liver biopsy		142 (5.9)
Liver transplantation		143 (5.9)
Death, n (%)	N/A	780 (32.3)

Disclosures: Jayashri Desai: Nothing to Disclose, Scott Bunner: Nothing to Disclose, Marty Masek: Nothing to Disclose, Dannielle Lebovitch: Nothing to Disclose, Thomas Capozza: Intercept Pharmaceuticals/Alfasigma Group: Employee, Amon Asgharpour: Galectin: Clinical Endpoint Committee, NovoNordisk: Advisor, Madrigal: Advisor, Chronic Liver Disease Foundation: Speaking and Teaching, Intercept: Consultant

1547 | TRENDS IN LIVER TRANSPLANTATION FOR ALCOHOL-ASSOCIATED LIVER DISEASE IN THE US FROM 2018 TO 2024: A DESCRIPTIVE ANALYSIS OF UNOS DATA

Jayashri Desai[1] Scott Bunner[2] Marty Masek[2] Dannielle Lebovitch[2] Thomas Capozza[1], [1]Intercept Pharmaceuticals, Inc., Morristown, New Jersey, USA, [2]Genesis Research Group, Hoboken, New Jersey, USA

Background: Alcohol-associated liver disease (ALD) has emerged as a leading indication for liver transplantation (LT) in the US, reflecting evolving practices in candidacy evaluation amid rising cases of ALD. While earlier studies characterized ALD-related LT trends through 2019, little is known about post–pandemic patterns, regional variability, and demographic shifts through 2024. **Methods:** We conducted a retrospective descriptive analysis of the United Network for Organ Sharing (UNOS) database from 2018 to 2024. LT recipients with diagnoses related to ALD—including alcohol-associated hepatitis, alcoholic cirrhosis, metabolic dysfunction and ALD (metALD), and acute hepatic necrosis with unknown etiology—were included. Annual LT trends for adults (aged ≥ 18 years) were stratified by gender and age group (18–34, 35–49, 50–64, and ≥ 65 years). Annual LT trends for all ages were stratified by region (Organ Procurement and Transplantation Network [OPTN]-defined) and waitlist status (at the time of LT). Chi-square testing assessed distributional differences across strata. **Results:** LTs overall and ALD-related LTs in the US rose steadily between 2018 and 2024, with the proportion of ALD-related LTs increasing from 23.77% (2018) to 37.12% (2024; Figure). Among ALD-related LT recipients, male patients predominated annually, but the gender gap narrowed as the absolute number of female patients tripled from 2018 (530) to 2024 (1440). The 35–49-year age group showed a notable increase in ALD-related LTs, while proportions declined in the 50–64-year age group. Significant variation in ALD-related LTs occurred across OPTN regions, with the highest proportions over time being in region 5 (AZ, CA, NV, NM, UT) and region 3 (AL, AR, FL, GA, LA, MS, PR; $P < .001$). Significant variation was observed by waitlist status and Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease score. **Conclusion:** From 2018 to 2024, ALD-related LTs increased (count and proportion of overall) across most demographic and geographic subgroups, reflecting broader clinical acceptance and shifting transplant policy. ALD-related LTs occurred more frequently over time in younger adults and women, although male predominance remains. Regional variability, despite the 2020 implementation of acuity circles, highlights the potential need for standardized selection criteria and enhanced upstream interventions for alcohol use disorder. Further studies are warranted to evaluate long-term post-LT outcomes and ensure equity in LT access.

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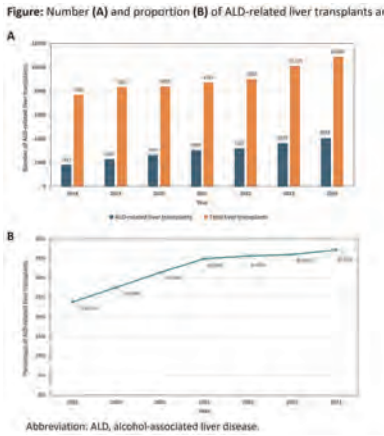

Disclosures: Jayashri Desai: Nothing to Disclose, Scott Bunner: Nothing to Disclose, Marty Masek: Nothing to Disclose, Dannielle Lebovitch: Nothing to Disclose, Thomas Capozza: Intercept Pharmaceuticals/ Alfasigma Group: Employee

1548 | ACUTE PHASE RESPONSE ACTIVATION IN HEPATOCYTES PROMOTES LIVER NICHE REMODELING REQUIRED FOR FIBROSIS RESOLUTION AFTER ALCOHOL CESSATION

Michael Schonfeld[1] Kruti Nataraj[1] Samson Mah[1] Steven Weinman[1] Irina Tikhanovich[1], [1]University of Kansas Medical Center

Background: Abstinence is beneficial for patients with Alcohol-associated liver disease (ALD). However, disease resolution after alcohol cessation is not uniform. We aimed to study the mechanism of fibrosis resolution in ALD following alcohol cessation to uncover potential therapeutic targets. **Methods:** Mice were fed western diet with 20% alcohol in the drinking water for 20 weeks to induce liver fibrosis, mice were then put on chow diet with plain water for 4 weeks. Livers were analyzed by scATAC-seq, 1000 plex CosMx spatial transcriptomics (Nanostrings) and RNA-seq analysis. To assess the role of Serum amyloid A, mice were treated with recombinant SAA or SAA-rich HDL. Fibrosis resolution was assessed by Sirius Red staining and COL1A1 immunohistochemistry. To evaluate relevance of SAA in human ALD niche remodeling, liver sections from Donors (N = 7), ASH (N = 8) and ALD cirrhosis (N = 5) were analyzed by spatial transcriptomics using 5k Xenium panel (10x Genomics). The role of lipid metabolites in functional niche changes was assessed with spatial metabolomics. **Results:** We identified a unique hepatocyte cluster expressing several acute phase response genes (*Saa1, Saa2, Crp*) enriched in fibrolytic niche of mouse livers after alcohol cessation. Serum amyloid A, SAA, was the top upregulated acute phase protein in these hepatocytes. We found that SAA gene and protein expression associated with fibrolytic niches in mice and humans. *In vitro* analysis confirmed that *Saa1/2* expressing hepatocytes promoted fibrolytic function in liver macrophages; moreover, *Saa1* overexpression stimulated, while SAA antibody-mediated depletion blocked pro-fibrolytic change in macrophages. *In vivo* recombinant SAA supplementation promoted fibrosis resolution after alcohol cessation in mice. In addition, we found that SAA function depended on its association with HDL. SAA-enriched HDL showed potent pro-fibrolytic properties *in vitro* and *in vivo* by promoting pro-resolving macrophage phenotype, liver niche composition change and collagen degradation. Supporting the role of lipid mediators in fibrosis resolution we identified spatially distinct lipid metabolite changes in ALD resolution livers that correlated with fibrosis persistence or resolution. **Conclusion:** Acute phase response activation after alcohol cessation triggers intrahepatic cell-cell communication changes that stimulate niche remodeling for efficient fibrosis resolution in ALD.

Disclosures: Michael Schonfeld: Nothing to Disclose, Kruti Nataraj: Nothing to Disclose, Samson Mah: Nothing to Disclose, Steven Weinman: Nothing to Disclose, Irina Tikhanovich: Nothing to Disclose, Nothing to Disclose

1549 | REAL-WORLD IMPACT OF ALCOHOL USE DISORDER PHARMACOTHERAPY ON HEALTHCARE UTILIZATION, COSTS, AND COST-EFFECTIVENESS IN THE U.S.

Chi Mai Nguyen[1] Hanna Blaney[2] Samer Gawrieh[3] Shihui Jiang[1] Wanzhu Tu[1] Suthat Liangpunsakul[3], [1]Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, IN, [2]Georgetown University, [3]Division of Gastroenterology and Hepatology, Indiana University, Indianapolis, IN

Background: Alcohol Use Disorder (AUD) is a leading preventable cause of death and a major driver of healthcare utilization and costs in the U.S. It also significantly contributes to the burden of alcohol-associated liver disease (ALD). Although several pharmacological treatments for AUD are effective, they remain underutilized, and their real-world impact on healthcare use and costs is not well established. The goal of this study is to assess the impact of pharmacological treatment for AUD on alcohol-related healthcare utilization and costs, and to evaluate its cost-

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effectiveness using national claims data. **Methods:** We conducted a retrospective cohort study using deidentified claims data from Optum's Clinformatics® Data Mart, including adults with an AUD diagnosis between January 1, 2017, and December 31, 2023. Patients with continuous insurance for ≥ 1 year were included. Those initiating AUD medications within one year of diagnosis were defined as treated and matched 1:1 to untreated controls using inverse propensity score weighting and exact matching on demographics and comorbidities. Alcohol-related outpatient (OP), emergency department (ED), and inpatient (IP) charges were analyzed using Wilcoxon signed-rank tests. All costs were inflation-adjusted to 2023 U.S. dollars. Incremental cost-effectiveness ratio (ICER) was also calculated. **Results:** The cohort included 579,018 adults with AUD; 148,551 received pharmacotherapy (gabapentin, ondansetron, naltrexone, baclofen, topiramate, varenicline, acamprosate, or disulfiram) and were matched to untreated individuals. Mean age was 57.5 years ($\pm$15.7); 58.1% were male and 63.3% white. Gabapentin (52.3%), ondansetron (19.3%), and naltrexone (12.0%) were most commonly prescribed. Within one year, alcohol-related ED visits occurred in 16.6% of treated vs. 21.1% of untreated patients, and IP admissions in 26.1% vs. 41.4%, respectively. Average alcohol-related charges were significantly lower in the treated group ($41,105 vs. $51,905; $P < 0.001$), largely due to reduced inpatient costs ($33,102 vs. $44,891; $P < 0.001$). ED charges were modestly lower ($2,586 vs. $2,764; $P < 0.001$), while OP charges were higher among treated individuals ($5,417 vs. $4,250; $P < 0.001$), possibly reflecting increased engagement with ambulatory care (Table 1). Medication costs averaged $602, with an ICER of –0.01, indicating every $1 saved in medical costs required only $0.01 in treatment spending.
Conclusion: Pharmacotherapy for AUD is associated with significantly lower alcohol-related ED visits, hospitalizations, and overall healthcare costs. These findings support broader adoption of AUD medications as a cost-effective strategy to reduce alcohol-related healthcare burden and potentially mitigate the progression of alcohol-associated liver disease.

Table 1: Comparison of Alcohol-Related Healthcare Charges by Treatment Status and Care Setting

	Untreated group	Treated group	P
Alcohol-related medical charges ($2023)			
Mean (SD)	$51,905 (146724.5)	$41,105 (136889.2)	<0.001
Alcohol-related charges by care-settings ($2023)			
Alcohol-related OP charges, Mean (SD)	$4,250 (17299.7)	$5,417 (22807.9)	<0.001
Alcohol-related ED charges, Mean (SD)	$2,764 (10200.3)	$2,586 (11155)	<0.001
Alcohol-related IP charges, Mean (SD)	$44,891 (144241.6)	$33,102 (131616.3)	<0.001

Disclosures: Chi Mai Nguyen: Nothing to Disclose, Hanna Blaney: Nothing to Disclose, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, Shihui Jiang: Nothing to Disclose, Wanzhu Tu: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant

1550 | LOSS OF HEPATIC PEROXIN 3 AGGRAVATES ALCOHOL-INDUCED LIVER INJURY VIA BILE ACID INTERMEDIATE ACCUMULATION IN MICE

Yantao Zhao[1] Weiran Wang[1] Carolina Hogerty[1] Steven Weinman[1] Zhanxiang Zhou[2] Wei Zhong[1], [1]University of Kansas Medical Center, [2]University of North Carolina at Greensboro

Background: Alcohol-associated liver disease (ALD) remains a leading cause of chronic liver injury worldwide, yet the contribution of hepatic peroxisomal dysfunction to its progression is not well understood. This study aimed to investigate the mechanisms by which impaired hepatic peroxisomal function contributes to ALD pathogenesis. **Methods:** Peroxisomal biogenesis factors were analyzed in liver tissues from both ALD patients and alcohol-fed mice. Liver-specific *Pex3* knockout mice were generated and examined for metabolic alterations. Bile acid intermediates that accumulated due to peroxisomal dysfunction were administered to wild-type mice and cultured hepatocytes to assess their direct effects. Additionally, *Pex3*-deficient mice were subjected to alcohol feeding to evaluate their susceptibility to liver injury. **Results:** Liver tissues from ALD patients and alcohol-fed mice showed a marked reduction in peroxin 3 (PEX3), a key regulator of peroxisomal biogenesis, along with decreased expression of the peroxisomal membrane protein PMP70. Liver-specific *Pex3* knockout mice exhibited impaired hepatic metabolism and accumulation of bile acid intermediates, indicating disrupted bile acid biosynthesis. Notably, these intermediates were also elevated in the livers of ALD patients and alcohol-fed mice. Administration of 3α,7α,12α-trihydroxy-5β-cholestanoic acid (THCA), a representative bile acid intermediate, at 50 mg/kg for five consecutive days induced significant liver injury in wild-type mice, as evidenced by elevated serum ALT and AST levels and increased hepatic inflammation. Bulk RNA sequencing of livers from THCA-treated mice revealed transcriptional signatures indicative of mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and impaired antimicrobial defense. *In vitro* treatment of Hepa1c1c7 cells with THCA led to dose-dependent cell death and upregulation of pro-inflammatory cytokines such as *Cxcl1* and

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Lcn2, along with protein markers of mitochondrial and ER damage. Furthermore, liver-specific *Pex3*-deficient mice demonstrated heightened sensitivity to alcohol-induced liver injury, suggesting a synergistic effect between peroxisomal dysfunction and alcohol exposure. **Conclusion:** These findings establish hepatic peroxisomal impairment as a crucial driver of bile acid dysregulation and alcohol-related liver injury, offering new insights into the molecular mechanisms underlying ALD and highlighting peroxisomal maintenance as a potential therapeutic target.

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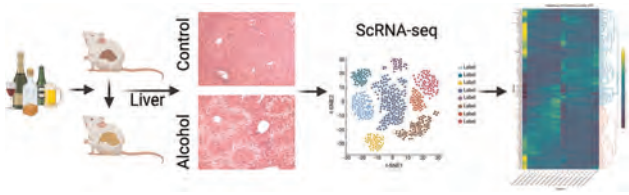
1551 | ZONE-SPECIFIC HEPATIC GENE DYSREGULATION IN ALCOHOL-ASSOCIATED LIVER DISEASE: EVIDENCE FROM SCRNA-SEQ AND HUMAN VALIDATION

Yanchao Jiang[1] Nazmul Huda[1] THEMIS THOUDAM[1] Hui Gao[1] Ge Zeng[1] Jing Ma[1] Xinshou Ouyang[2] Suthat Liangpunsakul[1] Zhihong Yang[1], [1]Indiana University, [2]Yale University

Background: Recent advances in single-cell RNA sequencing (scRNA-seq) have enabled to study gene expression in individual cell level, offering an unbiased and comprehensive view of cellular states and spatial organization within the liver. Alcohol use can damage the liver's structure and function, leading to alcohol-associated liver disease (ALD). However, it is still unclear how alcohol affects liver zonation—the specific patterns of gene expression in different regions of the liver, which is the objective of current study. **Methods:** C57BL/6 mice were fed using the NIAAA ethanol-plus-binge model, and their livers were collected 9 hours post gavage. Liver tissues were processed for immunohistochemistry (IHC). ScRNA-seq data from the GEO database were reanalyzed in R, Python and Matlab. Liver samples from patients with alcohol-associated cirrhosis (AC) were obtained from the Liver Tissue Procurement and Distribution System (Minneapolis, MN). **Results:** Alcohol exposure significantly disrupted the normal pattern of gene expression across liver zones. Immunohistochemistry (IHC) showed altered expression of zonation markers, and analysis of scRNA-seq data revealed increased expression of pericentral (PC, zone 3) genes such as Cyp2e1, Cyp4a14 and Glul, while periportal (PP, zone 1) genes like Mup21, Saa2, Cyp2f2, and Gls2 were reduced. Pathway analysis showed that upregulated genes were linked to cell death and immune responses, while downregulated genes were involved in lipid, cholesterol, and sterol metabolism. Zonation analysis identified 152 genes with consistent zonal patterns in both control and alcohol-fed mouse livers. However, 808 genes lost their zonation pattern, and 1,050 genes gained new zonal expression after alcohol exposure. Genes uniquely zonated in alcohol-fed livers were enriched in pathways related to RNA binding and transferase activity. In liver samples from patients with AC, IHC confirmed high expression of pericentral markers such as GS and CYP2E1, and reduced expression of periportal markers like E-CAD and CYP2F2. **Conclusion:** These findings show that alcohol consumption causes major changes in the spatial organization of gene expression in the liver, with increased activity of pericentral genes involved in alcohol metabolism and stress response. This underscores the importance of spatial gene regulation in liver function and suggests that therapies targeting specific liver zones may offer new precision treatment options for ALD.



Disclosures: Yanchao Jiang: Nothing to Disclose, Nazmul Huda: Nothing to Disclose, THEMIS THOUDAM: Nothing to Disclose, Hui Gao: Nothing to Disclose, Ge Zeng: Nothing to Disclose, Jing Ma: Nothing to Disclose, Xinshou Ouyang: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Zhihong Yang: Nothing to Disclose

1552 | RISING TIDE: SHIFTS IN ALCOHOL-ASSOCIATED LIVER TRANSPLANTATION IN THE UNITED STATES, 2012 – 2023

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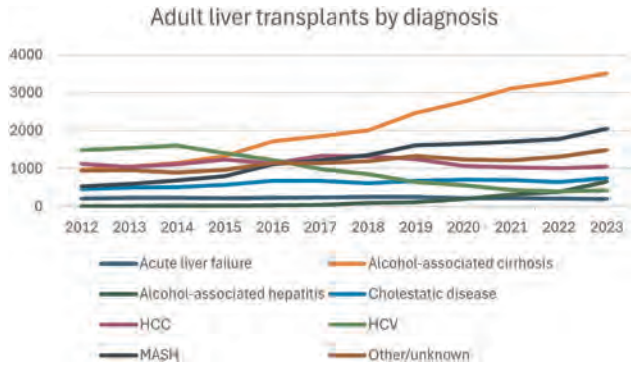
Background: Alcohol-associated liver disease (ALD) is now the most common indication for liver transplantation (LT) in the United States. This rise is largely attributed to increasing alcohol use nationwide and the broader adoption of early transplantation for alcohol-associated hepatitis. The decline in hepatitis C virus (HCV)-related transplants following the widespread use of curative antiviral therapies has further contributed to ALD's prominence. As ALD continues to reshape the liver transplant landscape, understanding these trends is critical for guiding resource allocation, optimizing patient care, and integrating evidence-based management of alcohol use disorder throughout the transplant process. **Methods:** We used data from the United Network for Organ Sharing (UNOS) database, which includes information on all liver transplants in the United States. Adult patients (aged 18 years or older) who underwent a first-time liver transplant between 2013 and 2022 were included in the analysis. Alcohol-associated liver disease (ALD) was identified using diagnosis codes for alcohol-associated cirrhosis and alcohol-associated hepatitis (AAH). We examined how the number of ALD-related transplants changed over time and looked at trends in patient age, sex, and transplant outcomes. **Results:** From 2012 to 2023, a total of 27,075 liver transplants were performed in the United States for alcohol-associated liver disease (ALD), including 25,211 for alcohol-associated cirrhosis and 1,864 for alcohol-associated hepatitis. • During this time, ALD-related transplants increased from 976 in 2012 to 4,163 in 2023. By 2016, ALD had surpassed hepatitis C virus (HCV) as the most common reason adults were added to the liver transplant waitlist. Alcohol-associated hepatitis (AAH)—a more severe form of ALD—grew even faster, from just 5 cases in 2012 to 658 in 2023, a 13,060% increase and a 56% annual growth rate. • Alcohol-associated cirrhosis (AC) transplants increased from 971 in 2012 to 3,505 in 2023, a 261% rise, with an average growth rate of 12.4% per year. • When combined, ALD-related transplants rose from 976 in 2012 to 4,163 in 2023, a 326% increase, with an annual growth rate of 14.1%. Over the same period, total liver transplants for all causes increased from 5,731 to 10,406, meaning ALD now accounts for 41% of all adult liver transplants, compared to just 17% in 2012. **Conclusion:** Alcohol-associated liver disease (ALD) has emerged as the leading indication for liver transplantation in the United States, accounting for over 40% of all adult liver transplants by 2023. The rapid growth in AAH transplants, younger recipient age, and rising representation of women reflect important demographic and clinical changes in the transplant population. These findings highlight the critical need for transplant centers to implement comprehensive, evidence-based strategies for alcohol use disorder treatment before and after transplantation.



Disclosures: Ashraf Ullah: Nothing to Disclose, Mati Ullah Dad Ullah: Nothing to Disclose, Hamnah Tayyab: Nothing to Disclose, Rohullah Rasikh: Nothing to Disclose, Saeed Ahmad: Nothing to Disclose

1553 | COMPARATIVE EFFECTIVENESS OF BARIATRIC SURGERY VERSUS GLP-1 RECEPTOR AGONISTS IN PATIENTS WITH METABOLIC DYSFUNCTION–ASSOCIATED ALCOHOL-RELATED LIVER DISEASE

Amir Hossein Gougol[1] Paul Kwo[2] Seyedbabak Mirminachi[3] Willian Pike[4] Mehdi Farokhnia[5], [1]Stanford, [2]Stanford University Medical Center, [3]University of Pittsburgh Medical Center, [4]Atropos Health, [5]NIH

Background: Alcohol use disorder (AUD) and metabolic dysfunction (MetD) frequently co-occur in patients with steatotic liver disease (SLD). According to new nomenclature, these patienst are classified as Metabolic Dysfunction–Associated Alcohol-Related Liver Disease (MetALD) and alcohol-related liver disease (ALD), relative to degree of alcohol intake. While both bariatric surgery and glucagon-like peptide-1 receptor agonists (GLP-1RA) are effective in managing MetD, their impact on AUD and liver-related outcomes in patients with MetALD and ALD with metD remain unclear. In this study, we aim to compare clinical outcomes between bariatric surgery and GLP-1RA therapy in patients with MetALD and ALD with MetD. **Methods:** This was a retrospective observational cohort study of patients with MetALD and ALD with MetD. MetD was defined as the presence of obesity [body mass index (BMI) >35 kg/m^2], diabetes mellitus (DM), or both. Patients were grouped based on exposure to either bariatric surgery or GLP-1RA therapy for at least six months. Outcomes included changes in weight, BMI, and hemoglobin A1c (HbA1c) over two years from the index intervention. Longitudinal outcomes included cardiovascular events, liver-related complications, and

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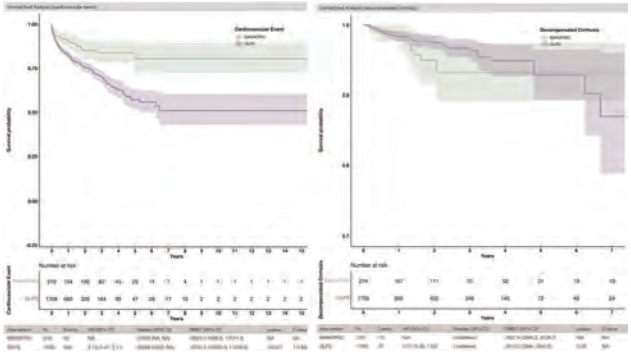
hospitalizations. Propensity score matching was employed to reduce effects of confounding factors. **Results:** A total of 127 patients underwent bariatric surgery and 450 received GLP-1RA therapy. Bariatric surgery patients were younger (47 vs. 53 years), more often female (59% vs. 47%), had a higher baseline BMI (43.4 vs. 38.1), and a lower prevalence of DM (47% vs. 84%), compared to the GLP-1RA group. Mean follow-up duration was 5.2 years. Bariatric surgery was associated with greater reductions in weight and HbA1c. Additionally, the bariatric group had a lower incidence of cardiovascular adverse outcomes. However, no significant differences were observed between groups in the incidence of decompensated cirrhosis or its components. Rates of hospital readmission and infections were also comparable. **Conclusion:** Although bariatric surgery achieved superior metabolic outcomes compared to GLP-1RA therapy, it did not confer additional benefit in reducing liver decompensation in patients with MetALD and ALD with MetD. Further research is warranted to elucidate the effects of bariatric surgery and GLP-1RA on alcohol consumption which may explain dissociation between metabolic improvement and hepatic outcomes.



Disclosures: Amir Hossein Gougol: Nothing to Disclose, Nothing to Disclose, Paul Kwo: Nothing to Disclose, Seyedbabak Mirminachi: Nothing to Disclose, Willian Pike: Nothing to Disclose, Mehdi Farokhnia: Nothing to Disclose

1554 | BRUTON'S TYROSINE KINASE INHIBITION AS A NOVEL MULTIMODAL THERAPY FOR ALCOHOL-ASSOCIATED HEPATITIS

Prashanth Thevkar Nagesh[1] Marti Ortega Ribera[2] Arman Patel[3] Veronika Brezani[2] Viliam Brezani[2] Aditi Ashish Datta[2] Yuan Zhuang[4] Scott Minchenberg[4] Deepika Deepika[2] Bruna Santos[2] Radhika Joshi[2] Stephen Varghese Samuel[2] Yeshaswini Katkoori[2] Gyongyi Szabo[4], [1]Beth Israel Medical Center, Harvard Medical School, [2]BIDMC - Harvard Medical School, [3]Beth Israel Deaconess Medical Centre, [4]Beth Israel Deaconess Medical Center

Background: Alcohol-associated hepatitis (AH) is a severe and life-threatening form of alcohol-associated liver disease with poor clinical outcomes. AH pathogenesis involves hepatic steatosis, neutrophil infiltration, neutrophil extracellular traps (NETs) formation, and NLRP3 inflammasome activation in macrophages. Identifying a therapeutic target common to these cellular pathways remains challenging. We recently identified Bruton's tyrosine kinase (BTK) as a critical mediator of neutrophil-driven liver injury in AH. Our findings suggest a broader multicellular role for BTK in AH that remains unexplored. We hypothesized that alcohol induces BTK phosphorylation (pBTK), and that pharmacological BTK inhibition could attenuate AH. **Methods:** Female C57BL/6J mice (12 weeks; wild-type [WT], global BTK-/-, myeloid-BTK-/-, hepatocyte-BTK-/-) received Lieber-DeCarli alcohol diet for 11 days followed by a binge (AH model) or a calorie-matched control diet. WT mice received daily oral gavage of evobrutinib (BTK inhibitor; BTKi, 5mg/kg) or DMSO (vehicle control) for 11 days. Serum ALT and cytokines were measured by ELISA. pBTK was assessed in human and mouse livers via Western blot. Hepatic steatosis markers were analyzed by qPCR and liver triglyceride content. NET markers (citrullinated histone H3, neutrophil elastase) were measured in liver lysates. Circulating and liver monocytes, neutrophils, and ASC specks were evaluated via flow cytometry. BTK-NLRP3 interaction was examined in mouse bone marrow-derived macrophages (BMDMs) via co-immunoprecipitation. **Results:** In vitro, alcohol rapidly induced pBTK in primary human/mouse hepatocytes, neutrophils, and monocytes. AH patient and mouse livers showed increased pBTK vs. controls. Alcohol-induced increases in serum ALT, cytokines (IL-1β, TNF-α, MCP-1), steatosis (triglycerides, Fasn, Fatp5, Pparα), and immune cell infiltration were all reduced in BTK-/-, myeloidBTK-/-, and hepatocyteBTK-/- mice. Mechanistically, alcohol-induced pBTK (Y223) acted upstream of pSTAT3 (Y705), regulating steatosis. Co-immunoprecipitation showed pBTK interaction with NLRP3, promoting inflammasome activation. Genetic deletion of BTK (all 3 models) reduced ASC specks and NET formation, in vivo. In the AH model, BTKi significantly attenuated steatosis, inflammation, and NETs, mimicking the effects observed in global BTK-/- mice. **Conclusion:** Alcohol-induced BTK activation occurs in parenchymal and immune cells in the liver and drives steatosis, inflammation, NLRP3 inflammasome activation, and NET formation in AH involving hepatocytes and immune

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cells. BTK inhibition in multiple cell types may serve as a promising therapeutic strategy for AH.

Disclosures: Prashanth Thevkar Nagesh: Nothing to Disclose, Marti Ortega Ribera: Nothing to Disclose, Arman Patel: Nothing to Disclose, Veronika Brezani: Nothing to Disclose, Viliam Brezani: Nothing to Disclose, Aditi Ashish Datta: Nothing to Disclose, Yuan Zhuang: Nothing to Disclose, Scott Minchenberg: Nothing to Disclose, Deepika Deepika: Nothing to Disclose, Bruna Santos: Nothing to Disclose, Radhika Joshi: Nothing to Disclose, Stephen Varghese Samuel: Nothing to Disclose, Yeshaswini Katkoori: Nothing to Disclose, Gyongyi Szabo: CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/ Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/ Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property

1555 | THE EFFECT OF MEDICAL ASSISTED THERAPY ON LIVER-RELATED OUTCOMES IN PATIENTS WITH ALCOHOL USE DISORDER AFTER TRANSPLANTATION

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Background: Alcohol-associated liver disease (ALD) remains the leading cause of cirrhosis and indication for liver transplantation (LT) in the United States. Despite controversy regarding the 6 months of mandated sobriety in patients with ALD pre-LT, post-LT alcohol relapse remains high, ranging from 15-50%. Minimal data exists on the effect of post-LT medical assisted therapy (MAT) for patients with alcohol use disorder (AUD). This study aims to evaluate early post-LT outcomes in patients using MAT for AUD. **Methods:** This analysis was completed using a TriNetX query of the United States Collaborative Network- a network of 70 healthcare organizations. Patients with ALD cirrhosis, AUD and LT between 2010-2022 were identified using ICD-10 codes. The study cohort included patients who were prescribed MAT within 90 days of LT and the control group included those without a history of MAT use pre-or post-LT. Propensity score matching (PSM) was used to balance cohorts by age, sex, and ethnicity. Outcomes included graft rejection, mortality, readmissions, need for Endoscopic Retrograde Cholangiopancreatography (ERCP) and liver biopsy. The probability of each outcome was compared using Chi-squared test and Kaplan-Meier analyses. Data was analyzed using TriNetX and statistical significance was evaluated at $p < 0.05$. **Results:** A total of 546 patients were included. Patients precribed MAT were more likely to be older (57 years old $\pm$ 9.55 vs. 55 $\pm$ 10.2, $p < 0.01$) and female (31% vs. 22%, $p < 0.01$).After PSM patients using MAT were found to have a lower risk of graft rejection (OR 0.43, 95% CI 0.23-0.61, $p < 0.01$) and liver biopsy (OR 0.50, 95% 0.25-0.99, $p = 0.04$) compared to those not on MAT after 1 year. There was no significant difference in mortality or readmission after 1 year. Furthermore, after 3 years patients on MAT had a lower risk of graft rejection (OR 0.43, 95% CI 0.28-0.66, $p < 0.01$), liver biopsy (OR 0.48, 95% CI 0.26-0.90, $p = 0.02$), and ERCP (OR 0.5, 95% CI 0.27-0.92, $p = 0.03$). Additionally, MAT was associated with an increased risk of 3-year (OR 1.77 95% CI 1.10-2.85, $p = 0.02$) and 5-year mortality (OR 1.75, 95% CI 1.17-2.53, $p < 0.01$). **Conclusion:** MAT use post-LT in patients with AUD may reduce the risk of graft rejection and need for procedures such as liver biopsy and ERCP, likely due increased abstinence from alcohol

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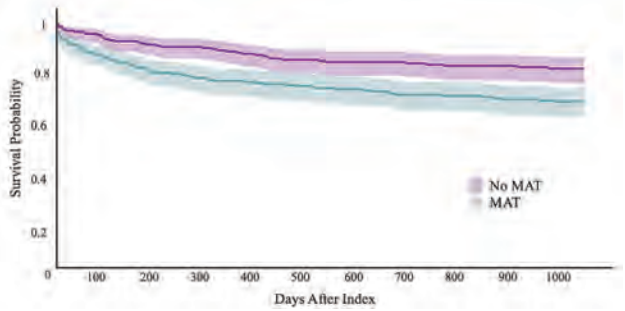
and reduced liver injury. Despite the high rates of alcohol relapse post-LT MAT is underutilized. The increased risk of mortality seen in the MAT group is more likely a consequence of the group's higher propensity for alcohol relapse, rather than an effect of MAT itself. This study further highlights the need for better management of AUD with MAT in patients post-LT, especially given possible improved graft outcomes.

Figure 1. A greater proportion of patients on MAT post-LT had rejection free survival compared to no MAT after 3 years.

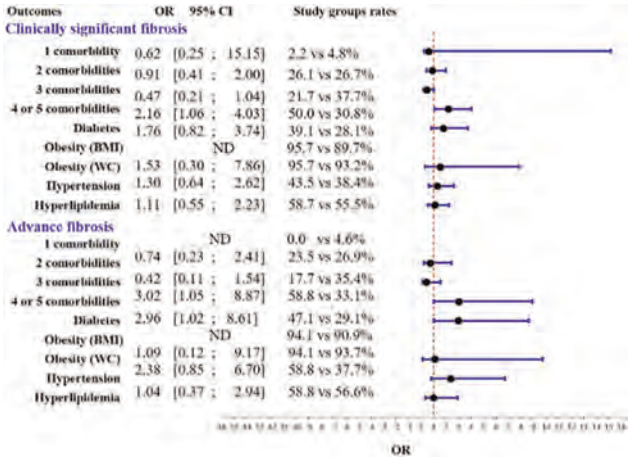


Disclosures: Ami Patel: Nothing to Disclose, Anita Krishnarao: Nothing to Disclose

1556 | FACTORS ASSOCIATED WITH INCREASED LIVER FIBROSIS IN ADULTS WITH METALD: DATA FROM US NHANES 2017 - 2023

Alex Chang[1] Joao Filipe Monteiro[1] Adam Burton[1] Andrew Petrou[1] Neha Wadhavkar[1] Kittichai Promrat[1], [1]Warren Alpert School of Medicine of Brown University

Background: MetALD is recent nomenclature describing steatotic liver disease (SLD) patients with cardiometabolic risk factors (CMRFs) and concurrent alcohol use. Limited literature exists on the major factors predicting advanced fibrosis in this recently labeled MetALD population. Additionally, since alcohol use is a risk factor for CMRFs, studies have questioned whether diagnosing MetALD should require more than one CMRF. The current study looks at patients with MetALD from the US NHANES 2017 - 2023 cohorts and identifies the major risk factors associated with increased fibrosis in these patients. **Methods:** The NHANES 2017-2020 and 2021-2023 datasets, comprising of 17,843 adult participants, was utilized. Participants without a complete transient elastography (TE) examination, with past history of viral or autoimmune hepatitis, or without evidence of steatosis on TE (CAP $<$ 285) were excluded. Participants who had at least one CMRF and for men, consumed between 210 and 420g of alcohol weekly and for women, consumed between 140 - 350 g of alcohol weekly were included in the study as patients with MetALD. Clinically-significant fibrosis (CSF) was defined as LSM $\geq$ 8 kPa on TE while advanced fibrosis (AF) was defined as LSM $\geq$ 12 kPa. The number of CMRFs was determined in accordance to AASLD guidelines and includes diabetes, obesity (BMI), obesity (waist circumference), hyperlipidemia, and hypertension. Multivariable logistic regression models, accounting for relevant covariates, were used to identify independent associations with fibrosis outcomes. All statistical tests were performed using SAS version 9.4 **Results:** 192 participants met MetALD criteria. CSF affected 24.0% while AF affected 8.9% (Table 1). Individuals with four or five comorbidities had significantly higher odds (OR 2.16; 95% CI: 1.06–4.03) for CSF compared to those with fewer comorbidities (Figure 1). Diabetes was associated with increased odds of CSF (OR 1.76; 95% CI: 0.82–3.74), though this was not significant. For AF, the presence of four or five comorbidities was again significantly associated with increased risk (OR 3.02; 95% CI: 1.05–8.87). Diabetes was also significantly associated with increased risk of AF (OR 2.96; 95% CI: 1.02–8.61), while hypertension and obesity had no clear association with fibrosis. For individuals with one or two comorbidities, the odds of AF were not significantly associated. **Conclusion:** Patients who meet criteria for MetALD have risk factors for steatosis related to both alcohol consumption and cardiometabolic disease. The current study would support that diabetes is associated with highest risk of developing AF in patients with MetALD. Additionally, risk of fibrosis is increased in patients with 4 or 5 compounded CMRFs as opposed to 1 or 2 CMRFs. Future studies should continue to delineate differences in risk factors for fibrosis between patients with MASLD, MetALD, and ALD to better inform clinical practices.



Disclosures: Alex Chang: Nothing to Disclose, Joao Filipe Monteiro: Nothing to Disclose, Adam Burton: Nothing to Disclose, Andrew Petrou: Nothing to Disclose, Neha Wadhavkar: Nothing to Disclose, Kittichai Promrat: Nothing to Disclose

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1557 | OMEGA-5 FATTY ACID AS AN ADJUVANT REDUCES INFLAMMA-OXIDATION IN PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS NEW SUBMISSION

Gabriela Gutierrez-Reyes[1] Moises Martinez-Castillo[1] Abigail Hernandez-Barragan[1] Marisela Hernandez-Santillan[1] Froylan Martinez-Sanchez[2] Daniel Santana-Vargas[3] Erik Bojorges-Valdez[4] Adrian Flores-Sanchez[1] Danna Mercado-Herrera[1] Jacqueline Cordova-Gallardo[2], [1]Universidad Nacional Autonoma de México, [2]Hospital General Dr. Manuel Gea Gonzalez, [3]Hospital General de Mexico "Dr. Eduardo Liceaga", [4]Universidad Iberoamericana

Background: Severe alcohol-associated hepatitis (SAAH) is associated with high mortality, particularly in patients who are unresponsive to corticosteroid therapy. That is also characterized by antioxidant deficiencies and heightened inflammation, both of which contribute to the progression and severity of liver injury. Omega-5 fatty acid (nano) has been shown antioxidant and anti-inflammatory properties, offering a potential new therapy. Aim: To evaluate the efficacy of Omega-5 fatty acid (nano) as an adjuvant to prednisone in modulating oxidative and inflammatory parameters in SAAH patients. **Methods:** This randomized, double-blind, placebo-controlled clinical trial (NCT 03732586) was conducted at a single center in Mexico between 2018 and 2020. Patients with confirmed SAAH (MDF ≥ 32) were randomly assigned to Group P (prednisone 40 mg/day + placebo) or Group T (prednisone 40 mg/day + Omega-5 at 1.28 g/day). Both regimens were administered for 28 days. Biochemical markers of liver function, nutritional evaluation, malondialdehyde (MDA), protein carbonyls (PC), reduced glutathione (GSH), oxidized glutathione (GSSG), and the GSH/GSSG ratio in blood were assessed. Additionally, cytokines (IL-1a, IL-10, IL-6, TNF-alpha, IFN-gamma, IL-1b, IL-1RA), chemokines MCP-1, CXCL-8 and 10) and growth factors (IGFBP-1 to 7), were measured at baseline (day 0) and on days 7, 14, and 28. **Results:** Baseline characteristics included nutritional parameters were similar between groups. Both groups exhibited similar steroid responses with no significant difference in Lille scores (Group P: 0.46 $\pm$ 0.33; Group T: 0.36 $\pm$ 0.28). Liver function tests revealed improved ALT, AST, and bilirubin levels in Group T by day 28 ($p < 0.05$). Analysis for oxidative markers showed that lipid peroxidation (MDA) was improved ($p = 0.001$) at 28 days in group T vs group P. The GSH/GSSG ratio also showed differences with the use of Omega-5. IL-10 levels (pg/mL) significantly increased in Group T, while MCP-1, CXCL-8 and CXCL10 levels (pg/mL) showed marked reduction by day 28 vs day 0. Additionally, IGFBP 1, 2,3 and 7 levels (ng/mL) in Group T were significantly reduced. **Conclusion:** Addition to Omega-5 fatty acid (nano) to prednisone strongly showed a beneficial effect, promoting the reduction of oxidative stress, while modulating cytokine /chemokines profiles and IGFBP levels. These findings support the potential of Omega-5 as an effective adjuvant therapy in SAAH. A phase 3 clinical trial is performed to further elucidate its molecular mechanisms and explore the correct dosing regimens.

Disclosures: Gabriela Gutierrez-Reyes: Nothing to Disclose, Moises Martinez-Castillo: Nothing to Disclose, Abigail Hernandez-Barragan: Nothing to Disclose, Marisela Hernandez-Santillan: Nothing to Disclose, Froylan Martinez-Sanchez: Nothing to Disclose, Daniel Santana-Vargas: Nothing to Disclose, Erik Bojorges-Valdez: Nothing to Disclose, Adrian Flores-Sanchez: Nothing to Disclose, Danna Mercado-Herrera: Nothing to Disclose, Jacqueline Cordova-Gallardo: Nothing to Disclose

1558 | INTEGRATED SPATIAL ANALYSIS REVEALS HEPATOCELLULAR CHANGES AS A PATHOGENIC HALLMARK OF ALCOHOL-ASSOCIATED HEPATITIS

Susmita Bhattarai[1] Sizhe Wan[1] Sehrish Naz[2] Sofia Izunza Barba[2] Hua Xu[2] Zhengsheng Zhang[2] Chi Chan[2] Shuli Luo[2] Prashanth Nagesh[2] Sizun Jiang[2] Zhenghui Jiang[2], [1]BIDMC/ Harvard Medical School, [2]BIDMC/ Harvard Medical School

Background: Alcohol-associated hepatitis (AH) remains a severe subacute liver failure associated with high mortality. Medical treatment for AH is limited due to the lack of proper understanding of disease pathogenesis. Although AH and alcohol-associated cirrhosis (AC) can co-exist, AH can also differ from AC by the presence of hepatomegaly rather than liver atrophy, faster progression to decompensation, higher rate of mortality, and potential reversibility. The spatial profiling of liver tissue can provide deep insights in disease pathogenesis and ultimately offer novel therapeutic strategies. Specifically, interrogating hepatocellular changes in AH could provide better mechanistic understanding of the molecular traits of AH that is distinct from AC. **Methods:** Human liver tissues from patients with AH, AC and healthy controls were identified for this study. We used RT-PCR and Basescope to assess the expression of critical genes in hepatocytes that shape the hepatocellular phenotype. CosMx Spatial Molecular Imager platform and CosMx™ Human Universal Cell Characterization Panel (RNA, 1000 Plex) was used for cell typing and gene detection. Spatial transcriptomics were employed to identify the AH transcriptomic

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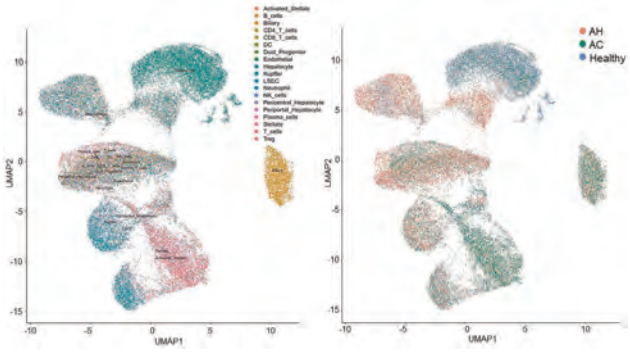
signature in comparison to AC. **Results:** RT-PCR analysis and Basescope analysis in human tissues show reduced expression of essential liver genes associated with hepatocellular phenotype such as HNF4α, HNF1α, ALB, HNF4α-AS1 and OTC in AH tissues. However, HNF1α, OTC and ALB were not significantly altered in cirrhosis samples compared to healthy controls. Basescope and immunohistological analysis revealed that HNF4α-P1, a transcription factor critical for the maintenance of mature hepatocyte phenotype was significantly reduced in AH samples. With CosMx Spatial imaging, AH liver tissue demonstrates a profoundly altered cellular landscape compared to AC and healthy liver tissues. Furthermore, AH hepatocytes exhibit remarkable transcriptomic changes in comparison to hepatocytes in AC and healthy liver. Specifically, HNF4α dysregulation was associated with hepatocellular dysfunction in AH. Fig:1 Spatial transcriptomics reveals disease-specific and cell-specific transcriptomic profiles. UMAP representation of the cell types in the human liver tissues and different diseased states. **Conclusion:** Altered hepatocellular transcriptome is a hallmark of AH, suggesting that a viable therapeutic strategy could target mechanisms that drive hepatocellular regeneration and differentiation.



Disclosures: Susmita Bhattarai: Nothing to Disclose, Sizhe Wan: Nothing to Disclose, Sehrish Naz: Nothing to Disclose, Sofia Izunza Barba: Nothing to Disclose, Hua Xu: Nothing to Disclose, Zhengsheng Zhang: Nothing to Disclose, Chi Chan: Nothing to Disclose, Shuli Luo: Nothing to Disclose, Prashanth Nagesh: Nothing to Disclose, Sizun Jiang: Nothing to Disclose, Zhenghui Jiang: Nothing to Disclose

1559 | AQUAPORINS FACILITATE HEPATIC ACETALDEHYDE TRANSPORT AND MODULATE ALCOHOL-ASSOCIATED LIVER DISEASE

Cheng Chen[1] Yuhong Lin[1] Dechun Feng[1] Yaojie Fu[1] Yukun Guan[1] Yang Wang[1] Luca Maccioni[1] Deniz Seyhan[1] Shoupeng Wei[1] Tiantian Yao[1] Li Zhang[1] George Kunos[2], [1]NIH/NIAAA, [2]National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Background: Our previous study revealed that biliary acetaldehyde (AcH) levels are significantly higher than those in serum, suggesting that bile excretion plays a key role in AcH clearance within the enterohepatic circulation. This uneven distribution implies the existence of a specific AcH transporter; however, none have been identified to date. Aquaporins (AQPs) are known to facilitate the transport of water and small solutes. Among them, AQP8 and AQP9 are predominantly localized on the canalicular and basolateral membranes of hepatocytes, respectively. Given that AcH is a water-soluble metabolite and highly carcinogenic, we hypothesized that AQP8 and AQP9 may mediate AcH transport and thereby contribute to hepatic AcH clearance, which may affect the pathogenesis of alcohol-associated liver disease (ALD). **Methods:** 1. *In situ* liver perfusion with 25% ethanol (EtOH) and 100 mg/kg AcH i.p. injection were performed in *Aqp8*$^{-/-}$ and *Aqp9*$^{-/-}$ mice, followed by measurement of AcH and EtOH levels in the liver, bile, and blood. 2. Primary hepatocytes isolated from *Aqp8*$^{-/-}$ and *Aqp9*$^{-/-}$ mice were incubated with EtOH or AcH, and intra- and extracellular AcH levels were quantified. 3. Dynamic bile flow and biliary AcH concentrations were assessed via gallbladder cannulation in *Aqp8*$^{-/-}$ mice, with or without EtOH exposure. 4. *Aqp8*$^{-/-}$ and *Aqp9*$^{-/-}$ mice were subjected to an ALD model, and liver injury markers were evaluated. Meanwhile, their expressions were evaluated in the severe alcoholic hepatitis (sAH) patients' liver. **Results:** 1. *Aqp8* deletion significantly reduced biliary and extracellular AcH levels following EtOH perfusion in the liver and EtOH incubation with isolated hepatocytes, despite comparable intrahepatic AcH accumulation. These findings suggest that AQP8 drives hepatic AcH efflux. 2. *Aqp9* deletion markedly decreased liver and intracellular AcH levels following AcH i.p. injection *in vivo* and AcH incubation with isolated hepatocytes, suggesting that AQP9 facilitates AcH influx to hepatocytes. 3. *Aqp8*$^{-/-}$ mice exhibited markedly reduced bile volume and biliary AcH concentrations, indicating impaired AcH clearance and altered bile secretion. 4. *Aqp8*$^{-/-}$ mice demonstrated significantly reduced serum ALT levels and liver damage compared to WT controls in the ALD model. AQP9 was identified as being specifically suppressed in the liver of sAH patients, suggesting that AQP8 and AQP9 are involved in the progression of different stages of ALD. **Conclusion:** This study identifies hepatic AQP8 and 9 as novel AcH transporters facilitating AcH efflux and influx in the liver, which may contribute to the progression of different stages of ALD.

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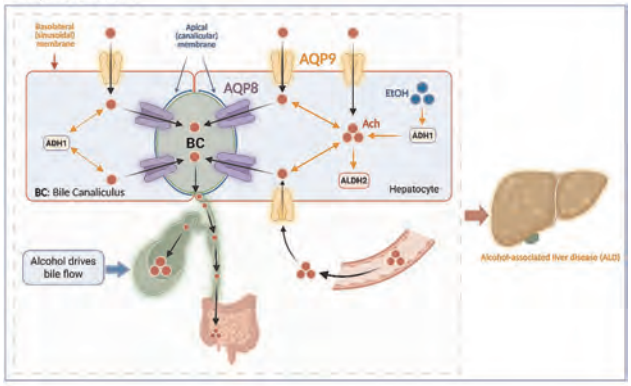
Graphic Abstract

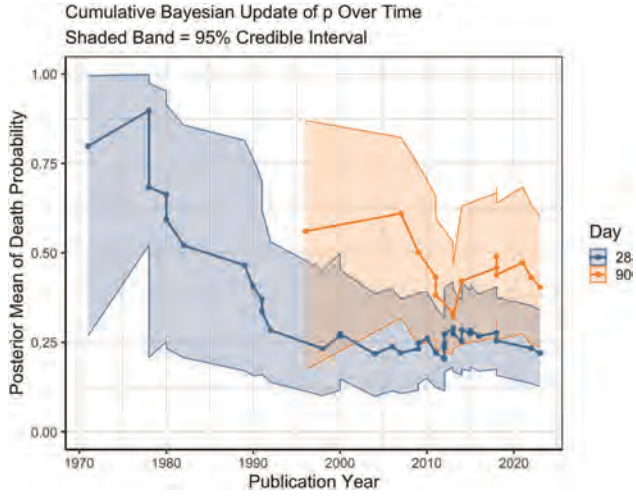


Disclosures: Cheng Chen: Nothing to Disclose, Yuhong Lin: Nothing to Disclose, Dechun Feng: Nothing to Disclose, Yaojie Fu: Nothing to Disclose, Yukun Guan: Nothing to Disclose, Yang Wang: Nothing to Disclose, Luca Maccioni: Nothing to Disclose, Deniz Seyhan: Nothing to Disclose, Shoupeng Wei: Nothing to Disclose, Tiantian Yao: Nothing to Disclose, Li Zhang: Nothing to Disclose, George Kunos: Nothing to Disclose

1560 | MORTALITY TRENDS AND RISK FACTORS IN ALCOHOL-ASSOCIATED HEPATITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Francisco Idalsoaga[1] Mushfiqur R. Siddique[2] Muzzafar Haque[3] Luis Antonio Diaz[4] Gene Im[5] Ashwani K. Singal[6] Stephen Hoang[7] Mohammad Qasim Khan[8] Juan Pablo Arab[7], [1]Pontificia Universidad Católica de Chile, Western University, [2]Jamaica Hospital Medical Center, New York, USA, [3]College of Medicine, University of Saskatchewan, Saskatchewan, Canada., [4]Pontificia Universidad Católica de Chile, University of California San Diego, La Jolla, California., [5]Columbia University, Vagelos College of Physicians and Surgeons, New York, NY, USA., [6]University of Louisville School of Medicine and University of Louisville Alcohol Research Center, [7]Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA., [8]Western University, London, Ontario, Canada

Background: Severe alcohol-associated hepatitis (sAH) is a life-threatening condition. Despite advances in clinical management, prognosis remains poor and the long-term effectiveness of available therapies is uncertain. We conducted a systematic review and meta-analysis to evaluate mortality trends in sAH over the past five decades. **Methods:** We searched PubMed, EMBASE, and Scopus from inception to February 2024 for studies reporting 28-, 60-, and 90-day mortality in patients with sAH. Pooled mortality estimates were calculated using a mixed-effects model. We assessed heterogeneity using the I^2 statistic and explored sources of heterogeneity through subgroup and meta-regression analyses. Bayesian mixed-effects meta-analyses estimated the posterior distribution of mortality probability across studies. **Results:** Forty-five studies, including 5,632 patients with sAH were analyzed. Pooled mortality rates were 28.3% (95% CI: 22.5–34.8%) at 28 days, 38.3% (95% CI: 31.5–45.5%) at 60 days, and 48.7% (95% CI: 39.2–58.3%) at 90 days. Substantial heterogeneity was observed ($I^2 > 80\%$). Although Bayesian analyses showed a decline in 28-day mortality from over 50% in the 1970s to approximately 25% after 2000, no significant overall improvement in short-term mortality was detected. No consistent associations were found between mortality and mDF, HRS, age, sex ratio, or publication year. However, higher MELD scores were significantly associated with increased mortality ($\beta = +0.20$ per point; 95% CI: +0.01 to +0.39; $p = 0.037$). The reported use of corticosteroids, NAC, or G-CSF did not result in meaningful differences in log-odds of mortality across studies. **Conclusion:** Short-term mortality in sAH remains high and has not improved in recent decades. Our findings highlight the urgent need for effective therapies and may improve candidate assessment for early liver transplantation in sAH.



Disclosures: Francisco Idalsoaga: Nothing to Disclose, Mushfiqur R. Siddique: Nothing to Disclose, Muzzafar Haque: Nothing to Disclose, Luis Antonio Diaz: Nothing to Disclose, Gene Im: KorroBio: Consultant, Echosens: Device support for research, Novo Nordisk: Advisor, Alimentiv: Consultant, Ashwani K. Singal: Nothing to Disclose, Stephen Hoang: Nothing to Disclose, Mohammad Qasim Khan: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose

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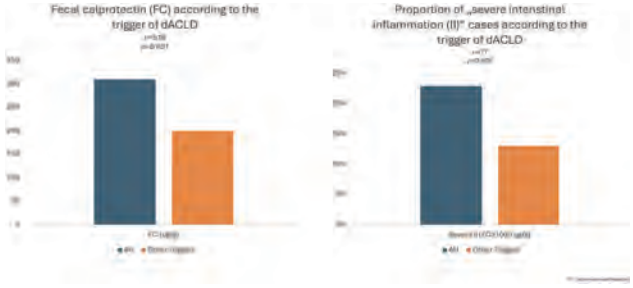
1561 | INTESTINAL INFLAMMATION (II) MEASURED BY FECAL CALPROTECTIN (FC) IN DECOMPENSATED ADVANCED CHRONIC LIVER DISEASE (DACLD) INPATIENTS IS HIGHER WHEN TRIGGERED BY ALCOHOL-ASSOCIATED HEPATITIS (AH), BUT: DO II/FC INDEPENDENTLY ASSOCIATE WITH ADVERSE OUTCOME?

Lubomir Skladaný[1] Tomas Koller[2] Petra Vrbova[3] Daniela Zilincanova[4] Svetlana Adamcova Selcanova[4] Daniel Jan Havaj[4] Juan Pablo Arab[5], [1]Faculty Hospital FD Roosevelt, [2]Dept Internal Medicine V, Komensky University Faculty of Medicine, University Hospital Bratislava, [3]Dept Internal Medicine V, Komensky University Faculty of Medicine, University Hospital Bratislava Ru, [4]Dept Int Medicine 2, Slovak Medical University Faculty of Medicine, F.D.Roosevelt Hosp, B. Bystrica, [5]Virginia Commonwealth University

Background: Gut-liver axis (GLA) when deranged by dysbiosis, intestinal inflammation (II) and barrier disruption plays a critical role in the pathogenesis of ACLD. GLA involvement seems to be especially pronounced in alcohol-associated liver disease (ALD) and AH-triggered dACLD. Fecal calprotectin (FC) is an established marker of II; our group has recently reported elevated levels of FC in dACLD with independent, dose-dependent, and phenotype-specific prognostic significance. However, FC has not been fully investigated against various etiologies and triggers of dACLD, especially ALD and AH. Therefore, we aimed to assess how FC relates to the severity and prognosis of dACLD triggered by AH in comparison to other causes of decompensation. **Methods:** RH7 cirrhosis registry prospectively records data from consecutive hospitalized cases with ACLD at the tertiary liver & transplant unit for more than 10 years (NCT04767945). FC has been added to RH in 2021. Here, we included ACLD cases with FC and a follow-up of at least 6 months or predefined adverse outcome (liver transplantation or death of any cause). We compared FC values and their predictive power for transplant-free survival between AH and other causes of decompensation of ACLD. **Results:** From August 2021 to March 2025 we enrolled 518 patients, with M/F ratio 325/193, a median age 57.4 years, MELD-Na score 20, Child-Pugh-Turcotte (CPTS) score 9, with refractory ascites in 117 (22.8%) and median FC of 236 ug/g (4.7 times the upper limit of normal of 50 ug/g). One hundred and thirteen cases (21,8%) had AH as a trigger of dACLD: AH patients were significantly younger (median age 48.8 vs. 59.2), had higher MELD-Na (28.0 vs. 18.0), CPTS (10 vs. 8), CRP (29.7 vs. 10.4) mg/l, with no gender difference (35% vs. 38%); patients with AH had higher FC 310.2 (IQR 120-914) vs. 200.3 (IQR 57.8-593 ug/g, $P < 0.001$). Seventy-seven (14.9%) patients had evidence of severe intestinal inflammation with FC > 1000 ug/g, 23% in the AH, and 12,6% in the non-AH group ($P = 0.006$). The Cox model for the entire cohort showed that age, MELD-Na, CRP, CTPS, and FC > 1000, but not AH, were independent risk factors of adverse outcome. In the log-rank test, patients with FC > 1000 had a significantly higher risk of adverse outcomes in both AH and non-AH groups, respectively (HR = 2.01; 95% CI 1.02-3.98 vs. 2.11; 1.24-3.56). AH cases having FC > 1000 compared to those with FC < = 1000 had significantly higher MELD-Na (30 vs. 26), and lower sodium (130 vs. 132). **Conclusion:** Patients with dACLD triggered by AH have evidence of a more pronounced intestinal inflammation reflected by *i)*significantly higher FC and *ii)*significantly higher proportion of patients with "severe intenstinal inflammation" (Graph). However, FC has not came out as an independent predictor of bad outcome and prognosis appears to be associated with the severity of the liver injury rather than a specific AH → II pathogenesis.



Disclosures: Lubomir Skladaný: Worwag: Speaking and Teaching, ProMed: Speaking and Teaching, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, RegPharm: Speaking and Teaching, Astellas: Speaking and Teaching, Tomas Koller: Abbvie: Speaking and Teaching, Gilead: other, Johnson and Johnson: Advisor, NovoNordisk: clinical study, Petra Vrbova: Nothing to Disclose, Daniela Zilincanova: Nothing to Disclose, Svetlana Adamcova Selcanova: Nothing to Disclose, Daniel Jan Havaj: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose

1562 | HIGH-SALT DIET EXACERBATES ALCOHOL-RELATED LIVER DISEASE BY RESHAPING THE GUT MICROBIOTA AND UPREGULATING SIK1 EXPRESSION IN LSECS

Hua Wang[1] Haiyuan Shen[2] Li Zuo[1], [1]Anhui Medical University, [2]the First Affiliated Hospital of Anhui Medical University

Background: Alcohol-related Liver Disease (ALD) is a form of hepatic pathology primarily induced by chronic excessive alcohol consumption, ranking as one of the foremost causes of liver-related mortality globally. Compounded by pervasive risk factors such as suboptimal dietary patterns, the global outlook for ALD

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remains concerning. This study aims to investigate the impact of a high-salt diet on ALD and explore its molecular regulatory mechanism, as well as identify potential therapeutic targets. **Methods:** C57BL/6 mice were employed as experimental subjects, utilizing the Gao-binge alcoholic liver model. Mice were subjected to high or normal salt diets. The extent of alcohol-induced liver damage, steatosis, and inflammation was assessed across different groups. To elucidate the regulatory pathways, comprehensive analyses were conducted using microbial community amplicon sequencing, metabolomics, proteomics, and genetic engineering techniques. **Results:** High-salt diet reduced the abundance of beneficial bacteria such as *Akkermansia muciniphila* and *Lactobacillus rhamnosus* while promoting the growth of harmful bacteria like *Enterococcus faecalis*. The disruption of the intestinal barrier allowed pathogen-associated molecular patterns to translocate into the liver, thereby exacerbating hepatic inflammation. Additionally, high-salt diet reshaped the immune landscape within the liver by promoting neutrophil migration into liver while exacerbating alcohol-induced liver damage in mice. Mechanistically, a high-salt diet induces the upregulation of salt-inducible kinase 1 (Sik1) expression in liver sinusoidal endothelial cells (LSECs), leading to the release of selectin and intercellular adhesion molecule-1 (ICAM-1). **Conclusion:** High-salt intake exacerbates ALD progression by altering the gut microbiome composition. While high-salt diet facilitates neutrophil infiltration into the liver by promoting selectin and ICAM-1 expression in LSECs, thereby causing tissue damage through inflammation. These findings elucidate novel molecular mechanisms underlying alcoholic liver injury and suggest potential therapeutic strategies for ALD involving dietary modifications and probiotic interventions. Additionally, this research underscores the critical importance of maintaining a balanced diet for overall health.

Disclosures: Hua Wang: Nothing to Disclose, Haiyuan Shen: Nothing to Disclose, Li Zuo: Nothing to Disclose

1563 | STAT5 AND REV-ERBA COOPERATIVELY REGULATE CYP4A EXPRESSION DURING THE PROGRESSION OF ALCOHOL-ASSOCIATED LIVER DISEASE.

Haibo Dong[1] Wei Zhong[1] Wei Guo[1] Xinguo Sun[1] Zhanxiang Zhou[1], [1]University of North Carolina at Greensboro

Background: Members of the cytochrome P450 4A (CYP4A) subfamily play key roles in the metabolism of long-chain fatty acids and have been linked to the development of alcohol-associated liver disease (ALD). However, how CYP4A expression changes over the course of ALD and what regulates these changes remain poorly understood. This study aimed to characterize the stage-specific expression patterns of CYP4A and to explore the underlying transcriptional mechanisms. **Methods:** To model early-stage ALD, mice were fed ethanol chronically for 8 weeks. For advanced disease, liver samples from patients with alcohol-associated cirrhosis (AC) and severe alcohol-associated hepatitis (sAH) were analyzed. Liver histology was used to evaluate disease severity. CYP4A expression and related metabolic pathways were assessed using RNA-seq, RT-qPCR, and Western blotting. A hepatocyte-specific STAT5 knockout mouse model and luciferase reporter assays were used to investigate transcriptional regulation. **Results:** RNA-seq analysis of liver tissues from chronic alcohol-fed (AF) mice and alcohol-associated hepatitis (AH) patients revealed that genes of the CYP4A family are enriched in long-chain fatty acid metabolism, including arachidonic acid and linoleic acid pathways. Furthermore, analysis of CYP4A isoforms showed that chronic alcohol feeding increased the expression of Cyp4a10 and Cyp4a14, but decreased Cyp4a12a/b in mice with early-stage ALD. However, In contrast, in human liver samples from advanced ALD, CYP4A11 (the human homolog of Cyp4a10/14) was downregulated in both AC and sAH, while CYP4A22 (homologous to Cyp4a12a/b) was upregulated in AC but decreased in sAH. Mechanistic studies revealed that the dynamic changes in Cyp4a expression may depend on the coordinated actions of the transcription factors STAT5 and REV-ERBα. **Conclusion:** In early ALD, REV-ERBα appears to be the primary regulator, whereas in later stages, STAT5 takes on a more dominant role. Moreover, STAT5 was found to repress REV-ERBα expression.

Disclosures: Haibo Dong: Nothing to Disclose, Wei Zhong: Nothing to Disclose, Wei Guo: Nothing to Disclose, Xinguo Sun: Nothing to Disclose, Zhanxiang Zhou: Nothing to Disclose

1564 | DISRUPTION OF HUR AGGRAVATES ALCOHOL-INDUCED LIVER INFLAMMATION THROUGH ALTERED BILE ACID SIGNALING AND H19 UPREGULATION

NAN WU[1] Yun-Ling Tai[1] Derrick Zhao[1] Hui Li[1] Grayson Way[1] Meiyi Song[1] Sareh Bayatpour[1] Lianyong Su[1] Xuan Wang[1] Emily Gurley[1] Phillip Hylemon[1] Arun Sanyal[1] Huiping Zhou[1], [1]Virginia Commonwealth University

Background: Alcohol-associated liver disease (ALD) involves hepatic steatosis, inflammation, and disrupted bile acid homeostasis, processes partly regulated post-

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transcriptionally. HuR (ELAVL1), an RNA-binding protein, stabilizes transcripts involved in metabolic and inflammatory pathways. Prior studies show that HuR suppresses *H19* expression, reducing ER stress and lipotoxicity. Metabolic stress suppresses HuR expression. However, HuR's role in ALD pathogenesis remains poorly defined and is the focus of this study. **Methods:** Twenty-four-week-old male HuR floxed and liver-specific HuR knockout (LKO) mice were fed a Lieber-DeCarli ethanol or control diet for 10 days, followed by a single ethanol binge or isocaloric maltose dextrin gavage. HuR deletion was confirmed by IHC and Western blot. Hepatic lipid accumulation was evaluated by H&E staining. Hepatic gene expression was profiled using the NanoString nCounter® Metabolic Pathways Panel with ROSALIND® analysis. *H19* expression was measured by qPCR. Hepatic bile acid composition was assessed via LC-MS and liver inflammation was evaluated via F4/80 IHC. **Results:** Following ethanol exposure, LKO mice exhibited increased F4/80$^+$ macrophage infiltration, indicating enhanced hepatic inflammation. NanoString analysis revealed upregulation of genes linked to stress responses, immune activation, and profibrogenesis—including *c-Myc*, Runt-related transcription factor 1, and protein tyrosine kinase 2—suggesting activation of stress signaling pathways and promotion of inflammatory and fibrotic remodeling. LC-MS analysis demonstrated altered bile acid composition in ethanol-fed LKO mice, with significant elevations in GCA, GβMCA, and TβMCA. However, LKO mice displayed reduced hepatic steatosis and lower serum triglyceride levels, potentially due to downregulation of *Fasn* and *Scd1*, which may impair lipid droplet formation and monounsaturated fatty acid synthesis. **Conclusion:** Liver-specific HuR deletion reprograms hepatic gene expression, alters bile acid composition, and modulates lipid metabolism in response to ethanol exposure. Although steatosis is attenuated, increased *H19* expression and activation of pro-inflammatory pathways indicate a pathological shift from lipid accumulation to inflammation-driven liver injury. Additionally, elevated levels of GCA and TβMCA may exacerbate hepatic inflammation by activating sphingosine-1-phosphate receptor 2 and antagonizing farnesoid X receptor signaling, respectively.

Disclosures: NAN WU: Nothing to Disclose, Yun-Ling Tai: Nothing to Disclose, Derrick Zhao: Nothing to Disclose, Hui Li: Nothing to Disclose, Grayson Way: Nothing to Disclose, Meiyi Song: Nothing to Disclose, Sareh Bayatpour: Nothing to Disclose, Lianyong Su: Nothing to Disclose, Xuan Wang: Nothing to Disclose, Emily Gurley: Nothing to Disclose, Phillip Hylemon: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (< 5K), Terns (< 5K), Merck (< 5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (< 5K),: Consultant, Novo Nordisk: Consultant, Regeneron (< 5K), Alnylam (< 5K), Akero (< 5K),: Consultant, Tern (< 5K), Histoindex (< 5K), Corcept (< 5K),: Consultant, Path AI (< 5K), Genfit (< 5K), Mediar (< 5K),: Consultant, Satellite Bio (< 5K), Echosens (< 5K), Abbott (< 5K),: Consultant, Promed (< 5K), Glaxo Smith Kline (~11K), Arrowhead (< 5K): Consultant, Zydus (> 60K), Boston Pharmaceutical (< 5K), Myovent (< 5K),: Consultant, Variant (< 5K), Cascade (< 5K), Northsea (< 5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Huiping Zhou: Nothing to Disclose

1565 | A SUPEROXIDE DISMUTASE-MIMETIC (BMX-001) MITIGATES LIPID PEROXIDATION IN A MOUSE MODEL OF ALCOHOL-ASSOCIATED LIVER DISEASE.

Delia Omar[1] Micah Schott[1] Nourhan Mostafa[1] Rebecca Deegan[1], [1]University of Nebraska Medical Center

Background: Alcohol-associated liver disease (ALD) is a growing public health concern. Hepatic steatosis represents the earliest stage of ALD and is marked by extreme accumulation of lipid droplets (LDs) within hepatocytes that are central to ALD progression. Additionally, hepatocytes accumulate reactive oxygen species (ROS) following ethanol (EtOH) metabolism, which then reacts with polyunsaturated fatty acids (PUFA), leading to increased lipid peroxidation. However, it is unclear whether ROS can be targeted therapeutically to decrease lipid peroxidation and improve ALD. A promising antioxidant therapy uses the superoxide dismutase SOD-mimetic (BMX-001), a lipophilic manganese porphyrin that scavenges excess intracellular ROS and is currently in Phase 2 clinical trials as a radioprotector in cancer patients. Pharmacokinetics data showed that BMX-001 stably accumulates within mouse livers in a dose dependent manner. However, its efficacy to mitigate ROS-driven hepatocyte damage in ALD has not been explored. **Methods:** C57BL6 mice were subjected to a diet enriched in PUFA with a chronic 10-day EtOH feeding followed by a single binge of EtOH or an isocaloric control-PUFA rich diet with a single binge of maltose dextrin. Mice were randomly assigned to four groups: Control + PBS, Control + BMX-001, EtOH + PBS, EtOH + BMX-001,

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and the drug was administered by intraperitoneal injection four times. At 7 hours post binge, mice were euthanized, liver tissues and blood serum were collected for analysis. **Results:** Findings demonstrated a remarkable increase in the liver / body weight ratio (P-value < 0.05), and a significant elevation in the hepatic triglyceride level (P-value < 0.0001) in EtOH-fed mice compared with controls (P-value < 0.0001). Serum alanine aminotransferase, and cholesterol levels didn't reveal significant differences between groups. Liver tissue immunofluorescence (IF) staining with LD marker perilipin-2 (PLIN2) revealed a remarkable increase in the mean fluorescence intensity (MFI) in EtOH-fed mice compared with controls. IF staining for lipid peroxidation using 4-Hydroxynonenal (4HNE) antibody showed a significant reduction in the MFI by BMX-001 (P-value < 0.05) compared with PBS in EtOH-fed mice. Interestingly, 4HNE staining was observed around LDs and was strongly colocalized with PLIN2. We also observed sex variability in 4HNE staining, where male mice showed elevated lipid peroxidation compared with female mice. Lipid peroxidation measurements were complemented by malondialdehyde (MDA) immunofluorescence, which confirmed the reduction by BMX-001 in EtOH-fed mice compared to PBS-EtOH. **Conclusion:** Our data suggests that LDs may serve as central organelles for the storage and trafficking of lipid peroxides in ALD, and that BMX-001 therapy mitigates lipid peroxidation in hepatocytes. Furthermore, sex-specific differences exist with respect to EtOH-induced lipid peroxidation in male and female mice.

Disclosures: Delia Omar: Nothing to Disclose, Micah Schott: Nothing to Disclose, Nourhan Mostafa: Nothing to Disclose, Rebecca Deegan: Nothing to Disclose

1566 | PATTERNS OF PRE-ALCOHOL-ASSOCIATED HEPATITIS HEALTHCARE UTILIZATION AND OUTCOMES AMONG ADOLESCENTS AND YOUNG ADULTS IN ONTARIO

Gabrielle Jutras[1] Maya Djerboua[2] Jennifer Lai[3] Norah Terrault[4] Oyedeji Ayonrinde[5] Jennifer Flemming[6], [1]University of California, San Francisco, [2]ICES, Queen's University, Kingston, Ontario, Canada, [3]Division of Gastroenterology and Hepatology, Department of Medicine, UCSF, [4]University of Southern California, [5]Department of Psychiatry, Queen's University, [6]Queen's University Cancer Research Institute

Background: Rates of alcohol-associated hepatitis (AH) in adolescents and young adults (AYAs) have tripled, with >20% dying in 5-years. Early identification and treatment of high-risk alcohol use and alcohol use disorder (AUD) may prevent AH. We examined pre-AH healthcare use among AYAs ultimately diagnosed with AH and described liver-related outcomes and mortality. **Methods:** Using Ontario administrative data (2000-2023), we identified AYAs (13-39 years) with a first AH presentation. Hierarchical agglomerative cluster analysis was used based on healthcare utilization in the 2-years preceding AH (emergency department [ED], hospitalizations, outpatient, etc.) to identify distinct patterns of usage. We described each cluster and evaluated 5-year outcomes post-AH (liver-related events, overall mortality) using cumulative incidence (CI) function estimates from competing risks analysis. **Results:** We included 3,340 AYAs with AH (median age 33, 36% female) and identified five distinct healthcare utilization clusters. In the two-years prior to AH, overall, 40% had alcohol-related ED visits (range between clusters: 27-80%) and 17% had alcohol-related admissions (6-65%). As outpatients, 86% saw a primary care provider (PCP) (81-97%), 19% saw a psychiatrist (1-84%), and 9% saw a gastroenterologist (GI)/hepatologist (0-89%). Five-year overall CI of mortality post-AH ranged from 15% to 31% ($p < .001$; Figure A). Liver-related events beyond six months post-AH ranged from 16% to 30% ($p < .001$; Figure B). The highest-mortality cluster (31%; cluster 5) included 40% females, 38% in the lowest income quintile, and 95% with mental illness. This cluster had the highest alcohol-related healthcare usage pre-AH (ED [80%], hospitalization [65%], outpatient [66%]), but only 10% received AUD pharmacotherapy and 14% saw GI/hepatology pre-AH. The cluster with the highest liver-related events (30%; cluster 4), 31% were female, 31% living in low-income areas and 63% had mental illness. Few had a GI/Hepatology visit pre-AH (23%), 3% received AUD pharmacotherapy, with 47% having an alcohol-related admission. **Conclusion:** Distinct patterns of healthcare use precede AH among AYAs. Despite extensive alcohol-related healthcare contact, many AYAs still present with AH, suggesting missed opportunities or limited effectiveness of current interventions on harmful alcohol use. These results can inform development of early identification and interdisciplinary intervention strategies to prevent AH.

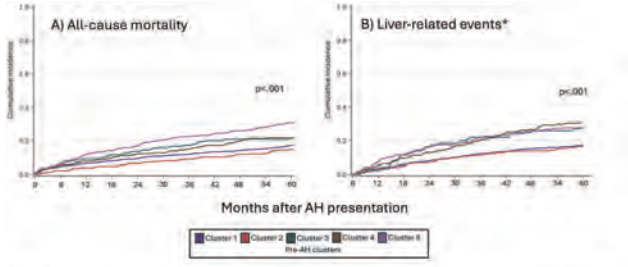

Figure: Cumulative incidence of a) mortality (competing event = liver transplant) and b) liver related events (competing event = non-liver related mortality) among adolescents and young adults with AH. *Liver events include cirrhosis, decompensation, liver transplant, hepatocellular carcinoma, liver-related death; AH: alcohol-associated hepatitis.

Disclosures: Gabrielle Jutras: Nothing to Disclose, Maya Djerboua: Nothing to Disclose, Jennifer Lai:

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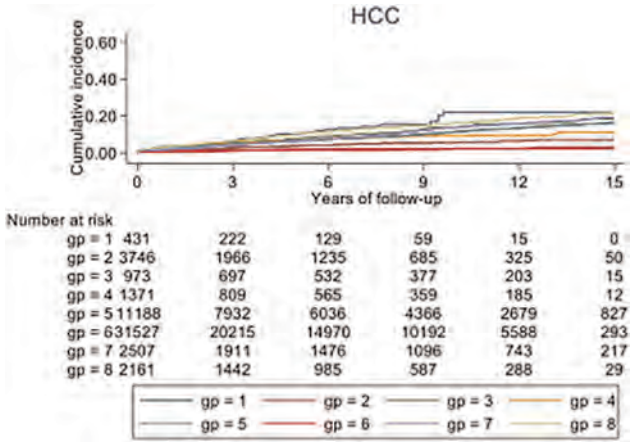
1567 | CLINICAL OUTCOMES BETWEEN ALCOHOL-ASSOCIATED LIVER DISEASE AND CHRONIC VIRAL HEPATITIS IN TAIWAN

Chun-Ming Hong[1] Tung-Hung Su[1] Shih-Jer Hsu[1] Tai-Chung Tseng[1] Chen-Hua Liu[1] Hung-Chih Yang[1] Shang-Chin Huang[2] Jia-Horng Kao[1] Chun-Jen Liu[1] Pei-Jer Chen[1], [1]National Taiwan University Hospital, [2]National Taiwan University Hospital Bei-Hu Branch

Background: Alcohol-associated liver disease (ALD) is becoming increasingly important after effective control of viral hepatitis. This issue has become even more serious after the COVID-19 pandemic. However, studies of ALD are not easily conducted in Taiwan because of lack of effective therapies and of stigma. On the contrary, managements towards viral hepatitis have been improving over the decades. Our study tried to investigate the difference between ALD and viral hepatitis and hence to improve managements towards ALD. **Methods:** We conducted a retrospective study by looking into Integrative Medical Database in National Taiwan University Hospital (NTUH-iMD) from 2009 to 2021. ICD-9 (International Classification of Diseases, ninth edition) and ICD-10 were used for disease coding. The inclusion criteria are patients whose diagnosis was made once at outpatient or inpatient and over 20 years old, while the exclusion criteria are those who had hepatocellular carcinoma (HCC), liver transplantation, or death before the index date. The index date was the first time when the patient was diagnosed inpatient or outpatient. **Results:** From 2009 to 2021, 63256 patients were enrolled. Among them, 3966 were ALD patients, 58853 had chronic viral hepatitis, and 437 had both ALD and chronic viral hepatitis. We further divided chronic viral hepatitis patients into several groups and each with/without antiviral therapy: chronic HBV/HCV co-infection, chronic hepatitis B, and chronic hepatitis C. As shown in Figure 1 and 2, patients with both ALD and chronic viral hepatitis had highest incidence of HCC and ALD patients had highest mortality. In addition, patients with both ALD and chronic viral hepatitis had highest incidence of liver transplantation. **Conclusion:** Our retrospective study presents a preliminary understanding of ALD versus chronic viral hepatitis in Taiwan. Compared to chronic viral hepatitis, ALD caused less HCC. However, ALD patients had the highest mortality indicating the cause of death in ALD patients was related to non-HCC mostly. Many unmet needs towards ALD warrant further studies.



Disclosures: Chun-Ming Hong: Nothing to Disclose, Tung-Hung Su: Gilead Sciences: Consultant, AbbVie: Speaking and Teaching, Bristol-Myers Squibb: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Merck Sharp and Dohme: Speaking and Teaching, Roche: Speaking and Teaching, Sysmex: Speaking and Teaching, Eisai: Speaking and Teaching, Shih-Jer Hsu: Nothing to Disclose, Tai-Chung Tseng: Nothing to Disclose, Chen-Hua Liu: Nothing to Disclose, Hung-Chih Yang: Nothing to Disclose, Shang-Chin Huang: Gilead Sciences: Speaking and Teaching, Jia-Horng Kao: Nothing to Disclose, Chun-Jen Liu: Nothing to Disclose, Pei-Jer Chen: Nothing to Disclose

1568 | SAFETY AND EFFECTIVENESS OF PHENOBARBITAL VS. BENZODIAZEPINES FOR SEVERE ALCOHOL WITHDRAWAL IN ALCOHOL-ASSOCIATED LIVER DISEASE

Rajalakshmi Govalan[1] Shengchen Hao[1] Michael Kenes[1] Jakob McSparron[1] Elliot Tapper[2], [1]University of Michigan, [2]University of Michigan Medical Center

Background: Severe alcohol withdrawal syndrome (SAWS) in patients with alcohol-associated liver disease (ALD) presents unique management challenges due to altered drug metabolism and increased drug-related toxicity. While benzodiazepines (BZDs) remain

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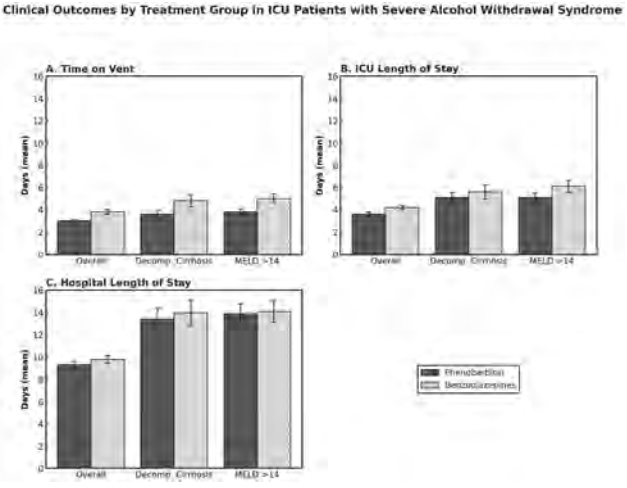
standard treatment, concerns about over-sedation, hepatic encephalopathy, and respiratory depression have prompted interest in phenobarbital as an alternative. **Methods:** This retrospective cohort study utilized the MIMIC-IV database (2008–2019) to compare the safety and efficacy of phenobarbital versus BZDs in ICU patients with ALD and SAWS. Patients receiving either drug as initial treatment were identified. To reduce confounding, inverse probability of treatment weighting (IPTW) was applied based on propensity scores derived from logistic regression using all baseline variables. The model demonstrated good discrimination with an area under the curve (AUC) of 0.7636. Primary outcomes included in-hospital mortality, need for mechanical ventilation, ICU length of stay, and overall hospital stay. Weighted logistic regression was used for binary outcomes, and weighted linear regression models were used for continuous outcomes. **Results:** Among 763 phenobarbital-treated and 2,863 BZD-treated patients, in-hospital mortality was slightly lower for the phenobarbital group (OR 0.80; 95% CI: 0.63–1.01). Phenobarbital was associated with a reduced need for mechanical ventilation (34.7% vs. 39.3%; OR 0.82; 95% CI: 0.74–0.91), shorter duration of ventilation (3.0 vs. 3.8 days; $p = 0.0005$), ICU length of stay (3.6 vs. 4.2 days; $p < 0.0001$), and a trend towards slightly shorter hospital stay (9.3 vs. 9.8 days; $p = 0.05$). Among patients with decompensated cirrhosis and those with severe liver disease (MELD > 14), phenobarbital remained associated with improved ICU and ventilatory outcomes without significant difference in in-hospital mortality compared to benzodiazepines. **Conclusion:** In this large cohort study, the first to examine patients with severe liver disease, phenobarbital was associated with better respiratory and ICU outcomes than BZDs in ALD patients with SAWS, without increased mortality. These findings support phenobarbital as a promising alternative; prospective studies are warranted to confirm these results and guide clinical management.



Disclosures: Rajalakshmi Govalan: Nothing to Disclose, Shengchen Hao: Nothing to Disclose, Michael Kenes: Nothing to Disclose, Jakob McSparron: Nothing to Disclose, Elliot Tapper: Madrigal: Grant/Research Support

1569 | HEPATIC SIRT7 PROMOTES PMN-MDSCS DIFFERENTIATION AND ALCOHOL RELATED LIVER INJURY VIA FXR-DEPENDENT BILE ACID METABOLISM

ZHUAN LI[1], [1]Hunan Normal University Healthy Science Center

Background: As the most recently identified subpopulation of neutrophil, polymorphonuclear myeloid derived suppressor cells (PMN-MDSCs) are crucial in regulating cancer progression via immunosuppression. Clinical evidence has suggested PMN-MDSCs involves in alcohol related liver disease (ALD) but the precise mechanisms remain elusive. The aim of the current study was to investigate mechanisms underly PMN-MDSCs differentiation and their role in ALD. **Methods:** $SIRT7^{flox/flox}$ mice were crossed with Alb-Cre mice to generate liver-specific SIRT7 gene knockout mice (Alb-$SIRT7^{-/-}$). Mice were fed with *Liber DeCarlie* diet for 4 week and the liver injury were assessed by ALT levels and histological evaluation. Unbiased metabolomics was used to identified changes in bile acid synthesis and metabolism. Western blot and qRT-PCR were utilized to evaluate protein and mRNA expression while Co-IP was employed to assess protein-protein interaction. Primary hepatic cells were isolated and evaluated and in vitro co-culture system was utilized to evaluate cell-cell communications. **Results:** Knockdown of SIRT7 in hepatocyte significantly impaired expression of genes that responsible for bile acid synthesis including *CYP27A1* and *CYP7A1*. Through unbiased metabolomics, we revealed that components of bile acid were significantly changed and secretion of deoxycholic acid (DCA) were decreased in Alb-$SIRT7^{-/-}$ mice. After 4 weeks of *Liber DeCarlie* alcohol feeding, Alb-$SIRT7^{-/-}$ mice exhibited significantly ameliorated alcohol induced liver injury and inflammation, which was associated with decreased expression of CD300ld, a recently identified PMN-MDSCs surface marker. Primary neutrophile isolated from mice after alcohol confirmed that PMN-MDSCs activation were significantly repressed in Alb-$SIRT7^{-/-}$ mice. Most importantly, we found that DCA was sufficient to promote PMN-MDSCs differentiation and activation *in vitro*. At molecular level, we demonstrated that SIRT7 interacted with and induced FXR deacetylation which was critical in regulating of bile acid synthesis via suppression of *CYP27A*, *CYP8B1* and *NTCP* gene expression. Finally,

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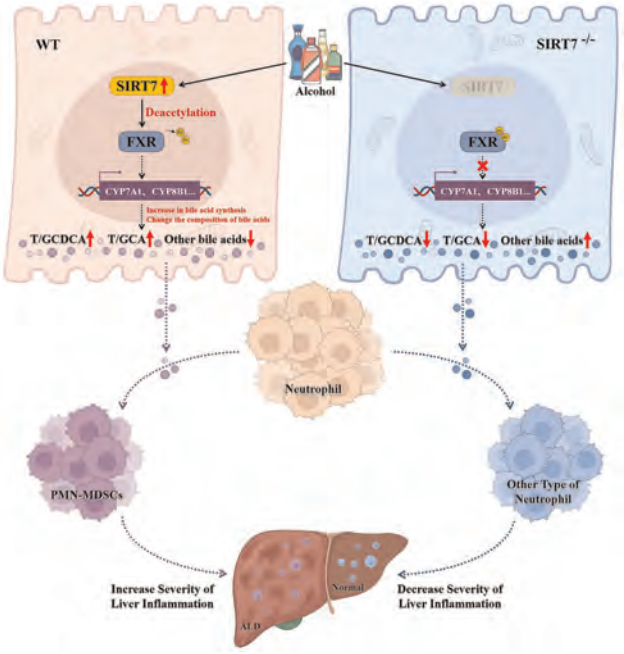
we found that expression of CD300ld were significantly elevated in clinical samples from ALD patients. **Conclusion:** Our data thus uncovered previously unidentified role of hepatic SIRT7 in promoting PMN-MDSCs differentiation and ALD progression via FXR deacetylation and bile acid metabolism. Targeting SIRT7 mediated FXR modulation and bile acid metabolism might offer therapeutic options against ALD.

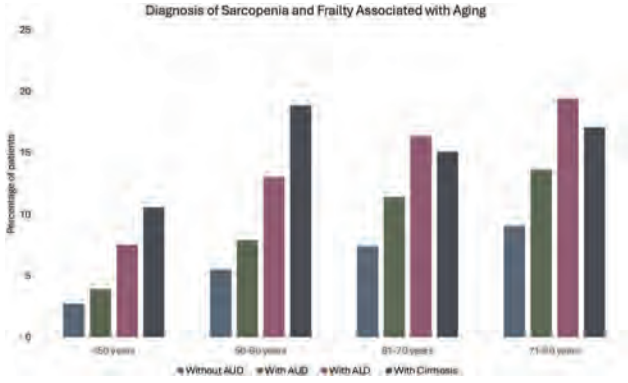


Disclosures: ZHUAN LI: Nothing to Disclose

1570 | AGE RELATED IMPACT OF OUTCOMES IN HOSPITALIZED PATIENTS WITH CIRRHOSIS AND ALCOHOL-ASSOCIATED LIVER DISEASE

Dhweeja Dasarathy[1], [1]*Stanford University, Department of Medicine*

Background: The prevalence and incidence of alcohol-use disorder (AUD) and alcohol-associated liver disease (ALD) continue to increase in the United States. Among patients with chronic liver disease, ALD is one of the most frequent etiologies. There is limited data on the incidence and consequences of alcohol intoxication and AUD in the hospitalized aging population, especially in those with liver disease. We investigated the impact of aging on clinical outcomes in a cohort with alcohol-associated liver injury. **Methods:** Data from 1/2017 to 12/2020 from the Nationwide Inpatient Sample were analyzed. Baseline population included patients (18–80 years old) with a clinical diagnosis of AUD (n = 523,464), without AUD (n = 238,678), alcoholic cirrhosis (n = 73,094), and ALD (n = 15,411) as defined by ICD-10 discharge codes. Primary and secondary diagnoses with ICD codes were analyzed. Clinical outcomes (length of stay, healthcare cost, mortality, sarcopenia, and frailty) were analyzed. Multivariate regression analyses were performed for each age category to identify independent associations with ALD and cirrhosis on clinical outcomes. **Results:** Among patients across all age groups with cirrhosis and ALD, healthcare utilization, social determinants of health, and comorbidities, as determined by the Elixhauser score, were significantly higher. As age increased, there was a stepwise increase in sarcopenia and frailty, with the highest prevalence in those with ALD > 70 years old (Figure 1). For all age categories, there was an independent effect of AUD associated with adverse outcomes, including sarcopenia, frailty, healthcare cost, length of stay, and discharge status. We then performed multivariate regression analyses stratified by age, and adjusted for race, sex, and comorbidities. We noted that AUD, AUD and ALD, AUD and alcoholic cirrhosis each increased risk for adverse clinical outcomes significantly. When controlling for aging, AUD, AUD and ALD, and AUD and cirrhosis also were highly associated with a diagnosis of sarcopenia, frailty, or both sarcopenia and frailty. **Conclusion:** We noted a significant association between ALD and cirrhosis on adverse clinical outcomes with increasing age including sarcopenia, frailty, and healthcare utilization. A diagnosis of sarcopenia and frailty conferred greater mortality risk than either alone in patients with ALD or cirrhosis with increasing age. Our findings highlight the need for targeted alcohol interventions in the aging population, especially in those with liver disease.



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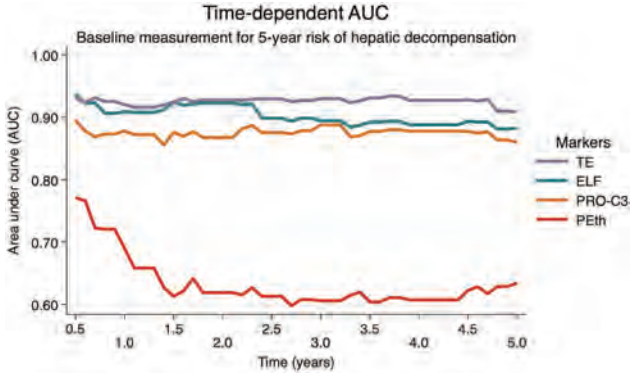
1571 | PHOSPHATIDYLETHANOL PREDICTS SHORT-TERM HEPATIC DECOMPENSATION BUT SHOWS RAPID DECLINE IN PROGNOSTIC DISCRIMINATION

Nikolaj Torp[1] Stine Johansen[1] Ellen Lyngbeck Jensen[1] Georg Semmler[1] Katrine Tholstrup Bech[1] Markus Maagaard[1] Helle Schnefeld[1] Katrine Prier Lindvig[1] Katrine Thorhauge[1] Ellen Elise Petersen[1] Johanne Kragh Hansen[1] Ida Falk Villesen[1] Peter Andersen[1] Diana Leeming[2] Morten Karsdal[2] Camilla Dalby Hansen[1] Maja Thiele[1] Mads Israelsen[1] Aleksander Krag[1], [1]Odense University Hospital, [2]Nordic Bioscience

Background: Phosphatidylethanol (PEth) reflects recent alcohol intake, while transient elastography (TE), ELF, and PRO-C3 are non-invasive tests (NITs) for liver fibrosis. The combined utility of PEth and liver fibrosis NITs for predicting hepatic decompensation and all-cause mortality, as well as the time-dependent prognostic performance of PEth, is unknown. **Methods:** We included 411 adults at risk of SLD due to a history of excessive alcohol consumption ($\geq$36 g/day men, $\geq$24 g/day women for $\geq$1 year). Known chronic liver disease and prior hepatic decompensation were key exclusion criteria. PEth, TE, ELF and ELISA PRO-C3 (Nordic-PRO-C3^{TM}) were measured at baseline. PEth was considered moderate-high if $\geq$80 ng/mL and high if $\geq$200 ng/mL. NIT cut-offs for liver fibrosis were TE $\geq$15 kPa, ELF $\geq$9.8, PRO-C3 $\geq$15.6 ng/mL. Hepatic decompensation (Baveno VII criteria) and mortality was assessed for up to 5 years. Competing risk (death prior to decompensation), Cox regression and time-dependent AUCs evaluated prognostic performance. **Results:** Median age was 58 years, 76% were male. Median PEth was 338 ng/mL, where 70% had a moderate-high PEth ($\geq$80 ng/mL) and 59% a high ($\geq$200 ng/mL). NITs suggestive of liver fibrosis were found in 22% (TE), 33% (ELF), 38% (PRO-C3). During follow-up, 60 patients died (15%) and 49 (12%) developed hepatic decompensation: ascites (n=27), encephalopathy (n=13), variceal bleed (n=9). PEth predicted hepatic decompensation (sHR=1.03, 95% CI: 1.01-1.06) and all-cause mortality (aHR=1.04, 95% CI: 1.02-1.06) independently of all NITs. A combined high PEth ($\geq$200 ng/mL) and elevated NIT (TE $\geq$15 kPa/ELF $\geq$9.8/PRO-C3 $\geq$15.6 ng/mL) identified a subgroup at high risk of decompensation within 1 year (PEth+TE: n=11/52, 21%; PEth+ELF: n=12/82, 15%; PEth+PRO-C3: 13/95, 14%). No additional decompensation episodes within 1 year were captured by using the moderate-high PEth threshold of $\geq$80 ng/mL (PEth+TE: n=11/57, 19%; PEth+ELF: n=12/92, 13%; PEth+PRO-C3: 13/105, 12%). Notably, the time-dependent AUC for hepatic decompensation declined for PEth from 0.77 at 0.5 years to 0.69 after 1 year and further to 0.62 at 2 years (Figure). At the same time, the time-dependent AUC for the liver fibrosis NITs remained stable throughout at around 0.90. **Conclusion:** PEth predicts hepatic decompensation and all-cause mortality independently of liver fibrosis NITs. Using established cut-offs for PEth and NITs identifies individuals at high short-term risk of decompensation. However, the prognostic discrimination of PEth diminish rapidly over time, underscoring the need for repeated PEth measurements to accurately risk stratify patients.



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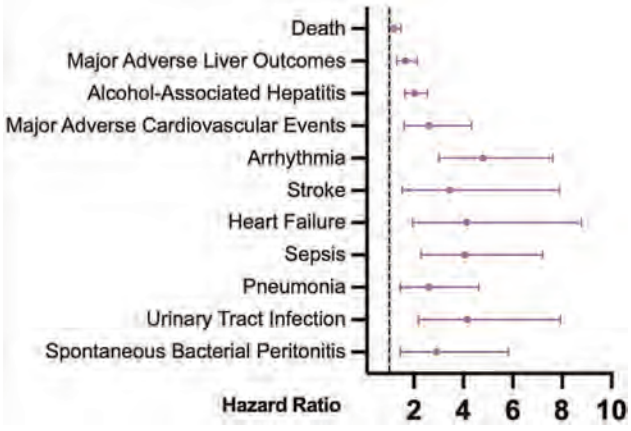
1572 | CLINICAL OUTCOMES ACROSS ORGAN SYSTEMS IN ALCOHOL-ASSOCIATED LIVER DISEASE WITH METABOLIC RISK

Pojsakorn Danpanichkul[1] Donghee Kim[2] Krittameth Rakwong[3] Peerapun Jit-are-roon[3] Phuuwadith Wattanachayakul[4] Thitiphan Srikulmontri[4] Shu-Yen Chan[5] Vincent Chen[6] Christos Mantzoros[7] Mazen Noureddin[8] Karn Wijarnpreecha[9], [1]Texas Tech University Health Sciences Center, [2]Stanford University Medical Center, [3]Chiang Mai University, [4]Jefferson University, [5]Weiss Memorial Hospital, [6]University of Michigan, [7]BIDMC, [8]Houston Methodist Hospital, [9]University of Arizona College of Medicine-Phoenix

Background: Alcohol-associated liver disease (ALD) is a major cause of liver-related morbidity and mortality. The impact of metabolic risks in ALD remains poorly understood. This study aimed to evaluate the association between metabolic risk and outcomes in patients with ALD. **Methods:** We conducted a retrospective cohort study using the TriNetX research network. Adults with ALD were stratified by the presence or absence of metabolic risk factors. Propensity score matching (1:1) balanced demographics, comorbidities, and medication use. The primary outcome was all-cause mortality; secondary outcomes included alcohol-associated hepatitis (AH), cardiovascular complications, infections, and major adverse liver outcomes (MALO). Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI) over a 1-year follow-up. **Results:** After matching, 3,532 patients (1,766 per group) were included. No significant difference in all-cause mortality was observed between groups (HR: 1.20, 95% CI: 0.98–1.48, $p = 0.073$). However, ALD with metabolic risk was associated with higher risks of MALO (HR: 1.67, 95% CI: 1.31–2.13, $p < 0.001$), AH (HR: 2.04, 95% CI: 1.64–2.54, $p < 0.001$), major adverse cardiovascular events (HR: 2.64, 95% CI: 1.60–4.34, $p < 0.001$), and sepsis (HR: 4.07, 95% CI: 2.30–7.21, $p < 0.001$). **Conclusion:** Among patients with ALD, metabolic risk was associated with markedly higher hepatic, cardiovascular, and infectious complications. These findings highlight the need to recognize ALD with metabolic risk as a distinct high-risk subgroup requiring targeted clinical and public health strategies.



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1573 | ABSTRACT WITHDRAWN

1574 | MULTICENTER VALIDATION OF PREDICTION MODELS FOR TRANSPLANT-FREE SURVIVAL IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS

Elina Stoffel[1] Olivia Blocker[2] Himel Mallick[2] Jialin Gao[2] Ziyu Liu[2] Robert Brown[2] Gene Im[3] Elizabeth Verna[1] Stephanie Rutledge[2], [1]Columbia University Medical Center, [2]Weill Cornell Medicine, [3]Center for Liver Disease and Transplantation, Division of Digestive and Liver Diseases Columbia Univ

Background: Alcohol-associated hepatitis (AH) is the fastest-growing indication for liver transplantation (LT) in the United States. Patients with severe AH (sAH), especially with acute-on-chronic liver failure (ACLF), face high short-term mortality risk. Among patients not responding to medical therapy, few qualify for early LT, and outcomes in those declined are poorly defined. A single center prediction model

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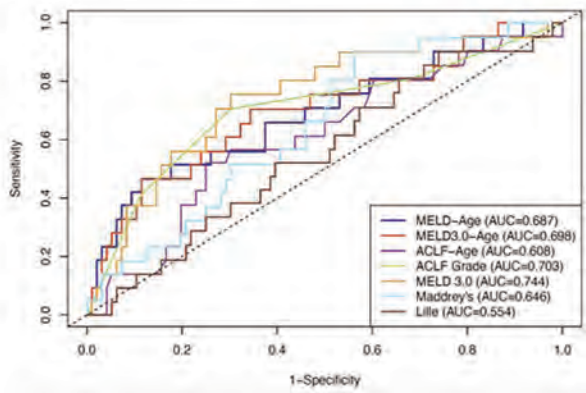
found that adding age to MELD score or ACLF grade enhances survival prediction at the time of waitlisting decision. We aimed to validate MELD-Age and ACLF-Age models in predicting transplant-free survival (TFS) in patients with sAH evaluated for early LT. **Methods:** We conducted a retrospective cohort study of patients >18 years old hospitalized with probable or definite sAH (per NIAAA criteria, MELD >20) who underwent eLT evaluation at two centers between January 2012 and May 2025. We analyzed 180-day TFS as a composite endpoint using Cox regression. Model performance was assessed using a time-dependent area under the receiver operating characteristic curve (AUROC). **Results:** Between 2012 and 2025, 133 patients with sAH were evaluated for eLT: 82/133 (61%) were accepted, 36/133 (27%) were declined and 15/133 (11%) were deferred. Of those deferred, 3/15 (20%) were later accepted. Overall, 65/133 (48%) underwent LT. The most common reasons for denial or deferral were psychosocial factors (35/51, 69%) and medical contraindications (10/51, 20%). The mean age was 44 years (SD 10) and 37% were female. 57% of patients identified as White, 16% as Black, and 7.5% as Hispanic. 58% were treated with corticosteroids. The mean MELD 3.0 was 32.6 (8.0) and mean Maddrey's DF (MDF) was 85 (56). A total of 95/133 (71%) patients met criteria for ACLF, of whom 51/133 (37%) had grade 2 or 3. Median time from admission to listing decision was 12 days (IQR 7-19.3). Over a median follow-up of 528 days (IQR 1-1161), 27/133 (20%) patients died, with 17/27 (63%) dying during index admission. The 90- and 180-day cumulative incidence of death was 12.8% and 15%, respectively. For 180-day TFS, AUROC for MELD-Age was 0.69, and 0.61 for ACLF-Age, but MELD 3.0 performed best (AUROC of 0.74). **Conclusion:** Patients with sAH evaluated for eLT have high short-term mortality. In this cohort, MELD 3.0 performed better than ACLF in predicting 180-day transplant-free survival, perhaps because of relatively low numbers with ACLF grade 2 or 3. Interestingly, adding age to MELD 3.0 or ACLF grade worsened their predictive ability. This may be because the scores incorporating age were originally designed to evaluate the natural history of sAH in the absence of eLT and it is likely that some of this cohort who underwent eLT (probably the younger patients) would have survived to 180 days. As a subset will recover without eLT, more accurate survival prediction is needed to guide decision-making in sAH and ensure judicious use of scarce organs.

Figures 1: AUROC of Tested Prediction Models



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1575 | ACCELERATED PROGRESSION TO CIRRHOSIS AND HEPATIC DECOMPENSATION IN METALD AND ALD COMPARED TO MASLD: A GLOBAL STUDY

Luis Antonio Diaz[1] Ming-Hua Zheng[2] Natalia Baeza[3] Francisco Idalsoaga[4] Gustavo Ayares[3] Terry Cheuk-Fung Yip[5] Vincent Wai-Sun Wong[5] Grace Lai-Hung Wong[5] Jimmy Che-To Lai[5] Rakhi Maiwall[6] Shiv Kumar Sarin[6] YU JUN WONG[7] Xin En Goh[7] May Xuan Goh[7] David Marti-Aguado[8] Cristiane Villela-Nogueira[9] nATHALIE Carvalho Leite[9] Gil Fernando Salles[9] Claudia Regina Lopes Cardoso[9] Sebastián Marciano[10] Jorge Martínez Morales[10] María José Acosta[10] Adrián Gadano[10] Claudia P. Oliveira[11] Mario G. Pessoa[11] Adelina Lozano[12] Anand V. Kulkarni[13] Ramagundam Ramyasri[13] Mohamed El-Kassas[14] Mario Reis Alvares-da-Silva[15] Bruno Basso[15] Gabriella Jonko[15] Fátima Higuera de la Tijera[16] Daniza Alexandra Contreras De

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Background: The natural history of metabolic dysfunction and alcohol-associated liver disease (MetALD) remains poorly characterized. In a large global cohort, we compared the natural history of the main steatotic liver disease (SLD) subtypes in terms of liver fibrosis progression, hepatic decompensation, and incidence of hepatocellular carcinoma (HCC). **Methods:** This is a retrospective cohort study of well-characterized adult participants with SLD evaluated between 2003 and 2025, including metabolic dysfunction-associated steatotic liver disease (MASLD), MetALD, and alcohol-associated liver disease (ALD) according to the 2023 SLD criteria. Sociodemographic and clinical data, vibration-controlled transient elastography (VCTE) parameters, and liver biopsy (when available) were recorded. Patients with other causes of liver disease (including viral hepatitis) were excluded. The primary outcome was progression to cirrhosis in those without cirrhosis at baseline (defined by 1. liver biopsy, or 2. VCTE $\geq$13.6 kPa, or Fibrosis-4 [FIB-4] $>$3.25 if other techniques were missing). Secondary outcomes were incidence of hepatic decompensation (ascites, hepatic encephalopathy, variceal bleeding, or hepatorenal syndrome) and HCC. A multivariable Cox regression adjusted by age, sex, race, body mass index, diabetes, hypertension, hyperlipidemia, and smoking (for HCC) was performed. **Results:** The total cohort included 150,306 participants from 15 countries; 87.5% MASLD, 7.9% MetALD, and 4.6% ALD. Overall, the median age was 61 years [IQR 51–70]; 52.8% men, and 97.6% Asian. At baseline, 12.2% of the cohort had a liver biopsy with F4 or a VCTE/FIB-4 suggestive of cirrhosis. During a median follow-up of 2.1 years [IQR 0.6–4.7], 0.9% of participants progressed to cirrhosis, 0.4% had hepatic decompensations, and 1.3% developed HCC. Individuals with MetALD and ALD exhibited a higher risk of progression to cirrhosis (MetALD aHR 1.34, 95%CI: 1.06–1.68, $p=0.013$; ALD aHR 1.82, 95%CI: 1.41–2.35, $p<0.0001$; MASLD: reference) and of hepatic decompensation (MetALD aHR 9.33, 95%CI: 6.32–13.75, $p<0.0001$; ALD aHR 20.56, 95%CI: 13.86–30.48, $p<0.0001$) (Figure). The incidence of HCC was higher in individuals with ALD than MASLD (aHR 1.26, 95%CI: 1.02–1.55, $p=0.029$). **Conclusion:** In this multi-ethnic global cohort, MetALD and ALD were associated with more rapid cirrhosis progression and greater decompensation rates than MASLD, independent of cardiometabolic factors. These findings may support early intervention in MetALD and ALD.

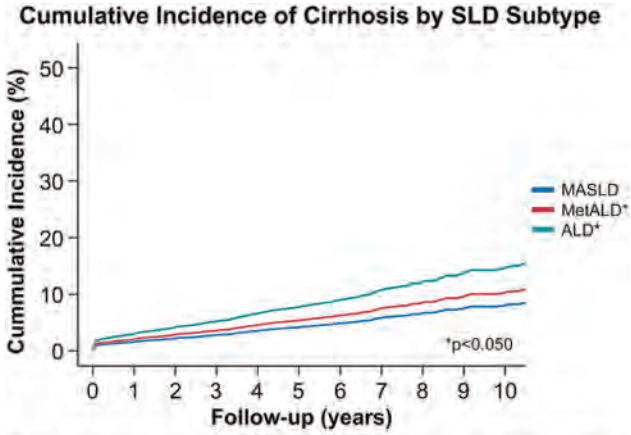

Figure. Cumulative incidence of incident cirrhosis by steatotic liver disease subtype. Participants with baseline cirrhosis—defined by (1) histologic stage F4, (2) liver stiffness ≥13.6 kPa on vibration-controlled transient elastography, or (3) Fibrosis-4 index >3.25—were excluded. Cox models were adjusted for age, sex, race, body mass index, diabetes, hypertension, and hyperlipidemia.

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1576 | GREATER LIVER DISEASE–RELATED STIGMA AMONG PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE COMPARED TO NON–ALCOHOL-RELATED LIVER DISEASE

Wei Zhang[1] Kelly Hsu[2] Edward Wu[1] Ellen Zhen[1] Ana Ivkovic[1] Heidi Yeh[1] Emily Bethea[1] Sarah Wakeman[1] Russell Goodman[1] Esperance Schaefer[1] Jay Luther[1] Nneka Ufere[1] Raymond Chung[1] Annie Fox-Galalis[3], [1]Massachusetts General Hospital, [2]Tuft University School of Medicine, [3]MGH Institute of Health Professions

Background: Stigma is a critical barrier to care in patients with liver disease, particularly for those with alcohol-associated liver disease (ALD). ALD carries

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added layers of moral judgment and blame, often rooted in perceptions of personal responsibility for illness. While prior studies have described stigma in patients with ALD, few have quantitatively assessed stigma severity across liver disease etiologies using a validated, liver-specific instrument. Understanding how stigma differs by etiology is essential to developing equitable, stigma-informed care. **Methods:** We administered the Liver Disease Stigma Scale (LDSS), a newly developed 28-item instrument assessing internalized, anticipated, and experienced stigma, to 221 adults with liver disease at a tertiary care center. The sample included 133 patients with ALD and 88 with non–alcohol-related liver disease (non-ALD). Compared to non-ALD participants, the ALD group was more likely to be male and have lower educational attainment ($p < .01$). LDSS subscale scores were compared between groups using t-tests. We also examined attitudes toward liver disease and liver disease treatment using theory-informed, pilot-tested measures designed to assess negative treatment beliefs and perceived undeservingness. **Results:** Patients with ALD reported significantly higher stigma across all LDSS subscales, including experienced stigma (mean [SD]: 1.75 [0.90] vs. 1.23 [0.46], $p < .001$), anticipated stigma (1.57 [0.77] vs. 1.24 [0.50], $p < .001$), and internalized stigma (2.34 [1.12] vs. 1.54 [0.84], $p < .001$). Differences were observed in both family- and healthcare-related stigma domains. ALD patients also endorsed more negative attitudes toward liver disease (2.11 [0.87] vs. 1.44 [0.59], $p < .001$) and liver disease treatment (1.38 [0.54] vs. 1.21 [0.39], $p = .008$). **Conclusion:** Patients with alcohol-associated liver disease experience significantly greater liver disease–related stigma than those with non–alcohol-related liver disease. These findings highlight the role of stigma as a modifiable barrier to equitable care in ALD and emphasize the need for etiology-sensitive, stigma-reducing interventions within hepatology.

Table: Comparison of liver disease stigma and treatment attitudes between patients with alcohol-associated liver disease (ALD) and non–alcohol-related liver disease (non-ALD).

Mechanism	ALL	ALD	Non-ALD	P value
LD Experienced Stigma	1.54 (0.79)	1.75 (0.90)	1.23 (0.46)	<0.001
LD Experienced Stigma-Family	1.55 (0.91)	1.79 (1.07)	1.19 (0.37)	<0.001
LD Experienced Stigma-Healthcare	1.53 (0.85)	1.71 (0.93)	1.27 (0.62)	<0.001
LD Anticipated Stigma	1.44 (0.69)	1.57 (0.77)	1.24 (0.50)	<0.001
LD Anticipated Stigma-Family	1.40 (0.74)	1.53 (0.85)	1.20 (0.46)	<0.001
LD Anticipated Stigma-Healthcare	1.48 (0.78)	1.61 (0.87)	1.28 (0.60)	0.002
LD Internalized Stigma	2.01 (1.09)	2.34 (1.12)	1.54 (0.84)	<0.001
Attitudes toward LD Treatment	1.31 (0.49)	1.38 (0.54)	1.21 (0.39)	0.008
Attitudes toward LD	1.84 (0.84)	2.11 (0.87)	1.44 (0.59)	<0.001

LD: Liver Disease, ALD: alcohol associated liver disease, Non-ALD: Non-alcohol associated liver disease

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1577 | LOSS OF MAP3K8 IN MYELOID CELLS PROTECTS AGAINST PRECLINICAL ALD AND METALD

Alejandro H. Gutierrez[1] Sara García[1] Douglas Maya Miles[2] Javier Vaquero[3] Rafael Bañares Cañizares[3] Rocío Gallego Durán[2] Javier Ampuero Herrojo[2] Manuel Romero-Gómez[2] Yulia Nevzorova[1] Carlos Sanz-García[1] Francisco Javier Cubero[1], [1]Department of Immunology, Ophthalmology & ORL, Complutense University of Madrid, Madrid, Spain, [2]Instituto de Biomedicina de Sevilla, IBiS/Hospital Virgen del Rocío/CSIC/University Sevilla, Spain, [3]Servicio de Aparato Digestivo, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Background: Heterogeneity of macrophages and other immune cells is a recently reported hallmark of alcohol-related liver disease (ALD) and metabolic dysfunction and alcohol-related steatotic liver disease (MetALD). MAP3K8, also known as TPL2 or COT, is a serine/threonine kinase (STK) which plays a critical role in the regulation of the immune response. Here, we investigated the cell-specific role of MAP3K8 in macrophages and myelomonocytic cells during ALD/MetALD. **Methods:** C57BL/6J mice with specific deletion of MAP3K8 in Kupffer ($\Delta^{\varnothing}$) and myeloid cells (Δ^{LysM}), and its respective controls (floxed mice, $\Delta^{f/f}$) were generated. Two experimental models of ALD (Lieber-DeCarli diet for 4 days and 25 days) and MetALD (DuAL model for 23 weeks). Samples were processed for histopathological examination and protein (IF, IHC and WB), mRNA expression was evaluated by qRT-PCR and flow citometry. The expression of MAP3K8 was analyzed in cohorts of ALD and MetALD patients. **Results:** Δ^{LysM} mice showed significantly reduction markers of liver injury (AST, ALT, LDH), liver inflammation (BW/LW ratio), cytokines and immune cell infiltration ($CD45^+$ and $CD11b^+$ cells), cell death (necrosis, TUNEL) and cell proliferation (PCNA, Ki-67), associated to pERK1/2 overexpression and downregulation of pJNK compared with $\Delta^{f/f}$ animals, both in preclinical ALD and MetALD. Moreover, collagen deposition - evaluated as Sirius red (SR) staining – and markers of hepatic fibrosis and hepatic stellate cell (HSC) activation including αSMA were significantly reduced in Δ^{LysM} mice, after 23w of DuAL diet. On the other hand, $\Delta^{\varnothing}$ mice displayed overexpression of pERK and downregulation of pJNK without variations in markers of liver injury, inflammation, cell death or fibrosis. Moreover, a significant increase in MAP3K8/pERK/pJNK expression was observed in patients with MetALD, specifically

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associated with high NAS and fibrosis score, and cirrhosis. **Conclusion:** Depletion of MAP3K8 in Δ^{LysM} positive cells protected against ALD and MetALD by decreasing liver injury, inflammation, and fibrosis via activation of ERK phosphorylation, indicating that MAP3K8 could be a novel therapeutic avenue for the treatment of these liver diseases.

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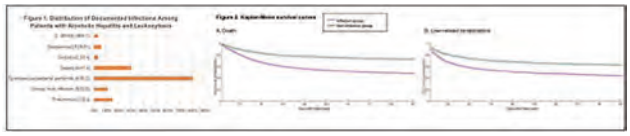
1578 | INFECTION AS A PREDICTOR OF MORTALITY AND DECOMPENSATION IN ALCOHOL-ASSOCIATED HEPATITIS WITH LEUKOCYTOSIS

Romelia Barba[1] Khawaja Hassam[2] Pojsakorn Danpanichkul[3] Ana Marenco-Flores[4] Natalia Rojas-Amaris[4] Denisse Rubio Cruz[4] Zeyad Elharabi[1] Gloria Erazo[1] Kanak Das[1] Hakan Akin[1], [1]Texas Tech University, [2]Lahey Hospital and Medical Center, [3]Texas Tech University Health Sciences Center, [4]Beth Israel Deaconess Medical Center

Background: Alcohol-associated hepatitis (AH) is a severe inflammatory liver condition often presenting with leukocytosis. While leukocytosis supports the diagnosis of AH, it may also signal a superimposed bacterial infection —a critical distinction, as corticosteroids, the only specific treatment for severe AH, are contraindicated in the presence of infection. Differentiating systemic inflammation from infection is clinically challenging, and misclassification may lead to inappropriate immunosuppression or delayed treatment. Despite this, limited large-scale data exist on the burden and prognostic implications of infection among AH patients with leukocytosis. We aimed to evaluate the prevalence and outcomes associated with infection in this high-risk population using a national real-world dataset. **Methods:** We conducted a retrospective cohort study using the TriNetX U.S. Collaborative Network, a federated EHR platform comprising 67 healthcare organizations. Adults ($\geq$18 years) with AH (ICD-10 K70.10 or K70.11) and leukocytosis (WBC $\geq$12 x10³/μL) between 2016–2025 were included. Patients were stratified by the presence or absence of documented infection (e.g., sepsis, pneumonia, spontaneous bacterial peritonitis [SBP], UTI) occurring within $\pm$2 days of AH diagnosis. Outcomes included 28- and 90-day all-cause mortality (primary), major adverse liver outcomes (hepatic encephalopathy, ascites, gastrointestinal bleeding, and hepatorenal syndrome), hepatorenal syndrome (HRS), and liver transplant (secondary). Kaplan-Meier and Cox proportional hazards analyses were performed. **Results:** Among 12,329 hospitalized patients with AH and leukocytosis, 5,334 (43.3%) had a documented infection. The most common infections were sepsis (30%), followed by pneumonia (15%), UTI (11%), and SBP (8%); less frequent infections included bacteremia (6%), cellulitis (3%), and C. *difficile* (3%) (Figure 1). At 28 days, AH patients with infection had significantly higher mortality (39.81% vs. 20.59%; HR 2.18, 95% CI 2.02-2.34, $p < 0.001$), a trend that persisted at 90 days (52.16% vs. 27.51%; HR 2.25, 95% CI 2.11–2.40, $p < 0.001$). Infection was also associated with higher rates of liver-related complications (46.45% vs. 29.81%; HR 1.78, 95% CI 1.67-1.89, $p < 0.001$), and ICU admission (40.42% vs. 14.03%; HR 3.46, 95% CI 3.19-3.75, $p < 0.001$) (Figure 2). Liver transplant rates were low and similar between groups (0.6% vs. 0.3%; HR 2.12, 95% CI 1.11-4.07, $p = 0.02$). **Conclusion:** Our findings showed that infection was present in over 40% of hospitalized AH patients with leukocytosis and was associated with significantly increased mortality and complications. The early excess in mortality among those with infection was especially notable.



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1579 | SIRPA$^{-/-}$ MICE DEVELOPED EXACERBATED ALCOHOL-ASSOCIATED HEPATITIS ASSOCIATED WITH EXCESSIVE INFLAMMATION

Josiah Hardesty[1] Rui Treves[1] Tyler Gripshover[1] Ashwani Singal[1], [1]University of Louisville

Background: Alcohol-associated hepatitis (AH) is a clinical manifestation of alcohol-associated liver disease (ALD) that has poor prognosis. Corticosteroids are a standard anti-inflammatory treatment used for AH patients; however, corticosteroids have limited efficacy in preventing disease progression. There is a need to

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identify new therapeutic targets and to improve the treatment options for AH patients. Signal regulatory protein alpha (SIRPa) is an immune cell receptor that regulates efferocytosis and inflammatory responses. SIRPa is cleaved by ADAM metallopeptidase domain 10 (ADAM10) and released into the plasma in inflammatory conditions but has not yet been studied in ALD. We hypothesized that *Sirpa*$^{-/-}$ mice would develop exacerbated AH and use of an ADAM10 inhibitor would restore immunological balance. **Methods:** WT and whole body *Sirpa*$^{-/-}$ male and female experimental mice were used in an experimental model of AH. Mice were fed an 5% ethanol (EtOH) diet for 11 days and injected with galactosamine (500 mg/kg) on days 9-11 to induce parenchymal necrosis. On day 11 mice received an oral gavage of EtOH (5 g/kg) and were euthanized 9 hours later followed by tissue collection, cryopreservation, and analysis. Mouse immune cells were assayed for inflammatory endpoints. **Results:** *Sirpa*$^{-/-}$ mice developed impaired liver function (reduced albumin) and enhanced liver injury (increased ALT), and exacerbated inflammation (increased liver TNFa and IL-1b). WT bone marrow-derived macrophages (BMDMs) treated with EtOH+lipopolysaccharide (LPS) had increased SIRPa release into the supernatant and elevated ADAM10 activity. Further, Mouse peripheral blood mononuclear cells (PBMCs) from *Sirpa*$^{-/-}$ mice had increased EtOH+LPS induced TNFa production but reduced IL-4 production *ex vivo*. In mouse PBMCs pretreated with an ADAM10 inhibitor (GI254023X), there was a reduction in EtOH+LPS induced SIRPa and TNFa release, but an increase in IL-4 *ex vivo*. **Conclusion:** Mice with ablated *Sirpa* developed exacerbated AH in this experimental ALD model. Pro-inflammatory cytokine production was higher in *Sirpa*$^{-/-}$ mice and immune cells. Treatment with an ADAM10 inhibitor reduced SIRPa shedding *ex vivo* and may be a potential therapeutic option. Future studies are required to identify how cleavage or loss of SIRPa expression contributes to AH pathogenesis.

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1580 | FECAL MICROBIOTA TRANSPLANT FROM SPECIFIC HUMAN DONORS REDUCE ALCOHOL PREFERENCE AND INTAKE IN CONVENTIONAL FEMALE MICE

Lauren May[1] Alexander Khoruts[2] Jennifer Wolstenholme[1] Jasmohan Bajaj[1], [1]Virginia Commonwealth University, [2]University of Minnesota

Background: Reducing alcohol consumption in patients with cirrhosis and alcohol use disorder (AUD) is critical to improve long-term prognosis. But current therapies have modest success. In a phase 1b trial, fecal microbiota transplant (FMT) from one donor reduced alcohol intake in men with cirrhosis, which was transmitted to germ-free (GF) male mice. However, we need to expand donor-recipient matching, use non-GF mice to ensure immune system integrity, and study females. Aim: Define impact of differing human FMT donors on alcohol consumption in conventional female mice. **Methods:** Adult female C57BL/6 mice (10-15 wks, n = 10-12/group) were treated with a course of antibiotics (ABX) prior to FMT administration to encourage FMT donor engraftment (Fig. A). The antibiotics were a cocktail of absorbable (ampicillin, cefoperazone & clindamycin hydrochloride) and non-absorbable (ertapenem, neomycin & vancomycin) ones that have been shown to allow engraftment in conventional mice. Three healthy human donor stools from a GMP facility were selected. These donors are in the pool for clinical human FMT studies. These stools were administered to female mice via gavage for 3 days and voluntary alcohol intake and preference were assessed for 4 weeks using the validated 2-bottle choice (2B-C) test. This test evaluates a weight-dependent (alcohol intake) and weight independent (preference) analysis of alcohol intake. Additional behavioral testing to measure locomotive and anxiety-like behaviors were also assessed using open-field test after FMT and during alcohol drinking sessions. We had 5 groups: no-ABX or control, ABX then PBS, and 3 groups of ABX followed by individual FMT donors (Donors 1, 2 or 3). **Results:** All mice tolerated ABX and subsequent FMT procedures. Following one week of FMT, alcohol intake and preference were decreased in mice following the FMT. Antibiotic treatment decreased alcohol intake and preference in all groups, however, FMT donor 1 further significantly decreased alcohol preference as compared to mice given antibiotics but no FMT. FMT donor 1 significantly reduced alcohol preference which peaked in weeks two and three, but was attenuated at the four week timepoint (Fig C/D). Alcohol intake showed a similar trend, but did not reach significance since administration of ABX slightly increased body weights in all groups (Fig B). Other behavioral tests: we report no changes in anxiety phenotypes or locomotor behavior following FMT engraftment or alcohol drinking. **Conclusion:** FMT from specific healthy humans resulted in reduced alcohol preference and intake in female conventional mice after a validated antibiotic pre-treatment protocol. This effect was restricted to stools from one donor but not the rest. The study provides a model for donor-recipient matching for human FMT studies using immunocompetent mice that include both sexes.

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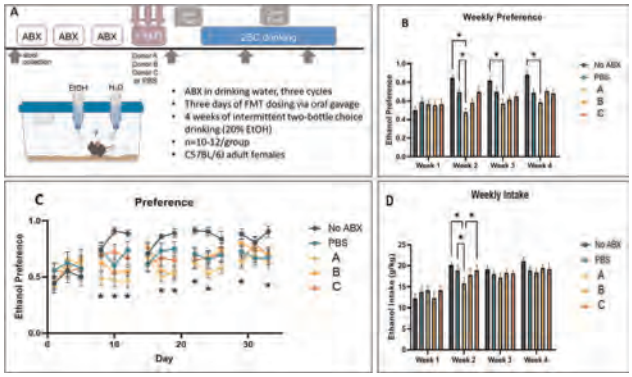

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1581 | PRIVATE INSURANCE AND A DIAGNOSIS OF ALCOHOL-ASSOCIATED HEPATITIS ARE ASSOCIATED WITH HIGHER PARTICIPATION IN VIRTUAL GROUP-BASED POST-LIVER TRANSPLANT RELAPSE PREVENTION THERAPY

Sasha Deutsch-Link[1] Sophia Hurr[1] Heather Gallagher[1] Ellen Green[2] Christian Hendershot[3] Marie-Josee Lynch[4] Daniel Velez[1] Hersh Shroff[1], [1]UNC Chapel Hill, [2]University of North Carolina, Chapel Hill, NC, USA, [3]Keck School of Medicine at USC, [4]University of Toronto

Background: Early liver transplant (LT) for alcohol-associated hepatitis (AAH) is associated with favorable outcomes in select patients with minimal abstinence prior to LT. As a result, there is a growing trend toward transplanting patients for alcohol-associated liver disease (ALD) with more severe alcohol use disorder (AUD), including some who have received little to no formal AUD treatment before LT. These patients are particularly likely to benefit from robust post-transplant AUD treatment; however, standardized treatment protocols in this setting remain limited. In response to this need, our center implemented a monthly group-based relapse prevention therapy (RPT) program for liver transplant recipients (LTRs) transplanted for ALD. This study examines patient-level factors associated with post-LT RPT participation. **Methods:** Our transplant center's psychosocial team contacted LTRs transplanted for ALD about their interest in a monthly virtual group-based RPT program. A licensed clinical addictions specialist (LCAS) completed individual assessments of each patient at enrollment. Monthly virtual counseling sessions were conducted by a LCAS. The RPT manual was previously developed by an external organ donation agency for use in LT candidates and modified for our center's purposes (with permission). Baseline chart review variables were collected via our center's electronic health record. A joint effects multivariable logistic regression assessed patient-level factors associated with group-based RPT attendance defined as attending at least 25% of counseling sessions. **Results:** Of 46 patients contacted, 19 (41%) decided to enroll, 14 (30%) attended at least one group counseling session, and 12 (26%) attended at least 25% of counseling sessions. 28 (61%) of patients were male and 33 (72%) were transplanted for alcohol-associated cirrhosis and 13 (28%) for AAH. A joint effects multivariable logistic regression model demonstrated that private insurance (OR 6.16, 95% CI 1.02-37.32) and a diagnosis of AAH (OR 6.78, 95% CI 1.30-35.43, compared to ALD cirrhosis) were associated with increased likelihood of RPT attendance. Alcohol relapse post-LT prior to intervention enrollment was associated with reduced RPT attendance (OR 0.13, 95% CI 0.01-1.67), but this did not reach statistical significance. (Table 1). **Conclusion:** In an era of rising LT for ALD in patients with higher-risk AUD profiles, optimizing post-LT AUD treatment is imperative. Our study demonstrated that a virtual monthly group-based RPT program was more likely to be attended by patients with private insurance and a diagnosis of alcohol-associated hepatitis; post-LT alcohol relapse may reduce participation. This study highlights the need for diverse treatment paradigms to meet the needs of patients who have relapsed ato alcohol post-LT, who are on public insurance, and with a pre-LT diagnosis of ALD cirrhosis.

Table 1. Patient-Level Factors Associated with Post-Liver Transplant Virtual Group-Based Relapse Prevention Therapy Attendance

Variable	Odds Ratio	P-Value	95% CI
Final/Reduced Model			
Private insurance	6.16	0.048	1.02-37.32
Alcohol-Associated Hepatitis	6.78	0.023	1.30-35.43
Alcohol relapse prior to intervention enrollment	0.13	0.118	0.01-1.67
Full Model			
Female gender	1.30	0.790	0.19-8.98
Age ≥ 50	1.24	0.862	0.11-14.34
Private insurance	12.24	0.044	1.08-139.20
Months post-LT	0.98	0.218	0.95-1.01
Alcohol-Associated Hepatitis	8.77	0.117	0.58-132.23
MELD 3.0 at LT	1.14	0.277	0.90-1.45
Pre-LT AUD treatment	0.62	0.722	0.05-8.34
Duration of abstinence pre-LT	1.02	0.167	0.99-1.05
Alcohol relapse prior to intervention enrollment	0.12	0.144	0.01-2.05

CI, confidence interval; LT, liver transplant.

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Christian Hendershot: Nothing to Disclose, Marie-Josee Lynch: Nothing to Disclose, Daniel Velez: Nothing to Disclose, Hersh Shroff: Nothing to Disclose

1582 | SPATIAL AND MOLECULAR PROFILING REVEALS DISTINCT IMMUNE AND FIBROTIC SIGNATURES IN MASLD/MASH VERSUS METABOLIC ALCOHOL-ASSOCIATED LIVER DISEASE (METALD)

Omar Saldarriaga[1] Esteban Arroyave[1] Timothy Wanninger[1] Monique Ferguson[1] Daniel Bao[1] Vincent Yang[1] Michael Kueht[1] Shi Ziyu[1] Zhiyuang Song[1] Haiqing Zhao[1] Heather Stevenson-Lerner[1], [1]University of Texas Medical Branch

Background: Recent updates in liver disease nomenclature have defined metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), along with a new classification—MetALD—for patients with MASLD who also exhibit excessive alcohol use. Despite these advances, the molecular and spatial mechanisms driving disease progression and heterogeneity in MetALD remain poorly understood. In particular, the impact of alcohol on the hepatic immune microenvironment in the setting of MASLD is underexplored. **Methods:** We performed a multi-modal analysis integrating publicly available single-cell RNA sequencing (scRNA-seq) data from controls and patients with MASH, MetALD, and ALD (total n = 46), alongside liver biopsy specimens from control individuals, patients with MASLD/MASH with minimal or advanced fibrosis, and MetALD with advanced fibrosis (total n = 44). Bulk gene expression was profiled using the NanoString nCounter PanCancer Immune panel. Spatial protein expression was assessed using multiplex immunofluorescence (CD163, CCR2, Galectin-3, Mac387, Cytoglobin, DAPI) and spectral imaging and AI-based algorithms for cell clustering and phenotypic mapping. **Results:** In MASLD/MASH, we observed enrichment of genes linked to T cell and dendritic cell recruitment and activation (e.g., CCL19, CXCL9, CCL5, ZAP70, TCF7, ITGAE, LCP1, CD74). Conversely, MetALD with advanced fibrosis showed elevated expression of genes promoting monocyte/macrophage recruitment (e.g., CCL2, CCL15, CXCL12, CXCL14), and a predominance of M2-like, anti-inflammatory, and profibrotic macrophages (e.g., NFKBIA, MSR1, F13A1, COL3A1, LGALS3, CD163). Spatial analysis confirmed regional enrichment of profibrotic immune cell populations and druggable protein targets. The public single-cell database results closely matched those obtained from liver biopsies analyzed at our institution. **Conclusion:** MASLD/MASH and MetALD are characterized by distinct immune and fibrotic molecular profiles, with MetALD shifting toward macrophage-dominant, fibrogenic responses. These findings underscore the heterogeneous nature of steatotic liver diseases and identify potential spatially resolved, druggable targets that may inform precision therapeutic strategies. Notably, findings from the public single-cell RNA-seq dataset mirrored those from liver biopsies analyzed at our institution using a smaller, cost-effective, and clinically scalable gene panel.

Disclosures: Omar Saldarriaga: Nothing to Disclose, Esteban Arroyave: Nothing to Disclose, Timothy Wanninger: Nothing to Disclose, Monique Ferguson: Nothing to Disclose, Daniel Bao: Nothing to Disclose, Vincent Yang: Nothing to Disclose, Michael Kueht: Nothing to Disclose, Shi Ziyu: Nothing to Disclose, Zhiyuang Song: Nothing to Disclose, Haiqing Zhao: Nothing to Disclose, Heather Stevenson-Lerner: Nothing to Disclose

1583 | AREA-LEVEL DEPRIVATION STRONGLY CONTRIBUTES TO DISPARITIES IN ACCESS TO LIVER TRANSPLANTATION AND OUTCOMES AMONG PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS: RESULTS: FROM A PROSPECTIVE MULTICENTER STUDY

Lauren Nephew[1] Thomas Cotter[2] Ashwani Singal[3] Juan Pablo Arab[4] Jaideep Beharry[5] Qing Tang[6] Samer Gawrieh[7] Wanzhu Tu[7] Naga Chalasani[8], [1]Indiana University, [2]UT Southwestern Medical Center, [3]University of Louisville, [4]Virginia Commonwealth University, [5]University of Pittsburgh Medical Center, [6]Departmen tof Biostatitics & Health Data Science, Indiana University School of Medicine, [7]Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of, [8]Indiana University Medical Center

Background: Severe alcohol-associated hepatitis (sAH) is a life-threatening manifestation of alcohol-related liver disease and a growing indication for liver transplantation (LT). While early LT can be life-saving, access remains inequitable. Most prior studies are retrospective and lack detailed data on social determinants of health (SDOH), which may disproportionately impact LT access in the time-sensitive context of sAH. We aimed to evaluate how clinical severity and SDOH jointly influence access to LT and short-term survival in a prospective multicenter cohort. **Methods:** We performed a secondary analysis of data from a prospective, multi-center observational study of 325 patients hospitalized with sAH (MELD ≥20) across five sites in the

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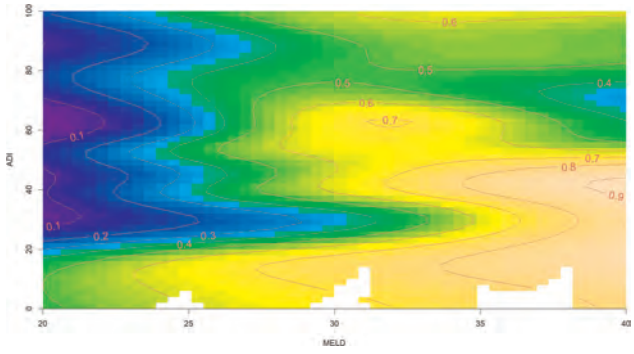
Alcoholic Hepatitis Network (AlcHepNet). Demographic, clinical, and SDOH data, including the Area Deprivation Index (ADI), were collected at baseline. Outcomes included referral, waitlisting, transplant receipt, and 180-day mortality. We used generalized additive models (GAMs) with a logit link function to evaluate factors associated with each outcome and interactions between disease severity (MELD) and neighborhood disadvantage (ADI). **Results:** The study cohort had a mean age of 44.8 years, comprised 39.4% females, 9.2% Black individuals, and 12.0% Hispanic individuals, with a high disease and social burden (mean MELD 29.2; ADI 56.2). Only 37% of patients were referred for LT, with marked attrition throughout the transplant cascade. MELD scores were higher in those referred (OR 1.13, 95% CI: 1.07–1.18), waitlisted (OR 1.10, 95% CI: 1.02–1.18), and transplant recipients (OR 1.24, 95% CI: 1.07–1.44). Higher ADI was associated with lower odds of waitlisting (OR 0.98, 95% CI: 0.96–1.00, $p = 0.017$) and trended toward lower referral (OR 0.99 per point, 95% CI: 0.97–1.00, $p = 0.059$). In GAMs, MELD × ADI interactions were significant for referral ($p = 0.014$), waitlisting ($p = 0.004$), and mortality ($p = 0.01$), with the largest effects at MELD 20–30. For example, referral probability ranged from 10% at ADI > 80 to 50% at ADI < 20 (Figure 1). Overall, 180-day mortality was 25.5%; among patients with MELD < 30, predicted mortality doubled from 20% at ADI < 20 to > 40% at ADI > 80. Figure 1 Estimated probability of referral by MELD score and ADI. This contour plot shows referral probability by MELD and ADI. Warmer colors indicate higher probability; cooler colors indicate lower. Probability increases with MELD but drops with higher ADI, especially at MELD 20–30. Contour labels show estimated probabilities. **Conclusion:** Both clinical severity and social disadvantage contribute to disparities in LT access and outcomes among patients with sAH. Given a quarter of patients died within 180 days, timely referral is critical for survival. These findings suggest the need for care pathways that explicitly incorporate social determinants of health to promote equitable access to LT.



Disclosures: Lauren Nephew: NovoNordisk: Consultant, Thomas Cotter: Nothing to Disclose, Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, GSK: Grant/Research Support, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, Avera Medical Group: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other, Juan Pablo Arab: Nothing to Disclose, Jaideep Beharry: Nothing to Disclose, Qing Tang: Nothing to Disclose, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, Wanzhu Tu: Nothing to Disclose, Naga Chalasani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose

1584 | SARCOPENIA AND ALCOHOL-ASSOCIATED LIVER DISEASE: INFLUENCE ON INPATIENT OUTCOMES &MDASH; A NATIONWIDE COHORT ANALYSIS

Carla Barberan Parraga[1] Talal Bhatti[2] Kundan Jana[1] Nicole Villa[3] Leandro Sierra[4] Marwan Alsaqa[5] James Park[2] Shirley Eng[2] Sanjaya Satapathy[2], [1]Maimonides Medical Center, [2]NorthWell Health, [3]NYMC Metropolitan Hospital, [4]Cleveland Clinic Foundation, [5]BIDMC Harvard Medical School

Background: Sarcopenia, defined as the loss of skeletal muscle mass and function, is an established predictor of poor outcomes in cirrhotic patients. However, its impact among patients with alcohol-associated liver disease (ALD) without cirrhosis remains underexplored. This study aims to evaluate the influence of sarcopenia on inpatient outcomes in a nationally representative cohort of hospitalized ALD patients. **Methods:** Using the National Inpatient Sample (2016–2021), we identified adult patients (≥ 18 years) with ALD using ICD-10 codes. Patients were stratified based on the presence or absence of sarcopenia. Survey-weighted methods accounted for complex survey design. Categorical and continuous variables were analyzed using Rao–Scott chi-square and Student's t-tests, respectively. Logistic regression models (univariate and multivariate) assessed associations between sarcopenia and inpatient outcomes, adjusting for relevant covariates ($p < 0.1$ in univariate analysis). Statistical significance was defined as $p < 0.05$. Data extraction was performed in Python (v3.9.1) and statistical analysis in R (v3.6.2). **Results:** A total of

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30,860 hospitalized patients with ALD were included. Baseline characteristics were comparable between sarcopenic and non-sarcopenic patients: predominantly non-Hispanic white (62.6% vs. 65.9%), male (65.7% vs. 61.5%), under age 50 (40.0% vs. 37.4%), and Medicaid-insured (41.3% vs. 38.3%). Sarcopenic patients had significantly longer hospital stays (mean 21.3 vs. 12.5 days, $p < 0.001$) and higher hospitalization costs ($380,310 vs. $193,526, $p < 0.001$). On multivariate analysis, sarcopenia was independently associated with increased odds of vasopressor use (OR 1.02; 95% CI, 1.01–1.04; $p = 0.02$), acute kidney injury (OR 1.06; 95% CI, 1.03–1.09; $p < 0.001$), and need for hemodialysis (OR 1.07; 95% CI, 1.05–1.09; $p < 0.001$). Interestingly, sarcopenia was associated with slightly reduced in-hospital mortality (OR 0.97; 95% CI, 0.95–0.99; $p = 0.03$) and was not significantly associated with mechanical ventilation (OR 1.02; 95% CI, 0.99–1.04; $p = 0.20$). **Conclusion:** In patients hospitalized with ALD, sarcopenia is associated with significantly increased healthcare utilization, including longer length of stay, higher costs, and greater risk of inpatient complications such as vasopressor requirement, acute kidney injury, and dialysis. These findings underscore the clinical relevance of sarcopenia as a prognostic marker in ALD, even in the absence of cirrhosis, and highlight the need for early detection and targeted interventions to mitigate adverse outcomes.

Table 1. Comparison of Inpatient Characteristics and Outcomes in Alcohol-Associated Liver Disease (ALD) Patients With and Without Sarcopenia

Variable	Sarcopenia	No Sarcopenia	OR (95% CI)	p-value
Demographics				
Non-Hispanic White (%)	62.6	65.9	—	NS
Male (%)	65.7	61.5	—	NS
Age < 50 years (%)	40.0	37.4	—	NS
Medicaid Insurance (%)	41.3	38.3	—	NS
Inpatient Outcomes				
Mean Length of Stay (days)	21.3	12.5	—	<0.001
Mean Hospitalization Cost ($)	$380,310.90	$193,526.05	—	<0.001
Vasopressor Use (%)	Higher	Reference	1.02 (1.01–1.04)	0.02
Acute Kidney Injury (%)	Higher	Reference	1.06 (1.03–1.09)	<0.001
Hemodialysis Requirement (%)	Higher	Reference	1.07 (1.05–1.09)	<0.001
In-hospital Mortality (%)	Lower	Reference	0.97 (0.95–0.99)	0.03
Mechanical Ventilation (%)	No difference	Reference	1.02 (0.99–1.04)	0.20

Abbreviations: OR = Odds Ratio; CI = Confidence Interval; NS = Not Significant

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1585 | CALPAIN INHIBITION ATTENUATES EXPERIMENTAL ALCOHOL-INDUCED LIVER INJURY THROUGH REGULATION OF CHOLESTEROL METABOLISM

Noriko Kitano[1] Jiang Li[1] Charis-Marie Vanderpuye[1] Pooja Muddasani[1] Yekaterina Krutsenko[1] Hamda Siddiqui[1] Samuel Taborski[1] Juliane Beier[1] Gavin Arteel[1], [1]University of Pittsburgh

Background: Alcohol-related liver disease (ALD) represents a significant global health burden with limited therapeutic options. Ethanol consumption disrupts hepatic homeostasis, resulting in fatty liver development in most ALD patients. Recent evidence suggests that calpain, a calcium-dependent protease family, plays a critical role in liver inflammation and fibrosis. Calpain activity is primarily controlled by its essential modulatory subunit, calpain-4 (Capn4), which stabilizes and governs catalytic isoforms calpain-1 and calpain-2. **Methods:** To investigate calpain's influence on ethanol-induced liver injury, six-week-old male C57Bl6/J mice were injected with rAAV8 vectors encoding either Capn4-specific shRNA or control vectors, with transgene expression driven by the hepatocyte-specific TBG promoter. After four weeks, mice underwent a 10-day chronic-plus-binge ethanol feeding protocol with a single ethanol gavage on day 11. Liver tissues and blood samples were analyzed for histological, biochemical, and gene expression changes. **Results:** Capn4 knockdown significantly ameliorated ethanol-induced microvesicular steatosis. While triglyceride and free fatty acid levels showed no significant alterations, cholesterol levels were markedly reduced in ethanol-exposed mice with Capn4 knockdown. Mechanistically, Capn4 silencing upregulated expression of NR1H3 (encoding LXRα), ABCA1, ABCG1, and CPT1, suggesting enhanced cholesterol efflux and fatty acid oxidation. Western blot analysis revealed an increased ratio of cleaved-HMGCR to pro-HMGCR in Capn4 knockdown mice, indicating reduced HMG-CoA reductase activity and suppressed cholesterol biosynthesis. While ethanol exposure primarily increased cytoplasmic NR1H3 expression, Capn4 knockdown promoted its nuclear relocalization, consistent with functional LXRα activation. **Conclusion:** This study identifies a previously unrecognized link between calpain activity and cholesterol metabolism in ALD pathogenesis. Calpain inhibition mitigates ethanol-induced lipid accumulation primarily through modulation of cholesterol metabolism

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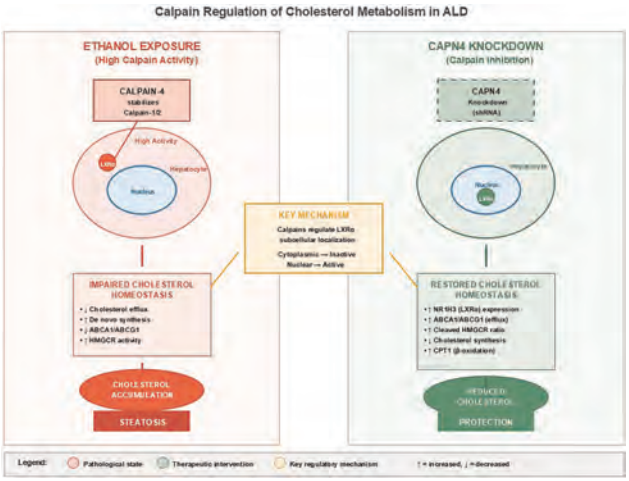
rather than effects on triglycerides or free fatty acids. The beneficial effects involve LXRα activation, enhanced cholesterol efflux, and reduced de novo cholesterol synthesis. These findings provide a mechanistic rationale for exploring calpain inhibitors as a therapeutic approach for alcohol-related hepatitis.



Disclosures: Noriko Kitano: Nothing to Disclose, Jiang Li: Nothing to Disclose, Charis-Marie Vanderpuye: Nothing to Disclose, Pooja Muddasani: Nothing to Disclose, Yekaterina Krutsenko: Nothing to Disclose, Hamda Siddiqui: Nothing to Disclose, Samuel Taborski: Nothing to Disclose, Juliane Beier: Nothing to Disclose, Gavin Arteel: Nothing to Disclose

1586 | THE USE OF WEARABLE ALCOHOL MEASUREMENT DEVICES INCREASES PRECISION OF ALCOHOL INTAKE ACCESSMENT IN PATIENTS WITH ALCOHOL-ASSOCIATED HEPATATIS

Ekaterina Smirnova[1] Albert Arias[1] Juan Pablo Arab Verdugo[1] Amon Asgharpour[1] Sara O'Connor[1] Frederick Moeller[1] Arun Sanyal[1], [1]Virginia Commonwealth University

Background: Alcohol-associated liver disease (AALD) has risen sharply in the last decades and became the leading cause of liver-related morbidity and mortality. Alcohol intake is one of the major factors leading to progression of AALD. However, accurate assessment of the amount, duration and time of alcohol intake is challenging due to unreliable self-reports and inability to frequently administer alcohol biomarkers in the everyday living environment. AIMS: (1) To establish validity of real-time alcohol measurement using wrist-worn alcohol detection devices in AALD patients; (2) To improve the detection of drinking episodes over the self-reported ecological momentary assessment (EMA). **Methods:** The study consisted of n = 13 patients with AALD followed daily over a period of 60 days. The alcohol intake was monitored using BACtrack Skyn Transdermal Alcohol Concentration (TAC) wrist-worn biosensor that measures alcohol concentration in the skin. Self-reported alcohol intake was assessed by EMA using phone app daily questions. Drinking episodes were detected using TAC peak values > 15mg of alcohol per liter (mg/L) in the 30-min centered average smoothed TAC data. **Results:** Among n = 13 participants, 11 had at least 1 day of alcohol sensor data, and 5 had matching dates of alcohol sensor and EMA data. Among 5 participants with complete alcohol sensor and EMA data, 3 self-reported at least one drinking episode. Among a total of 32 self-reported drinking days in these 3 participants, 21 were detected by the alcohol sensor. Additionally, n = 26 days of alcohol consumption were detected by the sensor out of n = 31 days when these participants did not self-report drinking episodes. **Conclusion:** Wearable alcohol biosensor was able to detect more than 65 % of reported episodes and additional unreported drinking episodes. These data support further validation efforts to further refine its performance as a tool to be used in clinical trials and in the management of alcohol related disorders.

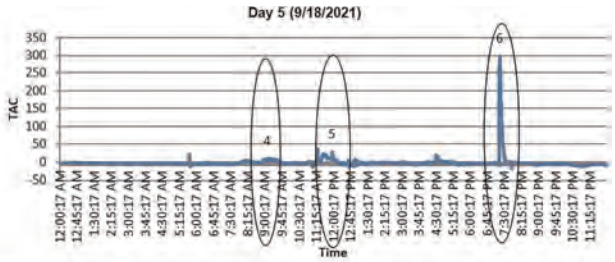


Figure 1. Alcohol intake episodes detected by the alcohol biosensor over one day (Day 5 in the study) for one study participant. Three peak values of Transdermal Alcohol Concentration (TAC) concentration (y-axis) annotated by the 3 ovals are indicate 3 drinking episodes for this day.

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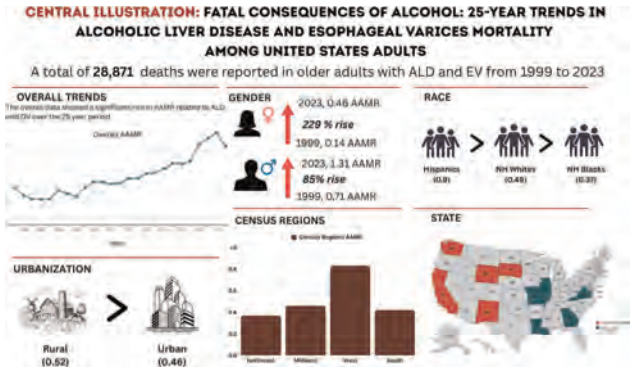
1587 | FATAL CONSEQUENCES OF ALCOHOL: 25-YEAR TRENDS IN ALCOHOLIC LIVER DISEASE AND ESOPHAGEAL VARICES MORTALITY AMONG UNITED STATES ADULTS

Simran Joshi[1] Muhammad Faizan[2] Husnain Ahmad[3] Sushrut Ingawale[4] Muhammad Khan[5] Jeevin Sandhu[6] Matthew Manoj[7] Marquise Soto[8] Muhammad Usman Arshad[3] Muhammad Shees Hunain[3] Corinne Caissie[1] Akshay Sharma[9] Salman Attari[10] Saman Javaid[11] Sherif Eltawansy[12] Charitha Karanam Ramapathy[13] Cheng-Hung Tai[14] Mohammad Islam[1], [1]Yale New Haven Health/Yale University School of Medicine, [2]Jinnah Postgraduate Medical Center, [3]Shalamar medical and dental college, [4]Quinnipiac University - Frank H Netter MD School of Medicine, [5]Bacha Khan Medical College, [6]Methodist Dallas Medical Center, [7]Beth Israel Deaconess Medical Center/Harvard Medical School, [8]Massachusetts General Hospital/Harvard Medical School, [9]Luminis Health/Anne Arundel Medical Center, [10]Asian Institute of Medical Sciences, [11]CMH Kharian Medical College, [12]Jersey Shore University Medical Center, [13]UAB Montgomery program/ Heersink school of Medicine, [14]Yale New Haven Health/Yale School of Medicine

Background: Alcoholic liver disease (ALD) and esophageal varices (EV) frequently coexist as complications of progressive liver dysfunction, yet national trends in comorbid ALD–EV mortality remain poorly defined. This study evaluates 25-year mortality patterns among U.S. adults with coexisting ALD and EV, highlighting demographic and regional disparities to inform targeted public health interventions. **Methods:** Mortality data from the CDC WONDER database (1999–2023) were analyzed using Joinpoint regression to assess ALD and EV-related deaths among U.S. adults aged 25 and older. Age-adjusted mortality rates (AAMRs) per hundred thousand were calculated, along with the average annual percent change (AAPC) and corresponding 95% confidence intervals (CI). **Results:** ALD among individuals with EV accounted for 28,871 deaths over 25 years. Between 1999 and 2023, the overall AAMR surged from 0.39 to 0.83, indicating a percent increase of 112.8%, with a staggering AAPC of 3.82 (95% CI: 2.80–5.97, $p < 0.000001$). Males consistently exhibited higher mortality rates than females (AAMR: 0.83 vs. 0.22); however, the trajectory of increase was steeper in females (AAPC: 5.40, 95% CI: 4.16–8.28, $p < 0.000001$) compared to males (AAPC: 3.08, 95% CI: 2.35–4.75, $p < 0.000001$). Among racial groups, Hispanics had the highest AAMR (0.90) followed by Non-Hispanic (NH) Whites (0.49) and NH Blacks (0.37). NH White individuals experienced the sharpest rise (AAPC: 4.56, 95% CI: 3.58–6.37, $p < 0.000001$), followed by Hispanic or Latino populations (AAPC: 1.43, 95% CI: 0.42–3.22, $p = 0.007998$). The highest AAMR was documented in the West (0.83), followed by the Midwest (0.45) and the South (0.42). However, the Northeast saw the most pronounced increase (AAPC: 5.41, 95% CI: 4.45–6.57, $p < 0.000001$), followed by the Midwest (AAPC: 4.98, 95% CI: 3.71–7.20, $p < 0.000001$), where the states with the highest AAMRs were South Dakota (0.98), North Dakota (0.70), and the Nebraska (0.60). Rural areas exhibited slightly higher AAMRs than urban areas (0.52 vs. 0.46), and the mortality trajectory was also steeper in rural populations (AAPC: 4.07, 95% CI: 2.74–6.32, $p < 0.000001$) compared to urban areas (AAPC: 2.85, 95% CI: 1.77–4.35, $p < 0.000001$). Age-stratified analysis revealed that individuals aged ≥ 65 years bore the highest mortality burden, with an AAPC of 4.86 (95% CI: 3.77–6.46, $p < 0.000001$), significantly outpacing the rise observed in the 45-64 years (AAPC: 4.64, 95% CI: 4.07–5.43, $p < 0.000001$) and 25-44 years (AAPC: 3.45, 95% CI: 2.17-5.82, $p < 0.000001$). **Conclusion:** ALD and EV-related mortality has escalated over the past 25 years, with the most notable increases seen in females, individuals aged ≥ 65 years, NH Whites, rural areas, and the Northeast region.These disparities emphasize the urgent need for targeted interventions to address the growing mortality burden, especially among vulnerable populations.



Disclosures: Simran Joshi: Nothing to Disclose, Muhammad Faizan: Nothing to Disclose, Husnain Ahmad: Nothing to Disclose, Sushrut Ingawale: Nothing to Disclose, Muhammad Khan: Nothing to Disclose,

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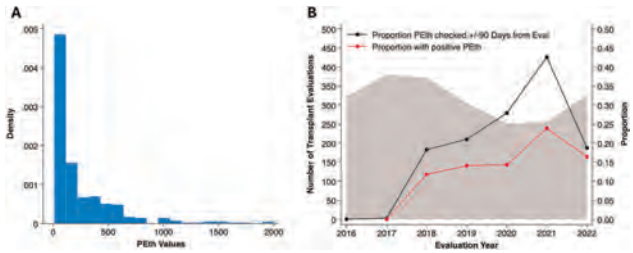
1588 | TRENDS IN PHOSPHATIDYLETHANOL TESTING FOR LIVER TRANSPLANT EVALUATION

Natalia Salinas Parra[1] Marina Serper[2] Nadim Mahmud[1], [1]Hospital of the University of Pennsylvania, [2]University of Pennsylvania Health System

Background: Phosphatidyethanol (PEth) is a highly sensitive direct serum biomarker for quantifying and assessing alcohol use in patients. Accurate identification of alcohol use is valuable in liver transplant evaluation and especially useful in situations where self-reported alcohol use can be unreliable. We aimed to evaluate trends in PEth monitoring at our institution over time surrounding initial liver transplant evaluation. **Methods:** This retrospective cohort study identified adult patients evaluated for liver transplant at the Hospital of the University of Pennsylvania between 1/2016 and 12/2022. Data was extracted on whether PEth testing was performed within +/- 90 days of the transplant evaluation date. Linear regression analysis was performed to assess temporal trends in the proportion of patients checked for PEth levels each evaluation year. **Results:** A total of 3,330 patients underwent liver transplant evaluations during the study time period. Of these patients, 896 (26.9%) had PEth testing checked, with 195 (21.8%) resulting in positive tests. In this cohort, the median PEth level was 214 ng/mL (IQR: 26, 239; Figure panel A), corresponding with heavy alcohol consumption. Over this period, there was a significant increase in the proportion of patients with PEth testing per year ($\beta = 0.054$, 95% CI 0.003-0.104, $p = 0.04$). The proportion of PEth positive patients also showed a significant upward trend over time ($\beta = 0.038$, 95% CI 0.008-0.059, $p = 0.02$; Figure panel B). **Conclusion:** At our large transplant center, descriptive data show rising rates of PEth checks over time. Notably, there is a rising rate of positive PEths around the time of evaluation, with almost a quarter of patients testing positive. This may suggest that PEth checks should be employed even more routinely as they may detect surreptitious alcohol use that could significantly impact transplant candidacy.



Disclosures: Natalia Salinas Parra: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Eurofins: Grant/Research Support, Nadim Mahmud: Grifols: Grant/Research Support

1589 | MORTALITY AND HEPATIC OUTCOMES OF SGLT2 INHIBITORS IN PATIENTS WITH ALCOHOLIC CIRRHOSIS, OBESITY, AND DIABETES: A GLOBAL COHORT STUDY

Mohamad Mahdi Osman[1] Mohamad-Noor Abu-Hammour[1] Walid Hazem[2] Leandro Sierra[1] Omar Sims[1] Dian Chiang[3], [1]Cleveland Clinic Foundation, [2]University Hospitals, [3]Cleveland Clinic

Background: Sodium-glucose co-transporter 2 inhibitors (SGLT2-i) are guideline-recommended therapies for patients with type 2 diabetes mellitus (T2DM) and obesity, with emerging benefits in cardiorenal protection. However, their safety and efficacy in patients with advanced liver disease—particularly alcoholic cirrhosis—remain poorly defined. Given the growing burden of metabolic comorbidities in this population, we aimed to evaluate the impact of SGLT2-i use on clinical outcomes in patients with alcoholic cirrhosis, coexisting T2DM, and obesity. **Methods:** Using the TriNetX research network, we identified adult patients with alcoholic cirrhosis, T2DM, and obesity who were prescribed SGLT2-i. Patients were divided into two cohorts: those prescribed SGLT2-i and those with no SGLT2-i use. Propensity score matching (1:1) was performed based on demographics, liver function tests, MELD components, and cardiometabolic comorbidities. Clinical outcomes were assessed using time-to-event analysis. The primary outcome was all-cause mortality. Secondary outcomes included all-cause hospitalizations, spontaneous bacterial peritonitis (SBP), ascites, and variceal bleeding. **Results:** After matching, SGLT2-i use was associated with a significantly lower risk of all-cause mortality [HR 0.769; 95% CI 0.719–0.823; $p < 0.0001$], all-cause hospitalizations [HR 0.937; 95% CI 0.900–0.976; $p < 0.0001$], incidence of ascites [HR

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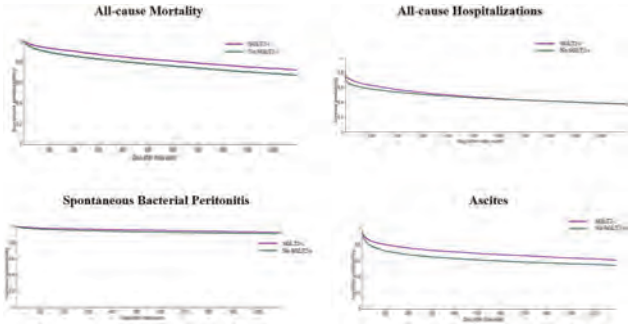
0.755; CI 0.716–0.795; p < 0.0001, and incidence of SBP [HR 0.728; 95% CI 0.636–0.833; p = 0.0008] (Figure 1). There was an associated reduction in variceal bleeding, though it did not show statistical significance. **Conclusion:** In this large real-world cohort, SGLT2-i use was associated with improved survival and lower hospitalization rates in patients with alcoholic cirrhosis, T2DM, and obesity. Additionally, SGLT2-i use correlated with significantly reduced risk of SBP and ascites and a favorable trend toward fewer variceal bleeding events. These findings support the potential utility of SGLT2-i in this high-risk population and warrant prospective evaluation to confirm safety and long-term benefit in cirrhosis management.



Disclosures: Mohamad Mahdi Osman: Nothing to Disclose, Mohamad-Noor Abu-Hammour: Nothing to Disclose, Walid Hazem: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Omar Sims: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Dian Chiang: Ipsen: Advisor

1590 | A DEADLY COMBINATION? EXPLORING THE BURDEN OF SEPTICEMIA IN PATIENTS WITH ALCOHOLIC LIVER DISEASE IN THE UNITED STATES (1999–2023)

Simran Joshi[1] Muhammad Ali[2] Matthew Manoj[3] Husnain Ahmad[4] Susan Feldman[5] MANJEET GOYAL[6] Muhammad Khan[7] Muhammad Hermain Amin[4] Jeevin Singh[8] Corinne Caissie[1] Muhammad Abdullah[4] Salman Attari[9] Saman Javaid[10] Sherif Eltawansy[11] Susan Feldman[5] Mohammad Islam[1] Cheng-Hung Tai[1], [1]Yale New Haven Health/Yale University School of Medicine, [2]Jinnah Postgraduate Medical Center, [3]Beth Israel Deaconess Medical Center/Harvard Medical School, [4]Shalamar Medical and Dental College, [5]University of South Carolina/Prisma Health, [6]Cleveland Clinic/Akron, [7]Bacha Khan Medical College, [8]Methodist Dallas Medical Center, [9]Asian Institue of Medical Sciences, [10]CMH Kharian Medical College, [11]Jersey Shore University Medical Center

Background: Alcoholic liver disease (ALD), a consequence of chronic alcohol consumption, compromises hepatic immune function, rendering patients more vulnerable to systemic infections. Among these, septicemia stands out as a critical cause of acute deterioration and death. The impaired host defense in ALD may predispose individuals to sepsis at a higher rate than the general population, yet national trends exploring this intersection remain under-investigated. In this study, we analyze mortality trends from 1999 to 2023 to assess whether adults with ALD are experiencing a disproportionate burden of septicemia-related deaths, while also exploring demographic and regional disparities across the United States. **Methods:** Mortality data from CDC WONDER (1999–2023) were analyzed using Joinpoint regression to evaluate ALD- and septicemia-related deaths in U.S. adults aged 25+. Age-adjusted mortality rates (AAMRs) per 100,000 and average annual percent change (AAPC) with 95% confidence intervals were calculated. **Results:** Sepsis among individuals with ALD accounted for 58,728 deaths over 25 years. Between 1999 and 2023, the overall AAMR surged from 0.49 to 1.75 per hundred thousand, with a staggering AAPC of 6.67 (95% CI: 5.97–8.45, $p < 0.000001$). Males consistently exhibited higher mortality rates than females (AAMR: 1.42 vs. 0.66); however, the trajectory of increase was steeper in females (AAPC: 7.83, 95% CI: 7.33–8.78) compared to males (AAPC: 5.82, 95% CI: 5.22–7.21,), both with $p < 0.000001$. Among racial groups, Hispanics had the highest AAMR (1.61) followed by Non-Hispanic (NH) Whites (0.97) and NH Blacks (0.83). NH White individuals experienced the sharpest rise (AAPC: 6.10, 95% CI: 5.39–7.39, $p < 0.000001$), followed by Hispanic or Latino populations (AAPC: 4.43, 95% CI: 3.91–5.24, $p < 0.000001$). The West saw the most pronounced increase (AAPC: 6.72, 95% CI: 5.85–7.93, $p < 0.000001$), followed by the Midwest (AAPC: 6.37, 95% CI: 5.52–7.87, $p < 0.000001$), where the states with the highest AAMRs were South Dakota (5.26), North Dakota (2.98), and Minnesota (1.85). Urban areas exhibited slightly higher AAMRs than rural areas (0.96 vs. 0.93), but the mortality trajectory was steeper in rural populations (AAPC: 7.91, 95% CI: 6.93–9.19, $p < 0.000001$) compared to urban areas (AAPC: 6.87, 95% CI: 6.24–7.84,$p < 0.000001$). Individuals aged ≥ 65 years bore the highest mortality burden, with an AAPC of 4.86 (95% CI: 3.77–6.46, $p <$ 0.000001), significantly outpacing the rise observed in the 45-64 years (AAPC: 4.64, 95% CI: 4.07–5.43) and 25-44 years (AAPC: 3.45, 95% CI: 2.17-5.82). **Conclusion:** ALD and sepsis-related mortality has escalated over the past 25 years, with the most notable increases seen in females, NH Whites, the West, rural areas and

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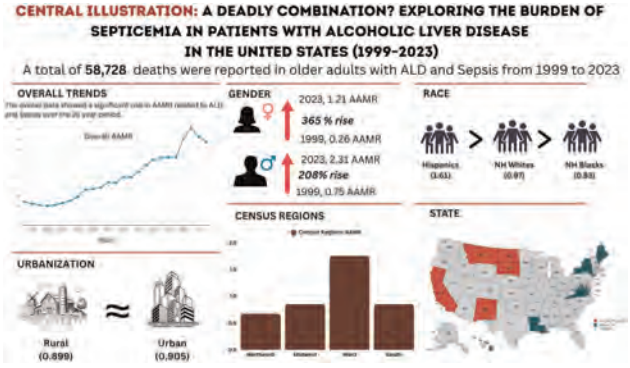
older adults. These disparities emphasize the urgent need for targeted interventions to address the growing mortality burden, especially among vulnerable populations.



Disclosures: Simran Joshi: Nothing to Disclose, Muhammad Ali: Nothing to Disclose, Matthew Manoj: Nothing to Disclose, Husnain Ahmad: Nothing to Disclose, Susan Feldman: Nothing to Disclose, Nothing to Disclose, MANJEET GOYAL: Nothing to Disclose, Muhammad Khan: Nothing to Disclose, Muhammad Hermain Amin: Nothing to Disclose, Nothing to Disclose, Jeevin Singh: Nothing to Disclose, Corinne Caissie: Nothing to Disclose, Muhammad Abdullah: Nothing to Disclose, Salman Attari: Nothing to Disclose, Nothing to Disclose, Saman Javaid: Nothing to Disclose, Sherif Eltawansy: Nothing to Disclose, Susan Feldman: Nothing to Disclose, Nothing to Disclose, Mohammad Islam: Nothing to Disclose, Cheng-Hung Tai: Nothing to Disclose

1591 | ONE FIFTH OF INDIVIDUALS HAVING ALCOHOL USE DISORDER ARE SARCOPENIC

Chittaranjan Panda[1] Sananda Kumar Sethi[2] Rakesh Mohanty[2] Prajna Anirvan[2], [1]S. C. B. Medical College, Cuttack, Odisha, India, [2]S.C.B. Medical College, Cuttack, Odisha, India

Background: Sarcopenia in patients with Alcohol Use Disorder (AUD) without cirrhosis of liver or other risk factors is often underdiagnosed. Given the limited literature on this subject both globally and within India, we conducted this study to determine the prevalence of sarcopenia in individuals with AUD, identify associated risk factors, and evaluate the diagnostic accuracy of various assessment modalities for sarcopenia in this population. **Methods:** 200 consecutive patients diagnosed with AUD without liver cirrhois or other risk factors for sarcopenia were enrolled. The assessment of sarcopenia was carried out using the EWGSOP2 criteria. Initial screening was performed using the SARC-F questionnaire. Muscle strength, muscle mass and physical performance were measured by handgrip strength (HGS), CT-Skeletal Muscle Index (SMI) and gait speed of a 4-meter walk test (4MWT). Emerging modality like B-mode ultrasound measurement of rectus femoris muscle thickness (USG-MTRF) using the LOGIQ e device, was also employed and recorded in centimeters. **Results:** Sarcopenia was observed in 41 patients (20.5%), while severe sarcopenia was identified in 13 patients (6.5%). Significant association was found between sarcopenia and severity of AUD ($p = 0.02$); prevalence of sarcopenia increased with AUD severity; 7.92% (8/101) in mild AUD, 19.64% (11/56) in moderate AUD, 48.83% (21/43) in severe AUD. No significant association was observed between sarcopenia and gender, age, type of alcohol consumed. Sarcopenic patients had significantly higher mean alcohol intake (452.01 $\pm$ 101.47 g/wk vs 346.29 $\pm$ 68.90 g/wk,non-sarcopenic patients, $p = 0.05$). Mean daily caloric intake (1943.90 $\pm$ 545.45 kcal vs. 2215.1 $\pm$ 668.85 kcal;$p = 0.01$) and daily protein intake (33.29 $\pm$ 5.65 g vs. 36.03 $\pm$ 7.62 g, $p = 0.03$) were significantly lower. Significant negative correlation was noted between amount of alcohol consumption and SMI and HGS(-0.382 and -0.389, respectively;$p \leq 0.05$). No significant correlation was found between alcohol intake and physical performance (4MWT). SMI demonstrated the highest accuracy (sensitivity-95.12%, specificity-89.31%).USGMTRF had a sensitivity of 82.93% and specificity of 70.44%. Mid-arm circumference (MAC) also showed a sensitivity of 65.85% and specificity of 82.39%. SARC-F questionnaire was found to have a sensitivity of 90.24% sensitivity and specificity of 71.07%. Low physical activity level increased the risk of sarcopenia by 10.37 times, higher alcohol intake (> 210 g/week) increased this risk by 1.1 times and severe AUD increased this risk by 11.56 times in regression analysis. **Conclusion:** Sarcopenia among individuals with AUD was even higher than already reported general adult population (10.1%) and even the elderly population (14.2%–15.2%) in India. Its occurence increases with the severity of AUD. Skeletal muscle ultrasound was observed to be a simple and effective tool for quantifying muscle mass in this population.

Disclosures: Chittaranjan Panda: Nothing to Disclose, Sananda Kumar Sethi: Nothing to Disclose, Rakesh Mohanty: Nothing to Disclose, Prajna Anirvan: Nothing to Disclose

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1592 | TARGETING PDK4-MEDIATED SEPT2 PHOSPHORYLATION TO COMBAT MITOCHONDRIAL DYSFUNCTION IN ALCOHOL-ASSOCIATED LIVER DISEASE

THEMIS THOUDAM[1] Hui Gao[1] Ge Zeng[1] Nazmul Huda[1] Yanchao Jiang[1] Jing Ma[1] Zhihong Yang[1] Suthat Liangpunsakul[1], [1]Indiana University

Background: Alcohol-associated liver disease (ALD) remains a global health challenge, yet the molecular mechanisms driving its progression are not fully elucidated. Mitochondrial dysfunction, marked by excessive fragmentation and heightened production of reactive oxygen species (ROS), plays a pivotal role in ALD pathogenesis. Our prior research identified pyruvate dehydrogenase kinase 4 (PDK4) as a key regulator of mitochondrial fragmentation, acting through direct phosphorylation of Septin 2 (SEPT2) at serine 218 (S218). This modification enhances SEPT2's interaction with Dynamin-related protein 1 (DRP1), facilitating mitochondrial fission. However, the detailed role of PDK4-mediated SEPT2 phosphorylation in mitochondrial dysfunction within ALD remains poorly understood. This study investigates the role of PDK4-mediated phosphorylation of SEPT2 in promoting mitochondrial dysfunction during ALD progression. **Methods:** We utilized a combination of ethanol-fed mice, liver samples from ALD patients, and ethanol-treated hepatocyte cultures to assess mitochondrial dynamics. Mechanistic insights were explored through the use of SEPT2 phosphorylation-deficient and phospho-mimetic mutants. **Results:** In a mouse model of ALD, transmission electron microscopy revealed a reduced mitochondrial perimeter in ethanol-fed mice, indicating enhanced mitochondrial fragmentation. Ethanol exposure led to increased PDK4 expression, heightened SEPT2 phosphorylation, and augmented mitochondrial localization of DRP1, supporting a PDK4-driven SEPT2–DRP1 signaling axis. Elevated PDK4 and phosphorylated SEPT2 were also detected in liver biopsies from patients with alcohol-related cirrhosis, confirming the clinical relevance of this pathway. In vitro, ethanol treatment of AML12 hepatocytes promoted SEPT2 phosphorylation, which facilitated its interaction with DRP1, resulting in mitochondrial fragmentation—a process that was reversed by a phosphorylation-deficient SEPT2 mutant. Additionally, ethanol exposure in primary hepatocytes resulted in mitochondrial fragmentation, increased ROS production, and diminished mitochondrial respiration. However, Pdk4 knockout hepatocytes were protected from these detrimental effects. Finally, hepatocyte-specific Pdk4 knockout mice exhibited reduced serum transaminases and mitigated hepatic steatosis. **Conclusion:** Our findings uncover a novel molecular mechanism driving mitochondrial dysfunction and ALD progression through PDK4-mediated SEPT2 phosphorylation. Targeting this pathway could offer a promising therapeutic strategy for managing ALD.

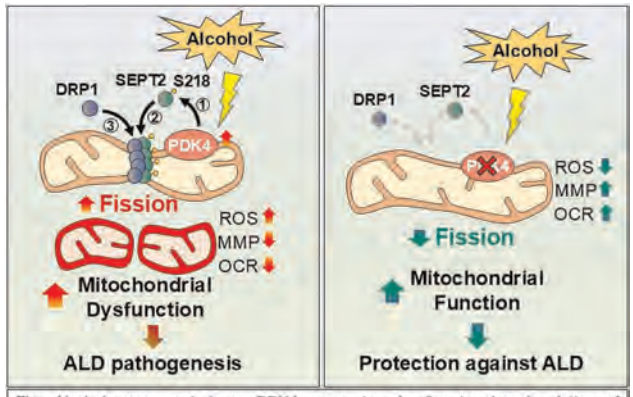

Fig. Alcohol exposure induces PDK4 expression, leading to phosphorylation of SEPT2 at serine 218. This modification promotes DRP1 recruitment to mitochondria, enhancing mitochondrial fission and dysfunction in ALD models. Genetic deletion of Pdk4 or expression of a non-phosphorylatable SEPT2 mutant mitigates these effects and preserves mitochondrial function, supporting the PDK4–SEPT2–DRP1 axis as a key mediator of alcohol-induced mitochondrial damage in ALD pathogenesis.

Disclosures: THEMIS THOUDAM: Nothing to Disclose, Hui Gao: Nothing to Disclose, Ge Zeng: Nothing to Disclose, Nazmul Huda: Nothing to Disclose, Yanchao Jiang: Nothing to Disclose, Jing Ma: Nothing to Disclose, Zhihong Yang: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant

1593 | IN VIVO PROTEIN HALF-LIFE ANALYSIS UNVEILS THE ROLE OF THE SREBF1-SLC27A5 AXIS IN ALLEVIATING ALCOHOL-INDUCED LIVER DAMAGE

NUPUR SHARMA[1] Sadam Bhat[1] Shweta Choudhary[2] Babu Mathew[1] sushmita pandey[1] Sanju Yadav[1] manisha yadav[1] Vasundhra Bindal[1] gaurav tripathi[1] neha sharma[1] Vipul Sharma[1] Ranjan Nanda[2] Ranjan Nanda[2] Anupama Parasar[1] Shvetank Sharma[1] jaswinder singh Maras[3], [1]Institute of Liver and Biliary Sciences, [2]International Centre for Genetic Engineering and Biotechnology, [3]NSTITUTE OF LIVER AND BILIARY SCIENCES

Background: Alcohol-related associated liver disease (ALD) is a leading cause of liver dysfunction and is is characterized by inflammation, steatosis, and fibrosis. Abstinence reverses liver damage, but its effects on protein half-lives in the liver, plasma, and intestine are unclear. This study investigates site-specific protein half-life changes, its transcription regulation, and its their roles in ALD pathophysiology and damage reversal upon alcohol abstinence. **Methods:** Long-Evans rats were fed control or ethanol Lieber De Carli diets for 24 weeks to develop ALD. A separate group of ALD rats was switched to a control diet for 7 days to induce abstinence. Protein half-life was measured using

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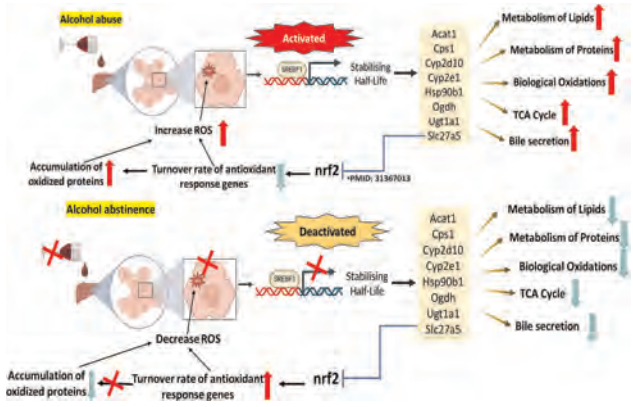
stable isotope labellinglabeling with deuterium oxide usingand, D2ome software. Protein half-life analysisomic analyses were was complemented with the pathway enrichment of important pathways and and transcription factors (TF) analyses. Expression of The iIdentified transcription regulator and linked associated genes were validated in rat model of ALD, human biopsy of ALD and rats under alcohol abstinence in rat model of ALD followed by, validation on human biopsy of ALD. **Results:** Liver histology showed increased steatosis (28%) and fibrosis (15%) in ALD rats, both reduced with abstinence ($<20\%$, $<12\%$, $p<0.05$). Liver function and lipid profiles improved, while alcohol-metabolizing and inflammatory markers were decreased (>1.5-fold, $p<0.05$) following abstinence. Site-specific protein half-life analysis in ALD rats revealedALD induced change in protein half-life specific to liver (82↑, 54↓), intestine (26↑, 30↓), and plasma (11↑, 17↓). Abstinence modulated; liver (64↑, 62↓), intestine (13↑, 25↓), and plasma (10↑, 12↓; FC >1.5, $p<0.05$). Notably, abstinence reversed protein half-lives linked to lipid metabolism and protein localization in the liver, neurodegeneration and and cell death in the intestine, and NET formation in plasma ($p < 0.05$). Abstinence restored protein half-lives of Cyp2d10, Ugt1a1, Slc27a5, and Hsp90b1, regulated by Srebf1. Proteomic validation confirmed increased Acat1, Ugt1a1, and Slc27a5 in ALD, linked to steatosis and inflammation, which decreased with abstinence. Further validation on liver biopsy of Severe alcoholic hepatitis patients also documented that abstinence work on modulating protein turnover under the Srebf1-Slc27a5 axis and thereby ameliorate liver damage. **Conclusion:** Alcohol consumption causes site-specific changes in protein half-life, some of which are reversed by abstinence. Targeting the transcriptional regulation of SREBF1-Slc27a5 axis a key regulator of protein stability linked to inflammation, hepato-steatosis, and antioxidant response offers potential for treating alcohol-induced liver damage.



Disclosures: NUPUR SHARMA: Nothing to Disclose, Sadam Bhat: Nothing to Disclose, Shweta Choudhary: Nothing to Disclose, Babu Mathew: Nothing to Disclose, sushmita pandey: Nothing to Disclose, Sanju Yadav: Nothing to Disclose, manisha yadav: Nothing to Disclose, Vasundhra Bindal: Nothing to Disclose, gaurav tripathi: Nothing to Disclose, neha sharma: Nothing to Disclose, Vipul Sharma: Nothing to Disclose, Ranjan Nanda: Nothing to Disclose, Nothing to Disclose, Ranjan Nanda: Nothing to Disclose, Nothing to Disclose, Anupama Parasar: Nothing to Disclose, Shvetank Sharma: Nothing to Disclose, jaswinder singh Maras: Nothing to Disclose

1594 | CLINICAL UTILITY OF PHOSPHATIDYLETHANOL AS AN OBJECTIVE BIOMARKER FOR QUANTIFYING ALCOHOL USE IN STEATOTIC LIVER DISEASE: EVIDENCE FROM THE SAN DIEGO LIVER STUDY

Federica Tavaglione[1] Luis Díaz[2] Veeral Ajmera[1] Egbert Madamba[1] Seema Singh[1] Ricki Bettencourt[1] Lisa Richards[1] Rohit Loomba[1], [1]University of California San Diego, [2]Pontificia Universidad Católica de Chile

Background: The 2023 subclassification of steatotic liver disease (SLD) relies on self-reported alcohol use, which lacks diagnostic precision in routine clinical practice. Phosphatidylethanol (PEth) is a quantitative, objective alcohol biomarker with high sensitivity and specificity. In this study, we aimed to estimate the prevalence of underreported alcohol use, identify its independent predictors, and enhance SLD subclassification using PEth in a large, population-based cohort of individuals with overweight/obesity and SLD in the United States. **Methods:** This is a cross-sectional analysis of a prospective study including 391 community-dwelling adults with overweight/obesity and SLD, as defined by MRI-PDFF $\geq$ 5%, residing in Southern California. Participants underwent a standardized clinical research visit, including PEth testing and advanced liver imaging using MRI-PDFF and MRE. Participants were subclassified as having metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-related liver disease (MetALD) or alcohol-related liver disease (ALD) in accordance with the new AASLD–EASL–ALEH nomenclature guidance. Underreported alcohol use was defined as individuals originally classified as MASLD with PEth $\geq$ 25 ng/mL or individuals originally classified as MetALD with PEth $\geq$ 200 ng/mL. Sensitivity analyses were performed using PEth cut-points of 20 ng/mL and 35 ng/mL to differentiate between no/light and moderate drinking. **Results:** The mean (SD) age and body mass index (BMI) were 51 (13) years and 33 (6) kg/m^2, respectively. 15.9% (95% CI: 12.2%–19.5%) of individuals with SLD underreported their alcohol consumption

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(Table). Male gender (OR 2.39, 95% CI: 1.31–4.51; p = 0.006), White race (OR 1.83, 95% CI: 1.02–3.32; p = 0.044), and the absence of type 2 diabetes (OR 3.30, 95% CI: 1.58–7.59; p = 0.003) were the strongest independent factors associated with alcohol underreporting. The use of PEth in addition to self-reported alcohol use resulted in a 4-fold and 3-fold increase in MetALD and ALD diagnoses, respectively. PEth and self-reported alcohol use showed a moderate positive correlation ($\rho = 0.52$, 95% CI: 0.45–0.59; $p < 0.001$), while the agreement was low ($\kappa = 0.22$, 95% CI: 0.09–0.35; $p < 0.001$). When stratified by gender, PEth and self-reported alcohol use remained similarly correlated in men ($\rho = 0.49$, 95% CI: 0.37–0.59; $p < 0.001$) and women ($\rho = 0.48$, 95% CI: 0.37–0.58; $p < 0.001$), but agreement was higher in women ($\kappa = 0.47$, 95% CI: 0.29–0.65; $p < 0.001$) compared to men ($\kappa = 0.10$, 95% CI: -0.05–0.26; p = 0.10). Sensitivity analyses yielded results substantially similar to those of the main analysis. **Conclusion:** PEth may objectively quantify alcohol use and help identify SLD subcategories alongside clinical history, mitigating diagnostic misclassification.

Table: Distribution of PEth-defined categories of alcohol use across SLD subcategories.

PEth, ng/mL	MASLD	MetALD	ALD	Total
<25: no/light drinking	312 (84%)	4 (29%)	4 (57.1%)	320
≥25-80: moderate drinking, lower range	34 (9%)	3 (21%)	1 (14.3%)	38
≥80-200: moderate drinking, upper range	14 (4%)	3 (21%)	1 (14.3%)	18
≥200: heavy drinking	10 (3%)	4 (29%)	1 (14.3%)	15
Total	370	14	7	391

Outlined boxes indicate agreement between PEth levels and self-reported alcohol consumption.
Gray-shaded boxes indicate underreporting of alcohol consumption compared to PEth levels.
Unshaded boxes indicate overreporting of alcohol consumption compared to PEth levels.
Abbreviations: ALD, alcohol-related liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-related liver disease; PEth, phosphatidylethanol.

Disclosures: Federica Tavaglione: Nothing to Disclose, Luis Díaz: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Egbert Madamba: Nothing to Disclose, Seema Singh: Nothing to Disclose, Ricki Bettencourt: Nothing to Disclose, Lisa Richards: Novo Nordisk: Advisor, Madrigal: Advisor, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder

1595 | MULTIDISCIPLINARY MANAGEMENT OF ALD: IMPROVED PATIENT OUTCOMES AND REDUCED HEALTHCARE UTILIZATION

Nabeeha Mohy-ud-din[1] Mark Guy[2] Gursimran Kochhar[1], [1]Division of Gastroenterology, Hepatology and Nutrition, Allegheny Health Network, Pittsburgh, PA, [2]Allegheny Health Netowrk Center for Inclusion Health, Pittsburgh, PA

Background: Alcohol associated liver disease (ALD) is a leading cause of liver-related mortality, with approximately half of the cirrhosis related hospitalizations occurring due to alcohol use with an annualized cost per decompensated patient of $36,384. ALD has traditionally fallen under the purview of hepatologists, however, there is increasing evidence to show that patients with ALD treated in multi-disciplinary settings have superior outcomes when alcohol use disorder (AUD) is concurrently managed. We established a multi-disciplinary clinic in conjunction with addiction medicine, at our tertiary care center with the aim of improving care for patients with ALD and decreasing health care utilization. **Methods:** Data was collected retrospectively for patients with ALD seen in a multi-disciplinary clinic (by transplant hepatology and addiction medicine) over a 6-month period (October 2024 - March 2025). Demographics, management data (including medications for AUD and behavioral interventions), outcomes data (downstream healthcare utilization), and patient satisfaction questionnaires were collected. **Results:** A total of 32 patients were seen in our multi-disciplinary ALD clinic. The average age was 50, 75% (n = 24) were men and 78% (n = 25) Caucasians. 87.5% (n = 28) patients had liver cirrhosis with a mean MELD of 17 (range 9-28). 84% (n = 27) patients had an average of 3 ER visits in the 12-month period prior to being seen in our clinic, and 60% (n = 19) were hospitalized within the 30 days prior to the clinic visit. 69% (n = 22) patients were prescribed medications for AUD, 85% (n = 27) patients reported no or decreased alcohol use at the 6-month follow-up. Only 2 patients required

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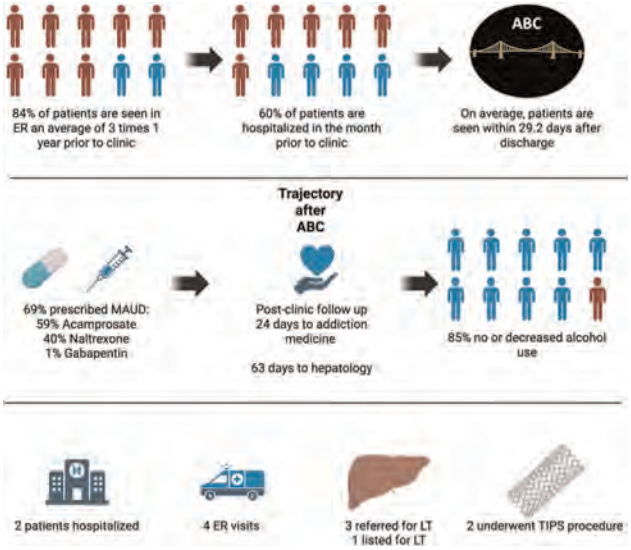
hospitalization during the follow-up period. 90% (n = 29) of patients reported increased likelihood of positive lifestyle changes and improved symptom management after being seen in clinic. **Conclusion:** Patients with ALD managed in a multi-disciplinary setting with co-located hepatology/addiction medicine have increased sobriety and high patient satisfaction. Our multidisciplinary clinic reduced hospitalizations by 89% during our follow-up period, thereby reducing health care costs.



Disclosures: Nabeeha Mohy-ud-din: Nothing to Disclose, Mark Guy: Nothing to Disclose, Gursimran Kochhar: Nothing to Disclose

1596 | EVALUATING SERUM BIOMARKERS FOR ADVANCED LIVER FIBROSIS SCREENING AND DISEASE PROGRESSION IN ACTIVELY DRINKING HOSPITALIZED PATIENTS WITH ALCOHOL USE DISORDER

Michael Butler[1] Chantelle Marshall[2] Prasanna Challa[1] Rachael Mahle[1] Wei Zhang[1] Russell Goodman[2] Esperance Schaefer[3] Jay Luther[2], [1]MGH, [2]Massachusetts General Hospital, [3]Brigham and Women's Hospital

Background: Hospitalized patients with heavy alcohol consumption constitute a high-risk group for advanced liver disease, with an estimated prevalence of undiagnosed advanced fibrosis or cirrhosis in approximately 20%. Despite this, there is a lack of accurate and clinically available screening tools to guide targeted assessment in this patient population, especially in those with active alcohol use. We evaluated the performance of commonly used non-invasive tests for advanced fibrosis in a cohort of actively drinking, hospitalized patients with alcohol use disorder (AUD). **Methods:** We conducted a prospective study (2019-2023) of 6 liver fibrosis markers—APRI, FIB-4, FibroTest, Forns Score, GAPRI, and MELD-Na—in hospitalized AUD patients with no known history of liver disease and reported ongoing alcohol consumption. Biomarkers were obtained on the day of admission. All participants underwent liver elastography. Elastography results served as the reference standard for the presence of advanced fibrosis, defined as $\geq$11 kPa on FibroScan or $\geq$1.7 m/s on US elastography. These thresholds were validated using liver biopsy results from 20 patients who underwent both elastography and biopsy, demonstrating concordant detection of advanced fibrosis. We calculated AUROC, sensitivity, specificity, predictive values, and likelihood ratios at established literature-based cutoff values. Calibration of each test was evaluated using the Brier score. To assess the prognostic utility for future hepatic decompensation events, we calculated a Harrell's C-index for each test. **Results:** 455 patients were studied, 27.1% who were found to have advanced fibrosis as determined by elastography. There were no differences in clinical demographics—age, sex, ethnicity, BMI, diabetes mellitus, viral hepatitis, or hyperlipidemia—between patients with and without advanced fibrosis (all $P > 0.05$). Among the evaluated serum biomarkers, GAPRI demonstrated the highest sensitivity as a screening tool, with a sensitivity of 98.1% (95% CI: 94.5–100.0), a NPV of 96.6% (95% CI: 89.9–100.0), and a negative LR of 0.10. No biomarker reliably predicted the presence of advanced fibrosis. FibroTest exhibited the best overall diagnostic performance in this regard, with an area AUROC of 0.756 (95% CI: 0.684–0.823) and a Brier score of 0.183. During the follow-up period, 61 patients experienced a major hepatic decompensation event. These patients had lower ALT and higher bilirubin comparitively. None of the fibrosis biomarkers demonstrated adequate predictive accuracy for these events, with the MELD-Na score yielding the highest prognostic discrimination (Harrell's C-index = 0.685). **Conclusion:** GAPRI at the time of hospital admission is a readily available and effective screening tool to rule out advanced hepatic fibrosis in the highly prevalent group of high-risk, actively drinking hospitalized AUD patients. The need for predictive biomarkers remains.

Disclosures: Michael Butler: Nothing to Disclose, Chantelle Marshall: Nothing to Disclose, Prasanna Challa: Nothing to Disclose, Rachael Mahle: Nothing to Disclose, Wei Zhang: Nothing to Disclose, Russell Goodman: Nothing to Disclose, Esperance Schaefer: Nothing to Disclose, Jay Luther: Nothing to Disclose

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1597 | COMPARATIVE OUTCOMES IN ALCOHOL-RELATED LIVER DISEASE VERSUS NAFLD: A RETROSPECTIVE COHORT STUDY

Abdallah Hussein[1] Islam Rajab[2] Ahmed Salem[3] Nyan Latt[4] Mohamed Eldesouki[5] Abdallatif Hussein[6], [1]Virtua health Inc, [2]St Joseph University Medical Center, [3]Maimonides Medical Center, [4]Virtua Health, [5]New York Medical College at Saint Michael Medical Center, [6]Al-Najah University

Background: Non-alcoholic fatty liver disease (NAFLD) and alcohol-related liver disease (ALD) are leading causes of hepatic fibrosis, cirrhosis, and subsequent decompensation. We sought to compare rates of cirrhosis progression, acute hepatic failure, liver transplantation, and mortality between these two etiologies. **Methods:** Using the TriNetX database, we identified adults ($\geq$18 years) who had both a diagnosis of NAFLD (ICD-10 K76.0, K75.81) or alcohol-related liver disease (ICD-10 F10.x, K70.x). To ensure two mutually exclusive cohorts, patients in the NAFLD arm were required to have no alcohol-related codes, and those in the alcohol-related arm were required to have no NAFLD codes. The index date was defined as the first cirrhosis diagnosis following the NAFLD or alcohol-related code. We then performed 1:1 propensity-score matching on age, sex, race/ethnicity, and key comorbidities, yielding 81,925 patients in each cohort. Patients were followed for 12 months from index; outcomes assessed included cirrhosis-related complications, acute hepatic failure, need for liver transplantation, and all-cause mortality. Risk ratios (RRs), 95% confidence intervals (CIs), and p-values were calculated for each outcome. **Results:** Risk of progression to liver cirrhosis over one year was lower in ALD, 41.34% versus 47.97% in NAFLD (RR 0.862; 95% CI 0.853-0.871; $p < 0.0001$), and association with hepatic failure occurred in 21.40%, versus 6.98% respectively (RR 3.03; 95% CI 2.978,3.151; $p < 0.0001$). ALD patients also had higher mortality (5.11% vs 17.07%; RR 3.33; 95% CI 3.228-3.45; $p < 0.0001$) and increased need for liver transplantation (1.79% vs 0.87% ; RR 2.045; 95% CI 1.871-2.235; $p < 0.0001$). **Conclusion:** Although NAFLD patients were more likely to develop cirrhosis over one year, they experienced significantly lower risks of acute hepatic failure, liver transplantation, and death compared with matched ALD patients.

Disclosures: Abdallah Hussein: Nothing to Disclose, Islam Rajab: Nothing to Disclose, Ahmed Salem: Nothing to Disclose, Nyan Latt: Nothing to Disclose, Mohamed Eldesouki: Nothing to Disclose, Abdallatif Hussein: Nothing to Disclose

1598 | PATIENTS WITH HIGHER MELD SCORES MAY BE AT HIGHER RISK OF BEING MISCLASSIFIED AS LOW RISK FOR ALCOHOL RELAPSE BY PRE-TRANSPLANT SIPAT EVALUATION

Alex Chang[1] Aditya Sood[2] Reanay Berezovskiy[2] Christopher Dorizas[2] Nishi Joshi[2] Sanjaya Satapathy[2], [1]Warren Alpert School of Medicine of Brown University, [2]Zucker School of Medicine at Hofstra/Northwell

Background: The Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) is increasingly used to assess relapse risk in candidates undergoing liver transplantation for alcohol-associated liver disease (ALD). However, the subjective nature of SIPAT scoring —especially elements such as social support—can result in variability across institutions and evaluators. This study aimed to examine the predictive accuracy of SIPAT scores in assessing alcohol relapse post-transplant and identify pre-transplant patient characteristics associated with misclassification of relapse risk, particularly among those with high Model for End-Stage Liver Disease (MELD) scores. **Methods:** This retrospective cohort study included 60 patients who underwent liver transplantation for ALD from 2019–2023 at a single transplant center and had pre-transplant SIPAT scores. Risk categories were defined as follows: SIPAT 0–10 (low-risk), 11–20 (intermediate-risk), and >20 (high-risk). Relapse was categorized as either a slip (any alcohol use not requiring hospitalization) or harmful relapse (alcohol use resulting in hospitalization or >3 drinks/week). Misclassification was defined as follows–misclassified low-risk is a SIPAT ≤ 20 with harmful relapse or SIPAT <10 with slip or harmful relapse. Misclassified high-risk is a SIPAT >20 without any relapse. Univariate binary logistic regression was used to analyze associations between misclassification and demographic or clinical variables. **Results:** A total of 7 of 32 patients (21.9%) were misclassified low-risk. A total of 20 of 29 patients (69.0%) were misclassified high-risk. A SIPAT <10 had a negative predictive value (NPV) of 72.7% for any relapse and 90.9% for harmful relapse. SIPAT <20 had a similarly high NPV of 81.0% for harmful relapse. However, SIPAT >20 had a low positive predictive value (PPV) of 28.6% for harmful relapse. Among variables analyzed, higher MELD scores were associated with an increased likelihood of being misclassified as low-risk (mean MELD 33.6 vs 27.9, $p = 0.055$) (Figure 1). Other factors, including age, sex, race, employment, insurance, education, and abstinence duration, were not significantly associated with misclassification. **Conclusion:** While SIPAT scores <20 are effective in ruling out harmful relapse post-transplant, high SIPAT scores lack specificity in predicting relapse. Importantly, patients with higher

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MELD scores may be at risk of being underestimated for relapse potential, potentially due to under-reporting or evaluator bias during psychosocial evaluation. These findings suggest a need for more objective and standardized assessments of relapse risk, particularly in critically ill patients.

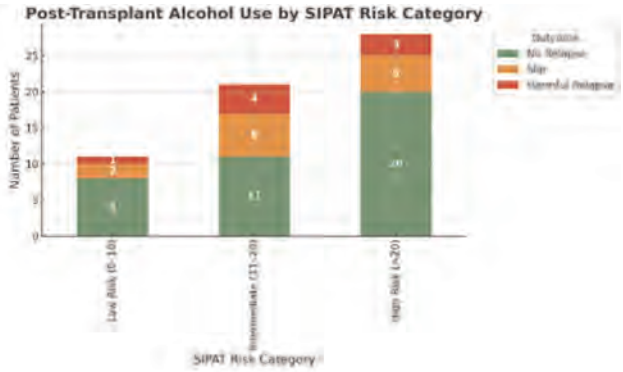

Table: Comparison of Characteristics – Misclassified vs Correctly Classified (Low-Risk Patients Only)

Variable	Misclassified (n=7)	Correctly Classified (n=24)	p-value	Odds Ratio (95% CI)
Age (mean ± SD)	51.4 ± 14.0	54.0 ± 10.4	0.592	0.979 (0.908 – 1.060)
MELD Score (mean ± SD)	33.6 ± 4.9	27.9 ± 6.3	0.055	1.22 (0.995 – 1.50)
Sex (% Male)	85.7%	75.0%	0.556	2.00 (0.199 – 20.15)
Employment (% Unemployed)	71.4%	45.8%	0.245	2.96 (0.476 – 18.34)
Education ≥ Bachelor's (%)	85.7%	54.2%	0.160	0.197 (0.020 – 1.90)
Abstinence >6 months (%)	28.6%	41.7%	–	–

Disclosures: Alex Chang: Nothing to Disclose, Aditya Sood: Nothing to Disclose, Reanay Berezovskiy: Nothing to Disclose, Christopher Dorizas: Nothing to Disclose, Nishi Joshi: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support

1599 | EXERCISE IS A FEASIBLE MECHANISTIC INTERVENTION FOR SARCOPENIA IN ALCOHOL-RELATED LIVER DISEASE (ALD)

Nicole Welch[1] Annette Bellar[1] Amy Attaway[1] Saurabh Mishra[1] Jasmin Cunningham[1] Pugazhendhi Kannan[1] Seshu Pothabathula[1] Vandana Agrawal[1] Maxmillian Hanlon[1] Laura Nagy[2] Takhar Kasumov[3] Srinivasan Dasarathy[1], [1]Cleveland Clinic, [2]Cleveland Clinic Foundation, [3]NEOMED

Background: Sarcopenia and impaired contractile function are frequent complications in patients with alcohol related liver disease (ALD). Sarcopenia/contractile dysfunction in ALD is frequent, severe and progressive. Alcohol use disorder (AUD) is the primary causal factor for ALD with no therapies/interventions that target ALD/AUD. Exercise improves functional capacity (VO2max) and muscle mass in patients with cirrhosis. Mechanistic studies on preclinical models of exercise have been limited by concerns regarding impaired activity during ethanol treatment. Exercise also lowers alcohol consumption/cravings (alcohol use disorder) but there are no systematic studies on the effect of alcohol ingesion on physical activity in preclincal models. We studied voluntary activity and alcohol consumption in mice before and after ethanol treatment. **Methods:** Wild type C57BL/6J mice were assigned to voluntary wheel running (VWR) or usual activity (UA) and ad-lib water and chow for 28-days (n = 4 male and 4 female mice in each group). On day 28, free water was removed and 2-bottle choice: Ethanol in escalating doses every 2 days until endpoint (2% day 28-30, 4% day 30-32, 8% day 32-34) or water were provided and the bottle positions switchd daily. Total fluid and ethanol consumption, and blood alcohol concentrations were measured at the end of the study. Mean rotations, distance run, and hourly rotations/distance run were calculated over the full 24-hour period for each mouse evey day of the 6 days prior to and during the 2-bottle choice. Dark (1900-0659) and light (0700-1859) cycles were also analyzed separately in secondary analyses. Paired t-tests were used to compare activity in each individual mouse in the week pre- and post-ethanol exposure and in the light vs dark cycles. **Results:** Since there were no differences between male and female VWR (rotations,distance run) during the water only or 2-bottel choice periods of the study ($p > 0.05$) (Fig 1A). Hence, all 8 mice were analyzed together pre- and post-ethanol exposure. There was no statistically significant difference between running counts the week before ethanol and the 6 days of ethanol exposure as a 2 bottle choice ($t = 1.50$, $p = 0.178$) (Fig 1B). There were no differences in wheel running activity at different ethanol doses (2% vs 4%: $p = 0.131$, 4% vs 8%: $p = 0.944$, 2% vs 8%: $p = 0.101$) (Fig 1C). Greater wheel running during the dark vs. light cycle ($t = 8.21$, $p = 7.71 \times 10^{-5}$) is consistent with the nocturnal activity of mice. Wheel running activity also did not change between the week before and after ethanol exposure during the light cycle ($t = -0.13$, $p =$

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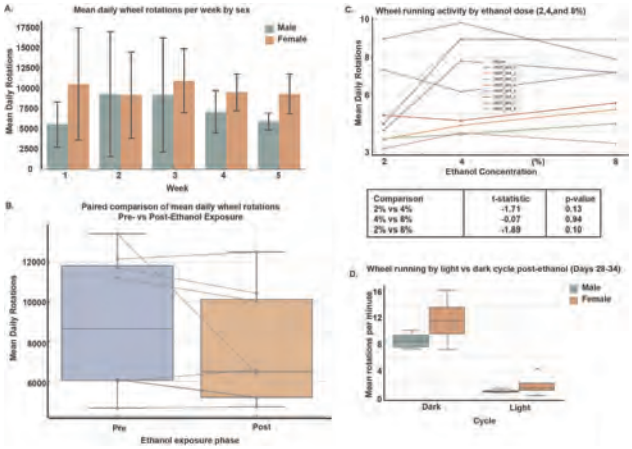
0.899) or dark cycle (t = 1.55, p = 0.165) (Fig 1D). **Conclusion:** Ethanol exposure did not alter voluntary locomotor activity in mice when analyzed within/between groups, stratified by light/dark cycle, or increasing ethanol concentrations. VWR, a model that replicates human activity, in mice can be used to study the effects of alcohol responses in mice.



Disclosures: Nicole Welch: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Saurabh Mishra: Nothing to Disclose, Jasmin Cunningham: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Seshu Pothabathula: Nothing to Disclose, Vandana Agrawal: Nothing to Disclose, Maxmillian Hanlon: Nothing to Disclose, Laura Nagy: Nothing to Disclose, Takhar Kasumov: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

1600 | IMPLEMENTING A PARTICIPATORY PROCESS TO SUSTAIN BIO-PSYCHO-SOCIAL SUPPORT FOR AUD, METALD, AND ALD PATIENTS

Jennifer Jones[1] Neeraj Mistry[2] Suthat Liangpunsakul[3], [1]Sober Livers, [2]Fatty Liver Foundation, [3]Indiana University School of Medicine

Background: Contemporary medicine increasingly acknowledges that health outcomes are shaped not only by disease progression but also by patients' psychological and social context. Alcohol use disorder (AUD) and alcohol-associated liver disease (ALD) exemplify the bio-psycho-social complexity that demands a multifaceted approach to harm reduction, treatment, recovery, and rehabilitation. Effective interventions must be informed by scientific advances, stakeholder engagement, and the lived experiences of those affected. Given the spectrum of AUD and alcohol-associated disease severity, patient-centered and participatory models are essential to "meet patients where they are." Sober Livers is a patient-led organization supporting individuals with AUD, MetALD, and ALD, including pre- and post- liver transplant patients. The organization launched HOPE (Healing Ourselves with Peers and Education), a virtual peer community supported by the Whole Health Advisory Committee (WHAC) of scientific and clinical experts. **Methods:** HOPE and WHAC adopt a bio-psycho-social theory of change that leverages compassionate, empathic peer engagement to promote behavior change and enhance treatment outcomes. Initial data were gathered through Knowledge, Attitudes, and Practices (KAP) assessments to guide the development of a comprehensive mixed-methods evaluation framework. **Results:** Preliminary feedback and findings from the qualitative KAP assessments include: an expressed need and appreciation for peer-led AND expert-input education and information sharing; a sense of solidarity and support through the HOPE community; and support for more holistic approaches to managing AUD and ALD. More details will be presented at AASLD's The Liver Meeting (TLM) including a framework with qualitative and quantitative metrics of patient well-being; experiences of shame, stigma, and empowerment; alcohol consumption patterns; biochemical markers; and liver health. These metrics illustrate the multi-dimensional impact of peer-led engagement for behavior change and recovery outcomes. **Conclusion:** AUD/ALD care and treatment success varies, underscoring the need for holistic and personalized approaches. Supporting individuals with AUD/ALD requires a bio-psycho-social approach to address holistic patient needs. Combining peer support with medical expertise offers a strong foundation for multidisciplinary and multistakeholder engagement, enhancing the impact and reach of interventions within the patient community.

Disclosures: Jennifer Jones: Boehringer Ingelheim: Independent Contractor, GlaxoSmithKline: Patient Council, Boehringer Ingelheim: Advisor, GSK: Advisor, Neeraj Mistry: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant

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1601 | PRE-TRANSPLANT ALCOHOL-RELATED LIVER DISEASE CLINIC: A MULTIDISCIPLINARY CLINIC APPROACH TO TREATMENT OF ALCOHOL-RELATED LIVER DISEASE AND ALCOHOL USE DISORDER

Jasleen Singh[1] Eshan Walia[1] Amy Richards[1] Julio Meza[1] Akshay Shetty[1] Sammy Saab[2], [1]UCLA, [2]University of California, Los Angeles

Background: Alcohol-related liver disease (ALD) is the leading indication for liver transplantation (LT) in the United States. The underlying alcohol use disorder (AUD) is critical to address, especially when evaluating patients for LT. AUD treatment has also been shown to improve survival. A multidisciplinary clinic with hepatology and addiction medicine may further inform decision-making prior to LT, improve rates of re-compensation and may decrease risk of alcohol relapse. **Methods:** Patients with decompensated ALD and AUD referred to PAC (Pre-transplant Alcohol-related liver disease Clinic) were included in this study. In addition to sociodemographic and clinical variables, AUD treatment, TIPS, receipt of LT and mortality were collected. Re-compensation, defined as the resolution of portal hypertensive complications and normalization of liver function, was also included. Descriptive statistics were used. **Results:** From March 2024 to January 2025, 62 patients were evaluated in PAC at University of California-Los Angeles, with a mean follow up time of 236 (± 90.4) days. Most patients were male (59.7%), Caucasian (46.8%), with private PPO insurance (43.5%) and were English-speaking (85.5%). Mean MELD of patients at initial visit was 18.3 (± 8.0). Twenty patients were on naltrexone, acamprosate or a combination of both. Of those on medication, 4 discontinued treatment during the study period. Of the 62 patients, 24 patients re-compensated and 37.5% of those patients were on AUD therapy. A quarter of patients relapsed after the initial visit in PAC, and 10 (62.5%) of those 16 patients who relapsed were prescribed AUD treatment. Ultimately 39 patients were evaluated for LT and 20 were listed for LT. Five of the 20 listed patients received LT through January 2025. The full characteristics of the cohort are described in the table. **Conclusion:** In this multidisciplinary clinic with hepatology and addiction medicine, we describe a cohort of patients with ALD and AUD. While most of the patients were ultimately evaluated for liver transplant, many patients also re-compensated in this time period. Concurrent treatment of ALD and AUD may benefit this patient population, improve LT candidacy and potentially promote re-compensation, obviating the need for LT. Longer term follow up with a larger cohort is necessary to explore associations amongst these variables.

Characteristics of Patients Referred to PAC from March 2024-January 2025.

Characteristic	n (%)	Mean (SD)
Age (years)		48.4 (11.9)
Sex		
Male	37 (59.7%)	
Female	25 (40.3%)	
Race		
Caucasian	29 (46.8%)	
Other	25 (40.3%)	
African American	3 (4.8%)	
Multiracial	2 (3.2%)	
Asian	1 (1.6%)	
Unknown	2 (3.2%)	
Ethnicity		
Hispanic/Latino	27 (43.5%)	
Non-Hispanic/non-Latino	31 (50%)	
Unknown	4 (6.5%)	
Insurance		
Private PPO	27 (43.5%)	
Medicare PPO	6 (9.7%)	
Medicaid	25 (40.3%)	
Self-pay/uninsured	4 (6.5%)	
Preferred Language		
English	53 (85.5%)	
Spanish	9 (14.5%)	
Employed	33 (53.2%)	
Married	29 (46.8%)	
Social support present	53 (85.5%)	
Psychiatric diagnosis	35 (56.4%)	
Concomitant MASH	3 (4.8%)	
Diabetes	13 (21.0%)	
Alcohol-associated hepatitis	23 (37.1%)	
History of tobacco use	21 (33.9%)	
History of Illicit drug use	11 (17.7%)	
MELD 3.0 (at initial visit)		18.3 (8.0)
Ascites	55 (88.7%)	
Variceal bleed	26 (41.9%)	
Hepatic encephalopathy	41 (66.1%)	
Any Positive PeTH	30 (48.4%)	
AUD Therapy		
Naltrexone	11 (17.7%)	
Acamprosate	3 (4.8%)	
Naltrexone + acamprosate	2 (3.2%)	
Naltrexone discontinued	3 (4.8%)	
Acamprosate discontinued	1 (1.6%)	
None	42 (67.7%)	
Presence of TIPS	5 (8.1%)	
Re-compensation	24 (38.7%)	
Alcohol Relapse after initial visit	16 (25.8%)	
Evaluated for LT	39 (62.9%)	
Listed for LT	20 (32.3%)	
Received LT	5 (8.1%)	
Mortality	1 (1.6%)	

Disclosures: Jasleen Singh: Madrigal: Speaking and Teaching, Eshan Walia: Nothing to Disclose, Amy Richards: Nothing to Disclose, Julio Meza: Nothing to Disclose, Akshay Shetty: Nothing to Disclose, Sammy Saab: Nothing to Disclose

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1602 | PREDICTING ALCOHOL RELAPSE IN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE AFTER TRANSPLANT EVALUATION

Mohamad Ali Ibrahim Nagham Ramadan[1] Sherry Fares[1] Caroline Ankoma-Sey[1] Megha Bhongade[1] Mazen Elsheikh[1] Sohm Manzoori[1] Islam Mohamed[2] Youseph Karouni[1] Karim Adhem[1] Ximena Ramirez-Morales[1] Manal Hassan[3] Prasun Jalal[1], [1]Baylor College of Medicine, [2]The Cleveland Clinic Foundation-Fairview hospital, [3]The University of Texas MD Anderson Cancer Center

Background: Alcohol-associated liver disease (ALD) is the leading indication for liver transplantation (LT) in the United States. However, alcohol relapse (AR) after LT remains a major concern, associated with poor graft outcomes and reduced survival. Existing predictive models focus on the post-LT period and are limited in clinical applicability. This study aims to identify predictors of AR in ALD and MetALD patients undergoing LT evaluation. **Methods:** We conducted a retrospective cohort study of 181 patients with ALD or MetALD referred for LT evaluation at Baylor College of Medicine between October 2021 and August 2023. AR was defined as a positive phosphatidylethanol (PEth) test >20 ng/mL after evaluation. Baseline clinical, psychosocial, and alcohol history data were collected. Multivariable logistic regression was used to identify independent predictors of AR. Subgroup analysis included only patients listed or transplanted, excluding patients declined for listing. **Results:** Among 181 patients (mean age 53 $\pm$ 11 years, 43% female), 30 (16%) experienced AR after evaluation. Of these, 23% relapsed while listed, 37% after LT, and 40% after being declined. The AR group was more likely to have a positive PEth at evaluation (55% vs. 21%, $p<0.001$), earlier age of alcohol initiation (17 vs. 22 years, $p=0.029$), and history of alcohol-related legal issues (40% vs. 20%, $p=0.016$). In multivariable analysis, the strongest predictors of AR were positive PEth (OR 7.34, $p=0.002$), earlier alcohol initiation (OR 0.88, $p=0.039$), and alcohol-related legal issues (OR 3.58, $p=0.046$). LT listing, receipt, and recompensation rates were similar between patients who relapsed and those who didn't. In the subgroup excluding non-listed patients, active substance abuse (OR 12.46, $p=0.013$) and alcohol-related legal issues (OR 4.54, $p=0.010$) remained significant predictors. We developed two scores to estimate AR in our patients. In the overall cohort, the model included PEth positivity, age at alcohol initiation, and legal history (AUC = 0.819). In the waitlisted/transplanted subgroup, it included active substance use and legal history (AUC = 0.729). **Conclusion:** Factors including positive PEth, early age of alcohol initiation, alcohol-related legal issues, and active substance abuse on LT evaluation are strong predictors of alcohol relapse after LT evaluation. These findings support early identification of high-risk patients during LT evaluation and highlight the need for targeted interventions prior to listing and LT.

Disclosures: Mohamad Ali Ibrahim: Nothing to Disclose, Nagham Ramadan: Nothing to Disclose, Sherry Fares: Nothing to Disclose, Caroline Ankoma-Sey: Nothing to Disclose, Megha Bhongade: Nothing to Disclose, Mazen Elsheikh: Nothing to Disclose, Sohm Manzoori: Nothing to Disclose, Islam Mohamed: Nothing to Disclose, Youseph Karouni: Nothing to Disclose, Karim Adhem: Nothing to Disclose, Ximena Ramirez-Morales: Nothing to Disclose, Manal Hassan: Nothing to Disclose, Prasun Jalal: Nothing to Disclose

1603 | OUTCOMES IN METABOLIC DYSFUNCTION AND ALCOHOL-RELATED LIVER DISEASE COMPARED TO ALCOHOL-ASSOCIATED LIVER DISEASE IN PATIENTS REFERRED FOR LIVER TRANSPLANT EVALUATION

Mohamad Ali Ibrahim[1] Nagham Ramadan[1] Islam Mohamed[2] Caroline Ankoma-Sey[1] Sherry Fares[1] Eric Nguyen[1] Mazen Elsheikh[1] Megha Bhongade[1] Youseph Karouni[1] Ximena Ramirez-Morales[1] Karim Adhem[1] Manal Hassan[3] Prasun Jalal[1], [1]Baylor College of Medicine, [2]The Cleveland Clinic Foundation-Fairview hospital, [3]The University of Texas MD Anderson Cancer Center

Background: Metabolic dysfunction and alcohol-related liver disease (MetALD) is a recently defined entity combining metabolic syndrome and moderate-to-high alcohol consumption (140-350g/week for females and 210-420g/week for males). Its distinction from alcohol-associated liver disease (ALD) remains underexplored, particularly regarding liver transplant (LT) evaluation outcomes. **Methods:** We conducted a retrospective cohort study of 194 patients referred for LT evaluation between October 2021 and August 2023 at a single U.S. transplant center. Patients were categorized as ALD or MetALD per Delphi consensus definitions. The primary outcomes were liver recompensation (LR) within 12 months (defined as MELD-Na <15 and absence of ascites, hepatic encephalopathy, cirrhosis-related gastrointestinal bleeding, and jaundice), LT and mortality rates. Predictors were analyzed using multivariable Cox regression. **Results:** Of the 194 patients, 135 (70%) had ALD and 59 (30%) MetALD. Baseline characteristics showed significantly higher BMI (31 vs. 28 kg/m², $p=0.001$), chronic kidney disease (32% vs. 17%, $p=0.025$), and lower Karnofsky scores

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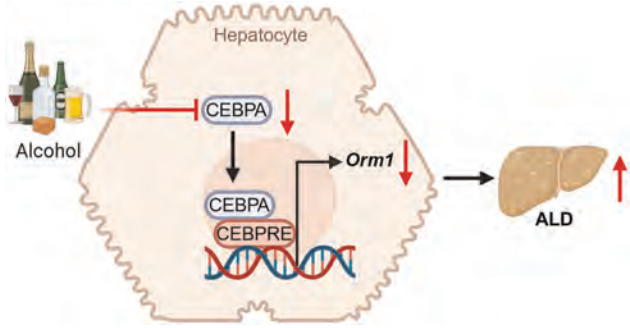
(51 vs. 62, p = 0.014) in the MetALD group. While no statistical difference was found in listing and LT rates between groups, LR occurred significantly less often in MetALD compared to ALD (3% vs.18%, p = 0.006). On multivariable analysis, MetALD independently predicted lower LR (HR 0.21, 95% CI: 0.05–0.91). Hypertension (HR 0.38, 95% CI: 0.16–0.89) and increasing BMI (HR 0.91, 95% CI: 0.84–0.99) were also significantly associated with lower LR. While overall mortality was higher in the MetALD group (42% vs. 26%, p = 0.029), MetALD was not an independent mortality predictor after adjustment. Higher MELD-Na score and older age were associated with increased mortality, while LT was protective. **Conclusion:** Compared to ALD, MetALD is associated with significantly lower LR and higher unadjusted mortality following LT evaluation. These findings emphasize the prognostic impact of metabolic comorbidities and support the need for tailored strategies in this emerging high-risk liver disease phenotype. **Disclosures:** Mohamad Ali Ibrahim: Nothing to Disclose, Nagham Ramadan: Nothing to Disclose, Islam Mohamed: Nothing to Disclose, Caroline Ankoma-Sey: Nothing to Disclose, Sherry Fares: Nothing to Disclose, Eric Nguyen: Nothing to Disclose, Mazen Elsheikh: Nothing to Disclose, Megha Bhongade: Nothing to Disclose, Youseph Karouni: Nothing to Disclose, Ximena Ramirez-Morales: Nothing to Disclose, Karim Adhem: Nothing to Disclose, Manal Hassan: Nothing to Disclose, Prasun Jalal: Nothing to Disclose

1604 | HEPATOCYTE CEBPA-ORM1 AXIS RESTRICTS ALCOHOL-ASSOCIATED LIVER DISEASE

Tingting Yan[1] Nana Yan[2] Yangliu Xia[3] Haiping Hao[1] Frank Gonzalez[3], [1]China Pharmaceutical University, [2]China Pharmaceutical University; National Cancer Institute, [3]National Cancer Institute

Background: Alcohol-associated liver disease (ALD) represents a major global health burden with limited therapeutic options. Although hepatocyte CCAAT/enhancer-binding protein α (CEBPA) critically regulates hepatocyte maturation, differentiation, glycogen metabolism, and liver fibrosis progression, its contribution to ALD pathogenesis remains undefined. **Methods:** The role of the hepatocyte CEBPA-ORM1 axis in ALD was investigated using hepatocyte-specific constitutive/inducible Cebpa-knockout mice, adeno-associated virus serotype 8 (AAV8)-mediated overexpression or knockdown, and preclinical ALD models. Mechanistic insights into CEBPA-ORM1 signaling were elucidated using chromatin immunoprecipitation (ChIP) and luciferase reporter assays, complemented by translational analyses of human ALD serum and liver specimens to establish its clinical and pathophysiological relevance. **Results:** Hepatic CEBPA expression was found to be decreased during ALD progression in human patient cohorts. Hepatocyte-specific *Cebpa*-knockout (*Cebpa*$^{\Delta Hep}$) mice exhibited exacerbated alcohol-associated steatosis in both acute and chronic ALD models. Inducible ablation of CEBPA in hepatocytes during late-stage ALD accelerated disease progression, demonstrating its persistent protective function. Mechanistically, CEBPA directly activates orosomucoid 1 (*Orm1*) transcription by binding to CEBP response elements within the *Orm1* promoter. Loss of CEBPA suppressed ORM1, a hepatokine whose hepatic production and circulating levels are inversely correlated with ALD severity in patients. Loss of hepatocyte ORM1 worsened ALD in mice, whereas restoring CEBPA or ORM1—via AAV8-mediated gene delivery or recombinant protein administration—rescued hepatic lipid metabolism and reduced disease progression. **Conclusion:** Hepatocyte CEBPA-ORM1 axis acts as a critical suppressor of ALD, which provides a compelling therapeutic target for ALD treatment and nominates serum ORM1 as a potential biomarker for staging ALD severity.



Disclosures: Tingting Yan: Nothing to Disclose, Nana Yan: Nothing to Disclose, Yangliu Xia: Nothing to Disclose, Haiping Hao: Nothing to Disclose, Frank Gonzalez: Nothing to Disclose

1605 | METABOLIC AND ALCOHOL-ASSOCIATED (METALD) LIVER DISEASE RELATED CIRRHOSIS HAS WORSE DISEASE SEVERITY AND HIGHER MORTALITY THAN OTHER ETIOLOGIES

Nicole Welch[1] Ana Ostojic[1] Annette Bellar[1] Amy Attaway[1] Lars Deutz[1] Ryan Musich[1] John McMichael[1] Lopa Mishra[2] Srinivasan Dasarathy[1], [1]Cleveland Clinic, [2]Feinstein Institutes for Medical Research & Cold Spring Harbor Laboratory

Background: We evaluated if etiology of cirrhosis impacts adverse cliinical outcomes including

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decompensation and hepatocellular carcinoma (HCC). **Methods:** 29,999 patients with cirrhosis rom January 2000-December 2024 were evaluated at a large transplant center were evaluated from their electronic medical records (EMR). Etiologies were identified by ICD9 and ICD10 codes. To standardize the cohort, patients were included if they had compensated cirrhosis or decompensated cirrhosis without recompensation (identified by bleeding, encephalopathy, and ascites). The cohort was further stratified by etiology into metabolic associated steatotic liver disease (MASLD), alcohol associated (ALD), metabolic and alcohol-associated (MetALD, had a diagnosis code for both MASLD and ALD), viral hepatitis-associated (VLD), and other liver disease. HCC was determined by biopsy, imaging, or physician documentation with corroborative evidence. A random sample of subject data were verified by investigator evaluation of the EMR. **Results:** The majority of patients in the cohort had cirrhosis from MASLD (n = 13560; 45.2%), ALD (n = 8533, 28.4%), VLD (n = 3049;10.2%), Other (n = 2764; 9.2%), MetALD(n = 2093,7.0%). Of the steatotic disease etiologies, MetALD cirrhosis patients were more likely (21.1 MetALD, 16 ALD, and 12.6% MASLD) to be on dialysis and to report abstinence from alcohol (66.8% MetALD; 61.4% MASLD; 54.9% ALD). Patients with ALD (n = 2986/8533; 35.0%) were more likely ($p < 0.001$) to report active drinking than either those with MASLD (n = 2973, 21.9%) or MetALD (n = 554/2093,26.5%). Ascites was the most frequent cause of initial decompenstation in all etiologies. Patients with ALD and MetALD were more likely to have decompensated disease (ALD:5150/8533, 60.4%; MetALD:1459/2093, 69.7%) while patients with MASLD, VLD, and other etiologies were more likely to have compensated disease (MASLD:8342/13560, 61.5%; VLD:2044/3049, 67.0%; Other: 1965/2764, 71.1%). Of the patients with HCC (n = 2489), patients with MASLD, ALD, and MetALD were more likely to have decompensated HCC while patients with VLD and other etiologies were more likely to have compensated HCC (Table 1). Of those patients who had fibroscans, patients with ALD and MetALD were more likely ($p < 0.001$) to have KPA scores $\geq$ 15 compared to patients with other etiologies of liver disease. At the end of follow-up, mortality rate was highest ($p < 0.001$) in those with MetALD (47%) compared to that in the other etiologies (ALD:46.5, MASLD:46.6, VLD:40.4, and Other:29.5%). **Conclusion:** In this large single center cohort of patients evaluated over a 24-year period, patients with MetALD cirrhosis had higher rates of alcohol use, decompensation, dialysis dependence, stiffness scores on fibroscan, and higher rates of HCC. MetALD was associated with the highest overall mortality, suggesting the need for improved clinical recognition and management strategies, especially for alcohol cessation.

Table 1. Disease and hepatocellular carcinoma (HCC) status

Etiology of cirrhosis	MASLD	ALD	MetALD	VLD	Other	Totals
No HCC compensated (%)	7881 (58.1)	3181 (37.3)	573 (27.4)	1791 (58.7)	1901 (68.8)	15327 (51)
No HCC decompensated (%)	4892 (34.6)	4703 (55.1)	1262 (60.3)	774 (25.4)	751 (27.2)	12182(41)
HCC compensated (%)	461 (3.4)	201 (2.4)	61 (2.9)	253 (8.3)	64 (2.3)	1040(3)
HCC decompensated (%)	526 (3.9)	448 (5.3)	197 (9.4)	231 (7.6)	48 (1.7)	1450(5)
Total	13560 (45.2)	8533 (28.4)	2093 (69.8)	3049 (10.2)	2764 (9.2)	29999

ALD: alcohol-associated liver disease, MASLD: Metabolic-associated liver disease, MetALD: Features of both metabolic and alcohol associated liver disease, VLD: Viral hepatitis-associated liver disease.

Disclosures: Nicole Welch: Nothing to Disclose, Ana Ostojic: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Lars Deutz: Nothing to Disclose, Ryan Musich: Nothing to Disclose, John McMichael: Nothing to Disclose, Lopa Mishra: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

1606 | PROTOCOL FOR INITIATION OF MEDICATIONS FOR ALCOHOL USE DISORDER (MAUD) AT INDEX HOSPITALIZATION FOR LIVER TRANSPLANTATION IN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE

Rachel Zuzul[1] Andrew Muir[1] Stephanie Garbarino[1], [1]Duke University

Background: There has been a shift in the attitude on prolonged alcohol abstinence prior to transplant for patients with alcohol-associated liver disease (ALD) over the recent years with a focus on earlier liver transplantation (LT) in this population. However, patients with ALD who experience relapse have worse outcomes. Addressing underlying alcohol use disorder (AUD) using a multi-modal approach like pharmacotherapy, has been shown to be effective. Identifying patients at high risk for relapse post-LT and initiating medications for alcohol use disorder (MAUD) is feasible and safe and may reduce rates of relapse and improve post-transplant outcomes. The aim of this study was to evaluate the feasibility of a post-LT MAUD protocol. **Methods:** This was a single center, retrospective analysis. An internal protocol was implemented in January 2024 where all patients with ALD who were deemed high risk for relapse by prespecified criteria determined by a multi disciplinary psychosocial team at the time of listing were started on post-LT MAUD at the index hospitalization (Figure 1). Choice of MAUD agent was determined primarily by renal function with the first line agent being acamprosate. Patients were continued on MAUD for at least one year post-transplant. The primary endpoint was relapse after transplant. Phosphatidyl ethanol (PEth) levels were collected every 3 months for the two years post-LT to detect alcohol relapse, definited as a PEth > 20. **Results:** Sixty-three patients underwent LT for

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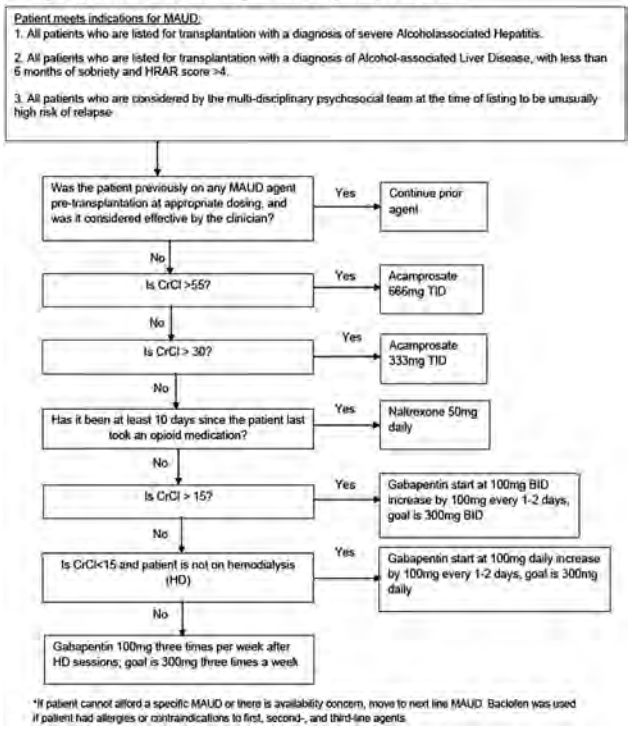
ALD between January 1, 2024 and April 14, 2025. Forty-two patients (67%) met the protocol indications for MAUD, and 42/42 (100%) initiated MAUD. Treatment regimens were acamprosate for 23 (55%) patients, gabapentin for 18 (43%), and naltrexone for one. Zero patients received baclofen. The median follow-up time for this patient cohort was 9 months (range 1-15 months). At the time of this analysis, 1/42 (2.4%) experienced relapse, and that patient prematurely discontinued their MAUD after 2 months of therapy due to reported lack of alcohol cravings. Of the patients who did not meet the protocol criteria for MAUD, 2/21 (9.5%) experienced relapse. **Conclusion:** Data on the use of MAUD in the post-transplant setting is limited, and this study found that implementation of a post-transplant MAUD protocol for patients undergoing LT with ALD that are deemed high risk for relapse was feasible. Early outcome data suggests low relapse rates for post-LT patients undergoing MAUD treatment. Two of the three patients with relapse were not on MAUD, suggesting there could be expansion of the eligibility criteria for MAUD in the protocol. Limitations include that this is a single-center, retrospective analysis and the limited follow-up time. Further research is needed to refine the criteria for MAUD therapy after LT and to understand the long-term outcomes of LT for AUD with MAUD.

Figure 1: Protocol for choice of MAUD agent for liver transplant in patients with ALD



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1607 | DIETARY QUERCETIN SUPPLEMENTATION ATTENUATES ALCOHOL INDUCED HEPATIC ER STRESS AND APOPTOSIS BY DECREASING KYNURENINE LEVELS

Leila Gobejishvili[1] Walter Rodriguez[2] Yali Wang[2] JingWen Zhang[2] Shirish Barve[2] Craig McClain[2],
[1]University of Louisville, [2]School of Medicine, University of Louisville, Louisville, KY, USA.

Background: Alcohol mediated production of hepatic kynurenine (KYN) has been shown to contribute to dysregulated lipid metabolism in a mouse model of alcohol-associated liver disease (ALD). This effect was mediated by activation of hepatic aryl hydrocarbon receptor (Ahr) by KYN. Hepatocyte specific Ahr deletion prevented alcohol induced lipid accumulation in the liver. The dietary flavonol, quercetin has been shown to alleviate alcohol induced steatosis, however the exact underlying molecular mechanisms are not known. Hence, the present work was performed to investigate quercetin mediated protection of alcohol induced steatosis and injury involving pathogenic hepatic KYN/Ahr signaling. **Methods:** C57Bl/6 mice were used in a chronic plus binge of ALD (10 plus one, NIAAA model). Mice were fed control and alcohol diet with and without quercetin, which was dissolved in the diet. Daily quercetin dose was calculated based on the amount of food consumed (100 mg/kg body weight daily). At the end of experiment plasma and liver tissues were collected. Plasma was used to analyze liver injury markers; liver tissue was used for metabolomic and gene expression analyses. Formalin fixed liver tissues were evaluated for hepatocyte apoptosis using terminal deoxynucleotidyl transferase dUTP nick end labeling ((TUNEL). Statistical analysis was carried out using one-way ANOVA. **Results:** Metabolomic analysis of liver tissues revealed that alcohol markedly increased kynurenine and decreased quercetin levels. Notably, quercetin supplementation decreased liver kynurenine levels and activation of Ahr as demonstrated by decreased the Ahr target gene, *Cyp1a1*. Pearson correlation analysis showed that high liver KYN levels significantly correlated with the liver injury marker, alanine transaminase (ALT) ($r = 0.66$, $P = 0.0002$) and negatively correlated with liver quercetin levels ($r = -0.55$, $P = 002$). Notably high liver quercetin levels were associated with lower ALT ($r = -0.525$, $P = 0.004$). Alcohol increased the liver to body weight ratio, which was prevented by quercetin. Alcohol induced liver endoplasmic reticulum (ER) stress was decreased by quercetin as demonstrated by significantly lower mRNA levels of ER stress markers *Chop, Atf3, Gadd45a,* and *Gadd45b*. Alcohol induced hepatocyte apoptosis was also markedly attenuated by quercetin supplementation. **Conclusion:** Alcohol induced liver injury in mice is

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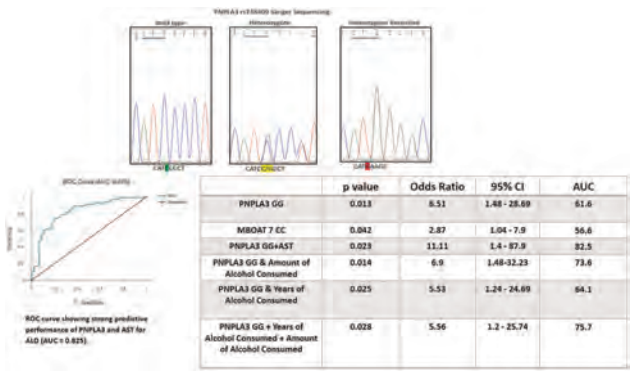
associated with decreased hepatic quercetin levels and increased production of kynurenine. Dietary quercetin supplementation decreases the levels and pathogenic signaling of kynurenine caused by alcohol.

Disclosures: Leila Gobejishvili: Nothing to Disclose, Walter Rodriguez: Nothing to Disclose, Yali Wang: Nothing to Disclose, JingWen Zhang: Nothing to Disclose, Shirish Barve: Nothing to Disclose, Craig McClain: Nothing to Disclose

1608 | PNPLA3 RS738409 RISK VARIANT OUTPERFORMS MBOAT7 RS641738 POLYMORPHISM IN PREDICTING ALCOHOL RELATED LIVER DISEASE (ALD) AND SHORT LEUKOCYTE TELOMERE LENGTH IS ASSOCIATED WITH HIGH FIB4 SCORE

Vaishali Yadav[1] Saggere Muralikrishna Shasthry[2] Kanica Kaushal[2] Mohit Varshney[2] Satender Singh[2] GURESH KUMAR[2] Rishabh Sharma[2] Nirupama Chatterjee[3] Nirupma Trehanpati[2] Shiv Kumar Sarin[2], [1]Institute of Liver and Biliary Sciences, [2]Institute of Liver and Biliary Sciences New Delhi, India, [3]Artemis Education & Research Artemis Hospital, Gurugram, India

Background: Alcohol related liver disease (ALD) is the leading cause of cirrhosis globally and in India. Despite heavy drinking, only ~30% develop steatohepatitis, suggesting a strong genetic influence. This study evaluated *PNPLA3* rs738409 (148M) and *MBOAT7* rs641738 risk variants as predictors of ALD and assessed whether combining them with clinical markers and leukocyte telomere length improves prediction. **Methods:** Patients with ALD (N = 183) and alcohol use disorder (AUD) without liver disease (N = 55) were enrolled. *PNPAL3* was genotyped by PCR-Sanger sequencing and TaqMan Assay was used for *MBOAT7*. Leukocyte telomere length was measured by qPCR and expressed as the T/S ratio. **Results:** Amongst the various clinical parameters AST (IU/L) (Aspartate Aminotransferase) levels were significantly high in patients with ALD compared to those with AUD with [108 (23.7–1179) vs. 30.7 (23–44), $p < 0.001$]. Interestingly, individuals with AUD had higher overall alcohol intake, both in quantity (155.6 ± 63.13 g vs. 120.6 ± 61.9 g, $p = 0.0004$) and duration (17.21 ± 10.07 years vs. 13.88 ± 5.99 years, $p = 0.0029$). The PNPLA3 rs738409 risk variant (CG/GG) was more prevalent in ALD than AUD (G = 0.355 vs. G = 0.214, $p < 0.01$). Similarly, MBOAT7 rs641738 risk variants (TC/CC) were also more frequent in ALD (C = 0.495 vs. C = 0.391, $p < 0.01$). AUC for PNPLA3 and MBOAT7 to predict ALD was 0.616 (95% CI: 0.92–3.45) and 0.566 (95% CI: 1.04–7.9), respectively. Combining both variants together offered little benefit and only PNPLA3 remained significant. Hence, PNPLA3-based models were tested for ALD: Model 1 (adjusted for AST) PNPLA3 GG genotype had OR 11.11 (CI: 1.4–87.9), AUC = 0.82. Model 2 (adjusted for alcohol amount): OR = 6.9 (CI: 1.48–32.23), AUC = 0.736. Model 3 (adjusted for duration): OR = 5.53 (CI: 1.24–24.69), AUC = 0.641. Model 4 (adjusted for both): OR = 5.56 (CI: 1.2–25.79), AUC = 0.757. A negative coefficient for alcohol usage in Models 2–4 suggests PNPLA3 adds genetic susceptibility to liver disease even at lower alcohol levels. Leukocyte telomere length (T/S ratio) was significantly shorter in ALD than AUD (8.545 ± 1.002 vs. 8.943 ± 0.9832, $p = 0.0193$), and inversely correlated with fibrosis severity (FIB-4: r = –0.64, $p < 0.001$). **Conclusion:** *PNPLA3* rs738409 is an independent ALD predictor, with *MBOAT7* showing weaker association. Combining *PNPLA3* with AST or alcohol intake improves risk prediction. And risk GG genotype of PNPALA3 increases ALD risk even at lower alcohol exposure.



	p value	Odds Ratio	95% CI	AUC
PNPLA3 GG	0.013	8.51	1.48 - 28.69	61.6
MBOAT 7 CC	0.042	2.87	1.04 - 7.9	56.6
PNPLA3 GG+AST	0.023	11.11	1.4 - 87.9	82.5
PNPLA3 GG & Amount of Alcohol Consumed	0.014	6.9	1.48-32.23	73.6
PNPLA3 GG & Years of Alcohol Consumed	0.025	5.53	1.24 - 24.69	64.1
PNPLA3 GG + Years of Alcohol Consumed + Amount of Alcohol Consumed	0.028	5.56	1.2 - 25.74	75.7

Disclosures: Vaishali Yadav: Nothing to Disclose, Saggere Muralikrishna Shasthry: Nothing to Disclose, Kanica Kaushal: Nothing to Disclose, Mohit Varshney: Nothing to Disclose, Satender Singh: Nothing to Disclose, GURESH KUMAR: Nothing to Disclose, Rishabh Sharma: Nothing to Disclose, Nirupama Chatterjee: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

1609 | PEPTIDE YY REDUCES CYTOTOXICITY OF CANDIDA ALBICANS IN ALCOHOL-ASSOCIATED LIVER DISEASE

Henriette Kreimeyer[1] Marcos F. Fondevila[1] Aenne Harberts[1] Fernanda Raya Tonetti[1] David Ben Schoeler[2] Eliane Münte[1] Phillipp Hartmann[3] Cristina Llorente[3] Bernhard Hube[4] Salomé LeibundGut-Landmann[5] Peter

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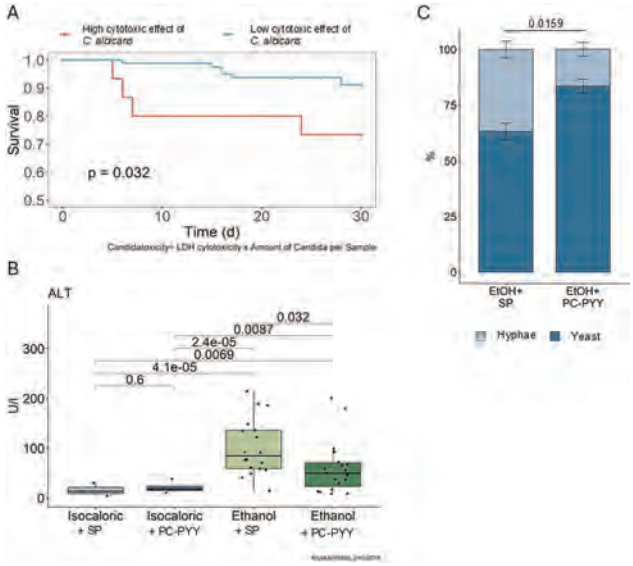
Stärkel[6] AlcHepNet Investigators[7] Bernd Schnabl[3], [1]University of California San Diego, [2]UCSD, [3]University of California, San Diego, [4]Leibniz Institute for Natural Product Research and Infection Biology, Jena; Germany, [5]University of Zurich, University of Exeter, [6]Cliniques universitaires Saint-Luc, Brussels, [7]Indiana University School of Medicine

Background: Transitioning from yeast to hyphal morphology enables *Candida albicans* to secrete the exotoxin candidalysin, invade the intestinal mucosa, and translocate to the bloodstream. Patients with alcohol-associated hepatitis have an increased abundance of *C. albicans* in the intestinal microbiome, and fecal presence of the gene encoding candidalysin is associated with reduced survival. Paneth cell-derived peptide YY (PC-PYY) inhibits hyphal growth of *C. albicans*. In this study, we evaluated the potential of different *C. albicans* strains isolated from patients with alcohol-associated hepatitis to induce cytotoxicity and explored the therapeutic potential of PC-PYY in a mouse model of ethanol-induced liver disease. **Methods:** *C. albicans* strains isolated from fecal samples of patients with alcohol-associated hepatitis were co-cultured with intestinal epithelial Caco-2 cells to assess in vitro cytotoxicity. Caco-2 cells and primary mouse hepatocytes were incubated with *C. albicans* and PC-PYY. Mice were subjected to chronic plus binge ethanol feeding. **Results:** *C. albicans* strains isolated from stool of patients with alcohol-associated hepatitis induced significant cytotoxicity in Caco-2 cells, and high cytotoxicity was associated with worse 30-day survival (Fig. A). This functional cytotoxicity is primarily associated with the hyphal form, largely driven by candidalysin. *C. albicans* strains which expressed candidalysin induced higher cytotoxicity in primary mouse hepatocytes compared with strains expressing no candidalysin. PC-PYY significantly reduced *C. albicans*-induced cytotoxicity in Caco-2 cells and primary mouse hepatocytes compared with a scrambled peptide as a control by inhibiting hyphal morphology. Peptide YY to chromogranin A ratio in intestinal crypts was significantly elevated in ethanol-fed mice compared with both isocaloric and antifungal-treated controls indicating that fungal overgrowth in ethanol-fed mice stimulates PC-PYY release. Immunofluorescence showed that in ethanol-fed mice, PC-PYY is increased compared with isocaloric controls. In mice subjected to the chronic plus binge ethanol feeding model, PC-PYY administration attenuated liver injury and steatosis, and reduced hyphae formation in the feces (Fig. B-C). **Conclusion:** PYY inhibits filamentous growth of *C. albicans* in vitro and alleviates ethanol-induced liver disease in mice, highlighting its potential as a therapy for patients with alcohol-associated liver disease.



Disclosures: Henriette Kreimeyer: Nothing to Disclose, Marcos F. Fondevila: Nothing to Disclose, Aenne Harberts: Nothing to Disclose, Fernanda Raya Tonetti: Nothing to Disclose, David Ben Schoeler: Nothing to Disclose, Eliane Münte: Nothing to Disclose, Phillipp Hartmann: Nothing to Disclose, Cristina Llorente: Nothing to Disclose, Bernhard Hube: Nothing to Disclose, Salomé LeibundGut-Landmann: Nothing to Disclose, Peter Stärkel: Nothing to Disclose, AlcHepNet Investigators: Nothing to Disclose, Bernd Schnabl: Nothing to Disclose

1610 | LIVER SINUSOIDAL ENDOTHELIAL CELLS EXHIBIT TRAINED IMMUNITY FEATURES FOLLOWING POLY I:C EXPOSURE

Weizhe Zhong[1] Benjamin Swartzwelter[1] Fiona Xhafi[1] Mengfei Liu[2], [1]Division of Digestive Disease, Internal Medicine, Yale University; Yale Liver Cente, Yale University, [2]Division of Digestive Disease, Internal Medicine, Yale University;Yale Liver Center, Yale University

Background: Trained immunity refers to the long-term functional reprogramming of innate immune cells, resulting in an altered response upon secondary stimulation. This concept was first described in myeloid cells, where prior exposure to microbial stimuli leads to epigenetic and metabolic changes that influence secondary responses to pathogen challenge. Liver sinusoidal endothelial cells (LSECs) form the primary barrier between circulating blood and hepatic parenchymal cells. Beyond their structural role, LSECs possesses multiple innate-like immune functions by secreting

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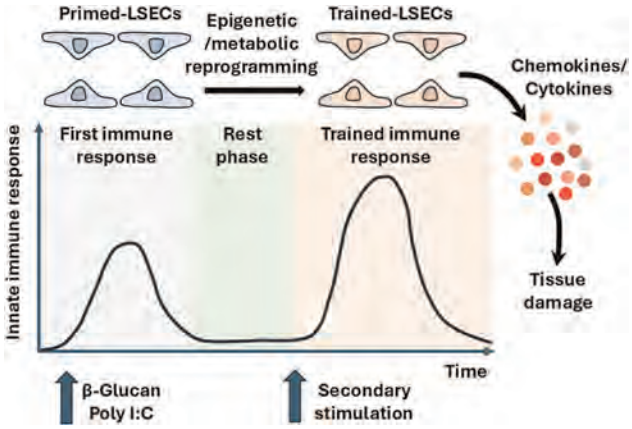
inflammatory cytokines and interacting with immune cells. However, whether and how LSECs undergo trained immunity remains unknown. This study aims to determine whether LSECs can acquire a trained immunity–like phenotype in response to microbial stimuli. **Methods:** We established an *ex vivo* model to assess innate immune memory in LSECs. Mice were intraperitoneally injected with either PBS (control), 1 mg of β-glucan, or 200 μg of Poly I:C. After a 7-day resting period, mice were sacrificed and livers harvested. Liver tissues were processed by perfusion and enzymatic digestion. LSECs were enriched using magnetic bead-based selection for CD146-positive cells. Purified LSECs were restimulated with IFNγ, IFN-β, LPS, or TNF-α, and immune gene expression was assessed by PCR. In parallel, bone marrow cells were isolated from the femurs and tibias of treated mice and differentiated into bone marrow–derived macrophages (BMDMs) using colony-stimulating factor (CSF). Inflammatory cytokine expression in BMDMs was similarly analyzed by PCR. **Results:** Poly I:C priming induced a pronounced proinflammatory response in LSECs upon secondary stimulation, characterized by significantly elevated expression of inflammatory mediators (*Cxcl9* and *Il6*). This enhancement was particularly evident following IFN-β and LPS challenges. In addition, increased expression of *Ccl2*, *Cxcl1*, and *Vcam1* was observed across multiple stimuli in Poly I:C–primed LSECs, supporting the acquisition of a trained immunity phenotype. A comparable effect was observed in BMDMs, where LPS stimulation led to a marked upregulation of *Il6* mRNA expression in cells primed with either β-glucan or Poly I:C, relative to PBS-treated controls. These data are consistent with the induction of trained immunity in both endothelial and myeloid compartments following exposure to stimuli. **Conclusion:** Our findings provide the first evidence that LSECs are capable of developing innate immune memory in the form of trained immunity. This observation expands our understanding of the potential roles of liver structural cells in innate immune responses of the liver.



Disclosures: Weizhe Zhong: Nothing to Disclose, Benjamin Swartzwelter: Nothing to Disclose, Fiona Xhafi: Nothing to Disclose, Mengfei Liu: Nothing to Disclose

1611 | FIRST IN LINE: A SUCCESSFUL EARLY LIVER TRANSPLANT FOR CATASTROPHIC SEVERE ALCOHOL-ASSOCIATED HEPATITIS USING THE ELFSAH PROTOCOL AT A TERTIARY CENTER

Rachel Patel[1] Caty Davenport[1] Daniel Logatto[1] Asuwin Anandaram[1] Fahad Khan[1] Samir Patel[1] George Rofaiel[1] Shahid Malik[1], [1]Lehigh Valley Health Network

Background: Severe alcohol-associated hepatitis (SAH), defined by a MELD-Na ≥20 or Maddrey's DF ≥32, is associated with high short-term mortality. In catastrophic SAH (MELD-Na ≥35 or DF ≥100), outcomes are especially poor. Corticosteroids, once the mainstay of treatment, show limited efficacy in this subgroup and may delay transplant. The Expedited Liver Transplantation as First-Line Therapy for Severe Alcohol-Associated Hepatitis (ELFSAH) protocol recommends deferring steroids and prioritizing transplant in these patients. We describe the first successful application of the ELFSAH protocol at a large tertiary center. **Methods:** A 31-year-old woman with alcohol use disorder presented with jaundice, abdominal pain, and acute decompensation. Imaging revealed cirrhosis, steatosis, ascites, and pleural effusions. Labs showed bilirubin 20 mg/dL, INR 5.5, creatinine >4 mg/dL, MELD-Na >40, and DF 120—consistent with catastrophic SAH. She developed multi-organ failure requiring ICU care and renal replacement therapy. In accordance with ELFSAH, corticosteroids were deferred and transplant evaluation was initiated. **Results:** The patient was evaluated by transplant hepatology, surgery, psychiatry, and social work. She had strong psychosocial support and commitment to abstinence. She was listed and successfully transplanted within 3 days. Explant pathology confirmed cirrhosis with superimposed SAH. Postoperatively, she recovered well, was discharged in one week, and remains abstinent with normal liver function on outpatient follow-up. Her management includes behavioral therapy, acamprosate, and serial PETH testing. **Conclusion:** The application of the ELFSAH protocol in this case of catastrophic SAH resulted in a successful liver transplant and recovery for a patient who would likely not have survived under traditional management. As liver transplant programs increasingly adopt early transplantation strategies for SAH, this case serves as

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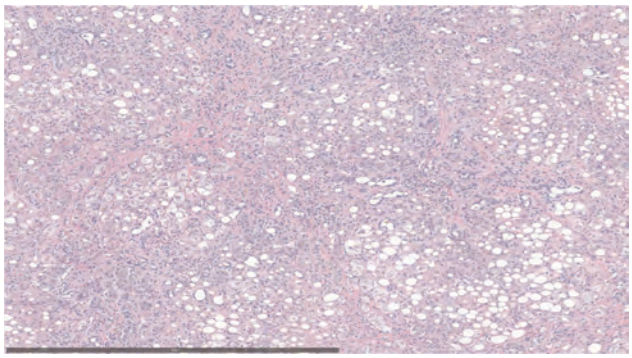
a powerful example of how evidence-based, patient-centered care can redefine outcomes in one of the most challenging areas of transplant hepatology.

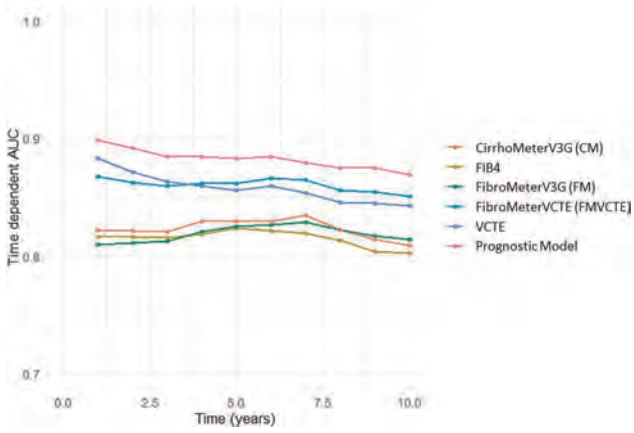


Disclosures: Rachel Patel: Nothing to Disclose, Caty Davenport: Nothing to Disclose, Daniel Logatto: Nothing to Disclose, Asuwin Anandaram: Nothing to Disclose, Fahad Khan: Nothing to Disclose, Samir Patel: Nothing to Disclose, George Rofaiel: Nothing to Disclose, Shahid Malik: Nothing to Disclose

1612 | NON-INVASIVE TESTS FOR PROGNOSTICATION IN STEATOTIC LIVER DISEASES: RESULTS: FROM A LONG TERM FOLLOW-UP COHORT OF 3,442 PATIENTS

Jérôme Boursier Marc De Saint Loup[1] Marine Roux[2] Marc Fadel[1] Jean-Marie Chrétien[1] Valerie MOAL[1] LANNES ADRIEN[1] Isabelle Fouchard[1] Pierre Celea[1] Sandra Girre[1] Audrey Morisset[1] Andrea Klingberg[1] Nathanaelle Cornet[1] Jeanne Fichez[1] Anita Paisant[2] Sophie Michalak[1] Christophe Aube[2] frederic oberti[1] Paul Cales[2], [1]Angers University Hospital, [2]Angers University

Background: Cross-sectional studies in steatotic liver diseases (SLD) have shown that elastography and specialized blood tests are more accurate than simple blood tests for diagnosing liver fibrosis, and that combination of biology with elastography offers the highest accuracy. We aimed to evaluate how this ranking of diagnostic tests translates into prognostic accuracy in a large cohort with long-term follow-up. **Methods:** 3,442 patients with SLD (MASLD or alcohol) who underwent non-invasive testing in the Hepatology department of a tertiary care center between 06/2004 and 12/2022 were included. All patients had vibration-controlled transient elastography (VCTE) and four blood tests: the simple blood test FIB4, the specialized blood tests FibroMeter^{V3G} (FM, for advanced fibrosis) and CirrhoMeter^{V3G} (CM, for cirrhosis), and the FibroMeter^{VCTE} (FMVCTE, combination of VCTE with biology for advanced fibrosis). Clinical events during the follow-up were retrieved using CIM10 codes. Liver-related event (LRE) was defined as cirrhosis complication or hepatocellular carcinoma. **Results:** Median age was 59.4 years, 72% of patients were male, and median VCTE result was 9.5 kPa (IQR: 6.1-19.6). 1,440 patients (42%) had MASLD and 2,002 (58%) had excessive alcohol consumption (MetALD/ALD). 733 LRE occurred during the median 5.0 years follow-up (IQR: 2.2-9.0). AUC(t) for predicting LRE at 3 years was 0.82 ± 0.02 for FIB4, FM: 0.81 ± 0.02, CM: 0.82 ± 0.02, VCTE: 0.86 ± 0.03, and FMVCTE: 0.86 ± 0.02. AUC(t) for 5-year prediction was 0.82 ± 0.02 for FIB4, FM: 0.82 ± 0.03, CM: 0.83 ± 0.02, VCTE: 0.86 ± 0.03, FMVCTE: 0.86 ± 0.02. AUC(t) for 10-year prediction was 0.80 ± 0.02 for FIB4, FM: 0.81 ± 0.02, CM: 0.81 ± 0.02 VCTE: 0.84 ± 0.02, FMVCTE: 0.85 ± 0.02. There was no significant difference in AUC(t) between the three blood tests (FIB4, FM, CM) at each time horizon. VCTE and FMVCTE had significantly higher AUC(t) than the three blood tests, with no significant difference between VCTE vs FMVCTE. VCTE, prothrombin time, α2macroglobulin, gammaGT and etiology (MASLD vs alcohol) were independent predictors of LRE. A score combining these five parameters provided the highest AUC(t) (3-year prediction: 0.88 ± 0.02, 5-year: 0.88 ± 0.02, 10-year: 0.87 ± 0.02), with significant difference compared to the five non-invasive tests evaluated (all p values ≤ 0.010). Sensitivity analysis yielded similar results in MASLD and alcohol groups. At fixed results of non-invasive tests, hazard ratio for LRE was higher in patients with excessive alcohol consumption, confirming that alcoholic liver disease has a more aggressive course than MASLD. **Conclusion:** Non-invasive diagnostic tests have very good prognostic accuracy in SLD, with elastography being more accurate than blood tests. However, a specific risk score outperforms diagnostic tests for prognostication. Efforts should be made to develop new risk scores calibrated on events rather than liver lesions to stratify the disease risk.



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1613 | MUSCLE INJURY IS CLOSELY RELATED TO HEPATIC ENCEPHALOPATHY IN MALE CHINESE PATIENTS WITH ALCOHOL - RELATED LIVER DISEASE

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Background: Alcohol-related liver disease (ALD) is a series of liver damage caused by long-term excessive alcohol consumption. Its pathological process includes alcoholic hepatitis (AH), alcohol-related cirrhosis (AC), and acute alcoholic hepatitis manifested as acute-on-chronic liver failure. In this process, hepatic encephalopathy (HE), sarcopenia, and myosteatosis are common complications, with complex interactions among them, which may affect their survival. This study aimed to evaluate the occurrence of hepatic encephalopathy and muscle damage (sarcopenia, myosteatosis) in male ALD patients in China, the association between muscle damage and hepatic encephalopathy, as well as the risk factors and prognosis of hepatic encephalopathy. It was determined by using the skeletal muscle index at the third lumbar vertebra level (L3-SMI), BMI, mean, etc. **Methods:** ALD patients hospitalized in Beijing Ditan Hospital affiliated to Capital Medical University and the Fourth People's Hospital of Qinghai Province from 2015 to 2024 were retrospectively included, and their survival status was evaluated through 6-month, 12-month, and 24-month follow-up based on the baseline time. The Cox proportional hazards regression model was used to estimate the survival factors of patients. **Results:** This study included 338 ALD patients, who were followed up for 6 months, 12 months, and 24 months respectively or until the end of the study. Among the ALD patients, 162 had sarcopenia, 241 had myosteatosis, 137 had myosteatosis combined with sarcopenia, 75 had no muscle damage, and 74 had hepatic encephalopathy. The L3-SMI of patients with hepatic encephalopathy was lower than that of patients without hepatic encephalopathy (39.68 ± 8.47cm2/m2 vs 43.65 ± 9.89cm2/m2). The prevalence of myosteatosis in patients with alcohol-related liver disease was significantly higher than that of sarcopenia and hepatic encephalopathy (71.3% vs 47.93% vs 21.89%). L3-SMI, alcoholic hepatitis, alcoholic cirrhosis, liver failure, myosteatosis, ascites, rupture and bleeding of esophagogastric varices, aspartate aminotransferase, total bilirubin, albumin, PT, INR, WBC, PLT, CR, serum sodium, hemoglobin, etc. may be related to hepatic encephalopathy. The 338 ALD patients were followed up for 6 months, 12 months, and 24 months respectively according to the baseline time (patients who did not reach the follow-up time were excluded according to the follow-up time), and the overall survival rates were 90.53% (306/338), 87.57% (296/338), and 78.31% (195/249) respectively. The mortality of patients with liver failure, sarcopenia, decreased albumin, infection, and ascites increased significantly. Multivariate Cox regression analysis showed that liver failure and infection were independent risk factors for short-term death, while liver failure and sarcopenia were independent risk factors for death at 12 and 24 months, and ascites was an independent risk factor for death at 12 months. The hazard ratios for death at 6 months (95% confidence interval) were 0.287 (0.129 - 0.639) and 1.090 (1.021 - 1.184) respectively; the hazard ratios for death at 12 months (95% confidence interval) were 0.449 (0.263 - 0.768), 0.583 (0.347 - 0.981), and 2.321 (1.222 - 4.410) respectively; the hazard ratios for death at 24 months (95% confidence interval) were 0.390 (0.211 - 0.720) and 1.849 (1.020 - 3.350) respectively. **Conclusion:** Hepatic encephalopathy is significantly associated with sarcopenia. Sarcopenia is more likely to lead to hepatic encephalopathy and is an independent risk factor for hepatic encephalopathy. Compared with sarcopenia, myosteatosis is more likely to occur in ALD patients, but there is no significant correlation between myosteatosis and hepatic encephalopathy. Sarcopenia and liver failure are independent risk factors for the onset of hepatic encephalopathy. Sarcopenia and liver failure are independent risk factors for death of patients with alcohol-related liver disease at 12 and 24 months, while sarcopenia has little impact on short-term death.

Disclosures: xiaoting Ma: Nothing to Disclose, Yu Zhang: Nothing to Disclose, Song Yang: Nothing to Disclose, Guoying Yu: Nothing to Disclose

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1614 | POLYENE PHOSPHATIDYLCHOLINE INJECTION REGULATES LIPID HOMEOSTASIS VIA AKT-PDE3-PKA IN MICE

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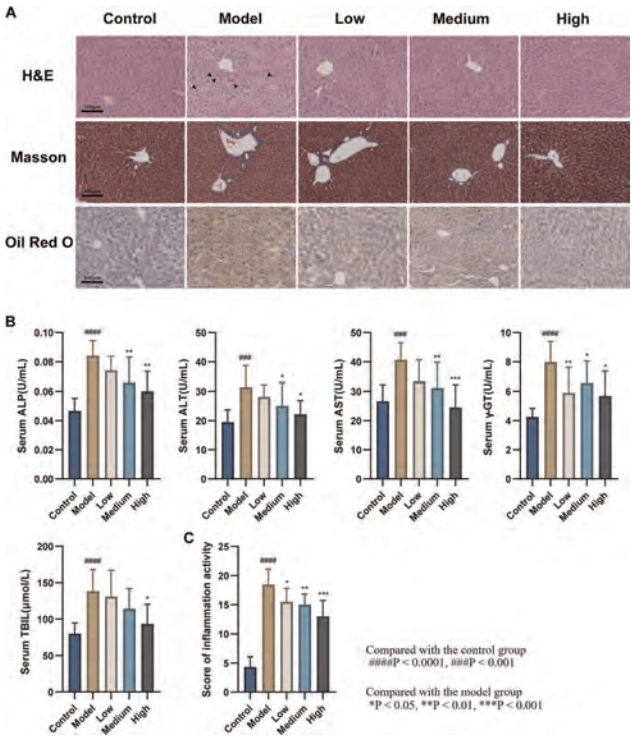
Background: Alcoholic liver disease (ALD) is a common liver injury disorder and a growing health concern worldwide.Clinically, the prevention and treatment of alcoholic liver disease are best achieved through abstinence from alcohol, accompanied by the use of hepatoprotective drugs and nutritional support during the period of alcohol cessation.Polyene phosphatidylcholine (PPC) is commonly used as a hepatoprotective medication for a variety of liver diseases in China.The aim of the study is to investigate the mechanisms of PPC in preventing and treating ALD in mice. **Methods:** Ninety standard inbred strain C57BL/6J male mice aged 6 weeks were randomly divided into five groups, with 18 mice in each group. The groups were as follows: the control group was fed a non-alcoholic liquid diet; the alcoholic liver injury model group; the group fed an alcoholic liquid diet + PPC (50 mg/kg); the group fed analcoholic liquid diet + PPC (100 mg/kg); and the group fed an alcoholic liquid diet + PPC (200mg/kg). The feeding period lasted for 12 weeks. After the confirmation of alcoholic liver injury through blood and liver tissue slice analyses in the alcohol-administered groups, indicating the successful establishment of the alcoholic liver injury model, the corresponding concentration of drug intervention treatment was initiated. Histopathological analyses were measured by standard hematoxylin and eosin (H&E) staining、Masson's trichrome staining and Oil Red O staining. Liver damage was assessed by serum ALT, AST,ALP,γ-GGT,TBIL. Lipid metabolism levels were assessed by TG,TC,HDL-c,LDL-c. The level of oxidative stress were assessed by MDA,GSH,SOD. Serum inflammatory index were assessed by TNF-α,IL-6,IL-1β, TGF-β,LPS. RNA-seq technology was performed to search for specific differential genes and related signaling pathways. Western blotting was used to detect differentially expressed genes and related signaling pathway changes in the liver tissue. **Results:** PPC injection significantly improved the pathological damage and steatosis (Figure A), reduced the content of serum liver injury-related indexes(Figure B,C), improved lipid metabolism in serum and liver tissues, improved the levels of oxidative stress in the serum and liver tissues, reduced serum endotoxin LPS content and expression of inflammation-related factors TNF-α, IL-6, IL-1B and TGF-βin mice with alcoholic liver injury model. The three genes(Akt1, Prkaca, and Pde3b) played an important role in drug regulation for the treatment of alcoholic liver disease. **Conclusion:** The improvement in liver function by PPC injectiom was a complex, multi-pathway process. PPC injection prevented and treated ALD potentially by regulating the Akt-PDE3-PKA signaling pathway to modulate lipid homeostasis.



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1615 | SERUM LEVELS OF CANDIDA ALBICANS 65-KDA MANNOPROTEIN (CAMP65P) CORRELATE WITH LIVER DISEASE IN PATIENTS WITH ALCOHOL USE DISORDER

Julia Schnabl[1] Silvia Sandini[2] Peter Starkel[3] Phillipp Hartmann[4], [1]University of California, [2]National Centre

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Background: **Background:** Alcohol-associated liver disease is a global health burden with high morbidity and mortality, and the fungal microbiome is important for its progression. In particular, *Candida albicans* and *C. albicans*-reactive T helper 17 (Th17) cells contribute to alcohol-associated liver disease. Specific *C. albicans* antigens that activate Th17 cells during this disease are unknown. The *C. albicans* 65-kDa mannoprotein (CaMp65p) is one of the most abundant and immunodominant proteins of *C. albicans*, and is capable to elicit robust T cell and interleukin (IL)-17A responses. The aim of this study was to measure levels of CaMp65p in serum of patients with alcohol use disorder and liver disease. **Methods:** **Methods:** Serum CaMp65p levels were measured in the serum of 60 patients with alcohol use disorder using an indirect competitive Enzyme-Linked Immunoabsorbent Assay (ELISA). Serum CaMp65p levels were correlated with liver disease severity. **Results:** **Results:** Serum CaMp65p levels positively correlated with several clinical and biochemical markers of liver injury and disease within the patient group with alcohol use disorder, including serum aspartate aminotransferase (AST; $R = 0.33$, $P = 0.0092$), alanine amino-transferase (ALT; $R = 0.27$, $P = 0.037$), gamma-glutamyl transferase (GGT; $R = 0.35$, $P = 0.0055$) and alkaline phosphatase ($R = 0.36$, $P = 0.0052$), and with the circulating M65 fragment of cytokeratin 18 (CK18-M65; $R = 0.51$, $P = 0.0012$), a marker of hepatocyte death. In addition, patients with alcohol use disorder in the upper quartile had significantly higher liver stiffness ($P = 0.0022$). Serum CaMp65p was significantly higher in patients with fibrosis stage F2–F4 as compared with patients with no or minimal fibrosis F0–F1 ($P = 0.0082$). The area under curve (AUC) for detecting F2–F4 fibrosis was 0.70. **Conclusion:** **Conclusion:** Elevated serum CaMp65p levels are associated not only with more severe hepatic injury, but also liver fibrosis in patients with alcohol use disorder. Therefore, CaMp65p may serve as a non-invasive biomarker for fibrosis assessment in patients with alcohol use disorder.

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1616 | ENDOSCOPIC SLEEVE GASTROPLASTY IS ASSOCIATED WITH LOWER RISK OF ALCOHOL-RELATED HARM THAN SLEEVE GASTRECTOMY: A MATCHED COHORT ANALYSIS OF 608 PATIENTS

Brittany Bromfield[1] Esperance Schaefer[1] Pichamol Jirapinyo[1] Nikroo Hashemi[1], [1]Brigham and Women's Hospital

Background: Sleeve gastrectomy (SG) is the most performed bariatric surgery, which is effective for metabolic dysfunction associated liver disease but may increase alcohol use disorder (AUD) risk and risk of alcohol-related liver disease. Changes in gastric anatomy may accelerate alcohol absorption and systemic exposure. Endoscopic sleeve gastroplasty (ESG) is an anatomy-sparing, minimally invasive endoscopic bariatric procedure. We evaluated the comparative incidence of alcohol-related outcomes in matched patients undergoing ESG versus SG. **Methods:** We conducted a retrospective, 1:1 matched cohort study of patients undergoing ESG ($n = 304$) or SG ($n = 304$) from January 2013–May 2024 within a single center healthcare system. Patients were matched based on age, sex, race, and comparative health (comorbidity burden, medical visit frequency). Excluded patients with pre-existing AUD (ICD-10 codes, manual review). Primary outcome: incident AUD defined by ICD-10 diagnosis, AUD-related hospitalization, or AUDIT-C ≥ 7; Secondary: conversion from a negative baseline screen (AUDIT-C < 3 for females, < 4 for males) to at-risk drinking (AUDIT-C $\geq 3/\geq 4$). Statistical comparisons used Fisher's exact test, Kaplan-Meier analysis, and logistic regression with subgroup analyses (female, BMI < 40 or > 40, baseline non-drinkers). **Results:** A total of 608 patients with BMI ≥ 30 kg/m² were included. Cohorts comparing ESG to SG were balanced in age (mean 45.9 vs. 45.5 years), sex (90.5% vs. 92.1% female), and psychiatric comorbidity (43.4% vs. 48.7%). Mean baseline AUDIT-C scores were low and similar between groups (0.73 ± 1.0 for ESG vs. 0.86 ± 1.1 for SG). ESG patients had lower baseline BMI (38.1 ± 7.0 vs 43.0 ± 6.4 kg/m²; $p < 0.001$), consistent with real-world clinical selection. Over a median follow-up of 2.8 years (IQR 1.5–4.2), 0/304 ESG patients (0.0%) developed incident AUD compared to 23/304 SG patients (7.6%) ($p < 0.001$, exact test) (Figure 1a). Among SG patients, median time to AUD diagnosis

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was 1.1 years (IQR 0.8–1.7). Among 544 patients with negative baseline screens and pre/post AUDIT-C data, conversion to at-risk drinking was lower after ESG than SG (5.8% vs. 13.3%; OR 2.48, 95% CI 1.34–4.59; $p = 0.0033$), with divergence evident by 12 months (log-rank $p < 0.001$). Subgroup analysis demonstrated the protective effect of ESG was most pronounced among: Females: 6.2% ESG vs. 13.6% SG (OR 2.37, NNT = 14), baseline non-drinkers: 3.0% ESG vs. 9.9% SG (OR 3.50, NNT = 15) and BMI < 40 kg/m²: 5.0% ESG vs. 16.7% SG (OR 3.82, NNT = 9) (Figure 1b). **Conclusion:** In this first-ever study comparing alcohol-related outcomes after ESG vs. SG, ESG was associated with no incident AUD and lower risk of at-risk drinking. The protective association was consistent across key subgroups. Findings provide compelling evidence that procedural choice may influence alcohol-related harm, with ESG emerging as a safer alternative. Prospective studies are needed to validate these findings.

Figure 1A. Time to Incident Alcohol Use Disorder After ESG vs. SG.

Figure 1B. Conversion to At-Risk Drinking by Subgroup After ESG vs. SG.

Figure 1. Comparative Risk of Alcohol-Related Outcomes Following Bariatric Procedures. (A) Kaplan-Meier analysis shows probability of remaining free from alcohol use disorder (AUD) among matched patients undergoing endoscopic sleeve gastroplasty (ESG) versus sleeve gastrectomy (SG). Over a median follow-up of 2.8 years, no ESG patients developed AUD, while 7.6% of SG patients did (log-rank p = 0.00051). (B) displays rates of conversion to at-risk drinking, defined by sex-specific AUDIT-C thresholds, across key subgroups. ESG conferred significantly lower risk than SG in all strata: overall (5.8% vs. 13.3%, p = 0.003; NNT = 13), females (6.2% vs. 13.6%, p = 0.007; NNT = 14), baseline non-drinkers (3.0% vs. 9.9%, p = 0.019; NNT = 14), and patients with BMI <40 kg/m² (5.0% vs. 16.7%, p = 0.010; NNT = 9). These findings highlight the protective effect of ESG against postoperative escalation in alcohol use.

Disclosures: Brittany Bromfield: Nothing to Disclose, Esperance Schaefer: Nothing to Disclose, Pichamol Jirapinyo: Bariendo: Co-Founder, Boston Scientific: Consultant, Cook Medical: Consultant, EndoSim: Royalties or patent beneficiary, ERBE: Consultant, Fractyl: Consultant, Madrigal: Consultant, Merit Medical: Consultant, Morphic Medical: Consultant, Olympus: Consultant, Spatz Medical: Consultant, USGI Medical: Consultant, Nikroo Hashemi: Nothing to Disclose

1617 | SHIFTING THE PROGNOSTIC WINDOW: DAY-4 LILLE SCORE AS A TOOL FOR EARLY CLINICAL DECISION-MAKING IN ALCOHOLIC HEPATITIS

Harisimha Godha[1] Mallikarjun Patil[1] Sunu Sara Kurien[1] Harshad Devarbhavi[2], [1]St. John's Medical College, Bengaluru, [2]St. Johns Medical College, Bengaluru

Background: Severe alcoholic hepatitis (SAH) carries high short-term mortality. Corticosteroids remain standard therapy for eligible patients, but their benefits are limited to responders. The Lille score, calculated on Day 7 of therapy, is widely used to assess steroid response. However, a 7-day wait may delay critical decisions, including therapy discontinuation and early transplant referral. Emerging evidence suggests that Day-4 Lille score may offer comparable prognostic accuracy, enabling earlier clinical intervention and reduced steroid-related complications. This study aimed to assess the prognostic performance of the Day-4 Lille score in predicting 28-day mortality and its concordance with Day-7 scores. **Methods:** In this prospective observational study conducted from March 2023 to March 2025, 154 patients with SAH were screened; 79 met inclusion criteria and were initiated on oral prednisolone (40 mg daily with 10 mg/week taper). Exclusions were due to AKI (25.5%), GI bleed (18.4%), or SBP (14.2%). Baseline and follow-up clinical data were collected, including Day-4 and Day-7 Lille scores. Responders were defined as Lille score < 0.45. Outcomes included 28-day mortality, Lille score concordance, and complication rates. **Results:** Baseline characteristics are summarized in Table 1. Mean age was 41.3 years. Baseline bilirubin was 20.5 mg/dL, decreasing to 17.1 mg/dL by Days 4 and 7. Mean MELD score was 25.7; MDF was 79.3. Among 79 patients with complete data, 84.8% were responders on Day 4 and 77.2% on Day 7. Concordance between Day-4 and Day-7 classifications was 87.3%. Pearson's $r = 0.69$ and Spearman's $\rho = 0.68$, indicating strong correlation. A total of 19 episodes of infections (24%) were recorded, with 9 (11%) occurring between days 4 and 7. **Conclusion:** The Day-4 Lille score is a reliable early predictor of steroid response and 28-day mortality in SAH. High concordance with Day-7 classification supports its use for earlier clinical decision-making. Early identification of non-responders may allow timely corticosteroid discontinuation, potentially reducing steroid-related complications. Routine use of the Day-4 Lille score may enhance risk stratification and patient safety in SAH management.

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Table 1: Baseline demographics, clinical characteristics and outcomes.

Variable	n = 79
Age, years (Mean, ±SD)	41.3 ± 7
Jaundice	100%
Ascites	30%
Albumin g/dL (Mean, ±SD)	2.73 ±0.65
Total Bilirubin mg/dL (day 1) (Mean, ±SD)	20.5 ± 8.33
Total Bilirubin mg/dL (day 4) (Mean, ±SD)	17.1 ± 7.74
Total Bilirubin mg/dL (day 7) (Mean, ±SD)	17.1 ± 9.4
AST U/L (Mean, ±SD)	169.5 ± 83.86
ALT U/L (Median, IQR)	44.5 ± 26.5
Serum Creatinine mg/dL on admission (Median, IQR)	0.65 ± 0.31
Prothrombin time (Median, IQR)	23 ± 8.85
International normalized ratio (Mean, ±SD)	2.12 ± 0.64
MDF	79.3 ± 34.61
MELD	25.7 ± 4.64
ABIC	7.87 ± 0.97
Lille score-day 4 (Median, IQR)	0.19 ± 0.30
Lille score-day 7 (Median, IQR)	0.15 ± 0.339
Total infections at 28 days	19 (24%)
Infections between day 4 and day 7	9 (11.5%)
Pearson correlation coefficient	0.69
Mortality at 28 days (18/79)	22%

Abbreviation: AST-Aspartate Aminotransferase; ALT-Alanine Aminotransferase; MDF-Maddrey discriminant function; ABIC – age-bilirubin-INR- creatinine.

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1618 | TARGETING THE LEUKOTRIENE-MEDIATED PATHWAY IMPROVES ALCOHOL-ASSOCIATED LIVER DAMAGE IN A MOUSE MODEL

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Background: Alcoholic hepatitis (AH) is frequently accompanied by cholestasis or impairment in bile formation or flow, resulting in fatigue, pruritus, jaundice, and high levels of AST. Oxylipin profiles are altered in serum and fecal samples from patients with ALD; however, the impact of oxylipins on the pathogenesis of ALD remains unclear. **Methods:** Mice were given chronic ethanol (EtOH) feeding for 4 weeks and then subjected to a sub-toxic dose of α-naphthylisothiocyanate (ANIT) to establish alcohol-associated cholestasis and hepatitis (AlChoHep). Targeted metabolomics was applied to determine oxylipin profiles in liver samples from mice following pair-feeding, EtOH-feeding, and EtOH-feeding with ANIT. Data from mouse models were compared with previously published data from ALD patients to identify oxylipins with translational significance. Leukotrienes (LTs) are a family of pro-inflammatory mediators mainly derived from arachidonic acid. Montelukast, a leukotriene receptor antagonist (LTRi), was administered via intraperitoneal injection to inhibit the CysLT1 receptor, beginning ~16 hours before ANIT treatment and continued daily thereafter. **Results:** Hepatic levels of 57 out of 117 oxylipins were significantly altered in EtOH-fed mice, which were more dominant in EtOH-fed mice with ANIT. Levels of 16 oxylipins were also altered in patients with ALD. Interestingly, among these significantly altered oxylipins, oxylipins derived from arachidonic acid are enriched. In AlChoHep mice, LTRi treatment decreased serum levels of ALT, AST, and ALP, indicating improved liver injury. LTRi also reduced hepatic total bile acids (TBA) levels and gall bladder weight. Histologically, AlChoHep mice showed less necrosis and inflammation in the liver following LTRi treatment. **Conclusion:** Taken together, our results indicate that oxylipins are altered in ALD, and treatments targeting LT-mediated pathways can be beneficial.

Disclosures: Elijah Burks: Nothing to Disclose, Xiao-Ming Yin: Nothing to Disclose, Shengmin Yan: Nothing to Disclose

1619 | TRENDS IN ALCOHOLIC HEPATITIS, LIVER CIRRHOSIS PROGRESSION, AND LIVER TRANSPLANTATION BEFORE AND AFTER THE COVID-19 PANDEMIC: A 10-YEAR RETROSPECTIVE ANALYSIS

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Background: Alcohol-related liver disease (ALD) remains a significant public health concern, with evolving patterns potentially influenced by the COVID-19 pandemic. This study examines national trends in alcoholic hepatitis, progression to liver cirrhosis, and liver transplantation across a 10-year span, including pre- and post-COVID eras. **Methods:** We conducted a retrospective study using the TriNetX database, analyzing inpatient admissions from 2015–2024. New incidence of alcoholic hepatitis (ICD-10 K70.1), progression to cirrhosis and liver transplant were

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identified and compared pre- and post-COVID across time, sex, age, race, and ethnicity. **Results:** Out of a total cohort of 15,003,014 individuals, 100,834 cases of alcoholic hepatitis were identified between 2015 and 2024. The incidence proportion rose significantly from 0.057% (3,907 cases) in 2015 to 0.125% (7,828 cases) in 2024 ($p < 0.01$). Among males, incidence increased from 0.095% (2,593) to 0.209% (5,088), while among females, it rose from 0.032% (1,253) to 0.072% (2,647) ($p < 0.01$ for both). Hispanic or Latino individuals experienced the most notable rise, from 0.071% (420) to 0.189% (1,036) over the same period ($p < 0.01$). In the pre-COVID period (2019), the incidence was 0.091% (8,067). During the early COVID phase (2020–2021), it rose to 0.107% (9,323) and 0.11% (9,516), respectively. In the post-COVID phase (2022–2024), incidence continued to climb from 0.11% (8,813) in 2022 to 0.125% (7,828) in 2024. The progression to liver cirrhosis also showed a marked increase, from 5.664% (2,722) in 2015 to 17.8% (4,690) in 2024. Correspondingly, the need for liver transplantation rose sharply, from 0.197% (100 cases) in 2015 to 1.405% (569 cases) in 2024. **Conclusion:** The incidence of alcoholic hepatitis and its progression to cirrhosis and liver transplantation increased significantly over the past decade, with a notable acceleration during and after the COVID-19 pandemic. These findings underscore the pandemic's potential role in amplifying alcohol-related liver disease burden across demographic groups.

	Alcohol hepatitis		Liver cirrhosis		Liver transplant	
	2015	2024	2015	2024	2015	2024
Gender						
Male	0.095	0.209	5.761%	17.219	0.626%	1.567%
Female	0.032	0.072	5.342%	19.298%	0.418%	1.668%
Race						
American Indian or Alaska Native	0.392%	0.597%	7.208%	25.049%	0.335%	1.533%
Asian	0.026%	0.066%	6.21%	23.992%	0.518%	1.382%
Black or African American	0.047%	0.089%	3.929%	11.647%	0.271%	0.718%
Native Hawaiian or Other Pacific Islander	0.021%	0.099%	6.093%	21.212%	0.776%	1.383%
Unknown Race	0.056%	0.107%	8.294%	19.863%	0.656%	1.666%
White	0.058%	0.126%	5.639%	17.839%	0.578%	1.664%
Other Race	0.069%	0.262%	5.96%	23.992%	0.924%	2.405%
Ethnicity						
Hispanic or Latino	0.071 %	0.189%	6.221%	21.696%	0.833%	2.01%
Not Hispanic or Latino	0.056 %	0.119%	5.448%	16.897%	0.506%	1.519%
Unknown Ethnicity	0.055 %	0.118%	6.1%	18.52%	0.542%	1.552%
Age						
20 - 24	0.015 %	0.045 %	0.435%	15.287%	0.308%	1.949%
25 - 29	0.052 %	0.121 %	2.089%	16.403%	0.158%	1.84%
30 - 34	0.072 %	0.183 %	3.105%	18.175%	0.214%	1.831%
35 - 39	0.105 %	0.228 %	4.524%	18.54%	0.328%	1.832%
40 - 44	0.123 %	0.265 %	6.151%	20.101%	0.312%	1.981%
45 - 49	0.134 %	0.259 %	6.905%	20.812%	0.481%	1.881%
50 - 54	0.123 %	0.220 %	7.554%	19.925%	0.57%	2.036%
55 - 59	0.088 %	0.185 %	8.283%	18.473%	0.803%	1.798%
60 - 64	0.055 %	0.134 %	8.67%	15.891%	0.935%	1.534%
65 - 69	0.029 %	0.075 %	8.541%	13.997%	0.832%	1.599%
70 - 74	0.011 %	0.036 %	5.949%	10.689%	0.492%	0.766%
75 - 79	0.009 %	0.013 %	5.932%	7.692%	0.353%	0%
80 - 84	0.004 %	0.009 %	13.699%	10%	0.915%	0%
85 and older	0.005 %	0.003 %	30.303%	11.364%	0%	0%

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1620 | RECOMPENSATION AMONG PATIENTS WITH BIOPSY-PROVEN ACUTE ALCOHOL-ASSOCIATED HEPATITIS SUPERIMPOSED ON CIRRHOSIS

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Background: Previous studies have shown that up to 18% of patients with decompensated alcohol-related cirrhosis achieve recompensation with alcohol abstinence. It is uncertain whether recompensation occurs in the setting of alcohol-associated hepatitis (AH) superimposed on alcohol related cirrhosis. Therefore, we aimed to evaluate the rate and characteristics of patients with biopsy-proven AH superimposed on cirrhosis achieving recompensation. **Methods:** Patients admitted with AH to a tertiary care hospital from 2013-2022 and who had a liver biopsy during hospitalization were identified retrospectively. From this cohort, patients who presented with first decompensation (ascites, variceal hemorrhage [VH] and or encephalopathy [HE]) within 60 days of a liver biopsy confirming presence of both AH and cirrhosis were selected. Primary outcome was recompensation per Baveno VII criteria, defined as normal serum albumin and bilirubin, no ascites (off diuretics), no VH and no HE for at least a year. Patients were followed from the date of biopsy until recompensation, death, transplant, or last follow up, for a maximum of 5 years. Patients with less than 90 days of follow up and not meeting the above end points were considered lost to follow up. **Results:** A total of 138 patients with biopsy proven AH superimposed on cirrhosis presenting with first decompensation were included. Baseline characteristics are shown in the Table. Median time from admission to biopsy was 5 days. Thirteen patients (9%) were lost to follow up after discharge, 70 (51%) died (all decompensated at the time of death, except for 3 with unknown status) and 8 (6%) were transplanted. Median time from liver biopsy to death was 68 days (range 3 to 1640), and to transplant was 88 days (range 25 to 295). Among 47 transplant-free survivors (median follow up

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3.6 years), only 10 (7.2%) achieved recompensation. The median time from the initial presentation to recompensation was 2.9 years (range 1.7 - 3.9); the median follow-up of 37 patients who did not achieve recompensation was 4 years. All recompensated patients discontinued alcohol use within 4 months of liver biopsy. Patients who recompensated were younger and had a higher AST compared to the rest of the cohort. Severity of disease based on MELD 3.0 was similar between the two groups. **Conclusion:** Our study shows that among patients with AH superimposed on cirrhosis presenting with first decompensation, recompensation is a rare event (~7%) that occurs after a long period ($\geq$ 1.5 years) of alcohol abstinence.

Table - Baseline Characteristics

	Did not recompensate N= 128	Recompensated N= 10
Demographics		
Sex = male (%)	64 (50%)	5 (50%)
Age (median [IQR])	49 [40, 55] *	34 [32, 45] *
Ethnicity = Not Hispanic or Latino (%)	112 (88%)	10 (100%)
Race (%)		
Black	7 (6%)	1 (10%)
White	100 (90%)	9 (90%)
Other	4 (4%)	0 (0%)
BMI (median [IQR])	29 [26, 34]	27 [23, 31]
Labs		
AST (median [IQR])	142 [99, 199] *	211 [163, 292] *
WBC (median [IQR])	11.8 [7.8, 17.5]	10.6 [6.5, 15.8]
Bilirubin (median [IQR])	15.0 [8.3, 25.2]	20.5 [14.8, 23.6]
Creatinine (median [IQR])	0.80 [0.52, 1.82]	0.73 [0.56, 0.88]
INR (median [IQR])	1.8 [1.6, 2.1]	1.7 [1.5, 1.8]
Sodium (median [IQR])	133 [131, 137] *	128 [123, 131] *
Albumin (median [IQR])	2.7 [2.5, 3.2]	2.7 [2.5, 3.0]
MELD 3.0 (median [IQR])	28.5 [24, 34]	28 [24, 29]
Baseline decompensation/status		
Ascites = Y (%)	126 (98%)	10 (100%)
Hepatic encephalopathy = Y (%)	95 (74%)	8 (80%)
Variceal bleeding = Y (%)	8 (6%)	1 (10%)
Hepatorenal syndrome = Y (%)	15 (12%)	0 (0%)
Mechanical ventilation (MV)= Y (%)	25 (20%)	1 (10%)
Shock requiring pressors = Y (%)	30 (23%)	1 (10%)
Renal replacement therapy (RRT)= Y (%)	22 (17%)	1 (10%)
ICU admission for shock, MV, or RRT = 1 (%)	35 (27%)	1 (10%)

* p value < 0.05 compared to no recompensation
Fisher exact test used for categorical variables; Wilcoxon rank-sum test used for continuous variable

Disclosures: Beatriz Sordi Chara: Nothing to Disclose, Anahita Rabiee: Grifols: Investigator-initiated studies (IIS), Praveena Narayanan: Nothing to Disclose, Daniela Goyes: Nothing to Disclose, Pramod Mistry: Nothing to Disclose, Guadalupe Garcia-Tsao: Nothing to Disclose

1621 | HEALTH CARE UTILIZATION, COSTS, AND ADVANCE CARE PLANNING IN SEVERE ALCOHOLIC HEPATITIS PATIENTS

Tanisha Ronnie[1] *Irene Helenowski*[1] *Scott Cotler*[1] *Steven Scaglione*[2], [1]*Loyola University Medical Center,* [2]*Loyola University Health System*

Background: Severe alcoholic hepatitis (sAH) is associated with high morbidity, mortality, and healthcare burden. Limited research exists evaluating the utility of palliative care (PC), cost, and advance care planning (ACP) in patients with sAH. This study aimed to assess end-of-life care (EOL), health care utilization, and ACP documentation rates in the sAH population. **Methods:** This single center, retrospective study analyzed 298 patients, admitted between 2012-2020, who met NIAAA criteria for sAH and died by 11/1/2024. We compared health care utilization, costs, and EOL care between survivors (n = 193) and decedents (n = 105) following the initial admission for sAH. Demographic and clinical variables included MELD-NA, Maddrey's discriminant function (MDF), time to death, code status, length of stay(LOS), hospitalizations, PC consultation, and ACP documentation. Statistical differences were assessed using the Wilcoxon rank-sum and Fisher's exact tests. **Results:** The median age was 48 (IQR: 39,55) years, with 37.2% male and 62.8% female. Medicaid was the primary insurance (42.3%), followed by Other (26.5%), Private (16.4%), Medicare (9.4%), and Uninsured (5.4%). Marital status was similar between survivors and decedents: 42.3% single, 37.2% married, 18.4% divorced/legally separated, and 2% widowed. The mean MELD-NA was 29 and mean MDF was 67 for both groups. Of the 298 patients, 35% died, with a mean time of 1.2 years from initial diagnosis of sAH to death. Most decedents (70%) died in-hospital, with 53% in an ICU. Of out-of-hospital deaths, 21% occurred in hospice and 8.5% occurred at home. Decedents were more likely to be DNR/DNI at discharge (74.29% vs 5.7%, $p < 0.001$) and had a higher likelihood of their code status changing from Full Code to DNR/DNI (93.3% vs 25.7%, $p < 0.001$). Among those who died, 64.4% of patients were admitted to an ICU, with a mean LOS of 7.82 days. Many underwent life sustaining procedures including intubation (10.5%), CPR (41%), dialysis (29.5%), blood transfusion (41%), vasopressors (42.9%), and arterial (42.9%), and central line placement (42.9%). Both groups had a mean of seven hospitalizations post-diagnosis, with a significant association between hospitalization frequency and survival (3(IQR: 0,11) vs 1(IQR: 0,6), $p = 0.003$). Decedents were more likely to have PC consulted (16.2% vs 2.6%, $p < 0.001$), inpatient palliative referrals (15.2% vs 2.6%, $p < 0.001$), ACP documentation (24.8% vs 15%, $p = 0.037$); higher initial admission hospitalization costs for palliative vs. non-palliative care ($16,471 vs $10,675, $p = 0.031$). The average cost of initial hospitalization was $11,000.86. **Conclusion:** Despite the high mortality in sAH patients, ACP documentation and PC consultation regarding EOL care are

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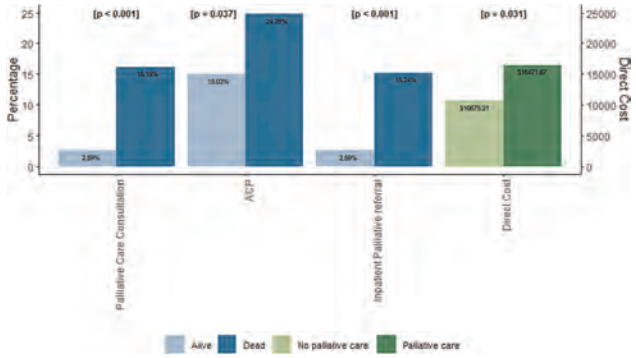
uncommon. These patients also have substantial health care utilization and costs. Further studies should be performed to improve EOL care outcomes and reduce the health care burden for these patients.



Disclosures: Tanisha Ronnie: Nothing to Disclose, Irene Helenowski: Nothing to Disclose, Scott Cotler: Nothing to Disclose, Steven Scaglione: Nothing to Disclose

1622 | DISPARATE REFERRAL PATTERNS FOR PATIENTS WITH ALCOHOL USE DISORDER REFERRED TO HEPATOLOGY CLINICS

Elizabeth Sun[1] Donald Sengstack[1] Jackson Resser[1] Qingxia Chen[1] Ashley Spann[1], [1]Vanderbilt University Medical Center

Background: Approximately 29.5 million individuals suffer from alcohol use disorder (AUD) in the United States, yet only 7.6% receive treatment. While treatment for AUD is increasingly available, literature on referral patterns and direct pharmacological treatment for AUD in hepatology clinics remains sparse. We aimed to evaluate AUD referral patterns for hepatology patients at a single tertiary care center. **Methods:** Retrospective data was extracted from the electronic health record for all new patient evaluations in hepatology clinics from 01/2019 – 12/2023 at a tertiary liver transplant center. Inclusion criteria were adults with current or prior documentation of alcohol use either by visit-related clinical documentation or by elevated phosphatidylethanol (PETH) levels prior to or within 30 days of initial visit. Patients without documented alcohol use or positive PETH data were excluded, along with patients with fewer than one day of survival time for the outcome of interest. The primary outcome was behavioral health referrals (BHR). The secondary outcome was prescription of medications utilized for AUD pharmacotherapy (MAUD). Cox proportional hazards ratios analysis for time to event analysis to evaluate for potential differences in referral rates/timing between subgroups of interest. **Results:** 2457 patients were seen for an initial hepatology visit during the study period. 856 (34.8%) met inclusion criteria. Of these patients, 298 (34.8%) had a diagnosis of cirrhosis at the initial visit. A total of 93 (10.9%) patients received a BHR. Hispanic patients were more likely to have BHR ordered than non-Hispanic white patients [HR = 2.99 (1.24, 7.2)], as were patients with at least one hospitalization in the year prior to the visit relative to patients with no prior hospitalizations [HR = 2.39 (1.41, 4.1)]. 164 patients (19.2%) were prescribed MAUD during this period. Female patients were more likely to be ordered a MAUD prescription than male patients [HR = 1.42 (1.04, 1.0)], as were non-Hispanic black patients relative to non-Hispanic white patients [HR = 2.01 (1.30, 3.1)] and patients with at least one prior hospitalization relative to patients with no prior hospitalizations [HR = 2.16 (1.55, 3.0)]. **Conclusion:** BHR referrals are low among eligible patients seen in hepatology clinics. MAUD initiation remains low as well with racial and gender disparities among patients with documented alcohol use attending hepatology clinics.

Table 1: Outcomes of Behavioral Health Referral and Prescriptions for Medications for Alcohol Use Disorder

	Behavioral Health Referral (n)	Hazard Ratio (95% CI)	Prescriptions for AUD Medications (n)	Hazard Ratio (95% CI)
Age at Appointment		0.98 (0.96, 1.00)		1.00 (0.98, 1.01)
Sex				
Male Sex	38	REF	84	REF
Female Sex	25	0.91 (0.54, 1.52)	76	1.42 (1.04, 1.94)
Race/Ethnicity				
Non-Hispanic White	48	REF	123	REF
Non-Hispanic Black	4	0.71 (0.25, 1.98)	25	2.01 (1.30, 3.12)
Hispanic	6	2.99 (1.24, 7.22)	8	1.60 (0.77, 3.31)
Other Race/Eth or Unknown	5	1.53 (0.60, 3.89)	4	0.48 (0.18, 1.31)
Insurance Type				
Private/Commercial Insurance	39	REF	85	REF
Govt Insurance	21	1.01 (0.55, 1.84)	69	1.18 (0.82, 1.70)
Liability/Uninsured	3	0.69 (0.21, 2.26)	9	0.71 (0.31, 1.63)
Primary Care Provider Status				
No VUMC PCP at Visit	1	REF	5	REF
VUMC PCP at Visit	62	1.55 (0.21, 11.27)	155	0.77 (0.31, 1.89)
Clinic Site				
Main Campus (VAV and TVC)	52	REF	130	REF
Outreach Clinic	11	0.75 (0.38, 1.46)	30	0.83 (0.55, 1.25)
Prior Healthcare Utilization				
No Hospitalizations in Year Prior to Visit	39	REF	102	REF
>= 1 Hospitalization in Year Prior to Visit	24	2.39 (1.41, 4.06)	58	2.16 (1.55, 3.01)
No ED Visits in Year Prior to Visit	48	REF	126	REF
>= 1 ED Visit in Year Prior to Visit	15	0.96 (0.53, 1.72)	34	0.77 (0.52, 1.13)

Disclosures: Elizabeth Sun: Nothing to Disclose, Donald Sengstack: Nothing to Disclose, Jackson Resser: Nothing to Disclose, Qingxia Chen: BeiGene: Data Monitor Committee, Ashley Spann: Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support,

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Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant

1623 | INTERACTION OF ALCOHOL AND DIETARY FAT INTAKE ON STEATOSIS AND FIBROSIS IN METABOLIC ALCOHOL-ASSOCIATED LIVER DISEASE (METALD): A CROSS-SECTIONAL NHANES STUDY

Katharine Tippins[1] Adnan Said[2], [1]University of Wisconsin Hospitals and Clinics, [2]University of Wisconsin School of Medicine and Public Health

Background: Metabolic alcohol-associated liver disease (MetALD) is a newly recognized phenotype of steatotic liver disease (SLD) characterized by concurrent metabolic dysfunction and moderate alcohol intake. While both alcohol and dietary fat independently contribute to liver injury, their synergistic effects - particularly within MetALD - remain poorly understood. This study examined the interaction of alcohol and dietary fat intake on hepatic steatosis and fibrosis across distinct SLD subgroups. **Methods:** We analyzed data from NHANES 2017–2020 survey information, restricting to adults ($\geq$18 years) with valid transient elastography data and hepatic steatosis (CAP $\geq$285 dB/m). Participants were classified into mutually exclusive groups: MASLD (metabolic dysfunction + low alcohol), MetALD (metabolic dysfunction + moderate alcohol), AUD (high alcohol + no metabolic dysfunction), and "Other" (i.e., viral hepatitis, hemochromatosis, cryptogenic). Alcohol intake was defined as moderate for men $>$20 - 50 g/day and women $>$10 - 30 g/day. Total dietary fat intake was derived from 24-hour recall. Survey-weighted multivariable regression models examined CAP (continuous) and significant fibrosis (LSM $\geq$8.0 kPa), testing for interaction between alcohol and fat intake. Models were adjusted for age, sex, race/ethnicity, and energy intake. Sensitivity analyses excluded "lean MASLD" (individuals with BMI $<$25 and without metabolic dysfunction) and applied stricter fibrosis thresholds. **Results:** Among 2,992 participants with CAP $\geq$285 dB/m, 663 had identifiable MASLD, 224 MetALD, and 15 AUD. The weighted mean CAP score was 332.2 dB/m (SE $\pm$2.27). In unweighted models, both alcohol and dietary fat intake were independently associated with higher CAP, with a significant alcohol $\times$ fat interaction ($p = 0.049$), primarily driven by the MetALD group. However, this interaction did not remain statistically significant in survey-weighted models ($p = 0.44$). No significant predictors or interactions were associated with fibrosis $\geq$8.0 kPa. Male sex was the only consistent predictor of fibrosis. Sensitivity analyses yielded similar findings. **Conclusion:** In this nationally representative sample of U.S. adults with steatosis, the interaction between alcohol and dietary fat intake was directionally consistent with synergy but did not reach statistical significance after applying NHANES survey weights. These findings support MetALD as a distinct clinical phenotype and underscore the importance of behavioral risk factors in liver fat accumulation. Further prospective research is needed to clarify their contribution to fibrosis progression.

Disclosures: Katharine Tippins: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Advisor

1624 | PLATANOSIDES INCREASES MITOCHONDRIAL BIOGENESIS (MB) AFTER CHRONIC-BINGE ETHANOL (CBE) TREATMENT IN MICE

Devadoss Samuvel[1] Menny Benjamin[1] Cody Dickinson[1] Amir Richardson[1] John Lemasters[1] Mark Hamann[1] Zhi Zhong[1], [1]Medical University of South Carolina

Background: We showed previously that mitochondrial depolarization and mitophagy/lysosomal processing dysregulation develop after CBE. MB must occur after mitochondrial damage to restore mitochondrial homeostasis and recover mitochondrial function. In *in silico* studies, we showed that PTS isolated from American sycamore trees are good ligands for the Keap1/Nrf2 complex, which likely promotes Keap1/Nrf2 dissociation and subsequent Nrf2 pathway activation. Since Nrf2 activation reportedly increases expression of PGC1α, the master regulator of MB, we examined whether PTS treatment alters MB after CBE treatment in mice. **Methods:** Mice were fed a liquid diet containing 5% ethanol for 10 days and then gavaged once with ethanol (5 g/kg) on day 11. Liver and blood were harvested 9h later. PTS (10 mg/kg, i.p.) or vehicle were injected daily during feeding of ethanol-containing liquid diet and 30 min before gavage. **Results:** After CBE, PGC1α decreased by 55%. PGC1α regulates expression of nuclear DNA (nDNA)-encoded mitochondrial proteins as well as TFAM, a transcription factor that controls mitochondrial DNA (mtDNA) replication and transcription. TFAM decreased by about 60%, and mtDNA copy number decreased 44% after CBE. Expression of COX-IV and ND3, mitochondrial oxidative phosphorylation proteins encoded by nDNA and mtDNA, respectively, decreased by 58% and 61%, signifying suppressed MB. PTS blunted alterations of PGC1α, TFAM, mtDNA copy number, and mitochondrial oxidative phosphorylation proteins in liver tissue

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after CBE. Mitochondria catalyze fatty acid β-oxidation. CBE decreased hepatic fatty acid oxidation (FAO) by 63% and increased hepatic triglycerides by 160%, which PTS partially reversed. By preventing mitochondrial dysfunction, PGC1α also mitigates inflammasome activation. After CBE, NLRP3 increased 280%, cleaved caspase-1 increased 188%, and interleukin-1β increased 167%, signifying inflammasome activation, which PTS blunted. Disruption of mitochondrial homeostasis can increase tissue injury and/or suppress tissue repair after damage. After CBE, serum ALT increased to ~360 U/L, which PTS decreased by 48%. Histology showed moderate hepatic steatosis, ballooning, scattered necrotic cell death, and increased leukocyte infiltration. PTS attenuated all histological alterations. **Conclusion:** MB is suppressed after CBE exposure. PTS decreases liver injury and improves liver function after CBE, at least in part, by increasing PGC1α and MB.

Disclosures: Devadoss Samuvel: Nothing to Disclose, Menny Benjamin: Nothing to Disclose, Cody Dickinson: Nothing to Disclose, Amir Richardson: Nothing to Disclose, John Lemasters: Nothing to Disclose, Mark Hamann: Nothing to Disclose, Zhi Zhong: Nothing to Disclose

1625 | TRANSIENT ELASTOGRAPHY AS THERANOSTIC INTERVENTION IN ALCOHOL-ASSOCIATED LIVER DISEASE: SYSTEMATIC REVIEW AND META-ANALYSIS

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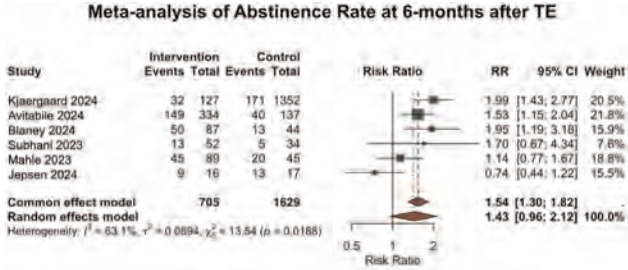
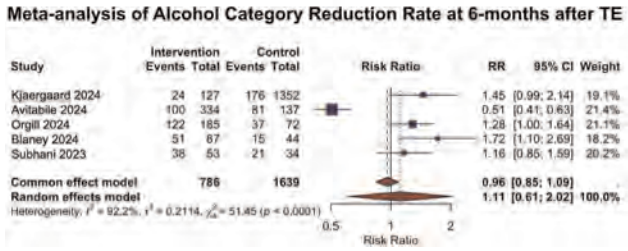
Background: Several recent studies have demonstrated the potential of transient elastography (TE) as a theranostic intervention in patients with or at-risk for steatotic liver disease (SLD), particularly alcohol-associated liver disease (ALD). TE offers convenient, accurate, and actionable results about liver health in real-time that can be leveraged as an opportunistic intervention of diagnosis and therapy (theranostic) to promote alcohol harm reduction and/or abstinence. We conducted a systematic review and meta-analysis to evaluate the effect of TE on alcohol-associated outcomes in patients at-risk for ALD. **Methods:** We searched PubMed, EMBASE, Scopus, and Google Scholar from inception to 5/2025, and abstracts from AASLD, DDW, EASL in the past year using keywords for studies of alcohol and metabolic outcomes after performance of TE. The primary and secondary endpoints were self-reported abstinence from alcohol and alcohol category reduction at 6 months, respectively. MOOSE guidelines were followed for design, implementation, and reporting. The Newcastle-Ottawa Scale was used for quality assessment. Analyses of abstinence and alcohol category reduction at 6 months were calculated using common effect and random effects modeling using R version 4.5.0. Heterogeneity was assessed by the I² statistic. **Results:** Our search identified 172 citations with 13 studies meeting our inclusion criteria. Six studies (3 alcohol, 3 metabolic outcomes) were excluded for low quality (lacking controls or uniform outcomes). The remaining 7 studies included 2,591 at-risk individuals for ALD undergoing TE in mostly outpatient settings identified prospectively (5 out of 7, 71%). Six studies were included for the primary analysis, and 5 for the secondary analysis: 3 reported AUDIT-C, 1 NIAAA, and 1 WHO drinking categories. Individuals at-risk for ALD undergoing TE had significantly increased rates of abstinence at 6-months compared to controls (RR 1.54; 95% CI: 1.30-1.82, $p < 0.001$) with moderate heterogeneity ($I^2 = 63.1\%$) on common effect modeling. This represents a 54% increased likelihood of achieving abstinence compared to controls. In contrast, no significant reduction of alcohol categories after TE was seen compared to controls (RR 0.96; 95% CI: 0.85-1.09, $p = 0.54$] with very high heterogeneity ($I^2 = 92.2\%$). On sensitivity analysis with exclusion of 1 outlier study ($n = 4$), there was a significant reduction of alcohol categories after TE (RR 1.33; 95% CI: 1.13-1.56, $p = 0.001$), with low heterogeneity ($I^2 = 0\%$). On random effects modeling, there were no differences between TE and controls for abstinence (RR 1.43; 95% CI: 0.96-2.12, $p = 0.07$) and alcohol category reduction (RR 1.11; 95% CI: 0.61-2.02, $p = 0.65$). **Conclusion:** TE as a theranostic intervention is associated with improved abstinence at 6-months in individuals at-risk for ALD. These findings highlight the potential for theranostics in ALD by leveraging TE and the need for future studies.





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Disclosures: Gene Im: KorroBio: Consultant, Echosens: Device support for research, Novo Nordisk: Advisor, Alimentiv: Consultant, Stephanie Rutledge: Paige AI: Stock – privately held company, Intercept Pharmaceutical: Consultant, Giuseppe Cullaro: Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant

1626 | OUTCOMES OF PATIENTS WITH ALCOHOL-ASSOCIATED HEPATITIS EVALUATED FOR EARLY LIVER TRANSPLANTATION

Darine Daher[1] Hassan Azhari[2] Omar Mousa[3] Kymberly Watt[1] William Sanchez[1] Timucin Taner[3] Terry Schneekloth[1] Douglas Simonetto[3], [1]Mayo Clinic, [2]Memorial Sloan-Kettering Cancer Center, [3]Mayo Clinic Rochester

Background: The Dallas Consensus Conference set forth candidacy criteria for early liver transplantation (LT) in severe alcohol-associated hepatitis (AAH). These criteria, based on expert opinion, include first presentation of decompensated disease and rigorous psychosocial evaluation, diverging from traditional 6-month abstinence rule. This remains controversial in part because of concern for higher alcohol relapse, and for potential recovery obviating need for transplant. Our study aims to explore outcomes of those transplanted (LT-AAH) compared to those not approved for LT (Non-LT AAH). **Methods:** Consecutive patients evaluated at transplant selection committee at Mayo Clinic, Rochester, between January 1, 2018 and December 31, 2023, with a primary indication of AAH were retrospectively reviewed. Patients were divided into those who received LT and those who were deferred or denied. T-tests were used to compare the means of 2 groups when needed. **Results:** We identified 27 patients with AAH who were considered for early LT, 17 receiving LT (63%) while 10 did not (37%). Mean age at evaluation was similar in both LT-AAH and non-LT AAH groups (40.1 vs 39.1 years), with most patients being Non-Hispanic White (88% vs 80%). Among the 10 who did not receive LT, 4 were denied, 5 were deferred, and 1 was waitlisted but then de-listed due to not completing chemical dependency treatment. Reasons for deferral or denial included no insight to alcohol as cause of illness (n = 5), lack of identifiable sober system (n = 3), not first decompensating event (n = 2), unwillingness to complete alcohol use disorder treatment (n = 2), > 2 prior alcohol treatment programs with relapse (n = 2), evidence of polysubstance abuse (n = 1), not at high risk for mortality from AAH (n = 1), and presence of other life limiting conditions (n = 1) (Figure 1). Alcohol consumption was observed in 4 patients after transplant in LT-AAH group (24%), compared to 4 patients after evaluation in non-LT AAH group (40%). Mean time to first drink was 23 weeks (95CI% 3 – 42 weeks) in LT-AAH group compared to 16 weeks (95%CI 4 – 29 weeks) in non-LT AAH group (p = 0.6). There were 2 deaths in LT-AAH (12%) with 1 alcohol-related death, compared to 5 in non-LT AAH (50%) group, all of which were alcohol-related. 4 out of the 5 surviving patients in non-LT AAH group achieved recompensation with sustained alcohol abstinence. **Conclusion:** Our findings suggest that despite being deferred or denied transplant due to suspected high risk of alcohol relapse, most of these patients remain abstinent, and 40% successfully achieve recompensation. Further studies are needed to better individualize approach to early LT in patients with severe AAH.

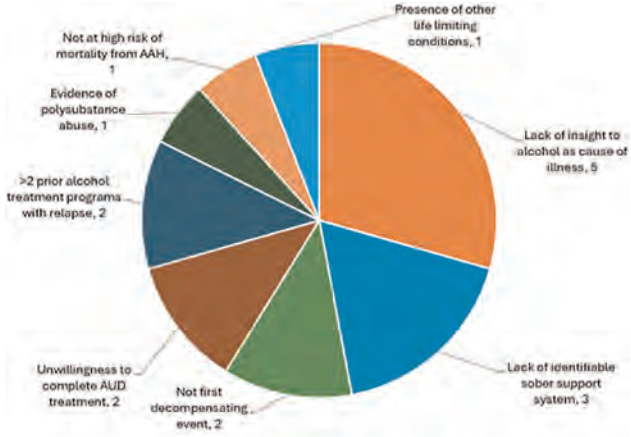

Figure 1. Reasons for early LT deferral or denial in patients with AAH.

Disclosures: Darine Daher: Nothing to Disclose, Hassan Azhari: Nothing to Disclose, Omar Mousa: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Madrigal: Stock - publicly traded company, Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Viking: Stock - publicly traded company, Viking: Stock - publicly traded company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock - publicly traded company, Madrigal: Stock - publicly traded company, Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Viking: Stock - publicly traded company, Viking: Stock - publicly traded company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock - publicly traded company, Madrigal: Stock - publicly traded company, Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Viking: Stock - publicly traded company, Viking: Stock - publicly traded company, Novo Nordisk: Speaking and Teaching, William Sanchez: Nothing to Disclose, Timucin Taner: Nothing to Disclose, Terry Schneekloth: Nothing to Disclose, Douglas Simonetto: Mallinckrodt:

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Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant

1627 | SIGNIFICANT LIVER DISEASE AMONG INCREASED ALCOHOL CONSUMERS TRIPLED FROM 1999-2018 ALONGSIDE EVOLVING US POPULATION DEMOGRAPHICS

Kalpana Gopalkrishnan[1] Jennifer Dodge[2] Brian Lee[3], [1]Keck School of Medicine, University of Southern California, [2]Keck School of Medicine at USC, [3]Keck School of Medicine

Background: According to current teaching, 10-20% of increased alcohol consumers develop progressive liver disease in a lifetime. However, changes to U.S. population demographics may influence current risk. This study used national data to assess trends and contributors to the risk of developing alcohol associated liver disease (ALD) among increased alcohol consumers. **Methods:** The nationally-representative National Health and Nutrition Examination Survey (NHANES) was analyzed from 1999-2018. Adults aged $\geq$20 years were included and those with viral hepatitis (B or C) or unknown alcohol or Fibrosis-4 (FIB-4) score were excluded. Increased alcohol consumption was defined as $\geq$20 grams/day for women and $\geq$30 grams/day for men in the past 12 months. Demographic trends were examined from 1999-2004, 2005-2012, and 2013-2018 using survey-weighted prevalence and mean estimates. Survey-weighted prevalence of high FIB-4 (defined as $>$2.67) was estimated among those with vs. without increased alcohol consumption and stratified by demographic variables. Confidence intervals were determined using Taylor linearization. **Results:** National prevalence of high FIB-4 increased over time from 1.8% (95% CI 1.0-3.3%) in 1999-2004 to 5.6% (3.7-8.3%) in 2013-2018 among increased alcohol consumers, and from 0.1% (0.1-0.2%) to 0.2% (0.2-0.3%) among those without increased alcohol consumption. Among increased alcohol consumers, mean age increased over time, as well as the proportion of female consumers and those living in poverty. Prevalence of metabolic syndrome increased from 26.4% (23.5-29.6%) in 1999-2004 to 37.6% (32.5-43.1%) in 2013-2018 among increased alcohol consumers. Among increased alcohol consumers, mean alcohol use was similar across eras (Table 1), but prevalence of high FIB-4 increased for this group overall and among all age, sex, and ethnicity groups from 1999-2004 to 2013-2018. **Conclusion:** The national risk of significant liver fibrosis among heavy drinkers increased over 3-fold, despite *similar* alcohol use between 1999-2018. We identified increasing metabolic syndrome and changing demographics of heavy drinkers (age, women, living in poverty) as contributors to these alarming trends. These results show the importance of updated recommendations regarding screening of liver disease among increased alcohol users, and the need to address co-factors of ALD progression.

Table 1. Characteristics of US Adults with and without Increased Alcohol Consumption in NHANES between 1999-2018

	With Increased Alcohol Consumption (N=3,275)						Without Increased Alcohol Consumption (N=39,954)					
	1999-2004		2005-2012		2013-2018		1999-2004		2005-2012		2013-2018	
Characteristic	No.	Mean (n) or Prevalence (95% CI)	No.	Mean (n) or Prevalence (95% CI)	No.	Mean (n) or Prevalence (95% CI)	No.	Mean (n) or Prevalence (95% CI)	No.	Mean (n) or Prevalence (95% CI)	No.	Mean (n) or Prevalence (95% CI)
Age, mean (95% CI)	814	44.0 (42.5-45.7)	992	44.4 (43.2-45.6)	669	45.3 (43.6-47.0)	11,003	46.4 (45.8-47.0)	18,400	47.2 (46.6-47.9)	12,542	48.1 (47.5-48.8)
Male Sex	434	68.9 (64.3-73.0)	710	70.0 (65.9-73.8)	441	64.0 (58.9-68.8)	5,151	47.3 (46.3-48.1)	7,910	47.4 (46.7-48.1)	12,542	47.8 (46.8-48.9)
Smoking (at least 100 cigarettes during lifetime)	492	75.7 (74.4-82.4)	746	77.0 (73.8-80.1)	581	71.1 (65.2-76.3)	5,146	37.9 (46.0-49.8)	7,275	34.2 (42.3-45.7)	5,125	41.3 (32.6-43.0)
Metabolic Syndrome	189	26.4 (23.5-29.6)	341	31.4 (27.9-35.2)	253	37.6 (32.5-43.1)	3,862	32.0 (30.5-33.5)	6,602	37.1 (35.6-38.6)	5,509	40.4 (38.7-42.2)
BMI	814	28.8 (26.3-27.3)	992	27.1 (26.7-27.6)	669	28.9 (28.2-29.4)	11,003	28.1 (27.9-29.0)	18,400	28.6 (28.6-29.)	12,542	29.5 (29.2-29.8)
Poverty Index < 100%	55	8.5 (6.3-11.5)	227	15.7 (13.4-18.2)	144	13.5 (10.9-17.0)	1,765	12.7 (11.4-14.2)	3,019	12.9 (11.8-14.1)	2,213	13.1 (11.8-14.7)
Race												
Non-Hispanic White	383	79.2 (75.2-82.7)	592	78.4 (74.9-81.6)	307	71.2 (66.0-75.9)	5,678	73.2 (69.7-76.4)	7,702	70.5 (67.0-73.7)	4,793	65.4 (61.8-69.1)
Non-Hispanic Black	98	7.6 (5.8-10.0)	176	8.1 (6.5-10.0)	163	10.8 (8.4-13.8)	1,919	9.6 (7.9-11.7)	3,319	10.3 (8.7-12.1)	2,535	10.3 (8.5-12.5)
Hispanic	137	10.0 (7.3-13.7)	213	10.2 (8.2-12.6)	136	11.3 (8.3-15.1)	3,043	12.9 (10.0-16.3)	5,257	13.1 (11.0-15.7)	3,281	15.4 (12.8-18.4)
Other	16	3.2 (1.7-6.0)	41	3.3 (2.1-4.9)	63	6.8 (4.5-10.0)	363	4.3 (3.5-5.3)	1,121	6.0 (5.2-6.9)	1,933	8.8 (7.8-10.1)
Education: Less than high school	191	20.7 (17.7-24.1)	265	19.3 (16.7-22.2)	135	11.5 (9.0-14.7)	3,445	19.4 (18.1-20.7)	4,338	17.2 (15.8 - 18.8)	2,550	12.6 (11.1-14.2)
High school grad/ GED or equivalent	172	31.3 (27.2-35.6)	268	29.1 (6.5-10.0)	200	30.0 (25.7-34.7)	2,585	28.6 (28.0-27.3)	3,751	22.6 (21.4-23.9)	2,818	22.9 (21.4-24.5)
Some college or college graduate	251	48.0 (42.9-53.0)	419	51.6 (47.2-55.9)	333	58.4 (53.2-63.5)	4,975	50.0 (52.9-57.2)	8,329	60.1 (57.9-62.3)	7,169	64.5 (62.1-66.9)
Alcohol use, mean (grams per day)	814	49.9 (47.4-52.5)	992	49.6 (47.3-51.8)	669	50.9 (47.4-54.4)	11,003	3.7 (3.4-4.0)	18,400	4.1 (3.9-4.3)	12,542	3.9 (3.7-4.1)
High FIB-4	16	1.8 (1.0-3.3)	51	3.7 (2.5-5.2)	39	5.6 (3.7-8.3)	278	0.1 (0.1-0.2)	545	0.2 (0.2-0.3)	461	0.2 (0.2-0.3)

High FIB-4: fibrosis-4 score >2.67

Disclosures: Kalpana Gopalkrishnan: Nothing to Disclose, Jennifer Dodge: Nothing to Disclose, Brian Lee: NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, DURECT: Advisor, HepaTx: Advisor, CymaBay: Consultant, Ipsen: Consultant, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor, Assertio: Consultant

1628 | PHOSPHORYLATED UBIQUITIN CONJUGATING ENZYME 9 AS A NOVEL REGULATOR OF LIPOGENESIS IN ALCOHOL-ASSOCIATED LIVER DISEASE

Swati Chandla[1] Youngyi Lim[1] Michael Mazarei[1] Xi Yang[1] TAKASHI TSUCHIYA[1] Manisha Dagar[1] Monica Justo[1] Komal Ramani[1] Maria Lauda Tomasi[1], [1]CEDARS-SINAI MEDICAL CENTER

Background: Alcohol abuse promotes the activation of liver-resident macrophages, known as Kupffer cells (KCs), by enhancing the gut-derived endotoxins translocation into the portal circulation. Activated KCs secrete the pro-inflammatory cytokines that promote the expression of the de novo lipogenesis mediators in hepatocytes including *SrebF1* and *CEBP-β*, via an NF-κB dependant pathway. We previously reported that alcohol causes NF-κB activation in KCs through phosphorylation of ubiquitin conjugating enzyme 9

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(pUBC9), the unique E2 conjugating enzyme for SUMOylation. This study aims to investigate the role of pUBC9 in modulating de novo lipogenesis in alcohol-associated liver disease (AALD). **Methods:** Primary mouse KCs and hepatocytes were used for in vitro experiments which were further validated using the NIAAA mouse model. Techniques including phosphopeptide mapping, phosphomimetic peptide treatment, Western blot, ELISA, RT-PCR, CRISPR/Cas9-mediated UBC9 Y68 editing in vivo, immunofluorescence (IF), BODIPY and H&E staining and ChIP assay were used to examine the functional role of UBC9 phosphorylation at specific residues. **Results:** Alcohol administration induced UBC9 phosphorylation at tyrosine Y68 residue (UBC9Y68) in KCs both in vitro and in vivo. The use of phosphomimetic peptide promoted the expression of pro-inflammatory cytokines, while CRISPR/Cas9-mediated UBC9 mutation of tyrosine 68 residue to phenylanine (UBC9Y68F) prevented UBC9 phosphorylation and decreased the cytokine production as well as secretion in KCs. In NIAAA model, editing of UBC9 prevented its phosphorylation that attenuated liver injury, hepatic lipid accumulation and reduced *SrebF1* and *CEBPβ* expression by lowering their promoter binding with p65, known as their main transcription factor. **Conclusion:** Phosphorylation of UBC9 at Y68 residue in KCs causes lipid accumulation promoting lipogenic genes expression. These findings identify phosphorylated UBC9 Y68 as a novel and promising therapeutic target for the treatment of AALD. **Disclosures:** Swati Chandla: Nothing to Disclose, Youngyi Lim: Nothing to Disclose, Michael Mazarei: Nothing to Disclose, Xi Yang: Nothing to Disclose, TAKASHI TSUCHIYA: Nothing to Disclose, Manisha Dagar: Nothing to Disclose, Monica Justo: Nothing to Disclose, Komal Ramani: Nothing to Disclose, Maria Lauda Tomasi: Nothing to Disclose

1629 | COMPARATIVE EFFECTIVENESS AND SAFETY OF NALTREXONE AND ACAMPROSATE IN PATIENTS WITH CIRRHOSIS: A RETROSPECTIVE COHORT STUDY

Brooke Rice[1] Prasanna Challa[1] Tracey Simon[1], [1]Massachusetts General Hospital

Background: Medications for alcohol use disorder are underutilized in patients with advanced liver disease due to a lack of data, with concerns regarding naltrexone use due to hepatic metabolism and potential hepatotoxicity. **Methods:** We identified all new initiators of naltrexone or acamprosate after diagnosis of cirrhosis within the Mass General Brigham health care system (1993 – 2024). After 1:1 propensity score matching to emulate a target trial, we estimated Cox proportional hazard ratios (HRs) and 95% CIs for the primary outcomes of death or hospitalization for liver decompensation (i.e. ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal hemorrhage, hepatocellular carcinoma, or hepatorenal syndrome). Subgroup analyses separately analyzed those with compensated and decompensated cirrhosis. **Results:** The PS-matched cohort included 1418 patients with cirrhosis, including 819 (57.8%) with prior decompensation. In the full population, no significant differences were found between initiator groups for the primary composite outcome (HR 0.95 [95% CI = 0.79-1.15]). However, among patients with compensated cirrhosis at baseline, initiators of acamprosate had significantly higher rates of incident major decompensation events (HR = 1.69 [95% CI = 1.07 – 2.67]) with a nonsignificant trend towards increased mortality (HR 1.46 [95% CI = 0.89 – 2.41]). In contrast, among patients with decompensated cirrhosis, no significant differences were found between exposure groups for recurrent decompensation or death. **Conclusion:** Among patients with cirrhosis, initiators of naltrexone versus acamprosate had similar hazards of decompensation and death. In patients with baseline compensated cirrhosis, acamprosate initiation was associated with higher hazard of decompensation requiring hospitalization.
Disclosures: Brooke Rice: Nothing to Disclose, Prasanna Challa: Nothing to Disclose, Tracey Simon: Nothing to Disclose

1630 | EXCELLENT OUTCOMES FOLLOWING RENAL REPLACEMENT THERAPY IN YOUNG PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS: IS IT TIME FOR A CHANGING PARADIGM IN THE ERA OF EARLY LIVER TRANSPLANT?

Emily Harding-Theobald[1], [1]DENVER HEALTH

Background: The increasing prevalence of life-threatening alcohol-associated hepatitis (AH) among otherwise healthy young adults represents a significant challenge in modern hepatology. Patients who have very recent alcohol use are typically not considered candidates for liver transplant, and are left with no therapeutic options if anuric renal failure (ARF) develops secondary to acute tubular necrosis (ATN) or hepatorenal syndrome (HRS). Historically, renal replacement therapy (RRT) has not been offered to patients with alcohol-associated hepatitis if they are not transplant candidates, based on data suggesting dismal survival in patients with chronic decompensated cirrhosis of about 25-30% at 6 months. We describe a small case series of patients age < 50 with acute AH whose 83% survival at 6 months significantly exceeds the historic figures described for cirrhosis, suggesting that RRT as a bridge to transplant may be feasible and life-

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saving in the era of early liver transplant for AH. **Methods:** We describe the experience of an integrated alcohol-associated liver disease clinic with embedded addiction medicine at a major referral center. The total cohort included 53 patients with an initial MELD score of >20 (median MELD 29) who were followed for a minimum of 6 months following an index admission for acute AH. All patients were not candidates for transplant due to recent alcohol use. 15 patients developed anuric renal failure within one month of their index admission for AH. Because of geographically remote referring hospitals, 9 patients were initiated on CRRT and transitioned to intermittent hemodialysis (iHD). 5 patients were felt by local nephrologists to have primary HRS, 4 patients were felt to have renal failure secondary to ATN. **Results:** Among 15 patients who developed ARF, 6 were not offered RRT because they were not considered transplant candidates at that time. All 6 patients died during that admission after transitioning to hospice. 9 patients were offered RRT, of whom 2 were over age 50. Both patients over age 50 died within 3 months of initiating iHD, similar to previously reported poor survival. 1 patient < 50 relapsed to alcohol use within the first 30 days and died from recurrent AH. 6 patients were offered RRT and maintained strict PETH-proven sobriety for 6 months. Of that population, 5 patients (83%) survived to 6 months. All were transitioned off iHD and now have between stage 2-3 CKD. **Conclusion:** In the era of early liver transplant for AH, the canonical teaching that RRT in AH is a 'bridge to nowhere' needs to be rigorously challenged. RRT and iHD are an unlimited resource, and increase the survival chances of young adults significantly above zero. These patients likely have different physiology than chronic decompensated cirrhotics. With the additional survival time they benefit from, many of these patients will recover well, maintain sobriety, and potentially survive to liver transplant.

Disclosures: Emily Harding-Theobald: Nothing to Disclose

1632 NEW SUBMISSION | COMPARATIVE INPATIENT OUTCOMES AND COMORBIDITY PROFILES IN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE WITH AND WITHOUT METABOLIC SYNDROME: INSIGHTS FROM A NATIONALLY REPRESENTATIVE DATABASE

Talal Bhatti Carla Barberan Parraga[1] Kundan Jana[2] Sanjaya Satapathy[3] Sajid Jalil[4] Shahzad Ashraf[5] Amir Saleem[6] Madeha Irfan[7] Lubna Kamani[8] Tanveer Hussain[9] Wasim Jafri[10] Taimur Aslam[11], [1]Maimonides Medical Center, NY, [2]Maimonides medical Center NY, [3]Northwell Health, [4]Stanford University, [5]NUMS Islamabad, Pakistan, [6]SZABMU Islamabad, [7]UHS, Lahore Pakistan, [8]LNH Karachil, [9]HFH, RMU Rawalpindi, [10]AKU Karachi, [11]Northwell

Background: The intersection of metabolic syndrome and alcohol-associated liver disease (ALD) is increasingly recognized as a unique phenotype termed MetALD. However, data comparing clinical characteristics and inpatient outcomes between ALD patients with and without metabolic syndrome remain limited. **Methods:** We identified adult patients (≥18 years) hospitalized with a principal diagnosis of ALD between 2016 and 2021 using the National Inpatient Sample (NIS) and ICD-10 codes. Patients were stratified into two groups based on the presence or absence of metabolic syndrome, defined by ≥ 3 components out of obesity (BMI ≥30), diabetes, hypertension, and hyperlipidemia. Weighted analyses were performed to account for the complex survey design. Baseline characteristics were compared using Rao-Scott chi-square and Student's t-tests. Multivariate regression models were developed to assess the impact of Metabolic Syndrome associated ALD (MetS +ALD) on in-hospital outcomes, adjusting for variables with $p < 0.1$ in univariate analysis. **Results:** A total of 936,645 weighted hospitalizations were included (ALD: 759,680 [81.1%]; MetS + ALD: 6,965 [18.9%]). Met S+ ALD patients were older (57.8 vs. 52.2 years, $p < 0.001$) and more likely male (80.1% vs. 67.4%, $p < 0.001$). MetS + ALD was significantly associated with higher prevalence of diabetes (91.7% vs. 17.9%), hypertension (96.1% vs. 44.6%), hyperlipidemia (91.7% vs. 12.2%), and chronic kidney disease (25.0% vs. 10.0%; all $p < 0.001$). Despite a higher burden of comorbidities, MetS + ALD patients had lower in-hospital mortality (3.0% vs. 4.9%, $p = 0.0024$) and reduced need for mechanical ventilation (4.2% vs. 5.8%, $p = 0.0125$). No significant differences were noted in length of stay or total hospital charges. **Conclusion:** Patients with MetS + ALD represent a distinct clinical subgroup of ALD with greater metabolic comorbidity burden but paradoxically lower inpatient mortality and respiratory support needs. These findings support further investigation into the natural history and tailored management strategies for MetS + ALD.

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Variable	No metabolic syndrome (ALD)	With metabolic syndrome	P_Value
FEMALE	247615 (32.6%)	1385 (19.9%)	0
Male	512065 (67.4%)	5580 (80.1%)	0
DIED: 1	37005 (4.9%)	210 (3.0%)	0.0024
White	492750 (66.7%)	4770 (70.1%)	0.0085
Hispanic	131770 (17.8%)	1190 (17.5%)	0.7503
Black	64650 (8.8%)	545 (8.0%)	0.3356
Asian/ Pac	9250 (1.3%)	50 (0.7%)	0.0862
Other	23370 (3.2%)	125 (1.8%)	0.0053
Native ame	16955 (2.3%)	120 (1.8%)	0.1888
Medicaid	286615 (37.8%)	1660 (23.9%)	0
Medicare	174060 (23.0%)	2760 (39.7%)	0
Self Pay	79020 (10.4%)	320 (4.6%)	0
Private Insi	185530 (24.5%)	1945 (27.9%)	0.0033
Other	26045 (3.4%)	235 (3.4%)	0.9107
No Charge	7040 (0.9%)	40 (0.6%)	0.1657
Fringe Cou	178235 (23.7%)	1875 (27.0%)	0.0062
Counties in	68960 (9.2%)	615 (8.9%)	0.6747
Counties in	163365 (21.8%)	1530 (22.0%)	0.8147
Not metrop	42650 (5.7%)	400 (5.8%)	0.9
Micropolita	61150 (8.1%)	575 (8.3%)	0.8556
"Central" c	236500 (31.5%)	1950 (28.1%)	0.0073
Northeast	139200 (18.3%)	1105 (15.9%)	0.0285
Midwest	156190 (20.6%)	2010 (28.9%)	0
South	285320 (37.6%)	2385 (34.2%)	0.0163
West	179070 (23.6%)	1465 (21.0%)	0.0333
Medium	218055 (28.7%)	1815 (26.1%)	0.0372
Small Hosp	151655 (20.0%)	1425 (20.5%)	0.6588
Large	390070 (51.3%)	3725 (53.5%)	0.1311
Urban Tea	557120 (73.3%)	5155 (74.0%)	0.5746
Urban Non	155805 (20.5%)	1415 (20.3%)	0.8643
Rural	46855 (6.2%)	395 (5.7%)	0.4421
Median Ho	132990 (18.0%)	1235 (18.1%)	0.9441
Median Ho	176235 (23.8%)	1670 (24.4%)	0.6196
Median Ho	234435 (31.7%)	2075 (30.3%)	0.2853
Median Ho	195990 (26.5%)	1860 (27.2%)	0.5687
Hospital Di	46455 (6.1%)	470 (6.7%)	0.3731
HOSP_DI\	92745 (12.2%)	635 (9.1%)	0.0009
HOSP_DI\	108815 (14.3%)	1535 (22.0%)	0
HOSP_DI\	47375 (6.2%)	475 (6.8%)	0.3719
HOSP_DI\	152960 (20.1%)	1320 (19.0%)	0.3004
HOSP_DI\	42075 (5.5%)	320 (4.6%)	0.1362
HOSP_DI\	90285 (11.9%)	745 (10.7%)	0.2035
HOSP_DI\	62510 (8.2%)	335 (4.8%)	0
HOSP_DI\	116560 (15.3%)	1130 (16.2%)	0.3864
OBESITY:	69705 (9.2%)	6515 (93.5%)	0
PREDM: 1	3065 (0.4%)	190 (2.7%)	0
HLD: 1	92745 (12.2%)	6390 (91.7%)	0
METSYN:	0 (0.0%)	865 (12.4%)	0
ECMO: 1	105 (0.0%)	0 (0.0%)	0.6874
HD: 1	23255 (3.1%)	275 (3.9%)	0.061
MV: 1	44135 (5.8%)	290 (4.2%)	0.0125
ESRD: 1	18840 (2.5%)	215 (3.1%)	0.1442
CKD: 1	76185 (10.0%)	1740 (25.0%)	0
AMI: 1	10955 (1.4%)	115 (1.7%)	0.5143
CHF: 1	55150 (7.3%)	1680 (24.1%)	0
PVD: 1	19820 (2.6%)	255 (3.7%)	0.0126
CVA: 1	8405 (1.1%)	120 (1.7%)	0.0347
DEMENTI	13715 (1.8%)	140 (2.0%)	0.5652
CTD: 1	9625 (1.3%)	125 (1.8%)	0.0813
COPD: 1	81725 (10.8%)	1360 (19.5%)	0
PUD: 1	28490 (3.7%)	265 (3.8%)	0.9138
HEMIPLE	2560 (0.3%)	30 (0.4%)	0.5483
AIDS: 1	2340 (0.3%)	10 (0.1%)	0.27
Malignanc	33700 (4.4%)	295 (4.2%)	0.7262
DM: 1	136120 (17.9%)	6390 (91.7%)	0
HTN: 1	338990 (44.6%)	6690 (96.1%)	0
surrogate:	0 (0.0%)	6100 (87.6%)	0
AGE	52.2 (0.0)	57.8 (0.3)	0
LOS	5.9 (0.0)	5.8 (0.2)	0.4549
TOTCHG	69234.9 (938.3)	68049.7 (2746.8)	0.6656

Disclosures: Talal Bhatti: Nothing to Disclose, Carla Barberan Parraga: Nothing to Disclose, Kundan Jana: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, Sajid Jalil: Nothing to Disclose, Shahzad Ashraf: Nothing to Disclose, Amir Saleem: Nothing to Disclose, Madeha Irfan: Nothing to Disclose, Lubna Kamani: Nothing to Disclose, Tanveer Hussain: Nothing to Disclose, Wasim Jafri: Nothing to Disclose, Taimur Aslam: Nothing to Disclose

1633 | MACROPHAGE DYSFUNCTION, NOT HEPATOCYTE OR NEUTROPHIL IMPAIRMENT, DRIVES ALCOHOL-INDUCED SUSCEPTIBILITY TO KLEBSIELLA PNEUMONIAE INFECTION

Tiantian Yao[1] Yukun Guan[1] Bryan Mackowiak[2] Luca Maccioni[1] Yang Wang[1] Yaojie Fu[1] Deniz Seyhan[1] Cheng Chen[1] Yuhong Lin[1] Dechun Feng[1] Bin Gao[1], [1]NIH, [2]National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Background: Alcohol consumption increases mortality in mice infected with *Klebsiella pneumoniae* (KP), a clinically relevant pathogen. However, the mechanisms underlying this increased susceptibility remain poorly understood. While it is known that alcohol impairs various immune responses, whether alcohol compromises hepatocyte production of acute-phase proteins or neutrophil bactericidal function during KP infection remains unclear. **Methods:** We utilized a murine model of chronic-plus binge ethanol exposure followed by intraperitoneal KP infection to assess survival and immune response. Hepatic transcriptional responses were evaluated by bulk and single cell RNA sequencing. Neutrophil antibacterial function and hepatocyte acute-phase protein production were assessed using in vitro assays. The role of macrophages and Kupffer cells in alcohol promotion of KP infection was tested by cell depletion and ablation. **Results:** Chronic plus binge alcohol challenge significantly increased the mortality in mice following KP infection. Singl cell RNA seq analysis identified hepatocytes are the major sources to produce acute phase proteins, which play a key role in controlling bacterial infection. Alcohol feeding did not impair hepatocyte synthesis of key acute-phase proteins (APPs). Neutrophils are known to play important roles in controlling bacterial infection, alcohol consumption upregulated hepatic CXCL1, a key chemokine to induce neutrophil migration, and neutrophil NCF1, a key factor to promote neutrophil ROS production. Neither hepatic specific Cxcl1 deletion nor neutrophil specific Ncf1 deletion affected alcohol promotion of KP infection-induced mortality. Macrophages and Kupffer cells play an important role in controlling bacterial infection. Interestingly, we found that alcohol exposure markedly reduced macrophages in the liver and lung. Depletion of all macrophages using clodronate liposomes markedly increased the mortality in mice following KP infection, while depletion of Kupffer cells did not increase the mortality induced by KP infection. **Conclusion:** Our findings suggest that macrophage dysfunction is a key driver of alcohol-induced susceptibility to bacterial infection, rather than impaired hepatocyte or neutrophil responses. These results highlight the central role of macrophages in the innate immune defense against KP

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and provide insight into how alcohol compromises host resistance through innate immune dysregulation.
Disclosures: Tiantian Yao: Nothing to Disclose, Yukun Guan: Nothing to Disclose, Bryan Mackowiak: Nothing to Disclose, Luca Maccioni: Nothing to Disclose, Yang Wang: Nothing to Disclose, Yaojie Fu: Nothing to Disclose, Deniz Seyhan: Nothing to Disclose, Cheng Chen: Nothing to Disclose, Yuhong Lin: Nothing to Disclose, Dechun Feng: Nothing to Disclose, Bin Gao: Nothing to Disclose

1634 | SERUM IMMUNOGLOBULIN A LEVELS: A CORRELATE OF SEVERITY AND POTENTIAL STRATIFICATION TOOL IN ALCOHOL-ASSOCIATED CIRRHOSIS

Yanxu Hao[1] Yuxuan Song[2] Jiarui Zheng[2] Bo Feng[2] Yandi Xie[2], [1]Beijing Jingmei Group General Hospital, Beijing, [2]Peking University People's Hospital, Peking University Hepatology Institute

Background: To investigate the relationship between serum immunoglobulin A (IgA) levels and alcohol-associated cirrhosis (AC) severity, and to evaluate IgA's potential for stratifying AC severity. **Methods:** This retrospective study included 379 individuals with AC admitted to our hospital between January 2012 and December 2023. Patients were stratified into groups based on Child-Pugh score (CPs). Baseline characteristics, liver function indicators, and immunoglobulin levels were compared across groups to assess IgA's role in AC severity. Spearman correlation analysis was performed to examine the relationship between IgA levels and established severity indices (ALBI score, MELD score, CPs). Additionally, correlations between IgA and relevant serological indicators were analyzed. Finally, we evaluated the utility of combining IgA with specific serological markers for stratifying AC severity. **Results:** The 379 AC patients were divided into CPs-A, CPs-B, and CPs-C groups. Serum IgA levels were significantly higher in the CPs-C group [6.9 (5.74, 9.56)] compared to both the CPs-A [3.95 (2.63, 5.94); $p < 0.001$] and CPs-B groups [5.35 (3.63, 6.76); $p < 0.001$]. Spearman analysis revealed significant positive correlations between IgA levels and CPs, ALBI score, and MELD score. Heatmap analysis indicated that IgA correlated significantly with all other serological indicators showing statistically significant differences among the AC severity groups. Notably, the combination of IgA and albumin (ALB) demonstrated superior diagnostic ability compared to other tested indices in distinguishing between compensated and decompensated AC subgroups. **Conclusion:** Serum IgA levels correlate significantly with the severity of alcohol-associated cirrhosis and hold significant value for the stratified diagnosis of AC, particularly when combined with albumin.
Disclosures: Yanxu Hao: Nothing to Disclose, Yuxuan Song: Nothing to Disclose, Jiarui Zheng: Nothing to Disclose, Bo Feng: Nothing to Disclose, Yandi Xie: Nothing to Disclose

1635 | LOWER HANDGRIP STRENGTH SCORES AND LIVER INJURY SEVERITY IN ALCOHOL-ASSOCIATED HEPATITIS

Harsh Tiwari[1] Henry Shay[1] Mack Mitchell[2] Gyongyi Szabo[3] Srinivasan Dasarathy[4] Bruce Barton[5] Laura Nagy[4] Maiying Kong[1] Vatsalya Vatsalya[1] Craig McClain[1], [1]University of Louisville, [2]University of Texas Southwestern Medical Center, [3]Beth Israel Deaconess Medical Center, [4]Cleveland Clinic Foundation, [5]University of Massachusetts

Background: Reduced handgrip strength (HS) is frequently observed in patients with liver disease, though its characterization in alcohol-associated hepatitis (AH) remains limited. There has yet to be an established relationship between HS and severity of liver injury or mortality in AH. This study aims to characterize HS in patients with AH and investigates the correlation between diminished HS and worsened liver injury or increased mortality. **Methods:** A total of 55 adult subjects (male and female, aged 21-67 years) were enrolled in this study. Subjects were categorized as healthy controls (HC; $n = 11$) or classified according to severity of AH using the Model for End Stage Liver Disease (MELD) score as either moderate AH (mAH, MELD ≤ 19; $n = 10$) or severe AH (sAH, MELD ≥ 20; $n = 34$). Clinical measures and laboratory data collected at a single point in time in this cross-sectional clinical investigation included demographics, alcohol consumption metrics (Alcohol Use Disorders Identification Test [AUDIT], Lifetime Drinking History [LTDH]), Controlling Nutritional Status (CONUT) scores, comprehensive metabolic panel (CMP), complete blood count (CBC), coagulation profile (PT/INR), and MELD scores. HS was measured three times for each subject. HS scores were assessed in relation to clinical parameters, biomarkers of liver injury and disease severity, and 90-day survival/mortality risk. **Results:** On average, patients with AH were in their 40s and overweight. All patients with AH reported 20+ years of drinking. Their AUDIT scores were > 20 (indicative of alcohol dependence and need for intervention) (Table 1). HS scores demonstrated a statistically significant 2-fold drop in patients with AH compared to the HC group. There was no significant difference in HS scores between the mAH and sAH groups. Average HS and ABIC scores correlated significantly ($p = 0.043$) in patients with

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sAH. There was a statistically significant correlation between 90-day survival and first handgrip scores with a good performance level of model fit (AUC = 0.708 ± 0.093 [SE], 95% CI [0.527, 0.890]; p = 0.025). There was a significant association between average HS and albumin levels (p = 0.043) among all patients with AH. In the mAH group, there was a significant association between average HS and MELD scores (adjusted $R^2 = 0.529$, p = 0.010). In the sAH group, female patients demonstrated a statistically significant reduction in average HS (>40%, 95% CI [-34.59, -4.21]; p = 0.014) compared to their male counterparts. **Conclusion:** HS decreases significantly in patients with AH. HS serves as a significant constituent phenotype in the clinical presentation of AH and correlates closely with 90-day survival/mortality risk. Reduced HS score can suggest functional deficits as noted by the correlation between HS scores and albumin levels. Sex differences in HS scores were observed in patients with sAH, highlighting a vulnerability among females.

Table 1. Demographic, drinking, and hand grip data of healthy controls and moderate and severe alcohol-associated hepatitis (AH) groups.

Variables	Healthy Controls (M = 5; F = 0)	Moderate AH (M = 5; F = 5)	Severe AH (M = 25; F = 9)
Age (yrs.) [a b]	32.50 ± 10.7	45.96 ± 9.3	46.10 ± 8.8
Weight (Lbs.) [a]	159.57 ± 26.5	236.86 ± 85.8	194.56 ± 54.6
LTDH (yrs.)	12.82 ± 11.7	22.10 ± 11.8	21.38 ± 13.8
AUDIT (Unit Score) [a b]	3.82 ± 4.9	23.50 ± 8.1	23.88 ± 7.5
1st Handgrip test [a b](/100 unit)	75.52 ± 29.6	35.73 ± 23.9	38.65 ± 19.6
2nd Handgrip test [a b](/100 unit)	73.36 ± 28.2	34.62 ± 22.3	51.77 ± 26.9
3rd Handgrip test [a b](/100 unit)	71.09 ± 28.6	32.6 ± 20.5	37.96 ± 18.7
Average Handgrip	73.32 ± 28.21	34.33 ± 22.02	39.26 ± 18.93

AH: alcohol-associated hepatitis; LTDH: Lifetime Drinking History; AUDIT: Alcohol Use Disorder Identification Test; M: Males; F: Females. (a) Significant difference between healthy controls and the moderate AH group. (b) Significant difference between the healthy controls and severe AH groups. Data presented as Mean ± Standard Deviation. Statistical significance was set at p<0.05.

Disclosures: Harsh Tiwari: Nothing to Disclose, Henry Shay: Nothing to Disclose, Mack Mitchell: Nothing to Disclose, Gyongyi Szabo: CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, Srinivasan Dasarathy: Nothing to Disclose, Bruce Barton: Nothing to Disclose, Laura Nagy: Nothing to Disclose, Maiying Kong: Nothing to Disclose, Vatsalya Vatsalya: Nothing to Disclose, Craig McClain: Nothing to Disclose

1636 | THERAPEUTIC PLASMA EXCHANGE-INDUCED SHIFTS IN BILE SALT COMPOSITION IN ALCOHOL-RELATED HEPATITIS: INSIGHTS INTO MECHANISMS AND THERAPEUTIC POTENTIAL

Francisco Idalsoaga[1] Paula Rivera[2] Luis Antonio Diaz[3] Fidel Allende[4] Sandra Solari[5] Nancy Solis[6] Daniel Jan Havaj[7] Karolina Sulejova[7] Daniela Žilinčanová[7] Svetlana Selčanová[7] Libor Vítek[8] Anand Kulkarni[9] Juan Pablo Arab[10] Lubomir Skladaný[7], [1]Pontificia Universidad Católica de Chile, Western University, [2]Pontificia Universidad Catolica de Chile, [3]Departamento De Gastroenterología, Escuela De Medicina, Pontificia Universidad Católica dDe Chile, S, [4]Department of Clinical Laboratories, School of Medicine, Pontificia Universidad Católica de Chile, [5]Department of Clinical Laboratories, School of Medicine, Pontificia Universidad Católica de Chile, S, [6]Departamento de Gastroenterología, Escuela de Medicina, Pontificia Universidad Católica de Chile, [7]Slovak Medical University, F. D. Roosevelt University Hospital, Banská Bystrica, Slovak Republic, [8]Charles University and General University Hospital in Prague, Prague, Czech Republic., [9]Department of Hepatology, AIG Hospitals, Hyderabad, India., [10]Virginia

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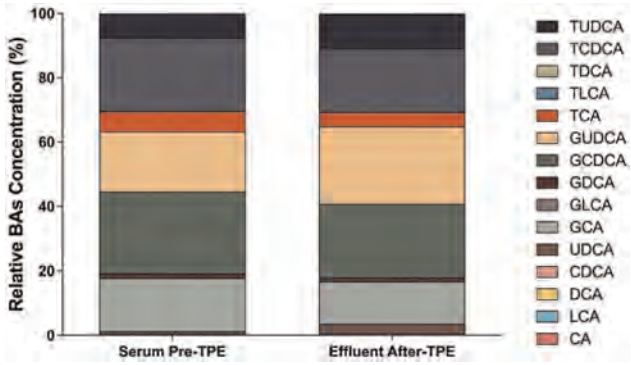
Commonwealth University School of Medicine, Richmond, VA, USA.

Background: Severe alcohol-associated hepatitis (sAH) is an acute condition with high mortality. Recent studies suggest that therapeutic plasma exchange (TPE) may improve 30- and 90-day survival in patients with ACLF; however, there is no evidence of the TPE efficacy in sAH. This pilot study aimed to evaluate the effect of TPE on BA profiles and clinical outcomes. **Methods:** We conducted a retrospective study of patients with sAH who underwent TP (five sessions), collecting clinical and laboratory data. Serum levels of total, conjugated, and unconjugated bile acids (BA) were measured in serum samples before plasmapheresis and in the post-procedure effluent using high-performance liquid chromatography-tandem mass spectrometry. **Results:** We included a total of 11 patients with sAH from a single center in Banská Bystrica, Slovakia. The median age was 48.7 years [IQR: 40–60], with two patients (18%) being women. The median MELD before and after TPE was 34.3 [32–39] and 24.6 [21–29], respectively. The mean time from admission to the start of TPE was 10.1 ± 7.9 days. Overall, five patients (45.5%) died. We identified significant differences on the ursodeoxycholic acid (UDCA) (Median 399.6 [202.6 - 541.9] vs. 669.4 [520-3412.5] ng/mL; $p = 0.04$) concentrations between serum and effluent. BA composition seems to be similar ($p = 0.689$). Before TPE, participants who died had significantly higher serum levels of total BA (Median 75213.03 [72478.1 - 77677.6] vs. 44736.3 [35823.4 - 53761.8] ng/mL; $p = 0.026$), glycine-conjugated BA (Median 49769.4 [49246.7 - 52276.7] vs. 28350.1 [20241.5 - 33597.5] ng/mL; $p = 0.0132$), total conjugated BA (glycine + taurine; Median: 73836.7 [71764-77112.7] vs. 43881.4 [35100.8 - 53290.8]ng/mL; $p = 0.026$), Glycoursodeoxycholic acid (G-UDCA) (Median 19038.1 [17669.9-19872.3] vs. 7819.2 [3659.4-11428.3] ng/mL; $p = 0.021$), lithocholic acid (LCA) (Median 6.34 [5-8-6.37] vs. 4.62 [3.62-5.41]ng/mL; $p = 0.0476$), and Glycochenodeoxycholic acid (G-CDCA) (Median 21132.1[19249.2-21307] vs. 11370 [9173.9- 14514,9] ng/mL; $p = 0.012$) than in those alive at the end of follow-up. After TPE, deceased participants also showed higher levels of total unconjugated BA (Median 3512.4 [3206.7-3909.5] vs. 871.3 [631.9-911.6] ng/mL; $p = 0.0324$), UDCA (Median 3352.8 [2425.9-3472.3] vs. 520.01 [243.2-636.6]ng/mL; $p = 0.026$), and DCA (Median 25.9[22.6-31.2] vs. 17.49 [14.5-20.7] ng/mL; $p = 0.047$) on the effluent. **Conclusion:** TPE may induce changes in serum bile acid composition in patients with sAH. Patients who died showed a distinct bile acid profile both before TPE and in the effluent. Further research should explore post-TPE BA changes and their clinical significance.



Disclosures: Francisco Idalsoaga: Nothing to Disclose, Paula Rivera: Nothing to Disclose, Luis Antonio Diaz: Nothing to Disclose, Fidel Allende: Nothing to Disclose, Sandra Solari: Nothing to Disclose, Nancy Solis: Nothing to Disclose, Daniel Jan Havaj: Nothing to Disclose, Karolina Sulejova: Nothing to Disclose, Daniela Žilinčanová: Nothing to Disclose, Svetlana Selčanová: Nothing to Disclose, Libor Vítek: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Lubomir Skladaný: Worwag: Speaking and Teaching, ProMed: Speaking and Teaching, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, RegPharm: Speaking and Teaching, Astellas: Speaking and Teaching

1637 | DOES A DIAGNOSIS OF ALCOHOL-ASSOCIATED LIVER DISEASE INCREASE PRESCRIPTION OF ALCOHOL USE DISORDER MEDICATION? DANISH AND ENGLISH COHORT STUDIES

Gro Askgaard[1] Adina Olaru[2] Peter Jepsen[3] Colin Crooks[2], [1]Zealand University Hospital, [2]University of Nottingham, [3]Aarhus University Hospital

Background: Alcohol abstinence is key to survival in alcohol-associated liver disease (ALD) and medications to treat alcohol use disorder may help towards this goal. We investigated the pattern of prescriptions of alcohol use disorder medications before and after the time of diagnosis of ALD in Denmark and England. **Methods:** Patients with newly diagnosed ALD and their prescriptions to treat alcohol use disorder (acamprosate, naltrexone, nalmefene and disulfiram) were identified from population-based health registries of the nationwide Danish registers (2011-2024) and UK Clinical Practice Research Datalink (2011-2018). We calculated the percentage of patients being covered with a prescription every day in the two years before and after ALD diagnosis, censoring patients at death or emigration. We used a poisson regression model to evaluate predictors of any alcohol use disorder prescription one

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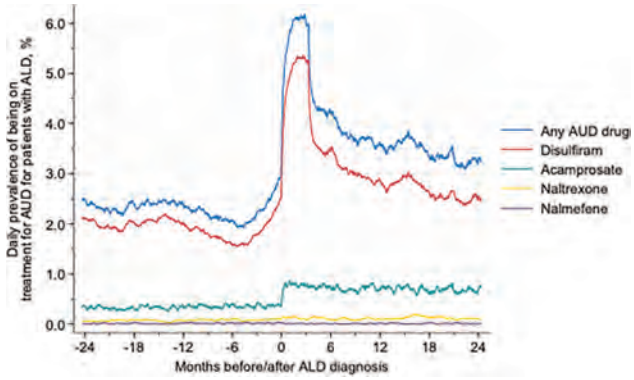
year after ALD diagnosis. **Results:** Cirrhosis was present in 69% of 17,657 Danish and in 43% of 56,240 English newly diagnosed patients with ALD. In both countries, the percentage of patients covered with prescriptions to treat alcohol use disorder increased at ALD diagnosis (Figure 1 shows Danish data, n = 17,657): the percentage of patients covered each day was 2.4% one year before diagnosis, it peaked at 6.1% shortly after diagnosis, and then decreased to 3.5% one year after diagnosis. For England, the percentages were 2.1%, 4.0% and 2.5% for patients being covered by a prescription to treat alcohol use disorder 1 year before, shortly after diagnosis and 1 year after ALD diagnosis. Disulfiram was the most prescribed drug in Denmark whereas it was acamprosate in England. Naltrexone and nalmefen were prescribed in less than 0.5% of ALD patients in Denmark and England during the 2-year observation period. The predictors for being prescribed a medication to treat alcohol use disorder were younger age, female sex, lower socioeconomic position, and non-cirrhotic state of ALD. **Conclusion:** Diagnosis of ALD increases the likelihood of prescription of alcohol use disorder medications. Still, few patients are prescribed these medications indicating missed opportunities to support abstinence.



Disclosures: Gro Askgaard: Nothing to Disclose, Adina Olaru: Nothing to Disclose, Peter Jepsen: Nothing to Disclose, Colin Crooks: Nothing to Disclose

1638 | NUTRITIONAL MANAGEMENT IN PATIENTS WITH ALCOHOL RELATED HEPATITIS- A QUALITY IMPROVEMENT PROJECT

Tyler Wark[1] Chandler Patton[2] She-Yan Wong[2] Cristina Angelo[2], [1]Lehigh Valley Health Network, [2]Lehigh Valley Health

Background: Alcohol related hepatitis (AH) is a type of alcohol related liver disease associated with significant morbidity and mortality. Treatment options are limited and steroids are the mainstay of therapy. Patients with AH are often malnourished; therefore, nutrition therapy is an important part of treatment. Studies show that meeting certain calorie/protein goals was noninferior to steroids in regard to mortality in patients with acute severe AH. We aimed to increase the number of hospitalized patients with AH who received a high calorie, high protein diet. **Methods:** This quality improvement study was conducted at Lehigh Valley Hospital (LVH) in Allentown, PA with data collected between 1/2018 and 2/2025. In conjunction with the nutrition team, a new diet order was created and implemented in the electronic medical record under GI/Hepatology as "hi calorie/hi protein diet" on 7/2024, after which all data collected was considered post intervention data including the number of patients on the new diet order, demographics, and 30-day mortality. Education on the diet and its indication was provided via a PowerPoint presentation to internal medicine residents and faculty attendings on 08/2024. Adults hospitalized with AH were identified with ICD 10 codes K70.9, K70.10, and K70.11 and diet order data were collected at two LVH campuses. **Results:** A total of 108 patients were admitted with AH during our data collection period. The patient cohort was 61% male, 90% white, and average age was 50 years old. Only 2/91 (2%) patients were on a high protein/calorie diet pre- intervention, compared to 7/15 (46%) patients post-intervention. At baseline, 22/91 (24%) patients were readmitted within 30 days compared to 1/17 (5%) following intervention. 30-day mortality was 11% (10/91) and 6% (1/17) pre and post-interventions, respectively. At the conclusion of the project, a QI forum with hospitalists and other departments associated with research was held to provide updates on the project. **Conclusion:** Though nutrition therapy is one of the few known treatments of AH, this study highlights that it is underutilized. Through creation of a liver specific diet order and increasing awareness, we increased the number of patients hospitalized with AH who received standard of care nutrition requirement, and 30 day readmission rates and mortality were improved. With ongoing education, nutrition assessments, and placing inpatients on standard of care diets, we hope to improve overall outcomes in this patient population.

Disclosures: Tyler Wark: Nothing to Disclose, Chandler Patton: Nothing to Disclose, She-Yan Wong: Nothing to Disclose, Cristina Angelo: Nothing to Disclose

1639 | INSTITUTIONAL APPROACHES TO ALCOHOL MONITORING AND TREATMENT AFTER LIVER TRANSPLANTATION (LT) FOR ALCOHOL-ASSOCIATED LIVER DISEASE (ALD): A MULTICENTER PROTOCOL-BASED COMPARISON

Sheila Eswaran[1] Esra Alagoz[2] Megan Saucke[2] Brian Fisher[2] Marina Serper[3] Keren Ladin[4] John Rice[2] Brian

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Background: There is currently no consensus for monitoring or treatment of alcohol use disorder (AUD) after LT in patients with ALD. Our study evaluates institutional variability in guidance documents from 8 LT centers in the ACCELERATE consortium. **Methods:** Based on the principles qualitative document analysis, using inductive content analysis, we reviewed all internal protocols related to alcohol use after LT from 8 geographically diverse US LT centers. The protocols had been updated between 2019-2025. **Results:** Our review highlights the following themes: psychosocial team engagement, alcohol testing, AUD counseling, and AUD treatment with pharmacotherapy. Elements of the documents were characterized as "vague", "specific" or "no guidance" (Table1). Five centers outlined preemptive psychosocial team engagement post-LT, among which 2 had guidelines for follow up by the psychosocial team at specific time intervals and 3 centers proposed psychosocial team follow up on an *as needed* basis (advice that we characterized as 'vague'). No guidance on engagement by psychosocial services was prescribed at 3 centers. Seven centers required surveillance for alcohol use post-LT: monthly whole blood Phosphatidylethanol (PEth) testing for one year in 4 centers, PEth testing every 3 months at 2 centers, while 1 center did not specify type or frequency of testing. One center did not have guidance on the requirement of any alcohol testing. Five centers described AUD counseling post-LT: preemptive in 3 and reactive after evidence of drinking in 2. Four centers outlined in detail the location, frequency, and duration of AUD counseling. Pharmacotherapy for AUD post-LT was addressed in documents from 2 centers only. Two centers had patient facing documents vaguely outlining the monitoring or treatment of AUD post-LT. **Conclusion:** Our study shows inter-institutional variability in post-LT guidance for patients transplanted with ALD regarding testing for alcohol use, and approaches to prevent or respond to episodes of return to drinking. This variance may contribute to disparate patient experiences and center outcomes. Further study is needed to determine the relative effectiveness of different protocols for management of AUD post-LT, which can inform efforts to standardize best practices in LT for ALD care.

Table 1: Summary of Post-LT Documents from 8 centers

	Center 1	Center 2	Center 3	Center 4	Center 5	Center 6	Center 7	Center 8
Post-LT Psychosocial Team Engagement	Specific	Specific	Vague	No Guidance	Vague	Vague	No Guidance	No Guidance
Post-LT Alcohol Testing	Specific	Specific	Specific	Specific	Vague	Specific	Specific	No Guidance
Post-LT AUD Counseling	Specific	Specific	Specific	Specific	Vague	No Guidance	No Guidance	No Guidance
Post-LT AUD Pharmacotherapy	Vague	No Guidance	No Guidance	No Guidance	No Guidance	No Guidance	No Guidance	Specific
Post-LT AUD Patient Facing Documents	No Guidance	No Guidance	Vague	No Guidance	Vague	No Guidance	No Guidance	No Guidance

Disclosures: Sheila Eswaran: Nothing to Disclose, Esra Alagoz: Nothing to Disclose, Megan Saucke: Nothing to Disclose, Brian Fisher: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Eurofins: Grant/Research Support, Keren Ladin: Nothing to Disclose, John Rice: Nothing to Disclose, Brian Lee: NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, DURECT: Advisor, HepaTx: Advisor, CymaBay: Consultant, Ipsen: Consultant, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor, Assertio: Consultant, Norah Terrault: Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, ImmunoCore: Grant/Research Support, HBV Foundation: Board member, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, George Therapondos: Novo Nordisk: Consultant, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Ipsen: Speaking and Teaching, Gilead: Speaking and Teaching, Mohamed Shoreibah: Nothing to Disclose, R. Mark Ghobrial: Nothing to Disclose, Christine Hsu: Nothing to Disclose, Amol Rangnekar: Nothing to Disclose, Ethan Weinberg: PharmaIN: Consultant, BioVie: Consultant, Sequana: Consultant, Novo Nordisk: Advisor, Amgen: Consultant, Astra Zeneca: Consultant, Kezar: Consultant, Kirti Shetty: Nothing to Disclose, Neha Jakhete: Nothing to Disclose, Michael Lucey: Nothing to Disclose

1640 | UNDERLYING CIRRHOSIS IN PATIENTS RECEIVING LIVER TRANSPLANTATION FOR ALCOHOL-ASSOCIATED HEPATITIS: A HISTOPATHOLOGIC AND CLINICAL ANALYSIS

Qusai Al Zureikat[1] Sarah Wang Bu[2] Ahmad Abdulraheem[1] Brototo Deb[1] Amol Rangnekar[3] Hanna

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Background: Alcohol-associated hepatitis (AH) is the most severe presentation of alcohol-associated liver disease and is increasingly recognized as an indication for liver transplantation (LT). A substantial proportion of patients with AH have coexisting cirrhosis, with literature estimating prevalence rates of 50–70%. Clinical overlap between AH and cirrhosis complicates accurate diagnosis without histologic confirmation. Improved recognition of cirrhosis in this setting has implications for prognostication and long-term management. This study aimed to assess the prevalence of cirrhosis in patients with AH undergoing LT and to identify clinical features distinguishing patients with AH alone from those with AH and underlying cirrhosis. **Methods:** We conducted a retrospective review of patients who underwent LT for AH at a single center. Patients were stratified based on the presence or absence of histologic cirrhosis on explant pathology. Demographic, clinical, and laboratory variables at the time of transplant were compared between groups. Statistical significance was defined as $p < 0.05$. **Results:** Of 71 patients who received LT for AH, 68 (95.8%) had histologically confirmed cirrhosis, with only 3 (4.2%) without underlying cirrhosis. Compared to patients without cirrhosis, those with cirrhosis had significantly lower neutrophil percentages (34.59% ± 38.97 vs. 85.10% ± 8.51, $p = 0.029$), lower platelet counts (153 ± 97 vs. 313 ± 139 x10³/μL, $p = 0.021$), and were significantly less likely to have histologic evidence of inflammation on explant (41% vs. 100%, $p = 0.007$). MELD 3.0 scores were similar between groups (mean 36.0 ± 4.36 in patients without cirrhosis vs. 38.57 ± 10.18 in patients with cirrhosis, $p = 0.558$ using Welch's t-test). No statistically significant differences were observed in age, time from last drink, white blood cell count, ferritin, or albumin levels. On imaging, patients with cirrhosis were significantly more likely to have radiographic evidence of cirrhosis (90% vs. 0%, $p = 0.002$), while no significant differences were observed in rates of hepatomegaly (43% vs. 67%, $p = 0.580$), splenomegaly (79% vs. 33%, $p = 0.129$), or hepatic steatosis (79% vs. 67%, $p = 0.515$). **Conclusion:** Our findings demonstrate that the vast majority of patients undergoing LT for AH have underlying cirrhosis, which is often under-recognized in clinical assessment. These results suggest a much higher prevalence of cirrhosis in the AH LT population than previously reported. This likely reflects more advanced disease in those who receive LT. Features such as thrombocytopenia, reduced neutrophil percentage, and imaging may offer subtle clues to the presence of underlying cirrhosis.

Category	Variable	Cirrhosis Absent (n=3)	Cirrhosis Present (n=68)	p-value
Demographics	Age at time of transplant (yrs)	51.3 ± 12.7	43.6 ± 10.2	0.285
	Time since last drink to transplant (days)	171.0 ± 224.3	182.9 ± 668.6	0.539
Laboratory results (mean ± SD)	WBC (x10³/μL)	22.2 ± 2.3	15.9 ± 7.6	0.113
	Neutrophil (%)	85.1 ± 8.5	34.6 ± 39.0	0.029
	Lymphocytes (%)	5.7 ± 2.6	8.8 ± 12.7	0.764
	Monocytes (%)	6.6 ± 4.0	37.9 ± 181.6	0.853
	Platelet count (x10³/μL)	313.0 ± 138.6	152.9 ± 97.1	0.021
	MCV (fL)	97.7 ± 4.9	98.2 ± 14.7	0.764
	Creatinine (mg/dL)	2.39 ± 1.48	5.73 ± 23.78	0.966
	Sodium (mmol/L)	133.0 ± 6.2	132.0 ± 6.1	0.683
	Total bilirubin on admission (mg/dL)	20.1 ± 16.2	24.1 ± 12.1	0.679
	Total bilirubin 4 days after admission (mg/dL)	16.7 ± 16.6	29.5 ± 45.8	0.395
	ALP (U/L)	234.7 ± 103.7	174.2 ± 84.7	0.265
	AST (U/L)	91.3 ± 63.6	185.1 ± 235.1	0.241
	ALT (U/L)	29.3 ± 21.1	78.2 ± 127.2	0.141
	Albumin (g/dL)	2.83 ± 1.06	2.95 ± 0.59	0.943
	Ferritin (ng/mL)	1005.5 ± 329.7	1087.9 ± 1155.1	0.617
Scores (mean ± SD)	MELD 3.0 Score	36.0 ± 4.36	38.57 ± 10.18	0.558
Histology n (%)	Steatosis	2 (67%)	54 (79%)	0.515
	Inflammation	3 (100%)	28 (41%)	0.007
	Mallory-Denk Bodies	2 (67%)	43 (63%)	1.000
Imaging n (%)	Consistent with Cirrhosis	0 (0%)	59 (87%)	0.002
	Hepatomegaly	2 (67%)	29 (43%)	0.708
	Splenomegaly	1 (33%)	53 (78%)	0.174
	Hepatic Steatosis	2 (67%)	54 (79%)	1

Disclosures: Qusai Al Zureikat: Nothing to Disclose, Sarah Wang Bu: Nothing to Disclose, Ahmad Abdulraheem: Nothing to Disclose, Brototo Deb: Nothing to Disclose, Amol Rangnekar: Nothing to Disclose, Hanna Blaney: Nothing to Disclose

1641 | ALCOHOL-RELATED LIVER CIRRHOSIS MORTALITY TRENDS IN OLDER ADULTS IN THE UNITED STATES (1990–2021): AGE, SEX AND SOCIODEMOGRAPHIC INDEX STRATIFIED INSIGHTS

MOHAMED A ELNAGGAR[1] Ayah Obeid[2] Ismail Elkhattib[1] Mohamad Elgozair[3] Omar Abbas[4] Mohamed Abd El Aziz[5] Raffi Karagozian[6], [1]Hartford Healthcare, [2]Saint Luke's University Health Network, [3]Danbury Hospital/Yale New Heaven, [4]Al-Azhar University, School of Medicine, [5]Deaconess health system, Henderson, KY, [6]Tufts University School of Medicine

Background: The burden of alcohol-related liver cirrhosis is increasing worldwide, but mortality trends in older adults remain underexplored. We analyzed trends in alcohol-related cirrhosis deaths among U.S. adults aged ≥70 years between 1990 and 2021, with stratification by age group, sex, and Socio-demographic Index (SDI) level. **Methods:** We used data from the Global Burden of Disease (GBD) 2019 study to examine mortality trends from 1990 to 2021. Analyses were stratified by age group (70–74, 75–79, 80–84, 85–89, 90–94, and ≥95 years), sex, and global SDI level. We calculated Average Annual Percent Change (AAPC) using log-linear regression models and visualized

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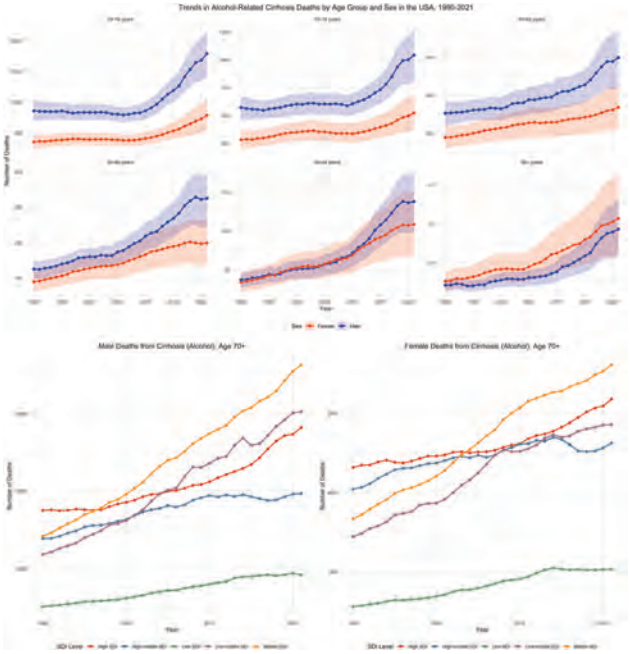
results with 95% uncertainty intervals (UIs). **Results:** In 2021, the highest alcohol-related cirrhosis mortality was observed among U.S. males aged 70–74 years (2,135 deaths; 95% UI: 1,681–2,607). A consistent upward trend was observed across all age groups and both sexes, with AAPC ranging from 2.15% to 3.19%. Globally, the Middle SDI group experienced the highest AAPC for both sexes (male: 3.18%, female: 3.22%). High SDI countries like the U.S. showed lower AAPC values but high absolute mortality. **Conclusion:** Alcohol-related cirrhosis mortality has risen significantly in U.S. adults ≥70 years, with the most rapid increases seen in the oldest age groups and in middle-SDI countries globally. These findings highlight an urgent need for targeted preventive strategies in aging populations. Keywords: Alcohol-related cirrhosis; Global Burden of Disease; older adults; mortality trends; SDI; liver disease



Disclosures: MOHAMED A ELNAGGAR: Nothing to Disclose, Ayah Obeid: Nothing to Disclose, Ismail Elkhattib: Nothing to Disclose, Mohamad Elgozair: Nothing to Disclose, Omar Abbas: Nothing to Disclose, Mohamed Abd El Aziz: Nothing to Disclose, Raffi Karagozian: Nothing to Disclose

1642 | LONG-TERM MAJOR ADVERSE LIVER OUTCOMES IN LEAN AND NON-LEAN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE

Pojsakorn Danpanichkul[1] Yanfang Pang[2] Vincent Chen[3] Donghee Kim[4] Karn Wijarnpreecha[5], [1]Texas Tech University Health Sciences Center, [2]Chiang Mai University, [3]University of Michigan Medical Center, [4]Stanford University, [5]University of Arizona College of Medicine-Phoenix

Background: Although differences in liver outcomes among lean and non-lean individuals with MASLD are well established, the major adverse liver outcomes (MALO) in patients with lean and non-lean ALD remain unexplored. This study leverages a large-scale federated database to investigate these differences. **Methods:** We conducted a retrospective cohort study utilizing anonymized electronic health records from the TriNetX network. Two cohorts were identified: individuals with ALD who were lean (body mass index [BMI] < 25 kg/m2) and those who were non-lean (BMI ≥ 25 kg/m2). The study focused on individuals without a prior history of liver decompensation, with a follow-up duration of median 5 years. The primary outcomes included MALO and its subcategories. To minimize confounding, 1:1 propensity score matching was performed, accounting for baseline demographics, socioeconomic factors, substance use disorder, mental health conditions, medication use, and laboratory values. **Results:** The study included 90,712 individuals with ALD, evenly distributed between the lean (n = 45,356) and non-lean patients with ALD (n = 45,356), post propensity score matching. Compared to the non-lean group, the lean ALD group was associated with a lower risk of hepatic encephalopathy (hazard ratio [HR]: 0.93, 95% confidence interval [CI] 0.87 to 1.00), variceal bleeding (HR: 0.90, 95% CI 0.82 to 0.99), hepatorenal syndrome (HR: 0.84, 95% CI 0.78 to 0.90), and portal hypertension (HR 0.91, 95% CI 0.87 to 0.94). However, the lean ALD group was associated with a higher risk of ascites (HR: 1.10, 95% CI 1.06 to 1.14) and spontaneous bacterial peritonitis (HR: 1.10, 95% CI 1.10, 95% CI 1.02 to 1.19). However, there is no difference between overall MALO in the two groups (HR: 0.97, 95% CI 0.94 to 1.01). **Conclusion:** In **Conclusion:**, this multicenter study offers preliminary evidence suggesting that lean patients with ALD have different MALO than non-lean ALD patients.

Table 1 Major Adverse Liver Outcomes different between lean and non-lean patients with alcohol-associated liver disease

Outcome	Hazard Ratio (95% CI)	p-value
Major Adverse Liver Outcomes	0.97 (0.94–1.01)	0.127
Ascites	1.10 (1.06–1.14)	**<0.001**
Hepatic Encephalopathy	0.93 (0.87–1.00)	**0.049**
Variceal Bleeding	0.90 (0.82–0.99)	**0.027**
Hepatorenal Syndrome	0.84 (0.78–0.90)	**<0.001**
Portal Hypertension	0.91 (0.87–0.94)	**<0.001**
Spontaneous Bacterial Peritonitis	1.10 (1.02–1.19)	**0.016**

Disclosures: Pojsakorn Danpanichkul: Nothing to Disclose, Yanfang Pang: Nothing to Disclose, Vincent Chen: AstraZeneca: site PI on industry-sponsored trial,

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Ipsen: site co-I on industry-sponsored trial, Kowa: site co-I on industry-sponsored trial, Donghee Kim: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose

1643 | INTEGRATED LIVER TRANSPLANT ENGAGEMENT & RECOVERY NETWORK: A PERSON-CENTERED APPROACH TO ALCOHOL-ASSOCIATED LIVER DISEASE

Luis Seija[1] Shimrit Keddem[1] Allison Schachter[1] Vinayak Ahluwalia[1] James Guevara[2] Jonathan Nahas[1] Marina Serper[3] Marilyn Schapira[1] Tamar Klaiman[1] Ethan Weinberg[1] Robert Weinrieb[1] Arpita Goswami Banerjee[1] Therese Bittermann[4], [1]University of Pennsylvania, [2]Children's Hospital of Philadelphia, [3]University of Pennsylvania Health System, [4]Perelman School of Medicine

Background: Alcohol-associated liver disease (ALD) is the leading indication for liver transplantation in the U.S. Patients with ALD often have co-occurring alcohol use disorder (AUD), psychiatric co-morbidities, complex psychosocial needs, and systemic barriers to care, frequently without access to coordinated, multidisciplinary treatment. While integrated care models offer a promising approach, there is limited information on how patients experience these interventions. The Integrated Transplant Engagement & Recovery Network (ILEARN), a person-centered, team-based clinic, was developed to strengthen relational continuity, improve care coordination, and enhance quality of care for patients with ALD and AUD pre- and post-transplant. This qualitative study explores how patients perceive and engage with the ILEARN model to inform future program design, implementation strategies, and opportunities to embed equity throughout the transplant pathway. **Methods:** We conducted a single-center qualitative study utilizing modified grounded theory. Between February and May 2025, we purposively sampled both pre- and post-transplant patients with documented ILEARN visits. In-depth, semi-structured interviews explored five domains: illness and transplant experience, perceptions of integrated care, barriers and facilitators to treatment engagement, and caregiver roles. Interviews continued until thematic saturation. Data were analyzed thematically. Sociodemographic information, clinical characteristics, and self-reported health data were also collected. The study followed COREQ guidelines. **Results:** Seventeen patient interviews yielded four major themes: Lived Experience of Illness & Recovery, Navigating Systems of Care, Perceptions of Multidisciplinary Care, and Relational Context & Family Systems. ILEARN was perceived as more supportive, coordinated, and behaviorally inclusive than prior care, offering a sense of stability during a time of emotional and identity disruption. Barriers included insurance obstacles, difficulty navigating transplant processes, emotional fatigue, and lack of clarity around clinic structure and AUD pharmacotherapy. Relational support, provider trust and communication, and personalized care emerged as powerful facilitators. Findings informed a patient-derived integrated care framework and key clinician-facing implementation considerations. **Conclusion:** To our knowledge, this is the first study to center the patient voice in evaluation of a multidisciplinary ALD clinic. Findings underscore the potential of integrated, person-centered models like ILEARN while revealing structural gaps and opportunities for practice change. Patient narratives offer actionable insights to inform future implementation and reshape transplant care around the lived experiences of those it aims to serve.

Theme	Theme Description	Illustrative Quote(s)
Lived Experience of Illness & Recovery	Emotional, functional, and identity-related experiences of living with ALD and/or AUD, offering narrative insight into how patients understand and adapt to illness and recovery	*"Being sober now is like a second chance, I'm finally living."* *"I was functioning just fine on the outside. No one knew I had a problem until it was too late."* *"Doctors told me if this transplant hadn't happened, I had maybe two weeks to live."*
Navigating Systems of Care	Describes patients' structural and interpersonal experiences with healthcare systems, highlighting feasibility, accessibility, and system-level barriers or facilitators	*"MyChart has been amazing because my nurse practitioner is so responsive, even with questions about vitamins. I trust the information she gives me."* *"I had no liver specialist nearby. Local doctors just weren't equipped for this."* *"Insurance slowed everything down, I didn't even know what I was eligible for."*
Perceptions of Multidisciplinary & Integrated Care	Reflects how patients interpret and emotionally respond to team-based models like ILEARN with implications of care acceptability and future implementation	*"You're not just seeing a doctor; you're seeing a whole care team."* *"They treated me with dignity, not pity. That changed everything."* *"They workshopped my case together - it was about me, not just the disease."* *"Everything I know about this process came from them. I'd be lost without my team."*
Relational Context & Family Systems	Highlights the role of caregivers, family dynamics, and social context in shaping patient experiences and engagement throughout the transplant journey	*"My partner carried the whole thing. He was the one coordinating and holding it all together."* *"Telling my family was the hardest part. But it kept me accountable."* *"My mom was saying goodbye over dinner the night before surgery. I just didn't know it yet."*

Themes + Illustrative Quotes *Overview of major themes identified by thematic analysis, supported by illustrative quotes*

Disclosures: Luis Seija: Nothing to Disclose, Shimrit Keddem: Nothing to Disclose, Allison Schachter: Nothing to Disclose, Vinayak Ahluwalia: Nothing to Disclose, James Guevara: Nothing to Disclose, Jonathan Nahas: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Eurofins: Grant/Research Support, Marilyn Schapira: Nothing to Disclose, Tamar Klaiman: Nothing to Disclose, Ethan Weinberg: PharmaIN: Consultant, BioVie: Consultant, Sequana: Consultant, Novo Nordisk: Advisor, Amgen: Consultant, Astra Zeneca: Consultant, Kezar: Consultant, Robert

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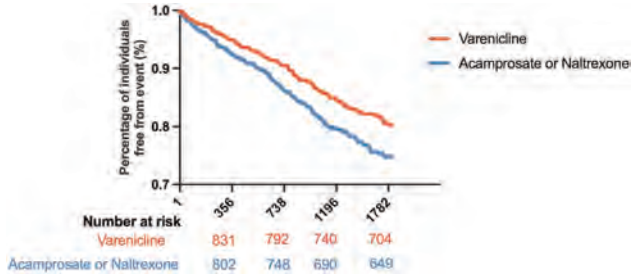
Weinrieb: Nothing to Disclose, Arpita Goswami Banerjee: Nothing to Disclose, Therese Bittermann: Nothing to Disclose

1644 | EVALUATING THE IMPACT OF VARENICLINE ON MAJOR ADVERSE LIVER OUTCOMES IN ALCOHOL-ASSOCIATED LIVER DISEASE

Pojsakorn Danpanichkul[1] Yanfang Pang[2] Donghee Kim[3] Andrew Ibrahim[4] Benjamin Nah[5] Mazen Noureddin[6] Karn Wijarnpreecha[7] Suthat Liangpunsakul[8], [1]Texas Tech University Health Sciences Center, [2]Chiang Mai University, [3]Stanford University Medical Center, [4]Texas Tech University, [5]National University of Singapore, [6]Houston Methodist Hospital, [7]University of Arizona College of Medicine-Phoenix, [8]Indiana University

Background: Varenicline, an FDA-approved medication for smoking cessation, has shown promise in supporting alcohol abstinence. However, its impact on mortality and major adverse liver outcomes (MALO) among individuals with alcohol use disorder (AUD) and alcohol-associated liver disease (ALD) remains uncertain. This study utilizes a large federated database to assess varenicline's association with long-term outcomes in this population. **Methods:** A retrospective cohort study was conducted using anonymized electronic health records from the TriNetX network. Two cohorts were established, including individuals with ALD and AUD. The index event was initiation of either FDA-approved AUD pharmacotherapies (naltrexone or acamprosate) or varenicline. Outcomes were evaluated in patients without prior liver decompensation over a follow-up period of up to 10 years. The primary outcomes were MALO and all-cause mortality. To minimize confounding, propensity score matching (1:1) was applied, accounting for demographics, socioeconomic factors, substance use disorder, mental health conditions, medication use, and laboratory values. **Results:** The study included 2,272 individuals with ALD and AUD, equally divided between the FDA-approved pharmacotherapy group (n = 1,136) and the varenicline group (n = 1,136). Varenicline use was associated with a lower risk of mortality (HR: 0.76, 95% CI: 0.62–0.94, p = 0.009), MALO (HR: 0.74, 95% CI: 0.59–0.94, p = 0.012), and portal hypertension (HR: 0.70, 95% CI: 0.53–0.92, p = 0.011) compared to FDA-approved pharmacotherapy. **Conclusion:** These findings suggest that varenicline may provide clinical benefits for individuals with ALD and AUD, potentially reducing mortality and serious liver complications relative to FDA-approved AUD pharmacotherapies.



Disclosures: Pojsakorn Danpanichkul: Nothing to Disclose, Yanfang Pang: Nothing to Disclose, Donghee Kim: Nothing to Disclose, Andrew Ibrahim: Nothing to Disclose, Benjamin Nah: Nothing to Disclose, Mazen Noureddin: Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor: Terns,Takeda, Zydus., Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK: Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, Rivus Pharma, Cytodyn, and ChronWell: Stock – privately held company, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharmaceuticals: Consultant, Cytodyn: Consultant, GSK: Consultant, Eli Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Terns: Consultant, Takeda: Consultant, Allergan: Principal Investigator for a Drug Study, Akero: Principal Investigator for a Drug Study, BI: Principal Investigator for a Drug Study, BMS: Principal Investigator for a Drug Study, Gilead: Principal Investigator for a Drug Study, Galectin: Principal Investigator for a Drug Study, Genfit: Principal Investigator for a Drug Study, GSK: Principal Investigator for a Drug Study, Conatus: Principal Investigator for a Drug Study, Corcept: Principal Investigator for a Drug Study, Enanta: Principal Investigator for a Drug Study, Madrigal: Principal Investigator for a Drug Study, Novartis: Principal Investigator for a Drug Study, Novo Nordisk: Principal Investigator for a Drug Study, Shire: Principal Investigator for a Drug Study, Takeda: Principal Investigator for a Drug Study, Terns: Principal Investigator for a Drug Study, Viking: Principal Investigator for a Drug Study, Zydus: Principal Investigator for a Drug Study, Rivus Pharmaceuticals: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speaking and Teaching, Akero: Stock – privately held company, Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator,

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1645 | IMPACT OF ALCOHOL-RELATED HEPATITIS ON PATIENTS WITH ALCOHOL INDUCED PANCREATITIS; A NATIONWIDE ANALYSIS

Adham Obeidat[1] Hareesh Gundlapalli[2] Jawairia Memon[2] Gicel Jacklin Aguilar[2] Ahmad Abou Yassine[2] Christopher Chang[2], [1]Presbyterian Medical Group, [2]University of New Mexico

Background: Acute pancreatitis (AP) is caused by the destruction of exocrine cells due to the infiltration of inflammatory cells. Alcohol consumption is responsible for 17% to 25% of acute pancreatitis cases globally, making it the second most common cause of AP after gallstones. Additionally, excessive alcohol intake can result in steatosis, alcohol-related hepatitis (AH), and cirrhosis. This retrospective study aims to assess the potential impact of concurrent AH in patients hospitalized with alcohol-induced AP. **Methods:** The United States Nationwide Inpatient Sample (NIS) database was utilized to extract hospitalization data for patients admitted between 2019 and 2021. Using ICD-10 revision codes, we identified adults diagnosed with alcohol-induced AP and concurrent alcohol-related hepatitis (AH). The control group consisted of AP patients without AH. The primary outcome was in-hospital mortality. Secondary outcomes included sepsis, encephalopathy, pulmonary edema, respiratory failure (RF), acute kidney injury (AKI), pulmonary embolism (PE), cardiac arrest, malnutrition and length of stay (LOS). Multivariate logistic regression was used to adjust for relevant variables. **Results:** 74,756 patients were admitted with alcohol induced AP. Of these, 11,366 patients had a concurrent diagnosis of AH. In the AH group, the mean age was 43.31 years. 34.38% were females and 65.3% were Caucasians. In the AH group, 9.06% were malnourished and 11.4% were obese. 2.6% of AP patients with AH died during hospitalization compared to 1.3% in those without AH. Further, total hospital charges were more in the AH group (62,464.99$ vs 53,132.45$.). When adjusted to other relevant variables, AH was associated with increased in-hospital mortality in AP patients (OR 2.21; P-value $<$ 0.001). Congestive heart failure, malnutrition, age, male gender and Caucasian race were also associated with increased in-hospital mortality. On univariate and multi-variate analysis, AH was associated with an increased chance of developing sepsis, encephalopathy, AKI, malnutrition, pulmonary edema, RF, cardiac arrest and prolonged LOS. Interestingly, patients with AH had a lower chance for PE (see Table 1). **Conclusion:** The mortality rate in patients with alcohol-induced AP is approximately 36 times higher than in the general population, with nearly 50% of these patients dying within 20 years of diagnosis. The prevalence of concurrent alcohol-related liver disease, including AH, in patients with alcohol-induced AP varies significantly, ranging from 1.4% to 70%. In this study, we observed increased in-hospital mortality, additional complications, and a higher financial burden for patients with both alcohol-induced AP and concurrent AH. As a result, we recommend that clinicians closely monitor patients with these coexisting conditions and consider more aggressive treatment early in their hospitalization.

Complication	Univariate	P-Value	Multivariate	P-Value
Sepsis	1.29	< 0.001	1.36	< 0.001
AKI	1.34	< 0.001	1.58	< 0.001
Pulmonary edema	1.53	< 0.001	1.56	< 0.001
Respiratory Failure	1.43	< 0.001	1.67	< 0.001
Hepatic Encephalopathy	1.87	< 0.001	2.1	< 0.001
Cardiac arrest	1.47	< 0.001	1.63	< 0.001
Pulmonary embolism	0.61	< 0.001	0.68	< 0.001
Malnutrition	1.14	< 0.001	1.29	< 0.001
LOS	1.67	< 0.001	1.76	< 0.001

Table 1. Univariate and multivariate analysis of odds ratios (OR) for alcohol-related hepatitis as a potential predictor of in-hospital complications in patients hospitalized with alcohol-induced pancreatitis.

Disclosures: Adham Obeidat: Nothing to Disclose, Hareesh Gundlapalli: Nothing to Disclose, Jawairia Memon: Nothing to Disclose, Gicel Jacklin Aguilar: Nothing to Disclose, Ahmad Abou Yassine: Nothing to Disclose, Christopher Chang: Nothing to Disclose

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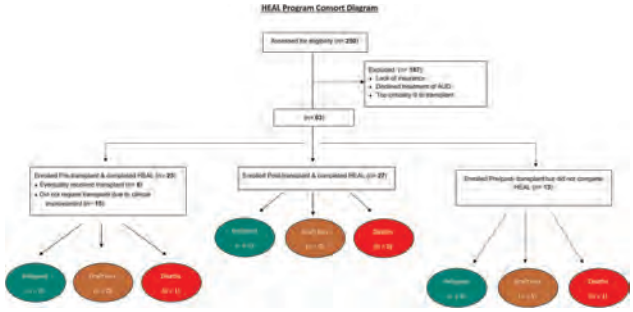
1646 | A NOVEL PROGRAM FOR MANAGEMENT OF ALCOHOL USE DISORDER IN A LIVER TRANSPLANT PROGRAM

Lynda Coraluzzi[1] Kevin Robinson[2] Victor Navarro[3], [1]Jefferson Health Transplant Institute, [2]Department of Medicine Jefferson Einstein, [3]Jefferson Health System

Background: There is no universally agreed upon approach to alcohol use disorder (AUD) for patients with end stage alcohol-related liver disease (ARLD) who require liver transplant (LT), and data indicates relapse rates post-LT of up to 50%.1 Involvement of an addiction specialist (AS) as a part of a multidisciplinary team reduces relapse rates when there is continuity of treatment pre- and post-LT. 2 A major challenge faced by this patient population is the inability to attend in-person outpatient AUD treatment sessions. Consequently, only about 10% of these patients receive adequate AUD treatment. 3. The HEAL (Hope, Empowerment, Acceptance, Life) program was designed to reduce relapse rates in ARLD patients post-LT. **Methods:** The AS assessed 250 patients from a single LT center for eligibility between April 2023 and October 2024. 187 were excluded due to lack of insurance or social support, or poor insight into their AUD and refusal of AUD treatment. 63 eligible patients, both pre- and post-LT, were invited to enroll in the HEAL program, which consisted of 12 weeks of virtual group and individual counseling sessions totaling 3.5 hours weekly. The curriculum was based on cognitive behavioral therapy (CBT) and psychoeducation, with the aim of increasing insight, educating on AUD, and motivating change. Monitoring for relapse was performed via self-reporting and monthly phosphatidyl ethanol (PEth) testing. Post-LT graft loss and patient deaths were recorded. **Results:** Of the 63 patients enrolled, 50 (79%) completed the HEAL program. 23 patients enrolled pre-LT and 27 enrolled post-LT. Among the 23 who enrolled pre-LT, 8 underwent LT and 15 did not require LT due to clinical improvement. One patient expired among the LT recipients who enrolled pre-LT, but there were no instances of graft loss in this group. Among the 27 who enrolled post-LT, 3 relapsed. This represents 6% relapse, 0% graft loss, and 2% death rate among all participants who enrolled both pre-LT and post-LT and completed HEAL. Among the 13 who did not complete HEAL, 6 relapsed-one of whom eventually suffered graft loss and subsequently expired. This represents 46% relapse, 7% graft loss, and 8% death rate among non-completers. **Conclusion:** This study demonstrates the benefit of LT centers investing in programs such as HEAL for patients with AUD. Results showed a favorable outcome among participants who completed the HEAL program, evidenced by a lower rate of recurrence of alcohol use and graft loss compared to participants who did not complete the program.



Disclosures: Lynda Coraluzzi: Nothing to Disclose, Kevin Robinson: Nothing to Disclose, Victor Navarro: Nothing to Disclose

1647 | CARDIOVASCULAR MORTALITY IN ALCOHOL-RELATED LIVER DISEASE: NATIONAL TRENDS ANALYSIS

Pojsakorn Danpanichkul[1] Donghee Kim[2] Thanida Auttapracha[3] Luis Antonio Diaz[4] Juan Pablo Arab[5] Karn Wijarnpreecha[6] Amit Singal[7] Ju Dong Yang[8] Suthat Liangpunsakul[9], [1]Texas Tech University Health Sciences Center, [2]Stanford University, [3]Chiang Mai University, [4]UCSD, [5]VCU, [6]University of Arizona, [7]UTSW, [8]CSHS, [9]Indiana University

Background: People with alcohol-associated liver disease (ALD) are at heightened risk for cardiovascular disease (CVD)-related deaths, yet comprehensive data on this association remain scarce. This study aimed to evaluate national trends in CVD-related mortality among U.S. adults with ALD. **Methods:** We utilized mortality data from the US Census and the National Center for Health Statistics mortality records database spanning 1999 to 2020 to investigate CVD-related deaths in adults diagnosed with ALD. Age-adjusted mortality rates (AAMRs) per 100,000 population and annual percent change (APC) were calculated to assess temporal trends. **Results:** In 2020, a total of 1,840 CVD-related deaths were recorded among individuals with ALD in the United States—marking a 240% rise compared to 1999. While CVD mortality declined in the general population (APC: -2.20%, 95% CI: -2.73 to -1.73%), it significantly increased in the ALD cohort (APC: 4.19%, 95% CI: 0.65 to 7.85%). Although males exhibited higher AAMRs than females, the rate of increase was steeper among females (APC: 6.57%, 95% CI: 4.98 to 8.18%) than males (APC: 0.74%, 95% CI: 0.70 to 0.78%). American Indian and Alaska Native populations bore the highest AAMRs across racial/ethnic groups. The predominant causes of CVD-related deaths among ALD patients were ischemic heart disease (38%), hypertensive disorders (19%), and cerebrovascular conditions (15%). **Conclusion:**

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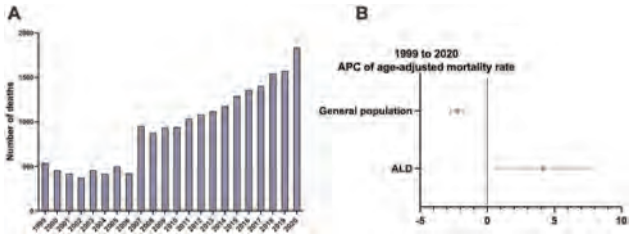
Contrary to the downward trend in cardiovascular mortality within the general U.S. population, individuals with ALD are experiencing a significant rise in CVD-related deaths—particularly women. These findings underscore the urgent need for sex- and population-specific strategies to mitigate cardiovascular risk in this at-risk group.



Disclosures: Pojsakorn Danpanichkul: Nothing to Disclose, Donghee Kim: Nothing to Disclose, Thanida Auttapracha: Nothing to Disclose, Luis Antonio Diaz: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Ju Dong Yang: Exact Sciences: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Exelixis: Consultant, Fujifilm Medical Sciences: Consultant, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant

1648 | INTEGRATIVE TRANSCRIPTOME META-ANALYSIS IDENTIFIES UPSTREAM REGULATORY TARGETS IN ALCOHOLIC HEPATITIS ACROSS LIVER AND BLOOD

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Background: Alcoholic liver disease is recognized as a complex condition caused by alcohol abuse, encompassing a wide range of liver disorders. Severe alcoholic hepatitis (SAH) is a major disease that causes liver damage and inflammation, highlighting the need for effective treatment development. Therefore, to identify therapeutic targets and validate selected genes through meta-analysis, genes that play a critical role in the onset and progression of SAH were selected, and their therapeutic potential was evaluated in an SAH animal model. **Methods:** Using bioinformatics data, we collected gene expression information related to SAH and analyzed genetic data and biological pathways from multiple databases. Changes in gene expression, selected through meta-analysis, were confirmed in liver tissues of SAH animal models using molecular biological techniques, including qPCR and western blot. **Results:** Meta-analysis results showed that specific genes cause significant changes in SAH and are promising candidates as therapeutic targets. First, it was confirmed that the expression of TNF-α and iNOS, genes related to inflammation, increased in the liver tissue of the animal model, creating an animal model that reflects SAH well. In addition, among the 10 genes that showed an increase in the AH genes selected by the meta-analysis, TGF-b1, LYN, TLR2, HDAC9, MAPK3, and AFP showed a significant increase in expression, and among the 18 genes that showed a decrease, GSTP1, SREBF2, CBS, PCBP2, PPARA, AGT, MAPK8, MET, LPIN1, DNAJB1, NR3C1, and LIPC showed a significant decrease in expression. **Conclusion:** These results not only provide important basic data for the development of diagnostic and therapeutic strategies for SAH, but also show the possibility of suggesting new therapeutic approaches in future studies. This study provides an important step toward discovering new targets for SAH treatment and demonstrates the usefulness of bioinformatic analysis.

Disclosures: Seul Ki Han: Nothing to Disclose, Moon Young Kim: Nothing to Disclose, Soon Koo Baik: Nothing to Disclose

1650 | HYALURONAN 35 PREVENTS ENDOTOXIN MEDIATED DYSREGULATED SKELETAL MUSCLE PROTEOSTASIS IN ALCOHOL RELATED LIVER DISEASE

Nicole Welch[1] Annette Bellar[1] Pugazhendhi Kannan[1] Elif Ertugral[2] Amy Attaway[1] Saurabh Mishra[1] Seshu Pothabathula[1] Carol de la Motte[1] Laura Nagy[3] Chandrasekhar Kothapalli[2] Srinivasan Dasarathy[1],
[1]Cleveland Clinic, [2]Cleveland State University, [3]Cleveland Clinic Foundation

Background: Despite pre-clinical and human data in alcohol related liver disease (ALD) that a number of signaling and functional perturbations contribute to sarcopenia, there are no effective treatments. Hyaluronans are glycosaminoglycan polymers with size specific homeostatic and signal regulatory functions. Hyaluronans with ~35 Kd molecular weight (HA35) are beneficial in hepatic and macrophage functions in ALD and modulate responses to TLR4, a lipopolysaccharide (LPS) receptor and CD44, an HA receptor. Whether low grade endotoxemis contributes to and if HA35 reverses sarcopenia of ALD were studied. **Methods:** Based on concentration and time course of ethanol/LPS treatment that replicate the phenotype,molecular, metabolic, and functional responses of skeletal muscle in human ALD,

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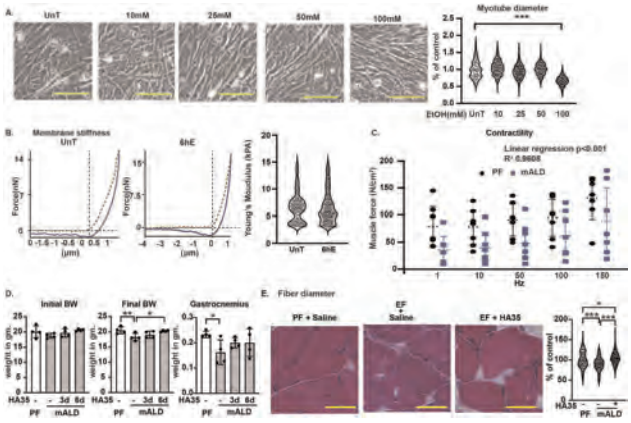
responses to ethanol, LPS, and HA35 were studied in differentiated murine C2C12 and human induced pluripotent stem cell derived myotubes trearted with 100mM ethanol for 6h. In vivo studies were done in mouse models of ALD (mALD). Signaling responses and measures of protein homeostasis (proteostasis) were quantified by immunoblots, and mitochondrial oxidative function determined by high-sensitivity respirofluorometry. Membrane elasticity with ethanol treatment in myotubes was determined by atomic force microscopy (AFM), and contractile responses in skeletal muscle from mALD were determined. Integrated multiomics of untargeted data and image analyses were also performed. **Results:** Ethanol caused a sarcopenic phenotype in myotubes at 100mM for 6h and in mALD (lower myotube/myofiber diameter, muscle mass, protein synthesis, impaired mTORC1 signaling, and higher autophagy markers) without altering membrane elasticity and no membrane tethering on AFM at the dose/duration of ethanol treatment (Fig 1, A-C). Expression of LPS (TLR2, TLR4) and HA (CD44) receptors were upregulated by ethanol. In myotubes and muscle tissue from mALD, LPS caused a sarcopenic phenotype with impaired proteostasis signaling. Sarcopenic molecular/phenotype responses were observed at lower concentrations of ethanol/LPS treatment in myotubes showing increased LPS sensitivity in ALD. Treatment of myotubes and mALD with HA35 reversed proteostasis and prevented ethanol/LPS-induced lower protein synthesis, increased phosphorylation of p65-NFkB and myostatin expression, and impaired mTORC1 signaling (Fig 1, D-E). Consistently, HA35 treatment reversed the sarcopenic phenotype/signaling and functional perturbation in mALD without changes in ethanol-induced perturbations in muscle HA concentrations. **Conclusion:** Sarcopenic phenotype with signaling/molecular/functionalperturbation in ALD are worsened by lower concentrations of LPS and reversed by HA35. Safety of HA35 in humans (PMID 31121841) and sarcopenia reverasl in preclinical models provide the rationale for clinical translation (clinicaltrials.gov. NCT05018481).



Disclosures: Nicole Welch: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Elif Ertugral: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Saurabh Mishra: Nothing to Disclose, Seshu Pothabathula: Nothing to Disclose, Carol de la Motte: Nothing to Disclose, Laura Nagy: Nothing to Disclose, Chandrasekhar Kothapalli: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

1651 | OUTCOMES OF EARLY AND LATE ALCOHOL RELAPSE IN LIVER TRANSPLANT RECIPIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE

Garren Montgomery[1] Ayato Obana[1] Antonio Alvarez Castaneda[1] Benjamin Davies[2] Sylvester Black[1] Khalid Mumtaz[1], [1]Ohio State University Medical Center, [2]Ohio State University School of Medicine

Background: Alcohol-associated liver disease (ALD) is among the most common indications for liver transplantation (LT) in the United States. Candidacy for LT is influenced by the risk of alcohol relapse (AR) in LT recipients (LTRs). Early AR among LTRs for alcoholic hepatitis (AH) has been associated with poorer survival compared to late AR. However, the impact of early AR on LTR outcomes in the overall ALD transplant population is less clear. Therefore, we sought to study the impact of early and late AR on the outcomes of overall survival, graft survival, and risk of rejection among LTRs for ALD. **Methods:** We performed a retrospective study of LTRs for ALD at a single large LT center between 1/1/2016 and 11/30/2023. LTRs with AR were divided into early relapse (ER, defined as alcohol relapse within the first 12 months after LT) and late relapse (LR, alcohol relapse >12 months after LT). Cumulative risk of T cell-mediated rejection (TCMR), graft survival, and the overall survival were compared between ER, LR, and no relapse using the log-rank test. Cox proportional hazards regression analysis adjusting for age, male gender, MELD score, and type of deceased donor (donation after brain death; DBD vs donation after cardiac death; DCD) was also performed. **Results:** Out of 383 LTRs, 80 experienced AR - twenty-eight (35%) LTRs had ER while 52 (65%) LTRs had LR. The cumulative risk of TCMR was significantly higher among LTRs with ER compared to no relapse (log-rank $p=0.01$). On multivariate analysis (Table 1), using LTRs with no relapse as the reference, those with ER had a higher risk of TCMR (HR: 2.11; 95% CI: 1.03-4.32; $p=0.04$) adjusting for age (HR: 0.96; $p<0.005$), male sex (HR: 0.60; $p=0.04$), MELD score ($p=0.3$), and DCD graft type ($p=0.65$). LR was not associated with TCMR (HR: 1.19; 95% CI: 0.65-2.18; $p=0.58$).

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Neither ER nor LR were associated with an increased risk of death (ER, HR: 1.47, p = 0.47; LR, HR: 0.53, p = 0.15) or graft loss (ER, HR: 1.37, p = 0.55; LR, HR: 0.72, p = 0.39). Potential limitations to statistical power in this study included the small sample size of the ER group. **Conclusion:** Early relapse, but not late relapse, is an independent risk factor for TCMR in LTRs for ALD. However, neither ER nor LR was associated with a higher risk of graft loss or death. These observations suggest that early intervention for alcohol use disorder among LTRs with ALD is an important component of preventing TCMR in these patients.

Table 1: Multivariable Cox Regression Analyses to Determine Association of Early and Late Relapse with Rejection, Overall Survival, and Graft Survival

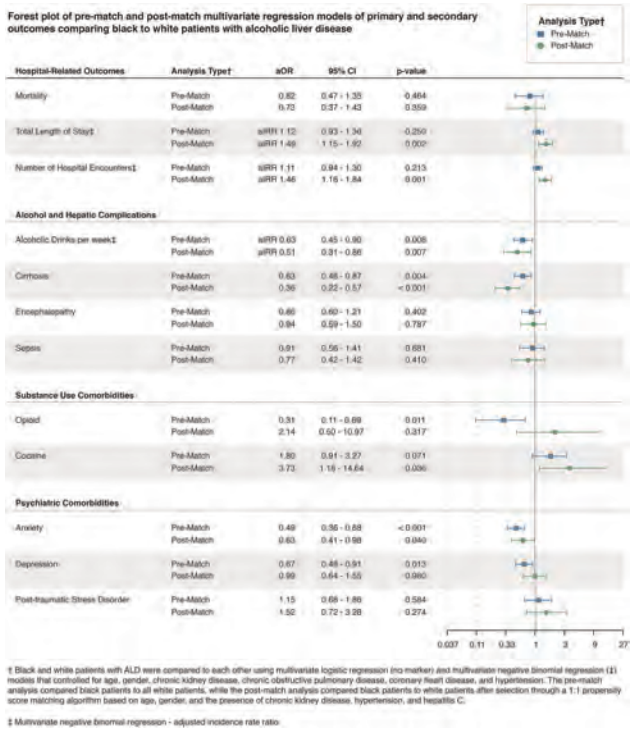
	Rejection		Overall Survival		Graft Survival	
Variable	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Early Relapse	2.11 (1.03-4.32)	0.04	1.47 (0.52-4.15	0.47	1.37 (0.48-3.85)	0.55
Late Relapse	1.19 (0.65-2.18)	0.58	0.53 (0.22-1.25)	0.15	0.72 (0.34-1.52)	0.39
No Relapse	Ref		Ref		Ref	
Age	0.96 (0.94-0.99)	<0.005	1.02 (0.99-1.05)	0.15	1.03 (1.0-1.06)	0.06
Male Sex	0.6 (0.37-0.97)	0.04	0.98 (0.5-1.84)	0.90	0.99 (0.53-1.85)	0.98
MELD Score at LT	0.99 (0.96-1.01)	0.30	0.99 (0.96-1.03)	0.69	1.0 (0.97-1.03)	0.93
DCD graft type (vs DBD)	1.13 (0.67-1.89)	0.65	1.05 (0.56-1.96)	0.87	0.91 (0.49-1.69)	0.77

Disclosures: Garren Montgomery: Nothing to Disclose, Ayato Obana: Nothing to Disclose, Antonio Alvarez Castaneda: Nothing to Disclose, Benjamin Davies: Nothing to Disclose, Sylvester Black: Nothing to Disclose, Khalid Mumtaz: Nothing to Disclose

1652 | BLACK PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE IS ASSOCIATED GREATER INCIDENCE OF COMPLICATIONS AND HOSPITAL-RELATED OUTCOMES

Ki Jung Lee[1], [1]*Tufts Medical Center*

Background: Alcohol-associated liver disease (ALD) is one of the leading causes of advanced liver disease in the United States and the world. Given the scarcity of race-specific data, this study examines the effects of race, specifically Black patients, on hospital outcomes and associated psychiatric conditions with ALD to assess for the racial disparities. **Methods:** Patients hospitalized with ALD from 2020 to 2024 at a tertiary care center were retrospectively reviewed. The cohort was stratified into White (reference group) and Black (exposure group). Primary endpoints included lengths of stay (LOS), number of readmissions, psychiatric comorbidities, and hepatic complications. Multivariate regression models were used for categorical outcomes, while negative binomial regression models assessed discrete outcomes. Exposure and reference cohorts were 1:1 propensity-score matched for age, race, gender, as well as the presence of chronic kidney disease, hypertension, hepatitis C. **Results:** The analysis included 3,179 patients: 239 Black (8.20%) and 2,674 White (91.80%). Black patients were younger and had lower BMI (p = 0.002). They consumed less alcohol per week than White patients (aOR 0.63, 95% CI 0.45-0.90, p = 0.008). Black population experienced longer average LOS compared to White population (aOR 1.17, 95%CI 1.00-1.37, p = 0. In the matched analysis, Black patients exhibited a significantly longer total LOS (aOR 1.49, 95% CI 1.15-1.92, p = 0.002) and more frequent hospital encounters (aOR 1.46, 95% CI 1.16-1.84, p = 0.001). Compared to White patients, Black patients had notably fewer drinks per week (aOR 0.51, 95% CI 0.31-0.86, p = 0.007) and a lower incidence of cirrhosis (aOR 0.36, 95% CI 0.22-0.67, p < 0.001). Regarding psychiatric comorbidities, Black patients had lower anxiety rates (aOR 0.63, 95% CI 0.41-0.98, p = 0.04) but higher schizophrenia rates (aOR 4.79, 95% CI 1.20-31.90, p = 0.05). Cocaine use (aOR 3.73, 95% CI 1.18-14.64, p = 0.04) and multiple substance use disorders (aOR 2.61, 95% CI 1.59-4.37, p < 0.001) were more prevalent among Black patients **Conclusion:** Black patients with ALD encountered longer hospital LOS, more frequent hospitalizations, and higher rates of sepsis, despite lower alcohol consumption and fewer substance use comorbidities. However, they had higher rates of psychiatric comorbidities such as schizophrenia and cocaine use. These disparities highlight the need for multidisciplinary, tailored care approaches to address the unique challenges faced by this vulnerable population.



Disclosures: Ki Jung Lee: Nothing to Disclose

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1653 | ROLE OF SHEAR WAVE VISCOSITY (SWV) AS AN IMAGING BIOMARKER FOR EVALUATION OF ALCOHOLIC HEPATITIS NEW SUBMISSION

Carmen Fierbinteanu Braticevici[1] Vlad-Teodor Enciu[2] Priscila Madalina Ologeanu[2] Alexandru Constantin Moldoveanu[2], [1]University Hospital Bucharest, "Carol Davila" University of Medicine and Pharmacy, [2]University Hospital Bucharest, "Carol Davila" University of Medicine and Pharmacy

Background: Acute hepatitis is an acute and potentially life-threatening liver disease associated with high morbidity and mortality. One of the more common types of acute hepatitis is alcoholic hepatitis, which is of varying degrees of severity. Accurate assessment of the severity of the inflammation can help guide treatment choice in these patients. Shear Wave Viscosity (SWV), a novel ultrasound technique, quantifies liver tissue viscosity and may serve as an imaging biomarker for inflammation. Objective: To investigate the accuracy of liver viscosity as measured by SWV in predicting the severity of liver inflammation in alcoholic hepatitis. **Methods:** We conducted a prospective study including patients with alcoholic hepatitis. All patients underwent liver ultrasound using Shear Touch Viscosity (Resona A20 – Mindray). The machine has a module, a multi-parametric combined analysis tool, that enables real-time same-screen of attenuation, viscosity and stiffness. Laboratory evaluation included markers that are typically increased in alcoholic hepatitis: leukocyte count, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), transaminases, total bilirubin, prothrombin time (PT) and international normalized ratio (INR), gamma glutamyl transpeptidase (GGT), alkaline phosphatase. The Maddrey Discriminant Function (DF) was calculated using the standard formula. The viscosity results were compared to the laboratory results, and analyzed using python. **Results:** Thirty-nine patients were included in the study. The viscosity measurements in our patients were included between 1.6 - 5 Pa.s.There was a significant correlation between liver viscosity and biological markers in univariate analysis (CRP – $p < 0.001$; ESR $p = 0.021$; AST $p < 0.001$; PT $p < 0.001$; INR $p < 0.001$; DF $p < 0.001$). Bivariate analysis shows strong positive correlations between liver viscosity and laboratory results: CRP 0.66; AST 0.80; PT 0.70; INR 0.69; DF 0.68. A ROC analysis was performed for the prediction of severe disease (DF > 32), with an AUROC of 0.95 [95% CI 0.87 – 1.00]. Using a cutoff value of 2.6, we obtain a sensitivity of 100% and a specificity of 90%. **Conclusion:** Liver viscosity correlates significantly with hepatic inflammatory activity and clinical severity in alcoholic hepatitis and may be an accurate marker of liver inflammation. Further studies are required to asses accuracy in other acute liver pathologies.

Disclosures: Carmen Fierbinteanu Braticevici: Nothing to Disclose, Vlad-Teodor Enciu: Nothing to Disclose, Priscila Madalina Ologeanu: Nothing to Disclose, Alexandru Constantin Moldoveanu: Nothing to Disclose

1654 | GLUTAMATE RELEASE FROM VGLUT3 GRANULES EXACERBATES ASH BY ACTIVATING MGLUR5 ON KUPFFER CELLS VIA METABOLIC SYNAPSE

Kwang Woo LEE[1] Keungmo Yang[2] Kyurae KIM[1] Sung Eun Choi[3] Min Jeong Kim[1] Katherine Po Sin Chung[3] Eunmi Lee[1] Jihyo Byun[1] Jaewoo Oh[1] Seungryong Choo[1] WON-IL JEONG[1], [1]KAIST, [2]College of Medicine, The Catholic University of Korea, [3]Korea Advanced Institute of Science and Technology

Background: Glutamate, an essential component in amino acid metabolism, has been relatively unexplored in the development of alcohol-associated steatohepatitis (ASH). This study investigates the underlying mechanism by which hepatic glutamate induces reactive oxygen species (ROS) production in Kupffer cells (KCs) and leads liver injury through bidirectional interactions via pseudosynapse formation following alcohol consumption. **Methods:** ASH was induced in mice via 2-week ethanol feeding plus a binge. Hepatic immune cells were analyzed using flow cytometry analysis and immunostaining. Public and bulk RNA-seq data were used to assess glutamate synthesis and transporter expression. Glutamate-related proteins and vesicle formation were visualized via immunostaining and tissue expansion. Intravital imaging tracked calcium changes, and electron microscopy revealed hepatocyte–KC proximity. For in vivo and in vitro experiments, KC-specific metabotropic glutamate receptor 5 (mGluR5) or NADPH oxidase 2 (NOX2)-deficient mice and isolated primary Kupffer cells were used. **Results:** 2-week alcohol consumption induces the formation of hepatic glutamate vesicles, driven by the aryl hydrocarbon receptor-mediated expression of vesicular glutamate transporter 3 (VGLUT3). Simultaneously, alcohol-induced changes, including perivenous hepatocyte ballooning, microvilli loss, and mitochondrial Ca^{2+} accumulation, bring KCs into close contact with ballooned hepatocytes. Additional binge drinking alters intracellular Ca^{2+} levels, triggering the exocytosis of glutamate from VGLUT3 vesicles. This, in turn, activates NOX2 through mGluR5 in KCs, leading to ROS production and the promotion of ASH. Accordingly, genetic or pharmacological interference of mGluR5 and NOX2 in KCs attenuates ASH. In patients, plasma glutamate and VGLUT3 vesicles correlate with ASH development. **Conclusion:** Our findings suggest that hepatocytes and KCs

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form a pseudosynapse, allowing glutamatergic signaling to potentially exacerbate the development of ASH.
Disclosures: Kwang Woo LEE: Nothing to Disclose, Keungmo Yang: Nothing to Disclose, Kyurae KIM: Nothing to Disclose, Sung Eun Choi: Nothing to Disclose, Min Jeong Kim: Nothing to Disclose, Katherine Po Sin Chung: Nothing to Disclose, Eunmi Lee: Nothing to Disclose, Jihyo Byun: Nothing to Disclose, Jaewoo Oh: Nothing to Disclose, Seungryong Choo: Nothing to Disclose, WON-IL JEONG: Nothing to Disclose

1655 | SINGLE-CENTER COMPARATIVE ANALYSIS OF HOSPITAL ADMISSIONS FOR ALCOHOL-RELATED LIVER DISEASE AND ITS OUTCOMES: PRE- AND POST-COVID-19 PANDEMIC

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Background: Alcohol-Related Liver Disease (ALD) represents a significant public health concern worldwide, contributing to substantial morbidity, mortality, and healthcare costs. ALD is uniquely characterized by its association with modifiable risk factors, including alcohol consumption patterns, nutrition, and socioeconomic determinants of health. While studies from other regions have shed light on the COVID-19 pandemic's short-term impact on ALD, knowledge gaps persist in understanding its long-term effects on disease progression and healthcare utilization patterns. This retrospective study aims to analyze hospitalizations for ALD at The Ottawa Hospital (TOH) over a five-year period spanning the Pre-COVID, COVID, and Post-COVID eras. **Methods:** This single-center retrospective study examined all hospital admissions for ALD at TOH from March 1, 2018, to March 31, 2023. The inclusion criteria were as follows: admission to TOH during the specified study period, primary or contributing diagnosis of ALD, including alcoholic hepatitis, alcohol-related cirrhosis, or acute liver failure due to alcohol use disorder. The primary outcomes of interest were to compare hospital admissions, disease severity (MELD, Maddrey, and Child-Pugh scores), and mortality (in-hospital mortality rates and causes of death) across the three eras. **Results:** The total number of admissions was highest during the COVID era (429), followed closely by the Pre-COVID era (341), and was lowest in the Post-COVID era (217), ($p = 0.264$). Mean Maddrey scores were not statistically different between the 3 eras ($p = 0.695$). The highest mean MELD score was observed during the COVID era (34.5, $SD = 4.43$), without statistically difference between the eras ($p = 0.172$). The mortality rate was highest in the Pre-COVID era (28.7%), followed by the COVID era (25.4%), and the Post-COVID era (19.8%), ($p = 0.061$). The main cause of death in all eras was acute liver failure (80/250 deaths). COVID-19 was the main cause of death in only 2 patients. **Conclusion:** This study demonstrates the impact of the COVID-19 pandemic on ALD care and its outcomes, with implications for public health and healthcare systems. While there was not statistically significant difference in hospital admissions for ALD between the 3 eras, a modest increase in hospital utilization during the COVID era was seen. The high mortality seen among this population of severe liver disease patients may reflect the delay in seeking medical attention in all eras. These results highlight the need for proactive strategies to support ALD patients, continuously ensuring equitable access to care to reduce mortality.
Disclosures: Vivek Govardhanam: Nothing to Disclose, Valerie Lavigne: Nothing to Disclose, Kyle Tong: Nothing to Disclose, Mayan Alqahtani: Nothing to Disclose, Laila Shirzad: Nothing to Disclose, Fernanda Onofrio: Nothing to Disclose

1656 | LOW BLOOD UREA NITROGEN DURING ALCOHOL-ASSOCIATED ADMISSION PREDICTS CIRRHOSIS IN PATIENTS WITHOUT PRE-EXISTING LIVER DISEASE: RESULTS: FROM A LARGE NATIONWIDE VETERANS AFFAIRS DATABASE

Rahul Karna[1] Anders Westanmo[2] Amy Gravely[2] Khalid Ishani[3] Natalie Wilson[4] Mohammad Bilal[5] Tessa Steel[6] Robert Wong[7] Thad Abrams[8] Prowpanga Udompap[9], [1]Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, Minneapolis, MN, [2]Research Service, Minneapolis Veteran Affairs Medical Center, Minneapolis, MN, [3]University of Minnesota Medical School, Minneapolis, MN, [4]Department of Medicine, University of Minnesota, Minneapolis, MN, [5]Division of Gastroenterology & Hepatology, University of Colorado, Aurora, CO, [6]Division of Pulmonary, Critical Care and Sleep Medicine, University of Washington, Seattle, WA, [7]VA Palo Alto Healthcare System, [8]Department of Internal Medicine, University of Iowa, Iowa City, IA, [9]Minneapolis VA Medical Center, Minneapolis, MN

Background: Low Blood urea nitrogen (BUN) levels are common in individuals with alcohol use disorder (AUD) due to inadequate protein intake and impaired nutrient absorption which leads to reduced synthesis of urea in the liver. Protein metabolism may be

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impaired further among those with chronic liver disease due to the liver's reduced ability to synthesize urea which can result in low BUN. We hypothesize that the lower BUN in patients with AUD without pre-existing liver disease is associated with more severe AUD and likely alcohol-related liver disease. We therefore aim to determine whether low BUN during a hospitalization for AUD in patients without pre-existing liver disease is associated with an increased future risk of developing cirrhosis. **Methods:** This is a retrospective cohort study of adults hospitalized for AUD between 10/1/2015 to 12/31/2019. Data was obtained from the Veterans Health Administration Corporate Data Warehouse. The normal range for BUN at Veterans Affairs labs is 8–26 mg/dL for male and 6-21 mg/dL for females. Index cohort was classified into 3 groups, adjusted by sex based on the lowest BUN during hospitalization: Very Low (BUN <5), Low (BUN 5-8) and Not Low (BUN >8). Cirrhosis development was evaluated at 1, 3, and 5 years after hospital discharge, using ICD-9/10 codes. Patients with history of cirrhosis prior to the hospitalization, new diagnosis of cirrhosis within 6 months of discharge or any pre-existing liver diseases were excluded. A multivariate regression analysis was performed to explore the association of BUN and cirrhosis, controlling for the following variables: age, sex, race, ethnicity, BMI, eGFR, and Charlson comorbidity index. **Results:** Among a total of 15,093 patients with AUD and no pre-existing liver diseases included in the analysis, 22.16% had BUN $<$ 5 mg/dL (Very Low BUN), 29.37% had BUN 5-8 mg/dl (Low BUN) and 48.45% had BUN >8 mg/dL (Not Low). Interestingly, 7.1% developed cirrhosis in Very Low BUN cohort while, 5.6% had cirrhosis in Low BUN and 3.8% in Not Low BUN cohort at 5 years (Table 1). Multivariate regression analysis showed that Low BUN cohort (OR: 1.55, 95% CI:1.28-1.87) and Very Low BUN cohort (OR: 2.14; 95% CI: 1.77-2.58) had significantly high odds of developing cirrhosis than Not Low BUN cohort. Male sex (OR:1.5; 95% CI:1.03-2.26), hypertension (OR:1.5; 95% CI:1.22-1.84) and high FIB-4 score ($>=$ 2.67) (OR: 95% 1.25; 95% CI:1.04-1.49) were also associated with higher risk of cirrhosis development. The sensitivity analysis excluding the patients with baseline high FIB-4 score was also completed and showed that a strong association between very low BUN, low BUN and cirrhosis development remained unchanged. **Conclusion:** Our large database study suggests that Low BUN during the alcohol-related admission is associated with cirrhosis development in patients with AUD. The study could pave way for prognostication and risk stratification of patients with AUD with higher risk of cirrhosis development.

Table 1: Demographic data and cirrhosis development in patients with AUD stratified by lowest BUN during hospitalization

Variable	Total	Very Low BUN (BUN < 5 mg/dl)	Low BUN (BUN 5-8 mg/dl)	Not Low BUN (BUN >8 mg/dl)	P-Value
N	15093	3346	4434	7313	
Gender, N(%)					
Female	872 (5.78)	294 (8.79)	247 (5.57)	331 (4.53)	<0.0001
Male	14,220 (94.22)	3,052 (91.21)	4,186 (94.43)	6,982 (95.47)	
Age, in years					
Mean (S.D.)	52.39 (13.39)	51.23 (12.38)	51.21 (12.98)	53.61 (13.99)	
FIB-4 at baseline (%)					
Low (<1.3)	9,625 (68.24)	2,159 (68.8)	2,817 (67.44)	4,649 (68.47)	0.3179 *
Indeterminate (1.3-2.67)	1,415 (10.03)	291 (9.27)	449 (10.75)	675 (9.94)	
High (>2.67)	3,065 (21.73)	688 (21.92)	911 (21.81)	1,466 (21.59)	
COPD, N(%)	2,309 (15.31)	500 (15.01)	636 (14.35)	1,171 (16.03)	0.0447
Diabetes, N(%)	1,590 (10.53)	267 (7.98)	422 (9.52)	901 (12.32)	<0.0001
Hypertension, N(%)	11,007 (72.95)	2,382 (71.13)	3,173 (71.56)	5,454 (74.58)	0.0001
Cardiovascular Disease, N(%)	2,900 (19.21)	561 (16.77)	791 (17.84)	1,548 (21.17)	<0.0001
Smoking, N(%)					
Non-Smoker	2,419 (16.68)	567 (16.95)	793 (17.88)	1,059 (19.95)	<0.0001
Smoker	10,942 (72.8)	2,561 (76.54)	3,256 (73.43)	5,125 (70.09)	
Former Smoker	1,332 (8.83)	218 (6.52)	385 (8.68)	729 (9.97)	
Location, N(%)					
Urban	8,940 (67)	2,251 (68.36)	2,950 (67.74)	4,739 (65.94)	0.0239
Rural	4,896 (33)	1,042 (31.64)	1,405 (32.26)	2,448 (34.06)	
Outcomes					
Cirrhosis at 1 year, N(%)	118 (0.78)	40 (1.2)	48 (1.04)	32 (0.44)	<0.0001
Cirrhosis at 3 years, N(%)	459 (3.31)	150 (4.48)	176 (3.97)	173 (2.37)	<0.0001
Cirrhosis at 5 years, N(%)	763 (5.06)	238 (7.11)	247 (5.57)	278 (3.8)	<0.0001

Disclosures: Rahul Karna: Nothing to Disclose, Anders Westanmo: Nothing to Disclose, Amy Gravely: Nothing to Disclose, Khalid Ishani: Nothing to Disclose, Natalie Wilson: Nothing to Disclose, Mohammad Bilal: Boston Scientific: Consultant, Steris Endsocopy: Consultant, Cook endoscopy: Consultant, Tessa Steel: Nothing to Disclose, Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Thad Abrams: Nothing to Disclose, Prowpanga Udompap: Nothing to Disclose

◆ 2001 | VALIDATION AND PERFORMANCE OF A LIVER PDFF MEASUREMENT METHOD USING ARTIFICIAL INTELLIGENCE

Wenjie Pang[1], [1]*Resonance Health*

Background: Fatty liver related diseases can be closely associated to metabolic syndrome and increased risk of cardiovascular diseases in both adults and children. Magnetic Resonance Imaging (MRI) methods for hepatic steatosis measurement become the new gold standard with more benefits than liver biopsy and other non-invasive methods. The aim of this study is to validate and evaluate the performances of a Convolutional Neural Network (CNN) trained MRI-data processing method automatically quantifying multiple metrics related to hepatic steatosis in near real-time. **Methods:** 300 fully quarantined datasets previously processed within 5-year period by an FDA-cleared HepaFatScan manual method with the data scanned by different MRI makes, models and field strengths (1.5T and 3T) were recruited as a reference standard for validation of an FDA-cleared CNN (HepaFatSmart) method to simultaneously measure proton density fat fraction (PDFF), volumetric liver fat fraction (VLFF) and steatosis grade. Among them, 281 datasets passed

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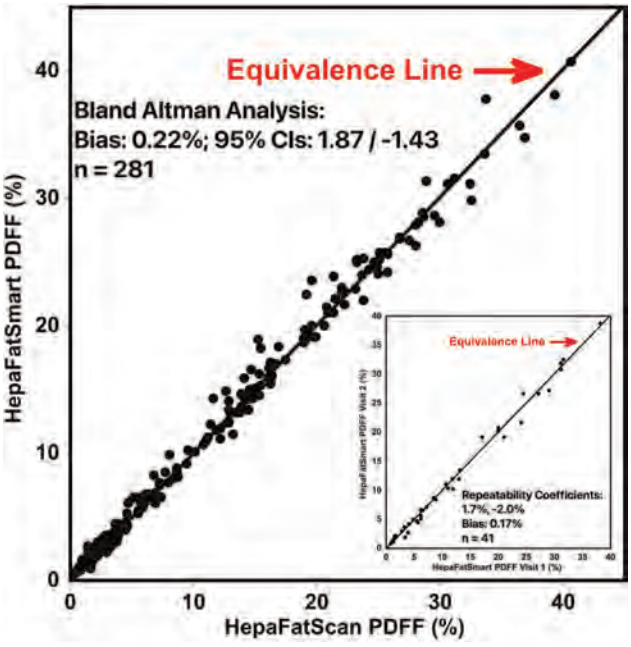
both the input quality control algorithms defined by both methods were successfully analysed. Additional 41 subjects with repeated scans were analysed by the AI method for evaluation of repeatability and comparison with manual HepaFatScan analysis. **Results:** CNN PDFF (HepaFatSmart) returned almost the same analysis results as the reference standard HepaFatScan. A small bias of 0.22% found in the validation dataset is very small and unlikely has any clinical relevance although it is statistically significant due to small standard deviation, indicating reliable and accurate measurement of liver fat by the AI device compared with the reference standard of HepaFatScan. In addition, HepaFatSmart repeatability coefficients showed a narrow range of -2.0% – 1.7% with a small bias of 0.17%, indicated robustness regarding not only reliable and consistent analysis outcomes but also slightly better repeatability than the manual HepaFatScan, which does not suggest yet the AI method is better than the manual method rather than due to historical reason when small ROIs were used in the past for the reference standard (Figure). An anomaly assessment mechanism can also automatically detect excessive liver iron level, evaluate the impact and determine when to stop as a safety measure. **Conclusion:** The accuracy and precision of the CNN PDFF method are comparable with the reference standard and the results are interchangeable. Using the ANN eliminates the need for image analysis or other technical expertise and speeds up reporting to an extent that point-of-care screening could be performed and costs associated with analysis greatly reduced. As an important measure within the quantitative MRI data analytics realm, the result is fully transparent and visible to the user to mitigate any potential residual risks of an AI method.



Disclosures: Wenjie Pang: Resonance Health: Employee

◆ 2002 | COMPARATIVE PERFORMANCE OF THE TWO-STEP CLINICAL CARE PATHWAY FOR DETECTING ADVANCED LIVER FIBROSIS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A PROSPECTIVE MULTICENTER BIOPSY-BASED STUDY

Yuping Chen[1] Bingtian Dong[2] Airong Hu[3] Xiao Liang[4] Yiling Li[5] Wei Gou[6] Qing-Lei Zeng[7] Chuan Liu[1] Minghua Zheng[8] Xiaolong Qi[1], [1]Zhongda Hospital, Southeast University, [2]The First Affiliated Hospital of Anhui Medical University, [3]Ningbo Institute of Liver Diseases, Ningbo No. 2 Hospital, [4]Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, [5]The First Hospital of China Medical University, [6]Qingdao Public Health Clinical Center, [7]The First Affiliated Hospital of Zhengzhou University, [8]The First Affiliated Hospital of Wenzhou Medical University

Background: Current clinical guidelines recommend screening for advanced liver fibrosis (AF) due to metabolic dysfunction-associated steatotic liver disease (MASLD) in patients with type 2 diabetes mellitus (T2DM), using a two-step approach: initial risk stratification with the Fibrosis-4 index (FIB-4), followed by liver stiffness measurement (LSM) via vibration-controlled transient elastography or other second-line noninvasive tests (NITs). This study aimed to evaluate the performance of the two-step clinical care pathway and compare different NIT-based strategies for identifying AF in patients with T2DM. **Methods:** We prospectively enrolled 321 biopsy-proven MASLD patients with T2DM from five hospitals in China between 2017 and 2024. The diagnostic accuracy of various NITs, including LSM, FIB-4, Agile 3+ score, metabolic dysfunction-associated fibrosis-5 (MAF-5) score, LiverRisk score, FibroScan-AST (FAST) score, and NAFLD fibrosis score (NFS), were evaluated using their respective established dual cut-off values. We further evaluated the performance of novel two-step algorithms combining FIB-4 with second-line NITs and explored alternative algorithms replacing FIB-4 with NFS, MAF-5 or LiverRisk score in the first step. **Results:** The median age of participants was 49.0 ± 12.8 years, median body mass index was 27.3 ± 3.9 kg/m^2, and 52.6% were male. The prevalence of AF (≥F3) was 21.8%. For detecting AF, the area under the ROC curve values were: Agile 3+ (0.795 [95% CI: 0.747-0.838]), LSM (0.783 [0.734-0.827]), FIB-4 (0.752 [0.701-0.798]), MAF-5 (0.719 [0.652-0.779]), FAST (0.717 [0.665-0.766]), NFS (0.704

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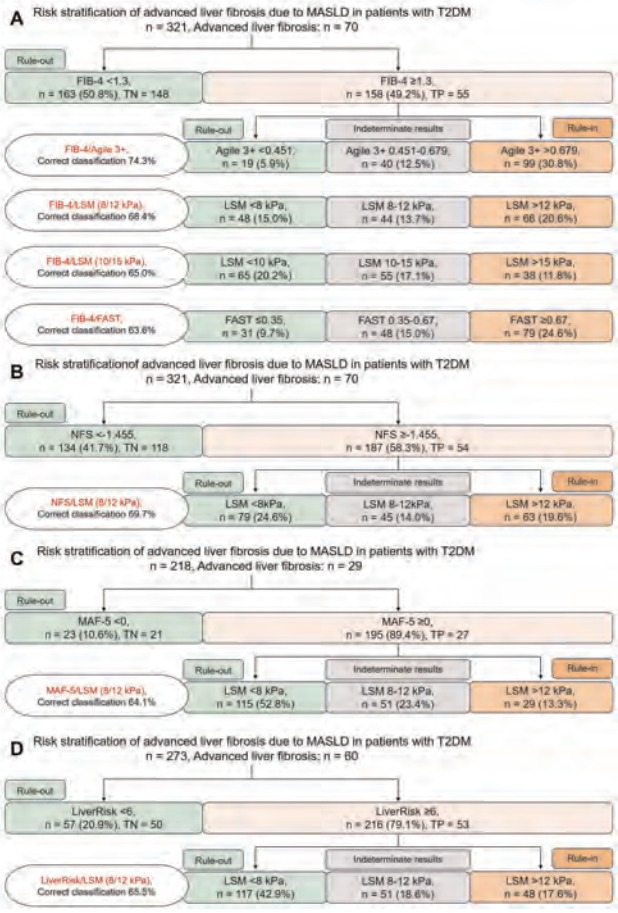
[0.651-0.753]), and LiverRisk (0.669[0.610-0.725]). Using predefined dual thresholds (Agile 3+: 0.451/0.679; LSM: 8/12 kPa), Agile 3+ achieved a higher correct classification rate than LSM (76.6% vs. 72.1%) and a lower indeterminate rate (18.4% vs. 26.2%). Moreover, when used as a second step following FIB-4 ($\geq$1.3 or $\geq$2.0 if age $\geq$65), Agile 3+ achieved the highest correct classification rate (74.3%) and the fewest indeterminate results (12.5%) among all tested combinations (See Figure 1 for more details). **Conclusion:** The two-step algorithm using FIB-4 followed by Agile 3+ outperformed other NIT-based strategies for AF risk stratification in T2DM patients, offering superior diagnostic accuracy and minimizing indeterminate classifications. This supports its clinical utility as an efficient noninvasive care pathway for AF screening in this high-risk population.

Figure 1: Risk stratification of advanced liver fibrosis due to metabolic dysfunction-associated steatotic liver disease in patients with type 2 diabetes mellitus



Disclosures: Yuping Chen: Nothing to Disclose, Bingtian Dong: Nothing to Disclose, Airong Hu: Nothing to Disclose, Xiao Liang: Nothing to Disclose, Yiling Li: Nothing to Disclose, Wei Gou: Nothing to Disclose, Qing-Lei Zeng: Nothing to Disclose, Chuan Liu: Nothing to Disclose, Minghua Zheng: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose

◆ 2003 | CROSS-NATIONAL VALIDATION OF FIBRO-SCOPE FOR LIVER FIBROSIS IN MASLD: INSIGHTS FROM JAPAN AND THE US

yuya seko[1] Georgia Sofia Karachaliou[2] Ayako Suzuki[2] Manal Abdelmalek[3] Kanji Yamaguchi[1] Toshihide Shima[4] Yoshito Itoh[1] Anna Mae Diehl[5] Takeshi Okanoue[6], [1]Kyoto Prefectural University of Medicine, [2]Division of Gastroenterology, Duke University Medical Center, Durham, NC, USA, [3]Mayo Clinic Rochester, [4]Saiseikai Suita Hospital, [5]Duke University, [6]Osaka Saiseikai Suita Hospital

Background: Fibro-Scope is an artificial intelligence-based neural network system generated non-invasive test designed to assess liver fibrosis in patients with metabolic dysfunction associated steatotic liver disease (MASLD) using 11 clinical parameters. In Japanese cohort of patients with MASLD, Fibroscope showed high specificity to diagnose advanced fibrosis among patients who were classified as intermediate risk by FIB-4 index of 1.3–2.67. This study aims to validate and compare the diagnostic performance of FibroScope in a US cohort of patients with biopsy-proven MASLD with Japanese cohorts. **Methods:** 229 U.S. patients and 796 Japanese with biopsy-proven MASLD were evaluated. The diagnostic accuracy of the FIB-4 index and Fibro-Scope was evaluated using the area under the receiver operating characteristic curve (AUROC). Cohort-specific Fibro-Scope cutoff values were adopted based on previous studies. **Results:** The U.S. cohort had significantly higher BMI and platelet counts, and lower levels of ALT, GGT, total cholesterol, and triglycerides compared to the Japanese cohort. Additionally, the Japanese cohort was significantly older than the U.S. cohort. The prevalence of advanced fibrosis (F3–F4) was 26.2% in the U.S. cohort and 18.1% in the Japanese cohort ($p = 0.008$). The AUROCs of the FIB-4 index and Fibro-Scope for detecting advanced fibrosis were 0.784 and 0.854 in the U.S. cohort, and 0.883 and 0.907 in the Japanese cohort, respectively. The prevalence of "intermediate zone" was significantly smaller in Fibro-Scope (4.8%) than FIB-4 index (32.6%). The sensitivity and specificity for F3-4 of Fibro-Scope were 71.7% and 87.6% in the U.S. cohort, and 76.4% and 86.3% in the Japanese cohort. The sensitivity of Fibro-Scope outperformed the FIB-4 index cutoff of $\geq$ 2.67 (advanced hepatic fibrosis) in both cohorts. Among patients aged $\geq$65 years, the sensitivity and specificity of Fibro-Scope were 78.6% and 83.3% in the U.S. cohort, and 90.0% and 72.4% in the Japanese cohort. **Conclusion:** Fibro-Scope demonstrated robust diagnostic performance for detecting advanced fibrosis in both US and Japanese MASLD cohorts with few intermediate ranges when using race-specific cutoff values.

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≥ 65 years old	Sensitivity	Specificity	PPV	NPV	AUROC
Japan cohort					
Fibroscope	90.0%	72.4%	54.5%	95.2%	0.900
FIB-4 index	93.8%	67.7%	51.7%	96.7%	0.905
U.S. cohort					
Fibroscope	78.6%	83.3%	78.6%	83.3%	0.786
FIB-4 index	57.1%	72.2%	61.5%	68.4%	0.698
< 65 years old					
Japan cohort					
Fibroscope	59.4%	93.3%	56.7%	94.0%	0.944
FIB-4 index	50.0%	94.3%	56.1%	92.8%	0.875
U.S. cohort					
Fibroscope	67.4%	88.1%	63.3%	89.9%	0.871
FIB-4 index	26.1%	94.7%	60.0%	80.8%	0.789

Disclosures: yuya seko: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Georgia Sofia Karachaliou: Nothing to Disclose, Ayako Suzuki: Nothing to Disclose, Manal Abdelmalek: 89Bio, Akero, Madrigal, Inventiva, Novo Nordisk, Intercept, Merck,: Advisor, Hanmi, Novo Nordisk: Consultant, Madrigal, Gilead, Inventiva, 89Bio, Akero, Hanmi: Research paid to my institution, Pfizer, Merck: Stock – privately held company, Medscape; Clinical Care Options; Fishawack Inc, LLC; CLDF: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Kanji Yamaguchi: Nothing to Disclose, Toshihide Shima: Nothing to Disclose, Yoshito Itoh: Nothing to Disclose, Anna Mae Diehl: Nothing to Disclose, Takeshi Okanoue: Nothing to Disclose

◆ 2004 | IMPROVEMENT OF HEPATIC STEATOSIS AND REDUCTION IN CARDIOVASCULAR EVENT IN PATIENTS WITH DIABETES MELLITUS: A PROSPECTIVE STUDY

Yoonseok Lee[1] Oh Sang Kwon[2] SEUNG KAK SHIN[2] Yun Soo Kim[2] Ju Hyun Kim[2] Kiyoung Lee[2] Young Sil Eom[2] Byung-Joon Kim[2], [1]Gachon University Gil Medical Center, [2]Department of Internal Medicine, Gachon University Gil Medical Center

Background: Patients with diabetes mellitus (DM) are at an increased risk of developing cardiovascular disease (CVD). Hepatic steatosis is common among patients with DM, but its impact on CVD risk remains unclear. This study aimed to prospectively assess the association between a reduction in hepatic steatosis and a lower risk of CVD in patients with DM. **Methods:** A total of 323 patients with DM were prospectively enrolled from January 2022, after excluding those with viral hepatitis, overt cirrhosis, and cancer. The following parameters and data were assessed: body weight (BW), body mass index (BMI), waist circumference (WC), laboratory data, presence of hypertension (HTN), dyslipidemia, alcohol consumption, smoking status, liver stiffness measurement (LSM), current anti-DM medications, and CVD events. Hepatic steatosis was quantified using the controlled attenuation parameter (CAP) measured by FibroScan® at baseline and after 2 years. CVD was defined as ischemic heart disease or ischemic/hemorrhagic stroke. **Results:** A total of 277 patients completed 2-year follow-up and underwent repeat CAP assessment. The mean age was 57 ± 12 years, and 56.3% were male. The baseline mean CAP was 274 ± 18 dB/m. A history of CVD was present in 86 (31%) patients, while 6 (3.2%) developed new CVD events during follow-up. CAP scores decreased in 176 patients (d-CAP group) and increased in 101 patients (i-CAP group). The mean CAP change was -33 ± 29 dB/m in the d-CAP group and $+24 \pm 18$ dB/m in the i-CAP group. Patients in the d-CAP group were older (58 ± 12 vs. 55 ± 12 years, $p = 0.012$) and had higher baseline CAP (284 ± 50 vs. 255 ± 47 dB/m, $p < 0.001$) than those in the i-CAP group. There were no significant differences in male proportion, BW, BMI, WC, laboratory data, HTN, dyslipidemia, alcohol consumption, smoking status, or baseline LSM between the two groups. The insulin use was lower in the d-CAP group than in the i-CAP group (5.1% vs. 12.9%, $p = 0.022$). When stratified by CAP change, the incidence of new CVD was 0% (0/55) in patients with CAP reduction of $\leq$-40 dB/m, 2% (4/201) in those with changes between -40 and +40 dB/m, and 9.5% (2/21) in those with CAP increases of $\geq$+40 dB/m ($p = 0.037$). **Conclusion:** A marked decrease in CAP score was associated with a lower risk of CVD in patients with DM. Therefore, CAP monitoring may be a valuable tool for assessing CVD risk. Efforts to reduce hepatic steatosis, as reflected by CAP reduction, may contribute to CVD prevention in this population.

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◆ 2005 | AI-POWERED CELL-FREE DNA METHYLATION PROFILING FOR NON-INVASIVE DIAGNOSIS OF AT-RISK MASH, WITH BIOLOGICAL PLAUSIBILITY VALIDATION VIA PATHWAY ANALYSIS: A MULTI-COHORT STUDY

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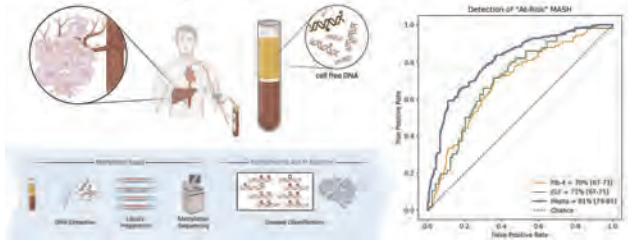
Background: MASH presents diagnostic challenges due to the invasive nature of liver biopsy. Cell-free DNA (cfDNA) methylation profiling offers a non-invasive alternative, capturing epigenetic alterations associated with disease progression. Intersection of genomics and built-for-purpose AI could enhance diagnostic accuracy and provide insights into underlying biological mechanisms. **Methods:** This international multi-cohort study includes 528 biopsy-confirmed MASLD patients (Control = 59, F0 = 88, F1 = 113, F2 = 106, F3 = 101, F4 = 61) from 3 independent cohorts across US and Europe: (1) Akero Therapeutics's SYNCHRONY Phase 3 program (n = 179), (2) Duke MASLD biobank (n = 276), (3) University Medical Center Mainz biobank (n = 73). Plasma samples were collected at baseline. Deep methylation sequencing of cfDNA was performed generating 33 terabytes of genomic data. We have developed a proprietary liquid biopsy-native AI platform which, using a 20,000 core dynamic compute cluster, enables the training of the model required to capture the molecular-level complexity across hundreds of millions of unique cfDNA molecules per sample. The negative binomial deep neural network model, with 89 million parameters, is trained to detect "at-risk MASH" (i.e. NAS $\geq$ 4 with F $\geq$ 2) and the 5-fold cross-validated performance is reported. Additionally, methylation signatures contributing to the classification algorithm were identified and subjected to pathway enrichment analysis to assess biological plausibility. **Results:** The AI model identified methylation signatures correlating with disease severity with AUC of 0.81 for detecting "at-risk MASH" compared to 0.70 for Fib-4 ($p < 0.01$). ELF score was available on a subset of Akero subjects (n = 172), on which our model had an AUC of 0.80 compared to ELF's AUC of 0.71 ($p < 0.01$). There was no significant difference in the model's performance across cohorts, demonstrating robustness and generalizability. Pathway analysis performed on the genomic features driving classification revealed enrichment in a substantial number of metabolic, fibrosis, and inflammation regulation pathways which align with known MASH pathophysiology and demonstrate the model's biological plausibility. **Conclusion:** By combining state-of-the-art AI with deep methylation profiling we have created and validated a powerful technology to study disease epigenetics, identify relevant methylation signatures, and diagnose "at-risk MASH". This innovative approach for blood-based biomarker provides mechanistic insights into disease pathobiology through pathway analysis and offers a novel promising direction for early detection of MASH and fibrosis, disease monitoring, risk stratification, with potential application in therapy selection based on the mechanistic characterization.

Cohort	Control	F0	F1	F2	F3	F4	Total
Akero SYNCHRONY	-	28	39	54	35	23	179
Duke Biobank	59	59	53	31	47	27	276
Mainz Biobank	-	1	21	21	19	11	73
Total	59	88	113	106	101	61	528



Disclosures: Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Soheil Damangir: Nothing to Disclose, Georgia Sofia Karachaliou: Nothing to Disclose, Jörn Schattenberg: Apollo Endoscopy, Boehringer Ingelheim, Gilead Sciences: Consultant, Intercept Pharmaceuticals: Consultant, Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals: Consultant, MSD, Northsea Therapeutics, Novartis, Novo Nordisk: Consultant, Pfizer, Roche, Sanofi, and Siemens Healthineers: Consultant, Boehringer Ingelheim, Siemens Healthcare GmbH: Grant/Research Support, Alentis, Alexion, Altimmune, Astra Zeneca, 89Bio,Bionorica,: Consultant, Boehringer

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◆ 2006 | VALIDATION OF NEW CLINICAL OBESITY CRITERIA FOR STEATOTIC LIVER DISEASE IN THE UNITED STATES

Luis Antonio Diaz[1] Nikhil Kalita[2] Federica Tavaglione[2] Patrick Corr[3] Chinar Sheth[2] Darryl Contrano[2] Veeral Ajmera[2] Rohit Loomba[2], [1]Pontificia Universidad Católica de Chile, [2]University of California San Diego, [3]Integrative Medicine, George Washington University School of Medicine & Health Sciences

Background: Obesity is highly prevalent in the United States and constitutes a leading cause of steatotic liver disease (SLD). However, the optimal anthropometric measures for identifying patients at risk of liver fibrosis remain uncertain. We aimed to compare body mass index (BMI) and waist circumference (WC) classifications in their association with liver fibrosis stages, applying the new 2025 clinical obesity definition. **Methods:** We performed a cross-sectional analysis of adult participants from the 2017–2023 NHANES cycles who underwent vibration-controlled transient elastography (VCTE). We included participants aged ≥12 years and excluded those with chronic hepatitis B or C infection. WC was classified both by standard (SWC) and metabolic-dysfunction–specific thresholds (MWC). Steatosis was defined by a CAP ≥288 dB/m, and significant fibrosis was defined by liver stiffness measurement ≥7.6 kPa. MASLD was diagnosed according to the 2023 criteria. We used multinomial logistic regression, adjusted for age, sex, race/ethnicity, diabetes, hypertension, hyperlipidemia, and alcohol use to estimate odds ratios (OR) for significant fibrosis across BMI and WC categories. We also incorporated restricted cubic splines (three knots) to model non-linear effects. Subgroup analyses were performed for SLD subtypes. **Results:** We included 27,493 individuals. The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) was 30.2%. The prevalence of significant fibrosis was 34.0% among individuals with BMI ≥35 kg/m², compared to 5.6% among those with BMI ≤25 kg/m². In adjusted models, participants with BMI ≥35 kg/m² had significantly higher odds of significant fibrosis compared to those with underweight/normal BMI (odds ratio [OR]: 8.29; 95%CI: 6.36–10.81). The very high SWC category (>110/120 cm for women/men) had an OR of 2.99 (95% CI: 2.19–4.09) for significant fibrosis compared to the very low SWC category (<70/80 cm for women/men), while the very high MWC category (>120/130 cm for women/men) had an OR of 13.09 (95%CI: 10.11–16.94) compared to the very low MWC reference (<90/100 cm for women/men). Adjusted non-linear models revealed an inflection point where significant fibrosis risk increases at BMI ≥28.4 kg/m² and WC ≥85 cm (Figure). Similar findings were observed when analyses were restricted to

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individuals with MASLD. **Conclusion:** Central adiposity measured by WC thresholds enhances identification of fibrosis risk beyond BMI alone. Routine incorporation of WC into screening algorithms may optimize early detection and referral for fibrosis assessment in clinical practice.

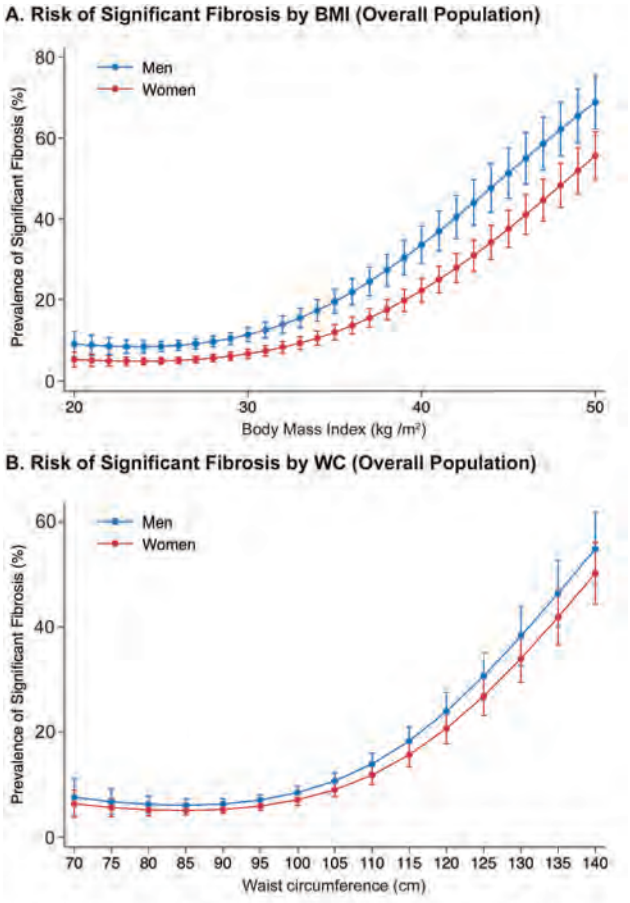

Figure. Nonlinear adjusted models to assess the prevalence of significant fibrosis (liver stiffness ≥7.6 kPa on vibration-controlled transient elastography) according to body mass index (BMI) and waist circumference (WC). Models were adjusted by age, sex, race/ethnicity, diabetes, hypertension, hyperlipidemia, and alcohol use.

Disclosures: Luis Antonio Diaz: Nothing to Disclose, Nikhil Kalita: Nothing to Disclose, Federica Tavaglione: Nothing to Disclose, Patrick Corr: Nothing to Disclose, Chinar Sheth: Nothing to Disclose, Darryl Contrano: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Rohit Loomba: Nothing to Disclose

◆ 2007 | PATIENTS WITH MASLD DECOMPENSATE AT A LOWER HEPATIC VENOUS PRESSURE GRADIENT THRESHOLD: DATA FROM A MULTICENTRIC RETROSPECTIVE COHORT STUDY

Xiao Yu Xie[1] Myriam Martel[2] Yu Jun Wong[3] Ikram Abow-Mohamed[2] Julien Bissonnette[4] Puneeta Tandon[5] Amine Benmassaoud[2], [1]Université de Montréal, [2]Division of Gastroenterology and Hepatology, Department of Medicine, McGill University Health Centre, [3]Division of Gastroenterology and Hepatology, Department of Medicine, University of Alberta, Edmonton, [4]University of Montreal Hospital Center, [5]University of Alberta

Background: Hepatic venous pressure gradient (HVPG) is the gold standard to predict hepatic decompensation in patients with advanced chronic liver disease (ACLD). However, the ability of clinically significant portal hypertension (CSPH) defined as HVPG ≥ 10 mmHg to predict decompensation in metabolic dysfunction-associated steatotic liver disease (MASLD) patients requires further validation. This study aimed to identify specific HVPG cutoffs to predict hepatic decompensation and liver-related events in MASLD patients. **Methods:** This is a retrospective cohort study from 3 Canadian tertiary centers including patients ≥18 years old with ACLD and portal hypertension diagnosed by HVPG ≥5 mmHg. Patients were identified through a prospective HVPG database from 2013 to 2024. Patients with non-cirrhotic portal hypertension, HVPG measured during acute hepatitis or acute-on-chronic liver failure, prior TIPS or liver transplant before HVPG measurement were excluded. We assessed the discriminatory abilities of HVPG to predict hepatic decompensation and liver-related events using the area under the receiver operating characteristic curve (AUROC) reporting with 95% confidence interval (CI). Cutoff values were derived based on Youden's Index. Hepatic decompensation is defined as new or worsening ascites, hepatic encephalopathy or variceal bleeding and liver-related events are defined as hepatic decompensation, liver transplant or death. **Results:** 409 patients with ACLD were included: 166 (40.6%) were women, mean age was 56.9 ± 13.2 years, mean HVPG was 13.1 ± 5.9 mm Hg, mean MELD Na score was 14.9 ± 8.0, 129 (31.5%) were MASLD patients. 149 (36.4%) patients had new hepatic decompensation, and 225 (55.0%) patients had new liver-related events. The HVPG thresholds to predict new hepatic decompensation in all patients and in MASLD patients were 11.0 mm Hg (AUROC = 0.62 (95%CI 0.56; 0.67)) and 5.9 mm Hg (AUROC = 0.67 (95%CI 0.58; 0.76)), respectively, both with a weak discriminatory ability. The HVPG thresholds to predict new liver-related events in all patients and in MASLD were 11.0 mm Hg with a weak discriminatory ability (AUROC = 0.69 (95%CI 0.64; 0.74)) and 8.5 mmHg with a fair discriminatory ability (AUROC = 0.73 (95%CI 0.65; 0.82)), respectively. **Conclusion:** HVPG demonstrated weak discriminatory ability to predict new hepatic decompensation and fair discriminatory ability to predict liver-related events in MASLD patients. Our

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study highlights that these thresholds are lower than for traditional CSPH.
Disclosures: Xiao Yu Xie: Nothing to Disclose, Myriam Martel: Nothing to Disclose, Yu Jun Wong: Nothing to Disclose, Ikram Abow-Mohamed: Nothing to Disclose, Julien Bissonnette: Nothing to Disclose, Puneeta Tandon: Nothing to Disclose, Amine Benmassaoud: Cook Medical: Speaking and Teaching, Jazz Pharmaceuticals: Advisor

◆ 2008 | HIGH-RESOLUTION COLLAGEN PROFILING REVEALS STAGE-SPECIFIC FIBROSIS PATTERNS IN PEDIATRIC MASLD USING DIGITAL PATHOLOGY AND UMAP

Li Chen Adi Lightstone[1] Mathieu Petitjean[1] Karenina Valdez[2] Cynthia Behling[2] Jeffrey Schwimmer[2], [1]Pharmanest, [2]University of California

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease in children. Despite its rising prevalence and characteristic zone 1–predominant steatosis and fibrosis, conventional histology lacks the resolution to assess fiber-level phenotypes or architectural complexity. To overcome this limitation, we applied FibroNest™, a high-resolution digital pathology platform, to quantify single-fiber collagen remodeling across fibrosis stages (NAS F0–F4) in pediatric MASLD liver biopsies. **Methods:** Liver biopsies from 67 pediatric MASLD patients (F0: 10, F1a: 9, F1b: 6, F1c: 23, F2: 8, F3: 8, F4: 3) were analyzed using FibroNest to quantify collagen quantity, fiber morphometry, and architectural complexity. Collagen fibers were segmented and profiled across three representative domains, selected from over 300 quantifiable fibrosis traits: Fiber Density (collagen quantity), Fiber Class (Fine vs Assembled reticulated collagen, and MFI (measures fiber structural maturity). Dimensionality reduction using Uniform Manifold Approximation and Projection (UMAP) enabled spatial visualization of collagen phenotypes across fibrosis stages. **Results:** UMAP analysis revealed distinct collagen phenotypes across fibrosis stages in pediatric MASLD, showing a clear progression from sparse, fine fibers in F0 to dense, mature, and complex structures in F3–F4. Within early-stage F1, subclassification revealed a gradient: F1a showed low fiber density and complexity; F1b had increased density and maturation; and F1c, with the highest collagen content and MFI, resembled F2, suggesting a transitional fibrotic state. Density UMAPs highlighted dispersed fibers in F0–F1 and dense, aggregated septa-like patterns in F2–F4. MFI increased with stage, with F3–F4 forming bright, compact clusters indicative of mature collagen. Fiber Class UMAPs showed a shift from fine collagen in early stages to assembled collagen in F2–F4, capturing architectural progression and dynamic collagen remodeling not apparent in conventional histology. **Conclusion:** FibroNest enables high-resolution, spatially resolved profiling of fibrosis in pediatric MASLD. UMAP visualization uncovered stage-specific collagen patterns and fibrosis progression. These findings support digital fiber phenotyping as a promising tool for improved disease staging and therapeutic monitoring in children with MASLD.
Disclosures: Li Chen: Nothing to Disclose, Adi Lightstone: Nothing to Disclose, Mathieu Petitjean: PHARM ANEST INC: Employee, PHARMANEST INC: Stock – privately held company, Karenina Valdez: Nothing to Disclose, Cynthia Behling: Nothing to Disclose, Jeffrey Schwimmer: Nothing to Disclose

◆ 2009 | DIFFERENT LIPIDOMIC SIGNATURE IN EXTRACELLULAR VESICLES IN PATIENTS WITH MASLD-HCC: ANALYSIS OF DIFFERENT STAGES OF MASLD

Mario Alvares-da-Silva[1] Melina Keingeski[1] Bruno Basso[1] Larisse Longo[1] José Tadeu Stéfano[2] Claudia Oliveira[2] Juan Pablo Arab[3] Carolina Uribe-Cruz[4], [1]Universidade Federal do Rio Grande do Sul, [2]Universidade de São Paulo, [3]Virginia Commonwealth University, [4]Facultad Católica de Misiones

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) ranges from isolated steatosis (STE) to steatohepatitis (MASH), cirrhosis (CIR) and hepatocellular carcinoma (HCC). Non-invasive markers have limited ability to identify different stages. Extracellular vesicles (EVs) are essential for cellular communication and could be useful as a liquid biopsy tool. This study aims to evaluate the lipid signature of EVs and their usefulness in disease progression. **Methods:** EVs were isolated using silica columns from serum of patients with different MASLD stages: STE (n = 25), MASH without fibrosis (MASH; n = 25), CIR (n = 25) and HCC (n = 18), and compared to controls (CON; n = 25). EVs were characterized by nanoparticle tracking analysis flow cytometry, and Western-Blot. Lipidomics was performed by mass spectrometric analysis of sphingolipids (Cer-20, Cer-22, Cer24-0, Cer24-0, S1P-d18-1, S-d18-1, C16-SM, C17-SM, C18-SM, C20-SM, C22-SM, C261-SM and C24DHC), oxysterols (7aHC, 7KC, 56a-EHC and CH) and bile acids (TaMCA, TbMCA, GbMCA, TCA, GCA, TCDCA, TDCA, CA, GDCA, TLCA, GLCA, LCA and CDCA-3-S). **Results:** Figure 1 shows a heatmap of lipid profiles across the groups. C24DHC was lower in all disease groups vs CON, suggesting early alterations in membrane lipid homeostasis during MASLD. C18-SM, C20-SM, C22-SM and Cer24-0 decreased in CIR and HCC vs CON, STE, and MASH, indicating progressive disruption of sphingolipid metabolism with disease

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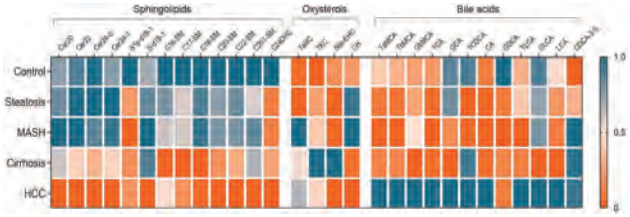
progression. C17-SM and C261-SM were significantly reduced in HCC vs CON, reflecting extensive lipid remodeling in late-stage disease. 7KC levels were significantly increased in HCC vs CON, STE, MASH, and CIR, consistent with enhanced oxidative stress specifically associated with advanced MASLD and hepatocarcinogenesis. Bile acids TCA and CA were higher in HCC vs other groups, pointing to dysregulation of bile acid pathways in late-stage disease. All differences, $p < 0.05$. **Conclusion:** The lipid composition of EVs may reflect key molecular changes during MASLD progression. The reduction of sphingolipids and accumulation of oxysterols and bile acids in advanced stages suggest disrupted lipid metabolism, oxidative stress, and hepatocellular dysfunction. These findings support the potential of EV lipidomics as a non-invasive tool for disease staging and mechanistic insight.



Disclosures: Mario Alvares-da-Silva: Nothing to Disclose, Melina Keingeski: Nothing to Disclose, Bruno Basso: Nothing to Disclose, Larisse Longo: Nothing to Disclose, José Tadeu Stéfano: Nothing to Disclose, Claudia Oliveira: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Carolina Uribe-Cruz: Nothing to Disclose

◆ 2010 | POPULATION SCREENING STRATEGIES FOR SIGNIFICANT FIBROSIS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN THE ERA OF DISEASE-SPECIFIC THERAPY

Winston Dunn[1] Naim Alkhouri[2] Terry Cheuk-Fung Yip[3] Nipun Verma[4] Laurent Castera[5] Ming-Hua Zheng[6] Leon Adams[7] Manal Abdelmalek[8] Ajay Duseja[9] Vincent Chen[10] Grace Lai-Hung Wong[3] Syed-Mohammed Jafri[11] Juan Pablo Arab[12] Vincent Wong[3] Bihui Zhong[13] Ashwani Singal[14], [1]University of Kansas Medical Center, [2]Summit Clinical Research, [3]The Chinese University of Hong Kong, [4]Postgraduate Institute of Medical Education and Research, [5]Hopital Beaujon, [6]The First Affiliated Hospital of Wenzhou Medical University, [7]University of Western Australia, [8]Mayo Clinic Rochester, [9]Postgraduate Institute of Medical Education & Research, [10]University of Michigan Medical Center, [11]Henry Ford Health System, [12]Virginia Commonwealth University, [13]The First Affiliated Hospital, Sun Yat-sen University, [14]University of Louisville

Background: Current clinical practice often employs the Fibrosis-4 (FIB-4) score as an initial screening tool, which is effective in identifying individuals at risk for advanced fibrosis and related complications. However, in the MAESTRO-NASH trial, the median FIB-4 among patients with significant (F2) to advanced (F3) fibrosis was only 1.3. Applying this as a cutoff would exclude nearly half of potentially eligible patients from further vibration-controlled transient elastography (VCTE) evaluation and subsequent resmetirom treatment. In this study, we compared two novel screening strategies—the Steatosis-Associated Fibrosis Estimator (SAFE) score and the mAchine Learning ADvanceD fibrosis and at-risk MASH Novel predictor (ALADDIN)-F2-Lab—against the traditional FIB-4 approach. **Methods:** We analyzed data from the 2017–2020 National Health and Nutrition Examination Survey (NHANES), the only cycle with VCTE data currently available. We included adults ($\geq$18 years) with hepatic steatosis (controlled attenuation parameter $>$248 dB/m), $\geq$1 metabolic risk factor, and alcohol intake consistent with MASLD, excluding those with viral hepatitis. We compared the performance of FIB-4, SAFE score, and ALADDIN-F2-Lab in identifying individuals with liver stiffness measurement (LSM) $\geq$8 kPa, the AASLD-recommended threshold for resmetirom treatment. All analyses incorporated survey design weights, strata, and primary sampling units. **Results:** In NHANES 2017–2020, 4,092 participants—projecting to 114.4 million U.S. adults—met criteria for MASLD, of whom 15.3% had liver stiffness measurement (LSM) $\geq$8 kPa. Using the current guideline of FIB-4 $\geq$1.3 as the initial screen, 28.5 million individuals would undergo VCTE to identify 5.2 million with LSM $\geq$8 kPa. In comparison, the SAFE score–based approach would identify 7.8 million individuals with LSM $\geq$8 kPa—a 51% increase in case detection—while requiring 1.1 million fewer VCTEs (a 4% reduction). The ALADDIN-F2-Lab–based approach would identify 9.4 million with LSM $\geq$8 kPa—an 81% increase in case detection—at the cost of 3.2 million additional VCTEs (an 11% increase). See Figure. **Conclusion:** In the era of disease-specific therapy for MASH, accurate and efficient non-invasive screening is critical for identifying patients with significant fibrosis eligible for treatment. The SAFE score improves upon the current FIB-4–based strategy by increasing case detection while reducing the number of required VCTEs. The ALADDIN-F2-Lab model provides even greater gains in identifying at-risk individuals, with a modest increase in VCTE use. Integrating SAFE or ALADDIN-F2-Lab into clinical workflows may enhance patient selection and expand access to therapy.

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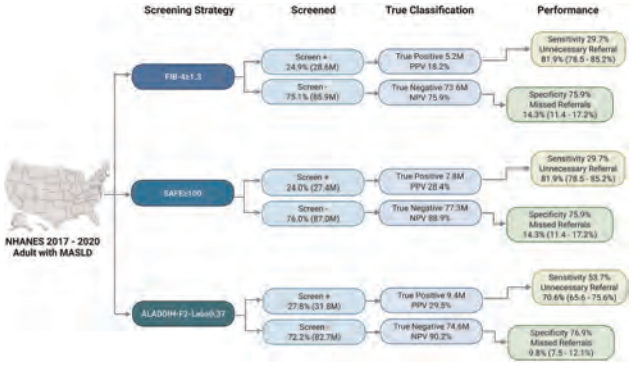

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◆ 2011 | MULTI-OMICS STUDY REVEALS IMMUNE PHENOTYPE ASSOCIATED WITH ELEVATED ADENOSINE DEAMINASE 2 IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

Sizhe Wan[1] David GUARDAMINO OJEDA[2] Scott Minchenberg[1] Denisse Rubio Cruz[1] Aaron Hakim[1] Kenneth Mukamal[1] Jerome Rotter[3] Z. Gordon Jiang[1],

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

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Background: Purine metabolites such as ATP, adenosine, inosine are potent immune regulators. The conversion from adenosine to inosine in the extracellular space is catalyzed by adenosine deaminase 2 (ADA2), an ecto-enzyme secreted by monocytes and macrophages. ADA2 deficiency can cause autoimmunity and vasculitis. However, the function of ADA2 remains elusive. We have previously reported that ADA2 promotes fibrogenesis in metabolic dysfunction associated steatotic liver disease (MASLD) by modulating monocyte differentiation. This study aims to interrogate the biology of ADA2 in MASLD leveraging the Trans-Omics for Precision Medicine (TOPMed) multi-omics data in Multi-Ethnic Study of Atherosclerosis (MESA). **Methods:** A total of 427 MASLD patients were identified from MESA based on medical history and the liver-to-spleen density ratio on CT. Among these individuals, ADA2 activity and components of Extended Liver Fibrosis panel were measured in the serum. We analyzed O-link proteomics and LC-MS metabolomics data of 320 MASLD patients and 2020 individuals without MASLD. Proteomics findings were further cross-examined in 110 individuals with RNA sequencing data of PBMC (n = 103), T cell (n = 40), and monocyte (n = 42). **Results:** ADA2 activity in the serum was significantly associated with ELF score ($r = 0.484$; $p < 0.0001$) in patients with MASLD. MASLD patients with high ADA2 activity (1 SD above mean) have elevated CXCL10, a monocyte specific chemokine, along with CXCL9 and CXCL11 in the serum. O-link proteomics analysis also revealed elevation of ADGRE1, CDCP1, LILRA6, CLEC6A, FCAR, and SIGLEC1, signatures of tissue-infiltrating proinflammatory monocytes-derived macrophages. Gene ontology pathway enrichment analysis indicated upregulation of leukocyte cell-cell adhesion, chemotaxis, and proliferation. These findings were supported by the upregulation of interferon (IFN)-induced genes (IFI27, IFIT3, IFI6, IGLV7-46), and cell migration regulators (CXCL10, CCR9, ITGA1, MIF) in PBMC transcriptome. We then performed hypothesis-free clustering analysis of circulating purine metabolites and identified three profiles. Besides the majority with low purine metabolites, individuals with high purine metabolites demonstrate two profiles: Type 1 (elevation in ATP, ADP, AMP, adenosine) and Type 2 (elevation in inosine, hypoxanthine, xanthine), with main differences at the rate of adenosine deaminase activating, potentially catalyzed by ADA2. **Conclusion:** Integrated multi-omics analyses indicate a strong role of ADA2 in shaping circulating purine metabolite profiles. Elevated ADA2 activity is associated with proteomic and transcriptomic signatures of tissue infiltration of monocytes with proinflammatory differentiation.

Disclosures: Sizhe Wan: Nothing to Disclose, David GUARDAMINO OJEDA: Nothing to Disclose, Scott Minchenberg: Nothing to Disclose, Denisse Rubio Cruz: Nothing to Disclose, Aaron Hakim: Olix Pharmaceuticals: Advisor, Deep Track Capital, LP: Consultant, Kenneth Mukamal: Nothing to Disclose, Jerome Rotter: Nothing to Disclose, Z. Gordon Jiang: Nothing to Disclose

◆ 2012 | WEIGHT LOSS-INDUCED METABOLIC REMODELING IN MASLD: A COHORT STUDY STRATIFIED BY POLYGENIC RISK

Torre Pietro[1] Jacopo Troisi[1] Luigi Schiavo[1] Benedetta Maria Motta[1] Martina Lombardi[1] Mariano Festa[1] Tommaso Sarcina[1] Mario Masarone[1] Marcello Persico[1], [1]University of Salerno, Italy

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the hepatic expression of systemic metabolic derangement, yet tools for tracking its regression remain limited. Metabolomics can provide dynamic biomarkers that reflect pathophysiological change. The objective of this study is to delineate serum metabolomic adaptations to a weight-loss-oriented Mediterranean diet in obese MASLD patients stratified by genetic risk. **Methods:** In a prospective cohort, 148 adults with ultrasound-confirmed MASLD started a personalized hypocaloric Mediterranean diet. Weight loss was classified as $< 5\%$, 5–10%, or $> 10\%$ of baseline. Single-nucleotide polymorphisms in PNPLA3, TM6SF2, MBOAT7 and GCKR were genotyped and combined into a weighted polygenic risk score. Untargeted gas chromatography–mass spectrometry profiled fasting serum samples at baseline and study end. Data were processed by partial least squares discriminant analysis, variable importance in projection scoring, and pathway enrichment. **Results:** Mean weight decreased by 8% and controlled attenuation parameter declined by 17%, with greatest steatosis reduction in PNPLA3 G-allele carriers. Metabolomic modelling achieved 92% classification accuracy and revealed fourteen key metabolites. Caproic acid, glycerol and hydroxypropanedioic acid increased consistently, whereas palmitic acid and D-galactose decreased. Enriched pathways included galactose, butanoate and glycerolipid metabolism. Metabolic shifts scaled with weight loss intensity and differed by genotype; high responders showed enhanced branched-chain amino acid catabolism. The figure shows a stratified metabolomic analysis by weight loss class after 6 months of dietary intervention; patients were divided into three groups based on the percentage

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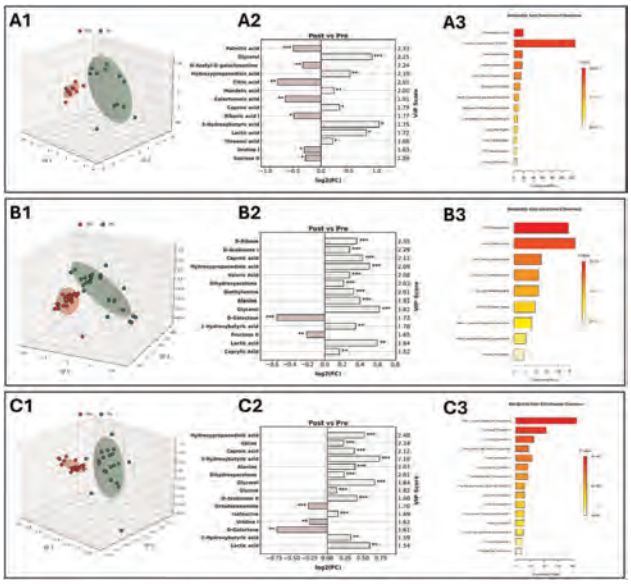
of body weight loss at 6 months: low (< 5%, panels A1–A3), mid (5–10%, panels B1–B3), and high (> 10%, panels C1–C3). **Conclusion:** Mediterranean diet-induced weight loss triggers rapid, weight-dependent and genotype-modulated metabolomic reprogramming that parallels hepatic fat clearance. Caproic acid, glycerol and hydroxypropanedioic acid constitute biomarkers and, combined with polygenic risk assessment, may support precision nutrition strategies for MASLD.



Disclosures: Torre Pietro: Nothing to Disclose, Jacopo Troisi: Nothing to Disclose, Luigi Schiavo: Nothing to Disclose, Benedetta Maria Motta: Nothing to Disclose, Martina Lombardi: Nothing to Disclose, Mariano Festa: Nothing to Disclose, Tommaso Sarcina: Nothing to Disclose, Mario Masarone: Nothing to Disclose, Marcello Persico: Nothing to Disclose

◆ 2013 | CURRENT CARE PATHWAY AND REFERRAL PATTERNS IDENTIFY GAPS IN SCREENING, DIAGNOSIS, AND TREATMENT OF MASLD/MASH IN AMBULATORY CARE SETTING

Rahul Sandella[1] Hee Yeon Kim[2] Andrew Davis[1] Mary Rinella[1], [1]The University of Chicago, [2]Bucheon St Mary's Hospital, The Catholic University of Korea

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is typically asymptomatic even with significant fibrosis, contributing to its under-diagnosis. Despite cross-society alignment in guidelines on the use of FIB-4 to screen at-risk populations, adherence to recommendations remains poor. We aimed to assess care patterns across FIB-4 risk strata in a large ambulatory cohort. **Methods:** We conducted a retrospective cohort study of patients aged 35-70 years seen between 2021 and 2025 across 35 ambulatory care clinics within a large academic health system. Data were extracted from the electronic health record using MDCLONE software. Patients with available ALT, AST, and platelet count were included. FIB-4 was calculated and categorized as low, intermediate, or high risk (table). We examined metabolic risk factors, liver biochemistries, medication use, hepatology referral, and visits across risk strata, using ANOVA and chi-squared testing. **Results:** Of 56,552 patients, 73% were low-risk, 20% intermediate-risk, and 7% high-risk according to FIB-4. Demographic and clinical characteristics differed significantly across FIB-4 strata (table). Use of GLP-1 receptor agonists was more common in low-risk patients, while SGLT-2 inhibitor use increased with fibrosis risk ($p < 0.001$ for both). Hepatology referral rates were low across groups, while actual hepatology visits were more frequent in high-risk patients ($p < 0.001$). High-risk patients were most likely to be referred, seen by hepatology, or undergo liver stiffness assessment when seen by gastroenterology (73%) or endocrinology (39%), and least likely when seen by cardiology, family medicine, or internal medicine (22-24%, $p < 0.001$). Among high-risk patients, Black patients were less likely to be referred or seen by hepatology compared to White patients ($p < 0.001$), and the presence of diabetes or obesity was not associated with higher referral rates. **Conclusion:** Despite 7% of patients meeting high-risk FIB-4 criteria, most were not referred to hepatology, while some low-risk patients were referred unnecessarily. Referral patterns varied significantly by provider specialty and patient demographics, suggesting potential disparities and inefficiencies in triage. System-level interventions are urgently needed to improve adherence to guidelines and ensure timely, risk-based, and equitable hepatology care to prevent major adverse liver outcomes in MASH patients.

Table. Patient characteristics and Hepatology referral across FIB-4 risk categories

Parameters (counts are n (%) or mean (SD))	FIB-4 Category			P-value
	Low-risk FIB-4 < 1.3 if < 65 y FIB-4 < 2.0 if ≥ 65 y N=41,525	Intermediate-risk FIB-4: 1.3 - 2.66 if < 65 y FIB-4: 2.0 - 2.66 if ≥ 65 y N=11,292	High-risk FIB-4 ≥ 2.67 N=3,735	
Female	25,056 (60%)	5,406 (48%)	1,551 (42%)	<0.001
White race	15,481 (37%)	3,955 (35%)	1,266 (34%)	<0.001
Black race	19,427 (47%)	5,853 (52%)	1,918 (51%)	<0.001
Age, years	52.5 (11.7)	57.9 (8.5)	61.0 (8.7)	<0.001
BMI, kg/m²	30.5 (7.3)	28.8 (7.0)	28.1 (6.9)	<0.001
Diabetes	5106 (17%)	1403 (18%)	560 (23%)	<0.001
LDL, mg/dL	102 (34)	95 (36)	79 (36)	<0.001
Triglycerides, mg/dL	108 (69)	106 (75)	113 (81)	<0.001
ALT, IU/L	22 (15)	29 (31)	55 (67)	<0.001
AST, IU/L	22 (9)	33 (24)	82 (75)	<0.001
GGT, IU/L	80 (157)	140 (359)	215 (439)	<0.001
Albumin, g/dL	4.2 (0.5)	4.1 (0.6)	3.6 (0.8)	<0.001
Ferritin, ng/mL	292 (980)	606 (1,457)	1,274 (4,928)	<0.001
Platelets, G/L	281 (69)	211 (50)	159 (62)	<0.001
GLP1-RA use	3,152 (8%)	487 (4%)	154 (4%)	<0.001
SGLT2i use	3,049 (7%)	1,084 (10%)	545 (15%)	<0.001
Liver stiffness (VCTE or MRE)	325 (0.8%)	161 (1.4%)	113 (3%)	<0.001
Hepatology referral	4,578 (11%)	1,125 (10%)	433 (12%)	0.002
Hepatology visit	2,235 (5%)	845 (8%)	714 (19%)	<0.001

Disclosures: Rahul Sandella: Nothing to Disclose, Hee Yeon Kim: Nothing to Disclose, Andrew Davis: Nothing to Disclose, Mary Rinella: akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant,

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◆ 2014 | MISSED OPPORTUNITIES FOR EARLY MASLD TREATMENT: TRENDS IN FIBROSIS BURDEN AND DISEASE AWARENESS IN THE U.S. POPULATION — RESULTS: FROM THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY 2017–2023

Jameel Alp[1] Giovanni Roldan[2] Jesse Fletcher[1] Amy Gravely[3] Lisa Smith[3] Pimsiri Sripongpun[4] Prowpanga Udompap[5], [1]Department of Medicine, University of Minnesota, Minneapolis, MN, [2]Division of Gastroenterology, Hepatology, and Nutrition, University of Minnesota, Minneapolis, MN, [3]Research Service, Minneapolis Veterans Affairs Health Care System, Minneapolis, MN, [4]Gastroenterology and Hepatology Unit, Prince Songkhla University, Hat Yai, Thailand, [5]Minneapolis VA Medical Center, Minneapolis, MN

Background: Metabolic dysfunction-associated liver disease (MASLD) has become a leading cause of chronic liver disease worldwide. MASLD patients with steatohepatitis (MASH)/moderate fibrosis (F2-F3) are eligible for resmetirom, the FDA-approved treatment for MASH that can potentially improve clinical outcomes. Yet, it remains challenging to capture MASLD population at-risk for disease progression and those eligible for resmetirom since majority of patients are asymptomatic, and the diagnosis required high index of suspicion from the providers. This study aims to evaluate temporal trends in the fibrosis burden as well as the awareness of their liver disease among U.S. adults with MASLD. **Methods:** Using the data from the National Health and Nutrition Examination Survey (NHANES) 2017-March 2020 (pre-pandemic) and August 2021-August 2023 (post-pandemic), adults aged ≥ 18 with valid vibration-controlled transient elastography and body mass index (BMI) were included. Hepatic steatosis (HS) was defined based on the controlled attenuation parameter ≥ 274 dB/m. Individuals with HS were categorized into MASLD, MASLD with increased alcohol intake (MetALD), or alcohol-associated liver disease (ALD) per current nomenclature. Liver fibrosis stage 2-3 (F2-F3) was defined by liver stiffness (LS) 8-15 kPa and compensated advanced chronic liver disease (cACLD) was defined by LS ≥ 15 kPa. **Results:** A total of 13,188 adults were included in the initial analysis which projected to a total of 219 million (M) Americans. Of these, 50.5M pre- and 30.4M post-pandemic had MASLD. 13.4% of MASLD participants in pre- and 15.7% in post-pandemic ($p = 0.15$) had LS of 8-15 kPa or F2-F3 fibrosis and deemed eligible for resmetirom. The prevalence of MASLD-related cACLD increased significantly from 3.7% pre- to 5.4% post-pandemic ($p = 0.02$). Interestingly, the awareness of liver disease remained low among all individuals with MASLD (6.3% pre- vs 6.7% post-pandemic ($p = 0.64$)). While the awareness of the liver disease among individuals with MASLD-related cACLD increased significantly from pre- (8.4%) to post-pandemic (20.4%), ($p = 0.02$), the awareness remained low among MASLD participants eligible for resmetirom (12.6% pre- vs 10.3% post-pandemic, ($p = 0.53$)). Factors associated with awareness included central obesity (OR 3.2; 95%CI [1.1, 9.9]), HTN (OR 1.5, 95%CI [1.1, 2.3]), diabetes (OR 1.7, 95%CI [1.1, 2.6]). **Conclusion:** The awareness of liver disease increased after the pandemic among MASLD individuals with cACLD; however, this group is already

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at high risk for complications and is no longer eligible for resmetirom. Approximately 13-15% of the MASLD population are eligible for resmetirom but only 1 in 10 individuals in this group are aware of their condition. These findings highlight an urgent need to expand screening efforts, improve risk stratification strategy and access to elastography in order to identify eligible individuals for intervention earlier.

Table 1: Characteristics of U.S. adults with valid vibration-controlled transient elastography and BMI data in NHANES, pre- and post-pandemic

	Pre-pandemic (2017-March 2020)	Post-pandemic (August 2021-August 2023)	p-value
Study Participants			
Number of US residents age ≥18 with valid elastography, and available BMI (in millions, (SE))	133.2 (5.5)	85.8 (4.5)	
Proportion of US residents with hepatic steatosis (%, (95%CI))	41.5 (39.7, 43.2)	39.2 (37.0, 41.4)	0.10
Subtype of steatotic liver disease (%, (95%CI))			
MASLD	91.4 (89.6, 93.0)	90.5 (88.7, 92.3)	0.01
MetALD	6.5 (5.1, 8.0)	5.6 (4.4, 6.7)	
ALD	1.9 (1.2, 2.6)	3.5 (2.4, 4.5)	
Characteristics of US adult with MASLD			
Number of US residents age >= 18 with MASLD (in millions, (SE))	50.5 (1.7)	30.4 (1.2)	
Age (years, (SE))	50.7 (0.6)	50.5 (0.5)	0.81
Male (%, (95%CI))	55.1 (52.2, 58.1)	53.7 (51.8, 55.7)	0.43
Race/ethnicity (%, (95%CI))			
Mexican American	12.0 (8.6, 15.4)	9.5 (3.7, 15.4)	0.64
Other Hispanic	7.6 (5.8, 9.3)	10.5 (7.1, 13.8)	
Non-Hispanic White	61.7 (56.3, 67.1)	59.6 (54.7, 63.4)	
Non-Hispanic Black	8.7 (6.3, 11.0)	9.3 (5.6, 12.9)	
Non-Hispanic Asian	5.7 (3.8, 7.6)	6.1 (3.0, 9.1)	
Other Races	4.3 (3.2, 5.4)	5.6 (4.1, 7.1)	
BMI categories (%, (95%CI))			
<18.5	0.02 (0.0, 0.06)	0.03 (0.0, 0.08)	0.99
18.5-25	5.5 (3.7, 7.2)	5.2 (3.3, 7.1)	
25-30	26.9 (23.8, 29.5)	27.6 (24.5, 30.7)	
≥ 30	67.6 (63.5, 71.7)	67.1 (63.1, 71.2)	
Proportion of US residents with MASLD eligible for resmetirom (%, (95%CI))	13.4 (10.9, 16.0)	15.7 (14.0, 17.3)	0.15
Proportion of US residents with MASLD-related cACLD (%, (95%CI))	3.7 (2.7, 4.7)	5.4 (4.1, 6.7)	0.02
Awareness of their liver disease among each subgroup (%, (95%CI))			
Individuals with MASLD	6.3 (4.7, 7.8)	6.7 (5.4, 8.1)	0.64
Individuals with MASLD eligible for resmetirom	12.6 (5.9, 19.3)	10.3 (6.4, 14.2)	0.53
Individuals with MASLD-related cACLD	8.4 (2.8, 14.1)	20.4 (13.8, 27.0)	0.02

Disclosures: Jameel Alp: Nothing to Disclose, Giovanni Roldan: Nothing to Disclose, Jesse Fletcher: Nothing to Disclose, Amy Gravely: Nothing to Disclose, Lisa Smith: Nothing to Disclose, Pimsiri Sripongpun: Nothing to Disclose, Prowpanga Udompap: Nothing to Disclose

◆ 2015 | GENETIC CORRELATION AND PHENOME-WIDE ASSOCIATION STUDIES PROVIDE INSIGHTS INTO THE METABOLIC FEATURES AND GENETIC SUBTYPES OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Ci Song[1] Wentao Yao[1], [1]Nanjing Medical University

Background: According to the latest diagnostic criteria, a diagnosis of metabolic dysfunction-associated steatotic liver disease (MASLD) requires individuals to exhibit hepatic steatosis alongside at least one cardiometabolic risk factor (CMRF). However, certain conventional metabolic factors, such as LDL cholesterol, are omitted from these criteria, and the relationship between the included factors and hepatic steatosis remains incompletely elucidated. **Methods:** We conducted a genome-wide association study (GWAS) meta-analysis of imaging-quantified hepatic fat content (HFC) in 34,309 Caucasian participants and 28,318 Han Chinese participants. Leveraging GWAS summary statistics from diverse sources, we estimated the genetic correlations between HFC and nine clinically relevant metabolic biomarkers, including those both within and outside the diagnostic criteria. Subsequently, using the colocalization probabilities from significant loci between HFC and each metabolic biomarker, we performed unsupervised clustering analysis and constructed polygenic risk scores (PRS) for the resulting latent subgroups, which were then used to conduct phenome-wide association studies (PheWAS). **Results:** We identified 18 lead SNPs associated with HFC at $P < 5 \times 10^{-8}$, including two novel signals. Genetic correlation analyses confirmed robust associations between HFC and the seven markers included in the current diagnostic criteria, irrespective of the specific sources of summary statistics. In contrast, two metabolic markers previously reported to be associated with MASLD—LDL cholesterol and total cholesterol—showed no correlation with HFC across any dataset. Colocalization-driven clustering analysis uncovered three distinct genetic subgroups: the first subgroup exhibited strong colocalization with HDL cholesterol, demonstrating robust associations with a broad spectrum of liver diseases while being linked to a reduced risk of cardiovascular disease; the second subgroup primarily colocalized with fasting glucose, showing weaker associations with liver disease but contributing to an elevated risk of cardiovascular disease; and the third subgroup displayed strong colocalization with both glucose markers and triglycerides, maintaining moderate associations with both liver and cardiometabolic diseases. Furthermore, we observed that MASLD patients without evident metabolic dysregulation exhibited a higher overall genetic burden, predominantly concentrated in the SNP subgroup colocalizing with HDL cholesterol. **Conclusion:** Our study supports the selection of CMRFs in the current diagnostic criteria and provides genetic insights into the heterogeneity of MASLD. Furthermore, these findings suggest that genetic factors likely play a significant role in MASLD among patients without metabolic dysregulation, potentially facilitating the diagnosis and management of cryptogenic MASLD cases.

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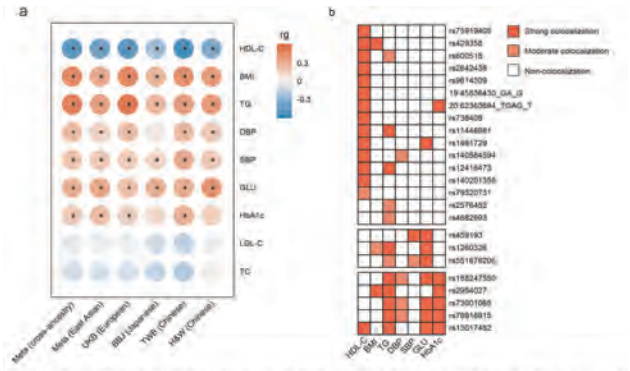


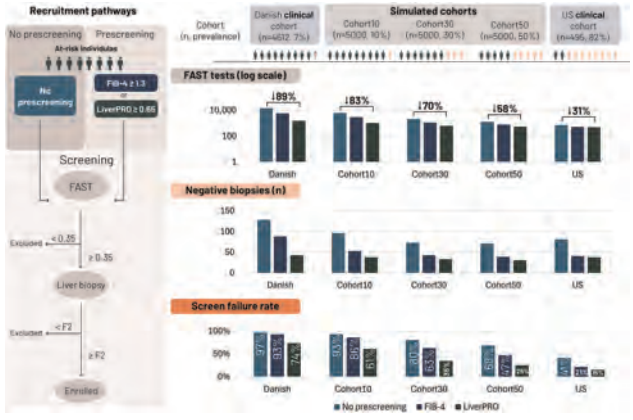
Figure | Genetic correlation and colocalization analyses reveal global and local metabolic features and potential genetic subtypes of MASLD. a, Using LDSC, we analyzed the genetic correlations between HFC-GWAS summary statistics derived from meta-analysis and summary statistics for nine cCMRFs from six sources (four association studies and two meta-analyses). The heatmap colors represent the magnitude of genetic correlation between HFC and the corresponding CMRF from specific sources, with asterisks indicating statistically significant correlations ($P < 0.05$). b, Based on Bayesian colocalization posterior probabilities (PP.H4) with seven CMRFs exhibiting genetic correlations, we performed unsupervised clustering of significant HFC loci. Strong colocalization (dark red) was defined as PP.H4 ≥ 0.8, moderate colocalization (light red) as PP.H4 between 0.4 and 0.8, and PP.H4 < 0.4 as non-colocalization (white). The final number of clusters was set to N = 3 based on the silhouette coefficient. UKB, UK Biobank; BBJ, BioBank Japan; TWB, Taiwan Biobank. H&W, HOPE cohort and WELLSPRING cohort; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; TG, triglycerides; DBP, diastolic blood pressure; SBP, systolic blood pressure; GLU, fasting glucose; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

Disclosures: Ci Song: Nothing to Disclose, Wentao Yao: Nothing to Disclose

◆ 2016 | LIVERPRO CAN OPTIMIZE TRIAL RECRUITMENT AND LOWER SCREEN FAILURE RATES IN STEATOTIC LIVER DISEASE

Julie Astono[1] Andreas Sand[1] Katrine Thorhauge[1] Georg Semmler[2] Rida Nadeem[3] Aarya Patel[3] Manal Chughtai[3] Sahasraara Hemant[3] Yasmeen Fallouh[3] Himanshi Kapoor[3] Camilla Dalby Hansen[2] Johanne Hansen[2] Stine Johansen[2] Helle Schnefeld[2] Peter Andersen[2] Katrine Bech[2] Nikolaj Torp[2] Søren Overgaard[1] Mads Israelsen[2] Katrine Lindvig[1] Maja Thiele[2] Aleksander Krag[4] Naim Alkhouri[3], [1]Evido Health, [2]Odense University Hospital, [3]Arizona Liver Health, [4]University of Southern Denmark

Background: Recruitment for clinical trials targeting moderate and severe fibrosis in steatotic liver disease (SLD) remains a major challenge due to high screen failure rates. Clinical trials often start by targeting individuals with cardiometabolic risk factors (CMRFs), followed by prescreening tools to enrich recruitment, but their performance varies across populations and disease prevalence. We evaluated LiverPRO, a non-invasive algorithm-based fibrosis tool, to improve recruitment efficiency compared to conventional strategies. **Methods:** We included two clinical cohorts from Denmark and the US, both representing populations at-risk of SLD. All participants underwent blood sampling and transient elastography (TE); liver biopsy was performed if TE ≥8 kPa (Denmark), or universally (US). To assess the impact of prevalence on diagnostic performance, we simulated three additional cohorts (n = 5,000 each) with predefined fibrosis prevalences (TE ≥8 kPa) of 10%, 30%, and 50%. We evaluated three recruitment pathways: no prescreening, FIB-4 ≥1.3, or LiverPRO ≥65%. In all three we considered follow-up Fibroscan-AST (FAST) test in those screening positive, and biopsy if FAST ≥0.35 to confirm significant fibrosis (≥F2). For each pathway and cohort, 500 trial recruitments were simulated to enroll 400 patients with significant fibrosis by sampling from a large population. Mean screen failure rates, number of FAST tests needed, and negative biopsies (F0-1) were compared across pathways and cohorts. **Results:** The Danish cohort included 4,612 individuals (52% male, median age 58 [interquartile range (IQR): 53 - 63] years) at-risk of SLD due to CMRFs, 322 (7%) had TE ≥8 kPa, and 147 (3%) biopsy-verified ≥F2. The US cohort included 495 participants (31% male, median age 58 [IQR: 49 - 65] years) with CMRFs at-risk of metabolic dysfunction-associated steatotic liver disease, 408 (82%) had TE ≥8 kPa and 356 (72%) had biopsy-verified ≥F2. When comparing the pathway simulations leading to 400 enrolled patients with biopsy confirmed significant fibrosis (≥F2), LiverPRO reduced the number of FAST tests by 31-89% compared to no prescreening and by 7-73% compared to FIB-4, with the greatest reductions observed in lower prevalence cohorts. Similarly, the number of negative (unnecessary) biopsies decreased by 53-66% versus no prescreening and by 7-51% versus FIB-4. Screen failure rates declined by 23-46 and 6-28 percentage points when using LiverPRO in prescreening versus no prescreening or FIB-4, respectively.
Conclusion: LiverPRO substantially improved screening efficiency across cohorts. For trial recruitment of SLD patients with ≥F2, employing LiverPRO resulted in lower screen failure rates, fewer FAST tests, and less negative biopsies than using no prescreening or FIB-4.



Disclosures: Julie Astono: Evido Health: Employee, Andreas Sand: Nothing to Disclose, Katrine Thorhauge: Nothing to Disclose, Georg Semmler: Amgen: Travel Support, Rida Nadeem: Nothing to Disclose, Aarya Patel: Nothing to Disclose, Manal Chughtai: Nothing to Disclose, Sahasraara Hemant: Nothing to Disclose, Yasmeen Fallouh: Nothing to Disclose, Himanshi Kapoor: Nothing to Disclose, Camilla Dalby Hansen: Nothing to Disclose, Johanne Hansen: Nothing to Disclose, Stine Johansen:

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◆ 2017 | IDENTIFICATION OF SIGNATURE GENES AND PATHWAYS IN THE PROGRESSION OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: A META-ANALYSIS IN LIVER TRANSCRIPTOMICS

Wei Zhang[1] Xiangwen Ji[2] Yangyang Sun[3] Leyi Wang[3] Xiangsha Kong[4] Lin Zhang[4] Zhengxi Wang[5] Long Zhang[3] Jing Zhou[4], [1]Peking University People's Hospital, Beijing, China, [2]Peking University Third Hospital, Beijing, China, [3]Peking University First Hospital, Beijing, China, [4]Peking University People's Hospital, Beijing, China, [5]Capital Medical University, Beijing, China

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is considered as the progression of steatosis and the primary driver of liver fibrosis. Then, changes of liver gene expression along with the progression of MASH should be not only as a predictor of liver histology but also as a potential target for treatment. By now, the association remains unclear. Therefore, the aim of our study was to explore differentially expressed genes (DEGs) in the progression of MASH patients (steatosis-steatohepatitis-fibrosis 3-4) whose histological features were assessed according to NASH CRN histological scoring systems. **Methods:** The Gene Expression Omnibus database (GEO) and PubMed were searched with key terms and MeSH terms. We combine results of individual studies using a random-effects model. The $\log_2$ fold changes ($\log_2$FC) and 95% confidence interval (CI) of genes between two groups were given and p value < 0.05 was considered as the significance cut-off for differential gene expression. For the gene functional enrichment analysis, we employed the single sample gene set enrichment

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analysis (ssGSEA) module. **Results:** The nine GEO datasets were included. Among 691 adult patients in these studies, 56% were female, and the ranges of age and BMI (mean) were 43.8 to 54 yrs and 30.2 to 47kg/m2, respectively. For metabolic abnormalities, 44.3% patients (274/618), 53.7% (139/259) and 56.6% (145/256) were diagnosed with diabetes, hyperlipidemia and hypertension, respectively. To identify DGEs and pathways which play important roles in the progress from steatosis to steatohepatitis and further severe fibrosis, we compared and overlapped results from the following meta-analyses: 1) NAS (0-3) versus Controls, 2) NAS (4-8) versus (0-3) and 2) Fibrosis stage (3 or 4) versus (0 or 1) in patients with NAS (4-8). 3,447, 5,639 and 4,474 DEGs were identified in the above comparisons. Among shared genes, 131 up-regulated and 83 down-regulated genes were identified (Fig.1) and the top 3 significant differentially expressed pathways included "low-density lipoprotein receptor particle metabolic process", "Release of apoptotic factors from the mitochondria" and "intracellular sphingolipid homeostasis". **Conclusion:** To the best of our knowledge, this is the first study to provide a comprehensive and robust analysis of DEGs in the progression of MASH patients whose histological features were assessed according to NASH CRN and identify important pathways in the progression.

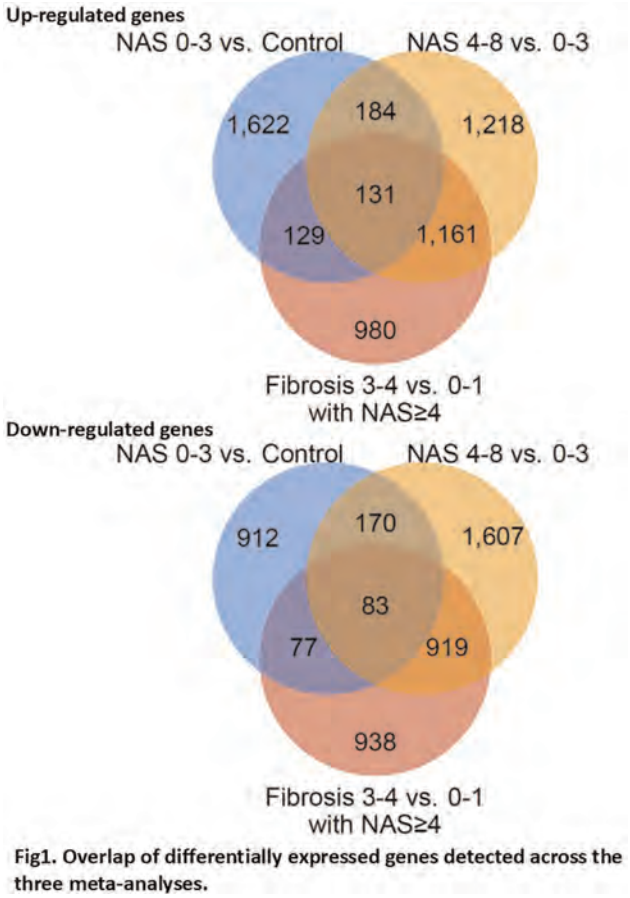

Fig1. Overlap of differentially expressed genes detected across the three meta-analyses.

Disclosures: Wei Zhang: Nothing to Disclose, Xiangwen Ji: Nothing to Disclose, Yangyang Sun: Nothing to Disclose, Leyi Wang: Nothing to Disclose, Xiangsha Kong: Nothing to Disclose, Lin Zhang: Nothing to Disclose, Zhengxi Wang: Nothing to Disclose, Long Zhang: Nothing to Disclose, Jing Zhou: Nothing to Disclose

◆ 2018 | THE SMELL OF MASLD: DISCRIMINATORY BREATH VOC SIGNATURE IN CHILDREN WITH MASLD; A PROSPECTIVE COHORT STUDY

Jennifer Panganiban[1] Amalia Berna[2] Sarah Abu Alreesh[1] Yang Liu[2] Aakanshya Aryal[2] Audrey Odom John[2], [1]Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia, [2]Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, US

Background: Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) is the most common cause of chronic liver disease in children, defined by hepatic steatosis with at least one cardiometabolic risk factor. Pediatric MASLD is often underrecognized, screening measures are inadequate and non-invasive tests validated in adults lack accuracy in pediatrics. Breath-based volatile organic compounds (VOCs) show promise for noninvasive diagnosis. A pediatric study by Alkhouri et al 2014, identified altered VOCs in presumed MASLD, diagnosed by ultrasound, using targeted analysis of 14 compounds. Our study builds on this by applying untargeted breath VOC analysis to better characterize diagnostic breath signatures in children. **Methods:** This is a prospective IRB-approved cohort study at the Children's Hospital of Philadelphia. Children aged 4–20 years were enrolled into either the MASLD or healthy control group. Inclusion criteria for the MASLD group were either: (1) BMI $\geq 85^{th}$ % for age and sex based on CDC growth charts, hepatic steatosis on imaging, Alanine aminotransferase (ALT) $\geq 2\times$ the upper limit of normal for sex (≥ 52 U/L for males ≥ 44 U/L for females); or (2) biopsy-confirmed MASLD $\leq$ 6 months from consent. Controls had BMI $\geq 85^{th}$% for age and sex based on CDC growth charts, normal hepatic ultrasound and normal ALT. Breath samples were analyzed via two-dimensional gas chromatography-mass spectrometry (GC×GC-MS). Raw data were processed using ChromSpace software (v2.0.1, SepSolve, UK). A Random Forest model was applied to evaluate the predictive capacity of identified VOCs. **Results:** 20 healthy controls and 22 MASLD patients were enrolled: 10 patients had biopsy-confirmed MASLD and 12 patients had non-biopsy MASLD. Breath analysis in children with MASLD had a distinct breath VOC profile than their healthy obese counterparts. Ten discriminatory molecules were found.

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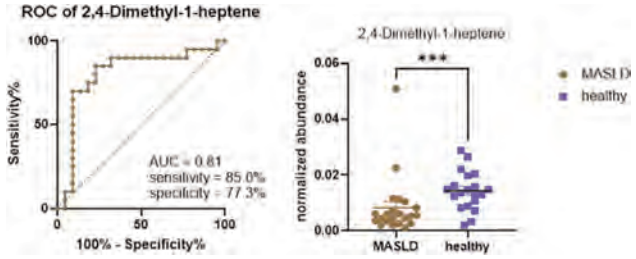
Random Forest applied to the data set indicates that VOCs can predict pediatric MASLD with 73% sensitivity and 65% specificity, with an area under the curve (AUC) of 0.84. Using the VOC with the highest Gini importance, 2,4-Dimethyl-1-heptene had a greater sensitivity of 85% and specificity 77.3% with AUC of 0.81. (Figure 1). **Conclusion:** This study demonstrates a distinct breath VOC signature associated with pediatric MASLD. These findings support the potential utility of breath analysis as an easy, noninvasive screening tool for MASLD in children. Limitations include the small sample size, and further studies are needed to validate these results.



Disclosures: Jennifer Panganiban: Nothing to Disclose, Amalia Berna: Nothing to Disclose, Sarah Abu Alreesh: Nothing to Disclose, Yang Liu: Nothing to Disclose, Aakanshya Aryal: Nothing to Disclose, Audrey Odom John: Nothing to Disclose

◆ 2019 | COMPARISON OF DIGITAL IMAGES VERSUS GLASS SLIDES FOR THE HISTOPATHOLOGICAL EVALUATION OF LIVER BIOPSY SAMPLES ACCORDING TO THE NASH-CRN SCORING SYSTEM FOR MASH: A VALIDATION PERFORMED AS PART OF THE NATIV3 STUDY

Carolin Lackner[1] Zachary Goodman[2] Dina Tiniakos[3] Prodromos Hytiroglou[4] Arun Sanyal[5] Sven Francque[6] Philippe Huot-Marchand[7] Lucile Dzen[7] Benoit Noel[7] Pierre Broqua[7] Martine Baudin[7] Michael Cooreman[8] Louis Griffel[7], [1]Medical University of Graz, [2]INOVA Fairfax Hospital, [3]Univeristy of Athens, GR & Visiting Professor, Translational & Clinical Res Inst, Newcastle Univ, UK, [4]Aristotle University of Thessaloniki, [5]Virginia Commonwealth University, [6]University of Antwerp, [7]Inventiva Pharma, [8]INVENTIVA

Background: Histopathologic assessment by liver biopsy remains the standard for diagnosis and assessing treatment response in metabolic dysfunction-associated steatohepatitis (MASH) clinical trials. Historically, this has been done by interpretation of glass slides. The development of digital technology has afforded a more efficient option that allows all pathologists to view a consistent digital image. **Methods:** As part of the NATiV3 trial (NCT04849728), we performed validation of histological scoring of digital images compared to glass slides of the same case. Three expert liver pathologists each scored 20 biopsies, each stained with hematoxylin & eosin and Masson trichrome. Glass slides representing the full MASH spectrum were used to generate digital images. Scoring of digital images and then of glass slides were performed at least 2-weeks apart, independently (results from 1st scoring not available at time of 2nd scoring) using both the NASH-CRN and SAF scoring systems. For each component (steatosis, lobular inflammation and ballooning grade, fibrosis stage), agreement rates between digital images and glass slides were calculated and intra-variability between the 2 scorings was measured with linear weighted Cohen's kappas and 95% confidence intervals. Results were pooled using the 3 pathologists' scores. **Results:** Agreement on fibrosis stage between digital images and glass slides was high with Kappa 0.81 [0.71-0.92] (agreement rate of 82%). Agreement on NAS steatosis, inflammation and ballooning were substantial with Kappas 0.68 [0.53-0.83], 0.63 [0.45-0.81] and 0.67 [0.52-0.81], respectively (agreements rates 77%, 83% and 72%). Similarly, agreements on SAF inflammation, ballooning and activity were substantial with Kappas 0.75 [0.57-0.93], 0.70 [0.52-0.88] and 0.72 [0.59-0.85], respectively (agreements rates 90%, 83% and 75%). Other studies that investigated intra-observer agreement on either glass slides or digital images reported ranges from 0.62 to 0.88 for steatosis, 0.21 to 0.76 for inflammation, 0.27 to 0.79 for ballooning, and 0.48 to 0.87 for fibrosis. [Ref 1.Langford 2022, 2.Kleiner 2019, 3.Davison 2020, 4.Iyer 2024, 5. Pulaski 2024] **Conclusion:** Concordance rates observed in our project between digital images and glass slides are comparable to or higher than published NASH CRN concordance estimates. These data support that the use of digital images does not introduce additional variability and is equivalent to glass slides, highlighting their suitability in clinical MASH trials.

Disclosures: Carolin Lackner: Inventiva: Consultant, Novo Nordisk: Consultant, 89bio: Consultant, Akero: Consultant, Regeneron: Consultant, Boehringer Ingelheim: Consultant, Zachary Goodman: Nothing to Disclose, Dina Tiniakos: Inventiva: Consultant, ICON: Consultant, CymaBay: Consultant, Prodromos Hytiroglou: Inventiva: Independent Contractor, ICON: Independent Contractor, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),:

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◆ 2020 | ZONE-SPECIFIC FIBROSIS REDUCTIONS INDUCED BY PEGOZAFERMIN OVER 24 WEEKS ARE SIMILAR IN NON-CIRRHOTIC (F2/F3) AND CIRRHOTIC (F4) MASH

Quentin Anstee[1] Maya Margalit[2] Arun Sanyal[3] Vlad Ratziu[4] Mildred Gottwald[2] Elaine Chng[5] Yukti Choudhury[5] Harpreet Nagra[2] Cynthia Hartsfield[2] Dean Tai[5] Hank Mansbach[2] Rohit Loomba[6], [1]Newcastle University, UK, [2]89bio, [3]Virginia Commonwealth University, [4]Service D' Hepatogastroenterologie (FR), [5]HistoIndex, [6]University of California, San Diego

Background: In the ENLIVEN trial, pegozafermin (PGZ), a glycoPEGylated FGF21 analog administered at 30mg every week (QW) or 44mg every 2 weeks (Q2W) for 24 weeks significantly improved fibrosis without worsening of MASH in F2-F3 patients. qFibrosis features in the portal, periportal, and zone 2 regions have previously been reported to be predictive of hepatic decompensation and all-cause mortality[1]. In this post-hoc study, qFibrosis zonal analysis was conducted to assess hepatic zone-specific effects of PGZ in non-cirrhotic and cirrhotic MASH. [1] Kendall et al. Liver Int. 2024. **Methods:** Paired, unstained biopsies from baseline (BL) and week 24 for qFibrosis analysis were available for a subset of subjects in ENLIVEN: 1) F2-F3 subjects [n = 122; placebo (PBO, n = 46), 30mg QW (n = 45), 44mg Q2W (n = 31)], and 2) F4 patients at BL (as re-read by a 3-panel consensus, not included in ENLIVEN main results) [n = 7; PBO (n = 1), 30mg QW and 44mg Q2W pooled (n = 6)]. Biopsies were imaged using second harmonic generation/two-photon excitation fluorescence microscopy and fibrosis changes were assessed across 5 hepatic zones: portal zone, periportal (zone 1), peri-sinusoidal (zone 2), central zone, and peri-central (zone 3). Steatosis-correction was applied to account for the effect of large reductions in steatosis by PGZ, on fibrosis quantification. **Results:** By qFibrosis zonal analysis, treatment of pathologist-determined F2-F3 patients with PGZ (30 mg QW and 44 mg Q2W) for 24 weeks led to significant reductions in fibrosis specifically in the portal zone, zone 1, and zone 2, compared to baseline ($p < 0.05$). No reduction was observed in PBO. In pathologist-determined F4 patients, similar pronounced fibrosis regression was seen in zones 1 and 2, with modest reductions in the other zones. Findings were aligned in subjects identified as qFibrosis stage F2/F3 or F4 at baseline. **Conclusion:** PGZ led to consistent patterns of qFibrosis portal zone, peri-portal (zone 1), and peri-sinusoidal (zone 2) regression in non-cirrhotic (F2-F3) and cirrhotic (F4) patients with MASH at 24 weeks. This is the first report of qFibrosis regression in these clinically meaningful zones induced by a therapeutic intervention in MASH cirrhosis. PGZ is currently being studied in Phase 3 studies in non-cirrhotic and cirrhotic MASH.

Disclosures: Quentin Anstee: AstraZeneca, Boehringer Ingelheim, Intercept.: Grant/Research Support, Alimentiv, Akero, AstraZeneca, Axcella, 89Bio: Consultant, Boehringer Ingelheim, Bristol Myers Squibb, Corcept: Consultant, Enyo Pharma, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKl: Consultant, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janss: Consultant, Madrigal, Medpace, Merck, Metadeq, NGMBio, North Sea T: Consultant, Novartis, Novo Nordisk, PathAI, Pfizer, Pharmanest: Consultant, Poxel, Prosciento, Resolution Therapeutics, Roche,: Consultant, Ridgeline Therapeutics, RTI, Shionogi, Terns: Consultant, Fishawack, Integritas Communications, Kenes,: Speaking and Teaching, Novo Nordisk, Madrigal, Medscape, Springer Healthcare: Speaking and Teaching, Elsevier Ltd: Royalties or patent beneficiary, Maya Margalit: 89bio Inc.: Stock and options holder, 89bio Inc.: Stock and options holder, 89bio Inc.: Employee, 89bio Inc.: Stock - publicly traded company, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above

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◆ ★ 2021 | VALIDATION OF AGILE-3+ AND AGILE-4 SCORES FOR NONINVASIVE DETECTION OF FIBROSIS AND CIRRHOSIS IN METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN LATIN AMERICA

Luis Antonio Diaz[1] Carlos Esteban Coronel-Castillo[2] Natalia Baeza[1] Francisco Idalsoaga[1] Daniel Cabrera[3] Fernando Barreyro[4] Sebastián Marciano[5] Jorge Martinez[5] Cristiane Villela-Nogueira[6] nATHALIE Carvalho Leite[6] Gil Salles[6] Claudia Cardoso[6] Claudia Couto[7] Rafael Theodoro[8] Misia Joyner de Sousa Dias Monteiro[8] Mario Pessoa[9] Mario Alvares-da-Silva[10] Bruno Basso[10] Gabriella Jonko[10] Fatima Higuera de la Tijera[2] Constanza Sabate[11] Manuel Mendizabal[11] Mazen Noureddin[12] Naim Alkhouri[13] Winston Dunn[14] Rohit Loomba[15] Claudia Oliveira[16] Adrián Gadano[5] Marco Arrese[1] Juan Pablo Arab[17], [1]Pontificia Universidad Católica de Chile, [2]Hospital General de México "Dr. Eduardo Liceaga", [3]Universidad de los Andes, [4]Universidad Nacional de Misiones, [5]Hospital Italiano de Buenos Aires, [6]Hospital Universitário Clementino Fraga Filho, [7]Federal University of Minas Gerais, [8]Hospital das Clínicas da Universidade Federal de Minas Gerais, [9]Universidade de São Paulo, [10]Hospital de Clínicas de Porto Alegre, [11]Hospital Universitario Austral, [12]Houston Methodist Hospital, [13]Summit Clinical Research, [14]University of Kansas Medical Center, [15]University of California San Diego, [16]University of Sao Paulo School of Medicine, [17]Virginia Commonwealth University

Background: Early detection of liver fibrosis in MASLD is crucial for preventing progression to cirrhosis. The Agile-3+ and Agile-4 scores are designed to identify advanced fibrosis and cirrhosis, respectively, but their performance in Latin American populations is unknown. This study aimed to validate Agile-3+ and Agile-4 scores in predicting advanced fibrosis and cirrhosis in a well-characterized cohort of Latin American patients with MASLD. **Methods:** We conducted a multicenter cross-sectional study with patients from 10 centers across Brazil, Argentina, Chile, and Mexico, all diagnosed with MASLD according to the 2023 definition. Liver fibrosis was assessed using liver biopsy and liver stiffness measurements (LSMs) by vibration-controlled transient elastography (VCTE) and liver biopsy was used as the standard for grading fibrosis. Biochemical and clinical studies were obtained to calculate FIB-4, Agile-3+, and Agile-4 scores. The diagnostic efficacy of non-invasive indices in detecting advanced fibrosis ($\geq$F3) and cirrhosis (F4) was evaluated using receiver operating characteristic (ROC) curve analysis and Youden index. **Results:** We included 770 adults with MASLD, with a median age of 59 years [51–66], 60% were men, and 64.5% were Hispanic. The median body mass index (BMI) was 33.3 $\pm$ 8.2 kg/m² and 69.6% had type 2 diabetes mellitus. The median liver stiffness on VCTE was 9.1 kPa [IQR 6.9–12.6]; 29.9% of participants had advanced fibrosis and 10.5% had cirrhosis. When comparing performance in predicting advanced fibrosis, Agile-4 had the highest performance (AUROC 0.765, 95%CI: 0.725–0.805; p = 0.037) compared to LSM by VCTE alone, while Agile-3+ did not show significant differences (AUROC 0.754, 95%CI:

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0.715–0.793; p = 0.213) (Figure A). Accuracy improved for cirrhosis, where Agile-4 achieved an AUROC of 0.875 (95% CI: 0.836–0.914, p = 0.003), outperforming Agile-3+ (AUROC 0.856, 95% CI: 0.813–0.899, p = 0.100) (Figure B). For Agile-4, the optimal cut-off to rule out cirrhosis (90% sensitivity) was ≥ 0.159, and the optimal cut-off to rule in cirrhosis (90% specificity) was ≥ 0.366. **Conclusion:** In this Latin American MASLD cohort, the Agile-4 score demonstrated superior noninvasive rule-out performance for advanced fibrosis and cirrhosis. Incorporating these Agile-4 thresholds into VCTE-based algorithms could reduce unnecessary biopsies and streamline MASLD care pathways across resource-variable settings (FONDECYT 1241450).

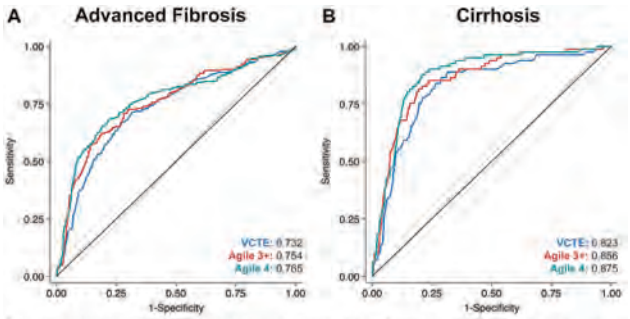

Figure. Receiver-operating characteristic curves comparing the performance of vibration-controlled transient elastography (VCTE) liver stiffness measurements with Agile-3+ and Agile-4 scores in predicting (A) advanced fibrosis and (B) cirrhosis.

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◆ 2022 | SINGLE CIRCULATING BIOMARKERS SVCAM-1 AND TSP2 ACHIEVED EFFECTIVE PROGNOSTIC PERFORMANCES FOR THE DETECTION OF FIBROSIS PROGRESSION TO CIRRHOSIS

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Background: Cirrhosis (F4) is the main source of complications and mortality for patients (pts) with chronic liver diseases. An early detection of pts at high risk of progression to F4 could optimize clinical management and reduce related health-care burden. We compared the prognostic performance of 40 single circulating biomarkers (BMs) vs ELF™ and VCTE-based tests for progression to cirrhosis in pts with MASH and fibrosis (F). **Methods:** Pts with non-cirrhotic MASH enrolled in the RESOLVE-IT Phase 3 trial (NCT02704403), with paired liver biopsies (baseline and end of study [EOS]) and available data at baseline for ELF, VCTE, Agile3+, Agile4 and 40 circulating BMs, were selected (N = 739). Placebo and treated arms were included as the evaluated agent did not significantly impact fibrosis evolution. AUC and associated Delong tests were used to compare the overall performance of the BMs vs ELF, VCTE, Agile3+ and Agile4 for the detection of fibrosis progression towards

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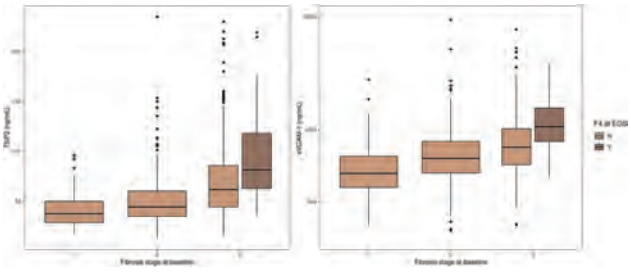
F4. For BMs with AUC not significantly lower than ELF, a single cutoff was derived to achieve same sensitivity (sen) as ELF at its threshold indicative of increased risk of progression to cirrhosis (9.8). Corresponding specificity (spe), PPV and NPV were computed. A subpopulation matched for baseline histology and clinical characteristics between progressors and non-progressors to F4 was also extracted using a propensity score matching (PSM) algorithm. **Results:** Mean follow-up was 19 months. All pts had MASH with F1-3 at baseline, mean age was 55 y and 54% were male. 5.4% of pts (n = 40) progressed to F4 at EOS; 40% of progressors were male, mean age was 59 y and all had F3 at baseline. ELF at baseline achieved an AUC of 0.778 for the detection of pts who progressed to F4 and had a spe of 0.61 and a sen of 0.78 at a cutoff of 9.8. Among the 40 BMs evaluated, 6 achieved similar AUC to ELF and were kept for further analyses: TSP2 (0.785, p = 0.86), sVCAM-1 (0.782, p = 0.90), YKL40 (0.739, p = 0.44), TIMP1 (0.736, p = 0.24), GGT (0.733, p = 0.37) and P3NP (0.725, p = 0.11). Among these BMs, only sVCAM-1 at a cutoff of 896 ng/mL and TSP2 at a cutoff of 63 ng/mL achieved significantly higher spe than ELF (resp: 0.69 vs 0.61, p < 0.001; 0.68 vs 0.61, p = 0.002) for the same sen. Among VCTE-based tests, Agile4 achieved the highest AUC (0.835). TSP2 and sVCAM-1 were the only BMs with AUC not significantly lower than Agile4. The PSM algorithm resulted in a cohort of n = 117 pts (39 progressors and 78 non-progressors to F4) with F3 at baseline, well-balanced for clinical characteristics. Within this population, a similar overall ranking was observed with VCTE-based tests performing best, followed by sVCAM-1, TSP2 and ELF. **Conclusion:** Single biomarkers sVCAM-1 and TSP2 predicted progression to cirrhosis with similar performance as VCTE-based tests (Agile4, Agile3+ and VCTE) and the composite marker ELF™, an FDA-approved tool for this indication. These two circulating BMs could represent valuable tools to predict progression to cirrhosis.



Disclosures: Vlad Ratziu: Novo-Nordisk: Consultant, Boehringer-Ingelheim: Consultant, Madrigal: Consultant, Akero: Consultant, 89Bio: Consultant, Sagimet: Consultant, Sven Francque: Nothing to Disclose, Bérénice Alard: GENFIT SA: Employee, Jérémy Magnanensi: Nothing to Disclose, Zouher Majd: Genfit: Employee, Genfit: Employee, Genfit: Employee, Genfit: Stock – privately held company, Dean Hum: Nothing to Disclose, Bart Staels: Genfit SA: Consultant, Quentin Anstee: AstraZeneca, Boehringer Ingelheim, Intercept.: Grant/Research Support, Alimentiv, Akero, AstraZeneca, Axcella, 89Bio: Consultant, Boehringer Ingelheim, Bristol Myers Squibb, Corcept: Consultant, Enyo Pharma, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKl: Consultant, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janss: Consultant, Madrigal, Medpace, Merck, Metadeq, NGMBio, North Sea T: Consultant, Novartis, Novo Nordisk, PathAI, Pfizer, Pharmanest: Consultant, Poxel, Prosciento, Resolution Therapeutics, Roche,: Consultant, Ridgeline Therapeutics, RTI, Shionogi, Terns: Consultant, Fishawack, Integritas Communications, Kenes,: Speaking and Teaching, Novo Nordisk, Madrigal, Medscape, Springer Healthcare: Speaking and Teaching, Elsevier Ltd: Royalties or patent beneficiary, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (< 5K), Terns (< 5K), Merck (< 5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (< 5K),: Consultant, Novo Nordisk: Consultant, Regeneron (< 5K), Alnylam (< 5K), Akero (< 5K),: Consultant, Tern (< 5K), Histoindex (< 5K), Corcept (< 5K),: Consultant, Path AI (< 5K), Genfit (< 5K), Mediar (< 5K),: Consultant, Satellite Bio (< 5K), Echosens (< 5K), Abbott (< 5K),: Consultant, Promed (< 5K), Glaxo Smith Kline (~11K), Arrowhead (< 5K): Consultant, Zydus (> 60K), Boston Pharmaceutical (< 5K), Myovent (< 5K),: Consultant, Variant (< 5K), Cascade (< 5K), Northsea (< 5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor

◆ 2023 | LIBRA (LIVER BREATH ANALYSIS) ASSESSMENT OF LIVER DYSFUNCTION FOR CIRRHOSIS DETECTION IN AT-RISK POPULATIONS

Giuseppe Ferrandino[1] Federico Ricciardi[1] Antonio Murgia[1] Edward Jackson[1] Liz Thompson[1] Olga Gandelman[1] M. Consuelo Cuquerella[1] Alice Thornton Smith[1] Daniela Fonseca[1] Huw Davies[1] Max Allsworth[1] Billy Boyle[1] Claudia ASENJO-LOBOS[2] Francisca Bascur[3] Daniela Riquelme[3] Alexandra Ginesta[4] Luis Mendez[4] Arun Shankar[5] Tapas Das[6] Naim Alkhouri[7],

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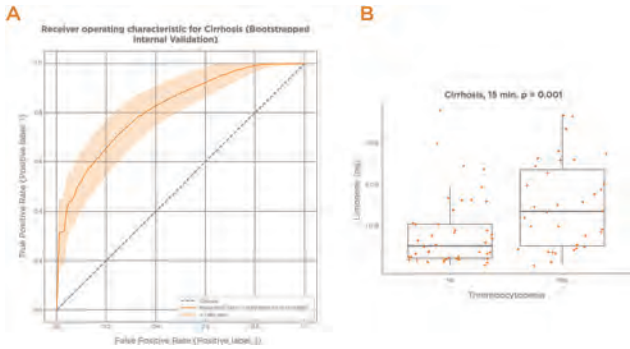
Background: Current methods for evaluating chronic liver disease primarily focus on structural alterations, markers of hepatic injury, or general biochemical indicators, providing limited information on the hepatic functional reserve. LIBRA is a novel non-invasive breath test designed to assess liver impairment by quantifying the metabolism of orally administered Exogenous Volatile Organic Compounds (EVOCs), which are processed by the liver and detected in exhaled breath. This study evaluates the diagnostic performance of LIBRA in identifying liver dysfunction associated with cirrhosis among individuals with relevant risk factors and clinical symptoms. **Methods:** This case-control multicentre study enrolled 171 participants with chronic liver disease of different aetiologies. Of these, 83 had cirrhosis confirmed through clinical and imaging assessments. Breath was sampled before, 15, and 30 minutes after EVOCs ingestion. Samples were analysed using thermal desorption-gas chromatography-mass spectrometry (TD-GC-MS), and classification models were refined using lasso logistic regression with bootstrap resampling **Results:** Presence of cirrhosis alters EVOCs breath levels at 15 min with higher limonene (Median: cirrhosis 862 ng, control = 326 ng ($p = 3.1e-7$)), and reduced conversion of 2-butanol (Median: cirrhosis 33.2 ng, control = 15.5 ng ($p = 2.2e-4$)) into its metabolite 2-butanone (Median: cirrhosis 491.7 ng, control = 995.4 ng ($p = 1.5e-4$)). LIBRA identified subjects with cirrhosis with an AUC of 0.82 (95% CI: 0.73-0.90) a sensitivity of 68% (95% CI: 47-86%), and a specificity of 79% (95% CI: 61-94%) at Youden index (Fig.1a). Across the cohort, EVOCs were associated with fibrosis stage estimated using FibroScan® ($p < 0.05$). In the cirrhosis group, breath limonene at 15 minutes correlated with FIB-4 ($r = 0.55$) and platelet count ($r = 0.65$). Analysis of Covariance (ANCOVA) showed a significant effect of platelet count on breath limonene levels in relation to cirrhosis status ($p = 0.04$). Within the cirrhosis group, subjects with thrombocytopenia showed higher limonene levels compared to those with normal platelets count ($p = 0.001$) (Fig.1B). **Conclusion:** The presented data demonstrates LIBRA clinical utility in assessing liver dysfunction associated with cirrhosis. Correlations between exhaled EVOCs and fibrosis staging support breath analysis to assess liver disease severity. Moreover, limonene association with thrombocytopenia, a well-established marker of portal hypertension, indicates its potential utility in monitoring this cirrhosis-related complication.



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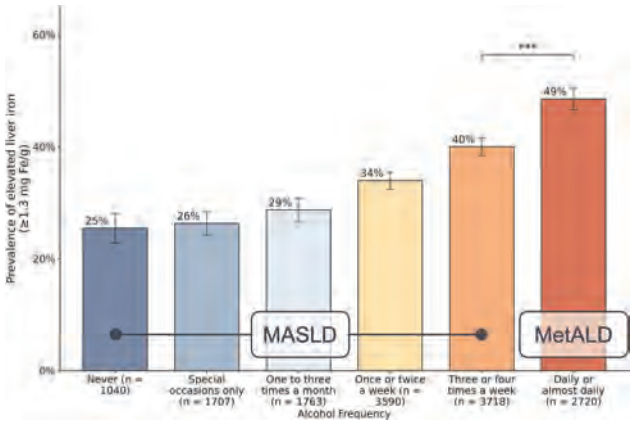
◆ 2024 | LIVER IRON CONCENTRATION CHARACTERISES PROGRESSION OF MASLD TO METALD

Edward Jackson[1] Anneli Andersson[1] Helena Thomaides Brears[1] Jacqueline O'Leary[2] Niharika Samala[3] Rohit Loomba[4] Vinod Rustgi[5] Carlos Duncker[6] Andrea Dennis[1] Rajarshi Banerjee[1], [1]Perspectum, Oxford, UK, [2]University of Texas Southwestern, Dallas, TX, USA, [3]Indiana University School of Medicine, Bloomington, IN, USA, [4]University of California at San Diego, CA, USA, [5]Rutgers Robert Wood Johnson Medical School, NJ, USA, [6]Pinnacle Clinical Research, San Antonio, TX, USA

Background: MetALD describes individuals whose liver pathology is in a continuum between metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD), depending on alcohol consumption. Diagnosis of MetALD poses challenges due to the limited reliability of self-reported alcohol consumption. Quantitative multiparametric MRI is increasingly used to diagnose and monitor chronic liver disease, with biomarkers of liver fat, iron and fibro-inflammation. Using population data from the UK biobank, this study aimed to identify how MRI biomarkers of liver health discern MASLD from MetALD and to risk stratify major liver related events (LRE) and new-onset diabetes. **Methods:** Multiparametric MRI (LiverMultiScan) was used to measure iron-corrected T1 (cT1, ms), liver fat content (LFC, %) and liver iron content (LIC, mg Fe/g) in 60,595 UK biobank participants. Self-reported daily/almost daily alcohol consumption stratified MetALD from MASLD in individuals with LFC >5% and at least one cardiometabolic risk factor. Associations between biomarkers and new onset diabetes and LRE were investigated using Cox proportional hazard models adjusted for age, sex and BMI. Adjusted hazard ratios (HR) are reported. **Results:** MASLD was diagnosed in 11,818 participants (aged 65 years, 57% male, 96% White) and MetALD in 2,720 (aged 67 years, 71% male, 98% White). After matching for age, sex, BMI and metabolic risk factors, patients with MetALD had small but statistically significant differences, a higher LFC (11.5 vs. 10.7%) and lower cT1 (740 vs. 748ms), higher LIC (1.36 vs 1.29 mg Fe/g), with a higher proportion of patients with hepatic iron above the 1.3 mg Fe/g threshold (49% vs 36%) (Figure 1). Higher cT1 was associated with LRE in MetALD (HR 2.4 (1.3, 4.4)) and in MASLD (HR 2.4 (1.3, 4.4)), LFC and cT1 were both associated with new onset diabetes (HR per SD increase, LFC 1.3 (1.1, 1.5) cT1: 1.5 (1.2, 1.9)). Increased LIC however was not associated with any outcome. **Conclusion:** In a large-scale population study, we find individuals with MetALD have significantly higher levels of LIC compared to MASLD. cT1 predicted LREs and both cT1 and LFC predicted new onset diabetes, similarly in both MASLD and MetALD. Liver iron content may accelerate disease, so should be measured in people with suspected MetALD.



Disclosures: Edward Jackson: Perspectum Ltd.: Employee, Anneli Andersson: Nothing to Disclose, Helena Thomaides Brears: Perspectum: Employee, Perspectum: Stock – privately held company, Jacqueline O'Leary: Genfit: Consultant, Grifols: Advisor, CVS: Stock - publicly traded company, Mallinckrodt: Advisor, Novo Nordisk: Advisor, PharmaIn: Advisor, Grifols: Consultant, Cellion: Advisor, Mallinckrodt: Advisor, PharmaIn: Consultant, Genfit: Consultant, PharmaIn: Consultant, Genfit: Consultant, Niharika Samala: Novo Nordisk: Consultant, Rohit Loomba: Nothing to Disclose, Vinod Rustgi: Nothing to Disclose, Carlos Duncker: Nothing to Disclose, Andrea Dennis: Nothing to Disclose, Rajarshi Banerjee: Nothing to Disclose

2025 | FAST AND CAP SCORES AS EARLY BIOMARKERS OF TREATMENT RESPONSE IN MASLD PATIENTS RECEIVING RESMETIROM: A REAL-WORLD STUDY

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Background: Resmetirom is the first FDA-approved medication for non-cirrhotic metabolic dysfunction-

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associated steatohepatitis (MASH) patients with significant (F2) to advanced (F3) fibrosis. Current AASLD guidance recommends assessing response at one year; however, reliable biomarkers indicating earlier clinical improvement are critically needed. This study evaluated the sensitivity of biomarkers, including liver enzymes (ALT, AST), fibrosis indicators (FIB4, Agile3, FAST), controlled attenuation parameter (CAP), and liver stiffness measurements (LSM) at 3 and 6 months post-treatment initiation in a real-world cohort. **Methods:** This observational study enrolled MASLD patients treated at six U.S. tertiary hepatology clinics (March–November 2024). Demographic data, laboratory values, LSM, CAP, and medications were collected at baseline, 3, and 6 months. Inclusion required meeting at least one AASLD criterion: (1) LSM 8–20 kPa, (2) ELF 9.2–11.3, or (3) biopsy fibrosis stage F2–F3. Paired t-tests assessed changes from baseline. Cohen's d (mean change divided by standard deviation) quantified standardized response magnitude independently of sample size. Treatment discontinuations were documented. **Results:** 485 patients initiated Resmetirom; 9 discontinued treatment. Baseline means were: ALT 53.9 U/L (SD 41.2), AST 43.7 U/L (SD 30.3), CAP 324 dB/m (SD 41.2), FAST 0.52 (SD 0.19), Agile3 0.56 (SD 0.22), and LSM 13 kPa (SD 9.6). At 3 months, FAST was the most responsive biomarker, demonstrating the largest standardized improvement (Cohen's d -0.64, $p = 0.0002$), followed by CAP score (Cohen's d -0.42, $p = 0.0008$). At 6 months, CAP emerged as the top-performing biomarker with even greater improvement (Cohen's d -0.94, $p < 0.0001$), followed by FAST (Cohen's d -0.63, $p < 0.0001$). ALT also improved at both 3 months (Cohen's d -0.19, $p = 0.008$) and 6 months (Cohen's d -0.42, $p < 0.0001$). Fibrosis-related biomarkers (LSM, Agile3, FIB4) showed minimal responsiveness within 6 months (Table 1). **Conclusion:** FAST was the most responsive biomarker at 3 months, while CAP provided the greatest standardized response at 6 months, highlighting their potential utility as early indicators of Resmetirom treatment effectiveness. Fibrosis markers showed minimal short-term changes, suggesting that fibrosis improvement may require longer treatment duration. Incorporating FAST and CAP into clinical practice could facilitate earlier assessment and optimization of therapy.

Month	Biomarker	N	Cohen's d	p-value	Interpretation
3	**FAST**	71	-0.64	0.0002	Largest early improvement
3	CAP Score	71	-0.42	0.0008	Moderate early improvement
6	**CAP Score**	74	-0.94	<0.0001	Largest overall improvement
6	FAST	74	-0.63	<0.0001	Continued large improvement
6	ALT	96	-0.42	<0.0001	Moderate delayed improvement

Note:

- Cohen's d indicates the magnitude of standardized improvement. Larger negative values represent greater treatment response.

Disclosures: Winston Dunn: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, GSK: Grant/Research Support, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, Avera Medical Group: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other, Imad Asaad: Madrigal: Speaking and Teaching, Edward Mena: Nothing to Disclose, Amreen Dinani: Madrigal Pharmaceutical: Consultant, Madrigal Pharmaceutical: Consultant, Novonordisk: Consultant, Novonordisk: Consultant, Kinetic: Advisor, Kinetic: Advisor, Madrigal Pharmaceutical: Consultant, Madrigal Pharmaceutical: Consultant, Novonordisk: Consultant, Novonordisk: Consultant, Kinetic: Advisor, Kinetic: Advisor, Savannah Nelson: Nothing to Disclose, Karthikeya Kodali: Nothing to Disclose, Rayan Ahmed: Nothing to Disclose, Phuong Nguyen: Nothing to Disclose, Wamda Ahmed: Nothing to Disclose, Sheel Patel: Nothing to Disclose, Sonal Kumar: Gilead Sciences: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Grant/Research Support, Gilead Sciences: Grant/Research Support, Madrigal Pharmaceuticals: Advisor, Gilead Sciences: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Ipsen: Advisor, Ipsen: Speaking and Teaching, Ipsen: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Intercept Pharmaceuticals: Speaking and Teaching, Intercept Pharmaceuticals: Advisor, Cymabay Therapeutics: Advisor, Cymabay Therapeutics: Grant/Research Support, Akero Therapeutics: Grant/Research Support, GSK: Consultant, GSK: Speaking and Teaching, Boehringer Ingelheim: Consultant, Madhavi Rudraraju: Nothing to Disclose, Mazen Noureddin: Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor: Terns,Takeda, Zydus., Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK: Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, Rivus Pharma, Cytodyn, and ChronWell: Stock – privately held company, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharmaceuticals: Consultant, Cytodyn: Consultant, GSK: Consultant, Eli Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Terns: Consultant, Takeda: Consultant, Allergan: Principal Investigator for a Drug Study, Akero: Principal Investigator for a Drug Study, BI: Principal Investigator for a Drug Study, BMS: Principal Investigator for a Drug Study, Gilead: Principal Investigator for a Drug Study, Galectin: Principal Investigator for a Drug Study, Genfit: Principal Investigator for a Drug Study, GSK: Principal Investigator for a Drug Study, Conatus:

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2026 | ALLYL NONANOATE: A BILE METABOLITE AND POTENTIAL BIOMARKER FOR HEPATIC FIBROSIS IN MASLD

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Background: Metabolic dysfunction-associated steatosis (MASLD) is a prevalent chronic liver disease with limited treatment options due to unclear pathophysiology. Bile acids play a critical role in MASLD progression; however, we hypothesized that serum or fecal bile acids may not directly reflect hepatic bile acid signaling due to their multi-step metabolic processing. To address this, we conducted metabolomic analysis to investigate distinguishing bile metabolites obtained from gallbladder samples of biopsy-proven MASLD patients compared to healthy controls. **Methods:** Primary bile samples and liver biopsies were collected from 68 patients undergoing cholecystectomy, including 19 healthy controls and 49 MASLD patients with varying degrees of hepatic fibrosis. Metabolomic profiling of bile acids was conducted using mass spectrometry to identify metabolites associated with hepatic fibrosis. RNA sequencing was performed on HT29 cells treated with the identified metabolite, and its fibrotic effects were further investigated using the human hepatic stellate cell line LX-2. **Results:** Among the metabolites increased in patients with fibrosis (139 in mild fibrosis and 173 in significant fibrosis) compared to controls, eight bile metabolites showed a positive dose-dependent correlation with fibrosis severity. Allyl nonanoate was ultimately identified as an elevated metabolite in fibrosis patients. Gene set enrichment analysis revealed downregulation of pathways related to cell cycle progression, including the G2/M checkpoint. In vitro, allyl nonanoate demonstrated a dose-dependent reduction in the mRNA expression of fibrosis markers FN1 and Col1A1. **Conclusion:** This study identified allyl nonanoate as a bile metabolite associated with hepatic fibrosis in MASLD patients. These findings highlight the

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potential of primary bile samples as a valuable resource for identifying novel biomarkers and therapeutic targets. **Disclosures:** Dae Won Jun: Nothing to Disclose, Hyo Young Lee: Nothing to Disclose, Hyun Woo Oh: Nothing to Disclose, Eileen Yoon: Nothing to Disclose, Sang Bong Ahn: Nothing to Disclose, HA IL KIM: Nothing to Disclose

2027 | DEVELOPMENT AND VALIDATION OF QINFLAMMATION: AN AI-DRIVEN DIGITAL PATHOLOGY ALGORITHM FOR DIFFERENTIATING PORTAL AND LOBULAR INFLAMMATION IN METABOLIC-ASSOCIATED STEATOHEPATITIS

Yayun Ren[1] Kutbuddin Akbary[1] Karoline Lackner[2] Daniela Allende[3] Feng Liu[4] David Kleiner[5] Dean Tai[6], [1]HistoIndex Pte Ltd, [2]Medical University of Graz, [3]Cleveland Clinic, [4]Peking University People's Hospital, [5]National Cancer Institute, Bethesda, [6]HistoIndex

Background: Accurate histopathological assessment is critical for evaluating treatment response in metabolic-associated steatohepatitis (MASH), yet differentiating lobular and portal inflammation—key markers of disease progression—remains challenging with traditional microscopy. AI-driven digital pathology enables standardized, reproducible quantification of histological features. This study describes the first-round development and performance of the qInflammation (qI) algorithm, with two additional optimization rounds planned. **Methods:** The qI algorithm was developed to detect portal and lobular inflammation in H&E-stained liver tissue digital images (3–5 mm tissue length, cropped from whole slides). Three rounds of iterative optimization were planned; the first round included 30 unrotated and 8 90°-rotated images. Three expert pathologists (DK, CL, DA) independently labeled labeled each algorithm-identified inflammation foci as "YES" (correct identification of portal/lobular inflammation focus), "NO" (algorithm-identified region not representing inflammation focus), or "Misclassification" (algorithm misassigned portal focus as lobular or vice versa). Performance metrics—true positive ratio (TPR), false positive ratio (FPR), misclassification ratio (MR)—were validated against pathological consensus, with algorithm updates applied in subsequent planned rounds. **Results:** In Round 1, unrotated images (n = 30) showed portal inflammation grades: I0 (33%), I1 (37%), I2 (30%); lobular grades: I0 (20%), I1 (30%), I2 (27%), I3 (23%). qI detected 155 portal and 614 lobular foci, with strong Spearman correlations between histological grades and focus counts (portal: $\rho = 0.87$; lobular: $\rho = 0.86$). Rotated images (n = 8) retained 87% focus detection, confirming rotational invariance. Pathologist-specific metrics for portal inflammation: TPRs 61% (DK), 73% (CL), 84% (DA); FPRs 26%, 10%, 5%; MRs 14%, 17%, 11%. For lobular inflammation: TPRs 45% (DK), 64% (CL), 68% (DA); FPRs 40%, 28%, 23%; MRs 15%, 8%, 10%. Consensus agreement (≥ 2 pathologists) yielded portal metrics: TPR = 77%, FPR = 8%, MR = 12%; lobular: TPR = 60%, FPR = 28%, MR = 9%. **Conclusion:** The first-round evaluation demonstrates qI's robust potential for automated quantification of portal/lobular inflammation in MASH. Planned subsequent optimization rounds will focus on enhancing lobular inflammation detection accuracy to further improve algorithm performance.

Table: True positive ratio (TPR), false positive ratio (FPR) and misclassification ration (MR) for portal inflammation and lobular inflammation were determined by the pathologists (DK – David Kleiner; CL - Carolin Lackner; DA - Daniela S. Allende).

Determined by	Portal Inflammation			Lobular Inflammation		
	TPR	FPR	MR	TPR	FPR	MR
DK	61%	26%	14%	45%	40%	15%
CL	73%	10%	17%	64%	28%	8%
DA	84%	5%	11%	68%	23%	10%
At least 1 pathologist	89%	31%	23%	77%	46%	19%
At least 2 pathologists	77%	8%	12%	60%	28%	9%
All 3 pathologists	51%	2%	6%	39%	16%	5%

Disclosures: Yayun Ren: HistoIndex Pte Ltd: Employee, Kutbuddin Akbary: HistoIndex Pte Ltd: Employee, Karoline Lackner: Nothing to Disclose, Daniela Allende: Mayo Clinic: Speaking and Teaching, Univ. of Ottawa: Speaking and Teaching, Educational Symposia: Speaking and Teaching, Feng Liu: Nothing to Disclose, David Kleiner: Nothing to Disclose, Dean Tai: Nothing to Disclose

2028 | IMPROVING THE PREDICTION OF MASLD WITH ADVANCED FIBROSIS AMONG PRIMARY CARE PATIENTS WITH OBESITY, DIABETES, OR BOTH: A PROSPECTIVE COHORT STUDY IMPLEMENTING SCREENING WITH FIB-4 AND SAFE SCORES

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Background: FIB-4 is recommended for screening primary care (PC) patients at risk for MASLD-related fibrosis, but its performance in general versus specialty populations is suboptimal. The steatosis-associated fibrosis estimator (SAFE) score adds BMI, type 2 diabetes mellitus (DM), and globulins to FIB-4, and may improve risk stratification. We aimed to evaluate the utility of SAFE compared to FIB-4 in a PC setting. **Methods:** We used EMR data from 2019-2023 to identify PC adults with three risk factor profiles: (1) obesity only, (2) DM only, or (3)

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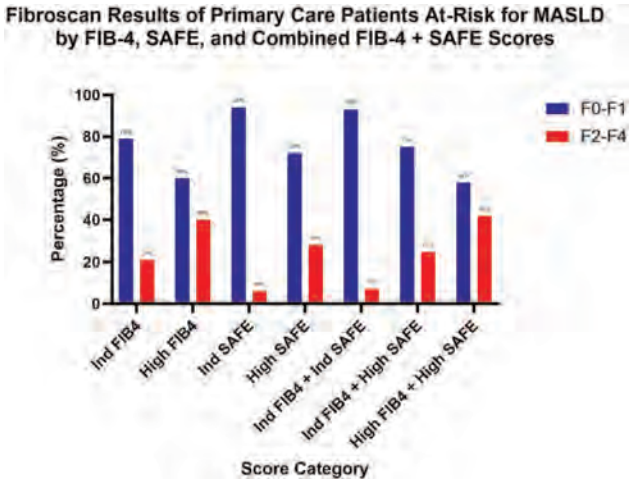
obesity + DM. Annual FIB-4 and SAFE scores were calculated. The most recent scores were used to categorize by age-based cutoffs into low-, indeterminate-, or high-risk for advanced fibrosis. Patients with indeterminate/high-risk FIB-4 and available SAFE were included; their primary care provider (PCP) was prompted in the EMR to refer for Fibroscan. The primary outcome was significant fibrosis (F2-4), defined as median liver stiffness $\geq$8kPa. We calculated descriptive statistics and conducted two multivariable logistic regressions to analyze F2-4 association with (1) risk factor profile, adjusting for age and sex, and (2) FIB4/SAFE category, adjusting for sex. **Results:** Of 22,806 PC patients, 7,027 (31%) met inclusion for one of three risk factor groups: obesity (n = 3,644), DM (n = 1,896), or both (n = 1,474). The majority had data for at least one FIB-4 (72%) and SAFE (63%). To date, n = 430 met the FIB-4/SAFE cohort inclusion criteria, prompting their PCP to order Fibroscan. The cohort mean age was 62 years; 43% had obesity, 31% DM, and 26% both. Most had indeterminate FIB-4 (85%) and high SAFE (77%). Among 104 who underwent Fibroscan, 25% had F2-4, including 40% of those with high FIB-4 (Figure 1). Compared to F0-1, F2-4 patients had higher FIB-4 (2.5 vs 2.0, p = 0.01) and higher SAFE (242 vs 156, p < 0.001). Obesity + DM but not DM alone was independently associated with F2–4, which remained significant in multivariable analysis adjusting for age and sex (OR 7.97, 95% CI 2.25–28.21), compared to obese only. The addition of high SAFE to indeterminate FIB-4 did not increase the odds of F2-4 fibrosis (OR 4.60, 95% CI 0.56–37.69), but the combination of high FIB-4 + high SAFE did (OR 10.29, 95% CI 1.10–95.99). **Conclusion:** In PC patients, those with obesity + DM were significantly more likely to have F2-4 fibrosis relative to DM or obesity alone. High FIB-4 yielded a higher percent of F2-4 fibrosis relative to high SAFE. Applying both scores, the detection of significant fibrosis by indeterminate FIB-4 did not improve when combined with high SAFE, but high FIB-4 may be improved when combined with high SAFE in the PC setting.



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2029 NEW SUBMISSION | A MACHINE LEARNING-VALIDATED MODEL CAN DIFFERENTIATE THREE SUBTYPES OF STEATOTIC LIVER DISEASE BASED ON SELF-REPORTED ALCOHOL USE: ANALYSIS OF NHANES DATABASE

Talal Bhatti Nicholas Dunn[1] Wanyu Zhang[2] Maiying Kong[3] Craig McClain[3] Winston Dunn[4] Ashwani Singal[3], [1]KUMC,KS, [2]University of Louisville School of Medicine, [3]University of Louisville, [4]University of Kansas Medical Center

Background: The new nomenclature of steatotic liver disease (SLD) based on self-reported alcohol use identified a new entity of metabolic dysfunction and alcohol associated liver disease (MetALD). There are challenges on accurately identifying MetALD given inaccurate reporting and changing alcohol use. ASH-NASH index (ANI) [PMID 17030176] can accurately distinguish patients with metabolic dysfunction associated liver disease (MASLD) and alcohol-associated liver disease (ALD). We analyzed NHANES database to develop a machine learning model (ANI 2.0) to differentiate three subtypes of SLD (MASLD, MetALD, and ALD). **Methods:** A random forest model was fitted on subjects with steatotic liver disease (SLD) in the NHANES database (1999–2006 and 2017–2020) using an iron panel (UIBC, TIBC, iron, ferritin, and transferrin), AST, ALT, MCV, demographics, GGT, folate, globulin, and CMRF. SLD was defined in presence of $\geq$1 cardiometabolic risk factor (CMRF), negative for hepatitis B or C virus, and with elevated ALT. We examined the model to distinguish SLD subtypes based on self-

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reported alcohol use, utilizing the new 2023 nomenclature. The dataset was randomly divided into 70% training and 30% test sets. We applied the synthetic minority over-sampling technique (SMOTE) on the training set to balance the sample sizes across groups. Performance was summarized with confusion matrices and one-versus-all ROC curves (with corresponding AUCs) for both the training and test datasets. **Results:** 7637 participants were stratified SLD subtypes: metabolic-dysfunction associated liver disease (MASLD, n = 7084), metabolic dysfunction and alcohol-associated liver disease (MetALD, n = 418), and alcohol-associated liver disease (ALD, n = 135). Three subtypes differed on baseline characteristics (Table). The model on the training dataset yielded a c-statistics of 0.98 for MASLD and 0.99 for both MetALD and ALD. In the test data, the model resulted in c-statistics of 0.79 for MASLD, 0.76 for MetALD, and 0.80 for ALD. Overall c-statistics (average of all pairwise AUCs) was 0.99 and 0.73 in training and test data respectively. The most important variables were five iron panel markers, age, AST, ALT, and MCV. **Conclusion: Conclusion:** A validated machine learning model (ANI 2.0) can accurately differentiate three subtypes of SLD. If confirmed in other prospective and retrospective cohorts, this could be clinically useful for clinical care pathway and for recruitment in research trials.

Table Demographic table across alcohol groups, for cycles with all iron variables available - All NA values are removed, for model fitting

	Total No,4762	MASLD No.4,426	MetALD No.258	AALD No.78	P-value
Age	45.7(±16.1)	45.9(±16.3)	44.8(±14.2)	42.9(±12.9)	0.37
Sex					< 0.0001
Male	1,526(32.0%)	1,334(87.4%)	132(8.7%)	60 (3.9%)	
Female	3,236(68.0%)	3,092(95.6%)	126(3.9%)	18(0.6%)	
Race					<0.0001
Non Hispanic White	2,125(44.6%)	1,941(91.3%)	153(7.2%)	31(1.5%)	
Hispanic	1,578(33.1%)	1,492(94.6)	58(3.7%)	28(1.8%)	
Non- Hispanic Black	719(15.1%)	672(93.5%)	37(5.1%)	10(1.4%)	
Other Race	340(7.1%)	321(94.4%)	10(2.9%)	9(2.6%)	
AST	30.4(±24.0)	29.7(±22.4)	38.3(±37.9)	45.6(±39.7)	<0.0001
ALT	37.1(±40.5)	36.5(±40.9)	43.6(±34.1)	51.4(±33.7)	<0.0001
GGT	42.5(±59.5)	39.4(±50.6)	71.9(±121.4)	118.5(±115.3)	<0.0001
MCV	89.5(±5.6)	89.3(±5.6)	92.5(±5.2)	92.6(±5.5)	<0.0001
MCHC	33.8(±0.8)	33.8(±0.8)	34.1(±0.8)	34.0(±0.9)	<0.0001
folate	839.8(±441.0)	840.3(±440.9)	845.1(±467.2)	793.0(±352.9)	0.81
Met_risk	2.1(±1.2)	2.1(±1.2)	1.9(±1.2)	2.0(±1.2)	0.043
Globulin	31.2(±4.4)	31.3(±4.4)	30.0(±4.2)	31.8(±4.3)	<0.0001
Transferrin	25.0(±11.3)	24.7(±11.2)	28.3(±11.6)	31.3(±11.6)	<0.0001
TIBC	362.7(±62.0)	363.0(±62.7)	359.7(±51.9)	357.4(±57.0)	0.92
UIBC	227.1(±120.5)	228.7(±120.9)	209.9(±110.3)	188.5(±120.7)	0.0005
Iron	88.0(±36.9)	86.8(±36.4)	100.3(±40.1)	110(±38.6)	<0.0001
Ferritin	144.7(±185.0)	136.7(±167.3)	227.1(±311.8)	327.0(±350.8)	<0.0001

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2030 | CIRCULAR RNA PROFILING REVEALS IGF2BP-LINKED REGULATORY NETWORKS IN HUMAN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Sareh Bayatpour[1] Hui Li[1] Grayson Way[2] NAN WU[1] Yunling Tai[1] Derrick Zhao[1] Meiyi Song[1] Lianyong Su[1] Emily Gurley[1] Xuan Wang[1] Phillip Hylemon[1] Arun Sanyal[2] Huiping Zhou[2], [1]VCU, [2]Virginia Commonwealth University

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is the progressive, inflammatory form of metabolic dysfunction-associated steatotic liver disease (MASLD), characterized by hepatic steatosis and lobular inflammation, with or without fibrosis. MASH has emerged as one of the most prevalent causes of chronic liver disease globally and is a leading indication for liver transplantation. Recent studies have reported altered circular RNA (circRNA) expression profiles in MASH mouse models; however, the circRNA landscape in human MASH remains largely unexplored. This study aims to identify circRNAs associated with MASH pathogenesis and to investigate their potential cellular and molecular mechanisms. **Methods:** Frozen liver tissues from MASH patients and healthy controls (HCs) were obtained through the Liver Tissue Cell Distribution System (Minneapolis, Minnesota), funded by NIH Contract# HSN276201200017C. Hepatic circRNA profiles were analyzed using the Arraystar Human circRNA Array V2 platform (n = 8, both male and female). Differentially expressed circRNAs were identified using circRNA-specific bioinformatics algorithms. Publicly available RNA-binding protein (RBP) databases (ENCORI and POSTAR3) were used to identify RBPs predicted to interact with the circRNA sequences. **Results:** The majority of detected circRNAs were exonic (75%). A total of 358 upregulated and 141 downregulated circRNAs were identified in MASH patients compared to HCs (fold change ≥ 2.5, $p < 0.05$). The top 10 upregulated circRNAs showed expression increases ranging from 25- to 193-fold. Bioinformatic analysis revealed that several of the most significantly upregulated circRNAs—circCNOT6L, circAHCY, circKIAA0319, circPOLR2A, and circPTPRF—are predicted targets of a shared group of RBPs: the IGF2BP family. IGF2BPs are known to regulate key oncofetal proteins such as MYC, IGF2, and β-catenin, and also act as readers of N6-methyladenosine (m^6A) RNA modifications, which are involved in cancer-related signaling pathways including PI3K/AKT, Wnt/β-catenin,

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and MAPK/ERK. **Conclusion:** These findings suggest that IGF2BPs may contribute to MASH pathogenesis by binding to and regulating key circRNAs, thereby altering hepatic metabolic and inflammatory responses. Future studies are warranted to validate the functional impact of these circRNA–IGF2BP interactions in vitro and in vivo, and assess their potential as diagnostic biomarkers or therapeutic targets in MASH.

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2031 | PREDICTORS OF LONGITUDINAL CHANGES IN LIVER CORRECTED T1 VALUE BASED ON UK BIOBANK COHORT

Ju Dong Yang[1] Minsun Kwak[2] Hyunseok Kim[3] Yufeng Wang[3] Lixia Wang[1] Walid Ayoub[1] Alexander Kuo[1] Paul Martin[1] Hirsh Trivedi[1] Aarshi Vipani[3] Yun Wang[1] Stephen Pandol[1] Debiao Li[1] Shelly Lu[1] Mohammad Saeid Rezaee-Zavareh[4] Abdelrahman Attia[1], [1]Cedars-Sinai Medical Center, [2]Seoul National University Hospital Gangnam Center, Seoul, South Korea, [3]Cedars Sinai Medical Center, [4]Middle East Liver Diseases (MELD) center, Tehran, Iran

Background: Corrected T1 (cT1), measured by liver MRI, is a non-invasive biomarker reflecting hepatic fibro-inflammation. Our recent study showed that a cT1 with a lower cut-off value (≥700ms) was associated with increased all-cause mortality, cardiovascular mortality and liver-related events. However, little is known about factors influencing longitudinal changes in liver cT1. The aim of this study was to investigate predictors of cT1 trajectory in individuals who underwent at least two liver MRI scans. **Methods:** Participants who performed two consecutive liver MRI were included among UK Biobank cohort. Participants were categorized into four groups based on serial cT1 measurements as follows; Group 1 (cT1 <700ms at both exam), Group 2 (cT1 <700ms at baseline, ≥700ms at follow-up), Group 3 (cT1 ≥700ms at baseline, <700ms at follow-up), Group 4 (cT1 ≥700 ms at both). Multinomial logistic regression adjusted by age, sex, number of cardiometabolic risk factors, smoking, alcohol, diet, physical activity, and PNPLA3 genotype was performed to compare Group 2 vs. Group 1 (worsening), and Group 3 vs. Group 4 (improved). **Results:** Among total of 2,467 participants with longitudinal MRI measurement, 1,132 (45.9%) were in Group 1, 312 (12.7%) in Group 2, 210 (8.5%) in group3, and 813 (33.0%) in Group 4. Median follow-up duration between the first and the follow-up MRI was 26.7 months (interquartile range 26.2-27.7 months). Compared to individuals with stable cT1 values below 700ms (Group 1), those whose cT1 values worsened to 700ms or higher at follow-up (Group 2) were more likely to be male (Relative Risk Ratio, 1.40, [95% confidence interval, 1.03–1.91]), have three or more cardiometabolic risk factors (1.67, [1.20–2.34]), and more likely to carry the PNPLA3 GG genotype (2.18, [1.07–4.43]). Conversely, compared to individuals who maintained high cT1 values ≥700ms (Group 4), those whose cT1 improved to below 700ms at follow-up (Group 3) were less likely to have three or more cardiometabolic risk factors (0.37, [0.25–0.54]), more likely to engage in moderate-to-vigorous physical activity (2.61, [1.21–5.62]). **Conclusion:** In summary, cardiometabolic burden and genetics (PNPLA3 GG genotype) were important predictors of worsening liver cT1, while physical activity and lower cardiometabolic risk were associated with cT1 improvement. These findings suggest that lifestyle interventions and cardiometabolic risk factor control may influence hepatic fibro-inflammation progression or resolution.

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Table. Predictors of worsening/improvement of liver cT1

	Group 2 (worsening of cT1) vs. Group 1 (baseline)		Group 3 (improved cT1) vs. Group 4 (baseline)	
	Relative risk ratio (95% CI)	P-value	Relative risk ratio (95% CI)	P-value
Age	0.99 (0.97-1.01)	0.30	1.01 (0.99-1.04)	0.37
Male sex	**1.40 (1.03-1.91)**	**0.03**	0.78 (0.54-1.14)	0.21
CMRFs≥3	**1.67 (1.20-2.34)**	**<0.01**	**0.37 (0.25-0.54)**	**<0.01**
Ever smoker	1.07 (0.78-1.46)	0.70	1.04 (0.71-1.52)	0.84
Alcohol, 10 gm/day	0.90 (0.81-1.001)	0.051	1.00 (0.89-1.13)	0.99
High quality diet	1.06 (0.76-1.46)	0.74	0.76 (0.50-1.16)	0.21
Moderate to vigorous physical activity	0.82 (0.45-1.48)	0.50	**2.61 (1.21-5.62)**	**0.01**
PNPLA3				
G heterozygote	1.09 (0.80-1.49)	0.57	0.96 (0.66-1.39)	0.83
G homozygote	**2.18 (1.07-4.43)**	**0.03**	0.58 (0.22-1.55)	0.28

CMRF, cardiometabolic risk factor; CI, confidence interval; cT1, corrected T1

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2032 | GENETIC CONTRIBUTIONS TO FATTY LIVER DISEASE–RELATED LIVER CANCER

Ching-Wen Chang[1], [1]GIMOS, Taipei Medical University

Background: Obesity has emerged as a major global health burden, markedly increasing the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH). These conditions are now recognized as key drivers of hepatocellular carcinoma (HCC), particularly in populations with rising obesity rates. Notably, liver cancer exhibits the strongest association with obesity among all cancer types, emphasizing the pivotal role of metabolic dysfunction in hepatic carcinogenesis. The growing incidence of MASH-related HCC, especially in Western countries, underscores the urgent public health challenge posed by obesity-linked liver diseases. Genetic susceptibility plays a critical role in determining MASLD and MASH outcomes. Among known variants, the PNPLA3 I148M allele is the most robustly associated with hepatic steatosis, inflammation, and fibrosis. However, interindividual differences in disease severity among carriers point to additional genetic modifiers. **Methods:** We searched genetic alleles among the 24 most significant alleles associated with body fat distribution from a genome-wide association study of 344,369 individuals and validated the top allele in 3 independent cohorts of American and European patients (N = 1380) with NAFLD/NASH/HCC. **Results:** Our research highlights DNAJA3, particularly the rs3747579-TT variant, as a novel contributor to MASH and MASH-related HCC. DNAJA3 encodes a mitochondrial chaperone that preserves mitochondrial integrity and cellular homeostasis. Its deficiency disrupts mitochondrial biogenesis, shifts energy metabolism toward glycolysis, and promotes lipid accumulation and cholesterol synthesis. We further observed a positive global correlation between MASH-related HCC prevalence and the frequency of the DNAJA3 eQTL variant, reinforcing its pathogenic relevance. Interaction analyses of DNAJA3 and PNPLA3 variants indicate that the convergence of mitochondrial and lipid dysregulation amplifies liver cancer risk. **Conclusion:** Together, our findings emphasize the importance of integrating genetic and metabolic insights in assessing liver cancer susceptibility in obesity. This work advances precision medicine by identifying actionable biomarkers for early detection and therapeutic targeting in MASH-related liver cancer.

Disclosures: Ching-Wen Chang: Nothing to Disclose

2033 | VCTE RADIOMICS FOR NON-INVASIVE ASSESSMENT OF HEPATIC FIBROSIS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Haoshuang Fu[1] Shuying Song[1] Yuelin Xiao[1] Bingying Du[1] Yan Huang[1] Qing Xie[1], [1]Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

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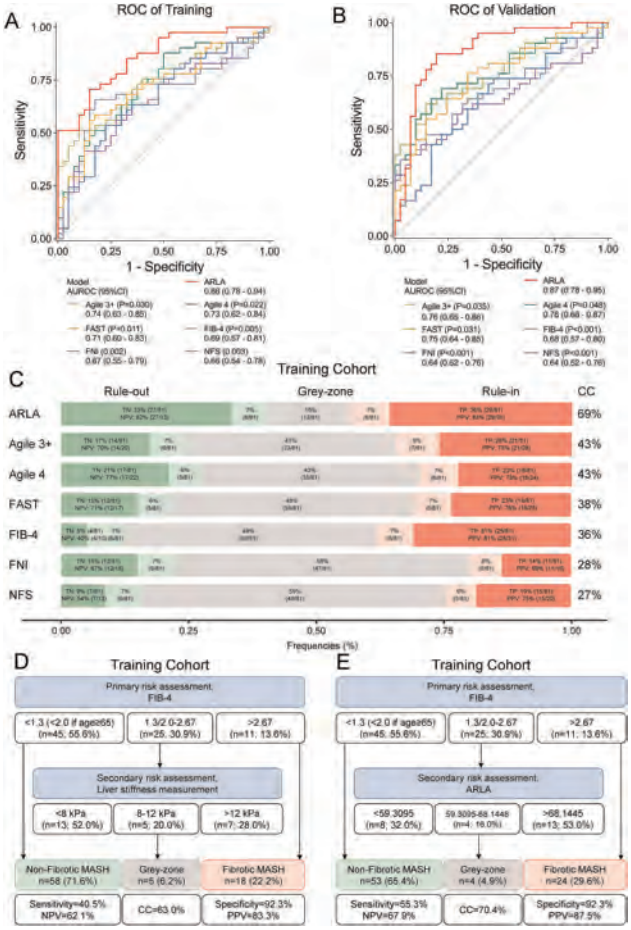
Background: Fibrotic metabolic dysfunction-associated steatohepatitis (MASH) is the leading cause of all-cause and liver-related mortality. Radiomics could predict disease progression. We developed a diagnostic model for identifying fibrotic MASH using radiomics analysis based on hepatic vibration-controlled transient elastography (VCTE). **Methods:** A total of 163 patients with biopsy-proven metabolic dysfunction-associated steatotic liver disease (MASLD) were enrolled and divided into training (50%) and validation (50%) cohorts. The outcome was defined as Fibrotic MASH (NAS $\geq$4 and fibrosis stage $\geq$2). VCTE images were obtained and extracted 1209 radiomics feature, where 7 features were selected using Least absoluteshrinkage and selection operator regression. R Score was established using support vector machines based on selected features. The diagnostic model was constructed using multiple logistic regression based on R Score and clinical data, which performance was compared with previous models (Agile 3+, Agile 4, FAST, FIB-4, FNI, NFS). **Results:** Fibrotic MASH patients presented elder ages, higher AST, and higher liver stiffness measurement (LSM) than Non-Fibrotic MASH patients. The AST, R Score, LSM and age were combined to construct diagnostic model (ARLA). The ARLA model yielded best accuracy with AUROC of 0.86 (95% CI = 0.78-0.94) and 0.87 (95%CI = 0.78-0.95) in training and validation cohorts, respectively (Figure1 A-B). The decision curve analysis showed the ARLA model offered more benefit than other models in both cohorts. The calibration curves showed the ARLA model demonstrated acceptable consistency between predictive and actual outcomes in both cohorts. Moreover, the ARLA model exhibited highest correct classified proportion of 69% and 70% with the smallest grey zone of 16% in both cohorts (Figure 1C). Furthermore, the two-step approach based on FIB4 and ARLA exhibited smaller grey zone (4.9%) and higher correct classified proportion (70.4%) than traditional two-step approach based on FIB-4 and LSM (grey zone = 6.2% and correct classified proportion = 63.0%) (Figure 1D-E). The nomogram based on ARLA model was developed for clinical practice. **Conclusion:** The ARLA model satisfactorily identified the Fibrotic MASH patients with high accuracy, cost-effectiveness, and acceptability, which could be an effective and noninvasive tool for optimal management of MASLD patients.



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2034 | HEPATOCELLULAR CARCINOMA RISK STRATIFICATION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Huapeng LIN[1] Fangkun Yang[2] Terry Cheuk-Fung Yip[3] Hye Won Lee[4] Emmanuel Tsochatzis[5] Salvatore Petta[6] Dong Wang[1] Xiangjun Meng[1] Elisabetta Bugianesi[7] Masato Yoneda[8] Ming-Hua Zheng[9] Hannes Hagström[10]

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Jerome Boursier[11] Li Chen[1] Jose Luis Calleja[12] Boon Bee George Goh[13] Wah Kheong Chan[14] Rocio Gallego-Durán[15] Arun Sanyal[16] Philip Newsome[17] Jian-Gao Fan[1] Laurent Castéra[18] Michelle Lai[19] Lijun Chang[20] Celine Fournier[21] Seung Up Kim[4] Vincent Wong[3], [1]Shanghai Jiao Tong University, [2]Ningbo University, [3]The Chinese University of Hong Kong, [4]Yonsei University, [5]Royal Free Hospital and UCL, [6]University of Palermo, [7]University of Turin, [8]Yokohama City University, [9]Wenzhou Medical University, [10]Karolinska Institutet, [11]Angers University, [12]Hospital Universitario Puerta de Hierro Majadahonda, [13]Singapore General Hospital, [14]University of Malaya, [15]Virgen Del Rocío University Hospital, [16]Virginia Commonwealth University, [17]University of Birmingham, [18]Université Paris Cité, [19]Beth Israel Deaconess Medical Center, [20]Shanxi Medical University, [21]Echosens

Background: Current clinical guidelines recommend hepatocellular carcinoma (HCC) surveillance in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and cirrhosis when annual incidence exceeds 1%, but the role of noninvasive tests (NITs) in identifying suitable candidates remains unclear. In our previous study, fibrosis-related NITs showed good accuracy for predicting cirrhotic complications, but limited value in forecasting HCC. **Methods:** This cohort study utilized data from a natural history cohort of patients with MASLD who underwent vibration-controlled transient elastography (VCTE) at 16 tertiary referral centers across the United States, Europe, and Asia. Patients were stratified according to liver stiffness measurement (LSM) thresholds of 8 and 12 kPa into three groups: advanced fibrosis (AF), gray-zone, and non-AF. We evaluated the performance of LSM-based HCC risk scores, such as PLEASE score, as well as etiology-agnostic scores such as aMAP. These scores were compared with fibrosis-related NITs. Sensitivity analyses were performed using alternative LSM thresholds (10 and 15 kPa), as well as a two-step pathway incorporating Fibrosis-4 index followed by LSM. The primary outcome of interest was the development of HCC. **Results:** A total of 16,603 MASLD patients with available LSM data were included. Over a median follow-up of 51.7 months (interquartile range, 25.2–85.2), 139 patients (0.8%) developed HCC. Among those with AF or in the gray-zone, the aMAP score consistently showed the best discrimination for 3-, 5-, and 8-year HCC risk, with the highest area under the receiver operating characteristic curve and C-index values. Toronto HCC Risk Index (THRI) also performed well, with all metrics above 0.75. These results held across different LSM cutoffs (8/12, 10/15 kPa) and with the two-step stratification. We used established score cutoffs to stratify HCC risk in AF patients. Regardless of the LSM threshold or two step method, patients classified as high-risk by aMAP or THRI had 5-year HCC rates above 7%, exceeding the 1% annual threshold for surveillance. Conversely, 5-year incidence in low-risk groups remained below 0.8% for both scores. Notably, THRI classified nearly 50% of patients as intermediate-risk, while this proportion was much lower for aMAP. **Conclusion:** Among AF patients, LSM-based HCC risk scores performed worse than aMAP and THRI. Although THRI classified nearly 50% of MASLD patients as intermediate-risk, it only requires age, sex, and platelet count, making it practical in real-world settings, especially when lab data are limited. When additional parameters like bilirubin and albumin are available, aMAP is preferred for risk stratification.

Table 1. HCC risk stratification by aMAP and Toronto HCC risk index.

Non-invasive tests	Risk groups	HCCs (N)	Percentage in total HCCs	5-year HCC (%)	HCC incidence per 1 000 PY (95% CI)
LSM ≥12 kPa					
aMAP	<50	7	8.4	0.8 (0.3-1.9)	2.2 (2.1-2.3)
	50-60	24	28.9	2.8 (1.6-4.6)	6.6 (6.5-6.7)
	≥60	52	62.7	11.5 (8.1-15.4)	26.4 (26.2-26.6)
Toronto HCC risk index	<120	2	2.4	0.4 (0.3-2.2)	1.3 (1.2-1.4)
	120-240	43	51.2	3.1 (2.0-4.5)	7.1 (6.9-7.2)
	>240	39	46.4	11.2 (7.6-15.6)	25.9 (25.6-26.2)
LSM ≥15 kPa					
aMAP	<50	4	5.9	0.5 (0.1-2.3)	2.3 (2.2-2.4)
	50-60	19	27.9	3.2 (1.7-5.6)	7.7 (7.6-7.9)
	≥60	45	66.2	13.6 (9.4-18.3)	31.1 (30.8-31.4)
Toronto HCC risk index	<120	1	1.5	-	1.3 (1.1-1.4)
	120-240	33	47.8	3.6 (2.2-5.4)	8.4 (8.3-8.5)
	>240	35	50.7	14.1 (9.4-19.7)	33.2 (32.8-33.5)
Two step pathway for AF					
aMAP	<50	2	2.4	0.2 (0.1-1.1)	0.9 (0.8-0.9)
	50-60	27	32.9	2.2 (1.4-3.5)	4.6 (4.5-4.7)
	≥60	53	64.6	8.6 (6.2-11.4)	17.4 (17.2-17.5)
Toronto HCC risk index	<120	1	1.2	-	0.9 (0.8-0.9)
	120-240	40	48.2	2.6 (1.7-3.8)	5.2 (5.1-5.3)
	>240	42	50.6	7.6 (5.2-10.6)	16.1 (15.9-16.3)

Notes: AF: advanced fibrosis; CI: confidence interval; HCC: hepatocellular carcinoma; LSM: liver stiffness measurement; PY: person-years.

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2035 | ABSTRACT WITHDRAWN

2036 | VALIDATION OF A NOVEL IN VITRO DIAGNOSTICS VERSION OF THE ADAPT ALGORITHM FOR NON-INVASIVE ASSESSMENT OF FIBROSIS SEVERITY FOR CLINICAL USE IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE – A SECONDARY ANALYSIS IN THE LITMUS STUDY COHORT

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Background: There is a need for accurate high throughput blood based non-invasive tests (NITs) for assessing fibrosis severity within Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD). The ADAPT algorithm has previously been calculated using a PRO-C3 ELISA technology with platelets, age, and diabetes status, however now transitioned to the Roche Cobas® e801 high throughput IVD analyzer. This study aimed to validate the diagnostic performance of the ADAPT algorithm using the Roche Elecsys® PRO-C3, within a well characterized European multicentre study cohort. **Methods:** This prospective, multicentre study included MASLD patients from the LITMUS study cohort with central read biopsy-confirmed fibrosis staging. In the current analysis a total of 1134 patients were included. ADAPT cut-offs were identified in a derivation cohort (n = 451) and tested in a validation cohort (n = 683) including all fibrosis stages: F0 (n = 84), F1 (n = 140), F2 (n = 207), F3 (n = 179), and F4 (n = 73) all originating from the LITMUS study cohort. PRO-C3 was assessed by the Cobas® e801 analyzer. The area under the receiver operating characteristic curve (AUROC) as well as sensitivity at given specificity was used to evaluate the performance in assessing fibrosis severity for significant- ($F \geq 2$), and advanced ($F \geq 3$), liver fibrosis and cirrhosis (F4). **Results:** Elecsys® PRO-C3 as part of the ADAPT algorithm demonstrated strong diagnostic accuracy for detecting fibrosis severity, with AUROC values of 74% (95% CI: 70%-78%) for significant fibrosis (F2-F4) with a cutoff of $\geq$ 10.03; 80% (95% CI: 77%-84%) for advanced fibrosis (F3-F4) with a cutoff of $\geq$ 10.18; and 85% (95% CI: 81%-89%) for cirrhosis (F4) with a cutoff of $\geq$ 11.07. The diagnostic performance at different ADAPT cutoffs were as follows: for significant fibrosis (F2-F4), specificity was 93% (95% CI: 89%-96%) and sensitivity was 34% (95% CI: 29%-38%); for advanced fibrosis (F3-F4), specificity was 90% (95% CI: 87%-93%) and sensitivity was 46% (95% CI: 40%-52%); for cirrhosis (F4), specificity was 91% (95% CI: 88%-93%) and sensitivity was 51% (95% CI: 40%-62%). **Conclusion:** Three potential ADAPT cut-offs were identified for clinically relevant target conditions in MASLD. It was shown, that the ADAPT algorithm is a tractable non-invasive tool for assessing the severity of fibrosis in MASLD, and that a

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comparison to other NITs is warranted. Its integration into clinical pathways could improve early detection of disease, fibrosis risk stratification and guide appropriate patient management.

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2037 | DOES SUBCUTANEOUS FIBROSIS PREDICT THE SEVERITY OF LIVER FIBROSIS?

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) in patients with severe obesity often progresses to advanced liver fibrosis or cirrhosis. Given the systemic nature of fibrotic processes in obesity, subcutaneous fibrosis may reflect hepatic disease severity. This study uses quantitative digital pathology image analysis to evaluate whether subcutaneous fibrosis can serve as a minimally-invasive predictor of liver fibrosis in patients with severe obesity, biopsy-confirmed MASH and F2-3 fibrosis. **Methods:** This retrospective cohort study included 40 patients with histologically confirmed MASH, diagnosed via liver biopsy and evaluated according to the NASH CRN criteria by expert pathologists. The cohort consisted of 20 patients with stage F2 fibrosis and 20 with stage F3 fibrosis. FFPE sections (~4 microns) of liver and subcutaneous adipose tissue biopsies were stained with Picrosirius Red. The slides were digitized (Ventana DP200 at 40X) and analyzed using FibroNest™ for quantitative image analysis. For each etiology, the fibrosis phenotype was described for its collagen content (12 traits), the morphometric traits of the collagen fibers (12), and fibrosis architecture traits (7). Each trait was quantified with 7 quantitative fibrosis traits parameters (qFTs) to account for severity, distortion, and variance, resulting in a total of 448 qFTs. As reported elsewhere (doi; 10.1111/liv.15768), the FibroNest Phenotypic Fibrosis composite score (Ph-FCS, established from a selection of qFT that best classify early from advanced liver fibrosis in patients with MASH). Similarly, qFTs that would exhibit a significant ($p < 0.05$) and meaningful ($> 20\%$) relative difference (group average) between the F2 and F3 groups of adipose tissue (AT) samples we selected and assembled in a equi-weighted phenotypic composite score Ph-PCS(AT). **Results:** Contrary to the Ph-FCS values that were well aligned with

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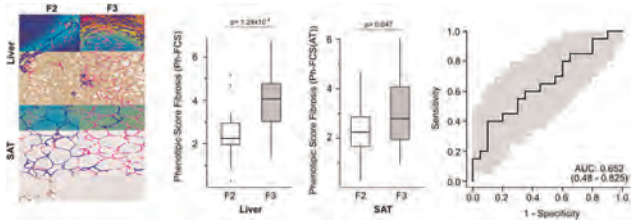
NASH-CRN fibrosis stages, the correspondence of the Ph-FCS(AT) with NASH-CRN fibrosis stages was moderate ($p = 0.047$. Ph-FCS(AT) showed a modest performance (AUROC = 0.652 [95%CI: 0.480 – 0.825] to help diagnose F2 from F3 patients from adipose tissue biopsies. **Conclusion:** Sophisticated quantitative Digital Pathology Image analysis found moderate associations between the histological fibrosis phenotypes of subcutaneous tissue and liver biopsies. Subcutaneous biopsies cannot be used to predict the associated Liver NASH-CRN stage with a performance that is acceptable in the context of clinical care.



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2038 | SERUM HISTAMINE N-METHYLTRANSFERASE AS A POTENTIAL BIOMARKER FOR LIVER HISTOLOGIC SEVERITY IN MASLD: INSIGHTS FROM IMMUNE-RELATED PROTEOMIC SIGNATURES

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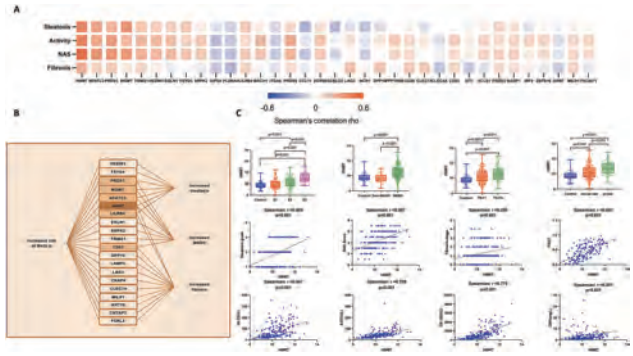
Background: Metabolic inflammation are believed to play important role in the development of metabolic-dysfunction associated steatotic liver disease (MASLD), the changes in peripheral immune proteomics might provide insights to pathogenesis of MASH and fibrosis. This study explored serum immune proteome panel in the patients of MASLD diagnosed by liver biopsy and aimed to evaluate the immune features associated with liver histological feature. **Methods:** In a MASLD cohort, which prospectively included healthy check-up subjects (n = 43), subjects diagnosed with MASLD (n = 221) by liver biopsy, in which 83.26% were metabolic-dysfunction associated steatohepatitis (MASH). Serum immune protein profiles using the Olink Proximity Extension Assay platform was assessed for association of histologic severities in MASLD and with other biomarkers as follows: anthropometric and inflammation biochemical indicators, and transient resonance elastography. **Results:** We identified 92 serum immune proteins in the MASLD cohort. There were distinct serum immune features between healthy control and MASLD subjects. In the subgroup analysis of histology features of steatosis, inflammation and fibrosis, we identified the top differentiated immune protein: histamine N-methyltransferase (HNMT), which showed the most prominent association with the histological severities of steatosis, steatohepatitis and fibrosis and the correlation analysis with serum inflammatory markers including aminotransferase, C-reactive protein and cytokeratin 18. **Conclusion:** The increased serum HNMT, which used to be associated hypersensitivity disease, might reflects the chronic low-grade inflammation status of MASLD. HNMT showed the prominent association with the histological severities especially in MASH in patients of MASLD, which might provide new targets for potential pathogenesis exploration and non-invasive marker.



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2039 | PROSPECTIVE COHORT STUDY IDENTIFIES DIETARY AND ORAL MICROBIAL SIGNATURES ASSOCIATED WITH SIGNIFICANT MASLD FIBROSIS

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Background: While gut microbiome has been extensively studied, the role of oral microbiome in liver fibrosis remains less explored. This prospective cohort study investigated associations between dietary intake, oral microbiome, host metabolites and proteins profiles and their collective relationship to MASLD fibrosis. **Methods:** Forty-four MASLD adults were prospectively enrolled, excluding those with viral hepatitis, excessive alcohol use, dental issues, other chronic liver diseases, or recent antibiotics/

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probiotics. Liver stiffness (kPa) was used as a fibrosis surrogate; ≥8 kPa indicated significant fibrosis, and >30% increase between sequential LSM assessments in previous year defined rapid progression. Dietary intake was assessed using NCI Dietary Screener Questionnaire. Oral microbiome (metagenomics), serum metabolomics (LC-MS), and plasma proteomics (Olink) were profiled. α-diversity (Shannon) was compared using Mann-Whitney U test. Differentially abundant microbial taxa associated with fibrosis progression were identified using MaAsLin2, while key metabolomic and proteomic signatures linked to significant MASLD fibrosis were visualized using volcano plots. Relationships among diet, key oral microbiota, metabolites and proteins were assessed via Spearman correlations. **Results:** At baseline, 44% of patients had significant MASLD fibrosis, and lower α-diversity (Shannon) was significantly associated with higher LSM ($\beta = -6.8$, $p = 0.035$). Patients with rapid fibrosis progression had higher relative abundances of *Streptococcus*, *Lautropia* and *Atopobium*, with lower relative abundances of *Prevotella*, *Veillonella* and *Alloprevotella*. Significant MASLD fibrosis was associated with higher levels of oxidative stress (e.g., 7-methylguanine, N-acetylputrescine), immune activation (e.g., IL-17C, CD8A, PD-L1), and matrix remodeling markers (e.g., MMP-10, uPA), and lower levels of antioxidants (e.g., taurine, piperine) and immune-regulatory markers (e.g., MCP-2, TRANCE) (Figure 1). No nutrients were associated with significant MASLD fibrosis, but added sugar intake correlated with pro-fibrotic taxa (e.g., *Atopobium*, $r = 0.44$, $p = 0.005$) and immune markers (e.g., IL-17C, $r = 0.38$, $p = 0.049$). **Conclusion:** Higher liver stiffness was associated with lower oral microbial α-diversity. Significant MASLD fibrosis was associated with elevated circulating markers of oxidative stress and immune activation, and lower levels of antioxidant and immune-regulatory markers. Fibrosis progression was linked to increased abundance of pro-fibrotic oral taxa. Added sugar intake was positively associated with pro-fibrotic microbes and immune activation. Given increased accessibility of oral microbiome samples at point of care, these findings may lead to novel approaches for tracking impact of interventions on oral-liver axis and understanding their mechanistic roles in driving fibrosis progression.

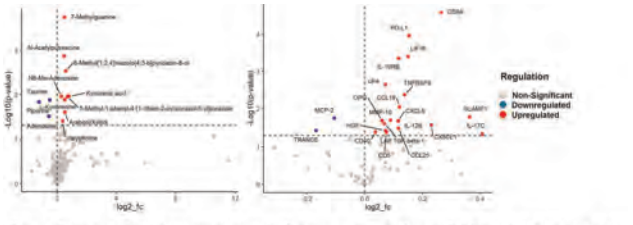

Figure 1. Serum metabolomics and plasma proteomics profiles associated with significant MASLD fibrosis (left: metabolomics; right: proteomics)

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2040 | LARGE LANGUAGE MODELS (LLMS) ACCURATELY EXTRACT VCTE MEASUREMENTS FROM UNSTRUCTURED DOCUMENTATION AND ENABLE AT-SCALE PREDICTIVE MODELING IN REAL-WORLD COHORTS

Aryana Far[1] Aryan Ayati[1] Jordan Guillot[1] Shadera Azzam[1] Vivek Rudrapatna[1] Jin Ge[1], [1]University of California, San Francisco

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a leading cause of cirrhosis. Vibration Controlled Transient Elastography (VCTE) measurements are commonly used to stratify disease severity, but they are often only available in unstructured documentation and therefore poorly available for clinical research. Recent advances in LLMs enable accurate extraction of clinical variables and measurements from unstructured notes, offering new opportunities for large-scale analyses in real-world cohorts of patients with compensated MASH cirrhosis. **Methods:** We used an established cohort of 493 patients with compensated MASH cirrhosis from the University of California, San Francisco (UCSF). We selected 1,670 de-identified clinical notes referencing VCTE and evaluated the accuracy of GPT-4o and Claude 3.5 Sonnet in extracting FibroScan stiffness and Controlled Attenuation Parameter (CAP) measurements. We used multivariate LASSO-Cox regressions to assess the association of these LLM-extracted measurements with the composite outcome of death or decompensation. **Results:** LLM-extraction identified 148 patients with stiffness and 117 with CAP available. Compared with manual chart review of a 20% random sample, GPT-4o achieved 100% accuracy for extracting stiffness and CAP, while Claude 3.5 Sonnet achieved 100% for stiffness and 92% for CAP. Extraction required about 6.5 million tokens for both models,

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costing approximately $0.012 per case for GPT-4o (~ $42.54 total) and $0.014 per case for Claude 3.5 Sonnet (~$48.34 total). GPT-4o was approximately 24% faster than Claude 3.5 Sonnet. In LASSO-Cox regression including 58 structured clinical variables (e.g., age, race/ethnicity, MELD, medications) and LLM-extracted measurements, stiffness (HR 1.02, 95% CI 1.00-1.05, p = 0.03) and CAP (HR 0.99, 95% CI 0.99-1.00, p = 0.05) were identified as significant predictors of the composite outcome. **Conclusion:** LLMs can extract FibroScan/VCTE parameters from clinical reports with high accuracy and low cost. When incorporated into regression modeling, extracted stiffness and CAP values are highly associated with progression to high-impact outcomes like mortality and decompensation. Given the scalability of LLM-based approaches and the growing availability of PHI-secure APIs to popular LLMs like GPT-4o and Claude, academic medical centers should facilitate their adoption for research and quality improvement for chronic liver diseases like MASH.

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2041 | PERFORMANCE OF FIB-4 VARIES GREATLY ACCORDING TO AGE GROUPS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): DATA FROM GLOBAL MASLD PROJECT

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Background: Fibrosis-4 (FIB-4) is a widely used first-line non-invasive test (NIT) for risk-stratification of patients with MASLD, with FIB-4 <1.30 (<2.0 in patients ≥ 65 years) indicating low risk and ≥ 2.67 or ≥ 3.25 suggesting elevated or high risk of advanced fibrosis. The aim was to assess performance of FIB-4 in patients with biopsy-proven MASLD across different age groups. **Methods:** The Global MASLD (G-MASLD) project enrolled MASLD patients with liver biopsy, and laboratory data (FIB-4). Cutoff values for predicting advanced fibrosis (F3-F4) were analyzed by age group. **Results:** 16,867 patients with biopsy and FIB-4 data from 40 countries were included: age 51 ± 13 years, 48% male, 46% type 2 diabetes (T2D), 35% advanced fibrosis. The crude AUC of FIB-4 for predicting advanced fibrosis was 0.80 (95% CI 0.79-0.81), with substantial variability across age-based subgroups: 0.72 (0.68-0.75) in <35 years, 0.78 (0.77-0.79) in 35-64 years, and 0.71 (0.69-0.73) in ≥ 65 years. The low risk cutoff of 1.30 returned pooled sensitivity of 74% (73%-75%) with specificity of 72% (71%-73%); that, however, included sensitivity of 20% (15%-25%) with specificity of 95% (94%-96%) in patients <35 years, 71% (70%- 73%) with 72% (71%-73%), respectively, in 35-64 years, and 92% (91%- 93%) with 26% (24%-29%), respectively, in ≥ 65 years; the respective positive and negative predictive values varied across the age groups from 31% to 62% and from 71% to 91%, respectively. In order to maintain consistent sensitivity of 80% (low risk criterion, to rule out advanced fibrosis), the FIB-4 cutoff of 0.50 would be needed in the <35 years group vs. 1.10 in 35-64 years group and 1.65 in the ≥ 65 years group; even more granular cutoff use may be warranted within those groups (Figure). Similarly, the cutoff of 2.67 returned pooled sensitivity/specificity of 28% (27-29%)/95% (94-96%) which was 4% (2-7%)/99% (98-99%) in the <35 years group, 24% (23-25%)/96% (95-96%) in 35-64 years, and 45% (42-47%)/84% (82-86%) in ≥ 65 years. For the specificity of

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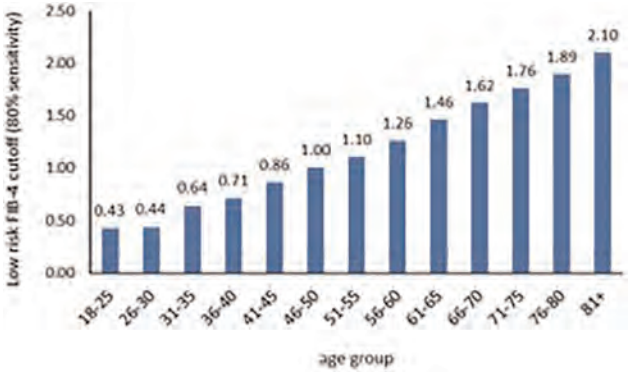
95% (high risk criterion, to rule in advanced fibrosis), the age-specific FIB-4 cutoffs would be as follows: 1.33 in <35 years, 2.60 in 35-64 years, and 3.95 in ≥ 65 years. **Conclusion:** The use of FIB-4 cutoff values without adjustment for age results in substantially varying accuracy. Given that FIB-4 is routinely used as the first line NIT, the use of granular age-specific cutoff values, particularly those identifying low-risk patients, may be needed.



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2042 | DEVELOPMENT OF A NEURAL NETWORK TO DETECT HEPATIC STEATOSIS IN METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Early identification of metabolic dysfunction-associated steatotic liver disease (MASLD) is critical for risk stratification and timely intervention. Conventional non-invasive indices (Fatty Liver Index (FLI), Hepatic Steatosis Index (HSI), Zhejiang University (ZJU) index, and MASLD index) are limited by linear assumptions and moderate predictive accuracy. We aimed to develop and externally validate a neural network model for non-invasive detection of hepatic steatosis. **Methods:** We used a retrospective cohort of 17,465 Japanese health checkup participants (2010–2020). The cohort was split into a development cohort (n = 8,426) and an internal validation cohort (n = 9,039). A feedforward neural network was trained using clinical and biochemical variables, including body mass index (BMI), abdominal circumference, and existing indices. External validation used the NHANES III cohort (n = 2,759), with hepatic steatosis defined by ultrasonography (GUPHSPFR ≥ 2). Model performance was assessed via area under the receiver operating characteristic curve (AUC), calibration, decision curve analysis (DCA), and subgroup analyses. **Results:** The neural network achieved an AUC of 0.922 (95% CI: 0.913–0.931) in internal validation and 0.924 (95% CI: 0.917–0.931) in external validation, outperforming FLI, HSI, ZJU, and MASLD indices (all $p < 0.001$). At the optimal Youden cutoff (0.357), sensitivity and specificity were 89% and 86%, respectively. Calibration analysis and DCA confirmed strong agreement between predicted and observed risk. Abdominal circumference and BMI were the most influential predictors. **Conclusion:** Our neural network model outperforms conventional indices in detecting moderate-to-severe hepatic steatosis and may facilitate early, scalable MASLD screening in primary care and low-resource settings.

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2043 | RISK OF SUBCLINICAL CARDIOVASCULAR DISEASE IN US ADULTS WITH LEAN MASLD: A POPULATION-BASED ASSESSMENT USING CARDIAC BIOMARKERS

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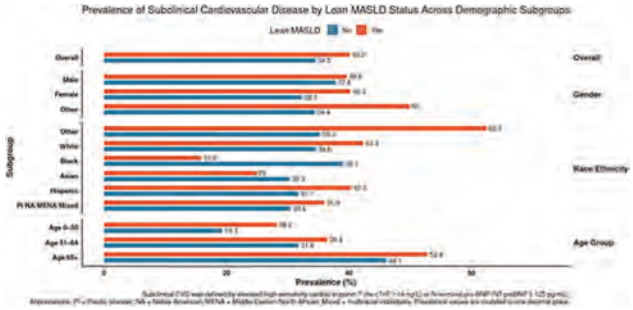
Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized as a systemic cardiometabolic disorder. While obesity is a hallmark feature of MASLD, its occurrence in lean individuals represents a clinically distinct and understudied phenotype. Cardiovascular disease (CVD) remains the leading cause of mortality in MASLD, yet the burden of subclinical CVD among lean individuals with MASLD remains poorly defined. Cardiac biomarkers such as high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) allow for early detection of myocardial injury and hemodynamic stress. We aimed to characterize the burden of subclinical CVD among US adults with lean MASLD. **Methods:** We used data from the All of Us Research Program (2016–2022) to identify adults aged ≥ 18 years without known CVD (including prior myocardial infarction, heart failure, atrial fibrillation, or stroke). We also excluded participants with a history of cancer, and those with missing covariates. Lean MASLD was defined as a diagnosis of MASLD and body mass index (BMI) < 25 kg/m². Subclinical CVD was defined as either elevated hs-cTnT (≥ 14 ng/L) or NT-proBNP (≥ 125 pg/mL). We estimated the prevalence of subclinical CVD among individuals with lean MASLD and compared it to those without MASLD. Poisson regression with robust standard errors was used to estimate adjusted relative risks (aRRs), controlling for age, sex, race/ethnicity, BMI, smoking status, medications, hypertension, hyperlipidemia, diabetes, and chronic kidney disease. **Results:** Among 6,871 adults included in the analysis, 493 (7.2%) had lean MASLD. Subclinical CVD was present in 40.2% of individuals with lean MASLD compared to 34.5% of those without MASLD. In fully adjusted models, lean MASLD was independently associated with elevated risk of subclinical CVD (aRR: 1.38, 95% CI: 1.07–1.70, $p = 0.015$). In stratified analyses, subclinical CVD prevalence increased with age—from 28.2% among adults < 50 to 52.8% in those ≥ 80 years. Prevalence was slightly higher among women (40.3%) than men (39.6%). Among racial/ethnic groups, Black adults with MASLD had the lowest prevalence (15.8%) compared to Hispanic (40.3%) and White (42.3%) individuals. **Conclusion:** Lean MASLD is independently associated with a higher burden of subclinical cardiovascular disease, even after accounting for traditional cardiometabolic risk factors. These findings suggest that lean individuals with MASLD should not be overlooked for CVD risk screening and may benefit from early biomarker-based surveillance strategies.



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2044 | UNSUPERVISED PARTITIONAL CLUSTERING OF HEMOGLOBIN A_{1C} (HBA_{1C}) LEVEL AND TRAJECTORY STRATIFY THE RISK OF LIVER-RELATED COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES (T2D)

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Background: The relationship between glycemic control indicated by HbA_{1c} levels and trajectories and liver-related complications in patients with T2D remains unclear. We aimed to examine whether HbA_{1c} level and early-stage trajectories impact the risk of liver-related complications, including hepatic decompensation, hepatocellular carcinoma, and liver-related death in patients with T2D, and to what extent optimal glycemic control would benefit patients at high risk of liver outcomes. **Methods:** A territory-wide retrospective cohort of patients with T2D from 2000-2016 was identified in Hong Kong. Patients with type 1 diabetes, chronic viral hepatitis, excessive alcohol use, or liver-related complications before baseline or follow-up < 5 years were excluded. Unsupervised partitional clustering was applied to identify trajectories by testing the number of clusters (k) from 1 to 6. Various distance measures with centroid calculation were employed, including Euclidean distance, dynamic time wrapping (DTW) and move-split-merge (MSM) with arithmetic mean, DTW with DTWbarycenter averaging (DBA), and MSM with MSM barycenter averaging (MBA). Cluster validity indices were summarized to determine the optimal k and the best-performing algorithm. The association between HbA_{1c}

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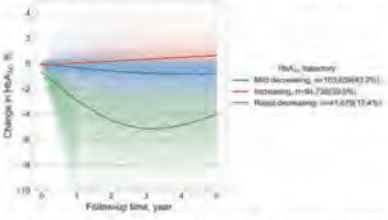
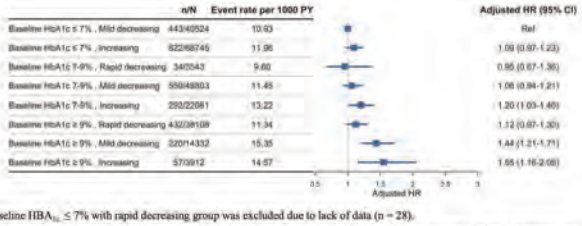
level and trajectories with liver-related complication risk was evaluated using cause-specific hazards models, with non-liver-related death as competing risk. Variation of each trajectory stratified by HbA_{1c} level was quantified by linear mixed models. **Results:** Among 240,076 patients, MSM-MBA identified 3 robust HbA_{1c} trajectories in the first 5 years after T2D diagnosis: mild decreasing (n = 103,659[43.2%]), increasing (n = 94,738[39.5%]) and rapid decreasing (n = 41,679[17.4%]). (Figure A) Patients with baseline $HbA_{1c} \geq 9\%$ had a higher risk (hazard ratio [HR], 1.42 [95% CI, 1.23-1.64]) compared to those with $HbA_{1c} \leq 7\%$. Compared to mild decreasing, patients with rapidly decreasing HbA_{1c} showed a lower risk(HR, 0.80 [95% CI, 0.69-0.92]), while those with increasing HbA_{1c} had a higher risk (HR, 1.10 [95% CI, 1.01-1.20]). Compared to a mild decreasing trajectory with $HbA_{1c} \leq 7\%$, patients with HbA_{1c} levels of 7-9% with an increasing trend, or $\geq 9\%$ with either a mild decreasing or increasing trend, had higher risks of liver-related complications (HR, 1.20 [95% CI, 1.03-1.40], 1.44 [95% CI, 1.21-1.71], and 1.55 [95% CI, 1.16-2.05], respectively), while notably, those with $HbA_{1c} \geq 9\%$ and a rapid decreasing trend did not show increased risk (HR, 1.12 [95% CI, 0.97-1.30]). (Figure B and C) **Conclusion:** Higher baseline HbA_{1c} levels and increasing trajectory are associated with a higher risk of liver-related complications in T2D, while rapid decreasing trajectory is associated with a lower risk. Good glycemic control over time mitigates the risk associated with higher baseline HbA_{1c} levels.

Figure A. HbA_{1c} trajectories across the first 5 years after T2D diagnosis identified by MSM-MBA.



* Individual data belonging to each trajectory was randomly sampled 1,000 times for visualization, and trajectories were fitted using generalized additive models with shrinkage cubic regression splines and 3 knots.

Figure B. Joint association between baseline HbA_{1c} level and HbA_{1c} trajectory and liver-related complications risk in patients with T2D.



* Baseline $HBA_{1c} \leq 7\%$ with rapid decreasing group was excluded due to lack of data (n = 28).

** HRs were adjusted by age, sex, albumin, total bilirubin, platelets, creatinine, ALT and ALT trajectories, cirrhosis, hypertension, dyslipidemia, and the use of statin, insulin, metformin, sulfonylureas, thiazolidinedione, DDP-4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists.

Abbreviations: CI = confidence interval, HbA_{1c} = hemoglobin A_{1c}, HR = hazard ratio, MSM-MBA = move-split-merge with MSM barycenter averaging, PY = person years, T2D = type 2 diabetes.

Figure C. Slope and 95% CI of trajectories stratified by baseline HbA_{1c} level group.

	Annual change in HbA_{1c} (95% CI)* (%/year)		
	Mild decreasing	Increasing	Rapid decreasing
Baseline $HbA_{1c} \leq 7\%$	-0.082 (-0.083 to -0.081)	0.152 (0.151 to 0.153)	-0.228 (-0.297 to -0.158)
Baseline HbA_{1c} 7-9 %	-0.180 (-0.181 to -0.179)	0.156 (0.154 to 0.159)	-0.348 (-0.355 to -0.341)
Baseline $HbA_{1c} \geq 9\%$	-0.381 (-0.385 to -0.377)	0.140 (0.129 to 0.150)	-0.700 (-0.704 to -0.696)

* Estimated by the linear mixed models with patients treated as a random effect.

Disclosures: Nana Peng: Nothing to Disclose, Sherlot Juan Song: Nothing to Disclose, Mary Yue Wang: Nothing to Disclose, Jimmy Che-To Lai: Nothing to Disclose, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company, Eli Lilly: Consultant, Merck: Consultant, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support

2045 | FIBRO-GPT: A LARGE LANGUAGE MODEL FOR ACCURATE PREDICTION OF ADVANCED LIVER FIBROSIS IN MASLD

Basile Njei[1] Nelvis Njei[2] Ysabel Ilagan-Ying[1] Omar Al Ta'ani[3] Sarpong Boateng[4] Yazan Al-Ajlouni[5] Bubu Banini[1], [1]Yale University, [2]Machine Learning and Artificial Intelligence Center, MD, USA, [3]Allegheny Health Network, [4]Yale New Haven Health, Bridgeport Hospital, [5]Department of Medicine, Staten Island University Hospital, NY, USA

Background: Noninvasive liver disease assessment (NILDA) tools, such as Fibrosis-4 index (FIB-4) and NAFLD fibrosis score (NFS), are frequently used to identify patients with metabolic dysfunction-associated steatotic liver disease (MASLD) at risk of advanced fibrosis ($\geq$F3). However, their predictive accuracy is limited. Unlike traditional tools, large language models (LLMs) can dynamically adapt to new data and provide contextual rationales for predictions. Fibro-GPT, a generative pre-trained transformer (GPT)-4-based LLM model, fine-tuned for tabular prediction, was developed to enhance the detection of advanced fibrosis in MASLD. **Methods:** The LLM-based pipeline was developed on a derivation cohort of adults with MASLD (N = 1487) from NHANES 2017–2020. MASLD was defined by hepatic steatosis (CAP $\geq$274 dB/m) assessed on vibration-controlled transient elastography

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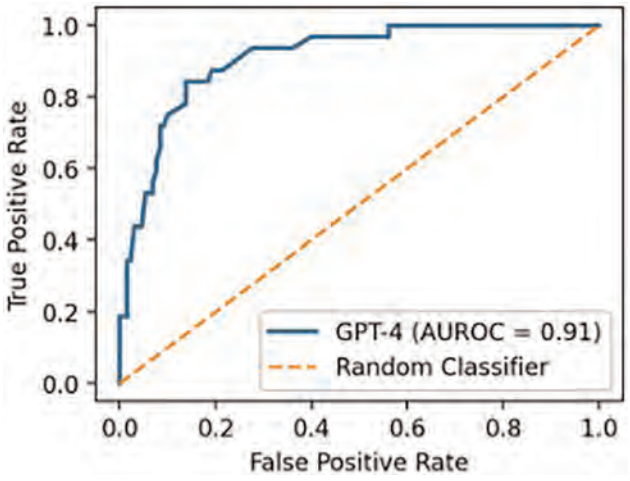
(VCTE) and at least one cardiometabolic criterion, excluding individuals with significant alcohol use (≥1 drink/day for women, ≥2 drinks/day for men) or viral hepatitis. Fibrosis stage was determined using a two-step method: blood-based NILDA tools (FIB-4, NFS), followed by VCTE. Patient data, including age, platelet count, HbA1c, eGFR, BMI, AST, and ALT, were formatted into standardized text prompts and submitted to GPT-4 via a secure Python Interface. Model performance was assessed by AUROC, sensitivity, specificity, Brier score, F1 score, and calibration plots, using bootstrapped 95% confidence intervals. For external validation, we applied the model to an independent biopsy-confirmed MASLD cohort from Yale (n = 105), where liver histopathology served as the gold standard for fibrosis staging. **Results:** In the derivation cohort, Fibro-GPT achieved an AUROC of 0.91, sensitivity of 84%, and specificity of 86% (Fig. 1). Fibro-GPT demonstrated superior predictive accuracy compared to FIB-4 (AUROC: 0.62; P < 0.001) for detecting advanced fibrosis. In the Yale biopsy cohort, Fibro-GPT maintained robust predictive performance, achieving an AUROC of 0.90 (95% CI 0.88–0.97), and outperformed FIB-4 (AUROC 0.75; p < 0.001). **Conclusion:** Fibro-GPT is a highly accurate LLM-based risk prediction model that improves the detection of advanced liver fibrosis compared to FIB-4 in patients with MASLD. These findings highlight the potential for LLMs to enhance the early detection of advanced liver fibrosis and support clinical decision-making in patients with MASLD. Prospective, multicenter studies are warranted to confirm real-world utility.



Disclosures: Basile Njei: Nothing to Disclose, Nelvis Njei: Nothing to Disclose, Ysabel Ilagan-Ying: Nothing to Disclose, Omar Al Ta'ani: Nothing to Disclose, Sarpong Boateng: Nothing to Disclose, Yazan Al-Ajlouni: Nothing to Disclose, Bubu Banini: Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Merck: Grant/Research Support

2046 | NOVEL MATRICELLULAR SERUM MARKER SCORES FOR IMPROVED PREDICTION OF LIVER FIBROSIS AND FIBROGENESIS IN PATIENTS WITH MASLD UNDERGOING BARIATRIC SURGERY

Rambabu Surabattula[1] Pierre Bel Lassen[2] Sudharani Myneni[1] Judith Aron-Wisnewsky[3] Laurent Genser[3] Jean-Daniel Zucker[4] Karine Clément[5] Detlef Schuppan[1], [1]University Medical Center Mainz, [2]Sorbonne Université, INSERM, Nutrition & Obesities: Systemic Approaches Research Group (NutriOmics)., [3]APHP, Nutrition and surgery departments, Pitié-Salpêtrière hospital), F-75013, Paris, France, [4]UMMISCO, Unité de Modélisation Mathématique et Informatique des Systèmes Complexes, [5]Sorbonne Université, INSERM, Nutrition & Obesities: Systemic Approaches Research Group (NutriOmics),

Background: Severe obesity is a risk factor for MAFLD, and the prevalence in patients eligible for bariatric surgery (BS) can reach 75-100%. We established novel serum markers for liver fibrosis and evaluated them in patients with severe obesity and MAFLD before and after undergoing BS. **Methods:** ELISA tests were established using combinations of recombinant proteins, commercial and self-produced monoclonal and polyclonal antibodies to measure the matricellular fibrosis markers TSP2 (thrombospondin 2), IGFBP7 (insulin like growth factor binding protein 7) and ADAMTS9 (a disintegrin and metalloprotease thrombospondin like-9) in 132 severely obese patients with matched liver biopsies. Sensitivity and specificity were optimized with less than 10% and 15% variation between serum and plasma tests, respectively. 54 patients had moderate to advanced fibrosis (stage F2-4) and 74 had stage F0-1 fibrosis. Follow-up fibrosis markers were analyzed in 51 patients 3 and 12 months after BS. **Results:** Patients with F2-4 vs F0-1 fibrosis displayed significantly higher mean baseline levels for TSP2 (88.6 vs 53.9) and IGFBP7 (208.8 vs 128 ng/ml). TSP2 & IGFBP7 were significantly higher in patients with severe fibrosis F3-4 (means 114.4 & 234.5 ng/ml, resp.) indicating more rapid fibrosis progression compared to fibrosis F0-2 (means 62 & 152.3 ng/ml, resp.). AUROC for fibrosis F2-4 or F3-4 vs F0-1 or F0-2 were 0.74 and 0.84 for TSP2, 0.84 and 0.78 for IGFBP7, and 0.72 and 0.70 for ADAMTS9. Given the good diagnostic performance of TSP2 & IGFBP7, we developed new algorithms (ADAPT-2 & ADAPTI) based on these 2 fibrosis markers along with age, diabetes and platelets. Both ADAPT-2 and ADPTI scores (AUROC: 0.86) out performed FIB4, ADAPT and TSP2 & IGFBP7 alone in detecting significant (≥F2) and advanced fibrosis (≥F3). Serum levels of matricellular markers were also correlated with insulin resistance and type 2 diabetes status. Levels of TSP2 were significantly

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decreased 3 months after BS – most prominently in patients with baseline F2-4 fibrosis. The underlying biochemistry as well as the results support a prominent role of TSP2 in liver fibrogenesis, and of IGFBP7 (ADAMTS9) in metabolic-fibrogenic inflammation. **Conclusion:** In patients undergoing BS, the markers TSP2 and IGFBP7, and especially the TSP2 and IGFBP7 based algorithms (ADAPT2 and ADAPTI) showed the highest predictive value for F2-4 fibrosis and the antifibrotic effect of BS.

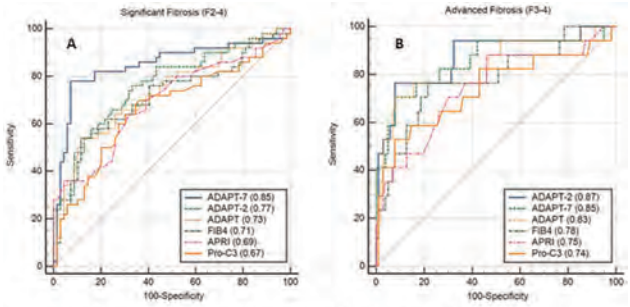

Figure 1. AUROCs to distinguish significant (A) and advanced fibrosis (B).

Disclosures: Rambabu Surabattula: Nothing to Disclose, Pierre Bel Lassen: Nothing to Disclose, Sudharani Myneni: Nothing to Disclose, Judith Aron-Wisnewsky: Nothing to Disclose, Laurent Genser: Nothing to Disclose, Jean-Daniel Zucker: Nothing to Disclose, Karine Clément: Nothing to Disclose, Detlef Schuppan: Nothing to Disclose

2047 | FAP INDEX: A NEW STATISTICAL MODEL IN IMPROVING TRIAGE FOR ADVANCED LIVER FIBROSIS IN OBESE OR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC INDIVIDUALS USING A SPECIFIC MARKER OF ACTIVATED STELLATE CELLS AND MYOFIBROBLASTS

Bobby Boumelhem[1] Ziqi Vincent Wang[1] William Bachovchin[2] Geraldine Ooi[3] Jacob George[4] Mohammed Eslam[4] Leon Adams[5] Hui Zhang[1] Geoffrey McCaughan[1] Avik Majumdar[6] Mark Gorrell[1], [1]The Centenary Institute, The University of Sydney, Sydney, Australia, [2]Tufts University, Boston, United States of America, [3]Monash University, Melbourne, Australia, [4]Westmead Institute of Medical Research, The University of Sydney, Sydney, Australia, [5]The University of Western Australia, Perth, Australia, [6]The Austin Hospital, The University of Melbourne, Melbourne, Australia

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) drives chronic liver injury leading to fibrosis. Fibrosis is the major correlate of adverse health outcomes in MASLD. Non-invasive tests (NITs) for liver fibrosis must accurately discriminate fibrosis severity while minimising indeterminate results. Accurate blood test-based NITs are especially needed for primary screening in general practice, diabetes and obesity clinics. Currently, most NITs include a statistical model based on markers of hepatocyte damage rather than products of activated mesenchymal cells (stellate cells and fibroblasts) that create and regulate fibrosis. Fibroblast activation protein (FAP) digests collagens and TGFbeta precursors and is highly expressed by myofibroblasts and activated stellate cells in cirrhosis. Here, we investigated the utility of circulating FAP (cFAP) to detect fibrosis in MASLD. **Methods:** FAP shed from cell surfaces is an active enzyme that is stable in human serum and plasma. We applied our quantitative, specific, rapid, one-step FAP enzyme assay to sera from a bariatric cohort (training cohort, $n = 160$, 36% diabetic, 20.3% F3-F4) and a bariatric/MASLD cross-validation cohort ($n = 332$, 30% diabetic, 11.4% F3-F4). **Results:** Fibrosis was associated with cFAP in MASLD cohorts ($p < 0.05$). We coined the term FAP Index for a multi-variate model that was developed combining cFAP with age, diabetes status and ALT to evaluate liver fibrosis risk, especially in individuals who had an indeterminate result in an NFS or FIB4 test. The training cohort AUROC was 0.875 with a negative prediction value of 92% and a positive prediction value of 95%, indicating high accuracy. The cross-validation cohort AUROC was 0.84, with 98.5% specificity and 55% sensitivity. By serial application of NFS or FIB4 then FAP Index, the proportion of indeterminate results more than halved, to $< 15\%$. Therefore, applying cFAP measurement as a reflex test following an indeterminate FIB4 or NFS would likely have economies of time and expense, and lower the need for obesity-specialised secondary testing. **Conclusion:** We present a novel, inexpensive fibrosis NIT for assessment and triage of individuals with diabetes, steatosis or obesity. We suggest that an advantage of including FAP Index in clinical fibrosis assessments is that FAP is strongly expressed by liver cell types that regulate the extracellular matrix.

Disclosures: Bobby Boumelhem: Nothing to Disclose, Ziqi Vincent Wang: Nothing to Disclose, William Bachovchin: Nothing to Disclose, Geraldine Ooi: Nothing to Disclose, Jacob George: Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, novo Nordisk: Advisor, Boehringer Ingleheim: Advisor, Boehringer Ingleheim: Speaking and Teaching, Roche: Advisor, Astra Zeneca: Advisor, Gilead: Advisor, Eisai: Advisor, Mohammed Eslam: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Dr Falk: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Boehringer Ingelheim: Speaking and Teaching, Hui Zhang: Nothing to Disclose, Geoffrey McCaughan: Nothing to Disclose, Avik Majumdar: Nothing to Disclose, Mark Gorrell: Nothing to Disclose

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2048 | DEVELOPMENT, VALIDATION, AND PROGNOSTIC EVALUATION OF OBESITYLIVER SCORE FOR SIGNIFIEANT LIVER FIBROSIS IN OVERWEIGHT AND OBESITY POPULATION: A MULTICOHORT STUDY

Bicheng Ye[1] Shanghao Liu[1] Jie Zhang[2] Yilin Zhang[1] Caihong Gu[3] Rong Hu[3] Haiying Feng[4] Xibin Liu[4] Zhenyu Dai[5] Pinglei Pan[5] Yijun Tang[6] Zhongji Meng[6] Puqiang Liu[7] Jianping Zhang[7] Xiao Liang[8] Yongfen Zhu[8] Huizhen Fan[9] Jianwen Sheng[10] Qing He[11] Fengjuan Chen[11] Yong Pan[12] Ruyu Liu[12] Ji JianSong[13] Yanru Xie[13] Manguo Zhao[14] Lingxiao Wang[14] Junhong Yang[14] Yan Yang[14] Yang Hui[15] Zhao Yajuan[15] Yang Bo[16] Jing Wang[16] Shuli Hao[17] Youfang Gao[17] Tongqin Han[18] Yuxia Qi[18] Yongyi Zeng[19] Guo Zhang[20] Wenjuan Wang[20] Qiang Yan[21] Zhaowei Tong[22] Gao-Jun Teng[23] Qi Xiaolong[23], [1]Southeast University, [2]Huai'an Hospital Affiliated to Xuzhou Medical University, [3]The First People's Hospital of Lianyungang, [4]Huanghua People's Hospital, [5]Affiliated Yancheng Hospital, School of Medicine, Southeast University, [6]Taihe Hospital, Hubei University of Medicine, [7]Puxian People's Hospital, [8]Sir Run-Run Shaw Hospital, [9]Yichun People's Hospital, Yichun, [10]Yichun People's Hospital,Yichun,J, [11]Shenzhen third People's Hospital, [12]Xuzhou Infectious Diseases Hospital, [13]The Fifth Affiliated Hospital of Wenzhou Medical University, [14]Baiyin Central Hospital, [15]The Second Affiliated Hospital of Guangzhou Medical University, [16]General Hospital of Ningxia Medical University, [17]Bozhou People's Hospital, [18]Qingdao Public Health Clinical Center, [19]Mengchao Hepatobiliary Hospital of Fujian Medical University, [20]Guangxi Hospita1 Division of The First Affiliated Hospital, [21]Huzhou Central Hospital, [22]Huzhou Key Laboratory of Precision Medicine Research and Translation for Infectious Diseases, [23]Zhongda Hospital, Medical School, Southeast University

Background: Overweight and obesity are closely associated with liver fibrosis and adverse hepatic outcomes. This study aimed to develop a reliable tool for assessing liver fibrosis risk in primary care settings for overweight and obese populations. **Methods:** The ObesityLiver score was developed and validated using five independent cohorts from China, the United States, and England. In the derivation cohort, we used elevated liver stiffness ($\geq$8 kPa) for variable selection and built the model with ten machine learning algorithms. The score was validated across all cohorts to predict elevated liver stiffness, significant liver fibrosis (histological stage $\geq$F2), and liver-related outcomes at 5, 10, and 15 years. Predictive performance was assessed using receiver operating characteristic curves and Kaplan-Meier survival analysis. **Results:** In a derivation cohort of 2,731 participants, we developed ten distinct machine learning models and ultimately selected a gradient boosting machine model based on five pivotal biomarkers including body mass index, gamma-glutamyl transferase, aspartate aminotransferase, glycated hemoglobin percentage, and platelet count. The ObesityLiver score showed good accuracy for predicting elevated liver stiffness in the derivation cohort (AUC 0.81, 95% CI 0.78–0.85) and validation cohorts 1 (n = 3,544; AUC 0.78, 95% CI 0.74–0.81) and 2 (n = 2,371; AUC 0.81, 95% CI 0.78–0.83). Validation cohort 3 (n = 311), which used liver biopsy, also demonstrated strong diagnostic performance with an AUC of 0.77 (95% CI 0.71–0.82) for predicting significant liver fibrosis. The ObesityLiver score outperformed the fibrosis-4 index, non-alcoholic fatty liver disease fibrosis score, aspartate aminotransferase to platelet ratio index, LiverRisk score, and others in predicting significant liver fibrosis and elevated liver stiffness. Furthermore, in the prognosis cohort, the ObesityLiver Score demonstrated robust predictive ability for liver-related outcomes at 5, 10, and 15 years, with AUCs ranging from 0.76 to 0.83. **Conclusion:** The ObesityLiver score reliably identifies clinically significant liver fibrosis and elevated liver stiffness, predicts the risk of liver-related events for overweight and obesity populations in primary care.

Figure

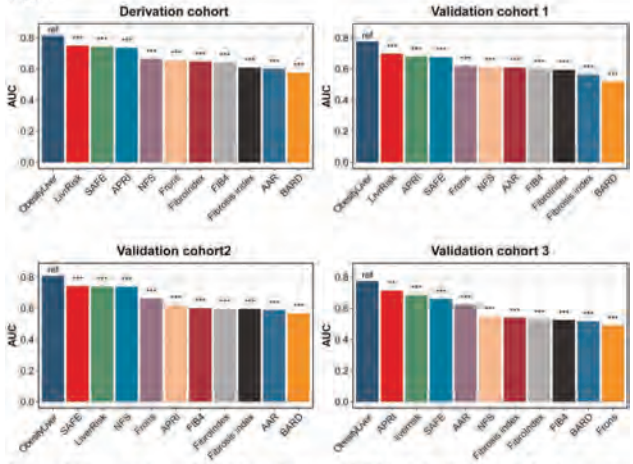

Figure 1. Comparison of non-invasive tests (NITs). A-C. Bar charts displaying the ability of multiple NITs to predict elevated liver stiffness (≥8 kPa) in the derivation cohort (**A**), validation cohort 1 (**B**), validation cohort 2 (**C**). **D.** Bar charts displaying the ability of multiple NITs to predict significant liver fibrosis (histological stage ≥F2) in the validation cohort 3. FIB-4=fibrosis-4. NFS=nonalcoholic fatty liver disease fibrosis score. APRI=aspartate aminotransferase-to-platelet ratio index. AAR=aspartate aminotransferase to alanine aminotransferase ratio. AUC=area under the receiver operating characteristic curve. Ref= reference. *p < 0.05; **p < 0.01; ***p < 0.001. P-values tested using DeLong method.

Disclosures: Bicheng Ye: Nothing to Disclose, Shanghao Liu: Nothing to Disclose, Jie Zhang: Nothing to Disclose, Yilin Zhang: Nothing to Disclose, Caihong Gu: Nothing to Disclose, Rong Hu: Nothing to Disclose, Haiying Feng: Nothing to Disclose, Xibin Liu: Nothing to Disclose, Zhenyu Dai: Nothing to Disclose, Pinglei Pan:

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2049 | PREDICTIVE VALUE OF NON-INVASIVE TESTS VARIES ACROSS NOVEL DATA-DRIVEN MASLD CLUSTERS

Nicolas Desmons[1] Guillaume Lassailly[1] Violeta Raverdy[1] Macine Bachir Abdelouahab[1] Robert Caiazzo[1] Helene Verkindt[1] Viviane Gnemmi[1] Emmanuelle Leteurtre[1] Philippe Mathurin[1] Guillemette Marot[1] Francois Pattou[1], [1]University of Lille

Background: Non-invasive tests (NITs) are increasingly used to identify patients with at-risk form of MASLD in the general population. The performance of NITs for detecting liver fibrosis and/or MASH may vary with patient characteristics (i.e. age or body mass index). Two novel data-driven endotypes of MASLD at risk for liver fibrosis and MASH have been recently identified (Raverdy et al., Nat Med, 2024 / PMID: 39653777) : the cardiometabolic (CM) cluster and the liver specific (LS) cluster. Despite displaying similar liver histological features, the newly described clusters are characterized by distinct underlying biological profiles and different clinical trajectories. The aim of this study was to compare the predictive value of common NITS to predict fibrotic MASH across novel data driven clusters. **Methods:** Participants in this retrospective study were unselected patients with class II–III obesity who underwent bariatric surgery, and for whom all necessary biological results and liver histology (CRN) were available. Patients were allocated to one MASLD cluster (CM, LS, or Control) using partionning around median hard clustering, based on six simple variables: age, BMI, HbA1c, ALT, LDL-cholesterol, and triglycerides, as initially described. We also calculated in each patient four NITs - fibrosis-4 index (FIB-4), NAFLD fibrosis score (NFS), NAFLD index (FNI), and Liver risk score (LRS) - and analyzed their predictive value to diagnose fibrotic MASH, defined as the coexistence of Steatostis, Ballooning, and Inflammation (≥ 1 each) and Fibrosis (≥ 2). The area under the receiver operating characteristic (AUROC) of the four NITs were calculated in each cluster and compared with DeLong's test. **Results:** A total of 1031 patients were enrolled (median age 42 years, 26% women; BMI 47 kg/m²; HbA1c 5.80%; ALT 27 IU/L; LDL 3.06 mmol/L; triglycerides 1.40 mmol/L). Among them, 132 (13%) were allocated to the CM, 73 (7%) to LS, and 826 (80%) to control cluster, with a prevalence of Fibrotic MASH of 13 (10%), 10 (14%) and 22 (3%) respectively ($p < 0.001$). Figure 1A displays median patient characteristics in each cluster. Figure 1B displays the AUROC (95% CI) to diagnose fibrotic MASH for each NITs across the three clusters. In CM, AUROC values were higher for FNI and LRS and significantly superior than for FIB-4 ($p < 0.001$) and NFS ($p < 0.001$). In LS, AUROC values were higher for NFS and FIB-4 but not significantly different from FNI and LRS. **Conclusion:** The performance of NITs to diagnose fibrotic MASH varied across novel data driven MASLD clusters. FIB-4 and NFS showed acceptable predictive value in patients with LS MASLD, but not in those with CM MASH. In the CM and control clusters, fibrotic MASH was best predicted by FNI and LRS. Our findings highlight the need to consider novel MASLD clusters when evaluating the predictive value of NITs.

A

B

NITs	Cardio-metabolic	Liver specific	Control	All patients
FIB-4	0.55 (0.37-0.74)	0.74 (0.59-0.89)	0.73 (0.62-0.85)	0.73 (0.65-0.8)
NAFLD Fibrosis Score	0.44 (0.27-0.62)	0.79 (0.67-0.91)	0.65 (0.53-0.77)	0.65 (0.58-0.73)
Liver Risk Score	0.75 (0.63-0.87)	0.61 (0.4-0.83)	0.85 (0.78-0.91)	0.82 (0.77-0.88)
Fibrotic Nash index	0.79 (0.66-0.93)	0.69 (0.55-0.83)	0.88 (0.81-0.96)	0.87 (0.82-0.91)

Disclosures: Nicolas Desmons: Nothing to Disclose, Guillaume Lassailly: Nothing to Disclose, Violeta Raverdy: Nothing to Disclose, Macine Bachir Abdelouahab: Nothing to Disclose, Robert Caiazzo: Nothing to Disclose, Helene Verkindt: Nothing to Disclose, Viviane Gnemmi: Nothing to Disclose, Emmanuelle Leteurtre: Nothing to Disclose, Philippe Mathurin: Nothing to Disclose, Guillemette Marot: Nothing to Disclose, Francois Pattou: Nothing to Disclose

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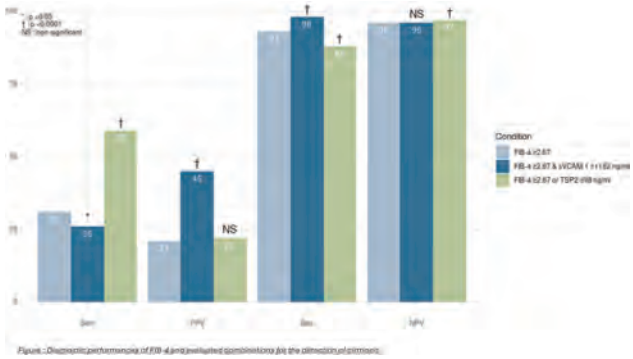
2050 | COMBINING SVCAM-1 OR TSP2 WITH FIB-4 FOR AN IMPROVED DETECTION OF PATIENTS WITH CIRRHOSIS

Sven Francque[1] Bérénice Alard[2] Jérémy Magnanensi[2] Zouher Majd[2] Dean Hum[3] Jerome Boursier[4] Bart Staels[5] Quentin Anstee[6] Vlad Ratziu[7] Arun Sanyal[8], [1]Department of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium, [2]GENFIT SA, [3]GENFIT CORP, [4]Angers University, [5]University Lille 2, [6]Newcastle University, UK, [7]Service D' Hepatogastroenterologie (FR), [8]Virginia Commonwealth University

Background: Prevalence of MASH-related liver cirrhosis (F4) is increasing worldwide. Screening for this largely asymptomatic condition in primary care settings is of major importance as patients (pts) with compensated cirrhosis are at high risk of acute decompensation, development of HCC and liver-related mortality, leading their clinical management to be adapted accordingly. We aimed to compare the diagnostic performances of FIB-4 with single blood-based biomarkers (BM) and evaluate combinations of those BMs with FIB-4 for an improved detection of pts with F4. **Methods:** Among pts screened for potential inclusion in the RESOLVE-IT Phase 3 trial (NCT02704403), those with FIB-4 available and complete values on 40 circulating BMs of interest were selected (discovery cohort, N = 1,640). AUC and associated Delong tests were used to compare the overall performance of the BMs vs FIB-4 for the detection of F4. For BMs with at least similar AUC as FIB-4, cutoffs were derived to achieve similar specificity (spe) as FIB-4 at its threshold indicative of pts referral to specialists (2.67). Corresponding sensitivity (sen), PPV and NPV were computed and compared with FIB-4 ones. Performances of concomitant uses of FIB-4 and single BMs with their associated cutoffs were evaluated to identify conditions that either maximize sen or PPV. An independent single-center (Angers University Hospital, France) cohort of N = 220 pts recruited with suspected MASLD was used to validate the results. **Results:** In the discovery cohort, 5.5% (n = 90) of pts had F4 and FIB-4 achieved an AUC of 0.780 for the detection of those pts. Among the 40 BMs evaluated, 6 achieved similar AUC as FIB-4 and were considered as potential substitutes or for concomitant uses with FIB-4: TSP2 (0.814), sVCAM-1 (0.796), hyaluronic acid (0.784), A2M (0.773), TIMP-1 (0.769) and YKL-40 (0.750). Among these BMs, sVCAM-1 with a cutoff of 1,182 ng/mL was the only marker which detected F4 with a significantly higher sen than FIB-4 (0.42 vs 0.31, p = 0.0253) while keeping similar spe (0.93). Among all concomitant uses of FIB-4 and single BMs, the condition [FIB-4 $\geq$ 2.67 and sVCAM-1 $\geq$ 1,182 ng/mL] achieved the highest PPV, significantly surpassing FIB-4 alone (0.45 vs 0.21, p $<$ 0.0001) with higher spe (0.98 vs 0.93, p $<$ 0.0001) but lower sen (0.26 vs 0.31, p = 0.0253). The condition [FIB-4 $\geq$ 2.67 or TSP2 $\geq$ 98 ng/mL] exhibited the highest sen, significantly surpassing FIB-4 alone (0.59 vs 0.31, p $<$ 0.0001) with similar PPV (0.22 vs 0.21, p = 0.71) but lower spe (0.88 vs 0.93, p $<$ 0.0001). In the validation cohort, 7.8% (n = 17) of pts had F4. Overall, findings were validated in this population. **Conclusion:** sVCAM-1 and TSP2 showed high performances for the detection of pts with cirrhosis. Their concomitant use with FIB-4 significantly surpassed the performances of FIB-4 alone and could thus represent valuable BMs to deploy on large scale for improving the referral pathway in primary care.



Disclosures: Sven Francque: Nothing to Disclose, Bérénice Alard: GENFIT SA: Employee, Jérémy Magnanensi: Nothing to Disclose, Zouher Majd: Nothing to Disclose, Dean Hum: Nothing to Disclose, Jerome Boursier: Nothing to Disclose, Bart Staels: Genfit SA: Consultant, Quentin Anstee: AstraZeneca, Boehringer Ingelheim, Intercept.: Grant/Research Support, Alimentiv, Akero, AstraZeneca, Axcella, 89Bio: Consultant, Boehringer Ingelheim, Bristol Myers Squibb, Corcept: Consultant, Enyo Pharma, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKl: Consultant, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janss: Consultant, Madrigal, Medpace, Merck, Metadeq, NGMBio, North Sea T: Consultant, Novartis, Novo Nordisk, PathAI, Pfizer, Pharmanest: Consultant, Poxel, Prosciento, Resolution Therapeutics, Roche,: Consultant, Ridgeline Therapeutics, RTI, Shionogi, Terns: Consultant, Fishawack, Integritas Communications, Kenes,: Speaking and Teaching, Novo Nordisk, Madrigal, Medscape, Springer Healthcare: Speaking and Teaching, Elsevier Ltd: Royalties or patent beneficiary, Vlad Ratziu: Novo-Nordisk: Consultant, Boehringer-Ingelheim: Consultant, Madrigal: Consultant, Akero: Consultant, 89Bio: Consultant, Sagimet: Consultant, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca ($<$ 5K), Terns ($<$ 5K), Merck ($<$ 5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis ($<$ 5K),: Consultant, Novo Nordisk: Consultant, Regeneron ($<$ 5K), Alnylam ($<$ 5K), Akero ($<$ 5K),: Consultant,

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2051 | LONGITUDINAL FOLLOW-UP OF A TGF-β PATHWAY-RELATED BIOMARKER PANEL THAT STRATIFIES HCC RISK IN CIRRHOTIC PATIENTS

Lopa Mishra[1] Xiyan Xiang[1] Richard Amdur[2] Brandon Mathew[3] Kirti Shetty[4] Herbert Yu[5] Linda Wong[6] Bibhuti Mishra[1] Sanjaya Satapathy[7] James Crawford[8] Lopa Mishra[1], [1]Feinstein Institutes for Medical Research & Cold Spring Harbor Laboratory, [2]The Institutes for Health Systems Science & Bioelectronic Medicine, [3]Feinstein Institutes for Medical Research, [4]University of Maryland, Baltimore, [5]University of Hawaii Cancer Center, [6]University of Hawaii, [7]Northwell Health and Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, [8]Northwell Health

Background: Current screening for early diagnosis of HCC remains suboptimal particularly in obese individuals with MASLD/MASH. We and others have identified a major role of the TGF-β pathway in fibrosis, MASH and HCC through human genomic analyses (Korkut, Cell Systems, 2018) and mechanistic insight from HCC models (Yang, Cell Reports, 2024). We hypothesized that the TGF-β pathway through its instrumental role in ongoing pathology from fibrosis to cirrhosis to cancer could provide functional markers predicting HCC risk. **Methods:** 7000 serum proteins (Somalogic) assayed in a total of 477 cirrhotic patients (125 with HCC) from four Institutions and revealed a strong TGF-β pathway signature in the retrospective cohort A (n = 216, Xiang, Genes & Cancer, 2024). Clustering analysis in the prospective cirrhotic cohort B (n = 312) was performed. Longitudinal follow up cohort B revealed 18 HCCs in 312 patients over a median of 5-years. ELISA validation was carried out for seven protein markers raised in HCC. A predictive model based on the TGF-β Pathway was developed using multivariable logistic regression analysis in the matched cohort C (109 pairs, n = 328). Model performance was 10-fold cross-validated across the entire cohort (n = 477). **Results:** TGF-β-related protein signature displayed a five-fold increased risk of HCC development (9.68% vs. 1.91%) in the longitudinal cohort B. Compared to cirrhosis, ELISA validated increases in serum MSTN, TGFBR2, and AFP in HCC (odds ratio = 1.4-2.9, $p < 0.05$); MSTN and SPTBN1 were elevated in HCCs with MASLD/ALD ($p < 0.05$); however, no significant alterations were observed for serum HMGB1, IL-6 and COL1A1. In a subsequent matched cohort C, 88 proteins were significantly altered in HCC ($p < 0.05$). The six-protein panel (TGFBR2, MSTN, AFP, COL18A1, GLUL, TP63) displayed a strong performance in this matched cohort C (AUC 0.87, sensitivity 0.88, specificity 0.72), with four clinical factors (Age, Sex, BMI, Bilirubin). This panel performed equally well in specific subgroups including obese and MASLD/ALD (AUC 0.90, 0.92) related patients, and in the longitudinal cohort B of patients with mild to moderate cirrhosis (AUC 0.86). **Conclusion:** TGF-β pathway-related markers can potentially stratify HCC risk in cirrhotic patients in support of our approach towards capturing ongoing pathology in the liver. Next steps will be large-scale validations of this biomarker panel in cirrhotic patients across larger populations in Phase II/III studies.

Disclosures: Lopa Mishra: Nothing to Disclose, Nothing to Disclose, Xiyan Xiang: Nothing to Disclose, Richard Amdur: Abbvie: Stock - publicly traded company, Brandon Mathew: Nothing to Disclose, Kirti Shetty: Nothing to Disclose, Herbert Yu: Nothing to Disclose, Linda Wong: Astra Zeneca: Speaking and Teaching, Bibhuti Mishra: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support, James Crawford: Project Santa Fe Foundation: Chair, Board of Directors; no remuneration, ClaraPath: Non-voting member, board of directors; no remuneration, Northwell Health Genomics Alliance: President; no remuneration, Lopa Mishra: Nothing to Disclose, Nothing to Disclose

2052 | PREVALENCE OF STEATOSIS AND LIVER FIBROSIS IN PATIENTS WITH MASLD/MASH FROM NON-HEPATOLOGY CENTERS IN THE USA AND EUROPE

Jörn Schattenberg[1] Julie Foucquier[2] Mamta Upadhyay[3] Kwabena Opuni[3] Victor de Lédinghen[2] Kenneth Cusi[4],

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

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Background: There are limited data among individuals on the prevalence of significant fibrosis in patients with MASLD/MASH outside tertiary hepatology centers (e.g. primary care, diabetology units). The aim of this study was to fill that gap in knowledge by determining the Vibration-Controlled Transient Elastography (VCTE FibroScan) prevalence of steatosis. **Methods:** This is a cross-sectional analysis of prospectively enrolled adults with MASLD/MASH (18 to 80 years) from primary care and private diabetology settings in the USA, Germany, Italy and Spain. Liver steatosis and fibrosis were assessed using FibroScan Go™, a connected device designed for upstream centers. All patients had at least 10 valid measurements and IQR/LSM (Liver Stiffness Measurement) ratio < 0.3. Steatosis was defined as CAP (Controlled Attenuation Parameter) $>$ 274 dB/m. The moderate fibrosis, advanced fibrosis and cirrhosis were defined as LSM between 8 and 12 kPa, between 12 and 15 kPa and $>$ 15 kPa, respectively. After a first selection of variables with univariate analyses at the 10% significance level, multivariate analyses were performed to determine the factors associated with CAP > 274 dB/m, with LSM ≥ 8 kPa and with both LSM ≥ 8 kPa and CAP > 274 dB/m (at the 5% significance level). **Results:** The cohort included 2050 participants, 1985 from USA (96.8%), 1072 (52.3%) female, 984 patients with an age between 50 and 70 years (48%) and 755 (36.8%) with a body mass index (BMI) > 30 kg/m²). Main setting was primary care (64.9%). Median (IQR) LSM was 5.1 (2.6) kPa and mean (SD) CAP was 261 (56) dB/m. The prevalence of steatosis (CAP $>$ 274 dB/m) was 38.8%. The prevalence of moderate fibrosis, advanced fibrosis and cirrhosis was 8.6%, 1.9% and 3.1%, respectively. A total of 8.8% of the patients had LSM $\geq$ 8 kPa and CAP $>$ 274 dB/m. By univariate analysis, factors associated with CAP > 274 dB/m were age, gender, BMI and country (US vs Europe). By multivariate analysis, factors associated with CAP > 274 dB/m were age, male gender, and BMI (irrespective of the BMI class). By univariate analysis, factors associated with LSM ≥ 8 kPa were age, gender, BMI, country (US vs Europe) and type 2 diabetes (T2D). By multivariate analysis, factors associated with LSM ≥ 8 kPa were age > 70 years old, male gender, having obesity (BMI) and T2D. By univariate analysis, factors associated with LSM $\geq$ 8 kPa and CAP $>$ 274 dB/m were age, gender, BMI, country and T2D. By multivariate analysis, factors associated with LSM $\geq$ 8 kPa and CAP $>$ 274 dB/m were age $>$ 70 years and male gender. **Conclusion:** The prevalence of moderate to advanced fibrosis and cirrhosis in patients with MASLD/MASH by VCTE is high (13.6%) in patients from centers other than that from tertiary hepatology centers. Therefore, screening with VCTE for clinically significant liver fibrosis in patients with MASLD/MASH offers a unique opportunity for early diagnosis in primary care and diabetes centers in private settings, especially in patients with T2D and obesity.

Disclosures: Jörn Schattenberg: Apollo Endoscopy, Boehringer Ingelheim, Gilead Sciences: Consultant, Intercept Pharmaceuticals: Consultant, Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals: Consultant, MSD, Northsea Therapeutics, Novartis, Novo Nordisk: Consultant, Pfizer, Roche, Sanofi, and Siemens Healthineers: Consultant, Boehringer Ingelheim, Siemens Healthcare GmbH: Grant/Research Support, Alentis, Alexion, Altimmune, Astra Zeneca, 89Bio, Bionorica,: Consultant, Boehringer Ingelheim, Gilead Sciences, GSK, Ipsen, Inventiva: Consultant, Madrigal Pharmaceuticals, Lilly, MSD, Northsea Therapeutics,: Consultant, Novo Nordisk, Pfizer, Roche, Sanofi, and Siemens Healthineer: Consultant, AbbVie, Academic Medical Education (AME),: Speaking and Teaching, Boehringer Ingelheim, Echosens: Speaking and Teaching, Forum für Medizinische Fortbildung (FOMF), Gilead Sciences: Speaking and Teaching, MedicalTribune, MedPublico GmbH, MedScape,: Speaking and Teaching, Novo Nordisk, Madrigal Pharmaceuticals,: Speaking and Teaching, Akero, Alentis, Alexion, Altimmune, Astra Zeneca, 89Bio: Consultant, Bionorica, Boehringer Ingelheim, Gilead Sciences, GSK,: Consultant, HistoIndex, Ipsen, Inventiva Pharma, Madrigal Pharmaceutical: Consultant, Kríya Therapeutics, Lilly, MSD Sharp & Dohme GmbH: Consultant, Northsea Therapeutics, Novartis, Novo Nordisk: Consultant, Pfizer, Roche, Sanofi, Siemens Healthineers,: Consultant, Summit Clinical, and Vantage Biosciences Research: Consultant, AbbVie, Boehringer Ingelheim, Gilead Sciences,: Speaking and Teaching, Ipsen Novo Nordisk,: Speaking and Teaching, Madrigal Pharmaceuticals, Worldwide Clinical Trials: Speaking and Teaching, Hepta Bio.: Stock – privately held company, Akero: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Ipsen: Consultant, Inventiva Pharma: Consultant, Madrigal: Consultant, Northsea Therapeutics: Consultant, Novo Nordisk: Consultant, Roche: Consultant, Siemens Healthineers: Consultant, Boehringer Ingelheim: Grant/Research Support, AGED diagnostics: Stock – privately held company, Hepta Bio: Stock – privately held company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock – privately held company, MedPublico GmbH: Speaking and Teaching, Julie Foucquier: Nothing to Disclose, Mamta Upadhyay: Novo Nordisk:

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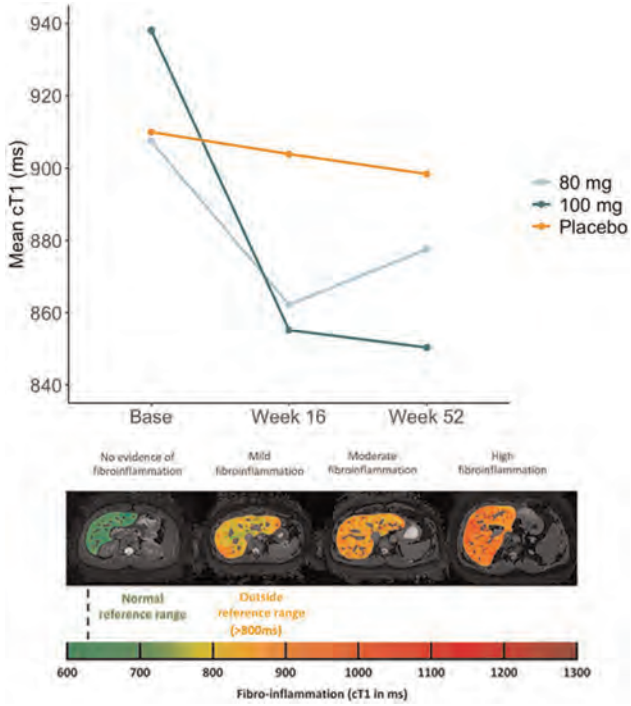
Employee, Kwabena Opuni: Nothing to Disclose, Victor de Lédinghen: Nothing to Disclose, Kenneth Cusi: Nothing to Disclose

2053 | NOVEL MULTIPARAMETRIC MRI IMAGING PREDICTS HISTOLOGIC RESPONSE IN RESMETIROM VERSUS PLACEBO IN THE MULTICENTRE, INTERNATIONAL, MAESTRO-NASH PHASE 3 TRIAL

Anneli Andersson[1] Hang Zhang[2] Andrea Dennis[1] Rebecca Taub[2] Dominic Labriola[2] Rohit Loomba[3], [1]Perspectum, [2]Madrigal Pharmaceuticals, [3]University of California, San Diego

Background: Resmetirom was approved by FDA in March 2024 and is indicated for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis. The Phase 3 trial MAESTRO-NASH (NCT03900429) evaluated the efficacy of resmetirom in patients with NASH and achieved its primary outcomes. For a subset of patients MRI-derived cT1, a marker of fibro-inflammation, was collected. A reduction in cT1 of 80ms has been identified as the optimal threshold associated histological response. We explored the cT1 responses observed in the MAESTRO-NASH trial. **Methods:** Adults with ≥3 metabolic risk factors, liver stiffness ≥8.5 kPa, hepatic fat ≥8%, biopsy-confirmed NASH with F1B-F3 fibrosis, and NAS ≥4 were eligible to participate in MAESTRO-NASH. cT1 was acquired using LiverMultiScan. Average changes in cT1 with increasing dose, and with histological response was assessed and summary descriptive statistics reported. cT1 responders were considered those who had an ≥80ms reduction in cT1 from baseline. **Results:** 156 patients had cT1 and histology data (mean age: 57 years old, 56% female, mean BMI: 37kg/m^2). cT1 and PDFF were positively correlated (Spearman's rho: 0.68 – 0.83) and cT1 increased with increasing fibrosis stage, PDFF did not. After 16-weeks of Resmetirom treatment, the mean reduction in cT1 was -48ms (SD: 101ms) in the 80mg group (N = 37) and -78ms (SD: 88ms) in the 100mg group (n = 46). There was minimal change in the in the placebo group (-8ms, (SD: 56ms), N = 51). This dose-dependent pattern in cT1 change was maintained at 52 weeks. Additionally, 25% and 36% met the cT1 response criteria in the 80mg and 100mg arms, respectively. cT1 reduction was larger in histological responders than non-responders for NASH Resolution in the 100mg arm (mean change -125ms vs. 46ms; cT1 responders 53% vs. 19%) and for fibrosis Improvement in both 80mg (mean change -84ms vs. 11ms) and 100mg arms (mean change -124ms vs. -74ms; cT1 responders 70% vs. 24%). **Conclusion:** A positive association with fibrosis stage and with MRI-PDFF was observed for cT1 in this subset analysis. cT1 demonstrated a dose dependent reduction with resmetirom treatment, with the greatest reductions in the 100mg group, and a negligible placebo response. A reduction incT1 of >80ms was associated with high likelihood of histological response. These data suggest cT1 may be a suitable test for monitoring response in patients being treated with resmetirom.



Disclosures: Anneli Andersson: Nothing to Disclose, Hang Zhang: Nothing to Disclose, Andrea Dennis: Nothing to Disclose, Rebecca Taub: Madrigal Pharmaceuticals: Employee, Madrigal Pharmaceuticals: Stock - publicly traded company, Madrigal Pharmaceuticals: Executive role, Dominic Labriola: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences:

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2054 | IMPACT OF PNPLA3 P.I148M VARIANT ON QFIBROSIS-BASED LIVER FIBROSIS FEATURES IN MASLD BIOPSIES IN THE MILAN BIOBANK COHORT

Giulia Periti[1] Kutbuddin Akbary[2] Francesco Malvestiti[3] Serena Pelusi[1] Marco Maggioni[1] Luisa Ronzoni[1] Sara Margarita[1] Alessandro Cherubini[4] Jessica Rondena[3] Roberta D'Ambrosio[1] Daniele Dondossola[3] Daniele Prati[1] Dean Tai[5] Luca Valenti[6], [1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano, [2]HistoIndex Pte Ltd, Singapore, [3]University of Milan, [4]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, [5]HistoIndex, [6]Fondazione Ca' Granda OMP Milano

Background: The PNPLA3 p.I148M variant (rs738409) is the main genetic determinant of steatosis and fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD), impacting both hepatocytes and hepatic stellate cells, greatly contributing to global liver disease burden. Its influence on fibrosis biology extends beyond traditional staging systems, yet its impact on collagen morphology has not been fully characterized. We aimed to evaluate the association between PNPLA3 p.I148M and quantitative collagen features using AI-based digital pathology analysis. **Methods:** Fifty liver biopsies from MASLD patients in the Milan Biobank with PNPLA3 genotyping and stain-free Second Harmonic Generation/Two Photon Excitation (SHG/TPE) microscopy imaging were analysed using qFibrosis (qF; HistoIndex Pte Ltd, Singapore). Features linked to qF stage, COMI-F (mortality risk), and CODI-F (decompensation risk) indices were assessed (Kendall et al. Liver Int. 2024). Data were normalized to SHG% area. Associations between PNPLA3 p.I148M genotype and collagen features were assessed using generalized linear models under an additive allelic model, adjusting for SHG% area. Correlation between pathologist-based and qF-derived staging was evaluated using generalized linear models, and correction for multiplicity was performed using the Bonferroni method. **Results:** Mean age was 55.8 ± 11.1 years, BMI 29.8 ± 4.4 kg/m², 90% male; 40% had advanced fibrosis (NASH-CRN stage F3–F4). PNPLA3 genotypes were I/I (28%), I/M (44%), M/M (28%). Pathologist-based NASH-CRN fibrosis staging correlated strongly with qF stage ($R^2 = 0.84$, $p < 0.0001$) and qF value ($\beta = 1.28 \pm 0.11$, $p < 0.0001$). PNPLA3 p.I148M was significantly associated with higher steatosis grade and NAS ($p < 0.05$). In unadjusted models, PNPLA3 variant correlated with greater number of long collagen strings in periportal regions ($\beta = 1.44 \pm 0.59$, $p = 0.018$). After SHG% normalization, PNPLA3 was significantly associated with qF stage ($\beta = 0.66 \pm 0.20$, $p = 0.0014$), COMI-F risk ($\beta = 0.17 \pm 0.07$, $p = 0.016$), and multiple periportal features including distributed thin and long strings (Fig. 1). These associations withstood correction for multiple testing. In cases with advanced fibrosis (F3-F4), PNPLA3 also influenced zone 2 and centrivenular collagen features ($p < 0.05$). **Conclusion:** The PNPLA3 p.I148M variant is associated with distinct collagen architectural patterns, especially in periportal regions, captured by SHG/TPE-based AI analysis. These features correlate with AI-digital analysis based fibrosis stage and clinical risk indices. Findings suggest genotype-specific fibrogenic patterns, which may support future efforts in patient stratification and monitoring of fibrosis improvement in MASLD clinical trials via AI-analysis based precision histology. Further validation in independent cohorts would strengthen these findings.

Table 1. Association of PNPLA3 p.I148M variant with collagen features contributing to qFibrosis stage and value and COMI-F/CODI-F indices

qFibrosis	Staging		COMI-F	Mortality		CODI-F	Decompensation	
Feature	Estimate±SE	p-value°	Feature	Estimate±SE	p-value°	Feature	Estimate±SE	p-value°
qFibrosis value	0.39±0.20	0.050	COMI-F index	-0.01±0.05	0.77	CODI-F index	0.04±0.03	0.17
qFibrosis stage	**0.66±0.20**	**0.0014***	**COMI-F risk**	**0.17±0.07**	**0.016**	CODI-F risk	0.12±0.08	0.14
# Strings	-72.2±43.3	0.10	# Long string PT	-0.87±2.45	0.68	# Intersections PT	-110±107	0.30
String area	0.33±3.84	0.93	String length PT Aggr	61.5±447	0.89	**# Thin strings PT**	**7.20±2.36**	**0.0035**
String length	-1589±1882	0.40	**# Long strings PP Distr**	**1.78±0.47**	**0.0003***	String length PP	1738±521	0.007
String area PT	-27641±1902	0.69	% Z2 Aggr	-0.24±0.22	0.28	**# Long strings PP Aggr**	**6.85±3.21**	**0.0093**
String length PT	2.26±5.22	0.96	**# Short strings Z2 Aggr**	**-86.1±36.4**	**0.021**	**# Thin strings PP Distr**	**3.08±1.29**	**0.0059**
String area Z2	-22.73±17917	0.21						
String length Z2	-3419±1945	0.083						
String area CV	377±2071	0.073						
String length CV	10.9±38.8	0.78						

#: number, PT: portal tract, PP: periportal, Z2: zone 2, CV: centrivenular, Aggr: aggregated, Distr: distributed. °At generalized linear models adjusted for SHG% area. * p-value<0.05 after Bonferroni correction for multiple comparisons.

Disclosures: Giulia Periti: Nothing to Disclose, Kutbuddin Akbary: HistoIndex Pte Ltd: Employee, Francesco Malvestiti: Nothing to Disclose, Serena Pelusi: Nothing to Disclose, Marco Maggioni: Nothing to Disclose, Luisa Ronzoni: Nothing to Disclose, Sara Margarita: Nothing to Disclose, Alessandro Cherubini: Nothing to Disclose, Jessica Rondena: Nothing to Disclose, Roberta D'Ambrosio: Nothing to Disclose, Daniele Dondossola: Nothing to Disclose, Daniele Prati: Nothing to Disclose, Dean Tai: Nothing to Disclose, Luca Valenti: Nothing to Disclose

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2055 | SERUM MULTIOMICS PREDICTS LIVER HISTOPATHOLOGY AND DISEASE PROGNOSIS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

Jasna Cotic[1] Paul Newcombe[2] Maria Jimenez Ramos[2] Felix Frauhammer[3] Rebecca Levinson[3] Jonathan Davitte[4] Lauren Brunner[5] Lara Murray[5] Geetika Singh[5] Robert Egger[5] Ylaine Gerardin[5] Tim Kendall[6] Jonathan Fallowfield[6] Michael Allison[7] Marc Goldfinger[1] Mark Harpel[4] Stephen Atkinson[2] Prerak Desai[4], [1]GSK, London, UK, [2]GSK, Stevenage, UK, [3]GSK, Heidelberg, Baden-Württemberg, Germany, [4]GSK, Upper Providence, PA, USA, [5]PathAI, Boston, MA, USA, [6]Institute for Regeneration and Repair, University of Edinburgh, Edinburgh, UK, [7]Cambridge Liver Unit, Cambridge NIHR Biomedical Research Centre, Cambridge University Hospitals NHS

Background: Metabolic dysfunction-Associated Steatohepatitis (MASH) is a complex disease consisting of hepatocyte ballooning and death, inflammation and fibrosis. Non-invasive metrics of disease activity and stage are limited in their ability to predict disease outcomes. Accelerated approval in MASH is dependent upon liver histology, posing significant challenges to drug development – cost, patient risk, sampling and scoring variability. This creates major bottlenecks in the development of novel MASH therapies. Here, we used a machine learning (ML)-based approach to predict liver histology scores from serum-derived multiomics data. **Methods:** Serum was obtained from >100 patients (Cambridge University Hospital, CUH) representing the full spectrum of MASH: steatosis, steatohepatitis and steatohepatitis with cirrhosis. We generated a multiomics dataset including proteomics, metabolomics, and lipidomics data, together with a panel of commercial serum-based biomarkers (Nordic Bioscience; liver disease biomarker panel). Liver fibrosis, hepatocyte ballooning, lobular inflammation, and steatosis Clinical Research Network (CRN) scores were provided by pathologists and by AIM-MASH* (PathAI, Boston, MA). XGBoost models were trained to predict histology scores. Bayesian Variable Selection was applied to construct a disease prognostic score for time to liver decompensation, liver transplantation, or all-cause death based on AI-derived histology features (Liver Explore*; PathAI, Boston, MA) in the SteatoSITE cohort (N~600 patients with up to 20 years follow-up). An XGBoost model was trained to predict this disease prognostic score from the serum multiomics data in the CUH cohort. Models were independently validated using data from UK Biobank, using available surrogate phenotypes. **Results:** Serum-based models achieved high performance for predicting histology scores (cross-validated R^2 as high as 0.75), as well as disease prognosis scores (cross-validated $R^2 = 0.57$). Validation in independent data from UK Biobank confirmed the ability of the models to generalize beyond the development cohort. **Conclusion:** We developed ML models providing reliable out-of-sample prediction of liver disease histopathology and prognosis, demonstrating the power of serum multiomics to capture complex biological signatures of liver disease. This work suggests a way towards less-invasive alternatives to liver biopsy to monitor disease progression and as surrogate endpoints in clinical trials.

* AIM-MASH and Liver Explore are for research use only; not for use in diagnostic procedures.

Disclosures: Jasna Cotic: GSK: Employee, Paul Newcombe: Nothing to Disclose, Maria Jimenez Ramos: Nothing to Disclose, Felix Frauhammer: GlaxoSmithKline: Employee, Rebecca Levinson: Nothing to Disclose, Jonathan Davitte: GSK: Employee, GSK: Stock - publicly traded company, Lauren Brunner: PathAI: Stock – privately held company, PathAI, Inc: Employee, PathAI, Inc: Stock – privately held company, Lara Murray: PathAI: Employee, PathAI: Stock – privately held company, Geetika Singh: PathAI: Employee, Robert Egger: Nothing to Disclose, Ylaine Gerardin: PathAI: Employee, Tim Kendall: Nothing to Disclose, Jonathan Fallowfield: Stimuliver: Advisor, Ipsen: Advisor, Kynos Therapeutics: Advisor, Resolution Therapeutics: Consultant, River 2 Renal Corp.: Advisor, Global Clinical Trial Partners: Advisor, Guidepoint: Consultant, GlaxoSmithKline: Grant/Research Support, Genentech: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Michael Allison: GSK: Grant/Research Support, Astra Zeneca: Research collaboration, Marc Goldfinger: Nothing to Disclose, Mark Harpel: GSK: Employee, Stephen Atkinson: GlaxoSmithKline: Employee, GlaxoSmithKline: Stock - publicly traded company, Prerak Desai: Nothing to Disclose

2056 | LONGITUDINAL ASSESSMENT OF FIBROSIS DISTRIBUTION CHANGES AFTER TREATMENT IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Daniela Allende[1] Laura Wilson[2] Cynthia Behling[3] Patricia Belt[4] Ryan Gill[5] Danielle Carpenter[6] Oscar Cummings[7] Cynthia Guy[8] Matthew Yeh[9] Bryce Hatfield[10] David Kleiner[11], [1]Cleveland Clinic, [2]Johns Hopkins University, [3]University of California, San Diego, [4]Johns Hopkins Bloomberg School of Public Health, [5]University of California, San Francisco, [6]Saint Louis University, [7]Indiana University School of Medicine, [8]Duke University, [9]University of Washington Medical Center, [10]Virginia Commonwealth University, [11]National Cancer Institute, Bethesda

Background: Fibrosis regression in MASLD poses challenges in the setting of recent therapies. This study aims to elucidate the impact of treatment and histologic response on fibrosis location. **Methods:** Biopsies from adult MASLD

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patients from the NASH CRN PIVENS and FLINT randomized clinical trials with baseline (BL) and end-of-treatment (EOT) biopsies were blindly assessed. Perisinusoidal fibrosis (PSF) grade was recorded as 0-none, 1-mild, or 2-moderate. Relative distribution of fibrosis by location was scored as portal fibrosis (PF) dominant, PSF dominant, equivocal, or undefined if no fibrosis was evident. The analysis included "responders" (>2 point decrease in NAS with no worsening of fibrosis) and non-responders for changes in PSF grade and predominance at BL and EOT. P-values for change were derived from ANCOVA models, relating the change from BL to EOT to response and BL value of the outcome. **Results:** This study included 399 patients (62% female, 84% white, mean age 49 years), with 214 cases from PIVENS (54%) and 185 from FLINT (46%). Patients were randomized to vitamin E ($N=76$), obeticholic acid ($N=93$), pioglitazone ($N=67$), or placebo ($N=162$). At BL, 85% of cases had fibrosis (15% 0, 32% 1a/b, 2% 1c, 25% 2, 25% 3, 1% 4). Among the 341 biopsies with fibrosis, PSF predominance was common (76%), followed by balanced PSF/PF (17%), and PF predominance (7%). PSF grade was none in 17%, mild in 26%, and moderate in 57% of cases. Among responders vs. non-responders, a decrease in PSF was identified when comparing BL versus EOT biopsies (-0.65 vs +0.04, $p<0.0001$). This change in PSF grade was similar across all treatment groups vs placebo (vitamin E: -0.37, obeticholic acid: -0.35, pioglitazone: -0.4 vs placebo: -0.02, $p\leq0.02$). In responders, a shift from PSF to PF predominance in EOT biopsies was seen in 15% of stage 2 and 19% of stage 3 cases vs controls (8% and 7%) ($p\leq0.05$) (Table 1). **Conclusion:** Histologic responders had a reduction in PSF severity and a shift in the fibrosis dominance towards less PSF at EOT, independent of therapy used. Decreased PSF suggests a sequence of fibrosis regression in treatment response which may have implications for prognosis or drug development.

Table 1 – Fibrosis stage, perisinusoidal fibrosis grade, and distribution by histologic response

	Histologic response		
	Responder (N=156)	Non-Responder (N=243)	P
Fibrosis stage, mean (SD)			
Baseline	1.8 (1.0)	1.6 (1.1)	
End-of-treatment	1.1 (1.0)	1.8 (1.2)	
Change (EOT-BL)	-0.71 (0.80)	+0.22 (0.87)	<0.0001
Perisinusoidal fibrosis grade, mean (SD)			
Baseline	1.5 (0.7)	1.3 (0.8)	
End-of-treatment	0.9 (0.8)	1.4 (0.8)	
Change (EOT-BL)	-0.65 (0.77)	+0.04 (0.74)	<0.0001
Change in predominant fibrosis location among fibrosis stage 2 at BL (N=101)			0.04
Central at BL – Central at EOT	14 (36%)	39 (63%)	
Central at BL – Portal at EOT	6 (15%)	5 (8%)	
Central at BL – No predominance at EOT	8 (21%)	11 (18%)	
Central at BL – Undefined at EOT (fibrosis stage 0 at EOT)	11 (28%)	7 (11%)	
Change in predominant fibrosis location among fibrosis stage 3 at BL (N=99)			0.05
Central at BL – Central at EOT	19 (44%)	29 (52%)	
Central at BL – Portal at EOT	8 (19%)	4 (7%)	
Central at BL – No predominance at EOT	13 (30%)	23 (41%)	
Central at BL – Undefined at EOT (fibrosis stage 0 at EOT)	3 (7%)	0 (0%)	

Disclosures: Daniela Allende: Mayo Clinic: Speaking and Teaching, Univ. of Ottawa: Speaking and Teaching, Educational Symposia: Speaking and Teaching, Laura Wilson: Nothing to Disclose, Cynthia Behling: Nothing to Disclose, Patricia Belt: Nothing to Disclose, Ryan Gill: Nothing to Disclose, Danielle Carpenter: Nothing to Disclose, Oscar Cummings: Nothing to Disclose, Cynthia Guy: Sagimet: Consultant, Madrigal: Consultant, HistoIndex: Consultant, Matthew Yeh: Nothing to Disclose, Bryce Hatfield: Nothing to Disclose, David Kleiner: Nothing to Disclose

2057 | SPATIAL COMPUTATIONAL HISTOLOGY STRATIFIED DENIFANSTAT FIBROSIS RESPONDERS IN THE PHASE 2B FASCINATE-2 MASH STUDY

Vlad Ratziu[1] Wen-Wei Tsai[2] Louis Petitjean[3] Marie O'Farrell[2] Mathieu Petitjean[3] Eduardo Martins[2] Philip Newsome[4] Rohit Loomba[5], [1]Service D' Hepatogastroenterologie (FR), [2]Sagimet Biosciences, [3]PHARMANEST, [4]Kings College School of Medicine, [5]University of California, San Diego

Background: Denifanstat (TVB-2640), an oral fatty acid synthase (FASN) inhibitor, demonstrated significant improvements in fibrosis and MASH resolution in the Ph2b FASCINATE-2 study, and prevented progression to cirrhosis. Fibrosis improvement was shown by both MASH CRN criteria and by AI-based digital pathology. In this exploratory analysis, we used single-fiber analysis to identify fibrotic phenotypes that predict denifanstat response. **Methods:** Liver biopsies were stained with Masson's Trichrome and read by a central pathologist using MASH CRN criteria. Paired biopsy images were available for single fiber analysis from placebo (PBO, $n=45$; F2: $n=22$, F3: $n=23$) and denifanstat ($n=81$ of which 78 analyzed; F2: $n=34$, F3: $n=44$) groups. Responders (F+) had $\geq$1-stage fibrosis reduction by CRN; non-responders (F–) had no change or progression. High resolution quantitative image analysis generated a single-fiber study data lake (sFD). 315 statistical descriptors of fiber populations (fibrosis traits, qFTs) were derived for each biopsy. qFTs differing by $\geq$20% between F+ and F- ($p<0.01$) were normalized and assembled in an equi-weighted response prediction score (RPS). UMAP, a dimensionality reduction technique that preserves both global structure and local relationships, was applied to the sFD to detect phenotypic clusters and spatial patterns associated with histological response. **Results:** 41 and 79 qFTs were identified for fibrosis response in the F3 and F2 baseline groups respectively (Panel A, Volcano plot). These qFTs were assembled to form the RPS(F3) (Panel B) and RPS(F2) respectively. Only 20

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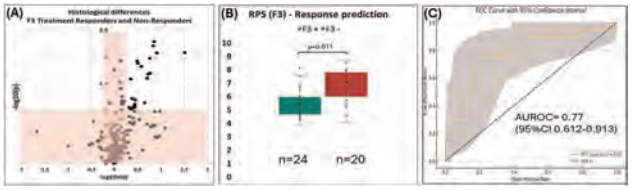
qFTs were shared from F2 and F3 phenotypes are distinct. RPS scores significantly discriminated responders from non-responders in both F3 and F2 baseline subgroups: F3+ from F3- : AUROC = 0.77 (95% CI: 0.61–0.91) (Panel C), $p = 0.011$ (F3+: $n = 24$; F3–: $n = 20$) and F2+ from F2-: AUROC = 0.81 (95% CI: 0.63–0.95), $p = 0.007$ (F2+: $n = 11$; F2-: $n = 9$). Patient-level FibroMAP constructed on the sFD identified clearly distinct histological phenotypic clusters for each F stage for baseline and end of study biopsies combined (N = 246) and identified single-fiber clusters enriched in denifanstat responders at baseline, regardless of their F stage. **Conclusion:** Quantitative single-fiber traits and clustering revealed fibrosis phenotypes that predict denifanstat response, supporting that computational pathology could be leveraged for response stratification.



Disclosures: Vlad Ratziu: Novo-Nordisk: Consultant, Boehringer-Ingelheim: Consultant, Madrigal: Consultant, Akero: Consultant, 89Bio: Consultant, Sagimet: Consultant, Wen-Wei Tsai: Sagimet: Stock share holder, Gordian: paid consultant service, Louis Petitjean: Nothing to Disclose, Marie O'Farrell: Nothing to Disclose, Mathieu Petitjean: PHARMANEST INC: Employee, PHARMANEST INC: Stock – privately held company, Eduardo Martins: Nothing to Disclose, Philip Newsome: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder

2058 | INNOVATIVE SCORING SYSTEM TO SIMULATE MAGNETIC RESONANCE ELASTOGRAPHY IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Isabel Fernandez-Lizaranzu[1] Vanessa Garcia-Fernandez[1] Paloma Carrillo-Fernandez[1] Pedro Montero-Pavon[1] Rocio Gallego-Duran[2] Javier Castell-Monsalve[3] Manuel Romero-Gómez[1], [1]Instituto de Biomedicina de Sevilla (IBiS), [2]Ibis- Biomedicine Institute of Sevilla, [3]Department of Diagnostic Radiology. Virgen del Rocío University Hospital. Seville, Spain

Background: Magnetic resonance elastography (MRE) has emerged as a preeminent non-invasive modality for the assessment of liver fibrosis, exhibiting superior diagnostic precision in both the identification and staging of liver fibrosis (Pavlides et al. EASL2025). However, its accessibility and widespread implementation remain limited. Consequently, this study aims to develop an alternative scoring system that replicates the diagnostic accuracy of MRE, based on widely available biomarkers and clinical parameters. **Methods:** In an estimation cohort comprising N = 85 patients referred from primary care due to MASLD-fibrosis who underwent MRE to stratify fibrosis stage. A logistic regression analysis was conducted to derive the ultimate formula of the score MR-SeLiver that incorporates transient elastography (TE) measurements (kPa), sex, age, and the Hepamet Fibrosis Score (HFS) as independent variables. The accuracy of this score was subsequently validated in a second independent cohort consisting of 178 patients diagnosed with biopsy-proven MASLD who underwent MRE. Advanced fibrosis was defined as F3-F4 on histological examination and a measurement exceeding 3.53 kPa on MRE (Liang et al. J Hep 2023). The area under the receiver operating characteristic curve (AUROC), Youden Index and diagnostic accuracy were calculated to assess the diagnostic capability of the newly developed score. **Results:** 178 patients with biopsy-proven MASLD were finally included in the validation cohort, 67% (121/178) had histologically confirmed advance fibrosis, 47% (32/68) were evaluated by MRE in a non-selected subcohort. Half (89/178) were female, 55.2 years median age, 52% (92/178) type two diabetes. MR-SeLiver demonstrated a diagnostic accuracy for detecting advanced fibrosis by MRE, with an AUROC of 0.845 (95% CI: 0.748, 0.941). When compared to histological

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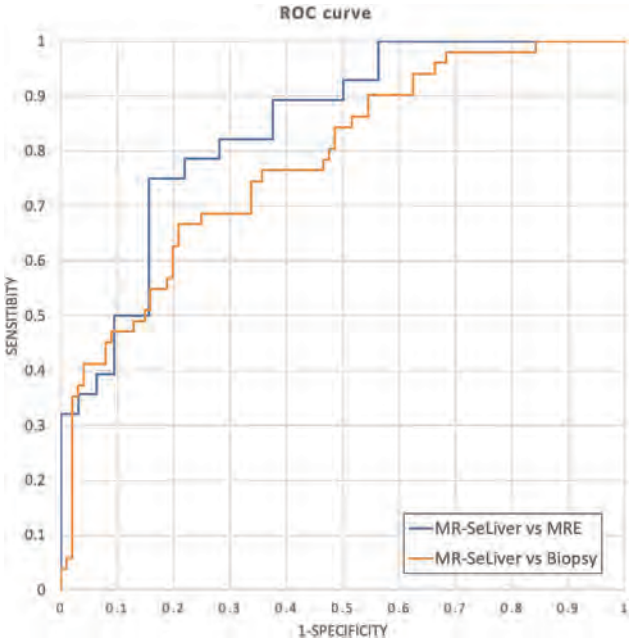
evaluation of advanced fibrosis, it achieved an AUROC of 0.784 (95% CI: 0.708, 0.860). Youden Index pointed 0.6 as the best cut-off for advance fibrosis prediction by MRE with a sensitivity of 75%, specificity of 84.3%, positive predictive value 80.7%, negative predictive value 79.4%, positive likelihood ratio 4.8 and negative likelihood ratio 0.29. **Conclusion:** Despite MRE's exceptional capability to diagnose advanced fibrosis with remarkable sensitivity and specificity, its limited accessibility remains a challenge. Score MR-SeLiver incorporates clinically available variables and standard biomarkers such as sex, age, TE, and HFS, emerges as a highly accessible and alternative score to MRE poised to revolutionize diagnostic of MASLD-fibrosis.



Disclosures: Isabel Fernandez-Lizaranzu: Nothing to Disclose, Vanessa Garcia-Fernandez: Nothing to Disclose, Paloma Carrillo-Fernandez: Nothing to Disclose, Pedro Montero-Pavon: Nothing to Disclose, Rocio Gallego-Duran: Nothing to Disclose, Javier Castell-Monsalve: Nothing to Disclose, Manuel Romero-Gómez: Nothing to Disclose

2059 | MULTI-OMICS SIGNATURES OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN CHILDREN AND YOUTH

Shiwen Li[1], [1]University of Southern California

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is emerging in pediatric and young adult populations, yet the molecular mechanism remains poorly characterized. Multi-omics integration offers a powerful framework to uncover protein–metabolite networks that can distinguish MASLD patients and may improve early detection. **Methods:** We included two cohorts: the Study of Latino Adolescents at Risk of Type 2 Diabetes (SOLAR) (aged 8–13 years; n = 130) with validation cohort from the Metabolic and Asthma Incidence Research (Meta-AIR) study (aged 17–23 years; n = 122). MASLD was defined as hepatic fat fraction > 5% on MRI plus ≥ 1 cardiometabolic risk factor. Plasma proteins (n = 346) were measured utilizing the proximity extension assay using an Olink Explore Cardiometabolic Panel I. Metabolome (n = 370) was determined using liquid-chromatography/high-resolution mass spectrometry. We then applied the Data Integration Analysis for Biomarker discovery using Latent cOmponents (DIABLO) model to integrate multi-omics data. We then evaluated model performance in the Meta-AIR cohort and extracted the significant multiomics features to conduct pathway analysis in Ingenuity Pathway Analysis. **Results:** The DIABLO model identified 25 proteins, and 5 metabolites linked to MASLD, implicating pathways of detoxification, amino-acid regulation, and energy metabolism. When applied to Meta-AIR, the SOLAR-trained model achieved a balanced error rate of 0.19. Pathway analysis highlighted the upregulation of tryptophan and branched-chain amino acid catabolism (adjusted $p < 0.05$) linking the multi-omics signature to hepatocellular carcinoma and liver-cell proliferation toxicity endpoints. **Conclusion:** This integrative multi-omics approach classified MASLD cases across independent cohorts and identified proteins and metabolites involved in tryptophan and branched-chain amino acid catabolic pathways as mechanistic biomarkers for MASLD detection.

Disclosures: Shiwen Li: Nothing to Disclose

2060 | ISOLATED HBCAB POSITIVITY IS NOT ASSOCIATED WITH HCC RISK IN PATIENTS WITH MASLD

Abdelrahman M Attia[1] Emily Truong[1] Naomy Kim[1] Hasmik Adetyan[1] Rami Hemadeh[1] Manaf Alsudaney[1] Jaeho Park[2] Aarshi Vipani[1] Hirsh Trivedi[1] Yun Wang[1] Walid S Ayoub[1] Alexander Kuo[1] Paul Martin[1] Hyunseok Kim[1] Ju Dong Yang[1], [1]Cedars-Sinai Medical Center, [2]University of Arkansas Medical Sciences

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a leading cause of hepatocellular carcinoma (HCC). The role of prior hepatitis B virus (HBV) exposure, indicated by hepatitis B core antibody (HBcAb) positivity in HCC risk among MASLD patients remains unclear. We investigated this association in a racially diverse case and control of MASLD patients. **Methods:** In this single center

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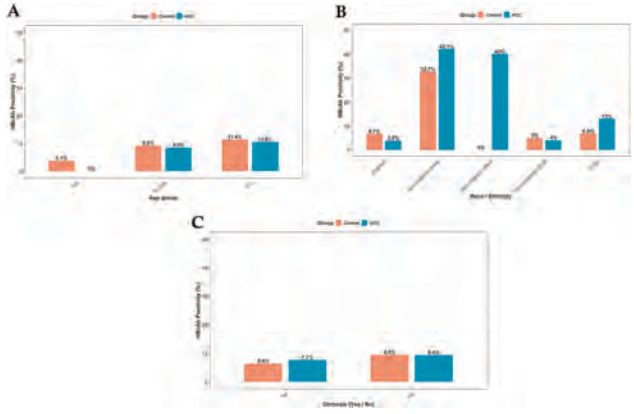
retrospective case-control study, we analyzed 1,098 MASLD patients (343 HCC cases, 755 controls) without other coexisting liver diseases (e.g., hepatitis C, HBsAg-positive HBV, HIV, alcohol-related liver disease) between 2013 and 2024. HBcAb status, demographics, metabolic comorbidities, and cirrhosis status were extracted via medical records review. Logistic regression was used to investigate the association between HBcAb and HCC risk, adjusting for age, sex, race, BMI, diabetes, hypertension, hyperlipidemia, and cirrhosis. Subgroup analyses focused on Non-Hispanic Asian and Black patients due to higher HBV exposure prevalence. **Results:** HBcAb positivity was higher in HCC cases than controls (11.2% vs 7.4%; $p = 0.062$). Univariate analysis showed HBcAb positivity is associated with HCC (OR 1.59, 95% CI 1.00–2.50, $p = 0.048$), but not in multivariable models (aOR 0.59, 95% CI 0.29–1.19, $p = 0.14$). In Non-Hispanic Asian and Black patients, HBcAb prevalence was high (42.1% and 40.0% in HCC cases and 32.7% and 0% in control), with a univariate association (OR 2.96, 95% CI 1.29–6.93, $p = 0.011$) but association was attenuated after adjustment (aOR 2.24, 95% CI 0.41–14.0, $p = 0.4$). In Hispanic and Non-Hispanic White, HBcAb prevalence was lower (3.9% and 4.0% in HCC cases and 6.7% and 5.0% in control), with no association at univariate (OR 0.86, 95% CI 0.41– 1.68, $p = 0.7$) or multivariable (aOR 0.40, 95% CI 0.15–1.02, $p = 0.06$) analysis. HBcAb positivity was slightly higher in cirrhotic patients (9.4% HCC vs. 9.5% control) than non-cirrhotics (7.7% HCC vs. 6.4% control). No significant association was found between HBcAb positivity and HCC in non-cirrhotics (aOR 0.98, 95% CI 0.03–13.4, $p > 0.9$) or cirrhotics (aOR 0.56, 95% CI 0.27–1.15, $p = 0.11$). **Conclusion:** HBcAb positivity is not independently associated with HCC risk in MASLD after adjusting for demographic and clinical risk factors. While higher HBcAb prevalence were noted in Non-Hispanic Asian and Black patients, there was no independent association with HCC risk.



Disclosures: Abdelrahman M Attia: Nothing to Disclose, Emily Truong: Nothing to Disclose, Naomy Kim: Nothing to Disclose, Hasmik Adetyan: Nothing to Disclose, Rami Hemadeh: Nothing to Disclose, Manaf Alsudaney: Nothing to Disclose, Jaeho Park: Nothing to Disclose, Aarshi Vipani: Nothing to Disclose, Hirsh Trivedi: Nothing to Disclose, Yun Wang: Nothing to Disclose, Walid S Ayoub: Nothing to Disclose, Alexander Kuo: Nothing to Disclose, Paul Martin: Nothing to Disclose, Hyunseok Kim: Nothing to Disclose, Ju Dong Yang: Exact Sciences: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Exelixis: Consultant, Fujifilm Medical Sciences: Consultant

2061 | VELACUR AS A NON-INVASIVE TEST FOR THE DETECTION OF PEDIATRIC HEPATIC STEATOSIS

Cristian Sanchez Torres[1] Ana Ramirez Tovar[2] Caitlin Schneider[3] Helaina Huneault[2] Kelsey Chatman[1] Geetika Khanna[1] Jack Knight-Scott[4] Adina Alazraki[1] Shasha Bai[2] Jean Welsh[1] Miriam Vos[1], [1]Emory University, Children's Healthcare of Atlanta, [2]Emory University, [3]Sonic Incytes, [4]Children's Healthcare of Atlanta

Background: Noninvasive, point-of-care tests to detect hepatic steatosis (HS) are needed for rapid diagnosis of MASLD in outpatient pediatric clinics, particularly in young children with early onset of the disease. Conventional ultrasound is the most widely used imaging modality due to its safety, tolerability, and ease of use in children. However, its performance is suboptimal, and it typically requires scheduling a separate appointment in radiology. Velacur is a non-invasive, point-of-care, ultrasound-based method for the assessment of attenuation and liver stiffness, demonstrated to be superior to Fibroscan for liver fat detection in adults (referenced to MRI-PDFF). **Methods:** This prospective, cross-sectional study included 113 Hispanic/Latino children prospectively recruited from the community as part of a MASLD prevention trial. Each participant underwent both MRI-PDFF (Proton Density Fat Fraction) and Velacur assessment on the same day. The primary outcome was the presence of liver steatosis ($\geq 5.2\%$) as measured by MRI-PDFF. The performance of Velacur attenuation coefficient estimate (ACE) was evaluated using Area Under Curve (AUC) analyses for hepatic steatosis thresholds of normal ($< 5.2\%$), mild (5.2 - 11%), and moderate ($> 11\%$) defined by MRI-PDFF. **Results:** A total of 113 Hispanic/Latino children, aged 6-9 years, were included in the study (mean age: 7.9 years (SD 1.05), 55% male). 34% of participants were categorized as obese, 18% overweight, and 48% as normal weight. Overall, 35% ($n = 40$) had HS $\geq 5.2\%$ as determined by MRI-PDFF. Velacur ACE had fair diagnostic performance for MASLD in children (AUC 0.76, CI 0.67 – 0.86). Using the optimal ACE cutoff of 250 dB/m, which maximized the combination of sensitivity and specificity, sensitivity was 70%, and specificity was 67%, Positive Predictive Value of 48% and Negative Predictive Value of 84%. For moderate steatosis ($> 11\%$) Velacur ACE

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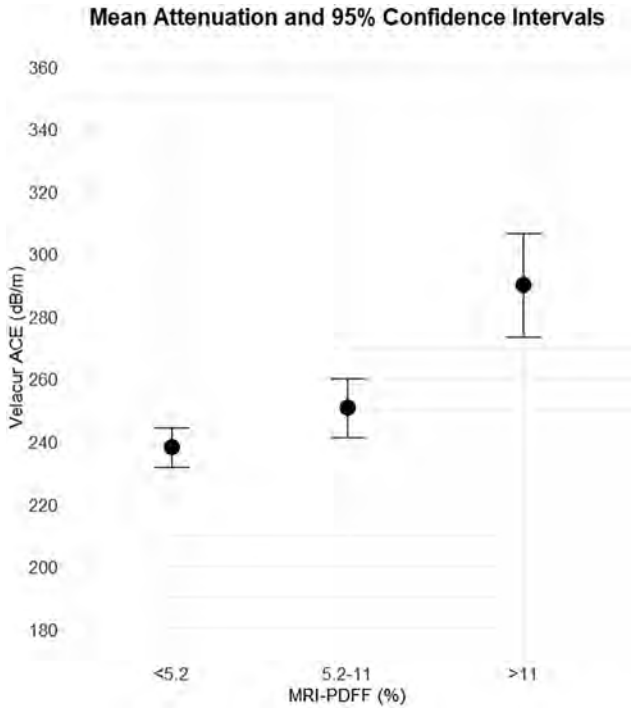
diagnostic performance improved to AUC 0.88 (CI 0.78 – 0.98). **Conclusion:** Velacur™ attenuation demonstrated fair to good performance in detecting hepatic steatosis in young children, particularly at higher levels of liver steatosis. While accuracy improves with increasing liver steatosis content, the overall negative predictive value of 84% supports clinical utility. Further validation in a larger more diverse pediatric population is needed.



Disclosures: Cristian Sanchez Torres: Nothing to Disclose, Ana Ramirez Tovar: Nothing to Disclose, Caitlin Schneider: Sonic Incytes Medical Corp: Employee, Helaina Huneault: Nothing to Disclose, Kelsey Chatman: Nothing to Disclose, Geetika Khanna: Nothing to Disclose, Jack Knight-Scott: Nothing to Disclose, Adina Alazraki: Nothing to Disclose, Shasha Bai: Nothing to Disclose, Jean Welsh: Nothing to Disclose, Miriam Vos: Boehringer Ingelheim: Consultant, Madrigal: Consultant, Eli Lilly: Consultant, Inventiva: Consultant, Alberio: Consultant, Target Real World Evidence: Advisor, Thiogenesis: Advisor, Tern Pharmaceuticals: Stock - publicly traded company, Dexcom: Grant/Research Support, Sonic Incytes Medical Corp: Grant/Research Support, Prosciento: Advisor

2062 | NEUTROPHIL-TO-LYMPHOCYTE RATIO PREDICTS RECURRENCE OF MASLD-SUSPECTED HEPATOCELLULAR CARCINOMA AFTER RADIOFREQUENCY ABLATION

Yuoh Namiki[1] Tomoharu Yamada[1] Takuma Kaneko[1] Keisuke Mabuchi[1] Yuki Matsushita[1] Takuma Nakatsuka[1] Masaya Sato[1] Tatsuya Minami[1] Mitsuhiro Fujishiro[1] Ryosuke Tateishi[1], [1]The University of Tokyo

Background: Neutrophil-to-lymphocyte ratio (NLR) reflects systemic inflammation and immune status, which has been reported as a prognostic marker in various cancers. However, its role in predicting recurrence after radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) remains unclear, particularly among patients suspected of having metabolic dysfunction-associated steatotic liver disease (MASLD). This study aimed to investigate whether NLR level is associated with recurrence risk after RFA in MASLD-suspected HCC. **Methods:** From October 1999 to September 2024, 1,854 patients with newly diagnosed HCC underwent RFA at our institution. After excluding cases of autoimmune hepatitis, primary biliary cholangitis, significant alcohol consumption ($\geq$30 g/day for men, $\geq$20 g/day for women), and viral hepatitis, 144 patients with up to three lesions (each $\leq$3 cm) and at least one cardiometabolic risk factor (obesity, hypertension, diabetes, or dyslipidemia) were identified as MASLD-suspected HCC. Cox proportional hazards regression was used to assess recurrence risk factors, including NLR, with a cut-off of 2.5. **Results:** Among the 144 patients, the median age was 72 years, 42% were male, and 78% were Child-Pugh A. Patients with NLR $\leq$2.5 accounted for 58%. Univariable analysis identified sex ($p = 0.053$), Child-Pugh class B vs. A ($p = 0.010$), albumin ($p = 0.014$), AST ($p = 0.023$), platelet count ($p = 0.001$), NLR ($p = 0.007$), tumor diameter ($p = 0.026$), and tumor number ($p = 0.006$) as factors associated with recurrence ($p < 0.1$). Notably, NLR $>$2.5 was associated with a lower recurrence risk (HR 0.56, 95% CI: 0.37–0.85). In multivariable analysis, platelet count $<$150,000/μL (HR 1.79, $p = 0.012$) and NLR $>$2.5 (HR 0.61, $p = 0.029$) remained independent predictors of recurrence. **Conclusion:** In MASLD-suspected HCC patients undergoing RFA, a lower NLR ($\leq$2.5) was associated with a higher recurrence risk. This finding contrasts with previous reports in other cancers, where higher NLR is typically linked to worse outcomes. The distinct recurrence pattern observed in MASLD-suspected HCC suggests a unique tumor-immune interaction, warranting further investigation and validation in larger cohorts.

Disclosures: Yuoh Namiki: Nothing to Disclose, Tomoharu Yamada: Eisai: Speaking and Teaching, Chugai Pharmaceutical: Speaking and Teaching, astrazeneca: Speaking and Teaching, Takuma Kaneko: Nothing to Disclose, Keisuke Mabuchi: Nothing to Disclose, Yuki Matsushita: Nothing to Disclose, Takuma Nakatsuka: Nothing to Disclose, Masaya Sato: Nothing to Disclose, Tatsuya Minami: Asahi Kasei Pharma Corporation: Speaking and Teaching, AstraZeneca K. K.: Speaking and Teaching, Mitsuhiro Fujishiro: Nothing to Disclose, Ryosuke Tateishi: EA Pharma: Speaking

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2063 | ENHANCING STEATOTIC LIVER DISEASE (SLD) DETECTION VIA OPPORTUNISTIC SCREENING

Vignesh Rajasekaran[1] Asad Aali[1] Andrew Johnston[1] Neera Ahuja[1] Paul Maggio[1] David Svec[1] Robert Boutin[1] Lisa Shieh[1] Allison Kwong[1] Nishita Kothary[1] Roger Sands[1] Jason Hom[1] Akshay Chaudhari[1] Laura Derry[1], [1]Stanford University Medical Center

Background: Steatotic liver disease (SLD), is highly prevalent, and disease progression to fibrosis can lead to major complications such as liver failure, portal hypertension (e.g., ascites, hepatic encephalopathy), hepatocellular carcinoma, and death. Steatosis alone has also been associated with worse outcomes, including reduced survival and increased morbidity. The 2025 AASLD Guidelines recommend the use of biomarker-based (e.g., FIB-4, APRI) and imaging-based tools (e.g., ultrasound, VCTE, MRI) to assess liver disease in high-risk individuals. However, biomarker-based tests lack sensitivity for SLD, and advanced imaging modalities such as MRI are resource-intensive and costly. While non-contrast computed tomography (CT) — and recently contrast-enhanced CT— has good performance for detecting SLD, limited data exists on the role of CT in screening. Given the widespread use of CT imaging, opportunistic CT paired with novel deep learning tools presents an automated, cost-effective, and scalable approach for detection. We aim to determine whether opportunistic CT paired with a novel deep learning algorithm can improve rates of detection of SLD. **Methods:** We used a novel deep learning algorithm, Comp2Comp, to retrospectively assess a cohort of 18,915 contrast-enhanced CT scans performed between 2013–2018 and 2021–2024 at a multisite academic center (Figure 1). SLD was identified using validated radiographic criteria: liver attenuation $\leq$ 90 Hounsfield units (HU) and a liver–spleen attenuation difference $\leq$ –19 HU. We compared detection rates by ICD coding, opportunistic CT image analysis, and the corresponding radiology reports. **Results:** Opportunistic CT image analysis identified SLD in 28% of patients, compared to only 12% in radiology reports and 4% via ICD coding. Among individuals identified by both Comp2Comp with opportunistic CT and radiology reports, only 24% were ICD-coded. Subgroup analysis comparing detection of SLD by opportunistic CT analysis and radiology reports across inpatient and outpatient CT scans revealed that outpatient cases were less likely to be coded (18.1% vs. 38.3%, $p < 0.001$). **Conclusion:** Opportunistic CT with deep learning offers a powerful, scalable, and automated solution for identifying patients with SLD who often remain undiagnosed in standard clinical workflows across the electronic health system. This population-based approach detected over twice as many cases than radiology reports. Although current guidelines allow ICD coders to assign diagnoses directly from outpatient radiology reports, SLD was significantly less likely to be coded in the outpatient setting. These findings highlight the need and opportunities for better integration of imaging data into diagnostic and clinical care pathways— both inpatient and outpatient— to improve early detection, linkage to subspecialty care, and treatment of SLD.

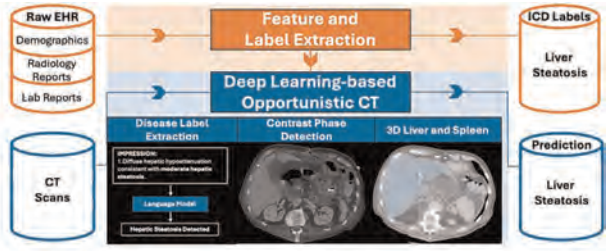

Figure 1. Pipeline for identifying steatotic liver disease using opportunistic CT image analysis, radiology reports, and ICD coding.

Disclosures: Vignesh Rajasekaran: Nothing to Disclose, Asad Aali: Nothing to Disclose, Andrew Johnston: Nothing to Disclose, Neera Ahuja: Nothing to Disclose, Paul Maggio: Nothing to Disclose, David Svec: Nothing to Disclose, Robert Boutin: GE Healthcare: Grant/Research Support, Lisa Shieh: Nothing to Disclose, Allison Kwong: Nothing to Disclose, Nishita Kothary: Nothing to Disclose, Roger Sands: Nothing to Disclose, Jason Hom: Cognita Imaging: Stock – privately held company, Akshay Chaudhari: Nothing to Disclose, Laura Derry: Nothing to Disclose

2064 | THE METAL SCORE (WESKEL-GP): A PRIMARY CARE FIBROSIS RISK TOOL FOR SILENT METALD – A GUIDELINE-ALIGNED RESPONSE TO THE MASLD CLASSIFICATION GAP

KSHEETIJ KOTHARI[1], [1]Sahyadri Hospital, Pune

Background: Up to 30% of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) report moderate alcohol use (100–200 g/week), forming a "Silent MetALD" subgroup per AASLD/EASL 2023 criteria. These patients face a 2.1-fold higher risk of fibrosis due to metabolic–alcohol synergy, yet lack

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dedicated risk-stratification tools. Current guidelines exclude them from MetALD classification ($\geq$140 g/week), and FIB-4 $<$1.3 fails to detect ~70% of F2 fibrosis, delaying hepatology referral by 18–24 months. Objective: To develop the METAL Score (WESKEL-GP) for identifying high-risk Silent MetALD using routine clinical parameters in primary care. **Methods:** The Weight-based Etiology Scoring with Key Elements for Liver Disease – Guided for Primary Care (WESKEL-GP) assigns weighted points based on meta-analytic odds: type 2 diabetes (2.0), BMI $>$30 or waist-to-height ratio $>$0.5 (1.5), ALT/AST $<$1 (1.5), GGT $>$1.5×ULN (1.0), family history (1.0), and sex-specific alcohol intake (women: 100–140 g/week = 1.5; men: 140–200 g/week = 2.0). A simulated MASLD cohort (n = 5,000), modeled using Agile 3+/LITMUS fibrosis data, assessed performance for F3+ fibrosis detection (AUROC vs. FIB-4 and NAFLD Fibrosis Score) **Results:** The METAL Score achieved an AUROC of 0.82 (95% CI: 0.79–0.85) for F3+ fibrosis, outperforming FIB-4 (0.78; Δ+0.04, p = 0.03) and NFS (0.75; p = 0.01). At a threshold of $\geq$5.0, it demonstrated 78% sensitivity and 76% specificity, reclassifying 22% of FIB-4 false-negatives. It reduced missed high-risk cases by 19% and avoided unnecessary referrals in one of four low-risk patients **Conclusion:** The METAL Score (WESKEL-GP) is the first clinically actionable tool designed explicitly for Silent MetALD, addressing a critical unmet need in the 2023 AASLD/EASL guidelines. By integrating six routine parameters—validated in a simulated cohort modeled on Agile 3+/LITMUS data—it enables early risk stratification in primary care, reducing delayed referrals by 19% and avoiding 1 in 4 unnecessary specialist consultations. To ensure equitable real-world application, we propose the PROSPECT-METAL trial (*target n = 5,000*), a global consortium initiative to: Refine sex- and ethnicity-specific thresholds, Optimize EHR integration for seamless adoption, Validate long-term outcomes (e.g., cirrhosis, mortality). Clinicians, researchers, and institutions worldwide are invited to join this urgent, guideline-aligned effort, advancing a tool poised to redefine metabolic-alcohol liver disease management.
Disclosures: KSHEETIJ KOTHARI: Nothing to Disclose

2065 | MACHINE LEARNING EXTRACTED FEATURES OF QUANTITATIVE ABDOMINAL IMAGING FINDS VISCERAL FAT AS PRIMARY PREDICTOR OF HEPATIC STEATOSIS

Wesley Dixon[1] Joseph Simeone[2] Jay Luther[2] Wei Zhang[2] Esperance Schaefer[1] Russell Goodman[2],

[1]Brigham and Women's Hospital, [2]Massachusetts General Hospital

Background: Machine learning (ML) algorithms can extract quantitative body composition metrics from abdominal computed tomography (CT) scans, but the relationship between body composition and hepatic steatosis has yet to be defined. These ML metrics may offer a novel approach to phenotyping patients beyond traditional measures like body mass index (BMI). **Methods:** We included adults (age $>$18 years) in the Mass General Brigham Biobank with a ML-processed contrast or non-contrast abdominal CT scan within one year of biospecimen collection. Body composition features, including skeletal muscle, visceral fat, and subcutaneous fat area, were extracted using automated Biobank ML algorithms and reported using z-scores relative to the corresponding demographic group. Hepatic steatosis was quantified using the Liver-to-Spleen Attenuation (L/S) Ratio; categories were defined as: minimal ($>$1.0), mild (0.9-1.0), moderate (0.8-0.9), and severe ($<$0.8). Results were expressed as n (%) or median (interquartile range) and compared using Kruskal-Wallis rank sum tests, Chi-squared tests, or area under the curve (AUC) values derived from univariable logistic regression. Robust scaling was used to allow for feature comparison in heatmaps. **Results:** Among 626 patients [age 69 (57-78) years, 46% female, 91% white], 45% had none or minimal, 20% had mild, 13% had moderate, and 22% had severe hepatic steatosis on abdominal CT (77% contrast-enhanced). Age, race, and gender were similar between steatosis categories (p = 0.40, 0.80, 0.15, respectively). Visceral fat, subcutaneous fat, skeletal muscle, BMI, ALT, and triglycerides, but not LDL, AST, or hemoglobin A1c, differed significantly between hepatic steatosis categories (Figure 1A). Comparing severe versus non-severe hepatic steatosis, visceral fat had the largest AUC (0.65), followed by ALT (0.64), BMI (0.63), subcutaneous fat (0.62), triglycerides (0.61), and skeletal muscle (0.61). When only including the 384 patients with BMI $<$30 kg/m^2 (51% none or minimal, 20% mild, 13% moderate, 17% severe hepatic steatosis), only visceral fat and ALT differed between steatosis categories (Figure 1B). In this non-obese population, comparing severe to non-severe steatosis, visceral fat again had the largest AUC (0.62), followed by ALT (0.61), triglycerides (0.58), and BMI (0.57). **Conclusion:** Visceral fat was the strongest imaging-derived correlate of hepatic steatosis, outperforming BMI and traditional lab markers, especially in non-obese patients. This offers a new approach to phenotyping patients with steatotic liver disease, further enabled by this cohort's banked blood samples.

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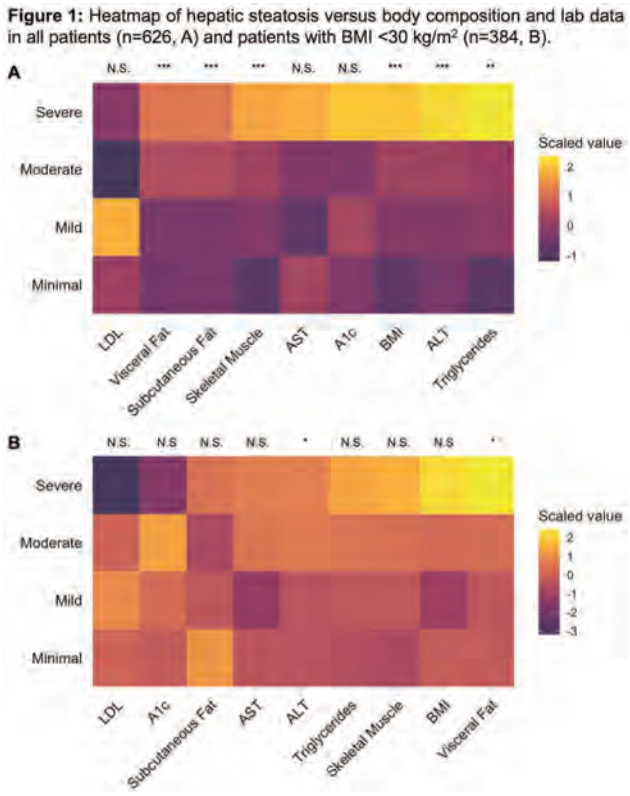

Figure 1: Heatmap of hepatic steatosis versus body composition and lab data in all patients (n=626, A) and patients with BMI <30 kg/m^2 (n=384, B).

Disclosures: Wesley Dixon: Nothing to Disclose, Joseph Simeone: Nothing to Disclose, Jay Luther: Nothing to Disclose, Wei Zhang: Nothing to Disclose, Esperance Schaefer: Nothing to Disclose, Russell Goodman: Nothing to Disclose

2066 | MACHINE LEARNING PREDICTION OF AT-RISK MASH USING SEVEN KEY PREDICTORS: DEVELOPMENT AND VALIDATION

Yousif Alyousifi[1] Chinmay Raut[1] Lishi Yin[1] Vincent Chen[2] Yanhua Chen[1] Antonino Oliveri[1] Elizabeth Speliotes[2], [1]University of Michigan, [2]University of Michigan Medical Center

Background: Metabolic dysfunction-associated steatohepatitis (MASH) affects up to 12% of Americans, and it can progress to cirrhosis, increasing the risk of liver-related complications. Early and accurate identification of at-risk MASH is essential for effective clinical management and disease prognosis. Traditional diagnostic methods, like liver biopsy and imaging, are invasive, costly, and sometimes unreliable. Proton density fat fraction (PDFF) and iron-corrected T1 (cT1) are MRI-based measures of liver fat accumulation and inflammation; however, they are expensive and not readily available. Here, we aim to leverage machine learning techniques using clinical, biochemical, and genetic data to develop and validate an efficient predictive model for at-risk MASH. **Methods:** The UK Biobank cohort includes individuals with cT1 measures (n = 33,966, mean age = 64.3 years, male = 47.6%). MASH was defined as cT1 > 800 and PDFF ≥ 5. The dataset was split into training (N = 27,467) and testing (N = 6,867) sets. BorutaShap algorithm selected 7 key predictors out of 338 initially considered, encompassing baseline characteristics, physical measures, metabolites, serum biomarkers, and genetics. These 7 selected predictors were then utilized to train six machine learning algorithms - CatBoost, XGBoost, Random Forest, Logistic Regression, K-Nearest Neighbors, and Multilayer Perceptron and evaluated on testing set using the area under the receiver operating characteristic curve (AUC) for identifying at-risk MASH. Hyperparameters of our models were tuned using Optuna algorithm with 10-fold cross-validation. External validation was conducted using the Michigan Genomics Initiative (MGI) cohort (n = 20,195; mean age = 62.3 years; 46.2% male), MASH was defined based on ICD-10 code K75.81 or via pathology staining, using only five predictors, as two of the original seven were not available in MGI. **Results:** Among the evaluated machine learning models, CatBoost achieved the best performance, with the highest test AUC of 0.87 (95% CI: 0.87 - 0.89) and 0.86 (95% CI: 0.85 - 0.88) in UKBB using 7 and 5 predictors, respectively, and a validated AUC of 0.78 (95% CI: 0.75 - 0.81) in MGI (Figure). **Conclusion:** Our model demonstrated high accuracy for identifying at-risk MASH. Implementing this model in the electronic medical record may allow for early intervention to reduce progression to advanced liver disease. We are working to generalize the model, perform time-to-event analysis, and compare its performance with existing scores.

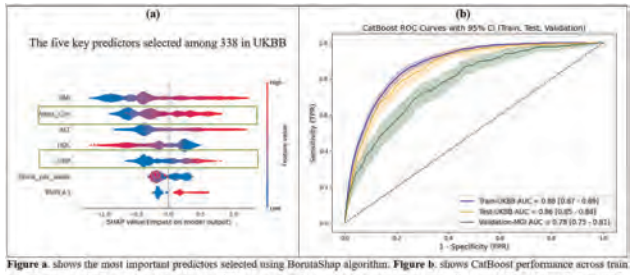

Figure a. shows the most important predictors selected using BorutaShap algorithm. **Figure b**. shows CatBoost performance across train and test sets in UKBB and the validated set in MGI cohort using five available predictors in both UKBB and MGI. **Abbreviations**: BMI, body mass index; HDL, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; CRP, C-reactive protein; Waist_Circ, waist circumference; Drink_per_week, alcohol consumption per week; PNPLA3 rs738408_dosage, genetic variant. **Note**: Waist_Circ and CRP were not available in the MGI dataset.

Disclosures: Yousif Alyousifi: Nothing to Disclose, Chinmay Raut: Nothing to Disclose, Lishi Yin: Nothing to Disclose, Vincent Chen: AstraZeneca: site PI on industry-sponsored trial, Ipsen: site co-I on industry-sponsored trial, Kowa: site co-I on industry-sponsored trial, Yanhua Chen: Nothing to Disclose, Antonino Oliveri: Nothing to Disclose, Elizabeth Speliotes: University of Michigan: Pending patent on use systems for MASLD/insulin resistance

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2067 | MASLD EXACERBATES CARDIOVASCULAR MORTALITY RISK IN ADVANCED STAGES OF CARDIOVASCULAR-KIDNEY-METABOLIC SYNDROME: A POPULATION-BASED COHORT STUDY

Tong Bu[1] Tianyuan Yang[1] Qi Wang[1], [1]Center of Liver Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China

Background: Background and Aims: The "cardiovascular-kidney-metabolic (CKM) syndrome" is a newly proposed staging framework aimed at enhancing the prevention, risk stratification, and multidisciplinary management of metabolic diseases. Metabolic dysfunction–associated steatotic liver disease (MASLD), recognized as a condition associated with adverse cardiovascular outcomes, may exert differential impacts on cardiovascular risk across various CKM stages. While previous studies have demonstrated varying cardiovascular risks across CKM stages, the distribution of CKM stages within the MASLD population is heterogeneous. This study aims to evaluate whether MASLD increases the risk of cardiovascular mortality across different CKM stages. **Methods:** This population-based prospective cohort study analyzed data from individuals aged 20 to 79 years who participated in the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2018 and NHANES III, with mortality follow-up data available through 2019. The Fine-Gray competing risk model was employed to evaluate the risk of adverse cardiovascular outcomes and to assess the association between MASLD and cardiovascular mortality across different CKM stages. The model was adjusted for potential confounders including age, sex, educational attainment, and poverty level, with further adjustments for comorbid conditions such as hypertension, diabetes mellitus, and dyslipidemia. **Results:** In the adjusted Model 1, MASLD was significantly associated with an increased risk of cardiovascular mortality among individuals with CKM stages 0–3 (HR = 1.25, 95% CI: 1.13–1.52, P = 0.003). Subgroup analysis by CKM stage revealed that this association remained significant in individuals with CKM stage 2 and stage 3 (HR = 1.42, 95% CI: 1.18–1.84, P = 0.001; HR = 1.35, 95% CI: 1.11–1.79, P = 0.006). However, in a further adjusted model(adjusted Model 2) accounting for additional confounding factors, the association between MASLD and cardiovascular mortality among CKM stage 0–3 individuals was no longer statistically significant (HR = 1.18, 95% CI: 0.91–1.35, P = 0.1). Nonetheless, the association remained significant in individuals with CKM stage 2 and stage 3 (HR = 1.32, 95% CI: 1.15–1.75, P = 0.003; HR = 1.29, 95% CI: 1.08–1.70, P = 0.02, respectively). **Conclusion: Conclusion:** MASLD significantly increased the risk of cardiovascular mortality among individuals with CKM syndrome, particularly in those at CKM stages 2 and 3. In clinical practice, special attention should be given to the management of MASLD in patients at CKM stages 2 and 3, with enhanced screening efforts aimed at reducing the risk of adverse cardiovascular outcomes.

Table. Hazard Ratios (HR) for Cardiovascular Mortality Risk in Different Stages of CKM Syndrome with MASLD as an Exposure.

	Adjustment Model 1			Adjustment Model 2		
Group	HR	(95%CI)	P value	HR	(95%CI)	P value
0-3 CKM group	1.25	(1.13-1.52)	0.003	1.18	(0.91–1.35)	0.1
CKM stage 1	1.40	(0.41-4.79)	0.59	1.26	(0.52–2.5)	0.68
CKM stage 2	1.42	(1.18-1.84)	0.001	1.32	(1.15-1.75)	0.003
CKM stage 3	1.35	(1.11-1.79)	0.006	1.29	(1.08-1.70)	0.02
CKM stage 4	1.56	(0.63-3.85)	0.33	1.45	(0.75–2.58)	0.25

The table presents the hazard ratios (HR) and 95% confidence intervals (CI) for cardiovascular mortality risk in individuals at different stages of cardiovascular-kidney-metabolic (CKM) syndrome, with metabolic dysfunction-associated steatotic liver disease (MASLD) as an exposure factor. Model 1 was adjusted for age, sex, education level, and poverty status. Model 2 further adjusted for additional confounding factors, including hypertension, diabetes, and hyperlipidemia.

Disclosures: Tong Bu: Nothing to Disclose, Tianyuan Yang: Nothing to Disclose, Qi Wang: Nothing to Disclose

2068 | DEEP LEARNING-BASED MODEL FOR ASSESSING HEPATIC STEATOSIS IN LIVING LIVER DONOR

Jonggi Choi[1] Hyunseok Lim[2] Chaeyeon Lim[3] Jina Park[3] Won-Mook Choi[3] Danbi Lee[3] Ju Hyun Shim[3] Kang Mo Kim[3] YOUNG-SUK LIM[3] Han Chu Lee[3] Namkug Kim[3], [1]University of Ulsan, Asan Medical Center, [2]University of Ulsan College of Medicine, ASAN medical Center, Seoul, South Korea, [3]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: Liver biopsy is the gold standard for diagnosing hepatic steatosis, but its invasiveness limits widespread use, particularly among potential living liver donors. With the growing prevalence of fatty liver disease, there is an urgent need for accurate, noninvasive diagnostic tools. This study aimed to develop a deep learning–based model that predicts hepatic steatosis by integrating clinical, laboratory, and CT imaging data. **Methods:** This retrospective study analyzed 6,259 individuals who underwent both liver biopsy and CT imaging during living donor evaluation at Asan Medical Center from January 2005 to April 2024. Of these, 4,370 had biopsy and CT within 30 days and were included in the modeling. Liver and spleen segmentation was applied to CT images to mask relevant regions of interest. Clinical and laboratory features used included sex, age, alcohol use, hypertension, AST, ALT, protein, albumin, cholesterol, and glucose. Data preprocessing involved outlier removal and minor label perturbations to address rounding bias in histological grading. Due to class imbalance, class-balanced sampling and augmentation techniques were employed. For model architecture, Inception v3 was used for CT imaging, FT-Transformer for tabular data, and the outputs were fused for prediction. **Results:** Median age was 29.5 years, 65.7% were male, and median BMI was 23.3 kg/m². Mild-to-

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moderate and heavy alcohol use were reported in 47.8% and 4.1% of participants, respectively. The training dataset included 3,791 samples, and the test set included 236 samples. Internal and external validation sets comprised 72 and 36 samples, respectively. In internal validation, the model achieved a concordance correlation coefficient (CCC) of 0.8802, RMSE of 0.0860, R^2 of 0.6740, and MAE of 0.0600. In external validation, CCC was 0.6467, RMSE was 0.0669, R^2 was 0.0380, and MAE was 0.0669. **Conclusion:** This deep learning–based model demonstrated strong performance in predicting hepatic steatosis using CT and clinical data, showing good correlation with histologic findings. The model offers a promising non-invasive alternative to liver biopsy, especially in evaluating living liver donor candidates amidst the rising global burden of fatty liver disease.

Disclosures: Jonggi Choi: GILEAD SCIENCE: Grant/Research Support, Hyunseok Lim: Nothing to Disclose, Chaeyeon Lim: Nothing to Disclose, Jina Park: Nothing to Disclose, Won-Mook Choi: Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, Roche: Consultant, Danbi Lee: Nothing to Disclose, Ju Hyun Shim: Nothing to Disclose, Kang Mo Kim: Nothing to Disclose, YOUNG-SUK LIM: Nothing to Disclose, Han Chu Lee: Roche: Grant/Research Support, BMS: Grant/Research Support, Astrazeneca: Grant/Research Support, Merck: Grant/Research Support, Namkug Kim: Nothing to Disclose

2069 | A REAL-TIME NATURAL LANGUAGE PROCESSING PIPELINE TO EXTRACT ELASTOGRAPHY RESULTS: FROM ELECTRONIC HEALTH RECORD

Lale Ertuglu[1] Christina Grimes[2] Dario Giuse[2] Cathy Jenkins[3] Qingxia Chen[3] Qingxia Chen[3] Ashley Spann[2], [1]Department of Medicine, Vanderbilt University Medical Center, [2]Vanderbilt University Medical Center, [3]Department of Biostatistics, Vanderbilt University Medical Center

Background: Shear wave (SWE) and magnetic resonance elastography (MRE) are crucial non-invasive diagnostic modalities for quantifying liver stiffness and assessing hepatic fibrosis. MRE provides quantification of liver fat as Proton Density Fat Fraction (PDFF). Traditionally, the extraction of these values from electronic health records (EHRs) for clinical studies has been manual, time-intensive, and prone to human error. This study aims to evaluate the accuracy of a novel real-time natural language processing (NLP) pipeline designed to automate the extraction of discrete data elements from liver elastography data from EHRs. **Methods:** An NLP pipeline was designed and embedded directly in the EHR system to facilitate extraction of real-time liver elastography data from all patients within the Vanderbilt University Medical Center Health System undergoing either SWE/MRE studies. The NLP pipeline was embedded in the EHR and prospectively validated from 02/11/2025 through 04/21/2025. We evaluated the NLP pipeline's performance for extraction of quantifiable liver stiffness (kPa) and liver steatosis (PDFF) data compared to manual review of the original SWE/MRE reports obtained during the study period. Evaluation metrics of the extraction methods were reported with their corresponding 95% Wilson confidence intervals. **Results:** A total of 415 studies (186 MRI, 229 SWE) were completed during the observation period. For fibrosis assessment, a small percentage of studies were either nondiagnostic (5/415; 1.2%) or did not have discrete fibrosis values documented in the report (10/415; 2.4%), representing the true negatives in our study. For both SWE and MRE, the NLP pipeline resulted in 100% sensitive, specific, and positive/negative predictive in extracting the resultant discrete fibrosis values, regardless of modality used to diagnose. For quantified steatosis assessments, the NLP pipeline successfully captured 182/186 (97.8%) PDFF values from the completed MRE studies. NLP sensitivity and positive predictive values for PDFF were 98% (95%, 99%) and 100% (98%, 100%), respectively. Discrepancies were primarily attributed to studies with both non-diagnostic kPa values but available PDFF data, and studies that reported the presence of a single PDFF value instead of a range. **Conclusion:** Our NLP pipeline demonstrates excellent test characteristics in extracting liver elastography data from EHRs, with substantial time savings over manual methods. This tool has the potential to streamline data extraction processes in clinical and research settings, facilitate guided decision support for clinicians, and enhance efficiency in longitudinal data registries.

Table. Test characteristics with 95% Wilson confidence intervals for manual vs NLP extraction of liver stiffness (kPa) and liver fat content (PDFF)

	Estimate	95% CI
Liver stiffness		
Overall (kPa)		
Sensitivity	1.00	(0.99, 1.00)
Specificity	1.00	(0.80, 1.00)
Positive Predictive Value	1.00	(0.99, 1.00)
Negative Predictive Value	1.00	(0.80, 1.00)
Shear wave elastography (kPa)		
Sensitivity	1.00	(0.98, 1.00)
Specificity	1.00	(0.74, 1.00)
Positive Predictive Value	1.00	(0.98, 1.00)
Negative Predictive Value	1.00	(0.74, 1.00)
MR elastography (kPa)		
Sensitivity	1.00	(0.98, 1.00)
Specificity	1.00	(0.51, 1.00)
Positive Predictive Value	1.00	(0.98, 1.00)
Negative Predictive Value	1.00	(0.51, 1.00)
Liver fat content		
MR elastography (PDFF)		
Sensitivity	0.98	(0.95, 0.99)
Specificity	-	-
Positive Predictive Value	1.00	(0.98, 1.00)
Negative Predictive Value	0.00	(0.00, 0.49)

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2070 | TRANSIENT ELASTOGRAPHY ENHANCED MACHINE LEARNING MODELS OPTIMIZE SENSITIVITY AND NEGATIVE PREDICTIVE VALUE FOR DETECTING SIGNIFICANT FIBROSIS IN MASLD

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a prevalent chronic liver condition associated with lifestyle changes and obesity. Current severity assessment relies on invasive liver biopsy, with significant fibrosis (stage $F \geq 2$) representing a critical threshold for markedly increased liver-related mortality. This study aimed to develop a diagnostic model integrating demographic, laboratory, and transient elastography (TE) data to improve noninvasive fibrosis staging in MASLD patients. **Methods:** A total of 791 patients with histologically confirmed MASLD were retrospectively enrolled from nine medical centers between July 2018 and July 2024. The cohort was divided into training/internal validation (712 patients from five centers) and external validation (79 patients from four centers) sets. Clinical variables included age, sex, BMI, diabetes status, hypertension history, laboratory parameters (ALT, AST, ALP, GGT, albumin, ferritin, uric acid, triglycerides, total cholesterol, LDL, HDL) and liver stiffness measurement (LSM) from fibroscan. Six machine learning algorithms—random forest (RF), elastic net regression (ENET), XGBoost, support vector machine (SVM), LightGBM, and k-nearest neighbors (KNN)—were employed to develop a base model. An enhanced model incorporating TE was subsequently constructed. Bootstrap resampling (1,000 iterations) was used to calculate confidence intervals, with DeLong's test comparing AUC differences between models. High-performing models underwent external validation. **Results:** Of 791 patients, 305 (38.6%) had $F \geq 2$ fibrosis. Enhanced models demonstrated superior diagnostic performance compared to base models, and LSM emerged as the top-contributing feature across all enhanced models. RF, ENET, and SVM enhanced models showed statistically significant AUC improvements and these models improved mainly in sensitivity and negative predictive value. Several models with an AUC above 0.75 in the internal validation also maintained high levels of sensitivity and negative predictive value in the external validation. Detailed performance metrics are presented in Table 1. **Conclusion:** Transient elastography significantly enhances noninvasive detection of significant fibrosis in MASLD. Enhanced machine learning models incorporating LSM demonstrate high sensitivity and NPV, suggesting clinical utility for excluding low-risk individuals in high-prevalence populations. This approach may reduce unnecessary biopsies while ensuring accurate risk stratification.

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Model	AUC (95% CI)	P Value	Sensitivity (95% CI)	Specitivity (95% CI)	PPV (95% CI)	NPV (95% CI)
Internal validation						
RF	0.703 (0.623-0.783)	0.013	0.6 (0.5-0.723)	0.727 (0.636-0.813)	0.579 (0.451-0.718)	0.744 (0.653-0.853)
RF*	0.774 (0.703-0.841)		0.745 (0.651-0.830)	0.614 (0.505-0.708)	0.547 (0.449-0.660)	0.794 (0.701-0.882)
Xgboost	0.720 (0.621-0.789)	0.195	0.745 (0.621-0.845)	0.625 (0.5404-0.698)	0.554 (0.444-0.655)	0.797 (0.700-0.883)
Xgboost*	0.744 (0.664-0.809)		0.764 (0.654-0.860)	0.614 (0.506-0.705)	0.533 (0.435-0.669)	0.806 (0.707-0.895)
ENET	0.724 (0.644-0.795)	0.009	0.745 (0.644-0.852)	0.625 (0.539-0.694)	0.554 (0.449-0.651)	0.797 (0.693-0.892)
ENET*	0.784 (0.711-0.854)		0.836 (0.712-0.933)	0.511 (0.397-0.583)	0.517 (0.402-0.601)	0.833 (0.715-0.936)
SVM	0.714 (0.632-0.793)	0.007	0.673 (0.570-0.772)	0.625 (0.524-0.705)	0.529 (0.417-0.628)	0.753 (0.669-0.836)
SVM*	0.785 (0.709-0.853)		0.782 (0.661-0.896)	0.602 (0.475-0.682)	0.551 (0.441-0.646)	0.815 (0.691-0.897)
LightGBM	0.728 (0.644-0.798)	0.299	0.764 (0.650-0.859)	0.636 (0.536-0.721)	0.568 (0.469-0.658)	0.812 (0.714-0.899)
LightGBM*	0.752 (0.671-0.830)		0.727 (0.575-0.821)	0.659 (0.528-0.756)	0.571 (0.471-0.672)	0.795 (0.687-0.868)
KNN	0.673 (0.581-0.771)	0.061	0.655 (0.518-0.773)	0.614 (0.509-0.699)	0.514 (0.378-0.615)	0.740 (0.614-0.829)
KNN*	0.713 (0.620-0.807)		0.673 (0.540-0.799)	0.625 (0.518-0.719)	0.529 (0.409-0.651)	0.753 (0.616-0.845)
External validation						
RF*	0.744 (0.634-0.848)		0.812 (0.666-0.934)	0.511 (0.363-0.615)	0.531 (0.404-0.657)	0.8 (0.661-0.933)
ENET*	0.725 (0.607-0.842)		0.875 (0.738-0.971)	0.362 (0.238-0.5)	0.483 (0.368-0.600)	0.810 (0.611-0.959)
SVM*	0.748 (0.642-0.854)		0.875 (0.757-0.971)	0.404 (0.279-0.540)	0.5 (0.366-0.612)	0.826 (0.681-0.957)
LightGBM*	0.741 (0.621-0.853)		0.906 (0.806-0.973)	0.426 (0.303-0.555)	0.518 (0.385-0.633)	0.870 (0.720-0.963)

Table1. Diagnostic accuracy of base models and enhanced models
*represents the enhanced model.

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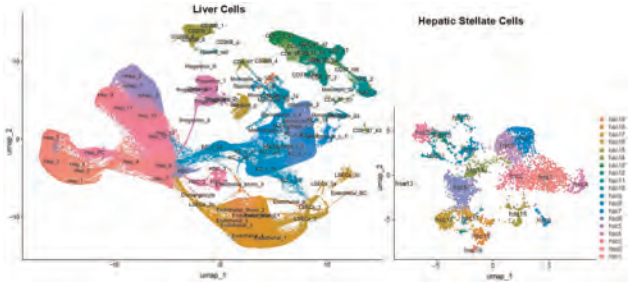
2071 | MOUSE HEPATIC STELLATE CELL ACTIVATION HETEROGENEITY IN THREE COMMONLY USED MASH DIETS

Simeng Wang[1], [1]*UT Southwestern Medical Center*

Background: MASH-induced fibrosis is a result of insulin resistance, and it requires triglyceride accumulation in hepatocytes and stellate cell activation. Here, we used single-cell sequencing (scRNA-seq) to define the time-dependent molecular events that lead to stellate cell activation and liver fibrosis induced by three distinct MASH diets. **Methods:** Mice (n = 30) were fed chow, High Sucrose/Fat (45% fat, 17% sucrose, 0.02 % cholesterol), Western (40% fat, 29% sucrose, 0.14% cholesterol), or AMLN (40% fat, 20% fructose, 9% sucrose, 2% cholesterol) diets for 26, 34, or 45 weeks. Livers were then harvested for histology, bulk RNA sequencing, and scRNA-seq. Analysis of scRNA-seq utilized Seurat, RNA velocity, and Cellrank. **Results:** A total of 96 high-yield cell clusters were identified that were composed of hepatocytes, nonparenchymal liver cells and their corresponding subpopulations. 6,391 single-cell transcriptomes of stellate cells were further analyzed. After 45 weeks, the AMLN diet caused the highest stellate cell activation (67%) and liver fibrosis, with a 22-fold increase in collagen production. The Western diet led to intermediate effects (26% activation, 15-fold collagen increase), while the high sucrose/fat diet had minimal impact (7% activation, 5-fold collagen increase). The expressions of genes related to actin cytoskeleton, myofibroblast differentiation, and fatty acid catabolism were significantly upregulated in stellate cells, especially in stellate cells from mice fed the AMLN diet. Among the fully activated stellate cells, a total of 24,897 differentially expressed genes are identified, 25 of which potentially serve as new hepatic stellate cell activation markers. Fras1 gene associated with extracellular matrix formation and interactions was exclusively induced in activated stellate cells from mice fed the Western diet, while Utp18 gene played a crucial role in cell growth and proliferation was uniquely induced in activated stellate cells from mice fed the high sucrose/fat diet. **Conclusion:** This study is the first to comprehensively quantify how hepatic stellate cell (HSC) activation varies over time in response to three commonly used MASH diets, using single-cell transcriptome analysis. The AMLN diet triggered the most robust HSC activation and proliferation. However, both Western and high sucrose/fat diets also significantly activated HSCs, each through distinct mechanisms.



Disclosures: Simeng Wang: Nothing to Disclose

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2072 | UNDERSTANDING THE FUNCTIONAL AND PHYSIOLOGIC HETEROGENEITY OF ADVANCED MASH AS DEFINED BY THE ORAL CHOLATE CHALLENGE TEST MAY ENHANCE CLINICAL TRIAL DESIGN

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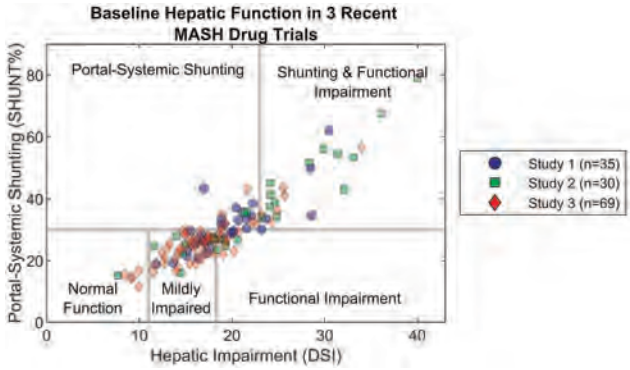
Background: Liver function in patients with advanced MASH may vary from normal to severe impairment and portal-systemic shunting which may impact treatment responses in drug trials. The oral cholate challenge test (HepQuant DuO) characterized baseline liver function and shunting in three recent MASH drug trials. **Methods:** Subjects were enrolled in 3 clinical trials linking the Test results to treatment response. Trial 1 was a Phase 2 trial conducted in patients with CP A MASH cirrhosis. Trial 2 was a Phase 3 open-label trial in patients with well-compensated CP A MASH cirrhosis. Trial 3 was a Phase 2 open-label trial in patients with MASH $\geq$F3 fibrosis. Test parameters were quantified from 20- and 60-min concentrations of orally administered d4-cholate. Serum was analyzed for cholate concentrations by LC-MS/MS. Baseline Test parameters, including the disease severity index (DSI) and portal systemic shunting (SHUNT%), were calculated. **Results:** A total of 134 subjects with MASH underwent the Test. Subjects were on average 61 $\pm$ 9 years of age, BMI 37 $\pm$ 8 kg/m^2, 99% overweight, 86% obese, 43% male, and 58% Hispanic ethnicity. A wide range of functional impairment and shunting was observed in these cohorts of patients with MASH. Mean ($\pm$ SD) values for the Test were 18.7 $\pm$ 5.5 for DSI and 29.4% $\pm$ 10.5% for SHUNT%. The diagram below, based on DSI (function) and SHUNT%, indicated 6 (4.4%) with normal function, 19 (14.2%) with only portal-systemic shunting, 67 (50%) with mild functional impairment, 18 (13.4%) with significant functional impairment, and 24 (18%) with significant functional impairment and shunting. Using the RISK ACE model (Kittelson 2025), the individual estimated 1-year risk for clinical outcome ranged from 0.4% (DSI 7.7) to 61.4% (DSI 40.0). **Conclusion:** The oral cholate challenge test (HepQuant DuO) uncovered significant heterogeneity in functional and physiologic impairment at baseline in patients enrolled in MASH drug trials. Quantitative functional assessment to risk stratify study populations to reach clinical liver events could improve efficiency and lower the cost of clinical trials by enhancing statistical power, thereby reducing sample size and study duration.



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2073 | FIB-4 SERVES AS A REFERRAL INDEX FOR CORONARY ARTERY CALCIFICATION IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Chung-Feng Huang[1] Ming-Lung Yu[2], [1]Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, [2]Kaohsiung Medical University/ Kaohsiung Medical University Hospital

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and liver fibrosis is linked to cardiovascular disease (CVD), but their association with coronary artery calcification (CAC) remains unclear. This study aimed to investigate the relationship between MASLD and CAC, and the diagnostic accuracy of non-invasive fibrosis marker in predicting CAC. **Methods:** The study included 6,058 subjects undergoing coronary computed tomography (CT) from 2015 to 2024. Steatotic liver disease (SLD) was identified via ultrasonography or a hepatic steatosis index (HSI) > 36. MASLD was defined as SLD with at least one of the five cardiometabolic risk factors (CMRFs). Liver fibrosis severity was assessed using the FIB-4 index to assess its association with CAC and predictive performance at different CAC thresholds. **Results:** 39.8% of participants (n = 2,411) were classified as having MASLD whereas the remaining 60.2% (n = 3646) were with non-MASLD. MASLD patients had a higher prevalence of CAC than non-MASLD individuals (51.1% vs. 42.5%, $p < 0.001$). Factors associated with the presence of CAC included age (odds ratio [OR]/95% confidence intervals [CI]: 1.117/1.106-1.128, $P < 0.001$), male gender (OR/CI: 4.448/3.660-5.406, $P < 0.001$), MASLD (OR/CI: 1.570/ .342–1.837, $P < 0.001$), and FIB-4 (OR/CI: 1.217/ 1.034–1.433, $P = 0.018$). Among MASLD subjects, prevalence of CAC increased with FIB-4 value and cardiometabolic burdens. FIB-4 values increased progressively in patients with higher CACS ranging from 0.91 in patients without CAC, 1.16 in patients with mild CAC, 1.39 in patients with moderate CAC to 1.52 in patients with severe CAC. (P trend = 0.0091). A FIB-4 cut-off of ≥ 2.67 provided the highest positive predictive value (PPV: 89.7%) for the presence of CAC, while a cut-off of 1.26 offered the best negative predictive value (NPV: 95.1%) for severe CAC

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(≥400). **Conclusion:** MASLD patients with liver fibrosis were at a greater risk of CAD. The FIB-4 index, with optimized cut-offs, served as a valuable tool for cardiovascular risk stratification in MASLD, helping identify individuals with high-risk CAD.

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2074 | RELIABLE MONITORING OF PATIENTS WITH MASLD USING IMAGING: SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS ON MEASUREMENT REPEATABILITY

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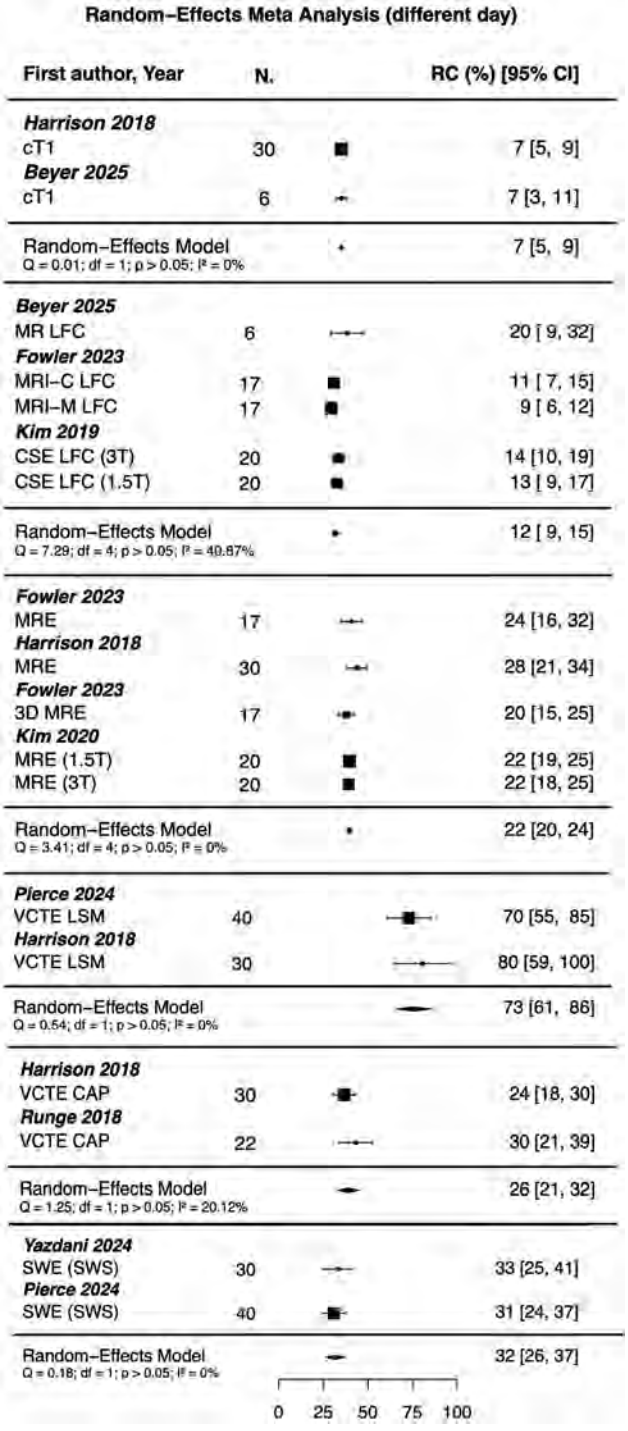
Background: As treatments for patients with metabolic dysfunction-associated steatotic liver disease (MASLD) emerge, monitoring of changes in liver health is becoming increasingly important. Reliable detection of treatment response requires quantitative metrics that are sensitive to change and highly reproducible. To assess the robustness of non-invasive imaging technologies in MASLD, we systematically reviewed the literature for same-day and different-day repeatability of various modalities. **Methods:** We searched PubMed Central and MEDLINE from 2015 to April 2025 for studies that examined the repeatability of non-invasive image-based technologies in adults with MASLD, specifically MRI iron-corrected T1 (cT1), MRI liver fat content (LFC; also known as proton density fat fraction, MRI-PDFF), magnetic resonance elastography (MRE), vibration controlled transient elastography liver stiffness measure (VCTE LSM), controlled attenuation parameter (CAP) and shear wave elastography shear wave speed (SWE-SWS). Two authors independently screened records and extracted data. The within subject standard deviations (wSD), mean and coefficient of variation (CV) were used to calculate the repeatability coefficient (RC) when not directly reported. The absolute (RC) and relative (%RC) for same-day (RC_{SD}) and different-day (RC_{DD}) repeat tests were summarized with a random-effects meta-analysis. **Results:** The searches resulted in 13 studies (cT1 n=2; LFC n=6; MRE n=4; VCTE n=3; CAP n=3; SWE n=2), with 328 individuals. The $\%RC_{SD}$ was 4% for cT1 and 21% for SWE-SWS, the random-effect average was 9% for LFC, 12% for MRE, 40% for VCTE LSM, and 21% for CAP. The random-effect average $\%RC_{DD}$ was 7% for cT1, 12% for LFC, 22% for MRE, 73% for VCTE LSM, 26% for CAP, and 32% for SWE-SWS, with a median time between repeat scans of 2.3 weeks. The RC_{SD} and average RC_{DD} for cT1 were 32ms and 65ms. To place these measurement variabilities in the context of monitoring in MASLD, the RC_{DD} can be compared to the established thresholds for clinically significant change for treatment responders: absolute change of 80ms for cT1 and relative reductions of 30% for LFC, 15% for MRE and 30% for VCTE, while not well established for CAP and SWE. **Conclusion:** This systematic review and meta-analysis showed that different day measurement repeatability is sufficiently robust for cT1 and LFC, not for MRE or VCTE, to detect individual clinically significant changes in liver health at treatment follow-up in MASLD.



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2075 | SOMASIGNAL DEFINED MASH DISEASE COMPONENTS ARE PROGNOSTIC OF SECONDARY CARDIOVASCULAR DISEASE – A POST-HOC ANALYSIS OF THE SELECT TRIAL

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Background: The SELECT trial confirmed the preventive effect of semaglutide vs placebo on secondary cardiovascular (CV) events in patients without diabetes but with a body mass index (BMI) ≥ 27 kg/m^2 and CV disease (CVD). The metabolic dysfunction associated steatohepatitis (MASH) SomaSignal® (SS) test uses protein profiling to predict histologic MASH disease components; however, the prevalence, and treatment effect of semaglutide on SS-MASH disease components within the SELECT trial population is unknown. Additionally, it is unknown if SS-MASH disease components are prognostic of 3-point major adverse CV events (3P-MACE) or CV- and all-cause mortality. **Methods:** This post-hoc, secondary analysis of SELECT participants with available SS-MASH data at baseline, weeks 20 and 104 used descriptive statistics and odds ratios (ORs) to determine the prevalence of SS-MASH disease components and the treatment effect of semaglutide 2.4 mg once weekly vs placebo on SS-MASH disease components at week 20 and 104, respectively. Cox proportional hazards regression adjusted for sex, age, BMI, pre-diabetes status and CV inclusion criteria were applied to analyse the association of baseline predicted disease components with time to event CV endpoints. **Results:** Of 17,604 participants, 11,568 (66%) (mean age 62 years, mean BMI 34 kg/m^2) had available SS-MASH data. SS-predicted steatosis was the most prevalent MASH disease component (39%), whilst lobular inflammation (grade ≥ 2) (6%), hepatocyte ballooning (6%), or fibrosis stage ≥ 2 (clinically significant fibrosis) (7%) were lower. Treatment with semaglutide statistically significantly reduced the odds of SS-MASH disease components at weeks 20 and 104. ORs (95% confidence interval [CI]) at week 104 were 0.22 (0.18-0.28) for steatosis, 0.28 (0.19-0.43) for lobular inflammation, 0.18 (0.11-0.28) for ballooning, and 0.43 (0.29-0.65) for fibrosis. In the placebo group, SS-predicted fibrosis was associated with subsequent CV-death (hazard ratio [HR], [95% CI] 2.29 [1.50-3.50]), all-cause death (2.06 [1.48-2.85]) and incident 3P-MACE (1.42 [1.04-1.94]) after adjustment for age, sex, BMI, CVD, and pre-diabetes status. SS-predicted hepatocyte ballooning was associated with subsequent CV-death (2.03 [1.25-3.29]) and all-cause death (2.10 [1.46-3.02]). There was a treatment effect of semaglutide vs placebo on 3P-MACE, CV- and all-cause death, and this was similar in the groups with or without baseline SS-predicted significant fibrosis. **Conclusion:** MASH SomaSignal® investigated the prevalence and semaglutide treatment effects on MASH disease components in a large CV outcome trial in a population with expected high prevalence of metabolic dysfunction associated steatotic liver disease, without biopsy data. We also established predicted MASH disease components as important secondary CV prognostic factors.

Disclosures: Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Steen Ladelund: Novo Nordisk: Employee, Michelle Long: Novo Nordisk A/S: stock, Sune Boris Nygård: Nothing to Disclose, Adel Belloum: Nothing to Disclose, Jörn Schattenberg: Apollo Endoscopy, Boehringer Ingelheim, Gilead Sciences: Consultant, Intercept Pharmaceuticals: Consultant, Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals: Consultant, MSD, Northsea Therapeutics, Novartis, Novo Nordisk: Consultant, Pfizer, Roche, Sanofi, and Siemens Healthineers: Consultant, Boehringer Ingelheim, Siemens Healthcare GmbH: Grant/Research Support, Alentis, Alexion, Altimmune, Astra

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2076 | NEW MASHFIB-12 MACHINE LEARNING MODEL: AFFORDABLE, SIMPLE, AND EFFECTIVE ALTERNATIVE TO CURRENT AGA/AASLD TWO-STEP GUIDELINES TO SCREEN MASLD

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Background: According to current AGA/AASLD guidelines, patients with metabolic dysfunction-associated steatotic liver disease (MASLD) at risk for advanced liver fibrosis should be screened using FIB-4 followed by transient elastography, FibroScan® (FIB-Fibro). In this study, we evaluated a new machine learning model, MASHFIB-12, and compared it to FIB-Fibro in risk-stratifying patients with MASLD. **Methods:** The new MASHFIB-12, a random forests model, was used to predict the risk of significant/advanced fibrosis in 763 prospectively followed patients with MASLD from multiple US centers with labs, FibroScan and liver biopsy performed within six months of one another. MASHFIB-12 uses 12 routine clinical/demographic features to make predictions. We split the cohort so that 80% was used for training MASHFIB-12 and 20% was used for testing MASHFIB-12 against FIB-4 alone, FibroScan alone, and sequential FIB-Fibro. Additionally, we tested sequential MASHFIB-12 followed by FibroScan (MASHFIB-12-Fibro) against FIB-Fibro. **Results:** In Table 1, results that are statistically significantly different from MASHFIB-12 ($p < 0.05$) are marked with an asterisk (*), while results that are significantly different from MASHFIB-12-Fibro ($p < 0.05$) are marked with a double asterisk (**). For low cutoffs ($\geq$F2), MASHFIB-12 had higher accuracy, AUC, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) versus FIB-4, and higher accuracy, AUC, specificity, and PPV versus FibroScan (all $p < 0.05$). For high cutoffs ($\geq$F3), it had higher accuracy, AUC, sensitivity, and NPV versus FIB-4, and higher AUC and sensitivity than FibroScan (all $p < 0.05$). There was no difference between MASHFIB-12 and FIB-Fibro in percentage of indeterminate-risk patients ($p > 0.05$). MASHFIB-12 displayed higher correctly classified (CC) measurement than FIB-Fibro, and MASHFIB-12-Fibro demonstrated higher CC and lower percentage of indeterminate-risk patients versus FIB-Fibro (all $p < 0.05$). **Conclusion:** MASHFIB-12 performs better than or similar to FIB-4 alone, FibroScan alone, and FIB-Fibro in several metrics while utilizing variables that can be quickly, easily, and inexpensively obtained, unlike FIB-Fibro, which requires FibroScan, a complex and costly imaging technology that is not frequently available in primary care settings. However, if FibroScan is available, MASHFIB-12-Fibro, which outperforms FIB-Fibro in all metrics, could be used instead for increased performance.

≥F2	Sensitivity	Specificity	Accuracy	AUC	PPV	NPV
MASHFIB-12	0.792 [0.755, 0.830]	0.767 [0.703, 0.829]	0.778 [0.756, 0.800]	0.844 [0.824, 0.863]	0.774 [0.750, 0.817]	0.794 [0.754, 0.835]
FIB-4	0.589 [0.559, 0.620] *	0.775 [0.743, 0.808]	0.685 [0.656, 0.710] *	0.785 [0.759, 0.810] *	0.722 [0.687, 0.757] *	0.657 [0.626, 0.688] *
FibroScan	0.813 [0.787, 0.840]	0.558 [0.535, 0.583] *	0.684 [0.663, 0.705] *	0.774 [0.755, 0.795] *	0.644 [0.618, 0.670] *	0.752 [0.717, 0.787]
≥F3	Sensitivity	Specificity	Accuracy	AUC	PPV	NPV
MASHFIB-12	0.774 [0.704, 0.844]	0.790 [0.736, 0.844]	0.785 [0.756, 0.810]	0.849 [0.833, 0.865]	0.645 [0.583, 0.709]	0.882 [0.845, 0.919]
FIB-4	0.241 [0.196, 0.286] *	0.946 [0.935, 0.957] *	0.720 [0.693, 0.746] *	0.793 [0.776, 0.811] *	0.672 [0.607, 0.737]	0.725 [0.697, 0.752] *
FibroScan	0.685 [0.655, 0.715] *	0.836 [0.818, 0.854]	0.788 [0.775, 0.798]	0.821 [0.803, 0.840] *	0.664 [0.629, 0.698]	0.849 [0.835, 0.863]
	Correctly Classified (CC) Measurement (%)	Indeterminate-Risk Patients (%)				
MASHFIB-12	66.405 [64.419, 68.391] **	10.654 [8.548, 14.758] **				
MASHFIB-12-Fibro	69.869 [68.073, 71.666] *	3.987 [2.334, 5.440] *				
FIB-Fibro	62.222 [60.145, 64.299] * **	9.083 [7.973, 10.197] **				

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2077 | MAXIMIZING THE DIAGNOSTIC YIELD OF NON-INVASIVE TESTS: SIMULTANEOUS OPTIMIZATION OF KEY PERFORMANCE METRICS FOR FIBROTIC LIVER DISEASE WITH A FIB-4 AND MASEF (OWLIVER) STRATEGY

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Background: Non-invasive tests (NITs) for metabolic dysfunction-associated steatotic liver disease (MASLD) diagnosis and staging face hurdles due to performance limits, especially the sensitivity-specificity trade-off. Robust NITs are needed. The low-cost, simple FIB-4 index is a recommended first-line tool for fibrosis risk. The Metabolomics-Advanced Steatohepatitis Fibrosis Score (MASEF) (part of the OWLiver test) accurately predicts MASH/at-risk MASH. This study evaluated a novel FIB-4 + MASEF strategy to maximize accuracy, sensitivity, specificity, PPV, and NPV, aiming to overcome current limitations. **Methods:** This multicenter study analyzed a cohort of 1122 patients at elevated

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risk for MASLD due to various metabolic comorbidities. FIB-4 and MASEF were determined and compared against the histopathological reference standard. To identify optimal diagnostic thresholds for FIB-4, a grid-based evaluation of all possible FIB-4 cutoff pairs was performed. For each pair, the MASEF score (part of the OWLiver test) was applied exclusively to the indeterminate zone (patients with FIB-4 values between the two cutoffs). This approach allowed for the systematic assessment of the combined strategy's performance across a multidimensional space. A rigorous statistical analysis, including ROC curve modeling and joint maximization of accuracy, sensitivity, specificity, PPV, and NPV, was conducted focusing on identifying a method capable of the simultaneous optimization of all five metrics. **Results:** Analysis of the 1122-patient cohort led to the identification of optimized FIB-4 thresholds (1.08 and 2.61) that enabled a balanced trade-off across all five key diagnostic metrics for detecting at-risk MASH. Using this strategy, the combined FIB-4 and MASEF (cutoff 0.33) approach achieved an accuracy of 78%, sensitivity of 71%, specificity of 82%, PPV of 64%, and NPV of 88%. **Conclusion:** This study demonstrates that the simultaneous maximization of all five key diagnostic metrics is an achievable benchmark for non-invasive testing with the combination of FIB-4 index and MASEF score (OWLiver test). This approach can enhance clinical confidence, streamline diagnostic pathways, and ultimately improve the management of patients with MASLD by providing a more complete and reliable assessment of disease severity.

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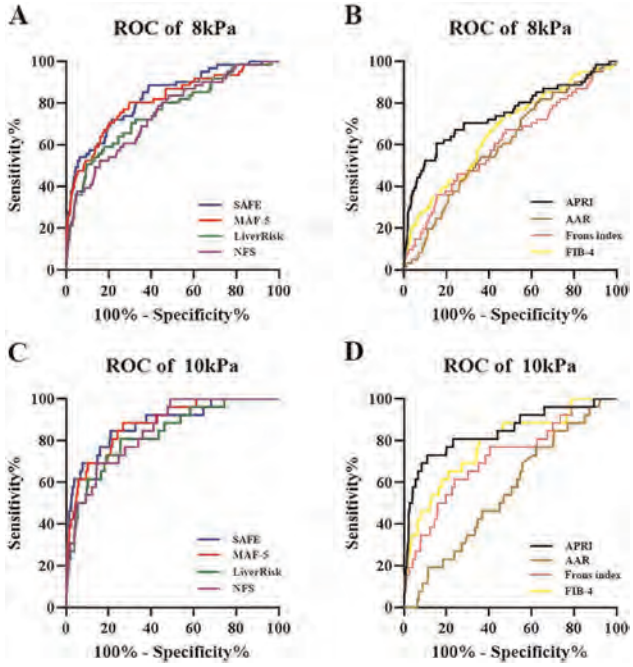
2078 | DIAGNOSTIC PERFORMANCE OF DIFFERENT NON-INVASIVE FIBROSIS SCORES IN THE GENERAL POPULATION WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Hui Shi[1] Xiaolin Wang[2] Rong Hu[1] Caihong Gu[1] Yilin Zhang[2] Shanghao Liu[2] Xiaolong Qi[2], [1]The First Affiliated Hospital of Kangda College of Nanjing Medical University, [2]Zhongda Hospital, Medical School, Southeast University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent condition associated with significant liver-related morbidity and mortality, primarily due to progressive liver fibrosis. Non-invasive fibrosis scores are widely used to assess fibrosis risk in MASLD patients. This study evaluates the diagnostic performance of various non-invasive fibrosis scores in identifying advanced fibrosis among MASLD patients in the general population. **Methods:** This study enrolled participants from Lianyungang, China, who underwent standardized health examinations in 2024. Comprehensive physical examination data, venous blood samples for serological biomarkers, and transient elastography for controlled attenuation parameter (CAP) values and liver stiffness measurements (LSM) were collected. Participants with CAP ≥ 248 dB/m and at least one cardiometabolic risk factor were included, excluding other causes of hepatic steatosis. Participants were stratified into two age groups: 18 - 60 years and ≥ 60 years. Eight non-invasive fibrosis scores, including SAFE, FIB-4, MAF-5, LiverRisk, NFS, APRI, AST/ALT Ratio, and Forns index, were calculated. Their diagnostic performance for clinically significant fibrosis (F2, LSM ≥ 8 kPa) and advanced fibrosis (F3, LSM ≥ 10 kPa) was assessed using ROC curve analysis, with AUC as the primary metric. **Results:** The study cohort included 985 MASLD patients (mean age: 49.09 years; 507 males, 478 females). F2 was identified in 61 patients (6.19%), and F3 in 26 patients (2.64%). All eight scores showed robust diagnostic performance for both fibrosis stages ($p < 0.01$). For F2, SAFE had the highest AUC (0.8273, 95% CI 0.76 - 0.89), followed by MAF-5 (AUC = 0.8081). For F3, SAFE (AUC = 0.8815), MAF-5 (AUC = 0.8784), APRI (AUC = 0.8431), and NFS (AUC = 0.8479) performed best. Age-stratified analyses confirmed the consistent reliability of SAFE, MAF-5, LiverRisk, and NFS. MAF-5 was the most stable predictor for F3, with AUC values of 0.9104 in the 18 - 60 age group and 0.8249 in those over 60 years. SAFE maintained strong performance across both age groups (AUC = 0.8909 for 18 - 60 years; AUC = 0.8202 for over 60 years). **Conclusion:** This study demonstrates that SAFE is the superior non-invasive score for detecting significant and advanced fibrosis in MASLD, with consistent diagnostic accuracy across all age groups (AUCs ranging from 0.89 to 0.80).



Disclosures: Hui Shi: Nothing to Disclose, Xiaolin Wang: Nothing to Disclose, Rong Hu: Nothing to Disclose, Caihong Gu: Nothing to Disclose, Yilin Zhang: Nothing to Disclose, Shanghao Liu: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose

2079 | EVALUATING THE NONINVASIVE DIAGNOSTIC PATHWAYS FOR IDENTIFYING MASH PATIENTS ELIGIBLE FOR RESMETIROM THERAPY

Larissa Lushniak[1] Alice Parish[1] Amreen Dinani[1], [1]Duke University

Background: Resmetirom was conditionally approved to treat individuals with metabolic dysfunction-

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associated steatohepatitis (MASH) and significant fibrosis ($\geq$ F2 fibrosis) in March 2024. The ongoing Phase 3 trial, which led to its approval, relied on biopsy-proven diagnosis, yet the real-world eligibility criteria can be determined with noninvasive tests (NITs). The aim of this study is to understand the pathways employed to assess eligibility for Resmetirom in a tertiary care center. **Methods:** A retrospective cohort of patients with MASH and significant fibrosis deemed eligible for Resmetirom was included (March 2024 to May 2025). Descriptive analysis was used to summarize patient characteristics, lab values, NITs, and, when available, liver biopsy data. Utilization of type and/or combination of NIT was assessed to confirm eligibility. **Results:** A total of 91 patients were considered eligible for Resmetirom prescription, 43 (47.3%) female, 74 (81.3%) white, with mean age of 57 years (SD 13.6), and mean BMI 33.5 (SD 6.2). Statins were the most common concurrent medication (61.5%), followed by GLP1 agonists (39.6%) and metformin (35.2%). Transient Elastography (TE) was the most employed NIT (87%) with mean liver stiffness measurement (LSM) of 10.6 kPa (SD 3.3), followed by Enhanced Liver Fibrosis (ELF) at 45% with mean score of 9.7 (SD 0.8), and MRI elastography (MRE) at 23% with mean LSM of 3.4kPa (SD 0.9). One NIT was performed in 51%, 2 NITs in 37%, and 3 NITs in 11%. One patient had a liver biopsy and no NITs. To determine stage of fibrosis via one NIT (N = 46), TE was utilized solely in 85%, ELF in 13%, and MRE in 6.5%. Among those evaluated by 2 NITs (N = 34), 71% had TE and ELF, 18% TE and MRE, and 12% ELF and MRE. Patient demographics, comorbidities, and laboratory data stratified by number of NITs are described in Table 1. The main reason for performing MRE was due to discordance between previous NITs (12/21, 57%). Liver biopsy was performed in 46 patients: 9% due to discordance in NITs. Of the 46 patients with biopsies, significant fibrosis was determined by histology in 93%, and a majority (72%) had NIT staging that correlated with histologic staging. **Conclusion:** This cohort of patients with MASH and significant fibrosis demonstrates how NITs can be employed to accurately identify individuals eligible for Resmetirom prescriptions. Despite heterogeneity in diagnostic approach, NITs demonstrate a high concordance with histologic staging, supporting their use in place of biopsy. These results provide reassurance and guidance on how to utilize NITs to diagnose MASH with significant fibrosis and guide the use of NITs in disease monitoring and response to treatment.

	Total (N=91)	1 NIT (N=46)	2 NITs (N=34)	3 NITs (N=10)
Sex (n, %)				
Female	43 (47.3)	20 (43.5)	18 (52.9)	4 (40.0)
Male	48 (52.7)	26 (56.5)	16 (47.1)	6 (60.0)
Race (n, %)				
White/Caucasian	74 (81.3)	35 (76.1)	28 (82.4)	10 (100.0)
Black	6 (6.6)	3 (6.5)	3 (8.8)	0 (0)
Asian	5 (5.5)	4 (8.7)	1 (2.9)	0 (0)
Other	6 (6.6)	4 (8.7)	2 (5.9)	0 (0)
Ethnicity (n, %)				
Hispanic or Latino	3 (3.3)	0 (0)	3 (8.8)	0 (0)
Non-Hispanic or Latino	88 (96.7)	46 (100.0)	31 (91.2)	10 (100.0)
Comorbidities (n, %)				
HLD	78 (85.8)	43 (93.5)	27 (79.4)	8 (80.0)
HTN	66 (72.5)	30 (65.2)	27 (79.4)	8 (80.0)
DM	49 (53.8)	21 (45.7)	22 (64.7)	5 (50.0)
Pre-DM	20 (22.2)	10 (22.2)	9 (26.5)	1 (10)
Age				
Mean (SD)	57 (13.6)	56 (14.1)	60 (13.1)	55 (13.1)
Median	60.0	58.5	61.0	57.5
BMI (kg/m^2)				
Mean (SD)	33.5 (6.2)	33.5 (5.8)	33.4 (7.2)	33.2 (5.4)
Median	33.3	33.4	32.4	32.2
Weight (kg)				
Mean (SD)	100.9 (26.2)	101 (22.3)	100.8 (31)	100.2 (29)
Median	100.0	101.8	97.5	87.5
Medications (n, %)				
ACE Inhibitor	22 (24.2)	11 (23.9)	8 (23.5)	3 (30.0)
ARB	25 (27.5)	11 (23.9)	10 (29.4)	4 (40.0)
Aspirin	24 (26.4)	11 (23.9)	11 (32.4)	2 (20.0)
GLP-1	36 (39.6)	14 (30.4)	16 (47.1)	6 (60.0)
Insulin	14 (15.4)	5 (10.9)	6 (17.6)	2 (20.0)
Metformin	32 (35.2)	14 (30.4)	14 (41.2)	3 (30.0)
Statin	56 (61.5)	25 (54.3)	22 (64.7)	8 (80.0)
Vit E	7 (7.7)	2 (4.3)	4 (11.8)	1 (10.0)
Data (mean, SD)				
ALP (U/L)	79.5 (48.3)	77.3 (26.3)	87.3 (71.5)	63.8 (23.8)
Total Bilirubin (mg/dL)	0.8 (0.3)	0.8 (0.3)	0.8 (0.4)	0.8 (0.2)
AST (U/L)	48.0 (35.4)	56.5 (45.6)	38.8 (16.0)	43.3 (18.8)
ALT (U/L)	59.1 (57.7)	71.1 (75.4)	48.1 (28.2)	45.7 (19.0)
Creatinine (mg/dL)	1.0 (0.3)	0.9 (0.2)	1 (0.4)	1 (0.3)
Platelet (10^3/L)	233.7 (65.9)	237 (61.2)	243 (72.9)	188 (50.4)
Hemoglobin A1c (%)	6.3 (1.2)	6.3 (1.1)	6.5 (1.5)	5.7 (0.8)
LDL (mg/dL)	87.0 (35.7)	91.3 (35.2)	87.7 (36.9)	70.8 (32.3)

NIT = Noninvasive Test, HLD = Hyperlipidemia, HTN = Hypertension, HLD = Hyperlipidemia, DM = Diabetes Mellitus, ALP = Alkaline Phosphatase, AST = Aspartate Aminotransferase, ALT = Alanine Transaminase, LDL = Low Density Lipoprotein

Table 1: **This table displays the demographics, co-morbidities, medications, and laboratory data for the population of patients who were prescribed Resmetirom between March 2024 and May 2025 (N=91), stratified by number of NITs performed. One individual prescribed Resmetirom had evidence of fibrosis on histologic staging, but no NIT evaluation.**

Disclosures: Larissa Lushniak: Nothing to Disclose, Alice Parish: Nothing to Disclose, Amreen Dinani: Madrigal Pharmaceutical: Consultant, Madrigal Pharmaceutical: Consultant, Novonordisk: Consultant, Novonordisk: Consultant, Kinetic: Advisor, Kinetic: Advisor, Madrigal Pharmaceutical: Consultant, Madrigal Pharmaceutical: Consultant, Novonordisk: Consultant, Novonordisk: Consultant, Kinetic: Advisor, Kinetic: Advisor

2080 | MODELING HIV- AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) USING IPSC-DERIVED MACROPHAGE- INCORPORATED LIVER ORGANOIDS

Zeinab Heidariyan[1] Volney Spalding[1] Nadia Al Atrakchi[1] Wenyu Lin[1] Min Xu[1] Yongtao Wang[1] Cecilie Siem Bach-Nielsen[1] Raymond Chung[1] Shadi Salloum[1], [1]Massachusetts General Hospital and Harvard Medical School

Background: Liver fibrosis is a major non-AIDS complication in people living with HIV (PLWH), despite effective antiretroviral therapy. Mechanistic insights are

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limited by the absence of in vitro human models that capture hepatic-immune interactions. We developed a macrophage-incorporated liver organoid (MILO) model from human induced pluripotent stem cells (iPSCs) to investigate fibrosis induced by HIV and metabolic stress. **Methods:** Human liver organoids (HLOs) were generated via a 25-day protocol to form 3D spheroids with hepatocyte- and hepatic stellate cell–like populations. In parallel, iPSCs were differentiated into $CD14^+$ macrophages using a feeder- and serum-free 32-day protocol. Pre-macrophages (day 25) were added to HLOs at a 1:4 ratio to generate MILOs. Organoids were treated with HIV or free fatty acids (FFAs) to model HIV and MASLD. qPCR, immunofluorescence, and flow cytometry were used to evaluate responses. Iodixanol gradients enabled cell-type–specific analysis. **Results:** Organoids exhibited hepatic function, including albumin production and FFA-induced lipid accumulation. Macrophages integrated into organoids and enhanced immune representation. HIV and/or FFA exposure led to nuclear translocation of Yes-associated protein (YAP; a key regulator of liver fibrosis) along with upregulation of fibrogenic genes (TIMP1, αSMA, COL1A1). HIV induced both M1 (CD80, CCR7, IL1B) and M2 (CD163, CD206, ARG1) markers, with M2 predominating. siRNA knockdown of PI3K, AKT, ERK, and JNK pathways downregulated YAP and reduced hepatic stellate cell activation. **Conclusion:** This iPSC-derived MILO model recapitulates HIV- and MASLD-associated fibrogenesis and enables cell-type–specific analysis. It represents a robust platform for dissecting mechanisms and testing antifibrotic therapies for HIV-related liver disease.

Disclosures: Zeinab Heidariyan: Nothing to Disclose, Volney Spalding: Nothing to Disclose, Nadia Al Atrakchi: Nothing to Disclose, Wenyu Lin: Nothing to Disclose, Min Xu: Nothing to Disclose, Yongtao Wang: Nothing to Disclose, Cecilie Siem Bach-Nielsen: Nothing to Disclose, Raymond Chung: Nothing to Disclose, Shadi Salloum: Nothing to Disclose

2081 | SOLUBLE CD46 AS A MARKER OF HEPATIC STEATOSIS IN LIVER SURGERY

Paul Kupke[1] Florian Bitterer[1] Laura Kupke[1] Gunther Glehr[1] Katja Evert[1] Ingo Einspieler[1] Matthias Hornung[1] Christian Stroszczynski[1] Hans Schlitt[1] Juergen Wenzel[1] Edward Geissler[1] James Hutchinson[1] Jens Werner[1], [1]University Hospital Regensburg

Background: We recently discovered interleukin-4-secreting ($IL\text{-}4^+$) iNKT cells to be overrepresented in steatotic liver. This could be attributed to stress-induction of matrix metalloproteases (MMP) in hepatocytes, which led to indiscriminate cleavage of immune receptors. Loss of cell-surface CD46 then resulted in unrepressed differentiation of $IL\text{-}4^+$ iNKT cells. Here, we asked whether sCD46 levels could predict steatosis in patients planned for liver surgery and thereby improve the detection of high-risk steatosis identifying patients that would benefit from alternative treatment options. **Methods:** sCD46 was measured in stored plasma from 156 prospective living liver donors and serum from 91 tumor patients. Steatosis was assessed by ultrasonography, computed tomography and liver histology. Clinical data were collected from hospital records. Waist circumference was measured from abdominal CT images. Significance tests and receiver operating characteristic (ROC) curve analyses were performed in R (4.3.3). ROC curves were compared with the DeLong test. Results were validated by training/validation sets and cross-validation. **Results:** Prospective living liver transplant donors and patients with liver tumors with moderate or severe steatosis had higher sCD46 levels than those without. After stratified random assignment of cases, we found that sCD46 performed well in classifying steatotic donors. In the validation set, the correct classification rate (CCR) was 78.8 %. We further demonstrated sCD46 was superior to Fatty Liver Index (FLI) in classifying steatotic donors. In liver tumor patients, histologically verified high-grade steatosis could be predicted with a CCR of 97.8%. The perfomance of sCD46 could be further improved by combination with pre-surgery computed tomography (AUC 0.956). **Conclusion:** sCD46 is a reliable diagnostic marker of hepatic steatosis, which can be conveniently and non-invasively measured in serum and plasma samples. Our work raises the possibility of using sCD46 as a biochemical screening tool for evaluating patients before liver surgery regarding high-risk steatosis.

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2082 | LIMITATIONS OF FIB-4 IN MASLD: ONE IN THREE CASES OF ADVANCED FIBROSIS MISSED IN BIOPSY-PROVEN COHORT

Tanya Jayakar[1] Ali Abdul Hussein[1] Jawad Aziz[1] Najwa Hussain[1] Mary Olayiwola[1] Atputhan Kuralarasu[1] Azeem Hassan[1] Maria Kalafateli[1] Michael Yee[1] Roberta Forlano[1] Benjamin Mullish[1] Mark Thursz[1] Pinelopi Manousou[1], [1]Imperial College London

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Background: The Fibrosis-4 (FIB-4) index is widely used to exclude advanced fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD), using a threshold of <1.3. However, its diagnostic accuracy varies, and misclassification may delay treatment. This study evaluated the negative predictive value of FIB-4 <1.3 using liver stiffness measurement (LSM) and liver biopsies as comparators, and identified factors associated with false negatives. **Methods:** MASLD patients referred for Fibroscan (2012–2016) were retrospectively identified. Clinical, biochemical, and anthropometric data were extracted from electronic health records. FIB-4 was compared with LSM ($\geq$8kPa), staging in liver biopsy, and clinical outcomes. Statistical analysis was performed using SPSS and R. **Results:** Among 832 patients (64% male; median age 51 years; median BMI 29.7 kg/m², 41% non-White), FIB-4 misclassified 31.4% (262/832) relative to LSM. Of 324 patients with FIB-4 ≥ 1.3, 55.6% had normal LSM; of 508 with FIB-4 <1.3, 16.1% had elevated LSM. Biopsy was performed in 299 patients; of 176 with FIB-4 <1.3, 33.5% had advanced fibrosis (stage ≥ 3, NASH CRN). False negatives were more likely in those with diabetes (T2DM) (26.8% vs 11.7%, $p<0.001$), hypertension (26.2% vs 12.3%, $p<0.001$), and BMI ≥ 27.5 kg/m² (21.6% vs 8.6%, $p=0.004$). On multivariate analysis, BMI (OR 1.11, 95% CI 1.04–1.18; $p<0.001$) and hypertension (OR 2.27, 95% CI 1.06–4.86; $p=0.036$) independently predicted false negatives. A combined predictive model including FIB-4, BMI, hypertension, and diabetes (P(advanced fibrosis) = 1/(1+e-(-5.5280+0.7499 (FIB-4)+0.0941(BMI)+0.3146(HTN)+0.8563(Diabetes) - coefficients were calculated using logistic regression models in R), outperformed FIB-4 alone (NRI 0.0433, $p=0.03$; IDI 0.2320, $p<0.001$). During follow-up, 14% of false negatives developed liver complications, 16% had cardiovascular events, and 2% died. Cox regression showed no significant differences in liver (HR 0.80–0.66, $p>0.3$), cardiovascular (HR 1.18–1.35, $p>0.4$), or mortality outcomes (HR 2.04–3.66, $p>0.2$) for false negative results, though trends suggest possible clinical implications. **Conclusion:** FIB-4 <1.3 misses advanced fibrosis in 1 in 6 patients by LSM and 1 in 3 by biopsy. Elevated BMI and hypertension increase the risk of false negatives. These findings support incorporating metabolic risk factors into MASLD fibrosis stratification to improve diagnostic accuracy and avoid delayed care.

Disclosures: Tanya Jayakar: Nothing to Disclose, Ali Abdul Hussein: Nothing to Disclose, Jawad Aziz: Nothing to Disclose, Najwa Hussain: Nothing to Disclose, Mary Olayiwola: Nothing to Disclose, Atputhan Kuralarasu: Nothing to Disclose, Azeem Hassan: Nothing to Disclose, Maria Kalafateli: Nothing to Disclose, Michael Yee: Nothing to Disclose, Roberta Forlano: Nothing to Disclose, Benjamin Mullish: Nothing to Disclose, Mark Thursz: Nothing to Disclose, Pinelopi Manousou: Nothing to Disclose

2083 | RISK STRATIFICATION USING NON-INVASIVE TESTS AND MAGNETIC RESONANCE ELASTOGRAPHY REVEALS SIMILAR PATTERNS IN METALD AND MASLD

Akash Roy[1] Shardhya Chakroborty[1] Surabhi Jajodia[2] Usha Goenka[2] Anand Kulkarni[3] Nipun Verma[4] Awanish Tewari[1] Nikhil Sonthalia[1] Uday Ghoshal[1] Rajender Reddy[5] Mahesh Goenka[1], [1]Apollo Hospitals, [2]Radiology, Apollo Hospitals, [3]AIG Hospitals, [4]PGIMER, Chandigar, [5]University of Pennsylvania

Background: Non-invasive tests (NITs) for fibrosis risk stratification are central to optimized care in metabolic dysfunction-associated steatotic liver disease (MASLD). However, data on their performance in individuals with metabolic dysfunction and alcohol-associated liver disease (MetALD) are scarce. We aimed to assess the performance of measures of NITs against magnetic resonance elastography (MRE) in this population. **Methods:** Adults ($\geq$ 18 years) meeting MASLD criteria based upon cardiometabolic risk factors (CMRFs) and evidence of hepatic steatosis were prospectively enrolled. Self-reported alcohol history, anthropometry indices (AI), and biochemical indices were recorded. Contemporaneous MRE served as the outcome measure with cut-offs for significant fibrosis (SF, $\geq$F2) and advanced fibrosis (AF, $\geq$F3) as 3.14kPa and 3.53kPa, respectively and compared with Fibrosis-4 (Fib-4), AST platelet ratio index (APRI), and NAFLD fibrosis score (NFS) in MASLD and Met-ALD. **Results:** Among 1010 individuals [44(35-54years),35.2%females] 842(83.3%) had MASLD and 168(16.6%) had MetALD. Anthropometric indices (AI) [BMI, 27.2(24.8-30.4) vs27.6(25.2-30.4), hip circumference [105(100-111) vs 105(100-110.5)], waist circumference [98.7 (91-104) vs 98(92.5-105)] and CMRF [diabetes,36.6% vs.30.9%, $p=0.15$], hypertension (38.2%vs.58 34.5% $p=0.36$), dyslipidaemia (31.5% vs 33.9%, $p=0.55$) were similar. The burden of fibrosis (SF, 21.6% vs 27.9%, $p=0.07$; AF,15.4% vs 18.4%, $p=0.33$) among MASLD and Met-ALD was also similar. Performance of APRI in the entire cohort was suboptimal [AUC 0.63(0.60-0.66 for AF)]. In MetALD, FIB-4 had an Sn, Sp, PPV, and NPV of 67.7%,73.7%,36.8% and 91%, respectively, for AF. Corresponding metrics for NFS were 77.4%,72.3%,38.7% and 93.4%. AUC for FIB-4 for MASLD and Met-ALD in predicting AF were similar [0.77(0.74-0.79), 0.78(0.71-0.84),$p=0.82$]. The AUC of NFS for MASLD and Met-ALD [0.80 (0.70.83) and 0.80 (0.73-0.86), $p=0.98$] were also similar. NFS performed better than FIB-4 in MASLD but showed equivalent performance in Met-ALD (AUC 0.80 vs 0.78, $p=0.48$) **Conclusion:** In a prospective cohort, MASLD and Met-ALD showed similar AI, CMRF, and fibrosis burden. Compared with MRE, FIB-4 and NFS show acceptable performance in MetALD, replicating MASLD performance, and may be used for Met-ALD risk stratification.

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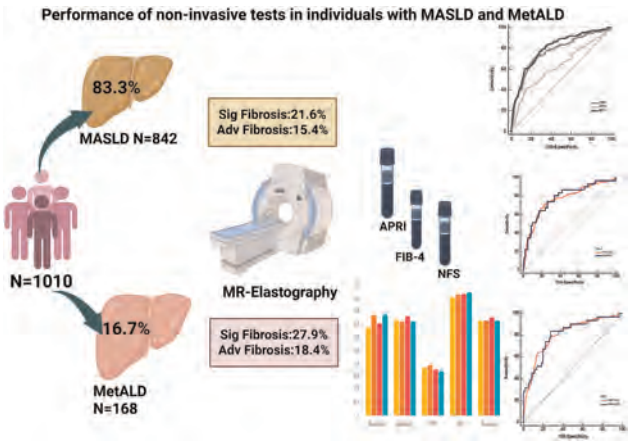

Disclosures: Akash Roy: Nothing to Disclose, Shardhya Chakroborty: Nothing to Disclose, Surabhi Jajodia: Nothing to Disclose, Usha Goenka: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Awanish Tewari: Nothing to Disclose, Nikhil Sonthalia: Nothing to Disclose, Uday Ghoshal: Nothing to Disclose, Rajender Reddy: Nothing to Disclose, Mahesh Goenka: Nothing to Disclose

2084 | EVALUATING ELASTOGRAPHY IN LEAN NASH PATIENTS: A SUPERIOR DIAGNOSTIC TOOL OVER ULTRASOUND?

Simardeep Singh[1] Boniface Mensah[1] Manish Arora[2], [1]MedStar Health Georgetown University (Baltimore) Program, [2]Decatur Morgan Hospital

Background: Fatty liver disease, particularly non-alcoholic steatohepatitis (NASH), often remains underdiagnosed. While liver biopsy is the diagnostic gold standard, its invasive nature limits widespread application. Ultrasound, commonly used for hepatic evaluation, may overlook fibrosis, especially in lean NASH patients. Elastography, with its enhanced sensitivity, may address this gap. This study assesses the utility of elastography in detecting fibrosis in patients with negative ultrasound findings but significant metabolic risk factors, particularly diabetes and hyperlipidemia. **Methods:** This retrospective cohort study, conducted between 2023 and 2024, included 450 adults without pre-existing liver disease who underwent screening via ultrasound and elastography. Patients with incomplete records or liver-impacting malignancies were excluded. The study focused on individuals with negative ultrasound findings for fatty liver but positive elastography results, meeting the inclusion criteria. Data were sourced from institutional electronic health records, with liver stiffness (kPa) measured by elastography serving as the primary variable. Secondary variables included demographics, BMI, diabetes, and hyperlipidemia. Statistical analyses involved descriptive statistics, chi-square tests, and logistic regression to identify predictors of fibrosis.

Results: In a cohort with a mean age of 63 years and an equal gender distribution, metabolic comorbidities were prevalent, with • 44% having diabetes, • 50% hyperlipidemia, and • 50% being classified as overweight or obese. Among 450 patients with negative ultrasound, 11% were diagnosed with fibrosis through elastography, with F2 fibrosis staging in 86%, F3 in 12%, and F4 in 2%. Notably, 18% of fibrosis cases were found in lean individuals (BMI < 25), highlighting the presence of lean NASH. Diabetes and HLD emerged as significant predictors of fibrosis ($p < 0.01$ and $p < 0.05$, resp.), with the highest risk observed in individuals with both conditions, accounting for 32% of fibrosis cases. **Conclusion:** Elastography significantly enhances fibrosis detection in patients with negative ultrasound findings, particularly in lean NASH cases. Metabolic risk factors such as diabetes and hyperlipidemia were more predictive of fibrosis than obesity. This underscores elastography's potential as a superior non-invasive tool for liver disease screening in at-risk populations. Future studies should incorporate larger cohorts and prospective designs to validate these findings.

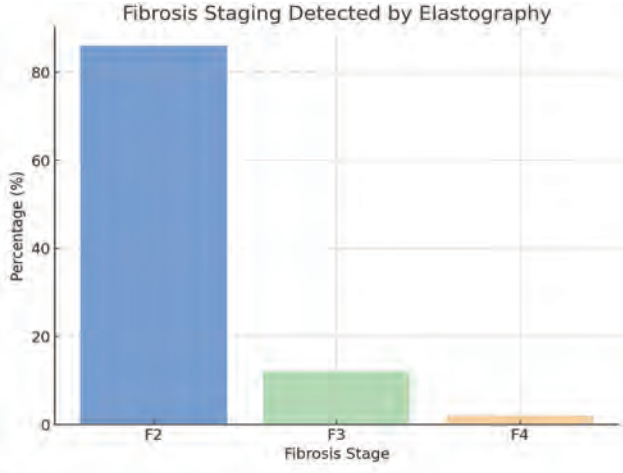

Fig 1:

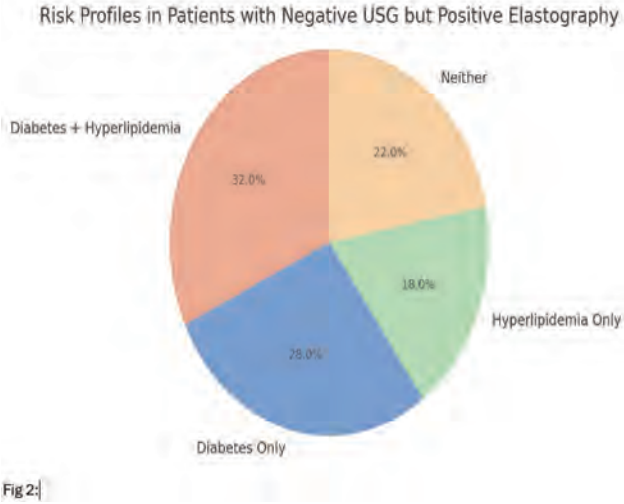

Fig 2:

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Disclosures: Simardeep Singh: Nothing to Disclose, Boniface Mensah: Nothing to Disclose, Manish Arora: Nothing to Disclose

2085 | ENHANCED LIVER FIBROSIS (ELF) TEST CORRELATES BETTER WITH MRE THAN VCTE IN A REAL-WORLD COHORT OF PATIENTS WITH SUSPECTED MASH

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Background: The Enhanced Liver Fibrosis (ELF) test, FDA-approved for prognostication, shows promise for identifying patients with at-risk metabolic dysfunction-associated steatohepatitis (MASH), but its real-world use remains underexplored. Magnetic Resonance Elastography (MRE) is limited by cost and availability, vibration-controlled transient elastography (VCTE) is less reliable in patients with obesity and is operator-dependent, while FIB-4 has a substantial indeterminate range. We evaluated ELF's ability to predict fibrosis severity assessed by MRE (kPa) compared with other non-invasive tests. **Methods:** This prospective study included patients evaluated for MASH at an urban, academic center who underwent FIB-4, VCTE, ELF, and MRE as part of routine care. Due to right-skewness and nonlinearity, ELF and MRE values were log-transformed to improve model fit. Model assumptions were confirmed via regression diagnostics. Spearman's correlation assessed ELF–MRE association. Univariable linear regression on log-transformed values was used, with β interpreted as percent change in stiffness per 1% change in ELF. This approach was applied consistently in subgroup analyses by diabetes status, sex, age, and indeterminate FIB-4 value. Variance explained was quantified by R^2. **Results:** The cohort ($n = 57$) had a mean age of 57.5 years (SE 2.0); 57% were female, and 60% Hispanic. MRE stiffness averaged 3.8 kPa (SE 0.20), and ELF 9.5 (SE 0.17). ELF was strongly correlated with MRE ($\rho = 0.68$, $p < 0.001$). In a log-log regression, a 1% increase in ELF was associated with a 2.01% increase in liver stiffness, explaining 50% of the variance. VCTE and FIB-4 explained 48% and 23% of variance, respectively. Subgroup analyses confirmed ELF's strong predictive power: in those with diabetes, ELF explained 51% variance; in males, 54%. Predictive strength was highest in younger patients and declined with age. ELF outperformed FIB-4 in all groups and VCTE in women and patients under 40 years old. In those with indeterminate FIB-4, ELF showed a stronger association with MRE than VCTE (table 1). **Conclusion:** In this real-world cohort, ELF outperformed VCTE and FIB-4 in predicting liver stiffness. ELF performed most consistently across all subgroups and added predictive value when FIB-4 was inconclusive. As an FDA-approved, blood-based test, ELF offers a scalable alternative when MRE is unavailable. These results support the potential use of ELF to identify patients eligible for MASH therapies and highlight the need for broader coverage and adoption in clinical practice, particularly in settings where patients may not have access to evaluation via MRE.

Table 1. Predictive Performance of ELF, VCTE, and FIB-4 for MRE-Assessed Liver Stiffness Using Linear Regression with Log-Transformed Variables

	N	ELF R^2	ELF β		VCTE R^2	VCTE β		FIB-4 R^2	FIB-4 β	
Total cohort	57	0.50	2.01	$p<0.001$*	0.48	0.41	$p<0.001$*	0.23	0.25	$p<0.001$*
Diabetes	31	0.51	1.85	$p<0.001$*	0.60	0.39	$p<0.001$*	0.16	0.22	$p=0.028$*
Non-diabetes	26	0.38	1.86	$p=0.001$*	0.45	0.44	$p<0.001$*	0.20	0.21	$p=0.021$*
Male sex	21	0.54	2.01	$p<0.001$*	0.67	0.47	$p<0.001$*	0.11	0.19	$p=0.146$
Female sex	31	0.52	2.17	$p<0.001$*	0.25	0.35	$p=0.005$*	0.35	0.30	$p<0.001$*
Age <40	8	0.61	3.74	$p=0.023$*	0.48	0.53	$p=0.057$	0.05	0.21	$p=0.594$
Age 40-59	19	0.59	2.29	$p<0.001$*	0.66	0.48	$p<0.001$*	0.37	0.48	$p=0.005$*
Age ≥ 60	30	0.30	1.68	$p=0.002$*	0.35	0.31	$p=0.001$*	0.11	0.16	$p=0.070$
Obesity	48	0.35	1.61	$p<0.001$*	0.33	0.36	$p<0.001$*	0.11	0.17	$p=0.022$
Indeterminate FIB-4 (1.30-2.67)	28	0.44	2.42	$p<0.001$*	0.48	0.45	$p<0.001$*	0.08	0.50	$p=0.147$

Disclosures: Cecilia Katzenstein: Nothing to Disclose, Anna Mageras: The Kinetix Group: Advisor, Novo Nordisk: Advisor, Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Mark Miller: Nothing to Disclose, Xiaotao Zhang: Nothing to Disclose, Meena Bansal: Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor

2086 | SECOND HARMONIC GENERATED IMAGING WITH QFIBROSIS PROVIDES QUANTITATIVE INFORMATION ON FIBROSIS SEVERITY AND PREDICTS THE FUTURE COURSE OF FIBROSIS IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

David Kleiner[1] Ekaterina Smirnova[2] Dean Tai[3] Cynthia Behling[4] Oscar Cummings[5] Ryan Gill[6] Patricia Belt[7] Daniela Allende[8] Danielle Carpenter[9] Cynthia Guy[10] Matthew Yeh[11] Shailaja Reddy[2] Faridoddin Mirshahi[2] Arun Sanyal[12], [1]National Cancer Institute, Bethesda, [2]Virginia Commonwealth University, Richmond, VA, [3]HistoIndex, [4]Department of Pediatrics, University of

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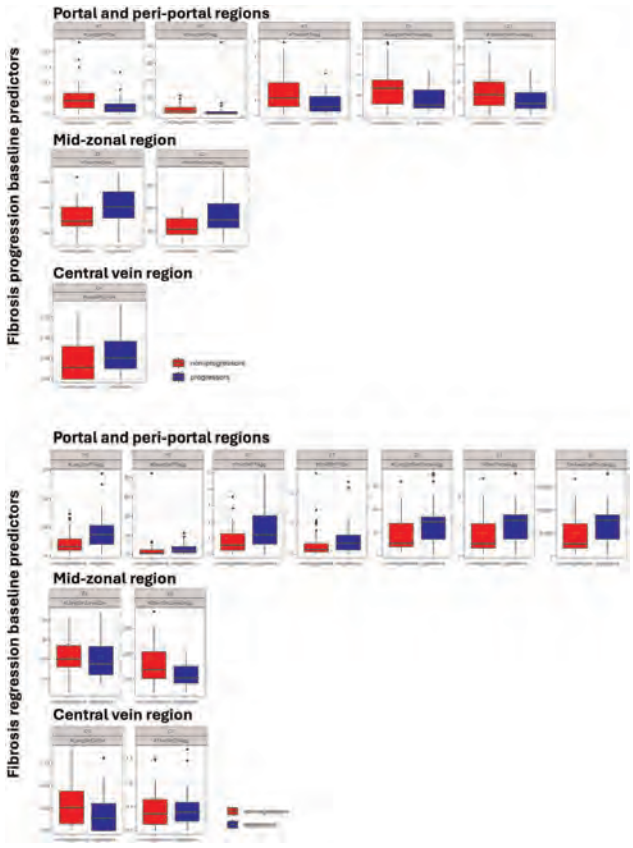
Background: Fibrosis progression or regression can occur in MASLD even without specific therapy. Conventional fibrosis stages do not predict the future course of fibrosis. Second harmonic generation/two-photon excitation (SHG/TPE) with qFibrosis analysis quantitatively captures collagen fibers which also correlates with fibrosis severity. Its ability to predict the future course of fibrosis is not known. This study aims to: (1) independently validate the qFibrosis scoring, and (2) evaluate the prognostic performance of qFibrosis parameters (qFPs) in MASLD. **Methods:** A retrospective ancillary study of the NIDDK NASH CRN cohort included subjects with ≥ 2 biopsies > 1 year apart, with no intervening treatment. The biopsies were read by the NASH CRN pathology committee using the NASH CRN system masked to qFibrosis stage. SHG/TPE imaging was performed on unstained tissue sections and quantitative fibrosis (qFibrosis) stage computed by investigators masked to NASH CRN pathology committee scores. Data analysis was performed by an independent statistician using a pre-specified analytical plan. Baseline biopsies were related to qFibrosis stage and continuous value. Baseline fibrosis parameters were related to progression, no change or regression in CRN stage using lasso regression. The changes were further quantified in portal, peri-portal, mid-zonal, pericentral and central vein regions. Model performance was assessed by area under receiver operating characteristic (AUROC) curves. **Results:** Baseline composite qFibrosis scores correlated strongly with CRN fibrosis staging ($r = 0.75$, $p < 0.001$). Zonal analysis revealed moderate to strong correlations between fibrosis severity and qFPs in periportal and portal regions (r ~0.68–0.75). Progressors exhibited an inverse correlation with periportal features and a direct correlation with midzonal collagen density, suggesting loss of collagen in periportal region and mid-zonal accumulation of collagen as indicators of worsening disease. In contrast, regressors demonstrated higher baseline periportal and portal collagen complexity, consistent with a preserved architecture conducive to fibrosis reversal. Predictive models achieved AUROCs of 0.773 (progression) and 0.802 (regression). **Conclusion:** qFibrosis stages and scores correlate well with NASH CRN fibrosis staging. SHG analysis of fibrosis may have prognostic utility in MASLD and be used to enrich study populations for patients most at risk for fibrosis progression. Additional modeling approaches are needed to further strengthen the predictive framework. A larger validation study involving over 1,000 biopsies is underway.



Disclosures: David Kleiner: Nothing to Disclose, Ekaterina Smirnova: Nothing to Disclose, Dean Tai: Nothing to Disclose, Cynthia Behling: Nothing to Disclose, Oscar Cummings: Nothing to Disclose, Ryan Gill: Nothing to Disclose, Patricia Belt: Nothing to Disclose, Daniela Allende: Mayo Clinic: Speaking and Teaching, Univ. of Ottawa: Speaking and Teaching, Educational Symposia: Speaking and Teaching, Danielle Carpenter: Nothing to Disclose, Cynthia Guy: Sagimet: Consultant, Madrigal: Consultant, HistoIndex: Consultant, Matthew Yeh: Nothing to Disclose, Shailaja Reddy: Nothing to Disclose, Faridoddin Mirshahi: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea

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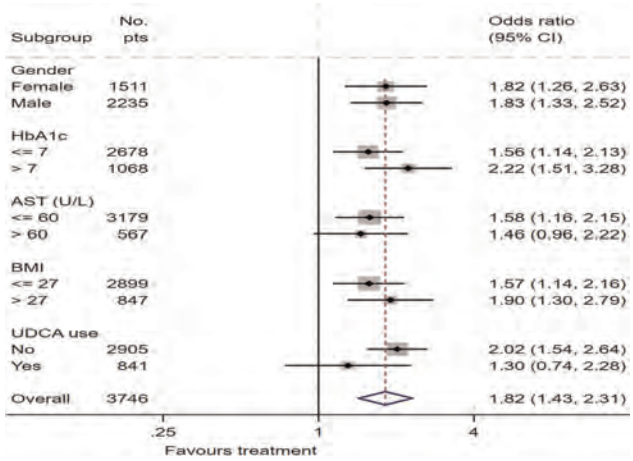
2087 | EFFECT OF VITAMIN E ON LIVER STIFFNESS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

seungteak Lee[1] Juneyoung Lim[1] Eun Sun Jang[2] Min Kyung Park[3] Jin-Wook Kim[1], [1]Seoul National University Bundang Hospital, [2]Seoul National University College of Medicine, [3]Seoul National University Hospital

Background: Current guidelines on the therapeutic efficacy of vitamin E on metabolic dysfunction-associated steatotic liver disease (MASLD) are based on limited evidence and it is not clear if vitamin E affects liver fibrosis in MASLD patients. Vibration-controlled transient elastography (VCTE) is a well-established non-invasive method for assessing liver fibrosis in MASLD. In this study, we evaluated the effect of vitamin E on the liver stiffness measured by VCTE in patients with MASLD. **Methods:** In this retrospective cohort study, we identified MASLD patients who underwent serial measurements of liver stiffness by VCTE. Patients with viral hepatitis were excluded. Administration of other hepatotonics, i.e., ursodeoxycholic acid, silymarin, biphenyl dimethyl dicarboxylate, were controlled as covariates by multivariate logistic regression analysis. **Results:** A total of 5,055 patients with MASLD received at least 2 measurements of liver stiffness by VCTE during the period between July 2020 and March 2025. After excluding 1,206 patients with chronic hepatitis B and 105 patients with chronic hepatitis C, 3,746 patients were finally selected for analysis. The median duration of follow-up was 724 days (interquartile range = 549). The median change in liver stiffness measurement (LSM) was -0.2 kPa, -3.6% from baseline (interquartile range = 2.2kPa, 40%). The median duration of vitamin E therapy was 455 days (interquartile range = 720). Multivariate logistic regression analysis showed that use of vitamin E for more than 3 months was associated with significant improvement in LSM: the odds ratio for improvement of LSM more than 50% from baseline was 2.40 (95% confidence interval, 1.68 – 3.43). **Conclusion:** Use of vitamin E was associated with significant improvement of LSM in MASLD patients.



Disclosures: seungteak Lee: Nothing to Disclose, Juneyoung Lim: Nothing to Disclose, Eun Sun Jang: Nothing to Disclose, Min Kyung Park: Nothing to Disclose, Jin-Wook Kim: Nothing to Disclose

2088 | NON-INVASIVE MACHINE LEARNING MODEL IMPROVES MID-STAGE FIBROSIS DETECTION IN MASLD

Laith Alomari[1] Zaid Al-Fakhouri[2] Tinsae Tsegaye Anebo[1] Emmanuel Otabor[1] Justin Riley Lam[1] Daniel Simadibrata[3] Jana Alomari[4] Karecia Byfield[1] Jordan Carty[1] Delano Carty[1] Thai Hau Koo[5] Oluwanifemi Balogun[1] Ghideon Ezaz[1], [1]Jefferson Einstein Philadelphia Hospital, [2]The MetroHealth System, CWRU, [3]MetroHealth Medical Center, Case Western Reserve University, [4]Faculty of Medicine, Jordan University of Science and Technology, [5]University of Sciences Malaysia Specialist Hospital

Background: Non-invasive tests like FIB-4 reliably distinguish both ends of the liver fibrosis spectrum but have limited performance at intermediate stages. We developed and validated a machine-learning classifier using routine demographics and laboratory values for two tasks: discriminating $\leq$ F2 versus $\geq$ F3 (advanced fibrosis) and separating mild fibrosis (F1 or F2) from F3 in biopsy-proven MASLD patients. Performance of the model was compared against FIB-4. **Methods:** Data from 452 consecutive MASLD patients obtained from NAFLD Adult database with contemporaneous liver biopsy and 16 baseline laboratory/demographic variables obtained within 6 months of liver biopsy were retrospectively analyzed. A LightGBM gradient-boosting classifier with class-balanced focal loss ($\alpha = 0.25$, $\gamma = 1.5$) was trained on 75 % of the cohort and evaluated on a held-out 25 % test set. Performance was evaluated by area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV); FIB-4

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was calculated on the same dataset for benchmarking. **Results:** In distinguishing ≤ F2 versus ≥ F3 (test n = 113), the classifier achieved an AUROC of 0.851 (95% CI: 0.826, 0.891), significantly outperforming FIB-4's AUROC of 0.788 ($p < 0.001$). It reached 95% sensitivity and NPV of 85% for ruling out advanced fibrosis and 73% specificity and 73.3% PPV for detecting ≥ F3 fibrosis. When separating milder fibrosis stages (F1 or F2) from F3 (excluding F0 and F4; test n = 72), it attained an AUROC of 0.801 (95% CI: 0.797, 0.825), with a specificity of 92% distinguishing F3 from F1 or F2. **Conclusion:** A focal-loss LightGBM model built on routine labs and demographics outperforms FIB-4 for ruling in advanced fibrosis and delivers actionable discrimination of mid-stage fibrosis. This non-invasive, scalable approach could enhance triage for imaging or biopsy and merits prospective validation.

Disclosures: Laith Alomari: Nothing to Disclose, Zaid Al-Fakhouri: Nothing to Disclose, Tinsae Tsegaye Anebo: Nothing to Disclose, Emmanuel Otabor: Nothing to Disclose, Justin Riley Lam: Nothing to Disclose, Daniel Simadibrata: Nothing to Disclose, Jana Alomari: Nothing to Disclose, Karecia Byfield: Nothing to Disclose, Jordan Carty: Nothing to Disclose, Nothing to Disclose, Delano Carty: Nothing to Disclose, Thai Hau Koo: Nothing to Disclose, Oluwanifemi Balogun: Nothing to Disclose, Ghideon Ezaz: Nothing to Disclose

2089 | IRON MARKERS IN MASLD AND METALD: A COMPARATIVE ANALYSIS FROM NHANES 2017-2020

Sheena Bhushan[1] Kris Kowdley[1], [1]Liver Institute Northwest

Background: Elevated serum ferritin (SF) levels have been associated with hepatic injury and fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD). Experimental evidence suggests that alcohol consumption may contribute to iron dysregulation, thereby exacerbating hepatic inflammation and fibrogenesis. However, to date, no population-based comparative studies have evaluated the role of iron-related biomarkers in MASLD and metabolic dysfunction-associated alcohol-related liver disease (metALD). The objective of this study is to compare serum ferritin (SF) and transferrin saturation (TSAT) levels and examine their associations with liver stiffness measurement (LSM) in individuals with MASLD and metALD. **Methods:** Data from the 2017–2020 cycles of the National Health and Nutrition Examination Survey (NHANES) were analyzed. The study population included 843 individuals who met the diagnostic criteria for MASLD, defined as a controlled attenuation parameter (CAP) ≥288 dB/m, and 67 individuals who met criteria for metALD. SF levels greater than 400 in men and gretaer than 300 in women were considered elevated. A TSAT greater than 45% was considered elevated. Statistical analyses included Mann–Whitney U tests for group comparisons and Spearman correlation coefficients to assess associations between variables. Multivariable logistic regression models were employed to adjust for potential confounders, including age, sex, BMI, diabetes mellitus, and dyslipidemia. **Results:** Individuals with meALD has significantly higher SF and TSAT levels compared to MASLD (ferrtin p = 0,0057; TSAT p = 0.0148), while liver stiffness did not differ significantly (p = 0.3808). LSM showed weak correlations with ferritin in MASLD (p = 0.08) and TSAT (p = -0.077), whereas LSM in metALD was more strongly correlated with both ferritin (p = 0.239) and TSAT (p = 0.204). **Conclusion:** Iron biomarkers were more strongly associated with LSM in metALD, thereby suggesting that SF and TSAT may have the potential to be utilized as makers for risk stratification. Our study is limited by a small sample size in the metALD group which may limit power to detect subtle associations.

Disclosures: Sheena Bhushan: Nothing to Disclose, Kris Kowdley: Nothing to Disclose

2090 | THE OBESITY-RELATED MUTATION GENES ON HEPATOCARCINOGENESIS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Jee-Fu Huang[1] Ming-Lun Yeh[2] Wan Long Chuang[1] Ming-Lung Yu[1] Shu-Chi Wang[1], [1]Kaohsiung Medical University, [2]National Sun Yat-Sen University

Background: In addition to liver injury, metabolic dysfunction-associated steatotic liver disease (MASLD) carries a potential risk for hepatocellular carcinoma (HCC) development. The study aimed to investigate the characteristics of obesity-related driver gene mutations in hepatocarcinogenesis. **Methods:** We investigated the impact of body mass index (BMI) on HCC survival by using the Cancer Genome Atlas Liver (TCGA-LIHC) dataset. To explore the effects of obesity-related gene mutations on HCC, we analyzed the driver mutation genes between 34 patients with obese BMI ≥ 27 kg/m^2 and 23 patients with BMI < 27 kg/m^2. We also validated the peripheral blood mononuclear cells (PBMC) and exosome samples for the variant rate by digital PCR in 96 MASLD patients. **Results:** Using Cbio-portal, we identified 414 driver mutation genes in patients with obesity and 127 driver mutation genes in their non-obese counterparts. Obesity HCC patients had significantly worse survival outcomes. Functional analysis showed that obese-related genes significantly enriched the regulated lipid and insulin pathways in HCC. The insulin secretion pathway in obese patients with HCC-specific survival identified ABCC8 and PRKCB as significant genes ($p < 0.001$). The significant differences in gene mutation

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and gene expression profiles were observed in obese patients compared to non-obese patients. The ABCC8 variants detected by digital PCR test in PBMC samples had a variant rate of 14.5%, which was significantly higher than that of non-obese MASLD patients. **Conclusion:** The study showed that an obesity-related gene mutation, ABCC8, predicted for HCC development in MASLD.

Disclosures: Jee-Fu Huang: Roche: Consultant, Gilead: Consultant, Sysmex: Consultant, Aligos: Consultant, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Merck: Speaking and Teaching, Sysmex: Speaking and Teaching, Novo Nordisk: Consultant, Berlinger-Ingelheim: Consultant, Ming-Lun Yeh: Nothing to Disclose, Wan Long Chuang: Nothing to Disclose, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching, Shu-Chi Wang: Nothing to Disclose

2091 | LIPIDOMIC ANALYSIS AND MACHINE LEARNING MODELS FOR PREDICTING SIGNIFICANT LIVER FIBROSIS IN PATIENTS WITH SEVERE OBESITY UNDERGOING BARIATRIC SURGERY

Chien-Hung Lu[1] Yin-Ru Hsieh[2] Shih-Yi Huang[2] Weu Wang[3] Ching-Wen Chang[4] Binar Panunggal[5] I-Wei Chang[6] Chi-Long Chen[6] Chun-Chao Chang[7] Wei-Yu Kao[1], [1]Division of Gastroenterology and Hepatology, Taipei Medical University Hospital, Taipei, Taiwan, [2]School of Nutrition and Health Sciences, Taipei Medical University, Taipei, Taiwan, [3]Division of Digestive Surgery, Taipei Medical University Hospital, Taipei, Taiwan, [4]Graduate Institute of Metabolism and Obesity Sciences, Taipei Medical University, Taipei, Taiwan, [5]Department of Nutrition Science, Faculty of Medicine, Diponegoro University, Semarang, Indonesia, [6]Department of Pathology, Taipei Medical University Hospital, Taipei, Taiwan, [7]TMU Research Center for Digestive Medicine, Taipei Medical University, Taipei, Taiwan

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) affects over 30% of the global population and is strongly associated with obesity. Significant liver fibrosis, an advanced stage of MAFLD, poses a major risk factor for hepatocellular carcinoma. Despite its increasing prevalence, the accuracy and cost-effectiveness of current non-invasive tools for liver fibrosis assessment remain limited, with liver biopsy still considered the gold standard. Lipidomic analysis offers a promising approach for identifying potential biomarkers across diverse lipid profiles. This study aimed to apply statistical methods and machine learning models to lipidomic data to identify potential biomarkers and predict significant liver fibrosis. **Methods:** This prospective study included 50 patients with severe obesity who underwent wedge liver biopsy and metabolic bariatric surgery at Taipei Medical University Hospital between September 2016 and December 2020. Significant liver fibrosis was defined as a fibrosis score of ≥ 2. Pre-surgery liver samples and both pre- and post-surgery serum samples were collected and prepared for mass spectrometric analysis. Statistical methods, including fold change analysis and one-way ANOVA with post-hoc tests were performed to identify lipid differences between groups. Additionally, machine learning algorithms, including Random Forest, logistic regression, support vector machine, AdaBoost, and XGBoost, were employed to predict significant liver fibrosis, with 70% of the entire dataset used for training and 30% for testing. **Results:** Patients with normal liver histology (n = 10), MASH without or with mild fibrosis (n = 19), and MASH with significant fibrosis (n = 21) were included. Lipidomic analysis identified the relative abundance of diradylglycerolipid 34:1 and triradylglycerolipid 52:3 as promising biomarkers for assessing liver fibrosis. Machine learning algorithms consistently demonstrated robust prediction of significant liver fibrosis (AUROC: 0.967–0.989) across different models and further identified phosphatidylinositol 36:2 as a key feature of importance. **Conclusion:** Lipidomic analysis using statistical methods and machine learning models is a promising and robust approach for predicting significant liver fibrosis. These findings provide insights into underlying mechanisms, therapeutic targets, and predictive biomarkers, and may be incorporated into current clinical tools for predicting significant liver fibrosis in patients with severe obesity and MAFLD.

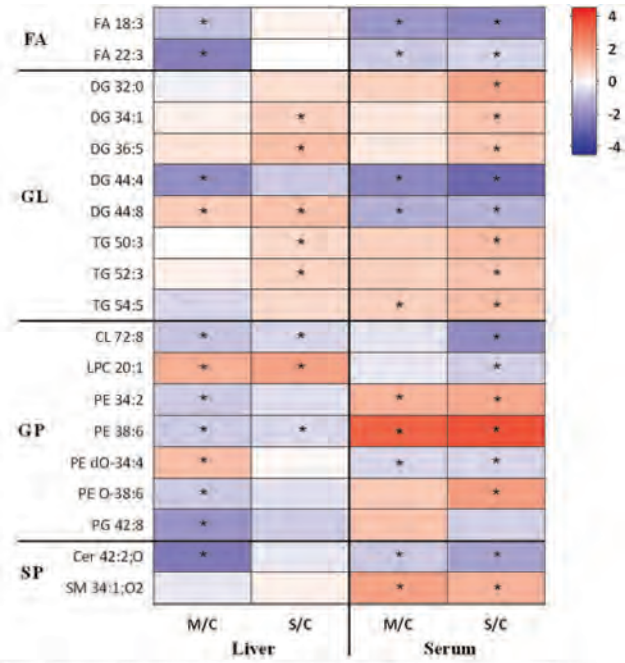

Figure. Statistical analysis of lipid species overlapping between liver and serum samples. Statistical analysis between groups was performed with fold change analysis and ANOVA with post-hoc tests. C, normal liver histology; M, MASH with no or mild fibrosis; S, MASH with significant fibrosis.

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2092 | CLINICAL OBESITY IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IS ASSOCIATED WITH ADVANCED FIBROSIS AND SEVERE STEATOSIS: VALIDATING CLINICAL OBESITY DEFINITION IN A MASLD COHORT

Karen Cheuk Ying Ho[1] Rex Wan-Hin Hui[1] Trevor Kwan-Hung Wu[1] Chi Ho Lee[1] David Tak-Wai Lui[1] Wai-Kay Seto[2] Man-Fung Yuen[2] Lung Yi Mak[2], [1]Department of Medicine, Queen Mary Hospital, The University of Hong Kong, [2]State Key Laboratory of Liver Research, The University of Hong Kong

Background: The Lancet Diabetes & Endocrinology Commission has proposed a new definition of clinical obesity due to inadequacy of current body mass index (BMI)-based measurements[1]. This study aims to apply clinical obesity criteria in a cohort of Asian patients with metabolic dysfunction associated steatotic liver disease (MASLD) to evaluate its associations with liver-specific parameters. **Methods:** We enrolled 642 patients with MASLD and valid vibration-controlled transient elastography (VCTE). A subgroup of 254 patients underwent additional bioelectrical impedance analysis (BIA). The diagnosis of clinical obesity required fulfillment of both anthropometric (waist circumference $\geq$90 cm in Asian male or $\geq$80 cm in Asian female, in addition to BMI $\geq$25 kg/m2) and clinical criteria (at least one signs or symptoms of ongoing dysfunction of organ system due to obesity, excluding liver disease). Univariate and multivariate analysis were applied to calculate p-value, odds ratio (OR) and 95% confidence intervals (95%CI). Severe steatosis and advanced fibrosis/cirrhosis (F3/F4) were defined by VCTE parameters, at-risk metabolic dysfunction-associated steaotohepatitis (MASH) was defined by FAST score[2] and major adverse cardiovascular events (MACE) were defined by acute myocardial infarction, cardiac revascularization procedure and stroke. **Results:** Among 642 MASLD patients (mean age 55.76+/-12.47 years; 49.20% male, mean BMI 28.24+/-4.66 kg/m^2, 76.0 % severe steatosis, 12.46% F3/F4), 46.11% of patients fulfilled the diagnosis of clinical obesity. Compared to BMI-based criteria, clinical obesity criteria identified more patients with F3/F4 (8.11% vs 20.61%, $p<0.001$), severe steatosis (67.57% vs 83.79%, $p<0.001$), at-risk MASH (0% vs 3.38%, $p=0.056$) and MACE (2.70% vs 11.15%, $p=0.006$). Clinical obesity was an independent predictor of F3/F4 (OR 4.07, 95%CI 2.20-7.56) and severe steatosis (OR 2.44, 95%CI 1.64-3.64). Other independent predictors of F3/F4 included aspartate transaminase level (OR 1.04, 95%CI 1.02-1.05), platelet count (OR 0.98, 95%CI 0.98-0.99), and diabetes mellitus (OR 2.70, 95%CI 1.53-4.74). Male gender (OR 3.35, 95%CI 1.77-6.35), age (OR 1.10, 95%CI 1.06-1.13) and hypertriglyceridemia (OR 3.65, 95%CI 1.58-8.40) were independent predictors of MACE. BIA revealed a lower appendicular skeletal muscle mass percentage (27.04% vs 41.09%, $P<0.001$) and a greater visceral fat index (15.0 vs 9.0, $p<0.001$) in patients fulfilling clinical obesity criteria versus BMI-based criteria.
Conclusion: Clinical obesity criteria effectively identify MASLD patients with advanced fibrosis, severe steatosis, at-risk MASH and MACE.
Disclosures: Karen Cheuk Ying Ho: Nothing to Disclose, Rex Wan-Hin Hui: Nothing to Disclose, Trevor Kwan-Hung Wu: Nothing to Disclose, Chi Ho Lee: Nothing to Disclose, David Tak-Wai Lui: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose, Man-Fung Yuen: Nothing to Disclose, Lung Yi Mak: Nothing to Disclose

2093 | THE UTILITY OF ROUTINELY COLLECTED NON-INVASIVE TESTS TO ASSESS MORTALITY RISK IN A LARGE REAL-WORLD COHORT OF PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS FROM THE UNITED STATES

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Background: Fibrosis Score 4 (FIB-4) is a well-established liver fibrosis risk assessment tool. Higher scores indicate more severe disease and are associated with increased mortality. Nevertheless, it is uncertain whether other biomarkers that are routinely collected, such as aspartate transaminase (AST), alanine transaminase (ALT), the AST/ALT ratio, platelet count, estimated glomerular filtration rate (eGFR), and glycated hemoglobin (HbA1c), can serve as prognostic indicators. This study aimed to establish predictors of prognosis as it is crucial for identifying high risk patients and facilitating healthcare providers to appropriately

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focus on early interventions. **Methods:** This was a retrospective cohort study using Optum Market Clarity data (2016-2021). MASH was identified by ICD10-CM code K75.81, with AST, ALT, and platelets tests within 3 months of diagnosis, excluding prior liver diseases. At MASH diagnosis, patients were classified by presence of cirrhosis based on ICD-10 codes and FIB-4 score was calculated. Fine-Gray models were used to assess the association between non-invasive tests (NITs) and all-cause mortality, and were adjusted for age, sex, region, and ethnicity. **Results:** A total of 18,710 MASH patients were included in the study. In the overall MASH population, a FIB-4 score greater than 2.67, compared to a score of 2.67 or lower, was a strong predictor of mortality, associated with a seven-fold increase in risk (adjusted hazard ratio [aHR] = 7.06; 95% confidence interval [CI] = 6.37–7.83). Elevated AST levels (>40 U/L vs. ≤ 40 U/L; aHR = 1.38, 95% CI = 1.24–1.53) and lower platelet counts ($<150 \times 10^3/\mu L$ vs. $\geq 150 \times 10^3/\mu L$; aHR = 2.83, 95% CI = 2.54–3.14) were linked to increased mortality. Additionally, reduced kidney function (eGFR <60 mL/min/1.73 m² vs. ≥ 60 mL/min/1.73 m²) was associated with a more than two-fold heightened risk of mortality. **Conclusion:** It is important to measure FIB-4, its components (AST or platelets) and eGFR in routine practice, as they showed potential as prognostic biomarkers for overall mortality. The eGFR association with mortality indicated that assessing kidney disease severity in MASH is also important. However, more research is needed to understand whether these biomarkers confirm their prognostic value in different populations and different countries. The findings from this study can inform future MASH clinical guidelines regarding risk stratification and clinical assessment.

Disclosures: Jörn Schattenberg: Apollo Endoscopy, Boehringer Ingelheim, Gilead Sciences: Consultant, Intercept Pharmaceuticals: Consultant, Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals: Consultant, MSD, Northsea Therapeutics, Novartis, Novo Nordisk: Consultant, Pfizer, Roche, Sanofi, and Siemens Healthineers: Consultant, Boehringer Ingelheim, Siemens Healthcare GmbH: Grant/Research Support, Alentis, Alexion, Altimmune, Astra Zeneca, 89Bio,Bionorica,: Consultant, Boehringer Ingelheim, Gilead Sciences, GSK, Ipsen, Inventiva: Consultant, Madrigal Pharmaceuticals, Lilly, MSD, Northsea Therapeutics,: Consultant, Novo Nordisk, Pfizer, Roche, Sanofi, and Siemens Healthineer: Consultant, AbbVie, Academic Medical Education (AME),: Speaking and Teaching, Boehringer Ingelheim, Echosens: Speaking and Teaching, Forum für Medizinische Fortbildung (FOMF), Gilead Sciences: Speaking and Teaching, MedicalTribune, MedPublico GmbH, MedScape,: Speaking and Teaching, Novo Nordisk, Madrigal Pharmaceuticals,: Speaking and Teaching, Akero, Alentis, Alexion, Altimmune, Astra Zeneca, 89Bio: Consultant, Bionorica, Boehringer Ingelheim, Gilead Sciences, GSK,: Consultant, HistoIndex, Ipsen, Inventiva Pharma, Madrigal Pharmaceutical: Consultant, Kríya Therapeutics, Lilly, MSD Sharp & Dohme GmbH: Consultant, Northsea Therapeutics, Novartis, Novo Nordisk: Consultant, Pfizer, Roche, Sanofi, Siemens Healthineers,: Consultant, Summit Clinical, and Vantage Biosciences Research: Consultant, AbbVie, Boehringer Ingelheim, Gilead Sciences,: Speaking and Teaching, Ipsen Novo Nordisk,: Speaking and Teaching, Madrigal Pharmaceuticals, Worldwide Clinical Trials: Speaking and Teaching, Hepta Bio.: Stock – privately held company, Akero: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Ipsen: Consultant, Inventiva Pharma: Consultant, Madrigal: Consultant, Northsea Therapeutics: Consultant, Novo Nordisk: Consultant, Roche: Consultant, Siemens Healthineers: Consultant, Boehringer Ingelheim: Grant/Research Support, AGED diagnostics: Stock – privately held company, Hepta Bio: Stock – privately held company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock – privately held company, MedPublico GmbH: Speaking and Teaching, Zuleika Aponte-Torres: Boehringer Ingelheim: Employee, Ronald Herrera: Nothing to Disclose, Mireia Raluy: Nothing to Disclose, Mark Yates: Nothing to Disclose, Ramy Younes: Nothing to Disclose, Claudio Sartini: Nothing to Disclose

2094 | CENTRAL OBESITY INDICES PROVIDE BETTER PROGNOSTIC VALUE WHILE ENSURING ROBUST MASLD DIAGNOSIS

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Background: Obesity is a significant risk factor for nonalcoholic fatty liver disease (NAFLD). While BMI remains part of the diagnostic criteria for metabolic dysfunction-associated steatotic liver disease (MASLD), its limitations in predicting prognosis and risk stratification have been noted. Central obesity indices may offer superior predictive value, prompting evaluation as potential replacements for BMI. **Methods:** We analyzed 12,156 adults from NHANES III, including 2,387 MASLD cases. Density plots assessed the variability of central obesity indices across BMI levels. Residuals from regression of central obesity indices on BMI were used as predictors in proportional hazards models, and Bayesian survival analysis compared model performance. Consistency between original and central obesity-based MASLD diagnostic criteria was also evaluated. **Results:** BMI was strongly correlated with WC ($r = 0.86$) and WHtR ($r = 0.89$), but weakly with CI, and showed

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negligible correlation with WHR. Despite these differing degrees of correlation, central obesity indices displayed considerable variability within specific BMI ranges, necessitating broad intervals to capture 95% of all observed values. Among 1,180 deaths, residual WC (HR: 1.41, $P = 0.001$), WHR (HR: 1.15, $P = 0.001$), WHtR (HR: 1.45, $P < 0.001$), and CI (HR: 1.22, $P < 0.001$) remained significant predictors even after adjusting for BMI (HR: 1.20, $P = 0.01$). Bayesian analysis confirmed that models incorporating central obesity indices outperformed those using BMI (Bayes factor for WHR = 2,392.5; for CI = 6,703.4). High consistency between original and central obesity-based criteria was observed (Cohen's Kappa $\geq$ 0.9). **Conclusion:** Central obesity indices demonstrate superior prognostic value over BMI in MASLD and support their use as diagnostic replacements, given high consistency with original criteria.

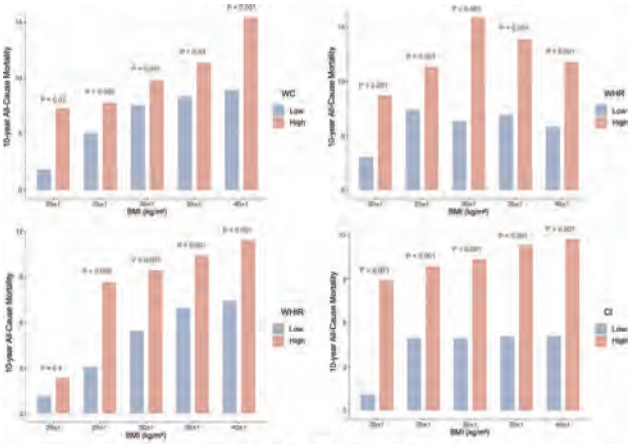

Figure 2. Ten-year risk of all-cause mortality for high vs. low levels of WC, WHR, WHtR, and CI Across Different BMI levels. This figure illustrates the 10-year Kaplan–Meier estimates of all-cause mortality for individuals with high (right bar, ≥1 SD above the mean) and low (left bar, ≤1 SD below the mean) levels of waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), and conicity index (CI) at varying BMI ranges (20, 25, 30, 35, and 40 kg/m² ±1).

Disclosures: Tianyuan Yang: Nothing to Disclose, Tong Bu: Nothing to Disclose, Qi Wang: Nothing to Disclose

2095 | LIFE'S ESSENTIAL 8 SCORE AS A PREDICTOR OF CARDIOVASCULAR MORTALITY IN MASLD PATIENTS: A NHANES-BASED COHORT STUDY

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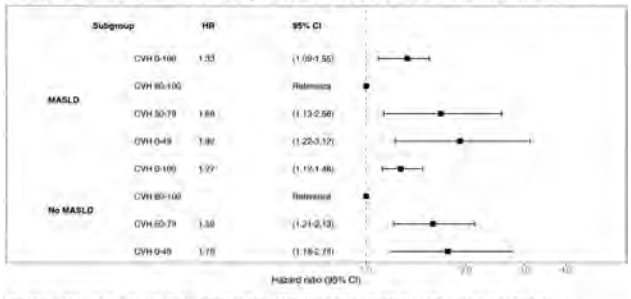
Background: The Life's Essential 8 (LE8) cardiovascular health score is a tool used to assess individual health behaviors and has been widely applied in the risk evaluation of various diseases. In patients with metabolic dysfunction–associated steatotic liver disease (MASLD), adverse cardiovascular outcomes are common complications. Although the LE8 score has been shown to be significantly associated with all-cause mortality among individuals with MASLD, its relationship with cardiovascular mortality risk in this population remains unclear and warrants further investigation. **Methods:** This study is a population-based prospective cohort study that analyzed data from individuals aged 20 to 79 years participating in the National Health and Nutrition Examination Survey (NHANES) and NHANES III from 2005 to 2018, with mortality follow-up data available through 2019. The Fine-Gray competing risk model was employed to evaluate the risk of adverse cardiovascular outcomes and to examine the association between LE8 cardiovascular health score and cardiovascular mortality among patients with MASLD. **Results:** A total of 21,726 participants were included in this study, of whom 6,582 (30.3%) were diagnosed with MASLD. The median follow-up duration was 15.6 years. The overall LE8 cardiovascular health score was significantly associated with cardiovascular mortality risk among MASLD patients (HR = 1.33, 95% CI: 1.09–1.55). Compared with individuals with ideal LE8 scores, those with intermediate and poor scores had a higher risk of adverse cardiovascular outcomes (intermediate: HR = 1.68, 95% CI: 1.13–2.56; poor: HR = 1.92, 95% CI: 1.22–3.12). Similar associations were observed among MASLD patients with liver fibrosis. **Conclusion:** The LE8 cardiovascular health score serves as a significant predictor of cardiovascular mortality risk among patients with MASLD. Incorporating the LE8 score into clinical risk assessment may enhance the identification of individuals at elevated risk for adverse cardiovascular outcomes. These findings highlight the importance of targeted interventions and effective management of health behaviors in MASLD patients to improve cardiovascular prognosis.

Table. Hazard Ratios for Cardiovascular Mortality Risk in MASLD Patients Based on LE8 Health Behavior Score



The table presents the hazard ratios (HR) and 95% confidence intervals (CI) for cardiovascular mortality risk in individuals with MASLD, based on LE8 health behavior scores. The analysis was adjusted for potential confounding factors, including age, sex, education level, hypertension, diabetes, and hyperlipidemia.

Disclosures: Tianyuan Yang: Nothing to Disclose, Tong Bu: Nothing to Disclose, Qi Wang: Nothing to Disclose

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2096 | DIVERGENT IMMUNE-INFLAMMATORY SIGNATURES IN STEATOTIC LIVER DISEASE PHENOTYPES WITH A UNIFIED LAB-BASED FIBROSIS PREDICTION TOOL

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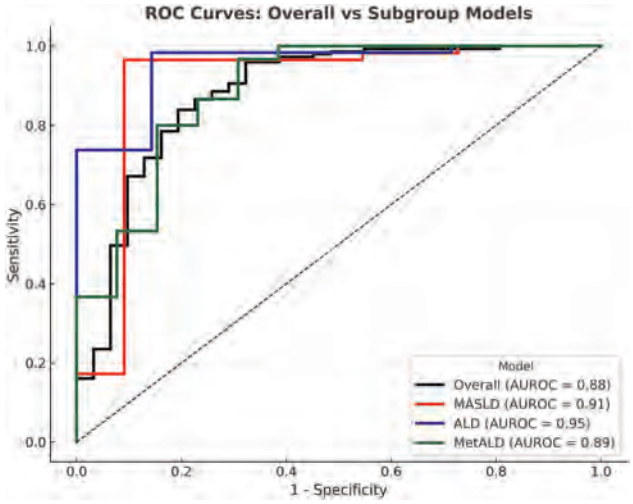
Background: Liver fibrosis is a major prognostic factor in chronic steatotic liver diseases, including Metabolic dysfunction-associated steatotic liver disease (MASLD), MetALD (metabolic and alcohol-associated liver disease), and Alcohol-related liver disease (ALD). As systemic inflammation is increasingly recognized as a central driver of fibrosis and adverse liver-related outcomes, understanding the differences in inflammatory signatures between these steatotic liver disease phenotypes is critical. This study aims to (1) compare systemic inflammation and fibrosis across phenotypes, (2) evaluate correlations between immune-inflammatory markers and fibrosis severity, and (3) develop a lab-based composite score to predict advanced fibrosis. **Methods:** A total of 180 patients were categorized into MASLD (n = 69), MetALD (n = 43), and ALD (n = 68) based on metabolic and alcohol criteria. Liver stiffness (FibroScan), FIB-4, APRI, MELD, CTP scores, and systemic immune inflammatory markers like Neutrophil Lymphocyte Ratio (NLR) and Lymphocyte Monocyte ratio (LMR), Systemic Immune-Inflammation Index (SII), Platelet–Lymphocyte Ratio (PLR) were assessed. Correlation and multivariate logistic regression analyses were performed to build a predictive score for advanced fibrosis ($\geq$F3). **Results:** ALD patients had the highest neutrophilic burden (mean NLR 6.56 $\pm$ 1.61), followed by MetALD (5.16 $\pm$ 1.36) and MASLD (4.30 $\pm$ 1.60) ($p < 0.001$). MASLD exhibited a lymphocyte-predominant profile (mean LMR 4.86 $\pm$ 1.17), as compared to MetALD (3.46 $\pm$ 0.74)and ALD (3.31 $\pm$ 0.98) ($p < 0.001$). Fibrosis burden followed a similar gradient: highest in ALD, intermediate in MetALD, lowest in MASLD. NLR (spearman coefficient, $\rho = 0.44$) and LMR ($\rho = -0.33$) significantly correlated with fibrosis severity. The derived composite score using inflammatory markers predicted advanced fibrosis with high accuracy (AUC = 0.90) with a excellent positive predictive value of 95.4%. The high positive predictive value (PPV) observed in our model indicates a strong capacity to accurately identify patients with advanced fibrosis ($\geq$F3) among those classified as positive by the algorithm. **Conclusion:** Despite overlapping clinical features, MASLD, MetALD, and ALD exhibit distinct inflammatory profiles. Systemic immune-inflammatory markers, especially NLR, are closely associated with fibrosis severity. The developed composite score, derived entirely from routine labs, offers a scalable, cost-effective tool for detecting advanced fibrosis across phenotypes in real-world settings.



Disclosures: Akshay Verma: Nothing to Disclose

2097 | C7 AS A PREDICTOR OF FIBROSIS AND LIVER-RELATED EVENTS IN MASLD

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Background: In metabolic dysfunction-associated steatotic liver disease (MASLD), advanced fibrosis and liver-related events (LRE) are major prognostic factors. However, current non-invasive biomarkers lack sufficient accuracy in predicting fibrosis and LRE risk. This study aimed to identify novel biomarkers for fibrosis severity and LRE prediction. **Methods:** Transcriptomic, proteomic, and spatial transcriptomic analyses were integrated to identify candidate biomarkers. Two independent MASLD cohorts were examined: a biopsy-proven cohort and a VCTE-based validation cohort. Kaplan–Meier analysis and Cox proportional hazards models were used to assess LRE risk. Single-nucleus RNA sequencing (snRNA-seq), in situ hybridization (ISH), and cell experiments were conducted to validate molecular relevance. **Results:** Complement component 7 (C7) emerged as a top candidate from hepatic transcriptomics and plasma proteomics. Spatial transcriptomics and ISH localized hepatic C7 expression mainly to hepatic stellate cells (HSCs) in fibrotic areas. Serum C7 levels correlated with liver stiffness and fibrosis stage, and levels $\geq$140 μg/mL were associated with significantly higher LRE risk ($p < 0.0001$), validated in a VCTE cohort. Multivariate analysis confirmed serum C7 as an independent predictor of LRE (HR 4.54, 95% CI 1.49–13.82, $p = 0.008$). Notably, C7 outperformed FIB-4,

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autotaxin, APRI, and AAR in ROC analysis (AUROC: 0.90 vs. 0.85, 0.84, 0.77, 0.67, respectively). C7 knockdown in LX-2 cells suppressed extracellular matrix genes such as LAMA2, LAMB1, and COL6A3. **Conclusion:** C7 is a robust biomarker for assessing fibrosis severity and predicting LRE in MASLD, outperforming conventional markers and offering potential for clinical application.
Disclosures: Shohei Kondo: Nothing to Disclose, Takefumi Kimura: Nothing to Disclose, Naoki Tanaka: Nothing to Disclose

2098 | ASSOCIATION OF CIRCULATING Z-POLYMER WITH HEPATIC FIBROSIS IN ADULTS AT-RISK FOR MASLD AND THE ALPHA-1 ANTITRYPSIN PI*MZ VARIANT

Monika Sigg[1] Catherine Chang[1] Kevin Larimore[1] Jack Brownrigg[1] Rohit Loomba[2], [1]BioMarin, [2]University of California, San Diego

Background: Mutations in the *SERPINA1* gene, which encodes alpha-1 antitrypsin (AAT), lead to the accumulation of polymers in hepatocytes, triggering cellular injury that leads to liver fibrosis. The E342K mutation (Pi*Z) produces a mutant AAT protein (Z-AAT) that is especially prone to polymerization. In individuals with MASH, the Pi*MZ genotype increases risk of liver disease progression. Gaining insights into the relationship between circulating AAT polymer levels and liver disease severity in individuals with MASLD and the Pi*MZ genotype could inform prognosis, enrich trial populations and allow monitoring of treatment response for this understudied patient population. **Methods:** To identify Pi*MZ individuals with or at-risk of MASLD, we screened 792 people with preexisting MASLD, cirrhosis, or diabetes and their relatives for the Pi*MZ proteotype using an AAT isoelectric focusing assay. We identified 15 individuals with the Pi*MZ proteotype. We measured both total and polymeric AAT plasma levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) in these individuals as well as 10 age-, sex-, and BMI-matched Pi*MM individuals. We then carried out a correlation analysis between plasma polymer concentration and non-invasive measures of fibrosis, steatosis, and for a subset of 8 individuals with available data, histological fibrosis and MASLD assessment (METAVIR and NAS, respectively). **Results:** As expected, plasma AAT polymers were not detected in most Pi*MM individuals, while all Pi*MZ individuals had measurable levels. Plasma AAT polymer correlated positively with multiple non-invasive measures of liver fibrosis: magnetic resonance elastography ($r = 0.75$, $p = 0.005$), vibration controlled transient elastography ($r = 0.54$, $p = 0.072$) and Fibrosis-4 ($r = 0.67$, $p = 0.006$). METAVIR fibrosis scores also showed a positive correlation with AAT polymer levels ($r = 0.52$, $p = 0.191$). Plasma AAT polymer did not correlate significantly with non-invasive measures of steatosis or NAS. Total AAT levels were lower in Pi*MZ individuals than Pi*MM and did not correlate significantly with fibrosis measures. **Conclusion:** The correlation between plasma AAT polymers and liver fibrosis in Pi*MZ individuals with or at-risk of MASLD suggests that polymeric AAT may be a key driver of hepatic fibrogenesis in this patient population. More studies with larger sample sizes and clinical outcome data are needed to better understand the relationship between MASLD and the Pi*MZ genotype.
Disclosures: Monika Sigg: Nothing to Disclose, Catherine Chang: Nothing to Disclose, Kevin Larimore: BioMarin Pharmaceutical Inc.: Employee, Jack Brownrigg: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder

2099 | DEVELOPMENT OF NONINVASIVE MRI TECHNOLOGIES FOR ASSESSMENT ON NHP MODELS OF OBESITY AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Lichuan Yang[1] Yuchao Zhao[1] Zhenghua Zhu[1] Dawei Wang[1] Shaohui Ji[1] Joseph Gabriel[1] Rosario Perez[1], [1]Kunming Biomed International

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Background: Liver biopsy, a current necessity for diagnosing metabolic dysfunction-associated steatohepatitis (MASH) and evaluating drug efficacy, is invasive and poses risks to patients. Thus, the development of non-invasive methods for assessing MASH lesions is a crucial research direction. **Methods:** MASH was induced in a group of diet-induced obese (DIO) male cynomolgus monkeys fed with a high-fat diet (40% fat, 0.5% cholesterol) to BMI > 35 kg/m² and fat mass > 25%. Hepatic MASH lesions in liver biopsy specimens were evaluated using a histopathological scoring system from the NIH MASH clinical network. A 3.0T SIEMENS MAGNETOM Prisma was employed for MRI imaging. Subcutaneous and visceral fat volumes were measured with a protocol that included structural localization and a Six-echo VIBE-Dixon gradient echo sequence. Liver proton density fat fraction (PDFF) images were obtained via the mge-6 echoes protocol and analyzed by VivoQuant 3.0 software. Liver extracellular volume (ECV) was determined by acquiring native and post-contrast (Magnevist) T1 mapping images with MOLLI/WIP780 sequences and calculated using T1 mapping parameters from selected liver regions of interest. Virtual MR elastography (vMRE) was performed using a fat-suppressed spin-echo echo-planar sequence and analyzed with ITK-SNAP software and custom MATLAB software. **Results:** 10 lean healthy and 34 obese monkeys were evaluated on their subcutaneous volumes (476.8 ± 52.8 vs. 1585.3 ± 623.6 cm^3) and visceral fat volumes (719.3 ± 181.4 vs. 1522.7 ± 482.4 cm^3). The obese monkeys treated with weight loss compound showed significant visceral fat reduction by over 30%. PDFF was elevated significantly elevated in DIO monkeys in contrast to lean healthy monkeys ($9.5 \pm 4.8\%$ vs. $4.3 \pm 0.5\%$) and a FGF-21 analogy reduced the elevated PDFF in DIO monkeys by 45%. The elevated PDFF is positively correlated with liver triglycerides analyzed by biochemical approach, and also positively correlated with the steatosis scoring by pathological approach. The calculated hepatic ECV was greatly increased in MASH/fibrosis monkeys compared to healthy animals and positively correlated with the fibrosis scores of liver biopsy specimen by pathology (F0 of $24.8 \pm 3.6\%$, F1 of $26.5 \pm 2.4\%$, F2 of $28.9 \pm 2.0\%$ and F3 of $35.2 \pm 5.2\%$). The vMRE reflects liver stiffness (kPa) which may implicate fibrosis in the liver of MASH monkeys. Significant elevation of kPa was observed in MASH monkeys ($n = 33$, 6.8 ± 3.3 kPa) in comparison to lean healthy monkeys ($n = 10$, 3.1 ± 0.5 kPa). MASH monkeys treated with a siRNA compound responded ~29% reduction in kPa at 12 week post the dosing. **Conclusion:** Noninvasive MRI procedures for have been validated in NHP models of obesity and MASH/fibrosis. The utilization of these translatable technologies in preclinical studies with NHP models should accelerate drug development targeting the obesity and MASH diseases.

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2101 | VALIDATING THE PERFORMANCE OF INSULIN RESISTANCE INDICES AND VISCERAL ADIPOSITY INDICES IN PREDICTING METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME AND CONSTRUCTING A NEW PREDICTIVE MODEL

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Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) and polycystic ovary syndrome (PCOS) have shared risk factors, but the risk of MAFLD is ignored in PCOS patients. The performance of clinical indices in predicting PCOS concurrent with MAFLD has not been fully validated. An accurate and efficient predictive model is needed for MAFLD screening in PCOS patients. **Methods:** A total of 357 PCOS patients who underwent abdominal ultrasonography were retrospectively enrolled from 2015 to 2024 at the Reproductive Medical Center of Peking University People's Hospital. The performance of eight insulin resistance indices (IRIs) (HOMA-IR, QUICKI, Bennet ISI, G/I ratio, TyG, TyG-BMI, METS-IR, and CHG) and eight visceral adiposity indices (VAIs)(Obesity level, ALT/TG ratio, TG/HDL ratio, HSI, LFS, FSI, ZJU, and MAFLD-S) in predicting concurrent MAFLD were validated. The least absolute shrinkage and selection operator (LASSO) regression was performed to select variables for model construction, which were included in a multivariate logistic regression model. The area under the receiver operating characteristic curve (AUC), Delong test, calibration curve and decision curve analysis (DCA) were applied to validate and compare the predictive efficacy of different indices and models. **Results:** In this cohort, 129 (36.1%) PCOS patients were concurrent with MAFLD. Among the sixteen clinical indices validated, VAIs demonstrated better performance in predicting MAFLD than IRIs in general. FSI (AUC 0.8293, sensitivity 0.860), ZJU (AUC 0.8244, sensitivity 0.880), TyG-BMI (AUC 0.8163, sensitivity 0.899), LFS (AUC 0.8079, sensitivity 0.791) and MAFLD-S (AUC 0.8054, sensitivity 0.814) were the five clinical indices with the highest AUC, but only showed moderate discrimination and sensitivity. Six clinical

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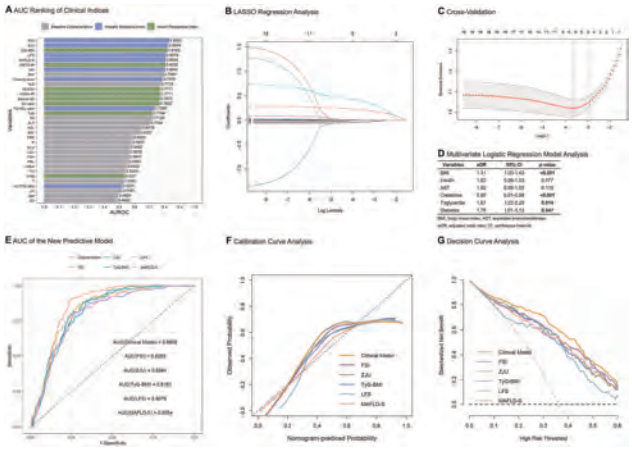
characteristics, including body mass index (BMI), insulin, aspartate transaminase (AST), creatinine, triglyceride and diabetes, were used to construct a new predictive model (AUC 0.8606, sensitivity 0.899). This predictive model showed a better discrimination than the AUC-top-five clinical indices (Delong $p < 0.05$) but had a similar calibration with these indices. In DCA, this new model also had a higher clinical usefulness and benefit in predicting PCOS concurrent with MAFLD than existing clinical indices. **Conclusion:** This new model has a better performance in predicting PCOS concurrent with MAFLD than existing IRIs and VAIs and can be helpful in MAFLD screening in PCOS patients.

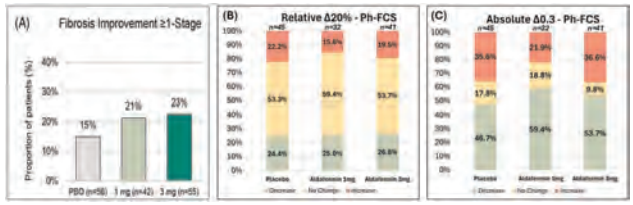


Disclosures: Zixiang Huang: Nothing to Disclose, Fang Fang: Nothing to Disclose, Nan Wu: Nothing to Disclose

2102 | DIGITAL PATHOLOGY IDENTIFIES INTRA-STAGE RESPONDERS IN THE ALPINE4 CIRRHOSIS STUDY

Lei Ling[1] Louis Petitjean[2] Mathieu Petitjean[2] Mary Rinella[3], [1]NGM Biopharmaceuticals, Inc, [2]PHARMANEST INC, [3]The University of Chicago

Background: The ALPINE 4 Phase 2b study evaluated aldafermin, an FGF19 analog, in 160 patients with MASH and compensated cirrhosis over 48 weeks. The primary endpoint (ELF reduction) was achieved at 3 mg. Fibrosis improvement ($\geq$1-NASH-CRN stage) was reported in 23% (3 mg), 21% (1 mg), and 15% (placebo), p = NS. We retrospectively reanalyzed the biopsies using a continuous digital pathology biomarker for fibrosis severity. **Methods:** Paired biopsies from placebo (n = 45), 1 mg (n = 32), and 3 mg (n = 41) groups were scanned at 40X and analyzed uploaded for analysis to FibroNest, a robust, high-resolution phenotypic digital pathology method generating a continuous fibrosis severity score (Ph-FCS) based on ~100 features quantiifying collagen deposition, fiber morphometry, and fibrosis architectural distortion (doi.org/10.1111/liv.15768). A $\geq$20% relative Ph-FCS change reflects a full NASH-CRN stage shift, and $\geq$0.3 absolute change indicates intra-stage improvement (doi:10.1097/HEP.0000000000000980). Additional metrics included Parenchymal Tissue Area %, Scar Tissue Area %, and faint and fine fiber count/mm² in the nodular parenchymal tissue. **Results:** Responder analysis using a 20% relative Ph-FCS reduction showed no significant differences (Pbo: 24.4%, 1 mg: 25.0%, 3 mg: 26.8%). When applying a 0.3 absolute Ph-FCS threshold, "no change" responder rates dropped (Pbo: 17.8%, 1 mg: 18.8%, 3 mg: 9.8%). Placebo-corrected response rates using $\geq$1-NASH-CRN stage reduction, 20% relative, or 0.3 absolute Ph-FCS reduction also showed no statistical significance: 1 mg (6%, 0.6%, 12.7%) and 3 mg (8%, 2.4%, 7%). Mean Ph-FCS changes from baseline also did not reach significance. For 20% relative change: Pbo: -0.033 ($\pm$0.283), 1 mg: -0.110 ($\pm$0.206), 3 mg: -0.080 ($\pm$0.366); p = NS. For 0.3 absolute change: Pbo: -0.131 ($\pm$1.306), 1 mg: -0.515 ($\pm$1.096), 3 mg: -0.313 ($\pm$1.725); p = NS. No significant changes were detected in tissue- or nodule-based markers. **Conclusion:** Continuous digital pathology biomarkers did not confirm a significant antifibrotic effect of aldafermin in patients with compensated cirrhosis. Across multiple analysis thresholds—including both relative and absolute Ph-FCS changes—and additional parenchymal-tissue based biomarkers, no dose group demonstrated a statistically meaningful improvement compared to placebo. These results underscore the value of continuous digital quantification in complementing traditional histological endpoints for the assessment of therapeutic impact.



Disclosures: Lei Ling: Nothing to Disclose, Louis Petitjean: Nothing to Disclose, Mathieu Petitjean: PHARMANEST INC: Employee, PHARMANEST INC: Stock – privately held company, Mary Rinella: akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant,

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2103 | ANALYSIS OF FACTORS ASSOCIATED WITH LIVER FIBROSIS IN TYPE 2 DIABETES PATIENTS AND THE PREDICTIVE VALUE OF CHI3L1 FOR LIVER FIBROSIS

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Background: The prevalence of Metabolic dysfunction–associated steatotic liver disease (MASLD) is significantly increased in patients with Type 2 diabetes mellitus (T2DM), elevating the risk of cirrhosis and hepatocellular carcinoma. Therefore, early diagnostic assessment of liver fibrosis in T2DM patients is critically important. Our study investigated the factors associated with liver fibrosis in T2DM patients with comorbid MASLD and evaluated the predictive value of chitinase-3-like protein 1 (CHI3L1) for liver fibrosis in these patients. **Methods:** This is a retrospective study that enrolled T2DM patients who received care at Tianjin Third Central Hospital between January 2023 and August 2024. Liver fibrosis was assessed in both the total T2DM population and in T2DM patients with comorbid MASLD using liver stiffness measurement (LSM) and non-invasive assessment indicators including APRI, FIB-4, and CHI3L1. The LSM value $\geq$ 8kPa was established as the threshold for significant liver fibrosis (SLF). Correlation analysis was applied to evaluate the relationships between LSM, CHI3L1, and other indicators. Logistic regression analyses were conducted to identify risk factors associated with liver fibrosis, and receiver operating characteristic (ROC) curve analysis was used to assess the predictive value of CHI3L1. **Results:** This study included 236 patients with T2DM, of whom 176 had comorbid MASLD (74.6%) and 89 had significant liver fibrosis (37.7%). Among T2DM-MASLD patients, 74 had significant liver fibrosis, with a prevalence rate of 42%.In the T2DM-MASLD population, patients with significant liver fibrosis demonstrated significantly higher levels of BMI, TSH, AST, GGT, LDH, CHI3L1, APRI, LSM, and CAP compared to the non-significant fibrosis subgroup, with all differences being statistically significant ($P < 0.05$). Conversely, the significant fibrosis subgroup exhibited significantly lower levels of PLT, LDL-C, and PWR compared to the non-significant fibrosis subgroup ($P < 0.05$).CHI3L1 showed positive correlation with LSM ($r = 0.48$, $P < 0.001$). Multivariate logistic regression analysis identified CHI3L1, APRI, and CAP as potential independent risk factors for significant liver fibrosis in T2DM-MASLD patients. The area under the ROC curve (AUC) for CHI3L1 in predicting significant liver fibrosis was 0.717 (95% CI: 0.638-0.796, $P < 0.05$), with an optimal cutoff value of 96.6 ng/mL. **Conclusion:** The prevalence of MASLD among T2DM patients was 74.6%, while the prevalence of significant liver fibrosis was 37.7%. T2DM patients with significant liver fibrosis exhibited higher levels of BMI, CHI3L1, AST, LDH, TSH, APRI, LSM, and CAP compared to those without significant liver fibrosis. Serum CHI3L1 demonstrated a significant correlation with liver fibrosis, suggesting that serum CHI3L1 may serve as a predictive indicator for liver fibrosis in T2DM patients.

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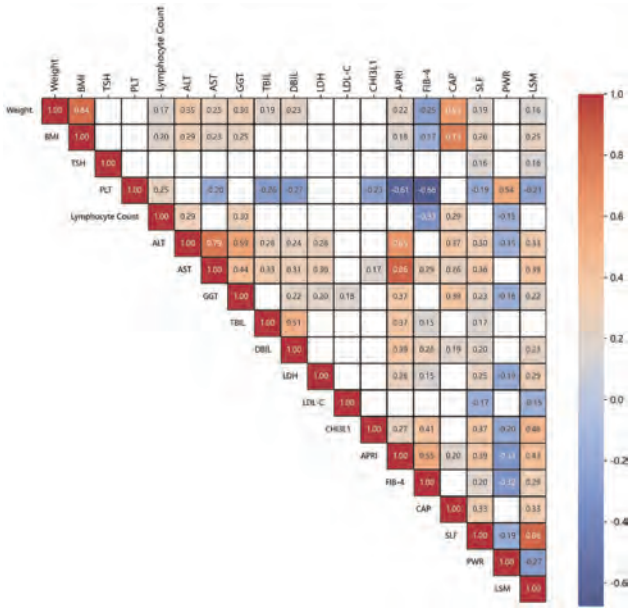

Disclosures: Lixia Sun: Nothing to Disclose, Shuangshuang Du: Nothing to Disclose, Aili Fan: Nothing to Disclose, Jiawen Feng: Nothing to Disclose, Fei Wang: Nothing to Disclose, Jia Lian: Nothing to Disclose, Qing Ye: Nothing to Disclose

2104 | EVALUATING THE IMPACT OF ELECTRONIC HEALTH RECORD (EHR) EMBEDDED METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) CARE PATHWAYS TO IMPROVE DETECTION OF ADVANCED FIBROSIS IN ADULTS WITH TYPE 2 DIABETES

Robert Schwartz[1] Sonal Kumar[2] Anna Mageras[3] Sujit Janardhan[4] Brendan McQuillen[4] Jihae Jeon[3] Jacob Debroff[3] Rama Hussein[3] Holly Jain[5] Mohanish Savanth[5] Kristi Cohn[5] Meena Bansal[6], [1]Weill Cornell Medical College, [2]Weill Cornell Medicine, [3]Icahn School of Medicine at Mount Sinai, [4]Rush University Medical Center, [5]MASHNET, [6]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) impacts ~38% of adults, including ~65% of patients with type 2 diabetes (T2D). Left undetected, it can progress to metabolic steatohepatitis (MASH), cirrhosis, hepatocellular carcinoma (HCC), or death. Guidelines recommend MASLD screening in high-risk populations, but clinical adoption is limited. Mount Sinai Health System (MSHS), Weill Cornell Medicine (WCM), and Rush University Medical Center (Rush) implemented EHR-embedded MASLD care pathways. **Methods:** MSHS, WCM and Rush developed unique approaches to embedding MASLD care pathways within their EHRs leveraging Passive (clinician activated) or Active (automatically activated) interventions and evaluated performance for ≥ 5 months using a common data framework. Passive approaches used by MSHS and WCM included implementation of an age-adjusted Fibrosis-4 (FIB-4) SmartPhrase, in which clinicians could type the phrase and subsequently receive a score, interpretation, and recommended next steps. Two active approaches were used by MSHS and Rush. MSHS leveraged a backend FIB-4 calculation, in which a FIB-4 was calculated for eligible patients, and high/indeterminate patients flagged for outreach. Rush built a series of silent best practice alerts (BPAs) using EPIC care paths, starting with an auto-calculated FIB-4 for patients with T2D. Both active and passive interventions were implemented in tandem with provider education in attending or teaching clinics. Statistical analyses were conducted at the site level and reported as population-level summary statistics. Primary endpoints were rate of FIB-4 calculation for eligible patients and rate of referral. Those eligible for screening included adults who were ≥ 18 years old, diagnosed with T2D, and had an encounter with a pilot provider. New screening eligibility was defined as individuals who had not been screened in the past 12-months. **Results:** 24,125 patients with T2D were seen over the pilot, and 13,631 (56.50%) were eligible for screening. 4,672 patients were newly screened, of which 774 (16.57%) were high-risk (> 2.67) and 1,945 (41.63%) were indeterminate risk (1.3-2.67 for < 65, 2.0-2.67 for 65+). Figure 1 represents the baseline and follow up screening rates of eligible patients at each institution by intervention type. **Conclusion:** Passive and active EHR-embedded interventions have utility in improving identification of patients at risk for advanced fibrosis, and trainees demonstrated greater receptivity to adopt new pathways.

Disclosures: Robert Schwartz: Miromatrix Inc: Advisor, Lime Therapeutics: Advisor, Otsuka Inc.: Grant/Research Support, Alnylam Pharmaceuticals: Speaking and Teaching, Alnylam Pharmaceuticals: Consultant, Sonal Kumar: Gilead Sciences: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Grant/Research Support, Gilead Sciences: Grant/Research Support, Madrigal

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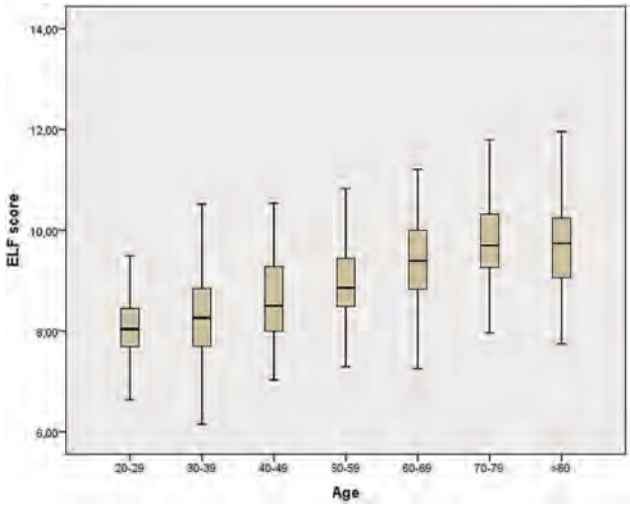
2105 | OPTIMIZING THE USE OF NON-INVASIVE TESTS FOR PATIENT SELECTION FOR MASLD PHARMACOTHERAPY

Vlad Ratziu[1] Antoine Pilon[2] Vittoria Zambon[3] Francisca Dora Copil[3] An Ngo Kim Tu[4] Raluca Pais[5] Leila Kara[3] Dominique Thabut Damais[6] Michel Vaubourdolle[7], *[1]Service D' Hepatogastroenterologie (FR), [2]Hopital St Antoine, [3]ICAN Institute for Cardiometabolism and Nutrition, [4]Hospital Pitié-Salpêtriere, Paris, France, [5]Pitié-Salpêtrière Hospital, [6]Hospital Pitié-Salpêtrière, Paris, [7]Hospital Saint Antoine*

Background: Selection of patients (pts) for MASLD pharmacotherapy relies on the diagnosis of stage 2&3 fibrosis based on non-invasive tests (NIT). However, concordance of NIT results and their optimal use (single or combined, algorithm, confounding factors) is unknown. **Methods:** Pts with chronic liver disease (CLD) including MASLD (steatosis on ultrasound or CAP > 280 dB/m and no other CLD) were assessed with NITs for liver fibrosis: liver stiffness (LSM) by vibration controlled transient elastography (VCTE), LSM by Shear wave elastography (SWE), ELF and FibroSure® (FS, LabCorp). Thresholds proposed to reflect stages 2 or 3 fibrosis for initiation of pharmacotherapy were used (PMID: 39038768). **Results:** 587 CLD pts (488 MASLD) were included: men 53% mean age 57.8 yrs (≥60yrs: 49.5%), BMI 29.6 kg/m² (sd 6.2), type 2 diabetes 34%. Eligibility based on a single or a pair of NITs. The proportion of pts eligible for pharmacotherapy when NITs were used alone was highly variable: 38% for ELF (9.2-10.5); 17.5% for FS (0.49-0.72); 10.5% for LSM and 7.2% for SWE (both 10-15 kPa). With 2 NITs the proportion of concordant results fell to 6% for ELF+LSM, 3.7% for ELF+SWE, 2.8% for FS+SWE and 2.4% for FS +LSM. Exclusion of mild fibrosis. Among pts not eligible for treatment based on ELF < 9.2 (N = 259), 93% were confirmed by LSM and 96% by SWE (< 10 kPa). Conversely, among 410 pts not eligible by LSM (< 10 kPa) only 59% were confirmed by ELF (< 9.2). Confirming eligibility based on advanced fibrosis. Among patients eligible for treatment based on ELF (9.8-10.49, N = 73), 75%-84% would have been underscored by LSM or SWE (< 10 kPa). For FS (0.49-0.72) the proportion was 79% for both LSM and SWE (< 10 kPa). Conversely, among pts eligible by LSM or SWE (10-15 kPa) only 25.5% or 17%, respectively, were underscored by ELF(< 9.2). Confounding factors. LSM was correlated with BMI ($r = 0.30$, $p < 0.001$). ELF was strongly correlated with age in both sexes, in MASLD and the whole cohort ($r = 0.49$, $p < 0.001$, Figure). In pts without fibrosis (LSM < 6kPa) median ELF increased with age: 8 if < 40 yrs; 8.29 if 40-49; 8.66 if 50-59; 9.07 if 60-69; 9.53 if > 70. Starting age 40 an age correction should be applied: ELFcorr = ELF-[0.3x(decade-4)]. **Conclusion:** NITs with current thresholds are highly discordant when used for selecting pts for pharmacotherapy. Exclusion of candidates can be based on ELF < 9.2 but not on LSM. Confirmation should rely primarily on LSM with concordant ELF. ELF should be age-corrected.



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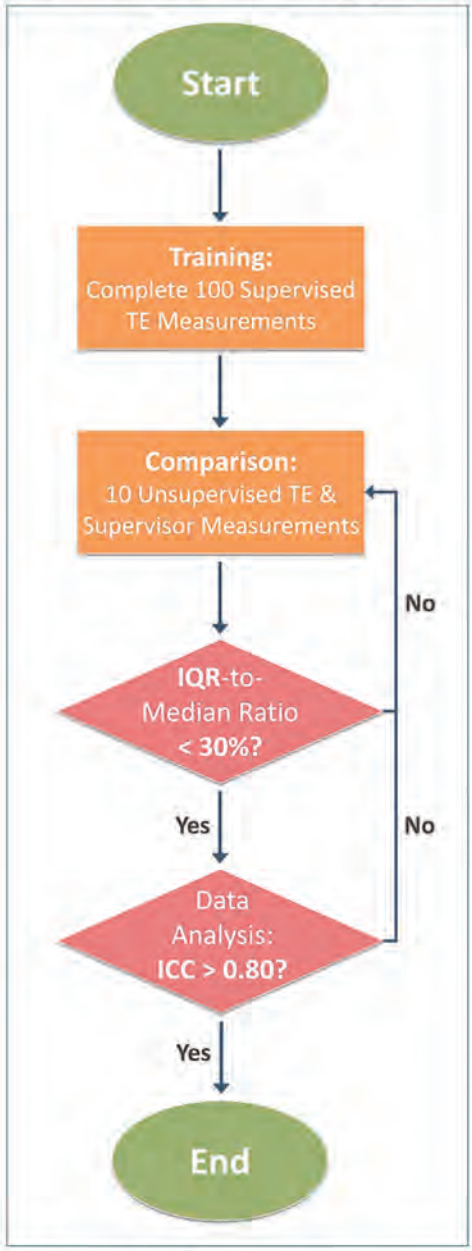
2106 | ACHIEVING OPERATOR COMPETENCY IN TRANSIENT ELASTOGRAPHY (TE): A STRUCTURED PROTOCOL FOR TRAINING NON-EXPERTS TO ASSESS METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) — A MULTICENTER EXPERIENCE

Faisal Abaalkhail[1] Shadan AlMuhaidib[1] Faisal Sanai[2] Duna Barakeh[1] Haifa Alotaibi[3] Saleh Alessy[1] Ali Hazazi[4] Sahar Alnasrallah[3] Alaa AlGhamdi[3] Abdulmohsen Alshammari[1] Mohammed Alghamdi[5] Mariam Seria[5] Waleed Alomaim[1] Bandar Aljudaibi[1] Waleed Alhazzani[3] Saleh Alqahtani[1], [1]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [2]King Abdulaziz Medical City, KAIMRC, Jeddah, Saudi Arabia, [3]Ministry of Defense Health Services, Riyadh, Saudi Arabia, [4]Alfaisal University, Riyadh, Saudi Arabia, [5]King Fahad Military Medical Complex, Dhahran, Saudi Arabia

Background: Non-invasive assessment of liver fibrosis and steatosis is critical in MASLD screening, with TE emerging as the preferred modality. Despite its procedural simplicity, reliability and diagnostic accuracy vary with operator proficiency. We aimed to develop and validate a standardized TE training protocol for implementation across multiple healthcare settings. **Methods:** A multicenter, prospective study was conducted between March 2024 and May 2025 across 6 centers in three main regions of Saudi Arabia. A team of hepatologists and gastroenterologists developed a standardized TE training protocol using FibroScan®. Nine healthcare workers, assigned as research coordinators and lacking prior TE experience, received structured hands-on training from 9 certified supervisors. Each trainee performed 100 supervised and 10 unsupervised TE scans with real-time feedback (Figure 1). Supervisors, blinded to the trainees' unsupervised results, performed parallel TE assessments on the same patients. We recorded the controlled attenuation parameter (CAP), liver stiffness measurements (LSM), and the interquartile range (IQR) for both trainee and supervisor measurements. LSMs were considered reliable if the IQR-to-median ratio was $<30\%$. We assessed inter-operator reliability using intraclass correlation coefficients (ICCs), with values >0.80 indicating strong concordance. **Results:** Trainees (55.6% female) had a median age of 28 years (range: 23–38) and four years of clinical experience (range: 0–13). Their backgrounds included nursing (44.4%), radiology (22.2%), genomics (22.2%), and pharmacy (11.1%). Supervisors (88.9% female) came from diverse disciplines: pharmacists (33.3%), hepatologists/gastroenterologists (22.2%), ultrasound technologists (11.1%), biochemists (11.1%), and genomics (11.1%). The median training period was 20 days (range: 14–22), with a median of 6 hours daily (4–8). Each trainee was supervised by a median of 2 supervisors (range: 1–3). Seven trainees (77.8%) achieved competency on first attempt; the median ICC for CAP was 0.95 (IQR: 0.92–0.98), and for fibrosis scores was 0.96 (0.82–0.99). Median IQR-to-median ratios were 13.5% for trainees and 14.0% for supervisors. **Conclusion:** A short-term, structured training protocol, involving 100 supervised TE assessments over ~20 days, can effectively train novice operators to achieve expert-level proficiency. This approach enhances diagnostic reliability and supports implementation across diverse healthcare settings.

Figure 1
Flowchart for training protocol



Abbreviation: ICC, intraclass correlation coefficient; IQR, interquartile range; TE, transient elastography.

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2107 | DEVELOPMENT OF A NOVEL MODEL USING MACHINE LEARNING ALGORITHMS TO PREDICT PRESENCE OF METABOLIC ASSOCIATED STEATOTIC LIVER DISEASE IMPROVING ON FIB-4 AND ELF. A POPULATION SCREENING TOOL

Charlene Cheong[1] Thomas Ashdown[2] Jorg Taubel[2] Ulrike Lorch[2] Dilshat Djumanov[3] James Rickard[4], [1]Richmond Research Institute, [2]Richmond Pharmacology Ltd, [3]King's College London, [4]Richmond Research Institiute

Background: Metabolic associated steatotic liver disease (MASLD) affects approximately one in four of the global adult population, and ranges in severity from benign fatty liver infiltration, to hepatitis, cirrhosis, hepatocellular carcinoma, and death. Routinely used clinical tools FIB-4 and ELF used to identify patients that require further diagnostic assessment. FIB-4 has limitations with extremes of age at best achieving 0.73 predictive power, with an aging population the score is falsely elevated, the ELF having a predictive power of 0.8. We set about to improve on FIB-4 and ELF for predictive power to offer a more accurate referral tool for further assessment of MASLD to reduce unnecessary diagnostics requested, using readily available clinical assessments. **Methods:** An observational cross-sectional study of 1970 volunteers was completed, Age range 18-90 years, collecting bioimpedance vector analysis (visceral fat%, total body fat% and skeletal muscle %), anthropometric measurement and laboratory bloods. A FibroScan is performed as a pragmatic gold standard 'outcome' for MASLD using $>$248dB/m or $>$7.6kPa as a positive. The data was divided into a training set of (75%) used to build the model, (25%) used to validate its predictive accuracy. Lasso Logistic Regression, Elastic Net Logistic Regression, Random Forest and XGBoost were then compared for model with highest performance. SHAP analysis was used to identify feature importance and remodelling with reduced features to simplify clinical data needed for the model. **Results:** All models achieved an AUROC $>$0.88, Elastic Net Logistic Regression produced the highest performing model using all features achieving AUROC 0.892, Accuracy 0.807, F1 score 0.796 and NPV 0.844. A reduced feature model developed with 5 features (Waist, Height, Weight, ALT & Age) using LASSO Logistic Regression achieving AUROC 0.888, Accuracy 0.809, F1 Score 0.801 and NPV 0.854. **Conclusion:** The model developed produces a highly accurate tool using waist circumference, height, weight, ALT and Age – all readily available in clinical settings. The data collected spans a wide demographic of participants to provide a representative population and current dataset as a foundation of this model. Implementation of this tool in the clinical setting has potential to reduce unnecessary Hepatology referral, Transient Elastography by 10% reducing patient burden and releasing diagnostic capacity to reduce clinic waiting lists on strained health systems.

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2108 | NORMAL LIVER ENZYMES IN PATIENTS WITH DIABETES MELLITUS AND ADVANCED FIBROSIS BY FIB-4

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Background: Diabetes mellitus (DM) is a risk factor for both metabolic-associated steatotic liver disease (MASLD) and morbidity and mortality in patients with MASLD. MASLD, even with advanced fibrosis, may exist without abnormal liver tests, potentially delaying diagnosis. The primary aim of this study was to describe patients with DM and Fibrosis-4 scores (FIB-4) suggesting advanced fibrosis in the absence of abnormal transaminases and to evaluate referral patterns for specialty liver care. **Methods:** Retrospective review of electronic medical records at a single center was performed. Adults aged 18-90 with DM seen in primary care from 2022-2024 were included. FIB-4 scores were calculated using ambulatory encounter labs within 2 years. Patients with viral hepatitis (B or C) and those seen in oncology or hepatology clinics were excluded to evaluate only undiagnosed patients with probable MASLD. Upper limit of normal (ULN) values for alanine transaminase (ALT) and aspartate transaminase were 44 IU/L and 40 IU/L, respectively, per our laboratory's standard. Patients were considered to have advanced

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fibrosis if maximum FIB-4 was > 2.67. Referrals to gastroenterology, hepatology, and vibration-controlled transient elastography (VCTE) for any reason were considered. **Results:** 3389 patients (1584 female) had FIB-4 > 2.67. 433 (18%) were between 35-65 years old; 2956 (87%) were older than 65 and 0 were between 18-34. Among patients aged 35-65 with FIB-4 > 2.67 (Table), all available levels of ALT and AST were below the ULN in 177 (40% of patients aged 35-65, 5% of all patients). 9 (5%) and 8 (5%) of these patients were referred for VCTE or hepatology, respectively. 31 females (42% of females with ALT and AST within normal limits per lab cut-off) had maximum levels of ALT and AST that were below the lab ULN but greater than the sex-adjusted cut-off of 20 IU/L. 1 (3%) and 3 (10%) of these patients were referred for VCTE or hepatology, respectively. **Conclusion:** Only a minority of patients with DM and possible advanced MASLD were referred to hepatology or VCTE regardless of whether transaminases were abnormal. Although 5% of patients with advanced fibrosis by FIB-4 did not have elevated transaminases, 43% of females with "normal" transaminases by lab cut-offs actually had elevated liver enzymes by sex-adjusted norms. These patients are at particularly high-risk for missed diagnosis of advanced liver disease, with the lowest demonstrated likelihood of specialty referral.

	All patients age 35-65 with ALT>44 or AST >40	All patients age 35-65 with ALT≤44 IU/L and AST ≤40 IU/L	Females age 35-65 with ALT 20-44 IU/L and AST 20-40 IU/L
Females (n, %)	83 (32.43%)	74 (41.81%)	31 (–)
Males (n, %)	173 (67.58%)	103 (58.19%)	–
FIB-4 (mean/STD)	4.67 (3.56)	3.49 (0.98)	3.97 (1.62)
Max ALT (IU/L) (mean/STD)	67.09 (41.80)	21.32 (8.79)	27.84 (4.78)
Max AST (IU/L) (mean/STD)	88.12 (62.89)	28.29 (6.83)	31.71 (5.18)
Max Platelets (10^3/uL) (mean/STD)	178.93 (71.83)	139.04 (49.13)	120.23 (50.97)
BMI (kg/m^2) (mean/STD)	30.37 (6.45)	29.28 (6.54)	30.69 (6.52)
Hemoglobin A1c (%) (mean/STD)	7.42 (1.86)	6.81 (1.51)	6.97 (1.43)
Age (years) (mean/STD)	57.62 (6.57)	60.47 (4.47)	60.42 (4.01)
Age group (years)			
35-50	40 (15.63%)	6 (3.57%)	1 (3.23%)
51-65	216 (84.38%)	171 (96.661%)	30 (96.77%)
Race/Ethnicity (n, %)			
Asian	26 (10.16%)	15 (8.93%)	5 (16.13%)
Non-Hispanic Black	41 (16.02%)	36 (20.34%)	3 (9.68%)
Non-Hispanic White	84 (32.81%)	47 (26.55%)	8 (25.81%)
Latino	61 (23.83%)	38 (21.47%)	7 (22.58%)
Other/Unknown	44 (17.19%)	34 (20.24%)	8 (25.81%)
VCTE referral	17 (6.64%)	9 (5.08%)	1 (3.23%)
Hepatology referral	47 (18.36%)	8 (4.52%)	3 (9.68%)
Gastroenterology referral	106 (41.41%)	72 (40.8%)	12 (38.71%)
Any referral	129 (50.39%)	75 (42.37%)	12 (38.71%)

ALT (alanine aminotransferase); AST (aspartate aminotransferase); BMI (body mass index); FIB-4 (Fibrosis-4 score); STD (standard deviation); VCTE (vibration-controlled transient elastography)

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2109 | DISTINCT TRANSCRIPTOMIC SIGNATURES IN PLATELET-DERIVED EXTRACELLULAR VESICLES (PEVS) ASSOCIATED WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Background: Platelet-derived extracellular vesicles (PEVs) are membrane-bound vesicles released by platelets during activation or apoptosis. They carry genetic and protein material from their cells of origin, acting as vectors for intercellular communication and contributing to the initiation, pathogenesis, and progression of various liver diseases. Both platelets and platelet-derived EVs interact with liver cells, playing a role in hepatic injury. Objectives: (i) To determine the use of platelet-derived EVs as biomarkers for the severity of MASLD, (ii) to determine the differential miRNA profile contained in platelet-derived EVs in patients with different severity degrees. **Methods:** A total of 97 biopsy-proven MASLD patients were recruited and classified into steatosis (n = 23) or steatohepatitis (n = 70) based on the SAF score. EVs quantification was performed by flow cytometry (LRS Fortessa) using Annexin V-PE and CD41-FITC antibodies. Isolation of EVs was carried out on the Facs Aria Fusion cell sorter (Becton Dickinson) in plasma from 16 patients with steatohepatitis and 8 patients with steatosis. The size and yield of particles isolated was determined by nanoparticle tracking analysis and CD41 + EVs were also characterized by transmission electron microscopy (TEM). Total RNA enriched in miRNAs was extracted using the miRNeasy Mini Kit (Qiagen), and the differential expression profile of microRNAs was determined by microarray (GeneChip miRNA 4.0 Assay

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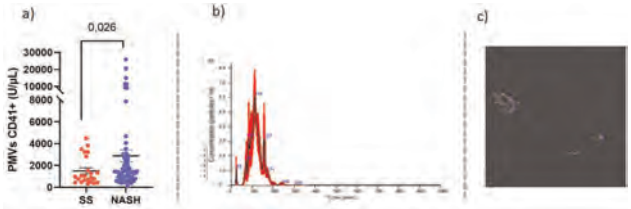
Affymetrix, ThermoFisher CA, USA). **Results:** CD41+ EVs levels were significantly elevated in patients with steatohepatitis compared to those with steatosis (1511 ± 268 vs. 2882 ± 542.5; $p = 0.04$). The results of the differential analysis showed that 8 microRNAs were upregulated in platelet-derived EVs from patients with steatohepatitis (fold change > 2, p-value < 0.05): miR-3141, miR-6791-5p, miR-6803-5p, miR-6786-5p, miR-6763-5p, miR-3656, miR-4763-3p y miR-4467; and one downregulated: miR-4679-1. After comparing transcriptomic profile in patients with advanced fibrosis (F3-F4), we found an overexpression of miR-139-3p. Specifically, overexpression of miR-6803-5p, miR-3656 and miR-139-3p has been previously associated with hepatocellular carcinoma, proliferation and metastasis. Furthermore, miR-4763-3p and miR-4467 are associated with liver inflammation **Conclusion:** Platelet-derived EVs are elevated in patients with steatohepatitis, suggesting their potential as biomarkers for disease severity. Furthermore, preliminary data indicate a distinct miRNA profile within PEVs, which may help explain their role in the progression of MASLD to more advanced stages.



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2110 | EXPERIENCE USING PORTABLE ULTRASOUND FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE DETECTION IN RURAL COLOMBIAN MUNICIPALITIES

Jimmy Daza[1] Sara Tamayo[2] Eduardo Mazuera[2] Juan Fernando Mesa Valencia[3] Yeinis Paola Espinoza Herrera[4] Vanessa Cuadrado Cardenas[4] Victor De La Espriella[4] Maria Cristina Navas[4] Andreas Teufel[1] Milena Alcázar Paternina[2], [1]Div. of Hepatology, Dep. of Medicine II, Medical Faculty Mannheim of Heidelberg University, Germany, [2]Department of Radiology, Universidad de Antioquia, Medellin, Colombia., [3]LivingLab Telesalud, Universidad de Antioquia, Medellín, Colombia., [4]Gastrohepatología Research Group, Universidad de Antioquia, Medellín, Colombia

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease, with a global prevalence of over 25%. Early detection is crucial but challenging in rural areas due to limited healthcare access and MASLD's asymptomatic nature in its initial stages. Although liver biopsy remains the gold standard, its invasive nature limits its use for population-wide screening. Non-invasive methods, such as portable ultrasound, emerge as viable alternatives, particularly in rural areas with limited healthcare access. This study evaluates portable ultrasound efficacy for MASLD detection and characterize disease prevalence in underserved Colombian rural populations. **Methods:** We conducted a cross-sectional study in adults (> 18 years) with cardiovascular risk factors from three rural Colombian municipalities (Gómez Plata, Leticia, and Frontino). Exclusion criteria included cirrhosis, hepatocellular carcinoma, or active viral hepatitis. Hepatic steatosis was assessed using Clarius® portable ultrasound with standardized grading protocols. Statistical analysis included descriptive statistics, comparative tests (Shapiro-Wilk, Student's t-test, Mann-Whitney U, χ^2) and logistic regression in Stata v14. **Results:** Among 271 participants (67% female, mean age 60.5 ± 12.3 years), hepatic steatosis prevalence was 63% (grade I: 34%, grade II: 23%, grade III: 7%). Obesity demonstrated the strongest association with MASLD (OR: 2.10, 95% CI: 1.23-3.58, $p = 0.007$), followed by diabetes mellitus (OR: 1.71, 95% CI: 1.02-2.86, $p = 0.041$). No significant associations were found with sex, age, or hypertension. Portable ultrasound enabled real-time imaging with cloud-based storage and telemedicine integration, facilitating remote expert consultation. **Conclusion:** Portable ultrasound represents an effective, accessible diagnostic tool for MASLD screening in rural populations. This technology enables early detection, timely interventions, and reduces geographic healthcare disparities, supporting decentralized care models in resource-limited settings.

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2111 | EARLY DIAGNOSIS OF SARCOPENIA IN PATIENTS WITH MASLD USING OXIDATIVE STRESS MARKERS

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Background: Sarcopenia is a common comorbidity in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and is a recognized risk factor for the progression of metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis. Oxidative stress is considered one of the key mechanisms underlying sarcopenia. We previously reported that human mercaptalbumin (HMA), the reduced form of albumin, serves as a sensitive marker of oxidative stress in patients with chronic liver disease. The aim of this study was to investigate the associations between oxidative stress markers—particularly HMA and advanced oxidation protein products (AOPPs)—and muscle strength and body composition in patients with MASLD/MASH. **Methods:** A total of 67 patients with MASLD/MASH who visited or were admitted to our department between June 2021 and May 2024 were included. Clinical assessments included grip strength, skeletal muscle mass, body fat percentage, and liver stiffness. Muscle mass and fat percentage were measured using bioelectrical impedance analysis (BIA). Additionally, computed tomography (CT) at the L3 vertebral level was used to evaluate skeletal muscle, subcutaneous fat, and visceral fat via a 3D imaging analysis system. Serum HMA was measured using electrospray ionization time-of-flight mass spectrometry (ESI-TOFMS), while AOPPs were measured using a commercial colorimetric assay kit. **Results:** Among the 67 patients analyzed, 11 were diagnosed with liver cirrhosis. The mean grip strength was 25.2 ± 6.9 kg, BIA-measured muscle mass was 10.3 ± 2.2 kg/m², body fat percentage was 24.2 ± 7.9%, and CT-measured muscle area at the L3 level was 48.2 ± 10.1 cm²/m². The mean HMA level was 2.83 ± 0.6 g/dL, and the mean AOPP concentration was 185.4 ± 61.7 μM. Notably, grip strength demonstrated a remarkably strong positive correlation with HMA ($r = 0.903$), while CT-assessed muscle mass at L3 showed a strong inverse correlation with AOPPs ($r = –0.718$) and a moderate positive correlation with HMA ($r = 0.536$). Despite the limited sample size, these findings provide compelling evidence that oxidative stress markers—particularly HMA and AOPPs—are closely linked to muscle strength and mass in patients with MASLD/MASH, underscoring their potential as clinically relevant biomarkers of early sarcopenic changes. **Conclusion:** Our findings suggest that HMA is associated with muscle strength, whereas AOPPs are more closely correlated with muscle mass in patients with MASLD/MASH. Given that AOPPs can induce reactive oxygen species, inflammatory cytokines such as TNF-α, and myokines, they may represent a novel therapeutic target for sarcopenia. Moreover, both HMA and AOPPs may serve as valuable biomarkers for the early detection of pre-sarcopenia in patients with MASLD/MASH.

Disclosures: Hiroko Setoyama: Nothing to Disclose, Toshinori Toyoda: Nothing to Disclose, Takahiro Mizuta: Nothing to Disclose, Daiki Maeda: Nothing to Disclose, Kentaro Tanaka: Nothing to Disclose, Hiroki Inada: Nothing to Disclose, Satoshi Narahara: Nothing to Disclose, Etsuko Iio: Nothing to Disclose, Yoko Yoshimaru: Nothing to Disclose, Takehisa Watanabe: Nothing to Disclose, Katsuya Nagaoka: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

2112 | PROGNOSTIC VALUE OF THE TLM3 BIOMARKER PANEL FOR EARLY FIBROSIS DEVELOPMENT IN MASLD WITHIN THE GENERAL POPULATION

Lars Verschuren[1], [1]TNO

Background: Fibrotic MASLD is associated with increased morbidity and mortality, often remaining asymptomatic until advanced stages of disease. Predicting fibrosis onset and progression would improve risk stratification and treatment allocation. This study aims to investigate whether a previously identified fibrosis biomarker panel for active fibrogenesis (TLM3) can serve as a prognostic marker panel for fibrosis development in a population at cardiometabolic risk of fibrotic MASLD. **Methods:** The temporal dynamics of a molecular fibrosis gene expression signature associated to histologically-proven fibrosis development was investigated in a diet-induced MASLD mouse model (LDLr-/-.Leiden). The corresponding proteins were measured in baseline serum from individuals at risk of MASLD from the general population HELIUS-cohort and correlated to established fibrosis proxies (ELF, VCTE and FIB4) at 7 years follow-up. **Results:** The molecular fibrosis gene expression signature was upregulated in a murine MASLD model before the onset of histopathological features of fibrosis. In humans, serum levels of IGFBP7, Ssc5D, Sema4D, VCAN, THBS1 and TNC at baseline correlated with fibrosis proxies at follow-up. IGFBP7 at baseline was able to predict new onset fibrosis, defined as ELF ³9.8 at

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follow-up in participants with ELF <9.8 at baseline, with an area under the curve (AUC) of 0.79 (95% CI: 0.64-0.94). **Conclusion:** Together, these findings indicate the potential predictive capacity of the TLM3 biomarker panel in early stages of MASLD-fibrosis, both in a murine model as well as in individuals from the general population at risk of MASLD.
Disclosures: Lars Verschuren: Nothing to Disclose

2113 | PREVALENCE AND ASSOCIATED FACTORS OF STEATOSIS, STEATOHEPATITIS AND FIBROSIS DIAGNOSED WITH NON-INVASIVE METHODS: DURING ANNUAL CHECK-UPS IN AN INDUSTRIAL WORKER POPULATION

Pietro Guerra[1] Javier Lopez Perez[2] Silvia Cagnin[1] Patrizia Pontisso[3] Maria Martinez Chantar[4] Andrea Martini[5], [1]University of Padova, [2]Bridgestone Hispania Manufacturing S.L, Bilbao, Spain, [3]Univeristy of Padova, [4]Liver Disease Lab, CIC bioGUNE, Basque Research and Technology Alliance, BRTA, Derio, Spain, [5]Department of Medicine, Azienda Ospedale-Università di Padova (AOPD), Padova, Italy

Background: Steatotic liver disease (SLD), which may progress to fibrosis and cirrhosis, is increasing due to the rising incidence of metabolic dysfunction-associated SLD (MASLD). Although general screening is not recommended, incidental findings should prompt evaluation. SLD with elevated liver enzymes (Setatohepatitis - SH) and fibrosis carries prognostic relevance. Non-invasive scores like FIB-4 and APRI can identify fibrosis risk. Using routine health data, we assessed the prevalence and associated factors of SLD, SH, and fibrosis among workers at the Bridgestone factory in Bilbao. **Methods:** 886 workers were enrolled during the 2024 annual checkups. Data included ultrasound, anthropometry, blood tests, and a qualitative alcohol questionnaire. Complete data were available for 362 individuals. Participants were grouped into: Healthy (no steatosis), SLD (steatosis, normal enzymes), and SH (steatosis, elevated enzymes). Group differences were analysed using ANOVA or Kruskal-Wallis and chi-square tests. Logistic and linear regressions identified predictors of SLD, SH, and fibrosis (FIB-4/APRI). **Results:** The Healthy Group accounted for 68% of the patients, while the remaining patients were divided into the other two groups (SLD 20%; SH 12%). Analysis of variance showed a statistical significant increase in age, BMI, creatinine, haemoglobin, triglycerides and serum glucose between healthy individuals, SLD and SH. A progressive increase also in individuals with arterial hypertension, with increased alcohol consumption and male sex was noted. At post-hoc analysis the only differences between SLD and SH patients were higher BMI, higher triglycerides and lower HDL. The prevalence of SLD diagnosed with ultrasound was 31.9%, [95% CI: 27.6%-36.6%]. Also, the prevalence of fibrosis diagnosed with FIB4 or APRI score was: 0.55% [0.15% - 1.9%], defined by a FIB4 score $>$ 2.67; and 0.2% [0.04% - 1.5%] defined by a APRI score $>$ 1.5. Factors associated with SLD at multivariable logistic regression were: BMI (aOR 1.18 [1.06, 1.33]), hypertension (aOR 2.69 [1.22, 6.03]), alcohol consumption (aOR 2.40 [1.16, 5.12]) and ALT (aOR 1.03 [1.00, 1.06]). Factors associated with SH at multivariable logistic regression were: BMI (aOR 1.33 [1.19, 1.50]) and triglycerides (aOR 1.00 [1.00, 1.01]). Predictors of FIB4 were sex (coefficient: 1.30 [1.15, 1.47]), serum magnesium (coefficient: 0.67 [0.52, 0.84]) and HDL (coefficient: 1.01 [1.01, 1.01]). The only predictor of APRI score was serum magnesium (coefficient: 0.85 [0.76, 0.95]). **Conclusion:** The prevalence of SLD and liver fibrosis in this working population was consistent with existing literature. Opportunistic screening with ultrasound and liver enzymes identified a subset of patients at increased risk (SH), emphasizing the value of incorporating liver assessments into routine occupational health evaluations.
Disclosures: Pietro Guerra: Nothing to Disclose, Javier Lopez Perez: Nothing to Disclose, Silvia Cagnin: Nothing to Disclose, Patrizia Pontisso: Nothing to Disclose, Maria Martinez Chantar: Nothing to Disclose, Andrea Martini: Nothing to Disclose

2114 | CHANGES IN THE FIBROSIS-4 (FIB-4) SCORE ACCURATELY REFLECTS THE DISEASE TRAJECTORY OF METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

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Background: A FIB-4 score of 1.3-2.6 reflects an intermediate risk stratum of MASLD where secondary tests with VCTE or repeat testing is recommended. VCTE is not however universally available and the utility of repeat FIB-4 testing to assess changes in clinical status in MASLD is not known. This is particularly relevant since MASLD can both progress and regress without specific intervention. We hypothesized that

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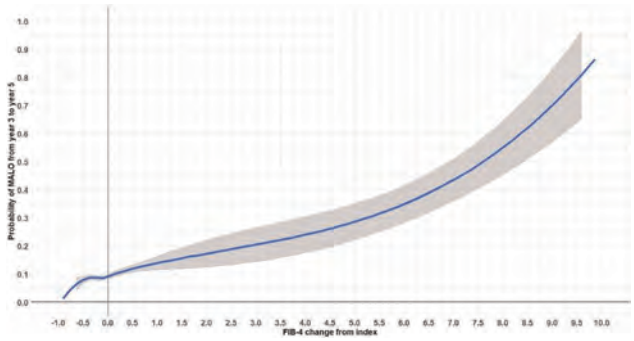
changes in FIB-4 will coordinately track the risk of clinical outcomes in MASLD. The aim of this study was to define the performance of changes in FIB-4 as a disease-monitoring test in MASLD. **Methods:** A retrospective analysis of a US cohort with MASLD followed prospectively in a non-interventional longitudinal registry (TARGET-NASH) was performed. MASLD was diagnosed by metabolic risk factors, histology or NITs, and AUDIT score < 7 (Am J Gastroenterol, 2024; 119 (8):1624-1627). Adults with FIB-4 between 1.3-2.6 who had 2 FIB-4 measurements > 6 mths apart within 3 years from baseline and a total of 5 years of follow up were included. Changes in FIB-4 from baseline up to yr. 3 was related to outcomes between yrs. 3-5. Key outcomes included death and major adverse liver outcomes (MALO) i.e. ascites, overt encephalopathy and variceal hemorrhage. Regression analysis was performed to determine if FIB-4 effects were independent of age, type 2 diabetes and other confounders. Bootstrap validation of the model was performed. **Results:** A total of 974 individuals were analyzed. Baseline data included: mean age 61 (9.7 SD) yrs, FIB-4 1.8 (0.34 S.D.) including T2DM (28%) and HTN (63%). 221 MALO events were noted by yr 3 and a total of 94 clinical events were noted between yr 3 and 5. From baseline to yr 3, FIB-4 declined by >10% in 434 patients and increased by >10% in 304 patients. MALO incidence decreased with decreasing FIB-4 and increased with rising FIB-4 (O.R. 1.4 (1.08-1.9)(Figure 1). Age and BMI did not impact outcomes while T2DM increased outcome risk (OR 2.36(1.5-3.8)). A total of 7 and 11 individuals died by yr. 3 and between yrs. 3-5 respectively; changes in FIB-4 were also associated with mortality risk. Bootstrap validation confirmed the robustness of the model. **Conclusion:** Changes in FIB-4 predict future risk of adverse health outcomes independent of age and changes in BMI. Thus, in this intermediate risk FIB-4 category especially with T2DM, repeat testing and change in FIB-4 can be used to assess prognosis and disease trajectory.



Disclosures: Vinay Jahagirdar: Nothing to Disclose, Nothing to Disclose, Breda Munoz-Hernandez: Nothing to Disclose, Andrea Mospan: Nothing to Disclose, Philip Newsome: Nothing to Disclose, Brent Neuschwander-Tetri: Akero: Consultant, Aligos: Consultant, Arrowhead: Consultant, Corcept: Consultant, GSK: Consultant, Hepion: Consultant, Histoindex: Consultant, Madrigal: Consultant, Merck: Consultant, Mirum: Consultant, Sagimet: Consultant, Senseion: Consultant, HepGene: Stock – privately held company, HeptaBio: Consultant, Abbvie: Consultant, Pliant: Consultant, Kenneth Cusi: Nothing to Disclose, A. Sidney Barritt IV: Nothing to Disclose, Michael Fried: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor

★ 2116 | PREVALENCE AND HEALTH CHECKUP-BASED DETECTION OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN JAPANESE YOUNG ADULTS

Satoko Tajirika[1] Takao Miwa[2] Tatsunori Hanai[2] Masahito Shimizu[2] Mayumi Yamamoto[1], [1]Gifu University, Gifu, Japan, [2]Graduate School of Medicine, Gifu University, Gifu, Japan.

Background: The new nomenclature of steatotic liver disease (SLD) has been announced for a clear definition based on cardiometabolic criteria and alcohol consumption. This study aimed to reveal the prevalence of SLD based on the new nomenclature in Japanese young adults. Additionally, health checkup-based markers to identify metabolic dysfunction-associated steatotic liver disease (MASLD) in this population were explored. **Methods:** We recruited Japanese young adults (aged 18–29 years) attending a health checkup. Abdominal ultrasonography and health checkup data were used to diagnose and classify SLD based on the

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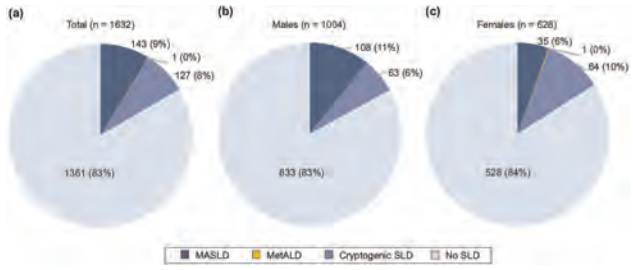
new nomenclature. Regarding health checkup-based markers to identify MASLD, the diagnostic ability of serum alanine aminotransferase (ALT), fatty liver index (FLI), and hepatic steatosis index (HSI) were evaluated using receiver operating characteristic curve analysis. **Results:** Of the 1632 participants, 1004 (62%) were male, and SLD was observed in 271 (17%). In the SLD subclass, 143 (9%), 1 (<1%), 0 (0%), and 127 (8%) were diagnosed with MASLD, metabolic and alcohol-related/associated liver disease, alcohol-associated/related liver disease, and cryptogenic SLD, respectively, which was more frequent males than females (Figure 1). Regarding markers of MASLD, ALT, FLI, and HSI had a favorable ability to identify MASLD with an area under the curve of 0.76, 0.85, and 0.84, respectively, in the total cohort, 0.81, 0.87, and 0.86, respectively, in males, and 0.63, 0.83, and 0.79, respectively, in females. The cutoff value of ALT to rule-in (specificity 0.90) MASLD was 31 IU/L. **Conclusion:** The prevalence of SLD and MASLD in Japanese young adults was 17% and 9%, respectively. Regarding health checkup-based markers for MASLD, FLI, HSI and ALT had favorable ability to identify MASLD. In addition, ALT >30 IU/L was identified as a reasonable cutoff value to identify MASLD in Japanese young adults.



Disclosures: Satoko Tajirika: Nothing to Disclose, Takao Miwa: Nothing to Disclose, Tatsunori Hanai: Nothing to Disclose, Masahito Shimizu: Nothing to Disclose, Mayumi Yamamoto: Nothing to Disclose

2117 | THE EFFICACY OF MEASURING NATURAL KILLER ACTIVATING RECEPTOR LIGANDS AND BILE ACIDS TO PREDICT THE PATHOGENESIS OF MASLD

Jun Arai[1] Akinori Okumura[1] Shun Futagami[1] Masato Yano[1] Tomoya Kitada[1] Satoshi Kimoto[1] Kazumasa Sakamoto[1] Rena Kitano[1] Tadahisa Inoue[1] Sayaka Nishimura[1] Kiyoaki Ito[1], [1]Department of Gastroenterology, Aichi Medical University, Nagakute, Aichi, Japan.

Background: The proportion of non-B/non-C hepatocellular carcinoma cases is increasing, and the principal cause is metabolic dysfunction-associated steatotic liver disease (MASLD). The degree of intrahepatic natural killer (NK) cell infiltration has been reported to correlate with MASLD progression. However, reports on MASLD are limited. Previous studies have also revealed that the disruption intrahepatic bile acid homeostasis could be one of the major mechanisms of progression to MASH. We aimed to investigate the involvement of NK cell-activating receptor ligands and bile acid in MASLD pathogenesis. **Methods:** This study cohort comprised 69 patients with biopsy-proven MASLD treated between 2012 and 2018 at our institute. The concentrations of major histocompatibility complex class I polypeptide-related sequences A and B (MICA and MICB, respectively) B7H6, total bile acids (TBA), and Chenodeoxycholic acid (CDCA) in patient sera were measured. Data were statistically compared between those with metabolic-associated steatotic liver (MASL, n = 25) and those with metabolic dysfunction-associated steatohepatitis (MASH, n = 44). The clinical characteristics related to higher concentrations of each NK cell-activating receptor ligand were also investigated. **Results:** The MASH group had a higher level of the ligands than the MASL group. Furthermore, the MASH group had a significantly higher level of the Mac-2-binding protein glycosylation isomer (M2BPGi) and Fib-4 index than the MASL group ($p < 0.001$). MICA and MICB were positively correlated, and all three ligands were strongly correlated with alpha-fetoprotein and protein induced by vitamin K absence 2. Although MICB levels positively correlated with aspartate transaminase and alanine transaminase levels ($p < 0.005$), patients with higher MICA and B7H6 levels had higher M2BPGi levels. Interestingly, concentrations of B7H6 were significantly correlated with portal inflammation ($p < 0.001$), rather than lobular inflammation. On the other hand, there were no significant differences in TBA and CDCA between MASL and MASH groups. CDCA shows significant positive correlations with age, M2BPGi, and Fib-4 index ($p < 0.001$). Furthermore, CDCA/TBA ratio was positively associated with MICB level ($\rho = 0.41$, $p < 0.001$). **Conclusion:** The three NK-activating receptor ligands were higher in the sera of the MASH group than those of the MASL group and strongly correlated with tumor markers, indicating the potential for hepatocarcinogenesis. Higher concentrations of serum B7H6 were correlated with advanced fibrosis and the degree of portal inflammation, which is a potential biomarker for predicting the pathogenesis of MASH. The CDCA/TBA ratio could predict the activation of the NK cells. **Disclosures:** Jun Arai: Nothing to Disclose, Akinori Okumura: Nothing to Disclose, Shun Futagami: Nothing to Disclose, Masato Yano: Nothing to Disclose, Tomoya Kitada: Nothing to Disclose, Satoshi Kimoto: Nothing to

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Disclose, Kazumasa Sakamoto: Nothing to Disclose, Rena Kitano: Nothing to Disclose, Tadahisa Inoue: Nothing to Disclose, Sayaka Nishimura: Nothing to Disclose, Kiyoaki Ito: Nothing to Disclose

2118 | PREDICTING HEPATIC STEATOSIS: A STUDY OF DECEASED LIVER DONORS

Jaimie Chang[1] Darren Nin[1] Stephanie Trautmann[1] Maria Charina Benavidez[1] Jarren Takaki[1] Kabeer Masih[1] John Klein[1] Edie Chan[1], [1]Rush University Medical Center

Background: Hepatic steatosis in donor grafts is associated with poorer liver transplantation outcomes. While liver biopsy remains the gold standard for diagnosis, it is not always readily available. This study aims to evaluate how donor risk factors and imaging features correlate with hepatic steatosis. **Methods:** This study used data from the Organ Procurement and Transplantation Network (OPTN). Adult liver donors in the United Stated between 2020-2024 with liver biopsy results and CT scans were identified from the OPTN database. Hounsfield units (HU's) of the liver, spleen, anterior abdominal wall thickness and dimensions of the waist and peritoneal cavity at the level of the umbilicus were measured on CT scans. **Results:** A total of 2972 donors with liver recovered met inclusion and exclusion criteria. 2673 had $<30\%$ steatosis and 299 had $\geq 30\%$ steatosis. The absolute intraclass correlation coefficient was high, ranging from 0.73-0.91 for HU measurements and between 0.84-0.99 for abdominal measurements. Younger age, Hispanic ethnicity, higher body mass index (BMI), Weight-Adjusted Waist Index (WWI), abdominal wall thickness, and peritoneal cavity area, lower liver to spleen (L/S) ratio, elevated total bilirubin, and a history of heavy alcohol use were identified as risk factors on the univariate analysis. On the adjusted analyses the only significant predictors of steatosis were Hispanic ethnicity [OR: 1.74, 95% CI:1.13-2.66] and L/S ratio [OR: 0.02, 95%CI: 0.01-0.04]. **Conclusion:** Donor related risk factors including BMI, bilirubin, and drinking, history, as well as CT measurements including waist dimensions, abdominal wall thickness, are all correlated to hepatic steatosis, but Hispanic ethnicity and L/S ratio were the most significant predictors on adjusted analysis. This may inform donor selection when biopsy is not available.

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2119 | META-ANALYSIS OF THE PERFORMANCE OF THE ENHANCED LIVER FIBROSIS (ELF) TEST TO IDENTIFY SIGNIFICANT FIBROSIS, ADVANCED FIBROSIS AND CIRRHOSIS IN PATIENTS WITH MASLD

Matthew Gee[1] Donald Chalfin[1] Edward De Vol[1] Mario Gutierrez Casale[1] Artem Boltyenkov[1] H. Roma Levy[1] Arun Sanyal[2], [1]Siemens Healthineers, [2]Virginia Commonwealth University

Background: Non-invasive tests, such as the ELF Test, are increasingly employed to evaluate the presence of liver fibrosis and the likelihood of disease progression in patients with MASLD. This meta-analysis aimed to determine the optimal ELF cutoffs for detecting histologically-staged significant fibrosis ($\geq$F2), advanced fibrosis ($\geq$F3), and cirrhosis (F4) in patients with MASLD; and to validate the accuracy of established cutoffs (9.00, 9.80, and 11.30). This study incorporates several reports not included in prior meta-analyses. Additionally, this is the first meta-analysis to evaluate the performance of the ELF Test in MASLD patients with cirrhosis. **Methods:** We searched MEDLINE (PubMed), EMBASE, the Cochrane Library, and CINAHL databases for studies reporting ELF Test performance published between 2004-01-01 and 2023-10-10, followed by an additional PubMed search in May 2024 for liver fibrosis and ELF. One author extracted data with confirmation by two reviewers. Study quality was assessed using the QUADAS-2 tool. Multiple thresholds published in the various reports were integrated into a hierarchical summary receiver operating characteristic (HSROC) model. For each fibrosis category ($\geq$F2, $\geq$F3, F4), a bivariate random-effects model was used to estimate sensitivity and specificity across thresholds, generating summary areas (AUCs) under the ROC curve. **Results:** Of 8004 articles identified by keyword search, 981 abstracts were screened, of which 107 articles were selected for whole article review. Upon review, 33 separate cohorts from 30 studies were extracted for inclusion in the meta-analysis. The AUC was 0.827 (95% CI: 0.787, 0.860) for $\geq$F2 fibrosis, 0.829 (95% CI: 0.791, 0.861) for $\geq$F3 fibrosis, and 0.773 (95% CI: 0.707, 0.826) for cirrhosis. For detection of $\geq$F2, the pre-established ELF threshold of 9.00 yielded 86% sensitivity and 63% specificity. The 9.80 cutoff was confirmed to be a balanced threshold for $\geq$F3 (sensitivity = 71%, specificity = 81%), while the recognized cutoff of 11.30 was useful to rule in F4 (sensitivity = 22%, specificity = 96%). A higher sensitivity cutoff of 10.50 was determined to be an effective alternate threshold for identification of cirrhosis (sensitivity = 51%, specificity = 86%). **Conclusion:**

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Incorporating the highest number of MASLD cohorts of any meta-analysis to date, our study confirms that the ELF Test accurately identifies significant fibrosis, advanced fibrosis, and cirrhosis in patients with confirmed or suspected MASLD. An ELF cutoff <9.00 may be useful to rule out significant fibrosis, while ≥ 9.80 represents a balanced cutoff to identify advanced fibrosis. For cirrhosis, ELF ≥ 11.30 is a high-specificity rule-in cutoff, whereas ≥ 10.50 offers higher sensitivity for F4 detection. These findings support recent MASH treatment initiation guidelines based on non-invasive determination of fibrosis stage.
Disclosures: Matthew Gee: Siemens Healthineers: Employee, Donald Chalfin: Nothing to Disclose, Edward De Vol: Nothing to Disclose, Mario Gutierrez Casale: Nothing to Disclose, Artem Boltyenkov: Siemens Healthineers: Employee, Siemens Healthineers: Stock - publicly traded company, H. Roma Levy: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock – publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor

2120 | EVALUATION FOR HEPATIC FIBROSIS RISK BY FIB4 SCORE, LIVER STIFFNESS (FIBROSCAN, SHEARWAVE), LIVERRISK SCORE AND EASL/AASLD-2 STEP APPROACH IN 1169 PATIENTS FOLLOWED FOR MASLD, NEW SUBMISSION

Denis Ouzan[1] Guillaume Maeva[2] Penaranda Guillaume[3] guivarch mathieu[4] guillouche Pauline[5] Chagneau Corinne[6] delasalle Patrick[7] Boussoukaya Samy[8] Toulemonde Pierre[9] Lim Annie[10] Maeva Salimon[10] Hanslik Bertrand[11] Jacques Liautard[12] Dukan Patrick[13] Ingiliz Patrick[14] Ouizeman Dann Joseph[15] Bonny Corinne[16] Ancel David[17] Marion Audibert Anne Marie[18] Debono Emmanuel[19] Fontanges Thierry[20] Vallin Melanie[20] Guillaud Olivier[21],
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Background: The STEATOLIB cohort was established to prospectively monitor patients with steatosis in hepatology private practice over a decade. This study focuses on liver fibrosis evaluation by FIB4 score, liver stiffness (Fibroscan, ShearWave), and LiverRisk score.
Methods: From February 2021 to June 2023, 18 centers enrolled 1,169 adult patients with morphological and/or histological steatosis and abnormal liver tests (ASAT, ALAT, GGT, and/or PAL) into the STEATOLIB cohort. **Results:** Among the 1,169 patients included, 56% were men, with a mean age of 56 years (SD: 13). Comorbidities included diabetes (37%), hypertension (45%), and dyslipidemia (36%). Weekly alcohol consumption was: no consumption (56%), 1–10 units (33%), and >10 units per week (11%). The mean BMI was 31 ± 5.8 kg/m². Fibrosis was assessed using the FIB-4 score in 936 patients: 69% had a low fibrosis risk (FIB-4 <1.3/<2, age-dependent), 23% had an intermediate (FIB-4: 1.3–2.67), and 8% had a high risk (FIB-4 >2.67). Liver stiffness measurement (LSM) was available in 836 patients: FibroScan (n = 407) showed a mean stiffness of 8.3 kPa (SD 6.1), with 66% <8 kPa, 19% between 8–12 kPa, and 15% >12 kPa, Shear Wave Elastography (n = 429) yielded similar results (mean: 8.0 kPa (SD 5.2)). The LiverRisk Score (LRS) was calculated in 654 patients: 41% had minimal risk (LRS <6), 51% had low risk (LRS <10), 7% had medium risk (LRS 10–15), and 1% had high risk (LRS >15). Advanced fibrosis (LSM ≥8 kPa) was significantly associated with diabetes, FIB-4 >1.3/> 2, and LRS >6. Liver biopsy, performed in 90 patients (8%), revealed fibrosis F2–F4 in 55 patients, significantly correlated with age, diabetes, and LSM. Using the EASL-recommended 2-step approach: low fibrosis risk by FIB-4 was confirmed by LSM (<8 kPa) in 79% and by LRS (<10) in 96% of cases. Intermediate FIB-4 risk was confirmed by LSM (≥8 kPa) in 55% of cases and

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by median or high-risk LRS ($\geq$10) in 16%. High FIB-4 risk was confirmed by LSM ($\geq$8 kPa) in 77% of cases and by medium or high-risk LRS ($\geq$10) in 30%. Using the AASLD- 2-step approach using FIB-4 then LSM measurement, low fibrosis risk was observed in 81 % and confirmed by LRS ($<$10) in 96% of cases, intermediate risk in 29% of cases confirmed by LRS ($\geq$10) in 24 % and high risk of fibrosis in 12% of cases confirmed and by LRS ($\geq$10) in 26 % of cases. LRS $<$6 was observed in: 52%, 20%, and 4% of patients with low, intermediate, and high FIB-4 risks, respectively ($p<0.001$), in 47% of patients with LSM $<$10 kPa vs. 4% with LSM $\geq$10 kPa ($p<0.001$). **Conclusion:** Hepatic fibrosis was confirmed in one-third of patients consulting for MASLD in hepatology private practice. The EASL and AASLD 2-step approaches are effective in identifying liver fibrosis. In resource-limited settings, second-line fibrosis testing can be restricted to patients with intermediate FIB-4 scores. While FIB-4 and LRS show strong concordance in low-risk zones, their agreement is more limited in the intermediate or high-risk zones of the FIB-4.

Disclosures: Denis Ouzan: Nothing to Disclose, Guillaume Maeva: Nothing to Disclose, Penaranda Guillaume: Nothing to Disclose, guivarch mathieu: Nothing to Disclose, guillouche Pauline: Nothing to Disclose, Chagneau Corinne: Nothing to Disclose, delasalle Patrick: Nothing to Disclose, Boussoukaya Samy: Nothing to Disclose, Toulemonde Pierre: Nothing to Disclose, Lim Annie: Nothing to Disclose, Maeva Salimon: Nothing to Disclose, Hanslik Bertrand: Nothing to Disclose, Jacques Liautard: Nothing to Disclose, Dukan Patrick: Nothing to Disclose, Ingiliz Patrick: Nothing to Disclose, Ouizeman Dann Joseph: Nothing to Disclose, Bonny Corinne: Nothing to Disclose, Ancel David: Nothing to Disclose, Marion Audibert Anne Marie: Nothing to Disclose, Debono Emmanuel: Nothing to Disclose, Fontanges Thierry: Nothing to Disclose, Vallin Melanie: Nothing to Disclose, Guillaud Olivier: Nothing to Disclose

2121 | DIAGNOSTIC PERFORMANCE OF FIB-4, LIVERRISK SCORE, SAFE AND MAF-5 AS INDEX SCREENING TOOL FOR LIVER FIBROSIS AMONG COMMUNITY-DWELLING INDIVIDUALS WITH HIGH METABOLIC RISK

Laurens van Kleef[1] Jesse Pustjens[1] Maja Thiele[2] Maurice Michel[3] Adriaan Holleboom[4] Manuel Castro Cabezas[5] Maarten Tushuizen[6] Harry Janssen[1] Jörn Schattenberg[7] Sven Francque[8] Zobair Younossi[9] Aleksander Krag[10] Willem Pieter Brouwer[1],

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Background: Screening for advanced liver disease is indicated in $>$60% of the US population, of whom up to 30% may require liver stiffness measurement (LSM) due to an elevated FIB-4. We investigated the diagnostic performance of FIB-4, LiverRisk score and MAF-5 in individuals at high risk for liver fibrosis. **Methods:** Using NHANES 2017-2020 data, we analysed high-risk individuals defined as having (1) diabetes with obesity and/or elevated ALT (2) or obesity – either class III, class II with elevated ALT or class I with elevated ALT and $\geq$ 3 cardiometabolic risk factors. Individuals with excessive alcohol consumption were excluded. Analyses included assessment of the proportion having FIB-4 $\geq$1.3 (or $\geq$2.0 in individuals aged $\geq$65), LiverRisk score $\geq$ 6, SAFE $\geq$0 and MAF-5 $\geq$1 together with the diagnostic characteristics. Analyses were repeated among individuals with diabetes (regardless obesity or ALT). **Results:** We included 1,408 individuals (mean age 51, 51% male) of whom 52.7% had diabetes, 95.3% obesity and 44.7% ALT $\geq$ 30. The median LSM was 6.1 kPa [4.9-8.0] and 25.8% had LSM $\geq$8 kPa. Among this high-risk population, 14.2% had an increased FIB-4, 39.3% had a LiverRisk score $\geq$6, 70.7% a SAFE $\geq$0 and 73.3% had a MAF-5 $\geq$ 1, indicating high risk of fibrosis. This translated into a sensitivity (for LSM $\geq$8 kPa) of 20.7% for FIB-4, 50.4% for LiverRisk score, 79.6% for SAFE and 90.4% for MAF-5 (specificity: 88.0, 64.5, 32.4 and 32.6, respectively). FIB-4 had a PPV of 37.5% and NPV of 76.1%, the LiverRisk score had a PPV of 32.8% and NPV of 79.1%, the SAFE had a PPV of 29.1% and NPV of 82.0% and MAF-5 had a PPV of 31.5% and NPV of 90.8%. Comparable differences in test performance were observed with higher LSM thresholds or when 1,045 individuals with diabetes (irrespective of ALT and class obesity) were assessed. **Conclusion:** Among individuals at high risk, the FIB-4 had the lowest sensitivity for detecting increased LSM and seems not suitable as a primary screening test. In contrast, MAF-5 identified the largest proportion of individuals, yet achieved a similar positive predictive value (PPV) as the FIB-4 and a markedly higher negative predictive value (NPV). To avoid inefficient screening pathways, alternative tests other than FIB-4, with better diagnostic performance, should be considered.

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Table 1: Diagnostic accuracy of NITs as index test in high-risk populations

	Sensitivity	Specificity	PPV	NPV
FIB-4	20.7	88	37.5	76.1
LiverRisk score	50.4	64.5	32.8	79.1
SAFE	79.6	32.4	29.1	82
MAF-5	90.4	32.6	31.5	90.8

Increased FIB-4 was defined as ≥ 1.3 (or ≥ 2.0 among individuals aged ≥ 65 years), increased LiverRisk score as ≥ 6, increased SAFE as ≥ 0 and increased MAF-5 as ≥ 1.

Disclosures: Laurens van Kleef: Nothing to Disclose, Jesse Pustjens: Nothing to Disclose, Maja Thiele: Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, GSK: Advisor, GSK: Advisor, GSK: Advisor, Novo Nordisk: Speaking and Teaching, GSK: Grant/Research Support, Evido: Co-founder, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, GSK: Advisor, GSK: Advisor, GSK: Advisor, Novo Nordisk: Speaking and Teaching, GSK: Grant/Research Support, Evido: Co-founder, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, GSK: Advisor, GSK: Advisor, GSK: Advisor, Novo Nordisk: Speaking and Teaching, GSK: Grant/Research Support, Evido: Co-founder, Maurice Michel: Nothing to Disclose, Adriaan Holleboom: Nothing to Disclose, Manuel Castro Cabezas: Nothing to Disclose, Maarten Tushuizen: Nothing to Disclose, Harry Janssen: Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Academic Medical Education: Consultant, H.C. 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2122 | RISK STRATIFICATION IN STEATOTIC LIVER DISEASES: CHANGING THE REFERENCE TO DEVELOP NEW NON-INVASIVE TESTS WELL ADAPTED TO THE CONTEXT OF USE

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Background: The Liver Risk Score (LRS) is a simple blood fibrosis test that was recently developed using vibration-controlled transient elastography (VCTE) as the reference rather than liver biopsy. We aimed to evaluate this concept of changing the reference for non-invasive tests of liver fibrosis. **Methods:** Cohort #1 included 1,510 patients with steatotic liver disease (MASLD or alcohol) who underwent liver biopsy, VCTE, and blood sampling in four tertiary care centers. This cohort was divided into a derivation (one center, n = 739) and a validation set (three other centers, n = 771). Cohort #2 included 2,526 consecutive patients with steatotic liver disease who underwent VCTE and blood sampling in the Hepatology department of a tertiary care center, with further follow-up for liver-related events (LRE: cirrhosis complication or hepatocellular carcinoma). **Results:** In cohort #1 (biopsy cohort), the calibration plot showed that LRS underestimated VCTE result. As a consequence, 76% of F3 patients and 49% of F4 patients were classified as minimal/low risk by LRS (LRS < 10, PMID 37572680). We hypothesized this poor diagnostic accuracy was due to the use of VCTE as reference when deriving LRS. We therefore developed two tests based on simple biology in the derivation set: one using VCTE as reference and the other using biopsy (target: F3/4). Both tests showed similar accuracy for F3/4 in the validation set, with respective AUROC at 0.76 ± 0.03 and 0.78 ± 0.03 (p = 0.098). We then hypothesized that underestimation by LRS was due to its development in a set with low prevalence of fibrosis (mean VCTE result: 5.9 kPa [SD: 5.8], PMID 37572680). We therefore recalibrated LRS in the derivation set (prevalence F3/4: 38%), which improved sensitivity: only 29% of F3 patients and 16% of F4 patients were classified as minimal/low risk in the validation set. All these results suggested that non-invasive tests could be developed using VCTE as reference, provided the derivation set has a sufficient prevalence of at-risk patients and covers the full range of VCTE results to ensure the best calibration. This led to develop a new test using VCTE as reference in cohort #2, an inception cohort corresponding to the context of use of liver specialists. The new test included 8 variables (AST, ALT, gamma-GT, ALP, albumin, platelets, glycaemia, HDL-cholesterol). Calibration between the new test and VCTE result was very good. AUC(t) for predicting LRE at 3 years was 0.86 ± 0.02 with the new test, versus 0.76 ± 0.03 with LRS (p < 0.001) and 0.86 ± 0.03 with VCTE (p = 0.700). AUC(t) for 5-year prediction was 0.86 ± 0.02 with the new test, versus 0.77 ± 0.03 with LRS (p < 0.001) and 0.85 ± 0.03 with VCTE (p = 0.500). **Conclusion:** VCTE can be used as reference for developing new non-invasive tests, without decreasing diagnostic and prognostic accuracy compared to tests developed using liver biopsy. This approach enables tests to be derived in the correct context of use, reducing bias in the development process.

Disclosures: Jérôme Boursier: Novo Nordisk: Consultant, Lilly: Consultant, Madrigal: Advisor, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Sanofi: Speaking and Teaching, Echosens: Grant/Research Support, Gilead: Grant/Research Support, Intercept: Grant/Research Support, Inventiva: Grant/Research Support, Ipsen: Grant/Research Support, Siemens: Grant/Research Support, Diafir: Grant/Research Support, Adele Delamarre: Nothing to Disclose, Charlotte Costentin: Nothing to Disclose, Christophe Bureau: Nothing to Disclose, Jeanne Fichez: Nothing to Disclose, Isabelle Fouchard: Nothing to Disclose, Adrien Iannes: Nothing to Disclose, frederic oberti: Nothing to Disclose, Marine Roux: Nothing to Disclose

2123 | EVALUATION OF NUTRITIONAL ABNORMALITIES AND FRAILTY INDICES IN PATIENTS WITH ALD, MASLD AND METALD

Anastasia Xynogala[1] Arpit Amin[1] Caprice Pierre[1] Tumininu Ayorinde[2] Yash Shah[1] Guergana Panayotova[1] Lianhua Jin[1] Nedine Abdelhamid[1] Grace Lee-Riddle[1] Flavio Paterno[3] Zaid Tafesh[1] Mumtaz Niazi[1] Vivek Lingiah[3] Paul Gaglio[1] James Guarrera[1] Keri Lunsford[1], [1]Rutgers New Jersey Medical School, [2]Rutgers New Jersey Medical Scool, [3]Rutgers University - New Jersey Medical School

Background: There is little information in the literature about differences in nutritional abnormalities and frailty indices in patients with alcohol-associated liver disease (ALD), metabolic dysfunction-associated liver disease (MASLD) and the overlap of these two conditions (MetALD). **Methods:** This is a single-center, prospective study evaluating nutritional abnormalities and different frailty indices in adult patients (n = 179) with ALD, MASLD and MetALD presenting for liver transplant evaluation from 12/2023 to 05/2025. We analyzed the micronutrient and vitamin levels in our study population. Additionaly, we performed a variety of frailty indices including Katz index (KI), Short Physical Performance Battery (SPPB), Fried Frailty Index (FFI) and Liver Frailty Index (LFI) in these patients. Categorical variables were analyzed with chi-square test and continuous variables were analyzed with one-way analysis of variance test. **Results:** The median age of patients with ALD (49 years) was significantly lower

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compared to those with MASLD (65 years) and MetALD (61 years) ($p = 0.001$). The median MELD 3.0 score at initial evaluation was significantly higher in ALD patients (27) compared to both MetALD (17) and MASLD (17) patients ($p < 0.001$). Greater proportion of ALD patients (66%) were evaluated in the inpatient setting compared to MetALD (40%) and MASLD (43%) patients ($p = 0.003$). Copper levels were significantly lower in patients with ALD and MetALD compared to patients with MASLD ($p = 0.036$). Zinc levels were significantly lower in the ALD group compared to the MetALD group ($p = 0.012$). Vitamin C levels were significantly lower in both ALD and MASLD patients compared to MetALD patients ($p = 0.026$). Vitamin D deficiency was noted in all three groups with ALD patients having significantly lower vitamin D levels compared to MASLD and MetALD patients ($p = 0.011$). Vitamin B1 levels were significantly lower in the MASLD group compared to ALD group ($p = 0.001$). Vitamin B12 levels were significantly lower in the MetALD group compared to ALD group ($p = 0.01$). Frailty assessment using the FFI showed MASLD patients to be significantly frail compared to ALD and MetALD patients ($p = 0.002$). No significant difference in frailty was observed across the three groups when assessed using the KI, SPPB, or LFI. **Conclusion:** We demonstrate that there are distinct patterns of micronutrient and vitamin deficiencies in patients with ALD, MASLD and MetALD underscoring the importance of targeted nutritional screening and nutritional supplementation.

	Alcohol (n=113)	MASLD (n=52)	MetALD (n=14)	p-value
Cooper [median (range)] Normal reference range (80-158 ug/dL)	72 (18-180)	89 (29-155)	70 (9-179)	0.036
Selenium [median (range)] Normal reference range (93-198 ug/dL)	83 (44-956)	89 (46-163)	83 (49-155)	0.944
Zinc [median (range)] Normal reference range (44-115 ug/dL)	49 (23-108)	52 (27-132)	55 (27-140)	0.012
Iron [median (range)] Normal reference range (59-158 ng/ml)	74 (17-302)	67 (18-246)	69 (22-198)	0.857
Vitamin A [median (range)] Normal reference range (22-66.9 ug/dl)	8 (2.5-75.7)	9.6 (2.5-62.8)	10.2 (2.8-28.7)	0.659
Vitamin B1 [median(range)] Normal reference range (66.5-200 nmol/L)	127.6 (31.2-460.5)	93.9 (45.6-218.8)	123.6 (53.7-252.2)	0.001
Vitamin B6 [median(range)] Normal reference range (34.2-65.2 ug/dL)	5.9 (1.4-100.2)	7.25 (0.2-62.4)	6.25 (2.1-62.1)	0.645
Vitamin B9 [median(range)] Normal reference range (4.8-24.2 ng/mL)	13.2 (4.7-38.8)	11.6 (5.8-990)	13 (5-34.4)	0.381
Vitamin B12 [median(range)] Normal reference range (232-1245 pg/mL)	1720 (438-2000)	1290 (387-2000)	928 (429-2000)	0.01
Vitamin C [median(range)] Normal reference range (0.4-2 mg/dL)	0.5 (0-2.3)	0.4 (0-1.6)	0.8 (0.4-2.8)	0.026
Vitamin D [median(range)] Normal reference range (30-100 mg/dL)	12.3 (3.5-98.7)	18.5 (3.9-55.6)	14.8 (7-54)	0.011
Vitamin E [median(range)] Normal reference range (9-29)	5.8 (1.5-30.3)	7.45 (1.2-17.8)	7.1 (1.9-12.1)	0.730
Vitamin K [median(range)] Normal reference range (0.1-2.2)	1.4 (10-71.5)	0.6 (0-40)	0.5 (0.25-17.4)	0.486

Disclosures: Anastasia Xynogala: Nothing to Disclose, Arpit Amin: Nothing to Disclose, Caprice Pierre: Nothing to Disclose, Tumininu Ayorinde: Nothing to Disclose, Yash Shah: Nothing to Disclose, Guergana Panayotova: Nothing to Disclose, Lianhua Jin: Nothing to Disclose, Nedine Abdelhamid: Nothing to Disclose, Grace Lee-Riddle: Nothing to Disclose, Flavio Paterno: Nothing to Disclose, Zaid Tafesh: Nothing to Disclose, Mumtaz Niazi: Nothing to Disclose, Vivek Lingiah: Nothing to Disclose, Paul Gaglio: Nothing to Disclose, Nothing to Disclose, James Guarrera: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Keri Lunsford: ROM Tech: Stock – privately held company, Johnson and Johnson: Stock - publicly traded company, Adaptive biotechnology: Stock - publicly traded company, Incyte: Stock - publicly traded company, Tandem Diabetes: Stock - publicly traded company

2124 | NO LONGER MISSING HALF: CONCURRENT FIB-4&GE;1.3 AND ELF &GE;9.4 ENHANCES FIBROTIC MASH DETECTION - EVIDENCE FROM A PROSPECTIVE STUDY

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Background: Societal guidelines recommend Enhanced Liver Fibrosis (ELF) score as second-line test for metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis in patients with FIB-4 ≥ 1.3, using a rule-out cutoff of < 7.7. However, this cutoff may be too low, and the performance of this algorithm is uncertain. We aimed to: 1) identify optimal ELF cutoffs for fibrotic MASH using biopsy and elastography as reference, and 2) assess guideline-recommended algorithm performance using ELF 7.7 vs. an optimized cutoff. **Methods:** In this prospective study, patients with/at risk for MASLD at liver or obesity clinics underwent FIB-4, ELF testing, liver stiffness measurement (LSM) by magnetic resonance elastography (MRE), and liver biopsy within one month. Histology was evaluated by two blinded pathologists. Fibrotic MASH was defined as fibrosis stage ≥ 2 by histology or LSM ≥ 3.1 kPa by MRE. We evaluated several diagnostic pathways using different ELF cutoffs applied sequentially (after FIB-4 ≥ 1.3) or concurrently (further evaluation needed if either test exceeds the cutoff). Pathway performance was assessed using area under the receiver operating curve (AUROC), sensitivity and specificity. **Results:** Among 237 participants, 186 had complete data. Median age was 51 (range 19–74), 69% were women, median BMI 40 (range 22–70) kg/m², and 36% had type

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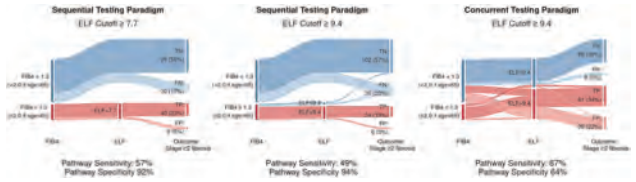
2 diabetes. Fibrotic MASH was present in 71 (38%), with median ELF 10.1 (IQR: 9.5–10.7). ELF alone yielded AUROC 0.77 (95% CI: 0.70–0.84); the optimal Youden cutoff was 9.4 (80% sensitivity, 65% specificity). Lower ELF cutoffs of 8.7 and 7.7 had sensitivity of ≥ 90% and 100%, respectively, with low specificity of 34% and 4%, respectively. FIB-4 ≥ 1.3 had 57% sensitivity and 92% specificity, missing 43% of fibrotic MASH, limiting sequential testing utility of a second-line test. A concurrent approach, applying both FIB-4 and ELF as first-line tests with follow-up if either is elevated, improved performance. Among candidate ELF rule-out thresholds (7.7, 8.7, 9.0, 9.4, 9.8), 9.4 offered the best balance (87% sensitivity, 64% specificity) (Figure). **Conclusion:** A first-line test should have high sensitivity (ideally > 80%) to minimize the false negative results, and FIB-4 lacks adequate sensitivity, missing nearly half of fibrotic MASH cases. A concurrent first-line strategy using FIB-4 ≥ 1.3 and ELF ≥ 9.4 improves fibrotic MASH detection and balances false positives and negatives. This approach may significantly enhance the performance of noninvasive tests pathway.



Disclosures: Alina Allen: Novo Nordisk: Grant/Research Support, Novo Nordisk: Advisor, Target Pharma: Grant/Research Support, Pfizer: Grant/Research Support, Boehringer Ingelheim: Advisor, Madrigal: Advisor, GSK: Advisor, Oncoustics: Grant/Research Support, Escopics: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Madrigal: Grant/Research Support, Siemens: Grant/Research Support, Olivia Bobek: Nothing to Disclose, Rachel Canning: Nothing to Disclose, Maysa Eslami: Nothing to Disclose, Joanne Benson: Nothing to Disclose, Fang-Shu Ou: Nothing to Disclose

2125 | THE NEW ASSAY TYPE IV COLLAGEN 7S (CLEIA) IS A USEFUL TEST TO IDENTIFY PROGRESSIVE FIBROSIS IN CHRONIC LIVER DISEASE: A STUDY BASED ON MAGNETIC RESONANCE ELASTOGRAPHY

Miwa Kawanaka[1] Masahiko Sue[1] Takuya Adachi[1] Hideki Onishi[1] YASUTO TAKEUCHI[1] Akinobu Takaki[1] Motoyuki Otsuka[2], [1]Faculty of Medicine, Dentistry and Phaemaceutical Sciences,Okayama University, [2]Okayama University

Background: Liver fibrosis is a critical prognostic factor for chronic liver disease that influences morbidity and mortality. While imaging-based methods such as magnetic resonance elastography (MRE) offer precise fibrosis staging, they are not widely available.Noninvasive serum biomarkers, such as the fibrosis-4 (FIB-4) index, M2BPGi, and hyaluronic acid, are widely used but have limitations, particularly in low inflammatory states or elderly patients. Type IV collagen 7S (T4C7S), a basement membrane component, reflects fibrotic extracellular matrix remodeling. With the advent of a new chemiluminescent enzyme immunoassay (CLEIA) method, this marker now allows for more sensitive quantification. We aimed to evaluate the diagnostic performance of CLEIA-based T4C7S against MRE as the reference standard and to explore a novel two-step stratification model using T4C7S to refine risk categorization within the intermediate FIB-4index. **Methods:** A total of 307 patients with chronic liver disease (235 with MASLD) were prospectively enrolled and underwent same-day MRE and biomarker measurement. Liver stiffness was categorized as F0–F4 based on kPa thresholds. Serum levels of T4C7S, FIB-4 index, M2BPGi, and hyaluronic acid were analyzed across fibrosis stages. The primary outcome was AUROC for detecting ≥ F2 fibrosis, with sensitivity, specificity, PPV, and NPV calculated using the Youden Index. Subgroup analyses were performed based on ALT levels (≤ 30 vs > 30 U/L) and age (≤ 60 vs > 60 years). A two-step diagnostic algorithm combining FIB-4 (cutoff 1.3–2.66) with T4C7S (cutoff ≥ 3.8 ng/mL) was tested to improve triage efficiency. **Results:** T4C7S showed the highest correlation with MRE ($\rho = 0.591$, $p < 0.001$), outperforming FIB-4 ($\rho = 0.532$), M2BPGi ($\rho = 0.503$), and hyaluronic acid ($\rho = 0.509$). For diagnosing ≥ F2 fibrosis, T4C7S achieved an AUROC of 0.795, versus 0.759 for FIB-4 and 0.745 for M2BPGi. Its diagnostic performance remained consistent across ALT and age subgroups, indicating greater robustness under low-inflammation and aging-related confounding. In the FIB-4 intermediate range (1.3–2.66), applying the T4C7S cutoff of ≥ 3.8 ng/mL improved specificity (from 55% to 78%) and PPV (from 54% to 67%), while only minimally reducing NPV (from 82% to 78%). This approach also reduced the number of unnecessary specialist referrals by 20%, highlighting its cost-effective potential. Among intermediate FIB-4 cases, 71% of ≥ F2 fibrosis cases were correctly reclassified using T4C7S. **Conclusion:** CLEIA-based type IV collagen 7S is a superior noninvasive biomarker for liver fibrosis, with strong correlation to MRE-derived stiffness. Its diagnostic robustness across ALT and age subgroups makes it especially valuable in populations where traditional markers underperform. Incorporating T4C7S into a two-step FIB-4-based model enhances diagnostic precision and reduces unnecessary referrals.

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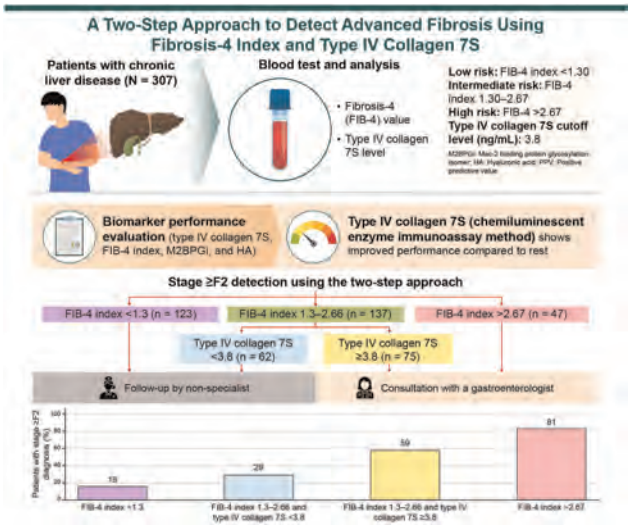

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2126 | DECREASE IN LIVER STIFFNESS IS NOT ASSOCIATED WITH REDUCED CARDIOVASCULAR EVENTS IN PATIENTS WITH DIABETES MELLITUS: A PROSPECTIVE STUDY

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Background: Patients with diabetes mellitus (DM) are at an increased risk of developing cardiovascular disease (CVD). Hepatic fibrosis is common among patients with DM and is associated with liver-related events. However, its impact on CVD risk remains unclear. This study aimed to prospectively assess the association between hepatic fibrosis and CVD risk in patients with DM. **Methods:** A total of 323 patients with DM were prospectively enrolled from January 2022, excluding those with viral hepatitis, overt cirrhosis, or cancer. The following parameters and data were assessed: body weight (BW), body mass index (BMI), waist circumference (WC), laboratory data, presence of hypertension (HTN), dyslipidemia, alcohol consumption, smoking status, liver steatosis measured by the controlled attenuation parameter (CAP) using FibroScan®, and CVD events. Hepatic fibrosis was quantified by liver stiffness measurement (LSM) using FibroScan®, assessed at baseline and after two years. CVD was defined as ischemic heart disease or ischemic/hemorrhagic stroke. **Results:** A total of 277 patients completed the 2-year follow-up and underwent repeat LSM. The mean age was 57 ± 12 years, and 56.3% were male. The baseline mean LSM was 6.9 ± 3.7 kPa. A history of CVD was present in 86 (31%) patients, while 6 (3.2%) developed new CVD events during follow-up. LSM decreased in 157 patients (d-LSM group) and increased in 120 patients (i-LSM group). The mean LSM change was -1.7 ± 2 kPa in the d-LSM group and +1.5 ± 1.3 kPa in the i-LSM group. The d-LSM group had significantly higher baseline ALT (39 ± 30 vs. 32 ± 21 IU/L, $p = 0.018$), CAP (281 ± 51 vs. 264 ± 49 dB/m, $p = 0.005$), and LSM (7.9 ± 4.2 vs. 5.7 ± 2.3 kPa, $p < 0.001$) than the i-LSM group. Alcohol consumption was more prevalent in the i-LSM group (30.8% vs. 17.8%., $p = 0.011$). There were no significant differences between the two groups in mean age, male proportion, BW, BMI, WC, HTN, dyslipidemia, laboratory results excluding ALT, or smoking status. When stratified by LSM change, the incidence of new CVD was 2% (1/49) in patients with a decrease LSM of ≤-2 kPa, 2% (4/198) in those with changes between -2 and +2 kPa, and 3.3% (1/30) in those with an increase of ≥+2 kPa ($p = 0.897$). **Conclusion:** Hepatic fibrosis, as measured by LSM, can change dynamically in patients with DM. A decrease in LSM was not associated with a reduced risk of CVD. Therefore, LSM monitoring may have limited value in assessing CVD risk in this population.

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2127 | ASSOCIATION BETWEEN NON-HIGH-DENSITY LIPOPROTEIN CHOLESTEROL TO HIGH-DENSITY LIPOPROTEIN CHOLESTEROL RATIO AND RISK OF DEVELOPING MASLD AND ITS SUBGROUPS

ge yidi[1] Wen Xie[1], [1]Beijing Ditan Hospital, Capital Medical University,

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), is a relatively common chronic liver disease. This study aimed to explore the relationship between the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and the risk of developing MASLD, and to explore the differences between the pure MASLD and

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metbolic and alcohol related/associated liver disease (MetALD) subgroups. We also compared other predictors, such as albumin-to-alkaline phosphatase ratio (AAPR), albumin-to-glutamyl transpeptidase ratio (AGTR), atherogenic index of plasma (AIP) and uric acid to high-density lipoprotein cholesterol ratio (UHR). **Methods:** We included 1,648 participants from the National Health and Nutrition Examination Survey in 2019- 2020. Logistic regression evaluated the relationship between NHHR and the risk of MASLD. The dose-response association between NHHR and MASLD was determined using restricted cubic splines, and the predictive power of NHHR in comparison to traditional lipid markers for MASLD was evaluated using receiver operating characteristic (ROC) curves. **Results:** We found that the NHHR was positively associated with the risk of MASLD [OR:14.11, 95%CI:5.37, 37.07]. We further discover the NHHR was positively associated with the risk of pure MASLD and MetALD, the results respectively are [OR:5.41, 95%CI: 2.91, 10.04], [OR: 5.05, 95%CI: 1.06, 24.07]. The RCS results showed that there was a linear relationship between NHHR and MASLD (P **Conclusion:** According to our research, NHHR may be a helpful biomarker for identifying individuals at risk of MASLD. Clinical risk assessment and early intervention methodologies could get advantages from it. Additional longterm studies are required to corroborate these findings and explore the mechanisms between NHHR and MASLD.

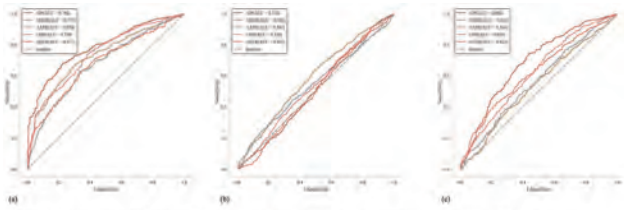

Figure 1 The ROC curve for internal validation between different predictors with the risk of MASLD. (a) The participants were diagnosis of MASLD. (b) The participants were diagnosis of pure MASLD. (c) The participants were diagnosis of MetALD. AAPR, albumin-to-alkaline phosphatase ratio; AGTR, albumin-to-glutamyl transpeptidase ratio; AIP, atherogenic index of plasma; NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; UHR, uric acid to high-density lipoprotein cholesterol ratio.

Disclosures: ge yidi: Nothing to Disclose, Wen Xie: Nothing to Disclose

2128 | DEFINING CUT-OFFS OF ANTHROPOMETRIC AND METABOLIC MARKERS IN MEXICO FOR EARLY DETECTION AND PREVENTION OF CHRONIC METABOLIC DISEASES

Leonardo Leal-Mercado[1] Sonia Roman[1] Arturo Panduro[1], [1]UNIVERSIDAD DE GUADALAJARA

Background: The main mortality causes in Mexico include diabetes, cardiovascular, liver, and kidney diseases, which are often underdiagnosed and detected at advanced stages. Current clinical cutoffs derived from European and North American populations underestimate risk in Mexicans, who exhibit distinct anthropometric and metabolic traits. This study aimed to identify the onset of metabolic risk factors (MRFs) and define anthropometric and metabolic cutoffs for Mexico. **Methods:** We conducted a cross-sectional analysis on 1,012 youngsters and adults from Mexico. We identified overweight, obesity, and metabolic risk factors (MRF) using standard clinical measures: Body mass index (BMI) ($\geq$25 kg/m²), triglycerides ($\geq$150 mg/dL), total cholesterol ($\geq$200 mg/dL), HOMA-IR ($\geq$2.5), glucose ($\geq$100 mg/dL), and liver enzymes (ALT and AST $\geq$40 U/L). We assessed the frequency of overweight and obesity and the presence of at least 1 MRF across BMI and age groups. Receiver operating characteristic (ROC) curve analysis helped us find the age and BMI when metabolic risk factors (MRF) start to appear and looked at how well different body measurements (waist circumference, waist-to-hip ratio, and waist-to-height ratio) and blood markers (triglycerides, cholesterol, glucose, HOMA-IR, ALT, and AST) perform. Finally, using the ROC curve results, we compared how well the standard thresholds work against the new thresholds to see if they improve our ability to identify people at risk. **Results:** We found a high prevalence (71.17%) of individuals with $\geq$1 MRF, and 53.31% of normal-weight subjects (BMI $<$25 kg/m²) had $\geq$1 MRF. MRFs and anthropometric markers were significantly higher in overweight/obese individuals ($<$0.05). Among youngsters (15–19 years), 32% were overweight/obese, and 40% had $\geq$1 MRFs. ROC analysis showed early MRF onset at 22.5 years, with insulin resistance as the first abnormality. MRFs emerged at a BMI of 23.4 kg/m², with hypercholesterolemia appearing earliest. Based on Youden index results, we propose lower cut-offs: BMI $\geq$23.4 kg/m², triglycerides $\geq$109.5 mg/dL, cholesterol $\geq$174.5 mg/dL, glucose $\geq$87 mg/dL, HOMA-IR $\geq$2.4, ALT $\geq$21.5 U/L, and AST $\geq$22 U/L. These changes helped find metabolic risk factors 28.8% more often, especially for liver enzymes (high AST increased by 32.4%, high ALT by 28.6%), glucose by 24.7%, and total cholesterol by 23.4%. **Conclusion:** These results underscore that current clinical guidelines underestimate metabolic risk within the Mexican population. Adopting these newly identified anthropometric and metabolic cutoffs can facilitate early detection, reducing the prevalence and progression of chronic metabolic diseases.
Disclosures: Leonardo Leal-Mercado: Nothing to Disclose, Sonia Roman: Nothing to Disclose, Arturo Panduro: Nothing to Disclose

2129 | A COMPARISON OF NON-INVASIVE DIAGNOSTIC METHODS: USED TO IDENTIFY HIGH-RISK PATIENTS ELIGIBLE FOR RESMETIROM THERAPY: A BIOPSY PROVEN STUDY FROM T&UUML; RKIYE

Hatice Karatas[1] Melike Baskan[1] Selin Karaman[1] Eda Kaya[2] Caglayan Keklikkiran[3] Yusuf Yilmaz[4], [1]School of Medicine, Recep Tayyip Erdogan University, Rize,

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Background: An algorithm incorporating non-invasive methods was proposed to guide the prescription of resmetirom, a newly introduced therapeutic option for metabolic dysfunction-associated steatotic liver disease (MASLD). The widespread use of these non-invasive diagnostic tools may lead to overprescription, potentially imposing an added financial burden on the healthcare system. In this study, we aim to analyze the Turkish NAFLD Biobank, which includes biopsy-confirmed MASLD cases, compare the performance of different diagnostic algorithms, and assess the clinical implications of resmetirom prescribing based on these proposed strategies. **Methods:** After excluding patients with missing FibroScan data, a total of 242 patients from the Turkish NAFLD Biobank database were included in the study. Non-invasive diagnostic criteria were applied using a three-step algorithm. In the first step, patients with a FIB-4 score <1.3 and a NAFLD Fibrosis Score (NFS) <-1.455 were excluded from further evaluation. In the second step, AST levels >17 U/L for female patients and >20 U/L for male patients, along with a controlled attenuation parameter (CAP) value ≥ 280 dB/m, were required. In the third step, patients were considered eligible for treatment if their liver stiffness measurement (LSM) was between 10 and 19.9 kPa or if their FAST score was ≥ 0.67. The patients with signs of cirrhosis or platelet count $\geq 140{,}000/\mu L$ were excluded. Finally, the concordance of this algorithm with histological diagnosis was analyzed. **Results:** A total of 139 patients (57.4%) had a FIB-4 score <1.3, and 103 patients (42.9%) with NFS $<$ -1.455 did not proceed to the next step of the algorithm. Among these, 56 patients (40.3%) and 37 patients (35.9%), respectively, actually met the MASH + F2–F3 fibrosis criteria. When the LSM-based algorithm was applied following the FIB-4 screening, 42 patients (17.4%) met the eligibility criteria. When the FAST algorithm was applied instead, 33 patients (13.6%) qualified. The LSM algorithm correctly identified 28 patients (23.3%) as eligible for treatment, while 14 patients (11.5%) would have been incorrectly prescribed the drug. In the FAST algorithm, these figures were 21 patients (17.5%) correctly identified and 12 patients (9.8%) incorrectly identified. Similar results were observed with the NFS-based algorithm. Both algorithms demonstrated poor concordance with the histological gold standard (Kappa values: 0.119 and 0.077 for FIB-4; 0.080 and 0.080 for NFS). Although the overall concordance slightly improved when FIB-4 or NFS pre-screening was omitted, agreement with histology remained weak (Kappa values: 0.130 for the LSM algorithm and 0.122 for the FAST algorithm). **Conclusion:** These findings suggest that non-invasive diagnostic algorithms may not be sufficiently reliable and prescribing resmetirom based on liver biopsy may represent a more cost-effective approach from a healthcare perspective.

Disclosures: Hatice Karatas: Nothing to Disclose, Melike Baskan: Nothing to Disclose, Selin Karaman: Nothing to Disclose, Eda Kaya: Nothing to Disclose, Caglayan Keklikkiran: Nothing to Disclose, Yusuf Yilmaz: Nothing to Disclose

2130 | TO VERIFY THE DIAGNOSTIC EFFICACY OF FAST SCORE FOR HIGH-RISK MASH IN PATIENTS WITH METABOLIC-RELATED FATTY LIVER DISEASE BASED ON LIVER BIOPSY

shicheng Ren[1] WU Xu[2] LI Xue[2] Dou Jing[3] Zhang Rong[3] LIU Ruonan[2] SUBINUR ·Kurban[2] Guo Feng[3] Wang Xiaozhong[3], [1]Affiliated Hospital of Traditional Chinese Medicine, Xinjian, [2]The Fourth Clinical Medical College of Xinjiang Medical University, [3]Traditional Chinese Medical Hospital Affiliated to Xinjiang Medical University

Background: The prevalence of MAFLD is increasing year by year in the world. MASH and liver fibrosis are the intermediate links of disease progression and are closely related to the long-term survival rate of patients. Noninvasive diagnostic methods have great potential in the diagnosis of MASH patients. The FAST score was used to assess the severity of MAFLD. This study will verify the diagnostic efficacy of FAST score for high-risk MASH in MAFLD patients based on liver biopsy, and analyze the clinical characteristics of high-risk MASH, in order to provide a basis for the early diagnosis of high-risk MASH. **Methods:** Patients who underwent liver biopsy and were diagnosed with NAFLD or MAFLD in the Department of Hepatology, the Fourth Clinical Medical College of Xinjiang Medical University from October 2018 to September 2024 were selected. The area under the receiver operating characteristic curve (AUROC) was used to analyze the diagnostic efficacy of FAST score for high-risk MASH in MAFLD patients. **Results:** Compared with the non-high-risk MASH group, the age and the proportion of drinking history in the high-risk MASH group were higher ($P < 0.05$), the levels of PLT, Alb, CHE, TG, TC and LDL-C were lower ($P < 0.05$), and the levels of PT, PT-INR and LSM were higher ($P < 0.05$). The AUROC value of FAST score in the diagnosis of high-risk MASH was 0.708 (95 % CI : 0.610-0.806). The AUROC values of FAST score in the diagnosis of high-risk MASH in patients with mild steatosis and non-obese patients were 0.762 (95 % CI : 0.655-0.868) and 0.731 (95 % CI : 0.609-0.854), respectively. **Conclusion:** FAST score has good diagnostic efficacy for high-risk MASH, and has higher

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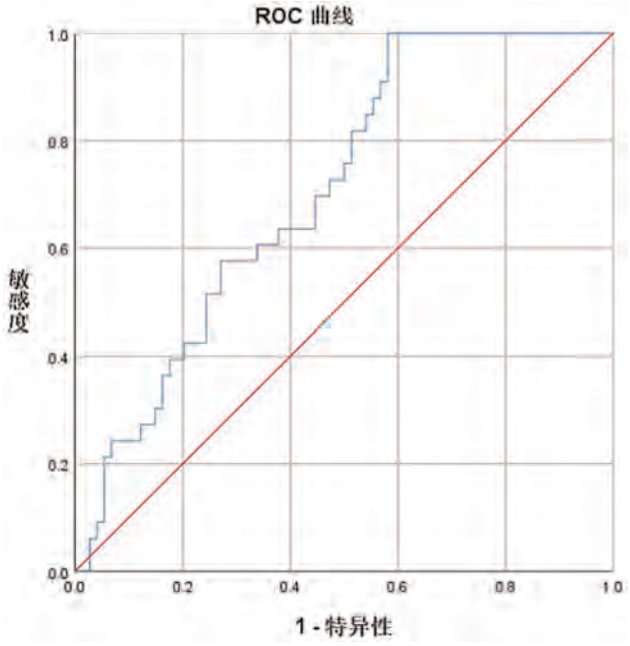
diagnostic efficacy for mild steatosis and non-obese patients, which is helpful for the prediction of high-risk MASH in MAFLD patients.



Disclosures: shicheng Ren: Nothing to Disclose, WU Xu: Nothing to Disclose, LI Xue: Nothing to Disclose, Dou Jing: Nothing to Disclose, Zhang Rong: Nothing to Disclose, LIU Ruonan: Nothing to Disclose, SUBINUR ·Kurban: Nothing to Disclose, Guo Feng: Nothing to Disclose, Wang Xiaozhong: Nothing to Disclose

2131 | AI-ASSISTED DIGITAL PATHOLOGY UNVEILS PATIENT HETEROGENEITY IN THE ANTIFIBROTIC RESPONSE FOLLOWING BARIATRIC SURGERY

Desiree Abdurrachim[1] Clare Yong[2] Sahana Abdul Rahim[1] Raluca Pais[3] Judith Aron-Wisnewsky[3] Frederic Charlotte[3] Serene Lek[4] Dean Tai[4] Elaine Chng[4] Gideon Ho[4] Richard Baumgartner[5] Chih-Liang Chin[6] Leila Kara[3] Saswata Talukdar[6] Asad Abu Bakar Ali[1] Vlad Ratziu[3], [1]Quantitative Biosciences, MSD, Singapore, [2]Chief Technology Office, MSD, Singapore, [3]Sorbonne Université, ICAN institute, Hôpital Pitié-Salpêtrière, Paris, France, [4]HistoIndex Pte. Ltd., Singapore, [5]Biostatistics and Research Decision Sciences, Merck & Co., Inc., Rahway, NJ, USA, [6]Cardiometabolic Diseases, Merck & Co., Inc., South San Francisco, CA, USA

Background: We compared AI-assisted digital pathology (DP) with conventional pathology to assess features and dynamics of fibrosis regression in patients undergoing bariatric surgery for morbid obesity. **Methods:** Unstained paired liver biopsies (pre and >1-year post-bariatric surgery) from 41 patients were staged by NASH-CRN: 17 early (F0-F2), 24 advanced (F3-F4). SHG/TPEF images (Histoindex®) extracted 184 zone-specific fibrosis features and the corresponding qFibrosis stage (qFst) and qFibrosis continuous score (qFcs). K-means clustering evaluated changes in fibrosis features post-bariatric surgery. Fibrosis response (R, defined as >1 stage F or qFst reduction or >2SD qFcs reduction), no change (NC) or progression was noted. **Results:** Fibrosis response was more frequently seen by DP (qFst: 71%, qFcs: 80.5%) than by NASH-CRN (44%) and with a higher sensitivity: 10 NC by NASH-CRN reclassified as R by DP. DP showed a time-dependent fibrosis reduction, 24% R at 3-6 years post-bariatric surgery vs 41.5% at >6 years, not visible by NASH-CRN (22% and 22%, respectively). A clear trend towards less fibrosis reduction in F3-F4 than F0-F2 patients was shown by qFst (58% vs 88%) and qFcs (71% vs 94%), but not by NASH-CRN (41% vs 46%). There was significant heterogeneity in the pattern of intralobular fibrosis changes following bariatric surgery: a strong reduction in portal and periportal fibrosis features and a reduction in chicken-wire fibrosis coexisted with no change or a slight increase in central and pericentral fibrosis parameters. Unsupervised clustering revealed four clusters (C) based on changes in zone-specific fibrosis features (Figure). Baseline characteristics (including fibrosis severity) were similar between clusters, as were changes post-bariatric surgery in BMI or metabolic parameters. However, the proportion of response was different: clusters C1 (N = 7) and C2 (N = 5) had 1 R each, while C3 (N = 18) had 10 R and C4 (N = 11) had 6 R. There was significant individual heterogeneity in the antifibrotic response post-bariatric surgery across clusters with more pronounced changes in C3-C4 than in C1-C2 and a higher rate of fibrosis regression (-0.21 qFst/yr and -0.16 qFcs/yr vs -0.03 to 0.02 qFst/yr and -0.04 to 0.08 qFcs/yr, respectively). **Conclusion:** AI-assisted DP characterizes the extent of antifibrotic effect with higher resolution and sensitivity than traditional pathology. It also unveils significant heterogeneity in the antifibrotic response at the tissue and the individual level. These findings should help better understand the potency of antifibrotic interventions and individual response.

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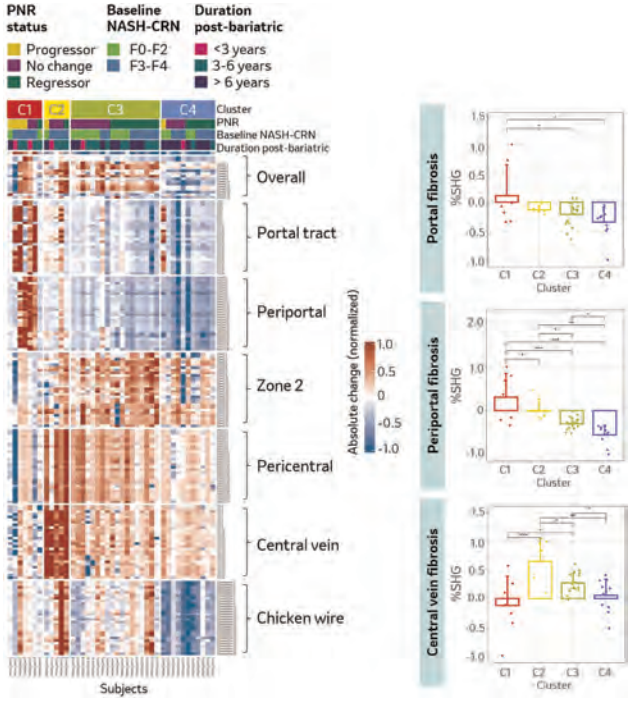

Disclosures: Desiree Abdurrachim: MSD: stockholder, MSD: Employee, Clare Yong: Nothing to Disclose, Sahana Abdul Rahim: Nothing to Disclose, Raluca Pais: Nothing to Disclose, Judith Aron-Wisnewsky: Nothing to Disclose, Frederic Charlotte: Nothing to Disclose, Serene Lek: Nothing to Disclose, Dean Tai: Nothing to Disclose, Elaine Chng: Nothing to Disclose, Gideon Ho: Nothing to Disclose, Richard Baumgartner: Nothing to Disclose, Chih-Liang Chin: Nothing to Disclose, Leila Kara: Nothing to Disclose, Saswata Talukdar: Nothing to Disclose, Asad Abu Bakar Ali: Nothing to Disclose, Vlad Ratziu: Novo-Nordisk: Consultant, Boehringer-Ingelheim: Consultant, Madrigal: Consultant, Akero: Consultant, 89Bio: Consultant, Sagimet: Consultant

2132 | COMPARING NON-INVASIVE FIBROSIS SCORES TO TRANSIENT ELASTOGRAPHY MEASUREMENTS ACROSS THE SPECTRUM OF STEATOTIC LIVER DISEASE: A US NHANES 2017–2020 STUDY

Alex Chang[1] Joao Filipe Monteiro[1] Neha Wadhavkar[1] Adam Burton[1] Kittichai Promrat[1], [1]Brown University School of Medicine

Background: Non-invasive fibrosis scores (NIFS) and transient elastography (TE) are important tools for screening patients for steatotic liver disease. While validated in patients with metabolic-associated steatotic liver disease, neither tool has been well-studied in patients with metabolic risk factors and concurrent alcohol consumption. The current study compares how well NIFS agree with TE measurements across the spectrum of steatotic liver disease in a national dataset. **Methods:** The NHANES 2017–2020 dataset, comprising 9,693 adult participants, was utilized for the current study. Clinically significant fibrosis (CSF) is defined as a liver-stiffness measurement (LSM) $\geq$ 8 kPa, and advanced fibrosis (AF) as LSM $\geq$ 12 kPa. Non-invasive fibrosis scores assessed in the study includes the APRI, BARD, FIB-4, and NAFLD fibrosis score (NFS). A total of 7,100 participants without a complete TE examination, with past history of viral or autoimmune hepatitis, or without evidence of steatosis on TE (CAP $<$ 285) were excluded. The final analytic sample consisted of 2,593 patients with steatotic liver disease (SLD)–MASLD, MetALD, or ALD. The determination of MASLD, MetALD, or ALD was based on weekly alcohol consumption cutoffs in accordance to the AASLD guidelines. The concordance of each NIF to TE was evaluated using receiver operating characteristic (ROC) curves, including calculations of the area under curve. All analyses were conducted using SAS version 9.4. **Results:** Using the 2017-2020 NHANES cohort, 2,431 participants met MASLD criteria, 104 met MetALD criteria and 58 met ALD criteria. CSF was detected in 19.1% of MASLD, 17.3% of MetALD and 19.0 % of ALD, while AF affected 6.7%, 5.8% and 6.9%, respectively. MASLD subjects were older (52.0 $\pm$ 16.6 years) with higher BMI (BMI 34.5 $\pm$ 7.5 kg/m^2) than those with MetALD (32.9 $\pm$ 7.7 kg/m^2) or ALD (32.0 $\pm$ 6.1 kg/m^2). Diabetes (53%) and hypertension (43%) were common in MASLD, whereas ALD participants were predominantly younger males (89%) with lower metabolic burden. NIFs were not significantly different at predicting clinically significant fibrosis (range of AUC from 0.549 - 0.742) on TE across the entire spectrum of SLD and were, in fact, better at predicting advanced fibrosis (range of AUC 0.836 - 0.945) on TE in patients with ALD compared to MetALD or MASLD (Figure 1). NFS was significantly better at predicting CSF and AF on TE than the BARD score for MASLD and MetALD patients, but not in ALD patients. **Conclusion:** While NIFS and TE have only been validated for patients with MASLD, the current study shows that concordance of NIFS and TE does not change significantly across the spectrum of SLD, incldiuing MetALD and ALD. NFS has closer concordance to TE measurements than the BARD score in SLD patients with cardiometabolic risk factors. Future studies should look to compare NIFS and TE measurements to liver biopsy results to validate NIFS and TE in the MetALD and ALD populations.

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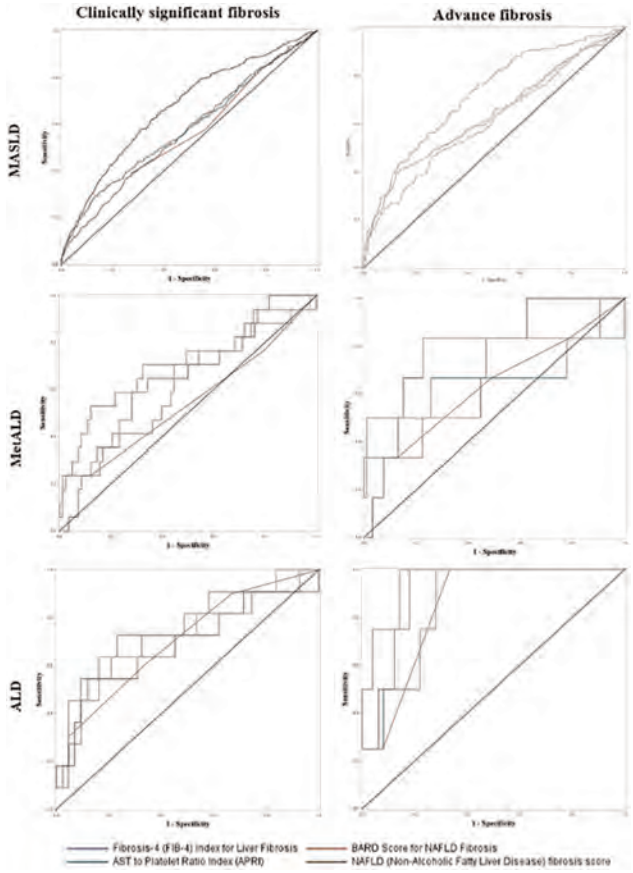


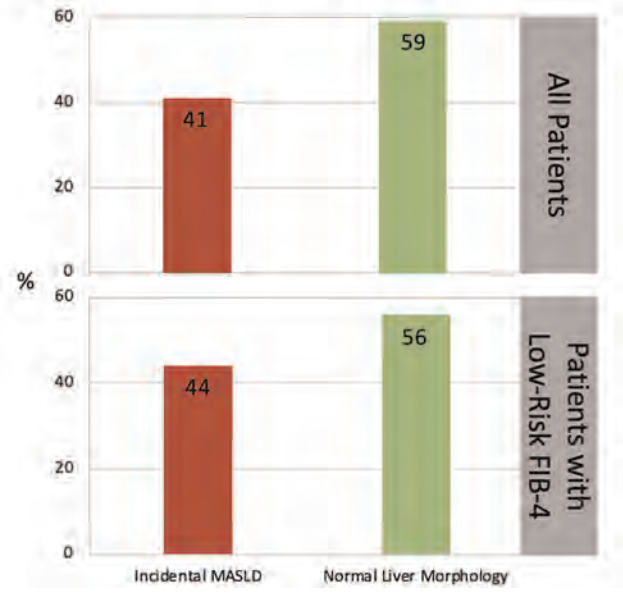
Disclosures: Alex Chang: Nothing to Disclose, Joao Filipe Monteiro: Nothing to Disclose, Neha Wadhavkar: Nothing to Disclose, Adam Burton: Nothing to Disclose, Kittichai Promrat: Nothing to Disclose

2133 | LIMITATIONS OF FIB-4 SCREENING FOR MASLD IN PATIENTS WITH OBESITY

Sanjna Shelukar[1] Ananya Venkatesh[1] Breanne McDermott[1] Julietta Gervase[1] Maria Winte[1] Rebecca Loh[1] Dina Halegoua-De Marzio[1], [1]Thomas Jefferson University Hospital

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease. Comorbidities such as obesity, hypertension, hyperlipidemia, and diabetes place patients at higher risk for developing MASLD. Early diagnosis is critical to prevent progression to advanced fibrosis. While the Fibrosis-4 (FIB-4) index is commonly used to assess fibrosis risk, there is currently no validated screening tool for MASLD, potentially contributing to underdiagnosis. We aimed to assess the prevalence of incidentally identified MASLD in patients with obesity who underwent abdominal imaging for non-screening purposes and would not have received further evaluation for MASLD otherwise. **Methods:** We conducted a retrospective chart review of patients with obesity at an urban resident-run primary care clinic. FIB-4 scores were calculated using available laboratory data, and patients were stratified into risk categories: low (< 1.30), indeterminate (1.30-2.67), and high (> 2.67). Abdominal imaging, when available for non-screening purposes (abdominal pain, kidney stones, trauma, etc.), was reviewed for findings consistent with MASLD. Relevant terminology included hepatic steatosis, hepatomegaly, fatty infiltration, increased echogenicity, and nodularity. **Results:** 172 patients with obesity were identified. All patients had BMI > 36 (range 36.4-70.3) and several had other risk factors for MASLD including hypertension (69%), hyperlipidemia (67%), and diabetes (46%). There were 108 females (63%), median age was 53 years (range 36-65), and racial composition was 45% Caucasian, 40% African American, and 9% Hispanic individuals. Of the 172 patients, 59 underwent abdominal imaging for non-screening purposes. Of these 59 patients, 24 (41%) had incidental MASLD. Notably within the low-risk FIB-4 subgroup (N = 144), 52 patients had imaging done for non-screening purposes. Of these 52 patients, 23 (44%) had incidental MASLD and one patient had nodularity suggesting advanced fibrosis (Figure 1). **Conclusion:** Nearly half of patients with obesity had incidental MASLD on abdominal imaging performed for non-screening purposes, including nearly half of those classified as low-risk by FIB-4. Current AASLD guidelines recommend periodic laboratory testing in low-risk patients, rather than further workup with elastography or specialized serum testing, which can delay diagnosis in patients with obesity. These findings highlight a critical limitation of the FIB-4 as a screening tool and suggest that obesity and other metabolic risk factors be more directly integrated into MASLD screening strategies.

Figure 1: Patients with Obesity with Incidental MASLD



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2134 | ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK USING THE TWO-STEP ALGORITHMS FROM THE KASL/EASL AND AGA GUIDELINES IN INDIVIDUALS WITH MASLD

Jungpyo Hong[1] Jaehong Jeong[1] Jae Seung Lee[1] Mi Na Kim[1] Beom Kyung Kim[1] Do Young Kim[1] Sang Hoon Ahn[1] Hye Won Lee[1] Seung Up Kim[1], [1]Yonsei University College of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is linked to cardiovascular disease (CVD) risk factors, and liver fibrosis severity importantly correlates with atherosclerotic cardiovascular disease (ASCVD) risk. Recent KASL/EASL and AGA guidelines introduced two-step algorithms using non-invasive tests (NITs) to help identify high-risk MASLD patients. This retrospective cohort study aimed to assess whether these algorithms can effectively evaluate ASCVD risk in individuals with MASLD. **Methods:** A total of 12,738 subjects undergoing health check-ups (2012-2020), including FIB-4 and vibration-controlled transient elastography (VCTE), were screened. Following 6,219 exclusions, 6,519 study subjects (mean age 50.3 years; 41.7% female) were ultimately selected[홍1]. ASCVD risk was then determined using the 2025 ACC/AHA Pooled Cohort Equations (PCE); High-risk ASCVD was specifically defined as a 10-year risk $\geq$20%. ANOVA and Chi-square tests were used for statistical analysis ($P < 0.05$). **Results:** High-risk ASCVD was identified in 375 subjects (5.8%) and was significantly associated with older age, a higher comorbidity prevalence, and elevated FIB-4 levels (all $P < 0.001$). Applying the KASL/EASL guidelines, mean ASCVD scores increased from 5.1% in low-risk individuals to 18.8% in high-risk individuals. The proportion of subjects with high ASCVD risk correspondingly rose from 4.7% (low-risk) to 38.6% (high-risk) (P trend < 0.001). Similarly, the AGA guidelines also showed an increase in mean ASCVD scores from 1.5% (very low-risk) to 8.2% (intermediate/high-risk). The proportion with high ASCVD risk also increased from 0.3% (very low-risk) to 9.1% (intermediate/high-risk) (P trend < 0.001). **Conclusion:** These findings indicate that the KASL/EASL and AGA proposed two-step algorithms can effectively assess ASCVD risk in MASLD subjects.

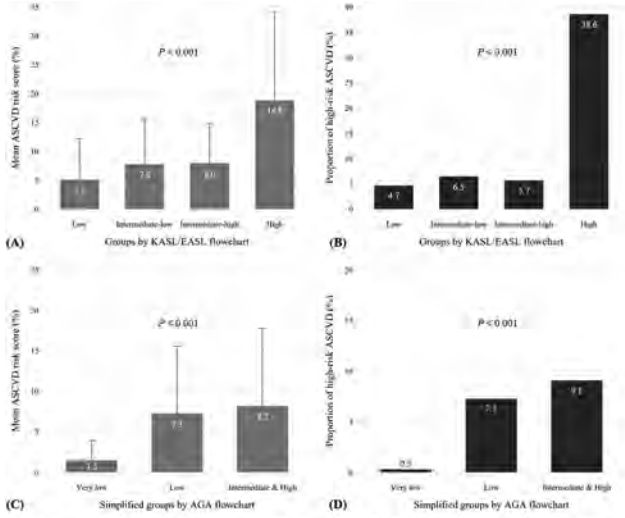

Figure 1. Comparison of ASCVD risk by groups stratified using KASL/EASL and AGA flowcharts. (A) Mean ASCVD risk scores in KASL/EASL flowchart-stratified groups. (B) Proportion of high-risk ASCVD (≥ 20%) in KASL/EASL flowchart-stratified groups. (C) Mean ASCVD risk scores in AGA flowchart-stratified groups. (D) Proportion of high-risk ASCVD (≥ 20%) in AGA flowchart-stratified groups. ASCVD, atherosclerotic cardiovascular disease; KASL, the Korean Association for the study of the Liver; EASL, the European Association for the Study of the Liver; AGA, the American Gastroenterological Association.

Disclosures: Jungpyo Hong: Nothing to Disclose, Jaehong Jeong: Nothing to Disclose, Jae Seung Lee: Nothing to Disclose, Mi Na Kim: Nothing to Disclose, Beom Kyung Kim: Nothing to Disclose, Do Young Kim: Nothing to Disclose, Sang Hoon Ahn: Nothing to Disclose, Hye Won Lee: Nothing to Disclose, Seung Up Kim: Nothing to Disclose

2135 | ELEVATED M2BPGI AS A NON-INVASIVE MARKER FOR BRAIN WHITE MATTER CHANGES IN OLDER ADULTS WITH MASLD: A CROSS-SECTIONAL STUDY

Katsuya Nagaoka[1] Maiko Nagaoka[2] Naoto Kajitani[3] Yoko Yoshimaru[1] Takehisa Watanabe[1] Hiroko Setoyama[1] Hirofumi Soejima[2] Noboru Fujise[4] Minoru Takebayashi[3] Yasuhito Tanaka[1], [1]Faculty of Life Sciences, Kumamoto University, [2]Kumamoto University, [3]Center for Metabolic Regulation of Healthy Aging, Faculty of Life Sciences, Kumamoto University, [4]Kumamoto University Hospital

Background: Mac-2 binding protein glycan isomer (M2BPGi), a non-invasive serum biomarker for liver fibrosis identified in 2013 (Kuno et al., Sci Rep 2013), is increasingly linked to systemic conditions including cardiovascular risk and silent atherosclerosis. We investigated the association between M2BPGi and cerebral white matter hypo-intensity (WMH), an

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indicator of ischemic changes using brain MRI in community-dwelling older adults, examining the modifying effects of MASLD status. **Methods:** This cross-sectional study included participants from a prospective population-based cohort in Arao City, Japan. Out of 1,448 residents aged 65 years or older who underwent a health survey between 2016 and 2017, we analyzed 607 participants after excluding those with histories of stroke, myocardial infarction, heart failure, cancer, head trauma, or current smoking to minimize confounders. Key measurements included serum M2BPGi, HbA1c, and diagnosis of steatotic liver disease (SLD), defined by a Fatty Liver Index $\geq$ 30, with MASLD confirmed according to recent criteria. Cerebral white matter hypointensities were quantified from T1-weighted brain MRI scans using FreeSurfer 5.3 software. Statistical analyses included chi-squared tests and linear regression, adjusted for age, sex, hypertension, and hyperlipidemia. **Results:** Among the 607 participants, 253 subjects (41.7%) met the criteria for MASLD. When the MASLD group was divided into two groups based on M2BPGi values of 0.9 or higher (n = 157, 48.5%) and less than 0.9 (n = 96, 36.4%), a chi-squared analysis demonstrated that MASLD participants were significantly more likely to have elevated M2BPGi levels (M2BPGi $\geq$ 0.9: 157 [48.5%] vs. M2BPGi $<$ 0.9: 96 [36.4%]; p = 0.03). Furthermore, within the MASLD group, higher M2BPGi levels (specifically M2BPGi $\geq$ 0.9) were significantly associated with an increase in WMH volumes (β = 1927.64, p = 0.017), even after adjusting for age, sex, hypertension, and hyperlipidemia. **Conclusion:** These findings suggest M2BPGi ($\geq$0.9) may be a useful non-invasive marker for early detection of silent brain ischemic disease in individuals with MASLD.

Disclosures: Katsuya Nagaoka: Nothing to Disclose, Maiko Nagaoka: Nothing to Disclose, Naoto Kajitani: Nothing to Disclose, Yoko Yoshimaru: Nothing to Disclose, Takehisa Watanabe: Nothing to Disclose, Hiroko Setoyama: Nothing to Disclose, Hirofumi Soejima: Nothing to Disclose, Noboru Fujise: Nothing to Disclose, Minoru Takebayashi: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

2136 | PERFORMANCE OF ATTENUATION IMAGING (ATI) COMPARED TO CONTROLLED ATTENUATION PARAMETER (CAP) FOR NON-INVASIVE ASSESSMENT OF HEPATIC STEATOSIS IN A COHORT OF MIXED CHRONIC LIVER DISEASES

Thales Saad[1] Joao Marcello de Araujo-Neto[2] Flavia Fernandes[3] Cristiane Villela-Nogueira[2] Priscila Pollo-Flores[4] Priscila Barreiro[5] Vania Cristina Nunes[5],

[1]Centro da Imagem Diagnósticos, [2]Federal University of Rio de Janeiro, [3]Hospital Federal de Bonsucesso, [4]Fluminense Federal University, [5]Clínica Diagnósticos Avançados

Background: While the Controlled Attenuation Parameter (CAP, FibroScan®) is widely validated, new ultrasound-based technologies such as Attenuation Imaging (ATI, Canon) have emerged as potential alternatives. This study aimed to assess the diagnostic performance of ATI in comparison with CAP for the detection and grading of hepatic steatosis. **Methods:** This prospective, cross-sectional study was conducted in a private diagnostic clinic specialized in liver diseases. Adult patients underwent CAP and ATI evaluations, performed on the same day by blinded operators. CAP values were classified according to Karlas et al. (2014): S0 ($<$234 dB/m), S1 (234–269), S2 (270–301), S3 ($>$301). ATI performance was assessed using ROC curve analysis with CAP as the reference standard for detecting any steatosis (S $\geq$ 1), moderate (S $\geq$ 2), and severe steatosis (S $\geq$ 3). Optimal ATI cutoff values were determined by maximizing Youden's index. **Results:** A total of 375 adult patients were included, with a mean age of 53.6 years ($\pm$13.3); 55.7% were female; median BMI was 30.1 kg/m² ($\pm$9.5). MASLD was the most frequent etiology (67.2%), followed by chronic hepatitis C (15.7%), hepatitis B (6.9%), and other causes (10.2%). The mean CAP was 272.9 $\pm$ 67.1 dB/m, and ATI was 0.69 $\pm$ 0.14 dB/cm/MHz. The prevalence of steatosis using CAP as reference was 68.8%. ATI values demonstrated a strong correlation with CAP (ρ = 0.750, p $<$ 0.001). – For S $\geq$ 1, ATI cutoff of 0.63 dB/cm/MHz showed AUROC 0.88, sensitivity 82.6%, specificity 81.2%. – For S $\geq$ 2, ATI cutoff of 0.69 dB/cm/MHz showed AUROC 0.91, sensitivity 82.4%, specificity 88.1%. – For S $\geq$ 3, ATI cutoff of 0.70 dB/cm/MHz showed AUROC 0.89, sensitivity 86.4%, specificity 78.6%. In the MASLD subgroup (n = 252), diagnostic performance remained high: – For S $\geq$ 1, AUROC was 0.84 with cutoff 0.68, sensitivity 73.9%, specificity 85.3%. – For S $\geq$ 2, AUROC was 0.89 with cutoff 0.69, sensitivity 83.1%, specificity 82.5%. – For S $\geq$ 3, AUROC was 0.83 with cutoff 0.74, sensitivity 77.9%, specificity 76.8%. **Conclusion:** In this double-blinded cross-sectional study with a large cohort of patients, ATI demonstrated strong correlation and excellent diagnostic performance for detecting hepatic steatosis, particularly among patients with MASLD. These findings support ATI as a reliable non-invasive tool in hepatology practice and highlight its applicability in routine liver assessment, especially in settings where CAP is unavailable or limited. The method's strong performance in the MASLD subgroup reinforces its relevance amid the growing burden of metabolic liver disease.

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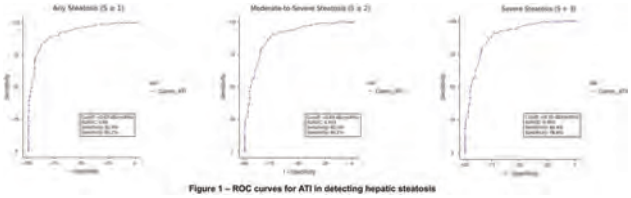


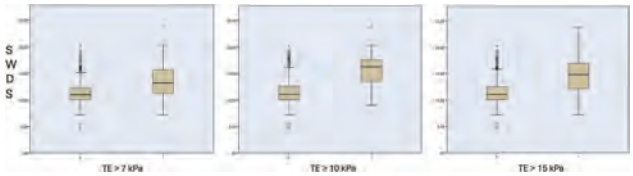
Figure 1 – ROC curves for ATI in detecting hepatic steatosis

Disclosures: Thales Saad: Nothing to Disclose, Joao Marcello de Araujo-Neto: Nothing to Disclose, Flavia Fernandes: Nothing to Disclose, Cristiane Villela-Nogueira: Nothing to Disclose, Priscila Pollo-Flores: Nothing to Disclose, Priscila Barreiro: Nothing to Disclose, Vania Cristina Nunes: Nothing to Disclose

2137 | LIVER SHEAR WAVE DISPERSION SLOPE MEASUREMENT IS HIGHER IN PATIENTS WITH SIGNIFICANT AND ADVANCED FIBROSIS DUE TO MASLD

Joao Marcello de Araujo-Neto[1] Thales Saad[2] Priscila Pollo Flores[3] Priscila Calvet Nelson-Smith Barreiro[4] Vania Cristina de Santana Roch Nunes[4] Flávia Ferreira Fernandes[4] Claudia Oliveira[5], [1]Federal University of Rio de Janeiro, [2]Centro da Imagem Diagnósticos, [3]Fluminense Federal University, [4]Clínica Diagnósticos Avançados, [5]University of Sao Paulo School of Medicine

Background: Shear-wave dispersion slope (SWDS), a parameter derived from two-dimensional shear-wave elastography, has been proposed as a non-invasive biomarker for hepatic inflammation and fibrosis. Previous studies have examined its diagnostic utility across various liver diseases, including Metabolic dysfunction-associated steatotic liver disease (MASLD). However, data from large-scale cohorts remain limited. **Methods:** A prospective, cross-sectional, multicentric study was conducted between October 2023 to May 2025 at a tertiary university hospital and a private hepatology clinic. Consecutive adult patients with suspected MASLD were assessed using transient elastography (TE), controlled attenuation parameter (CAP), conventional B-mode ultrasound, and SWDS (Canon Aplio i800). Steatosis severity was graded based on CAP as S0: < 234db/m, S1: 234 - 267 dB/m, S2: 268 - 304 dB/m, S3: > 304 dB/m. The characteristics of steatosis on B mode ultrasound were categorized according to the US-FLI score. **Results:** A total of 864 patients were included (mean age 55.6 ± 13.9 years; 52.3% female). Steatosis distribution according to CAP was: S0 – 3.9%, S1 – 14.9%, S2 – 15.4%, and S3 – 25.2%. The median liver stiffness (TE) was 5.2 kPa (range: 2–39 kPa) and 14.8% of patients exhibited liver stiffness >7 kPa, 6.5% >10 kPa, and 2.9% >15 kPa. The median SWDS was 11.2 m/s/kHz (range: 4.8–23.8). Patients with liver stiffness >7 kPa demonstrated significantly higher SWDS values compared to those with lower stiffness (13.3 *vs*. 11.3 m/s/kHz; $p < 0.001$). This association remained consistent across higher TE thresholds >10kPa (14.5 *vs* 11.3; p< 0,001) and > 15 kPa (15.5 *vs* 11.4; p< 0,001). No clinically meaningful correlation was observed between SWDS and steatosis severity assessed by CAP (11.8 vs. 11.4 vs 11.5 vs 11,5 m/s/kHz for S0, S1, S2, S3 respectively, p = 0,148). Similarly, no significant association was identified between SWDS and steatosis quantified by the US-FLI score (threshold: ≥4 points) (11.6 vs. 11.5 m/s/kHz; $p = 0.59$). **Conclusion:** In this large prospective cohort of patients with MASLD, SWDS was not associated with the degree of hepatic steatosis as assessed by either CAP or B-mode ultrasound. In contrast, SWDS demonstrated a robust and consistent association with liver fibrosis across various TE-defined thresholds. Given that hepatic inflammation is a key upstream event in fibrogenesis, these findings support further investigation into the utility of SWDS as a marker of liver inflammation in MASLD using alternative study designs.



Disclosures: Joao Marcello de Araujo-Neto: Nothing to Disclose, Thales Saad: Nothing to Disclose, Priscila Pollo Flores: Nothing to Disclose, Priscila Calvet Nelson-Smith Barreiro: Nothing to Disclose, Vania Cristina de Santana Roch Nunes: Nothing to Disclose, Flávia Ferreira Fernandes: Nothing to Disclose, Claudia Oliveira: Nothing to Disclose

2138 | BEYOND METABOLIC SYNDROME: ELEVATED FERRITIN PREDICTS HIGHER LIVER STIFFNESS IN ADULTS

Sheena Bhushan[1] Kris Kowdley[1], [1]Liver Institute Northwest

Background: Elevated Serum Ferritin (SF) is frequently observed in individuals with metabolic liver disease. However, the independent relationship between SF and liver stiffness measurement (LSM)- beyond the effects of metabolic syndrome and demographic factors- is unclear. The aim of this study is to evaluate whether an elevated SF level is independently

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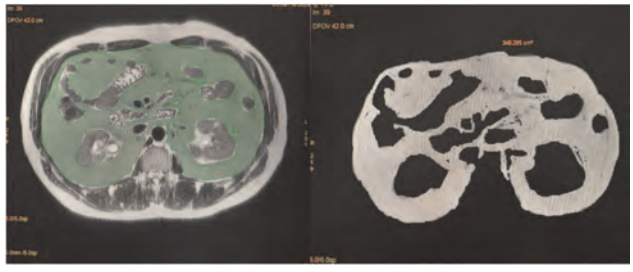
associated with increased liver stiffness measurement (LSM), after adjusting for relevant demographic and metabolic covariates. **Methods:** Data were analyzed from 2,473 participants in the 2017-2020 cycles of the National Health and Nutrition Examination Survey (NHANES) who underwent transient elastography (VCTE). Elevated SF was defined as levels >450 ng/mL in men and >300 ng/mL in women. Covariates included diabetes status, age, a proxy for menopausal status (women 50), and number of metabolic syndrome features. A robust linear regression model was used to estimate the independent association between elevated SF and LSM after adjusting for the aforementioned covariates. **Results:** An elevated SF level was independently associated with increased LSM ($\beta = 0.53$, 95% CI:0.28-0.78, $p < 0.001$). Other significant predictors included diabetes mellitus. ($\beta = 0.68$, $p < 0.001$), metabolic syndrome burden ($\beta = 0.24$ per feature, $p < 0.001$), and menopausal status ($\beta = -0.46$, $p < 0.001$). Interestingly, age was associated with a slightly LSM ($\beta = -0.009$ per year, $p < 0.001$). **Conclusion:** Elevated SF is independently associated with increased liver stiffness, even after controlling for key metabolic and demographic confounders. These findings support the role of SF as a clinically useful biomarker in non-invasive assessment and risk stratification of hepatic fibrosis, particularly in populations with metabolic risk.
Disclosures: Sheena Bhushan: Nothing to Disclose, Kris Kowdley: Nothing to Disclose

2139 | QUANTIFYING VISCERAL FAT ON MAGNETIC RESONANCE ELASTOGRAPHY (MRE)- A COMPARATIVE STUDY BETWEEN EARLY AND ADVANCED STAGES OF METABOLIC DYSFUNCTION-RELATED STEATOTIC LIVER DISEASE WITH HEALTHY CONTROLS

Ameet Mandot[1] Sachi Banker[2] Kevin Shah[1] Nafe Chinde[1] Ajay Bang[1] Samriddhi Poyekar[1] Chetan Kalal[1] Sitaram Sabane[1], [1]Gleneagles Hospital, Mumbai, [2]Gleneagles hospitals, Mumbai

Background: Obesity, especially visceral adiposity, is a significant risk factor for Metabolic Dysfunction-Related Steatotic Liver Disease (MASLD) and contributes to the progression of liver disease. MR Elastography (MRE) is the best non-invasive modality to diagnose various stages of MASLD, and can also be used to quantify visceral fat. Our aims were to correlate the amount of visceral fat on MRE in patients at various stages of MASLD with the severity of the disease and to compare the amount of visceral fat in normal subjects and those with MASLD. **Methods:** This retrospective observational study in a tertiary care hospital in Mumbai, India included 133 subjects: 48 patients with MASLD-related early and intermediate stages of fibrosis (F0-F3) -group 1, 43 patients with MASLD-related compensated cirrhosis -group 2 and 42 healthy liver donors as controls -group 3. Demographic, clinical and laboratory data were collected. The fat fraction and the Liver Stiffness Measurement (LSM) on MRE were noted. Visceral abdominal tissue (VAT) cross-sectional area was quantified at L3 vertebral level on MRE using semi-automated software. Statistical analyses included Welch's one-way ANOVA test, Tukey's post-hoc tests, and Pearson correlation. **Results:** Patients with group 1 and group 2 were notably older than healthy controls (group 3), had a higher BMI (group 1: 28.81kg/m^2, group 2: 27.44kg/m^2, group 3: 22.8kg/m^2) and a larger proportion of males. Diabetes, hypertension, and dyslipidemia were more prevalent in the MASLD groups. Mean LSM was 2.29 kPa in group 3, 2.9 kPa in group 1, and 7.44 kPa in group 2 patients. Fat fraction was found to be highest in the group 1 (11.77%). Mean VAT levels were significantly elevated in MASLD groups (group 1: 165.02m^3, group 2:155.28m^3) compared to healthy controls (group 3: 31.23m^3), although no significant difference existed between the two MASLD subgroups. VAT levels positively correlated with LSM, fat fraction, and HbA1C, and inversely with HDL levels. **Conclusion:** Our study provides compelling evidence of increased visceral fat in MASLD, irrespective of fibrosis stage. Our study did not find any significant difference in the amount of visceral fat in the various stages of MASLD. The consistently high VAT levels across all MASLD stages highlight visceral adiposity as a critical therapeutic target, underscoring the importance of lifestyle interventions to prevent, modulate, and mitigate cardiometabolic risks associated with MASLD.



Disclosures: Ameet Mandot: Nothing to Disclose, Sachi Banker: Nothing to Disclose, Kevin Shah: Nothing to Disclose, Nafe Chinde: Nothing to Disclose, Ajay Bang: Nothing to Disclose, Samriddhi Poyekar: Nothing to Disclose, Chetan Kalal: Nothing to Disclose, Sitaram Sabane: Nothing to Disclose

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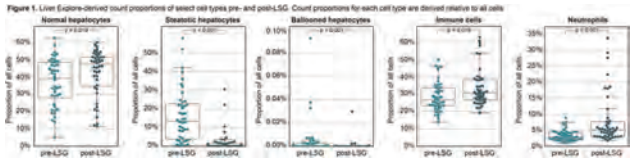
2140 | AI-POWERED PATHOLOGY REVEALS SURGERY-INDUCED CHANGES IN THE CELLULAR COMPOSITION OF THE LIVER IN PATIENTS WITH MASLD

Alina Iuliana Onoiu[1] Lara Murray[2] Ylaine Gerardin[2] Geetika Singh[2] Robert Egger[2] David Parada[3] Jorge Joven[4], [1]Unitat de Recerca Biomèdica, Universitat Rovira i Virgili, Reus, Spain, [2]PathAI Inc., Boston, MA, US, [3]Departament d'Anatomía Patològica, Hospital Universitari Sant Joan de Reus, Reus, Spain, [4]Unitat de recerca biomèdica, Hospital Universitari Sant Joan de Reus, Reus, Spain

Background: Severe obesity increases the risk of metabolic dysfunction-associated steatotic liver disease (MASLD), fibrosis, and related complications. Lifestyle changes, medications (e.g., Semaglutide), and bariatric surgery may lead to substantial weight loss. However, an opportunity remains to better understand the effects of these interventions on liver histology. In this study, we assessed changes in liver histology that occur with laparoscopic sleeve gastrectomy (LSG) in patients with severe obesity using Liver Explore[1], an AI-powered tool for the characterization of liver microarchitecture. **Methods:** Patients with severe obesity were enrolled in a cross-sectional observational study for LSG intervention (NCT0554224). Liver wedge biopsies were obtained prior to LSG, and a second biopsy was obtained from a subset of patients with MASLD (N = 44) after an average of 5 years. Biopsies were stained with hematoxylin and eosin, digitized (Ventana DP200, 40X), and analyzed using Liver Explore. Liver Explore-derived cell features from pre- and post-LSG were compared using non-parametric statistical analysis, specifically the Wilcoxon signed-rank test. Immunohistochemistry (IHC) was performed on serial biopsy sections using a Ventana BenchMark ULTRA autostainer (Roche, Indianapolis, IN, USA) and anti-CD15 monoclonal antibody (Roche, Indianapolis, IN, USA), and CD15 positivity was quantified using QuPath. **Results:** In the subset of patients assessed here, BMI was reduced from 52.4 to 40.6 kg/m^2 after LSG. Significant changes in liver composition were observed following LSG intervention (Fig. 1). The proportion of normal hepatocytes increased, while the proportions of steatotic and ballooned hepatocytes decreased. In addition, the proportion of immune cells increased, driven by an increase in neutrophils. This neutrophil increase was further validated by CD15+ IHC on neighboring sections. **Conclusion:** AI-based digital pathology allows objective, reproducible, and quantitative examination of histology and here provides precise evaluation of the effects of LSG on liver histology. These findings reveal that LSG may improve MASLD features, such as steatosis and ballooning, but may exacerbate inflammation, driven by a rise in neutrophil density. These findings underscore LSG's role in managing MASLD while highlighting the need to monitor inflammatory changes.
[1]Liver Explore is for research use only. Not for use in diagnostic procedures.



Disclosures: Alina Iuliana Onoiu: Nothing to Disclose, Lara Murray: PathAI: Employee, PathAI: Stock – privately held company, Ylaine Gerardin: PathAI: Employee, Geetika Singh: PathAI: Employee, Robert Egger: Nothing to Disclose, David Parada: Nothing to Disclose, Jorge Joven: Nothing to Disclose

2141 | POLYMORPHISM RS7903146 OF TCF7L2 GENE IS ASSOCIATED WITH TYPE 2 DIABETES AND CARDIOVASCULAR RISK BIOMARKER IN PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Brian Lam[1] James Estep[2] Mustafa Kanat[3] Mehmet Agirbasli[4] Maria Stepanova[5] Zobair Younossi[6], [1]INOVA Fairfax Hospital, [2]Beatty Liver and Obesity Research Program, Inova Health System, Falls Church, VA, [3]Diabetes Research Center (DIMER), Istanbul Medeniyet University, Istanbul, Turkey, [4]Department of Cardiology, Medeniyet University School of Medicine, Istanbul, Turkey, [5]Center for Outcomes Research in Liver Disease, [6]The Global NASH Council

Background: Components of metabolic syndrome (MS) have been linked to genetic risk factors. Our aim was to assess the impact of 2 polymorphisms in the *TCF7L2* gene on the clinical profile of patients with MASLD. **Methods:** Clinico-laboratory data were collected from consented MASLD patients. Genomic DNA was extracted from the whole blood and used for determination of minor allele frequency for genomic loci rs7903146 and rs12255372 in the *TCF7L2* gene. Individual alleles were evaluated for association with components of MS, liver disease severity [FIB-4 score, Enhanced Liver Fibrosis (ELF) score], coronary artery

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disease (by history or coronary angiography), metabolic biomarkers (fasting c-peptide and insulin), and cardiac biomarkers [high-sensitivity CRP (hsCRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin I (hs-cTnI)]. Associations of clinical and laboratory variables with minor alleles of *TCF7L2* gene were carried out using univariate and multivariate analysis. **Results:** We included 254 MASLD patients with at least one polymorphism available: mean ± SD age 61 ± 9 years, 84% male, BMI 30.9 ± 5.3, 33% type 2 diabetes (T2D), 61% with insulin ≥ 20 μIU/mL (insulin resistance), 72% with c-peptide < 1.0 ng/mL (impaired beta cell function). Of these patients, the distributions of alleles for 2 studied polymorphisms were as follows: rs7903146 – 43% CC, 54% CT, 3% TT; rs12255372 – 13% GG, 76% GT, 11% TT. Patients with CT/TT at rs7903146 had higher prevalence of T2D (40% vs. 24%, p = 0.018) and higher levels of hs-cTnI (median (IQR) = 6.5 (4.3-14.4) pg/ml vs. 4.6 (3.3-8.8) pg/ml, p = 0.030) in comparison to CC. Although there were no differences in clinical or laboratory parameters of MASLD by rs12255372 allele (all p > 0.05), hs-cTnI level trended to be higher in GT/TT vs. GG groups (median (IQR) = 6.3 (4.3-11.5) pg/ml vs. 4.0 (3.3-11.9) pg/ml, p = 0.086). In multivariate analysis, having C- > T minor allele in the rs7903146 locus was independently associated with an increased risk of T2D in MASLD: OR (95% CI) = 2.3 (1.2-4.6), p = 0.018. Other independent predictors of T2D included older age (OR = 1.059 (1.015-1.104) per year, p = 0.007) and higher BMI (OR = 1.138 (1.062-1.220) per kg/m2, p = 0.0003). **Conclusion:** In patients with MASLD, polymorphism rs7903146 in the *TCF7L2* gene is not only independently associated with T2D but also with higher troponin levels suggesting a potentially increased risk of cardiovascular disease in those patients.

Disclosures: Brian Lam: Madrigal: Speaking and Teaching, James Estep: Nothing to Disclose, Mustafa Kanat: Nothing to Disclose, Mehmet Agirbasli: Nothing to Disclose, Maria Stepanova: Nothing to Disclose, Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant

2142 | EVALUATION OF MULTISENSORIAL ELECTRONIC TECHNOLOGIES AS NONINVASIVE TOOLS FOR THE DETECTION OF FIBROTIC-MASH IN MASLD PATIENTS

Francesca Terracciani[1] Alessandro Zompanti[2] Simone Grasso[2] Antonio De Vincentis[3] Aldo Marrone[4] Paolo Gallo[1] Andrea Falcomatà[1] Valentina Flagiello[1] Maria Rocco[5] Riccardo Fuso[1] Alfredo Caturano[6] Ferdinando Carlo Sasso[6] Antonio Picardi[1] Marco Santonico[2] Giorgio Pennazza[2] Raffaele Antonelli Incalzi[7] Umberto Vespasiani-Gentilucci[1], [1]Research Unit of Hepatology, Università Campus Bio-medico di Roma, Italy, [2]Research Unit of Electronics for Sensor Systems, Università Campus Bio-Medico di Roma, Rome, Italy, [3]Unit of Internal Medicine, Università Campus Bio-medico di Roma, Italy, [4]Università della Campania, [5]4University of Campania Luigi Vanvitelli, Naples, Italy, [6]University of Campania Luigi Vanvitelli, Naples, Italy, [7]Research Unit of Internal Medicine, Università Campus Bio-medico di Roma, Italy

Background: Fibrotic-MASH, the progressive inflammatory phenotype of MASLD defined by significant necroinflammatory activity (NAS ≥ 4) and fibrosis (≥ stage 2), is the most clinically relevant and treatment-eligible form of the disease. Accordingly, noninvasive detection methods are a key focus of current research. In recent years, multisensory technologies such as the electronic nose (e-nose) and electronic tongue (e-tongue) have emerged as promising diagnostic and prognostic tools across various conditions, including liver diseases. This study aims to evaluate their performance as novel noninvasive tools for identifying fibrotic-MASH. **Methods:** Consecutive MASLD patients were prospectively enrolled at the Hepatology Unit of "Fondazione Policlinico Universitario Campus Bio-Medico" of Rome. MASLD was diagnosed by the presence of cardiometabolic criteria and either histological or ultrasonographic steatosis. Fibrotic-MASH was defined by Fibroscan-AST (FAST) score ≥ 0.67 or, histologically, by NAS ≥ 4 and fibrosis ≥ 2. All patients underwent breath collection for analysis via BIONOTE e-nose, and urine and saliva sampling for BIONOTE e-tongue analysis. Diagnostic performance for fibrotic-MASH was assessed using Partial Least Squares Discriminant Analysis (PLS-DA) and described by confusion matrices. **Results:** A total of 121 MASLD patients were enrolled (median age 57.4 years, 60% male, mean BMI 31.9 kg/m²), of which 75 in the non-invasive cohort and 46 in the histological cohort. Overall, FAST score was available in 107 cases. Fibrotic-MASH was identified in 15/107 patients by FAST and in 24/46 by histology. Suitable breath, urine, and saliva samples were obtained from 102, 118, and 116 patients, respectively. The accuracies of e-nose (breath) and e-tongue (saliva and urine) in predicting fibrotic-MASH according to FAST score were 77%, 80%, and 82%, respectively. In the histological cohort, e-tongue saliva showed the highest accuracy (79%), followed by e-nose (74%) and e-tongue urine (65%) in predicting fibrotic-MASH, while combining all three sample types resulted in a predictive performance of 79%. Overall, e-technologies outperformed FAST (68% accuracy) in predicting histologically confirmed fibrotic-MASH. **Conclusion:** E-technologies exhibit good

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accuracy in identifying fibrotic-MASH, outperforming FAST, one of the widely used noninvasive score. These findings highlight the potential of these tools for clinical risk stratification in MASLD/MASH, though confirmation in larger, prospective cohorts remains necessary.
Disclosures: Francesca Terracciani: Nothing to Disclose, Alessandro Zompanti: Nothing to Disclose, Simone Grasso: Nothing to Disclose, Antonio De Vincentis: Nothing to Disclose, Aldo Marrone: Nothing to Disclose, Paolo Gallo: Nothing to Disclose, Andrea Falcomatà: Nothing to Disclose, Valentina Flagiello: Nothing to Disclose, Maria Rocco: Nothing to Disclose, Riccardo Fuso: Nothing to Disclose, Alfredo Caturano: Nothing to Disclose, Ferdinando Carlo Sasso: Nothing to Disclose, Antonio Picardi: Nothing to Disclose, Marco Santonico: Nothing to Disclose, Giorgio Pennazza: Nothing to Disclose, Raffaele Antonelli Incalzi: Nothing to Disclose, Umberto Vespasiani-Gentilucci: Advanz Pharma: Advisor, Gilead: Speaking and Teaching, Ipsen: Advisor, Diasorin: Consultant, Novo Nordisk: Advisor, Astra Zeneca: Grant/Research Support, Astra Zeneca: Grant/Research Support

2143 | MULTIPLE QUANTITATIVE ULTRASOUND PARAMETERS FOR THE EVALUATION OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: A PROSPECTIVE STUDY

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Background: Metabolic dysfunction–associated steatohepatitis (MASH), a subtype of metabolic dysfunction-associated steatotic liver disease (MASLD), is characterized by inflammation and hepatocyte injury, leading to liver fibrosis and ultimately, cirrhosis. Early detection and treatment of individuals with hepatic steatosis may potentially prevent cirrhosis-related outcomes. This study aims to develop optimized models integrating multiple ultrasound parameters to evaluate at-risk MASH in liver biopsy-proven MASLD patients. **Methods:** In this prospective study, patients scheduled for liver biopsy due to clinical suspicion of MASH were enrolled. All abdominal ultrasound examinations were performed using the Resona A20 ultrasound system (Mindray, China) with a SC7-1U probe (1.0 – 7.0 MHz). After producing an M-Ref map, the multiple ultrasound parameters were measured, including the attenuation coefficient obtained with UltraSound ATtenuation Imaging Technology (USAT) (in dB/cm/MHz), shear wave speed (SWS) (in m/s), and viscosity (in Pa·s). The at-risk MASH was defined as MASH with F2-F3 fibrosis. Receiver operating characteristic curves (AUCs) were performed to assess the diagnostic performance of multiple ultrasound parameters. **Results:** From November 2023 to January 2025, 52 patients (median age of 46 years) were included. The risk score model from multiple ultrasound parameters was developed using USAT, viscosity values, and SWV, which were associated with the degree of hepatic steatosis, lobular inflammatory activity, and fibrosis (all $P < 0.05$). For the USAT, the risk score was assigned using the cutoff values of USAT for detecting hepatic steatosis as follows: score 1, USAT value between 0.55 and 0.58 dB/cm/MHz (S1); score 2, USAT value between 0.58 and 0.75 dB/cm/MHz (S2); and score 3, USAT value greater than 0.75 dB/cm/MHz (S3). The risk score of viscosity was assigned using the cutoff values of viscosity as follows: score 1, viscosity value between 2.00 and 2.05 Pa·s (A2); score 2, viscosity value between 2.05 and 2.11 Pa·s (A3); and score 3, viscosity value greater than 2.11 Pa·s (A4). The risk score of SWV was assigned using the cutoff values of SWV as follows: score 1, SWV value between 1.77 and 2.01 m/s (F2), and score 2, SWV value greater than 2.01 m/s (F3). The final at-risk score was defined as the unweighted sum of each score from USAT, viscosity, and SWV values, ranging from 0 to 8. The diagnostic performance of the risk score model for detecting at-risk MASH was higher than that of ultrasound parameters alone (AUC = 0.70 vs. AUC = 0.53 – 0.66). **Conclusion:** The risk score model integrating multiple ultrasound parameters (attenuation coefficient, viscosity, and SWV) improved noninvasive diagnostic performance for detecting at-risk MASH in patients with MASLD.
Disclosures: Yi Dong: Nothing to Disclose, Yunlin Huang: Nothing to Disclose, Ying Wang: Nothing to Disclose, Juan Cheng: Nothing to Disclose, Li Wei: Nothing to Disclose, Rui Cheng: Nothing to Disclose

2144 | IMPACT OF PNPLA3 RS738409 VARIANT ON IL-6-MEDIATED INFLAMMATION IN AFRICAN AMERICANS WITH MASLD

Morinne Osborne[1] Tanmoy Mondal[2] Coleman Smith[3] Christopher Loffredo[4] Ruth Quartey[2] Charles Howell[5] Brent Korba[4] Zaki Sherif[2] Gail Nunlee-Bland[2] Leanna Rucker[4] Gemeyel Moses[2] Somiranjan Ghosh[2], [1]Howard University College of Medicine, [2]Howard University, [3]Georgetown University Hospital, [4]Georgetown University, [5]Howard University Hospital

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a global health problem and is one of the primary causes of liver disease. An earlier study conducted at Howard University revealed

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that African Americans (AA) are moderately protected from MASLD due to a Single Nucleotide polymorphism (SNP) at position rs738409 on *PNPLA3* converting an amino acid from isoleucine to methionine. This conversion causes Interleukin 6 (*IL-6*) to be upregulated and overexpressed, causing an acute and chronic inflammatory response in the liver and in turn can cause hepatic steatosis. Due to allele frequencies in PNPLA3, other ethnic groups have a higher chance of developing fatty liver disease compared to AA. Within the gene, there are three possible alleles that the general population could have that affects inflammation activity (C/C, C/G, G/G). In this pilot study, we compared each of the three alleles to determine the upstream and downstream effects that the SNP has on IL-6. **Methods:** AA MASLD patients ($n = 11$; mean age 45 ± 8.15 y) were selected from the previous study cohort, along with non-MASLD AA controls ($n = 10$; mean age 27 ± 11.42 y) from the Washington DC area. Their sociodemographic, lifestyle exposures, and medical background information were recorded. To categorize the PNPLA3 polymorphism (rs738409), we performed SNP genotype analysis. RNA Sequence analysis and IPA (Qiagen) analysis were used to map the metabolic pathway of IL-6 and to understand the gene networks. **Results:** The SNP analysis revealed the following frequency of the three alleles: 62% for the wildtype allele (C/C), 29% for the heterozygous allele (C/G), and 10% for the homozygous allele (G/G). The differential gene expression analysis disclosed an activation of IL-6 when we compared the wild type with the mutated allele type. Additionally, we identified 10 key genes that are significantly ($p < 0.05$) up and downregulated ($> \pm 4$ fold), viz., RSS53, CORO7-PAM16, MAPK12, CNIH3, CATIP, WDR74, TPTE, UTP14C, H3C14, and CRYBB2. Hepatic Fibrosis Signaling Pathway and Hepatic Satellite cell activation are observed as key canonical pathways (CP) when compared with wildtype variants over the mutated type. Additionally, we observed activation of IL-1B, EXOSC3, PRTN3 and inactivation of MYOCD, MAP3K5, E2F1 through causal network analysis. **Conclusion:** This pilot study opens an opportunity to gain insight into MASLD disease dynamics at different polymorphisms levels of PNPLA3 in AA. This study may further help in developing molecular classifiers to identify the disease risks and the progression of MASLD in the future that necessitates further large-scale multiethnic population validation as well as using large sample size as well as comparisons of blood and liver biopsies is necessary to strengthen our findings.

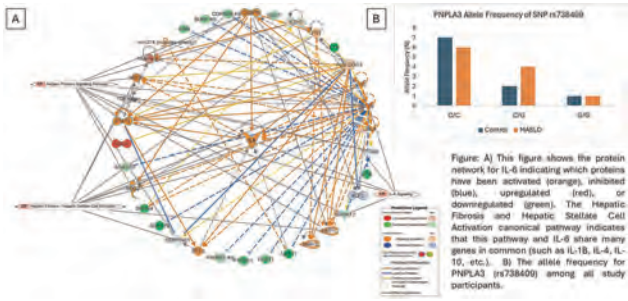

Figure: A) This figure shows the protein network for IL-6 indicating which proteins have been activated (orange), inhibited (blue), upregulated (red), or downregulated (green). The Hepatic Fibrosis and Hepatic Stellate Cell Activation canonical pathway indicates that this pathway and IL-6 share many genes in common (such as IL-1B, IL-4, IL-10, etc.). B) The allele frequency for PNPLA3 (rs738409) among all study participants.

Disclosures: Morinne Osborne: Nothing to Disclose, Tanmoy Mondal: Nothing to Disclose, Coleman Smith: Nothing to Disclose, Christopher Loffredo: Nothing to Disclose, Ruth Quartey: Nothing to Disclose, Charles Howell: Nothing to Disclose, Brent Korba: Nothing to Disclose, Zaki Sherif: Nothing to Disclose, Gail Nunlee-Bland: Nothing to Disclose, Leanna Rucker: Nothing to Disclose, Gemeyel Moses: Nothing to Disclose, Somiranjan Ghosh: Nothing to Disclose

2145 | EVALUATION OF ACCURACY OF AST TO PLATELET RATIO INDEX (APRI) IN VARIOUS AGE GROUPS WITH BIOPSY-PROVEN MASLD OR MASH: A COMPREHENSIVE RETROSPECTIVE STUDY

Frank Lin[1] Ayah Obeid[1] Parampreet Kaur[1] Kimberly Chaput[1] Hammad Liaquat[1], [1]St. Luke's University Health Network

Background: Metabolic dysfunction-associated steatotic liver disase (MASLD) can involve advanced fibrosis and has implications with cardiovascular and liver disease related mortality. The definitive diagnosis of MASLD and metabolic dysfunction-associated steatohepatitis (MASH) is liver biopsy. We aim to evaluate and compare the accuracy of the AST to platelet ratio index (APRI) in predicting hepatic fibrosis among various adult age groups with biopsy proven MASLD or MASH. **Methods:** We conducted a retrospective chart review to identify patients who were 18 years of age and over who underwent a liver biopsy between 2020 and 2023. Data was collected on patient demographics, comorbidities, and liver biopsy findings. Stage of fibrosis was determined using the Metavir Scoring System (F0-F4). Exclusion criteria for the study focused on identification of other causes of steatosis, steatohepatitis, and chronic liver disease. Patients were split into two age groups: young (18-44 years) and older (45 years or more). All statistical analyses were conducted using Stata V.18 to compute means and frequencies of patient data to determine accuracy of

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APRI. **Results:** A total of 254 patients were included with a mean age of 53.1 years, 62.2% females, and 80.3% Caucasians. The majority of patients had metabolic syndrome (50.8%), obesity (75.2%), hypertension (62.6%), and dyslipidemia (64.9%). APRI was interpretable in all 254 patients with a scoring threshold of 0.5. Of the 254 patients, 50.8% were predicted to have advanced fibrosis. Overall, APRI had higher sensitivity (72.7%) and lower specificity (50.2%) in predicting advanced fibrosis with the best outcomes seen in the older age group for sensitivity and negative predictive value (NPV) (Table 1). Area under the receiver operating characteristic (AUROC) curve analysis showed unsatisfactory accuracy of APRI in the overall sample, young, and older age groups with AUROC of 51.2%, 43.5%, and 53.7%, respectively. **Conclusion:** Our results suggest that APRI has good sensitivity for predicting fibrosis and even stronger predictability for non-advanced fibrosis (F0-F2) based on the NPV among all patients. APRI as a diagnostic tool and biomarker appears to have greater clinical utility for increasing the pre-test probability for non-advanced fibrosis. The results in the young age group can be further improved with a larger sample size. A comparison of results with other non-invasive liver fibrosis biomarkers is needed.

Table 1: AST to Platelet Ratio (APRI) Index scores in patients with biopsy proven MASLD or MASH.

Characteristics	All MASLD or MASH patients (n=254) n (%)	Age 18-44 years (n=62) n (%)	Age 45 years and above (n=192) n (%)
F0-F2 *(APRI ≤ 0.5)*	125 (49.2)	29 (46.8)	96 (50)
F0-F2 on APRI *and* liver biopsy	122 (48)	26 (41.9)	96 (50)
F0-F2 on APRI *but* F3-F4 on liver biopsy	3 (1.2)	3 (4.8)	0 (0)
F3-F4 *(APRI > 0.5)*	129 (50.8)	33 (53.2)	96 (50)
F3-F4 on APRI *and* liver biopsy	8 (3.1)	1 (1.6)	7 (3.6)
F3-F4 on APRI *but* F0-F2 on liver biopsy	121 (47.6)	32 (51.6)	89 (46.3)
Sensitivity / NPV, (%)	72.7 / 97.6	25 / 89.7	100 / 100
Specificity / PPV, (%)	50.2 / 6.2	44.8 / 3	51.9 / 7.3
AUROC (%)	51.2	43.5	53.7

PPV- positive predictive value; NPV- negative predictive value, AUROC - area under the receiver operating characteristic curve; CI - confidence interval.

Disclosures: Frank Lin: Nothing to Disclose, Ayah Obeid: Nothing to Disclose, Parampreet Kaur: Nothing to Disclose, Kimberly Chaput: Nothing to Disclose, Hammad Liaquat: Nothing to Disclose

2146 | DEVELOPMENT OF A NONINVASIVE MODEL FOR SIGNIFICANT FIBROSIS IN MAFLD USING LASSO REGRESSION

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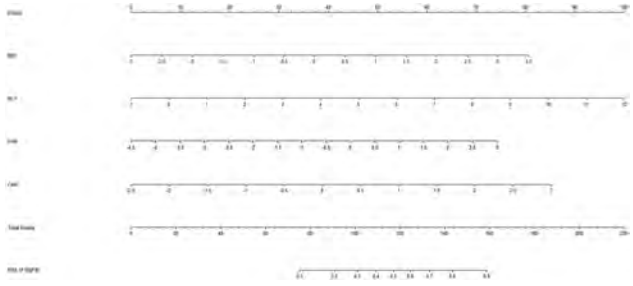
Background: The progression of liver fibrosis in patients with Metabolic dysfunction-Associated Fatty Liver Disease (MAFLD) is often insidious, and there remains a clinical unmet need for noninvasive diagnostic models capable of effectively identifying significant fibrosis in MAFLD (SigFib-MAFLD). This study aimed to develop an assessment model for the early identification of significant liver fibrosis in MAFLD patients. **Methods:** Patients with biopsy-confirmed MAFLD were enrolled from Beijing Ditan Hospital, Capital Medical University between 2008 and 2018. Predictors associated with significant fibrosis were selected using LASSO regression. A multivariable logistic regression model was then constructed based on the selected variables and internally validated using the bootstrap method. The predictive performance of the model was evaluated by receiver operating characteristic (ROC) curve analysis, with calculation of the area under the curve (AUC), and compared with existing indices (FIB-4, APRI, and LSM). Decision curve analysis (DCA) was performed to assess the clinical net benefit of the model. **Results:** A total of 466 patients with biopsy-confirmed MAFLD were ultimately included in this study. The final model incorporated four independent predictors: BMI (aOR = 1.92, 95% CI:1.51-2.44; Z = 5.42, P < 0.001), ALT (aOR = 1.50, 95% CI:1.10-2.04; Z = 2.59, P = 0.010), CHE (aOR = 1.68, 95% CI:1.34-2.12; Z = 4.41, P < 0.001), and CAP (aOR = 2.26, 95%CI:1.77-2.89; Z = 6.51, P < 0.001), all demonstrating significant positive associations with risk of significant fibrosis in MAFLD. The model achieved an AUC of 0.798 (95%CI:0.757-0.840), with diagnostic accuracy significantly superior to existing indices including FIB-4, LSM and APRI (all P < 0.05). Internal validation confirmed good model calibration, while decision curve analysis (DCA) demonstrated favorable clinical utility. **Conclusion:** The composite model comprising BMI, ALT, CHE, and CAP showed excellent diagnostic accuracy for detecting significant fibrosis in MAFLD (AUC 0.798, 95% CI 0.757-0.840).



Disclosures: Wen Deng: Nothing to Disclose, Yao Xie: Nothing to Disclose, Minghui Li: Nothing to Disclose

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2147 | COMBINATION OF ELF SCORE AND CYTOKERATIN-18 FRAGMENT FOR EFFICIENT DETECTION OF AT-RISK MASH

Takemi Akahane[1] Masafumi Oyama[1] NORIHISA NISHIMURA[1] Shinya Sato[1] Kosuke Kaji[1] Tadashi Namisaki[1] Hitoshi Yoshiji[1], [1]Nara Medical University

Background: The prognosis of MASLD/MASH is primarily determined by the degree of liver fibrosis progression. High-risk MASH (at-risk MASH), defined as NAFLD activity score (NAS) ≥ 4 with liver fibrosis stage $F \geq 2$, requires early intervention. Cytokeratin-18 fragment (CK18F) is released into the blood as a result of apoptosis in damaged hepatocytes. CK18F has been shown to be significantly elevated in MASH and is considered useful for MASH detection. Enhanced liver fibrosis (ELF) score is also valuable for diagnosing the degree of liver fibrosis progression. We investigated whether CK18F and ELF are useful for identifying at-risk MASH patients. **Methods:** We measured ELF and CK18F using stored serum samples from 108 MASLD patients who underwent liver biopsy at our hospital. We examined the associations between these biomarkers and biochemical tests as well as pathological findings, and developed a predictive model for detecting at-risk MASH using CK18F and ELF. **Results:** CK18F showed positive correlations with AST, ALT, and HOMA-IR. CK18F levels increased significantly with higher degrees of ballooning and were significantly higher in patients with $NAS \geq 4$ compared to $NAS \leq 3$. The cutoff value of CK18F for predicting ballooning or $NAS \geq 4$ was 329 U/L, with AUROCs of 0.714 and 0.775, respectively. Regarding liver fibrosis, CK18F was significantly higher in the $F \geq 2$ group compared to $F \leq 1$, with a cutoff value of 351 U/L for predicting $F \geq 2$ (AUROC: 0.723). In the at-risk MASH group, CK18F was significantly higher compared to the non-at-risk MASH group, with a cutoff value of 351 U/L for predicting at-risk MASH (AUROC: 0.714). ELF also increased significantly with higher inflammation and ballooning scores in NAS, and was significantly higher in the $F \geq 2$ group compared to $F \leq 1$. ELF was significantly higher in the at-risk MASH group compared to the non-at-risk MASH group, with a cutoff value of 9.91 (AUROC: 0.764). Decision tree analysis for predicting at-risk MASH revealed ELF in the first layer and CK18F in the second layer. **Conclusion:** Both CK18F and ELF reflect ballooning and liver fibrosis, and their combined use may enhance the predictive ability for at-risk MASH. The combination of ELF and CK18F enables efficient identification of at-risk MASH patients, potentially improving patient selection for early intervention and reducing unnecessary liver biopsies.

Disclosures: Takemi Akahane: Nothing to Disclose, Masafumi Oyama: Nothing to Disclose, NORIHISA NISHIMURA: Nothing to Disclose, Shinya Sato: Nothing to Disclose, Kosuke Kaji: Nothing to Disclose, Tadashi Namisaki: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose

2148 | EVALUATING THE CORRELATION BETWEEN NAFLD ACTIVITY SCORE (NAS) WITH NON-INVASIVE FIBROSIS-4 (FIB-4) AND AST TO PLATELET RATIO INDEX (APRI) IN VARIOUS AGE GROUPS WITH BIOPSY-PROVEN MASLD OR MASH: A TERTIARY HEALTH CARE NETWORK RETROSPECTIVE STUDY

Ayah Obeid[1] Frank Lin[1] Parampreet Kaur[1] Kimberly Chaput[1] Hammad Liaquat[1], [1]St. Luke's University Health Network

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) can lead to advanced fibrosis, increasing cardiovascular and liver-related mortality. Liver biopsy is the gold standard for diagnosing NAFLD and Metabolic Dysfunction-Associated Steatohepatitis (MASH), but non-invasive tests like the Fibrosis-4 (Fib-4) index and AST to Platelet Ratio Index (APRI) are increasingly used to assess fibrosis risk. This study evaluates the correlation between the NAFLD Activity Score (NAS) and these non-invasive markers in patients with biopsy-proven MASLD or MASH. **Methods:** We conducted a retrospective analysis of 252 patients with biopsy-proven MASLD or MASH (2020- 2023). Fibrosis risk from the liver biopsy was categorized into mild to moderate (score: 1-2) and advanced fibrosis (score: 3-4). NAS was divided into 0–2 (indeterminate), 3–4 (low to moderate risk), and 5–8 (high risk to advanced fibrosis). Fib-4 was divided into low likelihood of advanced fibrosis, high likelihood, and indeterminate (needs more testing). APRI scores were categorized as low (< 0.5), high (> 1.5), and indeterminate (0.5–1.5). Fib-4 and NAS were combined to create a composite variable, as were Fib-4 and APRI, to compare against the liver biopsy for detecting advanced fibrosis. Statistical tests included unpaired t-tests, Mann-Whitney U tests, Chi-square, and Fisher's exact tests. Diagnostic performance was assessed using sensitivity, specificity, predictive values, and the area under the curve (AUC). **Results:** The cohort had a mean age of 52.94 years (SD: 13.80), with 61.9% female participants. Advanced fibrosis was identified in 6.01% of patients. Among non-invasive markers, Fib-4 demonstrated the highest diagnostic accuracy, with a sensitivity of 66.67%, specificity of 67.86%, and an AUC of 67.26% (Table 1). APRI had lower accuracy, with a sensitivity of 40%, specificity of 77.5%, and an AUC of 58.75%. The NAS score exhibited limited diagnostic utility, with a

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sensitivity of 40%, specificity of 59.29%, and an AUC of 49.64%. Combining Fib-4 with APRI provided marginal improvement, achieving an AUC of 62.17% (Table 2). High NAS scores (5–8) were associated with increased likelihood of advanced fibrosis, with 22.45% and 10.20% of patients in this group classified as high risk by Fib-4 and APRI, respectively (Table 3). However, statistical significance was limited, with p-values of 0.350 for Fib-4 and 0.058 for APRI, reflecting the variability in correlation between NAS and these non-invasive markers. **Conclusion:** Fib-4 is the most reliable non-invasive marker for detecting advanced fibrosis as compared to NAS, APRI, Fib-4 & NAS combined, and Fib-4 & APRI combined. However, NAS alone provides limited diagnostic value, and combining Fib-4 with APRI offers only marginal improvement. These findings suggest that while Fib-4 is a valuable tool, further studies are needed to evaluate non-invasive markers and reduce the reliance on liver biopsy.

Table 1: Diagnostic accuracy of the Fib-4 test against the liver biopsy results for fibrosis.

Fib-4 Score	Liver Biopsy: Advanced fibrosis (3-4)	Liver Biopsy: Mild to moderate (1-2)	Total
High risk	4 (66.67%)	38 (32.14%)	40
Low risk	2 (33.33%)	78 (76.86%)	78
Total	6	112	118

Parameter	Score (95% C.I.)
Sensitivity	66.67% (52.19, 75.17)
Specificity	67.86% (59.43, 76.28)
Positive predictive value	10% (3.59, 15.61)
Negative predictive value	97.44% (94.68, 100)
Area under the curve	67.26% (46.15, 88.37)

Table 2: Diagnostic accuracy of the Fib-4 and APRI test combined against the liver biopsy results for fibrosis.

Fib-4 & APRI combined Score	Liver Biopsy: Advanced fibrosis (3-4)	Liver Biopsy: Mild to moderate (1-2)	Total
High risk (1-2)	4 (57.41%)	41 (32.80%)	45
Low risk (3-4)	3 (42.86%)	84 (67.20%)	87
Total	7	125	132

Parameter	Score (95% C.I.)
Sensitivity	57.14% (18.70, 85.09)
Specificity	67.20% (58.19, 75.21)
Positive predictive value	8.89% (4.03, 13.74)
Negative predictive value	96.55% (93.44, 99.66)
Area under the curve	62.17% (41.96, 82.38)

Table 3: Assessing the correlation between the NAFLD Activity Score (NAS) and non-invasive fibrosis markers (FIB-4, APRI) in patients diagnosed with MASLD or MASH.

Factor	NAS 0-2	NAS 3-4	NAS 5-8	p-value
N	4	51	49	
Fib-4 score				0.350
Indeterminate	0 (0.00%)	19 (38.00%)	23 (46.94%)	
Low likelihood	0 (0.00%)	20 (40.00%)	15 (30.61%)	
High likelihood	1 (100.00%)	11 (22.00%)	11 (22.45%)	
APRI score				0.058
Indeterminate	0 (0.00%)	27 (52.94%)	26 (51.22%)	
Low likelihood	0 (0.00%)	10 (27.25%)	14 (28.57%)	
High likelihood	1 (100.00%)	5 (9.80%)	5 (10.20%)	

Disclosures: Ayah Obeid: Nothing to Disclose, Frank Lin: Nothing to Disclose, Parampreet Kaur: Nothing to Disclose, Kimberly Chaput: Nothing to Disclose, Hammad Liaquat: Nothing to Disclose

2149 | ASSOCIATION OF SENSITIVITY TO THYROID HORMONES AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN EUTHYROID ADULTS

Hyun Woo Oh[1] Yoosoo Chang[1] Kyoung A Ko[1] Won Sohn[1] Seungho Ryu[1] Yong Kyun Cho[1] Byung Ik Kim[1], [1]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine

Background: Thyroid hormones are key regulators of hepatic lipid metabolism, and recent evidence highlights the potential role of thyroid hormone sensitivity, particularly the free triiodothyronine to free thyroxine (FT3/FT4) ratio, in the pathogenesis of metabolic dysfunction-associated steatotic liver disease (MASLD) among euthyroid individuals. However, most prior studies have been cross-sectional, limiting insight into temporal or causal associations. To overcome this limitation, we designed a longitudinal study to determine whether baseline FT3/FT4 ratio can predict the onset or progression of MASLD in a euthyroid population. **Methods:** We performed a prospective longitudinal cohort study of 209,729 South Korean euthyroid adults, free of MASLD at baseline, who participated in repeated health screening examination annually or biennially from January 1, 2011 to December 31, 2021. Steatotic liver disease was diagnosed by ultrasonography. FT4, FT3, and thyroid stimulating hormone levels were measured by ECLIA. The adjusted hazard ratio (aHR) with 95% confidence interval (CI) was estimated using a Cox proportional hazards model. **Results:** Mean age of 209,729 participants was 35.7 years. During a mean follow-up of 5.98 years, 51,205 participants (32.3%) developed MASLD. High FT3/FT4 levels were associated with elevated risk of MASLD with a corresponding multivariable aHR 1.32 (95% CI: 1.29-1.35) for men and 1.21 (95% CI: 1.16-1.27) for women. Subjects with higher FT3/FT4 quintiles were associated with progressively increased risks of MASLD in a dose-response manner in both men and women groups ($P < .001$). **Conclusion:** In a large cohort of euthyroid men and women, increased FT3/FT4 were significantly associated with development of MASLD. FT3/FT4 could be used as new indicators for predicting development of MASLD.

Table 1. Development of MASLD by **Free T3 - Free T4 ratio levels** among participants without MASLD at baseline (n = 209,729)

Quintile of Free T3 - Free T4 ratio	Person-years (PY)	Incident cases	Incidence density (/ 10^3 PY)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR* (95% CI) Model 1	Model 2	HR (95% CI)† in a model with time-dependent variables
Men (n=91,080)							
Q1 (<2.20)	94,603.5	5,545	58.6	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (2.20-2.37)	98,996.6	6,364	64.3	1.10 (1.06-1.14)	1.05 (1.01-1.09)	1.01 (0.97-1.04)	1.10 (1.06-1.15)
Q3 (2.38-2.53)	97,878.3	6,840	69.9	1.19 (1.15-1.23)	1.09 (1.05-1.13)	1.01 (0.97-1.05)	1.17 (1.13-1.22)
Q4 (2.54-2.72)	98,346.8	7,611	77.4	1.31 (1.27-1.36)	1.16 (1.12-1.20)	1.06 (1.02-1.09)	1.24 (1.19-1.28)
Q5 (≥2.73)	98,415.7	8,370	85.0	1.43 (1.39-1.48)	1.19 (1.15-1.23)	1.04 (1.01-1.08)	1.29 (1.25-1.34)
P for trend				<0.001	<0.001	0.001	<0.001
Per 1 increase				1.32 (1.29-1.35)	1.16 (1.13-1.19)	1.04 (1.01-1.07)	1.22 (1.19-1.25)
Women (n=118,649)							
Q1 (<2.20)	157,551.2	2,797	17.8	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (2.20-2.37)	156,620.5	2,981	19.0	1.08 (1.02-1.13)	1.03 (0.98-1.09)	0.99 (0.94-1.05)	1.08 (1.02-1.14)
Q3 (2.38-2.53)	156,557.7	3,365	21.5	1.22 (1.16-1.28)	1.13 (1.07-1.18)	1.06 (1.01-1.11)	1.20 (1.14-1.26)
Q4 (2.54-2.72)	151,915.9	3,525	23.2	1.32 (1.25-1.38)	1.16 (1.10-1.22)	1.06 (1.01-1.12)	1.30 (1.24-1.37)
Q5 (≥2.73)	143,147.3	3,807	26.6	1.51 (1.44-1.59)	1.21 (1.15-1.27)	1.08 (1.02-1.13)	1.44 (1.37-1.51)
P for trend				<0.001	<0.001	<0.001	<0.001
Per 1 increase				1.50 (1.44-1.56)	1.21 (1.16-1.27)	1.09 (1.04-1.14)	1.31 (1.27-1.35)

The P-value for the interaction of sex, and **quintile of Free T3 - Free T4 ratio** with the risk of MASLD was 0·525 (Model 1).
* Estimated from Cox proportional hazards models. Multivariable model 1 was adjusted for age, center, BMI(body mass index), year of screening exam, smoking status, alcohol intake, physical activity, educational level, history of diabetes, history of hypertension and medication for dyslipidemia; model 2: model 1 plus adjustment for hsCRP(high sensitivity C-reactive protein) and HOMA-IR(homeostasis model assessment of insulin resistance).
† Estimated from Cox proportional hazard models with **quintile of Free T3 - Free T4 ratio**, smoking, alcohol consumption, physical activity, BMI, history of diabetes, history of hypertension and medication for dyslipidemia as time-dependent variables, baseline age, center, year of screening exam, and education level as time-fixed variables.
Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio

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2150 | IMPROVING METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE SCREENING IN A RESIDENT CLINIC: A QUALITY IMPROVEMENT INITIATIVE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease worldwide and present in 32% of U.S. adults. A majority of U.S. Veterans have at least one cardiovascular risk factor increasing risk for MASLD. Fibrosis index (FIB-4) is a non-invasive test recommended for estimating liver fibrosis in patients with suspected MASLD. Despite its utility, only 14.8% of eligible patients at a single resident-run primary care clinic had a FIB-4 completed in the previous year. **Methods:** We implemented a quality improvement initiative to increase FIB-4 testing in Veterans aged 35-70 seen in a resident-run primary care clinic affiliated with the Durham Veterans Affairs Medical Center who had at least 1 cardiometabolic risk factor, including body mass index (BMI) $\geq$ 25 kg/m^2, diabetes mellitus type 2 (DM2), pre-diabetes (pre-DM), hypertension (HTN), or hyperlipidemia (HLD). Our intervention consisted of designing and sharing an infographic in clinical work areas with instructions on FIB-4 screening. Data was collected on FIB-4 screening and follow-up testing for 3 months (March-May 2025). We compared FIB-4 screening rates in the baseline and post-intervention periods using a Chi-squared test. **Results:** At baseline, 14.8% of eligible veterans had a FIB-4 completed in the past year. Following the intervention, we saw a 34% relative increase in FIB-4 testing among eligible patients to 230/1,154 (19.9%, $p < .001$). Characteristics of eligible and screened patients are shown in Table 1. The most common MASLD risk-factors among screened patients were HTN (57.1%) and HLD (33.2%). Among those with a FIB-4 score > 1.3 ($n = 78$), 16.7% had a vibration controlled transient elastrography scan (VCTE) ordered to measure their liver stiffness. Of these, 92.3% had VCTE completed, and 7.7% had VCTE discontinued. **Conclusion:** Our study shows that a simple, targeted infographic intervention effectively increased FIB-4 screening rates among Veterans at risk for MASLD in a resident-run primary care clinic. HTN and HLD were the most common risk factors among the screened population. Limitations include lack of data on abdominal imaging and hepatic steatosis assessments. Next steps include a larger cohort, longer follow-up, and improvements in appropriate follow-up testing among patients with elevated FIB-4 scores.

Demographics	Patients eligible for screening (N=1154)	Patients screened with FIB-4 (N=230)
Age (years)		
Mean (SD)	56.4 (10.2)	57.7 (10.6)
Median	59.0	61.0
Sex, n (%)		
Male	933 (80.8)	193 (83.9)
Female	221 (19.2)	37 (16.1)
Race, n (%)		
American Indian or Alaska Native	10 (0.9)	1 (0.4)
Asian	8 (0.7)	2 (0.9)
Black or African American	608 (52.7)	119 (51.7)
Native Hawaiian or other Pacific Islander	7 (0.6)	1 (0.4)
White	475 (41.2)	102 (44.3)
Declined to answer	42 (3.6)	5 (2.2)
Unknown	4 (0.3)	0 (0)
Ethnicity, n (%)		
Hispanic or Latino	38 (3.3)	6 (2.6)
Not Hispanic or Latino	1082 (93.8)	221 (96.1)
Declined to answer	23 (2.0)	1 (0.4)
Unknown	11 (1.0)	2 (0.9)
Co-morbidities		
HTN, n (%)	708 (61.4)	148 (57.1)
HLD, n (%)	418 (36.2)	86 (33.2)
DM2, n (%)	248 (21.5)	47 (18.1)
Obesity, n (%)	253 (21.9)	43 (16.6)
BMI, Mean (SD) (kg/m^2)	32.4 (5.3)	33.1 (6.4)
HbA1c, Mean (SD) (%)	7.5 (2.4)	7.7 (2.7)
HDL, Mean (SD) (mg/dL)	33.2 (5.1)	32.7 (6.8)

Table 1. This table displays the demographics and co-morbidities of the cohort of veterans eligible for MASLD screening and the cohort of veterans that underwent screening over the previous year.

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2151 | EXPLORING THE MULTIDIMENSIONAL STRUCTURE OF NONINVASIVE LIVER FIBROSIS ASSESSMENTS IN MASLD

stephanie Chang[1] Edward De Vol[2] Molly Ma[1] Yu Chen[1] Cecilia Miller[1] Miki Kwan[1] Alex Ma[1] Om Patel[1] Oluwademilade Dada[1] Vibhas Desphande[2] Daniel Ennis[3] Donald Chalfin[2] Ramsey Cheung[4], [1]VA Palo Alto Healthcare System, [2]Siemens Healthineers, [3]Stanford University, [4]Stanford University Medical Center

Background: Liver fibrosis is typically assessed using a combination of serologic, imaging, and demographic features. We analyzed 69 type II diabetic individuals from a larger cohort of 101 patients. Our goal was to understand how commonly used fibrosis-related features co-vary and supports the use of multivariate methods to explore the structure of imperfect proxy measures. **Methods:** We performed principal components analysis on seven standardized variables to assess fibrosis: Fibrosis-4 Index (FIB-4), Enhanced

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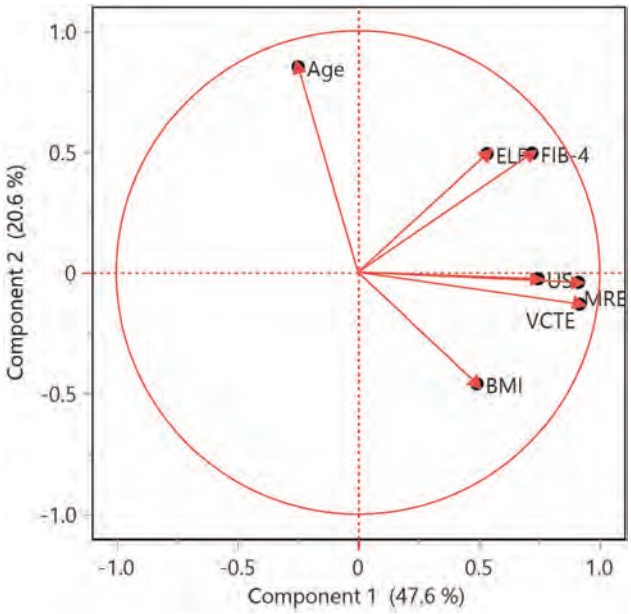
Liver Fibrosis (ELF), vibration-controlled transient elastography (VCTE), ultrasound auto-point shear wave elastography (auto-pSWE) (US), magnetic resonance imaging elastography (MRE), body mass index (BMI), and age. Only subjects with both diagnostic VCTE and MRE were included in the analysis. **Results:** Three principal components (PCs) appeared significant based on scree plot inspection, accounting for 48% (PC1), 21% (PC2), and 13% (PC3) of total variance. PC1 represented a general fibrosis severity axis, with strong loadings from MRE (0.91), VCTE (0.92), US (0.75), [SC1] FIB-4 (0.72), ELF (0.53), and BMI (0.49). This suggests these features collectively describe an underlying dimension of liver disease burden. PC2 was dominated by age (0.85), with moderate contributions from ELF (0.49) and FIB-4 (0.49), and a negative association with BMI (-0.46). This component may reflect an age-associated pattern of fibrosis expression or marker responsiveness. PC3 had high loading from BMI (0.69) and a strong negative loading from US (-0.56), possibly representing a BMI-US interaction, where adiposity may affect imaging performance. **Conclusion:** Our findings suggest that a set of underlying dimensions can capture key variations across noninvasive fibrosis-related measures to potentially streamline fibrosis assessment and support more efficient risk stratification. The first component supports combined use of VCTE, US, MRE, ELF, and FIB-4 to assess fibrosis burden, while the second highlights age-related differences in fibrosis profiles, potentially useful for refining stratification in older patients. The third supports an inverse relationship between BMI and US, highlighting how body composition may influence fibrosis interpretation. Overall, these findings reinforce the multi-factorial nature of liver fibrosis.



Disclosures: stephanie Chang: Siemens Healthineers: Grant/Research Support, Edward De Vol: Nothing to Disclose, Molly Ma: Nothing to Disclose, Yu Chen: Nothing to Disclose, Cecilia Miller: Nothing to Disclose, Miki Kwan: Nothing to Disclose, Alex Ma: Nothing to Disclose, Om Patel: Nothing to Disclose, Oluwademilade Dada: Nothing to Disclose, Vibhas Desphande: Nothing to Disclose, Daniel Ennis: Siemens Healthineers: Grant/Research Support, Donald Chalfin: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Nothing to Disclose

2152 | DESIGN OF A NON-INTERVENTIONAL STUDY TO ESTIMATE THE PREVALENCE OF UNDIAGNOSED MASH USING US REAL-WORLD DATA THROUGH MACHINE LEARNINGNEW SUBMISSION

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Background: The US prevalence of metabolic dysfunction-associated steatohepatitis (MASH; previously non-alcoholic steatohepatitis [NASH]) is estimated at 5%. Administrative databases rely on International Classification of Diseases (ICD) codes for NASH, so only patients who were assigned NASH-related ICD codes can be identified in these datasets. However, they inadequately describe the condition, particularly the stage of fibrosis, so MASH is often underdiagnosed and underreported in routine clinical care. This is compounded by the invasive and costly nature of liver biopsy for large-scale screening. Advances in non-invasive tests (NITs), and machine learning (ML) approaches, may offer new tools for MASH screening, using combinations of blood-based biomarkers. We aim to estimate how the prevalence of MASH in the US could vary using criteria that incorporate the use of ICD codes and NITs using different methods, including ML. **Methods:** This is an observational, non-interventional, retrospective study using electronic health record and claims data from the Optum Market Clarity US database between January 1, 2021, and December 31, 2023. Eligible individuals are aged ≥18 years as of January 1, 2021. Patients with liver disease etiologies other than

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MASH, and with missing age data, are excluded. Case definitions for different criteria used to define diagnosed and undiagnosed MASH, using ICD codes, Fibrosis-4 (FIB-4), and LiverPRO parameters are described in Table 1. LiverPRO is a novel, validated, algorithm-based medical device that estimates liver fibrosis risk using routinely collected NITs and patient age. **Results:** The primary outcome is the period prevalence of MASH, as indicated by the different case definitions, within the study population. Secondary and exploratory outcomes are patient demographics and clinical characteristics, number of cases of undiagnosed MASH for each case definition compared with specific ICD codes, distribution of patients diagnosed with MASH across fibrosis stages identified by LiverPRO or FIB-4 scores, and quantification of undiagnosed individuals with laboratory values indicative of MASLD. **Conclusion:** We predict that diagnosed prevalence will be low compared with undiagnosed prevalence. By leveraging advanced screening methods that combine traditional diagnosis codes with laboratory-based biomarkers, we aim to enhance the understanding of the clinical and demographic landscape of MASH, improve case detection, and inform future public health and clinical strategies.

Table 1. Operational case definitions of MASH and undiagnosed MASH

Case definition	Operational criteria	
	Inclusion criteria	Exclusion criteria
#1: ICD-10 based MASH (Diagnosed MASH)	At least one ICD-10 (K75.81) code for MASH	At least one ICD-10 code for liver disease other than MASLD/MASH, or selected alcohol-related diseases
#2: ICD-10 for MASLD and FIB-4 ≥1.3 (Undiagnosed MASH)	At least one ICD-10 code (K76.0) for MASLD and a FIB-4 score ≥ 1.3	Same exclusion criteria as listed for 1
#3: ICD-10 for MASLD and LiverPRO-identified F2, F3, F4 (Undiagnosed MASH)	At least one ICD-10 (K76.0) code for MASLD and LiverPRO predicting fibrosis stages F2, F3, or F4	Same exclusion criteria as listed for 1
#4: ICD-10 based MASLD (Diagnosed MASLD)	At least one ICD-10 code (K76.0) for MASLD	Same exclusion criteria as listed for 1
#5: FIB-4 ≥1.3 without ICD-10 codes for MASLD or MASH (Undiagnosed MASH)	Patients with a FIB-4 score ≥ 1.3	At least one ICD-10 code for MASLD (K76.0) or MASH (K75.81) or as listed for 1
#6: LiverPRO F2, F3, F4 without ICD-10 codes for MASLD or MASH (Undiagnosed MASH)	Patients meeting LiverPRO criteria for fibrosis stages F2, F3, or F4	At least one ICD-10 code for MASLD (K76.0) or MASH (K75.81) or as listed for 1

ICD-10, International Classification of Diseases, 10th Revision; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatosis liver disease.

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2153 | UTILIZATION OF ENHANCED LIVER FIBROSIS (ELF) TEST IN THE EVALUATION OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Identifying individuals who are at risk for significant liver fibrosis is key step in risk stratification for metabolic dysfunction-associated steatotic liver disease (MASLD). The Enhanced Liver Fibrosis (ELF) test is a non-invasive test (NIT) recommended by society guidelines as a secondary tool for liver fibrosis assessment. The purpose of this study was to examine the application of ELF across two hepatology clinics with differing diagnostic testing availability. **Methods:** This was a retrospective study including 287 adult patients referred for MASLD evaluation from September

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2023 and May 2024 at two clinics (Clinic 1: access to transient elastography [TE] and Clinic 2: no access to TE). 50 participants were excluded due to pre-existing diagnosis of cirrhosis or unmet MASLD criteria. Data included demographics, clinical characteristics, and modalities of fibrosis staging (ELF, TE, magnetic resonance elastography [MRE], liver biopsy). Differences in ELF utilization by clinic location were assessed with a chi-square analysis. Secondary analyses compared FIB-4 and ALT levels between ELF-tested and non-tested groups and correlated FIB-4 with ELF scores. **Results:** Our final cohort of 237 participants (140 in Clinic 1 and 97 in Clinic 2), with 43.5% male, mean age 53.1 years (SD 14.16), and mean BMI 34.1 kg/m² (SD 7.9). ELF testing was performed in 27.8% (66/237), with a mean score of 9.61 (SD 1.10). Of those tested, 59.1% (n = 39) had indeterminate risk for significant fibrosis (ELF 9.80–11.29), and 37.9% (n = 25) had high risk (ELF > 11.29). In Clinic 2, the primary reasons for ELF testing included indeterminate FIB-4 (30%, n = 9), age (20%, n = 6), and clinic location (20%, n = 6); in Clinic 1, indeterminate FIB-4 was the leading reason (36.1%, n = 13). Clinic location was not significantly associated with ELF test utilization ($\chi^2 = 3.06$, $p = 0.92$). In Clinic 2, 37.74% (n = 20) of patients with FIB-4 > 1.3 underwent ELF testing, compared to 23.26% (n = 10) with FIB-4 < 1.3. ELF scores showed a moderate correlation with FIB-4 ($R = 0.42$, $p < 0.05$). Among patients with high-risk ELF scores (> 11.29) who underwent further evaluation, TE (n = 18), MRE (n = 11), or liver biopsy (n = 8) confirmed advanced fibrosis in a subset (e.g., 33.3% of TE and MRE in Clinic 2 showed elevated stiffness; biopsies showed stages 0–4), supporting ELF's role in identifying at-risk patients, though small sample sizes limit definitive conclusions. **Conclusion:** ELF testing was utilized in over a quarter of MASLD patients and correlated moderately with FIB-4. Its application varied by clinic, with greater reliance in Clinic 2 due to the absence of TE. These findings suggest that ELF can enhance risk stratification in MASLD, particularly in resource-limited settings, warranting further prospective studies to validate its integration into clinical algorithms.

Table 1. Reason for ELF test by clinic location

	Clinic 1 (access to TE)	Clinic 2 (no access to TE)
Clinic location	4 (11.11%)	6 (20%)
Age	8 (22.22%)	6 (20%)
Indeterminate FIB4	13 (36.11%)	9 (30%)
Unsuccessful TE	0 (0%)	1 (3.33%)
Patient not NPO for TE	2 (5.56%)	1 (3.33%)
Patient or provider preference	3 (8.33%)	4 (13.33%)
Low FIB4	6 (16.67%)	3 (10%)

Disclosures: Amreen Dinani: Madrigal Pharmaceutical: Consultant, Madrigal Pharmaceutical: Consultant, Novonordisk: Consultant, Novonordisk: Consultant, Kinetic: Advisor, Kinetic: Advisor, Madrigal Pharmaceutical: Consultant, Madrigal Pharmaceutical: Consultant, Novonordisk: Consultant, Novonordisk: Consultant, Kinetic: Advisor, Kinetic: Advisor, Karen Young: Nothing to Disclose, Chukwuemeka Oko: Nothing to Disclose

2154 | THE NFS SCORE DEMONSTRATES SUPERIOR DIAGNOSTIC PERFORMANCE IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)-RELATED CIRRHOSIS

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Background: Early diagnosis of metabolic dysfunction-associated steatotic liver disease (MASLD)-related cirrhosis is critical for improving patient outcomes. However, liver biopsy, the traditional gold standard, is limited by its invasiveness. This study evaluated the diagnostic performance of non-invasive methodologies, including FIB-4, APRI, FAST, NFS, ABIDE, and SIRI. The results demonstrated that the NFS score exhibited superior diagnostic efficacy, thereby establishing itself as a highly efficient and safe screening tool for MASLD-related cirrhosis. **Methods:** Hospitalized patients diagnosed with non-alcoholic fatty liver disease (NAFLD) at the Fourth Affiliated Hospital of Xinjiang Medical University (January 2018–December 2024) were enrolled. Demographic, clinical, and serological data were collected. Non-invasive indices (FIB-4, APRI, FAST, NFS, ABIDE, SIRI) were calculated. Patients were stratified into cirrhosis and non-cirrhosis groups based on liver biopsy (gold standard). Multivariate logistic regression identified predictors of MASLD-related cirrhosis. Cut-off values were determined, and diagnostic performance was assessed using the area under the receiver operating characteristic curve (AUROC). **Results:** 1. Among 144 MASLD patients (50.23 ± 13.14 years), 49 (34%) had cirrhosis. 2. Multivariate analysis identified FAST [OR = 2.63, 95% CI: 1.16–5.94, P = 0.020] and NFS scores [OR = 2.02, 95% CI: 1.27–3.22, P = 0.003] as independent predictors of MASLD-related cirrhosis. 3. The AUROCs for NFS and FAST scores were 0.86 (95% CI: 0.80–0.92) and 0.68 (95% CI: 0.58–0.79), respectively, with optimal cut-off values of -0.91 and -0.75. Both scores demonstrated superior diagnostic performance compared to FIB-4 and APRI. **Conclusion:** The NFS and FAST scores serve as effective non-invasive tools for diagnosing MASLD-related cirrhosis, with the NFS score exhibiting significantly higher diagnostic accuracy.

Disclosures: SUN Wei: Nothing to Disclose, YU Hong: Nothing to Disclose, Dou Jing: Nothing to Disclose, WU Xu: Nothing to Disclose, LI Jingtao: Nothing to Disclose,

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Wang Xiaozhong: Nothing to Disclose, Guo Feng: Nothing to Disclose

2155 | COMMON SINGLE NUCLEOTIDE POLYMORPHISM DISTRIBUTION AND ASSOCIATIONS WITH A SURROGATE OF LIVER DISEASE SEVERITY IN MASLD PATIENTS FROM THE UNITED STATES (U.S.) AND TAIWAN

Maria Stepanova[1] Mei-Hsuan Lee[2] James Estep[3] Yan-Ling You[2] Xia-Rong Liu[2] Leyla de Avila[1] Brian Lam[1] Zobair Younossi[1], [1]The Global NASH Council (GNC), Washington DC, United States, [2]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, [3]Beatty Liver and Obesity Research Program, Inova Health System, Falls Church, VA, United States

Background: Genetic risk factors have been linked to liver disease severity in patients with MASLD. The association of the genetic factors with non-invasive tests (NITs) in various global populations is less well established. We aimed to assess the distribution of common Single Nucleotide Polymorphism and their association with FIB-4 as a surrogate of disease severity in MASLD. **Methods:** Two groups of MASLD patients from the U.S. (hepatology clinic) and Taiwan (Taiwan Biobank, community settings recruitment) were analyzed. Both groups had genomics data for loci rs738409 (*PNPLA3*), rs641738 (*MBOAT7*), and rs58542926 (*TM6SF2*). Individual alleles were evaluated for association with FIB-4 ≥ 1.30 (elevated) or ≥ 2.67 (high). **Results:** In comparison to the U.S. MASLD patients (n = 1,969), MASLD patients from Taiwan (N = 4477) were older (age 53 ± 10 years vs. 52 ± 13 years) and had a higher proportion of females (69% vs. 44%), while the U.S. patients had higher BMI (37 ± 10 vs. 26 ± 4 kg/m²), more type 2 diabetes (36% vs. 7%) and higher liver enzymes (AST, ALT), fasting glucose, and triglycerides (all $p < .01$). Genotypic analysis revealed differences in allele distributions of rs738409 (*PNPLA3*), rs58542926 (*TM6SF2*), and rs641738 (*MBOAT7*) between 2 groups (all $p < 0.01$). In Taiwanese and U.S. patients, the frequency of the *PNPLA3* GG (high-risk) genotype was 17% and 13%, while CC *PNPLA3* genotype (low-risk) was present in 35% vs. 47% ($p < 0.0001$). The *MBOAT7* TT and CC genotypes were observed in 6% (Taiwanese) vs. 14% (U.S.) and 58% (Taiwanese) vs. 30% (U.S.), respectively ($p < 0.0001$). Taiwanese patients had a lower frequency of the *TM6SF2* CT/TT genotypes (15%) compared to 18% in the U.S. ($p < 0.01$). The FIB-4 scores were lower in Taiwanese patients with MASLD than the U.S. patients (1.19 ± 0.52 vs. 1.54 ± 1.61, $p < 0.0001$). Logistic regression adjusted for age and sex showed that *PNPLA3* CC/CG alleles were significantly associated with elevated FIB-4 in both groups ($p < 0.05$) (Table). The *TM6SF2* CT/TT allele was associated with high FIB-4 in Taiwanese but not in the U.S. patients, while the minor alleles at rs641738 (*MBOAT7*) showed no association with high FIB-4 in either cohort (Table). **Conclusion:** The polymorphism rs738409 (C- > T) in the *PNPLA3* gene is associated with high FIB-4 score as a surrogate of disease severity in both the U.S. and Taiwanese patients with MASLD.

Table

Allele	Taiwanese patients with MASLD		U.S. patients with MASLD	
	OR (95% CI)	p	OR (95% CI)	p
Outcome: FIB-4 ≥1.30				
rs738409 (*PNPLA3*)				
CG (ref: CC)	1.18 (1.00-1.40)	0.0151	1.56 (1.24 - 1.96)	<.0001
GG (ref: CC)	1.28 (1.03-1.60)		3.11 (2.23 - 4.34)	
rs58542926 (*TM6SF2*)				
CT / TT (ref: CC)	1.33 (1.08-1.64)	0.0064	1.00 (0.71 - 1.41)	0.99
rs641738 (*MBOAT7*)				
CT (ref: CC)	1.02 (0.87-1.19)	0.76	0.97 (0.69 - 1.35)	0.64
TT (ref: CC)	1.05 (0.77-1.42)		1.12 (0.69 - 1.82)	
Outcome: FIB-4 ≥2.67				
rs738409 (*PNPLA3*)				
CG (ref: CC)	1.54 (0.85-2.81)	0.31	2.14 (1.55 - 2.96)	<.0001
GG (ref: CC)	1.39 (0.64-3.03)		3.86 (2.57 - 5.81)	
rs58542926 (*TM6SF2*)				
CT / TT (ref: CC)	1.82 (1.00-3.31)	0.0487	0.84 (0.45 - 1.57)	0.58
rs641738 (*MBOAT7*)				
CT (ref: CC)	1.07 (0.62-1.83)	0.73	0.99 (0.56 - 1.72)	0.79
TT (ref: CC)	0.57 (0.14-2.40)		0.89 (0.37 - 2.11)	

Disclosures: Maria Stepanova: Nothing to Disclose, Mei-Hsuan Lee: Nothing to Disclose, James Estep: Nothing to Disclose, Yan-Ling You: Nothing to Disclose, Xia-Rong Liu: Nothing to Disclose, Leyla de Avila: Nothing to Disclose, Brian Lam: Madrigal: Speaking and Teaching, Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant

2156 | NON-INVASIVE TESTS ACCURACY FOR LIVER FIBROSIS STRATIFICATION IN ADULTS WITH GRADE II-III OBESITY IN THE WAITING LIST FOR METABOLIC AND BARIATRIC SURGERY IN BRAZIL - A MULTICENTRIC STUDY

Thaís Guaraná[1] Fernando de Barros[2] Leonardo Pereira[3] Celso Nilo Didoné[4] Luis Fernando Ferreira[5] Carlos Frederico Campos[6] Cristiane Tovo[7] Claudia Alexandra Ivantes[4] Cristiane Villela-Nogueira[8], [1]Universidade Federal Fluminense, Niterói, RJ; Programa de Pós-Graduação em Clínica Médica, UFRJ, RJ, [2]Universidade Federal Fluminense and Hospital São Francisco da Providência, [3]Medical School, Universidade Federal Fluminense, Niterói, RJ, [4]Hospital Nossa Senhora das Graças, Curitiba, PR, [5]Programa de Pós-Graduação em Ciencias da Reabilitação, UFCSPA, [6]Fonte Patologia Oncológica SA, Rio de Janeiro, [7]Universidade Federal de Ciências da Saúde de Porto Alegre - UFCSPA, [8]Hospital

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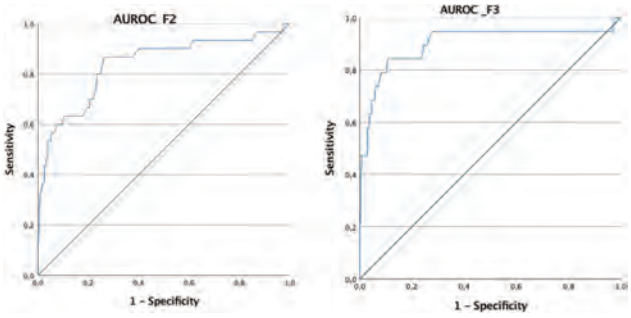
Universitário Clementino Fraga Filho- Universidade Federal do Rio de Janeiro

Background: Persons living with obesity are at high risk for metabolic dysfunction- associated steatotic liver disease (MASLD) and its complications. Few studies analyze the accuracy of non-invasive tests for detecting significant/advanced liver fibrosis in individuals with obesity grade equal or higher than grade II. This study evaluated FIB-4 data and VCTE accuracy in patients with grade II-III obesity. **Methods:** Individuals living with grade II-III obesity on the waiting list for bariatric and metabolic surgery (BMS) in three tertiary centers were included. Clinical and laboratory data were collected two months before surgery, and VCTE was performed by Fibroscan® 430 mini + with continuous CAP with XL probe (Echosens, Fr) one week before BMS. All patients performed a liver biopsy (LB) during BMS. Regarding FIB-4, the sensitivity (S), specificity (Sp), negative (NPV) and positive predictive values (PPV) were calculated for a cut-off of 1.3. AUROC curves were plotted to evaluate the accuracy of VCTE to identify significant and advanced fibrosis in this population. **Results:** A total of 474 individuals were included (79% women, 41.5 ± 10.2 yrs, BMI 44.1 ± 6.1 kg/m2, 82.7% obesity grade III). Exclusion due to unreliability of liver stiffness by Fibroscan® was only 1.1%. At LB, 94% were F0-F1, 2.5% F2, 2.1 % F3 and 1.9% F4. FIB-4 lower than 1.3 was identified in 93.1%; among those, only five patients (26.3%) had F ≥ 3. Regarding FIB-4 with a 1.3 cut-off, S of 73%, Sp of 93%, PPV = 31% and an NPV of 98% was found. The AUROC of VCTE for F ≥ 2 and F ≥ 3 were 0.83 (0.74-0.92; $p < 0.001$) and 0.93 (0.80 – 1.00; $p = 0.001$), respectively. **Conclusion:** FIB-4 is a valuable tool for excluding advanced fibrosis in individuals with obesity grade II or III. The accuracy of VCTE by 430 mini + with continuous CAP with XL probe showed good performance in stratifying liver fibrosis in both F2 and F3 individuals on the BMS waiting list, and it may be an useful non-invasive tool in this population.



Disclosures: Thaís Guaraná: Nothing to Disclose, Fernando de Barros: Nothing to Disclose, Leonardo Pereira: Nothing to Disclose, Celso Nilo Didoné: Nothing to Disclose, Luis Fernando Ferreira: Nothing to Disclose, Carlos Frederico Campos: Nothing to Disclose, Cristiane Tovo: Nothing to Disclose, Claudia Alexandra Ivantes: Nothing to Disclose, Cristiane Villela-Nogueira: Nothing to Disclose

2157 | HIGH CONCORDANCE OF MASLD AND NAFLD NOMENCLATURES IN PREGNANCY

Sindhu Chadalawada[1] Cecilia Katzenstein[2] Nina Rodriguez[2] Tatyana Kushner[3] Monika Sarkar[4], [1]University of California San Francisco, [2]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [3]Division of Gastroenterology & Hepatology, Weill Cornell Medicine, New York, NY, USA, [4]University of California, San Francisco

Background: Nonalcoholic fatty liver disease (NAFLD) diagnosis by traditional criteria has high concordance with the updated definitions for metabolic dysfunction-associated steatotic liver disease (MASLD). However, concordance of these entities has not been validated in pregnancy. **Methods:** This retrospective cohort study aimed to validate MASLD nomenclature in pregnancies with previously established NAFLD within obstetric practices at two large academic health systems. Chart review of all cases was used to confirm NAFLD and MASLD criteria among pregnant patients in their second trimester onwards seen at our centers between January 2013 to September 2024. Demographic and clinical data including imaging, transient elastography, and/or liver biopsy evidence of steatosis within 1.5 years of pregnancy, as well as pre-conception and gestational metabolic risk factors were noted. Descriptive statistics for continuous variables were reported for mean, median interquartile range (IQR), and standard deviation (SD). **Results:** Among 302 women with one or more pregnancies having a NAFLD diagnosis by imaging and/or biopsy confirmed steatosis, 100% were identified to have ≥ 1 metabolic risk factors (body mass index [BMI] > 25 kg/m2, HbA1c ≥ 5.7%, hypertension [HTN] or anti-HTN treatment, triglycerides > 150 mg/dL, HDL < 50 mg/dL or lipid lowering therapy), therefore meeting MASLD criteria in the absence of alternative causes of steatosis. Most patients reported Hispanic ethnicity (60.9%), with a mean age of 31 years (median 32 [IQR 27-36] SD 6.8), BMI of 36.3 kg/m2 (median 35 [IQR 32-40] SD 6.6), and HbA1c of 5.8% (median 5.5 [IQR 5.2-5.9] SD 1.5). All patients met MASLD criteria by BMI cutoff > 25 kg/m2 (> 23 kg/m2 for Asian race) (Table 1). Of these patients, five met NAFLD criterion when considering gestational diabetes (GDM) in place of pregestational diabetes. Pregnancy-specific metabolic conditions were evenly distributed within the cohort and included gestational hypertension (19.2%), preeclampsia (18.9%), and GDM (22.2%). **Conclusion:**

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Concordance of NAFLD and MASLD definitions was high in pregnancy at 98.3%. When polycystic ovarian syndrome (PCOS) and gestational risk factors were considered, there was a 100% concordance rate.

Table 1. Metabolic Risk Factors in Pregnancy

	UCSF N=74	Sinai N=228	Total N=302 (%)
Pre-conception Risk Factors			
BMI > 25 kg/m^2 (23 for Asian race)	74	228	302 (100%)
HgA1c ≥ 5.7% or T2DM	40	43	83 (27.2%)
HTN or Anti-HTN Rx	24	33	57 (18.9%)
TG > 150 or Lipid Rx	35*	6*	41 (13.6%)
HDL < 50 (F) or Lipid Rx	35*	6*	41 (13.6%)
Gestational Risk Factors			
Gestational HTN	13	45	58 (19.2%)
Preeclampsia	25	32	57 (18.9%)
Gestational Diabetes	33	34	67 (22.2%)
PCOS	23	22	45 (14.9%)

*May be underreported as lipid panels are not routinely ordered in pregnancy

Disclosures: Sindhu Chadalawada: Nothing to Disclose, Cecilia Katzenstein: Nothing to Disclose, Nina Rodriguez: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Monika Sarkar: GSK: Grant/Research Support, Zydus Pharmaceuticals: Grant/Research Support, Gilead Sciences: Grant/Research Support

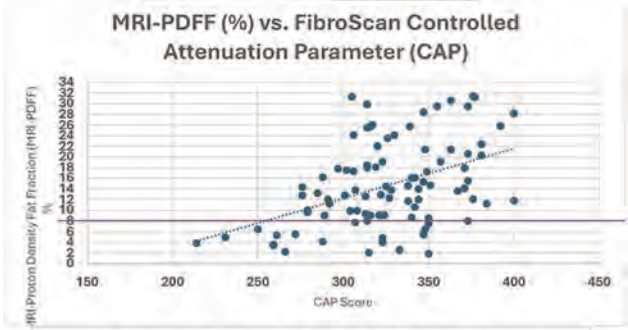
2158 | ASSOCIATED PARAMETERS THAT MAY AFFECT PDFF TRIAL OUTCOMES

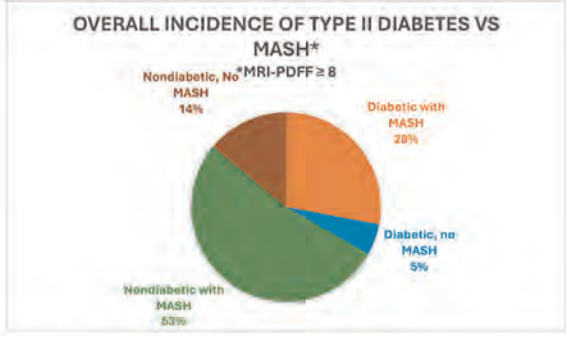
Elisabeth Verwest[1] Ian McCauley[1] Nicholas Kruzdlo[1] Dominika Budai[1] Cameron Rolph[1] Raymond Bell[1] Kyla Thiel[1] Yovanni Rosario[1] Isabelle Crotsley[1] Guy Neff[1], *[1]Covenant Metabolic Specialists, LLC*

Background: Metabolic associated steatohepatitis (MASH) has become the most prevalent form of chronic liver disease in the United States, with an adult incidence of 20% expected by 2030. Accurate non-invasive testing for chronic liver disease is vastly needed. In clinical research, MRI-PDFF (proton density fat fraction) is the most widely accepted non-invasive method to identify and quantify hepatic steatosis causing fibrosis and inflammation. The purpose of this study is to evaluate MRI-PDFF data to analyze and establish a link between various morbidity-associated diseases, as well as explore the extent to which these risk factors may serve as predictors of PDFF results. **Methods:** Data from 93 subjects of a MASH clinical trial was collected for retrospective analysis. Qualifying criteria for presumed MASH was a liver fat fraction of 8% or higher. FibroScan scores for controlled attenuation parameter (CAP) were compared with MRI-PDFF results to establish correlation using statistical analysis. Comorbid risk factors of BMI and Type II Diabetes Mellitus (T2DM) were collected and analyzed in association with CAP scores and PDFF values above and below 8% fat content. **Results:** The relationships between the patients' various comorbidities (i.e., T2DM, HbA1c, and BMI) were analyzed with CAP and MRI-PDFF scores. As predicted, MRI-PDFF and CAP score were positively correlated. In total, approximately 70% of those with CAP scores of at least 300 also had MRI-PDFF of 8% or higher, and 100% of CAP scores over 350 showed at least 8% liver fat in MRI. Only 10.8% of patients with CAPs below 300 resulted in MRI-PDFFs qualifying for MASH. Analysis of comorbidities revealed mixed results. While only 34.7% of patients with MRI-PDFF of 8% or above were type II diabetic, approximately 83.9% of all diabetic patients who completed MRI-PDFF met the criteria for MASH. Neither BMI nor HbA1c appeared to have any significant correlation with CAP or MRI-PDFF results. **Conclusion:** In support of the broader body of MASH research, the data analysis indicates that a variety of factors likely contribute to overall risk of MASH development and shows a correlation between T2DM and hepatic steatosis. The findings suggest direct parameters such as comorbidity incidence will help guide use of MRI-PDFF and other diagnostic tools. The potential to determine a level of predictiveness for comorbid risk factors of MASH may have applications in optimizing the screening process for clinical trials by increasing the probability of identifying subjects with elevated PDFF fat % values.

Total:	CAP≥300, ≥8%	CAP≥300, <8%	CAP<300, ≥8%	CAP<300, <8%
93	65	9	10	9

CAP ≥300, >8%	CAP ≥325, ≥8%	CAP >350, ≥8%
69.90%	89%	100%





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Disclosures: Elisabeth Verwest: Nothing to Disclose, Ian McCauley: Nothing to Disclose, Nicholas Kruzdlo: Nothing to Disclose, Dominika Budai: Nothing to Disclose, Cameron Rolph: Nothing to Disclose, Raymond Bell: Nothing to Disclose, Kyla Thiel: Nothing to Disclose, Yovanni Rosario: Nothing to Disclose, Isabelle Crotsley: Nothing to Disclose, Guy Neff: Nothing to Disclose

◆ 2159 | HOW THE CAUSE OF LIVER FAILURE SHAPES THE POST-TRANSPLANT JOURNEY: PATIENT-REPORTED OUTCOMES ACROSS ETIOLOGIC CATEGORIES

Lorrinda Gray-Davis[1] Richard Jaenisch[1] David Jaenisch[1] Karen Hoyt[1] Mustafa Behan[2] Jutta Kurz[2] Valeriia Aksakovska[2] Michael Tunkelrott[3] Rachma Purnama[3] Emmanuel Gorospe[4] Tarek Hassanein[5], [1]None, [2]Amsety, [3]Amsety LLC, [4]Burrell College of Osteopathic Medicine, [5]Southern California Liver Centers

Background: While one-year survival post-liver transplant (LTx) exceeds 93%, 38.1% of grafts fail by year ten. This pilot study suggests the underlying cause of liver failure, regardless of underlying etiology, significantly influences long-term experiences, needs, and complications over uniform survivorship model for post-transplant follow-up care. **Methods:** We conducted an exploratory survey (March–April 2025) of 200 LTx patients from a world-wide network, yielding 76 responses. The HIPAA-compliant Amsety database has over 650,000 U.S. individuals, including 13,000 self-identified LTx cases. Participants were stratified by transplant indication. Survey covered complications, follow-up frequency, medication changes, testing patterns, psychosocial stressors, and educational priorities. **Results:** Respondents with NASH/MASH reported the highest overall complication burden, including elevated liver enzymes and kidney problems, as well as the greatest unmet need for nutrition guidance, exercise support, and education about rejection signs. Alcohol-related recipients showed high rates of skin cancer and frequent medication adjustments and were more likely to cite adherence and mental health as ongoing challenges. By contrast, viral hepatitis recipients experienced fewer complications and greater medication stability, while autoimmune and drug-induced injury groups showed higher testing frequency and dynamic immunosuppression changes. Educational and support needs were strongly etiology-dependent. Nutrition was the most requested topic across all groups, but those with NASH/MASH or alcohol-related causes also emphasized peer support and mental health resources. As expected, the first post-transplant year emerged as the most vulnerable time, with the highest rates of complications and information needs. **Conclusion:** Transplant indication meaningfully shapes the post-transplant course. A uniform survivorship model may miss critical differences in complications, care engagement, and psychosocial needs. Etiology-specific approaches integrating nutrition, mental health, and long-term monitoring are likely warranted. This pilot study emphasizes the need for more research exploring etiology-specific survivorship care planning in liver transplantation.

Disclosures: Lorrinda Gray-Davis: Nothing to Disclose, Richard Jaenisch: Nothing to Disclose, David Jaenisch: Nothing to Disclose, Karen Hoyt: Nothing to Disclose, Mustafa Behan: Amsety GmbH: Founder and Co-Owner, Jutta Kurz: Nothing to Disclose, Valeriia Aksakovska: Amsety GmbH: Employee, Michael Tunkelrott: amsety: non-compensated advisor, Rachma Purnama: Amsety GmbH: Employee, Emmanuel Gorospe: Nothing to Disclose, Tarek Hassanein: AbbVie: Speaker and Research Support, Gilead: Speaker and Research Support, HepQuant Shunt: Advisor, Madrigal: Advisor and Research Support, Amgen: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer- Ingelheim: Grant/Research Support, COUR: Grant/Research Support, Escient: Grant/Research Support, Galectin: Grant/Research Support, Grifols: Grant/Research Support, Intercept: Grant/Research Support, Janssen: Grant/Research Support, Merck: Grant/Research Support, Mirum: Grant/Research Support, NeuroBo: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pfizer: Grant/Research Support, Regeneron: Grant/Research Support, Salix Pharmaceuticals: Grant/Research Support, Takeda: Grant/Research Support, Akero: Grant/Research Support, Ipsen: Grant/Research Support, Kowa: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, DURECT: Grant/Research Support, HepQuant: Grant/Research Support, Terns Pharmaceutical: Grant/Research Support, Mallinckrodt: Speaker and Research Support, Eli Lilly: Grant/Research Support, PharmaIn: Grant/Research Support, Sonic incytes: Grant/Research Support, Tensor Bio: Grant/Research Support, 89Bio: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Nterica: Consultant

2160 | IMPAIRED WORKING MEMORY IN INDIVIDUALS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND FATIGUE

Ali Weinstein[1] Leyla de Avila[2] Brian Lam[2] Jillian Price[2] Carey Escheik[2] Lynn Gerber[2] Zobair Younossi[2],

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[1]Department of Global and Community Health, George Mason University, Fairfax, VA, USA, [2]Beatty Liver and Obesity Research Program, Inova Health System, Falls Church, VA, USA

Background: Fatigue has been well-documented to negatively impact cognitive performance, including working memory. MASLD is associated with systemic inflammation and metabolic dysregulation both of which can affect brain health by influencing brain metabolism, thereby leading to cognitive performance deficits such as impaired working memory. However, the interactive effects of MASLD and fatigue on cognitive performance have not been well studied. The current project examined the working memory performance of individuals with MASLD and fatigue. **Methods:** Subjects enrolled in this cross-sectional study from a liver clinic. Subjects completed informed consent. Participants attended a one-time research visit where clinical, demographic, and cognitive performance data were collected. Working memory was tested using the WAIS-IV arithmetic and digit span tests. The scores from these tests were combined into a composite score that yields an overall working memory index (WMI). FACIT-Fatigue self-report tool was also completed. Presence of fatigue was defined as a score of 40 or less on the FACIT-Fatigue. MASLD was defined as presence of hepatic steatosis by ultrasonography or CAP $\geq$ 280 by transient elastography (TE) and at least 1 of 5 cardiometabolic risk factors (BMI $\geq$ 25, BP $\geq$ 130/85, type 2 diabetes, triglycerides $\geq$ 150 mg/dl; HDL cholesterol $\leq$ 40mg/dl). **Results:** There were 101 participants in the study, 65 MASLD [29 with MASLD and fatigue and MASLD without fatigue (n = 36)] and 36 controls without MASLD [Controls with fatigue (n = 14) and Controls without fatigue (n = 22)]. Those with MASLD and fatigue had statistically significantly higher BMI's than the others. The WMI was statistically significantly lower in those with MASLD and fatigue (99.7 ± 13.8) compared to the others (106.3 ± 14.8; $p = 0.04$). When we compared those with MASLD (n = 65) to those without (n = 36) and when comparing those with fatigue (n = 43) to those without fatigue (n = 58), the WMI was not statistically significantly different (p's > 0.10). **Conclusion:** Cognitive performance deficit (lower working memory performance) in MASLD seems to exist with fatigue. These findings suggest that fatigue negatively impacts cognitive performance in individuals with MASLD, and is likely an important factor to consider when managing MASLD-related health outcomes. Further research is warranted to explore the underlying mechanisms driving this association in MASLD.

Disclosures: Ali Weinstein: Nothing to Disclose, Leyla de Avila: Nothing to Disclose, Brian Lam: Madrigal: Speaking and Teaching, Jillian Price: Nothing to Disclose, Carey Escheik: Nothing to Disclose, Lynn Gerber: Nothing to Disclose, Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant

2161 | LIVERPAL: A FORMATIVE EVALUATION OF A LONGITUDINAL SPECIALTY-ALIGNED PALLIATIVE CARE INTERVENTION FOR HOSPITALIZED PATIENTS WITH ADVANCED LIVER DISEASE (ADVLD)

Nancy Mason[1] Erin Plews-Ogan[2] Alyssa Fenech[3] Samantha Berliss[4] Michaela Rowland[1] Kirsten Engel[1] Karen O'Brien[1] Michelle Diop[1] Sara Kenimer[1] Teresa Indriolo[5] Lucinda Li[6] Enya Zhu[7] Malia Armstrong[1] Grace Bizup[1] Anushka Dalvi[1] Brett Nava-Coulter[8] Anna Revette[8] Vicki Jackson[1] Raymond Chung[1] Areej El-Jawahri[1] Nneka Ufere[1], [1]Massachusetts General Hospital, [2]University of Virginia, [3]University of Delaware, [4]Legacy Health, [5]Stanford University, [6]UCLA, [7]Duke University, [8]Dana Farber Cancer Institute

Background: Hospitalized patients with AdvLD experience substantial symptom burden, frequent readmissions, and high mortality, yet palliative care is underutilized for this population. Much of the evidence base for inpatient palliative care interventions has come from oncology. However, instead of a "one-size-fits-all" approach, there have been increasing calls for population-specific (i.e., specialty-aligned) palliative care interventions that are targeted to the unique palliative care needs of patients with non-cancer serious illnesses. In response, we developed *LiverPal,* a longitudinal specialty-aligned inpatient palliative care intervention delivered by palliative care clinicians. We conducted a formative evaluation of a single-arm open pilot trial of *LiverPal* to refine the intervention in preparation for a larger efficacy RCT. **Methods:** Between 6/2022-9/2022, we conducted individual interviews with adult patients with AdvLD recently hospitalized at a large academic transplant center, their caregivers and their inpatient clinicians (internal medicine, hepatology, transplant surgery, critical care, palliative care) enrolled in the *LiverPal* pilot trial. We explored their perspectives regarding: 1) unique features of AdvLD care; 2) challenges to inpatient palliative hepatology care; and 3) benefits and areas of ongoing need regarding delivery of *LiverPal* to patients and caregivers (Figure). We conducted a team-based qualitative thematic analysis using a multistage iterative approach, including

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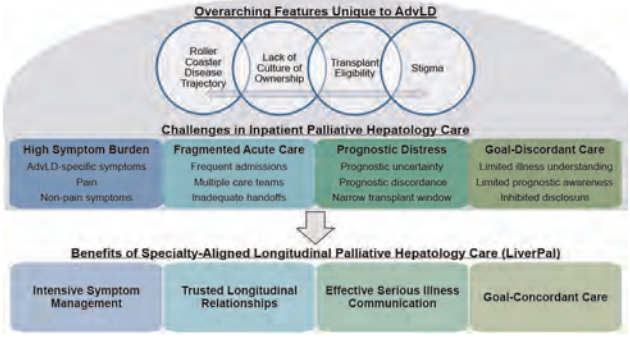
both prefigured and emergent dimensions. **Results:** Nineteen individuals (3 patients, 3 caregivers, 13 clinicians) participated in interviews. Participants identified the following unique features of AdvLD care: rollercoaster illness trajectory, lack of culture of ownership of AdvLD patients, the possibility of transplantation as cure, and stigma. These features resulted in challenges to inpatient palliative care delivery, including difficult symptom management, fragmented care, prognostic distress, and goal discordant care. Respondents highlighted the value of having one team that provided longitudinal care across multiple hospitalizations, which engendered trust from all participants and facilitated serious illness conversations and management of pain and mood symptoms by the LiverPal team. Areas of refinement included developing: 1) evidence-based symptom management manual in collaboration with a palliative care pharmacist, 2) serious illness communication scripts to support transplant and dialysis decision-making, and 3) AdvLD-specific care pathways for both end-of-life and transplant survivorship care. **Conclusion:** A longitudinal model of inpatient palliative care promoted trust and facilitated serious illness conversations and symptom management for hospitalized patients with AdvLD. Our refined *LiverPal* intervention is now being evaluated in an ongoing efficacy RCT.



Disclosures: Nancy Mason: Nothing to Disclose, Erin Plews-Ogan: Nothing to Disclose, Alyssa Fenech: Nothing to Disclose, Samantha Berliss: Nothing to Disclose, Michaela Rowland: Nothing to Disclose, Kirsten Engel: Nothing to Disclose, Karen O'Brien: Nothing to Disclose, Michelle Diop: Nothing to Disclose, Sara Kenimer: Nothing to Disclose, Teresa Indriolo: Nothing to Disclose, Lucinda Li: Nothing to Disclose, Enya Zhu: Nothing to Disclose, Malia Armstrong: Nothing to Disclose, Grace Bizup: Nothing to Disclose, Anushka Dalvi: Nothing to Disclose, Brett Nava-Coulter: Nothing to Disclose, Anna Revette: Nothing to Disclose, Vicki Jackson: Nothing to Disclose, Raymond Chung: GSK: Grant/Research Support, Salix: Grant/Research Support, GSK: Consultant, Precision Biosciences: Consultant, Boehringer: Grant/Research Support, BMS: Grant/Research Support, Areej El-Jawahri: Nothing to Disclose, Nneka Ufere: Nothing to Disclose

2162 | ACLF – THE ADVANCED PRACTICE PROVIDER EXPERIENCE FROM A LIVER ICU

Leah Psellas[1] Cheryl Milani[1] Alaina Miller[1] Wesam Aleyadeh[2] Kelly Bowen[3] Aanchal Kapoor[1] Christina Lindenmeyer[4], [1]Cleveland Clinic Foundation, [2]Toronto Centre for Liver Disease/Cleveland Clinic Akron General Hospital, [3]Cleveland Clinic Lerner College of Medicine, [4]Cleveland Clinic

Background: The Medical Intensive Liver Unit (MILU) at Cleveland Clinic was established in August 2018 to care for critically ill patients with acute and chronic liver disease, many of whom develop acute-on-chronic liver failure (ACLF). Advanced Practice Providers (APPs) are often frontline caregivers in the multidisciplinary teams caring for these patients, making the recognition of ACLF and initiation of early liver transplant (LT) referrals core responsibilities. Increased awareness and early identification of ACLF by APPs may inform prognosis and early referrals to LT centers. This analysis from a quaternary LT referral center's Hepatology APP team characterizes common ACLF presentations and outcomes to guide timely, informed intervention. **Methods:** Patients admitted to the MILU between 08/2018-08/2023 were prospectively enrolled in a patient registry. Out of 1570 admissions, 614 were for ACLF (EASL-CLIF criteria, 494 unique patients). We analyzed associated mortality and outcome profiles, according to the admitting diagnosis, to better understand early presentation patterns of ACLF. **Results:** Hepatology and Intensive Care Unit (ICU) APPs collaborate and lead the multi-disciplinary morning MILU huddle. Pending transfers are triaged, patients with ACLF are identified, and LT candidacy assessments are immediately reviewed with the interprofessional LT team. The most common admission diagnoses for ACLF patients identified in huddle by the APPs were shock/hypotension (n = 200), gastrointestinal bleeding (GIB, n = 118), altered mental status (AMS, n = 105), acute kidney injury (AKI, n = 99), and acute respiratory failure (ARF, n = 72). Shock/hypotension was associated with the highest in-hospital mortality rate (48%), followed by ARF (40%), AMS (35%), GIB (34%), and AKI (25%). 92% (564/614) of all admissions with ACLF were complicated by AKI, regardless of the admitting diagnosis. Ninety patients (18.2%) with ACLF underwent successful LT; 65 directly from MILU and 25 following ICU discharge. **Conclusion:** These findings underscore the critical role of frontline APPs in the prompt recognition of ACLF, the identification of patients at highest risk of mortality, the initiation of

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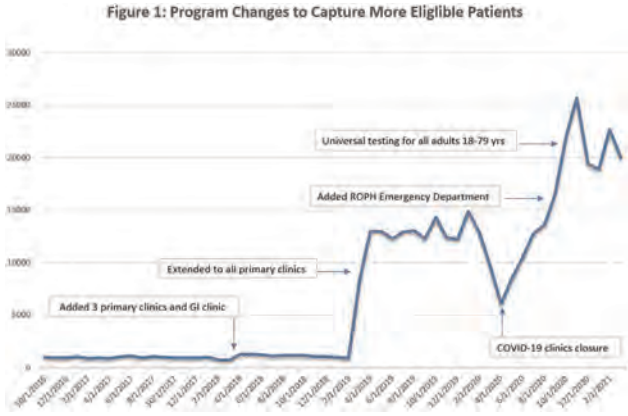
timely referrals to transplant, and the early anticipation of dialysis. Targeted education to increase awareness and empower frontline APPs in referring centers and ICUs may improve outcomes and facilitate access to LT in this high-risk population.

Disclosures: Leah Psellas: Nothing to Disclose, Cheryl Milani: Nothing to Disclose, Alaina Miller: Nothing to Disclose, Wesam Aleyadeh: Nothing to Disclose, Kelly Bowen: Nothing to Disclose, Aanchal Kapoor: Nothing to Disclose, Christina Lindenmeyer: Nothing to Disclose

2163 | NAVIGATING THE HEPATITIS C CARE CASCADE WITH ADVANCED PRACTICE PROVIDER AND ELECTRONIC HEALTH RECORD IN AN URBAN EMERGENCY DEPARTMENT AND OUTPATIENT CLINICS

Vicki Shah[1] Colleen Folkers[2] Nancy Reau[2] Bevelry Sha[2], [1]Rush University and Gilead Sciences, [2]Rush University Medical Center

Background: Centers for Disease Control and Prevention (CDC) and U.S. Preventive Services Task Force (USPSTF) recommended universal HCV screening at least once in a lifetime for all adults 18-79 years of age to correspond with World Health Organization (WHO) goal of eliminating hepatitis C virus (HCV) as a public health concern. There is a significant loss of individuals at each step of the HCV treatment cascade from screening to linkage to care. Our aim was to increase HCV screening, diagnosis, and linkage to care in an academic tertiary care system. **Methods:** Beginning October 2016, we utilized the electronic health record (EHR) and hepatology Advanced Practice Providers (APPs) to enhance HCV testing and linkage-to-care in patients seen in the emergency departments and ambulatory clinics. Strategies included auto-order HCV Ab test linked to complete blood count, use of a "best practice advisory" alert, and dedicated hepatology APPs to monitor HCV Ab results. **Results:** From October 2016 to March 2021, 385,683 patients met our testing criteria, and 36,922 (9.57%) HCV Ab tests were performed. 1261 of the 36,922 HCV Ab tests (3.42%) were reactive and 520 (1.41%) of patients tested were found to have detectable HCV viral load. For the 520 patients with HCV infection, 244 (46.9%) were linked for HCV treatment. **Conclusion:** With EHR modifications, HCV viral load reflex testing, and dedicated APPs, we demonstrated higher identification of HCV infected patients and removed several barriers in the HCV care cascade. Successful linkage-to-care varied greatly by where the patient was initially screened.



Disclosures: Vicki Shah: Gilead Sciences: Employee, Colleen Folkers: Gilead: HCV FOCUS Grant, Nancy Reau: Gilead: Grant/Research Support, eiger: Grant/Research Support, abbott: Consultant, Arbutus: Consultant, Gilead: Consultant, VIR: Consultant, Salix: Consultant, Salix: Grant/Research Support, AbbVie: Grant/Research Support, VIR: Grant/Research Support, Bevelry Sha: Gilead Sciences, Inc: Grant/Research Support, Merck: Grant/Research Support, ViiV Healthcare: Advisor

2164 | BARRIERS AND FACILITATORS TO ENGAGING IN ALCOHOL TREATMENT AMONG PERSONS WITH ALCOHOL-ASSOCIATED LIVER DISEASE: A MIXED-METHODS: SYSTEMATIC REVIEW

Sue Hyon Kim[1] Sasha Deutsch-Link[2] Alison Buttenheim[1] Laura Starbird[1] Michael Stawnychy[1] Marina Serper[3], [1]University of Pennsylvania, [2]UNC Chapel Hill, [3]University of Pennsylvania Health System

Background: Alcohol use disorder (AUD) treatment rates among patients with alcohol-associated liver disease (ALD) are low; 16% report active treatment engagement and less than 5% receive medications for alcohol use disorder (MAUD). Factors influencing stages of need recognition, initiation, and maintenance of AUD treatment are not clearly defined for ALD patients, resulting in limited actionable knowledge. **Methods:** We conducted a mixed methods systematic review synthesizing diverse study designs and data types on facilitators and barriers to AUD treatment engagement among individuals with ALD. Searches were performed in PubMed, CINAHL, Embase, and PsycINFO. We followed the convergent integrated

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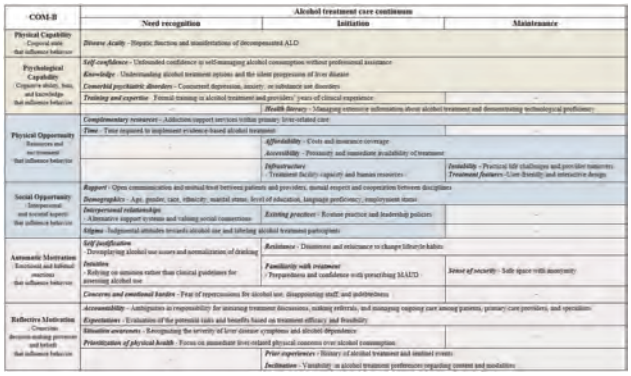
approach recommended by the Joanna Briggs Institute and performed directed content analysis based on the Capability, Opportunity, Motivation-Behavior (COM-B) model. **Results:** Twenty-three studies revealed COM-B elements uniquely influencing distinct stages of the AUD treatment care continuum (Table 1). We observed discordance between patients' and providers' treatment need recognition; patients had limited insight into their AUD treatment needs when they were asymptomatic, while providers mainly focused on AUD treatment during asymptomatic ALD. Patient confidence in self-management further reduced their desire for professional help. Their liver transplant (LT) status also influenced motivations for concealing alcohol use and limited their acceptance of AUD treatment; LT candidates feared reprimand or disqualification, and recipients felt shame. Provider training on MAUD was ineffective at increasing prescription rates due to persistent unfamiliarity with pharmacotherapy and practice norms that do not incorporate its routine use. Unclear delineation of responsibilities emerged across the care continuum, as patients relied on providers to recommend AUD treatment, providers cited patient unwillingness as a primary reason for non-referral, and role ambiguity between hepatology and addiction specialists disrupted continuity of care. **Conclusion:** We suggest the following strategies to enhance AUD treatment engagement among patients with ALD: (1) Deepen patient and provider insights into the importance of treating AUD in asymptomatic and symptomatic ALD (2) Normalize AUD treatment for LT candidates and recipients (3) Increase provider comfort with MAUD to promote prescription initiation (4) Offer collaborative multidisciplinary care models integrating addiction medicine with hepatology to maintain treatment engagement.



Disclosures: Sue Hyon Kim: Nothing to Disclose, Sasha Deutsch-Link: Nothing to Disclose, Alison Buttenheim: Nothing to Disclose, Laura Starbird: Nothing to Disclose, Michael Stawnychy: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Eurofins: Grant/Research Support

2165 | REDUCED HEALTH-RELATED QUALITY OF LIFE PREDICTS UNFAVORABLE OUTCOMES IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA TREATED WITH ATEZOLIZUMAB AND BEVACIZUMAB. NEW SUBMISSION

Masako Shomura[1] Haruka Okabe[1] Maya Sakakibara[1] Emi Sato[2] Koichi Shiraishi[3] Yoshitaka Arase[3] Kota Tsuruya[3] Shunji Hirose[3] Yusuke Mishima[3] Tatehiro Kagawa[4], [1]Faculty of Nursing, Tokai University School of Medicine, [2]Department of Nursing, University of Tokyo Health Science, [3]Division of Gastroenterology, Department of Internal Medicine, Tokai University School of Medicin, [4]Tokai University

Background: Patient-Oriented Outcomes (PRO), particularly Health-related Quality of Life (HRQoL), are vital for patients with hepatocellular carcinoma (HCC). These outcomes are increasingly important for evaluating new treatments like the combination of atezolizumab and bevacizumab (Atezo+Bev). HRQoL can be affected by cancer symptoms and treatment-related adverse events (AEs). This study aimed to identify factors related to treatment efficacy, duration, and overall survival (OS) in HCC patients receiving Atezo+Bev, focusing on their characteristics, including AEs and HRQoL assessed at three months. **Methods:** We followed up consecutive HCC patients treated with Atezo+Bev from November 2020 to March 2025, with tracking until May 2025, or the patient's death. Treatment efficacy was assessed using modified RECIST criteria at 6 to 9 weeks. HRQoL was monitored monthly with the EORTC-QLQ C30. We analyzed relationships between baseline characteristics, AEs, HRQoL, treatment efficacy, OS, and treatment duration using multivariate logistic regression and Cox's proportional hazards models. A nursing intervention program included education on self-monitoring, AE management, and telephonic consultations. **Results:** A total of 91 patients were enrolled in the study, mostly men (81%), with 56% aged 70 or older. Most had a Child-Pugh score of 5 (48%) and were classified as Barcelona Clinic Liver Cancer Stage C (36%). The disease control rate was 78.4%, and the objective response rate was 29.5%, with a median treatment duration of 8.6 months and an overall survival of 19.6 months. Common adverse events included fatigue (90%), hypoalbuminemia (80%), and thrombocytopenia (59%). HRQoL scores for general health, physical function (PF), role function (RF), and cognitive function (CF), along with symptoms like fatigue, nausea, and financial difficulties, significantly worsened in the first four months. CF score greater than 80 at 3 months (Odds Ratio [OR] 3.39, 95% Confidence Interval [CI]: 1.03–11.21, $p = 0.04$) was associated with a higher ORR. In contrast, TNM stage IV (OR 0.32, 95% CI: 0.12–0.87, $p = 0.02$) was associated

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with lower ORR. PF score of 80 or above (Hazard Ratio [HR] 0.48, 95% CI: 0.27–0.86, p = 0.01) and RF score of 80 or above (HR 0.53, 95%CI: 0.30-0.95) were associated with a more extended treatment duration, while DCP value greater than 1000 (HR 1.75, 95% CI: 1.75–2.85) was connected to shorter treatment duration. Predictors of longer OS included PF score of 80 or above (HR 0.50, 95% CI: 0.26-0.97) and RF score of 80 or above (HR 0.46, 95% CI: 0.25–0.86). Conversely, shorter OS was associated with grade 2 or more worsened hypoalbuminemia (HR 3.57, 95%CI: 1.48–8.59). **Conclusion:** HRQoL scores significantly declined by the fourth month of Atezo+Bev therapy in HCC patients. Decreased CF, PF, and RF scores indicated poorer prognosis. Managing AEs effectively with a multidisciplinary team can enhance HRQoL and improve outcomes during cancer treatment.

Disclosures: Masako Shomura: Nothing to Disclose, Haruka Okabe: Nothing to Disclose, Maya Sakakibara: Nothing to Disclose, Emi Sato: Nothing to Disclose, Koichi Shiraishi: Nothing to Disclose, Yoshitaka Arase: Nothing to Disclose, Kota Tsuruya: Eisai Co., Ltd.: Speaking and Teaching, Takeda Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, Chugai Pharmaceutical Co., Ltd.: Speaking and Teaching, ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, AbbVie GK: Speaking and Teaching, Shunji Hirose: Nothing to Disclose, Yusuke Mishima: Nothing to Disclose, Tatehiro Kagawa: Nothing to Disclose

◆ 2166 | TWO-DECADE TRENDS IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND ITS COMPLICATIONS IN THE MIDDLE EAST AND NORTH AFRICA (MENA) (2010–2021)

Zobair Younossi[1] James Paik[2] Yusuf Yilmaz[3] Mustafa Kanat[4] Mohamed El-Kassas[5] Said Al-Busafi[6] Khalid AlNaamani[7] Abdel-Naser Elzouki[8] Khalid Alswat[9] Ahmed Cordie[10] Ashraf Abdelaziz Osman[11] Nabil Debzi[12] Jawad Khamis[13] Mohammad Hassanein[14] Mohamed Abu-Farha[15] Fahd Al-Mulla[15] Faisal Aba-Alkhail[16] Asrar Alaklabi[17] Linda Henry[1] Shira Zelber-Sagi[18] Saleh Alqahtani[19], [1]The Global NASH Council, [2]Beatty Liver and Obesity Research Program, Inova Health System, Falls Church, VA, United States., [3]Recep Tayyip Erdoğan University, [4]Department of Medicine, DIMER Diabetes Research Center, Istanbul Medeniyet University, Istanbul, [5]Helwan University, [6]Gastroenterology and Hepatology Unit, Department of Medicine, College of Medicine and Health Scie, [7]Department of Medicine, Division of Gastroenterology and Hepatology, The Medical City for Militar, [8]Department of Medicine, Hamad Medical Corporation, College of Medicine-Qatar University and Weill, [9]King Saud University/KKUH, [10]Department of Endemic and Hepatology Faculty of Medicine Cairo University, Egypt, [11]Cairo University, [12]Department of Hepatology, Mustapha Bacha University Hospital Algiers -Algeria, [13]Salmaniya Medical Complex (SMC), Bahrain, Bahrain, [14]Dubai Hospital and Mohamed Bin Rashid University, Dubai, UAE, [15]Department of Translational Research, Dasman Diabetes Institute, Kuwait, [16]Gastroenterology Section, Department of Medicine, King Faisal Specialist Hospital and Research Cente, [17]Liver, Digestive, &Lifestyle Health Research Section, King Faisal Specialist Hospital and Research, [18]Tel-Aviv Sourasky Medical Center, [19]Liver Transplant Unit, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

Background: MENA region is undergoing rapid demographic and metabolic shifts that may contribute to the growing burden of MASLD and its complications. We assessed trends in MASLD prevalence and associated disease burden, including cirrhosis and liver cancer (LC), from 2010 to 2021 across MENA countries. **Methods:** This ecological study analyzed data from the Global Burden of Disease (GBD) study, United Nations Population Division, and the NCD Risk Factor Collaboration from 2010 to 2021 across 21 MENA countries. Annual percent change (APC) was estimated using Joinpoint regression. Prevalence of compensated (CC) and decompensated cirrhosis (DCC) due to MASLD was modeled using country-level regression models. All prevalence and mortality estimates are age-standardized rates based on the entire population, including both children and adults. **Results:** Between 2010 and 2021, MENA region experienced significant demographic growth, with the population increasing from 518 million to 623 million with progressive aging trends. Modest improvements were observed in the Socio-demographic Index, reflecting gains in education, income, and fertility-related indicators. Concurrently, the region underwent significant metabolic shifts, with adult diabetes prevalence rising from 7.4% to 12.1% and obesity increasing from 25.4% to 31.3%. During this period, MASLD prevalence increased from 26.3% (117.97 million) in 2010 to 27.7% (164.31 million) in 2021 (APC = 0.47%; 95% CI, 0.35-0.59), with a steeper increase among adults aged ≥ 20 years (from 37.1% to 41.0%; APC = 0.90%; 95% CI, 0.79-1.01). MASLD-related cirrhosis increased from 0.22% (1.13 million) to 0.28% (1.73 million) (APC = 2.18%; 95% CI, 2.05-2.31) [CC (0.20% to 0.25%; APC = 2.24%) and DCC (0.020% to 0.025%; APC = 2.23%)]. Algeria, Iraq, Morocco, and Turkey had the highest increases (APCs > 2.8% for both CC and DCC). MASH-related cirrhosis mortality (APC = 0.60%), and DALYs (APC = 0.47%) increased. MASH-LC also increased in prevalence (APC = 2.90%), incidence (APC = 2.90%), mortality from 0.50 to 0.69

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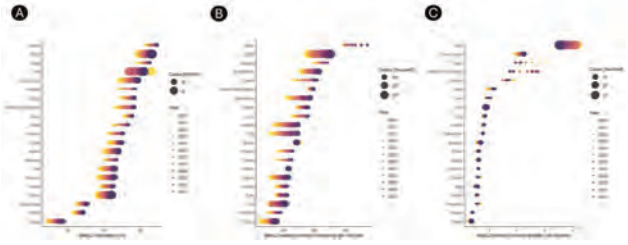
per 100,000 (APC = 2.87%), and DALYs (APC = 2.51%). Iran exhibited the most rapid increases (APC > 6%) for all LC outcomes, while Egypt accounted for over half of the region's LC DALYs in 2021. **Conclusion:** The prevalence of MASLD and associated complications, including cirrhosis and LC, increased substantially across MENA region from 2010 to 2021, with considerable variation across countries.

Figure. Trends in Age-Standardized (A) MASLD Prevalence (B) MASLD-related Cirrhosis Prevalence (C) MASLD-related Cirrhosis Mortality in the MENA Region, 2010–2021



Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, James Paik: Nothing to Disclose, Yusuf Yilmaz: Nothing to Disclose, Mustafa Kanat: Nothing to Disclose, Mohamed El-Kassas: Nothing to Disclose, Said Al-Busafi: Nothing to Disclose, Khalid AlNaamani: Nothing to Disclose, Abdel-Naser Elzouki: Nothing to Disclose, Khalid Alswat: Nothing to Disclose, Ahmed Cordie: Nothing to Disclose, Ashraf Abdelaziz Osman: Nothing to Disclose, Nabil Debzi: Nothing to Disclose, Jawad Khamis: Nothing to Disclose, Mohammad Hassanein: Nothing to Disclose, Mohamed Abu-Farha: Nothing to Disclose, Fahd Al-Mulla: Nothing to Disclose, Faisal Aba-Alkhail: Nothing to Disclose, Asrar Alaklabi: Nothing to Disclose, Linda Henry: Nothing to Disclose, Shira Zelber-Sagi: Nothing to Disclose, Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose

◆ 2167 | SEXUAL HEALTH AFTER LIVER TRANSPLANTATION: AN UNRECOGNIZED PROBLEM AFFECTING QUALITY OF LIFE

Chanattha Thimphitthaya[1] Alvaro Noriega Ramirez[1] Dyanna Gregory[1] Arjmand Mufti[1] Shannan Tujios[1] Lisa VanWagner[1] Amit Singal[1] Nneka Ufere[2] Sarah Lieber[1], [1]University of Texas Southwestern Medical Center, [2]Massachusetts General Hospital

Background: Sexual health (SH) is an overlooked aspect of patient experiences and is greatly impacted by chronic health conditions. It remains unclear what factors are associated with better or worse sexual outcomes after liver transplantation (LT) and associated health-related quality of life (HRQoL). **Methods:** We performed a cross-sectional study of all adult LT recipients (LTRs) at least 1-year post-LT being followed at a large U.S. transplant center. An electronic survey assessed: 1) sexual activity after LT, 2) sexual interest and satisfaction,3) HRQoL using validated questionnaires from Patient-Reported Outcomes Measurement Information System (PROMIS). Sociodemographic and clinical data were also captured. Scores were reported as T-scores, with scores <40 representing low sexual interest or satisfaction. Factors associated with lower sexual satisfaction for LTRs were assessed using bivariate and multivariate analysis adjusting for age, gender, comorbidity, income, and LT indication. **Results:** A total of 239 LTRs completed surveys (response rate 43.9%); 59.8% were male with median (IQR) age of 58 (47,67 years) and median (IQR) time of 5.0 (2.9, 7.5) years post-LT. LT indications were alcohol-related (34.3%), metabolic dysfunction-associated steatotic liver disease (19.7%) and viral hepatitis (14.7%). A majority (77.6%) of patients were sexually active since LT; median time to sexual activity was 4-6 months. The most common reason for sexual inactivity was lack of interest (40.8%). Mean (SD) sexual interest scores were 45.9 (11.9) while mean sexual satisfaction scores were 49.5 (8.3). Of all patients, 75 (32.2%) reported low sexual interest. Among sexually active LTRs, 15 (11.4%) had low sexual satisfaction scores. Sexual interest and satisfaction scores positively correlated with physical and mental HRQoL scores ($p < 0.01$), especially for male patients. Age > 65 years, female gender, lower-income, and alcohol use disorder were associated with lower sexual satisfaction score (although non-significant) (Table1). Interestingly, LTRs with higher Charlson comorbidity index (i.e., higher comorbidity) were less likely to report low sexual satisfaction (adjusted odds ratio 0.10, 95% CI 0.02-0.58). **Conclusion:** Most LTRs return to sexual activity within 4-6 months post-LT. Sexual interest and satisfaction scores positively correlated with physical and mental HRQoL. These findings highlight the need for more proactive, patient-centered approaches to sexual health assessment and support in long-term transplant survivorship care.

Table 1. Odd ratios of factors associated with low sexual satisfaction scores after LT

Variable	Unadjusted OR (95% CI) (N = 132)	Adjusted OR (95% CI) (N = 125)
Age ≥65	1.749 (0.54-5.67)	2.06 (0.56-7.49)
Female gender	1.05 (0.35-3.15)	1.60 (0.48-5.31)
Non-White	0.70 (0.15-3.32)	0.56 (0.06-4.96)
Income ($) <75K	1.58 (0.51-4.9)	1.56 (0.48-5.13)
Indication for LT (reference group MASLD)		
Alcohol	4.41 (0.87-23.3)	0.64 (0.15-2.67)
Viral hepatitis	2.15 (0.36-12.69)	0.65 (0.09-4.83)
Other	0.47 (0.04-5.44)	0.19 (0.03-1.24)
HCC	0.69 (0.18-2.62)	0.34 (0.05-2.34)
MELD3.0 at transplantation >25	0.50 (0.16-1.58)	0.47 (0.12-1.90)
Dual organ transplant	0.50 (0.08-3.30)	N/A
Pre-LT alcohol use	2.53 (0.76-3.39)	2.81 (0.55-14.53)
Diabetes		
Uncomplicated	1.76 (0.34-9.20)	1.08 (0.25-4.74) for the presence of any co-morbidities
With End-organ damage	0.79 (0.16-3.85)	
Hypertension	1.54 (0.46-5.14)	
Cardiovascular disease	0.96 (0.25-3.67)	
Charlson comorbidity index ≥ 2	0.49 (0.18-1.51)	**0.10 (0.02-0.58)**

Disclosures: Chanattha Thimphitthaya: Nothing to Disclose, Alvaro Noriega Ramirez: Nothing to Disclose,

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Dyanna Gregory: Nothing to Disclose, Arjmand Mufti: Nothing to Disclose, Shannan Tujios: Nothing to Disclose, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Nneka Ufere: Nothing to Disclose, Sarah Lieber: Nothing to Disclose

◆ 2168 | SOCIOECONOMIC DISPARITIES IN INCIDENCE, TREATMENT AND SURVIVAL AFTER HEPATOCELLULAR CARCINOMA IN ALCOHOL-ASSOCIATED CIRRHOSIS: NATIONWIDE DATA FROM DENMARK

Gro Askgaard[1] Morten Daniel Jensen[2] Joe West[3] Colin Crooks[3] Peter Jepsen[2], [1]Zealand University Hospital, [2]Aarhus University Hospital, [3]University of Nottingham

Background: Reducing socioeconomic disparities in health is a key strategic objective. This study investigated the socioeconomic pattern of hepatocellular carcinoma (HCC) incidence, treatment and mortality after HCC in patients with alcohol-associated (ALD) cirrhosis in a country with universal healthcare. **Methods:** We followed newly diagnosed patients with ALD cirrhosis identified in the nationwide Danish healthcare registries 2000-2018. Socioeconomic position was measured by educational length in four levels. First, we estimated the hazard ratio (HR) of HCC with increasing educational length in patients with ALD cirrhosis. Second, we followed the subset who developed HCC to examine the association between educational length and A) curative-intent HCC treatment (liver transplantation, liver resection or ablation), B) consultation with a specialized palliative care team, and C) mortality. All HRs were adjusted for age, sex, calendar-year, comorbidity and decompensation status. **Results:** During follow-up in 32,532 patients with ALD cirrhosis, HCC was diagnosed in 1430, and death occurred in 22,962 patients. There was a trend towards a higher HCC incidence in ALD cirrhosis patients with lower socioeconomic position compared to higher with a HR of 1.04 (0.99-1.09) per one-level decrease in socioeconomic position. Patients of lower socioeconomic position tended to be younger at HCC diagnosis and have more comorbidity, and they were less likely to receive curative intent-treatment and also less likely to have consultations with specialized palliative team (Table 1). For example, curative-intent HCC treatment was given to 25% versus 34% of patients of low versus high socioeconomic position. In addition, lower socioeconomic position was associated with increased mortality risk with a HR for mortality of 1.06 (1.00-1.11) per one-level decrease in socioeconomic position. **Conclusion:** Despite universal healthcare, we found socioeconomic disparities in the HCC incidence, treatment and mortality after HCC in patients with ALD cirrhosis. These findings highlight the need for individualized support for ALD patients.

Table 1. Treatment and survival after diagnosis of hepatocellular carcinoma in patients with alcohol-associated cirrhosis, according to socioeconomic position in Denmark 2000-2016.

Socioeconomic position	N	Men	Median age (IQR)	Curative-intent treatment*	Referral to specialised palliative care	Rate of death per 1000 person-years	Hazard ratio of all-cause death*
Low	583	79%	65 (60-71)	144 (25%)	137 (23%)	825 (755-898)	1.26 (1.03-1.70)
Medium-low	636	86%	66 (60-72)	176 (28%)	153 (24%)	787 (725-854)	1.16 (0.96-1.70)
Medium-high	158	82%	66 (60-71)	52 (33%)	41 (26%)	671 (569-792)	1.07 (0.77-1.50)
High	53	92%	58 (55-74)	18 (34%)	17 (32%)	704 (527-940)	(Reference)
Total	1430	83%	66 (60-72)	392 (27%)	348 (24%)	783 (741-827)	1.06 (1.00-1.11)

Disclosures: Gro Askgaard: Nothing to Disclose, Morten Daniel Jensen: Nothing to Disclose, Joe West: Nothing to Disclose, Colin Crooks: Nothing to Disclose, Peter Jepsen: Nothing to Disclose

◆ 2169 | NOURISHING THE MIND: FOOD INSECURITY IS A KEY DETERMINANT OF HEPATIC ENCEPHALOPATHY RISK IN CIRRHOSIS

Somaya Albhaisi[1] Jennifer Dodge[1] Diana Segura[1] Norah Terrault[1] Ani Kardashian[1], [1]University of Southern California

Background: Hepatic encephalopathy (HE), a debilitating complication of cirrhosis, impairs quality of life and worsens prognosis. While malnutrition is a known risk factor for HE, the role of social determinants of health—particularly food insecurity (FI)—in HE is unknown. We investigated the association of FI and diet quality (DQ) with HE in a diverse cohort of outpatients with cirrhosis. **Methods:** We performed a cross-sectional analysis of 177 adults with decompensated cirrhosis evaluated for liver transplant (July 2023-present) from a single-center prospective cohort. FI was assessed by the validated USDA Household Food Security Survey. Participants were categorized as food secure if they had high or marginal food security and food insecure if they had low or very low food security. Individual DQ components were assessed by the NCI Dietary Screener Questionnaire. Participants were categorized as having HE, the primary

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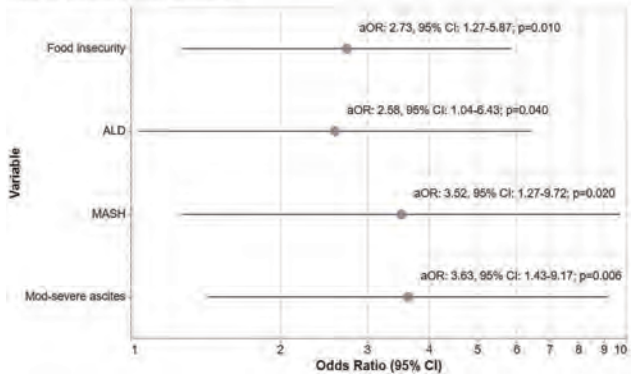
outcome, if they carried a chart diagnosis based on review of hepatology clinic notes and took 45 seconds to complete the Numbers Connect Test A. Logistic regression models examined the association of HE with (1) FI and (2) DQ, testing relevant covariates, (age, sex, ethnicity, cirrhosis etiology, BMI, income, MELD 3.0, and ascites severity), with the final models including only covariates with $p < 0.05$ per backward elimination. Results were reported as adjusted odds ratios (aOR) with 95% CI. **Results:** Of 177 participants (median age 56 years, 53% male, 74% Hispanic, median MELD 16), 24% experienced FI. HE was present in 35% of all participants and was more prevalent in the food insecure, compared to the food secure, group (52% vs 30%, $p = 0.007$). In multivariable analysis, odds of HE increased with FI (aOR for HE: 2.73, 95% CI: 1.27–5.87; $p = 0.01$) after adjusting for etiology [alcohol-associated liver disease (ALD), metabolic dysfunction-associated steatohepatitis (MASH)] and moderate-severe ascites (Figure 1). Individual dietary components (fruits, vegetables, added sugars, whole grains, dairy, fiber) were not associated with HE in unadjusted or adjusted models. **Conclusion:** FI is highly prevalent and linked to significantly increased odds of HE in decompensated cirrhosis. Given the lack of association with DQ, our findings suggest the FI-HE pathway may extend beyond conventional DQ and involve other mechanisms. Future studies should examine social factors that may present in the context of FI. Integrating social risk assessments into routine hepatology care may help identify high-risk individuals and improve HE outcomes, positioning FI as a modifiable factor directly impacting liver health equity.

Figure 1. Multivariable regression analysis demonstrating factors associated with greater odds of hepatic encephalopathy.



Disclosures: Somaya Albhaisi: Nothing to Disclose, Jennifer Dodge: Nothing to Disclose, Diana Segura: Nothing to Disclose, Norah Terrault: Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, ImmunoCore: Grant/Research Support, HBV Foundation: Board member, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Ani Kardashian: Nothing to Disclose

◆ 2170 | RISK FACTORS FOR LIVER INVOLVEMENT OF HYPERTENSIVE DISORDERS OF PREGNANCY

Sorvena Yoyo[1] Amy Shui[1] Cynthia Felton[1] Gabrielle Jutras[1] Roxanna Irani[1] Monika Sarkar[2], [1]University of California San Francisco, [2]University of California, San Francisco

Background: Hypertensive disorders of pregnancy (HDP) defined as gestational hypertension, pre-eclampsia, and Hemolysis, Elevated Liver Enzymes, Low Platelet (HELLP) syndrome may progress to liver involvement, adversely affecting maternal and fetal outcomes, and timing of delivery. However, risk factors for hepatic involvement of HDP are unknown, which is relevant to pregnancy counseling, risk stratification, and management. **Methods:** We evaluated risk factors for hepatic involvement of HDP (defined as pre-eclampsia plus ALT $\geq$ 50) or HELLP syndrome among all pregnancies at UCSF Health between 2014-2023 in patients aged 13-55, excluding those with chronic liver disease. Chart validation confirmed all HDP cases with liver involvement. Multivariable analysis included biologically relevant covariates, using generalized estimating equations models with exchangeable correlation structure to account for multiple pregnancies per patient. Risk factors for HDP with liver involvement were evaluated in the larger cohort of all pregnancies, with secondary analysis in the subgroup of pregnancies with HDP. **Results:** Among 50,517 pregnancies at our center, 6529 (13%) had an HDP, of which 430 (6.6%) manifested with liver involvement. In the HDP cohort without liver involvement, the racial/ethnic distribution was 31% White, 16% Asian, 6.9% Black or African American, and 15% Latina, vs 27% White, 12% Asian, 4.7% Black, and 25% Latina for those with HDP with liver involvement. Mean age was 34 vs 33 years in the HDP and HDP with liver involvement groups, and 19% vs 21% developed gestational diabetes (GDM), respectively. HDP subtypes included 1.2% with HELLP syndrome and $<1\%$ with eclampsia. On multivariable analysis of all pregnancies (Figure 1a), risk factors for liver involvement included BMI 25-29.9 (Adjusted OR 1.45, 95% CI 1.08-1.95), BMI $\geq$ 30 (AOR 2.54, 95% CI 1.88-3.44), GDM (AOR 1.32, 95% CI 1.03-1.68), and multiparity (AOR 4.81, 95% CI 3.58-6.47). Estimates overall persisted in the subgroup with HDP (Figure 1b), with Latina patients additionally having a higher risk for HDP with liver involvement (AOR 1.62, 95% CI 1.21-2.17). **Conclusion:** Liver involvement occurred in nearly 7% of pregnancies complicated by HDP. Risk factors for hepatic involvement included overweight/obesity, multiparity, GDM, and self-identified Latina ethnicity. These novel findings can inform risk-based counseling and management in the growing number of women at risk for hypertensive disorders of pregnancy.

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Figure 1: Risk factors for liver involvement among all pregnancies (Figure 1a) and among pregnancies with HDP (Figure 1b)

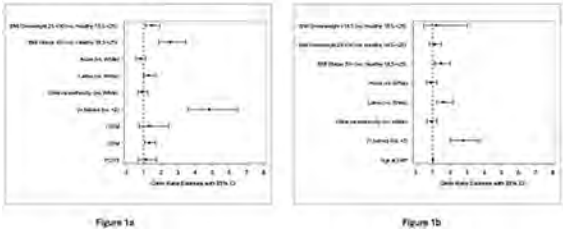

Figure 1a Figure 1b

Disclosures: Sorvena Yoyo: Nothing to Disclose, Amy Shui: Nothing to Disclose, Cynthia Felton: Nothing to Disclose, Gabrielle Jutras: Nothing to Disclose, Roxanna Irani: Nothing to Disclose, Monika Sarkar: GSK: Grant/Research Support, Zydus Pharmaceuticals: Grant/Research Support, Gilead Sciences: Grant/Research Support

◆ 2171 | DEMOGRAPHIC DISPARITIES IN RECRUITMENT FOR LIVER TRANSPLANT CLINICAL TRIALS IN THE UNITED STATES

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Background: Liver transplantation enhances survival rates and quality of life for patients with end-stage liver disease. However, concerns persist about the inclusivity of patient recruitment for clinical trials, leading to challenges in generalizing trial results to the broader population. Our goal is to compare the demographics of patients enrolled in clinical trials with those who receive liver transplants in the United States. **Methods:** We searched ClinicalTrials.gov for studies related to liver transplantation conducted between January 1, 2000, and December 31, 2024. National data on liver transplantation activity in the United States were obtained from the Organ Procurement and Transplantation Network (OPTN) website. We only included trials focused on the liver only as the transplanted organ, did not involved countries other the US, and that specified in their inclusion criteria that participants must be liver transplant reciepients or listed to recieve a live transplant. Statistical comparisons between the two groups were performed using IBM SPSS Statistics, version 26. **Results:** Based on OPTN data between 2000 and 2024, a total of 181,657 liver transplants were performed in the United States. We identified 141 liver transplantation studies conducted in the U.S. in the same time frame. Out of these, 86 studies met the inclusion criteria, involving 5,461 participants (Figure 1). 6 studies (7.0%) included participants under the age of 18, though two were limited to pediatric age ranges ("up to 12 only" and "3m–12y"). 78 studies (90.7%) included participants over the age of 65. The mean age of participants in studies that reported age (88.3%) was 54.5 years. From the 86 included trials, 62 (72.1%) were completed. Regarding transplant status, 45 trials (52.3%) included patients who had already received a transplant, while 38 (44.2%) included listed patients; only trials (3.5%) included both. Most studies were interventional (94.2%), with only 5 observational trials (5.8%). In terms of trial settings, 49 (57.0%) were single-center (Table 1). In the clinical trials, 1,748 participants (32.01%) were female, compared to 66,079 (36.4%) female liver recipients ($P < 0.001$). Race data were available from 48 studies, showing that 2,716 participants (82.4%) were White, compared to 126,651 (69.7%) White liver recipients ($P < 0.001$). Thirty-three trials reported ethnicity, with 359 (13.1%) participants identified as Hispanic, compared to 27,947 (15.4%) Hispanic liver recipients ($P = 0.001$) (Table 2) **Conclusion:** Liver transplant outcomes have been shown to vary based on demographics such as gender, race, and ethnicity. Our study found that women and racial minorities are underrepresented in liver transplantation trials compared to actual transplant recipients. This lack of diversity limits the generalizability of findings and underscores the need for more inclusive recruitment practices.

Table 1: Summary of Liver Transplant Clinical Trials (n = 86)

Category	Subcategory	Number of Trials	Percentage (%)
Trial Status	Completed	62	72.1%
	Terminated	24	27.9%
Transplant Inclusion	Received Only	45	52.3%
	Listed Only	38	44.2%
	Both Listed/Received	3	3.5%
Study Type	Interventional	81	94.2%
	Observational	5	5.8%
Center Type	Single-Center	49	57.0%
	Multi-Center	37	43.0%

Table 2: Difference in demographics of participants in liver transplant clinical trials and liver transplant recipients

Category	Clinical Trials, n(%)	Real World, n (%)	P-Value
Gender (Female)	1,748 (32.01%)	83,469 (37.6%)	<0.001
Race (White)	2,716 (82.4%)	126,651 (69.7%)	<0.001
Ethnicity (Hispanic)	359 (13.1%)	27,947 (15.4%)	0.001

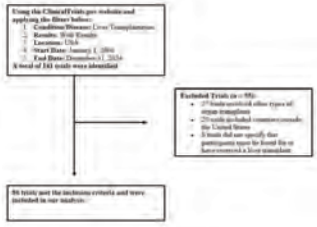

Figure 1: A flowchart showing how trials were identified

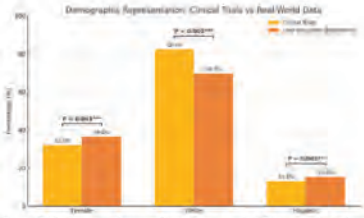

Figure 2: Difference in demographics of participants in liver transplant clinical trials and liver transplant recipients

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◆ 2172 | SIGNIFICANT DISPARITIES IN INPATIENT PALLIATIVE CARE CONSULTATION AND MORTALITY AMONG HOSPITALIZED ADULTS WITH DECOMPENSATED CIRRHOSIS

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Background: Patients with decompensated cirrhosis have decreased quality of life, higher healthcare resource utilization, and high mortality. Although palliative care (PalCare) services have the potential to enhance health-related quality of life, they are often underutilized in vulnerable populations. We assessed socio-demographic and racial/ethnic disparities in PalCare utilization and all-cause mortality among U.S. adults hospitalized with decompensated cirrhosis. **Methods:** Adult hospitalizations for decompensated cirrhosis were identified using relevant ICD-10 codes from the 2021 to 2022 National Inpatient Sample (NIS). PalCare utilization was compared between groups, and adjusted multivariable logistic regression models evaluated for independent predictors of receiving PalCare. Comparisons of all-cause inpatient mortality were similarly evaluated with adjusted multivariable logistic regression models. **Results:** Among 117,476 hospitalizations for decompensated cirrhosis (median age 58 years, 61% male, 65.2% non-Hispanic white (NHW), 16.9% Hispanic, 8.9% African American (AA), 4.1% Asian/Pacific Islander (API), 2.6% American Indian/Alaska Native (AI/AN), 67.3% publicly insured, and 31.1% < $25,000 annual household income), 12.0% received PalCare consultation. Compared with NHW patients, significantly lower odds of receiving PalCare was observed among AA (aOR, 0.92; 95% CI, 0.86-0.99, $P < 0.05$) and Hispanics (aOR, 0.75; 95% CI, 0.71-0.79, $P < 0.05$). Overall inpatient mortality among decompensated cirrhosis hospitalizations was 9.2%, which was significantly higher in non-white ethnic minorities (10.8% in AA, 10.7% in API, 10.5% in AI/AN) compared to NHW (8.9%). On multivariable regression, compared to NHW patients, significantly greater odds of inpatient mortality was observed among AA (aOR, 1.13; 95% CI, 1.05-1.21, $P < 0.05$), API (aOR, 1.21; 95% CI, 1.09-1.34, $P < 0.05$), and AI/AN patients (aOR, 1.18; 95% CI, 1.04-1.33, $P < 0.05$). Patients with lower annual household income also had significantly higher odds of mortality compared to those from higher income households (Table 1). **Conclusion:** Significant disparities in inpatient PalCare utilization and mortality persists among hospitalized adults with decompensated cirrhosis, particularly among racial/ethnic minorities and lower income groups. Further efforts should focus on enhancing access to appropriate PalCare services among vulnerable populations.

Table 1. Multivariable Logistic Regression Models for Receipt of Palliative Care Consultation and Inpatient Mortality

	Receipt of Palliative Care Consultation			Inpatient Mortality		
Characteristic	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Age, ref 18-39	—	—	—	—	—	—
40-59	1.31	1.22-1.42	<0.001	1.23	1.13-1.34	<0.001
60+	1.55	1.71-2.62	<0.001	1.57	1.44-1.72	<0.001
Gender, ref men	1.02	0.96-1.08	0.440	1.03	0.98-1.07	0.250
Race/Ethnicity, ref Non-Hispanic White	—	—	—	—	—	—
African American	0.92	0.86-0.99	0.018	1.13	1.05-1.21	0.001
Hispanic	0.75	0.71-0.79	<0.001	0.89	0.84-0.95	<0.001
Asian/Pacific Islander	1.01	0.93-1.11	0.768	1.21	1.09-1.34	<0.001
American Indian/Alaska Native	0.89	0.78-1.00	0.062	1.18	1.04-1.33	0.010
Insurance, ref Private	—	—	—	—	—	—
Medicare	1.19	1.13-1.25	<0.001	0.92	0.87-0.98	0.006
Medicaid	1.14	1.08-1.20	<0.001	0.99	0.93-1.05	0.809
Self-pay	1.23	1.12-1.35	<0.001	1.22	1.11-1.35	<0.001
No Charge	1.41	1.04-1.88	0.022	0.77	0.51-1.11	0.161
Other	1.64	1.46-1.82	<0.001	1.27	1.13-1.43	<0.001
Region, ref Northeast	—	—	—	—	—	—
Southeast	1.29	1.21-1.37	<0.001	0.94	0.89-1.00	0.060
West	1.19	1.12-1.26	<0.001	0.95	0.84-0.96	<0.001
Midwest	1.09	1.02-1.17	0.012	1.18	1.10-1.27	<0.001
Income quartile, ref upper	—	—	—	—	—	—
Lower	0.97	0.91-1.03	0.291	1.20	1.12-1.28	<0.001
Lower Middle	0.94	0.88-1.00	0.037	1.13	1.05-1.22	<0.001
Upper Middle	0.93	0.88-1.01	0.079	1.06	0.99-1.14	0.082
Year	0.94	0.92-0.97	<0.001	0.97	0.93-0.91	<0.001
ALD, ref non-ALD	1.55	1.46-1.65	<0.001	1.44	1.35-1.54	<0.001
Ascites	1.27	1.19-1.37	<0.001	1.07	0.99-1.16	0.083
SBP	1.80	1.69-1.79	<0.001	1.73	1.66-1.80	<0.001
Hepatic encephalopathy	2.35	2.24-2.46	<0.001	1.87	1.80-2.23	<0.001
Hepatorenal syndrome	3.72	3.55-3.89	<0.001	3.65	3.50-4.01	<0.001
Variceal Bleeding	1.10	0.98-1.42	0.081	1.33	1.09-1.61	0.004
HCC	2.41	2.25-2.58	<0.001	1.30	1.19-1.43	<0.001
Elixhauser variable	1.65	1.54-1.66	<0.001	1.62	1.51-1.63	<0.001

Disclosures: Shyam Patel: Nothing to Disclose, Sohil Patel: Nothing to Disclose, Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support

◆ 2173 | CHRONIC DAMAGE TO CANCER RISK: ALCOHOLIC LIVER DISEASE DRIVEN HEPATOCELLULAR CARCINOMA AMONG ADULTS AGED 45 AND OLDER IN THE UNITED STATES FROM 1999 TO 2023

Simran Joshi[1] Susan Feldman[2] Muhammad Ali[3] Husnain Ahmad[4] Pujitha Vallivedu Chennakesavulu[5] Saman Javaid[6] Sherif Eltawansy[7] Jeevin Sandhu[8] Matthew Manoj[9] Muhammad Khan[10] Salman Attari[11] Talha Qadeer[4] Muhammad Shees Hunain[4] Charitha Karanam Ramapathy[12] Mohammad Islam[1], [1]Yale New Haven Health/Yale University School of Medicine, [2]University of South Carolina/ Prisma health, [3]Jinnah Postgraduate Medical Center, [4]Shalamar Medical and

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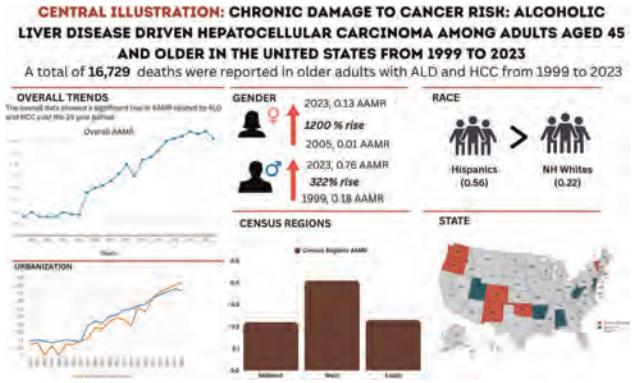
Dental College, [5]Quinnipiac University Frank H. Netter MD School of Medicine / St. Vincent's Medical Center, [6]CMH Kharian Medical College, [7]Jersey Shore University Medical Center, [8]Methodist Dallas Medical Center, [9]Beth Israel Deaconess Medical Center/ Harvard Medical School, [10]Bacha Khan Medical College, [11]Asian Institute of Medical Sciences, [12]UAB Montgomery program/Heersink school of Medicine

Background: Alcoholic liver disease (ALD) is a major contributor to chronic liver injury and a well-established risk factor for hepatocellular carcinoma (HCC). With rising alcohol consumption and earlier onset of liver dysfunction, ALD-driven HCC poses a growing public health concern in the United States. However, national-level mortality trends in ALD-associated HCC, particularly among older adults, remain underexplored. This study aims to analyze 25-year mortality trends of ALD-related HCC in U.S. adults aged 45 and older, with emphasis on demographic and regional disparities. **Methods:** Mortality data from the CDC WONDER database (1999–2023) were analyzed using Joinpoint regression to assess ALD and HCC-related deaths among U.S. adults aged 45 and older. Age-adjusted mortality rates (AAMRs) per million were calculated, along with the average annual percent change (AAPC) and corresponding 95% confidence intervals (CI). **Results:** Over the 25-year study period, ALD-associated HCC accounted for 16,729 deaths. From 1999 to 2023, the AAMR increased from 0.08 to 0.41 per 100,000, reflecting a 412.5% rise (AAPC: 6.86; 95% CI: 5.62 to 8.25; $p < 0.000001$). Females experienced a more pronounced increase compared to males (females: AAPC: 8.05; 95% CI: 5.24 to 11.26 vs. males: AAPC: 6.89; 95% CI: 5.66 to 7.98; both $p < 0.000001$). Among racial and ethnic groups, Hispanics or Latinos had the highest AAMR (0.56), indicating an 82.5% increase, followed by non-Hispanic (NH) Whites (AAMR: 0.21), reflecting a 457.14% increase. The steepest rise was seen among NH Whites (AAPC: 8.07; 95% CI: 6.83 to 10.11; $p < 0.000001$), followed by Hispanics or Latinos (AAPC: 3.66; 95% CI: 2.58 to 5.77; $p < 0.000001$). Regionally, the West bore the highest mortality burden (AAMR: 0.41), followed by the South (AAMR: 0.22) and the Midwest (AAMR: 0.21). The Midwest showed the fastest increase in mortality (AAPC: 8.77; 95% CI: 7.34 to 11.05; $p < 0.000001$), followed closely by the South (AAPC: 8.63; 95% CI: 7.67 to 9.89; $p < 0.000001$). States in the 90th percentile for mortality included Oregon, Vermont, and New Mexico, while those in the 10th percentile included New Jersey, West Virginia, and Arkansas. Urban and rural areas showed comparable AAMRs (0.23 vs. 0.22, respectively). Adults aged 65 and older consistently exhibited higher mortality rates than those aged 45–64 (AAMR: 0.52 vs. 0.43), with a steeper increase in the older age group (AAPC: 7.58 vs. 5.41; $p < 0.000001$ for both). **Conclusion:** ALD-related HCC mortality has surged by 412.5% over 25 years in the U.S., with the highest burden in adults aged 65+, females, non-Hispanic Whites, and Hispanics. The Midwest and South saw the fastest increases, while the West had the highest rates. These findings highlight the urgent need for targeted prevention in high-risk groups.



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◆ 2174 | NATIONAL TRENDS IN DIABETES-ASSOCIATED HEPATOCELLULAR CARCINOMA MORTALITY BY SEX, AGE, AND RACE, 1999–2023

Sarpong Boateng[1] Bubu Banini[2] Ece Tolgay[2], [1]Yale New Haven Health, [2]Yale University

Background: Diabetes Mellitus (DM) is a well-established risk factor for hepatocellular carcinoma (HCC), and its rising prevalence may be contributing to increased liver cancer mortality. However, national trends in DM-related HCC mortality and disparities across demographic groups remain poorly characterized. Understanding the burden of diabetes-related HCC deaths by sex, race, age, and ethnicity can inform prevention strategies and guide surveillance efforts. We aimed to characterize national trends in diabetes-related HCC mortality in the United States (US) from 1999 to 2023. **Methods:** We analyzed U.S. mortality data from the CDC Wide-ranging Online Data for Epidemiologic Research (WONDER) from 1999 to 2023. Decedents aged ≥15 years with both HCC (ICD-10 code C22.0) and DM (E10–E14) listed as causes of death were identified. Mortality rates (MRs) per 100,000 population were calculated and stratified by year, sex, race/

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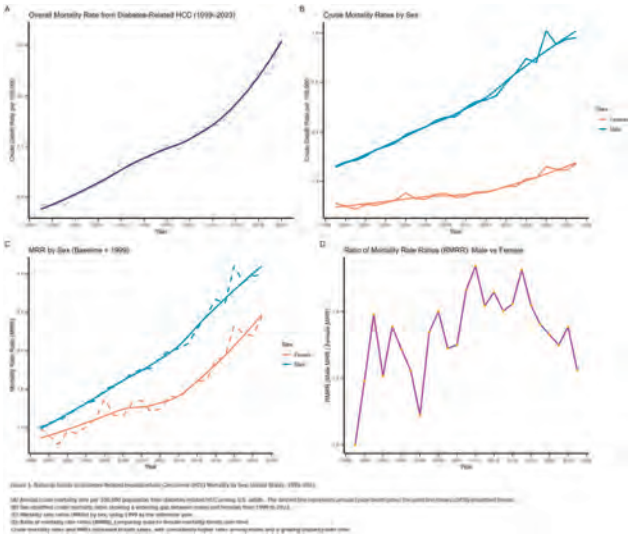
ethnicity, and 10-year age groups. Mortality rate ratios (MRRs) used 1999 as the reference year, and the ratio of MRRs (RMRRs) compared trends by sex. Joinpoint regression identified temporal inflection points and estimated annual percent changes (APCs) with 95% confidence intervals (CI). **Results:** Between 1999 and 2023, 27,729 diabetes-related HCC deaths were reported among U.S. adults. Crude mortality rates increased from 0.2 to 0.5 per 100,000. Males exhibited higher rates than females, with a widening gap over time. In 1999, mortality rates were 0.3 per 100,000 in males and 0.1 in females. By 2023, rates rose to 0.8 in males and 0.3 in females. Male MRR increased from 1.00 (95% CI: 0.77–1.15) to 2.99 (2.68–3.06), and female MRR from 1.00 (0.90–0.90) to 2.45 (1.79–2.69). Joinpoint regression showed significant increases in mortality for both sexes over the entire period: males had an APC of 4.66% (95% CI: 4.11–5.14%) and females 4.58% (3.01–6.03%). White and American Indian/Alaska Native (AI/AN) individuals experienced the highest increases in crude mortality. Among Whites, mortality rose from 0.2 to 0.5 per 100,000 (APC: 6.67%, 95% CI: 6.09–7.25%). AI/AN rates rose from 0.3 to 0.8 (APC: 5.20%, 3.83–6.60%). Increases were also observed among Black (APC: 3.66%, 2.68–4.65%) and Asian/Pacific Islander populations (APC: 2.05%, 1.07–3.04%). Age-stratified analyses showed mortality acceleration among older adults. For those aged ≥85 years, APC was 5.60% (95% CI: 4.43–6.62%). Among individuals aged 75–84, APCs were 2.65% (1.41–3.25%) from 1999–2018 and 11.08% (5.01–25.55%) from 2018–2023. **Conclusion:** Diabetes-related HCC mortality in the US has more than doubled over the past 25 years, with growing disparities by sex, race, and age. Males and older adults carry a disproportionate burden, and rates are rising fastest among AI/AN and White populations. Tailored prevention strategies, early intervention, and equitable access to DM and liver disease care are critical to addressing the shifting epidemiology of HCC.



Disclosures: Sarpong Boateng: Nothing to Disclose, Bubu Banini: Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Merck: Grant/Research Support, Ece Tolgay: Nothing to Disclose

2175 | HEPATOCELLULAR CARCINOMA (HCC) IN CIRRHOTICS VS NON-CIRRHOTIC PATIENTS: DEMOGRAPHICS, SURVIVAL GAPS, RACIAL DISPARITIES: A SEER REGISTRY DATA ANALYSIS (2011-2021)

Eunice Aregbesola[1] Chiamaka Nwachukwu[2] Jonas McCaffrey[1] Ali Ahmad[1] Jamal Ibdah[1], [1]University of Missouri, Columbia, [2]Tulane University

Background: Hepatocellular carcinoma (HCC) accounts for over 90% of liver tumors. Although well-known to be associated with liver cirrhosis, HCC can be identified in patients without liver cirrhosis. In our study, we compared demographic and stage at diagnosis, as well as outcomes, in individuals with and without cirrhosis using a large database cohort. **Methods:** We analyzed 17,481 HCC cases from SEER 17 Registries (2011-2021) in individuals aged 20 and older with documented histological data. Cases were categorized based on biopsy-proven cirrhosis status and we classified cirrhosis based on METAVIR and ISHAK scores of F4 and 5-6, respectively. We used descriptive statistics, multivariate logistic regression, and Kaplan-Meier survival analysis to evaluate group differences. **Results:** Cirrhosis was present in 81.2% of the cases, reinforcing its central role in the development of HCC, while 18.8% of the cases were not cirrhotic. Cirrhotic cases were generally older (peak 60-69 years), Most patients were non-Hispanic White (48.13%), Hispanic (23.25%), and Black (11.01%), with a male predominance. Gender did not significantly affect cirrhosis status ($p = 0.6626$), but being over 40 was linked to cirrhosis ($p < 0.05$). Non-Hispanic patients had lower odds of cirrhosis when compared with Hispanic patients. This was statistically significant among non-Hispanic Black (OR = 0.44, CI = 0.44- 0.53), non-Hispanic white (OR = 0.66 CI = 0.57-0.76) and Asian/Pacific Islanders (OR = 0.38 CI = 0.31-0.45). American Indian/Alaska natives had slightly lower odds, which was not statistically significant (OR = 0.90, CI = 0.54-1.57). Non-cirrhotic patients were more often diagnosed at a later stage (odds ratio = 0.8803, $p = 0.045$). Non-cirrhotic patients had better survival rates despite later diagnoses ($p < 0.001$). **Conclusion:** HCC is more common among older and non-Hispanic white patients. Cirrhosis is strongly linked to HCC, with Hispanic patients having a higher likelihood of being affected compared to non-Hispanic patients. The non-cirrhotic

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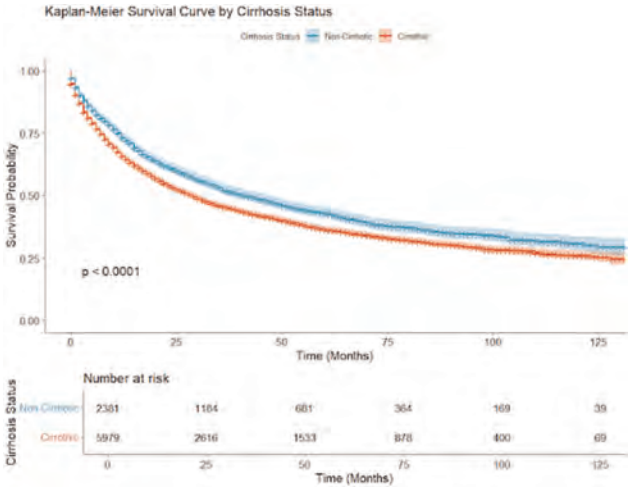
group was diagnosed at more distant stages compared to the cirrhotic group, which was diagnosed at earlier (regional and localized) stages. This difference is likely due to increased surveillance. However, despite being diagnosed earlier, the cirrhotic group had poorer survival outcomes. These findings highlight the need for targeted prevention, improved early detection strategies, and interventions to address disparities in liver cancer outcomes.



Disclosures: Eunice Aregbesola: Nothing to Disclose, Chiamaka Nwachukwu: Nothing to Disclose, Jonas McCaffrey: Nothing to Disclose, Ali Ahmad: Nothing to Disclose, Jamal Ibdah: Nothing to Disclose

2176 | REDUCED PULMONARY FUNCTION IS A LIVER FIBROSIS RISK FACTOR AMONG WORLD TRADE CENTER RESPONDERS BUT NOT AMONG THE GENERAL POPULATION

Ning Ma[1] Rowena Yip[1] Meena Bansal[2] michael crane[1] Sara Lewis[1] David Yankelevitz[1] Claudia Henschke[1] Andrea Branch[2], [1]Icahn School of Medicine at Mount Sinai, [2]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Exposure to the World Trade Center (WTC) dust cloud caused extensive pulmonary damage and may have injured additional vital organs. We investigated reduced forced expiratory volume in 1-second (FEV_1) as a risk factor for advanced liver fibrosis (LF), comparing WTC General Responders (WTC-GRs) to the U.S. population, while adjusting for toxic metal exposure and other established LF risk factors. **Methods:** We analyzed data of 20,905 WTC-GRs and 11,602 National Health and Nutrition Examination Survey (NHANES) participants (Fig.1A). Advanced-LF was indicated by FIB-4 $\geq$2.67 plus alanine aminotransferase (ALT) elevation ($\geq$40 IU/L men, $\geq$31 IU/L women); FEV_1 was determined by spirometry. Cadmium data was from WTC-GR self-reports of pre-9/11 exposure and NHANES blood measurements. Univariable/multivariable logistic regression models were used to estimate odds ratios (ORs). Regression models included no less than 10 cases of advanced-LF per predictor and alternative models were built with different sets of predictors to accommodate the limited number of cases. Propensity score matching by age and sex was used in sensitivity analyses (n = 7,568 per group). **Results:** Among WTC-GRs, FEV_1 and cadmium exposure were associated with advanced-LF, with ORs of 0.74 (95%CI: 0.58-0.95) and 1.73 (95%CI: 1.42-2.09), respectively. Among NHANES participants, FEV_1 was not significantly associated with advanced-LF (OR = 0.68, 95% CI: 0.36-1.27), while cadmium had an OR of 1.42 (95%CI: 1.01-2.0). In a sensitivity analysis of participants matched on age and sex (Fig.1A), FEV_1 was associated with advanced-LF among WTC-GRs (OR = 0.68, 95%CI: 0.48-0.97) after adjusting for the sets of covariates indicated in Figure 1B, but FEV_1 was not associated with advanced-LF among NHANES participants (Fig.1C); cadmium exposure was positively, but not significantly, associated with advanced-LF among WTC-GRs (OR = 1.84, 95% CI: 0.91-3.73), while the blood levels of cadmium were significantly associated with advanced-LF among NHANES participants (OR = 1.41, 95% CI: 1.00-1.99). **Conclusion:** People with lung damage caused by extremely high toxic exposures to the upper respiratory track may have increased risk of advanced liver fibrosis and may benefit from liver disease screening. Cadmium exposure should be considered when assessing liver disease risk in all populations.

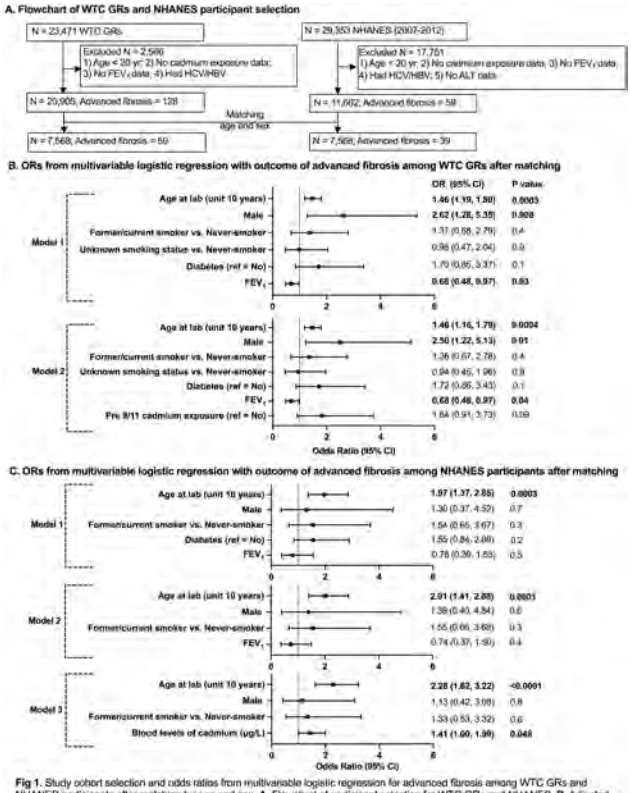


Fig 1. Study cohort selection and odds ratios from multivariable logistic regression for advanced fibrosis among WTC GRs and NHANES participants after matching by age and sex. **A.** Flowchart of participant selection for WTC GRs and NHANES. **B.** Adjusted odds ratios (ORs) for advanced fibrosis among WTC GRs after matching. **C.** Adjusted odds ratios (ORs) for advanced fibrosis among NHANES participants after matching.Abbreviations: OR, odds ratio; WTC GRs, World Trade Center General Responders; NHANES, National Health and Nutrition Examination Survey.

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Disclosures: Ning Ma: Nothing to Disclose, Rowena Yip: Nothing to Disclose, Meena Bansal: Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor, michael crane: Nothing to Disclose, Sara Lewis: Nothing to Disclose, David Yankelevitz: Nothing to Disclose, Claudia Henschke: Nothing to Disclose, Andrea Branch: Gilead Sciences: Research, Pfizer: Research

2177 | DIFFERENTIATING BETWEEN PREGNANCY- AND NON-PREGNANCY RELATED CAUSES OF LIVER ENZYME ELEVATIONS IN THE SECOND AND THIRD TRIMESTER: A MULTICENTER RETROSPECTIVE COHORT STUDY

Jeffrey Lowell[1] Nitzan Roth[2], [1]Northwell, Department of Medicine, New Hyde Park, NY, USA, [2]Northwell, Division of Hepatology, Department of Medicine, New Hyde Park, NY, USA and Zucker School

Background: Elevated liver enzymes in late pregnancy present a clinical dilemma given the need to rapidly differentiate between serious pregnancy-specific diagnoses and non-pregnancy-related liver disease to improve maternal-fetal outcomes through optimal delivery timing. Established diagnostic criteria for pregnancy-specific conditions may not effectively capture atypical presentations, leading to delayed recognition. We aimed to differentiate pregnancy- from non-pregnancy-related enzyme elevations in the second and third trimesters using patient and laboratory characteristics. **Methods:** We conducted a 5-year retrospective cohort study across two tertiary centers of 526 patients with elevated liver enzymes (AST and/or ALT ≥ 40 U/L) during the second or third trimester. Patients had peak antepartum liver enzyme levels ≤ 24 hours from delivery, and ≥ 2 antepartum measurements and ≥ 2 postpartum measurements peripartum. Liver injury was as classified pregnancy-related if both AST and ALT decreased postpartum prior to discharge or non-pregnancy-related otherwise. Demographic, clinical, and laboratory variables including diagnostic criteria for acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, preeclampsia, and HELLP syndrome were analyzed. **Results:** Comparing pregnancy-related to non-pregnancy-related cases (Table 1), peak liver enzyme levels were significantly higher (ALT 99 [54-192] vs. 47 [34-72]; AST 84 [53-151] vs. 51 [41-64] U/L; both $p < 0.001$) and rapidly normalized postpartum ($p < 0.001$), while AST:ALT ratio was lower (0.87 [0.69-1.18] vs. 0.96 [0.72-1.47], $p = 0.007$). Pregnancy-related injury associated with higher LDH (301 vs. 260.5 U/L, $p = 0.003$) and WBC (12.9 [10.4-15.6] vs. 11.9 [9.6-14.9] K/μL, $p = 0.043$), with more frequent fulfillment of preeclampsia features (≥ 2, $p < 0.001$; ≥ 3, $p = 0.004$) and HELLP syndrome criteria (≥ 1, $p < 0.001$; ≥ 2, $p = 0.02$). A simplified diagnostic approach using either platelet count ≤ 150 K/μL or LDH > 300 U/L had 75% positive predictive value for identifying pregnancy-related cases ($p = 0.002$). Peak ALT emerged as the strongest independent predictor in multivariate analysis ($p = 0.016$; cutoff 79.5 U/L, AUROC 0.73; Fig 1). **Conclusion:** Among patients with liver enzyme elevations peaking ≤ 24 hours before delivery, two-thirds had pregnancy-related injury characterized by higher absolute liver enzyme values but rapid postpartum normalization. Peak ALT value, AST:ALT ratio, LDH, WBC, and platelet count aid in discriminating between pregnancy- and non-pregnancy-related liver injury. While established diagnostic criteria for pregnancy-related liver diseases provide important clinical frameworks, simplified diagnostic approaches meeting fewer formal criteria may facilitate earlier recognition of atypical pregnancy-related liver disease presentations.

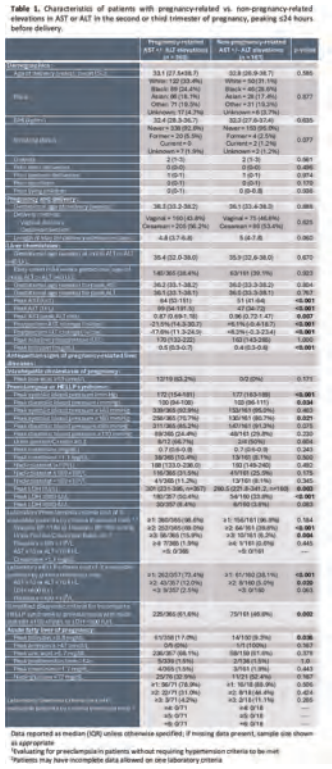

Figure 1: ROC Curve for Livery Injury Prediction Model

Disclosures: Jeffrey Lowell: Nothing to Disclose, Nitzan Roth: Nothing to Disclose

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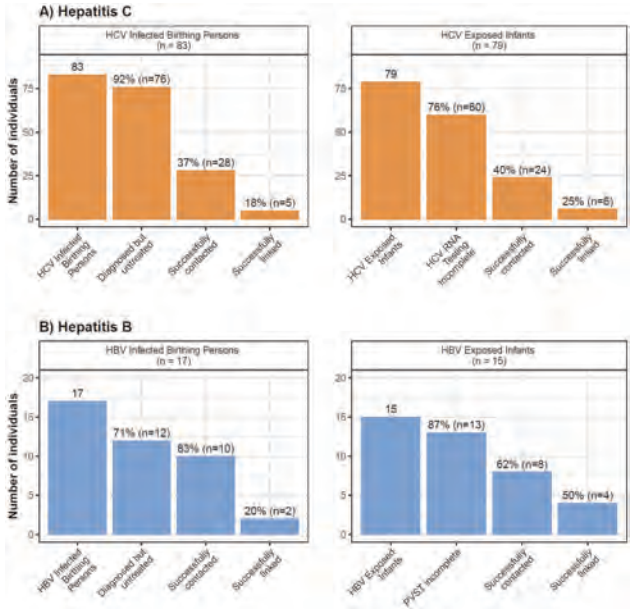
2178 | IMPROVING LINKAGE TO CARE FOR HBV/HCV-EXPOSED MOTHER–INFANT DYADS IN NORTH CAROLINA: UNIVERSITY OF NORTH CAROLINA RELINK PROGRAM

Cory Spencer[1] Lauryn Ursery[2] Carl Seashore[3] Andrea Knittel[3] Elisabeth Johnson[3] Richard Moore[3] Asher Schranz[3] Peyton Thompson[3], [1]School of Medicine, University of North Carolina, Chapel Hill, USA, [2]Gillings School of Global Public Health, University of North Carolina, Chapel Hill, USA, [3]University of North Carolina, Chapel Hill, USA

Background: Hepatitis B virus (HBV) and Hepatitis C virus (HCV) are leading causes of liver-related mortality, resulting in 1.3 million global deaths each year. Elimination efforts focus on preventing vertical transmission but follow-up for postpartum individuals and infants is insufficient. The University of North Carolina (UNC) Relink program seeks to identify pregnant or postpartum people and infants affected by HBV and HCV to (i) identify diagnosed but untreated patients, (ii) describe their demographic characteristics, and (iii) provide linkage to care and testing. **Methods:** We systematically searched UNC Health (15 hospitals, 15.6% of statewide births) records for HBV+ or HCV+ pregnant or postpartum individuals May 2023-June 2024. HBV positivity was defined by a positive HBV surface antigen test and HCV positivity by detectable HCV RNA viral load. Medical records were reviewed to collect demographic, socioeconomic, and health information and identify whether mother-infant dyads were connected to care. Unlinked patients, defined as diagnosed but not receiving hepatitis care, were contacted by phone or MyChart to link them to follow-up care. Medical record and linkage data were collected in REDCap, and summary statistics were computed in R. **Results:** We identified 83 HCV+ and 17 HBV+ pregnant or postpartum individuals across NC (23% in eastern, 54% in central and 23% in western NC). Among HCV+ and HBV+ birthing persons, 92% (n = 76) and 71% (n = 12), respectively, were unlinked to care. Most unlinked HCV+ birthing persons were White (88.2%, n = 67), 100% spoke English, and half (52.6%, n = 40) had a diagnosed opioid use disorder (OUD), whereas unlinked HBV+ birthing persons were more racially diverse (Asian: 50%, n = 6; Other race: 25%, n = 3), 50% (n = 6) were non-English speaking, and none had an OUD diagnosis. We successfully contacted 37% (n = 28) of HCV+ and 83% (n = 10) of HBV+ unlinked birthing persons. To date, 18% (n = 5) and 20% (n = 2) of contacted HCV+ and HBV+ birthing persons have been linked to care, respectively (Figure 1). We also identified 79 HCV-exposed and 15 HBV-exposed infants, of whom 76% (n = 60) and 87% (n = 13), respectively, had not yet undergone testing. We successfully contacted families of 40% (n = 24) of HCV-exposed and 62% (n = 8) of HBV-exposed infants, of whom 25% (n = 6) and 50% (n = 4) have been linked to testing, respectively. **Conclusion:** Major care gaps remain for postpartum people and infants affected by HCV and HBV, and linkage efforts must be enhanced to achieve hepatitis elimination. UNC's Relink project has highlighted these gaps and the need for interventions to link untreated patients to care.



Disclosures: Cory Spencer: Nothing to Disclose, Lauryn Ursery: Nothing to Disclose, Carl Seashore: Couplet Care, LLC: Scientific Advisor, Andrea Knittel: Nothing to Disclose, Elisabeth Johnson: Nothing to Disclose, Richard Moore: Nothing to Disclose, Asher Schranz: Nothing to Disclose, Peyton Thompson: Nothing to Disclose

2179 | HEPATOCELLULAR CARCINOMA CARE DELIVERY: WHO IS AT RISK FOR DELAYS?

Elizabeth Ayomide Fashakin[1] Varun Rohatgi[1] Robert Brown[1] Resmi Charalel[1], [1]Weill Cornell Medicine

Background: HCC is curable if found and treated at an early stage. Prior studies have demonstrated an ideal timeline of less than 28 days between presentation to diagnosis and less than 62 days between diagnosis and treatment. Still, many patients experience delays in screening and diagnosis of HCC and further delays in treatment once officially diagnosed. Here, we identify where gaps in care are most likely to occur within our tertiary care center and who is most at risk. **Methods:** Retrospective, single-center cohort study of patients presenting with a new diagnosis of HCC (new LI-RADS 4 or 5 lesion or positive biopsy) between Jan 2018-Dec 2020 and Jan 2023-Dec 2023. Patients diagnosed in 2021 and 2022 were excluded due to changes in cancer care workflow during the COVID-19 pandemic. EHR was reviewed for clinical data and general demographic

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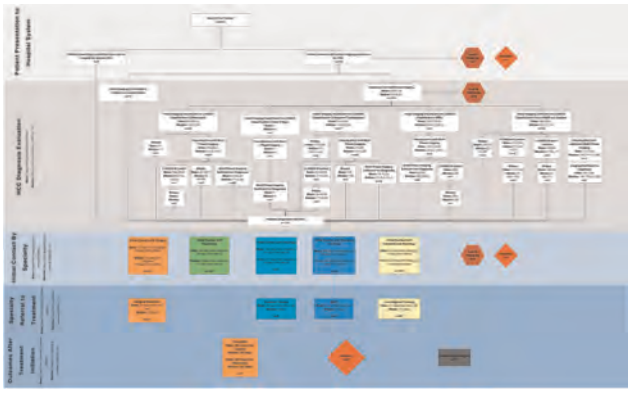
information including age at diagnosis, race, native language, medical comorbidities, cirrhosis etiology, and socioeconomic status (via patient zip code and insurance status). Milestone timepoints for each patient's care were evaluated including dates of initial presentation, HCC diagnosis, treatment initiation, and referral to/evaluation by multidisciplinary specialists. Delays in presentation to diagnosis and diagnosis to treatment were defined as >28 and >62 days respectively. Categorical data were evaluated using Chi-square and continuous data via Kruskal Wallis testing. Bonferroni correction was applied for pairwise comparisons. **Results:** Among 2,504 records screened, 194 presented with new lesions suspicious for a new HCC with 187 formally diagnosed with HCC and 135 receiving treatment. Mean age was 67 years and the study population was racially and ethnically diverse (40% White, 11% Black, 27% Asian, 18% Other/Combined, 3% Not Reported) with 15% identifying as Hispanic/Latino. 41/187 (22%) experienced delays in diagnosis and 36/187 (27%) experienced delays in treatment. Nine of 194 patients (4.64%) passed away prior to receiving treatment. The most commonly referred specialties were hepatology (137/187, 73.3%) with a median diagnosis-to-evaluation time of 9 days (IQR: 0.5, 41), interventional radiology (122/187, 65.2%) with median time of 23 days (10, 46.25), and surgery (111/187, 59.4%) with median time of 14 days (0, 34). Time to diagnosis was shorter for those with private insurance (15.6 days) compared to Medicaid (27.8 days, $p = 0.003$) or Medicare (21.8 days, $p = 0.0023$). Otherwise, there was no significant association found between diagnostic delays and racial group, native language, or liver disease etiology (all p-values > 0.05 or exceeded corrected alpha). **Conclusion:** While most HCC patients receive timely care, even in our tertiary medical center with well-equipped multidisciplinary teams, about one-quarter of patients continue to experience diagnostic and treatment delays, with longer times to diagnosis for those insured by Medicaid and Medicare.



Disclosures: Elizabeth Ayomide Fashakin: Nothing to Disclose, Varun Rohatgi: Nothing to Disclose, Robert Brown: Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant, Resmi Charalel: Nothing to Disclose

2180 | METABOLIC AND ALCOHOL-ASSOCIATED LIVER DISEASE IN HISPANICS: DISPARITIES IN OUTCOMES USING REAL-WORLD DATA

Mohamed Eldesouki[1] Ashlynn Black[2] Karimar Amador-Martinez[2] Ahmed Salem[3] Ahmed Ibrahim[4] Mohammed Youssef[5] Abdallah Hussein[6] Mona Ahmed[7] Nikki Duong[2], [1]New York Medical College at Saint Michael Medical Center, [2]Stanford University School of Medicine, [3]Maimonides Medical Center, [4]Medical University of South Carolina, [5]Hunt regional medical center, [6]Virtua our Lady Of Lourdes Hospital, [7]Mansoura University School of Medicine

Background: Metabolic and Alcohol-related Liver Disease (Met-ALD) is a newly defined subset of steatotic liver disease that combines ≥ 1 cardiometabolic risk factor with at-risk alcohol use. Liver-related outcomes in Hispanics with Met-ALD have been understudied. We used a large U.S. real-world data set to compare liver outcomes between Hispanic and non-Hispanic adults with Met-ALD. **Methods:** TriNetX U.S. Collaborative Network was queried for adults (≥ 18 y), diagnosed with Met-ALD. Patients were then stratified by ethnicity into Hispanic and non-Hispanic groups. Propensity-score matching (PSM) (1:1) balanced age, sex, body-mass index, diabetes, hypertension, dyslipidemia, and smoking. Matched patients were followed for up to three years from the Met-ALD index date. Study outcomes were cirrhosis, portal hypertension (HTN), variceal bleeding, acute liver failure (ALF), hepatocellular carcinoma (HCC), ascites, and hepatorenal syndrome (HRS). Adjusted odds ratios (aORs) with 95 % confidence intervals (CI) were calculated. **Results:** A total of 15,741 Hispanic and 120,507 non-Hispanic patients with Met-ALD were identified. After PSM, a total of 15,727 patients were identified in each group with balanced baseline covariates. BMI was 39.9 ± 22 in Hispanic group, and 38.4 ± 17.8 in non-Hispanics. (Table 1). After PSM, Hispanics had a higher rate of cirrhosis (14.37 vs. 12.15; OR = 1.21, 95% CI: 1.14–1.30, $p < 0.001$), portal HTN (9.15 vs. 7.36; OR = 1.27, 95% CI: 1.17–1.37, $p < 0.01$), ALF (7.55 vs. 6.87; OR = 1.11, 95% CI: 1.02–1.21, $p = 0.02$), variceal bleeding (1.20 vs. 0.86; OR = 1.41, 95% CI: 1.13–1.75, $p = 0.003$), and HCC (1.88 vs. 0.94; OR = 2.02, 95% CI: 1.66–2.46, $p < 0.01$) when compared to non-Hispanics. Ascites and HRS showed no significant difference (7.75 vs. 8.05; OR = 0.96, 95% CI: 0.89–1.04, $p = 0.30$), and (1.57 vs. 1.44; OR = 1.09, 95% CI: 0.91–1.31, $p = 0.35$), respectively. (Table 2). **Conclusion:** In this national cohort, Hispanic adults with Met-ALD experienced significantly greater liver-related morbidity including cirrhosis, portal

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hypertension, variceal bleeding, acute liver failure, and HCC risk versus non-Hispanics. These findings underscore the urgent need for culturally tailored alcohol-reduction programs, equitable access to hepatology care, and enhanced HCC surveillance to mitigate the disproportionate burden of Met-ALD in Hispanic patients.

Table 1 Baseline characteristics for the study cohorts before and after propensity score matching

Variable (%)	Hispanics 15,741	Non-Hispanics 120,597	P-value	Hispanics 15,727	Non-Hispanics 15,727	P-value
Age	46.3 ± 13.1	52 ± 13.2	< 0.01	46.3 ± 13.1	46.3 ± 13.1	0.96
Female	3,888 (24.72)	39,995 (33.3)	< 0.01	3,888 (24.72)	3,886 (24.71)	0.97
CKD	711 (4.5%)	6,686 (5.5)	< 0.01	711 (4.52)	694 (4.41)	0.64
HTN	5,067 (32.21)	53,001 (44.13)	< 0.01	5,067 (32.22)	5,056 (32.15)	0.8
DM	3,469 (22.06)	20,447 (17.02)	< 0.01	3,468 (22.05)	3,465 (22.03)	0.9
HB A1c	6.73 ± 2.14	6.28 ± 1.66	< 0.01	5,111 (32.49)	5,111 (32.49)	1
BMI	39.9 ± 22	30.2 ± 10	< 0.01	39.9 ± 22	38.4 ± 17.8	0.77
Opioid	5,111 (32.49)	42,809 (35.64)	< 0.01	5,111 (32.49)	5,111 (32.49)	1

Table 2 Outcomes in Hispanics and non-Hispanics patients with metabolic and alcohol-associated liver disease

Variable	Hispanics		Non-Hispanics		OR	95 % CI	P value
	Events	Rate	Events	Rate			
Hepatic failure	1,188	7.55	1,081	6.87	1.11	1.02 - 1.21	0.02
Hepatic encephalopathy	528	3.35	432	2.74	1.22	1.08 - 1.38	< 0.01
Ascites	1,220	7.75	1,266	8.05	0.96	0.89 - 1.04	0.3
Liver transplant	358	2.27	269	1.71	1.33	1.14 - 1.57	< 0.01
Cirrhosis	2,261	14.37	1,912	12.15	1.21	1.14 - 1.25	< 0.01
Variceal bleeding	189	1.20	135	0.86	1.41	1.13 - 1.75	0.003
Hepatocellular carcinoma	296	1.88	148	0.94	2.02	1.66 - 2.46	< 0.01
Hepatorenal syndrome	247	1.57	227	1.44	1.09	0.91 - 1.31	0.35
Portal hypertension	1,439	9.15	1,159	7.36	1.27	1.17 - 1.37	< 0.01

Disclosures: Mohamed Eldesouki: Nothing to Disclose, Ashlynn Black: Nothing to Disclose, Karimar Amador-Martinez: Nothing to Disclose, Ahmed Salem: Nothing to Disclose, Ahmed Ibrahim: Nothing to Disclose, Mohammed Youssef: Nothing to Disclose, Abdallah Hussein: Nothing to Disclose, Mona Ahmed: Nothing to Disclose, Nikki Duong: Nothing to Disclose

2181 | ADDRESSING FOOD INSECURITY AMONG PATIENTS WITH AND AT-RISK FOR MASLD: A QUALITATIVE STUDY TO OPTIMIZE A FOOD PHARMACY PROGRAM

Rebecca Kim[1] April Ballantyne[2] Hanna Hedges[2] Heather Williamson[2] Ellen Maxfield[2] John Inadomi[1] Molly Conroy[1] Andrew Gawron[1] Jennifer Price[3], [1]University of Utah Health, [2]University of Utah, [3]University of California, San Francisco

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), the liver disease concomitant with obesity, diabetes, hypertension, and metabolic syndrome, disproportionately impacts individuals with lower income. Food insecurity (FI), the lack of consistent access to healthy foods, has been associated with advanced fibrosis and all-cause mortality among patients with MASLD. Our Food Pharmacy Program (FPP) is a mobile trailer equipped with hospital-grade foodservice equipment, designed to serve patients experiencing FI and nutrition-related chronic disease. Patients receive six month food prescriptions redeemable for healthy foods or gift cards, along with personalized health coaching that includes nutrition education, meal planning, and strategies for preparing affordable, healthy meals. We aimed to understand the experiences of former participants with and at-risk for MASLD, to optimize the FPP in preparation for a MASLD focused FPP. **Methods:** Seventeen participants were recruited through outreach methods, screened for eligibility with REDCap surveys, and provided verbal consent prior to focus groups. Groups followed a semi- structured interview guide and were recorded. Participants were given $75. Thematic analysis was performed using a codebook developed from audit trails. **Results:** Overall, 94% were women, mean age 55 yrs, 18% Black, 18% Hispanic, 53% White; all had FI. 59% had diabetes, 41% had hypertension, 59% had obesity, 12% had heart disease, 12% with MASLD. Themes emerged including: 1) health and nutrition education, 2) program benefits, 3) engagement and motivation, 4) suggestions for improvement. Participants reported that the FPP enhanced their knowledge of healthy eating, leading to healthier eating habits, improved cooking skills using fresh ingredients, and a more comprehensive understanding of nutrition. Many participants noted the high quality and variety of food provided by the FPP. They also valued the coaching sessions and found virtual appointments to be convenient and facilitated greater accountability. Reported barriers to engagement in the FPP included restricted operating hours, lack of transportation, inadequate internet access, limited length of prescription, and prior negative experiences with dieticians. Participants recommended increasing FPP awareness to providers, expanding accessibility through additional locations, and extending FPP hours and food availability. **Conclusion:** Former FPP participants with or at-risk for MASLD found the program to be beneficial to improve nutrition knowledge, eating habits, and food access. Their feedback describes opportunities to enhance the program as it is adapted for the MASLD population.

Disclosures: Rebecca Kim: Nothing to Disclose, April Ballantyne: Nothing to Disclose, Hanna Hedges: Nothing to Disclose, Heather Williamson: Nothing to

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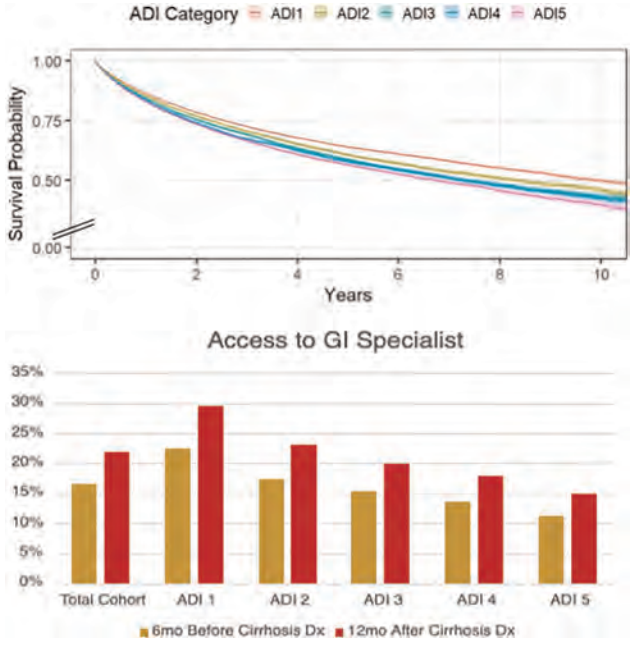
2182 | SOCIAL DEPRIVATION IS ASSOCIATED WITH AN INCREASED RISK OF DECOMPENSATION AND DECREASED ACCESS TO SPECIALTY CARE

Joy Obayemi[1] Mitchell Paukner[2] Bima Hasjim[3] Dominic Vitello[2] Aditya Jain[4] Federico Crippa[4] Kiarri Kershaw[5] Therese Banea[2] Lisa VanWagner[6] Lihui Zhao[2] Charles Manski[4] Daniela Ladner[2] Daniela Ladner[2], [1]University of Michigan / Northwestern University, [2]Feinberg School of Medicine, Northwestern University, [3]University of California, Irvine, [4]Department of Economics, Northwestern University, [5]Northwestern University, [6]Department of Medicine, University of Texas Southwestern Medical Center

Background: The transition from compensated to decompensated cirrhosis is associated with significant morbidity and mortality. Little is known about how structural and socioeconomic environments may correlate with the timing of this transition and access to specialty care. **Methods:** A longitudinal, retrospective, cohort study of patients with compensated cirrhosis using administrative claims data from 2011-2021 was conducted. Diagnoses, decompensation events, and access to gastroenterology (GI) specialists were defined by validated ICD/CPT/provider specialty codes. Structural and socioeconomic deprivation was categorized using the standardized Area Deprivation Index (ADI) [ADI1 = least deprived (0-20), ADI2 = less deprived (21-40), ADI3 = moderately deprived (41-60), ADI4 = more deprived (61-80), ADI5 = most deprived (81-100)]. Time-to-event analysis of first decompensation event was performed using a Cox model adjusted for clinicodemographic covariates and restricted mean survival time (RMST). Descriptive statistics were used to calculate median time to decompensation and access to specialty care. **Results:** Among 200,823 patients identified with cirrhosis, 51.8% (n = 104,095) were male and most patients had MASLD (n = 72,805; 36.25%), MetALD (n = 36,533; 18.19%) or ≥ 2 etiologies (n = 42,894; 21.36%). 28.6% (n = 57,489) experienced a decompensation in the 10-year follow-up period. Patients in areas of higher deprivation (ADI2 HR 1.06; ADI3 HR 1.12; ADI4 HR 1.16; ADI5 HR 1.13; all $p < 0.001$) were at higher risk of decompensation than those in the least deprived areas (ADI1) [Figure 1]. The median time to decompensation for patients in ADI5 was 9.89y (95% CI 9.49-10.30) compared to 6.73y (95%CI 6.45-6.96) in ADI 1 ($p < 0.001$). Patients in ADI 5 were expected to survive 6.69y (95% CI 6.65-6.74) in 10 years of follow-up without a decompensation event compared to an expected 5.98y for patients in ADI 1 (95% CI 5.92-6.03) (pairwise RMST $p < 0.001$). As deprivation increased, the proportion of patients who saw a GI specialist in the 6 months prior to cirrhosis diagnosis (ADI1 22.38% vs ADI5 11.14%) and in the 12 months following cirrhosis diagnosis (ADI1 29.53% vs ADI5 15.02%) decreased. **Conclusion:** Structural and socioeconomic deprivation is associated with faster decompensation and decreased access to GI specialists for patients with cirrhosis. This presents an opportunity for targeted patient interventions in deprived neighborhoods to slow disease progression.



Disclosures: Joy Obayemi: Nothing to Disclose, Mitchell Paukner: Nothing to Disclose, Bima Hasjim: Nothing to Disclose, Dominic Vitello: Nothing to Disclose, Aditya Jain: Nothing to Disclose, Federico Crippa: Nothing to Disclose, Kiarri Kershaw: Nothing to Disclose, Therese Banea: Nothing to Disclose, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, Lihui Zhao: Nothing to Disclose, Charles Manski: Nothing to Disclose, Daniela Ladner: Nothing to Disclose, Nothing to Disclose, Daniela Ladner: Nothing to Disclose, Nothing to Disclose

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2183 | LOW DISEASE AWARENESS AMONG METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND MASLD CIRRHOSIS IN THE UNITED STATES

Zobair Younossi[1] James Paik[2] Leyla de Avila[3] Brian Lam[4] Andrei Racila[1] Annette Paik[1] Arianna Nader[1] Asrar Alaklabi[5] Fatema Nader[1] Andrei Racila[1] Linda Henry[1] Saleh Alqahtani[5], [1]The Global NASH Council, [2]Beatty Liver and Obesity Research Program, [3]Beatty Liver and Obesity Research Program, Inova, [4]INOVA Fairfax Hospital, [5]Liver, Digestive, and Lifestyle Health Research Section, and Organ Transplant Center of Excellenc

Background: Despite the growing burden of MASLD, patients' awareness has been low. We assessed liver disease awareness among U.S. adults with MASLD. **Methods:** We analyzed data from U.S. adults participating in NHANES (2007–2023). MASLD was defined using either a validated U.S. Fatty Liver Index or controlled attenuation parameter (CAP $\geq$280 dB/m) in accordance with recent consensus. Chronic hepatitis B (HBV), chronic hepatitis C and cirrhosis were defined as HBsAg (+), HCV RNA (+) and liver stiffness measurement $\geq$20 kPa. Liver disease awareness was determined by self-reported current liver diseases including fatty liver, hepatitis, or cirrhosis. **Results:** The study included 24,676 participants (2007 to 2023). Over this period, liver disease awareness among MASLD increased from 4.39% to 5.76% (trend $p = 0.016$), while awareness among those with HBV or HCV remained stable ($p > 0.05$). In the most recent NHANES cycle (2017-2023, N = 12,976), 33.6% had MASLD, 1.2% MASLD-related cirrhosis, 0.9% HCV, and 0.3% HBV. In this period, awareness of fatty liver among MASLD was 4.8%, awareness of cirrhosis among MASLD-cirrhosis was 6.5% while awareness of hepatitis among HCV and HBV was 21.8% and 26.1%.Awareness of liver disease varied according to age [highest 45–64 yrs (5.9%)], race/ethnicity [lowest in Non-Hispanic Black individuals (1.0%) but highest among Other Hispanics (8.0%)] (all $p < 0.02$). According to the healthcare setting, attendees of Veterans Affairs (VA) medical center had the highest awareness (15.8%) compared to community health centers (6.4%), emergency departments (6.1%), and urgent care centers (4.9%) ($p < .017$). Awareness also differed by insurance: highest awareness among those with military health coverage (9.6%) and lowest among the uninsured (2.4%). Sociodemographic and metabolic conditions-adjusted model showed male sex and non-Hispanic Black race were significantly associated with lower awareness, while receiving care at a VA medical center was associated with higher awareness of liver disease. (Table). **Conclusion:** Despite some improvements, awareness among MASLD patients remains very low. This low awareness is especially concerning among MASLD with cirrhosis.

Table. Awareness of Liver Disease Among U.S. Adults with MASLD by Demographic and Healthcare Access Characteristics, NHANES 2017–2023

	Awareness % (95% CI)	p-value
Age Group		0.0364
18 - 29	2.07 (0.08 - 4.05)	
30 - 44	4.26 (1.88 - 6.64)	
45 - 64	5.86 (4.65 - 7.07)	
≥ 65	4.81 (3.28 - 6.34)	
Race		<.0001
Non-Hispanic White	4.69 (3.49 - 5.88)	
Non-Hispanic Black	0.95 (0.31 - 1.59)	
Mexican American	6.41 (3.41 - 9.41)	
Other Hispanic	7.97 (4.74 - 11.20)	
Asian	4.23 (2.47 - 5.99)	
Education		0.0109
Less than high school	5.06 (2.57 - 7.55)	
High School	5.59 (4.17 - 7.01)	
College	3.28 (2.26 - 4.29)	
Primary Source of Routine Healthcare		<.0001
Community Health Center / Clinic	6.37 (4.88 - 7.86)	
Emergency	6.11 (1.41 - 10.80)	
Urgent Care Facility	4.94 (-0.27 - 10.14)	
Veterans Affairs Medical Center	15.75 (5.58 - 25.92)	
Health Insurance		0.0174
Private Insurance	4.10 (2.85 - 5.36)	
Medicare	6.78 (4.25 - 9.32)	
Medicaid/CHIP & Other Govt	7.64 (3.97 - 11.30)	
Military Health Care	9.60 (-6.05 - 25.24)	
Uninsured	2.40 (0.66 - 4.14)	

Adjusted Odds Ratios of Factors Associated With Liver Disease Awareness Among U.S. Adults With MASLD, NHANES 2017–2023

	OR (95% CI)	P
Male	**0.43 (0.21 - 0.89)**	**0.0265**
Non-Hispanic Black	**0.13 (0.04 - 0.50)**	**0.0052**
Veterans Affairs Medical Center	**4.97 (1.61 - 15.32)**	**0.0084**

Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, James Paik: Nothing to Disclose, Leyla de Avila: Nothing to Disclose, Brian Lam: Madrigal: Speaking and Teaching, Andrei Racila: Nothing to Disclose, Annette Paik: Nothing to Disclose, Arianna Nader: Nothing to Disclose, Asrar Alaklabi: Nothing to Disclose, Fatema Nader: Nothing to Disclose, Andrei Racila: Nothing to Disclose, Linda Henry: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose

2184 | OVERLOOKED AND UNDERDOSED: HEPATITIS B TREATMENT INEQUITIES IN US MIGRANTS

Raissa Nana Sede Mbakop Forlemu[1] Anuj Sharma[1] Manasa Ginjupalli[1] Arnold Nongmoh Forlemu[1] Madhavi Reddy[1], [1]The Brooklyn Hospital Center

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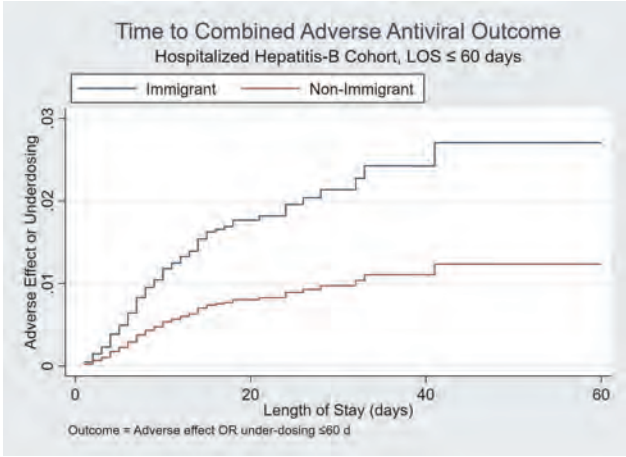
Background: Chronic hepatitis B (HBV) disproportionately affects migrants in the United States, particularly those from high-prevalence regions such as East and Southeast Asia, sub-Saharan Africa, and the Pacific Islands. Although effective treatments are available, many migrants face barriers to diagnosis and care, including language difficulties, lack of insurance, limited health literacy, and fear related to immigration status. These challenges contribute to delayed treatment and higher rates of liver complications such as cirrhosis and hepatocellular carcinoma. Despite national screening guidelines, significant disparities persist in HBV care among migrant populations. We evaluated adverse events and rates of underdosing of hepatitis B antiviral treatment in migrant Hepatitis B patients with the goal of informing policies and interventions that promote more equitable access to care. **Methods:** We included hepatitis B patient population seen in United States health care facilities from 2018-2022 using the Nationwide inpatient sample database. We further subdivided the migrants per geographic location in the US. Propensity score matching was used to balance confounding factors between migrants to natives. Time to hepatitis B treatment adverse events and dosing were estimated using Kaplan-Meier. Adjusted hazard odds ratios for hepatitis B treatment adverse events and dosing were estimated using Cox-proportional hazards regression models, while accounting for competing events. Adjusted hazard ratios (HR) and confidence intervals (CI) at 95% were reported. **Results:** The number of patients with hepatitis B was 352,860, 3.8% of them were immigrants. The mean age of study population was 55.6 years. Majority of immigrant hepatitis B patients were male at 76.4%. On regression analysis, Migrant patients with hepatitis B were more likely to have treatment related disparities including adverse events with a hazard ratio of 2.20 (CI 1.35-3.61, $p = 0.002$) compared to natives. Also, migrants were more likely to have their hepatitis B treatment underdosed with a hazard ratio of 3.65 (CI 2.15-6.19, $p = 0.001$), compared to natives. Time to event curves also showed a significant trend to underdosing and adverse events among immigrants compared to natives (Figure 1). No meaningful differences were observed between natives and migrant hepatitis B populations within geographic US regions. **Conclusion:** Migrants were more likely to have side effects to hepatitis B treatment and to be under dosed. It is known that many migrants have irregular access to care including insurance issues, making dose monitoring difficult. In addition, misunderstanding treatment instructions by migrants can lead to incorrect dosing, nonadherence, or combining with harmful substances. Addressing this requires policy reform, provider education, and tailored care models that account for the unique challenges faced by migrant populations.



Disclosures: Raissa Nana Sede Mbakop Forlemu: Nothing to Disclose, Anuj Sharma: Nothing to Disclose, Manasa Ginjupalli: Nothing to Disclose, Arnold Nongmoh Forlemu: Nothing to Disclose, Madhavi Reddy: Nothing to Disclose

2185 | MEDICAL MISTRUST AMONG PATIENTS WITH EARLY-STAGE ALCOHOL-ASSOCIATED LIVER DISEASE: INSIGHTS FROM THE PROSPECTIVE DALLAS DIONYSUS COHORT

Elias Rady[1] Hamza Dahshi[2] Ahmad Anouti[1] Bill Zhang[1] Courtney Roberts[3] Thomas Kerr[1] Nicole Rich[1] Amit Singal[1] Amit Singal[1] Mack Mitchell[1] Thomas Cotter[1], [1]University of Texas Southwestern Medical Center, [2]Case Western Reserve University School of Medicine, Medical Scientist Training Program, [3]University of Texas Southwestern Medical School

Background: Medical mistrust is a known barrier to care, particularly for stigmatized conditions like alcohol-associated liver disease (ALD), which frequently coexists with alcohol use disorder (AUD). Despite its potential impact on care delays and late-stage disease presentation, few studies have explored mistrust in patients with ALD. We aimed to characterize the prevalence of medical mistrust among patients with early-stage ALD to inform strategies for improving patient engagement with care. **Methods:** We conducted a survey among adults with early-stage ALD enrolled at UT Southwestern Medical Center and Parkland Health between September 2024 to present. Participants completed the validated 12-item Group-Based Medical

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Mistrust Scale (GBMMS), which evaluates perceived discrimination, lack of support and suspicion toward healthcare providers. Each item was rated on a 5-point Likert scale, with scores >3 indicating high mistrust (range 1-5). Surveys were administered in person by trained research staff. We calculated mean GBMMS scores and used Wilcoxon Rank Sum test or Kruskal-Wallis for categorical variables and linear regression for continuous variables to examine the association between mistrust and clinical, demographic, and psychosocial factors. **Results:** Among 88 patients approached, 70 (80%) participated in the survey (median age 54.6 years, 86% men, 20% Hispanic). Mean GBMMS scores ranged from 1.22 to 2.09 (mean 1.59; SD 0.79), with 10.1% of participants reporting high mistrust. Item 2 (doubts about doctors' intentions toward their ethnic group) exhibited the highest frequency of high mistrust at 22.7%, while the frequency for all other items remained below 14%. Higher mean GBMMS summary scores were significantly associated with younger age ($p < 0.01$), single marital status ($p = 0.027$), and immigrant status ($p = 0.031$). Hispanic patients were more likely than non-Hispanic counterparts to perceive information withholding by doctors (46% vs 2%; $p = 0.01$), have doubts about doctors' intentions toward their ethnic group (38% vs 19%; $p = 0.02$), and fear that information confided to healthcare providers may be used against them (23% vs 4%; $p = 0.04$). **Conclusion:** We found medical mistrust is common among patient with early-stage ALD, particularly among Hispanic, single, and immigrant individuals, and may be a barrier to ALD care. These findings highlight the opportunity for interventions to promote trust, increase care engagement, and improve ALD outcomes.

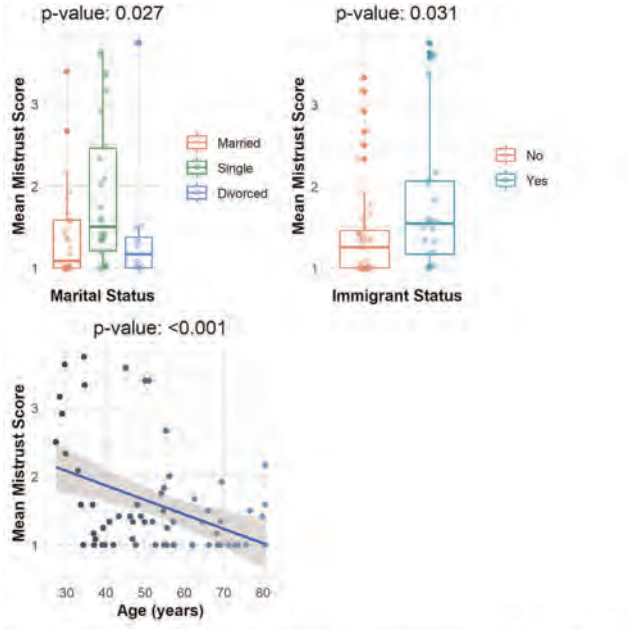

Figure 1 – Mean Group-Based Medical Mistrust Scale (GBMMS) scores by marital status, immigrant status, and age.

Disclosures: Elias Rady: Nothing to Disclose, Hamza Dahshi: Nothing to Disclose, Ahmad Anouti: Nothing to Disclose, Bill Zhang: Nothing to Disclose, Courtney Roberts: Nothing to Disclose, Thomas Kerr: Madrigal: Consultant, GSK: Grant/Research Support, Nicole Rich: AstraZeneca: Advisor, Genentech: Consulting, Exelixis: Advisor, Eisai: Advisor, Madrigal: Advisor, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Mack Mitchell: Nothing to Disclose, Thomas Cotter: Nothing to Disclose, Nothing to Disclose

2186 | ANALYZING THE READABILITY OF LLM-GENERATED PATIENT INFORMATION FOR LIVER DISEASES

Husayn Ramji[1] Aishwarya Gatiganti[1] Shaquille Lewis[1] Anveet Janwadkar[1] Jacob Lampenfeld[1] Stephanie Mrowczynski[1] Larry Zhou[1] Matthew Houle[1] Pooja Arumugam[1] Luis Morales[1] Sharan Poonja[1] Peng-

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Background: Numerous generative artificial intelligence (AI) tools are available today. Many large language models (LLMs), such as ChatGPT, are already being utilized to generate educational materials for patients on both an inpatient and outpatient basis. Although LLMs have made strides in providing evidence-based information, the degree to which they are consistently meeting the Agency for Healthcare Research and Quality's (AHRQ) recommendation of presenting information to patients at a sixth grade reading level or below remains to be seen. LLMs are powerful tools, but they must consistently be able to meet the needs of our patients to be reliable tools. This project is one of the first to analyze the readability of AI-generated educational materials in hepatology. **Methods:** ChatGPT 4o, Gemini 2.5, Claude 3.7, and OpenEvidence were each asked three distinct prompts: Prompt 1 ("Explain [condition]"), Prompt 2 ("I am a patient who was just diagnosed with [condition]. What is that?"), and Prompt 3 ("Explain [condition] to a patient"). The conditions that the LLMs were asked to explain were Cirrhosis, Hepatocellular Carcinoma (HCC), hepatitis, NAFLD, and MASLD. Each LLM was asked the same prompt three times for every condition, leading to a total of 180 outputs across the prompts and LLMs. The grade reading level of each output was assessed with the Sydney Health Literacy Lab (SHeLL) Health Literacy Editor tool, which provides the validated SMOG index measure of reading level, alongside other metrics. After testing for normality, appropriate analysis and significance testing took place for within-model comparisons across prompts, and for between-model comparisons with the same prompt, with $p < 0.05$ being deemed statistically significant. **Results:** All four LLMs demonstrated statistically significant improvements in reading level from Prompt 1 to Prompt 3 ($p < 0.001$), but none of the LLMs reached the goal of providing information at or below a sixth grade reading level. Of the LLMs, ChatGPT provided information that was the objectively easiest to read, going from an average reading level of 12.29 on Prompt 1 to an average of 10.23 ($p < 0.001$) on Prompt 3. The others ranged from 14.66 to 21.90 on Prompt 1, and 11.18 to 13.41 on Prompt 3. Gemini consistently provided the longest outputs, while OpenEvidence provided the most complex. **Conclusion:** Current leading LLMs require further refinement before they can be consistently utilized to address the health literacy gap and assist in educating patients about liver diseases. Until LLMs can consistently provide information at the reading level of the patient, utilization of LLMs on inpatient and outpatient settings must be approached with caution and oversight. Future directions will involve testing more specific prompts, formally evaluating the accuracy of outputs, and potentially testing liver-disease specific LLMs in their ability to educate patients effectively.

Table 1: Average SMOG Index by LLM, with within-model Prompt Comparisons

	ChatGPT	Gemini	Claude	OpenEvidence
Prompt 1 (P1) ± SD	12.29 ± 1.66	14.66 ± 0.75	14.97 ± 2.22	21.90 ± 3.30
Prompt 2 (P2) ± SD	10.97 ± 0.84	12.99 ± 0.47	13.87± 1.38	21.72 ± 3.19
Prompt 3 (P3) ± SD	10.23 ± 0.75	12.09 ± 0.47	11.18 ± 0.62	13.41 ± 1.13
Normal	No	Yes	No	No
Significance	p<0.001	p<0.001	p<0.001	p<0.001
P1 v P2	<0.05	<0.001	0.4076	0.8476
P1 v P3	<0.001	<0.001	<0.001	<0.001
P2 v P3	0.2668	<0.01	<0.01	<0.001

Disclosures: Husayn Ramji: Nothing to Disclose, Aishwarya Gatiganti: Nothing to Disclose, Shaquille Lewis: Nothing to Disclose, Anveet Janwadkar: Nothing to Disclose, Jacob Lampenfeld: Nothing to Disclose, Stephanie Mrowczynski: Nothing to Disclose, Larry Zhou: Nothing to Disclose, Matthew Houle: Nothing to Disclose, Pooja Arumugam: Nothing to Disclose, Luis Morales: Nothing to Disclose, Sharan Poonja: Nothing to Disclose, Peng-Sheng Ting: Nothing to Disclose

2187 | ALCOHOL, INEQUALITY, AND LIVER CIRRHOSIS: CAN DRINKING PATTERNS AND CARDIOMETABOLIC RISK FACTORS EXPLAIN THE SOCIOECONOMIC GAP?

Jonas Rønn[1] Gro Askgaard[1] Lone Madsen[1] Jessica Mellinger[2] Peter Jepsen[3] Matilde Winter-Jensen[4] Marie Eliasen[4] Merete Osler[4], [1]Zealand University Hospital, Køge, Denmark, [2]Department of Gastroenterology, Henry Ford Health System, Detroit, Michigan, USA, [3]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark, [4]Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Denmark

Background: There is socioeconomic inequality in the incidence of cirrhosis. We investigated 1) the contribution of alcohol drinking pattern and cardiometabolic factors to socioeconomic inequality in cirrhosis incidence, and 2) whether the association of these risk factors with cirrhosis risk depended on socioeconomic status. **Methods:** We included participants from the population-based Danish National Health Surveys 2010-2017 and followed them until December 31st, 2022, for an incident hospital diagnosis of cirrhosis, linking data from questionnaires and health registries. Socioeconomic position was measured by educational length. The socioeconomic inequality of cirrhosis incidence was estimated as the hazard ratio (HR) of cirrhosis in those with short ($<= 9$ years) vs. long (> 17 years) educational length. 1) The contribution of alcohol drinking pattern (drinks per week, drinking days per week, drinking outside of meals) and cardiometabolic factors (body mass index (BMI), diabetes, hypertension, dyslipidemia, smoking) to socioeconomic inequality of cirrhosis was measured by

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the socioeconomic inequality in HR for cirrhosis with versus without adjustments for these risk factors. 2) We used interaction tests to examine whether the association of alcohol and cardiometabolic risk factors on the incidence of cirrhosis depended on socioeconomic position. All analyses were weighted for sampling procedure and differential participation in the health surveys according to sociodemographic and health variables. **Results:** The study included 301,559 participants with a median age of 49 years (IQR 40.3-59.1), 50% were female, 19% had a short education length, and 12% had a long education length. With decreasing educational length, there was a gradual increase in the prevalence of drinking above 28 drinks/week, smoking, BMI >30, and the other cardiometabolic risk factors. During 2,711,309 person-years of follow-up, 1015 participants were diagnosed with cirrhosis. The HR for cirrhosis in short vs. long education length was attenuated from 3.85 (95% CI: 2.60; 5.71) in the age- and sex adjusted analysis to 3.60 (95% CI, 2.44; 5.32) when further adjusted for alcohol drinking pattern, and to 2.72 (95% CI, 1.84; 4.03) when fully adjusted for alcohol drinking pattern and cardiometabolic factors. The strength of the association between alcohol drinks per week and any cardiometabolic risk factor on cirrhosis risk did not depend on education length (p-values for interactions were all $>$ 0.4). Figure 1 shows the similar associations of drinks per week with cirrhosis incidence across socioeconomic position. **Conclusion:** When alcohol drinking pattern and cardiometabolic factors were considered, there was still a nearly three-fold higher incidence of cirrhosis in short vs. long educated. The relative harmful effect of alcohol was irrespective of educational level, and a similar pattern was observed for the influence of cardiometabolic factors.

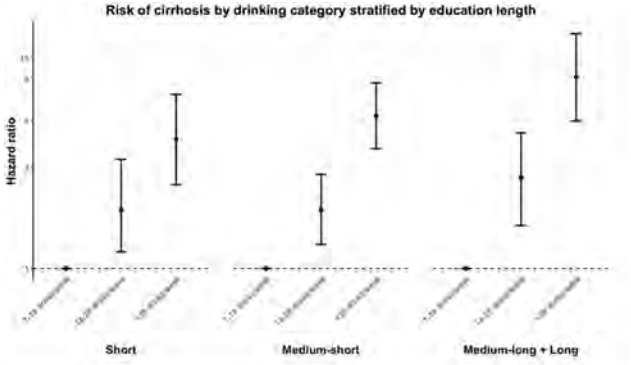

Figure 1. Incidence of cirrhosis according to alcohol consumption by education length. Hazard ratios for incident cirrhosis for participants in the Danish National Health Surveys 2010-2017 (n = 301,559) with follow-up until 31st December 2022. Hazard ratios are adjusted for age, sex, BMI, drinking days, drinking outside meals, smoking status, diabetes, hypertension, and dyslipidemia. Medium-long and Long educational groups have been pooled.

Disclosures: Jonas Rønn: Nothing to Disclose, Gro Askgaard: Nothing to Disclose, Lone Madsen: Nothing to Disclose, Jessica Mellinger: GlaxoSmithKline: Consultant, Novo Nordisk: Consultant, Boehringer Ingelheim: Consultant, Peter Jepsen: Nothing to Disclose, Matilde Winter-Jensen: Nothing to Disclose, Marie Eliasen: Nothing to Disclose, Merete Osler: Nothing to Disclose

2188 | HEPATOLOGY AND THE HOME: A NOVEL HOME-BASED ETHNOGRAPHIC APPROACH TO INFORMAL CAREGIVING FOR END-STAGE LIVER DISEASE IN A U.S. URBAN SAFETY NET SETTING

Ramón Casillas-Salazar[1] Simon Beaven[1] Shaun Chandna[1] Soma Wali[1] Arleen Brown[2] Philippe Bourgois[2] Utpal Sandesara[2], [1]Olive View-UCLA Medical Center, [2]University of California - Los Angeles

Background: End-stage liver disease (ESLD), a major cause of morbidity and mortality, exhibits significant socioeconomic disparities. While caregiving can be a critical determinant of health, we lack comprehensive analyses of ESLD caregivers' experiences, particularly in settings of poverty, linguistic/ethnic minority status, and limited healthcare access. Our aim is to ethnographically assess experiences of multiethnic informal caregivers for ESLD patients in close collaboration with a U.S. urban safety-net health system. **Methods:** This study leverages the strengths of inductive anthropological data collection and grounded theory analysis. We combine domestic observation, longitudinal home-based ethnographic interviews, clinical observation, and health system personnel interviews to explore how caregivers experience disease-specific learning, monitoring, management, communication, advance care planning, and caregiving assets and challenges. We are guided by a 6-member community action board that brings together researchers, hepatologists, community health workers, caregivers, and patients. **Results:** Based on preliminary in-depth engagement with 7 families (of an anticipated 24 total), we present 3 findings with bearing on practice and policy: (1) Caregiver and patient understandings of the liver's regenerative capacity can foster an optimism that belies the biological precarity of advanced fibrosis/cirrhosis, thereby hindering timely intervention to prevent progression. (2) Breakdowns in communication with providers who diagnose ESLD frequently position caregivers and families to potentially misunderstand the severity, nature, and volatility of the disease. (3) An ESLD diagnosis can reconfigure family dynamics, shifting power in ways that create new agency; this may allow caregivers to reclaim autonomy, reintegrate households, and better support patients. **Conclusion:** We lack comprehensive analyses of ESLD caregivers' experiences, particularly in the U.S. safety net. Deeper understandings of ESLD caregiving can guide direct interventions, clinical care adaptations, and upstream measures to improve health system-caregiver

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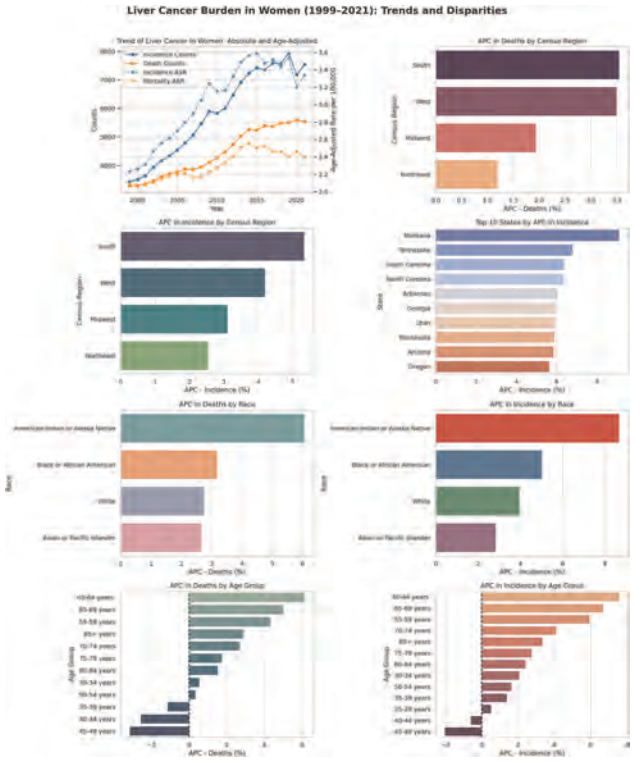
partnership. This project's community-engaged, anthropological approach shows how home-based research can inform better hepatologic care. Our findings suggest potentially untapped opportunities for partnering with caregivers to enhance ESLD prevention, improve disease knowledge, and leverage novel family dynamics to augment clinical interventions.

Disclosures: Ramón Casillas-Salazar: Nothing to Disclose, Simon Beaven: Alnylam: Speaking and Teaching, Shaun Chandna: Calliditas Therapeutics (previously Genkyotex): Grant/Research Support, Mirum Pharmaceuticals: Grant/Research Support, Lipocine: Grant/Research Support, Arrowhead Pharmaceuticals: Grant/Research Support, Mirum Pharmaceuticals: Consultant, Ipsen: Consultant, Soma Wali: Nothing to Disclose, Arleen Brown: Nothing to Disclose, Philippe Bourgois: Nothing to Disclose, Utpal Sandesara: Nothing to Disclose

2189 | ESCALATING LIVER CANCER BURDEN IN WOMEN ACROSS THE UNITED STATES: A 22-YEAR ANALYSIS OF GEOGRAPHIC, RACIAL, AND AGE-BASED DISPARITIES

Raghava Rao Alluri[1] Parvinder Kaur[2] Yashkumar Kamani[3] Sandeep Kotnani[4] Jainil Parikh[5] Mahir Modi[6] Madhu babu Adusumilli[7] Hardik Desai[8], [1]Prime South GME Consortium/Harlingen Medical Center Program, [2]The Crimean State Medical University named after S.I. Georgievsky, Simferopol, Ukraine, [3]"BronxCare Health System ", [4]Rutgers Monmouth Medical Center, [5]GMERS MEDICAL COLLEGE, GOTRI, VADODARA, [6]GCS Medical College Hospital and Research Centre, [7]HCA Ocala Florida hospital -UCF, [8]Independent Clinical and Public Health Researcher

Background: While breast, lung, and colorectal cancers remain the leading malignancies in U.S. women, liver cancer has shown one of the most rapid increases in incidence and mortality. Its rising burden, coupled with poor prognosis and modifiable risk factors, warrants focused epidemiologic evaluation across diverse subgroups. **Methods:** We utilized data from the CDC WONDER database spanning 1999–2021 to evaluate LC incidence and mortality in U.S. women. Annual counts and age-adjusted rates per 100,000 population were extracted. Annual Percent Change (APC) was computed using Joinpoint regression for both absolute and age-standardized rates, stratified by census region, state, race, Hispanic origin, and age group. **Results:** From 1999 to 2021, LC deaths among women increased from 3,287 to 5,538 (APC: +2.84%), with the age-adjusted mortality rate rising from 2.09 to 2.40 per 100,000 (APC: +0.95%); incidence counts rose from 3,432 to 7,539 (APC: +4.11%), and the age-adjusted incidence rate increased from 2.24 to 3.34 per 100,000 (APC: +2.14%). The most pronounced regional increases in LC mortality were observed in the South and West, with death counts rising annually by 3.55% and 3.50%, respectively. At the state level, Montana exhibited the most significant increase in incidence, rising from 22 cases in 1999 to 75 in 2021 (APC: 9.11%), followed by Tennessee (6.79%) and South Carolina (6.38%). Marked racial disparities were observed, with American Indian or Alaska Native women experiencing the highest escalation in both incidence (8.68%) and mortality (6.05%), while incidence among Black and White women rose by 5.02% and 3.96%, respectively. Hispanic women showed a steeper increase, with incidence rising from 413 to 880 cases (6.49%) and deaths from 291 to 528 (5.41%). Age-specific analyses revealed that women aged 60–64 years demonstrated the most accelerated rise in disease burden, with incidence increasing by 7.59% and mortality by 6.13% annually, followed by the 65–69 and 55–59 age groups. **Conclusion:** LC burden among U.S. women has escalated markedly over the past two decades, with disproportionate increases in the South and West, among American Indian or Alaska Native and Hispanic populations, and in women aged 60–69 years. These findings underscore the need for urgent, tailored public health strategies to mitigate rising LC disparities through improved screening, risk reduction, and equitable access to care.



Disclosures: Raghava Rao Alluri: Nothing to Disclose, Parvinder Kaur: Nothing to Disclose, Yashkumar Kamani: Nothing to Disclose, Sandeep Kotnani: Nothing to Disclose, Jainil Parikh: Nothing to Disclose, Mahir Modi: Nothing to Disclose, Madhu babu Adusumilli: Nothing to Disclose, Hardik Desai: Nothing to Disclose

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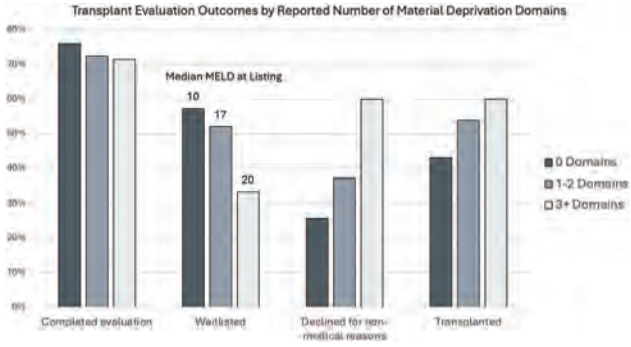
2190 | SOCIAL RISK SCREENING AMONG LIVER TRANSPLANT CANDIDATES: IMPACT OF MATERIAL DEPRIVATION ON TRANSPLANT OUTCOMES

Mark Wang[1] Christopher Wong[1] Kali Zhou[1], [1]Keck School of Medicine, University of Southern California

Background: Social barriers play a major role in successful navigation of the liver transplant (LT) process. Few studies have conducted prospective social risk screening among adult LT candidates. We examined frequency of material deprivation (lack of access to basic necessities) derived from a social risk screener and impact on transplant outcome. **Methods:** Adult LT candidates who completed an adapted AHC Health-Related Social Needs Screening Tool at initial LT evaluation clinic visit at a high-volume transplant center between 11/1/2021-12/31/2022 were included. Material deprivation was assessed across five domains: housing, food, finances, transportation, and social support insecurities. Sociodemographic, clinical, and LT outcome data (through 4/2025) were abstracted from medical records and compared by deprivation status. Associations of material deprivation (individual domains and categorized into 0, 1-2, or 3+ domains) with LT waitlisting were examined using univariate logistic regression. **Results:** 219 patients were screened with median follow-up of 14.4 (3.6-28.7) months. Median cohort age was 59 (52-65), 56% male, 64% Hispanic, and 42% alcohol etiology. Prevalence of material deprivation was as follows: 27% reported food insecurity, 15% transportation insecurity, 15% financial insecurity, 14% housing insecurity, and 5% social support insecurity. 59%, 32%, and 10% reported material deprivation in 0, 1-2, and 3+ domains, respectively. Candidates reporting material deprivation were more likely to be foreign-born, Medicaid-insured, unemployed, and lower income, with higher median MELD at evaluation (15 vs 12), more hepatic encephalopathy, and less hepatocellular carcinoma (all $p < 0.05$). Higher material deprivation categories had lower proportion waitlisted, but higher proportion transplanted, potentially driven by medical urgency evidenced by higher MELD at listing (Figure). Of the five domains, only housing insecurity was significantly associated with lower odds of listing (OR = 0.30, 95% CI 0.12-0.76, $p = 0.01$), while there was a trend towards lower odds of listing with 3+ domains (vs 0) (OR = 0.38, 0.13-1.11, $p = 0.08$). **Conclusion:** Over 40% of LT candidates report having material deprivation in at least one social risk domain. Housing insecurity and having more than three affected domains may impact likelihood of waitlisting. Studies are needed on the impact of material support interventions on increasing LT equity for populations experiencing social vulnerability.



Disclosures: Mark Wang: Nothing to Disclose, Christopher Wong: Nothing to Disclose, Kali Zhou: Gilead Sciences Inc: Grant/Research Support, Merck: Grant/Research Support

2191 | THE ROLE OF SOCIAL DETERMINANTS OF HEALTH ON HEPATITIS B DURING PREGNANCY IN MASSACHUSETTS AND WITHIN THE UNITED STATES

Ami Patel[1] Katherine Cooper[2] Alessandro Colletta[1] Deepika Devuni[2], [1]Univeristy of Massachusetts, [2]University of Massachusetts

Background: Hepatitis B Virus (HBV) is the leading cause of chronic hepatitis worldwide. HBV during pregnancy poses significant risk, in the absence of appropriate immunoprophylaxis the risk of vertical transmission is up to 90%. Given the high risk of transmission both the United States Preventive Services Task Force and the American Congress of Obstetricians and Gynecologists have recommended screening for HBV during pregnancy. **Methods:** In this study we evaluated the impact of social determinants of health (SDOH) on HBV during pregnancy leveraging state and national databases. Data was obtained from the Perinatal Hepatitis B Prevention Program (PHPP) housed by the Massachusetts Department of Public Health (MADPH). The PHPP is a case management program for women with HBV during pregnancy to ensure access to care. Baseline characteristics were reported among the cohort and compared to expected values in Massachusetts (MA). Next, United States (U.S) census data was used to overlay the percent living below poverty and percent born outside the US in each county from which patients were referred. A query of the TriNetX database was then used to validate these findings in database containing health record data from 70 health care organizations in the U.S using specific ICD-10 codes for SDOH (Z55-X65). Z-score was used to compare race of women with HBV to the MA population. **Results:** A total of 215 women (median age 36 years) were enrolled in PHPP in 2022. Most women were of Asian (30%, z = 0.39) or African (25%, z = 0.32) decent, which was disproportionately

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higher than expected compared to MA population (79% white, z = 1.25, 10% African, z = .0.13, 8% Asian, z = 0.10). A greater than expected proportion were also born outside the U.S. (53%, z = 0.72vs. 18%, z = 0.23). Most participants were from Suffolk County (23%) which had the highest proportion of women living below poverty per 2022 census data. Vertical transmission was 0% in neonates born to mothers who were positive for HBV and in PHPP. In a nationally representative cohort, 1,522 pregnant women with HBV were compared to 232,829 pregnant women without HBV. Women with HBV were older (32.1 ± 5.4 vs. 30.9 ± 5.9, $p < 0.01$), more likely to be Hispanic/Latino (33% vs. 18%, $p < 0.01$) and Asian (11% vs 5%, $p < 0.01$). Women with HBV during pregnancy were significantly more likely to have problems related to housing/economic insecurity (OR 2.75, 95% CI 2.10-3.39, $p < 0.01$) and social support (OR 2.53, 95% CI 1.78-3.51, $p < 0.01$). **Conclusion:** Women with HBV during pregnancy have complex SDH concerns. Immigration status, primary language, poor English literacy, and housing/economic instability contribute to HBV diagnosis during pregnancy. Further interventions are needed to target high-risk communities and increase access to care for both prevention and treatment. Lastly, programs such as PHPP allow for close monitoring of patients with HBV during pregnancy and are effective at reducing vertical transmission to neonates.

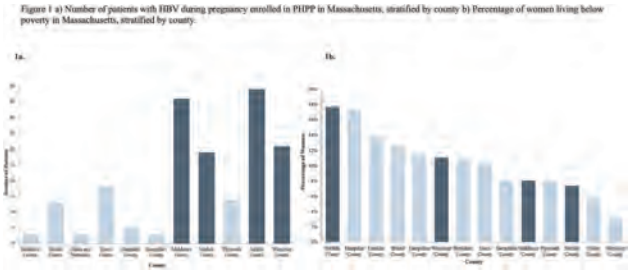

Figure 1 a) Number of patients with HBV during pregnancy enrolled in PHPP in Massachusetts, stratified by county b) Percentage of women living below poverty in Massachusetts, stratified by county.

Disclosures: Ami Patel: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Alessandro Colletta: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Avania Medical: Grant/Research Support, Intercept: Grant/Research Support

2192 | SEX-SPECIFIC DIFFERENCES IN CARDIOMETABOLIC RISK FACTORS AND RISK OF SIGNIFICANT LIVER FIBROSIS IN THE U.S. GENERAL POPULATION: AN ANALYSIS OF NHANES 2017-2020

Somaya Albhaisi[1] Steve Kim[2] Norah Terrault[1] Jennifer Dodge[1], [1]University of Southern California, [2]Keck/USC Department of Population and Public Health Sciences

Background: Cardiometabolic risk factors (CMRFs) are key drivers of metabolic dysfunction–associated steatotic liver disease, yet sex-specific links to advanced fibrosis remain unclear. Clarifying this can improve risk stratification, screening, and sex-informed management. This study examines the sex-stratified differential effect of CMRFs on significant fibrosis in U.S. adults. **Methods:** We conducted a population-based, cross-sectional analysis of U.S. adults ≥ 20 years without viral hepatitis using 2017–2020 NHANES data, which included transient elastography measurements. Primary outcome: significant fibrosis (defined as liver stiffness ≥ 8.0 kPa). CMRFs were defined per ATP III: waist circumference (WC) > 102cm [M]/ > 88cm[F]; fasting glucose ≥ 100 mg/dL or treatment; BP ≥ 130/85 mmHg or treatment; triglycerides ≥ 150 mg/dL or treatment; HDL < 40 mg/dL(M)/ < 50 mg/dL(F) or treatment. Obesity (BMI ≥ 30 kg/m² or ≥ 27.5 for Asians) was also assessed. Multivariable logistic regression evaluated associations between CMRFs and significant fibrosis, stratified by biologic sex, adjusting for age, race/ethnicity, smoking, and alcohol, with sex-by-CMRF interactions tested. Subgroup analyses were performed: (a) adults with severe steatosis (CAP ≥ 280 dB/m); (b) excluding heavy alcohol use (> 50 g/day women, > 60 g/day men). **Results:** Among 5,981 adults, women (N = 2992) compared to men (N = 2989) had a higher prevalence of high WC (69.0% vs 48.6%) and low HDL (42.6% vs 39.7%) and a lower prevalence of HTN (41.0% vs 44.9%), glucose intolerance (31.1% vs 41.7%) and hypertriglyceridemia (36.6% vs 48.8%). Obesity prevalence (41.9% vs 42.3%) was similar by sex. The prevalence of significant fibrosis was 6.9% (95%CI 5.4-8.8) in women and 10.7% (95%CI 8.8-12.9) in men. The association of significant fibrosis was significantly greater in women versus men for high WC (aOR 13.45 [95%CI 5.70–31.78] vs 4.44 [95%CI 3.00–6.57]; $p = 0.01$), glucose intolerance (2.94 [1.64–5.28] vs 1.51 [1.08–2.13]; $p = 0.04$), and presence of ≥ 2 CMRFs (10.22 [4.76–21.95] vs 2.87 [1.91–4.31]; $p = 0.002$) (Figure 1). In the subgroup with steatosis (N = 2,452), odds of significant fibrosis were disproportionately greater in women vs men for presence of ≥ 2 CMRFs (4.88 [1.62–14.74] vs 1.83 [0.98–3.42]; $p = 0.06$). Results were similar when individuals with heavy alcohol use were excluded with statistically significant differences for high WC (13.22 [5.55-31.50] vs 4.58 [3.01-6.95]; $p = 0.02$) and presence of ≥ 2 CMRFs (10.07 [4.70-21.60] vs 2.88 [1.88-4.40]; $p = 0.003$). **Conclusion:** In U.S. adults, women with ≥ 2 CMRFs had a nearly 5-fold higher likelihood of having significant fibrosis than men, revealing key sex-specific vulnerabilities. These findings suggest that women—despite historically being considered lower risk—may harbor a hidden burden of significant liver disease when multiple CMRFs are present and that

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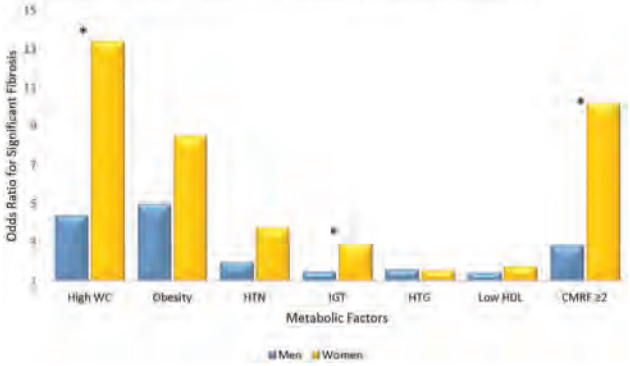
sex-specific screening strategies warrant consideration.

Figure 1. Comparison of Odds Ratios for Significant Fibrosis by Sex for Metabolic Factors in Overall Population.

* Interaction p < 0.05. IGT: Impaired Glucose tolerance; HTG: Hypertriglyceridemia.

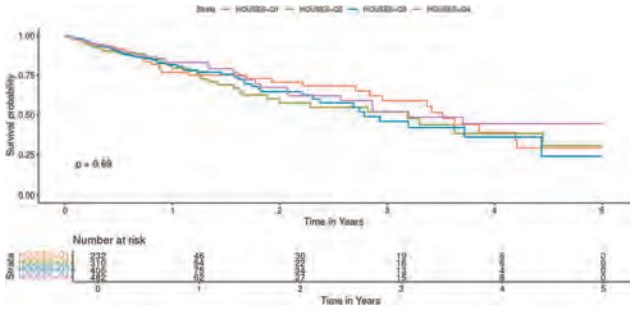


Disclosures: Somaya Albhaisi: Nothing to Disclose, Steve Kim: Nothing to Disclose, Norah Terrault: Elsevier: Royalties or patent beneficiary, GSK: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, Immuno-Core: Grant/Research Support, HBV Foundation: Board member, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Jennifer Dodge: Nothing to Disclose

2193 | THE IMPACT OF INDIVIDUALIZED SOCIOECONOMIC MEASURES ON LIVER TRANSPLANT WAITLIST OUTCOMES IN A MULTICENTERED STUDY

Saurav Panda[1] Bradley Johnson[1] Chung-Il Wi[2] Elizabeth Krusemark[1] Ummah Salma Nisar[3] Kymberly Watt[1], [1]Mayo Clinic Rochester, MN, [2]Mayo Clinic, Rochester, MN, [3]East Tennessee State University, Johnson City, TN

Background: Data suggests socio-economic factors impact outcomes on the liver transplant (LT) waitlist but lack granularity on an individual basis. We aimed to investigate the application of a novel socioeconomic index termed the HOUSES index for its impact on waitlist outcomes in a multicentered setting compared to Area deprivation index (ADI). **Methods:** This multicentered retrospective study included 1448 patients listed for LT between 2010-2020 specifically with diagnoses of MASH, cholestatic disorders and ALD. Baseline laboratory values, clinical characteristics and demographics were recorded at the time of listing and removal from the waitlist. The HOUSES index provides socioeconomic data derived for each patient, based on the individual addresses provided at the time of listing (analyzed by highest socio-economically disadvantaged quartile(Q1) to the least (Q4)) while the ADI state ranking is based on the census block group. Cox proportional hazards models were fit using HOUSES quartiles and ADI ranking to assess waitlist mortality at 5 years. **Results:** Mean age of the cohort was 56.4 (SD 10.2), 61% male and 87% non-Hispanic ethnicity. Patients with MASH or ALD were more prevalent in the lower HOUSES quartiles (Q1&2) than patients with cholestatic disease (39% and 41% vs 19%, $p = 0.03$). Of the 1448 patients waitlisted, 184 were removed due to death ($N = 97$) or being 'too sick' ($N = 87$) for LT, while 1264 received a LT. In the adjusted multivariate model, Quartile 2 (Q2) [HR:2.50; 1.14 – 5.50, $p < 0.022$], age [HR:1.05; 1.01 –1.09, $p = 0.008$], MELDNa at listing [HR: 1.11; 1.05 – 1.17, $p < 0.001$] and driving distance from transplant center between 180-360 miles [HR: 2.48; 1.04 – 5.91, $p = 0.041$] turned up as significant predictors for death/too sick waitlist removal. Candidates in Q2 had an 18% lower likelihood of receiving LT [aHR: 0.82; 0.70-0.95, $p < 0.011$] while those in Q3 it was 15% lower [aHR: 0.85; 0.74-0.99, $p < 0.03$], when compared to Q4. In contrast, the ADI model was unable to show any significant results for its ranking system when predicting waitlist mortality. Cohen's weighted test between the two indices showed a κ of 0.244 (0.212, 0.277),$p <$ 0.001, highlighting only meagre agreement. **Conclusion:** This study demonstrates the use of individualized socioeconomic measures (i.e., HOUSES index) are superior to area dependent indicators and may help identify increased risk of waitlist mortality. The ability to identify individual risk will allow for individualized intervention addressing these needs.



Disclosures: Saurav Panda: Nothing to Disclose, Bradley Johnson: Nothing to Disclose, Chung-Il Wi: Nothing to Disclose, Elizabeth Krusemark: Nothing to Disclose, Ummah Salma Nisar: Nothing to Disclose, Kymberly Watt: Madrigal: Stock - publicly traded company, Madrigal: Stock - publicly traded company, Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded company, Viking: Stock - publicly traded company, Viking: Stock - publicly traded company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock - publicly traded company, Madrigal: Stock - publicly traded company, Madrigal: Stock - publicly traded company, Viking: Stock - publicly traded

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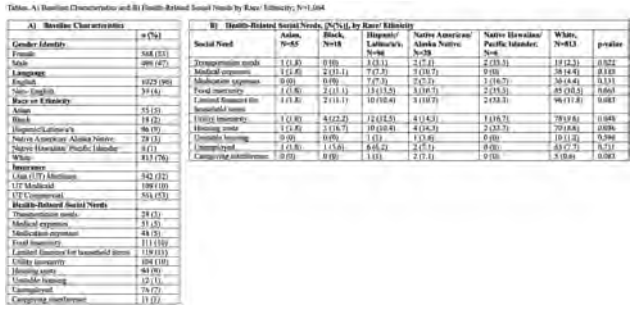
2194 | SOCIAL NEEDS SCREENING AND COMMUNITY RESOURCE REFERRALS INTEGRATED INTO ROUTINE HEPATOLOGY CARE

Rebecca Kim[1] April Ballantyne[1] Jia-Wen Guo[1] Bob Wong[1] John Inadomi[2] Molly Conroy[2] Jennifer Price[3] Andrea Wallace[1], [1]University of Utah, [2]University of Utah Health, [3]University of California, San Francisco

Background: Health-related social needs (HRSN) contribute to worse outcomes in chronic liver disease (CLD), yet routine HRSN screening remains uncommon in hepatology. To address this gap, we implemented HRSN screening in liver clinics at our academic medical center to integrate screening into clinical workflows and to connect patients with needs to available community resources. **Methods:** From 12/2024-03/2025, a validated 10-item HRSN screener was integrated into routine hepatology care through electronic health record-based workflows and staff training. Screening was completed via MyChart or in person during pre-visit check-in. Beginning 04/01/2025, patients reporting social needs and interested in assistance were referred to external support. Descriptive analyses included mean and frequency. Comparative analyses were performed using Chi-Square and Fisher's exact tests. **Results:** Among 1,064 liver clinic patients screened, 53% were female, 76% White, 9% Hispanic/Latino, 5% Asian, 3% Native American/Alaska Native (NA/AN), 2% Black, 1% Native Hawaiian/Pacific Islander (NH/PI). Most (96%) spoke English. Reported needs included limited finances for household items (11%), food insecurity (FI) (10%), utility insecurity (10%), and housing costs (9%). No significant differences in HRSN were found by gender, language (English vs. non-English), rural vs. urban residence, or clinic visit type (transplant vs. general hepatology). However, differences emerged by race/ethnicity: transportation needs were more common among NH/PI (33%) and NA/AN (7%) ($p = 0.022$). Utility insecurity differed significantly: Black (22%), NH/PI (17%), NA/AN (14%), Hispanic/Latino (13%) ($p = 0.048$). Similarly, housing cost challenges were reported by 33% NH/PI, 17% Black, 14% NA/AN, and 10% Hispanic/Latino patients ($p = 0.036$). There was a trend toward significance in FI by race/ethnicity ($p = 0.063$). Small sample sizes of subgroups may have impacted results. Of the 10 people referred to resources, 70% were male, 80% White, 10% NA/AN, 10% undisclosed race. High rates of reported HRSN were observed: limited finances for household items (60%), utility insecurity (60%), housing cost burden (80%), and unemployment (40%). An additional 110 patients selected "prefer not to answer" for one or more question, and were excluded from analysis. Over half (54%) of these patients selected "yes" for at least one social need. Therefore, this exclusion likley led to an underestimation of HRSN, as those declining to answer all questions disproportionately reported other HRSN. **Conclusion:** HRSN screening was successfully integrated into liver clinic workflows, revealing unmet social needs, particularly among racial/ethnic minority groups. However, these findings also demonstrate the need to further assess the acceptability of and stigma related to HRSN screeners among CLD patients.



Disclosures: Rebecca Kim: Nothing to Disclose, April Ballantyne: Nothing to Disclose, Jia-Wen Guo: Nothing to Disclose, Bob Wong: Nothing to Disclose, John Inadomi: Nothing to Disclose, Molly Conroy: Nothing to Disclose, Jennifer Price: AbbVie: Grant/Research Support, Gilead: Grant/Research Support, Genentech: Grant/Research Support, VIR: Grant/Research Support, Cepheid: Grant/Research Support, Aligos: Grant/Research Support, Andrea Wallace: Nothing to Disclose

2195 | DEMOGRAPHIC AND REGIONAL DISPARITIES IN GLP-1 RECEPTOR AGONIST CLINICAL TRIALS FOR WEIGHT LOSS WITH A SPECIFIC FOCUS ON MASLD/MASH: A COMPARATIVE META-ANALYSIS OF US AND INTERNATIONAL RCTS

Kimberly Ho[1] Taranika Sarkar Das[2] Joao Filipe Goncalves Monteiro[3] Sonali Paul[4] Paige McLean Diaz[5], [1]Brown University, [2]NYU Langone Health, [3]Brown Medicine, [4]University of Chicago Medical Center, [5]Brown Medicine/Brown University Health

Background: GLP-1 receptor agonists (GLP-1 RAs) treat obesity, a key driver of metabolic-dysfunction

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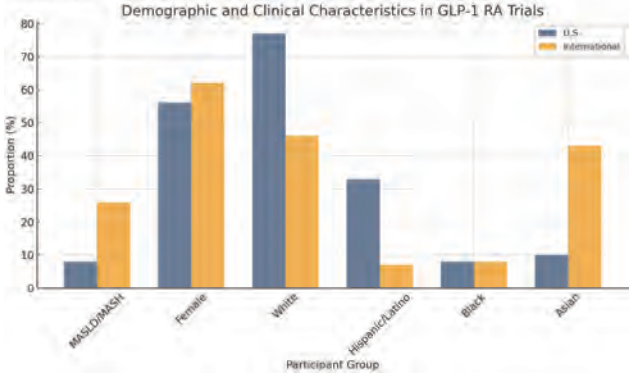
associated steatotic liver disease (MASLD) and steatohepatitis (MASH). The burden of these liver diseases is poorly defined in GLP-1 RA trials. We conducted a meta-analysis of RCTs to assess MASLD/MASH burden, lipid disorders, and global representation in GLP-1 trials. **Methods:** We reviewed 149 English-language RCTs that looked at GLP-1 RAs for weight loss from 2015 to 2024. Random-effects meta-analyses assessed demographic and clinical differences in US vs international trials using relative risk (RR). **Results:** Of the 149 studies screened, 24 met inclusion criteria and were included in the meta-analysis (N = 16,600), comprising 15 US-based studies (N = 12,906) and 9 international studies (N = 3,694). The pooled prevalence of MASLD/MASH was 18% (95% CI: 8%–27%, N = 6,479; I^2 = 99.47%). Prevalence was significantly lower in US RCTs at 8% (95% CI: 4%–13%) compared to 26% (95% CI: 11%–41%) in international RCTs. MASLD/MASH was 66% less likely among US participants (RR = 0.34 [0.20–0.49]). There was limited international data, including only 4 of 11 studies (573/962 subjects, 60%) that were conducted outside the US in Asia, Europe, and South America. No studies reported liver function test results or FibroScan data. Lipid disorders were reported in 45% of participants overall (95% CI: 34%–55%, N = 7,327, I^2 = 98.94%) with a slightly lower prevalence in US studies (41%, 95% CI: 25%–58%) than in international RCTs (48%, 95% CI: 35%–61%). Compared to international studies, US participants were 27% less likely to have lipid disorders (RR = 0.72 [0.63–0.82]). Across all studies, participants experienced a mean weight loss of 10.8% ± 5.8% from baseline. Weight reduction was slightly greater in US participants (11.3% ± 5.9%) compared to those in international studies (10.0% ± 5.7%). **Conclusion:** US GLP-1 RA RCTs reported MASLD and lipid data less often than international trials. Despite high US MASLD prevalence, only 8% included MASLD data, limiting the generalizability of GLP-1 RA efficacy in metabolic liver disease. Broader inclusion and greater focus on MASLD/MASH are needed to better guide GLP-1 RA use in obesity-related liver disease.

Figure 1. Demographic and MASLD/MASH data reported in US and international GLP-1 RA clinical trials.



Disclosures: Kimberly Ho: Nothing to Disclose, Taranika Sarkar Das: Nothing to Disclose, Joao Filipe Goncalves Monteiro: Nothing to Disclose, Sonali Paul: Intercept: Grant/Research Support, Target PharmaSolutions: Grant/Research Support, Eli Lilly: Stock - publicly traded company, Paige McLean Diaz: Nothing to Disclose

2196 | LONGITUDINAL ADHERENCE TO HEPATOCELLULAR CARCINOMA SURVEILLANCE FOLLOWING ULTRASOUND LI-RADS IMPLEMENTATION IN A SAFETY NET HEALTHCARE SYSTEM

Stephanie Kim[1] Kang Wang[1] Hailey Choi[1] Amy Shui[1] Mandana Khalili[2], [1]University of California San Francisco, [2]University of California, San Francisco

Background: Hepatocellular carcinoma (HCC) surveillance is suboptimal, especially in high-risk populations. The Ultrasound Liver Imaging Reporting and Data System (US LI-RADS) was recently introduced to standardize US reporting and follow-up for HCC surveillance. This study aims to assess longitudinal trends in adherence to HCC surveillance and its associated factors following US LI-RADS implementation in a safety net healthcare system. **Methods:** Radiology and medical records were retrospectively queried for demographic, clinical, and imaging data in patients who underwent US LI-RADS-based HCC surveillance between 6/1/2020 - 5/31/2021, follow-up was through 12/31/2024. Full adherence to radiologist recommendation was defined as US imaging follow-up in 5-7 months for US-1, 3-6 months for US-2, and CT/MRI in 2 months for US-3. Multivariable repeated measures logistic regression assessed factors associated with full (vs partial/none) adherence after adjusting for age, sex, race, time from 1st imaging, and including variables with $p < 0.1$ on univariable analysis. **Results:** Among 1004 patients (mean age 60 years; 56% men; 61% Asian) and a median follow-up of 50 months, full adherence to surveillance was 38% at 1st visit (33% non-adherent) and 64% by 4th visit. Liver disease etiologies were hepatitis B (65%), hepatitis C (18%), steatotic liver disease (metabolic 18%, alcohol related 12%); 36% had cirrhosis. 43% were current or past smokers, 23% reported current or past alcohol use, and 7.5% experienced homelessness. Multivariable analysis showed that older age, male sex, prior hepatology clinic visit, and longer time since 1st imaging were significantly associated with full adherence, whereas current or past smoking and current alcohol use were significantly associated with lower odds of adherence (Table 1). These associations did not significantly change when time variable was replaced by post-pandemic (vs pandemic) time in the model. **Conclusion:** Adherence to US LI-RADS HCC surveillance increased from 38% at 1st visit to 64% by 4th visit. On follow-up, higher adherence was associated with prior hepatology clinic visit and certain demographics while health risk behaviors such as alcohol and smoking use were

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associated with lower adherence. These findings highlight the effectiveness of US LIRADS uptake but also emphasize the need for lifestyle interventions, expanded access to specialty care, and integrated care models to improve surveillance for at-risk populations.

Table 1. Multivariable Analysis of Factors Associated with Full vs Partial/Non-Adherence

	Odds Ratio (95% CI)	P-value
Time since 1st visit (per 6 months)	1.20 (1.17, 1.24)	**<0.001**
Age (per decade)	1.16 (1.05, 1.27)	**0.003**
Male sex (vs female)	1.42 (1.16, 1.74)	**<0.001**
Ethnicity (vs non-Hispanic white)		
Asian	1.43 (0.94, 2.16)	0.094
Black	1.17 (0.76, 1.82)	0.47
Hispanic	0.67 (0.43, 1.04)	0.08
Other	1.44 (0.78, 2.69)	0.25
Non-English (vs English speakers)	1.18 (0.94, 1.50)	0.16
Number of comorbidities (> 2 vs ≤ 2)	0.91 (0.71, 1.16)	0.44
Diabetes	0.82 (0.67, 1.01)	0.07
Experiencing homelessness (vs not)	0.77 (0.50, 1.17)	0.21
Smoking (vs never)		
Current	0.69 (0.52, 0.91)	**0.009**
Former	0.78 (0.62, 0.99)	**0.04**
Alcohol use disorder (vs none)		
Current	0.59 (0.35, 0.98)	**0.042**
Past	0.70 (0.48, 1.01)	0.06
Illicit drug use (vs none)		
Current	0.71 (0.43, 1.19)	0.19
Past	1.01 (0.71, 1.46)	0.94
Etiology of liver disease*		
Hepatitis C	0.89 (0.63, 1.25)	0.51
Alcohol-related liver disease	1.34 (0.83, 2.14)	0.23
Metabolic-dysfunction associated steatotic liver disease	1.02 (0.81, 1.29)	0.87
Cirrhosis	1.06 (0.83, 1.36)	0.65
Decompensated cirrhosis	0.69 (0.44, 1.07)	0.10
Primary care location		
Outside (vs within institution)	1.03 (0.86, 1.24)	0.72
None (vs within institution)	0.74 (0.50, 1.12)	0.15
Hepatology clinic visit	2.78 (2.30, 3.35)	**<0.001**

*Hepatitis B was not included due to strong correlation with Asian or Pacific Islander race

Disclosures: Stephanie Kim: Nothing to Disclose, Kang Wang: Nothing to Disclose, Hailey Choi: Nothing to Disclose, Amy Shui: Nothing to Disclose, Mandana Khalili: gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant

2197 | CHRONIC LIVER DISEASE AND ASSOCIATED SOCIAL, BEHAVIORAL, AND METABOLIC RISK FACTORS IN TRANSGENDER AND GENDER-DIVERSE ADULTS: A 15-YEAR RETROSPECTIVE SAFETY-NET HOSPITAL COHORT STUDY

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Background: Introduction: Transgender and gender-diverse (TGD) individuals experience unique psychosocial stressors that affect social determinants of health and health behaviors, increasing their risk for chronic liver disease (CLD). However, data on CLD prevalence and associated risk factors in TGD populations remain limited. This study aims to compare CLD prevalence and risk factors between TGD and cisgender adults through a large retrospective cohort analysis. **Methods:** We conducted a retrospective cohort study from May 2010 to May 2025 at a safety-net hospital in the United States, identifying 528 TGD patients among 1,696,544 individuals using ICD-10 codes and medication records. The CLD cohort included alcohol-related liver disease, metabolic dysfunction-associated steatohepatitis, hepatic fibrosis, and cirrhosis, confirmed through ICD-10 codes, chart review, and imaging. We also collected data on housing instability, substance and alcohol use, metabolic risk factors (hypertension, dyslipidemia, diabetes, obesity), infectious comorbidities (HIV, hepatitis B and C), and mental health disorders. **Results:** Total cohort: TGD individuals had significantly higher prevalence ($p < 0.001$) of all measured risk factors and comorbidities compared to cisgender patients (Table 1). Notably, TGD patients exhibited higher rates of alcohol use disorder (18.4% vs. 1.2%), HIV infection (10.0% vs. 0.1%), housing instability (16.9% vs. 1.1%), and mental health disorders (65.2% vs. 3.7%). CLD sub cohort: TGD patients had a significantly higher prevalence of CLD compared to cisgender individuals (4.4% vs. 0.8%, $p < 0.001$). Compared to the general cohort, several disparities between TGD and cisgender patients were further amplified in the CLD subgroup, with TGD individuals experiencing greater burdens of alcohol use disorder (47.8% vs. 26.9%, $p = 0.04$), HIV infection (34.8% vs. 1.9%, $p < 0.001$), housing instability (39.1% vs. 13.0%, $p < 0.001$), and mental health disorders (73.9% vs. 34.2%, $p < 0.001$). **Conclusion:** TGD adults exhibited disproportionately high rates of chronic liver disease compared to cisgender peers. Key disparities among TGD patients with CLD included alcohol use disorder, HIV infection, housing instability, and mental health disorders. These risk factors and comorbidities were not only more prevalent in the overall cohort but were further amplified within TGD patients with CLD. These findings emphasize the need for tailored, culturally sensitive interventions addressing CLD and its unique disparities in TGD patients, delivered through a multidisciplinary approach to ensure equitable hepatology care.

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Table 1. Prevalence of Social, Behavioral, and Health Risk Factors in Total Cohort and Sub Cohort of Chronic Liver Disease

	Total Cohort			Chronic Liver Disease		
Risk Factor	Cisgender N= 1,696,016	Transgender and gender diverse N=528	P value	Cisgender N=13,639 (0.8%)	Transgender and gender diverse N=23 (4.4%)	P value
Alcohol use disorder	26,984 (1.2%)	97 (18.4%)	<0.001*	3,672 (26.9%)	11 (47.8%)	0.04**
Diabetes	37,594 (2.2%)	39 (7.4%)	<0.001*	4,609 (33.8%)	5 (21.7%)	0.32
Dyslipidemia	41,857 (2.5%)	46 (8.7%)	<0.001*	5,074 (37.2%)	3 (13.0%)	0.02**
Hepatitis B infection	6,882 (0.4%)	19 (3.6%)	<0.001*	2,668 (19.6%)	5 (21.7%)	1.00
Hepatitis C infection	4,078 (0.2%)	9 (1.7%)	<0.001*	1,204 (8.8%)	2 (8.7%)	1.00
HIV Infection	2,166 (0.1%)	53 (10.0%)	<0.001*	262 (1.9%)	8 (34.8%)	<0.001*
Housing instability	19,242 (1.1%)	89 (16.9%)	<0.001*	1,768 (13.0%)	9 (39.1%)	<0.001*
Hypertension	75,170 (4.4%)	91 (17.2%)	<0.001*	7,225 (53%)	9 (39.1%)	0.26
Injection drug use	116 (0.01%)	2 (0.4%)	<0.001*	13 (0.1%)	0	1.00
Mental health disorder	62,413 (3.7%)	344 (65.2%)	<0.001*	4,659 (34.2%)	17 (73.9%)	<0.001*
Obesity	31,314 (1.9%)	89 (16.9%)	<0.001*	4,388 (32.2%)	11 (47.8%)	0.17
Substance use disorder	56,474 (3.3%)	179 (33.9%)	<0.001*	4,930 (35.4%)	12 (52.2%)	0.14

*p < 0.001; **p < 0.05; p = 1.00 indicates no significant difference.

Disclosures: thanh nguyen: Nothing to Disclose, Christina Chou: Phathom: Speakers Bureau, George Cholankeril: Nothing to Disclose, Howard (Tzu-Hao) Lee: Abbvie: Consultant

2198 | BEYOND PRIMARY CARE: SPECIALIST DENSITY AS A DRIVER OF LIVER DISEASE MORTALITY IN NON-ALD POPULATIONS

Olivia Blocker[1] Xiaophan Ying[2] Robert Brown[3] Russell Rosenblatt[3], [1]Weill Cornell Medical Center, [2]Weill Cornell, [3]Weill Cornell Medicine

Background: Non-alcohol-associated liver disease (non-ALD), often due to metabolic dysfunction, is now the leading cause of liver- related mortality in the United States. Yet, this mortality is not equal as geographic disparities, particularly in rural and poorer populations, have limited access to care. While primary care providers (PCPs) manage chronic diseases, the role of Gastroenterologist (GI) availability in reducing liver-related mortality - especially in non-ALD remains underexplored. While previous research has shown that higher GI density is associated with reduced mortality in ALD, non-ALD likely has a different clinical trajectory. Therefore, this study examines the impact of GI density on non-ALD liver disease mortality.We hypothesized that GI density would be inversely associated with non-ALD liver mortality even after accounting for PCP density and county level health disparities. **Methods:** We conducted a retrospective analysis using CDC WONDER data (2018-2022) to calculate crude mortality rates for non-ALD liver disease and Hepatocellular Carcinoma (HCC), based on ICD-10 codes. Counties lacking sufficient mortality data were excluded. GI and family medicine (FM) physician densities were derived from HRSA. Given our focus was on rural communities, FM providers were used to represent PCPs. A Community Health Score (CHS, 0-40) was constructed from ten health indicators (County Health Rankings). Rurality was defined using USDA Rural-Urban Continuum Codes. Our Primary outcome was crude rate of death from non-ALD and HCC. Multivariable linear regression assessed the impact of GI density on mortality, controlling for FM density and an interaction term between CHS and rurality due to a significant interaction effect. **Results:** Median crude non-ALD mortality was 11/100,000 (100K)(IQR 7.8-14.9). The median GI density was 2/100K; FM median was 21/100K. Higher GI density was associated with decreased non-ALD mortality (coefficient = -0.52, 95% CI -1.02 to -0.02, P = 0.04), even when controlling for FM and CHS- rural interaction. FM density was also significantly associated with lower non-ALD mortality. For HCC mortality, GI density trended toward significance (coefficient = -0.13, 95% CI -0.26 to 0.00, P = 0.055). **Conclusion:** Our findings suggest that greater specialist density - particularly that of GIs - is associated with lower mortality from non-ALD liver disease. While no significant association was observed for HCC, this may reflect the complex, multidisciplinary care required for cancer management, including oncology, surgery, and hepatology. In contrast, the management for non-ALD may rely more directly on GI for early detection and intervention, in addition to the known impact of PCPs. These findings emphasize the need for targeted investment in specialist availiablity- particularly in rural or high-risk counties-to address liver disease disparities.

Outcome	Predictor	Adjusted Coefficient*	(95% CI)	P-value
Non-ALD Mortality	GI crude density	-0.52	(-1.02 to -0.02)	0.04
	FM crude density	-0.14	(-0.26 to -0.02)	0.02
HCC Mortality	GI crude density	-0.13	(-0.26 to 0.00)	0.06
	FM crude density	0.04	(-0.001 to 0.081)	0.06

* Controlled for the interaction of community health score and USDA Rural-Urban Continuum Codes

Disclosures: Olivia Blocker: Nothing to Disclose, Xiaophan Ying: Nothing to Disclose, Robert Brown: Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant, Russell Rosenblatt: Nothing to Disclose

2199 | RACIAL/ETHNIC DISPARITIES IN ACCESS TO LIVER TRANSPLANTATION - A SYSTEMATIC REVIEW AND META-ANALYSIS

Rajalakshmi Govalan Thomas Hunold[1] Elliot Tapper[2], [1]University of Michigan, [2]University of Michigan Medical Center

Background: Cirrhosis is the 10th leading cause of death in the United States, and liver transplantation (LT) remains the only definitive treatment. We must strive to provide equitable access to LT and to that end we must determine if there are disparities – and address them. We therefore conducted a systematic review and meta-analysis to evaluate racial disparities in LT access and disease severity at the time of listing between Black and

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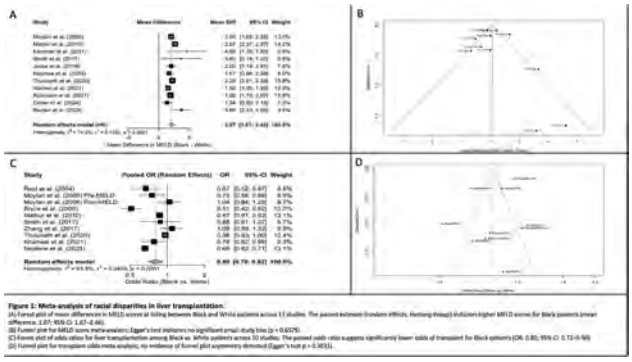
Non-Hispanic White patients in the U.S. **Methods:** We searched MEDLINE (2000–2024), identifying 1,753 studies. After independent screening and full-text review, 26 studies met inclusion criteria. Meta-analyses were conducted to assess pooled mean differences (MD) in MELD scores at listing and odds ratios (OR) for LT access between Black and Non-Hispanic White patients. Leave-one-out and duplicate cohort sensitivity analyses were performed. Publication bias was assessed using funnel plots and Egger's regression. Study quality was evaluated using the Newcastle-Ottawa Scale. **Results:** Among the 26 included studies, 11 reported MELD scores at listing, 10 reported odds of transplantation, 5 examined referral rates, and 3 assessed waitlisting odds by race. Two key findings emerged: 1. Black patients were listed with significantly more advanced liver disease, with a pooled mean MELD score difference of 2.07 (95% CI: 1.67–2.46). 2. Black patients had 20% lower odds of receiving a liver transplant compared to Non-Hispanic Whites (OR 0.80, 95% CI: 0.70–0.92). Substantial heterogeneity was observed, reflecting differences in healthcare practices, study design, and population demographics. Risk of bias across studies was rated mild to moderate. Sensitivity analyses confirmed the robustness of findings. No publication bias was detected. **Conclusion:** Our review and analysis highlights that Black patients not only have more severe liver disease at the time of listing but are also at lower odds of access to liver transplantation compared to Non-hispanic whites. Persistent racial disparities in liver transplant access and disease severity likely stem from a combination of social determinants of health, limited access to specialty care, implicit bias, and variability in referral practices. Tackling these inequities will require comprehensive strategies, including earlier screening, standardized referral pathways, and culturally tailored education. Future studies should examine region-specific and systemic contributors to inform targeted policy reforms.



Disclosures: Rajalakshmi Govalan: Nothing to Disclose, Thomas Hunold: Nothing to Disclose, Elliot Tapper: Madrigal: Grant/Research Support

2200 | CLINICIAN KNOWLEDGE AND PRACTICE OF TRANSGENDER AND GENDER DIVERSE HEALTHCARE IN LIVER TRANSPLANT

Sonali Paul[1] Ana Rossi[2] Elisa Gordon[3] Jody Jones[4] Wendy Balliet[5] Lisa Coscia[6] Goni Katz-Greenberg[7] Vineeta Kumar[8] Howard (Tzu-Hao) Lee[9] Rohan Ravirala[10] Alexandra Shingina[11] Laura Targownik[12] Monika Sarkar[10], [1]University of Chicago Medical Center, [2]Piedmont Healthcare, [3]Vanderbuilt University Medical Center, [4]University Hospitals Cleveland Medical Center-Transplant Institute, [5]Medical University of South Carolina, [6]Transplant Pregnancy Registry International, [7]Duke University School of Medicine, [8]University of Alabama at Birmingham, [9]Baylor College of Medicine, [10]University of California, San Francisco, [11]University of Michigan, [12]Sinai Health, Ontario Canada

Background: Nearly 1.6 million transgender and gender diverse (TGGD) individuals in the U.S. face significant health disparities driven by stigma, provider knowledge gaps, and systemic barriers. This survey assessed transplant professionals' knowledge, perceptions, and institutional support related to TGGD care. **Methods:** An online 33-question survey was administered through the American Society of Transplantation Communities of Practice member hubs. The survey assessed clinician knowledge, experience, communication practices, confidence, perceived barriers, and institutional infrastructure for TGGD care. Univariate analyses evaluated differences across transplant specialties. **Results:** Of 242 survey respondents, 125 completed the full survey. Most identified as female (68%) and White (80%); 44.8% were physicians. Transplant specialties included: kidney (67.2%), liver (48%), pancreas (41.6%), heart (20.8%), lung (14.4%), intestinal (9.6%), and vascularized composite allograft (2.4%). Most had previously cared for a TGGD patient (90.4%) and evaluated one for transplant (69.6%). Among liver transplant providers (n = 60, 48%), few reported feeling "very knowledgeable" about general (5%) and transplant-specific (3.3%) TGGD healthcare (Figure 1a). During initial evaluations, 27.8% asked about pronouns, and 22.2% asked about both gender identity and mental health (Figure 1b). Fewer inquired about sex assigned at birth (3.7%), gender affirmation steps (13.0%), or sexual orientation (5.5%). When evaluating TGGD patients for transplant, nearly half of liver transplant providers considered the impact of hormone therapy on transplant outcomes, immunosuppression interactions, and thrombosis risk (Figure 1c). About one-third accounted for prior (33.3%) or planned (28.3%) gender-affirming surgeries in their evaluations. Only 28.3% reported receiving required training on TGGD care, while half reported adequate institutional support in delivering gender-affirming liver transplant care. **Conclusion:** Liver transplant professionals report limited knowledge,

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confidence, and institutional support in providing care to TGGD patients. Our findings underscore a critical need for targeted education, resources, and institutional policy development to advance equitable, gender-affirming transplant care.

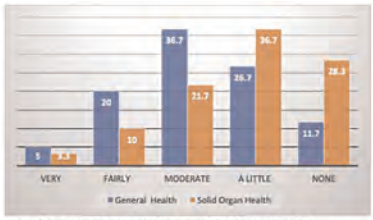

Figure 1a. Transgender and gender diverse health knowledge (%)

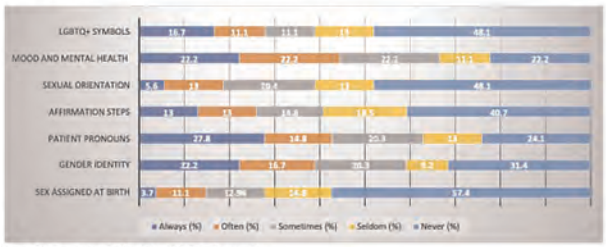

Figure 1b. Questions asked during initial clinical encounter

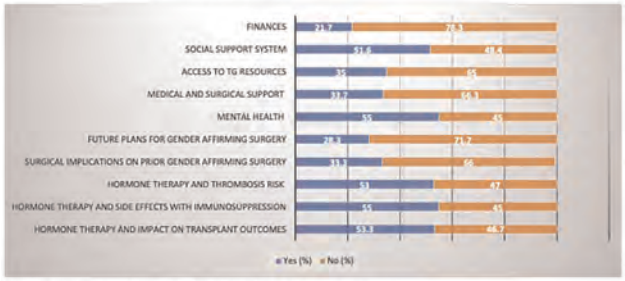

Figure 1c. Considerations in Transgender Health During Organ Transplant Evaluation

Disclosures: Sonali Paul: Intercept: Grant/Research Support, Target PharmaSolutions: Grant/Research Support, Eli Lilly: Stock - publicly traded company, Ana Rossi: Nothing to Disclose, Elisa Gordon: Nothing to Disclose, Jody Jones: Nothing to Disclose, Wendy Balliet: Nothing to Disclose, Lisa Coscia: Veloxis Pharmaceuticals: Grant/Research Support, Astellas: Grant/Research Support, Goni Katz-Greenberg: Nothing to Disclose, Vineeta Kumar: Alexion Pharmaceuticals: Consultant, United Therapeutics: Consultant, Vera Therapeutics: Consultant, Howard (Tzu-Hao) Lee: Nothing to Disclose, Rohan Ravirala: Nothing to Disclose, Alexandra Shingina: Nothing to Disclose, Laura Targownik: Nothing to Disclose, Monika Sarkar: GSK: Grant/Research Support, Zydus Pharmaceuticals: Grant/Research Support, Gilead Sciences: Grant/Research Support

2201 | WOMEN OF REPRODUCTIVE AGE WITH UNTREATED HCV: POSITIVE AND NEGATIVE PATIENT-REPORTED EXPERIENCES FROM A QUALITATIVE SURVEY

Mai Sedki[1] Jennifer Price[2] Matthew Caliz[2] Katrina Alcantara[2] Jeff McKinney[2] Tasha Toliver[2] Michael Helle[2] Rena Fox[3], [1]Stanford University, University of California San Francisco, [2]University of California San Francisco, [3]University of California, San Francisco

Background: Many patients with hepatitis C virus (HCV) do not complete the HCV care cascade. Understanding these patients' experience with the healthcare system is important to successfully relink them to care. Women of childbearing age are a particularly important population as only 17% of postpartum women initiated DAAs. We conducted a qualitative survey of women of reproductive age with untreated HCV to understand their prior HCV care. **Methods:** At a large urban tertiary health system, we identified all female patients aged 18-50 years seen between 2020-2024 with 1) current HCV viremia or 2) incomplete HCV diagnosis, defined by a reactive HCV Ab without RNA testing. A navigator called each patient, offered a clinician appointment, and conducted a phone survey. Patients were asked to answer on a Likert scale regarding their prior experience of HCV 1) overall care, 2) testing, 3) explanation of results, 4) education, 5) recommendation for treatment, 6) time with clinician, and 7) courtesy from clinic staff. Two open-ended questions were asked about how the healthcare system could be improved for patients and specifically women. No study incentives were offered to patients. **Results:** We identified 73 women who met criteria for outreach. Of those, 33 were successfully reached by phone within three attempts; 88% (29/33) completed the survey. The mean age of survey respondents was 38.9 years (SD 7.4), the majority were White (65%) and had Medi-cal insurance (14/29). Most were currently viremic (20/29) and the remainder were HCV Ab+ without any RNA testing. Only three had a primary care provider or had seen hepatology, and one had ever been prescribed a DAA, yet over a quarter (27%) were obese, two patients had cirrhosis, and one was decompensated. Of the 29 respondents, 41% reported they had received no prior healthcare for HCV, 45% had not been given or were dissatisfied with receiving their HCV results, 45% had no patient education or were dissatisfied, 48% had never been offered HCV treatment. Still, most responses were

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either positive or neutral. Patients' ideas about how healthcare for HCV could improve are shown in Table 1. **Conclusion:** In our cohort of young women with untreated HCV, patients reported a mix of positive and negative prior experiences. Although there was an 88% survey response rate, the study findings may be limited by small sample size. The women provided informative open-ended responses, and told us that attentive listening, more convenient care, and increased numbers of providers are ways that HCV care delivery could be improved for all and especially for women.

Table 1. Qualitative survey of women of childbearing age with untreated HCV: Free-response themes and quotes about how hepatitis C care can be improved

Response Theme	Question How can HCV care be improved for all patients?	Question Are there ways that hepatitis C care can be improved for women?
Improve how clinicians listen to patients	Having medical professionals give pts more information instead of treating every pt like they are the same person. We know that pts get Hep C for different reasons.	Listen to women when talking about HCV.
	It is important to make sure, that healthcare workers are caring and sensitive as possible because hepatitis C is a sensitive subject and painful because Hep C can cause physical and mental pain (depression) which can prevent people from getting treated.	Specifically for women, having available female specialists could make the care process more comfortable.
	Show awareness of how hep C is exposed	Someone being more present, actively asking questions and advocating testing.
		Talk and listen to women who have HCV.
Make HCV care more streamlined, convenient, and accessible	Help make patients' experience streamlined, like when the Rx was sent to the home directly. Make things more convenient.	Helping people who have problems with transportation
	If tests were positive, looping people in with providers.	Help people while they are doing treatment, such as if a patient has to care for children.
	Helping people with transportation for Hep C treatment	Investing more in healthcare for women
	Mobile testing sites.	
Make HCV care more affordable and investing more in HCV	Lower the financial barriers to testing. Provide free testing for people.	Universal healthcare.
	There needs to be more providers that will work with Medicaid, because there are limited providers. More availability.	Putting more money towards women's health
	Everyone should have universal healthcare/ access to healthcare.	
	More specialists that will handle HCV treatment.	
Continue current processes and this kind of outreach to patients	This hospital is doing a pretty good job in reaching out to previous patients.	Nothing to change, the process is straightforward.
	The fact that this institution is personally reaching out to patient's and taking initiative to call them is helpful on the patient's wellbeing.	Nothing else needed
	Care for Hep C is pretty decent	Nothing else needed

Disclosures: Mai Sedki: Nothing to Disclose, Jennifer Price: AbbVie: Grant/Research Support, Gilead: Grant/Research Support, Genentech: Grant/Research Support, VIR: Grant/Research Support, Cepheid: Grant/Research Support, Aligos: Grant/Research Support, Matthew Caliz: GILEAD Sciences: Grant/Research Support, Katrina Alcantara: Nothing to Disclose, Jeff McKinney: Nothing to Disclose, Tasha Toliver: Nothing to Disclose, Michael Helle: Nothing to Disclose, Rena Fox: Nothing to Disclose

2202 | MISSED OPPORTUNITIES FOR LIVER HEALTH IN WOMEN WITH SUBSTANCE USE DISORDER

Iva Kosuta[1] Lea Kozina[2] Paula Cizmic[3] Leo Kosuta[4] Anna Mrzljak[5] Zrnka Kovacic Petrovic[6], [1]Division of Intensive Care, Department of Internal Medicine, [2]University Psychiatric Hospital Vrapče, [3]School of Medicine, University of Zagreb, [4]School of Medicine, Univeristy of Zagreb, [5]University Hospital Center Zagreb, [6]University Psychiatric Hospital Vrapce

Background: Women with substance use disorder are at increased risk for liver disease yet liver health is rarely assessed systematically in psychiatric settings. This study aimed to determine the proportion of women treated for substance use disorder with advanced liver disease, based on non-invasive fibrosis scores, and to evaluate whether they had been appropriately referred for hepatology evaluation. **Methods:** We retrospectively analysed liver fibrosis risk using FIB-4 and APRI scores in hospitalized women with substance use disorder who had no previously known liver disease, applying standard cutoffs. Demographic, psychiatric, and biochemical data were reviewed to assess hepatology referral rates among at-risk patients. Additional analyses explored the association between fibrosis severity and socioeconomic indicators. **Results:** One hundred ninety-nine patients with a median age 50.1 years (IQR 39.8-59.5) were included. Alcohol use was documented in 91.5% of patients. Psychiatric comorbidities were frequent including personality, anxiety, and post-traumatic stress disorders. Based on FIB-4 score, 21.6% were at intermediate risk and 7.0% at high risk of fibrosis, but only 12.3% were referred to hepatology services. According to APRI score, 10.1% patients were classified as having significant fibrosis or probable cirrhosis, of whom only 15% were referred to hepatology services. FIB-4 scores differed significantly across education levels ($p = 0.004$), with both low and high educational attainment associated with higher fibrosis severity, suggesting a bimodal distribution. However, marital status was not associated with liver disease severity. **Conclusion:** Despite the availability of simple non-invasive tools to estimate liver fibrosis, many at-risk women were not referred to liver services. Lack of familiarity with the availability of such scores among psychiatric providers contribute to under-recognition and lack of referral. Improved training, a model of integrated care - collaboration between psychiatric and hepatology services and referral-pathways are needed

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to bridge a healthcare gap and support the development of holistic, low-threshold access models that address both medical and psychosocial needs in this vulnerable group.

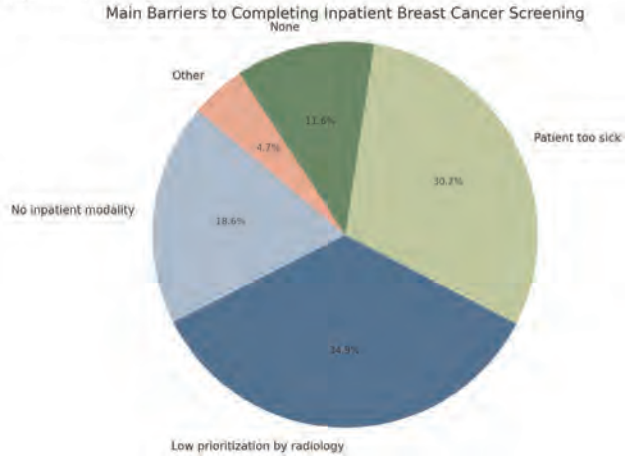
Disclosures: Iva Kosuta: Nothing to Disclose, Lea Kozina: Nothing to Disclose, Paula Cizmic: Nothing to Disclose, Leo Kosuta: Nothing to Disclose, Anna Mrzljak: Nothing to Disclose, Zrnka Kovacic Petrovic: Nothing to Disclose

2203 | BARRIERS TO OBTAINING BREAST CANCER SCREENING DURING LIVER TRANSPLANT EVALUATION: A CONTRIBUTOR TO SEX DISPARITIES IN LIVER TRANSPLANTATION LISTING

Madison Force[1] Caroline Conlon[2] Emily Chiacchiaro[2] Dina Halegoua-De Marzio[2] Danielle Tholey[2], [1]Thomas Jefferson University Hopsital, [2]Thomas Jefferson University Hospital

Background: Sex disparities persist in liver transplantation (LT), with women experiencing longer wait times and lower rates of transplant compared to men. This is due to differences in body habitus, access to care and until MELD3, lower GFR in women. We propose that completing inpatient breast cancer screening during liver transplant evaluation (LTE) is an additional barrier disadvantaging women. We examine the perceived impact of inpatient breast cancer screening on timely LTE in women at U.S. LT centers. **Methods:** Surveys were distributed via REDCap to the medical director (when available) or a single hepatologist at all 115 active adult LT centers listed in the Organ Procurement and Transplantation Network (OPTN) as of 5/1/2025. The survey included questions regarding breast cancer screening protocols for patients too ill to be discharged from the inpatient setting and perceived impact on listing timelines. Responses were collected anonymously. **Results:** In all, 31 centers completed the survey with a response rate of 27%. Survey responses were geographically diverse representing centers across 9 of the 11 OPTN regions and 20 US states. All responders reported that breast cancer screening was part of the inpatient LTE, but only 81% of centers had access to inpatient breast cancer screening. The most common screening tools used were mammography (77%), breast ultrasound (45%) and MRI (16%). 61% reported experiencing delays in completing breast cancer screening for inpatient LTE. On a 5-point difficulty scale, 63% of respondents rated the challenge of completing inpatient screening as moderate to high (scores of 3–5). The primary barriers cited are displayed in Figure 1. 24% of centers waive breast cancer screening in selected high MELD patients. Several centers attempted to overcome delays, via direct coordination with radiology and breast centers, developing pathways for same-day inpatient access, and using bedside breast exams or breast ultrasound when patients are too ill for a mammogram. **Conclusion:** A majority of participants reported logistical and clinical barriers to completing breast cancer screening for women undergoing inpatient LTE. Limited access to inpatient mammography, low prioritization by radiology, and the critical illness of candidates impede timely completion of required screening. These delays disproportionately affect women and represent a modifiable contributor to sex-based disparities in liver transplantation. Strategies to improve access to inpatient breast cancer screening are needed to promote equitable transplant listing.

Figure 1. Main barriers to completing inpatient breast cancer screening reported by survey responders.



Disclosures: Madison Force: Nothing to Disclose, Caroline Conlon: Nothing to Disclose, Emily Chiacchiaro: Nothing to Disclose, Dina Halegoua-De Marzio: Novo Nordisk: Advisor, Galectin: Grant/Research Support, Madigral: Advisor, Novo Nordisk: Grant/Research Support, Madigral: Advisor, Viking: Grant/Research Support, Akero: Grant/Research Support, Intercept: Grant/Research Support, 89Bio: Grant/Research Support, Danielle Tholey: Merck: I am an editor for the merck manual

2204 | SEX FOR THE PURPOSES OF MELD 3.0 CALCULATION: WHEN THIS DIFFERS FROM ASSIGNED SEX AT BIRTH AND IMPLICATIONS FOR POLICY

Nikki Duong[1] Daniel Huynh[2] Newsha Nikzad[3] W. Ray Kim[4] Neil Shah[5] Scott Biggins[6] Allison Kwong[7], [1]Stanford University, [2]University of Washington, [3]The University of Chicago Medical Center, [4]Mayo Clinic Arizona, [5]University of North Carolina at Chapel Hill,

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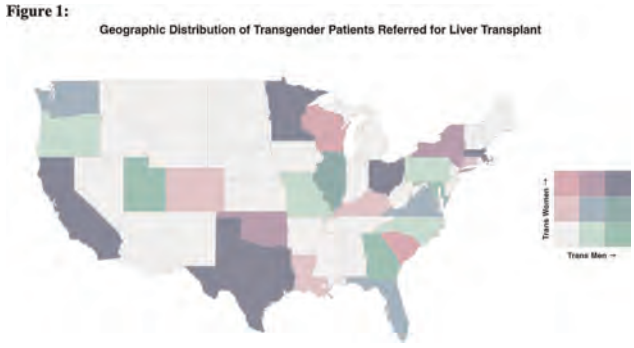
[6]University of Pittsburgh, [7]Stanford University Medical Center

Background: Adults with chronic liver disease are prioritized on the US liver transplant waiting list by their MELD 3.0 score, which was updated in July 2023 from MELD-Na to incorporate sex and albumin as additional variables. With MELD 3.0, women receive an additional 1.33 points to their MELD score, to better represent their waiting list mortality and correct a longstanding sex disparity in waiting list and transplant outcomes. With this policy update, the data field labeled "Gender" was relabeled as "Birth sex," and an additional field for adult liver transplant candidates was created "Sex for the Purposes of Adult MELD calculation." We evaluate the effect of this policy update in candidates who report their sex as different than their birth sex for MELD 3.0 calculation. **Methods:** We analyzed OPTN data for adult liver transplant candidates registered between July 2023 (when these data fields were created) and March 2025. The response to this data collection is left to the discretion of the transplant program in consultation with the candidate and their clinical team. OPTN guidance suggests that programs may consider the candidate's sex for the purposes of adult MELD calculation to be different from their birth sex, for example, if the candidate is taking gender-affirming hormone therapy. **Results:** Among 26,324 patients registered on the liver transplant list during the study period, 80 patients reported differing sex at birth and sex for the purposes of the MELD 3.0 calculation. 43 patients identified as female who reported male sex at birth (0.4% of women), and 37 patients identified as male and reported female sex at birth (0.3% of men). MELD 3.0 did not significantly differ between cisgender and transgender patients at listing ($p = 0.90$). Additionally, there were no significant differences between the groups in terms of age at the time of transplant evaluation, race, days to transplant, or waitlist mortality. There were no instances of patients being listed at multiple centers. **Conclusion:** The introduction of MELD 3.0 reflects continued efforts to mitigate sex-based disparities in liver transplant allocation. The OPTN database has the capacity to further illuminate implications of MELD 3.0 on health outcomes for transgender patients referred for transplantation. The addition of the field "Sex for the Purposes of Adult MELD calculation" is a critical step towards accurately stratifying mortality risk and promoting equitable allocation. This is an important study demonstrating that this variable appears to be used appropriately by transplant centers, or at the very least, not manipulated to gain waitlist advantage. However, ongoing vigilance is essential as more data become available.

Figure 1:



Disclosures: Nikki Duong: Nothing to Disclose, Daniel Huynh: Nothing to Disclose, Newsha Nikzad: Nothing to Disclose, W. Ray Kim: Nothing to Disclose, Nothing to Disclose, Neil Shah: GSK: Advisor, Ipsen: Advisor, GSK: Consultant, Ipsen: Consultant, Scott Biggins: Nothing to Disclose, Allison Kwong: Nothing to Disclose

2205 | EXPLORING INTERPERSONAL BIAS IN TRANSPLANTATION: A CROSS-SECTIONAL STUDY OF ATTITUDES, CULTURAL INTELLIGENCE, AND IMPLICIT BIAS AMONG ABDOMINAL TRANSPLANT CENTER EMPLOYEES

Joy Obayemi[1] Kenny Chen[2] Harika Reddy[2] Maggie Jones-Carr[3] Shaina Alexandria[2] Kiarri Kershaw[2] Dinee Simpson[2] Daniela Ladner[2], [1]University of Michigan / Northwestern University, [2]Feinberg School of Medicine, Northwestern University, [3]University of Alabama at Birmingham

Background: Black/African American patients are less likely to be waitlisted for abdominal organ transplantation and have poorer outcomes once transplanted. While the etiology of these disparities is multifactorial, little is known about the interpersonal biases held by transplant center employees, which may contribute to these findings. **Methods:** A cross-sectional study was performed using employee responses to a cultural assessment conducted at a large, metropolitan transplant center from July-September 2024. The assessment was created with iterative feedback from content experts in a multi-institutional consortium and included a race-based implicit association test (IAT), which assesses the speed of rapid association as an indirect measure of bias. The assessment was distributed to all patient-facing transplant center employees. Descriptive statistics were performed on respondent demographics and arithmetic mean response latency calculated with IAT data. **Results:** Of 178 employees of the transplant

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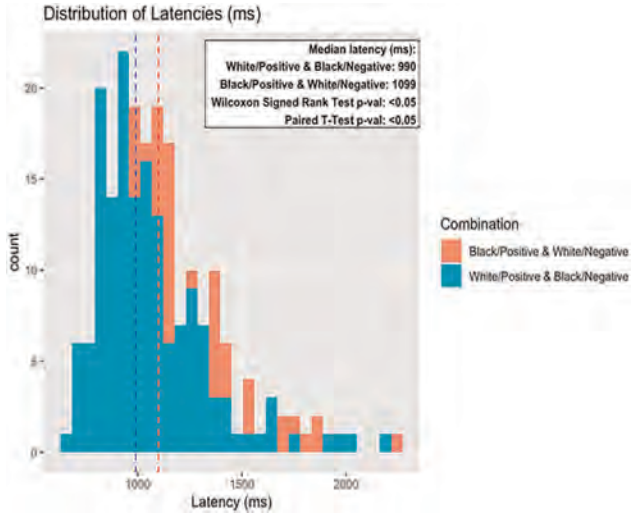
centers, 158 (88.8%) individuals completed the cultural assessment. Most respondents were female (n = 117;68.3%). 90 (57.0%) respondents were 18-40yo, 57 (36.1%) were 41-60yo, and 11 (7.0%) were ≥ 61yo. Most identified as White (n = 97, 61.4%), Asian (n = 25, 15.8%) or Black/African American (n = 20, 12.7%). 92 (58.3%) employees were non-Physician clinicians (i.e. nurse, APP, social worker, psychologist), 43 (27.2%) were office personnel, and 23 (14.6%) were physicians. The mean d score for the cohort was 0.26 (SD = 0.44) compared to a d score of 0, which would indicate no bias. This denotes a significant preference towards associating White people with positive words and Black people with negative words among the total cohort ($p < 0.001$, 95% CI 0.15,0.33) with a medium effect size (Cohen's d = 0.59) [Figure 1]. No significant differences in degree of bias were found when stratified by gender, age category, or position at the transplant center. Respondents who had been working in the transplant center for longer (> 10 years, d = 0.41) displayed more bias towards White individuals than those who were relatively new employees (0-5 years, d = 0.21)($p = 0.047$). **Conclusion:** These results suggest that anti-Black implicit bias exists among employees at a large metropolitan transplant center. This highlights the need for continued education and evidence-based efforts to mitigate bias, which has the potential to impact transplant access, outcomes, and experiences for minority patients.



Disclosures: Joy Obayemi: Nothing to Disclose, Kenny Chen: Nothing to Disclose, Harika Reddy: Nothing to Disclose, Maggie Jones-Carr: Nothing to Disclose, Shaina Alexandria: Nothing to Disclose, Kiarri Kershaw: Nothing to Disclose, Dinee Simpson: Nothing to Disclose, Daniela Ladner: Nothing to Disclose

2206 | UNEQUAL BURDEN: DISPARITIES IN CIRRHOSIS AND LIVER CANCER MORTALITY IN THE U.S.,1999–2022

Yousaf Zafar[1] Areesha Hafeez[2] Shanzay Akhtar[2] Syed Sarmad Javaid[3], [1]Cleveland Clinic Florida, [2]Karachi Medical and Dental College, [3]University of Mississippi Medical Center

Background: Cirrhosis is advanced liver scarring caused by chronic liver diseases, leading to impaired liver function. Hepatocellular carcinoma (HCC), on the other hand, is the most common type of primary liver cancer world-wide identifying as an aggressive cancer most common in people with advanced liver disease, like cirrhosis. This study analysed CDC WONDER data to examine trends in mortality in patients with cirrhosis and HCC in the United States (U.S). **Methods:** Using the CDC WONDER database, we queried mortality records from 1999 to 2022 among HCC-related deaths (ICD-10: C22.0) and cirrhosis-related deaths (ICD-10: K70.3, K74.5, K74.6) in adults aged 25+. Joinpoint regression analysis was utilized to assess trends in annual percentage change (APC) for contributing causes of death. Age-adjusted mortality rates (AAMR) were computed and compared cumulatively across subpopulation demographics. **Results:** From 1999 to 2022, Cirrhosis and hepatocellular carcinoma caused 63,484 deaths among U.S adults aged 25 years and older. Overall AAMR rose from 0.68 in 1999 to 1.58 in 2022. After the initial increase from 1999-2006 (APC: 2.13; 95% CI: 0.07 to 3.28), the mortality surged in the 2006-2017 period (APC: 5.57; 95% CI: 5.14 to 6.50), with a more gradual increase from 2017 to 2022 (APC: 1.78; 95% CI: 0.43 to 2.75) (Figure 1A). AAMR had an increasing trend in both sexes, men had consistently higher AAMR than women from 1999 (AAMR; men: 1.19 vs women: 0.25) to 2022 (AAMR; men: 2.60 vs women: 0.66) (Figure 1B). Among racial groups, Hispanics and Latino had the highest AAMRs, followed by Non-Hispanic (NH) Black or African American, and lastly NH White (2022; Hispanic or Latino: 2.98, NH Black: 1.48, NH White: 1.36) (Figure 2A). AAMR also showed significant regional variation, with the West region reporting the highest AAMR in 2022, and the Northeast region reporting the lowest (AAMR 2022; West: 2.10, South: 1.67, Midwest: 1.27, Northeast: 1.06) (Figure 2B). Across the states, Oregon reported the highest AAMR in 2022 (3.21), and West Virginia the lowest (0.73). **Conclusion:** This study highlights discrepancies in HCC mortality related to liver cirrhosis

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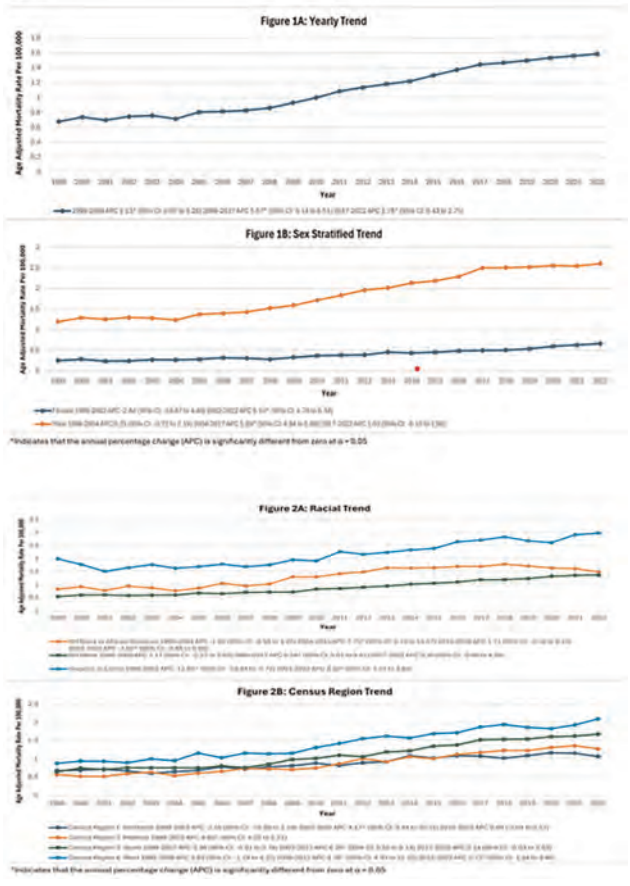
among U.S. adults. The steady rise in AAMRs from 1999 to 2022 underscores the need for specific public health interventions to address these growing inequalities. Our findings stress the importance of targeted, locally tailored programs and policies to reduce the dual mortality burden of HCC and cirrhosis.

Figures:



Disclosures: Yousaf Zafar: Nothing to Disclose, Areesha Hafeez: Nothing to Disclose, Shanzay Akhtar: Nothing to Disclose, Syed Sarmad Javaid: Nothing to Disclose

2207 | TRENDS IN MAT AND GLP-1 UTILIZATION AFTER LIVER TRANSPLANTATION BASED ON SOCIODEMOGRAPHIC VARIABLES: A NATIONAL COHORT ANALYSIS

Ami Patel[1] Taylor Seacor[2] Katherine Cooper[2] Anita Krishnarao[2], [1]Univeristy of Massachusetts, [2]University of Massachusetts

Background: Alcohol Associated Liver Disease (ALD) and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) are the most common etiologies of liver disease in the US. Medical assisted therapy (MAT) for alcohol use disorder and Glucagon-like peptide -1 agonists (GLP-1) for metabolic syndrome have been shown to improve outcomes pre-LT, although less is known about their impact and utilization after LT. Sociodemographic disparities have been identified regarding access to hepatology care and LT referral. This study aimed to evaluate if disparities in medication utilization persist even after gaining access to multidisciplinary care post-LT. **Methods:** This analysis was completed using a TriNetX query of the United States Collaborative Network- a network of 70 healthcare organizations. Patients who underwent transplantation between 2017-2025 and had either MASLD or ALD were identified using ICD-10 codes and those with prescriptions for MAT (Naltrexone, Acamprosate, and Disulfiram) and GLP-1 (Exenatide, Semaglutide, Liraglutide, Dulaglutide, and Tirzepatide) were included. Baseline characteristics such as age, sex, race, and ethnicity were analyzed in the MAT and GLP-1 group and then compared to no MAT and no GLP-1. Data was analyzed using TriNetX and statistical significance was evaluated at $p < 0.05$. **Results:** A total of 12,468 patients with ALD underwent LT, of which 744 (6%) were prescribed MAT post-LT. Patients on MAT were predominantly male (63%), non-Hispanic (67%), and white (78%). When compared to those without MAT, MAT recipients were younger (mean 49 vs. 54, $p < 0.01$) and more likely to be female (36% vs 27%, $p < 0.01$) with no differences in race or ethnicity: White (78% vs 75%, $p = 0.06$) or non-Hispanic (67% vs 67%, $p = 0.87$). Additionally, 15,514 patients with MASLD underwent LT, of which 1,925 (12%) were prescribed GLP-1 therapy post-LT. The GLP-1 cohort ($n = 1,925$) was again predominantly male (55%), non-Hispanic (66%), white (76%), and had a mean age of 59 years. When compared to the cohort without GLP-1, GLP-1 recipients were older (mean 59 vs. 56, $p < 0.01$) and more likely to be female (43% vs. 41%, $p = 0.02$). There were again no differences in race or ethnicity: White (76% vs 75%, $p = 0.26$) or non-Hispanic (66% vs 68%, $p = 0.19$). Notably, a majority of MAT (45%) and GLP-1 (47%) recipients resided in the southern US as compared to other regions. **Conclusion:** MAT and GLP-1 therapies are underutilized post-LT, despite their potential benefit. While there were fewer females overall in the post-LT cohort, there was a greater percentage of females in both the MAT and GLP-1 groups. In contrast to our hypotheses, there were no racial or ethnic differences related to MAT or GLP-1 utilization post-LT, though geography may play a role in prescribing practices. While MAT and GLP-1 utilization is low in the post-LT setting overall, the socioeconomic disparities related to healthcare access prior to LT do not seem to persist after our analysis.

Disclosures: Ami Patel: Nothing to Disclose, Taylor Seacor: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Anita Krishnarao: Nothing to Disclose

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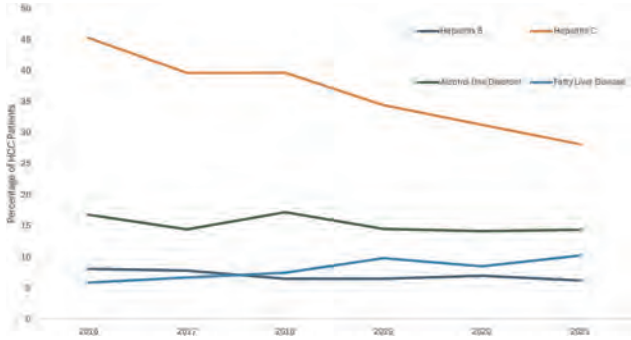
2208 | INCIDENCE OF ETIOLOGY OF HEPATOCELLULAR CARCINOMA BY SOCIAL DETERMINANTS OF HEALTH, A TREND FROM 2016-2021

Andrej Sodoma[1] James Pellegrini[2] Samuel Greenberg[3] Mark Baginski[4] Mary Thomas[4], [1]Northwell, [2]NUMC, [3]Stony Brook, [4]SSUH

Background: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults and the third leading cause of cancer-related deaths worldwide. Cirrhosis remains the predominant cause of HCC. The etiologies of cirrhosis over the years have changed with an increase in metabolic dysfunction-associated fatty liver disease (MAFLD) without much improvement in management while the primary prevention of virus-related cirrhosis and a decrease in rates of viral-related HCC. **Methods:** In this study, we used the National Inpatient Sample (NIS) from 2016-2021 to trend changes in the etiologies of HCC. The International Classification of Disease (ICD) 10 codes were used to identify patients with cirrhosis, HCC, and the leading causes of cirrhosis: Hepatitis B (Hep B), Hepatitis C (Hep C), Alcohol use disorder (AUD), and MAFLD. The groups were split by the cause of cirrhosis, creating four groups. Records were weighted per the NIS algorithm to produce accurate population estimates. The patients were analyzed for baseline characteristics: age, Charlson Comorbidity Index (CCI), sex, race, insurance, hospital size, region, income, hypertension (HTN), coronary artery disease (CAD), diabetes type two (DM2), current smoker, and opioid use. The percentage and number of patients for each cause of cirrhosis were organized, and the Cochran-Armitage test for trend significance was used. **Results:** A weighted total of 108,795 HCC patients from 2017-2021, with 7615 Hep B, 39765 Hep C, 16625 AUD, and 8745 MAFLD patients were analyzed. Patients were 65.1 years old on average ($p < 0.05$), average CCI of 7.65. Hep B and Hep C from 2016 to 2021 steadily decreased (Hep B: 8.04% 2016, 7.81% 2017, 6.44% 2018, 6.5% 2019, 6.94% 2020, 6.23% 2021 ($p < 0.0011$); Hep C: 45.19% 2016, 39.63% 2017, 39.6% 2018, 34.43% 2019, 31.24% 2020, 28.08% 2021 ($p < 0.0001$)). AUD Hep C remained relatively lateral from 2016 to 2021 (16.8% 2016, 14.46% 2017, 17.19% 2018, 14.54% 2019, 14.19% 2020, 14.38% 2021 ($p < 0.0024$)). MAFLD doubled from 2016 to 2021 (5.87% 2016, 6.66% 2017, 7.42% 2018, 9.78% 2019, 8.48% 2020, 10.19% 2021). **Conclusion:** The incidence of HCC is directly correlated with variations in the etiology of cirrhosis, as evidenced by the rise in MAFLD and the decline in the proportion of patients with HCC attributable to hepatitis B and C. The research methodology offers a clear and dependable framework for comprehending the trends associated with the etiology of HCC.



Disclosures: Andrej Sodoma: Nothing to Disclose, James Pellegrini: Nothing to Disclose, Samuel Greenberg: Nothing to Disclose, Mark Baginski: Nothing to Disclose, Mary Thomas: Nothing to Disclose

2209 | A REVIEW OF THE IMPACT OF BIAS IN ARTIFICIAL INTELLIGENCE IN ENSURING HEALTH EQUITY IN HEPATOLOGY

Sara Romero-Otero[1] Joaquín Dopazo[2] Manuel Romero-Gómez[2] Isabel Fernandez[1] Vanessa Garcia-Fernandez[1], [1]Instituto de Biomedicina de Sevilla (IBiS), [2]University Hospital Virgen del Rocío

Background: Artificial Intelligence (AI) has shown great promise as a tool for hepatology, both in routine clinical practice and in more specific forms of healthcare delivery. However, these technological advances have been noted to introduce new forms of statistic and social bias that may further broaden the systematic gap between socioeconomic minorities and their access to healthcare. As such, this review seeks to note the health inequities that have arisen or may arise from statistical and linguistic bias in AI used in routine clinical practice for hepatology, focusing specifically on how it has been shown to exacerbate gender disparities in liver transplant waitlists and worsen polyp detection in various ethnic minority groups. **Methods:** Scientific articles were collected through PubMed using the search criteria “Artificial Intelligence” + “bias” + “Hepatology” and limiting their publication date from 2020 to 2025. The platform offered 41 matches to the search criteria, 6 of which were classified as meta-analyses, 22 as reviews, and 16 as systematic reviews. All 41 articles were published in English, with only 2 of them featuring a female specialist as corresponding author. Other socioeconomic factors, such as the authors’ race or sexual identity, were later taken into consideration by contacting each corresponding author to request such information. **Results:** Our findings show that, while the impact of language and system bias on health equity has been somewhat reported in the field of hepatology,

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only 6 of the 41 articles offer a thorough analysis of the impact of bias on minorities' access to high-quality and accurate diagnosis, while also shedding light on the biases presents in AI chatbots used directly by patients to complement their treatment, as is the case with inappropriate and/or insensitive responses received when seeking advice for weight loss. Conversely, 11 of the 41 articles offer a brief discussion offer brief discussions of bias-related issues in hepatology, particularly in specific treatments and/or diagnostic procedures; 18 of them note bias mitigation as part of their methodology without discussing its socioeconomic impact; finally, 3 of them fail to address bias or do so from another medical specialty. **Conclusion:** These findings show that addressing bias in AI tools for hepatology remains an unmet need. It is of utmost importance to address these existing and/or potential biases in order to minimize racial and gender disparities within healthcare, both throughout the data collection process and through auditing processes once the devices have been deployed into routine clinical practice. The creation of an ethical framework applying specifically to the use AI in hepatology will also further help in mitigating any existing socioeconomic biases, while also enhancing the quality of care offered to all liver patients.

Table 1. Forms of language and system bias with impact on health equity observed in AI tools for hepatology and gastroenterology

Procedure/condition	Bias detected
Hepatocellular carcinoma and liver transplantation	HCC is 2 to 4 times more common in men, and as such the inclusion of this variable has been found to deprioritize women and perpetuate sex disparities: women are 20% less likely to receive a liver transplant and 8.6% more likely to die on the transplant waitlist
Alcohol Associated Liver Disease	Insufficiencies have been noted in the application of AI tools dependent on psychosocial variables, thus discriminating against socially vulnerable groups as candidates for liver transplantation
Weight loss	Inappropriate and/or insensitive responses to patient queries regarding forms of weight loss, thus affecting their treatment through stigmatization

Disclosures: Sara Romero-Otero: Nothing to Disclose, Joaquín Dopazo: Nothing to Disclose, Manuel Romero-Gómez: Nothing to Disclose, Isabel Fernandez: Nothing to Disclose, Vanessa Garcia-Fernandez: Nothing to Disclose

2210 | EPIDEMIOLOGICAL TRENDS AND DISPARITIES IN DIGESTIVE CANCERS AMONG HEPATITIS PATIENTS IN THE UNITED STATES: A CDC WONDER DATABASE ANALYSIS (1999-2022)

Simran Joshi[1] Muhammad Ali[2] Husnain Ahmad[3] Matthew Manoj[4] Jeevin Sandhu[5] Marquise Soto[6] Sushrut Ingawale[7] Corinne Caissie[1] Abhiraj Patel[1] Rishi Chowdhary[8] Shijia Li[1] Muhammad Abdullah Humayun[9] Simardeep Singh[10] Noor ul Ain Saleem[11] Faizan Ahmed[12] Cheng-Hung Tai[1] Atiqul Mohammad[1] Sandeep Nayak[1], [1]Yale New Haven Health/Yale University School of Medicine, [2]Jinnah Postgraduate Medical Center, [3]Shalamar Medical and Dental College, [4]Beth Israel Deaconess Medical Center, Harvard Medical School, [5]Methodist Dallas Medical Center, [6]Massachusetts General Hospital, Harvard Medical School, [7]Quinnipiac University - Frank H Netter MD School of Medicine, [8]MetroHealth Medical Center, [9]Mayo Clinic, [10]Medstar Health Georgetown University, [11]FMH College of medicine and dentistry, [12]Jersey Shore University Medical Center

Background: The prevalence of hepatitis-specific digestive cancer in the United States is underexplored, however, chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are well-established etiological agents for certain digestive cancers, particularly hepatocellular carcinoma (HCC) and gastric cancer. Long-term infection with either virus increases the risk of various GI malignancies, including colorectal, gastric, esophageal, and pancreatic cancers, likely due to mechanisms involving chronic inflammation, liver damage, and potential integration of viral DNA into host cells, leading to oncogenesis. Despite recent advances in antiviral therapies and public health interventions, disparities in digestive cancer mortality among hepatitis-infected individuals remain underexplored on a national scale. **Methods:** We conducted a retrospective study using CDC WONDER Multiple Cause of Death data from 1999 to 2022. Deaths were included if both DCs (ICD-10: C15–C26) and viral hepatitis (ICD-10: B15–B19) were listed. Age-adjusted mortality rates (AAMRs) per 100,000 were calculated using the 2000 U.S. standard population. Joinpoint regression was employed to estimate annual percent changes (APCs). Subgroup analyses stratified trends by sex, age, race/ethnicity, U.S. census region, and urban-rural classification. **Results:** A total of 80,310 deaths were attributed to concurrent DCs and viral hepatitis from 1999–2022. The overall AAMR increased from 0.56 in 1999 to a peak of 1.80 in 2012 (APC: +7.8%), followed by a steady decline to 1.25 in 2022 (APC: -6.2%). Men consistently exhibited higher mortality than women. HCC was the most common cause of death (68%), followed by lower GI and pancreatic cancers. Non-Hispanic (NH) Asians and NH Blacks had the highest AAMRs, with NH Asians demonstrating the most significant post-2012 decline. Regionally, the West had the highest mortality, and urban areas consistently exceeded rural counterparts. The most impacted age group was 55–74 years. Notably, states in the 90th percentile had AAMRs nearly three times higher

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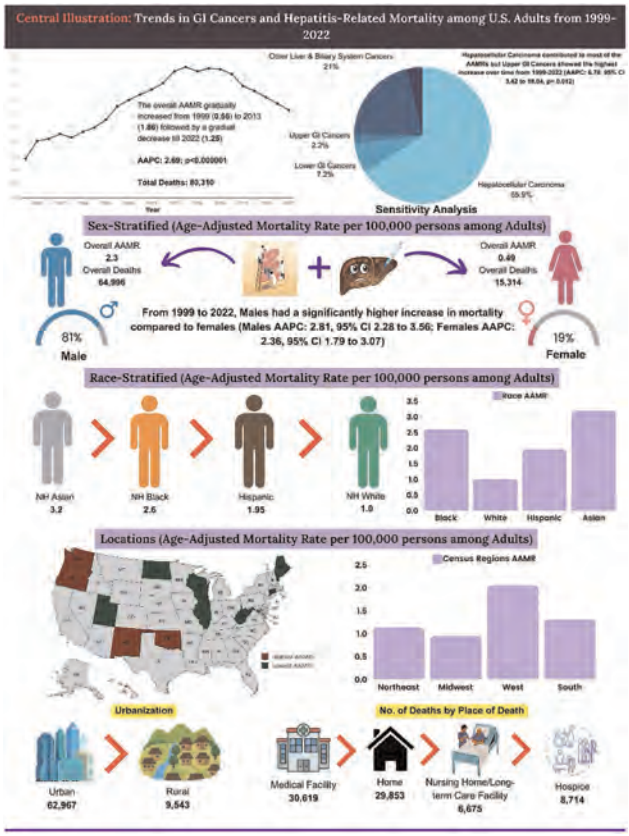
than those in the 10th percentile. **Conclusion:** While mortality from hepatitis-associated digestive cancers has declined over the past decade—likely due to improved screening, HBV vaccination, and direct-acting antivirals—significant disparities persist by sex, race, geography, and urbanization. HCC remains the predominant contributor to mortality. Targeted public health strategies are critical to address these inequalities and improve outcomes among hepatitis-infected populations.



Disclosures: Simran Joshi: Nothing to Disclose, Muhammad Ali: Nothing to Disclose, Husnain Ahmad: Nothing to Disclose, Matthew Manoj: Nothing to Disclose, Jeevin Sandhu: Nothing to Disclose, Marquise Soto: Nothing to Disclose, Sushrut Ingawale: Nothing to Disclose, Corinne Caissie: Nothing to Disclose, Abhiraj Patel: Nothing to Disclose, Rishi Chowdhary: Nothing to Disclose, Shijia Li: Nothing to Disclose, Muhammad Abdullah Humayun: Nothing to Disclose, Simardeep Singh: Nothing to Disclose, Noor ul Ain Saleem: Nothing to Disclose, Faizan Ahmed: Nothing to Disclose, Cheng-Hung Tai: Nothing to Disclose, Atiqul Mohammad: Nothing to Disclose, Sandeep Nayak: Nothing to Disclose

2211 | INFLUENCE OF SOCIAL VULNERABILITY ON COMPLICATIONS OF ALCOHOL-ASSOCIATED LIVER DISEASE

Pojsakorn Danpanichkul[1] Kanyaphak Charnpatanakorn[2] Donghee Kim[3] Thanathip Suenghataiphorn[4] Narathorn Kulthamrongsri[5] Karn Wijarnpreecha[6] Mazen Noureddin[7] Suthat Liangpunsakul[8], [1]Texas Tech University Health Sciences Center, [2]Faculty of Medicine, King Mongkut's Institute of Technology, Bangkok, Thailand, [3]Stanford University, [4]Griffin Hospital, [5]University of Hawaii, [6]University of Arizona, [7]Houston Methodist Hospital, [8]Indiana University

Background: Alcohol-associated liver disease (ALD) poses a significant and growing public health concern, with patient outcomes increasingly influenced by social determinants of health (SDoH). While factors such as poverty and social isolation are known to worsen outcomes in many medical conditions, their direct impact on ALD-related complications remains unclear. This study aimed to assess how social deprivation influences clinical outcomes in individuals with ALD. **Methods:** Using the TriNetX research network, which compiles real-time electronic health data from a broad range of U.S. healthcare institutions, we identified adults with a diagnosis of ALD. Social deprivation was defined by the presence of ICD-10-CM codes for extreme poverty (Z59.5), low income (Z59.6), or living alone (Z60.2). Patients were matched 1:1 using propensity scores to control for demographic characteristics, comorbidities, medications, and alcohol use disorder treatments. Cox proportional hazards models were applied to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for clinical outcomes. **Results:** The matched cohort consisted of 998 ALD patients, split evenly between socially deprived and non-deprived groups (499 each). Social deprivation was not significantly linked to all-cause mortality (20.1% vs. 19.5%; HR 0.93, 95% CI 0.70–1.22). However, socially deprived individuals had significantly higher risks of major adverse cardiovascular events (MACE) (20.6% vs. 11.4%; HR 1.76, 95% CI 1.22–2.56), arrhythmia (24.6% vs. 15.7%; HR 1.58, 95% CI 1.13–2.22), heart failure (13.5% vs. 6.2%; HR 2.15, 95% CI 1.34–3.43), alcohol-associated hepatitis (AH) (24.7% vs. 16.2%; HR 1.44, 95% CI 1.09–1.90), and sepsis (21.8% vs. 10.2%; HR 2.03, 95% CI 1.41–2.93). No meaningful differences were found in the rates of major adverse liver outcomes (MALO) or acute pancreatitis. **Conclusion:** Among patients with ALD, social deprivation

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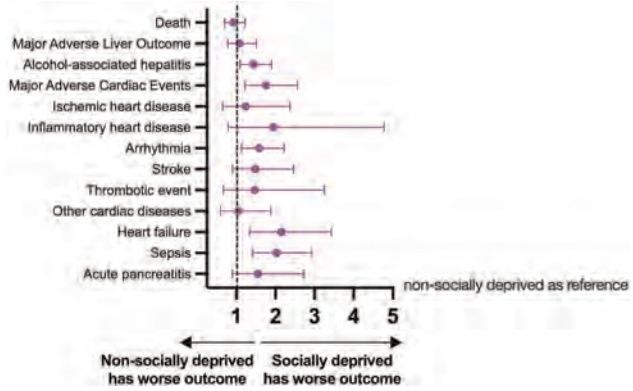
is independently linked to increased risks of cardiovascular events, sepsis, and alcohol-associated hepatitis. These results highlight the importance of addressing social vulnerabilities to improve health outcomes in this high-risk group.



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2212 | A LOWER SOCIAL DEPRIVATION INDEX IS ASSOCIATED WITH INCREASED MORTALITY AND MAJOR ADVERSE CARDIOVASCULAR EVENTS IN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE

Leith Ghani[1] Claire Faulkner[2] Majd Aboona[1] Pradhan Hariharan[1] Pooja Rangan[3] David Garcia[4] Vincent Chen[5] Donghee Kim[6] Juan Pablo Arab[7] Mazen Noureddin[8] Luis Díaz[9] Mike Fallon[10] Karn Wijarnpreecha[11], [1]University of Arizona College of Medicine - Phoenix, [2]Boston Medical Center, [3]Division of Clinical Data Analytics and Decision Support, University of Arizona College of Medicine, [4]University of Arizona Mel and Enid Zuckerman College of Public Health - Tucson, [5]University of Michigan Medical Center, [6]Stanford University Medical Center, [7]Virginia Commonwealth University, [8]Houston Methodist Hospital, [9]MASLD Research Center,Division of Gastroenterology and Hepatology,University of California San Diego, [10]University of Arizona, [11]University of Arizona College of Medicine-Phoenix

Background: Significant health disparities persist in alcohol-associated liver disease (ALD), largely driven

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by social determinants of health (SDOH). However, the influence of neighborhood-level SDOH on ALD outcomes remains underexplored. In this study, we aimed to evaluate how neighborhood-level SDOH impacts disease burden, comorbid conditions, and mortality in individuals with ALD. **Methods:** We conducted a retrospective cohort study of patients with ALD from 2012 to October 2024 in the Banner Health System, representing hospitals across Arizona, California, Nevada, Wyoming, and Colorado. We used ICD codes with a random chart review of over 250 cases to validate ICD codes for ALD and extrahepatic outcomes. Neighborhood-level SDOH were quantified using the Social Deprivation Index (SDI), a validated composite metric derived from American Community Survey data. Patients were stratified into quartiles based on SDI score, with Quartile 4 representing the most socioeconomically disadvantaged neighborhoods. Primary outcomes included the incidence of mortality, cirrhosis, liver-related events, type 2 diabetes mellitus, any cancer, and major adverse cardiovascular events (MACE). A multivariable competing risk analysis was performed adjusting for confounders. **Results:** Among 11,394 patients with ALD and available SDI data, 6,747 had $\geq$ 365 days of follow-up with average age 51 years and 65.6% are female. 68.8% were Non-Hispanic White, 19.7% Hispanic, 5.9% Native American/Alaskan Native (NA), 3.2% Black, and 0.4% Asian/Pacific Islanders. Patients residing in the most disadvantaged neighborhoods (Quartile 4) were significantly younger, more likely to be female, had higher average body max index, and more frequently reported a non-English primary language compared to those in the least disadvantaged areas (Quartile 1). Patients in the most deprived areas (Quartile 4) were more likely to be Hispanic, Black, or Native American/Alaska Native. Individuals in Quartile 4 were more likely to be uninsured or on Medicaid, whereas those in Quartile 1 predominantly had private insurance. Individuals in quartile 4 had an increased mortality (adjusted hazard ratio (aHR), 1.51; 95% Confidence Interval (CI) (1.11-2.04) and increased MACE (aHR 1.24; 95% CI, 1.02-1.51) compared to individuals in quartile 1. **Conclusion:** In this large and demographically diverse ALD cohort, residing in socioeconomically disadvantaged neighborhoods was associated with increased risk of mortality and MACE. These findings underscore the critical need for not only individualized clinical interventions but also broader intervention strategies that identify and target upstream social and environmental factors. Addressing neighborhood-level SDOH through community engagement, policy reform, and cross-sector collaborative partnerships may be essential to reducing health disparities in ALD.

Table 1. Competing risk analysis for death and incidence of disease by SDI quartile.

SDOH Quartile		Q1 SDI	Q2 SDI	Q3 SDI	Q4 SDI
Mortality[a]	aHR (95% CI)[b]	Referent	**1.45 (1.08-1.94)**	**1.24 (0.92-1.67)**	**1.51 (1.11-2.04)**
	p value		**0.01**	**0.16**	**<0.01**
Cirrhosis	aHR (95% CI)[b]	Referent	1.17 (0.95-1.46)	1.13 (0.90-1.41)	1.23 (0.97-1.56)
	p value		0.14	0.31	0.09
Liver-Related Events[c]	aHR (95% CI)[b]	Referent	1.08 (0.93-1.25)	1.10 (0.95-1.27)	1.04 (0.88-1.22)
	p value		0.33	0.21	0.65
Type 2 Diabetes Mellitus[d]	aHR (95% CI)[b]	Referent	1.18 (0.92-1.50)	**1.34 (1.06-1.70)**	1.26 (0.97-1.62)
	p value		0.19	**0.01**	0.08
Any Cancer	aHR (95% CI)[b]	Referent	1.08 (0.82-1.41)	0.83 (0.62-1.12)	0.92 (0.67-1.25)
	p value		0.58	0.22	0.58
MACE[e]	aHR (95% CI)[b]	Referent	1.16 (0.96-1.39)	1.06 (0.88-1.29)	**1.24 (1.02-1.51)**
	p value		0.12	0.53	**0.03**

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular event; SDI, Social Deprivation Index; SDOH, social determinants of health; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.
[a]Cox proportional hazards model was performed for mortality analysis.
[b]HR was adjusted for age, sex, race, insurance type, primary language, smoking status, type 2 diabetes mellitus, hypertension, hyperlipidemia, aspirin use, and statin use.
[c]Liver related events were defined as the incidence of hepatic encephalopathy, ascites, hepatocellular carcinoma, or variceal bleeding.
[d]For type 2 diabetes mellitus, HR was adjusted with the same confounders excluding type 2 diabetes mellitus.
[e]MACE is defined as the incidence of coronary artery disease, all-cause mortality, congestive heart failure, or cerebrovascular accident.

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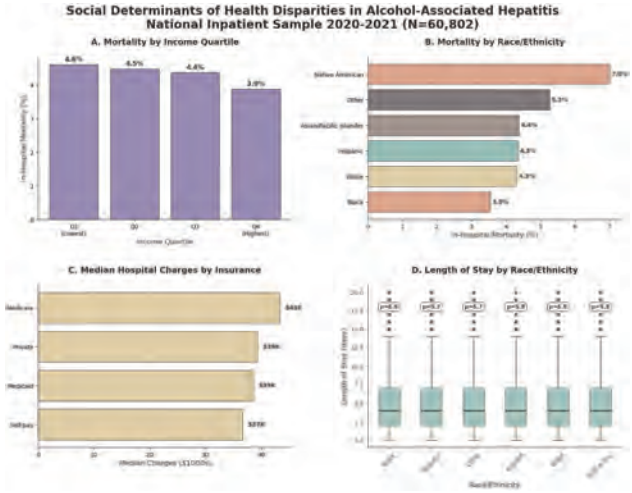
2213 | IMPACT OF SOCIAL DETERMINANTS OF HEALTH ON CLINICAL OUTCOMES IN ALCOHOL-ASSOCIATED HEPATITIS: A NATIONAL INPATIENT ANALYSIS 2020–2021

Nakul Ganju[1] Shubham Gupta[2] Shaunak Ganju[3] Juan Santiago-Gonzalez[1] Mesay Asfaw[1] Farshad Aduli[1], [1]Howard University Hospital, [2]Virtua Health, [3]Sidney Kimmel Medical College

Background: Alcohol-associated hepatitis (AH) is a severe liver disease with high morbidity and mortality, especially in hospitalized patients. AH-related hospitalizations are rising in the U.S., disproportionately among younger adults and women—a trend worsened by COVID-19. Though clinical outcomes are well studied, the role of social determinants of health (SDOH)—income, insurance, and geography—remains underexplored. **Methods:** We conducted a retrospective cohort study using 2020–2021 National Inpatient Sample (NIS) data to identify adults ($\geq$18) hospitalized with primary AH. Independent variables included income quartile, primary payer, and hospital location; outcomes were in-hospital mortality, length of stay (LOS), and total charges, adjusted via multivariable regression. **Results:** Among 31,273 AH hospitalizations, mortality was 4.9%, median LOS 4 days, charges $40,686. Lowest-income quartile had higher mortality (5.1% vs. 4.2%) and lower charges ($68,828 vs. $79,510) than highest; adjusted mortality odds were elevated (OR 1.22, 95% CI 0.99–1.51). Medicare patients had highest mortality (7.0%) and LOS (7.1 days); self-pay patients had lowest mortality (4.0%), LOS (5.5 days), charges ($60,843). Mortality was higher in rural hospitals (5.1%) vs. large metro centers (4.4%) and lowest in small metros. Black patients had shorter LOS, lower charges, and lower mortality ($\beta = -0.308$, $p = 0.0028$); Native Americans had higher mortality ($\beta = 0.496$, $p = 0.0007$). Asian/Pacific Islander, Hispanic, and other groups had higher charges without significant LOS or mortality differences. Disparities persisted after adjustment. Women had longer LOS despite similar mortality. SDOH differences suggest a need for stratified AH care. Resource use variation signals inefficiencies in care models. Subgroup trends may reflect delayed specialty access. Findings highlight equity gaps despite standardized settings. Unmeasured factors like alcohol severity or support may contribute. Regional variation in hospital capacity or care protocols may also influence disparities. Including clinical and behavioral data in future studies may improve precision. **Conclusion:** SDOH—including income, insurance, and race—independently influence AH outcomes and utilization. Persistent disparities, despite adjustment, imply systemic inequities in access, care quality, and resource allocation. This nationally representative analysis offers post-COVID insight into AH outcomes. The study quantifies cumulative SDOH effects, supporting their inclusion in risk models and care planning. Embedding SDOH in quality metrics may guide equity-focused reforms. Interventions addressing underinsurance, rural care gaps, and structural racism are essential to reduce disparities. Addressing these inequities is critical to improve AH survival and reduce alcohol-related liver disease burden.



Disclosures: Nakul Ganju: Nothing to Disclose, Shubham Gupta: Nothing to Disclose, Shaunak Ganju: Nothing to Disclose, Juan Santiago-Gonzalez: Nothing

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to Disclose, Mesay Asfaw: Nothing to Disclose, Farshad Aduli: Nothing to Disclose

2214 | DETERMINANTS OF CONTINUITY OF CARE BEYOND DIRECT-ACTING ANTIVIRAL INITIATION IN PATIENTS WITH HEPATITIS C

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Background: Hepatitis C virus (HCV), a major cause of chronic liver disease, affects an estimated 58 million people globally and remains a critical public health concern in the U.S. HCV disproportionately impacts underserved populations, including non-Hispanic Black individuals, those with a history of intravenous drug use (IVDU), and individuals of low socioeconomic status. While prior studies have assessed disparities in direct-acting antiviral (DAA) initiation, few have investigated the post-treatment continuum, including sustained virologic response (SVR-12) confirmation and ongoing hepatology follow-up. Here, we identify patient-level determinants of care continuity during and following DAA therapy. **Methods:** A retrospective cohort study was conducted among HCV patients who initiated DAA therapy between January 1, 2022 and December 15, 2024 within Northwell Health. Demographic and clinical variables included age, sex, race/ethnicity, language, insurance type, comorbidities, and route of infection. Primary outcome was continuity of care, defined by confirmed SVR-12 labs and post-treatment hepatology follow-up. Secondary analysis assessed AASLD-concordant HCC surveillance among cirrhotic patients. Logistic regression models adjusted for age, sex, and race were used to estimate odds ratios (OR) and 95% confidence intervals (CI). **Results:** Among 206 patients (mean age 60; 42.8% female), 47.1% were White and 23.5% Black. While continuity of care rates did not differ by race, patients with substance use disorder (SUD) enrolled in treatment programs had higher odds of missing SVR-12 labs (OR 4.2; $p = 0.008$), though this was attenuated after adjustment (aOR 2.9; $p = 0.073$). Mental health diagnoses remained significantly associated with lower SVR-12 lab completion (aOR 2.2; $p = 0.040$). Commercial insurance was protective (aOR 0.3 vs. Medicare; $p = 0.033$), and lower copay amounts were associated with continuity of care (aOR 0.9; $p = 0.044$). In cirrhotic patients ($n = 74$), younger age (OR 0.9; $p = 0.020$) and non-English language (OR 0.14; $p = 0.059$) were associated with increased adherence to HCC surveillance guidelines. **Conclusion:** Disparities in HCV care continuity persist even after DAA initiation. Psychiatric illness, substance use, insurance type, and out-of-pocket costs contribute to gaps continued follow up beyond DAA initiation. Surprisingly, non-English speakers demonstrated improved follow-up in cirrhotics, suggesting potential benefits of targeted language-concordant care. Culturally tailored, low-barrier interventions addressing mental health, substance use, and financial access are critical to achieving equity in HCV outcome.

Table 1. Baseline Characteristics

Covariates	N= 206
Age	60 [46 – 74]
Female Sex	89 (42.8%)
Race/Ethnicity	
White	98 (47.1%)
Black	49 (23.5%)
Hispanic	13 (6.3%)
Asian	14 (6.7%)
Other	22 (10.6%)
Unknown	11 (5.3%)
Primary Language	
English	171 (82.2%)
Spanish	14 (6.7%)
Other	22 (10.6%)
Percent below poverty level (Zip code)	9.2 (3.6 – 15.0)
Comorbidities	
Substance use disorder	33 (15.9%)
Substance use disorder (enrolled in a program)	16 (7.7%)
Alcohol use disorder	29 (13.9%)
Mental health diagnoses	38 (18.3%)
HIV	5 (2.4%)
Other medical comorbidities	160 (76.9%)
Insurance type	
Commercial	49 (23.6%)
Medicaid	59 (28.4%)
Medicare	93 (44.7%)
Uninsured	6 (2.9%)
Copay ($/month)	
Without Financial Aid	857.46 (±3,323.11)
With Financial Aid	74.62 (±532.39)
Number of patients with Financial Aid	47 (22.6%)

Disclosures: WonKyung Cho: Nothing to Disclose, Timea Csak: Nothing to Disclose, Ngan Nguyen: Nothing to Disclose

2215 | UNMASKING HEALTH DISPARITIES IN APPALACHIA: THE IMPACT OF THE COVID-19 PANDEMIC ON LIVER RELATED MORTALITY

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Background: According to the Centers for Disease Control and Prevention (CDC), chronic liver disease (CLD) was the 10th leading cause of death in the United States as of 2022. Previous studies have highlighted geographic hotspots for CLD mortality, with central Appalachia experiencing an increasing CLD prevalence prior to the COVID-19 pandemic. However, a study conducted in collaboration with the Appalachian Regional Commission (ARC) found no significant difference in CLD mortality between Appalachian counties (AC) and non-Appalachian counties (nAC) across the 13 states served by the ARC from 1999 to 2015. The

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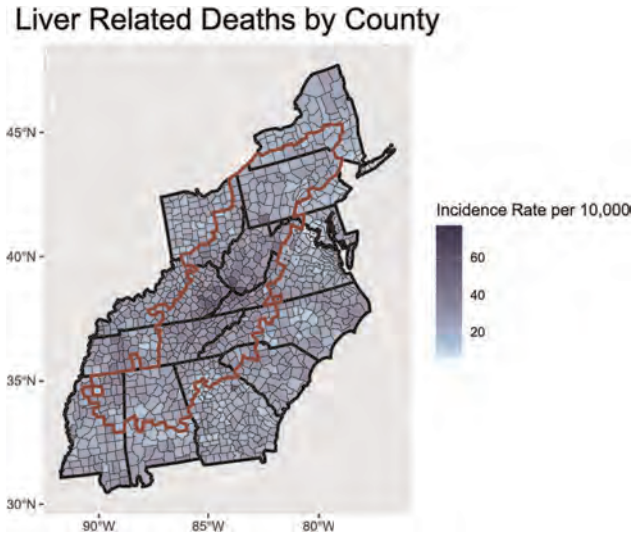
prevalence of the CLD has continues to rise through the COVID-19 pandemic with data from the ARC for 2019 showing increase in the rates of cirrhosis in both AC and nAC. Despite these trends, the disparities in CLD mortality between AC and nAC post-pandemic have not been adequately examined. This study aims to address this gap by investigating the evolving disparities in CLD mortality in wake of the COVID-19 pandemic. **Methods:** This cross-sectional study used mortality data from the CDC from 1/1/2018 – 9/15/2018 for the 13 states containing Appalachian counties. ICD-10 codes for alcohol-associated liver disease, cirrhosis, liver cancers, primary biliary cholangitis and primary sclerosing cholangitis were included. Counties with less than 10 deaths were excluded. Deaths per 10,000 were calculated as incidence ratios (IR) using 2020 U.S. Census data at the county level. Death rates were compared between AC and nAC, overall and at the state level. Statistical analyses were conducted using R-studio version 4.4.2 (R Foundation for Statistical Computing,Vienna, Austria). **Results:** 1,098 counties across 13 states were included. In all states, the AC had higher combined liver related deaths per 10,000 than nAC. The highest IRs by state were observed in West Virginia (WV) at 37.55 (36.65-38.46) followed by Kentucky at 32.33 (31.80-32.85). The AC in Kentucky had the highest crude IR at 42.22 (41.04-43.42). The lowest crude IR was New York at 16.80 (16.62-16.98). Virginia had the largest gap with ACIR being 23.69 points higher than nAC IR. Using geographical mapping, a mortality hotspot was identified in the Kentucky, West Virginia, and Virginia (figure 1). Using negative binomial regression, AC had an incidence rateratio of 1.30 ($p < 0.001$) compared to nAC. **Conclusion:** Previously, the ARC showed no difference between AC and nAC prior to 2019. As the incidence of CLD rises, we now identified that liver related mortality is 1.3 times higher in AC. Central Appalachia has the highest IR of liver deaths, likely related to the disproportionate increase in CLD previously documented in this region.



Disclosures: Jordan Woodard: Nothing to Disclose, Katharine Cook: Nothing to Disclose, Kory Heier: Nothing to Disclose, Kristen McQuerry: Nothing to Disclose, Nimish Thakral: Nothing to Disclose

2216 | PREVALENCE OF ADVANCED HEPATIC FIBROSIS AND STEATOSIS IN AN UNDERSERVED HISPANIC POPULATION

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Background: Increased risk of metabolic dysfunction-associated steatotic liver disease (MASLD) and cirrhosis in the Hispanic community is well-established.[1] However most studies have occurred in a healthcare setting and among those with health insurance and may not be representative of the Hispanic community as a whole which has among the lowest rates of health insurance coverage.[2] In order to assess the prevalence of MASLD and hepatic fibrosis in an underserved Hispanic community, we performed transient elastography measurements in patients presenting for free health services through the Ventanilla de Salud. **Methods:** The Ventanilla de Salud is a free service sponsored by the Mexican Consulate that provides free health services and screenings regardless of national origin, insurance, or immigration status. We performed transient elastography measurement in 209 consecutive patients who presented to the Ventanilla de Salud. MASLD was defined as a CAP score $\geq$ 285 dB/m, advanced fibrosis as a liver stiffness $\geq$ 8.5 kPa, and cirrhosis as liver stiffness $\geq$ 13 kPa. We also collected patient reported comorbidities, comprehensive metabolic panel, anthropomorphic measurements, and a brief survey about healthcare access. **Results:** Among 209 patients, 87 (42.2%) had evidence of MASLD and 31 (15%) had advanced fibrosis, and 9 (4.4%) had cirrhosis by transient elastography. The cohort had a mean age of 50 years, 21.9% had a known history of type 2 diabetes, 44.7% had a BMI $\geq$ 30 kg/m^2, 55.6% were uninsured, and 34.9% had a total household income $<$ \$35,000/year. Those with advanced fibrosis had a significantly higher BMI, AST, and ALT. Of note, none were aware of any prior diagnosis of liver disease. The primary reported reason for not having a routine source of healthcare was “seldom or never get sick” (44.2%) followed by lack of health insurance (15.4%). Nearly half (45.2%) of those with advanced fibrosis on transient elastography reported they do not seek medical care because they “seldom or never get sick” (Table 1). **Conclusion:** In an unselected cohort of Hispanic subjects with limited access to healthcare, the

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prevalence of MASLD was 42.2% and advanced fibrosis was 15%. While the majority of patients were uninsured (55.6%) and a significant proportion low income (34.9%), most patient reported they did not have a routine source of healthcare since they "seldom or never got sick". None were previously aware of any chronic liver disease. These findings point to improved screening, patient education, and community awareness as potential interventions to improve early diagnosis and management of MASLD in the Hispanic community.

Table 2. Demographics by advanced fibrosis (kPa ≥ 8.5)

	No advanced fibrosis (n = 175)	Advanced fibrosis (n = 31)	p value
Age (years, SD)	49.86 (12.3)	50.8 (12.8)	0.69
Male (n)	60 (34.3)	8 (25.8)	0.47
Type 2 diabetes (n)	34 (19.4)	10 (32.3)	0.17
Hypertension (n)	24 (13.7)	5 (16.1)	0.94
Coronary artery disease (n)	0 (0)	0	NA
Chronic liver disease (n)	0 (0)	0	NA
Chronic kidney disease (n)	0 (0)	1 (3.2)	0.33
BMI (kg/m2)	29.49 (5.47)	32 (6.2)	0.02
Obese (n, BMI ≥ 30 kg/m2)	75 (42.9)	17 (54.8)	0.3
Body fat percentage	38.34 (9.5)	41.1 (8.2)	0.13
Muscle	58.94 (46.1)	57 (17.9)	0.82
Creatinine (mg/dL)	0.8 (0.21)	0.71 (0.15)	0.01
ALT (U/L)	29.43 (13.68)	44 (28.7)	<0.001
Elevated ALT (n, ≥ 30)	60 (35.1)	18 (58.1)	0.03
AST (U/L)	28.45 (8.6)	43.9 (29.7)	<0.001
Total bilirubin (mg/dL)	0.93 (0.3)	0.95 (0.4)	0.75
Alkaline phosphatase (U/L)	89.89 (21.6)	89.4 (27.9)	0.03
CAP (dB/m)	270.5 (56)	278.9 (64.2)	0.45
MASLD (n, CAP ≥ 285 dB/m)	70 (40)	17 (54.8)	0.18
Liver stiffness (kPa)	4.77 (1.4)	20.5 (44.9)	<0.001
Insurance (n)			0.5
Private	47 (27.3)	10 (32.3)	
Public	31 (18.0)	3 (9.7)	
Uninsured	94 (54.7)	18 (58.1)	
Income (n)			0.53
<$10,000	8 (4.6)	0 (0)	
$10,001-$24,999	26 (14.9)	6 (19.4)	
$25,000-$34,999	25 (14.4)	7 (22.6)	
$35,000-$49,999	32 (18.4)	5 (16.1)	
$50,000-$74,999	42 (24.1)	3 (9.7)	
$75,000-$99,999	14 (8)	3 (9.7)	
$100,000-$199,999	14 (8)	4 (12.9)	
>$200,000	2 (1.1)	0 (0)	
Prefer not to answer	11(6.3)	3 (9.7)	
Is there a particular doctor's office, clinic, health center or other you would go to if you need advice about your health?			0.24
No	47 (26.9)	4 (12.9)	
Yes	128 (73.1)	27 (87.1)	
Would you go to one of these placed if you are sick?			0.18
No	43 (24.6)	3 (9.7)	
Yes	132 (75.4)	28 (90.3)	
What is the main reason you do not have a usual source of health care?			0.59
Seldom or never get sick	77 (44)	14 (45.2)	
No health insurance	21 (12)	7 (22.6)	
Other	23 (13.1)	7 (22.6)	
I don't know	5 (2.9)	0 (0)	
I don't know where to go for care	3 (1.7)	0 (0)	
I don't use doctors	1 (0.6)	0 (0)	
I have insurance	21 (12)	2 (6.5)	
I just changed insurance plans	6 (3.4)	0 (0)	
I go to different places for different health care needs	4 (2.1)	1 (3.2)	
Recently moved	10 (5.7)	0 (0)	
Usual source of health care no longer available	1 (0.6)	0 (0)	

Disclosures: Christopher Danford: Ipsen Pharmaceuticals: Advisor, Gabriela Portugal-Bouza: Nothing to Disclose, Silvia Rosas: Nothing to Disclose, Ivan Zendejas: Nothing to Disclose

2217 | PERSISTENT LIVER INJURY AND RECURRENCE AFTER HELLP SYNDROME: INCIDENCE AND OUTCOMES IN A RETROSPECTIVE COHORT (2009–2024)

Nina Rodriguez[1] Cecilia Katzenstein[1] Keith Sigel[1] Rhoda Sperling[1] Tatyana Kushner[2], [1]Icahn School of Medicine at Mount Sinai, [2]Weill Cornell Medicine

Background: Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is a severe obstetric complication with significant morbidity. While acute management is well described, data on hepatic recovery and outcomes in subsequent pregnancies is limited. We aim to characterize the acute complications and longitudinal hepatic and obstetric outcomes in patients with HELLP. **Methods:** We conducted a retrospective cohort study of singleton HELLP pregnancies at a large academic center (2009-2024). Data was extracted from the electronic medical record. We defined persistent ALT elevation as > 25 U/L within 6 months postpartum (PP). Variables were compared using Fisher's exact tests and t-tests. Time-to-event analysis was performed using a Cox proportional hazards model. **Results:** A total of 91 patients were identified (mean age 33 yrs; BMI 28 kg/m²); 51% were White, 19% Hispanic, 16% Black, 8% Asian. Six-month PP data was available for 53%; 76% had any post-delivery follow-up. Preexisting hypertensive disorders were present in 18%, prothrombotic conditions in 14%. Median gestational age at diagnosis was 36 weeks; 31% met Mississippi Class I criteria and 15% required ICU care. Acute hepatic complications were rare (two liver failures, one capsule rupture). Acute non-hepatic complications occurred in 16%: AKI (8%), pulmonary edema (4%), eclampsia (3%), DIC (2%), PRES (2%). Fetal outcomes include intrauterine demise (7%) and NICU admission (48%). ALT normalized in 52% by 6 months PP (median 34 days); 89% normalized at any point post-delivery (median 354 days). No preexisting factors were significantly associated with normalization (Table 1). Six-month PP follow-up was more common in patients with IVF pregnancies, ICU admission, higher peak ALT, and acute complications (all $p < 0.05$). Time to ALT normalization was shorter in those with acute non-hepatic complications (HR 2.5 95% CI 1.1-5.8). No new chronic liver diseases were documented in follow-up, though three patients had incidental hepatic steatosis on imaging. Among 27 patients with a subsequent pregnancy, HELLP recurred in 23% (median interval: 25 months). **Conclusion:** Liver injury persisted in many patients after HELLP, yet follow-up was inconsistent and more common in those with

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severe presentations. This raises concern that delayed hepatic recovery may go unrecognized in those perceived as lower risk. This underscores the need for structured surveillance after HELLP to ensure timely recognition of lingering hepatic injury. Given the risk of recurrence in future pregnancies, anticipatory counseling and interdisciplinary follow-up should also be integral to PP care.

Table 1. Demographic, Clinical, and Obstetric Characteristics by ALT Normalization Status Within 6 Months Postpartum

Variable	Normal ALT within 6 months PP (n=25)	Elevated ALT within 6 months PP (n=23)	p
Mean Age (years) (SD)	34.8 (6.4)	32.4 (5.5)	0.169
Mean BMI (kg/m²) (SD)	24.7 (6.9)	26.5 (4.6)	0.301
Hispanic ethnicity (%)	4 (16%)	8 (35%)	0.187
Race (%)			0.096
White	9 (36%)	12 (52%)	
Black	8 (32%)	1 (4%)	
Asian	3 (12%)	2 (9%)	
Other	5 (20%)	7 (40%)	
Past medical history			
Genetic or acquired hypertensive disorder (%)	6 (24%)	5 (22%)	1.00
Type II diabetes mellitus (%)	2 (8%)	-	0.490
Autoimmune disease (%)	4 (16%)	6 (26%)	0.487
Prothrombotic condition (%)	4 (16%)	3 (13%)	1.00
Obstetric characteristics (%)			
Gestational age at diagnosis (days) (IQR)	247 (218-263)	257 (223-268)	0.556
IVF pregnancy (%)	6 (24%)	4 (17%)	0.727
Nulliparity (%)	11 (44%)	15 (65%)	0.161
Gestational diabetes (%)	3 (12%)	4 (17%)	0.696
Suspected intrahepatic cholestasis of pregnancy (%)	3 (12%)	1 (4%)	0.610
Fetal growth restriction (%)	4 (16%)	5 (22%)	0.719
Cesarean section (%)	16 (64%)	17 (74%)	0.542
NICU admission (%)	15 (60%)	7 (33%)	0.085
Fetal demise (%)	2 (8%)	4 (17%)	0.407
Laboratory values			
Median peak ALT (IQR)	315 (175-442)	377 (145-613)	0.799
Median peak AST (IQR)	335 (178-513)	404 (158-678)	0.556
Median peak LDH (IQR)	727 (498-1109)	704 (461-1166)	0.892
Median minimum platelets (IQR)	63 (32-73)	55 (28-95)	0.732
Mississippi Class I (%)	8 (32%)	11 (48%)	0.377
ICU admission (%)	9 (36%)	4 (17%)	0.200
Composite acute non-hepatic complication (%)	8 (32%)	4 (17%)	0.324
Acute hepatic complication (%)	2 (8%)	1 (4%)	1.00

Disclosures: Nina Rodriguez: Nothing to Disclose, Cecilia Katzenstein: Nothing to Disclose, Keith Sigel: Nothing to Disclose, Rhoda Sperling: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support

2218 | HBV VACCINATION STATUS AMONG INDIVIDUALS IN THE NYC JAIL SYSTEM BORN BEFORE AND AFTER US UNIVERSAL CHILDHOOD VACCINATION RECOMMENDATIONS

Chibuzo Enemchukwu[1] Batya Koenigsberg[1] Raphael Simonson[1] Malia Mackey[1] Natalia Gonzalez Varela[1], [1]NYC Health+Hospitals

Background: Hepatitis B virus (HBV) vaccination is critical for the prevention of HBV infection and potential sequelae. Vaccination is recommended for adults 18-59 years, and for all adults with risk, such as incarceration. Additionally, universal vaccination of all infants has been recommended in the US since 1991. HBV vaccination status is not well studied in the jail setting. This study aims to examine HBV vaccination status among persons in the NYC jail system born before and after universal infant vaccination recommendations. Results will provide critical insights into potential HBV prevention strategies for short-stay carceral settings. **Methods:** This retrospective study included all individuals in the NYC jail system between October 2019 and December 2023 who had HBV serologic testing in our system. We divided the sample into two cohorts: (1) those born before November 22, 1991 (pre-recommendation (pre-rec)), and (2) those born after (post-recommendation (post-rec)). We used multivariate regression to examine differences in HBV susceptibility, vaccination status, and past infection (HBV core-antibody positivity) by birth cohort. Regressions were adjusted for histories of serious mental illness, select substance use disorders, HIV, hepatitis C, housing status, jail length of stay, gender, and number of previous incarcerations in the prior year. **Results:** Our study comprised 2282 persons, of whom 2014 (88.3%) were men, and 268 (11.7%) women. 1912 persons (83.8%) were in the pre-rec cohort, and 370 persons (16.2%) in the post-rec cohort. The post-rec cohort had higher odds of susceptibility to HBV (adjusted odds ratio [aOR] = 1.42, 95% CI: 1.12-1.82), higher odds of HBV vaccination (aOR = 1.71, 95% CI: 1.35-2.15), and lower odds of past HBV infection (aOR = 0.181, 95% CI: 0.117-0.278) when compared to the pre-rec cohort. **Conclusion:** Individuals born after universal HBV infant vaccination recommendations were more likely to be vaccinated for HBV, yet were also more likely to be susceptible to HBV and therefore vaccine-eligible. We found that these individuals were also less likely to have had past HBV infection, compared to those born before universal infant HBV vaccine recommendations. These findings suggest that birth cohort stratification may not be an effective strategy for targeted HBV screening and prevention protocols in short-stay carceral settings.

Disclosures: Chibuzo Enemchukwu: Nothing to Disclose, Batya Koenigsberg: Nothing to Disclose, Raphael Simonson: Nothing to Disclose, Malia Mackey: Nothing to Disclose, Natalia Gonzalez Varela: Nothing to Disclose

2219 | HIGHER MORTALITY AMONG WHITE PATIENTS AND LOWER WAITLISTING AMONG BLACK PATIENTS WITH CIRRHOSIS: A RETROSPECTIVE STUDY USING REAL-WORLD DATA

Saad Hussain[1] Paola Barrios[1] Suyanpeng Zhang[1] Dominic Vitello[1] Sijia Wei[1] Salva Balbale[1] Oriana

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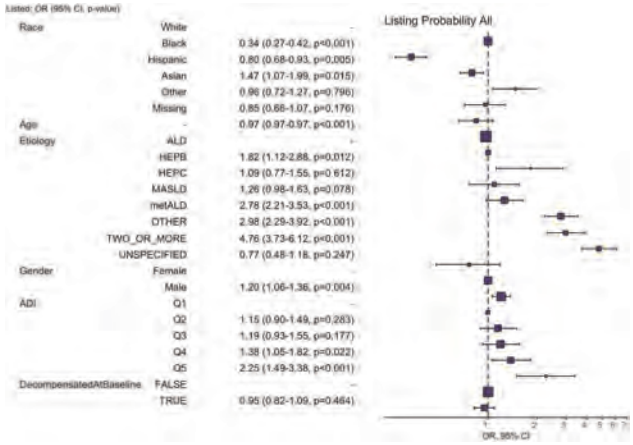
Dentici[1] Al'ona Furmanchuck[1] Nikhilesh Mazumder[2] Lisa VanWagner[3] Lihui Zhao[1] Andres Duarte-Rojo[4] Sanjay Mehrotra[1] Daniela Ladner[1], [1]Northwestern University, Chicago, IL, [2]University of Michigan Hospitals and Health Centers, [3]University of Texas Southwestern Medical Center, [4]Northwestern Medicine

Background: Liver transplant is a curative treatment for patients with cirrhosis. We examined mortality, waitlisting and liver transplant rates by race/ethnicity.
Methods: CAPriCORN, a large EHR data repository across 7 health care systems in a large US metropolitan area, was used to identify adult patients with cirrhosis from 2016-2021. Demographics and clinical factors were collected including age, sex, race/ethnicity, etiology, Area Deprivation Index (ADI) [Q1: high resourced, Q5: low resourced) and decompensation. Outcomes included all-cause mortality, waitlisting and transplant. HCC was excluded from mortality but included in waitlisting and transplant analyses. Multivariable Cox proportional hazard models were used to assess mortality and multivariable logistic regression to assess waitlisting and transplant probability. Significance = $P < 0.05$. **Results:** 18,718 patients with cirrhosis were included. Mean age was 59.8, 43.1% were women, 45% were white, 19% black, 21% Hispanic. Most common etiologies were MASLD (28.6%), MetALD (23.1%), ALD (12.8%). ADI (Q1: 5.7%, Q2: 30.8%, Q3: 36.4%, Q4: 23.6%, Q5: 2.4%). 29.7% were decompensated at inclusion. Mortality per 100 PY was 13.26 (white: 16.13, black: 9.08, Hispanic: 8.86 per 100PY). Waitlisting occurred in 9.63% of white, 3.83% of black, and 7.48% of Hispanic patients. Transplant occurred in 7.26% of white, 2.8% of black patients and 7.06% of hispanic patients. Adjusted mortality was highest in white patients; black (HR 0.52, 95% CI 0.46–0.60) and Hispanic (HR 0.59, 95% CI 0.52–0.67) patients had significantly lower mortality ($P < 0.001$). Black patients had lower odds of waitlisting compared to white patients (OR 0.34, 95% CI 0.27–0.42, $P < 0.001$), but similar odds of transplant once listed (OR 0.86, 95% CI 0.51–1.51, $P = 0.6$). (Figure) **Conclusion:** In a real-world cohort of patients with cirrhosis living in a metropolitan area, white patients have the highest all-cause mortality, while black patients were significantly less likely to be waitlisted. However, transplant probability was similar for white and black patients once waitlisted, suggesting differences in transplant access.



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2220 | RACIAL DIFFERENCES IN FIBROSIS PROGRESSION AFTER LIVER TRANSPLANTATION

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Background: Liver transplant remains an important tool in the treatment of end stage liver disease. However, the progression of post-transplant fibrosis has not been studied thoroughly in different racial groups. We hypothesized that the progression of post-transplant fibrosis varies in different racial groups, and examined this progression histologically. **Methods:** We examined all adults who had a liver biopsy with a transplant at our institution from January 1, 2013 through July 1, 2021. Histology, fibrosis stage, rejection activity index (RAI) and complete clinical data were abstracted via the medical record. We included only patients who had undergone liver transplantation, and excluded patients having a biopsy specifically to

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evaluate liver lesions. The median time to developing fibrosis levels (F0-F4) was calculated. Race was self-identified by patients. **Results:** Of 515 transplant patients having a liver biopsy, we identified 206 White and 69 Black patients who had fibrosis staged (a total of 688 biopsies among these patients). White patients were significantly older than Black patients at the time of transplant (53 (+/- 0.7) vs 46 (+/- 1.7) years, respectively ($p < 0.01$)). White patients were significantly more likely to be male, and Black patients were significantly more likely to be female. White patients were significantly more likely to have ALD and MASLD than Black patients (44/206 (21%) vs 2/69 (3%);32/206 (16%) vs 2/69 (3%), respectively; each $p < 0.01$), whereas Black patients were significantly more likely to have AIH, PBC, and PSC than White patients (20/69 (29%) vs 19/206 (9%); 7/69 (10%) vs 6/206 (3%); 9/69 (13%) vs 6/206 (3%), respectively; each $p < 0.01$). The median time to develop F4 fibrosis was 6 years in White patients and 9 years in Black patients (Figure 1). Sensitivity analysis of liver disease etiology by race demonstrated that this trend of more rapid fibrosis progression was preserved in White patients, with the exception of HCV, where Black patients had a slightly higher rate of fibrosis progression. **Conclusion:** In conclusion, White patients appear to have more rapid fibrosis progression than Black patients after liver transplantation. It should be recognized that the causes of liver disease leading to transplant are different in Black and White patients, and may represent a confounding factor for fibrosis progression; however, sensitivity analysis of this generally demonstrated the same trend.

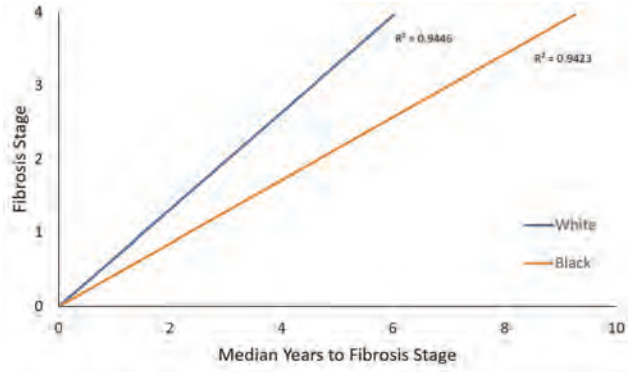

Figure 1. Median years to fibrosis stage. All liver biopsies taken in Black and White patients were analyzed and the median time to develop each stage of fibrosis was calculated and plotted. Biopsies in White patients: n = 480; Biopsies in Black patients: n = 208

Disclosures: Michael Attanasi: Nothing to Disclose, Mathew Gregoski: Nothing to Disclose, Don Rockey: WL Gore and Associates: Consultant, Cook Medical: Consultant, BD Medical: Consultant, AstraZeneca: Grant/Research Support, Bio89: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Durect: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Intercept: Grant/Research Support, Inventiva: Grant/Research Support, Madrigal: Grant/Research Support, Ocelot: Grant/Research Support, Salix: Grant/Research Support, Novonordisk: Grant/Research Support, Galectin: Grant/Research Support, Versantis: Grant/Research Support, Viking: Grant/Research Support

2221 | GLOBAL BURDEN AND TRENDS OF LIVER CANCER IN INDIVIDUALS < 20 YEARS IN 204 COUNTRIES AND ITS TERRITORIES: A 30-YEAR GLOBAL EPIDEMIOLOGICAL PERSPECTIVE

Sandeep Kotnani[1] Raghava Rao Alluri[2] Ker Patel[3] Parvinder Kaur[4] Madhu babu Adusumilli[5] Mili Ashar[6] JUHI PATEL[7] Yashkumar Kamani[8] Hardik Zinzala[9] VISHRANT AMIN[10] Hardik Desai[11], [1]Rutgers Monmouth Medical Center, [2]Prime South GME Consortium/Harlingen Medical Center Program, [3]Surat Municipal Institute of Medical Education and Research, Surat,India, [4]The Crimean State Medical University named after S.I.Georgievsky, Simferopol, Ukraine, [5]HCA Ocala Florida hospital -UCF, [6]Rural Medical College, Lonhi, Maarashtra (Pravara Institute of Medical Sciences), [7]GMERS Medical College Valsad, [8]"BronxCare Health System ", [9]Jonelta foundation school of medicine, [10]HMH JFK University Medical Center, [11]Independent Clinical and Public Health Researcher

Background: Although liver cancer is typically associated with adult populations, its occurrence in individuals under 20 years of age poses a significant yet underexplored public health concern. Emerging evidence highlights distinct etiologies, such as viral hepatitis, alcohol use, non-alcoholic steatohepatitis (NASH), and hepatoblastoma, which contribute to this burden. Understanding long-term trends in prevalence, incidence, and mortality is crucial for informing early interventions and global pediatric cancer strategies. **Methods:** We utilized data from the Global Burden of Disease (GBD) 2021 framework to assess liver cancer trends among individuals aged < 20 years across 204 countries and territories between 1990 and 2021. We examined temporal changes in prevalence, incidence, and deaths due to various liver cancer etiologies and calculated the Annual Percentage Change (APC) to quantify trends. Subgroup analyses were conducted by region, age, sex, and cause-specific attribution. **Results:** The greatest rise in global prevalence was attributed to liver cancer due to NASH, with an APC of +1.96% (from 176 in 1990 to 283 in 2021), followed by alcohol use (+0.94%; from 16 to 21), hepatitis C (+0.55%; from 41 to 48), and other causes (+0.20%; from 508 to 541). In contrast, hepatoblastoma showed a marked decline (APC: –1.28%; from 56,183 to 33,829), along with

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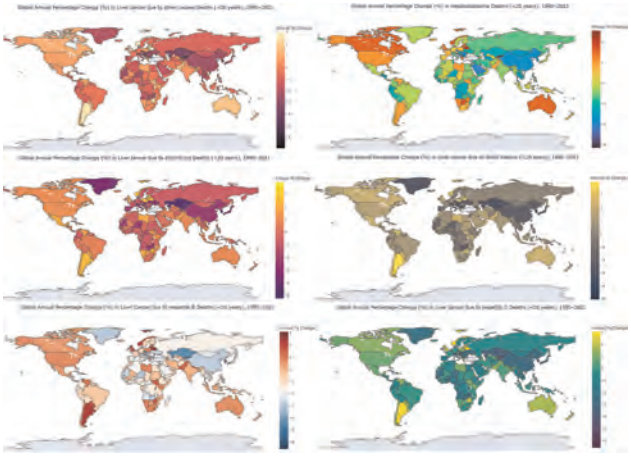
hepatitis B (–0.81%; from 1,565 to 1,169). Regionally, Sub-Saharan Africa reported the highest APC in liver cancer incidence (+0.26%) and deaths (+0.35%), whereas other regions experienced a decline. Among age groups, the highest incidence rate in 2021 was noted in infants aged 6–11 months (1.23 per 100,000; 95% UI: 0.93–1.59). Notably, the 15–19-year age group experienced the highest total percentage change (TPC) in incidence due to hepatitis C (24%), alcohol use (23%), and NASH (55%). Gender-specific analysis revealed a greater TPC in deaths among females compared to males for NASH (55% vs 39%), alcohol-related liver cancer (25% vs 12%), and hepatitis C (18% vs 4%). **Conclusion:** Liver cancer in the pediatric and adolescent population shows a heterogeneous pattern across causes and regions. The rising burden of NASH and alcohol-related liver cancer, particularly among older adolescents and females, underscores the need for early life preventive strategies and global pediatric oncology surveillance. Focused interventions targeting metabolic and infectious etiologies could curb this emerging burden in youth populations.



Disclosures: Sandeep Kotnani: Nothing to Disclose, Raghava Rao Alluri: Nothing to Disclose, Ker Patel: Nothing to Disclose, Parvinder Kaur: Nothing to Disclose, Madhu babu Adusumilli: Nothing to Disclose, Mili Ashar: Nothing to Disclose, JUHI PATEL: Nothing to Disclose, Yashkumar Kamani: Nothing to Disclose, Hardik Zinzala: Nothing to Disclose, VISHRANT AMIN: Nothing to Disclose, Hardik Desai: Nothing to Disclose

2222 | DISPARITIES IN MORTALITY TRENDS OF ALCOHOLIC LIVER FAILURE WITH MENTAL AND BEHAVIORAL DISORDERS IN THE U.S., 1999–2020: INSIGHTS FROM THE CDC WONDER DATABASE

Sandeep Kotnani[1] Yashkumar Kamani[2] Raghava Rao Alluri[3] Mahendra Kumar[4] Fagun Viramgama[5] Nimrat Dhillon[6] Nivid Patel[7] Mahir Modi[8] VISHRANT AMIN[9] Dhrumil Sakariya[10] Hardik Desai[11], [1]Rutgers Monmouth Medical Cente, [2]BronxCare Health System, [3]Prime South GME Consortium/Harlingen Medical Center Program, [4]Sardar Patel Medical College, Bikaner, India, [5]Surat Municipal Institute of Medical Education and Research (SMIMER),Surat, India, [6]Sri guru Ram das institute of medical sciences and research, vallah, Amritsar, Punjab, [7]American university of Barbados, [8]GCS Medical College Hospital and Research Centre, [9]HMH JFK University Medical Center, [10]Davao Medical School Foundation Poblacion District,Davao City, Philippines, [11]Independent Clinical and Public Health Researcher

Background: Alcoholic liver failure (ALF) is a medical emergency with high fatality, increasingly linked to the rising burden of mental and behavioral disorders (MBDs) in the U.S. Disorders such as alcohol use disorder, depression, and schizophrenia not only drive chronic alcohol misuse but also delay management of liver injury. Despite this critical overlap, the contribution of MBDs to ALF remains poorly quantified. **Methods:** We utilized nationally representative mortality data to assess the burden of ALF with coexisting MBDs in the U.S. from 1999 to 2020. Both absolute and age-standardized mortality rates were used to calculate the annual percent change (APC). Analyses were stratified by age, sex, year, race, location to identify demographic and geographic disparities. **Results:** From 1999 to 2020, the total number of deaths increased from 3,461 to 6,370, with a sharp rise observed between 2007-2020 at an APC of 8.83%. Across U.S. Census Regions, the Midwest showed the highest annual percent change (APC) in deaths at +1.91%, followed by the South (+0.54%), while the West experienced a decline (–1.79%). By 2013 urbanization levels, the highest APC was noted in small metro areas (+1.72%) and micropolitan nonmetro regions (+1.68%), with the lowest in large fringe metro areas (+0.34%). State-level analysis revealed the most pronounced increases in Indiana (+6.16%), Minnesota (+5.38%), and Iowa (+4.32%). Racial disparities were evident, with American Indian or Alaska Native populations experiencing the highest APC (+1.36%), while Black or African American populations showed a decline (–2.25%). By Hispanic origin, deaths increased among non-Hispanic individuals (+0.11%) but declined significantly among Hispanic or Latino populations (–1.71%). Age-wise, the sharpest rise was observed in the 55–64 age group (+2.64%), followed by 25–34 years (+2.15%), whereas a decline was noted in those aged 75–84 (–1.72%). Lastly, gender-based trends indicated an increase among females (+0.45%) and a slight decline among males (–0.33%). **Conclusion:** The rising mortality from ALF in individuals with MBDs—especially among American Indian populations,

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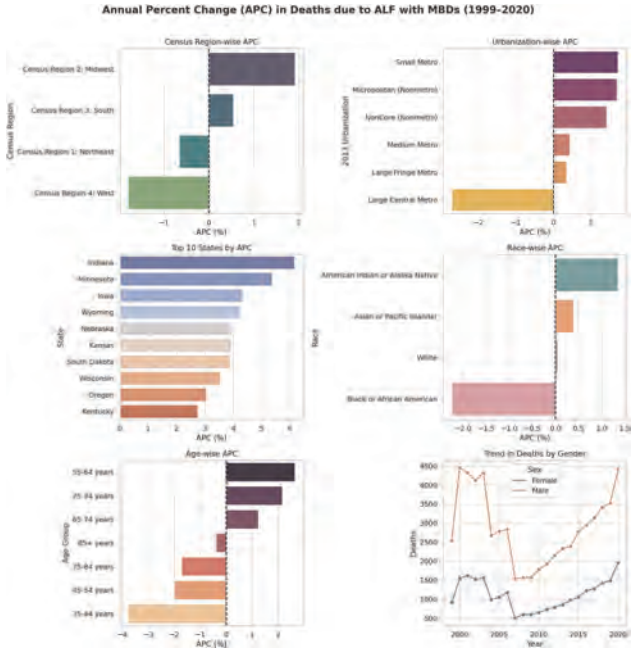
midwestern states, and adults aged 25–64—highlights a growing syndemic. This trend demands urgent, integrated strategies that combine mental health and liver care, with culturally tailored interventions and expanded access in high-risk, underserved communities.



Disclosures: Sandeep Kotnani: Nothing to Disclose, Yashkumar Kamani: Nothing to Disclose, Raghava Rao Alluri: Nothing to Disclose, Mahendra Kumar: Nothing to Disclose, Fagun Viramgama: Nothing to Disclose, Nimrat Dhillon: Nothing to Disclose, Nivid Patel: Nothing to Disclose, Mahir Modi: Nothing to Disclose, VISHRANT AMIN: Nothing to Disclose, Dhrumil Sakariya: Nothing to Disclose, Hardik Desai: Nothing to Disclose

2223 | ALCOHOL INTAKE ADJUSTMENT AND PREVIOUS HISTORY OF ALCOHOL USE UNCOVER HIDDEN RISK OF PREMATURE MORTALITY AMONG PATIENTS WITH STEATOTIC LIVER DISEASE

James Paik[1] Dana Ivancovsky Wajcman[2] Shira Zelber-Sagi[3] Andrei Racila[2] Saleh Alqahtani[4] Zobair Younossi[2], [1]Beatty Liver and Obesity Research Program, [2]The Global NASH Council, [3]Tel-Aviv Sourasky Medical Center, [4]Liver, Digestive, and Lifestyle Health Research Section, and Organ Transplant Center of Excellenc

Background: SLD encompasses a spectrum from metabolic dysfunction–associated SLD (MASLD), metabolic dysfunction–associated alcohol-related liver disease (MetALD) and alcohol-related liver disease (ALD). Self-reports often underestimate current and previous alcohol intake. This study aimed to compare the risk of premature mortality across the SLD spectrum using U.S. per capita–adjusted alcohol intake estimates. **Methods:** The National Health and Nutrition Examination Survey (1988-1994) with mortality follow-up to 2019 was used. Alcohol intake was adjusted to align with 1990 U.S. per capita alcohol consumption estimates based on national sales data. Participants were categorized as: abstainers (<12 drinks lifetime), former drinkers (≥ 12 drinks lifetime but none in past 12 months), low ($<20/30$ g/day for W/M), moderate (20–49.9/30–59.9 g/day), or heavy ($\geq 50/60$ g/day). SLD was diagnosed by ultrasound and sub-grouped according to the recent consensus to MASLD, MetALD and ALD. Premature mortality (death $\leq 80/75$ years for W/M) and age-standardized mortality rates (per 1,000 person-years) were calculated using the 2000 U.S. standard population. **Results:** Among 12,927 adults (mean age 42.8 years; 48.1% men), 19.0% had SLD ($n=2,807$, (79.9% MASLD, 8.4% MetALD, and 11.7% ALD). Within the MASLD group, 45.1% were former drinkers. Compared to MASLD-abstainers who never drunk, MASLD-former drinkers had higher fibrosis scores (FIB-4 >2.67: 2.01% vs. 0.44%, $p=0.038$), but lower than MetALD and ALD groups (FIB-4 >2.67: 4.21% and 6.56%, respectively). Premature mortality rates were also highest among individuals with ALD (13.5 per 1,000 person-years), followed by MetALD (11.5), MASLD (8.3), and non-SLD groups (Table). In Cox models adjusted for sociodemographic and lifestyle factors, the risk of premature death was greatest for ALD, followed by MetALD, and MASLD-former drinkers as compared to non-SLD abstainers, while no significant increase in risk of death was observed for MASLD-abstainers (Table). **Conclusion:** This U.S. study, using per capita–adjusted alcohol intake, highlight that both current and past alcohol use significantly increase premature mortality risk across SLD subtypes. ALD, MetALD, and MASLD with a history of alcohol use were all associated with increased premature mortality risk.

Table. Hazard Ratios for Premature Mortality by SLD and Alcohol Use Categories

	Premature Mortality (per 1,000)	Sociodemographic- and lifestyle-adjusted model	
		HR (95% CI)	P-value
Non-SLD (Abstainer)	5.93	Reference	
MASLD (Abstainer)	6.69	1.26 (0.82 - 1.92)	0.282
MASLD (Former drinkers)	9.87	**1.55 (1.11 - 2.16)**	**0.011**
MetALD	11.54	**1.77 (1.01 - 3.09)**	**0.046**
ALD	13.46	**1.80 (1.13 - 2.87)**	**0.014**

Abbreviations: HR, Hazard ratio.
Hazard ratios estimated using Cox proportional hazards models adjusted for age, sex, race/ethnicity, educational attainment, household income, Healthy Eating Index (<56.9), and no physical activity.

Disclosures: James Paik: Nothing to Disclose, Dana Ivancovsky Wajcman: Nothing to Disclose, Shira Zelber-Sagi: Nothing to Disclose, Nothing to Disclose,

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Andrei Racila: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant

2224 | HEPATORENAL MORTALITY TREND AND HEALTHCARE DISPARITIES IN THE UNITED STATES (1999–2020)

Tooba Laeeq[1] Ayesha Saleem[2] Syed Ali Hussain[2] Muhammad Asjad Saleem[3] Khadija Mohib[4], [1]University of Nevada Las Vegas, [2]Dow University of Health Sciences, [3]The Indus Hospital, [4]University of Nevada, Las Vegas

Background: Hepatorenal syndrome (HRS) is a severe liver disease complication marked by progressive renal failure. Despite clinical gains, mortality remains high. This study examines long-term HRS mortality trends in U.S. adults aged 55+, highlighting gender, ethnic, geographic, and urbanization differences from 1999-2020. **Methods:** Data from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) Multiple Cause of Death database were used to identify hepatorenal syndrome deaths (ICD-10 code K76.7) in U.S. adults aged 55 years and older from 1999 to 2020. Age-adjusted mortality rates (AAMRs) per 100,000 population were calculated using the 2000 U.S. Standard Population. Analyses were stratified by sex, race/ethnicity, urbanization (metropolitan vs. non-metropolitan), and U.S. Census region. Temporal trends were assessed using the Joinpoint Regression Program (v5.3.0) to estimate annual percent change (APC) and average annual percent change (AAPC), with 95% confidence intervals. Statistical significance was set at $p < 0.05$. **Results:** Between 1999 and 2020, a total of 63,389 hepatorenal-related deaths were recorded in the U.S. The AAMR declined from 4.63 in 1999 to 4.07 in 2020. In 1999, the highest AAMR was observed among NH American Indian/Alaska Natives (9.44), males (6.52), residents in the West (5.30), and non-metropolitan areas (4.98); the lowest were seen among NH White individuals (4.27), females (3.15), Midwest residents (4.12), and metropolitan areas (4.56). In 2020, the highest AAMR persisted among NH American Indian/Alaska Natives (11.32), males (5.44), West (5.01), and non-metropolitan areas (5.38); the lowest were among NH Asian/Pacific Islanders (2.12), females (2.95), Northeast (3.28), and metropolitan areas (3.84). Females showed a smaller decline (AAPC: −0.59%; 95% CI: −0.97, −0.27), while males had a greater decline (AAPC: −1.26%; CI: −1.57, −0.93). The Northeast experienced the most significant decline (AAPC: −1.93%; CI: −2.24, −1.62), while the Midwest showed the most significant increase post-2018 (APC: +9.24%; CI: 1.30, 13.87). The smallest decline was in the West -0.67(-1.30,-0.17).NH Asian/Pacific Islanders had the steepest decline (AAPC: −3.54%; CI: −4.73, −2.63), while NH American Indian/Alaska Natives showed the least change (AAPC: −0.20%; CI: −1.26, 1.15), which was not significant. White showed a statistically significant least decline with an AAPC -0.37% (-0.69,-0.12). Metropolitan areas had a notable decrease (AAPC: −1.18%; CI: −1.46, −0.86), compared to non-metropolitan areas (AAPC: -0.19%; CI -0.78,0.49). **Conclusion:** Despite the overall decline in hepatorenal mortality, sharp increases after 2018 in the Midwest with persistent gaps, especially in NH American Indian/Alaska Natives and rural areas, highlight ongoing inequities. Addressing this need requires culturally and regionally tailored public health efforts.
Disclosures: Tooba Laeeq: Nothing to Disclose, Ayesha Saleem: Nothing to Disclose, Syed Ali Hussain: Nothing to Disclose, Muhammad Asjad Saleem: Nothing to Disclose, Khadija Mohib: Nothing to Disclose

2225 | CHALLENGES FACING PATIENTS WITH CIRRHOSIS

Deanna Oliver[1] Anna Marie Hefner[1] Julian Diaz-Moreno[1] Ahmed Atalla[1] Usman Gul[1] Mustafa Behan[2] Jutta Kurz[2] Valeriia Aksakovska[2] Michael Tunkelrott[3] Emmanuel Gorospe[4] Fatma Barakat[5] Tarek Hassanein[1], [1]Southern California Liver Centers, [2]Amsety, [3]Amsety LLC, [4]Burrell College of Osteopathic Medicine, [5]SCTI Research Foundation

Background: Up to 8% of patients with cirrhosis develop liver cancer (LC). Over 10 years, the risk for LC can reach 30%, particularly in high-risk populations. Given new treatments for LC, early identification is essential for timely intervention. The aim of this analysis is to identify data-driven challenges for patients with cirrhosis. **Methods:** The Amsety database comprises of 650,000 participants (pts) in the United States with a history of liver disease. Out of those, about 36,000 have cirrhosis. In March 2025, 200 pts were asked to answer additional questions about their cirrhosis diagnosis and management. **Results:** Average age of respondents was 53 years. 62% were overweight, obese, morbidly obese. 27% were diagnosed with cirrhosis within the previous year, 46% between 1 and 5 years, 12% between 5 and 10 years, and 10% more than 10 years earlier. Etiology: 29% NAFLD/MASLD, 23% alcohol, 8% chronic viral hepatitis. Prior to cirrhosis diagnosis: 27% struggled with unusual fatigue and 23% experienced abdominal discomfort. 19% had swelling (legs, ankles, or abdomen), 12% itchy skin/jaundice. After diagnosis: 31% adopted a healthier diet, 21% reduced or eliminated alcohol consumption, 20% limited over-the-

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counter medications use, increased physical activity, started supplements, or focused on mental health. Monitoring: 35% followed by a liver specialist and 55% by primary care physicians. 19% visit their doctor once a month, 43% every 3 months, 29% every 6 months, 4% once a year or less. 62% reported monitoring their disease progression by blood tests vs. imaging in only 12%. Pt concerns: 46% disease progression, 25% development of LC, 17% future need for liver transplant. 48% cited healthcare providers as primary source of information, 27% used online resources, 10% relied on social media/online communities, 10% support groups/family and friends. **Conclusion:** Per patient reporting, 1) screening for LC is still not enforced and underutilized, 2) pts seek more education, support/monitoring, 3) pts lack consistent care and face barriers to early disease detection and intervention, 4) lifestyle changes are often initiated but not uniformly adopted. As the acceptance of digital tools is high, a liver-specific Gen AI solution could provide accessible, personalized information and guidance. Such tools may empower patients to better manage their condition, improve engagement, and potentially delay or prevent progression.

Disclosures: Deanna Oliver: Nothing to Disclose, Anna Marie Hefner: Nothing to Disclose, Julian Diaz-Moreno: Nothing to Disclose, Ahmed Atalla: Nothing to Disclose, Usman Gul: Nothing to Disclose, Mustafa Behan: Amsety GmbH: Founder and Co-Owner, Jutta Kurz: Nothing to Disclose, Valeriia Aksakovska: Amsety GmbH: Employee, Michael Tunkelrott: amsety: non-compensated advisor, Emmanuel Gorospe: Nothing to Disclose, Fatma Barakat: Nothing to Disclose, Tarek Hassanein: AbbVie: Speaker and Research Support, Gilead: Speaker and Research Support, HepQuant Shunt: Advisor, Madrigal: Advisor and Research Support, Amgen: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer- Ingelheim: Grant/Research Support, COUR: Grant/Research Support, Escient: Grant/Research Support, Galectin: Grant/Research Support, Grifols: Grant/Research Support, Intercept: Grant/Research Support, Janssen: Grant/Research Support, Merck: Grant/Research Support, Mirum: Grant/Research Support, NeuroBo: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pfizer: Grant/Research Support, Regeneron: Grant/Research Support, Salix Pharmaceuticals: Grant/Research Support, Takeda: Grant/Research Support, Akero: Grant/Research Support, Ipsen: Grant/Research Support, Kowa: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, DURECT: Grant/Research Support, HepQuant: Grant/Research Support, Terns Pharmaceutical: Grant/Research Support, Mallinckrodt: Speaker and Research Support, Eli Lilly: Grant/Research Support, PharmaIn: Grant/Research Support, Sonic incytes: Grant/Research Support, Tensor Bio: Grant/Research Support, 89Bio: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Nterica: Consultant

2226 | CLINICAL OUTCOMES OF NATIVE AMERICANS WITH ALCOHOL-ASSOCIATED LIVER DISEASE: A RETROSPECTIVE COHORT STUDY

Pojsakorn Danpanichkul[1] Supapitch Sirimangklanurak[2] Romelia Barba Bernal[3] Ana Marenco-Flores[4] Thanathip Suenghataiphorn[5] Omar Al Ta'ani[6] Khawaja Hassam[7], [1]Texas Tech University Health Sciences Center, [2]Chiang Mai University, [3]Texas Tech University, [4]BIDMC, [5]Griffin Hospital, [6]Allegheny Hospital, [7]Lahey Hospital

Background: Alcohol-associated liver disease (ALD) is a significant contributor to liver mortality. Despite this, limited evidence exists regarding clinical outcomes among American Indian and Alaska Native (AI/AN) populations affected by ALD. Recent data show that AI/AN communities experienced a sixfold higher death rate than Whites. This study aims to evaluate disparities in clinical outcomes between AI/AN and non-AI/AN patients with ALD over 10 years. **Methods:** We conducted a retrospective cohort study utilizing the TriNetX network to examine patients diagnosed with ALD. The study compared outcomes between AI/AN and non-AI/AN patients with ALD. To reduce potential confounding, we applied 1:1 propensity score matching based on demographics, comorbidities, and medication use. The primary outcome assessed was all-cause mortality, while secondary outcomes included liver-related and cardiovascular complications. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards models over a five-year follow-up. **Results:** A total of 3,652 patients with ALD were included after propensity score matching. After propensity score matching, AI/AN individuals with ALD had a significantly higher risk of death from any cause compared to non-AI/AN patients (HR: 1.32; 95% CI: 1.14–1.52). They were also more likely to experience major adverse liver outcomes (HR: 1.35; 95% CI: 1.14–1.61). The rate of hepatocellular carcinoma did not differ significantly between groups (HR: 0.73; 95% CI: 0.24–2.23). Cardiovascular outcomes—including major adverse cardiac events (HR: 1.01; 95% CI: 0.81–1.26), ischemic heart disease (HR: 1.25; 95% CI: 0.74–2.10), arrhythmias (HR: 0.96; 95% CI: 0.79–1.16), stroke (HR: 1.20; 95% CI: 0.86–1.67), thrombotic events (HR: 1.51; 95% CI: 0.86–2.66), and heart failure (HR: 0.96; 95% CI: 0.73–1.28)—were not significantly different between the two cohorts. **Conclusion:** AIAN individuals with ALD face a markedly

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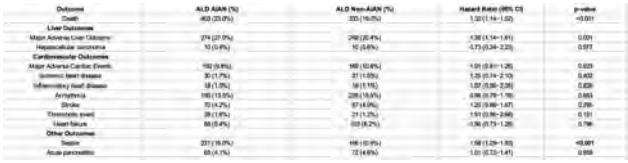
elevated risk of mortality and severe liver complications when compared to other racial and ethnic groups. These disparities necessitate targeted public health efforts and customized clinical strategies to enhance liver-related health outcomes in AI/AN communities.



Disclosures: Pojsakorn Danpanichkul: Nothing to Disclose, Supapitch Sirimangklanurak: Nothing to Disclose, Romelia Barba Bernal: Nothing to Disclose, Ana Marenco-Flores: Nothing to Disclose, Thanathip Suenghataiphorn: Nothing to Disclose, Omar Al Ta'ani: Nothing to Disclose, Khawaja Hassam: Nothing to Disclose

2227 | DIGITAL HEALTH LITERACY IS IMPAIRED IN LIVER CIRRHOSIS PATIENTS WITH A LOWER EDUCATION LEVEL: A CROSS-SECTIONAL MULTI-CENTER STUDY

Britt van Ruijven[1] Yunike Budiono[1] Luuk Mom[2] Matthijs Kramer[1] Marieke Pierik[1] Roos van der Vaart[3] Joost Drenth[4] Govert Veldhuijzen[2] Tom Gevers[1], [1]Maastricht University Medical Center, [2]Gelre Ziekenhuizen, [3]De Haagse Hogeschool, [4]Amsterdam University Medical Center

Background: Although healthcare increasingly adopts digital technologies, the impact of digital health literacy in patients with liver cirrhosis remains limited. We performed a comprehensive analysis of the digital health skills of liver cirrhosis patients using the Digital Health Literacy Instrument (DHLI) 2.0. **Methods:** A cross-sectional, multicenter questionnaire study was conducted involving liver cirrhosis patients identified by ICD-10 codes, treated at a secondary and tertiary medical center in the Netherlands. Eligible patients were diagnosed with liver cirrhosis and had a liver cirrhosis-related consultation in the past year. The DHLI 2.0 questionnaire was distributed through email. All non-responders and patients without a known e-mail address were invited by regular mail and received a reminder in case of no response. DHLI scores are reported on a 1-4 scale, with 4 indicating optimal digital health literacy. The questionnaire separately investigated digital device access, and education level categorized into low (no education, primary school, or lowest high school level), middle (higher levels of high school, or secondary vocational education), or high (bachelor's degree or higher). Patient demographics and disease characteristics, including MELD score, Child-Pugh score, and decompensation state according to Baveno VII at time of at last consultation, were collected from electronic patient records. Statistical analyses included Independent T-Tests, Kruskal-Wallis Tests, Mann-Whitney Tests, Spearman's Rank Correlations, and Generalized Linear Models. **Results:** Of 331 invited patients, 87 participated in this study (26.3%). Response rates for digital and physical DHLI 2.0 were 19.3% and 19.7%, respectively (27/140 vs. 60/304). Patients were predominantly male (71.3%), with a median age of 69.8 (IQR 64.1-75.6), treated in the tertiary center (65.5%), and with a lower education level (31.0%). Liver cirrhosis was caused by alcohol (34.5%) or MASLD (27.6%), most patients were compensated at time of participation (92.0%; 77% with Child-Pugh A). The majority of patients reported access to internet (79.3%), a smartphone (72%), and a computer or laptop (60%). The mean DHLI score was 3.1, and patients with low education demonstrated lower DHLI scores compared to middle or high education levels in the univariate analysis ($p = 0.026$) and Generalized Linear Model ($p = 0.034$). No statistically significant differences in DHLI scores were observed amongst liver cirrhosis etiologies ($p = 0.855$), (de)compensation ($p = 0.171$), Child-Pugh score ($p = 0.782$), MELD score ($p = 0.847$), or age ($p = 0.956$). **Conclusion:** This cross-sectional, multicenter study demonstrated lower digital healthcare literacy in liver cirrhosis patients with lower education levels, but showed no association with etiology or disease stage. The next step is to investigate how lower digital health literacy impacts the digital care of patients with liver cirrhosis.

Disclosures: Britt van Ruijven: Nothing to Disclose, Yunike Budiono: Nothing to Disclose, Luuk Mom: Nothing to Disclose, Matthijs Kramer: Nothing to Disclose, Marieke Pierik: Nothing to Disclose, Roos van der Vaart: Nothing to Disclose, Joost Drenth: Nothing to Disclose, Govert Veldhuijzen: Nothing to Disclose, Tom Gevers: Nothing to Disclose

2228 | RACIAL DISPARITIES IN INCIDENCE OF CIRRHOSIS AND EXTRAHEPATIC MANIFESTATIONS IN ALCOHOL-ASSOCIATED LIVER DISEASE

Majd Aboona[1] Pradhan Hariharan[1] Janet Foote[2] Leith Ghani[1] Vanessa Eller[1] Ryan Toledo[1] Pooja Rangan[1] David Garcia[2] Vincent Chen[3] Donghee Kim[4] Juan Pablo Arab[5] Mazen Noureddin[6] Luis Díaz[7] Mike Fallon[8] Karn Wijarnpreecha[9], [1]University of Arizona College of Medicine - Phoenix, [2]University of Arizona Mel and Enid Zuckerman College of Public Health, [3]University of

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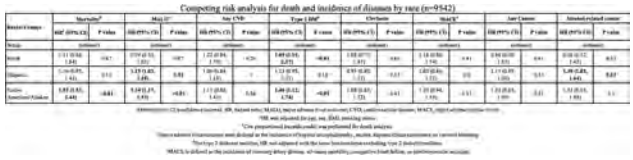
Michigan Medical Center, [4]Stanford University Medical Center, [5]Virginia Commonwealth University, [6]Houston Methodist Hospital, [7]University of California San Diego, [8]University of Arizona, [9]University of Arizona College of Medicine-Phoenix

Background: Alcohol-associated liver disease (ALD) is the leading cause of cirrhosis in Western countries. Alcohol can also contribute to the development of multiple extrahepatic manifestations. However, there is limited literature regarding the extrahepatic outcomes of ALD among diverse patient populations especially among the Native American population. We conducted a study to assess racial disparities in the incidence of cirrhosis and extrahepatic manifestations in ALD from a racially diverse cohort in the US. **Methods:** We conducted a study on ALD patients seen at the Banner Health System, representing hospitals across Arizona, California, Nevada, Wyoming and Colorado from 2012 to October 2024 using ICD codes with randomly selected chart review over 250 cases to validate ICD codes for ALD and extrahepatic outcomes. We excluded patients with other causes of liver disease and decompensated cirrhosis at baseline. Primary outcomes included incidence of mortality, major adverse liver outcomes (MALO), cardiovascular disease, type 2 diabetes mellitus (T2D), cirrhosis, major adverse cardiovascular events (MACE), any cancer, and alcohol-related cancer [gastrointestinal tract, liver, breast, prostate, and oropharyngeal cancer]. A multivariate analysis was performed and adjusted for variables such as age, sex, body mass index, and smoking status. **Results:** We included 9,542 patients with ALD. The median age in the cohort was 49.9 years, 66.3% were male, 67.0% were Non-Hispanic White (NHW), 18.4% Hispanic, 11.0% Native American (NA), and 3.2% Black. Compared to NHW patients, NAs had increased mortality (adjusted hazard ratio (aHR) 1.93; 95% Confidence Interval (CI): 1.53-2.44), higher incidence of MALO (aHR 1.34; 95% CI 1.17-1.53), and T2D (aHR 1.40; 95% CI 1.12-1.74). Hispanic patients had a higher incidence of MALO (aHR 1.50; 95% CI: 1.03-1.28) and higher incidence of alcohol-related cancer (aHR 1.30; 95% CI 1.03-1.64). Cardiovascular disease, any cancer, cirrhosis, MACE were nonsignificant among racial groups. **Conclusion:** In this multicenter cohort of patients with ALD, the NA population has a significantly disproportionately higher mortality than NHWs likely secondary to the higher incidence of MALO. Similarly, Hispanic patients had a high incidence in MALO, likely contributing to higher alcohol-related cancer. Attention to racial disparities is critical in ALD, highlighting the importance of earlier intervention to prevent MALO in underserved populations.



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2229 | HIGH ADHERENCE TO A PLANETARY HEALTH DIET IS ASSOCIATED WITH LOWER RISK OF HEPATOCELLULAR CARCINOMA

Roselyn Tanghal[1] Zhenjiang Li[1] Adelynn Paik[1] Jesse Goodrich[1] David Conti[1] Douglas Walker[2] Lynne Wilkens[3] Veronica Setiawan[1] Lida Chatzi[1], [1]University of Southern California, [2]Emory University, [3]University of Hawai'i

Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths globally, with increasing incidence in the U.S. Current prevention strategies are limited, underscoring the urgent need for modifiable risk factors. Diet is a key determinant of liver cancer risk, and dietary patterns that prioritize plant-based foods and limit red and processed meat intake may offer protection. The Planetary Health Diet (PHD), a new dietary framework proposed by the EAT-Lancet Commission to promote both human and environmental health, provides a diet-model characterized by increased consumption of plant-based foods and decreasing processed meat consumption. However, its role in HCC prevention remains unclear. This study examines the association between PHD adherence and HCC risk in a diverse population in the U.S. and explores potential biological mechanisms using metabolomics data. **Methods:** We evaluated the association between PHD and HCC risk in the Multiethnic Cohort, a large prospective cohort in the U.S. PHD adherence was quantified using the Planetary Health Diet Index (PHDI), derived from validated food frequency questionnaires. HCC cases were identified through cancer registry linkage. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for HCC across quintiles of PHDI scores. Pre-diagnostic plasma samples from 477 participants were analyzed using untargeted metabolomics via liquid chromatography coupled with high-resolution mass spectrometry (LC-HRMS). A meet-in-the-middle approach was applied to identify metabolites mediating the association. **Results:** Among 186,735 participants followed for an average of 20 years, we identified 1,003 incident HCC cases. High adherence to the PHD was significantly associated with reduced HCC risk (Q5 vs. Q1 HR: 0.75, 95% CI: 0.61, 0.93, P trend = 0.002). The association was consistent across racial and ethnic groups, with the strongest inverse association observed among Japanese Americans (Q5 versus Q1 HR: 0.62, 95% CI: 0.43,0.89; P trend = 0.002). Metabolomics analysis identified Hippurate, a gut-derived metabolite linked to plant-based diets, as a significant mediator, mediating approximately 15% of the total effect of PHDI on HCC risk ($p = 0.018$). **Conclusion:** Greater adherence to a nutritionally balanced and environmentally sustainable diet is inversely associated with HCC risk. These findings highlight the potential clinical utility of dietary modification as a primary prevention strategy for liver cancer and support public health efforts to promote sustainable dietary patterns.

Disclosures: Roselyn Tanghal: Nothing to Disclose, Zhenjiang Li: Nothing to Disclose, Adelynn Paik: Nothing to Disclose, Jesse Goodrich: Nothing to Disclose, David Conti: Nothing to Disclose, Douglas Walker: Nothing to Disclose, Lynne Wilkens: Nothing to Disclose, Veronica Setiawan: Nothing to Disclose, Lida Chatzi: Nothing to Disclose

2230 | FOOD INSECURITY EXPERIENCES IN LIVER DISEASE: A PILOT OF FOOD INSECURITY SCREENING IN PATIENTS WITH CIRRHOSIS

Ollie Desrochers[1] Therese Bittermann[2] David Goldberg[3] Grace Jung[1] Sahana Kannan[1] Harlene Kaur[1] Victoria Younes[1] Elena Byhoff[1], [1]UMass Chan Medical School, [2]Perelman School of Medicine, [3]University of Miami

Background: Food insecurity is the condition of not having consistent access to sufficient food for an active healthy life. Patients with cirrhosis may be more vulnerable to the health effects of food insecurity and may face additional barriers related to complex dietary recommendations. **Methods:** This

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was a cross-sectional study of adult outpatients with cirrhosis who were screened for food insecurity using the validated 2-item Hunger Vital Sign tool and two additional questions on perceived difficulties in making cirrhosis-specific dietary choices. Patients competed the survey in the waiting room on the day of their appointment. All survey responses were then linked to electronic medical record data for demographic, comorbidity, and healthcare utilization data. Descriptive statistics were calculated for patients who were food insecure vs food secure.Of 150 survey respondents, 25% (n = 38) screened positive for food insecurity using the Hunger Vital Sign. In total, 69% (n = 104) reported difficulty making the best food choices for their cirrhosis, 89% (n = 34) among food insecure and 54% (n = 60) among food secure. Not knowing which foods were appropriate for their cirrhosis was the most common difficulty reported by patients, followed by difficulty affording the best foods for their cirrhosis. Compared to food secure individuals, those with food insecurity were younger (mean age 58.1 vs. 63.5 years, $p = 0.02$), had lower BMI (mean 27.9 vs. 30.9, $p = 0.03$), and were more likely to be Hispanic (15.8% vs. 4.5%, $p = 0.05$) and Medicaid-insured (28.9% vs. 10.7%, $p = 0.01$). Both groups had similar cirrhosis etiologies, co-morbidities, decompensation events and number of ED visits and inpatient hospital days within 12 months prior to their screening date. **Results:** Of 150 survey respondents, 25% (n = 38) screened positive for food insecurity using the Hunger Vital Sign. In total, 69% (n = 104) reported difficulty making the best food choices for their cirrhosis, 89% (n = 34) among food insecure and 54% (n = 60) among food secure. Not knowing which foods were appropriate for their cirrhosis was the most common difficulty reported by patients, followed by difficulty affording the best foods for their cirrhosis. Compared to food secure individuals, those with food insecurity were younger (mean age 58.1 vs. 63.5 years, $p = 0.02$), had lower BMI (mean 27.9 vs. 30.9, $p = 0.03$), and were more likely to be Hispanic (15.8% vs. 4.5%, $p = 0.05$) and Medicaid-insured (28.9% vs. 10.7%, $p = 0.01$). Both groups had similar cirrhosis etiologies, co-morbidities, decompensation events and number of ED visits and inpatient hospital days within 12 months prior to their screening date. **Conclusion:** One in four patients with cirrhosis experience food insecurity with a higher burden experienced by Hispanic and publicly-insured individuals. Notably, over 69% of patients report difficulties with making cirrhosis-specific food choices, most of whom did not screen positive for food insecurity.

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2231 | A CAPACITY BUILDING INITIATIVE TO EXPAND HEPATITIS B AND C SCREENING AND TREATMENT IN VULNERABLE COMMUNITIES

Brianna Norton[1] Mark Sulkowski[2] Su Wang[3] Melissa Rodriguez[4] Jenniffer Meza Jimenez[4] Jeffrey Carter[4] Laura Simone[4] Leah Molloy[4], [1]Albert Einstein College of Medicine, Bronx, NY, [2]Johns Hopkins Medicine, [3]Cooperman Barnabas Medical Center, [4]PRIME Education

Background: Community clinics can play a frontline role in hepatitis elimination, but implementation barriers persist. This project aimed to identify gaps and improve HBV/HCV screening and linkage to care. **Methods:** Baseline surveys were completed by 76 healthcare professionals (HCPs) in 5 community clinics assessing current practices and barriers in HBV/HCV screening and treatment. Responses informed the development of live clinic-based audit-feedback sessions at the clinics from 11/2024 – 2/2025, each additionally attended by leaders from local community-based organizations to share community perspectives. Pre- and post-program surveys were administered, team-based action plans developed, and follow-up surveys completed 2-3 months later. **Results:** On baseline surveys, clinics reported inconsistent performance of one-time universal HBV/HCV screening: 65% of respondents reported that their practices offer this service, 17% did not and 18% were unsure. Most reported managing only 10% or fewer patients with HBV or HCV independently without specialist referral (58% and 52%, respectively). The top reported challenges in routine screening and treatment initiation were low patient awareness (66%) and selecting appropriate treatment (43%), respectively. Patients with ongoing substance use disorders were most frequently identified as the population for which HCPs were most hesitant to implement hepatitis treatment without specialist involvement (47%). Among the 160 HCPs who attended the live sessions, knowledge of HCV treatment for people who inject drugs was low and improved after education (Figure 1). Action plans prioritized by the HCPs following the sessions included: public outreach to improve screening (64%), expanding education and support for people diagnosed with HBV/HCV (64%), and establishing clinical criteria to differentiate patients with hepatitis who may be managed in a primary care setting from those who require specialist referral (40%). Follow-up surveys were completed by 15 HCPs. Respondents reported caring for a combined 46 patients with HCV

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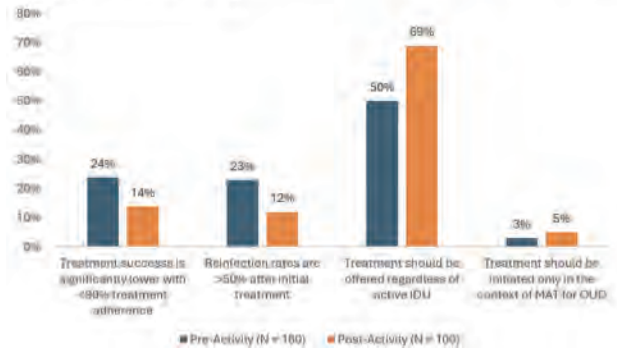
and 32 patients with HBV since participating in the initiative, 57% (26/46) and 59% (19/32) of whom were managed independently in clinic without specialist referral, respectively. **Conclusion:** Tailored discussion with live audit-feedback and action planning informed by community perspectives in community clinics led to measurable improvements in HBV/HCV knowledge and practice. These outcomes may inform other practice-changing implementation needs.

Figure 1. HCP responses to: "Which of the following is true about HCV treatment among people who inject drugs?"



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2232 | ASSOCIATION BETWEEN COUNTRY OF BIRTH AND LIVER FIBROSIS SEVERITY IN OBESE U.S. ADULTS: AN NHANES 2017–2023 STUDY

Mahinaz Mohsen[1] Ziad Mohsen[2] Rohan Karkra[1] David Kim[1] John Esli Medina Morales[1] Michael Bebawy[1] Menna-Allah Elaskandrany[3] Paul Gaglio[1], [1]Rutgers New Jersey Medical School, [2]Rutgers University, [3]Lenox Hill Hospital

Background: Obesity is a key contributor to metabolic dysfunction-associated steatotic liver disease (MASLD), with liver fibrosis severity serving as a critical marker of disease progression. Identifying factors associated with liver fibrosis severity is essential for risk stratification and targeted care in patients with MASLD. While prior studies have noted racial and ethnic disparities in hepatic fibrosis, the impact of nativity (U.S.-born vs. foreign-born) remains underexamined. This study investigates whether foreign-born status is associated with increased liver fibrosis severity among obese U.S. adults. **Methods:** This is a retrospective database analysis using combined data from the National Health and Nutrition Examination Survey (NHANES) from 2017 to 2023. Adults aged ≥ 18 with obesity (BMI ≥ 30) and no history of viral hepatitis were included. Participants with missing data or unreliable liver stiffness measurements, as defined by NHANES, were excluded. Liver fibrosis severity was measured by median liver stiffness. Univariate analyses were performed using IBM SPSS Statistics 25. Weighted multivariable analysis was performed using R (4.4.1). Significance was set at $p < 0.05$. **Results:** Out of 27,493 participants, 1,729 met inclusion criteria (84% U.S.-born, 16% foreign-born). The average age was 51 ($\pm$ 16), with 46% male and 48% white participants. Average BMI was 36.2 ($\pm$ 5.7). Univariate analysis showed that median liver stiffness was lower in foreign-born individuals, but the difference was not statistically significant ($p = 0.742$). Foreign-born individuals had significantly higher levels of hyperlipidemia ($p = 0.028$), less access to healthcare ($p < 0.05$), and a lower poverty income ratio ($p < 0.05$). Multivariable analysis (Table 1) showed that country of birth was not significantly associated with liver stiffness severity ($p = 0.598$). However, older age ($p = 0.002$), male gender ($p < 0.001$), higher BMI ($p < 0.001$), and lower income ($p = 0.0365$) were linked to increased fibrosis severity. Black ethnicity was associated with lower fibrosis severity ($p = 0.004$). **Conclusion:** In this nationally representative sample of obese U.S. adults, country of birth was not independently associated with liver fibrosis severity. However, older age, male gender, higher BMI, and lower income were significantly associated with increased fibrosis, while Black ethnicity was protective. This highlights metabolic and social determinants of health over nativity as possible risk factors in the development of liver fibrosis in immigrant patients.

Table 1. Weighted Multivariable Linear Regression Analyses of Comorbidities and Risk Factors for Liver Fibrosis in Obese Patients

		β Coefficient (95% CI)	p-value
Country of Birth, U.S.		0.16 (-0.47 to 0.74)	0.598
Age		0.040 (0.02 to 0.07)	**0.002**
Male		1.28 (0.74 to 1.95)	**<0.001**
Ethnicity*	Asian	1.38 (-0.08 to 3.20)	0.075
	Black	-0.90 (-1.52 to -0.39)	**0.004**
	Mexican American	0.050 (-0.86 to 0.83)	0.925
	Other Hispanic	-0.10 (-0.85 to 0.55)	0.799
	Other	-0.45 (-1.40 to 0.48)	0.361
BMI		0.22 (0.16 to 0.29)	**<0.001**
Diabetes		0.89 (0.11 to 1.6)	0.076
Hypertension		0.032 (-0.55 to 0.53)	0.878
Hyperlipidemia		-0.13 (-0.78 to 0.59)	0.658
Alcohol Use		0.25 (-0.56 to 1.06)	0.425
Access to Healthcare		-0.41 (-1.78 to 0.50)	0.451
Poverty Income Ratio		-0.24 (-0.47 to -0.050)	**0.0365**

*Ethnicity association with liver fibrosis was in comparison to the white reference group

Disclosures: Mahinaz Mohsen: Nothing to Disclose, Ziad Mohsen: Nothing to Disclose, Rohan Karkra: Nothing to Disclose, David Kim: Nothing to Disclose, John Esli Medina Morales: Nothing to Disclose, Michael Bebawy: Nothing to Disclose, Menna-Allah Elaskandrany: Nothing to Disclose, Paul Gaglio: Nothing to Disclose, Nothing to Disclose

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2233 | BREAST CANCER SCREENING AS A BARRIER TO EXPEDITED LIVER TRANSPLANT LISTING IN INPATIENTS: A RETROSPECTIVE CHART REVIEW

Madison Force Caroline Conlon[1] Emily Chiacchiaro[1] Khoa Nguyen[1] Danielle Tholey[1] Dina Halegoua-De Marzio[1], [1]Thomas Jefferson University Hospital

Background: Women receive liver transplantation (LT) less often than men. In 2023, MELD3.0, which includes sex, was introduced to help address sex disparities. We propose that difficulty accessing inpatient breast cancer screening during liver transplant evaluation (LTE) contributes to delayed listing for women. **Methods:** From 8/22/23-2/5/2025, we retrospectively reviewed consecutive, adults referred for inpatient LTE at a large, high MELD, LT center. Variables included: demographics, MELD 3.0 scores at referral and activation, and key transplant timeline dates (referral, activation, transplant, death, or lost to follow-up). For females aged $\geq$40, we reviewed prior breast cancer screening, inpatient imaging orders, modality, and completion time. Time to activation and LT were analyzed with Kaplan-Meier curves and compared by sex using log-rank tests. Patients who were not activated, transplanted, or died by the end of the study period (or were lost to follow-up) were considered censored; their time-to-event was calculated up to their last available evaluation date. Activation rates were assessed using chi-square tests. **Results:** Among 139 patients, 129 had valid dates for activation or eval date closure; 70 were female. Mean age was 56.5 years (SD = 9.39), and 74.4% were White. MELD 3.0 scores at referral and activation were similar between males and females. Activation rate was lower for females (34.3% vs. 39%), but not statistically significant ($\chi^2(1) = 0.31$, p = 0.58). Median time to activation or censoring was longer for females (9 vs. 7 days), but hazard distributions were not different ($\chi^2(1) = 0.90$, p = 0.40). Among activated patients, median time to transplant was 4 days for men and 7.5 days for women ($\chi^2(1) = 0.01$, p = 0.90). Of 70 female patients, 24 (34.3%) had prior screening; 20 (28.6%) had inpatient screening ordered. Median time from order to imaging was 2 days; from order to activation was 5.5 days. Transplant rate was 23.7% for males (n = 14) and 20% for females (n = 14). Deaths occurred in 32.2% of males (n = 19) and 31.4% of females (n = 22). **Conclusion:** Breast cancer screening requirements did not lead to statistically significant delays in LT activation for female inpatients, but modest delays were observed. All imaging was done via breast ultrasound, a less sensitive modality than mammography. These findings highlight a gap in screening access for high MELD female patients and the need for transplant-specific protocols that consider inpatient imaging limitations and listing urgency. Ongoing analysis with a larger cohort and subdistribution hazard models for competing risks are planned to determine whether these observed delays reach statistical significance. Results may be positively biased by our center's access to bedside breast imaging and buy-in from radiology.

Table 1. MELD 3.0 scores at referral to and activation on transplant list in men and women.

	Females		Males		
	M	SD	M	SD	t-test
MELD3 at Referral	30.18	7.09	29.29	8.46	t(152) = 0.71, p = 0.48
MELD3 at Activation	31.61	6.97	32.19	8.56	t(58) = 0.29, p = 0.78

Disclosures: Madison Force: Nothing to Disclose, Caroline Conlon: Nothing to Disclose, Emily Chiacchiaro: Nothing to Disclose, Khoa Nguyen: Nothing to Disclose, Danielle Tholey: Merck: I am an editor for the merck manual, Dina Halegoua-De Marzio: Novo Nordisk: Advisor, Galectin: Grant/Research Support, Madigral: Advisor, Novo Nordisk: Grant/Research Support, Madigral: Advisor, Viking: Grant/Research Support, Akero: Grant/Research Support, Intercept: Grant/Research Support, 89Bio: Grant/Research Support

2234 | LIVER TRANSPLANT ACCESS FOR UNDOCUMENTED IMMIGRANTS IS CONSTRAINED BY POLICY AWARENESS, INSTITUTIONAL PROTOCOLS, AND SOCIAL VULNERABILITY: A MIXED-METHODS: STUDY

Carolyn Singleton[1] Amanda Thayer[1] Lauren Nephew[2], [1]Indiana University School of Medicine, [2]Indiana University

Background: Undocumented immigrants with end-stage liver disease face significant structural barriers to liver transplantation (LT). While some U.S. states have adopted policies supporting access to LT for this population, national-level data on provider attitudes, practices, and policy awareness remain limited. **Methods:** We conducted a cross-sectional, mixed-methods survey of transplant hepatologists and surgeons in 16 states (emails sent to 808). The survey assessed provider attitudes, center protocols, and perceived barriers. To explore the role of policy and precedent, we classified states into a 2×2 matrix based on whether they (1) had ever performed LT in an undocumented

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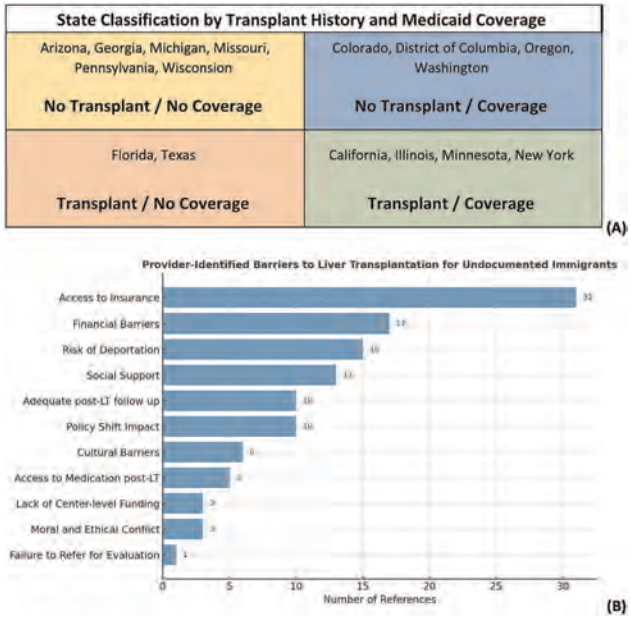
immigrant and (2) offered expanded Medicaid coverage (Figure 1A). Quantitative data were summarized descriptively; two open-text responses underwent rapid qualitative analysis. **Results:** Among 55 respondents from 12 states, 75.4% practiced in states with a history of LT in undocumented patients. Most were transplant hepatologists (58.6%). While 77.8% agreed they had an ethical obligation to evaluate undocumented patients, only 52.0% reported their center had ever listed undocumented patients. Although insurance was frequently cited as a barrier, 46.3% of respondents were unsure if their state offered expanded coverage. Only 14.8% reported clear center-level guidelines, more common in states with expanded Medicaid (62.5% vs 37.5%, $p = 0.046$). Most respondents (77.8%) reported no change in their willingness to evaluate or list undocumented immigrants following recent Executive Orders, but 20.4% were less willing or uncertain. The 2x2 policy matrix revealed four states (Colorado, Oregon, Washington, and District of Columbia) with expanded coverage but no reported LT history—highlighting gaps between permissive policy environments and clinical practice (Figure 1A). Qualitative themes (75 responses from 54 participants) included lack of insurance (31 references), financial concerns (17), risk of deportation (15), limited social support (13), and poor post-LT follow-up (10). Ten respondents identified immigration policy shifts, including Executive Orders, as direct barriers to care. **Conclusion:** Transplant providers broadly support equitable access to LT for undocumented immigrants but face persistent institutional and policy-related barriers. Greater policy transparency, provider education, and standardized protocols may help align ethical intent with practice, particularly in states where permissive policies remain underutilized.



Disclosures: Carolyn Singleton: Nothing to Disclose, Amanda Thayer: Nothing to Disclose, Lauren Nephew: NovoNordisk: Consultant

2235 | LIVER ABSCESSES IN A MEDICALLY UNDERSERVED, PREDOMINANTLY BLACK POPULATION: A RETROSPECTIVE STUDY FROM 2013 TO 2024 AT A U.S. SAFETY-NET HOSPITAL

Nakul Ganju[1] Jinal Makhija[1] Ahmed Ebeid[1] Sameer Garlapati[1] Pinky Bai[1] Hetu Patel[1] Ali Chand[1] Abay Gobezie[1] Lakshmi Chirumamilla[1] Fatemeh Homayounieh[1] Sneha Adidam[1] Farshad Aduli[1] Jhansi Gajjala[1], [1]Howard University Hospital

Background: Pyogenic liver abscesses (PLAs) are uncommon but serious infections. Their impact on younger, underserved patients with comorbidities and structural barriers remains undercharacterized, as most U.S. data focus on older, insured, non-minority populations. This study examines clinical, microbiologic, and socioeconomic features of PLA patients at a Washington, DC safety-net hospital **Methods:** We retrospectively reviewed radiologically confirmed PLA cases from 2013–2024, analyzing demographic, clinical, microbiologic, and socioeconomic variables, including Area Deprivation Index (ADI) and insurance status. Hospital length of stay (LOS) was analyzed and further stratified by cofactors. Descriptive statistics were used, and group comparisons were performed using t-tests and chi-square or Fisher's exact test, where appropriate. **Results:** Among 37 patients, 70.3% were Black, with a mean age of 55.2 years (range 19–88), younger than national PLA cohorts (mean ~63 years). Most were uninsured (48.6%), and 75.7% lived in the two highest ADI quartiles. Median LOS was 19.0 days, exceeding national medians of 9–12; mortality rate was 5.4%. LOS and mortality differences across subgroups were not statistically significant. Uninsured and Medicaid patients had longer LOS (21.0–22.0 days) and 11.1% mortality. Highest ADI quartile had the longest LOS (25.0 days) and 11.1% mortality. Drainage, performed in 86.5%, was linked to longer LOS (20.0 vs. 14.0 days) and lower mortality (3.1% vs. 20.0%), neither significant. Cultures were positive in 83.3%, most commonly E. coli, with frequent polymicrobial infections. Colonoscopy in 13 patients identified one colorectal adenocarcinoma. **Conclusion:** This cohort challenges prevailing PLA paradigms, revealing a younger, predominantly African American population with limited insurance and high comorbidity—features rarely reflected in national data. Elevated polymicrobial and post-procedural rates suggest delayed diagnoses and

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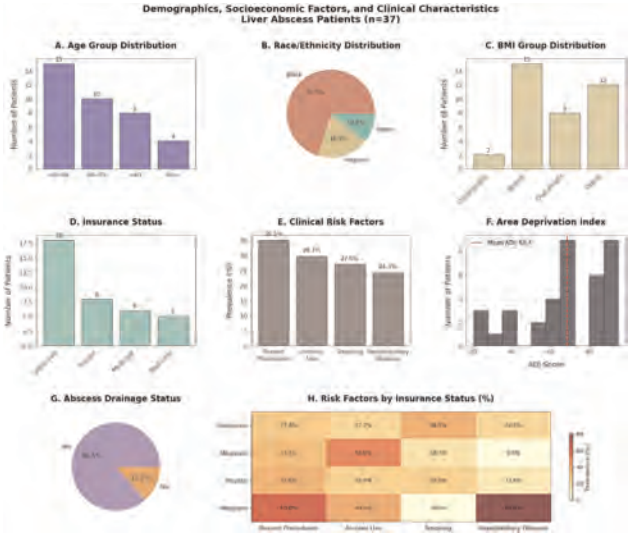
systemic barriers to care. Socioeconomic disadvantage, captured by ADI and insurance status, strongly correlated with prolonged hospitalization, indicating deprivation worsens clinical outcomes. This is among the few U.S. studies to longitudinally characterize PLA in a predominantly Black, uninsured population. Our findings highlight the urgent need to incorporate social determinants into PLA management and hepatology research frameworks. Our findings fill a critical knowledge gap by characterizing PLA in a U.S. safety-net population—a setting largely absent from prior studies. These data support targeted interventions to improve early recognition, diagnostic efficiency, procedural access, and equitable outcomes in underserved communities. Closing these persistent gaps requires collaboration across hepatology, public health, and health policy sectors to reduce disparities and improve care delivery.



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2236 | IDENTIFYING PROVIDER PRESCRIBING PRACTICES FOR GLP1RAS AND SGLT-2IS IN PATIENTS WITH TYPE 2 DIABETES TO ADDRESS PHARMACOINEQUITY IN LIVER DISEASE

Parnnate Wongsirisakul[1] Vincent Chen[1] Ponni Perumalswami[1], [1]University of Michigan Medical Center

Background: Evidence-based treatment of metabolic dysfunction-associated steatotic liver disease in patients with type 2 diabetes (T2DM) focuses on glycemic control and lifestyle modification to achieve weight loss, which slows the progression of liver disease and reduces the risk of liver-related complications. In the past 20 years, two newer classes of more effective T2DM medications became available in the United States—glucagon-like peptide receptor agonists (GLP-1RAs) and sodium/glucose cotransporter 2 inhibitors (SGLT-2is). However, studies observed racial and ethnic disparities in prescription rates despite controlling for high cost-sharing. **Methods:** We identified a cohort of 189 outpatient adult primary care providers who cared for at least 50 annual T2DM patients in a tertiary academic health system in 2021. GLP-1RA and SGLT-2i prescribing rates were crudely calculated with a median rate of 0.494 (IQR 0.594-0.393). Nine providers from the high prescribing quartile (prescribing rate 59.5-78.6%) and eight from the low (prescribing rate 4.8-39.3%) participated in 1:1 interviews guided by the Consolidated Framework for Implementation Research, which considers individual and system level factors. **Results:** On average, high prescribing providers had more patient-facing hours and exposure to GLP-1RAs and SGLT-2is in residency. In general, all providers cited task-sharing, patient-provider relationship longevity, and medication effectiveness as facilitators of GLP-1RA and SGLT-2i prescription. Barriers included patient mistrust of new therapies, insufficient access to care, and prescription inertia. However, medication costs and insurance prior authorization processes were the most mentioned deterrents, which varied along socioeconomic lines. High prescribers mitigated cost barriers by directing patients to in-system financial programs and leveraging prior authorization teams as opposed to low prescribers, who lacked prior authorization personnel and struggled to navigate cost issues sustainably. These factors allowed providers with strong administrative support systems to start metformin and GLP1-RAs co-first line but fostered hesitancy in prescription initiation for resource-deprived providers. Using the Expert Recommendations for Implementing Change, we mapped provider-proposed solutions to address concerns such as patient expectations, insurance gaps, and staff shortages in pursuit of pharmacoequity. **Conclusion:** This interview series revealed the GLP1-RA and SGTL-2i prescribing determinants and treatment approaches of primary care providers. Implementation strategies may help address determinants and improve prescribing newer, highly effective treatments in patients with T2DM.

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High Versus Low GLP-1RA and SGLT-2i Prescribing Provider Determinants

Determinant	High Providers	Low Providers	Quotes
Cost mitigation	Willing to navigate in-system resources	Cost issues seem insurmountable; unsustainable options	"It's a lot of work, but we have several patients, though, who we were able to get them [GLP-1RAs] through the patient assistance program." – High provider 8 "When I think about it [GLP-1RAs or SGLT-2is], or a patient asks about it, I kind of get like a visceral reaction like, 'Oh, God. I'm going to have to go through this circus of what does your insurance cover?'" – Low provider 17
Insurance processes	Effective in-clinic prior authorization teams	Poor prior authorization due to centralization and overwork	"We have a prior auth team now that helps, you know, get the medicines approved or denied without the burden on the clinics as much as it used to be." – High provider 4 "We used to do prior for these medications on site at our clinic. And then they centralized it. And the centralized version just does not work that well...They don't spend the time like looking through the patient's chart. They just route everything back to you a zillion times." – Low provider 2
Support	Strong reliance on embedded pharmacist	Opts for specialist referrals or search engines	"I get most of my information from the pharmacist. She sends me updated information on comparisons between the different medications, what the hemoglobin a1c reductions are" – High provider 13 "I've never done this, but if I had a question, in theory, I would do probably an E-consult just to run it by them (a specialist). If I have questions about the medications, I'll usually use UpToDate or ChatGPT" – Low provider 15
Treatment approach	Metformin and GLP1-RAs co-first line	Emphasis on lifestyle modification first	"I actually prefer a GLP-1RA to Metformin, depending on what else they have. If somebody comes in and they have obesity, even if their a1c is 6.5, and they are open to being on an injection medication, I will pretty much always do a GLP-1RA first." – High provider 14 "The first thing is always exploring lifestyle, which is probably better than any medication we're going to prescribe." – Low provider 9
Major concerns	Side effects and patient preference	Polypharmacy and lack of long-term research for newer meds	"First, I talk to the patient about what they might prefer and make sure they understand the side effects. I have some patients, for example, with the SGLT-2is that don't want to even try them if they already have issues with urinary symptoms or recurrent yeast infections." – High provider 5 "These medications add to the pill burden, and so we have to justify why we have to utilize this. If they have multiple reasons to be on this medication, that way, we're checking off multiple boxes with one pill." – Low provider 3

Disclosures: Parnnate Wongsirisakul: Nothing to Disclose, Vincent Chen: AstraZeneca: site PI on industry-sponsored trial, Ipsen: site co-I on industry-sponsored trial, Kowa: site co-I on industry-sponsored trial, Ponni Perumalswami: Nothing to Disclose

2237 | MELD AND THE RISK OF MORTALITY IN BLACK AND WHITE PATIENTS WITH ADVANCED FIBROSIS

Michael Attanasi[1] Mathew Gregoski[2] Don Rockey[2], [1]Northwell Health, [2]Medical University of South Carolina

Background: MELD has been well established as the gold standard metric for predicting mortality in patients with cirrhosis. Here, we hypothesized that race is an important factor in predicting mortality in patients with cirrhosis. **Methods:** All adults who had a liver biopsy showing F3 or F4 fibrosis at our institution from January 1, 2013 through July 1, 2021 were identified. Histology, fibrosis stage, and complete clinical data were abstracted via the medical record. Patients were propensity matched based on age, gender, Charlson Comorbidity Index, and the CDC/ATSDR Social Vulnerability Index Themes 1,2, and 4. Logistic regression analysis was performed comparing race, MELD 3.0, and their interaction on ninety-day mortality. **Results:** Of 3,572 patients having a liver biopsy, 92 Black and 372 White patients had F3/F4 fibrosis. Final propensity matching resulted in 143 White patients and 89 Black patients. Hypertension and chronic kidney disease were more prevalent in Black patients than in White patients (respectively: 63/89 (71%) vs 71/143 (50%); 12/89 (13%) vs 4/143 (3%); $p < 0.01$). HCV and AIH were more prevalent in Black patients than White patients (respectively: 23/89 (26%) vs 17/143 (12%); 18/89 (20%) vs 10/143 (7%); $p < 0.001$), and ALD and MASLD were more prominent in White patients than Black patients (respectively: 59/143 (41%) vs 20/89 (23%); 27/143 (19%) vs 3/89 (3%); $p < 0.001$). White patients were more likely to have hepatic encephalopathy (58/143 (41%) vs 22/89 (25%), $p < 0.05$) than Black patients. No significant differences between these groups existed for MELD scores. Liver-related mortality at ninety days and five years was not significantly different between White and Black patients (Figure 1). Logistic regression analysis did not reveal an association of race with liver-related mortality. ROC curves examined the relationship between race and MELD 3.0 demonstrated an AUC of 0.915 for White patients and 0.910 for Black patients. **Conclusion:** Black and White patients with similar comorbidities and social vulnerabilities had comparable liver-related mortality at similar MELD 3.0 scores in spite of increased evidence of portal hypertension and morbidity in White patients. The data suggest that the MELD 3.0 score is equally predictive of mortality in Black and White patients.

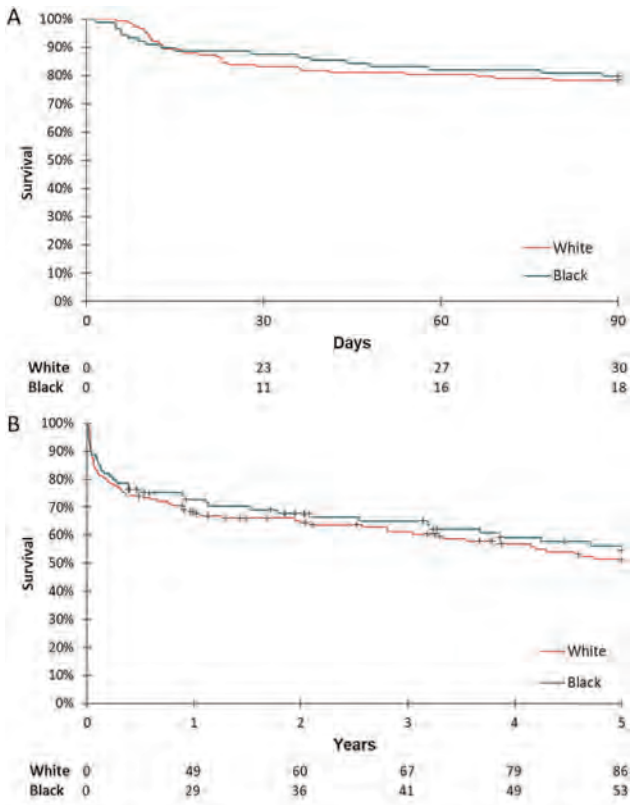

Figure 1. Kaplan Meier liver-related mortality at 90 days and 5 years for overall cohort

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2238 | DISPARITIES AMONG SOCIAL DETERMINANTS OF HEALTH AMONG LIVER TRANSPLANT RECIPIENTS IN A DIVERSE NATIONAL COHORT: FINDINGS FROM THE ALL OF US DATABASE

Ashley Spann[1] Dameia Brewster[1] Qingxia Chen[1] Andrew Guide[1] Haoyang Yi[2] Monica Tincopa[3], [1]Vanderbilt University Medical Center, [2]Vanderbilt University, [3]University of California, San Diego

Background: Social determinants of health (SDOH) contribute significantly to disparities in receipt of liver transplantation within the United States. However, for patients who do undergo liver transplantation, the status of SDOH after transplantation are unclear. In this study, we sought to explore potential sex-based, racial, and ethnic differences in various SDOH domains among liver transplant recipients (LTR). **Methods:** The All of Us (AOU) database is a NIH-funded national dataset of electronic health records composed of diverse adult participants with an emphasis on recruiting individuals historically underrepresented in medical research. The database was queried for patients with prior liver transplantation as determined by ICD-9, ICD-10, or CPT coding. Liver transplant recipients with complete SDOH survey data were included in the analysis. The SDOH survey data includes 3 domains: social & community context, economic stability, neighborhood environment metrics, and health & healthcare. Each domain was summarized using predefined methodology. Resultant SDOH summary scores are outlined in Table 1 with pairwise comparisons of SDOH subdomain scores between subgroups of race, sex, and ethnicity. Statistical significance was determined by Benjamini-Hochberg thresholds to adjust for multiple comparison from two-sample t-test for continuous scores, with a significance level of alpha (False discovery rate) = 0.05 corresponding to a p value of 0.013 or less. **Results:** A total of 1019 LTR were identified, with 387 (38% of LTR) having available SDOH survey data. For the social & community context domain, Hispanic LTR reported significantly lower social support compared to non-Hispanic LTR. Daily spiritual experiences were of greater importance to female, non-white, and Hispanic LTR; with both women and non-white individuals reporting significantly higher attendance to religious services. Regarding the neighborhood and environment domain, greater neighborhood walkability was appreciated among non-white and Hispanic LTR. Additionally, significantly higher neighborhood crime was reported by male, white, and non-Hispanic LTR. Lastly, in the health and healthcare domain, Hispanic individuals more often delayed medical care than non-Hispanic individuals. **Conclusion:** Racial, ethnic, and sex-based disparities exist across various SDOH domains among LTR and awareness of these can facilitate the development of mitigating or promoting strategies to enhance post-transplant survivorship. Some determinants may be protective of post-transplant outcomes (e.g. spirituality and religiosity for females, non-white, and Hispanic LTR). In contrast, others may have negative impacts after transplant (e.g. poor social support & delaying medical care among Hispanic LTR). The influence of these differences should be further explored to understand their role in overall post-transplant graft survival and quality of life.

Table 1: Social Determinants of Health Scores Stratified by Subgroup Analyses for Sex, Race and Ethnicity

Social & Community Context Domain (mean, SD)	Sex at Birth			Race			Ethnicity		
	Male	Female	P (SMD)	White	Non-White	P (SMD)	Non-Hispanic	Hispanic	P (SMD)
Social Cohesion Among Neighbors Score Range: 0 – 5	2.06	2.16	0.353 [0.10]	2.06	2.25	0.026 [0.24]	2.09	2.29	0.075 [0.25]
Social Support Score Range: 0 – 5	3.93	3.94	0.926 [0.01]	3.99	3.77	0.060 [0.29]	3.98	3.55	0.006 [0.37]
Loneliness Score Range: 0 – 5	1.81	1.83	0.748 [0.03]	1.85	1.74	0.112 [0.17]	1.82	1.82	0.981 [0.0]
Perceived Discrimination Score Range: 0 – 5	0.72	0.63	0.246 [0.12]	0.64	0.76	0.187 [0.16]	0.65	0.81	0.140 [0.21]
Perceived Stress Score Range: 0 – 5	2.16	2.24	0.292 [0.11]	2.19	2.16	0.865 [0.02]	2.15	2.41	0.021 [0.33]
Daily Spiritual Experiences Score Range: 0 – 5	3.31	4.01	0.001 [0.45]	3.36	4.22	0.001 [0.66]	3.51	4.27	0.001 [0.62]
Religious Service Attendance Score Range: 0 – 5	1.47	1.88	0.013 [0.27]	1.45	2.04	0.002 [0.27]	1.64	1.73	0.702 [0.07]
Neighborhood & Build Environment Domain (mean, SD)	**Sex at Birth**			**Race**			**Ethnicity**		
	Male	Female	P (SMD)	White	Non-White	P (SMD)	Non-Hispanic	Hispanic	P (SMD)
Neighborhood Walkability Score Range: 0 – 5	2.75	2.68	0.424 [0.06]	2.60	2.87	0.001 [0.40]	2.66	3.04	0.007 [0.43]
Neighborhood Crime Score Range: 0 – 5	2.47	3.17	0.005 [0.29]	3.46	2.58	0.001 [0.44]	3.38	2.95	0.006 [0.39]
Neighborhood Physical Disorder Score Range: 0 – 5	1.57	1.65	0.167 [0.14]	1.56	1.71	0.019 [0.25]	1.58	1.73	0.067 [0.25]
Neighborhood Social Disorder Score Range: 0 – 5	1.81	1.86	0.407 [0.09]	1.79	1.92	0.037 [0.22]	1.81	1.77	0.060 [0.28]
Health & Healthcare Domain (mean, SD)	**Sex at Birth**			**Race**			**Ethnicity**		
	Male	Female	P (SMD)	White	Non-White	P (SMD)	Non-Hispanic	Hispanic	P (SMD)
Perceived Discrimination in Medical Settings Score Range: 0 – 5	1.47	1.58	0.059 [0.19]	1.52	1.51	0.976 [0.0]	1.52	1.50	0.853 [0.03]
Inability to Afford Prescriptions Score Range: 0 – 1	0.55	0.65	0.026 [0.24]	0.60	0.66	0.641 [0.02]	0.59	0.82	0.723 [0.06]
Delays in Medical Care Score Range: 0 – 1	0.41	0.47	0.332 [0.07]	0.41	0.61	0.327 [0.11]	0.37	0.91	0.001 [0.44]

Disclosures: Ashley Spann: Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Dameia Brewster: Nothing to Disclose, Qingxia Chen: BeiGene: Data Monitor Committee, Andrew Guide: Nothing to Disclose, Haoyang Yi:

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Nothing to Disclose, Monica Tincopa: Nothing to Disclose

2239 | HEALTH LITERACY AS A DETERMINANT OF FRAILTY IN PATIENTS WITH LIVER CIRRHOSIS

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Background: Health literacy (HL) is a critical social determinant of health, particularly in chronic conditions like cirrhosis, where successful disease management depends on patients' understanding and engagement. HL refers to the ability to access, comprehend, and apply health information to make informed decisions. Frailty, which reflects decreased physiological reserve and increased vulnerability to stressors, is strongly associated with poor clinical outcomes in cirrhotic patients. While the Liver Frailty Index (LFI) is widely used to assess physical frailty, the influence of HL on this condition remains understudied. Understanding this relationship could reveal modifiable targets for improving care and reducing disparities. **Methods:** We conducted a cross-sectional study in adults with confirmed liver cirrhosis attending outpatient hepatology clinics in Cartagena, Colombia, from September to December 2024. HL was measured using the Short Assessment of Health Literacy for Spanish Adults (SAHL-S), and frailty using the LFI, based on handgrip strength, chair stands, and balance testing. Trained clinicians administered all functional tests under standardized conditions using calibrated equipment. Clinical and demographic variables were collected through medical records and structured interviews, including age, sex, BMI, Child-Pugh score, and history of decompensation or variceal bleeding. Patients with encephalopathy or severe mobility limitations were excluded. Frailty was defined as LFI $\geq$ 4.5. Descriptive statistics were used, and univariable and multivariable logistic regression analyses identified independent predictors of frailty. **Results:** A total of 89 patients were included; 57.3% were women, with a mean age of 64.8 years. Most were Child-Pugh A (85.4%). Prior decompensation and variceal bleeding were reported in 24.7% and 13.5%, respectively. LFI classified 15.7% as robust, 65.2% as prefrail, and 19.1% as frail. In univariable analysis, age, decompensation, variceal bleeding, and HL level were associated with frailty. In multivariable analysis, low HL (OR 2.8; 95% CI 1.3–6.0) and variceal bleeding (OR 3.2; 95% CI 1.4–7.1) remained independent predictors. **Conclusion:** Low HL is an independent predictor of frailty in patients with cirrhosis, along with clinical history of variceal bleeding. These findings underscore the relevance of HL as a modifiable risk factor and support its integration into routine hepatology practice. Targeted education may help reduce frailty and improve quality of life in this vulnerable population.

Variable	Value (n)
Female sex	57.3% (51)
Arterial hypertension	49.4% (44)
Child Classification	
Child B	14.6% (13)
History of ascites	12.4% (11)
BMI	27.3 (5.6)
Albumin	3.9 (0.56)
Frailty	
Prefrail	65.2% (58)

Table 1. Baseline Characteristics

Variable	OR	95% CI	p-value
Age	1,07	1.01 – 1.14	0,017
History of decompensation	3,6	1.2 – 11.2	0,02
History of variceal bleeding	3,87	1.05 – 14.2	0,04
SAHL-S	0,84	0.73 – 0.95	0,009

Table 2. Univariate logistic regression analysis.

Variable	OR	95% CI	p-value
History of variceal bleeding	5,2	1.18 – 23.0	0,02
SAHL-S	0,86	0.76 – 0.98	0,03

Tabla 3. Multivariate logistic regression analysis

Disclosures: ISMAEL YEPES: Nothing to Disclose, NICOLE CHAMORRO: Nothing to Disclose, GUILLERMO DONADO: Nothing to Disclose

2240 | LONGITUDINAL CHANGES IN HEPATOCELLULAR CARCINOMA SURVEILLANCE PATTERNS AMONG SAFETY-NET HEALTH SYSTEM PATIENTS WITH CIRRHOSIS

Robert Wong[1] Patricia Jones[2] Bolin Niu[3] Paulo Pinheiro[4] Mae Thamer[5] Onkar Kshirsagar[6] Yi Zhang[6] Ronnie Fass[3] Daniela Prieto Bello[4] Lisa Quirk[7] George Therapondos[8] Amit Singal[7] Mandana Khalili[9], [1]VA Palo Alto Healthcare System, [2]University of North Carolina at Chapel Hill, [3]MetroHealth Medical Center, [4]University of Miami, [5]Medical Technology and Practice Patterns Institute, [6]Medical Technology and Pratice Patterns Institute, [7]University of Texas Southwestern, [8]Oschner Health System, [9]University of California, San Francisco

Background: Hepatocellular carcinoma (HCC) surveillance is suboptimal in patients with cirrhosis, particularly those with low socioeconomic status, which was further impacted by disruptions in care during the pandemic. Whether HCC surveillance has improved in recent years remains unclear. We aim to evaluate changes in HCC surveillance patterns among cirrhosis patients from pre-pandemic to four years following pandemic onset. **Methods:** We evaluated the proportion of cirrhosis patients who received HCC surveillance within 6 months of study entry among those who had $\geq$6 months of follow-up across three periods: 3/1/2018-2/29/2020 vs. 3/1/2020-2/28/2022 vs. 3/1/2022-2/29/2024. Patients with baseline HCC were excluded. Appropriate HCC surveillance was determined by CPT codes for imaging type and associated ICD-9/10-CM codes for indication. Proportions receiving HCC surveillance across the three periods were compared using

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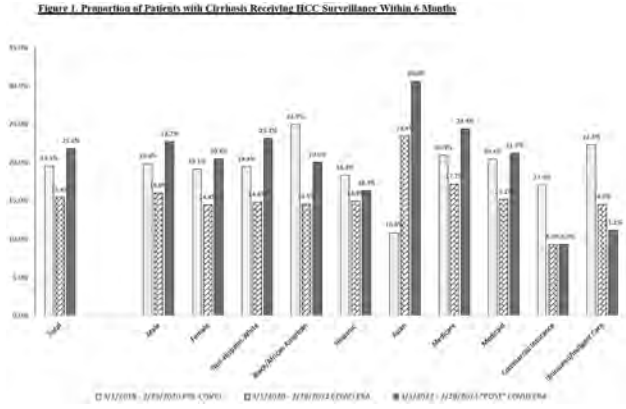
paired t-tests and stratified by gender, race/ethnicity, and insurance. **Results:** Among 4,229 patients with cirrhosis (60.3% men, mean age 56.8y, 72.3% non-White race/ethnicity, 28.3% Medicare, 25.8% Medicaid, 25.7% uninsured/indigent care), HCC surveillance declined from 19.5% to 15.4% following pandemic onset, but has improved to 21.8% in the "post" COVID-19 period (Figure). Similar patterns were observed by gender. Surveillance in all race/ethnic groups except Asians declined following pandemic and have since increased. However, surveillance among Hispanics and Black/African Americans remains below pre-pandemic levels. In the most recent years, HCC surveillance occurred in 30.6% of Asians vs. 23.1% in non-Hispanic whites ($p < 0.01$), the group with the next highest proportion. Medicare and Medicaid patients experienced lower HCC surveillance following pandemic onset, but have since increased to pre-pandemic levels. Surveillance in commercially insured patients declined and remained low. Surveillance among uninsured/indigent care patients continued to decline even 4 years following pandemic. **Conclusion:** Among a multi-center safety-net cohort of cirrhosis patients, declines in HCC surveillance following pandemic have since improved, with the exception of Black/African Americans, Hispanics, and commercially insured patients. HCC surveillance among uninsured/indigent care patients continued to decline even four years following pandemic onset, highlighting the need for novel targeted interventions to improve HCC surveillance among this high-risk group.



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2241 | SOCIO-DEMOGRAPHIC FACTORS ASSOCIATED WITH LINKAGE TO SPECIALTY CARE AMONG PATIENTS WITH CIRRHOSIS-RELATED DIAGNOSES AT TWO LARGE HOSPITAL SYSTEMS

Reid Grinspoon[1] Allison McCoy[2] Jianhua Li[3] Sara Horst[2] Julia Wattacheril[3], [1]NewYork-Presbyterian Hospital, [2]Vanderbilt University Medical Center, [3]Columbia University Irving Medical Center

Background: Specialty care from a gastroenterologist or hepatologist is associated with better outcomes in patients with liver disease. Sociodemographic factors are also associated with outcomes in liver disease, but the relationship between these factors and access to specialty care is not fully characterized, particularly within large hospital networks. **Methods:** Using electronic health record data from Vanderbilt University Medical Center (VUMC) and Columbia University Irving Medical (CUIMC), we identified patients whose records contained at least one of fifteen ICD 9/10 codes associated with cirrhosis with a clinical encounter at VUMC or CUIMC between 2/1/2020 and 8/31/2023. We determined if each patient had at least one outpatient visit with a gastroenterologist or hepatologist ('specialty care') in their hospital network in this period. We analyzed elements including gender, language, ethnicity, race, and primary insurance and compared patients with and without specialty care at each site. **Results:** There were 37899 patients that met criteria at VUMC and 24319 at CUIMC. 40% of patients at VUMC who met criteria had specialty care, versus 20.3% at CUIMC. At VUMC there was a higher proportion of female patients among those with specialty care (50.4% vs 45.9%, $p < 0.001$), but no significant difference at CUIMC. At VUMC, English as primary language was

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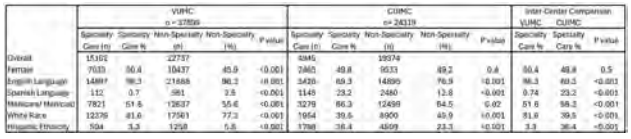
more common among specialty patients (98.3% vs 96.3%, p < 0.001), which was not seen at CUIMC (69.3% vs 76.9%, p < 0.001). At VUMC, Spanish as primary language was rarer among specialty patients (0.7% vs 2.4%, p < 0.001) in contrast with CUIMC where Spanish language was common and associated with specialty care (23.2% vs 12.8%, p < 0.001). At VUMC Medicare/Medicaid as primary insurance was less common in the specialty care group (51.6% vs 55.6%, p < 0.001), in contrast to CUIMC (66.3% vs 64.5%, p = 0.02). At VUMC, White race was more common (81.6% vs 77.2%, p < 0.001) and Hispanic ethnicity less common (3.3% vs 5.5%, p < 0.001) in the specialty group, while at CUIMC White race was less common (39.5 vs 45.9%, p < 0.001) and Hispanic ethnicity more common (36.4% vs 23.3%, p < 0.001) in the specialty group. **Conclusion:** The associations between select sociodemographic factors and linkage to specialty care varied significantly between sites. This reflects differences in patient populations, network practices, or other factors. Further study to better characterize these differences and contributing factors may lead to improved linkage to specialty care at large referral centers.

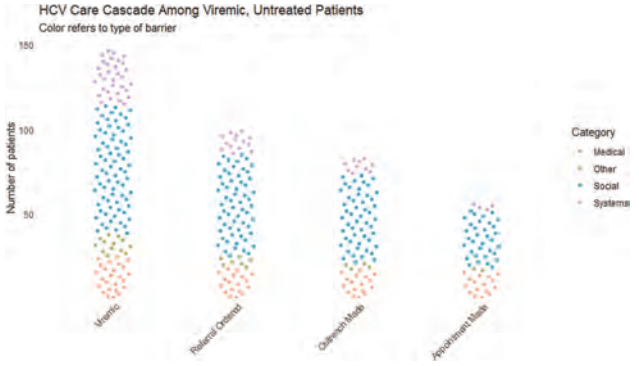


Disclosures: Reid Grinspoon: Nothing to Disclose, Allison McCoy: Nothing to Disclose, Jianhua Li: Nothing to Disclose, Sara Horst: J&J: Consultant, Abbvie: Consultant, Pfizer: Consultant, Takeda: Consultant, Biocon: Consultant, Celltrion: Consultant, Julia Wattacheril: Regeneron Pharmaceuticals: clinical trials, Galectin Therapeutics: clinical trials, Astra Zeneca: Advisor, GlaxoSmithKline: Advisor

2242 | REACHING THE REMAINING ONE-THIRD: A REVIEW OF BARRIERS TO HEPATITIS C ELIMINATION WITHIN A LARGE ACADEMIC MEDICAL CENTER

Hannah Laird[1] Margaret Hayden[2] Shaina Hasan[2] Tsola Efejuku[2] Neeral Shah[2] Kathleen McManus[3] Sanjay Kishore[2], [1]University of Virginia Medical Center, [2]University of Virginia, [3]Division of Infectious Diseases and International Health, University of Virginia Medical Center

Background: Hepatitis C elimination is a national priority. However, national data suggest fewer than 1 in 3 patients initiate treatment within a year of diagnosis. Reasons for a failure of linkage to care is poorly understood. We aimed to characterize gaps in the care cascade for those with a confirmed HCV RNA + but without treatment. **Methods:** The HCV cascade of care from January 2023 - February 2025 was analyzed using structured EHR queries at a single academic medical center. Chart reviews were performed on all patients with a detectable HCV viral load but without evidence of treatment. Descriptive statistics were used to compare patients who were treated and those that were not (Wilcoxon rank-sum test for continuous and Pearson's chi-square test for categorical variables). Finally, a primary barrier to treatment was characterized using thematic analysis. Treatment barriers were classified as a health systems gap (lack of referral, referral outside of system without follow-up), medical complexity (cancer diagnosis, transplant evaluation, advanced illness), or social determinants of health (incarceration, transportation, homelessness, inability to contact for follow-up). **Results:** Of 391 viremic patients, 245 (63%) had a record of treatment, there were no significant differences with the population by age, race, PCP, or fibrosis status; patients not prescribed antivirals were more likely to have documented mental health (74 vs. 51%; p < 0.001) and substance use diagnoses (41% vs. 26%; p < 0.001), and less likely to have commercial insurance (12% vs. 24%, p = 0.002). Of 146 patients without treatment, 68% had a referral, 58% had been contacted for future care, and 39% had an in-person appointment. Chart review revealed 53% had a social determinant, 18% had a medical barrier, and 22% for a health systems gap. **Conclusion:** Even within an academic medical center with above-average treatment rates, over one-third of patients with HCV RNA + remain untreated. Most had identifiable barriers ranging from incarceration and homelessness to terminal illness and missed referrals. Though much progress has been made, HCV elimination among may require proactive, decentralized interventions - including population health surveillance, inpatient/ED-initiated treatment, mobile outreach, telehealth, and enhanced data interoperability.



Disclosures: Hannah Laird: Nothing to Disclose, Margaret Hayden: Nothing to Disclose, Shaina Hasan: Nothing to Disclose, Tsola Efejuku: Nothing to Disclose, Neeral Shah: McGraw Hill Publishing: Royalties or

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◆ 2243 | PERFORMANCES OF BAVENO VII AND AASLD 2024 CRITERIA FOR IDENTIFYING CLINICALLY SIGNIFICANT PORTAL HYPERTENSION WITH GASTROESOPHAGEAL VARICES IN TREATMENT-NAIVE PATIENTS WITH HDV CIRRHOSIS: A MULTICENTER VALIDATION STUDY

Maria Paola Anolli[1] Elisabetta Degasperi[1] Giulia Tosetti[1] Martina Lucà[1] Liana Gheorghe[2] Alessandro Loglio[3] Alessia Ciancio[4] Gianpiero D'Offizi[5] Mathias Jachs[6] Christoph Schramm[7] Maurizia Brunetto[8] Florian van Bömmel[9] Serena Zaltron[10] Laura Turco[11] Caroline Zoellner[12] Teresa Santantonio[13] Ivana Carey[14] Alessandro Federico[15] Loredana Sarmati[16] Maria Buti[17] Mariana Cardoso[18] Filomena Morisco[19] Margarita Papatheodoridi[20] Francesco Paolo Russo[21] Alessandra Mangia[22] Pierluigi Toniutto[23] Nicola Coppola[24] Christopher Dietz Fricke[25] Jérome Dumortier[26] Edoardo Giovanni Giannini[27] Elena Rosselli Del Turco[28] Soo Aleman[29] Stella De Nicola[30] Mara Maracci[31] Letizia Marinaro[32] Michele Milella[33] Adriano Pellicelli[34] Biagio Pinchera[35] Massimo Puoti[36] Dominique Roulot[37] Lory Saveria Crocè[38] Ivana Maida[39] Uta Merle[40] Angelo Pan[41] Pietro Torre[42] Francesca Pileri[43] Antonietta Romano[44] Matteo Tonnini[45] Paola Vitiello[46] Rosa Zampino[47] Pietro Lampertico[1], [1]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [2]Center for Digestive Diseases and Liver Transplantation, Fundeni Clinical Institute, Bucharest, [3]Gastroenterology, Hepatology and Transplantation Division, ASST Papa Giovanni XXIII, Bergamo, Italy, [4]Gastroenterology Division of Città della Salute e della Scienza of Turin, University Hospital, Turin, [5]Istituto Nazionale per le Malattie Infettive "L. 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Background: Esophageal varices (EV) on esophagogastroduodenoscopy (EGD) indicate the presence of or characterize clinically significant portal hypertension (CSPH). Non-invasive tests (NITs) are used for assessing the risk for CSPH with EV in several liver diseases, but HDV specific cut-offs are yet to be defined. We sought NITs-based criteria to predict EV in CHD patients. **Methods:** Untreated patients with HDV cirrhosis and available liver stiffness measurement (LSM) and EGD from the multicenter SAVE-D and D-SHIELD studies were included. To "rule in" CSPH the Baveno VII and AASLD criteria were applied (LSM $\geq$25 kPa; LSM $>$20 kPa + platelets [PLT] $<$150x10^9/L). To "rule out" LSM $\leq$15 kPa plus PLT 150x10^9/L. Spleen stiffness measurement (SSM) was added to combined criteria: "rule in" if $\geq$2 of LSM $>$20 kPa + PLT $<$150 x10^9/L + SSM $>$50 kPa; "rule out" if $\geq$2 of LSM $\leq$ 15 kPa + PLT 150x10^9 + SSM $<$21 kPa. **Results:** 347/660 patients with HDV-related compensated cirrhosis from the SAVE-D and D-SHIELD studies were included. 154 (44%) showed EV. 53/85 (62%) fulfilling Baveno VII "rule in" criteria had EV (62%), but 101 (66%) with EV had LSM $<$25 kPa, corresponding to a Specificity (Sp) of 83% and a Positive Predictive Value (PPV) of 62%. 70/108 (65%) patients fulfilling the AASLD "rule in" criteria had EV. 84 (55%) patients with EV did not fulfill these "rule in" criteria, resulting in Sp of 80% and PPV 65%. The "rule out" criteria featured a Sensitivity (Sn) of 21% and a Negative Predictive Value (NPV) of 50%, with 41/46 (89%) patients with the "rule out" criteria not showing EV. 5 (11%) patients had missed varices. 216 (62%) and 185 (53%) patients fell in the "grey zone", with a prevalence of varices of 44% and 41%, respectively. Among 74 patients who performed SSM, the addition of SSM $>$50 kPa to the "rule in" criteria improved Sn (73% *vs.* 46%) but reduced Sp (73% *vs.* 80%) while PPV did not change (69% *vs.* 65%). As for "rule out" criteria, the addition of SSM $<$20 kPa improved both Sn (34% *vs.* 21%) and NPV (53% *vs.* 50%). **Conclusion:** The Baveno VII and AASLD criteria, show suboptimal performances in identifying HDV cirrhotics with clinically significant portal hypertension (CSPH) with gastroesophageal varices (EV), compared to other liver disease etiologies. Relying solely on NIT-based criteria to avoid endoscopic screening in these patients may misclassify individuals who have developed EV and are at increased risk of decompensating events.

Disclosures: Maria Paola Anolli: Nothing to Disclose, Elisabetta Degasperi: Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, IPSEN: Speaking and Teaching, Giulia Tosetti: Nothing to Disclose, Martina Lucà: Nothing to Disclose, Liana Gheorghe: Nothing to Disclose, Alessandro Loglio: Nothing to Disclose, Alessia Ciancio: Nothing to Disclose, Gianpiero D'Offizi: Nothing to Disclose, Mathias Jachs: Gilead Sciences Inc.: Speaker and/or consultant, Echosens Inc.: Speaking and Teaching, Christoph Schramm: Nothing to Disclose, Maurizia Brunetto: Nothing to Disclose, Florian van Bömmel: Nothing to Disclose, Serena Zaltron: Nothing to Disclose, Laura Turco: Nothing to Disclose, Caroline Zoellner: Nothing to Disclose, Teresa Santantonio: Nothing to Disclose, Ivana Carey: Nothing to Disclose, Alessandro Federico: Nothing to Disclose, Loredana Sarmati: Nothing to Disclose, Maria Buti: Nothing to Disclose, Mariana Cardoso: Nothing to Disclose, Filomena Morisco: Nothing to Disclose, Margarita Papatheodoridi: Nothing to Disclose, Francesco Paolo Russo: Nothing to Disclose, Alessandra Mangia: Gilead: Grant/Research Support, Madrigal: Consultant, Pierluigi Toniutto: Nothing to Disclose, Nicola Coppola: Nothing to Disclose, Christopher Dietz Fricke: Nothing to Disclose, Jérome Dumortier: Nothing to Disclose, Edoardo Giovanni Giannini: Ipsen: Advisor, Ipsen: Speaking and Teaching, Gilead: Advisor, Gilead: Speaking and Teaching, Roche: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Elena Rosselli Del Turco: Nothing to Disclose, Soo Aleman: Nothing to Disclose, Stella De Nicola: Nothing to Disclose, Mara Maracci: Nothing to Disclose, Letizia Marinaro: Nothing to Disclose, Michele Milella: Nothing to Disclose, Adriano Pellicelli: Nothing to Disclose, Biagio Pinchera: Nothing to Disclose, Massimo Puoti: Nothing to Disclose, Dominique Roulot: Gilead: Consultant, Lory Saveria Crocè: Nothing to Disclose, Ivana Maida: Nothing to Disclose, Uta Merle: Gilead: Speaking and Teaching, Falk: Speaking and Teaching, Microbiotica: Speaking and Teaching, Boehringer Ingelheim: Speaking and Teaching, GSK: Speaking and Teaching, Ipsen: Speaking and Teaching, CSL Behring: Advisor, Angelo Pan: Nothing to Disclose, Pietro Torre: Nothing to Disclose, Francesca Pileri: Nothing to Disclose, Antonietta Romano: Nothing to Disclose, Matteo Tonnini: Nothing to Disclose, Paola Vitiello: Nothing to Disclose, Rosa Zampino: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose

◆ 2244 | ONE-POT ASSAY BASED ON CRISPR/CAS13A TECHNOLOGY FOR HEV RNA POINT-OF-CARE TESTING

Feng Ren[1] Zihao Fan[1] Ling Xu[1], [1]Beijing Institute of Hepatology/Beijing Youan Hospital, Capital Medical University, Beijing, China

Background: Hepatitis E virus (HEV) poses a serious threat to both public health and animal food safety, thereby highlighting the demands for rapid, sensitive, and easy-to-use detection. This study aimed to develop a One-Pot assay using CRISPR/Cas13a for detecting HEV RNA, suitable for point-of-care testing (POCT) in resource-limited settings. **Methods:** We established, optimized, and evaluated the methods for HEV RNA detection using CRISPR/Cas13a combined with reverse transcription polymerase chain reaction (RT-

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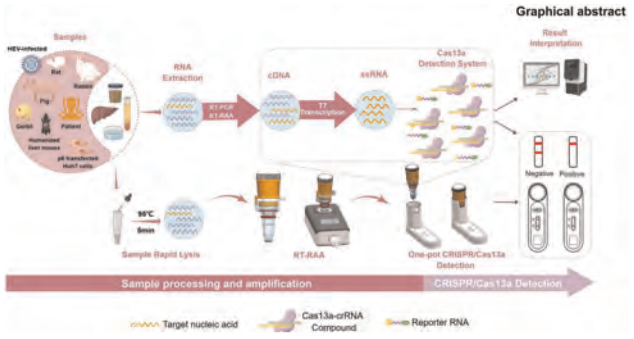
PCR) and reverse transcription recombinase-aided amplification (RT-RAA). Additionally, a large cohort of 154 HEV-infected patients and 74 HEV-infected animal specimens were utilized for application validation. **Results:** The RT-PCR/RT-RAA+CRISPR/Cas13a assays for HEV RNA detection (genotypes: HEV-1, HEV-3, and HEV-4) were established, optimized, and validated, achieving a limit of detection (LoD) of 1copy/μL and 100% specificity. In the HEV-infected application validation (ddPCR assay as the gold standard), the positivity rates of patients detected by RT-qPCR, RT-PCR-CRISPR and RT-RAA-CRISPR assays were 70.8%, 98.6%, and 79.2%, respectively, and among animals were 75.8%, 95.2%, and 87.1%, respectively, which were superior to those of RT-qPCR. Furthermore, sample rapid lysis, reagent lyophilization, and the One-Pot device were integrated to construct a One-Pot assay with an LoD of 102copies/μL. The 5-minute rapid lysis of processed specimens (serum and feces) significantly reduces the assay time to 35min, making it easy to perform, minimizing contamination, and meeting the requirements for screening. **Conclusion:** We developed a One-Pot assay for HEV RNA detection using CRISPR/Cas13a, which effectively achieves a "sample in, result out" POCT system, maximizes the potential for POCT implementation, and shows promise as a valuable tool for detecting and monitoring HEV infection.



Disclosures: Feng Ren: Nothing to Disclose, Zihao Fan: Nothing to Disclose, Ling Xu: Nothing to Disclose

◆ 2245 | PERSISTENT LOW VIREMIC RELAPSE VS HIGH VIREMIC RELAPSE AFTER THE END OF TREATMENT WITH BULEVIRTIDE WITH OR WITHOUT PEGYLATED INTERFERON IN PATIENTS WITH CHRONIC HEPATITIS DELTA VIRUS

Fabien Zoulim[1] Tarik Asselah[2] Soo Aleman[3] Maurizia Brunetto[4] Vladimir Chulanov[5] Adrian Streinu-Cercel[6] George Gherlan[7] Pavel Bogomolov[8] Tatiana Stepanova[9] Viacheslav Morozov[10] Olga Sagalova[11] Amos Lichtman[12] Dmitry Manuilov[12] Yuejiao Jiang[12] Heiner Wedemeyer[13] Pietro Lampertico[14], [1]Lyon Hepatology Institute, Lyon, France, [2]Hôpital Beaujon APHP, Université de Paris-Cité, INSERM UMR1149, Clichy, France, [3]Karolinska University Hospital/ Karolinska Institutet, Stockholm, Sweden, [4]University Hospital of Pisa; University of Pisa, Pisa, Italy, [5]Sechenov University, Moscow, Russian Federation, [6]NIID Prof Dr Matei Bals; University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania, [7]Dr Victor Babes Foundation; Univ of Medicine & Pharmacy "Carol Davila" Bucharest, Bucharest, Romania, [8]M.F. Vladimirsky Moscow Regional Research and Clinical Institute, Moscow, Russian Federation, [9]LLC Clinic of Modern Medicine, Moscow, Russian Federation, [10]LLC Medical Company Hepatolog, Samara, Russian Federation, [11]South Ural State Medical University, Chelyabinsk, Russian Federation, [12]Gilead Sciences, Inc., [13]Hannover Medical School, Hannover, Germany, [14]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico and University of Milan, Milan, Italy

Background: Bulevirtide (BLV) 2 mg is approved for treatment of chronic hepatitis delta virus (HDV) infection. Previous analyses showed that achieving undetectable HDV RNA at end of treatment (EOT) is required to maintain undetectable viremia post-treatment; patients (pts) with low-level viremia at EOT are likely to have increased HDV RNA off treatment. This pooled analysis of BLV 2 or 10 mg monotherapy or combined with pegylated interferon alpha (PegIFNα) investigated the posttreatment outcomes in pts who achieved undetectable HDV RNA by EOT and had low viremic relapse with HDV RNA below the lower limit of quantitation (<LLOQ; target detected [TD]). **Methods:** Pts from the MYR204 (NCT03852433) and MYR301 (NCT03852719) studies were included; pts received BLV 2 mg + PegIFNα for 48 weeks (W) followed by 48W of BLV 2 mg monotherapy (n = 50); BLV 10 mg + PegIFNα for 48W followed by 48W of BLV 10 mg monotherapy (n = 50); BLV 10 mg for 96W (n = 100), BLV 2 mg for 144W (n = 49), or BLV 10 mg for 144W (n = 50) and were followed up (FU) for 48W (FU48) after EOT. HDV RNA was determined using RoboGene 2.0 (LLOQ = 50 IU/mL; limit of detection = 6 IU/mL). High viremic relapse was defined as HDV RNA levels ≥LLOQ. **Results:** At EOT, 131 of 299 (44%) pts achieved undetectable HDV RNA and had FU data available. Of these, 57 (44%) had undetectable HDV RNA at all posttreatment FU visits, 60 (46%) had high viremic relapse, and 14 (11%) had low-level viremia that remained <LLOQ. Pts with low viremic relapse maintained their rates of alanine aminotransferase (ALT) normalization in the posttreatment period: 9/14 (64%) at EOT and 11/14

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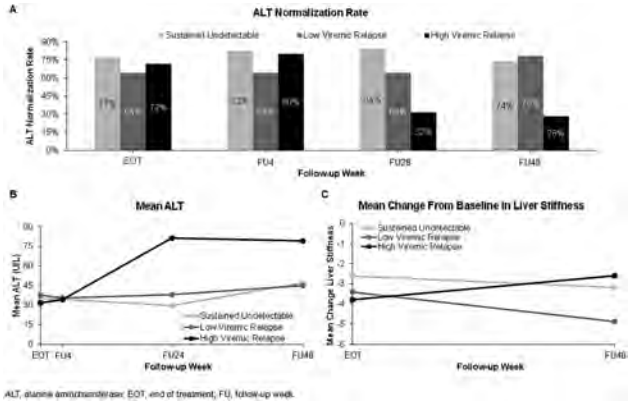
(79%) at FU48; results were similar in pts with no relapse (44/57 [77%] and 42/57 [74%] at EOT and FU48, respectively). In contrast, rates of ALT normalization in pts with high viremic relapse decreased during FU: 43/60 (72%) at EOT; 17/60 (28%) at FU48. Similar results were seen with mean ALT during FU. Mean liver stiffness increased only in pts with high viremic relapse. **Conclusion:** Most pts treated with BLV alone or in combination with PegIFNα who achieved undetectable HDV RNA at EOT either sustained undetectable HDV RNA post-treatment or had high viremic relapse, which was associated with loss of biochemical response. However, a small subset of pts had only low-level virological relapse (< 50 units) and maintained biochemical response; there was no progression to high viremic relapse after 1 year. The clinical significance of low-level viremia in the posttreatment period remains to be elucidated.



ALT, alanine aminotransferase; EOT, end of treatment; FU, follow-up week.

Disclosures: Fabien Zoulim: Ausperbio: Grant/Research Support, Ausperbio: Consultant, Blue Jay: Grant/Research Support, Blue Jay: Consultant, Aligos: Grant/Research Support, Aligos: Consultant, Gilead: Consultant, GSK: Consultant, nChroma: Consultant, Precision: Consultant, Tarik Asselah: GSK: Speaker, GILEAD: Consultant, VIR Biotechnology: Speaker, Roche: consultant, ABBVIE: Speaking and Teaching, Aligos therapeutics: Consultant, Bluejay Therapeutics: Consultant, Antios therapeutics: Consultant, GSK: Consultant, Soo Aleman: Nothing to Disclose, Maurizia Brunetto: Nothing to Disclose, Vladimir Chulanov: Nothing to Disclose, Adrian Streinu-Cercel: Nothing to Disclose, George Gherlan: Nothing to Disclose, Pavel Bogomolov: Nothing to Disclose, Tatiana Stepanova: Nothing to Disclose, Viacheslav Morozov: Nothing to Disclose, Olga Sagalova: Nothing to Disclose, Amos Lichtman: Nothing to Disclose, Dmitry Manuilov: Nothing to Disclose, Yuejiao Jiang: Nothing to Disclose, Heiner Wedemeyer: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose

◆ 2246 | IMPACT OF HDV GENOMIC SEQUENCE VARIATION ON VIRAL INFECTIVITY, INNATE IMMUNE RESPONSES, AND ANTIVIRAL TREATMENT EFFICACY IN PRIMARY HUMAN HEPATOCYTES

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Background: Hepatitis delta virus (HDV) is a subviral agent dependent on hepatitis B virus (HBV) that potently accelerates liver disease progression and, thus, poses a significant global health burden. HDV exhibits substantial genetic heterogeneity, forming eight distinct genotypes with unique geographic distributions. The genetic divergence among HDV genotypes is postulated to influence clinical manifestations, such as the severity of hepatic necroinflammation, fibrosis progression, and hepatocellular carcinoma incidence. However, clinical outcomes may also be affected by genomic variability of co-infecting HBV strains, host genetics, and region-specific comorbidities. Thus, this study aims to decipher the poorly understood genotype- and strain-specific factors underlying HDV-associated clinical heterogeneity using our state-of-the-art in vitro primary human hepatocyte (PHHs) culture system. **Methods:** We selected 16 distinct HDV strains across all eight genotypes, with each genotype represented by clinically aggressive strains and genetically distinct counterparts. For each strain, a 1.2-fold full-length HDV genomic RNA sequence flanked by ribozyme sites was cloned into a pcDNA3.1(+) expression vector. Each HDV-encoding plasmid was co-transfected with an HBsAg-expressing plasmid into Huh7.5 cells to produce HDV infectious particles. These particles were used to mono-infect or HBV-HDV coinfect PHHs maintained under optimized culture conditions that preserve the genuine characteristics of human hepatocytes. Following infection, intracellular and extracellular HDV RNA, HBV DNA, and virus-host interactions were genetically quantified. **Results:** Each HDV strain demonstrated substantial variability in viral replication efficiency and activation of innate antiviral responses, as quantified by the induction of interferon-stimulated genes (ISGs). Notably, these differences were not only genotype-specific but also strain-specific. Intergenotype comparison revealed that HDV-3c and HDV-1a exhibited the highest replication efficiencies, which correlated with strong activation of the innate antiviral response. Within each HDV genotype, subgenotype strains presented significant variability in ISG induction, replication efficiency, and sensitivity to IFN-based antiviral treatment. **Conclusion:** This study presents the first comprehensive cross-sectional comparison of multiple strains within each of the eight HDV genotypes and subgenotypes utilizing the most physiologically relevant model available. Our observations highlight

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genotype- and strain-specific differences in viral fitness, activation of hepatic innate antiviral responses, and responsiveness to antiviral therapy. These factors underscore the strain-specific nature of HDV, potentially influencing natural history of the disease and therapeutic outcomes. **Disclosures:** Daniel Pinski: Nothing to Disclose, Ju Won Kim: Nothing to Disclose, Masashi Okawa: Nothing to Disclose, Yein Woo: Nothing to Disclose, Garnik Arustamyan: Nothing to Disclose, Meng Li: Nothing to Disclose, Takeshi Saito: PhoenixBio: Grant/Research Support, Sekisui USA: Grant/Research Support, EA Pharma: Consultant, Quotient Therapeutics: Consultant, CytoPathfinder, Inc.: Consultant

◆ 2247 | RATES OF HDV RNA UNDETECTABILITY DURING LONG-TERM BULEVERTIDE MONOTHERPAY IN PATIENTS WITH CHD ARE ASSAY-DEPENDENT

Maria Paola Anolli[1] Sara Uceda Renteria[1] Elisabetta Degasperi[1] Floriana Facchetti[1] Dana Sambarino[1] Marta Borghi[1] Riccardo Perbellini[1] Roberta Soffredini[1] Sara Monico[1] Annapaola Callegaro[1] Pietro Lampertico[1], [1]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Background: A recent pooled analysis from the MYR2 204 and MYR301 studies suggested that, in patients with compensated CHD, the achievement of undetectable HDV RNA at EOT predicts maintaining undetectable viremia in the posttreatment period. [PL1] In this study, we compared two sensible methods for HDV-RNA quantification in long-term Bulevirtide (BLV)-treated CHD patients. **Methods:** Frozen plasma samples from BLV–treated CHD patients were tested in parallel on the same day by 2 different sensitive commercially available assays: Robogene HDV-RNA Quantification Kit 2.0 [Roboscreen GmbH; Lower Limit of Detection (LOD) 6 IU/mL)], and AltoStar HDV RT-PCR RUO Kit 1.5 (Altona Diagnostics GmbH, estimated LOD 1.12 IU/mL). **Results:** 173 plasma samples collected from 69 BLV-treated compensated CHD patients were studied by 2 different assays (overall 346 tests): median age was 54 (43-62), 71% were men, 90% had cirrhosis, 100% were HDV genotype 1 (available in 68 patients), 91% were HBeAg negative. Median ALT levels were 33 (27-40) IU/mL. Overall, HDV RNA levels were 2.79 (1.87-4.11) Log IU/mL with Robogene 2.0, and 2.78 (1.99-4.18) IU/mL with AltoStar ($p < 0.001$). Rates of HDV RNA undetectability, defined as target not detected (TND), during BLV therapy differed between the two assays after a median duration of BLV monotherapy of 60 weeks (IQR 36-120), 28 (16%) samples tested TND with Robogene 2.0 and 15 (9%) with AltoStar ($p = 0.049$). Of the 28 samples TND by Robogene 2.0, 16 (57%) tested positive with AltoStar, median HDV RNA being 0.54 (IQR 0.30-1.01) log IU/mL. Conversely, only 2 (13,3%) samples of the 15 testing TND with AltoStar resulted positive with Robogene 2.0, HDV RNA being 2.27 and 1.0 Log IU/mL, respectively. **Conclusion:** The proportion of patients achieving HDV RNA TND during long-term BLV monotherapy significantly differed according to the quantification assay used. These findings call attention to the urgency for further studies in this clinical setting to adequately identify patients who could safely withdraw BLV monotherapy.
Disclosures: Maria Paola Anolli: Nothing to Disclose, Sara Uceda Renteria: Nothing to Disclose, Elisabetta Degasperi: Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, IPSEN: Speaking and Teaching, Floriana Facchetti: Nothing to Disclose, Dana Sambarino: Nothing to Disclose, Marta Borghi: Nothing to Disclose, Riccardo Perbellini: Nothing to Disclose, Roberta Soffredini: Nothing to Disclose, Sara Monico: Nothing to Disclose, Annapaola Callegaro: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose

◆ 2248 | PLASMA METABOLOMICS AND 16S RRNA SEQUENCING IDENTIFIES DISTINCT SIGNATURES OF WORSE OUTCOMES IN HEPATITIS A-INDUCED ACUTE LIVER FAILURE COMPARED TO DRUG INDUCED LIVER FAILURE

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Background: Acute liver failure due to Hepatitis A (ALF-A), is an important cause of ALF in Asia. Outcomes in ALF depend on gut microbiota, immunity, systemic inflammation and altered metabolic milieu. We aimed to identify distinct signatures in ALF-A versus drug induced ALF to identify etiology specific signatures, specially predicting 90-day survival. **Methods:** One-hundred seventeen subjects (aged 26 ± 9 yrs) were compared: 1)acute viral hepatitis (IgM HAV positive,AVH-A, $n = 27$, ALT/AST > 10xULN), 2)acute liver failure (ALF-A, $n = 33$, ALT/AST > 10xULN with INR > 1.5 and hepatic encephalopathy), 3)drug-induced acute liver failure (ALF-D, $n = 37$, ALF features with definite evidence of DILI, and 4)healthy controls

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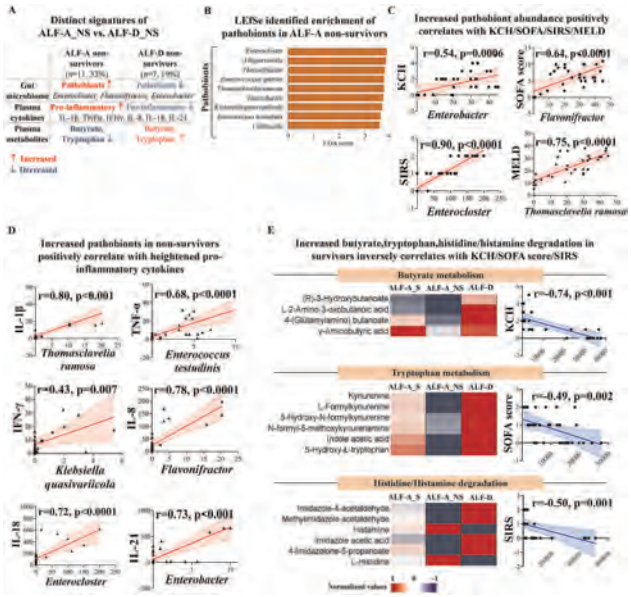
(HC, n = 20). 16SrNA sequencing was performed in stool at baseline; plasma metabolomics and multiplex cytokines were assessed till one week. Clinical and biochemical parameters and indices were compared in survivors (S) and non-survivors (NS) in ALF-A vs ALF-D upto 90 days. **Results:** ALF-A patients had worse outcomes;21% meeting KCH criteria,SOFA score 7.97 ± 2.89, 60.6% with SIRS and 39% required mechanical ventilation compared to ALF-D (11% met KCH criteria, SOFA score 5.87 ± 2.32, 18.4% SIRS and 21% required mechanical ventilation). Within 90 days, 33% were NS in ALF-A (11/33) compared to 19% in ALF-D (7/37)(Fig.A). ALF-A_NS exhibited marked enrichment of inflammatory and mucin-degrading pathobionts (LDA > 3); *Enterocloster*, *Flavonifractor*, *Thomasclavelia ramosa*, *Enterobacter*, *Klebsiella quasivariicola*, *Enterococcus testudinis* compared to ALF-D_NS (Fig.B). This altered pathobiont positively correlated with KCH, SOFA, SIRS, MELD scores ($r > 0.5$, $p < 0.05$) (Fig.C). These pathobionts also positively correlated with pro-inflammatory cytokines, such as IL-1β, TNFα, IFN-γ, IL-8, IL-18, IL-21 in ALF-A_NS(Fig.D). On the other hand, significant increase in butyrate, tryptophan, histidine/histamine degradation in ALF-A_S patients was seen compared to ALF-A_NS, which inversely correlated with KCH, SOFA scores,SIRS ($r < -0.5$, $p < 0.05$)(Fig.E). ALF-D_NS were uniquely characterized by enrichment of fatty acid, glycerophospholipid metabolism, histidine degradation, distinguishing them from ALF-A_NS. **Conclusion:** In ALF-A non-survivors, enrichment of inflammatory pathobionts positively correlated, while depleted butyrate/tryptophan negatively correlated with clinically established mortality predictors- KCH, SOFA, SIRS, MELD scores, serving as unique mechanistic biomarkers that predict poor 90-day survival beyond clinical risk scores.



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◆ 2249 | HEPATITIS D IN PRISON POPULATIONS: HIGH PREVALENCE, COINFECTION WITH HCV/HIV, AND LIMITED TREATMENT ACCESS IN SPAIN

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Background: Prisons provide a valuable setting for screening and monitoring of blood-borne diseases, which are typically more common among inmates. In 2023, the prevalence of HBsAg in Spanish prisons was 1.7%, being 0.7% among Spanish inmates and 2.6% among immigrant inmates. Unlike hepatitis B and C, testing for hepatitis D still remains infrequent in prison settings. The aim of the current study was to characterize individuals who tested positive for anti-HDV antibodies and to assess their co-infection rates with HCV and HIV across 9 Spanish prisons. **Methods:** A multicenter prospective study was conducted, including all HBsAg+ samples analyzed at 9 Spanish prisons. A double reflex testing for anti-HDV and HDV RNA was performed, as well as HCV and HIV screening. Demographic, epidemiological, clinical and laboratory data for all anti-HDV positive patients were recorded on a digital platform. **Results:** From Jan 1, 2024 to 31 Mar, 2025 a total of 71 anti-HDV+ subjects were identified from the participant prisons. The median age was 42 (36-43), 93% were male, 83% were immigrants (mostly from Romania [17%] and Morocco [15%]). Seven (10%) subjects presented detectable HDV-RNA. Twenty-four (34%) had elevated ALT levels and 6/33 (18%) were cirrhotic. A total of 13 (18%) had HCV coinfection, 1 of them with active HCV infection, and 9 (13%) were anti-HIV+, 3 of them with active HIV infection. Two had a liver decompensation event (ascitis in both cases), and 1 developed an hepatocellular carcinoma. No subject underwent liver transplant or died of a liver-related cause. No viremic patients received Bulevirtide treatment during these 15 months. The majority of subjects (70%) reported no risk factors, while the most common identified risk was injection drug use (7%), followed by sexual risk behavior (4%) and blood transfusions pre-1975 (3%). **Conclusion:** This study highlights a notable presence of anti-HDV positivity among

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HBsAg+ inmates in Spanish prisons, predominantly affecting middle-aged immigrant men, with a 31% rate of HCV/HIV co-infection. These findings show the need for targeted, integrated blood-borne diseases screening programs and improved access to antiviral therapies in prison settings. This study has been financed by Gilead Sciences (IN-ES-980-7058).

Disclosures: Adriana Palom: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Indiana Abdo: Nothing to Disclose, Ariadna Rando-Segura: Nothing to Disclose, Josefina Ayats: Nothing to Disclose, Andrés Marco: Nothing to Disclose, Maria Buti: Nothing to Disclose

◆ 2250 | TWO DECADES OF HEPATITIS D IN THE UNITED STATES: ESCALATING INCIDENCE, SEX- AND RACE-SPECIFIC PATTERNS, AND NEARLY-DOUBLED RISKS OF CIRRHOSIS AND DECOMPENSATION AMONG ADULTS WITH CHRONIC HEPATITIS B

Himsikhar Khataniar[1] Renuka Verma[2] Leandro Sierra Carrero[3] Kaitlyn Gernhard[1] Daniel Huynh[4] Hany Habib[1] Nabeeha Mohy-ud-din[1] Nikki Duong[5], [1]Allegheny General Hospital, [2]UNLV, [3]Cleveland Clinic, [4]University of Washington, [5]Stanford University

Background: Globally, an estimated 12 million people are affected by hepatitis D virus (HDV), a co-infection known to accelerate the progression of chronic hepatitis B (CHB). Although the WHO recommends testing for all individuals with CHB, the AASLD recommends a risk-based screening approach. However, national real world data examining temporal and demographic trends in this population remain limited. **Methods:** Adults ≥18 years with laboratory-confirmed or ICD-coded CHB were identified across 67 health-care organizations (January 1st 2005–December 31st 2024). HDV infection was ascertained by antibody, antigen, or RNA positivity. Prevalence and incidence rates were calculated within successive five-year epochs (2005-10, 2010-15, 2015-20, 2020-25). Two separate multivariable Cox proportional-hazard models compared (A) time to first diagnosis of fibrosis/cirrhosis (ICD-10: K74) and (B) composite decompensating events (ascites, variceal bleeding, or hepatic encephalopathy) between CHB + HDV and CHB-alone cohorts. Covariates included sex, race, and Hispanic ethnicity. **Results:** Among 21,247 adults with CHB, the incident proportion of HDV infection increased 80-fold—from 0.17 % in 2005–2010 to 13.5 % in 2020–2025. Similar trends in HDV prevalence were noted, with an increase from 0.17% to 19.0%. In the most recent interval from 2020-2025, the incidence was higher in males than in females (14.2% vs 12.7%). Incidence rates also varied among the racial groups: American Indian/Alaska Native 30%, Black 17%, White 15%, and Asian 11%, though the AI/AN estimate was limited by small cell counts. Multivariable Cox analysis of 114,304 patients (4,506 with CHB + HDV and 109,798 with CHB alone) showed that HDV co-infection independently predicted both fibrosis/cirrhosis (adjusted hazard ratio [aHR] 1.96, 95 % CI 1.86–2.07; P < 0.001) and hepatic decompensation (aHR 1.79, 95 % CI 1.66–1.94; P < 0.001). Across both models, male sex (aHR = 1.7) and White race (aHR = 1.4–1.5) were linked to higher risks, whereas Black and Asian race conferred lower risks, and Hispanic ethnicity conferred moderately increased risks. **Conclusion:** This is the first study using real-world data to demonstrate that HDV increases the risk of developing cirrhosis and hepatic decompensation by nearly two-fold in patients with CHB. With rising rates of HDV over the last two decades, we must continue to prioritize our understanding of patients who are co-infected. This should begin with mandating universal HDV screening of all HBsAg-positive individuals and targeted outreach to high-risk demographic groups highlighted in our study. These findings address key knowledge gaps surrounding hepatitis D—a silent yet lethal virus—and underscore the urgent need for future research into emerging therapies and the social determinants of health that contribute to disparities in HDV-related outcomes.

Figure 1. Incidence proportion (%) of newly detected HDV per 100 adults with chronic HBV across four five-year intervals (TriNetX 2005–2025).

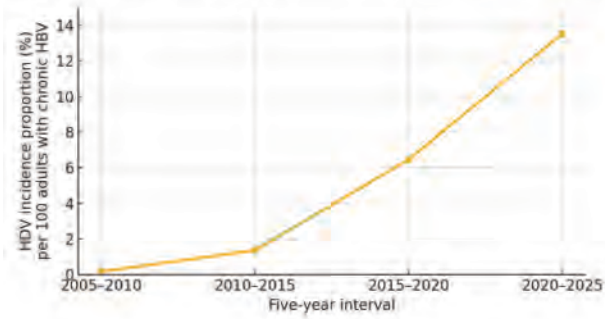

Table 1. Adjusted hazard ratios for HDV co-infection and demographic covariates

Predictor	Outcome: Fibrosis/Cirrhosis aHR (95 % CI)	Outcome: Decompensation aHR (95 % CI)
HDV co-infection	1.96 (1.86–2.07)	1.79 (1.66–1.94)
Male vs Female	1.77 (1.72–1.82)	1.73 (1.66–1.81)
White vs Other*	1.41 (1.35–1.47)	1.49 (1.40–1.58)
Black vs Other*	0.86 (0.82–0.91)	0.85 (0.79–0.91)
Asian vs Other*	0.87 (0.83–0.91)	0.68 (0.64–0.73)
Hispanic vs Non-Hispanic	1.20 (1.14–1.27)	1.27 (1.18–1.38)

*Reference category for race in TriNetX is "All Other Categories".
All p-values <0,001

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◆ 2251 | MAINTAINED HDV RNA UNDETECTABILITY DURING LONG-TERM BULEVIRTIDE MONOTHERAPY IN PATIENTS WITH HDV-RELATED COMPENSATED CIRRHOSIS: A SUBANALYSIS OF THE RETROSPECTIVE MULTICENTER EUROPEAN STUDY (SAVE-D)

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Background: Bulevirtide (BLV) monotherapy achieved >70% virological response in patients with chronic hepatitis D (CHD), however, rates of HDV RNA undetectability are lower and data about maintenance of HDV RNA undetectability during long-term treatment are still limited. **Methods:** CHD patients achieving undetectable HDV RNA at week 48 upon BLV 2 mg/day monotherapy in the retrospective European multicenter SAVE-D study were enrolled. HDV-RNA undetectability was defined as HDV RNA below the lower limit of quantification (1 log increase of HDV-RNA compared to previous levels. Virological (HDV-RNA undetectable or ≥2-log decline *vs.* baseline), biochemical (ALT <40 U/L), combined response (biochemical + virological), and liver-related events were also assessed. **Results:** Among 261 CHD patients with cirrhosis treated with BLV monotherapy for at least 48 weeks in the SAVE-D study, 70 (27%) patients achieved HDV RNA undetectability at week 48. At the same timepoint, overall rates of virological, biochemical and combined response resulted 66%, 66% and 46%, respectively. Among the 70 HDV RNA undetectable patients, paired HDV RNA data between W48 and W96 were available for n = 41, and W96-W144 data for n = 23, respectively. In W48-W96 analysis, 32/41 (78%) maintained persistent HDV RNA undetectable, 4 (10%) patients showed a transient VBK at week 72 and then returned undetectable at week 96, while 5 (12%) patients showed a stable VBK (~1 Log_{10}IU/mL in 2; ≥2 Log_{10}IU/mL in 3). Among VBK patients, biochemical response was maintained in all but one case. In the paired W96-W144 analysis, 15/23 (65%) of patients maintained HDV RNA undetectability throughout week 144, 3 (13%) showed transient VBK then returning undetectable at week 144, and 5 (22%) showed a stable VBK (~1 Log_{10}IU/mL in 3; ≥2 Log_{10}IU/mL in 2). VBK occurred mostly after W96; at the time of VBK, 3/5 patients maintained the biochemical response. De-novo liver-related events were observed in 3 patients with maintained HDV RNA undetectability (HCC n = 2; ascites n = 1) and 1 VBK (HCC); 1 VBK patient showed ascites recurrence. **Conclusion:** During long-term BLV monotherapy in CHD patients with cirrhosis, HDV RNA undetectability at week 48 was maintained overtime in most of the patients. Only few patients experienced a stable VBK and most maintained biochemical response.

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◆ 2252 | CLINICO-PATHOLOGICAL SPECTRUM AND OUTCOMES OF HEPATITIS-A OUTBREAK IN SOUTHERN INDIA: A MULTICENTRIC CROSS-SECTIONAL STUDY AND AN UPDATED ANALYSIS

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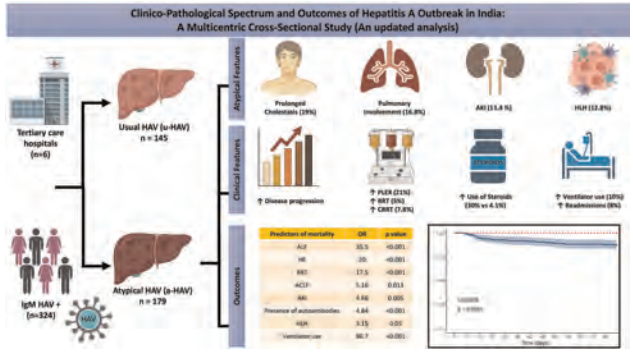
Background: Hepatitis A virus (HAV) infection is classically considered a self-limiting disease, however, a recent resurgence of HAV in Kerala State, India, raised public health concerns. Physicians reported atypical clinical phenotypes marked by persistent fever, early renal and pulmonary involvement, and occurence of hemophagocytic lymphohistiocytosis (HLH). **Methods:** We conducted a multi-centre, cross-sectional study across six tertiary care hospital in serologically confirmed acute HAV infection who were prospectively enrolled and grouped into :usual HAV (u-HAV) and atypical HAV (a-HAV). Detailed demographic, epidemiological, and clinicopathological data were collected. **Results:** A total of 324 patients (a-HAV = 179, u-HAV = 145), with the mean age of 32 ± 12.8 years, 68.2% males constitued the cohort. Clinically, a-HAV cases had significantly higher incidence of persistent fever (93% vs 12%), hepatomegaly (64% vs 44%), splenomegaly (30% vs 17%), ascites (30% vs 9%). Atypical complications like prolonged cholestasis (16%), clinical HLH (13%), acute kidney injury (AKI) (13%), metabolic acidosis (6.7%), autoantibody positivity (18% vs 0.7%; $p < 0.001$). Lab parameters reflected severe disease in a-HAV, with higher mean bilirubin (12.9 vs 6.9 mg/dL), AST (3306 vs 1880 IU/L), ALT (3350 vs 2492 IU/L), triglycerides (218.7 vs 171.4 mg/dL), ferritin (19385 vs 3154 IU/L), LDH (1955 vs 502 IU/L), INR (2.5 vs 1.5), and ammonia (99.3 vs 56.8 μmol/L). There was increased steroid use (30% vs 4.1%), plasma exchange (PLEX) (21%), continuous renal replacement therapy (CRRT) (5%), development of ACLF (7.3%), mechanical ventilation (10%), readmissions (9%) in a-HAV group. Multivariable analysis identified ALF presentation, any grade HE, RRT, ACLF, AKI, presence of autoantibodies, HLH, and mechanical ventilation independent predictors of mortality. Overall mortality in the cohort was 13%. Genotypic analysis of 56 samples identified genotype IIIA, consistent with the endemic variant. **Conclusion:** This study provides strong evidence for achanging clinico-pathological profile and possibly altered virulence of hepatitis A virus. Unlike previous outbreaks, a significant proportion of patients in our cohort had severe immune dysregulation, and multi-organ involvement. These findings underscore the need for clinical vigilance, early identification of atypical presentations, and the need for tailored management strategies to improve patient outcomes.



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◆ 2253 | SAFETY, EFFECTIVENESS AND CLINICAL OUTCOMES IN PATIENTS WITH CHRONIC HEPATITIS DELTA TREATED WITH BULEVIRTIDE MONOTHERAPY: A POOLED ANALYSIS ON 689 PATIENTS ENROLLED IN THE SAVE-D AND D-SHIELD STUDIES

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Background: Bulevirtide (BLV) 2 mg/day monotherapy demonstrated safety and effectiveness in patients with chronic hepatitis Delta (CHD), however data in large real-world cohorts of patients is lacking. **Methods:** Consecutive CHD patients starting BLV monotherapy from the multicenter SAVE-D and D-SHIELD studies were included. Virological (HDV-RNA undetectable or $\geq$2-log decline *vs.* baseline), biochemical (ALT $<$40 U/L), combined response (biochemical + virological), and liver-related events were assessed. HDV RNA was tested locally. Viral breakthrough (VBK) was defined as at least 1 Log_{10}IU/mL HDV-RNA increase from nadir. **Results:** 689 CHD patients treated with BLV 2 mg/day were enrolled. At BLV start, age was 52 (IQR 42-60) years, 58% men, ALT 75 (34-50) U/L, liver stiffness measurement 14.4 (10.4-22.3) kPa, platelets 116 (77-166) x 10^3/mm^3, 84% with cirrhosis, 33% with varices, 52% IFN-experienced, 8% HIV-positive, 93% on NUC, 6% with history of ascites and 7% of HCC. Baseline HBsAg and HDV-RNA levels were 3.7 (3.2-4.1) and 5.3 (4.1-6.3) Log_{10}IU/mL, respectively. Following 48 weeks of BLV monotherapy, 67% of patients achieved a virological, 66% biochemical, and 48% combined response, 30% HDV-RNA undetectability. At week 72, the corresponding rates were 66%, 64%, 49%, and 35%, respectively. 18% of patients had $<$1 Log HDV-RNA decline *vs.* baseline (non-virological response, NR), and 16% 1-2 Log decline (partial virological response, PR). 45% of patients with a suboptimal response (NR or PR, n = 95) achieved a biochemical response, 16% without biochemical response had at least a 50% ALT decrease compared to baseline. Among 261 patients with paired W24-48-72 data, 14 patients (5%) who had achieved a week 24 virological response had a VBK at week 48: prolonged BLV treatment rescued virological response in 4, 2 patients achieved a PR, 8 remained NR (normal ALT in 50%). In the overall population, no significant effect of BLV on HBsAg levels was observed. At multivariate analysis, lower baseline HDV RNA levels were associated with HDV RNA undetectability at week 48. De-novo liver-related events occurred in 20 cirrhotic patients: 14 HCC and 6 decompensations. **Conclusion:** BLV monotherapy 2 mg/day confirmed effectiveness and safety in two large multicenter cohorts of real-world CHD patients, independently of baseline cirrhosis. Lower baseline HDV RNA levels predicted HDV RNA undetectability at week 48. VBK and liver-related events occurred in few patients only.

Disclosures: Elisabetta Degasperi: Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, IPSEN: Speaking and Teaching, Maria Paola Anolli: Nothing to Disclose, Gianpiero D'Offizi: Nothing to Disclose, Alessia Ciancio: Nothing to Disclose, Liana Gheorghe: Nothing to Disclose, Alessandro Loglio: Nothing to Disclose, Maurizia Brunetto: Nothing to Disclose, Christoph Schramm: Nothing to Disclose, Serena Zaltron: Nothing to Disclose, Thomas Reiberger: Nothing to Disclose, Mariana Cardoso: Nothing to Disclose, Juliette Foucher: abbvie: Speaking and Teaching, GSK: Consultant, gilead: Speaking and Teaching, Maria Buti: Nothing to Disclose, Michele Milella: Nothing to Disclose, Alessandro Federico: Nothing to Disclose, Elena Rosselli Del Turco: Nothing to Disclose, Teresa Santantonio: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose, Laura Turco: Nothing to Disclose, Caroline Zollner: Nothing to

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2254 | INTEGRATED VIROLOGY ANALYSIS OF BULEVIRTIDE (BLV) MONOTHERAPY IN CHRONIC HEPATITIS DELTA: POOLED DATA THROUGH 96 WEEKS OF TREATMENT

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Background: Bulevirtide (BLV) is an entry inhibitor for chronic hepatitis delta virus (HDV) infection. This study presents integrated virology analyses from the MYR204 and MYR301 clinical trials, evaluating the virological response to BLV and assessing whether treatment was associated with emergent substitutions in the HBV PreS1 region, HDAg, or phenotypic shifts in clinical isolates from patients receiving BLV monotherapy. **Methods:** A total of 199 patients received BLV monotherapy (BLV 2 mg, N = 49; BLV 10 mg, N = 150). A control group included n = 51 patients who remained untreated during a delayed-treatment phase. Virologic response (VR): HDV RNA drop ≥ 2 $\log_{10}$ IU/mL from baseline (BL) or undetectable. The Resistance Analysis Population (RAP) included BLV-treated patients meeting virologic nonresponder (NR; < 1 $\log_{10}$ IU/mL decline at specified points through Week 144) or virologic breakthrough (VB; two consecutive HDV RNA $\geq$ LLOQ post-LLOQ, or confirmed ≥ 1 $\log_{10}$

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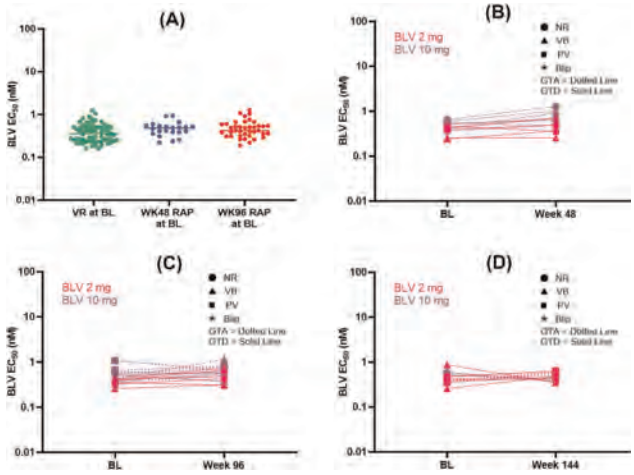
IU/mL rise from nadir at two visits) criteria. Resistance testing included sequencing analyses of HBV PreS1 BLV region, HDAg, NTCP, as well as in vitro BLV EC50 evaluation. **Results:** Among the HDV clinical isolates in this cohort, HBV genotype D (GTD) was the most prevalent (176 of 199, 88%), followed by genotype A (GTA, 14 of 199, 7%). At Week 96, 87% of patients receiving BLV 10 mg with HBV GTD (N = 129) achieved VR. Among patients with GTA (N = 12), 50% achieved VR and 58% attained ALT normalization. These endpoints were rarely achieved aamong patients in the control group. A total of 48 patients on BLV monotherapy qualified as RAP. No treatment-emergent amino acid substitutions were identified in the HBV BLV homologous region or conserved HDAg sites. NTCP polymorphisms were rare and also showed no association with BLV treatment outcome. Phenotypic analysis showed that BLV EC50 values were similar between VR and RAP isolates at BLand during BLV monotherapy through Week 144 (Fig. A-D). BLV EC50 values remained within assay variation across all subgroups, regardless of HBV/HDV polymorphisms (Fig A-D). **Conclusion:** BLV monotherapy demonstrated efficacy in patients with chronic HDV, including those with HBV GTD and GTA. Integrated virology and resistance analysis through Week 96 did not identify genotypic or phenotypic resistance to BLV, supporting its continued use as a monotherapy for the treatment of HDV infection.



Disclosures: Christopher Richards: Gilead Sciences: Employee, Tarik Asselah: GSK: Speaker, GILEAD: Consultant, VIR Biotechnology: Speaker, Roche: consultant, ABBVIE: Speaking and Teaching, Aligos therapeutics: Consultant, Bluejay Therapeutics: Consultant, Antios therapeutics: Consultant, GSK: Consultant, Fabien Zoulim: Ausperbio: Grant/Research Support, Ausperbio: Consultant, Blue Jay: Grant/Research Support, Blue Jay: Consultant, Aligos: Grant/Research Support, Aligos: Consultant, Gilead: Consultant, GSK: Consultant, nChroma: Consultant, Precision: Consultant, Savrina Manhas: Nothing to Disclose, Silvia Chang: Nothing to Disclose, Jiani Li: Nothing to Disclose, Pui Yan Ho: Gilead Sciences, Inc: Stock, Yu Hu: Nothing to Disclose, Mingyang Li: Nothing to Disclose, Chunfeng Li: Nothing to Disclose, Soo Aleman: Nothing to Disclose, Maurizia Brunetto: Nothing to Disclose, VLADIMIR CHULANOV: Nothing to Disclose, Adrian Streinu-Cercel: Nothing to Disclose, George Gherlan: Nothing to Disclose, Pavel Bogomolov: Nothing to Disclose, Tatiana Stepanova: Nothing to Disclose, VIACHESLAV MOROZOV: Nothing to Disclose, Olga Sagalova: Nothing to Disclose, Amos Lichtman: Nothing to Disclose, Dmitry Manuilov: Nothing to Disclose, Ross Martin: Gilead Sciences: Employee, Hongmei Mo: Nothing to Disclose, Evguenia Maiorova: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose

2255 | COMPARATIVE PERFORMANCE OF COMMERCIAL HDV ASSAYS

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Background: Chronic hepatitis D (CHD) is associated with faster progression to cirrhosis, hepatic decompensation, and an increased risk of liver cancer compared to other chronic hepatotropic viral infections. The approval of safe and effective therapy in Europe, highlights the need to identify cases of CHD. However, there is no approved screening assay for CHD in the U. S and how available anti-HDV assays compare in performance is unknown. Our aim was to evaluate the performance of a fully automated anti-HDV assay, LIAISON® XL MUREX Anti-HDV (LXL) compared to three commercially available, non-FDA approved, manual laboratory developed anti-HDV assays. **Methods:** Serum samples from HBsAg positive patients at a tertiary liver clinic were tested concurrently for anti-HDV using three Laboratory Developed Tests (LDTs) as well as the LXL (Research Use Only). Specimens were categorized as positive if two of the three LDTs results were reactive, independent of the LXL Anti-HDV assay result. An equivocal result was considered positive for this analysis. Performance characteristics (sensitivity, specificity, and concordant and discordant rates) were compared among the four assays. **Results:** Among 900 samples obtained from HBsAg positive individuals 10 had quantity not sufficient (QNS) for testing. The mean subject age was 57 years and 61% were men, 29.2% White 23.5% Black 41.9% Asian, and 5.4% of unknown or other race. The prevalence of anti-HDV ranged from 16.7%-19.7%. Using 2/3 consensus among tests sensitivity ranged from 94%-100% and specificity from

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98.4%-99.4%. Alternative consensus methods were evaluated by including the LXL results in the consensus. Using a consensus of 3/4 tests, 133 were considered positive with the LXL yielding 3 false positives, LDT 1 12 false positives, LDT 2 10 false positives and LDT 3 4 false positives. 553 samples were classified as negative. LXL and LDT 2 yielded no false negative results, LDT 1 reported 8 false negatives and LDT 3 had 1 false negative result; 211 specimens were QNS for testing by all methods. Consensus could not be determined in 3 samples because results were discordant. Consensus (4/4) could be determined for 648 specimens with 524 specimens resulting negative by all four methods and 124 specimens resulting positive; 31 specimens could not be categorized as at least one test reported discordant results. **Conclusion:** A high rate of discordance, affecting sensitivity, was observed among commercially available, non-approved anti-HDV tests potentially impeding efforts to introduce universal HDV screening in the U.S. An accepted standard for anti-HDV testing is urgently needed to enable screening efforts for CHD to identify persons who may benefit from emerging therapies.

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2256 | IMPACT OF A PHARMACIST-LED SUPPORT PROGRAM ON PATIENT-REPORTED OUTCOMES (PROS) IN PATIENTS WITH CHRONIC HEPATITIS DELTA UNDERGOING BULEVIRTIDE THERAPY: 60-WEEK RESULTS: FROM THE EXPLAIN STUDY

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Background: Bulevirtide (BLV) has shown efficacy in reducing viral load and improving liver tests in patients with chronic hepatitis delta (CHD), the most severe form of viral hepatitis. However, real-world data on patient-reported outcomes (PROs), including health-related quality of life (HRQoL), adherence, and safety, remain limited. Here we analysed the long-term impact of the EXPLAIN program – a pharmacist-led intervention combining medication counselling with proactive surveillance and individualized support – on adherence, HRQoL, and adverse effects (AEs) in CHD patients receiving BLV. **Methods:** Thirty-one CHD patients initiating BLV therapy at Padua University Hospital, Italy, were prospectively enrolled and followed for 60 weeks. Virological (HDV-RNA undetectable or $\geq$2log decline from baseline), biochemical (ALT **Results:** BLV led to a significant reduction of HDV RNA by week 24, with continued decline through weeks 48 and 60. Liver enzymes improved at week 24 and remained stable thereafter. Combined response rates increased significantly from 14.8% at week 24, to 36.4% and 43.7% at week 48 and 60, respectively ($p < 0.01$). Optimal adherence (PDC $\geq$90%) was achieved by 87.1% patients at week 24 and consistently maintained throughout follow-up. HRQoL improve significantly, with mean VAS scores increasing from 72.4 ($\pm$17.88) at baseline to 83 ($\pm$15.07) at week 24 ($p = 0.01$), 83.11 ($\pm$ 12.14) at week 48 and 84.6 ($\pm$ 10.74) at week 60 (+12.2, $p = 0.03$). EQ-5D-5L showed significant improvement in usual activities and anxiety/depression domains, while the other domains remained either stable or slightly improved. AEs were infrequent, mild, and rarely led to treatment discontinuation. **Conclusion:** In this real-world cohort, the EXPLAIN program was associated with excellent adherence, favourable virological, biochemical, and combined response, and significant HRQoL improvements during 60-weeks of BLV therapy. These findings support the integration of structured pharmacist-led education programs into routine care to enhance long-term outcomes in CHD management.

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2257 | HEPATITIS D VIRUS INFECTION PREVALENCE IN PERSONS WITH HUMAN IMMUNODEFICIENCY VIRUS AND HEPATITIS B VIRUS COINFECTION: A THREE-COUNTRY, CROSS-SECTIONAL STUDY IN EUROPE

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Background: People with human immunodeficiency virus (PWH) who have hepatitis B virus (HBV) are at increased risk of also having hepatitis D virus (HDV) given the shared transmission pathways. Accordingly, the guidelines of the European AIDS Society (EACS) recommend HDV screening in all PWH and concomitant HBV. However, the current prevalence of HDV among people with HIV/HBV is not well established. **Methods:** Across 47 HIV treatment centers (Germany, $N = 20$; Spain, $N = 21$; Poland, $N = 6$), all people with a confirmed HIV diagnosis and hepatitis B surface antigen positive serology for more than 6 months, aged ≥ 18 years, and actively in care on December 31, 2023 were recruited. We assessed HDV testing rates in the total cohort. In addition, we calculated the prevalence of individuals who ever had an anti-HDV positive serology (i.e., past/current infection) and the prevalence of individuals whose last HDV RNA result was positive (i.e., active infection). **Results:** Overall, 1,253 PWH and HBV coinfection were included (Germany, $n = 419$; Spain, $n = 774$; Poland, $n = 60$). The majority were male ($n = 1057$, 85.5%) and median age was 56 years (IQR = 48-61). Almost all individuals were on antiretroviral therapy ($n = 1231$, 98.3%), of whom 1082 (87.8%) had undetectable HIV viral load, 1162 (94.3%) were receiving antiviral dual active therapy, and 1111 (90.2%) had undetectable HBV-DNA. Anti-HDV antibody results were available in 981 (78.3%) individuals. Of them, 176/981 (17.9%) had past/current HDV infection. 110/176 individuals with HDV-positive serology had an HDV-RNA determination, of whom 53/110 (48.2%) were positive and thus had active infection. The resulting overall prevalence of active infection was 5.4% (95%CI = 4.1-7.1; $n = 53/981$). All individuals with active HDV infection were in Spain ($n = 39$) or Germany ($n = 14$), and the majority likely acquired HDV from injection drug use ($n = 34$) or sexual contact between males ($n = 10$). **Conclusion:** In this contemporary cohort of PWH with HBV from European centers, HDV serology was performed in roughly 75%, and HDV-RNA testing in two-thirds of those seropositive. Considering the overall 5% prevalence of active HDV, these findings highlight that HBV/HDV coinfection is not uncommon and reveal significant gaps in screening within this vulnerable population.

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2258 | ECLIPSE: A PIVOTAL PROGRAM EVALUATING ONCE-MONTHLY COMBINATION THERAPY WITH TOBEVIBART AND ELEBSIRAN FOR CHRONIC HDV INFECTION - RATIONALE, STUDY DESIGN, AND OBJECTIVES

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Background: Chronic hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis, with no approved therapies in the US and limited options globally. Tobevibart (VIR-3434), a broadly neutralizing anti-HBsAg monoclonal antibody that blocks HBV + HDV entry into hepatocytes and clears circulating viral particles, and elebsiran (VIR-2218), an HBV-targeted small interfering RNA that degrades HBV transcripts to reduce HBsAg production, are investigational agents with complementary mechanisms against HDV. In the Phase 2 SOLSTICE study, monthly subcutaneous administration of tobevibart+elebsiran led to HDV RNA $<$ LLOQ (63 IU/mL) in 100% of participants and 41% achieved HDV RNA $<$ LLOQ, target not detected (TND) (HDV RNA TND) by Week 24. This investigational combination has the potential to address a global unmet need for people with chronic HDV infection. **Methods:** ECLIPSE, a global registrational program launched in March 2025, evaluates monthly combination therapy with tobevibart+elebsiran in chronic HDV infection and consists of 3 global trials addressing 3 distinct HDV populations (see table). ECLIPSE 1, placebo-controlled, enrolls participants with elevated ALT who either have no approved therapy options or decline existing therapy. ECLIPSE 2 compares tobevibart+elebsiran vs bulevirtide (BLV) monotherapy in participants who have not achieved HDV RNA TND

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on BLV. ECLIPSE 3, head-to-head, evaluates tobevibart+elebsiran vs. BLV monotherapy in BLV-naive participants. Eligible participants are adults (18 to 70 years) with all stages of liver fibrosis and compensated cirrhosis. ECLIPSE will be conducted across North America, Europe, and Asia-Pacific. The long-term efficacy and safety of tobevibart+elebsiran therapy will be evaluated over 5 years. Additionally, impact on ALT, HBV serologies including HBsAg levels, liver fibrosis changes over time and occurrence of liver-related events will be assessed. **Results:** ECLIPSE 1, planned in 13 countries, was activated in early 2025. As of May 2025, ECLIPSE was initiated in the US, Canada, and several European countries. ECLIPSE 2 and 3 are projected to be initiated mid-2025 in 7 and 12 countries, respectively. Updated country/site activation, screening, and enrollment data will be presented. **Conclusion:** Tobevibart+elebsiran combination therapy has the potential to address a significant unmet need in chronic HDV infection, including in participants who do not have an approved treatment and those who did not achieve HDV RNA TND on BLV monotherapy.

ECLIPSE PIVOTAL DEVELOPMENT PROGRAM OVERVIEW

STUDY	DESIGN	SAMPLE SIZE	PRIMARY ENDPOINTS
ECLIPSE 1 Phase 3 NCT06903338 EU CT: 2024-515919-22-00	Immediate vs. delayed treatment with tobevibart+elebsiran	N=120 Randomized 2:1	• HDV RNA TND + ALT normalization at Week 48* • Incidence of Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) through Week 12
ECLIPSE 2 Phase 3	Tobevibart+elebsiran vs. continued bulevirtide in participants who failed to achieve HDV RNA TND with ≥ 6 months of bulevirtide	N=150 Randomized 2:1	Primary Part 1 (on treatment): • HDV RNA TND at Week 24 • Incidence of TEAEs and SAEs through Weeks 24, 48 and 96 Primary Part 2 (off treatment): • HDV RNA TND 24 weeks after end of treatment • Incidence of AEs and SAEs and lab abnormalities from Week 96 through Week 240
ECLIPSE 3 Phase 2b	Head-to-head tobevibart+elebsiran vs bulevirtide in bulevirtide naive participants	N=100 Randomized 2:1	Primary Part 1 (on treatment): • HDV RNA TND at Week 48 • Incidence of TEAEs and SAEs through Week 48 Primary Part 2 (off treatment): • HDV RNA TND 24 weeks after end of treatment

*HDV RNA TND will be a key secondary endpoint

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2259 | A CONSERVED G-QUADRUPLEX IN HEPATITIS E VIRUS NEGATIVE-STRANDED RNA PROMOTES VIRAL REPLICATION VIA RNA STABILIZATION

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Background: Hepatitis E virus (HEV) is one of the most common causes of acute hepatitis worldwide, it results in 20 million infections at least annually with approximately 3.3 million cases of acute illness. G-quadruplex (G4) is a kind of non-canonical structure formed in DNA or RNA which is composed of four guanine stretches into stacked quartets. Because the genetic material of viruses is also nucleic acids, which have the structural basis for the formation of G4s. Currently, G4s have been found in the genomes of many species of viruses, and they play an important role in the regulation of viral life cycle. The presence of G4s within the HEV genomic RNA remains unknown and their potential involvement in regulating viral replication warrants investigation. **Methods:** First, comparative genomic alignment of eight HEV genotypes was performed to identify conserved contiguous guanine(G)-rich sequences. Then, the genome of HEV Kernow-C1/p6, was predicted for Potential G-quadruplex Sequences (PQSs) by using QGRS Mapper online tool, and the multiple sequence alignment analysis of PQSs using 497 complete genomic sequences of HEV retrieved from the NCBI database. To validate the existence of G4s in HEV, three G4 ligands (PDS, CX-5461, TMPyP4) were used to diverse HEV infection models (HepG2/C3A, Caco-2, Primary Gerbil Hepatocytes) for antiviral efficacy assessment. G4 formation of candidate PQSs was validated in vitro through Circular Dichroism (CD) spectroscopy and native polyacrylamide gel electrophoresis, followed by functional characterization of critical PQSs using the HEV replicon system. **Results:** Comparative alignment of eight genotypes of HEV genomic RNA sequence revealed eight conserved contiguous guanine-rich motifs. In silicon analysis and scoring using the HEV Kernow-C1/p6 strain validated evolutionary conservation of eight PQSs. Meanwhile, three G4 ligands (PDS, CX-5461, TMPyP4) demonstrated antiviral efficacy against multiple HEV strains in diverse cellular models including HepG2/C3A, Caco-2, and Primary Gerbil Hepatocytes (PGHs). CD and Native PAGE analyses demonstrated that four of eight

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candidate PQSs could form G4 structure in vitro, with two localized to the positive-stranded RNA and two to the negative-stranded RNA of HEV. An optimized Gaussia Luciferase reporter system based on HEV Kernow-C1/p6 was developed, and combined with a full-length HEV replicon system, demonstrated the critical role of the negative-strand-localized NPQS-2 in viral replication. Finally, synonymous mutations disrupting G4 formation of NPQS-2 significantly accelerated viral RNA degradation. **Conclusion:** Collectively, these results demonstrate four conserved PQSs in HEV RNA capable of folding into stable parallel G4 structures in vitro. Notably, the NPQS-2 located on the HEV negative-stranded RNA is crucial for HEV, facilitating viral replication through RNA stabilization.

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2260 | NATIONWIDE HDV DIAGNOSIS AND CHARACTERIZATION IN SPAIN: INSIGHTS FROM THE DELTA DOUBLE REFLEX (DDR) STUDY

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Background: Hepatitis delta virus (HDV) infection, in patients coinfected with hepatitis B virus (HBV) accelerates liver disease progression and is linked to higher rates of cirrhosis and hepatocellular carcinoma. The DDR Spain study aims to standardize HDV screening by implementing a reflex anti-HDV and HDV-RNA testing strategy nationwide, and characterize HDV-infected individuals in Spain. **Methods:** DDR Spain is a multicenter, national, ambispective observational study, comprising a retrospective evaluation of DDR implementation during 2022–2023 and a prospective phase starting in 2024. The prospective phase, launched in Q3 2024, includes clinical, demographic, and virological data collection in anti-HDV-positive patients across participating centers. **Results:** From 2022 to 2024, 65,763 HBsAg-positive individuals were included from 80 centers across 16 out of Spain's 17 Autonomous Communities. Reflex anti-HDV testing increased from 55.1% (2022) to 64.8% (2023), and to 85.9% (2024) ($p < 0.05$), with anti-HDV prevalences of 5.6%, 4.9%, and 4.8%, respectively. Regional differences persisted throughout. HDV-RNA testing coverage improved from 72.6% in 2022 to 91% in 2024 ($p < 0.05$). Active HDV infection decreased from 40.2% (2022) to 31.1% (2024). By May 2025, the prospective cohort had enrolled 288 anti-HDV-positive patients. Median age was 55 years (IQR 43–61), 57.4% were male, and 52.3% were of Spanish origin. Genotyping revealed 90% were genotype 1. Co-infections were found in 17.9% (HIV) and 21.9% (HCV). Advanced fibrosis was common: 29.7% had FIB-4 >2.67, 17.3% had APRI >1.5, and in 123 patients with available transient elastography, the mean liver stiffness was 7.4 kPa. According to METAVIR staging, 15% had F3 and 30% had F4 fibrosis, highlighting the severity of liver disease. Prior hepatic decompensation was recorded in 23% of evaluable cases. **Conclusion:** DDR Spain is the largest HDV diagnostic initiative in Spain to date. It demonstrates substantial improvements in HDV reflex testing, while revealing persistent regional disparities. The prospective phase offers a detailed snapshot of the current HDV population. These findings support the need for unified screening policies, continued clinical education, and greater awareness to improve detection and management of HDV nationwide.

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2261 | LONAFARNIB AS FINITE TREATMENT FOR CHRONIC HEPATITIS D: LONG-TERM FOLLOW-UP DATA

Cihan Yurdaydin[1] Müge Gülnar[1] Olga Metin[2] Ozgur Aktas[3] Esra Yurdcu[4] Selin Ozer[5] Onur Keskin[6] Mesut Gumussoy[6] Emin Bodakci[6] Xheni Deda[6] Sevda Aghayeva[6] Genco Gencdal[7] Müjdat Zeybel[7] Ramazan Idilman[6] Mithat Bozdayi[4] Ingrid Choong[8] Jeffrey Glenn[9], [1]Koç University Hospital, Istanbul, Türkiye, [2]Prof. Dr. Cemil Tascioglu Sehir Hastanesi, Istanbul, Turkey, [3]Faculty of Medicine, Koç University School of Medicine, [4]Hepatology Institute, Ankara University, Ankara, Turkey, [5]Koç University Medical School, Istanbul, Türkiye, [6]Department of Gastroenterology, Ankara University Medical School, Ankara, Turkey, [7]Department of Gastroenterology and Hepatology Koç University, İstanbul, Türkiye, [8]Eiger BioPharmaceuticals, Inc., Palo Alto, California, USA, [9]Palo Alto Veterans Administration, Palo Alto, California, USA

Background: Hepatitis delta virus (HDV) infection leads to the most severe form of viral hepatitis. New treatment options are urgently needed. The farnesyl transferase inhibitor lonafarnib (LNF) may be an option for finite treatment as it possesses a dual mode of action: it interferes with virion assembly (Glenn et al Science 1992) and also has immunomodulatory properties (Lempp et al, Nat Commun 2019). The aim of this study was to assess if finite treatment with a LNF-based regimen is able to prevent hard endpoints such as complications of liver disease and death from liver disease on long-term follow-up (LTFU). **Methods:** All patients subject to this study had received LNF-based treatment in two phase 2 (LOWR 1 and 2) and one phase 2 (LIFT) studies in Ankara (TR) and NIH (USA), respectively, and one phase 3 (DLIVR) study in Istanbul (TR). LOWR 1 and 2 studies contained 21 and 55 patients, respectively, the LIFT study 26 and the phase 3 Istanbul study contained 27 patients with a LNF-based treatment. Start date used for LTFU (median 79.5 months (0-134, n = 97) and survival analysis was EOT date of LNF-based treatment. End of follow-up (EOFU) was set to either the last date of data collection (March 2025), or the date of liver-related event, the start date of a new potential treatment against HDV or loss to follow-up. Short-term viral response (STVR) was defined as undetectable HDV RNA or a ³ 2 log decline of HDV RNA compared to baseline and biochemical response (BR) as ALT normalization at off treatment month 6. BR and VR were the co-primary endpoints. Cumulative probabilities of any event occurrence were estimated by the Kaplan-Meier method and compared with the log-rank test. Uni- and multivariate logistic regression models with forward Wald deletion were used to estimate the effect of various on and off-treatment variables on clinical outcome. **Results:** STVR was achieved in 12 patients. On LTFU none of these patients developed a clinical event in up to 10 years of follow up. Out of 85 patients without VR+BR, 17(20%) developed an event (Figure, $p < 0.05$ by the log rank test). **Conclusion:** Patients achieving a 2 log drop in HDV RNA from baseline and normal ALT at 6 months after stopping any finite lonafarnib-based treatment regimen have no major clinical events (liver decompensation, liver cancer, or death) in up to 10 years of follow up.

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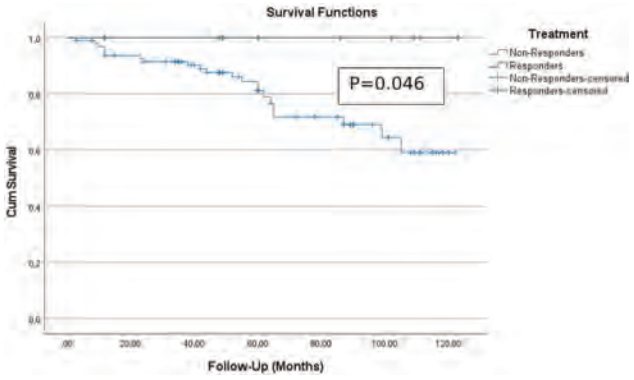
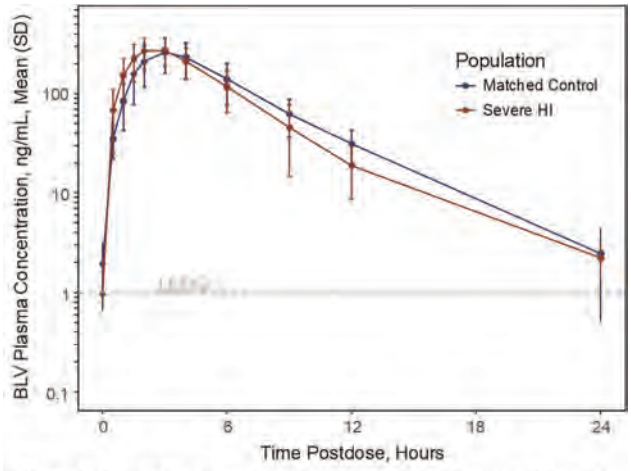


Disclosures: Cihan Yurdaydin: Nothing to Disclose, Müge Gülnar: Nothing to Disclose, Olga Metin: Nothing to Disclose, Ozgur Aktas: Nothing to Disclose, Esra Yurdcu: Nothing to Disclose, Selin Ozer: Nothing to Disclose, Onur Keskin: Nothing to Disclose, Mesut Gumussoy: Nothing to Disclose, Emin Bodakci: Nothing to Disclose, Xheni Deda: Nothing to Disclose, Sevda Aghayeva: Nothing to Disclose, Genco Gencdal: Nothing to Disclose, Müjdat Zeybel: Nothing to Disclose, Ramazan Idilman: Nothing to Disclose, Mithat Bozdayi: Nothing to Disclose, Ingrid Choong: Nothing to Disclose, Jeffrey Glenn: Eiger BioPharmaceuticals, Inc.: Board member, Riboscience, LLC: Board member, I-Cubed Therapeutics, LLC: Board member, 4J Therapeutics, Inc.: Board member, EITPharma: Board member

2262 | PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF BULEVIRTIDE 10 MG ONCE DAILY FOR 6 DAYS IN PARTICIPANTS WITH SEVERE HEPATIC IMPAIRMENT AND IN MATCHED CONTROL PARTICIPANTS WITH NORMAL HEPATIC FUNCTION

Parag Kumar[1] Wildaliz Nieves[1] David Pan[1] Jack Chang[1] Steve Tseng[1] Yuejiao Jiang[1] Yehong Wang[1] Ann Qin[1] Teckla Akinyi[1] Renee-Claude Mercier[1], [1]Gilead Sciences, Inc.

Background: Bulevirtide (BLV) 2 mg once-daily (QD) is approved in the EU, United Kingdom, Switzerland, Russia, and Australia for the treatment of chronic hepatitis delta virus (HDV) in patients with compensated liver disease. BLV binds to the sodium taurocholate cotransporting polypeptide (NTCP) receptor, resulting in asymptomatic and transient elevations in bile acids (BAs). Evaluations exploring potential benefits of an increased 10 mg QD dose are in progress. This study evaluated the effect of severe hepatic impairment (HI) on the pharmacokinetics (PK), pharmacodynamics (PD), and safety of BLV 10 mg. **Methods:** This was a Phase 1, open-label, parallel-group, multiple-dose study in participants (pts) without HDV with severe HI (Child-Turcotte-Pugh class C, n = 8) and matched controls (MCs) with normal hepatic function (matched for age [± 10 years], sex, and body mass index [± 20%]; n = 8) who received BLV 10 mg subcutaneously QD for 6 days, with intensive serial sampling for BLV PK and PD (total BAs). Geometric least-squares mean ratios (GLSMRs) and 90% CIs of maximum plasma concentration (C_{max}; ng/mL) and the area under the time-vs-concentration curve over 24 hours (AUC_{24h}, ng·h/mL) or extrapolated to infinity (AUC_{inf}, ng·h/mL) were evaluated for PK; those of C_{max} (μM), AUC_{24h} (μM·h), and baseline-adjusted AUC (NetAUC; μM·h) were evaluated for total BAs. Safety was assessed by clinical laboratory tests and evaluation of adverse events (AEs). **Results:** After 6 days of BLV 10 mg QD dosing, PK exposures were similar in pts with severe HI and MCs (GLSMR [90% CI]: 1.14 [0.81, 1.61], 0.95 [0.73, 1.24], 0.95 [0.73, 1.24] for C_{max}, AUC_{24h}, and AUC_{inf}, respectively). Transient elevations in total BAs were observed on days 1 and 6 in both groups and returned to approximate predose levels within 24–48 h of dosing. After 6 days, the elevations in total BAs were higher in pts with severe HI (GLSMR [90% CI]: 1.76 [1.38, 2.25], 2.47 [1.88, 3.24], 1.44 [1.04, 2.01] for C_{max}, AUC_{24h}, and NetAUC, respectively). There were no Grade ≥3 treatment-emergent AEs (TEAEs), serious AEs, or AEs leading to BLV discontinuation. The TEAEs were mild, with no increased severity compared with the MCs. **Conclusion:** There were no differences in steady-state PK exposure or safety findings observed in pts with severe HI compared with MCs with normal hepatic function following 10 mg QD BLV dosing for 6 days. Baseline-adjusted elevations in total BAs at BLV steady-state were approximately 44% higher in pts with severe HI compared to MCs.



LLOQ was set at 1 ng/mL. PK samplings relative to BLV dose were taken on day 6 predose (≤30 minutes before dose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24 (day 7), and 48 (day 8) hours postdose
BLV, bulevirtide; HI, hepatic impairment; LLOQ, lower limit of quantitation; PK, pharmacokinetic; QD, once-daily.

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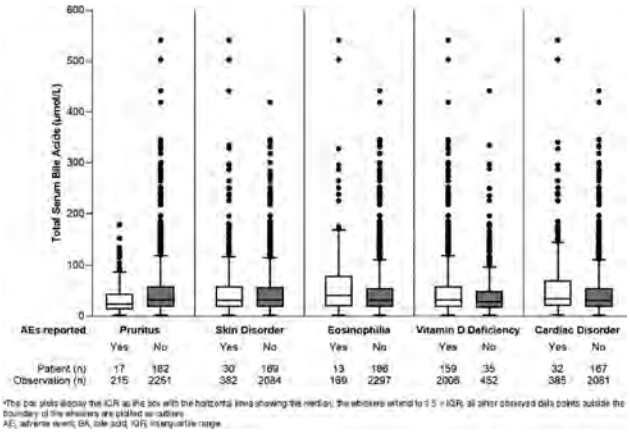
2263 | ELEVATIONS IN TOTAL SERUM BILE ACIDS DURING BULEVIRTIDE TREATMENT ARE ASYMPTOMATIC AND NOT ASSOCIATED WITH ADVERSE EVENTS OF INTEREST IN PATIENTS WITH CHRONIC HEPATITIS DELTA

Pietro Lampertico[1] Soo Aleman[2] Tarik Asselah[3] Adrian Streinu-Cercel[4] Pavel Bogomolov[5] Viacheslav Morozov[6] Tatiana Stepanova[7] Stefan Lazar[8] Maurizia Brunetto[9] Sreenivasu Yalamanchili[10] Amos Lichtman[10] Mingyang Li[10] Renee-Claude Mercier[10] Dmitry Manuilov[10] Heiner Wedemeyer[11], [1]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico and University of Milan, Milan, Italy, [2]Karolinska University Hospital/Karolinska Institutet, Stockholm, Sweden, [3]Hôpital Beaujon APHP, Université de Paris-Cité, INSERM UMR1149, Clichy, France, [4]NIID Prof Dr Matei Bals; University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania, [5]M.F. Vladimirsky Moscow Regional Research and Clinical Institute, Moscow, Russian Federation, [6]LLC Medical Company Hepatolog, Samara, Russian Federation, [7]LLC Clinic of Modern Medicine, Moscow, Russian Federation, [8]Univ of Med & Pharm "Carol Davila" Bucharest; Inf & Trop Dis Hospital "Dr Victor Babes," Bucharest, [9]University Hospital of Pisa; Dept of Clinical and Experimental Medicine, University of Pisa, Pisa, I, [10]Gilead Sciences, Inc., [11]Hannover Medical School, Hannover, Germany

Background: Bulevirtide (BLV) inhibits hepatitis delta virus (HDV) entry by binding to the sodium taurocholate cotransporting polypeptide (NTCP) receptor, a bile acid (BA) transporter expressed in hepatocytes. As such, BLV treatment leads to increases in serum BAs, which are similar in mechanism to those observed with genetic NTCP deficiency without hyperbilirubinemia, pruritus, or jaundice. This analysis assessed the impact of BA level increases during BLV treatment on adverse events (AEs). **Methods:** Data from an integrated analysis of up to 96 weeks of BLV treatment in 199 patients with HDV who received BLV 2 mg (n = 49) or 10 mg (n = 150) monotherapy once daily in one Phase 2 study (MYR204; NCT03852433) and one Phase 3 study (MYR301; NCT03852719) were analyzed. AEs of interest included pruritus, skin disorders, eosinophilia, vitamin D deficiency (defined as below lower limit of normal on laboratory tests at any on-treatment visit), and cardiac disorders. On-treatment BA levels were compared between patients with and without AEs of interest. **Results:** Median (Q1, Q3) baseline BA levels were 12.2 (8.6, 17.8) and 10.1 (6.5, 16.3) μmol/L in BLV 2 and 10 mg groups, respectively. At week 96, change from baseline in median (Q1, Q3) BA levels were 3.1 (−2.8, 10.7) and 19.9 (7.3, 56.5) μmol/L, respectively. Overall, across both groups, 6% of patients maintained BA values within the normal range (ie, 0–10 μmol/L Russia site, 0–9.9 μmol/L other sites) at both the baseline and at week 96, 39% had values that increased from normal at baseline to high (ie, > 10 μmol/L Russia site, > 9.9 μmol/L other sites), 6% had values that decreased from high to normal, and 49% had values that remained high from baseline to week 96. While pruritus and eosinophilia are known effects of BLV treatment, BA levels were not related to these AEs (Figure). Alanine aminotransferase (ALT) levels did not correlate with BA levels: median (Q1, Q3) on-treatment BA levels were 36.4 (20.7, 75.4) and 31.0 (18.4, 55.5) μmol/L in visits with and without concurrent ALT increases, respectively. Total serum BA concentrations did not differ based on cirrhosis status: median (Q1, Q3) on-treatment BA levels were 31.7 (18.4, 62.9) and 31.5 (18.5, 53.5) μmol/L in patients with and without cirrhosis, respectively. **Conclusion:** Median total BA levels increased in a dose-dependent manner following BLV dosing. There was substantial on-therapy intra-patient variability in BA levels; however, no association was observed between BA levels and AEs.



Disclosures: Pietro Lampertico: Nothing to Disclose, Soo Aleman: Nothing to Disclose, Tarik Asselah: GSK: Speaker, GILEAD: Consultant, VIR Biotechnology: Speaker, Roche: consultant, ABBVIE: Speaking and Teaching, Aligos therapeutics: Consultant, Bluejay Therapeutics: Consultant, Antios therapeutics: Consultant, GSK: Consultant, Adrian Streinu-Cercel: Nothing to Disclose, Pavel Bogomolov: Nothing to Disclose,

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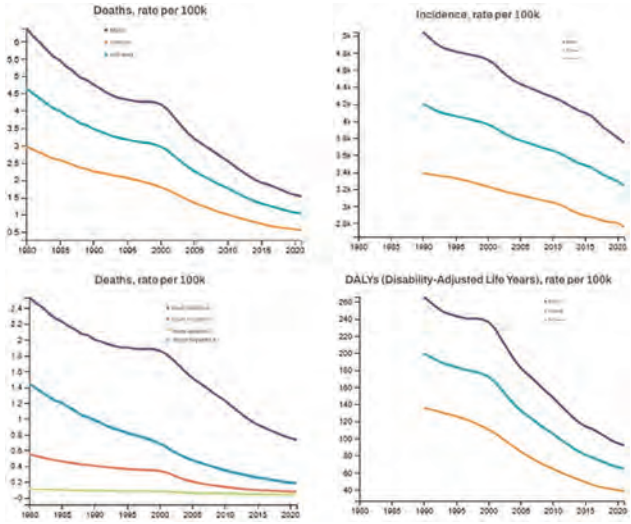
2264 | DECLINING BURDEN OF ACUTE VIRAL HEPATITIS IN ADOLESCENTS AND ADULTS AGES 15-45 IN AFRICA, 1991-2021: A GLOBAL BURDEN OF DISEASE STUDY

Mohammed Youssef[1] Mohamad Elgozair[2] Lewis Roberts[3], [1]Hunt Regional Medical Center, [2]Danbury Hospital, CT, [3]Mayo Clinic Rochester

Background: Acute viral hepatitis remains a significant public health concern in Africa, particularly among younger adults. While global targets for hepatitis elimination have been set, understanding how the burden has changed within Africa is crucial to guide local responses and priorities. This study examines trends in incidence, mortality, and disability-adjusted life years (DALYs) from acute hepatitis A, B, C, and E in Africa between 1990 and 2021, with a focus on differences between males and females. **Methods:** We used data from the Global Burden of Disease (GBD) 2021 study to assess hepatitis burden among individuals aged 15–49. Trends in incidence (both total cases and rates per 100,000), deaths, and DALYs were analyzed across hepatitis types and by sex. Findings were summarized descriptively and visualized using time-series graphs. **Results:** The death rate from acute hepatitis decreased from 3.406 (95% CI 2.28-4.90) in 1991 to 1.03 (CI 0.78-1.35) in 2021. Gender specific data showed that the mortality rates in males and females in 1991 were 4.64 (CI 7.1-2.7) and 2.2 (CI 3.0-1.66) per 100,000 respectively. By 2021 the rates had decreased to 1.52 (CI 1.09-2.08) in males and 0.55 (CI 0.44-0.66) per 100,000 in females. Acute hepatitis B remained the leading cause of acute hepatitis-related mortality in adolescents between 15-49 with rates of 1.97 (CI 1.15-3.11) in 1991 and 0.73 (CI 0.5-1.01). Acute hepatitis A is the second leading cause of acute hepatitis related deaths, with rates of 0.94 (CI 0.55-0.94) per 100,000 in 1991 and 0.18 CI (0.43-0.10) in 2021. The DALY from acute viral hepatitis decreased from 195.8 (CI 133-279) in 1991 to 64.66 (CI 50.6-83.1) in 2021. The incidence rate decreased from 4164 CI (3347-5015) per 100,000 in 2023[LR1] to 3241.24 CI (2684.4-3907.5) in 2021. **Conclusion:** The burden of acute hepatitis decreased significantly over 30 years, in adolescents and adults between 15-49 in Africa. Hepatitis B remains a key contributor to mortality among young adults. Continued investment in prevention, vaccination, and gender-targeted interventions is essential to sustain these gains and achieve hepatitis elimination goals.



Disclosures: Mohammed Youssef: Nothing to Disclose, Mohamad Elgozair: Nothing to Disclose, Lewis Roberts: Astra Zeneca: Advisor, Astra Zeneca: Grant/Research Support, Bayer: Advisor, Bayer: Grant/Research Support, Boston Scientific: Grant/Research Support, Eisai: Advisor, Exact Sciences: Advisor, Exact Sciences: Grant/Research Support, Focal Medical Communications: Speaking and Teaching, Fujifilm Medical Systems: Grant/Research Support, Genentech: Grant/Research Support, Gilead Sciences: Advisor, Gilead Sciences: Grant/Research Support, Glycotest: Grant/Research Support, GRAIL: Advisor, HERMES: Grant/Research Support, Hepion Pharmaceuticals: Consultant, Innovo Bioanalysis: Grant/Research Support, Medscape: Speaking and Teaching, AiCME: Speaking and Teaching, Novartis Venture Fund: Consultant, Olympus: Grant/Research Support, Pontifax: Consultant, Prometrika - Surface Oncology: Consultant, RedHill Biopharma: Grant/Research Support, Regeneron Genetics Center: Grant/Research Support, TARGET RWE: Grant/Research Support

2265 | THE NUCLEOSIDE ANALOGUE NITD008 USED ALONE OR IN COMBINATION WITH RIBAVIRIN STRONGLY SUPPRESSES VIRAL REPLICATION IN IMMUNODEFICIENT HUMANIZED MICE STABLY INFECTED WITH THE HEPATITIS E VIRUS

Maura Dandri[1] Annika Volmari[1] Tassilo Volz[2] Florian Hinte[1] Marc Lütgehetmann[1], [1]University Medical Center Hamburg-Eppendorf, [2]University Medical Centre Hamburg-Eppendorf

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Background: Hepatitis E virus (HEV) infection has an emerging clinical relevance for patients worldwide, but there is currently no approved antiviral therapy. For immunosuppressed people with chronic HEV, off-label treatment with ribavirin (RBV) is used in daily clinical practice, although it is effective in 80% of patients. Thus, there is an urgent need for effective antiviral drugs against HEV. The adenosine nucleoside analogue NIDT008 was shown to be effective in preclinical studies against a broad range of RNA viruses. The aim of this study was to evaluate the efficacy of NITD008 alone or in combination with ribavirin in HEV-infected human liver chimeric mice. **Methods:** Immunodeficient human-liver chimeric mice were infected with HEV (GT-1) via the co-housing fecal-oral route. After achieving stable viremia (median $1.5x10^7$ IU/ml HEV RNA), mice received either 20mg/Kg/day of NITD008 alone by oral gavage for up to 2 weeks, or 5mg/Kg NITD008 in combination with RBV (50mg/Kg), while other mice received mock treatment or RBV monotherapy. Viral changes were determined by qPCR in faeces and blood. Intrahepatic analyses (immunohistochemistry, RNA-ISH and qPCR) were performed at sacrifice. **Results:** NITD008 monotherapy effectively reduced fecal HEV loads (Δlog:-4log) already after 1 week of treatment. All mice had undetectable serum HEV titers (LloQ) after 7 days, while controls showed no decrease in fecal and serum titers. Intrahepatic analysis showed a Δlog:-2.5 reduction in HEV RNA levels in treated mice compared to controls after 14 days of treatment. RNA-ISH analysis confirmed the strong reduction of HEV-RNA-positive human hepatocytes in treated mice, whereas approximately 95% of human hepatocytes were positive in control animals. NITD008 administration did not induce ALT elevation. 11 days of combination therapy induced much stronger suppression of HEV RNA in faeces (Δlog:-5.02) then ribavirin monotherapy (Δlog:-1.08), despite using lower NITD008 amounts. **Conclusion:** This study demonstrates the efficacy and non-toxicity of NITD008 towards human hepatocytes in HEV infected humanized mice. NITD008 displayed more potent antiviral activity compared to ribavirin and combination regimens with ribavirin and lower NITD008 concentrations showed strong synergistic antiviral activity. The study suggests that HEV clearance may be achieved even in immunosuppressed patients by using and further developing this class of direct antiviral drugs.

Disclosures: Maura Dandri: Gilead Science, US: Grant/Research Support, Vir.Bio: Grant/Research Support, Annika Volmari: Nothing to Disclose, Tassilo Volz: Nothing to Disclose, Florian Hinte: Nothing to Disclose, Marc Lütgehetmann: Nothing to Disclose

2266 | SHIFTING EPIDEMIOLOGY OF HEPATITIS A AND ITS IMPACT ON UNVACCINATED ADOLESCENTS/ YOUNG ADULTS IN NORTH INDIA: A GEOSPATIAL ANALYSIS

Samagra Agarwal[1] Ayush Agarwal[1] Ginni Bharti[2] Sagnik Biswas[1] Rojaleen Das[2] Suneeta Meena[2] Baibaswata Nayak[1] . Shalimar[1], [1]Department of Gastroenterology and HNU, All India Institute of Medical Sciences, New Delhi, India, [2]Department of Laboratory Medicine, All India Institute of Medical Sciences, New Delhi, India

Background: Hepatitis A virus (HAV) may cause acute hepatitis rarely leading to acute liver failure (ALF). Most children in high endemicity zones are infected by 10 years of age, but access to improved drinking water and improved sanitation may shift epidemiology, making unvaccinated adolescents/ young adults more susceptible to HAV infection and paradoxically increasing the risk of ALF. While sero-surveys have indicated this epidemiological shift, direct clinical evidence of this change is lacking. **Methods:** In a retrospective hospital-based cohort study, we evaluated demographics of individuals with deranged liver enzymes tested for IgM HAV from January to June 2024 and assessed clinical outcomes of IgM HAV positive patients. Spatial analysis was performed for identifying HAV hotspots, and association of seropositivity with population density (kontur dataset 2023), access to clean water and sanitation (NFHS-5 database 2019-2021). Boruta algorithm was used to identify relevant features associated with seropositivity. **Results:** We identified 9996 unique individuals (median age 34 (IQR 25-50) years; 44.8% females) of whom 164 (1.64%) were IgM HAV positive; median age 13 (IQR 8-20) years. HAV positivity was concentrated in age-groups 5-10 yrs: 34/259(13.1%), 10-15 yrs: 42/283 (14.8%), 15-20 yrs (25/433; 5.8%) and 20-25 yrs (31/747; 4.2%). Elevated INR developed in 11, with ALF in 8 patients, of whom 4 succumbed to their illness, with 3 of 4 being older than 10 years. Most individuals were from Delhi and surrounding districts, with no hotspots (Figure 1) or seasonal trend. HAV infection was associated with higher population density [median 13730 (IQR: 6445 – 20451) vs 10310 (4492 – 18614) /km2; $p = 0.002$], but not with access to improved drinking water [99.8 (99.1-100)% vs 99.7 (99.1-100)%; $p = 0.32$] or improved sanitation [83.8 (76.8-84.5)% vs 79.7 (69.6-84.5)%; $p = 0.06$]. Boruta analysis identified being adolescent (age 10-25 years) and living in high population density areas as the most important factors associated with developing HAV infection. **Conclusion:** HAV hepatitis was common

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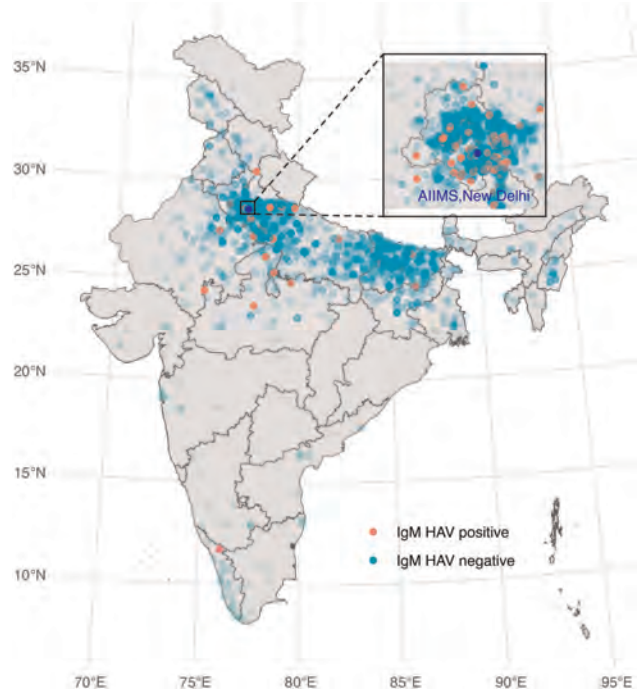
beyond 10 years of age, indicating persistent susceptibility and increased risk of ALF and mortality. Adolescents living in high population-density areas were at maximum risk. Our results support the epidemiological shift of north Indian population to intermediate endemicity for HAV and highlight the need for universal HAV vaccination.



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2267 | 3 YEARS OF BULEVIRTIDE MONOTHERAPY IN PATIENTS WITH HDV-RELATED COMPENSATED CIRRHOSIS: VIROLOGIAL OUTCOMES AND SAFETY DATA FROM THE RETROSPECTIVE MULTICENTER EUROPEAN STUDY (SAVE-D)

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Background: Bulevirtide (BLV) monotherapy up to 144 weeks was safe and effective in patients with chronic hepatitis Delta (CHD) in the MYR-301 trial, however real-world data in patients with cirrhosis are lacking. **Methods:** Consecutive CHD patients with cirrhosis reaching week 144 (3 years) of BLV 2 mg/day monotherapy in the retrospective multicenter European study (SAVE-D) were included. Virological (HDV-RNA undetectable or $\geq$2-log decline *vs.* baseline), biochemical (ALT $<$40 U/L), combined response (biochemical + virological), adverse events and liver-related events were assessed. HDV RNA was tested locally. **Results:** Among 130 patients starting BLV monotherapy between September 2019 and April 2022, 78 patients with available data up to 144 weeks were enrolled: age 50 (IQR 40-58) years, 54% men, ALT 93 (57-145) U/L, liver stiffness measurement (LSM) 18.8 (14.1-26.8) kPa, platelets 83 (58-132) x 10^3/mm^3, 99% Child-A, 49% with varices, 6% HIV-positive, 9% with previous decompensation, 4% with active HCC, 100% on NUC. Baseline HBsAg levels and HDV-RNA were 3.8 (3.4-4.1) $\log_{10}$IU/mL and 5.2 (4.4-6.3) $\log_{10}$IU/mL, respectively. Following 144 weeks of BLV monotherapy, 69% patients achieved a virological response, 63% a biochemical response, 51% a combined response, 41% HDV RNA undetectability. 10 (13%) patients had $<$1 log HDV RNA decline *vs.* baseline, whereas 14

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(18%) achieved >1 but <2 log HDV RNA decline. 11 out of these 24 (46%) patients with a suboptimal response (< 2 Log HDV RNA decline) had ≥50% ALT decrease *vs.* baseline. During long-term BLV monotherapy, AST, GGT, IgG and AFP levels significantly declined, as well as LSM values and serological non-invasive tests of fibrosis (FIB-4, APRI score). No baseline predictors of HDV RNA undetectability at week 144 (baseline ALT, HBsAg levels HDV RNA levels, bile acids) were identified. Bile acids levels increased under BLV therapy, 19% of patients reported mild and transient pruritus, independently of bile acid levels. During 144 weeks of BLV treatment, de-novo HCC and ascites occurred in 2 and 3 patients, respectively. For 27 patients with available week 192 data (4 years), rates of virological (81%), biochemical (67%) and combined (56%) were comparable to week 144, while 33% had undetectable HDV RNA. **Conclusion:** A 3-year course of BLV monotherapy 2 mg/day is effective and safe in patients with HDV-related compensated cirrhosis also in real-world setting. Liver-related events were rare under BLV therapy.

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2268 | DISEASE PROGRESSION AMONG COMMERCIALLY INSURED PATIENTS INFECTED WITH HEPATITIS DELTA VIRUS IN THE UNITED STATES

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Background: Hepatitis delta virus (HDV) infection occurs as a coinfection with hepatitis B virus (HBV) and causes the most severe form of viral hepatitis. HDV leads to a greater risk of cirrhosis, hepatocellular carcinoma (HCC), liver transplant (LT), and mortality vs HBV monoinfection. Here, we compared the rate of disease progression by disease state in adults with HDV. **Methods:** A retrospective observational analysis of the PharMetrics database identified commercially insured patients aged ≥18 years with an HDV diagnosis within the study period (1/1/2006–5/31/2024). The index date was defined as the first HDV diagnosis claim between 1/1/2007 and 5/31/2023. Patients were required to have ≥12 months of continuous enrollment pre-index and 1 day post-index date. Disease progression from baseline (BL) to the next disease state was assessed using Kaplan-Meier curves and a multivariable Cox proportional-hazards regression model adjusting for patient characteristics. Disease states include noncirrhotic (NC), compensated cirrhosis (CC), decompensated cirrhosis (DCC), HCC, and LT. **Results:** Of the 126,380,914 patients identified within the database, 1,106 with HDV met the enrollment criteria, and 1,064 were analyzed after excluding patients with LT at BL. Overall, patients had a mean (SD) age of 48 (11.6) years. The proportions of patients within each disease state at BL were NC, 730/1,064 (69%); CC, 60/1,064 (6%); DCC, 205/1,064 (19%); HCC, 69/1,064 (6%). Compared to patients with HDV and NC disease at BL, those with BL CC demonstrated a higher rate of progression to DCC; those with BL DCC demonstrated a higher rate of progression to HCC and LT; those with BL HCC demonstrated a higher rate of progression to LT (log rank $P < .05$ for all). Further,

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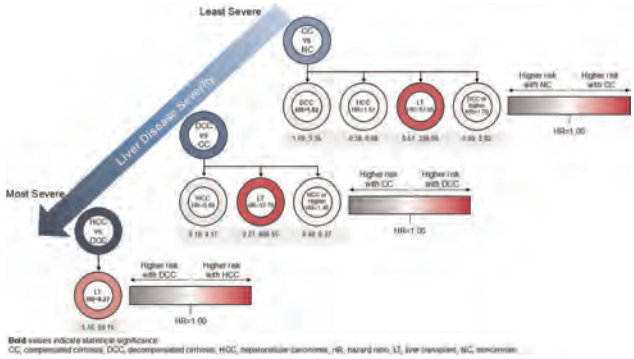
patients with BL HCC demonstrated a higher rate of progression to LT vs those with CC or DCC at BL (log rank $P < .05$ for both). Compared to patients with HDV and NC at BL, those with CC were at a higher risk of transitioning to DCC (hazard ratio [HR]: 1.92, 95% CI: 1.09–3.35, $P < .05$), those with DCC or HCC were at a higher risk of transitioning to LT (HR: 6.21, 95% CI: 2.09–18.45; HR: 180.67, 95% CI: 8.18–3,991.11, respectively; $P < .05$ for both). Patients with HDV and HCC at BL were also at a higher risk of transitioning to LT vs those with DCC at BL (HR: 8.27, 95% CI: 1.16–59.19, $P < .05$). **Conclusion:** These findings underscore the need for earlier identification, diagnosis, and treatment of HDV to mitigate future disease progression and associated burden of disease.



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2269 | CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF 92 HEPATITIS E PATIENTS

Lihua Yuan[1] Minghui Sun[1] Rui Hua[1] Yue Qi[1] Fang Xu[1] Hao Zhou[1], [1]The First Hospital of Jilin University, Changchun, China

Background: To investigate the clinical features and epidemiological characteristics of 92 sporadic Hepatitis E patients admitted to our hospital, and to compare the detection rates of Hepatitis E virus (HEV) in different specimens. **Methods:** Clinical data of 92 hospitalized Hepatitis E patients with positive anti-IgM antibodies from May 2023 to March 2025 at the First Hospital of Jilin University were collected. Hepatitis E virus nucleic acid was analyzed in blood and fecal specimens from 67 patients, and genotype testing was performed. Among them, 54 patients underwent urine antigen testing. Statistical analysis was conducted using SPSS 27.0. **Results:** Among them, there were 62 males (67%) and 30 females (33%),with 5 patients (5%) in the young group (age $\leq$40 years) and 87 patients (95%) in the middle-aged and elderly group (age $>$ 40 years). Cases were sporadic throughout the year, with a predominance in spring and winter (74%). 74 (80%) had simple infections, and 18 (20%) had overlapping infections or other liver diseases(hepatitis A, B, C, autoimmune liver diseases, etc.). Only 8 (9%) of the 92 hepatitis E patients were discharged automatically due to deterioration of condition (including 1 cases with liver cancer, 1 case with Hepatitis B cirrhosis, 1 case with Sjogren syndrome, and 3 cases with co-infections).The median hospital stay for the 74 patients with simple infections was 9 days. Patients with a hospital stay of $\geq$9 days were in Group A, and those with a hospital stay of $<$9 days were in Group B. Group A patients had lower levels of CHE, ALB, HDL-C, and PTA compared to Group B patients($P < 0.05$), while Group A patients had higher levels of TBIL, TBA, Scr, PT, and INR compared to Group B patients($P < 0.05$).Among the 67 patients, 43 (64%) were positive for blood nucleic acid,57 (85%) were positive for fecal nucleic acid, and 44 (81%) were positive for urine antigen. All patients had genotype 4 infection. **Conclusion:** Hepatitis E patients are mainly caused by genotype 4 hepatitis E virus infection, middle-aged and elderly patients, mainly in spring and winter. Co-infection with pathogens is a risk factor for disease progression and poor prognosis. Compared with blood and fecal nucleic acid detection, the positive rate of urine antigen is similar to that of fecal nucleic acid, but urine antigen detection is convenient, economical and has more diagnostic advantages.

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2270 | LONAFARNIB AS FINITE TREATMENT FOR CHRONIC HEPATITIS D: LONG-TERM FOLLOW-UP DATA

Jeffrey Glenn[1], [1]Stanford University School of Medicine

Background: Hepatitis delta virus (HDV) infection leads to the most severe form of viral hepatitis. New treatment options are urgently needed. The farnesyl transferase inhibitor lonafarnib (LNF) may be an option for finite treatment as it possesses a dual mode of action: it interferes with virion assembly (Glenn et al Science 1992) and also has immunomodulatory properties (Lempp et al, Nat Commun 2019). The aim of this study was to assess if

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finite treatment with a LNF-based regimen is able to prevent hard endpoints such as complications of liver disease and death from liver disease on long-term follow-up (LTFU). **Methods:** All patients subject to this study had received LNF-based treatment in two phase 2 (LOWR 1 and 2) and one phase 2 (LIFT) studies in Ankara (TR) and NIH (USA), respectively, and one phase 3 (DLIVR) study in Istanbul (TR). LOWR 1 and 2 studies contained 21 and 55 patients, respectively, the LIFT study 26 and the phase 3 Istanbul study contained 27 patients with a LNF-based treatment. Start date used for LTFU (median 79.5 months (0-134, n = 97) and survival analysis was EOT date of LNF-based treatment. End of follow-up (EOFU) was set to either the last date of data collection (March 2025), or the date of liver-related event, the start date of a new potential treatment against HDV or loss to follow-up. Short-term viral response (STVR) was defined as undetectable HDV RNA or a ³ 2 log decline of HDV RNA compared to baseline and biochemical response (BR) as ALT normalization at off treatment month 6. BR and VR were the co-primary endpoints. Cumulative probabilities of any event occurrence were estimated by the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate logistic regression models with forward Wald deletion were used to estimate the effect of various on- and off-treatment variables on clinical outcome. **Results:** STVR and BR was achieved in 12 patients. On LTFU none of these patients developed a clinical event in up to 10 years of follow up. Out of 85 patients without VR+BR, 17(20%) developed an event (Figure, $p < 0.05$ by the log rank test). **Conclusion:** Patients achieving a 2 log drop in HDV RNA from baseline and normal ALT at 6 months after stopping any finite lonafarnib-based treatment regimen have no major clinical events (liver decompensation, liver cancer, or death) in up to 10 years of follow-up.

Disclosures: Jeffrey Glenn: Eiger BioPharmaceuticals, Inc.: Board member, Riboscience, LLC: Board member, I-Cubed Therapeutics, LLC: Board member, 4J Therapeutics, Inc.: Board member, EITPharma: Board member

2271 | LOW HEPATITIS D VIREMIA AND CIRRHOSIS BURDEN AMONG AFRICAN PATIENTS: A MULTICENTER PROSPECTIVE STUDY

Adriana Palom[1] Ariadna Rando-Segura[2] Tomás Balari[3] ROSA MARIA MORILLAS CUNILL[4] Adrià Rodríguez[5] Patricia Huelin[6] Carmen Lopez[7] Darly Salazar[8] Joana Villaverde[9] Indiana Jesús Abdo Sanmartino[10] José Castellote[3] Joan Carles Quer[5] Carles Aracil Blanch[6] Andrés Marco[10] Maria Buti[1], [1]Liver Unit, Hospital Universitari Vall d'Hebron, CIBERehd, Barcelona, Spain, [2]Microbiology Unit, Hospital Universitari Vall d'Hebron, CIBERehd, Barcelona, Spain, [3]Gastroenterology Department, Hospital Universitari de Bellvitge, Barcelona, Spain, [4]Gastroenterology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [5]Gastroenterology Department, Hospital Universitari Joan XXIII, Tarragona, Spain, [6]Gastroenterology Department, Hospital Universitari Arnau de Vilanova, Lleida, Spain, [7]Gastroenterology Department, Hospital Universitari Doctor Josep Trueta, Girona, Spain, [8]Gastroenterology Department, Hospital de Tortosa Verge de la Cinta, Tortosa, Spain, [9]Gastroenterology Department, Hospital de Viladecans, Barcelona, Spain, [10]Group of infectious diseases in Prisons of Catalonia (GRUMIP), Barcelona, Spain

Background: Hepatitis D infection is a severe form of viral hepatitis, often leading to cirrhosis and liver failure. Its prevalence varies by geography and ethnicity, yet its distribution in Catalonia remains underexplored. This study examines the rate of HDV viremia across different ethnic groups in Catalonia, Spain. **Methods:** Multicenter prospective study that evaluated all anti-HDV positive patients detected in 15 months in the seven Catalan Health Institute laboratories. Demographic, epidemiological, clinical and laboratory data for all anti-HDV positive patients was recorded on a digital platform. HDV-RNA determination was centralized and quantified with an in-house RT-qPCR using the HDV-RNA WHO international standard. **Results:** From January 1, 2024, to March 31, 2025, a total of 215 anti-HDV-positive patients were identified; 128 Caucasian, 54 African, 10 Asian and 6 Hispanic. Table 1 shows the baseline characteristics from the two most prevalent groups. African patients were more often younger, had a lower percentage of cirrhosis and had more normal ALT levels and undetectable HDV-RNA. The multivariate analysis showed that older age and detectable HDV RNA were associated with a higher risk of cirrhosis while African ethnicity was strongly associated with a lower risk of cirrhosis compared to Caucasians (OR 0.12, $p < 0.001$). Moreover, among Caucasians, Eastern European patients (n = 43) had a higher proportion of detectable HDV-RNA (72% [31/43] vs. 26% [22/85], $p < 0.001$), and qHDV-RNA levels (median 5.0 (4.2–5.8) vs. 4.3 (3.8–4.8) log IU/mL ($p = 0.032$), than those from Western Europe. However, the proportion of cirrhosis was similar in Eastern and Western Europeans (18 [42%] vs 29 [34%], respectively) ($p = 0.439$). Among the 10 Asian patients, 4 (40%) were viremic and 2 (20%) had liver cirrhosis. No Hispanic patients presented detectable viremia or liver cirrhosis. **Conclusion:** African patients with HDV infection in Catalonia have a milder disease profile; characterized by lower viremia rates, lower cirrhosis prevalence, and younger age at diagnosis compared to other ethnic groups. These findings underscore the importance of considering ethnic background in the clinical assessment and management of HDV infection.

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Table 1. Baseline characteristics of Caucasian and African anti-HDV positive patients.

	Caucasian (n=128)	African (n=54)	p-value
Age, years	56 (46-60)	42 (33-51)	<0.001
Male	92 (72%)	32 (59%)	0.117
Elevated ALT	41/123 (33%)	13/52 (25%)	0.370
Liver cirrhosis	47 (37%)	4 (7%)	<0.001
Detectable HDV-RNA	53 (41%)	15 (28%)	0.094
qHDV-RNA, log IU/ml	4.8 (4.0-5.8)	5.3 (3.5-5.8)	0.597
Normal ALT and undetectable HDV-RNA	62/82 (76%)	35/39 (90%)	0.068

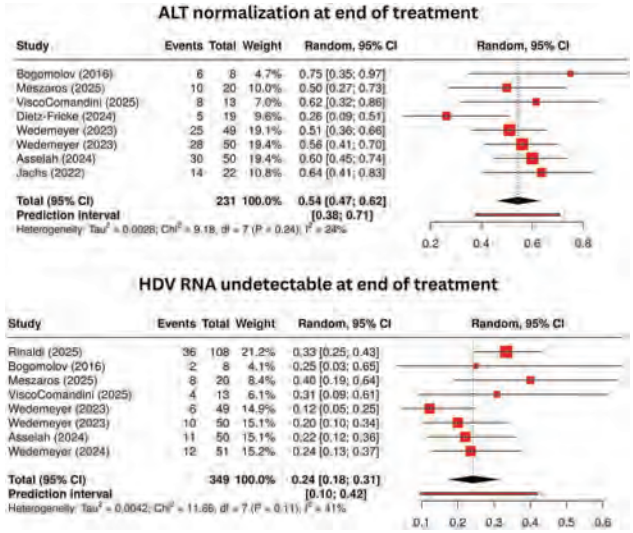
Qualitative variables are expressed as n (%) and quantitative variables are expressed as md (IQR)

Disclosures: Adriana Palom: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Ariadna Rando-Segura: Nothing to Disclose, Tomás Balari: GILEAD: Independent Contractor, GILEAD: Specific financing, AbbVie: Specific financing, ROSA MARIA MORILLAS CUNILL: Nothing to Disclose, Adrià Rodríguez: Nothing to Disclose, Patricia Huelin: Nothing to Disclose, Carmen Lopez: Nothing to Disclose, Darly Salazar: Nothing to Disclose, Joana Villaverde: Nothing to Disclose, Indiana Jesús Abdo Sanmartino: Nothing to Disclose, José Castellote: Nothing to Disclose, Joan Carles Quer: Nothing to Disclose, Carles Aracil Blanch: Nothing to Disclose, Andrés Marco: Nothing to Disclose, Maria Buti: Nothing to Disclose

2272 | EVALUATING THE EFFICACY OF BULEVIRTIDE MONOTHERAPY IN SUPPRESSING HEPATITIS DELTA VIRUS (HDV) RNA AND ACHIEVING ALT NORMALIZATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Rohan Karkra[1] Joshua Pagán-Busigó[1] Mahinaz Mohsen[1] Michael Bebawy[1] Muhammad Hassaan Arif Maan[1] Paul Gaglio[1], [1]Rutgers New Jersey Medical School

Background: The Hepatitis D Virus (HDV), a defective virus requiring Hepatitis B surface antigen (HBsAg) to replicate, affects 10-20 million people globally. Patients with Chronic Hepatitis Delta (CHD) are at an increased risk of advanced hepatic fibrosis, cancer, and mortality, with an estimated 50,000 deaths every year. Peginterferon alpha has traditionally been used for therapy, but its effectiveness is variable. Bulevirtide, a novel antiviral drug for treating chronic Hepatitis D, was recently authorized in Europe. It blocks the Sodium Taurocholate Co-Transporting Polypeptide (NTCP) receptor on hepatocytes, preventing viral entry into liver cells. This meta-analysis will evaluate Bulevirtide monotherapy's efficacy in managing CHD. **Methods:** We conducted a comprehensive search of electronic databases – PubMed, Embase, and Cochrane to date to identify all trials and studies that investigated the efficacy of Bulevirtide, irrespective of dosing regimen, for CHD. Eligible studies were restricted to single-arm investigations reporting clinical outcomes. Three reviewers performed data extraction. Pooled proportions were calculated using a random-effects model, with heterogeneity assessed via the DerSimonian–Laird method. Doses were pooled to represent Bulevirtide as a therapeutic class. Analyses adhered to PRISMA guidelines, and the results were visually represented using forest plots. **Results:** A total of 9 studies were included, involving 390 patients. Statistical heterogeneity was insignificant ($p > 0.05$), supporting the consistency of findings across studies. The pooled proportion of patients achieving biochemical response (ALT normalization) was 54% (95% CI: 47%–62%, $p < 0.05$). The proportion of patients attaining undetectable HDV RNA was 24% (95% CI: 18%–31%, $p < 0.05$). 46% (95% CI: 32%-60%, $p < 0.05$) of patients had a sustained combined response, defined as either ≥ 2 log decrease in HDV RNA or undetectable RNA, with ALT normalization at follow-up, at least 6 months later. **Conclusion:** In this analysis, over half of the patients receiving Bulevirtide demonstrated biochemical improvement, and approximately one-quarter achieved virological suppression at the end of treatment. Close to 50% had a sustained combined response ≥ 24 weeks after treatment. Despite the absence of comparator arms, these findings suggest that Bulevirtide offers clinically meaningful benefits in chronic hepatitis D, a historically challenging disease with limited therapeutic options. Given the relatively recent introduction of Bulevirtide and the scarcity of head-to-head trials, these results underscore the drug's potential role in treatment algorithms. Larger, randomized controlled studies, including combinations with interferons, are warranted to establish its efficacy further and optimize its clinical application.



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Disclosures: Rohan Karkra: Nothing to Disclose, Joshua Pagán-Busigó: Nothing to Disclose, Mahinaz Mohsen: Nothing to Disclose, Michael Bebawy: Nothing to Disclose, Muhammad Hassaan Arif Maan: Nothing to Disclose, Paul Gaglio: Nothing to Disclose, Nothing to Disclose

2273 | REAL-WORLD PERSISTENCY OF BULEVIRTIDE THERAPY IN CHRONIC HEPATITIS D PATIENTS IN GERMANY: A RETROSPECTIVE OBSERVATIONAL ANALYSIS

Dirk Nierhoff[1] Marianna Schwenken[2] Monika Weischenberg[2] Markus Cornberg[3] MEHTAP GUENDOGDU[2] Kyung min Kwon[4] AMANDA SINGER[4] MICHAEL MERTENS[4] Joerg Petersen[5], [1]University Hospital Cologne, [2]Gilead Sciences GmbH, [3]Hannover Medical School, [4]GILEAD SCIENCES, INC., [5]IFI Institute for Interdisciplinary Medicine Hamburg

Background: Bulevirtide (BLV) is the only approved therapy for the treatment of chronic hepatitis D (CHD) in the European Union. Administered as daily subcutaneous injections, BLV therapy should be continued as long as clinical benefit persists. Real world (RW) persistency is key to sustained outcomes. In 2020, Germany was the first country with availability of BLV for routine medical care, but RW persistency data are yet to be described. **Methods:** This retrospective, observational analysis used the German IQVIATM LRx prescription database (~80% of national statutory insurance coverage) to evaluate BLV persistency rates (PRs) in two cohorts: early (EC, 2020 – 2022 initiators, 24 months follow-up), and late (LC, 2023 initiators, 12 months follow-up). The rationale for selecting the two cohorts was based on assumed differences in clinical practice in Germany, historically prioritizing patients with higher disease burden for BLV initiation. Reasons for discontinuations were not captured. Data were stratified by demographics and comedication prescription (CP) (utilizing the Anatomical Therapeutic Chemical Classification – Level 3 (ATC3)). Persistency, defined as the probability of remaining on treatment, was estimated by Kaplan-Meier allowing therapy breaks of < 3 months. Predictors of 12-month PR were analyzed using logistic regression. **Results:** EC and LC included 219 and 87 patients, respectively. Baseline (BL) characteristics and CPs are shown in Table 1. In EC, the 12-months and 24-months PRs were 82%, and 73%, respectively. In LC, the 12-months PR was 79%. Nucleos(t)ide analogues (NUCs) were the most frequent CP at BL (66 – 68%) and during therapy (77 – 79%) in both cohorts. Pegylated Interferon alpha (Peg-IFN α) CP at BL was rare (1 – 2%) with no CP after 3 months of BLV-treatment. In pooled univariate analysis for preselected CPs at 12 months, NUCs during therapy were positively associated with persistency (OR = 7.78; 95% CI: 2.64 – 22.93; p < 0.001), while N02B analgesics /antipyretics were negatively associated (OR = 0.38; 95% CI: 0.19 – 0.79; p = 0.009). **Conclusion:** The current analysis demonstrated high real world BLV persistency, with 12-months rates of 79 – 82% and 24-months rate of 73% highlighting the sustained BLV use in clinical care. High persistency rates often serve as surrogate for overall clinical utility such as safety and effectiveness. RW associations with CPs such as NUCs were observed and require further validation.

Table 1:

		Early BLV cohort (EC)		Late BLV cohort (LC)	
Baseline (BL) characteristics	Parameter	Patients* count	Patients* share (%)	Patients* count	Patients* share (%)
n		219	100%	87	100%
Gender	female	73	33%	21	24%
	male	120	55%	60	69%
	unknown	26	12%	16	18%
Age in years	mean (SD)	46.9 (11.14)		46.9 (10.85)	
	18-49	76	17%	12	14%
	50-65	130	59%	56	64%
	>65	51	23%	19	22%
Total initiating specialty	Outpatient centers / clinics	147	67%	51	59%
Comedication (prescription) (CP)					
BL: BLV initiation (prior to 6 months)	Most prescribed substance: Nucleos(t)ide analogues (NUCs)	144	66%	59	68%
	TOP 5 prescribed WHO ATC3 classes for the interval (excluding NUCs)				
	A02B PEPTIC ULCER AND GORD	39	17%	13	15%
	C07A BETA BLOCKING AGENTS	34	16%	14	16%
	M01A ANTIINFLAM. AND ANTIRHEUMATICS NON-STEROIDS	21	10%	5	7%
	C03C HIGH-CEILING DIURETICS	17	8%	1	1%
	N02B OTHER ANALGESICS AND ANTIPYRETICS	16	7%	8	9%
	C09A ACE INHIBITORS, PLAIN	14	6%	4	5%
	Other drugs of interest:				
	Peg-IFN α	4	2%	1	1%
	HIV	3	1%	4	5%
	Diabetes	6	3%	4	5%
	HDV	-	-	-	-
During therapy (> 0 - 12 months after BLV initiation)	Most prescribed substance: Nucleos(t)ide analogues (NUCs)	173	79%	67	77%
	TOP 5 prescribed WHO ATC3 classes for the interval (excluding NUCs)				
	A02B DRUGS FOR PEPTIC ULCER AND GORD	69	32%	19	22%
	C07A BETA BLOCKING AGENTS	54	25%	19	22%
	N02B OTHER ANALGESICS AND ANTIPYRETICS	45	21%	16	18%
	M01A ANTIINFLAM. AND ANTIRHEUMATIC, NON-STEROIDS	43	20%	7	8%
	C03C HIGH-CEILING DIURETICS	23	11%	6	7%
	N06A ANTIDEPRESSANTS	22	10%	5	6%
	Other drugs of interest:				
	Peg-IFN α	1	-	-	-

Disclosures: Dirk Nierhoff: AbbVie: Advisor, AbbVie: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Ipsen: Advisor, Astra Zeneca: Speaking and Teaching, Marianna Schwenken: Gilead Sciences: Employee, Gilead Sciences GmbH: Employee, Gilead Sciences: Stock - publicly traded company, Monika Weischenberg: Nothing to Disclose, Markus Cornberg: Nothing to Disclose, MEHTAP GUENDOGDU: Nothing to Disclose, Kyung min Kwon: Gilead sciences: Employee, Gilead Sciences: own stock, AMANDA SINGER: Gilead Sciences: Employee and own stock, MICHAEL MERTENS: Nothing to Disclose, Joerg Petersen: Gilead Sciences: Speaking and Teaching

2274 | EFFECT OF 48-WEEK BULEVIRTIDE THERAPY ON NON-INVASIVE MARKERS OF LIVER FIBROSIS IN PATIENTS WITH HBEAG NEGATIVE CHRONIC HEPATITIS B/D

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

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Background: Treatment with Bulevirtide (BLV) in chronic hepatitis B/D (CHB/D) results in biochemical (BR), virologic (VR) or combined response in a significant proportion of patients. However, there is limited knowledge regarding changes in non-invasive fibrosis tests (NITs) during treatment. Our aim was to explore the changes in NITs after 48 weeks of 2mg daily BLV. **Methods:** We included patients with CHB/D who completed 48 weeks of BLV and had available liver stiffness values (LS) measured by transient elastography at the beginning of treatment (T0) and 48 (± 8) weeks later (T1). The AST to Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4) scores were also calculated. Cirrhosis was diagnosed based on clinical or imaging findings or LS >10.0 kPa. BR and VR were defined as ALT ≤ 40 IU/l and a reduction of HDV-RNA by 2 $\log_{10}$, respectively. **Results:** Of 31 patients followed at our Unit, 19 patients [36.8% males, median age 53 (41-63 years] fulfilled the inclusion criteria and were included in the analysis. After 48 weeks of BLV, 47.4% had BR and 78.9% VR. The LS at T0 was 11.9 (8.0-18.2) vs 8.4 (6.5-12.3) kPa ($p<0.001$) at T1. Seventy-five percent of patients showed a reduction in LS, while for 8/19 the reduction was >2 kPa. At T0, LS was >10 kPa in 13/19 patients (68.4%) compared to 7/19 (36.8%) at T1 ($p=0.024$). The reduction in LS was greater for cirrhotics compared to non-cirrhotics {-6.5 [-9.8-(-0.4)] vs -0.35 (-1.4-0.5) kPa, $p=0.103$}. LS was non-significantly greater among patients who did or did not achieve VR {-5.8 [-9.7-(-0.8)] vs -0.2 [-0.5-(-0.2)] kPa, $p=0.333$] and those with or without BR {-5.8 (-9.7-0.25) vs -1.9 (-8.4-0.1) kPa, $p=0.394$]. The APRI showed a non-statistically significant decrease between T0 and T1 in the total population [1.29 (0.62-2.04) vs 0.62 (0.56-1.03), $p=0.155$]. However the change was statistically significant greater between those with and without BR {-0.99 [-4.31 - (-0.45) vs 0.14 (-0.38-0.59), $p=0.004$}, while it did not differ when based on VR ($p=0.230$). A non-statistically significant decrease was also observed for FIB-4. Changes in FIB-4 followed similar trends to those of APRI. No correlation was observed between the changes in LS and those of APRI ($r=-0.079$, $p=0.829$) or between LS and FIB-4 ($r=0.006$, $p=0.98$). However, changes in APRI and FIB-4 showed a strong correlation ($r=0.937$, $p<0.001$). **Conclusion:** Treatment with BLV for 48 weeks is associated with a reduction in the NIT's particularly in LS values by transient elastography. Changes in NIT's based on serology (APRI and FIB-4) are clearly related to the biochemical response; therefore the profile of biochemistry during treatment should be taken into account when evaluating progression / regression of liver disease with APRI or FIB-4.

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2275 | SPECTRUM AND OUTCOMES OF HEPATITIS A VIRUS-ASSOCIATED ACUTE LIVER FAILURE: INSIGHTS INTO EXTRAHEPATIC MANIFESTATIONS AND ROLE OF EXTRACORPOREAL THERAPIES

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Background: Hepatitis A virus (HAV) remains a leading cause of acute liver failure (ALF) in developing countries. While hepatic dysfunction is well recognized, the spectrum of extrahepatic manifestations is increasingly appreciated. This study aimed to characterize the clinical profiles, extrahepatic involvement, and outcomes of patients with HAV-related ALF, with a focus on the impact of extracorporeal therapies. **Methods:** A retrospective analysis was conducted on patients with HAV-associated ALF and cerebral edema admitted to the Institute of Liver and Biliary Sciences (ILBS), New Delhi, between April 2022 and April 2024. Patients were stratified into two groups: Group 1 (liver-dominant), fulfilling King's College Hospital (KCH) criteria for liver transplantation, and Group 2 (non–liver-dominant), not meeting KCH criteria but with significant extrahepatic organ involvement. Clinical, biochemical, and outcome variables were compared. **Results:** Of 82 ALF cases, 56 (68.3%) were attributed to HAV (mean age: 23.6 years; 64% male). Among these, 12 (21.8%) were liver-dominant (Group 1) and 44 (78.2%) were non–liver-dominant (Group 2). Group 1 had higher INR (4.48 $\pm$ 2.34 vs. 2.52 $\pm$ 1.07; $p=0.014$), while Group 2 had higher SOFA scores (8.25 $\pm$ 1.67 vs. 7.08 $\pm$ 1.62; $p=0.031$) and CRP levels (38.5 ± 19.2 vs 67.8 ± 42.4; $p=0.02$). Therapeutic plasma exchange (TPE) was performed in 66% (Group 1) and 65% (Group 2); continuous renal replacement therapy (CRRT) was required in 83% and 56%, respectively. Extrahepatic manifestations included renal dysfunction (42%), pulmonary involvement (39%), hemolysis (5.6%), cardiac injury (7.5%), pancreatitis (7.5%), non-edema-related neurological symptoms (7.4%), and hemophagocytic lymphohistiocytosis (HLH) in 16%. Group 2 had

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higher mean and peak serum creatinine levels (1.92 ± 0.07 vs. 1.1 ± 0.8 mg/dL; 9.7 vs. 3.9 mg/dL; $p < 0.001$) and greater incidence of glomerulonephritis (58% vs. 33%; $p = 0.06$) and extrapulmonary ARDS (25% vs. 77%; $p = 0.03$). Despite greater extrahepatic involvement, Group 2 had better 28-day survival (84% vs. 41%; $p = 0.002$) and longer hospital stays (16.6 ± 14.3 vs. 12.2 ± 19.5 days; $p = 0.054$). Liver transplantation was performed more frequently in Group 1 (25% vs. 2.2%; $p = 0.028$). **Conclusion:** HAV-associated ALF exhibits a wide array of extrahepatic manifestations. Patients with non–liver-dominant HAV-related illness, despite greater multi-organ involvement, demonstrated better survival outcomes and favourable responses to extracorporeal therapies

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2276 | A NEW NON-INVASIVE DIAGNOSTIC APPROACH: RESEARCH ON THE DIAGNOSTIC VALUE OF URINE HEV RNA/ ANTIGEN DETECTION IN HEPATITIS E

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Background: Hepatitis E virus (HEV) is the main cause of acute and chronic viral hepatitis. Hepatitis E virus (HEV) is known to be excreted through feces, but there is little research on its presence in urine. This study investigated the presence and dynamic changes of antigens (HEV Ag) in urine. **Methods:** Virus markers were detected in the urine and serum of acute and chronic HEV patients to evaluate the diagnostic utility of HEV Ag in predicting HEV infection outcomes. **Results:** HEV RNA and HEV Ag were continuously detected in the blood of 4 patients with chronic HEV infection, and HEV Ag was continuously detected in the urine. The dynamic change of HEV Ag in blood was consistent with the dynamic change of HEV RNA in blood. Among 41 patients with acute HEV, 97.56% (40/41) had HEV Ag detected in their urine, and the specificity of HEV Ag in urine was 100%. Among 63 patients with acute HEV, 93.65% (59/63) had HEV Ag detected in their serum, although 2 cases were negative for anti-HEV IgM. We also identified 24 patients with hepatitis E complicated with hematological diseases. Among them, 13 patients underwent bone marrow transplantation, including 8 patients who underwent haploid hematopoietic stem cell transplantation and 5 patients who underwent fully compatible bone marrow hematopoietic stem cell transplantation. All 24 patients had positive HEV RNA. 87.5% of the patients had positive serum HEV Ag. Only 19 patients had urine samples, and 100% of the patients had positive urine HEV Ag. **Conclusion:** Detecting HEV Ag in urine may have important value in diagnosing acute and chronic HEV infections and monitoring persistent infections.

Disclosures: Haiying Zhang: Nothing to Disclose, Yuyuan Jia: Nothing to Disclose, Huiying Rao: Nothing to Disclose

2277 | THE IMPORTANCE OF INTERFERON AND WNT-RELATED SIGNALING PATHWAYS IN ACUTE HEPATITIS A: INSIGHTS FROM A MOUSE XENOGRAFT MODEL

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Background: Hepatitis A outbreak was declared in Los Angeles County last year, and the case counts continued to climb throughout the early part of this year. However, no potent anti-HAV drugs are currently available in clinical use, and there are no easily accessible or practical *in vivo* models for HAV drug screening, especially HAV genotype (GT)-III. In this study, we established a HAV GT-IIIA *in vivo* model using BALB/cAJcl-nu/nu (nude) xenograft mice and treated with several medicines. Moreover, we investigated how HAV induces gut microbiota dysbiosis, which may contribute to its survival. **Methods:** 1) Human hepatoma cells were infected with HAV, then transplanted as xenografts into the back of nude mice, which were subsequently treated with mouse IFN. 2) HAV-RNA were measured by real-time RT-PCR in liver tissues, intestinal tissues, feces, sera and xenografts of the mice. 3) Tissues samples were evaluated by hematoxylin and eosin staining. 4) Serum aminotransferase protein levels were quantified by ELISA. 5) HAV-RNA in the infected mouse liver was investigated by *in situ* hybridization. 6) RNA-Seq was performed to identify transcripts specifically associated with HAV infection. 7) Proteomic analysis was performed to

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identify the proteome profile of the conditioned medium from HAV infected hepatocytes. 8) The composition of the gut microbiota was determined by sequencing the V3-V4 region of the 16S rRNA gene. **Results:** 1) There was no difference in body weight between HAV infected and uninfected mice. 2) HAV-RNA levels were detected in liver tissues, intestinal tissues, feces, sera, and xenografts. HAV-RNA levels tend to be inhibited in IFN treated xenograft mice. Hepatic necroinflammation was observed in the liver with a slight elevation of serum aminotransferase levels in HAV infected xenograft mice and serum aminotransferase levels were significantly inhibited in IFN treated xenograft mice. 3) RNA sequencing and proteome analysis showed that HAV infection altered Wnt-related signaling pathways. 4) Gut microecological dysregulation was observed in HAV infected xenograft mice. **Conclusion:** We have established and utilized an *in vivo* HAV GT-IIIA model for anti-HAV drugs screening. In this model, inflammation was observed histopathologically in the liver tissues and intestinal tissues where HAV-RNA was detected, and IFN treatment tends to inhibit quantitative HAV-RNA levels. The Wnt-related signaling pathways altered by HAV infection may contribute to gut microecological dysregulation in HAV infected xenograft mice.

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2278 | PATIENT-REPORTED BURDEN AND HEALTH-RELATED QUALITY OF LIFE AMONG PATIENTS WITH HEPATITIS DELTA: RESULTS: FROM A REAL-WORLD STUDY IN EUROPE

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Background: Evidence surrounding the impact of bulevirtide (BLV) on health-related quality of life (HRQoL) among patients with hepatitis delta virus (HDV) infection is limited. We aimed to describe the demographics and HRQoL outcomes of patients with HDV infection in a real-world setting who were treatment naïve or prescribed BLV. **Methods:** Data were drawn from the Adelphi Real World Hepatitis Disease Specific Programme™, a cross-sectional survey with retrospective data collection of physicians and their patients with HDV in France, Italy, Spain, and the UK from June 2024 to December 2024. Physicians consulting 4 patients with HDV diagnosis for routine care collected physician-reported patient demographics and patients' HRQoL impact via patient-reported outcome measures (PROMs). Each physician reported on 2 patients who were prescribed BLV and 2 patients with or without a prescribed treatment. Descriptive analyses focused on patients who received BLV monotherapy for ≥6 months (BLV mono ≥6 m) and treatment-naïve patients. Patients prescribed interferon monotherapy or combination therapy were excluded from the analysis. **Results:** Overall, 34 physicians (France, 10; Italy, 7; Spain, 12; UK, 5) reported data on 102 patients (France, 24; Italy, 20; Spain, 28; UK, 30). Mean (SD) patient age was 45 (15.3) years; 68% were male, and 73% were White. Mean (SD) time since HDV diagnosis was 4 (7.4) years. Half (n = 51) of patients were prescribed BLV monotherapy and 41% were treatment naïve (n = 42). Of the 51 patients prescribed BLV monotherapy, 37 (73%) were BLV mono ≥6 m patients. Mean (SD) Fatigue Severity Scale, 7-item (1–7 scale; higher scores indicate more fatigue) scores were 3.7 (1.75) and 3.9 (1.39) for BLV mono ≥6 m and treatment-naïve patients, respectively (Table). Mean (SD) Hepatitis B Quality of Life (HBQoL; 0–100 scale; higher scores indicate worse HRQoL) overall and HBQoL viral response scores were 36 (18.7) and 34 (18.4), respectively, for BLV mono ≥6 m patients and 45 (14.1) and 48 (19.0) for treatment-naïve patients. Mean (SD) EuroQoL 5-Dimension 5-Level (EQ-5D-5L; 0–1 scale; 1 represents the best health) and EQ-5D Visual Analog Scale (0–100 scale; 100 represents the best health) scores for BLV mono ≥6 m patients were 0.7 (0.26) and 66 (21.7), respectively, and 0.8 (0.18) and 73 (14.3) for treatment-naïve patients. **Conclusion:** Disease- and symptom-specific PROMs show that patients prescribed BLV monotherapy for ≥6 months have better HRQoL outcomes compared with patients not on HDV treatment. General measures of HRQoL, which may be less sensitive, show minimal differences between the groups.

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Table. Patient-Reported HRQoL Among Patients With HDV Receiving BLV vs Treatment-Naïve Patients

HRQoL Measure	BLV Monotherapy ≥6 Months (n = 37)	Treatment-Naive (n = 42)
Disease- and symptom-specific PROMs		
FSS-7[a]	3.7 (1.75)	3.9 (1.39)
HBQoL[b] measures		
Overall	36 (18.7)	45 (14.1)
Viral response	34 (18.4)	48 (19.0)
Transmission	38 (24.0)	50 (21.0)
Psychological well-being	35 (21.0)	39 (18.0)
Anticipation anxiety	46 (25.7)	54 (17.2)
Vitality	35 (19.7)	39 (15.7)
Stigmatization	29 (22.2)	39 (18.7)
Vulnerability	34 (20.9)	46 (19.5)
General measures of HRQoL		
EQ-5D-5L[c]	0.7 (0.26)	0.8 (0.18)
EQ-5D VAS[d]	66 (21.7)	73 (14.3)

Values in table represent mean (SD). The *n* values indicate the overall group size; not all HRQoL measures include all patients.
[a]FSS-7 scale: 1-7, where higher scores indicate more fatigue. [b]HBQoL scale: 0-100, where 0 represents the best possible HRQoL. [c]EQ-5D-5L scale: 0-1, where 1 represents the best health the patient can imagine. [d]EQ-5D VAS scale: 0-100, where 100 represents the best health the patient can imagine.
BLV, bulevirtide; EQ-5D-5L, EuroQoL 5-Dimension 5-Level; EQ-5D VAS, EuroQoL 5-Dimension Visual Analog Scale; FSS-7, Fatigue Severity Scale, 7-item; HBQoL, Hepatitis B Quality of Life; HDV, hepatitis delta virus; HRQoL, health-related quality of life; PROM, patient-reported outcome measure.

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2279 | HDV MOLECULAR CHARACTERIZATION IN SPAIN: GENOTYPE DISTRIBUTION VIA WHOLE-GENOME SEQUENCING

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Background: Hepatitis delta virus (HDV) displays wide genetic variability, with eight known genotypes differing in geographic distribution and clinical relevance. Understanding circulating genotypes is essential for improving diagnosis, anticipating disease progression, and optimizing treatment strategies. This study analyzes the genotype distribution of HDV in Spain using whole-genome sequencing (WGS) in patients with active infection. **Methods:** A retrospective observational study was conducted from August 2019 to June 2024 in Andalusia, Murcia, and the Canary Islands, including HDV RNA-positive patients. Following the launch of the national Delta Double Reflex (DDR) project, additional samples from other Spanish regions were incorporated. WGS was performed using overlapping primers and Illumina NextSeq 1000 technology. Genotypes were assigned by alignment with HDVdb references. Phylogenetic analysis, including only sequences with $>90\%$ coverage, was performed using the Neighbor-Joining method (MEGA software). Recombination was evaluated with RDP5.63. **Results:** A total of 151 patients were included; 52.3% were of Spanish origin. Median HDV RNA level was 4.9 log IU/mL (IQR: 3.9–6). Genotyping was successful in 144 cases (95.4%), with mean genome coverage of 98% (range 70–100%). Genotype 1 (G1) predominated (88.2%), mostly among Spanish-born patients. Genotype 5 (G5) was found in 15 cases (10.4%), exclusively in individuals from West Africa. One case (0.7%) of genotype 7 (G7) was identified in a patient from Equatorial Guinea, and one case (0.7%) of genotype 3 (G3) in a patient from Bolivia. Seven samples could not be genotyped due to low amplification or insufficient coverage. Phylogenetic analysis (140 sequences) showed that subgenotype 1d was identified in 86.6% of G1 cases, and subgenotype 5b in 64.3% of G5 cases. No recombination events were detected. **Conclusion:** Genotype 1 is the predominant HDV strain in Spain, particularly among native patients, while genotype 5 is restricted to individuals from West Africa. This study contributes to understanding the molecular epidemiology of HDV in Spain and supports the relevance of genotyping in HDV management and surveillance.

Disclosures: Ana Alberola Romano: Nothing to Disclose, Adolfo De Salazar: Nothing to Disclose, Lucía Chaves Blanco: Nothing to Disclose, Marta Illescas López: Nothing to Disclose, Ana Fuentes: Nothing to Disclose, Alberto Vázquez Blanquiño: Nothing to Disclose, M Teresa Cabezas Fernández: Nothing to Disclose, Carolina Freyre: Nothing to Disclose, Berta Becerril Carral: Nothing to Disclose, Isabel Viciana: Nothing to Disclose, Inmaculada López Rodríguez: Nothing to Disclose, Natalia Montiel Quezel-Guerraz: Nothing to Disclose, Samuel Bernal: Nothing to Disclose, María del Pilar Luzón-García: Nothing to Disclose, Encarnación Ramírez Arellano: Nothing to Disclose, Carmen Liébana: Nothing to Disclose, Francisco Franco Álvarez de Luna: Nothing to Disclose, M Carmen Lozano Domínguez: Nothing to Disclose, Begoña Palop: Nothing to Disclose, Antonio Sampedro: Nothing to Disclose, Ana Belén Pérez: Nothing to Disclose, Sonia Algarate Cajo: Nothing to Disclose, Marta Álvarez Argüelles: Nothing to Disclose, Pablo Fraile Ribot: Nothing to Disclose, Dolores Ocete: Nothing to Disclose, María Jesús Alcaraz Soriano: Nothing to Disclose, Juan Carlos Rodriguez Díaz: Nothing to Disclose, Francisco Javier Hernández Felices: Nothing to Disclose, Olalla Martinez Macias: Nothing to Disclose, María Victoria Domínguez Márquez: Nothing to Disclose, Nieves Orta Mira: Nothing to Disclose, María Dolores Gómez Ruiz: Nothing to Disclose, Jorge Camacho Marín: Nothing to Disclose, Susana Sabater Vidal: Nothing to Disclose, Luis Ángel Iglesias Sánchez: Nothing to Disclose, Yasmina Martín:

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◆ 2280 | PREDICTING PORTAL HYPERTENSION SEVERITY USING THREE-DIMENSIONAL MR ELASTOGRAPHY-BASED MACHINE LEARNING MODEL IN PATIENTS WITH ADVANCED CHRONIC LIVER DISEASE

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Background: Hepatic venous pressure gradient (HVPG) is the gold standard for assessing portal hypertension (PH) severity but is limited by its invasive nature. This study developed and validated machine learning models (MLMs) integrating three-dimensional magnetic resonance elastography (3D-MRE) and laboratory parameters to establish a noninvasive PH risk stratification system for patients with advanced chronic liver disease (ACLD). **Methods:** The multicenter study enrolled patients with ACLD undergoing HVPG measurements and dual-frequency (30Hz/60Hz) 3D-MRE with dual drivers (spleen/liver) from six independent institutions between 2022 and 2024. Viscoelastic parameters were extracted from 3D-MRE data, with MLMs trained and validated in a 7:3 cohort split based on viscoelastic and laboratory parameters. External validation included a prospective cohort (n = 85, 2015-2019 HVPG measurements) and a retrospective cohort (n = 631, 2012-2024 3D-MRE and endoscopy data). **Results:** The primary cohort (n = 172) showed comparable HVPG between training (n = 120, median 9.5 mmHg) and validation (n = 52, median 8 mmHg) sets. Two optimized MLMs emerged: the MRE model (splenic shear stiffness at 60Hz, liver shear stiffness at 60Hz, and splenic damping ratio at 30Hz) and MRE-combined clinical model (MRE-ig) (adding international normalized ratio [INR] and gamma-glutamyl transferase). Both showed exceptional performance for clinically significant PH (CSPH, i.e., HVPG ≥ 10mmHg: train-AUC: 0.990/0.990, validation-AUC: 0.957/0.961, HVPG ≥ 12

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mmHg: train-AUC 0.978/0.982, validation-AUC: 0.961/0.967, HVPG ≥ 16mmHg: train-AUC: 0.949/0.964, validation-AUC: 0.937/0.942, and HVPG ≥ 20mmHg: train-AUC: 0.924/0.939, validation-AUC: 0.931/0.931), significantly outperforming transient elastography (AUC 0.792-0.840) and serum-based models, such as the 3P (platelet count, bilirubin, INR) or 3P+LSM models (AUC: 0.742~0.872) (mostly $p < 0.001$). Prospective validation confirmed robust performance (CSPH: 0.912/0.924, PH12: 0.864/0.887, PH16: 0.830/0.842, PH20: 0.821/0.826), significantly outperforming serum-based 3P models (CSPH: 0.805, PH16: 0.561, all $p < 0.001$), while retrospective analysis revealed strong correlation with the six-stage PH severity classification ($r = 0.732/0.756$, both $p < 0.0001$). Notably, in 341 non-cirrhotic/compensated cirrhosis patients, both models effectively identified patients who needed screening esophageal varices (VNT, AUC 0.858/0.864, both $p < 0.001$) (Figure 1). **Conclusion:** 3D-MRE-based MLMs offer a practical alternative to invasive HVPG measurements, enabling improved risk stratification and clinical decision-making for patients with advanced chronic liver disease.

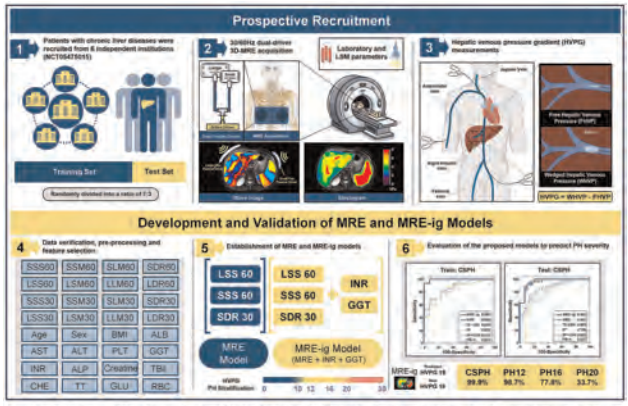

Figure 1: Flowchart of the study. (1-3) Prospective patient recruitment. (4-6) Development and validation of MRE and MRE-ig models.

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◆ 2281 | A PROSPECTIVE RANDOMIZED CONTROLLED, OPEN LABELED, TWO ARM PILOT STUDY WITH BLINDED ENDPOINTS TO EVALUATE THE EFFICACY OF TORSEMIDE-SPIRONOLACTONE VERSUS FUROSEMIDE-SPIRONOLACTONE COMBINATION IN CIRRHOSIS PATIENTS WITH NEWLY DIAGNOSED ASCITES

Arun Valsan[1] Arathi Venu[1] Nipun Verma[2] Marva Abdul Khader[3] Shreya Haridas[3] Ruby Renji[3] Bonny Thankachan[3] Gowri Priya Nair[1] Zubair Mohamed[1] Sudhindran Surendran[1] Priya Nair[1] Anoop K Koshy[1] Nimitha Mohan[4] Yashowardhan Taparia[1] Dr George Eapen Puthusseril[1] Ajay Nathan[5] Ajay Duseja[6], [1]Amrita Institute of Medical Sciences, Kochi, [2]Postgraduate Institute of Medical Education and Research, Chandigarh, [3]Amrita School of Pharmacy, [4]Aster Medcity, Kochi, [5]INHS Sanjivani, [6]Postgraduate Institute of Medical Education & Research

Background: Ascites is the most common complication of liver cirrhosis, often associated with poor prognosis and reduced survival. In addition to salt restriction, diuretics such as furosemide and torsemide in combination with spironolactone are widely used to manage ascites in cirrhotic patients. However, comparative evidence on their efficacy in controlling ascites and safety remains limited. **Methods:** We conducted a prospective, open label, randomized trial with blinded endpoints assessment at a tertiary-care center between May 2024 and Apr 2025. Adult patients (> 18years) with cirrhosis and newly diagnosed ascites without SBP, poorly controlled diabetes, pregnancy or SIADH, were randomized to receive either Furosemide-Spironolactone (FS) or Torsemide-Spironolactone (TS). The patients were followed-up for a period of 28 days or until death or liver transplantation whichever occurred first. Laboratory investigations were done on days 0, 4 and weekly till day 28. Body weight and abdominal girth were recorded every 4 days as surrogate for ascites control. Dose modification was done based on the degree of ascites control as per the treating physician. The primary end point was to assess the efficacy of treatment in controlling ascites and secondary endpoints were treatment emergent adverse effects and survival.Mixed-effects model was used to compare parameters over time between the groups. **Results:** A total of 103 patients (FS-49,TS-54) were enrolled, with a mean age of 52 ± 9.2 years. The cohort was predominantly male (90%) with alcohol being the most common underlying etiology (54%). Both groups demonstrated a significant reduction in abdominal girth over time ($p < 0.001$), without significant group-time differences ($p = 0.999$). There was significant weight reduction

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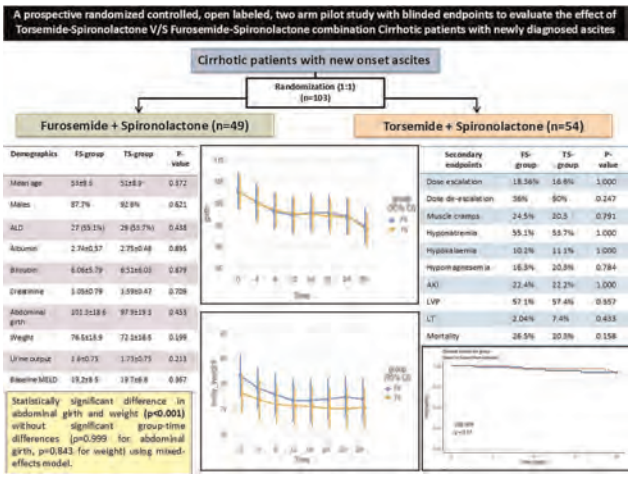
within each group ($p < 0.001$), without a significant interaction between group and time ($p = 0.843$). Dose escalation was required in 17.47% (18.36% vs 16.6%), while de-escalation was implemented in 43.68% (36% vs 50%) due to effective ascites control. The occurrence of muscle cramps (24.5% vs 20.3%, $p = 0.79$), hyponatremia (55.1% vs 53.7%, $p = 1.00$), hypokalemia (10.2% vs 11.1%, $p = 1.00$), hypomagnesemia (16.3% vs 20.3%, $p = 0.78$), incidence of AKI (22.4% vs 22.2%, $p = 1.00$) were similar in both groups. Liver transplantation was done in 2.04% patients in FS and 7.4% patients in TS group. There was no statistically significant difference in survival between the two groups, with a HR of 0.89 ($p = 0.87$). **Conclusion:** Both the FS and TS combinations were equally effective in achieving ascites control, with significant reductions in abdominal girth and mean body weight. No significant differences were observed between the groups in terms of efficacy, safety or survival. The findings suggest that both the regimens are equally effective and well tolerated for the management of new onset ascites.



Disclosures: Arun Valsan: Nothing to Disclose, Arathi Venu: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Marva Abdul Khader: Nothing to Disclose, Shreya Haridas: Nothing to Disclose, Ruby Renji: Nothing to Disclose, Bonny Thankachan: Nothing to Disclose, Gowri Priya Nair: Nothing to Disclose, Zubair Mohamed: Nothing to Disclose, Sudhindran Surendran: Nothing to Disclose, Priya Nair: Nothing to Disclose, Anoop K Koshy: Nothing to Disclose, Nimitha Mohan: Nothing to Disclose, Yashowardhan Taparia: Nothing to Disclose, Dr George Eapen Puthusseril: Nothing to Disclose, Ajay Nathan: Nothing to Disclose, Ajay Duseja: Nothing to Disclose

◆ 2282 | POCUS-GUIDED FLUID RESUSCITATION COMPARING PLASMALYTE PLUS 20% ALBUMIN VS 5% ALBUMIN IN CIRRHOSIS WITH SEPSIS-INDUCED HYPOTENSION: A RANDOMIZED CONTROLLED TRIAL (ALPS PLUS)

Ayush Jain[1] Rakhi Maiwall[2] Harsh Vardhan Tevethia[3] Omkar Rudra[3] Prashant Agarwal[3] Chhagan Bihari[3] Guresh Kumar[3] Mradul Daga[1] Shiv Kumar Sarin[1], [1]ILBS, New Delhi, [2]Institute of Liver and Biliary Sciences, [3]ILBS New Delhi

Background: In critically ill cirrhosis patients (CIC) with sepsis-induced hypotension (SIH), 5% albumin, plasmalyte and 20% albumin have been evaluated for fluid resuscitation. Point-of-care ultrasound (POCUS) can guide fluid resuscitation and reduce the incidence of pulmonary complications. However, no study has evaluated 5%Albumin (5%Alb) versus plasmalyte combined with slow infusion of 20% albumin (P+Alb20) using a POCUS -guided fluid resuscitation strategy. **Methods:** CIC patients with SIH were randomized in a 1:1 open-label design to receive either 5%Alb (5 ml/kg bolus over 30 minutes, followed by 50 ml/hr) or PlasmaLyte (30 ml/kg bolus over 30 minutes, followed by 100 ml/hr) along with 20–40 g of 20% albumin. Subsequent fluid management was guided by hourly POCUS (including IVC variablility and lung USG) assessment for 3 hours. The primary outcome was achievement of a mean arterial pressure (MAP) > 65 mmHg without vasopressor support at 3 hours. **Results:** Baseline characteristics including MAP(mm of Hg) (58.55 ± 4.16 vs 59.48 ± 2.90; $p = 0.157$), arterial lactate(mmol/L) (2.37 ± 1.63 vs 2.58 ± 1.68; $p = 0.502$), SOFA score (9.00 ± 2.35 vs 8.87 ± 2.54; $p = 0.766$), MELD score (28.28 ± 9.98 vs 29.25 ± 9.54; $p = 0.589$), IVC diameter(mm) (14.61 ± 3.63 vs 15.14 ± 4.36; $p = 0.484$), and initial POCUS findings (all A pattern) were comparable between groups. Shock reversal rates at 3 hours (43.3% vs 54.2%; $p = 0.234$) and 24 hours (55.9% vs 67.9%; $p = 0.193$) were similar across both arms. Fluid volume(ml) administered by 3 hours was significantly greater in the P+Alb20 group (600.83 ± 242.77 vs 2202.54 ± 658.52; $p < 0.001$), whereas daily albumin dose was higher in the 5%Alb group (67.01 ± 20.03 vs 34.44 ± 9.64; $p < 0.001$). POCUS identified a higher incidence of B-lines at 3 hours in the 5% Alb group compared to the P+Alb20 group (28.3% vs 10%, $p = 0.01$). However, by 24 hours, the proportion of patients with B-lines was comparable between the groups (20% vs 15%, $p = 0.487$), and the

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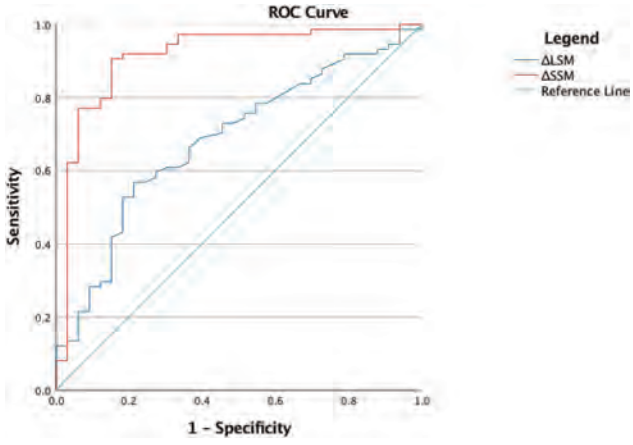
change in IVC measurements over time was similar in both groups. Time to norepinephrine initiation (in hours) (3.45 ± 4.47 vs 3.37 ± 3.50; $p = 0.960$) and cumulative dose of norepinephrine equivalents (1.83 ± 1.93 vs 1.30 ± 1.90; $p = 0.135$), changes in arterial lactate ($p = 0.336$), and requirement for renal replacement therapy (51.7% vs 47.5%; $p = 0.646$) were comparable. At 28 days, mortality (50% vs 43.3%; $p = 0.619$), incidence of hyperchloremic metabolic acidosis (23.3% vs 15.3%; $p = 0.26$), hypernatremia (10% vs 8.5%; $p = 0.774$), and respiratory distress (10% vs 11.6%; $p = 0.976$) were similar between groups. **Conclusion:** Plasmalyte combined with low-dose 20% albumin, guided by dynamic POCUS assessment, is as effective as 5% albumin for fluid resuscitation in cirrhosis with SIH. The POCUS allows tailored resuscitation and may lower the risk of pulmonary complications, highlighting its utility in critical care hepatology.
Disclosures: Ayush Jain: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, Harsh Vardhan Tevethia: Nothing to Disclose, Omkar Rudra: Nothing to Disclose, Prashant Agarwal: Nothing to Disclose, Chhagan Bihari: Nothing to Disclose, Guresh Kumar: Nothing to Disclose, Mradul Daga: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

◆ 2283 | SPLEEN STIFFNESS MEASUREMENT RELIABLY ASSESSES THE RESPONSE TO β-BLOCKER THERAPY (SPARE-B) FOR PRIMARY PROPHYLAXIS OF HIGH-RISK VARICES

Omkar Rudra[1] Jaifrin Daniel[1] Ayush Jain[1] SAURAV PAUL[1] Babu Lal Meena[1] VINOD ARORA[1] Akhil Deshmukh[1] Sherin Thomas[1] GURESH KUMAR[1] Manoj Sharma[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences

Background: HVPG is the gold standard for measurement of the presence and severity of portal hypertension. Clinically Significant Portal Hypertension (CSPH) is defined as HVPG $\geq$ 10 mmHg. Use of non-selective beta blockers (NSBB) has been associated with a positive effect on survival. Response to NSBB therapy is defined as a reduction of HVPG by 10% or to $\leq$ 12 mmHg. Non-invasive tests (NIT) to predict CSPH have been defined, but not assessed for predicting response to NSBB for primary prophylaxis. **Methods:** Patients $>$ 18 years of age with cirrhosis and small or large high-risk esophageal varices and no prior variceal bleed were enrolled. After a thorough assessment, carvedilol was initiated and titrated to the maximum tolerated dose within 7 days. Fibroscan, NIT and HVPG were performed at baseline and repeated after 4 weeks of maximum tolerated dose. NITs were evaluated to predict change in HVPG. **Results:** 130 patients were enrolled. 14 patients were lost to follow-up. 5 patients had a variceal bleed and 4 patients expired prior to follow-up. 107 patients analysed. 74 (69%) patients were HVPG responders and 33 (31%) were non-responders. HVPG at baseline was 17.5 ± 2.6 mmHg in non-responders and 16.8 ± 3.3 mmHg in responders ($p = 0.289$). MELD was comparable between the groups ($p = 0.990$). Mean dose of carvedilol was 18.5 ± 7.4 mg/day in non-responders and 20.2 ± 6.6 mg/day in responders ($p = 0.263$). Target heart rate achieved in 9 (27%) non-responders versus 19 (25%) responders ($p = 0.862$). At 5 weeks, HVPG was 16.7 ± 2.6 mmHg in non-responders and 13.6 ± 2.7 mmHg in responders ($p < 0.001$). SSM reduced by 18.8 ± 13.6 kPa in responders but had increased by 0.6 ± 10.9 kPa in non-responders. Reduction of SSM by $\geq$ 6kPa predicted HVPG response to carvedilol with 85% sensitivity, 84.8% specificity (AUROC 0.913). Reduction in LSM by $\geq$ 2kPa predicted HVPG response with 63% sensitivity and specificity and 68% accuracy. von-Willebrand factor (vWF) and vWF/ADAMTS ratio had an AUROC of 0.664 and 0.653 ($p = 0.007$ and 0.014 respectively). **Conclusion:** Change in SSM at 5 weeks can predict HVPG responders to carvedilol with good accuracy. A reduction of $\geq$6 kPa in SSM reliably reflects response to carvedilol and is a good alternative to repeat HVPG measurement for the primary prophylaxis of high-risk varices. [Trial Registration - NCT06050837]



Disclosures: Omkar Rudra: Nothing to Disclose, Jaifrin Daniel: Nothing to Disclose, Ayush Jain: Nothing to Disclose, SAURAV PAUL: Nothing to Disclose, Babu Lal Meena: Nothing to Disclose, VINOD ARORA: Nothing to Disclose, Akhil Deshmukh: Nothing to Disclose, Sherin Thomas: Nothing to Disclose, GURESH KUMAR: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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◆ 2284 | PROTON PUMP INHIBITOR TO PREVENT RECURRENT BLEEDING EPISODES AND MORTALITY AFTER ENDOSCOPIC VARICEAL LIGATION FOR ACUTE VARICEAL BLEEDING IN PATIENTS OF LIVER CIRRHOSIS: A RANDOMIZED CONTROLLED TRIAL

ABHISHEK YADAV[1] HARSHAL S MANDAVDHARE[1] VISHAL SHARMA[1] JIMIL SHAH[1] ATUL SAROCH[2] VANEET JEARTH[1] JAYANTA SAMANTA[1] ANUPAM SINGH[1] SAROJ SINHA[1], [1]Department of Gastroenterology, Postgraduate Institute of Medical Education & Research, Chandigarh, [2]Department of Internal Medicine, Postgraduate Institute of Medical Education & Research, Chandigarh

Background: Acute variceal bleeding is a life-threatening decompensating event in the natural history of cirrhosis. Endoscopic variceal ligation (EVL) along with non-selective beta blockers or carvedilol are current standard of care for patients with acute esophageal variceal bleeding. Use of proton pump inhibitors (PPI) in post EVL period is more of a personal choice as various society guidelines do not recommend continuation of PPI after EVL owing to low quality of evidence to support their use. **Methods:** We conducted a single centre, outcome assessor blinded prospective randomized controlled trial where patients of liver cirrhosis with acute variceal bleeding were enrolled and those who underwent EVL were randomized into PPI or No-PPI group after EVL. Patients in the PPI group received Tab Esomeprazole 40 mg once a day in addition to the standard of care for all patients. Both groups were followed up at 2 weeks post index EVL to assess occurrence of rebleeding and a repeat upper gastrointestinal endoscopy (UGIE) was done to document presence or absence of post EVL ulcers, their number and size. All patients were again followed up at 3 months to assess development of recurrent bleeding, mortality and adverse effects like pain and dysphagia post EVL. Primary outcome was to compare the rate of recurrent bleeding between the 2 groups. Secondary outcomes were to assess the difference in mortality, number and size of post EVL ulcers and adverse effects in the form of pain and dysphagia post EVL **Results:** A total of 246 patients were screened between June 2023 to April 2024 and after exclusion, 147 patients were randomized to both the groups. Baseline parameters were comparable between both the groups. In the primary outcome, recurrent bleeding was significantly more in the no PPI group [23 (31.94%) vs 7 (10.45%), p-0.002]. Among the secondary outcomes, incidence of mortality was higher in the no-PPI group [15 (20.83%) vs 11 (16.42%), p-0.505]. All the deaths in the no-PPI group were related to rebleeding episode [15 (100%) vs 3 (27.27%), $p = 0.00011$]. Incidence of post EVL ulcers was significantly more in the no- PPI group [58 (89.23%) vs 21 (34.43%) respectively; $p < 0.001$]. Median post EVL ulcer number and size were also significantly higher in the no-PPI group [1 (IQR 1,2) vs 0 (IQR 0,1) ($p = < 0.001$); 6 mm (IQR 5,8) vs 5 mm (IQR 5,5.5) ($p = 0.001$) respectively]. At 2 weeks, chest pain was reported by 5 (7.69%) patients in no PPI group vs 1 (1.63%) patient in PPI group ($p = 0.11$). No patient reported dysphagia at 2 weeks. No patient reported chest pain or dysphagia at 3 months. **Conclusion:** Prescription of PPI after EVL in patients of liver cirrhosis with acute esophageal variceal bleeding is beneficial as it significantly decreases the recurrent bleeding episodes as well as mortality in such patients.

Disclosures: ABHISHEK YADAV: Nothing to Disclose, HARSHAL S MANDAVDHARE: Nothing to Disclose, VISHAL SHARMA: Nothing to Disclose, JIMIL SHAH: Nothing to Disclose, ATUL SAROCH: Nothing to Disclose, VANEET JEARTH: Nothing to Disclose, JAYANTA SAMANTA: Nothing to Disclose, ANUPAM SINGH: Nothing to Disclose, SAROJ SINHA: Nothing to Disclose

◆ 2285 | REVERSAL OF HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY DOES NOT IMPACT LIVER TRANSPLANT RATES

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Background: Liver transplant (LT) is the definitive treatment for hepatorenal syndrome-acute kidney injury (HRS-AKI). Reversal of HRS-AKI may lower Model for End-Stage Liver Disease (MELD) score, which could impact LT access. We examined if HRS-AKI reversal impacts LT rates. **Methods:** This study analyzed a pooled cohort of patients with HRS-AKI enrolled in the Phase III CONFIRM (NCT02770716), REVERSE (NCT01143246), and OT-0401 (NCT00089570) clinical trials of terlipressin vs placebo. Patients were excluded if they met any of the following criteria at baseline: serum creatinine (SCr) ≥ 5 mg/dL, acute-on-chronic liver failure grade 3, or MELD score ≥ 35. The analysis cohort reflected the FDA label-specific population for terlipressin who are most likely to derive benefit from treatment. Patients were compared by baseline SCr (< 3 mg/dL vs ≥ 3 mg/dL) and by HRS reversal. The main outcome of interest was LT within 90 days. Rates of LT were compared across SCr and HRS reversal groups using Fine and Gray competing risks

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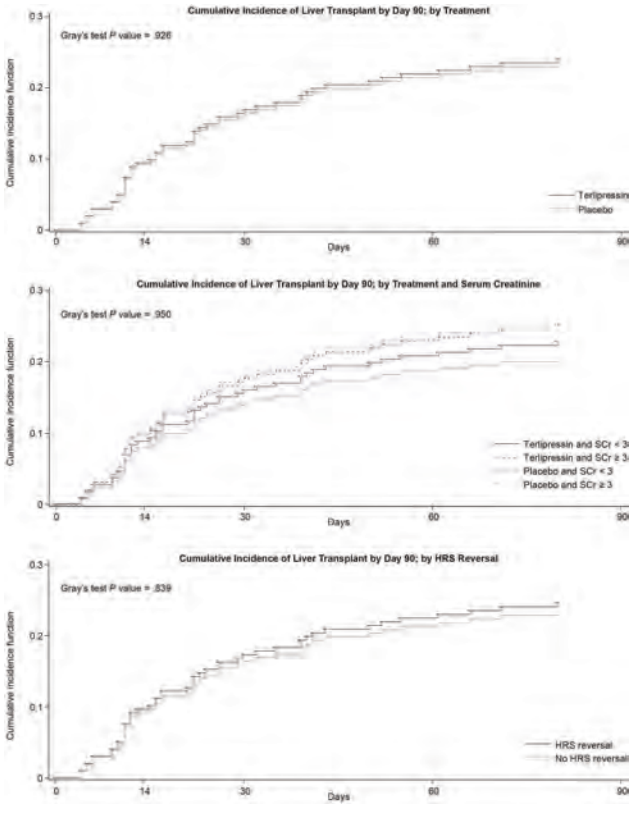
regression, with death during follow-up considered as a competing risk. Cumulative incidence functions were generated, and differences between groups were assessed using Gray's test. **Results:** Among 207 patients included (terlipressin, n = 136; placebo, n = 71), 45 were listed for LT at baseline. In total, the cumulative incidence of LT by Day 90 was 23.9% (95% confidence interval [CI] 18.0–31.7). There was no difference in cumulative incidence of LT by Day 90 between terlipressin (24.1% [95% CI 17.9–32.4]) and placebo (23.5% [95% CI 15.1–36.5]) groups overall ($P = .926$) or compared by SCr ($P = .950$; Figure). There was no difference in cumulative incidence of LT by Day 90 between patients who achieved HRS reversal (23.4% [95% CI 16.8–32.8]) and those who did not (24.7% [95% CI 16.6–36.6]) ($P = .839$; Figure). After adjusting for age, sex, and MELD score, there was no difference in cumulative incidence of LT by Day 90 between patients who achieved HRS reversal (24.2% [95% CI 17.1–31.3]) and those who did not (23.6% [95% CI 17.7–29.4]) ($P = .701$; adjusted subhazard ratio, 1.03 [95% CI 0.85–1.82; $P = .918$]); likewise, no difference was observed in the subgroup of patients listed for LT at baseline ($P = .341$). **Conclusion:** In this pooled analysis, terlipressin treatment and achieving HRS reversal were not associated with lower cumulative incidence of liver transplant at 90 days. These findings support the use of terlipressin in appropriate candidates without concern for compromising timely access to liver transplant.



Disclosures: Kavish Patidar: Madrigal Pharmaceuticals: Medical Advisory Board, Mallincrodt Pharmaceuticals: Consultant, Andrew Allegretti: Nothing to Disclose, Giuseppe Cullaro: Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant, Sumeet Asrani: Nothing to Disclose, Stevan Gonzalez: Mallinckrodt Pharmaceuticals: Speaking and Teaching, Mallinckrodt Pharmaceuticals: Consultant, Sanaz Cardoza: Mallinckrodt: Full Time Employee, Richard Wu: mallinckrodt: Employee, Chandrashekhar Kubal: Nothing to Disclose, R. Todd Frederick: Mallinckrodt: Consultant, Salix: Grant/Research Support, Astra Zeneca: Grant/Research Support, River2Renal: Grant/Research Support, Ipsen: Consultant

◆ 2286 | THE ASSOCIATION BETWEEN ALBUMIN ADMINISTRATION AT OUTPATIENT PARACENTESIS AND INCIDENT AKI HOSPITALIZATION IN A LARGE VETERANS AFFAIRS COHORT

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

Background: Guidelines recommend albumin infusion after paracenteses where more than 5 liters of ascites are removed. This recommendation, however, is based on small randomized controlled trials limited to a few centers. The current study aimed to evaluate if albumin infusion after outpatient paracentesis in patients with cirrhosis is associated with change in risk of hospitalization with acute kidney injury (AKI) and to further identify patient subgroups in which this association may vary. **Methods:** This was a retrospective cohort study using data from the Veterans Health Administration comprising 128 centers. All outpatient paracenteses in patients with established cirrhosis were identified. Detailed patient-level and paracentesis-related data were obtained, including a natural language processing-based approach to ascertain volume removal, as well as albumin administration per prior methods. Mixed-effects logistic regression was performed to evaluate the adjusted association between (1) albumin administration and (2) incident AKI hospitalization, accounting for key *a priori* covariates; an interaction between albumin administration and baseline creatinine category was also evaluated. **Results:** The analytic cohort comprised of 56,941 patients, 97.1% of which were male, 72.3% were white, with the most common etiology of liver disease being alcoholic liver disease at 32.9% followed by MASLD at 22.8%. The median MELD-Na score was 16 (IQR 11-20). The distribution of volume removal across all paracenteses is shown in Figure Panel A; albumin was administered in 17.0% of paracenteses. In adjusted analysis for the first

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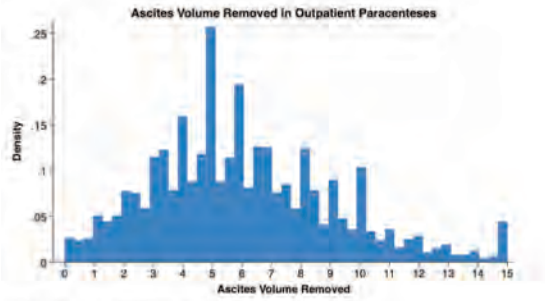
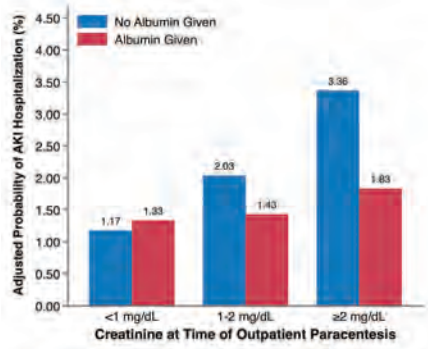
outcome, higher baseline creatinine (Cr) was associated with increased odds of albumin administration, for instance an OR 1.48 for Cr 1-2 (95% CI 1.35–1.62) and OR 3.10 for Cr >2 (95% CI 2.74–3.52) relative to Cr <1. In adjusted analysis for the second outcome, albumin administration was associated with reduced odds of AKI hospitalization (OR 0.67, 95% CI 0.55–0.82). A significant interaction between albumin administration and baseline Cr was identified such that albumin administration had a greater effect in reducing the probability of AKI hospitalization in patients with higher baseline creatinine ($p=0.01$) (Figure Panel B). **Conclusion:** Albumin administration after outpatient paracentesis was found to reduce the probability of hospitalization with AKI; this effect intensified in patients with higher creatinine at time of paracentesis.

Figure 1a – Distribution of Volume Removal in All Outpatient Paracenteses*



* Note that "15" corresponds to "15+"

Figure 1b – Interaction between Albumin Administration and Creatinine at Time of Paracentesis on AKI Hospitalization



* Interaction p=0.01 from mixed-effects model

Disclosures: Max Schechter: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Eurofins: Grant/Research Support, Siqi Zhang: Nothing to Disclose, David Kaplan: AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Sirtex: Advisor, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research Support, Nadim Mahmud: Grifols: Grant/Research Support

◆ 2287 | A MACHINE LEARNING APPROACH TO NON-INVASIVELY PREDICT HEPATIC DECOMPENSATION IN ADVANCED CHRONIC LIVER DISEASE

Georg Kramer[1] Anders Hildeman[2] Caterina Tozzi[2] Roza Maghshood[2] Vinusha Kalatharan[3] Hyewon Nina Koo[2] Kinga Jastrzębska[2] Nils Svangård[2] Claire Donoghue[2] Benedikt Simbrunner[1] Mattias Mandorfer[1] Benedikt Hofer[1] Thomas Reiberger[1] Jan Oscarsson[2] Philip Ambery[2], [1]Medical University of Vienna, [2]AstraZeneca, [3]Astra Zeneva

Background: Clinically significant portal hypertension (CSPH, i.e. hepatic venous pressure gradient [HVPG] ≥ 10 mmHg) indicates compensated advanced chronic liver disease (cACLD) at risk of decompensation. Invasive HVPG measurement is the gold standard for CSPH assessment, needing non-invasive alternatives. We developed and validated the Cirrhosis Risk Identifier (CIRI) model – a machine-learning tool trained to predict first decompensation using 11 general demographic and routine laboratory parameters. CIRI's performance was benchmarked with HVPG and liver stiffness measurement (LSM) in an external validation cohort. **Methods:** cACLD patients were included from the U.S. Optum's de-identified Clinformatics® Data Mart Database (Optum® CDM) cohort and an external validation cohort, prospectively recruited in the VICIS study (Vienna, Austria). Event of interest was first hepatic decompensation (ascites, overt hepatic encephalopathy, variceal bleeding) with HCC and death as competing events. The cACLD and decompensating event diagnoses in the Optum® CDM cohort were identified using ICD 9/10 codes. **Results:** In the Optum® CDM collective, we trained CIRI on 25,531 patients and validated it in an independent set of 18,852. The leading etiology in the Optum® CDM validation cohort was metabolic dysfunction-associated steatotic liver disease (MASLD) (34%), with a median MELD of 8 (IQR 6-11), and a median follow-up of 47 (IQR 18-102) months. The VICIS cohort included 216 patients with predominantly viral hepatitis (25%) and alcohol-related liver disease (22%), with a median MELD of 9 (IQR 8-12) and median follow-up of 70 (IQR 54-88) months. The CIRI model showed high time-dependent AUROCs for predicting decompensation at 1 and 2 years (Optum® CDM: 0.821, 0.819; VICIS: 0.846, 0.803), comparable to HVPG (0.837, $p=0.993$; 0.817, $p=0.955$) and outperforming LSM ($p=0.002$; $p=0.006$) in the VICIS cohort. In Fine-Gray competing risk regression analysis adjusted for non-selective beta-blocker intake, CIRI was independently linked to a higher decompensation risk (Optum® CDM: adjusted subdistribution hazard ratio [aSHR]: 1.67, $p<0.001$; VICIS: 2.25, $p<0.001$). **Conclusion:** The machine-

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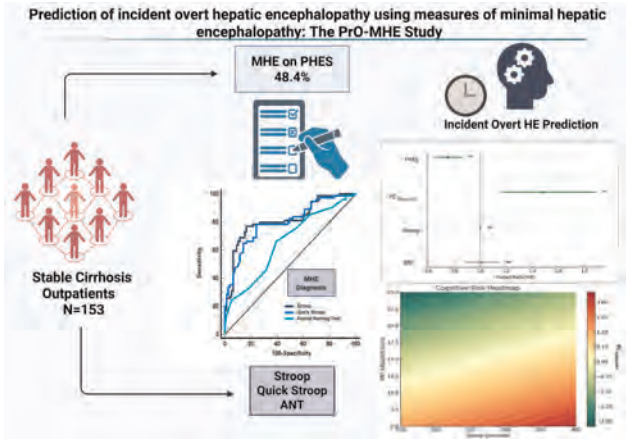
learning-based CIRI model showed robust prognostic performance and effective risk stratification in cACLD patients. Its predictive accuracy was confirmed in both a large U.S. and a European validation cohort, where CIRI's discrimination of decompensation risk was comparable to that of HVPG, thus highlighting its potential future utility as a non-invasive tool to identify "at-risk" cACLD patients.

Disclosures: Georg Kramer: Nothing to Disclose, Anders Hildeman: AstraZeneca: Employee, Caterina Tozzi: Nothing to Disclose, Roza Maghshood: Nothing to Disclose, Vinusha Kalatharan: Nothing to Disclose, Hyewon Nina Koo: AstraZeneca: Employee, Kinga Jastrzębska: AstraZeneca: Employee, Nils Svangård: Nothing to Disclose, Claire Donoghue: Nothing to Disclose, Benedikt Simbrunner: Nothing to Disclose, Mattias Mandorfer: Echosens: Speaking and Teaching, Echosens: Grant/Research Support, Ipsen: Consultant, Takeda: Consultant, Takeda: Speaking and Teaching, W.L. Gore & Associates: Speaking and Teaching, Eli Lilly: Consultant, Eli Lilly: Speaking and Teaching, Benedikt Hofer: IPSEN: Travel support, FALK: Travel support, Thomas Reiberger: Nothing to Disclose, Jan Oscarsson: Nothing to Disclose, Philip Ambery: AstraZeneca: Employee

◆ 2288 | PREDICTION OF INCIDENT OVERT HEPATIC ENCEPHALOPATHY USING MEASURES OF MINIMAL HEPATIC ENCEPHALOPATHY: THE PRO-MHE STUDY

Akash Roy[1] Uttkarsh Bhattad[2] Awanish Tewari[1] Nikhil Sonthalia[1] Shardhya Chakroborty[1] Nipun Verma[3] Anand Kulkarni[4] Madhumita Premkumar[3] Uday Ghoshal[1] Rajender Reddy[5] Mahesh Goenka[1], [1]Apollo Hospitals, [2]Apollo Hospitals,Kolkata, [3]PGIMER, Chandigarh, [4]AIG, Hospitals, [5]University of Pensylvania

Background: Psychometric hepatic encephalopathy score (PHES) is the gold standard for diagnosing minimal hepatic encephalopathy (MHE) and may predict incident overt hepatic encephalopathy (OHE). However, it is cumbersome, thus mandating increased use of simpler tests, such as EncephalApp (Stroop), QuickStroop, and Animal Naming Test (ANT). While these tests are good surrogates for MHE, their role in predicting OHE remains unclear. We aimed to ascertain the predictive performance of MHE scores for incident OHE. **Methods:** Stable outpatients without baseline or recent ($\leq$3 months) OHE were prospectively recruited to undergo PHES, Stroop, Quickstroop, and ANT. For MHE diagnosis at baseline, area under the receiver operating curves (AUROC) were generated using PHES as the gold standard ($\leq$-5 cut-off as prior validated local norm). Patients were followed up for at least six months to assess incident OHE as the primary outcome, and predictors were analyzed using Cox proportional hazards regression. To reduce dimensionality and avoid overlap among cognitive metrics, an exploratory principal component analysis (PCA) was conducted using Stroop and ANT to generate a composite measure of cognitive dysfunction ($PC_{Stroop-ANT}$) and assessed for OHE prediction. **Results:** 153patients [54(46-61) years), females 21%, MELD,10 (9-12), prior OHE 11.1%, CTP A/B 46.4%/48.4%) were enrolled. At baseline, 74(48.4%) had MHE by PHES. Stroop, Quickstroop, and ANT had an AUROC of 0.81 (0.74-0.87), 0.79 (0.72-0.85), and 0.65 (0.57-0.73), respectively, for MHE. Twenty-nine (19%) developed OHE on follow-up. On univariable Cox regression, Stroop [(HR, 1.03, (1.01-1.05), $p = < 0.01$] and PHES [0.74(0.65-0.85), $p = < 0.01$] but not ANT [0.89(0.77-1.01, $p = 0.08$)] predicted OHE. On multivariable analysis adjusted for MELD, only PHES was independently predictive of OHE (aHR,0.76(0.66-0.890)[Stroop, 1.00 (0.99-1.00), ANT,1.01(0.89-1.2)]. Only PHES was associated with all-cause non-elective hospitalization [0.84 (0.76-0.92), $p < 0.01$]. The composite cognitive score ($PC_{Stroop-ANT}$) was significantly associated with incident OHE (aHR: 1.48; 95% CI: 1.17–1.89; $p = 0.001$), and was only marginally inferior to PHES alone (Model Information criteria Akaike/Bayesian: PHES,267.7/273.8, $PC_{Stroop-ANT}$278.9/285). **Conclusion:** Among the various MHE tests, PHES most strongly predicts incident OHE. While individually simpler tests of Stroop, Quickstroop, and ANT are not as predictive, an exploratory composite measure, $PC_{Stroop-ANT,}$ closely approximates prediction by PHES.



Disclosures: Akash Roy: Nothing to Disclose, Uttkarsh Bhattad: Nothing to Disclose, Awanish Tewari: Nothing to Disclose, Nikhil Sonthalia: Nothing to Disclose, Shardhya Chakroborty: Nothing to Disclose, Nipun

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Verma: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, Uday Ghoshal: Nothing to Disclose, Rajender Reddy: Nothing to Disclose, Mahesh Goenka: Nothing to Disclose

◆ 2289 | EFFICACY AND SAFETY OF LOW-DOSE VERSUS CONVENTIONAL DOSE ALBUMIN FOR PREVENTION OF ACUTE KIDNEY INJURY IN CIRRHOSIS AND HIGH-RISK SPONTANEOUS BACTERIAL PERITONITIS: A RANDOMIZED CONTROLLED TRIAL

SAURAV PAUL[1] Manoj Kumar Sharma[2] Rakhi Maiwall[2] Shiv Kumar Sarin[2] Priyanka Saha[3] Babu Lal Meena[4] Omkar Rudra[4], [1]Institute of Liver and Bilary Sciences, Delhi, India, [2]Institute of Liver and Biliary Sciences, Delhi, India, [3]All India Institute of Medical Sciences, Delhi, India, [4]Insititute of Liver and Biliary Sciences, Delhi, India

Background: Patients with cirrhosis and high-risk spontaneous bacterial peritonitis (SBP) are prone to acute kidney injury (AKI), and albumin infusion can reduce this risk. However, conventional dosing often leads to infusion-related complications such as circulatory overload, and evidence for lower or individualized dosing is limited. This study evaluated the efficacy and safety of low-dose versus conventional-dose albumin for preventing new-onset or progressive AKI in this high-risk population. **Methods:** This randomized, open-label, non-inferiority trial at a tertiary center in northern India enrolled adults with cirrhosis and high-risk SBP (bilirubin >4 mg/dL and/or creatinine >1 mg/dL). Patients were randomized to receive either conventional (1.5 g/kg on day 1; 1.0 g/kg on day 3) or low-dose albumin (1.0 g/kg on day 1; 0.5 g/kg on day 3), infused as 20% solution over 18–24 hours. Analyses followed the intention-to-treat principle. The primary outcome was AKI onset or progression by day 4; secondary outcomes included SBP resolution, circulatory overload, biomarker changes, and mortality at days 7, 28, and 90. **Results:** Of the 263 patients screened for spontaneous bacterial peritonitis (SBP), 168 met the inclusion criteria and were randomized to receive either conventional-dose albumin (Group I, $n=83$) or low-dose albumin (Group II, $n=85$). Median ages were similar between groups (49 years [IQR: 43–58] vs. 50 years [IQR: 43–56]; $p=0.21$). The predominant causes of cirrhosis were alcohol-related liver disease (Group I: 47%; Group II: 51.8%) and non-alcoholic steatohepatitis (Group I: 39.8%; Group II: 34.1%). Most patients were Child-Pugh Class C (Group I: 73.5%; Group II: 70.6%; $p=0.78$), with comparable median MELD scores (24 [IQR: 22–29] vs. 24 [IQR: 20–28]; $p=0.21$). Circulatory overload occurred significantly more often in the conventional-dose group on both day 1 (81.9% vs. 31.8%) and day 3 (86.7% vs. 5.9%; $p<0.001$). Among patients without baseline AKI, new-onset AKI rates were similar (16.1% vs. 22.2%; $p=0.786$). However, among those with baseline AKI, progression occurred in 26.9% of Group I compared to 6.8% of Group II ($p=0.011$), favoring the low-dose group. Mortality and SBP resolution rates did not differ significantly between groups. **Conclusion:** This study demonstrated that low-dose albumin was non-inferior to conventional-dose albumin for new onset or progression of AKI among high-risk patients with SBP, while resulting in significantly reduced infusion-related complications. These findings suggest for adopting individualized, tolerance-guided albumin dosing strategies in the management of cirrhosis patients with high risk SBP. Clinical trial: gov (identifier: NCT06026267) Keywords: Spontaneous bacterial peritonitis, Acute kidney injury, Low dose albumin, Conventional dose albumin, Randomized controlled trial

Disclosures: SAURAV PAUL: Nothing to Disclose, Manoj Kumar Sharma: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Priyanka Saha: Nothing to Disclose, Babu Lal Meena: Nothing to Disclose, Omkar Rudra: Nothing to Disclose

◆ 2290 | IMPACT OF CIRRHOTIC CARDIOMYOPATHY AND CARDIOMETABOLIC RISK ON HEPATIC DECOMPENSATION AND SURVIVAL IN PATIENTS WITH CIRRHOSIS

Madhumita Premkumar[1] Kamal Kajal[2] Manhal Izzy[3] Prerna Sharma[2] Anchal Sandhu[2] Bhupendra Sihag[2] Ajay Bahl[2] Ankur Gupta[2] Jasvinder Nain[2] Ajay Duseja[1] Anand Kulkarni[4] Ashwani Sood[2] Arka De[2] K Rajender Reddy[5], [1]Postgraduate Institute of Medical Education & Research, [2]PGIMER, [3]Vanderbilt University Medical Center, [4]Asian Institute of Gastroenterology, [5]University of Pennsylvania

Background: Left ventricular diastolic dysfunction (LVDD) and Cirrhotic cardiomyopathy (CCM) are under-recognized, while not uncommon, in patients with advanced liver disease. Herein, we aimed to assess, in those with cardiometabolic risk factors,

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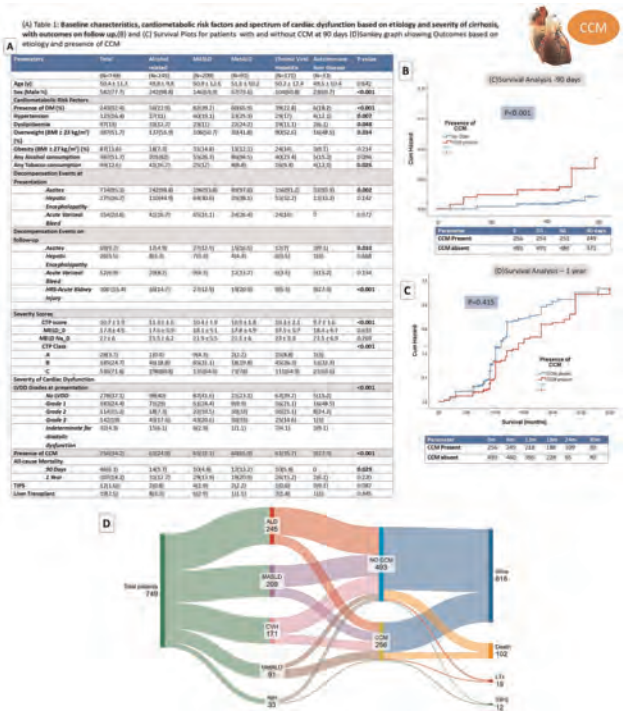
changes in cardiac function, hepatic decompensation events, and survival based on the etiology of cirrhosis. **Methods:** Prospective patients with cirrhosis of any etiology between January 2020 and January 2025 presenting to the outpatient liver clinic were screened with transthoracic echocardiography (TTE). speckle tracking, and tissue Doppler imaging for presence of LVDD as per 2020 CCM consortium criteria; ischemic heart disease, porto-pulmonary hypertension, valvular heart disease, anemia, and hepatocellular carcinoma were exclusions. Assessments were done every 6m; clinical and survival data, TTE and cardiac imaging, and biomarkers (NT-proBNP, aldosterone, norepinephrine) were collected. **Results:** Of 749 patients with cirrhosis enrolled (77.7%men, 50.4 ± 11.4y, with mean MELD-Na 20.7 ± 5.6), 32.4% with DM-2, 16.4% with hypertension, 9.% obese, with etiology being 245(32.7%), 209(27.9%), 91(12.1%), (171,22.8%), and (33,4.4%) due to alcohol-associated disease(ALD), metabolic-dysfunction associated steatotic liver disease(MASLD), Met-ALD, chronic viral hepatitis and autoimmune etiology respectively. Of them, 255(34%) met criteria for CCM (grades II-III LVDD), with increased prevalence in patients with MASLD (31%) and MetALD (65%). Overall, 270(36%), 184(24.6%), 121(16.2%), 142(19%) had no LVDD, or grades I, II,III LVDD, respectively, with 32(4.3%) being indeterminate for diastolic function. In patients with CCM, liver decompensation events were more frequent, with recurrence of ascites (18% vs 4.7%), hepatic encephalopathy (7.4% vs 1.4%,), HRS-AKI (28.9% vs 5.3) and variceal bleeding (13.3% vs 3.7%, $P < 0.001$) (Figure 1) The overall mortality at 90-days (13.3% vs 2.4%, $p < 0.001$) and 1 year(18%vs 12.4%, $P = 0.047$) was higher in patients with CCM, On multivariable regression for competing risks of deaths vs TIPS/transplantation, CCM (SHR1.3, 95%CI-1.2-1.7,$P = 0.034$), and MELDNa (SHR 1.14, 95%1.04-1.2,$P < 0.001$) predicted mortality at 1 year, independent of age, gender, diabetes, and disease etiology. (A) Table 1: Baseline characteristics, cardiometabolic risk factors and spectrum of cardiac dysfunction based on etiology and severity of cirrhosis, with outcomes on follow up.(B) and (C) Survival Plots for patients with and without CCM at 90 days /1 year (D) Sankey plot-outcomes **Conclusion:** Consistent with prior reports from the United States and EU, CCM is prevalent in approximately 1/3 rd of patients with advanced liver disease from the Indian subcontinent and is associated with increased risk of hepatic decompensation and 1 year mortality independent of age, gender, DM-2 and etiology of liver disease. Recognition of CCM may help in modifying care.



Disclosures: Madhumita Premkumar: Nothing to Disclose, Kamal Kajal: Nothing to Disclose, Manhal Izzy: Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Prerna Sharma: Nothing to Disclose, Anchal Sandhu: Nothing to Disclose, Bhupendra Sihag: Nothing to Disclose, Ajay Bahl: Nothing to Disclose, Ankur Gupta: Nothing to Disclose, Jasvinder Nain: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Ashwani Sood: Nothing to Disclose, Arka De: Nothing to Disclose, K Rajender Reddy: Nothing to Disclose

◆ 2291 | REDUCED RISK OF HEPATIC DECOMPENSATION AND OVERALL MORTALITY IN PATIENTS WITH COMPENSATED CIRRHOSIS AND STATIN THERAPY: A PROPENSITY SCORE-MATCHED ANALYSIS OF A POPULATION BASED COHORT OF 14,034 ADULTS

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Background: Statin use is often avoided in cirrhosis due to hepatotoxicity concerns. However, emerging data suggests a potential clinical benefit of statins in compensated cirrhosis. The aim of this study was to assess the impact of statin therapy on risk of hepatic decompensation, hepatocellular carcinoma (HCC) and overall mortality in a large population-based cohort. **Methods:** Using a large, federated electronic health based (EHR) database (TriNetX), we identified patients with compensated cirrhosis using ICD-10 codes. Statin users were defined as individuals taking statins at any dose for at least 1 year. Statin users were propensity score-matched 1:1 using demographics, labs, BMI, alcohol use, medical comorbidities, cirrhosis etiology, beta-blocker, opioid, and benzodiazepine use. Outcomes assessed at 1 and 4 years included composite hepatic decompensation [ascites, variceal bleeding, hepatic encephalopathy (HE), hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP) or hepatocellular carcinoma (HCC)]. Secondary outcomes included individual decompensation outcomes and overall mortality. **Results:** After matching, 14,034 patients were included in each group for 1-year outcomes, and 13,853 for 4-year outcomes. Statin use was associated with significantly lower 1-year rates of composite hepatic decompensation (6.4% vs. 9.8%; OR: 0.64; 95% CI: 0.58–0.70; $p < 0.0001$) and overall mortality (4.5% vs. 8.5%; OR: 0.51; 95% CI: 0.46–0.57; $p < 0.0001$) (Table 1a). At 4 years, the statin group continued to show reduced risk of composite hepatic decompensation (10.8% vs. 14.8%; OR: 0.70; 95% CI: 0.65–0.75; $p < 0.0001$) and overall mortality (14.6% vs. 20.8%; OR: 0.65; 95% CI: 0.61–0.69; $p < 0.0001$) (Table 1b). Statin use was particularly associated with reduced rates of ascites and portal hypertension, though not with reduced risk of HCC. **Conclusion:** In a large population-based propensity score-matched cohort of patients with compensated cirrhosis, statin therapy was associated with significantly lower rates of hepatic decompensation and overall mortality at 1 and 4 years of follow-up. These data suggest potential preventative benefit of statin therapy in adults with compensated cirrhosis that should be further assessed in future randomized clinical trials.

Table 1a. Outcome over one year

Outcome	Statin Group (n=14,034)	Control Group (n=14,034)	Odds Ratio (95% CI)	p-value
Hepatic Decompensation	911 (6.4%)	1,379 (9.8%)	0.63 (0.58–0.69)	**<0.0001**
Esophageal Varices with Bleeding	82 (0.5%)	96 (0.6%)	0.85 (0.63–1.14)	0.29
Hepatorenal Syndrome	16 (0.1%)	22 (0.1%)	0.72 (0.38–1.38)	0.33
Ascites	800 (5.7%)	1,2 (9.0%)	0.60 (0.55–0.66)	**<0.0001**
Portal Hypertension	689 (4.9%)	801 (5.7%)	0.85 (0.76–0.94)	**0.002**
Hepatic Encephalopathy	70 (0.4%)	60 (0.4%)	1.16 (0.82–1.65)	0.37
Spontaneous Bacterial Peritonitis	≤10 (0.07%)	17 (0.1%)	0.58 (0.26–1.28)	0.17
Hepatocellular Carcinoma	83 (0.5%)	88 (0.6%)	0.94 (0.69–1.27)	0.70
Overall Mortality	640 (4.5%)	1,198 (8.5%)	0.51 (0.46-0.56)	**<0.0001**

Table 1b. Outcome over 4 years

Outcome	Statin Group (n=13,853)	Control Group (n=13,853)	Odds Ratio (95% CI)	p-value
Hepatic Decompensation	1,500 (10.8%)	2,051 (14.8%)	0.69 (0.65–0.75)	**<0.0001**
Esophageal Varices with Bleeding	172 (1.2%)	204 (1.4%)	0.84 (0.68–1.03)	0.09
Hepatorenal Syndrome	31 (0.2%)	52 (0.3%)	0.59 (0.38–0.92)	**0.02**
Ascites	1,298 (9.3%)	1,842 (13.2%)	0.67 (0.62–0.72)	**<0.0001**
Portal Hypertension	1,389 (10.0%)	1,545 (11.1%)	0.88 (0.82–0.95)	**0.002**
Hepatic Encephalopathy	160 (1.1%)	165 (1.1%)	0.96 (0.77–1.20)	0.78
Spontaneous Bacterial Peritonitis	≤10 (0.07%)	43 (0.3%)	0.23 (0.11–0.46)	**<0.0001**
Hepatocellular Carcinoma	195 (1.4%)	193 (1.3%)	1.01 (0.82–1.23)	0.91
Overall Mortality	2,027 (14.6%)	2,894 (20.8%)	0.64 (0.61–0.69)	**<0.0001**

Disclosures: Monica Tincopa: Nothing to Disclose, Abdallah Hussein: Nothing to Disclose, Bisher Sawaf: Nothing to Disclose, Yusuf Hallak: Nothing to Disclose, Sana Rabeeah: Nothing to Disclose, Mohammed Abu-Ramaileh: Nothing to Disclose

◆ 2292 | PREHABILITATION IMPROVES PHYSICAL FITNESS METRICS PRIOR TO LIVER TRANSPLANTATION AND EXPANDS THE POOL OF TRANSPLANT-ELIGIBLE PATIENTS

Louis Guzman[1] Susanna Miranda[2] Joshua Sepic[3] Brittany Zelikoff[2] Daniela Ladner[4] Daniel Borja-Cacho[4] Satish Nadig[4] Richard Lieber[3] James Sliwa[3] Andres Duarte-Rojo[2], [1]Norhwestern University, [2]Northwestern Medicine, [3]Shirley Ryan Ability Lab, [4]Northwestern

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Background: Poor physical fitness (PhysFit), including frailty/sarcopenia, is highly prevalent in advanced chronic liver disease (AdvCLD) and significantly increases morbidity and mortality in liver transplant (LT) waitlisted candidates. Prehabilitation, the optimization of a candidate's physiologic reserve through a lifestyle intervention prior to surgery, improves PhysFit in LT candidates. In May/2024, Northwestern's Comprehensive Transplant Center opened a Prehabilitation Clinic for patients undergoing evaluation or waitlisted for LT. Herein, we present our first-year experience, highlighting clinical outcomes and improvements in PhysFit metrics among LT candidates. **Methods:** Frailty was assessed with the liver frailty index (LFI) and cardiorespiratory fitness with the 6-minute walk test (6MWT). At each visit, all patients were seen by a nurse practitioner, a dietician, two exercise professionals, and one hepatologist. An individualized exercise and dietary prescription was provided, and adherence monitored through phone calls and clinic visits every 2-6 weeks. Paired t-test was used for comparisons. **Results:** A total of 43 patients (age 63 $\pm$ 7, male 63%) were referred for frailty during a 1-year period, and 38 attended the clinic (70% during evaluation phase) for a median of 2 visits (32% attended $\geq$3 visits). Most patients had steatotic liver disease (35% ALD, 19% MASLD, 16% MetALD), and all were decompensated (ascites 94%, encephalopathy 72%) with a MELDNa of 17 $\pm$ 7; falls were reported by 36%. A total of 17 patients underwent LT: 6 newly waitlisted and 10 reactivated, following improvement of their PhysFit metrics; 1 inpatient who could not attend the clinic also underwent LT. Seven patients died (6 pre-LT, 1 post-LT) and none of them engaged with the program or showed adherence with recommendations. There were no differences in LFI at baseline between patients who were alive (4.98 $\pm$ 0.57) or deceased (5.01 $\pm$ 0.55) at the end of follow-up. Improvement in PhysFit metrics during prehabilitation is shown in *Table*. **Conclusion:** We successfully optimized 16 frail patients with AdvCLD who were initially deemed ineligible for LT, enabling them to meet listing criteria. Transplant approval was contingent upon sustained engagement in prehabilitation, observed physical resilience, and clinically meaningful improvement in objective physical fitness measures—defined as a $\geq$0.4-point reduction in LFI or an increase of $\geq$30 meters in 6MWT. While implementing LT prehabilitation is challenging, LFI and 6MWT trajectories offer actionable guidance for exercise and dietary interventions. While our findings are encouraging, they underscore the need for validation through a randomized controlled trial.

All (n=24)	Baseline	Second Visit	Difference	p-value
LFI	4.95 ± 0.62	4.79 ± 0.68	0.15	0.33
6MWT (m)	222 ± 72	230 ± 78	-7	0.58
Transplant (n=11)	**Baseline**	**Second Visit**	**Difference**	**p-value**
LFI	4.90 ± 0.57	4.45 ± 0.17	0.45	0.03
6MWT (m)	248 ± 57	283 ± 70	-35	0.03

Disclosures: Louis Guzman: Nothing to Disclose, Susanna Miranda: Nothing to Disclose, Joshua Sepic: Nothing to Disclose, Brittany Zelikoff: Nothing to Disclose, Daniela Ladner: Nothing to Disclose, Daniel Borja-Cacho: Nothing to Disclose, Satish Nadig: Pandorum Technologies: Consultant, Richard Lieber: Nothing to Disclose, James Sliwa: Nothing to Disclose, Andres Duarte-Rojo: Echosens: Grant/Research Support

◆ 2293 | ALLOPURINOL USE IS ASSOCIATED WITH DECREASED INCIDENCE OF HEPATIC DECOMPENSATION AND OVERALL MORTALITY AMONG ADULTS WITH COMPENSATED CIRRHOSIS: A POPULATION-BASED PROPENSITY-MATCHED COHORT STUDY OF 10,716 INDIVIDUALS

Monica Tincopa[1] Bisher Sawaf[2] Mohammad Al Hayek[3] Yusuf Hallak[4] Shahem Abbarh[5] Mohammed Beshr[6] Mohammed Elhadi[7] Mohammed Abu-Rumaileh[4], [1]University of California, San Diego, [2]Univeristy of Toledo, [3]Damascus University, [4]University of Toledo, [5]MedStar, [6]Sana'a University, [7]Korea University

Background: Recent studies highlight the potential role of allopurinol in reducing incident hepatic decompensation in compensated cirrhosis given its anti-inflammatory and anti-oxidant properties. The aim of this study was to evaluate the association of allopurinol use with incidence of hepatic decompensation and overall mortality in patients with compensated cirrhosis in a large, population-based propensity-matched cohort. **Methods:** Using a large electronic health-based database (TriNetX), we identified patients with compensated cirrhosis using ICD-10 codes. Allopurinol use was defined as having received allopurinol during $\geq$ five visits or hospital stays before follow-up and on or after cirrhosis diagnosis. Allopurinol use was assessed at: any dose, 100 mg and 300 mg. 1:1 propensity-score matching was done using demographics, labs, BMI, alcohol use, medical comorbidities, cirrhosis etiology, beta-blocker, opioid, benzodiazepine and statin use. The primary outcome was the incidence of composite hepatic decompensation [ascites, variceal bleeding, hepatic encephalopathy (HE), hepatorenal syndrome (HRS) or spontaneous bacterial peritonitis (SBP)]. Secondary outcomes included individual decompensation outcomes, hepatocellular carcinoma (HCC), and overall mortality. Outcomes were assessed at 6, 12, and 18 months. **Results:** After propensity-score matching, each group in the any dose exposure included 5358 patients, 2124 in each group for 100 mg, and 1020 in each group for 300 mg. At 18 months, statistically significantly lower incidence of hepatic decompensation was seen in the overall allopurinol

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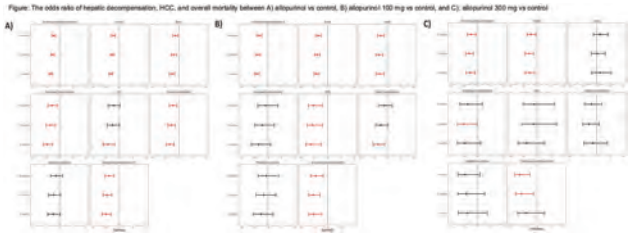
exposure cohort (OR: 0.77; 95% CI: 0.70-0.84), the 100 mg cohort (OR: 0.66; 95% CI: 0.57 to 0.76), and 300 mg cohort (OR: 0.76, 95% CI: 0.62 to 0.94). Allopurinol exposure was associated with a decreased incidence of esophageal variceal bleeding (OR: 0.71 95% CI: 0.55 to 0.92), ascites (OR: 0.77 95% CI: 0.69 to 0.84), HE (OR: 0.76 95% CI: 0.63 to 0.92), SBP (OR: 0.61 95% CI: 0.46 to 0.80), and overall mortality (OR: 0.86 95%% CI: 0.77 to 0.96) compared to the control group (Figure). **Conclusion:** In a propensity-score matched analysis of a large national database, individuals with compensated cirrhosis and allopurinol use had significantly lower risk of hepatic decompensation and overall mortality. These findings suggest that allopurinol may play a potential role in managing cirrhosis. Future randomized clinical trials are needed to confirm these findings.



Disclosures: Monica Tincopa: Nothing to Disclose, Bisher Sawaf: Nothing to Disclose, Mohammad Al Hayek: Nothing to Disclose, Yusuf Hallak: Nothing to Disclose, Shahem Abbarh: Nothing to Disclose, Mohammed Beshr: Nothing to Disclose, Mohammed Elhadi: Nothing to Disclose, Mohammed Abu-Rumaileh: Nothing to Disclose

◆ 2294 | RIFAXIMIN MONOTHERAPY REDUCES THE RISK OF NEW-ONSET HEPATIC ENCEPHALOPATHY AND MORTALITY COMPARED TO LACTULOSE MONOTHERAPY IN COMPENSATED CIRRHOSIS: A REAL-WORLD PROPENSITY-MATCHED STUDY

Himsikhar Khataniar[1] Renuka Verma[2] Kaitlyn Gernhard[1] Daniel Huynh[3] Leandro Sierra[4] Nabeeha Mohy-ud-din[1] Nikki Duong[5], [1]Allegheny General Hospital, [2]UNLV, [3]University of Washington, [4]Cleveland Clinic Foundation, [5]Stanford University

Background: Lactulose is the first-line therapy for hepatic encephalopathy (HE), but its real-world efficacy is often limited by the side effect profile (flatulence, nausea, diarrhea). Although rifaximin has shown benefit as an adjunct, less is known regarding its efficacy to prevent new-onset HE as monotherapy. Post hoc analyses from trials suggest rifaximin may be a superior alternative in decompensated patients, but real-world comparative data in patients with compensated cirrhosis are lacking. **Methods:** This is a retrospective cohort study using the TriNetX US Collaborative Network. Adult patients aged 18–90 years with cirrhosis and preserved hepatic function (defined by MELD surrogate labs: INR <1.5, bilirubin <1.9 mg/dL, creatinine <1.3 mg/dL, and albumin >3.5 g/dL) who initiated rifaximin or lactulose monotherapy between January 2010 and December 2023 were included. Individuals with any prior hepatic decompensation—including overt hepatic encephalopathy (OHE), ascites, or variceal bleeding—were excluded to specifically evaluate the incidence of new-onset OHE. Propensity score matching using 59 covariates generated two well-balanced cohorts ($N=1814$). Outcomes were assessed up to one year. Primary outcomes were new-onset HE and all-cause mortality. Secondary outcomes included major adverse liver events (MALO), progression to decompensated cirrhosis, all-cause hospitalization, hepatocellular carcinoma (HCC), and liver transplantation (LT). **Results:** At 1 year, new-onset OHE was lower with rifaximin (1.0% vs. 2.1%; HR 0.48, 95% CI 0.27–0.84; $p=0.009$; NNT 91). All-cause mortality was lower in the Rifaximin cohort (5.0% vs. 7.4%; HR 0.67, 95% CI 0.51–0.88; $p=0.003$). Rifaximin had lower rates of MALO (11.6% vs. 16.3%; HR 0.70, $p=0.002$), decompensations (6.9% vs. 8.8%; HR 0.78, $p=0.048$), and hospitalizations (6.1% vs. 10.0%; HR 0.62, $p=0.004$). No significant differences were seen in HCC (1.1% vs. 1.3%; HR 0.84; $p=0.59$) or LT (0.6% vs 0.6%; HR 1.26; $p=0.65$). **Conclusion:** In this large, multicenter real-world analysis of patients with compensated cirrhosis and no prior decompensation, rifaximin monotherapy reduced the risk of new-onset hepatic encephalopathy by almost 50% as well as all-cause mortality compared to lactulose. Additionally, rifaximin was associated with fewer liver-related complications and hospitalizations. These findings support a re-evaluation of rifaximin as potential first-line therapy for HE prevention due to the poor tolerability of lactulose, though costs and insurance approval may be limit widespread access.

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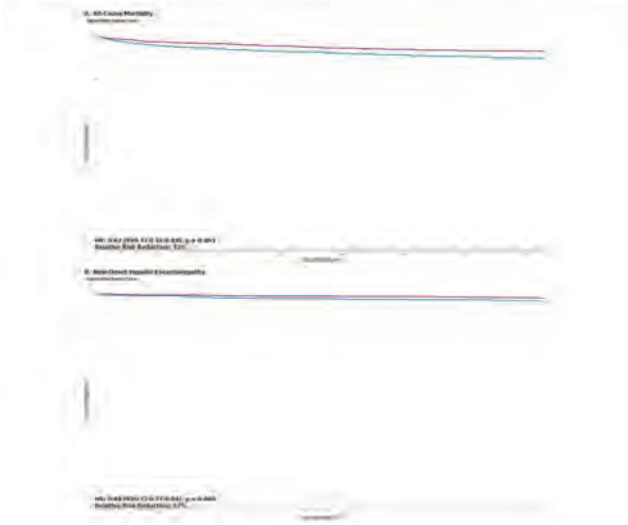
Table 1: Comparative Effectiveness of Rifaximin vs. Lactulose Monotherapy in Compensated Cirrhosis

Outcome	Rifaximin (n, %)	Lactulose (n, %)	HR (95% CI)	p-value
Hepatic Encephalopathy (HE)	18 / 1,723 (1.0%)	37 / 1,733 (2.1%)	0.48 (0.27–0.84)	**0.009**
All-Cause Mortality	91 / 1,807 (5.0%)	133 / 1,798 (7.4%)	0.67 (0.51–0.88)	**0.003**
MALO	121 / 1,044 (11.6%)	169 / 1,036 (16.3%)	0.70 (0.55–0.88)	**0.002**
Decompensated Cirrhosis	107 / 1,543 (6.9%)	136 / 1,539 (8.8%)	0.78 (0.60–1.00)	**0.048**
All-Cause Hospitalization	65 / 1,070 (6.1%)	87 / 866 (10.0%)	0.62 (0.45–0.86)	**0.004**
Hepatocellular Carcinoma (HCC)	19 / 1,748 (1.1%)	22 / 1,739 (1.3%)	0.84 (0.46–1.56)	0.59
Liver Transplantation (LT)	≤10 / 1,796 (0.6%)	≤10 / 1,795 (0.6%)	1.26 (0.47–3.37)	0.65

*≤ 10 indicates suppressed cell counts for privacy compliance by TriNetX database.
*Particular number of patients in Cohort 1 and Cohort 2 were excluded from each results because they had the outcome prior to the time window.

Figure 1: Kaplan–Meier Survival Estimates for All-Cause Mortality and New-Onset Hepatic Encephalopathy in Compensated Cirrhotic Patients Treated With Rifaximin vs. Lactulose



Disclosures: Himsikhar Khataniar: Nothing to Disclose, Renuka Verma: Nothing to Disclose, Kaitlyn Gernhard: Nothing to Disclose, Daniel Huynh: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Nabeeha Mohyud-din: Nothing to Disclose, Nikki Duong: Nothing to Disclose

◆ 2295 | LATENT CLASS ANALYSIS (LCA) IDENTIFIES DISTINCT ASCITES PHENOTYPES ASSOCIATED WITH CLINICAL OUTCOMES AND WITH IMPLICATIONS FOR TARGETED THERAPY IN PATIENTS WITH DECOMPENSATED CIRRHOSIS AND ASCITES

Giuseppe Cullaro[1] Andrew Allegretti[2] Kavish Patidar[3] Jennifer Lai[4] Elizabeth Verna[5], [1]Columbia University Irving Medical Center, [2]MGH, [3]Houston Methodist Hospital, [4]University of California San Francisco, [5]Columbia University Medical Center

Background: Ascites results from complex pathophysiologic mechanisms including portal hypertension, systemic vasodilation, and renal dysfunction. Traditional classifications—dependent on the degree or responsiveness to treatment—inadequately capture the heterogeneity of underlying mechanisms. We hypothesized that LCA could identify distinct phenotypes with differing clinical profiles and treatment implications. **Methods:** We performed LCA on 776 decompensated cirrhosis participants with ascites from two centers. 7 parameters were included: systolic blood pressure (SBP), portal vein thrombosis (PVT) status, platelet count (plt), albumin, total bilirubin, eGFR, and ascites grade. Continuous variables were modeled as deciles. We used a cross-validation approach with 80/20 split (derivation/validation) stratified by center. Optimal model selection was guided by BIC values and clinical interpretability. We assessed class-specific clinical characteristics and outcomes, including acute kidney injury (AKI) and transplantation through competing risk analysis. **Results:** LCA identified three distinct phenotypes: Class 1 "Kidney-Metabolic" (25%): characterized by highest albumin median(q1-q3): 3.80(3.40-4.10) g/dL, lowest bilirubin: 0.9(0.6-1.2) mg/dL, highest SBP: 131(116-150) mmHg, highest plts: 135(105-188) K/μL, and greatest burden of ≥ Stage 3b CKD (21%); Class 2 "Vasodilatory" (47%): distinguished by lowest albumin: 2.90(2.50-3.30) g/dL, highest bilirubin: 4.8 (3.0-8.3) mg/dL, lowest SBP: 115(104-127) mmHg, and intermediate burden of ≥ Stage 3b CKD (11%); Class 3 "PVT" (28%): exhibiting intermediate values with moderate albumin: 3.30(2.90-3.60) g/dL, intermediate bilirubin: 1.9(1.5-2.6) mg/dL, intermediate SBP: 124(112-139) mmHg, but notably highest PVT burden (27%), lowest plts: 58(46-73) K/μL, and lowest burden of ≥ Stage 3b CKD (8%) (Figure 1). In competing risk analysis, Class 2 demonstrated significantly higher cumulative incidence of AKI compared to Class 1 (sHR: 3.5, 95CI: 2.0-6.0) and higher rates of liver transplantation (sHR: 3.0, 95CI: 2.1-4.1), while Class 3, as compared to Class 1, showed no significant difference in AKI risk (sHR: 0.9, 95CI: 0.4-1.8) or transplantation (sHR: 1.0, 95CI: 0.7-1.6) (Figure 1). 4.6% of patients showed overlapping phenotypes, suggesting concurrent pathophysiological processes, without any significant differences in AKI ($p = 0.7$) or waitlist outcomes ($p = 0.4$) when compared to those with clear phenotypes. **Conclusion:** Our LCA reveals three clinically distinct ascites phenotypes with varying pathophysiologic mechanisms, crucial for therapy selection. The "Vasodilatory" phenotype (lower SBP) may benefit from vasoconstrictive therapies, while the "Kidney-Metabolic" phenotype (higher SBP, lower eGFR) may benefit from renoprotective interventions. This framework enables personalized treatment for cirrhotic patients with ascites.

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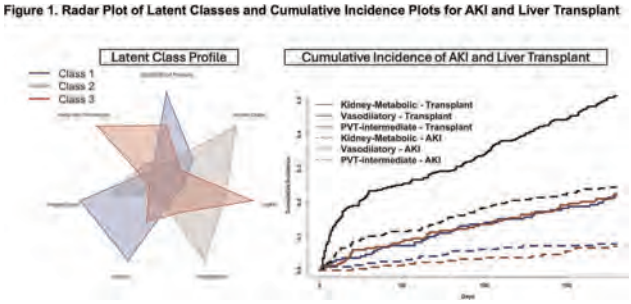

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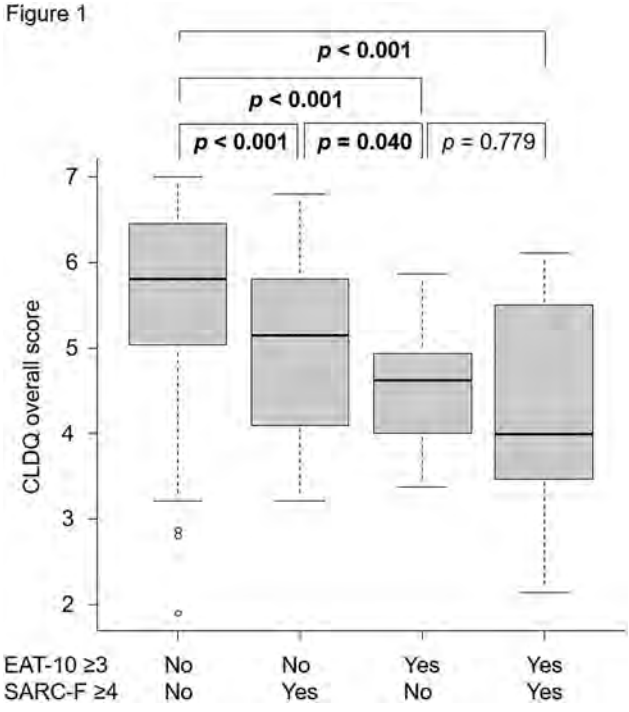
◆ 2296 | DYSPHAGIA IMPAIRS HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH CHRONIC LIVER DISEASE

Takao Miwa[1] Tatsunori Hanai[1] Itsuki Hayashi[1] Shinji Unome[1] Kenji Imai[1] Atsushi Suetsugu[1] Koji Takai[1] Masahito Shimizu[1], [1]Gifu University Hospital

Background: Dysphagia refers to the dysfunction or deterioration of swallowing and is usually a multidimensional syndrome rather than a localized disease specific to the oropharynx. Many patients with chronic liver disease (CLD), especially those with older age, malnutrition, and sarcopenia, can be at high risk for complications of dysphagia. However, very few studies have been conducted on the prevalence, clinical characteristics, and impact on outcomes of dysphagia in patients with CLD. This study aimed to reveal the prevalence and characteristics of dysphagia in patients with CLD and its association with health-related quality of life (HRQOL). **Methods:** This cross-sectional study included outpatients with CLD in Gifu University Hospital. Dysphagia, sarcopenia risk, malnutrition risk, and HRQOL were assessed using the Eating Assessment tool-10 (EAT-10), SARC-F, Royal Free Hospital-Nutrition Prioritizing Tool (RFH-NPT), and Chronic Liver Disease Questionnaire (CLDQ), respectively. Dysphagia and low HRQOL were based on EAT-10 ≥ 3 and CLDQ overall score < 5, respectively. Factors associated with dysphagia and low HRQOL were assessed using the logistic regression model. **Results:** Of the 335 outpatients with CLD, patients with dysphagia, at risk of sarcopenia, and at risk of malnutrition were, 33 (10%), 51 (15%), and 68 (20%), respectively. The median CLDQ overall score was 5.55, and 103 (31%) were diagnosed with low HRQOL based on a CLDQ overall score < 5. Patients with dysphagia were older, had lower liver functional reserve, were at higher risk for sarcopenia and malnutrition, and showed lower CLDQ overall score (median, 4.41 vs. 5.69; $p < 0.001$) than in those without. After adjustment, SARC-F (odds ratio [OR], 1.24; 95% confidence interval [CI], 1.02–1.50; $p = 0.029$) and RFH-NPT (OR, 1.71; 95% CI, 1.04–2.81; $p = 0.034$) scores were independently associated with dysphagia in patients with CLD. EAT-10 (OR, 1.17; 95% CI, 1.04–1.30; $p = 0.008$) and SARC-F (OR, 1.37; 95% CI, 1.18–1.59; $p < 0.001$) scores were also independently associated with low HRQOL. In addition, patients with dysphagia alone had significantly lower CLDQ score than those with sarcopenia risk alone ($p = 0.040$; Figure 1). **Conclusion:** Dysphagia was prevalent in approximately 10% of patients with CLD and was associated with a risk of sarcopenia and malnutrition. Furthermore, dysphagia was related to HRQOL in patients with CLD.

Figure 1



Disclosures: Takao Miwa: Nothing to Disclose, Tatsunori Hanai: Nothing to Disclose, Itsuki Hayashi: Nothing to Disclose, Shinji Unome: Nothing to Disclose, Kenji Imai: Nothing to Disclose, Atsushi Suetsugu: Nothing to Disclose, Koji Takai: Nothing to Disclose, Masahito Shimizu: Nothing to Disclose

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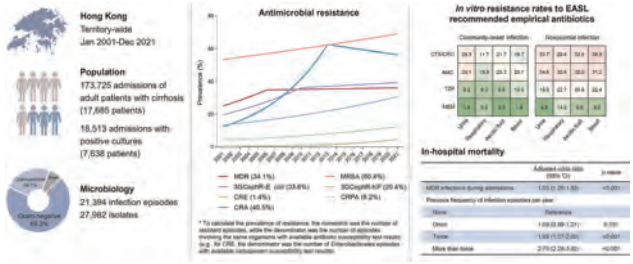
◆ 2297 | MICROBIOLOGICAL PROFILE OF BACTERIAL INFECTIONS IN PATIENTS WITH CIRRHOSIS OVER TIME: A 20-YEAR TERRITORY-WIDE STUDY

Jie Cai[1] Terry Cheuk-Fung Yip[2] Grace Lai-Hung Wong[2] Vincent Wong[2] Grace Lui[2] Jian Sun[3] Jimmy Che-To Lai[2], [1]Southern Medical University; The Chinese University of Hong Kong, [2]The Chinese University of Hong Kong, [3]Southern Medical University

Background: Antimicrobial resistance (AMR) complicates the management of bacterial infections in cirrhosis, while detailed microbiology data remain scarce. This study aimed to characterise the microbiological landscape of bacterial infections in patients with cirrhosis and assess their impact on mortality. **Methods:** All admissions of adult patients with cirrhosis between 2001-2021 were identified using a territory-wide database in Hong Kong. Temporal trends in bacteriology and AMR patterns were assessed using joinpoint regressions. In vitro non-susceptibility to empirical antibiotics recommended by the European Association for the Study of the Liver was evaluated across specimen types. The survival status of all patients at their last admissions was assessed, and patient-based multivariable logistic regressions were conducted. **Results:** A total of 173,725 admissions from 17,685 patients were included in the study, among which 18,513 admissions from 7,638 patients had positive cultures, involving 24,110 samples, 27,982 isolates and 21,394 episodes. Gram-negative bacteria predominated (69.3%), but their proportion decreased from 2010 to 2021 (annual percent change [APC] -0.6%, 95% CI: -1.8 to -0.1). Multidrug-resistant (MDR) organisms were isolated in 34.1% of episodes, with a significant rise during 2001-2006 (APC 6.8%, 95% CI: 3.0 to 17.7). A heterogeneous increase in drug-resistant bacteria was observed. The total number (and prevalence of resistance among the same organism) of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, third-generation cephalosporins-resistant *Enterobacterales*, carbapenem-resistant *Enterobacterales*, carbapenem-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Acinetobacter* episodes was 1,484 (60.4%), 20 (0.8%), 3,122 (28.7%), 135 (1.4%), 119 (6.2%) and 254 (40.5%), respectively. Amoxicillin/clavulanic acid showed comparable *in vitro* resistance rates to third-generation cephalosporins in community-onset infections. MDR infections during admissions (adjusted odds ratio [aOR] 1.55, 95% CI: 1.26-1.93, $p < 0.001$) and a history of two (aOR 1.65, 95% CI: 1.37-2.00, $p < 0.001$) or more (aOR 2.75, 95% CI: 2.28-3.32, $p < 0.001$) infection episodes per year were independently associated with increased in-hospital mortality. **Conclusion:** AMR is rising in patients with cirrhosis. Multidisciplinary effort is crucial to combat AMR and manage bacterial infections in cirrhosis.



Disclosures: Jie Cai: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Consultant, Boehringer Ingelheim: Consultant, Echosens: Speaking and Teaching, Eli Lilly: Consultant, Gilead: Consultant, Gilead: Grant/Research Support, Intercept: Consultant, Inventiva: Consultant, Illuminatio Medical Technology: Stock – privately held company, Merck: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet: Consultant, TARGET PharmaSolutions: Consultant, Unilab: Speaking and Teaching, Visirna: Consultant, AstraZeneca: Consultant, Grace Lui: Nothing to Disclose, Jian Sun: Nothing to Disclose, Jimmy Che-To Lai: Nothing to Disclose

◆ 2298 | FIRST DECOMPENSATION TYPE IN THREE LARGE BIOBANKS IS ASSOCIATED WITH ETIOLOGY OF LIVER DISEASE: A SIGN OF VENOUS REMODELING?

Nikhilesh Mazumder[1] Emma Ulrich[2] Chinmay Raut[3] Lishi Yin[3] Yanhua Chen[3] Antonino Oliveri[3] Elizabeth Speliotes[4], [1]University of Michigan Hospitals and Health Centers, [2]Division of Gastroenterology, [3]University of Michigan, [4]University of Michigan Medical Center

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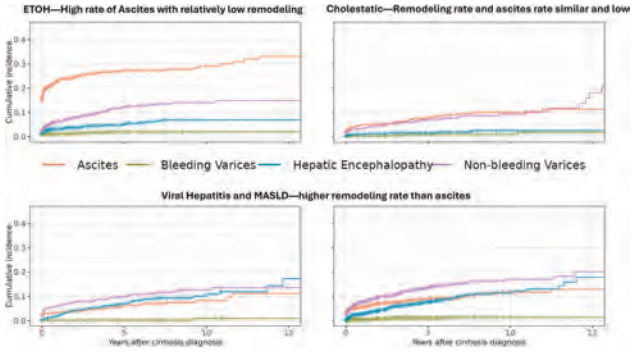
Background: Current models of disease progression (i.e. Baveno stages) propose a monotonic progression of portal hypertensive complications starting with ascites; however, clinically many patients present outside this schema. We hypothesize that patients with cirrhosis due to metabolic dysfunction [MASLD], cholangitis [CS], or viral hepatitis [VHEP]) progress slowly, allowing for venous remodeling while cirrhosis due to alcohol [ETOH] increases portal pressure rapidly leading to variceal rupture and/or symptomatic ascites. Here we examine how participants with cirrhosis of various etiologies first decompensate in three large biobanks, the UK Biobank, the All of Us Research Program, and The Michigan Genomics Initiative. **Methods:** Patients were included at time of first cirrhosis diagnosis using ICD codes. We defined decompensation as new diagnosis of ascites, encephalopathy (HE), or bleeding varices (BV) using ICD codes and/or their treatment procedure codes based on validated criteria. We excluded individuals that had decompensation codes before their inclusion date or if they had abnormal albumin, platelets or bilirubin within 12 months prior to inclusion date. To estimate venous remodeling, we used codes for non-bleeding varices (V). We limited our analyses to individuals with a single etiological cause of cirrhosis. We carried out a Fine Gray competing risk analysis in R 4.4.0. **Results:** A total of 3,361 patients were included (AoU n = 1,750, MGI n = 387, UKBB n = 1,124) with a mean follow up of 4.0 years comprising a total of 13,444 person years of follow up. Patients were an average age of 61 years old at cirrhosis diagnosis, 48% female, and 74.1% of European ancestry. Etiology of liver disease was 31.1% ETOH, 39.2% MASLD, 15.0% CS, and 14.7% VHEP. At the end of follow up, 1,035 (30.8%) patients experienced their first decompensation, with ascites in 447 (13.3%), HE in 197 (5.9%), V in 354 (10.5%), and BV in 37 (1.1%). ETOH cirrhosis more commonly presented with ascites and variceal bleeding as first decompensation while patients with CS, MASLD, and VHEP experienced higher early V formation prior to decompensation (Figure). Individuals with ETOH decompensated more than other causes in all categories (all $P < 0.05$). **Conclusion:** Our results suggest that decompensation pattern is influenced by the liver disease etiology. These findings support our hypothesis that rapidly progressing liver diseases like ETOH exceed compensatory venous remodeling to cause ascites and variceal bleeding more than slowly progressive liver diseases (CS, MASLD, VHEP). Future work can examine genetic predictors of venous remodeling to personalize care for patients with portal hypertension.



Disclosures: Nikhilesh Mazumder: Nothing to Disclose, Emma Ulrich: Nothing to Disclose, Chinmay Raut: Nothing to Disclose, Lishi Yin: Nothing to Disclose, Yanhua Chen: Nothing to Disclose, Antonino Oliveri: Nothing to Disclose, Elizabeth Speliotes: University of Michigan: Pending patent on use systems for MASLD/insulin resistance

◆ 2299 | ROTATIONAL THROMBOELASTOMETRY-GUIDED BLOOD COMPONENT ADMINISTRATION VERSUS STANDARD OF CARE IN PATIENTS WITH CIRRHOSIS AND COAGULOPATHY UNDERGOING INVASIVE PROCEDURES (RECIPE): FINAL RESULTS: FROM A MULTI-CENTRE AUSTRALIA-WIDE RANDOMISED CONTROLLED TRIAL (RCT)

Natasha Janko[1] William Kemp[2] Simone Strasser[3] Marcus Robertson[4] Fadak Mohammadi[3] Rohit Sawhney[1] Avik Majumdar[5] Karen Waller[3] Gerry MacQuillan[6] Thomas Goodwin[2] Paul Gow[5] Chris Hogan[5] Harshal Nandurkar[2] Ammar Majeed[2] Stuart Roberts[7], [1]Eastern Health, [2]Alfred Health, [3]Royal Prince Alfred, [4]Peninsula Health, [5]The Austin, [6]Sir Charles Gairdner Hospital, [7]Alfred Hospital

Background: Prophylactic transfusion of blood products remains common before invasive procedures in patients with cirrhosis. We assessed the efficacy and safety of a ROTEM-based algorithm to guide prophylactic transfusions in subjects with cirrhosis and coagulopathy. **Methods:** This single-blinded, multicentre RCT conducted at six Australian sites included adults with cirrhosis and coagulopathy (INR value or platelet count requiring pre-procedural correction as per

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local practice) scheduled for invasive procedures. Patients were randomized 1:1 to receive ROTEM-guided transfusions or standard of care (SOC) with stratification by bleeding risk (high vs low), INR ($<$/2), and platelet count ($<$/30$\times 10^9$/L). The primary outcome was the proportion of procedures requiring prophylactic blood product transfusion; secondary outcomes included procedure-related bleeding, thrombosis, transfusion-related complications, length of stay and mortality. **Results:** 114 patients were screened with 57 randomised (28 in ROTEM, 29 in SOC). 44 (77%) were high bleeding risk procedures: 13 dental procedures, 10 liver biopsies (7 percutaneous, 3 trans-jugular), 4 other solid organ biopsies, 4 trans-jugular intrahepatic portosystemic shunts, 4 abdominal surgeries, 4 endoscopic or image-guided hepatobiliary procedures, 3 radiological hepatocellular carcinoma treatments, one hip replacement, one muscle biopsy. Baseline demographics, coagulation profile and types of procedures were similar between the two groups. Prophylactic blood products were given before 20 procedures in the ROTEM group compared with 28 in SOC (71% vs. 97%, $p < 0.01$). The median volume of total blood components transfused was significantly lower in the ROTEM compared to SOC group (325 ml *vs.* 570ml, $p = 0.03$). The pattern of blood product usage differed between the groups, with less FFP and more cryoprecipitate given in the ROTEM group compared to SOC (see Table 1). There was no difference in procedure-related bleeding (1 ROTEM *vs.* 2 SOC, $p = 0.60$; no recorded major bleeding), thrombosis, transfusion-related complications, length of stay or mortality between the two groups. **Conclusion:** ROTEM-guided management significantly reduced blood product use in patients with cirrhosis undergoing invasive procedures without increasing bleeding risk or adverse outcomes. Future studies should refine ROTEM thresholds to enhance transfusion efficiency and patient safety.

Table 1. Comparison of blood product prophylaxis between the two groups

	ROTEM	SOC	p-value
Proportion of procedures where prophylaxis given,n (%)			
Any blood product	20 (71)	28 (97)	**0.009**
Fresh frozen plasma (FFP)	8 (29)	19 (66)	**0.005**
Platelets	7 (25)	14 (48)	0.069
Cryoprecipitate	10 (36)	3 (10)	**0.022**
Volume (ml) of prophylactic blood component transfused, median (interquartile range IQR)			
Total blood product	325 (0-570)	570 (285-570)	**0.031**
FFP	0 (0-285)	285 (0-570)	**0.002**
Platelets	0 (0-135)	0 (0-270)	0.133
Cryoprecipitate	0 (0-325)	0 (0-0)	**0.032**

Disclosures: Natasha Janko: Nothing to Disclose, William Kemp: Nothing to Disclose, Simone Strasser: Nothing to Disclose, Marcus Robertson: Nothing to Disclose, Fadak Mohammadi: Nothing to Disclose, Rohit Sawhney: Roche Diagnostics: Consultant, Gilead: Speaking and Teaching, Avik Majumdar: Nothing to Disclose, Karen Waller: Nothing to Disclose, Gerry MacQuillan: Nothing to Disclose, Thomas Goodwin: Nothing to Disclose, Paul Gow: Nothing to Disclose, Chris Hogan: Nothing to Disclose, Harshal Nandurkar: Nothing to Disclose, Ammar Majeed: Nothing to Disclose, Stuart Roberts: Nothing to Disclose

◆ 2300 | MACHINE LEARNING–DRIVEN TRANSPLANT RISK STRATIFICATION AND TIME-TO-TRANSPLANT FORECASTING IN CIRRHOSIS VIA RANDOM SURVIVAL FORESTS

Sri Harsha Boppana[1] Manaswitha Thota[2] Gautam Maddineni[3] Sachin Sravan Kumar Komati[4] Sai Lakshmi Prasanna Komati[5] C. David Mintz MD PhD[6], [1]Nassau University Medical Center / Johns Hopkins University, [2]Virginia Commonwealth University, [3]Creighton university school of medicine, [4]Florida International University, [5]Government Medical College, Ongole, [6]Johns Hopkins University

Background: Patients with cirrhosis experience highly variable disease trajectories, and there remains a critical need to identify, at the earliest possible stage, those most likely to progress to liver transplantation. To address this, we constructed a random survival forest algorithm that combines routinely obtained laboratory results with three novel derived metrics—age-normalized enzyme ratios, binary indicators of treatment response, and a unified severity index—to predict transplant-free survival and to surface the most influential prognostic variables. **Methods:** Using a de-identified dataset from a tertiary-care center, we selected adult cirrhosis cases and extracted key variables: age, total bilirubin, serum glutamic–oxaloacetic transaminase, serum albumin, validated comorbidity scores, and recorded treatment histories. We then generated three engineered features: liver enzyme ratios adjusted for patient age; binary flags denoting documented response to therapy; and a composite score reflecting overall disease severity. Missing continuous values were imputed with the mean, and categorical gaps were filled with the mode. The cohort was split 80:20 into training and held-out test sets. A random survival forest of 100 trees was trained using the sksurv package, with hyperparameters (split rule and minimum node size) optimized via five-fold cross-validation. Model performance was evaluated by the concordance index, and risk stratification was visualized through Kaplan–Meier survival curves. Finally, we employed permutation importance to rank the predictors of time until transplant. (Figure 1,2,3,4) **Results:** On the training data, the model achieved a concordance index of 0.94 and maintained strong performance on the test set with a concordance index of 0.82. Permutation analysis identified age, bilirubin levels, and serum glutamic–oxaloacetic transaminase as the three most impactful predictors of transplant risk.

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Patients were categorized into low-, intermediate-, and high-risk strata, comprising 29 percent, 37 percent, and 34 percent of the cohort, respectively. Median transplant-free survival times were 2,450 days for the low-risk group, 1,520 days for the intermediate group, and 890 days for the high-risk group. Kaplan–Meier curves for each stratum showed statistically significant separation (log-rank $p < 0.001$), confirming the model's ability to discriminate among risk tiers. **Conclusion:** The proposed random survival forest model delivers high discriminative accuracy in stratifying cirrhosis patients by transplant risk, with clear differences in median transplant-free survival across risk groups (log-rank $p < 0.001$). Integrating engineered features with conventional laboratory measures offers a promising avenue for personalized guidelines on transplant referral timing. Prospective external validation is warranted to establish clinical applicability and generalizability.

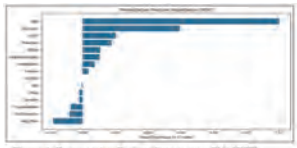
Figure 1. Permutation Feature Importance Plot (RSF)

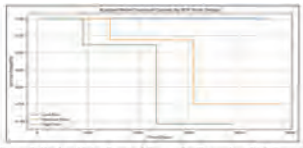
Figure 2: Kaplan-Meier Survival Curves for Transplant Risk Groups

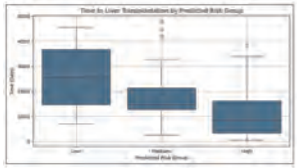
Figure 3: Time to liver transplantation by Prediction risk group.

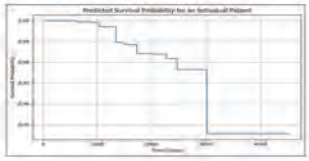
Figure 4 : Predicted Survival Probability for Individual Patients.

Disclosures: Sri Harsha Boppana: Nothing to Disclose, Manaswitha Thota: Nothing to Disclose, Gautam Maddineni: Nothing to Disclose, Sachin Sravan Kumar Komati: Nothing to Disclose, Sai Lakshmi Prasanna Komati: Nothing to Disclose, C. David Mintz MD PhD: Nothing to Disclose

◆ 2301 | UNDERSTANDING THE IMPACT OF CIRRHOSIS ETIOLOGY ON RISKS OF COMPLICATION, REGIONAL PATTERNS, AND TRENDS OVER TIME IN THE UNITED STATES

Arun Jesudian[1] Patrick Gagnon-Sanschagrin[2] Rebecca Burne[2] Anaïs Lemyre[2] Nathan Gobeil[2] Kana Yokoji[2] Tom Cornwall[2] Olamide Olujohungbe[3] Annie Guérin[2] Shweta Kiran Shah[3], [1]Weill Cornell Medicine, [2]Analysis Group, Inc., [3]Bausch Health

Background: Cirrhosis often leads to serious complications, with risk and prognosis varying by etiology. Understanding regional and temporal patterns is critical to identifying high-risk populations, guiding care, and informing future public health strategies. **Methods:** This retrospective cohort study using Komodo Research Data (2016-2023) included adults with cirrhosis. Newly diagnosed patients with cirrhosis were followed from an index date – defined as diagnosis onset or earliest complication (ascites, overt hepatic encephalopathy (OHE), varices with/without bleeding) – until the earliest of: end of continuous enrollment, liver transplant, secondary malignant neoplasm of liver, death, or end of data availability. Complications were descriptively reported for all patients and stratified by etiologies (alcohol-associated liver disease [ALD], metabolic dysfunction-associated steatohepatitis [MASH], viral hepatitis, or other/unspecified). Time to first complication after the index date was assessed using Kaplan-Meier methods. The geographic distribution of etiologies was described by U.S. region. Finally, trends in etiology were projected by linear extrapolation of patterns observed from 2017 to 2022 through 2030. **Results:** In total, 110,359 adults with cirrhosis (median age: 60 years; 55.5% male; 56.9% identified as White; median follow-up: 23.5 months) were included in the study. Of those, 34.7% had ALD, 22.8% MASH, 13.8% viral hepatitis, and 28.8% other or unspecified etiologies. Higher prevalence of ALD cirrhosis was observed in Midwest (6.9% above national average, Panel A); viral hepatitis-related cirrhosis in West (24.3% above national average; Panel B), and MASH in the South (8.7% above national average). By 36 months, 62.3% (95% CI: 62.0–62.6) of all patients developed a complication, with the highest rate observed in patients with ALD (84.6%; 95% CI: 84.2–85.0) and the lowest in patients with viral hepatitis (41.5%; 95% CI: 40.7–42.4; Panel C). The first complication observed was most commonly ascites (63.6%), followed by varices without bleeding (27.2%), OHE (14.6%), and varices with bleeding (8.5%; Panel D). Based on trends observed from 2017 to 2022, the proportion of incident cirrhosis attributable to viral hepatitis in 2030 is expected to decline by 78.5% relative to 2023, driven by a steep decline in cases due to hepatitis C. In the same period, the proportion of new cirrhosis cases due to ALD and MASH in 2030 is projected to increase by 12.0% and 17.7%, respectively. **Conclusion:** Cirrhosis etiology is a strong determinant of complication risk, with notable geographic variation across the U.S. The growing prevalence of ALD and MASH etiologies associated with the highest risk suggests a shift toward a more clinically severe cirrhosis population. These findings underscore the need for continued research to understand the evolving burden and its implications for clinical outcomes.

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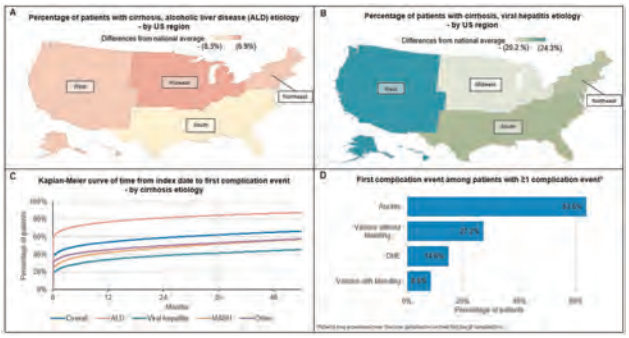

Disclosures: Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant, Mallinckrodt Pharmaceuticals: Consultant, Mallinckrodt Pharmaceuticals: Speaking and Teaching, Patrick Gagnon-Sanschagrin: Nothing to Disclose, Rebecca Burne: Nothing to Disclose, Anaïs Lemyre: Nothing to Disclose, Nathan Gobeil: Nothing to Disclose, Kana Yokoji: Nothing to Disclose, Tom Cornwall: Analysis Group, Inc.: Employee, Olamide Olujohungbe: Bausch Health: Employee, Bausch Health: Stock – privately held company, Annie Guérin: Nothing to Disclose, Shweta Kiran Shah: Nothing to Disclose

◆ 2302 | METABOLIC AND CARDIOVASCULAR EFFECTS OF ZIBOTENTAN AND DAPAGLIFLOZIN IN PATIENTS WITH CIRRHOSIS: A RANDOMIZED PLACEBO-CONTROLLED 6-WEEK STUDY

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Background: Endothelin-1 is a strong vasoconstrictor linked to intrahepatic vasoconstriction and portal hypertension (PH) in cirrhosis. Endothelin receptor antagonists (ERAs) can potentially lower PH but often cause fluid retention. Sodium-glucose co-transporter 2 inhibitors (SGLT2i) may normalize extracellular water volume. This phase 2b study examined effects of zibotentan (zibo), a selective ERA as monotherapy or combined with dapagliflozin (dapa), a selective SGLT2i, verses placebo (pbo) on different measures of fluid retention and safety biomarkers. **Methods:** Patients with clinically significant PH (CSPH) with compensated or decompensated cirrhosis (MELD <15 and Child Pugh score <10) were randomized to receive 5 mg zibo/10 mg dapa (n = 24), 5 mg zibo (n = 25), or placebo (n = 24) in a 6-week double-blind study. Key measures included body weight, total body water, loop diuretic use, adverse events (AEs) of fluid retention, systolic and diastolic blood pressures (SBP, DBP). Exploratory objectives included changes in eGFR, AST, ALT, MELD score, and liver stiffness. **Results:** Seventy-two treated patients with mean age of 60.8 years, 70.8 % males, 30.6% type 2 diabetes, 30.6% decompensated. Main etiology was alcoholic liver disease (47.2%) or metabolic dysfunction–associated steatotic liver disease (34.7%), with mean MELD and Child-Pugh scores of 8.4 and 5.8, respectively. Comparing zibo/dapa to zibo alone change from baseline over 6 weeks, estimated differences were: body weight -1.72 kg (90% CI: −2.82, −0.62), body fat -1.45 kg (90% CI: -2.48, −0.43), and body water -0.3 L (90% CI: −1.10,0.49). Difference in blood pressure change from baseline for zibo/dapa vs pbo were SBP -11.9 mmHg (90% CI: −17.7, −6.1); DBP-2.5 mmHg (90% CI: −17.7, −6.1). For zibo vs. pbo: SBP -10.8 mmHg (90% CI: −14.1, −7.6), DBP-4.3 mmHg (90% CI: −7.4, −1.1). In both zibo arms, median transaminase reductions were greater (2.5-4.5 U/L) than pbo (-0.5-0 U/L). Most AEs were mild/moderate, the most common being headache. One unrelated case of hepatitis E, 4 SAEs, and 6 subjects withdrew. No observed DILI events. **Conclusion:** Six weeks of treatment with both zibo/dapa and zibo alone were well tolerated, with no significant difference in fluid retention-related events between the active arms. Dapagliflozin may mitigate fluid retention associated with a lower dose of zibo. Both active treatment groups lowered blood pressure and transaminase levels.

Disclosures: Kristin Fiorino: Nothing to Disclose, phil ambery: AstraZeneca: Employee, Jan Oscarsson: Nothing to Disclose, Lynsey Corless: Nothing to Disclose, Emma Wijkmark: AstraZeneca: Employee, Agata Oruba: Nothing to Disclose, Eric Lawitz: 89Bio: Grant/Research Support, Akero Therapeutics: Grant/Research Support, Astrazeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, Cour Pharmaceuticals: Grant/Research Support, Cymabay Therapeutics: Grant/Research Support, Eli Lilly and Company: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Hanmi Pharmaceuticals: Grant/Research Support, Hightide Biopharma: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Inventiva: Grant/Research Support,

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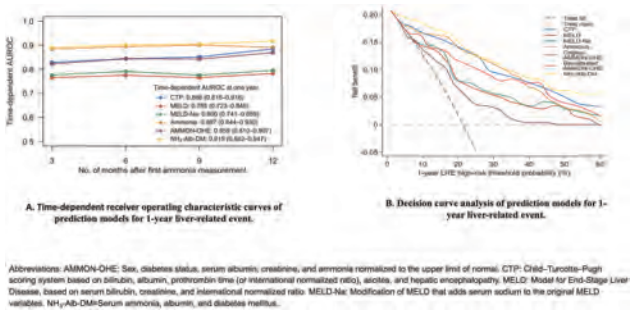
◆ 2303 | DEVELOPMENT OF A NEW MODEL TO PREDICT HOSPITALIZATION FOR LIVER-RELATED EVENTS: THE SOLIDARITY-DAM (DIABETES, ALBUMIN, AMMONIA) SCORE

Gayathry Morvil[1] Pooi Ling Loi[1] Xuan Han Koh[1] Daniel Lim[1] Chin Kimg Tan[1] YU JUN WONG[1] Jessica Tan[1] Andrew Boon Eu Kwek[1] Tiing Leong Ang[1] Marianne De Roza[2] Hiang Keat Tan[3] Chanda Ho[3] Jason Chang[3] Prema Raj Jeyaraj[3] Rahul Kumar[1], [1]Changi General Hospital, [2]Sengkang General Hospital, [3]Singapore General Hospital

Background: Predicting liver-related events (LREs) in cirrhosis is crucial. Traditional scoring models like MELD and CTP perform poorly due to incomplete pathophysiological integration and a shift in the etiological curve towards MASLD. New models, such as AMMON-OHE, are limited to predicting HE and mortality, not LREs. We developed and validated a new DAM (Diabetes, Albumin, aMmonia) model for predicting hospitalisation due to LRE. **Methods:** A total of 280 consecutive patients with cirrhosis were enrolled. Baseline and periodic data were collected on biochemical, clinical, demographic, and radiological parameters. Patients were then followed up prospectively for the primary endpoints, which were a composite of hospitalization within one year for new or worsening ascites, variceal bleeding, HE, or bacterial infection (LRE). Cox proportional hazards regression was used to derive a prognostic index (PI) for 1-year LRE. TRIPOD+AI guidance and decision curve analysis were carried out to interrogate the performance characteristics of competing models. Model discrimination was assessed by estimating the time-dependent area under the receiver operating characteristic curve (AUROC) at 90, 180, 270, and 360 days from study enrolment. **Results:** Most patients were male (60.7%) with a mean age of 66.1 ± 10.3 years. MASLD was the most common etiology (43.7%). Median CTP and MELD were 6 (IQR: 5-7) and 8 (IQR: 6-11). Overall, 60 (21.4%) developed LRE at one year, and 23 (8.2%) died. The PI of DAM for 1-year LRE was PI = 0.0247×ammonia (μmol/L)-0.126×albumin (g/L)+0.755×DM. The model-estimated baseline 1-year LRE-free survival was $\hat{S}_0(1y) = 0.904$. The DAM model outperformed others (AMMON-OHE, CTP, MELD, MELD-Na; Figure 1). AMMON-OHE predicted LRE with a time-dependent AUROC of 0.859 (CI: 0.810-0.907), outperforming MELD ($p = 0.014$) but similar to CTP (p = NS), underestimating LRE. Best prediction for LRE was achieved by the DAM (Diabetes, Albumin, aMmonia) model, yielding an AUROC of 0.915 (CI: 0.882 -0.947) and Brier score of 0.075 (CI: 0.038-0.119). A 1 g/L increase in albumin correlated with a 12% lower hazard of 1-year LRE (HR 0.88, 95% CI 0.85 to 0.92; $P < 0.001$). Patients with DM showed a 2.1 times higher hazard rate for 1-year LRE (HR 2.13, 95% CI 1.25 to 3.63; $P = 0.006$). Each 10 μmol/L rise in ammonia linked to a 28% higher hazard rate of 1-year LRE (HR 1.28, 95% CI 1.19 to 1.38; $P < 0.001$). **Conclusion:** We developed and internally validated a new LRE prediction model, the DAM (Diabetes, Albumin, aMmonia), which outperforms others. External validation is needed.



A. Time-dependent receiver operating characteristic curves of prediction models for 1-year liver-related event.

B. Decision curve analysis of prediction models for 1-year liver-related event.

Abbreviations: AMMON-OHE: Sex, diabetes status, serum albumin, creatinine, and ammonia normalized to the upper limit of normal. CTP: Child–Turcotte–Pugh scoring system based on bilirubin, albumin, prothrombin time (or international normalized ratio), ascites, and hepatic encephalopathy. MELD: Model for End-Stage Liver Disease, based on serum bilirubin, creatinine, and international normalized ratio. MELD-Na: Modification of MELD that adds serum sodium to the original MELD variables. NH_3-Ab-DM=Serum ammonia, albumin, and diabetes mellitus.

Disclosures: Gayathry Morvil: Nothing to Disclose, Pooi Ling Loi: Nothing to Disclose, Xuan Han Koh: Nothing to Disclose, Daniel Lim: Nothing to Disclose, Chin Kimg Tan: Nothing to Disclose, YU JUN WONG: Nothing to Disclose, Jessica Tan: Nothing to Disclose, Andrew Boon Eu Kwek: Nothing to Disclose, Tiing Leong Ang: Nothing to Disclose, Marianne De Roza: Nothing to Disclose, Hiang Keat Tan: Nothing to Disclose, Chanda Ho: Nothing to Disclose, Jason

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◆ 2304 | THE HEPATORENAL HIT: NATIONWIDE TRENDS IN CHRONIC LIVER DISEASE AND ACUTE KIDNEY INJURY RELATED MORTALITY IN THE U.S. (1999–2023)

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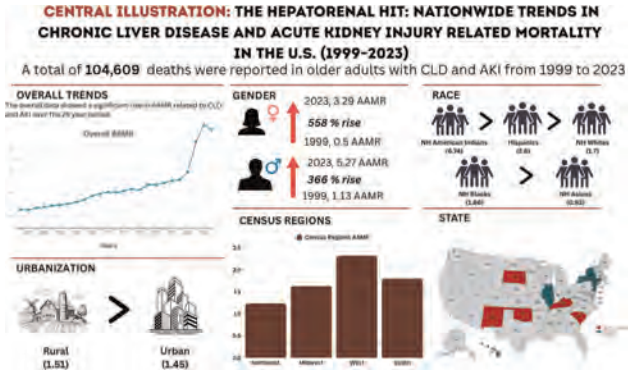
Background: Chronic Liver Disease (CLD) remains a major cause of morbidity and mortality in the United States, often progressing to advanced stages with systemic complications. Among these, Acute Kidney Injury (AKI) is a frequent and serious complication, markedly increasing the risk of in-hospital mortality and adverse outcomes in CLD patients. Despite its clinical significance, national trends in mortality associated with comorbid CLD and AKI have not been well characterized. This study examines 25-year trends in CLD and AKI–related mortality among U.S. adults, with a focus on demographic and regional disparities. **Methods:** Mortality data from the CDC WONDER database (1999–2023) were analyzed using Joinpoint regression to assess CLD and AKI-related deaths among U.S. adults aged 25 and older. Age-adjusted mortality rates (AAMRs) per million were calculated, along with the average annual percent change (AAPC) and corresponding 95% confidence intervals (CI). **Results:** AKI among individuals with CLD accounted for 104,609 deaths in adults aged 25 years and older. Between 1999 and 2023, the overall AAMR surged from 0.79 to 4.26 with an AAPC of 7.79 (95% CI 7.17- 8.5, $p < 0.000001$). Males consistently exhibited higher mortality rates than females (AAMR; 2.34 vs 1.27) however, the trajectory of increase was steeper in females (AAPC: 8.75; 95% CI 8.11- 9.55) as compared to males (AAPC: 7.07; 95% CI 6.42- 7.85) both with $p < 0.000001$). Among the racial groups, American Indian or Alaska Native (AI/AN) had the highest AAMR (6.74) followed by Hispanics (2.60), Non-Hispanic (NH) White (1.70) and NH Black individuals (1.66). NH Asian had the lowest mortality among all races (AAMR; 0.93). AI/AN experienced the sharpest rise (AAPC: 8.901; 95% CI 7.53- 10.87), followed by White population (AAPC: 8.42 95% CI 7.81- 9.19), Asians (AAPC: 5.91; 95% CI 0.64- 11.83), Hispanics (AAPC: 5.88; 95% CI 5.17- 6.72), Blacks (AAPC: 5.61; 95% CI 4.93- 6.43) and NH Asians (AAPC: 3.11; 95% CI 1.74- 4.86). The Midwest experienced the highest increase in mortality (AAPC: 7.98; 95% CI: 7.23–8.91), followed by the West (7.96), South (7.75), and Northeast (5.84). States with the highest AAMRs were Oklahoma (12.04), New Mexico (9.09), and South Dakota (8.70). Rural areas had higher AAMRs than urban areas (1.55 vs. 1.51) and a steeper rise in mortality (AAPC: 7.07 vs. 5.03). Individuals aged ≥ 75 had the highest mortality (AAMR: 3.52), followed by those aged 45–74 (2.70), and < 45 (0.53). However, the sharpest increase was in the younger population (AAPC: 8.81), followed by older (7.69) and middle-aged adults (7.29). **Conclusion:** CLD and AKI-related mortality has escalated over the past 25 years with the most notable increases observed in AI/AN, females, Whites, young adults, rural areas and in the Midwest region. These disparities emphasize the urgent need for targeted intervention and care to address the growing mortality burden, especially among vulnerable populations



Disclosures: Simran Joshi: Nothing to Disclose, MANJEET GOYAL: Nothing to Disclose, Muhammad Faizan Ali: Nothing to Disclose, Husnain Ahmad: Nothing to Disclose, Susan Feldman: Nothing to Disclose, Muhammad Khan: Nothing to Disclose, Muhammad Rahim: Nothing to Disclose, Salman Attari: Nothing to Disclose, Nothing to Disclose, Sherif Eltawansy: Nothing to Disclose, Saman Javid: Nothing to Disclose, Preethi Jagannath: Nothing to Disclose, Mayssaa Hoteit: Nothing to Disclose

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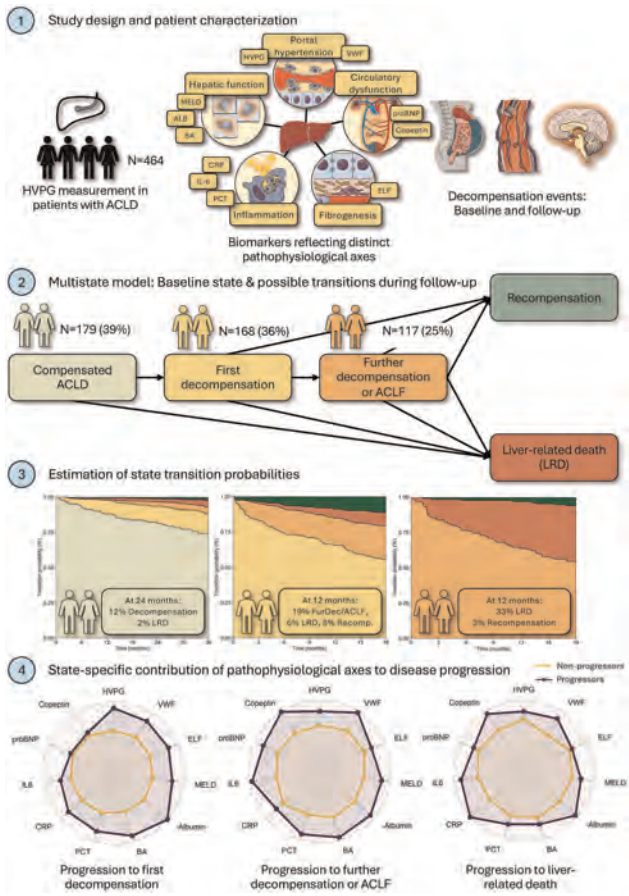
◆ 2305 | STAGE-SPECIFIC DRIVERS OF CLINICAL PROGRESSION IN ADVANCED CHRONIC LIVER DISEASE

Benedikt Simbrunner[1] Georg Semmler[1] Marta Bofill Roig[1] Elias Meyer[1] Lorenz Balcar[1] Mathias Jachs[1] Lukas Hartl[1] Benedikt Hofer[1] Georg Kramer[1] Paul Thoene[1] Christian Sebesta[1] Nina Dominik[1] Bernhard Scheiner[1] Philipp Schwabl[1] Albert Stättermayer[1] Michael Trauner[1] Thomas Reiberger[1] Mattias Mandorfer[1], [1]Medical University of Vienna

Background: Different pathophysiological mechanisms contribute to the progression of advanced chronic liver disease (ACLD). We investigated the clinical trajectory of ACLD in a contemporary cohort and evaluated biomarkers reflecting key pathophysiological mechanisms for their stage-specific prognostic value. **Methods:** We prospectively recruited 464 ACLD patients at hepatic venous pressure gradient (HVPG) measurement between 2017 and 2021 (VICIS; NCT03267615; see figure, panel 1). Clinical states at baseline and follow-up were defined as compensated ACLD (cACLD), first decompensation, further decompensation/ACLF (acute-on-chronic liver failure; combined), liver-related death (LRD), and recompensation (see figure, panel 2). Multistate modeling was used to investigate the risk of stage transitions during follow-up (median: 29 months). The association of biomarkers for portal hypertension (HVPG), endothelial dysfunction (VWF), liver fibrogenesis (ELF), liver function (MELD/albumin/bile acids), systemic inflammation (CRP/IL-6/procalcitonin), and circulatory dysfunction (proBNP/copeptin) with stage transitions was evaluated. **Results:** In cACLD, 12% developed first decompensation at 24 months, 3.2% further decompensation/ACLF, 2.1% LRD; and 1.1% recompensation after decompensation (see figure, panel 3). In decompensated cirrhosis, 19% developed further decompensation/ACLF, 6.3% LRD while 8.8% achieved recompensation. Among patients with further decompensation at baseline, 33% experienced LRD and 3.0% recompensation at 12 months.

Portal hypertension, endothelial dysfunction, fibrogenesis, and liver function were indicative of progression in cACLD, shifting towards SI and liver function in decompensated cirrhosis, with the additional contribution of circulatory dysfunction in further decompensation (see figure, panel 4). HVPG and albumin provided independent prognostic information in cACLD, CRP in decompensated cirrhosis, and copeptin in further decompensation. **Conclusion:** Targeting PH should be prioritized in cACLD, while modulating systemic inflammation and circulatory dysfunction is crucial for preventing disease progression in decompensated cirrhosis. Precision medicine based on individual biomarker profiles could optimize patient outcomes in future clinical trials.



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2306 | IMPAIRED COGNITION AND A HISTORY OF HEPATIC ENCEPHALOPATHY ARE ASSOCIATED WITH DISORDERED SLEEP AS MEASURED BY SHORT TERM MONITORING WITH COMMERCIAL WEARABLE TECHNOLOGY

Jessica Siguencia[1] Ziyu Liu[1] Brian McSteen[1] Olivia Blocker[1] Jialin Gao[1] Avesh Thuluvath[2] Elizabeth Verna[2] Ana Krieger[1] Himel Mallick[1] Robert Brown[1] Adam Buckholz[1], [1]Weill Cornell Medicine, [2]Columbia University Irving Medical Center

Background: Hepatic encephalopathy (HE) is common in cirrhosis but is often difficult to diagnose and assess longitudinally due to its dynamic nature and the subjective nature of gold standard cognitive assessment tools. Patients with both covert (CHE) and overt (OHE) HE often report disturbed sleep. We hypothesized that cognitive impairment and/or HE would be associated with objectively worse measured sleep when tracked by a commercial wearable device. **Methods:** We enrolled patients with cirrhosis and longitudinally monitored sleep for 6 months. For this study, we included participants with complete baseline cognitive assessment by Psychometric Hepatic Encephalopathy Score (PHES) and sleep data for at least 14/28 days after enrollment, analyzing the first 14 consecutive days recorded per participant. A PHES $\leq$ -4 was considered abnormal cognition. Primary comparison groups were those with vs. without impaired cognition at baseline, and those with a history of OHE or therapy for HE at enrollment compared to those without. Assessed sleep metrics included total sleep time, REM sleep duration, sleep efficiency (%SE), time in bed/time in bed variability and sleep midpoint/midpoint variability. A mixed effects model (MEM), log transformed where applicable, assessed outcomes, with primary analysis adjusting for age, gender, BMI and MELD. **Results:** Of 117 participants, 81 met adherence criteria, with 1134 baseline sleep nights analyzed. Patients with impaired cognition at enrollment had significantly reduced nightly time in bed (463 vs 495 min, $p = 0.01$) and REM sleep (64.4 vs 81.4 min, $p = 0.01$) (A, B). In MEM adjusted for age, gender, BMI, and MELD score, the association remained significant for both reduced time in bed ($\beta =$ -.594, $p = 0.01$) and REM ($\beta =$ -14.1, $p = 0.03$). Measured %SE was similar between groups. There was no difference in nightly REM time among those with a history of OHE compared to those without. In the adjusted MEM, sleep midpoint was numerically later in those with compared to without OHE history (4:21 vs 4:51, $p = 0.07$) (C), but there was significantly higher variability in sleep midpoint in those with prior OHE ($\beta = 0.25$, $p < 0.001$). In a subgroup analysis including only those with normal baseline cognition, there remained increased midpoint variability among those with a history of OHE compared to those without ($\beta = 0.19$, $p = 0.003$) (D). **Conclusion:** In cirrhosis, impaired cognition at baseline was associated with reduced REM and nightly time in bed, while a history of diagnosed encephalopathy, even if treated or covert, was associated with increased variation in sleep midpoint. A stable sleep midpoint is a marker of circadian health, and high variation has been associated with circadian rhythm dysfunction. Reduced REM may be more associated with sleep physiology or fragmentation. Further studies developing sleep as a biomarker and circadian dysfunction as a therapeutic target for HE should be considered.

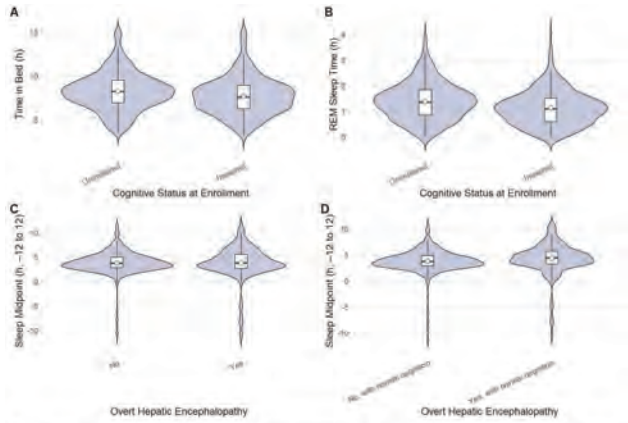

Figure. Violin plots showing distribution of analyzed nights and reduced measured time in bed **(A)** and REM sleep duration **(B)** among those with impaired cognition (CHE or OHE) at enrollment. Additionally, violin plots demonstrating distribution of sleep measured sleep midpoint, which showed higher variability among those with any history of overt hepatic encephalopathy **(C)**, even among those with normal enrollment cognition **(D)**. All differences were significant at p<0.01.

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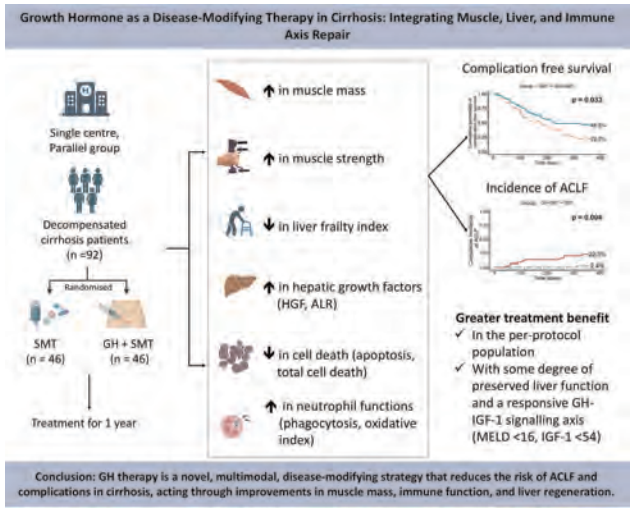
2307 | GROWTH HORMONE AS A DISEASE-MODIFYING THERAPY IN CIRRHOSIS: INTEGRATING MUSCLE, LIVER, AND IMMUNE AXIS REPAIR

Parminder Kaur[1] Nipun Verma[2] Pratibha Garg[3] Pinaki Dutta[2] Gaurav Sharma[2] Naveen Kalra[2] Sunil Taneja[2] Ajay Duseja[3] Virendra Singh[4], [1]Post Graduate Institute of Medical education and Research, [2]Post Graduate Institute of Medical Education and Research, Chandigarh, India, [3]Postgraduate Institute of Medical Education & Research, [4]Punjab Institute of Liver and Biliary Sciences, Mohali, Punjab, India

Background: Perturbed growth hormone (GH) - insulin-like growth factor (IGF-1) axis is linked to complications and mortality in cirrhosis. We evaluated the impact of GH therapy on complication-free survival (CFS), malnutrition, neutrophil function, and hepatic regeneration in patients with decompensated cirrhosis (DC). **Methods:** In a single-centre, parallel-group, open-label trial, 92 DC patients were randomized to standard medical therapy (Group A: SMT) (n = 46) or GH+SMT (Group B) (n = 46). GH was administered subcutaneously daily at 2 IU/day for 12 months, with dosing titration based on IGF-1 levels. Primary end point was CFS. Secondary end points were assessment of GH-IGF1 (by CLIA), malnutrition (muscle mass – CT-SMI, muscle function – handgrip strength), hepatic growth factors (hepatocyte growth factor: HGF, augmenter of liver regeneration: ALR - ELISA), and cell death makers (apoptosis: M30, total cell death: M65 – ELISA), neutrophil function (oxidative burst – ROS production and phagocytic capacity – flow cytometry). Patients achieving normal IGF-1 levels were classified as IGF-1 responders. Causal tree analysis was used to identify subgroups with maximum benefit. **Results:** Median age of patients was comparable (50.0 vs 45.5, p = 0.600) and 96.7% were males. Median MELD score was comparable in both (14.7 vs 14.8, p = 0.685). GH+SMT significantly improved 12-month CFS (HR: 0.58, p = 0.035; RR: 0.69, p = 0.021; NNT = 4.2) with a stronger effect in the per-protocol (HR: 0.46, p = 0.007) and IGF-1 responders (HR: 0.18, p = 0.001). Overall survival was better in per-protocol (HR:0.19, p = 0.027). Incidence of ACLF significantly reduced in GH+SMT comapred to SMT (2.4% vs 22.3%, p = 0.004). MELD score improved significantly in only GH+SMT (p = 0.015). IGF-1 levels (%ΔIGF-1: 79.3 vs 0.0, p < 0.001), muscle mass (%ΔSMI: 11.8 vs 1.2, p = 0.006), muscle strength (%ΔHGS: 4.8 vs 0.0, p = 0.017), frailty (%ΔLFI: –7.0 vs –0.2, p = 0.001) improved significantly along with reduction in circulating myostatin levels (%Δ: –27.8 vs –8.8, p < 0.001). Hepatic growth factor levels increased (%ΔHGF: 7.5 vs 1.2; ALR: 32.8 vs 5.2, p < 0.05 both), alongside reduced cell death markers (M30: –17.7 vs –11.6, p = 0.026; M65: –25.4 vs –14.0, p < 0.05 both). Neutrophil function improved with reduced resting ROS (%Δ: –56.1 vs 5.1, p = 0.009) and enhanced phagocytosis (%Δ: 35.2 vs –6.6, p = 0.03); with trend in oxidative index (%Δ: 14.6 vs –16.3, p = 0.179). No significant changes were observed in SMT. No HCC or grade ≥ 3 adverse events occurred with GH. Best treatment benefit was observed in patients with MELD < 16 and IGF-1 < 54, and albumin ≥ 3.7. **Conclusion:** GH therapy is a novel, multimodal, disease-modifying strategy that reduces the risk of ACLF and complications in cirrhosis, acting through improvements in muscle mass, immune function, and liver regeneration. Further studies are needed to optimise GH administration, enhance IGF-1 response, and validate multimodal improvement in cirrhosis.



Disclosures: Parminder Kaur: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Pratibha Garg: Nothing to Disclose, Pinaki Dutta: Nothing to Disclose, Gaurav Sharma: Nothing to Disclose, Naveen Kalra: Nothing to Disclose, Sunil Taneja: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, Virendra Singh: Nothing to Disclose

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2308 | DYNAMIC HEPATIC SEGMENTAL NETWORKS: A NOVEL IMAGING EARLY-WARNING SYSTEM FOR CIRRHOSIS DECOMPENSATION

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Background: Alterations in inter-segmental communication networks – driven by fibrotic bridging, vascular shunting, and metabolic dysfunction – serve as latent biomarkers for impending cirrhotic decompensation. However, the dynamic hepatic connectomes and its role in signaling decompensation remain unexplored. **Methods:** Study Cohort □Inclusion: Cirrhotic patients (with/without HCC) from our medical center (2022–2025) undergoing gadoxetic acid-enhanced upper abdominal MRI with ≥5 imaging phases (non-contrast, arterial, portal venous, equilibrium, delayed). □Exclusion: Poor image quality, honeycombing, macrocysts/large masses, uncorrected inter-sequence misalignment. □Study outcome: Cirrhosis decompensation (including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal bleeding, sepsis, hepatorenal syndrome, jaundice, or other clinically determined decompensation events, whichever occurs first). Imaging Acquisition Dynamic contrast-enhanced T1-weighted MRI using a GE Discovery 750 3.0T or Siemens Prisma 3.0T scanner with standardized axial acquisition (FOV = 38 cm), performed prior to and following intravenous injection of 0.1–0.2 mL/kg gadoxetic acid disodium (Bayer AG, Germany). Hepatic Segmental Division Liver partitioned into 8 segments (I-VIII, Couinaud classification). Representative slices: □Upper hepatic level: Middle/right hepatic veins (or fissures if veins indistinct), ensuring analyzable Segment I. □Splenic vein level: Right portal vein branch as reference if indistinct. □All sequences registered to portal venous phase (Phase 2) with manual correction when needed. MR Feature Quantification □ROI selection: Circular ROIs placed centrally in Segments I–VIII, avoiding vessels and lesions □Feature extraction: 837 radiomic features per segment extracted via PyRadiomics (first-order, GLCM, GLDM, GLSZM, NGTDM, wavelet features). □Feature screening: Phase 2 average values across segments showed both statistical and clinical differences between compensation and decompensation states, leading to their selection for network construction. Dynamic Network Analysis □Network construction: Sliding window (window size = 3 phases) applied to build topological networks. Inter-segmental connectivity quantified by Pearson correlation, with sparsity controlled at 0.2. □Network metrics: Small-worldness (sigma, clustering, path length), modularity, hub distribution, nodal centrality (degree, strength, betweenness, closeness, eigenvector). Clinical Value Evaluation Patients stratified into low/medium/high-risk groups by network features. Decompensation prediction assessed via Cox regression (Hazard Ratios, HRs). **Results:** Limited Predictive Value of Aggregate Radiomics Among 426 scans (224 [52.6%] pre-decompensation ≥30 days), only 2/837 average features across Segments I-VIII showed clinically (|fold change| > 2.5) and statistically significant differences between decompensation and compensation states. This underscores the critical need to account for spatial heterogeneity and segmental interactions. Inter-Segmental Network Remodeling in Decompensation Significant network reorganization was observed in decompensated compared to compensated livers within the arterial-portal venous-equilibrium window. This included an increase in modularity (indicating functional fragmentation: 0.066 vs. 0.038), sigma (reflecting heightened randomness: 1.514 vs. 1.434), and a decrease in path length (suggesting impaired information transfer efficiency: 0.786 vs. 0.818); all $P < 0.05$. Decentralization of Hub Nodes Signifies Hepatic Network Instability Segment V dominated the liver network in compensation (20% hub prevalence, consistent with its anatomical centrality). Decompensation triggered hub redistribution: Peripheral Segments II-V & VII-VIII: 12–15%; Marginal Segments I & VI: 8–10%. This indicate collapse of compensatory network. Segment I Centrality as an Effective Risk Gauge The betweenness centrality of Segment I (measure of its information-bridging role) predicted decompensation risk: 18.2%, 54.2%, and 83.3% in low, medium and high risk stratus, respectively. High-risk groups showed significantly elevated HRs for onset of ascites, hepatic encephalopathy and variceal bleeding; all $P < 0.05$. The findings were robust in sensitivity analyses (demographics and scanner-independent). **Conclusion:** This study pioneers a dynamic network paradigm for cirrhosis prognostication, shifting from isolated segmental biomarkers to system-level monitoring. The arterial-portal-equilibrium phase offers a critical window for detecting connectome-driven decompensation signals, with Segment I centrality emerging as a clinically important predictor.

Disclosures: Wang Zixing: Nothing to Disclose

2309 | REAL-WORLD TREATMENT PATTERNS AND UTILIZATION OF ALBUMIN AMONG PATIENTS WITH CIRRHOSIS AND ASCITES IN THE UNITED STATES

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Background: Decreases in serum albumin play a central role in the development and worsening of several complications of decompensated cirrhosis, including ascites, spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome-acute kidney injury (HRS-AKI). Human albumin (HA) infusions are commonly used in accordance with clinical guidelines—for example, after large-volume paracentesis (LVP), alongside antibiotics for SBP, or in combination with vasoconstrictors for HRS-AKI. However, patterns of HA use beyond these established indications remain poorly characterized. This study evaluates HA utilization among patients with decompensated cirrhosis and ascites in the United States. **Methods:** US adult patients with ICD-10-coded cirrhosis and concurrent ascites (loop or potassium-sparing diuretic use) who received ≥1 albumin infusion between Jan 2021–Dec 2023 were identified in the TriNetX database. Demographics, clinical characteristics, and treatment patterns (dosing, setting, and frequency) were examined, including the use of HA for cirrhosis-related complications in alignment with AASLD guidelines and international expert consensus. **Results:** A total of 18,937 adult patients were identified, with a median age of 59.0 years (IQR 49.0, 67.0) and 56.7% male. Alcohol-associated liver disease was the most common etiology of cirrhosis (65.0%). The median Charlson Comorbidity Index was 4.0 (IQR 3.0, 6.0). At identification (index of ascites diagnosis or diuretic receipt), patients had a MELD-3 score of 20.0 (IQR 15.0, 26.0) and a Child-Pugh score of 9.0 (IQR 8.0, 11.0). HA was administered primarily in the inpatient setting (90.8%), predominantly for LVP for ascites (59.0%), HRS-AKI (60.6%), and SBP (16.4%). Among patients with available dosing data (n = 5,562), the median per-encounter average albumin dose was 1.8 g/kg (IQR 0.6, 5.5) overall. Over 75% of patients received the vast majority of infusions (≥80%) acutely in a single care setting (inpatient or outpatient). HA use beyond AASLD guideline-recommended indications (e.g., LVP, SBP, or HRS-AKI), was less frequent. **Conclusion:** This real-world study highlights that HA use in the US remains largely acute and confined to inpatient care, primarily for guideline-based indications such as LVP, HRS-AKI, and SBP. Use across care settings was highly siloed, with minimal continuity into the outpatient setting, and limited adoption beyond well-established indications.

Table 1: Use of albumin across cirrhosis-related complications/events and infusion-related characteristics by care setting

Treatment Characteristics	Overall Cohort (N = 18,937)	Inpatient Setting[a] (N = 17,195)	Outpatient Setting[b] (N = 5,129)
Albumin use for complications/events based on both AASLD guidelines and international expert consensus			
Large-volume paracentesis (LVP), n (%)	11,564 (61.2%)	10,150 (59.0%)	3,693 (72.0%)
Hepatorenal syndrome-Acute kidney injury (HRS-AKI), n (%)	10,485 (55.4%)	10,413 (60.6%)	235 (4.6%)
Spontaneous bacterial peritonitis (SBP), n (%)	2,840 (15.0%)	2,813 (16.4%)	67 (1.3%)
Albumin use beyond guideline-based indications			
Hepatic encephalopathy (HE), n (%)	4,626 (24.4%)	4,525 (26.3%)	213 (4.2%)
Hyponatremia, n (%)	13,573 (71.7%)	13,256 (77.1%)	1,010 (19.7%)
Septic shock, n (%)	3,146 (16.6%)	3,129 (18.2%)	21 (0.4%)
Gastrointestinal bleeding, n (%)	5,022 (26.5%)	4,962 (28.9%)	97 (1.9%)
Muscle cramps, n (%)	100 (0.5%)	90 (0.5%)	12 (0.2%)
Acute-on-chronic liver failure (ACLF), n (%)	508 (2.7%)	502 (2.9%)	8 (0.2%)
Albumin infusion-related characteristics			
Infusions (per patient per year)			
Median [IQR]	3.0 [1.0, 7.0]	3.0 [1.0, 6.0]	2.0 [1.0, 6.0]
Total dose per patient per year (g/patient/year)			
n (dosing data available)	7,810 (41.2%)	6,946 (40.4%)	2,229 (43.5%)
Median [IQR]	198.8 [50.0, 637.5]	162.5 [50.0, 525.0]	150.0 [42.5, 550.0]
Average dose per encounter (g/kg/encounter)			
n (dosing data available)	5,562 (29.4%)	4,871 (28.3%)	1,753 (34.2%)
Median [IQR]	1.8 [0.6, 5.5]	2.1 [0.7, 6.1]	0.6 [0.3, 3.6]
Distribution of patients receiving albumin infusions by care setting[c], n (%)			
Inpatient			
0-20% of total infusions	2,377 (12.6%)	–	–
21-50% of total infusions	1,159 (6.1%)	–	–
51-80% of total infusions	1,018 (5.4%)	–	–
81-100% of total infusions	14,383 (76.0%)	–	–
Outpatient			
0-20% of total infusions	14,519 (76.7%)	–	–
21-50% of total infusions	1,284 (6.8%)	–	–
51-80% of total infusions	847 (4.5%)	–	–
81-100% of total infusions	2,287 (12.1%)	–	–

[a] Length of stay ≥ 2 days = inpatient care; [b] Length of stay ≤ 1 day (i.e., same-day discharge) = outpatient care
[c] Calculated based on the proportion of patients' total albumin infusions received in each setting

Disclosures: Cristina Coll-Ortega: Grifols: Employee, Rahul Rajkumar: Grifols: Consultant, Mallinckrodt Pharmaceuticals: Consultant, Thomas Ardiles: Grifols: Employee, Peter Nelson: Nothing to Disclose, Jonathan Lilley: Mallinckrodt: Consultant, Grifols: Consultant, Apeksha Shenoy: Boston Strategic Partners, Inc.: Employee, Boston Strategic Partners, Inc.: Independent Contractor, Miquel Barceló: Grifols: Employee, Dermot Whyms: Nothing to Disclose, Fiona McCarthy: Nothing to Disclose, Elisabet Viayna: Grifols SA: Employee

2310 | HEPATIC RECOMPENSATION AND PREDICTIVE FACTORS AFTER EUS-GUIDED THERAPY OR TIPS IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

Chenyue Zhang[1] You Deng[1] Weina Lu[2] Xinyan Zhao[1] Yu Wang[1] Peng Li[3] Jidong Jia[1] Junxiong Wang[3] Fuliang He[1], [1]Liver Research Center, Beijing Friendship Hospital, Capital Medical University, [2]Center of Liver Disease, Shijiazhuang fifth hospital, Shijiazhuang, China, [3]Department of Gastroenterology, Beijing Friendship Hospital, Capital Medical University

Background: Gastric fundus variceal bleeding (GFVB) is a life-threatening complication of portal hypertension and a major trigger of acute decompensation in cirrhosis. Both endoscopic ultrasound (EUS)-guided therapy and transjugular intrahepatic portosystemic shunt (TIPS) are effective for hemorrhage control, although each carries distinct risks and clinical implications. Hepatic recompensation, defined as a state of clinical and biochemical recovery, has emerged as a meaningful therapeutic endpoint. However, the long-

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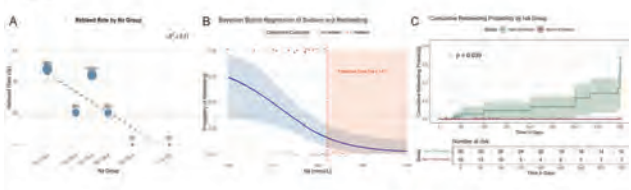
term rates of recompensation following EUS or TIPS remain unclear in patients with prior decompensation. Identifying real-world outcomes and potential predictors of recompensation may inform individualized secondary prevention strategies. **Methods:** We conducted a retrospective single-center study including 119 cirrhotic patients with at least one episode of GFVB and evidence of hepatic decompensation, treated between December 2017 and October 2024. Patients received either EUS-guided therapy (n = 56) or TIPS (n = 63). Hepatic recompensation was defined as the absence of decompensating events within one year. We compared recompensation rates and changes in liver function parameters between groups. Given the high rebleeding rate in the EUS group (26.8%, 15/56) and the high incidence of hepatic encephalopathy (HE) in the TIPS group (36.5%, 23/63), we performed univariate and multivariate logistic regression to identify risk factors. Binomial Curve and restricted cubic spline modeling were used to explore the optimal threshold of serum sodium. **Results:** At baseline, patients in the TIPS group had higher proportions of Child-Pugh class B/C (74.6% 47/63 vs. 42.9% 24/56, $p = 0.001$), portal vein thrombosis (61.9% 39/63 vs. 23.2% 14/56, $p < 0.001$), and ≥ 3 prior bleeding episodes (61.9% 39/63 vs. 14.3% 8/56, $p < 0.001$). Hepatic recompensation was achieved in 68% (81/119) of the overall cohort, with no significant difference between groups (EUS 67.9% 38/56 vs. TIPS 68.3% 43/63, $p > 0.999$). After a median follow-up period of 18.5 months (IQR 6–24), TIPS patients showed significantly higher total bilirubin (40.1 vs. 18.8 μmol/L, $p < 0.0001$), lower albumin (31.2 vs. 31.7g/L, $p < 0.0001$), and worsened Child-Pugh scores (median 8 vs. 7, $p < 0.001$). In the EUS group, no significant changes were observed in total bilirubin or Child-Pugh score ($p > 0.05$), while albumin levels improved significantly (from 32 to 33.8 g/L, $p = 0.005$). No independent predictors of HE were identified in the TIPS group. In contrast, in the EUS group, serum sodium emerged as an independent predictor of rebleeding. Sodium levels ≥ 141 mmol/L were associated with a significantly lower rebleeding risk [OR(95% CI): 0.82 (0.66–0.98), p = 0.041]. **Conclusion:** Both EUS and TIPS led to high rates of hepatic recompensation in GFVB. In the EUS group, higher serum sodium independently predicted lower rebleeding risk, Na 141 is a good cut-off.

Figure 1



(A) bubble plot demonstrated a strong linear correlation (R^2=0.71); (B) analysis confirmed a non-linear relationship; (C) Stratified analysis revealed a threshold effect at 141 mmol/L, with significantly lower cumulative rebleeding rates over 2 years in the ≥141 mmol/L subgroup (log-rank p=0.039)

Disclosures: Chenyue Zhang: Nothing to Disclose, You Deng: Nothing to Disclose, Weina Lu: Nothing to Disclose, Xinyan Zhao: Nothing to Disclose, Yu Wang: Nothing to Disclose, Peng Li: Nothing to Disclose, Jidong Jia: Nothing to Disclose, Junxiong Wang: Nothing to Disclose, Fuliang He: Nothing to Disclose

2311 | CONTEMPORARY NATURAL HISTORY OF COMPENSATED CIRRHOSIS: RESULTS: FROM THE POPULATION-BASED INDIANA CIRRHOSIS COHORT

Maaz Arif[1] Eric Orman[1] Lauren Nephew[1] Marwan Ghabril[1] LaKeisha Boyd[1] Yang Li[1] James Slaven[1] Naga Chalasani[1] Archita Desai[1], [1]Indiana University

Background: Contemporary real-world data on longitudinal trajectories of decompensation in patients with cirrhosis are lacking. We investigated a statewide cohort to characterize the contemporary natural history of patients with compensated cirrhosis. **Methods:** The Indiana Cirrhosis Cohort (ICC) was constructed digitally using the Indiana Network for Patient Care, a well-recognized, statewide health information exchange with manual validation of cirrhosis diagnosis. The ICC consists of 13,264 adults diagnosed with cirrhosis between 2018 and 2020; of whom 10,398 had compensated cirrhosis (study cohort). Baseline demographics, comorbidities, and cirrhosis-related characteristics were extracted. Outcomes were initial decompensation event [IDE: ascites, hepatic encephalopathy (HE), variceal bleeding (VB), or multiple concurrent events (MCE; 2+ events occurring within 30days)], hepatocellular carcinoma (HCC), liver transplant (LT), and death. Kaplan–Meier and log-rank tests assessed LT-free survival (TFS); multivariable logistic regression identified predictors of IDE. **Results:** The study cohort is described in the Figure. The median age was 61 years (IQR:53-68), 51% were male, and 86% were White. The most common etiologies were MASH (33%), viral hepatitis (25%), and alcohol-related liver disease (ALD, 21%). Baseline median MELD3.0 score was 11 (IQR:9 – 16). IDE or HCC occurred in 43% (n = 4,496) during a median follow-up of 4.4 years (IQR:2.7-5.8). Initial event was ascites in 34% (n = 1,515), HE in 34% (n = 1,531), MCE in 16% (n = 719), HCC in 12% (n = 550) and VB in 4% (n = 181). Time to IDE was 1.7 to 1.9 years from cirrhosis diagnosis. In a model fitted with age, sex, race, insurance, etiology, alcohol use disorder, and a categorical MELD 3.0 score, modeled as a binary variable (≥ 15 vs. < 15), an event was more likely in males vs. females (aOR 1.10, p = .02), in those with ALD vs. MASH (aOR 2.45, p < .001), and those with

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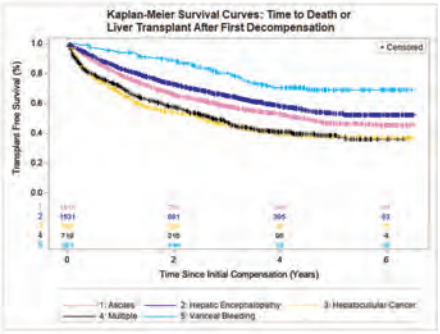
MELD3.0 ≥ 15 vs. < 15 (aOR 1.41, p < .001). Comorbid conditions were not significantly associated with decompensation/HCC. After IDE or HCC, median TFS ranged from 1.35 years (HCC) and 1.61 years (MCE) to 3.56 years (VB) and significantly differed by first event type on all pairwise comparisons, except between HCC and MCE (*log-rank* $p < 0.05$; Figure). **Conclusion:** In this contemporary, real-world cirrhosis cohort, decompensation or HCC occurs frequently within 3–5 years of initial diagnosis, with risk factors extending beyond MELD 3.0. The first decompensating event is not merely descriptive—it is prognostic, with outcomes shaped by both event phenotype and concurrent presentations, reinforcing the need for a dynamic model of cirrhosis progression, early risk stratification, and individualized care.

Variables	Study Cohort (N=10,398)
Age (years, median, IQR)	61 (53 – 68)
Male Gender (N, %)	6314 (51.1%)
Race (N, %)	
White	8859 (86.2)
Black or African American	986 (9.5)
Other	274 (3.6)
Asian or Pacific Islander	154 (1.3)
Insurance/Payer (N, %)	
Medicaid	4435 (42.68)
Commercial	2841 (27.32)
Medicare	2521 (24.25)
Other/Unknown	601 (5.75)
Etiology of Cirrhosis (N, %)	
NASH	3432 (32.9)
Hep C/Hep B	2563 (24.6)
Alcohol	2187 (21.0)
AIH/PBC/PSC	1267 (12.2)
HCT/Wilsons/A1At/Unknown	969 (9.3)
Comorbid Conditions (N, %)	
Diabetes Type II	3399 (32.7)
Coronary Artery Disease (CAD)	1600 (15.4)
Alcohol Use Disorder (AUD)	1419 (13.6)
Obesity	730 (7.0)
Substance Use Disorder (SUD)	653 (6.3)
MELD 3.0 score (median, IQR)	11 (9 – 16)



Disclosures: Maaz Arif: Nothing to Disclose, Eric Orman: Sitero: Consultant, Biovie: Advisor, Lauren Nephew: NovoNordisk: Consultant, Marwan Ghabril: Nothing to Disclose, LaKeisha Boyd: Nothing to Disclose, Yang Li: Nothing to Disclose, James Slaven: Nothing to Disclose, Naga Chalasani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Archita Desai: Nothing to Disclose

2312 | COMPARISON OF STANDARD-DOSE REPEATED BOLUS INJECTION VS. LOW-DOSE CONTINUOUS INTRAVENOUS INFUSION OF TERLIPRESSIN FOR ACUTE ESOPHAGEAL VARICEAL BLEEDING IN PATIENTS WITH LIVER CIRRHOSIS: A PROSPECTIVE MULTICENTER RANDOMIZED TRIAL

Hyung Joon Yim[1] Seong Hee Kang[1] Taehyung Kim[2] Moon Young Kim[3] Seul Ki Han[3] Yeon Seok Seo[2] Sun Young Yim[2] sang gyune kim[4] Seong Kyun Na[5] Hanah Lee[6] Eileen Yoon[7] Jae Young Jang[8] Young-Sun Lee[9] Young Kul Jung[1] Ji Hoon Kim[9], [1]Korea University Ansan Hospital, [2]Korea University Anam Hospital, [3]Yonsei University Wonju Severance Hospital, [4]Soon Chun Hyang University Bucheon Hospital, [5]Inje University Sangye Paik Hospital, [6]Chung Ang University Hospital, [7]Hangyang University Hospital, [8]Soon Chun Hyang University Seoul Hospital, [9]Korea University Guro Hospital

Background: Acute esophageal variceal bleeding (AVB) is one of the most serious complications of liver cirrhosis. For the emergent management of variceal bleeding, administration of a vasoconstrictor is essential for hemostasis together with endoscopic variceal ligation (EVL). Standard-dose repeated bolus injection (SDRBI) of terlipressin 4-6 times daily is most widely employed before and after EVL, but the adverse effects of terlipressin cannot be overlooked. To minimize the ischemic side effect, low-dose continuous infusion (LDCI) of terlipressin has been proposed for hepatorenal syndrome in patients with liver cirrhosis. However, data from prospective comparisons between the two methods for AVB are sparse. This study aims to compare the safety and efficacy of the two methods for the management of AVB. **Methods:** This study is a randomized controlled trial to compare SDRBI and LDCI of terlipressin in patients with AVB. A total of 125 patients were enrolled and randomly assigned to the SDRBI group (n = 63, 1 mg bolus injection every 6 hours after initial 2 mg of terlipressin) or LDCI group (n = 62, 2 mg/day of terlipressin infusion) after EVL. Patients with gastric varices on the fundus, failure of initial endoscopic therapy, or advanced hepatocellular carcinoma were excluded. **Results:** The baseline characteristics of the patients were not significantly different. Re-bleeding incidence after initial successful EVL was observed for 5 days. The success rate of maintaining hemostasis was 98.4% in both groups (Crude odd ratio = 0.98 [0.06-6.09], P = 0.991). One patient died in the SDRBI group. Decrease of Hb more than 3 g/dL or adjusted blood requirement index over 0.75 to maintain Hb > 8.0 g/dL were observed in 7 patients (11.1%) in the SDRBI and 9 (14.5%) in the LDCI group (P = 0.763), respectively, without newly developed hematemesis or melena. The overall incidence of gastrointestinal, cardiovascular, metabolic, or neurologic adverse events was significantly higher in the SDRBI group than in the LDCI group during 5 days (P < 0.05). **Conclusion:** Compared with SDRBI, LDCI of terlipressin shows comparable efficacy and better safety for managing AVB in patients with liver cirrhosis.

Disclosures: Hyung Joon Yim: Nothing to Disclose, Seong Hee Kang: Nothing to Disclose, Taehyung Kim: Nothing to Disclose, Moon Young Kim: Nothing to Disclose, Seul Ki Han: Nothing to Disclose, Yeon Seok Seo: Nothing to Disclose, Sun Young Yim: Nothing to Disclose, sang gyune kim: Nothing to Disclose, Seong Kyun Na: Nothing to Disclose, Hanah Lee: Nothing to

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2313 | OUTCOMES OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS) CREATION PRIOR TO SURGERY IN PATIENTS WITH CIRRHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Archit Garg[1] Mehak Bassi[1] Aashi Garg[2] Aadhithyaraman Santharaman[1] Abhishek Chouthai[1] Marcella Pimpinelli[1] umesh bhagat[3] Arkady Broder[1], [1]Saint Peter's University Hospital, [2]Boston University School of Public Health, [3]Cleveland Clinic, Cleveland

Background: Patients with cirrhosis undergoing surgery have higher rates of morbidity and mortality. Transjugular intrahepatic portosystemic shunt (TIPS) placement prior to surgery has shown favorable postoperative outcomes. The objective of our study was to compare the outcomes of TIPS versus no TIPS prior to surgery in cirrhotic patients. **Methods:** e searched multiple databases including Medline, Web of Science, Cochrane Library, Pubmed, Embase and conference proceedings from inception through November 2024 for articles reporting outcomes of TIPS vs no TIPS in cirrhotic patients undergoing surgical intervention. We studied liver failure, hepatic encephalopathy, postoperative ascites, mortality rates and blood transfusion requirements. Standard meta-analysis methods were employed using the random-effects model, and heterogeneity was studied by I2 statistics. **Results:** We analyzed 7 retrospective studies involving 561 subjects. 255 patients (70.56% males and mean age 58.13 years) in the TIPS group and 306 subjects (67.32% males and mean age 62.57 years) in the TIPS group. Postoperative ascites was significantly lower in TIPS group, 53.1% [CI 41.2-65.0%; I2 = 0.0%] compared to no TIPS group, 89.4% [CI 55.1-123.8%; I2 = 80.7%] with RR 0.46 [0.26-0.81; p 0.023]. TIPS were associated with lower incidence of hepatic encephalopathy, 49.0% [CI 38.9-59.1%; I2 = 15.0%] compared to no TIPS 58.3% [CI 38.9-77.8%; I2 = 73.9%]; RR 0.72 [0.56-0.93; p 0.022]. The pooled rate of liver failure was 40.9% [CI 34.9-46.8%; I2 = 0.0%] in TIPS group and 47.8% [10.3-85.3%; I2 = 84.1%] in no TIPS group with RR 0.52 [0.25-01.09; p 0.068]. The infection rates were comparable between the two groups, 7.3% [CI 41.6-73.0%; I2 = 62.6%] with TIPS and 58.3% [CI 38.9-77.8%; I2 = 73.9%] with no TIPS; RR 0.87 [0.40-1.89; p 0.673]. Intraoperative blood transfusion requirement was 53% [CI 42.6-63.5%; I2 = 6.6%] with TIPS and 51.5% [CI 33-70%; I2 = 73.6%] with no TIPS; RR 1.11 [0.69-1.78; p 0.585]. The pooled postoperative blood transfusion requirement was 48.7% [CI 23.7-73.8%; I2 = 61.4%] in TIPS group and 50.0% [CI 4.9-95.1%; I2 = 94.8%] in no TIPS group with RR 0.71 [0.31-1.63; p 0.330]. The bleeding complication rate with TIPS and no TIPS was 40.2% [CI 7.5-88.0%; I2 = 76.2] and 53.1% [CI 12.2-94.0%; I2 = 88.1%] respectively, RR 0.66 [0.03-13.88; p 0.692]. The overall mortality rate was 45.6% [CI 33.2-57.9; I2 = 54.7%] with TIPS compared to 54.5% [CI 38.9-70%; I2 = 82.4%] with no TIPS; RR 0.70 [0.44-1.09; p 0.095]. Further results are summarized in Table 1. **Conclusion:** Based on this meta-analysis, TIPS demonstrated significantly lower rates of hepatic encephalopathy (49% vs 58.3%) and ascites (53.1% vs 89.4%) compared to those who did not undergo TIPS prior to surgery. There was no significant difference in mortality rates. Preoperative TIPS can be considered as a bridge prior to surgery to lower the rates of postoperative adverse events.

Outcomes	Pooled rates (95% Confidence Interval), I2		Risk Ratio (95% CI); I2%; Studies	p-value
	TIPS	No TIPS		
Intraoperative Blood Transfusion	53.0% (42.6-63.5%); 6.6%	51.5% (33.0-70.0%); 73.6%	1.11 (0.69-1.78); 1.5%; 5 studies	0.585
Post-Op Blood Transfusion	48.7% (23.7-73.8%); 61.4%	50.0% (4.9-95.1%); 94.8%	0.71 (0.31-1.63); 64.5%; 4 studies	0.330
Liver Failure	40.9% (34.9-46.8%); 0.0%	47.8% (10.3-85.3%); 84.1%	0.52 (0.25-1.09); 2.7%; 4 studies	0.068
Hepatic Encephalopathy	49.0% (38.9-59.1%); 15.0%	58.3% (38.9-77.8%); 73.9%	0.72 (0.56-0.93); 0.0%; 6 studies	0.022
Postoperative Ascites	53.1% (41.2-65.0%); 0.0%	89.4% (55.1-123.8%); 80.7%	0.46 (0.26-0.81); 15.2%; 4 studies	0.023
Infectious Complications	57.3% (41.6-73.0%); 62.6%	60.1% (36.5-83.7%); 86.4%	0.87 (0.40-1.89); 60.8%; 6 studies	0.673
Bleeding Complications	40.2% (-7.5-88.0%); 76.2%	53.1% (12.2-94.0%); 88.1%	0.66 (0.03-13.88); 83.8%; 3 studies	0.614
Mortality	45.6% (33.2-57.9%); 54.7%	54.5% (38.9-70.0%); 82.4%	0.70 (0.44-1.09); 9.6%; 7 studies	0.095
Any Type of Leak from surgical site	39.6% (7.8-71.4%); 0.0%	41.1% (-13.6-95.9%); 0.0%	0.92 (0.01-116.98); 0.0%; 2 studies	0.863

Disclosures: Archit Garg: Nothing to Disclose, Mehak Bassi: Nothing to Disclose, Aashi Garg: Nothing to Disclose, Aadhithyaraman Santharaman: Nothing to Disclose, Abhishek Chouthai: Nothing to Disclose, Marcella Pimpinelli: Nothing to Disclose, umesh bhagat: Nothing to Disclose, Arkady Broder: Nothing to Disclose

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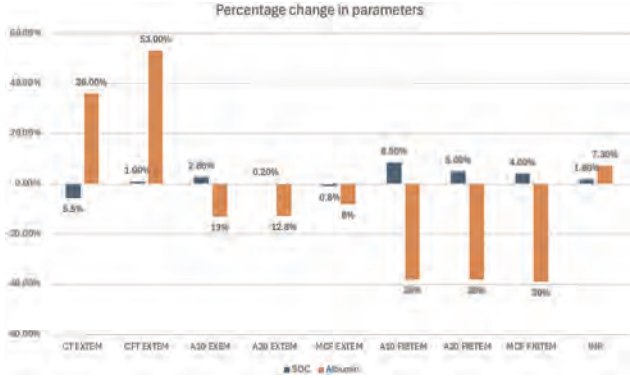
2314 | COAGULATION PARAMETERS WITH ALBUMIN IN DECOMPENSATED CIRRHOSIS (COPA-D): AN OPEN-LABEL RANDOMIZED CONTROL TRIAL

Omkar Rudra[1] Ayush Jain[1] SAURAV PAUL[1] Jaifrin Daniel[1] Babu Lal Meena[1] VINOD ARORA[1] Chhagan Bihari[1] Varsha Shasthry[1] Jaswinder Maras[1] Imran Khan[1] Satyakam Pandey[1] Manoj Sharma[1] GURESH KUMAR[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences

Background: Human albumin solution (HAS) has multiple indications in decompensated cirrhosis (DC); long-term administration serves as a disease-modifier. Cirrhosis is a state of dysregulated coagulation. Whether HAS infusion alters coagulation parameters and has clinical relevance was prospectively and dynamically studied in a randomised clinical trial. **Methods:** DC patients (>18yr.) with serum albumin ≤2.5 g/dl, were randomized to standard-of-care (SOC) plus albumin (Gr. A) or SOC arm (Gr. B). Those in albumin arm received daily 20% HAS to raise serum albumin ≥3 g/dl along with standard medical treatment (SMT). Those in SOC arm received SMT without HAS. Coagulation was assessed by a battery of tests and rotational thromboelastometry (ROTEM) at day 0, 1 and 3. Clinical bleeding events were recorded for 3 days. **Results:** 120 DC patients were enrolled; 9 [3 (7%) in albumin, 6 (12%) in SOC] were excluded as they required urgent coagulation correction for therapeutic interventions. 98 patients (albumin-50, SOC-48) with complete follow-up is analysed per-protocol. Baseline parameters including MELD score (17.2±4.9 in albumin vs 17.2±4.7 in SOC; p=0.970) was comparable. Mean dose of albumin received was 55.8 gram on day 0, 39.4 gram on day 1, 30 gram on day 2 and 23.6 gram on day 3. 60% patients received full prescribed dose of albumin and 63% achieved target albumin levels. After HAS infusion, albumin arm compared to SOC arm showed increase in clotting time (CT) of the extrinsically activated thromboelastometric test (EXTEM) {increase by 36% vs. reduction by 5.5%, p <0.001}, clot formation time (CFT) EXTEM {increase by 53% vs. decrease by 1%, p<0.001} by day 3. In albumin arm, EXTEM A10, A20 reduced by 13% and 12.8% versus increase by 2.8% and 0.2% in SOC arm {p<0.001 for both}. The maximum clot firmness (MCF) EXTEM reduced by 8% in albumin arm vs.0.8% in SOC, p=0.003. Fibrinogen-based thromboelastometry (FIBTEM) showed 38% reduction in A10 and A20 in albumin arm versus an increase by 8.5% and 5% respectively in the SOC arm {p<0.001 for both}. MCF FIBTEM showed a 39% reduction with albumin and 4% increase in SOC {p<0.001}. INR increased by 7.3% with albumin and 1.8% in SOC {p = 0.029}. No clinically significant muco-cutaneous or spontaneous bleeding developed in any of the patients. **Conclusion:** HAS in standard doses causes significant derangement in ROTEM-based coagulation parameters within 24-72 hours in patients with decompensated cirrhosis. Deranged coagulation indices may pose clinical challenges if patients receive regular albumin infusions during hospitalizations. Monitoring of coagulation by ROTEM and clinical bleeding events is advisable in DC patients receiving HAS. [Trial registration - NCT05937048]



Disclosures: Omkar Rudra: Nothing to Disclose, Ayush Jain: Nothing to Disclose, SAURAV PAUL: Nothing to Disclose, Jaifrin Daniel: Nothing to Disclose, Babu Lal Meena: Nothing to Disclose, VINOD ARORA: Nothing to Disclose, Chhagan Bihari: Nothing to Disclose, Varsha Shasthry: Nothing to Disclose, Jaswinder Maras: Nothing to Disclose, Imran Khan: Nothing to Disclose, Satyakam Pandey: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, GURESH KUMAR: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

2315 | CORRELATION OF RACE-NEUTRAL GLOMERULAR FILTRATION RATE ASSESSMENT IN LIVER DISEASE (GRAIL 2.0) WITH HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY REVERSAL IN PATIENTS RECEIVING TERLIPRESSIN

R. Todd Frederick[1] Kavish Patidar[2] Giovanna Saracino[3] Richard Wu[4] Sanaz Cardoza[4] Melissa Thompson Bastin[4] Sumeet Asrani[3], [1]California Pacific Medical Center, San Francisco, CA, USA, [2]Division of Gastroenterology and Hepatology, Houston Methodist Hospital, Houston, TX, USA, [3]Baylor University Medical Center, Baylor Scott and White, Dallas, TX, USA, [4]Mallinckrodt Pharmaceuticals, Bridgewater, NJ, USA

Background: Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a life-threatening but potentially reversible condition that occurs in patients (pts) with

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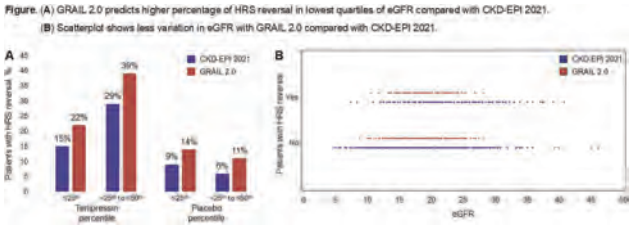
decompensated cirrhosis and ascites. Terlipressin (terli), the only FDA-approved therapy for adult pts with HRS-AKI, can reverse HRS and improve kidney function. While pts with low baseline serum creatinine (SCr) tend to respond more favorably to terli, SCr alone is a poor estimate of kidney dysfunction in pts with cirrhosis for assessment of optimal initiation of terli. GRAIL 2.0, a recently validated race-neutral equation in pts with cirrhosis designed to estimate glomerular filtration rate (GFR), has shown improved performance in predicting true GFR compared with CKD-EPI 2021. **Methods:** Pts with available baseline characteristics needed to calculate GRAIL 2.0 and CKD-EPI 2021 were pooled from the Phase III OT-0401 (NCT00089570), REVERSE (NCT01143246), and CONFIRM (NCT02770716) studies of terli versus placebo in pts with HRS-AKI. Estimated GFR (eGFR) was calculated using GRAIL 2.0 and CKD-EPI 2021. The main outcome of interest was HRS reversal. Scatter plots were constructed to visualize the relationship between eGFR calculations, treatment with terli, and clinical outcomes. **Results:** Among evaluable pts (terli, n = 323; placebo, n = 238), GRAIL 2.0-based eGFR identified HRS responders over a broader range of eGFR compared to CKD-EPI 2021. More pts in the 25th and 50th percentiles (low eGFR) by GRAIL 2.0 achieved HRS reversal than with CKD-EPI 2021 (Figure A). The variance of GRAIL 2.0-based eGFR was smaller, providing a more precise estimate than with CKD-EPI 2021 across terli and placebo groups (Figure B). **Conclusion:** GRAIL 2.0 identified more pts with HRS reversal despite lower eGFR compared with CKD-EPI 2021. Additionally, GRAIL 2.0 estimated GFR with smaller variance, suggesting greater consistency and potentially greater precision. However, GRAIL 2.0-based assessment did not enhance overall ability to predict terli response. Notably, our study population had already received substantial exogenous albumin and exhibited near normal serum albumin levels at enrollment, which could negatively influence GRAIL 2.0 performance. These results suggest that HRS reversal, while more common in pts with lower baseline SCr, may not be due entirely to a higher baseline eGFR and that other patient characteristics or factors may be contributing to response. Further validation of GRAIL 2.0 should be conducted in pts with advanced cirrhosis.



Disclosures: R. Todd Frederick: Mallinckrodt Pharmaceuticals: Consultant, AstraZeneca: Grant/Research Support, River 2 Renal Corp.: Grant/Research Support, Miromatrix Medical: Consultant, Salix Pharmaceuticals: Grant/Research Support, TenNor Therapeutics: Consultant, Kavish Patidar: Madrigal Pharmaceuticals: Medical Advisory Board, Mallincrodt Pharmaceuticals: Consultant, Giovanna Saracino: Nothing to Disclose, Richard Wu: mallinckrodt: Employee, Sanaz Cardoza: Mallinckrodt: Full Time Employee, Melissa Thompson Bastin: Nothing to Disclose, Sumeet Asrani: Nothing to Disclose

2316 | CHARACTERIZATION AND PROGNOSTIC IMPLICATIONS OF BIOMARKERS OF SYSTEMIC INFLAMMATION AND PORTAL HYPERTENSION ACROSS DISTINCT STAGES OF CIRRHOSIS

Georg Kramer[1] Dalila Costa[2] Benedikt Hofer[1] Ana Frias[2] Ricardo Silvestre[2] Joana Camoesneves[2] Joao Belmiro Martins[2] Kerstin Zinober[1] Vlad Taru[1] Mathias Jachs[1] Lukas Hartl[1] Lorenz Balcar[1] Christian Sebesta[1] Marlene Hintersteininger[1] Paul Thöne[1] Nina Dominik[1] Georg Semmler[1] Benedikt Simbrunner[1] Michael Trauner[1] Mattias Mandorfer[1] Carla Rolanda[2] Thomas Reiberger[1], [1]Medical University of Vienna, [2]University of Minho

Background: Systemic inflammation (SI) and portal hypertension (PH) are prominent drivers of disease progression in cirrhosis. In this study, we analyzed stage-specific differences of surrogates of PH/endothelial dysfunction (von Willebrand Factor Antigen [vWF]) and SI (Interleukin-6 [IL6]) in compensated (CC), decompensated (DC) and recompensated (RC) cirrhosis and their prognostic value for disease progression or regression. **Methods:** Patients with cirrhosis were prospectively enrolled at two tertiary centers (Vienna, Austria, and Braga, Portugal) between 01/2017 and 12/2023 and underwent measurement of IL-6 and vWF. Biomarker levels were compared cross-sectionally across CC, DC and RC. In CC, the primary endpoint was first hepatic decompensation. In DC, progression was defined as a composite endpoint comprising further decompensation or acute-on-chronic liver failure, while regression was defined as achieving recompensation (as per Baveno VII). Prognostic value of IL-6 and vWF was evaluated using uni- and multivariable Fine-Gray competing risks regression models, adjusted for MELD. **Results:** Among the 394 included patients (mean age 59.3 ± 10.6 years; 66.6% male; alcohol-related liver disease (ALD) in 65.7%), 88 patients (22.3%) had CC, 57 (24.5%) RC and 249 (63.2%) DC. MELD did not differ significantly between CC and RC (median 9 [IQR: 7-11] vs. 9 [IQR: 8-11], p = 0.845) but was significantly higher in DC (12 [IQR: 10-15], p < 0.001). IL6 levels

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were numerically lowest in RC (6.3 vs. CC: 8.7 pg/mL, $p = 0.194$) and highest in DC (21.4 pg/mL, $p < 0.001$ vs. CC/RC). A similar pattern was observed for vWF, which was comparable in CC (median: 211%) and RC (median: 192%, $p = 0.503$ vs. CC), yet significantly elevated in DC (median: 307%; $p < 0.001$ vs. CC/RC). During a median follow up of 24 (IQR: 14-32) months, 23 (26.1% of CC) patients experienced first decompensation, 70 (28.1% of DC) patients had disease progression and 45 (19.8% of DC with abstinent ALD or cured/suppressed viral hepatitis) achieved recompensation. In CC, IL-6 (subdistribution hazard ratio [SHR]: 1.03, $p = 0.010$) and vWF (SHR: 1.01, $p = 0.014$) were associated with first decompensation in univariable analysis, yet did not remain significant predictors after adjusting for MELD. In DC, IL-6 (adjusted SHR [aSHR]: 1.09, $p < 0.001$) and vWF (aSHR: 1.04, $p = 0.031$) remained independent risk factors for disease progression. Neither IL-6 nor vWF predicted recompensation. **Conclusion:** Surrogates of SI and PH are markedly elevated in DC and both, IL-6 and vWF, predict disease progression independently of liver function (MELD). In CC, IL-6 and vWF were also associated with the occurrence of first hepatic decompensation. Notably, recompensated patients tended to have lower levels of SI than those with CC, possibly reflecting disease trajectory.

Disclosures: Georg Kramer: Nothing to Disclose, Dalila Costa: Nothing to Disclose, Benedikt Hofer: IPSEN: Travel support, FALK: Travel support, Ana Frias: Nothing to Disclose, Ricardo Silvestre: Nothing to Disclose, Joana Camoesneves: Nothing to Disclose, Joao Belmiro Martins: Nothing to Disclose, Kerstin Zinober: Nothing to Disclose, Vlad Taru: Nothing to Disclose, Mathias Jachs: Gilead Sciences Inc.: Speaker and/or consultant, Echosens Inc.: Speaking and Teaching, Lukas Hartl: Nothing to Disclose, Lorenz Balcar: Nothing to Disclose, Christian Sebesta: Nothing to Disclose, Marlene Hintersteininger: Nothing to Disclose, Paul Thöne: Nothing to Disclose, Nina Dominik: Nothing to Disclose, Georg Semmler: Amgen: Travel Support, Benedikt Simbrunner: Nothing to Disclose, Michael Trauner: Albireo: Grant/Research Support, Alnylam: Grant/Research Support, Cymabay: Grant/Research Support, Falk: Grant/Research Support, Gilead: Grant/Research Support, Intercept: Grant/Research Support, MSD: Grant/Research Support, Takeda: Grant/Research Support, Ultragenyx: Grant/Research Support, Abbvie: Travel Grants, Falk: Travel Grants, Gilead: Travel Grants, Intercept: Travel Grants, Janssen: Travel Grants, Abbvie: Advisor, Albireo: Advisor, BiomX: Advisor, Boehringer Ingelheim: Advisor, Falk Pharma GmbH: Advisor, Genfit: Advisor, Gilead: Advisor, Hightide: Advisor, Intercept: Advisor, Ipsen: Advisor, Janssen: Advisor, MSD: Advisor, Novartis: Advisor, Phenex: Advisor, Pliant: Advisor, Regulus: Advisor, Siemens: Advisor, Shire: Advisor, BMS: Speaking and Teaching, Falk: Speaking and Teaching, Gilead: Speaking and Teaching, Intercept: Speaking and Teaching, Ipsen: Speaking and Teaching, Madrigal: Speaking and Teaching, MSD: Speaking and Teaching, Medical Universities of Graz and Vienna: Co.Inventor of patents for medical use of norUDCA filed by, Genentech: Grant/Research Support, Mirum: Advisor, Agomab: Advisor, Chemomab: Advisor, ProQR Therapeutics: Advisor, Rectify: Advisor, Mattias Mandorfer: Echosens: Speaking and Teaching, Echosens: Grant/Research Support, Ipsen: Consultant, Takeda: Consultant, Takeda: Speaking and Teaching, W.L. Gore & Associates: Speaking and Teaching, Eli Lilly: Consultant, Eli Lilly: Speaking and Teaching, Carla Rolanda: Nothing to Disclose, Thomas Reiberger: Nothing to Disclose

2317 | CACHEXIA IS AN INDEPENDENT PREDICTOR OF MORTALITY IN PATIENTS WITH CIRRHOSIS

Takao Miwa[1] Goki Suda[2] Ryosuke Tateishi[3] Tatsunori Hanai[4] Masatsugu Ohara[2] Yasuhiro Hagiwara[3] Shinji Unome[4] Kazuya Okushin[3] Mina Nakagawa[5] Naoya Sakamoto[2] Masahito Shimizu[4], [1]Gifu University Hospital, [2]Hokkaido University, [3]The University of Tokyo, [4]Gifu University, [5]Science Tokyo Hospital

Background: Cachexia is a systemic response syndrome characterized by disabling wasting during disease progression. We hypothesized that the diagnosis of cachexia can stratify the risk of mortality independent of liver functional reserves by reflecting devastating condition of cirrhosis. Furthermore, it is necessary to clarify whether cirrhosis is a predisposing condition for cachexia. This study aimed to elucidate factors associated with cachexia in patients with cirrhosis and to examine the impact of cachexia on patient survival. **Methods:** This multicenter cohort study included patients with cirrhosis admitted to two distinct institutes in Japan. Cachexia was diagnosed according to the criteria proposed by the Asian Working Group for Cachexia assessing weight loss, body mass index, anorexia, handgrip strength, and C-reactive protein. Factors associated with cachexia and the prognostic impact of cachexia were assessed using logistic regression and Cox proportional hazards regression, respectively. **Results:** Of the 723 patients enrolled (median [interquartile range] age, 71 [64–77] years; 456 [63%] were male; and 390 [54%] had viral hepatitis), 200 (28%) met the criteria for cachexia diagnosis, with the prevalence increasing with Child–Pugh class from A (17%) to B (40%) and C (66%). Multivariable logistic regression analysis revealed that age and indices of liver function reserve, including Child–Pugh score (adjusted odds ratio, 1.59; 95% confidence interval

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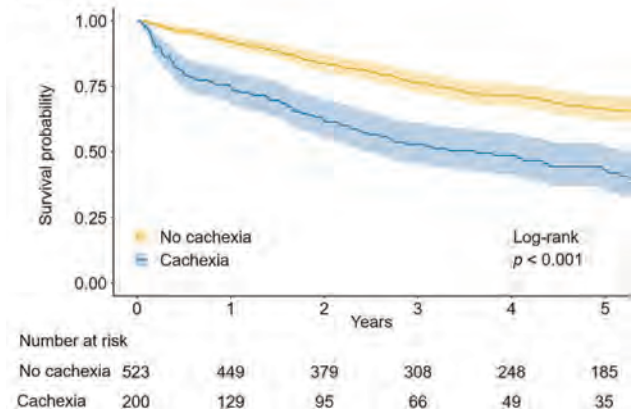
[CI], 1.43–1.76; $p < 0.001$), were associated with cachexia, whereas sex, etiology of cirrhosis, and complications with hepatocellular carcinoma were not. During a median follow-up period of 3.2 years, 264 (37%) patients died. Patients with cachexia had significantly lower survival rates than those without cachexia (overall survival rates at 1-, 3, and 5 years: 75%, 53%, and 43% vs. 92%, 76%, and 66%) (Figure 1). Multivariable Cox regression analyses showed that cachexia was independently associated with increased mortality (adjusted hazard ratio, 1.59; 95% CI, 1.24–2.12; $p < 0.001$), along with factors related to liver function, hepatocellular carcinoma, and alcohol-associated liver disease as the etiology. **Conclusion:** Cachexia is associated with poor liver function in patients with cirrhosis and is an independent prognostic factor.

Figure 1



Disclosures: Takao Miwa: Nothing to Disclose, Goki Suda: Nothing to Disclose, Ryosuke Tateishi: EA Pharma: Speaking and Teaching, MSD: Speaking and Teaching, Aska Pharma: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Abbvie: Speaking and Teaching, Eisai: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Covidien: Speaking and Teaching, Bayer: Speaking and Teaching, Century Medical: Speaking and Teaching, Canon Medical: Speaking and Teaching, Asahikasei Pharma: Speaking and Teaching, Terumo: Speaking and Teaching, TechsoMed: Speaking and Teaching, Sumitomo Pharma: Speaking and Teaching, Taisho Pharmaceutical: Speaking and Teaching, Daiichi-Sankyo: Speaking and Teaching, Chugai: Speaking and Teaching, Fujifilm: Speaking and Teaching, Tatsunori Hanai: Nothing to Disclose, Masatsugu Ohara: Nothing to Disclose, Yasuhiro Hagiwara: Nothing to Disclose, Shinji Unome: Nothing to Disclose, Kazuya Okushin: Nothing to Disclose, Mina Nakagawa: Nothing to Disclose, Naoya Sakamoto: Gilead Sciences, Eisai, AbbVie, Chugai: Speaking and Teaching, Masahito Shimizu: Nothing to Disclose

2318 | PREDICTING CARDIOVASCULAR OUTCOMES AFTER TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS) USING MACHINE LEARNING: AN ALTA GROUP STUDY

Shoma Bommena[1] Lisa VanWagner[2] Elizabeth Verna[3] Justin Boike[4] Kanti Kolli[5] Bartley Thornburg[6] Adnan Said[7] Catherine Frenette[8] Aparna Goel[9] Jennifer Lai[5] Sumeet Asrani[10] Consuelo Soldevila-Pico[11] Mary Thomson[12] Arun Jesudian[13] Adam Deising[14] Sonali Paul[15] Douglas Simonetto[16] Erin Spengler[17] Mehnush Hameie[6] Cynthia Padilla[6] Dyanna Gregory[2] Mike Fallon[1], [1]University of Arizona, [2]University of Texas Southwestern Medical Center, [3]Columbia University Medical Center, [4]Northwestern Memorial Hospital/ Northwestern University, [5]University of California San Francisco, [6]Northwestern University, [7]University of Wisconsin School of Medicine and Public Health, [8]Gilead Sciences, Inc., [9]Stanford University Medical Center, [10]Liver Consultants of Texas, [11]University of Florida, [12]University of Minnesota, [13]Weill Cornell Medicine, [14]Scripps Clinic, [15]University of Chicago Medical Center, [16]Mayo Clinic Rochester, [17]University of Wisconsin

Background: Cardiovascular complications after TIPS are associated with adverse outcomes; yet, identifying patients at risk remains challenging. Prior studies primarily focused on predictors of heart failure (HF), without comprehensively evaluating a broader spectrum of cardiovascular events (CVEs). Validated machine learning (ML) models for predicting these outcomes are also lacking. We assessed whether a ML model using baseline clinical data from a large multicenter prospective cohort could predict post-TIPS CVEs in patients with cirrhosis. **Methods:** Advancing Liver Therapeutic Approaches in Portal Hypertension (ALTA) is a multicenter prospective study across 13 U.S. centers of adults ($\geq$18 years) scheduled for TIPS from 7/2019 to 1/2025. Participants with TIPS for any indication without prior liver transplantation (LT) were included in this analysis. The primary outcome was post-TIPS CVE, defined as decompensated HF, myocardial infarction, cardiac arrest, arrhythmia requiring intervention, or stroke. We assessed the association between CVEs and all-cause mortality using competing risk analysis, with LT as a competing event. ML models, including Elastic Net, Least Absolute Shrinkage and Selection Operator, Random Forest (RF), Gradient Boosting Machine, and Support Vector Machine, were developed and internally validated. The training set included 635 participants and testing set 157. Model performance was assessed via 5-fold cross-validation, with area under the receiver operating characteristic curve (AUROC) as the primary metric. **Results:** We included

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792 participants (median age 59.2 years; 57.3% male, 75% Caucasian, 21% Hispanic). Median MELD was 10.9. Over median follow-up of 262 days, 64 participants (8.1%) developed post-TIPS CVEs; 8 (1.0%) had HF requiring hospitalization. Participants with CVEs were older and had higher MELD, more ascites, impaired renal function, and more cardiovascular risk factors. Mortality was significantly higher among those with CVEs (43% vs.17%, $P < 0.001$; Fig.1a), with a 1.5-fold increased sub-hazard for death after adjusting for MELD and TIPS indication (sHR 1.5, 95% CI 1.01-2.3). Among ML models, RF showed the highest predictive performance for post-TIPS CVEs, with an AUROC of 0.811 (95% CI, 0.74-0.93; Fig.1b) and 86% accuracy. Top predictors included renal dysfunction and history of HF, valvular disease, or atrial fibrillation. **Conclusion:** In this large US cohort, CVEs occurred in 8.1% of participants and were independently associated with increased post-TIPS mortality. ML models, particularly RF, showed high specificity in predicting post-TIPS CVEs using readily available clinical variables, especially renal dysfunction and cardiac history. Ongoing work incorporating echocardiographic features and external validation aims to enhance predictive performance, enabling more accurate pre-TIPS cardiovascular risk stratification and informed patient selection.

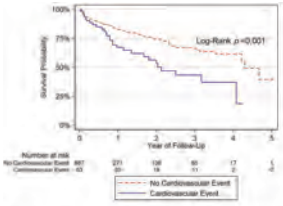

Fig. 1a: Kaplan-Meier Curves for post-TIPS CVE vs. No CVE

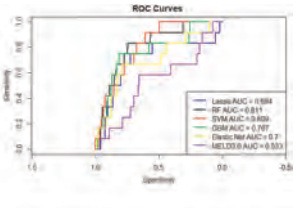

Fig. 1b: ROC Curves for Predicting Post-TIPS CVE

Disclosures: Shoma Bommena: Nothing to Disclose, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, Elizabeth Verna: Nothing to Disclose, Justin Boike: W. L. Gore and Associates: Grant/Research Support, Eurofins Transplant Genomics: Advisor, Echosens: Consultant, W. L. Gore and Associates, Inc.: Consultant, Kanti Kolli: Nothing to Disclose, Bartley Thornburg: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Advisor, Catherine Frenette: Gilead Sciences: Employee, Aparna Goel: Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Sumeet Asrani: Nothing to Disclose, Consuelo Soldevila-Pico: Nothing to Disclose, Mary Thomson: Nothing to Disclose, Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant, Mallinckrodt Pharmaceuticals: Consultant, Mallinckrodt Pharmaceuticals: Speaking and Teaching, Adam Deising: Nothing to Disclose, Sonali Paul: Intercept: Grant/Research Support, Target PharmaSolutions: Grant/Research Support, Eli Lilly: Stock - publicly traded company, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Erin Spengler: Nothing to Disclose, Mehnush Hameie: Nothing to Disclose, Cynthia Padilla: Nothing to Disclose, Dyanna Gregory: Nothing to Disclose, Mike Fallon: Nothing to Disclose

2319 | TRAINING AND VALIDATION OF THE PHASE ANGLE (PA)/C-REACTIVE PROTEIN (CRP) INDEX (PAC-I) AS A NOVEL NON-INVASIVE TOOL ACCURATELY PREDICTING SARCOPENIA AND FURTHER DECOMPENSATION EVENTS REQUIRING HOSPITALIZATIONS IN MASLD-RELATED DECOMPENSATED CIRRHOSIS

Mario Romeo[1] Fiammetta Di Nardo[1] Annachiara Coppola[1] Giuseppina Martinelli[1] Claudio Basile[1] Carmine Napolitano[1] Paolo Vaia[1] Alessandro Federico[1] Marcello Dallio[1], [1]University of Campania Luigi Vanvitelli

Background: Phase Angle (PA) represents a Bioelectrical impedance analysis (BIA)-assessable marker of sarcopenia, accurately predicting hospitalizations in advanced chronic liver disease (ACLD). Systemic inflammation severely burdens sarcopenia and, simultaneously with clinically significant portal hypertension (CSPH), constitutes the main driver of decompensation. Considering the high prevalence of sarcopenia in Metabolic dysfunction-associated Steatotic Liver Disease (MASLD) ("sarcopenic obesity" paradox), we evaluated the accuracy of the PA/C-reactive-protein (CRP) index (PAC-I) in predicting sarcopenia and 3-month further liver-related events (LREs)-determining hospitalizations in MASLD decompensated-ACLD (dACLD). **Methods:** Between December 2022 and January 2024, 50 MASLD-dACLD patients were consecutively enrolled, collecting baseline anthropo-biochemical, nutritional (BIA), and clinical [including Liver Stiffness Measurement (LSM) and varices severity] data. EWGSOP2 criteria diagnosed sarcopenia. Patients were followed up, and further LRE-determining

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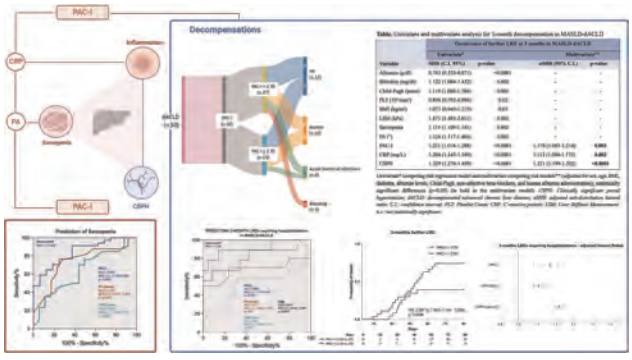
hospitalizations in the subsequent 3 months were recorded. Between March 2024 and January 2025, 40 MASLD-dACLD patients were enrolled [validation cohort]. **Results:** PA values inversely correlated with LSM [R: -0.711, $p < 0.0001$] and with CRP [-0.945, p:0.001], emerging as significantly higher in $\geq$F2 varices-affected patients ($p < 0.0001$). Multivariate analysis identified PAC-I (HR: 1.178, p: 0.03), CRP (HR: 1.112, p: 0.02), and CSPH (HR: 1.221, $p < 0.0001$) as variables associated with decompensation. ROC analysis showed a superior accuracy of PAC-I (AUC:0.843) compared to PA alone (AUC:0.721) and CRP alone (AUC:0.592) in predicting sarcopenia, as well as the superiority of PAC-I (AUC: 0.893) compared with LSM (0.814), PA (0.717), and CRP (0.581) (all $p < 0.05$) in predicting 3-month further LREs' occurrence, identifying PAC-I < 2.35 as the best cut-off. Consistently, dACLD patients showing baseline PAC-I < 2.35 presented a higher risk [HR: 2.287, p:0.032] of further LREs (Figure 1). The superiority of PAC-I in predicting sarcopenia [AUC PAC-I: 0.821, AUC PA: 0.709, AUC CRP: 0.611; all $p < 0.001$] and further LREs at 3 months [AUC PAC-I: 0.852, AUC LSM: 0.792, AUC PA: 0.711, AUC CRP: 0.572; all $p < 0.0001$] was confirmed in the validation cohort. **Conclusion:** In MASLD-dACLD, PAC-I represents a useful noninvasive tool in predicting sarcopenia and liver-related hospitalizations.



Disclosures: Mario Romeo: Nothing to Disclose, Fiammetta Di Nardo: Nothing to Disclose, Annachiara Coppola: Nothing to Disclose, Giuseppina Martinelli: Nothing to Disclose, Claudio Basile: Nothing to Disclose, Carmine Napolitano: Nothing to Disclose, Paolo Vaia: Nothing to Disclose, Alessandro Federico: Nothing to Disclose, Marcello Dallio: Nothing to Disclose

2320 | SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS OF THE CARDIOVASCULAR EFFECTS OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT CREATION

Wali Badar[1] Ramzy Khabbaz[1] Kashif Osmani[2] Sarah Shalaby[3] Anna Baiges[3] Juan Carlos Garcia-Pagan[3] Ron Gaba[1], [1]University of Illinois at Chicago, [2]University of Illinois-Chicago, [3]Hospital Clinic of Barcelona

Background: To characterize the cardiovascular (CV) effects of transjugular intrahepatic portosystemic shunt (TIPS) through systematic literature review and meta-analysis. **Methods:** A systematic literature review was performed using PubMed from inception through April 2025. The search strategy was: (Transjugular intrahepatic portosystemic shunt[Title]) OR Transjugular intrahepatic portosystemic[Title] OR Transjugular intrahepatic shunt[Title] OR Transjugular shunt[Title] OR TIPS[Title]) AND (Heart[Title] OR Cardiac[Title] OR Cardiovascular[Title] OR Mitral[Title] OR Atrial[Title] OR Ventricular[Title] OR Pulmonary[Title] OR Systemic[Title]) AND (Effects[Title] OR Changes[Title] OR Impact[Title] OR Survival[Title] OR Mortality[Title] OR Function[Title] OR Parameters[Title] OR Decompensation[Title] OR Follow-up[Title] OR Outcomes[Title]). Eligible articles were English language studies >5 patients reporting CV outcomes after TIPS. Outcome measures included hemodynamic changes, CV index alterations, CV decompensation, and mortality. Continuous outcomes were compared using the random effects method for meta-analysis. Statistical analysis was performed using R Studio 3.6.1. **Results:** Thirty-two articles with 4,452 patients met inclusion criteria. In 17 articles with 2,201 patients, right atrial pressure (RAP) significantly increased vs. baseline (+5.2 mm Hg, 95% CI: 4.0-6.3; $P < 0.001$). In 22 articles with 1,231 patients, cardiac output (CO) (+1.9 L/min, 95% CI: 1.1-2.7), cardiac index (CI) (+1.0 L/min/m2, 95% CI: 0.6-1.4), pulmonary artery pressure (PAP) (+8.6 mm Hg, 95% CI: 4.1-13.1), pulmonary capillary pressure (PCWP) (+5.7 mm Hg, 95% CI: 2.1-9.3), and E/A ratio (+0.2, 95% CI: 0.1-0.4) significantly increased vs. baseline ($P < 0.001$-0.006), but were not different $\geq$3 months post-TIPS ($P > 0.05$). Pre-TIPS portosystemic pressure gradient (PPG), RAP, PAP, and PCWP, and post-TIPS PPG and RAP, were higher when TIPS was performed under general anesthesia compared to moderate sedation ($P < 0.001$-0.004). In 8 articles with 1,914 patients, pooled incidence of symptomatic heart failure was 9%. In 10 articles with 1,967 patients, 1-year mortality rate was 30%. Diastolic dysfunction was associated with increased 1-year post-TIPS mortality (OR: 2.85, $P = 0.013$). In 5 articles with 413 patients, 9% of all post-TIPS mortality was attributable to cardiac decompensation. **Conclusion:** Transient CV changes occur after TIPS and may result in cardiac decompensation and mortality.

Disclosures: Wali Badar: Nothing to Disclose, Ramzy Khabbaz: Nothing to Disclose, Kashif Osmani: Nothing to Disclose, Sarah Shalaby: Nothing to Disclose, Anna Baiges: Nothing to Disclose, Juan Carlos Garcia-Pagan: Nothing to Disclose, Ron Gaba: Guerbet:

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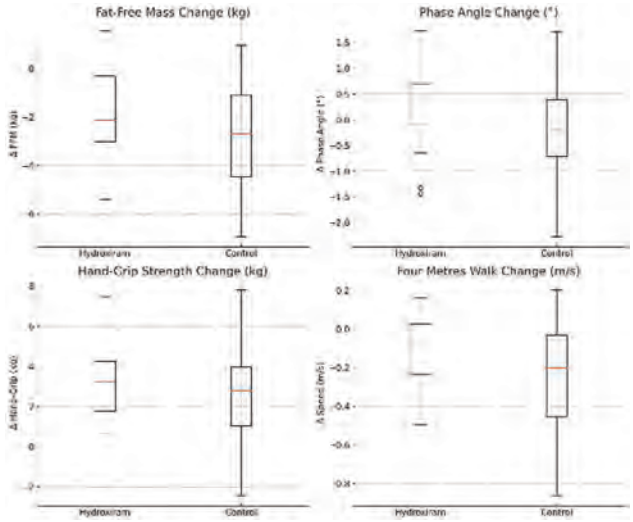
2321 | SARCIRAM: A PILOT STUDY ON THE IMPACT OF HYDROXIRAM D SUPPLEMENTATION ON SARCOPENIA IN PATIENTS WITH LIVER CIRRHOSIS

Paolo Gallo[1] Dafne Marcelli[1] Lucrezia Santoro[1] Valentina Flagiello[1] Francesca Terracciani[1] Andrea Falcomatà[1] Antonio Picardi[1] Umberto Vespasiani-Gentilucci[1], [1]Medicina Clinica ed Epatologia Campus Biomedico di Roma

Background: Background & Aims: Sarcopenia is a common complication of chronic liver disease and is associated with poor prognosis. Emerging evidence supports the role of branched-chain amino acids (BCAAs) and their metabolite β-hydroxy-β-methylbutyrate (HMB) in sarcopenia. The SARCIRAM pilot trial evaluated Hydroxiram D (BCAAs, calcium HMB, vitamin D) on sarcopenia progression in MASLD-related cirrhosis. **Methods:** In this single-center, open-label, randomized (1:1) pilot study, adults with compensated MASLD-related cirrhosis (Child-Pugh A) were assigned to receive Hydroxiram D twice daily plus standard care or standard care alone for 6 months. Bioelectrical impedance analysis measured fat- free mass (FFM), phase angle (PA), and appendicular skeletal muscle mass index (ASMM/h²). Ultrasound assessed quadriceps thickness index, cross-sectional rectus index, psoas height-to-width ratio, and diaphragm excursion. Muscle function was tested by handgrip strength (HGS) and 4 m walk test (4mWT). Within-group changes were analysed with paired-sample t-tests; between-group differences with baseline-adjusted ANCOVA. **Results:** Forty patients were randomized; 32 completed the study. Exclusions included five lost to follow-up, two with hepatocellular carcinoma detected at baseline, and one statistical outlier. Baseline anthropometric characteristics, age, sex, laboratory data and muscle parameters were comparable between groups (all $p > 0.05$). After 6 months, the adjusted mean change in FFM was –1.89 kg in the Hydroxiram D group versus –2.69 kg in controls ($p = 0.431$). PA changed by +0.20° versus –0.34° ($p = 0.242$), and ASMM/h² by –0.28 versus –0.44 kg/m² ($p = 0.343$), respectively. Although these between-group differences did not reach statistical significance, Hydroxiram D was associated with trends toward smaller declines in FFM and ASMM/h² and an increase in PA. Between-group differences in muscle function [ΔHGS +2.36 kg vs +1.80 kg ($p = 0.700$) and Δ4mWT –0.142 m/s vs –0.210 m/s ($p = 0.290$)] were not significant; however, within-group analysis showed a significant HGS improvement in the Hydroxiram D group ($p = 0.044$) and a greater decline in 4mWT in controls ($p = 0.004$). No significant changes were observed in ultrasound-derived indices or laboratory parameters. No safety concerns or adverse events were reported. **Conclusion:** Six months of Hydroxiram D supplementation was associated with improved muscle strength and physical performance in patients with compensated MASLD-related cirrhosis,
alongside favorable trends in nutritional status and muscle mass preservation. These pilot data support further investigation in larger, adequately powered trials to confirm efficacy and assess long-term clinical and functional outcomes in cirrhosis-related sarcopenia.



Disclosures: Paolo Gallo: Nothing to Disclose, Dafne Marcelli: Nothing to Disclose, Lucrezia Santoro: Nothing to Disclose, Valentina Flagiello: Nothing to Disclose, Francesca Terracciani: Nothing to Disclose, Andrea Falcomatà: Nothing to Disclose, Antonio Picardi: Nothing to Disclose, Umberto Vespasiani-Gentilucci: Advanz Pharma: Advisor, Gilead: Speaking and Teaching, Ipsen: Advisor, Diasorin: Consultant, Novo Nordisk: Advisor, Astra Zeneca: Grant/Research Support, Astra Zeneca: Grant/Research Support

2322 | DEVELOPMENT AND VALIDATION OF A NOMOGRAM INCORPORATING NUTRITIONAL FACTORS FOR PREDICTING PROGNOSIS IN CIRRHOSIS PATIENTS

Jianchun Shen[1] Yang Xu[1] Yanli Yang[1] Jiaoxia He[1] Luwen Liang[1] Dazhi Zhang[1] Dachuan Cai[2] Juan Kang[2], [1]The Second Affiliated Hospital, Chongqing Medical

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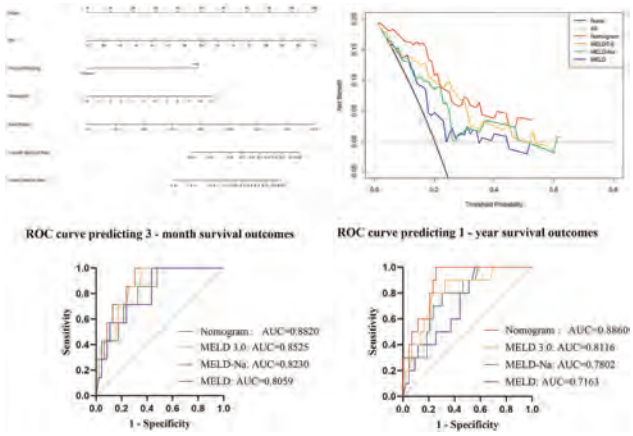
University, [2]The Second Affiliated Hospital of Chongqing Medical University

Background: Malnutrition is a prevalent complication in cirrhosis patients, significantly impacting prognosis. Existing prognostic models for cirrhosis inadequately address the impact of nutritional factors. This study aimed to identify key nutritional indicators associated with prognosis and develop a nomogram-based predictive model. **Methods:** Clinical data of 53 hospitalized cirrhosis patients admitted to the Second Affiliated Hospital of Chongqing Medical University (Feb 2023–Feb 2025) were analyzed. Body mass index (BMI), prognostic nutritional index (PNI), geriatric nutritional risk index (GNRI), Model for End-Stage Liver Disease (MELD), MELD-Na, and MELD 3.0 scores were calculated. Blood samples underwent non-targeted metabolomics to screen marker metabolites based on MELD 3.0. Patients were followed up at 3 months, 6 months, 1 year, and 2 years to record survival rates, adverse liver events, and complications. Univariate Cox regression ($P < 0.2$ threshold) identified prognostic indicators, which were entered into least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation to optimize the λ parameter and avoid overfitting. Multivariate Cox regression ($P < 0.05$) selected independent predictors for nomogram construction. Model performance was evaluated via AUC, C-index, calibration curves, and decision curve analysis (DCA). **Results:** Multivariate analysis identified PNI, esophageal-gastric variceal bleeding, and neutrophil count as independent risk factors. The nomogram assigned scores as follows: −7 points per 2-unit PNI increase, +48 points for variceal bleeding (0 if absent), and +5 points per 1×10^9/L neutrophil increase. The model showed a C-index of 0.8698. For 3-month and 1-year outcomes, AUC values were 0.8820 [95% CI (0.7787, 0.9852), $P < 0.001$] and 0.8860 [95% CI (0.7952, 0.9769), $P < 0.001$], surpassing MELD (0.8059, 0.7163), MELD-Na (0.8230, 0.7802), and MELD 3.0 (0.8525, 0.8116). Calibration curves showed close agreement between observed and predicted mortality. DCA revealed significantly higher net benefit than traditional models, validating robust predictive capability. **Conclusion:** The nomogram integrating PNI, variceal bleeding, and neutrophil count demonstrated superior prognostic performance for cirrhosis compared to traditional models, enabling more objective, comprehensive, and accurate clinical evaluation.



Disclosures: Jianchun Shen: Nothing to Disclose, Yang Xu: Nothing to Disclose, Yanli Yang: Nothing to Disclose, Jiaoxia He: Nothing to Disclose, Luwen Liang: Nothing to Disclose, Dazhi Zhang: Nothing to Disclose, Dachuan Cai: Nothing to Disclose, Juan Kang: Nothing to Disclose

2323 | HIGHER RISK OF FIRST ACUTE VARICEAL BLEEDING (AVB) IN MASLD DECOMPENSATED ADVANCED CHRONIC LIVER DISEASE PATIENTS (DACLD) RECEIVING CARVEDILOL-BASED PRIMARY PROPHYLAXIS: A MATTER OF INSULIN RESISTANCE. IS IT TIME TO PERSONALIZE PREVENTION STRATEGIES OF AVB ACCORDING TO THE ETIOLOGY?

Mario Romeo[1] Fiammetta Di Nardo[1] Carmine Napolitano[1] Paolo Vaia[1] Simone Olivieri[1] Claudio Basile[1] Giuseppina Martinelli[1] Alessandro Federico[1] Marcello Dallio[1], [1]University of Campania Luigi Vanvitelli

Background: In the *panorama* of chronic liver disease disorders, Metabolic dysfunction-associated Steatotic Liver Disease (MASLD) is dramatically supplanting viral etiologies worldwide. The recently published "CAVARLY trial" has demonstrated the superiority of combining variceal band ligation (VBL) with non-selective beta-blocker administration (NSBB) compared to each strategy alone for the primary prophylaxis of acute variceal bleeding (AVB) in patients with decompensated

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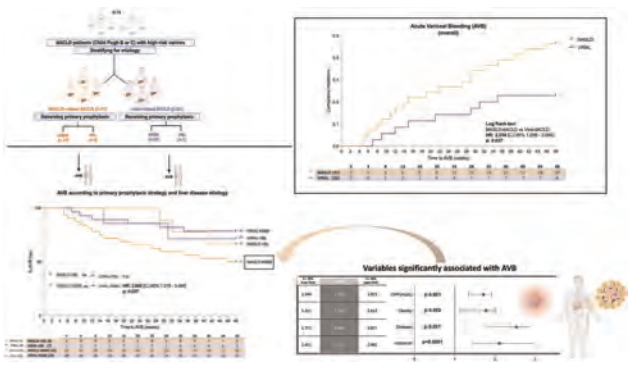
advanced chronic liver disease (dACLD) and high-risk varices (HRV). Notably, the monotherapy group receiving carvedilol exhibited a higher AVB incidence, highlighting a significant proportion of NSBB-not hemodynamically responding individuals among MASLD patients. Consistently, type 2 diabetes mellitus (T2DM) and obesity have already been demonstrated to impair the hemodynamic response to NSBB, thus predisposing to hepatic decompensation. However, the impact of the dysmetabolic etiology in conditioning the effectiveness of NSBB- and VBL-based strategies in preventing the first AVB in dACLD with HRV has never been systematically investigated. **Methods:** From July 2022 to April 2024, we consecutively enrolled and followed over 12 months, 76 (35 viral-related and 41 MASD-related) dACLD individuals presenting HRV. Patients received carvedilol-based primary prophylaxis (32 MASLD; 28 viral-related), reserving VBL for NSBB-intolerant subjects (9 MASLD; 7 viral-related). Baseline anthropometrical, biochemical, and clinical data were collected. NSBB-compliance was monitored by arterial pressure measurements and a self-compiled diary. **Results:** Unlike patients undergoing VBL, in the carvedilol-receiving group, MASLD patients showed a significantly higher rate of AVB compared to the viral-related CLD individuals (HR: 2.806, p: 0.027). Cox regression analysis [adjusted for sex, age, Child-Pugh, body mass index (BMI), and endoscopic varices features] revealed obesity (aHR: 1.781, p:0.002), T2DM (aHR: 2.541, p:0.001), C-reactive protein (aHR:1.72, p:0.001), and Homeostasis Model Assessment for Insulin Resistance (aHR: 2.112, $p < 0.0001$) as the variables significantly associated with this outcome (Figure 1). **Conclusion:** In the Era of Precision Medicine, personalizing the first AVB-prevention strategy for dACLD patients with HRV according to CLD etiology represents an urgent need.



Disclosures: Mario Romeo: Nothing to Disclose, Fiammetta Di Nardo: Nothing to Disclose, Carmine Napolitano: Nothing to Disclose, Paolo Vaia: Nothing to Disclose, Simone Olivieri: Nothing to Disclose, Claudio Basile: Nothing to Disclose, Giuseppina Martinelli: Nothing to Disclose, Alessandro Federico: Nothing to Disclose, Marcello Dallio: Nothing to Disclose

2324 | A MACHINE LEARNING MODEL TO REDUCE UNNECESSARY PARACENTESIS FOR SBP EXCLUSION HAS EXCELLENT PERFORMANCE IN A RECENT NATIONWIDE CIRRHOSIS COHORT

Jacqueline O'Leary[1] Jasmohan Bajaj[2] Scott Silvey[2] Nilang Patel[2] Heather Patton[3] Timothy Morgan[4] Sofia Jakab[5] Shari Rogal[6], [1]Dallas VAMC, [2]Virginia Commonwealth University, [3]VA San Diego Healthcare, [4]VA Long Beach Healthcare System, [5]West Haven VA, [6]University of Pittsburgh

Background: Lack of timely paracentesis to exclude spontaneous bacterial peritonitis (SBP) leads to poor outcomes. A machine learning (ML) model developed using demographics & blood tests from the Veterans Affairs Corporate Data Warehouse (VA-CDW) during pre-COVID era (2009-19) had excellent negative predictive value (NPV) for SBP. During/post-pandemic, there was disruption of inpatient/outpatient care. Aim: Validate a ML model to exclude SBP using clinical variables in cirrhosis inpatients enrolled after 2020. **Methods:** The derivation ML model included admitted Veterans with cirrhosis who received timely paracentesis between 2009-2019 (Fig 1A). We studied a similar cohort of patients 2020-2023 without prior SBP, and key variables were used to calculate SBP risk on admission using the established ML model. Predicted probabilities were assessed for overall calibration and NPV at thresholds of $<5\%$, $<10\%$, and $<15\%$ risk. Cohort characteristics were summarized between SBP/no-SBP groups, and compared to the 2009-19 derivation cohort used to train the ML model. Decision-curve analysis was applied in order to measure the potential net benefit of the ML model over a paracentesis-for-all scenario. **Results:** From 2020-2023, we identified 4192 Veterans (15.0% w/SBP) who met the inclusion criteria. SBP patients were significantly older, with lower BMI, less likely to have alcohol cirrhosis, and were more likely to be on SBPPr (Fig 1C). SBP pts. had higher total WBC, neutrophil%, platelets, INR, BUN, potassium, temperature on admission, and lower Hgb, eosinophil%, AST, ALP, eGFR, CO2, and blood pressure on admission. Compared to the pre-COVID derivation cohort ($n = 9643$, Figure 1A), these pts had significantly lower Hgb, AST, ALT, bilirubin, eGFR, CO2, and higher neutrophil/eosinophil%, platelets, INR, and albumin, although absolute differences were minor. Model validation: We found high NPVs of 93.6% [89.6%-96.4%] (219/234 pts. correctly predicted SBP-negative) at the $<5\%$ risk threshold, 92.0% [90.6%-93.3%] (1647/1791 correct) at the $<10\%$ threshold, and 90.9% [89.7%-91.9%] (2523/2777 correct) at the $<15\%$ threshold. Sensitivities were also high at the three risk levels (97.6%/77.1%/59.7%) indicating low false

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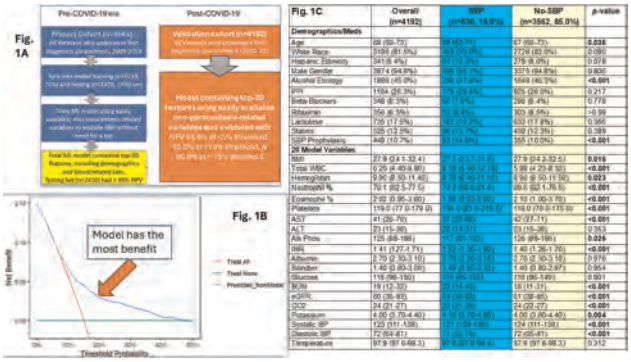
negativity rate. Predicted probabilities ranged from 2.8%-88.8% and were well-calibrated (brier score = 0.119, slope: 0.891, $p = 0.639$), implying that the predicted risk was similar to the true SBP risk over all levels. Decision curve analysis demonstrated superiority of the ML model over a paracentesis-for-all strategy (Fig 1B). **Conclusion:** In a nationwide cohort of Veterans with cirrhosis, a machine learning model derived in the pre-COVID era using routinely collected variables without paracentesis had excellent NPV, sensitivity, calibration & decision curve support to exclude SBP in a current cohort. Using this robust model could reduce the need for unnecessary paracentesis by excluding those unlikely to have SBP.



Disclosures: Jacqueline O'Leary: Genfit: Consultant, Grifols: Advisor, CVS: Stock - publicly traded company, Mallinckrodt: Advisor, Novo Nordisk: Advisor, PharmaIn: Advisor, Grifols: Consultant, Cellion: Advisor, Mallinckrodt: Advisor, PharmaIn: Consultant, Genfit: Consultant, PharmaIn: Consultant, Genfit: Consultant, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Genfit: Grant/Research Support, Enterobiotix: Advisor, Boehringer Ingelheim: Advisor, Scott Silvey: Nothing to Disclose, Nilang Patel: Nothing to Disclose, Heather Patton: Bristol-Myers Squibb: Spouse is employee of BMS, Timothy Morgan: Nothing to Disclose, Sofia Jakab: Nothing to Disclose, Shari Rogal: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose

2325 | IMPACT OF BACTERIAL INFECTION ON CLINICAL OUTCOMES IN PATIENTS WITH ACUTE DECOMPENSATION: REAL-WORLD EVIDENCE INSIGHTS

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Background: Acute decompensation (AD) of liver cirrhosis is associated with an increased risk of acute-on-chronic liver failure and short-term mortality. It is characterized by the acute development or worsening of ascites, gastrointestinal bleeding (GB), and/or hepatic encephalopathy (HE). Additionally, bacterial infections (BI) contribute to precipitating or aggravating decompensation but it remains controversial whether BI needs to be regarded as an AD event on its own. Using real-world data, we assessed the impact of BI on patient (pts) outcomes either alone or in combination with other AD events. **Methods:** All hospitalizations of pts with chronic liver disease associated with at least one AD event recorded on the date of admission between January 2023 and April 2025 in Komodo's Healthcare Map US real-world database were included. Hospitalizations were categorized by types of AD events (ascites, GB, HE) recorded during the hospital stay, accounting for BI reported within 48h after admission. Mortality at 90/180d, liver transplant-free survival at 90d, and rate of re-hospitalization within 90d for the occurrence of an additional AD event were compared between categories of hospitalization with or without BI using fold changes (FC) with 95% confidence intervals. **Results:** The data from 118,457 hospitalizations in 82,741 pts were analyzed (male: 59%, mean age at admission: 55y, median duration of hospitalization: 5d). BI was reported within 48h after admission in 48% of hospitalizations. During the hospital stay, ascites was the most common event (44%), followed by GB (32%), and HE (16%). In 29% of hospitalizations, BI was the only event. GB or BI alone were associated with the lowest 90/180d mortality (3/4% and 4/5% respectively) while HE or ascites alone showed higher rates (7/10%

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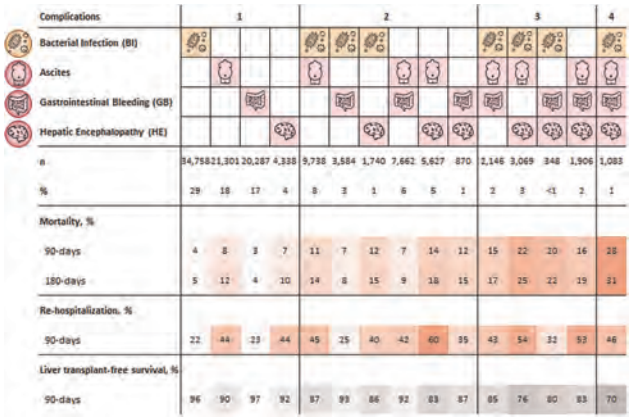
and 8/12%, respectively). Overall, mortality increased with the number of different types of AD events (1-4) experienced during hospital stay (90d: 5, 10, 18, 28%; 180d: 7, 13, 21, 31%). Pts admitted with BI and reporting of any other single type of AD event during their hospital stay had higher 90d mortality rate than pts with the same type of AD event recorded but without BI at admission: FC = 1.4 [1.3, 1.4] (11 vs 8%) for ascites, 1.7 [1.5, 1.9] (12 vs 7%) for HE and 2.3 [2.2, 2.5] (7 vs 3%) for GB. Irrespective of the number of different types of AD events reported during hospitalization, BI at admission did not impact the rate of re-hospitalization (FC: 0.9-1.1) but increased 90d (FC: 1.4-2.3) and 180d (FC: 1.2-2.0) mortality. Experiencing all 4 types of AD events resulted in a transplant-free survival rate of 70% vs 83% without the presence of BI at admission. **Conclusion:** While BI alone was associated with low risk of mortality and re-hospitalization, experiencing BI in addition to any other AD event consistently increased mortality rates. These findings support considering BI as an aggravating factor in pts with AD (ascites, GB, and/or HE), rather than an AD event on its own.



Disclosures: Javier Fernandez: GRIFOLS: Advisor, Yacine Hajji: GENFIT S.A.: Employee, Jonel Trebicka: Nothing to Disclose, Thierry Artzner: Nothing to Disclose, William Bernal: Genfit: Advisor, Flagship Pioneering: Advisor, Joan Claria: Nothing to Disclose, Lise Lotte Gluud: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Jacqueline O'Leary: Genfit: Consultant, Grifols: Advisor, CVS: Stock - publicly traded company, Mallinckrodt: Advisor, Novo Nordisk: Advisor, PharmaIn: Advisor, Grifols: Consultant, Cellion: Advisor, Mallinckrodt: Advisor, PharmaIn: Consultant, Genfit: Consultant, PharmaIn: Consultant, Genfit: Consultant, Pierre-Emmanuel Rautou: Nothing to Disclose, Debbie Shawcross: EnteroBiotix: Consultant, MRM Health: Advisor, Satellite Bio: Consultant, Norgine: Grant/Research Support, Apollo Therapeutics: Consultant, Genfit: Advisor, Alfa Sigma: Advisor, Bart Staels: Genfit SA: Consultant, Florence Wong: Mallinckrodt: Consultant, Mallinckrodt Pharmaceutical Inc: Grant/Research Support, River 2 Renal: Consultant, Sequana Medical: Consultant, sequana Medical: Grant/Research Support, Inventiva: Grant/Research Support, Inventiva: Consultant, Cristina Sánchez-Garrido: Nothing to Disclose, Eva Usón-Raposo: Nothing to Disclose, Carol Addy: GENFIT: GENFIT stock options, Maxime Anné: Nothing to Disclose, Stéphanie Ferreira: Nothing to Disclose, Dean Hum: Nothing to Disclose, Jérémy Magnanensi: Nothing to Disclose, Pierbruno Ricci: Nothing to Disclose, Katharina Staufer: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Richard Moreau: Nothing to Disclose, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Genfit: Grant/Research Support, Enterobiotix: Advisor, Boehringer Ingelheim: Advisor, Paolo Angeli: Nothing to Disclose

2326 | OLFACTORY AND GUSTATORY IMPAIRMENT IN CIRRHOSIS CORRELATES WITH RENAL INSUFFICIENCY AND COGNITIVE IMPAIRMENT AND NEGATIVELY IMPACTS PERCEIVED ABILITY TO EAT

Nilang Patel[1] Andrew Fagan[2] Mary Leslie Gallagher[3] Michael Fuchs[4] Brian Davis[5] Puneet Puri[1] Jasmohan Bajaj[1], [1]Virginia Commonwealth University, [2]Richmond

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Background: Cirrhosis is linked with poor nutrition, which could partly be due to anorexia & coexistent end-stage renal disease (ESRD). Taste & smell perception affect appetite but their role in pts with cirrhosis and ESRD are unclear. Aim: Define taste & smell perception in pts with cirrhosis ± ESRD & impact on eating. **Methods:** Healthy controls (Ctrls) & outpts with cirrhosis, ESRD only & both cirrhosis+ESRD underwent taste & smell tests, cognitive testing using (PHES, high = better, Stroop, lower = better) & SAS questionnaire for olfactory impact on life (high = worse). Patients with past/current COVID-19, dentures, current/recent alcohol or tobacco use were excluded. We used WETT taste test which studies sweet, sour, salty, brothy & bitter taste, while smell was tested using the NIH Olfactory toolbox system. Quality-of-life (QOL) testing was performed using Sickness Impact Profile (SIP high = worse) which has physical & psychosocial domains & one specifically for eating. Taste & smell results were compared between groups & correlated with eating SIP. Multi-variable analysis for eating SIP/taste/smell testing was performed using demographics, disease type, medications & cognitive testing **Results:** We enrolled 94 subjects [24 ctrl, 40 cirrh (20 comp/decomp), 20 ESRD only & 10 cirrhosis+ESRD]. Controls were younger & were free of diabetes; gender was similar. Diabetes trended higher in ESRD groups. Taste and smell: Ctrls had the best taste discrimination while cirrhosis & ESRD pts were similar. All taste sensations were more impaired in diseased vs controls, but sweet, sour & bitter tastes were most affected. Diseased groups admitted to more impact of smell-related impairment on the SAS questionnaire. Correct taste identification was linked with correct smell identification ($r = 0.5, p < 0.001$). Diabetes did not affect taste or smell results. QOL: QOL was worst in decomp cirrhosis, ESRD and both vs controls and comp cirrhosis. Eating portion of SIP was poor in all diseased groups and worst in pts with both cirrhosis+ESRD; this correlated with subjective impact of smell impairment (Fig B). Cognition: PHES, Stroop were best in ctrls & worsened with disease; worst in cirrhosis+ESRD pts. PHES linked with taste while Stroop linked with smell (Fig C/D). Multivariable analysis: For eating SIP, higher total SAS ($t = 0.3$, $p = 0.001$), advancing disease (1.04, $p = 0.05$) and age (1.0, $p = 0.05$) were contributory. For smell percentile Stroop was negatively ($t = -0.2$, $p = 0.005$), while age and taste ($p = 0.05$ each) were positively contributory while for taste age ($t = -0.2$, $p = 0.02$), PHES (0.6, $p = 0.03$) and smell performance (0.1, $p = 0.04$) were significant. **Conclusion:** Smell and taste impairments affect ability to eat in cirrhosis, which worsens with coexistent end-stage renal disease. Cognitive impairment are correlated with smell and taste impairment. Focusing on smell and taste improvement could beneficially impact nutrition and reduce sarcopenia.

Figure A	Healthy (n=24)	Comp cirrhosis (n=20)	Decomp Cirrhosis (n=20)	ESRD only (n=20)	Cirrhosis & ESRD (n=10)	P value (all groups)
Age	53.4±10.2	68.3±8.6	64.8±9.8	64.8±13.1	68.4±7.0	<0.0001
Male Gender	19 (79%)	20 (100%)	18 (90%)	19 (95%)	10 (100%)	0.78
Diabetes	0 (0%)	12 (60%)	12 (60%)	15 (75%)	7 (70%)	<0.0001
Cognition						
PHES (↑=good)	-0.0±1.9	-3.2±3.6	-2.5±3.0	-4.7±3.8	-5.8±3.5	<0.0001
Stroop time (↑=poor)	148.9±27.8	202.9±31.8	190.3±39.0	235.6±85.9	260.6±47	<0.0001
Taste (↑=good)						
Total correct	27.5±7.8	16.1±7.1	20.3±7.2	16.2±7.9	21.7±6.9	<0.0001
Sweet correct	5.6±2.3	2.8±2.3	3.6±2.3	2.3±2.4	3.9±2.9	<0.0001
Sour correct	5.7±1.1	4.6±2.0	5.3±2.2	4.5±2.5	5.0±1.0	0.001
Salty correct	6.0±2.1	4.1±2.2	4.9±2.5	4.3±2.6	5.7±1.8	0.04
Brothy correct	4.5±2.8	2.5±1.9	3.2±2.2	2.4±2.4	4.0±2.8	0.03
Bitter correct	4.7±2.7	2.2±1.8	3.3±2.1	2.7±2.6	3.3±2.3	0.006
Smell (↑=good)						
National % (↑=good)	47.4±31.8	39.2±30.9	34.9±29.1	32.5±32.9	26.1±22.5	0.40
PROs						
SAS questionnaire (↑=worse)	4.6±9.3	3.6±7.3	5.9±6.2	9.6±10.7	22.0±17.6	<0.0001
SIP (↑=worse)						
Total SIP	13.1±19.3	12.6±15.3	17.4±13.5	17.0±10.6	27.9±22.5	0.23
Physical	5.3±7.6	12.3±15.5	14.6±12.8	14.8±15.4	28.1±26.5	0.007
Psychosocial	10.3±13.6	11.1±17.6	16.4±16.9	10.9±9.1	24.1±25.0	0.23
Eating	2.1±3.7	5.5±7.2	6.9±7.9	7.7±8.5	11.9±7.4	0.005

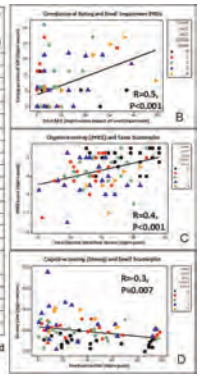

Fig A: comparison between groups, Fig B: Correlation between eating and smell-related PROs, Fig C: correlation of PHES and taste, Fig D: correlation of Stroop and smell

Disclosures: Nilang Patel: Nothing to Disclose, Andrew Fagan: Nothing to Disclose, Mary Leslie Gallagher: Nothing to Disclose, Michael Fuchs: Nothing to Disclose, Brian Davis: Nothing to Disclose, Puneet Puri: Nothing to Disclose, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Genfit: Grant/Research Support, Enterobiotix: Advisor, Boehringer Ingelheim: Advisor

2327 | DEVELOPMENT AND VALIDATION OF AN AMBULATORY ADMINISTRATIVE FRAILTY INDEX FOR PATIENTS WITH CIRRHOSIS

Lucia Calthorpe[1] Jessica Rubin[2] Catherine Lee[1] Garrett Roll[2] Sandy Feng[1] Jennifer Lai[1], [1]University of California San Francisco, [2]University of California, San Francisco

Background: Frailty is highly prevalent among patients with cirrhosis and is strongly associated with health outcomes. While numerous tools have been developed to assess frailty in administrative data, they are not specific to patients with cirrhosis, nor have they been developed against gold standard measures of physical frailty. **Methods:** Adult ambulatory patients listed for liver transplantation with in-person frailty assessments were identified from a single center from 2017 to 2024. Frailty was assessed with the Liver Frailty Index (LFI). The electronic health record was searched to identify all ICD-10 codes associated with inpatient, outpatient, and emergency department encounters for the two years prior to in-person frailty assessment. Codes with a frequency > 50 (n = 143) were considered for inclusion in the model. The cohort was randomly split into training

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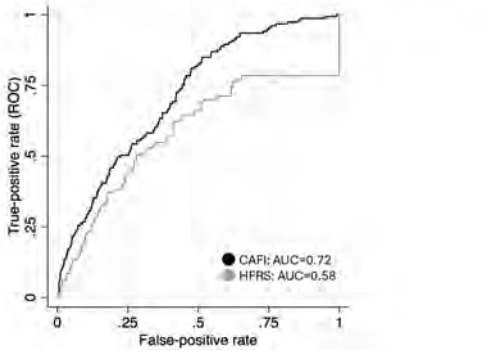
and validation sets (65% and 35% respectively), and lasso regression was used to select ICD-10 codes which predict LFI. Model performance was assessed in the validation cohort in terms of discrimination (AUC) and calibration (observed vs. expected outcomes). **Results:** Among 2419 patients, 63% were male, with a median age of 60, and 18.5% were frail by LFI. Patients had an average of 19 ICD-10 codes associated with their inpatient and outpatient encounters in the two years prior to their in-person LFI assessment. Lasso regression was used to generate the cirrhosis administrative frailty index (CAFI). We identified 30 codes which predict LFI > 4.5 with an AUC of 0.72. In comparison, the commonly used Hospital Frailty Risk Score predicted LFI with an AUC of 0.58. The CAFI was associated with pretransplant mortality and delisting secondary to illness (OR = 1.40, 95% CI: 1.18, 1.66). **Conclusion:** We developed the cirrhosis administrative frailty index, the first ICD-based frailty tool built to predict an in-person gold standard frailty metric. While numerous administrative frailty indices have been developed and correlate strongly with outcomes like in-hospital mortality, they correlate poorly with physical frailty (e.g., Fried Frailty Index, chair stands, falls). An administrative frailty index for ambulatory patients with cirrhosis will facilitate population-level research to understand the burden of frailty among patients with cirrhosis and quantify its impact on healthcare utilization and outcomes. Further, it will allow researchers to account and adjust for frailty in large-scale data analysis.

Figure 1. Area under the ROC for CAFI as compared to HFRS in predicting LFI, Validation cohort (n=827)



Disclosures: Lucia Calthorpe: Nothing to Disclose, Jessica Rubin: Nothing to Disclose, Catherine Lee: Nothing to Disclose, Garrett Roll: Nothing to Disclose, Sandy Feng: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI

2328 | RISK FACTORS FOR INFECTION AFTER TIPS

Shannon Sanda[1] John Martens[1] M. Katherine Dokus[2] Bandar Aljudaibi[1], [1]University of Rochester Medical Center, [2]University of Rochester

Background: Transjugular intrahepatic portosystemic shunt (TIPS) is a crucial intervention for complications of portal hypertension. While effective, TIPS procedures carry a risk of complications, with infection being a significant concern contributing to prolonged hospital stays, increased healthcare costs, and poor outcomes in an already vulnerable cirrhotic population. Despite the known risk, specific patient characteristics and procedural indications that independently predispose individuals to infection after TIPS are not fully elucidated. **Methods:** This was a retrospective cohort study of 293 adult patients who underwent TIPS placement at a single center (Mar 2011 – July 2020). The primary outcome was the occurrence of any infection within 30 days post-TIPS, confirmed by clinical diagnosis, culture results, or need for antimicrobial therapy. Univariate analyses were performed to compare characteristics between patients with and without 30-day infection. A multivariate backwards stepwise logistic regression was then completed to identify independent predictors of 30-day infection. **Results:** Among 293 patients, 59 (20.1%) developed infections: Pneumonia (31%), undifferentiated sepsis (28%), urinary tract infection (16%), bacteremia (12%), spontaneous bacterial peritonitis (5%), cellulitis (3%), fungemia (2%), tracheitis (2%), and viral infection (2%). The mean age was 56.6 years and 36% were female. The univariate predictors of infection included female sex (49.2% vs. 32.5%; p = 0.018), initial TIPS vs. revision (96.6% vs. 82.1%; p = 0.005), higher MELD-Na (median 20 vs. 17; p < 0.001), elevated Child-Pugh scores (p = 0.035), and variceal bleeding indication (45.8% vs. 20.9%; p < 0.001). Multivariate analysis identified independent predictors: diabetes (OR = 1.9, 95% CI:1.1–3.8; p = 0.019), variceal bleeding indication (vs. ascites; OR = 2.1, 1.1–3.8; p = 0.012), and MELD score (OR = 1.03 per unit; 1.03–1.12; p < 0.001). **Conclusion:** Diabetes, variceal bleeding as the TIPS indication, and higher MELD scores independently predict 30-day post-TIPS infection. These findings underscore the need for enhanced pre-procedural risk stratification and targeted antimicrobial prophylaxis in high-risk cohorts. Future studies should validate preventive strategies.

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Characteristic	Total n=293	Infection 30 Day n=59	No Infection 30 Day n=234	p value
Age, mean ± SD	56.6 ± 8.9	57.2 ± 9.6	56.4 ± 8.8	0.608
Female Sex	105 (35.8)	29 (49.2)	76 (32.5)	0.018
TIPS type				
Initial	249 (85)	57 (96.6)	192 (82.1)	0.005
Revision	44 (15)	2 (3.4)	42 (17.9)	
MELD-NA, median (IQR)	17 (13-23)	20 (15-27)	17 (13-22)	<0.001
Cirrhosis etiology				
ETOH/MASLD/Mixed	220 (75.1)	51 (86.4)	169 (72.2)	0.095
Chronic Viral Hepatitis	28 (8.9)	4 (6.8)	22 (9.4)	
A1AT deficiency and hemochromatosis	5 (1.74)	0 (0)	5 (2.1)	
PSC/PBC/autoimmune	14 (14.8)	3 (5.1)	11 (4.7)	
Other	28 (9.6)	1 (1.7)	27 (11.5)	
TIPS Indication				
Ascites	161 (54.9)	27 (45.8)	134 (57.3)	<0.001
Variceal Bleeding	76 (25.9)	27 (45.8)	49 (20.9)	
TIPS Malfunction	49 (16.7)	3 (5.1)	46 (19.7)	
Other	7 (2.4)	2 (3.4)	5 (2.1)	
Rifaximin Use	120 (41)	22 (37.3)	98 (41.9)	0.522
Prior SBP	29 (9.9)	6 (10.2)	23 (9.8)	0.938
Child-Pugh Score				
A	25 (8.7)	3 (5.1)	22 (9.7)	0.454
B	188 (65.7)	34 (57.6)	154 (67.8)	
C	73 (25.5)	22 (37.3)	51 (22.5)	0.035
Diabetes	127 (43.3)	25 (42.4)	102 (43.6)	0.866
CKD	97 (33.1)	21 (35.6)	76 (32.5)	0.65
Hypertension	169 (57.7)	37 (62.7)	132 (56.4)	0.382

Disclosures: Shannon Sanda: Nothing to Disclose, John Martens: Nothing to Disclose, M. Katherine Dokus: Nothing to Disclose, Bandar Aljudaibi: Nothing to Disclose

2329 | PATHOMECHANISTIC BIOMARKERS LINK BACTERIAL TRANSLOCATION TO ENDOTHELIAL DYSFUNCTION AND HEPATIC FIBROGENESIS ACROSS DIFFERENT STAGES OF CIRRHOSIS

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Background: Liquid biomarkers may reflect specific pathomechnisms of cirrhosis including bacterial translocation (BT), macrophage activation, systemic inflammation, endothelial dysfunction, and fibrogenesis, but their dynamics across disease stages and specific etiologies remain unclear. **Methods:** Patients with advanced chronic liver disease were prospectively included in the Vienna Cirrhosis Study (VICIS). Ten pre-selected biomarkers were analyzed by ELISA and compared between compensated (CC), decompensated (DC) cirrhosis patients and liver-healthy controls (HC), as well as across alcohol-related (ALD) vs. viral hepatitis B and C (VIRAL) vs. metabolic dysfunction-associated (MASH) cirrhosis etiologies. Multivariable linear regression models were used to evaluate the independent association between biomarkers (log10-transformed), adjusted for liver disease severity. **Results:** Forty HC and 200 patients, comprising 100 CC (MELD: 10 [4]; HVPG: 13 [9]) and 100 DC (MELD: 14 [8]; HVPG: 19 [6]) were included. The main etiology was ALD in 106 (53%) patients, followed by MASH in 45 (22.5%), VIRAL in 41 (20.5%) and others in 8 (4%). BT, indicated by increased circulating levels of LPS-binding protein (LBP) was already increased in CC and peaked in DC (HC vs. CC vs. DC: 5.8 [1.8] vs. 7.0 [2.8] vs. 7.7 [4.8] µg/mL, $p = 0.002$). Soluble CD14 (sCD14), an LPS co-receptor that activates toll-like receptor 4 (TLR4), was elevated in DC compared to CC (1.93 [0.77] vs. 1.56 [0.47] µg/mL, $p < 0.001$). In DC patients, sCD14 levels correlated with LBP (Spearman's rho = 0.50, $p < 0.001$), and this association was consistent across all etiologies, supporting a key role of BT-driven TLR4 activation in DC. Systemic inflammation (IL-6 and TNF-α) was more pronounced in DC than in CC and correlated with sCD14 (IL-6: rho = 0.43; TNF-α: rho = 0.45; both $p < 0.001$). Notably, sCD14 was independently associated with markers of endothelial dysfunction (von Willebrand factor antigen, VWF) and liver fibrogenesis (tissue inhibitor of metalloproteinases 1, TIMP1; and Enhanced Liver Fibrosis [ELF] test) when adjusted for HVPG and MELD (VWF: $\beta = 0.139$, $p = 0.003$; TIMP1: $\beta = 0.254$, $p = 0.002$; ELF: $\beta = 0.04$, $p = 0.012$). **Conclusion:** Biomarkers reflecting inflammation, BT and macrophage activation are elevated in patients with DC, regardless of the underlying etiology. Increased sCD14 levels in DC suggest a contribution of BT-driven innate immune activation to endothelial dysfunction and fibrogenesis during cirrhosis progression.

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2330 | BIOELECTRICAL IMPEDANCE ANALYSIS PROVIDES NOVEL INSIGHTS INTO FACTORS ASSOCIATED WITH SARCOPENIA IN DECOMPENSATED CIRRHOSIS

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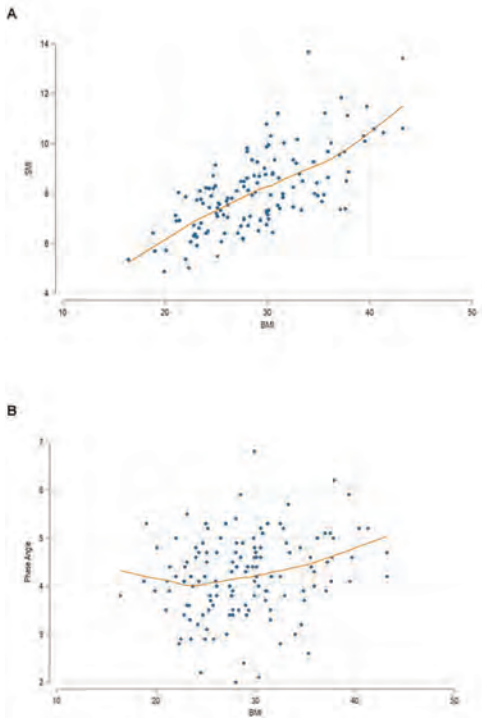
Background: Sarcopenia predicts poor outcomes in cirrhosis. Optimal assessment and modifiable risk factors remain ill-defined. Bioelectrical impedance analysis (BIA), specifically phase angle (PA) and appendicular skeletal muscle index (SMI), offers a non-invasive, objective assessment. Our study investigated factors associated with sarcopenia in outpatients with decompensated cirrhosis. **Methods:** We performed a cross-sectional analysis of 134 adults with decompensated cirrhosis evaluated for liver transplant (July 2023-present) from a single-center prospective cohort. Sarcopenia was assessed using BIA-derived PA ($\leq$5.6° in males, $\leq$5.4° in females) and SMI ($\leq$11.1 kg/m^2 in both sexes). Multivariable linear regression evaluated associations of demographic, clinical, and socioeconomic factors with PA and SMI, adjusting for sex, BMI, MELD-3.0, ascites grade, and cirrhosis etiology. Locally weighted scatterplot smoothing (lowess curves) was used to visualize the association between BMI and sarcopenia and derive potential BMI thresholds with the optimal BMI threshold confirmed in linear regression (i.e. highest adjusted R-squared). **Results:** Of 134 participants, median age was 55 years, 56% were male, 72% were Hispanic, median MELD was 16, and median BMI was 29. Major cirrhosis etiologies were ALD (49%) and MASH (25%); 49% were married, 29% unemployed, and 52% had income 25,000/year. Sarcopenia prevalence was high overall (PA: 96%, mean PA 4.2 [SD 0.9]; SMI: 94%, mean SMI 8.1 [SD 1.7]); highest among Hispanics (PA: 98%, SMI: 96%). Multivariable analysis showed female sex ($\beta = -0.52$, $p < 0.001$), MASH ($\beta = -0.46$, $p = 0.006$), moderate/severe ascites ($\beta = -0.39$, $p = 0.012$), and higher MELD ($\beta = -0.04$, $p = 0.005$) were independently associated with lower PA. Female sex ($\beta = -1.32$, $p < 0.001$) and Hispanic ethnicity ($\beta = -0.65$, $p < 0.001$) were associated with lower SMI. Higher BMI was strongly associated with higher PA ($\beta = 0.03$ per 1-unit BMI increase, $p = 0.027$) and greater SMI ($\beta = 0.18$, $p < 0.001$). Lowess curves showed a linear relationship between BMI and SMI (Fig 1A) and an inflection point in BMI on PA (Fig 1B). An optimal BMI threshold of 26 kg/m^2 was identified above which BMI had a protective effect on PA ($\beta = 0.05$, $p = 0.004$); in other words, each 1-unit BMI increase above 26 kg/m^2 was associated with a 0.05 PA increase. **Conclusion:** Sarcopenia prevalence is high in decompensated cirrhosis. Female sex, liver disease severity, and MASH were independently associated with poorer muscle quality. Female sex and Hispanic ethnicity were also independently associated with lower muscle mass. Higher BMI, particularly $\geq$26 kg/m², was protective against sarcopenia. These findings underscore the need for targeted interventions to mitigate sarcopenia in this vulnerable population, especially for women and Hispanics, and highlight the need for nuanced nutritional and functional assessments beyond BMI.

Figure 1. Association of BMI with (A) skeletal muscle index (SMI) and (B) Phase Angle (PA)



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2331 | COMBINATION OF CARVEDILOL AND ENDOSCOPIC VARICEAL LIGATION IS SUPERIOR TO CARVEDILOL ALONE FOR PRIMARY PROPHYLAXIS OF VARICEAL BLEEDING IN HIGH-RISK CIRRHOTICS: A RANDOMIZED CONTROLLED TRIAL

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Background: Primary prophylaxis against variceal hemorrhage in cirrhosis typically involves non-selective beta-blockers (NSBBs) or endoscopic variceal ligation (EVL). Carvedilol, a potent NSBB with α1-blocking activity, has shown superior portal pressure reduction compared to propranolol. However, its efficacy in combination with EVL in preventing first variceal bleed in high-risk cirrhotic patients remains inadequately studied. **Methods:** This single-center, open-label, randomized controlled trial enrolled 80 cirrhotic patients(July 2022–July 2023) with large varices or red color signs and no history of prior bleeding. Patients were randomized 1:1 to receive either (1) carvedilol alone or (2) carvedilol plus serial EVL until variceal eradication. The primary outcome was first variceal bleed within 1 year. Secondary outcomes included all-cause mortality, hospitalization for bleeding, and adverse events. **Results:** 72 patients (n = 36 per group) completed follow-up. First variceal bleeding occurred in 8.3% in the EVL+carvedilol group versus 25.0% with carvedilol alone (p = 0.041). All-cause mortality was significantly lower in the combination group (11.1% vs 27.8%, p = 0.048).Fewer hospitalizations due to bleeding were observed in the EVL+ carvedilol group (5.5% vs 22.2%, p = 0.031). Adverse event rates were similar between groups. **Conclusion:** Among cirrhotic patients with high-risk varices, combining EVL with carvedilol significantly reduces first variceal bleeding and mortality compared to carvedilol monotherapy. This dual-modality approach may represent a superior prophylactic strategy in selected high-risk populations.

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2332 | PROTON PUMP INHIBITOR USE AND RISK OF HEPATIC ENCEPHALOPATHY IN CIRRHOTIC PATIENTS: A META-ANALYSIS OF OBSERVATIONAL STUDIES

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Background: Hepatic encephalopathy (HE), a common complication of cirrhosis, contributes to cognitive dysfunction, reduced quality of life, and higher healthcare utilization. Proton pump inhibitors (PPIs) are frequently prescribed, often beyond evidence-based indications. Observational studies have linked PPI use to increased HE risk, possibly due to altered gut microbiota, infections, or intestinal permeability changes. Findings vary. This meta-analysis aimed to quantify the association between PPI use and HE in cirrhotic patients using adjusted effect estimates from observational data. **Methods:** A meta-analysis of observational studies was performed. Included studies reported adjusted odds ratios (ORs) or hazard ratios (HRs) assessing the association between PPI use and hepatic encephalopathy in adult cirrhotic patients. Data extracted: study design, population characteristics, outcome definitions, exposure classification, and adjusted effect sizes with 95% confidence intervals (CIs). Pooled ORs were calculated using a random-effects model (DerSimonian–Laird). Heterogeneity was assessed using I^2 and τ^2. Publication bias was evaluated via funnel plot with visual inspection for asymmetry. **Results:** Four observational studies (n = 169,090 cirrhotic patients) were included: two case-control, one prospective cohort, and one retrospective Medicare cohort. HE definitions varied, minimal, overt, and incident HE during follow-up. The pooled odds ratio for HE in PPI users was 3.48 (95% CI: 1.65–7.34), with high heterogeneity (I^2 = 88.7%, τ^2 = 0.3583). Zhu et al.'s inpatient study showed the largest effect; Tapper et al.'s Medicare cohort the smallest. Variability in setting, outcome definitions, and exposure classification likely contributed. Funnel plot showed asymmetry; smaller studies reported stronger effects. This meta-analysis shows a significant association between PPI use and HE in cirrhosis. Direction and magnitude were consistent despite heterogeneity. The indications for PPI use were not readily apparent on these studies. Given PPIs are often used in patients with gastrointestinal bleeding (GIB) and GIB is a risk factor for development of hepatic encephalopathy, it is possible that this may be a reason for the associated increased risk; thus, further prospective studies are needed to characterize this association. **Conclusion:** PPI use in cirrhotic patients was associated with increased odds of hepatic encephalopathy across four observational studies. The pooled effect estimate was statistically significant, with substantial between-study heterogeneity. Differences in study design, population setting, and outcome definitions may explain the observed variability. Future studies using

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prospective designs, standardized definitions of hepatic encephalopathy, and rigorous confounder adjustment will be necessary to further characterize this association.

Table 1: PPI use and Risk of HE in Cirrhosis

Figure 1: Forest plot showing individual and pooled odds ratios for hepatic encephalopathy associated with PPI use in cirrhotic patients.

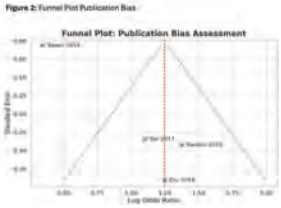

Figure 2: Funnel Plot Publication Bias

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2333 | AGE AS A PREDICTOR OF POST-TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT HEPATIC ENCEPHALOPATHY

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Background: Age is a known risk factor for adverse outcomes in various medical conditions, but its role as a predictor of complications following transjugular intrahepatic portosystemic shunt (TIPS) procedures, particularly hepatic encephalopathy (HE), remains unclear. Therefore, we aimed to evaluate the impact of age on 90-day post-TIPS outcomes, including HE, gastrointestinal (GI) bleeding, infections, hospital readmissions, and all-cause mortality. **Methods:** We used the TriNetX database to examine adult patients ($\geq$ 18 years) who underwent a TIPS procedure (2010-2025), stratified into two cohorts: those $>$70 years and those $<$70 years. Groups were propensity matched based on age, sex, race/ethnicity, cardiometabolic risk factors, medications (diuretics, beta-blockers), MELD, and Child-Pugh scores. Diagnoses, procedures, and medication use were extracted using ICD-9/10-CM, ICD-10-PCS, CPT®, and RxNorm codes. The primary outcome was incident HE, while secondary outcomes included mortality, GI bleeding, infections, and readmissions. **Results:** A total of 18,443 cirrhotic patients who underwent TIPS, including 6,090 patients $>$ 70 years (3,506 $>$ 75 years) were identified. Before matching, younger patients had a higher frequency of variceal hemorrhage (44% vs. 28%, $p < 0.001$), and ascites (45% vs. 41%, $p < 0.001$) compared to those $>$ 70 years, as well as higher bilirubin, ALT, and AST. After matching, 5,585 pairs were well-balanced. The mean age in the older group was 72 $\pm$ 6 years vs. 49 $\pm$ 12 years in the younger group. The majority of patients in both cohorts were White males and were evenly matched regarding cardiometabolic risk factors, and liver disease severity. Alcohol-associated cirrhosis was the most common underlying etiology of cirrhosis, followed by MASH-related cirrhosis, and viral hepatitis-associated cirrhosis. At 90 days post-TIPS procedure, the older cohort had significantly higher rates of HE (27% vs. 25%, $p = 0.02$) and all-cause mortality rates (11% vs. 7%, $p < 0.001$), as compared to the younger group. However, there were no significant differences in hospital readmissions, infections, or GI bleeding between both groups. Finally, a Cox proportional hazard model analysis demonstrated that older age was independently associated with a higher risk of developing HE after TIPS. Elevated bilirubin levels and INR (markers of more severe liver disease) were also significant predictors of increased risk of HE post-TIPS. **Conclusion:** Advanced age appeared to be a significant predictor of poorer outcomes following TIPS, particularly regarding hepatic encephalopathy and mortality. However, there were no significant differences in the incidence of infection or GI bleeding between groups. These findings highlight that tailored post-TIPS management strategies, particularly focused on HE prevention and treatment in older adults, are warranted.

Table 1. Demographic and clinical features in TIPS (stratified by age)

Baseline characteristics	Before propensity score matching			After Propensity score matching		
	Age<70 N=12,353	Age>70 N=6,090	Std diff	Age<70 N=5,585	Age>70 N= 5,585	Std diff
Age at diagnosis (yrs, mean, ±SD)	49±12	72±6	2.0	49±12	72±6	2.0
Women, n (%)	4,839 (39)	2,751 (45)	0.1	2,391 (43)	2,484 (44)	0.03
White, n (%)	9,181 (74)	4,802 (79)	0.1	4,371 (78)	4,354 (78)	0.007
Black, n (%)	1,023 (8)	393 (6)	0.1	397 (7)	378 (7)	0.01
BMI (mean, ±SD)	30±8	29±7	0.1	29±7	29±7	0.03
Diabetes mellitus type II, n (%)	2,764 (22)	1,976 (32)	0.2	1,697 (30)	1,661 (30)	0.01
Hypertension, n (%)	3,945 (32)	2,738 (45)	0.3	2,295 (41)	2,285 (41)	0.004
Obesity, n (%)	2,036 (16)	933 (15)	0.03	1,165 (21)	786 (15)	0.1
Hyperlipidemia, n (%)	1,559 (13)	1,551 (25)	0.3	1,174 (21%)	1,159 (21)	0.007
CKD, n (%)	1,435 (12)	1,030 (17)	0.2	702 (13)	886 (16)	0.1
Cirrhosis etiology						
Alcohol, n (%)	4,866 (39)	1,191 (20)	0.4	1,224 (22)	1,185 (21)	0.02
MASH, n (%)	1,084 (9)	584 (10)	0.03	530 (9)	521 (9)	0.01
Viral, n (%)	1,298 (11)	527 (9)	0.1	523 (10)	495 (7)	0.1
Liver-related decompensation events						
Ascites, n (%)	5,524 (45)	2,514 (41)	0.1	2,454 (44)	2,318 (42)	0.05
Variceal hemorrhage, n (%)	5,435 (44)	1,705 (28)	0.3	1,620 (29)	1,676 (30)	0.003
Medications						
Diuretics, n (%)	5,959 (48)	3,025 (50)	0.02	2,775 (50)	2,689 (48)	0.03
Beta blockers, n (%)	2,291 (19)	1,029 (17)	0.04	977 (17)	944 (17)	0.01
Albumin (g/dL, mean, ±SD)	3.1±0.7	3.2±0.7	0.04	3.2±0.7	3.1±0.7	0.04
Bilirubin (mg/dL, mean, ±SD)	2.1±3.6	1.4±2.2	0.2	1.7±2.9	1.4±2.2	0.1
INR (mean, ±SD)	1.4±0.5	1.4±0.5	0.1	1.4±0.5	1.4±0.5	0.1
Creatinine (mg/dL, mean, ±SD)	1.0±0.9	1.2±0.8	0.2	1.0±1.0	1.2±0.8	0.05

Abbreviations- TIPS: transjugular intrahepatic portosystemic shunt; BMI: body mass index; CKD: chronic kidney disease; MASH: metabolic dysfunction-associated steatotic liver disease; INR: international normalized ratio

Table 2. 90-day clinical outcomes post-TIPS (stratified by age)

Outcomes	Age<70 N (%)	Age>70 N (%)	HR (95% CI)	P value
HE, n (%)	791/3,166 (25.0)	933/3,408 (27.4)	1.12 (1.02-1.23)	**0.02**
*Infections, n (%)	233/4,504 (5.2)	245/4,692 (5.2)	1.02 (0.85-1.22)	0.9
GI bleeding, n (%)	118/4,217 (2.8)	127/4,300 (3.0)	1.07 (0.83-1.38)	0.6
Hospital readmission, n (%)	137/1,100 (12.5)	137/1,150 (11.9)	0.95 (0.75-1.21)	0.7
All-cause mortality, n (%)	416/5,585 (7.4)	362/5,585 (10.5)	1.44 (1.27-1.64)	**<0.001**

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2334 | ALBUMIN INFUSION MEDIATED INCREASE IN STRUCTURAL AND FUNCTIONAL MODIFICATION CAN EXACERBATE LIVER INJURY IN DECOMPENSATED CIRRHOSIS

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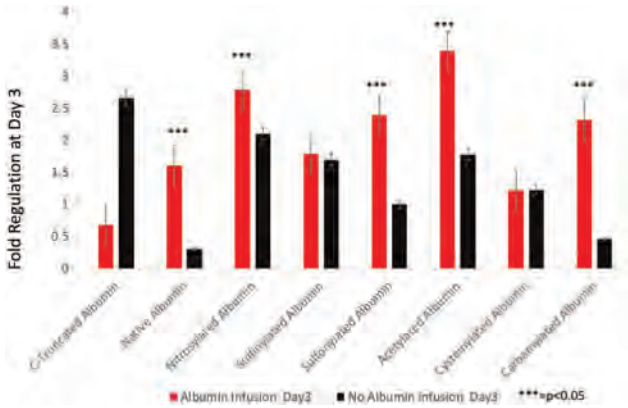
Background: Human albumin solution (HAS) is widely used for managing various complications in decompensated cirrhosis (DC), with long-term infusion considered a disease-modifying intervention. However, the impact of infused albumin on the structural and functional dynamics including advance oxidation of protein along with Ischemia modification of circulating albumin and its correlation with disease severity remains insufficiently explored and was studied in an RCT in DC patients [Trial registration - NCT05937048]. **Methods:** Decompensated cirrhosis patients aged ≥ 18 years with serum albumin ≤ 2.5 g/dL were allocated to two groups. Group A received standard-of-care (SOC) plus daily 20% HAS to maintain serum albumin ≥ 3 g/dL, along with standard medical therapy (SMT). Group B received SOC and SMT alone. High-resolution mass spectrometry and biochemical assays assessed albumin modifications at baseline, Day 1, and Day 3. Inflammatory markers (IL-6, TNF-α, CRP) and clinical parameters (MELD score, ABIC, AGE, IMA, AOPP) were also measured. **Results:** Baseline level of all albumin modification (Native, cysteinylated, Sulfinylated, Sulfonylated C-Truncated, Nitrosylated, Acetylated and Carbamylated Albumin) were comparable between Group A and Group B respectively. Albumin infusion by Day 3 significantly increased native albumin by 5 folds ($p < 0.05$) in Group A along with significant increase in Sulfonylated albumin (pro-inflammatory) by 3 folds, Carbamylated albumin (5.2 folds; pro-inflammatory) and acetylated albumin (4 folds; known for reduction of bilirubin binding $p < 0.05$) as compared to Group B. Increase in pro-inflammatory and dysfunctional albumin phenotype by Day 3 in Group A significantly correlated with increase in Advance Glycosylated End products (AGE; >2Folds), Ischemia Modified albumin (IMA, IMAr; >2Folds), Advance oxidation proteins products (AOPP >2Folds) levels, MELD score (>2Folds,$p < 0.045$) and CRP levels (>2FC,$p < 0.05$) respectively. Interestingly the levels of ABIC (albumin binding capacity) was significantly decreased in Group A as compared to Group B (>2FC, $p < 0.05$) suggesting decrease in albumin functionality and also suggestive of increase in liver severity in Group A respectively. Day-3 increase in carbamylated albumin documented the highest diagnostic efficiency of AUC $>$ 0.89 $p < 0.05$ for prediction of pro-inflammatory conversion of albumin in DC patients. **Conclusion:** Standard-dose human albumin solution (HAS) induces pro-inflammatory structural and functional changes in circulating albumin. Elevated carbamylated albumin levels serve as an indicator for this pro-inflammatory shift. Monitoring albumin carbamylation is recommended in decompensated cirrhosis patients receiving HSA



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2335 | IMPACT OF FRAILTY ON CLINICAL OUTCOMES AMONG HOSPITALIZED PATIENTS WITH HEPATORENAL SYNDROME: A NATIONWIDE ANALYSIS FROM 2018–2022

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Background: Hepatorenal syndrome (HRS) is a life-threatening complication of advanced liver disease

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characterized by rapid renal dysfunction and high inpatient mortality. While frailty has emerged as a key prognostic factor in chronic liver disease, its impact on hospitalized patients with HRS remains unclear. We aimed to evaluate the association between frailty and inpatient outcomes in HRS hospitalizations using a nationally representative database. **Methods:** We conducted a retrospective cohort study using the National Inpatient Sample (NIS) from 2018 to 2022 to identify adult hospitalizations with a principal diagnosis of HRS. Frailty was assessed using the Hospital Frailty Risk Score (HFRS), categorized as low (<5), intermediate (5–15), and high (>15). Descriptive analyses were performed to estimate unadjusted incidence rates of in-hospital outcomes. Multivariable logistic and linear regression models were used to determine adjusted odds ratios (aOR) and 95% confidence intervals (CI), controlling for demographics, comorbidity index, income, insurance and hospital-level variables. **Results:** A total of 18,315 HRS hospitalizations were identified, with 29.9% classified as low frailty (n = 5,480), 67.7% intermediate (n = 12,390), and 2.4% high frailty (n = 445). Descriptive analysis showed an increasing trend of adverse outcomes with higher frailty scores, including in-hospital mortality (17.8% low vs. 29.2% high), ICU admission (6.1% vs. 20.2%), respiratory failure (5.2% vs. 20.2%), and sepsis (1.8% vs. 15.7%). LOS and total hospital charges also increased with frailty (mean LOS: 7.1 vs. 13.6 days; charges: $83,711 vs. $166,273; $p<0.001$ for all comparisons). Adjusted regression analysis revealed that high frailty was independently associated with higher mortality (aOR: 2.02 [1.20–3.40], $p=0.008$), ICU admission (aOR: 4.41 [2.37–8.16], $p<0.001$), respiratory failure (aOR: 4.40 [2.37–8.16], $p<0.001$), sepsis-related complications (aOR: 10.01 [4.57–21.95], $p<0.001$), and cerebrovascular accident (aOR: 7.18 [1.47–35.10], $p=0.015$). LOS costs also remained significantly elevated in the high frail adjusted models (aOR: 7.09 [4.51 – 9.67], $p<0.001$). **Conclusion:** Our study reveals a substantial association between higher frailty scores and adverse clinical outcomes among HRS-related hospitalizations. These findings highlight the importance of frailty assessment in managing patients with hepatorenal syndrome, emphasizing the need for targeted interventions and resource allocation for frail individuals to improve outcomes and reduce healthcare burden. Incorporating the Hospital Frailty Risk Score into clinical workflows may enhance risk stratification and guide personalized management strategies for this high-risk population.

Table 1.- Descriptive and Adjusted Inpatient Outcomes Among Hospitalizations for Hepatorenal Syndrome (N= 18315) Stratified by Frailty Risk (HFRS)

Disclosures: Daniel Gonzalez Mosquera: Nothing to Disclose, Maria Mateo Chavez: Nothing to Disclose, Mariana Nunes Ferreira: Nothing to Disclose, Sakina Paracha: Nothing to Disclose, Carolina Gonzalez Mosquera: Nothing to Disclose, Juan Martinez-Ortega: Nothing to Disclose, Yassine Kilani: Nothing to Disclose, Cynthia Victor-Prophete: Nothing to Disclose

2336 | AETIOLOGY-SPECIFIC PATTERNS OF HEPATIC RECOMPENSATION IN ALCOHOL-RELATED AND VIRAL HEPATITIS B AND C CIRRHOSIS: A BAVENO MULTICENTRE STUDY

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Background: Removal of the primary aetiological factor ('cure') may result in hepatic recompensation in patients with decompensated cirrhosis. This study assessed aetiology-specific differences in the incidence of recompensation and its impact on transplant-free survival. **Methods:** In this multicentre Baveno-endorsed study, patients with decompensated cirrhosis due to alcohol-related liver disease (ALD), hepatitis B (HBV) or hepatitis C (HCV) were included at time of aetiological treatment (abstinence or start of antiviral treatment) until December 2022. According to Baveno VII, recompensation was defined by (i) resolution of ascites and hepatic encephalopathy, (ii) no variceal bleeding for 1 year, and (iii) improved hepatic function. Alcohol relapse or viral reinfection/relapse led to censoring. **Results:** Among 1793 included patients (68.6% male; median age: 57 years), the underlying aetiology was ALD in 35.3% (n = 633), HBV in 35.6% (n = 639) and HCV in 29.1% (n = 521). Baseline MELD was highest in ALD (median: 17, IQR: 13-21), followed by HBV (median 13, IQR: 11-17) and HCV (median: 11, IQR: 9-14) ($p < 0.001$). Over a median follow-up of 54.6 months, 662 patients (36.9%) achieved recompensation. The overall 3-year cumulative incidence of recompensation was 34.0%, with 28.8% in ALD, 35.5% in HBV and 37.6% in HCV. Nevertheless, the aetiology was not significantly linked to the likelihood of recompensation after accounting for MELD, age and sex with an adjusted subdistribution hazard ratio of 1.010 (95% CI: 0.478-2.135; $p = 0.980$) for HBV vs. ALD and 1.228 (95%CI: 0.477-3.163; $p = 0.670$) for HCV vs. ALD. During the study period, 617 patients died: n = 123 in ALD (19.4%), n = 278 in HBV (43.5%) and n = 216 in HCV (41.5%). At 5 years, the cumulative incidence of all-cause mortality was 32.8% overall, with 19.2% in ALD, 47.7% in HBV and 29.9% in HCV. After adjusting for MELD, age and sex, recompensation (included as time-varying covariate) was associated with a significantly reduced risk of all-cause mortality across all aetiologies. Specifically, in ALD the adjusted hazard ratio was 0.223 (95%CI: 0.111-0.449; $p < 0.001$), in HBV 0.511 (95%CI: 0.304-0.860; $p = 0.011$) and in HCV 0.566 (95%CI: 0.417-0.769; $p < 0.001$). **Conclusion:** The incidence of hepatic recompensation is comparable between ALD, HBV and HCV after accounting for disease severity at baseline. Recompensation improves transplant-free survival across all treatable aetiologies.
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2337 | READMISSION RATES FOR PATIENTS WITH CIRRHOSIS IN SASKATOON

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Background: Cirrhosis is a major global health burden, causing over 1.5 million deaths annually. In the U.S., cirrhosis-related deaths rose by 65% between 1999 and 2016. In Canada, prevalence is projected to double by 2040, driven by increasing rates of alcohol-associated liver disease (ALD) and metabolic-associated steatotic liver disease (MASLD). Hospitalizations are frequently due to complications of portal hypertension such as ascites, variceal hemorrhage, hepatic encephalopathy (HE), and hepatorenal syndrome (HRS). Identifying predictors of readmission and mortality is critical to improving outcomes. **Methods:** We conducted a retrospective cohort study of 768 adult patients hospitalized with cirrhosis at Royal University Hospital and St. Paul's Hospital in Saskatoon, Saskatchewan, Canada (2016–2022). Patients with hepatocellular carcinoma or receiving palliative care were excluded. Data included demographics, etiology, MELD-Na, Child-Pugh class, complications, length of stay (LOS), discharge status, and readmissions at 30, 60, 90, and > 90 days. Univariate and multivariate analyses were used to identify predictors of 30-day readmission. Mortality was analyzed by complication type and burden. **Results:** The 30-day readmission rate was

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23.4%, with 44.4% readmitted beyond 90 days. ALD was the leading etiology (49.7%), followed by MASLD and hepatitis C. LOS increased with MELD-Na category (<15, 15–20, >20), ranging from 7.0 to 12.0 days. Patients with MELD-Na >20 had the highest 30-day readmission rate (31.0%, $p=0.0099$). On multivariate analysis, higher Child-Pugh class was an independent predictor of 30-day readmission ($p=0.018$). Mortality was strongly associated with complication burden: patients with ≥ 4 complications had a 1-year mortality of 59.3%. HRS ($p<0.0001$) and HE ($p=0.021$) were the strongest individual predictors of death. ALD and mixed ALD/HCV etiologies were associated with higher readmission and mortality rates. **Conclusion:** In this Canadian dual-centre cohort, cirrhosis-related readmissions and mortality were highest in patients with advanced liver disease, multiple complications, and alcohol-related etiologies. HRS and HE were the most lethal complications. These findings support the need for risk-based discharge planning, outpatient follow-up, and integrated care models targeting high-risk subgroups.

Readmission Rates for Patients with Cirrhosis in Saskatoon

Disclosures: Sushila Pathak: Nothing to Disclose

2338 | MEASURED SLEEP QUALITY AND CONSISTENCY ARE ASSOCIATED WITH IMPAIRED QOL AND SLEEP FUNCTION IN PATIENTS WITH CIRRHOSIS

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Background: Many patients with cirrhosis report poor sleep quality, but formal assessment is rarely performed in clinical practice, making diagnosis and intervention difficult. Wearable devices offer a non-invasive, longitudinal method to track and characterize sleep but are understudied in this population. We hypothesized that worse measured short-term sleep would be associated with reduced patient reported sleep quality and overall quality of life (QoL). **Methods:** A prospective cohort of patients with cirrhosis were enrolled from 8/2023-5/2025. At baseline we collected clinical, laboratory, and survey data including the Pittsburgh Sleep Quality Index (PSQI) and the Chronic Liver Disease Questionnaire (CLDQ), where PSQI ≥ 5 and CLDQ <5 represented poor sleep and poor QoL, respectively. Sleep was longitudinally tracked for 6 months with a commercial wearable, the Oura Ring. We analyzed the first 14 recorded nights among participants with $\geq$ 14 nights of sleep data within 28 days of enrollment. Sleep data included total sleep time (TST), REM and deep sleep time, sleep efficiency (%SE), bedtime variability, wake after sleep onset (WASO), and sleep midpoint. Multivariable mixed effects models adjusting for age, gender, CTP score, and BMI were used to evaluate associations between objective and subjective measures of sleep quality and QoL. **Results:** Of 117 enrolled participants, 83 had ≥ 14 full nights of analyzable Oura data (n = 1162 nights). Among these, 73% had PSQI ≥ 5 and 55% CLDQ <5. Mean CTP scores were higher in those who reported poor sleep by PSQI (7.0 vs. 5.9, $p=0.03$), as well as lower QoL by CLDQ (7.1 vs 6.2, $p=0.049$). Mean TST was 388 minutes, with 75 min REM, 66 min deep sleep, 98 min WASO and 80% SE, with a mean sleep midpoint at 3:31 AM. Compared to those reporting good sleep, participants with poor sleep had Lower % SE (–4.9%, CI: –8.0 to –1.8, $p = 0.002$) Later average sleep midpoint (3:51 AM vs. 2:49 AM, $p < 0.001$) and Greater night-to-night variability in sleep midpoint (7.96 vs. 5.32 hours, $p < 0.001$), Higher %SE and lower WASO were associated with improved overall QoL. These associations remained significant in mixed-effects models adjusting for age, gender, BMI, and CTP score, except for WASO, which approached significance ($p = 0.056$). **Conclusion:** Impaired sleep efficiency and sleep consistency measured over a short period, 14 days, were associated with reduced QoL and self-reported sleep quality in cirrhosis. These findings suggest the clinical potential of wearable technology to identify sleep-related impairment and improve clinical monitoring in liver disease care. Later sleep midpoints and more variability in sleep period timing have been associated with circadian rhythm dysfunction, which may offer a therapeutic target for future studies to improve sleep and wellbeing in cirrhosis.

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Sleep Measure	Poor Reported Sleep (PSQI ≥ 5)		Impaired Overall QoL (CLDQ < 5)	
	Univariable Regression β [95% CI]	Multivariable Regression β [95% CI]	Univariable Regression β [95% CI]	Multivariable Regression β [95% CI]
Total Sleep time (min)	-48.9 [-75.2, -22.6] *	-41.6 [-66.7, -16.5]*	-5.1[-30.7,20.5]	-10.9[-33.9,13.8]
Sleep efficiency (%)	-0.05 [-0.79, -0.18]*	0.04 [-0.07, -0.01] *	-0.03 [-0.06, -0.001] *	-0.04 [-0.06,0.01] *
Wake after sleep onset (min)	21.4 [3.2,39.7] *	16.99[-0.4,34.4]	18.4 [1.8,34.9] *	19.64 [4.3,35.1] *
Average sleep midpoint (hours past 00:00)	1.02 [0.38,1.6] *	1.11[0.48,1.8] *	0.45 [-0.15,1.05]	0.31 [-0.29,0.92]
Midpoint variability (hours)	0.95 [0.52,1.4]*	1.02 [0.45,1.5] *	0.41 [-0.14,0.97]	0.41 [-0.29,1.09]

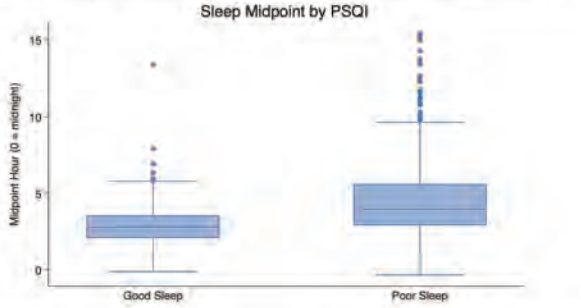

Table. Associations between objective sleep measures and subjective sleep quality and quality of life in patients with cirrhosis. **Figure.** Bar plot of the measured sleep midpoint, where box represents intraquartile range and whiskers represent upper and lower adjacent values. Abbreviations: PSQI: Pittsburgh sleep Quality Index, CLDQ: Chronic Liver Disease Questionnaire, Multivariable regression adjusting for age, gender, CTP score, and BMI, * Significant at $p<0.05$

Disclosures: Olivia Blocker: Nothing to Disclose, Ziyu Liu: Nothing to Disclose, Brian McSteen: Nothing to Disclose, Jessica Siguencia: Nothing to Disclose, Jialin Gao: Nothing to Disclose, Avesh Thuluvath: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose, Ana Krieger: Nothing to Disclose, Himel Mallick: Nothing to Disclose, Robert Brown: Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant, Adam Buckholz: Nothing to Disclose

2339 | DIRECT ORAL ANTICOAGULANTS VERSUS ENOXAPARIN FOR PORTAL VEIN THROMBOSIS IN CIRRHOSIS WITHOUT HCC:A REAL-WORLD COMPARATIVE STUDY

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Background: Direct oral anticoagulants (DOACs) are increasingly used for managing portal vein thrombosis (PVT) in cirrhotic patients without hepatocellular carcinoma, but comparative real-world data are limited. We compared clinical outcomes in cirrhotic patients receiving apixaban, rivaroxaban, or enoxaparin. **Methods:** Adult cirrhotic patients with PVT initiating apixaban (n = 2,259), rivaroxaban (n = 442), or enoxaparin (n = 6,262) were identified from the TriNetX database. Propensity score matching balanced demographic, clinical, and laboratory characteristics. Outcomes included a primary composite of ascites, hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), variceal bleeding, and all-cause mortality. Secondary outcomes included individual components of the primary composite, liver transplantation, transjugular intrahepatic portosystemic shunt (TIPS) placement, and intestinal ischemia. Patients with hepatocellular carcinoma (HCC) were excluded. Outcomes were assessed using odds ratios (OR), 95% confidence intervals (CI), and two-sided p-values. **Results:** Demographic and clinical characteristics of our study population can be found in Table 1. After matching, the primary composite was noted to occur similarly between apixaban and rivaroxaban cohorts, (60.8% vs 59.2%; OR 1.07, 95% CI [0.82–1.40], p = 0.63) and there was no significant difference in risk of variceal bleed. Use of apixaban was associated with higher liver transplant rates (12.7% vs 5.7%; OR 2.42, 1.48–3.96, p < 0.001), but lower events of intestinal ischemia (9.1% vs 14.7%; OR 0.58, 0.38–0.88, p = 0.009), when compared to use of rivaroxaban. Compared to enoxaparin, apixaban significantly reduced the primary composite outcome (59.1% vs 72.5%; OR 1.82, 1.60–2.06, p < 0.001), all-cause mortality (21.4% vs 39.7%; OR 2.43, 2.13–2.77, p < 0.001), and incidence of variceal bleeding (19.9% vs 24.9%; OR 1.33,1.16–1.53, p < 0.001). Liver transplant rates were similar between apixaban and enoxaparin cohorts (11.9% vs 11.8%; OR 0.98, 0.82–1.18, p = 0.853). Compared to patients on rivaroxaban, those on enoxaparin had an increased risk of primary composite outcome (67.2% vs 58.8%; OR 1.44, 1.09–1.89, p = 0.01), and all-casue mortality (31.9% vs 25.1%; OR 1.40, 1.04–1.88, p = 0.025), and no significant difference in risk of variceal bleeding (25.3% vs 21.4%; p = 0.175). Additional findings are outlined in Table 2. **Conclusion:** In cirrhotic patients with PVT, DOACS demonstrated superior effectiveness and safety—markedly lowering hepatic decompensation, intestinal ischemia, and all-cause mortality—compared with enoxaparin. These findings support DOACs as the preferred anticoagulation strategy for this population.

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Table 1

Characteristic	Apixaban (n=2,258)	Rivaroxaban (n=442)	Enoxaparin (n=6,282)
Demographics			
Age at Index (mean ± SD)	60.8 ± 12.4	59.4 ± 12.8	57.9 ± 13.1 (100%)
White	1722 (76.2%)	348 (78.7%)	4,657 (74.5%)
Black or African American	163 (7.2%)	34 (7.7%)	484 (7.7%)
Hispanic or Latino	220 (9.7%)	35 (7.9%)	758 (12.1%)
American Indian or Alaska Native	13 (0.6%)	10 (2.3%)	102 (1.6%)
Asian	58 (2.6%)	10 (2.3%)	159 (2.5%)
Native Hawaiian/Pacific Islander	10 (0.4%)	10 (2.3%)	22 (0.4%)
Not Hispanic or Latino	1583 (70.1%)	317 (71.7%)	4,247 (67.9%)
Female	929 (41.1%)	177 (40%)	2,705 (43.3%)
Male	1288 (57%)	261 (59%)	3,414 (54.6%)
Clinical Diagnoses			
Type 2 diabetes mellitus	862 (38.2%)	145 (32.8%)	2,351 (37.6%)
Essential hypertension	1278 (56.6%)	231 (52.3%)	3,574 (57.1%)
Hyperlipidemia	743 (32.9%)	130 (29.4%)	1,776 (28.4%)
Coronary artery disease	454 (20.1%)	70 (15.8%)	1,025 (16.4%)
Chronic kidney disease	444 (19.7%)	61 (13.8%)	1,023 (16.4%)
Atrial fibrillation	309 (13.7%)	52 (11.8%)	529 (8.5%)
Pulmonary embolism	152 (6.7%)	35 (7.9%)	296 (4.7%)
DVT lower extremity	131 (5.8%)	45 (10.2%)	280 (4.5%)
Alcohol abuse	395 (17.5%)	68 (15.4%)	1,728 (27.6%)
Nicotine dependence	475 (21%)	96 (21.7%)	1,836 (29.4%)
Medications			
Aspirin	608 (26.9%)	118 (26.7%)	1,668 (26.6%)
Clopidogrel	129 (5.7%)	21 (4.8%)	242 (3.9%)
Ticagrelor	12 (0.5%)	10 (2.3%)	24 (0.4%)
Warfarin	181 (8%)	51 (11.5%)	798 (12.8%)
Laboratory			
ALT (mean ± SD)	46.7 ± 118.1 (88.6%)	41.0 ± 106.1 (81.4%)	46.3 ± 83.7 (90.8%)
AST (mean ± SD)	56.4 ± 122.0 (88%)	50.3 ± 91.9 (80.5%)	71.4 ± 144.0 (90.3%)
ALP (mean ± SD)	157.8 ± 155.9 (87.9%)	150.3 ± 144.5 (80.5%)	176.9 ± 170.8 (89.5%)
Bilirubin (mean ± SD)	1.8 ± 2.6 (87.9%)	1.4 ± 1.6 (80.5%)	3.2 ± 5.0 (89.5%)
INR (mean ± SD)	1.4 ± 0.4 (82.9%)	1.4 ± 0.6 (75.1%)	1.5 ± 0.5 (85.1%)
Creatinine (mean ± SD)	1.0 ± 0.5 (87.1%)	0.9 ± 0.4 (80.1%)	0.9 ± 0.5 (89.7%)
Albumin (mean ± SD)	3.3 ± 0.7 (87%)	3.4 ± 0.7 (78.5%)	3.0 ± 0.7 (88.0%)
Platelets (mean ± SD)	156.2 ± 130.0 (88.9%)	179.4 ± 144.6 (81.7%)	148.3 ± 113.6 (90.8%)

Table 2

Outcome	Risk % (Apixaban)	Risk % (Rivaroxaban)	Odds Ratio (95% CI)	p-value
Primary composite	60.8	59.2	1.07 (0.82–1.40)	0.63
Mortality	21.3	25.4	0.80 (0.58–1.09)	0.152
Variceal bleed	22.2	21.5	1.04 (0.76–1.43)	0.807
SBP	6.1	2.9	2.15 (1.09–4.22)	0.023
Ascites	38.8	35.6	1.15 (0.87–1.51)	0.329
Transplant	12.7	5.7	2.42 (1.48–3.96)	<0.001
Hepatic encephalopathy	18.6	13.8	1.42 (0.99–2.04)	0.055
HRS	5.2	3.9	1.37 (0.72–2.61)	0.332
TIPS	2.3	2.3	1.00 (0.41–2.43)	1
Intestinal ischemia	9.1	14.7	0.58 (0.38–0.88)	0.009
Outcome	**Risk (%) (Enoxaparin)**	**Risk (%) (Apixaban)**	**Odds Ratio (95% CI)**	**p-value**
Primary composite	72.5	59.1	1.82 (1.60–2.06)	<0.001
Mortality	39.7	21.4	2.43 (2.13–2.77)	<0.001
Variceal bleed	24.9	19.9	1.33 (1.16–1.53)	<0.001
SBP	9.4	5.1	1.91 (1.51–2.42)	<0.001
Ascites	46.3	40.4	1.27 (1.13–1.44)	<0.001
Transplant	11.8	11.9	0.98 (0.82–1.18)	0.853
Hepatic encephalopathy	21.2	17.7	1.25 (1.08–1.45)	0.003
HRS	6.9	4.3	1.65 (1.27–2.14)	<0.001
TIPS	2.5	2.4	1.06 (0.73–1.54)	0.773
Intestinal ischemia	6.8	11.9	0.54 (0.44–0.67)	<0.001
Outcome	**Risk % (Enoxaparin)**	**Risk % (Rivaroxaban)**	**Odds Ratio (95% CI)**	**p-value**
Primary composite	67.2	58.8	1.44 (1.09–1.89)	0.01
Mortality	31.9	25.1	1.40 (1.04–1.88)	0.025
Variceal bleed	25.3	21.4	1.24 (0.91–1.70)	0.175
SBP	9.8	3	3.56 (1.89–6.72)	<0.001
Ascites	48.5	35.1	1.74 (1.33–2.29)	<0.001
Transplant	13	5.7	2.47 (1.51–4.04)	<0.001
Hepatic encephalopathy	19.6	13.7	1.54 (1.07–2.21)	0.018
HRS	5.5	3.6	1.53 (0.80–2.92)	0.195
TIPS	3.4	2.3	1.52 (0.67–3.42)	0.31
Intestinal ischemia	7.3	14.8	0.45 (0.29–0.71)	<0.001

Disclosures: Mohamed Nadeem: Nothing to Disclose, Shilpa Junna: Nothing to Disclose, Archana Kharel: Nothing to Disclose

2340 | POPULATION-LEVEL PATTERNS OF RECOMPENSATION IN CIRRHOSIS AND THEIR IMPACT ON MELD-NA TRAJECTORIES

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Background: Cirrhosis has traditionally been viewed as a progressive, unidirectional disease advancing from compensation to decompensation. However, emerging preliminary data support the concept of recompensation, wherein patients with decompensated cirrhosis can achieve a return to a compensated state. Understanding the frequency and biochemical markers of recompensation at the population level may have important implications for prognostication and disease management. This study aimed to characterize recompensation across distinct etiologies of liver disease and to evaluate longitudinal changes in MELD-Na trajectories among recompensated versus non-recompensated patients. **Methods:** This was a retrospective cohort study using data from the Veterans Health Administration. Patients with established cirrhosis due to MASLD, ALD, MetALD, HCV, or ALD+HCV who experienced an incident decompensation were included. Decompensation was identified based on paracentesis data, use of medications (diuretics, lactulose, rifaximin), and documented variceal bleeding. From the time of decompensation, patients were followed for up to 18 months. Recompensation was defined as the absence of paracentesis or decompensation-related medications for at least 12 consecutive months, with status also assessed at 18 months. MELD-Na trajectories were compared between recompensated and non-recompensated patients using linear regression. **Results:** A total 20,119 patients with cirrhosis and incident decompensation were included; the majority were MASLD (10,509), followed by HCV (7,376), ALD (5,919), MerALD (3,214), and ALD+HCV (2,101). There were significant differences in observed recompensation rates at 12 and 18 months across etiologies of liver disease (each $p < 0.001$), with HCV demonstrating the highest recompensation rates and ALD the lowest. For instance, 18% of patients with HCV had recompensation through 18 months, versus 12.4% MASLD and 11.7% ALD (Table 1). In comparing patients who remained recompensated through 18 months versus not, there were significant differences in MELD-Na trajectories. Significant declines in median MELD-Na were observed in recompensated patients (beta -0.34/month, $p = 0.04$), while there was no significant change in non-recompensated patients (beta -0.12/month, $p = 0.12$; Figure 1). **Conclusion:** Recompensation was observed across steatotic liver disease phenotypes and in HCV-related cirrhosis within this population-level dataset, with rates varying by etiology. Patients who achieved recompensation showed a significant decline in MELD-Na over time, supporting its association with measurable biochemical improvement. These results highlight recompensation as a clinically meaningful outcome and support the need for further investigation into its role as a prognostic marker and treatment target.

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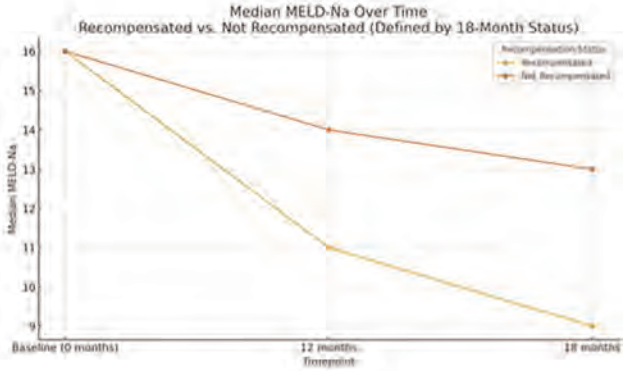
Table 1.

Factor	ALD	ALD+HCV	HCV	MASLD	MetALD	p-value
N	5919	2101	7376	10509	3214	
Recompensation at 12 months*	639 (14.6%)	308 (19.3%)	1135 (21.1%)	1097 (14.8%)	389 (15.3%)	<0.001
Recompensation at 18 months*	503 (11.7%)	272 (17.4%)	943 (18.0%)	898 (12.4%)	330 (13.2%)	<0.001

* Computed among patients with follow-up through timepoint

Figure 1.



Disclosures: Anna Goebel: Nothing to Disclose, Siqi Zhang: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Eurofins: Grant/Research Support, David Kaplan: AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Sirtex: Advisor, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research Support, Nadim Mahmud: Grifols: Grant/Research Support

2342 | HIGHER PLATELET COUNTS DEFINE A LOW-RISK SUBGROUP AMONG RECOMPENSATED HBV CIRRHOSIS: A PROPENSITY-MATCHED COHORT STUDY

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Background: Recompensation could be achieved by effective etiological treatment in patients with HBV-related decompensated cirrhosis. However, it remains unclear whether the clinical prognosis of those who achieve recompensation is comparable to that of patients with compensated cirrhosis who have never experienced decompensation. **Methods:** Patients with HBV-related cirrhosis treated with first-line nucleos(t)ide analogues were enrolled from two cohorts: a retrospective cohort with treatment-naïve decompensated cirrhosis; a prospective cohort with treatment-naïve HBV-related compensated cirrhosis. Participants were classified into 2 groups: (1) compensated group, (2) recompensated group according to Baveno VII criteria. Propensity score matching (1:1) matched recompensated patients at their recompensation time point to compensated patients at 1 year of antiviral therapy. The primary outcomes included overall survival, liver-related mortality, incidence of decompensation, and hepatocellular carcinoma (HCC). Kaplan-Meier analysis and Cox proportional hazards models were used to compare outcomes between groups. **Results:** A total of 223 patients with recompensated cirrhosis and 859 patients with compensated cirrhosis following one year of anti-HBV treatment were enrolled in this study. After propensity score matching, well-balanced cohorts were obstained. During a median follow-up of 45.0 months (IQR: 31.0–53.0), patients with recompensated cirrhosis had a significantly higher risk of developing decompensation and HCC compared to those with compensated cirrhosis (HR = 1.95, 95%CI:1.29-2.95 for re-decompensation; HR = 3.38, 2.27-5.02 for HCC; Figure 1a). Subgroup analyses indicated that neither the type of initial decompensating event nor albumin levels at recompensation adequately discriminate patients with favorable prognoses (HR = 1.90-3.69 for HCC, HR = 2.05-3.74 for re-decompensation, compared with compensated cirrhosis; Figure 1b). Notably, among recompensated patients with higher platelet counts ($\geq 100\times10^9$/L), the risks of HCC and subsequent decompensation was comparable to those observed in patients with compensated cirrhosis (HCC: HR = 1.03, 95%CI: 0.43-2.49, $P = 0.944$; re-decompensation: HR = 0.86, 95%CI: 0.38-1.95, $P = 0.718$). **Conclusion:** Among patients with HBV-related cirrhosis who

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achieving recompensation, those with higher levels of platelet counts demonstrate a promising prognosis similar to that of compensated cirrhosis. However, the remaining patients remain at elevated risk for subsequent decompensation and HCC.

Figure 1a. Cumulative incidence of liver related events in recompensated and compensated patients after recompensation or one year of antiviral therapy.

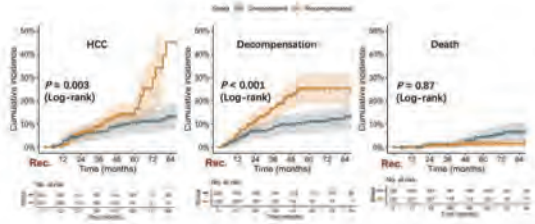
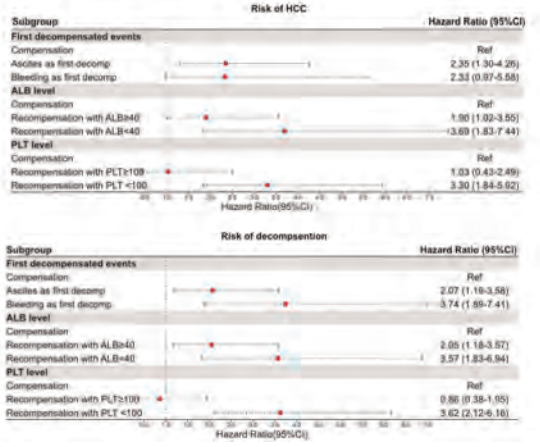


Figure 1b. Forest plot of hazard ratios of decompensation risk in recompensated vs compensated cirrhosis across different stratifications. Stratified by first decompensation type: Ascites and Bleeding. Stratified by serum albumin level. Stratified by platelet count.



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2343 | SPLEEN AND LIVER SSI-SHEAR WAVE ELASTOGRAPHY ACCURATELY ASSESS THE RISK FOR CLINICALLY SIGNIFICANT PORTAL HYPERTENSION – THE PROSPECTIVE AIXPLORE STUDY

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Background: Liver stiffness (LSM) and spleen stiffness (SSM) are closely correlated with the hepatic venous pressure gradient (HVPG), which is the minimal invasive reference standard for diagnosing clinically significant portal hypertension (CSPH; defined as HVPG $\geq$10 mmHg). Measurements of LSM, SSM, and related scores or models can be used to non-invasively estimate the risk of CSPH. **Methods:** In the prospective AIXPLORE study, 103 patients with compensated advanced chronic liver disease (cACLD) — 64% of whom had CSPH — were enrolled between July 2020 and August 2023. LSM and SSM were measured using 2D shear-wave elastography from SuperSonic Imagine (SSI). We evaluated: (i) the correlation of LSM and SSM with HVPG, (ii) optimal reliability criteria, and (iii) the diagnostic accuracy (AUC) of the measurement methods and multivariable models, including the resulting diagnostic gray zones and their accuracy for CSPH prediction. **Results:** The optimal reliability criterion for LSM was an interquartile range to median ratio (IQR/Median) $\leq$0.30 (met in 82.5% of cases), and for SSM a standard deviation $<$15 kPa (met in 70.9%). Both LSM and SSM showed good predictive value for identifying CSPH (AUCs $>$0.79). Multivariable models combining SSI-based LSM and SSM (the Anticipate-SSI model) with platelet count (PLT, used for LPS-SSI) significantly narrowed the diagnostic gray zone and achieved excellent discriminatory performance (AUCs $>$0.90). **Conclusion:** SSI-based measurements of spleen and liver stiffness allow for accurate non-invasive diagnosis of CSPH, particularly when applying the defined reliability criteria. Combined models incorporating SSI-SSM, SSI-LSM, and platelet count deliver the highest diagnostic precision while minimizing diagnostic uncertainty.

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2344 | PROGNOSTIC PERFORMANCE OF THE ENHANCED LIVER FIBROSIS (ELF) TEST IN PATIENTS WITH ADVANCED CHRONIC LIVER DISEASE

Georg Kramer[1] Benedikt Simbrunner[1] Benedikt Hofer[1] Nina Dominik[1] Lorenz Balcar[1] Lukas Hartl[1] Mathias Jachs[1] Michael Schwarz[1] Christian Sebesta[1] Georg Semmler[1] Paul Thoene[1] Philipp Schwabl[1] Michael Trauner[1] Mattias Mandorfer[1] Thomas Reiberger[1], *[1]Medical University of Vienna*

Background: The enhanced liver fibrosis (ELF) test based on serum biomarkers was initially developed for fibrosis staging. This study aimed to evaluate its prognostic utility in a tertiary care cohort of patients with compensated (cACLD) and decompensated (dACLD) advanced chronic liver disease. **Methods:** Patients enrolled in the prospective VICIS study (NCT03267615) who underwent hepatic venous pressure gradient (HVPG), liver stiffness measurement (LSM) and ELF testing were included. Individuals were grouped as cACLD or dACLD (ascites, overt hepatic encephalopathy, variceal bleeding). In cACLD, the primary outcome was first hepatic decompensation. For dACLD, the composite outcome for disease progression (DP) included further decompensation, acute-on-chronic liver failure (ACLF) or liver-related death. Prognostic performance was evaluated using multivariable Fine-Gray competing-risks regression models, adjusting for age, sex, HVPG and body mass index. **Results:** Among 573 patients (230 cACLD, 343 dACLD), alcohol-related liver disease (ALD) was the leading etiology (44.7%). Median ELF (12.00 vs. 10.79, $p < 0.001$) and HVPG (19 vs. 11 mmHg, $p < 0.001$) were significantly higher in dACLD. Over a median follow-up of 18.7 months, first decompensation occurred in 51 cACLD patients (22%), while 168 dACLD patients (49%) experienced LRE. In cACLD, ELF yielded time-dependent area under the receiver operating characteristic curves (td-AUROCs) of 0.765 (1 year) and 0.754 (2 years) for first decompensation. Moreover, ELF was independently associated with decompensation (adjusted subdistribution hazard ratio [aSHR]: 1.35, $p = 0.002$). Stratification using ELF separated high risk patients (≥ 11.1) from medium-risk (10.1–11.09 vs. ≥ 11.1, Gray's test $p = 0.006$) and lower-risk (< 10.1 vs. ≥ 11.1, $p < 0.001$) ACLD groups. In dACLD, ELF showed moderate discrimination for DP (td-AUROCs: 0.585 and 0.649 at 1 and 2 years). ELF remained an independent predictor of DP (aSHR: 1.15, $p = 0.008$). Risk stratification differentiated high-risk (≥ 14.0) from medium-risk (12.5–13.9 vs. ≥ 14.0, $p = 0.003$) and lower-risk (< 12.5 vs ≥ 14.0, $p < 0.001$) groups, albeit with less balanced distribution than in cACLD. **Conclusion:** The ELF test is a valuable prognostic tool both in cACLD and dACLD. ELF effectively predicts first decompensation in cACLD and disease progression in dACLD patients, respectively, and thereby facilitates individualized risk stratification and selection of appropriate, potentially intensified therapies.

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2345 | PROGNOSTICATION OF LIVER DISEASE PATIENTS VIA ARFI-BASED LIVER STIFFNESS MEASUREMENT USING THE WFUMB &LDQUO;RULE-OF-4&RDQUO; ALGORITHM

Christian Sebesta[1] Mathias Jachs[1] Lukas Hartl[1] Michael Schwarz[1] Lorenz Balcar[1] Benedikt Hofer[1] Nina Dominik[1] Georg Kramer[1] Paul Thoene[1] Bernhard Scheiner[1] Albert Friedrich Stattermayer[1] Benedikt Simbrunner[1] Till Schöchtner[1] Nicolas Balutsch[1] Friedrich Haimberger[1] Michael Trauner[1] Mattias Mandorfer[1] Thomas Reiberger[1] David Bauer[1], [1]Medical University of Vienna

Background: Liver stiffness measurement (LSM) using Acoustic Radiation Force Impulse (ARFI) technology represents a valuable tool for assessing liver disease severity. The recently proposed "rule-of-4" offers a comprehensive framework: values ≥ 13 kPa suggest advanced chronic liver disease (ACLD), while measurements > 21 kPa indicate a high likelihood of clinically significant portal hypertension (CSPH), which is associated with an elevated risk for liver-related events (LRE). **Methods:** We conducted a prospective study including 127 individuals with chronic liver disease who underwent ARFI-LSM via 2D-shear wave elastography (Aixplorer® Ultimate) and same-day hepatic venous pressure gradient (HVPG) measurements. Three groups were stratified based on LSM: < 13 kPa, 13–21 kPa, and > 21 kPa. All patients were followed for LRE defined by hepatic decompensation or liver-related death. Cumulative incidence of LRE was assessed using competing risk analysis across the three ARFI-based risk groups. **Results:** Among the participants, 17 (13.4%) had LSM values < 13 kPa (non-ACLD), 28 (22.0%) had values between 13 and 21 kPa (ACLD), and 82 (64.6%) had values > 21 kPa (CSPH). Median HVPG values increased progressively across the groups: 5 [IQR: 4-7] mmHg, 10 [8-12] mmHg, and 17 [12-20] mmHg, respectively, with corresponding CSPH prevalences of 11.8% in the < 13 kPa group, and 90.2% in the > 21 kPa group. Over a 12-month follow-up LREs occurred in 0% of non-ACLD, 7.1% of ACLD, and in 26.8% of the CSPH groups ($p = 0.007$). HVPG demonstrated the highest accuracy for predicting LREs (AUC: 0.79). ARFI-LSM and vibration-controlled transient elastography (VCTE) showed comparable performance (AUCs: 0.71 and 0.74, respectively; $p = 0.386$). Competing risk analysis showed LRE rates of 0%, 8%, and 30% for the three ARFI groups. **Conclusion:** Applying ARFI-LSM within the "rule-of-4" framework offers a non-invasive method to estimate liver disease progression and the risk of LRE. Patients with LSM values ≥ 13 kPa are at increased risk for LRE, with risk markedly elevated above 21 kPa. These findings support the broader integration of ARFI-LSM for liver disease prognostication.

Disclosures: Christian Sebesta: Nothing to Disclose, Mathias Jachs: Gilead Sciences Inc.: Speaker and/or consultant, Echosens Inc.: Speaking and Teaching, Lukas Hartl: Nothing to Disclose, Michael Schwarz: Nothing to Disclose, Lorenz Balcar: Nothing to Disclose, Benedikt Hofer: IPSEN: Travel support, FALK: Travel support, Nina Dominik: Nothing to Disclose, Georg Kramer: Nothing to Disclose, Paul Thoene: Nothing to Disclose, Bernhard Scheiner: AstraZeneca: Consultant, AstraZeneca: Grant/Research Support, AstraZeneca: Travel support, Roche: Travel support, Eisai: Speaking and Teaching, Eisai: Grant/Research Support, Albert Friedrich Stattermayer: Nothing to Disclose, Benedikt Simbrunner: Nothing to Disclose, Till Schöchtner: Nothing to Disclose, Nicolas Balutsch: Nothing to Disclose, Friedrich Haimberger: Nothing to Disclose, Michael Trauner: Albireo: Grant/Research Support, Alnylam: Grant/Research Support, Cymabay: Grant/Research Support, Falk: Grant/Research Support, Gilead: Grant/Research Support, Intercept: Grant/Research Support, MSD: Grant/Research Support, Takeda: Grant/Research Support, Ultragenyx: Grant/Research Support, Abbvie: Travel Grants, Falk: Travel Grants, Gilead: Travel Grants, Intercept: Travel Grants, Janssen: Travel Grants, Abbvie: Advisor, Albireo: Advisor, BiomX: Advisor, Boehringer Ingelheim: Advisor, Falk Pharma GmbH: Advisor, Genfit: Advisor, Gilead: Advisor, Hightide: Advisor, Intercept: Advisor, Ipsen: Advisor, Janssen: Advisor, MSD: Advisor, Novartis: Advisor, Phenex: Advisor, Pliant: Advisor, Regulus: Advisor, Siemens: Advisor, Shire: Advisor,

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2346 | NOVEL THERAPEUTIC STRATEGY FOR PORTOPULMONARY HYPERTENSION TARGETING PORTOSYSTEMIC SHUNTS

Tsuyoshi Ishikawa[1] Aika Kirihara[1] Natsuko Nishiyama[1] Daiki Kawamoto[1] Ryo Sasaki[1] Tatsuro Nishimura[1] Taro Takami[1], [1]Yamaguchi University Graduate School of Medicine

Background: Portosystemic shunt (PSS) development is considered to be a major risk factor for portopulmonary hypertension (PoPH), and reportedly contributes to PoPH onset through pulmonary arterial pressure elevation by increasing pulmonary arterial blood flow due to hyperdynamic state progression and pulmonary vascular resistance following humoral factor-mediated pulmonary vasoconstriction. However, there have been no studies on PSSs as a therapeutic target for PoPH. We previously reported a suggestive case in which PSS occlusion by balloon-occluded retrograde transvenous obliteration (BRTO) for refractory encephalopathy could successfully control pathophysiology of existing PoPH in alcoholic decompensated cirrhosis (J Vasc Interv Radiol. 2024). According to our case, the present study aimed to investigate changes in pulmonary arterial hemodynamics as well as those in systemic hemodynamics and humoral factors by PSS occlusion in patients with portal hypertension. **Methods:** Of patients who underwent BRTO at our hospital by November 2024, 25 patients who underwent transthoracic echocardiography (TTE) both before and after the procedure were enrolled in this retrospective study. Tricuspid valve systolic pressure gradient (TRPG) and cardiac output (CO) measured by TTE and blood levels of endothelin-1 (ET-1) and 5-hydroxytryptamine (5-HT) pre- and at 1month post-BRTO were statistically analyzed. **Results:** BRTO decreased TRPG in 20 of 25 patients (80%), and the postoperative reduction was statistically significant (24.9 ± 10.9 to 22.4 ± 9.6 mmHg, $p < 0.01$). In addition, following the procedure, ET-1 levels were significantly reduced (1.37 ± 0.79 to 1.13 ± 0.64 pg/mL, $p < 0.05$), and 5-HT levels showed a decreasing trend (51.6 ± 32.6 to 46.5 ± 27.1 ng/mL, $p = 0.10$). The CO was also significantly decreased postoperatively (5.3 ± 1.2 to 4.9 ± 0.7 L/min, $p < 0.05$). The maximum diameter of PSSs was the only preoperative parameter showing a significant difference between 20 patients with decreased TRPG and 5 patients with non-decreased TRPG (17.4 ± 4.6 vs. 11.8 ± 5.3 mm, $p < 0.05$), and the optimal cutoff value by receiver operating characteristic curve analysis was 12.17 mm (AUROC, 0.780; sensitivity, 90%; specificity, 60%). **Conclusion:** BRTO can control PoPH pathogenesis via both hemodynamic-related and humoral factor-related mechanisms. In addition, novel therapeutic strategy for PoPH can be expectedly developed with the prediction of TRPG reduction using the maximum diameter of PSSs.

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2347 | RIFAXIMIN MONOTHERAPY IS SUPERIOR TO LACTULOSE MONOTHERAPY IN REDUCING THE RISK OF HEPATIC ENCEPHALOPATHY RECURRENCE: INSIGHTS FROM A SUBGROUP ANALYSIS BY BASELINE CHARACTERISTICS

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Background: Lactulose monotherapy is recommended as secondary prophylaxis after an initial overt HE (OHE) episode, with rifaximin added when subsequent episodes occur. However, non-lactulose–based management approaches may be required due to patient nonadherence or tolerability issues (eg, GI adverse events leading to dehydration/electrolyte imbalances and precipitating OHE, as well as issues with lactulose dosing/volume/unpleasant taste). The aim was to assess the impact of baseline parameters on the risk of OHE recurrence in patients treated with rifaximin monotherapy vs lactulose monotherapy. **Methods:** Data were pooled post hoc from 2 randomized trials (1 phase 3 double-blind; 1 phase 4 open-label) of 270 adults with cirrhosis and a history of OHE occurrence in the previous 6 months (currently in remission [Conn score ≤1]). Analysis included patients treated for up to

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6 months with rifaximin 550 mg twice daily (ie, rifaximin monotherapy) or placebo plus lactulose (titrated [2-3 soft stools/d]; ie, lactulose monotherapy). The primary efficacy endpoint in both trials was time to first breakthrough OHE episode (Conn score ≥ 2). Patients were subgrouped by select baseline demographic/clinical characteristics. **Results:** 125 and 145 patients were treated with rifaximin monotherapy and lactulose monotherapy, respectively. The median (range) age in rifaximin vs lactulose groups was 58 y (32-83 y) vs 57 y (21-78 y); 60.0% vs 68.3% were male; 51.2% vs 46.2% were Child-Pugh (C-P) class B; and median Model for End-Stage Liver Disease score was 12 for both. Overall, significantly fewer patients treated with rifaximin monotherapy had an OHE episode vs lactulose monotherapy, with a 60% reduction in risk of a breakthrough OHE episode during 6 months of treatment (hazard ratio, 0.40; 95% CI, 0.26-0.62 [Table]). When analyzed by baseline parameters, rifaximin monotherapy was superior to lactulose monotherapy for all subgroups evaluated, except C-P class B or C and >2 HE episodes during previous 6 months (Table). The number needed to treat with rifaximin vs placebo to prevent an OHE episode was 4 for the overall population and ranged from 2 to 4 for the subgroups, showing significant differences between the 2 treatments. **Conclusion:** Rifaximin monotherapy demonstrates superior efficacy compared with lactulose monotherapy in reducing the risk of OHE recurrence in patients with cirrhosis and a history of OHE across a diverse range of demographic and baseline clinical characteristics.

Table. Percentage of Patients With Breakthrough OHE Episode*

Baseline characteristic, n/n (%)	Rifaximin monotherapy	Lactulose monotherapy	*P* value	HR (95% CI)†
Overall	29/125 (23.2)	71/145 (49.0)	<0.0001	0.40 (0.26, 0.62)
Age, y				
<65	21/96 (21.9)	53/116 (45.7)	<0.001	0.42 (0.26, 0.70)
≥65	8/29 (27.6)	18/29 (62.1)	<0.01	0.32 (0.14, 0.74)
Sex				
Male	17/75 (22.7)	46/99 (46.5)	<0.01	0.42 (0.24, 0.74)
Female	12/50 (24.0)	25/46 (54.3)	<0.01	0.36 (0.18, 0.71)
Diabetes diagnosis				
Yes	12/49 (24.5)	26/51 (51.0)	<0.01	0.37 (0.19, 0.74)
No	17/76 (22.4)	45/94 (47.9)	<0.01	0.42 (0.24, 0.73)
Child-Pugh class‡				
A	5/54 (9.3)	26/49 (53.1)	<0.0001	0.13 (0.05, 0.35)
B	20/64 (31.2)	31/67 (46.3)	0.10	0.62 (0.36, 1.1)
C	4/7 (57.1)	8/13 (61.5)	0.74	0.82 (0.24, 2.74)
Conn score				
0	22/86 (25.6)	43/98 (43.9)	0.01	0.52 (0.31, 0.86)
1	7/39 (17.9)	28/47 (59.6)	<0.001	0.23 (0.10, 0.53)
MELD score				
≤10	6/46 (13.0)	13/39 (33.3)	0.03	0.36 (0.14, 0.95)
≥11	23/79 (29.1)	58/105 (55.2)	<0.001	0.44 (0.27, 0.71)
Time since first HE diagnosis, mo				
<15	14/66 (21.2)	43/85 (50.6)	<0.001	0.34 (0.18, 0.62)
≥15	15/59 (25.4)	28/60 (46.7)	0.03	0.50 (0.27, 0.94)
# episodes in previous 6 mo‡				
≤3	24/106 (22.6)	42/99 (42.4)	<0.01	0.48 (0.29, 0.79)
>3	2/8 (25.0)	28/45 (62.2)	0.09	0.31 (0.07, 1.32)
HE remission duration, days				
≤90	18/71 (23.4)	52/99 (52.5)	<0.001	0.40 (0.23, 0.68)
>90	11/54 (20.4)	18/45 (40.0)	0.049	0.48 (0.23, 1.01)

*Through Day 168. †Reduction in risk of breakthrough overt HE with rifaximin vs lactulose monotherapy during 6 mo of treatment. ‡Data missing for 16 patients in lactulose group. §Data missing for 11 and 1 patients in rifaximin and lactulose groups, respectively. HE = hepatic encephalopathy; HR = hazard ratio; MELD = Model for End-Stage Liver Disease.

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2348 | THE EFFECT OF HEPATIC ENCEPHALOPATHY SERUM ON THE FIRING PATTERNS OF PRIMARY RAT NEURONS

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Background: Hepatic encephalopathy (HE) ranges from minimal HE where patients show subtle cognitive and behavioral changes, to overt HE with asterixis, disorientation, lethargy, and ultimately coma. Its mechanism is incompletely understood, however assumed to be connected to gut-derived toxins. Multielectrode arrays (MEA) are special tissue culture plates containing a grid of small electrodes embedded in the bottom of each well and are used to record extracellular action potentials from neuronal cells cultured directly on top of the recording electrodes. Simultaneous recording of spiking activity from multiple spatial locations within a culture allows for the interrogation of population-wide firing activity, and understanding of how network dynamics may be altered in disease states. We aimed to investigate the effects of HE serum on the firing patterns of primary rat neurons (PRN) using a MEA. **Methods:** Cortical PRN cultures were grown on 16x24-electrode MEA dishes. Serum samples from 6 healthy donors and 4 patients with cirrhosis exhibiting clinical or laboratory signs suggestive of HE (Grade I–II HE) were applied to a separate neuronal culture that had established baseline activity. Spiking, bursting, and network connectivity patterns were recorded (Figure 1,a). **Results:** Recorded neuronal activity demonstrated comparable spike rates (Figure 1, b). However, HE serum significantly reduced burst frequency (c), shortened burst duration (d), decreased spikes per burst (e), and disrupted synchrony, as shown by lower cross-correlation values. **Conclusion:** This pilot study demonstrates that HE serum induces reproducible and quantifiable alterations in PRN function over time possibly contributing to cognitive impairment in HE.

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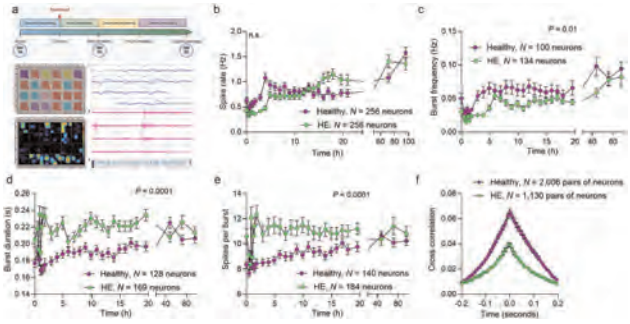

Disclosures: David Yardeni: Nothing to Disclose, Daniel Kimhi: Nothing to Disclose, Ohad Etzion: Nothing to Disclose, Shira Knafo: Nothing to Disclose

2349 | HIGH-FIDELITY NATURAL LANGUAGE PROCESSING MODEL FOR AUTOMATED EXTRACTION OF RADIOLOGIC BIOMARKERS TO STUDY CIRRHOSIS OUTCOMES

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Background: Radiological findings are key biomarkers for cirrhosis prognosis but remain underutilized due to unstructured reports and resource-heavy image analysis. Many deep learning models, while powerful, suffer from non-interpretable “black-box” features that hinder clinical adoption. We address these gaps with a natural language processing (NLP) framework that automates accurate extraction of imaging biomarkers from free-text radiology reports, enabling risk-stratified analysis of liver decompensation and 30-day hospitalization. **Methods:** We conducted a retrospective multicenter cohort study of 19768 adult patients with compensated cirrhosis from the Mass General Brigham healthcare system, from 1990 to 2024. The Clinical Longformer NLP model with data augmentation by Llama 3.1 was trained to extract 16 predefined imaging biomarkers of cirrhosis severity and portal hypertension from abdominal imaging reports (CT, US, MRI). NLP performance was manually validated in 1252 radiology reports. These validated features subsequently informed a Cox regression model to evaluate rates of incident major liver decompensation events and 30-day hospitalizations, among patients with compensated cirrhosis. **Results:** For all cirrhosis-related imaging features, the NLP algorithm yielded positive predictive values and sensitivity from 83.3% to 100%, with all negative predictive values between 97.9% and 100% (Table 1). Among 19768 patients with compensated cirrhosis, imaging features associated with higher rates of decompensation events included splenomegaly (HR 1.22, 95% CI 1.17-1.27), varices (HR 1.09, 95% CI 1.03-1.16), any ascites (HR 1.58, 95% CI 1.50-1.66), presence of TIPS (HR 1.36, 95% CI 1.17-1.58), abnormal venous flow (HR 1.19, 95% CI 1.08-1.31), and thrombus (HR 1.51, 95% CI 1.39-1.64). Any ascites (HR 1.62, 95% CI 1.44-1.82) and thrombus (HR 1.31, 95% CI 1.09-1.59) were also associated with higher rates of 30-day hospitalization (Table 2). **Conclusion:** The validated NLP algorithm enables accurate, automatic identification of key features of cirrhosis from radiology reports. In a large cohort of patients with compensated cirrhosis, presence of any ascites and thrombus on imaging are associated with higher rates of liver decompensation and 30-day hospitalization.

Table 1: Performance characteristics of natural language processing algorithm for identification of radiologic features in cirrhosis in test set (*n* = 188)

Feature	Accuracy %	Sensitivity/recall %	Specificity %	PPV*/Precision %	NPV* %	F_1 score	Support
Cirrhosis	98.9	99.2	98.6	99.2	98.6	0.99	119
Nodularity	96.8	96.7	95.5	93.9	99.1	0.96	78
Coarse echotexture	96.8	90.9	98.1	90.9	98.1	0.91	33
Caudate lobe hypertrophy	99.5	100	99.3	97.4	100	0.99	37
Any liver atrophy	97.3	95.7	97.9	93.6	98.6	0.95	46
Segment IV atrophy	100	100	100	100	100	1.00	23
Expanded gallbladder fossa	100	100	100	100	100	1.00	12
Portal hypertension	98.9	96.8	100	100	98.4	0.98	63
Splenomegaly	94.1	97.7	91.1	90.4	97.9	0.94	87
Varices	98.9	100	98.6	95.7	100	0.98	45
Any ascites	97.9	100	96.5	94.9	100	0.97	75
Trace ascites	99.5	100	99.4	94.4	100	0.97	17
Portosystemic shunt	95.2	97.9	94.3	85.5	99.3	0.91	48
Presence of TIPS	100	100	100	100	100	1.00	18
Abnormal venous flow	98.4	90.9	98.9	83.3	99.4	0.87	11
Presence of thrombus	97.3	100	96.9	83.9	100	0.91	26

*PPV: Positive predictive value; NPV: Negative predictive value

Table 2: Association between imaging features and the incidence of liver decompensation and 30-day hospitalization*

	Decompensation		Decompensation with 30-day Hospitalization	
Feature	HR (95% CI)†	p-value	HR (95% CI)†	p-value
Cirrhosis	1.32 (1.26–1.38)	<0.001	1.08 (0.96–1.21)	0.211
Nodularity	0.95 (0.91–0.99)	0.029	0.97 (0.86–1.09)	0.611
Coarse echotexture	0.88 (0.84–0.92)	<0.001	0.93 (0.83–1.05)	0.258
Caudate lobe hypertrophy	0.97 (0.90–1.04)	0.363	0.90 (0.73–1.12)	0.353
Any liver atrophy	1.01 (0.93–1.10)	0.807	0.99 (0.81–1.22)	0.952
Segment 4 atrophy	0.91 (0.73–1.14)	0.419	1.25 (0.67–2.34)	0.488
Expanded gallbladder fossa	0.98 (0.76–1.38)	0.919	1.22 (0.45–3.30)	0.690
Portal hypertension	1.04 (0.98–1.10)	0.221	1.00 (0.87–1.16)	0.960
Splenomegaly	1.22 (1.17–1.27)	<0.001	1.09 (0.98–1.21)	0.125
Varices	1.09 (1.03–1.16)	0.004	0.92 (0.78–1.09)	0.344
Any ascites	1.58 (1.50–1.66)	<0.001	1.62 (1.44–1.82)	<0.001
Trace ascites	0.85 (0.79–0.92)	<0.001	0.79 (0.66–0.94)	0.007
Portosystemic shunt or collateralization	1.04 (0.98–1.10)	0.224	0.94 (0.80–1.10)	0.444
Presence of TIPS	1.36 (1.17–1.58)	<0.001	1.14 (0.80–1.62)	0.461
Abnormal venous flow	1.19 (1.08–1.31)	<0.001	1.05 (0.88–1.28)	0.637
Presence of thrombus	1.51 (1.39–1.64)	<0.001	1.31 (1.09–1.59)	0.005

* Adjusted for age, sex, race, BMI, and lab values (sodium, creatinine, alanine aminotransferase (ALT), albumin, total bilirubin, and international normalized ratio (INR))

† HR: Hazard ratio; CI: Confidence interval

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Nothing to Disclose, Gregory Fricker: Nothing to Disclose, Rebecca Liu: Nothing to Disclose, Tracey Simon: Nothing to Disclose

2350 | ENDOSCOPIC ULTRASOUND GUIDED LIVER BIOPSY AND PORTAL PRESSURE GRADIENT MEASUREMENT COMPARED TO THE TRANSJUGULAR APPROACH: A RANDOMIZED CONTROLLED TRIAL

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Background: The transjugular (TJ) technique is the gold standard to simultaneously evaluate portal hypertension and liver fibrosis, with the hepatic venous pressure gradient (HVPG) and liver biopsy (LB), respectively. Recently, Endoscopic Ultrasound (EUS) has emerged as a novel approach capable of measuring portal pressure gradient (PPG) and performing LB. We hypothesize that EUS will yield higher-quality LB than TJ and also provide consistent PPG measurements. To date, no randomized controlled trial (RCT) has compared EUS to TJ. **Methods:** This single center RCT included adults evaluated for liver fibrosis and portal hypertension. Participants were randomly assigned to EUS or TJ for simultaneous PPG and LB. The TJ technique was performed as per standard of care (low-dose midazolam, 18G TJ-LB system, and balloon-occlusion HVPG). EUS was performed under conscious sedation with ketamine and low-dose midazolam. EUS-PPG was done using a 25G needle (EchoTip Insight, Cook Medical) and LB with a 19G needle (Acquire, Boston Scientific). The primary endpoint was the proportion of high-quality LB (AASLD criteria: $\geq$25mm total aggregate length and $\geq$11 complete portal tracts using 2 or 3 passes) with consistent PPG (duplicate or triplicate measures within $\leq$1mmHg). Secondary endpoints included technical success (obtaining a LB and PPG), procedure time, LB- and PPG-related outcomes, adverse events (AE, ASGE grading at day 7) and patient satisfaction (patient sedation satisfaction instrument, PSSI). We conducted an intent-to-treat analysis, reporting n (%) and mean (SD), with statistical significance defined as a two-tailed p-value ≤ 0.05. **Results:** A total of 58 patients were randomized, 29 to EUS and 29 to TJ (56.6 [14.7] years old, 37.9% female, 50% MASLD, 67.2% cirrhosis). The primary endpoint was met in 24 (82.8%) for EUS vs 12 (41.4%) for TJ ($p < 0.01$). Technical success occurred in 26 (90.0%) for EUS vs 28 (96.6%) for TJ ($p = 0.61$). The procedure time was 20.7 (4.8) minutes for EUS and 48.8 (14.0) minutes for TJ ($p < 0.01$). Mean total aggregate length was EUS: 117 (83.7) mm vs TJ: 29.2 (9.5) mm ($p < 0.01$), complete portal tracts per specimen: EUS: 29.2 (18.7) vs TJ: 11.2 (5.8) ($p < 0.01$), longest core: EUS: 25.3 (17.1) mm vs TJ: 13.6 (3.8) mm ($p < 0.01$), number of passes: EUS: 2.1 (0.3) vs TJ: 2.3 (0.5) ($p = 0.02$). Consistent PPG was obtained in 26 (89.7%) for EUS vs 17 (58.6%) for TJ ($p < 0.01$). All AEs were mild, including 2 (6.9%) for EUS and 3 (10.3%) in TJ. As per PSSI, total patient satisfaction with sedation was higher for EUS ($p < 0.01$). **Conclusion:** While both procedures had similar technical success and safety profile, EUS is superior to TJ for the simultaneous acquisition of high-quality LB, consistent PPG, and patient satisfaction with sedation. In the well-selected cases, EUS is therefore preferable to TJ, paving the way for a significant shift in practice.

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2351 | PREDICTORS AND SIGNIFICANCE OF ELEVATED LIPASE IN PATIENTS UNDERGOING EXPEDITED LIVER TRANSPLANT EVALUATION

Peyton Crest[1] Francis Yao[1] Chris Freise[1] John Roberts[1] Nghiem Ha[1], [1]University of California, San Francisco

Background: Serum lipase is a common but non-specific marker for pancreatitis and may be elevated in extra-pancreatic conditions. Among patients undergoing expedited liver transplant evaluation, lipase elevations are frequent yet unclear in significance. Accurate interpretation is crucial to avoid listing delays or unnecessary interventions. We aimed to identify predictors of clinically significant lipase elevation and assess its association with radiographic (RP) or intraoperative (IOP) pancreatitis. **Methods:** Retrospective cohort study of adults undergoing expedited liver transplant evaluation between 1/2020 and 3/2025 with elevated lipase ($\geq$78 U/L) within 14 days of pre-transplant, listing, or deferral/decline. RP was defined as imaging evidence of peripancreatic inflammation, necrosis, or fluid collections. IOP was defined as gross evidence of inflammation, necrosis, firmness, or surrounding saponification. Logistic regression identified predictors of clinically significant elevated lipase $\geq$3xULN and RP/IOP. **Results:** Among 178 patients, 47% were male with median age of 56; etiologies included alcohol-associated (43%), metabolic-associated (17%), viral hepatitis (14%), and cholestasis-associated (5%). Of these, 90 (51%) were transplanted, 40 (22%) waitlisted and 48 (27%) deferred/declined—primarily for psychosocial (19%), frailty (15%), or comorbidities (6%). Deferred/declined were younger (median age 53 vs 58 years, $p = 0.01$) and more likely to have alcohol-associated disease (67% vs 35%, $p < 0.001$). Independent predictors of lipase $\geq$3xULN were acute liver failure/Status 1A (OR 4.11, 95%CI 1.49-11.34) and GI-related infection (OR 2.03, 95%CI 1.02-4.01), after adjusting for age, alcohol-associated, kidney function, and MELD. While lipase $\geq$3xULN was not associated with RP/IOP, lipase $\geq$5xULN was predictive of RP/IOP (OR 6.92, 95%CI 2.04-23.52), and remained significant after adjusting for age, alcohol-associated, kidney function, MELD, and GI-related infection (OR 6.32, 95%CI: 1.78-22.47). **Conclusion:** Among patients undergoing expedited liver transplant evaluation, acute liver failure with Status 1A and GI infections predict lipase $\geq$3xULN, though not radiographic/intraoperative pancreatitis. However, lipase levels $\geq$5xULN may serve as a threshold for identifying individuals at increased risk for clinically relevant pancreatitis. These findings can guide interpretation of elevated lipase in transplant candidates and inform risk stratification and management.

Table 1. Univariable and multivariable logistic regression model for clinically significant lipase elevation (≥3xULN).

	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (years)	0.99	0.97-1.02	0.62	1.00	0.97-1.02	0.77
Alcohol-Associated	0.55	0.30-1.01	0.06	0.71	0.36-1.42	0.33
Creatinine (mg/dL)	1.14	0.90-1.43	0.27	1.04	0.93-1.17	0.46
Acute Liver Failure/Status 1A	4.36	1.81-10.50	0.001	4.11	1.49-11.34	<0.001
MELD	1.04	1.00-1.08	0.07	1.00	0.96-1.05	0.97
Gastrointestinal-Related Infection	1.48	0.97-3.49	0.06	2.03	1.02-4.01	0.04

Disclosures: Peyton Crest: Nothing to Disclose, Francis Yao: Nothing to Disclose, Chris Freise: Nothing to Disclose, John Roberts: Nothing to Disclose, Nghiem Ha: Nothing to Disclose

2352 | ELECTIVE TIPS AND KIDNEY FUNCTION: PROSPECTIVE ASSESSMENT OF EGFR TRAJECTORIES AND IMPACT ON CLINICAL OUTCOMES IN THE ADVANCING LIVER THERAPEUTIC APPROACHES (ALTA) STUDY GROUP

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Background: Transjugular Intrahepatic Portosystemic Shunt (TIPS) is widely used for portal hypertension complications, yet its effects on kidney function, particularly long-term outcomes, remain incompletely characterized. We examined longitudinal eGFR changes after TIPS creation and explored relationships between kidney parameters and clinical outcomes. **Methods:** The Advancing Liver Therapeutic Approaches in Portal Hypertension (ALTA) study is a multi-center prospective cohort study across 13 U.S. centers of adults ($\geq$18 years) who were scheduled for TIPS between 7/19-1/25. We included 522 subjects with 3-month post-TIPS creatinine data. CKD-EPI 2021 eGFR changes from baseline to 1, 3, 6, and 12 months post-TIPS were analyzed using linear mixed effects models. Subjects were categorized as "improved" ($>$10% increase), "stable" (within $\pm$10%), or "declined" ($>$10% decrease) based on baseline-to-3-month eGFR change. We assessed associations, including baseline eGFR and eGFR response, with hospitalizations with hepatic encephalopathy (HE) and, for those with ascites, number of paracenteses during 12-month

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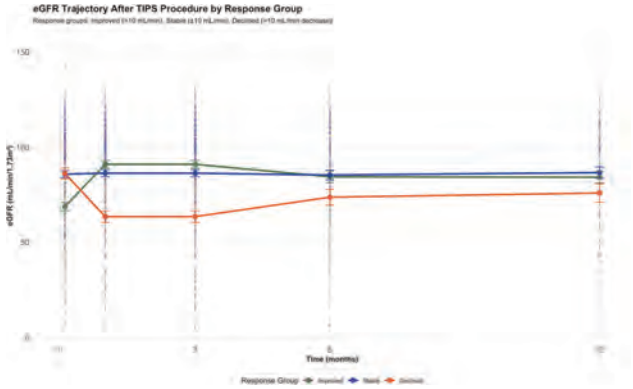
follow-up. **Results:** Among these 522 subjects, mean baseline eGFR was 79.2 ± 27.9 mL/min/1.73m². eGFR significantly increased at 1 and 3 months post-TIPS (84.0 ± 29.2, mean improvement 5.2 mL/min/1.73m², $p < 0.001$), with attenuated but sustained benefits at 6 and 12 months (Figure 1). Response distribution: 31% improved, 54% stable, 10% declined. The improved group had significantly lower baseline eGFR (69.6 ± 21.6 vs 84.4 ± 30.0 vs 80.7 ± 26.3 mL/min/1.73m² for improved, stable, and declined groups, $p < 0.001$) and greater Stage 3 CKD (37% v. 27%, $p < 0.001$). Factors associated with eGFR trajectory in univariable analyses included baseline eGFR (B = -0.01 ml/min/month, $p < 0.001$) and hepatorenal syndrome (HRS-AKI) history (B = 1.2 ml/min/month, $p < 0.001$). In the final multivariable model, only baseline eGFR (B = -0.01 ml/min/month, $p = 0.001$), HRS-AKI history (B = 0.9 ml/min/month, $p = 0.02$), and Asian race (B = -3.3 ml/min/month, $p = 0.01$). Only the baseline eGFR ($r = -0.01$, $p = 0.04$), but not the eGFR change over 12-months ($r = 0.01$, $p = 0.64$), was significantly correlated with the number of hospitalizations with HE over the 12-months after TIPS. Among the 249 (48%) subjects with ascites as an indication for TIPS, baseline eGFR ($r = -0.10$, $p < 0.001$), but not eGFR changes post-TIPS correlated with post-TIPS paracentesis requirements ($r = -0.02$, $p = 0.68$). **Conclusion:** TIPS creation is associated with early kidney function improvement, particularly in subjects with moderate baseline renal dysfunction. Baseline eGFR, but not eGFR improvement post-TIPS, was associated with post-TIPS hospitalizations with HE, and among those with ascites as a primary indication, baseline eGFR—not eGFR improvement—predicts need for post-TIPS paracenteses. These findings help inform the natural history of kidney function after elective TIPS creation.



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2353 | NECROTIZING FASCIITIS IN CIRRHOSIS: A PROSPECTIVE STUDY OF CLINICAL FEATURES AND OUTCOMES COMPARED TO NON-CIRRHOTIC PATIENTS

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Background: Cirrhosis-associated immune dysfunction predisposes patients to severe bacterial infections, including necrotizing fasciitis (NF)—a rapidly progressive and life-threatening soft tissue infection. NF in cirrhotic patients is frequently under-recognized early due to non-specific clinical features. While early surgical intervention is crucial, data comparing NF in cirrhotic vs. non-cirrhotic patients are limited and mostly retrospective. This prospective study aimed to evaluate differences in clinical presentation, microbiological profiles, and outcomes in patients with and without cirrhosis. **Methods:** This prospective observational study included all consecutive adult patients diagnosed with NF in both cirrhotic and non-cirrhotic at tertiary care university hospital. Diagnosis of NF was based on clinical, surgical, and histopathological criteria. Patients were stratified based on the presence of cirrhosis. Data on demographics, clinical features, laboratory parameters, microbial isolates, and outcomes were recorded. Cirrhosis severity was classified using Child-Pugh and MELD scores. ACLF was defined by APASL criteria. Statistical comparisons were performed using t-tests or Wilcoxon rank-sum tests, with $p < 0.05$ considered significant. **Results:** The demographic and clinical characteristics of patients are shown in Table 1. Eighty-eight patients were included (35 with cirrhosis, 53 without). Alcohol was the predominant cause of cirrhosis (74%). Cirrhotic patients presented at a younger age (mean 48 vs. 55 years, $p = 0.008$), and 34% had ACLF. Mortality was significantly higher in the cirrhosis group (45.7% vs. 18.8%, $p = 0.006$), as was the incidence of shock (42% vs. 15%, $p = 0.008$). Gram-negative organisms were predominant in cirrhosis (60% vs. 4%, $p < 0.001$). All patients underwent surgical debridement and one third in both groups required re-intervention (range,1-3) and skin grafting. **Conclusion:** NF in cirrhosis presents earlier, is commonly caused by gram-negative organisms, and carries significantly higher morbidity and mortality. High clinical vigilance and early surgical debridement are

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critical for improving outcomes in this high-risk population.

Table 1: Baseline Demographics, Clinical Characteristics, and Outcomes

Variable	NF in patients with Cirrhosis (n= 35)	NF in patients without cirrhosis (n=53)	P-value
Age, years (Mean, ±SD)	48.08 ± 11.58	55.6 ± 15.59	0.0084
Diabetes mellitus	11	37	0.0004
Other comorbidities (Hypertension)	8	20	0.1425
Pain	35	53	1
Fever	28	40	0.796
Shock	15 (42%)	8 (15%)	0.008
Haemoglobin g/dL (Mean, ±SD)	8.88 ± 1.71	10.5 ± 2.07	0.0001
Total leukocyte count cells/µL (Mean, ±SD)	14871 ± 9287.46	14152 ± 6155.82	0.33
Platelet cells/µL (Mean, ±SD)	96571 ± 53022.9	291156 ± 118911.12	0.00001
International normalized ratio (INR) (Mean, ±SD)	1.88 ± 1.52	1.24 ± 0.19	0.00003
Acute on Chronic liver failure	12 (34.28 %)	NA	NA
MELD score (Mean, ±SD)	23.76 ± 8.76	NA	NA
CTP (Median)	C	NA	NA
Total protein g/dL (Mean, ±SD)	6.17 ± 0.9	6.06 ± 1.12	0.34679
Albumin g/dL (Mean, ±SD)	2.11 ± 0.51	2.62 ± 0.48	0.00013
Total Bilirubin mg/dL (Mean, ±SD)	5.62 ± 5.9	1.38 ± 1.64	0.00058
Direct Bilirubin mg/dL (Median, IQR)	1.8 ± 3.85	0.5 ± 0.54	0.00145
AST U/L (Mean, ±SD)	68.6 ± 49.8	23.2 ± 15.12	0.00003
ALT U/L (Mean, ±SD)	30.8 ± 49.8	19.6 ± 12.26	0.00178
ALP U/L (Mean, ±SD)	123 ± 53.32	146.5 ± 112.98	0.14407
GGT U/L (Mean, ±SD)	77.5 ± 54.41	109.5 ± 120.87	0.86865
Serum Creatinine on admission, mg/dL (Median, IQR)	1.19± 1.51	1.1 ± 0.67	0.87456
Blood/Tissue culture: Gram negative bacteria (E. coli and K. Pneumoniae) Gram positive bacteria (S. Pyogenes and S. aureus) Polymicrobial bacteria (aerobe and anaerobic bacteria)	33 (94%) 20 (60%) 12 (36%) 1 (3%)	51 (96%) 2 (4%) 35 (68%) 14 (27%)	
Mortality	16 (45.7 %)	10 (18.8 %)	0.006

Abbreviation: AST- Aspartate Aminotransferase, ALT- Alanine Aminotransferase, ALP- Alkaline phosphatase; GGT- Gamma-glutamyl Transferase; CTP-Child-Turcotte-Pugh score

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2355 | PRE-ADMISSION RIFAXIMIN USE IS NOT ASSOCIATED WITH INFECTION WITH DRUG RESISTANT ORGANISMS IN A GLOBAL COHORT OF INPATIENTS WITH CIRRHOSIS

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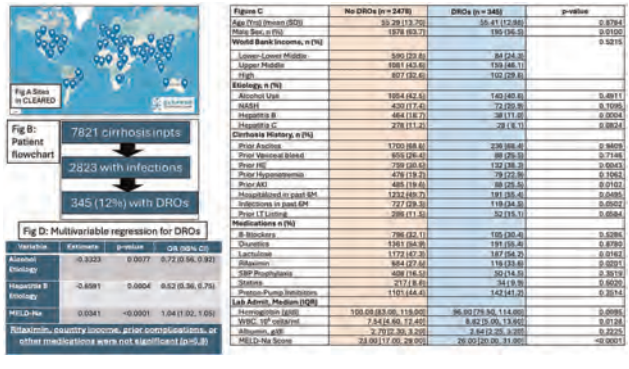
Background: Patients with cirrhosis are at risk of developing drug-resistant organisms (DRO) infections which can lead to poor outcomes. A recent study indicated that rifaximin could increase this risk, especially with daptomycin (dapto). There are global variations in rifaximin use & DRO prevalence. Aim: Determine the predictors of DROs in a global cohort of cirrhosis inpatients with infections and focus on pre-admission rifaximin. **Methods:** CLEARED consortium enrolls cirrhosis inpatients globally (FigA). Data re: pre-admission demographics, cirrhosis severity, complications, and medications on admission are recorded. We included those with infections either on admission or during the hospitalization only. The primary outcome was DROs (Vancomycin resistant Enterococcus (VRE), MRSA, carbapenem/fluroquinolone resistance), whether admission rifaximin was related & country-income level variations were studied. Logistic regression for DRO emergence was performed. **Results:** 7821 pts, of which 2823 had infections were enrolled (Fig B). 345 (12%) had DROs & 800 (28%) were on rifaximin. Mean age was 55 yrs with 63% men with mostly alcohol (42%) etiology were included. 24% were from LMICs, 44% UMIC & 32% HICs. Most had ascites (69%), 48% were on lactulose, 55% on diuretics, 16% on SBP prophylaxis & 44% on PPIs. Rifaximin use was highest in LLMICs, lowest in UMICs & intermediate in HICs ($p < 0.0001$). More males were on rifaximin (69 vs 61%), as well more people with alcohol (48 vs 40%) & MASH (22 vs 16%), while it was lower in HBV (10 vs 20%). Pts on rifaximin had more advanced cirrhosis with ascites (81 vs 63%), prior HE (63 vs 19%), AKI (34 vs 15%) prior infections (40 vs 26%). They had ↑admit MELDNa (26 vs 22, $p < 0.0001$) & WBC (8.5 vs 7.5, $p < 0.0001$). Dapto use was similar (1.9 vs 1.3%, $p = 0.29$). DROs (Fig C): Those with DRO were less likely to be men, have HBV, & more with MASH, lactulose/rifaximin use, & AKI. Country-incomes were similar. More DRO pts had dapto use (5.2 vs 1.0%, $p < 0.0001$). DROs resulted in higher in-hospital (29 vs 17%, $p < 0.0001$) & 30-day mortality (37 vs 27%, $p < 0.001$). Rifaximin and DROs crude/multivariable comparisons: No differences in VRE (2.1 vs 1.3, $p = 0.13$), MRSA (1.2 vs 1.3%, $p = 0.94$), fluoroquinolones (3.8 vs 3.6%, $p = 0.86$) was seen; carbapenem resistance was higher (4.4 vs 2.2%, $p = 0.003$) with rifaximin. On Multivariable analysis (Fig D) however, rifaximin was not significant; alcohol & HBV etiology linked with lower while MELD-Na was associated with higher DRO. **Conclusion:** 12% of inpatients with cirrhosis and infections had DROs which were associated with high mortality but were not different between country income types. Rifaximin pre-admission did not affect DROs in general or VRE specifically when adjusted on logistic regression. Daptomycin was used in $< 2\%$ of patients and unaffected by rifaximin. Rifaximin use is not associated with DRO emergence in a global cohort of inpatients with cirrhosis.



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2356 | PREVALENCE AND CLINICAL OUTCOMES OF RECOMPENSATION IN DECOMPENSATED CIRRHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Patients with decompensated cirrhosis may experience recompensation following effective

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etiological cure. However, the prevalence and clinical outcomes of decompensated patients who achieved recompensation remains unclear. We performed a systematic review and meta-analysis to determine the prevalence and clinical outcomes in decompensated patients who achieved recompensation. **Methods:** We systematically searched PubMed and EMBASE from inception to include all studies of patients with decompensated cirrhosis who achieved recompensation, evaluated the prevalence of clinical outcomes, specifically death and hepatocellular carcinoma (HCC), and compared them to patients who did not achieve recompensation. The primary outcome was the pooled prevalence of recompensation, and secondary outcomes included HCC occurrence and death. To improve precision of our analysis on the prognostic impact of recompensation, we applied a strict definition of recompensation, requiring both etiological cure and absence of liver decompensating events for one year, and minimum follow-up of two years. **Results:** A total of 26 studies encompassing 8,261 patients with decompensated cirrhosis were analyzed. The overall pooled prevalence of recompensation was 32% (95% CI: 24-41%). Recompensation prevalence was the highest among viral-related cirrhosis 46% (95%CI: 37-55%), followed by alcohol-related cirrhosis 21% (95%CI: 15-28%), and other etiologies 15% (95%CI: 2-37%). The pooled prevalence of recompensation was also higher in studies with lower median MELD (<15) and smaller sample sizes ($p<0.05$), but was not influenced by publication type or risk of bias. Over a median follow-up ranging from 2 to 8 years after recompensation, patients achieving recompensation had lower odds of HCC occurrence (OR: 0.60, 95%CI: 0.40-0.91, 6 studies) and death (OR: 0.34, 95%CI: 0.19-0.61, 5 studies). The clinical benefit of recompensation did not significantly differ between studies using the standard versus the expanded Baveno-VII criteria. Despite achieving recompensation, further decompensating events occurred in 13% (95%CI: 5%-23%). **Conclusion:** Recompensation occurred in approximately a quarter of decompensated cirrhosis patients who achieved etiological control. Recompensation was associated with a lower risk of death and possibly HCC, suggesting that recompensation could represent a clinically meaningful endpoint in patients with decompensated cirrhosis undergoing etiological treatment.

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2357 | EFFICACY OF INTRAVENOUS ALBUMIN FOR MANAGEMENT OF CELLULITIS AMONG PATIENTS WITH LIVER CIRRHOSIS

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Background: Cellulitis is one of the major bacterial infections in cirrhosis. Albumin is beneficial in spontaneous bacterial peritonitis but there is no data on efficacy of albumin in patients with cirrhosis and cellulitis. **Methods:** We conducted a open label study on adult patients with cirrhosis and new-onset cellulitis. One arm received Standard Medical Therapy (SMT) along with 20% albumin (20g/d) for 5 days and the other arm received SMT alone. Same antibiotics protocol was followed in both arms. The primary outcomes included 30-days mortality and time to cellulitis resolution (judged by an independent blinded investigator). Secondary outcomes were improvement in renal function, duration of hospital stay, improvement in CTP and MELD scores and requirement of surgical intervention. **Results:** A total 60 patients were included; 30 in each arm. Baseline characteristics were comparable in both arms. Duration of cellulitis resolution was significantly shorter in the albumin arm (median 6 vs. 8 days, $p=0.003$). The 30 days mortality was similar (6.7% vs. 10%, $p=0.64$). Overall hospital stay was significantly shorter in the albumin arm (8 vs 10 days, $p=0.01$). Decrease in serum creatinine at day 5, improvement in CTP and MELD score sat day 5 were comparable in both arms. There was a trend towards higher surgical intervention the SMT arm (36.7% vs. 16.7%, $p=0.08$). **Conclusion:** Intravenous albumin in patients with cirrhosis and cellulitis was associated with faster resolution of cellulitis and shorter hospital stay, without any difference in mortality.

Baseline Characteristics

Parameters	SMT + Albumin Arm	SMT Arm	P Value	Parameters	SMT + Albumin Arm	SMT Arm	P Value
Demographics				Lab Parameters on Day1			
Age (Median, IQR)	44 (40.75 – 53)	49.5 (40.5 – 56.25)	0.23	Total Leucocyte Count	16000 ± 10000	14000 ± 7100	0.37
Gender (Male)	25 (86.67%)	25 (83.33%)	0.72	Total Bilirubin	7.90 ± 3.93	5.87 ± 3.45	0.06
Etiology of Cirrhosis (Alcohol)	23 (76.67%)	21 (70%)		Serum Albumin	2.81 ± 0.35	2.74 ± 0.43	0.22
Site of Cellulitis				Creatinine	1.89 ± 0.63	1.82 ± 0.57	0.28
Right Lower Limb	16 (53.33%)	12 (40%)		INR	2.12 ± 0.66	2.02 ± 0.58	0.5
Left Lower Limb	8 (20%)	14 (46.67%)		CTP	12 (9.5 – 13)	13.5 (13, 14)	0.11
Bilateral Lower Limb	6 (20%)	4 (13.33%)		MELD	24 (22 – 27)	29 (27, 31)	0.22

Outcomes

Parameters	SMT + Albumin Arm	SMT Arm	P Value
Time to Resolution (Days)	6 (5 – 7.75)	8 (7 – 9)	0.003
Length of Hospital Stay (Days)	8 (6 – 10)	10 (9 – 11)	0.01
Need for Surgical Intervention	5	11	0.08
Need of RRT	4	2	0.39
Δ Creatinine	0.35 ± 0.56	-0.30 ± 1.27	0.18

Disclosures: Chetan Saner: Nothing to Disclose, Arun Vaidya: Nothing to Disclose, Akash Shukla: Nothing to Disclose

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2358 | A SIMPLE SCORE OF SARCOPENIC OBESITY PREDICTS ALL-CAUSE MORTALITY IN PATIENTS WITH CIRRHOSIS

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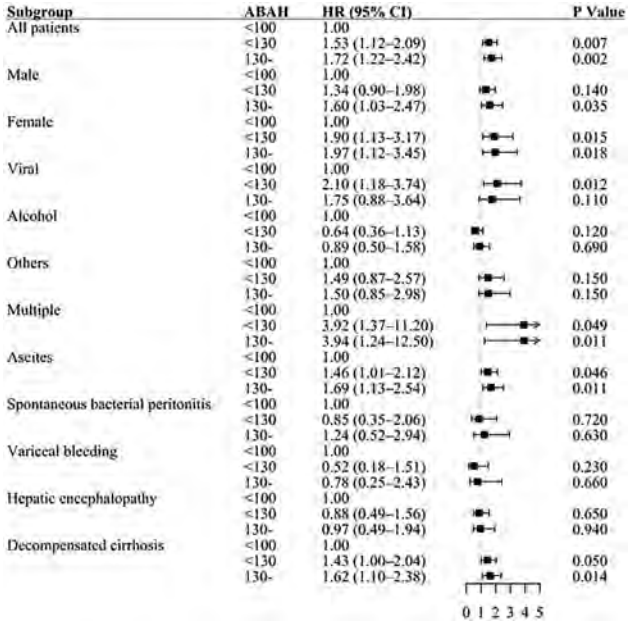
Background: Sarcopenic obesity (Sa-O) is linked to poor prognosis in liver cirrhosis (LC), and Computed Tomography (CT)-based body composition parameters offer diagnostic value of Sa-O. This study aimed to evaluate the incidence, predictors, and prognostic impact of Sa-O on all-cause mortality in cirrhotic patients. **Methods:** This retrospective cohort included patients diagnosed with cirrhosis from November 2008 to September 2022. Sa-O was defined via L3-level CT as skeletal muscle index (SMI) <42 cm²/m² (men) or <38 cm²/m² (women) with visceral adipose tissue area (VATA) >100 cm². Clinical data was collected via medical records. The primary outcome was all-cause mortality. Predictors were identified using univariable and multivariable analyses. A nomograph was developed and the total points formed the ABAH (Age-BMI-Alcohol-Hypertension) score by the predictors. Subgroups analysis was conducted to calculate the hazard ratio of death (HR) by categorized ABAH level (low: <100, medium: 100-130, high: >130). **Results:** Among 769 patients (60.1% male; 45.5% ≥ 60 years; median follow-up duration: 1557 days), 281(36.5%) was diagnosed as Sa-O. Multivariable analysis identified age ≥ 60 years (OR 1.813, 95% CI 1.210-2.718, P = 0.0040), obesity and overweight (BMI ≥ 28 kg/m²: OR 0.076, 95% CI 0.018-0.317, P = 0.0011; 24-28 kg/m²: OR 0.650, 95% CI 0.442-1.001, P = 0.0352), alcoholic liver disease (OR 1.685, 95% CI 1.078-2.634, P = 0.0220), and hypertension (OR 1.801, 95% CI 1.184-2.739, P = 0.0059) as independent predictors of Sa-O. The average probability of Sa-O was respectively 8.4% (low), 18.7% (medium) and 30.5% (high), with an increasing trend (P = 0.0260). Subgroups analysis in cirrhotic patients with sarcopenic obesity found ABAH (medium vs. low: HR 1.53, 95% CI, 1.12-2.09, P = 0.007; high vs. low: HR 1.72, 95% CI, 1.22-2.42, P = 0.002) having predictive value for all-cause mortality. In females, both medium ABAH (HR 1.90, 95% CI 1.13-3.17, P = 0.015) and high ABAH (HR 1.97, 95% CI 1.12-3.45, P = 0.018) significantly increased mortality compared to the low ABAH, whereas in males (HR 1.60, 95% CI 1.03-2.47, P = 0.035) and viral hepatitis subgroup (HR 2.10, 95% CI 1.18-3.74, P = 0.012), only high ABAH showed a significant effect. Other high-risk subgroups included patients with multiple liver disease etiologies (medium vs. low: HR 3.92, 95% CI 1.37-11.20, P = 0.049; high vs. low: HR 3.94, 95% CI 1.24-12.50, P = 0.011), ascites (medium vs. low: HR 1.46, 95% CI 1.01-2.12, P = 0.046; high vs. low ABAH: HR 1.69, 95% CI 1.13-2.54, P = 0.011), and decompensated cirrhosis (medium vs. low: HR 1.43, 95% CI 1.00-2.04, P = 0.050; high vs. low ABAH: HR 1.62, 95% CI 1.10-2.38, P = 0.014) (Figure 1). **Conclusion:** Sa-O in cirrhotic patients was associated with Age, BMI, Alcoholic etiology, and Hypertension, the new ABAH score being predictive of their all-cause mortality.



Disclosures: Yuteng Yang: Nothing to Disclose, Tingyang Wei: Nothing to Disclose, Zixing Wang: Nothing to Disclose, Rui Huang: Nothing to Disclose

2359 | STATIN USE IN LIVER TRANSPLANT CANDIDATES WITH DECOMPENSATED CIRRHOSIS: A MULTICENTER SAFETY ANALYSIS

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Background: Despite evidence of liver-specific benefits, statin use in patients with decompensated cirrhosis is often avoided due to concerns about complications such as rhabdomyolysis. This may increase cardiovascular risk and overlook potential hepatoprotective effects. We evaluated the safety of statin therapy in liver transplant (LT) candidates with decompensated cirrhosis. **Methods:** This multicenter retrospective study (Cleveland Clinic OH & FL) included 4,906 adult LT candidates listed between January 2000 and October 2023. Statin users (n = 277, 5.6%) had active prescriptions for ≥ 60 days prior to and after listing; non-users

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(n = 4,629, 94.4%) served as controls. Patients with acute liver failure or re-transplantation were excluded. Outcomes included hepatic complications, rhabdomyolysis, and major adverse cardiovascular events (MACE) within 1 year post-listing. Hospital encounters were reported per 100 patients. Wilcoxon rank sum, Pearson's Chi-square, and Fisher's exact tests were used for comparisons. **Results:** The median age of the cohort was 64.0 years, 61.6% were male, with a median BMI of 27.9 and MELD 3.0 score of 12.2 at listing. Rates of hospital encounters per 100 patients were lower in statin users for variceal bleeding (2.68 vs. 6.05, p = 0.004), but higher for hepatic encephalopathy (89.7 vs. 58.6, p = 0.001). Rates were similar for ascites (118.4 vs. 124.6, p = 0.421), spontaneous bacterial peritonitis (SBP) (8.71 vs. 8.48, p = 0.912), and rhabdomyolysis (1.34 vs. 0.32, p = 0.097), which was rare. MACE rates at 1-year post-listing were not significantly different between groups (4.3% vs. 2.5%, p = 0.086). **Conclusion:** In this large multicenter cohort of LT candidates with decompensated cirrhosis, statin use was not associated with increased risk of rhabdomyolysis, cardiovascular events, or most liver-related complications. Statin users had lower rates of variceal bleeding, though higher rates of hepatic encephalopathy were observed. These findings support the overall safety of statin use in this population and highlight the need for further prospective studies.

Outcome	[ALL] n= 4,906	Statin users (n=277 (5.6%))	Non-statin users (n=4,629 (94.4%))	p-value
Overall Demographics Median [25th;75th]				
Age	64.0 [55.0;71.0]	67.0 [61.0;72.0]	63.0 [54.0;70.0]	<0.001
BMI	27.9 [24.3;32.3]	29.6 [26.2;34.4]	27.8 [24.2;32.2]	<0.001
Male	3024 (61.6%)	180 (65.0%)	2844 (61.4%)	
MELD 3.0 at Listing	12.2 [8.6;16.3]	12.5 [8.4;16.4]	12.1 [8.6;16.3]	0.913
Non-transplant hospitalizations	2.0 [0.0;3.0]	2.0 [0.0;4.0]	2.0 [0.0;3.0]	0.617
Days spent on waitlist	217.0 [36.0;946.2]	158.0 [38.0;536.0]	220.0 [36.0;996.0]	0.005
Rate of hospital encounter/ 100 patients at 1 year post listing				
Ascites		124.6	118.4	0.421
SBP		8.48	8.71	0.912
Variceal Bleed		2.68	6.05	0.004
Hepatic encephalopathy		89.7	58.57	0.001
Rhabdomyolysis		1.34	0.32	0.097
Major adverse cardiovascular events at 1 year post listing (percentage)		12 (4.3)	114 (2.5)	0.086

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2360 | EVALUATION OF SARCOPENIA-RELATED MUSCLE DECLINE IN PATIENTS WITH LIVER CIRRHOSIS FOR REHABILITATION

Hiroyuki Abe[1] Hiroteru Kamimura[1] Suguru Miida[1] Hiroki Maruyama[1] Saori Endo[1] Hitoshi Yoshiji[2] Masahito Shimizu[3] Takumi Kawaguchi[4] Tetsuya Tsuji[5] Shuji Terai[1], [1]Niigata University, [2]Nara Medical University, [3]Gifu University, [4]Kurume University, [5]Keio University

Background: Liver disease is a representative cause of secondary sarcopenia, and liver cirrhosis (LC) complicated by sarcopenia is associated with poor prognosis. Therefore, controlling sarcopenia progression is crucial. This study aimed to analyze factors related to muscle mass decline using the skeletal muscle index at the third lumbar vertebra (L3-SMI; cm²/m²), a representative indicator of sarcopenia. We establish and validate a predictive model for muscle mass decline in LC patients. **Methods:** This multicentered retrospective study included 612 LC patients (375 males; mean age: 70 years) from four facilities who underwent annual CT imaging, including the pelvis, over five years. L3 SMI (Skeletal Muscle Index) (cm²/m²) is calculated by dividing the skeletal muscle area at the L3 vertebral level (cm²) by the square of the individual's height (meters). L3-SMI was measured annually, and factors related to muscle mass decline were analyzed. A linear regression model predicting L3-SMI at year five (SMI_5) based on L3-SMI at year one (SMI_1) was developed using our institution's data and validated using external data from three other facilities. **Results:** For the predictive model derived from data on 175 patients, we validated its accuracy using a dataset of 343 patients from three other institutions. The model's performance was assessed using the root mean squared error (RMSE) and the coefficient of determination (R^2 score). Patients were categorized by Child-Pugh score (A: n = 466, B: n = 135, C: n = 11). The average annual decline rates in L3-SMI were significantly steeper in Child C patients (-1.79 ± 1.92 cm²/m²/year) than in Child A (-0.99 ± 0.70 cm²/m²/year, p = 0.002). A multiple regression analysis yielded the following predictive formula: SMI_5 = -1.194 + 0.731SMI_1 - 2.609 (male) + 0.081BMI - 0.033*age - 4.077 (Child B) - 23.085 (Child C) Validation with data from 343 external patients demonstrated high accuracy (R^2 = 0.0079; root mean squared error [RMSE] = 24.9328). In addition to factors significantly associated with SMI, males tended to have significantly higher SMI

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values than females (regression coefficient: 6.829, P value < 0.01), higher albumin values tended to have higher SMI values (regression coefficient: 1.179, P value < 0.01), and SMI values with loop diuretics were lower than those without (regression coefficient: -1.025, P value < 0.01). The same results were also observed for Child-Pugh diuretics (regression coefficient: -1.275, P value < 0.01). **Conclusion:** This study identified a significant correlation between liver functional reserve (Child-Pugh score) and the rate of muscle mass decline, with worse liver reserve associated with accelerated muscle loss. The developed model accurately predicts future L3-SMI values based on current L3-SMI,age, BMI, and Child-Pugh score. These findings support the potential for personalized hepatic rehabilitation protocols targeting sarcopenia in LC patients.

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2361 | INCIDENCE, RISK FACTORS, AND OUTCOMES OF MAJOR ADVERSE KIDNEY EVENTS IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

Rakhi Maiwall[1] Sumeet Asrani[2] Gnana Kavitha[1] Neha Chauhan[1] Chhagan Bihari[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences, [2]Baylor University Medical Center, part of Baylor Scott & White Health

Background: Patients with cirrhosis have significant hemodynamic alterations and require continuous medications, predisposing them to the development of major adverse kidney events (MAKE). However, limited studies have evaluated risk factors for MAKE in cirrhosis **Methods:** We investigate a large retrospective cohort of decompensated cirrhosis (n = 3708) patients, from index hospitalization, risk factors for development of MAKE at 1 year. MAKE was defined as a composite of ≥25% decline in eGFR, development of de-novo chronic-kidney-disease (CKD) stage ≥3 or CKD progression (≥50% reduction in eGFR compared with baseline) or new haemodialysis or death. eGFR was measured every 3-6 months. Competing risk survival analysis was performed to identify risk factors of MAKE. **Results:** Patients {mean age 48 ± 15 years, 86% males, MELDNa 24 ± 10, eGFR 92.23 ± 51.54 ml/m^2, alcohol-related liver disease (ALD) in 38.5% } admitted with decompensated cirrhosis, 20% without acute kidney injury (no AKI 76.5%, CKD (32% CKD) or AKI on CKD (29%) while CKD without AKI (2.9%) were followed for a median of 220 days (IQR 198-354). Altogether, 63% developed MAKE (50% showed eGFR decline, 31% developed de-novo CKD, 15% had CKD progression, 38% required dialysis), 28% died while 5% and 2% underwent LT or TIPS respectively. MAKE was an independent predictor of mortality (HR 1.25, 95% CI 1.08-1.46). On multivariable analysis, patients with AKI on CKD had the highest risk (HR 2.42, 2.12-2.76), followed by CKD without AKI (HR 1.76, 1.45-2.14) while presence of AKI alone (sHR 0.96, 0.86-1.08) ref (no AKI or CKD), sepsis (sHR 1.82, 1.62-2.05), refractory ascites (sHR 1.79, 1.59-1.99) higher leucocyte counts (sHR 1.02, 1.001-1.03) and MELDNa (sHR 1.03, 1.02-1.04) were risk factors for MAKE. Patients with MAKE had more frequent hospitalizations (OR 3.84, 3.53-4.17), new episodes of AKI (OR 1.87, 1.53-2.30), hepatic encephalopathy (OR 1.38, 1.17-1.63) and worsening of ascites (OR 5.03, 4.33-5.84). Cystatin C was available in 436 patients and was found to be an independent risk factor for MAKE (sHR 1.74,1.54 -1.97). **Conclusion:** MAKE develops in almost two-thirds of patients with decompensated cirrhosis which is associated with higher risk of major adverse liver outcomes and mortality. Patients with background CKD and those with risk factors of MAKE should be closely monitored with biomarkers or eGFR equations for institution of appropriate therapeutic interventions for prevention and consideration of an early liver transplant.

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2362 | PHYSICAL ACTIVITY MEASURED BY DIGITAL WEARABLE TECHNOLOGY INVERSELY CORRELATES WITH SEVERITY OF LIVER DISEASE AND FRAILTY IN PATIENTS WITH CIRRHOSIS

Avesh Thuluvath[1] Kamaryn Tanner[2] Jessica Siguencia[3] Olivia Blocker[3] Nayda Pichardo-Fernandez[1] Brian McSteen[1] Ziyu Liu[4] Jialin Gao[4] Robert Brown[3] Alan Cohen[2] Adam Buckholz[3] Elizabth Verna[1], [1]Division of

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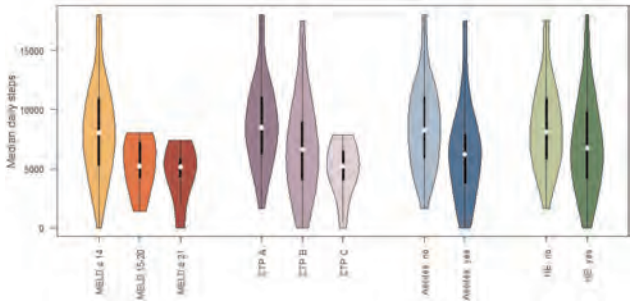
Background: Frailty is strongly associated with mortality in cirrhosis and may be exacerbated by decreased physical activity as liver disease progresses. Digital wearable technology, such as Oura™ rings, present a potential strategy to longitudinally monitor physical activity. We used Oura rings to study the association between severity of liver disease, frailty and physical activity in patients with cirrhosis. **Methods:** Adults with cirrhosis were prospectively enrolled at two centers in New York City from 8/2023-5/2025 and provided with an Oura ring for 6 months. Frailty was measured in a subset of patients using the Liver Frailty Index (LFI: grip, chair stands and balance testing). Daily total steps from each patient were extracted from the 1st month after enrollment. Data from the first 14 days in which the patient wore the ring $\geq$ 90% of the day were analyzed. Linear mixed effects models were used to estimate the association between daily total steps, indicators of liver disease severity (MELD, Child-Turcotte-Pugh Score [CTP], history of ascites, hepatic encephalopathy [HE] and variceal hemorrhage) and frailty. **Results:** Of the 111 enrolled participants, 109 had $\geq$ 1 day with $\geq$ 90% wear-time within the first month after enrollment; 50% were male, the mean age was 55.1 ($\pm$11.2) years and the most common etiologies of cirrhosis were alcohol-associated liver disease (35%) and metabolic dysfunction-associated steatotic liver disease (33%). The mean MELD was 10.6 ($\pm$4.8); 53% were CTP A, 33% CTP B and 14% CTP C, while 52% were decompensated. Among participants who underwent baseline LFI, mean LFI was 3.61 ($\pm$0.62). After adjusting for sex and age, a 1-point increase in MELD was associated with a 4% decrease in daily step count (95% CI: -2%, -7%, $p<0.01$) (Figure 1). Compared to CTP A, CTP B (-32%, 95% CI: -12%, -48%, $p<0.01$) and CTP C (-55%, 95% CI: -34%, -69%, $p<0.01$) were inversely associated with daily step count, as was a history of ascites (-40%, 95% CI: -48%, -12%, $p<0.01$) or HE (-27%, 95% CI: -44%, -4%, $p=0.03$). A 1-point increase in LFI was associated with an estimated 37% decrease in daily step count (95% CI: -57%, -7%, $p=0.04$) after adjusting for age, sex and MELD score. **Conclusion:** Physical activity measured by digital wearable technology is significantly associated with severity of liver disease and frailty in patients with cirrhosis. These findings demonstrate the potential for Oura rings to track physical activity in patients with cirrhosis and potentially even monitor response to frailty interventions and predict progression of both frailty and liver disease.

Figure: Violin Plots of Median Daily Steps, Stratified by Severity of Liver Disease and Frailty



Disclosures: Avesh Thuluvath: Nothing to Disclose, Kamaryn Tanner: Nothing to Disclose, Jessica Siguencia: Nothing to Disclose, Olivia Blocker: Nothing to Disclose, Nayda Pichardo-Fernandez: Nothing to Disclose, Brian McSteen: Nothing to Disclose, Ziyu Liu: Nothing to Disclose, Jialin Gao: Nothing to Disclose, Robert Brown: Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant, Alan Cohen: Nothing to Disclose, Adam Buckholz: Nothing to Disclose, Elizabth Verna: Nothing to Disclose

2363 | REAL-WORLD COMPARATIVE OUTCOMES OF TERLIPRESSIN USE IN HEPATORENAL SYNDROME: A PROPENSITY SCORE-MATCHED ANALYSIS OF U.S. HOSPITALIZED PATIENTS

Romelia Barba[1] Khawaja Hassam[2] Ana Marenco-Flores[3] Natalia Rojas-Amaris[3] Daniela Goyes[4] Denisse Rubio Cruz[3] Leo Yamaguchi[1] Kanak Das[1] Hakan Akin[1] Michael Curry[3], [1]Texas Tech University, [2]Lahey Hospital and Medical Center, [3]Beth Israel Deaconess Medical Center, [4]Yale School of Medicine

Background: Hepatorenal syndrome–acute kidney injury (HRS-AKI) is a life-threatening but reversible complication of cirrhosis. Terlipressin, a vasopressin analog, is FDA-approved and guideline-recommended for HRS-AKI, yet trials (OT-0401, REVERSE, CONFIRM) did not demonstrate a mortality benefit, likely due to limited power and inclusion of patients with advanced disease. Real-world data are needed to assess its effectiveness and safety in U.S. clinical practice. **Aim:** To evaluate real-world outcomes of terlipressin versus standard therapy in hospitalized adults with HRS-AKI. **Methods:** We conducted a retrospective cohort study using the TriNetX U.S. Collaborative Network, a federated research platform aggregating de-identified

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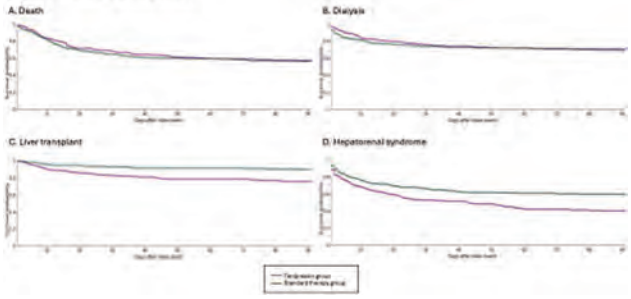
electronic health record data from multiple healthcare organizations. Among 13,888 hospitalized adults with HRS from September 14, 2022, through May 2025, 378 patients treated with terlipressin were 1:1 propensity score-matched to 378 patients receiving albumin and/or norepinephrine, midodrine, or octreotide. Matching included MELD 3.0 variables: serum sodium, creatinine, total bilirubin, INR, and albumin. Outcomes within 90 days included mortality, dialysis, liver transplant, and recurrent HRS. Odds ratios (OR), hazard ratios (HR), and Kaplan-Meier analyses were used. **Results:** After matching, mortality was slightly lower in the terlipressin group compared to controls (38.4% vs. 40.2%; OR 0.93, 95% CI 0.69–1.24; $p = 0.60$), as was dialysis initiation (24.1% vs. 26.7%; OR 0.87, 95% CI 0.63–1.21; $p = 0.40$), though neither reached statistical significance. In contrast, terlipressin-treated patients had higher rates of liver transplantation (17.7% vs. 7.4%; OR 2.67, 95% CI 1.69–4.29; $p < 0.001$) and recurrent HRS (49.7% vs. 35.2%; OR 1.82, 95% CI 1.36–2.44; $p < 0.001$). Kaplan-Meier analysis showed increased hazards for both recurrent HRS (HR 1.60, 95% CI 1.28–1.99; $p < 0.001$) and transplant (HR 2.63, 95% CI 1.69–4.09; $p < 0.001$) in the terlipressin group. **Conclusion:** In this multi-center matched cohort, terlipressin was not associated with significant reductions in mortality or dialysis, which is consistent with findings from prior trials. Higher transplant and recurrent HRS rates may reflect greater illness severity, treatment timing, or differential access to transplant. Due to de-identified data, site-level variation and practice patterns could not be assessed. Additionally, competing risks (e.g., death prior to transplant) were not formally modeled, which may influence the interpretation of non-fatal outcomes. These findings underscore the complexity of real-world terlipressin use and the need for prospective studies to clarify its role and guide MELD policy recalibration in transplant-listed patients.

Figure 1. Kaplan-Meier survival curves



Disclosures: Romelia Barba: Nothing to Disclose, Khawaja Hassam: Nothing to Disclose, Ana Marenco-Flores: Nothing to Disclose, Natalia Rojas-Amaris: Nothing to Disclose, Daniela Goyes: Nothing to Disclose, Denisse Rubio Cruz: Nothing to Disclose, Leo Yamaguchi: Nothing to Disclose, Kanak Das: Nothing to Disclose, Hakan Akin: Nothing to Disclose, Michael Curry: Mallinckrodt: Consultant, Pfizer: Independent Contractor, International Healthcare Inc: Independent Contractor, CareDx: Grant/Research Support, Intercept: Grant/Research Support, Sonic Incytes: Grant/Research Support

2364 | PLASMA AMMONIA LEVELS OVER THE COURSE OF A HOSPITALISATION FOR OVERT HEPATIC ENCEPHALOPATHY

Davide Erminelli[1] Chiara Mangini[2] Dario Gapeni[2] Lisa Zarantonello[2] Sara Montagnese[2], [1]University of Padova, Department of Medicine, [2]University of Padova

Background: The diagnostic and prognostic role of ammonia in the assessment of Overt Hepatic Encephalopathy (OHE) remains debated. The aim of the present study was to assess the time-course of ammonia levels during an OHE-related hospitalisation in relation to OHE duration/severity and the length of hospitalisation. **Methods:** All patients admitted to the Liver Unit, Padova University Hospital (Italy) between January 2021 and July 2024 with a verified discharge diagnosis of OHE were included ($n = 104$; 77% males, 72 ± 11 years). Clinical and laboratory indices, including ammonia levels prior to admission/after discharge (time frame: ± 6 month from hospitalisation) and during the hospitalisation (average of 3 measurements, up to 10) were recorded, along with duration of hospitalisation, precipitants, ongoing ammonia-lowering and psychoactive treatment. **Results:** Over the studied time frame, 58 (56%) patients had a single OHE hospitalisation while 20 (19%) had 2-7 OHE hospitalisations. Of the 104 hospitalisations, 31 (30%) were for grade II, 66 (63%) grade III and 7 (7%) grade IV OHE. Of the 58 single hospitalisations, 23 (40%) were for grade II, 33 (57%) for grade III and 2 (3%) for grade IV OHE. Ammonia levels increased progressively and significantly with increasing OHE grade (II: 118 ± 47 μmol/L; III: 155 ± 62 μmol/L; IV: 219 ± 65 μmol/L; $p < 0.001$, grade II vs grade III and IV, $p < 0.05$ and $p < 0.01$ respectively). Ammonia levels prior to admission/after discharge (87 ± 35 μmol/L and 79 ± 42 μmol/L, respectively) were significantly lower than those on admission (148 ± 63 μmol/L; $p < 0.0001$, Figure 1A). Hospitalisations for grade IV OHE were longer (12.3 ± 6.5 days) than those for grade III (5.8 ± 4.8 days $p < 0.01$). Lower levels of ammonia on admission were found in patients qualified as not fully recovered on discharge (124 ± 60 μmol/L) and those on chronic treatment with psychoactive drugs (117 ± 57 μmol/L) compared to their counterparts (155 ± 63 μmol/L, $p < 0.05$; 158 ± 62 μmol/L, $p < 0.01$ respectively). All the above held true when analyses were restricted to the 58 single hospitalisations (Figure 1B). **Conclusion:** OHE presence and

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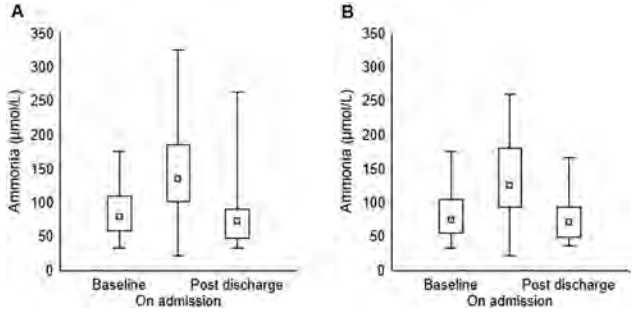
severity correlated both with ammonia levels and with the duration of hospitalisation. Ammonia on admission was significantly higher to baseline ammonia levels prior to admission and after discharge. Incomplete recovery and chronic treatment with psychoactive drugs were associated with lower ammonia levels, suggesting confounding in the expression of OHE phenotype.



Disclosures: Davide Erminelli: Nothing to Disclose, Chiara Mangini: Nothing to Disclose, Dario Gapeni: Nothing to Disclose, Lisa Zarantonello: Nothing to Disclose, Sara Montagnese: Nothing to Disclose

2365 | ULTRASOUND MUSCULAR THICKNESS-BASED MODEL TO IDENTIFY SARCOPENIA IN PATIENTS WITH PORTAL HYPERTENSION (PH): A CROSS-SECTIONAL SINGLE-CENTER OBSERVATIONAL STUDY

Martina Lucà[1] Lorenzo Argiento[1] Giulia Tosetti[1] Valentina Cardone[1] Sofia Ridolfo[1] Edoardo Acquati[1] Francesco Cicchetti[1] Edon Xhepa[1] Matilde Pavan[1] Chiara Grilli[1] Pierpaolo Biondetti[1] Salvatore Alessio Angileri[1] Simona Stella[2] Gianpaolo Carrafiello[1] Pietro Lampertico[1], [1]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [2]Occupational Health Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Background: Sarcopenia is a prevalent complication in cirrhosis (affecting 40–70% of patients) and an independent predictor of poor outcomes. Although CT imaging is the diagnostic gold standard, its use is limited by cost, radiation, and availability. Therefore, reliable, reproducible, and non-invasive tools are needed for routine sarcopenia screening and follow-up. **Methods:** This cross-sectional, single-center study included consecutive outpatients with cirrhotic or non-cirrhotic PH who had recent abdominal CT scans. Ultrasound (US) assessment of muscle thickness was performed at four sites—biceps brachii (BB), rectus abdominis (RA), rectus femoris (RF), and thigh muscles (TM)—by two blinded, trained operators. Clinical, anthropometric, biochemical, and nutritional data were collected. Sarcopenia was defined by CT using EASL/AASLD-endorsed L3 skeletal muscle index (L3-SMI) cut-offs. Associations between sarcopenia and clinical or US parameters were analyzed. **Results:** A total of 102 patients were enrolled (median age 61, 63% male, 84% cirrhotic, median BMI 25.7 kg/m²). Sarcopenia prevalence was high in both cirrhotic and non-cirrhotic PH patients (54.1% vs. 61.5%, $p = 0.58$), without significant sex-related differences. Among the parameters evaluated, US-RF thickness and BMI showed the strongest inverse correlations with sarcopenia: OR 0.79 (95% CI: 0.69–0.91, $p < 0.01$) and OR 0.80 (95% CI: 0.63–0.91, $p < 0.01$), respectively. Based on these findings, a sex-specific model was developed, combining BMI with US-RF thickness. The model showed best performance in cirrhotic men and in women overall, using BMI thresholds of 28.6 kg/m² for men and 21.7 kg/m² for women, with US-RF thickness cut-offs of 15 mm and 10 mm, respectively. These cut-offs yielded good diagnostic accuracy, with an overall AUC of 0.78. Intra- and inter-operator reproducibility of US measurements was excellent (ICC > 0.95). **Conclusion:** Ultrasound assessment of muscle thickness, especially when integrated with BMI, appears to be a reliable, non-invasive, and reproducible bedside method for identifying sarcopenia in patients with portal hypertension. Future studies on larger, sex-stratified cirrhotic cohorts are warranted to assess its prognostic value.

Disclosures: Martina Lucà: Nothing to Disclose, Lorenzo Argiento: Nothing to Disclose, Giulia Tosetti: Nothing to Disclose, Valentina Cardone: Nothing to Disclose, Sofia Ridolfo: Nothing to Disclose, Edoardo Acquati: Nothing to Disclose, Francesco Cicchetti: Nothing to Disclose, Edon Xhepa: Nothing to Disclose, Matilde Pavan: Nothing to Disclose, Chiara Grilli: Nothing to Disclose, Pierpaolo Biondetti: Nothing to Disclose, Salvatore Alessio Angileri: Nothing to Disclose, Simona Stella: Nothing to Disclose, Gianpaolo Carrafiello: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose

2366 | INTERPRETING SPLEEN STIFFNESS MEASUREMENT: THE ROLE OF TECHNICAL RELIABILITY CRITERIA IN CLINICAL DECISION-MAKING

Elizabeth Williams[1] Regina Weber[1] Archita Desai[1] Raj Vuppalanchi[1], [1]Indiana University

Background: The interquartile range to median ratio (IQR/M) is a widely accepted reliability criterion for liver stiffness measurement (LSM), where values ≤10% are considered very reliable, 10–30% reliable, and > 30% unreliable in cases with ≥10 valid measurements.

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However, equivalent criteria have not been established for spleen stiffness measurement (SSM). This study aimed to evaluate the utility of IQR/M as a reliability metric for SSM and its impact on diagnostic accuracy in detecting esophageal and/or gastric varices. **Methods:** In this cross-sectional study, 170 patients underwent 220 paired SSM and upper endoscopy exams within six months. SSM was measured using vibration-controlled transient elastography (FibroScan 630 Expert). We assessed the diagnostic accuracy of SSM $>$ 50 kPa —a threshold aligned with the Baveno VII guideline for high-risk varices—across varying IQR/M levels. **Results:** SSM and endoscopy were performed on the same day in 55 patients, with a median interval of 1.2 months (IQR 0–3). The median patient age was 60 years (range 20–83), with 55.3% male and 90% White. Common liver disease etiologies included metabolic dysfunction-associated steatotic liver disease (33.5%) and alcohol-associated liver disease (22.9%). Mean platelet count was $116 \pm 91 \times 10^3/\mu L$, INR 1.3 ± 0.5, and MELD score 12 ± 4. The prevalence of SSM $>$ 50 kPa was 68%, with only 6.7% meeting the unreliability criteria of IQR/M $>$ 30%. Without applying reliability criteria, the presence of varices was accurately identified in 125 patients (83.3%). When applying IQR/M $\leq$ 30%, diagnostic accuracy increased to 86.4% (121/140). Stricter thresholds (IQR/M $\leq$20% and $\leq$10%) were associated with lower diagnostic accuracy (Table 1). **Conclusion:** In patients with suspected portal hypertension and SSM $>$ 50 kPa, unreliable measurements (IQR/M $>$30%) were rare (6.6%). Applying IQR/M $\leq$ 30% as a reliability threshold modestly improved diagnostic accuracy for detecting varices. However, using more stringent thresholds paradoxically reduced diagnostic performance, suggesting that while reliability criteria enhance confidence, overly restrictive cutoffs may exclude valid clinical data.

Table 1. Diagnostic Accuracy of Spleen Stiffness Measurements in Identifying Esophageal and/or Gastric Varices Based on Interquartile Range/Median

	IQR/M ≤ 30% (n=140)	IQR/M > 30% (n=10)	P-value	Accuracy	IQR/M ≤ 20% (n=116)	IQR/M > 20% (n=34)	P-value	Accuracy	IQR/M ≤ 10% (n=69)	IQR/M > 10% (n=81)	P value	Accuracy
			0.001	84.7%			0.005	75.3%			0.048	53.3%
SSM > 50 kPa + Varices, n (%) Accurate	121 (86.4)	4 (40.0)			102 (87.9)	23 (67.6)			62 (89.9)	63 (77.8)		
SSM > 50 kPa + No Varices, n (%) Inaccurate	19 (13.6)	6 (60.0)			14 (12.1)	11 (32.4)			7 (10.1)	18 (22.2)		

IQR/M: Interquartile Range (IQR)/Median (M)

Disclosures: Elizabeth Williams: Nothing to Disclose, Regina Weber: Nothing to Disclose, Archita Desai: Nothing to Disclose, Raj Vuppalanchi: Eli LIlly: Grant/Research Support, GSK: Consultant, Madrigal: Consultant, Zydus Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Kowa: Grant/Research Support, Takeda: Grant/Research Support, GSK: Consultant, UBC: Consultant, Gilead: Grant/Research Support, GSK: Grant/Research Support, 89 Bio: Consultant

2367 | PREDICTORS OF POST TIPS PERSISTENT ASCITES

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Background: TIPS is used to lower portal pressure in refractory ascites. However, a proportion of patients require therapeutic paracentesis despite adequate portal pressure reduction and on optimum tolerable diuretic dose. This study investigated factors responsible for 'post-TIPS ascites persistence". **Methods:** EMRs of patients who underwent TIPS for refractory ascites over 5 years were reviewed. Ascites persistence was defined as the need for paracentesis $>$1 month post-TIPS despite max tolerable dose of diuretics and no shunt stenosis defined as angiographic evaluation of greater than 50% stenosis, PSG $>$12 mmHg or Doppler criteria. Follow-up: 1 month post-TIPS, then every 3 months. Patients needing paracentesis were evaluated for cardiac, renal, or shunt-related causes. Data included: Pre-TIPS labs and echo, TIPS procedure details, Post-TIPS outcomes SPSS v30; paired t-test, univariate and multivariate regression. $p<0.05$ significant. **Results:** 384 patients underwent TIPS placement during this period. TIPS placement due to variceal bleed (n=96), Budd-Chiari Syndrome (n=65) or miscellaneous reasons (n=6) or received liver transplant (n=32) or had incomplete data (n=185) were excluded. Finally, 107 patients were taken for assessment and follow-up Patients requiring therapeutic paracentesis after one month of TIPS (Group A) were compared with those who did not require tapping (Group B). Mean age Group A [n=39 (36.4%)] 53.05 $\pm$ 11.03 and Group B [n=68 (63.6%)] 53.14 $\pm$ 13.35 was comparable. Median MELD in group A was higher than group B {17.05 $\pm$ 5.14 vs.14.75 $\pm$ 4.13, p= 0.016} along with CTP score {8.82 $\pm$ 1.57 vs 7.95 $\pm$ 1.33, p 0.004}. The pre-TIPS cardiac ECHO parameters in Gr. A vs. B {RA dimension pre-TIPS 34.08 $\pm$ 5.31 vs 32.90 $\pm$ 6.71, p 0.35}, E/e' ratio Group A vs Group B {pre and post TIPS 8.46 $\pm$ 2.10 vs 6.6 $\pm$ 4.85 p 0.31, 8.96 $\pm$ 2.00 vs 8.08 $\pm$ 4.20 p values 0.11} were not statistically significant. Baseline Plasma Renin Activity had a mean of 11.80 $\pm$ 1.47 in the entire TIPS cohort, NT Pro BNP 967.51 $\pm$ 238.10 taking log into account. Pre and Post-TIPS plasma renin levels (p=0.04) were significantly higher in group A, possibly contributing to ascites recurrence. MELD, CTP, serum ALT, total protein, haemoglobin, and LA dimension were variables considered in univariate analysis. Multivariate analysis- MELD and CTP were the only variables contributing to post-TIPS ascites persistence. Post-TIPS, RA Pressure increased from 4.95 $\pm$ 3.24 to 9.44 $\pm$ 3.81 (p-value $<$0.01) in Group A. Portal Pressure reduction was significant in both groups (p-value $<$0.01) The average stent diameter in Group A patients was 8mm compared to group B, where 10mm stent was placed. **Conclusion:** Post-TIPS ascites persisting beyond 1 month, can be attributed to higher MELD, and CTP score, higher

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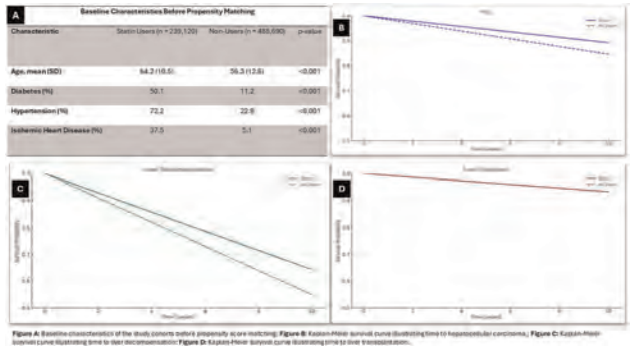
baseline PRA and or smaller diameter stent that may attribute to delayed ascitic fluid mobilization as one of the factors for therapeutic paracentesis, despite optimum portal pressure reduction.

Disclosures: JAYASHREE BISWAS: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, VINOD ARORA: Nothing to Disclose, AMAR MUKUND: Nothing to Disclose, YASHWANT PATIDAR: Nothing to Disclose

2368 | UNDERUTILIZATION OF STATINS IN YOUNGER CIRRHOTIC PATIENTS DESPITE HEPATOPROTECTIVE BENEFITS: A PROPENSITY-MATCHED REAL-WORLD STUDY

Mohammad Adam[1] Fatima Elmustafa[2] Abdellatif Ismail[3] Abdelhaleem Sideeg[4] John Helzberg[5] Ashwani Singal[6], [1]University of Missouri - Kansas City School of Medicine, Kansas City, MO, [2]Henry Ford Health System, Warren, MI, [3]University of Maryland Medical Center Midtown Campus, Baltimore, MD, [4]Virginia Mason Medical Center, Seattle, WA, [5]University of Missouri-Kansas City, Saint Luke's Liver transplant Program, [6]University of Louisville

Background: Despite historical concerns regarding hepatotoxicity, emerging evidence suggests statins may offer hepatoprotective effects in patients with cirrhosis. Using real-world data from a large, multicenter electronic health record network, we evaluated the association between statin use and liver-related outcomes. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network. Adults (≥18 years) with alcoholic or unspecified cirrhosis were categorized into statin-exposed and statin-naïve groups. Propensity score matching (1:1) was performed based on demographics, comorbidities, and labs. Outcomes included hepatocellular carcinoma (HCC), liver decompensation (ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome), and liver transplantation (LT). Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. **Results:** Before matching, statin users (n = 239,120) were older (mean age: 64.2 vs. 56.3) and had more comorbidities than non-users (n = 488,690). After matching, yielding 136,091 patients per group, baseline characteristics were balanced. Statin users had a lower risk of HCC (HR 0.66; 95% CI: 0.64–0.69; p < 0.001) and liver decompensation (HR 0.70; 95% CI: 0.68–0.71; p < 0.01). Transplant-free survival was similar (HR 1.02; p = 0.14). **Conclusion:** In this large real-world cohort, statin use was associated with a reduced risk of HCC and liver decompensation in patients with cirrhosis. These findings suggest that statin therapy should not be discouraged and may, in fact, be encouraged for its hepatoprotective benefits, particularly in younger cirrhotic patients.



Disclosures: Mohammad Adam: Nothing to Disclose, Fatima Elmustafa: Nothing to Disclose, Abdellatif Ismail: Nothing to Disclose, Abdelhaleem Sideeg: Nothing to Disclose, John Helzberg: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, GSK: Grant/Research Support, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, Avera Medical Group: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other

2369 | RISING SEPSIS-RELATED MORTALITY IN CIRRHOTIC PATIENTS IN THE UNITED STATES (1999–2020): A CDC WONDER ANALYSIS

Corinne Caissie[1] Simran Joshi[2] Saman Javid[3] Gaurav Sharma[4] Laksh Kumar[5] Aseef Rehman[6] Faizan Saqib[7] Sardar Noman Qayyum[8] Revathi Rajendran[9] Muhammad Faizan Ali[10] Preethi Jagannath[11] Marquise Soto[12] Jeevin Singh Sandhu[13] Matthew Manoj[14], [1]Yale New Haven Health, Brigeport Hospital, CT, [2]Yale New Haven Health, Bridgeport Hospital, [3]CMH Kharian Medical College, Kharian, Pakistan, [4]JNU Medical College, Jaipur, [5]Shaheed Mohtarma Benazir Bhutto Medical College, Lyari, [6]University College of Medicine and Dentistry, Lahore, Pakistan, [7]House Officer, CMH Kharian, [8]Bacha Khan Medical College, Mardan, Pakistan, [9]Sri Lalithambigai Medical College and Hospital, [10]Jinnah Postgraduate Medical Center, [11]Mayo Clinic, Rochester, MN, [12]Massachusetts General Hospital, Boston, MA, [13]Methodist Dallas Medical Center, Dallas, TX, [14]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background: Patients with cirrhosis are at elevated risk for sepsis due to profound immune dysfunction, impaired hepatic clearance, and increased gut permeability. Sepsis—a dysregulated host response to infection leading to life-threatening organ dysfunction—remains a major contributor to mortality in this population. Monitoring long-term mortality

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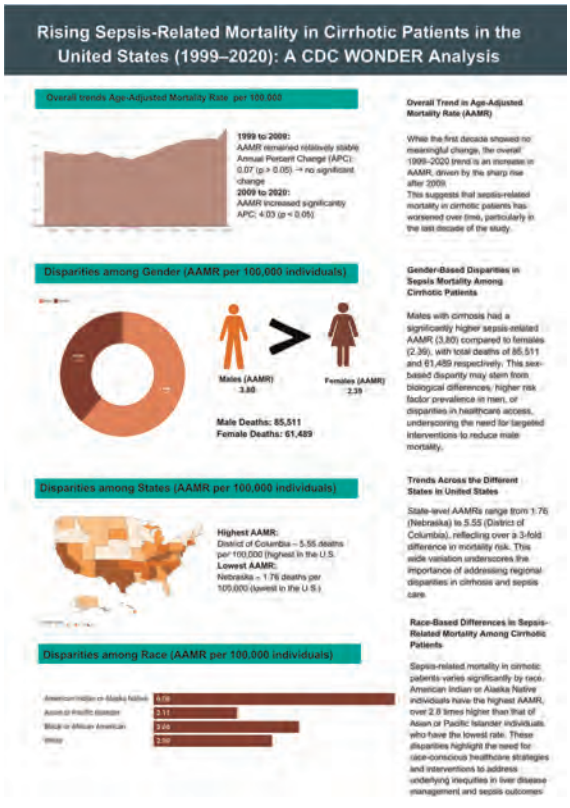
trends is critical to understanding disease burden and informing targeted clinical interventions. **Methods:** We conducted a retrospective, population-based study using age-adjusted mortality data from the CDC Wide-ranging Online Data for Epidemiologic Research (WONDER) database to assess trends in sepsis-related deaths among individuals with cirrhosis in the United States from 1999 to 2020. Joinpoint regression analysis was applied to identify statistically significant inflection points in mortality trends. Annual percent change (APC) and corresponding 95% confidence intervals were calculated to quantify temporal shifts. **Results:** The analysis revealed two distinct mortality trends. From 1999 to 2009, sepsis-related mortality among cirrhotic patients remained relatively stable (APC: 0.07; $p > 0.05$). In contrast, the period from 2009 to 2020 demonstrated a significant upward trajectory (APC: 4.03; $p < 0.05$), indicating a substantial increase in sepsis-associated deaths. This shift suggests a worsening clinical outlook for cirrhotic patients in the context of systemic infection over the last decade. **Conclusion:** The observed rise in sepsis-related mortality in patients with cirrhosis underscores an urgent need for improved surveillance, early detection, and management strategies tailored to this high-risk group. Potential contributors include increasing cirrhosis prevalence, evolving microbial resistance, suboptimal care pathways, and delayed diagnosis. Future research should focus on identifying modifiable risk factors and developing evidence-based protocols to reduce mortality and improve outcomes in cirrhosis-associated sepsis.



Disclosures: Corinne Caissie: Nothing to Disclose, Simran Joshi: Nothing to Disclose, Saman Javid: Nothing to Disclose, Gaurav Sharma: Nothing to Disclose, Laksh Kumar: Nothing to Disclose, Aseef Rehman: Nothing to Disclose, Faizan Saqib: Nothing to Disclose, Sardar Noman Qayyum: Nothing to Disclose, Revathi Rajendran: Nothing to Disclose, Muhammad Faizan Ali: Nothing to Disclose, Preethi Jagannath: Nothing to Disclose, Marquise Soto: Nothing to Disclose, Jeevin Singh Sandhu: Nothing to Disclose, Matthew Manoj: Nothing to Disclose

2370 | OVERALL MORTALITY TRENDS IN LIVER CIRRHOSIS AND GASTROINTESTINAL HEMORRHAGE (1999–2020)

Corinne Caissie[1] Simran Joshi[1] Saman Javid[2] Gaurav Sharma[3] Laksh Kumar[4] Sushrut Ingawale[5] Preethi Jagannath[6] Marquise Soto[7] Jeevin Sandhu[8] Matthew Manoj[9], [1]Yale New Haven Health, Bridgeport Hospital, CT, [2]CMH Kharian Medical College, Kharian, Pakistan, [3]JNU Medical College, Jaipur, [4]Shaheed Mohtarma Benazir Bhutto Medical College, Lyari, [5]Quinnipiac University Frank H. Netter MD School of Medicine / St. Vincent's Medical Center, Bridgepo, [6]Mayo clinic, Rochester, MN, [7]Massachusetts General Hospital, Boston, MA, [8]Methodist Dallas Medical Center, [9]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background: Liver cirrhosis and gastrointestinal (GI) hemorrhage remain significant contributors to morbidity and mortality in the United States. Understanding long-term mortality trends is essential for informing public health strategies and resource allocation. Our objective is to evaluate national trends in mortality from liver cirrhosis and GI hemorrhage in the U.S. between 1999 and 2020 using joinpoint regression analysis. **Methods:** Age-adjusted mortality rates were obtained from the CDC WONDER database. Joinpoint regression modeling was used to identify statistically significant changes in temporal trends. Annual Percent Changes (APCs) and corresponding 95% Confidence Intervals (CIs) were calculated for each trend segment. **Results:** From 1999 to 2007, mortality from liver cirrhosis and GI hemorrhage declined significantly, with an APC of –4.97% (95% CI: –7.04 to –3.69; $p = 0.004$). This trend reversed between 2007 and 2018, with a modest, non-significant increase in mortality (APC = +1.85%, 95% CI: –0.65 to 3.00; $p = 0.080$). A marked and statistically significant increase was observed from 2018 to 2020, with an APC of +12.70% (95% CI: 4.29 to 17.36; $p < 0.000001$), indicating a concerning resurgence in mortality in recent years. **Conclusion:** Following a period of improvement from 1999 to 2007, mortality from liver cirrhosis and GI hemorrhage plateaued and then rose sharply beginning in 2018. This recent surge

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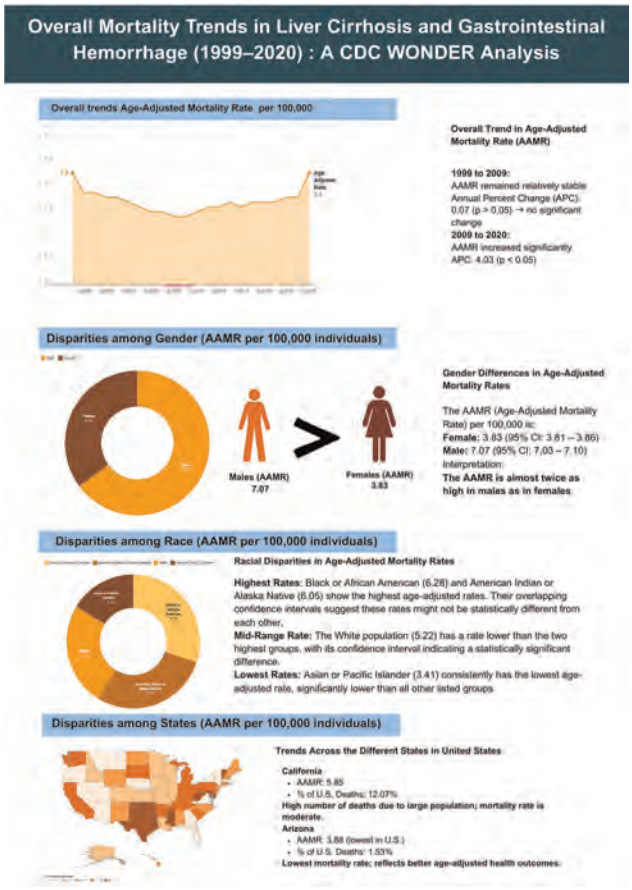
is both statistically and clinically significant, underscoring the urgent need for renewed public health efforts aimed at liver disease prevention and early intervention.

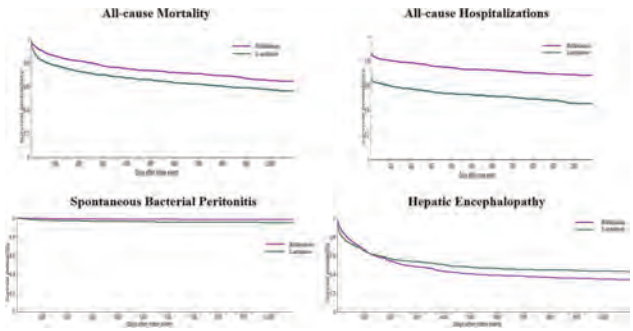


Disclosures: Corinne Caissie: Nothing to Disclose, Simran Joshi: Nothing to Disclose, Saman Javid: Nothing to Disclose, Gaurav Sharma: Nothing to Disclose, Laksh Kumar: Nothing to Disclose, Sushrut Ingawale: Nothing to Disclose, Preethi Jagannath: Nothing to Disclose, Marquise Soto: Nothing to Disclose, Jeevin Sandhu: Nothing to Disclose, Matthew Manoj: Nothing to Disclose

2371 | RIFAXIMIN USE IS ASSOCIATED WITH REDUCED MORTALITY AND HOSPITALIZATIONS IN CIRRHOTIC PATIENTS: A GLOBAL COHORT STUDY

Mohamad Mahdi Osman[1] Mohamad-Noor Abu-Hammour[1] Walid Hazem[2] Leandro Sierra[1] Omar Sims[1] Dian Chiang[3], [1]Cleveland Clinic Foundation, [2]University Hospitals, [3]Cleveland Clinic

Background: Lactulose and Rifaximin with or without lactulose are recommended therapy for prevention of recurrent hepatic encephalopathy (HE) in patients with cirrhosis. While rifaximin is often added as adjunct therapy, it is sometimes used alone in patients who are intolerant to lactulose. This retrospective study evaluates the effectiveness of rifaximin monotherapy versus lactulose monotherapy using a large global database. **Methods:** Using the TriNetX research network, we identified adult patients with cirrhosis and hepatic encephalopathy who were prescribed either rifaximin or lactulose alone. The rifaximin cohort included 1,737 patients, and the lactulose cohort included 12,950 patients. After 1:1 propensity score matching based on demographics, liver function tests, comorbidities, and MELD components, 1,734 matched pairs were analyzed. The primary composite outcome was recurrent HE and all-cause mortality. Secondary outcomes included all-cause hospitalizations, spontaneous bacterial peritonitis (SBP), and HE. **Results:** Rifaximin monotherapy was associated with a significantly lower risk of the primary composite outcome compared to lactulose monotherapy, driven largely by a reduction in all-cause mortality (HR 0.689; 95% CI 0.603–0.786; p = 0.003). Rifaximin also significantly reduced all-cause hospitalizations (HR 0.456; 95% CI 0.405–0.514; p = 0.045). While SBP was less frequent in the rifaximin group (HR 0.285; 95% CI 0.152–0.532), this difference did not reach statistical significance (p = 0.762). There was no significant difference in rates of HE (HR 1.045; 95% CI 0.940–1.160). **Conclusion:** In this large real-world cohort, rifaximin monotherapy was associated with reduced mortality and hospitalization rates compared to lactulose monotherapy in cirrhosis patients with hepatic encephalopathy, despite similar rates of recurrent HE. These findings suggest that rifaximin monotherapy may be superior to lactulose monotherapy in this population. Further risk stratification of HE patients and pharmacoeconomic study may help individualize treatment approach to prevent recurrent HE.



Disclosures: Mohamad Mahdi Osman: Nothing to Disclose, Mohamad-Noor Abu-Hammour: Nothing to Disclose, Walid Hazem: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Omar Sims: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Dian Chiang: Ipsen: Advisor

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2372 | COMPARATIVE OUTCOMES OF CIRRHOSIS ETIOLOGIES: A PROPENSITY SCORE–MATCHED ANALYSIS OF ALCOHOLIC VS NON-ALCOHOLIC CIRRHOSIS

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Background: Cirrhosis represents the terminal stage of chronic liver disease, yet clinical outcomes vary by etiology. While some analyses have contrasted single etiologies against all others combined, there remains a paucity of head-to-head comparisons across specific causes. This study aimed to compare long-term outcomes of several distinct cirrhosis etiologies—each matched to alcoholic cirrhosis (AC)—using a large real-world electronic health record dataset. **Methods:** We performed a retrospective cohort study using TriNetX, a US Collaborative Network comprising 69 tertiary institutions, to identify adults with cirrhosis due to autoimmune hepatitis (AIH); biliary diseases (BD) including primary biliary cholangitis and primary sclerosing cholangitis; chronic hepatitis B (CHB); chronic hepatitis C (CHC); metabolic dysfunction-associated steatotic liver disease (MASLD); and genetic metabolic liver diseases (GMLD) including Wilson disease, hemochromatosis, and alpha-1 antitrypsin deficiency. Each etiology was propensity score–matched 1:1 to AC based on demographics, MELD components, liver enzymes, and prior complications. Outcomes were assessed over 10 years and included hepatic encephalopathy (HE), hepatorenal syndrome (HRS), ascites, spontaneous bacterial peritonitis (SBP), upper gastrointestinal bleeding (UGIB), transjugular intrahepatic portosystemic shunt (TIPS), portal hypertension, hepatic vein thrombosis (HVT), portal vein thrombosis (PVT), hospitalization, emergency department (ED) visits, liver transplantation (LT), hepatocellular carcinoma (HCC), and a composite outcome. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and p-values. **Results:** Compared to AC, CHB and CHC had the most favorable profiles, showing lower risks of HE, ascites and hospitalization, though both had increased HCC risk (CHB: HR 2.873, $p < 0.001$; CHC: HR 2.634, $p < 0.001$). AIH and BD were associated with improved composite outcomes but showed elevated risks of HVT (AIH: HR 2.030, $p = 0.018$; BD: HR 2.084, $p = 0.002$), PVT (AIH: HR 1.261, $p = 0.005$; BD: HR 1.588, $p < 0.001$), and LT (AIH: HR 1.584, $p < 0.001$; BD: HR 2.274, $p < 0.001$). MASLD-related cirrhosis showed worse outcomes, including HE (HR 1.050, $p < 0.001$), UGIB (HR 1.259, $p < 0.001$), TIPS (HR 1.541, $p < 0.001$), HCC (HR 1.764, $p < 0.001$), LT (HR 2.488, $p < 0.001$), PVT (HR 1.820, $p < 0.001$), and HVT (HR 1.831, $p < 0.001$). GMLD-related cirrhosis showed better outcomes across most endpoints, though it was associated with increased HVT (HR 3.298, $p = 0.003$) and HCC (HR 1.326, $p < 0.001$). **Conclusion:** In this large cohort study, non-alcoholic cirrhosis etiologies were associated with more favorable outcomes than AC. Conversely, MASLD-related cirrhosis was linked to worse prognosis across multiple complications. These findings support etiology-specific risk stratification and emphasize the need for tailored management strategies in cirrhosis care.

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2373 | POINT-OF-CARE ULTRASOUND-BASED VOLUME STATUS METRICS AS PREDICTORS OF HEPATORENAL SYNDROME–ACUTE KIDNEY INJURY IN HOSPITALIZED PATIENTS WITH CIRRHOSIS: A PROSPECTIVE COHORT STUDY

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Background: Hepatorenal syndrome–acute kidney injury (HRS-AKI) was traditionally thought to result solely from renal vasoconstriction driven by splanchnic vasodilation and reduced effective circulating volume in cirrhosis. Recent evidence, however, suggests a multifactorial etiology that includes subclinical to overt cardiac dysfunction—the so-called hepatocardiorenal syndrome—as well as congestion-related renal impairment. Point-of-care ultrasound (POCUS) is increasingly used to assess systemic congestion and has been validated in patients with heart failure, but its role in cirrhosis remains underexplored. We evaluated whether POCUS-derived volume metrics—including ultrasound-estimated jugular venous pressure (uJVP), venous excess ultrasound (VExUS) score (integrating portal, hepatic, and renal vein Doppler), inferior vena cava (IVC) parameters, and lung B-line burden—predict the development of HRS-AKI in hospitalized patients with decompensated cirrhosis. **Methods:** We conducted a prospective observational study of 37 hospitalized patients with decompensated cirrhosis, including three readmissions treated as separate subjects, yielding 40 observations. All underwent comprehensive POCUS on admission, including uJVP (via internal jugular distension), IVC diameter and collapsibility, VExUS score, and lung B-line burden. Patients were monitored for HRS-

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AKI during hospitalization. HRS-AKI was defined as a creatinine rise of ≥ 0.3 mg/dL within 48 hours or ≥ 50% within 7 days, without response to diuretic withdrawal and albumin (1g/kg) for two days. **Results:** The cohort had a median age of 54; 63% were male, 68% Hispanic, and 68% had alcohol-associated liver disease. At admission, median MELD 3.0 was 23, median MAP was 79 mm Hg, and median creatinine was 0.92 (Table). Fourteen (35%) developed HRS-AKI. Compared to those without HRS-AKI, affected patients had significantly higher uJVP (mean 10.63 cm vs 7.89 cm, $p = 0.043$) and a trend toward higher VExUS scores: 25% of patients with HRS-AKI had a VExUS score ≥ 1, compared to 8.6% in those without ($p = 0.2$). IVC assessment was limited due to poor acoustic windows. Lung B-line burden did not differ between groups ($p = 0.9$). **Conclusion:** Higher uJVP and elevated VExUS scores—markers of right-sided filling pressure and venous congestion—may serve as early predictors of HRS-AKI in cirrhosis. These findings suggest underlying hemodynamic disturbances, such as reduced effective circulating volume, since venous congestion can impair the organ afterload, ultimately reducing organ perfusion. While not all associations reached statistical significance due to limited sample size, effect size trends were notable. POCUS-based volume assessment may aid in early risk stratification for HRS-AKI and warrants validation in larger cohorts.

Characteristic	Overall	HRS-AKI	No HRS-AKI	p-value2
	N = 401	N = 141	N = 261	
POCUS Parameters				
Jugular Venous Pressure Height				0.043
Median (Q1, Q3)	9.00 (6.00, 11.00)	10.00 (8.50, 12.50)	8.00 (5.00, 9.00)	
Total Number of Lung zones with B Line Pattern				0.9
Median (Q1, Q3)	2.00 (1.00, 4.00)	2.50 (1.00, 3.00)	1.50 (1.00, 5.00)	
IVC Diameter				0.8
< 1	3 (18%)	2 (25%)	1 (11%)	
1-2.1	12 (71%)	5 (63%)	7 (78%)	
>2.1	2 (12%)	1 (13%)	1 (11%)	
IVC Collapsible >50%	10 (59%)	5 (63%)	5 (56%)	>0.9
VExUS				
Hepatic Vein Doppler				0.4
S>D	35 (97%)	12 (92%)	23 (100%)	
S<D	1 (2.8%)	1 (7.7%)	0 (0%)	
S reversal	0 (0%)	0 (0%)	0 (0%)	
Portal Vein Doppler				>0.9
< 30	31 (97%)	10 (100%)	21 (95%)	
30-49	1 (3.1%)	0 (0%)	1 (4.5%)	
>50	0 (0%)	0 (0%)	0 (0%)	
Intrarenal Vein Doppler				0.6
Continuous monophasic flow	35 (95%)	12 (92%)	23 (96%)	
Discontinous biphasic flow withsystolic/diastolic phases	1 (2.7%)	1 (7.7%)	0 (0%)	
Discontinous monophasic flow withonly diastolic phase	1 (2.7%)	0 (0%)	1 (4.2%)	
Vexus Score				0.2
Grade 0	30 (86%)	9 (75%)	21 (91%)	
Grade 1	4 (11%)	3 (25%)	1 (4.3%)	
Grade 2	1 (2.9%)	0 (0%)	1 (4.3%)	
Grade 3	0 (0%)	0 (0%)	0 (0%)	

Disclosures: Daniel Alvarez: Nothing to Disclose, Suneet Waghmarae: Nothing to Disclose, Kelsie Pereyra-Bencosme: Nothing to Disclose, Nicholas Samel: Nothing to Disclose, Ashley Choi: Nothing to Disclose, Paola Mejia: Nothing to Disclose, Zoe Verzani: Nothing to Disclose, Abhilash Koratala: Nothing to Disclose, Benjamin Galen: Nothing to Disclose, Brett Fortune: Gilead Sciences: Consultant, Madrigal Pharma: Consultant, WL Gore and Associates: Consultant, BD medical: Consultant

2374 | CIRRHOSIS AS AN INDEPENDENT RISK FACTOR FOR MORTALITY IN HOSPITALIZED PATIENTS WITH ASPIRATION PNEUMONIA: A NATIONWIDE INPATIENT SAMPLE (NIS) STUDY

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Background: Aspiration pneumonia (AP) is a known complication in patients with multiple comorbidities, yet its interplay with cirrhosis remains under-characterized. This study aims to assess the burden, demographics, outcomes, and resource utilization among hospitalized patients with AP and coexisting cirrhosis using data from the NIS. **Methods:** Using NIS datasets (2018-2022), we identified admissions for AP with Cirrhosis vs without cirrhosis using relevant International Classification of Diseases(ICD), Tenth Revision codes. We compared the demographics, comorbidity burden (Elixhauser index), in- hospital outcomes and related comorbidities between the two groups. **Results:** Out of the 33,905,592 weighted adult hospitalizations, 678,739 had aspiration pneumonia, of which only 1.9% ($n = 13,035$) had cirrhosis. Cirrhotic cohorts were significantly younger (mean age 66 vs 73 years), males (66% vs 57%), higher Elixhauser comorbidity burden (98.9% vs 83.1%) and had higher proportions of Hispanic and Native American individuals than non-cirrhotic cohort (all $p < 0.001$). In-hospital mortality was higher in patients with cirrhosis (unadjusted odds ratio ≈1.52, $p < 0.001$). After adjusting for confounders, cirrhosis remained an independent predictor of mortality (design-based F-test, adjusted odds ratio[AOR] = 1.37, $p < 0.001$), alongside older age and higher comorbidity burden. Female sex was associated with slightly reduced mortality risk; race was not statistically significant in the adjusted model. Cirrhotics had longer LOS (+1.1 days, $p = 0.053$) and higher unadjusted hospital charges (+$23,800), though not significant after adjustment. Heptic Encephalopathy was significantly higher in cirrhotic cohort (11.9% vs 0.17%; AOR≈ 44, $p < 0.001$) but lower adjusted odds for dysphagia(AOR 0.65, $p < 0.001$), GERD(AOR 0.85, $p = 0.001$), PEM(AOR = 0.869, $p = 0.003$); suggesting potential confounding. **Conclusion:** In this large, nationally representative

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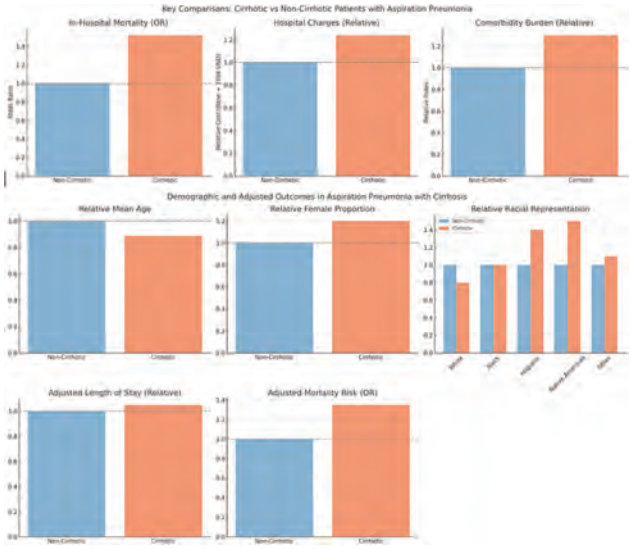
study, cirrhosis was present in a small subset (1.9%) of patients hospitalized with aspiration pneumonia but was independently associated with significantly increased in-hospital mortality, even after adjusting for demographic and clinical confounders. Cirrhotic patients exhibited a higher burden of comorbidities, were younger, and more likely to belong to Hispanic or Native American populations. While cirrhosis was associated with markedly higher rates of hepatic encephalopathy-nearly 44-fold increased odds-it was paradoxically linked to lower adjusted odds of dysphagia, GERD, and PEM, suggesting possible diagnostic or coding bias. These findings underscore the need for heightened clinical vigilance and targeted management strategies in cirrhotic patients hospitalized with aspiration pneumonia.



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2375 | BELAPECTIN MAINTAINS A FAVORABLE TREND IN REDUCING VARICEAL DEVELOPMENT OVER 36 MONTHS IN MASH CIRRHOSIS: RESULTS: FROM THE NAVIGATE TRIAL

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Background: Variceal development in patients with MASH cirrhosis and portal hypertension reflects disease progression and risk of decompensation. The NAVIGATE trial (NCT04365868) previously reported a statistically significant reduction in new varices at 18 months in the per-protocol population treated with belapectin 2 mg/kg LBW. This analysis reports outcomes at 36 months among subjects who completed the long-term follow-up. **Methods:** NAVIGATE is a Phase 2b/3 randomized, placebo-controlled trial of intravenous belapectin (2 mg/kg or 4 mg/kg LBW) administered bi-weekly in patients with MASH cirrhosis and portal hypertension without baseline varices. Endoscopies were performed at baseline, 18 months, and 36 months and were centrally read by multiple reviewers. The per-protocol (PP) population at 36 months included 57 subjects who completed 18 months of blinded therapy with evaluable endoscopy data. Subjects were stratified by type 2 diabetes mellitus (T2DM) status at baseline. The cumulative incidence of new varices was assessed using the Cochran-Mantel-Haenszel (CMH) test. **Results:** At 36 months, the per-protocol population included 57 subjects across three cohorts; placebo($n = 20$), 2mg ($n = 23$),4mg ($n = 14$). Incidence of new varices was 23.4%, 12.4% and 16.7% respectively in placebo, 2 and 4 mg cohorts. The cumulative trend observed in belapectin 2mg cohort at 18 months was maintained, with statistical significance for the 2 mg/kg group ($p = 0.04$ vs. placebo). The 4 mg/kg group showed no significant difference ($p = 0.24$). No new safety findings were observed at 36 months. Incidence of major adverse clinical events (MACE) was comparable across treatment arms, with a median follow-up of 24 months. **Conclusion:** In MASH cirrhosis with portal hypertension, belapectin 2 mg/kg continued to show a favorable trend in reducing new varices through 36 months in the per-protocol population. These findings show a continuous and sustained effect thru 36 month and support the long-term potential of galectin-3 inhibition for variceal prevention in patients with MASH cirrhosis and portal hypertension.

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publicly traded company, Akero: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Conatus: Principal Investigator, Gilead Sciences: Principal Investigator, Naga Chalasani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Raj Vuppalanchi: Eli LIlly: Grant/Research Support, GSK: Consultant, Madrigal: Consultant, Zydus Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Kowa: Grant/Research Support, Takeda: Grant/Research Support, GSK: Consultant, UBC: Consultant, Gilead: Grant/Research Support, GSK: Grant/Research Support, 89 Bio: Consultant, Edward Mena: Nothing to Disclose, Nadege Gunn: Nothing to Disclose, Zainab Abbas: Nothing to Disclose, Khurram Jamil: Mallinckrodt Pharmaceuticals: Employee, Galectin Therapeutics: Stock - publicly traded company, Galectin Therapeutics: Employee, Naim Alkhouri: Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research

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2376 | MICRONUTRIENT DEFICIENCIES IN PATIENTS WITH CIRRHOSIS: A CONTEMPORARY EVALUATION

Melinda Wang[1] Kathy Pariani[1] Fawzy Barry[1] Dorothea Kent[1] Jennifer Lai[1], [1]University of California San Francisco

Background: Despite the well-established relationship between micronutrient deficiencies and cirrhosis, little is known of micronutrient deficiencies among ambulatory cirrhosis patients awaiting liver transplant (LT). We aimed to characterize micronutrient deficiencies among cirrhosis patients awaiting LT and assess their association with frailty, a complication with high morbidity and mortality. **Methods:** Ambulatory adult patients with cirrhosis awaiting LT from 6/2024-3/2025 were tested for micronutrient deficiencies with a parsimonious panel in clinical practice. Multivariable modeling was used to assess the association between frailty and micronutrient deficiencies. **Results:** Of 154 patients, median (IQR) age was 60 (50-66) years and 66 (43%) were women. Median MELD 3.0 (IQR) was 17 (12-22) and 40 (26%) were frail. Micronutrient deficiencies were common, especially of zinc, vitamin D/E/B12, and selenium (Figure). Compared to patients who were not frail, frail patients were more likely to have vitamin E deficiency ($p = 0.01$). Frail patients had a 3.26 increased odds of vitamin E deficiency on multivariable analysis (95%CI 1.46-7.28, $p = 0.004$). **Conclusion:** Deficiencies of zinc, vitamin D/E/B12, and selenium are common in patients with cirrhosis awaiting LT and may represent a pragmatic panel of micronutrients to send in clinical practice. Vitamin E deficiency, in particular, was associated with frailty. In light of prior studies demonstrating that vitamin E supplementation improves sarcopenia and frailty in older adults, vitamin E supplementation may represent an important component of a multi-pronged approach to reversing frailty in cirrhosis patients.

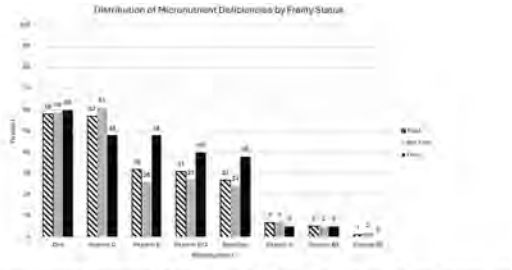

Figure 1. Distribution of Micronutrient Deficiencies by Frailty Status among Patients awaiting Phase 1 Liver Transplant Evaluations

Disclosures: Melinda Wang: Nothing to Disclose, Kathy Pariani: Nothing to Disclose, Fawzy Barry: Nothing to Disclose, Dorothea Kent: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI

2377 | DIET-FED HAMSTERS AS A MODEL OF MASH CIRRHOSIS-ASSOCIATED WEIGHT LOSS WITHOUT THE USE OF TOXINS FOR HIGH-THROUGHPUT IN VIVO SCREENING

Joanne Hsieh[1] Shengping Wang[1] Linda Chio[1] Ian Driver[1] Jingshu Chen[1] Christopher Carrico[1] Daniel Fuentes[1] Vinay Kartha[1] Hikaru Miyazaki[1] Arnav Gupta[1] Dimitry Popov[1] Smitha Shambhu[1] Gayathri Donepudi[1] Carmen Le[1] Jessica Nonora[1] Sophia Ruiz[1] Juana Cruz Sampedro[1] Chris Towne[1] Martin Borch Jensen[1] Francisco LePort[1], [1]Gordian Biotechnology

Background: Sarcopenia and osteopenia often co-occur with MASH and cirrhosis. An FGF21 analogue recently showed both antifibrotic and bone mineral density (BMD)-reducing effects in compensated MASH cirrhosis. There is a need for therapies that reduce fibrosis without compromising muscle mass or bone health, but discovery is limited by the tendency of diet-fed mouse models to progress to HCC rather than cirrhosis. **Methods:** Golden Syrian hamsters were given a “free choice” high fat, cholesterol, and fructose diet or chow, and 10% fructose water or plain water. AAV8 was delivered and livers were collected after 37 weeks then analyzed by single-nucleus RNA-Seq (snRNA-Seq). In a high-throughput *in vivo* screen, Gubra-Amylin (GAN) diet-fed mice were administered >100 barcoded AAV8 interventions. Hepatocyte responses were assessed by snRNA-Seq. **Results:** Hamsters displayed heterogeneous responses to the free choice diet, with lower body weight associated with more severe porto-portal fibrosis. In fibrotic livers, expression gradients of the periportal marker *Hal* and pericentral marker *Slco1b3* aligned, and hepatocytes showed upregulation of purine catabolism genes (*Nt5c2*, *Entpd5*) and steroid excretion transporters (*Abcc3*). Hepatocytes in severe fibrosis expressed the cholangiocyte markers *Sox9* and *Krt19*, indicating a biphenotypic hepatocyte state. AAV8 effectively transduced both zonated and biphenotypic hepatocytes. In the mouse screen, myotrophic IGF-1 overexpression suppressed purine breakdown genes, while spliced XBP-1 to mimick ER stress enhanced them. TGFBR2 overexpression induced steroid catabolism genes, suggesting a mechanistic link between fibrosis, sarcopenia, and osteopenia. FGF21 overexpression did not affect steroid catabolism pathways but rather reduced

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genes involved in the provision of micronutrients such as calciferol to peripheral tissues, suggesting its BMD-reducing effects are dissociated from liver fibrosis effects. The screen identified an overexpression candidate that increased micronutrient provision gene expression. When delivered as a saturating gene therapy to GAN-fed mice (62 weeks), this candidate reduced serum CK-18, TIMP1, and osteopontin while increasing body weight. **Conclusion:** In hamsters, 37 weeks of the free choice diet led to loss of hepatocyte zonation and acquisition of cholangiocyte-like features, paralleling changes seen in human cirrhosis. These aberrant hepatocytes remained transducible by AAV8, enabling parallelized *in vivo* screening. Differential gene expression analysis from this hamster model informed identification of a gene therapy candidate that mitigated fibrosis-related weight loss in MASH.

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2378 | LIVER STIFFNESS AS A PREDICTOR OF MYOPENIA AND FUNCTIONAL MUSCLE DECLINE IN ADVANCED LIVER DISEASE: A CALL FOR REFINED DIAGNOSTIC CUTOFFS

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Background: Transient elastography is widely used to assess liver fibrosis. However, few studies have examined the correlation between liver stiffness and indicators of muscle mass and function, and specific data on populations with advanced liver disease remain scarce. This study aimed to investigate whether liver stiffness (VCTE) and its categorization, including platelet levels, could serve as predictors of myopenia and declines in muscle function in patients with advanced liver disease. **Methods:** Patients aged 18 years or older with chronic liver disease and portal hypertension were included in this study. Liver stiffness was assessed using transient elastography with controlled vibration (VCTE, FibroScan®), analyzed as a continuous variable and categorized into groups: Group 1 (<15 kPa and platelets $\geq 150{,}000/mm^3$); Group 2 (≥ 15 kPa and platelets $<150{,}000/mm^3$); and Group 3 (≥ 25 kPa). Muscle parameters included Upper Arm Muscle Circumference (UAMC) and Handgrip Strength (HGS). The results were compared with established literature cutoffs (men: UAMC <24.2 cm and HGS <27 kgf; women: UAMC <21.5 cm and HGS <16 kgf). Linear and multiple logistic regression models were adjusted for covariates. **Results:** A total of 132 patients were included and categorized:Group 1 ($n=50$, 37.9%); Group 2 ($n=55$, 41.7%); and Group 3 ($n=27$, 20.5%). In the sex-stratified analysis, women had a median UAMC of 20.8 cm and median HGS of 15.8 kgf, values below the literature cutoffs (21.5 cm and 16 kgf). Among men, the medians were 24.8 cm and 26.8 kgf, with lower percentiles indicating impairment. In the adjusted linear model, each 1 kPa increase in liver stiffness was associated with a 0.45 kgf reduction in HGS (95%CI: –0.60 to –0.30; $p < 0.001$) and a 0.30 cm reduction in UAMC (CI: –0.42 to –0.18; $p < 0.001$). The coefficient for male sex was –1.10 (95% CI: –3.15 to 0.95; $p = 0.453$), indicating that although men had higher mean values, sex-adjusted effects did not alter the robustness of muscle predictors. In categorical analysis, Group 2 showed an average reduction of 3.0 kgf in HGS (95%CI: –4.5 to –1.5; $p < 0.001$) and 1.5 cm in UAMC (95%CI: –2.3 to –0.7; $p < 0.001$), while Group 3 exhibited reductions of 7.5 kgf and 3.0 cm, respectively ($p < 0.001$ for both). **Conclusion:** Liver stiffness is a significant predictor of myopenia and functional muscle impairment, independent of sex. Data suggest that in patients with advanced liver disease, median values in the most severe group (Group 3: UAMC 20.2 cm and HGS 18.3 kgf) fall below established cutoffs, indicating that current diagnostic methods may underestimate muscle impairment. Revising cutoffs and adopting an integrated approach—considering functional and compositional parameters alongside liver disease severity—are recommended for improved risk stratification and clinical management.

Disclosures: Lourianne Nascimento Cavalcante: Nothing to Disclose, Aloma Campeche-Leão: Nothing to Disclose, Ana Clara Batista: Nothing to Disclose, Monalisa Reis Arruda: Nothing to Disclose, Rosangela Passos: Nothing to Disclose, Lais Garcez: Nothing to Disclose, Helma Cotrim: Nothing to Disclose

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2379 | CHARACTERIZATION OF CIRRHOSIS-RELATED COMPLICATIONS IN A NATIONALLY REPRESENTATIVE DATABASE OF ELECTRONIC HEALTH RECORDS

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Background: Compensated cirrhosis can progress to life-threatening complications. Previous studies are limited due to the fragmentation of data sources, small sample sizes, and lack of national representation. We conducted a retrospective cohort study using a national dataset to characterize adults with cirrhosis and the timing and types of subsequent liver-related events. **Methods:** Adults with a first diagnosis of compensated cirrhosis (index date) between January 2015 and May 2024 were identified using ICD-10 codes in Epic Cosmos, a longitudinal dataset comprising >300 million patient records. Patients who developed a complication or received a liver transplant within 90 days of diagnosis were excluded. Subsequent occurrence of decompensation (variceal bleeding, encephalopathy, ascites, liver failure without encephalopathy), transplant, or hepatocellular carcinoma (HCC) was retrieved from diagnostic or procedural coding. Death dates were captured if recorded in patients' health records. Patients without an event were censored in May 2025. Cumulative-incidence functions were estimated using the Aalen–Johansen method. **Results:** Among 548,999 patients meeting inclusion criteria, the median age at first recorded cirrhosis diagnosis was 64 years (IQR 55-72), and 53.6% were male (Table 1). Median time to liver-related event or censoring was 2.3 years (IQR 1.2–4.2). First event was decompensation in 112,533 (20.5%), HCC in 11,426 (2.1%), transplantation in 79 (<0.1%), and death in 90,443 (16.5%). Median time from index to first decompensation was 1.4 years (IQR 0.7–2.7). Among patients who decompensated, 57,079 (50.7%) developed ascites, 14,729 (13.1%) liver failure without encephalopathy, 13,168 (11.7%) hepatic encephalopathy, 8,247 (7.3%) variceal bleeding, and 19,310 (17.2%) had multiple decompensation types. Of those who decompensated or developed HCC, 3,238 (2.6%) later underwent liver transplantation. At 1, 3, and 5 years, cumulative incidence estimates (accounting for censorship) were 7.9%, 18.3%, and 24.4% for any hepatic decompensation; 0.7%, 1.7%, and 2.5% for HCC; and 8.7%, 14.7%, and 18.9% for death. **Conclusion:** In this national retrospective study, we found that 20.5% of patients with cirrhosis progressed to decompensation, with ascites being the most frequent event, and 2.1% developed HCC. Among those who decompensated, 75% did so within 2.7 years of initial cirrhosis diagnosis, highlighting a critical window for preventative intervention.

Table 1: Characteristics and outcomes of patients diagnosed with cirrhosis in a national cohort (N = 548,999)

Sex		**First Outcome**	
Male	294,268 (53.6%)	Decompensation	112,533 (20.5%)
Female	254,692 (46.4%)	Hepatocellular Carcinoma	11,426 (2.1%)
Race		Transplantation	79 (<0.1%)
White	398,407 (72.6%)	Death	90,443 (16.5%)
Black	56,879 (10.4%)	**First Decompensation Etiology**	
Asian	9,946 (1.8%)	Ascites	57,079 (50.7%)
American Indian/Alaska Native	3,747 (0.7%)	Liver failure without encephalopathy	14,729 (13.1%)
Native Hawaiian or Pacific Islander	635 (0.1%)	Hepatic encephalopathy	13,168 (11.7%)
Multiracial	55,909 (10.2%)	Variceal bleeding	8,247 (7.3%)
Other/unknown	23,476 (4.3%)	Multiple decompensation etiologies	19,310 (17.2%)

Disclosures: James Haddad: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Advisor, Askar Safipour Afshar: Nothing to Disclose, Anoop Mayampurath: Nothing to Disclose, Majid Afshar: Nothing to Disclose, Matthew Churpek: Nothing to Disclose

2380 | INCIDENCE OF HEPATORENAL SYNDROME IN THE HOSPITALIZED U.S. PEDIATRIC POPULATION (2019–2023): A RETROSPECTIVE REAL-WORLD HEALTHCARE DATABASE ANALYSIS

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Background: Hepatorenal syndrome (HRS) is a rare and serious complication of severe liver disease characterized by marked impairment of kidney function. While HRS is well documented in adults, its incidence in children remains unclear, largely due to absence of standardized and published diagnostic criteria specific to pediatrics. **Methods:** Pediatric patients (<18 years) hospitalized with HRS were identified in the Premier database (Jan 2019–Dec 2023) using ICD-10 code K76.7 at admission and stratified by age, sex, and race. Concomitant chronic liver disease (CLD) and biliary atresia (BA) were evaluated using ICD-10 codes. National projections were calculated using discharge weights from the American Hospital Association. **Results:** Of 6,069,353 pediatric hospitalizations between 2019 and 2023, there were 90 admissions with an HRS diagnosis (0.0015%); 54.4% being female, and median age was 7.0 years (IQR 1.0, 14.0). Adolescents (12–17 years) accounted for the largest proportion (35.6%), followed by neonates/infants (0–<2 years; 27.8%). By race/ethnicity, 34.4% were White, 30.0% were Hispanic, and 21.1% were Black; notably, Black and Hispanic patients together

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accounted for over 50% of encounters overall and among infants and adolescents. Medicaid was the most common payer (62.2%), followed by managed care (12.2%) and commercial insurance (7.8%). Most cases (87.8%) were associated with concomitant CLD, including cirrhosis, while 12.2% had both CLD/cirrhosis and BA, which occurred predominantly (81.8%) in the neonate/infant age group. Over one-third of all pediatric HRS admissions resulted in in-hospital mortality (n = 33). Projected national estimates resulted in 251 pediatric HRS admissions during the 5-year study period, averaging 50.2 admissions per year (range: 39–75), with a consistent age group distribution across years. **Conclusion:** Based on U.S. data from 2019 to 2023, an estimated 50 pediatric HRS hospitalizations occured annually (range: 39–75), highlighting the rarity of this serious complication of advanced liver disease. Adolescents were most frequently affected, and CLD—including cirrhosis—was the predominant underlying etiology. Black and Hispanic patients accounted for over half of all encounters, particularly among infants and adolescents, highlighting potential disparities in disease burden that warrant further investigation. These findings provide national context on the incidence and associated mortality of pediatric HRS and may help inform future recognition and management strategies.

Table 1: Observed and projected annual incidence of hepatorenal syndrome (HRS) in pediatric patients stratified by age, race, and sex

Pediatric Admissions with HRS (N=90 patients)					
	Overall, n (%)	Neonates/Infants, (0–<2 years)	Early Childhood, (2–<6 years)	Middle Childhood, (6–11 years)	Adolescents, (12–17 years)
Age and Year, n (row%)					
2019	15 (16.7%)	5 (33.3%)	3 (20%)	2 (13.3%)	5 (33.3%)
2020	14 (15.6%)	3 (21.4%)	2 (14.3%)	3 (21.4%)	6 (42.9%)
2021	16 (17.8%)	7 (43.8%)	1 (6.3%)	4 (25%)	4 (25%)
2022	25 (27.8%)	5 (20%)	5 (20%)	5 (20%)	10 (40%)
2023	20 (22.2%)	5 (25%)	3 (15%)	5 (25%)	7 (35%)
Total	**90 (100%)**	**25 (27.8%)**	**14 (15.6%)**	**19 (21.1%)**	**32 (35.6%)**
Age and Race, n (%)					
White	31 (34.4%)	9 (36.0%)	7 (50.0%)	7 (36.8%)	8 (25.0%)
Hispanic	27 (30%)	11 (44.0%)	1 (7.1%)	2 (10.5%)	13 (40.6%)
Black	19 (21.1%)	3 (12.0%)	5 (35.7%)	3 (15.8%)	8 (25.0%)
Asian	3 (3.3%)	1 (4.0%)	0 (0.0%)	1 (5.3%)	1 (3.1%)
Other	5 (5.6%)	0 (0.0%)	1 (7.1%)	4 (21.1%)	0 (0.0%)
Unknown	5 (5.6%)	1 (4.0%)	0 (0.0%)	2 (10.5%)	2 (6.3%)
Total	**90 (100%)**	**25 (27.8%)**	**14 (15.6%)**	**19 (21.1%)**	**32 (35.6%)**
Age and Sex, n (%)					
Female	49 (54.4%)	15 (60%)	7 (50%)	13 (68.4%)	14 (43.8%)
Male	41 (45.6%)	10 (40%)	7 (50%)	6 (31.6%)	18 (56.3%)
Total	**90 (100%)**	**25 (27.8%)**	**14 (15.6%)**	**19 (21.1%)**	**32 (35.6%)**
HRS with concomitant CLD by Age and Year, n (row%)					
2019	14 (17.7%)	4 (28.6%)	3 (21.4%)	2 (14.3%)	5 (35.7%)
2020	10 (12.7%)	0 (0.0%)	2 (20%)	2 (20%)	6 (60.0%)
2021	15 (19%)	6 (40.0%)	1 (6.7%)	4 (26.7%)	4 (26.7%)
2022	21 (26.6%)	2 (9.5%)	5 (23.8%)	4 (19%)	10 (47.6%)
2023	19 (24.1%)	4 (21.1%)	3 (15.8%)	5 (26.3%)	7 (36.8%)
Total	**79 (100%)**	**16 (20.3%)**	**14 (17.7%)**	**17 (21.5%)**	**32 (40.5%)**
HRS with concomitant CLD and BA by Age and Year, n (row%)					
2019	1 (9.1%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2020	4 (36.4%)	3 (75.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)
2021	1 (9.1%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2022	4 (36.4%)	3 (75.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)
2023	1 (9.1%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	**11 (100%)**	**9 (81.8%)**	**0 (0.0%)**	**2 (18.2%)**	**0 (0.0%)**
AHA-weighted Pediatric Admissions with HRS (N=251 visits)					
Age and Year, n (row%)					
2019	39 (15.5%)	12 (30.6%)	6 (16.6%)	7 (17.2%)	14 (35.8%)
2020	40 (16%)	9 (21.2%)	7 (17.2%)	10 (25.8%)	14 (35.8%)
2021	44 (17.4%)	17 (39.3%)	3 (6.1%)	13 (30.5%)	11 (24.2%)
2022	75 (29.8%)	17 (22.8%)	12 (16%)	12 (15.6%)	34 (45.5%)
2023	54 (21.3%)	9 (15.9%)	7 (12.9%)	10 (17.9%)	29 (53.3%)
Total	**251 (100%)**	**63 (25.2%)**	**35 (13.9%)**	**52 (20.6%)**	**101 (40.4%)**
HRS with concomitant CLD by Age and Year, n (row %): N=218 visits (87%)					
2019	35 (16.5%)	9 (25.5%)	6 (17.8%)	7 (18.4%)	14 (38.3%)
2020	28 (13.0%)	0 (0.0%)	7 (24.5%)	7 (24.7%)	14 (50.8%)
2021	41 (18.8%)	14 (35.2%)	3 (6.5%)	13 (32.5%)	11 (25.8%)
2022	62 (28.4%)	7 (10.8%)	12 (19.4%)	9 (14.7%)	34 (55.2%)
2023	51 (23.3%)	6 (11.3%)	7 (13.7%)	10 (18.9%)	29 (56.2%)
Total	**218 (100%)**	**36 (16.5%)**	**35 (16.1%)**	**46 (20.9%)**	**101 (46.5%)**
HRS with concomitant CLD and BA by Age and Year, n (row %): N=34 visits (13.6%)					
2019	3 (8.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2020	12 (35.9%)	9 (71.5%)	0 (0.0%)	3 (28.5%)	0 (0.0%)
2021	3 (8.3%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2022	13 (39.4%)	10 (80.1%)	0 (0.0%)	3 (19.9%)	0 (0.0%)
2023	3 (8.4%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	**34 (100%)**	**28 (82.4%)**	**0 (0.0%)**	**6 (18.1%)**	**0 (0.0%)**

AHA: American Hospital Association; BA: Biliary atresia; CLD: Chronic liver disease; HRS: Hepatorenal syndrome

Disclosures: Xingyue Huang: Nothing to Disclose, Mary Panaccio: Mallinckrodt Pharmaceuticals: Consultant, Sanaz Cardoza: Mallinckrodt: Full Time Employee, Eva Tarau: Nothing to Disclose, Peggy Rooney: Mallinckrodt Pharmaceuticals: Employee, Stratatech, a Mallinckrodt Company: Employee, Chris Pappas: Nothing to Disclose, Jonathan Lilley: Mallinckrodt: Consultant, Grifols: Consultant, Rahul Rajkumar: Grifols: Consultant, Mallinckrodt Pharmaceuticals: Consultant

2381 | IT IS COST-EFFECTIVE TO SCREEN AND TREAT PATIENTS WITH DEMENTIA FOR UNDIAGNOSED HEPATIC ENCEPHALOPATHY

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Background: Cognitive impairment in older adults is frequently attributed to dementia. However, with the aging cirrhosis population & overlapping risk factors and symptoms between the conditions, approximately 10% of patients with dementia could have reversible but unrecognized hepatic encephalopathy (HE). Also, other cirrhosis complications (HCC/ascites) could be neglected in these patients. Aim: Evaluate cost-effectiveness of screening & treating patients with dementia for HE using FIB-4 ± GI consults. **Methods:** A decision-analytic cost-effectiveness model was developed to evaluate 7 strategies for HE detection and treatment & cirrhosis management (preventing/treating HCC, ascites) in dementia. These included: (1) no screening; (2–3) Empiric treatment using lactulose/rifaximin for those with a positive FIB-4 screen suggestive of cirrhosis; (4–5) hepatology referral and targeted therapy with lactulose/rifaximin for those with a positive FIB-4 screen suggestive of cirrhosis; and (6–7) empiric treatment of all dementia patients with lactulose/rifaximin. Transition probabilities across health states (dementia, cirrhosis with or without HE, recovery) and state-specific costs were based on predefined clinical assumptions based on published data. Outcomes included cumulative costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) over a 1-year cycle. **Results:** *Status quo* model projected $1.505 million cost & 45 QALYs (Figure). The most cost-effective approach was FIB-4 screening followed by GI consult and lactulose treatment (Strategy 4), which yielded 53 QALYs at a reduced cost of $1.472 million (ICER: $2.78 million/QALY). The most cost-saving approach was empiric lactulose treatment for all individuals with dementia (Strategy 6), which achieved

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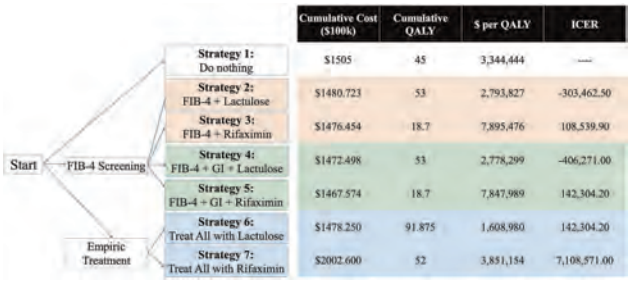
91.875 QALYs at $1.478 million (ICER: $1.6 million/QALY) but this would not be acceptable to providers or patients. Strategies involving rifaximin, either focused therapy or treat-all were substantially more costly with less favourable cost-effectiveness. **Conclusion:** Using focused GI/hepatology consults and lactulose therapy in patients with dementia and high FIB-4 was the most cost-effective strategy. This approach allows for the identification and management of potentially reversible cognitive impairment due to HE as well as preventing and managing HCC, ascites, and other cirrhosis complications. These findings support incorporating liver disease assessment into the diagnostic evaluation of cognitive decline, particularly in populations at risk for cirrhosis.



	Cumulative Cost ($100k)	Cumulative QALY	$ per QALY	ICER
Strategy 1: Do nothing	$1505	45	3,344,444	—
Strategy 2: FIB-4 + Lactulose	$1480.723	53	2,793,827	-303,462.50
Strategy 3: FIB-4 + Rifaximin	$1476.454	18.7	7,895,476	108,539.90
Strategy 4: FIB-4 + GI + Lactulose	$1472.498	53	2,778,299	-406,271.00
Strategy 5: FIB-4 + GI + Rifaximin	$1467.574	18.7	7,847,989	142,304.20
Strategy 6: Treat All with Lactulose	$1478.250	91.875	1,608,980	142,304.20
Strategy 7: Treat All with Rifaximin	$2002.600	52	3,851,154	7,108,571.00

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2382 | RECOMBINANT HUMAN ADAMTS13 ATTENUATES LPS-INDUCED ACUTE KIDNEY INJURY AND RENAL MICROANGIOPATHY IN MICE WITH LIVER CIRRHOSIS VIA CLEAVAGE OF VWF

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Background: Hepatorenal syndrome (HRS) has a poor prognosis among the complication of liver cirrhosis, yet treatment options are limited. Thrombotic microangiopathy with accumulation of von Willebrand factor (vWF) due to decreased a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13), a cleaving enzyme of vWF, has been reported to contribute to the pathogenesis of acute kidney injury (AKI) in liver cirrhosis. This study investigated the effect of recombinant human ADAMTS13 (rhADAMTS13) on acute kidney injury using a mouse model of HRS. **Methods:** To generate a mouse model of HRS (AKI-C mice), C57BL/6J mice received intraperitoneal administration of carbon tetrachloride (CCl_4) (0.5 ml/kg, twice a week) for eight weeks, subsequent administration of a double dose of CCl_4 (1.0 ml/kg) after 72 hrs, followed by intraperitoneal injection of LPS from *Klebsiella pneumonia* (6 mg/kg) after 24 hrs. AKI-C mice were subsequently injected intraperitoneally with saline as vehicle or rhADAMTS13 (10 μg/mouse equivalent to 2800 U/kg) 24 and 48 hrs after LPS administration and sacrificed 72 hrs later. Normal control mice received administration of saline instead of CCl_4, LPS and rhADAMTS13. Serological, histological and molecular analyses were performed to assess the effect of rhADAMTS13 on liver and kidney injuries in AKI-C mice. Tissue blood flow was also measured using a laser Doppler tissue blood flow meter to evaluate differences between the groups. **Results:** AKI-C mice showed a marked liver dysfunction as well as renal dysfunction with elevated serum level of AKI including Kidney Injury Molecule 1 (KIM-1), osteopontin and neutrophil gelatinase-associated lipocalin (NGAL). Plasma ADAMTS13 activity was reduced, and vWF antigen levels were increased. A decrease in blood flow in the liver and kidney tissues was also observed. In the rhADAMTS13-treated mice, plasma ADAMTS13 activity was increased, vWF antigen levels were decreased, and liver and kidney blood flow were improved as comoared to AKI-C mice. As a result, liver and kidney injuries were significantly alleviated. Furthermore, in the rhADAMTS13-treated mice, macrophage (F4/80-positive) infiltration and the increased expression of inflammatory cytokines observed in the AKI-C mice were suppressed. Accumulation of oxidative stress (4-HNE-positive) was also reduced. In addition, the deposition of CD41a-positive microthrombi in kidney tissues seen in the AKI-C mice was significantly suppressed in the rhADAMTS13-treated mice. This group also showed an increased expression of angiogenesis markers (Vegf) and a decreased expression of vascular inflammation markers (Vcam1, Icam1, Sele, Selp). **Conclusion:** Administration of rADAMTS13 may improve inflammation, oxidative stress, and reduced blood flow in liver and kidney, thereby mitigating HRS.
Disclosures: Kosuke Kaji: Nothing to Disclose, NORIHISA NISHIMURA: Nothing to Disclose, Shinya Sato: Nothing to Disclose, Tadashi Namisaki: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose

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2383 | WHEN THE MIND MEETS THE LIVER: A REAL-WORLD LOOK AT MOOD AND MORTALITY IN CIRRHOSIS

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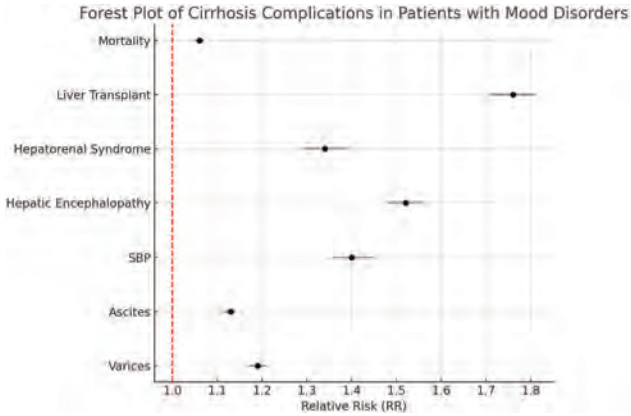
Background: Cirrhosis is a progressive liver disease associated with high morbidity and mortality, often leading to complications such as ascites, hepatic encephalopathy, and liver failure. Beyond physical symptoms, cirrhosis significantly impacts patients' quality of life, contributing to fatigue, disability, and social isolation. Mood disorders, including major depressive disorder (MDD) and stress-related conditions, are common in patients with chronic liver disease. These psychiatric conditions may worsen clinical outcomes through poor adherence, increased inflammation, and reduced engagement in care. Despite their prevalence, the effect of mood disorders on cirrhosis outcomes remains unclear. This study uses real-world data from the TriNetX network to assess whether mood disorders are associated with increased complications, lower transplant rates, or higher mortality in cirrhotic patients. **Methods:** We conducted a retrospective cohort study using TriNetX, a global federated health research network with de-identified electronic medical record data. Patients with cirrhosis were categorized into two cohorts: those with comorbid mood disorders (Cirrhosis + MDD) and those without (Cirrhosis – MDD). Propensity score matching (1:1) was performed based on demographics, cardiovascular, neurologic, pulmonary, renal, gastrointestinal, malignancy, and behavioral health conditions. Outcomes assessed in this study included key cirrhosis-related complications such as variceal bleeding, ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, and hepatorenal syndrome. In addition to these complications, liver transplantation and all-cause mortality were also evaluated as primary clinical endpoints. **Results:** The matched analysis revealed that patients in the Cirrhosis + Mood disorder group experienced significantly worse outcomes compared to the Cirrhosis without mood disorder group across all endpoints: · Esophageal/Gastric Varices: RR 1.19 [95% CI: 1.17–1.21]; $p < 0.001$ · Ascites: RR 1.13 [95% CI: 1.11–1.14]; $p < 0.001$ · Spontaneous Bacterial Peritonitis (SBP): RR 1.40 [95% CI: 1.35–1.45]; $p < 0.001$ · Hepatic Encephalopathy: RR 1.52 [95% CI: 1.48–1.56]; $p < 0.001$ · Hepatorenal Syndrome: RR 1.34 [95% CI: 1.29–1.39]; $p < 0.001$ · Liver Transplantation: RR 1.76 [95% CI: 1.71–1.81]; $p < 0.001$ · All-Cause Mortality: RR 1.06 [95% CI: 1.05–1.07]; $p < 0.001$ **Conclusion:** Cirrhotic patients with mood disorders experience worse clinical outcomes compared to those without, including higher rates of hepatic decompensation and mortality. They were also more likely to get a liver transplant as well. The study is limited by reliance on coded data, absence of data on treatment for depression (e.g., SSRIs, SNRIs, CBT), and lack of psychiatric severity assessment. These findings highlight the need for integrated psychiatric and hepatologic care and further prospective studies.



Disclosures: Muhammad Ali Ibrahim Kazi: Nothing to Disclose, Qetevan Gvazava: Nothing to Disclose, Siraj Ahmad: Nothing to Disclose, Zurabi Lominadze: Nothing to Disclose, Maia Tavadze: Nothing to Disclose

2384 | MUSCLE COMPOSITION MATTERS: MRI-BASED MYOSTEATOSIS STRONGLY CORRELATES WITH PHYSICAL FUNCTION IN CIRRHOSIS

Maria Rydfjord[1] Mohammad Siddiqui[2] Olof Dahlqvist Leinhard[3] Pontus Henriksson[4] Geneva Roache[2] Amon Asgharpour[2] Vaishali Patel[2] Mikael Forsgren[3] Danielle Kirkman[2], [1]Linköping University; AMRA Medical AB, [2]Virginia Commonwealth University, [3]AMRA Medical AB; Linköping University, [4]Linköping University

Background: Muscle fat infiltration (MFI), as a measurement of myosteatosis, is increasingly recognized as a predictor of functional decline in patients with liver cirrhosis, contributing to frailty and poor transplant outcomes. Traditionally, sarcopenia is assessed by identification of low muscle mass, but emerging evidence emphasizes also assessing MFI due to its links with strength, mobility, and endurance. Muscle volume z-score (MVZ), a standardized measure of muscle volume independent of sex and body size, has been developed to define sarcopenia and is associated with decreased mobility and adverse outcomes. This study examined the relationship between magnetic resonance imaging (MRI) derived muscle composition

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and standardized physical function tests in patients with decompensated cirrhosis. **Methods:** In this prospective study at Virginia Commonwealth University, USA, 26 patients (20 females) with decompensated cirrhosis undergoing liver transplant evaluation completed standardized physical function tests: 6-minute walk test (6MWT), Timed Get-Up-and-Go (GUG), gait speed (GS), sit-to-stand repetitions (STS), and isometric knee extensor strength (KES). AMRA® Researcher was used to measure thigh fat free muscle volume (FFMV), MVZ based on FFMV, and MFI based on MRI. Spearman correlation was used to evaluate associations between muscle composition and functional tests. Correlation strength was interpreted as weak ($\rho < 0.30$), moderate ($\rho = 0.30$-0.59), or strong ($\rho \geq 0.60$). **Results:** Higher MFI was strongly associated with poorer performance across multiple domains: reduced 6MWT distance ($\rho = -0.846$), slower GUG ($\rho = 0.77$), and fewer STS repetitions ($\rho = -0.642$), all $p < 0.001$ (Fig). MFI also showed a moderate correlation with slower GS ($\rho = 0.525$, $p = 0.007$), but was not significantly correlated with KES. Lower FFMV was strongly associated with reduced isometric KES ($\rho = 0.714$, $p < 0.001$), and moderately associated with 6MWT ($\rho = 0.42$, $p = 0.033$) and GUG time ($\rho = -0.489$, $p = 0.012$). Lower MVZ was moderately correlated with shorter 6MWT distance ($\rho = 0.426$, $p = 0.030$), slower GUG ($\rho = -0.51$, $p = 0.009$), and reduced isometric KES ($\rho = 0.584$, $p = 0.011$). Neither MVZ nor FFMV was associated with STS or GS. **Conclusion:** MFI, more than muscle volume alone, strongly predicts functional impairment in patients with decompensated cirrhosis. MFI correlated strongly with endurance and mobility measures, but not isolated strength measures, suggesting that MFI reflects broader physiological limitations. FFMV correlated more strongly with strength, highlighting its role in force generation. Despite a limited sample size, the wide range of functional performance supports generalizability. MRI-based muscle composition measurements may improve early identification of functional decline and enable targeted, preventative interventions to preserve function and enhance transplant readiness.

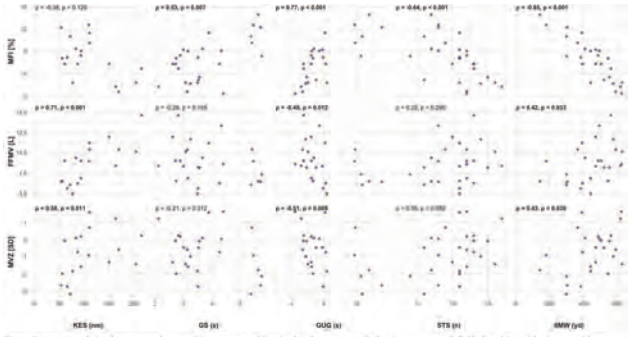

Figure. Spearman correlations between muscle composition measures and functional performance tests. Each point represents an individual participant. Muscle composition was assessed using (row 1) anterior thigh muscle fat infiltration [%], (row 2) fat free muscle volume of the anterior thigh [L], and (row 3) muscle volume Z score [SD]. Functional tests included knee extension strength (KES), gait speed (GS), get-up-and-go (GUG), sit-to-stand repetitions (STS), and six-minute walk distance (6MW. Each plot displays the Spearman correlation coefficient (ρ) and p-value.

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2385 | THE ROLE OF LIVER STIFFNESS IN ASSESSING THE SEVERITY OF PORTAL HYPERTENSION AND STRATIFYING LONG-TERM PROGNOSIS: A COMPARISON OF VIRAL AND NON-VIRAL ETIOLOGIES

Tatsuro Nishimura[1] Tsuyoshi Ishikawa[1], [1]Yamaguchi University Graduate School of Medicine

Background: The hepatic venous pressure gradient (HVPG) is one of the most useful tools for diagnosing the severity of portal hypertension (PH) and evaluating the risk of cirrhotic complications. Clinically significant portal hypertension (CSPH) is defined as HVPG $\geq$10 mmHg, severe portal hypertension (SPH) as HVPG $\geq$12 mmHg, and very severe portal hypertension (VSPH) as HVPG $\geq$16 mmHg. However, since HVPG measurement is invasive, it is necessary to develop a non-invasive alternative to its measurement. This study aimed to evaluate the correlation between liver stiffness (LS) and HVPG by etiology, and to examine the long-term prognosis. **Methods:** 111 patients with portal hypertension who underwent HVPG and LS at our hospital were enrolled in this retrospective study. The patients were separated into two groups, the viral group (n = 54, mean age: 66.3 years, male/female: 23/31, etiology of HBV/HCV: 4/50) and the non-viral group (n = 57, mean age: 63.9 years, male/female: 36/21, etiology of alcohol/MASH: 41/16). (Study1) The correlation between HVPG and LS in both groups was analyzed. (Study2) The best cutoff values defining CSPH, SPH and VSPH were examined. (Study3) Survival analysis was performed using the best cutoff value defined in Study 2. **Results:** Child-Pugh scores

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were not significantly different between the viral and non-viral groups (6.5 vs. 6.9, $p = 0.21$), while HVPG (11.1 vs. 12.9 mmHg, $p < 0.05$) and LS (25.1 vs. 29.5 kPa, $p < 0.05$) were significantly higher in the non-viral group. Fibrosis assessment markers such as type 4 collagen 7s and FIB4 index were also significantly higher in the non-viral group ($p < 0.05$). In addition, when LS was compared according to the severity of PH, it was significantly higher in the non-viral group in all CSPH, SPH and VSPH ($p < 0.01$). (Study 1) Correlation analysis showed a strong correlation between HVPG and LS in both the viral ($r = 0.68$, $p < 0.01$) and non-viral ($r = 0.68$, $p < 0.01$) groups. Significant correlations were also maintained in both groups for SPH and VSPH, which indicate severe PH. The cutoff values of CSPH, SPH and VSPH by LS were 20.6 kPa (AUROC: 0.78), 23.0 kPa (AUROC: 0.85) and 30.1 kPa (AUROC: 0. 92). On the other hand, the cutoff values for the non-viral group were 27.0 kPa (AUROC: 0.82), 30.4 kPa (AUROC: 0.81) and 35.3 kPa (AUROC 0.89). The cutoff values of LS at each HVPG level were significantly higher in the non-viral group. Survival analysis between the three groups based on HVPG and LS showed significant differences in MST in both groups ($p < 0.05$). **Conclusion:** LS represents a useful non-invasive surrogate marker for HVPG in cases of PH. The cutoff value of LS for CSPH, SPH and VSPH must be set for each etiology. LS may stratify survival and predict long-term prognosis similarly to HVPG.

Disclosures: Tatsuro Nishimura: Nothing to Disclose, Tsuyoshi Ishikawa: Nothing to Disclose

2386 | PREDICTORS OF ASCITES RESOLUTION IN PATIENTS WITH HEPATITIS C CIRRHOSIS AFTER ETIOLOGICAL CURE

Daniela Goyes[1] Anahita Rabiee[1] Nicolas Chong Lugon[1] Catherine Mezzacappa[1] David Kaplan[2] Tamar Taddei[1] Guadalupe Garcia-Tsao[1], [1]Yale University, [2]University of Pennsylvania

Background: Ascites is, by far, the most common decompensating event in cirrhosis. With etiological treatment of cirrhosis, ascites may resolve, no longer requiring diuretics, and this is one of the Baveno VII criteria defining cirrhosis "recompensation". Identifying predictors of ascites resolution could enhance prognostication and help refine the definition of cirrhosis recompensation. **Methods:** Retrospective cohort study of Veterans with HCV-related cirrhosis who achieved sustained virologic response (SVR) after direct-acting antiviral (DAA) therapy and who had ascites on abdominal imaging (ultrasound, computed tomography, or magnetic resonance) within six months prior to DAA initiation. Ascites (and absence of ascites) was determined via natural language processing (NLP) of imaging reports. Baseline was defined as DAA initiation. We excluded patients with hepatocellular carcinoma, heart failure, or chronic kidney disease at baseline, died within 24 weeks of DAA initiation, and those without follow-up imaging. The primary outcome was ascites resolution defined as absence of ascites, off diuretics, 12-18 months post-DAA initiation. Bivariate analyses were used to assess the associations between baseline parameters and ascites resolution. Variables with p value < 0.20 were included in a multivariable logistic regression model predicting resolution of ascites. **Results:** Of the 693 patients with available imaging 12-18 months after completing DAA treatment, 241 (35%) had resolution of ascites, 162 (23%) had no ascites but remained on diuretics, and 290 (42%) continued to have ascites (200 on diuretics and 90 off). Patients with ascites resolution had higher albumin and platelet count, and lower bilirubin and INR at baseline (Table 1). On multivariable analysis, the factor most strongly associated with ascites resolution was higher baseline serum albumin (OR 0.71, 95% CI 0.52–0.96). In contrast, baseline grade 2/3 ascites (versus grade 1) (OR 2.02, 95% CI 1.41–2.89), history of hepatic encephalopathy (OR 1.48, 95% CI 1.00–2.19), and variceal hemorrhage (OR 2.47, 95% CI 1.70–3.58) were associated with lower odds of ascites resolution. **Conclusion:** Resolution of ascites was observed in 35% of patients with HCV cirrhosis who achieve SVR after DAAs. Baseline serum albumin was the strongest predictor of ascites resolution.

Table 1. Cohort characteristics at baseline (initiation of DAA)

	Overall n = 693	Ascites resolution n = 241	No ascites resolution n = 452
Age, median [IQR]	60 [56, 64]	61 [57, 65]	60 [56, 64]
Male, n (%)	667 (96.2)	232 (96.3)	435 (96.2)
Race / Ethnicity, n (%)			
White	419 (60.5)	150 (62.2)	269 (59.5)
Black	162 (23.4)	58 (24.1)	104 (23.0)
Hispanic	38 (5.5)	6 (2.5)	32 (7.1)
Other	74 (10.6)	27 (11.2)	47 (10.3)
BMI, median [IQR]	27 [24, 31]	27 [24, 30]	27 [24, 31]
Etiology, n (%)			
HCV	553 (79.8)	194 (80.5)	359 (79.4)
HCV + Alcohol	140 (20.2)	47 (19.5)	93 (20.6)
Ascites grade at baseline, n (%)			
Grade 1	351 (50.6)	153 (63.5)	198 (43.8)
Grade 2&3	342 (49.4)	88 (36.5)	254 (56.2)
History of VH, n (%)	429 (61.9)	**113 (46.9)***	316 (69.9)
History of HE, n (%)	256 (36.9)	**62 (25.7)***	194 (42.9)
AST, median [IQR]	75 [54, 111]	79 [52, 115]	74 [54, 109]
ALT, median [IQR]	62 [39, 91]	66 [40, 95]	60 [38, 89]
Total bilirubin, median [IQR]	1.00 [0.70, 1.60]	**0.90 [0.60, 1.35]***	1.10 [0.70, 1.63]
Albumin, median [IQR]	3.20 [2.70, 3.60]	**3.40 [2.88, 3.80]***	3.06 [2.65, 3.55]
INR, median [IQR]	1.18 [1.09, 1.30]	**1.11 [1.06, 1.26]***	1.20 [1.10, 1.36]
Platelets, median [IQR]	100 [71, 139]	108 [70, 143]	97 [71, 136]
Creatinine, median [IQR]	0.81 [0.70, 0.99]	0.83 [0.70, 1.00]	0.80 [0.70, 0.95]
Sodium, median [IQR]	137 [135, 139]	137 [135, 139]	137 [135, 138]

DAA, direct-acting antiviral; BMI, body mass index; HCV, hepatitis C virus; VH, variceal hemorrhage; HE, hepatic encephalopathy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio
*p-value < 0.05 compared to no ascites resolution

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2387 | IMPACT OF CHRONIC KIDNEY DISEASE ON OUTCOMES OF ACUTE KIDNEY INJURY IN DECOMPENSATED CIRRHOSIS: A POST-HOC ANALYSIS OF THE INTERNATIONAL CLUB OF ASCITES GLOBAL-AKI STUDY

Kavish Patidar[1] Ann Ma[2] Adrià Juanola[3] Anna Barone[4] Simone Incicco[4] Anand Kulkarni[5] José Luis Pérez Hernández[6] Brian Wentworth[7] Sumeet Asrani[8] carlo alessandria[9] Nadia Abdelkader[10] YU JUN WONG[11] Qing Xie[12] Nikolaos Pyrsopoulos[13] Sung Eun Kim[14] yasser fouad[15] Aldo Torre[16] Eira Cerda Reyes[17] Javier Díaz Ferrer[18] Rakhi Maiwall[19] Douglas Simonetto[20] Maria Papp[21] Eric Orman[22] Giovanni Perricone[23] Cristina Sole[24] Christian Lange[25] Alberto Farias[26] Gustavo Pereira[27] Adrián Gadano[28] Paolo Caraceni[29] thevenot thierry[30] Nipun Verma[31] Jeong Han Kim[32] Julio Vorobioff[33] Jacqueline Cordova Gallardo[34] Vladimir Ivashkin[35] Juan Roblero[36] Raoel Maan[37] Claudio Toledo[38] Stefania Gioia[39] Eduardo Fassio[40] MONICA PATRICIA MARINO[41] Puria Nabilou[42] Victor Vargas[43] Manuela Merli[44] Luciana Goncalves[45] Liane Rabinowich[46] Aleksander Krag[47] Lorenz Balcar[48] Pedro Montes[49] Angelo Mattos[50] Tony Bruns[51] Abdulsemed Nur[52] Wim Laleman[53] ENRIQUE CARRERA ESTUPIÑAN[54] Maria Cecilia Cabrera[55] Marcos Girala[56] Hrishikesh Samant[57] Sarah Raevens[58] Joao Madaleno[59] W. Ray Kim[60] Juan Pablo Arab[61] Jose Presa[62] Carlos Noronha Ferreira[63] Antonio Galante[64] Andrew Allegretti[65] Bart Takkenberg[66] Sebastián Marciano[67] Shiv Kumar Sarin[19] François Durand[2] Pere Ginés[68] Paolo Angeli[69] ELSA SOLA[70] Salvatore Piano[69], [1]Houston Methodist Hospital, [2]Beaujon Hospital, [3]Hospital Clínic of Barcelona, [4]University and Hospital of Padova, [5]Asian Institute of Gastroenterology, [6]Hospital General de México, [7]University of Virginia, [8]Liver Consultants of Texas, [9]University of Turin, [10]Ain Shams University, [11]Changi General Hospital, [12]Ruijin Hospital, [13]NYU Grossman School of Medicine, [14]Hallym University Sacred Heart Hospital, [15]hoffman la roche, [16]Medical Center ABC, [17]Central Military Hospital, [18]Hospital Nacional Edgardo Rebagliati, [19]Institute of Liver and Biliary Sciences, [20]Mayo Clinic Rochester, [21]Hospital of Debrecen, [22]Indiana University, [23]Hospital Niguarda, [24]Corporacio Parc Tauli Hospital, [25]University of Munich, [26]University of Sao Paulo, [27]Hospital Federal de Bonsoccesso, [28]Hospital Italiano, [29]Università degli Studi di Bologna, [30]Jean Minjoz University Hospital, [31]Postgraduate Institute of Medical Education and Research, [32]Konkuk University Medical Center, [33]Universidad de Rosario, [34]Hospital General Dr Manuel Gea González, [35]University of Moscow, [36]Universidad de Chile, [37]Erasmus University Medical Center, [38]Universidad Australe de Chile, [39]Università Sapienza, [40]Hospital Nacional Prof. Alejandro Posadas, [41]Hospital de Gastroenterología, [42]Hvidovre Hospital, [43]Hospital Vall d'Hebron, [44]Policlinico Umberto I, [45]University Hospital Cassiano Antonio Moraes (HUCAM), [46]Tel Aviv Medical Center, [47]University of Southern Denmark, [48]University of Vienna, [49]Hospital D.A. Carrion, [50]Irmandade da Santa Casa de MIsericórdia de Porto Alegre, [51]University of Aachen, [52]Adera Medical Center, [53]KU Leuven, [54]Hospital de Especialidades Eugenio Espejo, [55]Hospital Nacional Guillermo Almenara, [56]Universidad Nacional de Asuncion, [57]Ochsner Medical Center, [58]Ghent University, [59]Centro Hospitalar e Universitário de Coimbra, [60]Mayo Clinic Arizona, [61]Virginia Commonwealth University, [62]Centro Hospitalar de Trás-os-Montes e Alto Douro, [63]Hospital de Santa Maria, [64]Ente Ospedaliero Cantonale and Università della Svizzera Italiana, [65]Massachusetts General Hospital, [66]Amsterdam University Medical Center, [67]Hospital Italiano de Buenos Aires, [68]Hospital Clínic of Barcelona, [69]University of Padova, [70]Standford University

Background: Acute kidney injury (AKI) is a common complication in decompensated cirrhosis, significantly increasing morbidity and mortality. However, the impact of pre-existing chronic kidney disease (CKD) on AKI outcomes in this population remains unclear. Using a large international cohort, we investigated how pre-existing CKD influences AKI outcomes in hospitalized patients with decompensated cirrhosis. **Methods:** We analyzed data from patients with decompensated cirrhosis and AKI enrolled in the International Club of Ascites GLOBAL-AKI study, a prospective, international observational study spanning 65 centers across 5 continents. Patients were categorized as AKI alone or AKI-CKD based on the absence or presence of pre-existing CKD. CKD was defined by an estimated glomerular filtration rate <60 mL/min for ≥ 3 months prior to AKI onset. Multivariable logistic regression and competing risk models were used to identify the independent factors associated with AKI resolution and 28-day mortality. **Results:** Among 1,456 patients with AKI, 239 (16.4%) had pre-existing CKD. Compared to AKI alone patients, AKI-CKD patients were older (64

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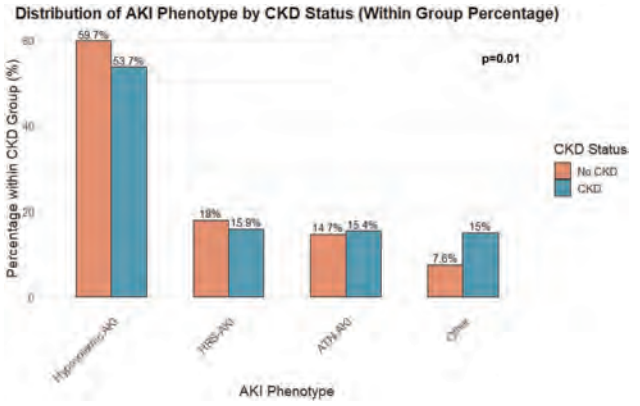
vs 57 years; $p < 0.01$), were more likely to have MASLD (44% vs 22%; $p < 0.01$), hypertension (57% vs 34%; $p < 0.01$), diabetes (53 vs 32%; $p < 0.01$), higher serum creatinine at baseline (1.5 vs 0.9 mg/dL; $p < 0.01$) and at AKI diagnosis (2.4 vs 1.8 mg/dl; $p < 0.01$), but lower MELD-Na score (24 vs 27; $p < 0.01$). AKI-CKD patients more often had AKI stage 1 at diagnosis (68 vs 51%; $p < 0.01$) and were less likely to have hypovolemic AKI (54% vs 60%) and hepatorenal syndrome-AKI (15.9% vs. 18%), while the prevalence of acute tubular necrosis phenotype was higher (15.4% vs. 14.7%) compared to AKI alone patients ($p = 0.01$) (Figure). AKI-CKD patients had significantly lower rates of AKI resolution (52 vs 60%, $p = 0.02$), but lower cumulative incidence of 28-day mortality (42% vs 50%, $p = 0.02$), compared to AKI alone patients. On multivariable analyses, AKI-CKD patients had lower odds of AKI-resolution (OR 0.53, 95%CI 0.38-0.73, $p < 0.01$), without a significant difference in risk for 28-mortality (sHR 0.76, 95%CI 0.56-1.03, $p = 0.08$). **Conclusion:** In patients with decompensated cirrhosis, pre-existing CKD significantly reduces AKI resolution rates without increasing short-term mortality risk, highlighting the need for tailored management strategies. These findings emphasize the importance of stratifying patients based on pre-existing CKD status in future clinical trials evaluating AKI interventions in cirrhosis.



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2388 | SEX-SPECIFIC EFFECT OF ESTRADIOL ON CHOLESTATIC LIVER CIRRHOSIS AND PORTAL HYPERTENSION

Fabian Schachteli[1] Sabine Klein[1] Robert Schierwagen[1] Maximilian Joseph Brol[1] Jonel Trebicka[1] Frank Erhard Uschner[1], [1]Department of Medicine B, University Hospital Münster, Münster, Germany

Background: Sex-specific differences have been observed in the etiology, clinical progression and therapeutic response of patients with chronic liver disease. Estradiol (E2) exerts its effects not only through the nuclear receptor alpha (ERα) but also via the G protein-coupled estradiol receptor (GPER). However, the role of GPER in liver cirrhosis with portal hypertension remains unclear. **Methods:** Cholestatic liver cirrhosis was induced in male rats via bile duct ligation (BDL). Female rats underwent BDL combined with either ovariectomy or a sham operation. The animals received one of the following: (i) a single dose of E2, (ii) an acute dose of a phosphodiesterase-5 inhibitor (PDE-5-I), (iii) a combination of both, or (iv) placebo. Portal and systemic hemodynamics were measured and the expression levels of E2 receptors and components of the nitric oxide (NO) signaling pathway (eNOS, PDE-5, VASP, p-VASP) were analyzed in liver and aorta using Western blot and qPCR. **Results:** In male BDL rats, E2 had no effect on hemodynamics, ER expression, or PDE-5-I efficacy. In female BDL rats, ovariectomy resulted in increased hepatic portal vascular resistance (HpVR), reduced hepatic GPER expression and decreased hepatic NO signaling activity, compared with non-ovariectomized females. Furthermore, ovariectomized females exhibited lower systemic vascular resistance and higher levels of GPER and ERα in the aorta. PDE-5-I significantly reduced portal pressure (PP) in female BDL rats but was ineffective after ovariectomy. Notably, E2 substitution in ovariectomized BDL rats significantly reduced HpVR and PP, while restoring PDE-5-I responsiveness. **Conclusion:** Estradiol deficiency after ovariectomy aggravates portal hypertension in female rats with cholestatic cirrhosis. Estradiol reverses this effect through activation of the cGMP-NO pathway. Combining estradiol substitution therapy with PDE-5 inhibition could represent a potential treatment strategy for postmenopausal women with portal hypertension.
Disclosures: Fabian Schachteli: Nothing to Disclose, Sabine Klein: Nothing to Disclose, Robert Schierwagen: Nothing to Disclose, Maximilian Joseph Brol: AbbVie: Consultant, Gilead: Speaking and Teaching, Falk Foundation: Speaking and Teaching, Jonel Trebicka: Nothing to Disclose, Frank Erhard Uschner: Nothing to Disclose

2389 | ALBUMIN IN THE MANAGEMENT OF HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY (HRS-AKI): IS THERE EVER TOO MUCH?

Florence Wong[1] Nicodemus Ong[2], [1]University of Toronto, [2]University Health Network

Background: Albumin (alb) at a dose of 20-40g/day is recommended as an adjunct therapy for HRS-AKI. Recent concerns of alb causing respiratory failure in patients (pts) with HRS-AKI have caused unease with excess alb use in these pts. Aim: to assess the outcomes of HRS-AKI pts who received more than the recommended daily alb dose. **Methods:** Retrospective study of all inpatients fulfilling the diagnostic criteria of HRS-AKI between Jan 2020 to Apr 2023 collected demographics, lab results, AKI treatment & course, admission outcomes and follow-up for 6Ms. Pts with alb dose of $\leq$50g/day were compared to those with $>$50g/day. **Results:** 195 pts (age 62 ± 12 yrs; male: 66%; MELD-Na: 27 ± 7) with 230 HRS-AKI events were identified. Group (Grp) A (alb $\leq$50g/day: 145 pts with 169 HRS-AKI events) had similar demographics as Grp B (alb $>$50g/day: 50 pts with 61 HRS-AKI events) except Grp B had a higher baseline serum creatinine (sCr) (102 ± 52 vs. Grp A $= 90 \pm 31$μmol/L, $p = 0.048$). HRS-AKI in Grp B was mostly precipitated by infections (46% vs.26.6% in Grp A) and less so by fluid shifts/loss (23% vs. 27% in Grp A) ($p = 0.025$). HRS-AKI stage distribution was similar at diagnosis between the 2 Grps. At peak sCr, significantly more Grp B pts reached stage 3 (59%), whereas 50% of Grp A pts remained in stage 1 HRS-AKI ($p < 0.0001$). 62.3% of Grp B pts fulfilled the old definition of type 1 HRS (vs.23.7% in Grp A, $p < 0.0001$). All Grp B pts received a mean of 66 ± 14g alb/day for a total of 8.1 ± 6.4days (total dose = 540 ± 379g), vs. a mean of 44 ± 10g alb/day ($p < 0.0001$) for a total of 4.7 ± 4.4days ($p < 0.0001$) (total dose = 221 ± 193g, $p < 0.0001$) in Grp A. Pts in Grp B received either midodrine (62%), octreotide (71%) or norepinephrine (28%), vs. 33%, 38%, and 16% respectively in Grp A. 65% of all Grp A pts had a complete response vs. 43% in Grp B ($p = 0.004$), mostly from stages 1 & 2 HRS-AKI. There was no difference in the HRS-AKI response for stage 3 between the Grps ($p = 0.554$). 3% of Grp A and 4% of Grp B pts developed respiratory failure ($p = 0.808$). Grp B patients had a

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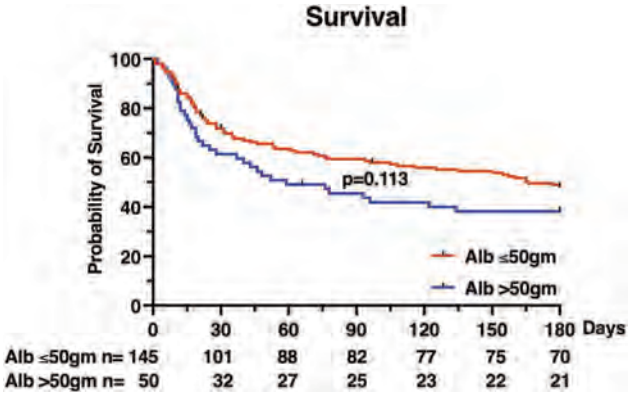
higher discharge MELD-Na (28 ± 9 vs. 24 ± 10 in Grp A, p = 0.002). There was no difference in length of hospital stay, readmission rate, or recurrent AKI in both Grps. Survival was the same (Figure). **Conclusion:** Pts with higher baseline sCr whose HRS-AKI is triggered by infection may need more than recommended alb dose, as they tend to have more severe AKI. The use of higher dose of alb may prevent a more serious outcome without causing respiratory compromise.



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2390 | ASCITIC NEUTROPHIL COUNT AT INITIAL PARACENTESIS IS ASSOCIATED WITH ADVERSE OUTCOMES IN CIRRHOSIS

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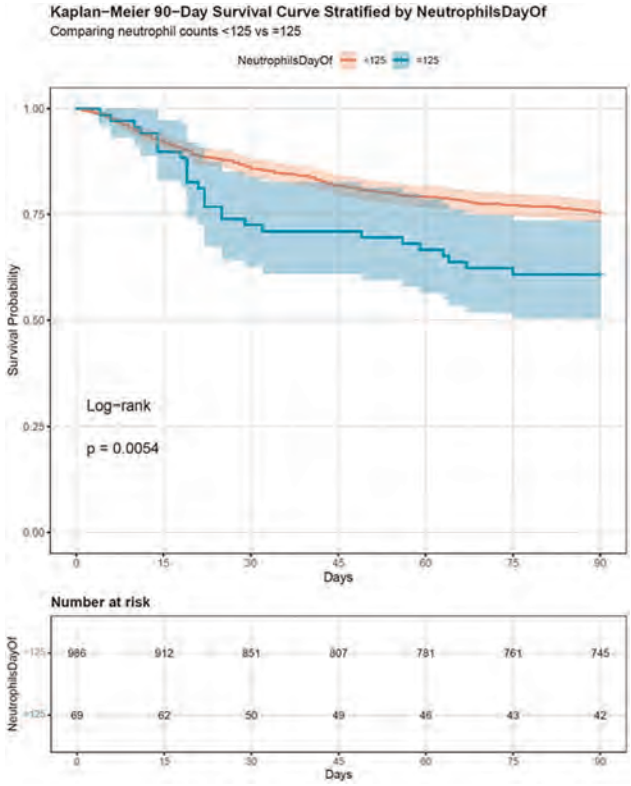
Background: Spontaneous bacterial peritonitis (SBP) is the most common source of infection in patients with cirrhosis and is a frequent precipitant of hepatic decompensation. While diagnosis is based on ascitic fluid neutrophil count, the prognostic significance of ascites neutrophil count (ANC) itself at initial paracentesis remains uncertain. **Methods:** We analyzed a cohort of patients with cirrhosis who underwent paracentesis at a tertiary healthcare center in the US Midwest between January 2015 and December 2024. The primary outcome was 90-day mortality; the secondary outcome was the development of SBP. Patients were stratified by ANC at the time of paracentesis (<125 cells/mm^3 vs. ≥ 125 cells/mm^3, defined as ascitic neutrophilia), and a Cox proportional hazards (PH) model was used to adjust for demographic and clinical confounders. Cumulative incidences of SBP and the composite outcome of death, liver transplant (LT), or TIPS placement were assessed using Gray's test, treating each as a competing risk for the other. **Results:** This retrospective cohort study included 1,053 patients. No significant demographic differences were noted other than white patients who were more likely to have an ANC < 125 cells/mm^3 (90.5% vs 84.2%, p = 0.017). Of the 1,053 patients, 269 died within 90 days. The 90-day mortality rate was higher in those with ascitic neutrophilia (39.1% vs. 24.6%, p = 0.012). In multivariable Cox PH model, ascitic neutrophilia remained an independent predictor of 90-day mortality (HR 1.77, 95% CI 1.18-2.64), alongside older age and lower BMI. Cumulative incidence of SBP was also higher amongst those with ascitic neutrophilia (7.2% vs. 4.0%) though it did not reach statistical significance (p = 0.18; Gray's test) and death, LT or TIPS were significantly higher in those with ascitic neutrophilia (40.6% vs. 27.7%, p = 0.012; Gray's test). **Conclusion:** An elevated neutrophil count in ascitic fluid at the index paracentesis is independently associated with increased 90-day mortality in patients with cirrhosis, and it may indicate a higher risk of developing SBP. This finding supports its utility not only as a diagnostic marker for current SBP but also as a prognostic indicator of adverse outcomes.



Disclosures: Alp Kahveci: Nothing to Disclose, Melis Celdir: Nothing to Disclose, Tomohiro Tanaka: Nothing to Disclose

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2391 | IMPACT OF INTRAVENOUS ALBUMIN ADMINISTRATION ON CLINICAL OUTCOMES AFTER VARICEAL HEMORRHAGE IN PATIENTS WITH CIRRHOSIS: A RANDOMIZED CONTROLLED TRIAL

Sagnik Biswas[1] Shubham Mehta[2] Shekhar Swaroop[1] Arnav Aggarwal[1] Sarthak Saxena[1] Shubham Jain[1] Samagra Agarwal[1] Shivanand Gamanagatti[1] . Shalimar[1], [1]All India Institute of Medical Sciences, New Delhi, [2]All India Institute of Medical Sciences

Background: Systemic inflammation plays a significant role in influencing clinical outcomes after variceal bleeding independent of the severity of underlying liver disease. Despite having anti-inflammatory and antioxidant properties, limited data exists on the efficacy of intravenous human albumin administration in improving clinical outcomes (overall survival, prevention of new onset organ failures [encephalopathy, renal failure] or spontaneous bacterial peritonitis [SBP]) after variceal bleeding in patients with cirrhosis. **Methods:** Consecutive patients with cirrhosis (Child-Pugh class B and C) with hypoalbuminemia (<3.5 g/dL) and esophageal variceal bleeding were randomized to receive either standard medical therapy (SMT) or SMT along with intravenous human albumin administration (40g per day) for 3 consecutive days after primary hemostasis. Hepatic venous pressure gradient (HVPG) was measured on day-1 and-3 of admission. Primary outcome was a composite of new onset renal failure, SBP, hepatic encephalopathy (HE) and all-cause mortality at 6 weeks. Secondary outcomes included 5-day treatment failure rate and need for rescue therapy. **Results:** From December 2022 to October 2024, 136 patients were randomized, of whom 123 patients received the allocated interventions (SMT: 63 patients, SMT+albumin: 60 patients). The median Child-Pugh score was 9 (8-10) and the model for end stage liver disease score was 14.8 (11.7-19.7). Alcohol use was the leading cause of cirrhosis (69/123 patients, 56.1%) with a male predominance (108, 87.8%). The median change in serum albumin levels (on day 3 as compared to day 1) among patients receiving SMT+albumin was higher (0.5 [0.2-0.8]) as compared to those receiving SMT (0 [-0.3 to 0.2]; $p<0.01$). However, patients receiving SMT +albumin had similar composite rates of HE, SBP, renal failure and all-cause mortality at 6 weeks (8 [13.3%, 95% CI: 5.9%-24.6%]) as compared to SMT alone (11 [17.5%, 95% CI: 9.1%-29.1%]; $p=0.53$). There were no differences in the rates of 5-day rebleeding (SMT alone: 3 [4.8%, 95% CI: 1.0%-13.3%] versus SMT+albumin: 5 [8.3%, 95% CI:2.7%-18.4%]; $p=0.42$) and mortality (SMT alone: 1 [1.6%, 95% CI: 0.04%-8.5%] versus SMT + albumin: 1 [1.7%, 95% CI: 0.04%-8.9%]; $p=0.97$) between the two groups. The median change in HVPG on day 3 compared to day 1 (SMT alone: 0 [-2 to +1.5] versus SMT+albumin: 0 [-2 to +2]; $p=0.41$) was also similar between both groups. Rescue therapy in the form of transjugular intrahepatic portosystemic shunt was required in 2 (3.2%, 95% CI: 0.4%-11.0%) patients in the SMT alone group as compared to 3 (5%, 95% CI: 1.0%-13.9%) patients in the SMT+albumin group ($p=0.61$). **Conclusion:** Intravenous albumin use is safe after an episode of variceal bleeding in patients with cirrhosis, but does not contribute to reduction in 6-week mortality or prevention of new onset SBP/organ failures [CTRI/2022/10/046898].

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2392 | ENDOSCOPIC VARICEAL LIGATION ALONE OR IN COMBINATION WITH NON-SELECTIVE BETA BLOCKERS FOR SECONDARY PROPHYLAXIS IN CHILDREN WITH NON-CIRRHOTIC PORTAL HYPERTENSION- A RANDOMIZED CONTROL TRIAL

Srinivas Srinidhi Vadlapudi[1] Anshu Srivastava[1] Anil Kumar Singh[1] Ujjal Poddar[1] Moinak Sen Sarma[1] Prabhaker Mishra[1], [1]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Background: Non-cirrhotic portal hypertension (NCPH) is the predominant cause of portal hypertension (PHT) and variceal bleed (VB) in children in the east. Baveno VII consensus recommends use of non-selective beta blockers (NSBB) with endoscopic variceal ligation (EVL) for secondary prophylaxis of esophageal VB (EVB). However, the role of NSBB in children with NCPH is not clearly established. Hence, the study was undertaken to address this issue. **Methods:** In this prospective randomized control trial (pilot study), consecutive children (age 2-17 years) of NCPH with VB were enrolled (September 2020-2023) and followed up for a year. Patients with contraindication for NSBB, large gastric varix (F3), prior endotherapy or shunt surgery were excluded. Randomization was done by computer generated random number tables. Subjects underwent 3 weekly EVL till variceal eradication followed by 3 monthly endoscopies for recurrence of varices (EVL done if $>/=$ grade 2 varix). Patients in EVL+NSBB arm were started on long acting propranolol (1-3mg/kg/day) targeting a 25% reduction in heart rate. Splenic artery resistivity index (RI) was measured by

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doppler to assess response to NSBB. Outcome measures included proportion of patients having rebleed (early-prior to variceal eradication or late- after variceal eradication), recurrence of esophageal varices (EV), change in gastric varices (GV), portal hypertensive gastropathy (PHG), tolerability and compliance to NSBB. **Results:** Seventy patients (9.2 ± 4.2 years, EVL = 36, EVL+NSBB = 34, extra hepatic portal venous obstruction [n = 64], non-cirrhotic portal fibrosis [n = 3], congenital hepatic fibrosis [n = 3]) were enrolled. Baseline characteristics were similar in the 2 groups. Patients got a dose of 1.6 ± 0.5 mg/kg of NSBB. There was no difference in overall rebleeding (16.1% *vs.* 12.5%, p = 0.73), early (9.1% *vs.* 12.1%, p = 1) or late rebleed (6.9% *vs.* 0%, p = 0.49) or the number of sessions needed for variceal eradication (3[1-9] *vs.* 3[1-10], p = 0.4) between the groups. Addition of NSBB was associated with significantly higher increase in RI, lower recurrence rate or need for further endotherapy of EV, maintained platelet counts and trend towards higher resolution of GV at 1year follow-up (table). There was no effect of NSBB on PHG. Four (11.8%) patients were non-compliant to NSBB and 4 (11.8%) did not achieve target heart rate due to hypotension (settled with reducing the dose of the drug). **Conclusion:** Addition of NSBB to EVL does not affect the rebleeding rate but reduces the recurrence or need for further endotherapy of EV in follow-up, maintains platelet count and downgrades GV in children with NCPH and EVB. NSBB are safe and well tolerated in children.

Table: Comparison between EVL and EVL+NSBB arms at baseline and at 1 year

Parameters	EVL arm (n=36)		EVL+NSBB arm (n=34)		p value			
	Baseline (n=36)	1 year (n= 30)	Baseline (n=34)	1 year (n=31)	*	@	#	$
Age (years)	9±4.4		9.5±4		0.6			
Gender (Male: Female)	20:16		17:17		0.64			
Ascites	3 (8.3%)	-	2 (5.9%)	-	1	-	-	
Spleen size (in cm on USG)	15±3.2	15.9±3.7	15.2±4.1	16.1±4.3	0.86	0.002	<0.01	0.85
Change in weight Z scores	0.19 ([-2.25] – [1.27])		0.1 ([-0.5] – [1.46])		0.49			
Change in height Z scores	0.1 ([-0.97] – [0.84])		0.14 ([-0.6] – [0.85])		0.34			
Change in BMI Z scores	0.1 ([-0.58] – [1.91])		-0.07 ([-0.84] – [1.59])		0.29			
Change in Hb (g/dL)	2.9±2.6		3.2±2.7		0.68			
TLC Change (/mm3)	-200 ([-9600] to [2340])		-50 ([-2970] to [2740])		0.62			
Platelet count change (/mm3)	-20000 (reduction) ([+170000] to [24000])		2000 (increase) ([-256000] to [82000])		0.02			
Change in RI	0.02±0.06		0.05±0.06		0.02			
Recurrence of EV	11 (36.7%)		5 (16.7%)		0.08			
Recurrence/need of endotherapy for EV at 1 year	16 (53.3%)		7 (23.3%)		0.02			
Gastric Varix (% patients seen)	31 (86.1%)	23 (76.7%)	29 (85.3%)	19 (61.3%)	0.92	0.32	0.028	0.2
PHG (% patients seen)	27 (75%)	26 (86.7%)	21 (61.8%)	22 (71%)	0.23	0.3	0.19	0.13

(All parameters expressed as mean±standard deviation or median[range]. Hb= hemoglobin, TLC- total leukocyte count, BMI- body mass index, USG- ultrasonography, EV- esophageal varices, GV- gastric varices, RI= resistivity index, PHG- portal hypertensive gastropathy. Change in weight Z score, height Z score, BMI Z score, Hb, TLC, platelet count and RI is the difference from 1 year follow up and baseline

p value: *Comparison between EVL vs EVL+NSBB at baseline

@ Comparison between EVL baseline vs. EVL at 1 year follow-up

Comparison between EVL+NSBB baseline vs. EVL+NSBB at 1 year follow-up

$ Comparison between EVL vs EVL+NSBB at 1year follow-up)

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2393 | TERLIPRESSIN USE LEADS TO A SIGNIFICANTLY REDUCED CREATININE AMONG HOSPITALIZED PATIENT WITH HEPATORENAL SYNDROME WHEN COMPARED WITH MIDODRINE/OCTREOTIDE IN A REAL-WORLD EXPERIENCE

Tanvi Goyal[1] David Kaplan[2] Jonathan Nahas[1],
[1]University of Pennsylvania, Penn Medicine, [2]University of Pennsylvania

Background: Hepatorenal syndrome (HRS) is a costly and often fatal complication of end-stage decompensated cirrhosis. Terlipressin (T) is the first FDA-approved treatment for HRS. Limited randomized controlled trial data showed superior outcomes for terlipressin relative to the prior off-label standard of care, midodrine/octreotide (MO). The objective of this study was to evaluate the efficacy of T relative to MO in a real-world setting. **Methods:** We performed a retrospective cohort study utilizing medical records review of inpatients admitted to our health system with a diagnosis of HRS in the 18 months prior to T formulary approval (January 2022-June 2023) and the 18 months following its introduction (July 2023-December 2024). Patients admitted at our main hospital, a tertiary referral and liver transplant center, were identified. [JN1] We collected laboratory values 48 hours prior to initiation of HRS therapy, at the time of initiation, 48 hours after initiation, and at maximal change in kidney function, length of stay (LOS) on medical floor and intensive care unit (ICU) and need for renal replacement therapy (RRT). We used non-parametric statistics and chi-square tests to compare demographic characteristics and the outcomes of interest. Linear and logistic regression models were evaluated to assess the association of treatment assignment and outcomes adjusting for key baseline covariates. **Results:** There were a total of 88 patients, with 59 in the MO cohort and 29 in the T cohort. Among patients admitted at our main hospital, 36 were in the MO cohort and 25 in T. At baseline, admission median creatinine was higher for the MO group, but at the start of HRS therapy, there were no significant differences in median creatinine or mean MELD-Na between the groups (Table 1). Post-treatment, patients in the T group demonstrated a significant improvement in creatinine, compared with a creatinine rise in the MO cohort. Patients in the T group had significantly higher rates of HRS reversal. Additionally, patients in the T group required fewer days of HRS treatment, and among those at our main hospital,

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had a lower fraction of inpatient days spent in ICU. There was also a trend towards decreased need for RRT in the T cohort. **Conclusion:** Among patients with HRS in a real-world clinical setting, T was associated with a greater improvement in creatinine and reversal of HRS, with a trend towards decreased need for RRT when compared to MO. Patients in the T group also required fewer days of HRS therapy and had less fractional time spent in ICU. Future work will compare the hospitalization costs of T versus MO to evaluate the cost-effectiveness of terlipressin in clinical practice.

	MO	T	p-value
Median Age in years	61[52-68.5]	59 [51-63]	0.31
Male	28 (47.5%)	16 (55.2%)	0.65
Race			
Asian	7 (11.9%)	1 (3.4%)	
Black	5 (8.5%)	3 (10.3%)	
Hispanic	8 (13.6%)	1 (3.4%)	
White	33 (55.9%)	22 (75.9%)	
Unknown	6 (10.2%)	2 (6.9%)	
Etiology of HRS %			
Hemorrhage	10.2%	6.9%	
Infection	32.2%	20.7%	
Paracentesis	10.2%	27.6%	
Unknown	47.5%	44.8%	
Admitting median Cr (mg/dl)	2.4 [1.9-3.4]	2.1[1.5-2.5]	0.017
Initial Median Cr (mg/dl)	2.7 [2.2-3.7]	2.4 [2.0-2.8]	0.122
Initial Median Cr (mg/dl) Main Hospital	2.7 [2.3-3.7]	2.4 [2.0-2.8]	0.081
Median Post-Treatment Cr (mg/dl)	3.0 [2.3-4.6]	1.5 [1.3-2.3]	<0.001
Median Post-Treatment Cr (mg/dl) Main Hospital	3.0 [2.0-4.4]	1.4 [1.2-2.3]	<0.001
Mean Initial MELD-Na	31[26-37]	31 [25-34]	0.38
Mean Post-Treatment MELD-Na	31[26-39]	27[19-33.5]	0.031
Change in Cr (mg/dl)	0.31	-0.95	
HRS Treatment Days Main Hospital	8.5 [5-12]	4 [2-7]	0.009
HRS Reversal (%)	6 (10.2)	13 (44.8)	0.001
Mean Total LOS (SD)	17.0 (12)	22.7 (15.6)	0.06
Mean ICU LOS (SD)	3.9 (8.3)	4.4 (11.6)	0.8
Fractional ICU LOS Mean (SD) Main Hospital	0.3 (0.39)	0.09 (0.22)	0.02
RRT (%)	24 (40.7)	6 (20.7)	0.105
RRT (%) Main Hospital	17 (47.2)	5 (20.0)	0.057

Table 1. Demographics and Results

Disclosures: Tanvi Goyal: Nothing to Disclose, David Kaplan: AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Sirtex: Advisor, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research Support, Jonathan Nahas: Nothing to Disclose

2394 | ULTRASOUND LOCALIZATION MICROSCOPY FOR DIAGNOSIS OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION: A PROSPECTIVE MULTICENTER STUDY

Wei Zhang[1] Chuan Liu[2] Yanping Ma[1] Yingchun Yuan[3] Xinde Gong[4] Xia Chen[5] Renmei Wu[6] Jia Li[7] Xiaolong Qi[2] Jie Ren[1], [1]The Third Affiliated Hospital of Sun Yat-sen University, [2]1.Liver Disease Center of Integrated Traditional Chinese and Western Medicine, Department of Radiolo, [3]General Hospital of Ningxia Medical University, [4]TaiHe Hospital (Affilated Hospital Of HuBei University Of Medcine), [5]Department of Ultrasound, The First Affiliated Hospital of USTC, Division of Life Sciences and Medic, [6]Suining Central Hospital, [7]Zhongda Hospital Southeast University

Background: Currently, hepatic venous pressure gradient (HVPG) remains the gold standard for diagnosing clinically significant portal hypertension (CSPH), but its use is restricted by invasiveness and accessibility. This multicenter study aims to apply ultrasound localization microscopy (ULM) to visualize and quantify hepatic microvasculature in cirrhotic patients, evaluating its potential in non-invasive CSPH diagnosis. **Methods:** This study enrolled patients aged 17 to 80 with clinical diagnosis of cirrhosis who underwent HVPG measurement between April 2024 and November 2024 based on clinical needs. Exclusion criteria included prior hepatosplenic surgery, TIPS, SonoVue allergy, hypovolemia, and HVPG contraindications. After informed consent, patients underwent ULM, with data acquisition in the portal phase. Real-time imaging was performed, followed by offline quantitative analysis of microvessel functional and morphological parameters. HVPG $\geq$ 10 mmHg was considered the gold standard for diagnosing CSPH. The Mann-Whitney U test was used to compare microvessel parameters between the CSPH and non-CSPH groups. Spearman correlation analysis assessed the correlation between microvessel parameters and HVPG values. Simple and multiple linear regression models evaluated independent predictors of HVPG. receiver operating characteristic curve was used to assess the diagnostic performance of microvessel parameters in identifying CSPH. **Results:** A total of 29 patients were enrolled, including 21 males, with an average age of 51 (range: 28-70) years. Among them, 12 had alcoholic cirrhosis (including 2 co-infected with hepatitis B), 11 had hepatitis B cirrhosis, 1 had non-alcoholic steatohepatitis, 2 had autoimmune hepatitis, and 3 had primary biliary cirrhosis. Eight patients were diagnosed with CSPH, and 3 were non-CSPH. Compared to the non-CSPH group, the CSPH group exhibited lower vessel density (VD) (57.8 $\pm$ 11.3 vs. 42.2 $\pm$ 4.7, $p = 0.001$) and perfusion index (PI) (12.7 $\pm$ 1.3 vs. 8.7 $\pm$ 1.4, $p = 0.002$). Moderate correlations were observed both between VD and HVPG ($r = -0.70$, $p < 0.001$), and between PI and HVPG ($r = -0.57$, $p = 0.001$). VD was an independent predictor of HVPG ($r^2 = 0.52$). The diagnostic performance of VD for CSPH (AUC = 0.98, $p = 0.01$) was higher than that of the CSPH risk score (AUC = 0.59, $p = 0.54$). **Conclusion:** ULM-based microvessel parameters were proposed with good diagnostic consistency for HVPG measurement.

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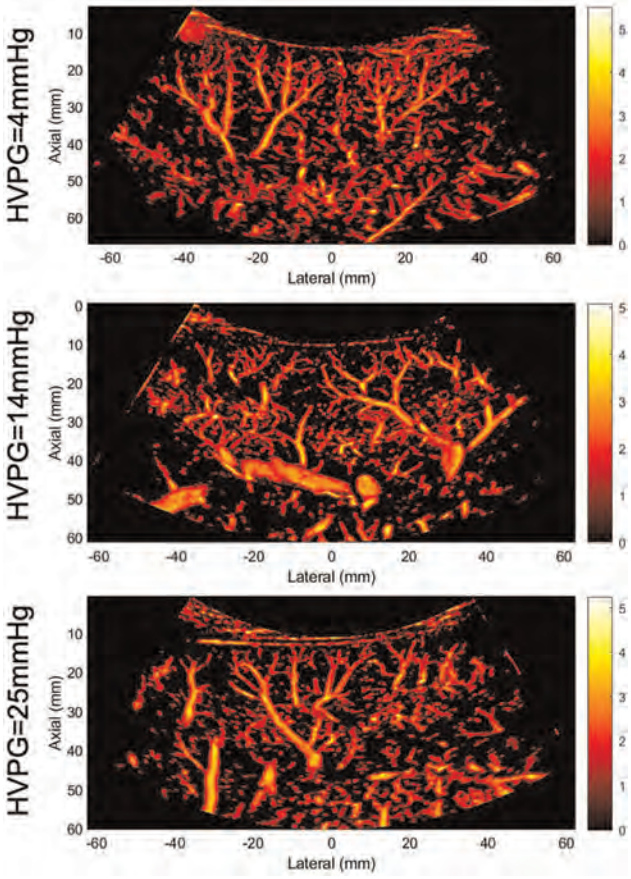


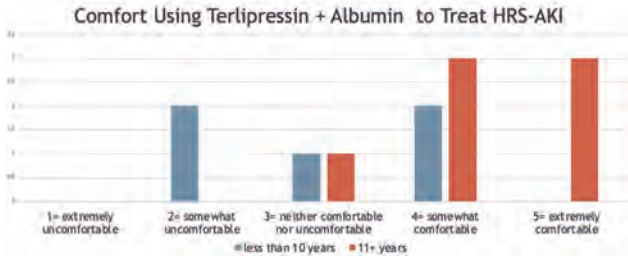
Disclosures: Wei Zhang: Nothing to Disclose, Chuan Liu: Nothing to Disclose, Yanping Ma: Nothing to Disclose, Yingchun Yuan: Nothing to Disclose, Xinde Gong: Nothing to Disclose, Xia Chen: Nothing to Disclose, Renmei Wu: Nothing to Disclose, Jia Li: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose, Jie Ren: Nothing to Disclose

2395 | HEPATOLOGISTS' EXPERIENCE IN USING TERLIPRESSIN FOR TREATMENT OF HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY

Prutha Shah[1] Rachel White[2] Morgan Elias[1] Rebecca Loh[3] Jonathan Fenkel[3] John Knorr[1] David Sass[3] Sarah Yeager[3] Jamie Schulte[3] Richard Kalman[1], [1]Jefferson Einstein Philadelphia Hospital, Philadelphia PA, [2]Sidney Kimmel Medical College, Philadelphia PA, [3]Thomas Jefferson University Hospital, Philadelphia PA

Background: Hepatorenal Syndrome-Acute Kidney Injury (HRS-AKI) is a complication of advanced liver disease. In September 2022, the FDA approved terlipressin + albumin for treating adults hospitalized with HRS-AKI. This study explores transplant hepatologists' experiences using the drug since its approval. **Methods:** A ten-question Qualtrics survey collected demographic data and assessed provider comfort, adverse effects, success rates, and optimal usage of terlipressin. The survey was distributed to 17 transplant hepatologists at two major liver transplant centers in Philadelphia, PA: Thomas Jefferson University Hospital and Jefferson Einstein Philadelphia Hospital. This study was IRB-exempt, voluntary, and responses were anonymized. Data analysis was conducted with Microsoft Excel. **Results:** Twelve transplant hepatologists responded to the survey (response rate 71%). Of the respondents, 83% found success with terlipressin 1/3 of the time, 17% found success 2/3 of the time, and none reported complete success or failure. Regarding adverse effects, 93% reported seeing hypoxia. Abdominal pain was the only other reported adverse reaction. When asked if the benefit outweighs the risks, 33% of providers said "it depends on the patient", 42% reported "most of the time", 25% reported "some of the time", and none reported "never" or "always". When asked about the minimum level of care, 75% of providers said the step-down unit, and 25% of providers answered the general medical floor. 58% of providers are less likely to prescribe terlipressin if the patient is listed for transplant, 8% are more likely, and 33% reported that transplant listing did not influence their decision. Providers with over 11 years of experience reported greater comfort using terlipressin than those with less than 10 years ($p < 0.05$) (Figure 1). Cost consideration influenced prescribing decisions for 8% of respondents. **Conclusion:** This study highlights transplant hepatologists' early experiences with terlipressin, showing success rates consistent with clinical trials. It underscores the need for targeted training for providers early in their careers and suggests further research to optimize usage. Our results confirm that despite the side effects and imperfect efficacy, transplant hepatologists at our centers believe there is a role for terlipressin in the treatment of HRS-AKI. Future research should explore experiences at other hospitals and identify specific patient populations who would benefit the most. Continued evaluation is critical to improving patient outcomes with this novel therapy.

Figure 1: Provider comfort using Terlipressin + Albumin based on years of experience



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Disclosures: Prutha Shah: Nothing to Disclose, Rachel White: Nothing to Disclose, Morgan Elias: Nothing to Disclose, Rebecca Loh: Nothing to Disclose, Jonathan Fenkel: Nothing to Disclose, John Knorr: Nothing to Disclose, David Sass: Gilead: Research support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Sarah Yeager: Nothing to Disclose, Jamie Schulte: Nothing to Disclose, Richard Kalman: Gilead: Speaking and Teaching

2396 | POST-POLYPECTOMY BLEEDING IN PATIENTS WITH CIRRHOSIS: A SYSTEMATIC REVIEW OF RISK, PREDICTORS, AND PROCEDURE-RELATED FACTORS

Sajid Jalil[1] Talal Bhatti[2] Mohammad Adam[3] Chencheng Xie[4] Ashwani Singal[5], [1]Stanford University, [2]Northwell Health Center for Liver Diseases and Transplantation, [3]University of Missouri - Kansas City School of Medicine, [4]Avera McKennan Hospital, [5]University of Louisville

Background: Patients with cirrhosis are considered at increased risk for post-polypectomy bleeding (PPB) due to coagulopathy, portal hypertension, and associated comorbidities. However, the frequency and predictors of bleeding, especially in the modern era of optimized endoscopic practice, remain incompletely characterized. This systematic review aims to quantify the incidence of immediate and delayed PPB in cirrhotic patients, evaluate procedure- and patient-level predictors, and propose practical implications for clinical endoscopy. **Methods:** This systematic review was conducted in accordance with the PRISMA 2020 guidelines. A comprehensive literature search was performed in databases for articles published up to April 2025. Retrospective or prospective studies in adults with a diagnosis of cirrhosis and undergoing colonoscopy were selected. Of these, those reporting outcomes on PPB, immediate (IPB) defined as intra-procedural or delayed (DPB) defined as bleeding within 30-d of procedure. Data were extracted on patient demographics, liver disease severity (Child-Pugh class, MELD, INR, platelet count), procedural characteristics (polypectomy technique, polyp size, number, location), and clinical outcomes (IPB and DPB, transfusion, hospitalization). Reported odds ratios (ORs) for bleeding predictors were collected when available. A formal meta-analysis was not conducted due to considerable heterogeneity across studies. **Results:** A total of five retrospective cohort studies, encompassing 4,345 cirrhotic patients, met inclusion criteria (Table). IPB occurred in 6.3–7.5%, and DPB in 0.3–5.9% of cirrhotic patients in comparison to the risk of 30-day PPB rate of $< 0.5\%$ in general population. Risk of significant bleeding (defined as requiring hospitalization or transfusion) was rare (0.3–2.0%). Risk factors for PPB from different studies included Child-Pugh B/C (OR: 19.7), decompensated cirrhosis (OR: 1.65), ascites (OR: 2.82), polyp size $\geq$ 10 mm (OR: 1.087 to 8.3). Prolonged INR was associated with increased risk of IPB ($r = 0.61$) and low platelet counts (below 50,000) was associated with DPB ($r = -0.58$). Colonoscopy with endoscopic mucosal resection (EMR) was associated with higher rates of IPB and DPB compared to snare polypectomy. Aspirin use was not associated with increased bleeding risk. Use of antiplatelets (e.g. clopidogrel) within 5 days was associated with increased risk of DPB (RR = 2.42). **Conclusion:** Rates of PPB in cirrhotic patients is higher compared to general population (6.1% vs. $< 1\%$). The use of EMR should be coupled with prophylactic strategies in high-risk patients. Careful patient selection using liver severity markers (Child-Pugh, platelet count, INR), lesion size, and polypectomy type can enable safe endoscopic practice. Future prospective studies should validate bleeding risk tools and assess the role of prophylactic clipping, cold resection techniques and hemostatic optimization.

Table: summary table with study variables

Variable	Lee 2015	Hasan 2021	Soh 2020	Huang 2016	Beran 2025
INR	1.07	1.20	1.09	1.20	NR
Platelet Count (10^3/μL)	151.6	145.8	138.8	140.6	NR
Age (years)	61.2	61.9	62.4	60.2	63.5
Immediate PPB (%)	NR	9.2	6.3	7.5	NR
Delayed PPB (%)	13.8	5.9	0.7	0.3	5.2
Cumulative (Mean)	1.14	144.2	61.8	7.7	5.2

INR: international normalized ratio, PPB: post polypectomy bleeding, NR: not reported

Disclosures: Sajid Jalil: Nothing to Disclose, Talal Bhatti: Nothing to Disclose, Mohammad Adam: Nothing to Disclose, Chencheng Xie: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, GSK: Grant/Research Support, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, Avera Medical Group: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other

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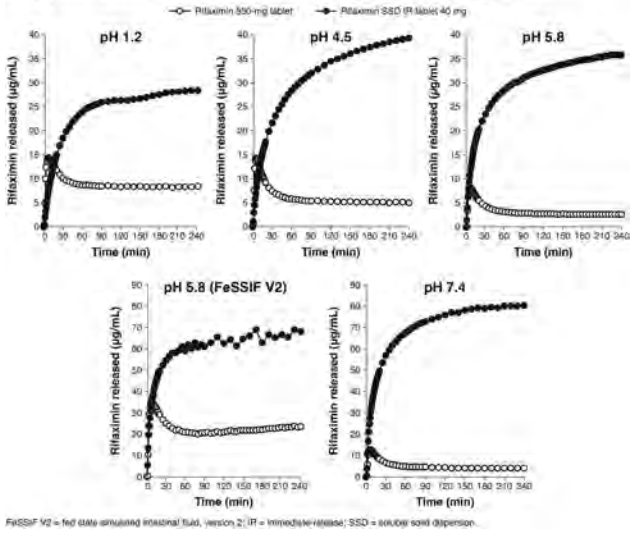
2397 | ENHANCED RIFAXIMIN DRUG RELEASE ACROSS GASTROINTESTINAL TRACT PH CONDITIONS WITH SOLUBLE SOLID DISPERSION (SSD) IMMEDIATE-RELEASE (IR) TABLETS: A COMPARATIVE IN VITRO STUDY VERSUS RIFAXIMIN 550 MG TABLET FORMULATION

Jasmohan Bajaj[1] RK Pillai[2] Sateesh Kandavilli[2] Saurabh Mishra[2] Christopher Allen[3] Arun Sanyal[1], [1]Virginia Commonwealth University, [2]Bausch Health US, LLC, [3]Salix Pharmaceuticals

Background: The current rifaximin 550-mg tablet is largely water insoluble and relies on small intestine bile acids (BA) to maximize solubility. Low intestinal BA levels in cirrhosis may reduce GI bioavailability. New formulations are needed to increase the applicability of rifaximin therapy across a wider range of cirrhosis/hepatic encephalopathy severity. Rifaximin SSD IR tablet 40 mg (SSD IR40) was designed to increase aqueous solubility of the rifaximin molecule throughout the lumen and minimize the need for BA. This is clinically important for patients with cholestasis/cirrhosis. The aim was to compare the in vitro dissolution profiles of rifaximin 550 mg and rifaximin SSD IR40 across a simulated range of fluid pH exposures likely to occur during GI transit. **Methods:** Dissolution rates of rifaximin 550 mg and rifaximin SSD IR40 were determined in 5 media to simulate portions of the GI tract (pH 1.2 [stomach], pH 4.5 [duodenum], pH 5.8 [small intestine], pH 5.8 [fed state simulated intestinal fluid, ver 2 (FeSSIF V2); small intestine], and pH 7.4 [colon]). Each test (N = 6) was conducted in 500 mL of medium at selected pH and maintained at 37 °C and 75 rpm (USP Apparatus 2 paddle method) for 240 min, with monitoring using an in situ UV fiber-optic 10-mm probe at λ_{max} = 325 nm (Opt-Diss 410, Distek, Inc). **Results:** The rifaximin release profile for both formulations is shown in the Figure. At 1 hour, for rifaximin SSD IR40 vs rifaximin 550 mg, there was a 2.7-, 4.9-, 9.1-, 2.8-, and 13.3-fold higher concentration of rifaximin at pH 1.2, 4.5, 5.8, 5.8 (FeSSIF V2), and 7.4, respectively. At 4 hours, there was a 3.4-, 7.7-, 13.6-, 2.9-, and 18.7-fold higher rifaximin concentration at pH 1.2, 4.5, 5.8, 5.8 (FeSSIF V2), and 7.4, respectively. Rifaximin 550-mg tablet dissolution was significantly enhanced at pH 5.8 in the presence of BA (FeSSIF V2 vs phosphate buffer pH 5.8); rifaximin SSD IR40 dissolution was not impacted. **Conclusion:** During exposure to pH conditions considered clinically relevant within segments of the lower GI tract, an ≈3- to 19-fold greater increase in rifaximin release was observed and sustained over time with rifaximin SSD IR40 vs rifaximin 550 mg. BA did not impact rifaximin SSD IR40 dissolution rate. These data support that rifaximin SSD IR may provide higher luminal bioavailability of rifaximin at a lower dosage throughout the lower GI tract vs the current rifaximin 550-mg tablet. Thus, rifaximin SSD IR40 may overcome low BA availability issues observed in cirrhosis progression.

Figure. Comparative Dissolution Profile of Rifaximin SSD IR Tablet 40 mg Versus Rifaximin 550-mg Tablet Across Various pH Values and FeSSIF V2 Medium Containing Bile Salts



FeSSIF V2 = fed state simulated intestinal fluid, version 2; IR = immediate-release; SSD = soluble solid dispersion.

Disclosures: Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Genfit: Grant/Research Support, Enterobiotix: Advisor, Boehringer Ingelheim: Advisor, RK Pillai: Nothing to Disclose, Sateesh Kandavilli: Bausch Health: Employee, Saurabh Mishra: Nothing to Disclose, Christopher Allen: Salix Pharmaceuticals: Employee, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (< 5K), Terns (< 5K), Merck (< 5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (< 5K),: Consultant, Novo Nordisk: Consultant, Regeneron (< 5K), Alnylam (< 5K), Akero (< 5K),: Consultant, Tern (< 5K), Histoindex (< 5K), Corcept (< 5K),: Consultant, Path AI (< 5K), Genfit (< 5K), Mediar (< 5K),: Consultant, Satellite Bio (< 5K), Echosens (< 5K), Abbott (< 5K),: Consultant, Promed (< 5K), Glaxo Smith Kline (~11K), Arrowhead (< 5K): Consultant, Zydus (> 60K), Boston Pharmaceutical (< 5K), Myovent (< 5K),: Consultant, Variant (< 5K), Cascade (< 5K), Northsea (< 5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant,

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Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor

2398 | VASCULAR GEOMETRIC MODEL FOR PREDICTING PORTAL PRESSURE GRADIENT IN PATIENTS WITH CIRRHOSIS

Ling Yang[1] Jiawei Zhang[1] Yechong Huang[2] Jiaqi Gu[1] Xiaolin Wang[3] Chuan Liu[3] Shaoting Zhang[2] Xiaolong Qi[3], [1]Zhongda Hospital, Medical School, Southeast University, [2]SenseTime Research, Shanghai, [3]Zhongda Hospital, Southeast University

Background: Measurement of the portacaval pressure gradient (PPG) is a crucial step in evaluating portal pressure in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) procedures. However, PPG assessment is limited by its invasive nature. Based on the inspiration provided by our previous study, we further explored the feasibility of non-invasively predicting PPG by utilizing 64 vascular geometric parameters derived from preoperative contrast-enhanced CT scans in patients scheduled for TIPS surgery. **Methods:** A retrospective cohort study was conducted from January to September 2024 across six university-affiliated medical centers, enrolling 39 patients scheduled for TIPS surgery. Invasive PPG measurements before TIPS surgery (PPG_Before) were obtained for all participants as the reference standard. We developed a comprehensive pipeline for the calculation of 64 geometric parameters from raw DICOM data using Python 3.6.1, encompassing data preprocessing, vessel segmentation, and vascular tree construction. Multivariate regression, logistic and linear regression analyses were used to identify predictive features. For clinical stratification, patients were dichotomized using a 20 mmHg PPG threshold - an established indicator for variceal rebleeding risk. **Results:** The cohort had a median age of 52.0 years (IQR 46.0–64.0), with 74.4% males (n = 29). Baseline PPG_Before measurements were available for 37 patients (mean 22.76 ± 6.12 mmHg). Logistic regression identified the main portal vein branch length as a particularly robust predictor during the portal venous phase (OR = 1.138, 95% CI: 1.016-1.275, $p < 0.05$). Linear regression models further established moderate but statistically significant correlations for both aortic phase vessel tortuosity (R = 0.437) and subbranch diameter (R = 0.348) with measured PPG_Before values. These findings informed the development of our convolutional neural network-derived predictive algorithm: PPG_{AI} = -0.175 × (Aorta_Average vessel tortuosity) + 0.149 × (Aorta_Subbranch diameter) + 0.130 × (Pv_Main branch length) - 1.657. The model achieved 83.8% accuracy in classifying patients above/below the 20 mmHg threshold. Through receiver-operating characteristic analysis, we established a clinically actionable cutoff value of PPG_{AI} = -0.3313, where values below this threshold indicated low rebleeding risk (negative predictive value = 90.0%), while values above suggested elevated risk requiring closer monitoring (positive predictive value = 81.5%). This stratification demonstrated good concordance with invasive PPG measurements (R = 0.576, $p < 0.001$), suggesting robust clinical utility for rebleeding risk assessment (Figure 1). **Conclusion:** In conclusion, the study proposed a PPG calculation model using anatomical imaging features, which may serve as a substitute for invasive PPG measurement.

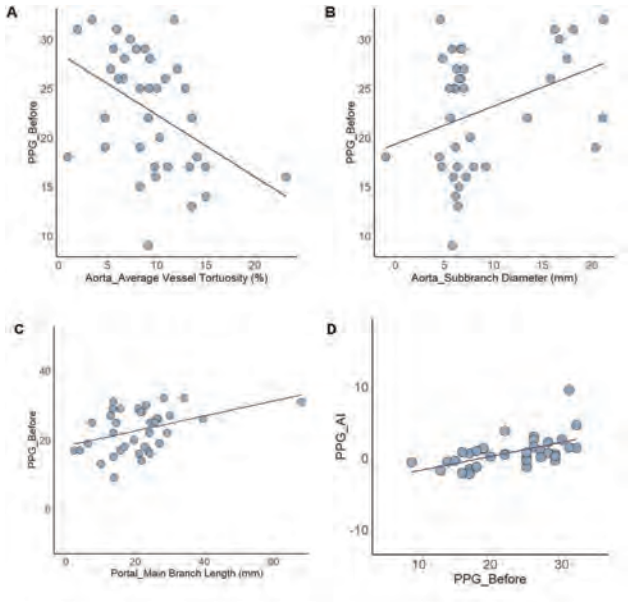

Figure 1: A-C: Scatter plot of average vessel tortursity, subbranch diameter in arterial phase and main branch length in portal phase and correlation with PPG_Before in linear regression. D: Scatter plot of PPG_AI and PPG_Before.

Disclosures: Ling Yang: Nothing to Disclose, Jiawei Zhang: Nothing to Disclose, Yechong Huang: Nothing to Disclose, Jiaqi Gu: Nothing to Disclose, Xiaolin Wang: Nothing to Disclose, Chuan Liu: Nothing to Disclose, Shaoting Zhang: Nothing to Disclose, Xiaolong Qi: Nothing to Disclose

2399 | RISK OF SERIOUS INFECTION AND MORTALITY IN PATIENTS WITH COMPENSATED CIRRHOSIS AND DECOMPENSATED CIRRHOSIS

Won Sohn[1] Jae Yoon Jeong[2] Ju-Yeon Cho[3] Jung Hee Kim[4] Hyun Woo Oh[1] Yongkyun Cho[1] Byung Kim[5] Kyoung A Ko[6], [1]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, [2]Ewha

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Womans University College of Medicine, [3]Chosun University Hospital, [4]Hallym University Dongtan Sacred Heart Hospital, [5]Kang Buk Samsung hospital, [6]Kangbuk Samsung Hospital

Background: It is unclear whether the risk of infection is different between chronic liver disease (CLD) without cirrhosis, compensated cirrhosis and decompensated cirrhosis. This study aimed to investigate the risk of serious infection and mortality in patients with compensated cirrhosis and decompensated cirrhosis. **Methods:** This study was conducted on 1,699,159 patients with CLD from the Korean National Health Insurance Service between 2009 and 2021. Serious infection was defined as acute meningitis, acute osteomyelitis, bacteremia, pneumonia, pyelonephritis, serious gastrointestinal infection, skin and soft tissue infections, spontaneous bacterial peritonitis, or COVID-19 infection. The primary outcome was all-cause mortality stratified by serious infection episodes (0, 1, and ≥ 2). We compared the development of serious infection, the admission of intensive care unit (ICU), and mortality between CLD without cirrhosis, compensated cirrhosis and decompensated cirrhosis. **Results:** The mean age of patients was 57.4 years, with 55.6% being men. Among them, the proportion of CLD without cirrhosis, compensated cirrhosis, and decompensated cirrhosis was 77.5% (N = 1,317,468), 17.5% (N = 296,617), and 5.0% (N = 85,074), respectively. During follow-up, there were 336,602 episodes of serious infections, with pneumonia being the most common, followed by serious gastrointestinal infection, pyelonephritis, and bacteremia. Mortality rates were 3.94, 41.58, and 114.03 per 1,000 person-years in patients with 0, 1, and ≥ 2 serious infections, respectively. Multivariable analysis indicated that adjusted hazard ratios (aHRs) for mortality were 6.04 (95% confidence interval [CI]: 5.96-6.13) for one infection and 13.40 (95% CI: 13.20-13.60) for ≥ 2 infections, compared to no infections. Compared to CLD without cirrhosis, the development of serious infection was higher in compensated cirrhosis (aHR: 1.99, 95% CI:1.97-2.02), and decompensated cirrhosis (aHR: 3.31, 95% CI:3.26-3.37). **Conclusion:** Patients with CLD exhibited a trend of increased mortality dependent on the number of serious infections and the degree of disease severity of CLD ranging from CLD without cirrhosis, compensated cirrhosis, and decompensated cirrhosis. Decompensated cirrhosis has more than 3-fold risk of infection than CLD without cirrhosis.

Disclosures: Won Sohn: Nothing to Disclose, Jae Yoon Jeong: Nothing to Disclose, Ju-Yeon Cho: Nothing to Disclose, Jung Hee Kim: Nothing to Disclose, Hyun Woo Oh: Nothing to Disclose, Yongkyun Cho: Nothing to Disclose, Byung Kim: Nothing to Disclose, Kyoung A Ko: Nothing to Disclose

2400 | REAL-WORLD OUTCOMES FOLLOWING TERLIPRESSIN USE IN HEPATORENAL SYNDROME: A MULTI-CENTER U.S. EHR ANALYSIS

Romelia Barba[1] Khawaja Hassam[2] Ana Marenco-Flores[3] Natalia Rojas-Amaris[3] Pojsakorn Danpanichkul[4] Daniela Goyes[5] Gloria Erazo[1] Zeyad Elharabi[1] Leo Yamaguchi[1] Kanak Das[1] Hakan Akin[1] Michael Curry[3], [1]Texas Tech University, [2]Lahey Hospital and Medical Center, [3]Beth Israel Deaconess Medical Center, [4]Texas Tech University Health Sciences Center, [5]Yale School of Medicine

Background: Hepatorenal syndrome–acute kidney injury (HRS-AKI) is a life-threatening but potentially reversible complication of cirrhosis characterized by rapid deterioration in kidney function. Terlipressin, a vasopressin analog, is FDA-approved (in combination with albumin) for the treatment of adult patients with HRS and is recommended as first-line therapy for HRS-AKI in recent AASLD and EASL guidelines. Despite demonstrated efficacy in clinical trials, real-world comparative data on terlipressin use remain limited in U.S. practice. **Aim:** To evaluate real-world outcomes in patients with HRS treated with terlipressin using a large multi-institutional electronic health record (EHR) database. **Methods:** We conducted a retrospective, single-arm outcomes analysis using the TriNetX U.S. Collaborative Network, a federated platform aggregating de-identified EHR data—including diagnoses, procedures, medications, labs, and outcomes—from 68 U.S. healthcare organizations. Adults (≥ 18 years) diagnosed with HRS who received terlipressin on or after September 14, 2022, were included. The date of terlipressin initiation served as the index event. Risk and Kaplan-Meier survival analyses were performed for all-cause mortality, dialysis initiation, liver transplantation, and recurrent HRS, assessed at 30, 60, 90, and 180 days. Competing risks (e.g., death before transplant) were not formally modeled. **Results:** A total of 380 patients were identified (mean age 54.5 years; 59% male; 74.7% White). Within 30 days, 30% had died, 21.3% initiated dialysis, 17.4% underwent liver transplantation, and 42.6% experienced recurrent HRS. These risks increased modestly at 60 days (36%, 23.4%, 21%, and 48.7%, respectively) and again by 90 days (38.4%, 24%, 22%, and 49.7%). At 180 days, 40.5% had died, 25.5% started dialysis, 24.2% underwent transplant, and 51.1% had recurrent HRS. Kaplan-Meier analysis showed the steepest risk increase in the first 30 days (Figure 1). The 180-day survival probabilities were 53.1% for overall survival, 66.0% dialysis-free, 61.4% transplant-free, and 36.6% HRS-free. Median time to event dropped below 50% only for recurrent HRS (43 days). **Conclusion:** In this real-world, multi-center cohort of adults with HRS treated with terlipressin,

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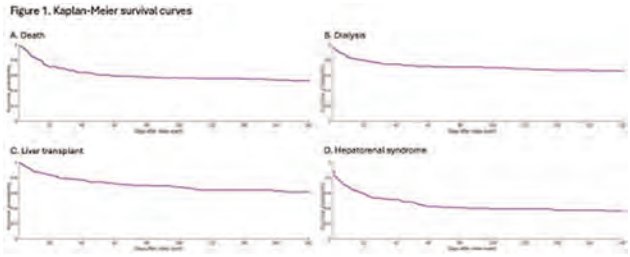
nearly half experienced death or recurrent HRS within six months, and one in four required dialysis or liver transplantation. These findings highlight the high acuity of the HRS population and suggest that while terlipressin may reverse renal dysfunction, it does not alter the underlying trajectory of advanced liver disease. Real-world data such as ours is essential to complement trial results and guide treatment decisions in this complex population. Limitations include the inability to model competing risks and the lack of site-level data, which may influence transplant-related outcomes.



Disclosures: Romelia Barba: Nothing to Disclose, Khawaja Hassam: Nothing to Disclose, Ana Marenco-Flores: Nothing to Disclose, Natalia Rojas-Amaris: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Daniela Goyes: Nothing to Disclose, Gloria Erazo: Nothing to Disclose, Zeyad Elharabi: Nothing to Disclose, Leo Yamaguchi: Nothing to Disclose, Kanak Das: Nothing to Disclose, Hakan Akin: Nothing to Disclose, Michael Curry: Mallinckrodt: Consultant, Pfizer: Independent Contractor, International Healthcare Inc: Independent Contractor, CareDx: Grant/Research Support, Intercept: Grant/Research Support, Sonic Incytes: Grant/Research Support

2401 | REAL-WORLD TREATMENT PATTERNS AND OUTCOMES AMONG HOSPITALIZED U.S. ADULTS WITH HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY TREATED WITH TERLIPRESSIN

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Background: Hepatorenal syndrome–acute kidney injury (HRS-AKI), is a life-threatening complication of advanced liver disease marked by rapid renal decline. This study examined early real-world use and outcomes of terlipressin, a vasopressin analogue recently approved in the U.S. to improve kidney function in adults with HRS. **Methods:** We identified adults hospitalized with HRS-AKI who received terlipressin for ≥ 2 consecutive days between Sep 2022–Feb 2025 using the Premier Healthcare Database. We evaluated treatment patterns and outcomes, including HRS reversal, which were also assessed among patients with alcohol-associated liver disease (ALD) and those on the liver transplant waitlist. Diagnoses, medication use, and outcomes were identified using ICD-10, National Drug Codes, and billing data. **Results:** We identified 285 patients [median age 56.0 years (IQR 47.0, 66.0), 63.5% male], of whom 68.1% were hospitalized at large-volume health systems (500+ beds). Most patients were White (64.2%), and Medicare was the most common payer type (33.0%). ALD was the most common cirrhosis etiology (70.5%). Overall median time to terlipressin initiation was 4.0 days (IQR 2.0, 8.0). First-line treatment included terlipressin (22.5%), same-day midodrine and octreotide (26.0%), or norepinephrine (3.2%). The remaining 48% received midodrine or octreotide monotherapy, or other combination therapies. In-hospital mortality was 16.8%, with 16.5% discharged to hospice and 45.6% discharged home. Median length of stay was 16 days (IQR 10.0, 27.0). Renal replacement therapy was required in 26.3% of patients. Among 36 patients with available SCr data, HRS reversal, defined as post-treatment SCr to ≤ 1.5 mg/dL, was achieved in overall 52.8% of patients, with median SCr declining from 2.2 mg/dL (IQR 1.7, 3.1) to 1.2 mg/dL (IQR 1.0, 1.4). HRS reversal was more frequent in ALD patients (60.7%) than in non-ALD patients (25.0%). Among those on the transplant waitlist, 75.0% achieved reversal compared with 50.0% of those not listed. **Conclusion:** In this real-world HRS cohort treated with terlipressin, most were managed at high-volume centers and had underlying ALD. Although terlipressin was infrequently used first-line, meaningful rates of HRS reversal were observed, particularly in ALD. With nearly half of all patients discharged home and in-hospital mortality under 20%, these findings highlight the potential for terlipressin to improve renal function and overall clinical outcomes–reinforcing the importance of early recognition and treatment.

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Table 1: Patient and hospital characteristics

Patient Demographics	Overall Cohort (N = 285)
Age (years), Median (IQR)	56.0 (47.0, 66.0)
Sex, n (%)	
Female	104 (36.5%)
Male	181 (63.5%)
Ethnicity, n (%)	
White or Caucasian	183 (64.2%)
Hispanic	41 (14.4%)
Black or African American	21 (7.4%)
Asian	16 (5.6%)
Other or unspecified	24 (8.4%)
Payer, n (%)	
Medicare	94 (33.0%)
Medicaid	87 (30.5%)
Managed care	47 (16.5%)
Commercial	34 (11.9%)
Other[a]	17 (6.0%)
Self	6 (2.1%)
Hospital Characteristics	
Hospital bed size, n (%)	
≥500	194 (68.1%)
<500	91 (31.9%)
Setting, n (%)	
Urban	280 (98.2%)
Rural	5 (1.8%)
Teaching hospital, n (%)	126 (44.2%)
Clinical Characteristics	
Etiology of liver disease[b], n (%)	
ALD	201 (70.5%)
MASH/MASLD	78 (27.4%)
Viral hepatitis	15 (5.3%)
Liver transplantation waitlist status, n (%)	36 (12.6%)
Pre-treatment SCr availability, n (%)	36 (12.6%)
Median (IQR), mg/dL	2.4 (1.8, 3.2)
Treatment Patterns	
Time to first terlipressin receipt, days	
Median (IQR)	4.0 (2.0, 8.0)
Duration of terlipressin therapy, days	
Median (IQR)	4.0 (3.0, 7.0)
First-line treatment, n (%)	
Terlipressin	64 (22.5%)
Midodrine and Octreotide (same day)	74 (26.0%)
Norepinephrine	9 (3.2%)
Midodrine	82 (28.8%)
Octreotide	43 (15.1%)
Multi-therapy	13 (4.6%)
Clinical Outcomes	
Post-treatment SCr availability, n (%)	36 (12.6%)
Median (IQR), mg/dL	1.5 (1.2, 2.1)
HRS reversal[c]	
n (% of post-treatment SCr availability)	19 (52.8%)
Discharge status, n (%)	
In-hospital mortality	48 (16.8%)
Discharge to hospice	47 (16.5%)
Home or home health organization	130 (45.6%)
Transfer to another facility[d]	55 (19.3%)
Left against medical advice	5 (1.8%)
Renal replacement therapy, n (%)	75 (26.3%)
Hospital LOS, days	
Median (IQR)	16.0 (10.0, 27.0)
ICU admission[e], n (%)	126 (44.2%)

[a]Includes other, charity, and government payors; [b]90 day lookback period used, not mutually exclusive; [c]Defined as return of pre-treatment SCr to ≤1.5 mg/dL; [d]Other facility, skilled nursing facility, health institution not in list, other rehab facility; [e]Identified using the speciality (critical care medicine) of the attending physician or an ICU room and board charge associated with the encounter
ALD: Alcohol-associated liver disease; IQR: Interquartile range; LOS: Length of stay; MASH/MASLD: Metabolic dysfunction-associated steatohepatitis/Metabolic dysfunction-associated steatotic liver disease; SCr: Serum creatinine

Disclosures: Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant, Target-RWE: Consultant, Madrigal Pharmaceuticals: Consultant, Merck (Any division): Consultant, Boehringer Ingleheim: Consultant, Robert Wong: Theratechnologies: Grant/Research Support, Durect: Grant/Research Support, Gilead Sciences: Grant/Research Support, Exact Sciences: Grant/Research Support, Theratechnologies: Grant/Research Support, Durect Corporation: Grant/Research Support, Kavish Patidar: Madrigal Pharmaceuticals: Medical Advisory Board, Mallincrodt Pharmaceuticals: Consultant, Nisha Wadhwani: Mallinckrodt Pharmaceuticals: Consultant, Jonathan Lilley: Mallinckrodt: Consultant, Grifols: Consultant, Rahul Rajkumar: Grifols: Consultant, Mallinckrodt Pharmaceuticals: Consultant, Xingyue Huang: Nothing to Disclose, Mary Panaccio: Mallinckrodt Pharmaceuticals: Consultant

2402 | COMPARATIVE VALIDATION OF PROGNOSTIC MODELS FOR TRANSPLANT-FREE SURVIVAL IN TIPS: THE ADVANCING LIVER THERAPEUTIC APPROACHES IN PORTAL HYPERTENSION (ALTA) STUDY

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Background: Despite advances in transjugular intrahepatic portosystemic shunt (TIPS) technique and patient selection, short-term mortality still varies widely (9-80% depending on patient characteristics). Prognosis is usually guided by MELD-based or Child-Turcotte-Pugh (CTP) scores, yet newer models derived in non-US based populations – the Freiburg Index of Post-TIPS Survival (FIPS) and the Modified TIPS Score (MOTS) – may offer better discrimination. We aimed to comparatively validate prognostic models for post-TIPS mortality in a large prospective multicenter US-based cohort. **Methods:** Advancing Liver Therapeutic Approaches in Portal Hypertension (ALTA) is a multi-center prospective cohort study across 13 US centers of adults (≥18 years) who were scheduled for TIPS between 7/2019-1/2025. Those who underwent successful TIPS creation with complete data for modeling were included in this analysis. Descriptive statistics were summarized using t-tests and ANOVA, or Chi-squared and Fisher, as appropriate. Fine and Gray competing risk models were fitted to evaluate time to death with transplant treated as a competing event and covariates

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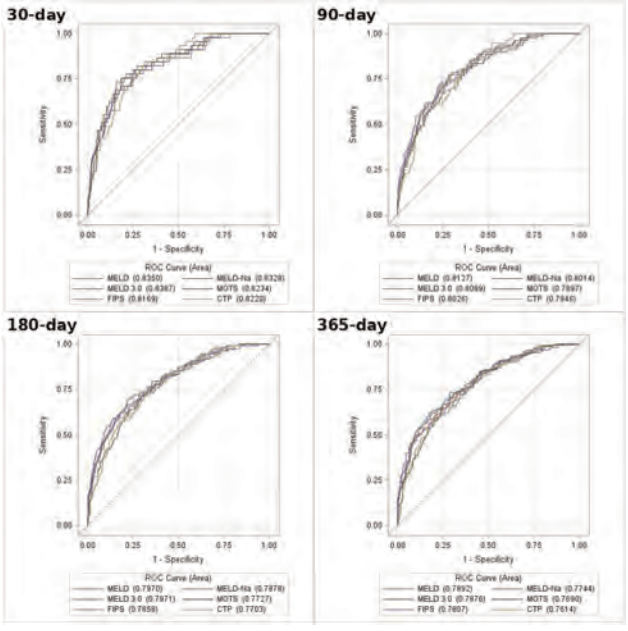
(sex, race/ethnicity, TIPS indication and urgency, portal-hypertension cause, transplant intent) held constant. Six candidate scores – MELD, MELD-Na, MELD-3.0, CTP, FIPS and MOTS – were evaluated. Discrimination for transplant-free survival (TFS) at 30, 90, 180 and 365 days was assessed using area under the receiver operating characteristic curves (AUROC). **Results:** A total of 501 subjects (mean age 56.7 years, 43.1% female, 80.6% White, 20.8% Hispanic) were included with mean follow up 427 days. Median (IQR) MELD was 11.4 (9.3-14.5), MELD-Na 13.1 (9.9-17.1), and MELD-3.0 13.6 (10.2-17.2). The 3 MELD-based scores provided the strongest and most consistent associations with death: each point increase in MELD-3.0 raised the instantaneous hazard by 7 % (HR 1.07, $p = 0.002$), and MELD-Na and original MELD produced similar effects (HR 1.06, $p = 0.003$ and 0.006, respectively). CTP score was also significant (HR 1.24, $p = 0.026$) but, because it spans only 5–15 points, offered less patient-level discrimination (i.e., ability to separate higher from lower-risk individuals). MOTS met significance (HR 1.50, $p = 0.032$), while FIPS was not associated with mortality ($p = 0.25$). MELD-3.0 and MELD yielded the highest 30 and 90-day AUROCs, but all 6 scores converged ≈0.78 by 1 year (Figure). In stratified analyses by cirrhosis status, sex, race and ethnicity, only MELD-3.0 and/or MELD-Na significantly predicted mortality. **Conclusion:** In a large contemporary US-based prospective cohort of TIPS recipients, MELD scores showed the most consistent hazard associations with short-term death post-TIPS across multiple subgroups. These findings suggest MELD-based scores remain reliable short-term guides. Additional studies are needed to improve risk discrimination for longer term survival post-TIPS.



Disclosures: Ludovic Saba: Nothing to Disclose, Justin Boike: W. L. Gore and Associates: Grant/Research Support, Eurofins Transplant Genomics: Advisor, Echosens: Consultant, W. L. Gore and Associates, Inc.: Consultant, Michael Fallon: Nothing to Disclose, Pallav Kolli: Nothing to Disclose, Bartley Thornburg: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Advisor, Carrie Frenette: Gilead Sciences: Employee, Aparna Goel: Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Sumeet Asrani: Nothing to Disclose, Giuseppe Joseph Morelli: Nothing to Disclose, Nicholas Lim: Nothing to Disclose, Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant, Mallinckrodt Pharmaceuticals: Consultant, Mallinckrodt Pharmaceuticals: Speaking and Teaching, Adam Deising: Nothing to Disclose, Sonali Paul: Intercept: Grant/Research Support, Target PharmaSolutions: Grant/Research Support, Eli Lilly: Stock - publicly traded company, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Margarita German: Nothing to Disclose, Dyanna Gregory: Nothing to Disclose, Mehnush Hameie: Nothing to Disclose, Cynthia Padilla: Nothing to Disclose, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support

2403 | TIPS-ATTRIBUTABLE MORTALITY IS PREDICTED BY MELD VARIANTS, NOT NON-TIPS DEATHS: EVIDENCE FROM THE ALTA STUDY GROUP

Heesoo Yoo[1] Justin Boike[2] Michael Fallon[3] K. Pallav Kolli[4] Bartley Thornburg[5] Elizabeth Verna[6] Adnan Said[7] Carrie Frenette[8] Aparna Goel[9] Jennifer Lai[4] Sumeet Asrani[10] Consuelo Soldevila-Pico[11] Mary Thomson[12] Arun Jesudian[13] Adam Deising[14] Sonali Paul[15] Douglas Simonetto[16] Margarita German[17] Mehnush Hameie[5] Dyanna Gregory[18] Lisa VanWagner[18], [1]University of Texas Southwestern, [2]Northwestern Memorial Hospital/ Northwestern University, [3]University of Arizona, [4]University of California San Francisco, [5]Northwestern

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University, [6]Columbia University Medical Center, [7]University of Wisconsin School of Medicine and Public Health, [8]Gilead Sciences, [9]Stanford University Medical Center, [10]Liver Consultants of Texas, [11]University of Florida, [12]University of Minnesota, [13]Weill Cornell Medicine, [14]Scripps Clinic, [15]University of Chicago Medical Center, [16]Mayo Clinic Rochester, [17]University of Wisconsin, [18]University of Texas Southwestern Medical Center

Background: TIPS is a key intervention for portal hypertension, and MELD-based scores are widely used to assess procedural risk. While they were developed to predict post-TIPS mortality, they also predict mortality in cirrhosis. Their ability to distinguish TIPS-attributable deaths (TAD) from non-attributable deaths (TNAD) remains unclear. We aim to evaluate this distinction. **Methods:** Advancing Liver Therapeutic Approaches in Portal Hypertension (ALTA) is a multi-center prospective cohort study across 13 U.S. centers of adults ($\geq$18 years) who were scheduled for TIPS between 7/2019-1/2025. Those who underwent successful TIPS creation with complete data for modeling were included; those with unknown cause of death were excluded. A committee of interventional radiologists and hepatologists adjudicated deaths as TIPS-related (TAD) or non-attributable (TNAD) by unanimous agreement. Fine-Gray subdistribution hazard models were used to assess associations between MELD scores and TAD/TNAD. TAD/transplant and TNAD/transplant were treated as competing risks in the TNAD and TAD models, respectively. **Results:** A total of 609 participants (mean age 57.2 years; 44.3% female; 82.2% White; 20.6% Hispanic) were included. TNAD group was older (67.4 vs. 61.8 years, $p = 0.02$); other demographics were similar between groups. Mean follow-up was 398 days. Overall post-TIPS mortality was 17.1% ($n = 104$), with 26.9% ($n = 28$) attributable to TIPS. Most common causes of TAD death were multiple organ system failure (28%), renal failure (14%), and cardiovascular and infection (11% each). TNAD were infection (18%), multiple organ system failure (14%), and malignancy (12%). Time to death was shorter in TAD vs. TNAD (110.6 vs. 366.1 days; $p < 0.001$). In adjusted models, all MELD scores were significantly associated with overall mortality and TAD but not associated with TNAD (Table). In stratified analyses, MELD variants were associated with increased risk of TAD in females, non-Hispanics, TIPS done for ascites, and patients with cirrhotic portal hypertension. Traditional MELD was associated with increased risk of TAD in patients in alcohol-associated cirrhosis. MELD-Na was associated with increased risk of TAD in patients with noncirrhotic portal hypertension. **Conclusion:** In this large multicenter study, MELD scores predicted overall and TIPS-attributable mortality, but not non-TIPS-related deaths. These findings suggest that MELD-based risk stratification specifically reflects vulnerability to TIPS-related complications rather than general post-procedure mortality. Risk assessment tools should account for this distinction to better guide TIPS candidacy and counseling.

Table. Subdistribution hazard ratios (95% CI) for MELD score variants stratified by clinical characteristics among TIPS recipients

	MELD		MELD-Na		MELD 3.0	
	TAD	TNAD	TAD	TNAD	TAD	TNAD
Overall	**1.10 (1.05, 1.16)**	1.02 (0.98, 1.06)	**1.10 (1.04, 1.16)**	1.02 (0.98, 1.06)	**1.10 (1.04, 1.18)**	1.03 (0.99, 1.07)
Sex						
Male	1.08 (0.99, 1.19)	1.03 (0.98, 1.09)	1.08 (0.99, 1.18)	1.03 (0.97, 1.08)	1.09 (1, 1.18)	1.03 (0.99, 1.08)
Female	**1.12 (1.07, 1.17)**	0.99 (0.93, 1.07)	**1.14 (1.07, 1.21)**	1.01 (0.96, 1.07)	**1.17 (1.08, 1.26)**	1.02 (0.96, 1.08)
Race						
White	**1.1 (1.05, 1.15)**	1.01 (0.97, 1.06)	**1.1 (1.05, 1.17)**	1.02 (0.97, 1.06)	**1.11 (1.03, 1.18)**	1.02 (0.99, 1.07)
Non-white	NA	1.02 (0.97, 1.18)	NA	1.06 (1.02, 1.11)	NA	1.07 (0.94, 1.22)
Ethnicity						
Non-Hispanic	**1.09 (1.03, 1.16)**	1.03 (0.99, 1.07)	**1.05 (1.01, 1.16)**	1.04 (1, 1.08)	**1.1 (1.02, 1.18)**	1.04 (1, 1.09)
Hispanic	1.21 (0.94, 1.55)	0.84 (0.71, 0.99)	1.23 (0.96, 1.56)	0.85 (0.73, 0.99)	1.18 (0.96, 1.46)	0.97 (0.79, 1)
TIPS Indication						
Ascites	**1.12 (1.06, 1.18)**	0.99 (0.92, 1.06)	**1.11 (1.03, 1.2)**	0.99 (0.93, 1.05)	**1.12 (1.03, 1.23)**	1 (0.94, 1.06)
Varices	1.01 (0.87, 1.18)	0.95 (0.7, 1.3)	1.03 (0.91, 1.16)	0.98 (0.8, 1.24)	1.06 (0.95, 1.19)	1.0 (0.94, 1.2)
Other indication	1.19 (0.95, 1.44)	1.03 (0.96, 1.11)	**1.27 (1.04, 1.54)**	1.04 (0.97, 1.11)	**1.26 (1.01, 1.56)**	1.04 (0.97, 1.11)
Source of portal hypertension						
Non-cirrhotic	**1.1 (1.04, 1.16)**	1.01 (0.96, 1.05)	**1.23 (1.01, 1.5)**	1.11 (0.98, 1.26)	1.34 (0.95, 1.9)	1.15 (0.97, 1.36)
Cirrhotic	1.01 (0.96, 1.06)	1.01 (0.92, 1.1)	**1.09 (1.03, 1.16)**	1.01 (0.97, 1.06)	**1.1 (1.03, 1.18)**	1.02 (0.97, 1.06)
Cirrhosis etiology						
MASLD	1.02 (0.85, 1.22)	1 (0.91, 1.1)	1.04 (0.91, 1.19)	1.02 (0.94, 1.1)	1.03 (0.9, 1.18)	1.02 (0.94, 1.09)
Alcohol	**1.16 (1.01, 1.33)**	1.01 (0.91, 1.11)	1.11 (0.97, 1.27)	1.02 (0.94, 1.11)	**1.15 (1.01, 1.31)**	1.02 (0.94, 1.1)
Viral hepatitis	0.89 (0.6, 1.32)	0.86 (0.5, 1.46)	0.96 (0.61, 1.14)	0.91 (0.66, 1.21)	0.95 (0.6, 1.12)	0.94 (0.72, 1.21)
Other cirrhosis etiology	**1.11 (1.06, 1.16)**	1.02 (0.95, 1.1)	**1.14 (1.09, 1.19)**	1 (0.93, 1.07)	**1.18 (1.11, 1.26)**	1.02 (0.95, 1.1)

All models adjusted for sex, race, ethnicity, TIPS indication, portal hypertension etiology, and TIPS urgency
Values in bold are statistically significant

Disclosures: Heesoo Yoo: Nothing to Disclose, Justin Boike: W. L. Gore and Associates: Grant/Research Support, Eurofins Transplant Genomics: Advisor, Echosens: Consultant, W. L. Gore and Associates, Inc.: Consultant, Michael Fallon: Nothing to Disclose, K. Pallav Kolli: Nothing to Disclose, Bartley Thornburg: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Advisor, Carrie Frenette: Gilead Sciences: Employee, Aparna Goel: Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Sumeet Asrani: Nothing to Disclose, Consuelo Soldevila-Pico: Nothing to Disclose, Mary Thomson: Nothing to Disclose, Arun Jesudian: Salix Pharmaceuticals: Consultant, Salix Pharmaceuticals: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Orphalan: Consultant, Mallinckrodt Pharmaceuticals: Consultant, Mallinckrodt Pharmaceuticals: Speaking and Teaching, Adam Deising: Nothing to Disclose, Sonali Paul: Intercept: Grant/Research Support, Target PharmaSolutions: Grant/Research Support, Eli Lilly: Stock - publicly traded company, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant, Margarita German: Nothing to Disclose, Mehnush Hameie: Nothing to Disclose, Dyanna Gregory: Nothing to Disclose, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights:

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2404 | PHASE 1, SINGLE-ASCENDING DOSE RESULTS: FROM THE PHIN-001 STUDY OF PHIN-214 IN COMPENSATED AND DECOMPENSATED PATIENTS WITH CIRRHOSIS

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Background: Portal hypertension is a key driver of decompensation in cirrhosis patients, yet effective chronic pharmacologic interventions are limited. PHIN-214 is a novel vasopressin analogue exhibiting partial V1a receptor agonism, reduced V2 activity, and a broad therapeutic index, that is being developed for subcutaneous, once daily self-injection for out-patient management of portal hypertension and associated complications. **Methods:** PHIN-001 (NCT05490888) is an ongoing phase 1 dose-optimization study evaluating single and multiple doses of PHIN-214 in adults with Child-Pugh (CP) A and B cirrhosis. Primary objectives include safety, tolerability, pharmacokinetic, and pharmacodynamic assessments. **Results:** Fifteen (15) subjects, 8 men and 7 women, were treated across eight (8) single-ascending dose levels. The subjects were mostly CP-A (73%) with a mean MELD-Na score of 10 (range 6-14) and an average age of 56 (range 42-72). Overall exposure to PHIN-214 and PHIN-156 (the active PHIN-214 metabolite) appear dose-proportional. PHIN-214 was generally well tolerated with a safety profile consistent with on-target V1a engagement. Possibly or likely drug-related adverse events included injection site blanching, abdominal pain/cramping, diarrhea, hematochezia and hypertension. An asymptomatic decrease in serum sodium was observed in all cases with a mean decrease of 6.2 (mmol/L) (95% CI: 4.6, 7.8) and mean minimum of 133 mmol/L (95% CI: 131.6, 134.4). Evidence of potential clinical benefit was demonstrated by improved estimated glomerular filtration rate (eGFR) in all subjects, irrespective of CP classification or baseline eGFR. Mean eGFR rose 40.2% within 12 hours (95% CI: 28–52.5%) and was sustained up to 24 hours in most cases. A strong positive correlation ($r > 0.80$, $P < 0.01$) was observed between PHIN-156 and eGFR improvement, particularly at higher doses. The single ascending dose phase of the study is complete; the multi-ascending dose phase is now enrolling to assess safety and sustained benefit with 28-day once daily dosing. **Conclusion:** A single subcutaneous dose of PHIN-214 was safe, well tolerated and showed a physiologic profile consistent with V1a activation. Early signs of clinical activity as evidenced by improvement in eGFR and a strong correlation with PHIN-156 exposure support continued development of PHIN-214 as a once-daily, self-administered treatment for portal hypertension in cirrhosis. Complete single-dose and emerging multi-dose data will be presented.

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2405 | BARIATRIC SURGERY IS ASSOCIATED WITH REDUCED RISK OF HEPATIC DECOMPENSATION AND IMPROVED SURVIVAL IN OBESE PATIENTS WITH CIRRHOSIS: A PROPENSITY-MATCHED TRINETX STUDY

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Background: Obesity often coexists with chronic liver disease and cirrhosis, yet the impact of bariatric surgery on decompensation remains unclear.We aimed to see whether bariatric surgery lowers decompensation risks in obese cirrhotic adults, using real-world data. **Methods:** We queried the TriNetX Research Network (101 healthcare organizations) to identify adults ($\geq$ 18 years) with a diagnosis of cirrhosis (ICD-10: K74 or K70.3) and obesity (E66) between Jan 1, 2010 and Apr 28, 2025. Patients with prior liver transplant, hepatic or gastric malignancy, or pregnancy were excluded. Two cohorts were defined: (1) those undergoing bariatric surgery (n = 4,411) and (2) non-surgical controls without weight loss intervention (n = 234,617). After 1:1 propensity score matching on age, sex, race, labs (Na, INR, total bilirubin), BMI, and comorbidities, 4,286 patients were retained per group. Outcomes assessed over a 3-year follow-up included ascites (R18), variceal bleeding (I85.01/I85.11), spontaneous bacterial peritonitis (SBP, K65.2), hepatocellular carcinoma (HCC, C22), hepatorenal syndrome (HRS, K76.7), and hepatic encephalopathy (HE, K72.9). **Results:** Following propensity score matching, the final study included 8,572 patients (4,286 per group). The cohorts were well-balanced in terms of age (mean 50 $\pm$ 12.2 years), sex (71.4% female), and metabolic comorbidities (94.9% with endocrine/metabolic disease). Post-matching standardized differences for all variables were < 0.01, indicating excellent covariate balance. During a 3-year follow-up, patients in the bariatric surgery group experienced significantly fewer liver-related decompensation events compared to those without any intervention. Ascites developed in 9.1% of the bariatric group versus 19.0% in the control group (HR 2.49, 95% CI 2.20–2.81; $p < 0.001$). Spontaneous bacterial peritonitis occurred in 0.8% vs 2.9% (HR 4.45, 95% CI 3.03–6.53; $p < 0.001$), and variceal bleeding was reduced among surgical patients (0.5% vs 2.9%; HR 6.38, 95% CI 4.09–9.96; $p < 0.001$). Other significant differences included a reduced incidence of hepatic encephalopathy in the bariatric cohort (4.2% vs 12.5%; HR 3.56, 95% CI 3.00–4.21; $p < 0.001$), hepatocellular carcinoma (1.8% vs 3.9%; HR 2.43, 95% CI 1.86–3.19; $p < 0.001$), and hepatorenal syndrome (0.9% vs 3.0%; HR 4.04, 95% CI 2.80–5.82; $p < 0.001$). Kaplan–Meier analysis showed significantly higher event-free survival across all outcomes in the bariatric cohort, three year event free survival were notably higher for ascites (89.6% vs 77.3%), HE (95.0% vs 84.6%), and HCC (97.9% vs 95.2%). **Conclusion:** Among patients with cirrhosis and obesity, bariatric surgery is associated with significantly reduced risk of hepatic decompensation with ascites, encephalopathy, variceal bleeding, and HCC. These findings suggest a possible disease-modifying role of metabolic surgery in selected cirrhotic populations and support prospective evaluation.

Figure 1:Bariatric surgery was associated with significantly lower 3-year cumulative risk for multiple complications:

Outcome	Non-intervention Cohort (%)	Bariatric Cohort (%)	Hazard Ratio (95% CI)	p-value
Ascites	19.0	9.1	2.49 (2.20–2.81)	<0.001
Variceal Bleed	2.9	0.5	6.38 (4.09–9.96)	<0.001
SBP	2.9	0.8	4.45 (3.03–6.53)	<0.001
HCC	3.9	1.8	2.43 (1.86–3.19)	<0.001
HRS	3.0	0.9	4.04 (2.80–5.82)	<0.001
HE	12.5	4.2	3.56 (3.00–4.21)	<0.001

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2406 | TARGETING THE HIDDEN RISK: RIFAXIMIN LOWERS THE RISK OF NEW ONSET OF HEPATIC ENCEPHALOPATHY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AND SPLENORENAL SHUNT RECEIVING LENVATINIB

Takumi Kawaguchi[1] Shigeo Shimose[1] Hideki Iwamoto[2] Takashi Niizeki[1] Tomotake Shirono[1] Etsuko Moriyama[1], [1]Kurume University School of Medicine, [2]Iwamoto Internal Medicine Clinic

Background: Lenvatinib effectively inhibits tumor angiogenesis and growth of hepatocellular carcinoma (HCC), leading to an improvement in prognosis. However, hepatic encephalopathy (HE) is a serious adverse event of lenvatinib that requires discontinuation of the medication. Rifaximin is a minimally absorbed oral antimicrobial agent, which reduces the risk of recurrence of HE in patients with liver cirrhosis. The aim of this study is to investigate risk factors for HE in patients with HCC receiving lenvatinib. We also explored the usefulness of rifaximin for preventing HE and the dosage of lenvatinib. **Methods:** This is a two-center retrospective observational cohort study. We enrolled 216 patients with HCC receiving lenvatinib. HE was diagnosed according to the presence of asterixis and/or mental symptoms from disorientation through the coma. Before the initiation of LEN, patients with hyperammonemia ($\geq$80 μg/dL) were treated with oral rifaximin at a dose of 1,200 mg/day. The incidence of HE was evaluated (observational period 480 [1-3,657] days). The dosage of lenvatinib was assessed by relative dose intensity (RDI). A decision-tree algorithm was constructed to reveal the profiles associated with HE. **Results:** The incidence of HE was 8.8%. There was no significant difference in age, sex, BMI, and tumor stage between the HE and non-HE groups. Although there was no significant difference in blood ammonia level between the two groups, the prevalence of splenorenal shunt was significantly higher in the HE groups compared to the non-HE group. A multivariate analysis demonstrated that a splenorenal shunt was identified as an independent risk factor for HE (HR 16.4, 95%CI 5.2-52.6, $P < 0.001$). Decision-tree analysis revealed that, in the patients with splenorenal shunt and ALBI grade 2, HE occurred in 66.6% of the patients with no refaxmin. In contrast, 16.6% developed HE in the patients with rifaximin. Furthermore, the prevalence of RDI $>$70% was 20.0% and 66.7% in the patients with no rifaximin and rifaximin, respectively. **Conclusion:** Splenorenal shunt was an independent risk factor for HE in patients with HCC receiving lenvatinib. Moreover, rifaximin prevented HE and contributed to sufficient dosage of lenvatinib in patients with HCC, splenorenal shunt, and ALBI grade 2. Thus, rifaximin may be beneficial for the management of HCC patients receiving lenvatinib, especially in HCC patients with splenorenal shunt and hepatic dysfunction.

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2407 | TIMING MATTERS: COMPARATIVE ANALYSIS OF EARLY VS. LATE TIPS IN VARICEAL BLEED MANAGEMENT

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Background: Acute variceal bleeding is a life-threatening complication of portal hypertension in cirrhosis. Despite initial endoscopic and pharmacologic therapy, some patients require early or rescue Transjugular Intrahepatic Portosystemic Shunt (TIPS) to control bleeding and prevent rebleeding. The goal of this study is to identify the outcomes associated with delayed TIPS in acute variceal bleed. **Methods:** This is a retrospective cohort study using National Inpatient Sample data including adult patients hospitalized between 2019 and 2022 with history of cirrhosis and presenting with acute variceal bleed. The study compares patients who underwent early TIPS (between Day 0 and Day 2) to late TIPS (from Day 3 and onward) and assessed risk factors including demographics, chronic medical conditions and inpatient complications. Statistical analyses were all performed using STATA software. **Results:** Of the 11,740 patients with cirrhosis presenting with a variceal bleed, a majority of patients were males, however gender was not associated time of TIPS ($p > 0.05$). In general, the patients who underwent late TIPS were on average older (56.6 vs. 54.9 years old, $p < .05$). There was no statistical significance of race on time of TIPS ($p < 0.05$). Of the other comorbidities assessed in Table 1, we found later TIPS in patient with congestive heart failure (OR = 0.706 (0.521-0.958)), end-stage renal disease (OR = 0.447 (0.231-0.863)), obesity (OR = 0.792 (0.639-0.980)), cancer (OR = 0.648 (0.437-0.962)), and Charlson Comorbidity Index (CCI) of 7 or more (OR 0.522

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(0.392-0.696)). Patients with a CCI lower than 3 were more likely to have early TIPS (OR = 1.312 (1.111-1.550)). As outlined in Table 2, a statistically significant greater rate of mechanical ventilation and mortality was seen patients with early TIPS; there was no difference in the number of patients requiring blood transfusion ($p > 0.05$). Patients with later TIPS has greater average length of stay 12.2 days versus 7.4 days for earlier TIPS ($p < 0.05$). **Conclusion:** Our study showed that patients with later TIPS although associated with greater length of stay and cost, was associated with lower mortality and may potentially indicate the benefits of postponed TIPS. Furthermore, these patients who underwent late TIPS also had greater comorbidities. Our retrospective study may find this greater mortality correlation in early TIPS as it may potentially represent a more critical presentation and further studies are necessary to explore the benefits of delayed TIPS.

Table 1: Demographics and Comorbidities

	Early TIPS (n = 7,365)	Late TIPS (n = 4,375)	p value	Odds Ratio (95% Confidence Interval)
Mean Age, years	54.9	56.5	0.001	-
Gender, n				
Male	5020 (68.2%)	3000 (68.6%)	0.838	0.981 (0.817-1.778)
Female	2345 (31.8%)	1375 (31.4%)		
Race, n				
White	4695 (63.7%)	2885 (65.9%)	0.302	0.908 (0.756-1.091)
Black	345 (4.7%)	205 (4.7%)	0.999	1.000 (0.686-1.456)
Hispanic	1450 (19.7%)	850 (19.4%)	0.882	1.017 (0.817-1.264)
Asian or Pacific Islander	195 (2.6%)	80 (1.8%)	0.205	1.460 (0.811-2.629)
Native American	175 (2.4%)	100 (2.3%)	0.886	1.041 (0.605-1.789)
Other	285 (3.9%)	165 (3.8%)	0.904	1.027 (0.665-1.587)
Hypertension, n	2600 (35.3%)	1435 (32.8%)	0.229	1.118 (0.932-1.341)
Congestive Heart Failure, n	520 (7.1%)	425 (9.7%)	0.025	0.706 (0.521-0.958)
COPD, n	565 (7.7%)	395 (9.0%)	0.251	0.837 (0.618-1.135)
ESRD, n	80 (1.1%)	105 (2.4%)	0.014	0.447 (0.231-0.863)
Diabetes, n	2380 (32.3%)	1460 (33.4%)	0.592	0.953 (0.800-1.136)
Smoking History, n	3295 (44.7%)	1815 (41.5%)	0.129	1.141 (0.962-1.356)
Obesity, n	1195 (16.2%)	860 (19.7%)	0.032	0.792 (0.589-0.980)
Cancer, n	250 (3.4%)	225 (5.1%)	0.031	0.648 (0.437-0.962)
Charlson Comorbidity Index, n				
3 or less	3480 (47.3%)	1775 (40.6%)	0.001	1.312 (1.111-1.550)
4	2085 (28.3%)	1140 (26.1%)	0.223	1.121 (0.933-1.347)
5	975 (13.2%)	695 (15.9%)	0.089	0.808 (0.642-1.017)
6	350 (4.8%)	255 (5.8%)	0.265	0.806 (0.551-1.179)
7 or more	475 (6.4%)	510 (11.7%)	<0.001	0.522 (0.392-0.696)

Table 2: Hospitalization Outcomes

	Early TIPS (n = 7,365)	Late TIPS (n = 4,375)	p value	Odds Ratio (95% Confidence Interval)
Mechanical Ventilation, n	3265 (44.3%)	1260 (28.8%)	<0.001	1.969 (1.639-2.365)
Blood Transfusion, n	2470 (33.5%)	1490 (34.1%)	0.804	0.977 (0.812-1.174)
Mortality, n	1205 (16.4%)	400 (9.1%)	<0.001	1.944 (1.491-2.535)
Length Of Stay, days	7.4	12.2	<0.001	-
Cost of Admission, dollars	205680.0	261323.8	<0.001	-

Disclosures: Het Patel: Nothing to Disclose, Hammad Liaquat: Nothing to Disclose

2408 | EPIDEMIOLOGY AND OUTCOMES OF SYSTEMIC MYCOSES IN HOSPITALIZED PATIENTS WITH CIRRHOSIS: A 5-YEAR NATIONAL INPATIENT SAMPLE ANALYSIS

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Background: Patients with cirrhosis are prone to numerous complications, chief among them being infections. Although bacterial infections in this cohort have been well studied, there is a paucity of data on the impact of fungal infections in this population. We sought to establish the prevalence of different fungal infections in hospitalized patients with cirrhosis and the associated inpatient outcomes. **Methods:** We analyzed the National Inpatient Sample (NIS) across five years (2018-2022) to identify adult hospitalizations with a primary diagnosis of cirrhosis using validated ICD-10 codes. Subsequently, fungal infections were identified using diagnostic codes for systemic mycoses. Outcomes of interest included in-hospital mortality, length of stay (LOS), and total hospital cost. Survey-weighted logistic and linear regressions adjusted for demographics, comorbidities, ICU-level care, and hospital characteristics. Statistical analysis was done using STATA version 18. **Results:** Among an estimated 4.4 million weighted cirrhosis hospitalizations, 2.3% had a fungal infection. These patients had significantly increased mortality (15.2% vs. 6.7%), longer LOS (13.9 vs. 6.7 days), and greater costs resulting from admission ($192,567 vs. $93,218). Fungal infection was independently associated with increased adjusted odds of mortality (aOR 1.50, 95% CI 1.42–1.59), longer LOS ($\beta = 0.56$, $p < 0.001$), and higher costs ($\beta = 0.54$, $p < 0.001$). Subgroup analysis demonstrated that the association with mortality was still significant even when accounting for elective (aOR 2.46) and non-elective (aOR 2.23) admissions. **Conclusion:** Systemic mycoses are associated with markedly worse outcomes in this cohort of hospitalized cirrhotic patients. This underscores the need for early recognition and aggressive management, even in elective admissions, in this cohort, to reduce the burden of fungal-related morbidity and mortality.

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2409 | VALIDATING THE URINARY CHLORIDE DIPSTICK AS A POTENTIAL BIOMARKER FOR PREDICTING DECOMPENSATION IN PATIENTS WITH CIRRHOSIS

Susan Fischer[1] Britt van Ruijven[2] Govert Veldhuijzen[3] Annarein Kerbert[1] Michael Klemt-Kropp[4] Tom Gevers[2] Anton Jan Zonneveld[1] Minneke Coenraad[1] Kirill Basiliya[1], [1]Leiden University Medical Center, [2]Maastricht UMC+, [3]Gelre Ziekenhuizen, [4]Noordwest Ziekenhuisgroep

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Background: Easily applicable biomarkers to predict acute decompensation in patients with cirrhosis is an unmet need. While reduced urinary sodium excretion reflects disease severity in patients with cirrhosis, it is not feasible for routine use outside clinical settings. Urinary chloride excretion can be easily measured using a dipstick. This study examines the correlation between dipstick-measured urine chloride and urinary sodium/chloride concentrations, and explores its potential as a predictive biomarker for future decompensation in cirrhosis. **Methods:** In this prospective multicenter cohort study, consecutive hospitalized adult patients with cirrhosis were enrolled from four Dutch hospitals. A single urine sample was collected for dipstick-based chloride measurement with simultaneous laboratory analysis of urinary sodium and chloride. Clinical data were recorded at inclusion, with prospective follow-up at 3 months to assess the occurrence of acute decompensation and mortality. Primary outcome was the correlation between dipstick and lab-based urine electrolytes, secondary outcome was the predictive value of dipstick-measured chloride for acute decompensation of cirrhosis. **Results:** A total of 100 patients (62% male), were included. Median age was 64 years [IQR 53-70] and median MELD score was 13 [8-19]. At enrollment, 49 patients (49%) were acutely decompensated. Dipstick-measured urinary chloride in all patients showed strong positive correlations with laboratory urinary chloride concentration (Spearman's $\rho = 0.801$, $p < 0.001$) and urinary sodium concentration ($\rho = 0.757$, $p < 0.001$). Among patients with available follow-up data (n = 62), 21 patients (34%) developed a new decompensating event within 90 days. Seven patients (11%) died, all due to acute-on-chronic liver failure (ACLF). In univariate logistic regression, both urine sodium concentration and dipstick chloride concentration <50 mmol/L were associated with an increased risk of decompensation within 90-days (OR 6.00, CI 1.71-21.03 and OR 3.81, CI 1.09–13.37 respectively). **Conclusion:** Dipstick-measured urinary chloride concentration strongly correlates with laboratory urinary sodium and -chloride concentration, and low laboratory urinary sodium concentration and dipstick-measured urinary chloride concentration are associated with an increased risk of new decompensation in patients with cirrhosis. Given its simplicity, low-costs and non-invasive properties, urine chloride dipstick testing may serve as a practical tool for early risk stratification in the outpatient setting. Further clinical trials are warranted to evaluate the role of dipstick-measured urinary chloride-guided therapy in patients with cirrhosis.

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2410 | COMPARATIVE OUTCOMES FOLLOWING AKI VERSUS NON-AKI HOSPITALIZATIONS IN PATIENTS WITH DECOMPENSATED CIRRHOSIS: AN ANALYSIS OF POST-DISCHARGE TRAJECTORIES

Chip Bowman[1] Giuseppe Cullaro[1] Elizabeth Verna[2], [1]Columbia University, [2]Columbia University Medical Center

Background: Acute kidney injury (AKI) complicates 20-50% of liver disease hospitalizations, yet comparative post-discharge outcome data remain limited. Gaps persist regarding differential impacts of AKI versus non-AKI hospitalizations on paracentesis requirements, readmission patterns, transplant rates, and renal recovery trajectories, significantly limiting evidence-based post-discharge care. **Methods:** We conducted a retrospective cohort study of 422 hospitalizations among liver transplant candidates at Columbia University. Baseline values (7-365 days before admission) were obtained from the EHR: serum creatinine (sCr), total bilirubin (Bili), INR, albumin, sodium, and ascites severity from imaging. AKI was defined as a $\geq$50% creatinine (sCr) increase during hospitalizations from baseline sCr. We identified 211 AKI hospitalizations and propensity matched to 211 non-AKI hospitalizations based on baseline sCr/Bili, INR, albumin, sodium, and ascites severity, length of stay (LOS), and age. Cox regression evaluated rates of 90-day readmission, binomial regression assessed 90-day number of large-volume paracenteses (LVPs), competing risk analysis evaluated transplant rates accounting for death, and linear mixed-effects modeling examined post-discharge sCr trajectories. **Results:** Compared to non-AKI hospitalizations, AKI hospitalizations had longer LOS (12v10 days), lower baseline Bili (3.1v3.7 mg/dL), higher peak sCr (2.7v1.4 mg/dL), and higher sCr at discharge (1.8v1.2 mg/dL) ($p < 0.05$ for all). Groups were otherwise similar for baseline sCr, INR, albumin, sodium, MELD3.0, ascites grade, need for paracentesis during hospitalization, discharge Bili, INR, sodium, and ascites grade ($p > 0.05$ for all). Post-discharge there were no differences in paracentesis frequency (IRR 0.5, $p = 0.1$) or 90-day readmission rates (HR 0.9, $p = 0.7$). Competing risk analysis revealed AKI hospitalizations reduced transplant probability (SHR 0.63, $p = 0.007$) while increasing mortality risk (SHR 1.59, $p = 0.04$). Longitudinal mixed-effects modeling showed no differences in sCr trajectory but sustained sCr elevations in the AKI group at 7-day ($\beta = 0.5$, $p = 0.004$) and 90-day ($\beta = 0.4$, $p = 0.021$). **Conclusion:** Among patients with decompensated cirrhosis, AKI hospitalizations are linked to lower transplant rates, higher mortality, and persistent renal dysfunction despite similar post-discharge

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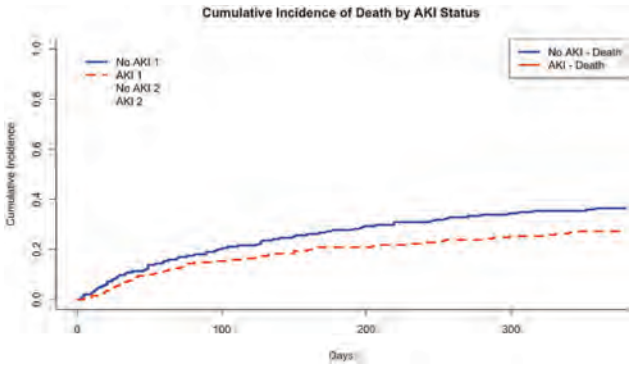
care utilization. These findings suggest AKI during hospitalization as a high-risk subgroup that may benefit from targeted post-discharge interventions to improve outcomes.



Disclosures: Chip Bowman: Nothing to Disclose, Giuseppe Cullaro: Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant, Elizabeth Verna: Nothing to Disclose

2411 | IN-HOSPITAL OUTCOMES AFTER PCI IN PATIENTS WITH CIRRHOSIS: A CONTEMPORARY NATIONWIDE INPATIENT SAMPLE ANALYSIS (2016–2022)

Abdullah Hafeez[1] Omar Alkasabrah[1] Ritu Tated[2] Siddharth Agrawal[1] Kriti Soni[3] Hritvik Jain[4] Faiza Jajja[1] Muhammad qasim Chaudhry[1] Sadia Rekhum[5] Tanuj Sharma[6], [1]NYMC/Landmark Medical Center, [2]New York Medical College, [3]MD, [4]All India Institute of Medical Sciences, Jodhpur, India, [5]Rahbar Medical And Dental College, [6]NYMC/Landmark Medical College

Background: Cirrhosis complicates the management of coexisting coronary artery disease, present in up to 37% of affected patients. Its coagulopathic and hemodynamic challenges raise concerns about the safety of percutaneous coronary intervention (PCI). Despite advances in hepatology and cardiology, large-scale, contemporary data on PCI outcomes in patients with cirrhosis remain limited **Methods:** We conducted a retrospective cohort study using the National Inpatient Sample (NIS) from 2016 to 2022, identifying adult patients ($\geq$18 years) who underwent PCI using ICD-10-PCS codes. Cirrhosis was identified via validated ICD-10-CM codes. The primary outcome was in-hospital mortality. Secondary outcomes included atrial fibrillation, heart failure, bleeding complications, and respiratory failure. Multivariable logistic regression was performed adjusting for age, sex, race, comorbidities, and hospital characteristics. **Results:** Of the 3,134,735 patients who underwent PCI between 2016 and 2022, 23,005 (0.73%) had a diagnosis of liver cirrhosis. Patients with cirrhosis were more likely to have comorbidities such as diabetes mellitus (64.6% vs. 51.2%), anemia (33.3% vs. 13.9%), chronic kidney disease stage $\geq$4 (29.6% vs. 17.1%), and coagulation disorders (22.6% vs. 6.3%) compared to those without cirrhosis. They also had significantly longer hospital stays (7.6 vs. 3.9 days, $P<0.001$) and were more frequently admitted to teaching hospitals. After multivariable adjustment, cirrhosis was independently associated with higher odds of in-hospital mortality (OR 1.28, 95% CI 1.22–1.37, $P<0.001$), atrial fibrillation (OR 1.09, 95% CI 1.06–1.13, $P<0.001$), heart failure (OR 1.27, 95% CI 1.23–1.31, $P<0.001$), and bleeding complications (OR 1.29, 95% CI 1.23–1.36, $P<0.001$). Although a lower odds ratio was observed for respiratory failure, this is likely attributable to selection bias, overlapping diagnostic codes, or inherent limitations of administrative data, rather than a true protective effect. **Conclusion:** In this large, nationally representative analysis, cirrhosis was independently associated with worse in-hospital outcomes following PCI, underscoring the need for liver-specific risk stratification and individualized, targeted pre-procedural planning in this high-risk population.

Table 1. Baseline Characteristics and In-Hospital Outcomes of PCI Patients With and Without Cirrhosis

Variable	No Cirrhosis (%)	Cirrhosis (%)	P value
Baseline Characteristics			
Number of Observations	99.27 (n=3,109,730)	0.73 (n=23,005)	—
Age 50–64	35.60	40.10	<0.001
Age 65–79	39.60	47.80	<0.001
Male	67.30	68.80	<0.001
Medicare/Medicaid as Primary Payer	63.40	76.40	<0.001
Hypertension	82.80	87.70	<0.001
Diabetes Mellitus	51.20	64.60	<0.001
Hyperlipidemia	67.50	57.60	<0.001
CAD	91.80	92.20	<0.001
Anemia	13.90	33.30	<0.001
CKD ≥ Stage 4	17.10	29.60	<0.001
Alcohol Use	2.80	15.70	<0.001
Coagulation Disorders	6.30	22.60	<0.001
Length of Stay (mean ± SD)	3.9 ± 5.1	7.6 ± 6.4	<0.001
In-Hospital Outcomes (Multivariable Analysis)			
Death (OR 1.28, 95% CI 1.22–1.37)	Reference	Increased	<0.001
Heart Failure (OR 1.27, 95% CI 1.23–1.31)	Reference	Increased	<0.001
Bleeding Complication (OR 1.29, 95% CI 1.23–1.36)	Reference	Increased	<0.001
Respiratory Failure (OR 0.78, 95% CI 0.74–	Reference	Decreased	<0.001

Disclosures: Abdullah Hafeez: Nothing to Disclose, Omar Alkasabrah: Nothing to Disclose, Ritu Tated: Nothing to Disclose, Siddharth Agrawal: Nothing to Disclose, Kriti Soni: Nothing to Disclose, Hritvik Jain: Nothing to Disclose, Faiza Jajja: Nothing to Disclose,

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Muhammad qasim Chaudhry: Nothing to Disclose, Sadia Rekhum: Nothing to Disclose, Tanuj Sharma: Nothing to Disclose

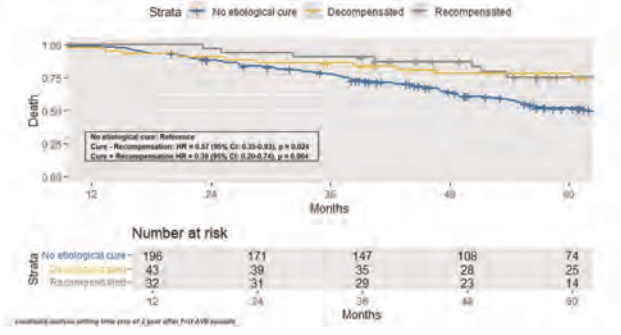
2412 | RECOMPENSATION IMPROVE SURVIVAL AND REDUCES FURTHER DECOMPENSATION IN A NATIONWIDE COHORT OF PATIENTS WITH ACUTE VARICEAL BLEEDING

May Xuan Goh[1] Alyssa Sim[2] Ian Yang Liew[2] Xin En Goh[3] Guan Wee Wong[4] Wei Rong Benjamin Tay[4] Pik Eu Jason Chang[5] Poh Hui Wee[5] Margaret Teng[6] Sophia Delu Lin[6] Garrett Kang[7] Guadalupe Garcia-Tsao[8] Juan Gonzalez-Abraldes[9] Yu Jun Wong[10], [1]Yong Loo Lin School of Medicine, NUS, [2]Department of Gastroenterology & Hepatology, Tan Tock Seng Hospital, Singapore, [3]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, [4]Division of Gastroenterology & Hepatology, Department of Medicine, Ng Teng Fong General Hospital, Si, [5]Department of Gastroenterology & Hepatology, Singapore General Hospital, Singapore, [6]Division of Gastroenterology & Hepatology, National University Hospital, Singapore, [7]Department of Gastroenterology & Hepatology, Sengkang General Hospital, Singapore, [8]Section of Digestive Disease, Yale University of Medicine, New Haven, USA, [9]Liver Unit, University of Alberta, Edmonton, Canada, [10]Department of Gastroenterology & Hepatology, Changi General Hospital, Singapore

Background: The natural history and clinical impact of recompensation following acute variceal bleeding (AVB) remains poorly understood. We aimed to evaluate the predictors and prognostic impact of recompensation in AVB patients. **Methods:** A nationwide cohort of well-characterized hospitalized AVB patients (2015 to 2020) were followed up (PMID:38381716). Patients with prior AVB or prior HCC were excluded. Primary predictor was recompensation, defined by the Baveno-VII (B7) criteria. Additionally, expanded Baveno-VII (eB7) criteria were evaluated for patients on low-dose diuretics and/or lactulose/rifaximin for 12 months. Landmark analysis was performed to compare the clinical outcomes after index AVB episode, with and without recompensation, by setting time zero at 1 year post AVB. **Results:** From 989 patients with AVB, 377 patients without prior AVB or HCC were included for analysis. 37% presented with more than 1 decompensating events at index AVB. While half of the cohort (53%) had potentially curable etiology of cirrhosis (28% were viral; 25% were alcohol), only 82 (22%) achieved etiological cure within a year of AVB. Among those achieving etiological cure, 32 (39%) achieved recompensation by B7 criteria, and 41 (50%) achieved recompensation by eB7 criteria. Predictors for achieving recompensation by B7 were a lower MELD score, lower bilirubin and higher albumin at index AVB. However, serum albumin at index AVB was the only independent predictors for both B7- and eB7-recompensation criteria in multivariable analysis. In landmark analysis, etiological cure after AVB was associated with a significantly lower risk of mortality, particularly when recompensation was achieved (Figure 1). Etiological cure also reduce further decompensation in patients presented with more than 1 decompensating events at index AVB. Importantly, recompensation was not only associated with a significantly less further decompensating events (HR: 0.43, 95%CI: 0.23-0.82), but also significantly better survival (HR: 0.50, 95%CI: 0.28-0.91). **Conclusion:** In this large cohort of patients with index AVB with predominantly viral-related cirrhosis, etiological cure leads to recompensation in nearly half of the patients at 1 year post AVB. Importantly, recompensation was associated with less further decompensating events and better survival, highlighting that recompensation is an achievable and clinically meaningful endpoint in patients with decompensated cirrhosis.

Figure 1

Risk of death after AVB in patients with and without achieving etiological cure and recompensation (B7)



Disclosures: May Xuan Goh: Nothing to Disclose, Alyssa Sim: Nothing to Disclose, Ian Yang Liew: Nothing to Disclose, Xin En Goh: Nothing to Disclose, Guan Wee Wong: Nothing to Disclose, Wei Rong Benjamin Tay: Nothing to Disclose, Pik Eu Jason Chang: Nothing to Disclose, Poh Hui Wee: Nothing to Disclose, Margaret Teng: Nothing to Disclose, Sophia Delu Lin: Nothing to Disclose, Garrett Kang: Nothing to Disclose, Guadalupe Garcia-Tsao: Nothing to Disclose, Juan Gonzalez-Abraldes: Nothing to Disclose, Yu Jun Wong: Nothing to Disclose

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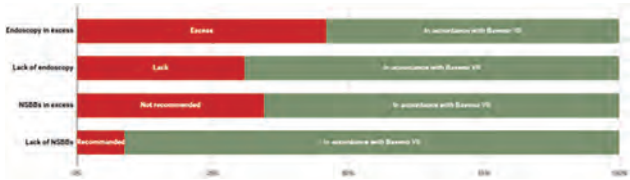
2413 | CONCORDANCE BETWEEN BAVENO VII RECOMMENDATIONS AND REAL-WORLD PRACTICE IN THE MANAGEMENT OF PORTAL HYPERTENSION IN CIRRHOSIS: A NATIONWIDE AUDITEW SUBMISSION

LUCY MEUNIER Christophe Bureau[1] Georges-Philippe Pageaux[2] Dominique Thabut Damais[3] Margaux Delhomme[2], [1]CHU Toulouse, [2]CHU Montpellier, [3]CHU La Pitié

Background: Portal hypertension (PH) is a key driver of liver-related morbidity and mortality in cirrhotic patients. The Baveno VII consensus provides structured recommendations to improve outcomes, but their application is complex due to the integration of multiple parameters, which may lead to practice variability and underutilization of evidence-based strategies. This study aimed to assess adherence to Baveno VII guidelines in clinical practice and to evaluate whether an automated decision-support tool could enhance compliance. **Methods:** A web-based, anonymous national survey was disseminated to French hepatogastroenterologists on April 20, 2025. The survey included 13 clinical vignettes representing core Baveno VII scenarios. For each vignette, participants selected a management strategy for three decision points: PH risk stratification, indication for upper gastrointestinal endoscopy, and initiation of primary prophylaxis using non-selective beta-blockers (NSBBs) or endoscopic variceal ligation. **Results:** A total of 100 physicians from 13 French regions completed the survey, comprising 22 residents, 28 general gastroenterologists without hepatology specialization, and 50 hepatology specialists. Across 3,900 individual decisions, overall adherence to Baveno VII was 59% (2,322 correct responses). Discordance was observed in 34% of PH stratification decisions, 42% of endoscopy indications, and 45% of prophylactic treatment decisions. Notably, 46% of endoscopies were performed without guideline-based indication, while 31% were omitted when recommended. NSBBs were incorrectly prescribed in 53% of scenarios where not indicated, and inappropriately withheld in 10% of cases where they were warranted (figure 1). The highest discordance rates (mean 52 ± 7.8%) were observed in scenarios involving intermediate-to-high liver stiffness in conjunction with thrombocytopenia. **Conclusion:** Adherence to Baveno VII recommendations remains suboptimal, particularly in complex cases requiring the integration of multiple clinical parameters. An automated clinical decision-support system could help standardize care, reduce unnecessary procedures, and enhance the management of portal hypertension in cirrhosis.



Disclosures: LUCY MEUNIER: Nothing to Disclose, Christophe Bureau: Nothing to Disclose, Georges-Philippe Pageaux: Nothing to Disclose, Dominique Thabut Damais: Nothing to Disclose, Margaux Delhomme: Nothing to Disclose

2414 | IMPACT OF CIRRHOSIS ON OUTCOMES IN ACUTE CHOLECYSTITIS: A NATIONWIDE ANALYSIS

Angelin Raju[1] Anish Jomy[2] Aashish Anunaya[1], [1]Texas Health Resources HEB/ Denton, [2]Methodist Richardson Medical Center

Background: This study used the Nationwide Inpatient Sample(NIS) to assess how liver cirrhosis(LC) affects outcomes in acute cholecystitis. Due to altered physiology, coagulopathy, and immunosuppression, LC may worsen risks of mortality, organ dysfunction, sepsis, surgical needs, and healthcare use. **Methods:** We performed a retrospective study of adult patients with Acute Cholecystitis (AC) utilizing the NIS database from 2018 to 2022. We compared AC outcomes in patients with and without LC. The primary outcome was all-cause inpatient mortality. Secondary outcomes were the length of stay (LOS), healthcare cost utilization, incidence of acute kidney injury (AKI), sepsis and surgical procedures. Statistical analyses were performed using STATA, version 19.5. Multivariable logistic and linear regression models were used to estimate adjusted odds ratios (AOR) for key outcomes, controlling for age, sex, race, and comorbidities (Elixhauser index). **Results:** From 2018 to 2022, 948,105 adult patients underwent AC admissions. Among the patients, 923,315 (97.4%) had AC without LC, and 24,790 (2.6%) had AC with LC. Cirrhotic patients were older (mean age 61.6 vs 56.6), more likely male (57% vs 43%), white (64.7% vs 60.3%) and had higher comorbidity burden (Elixhauser category 3: 89.6% vs. 42.1%)[all $p < 0.001$].Also they had a significantly higher likelihood of in-hospital mortality (AOR: 1.45, 95% CI: 1.11–1.90, $p = 0.006$), surgical interventions like Cholecystectomy (AOR: 1.34, $p = 0.012$) and Cholecystostomy (AOR: 1.12, $p = 0.023$). Odds of AKI (AOR: 0.75, $p < 0.001$) and healthcare utilization cost (-$3,544, $p = 0.001$) was lower even though unadjusted values were higher. Cirrhotic had longer

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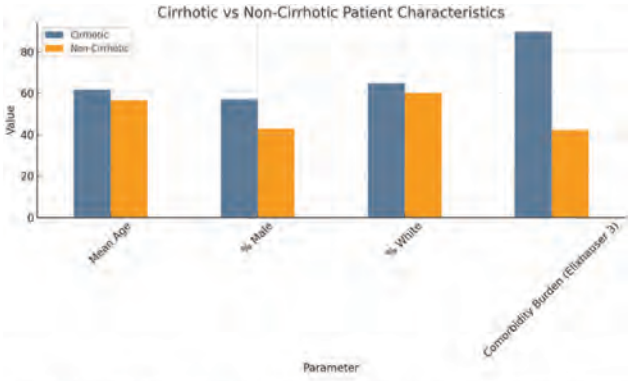
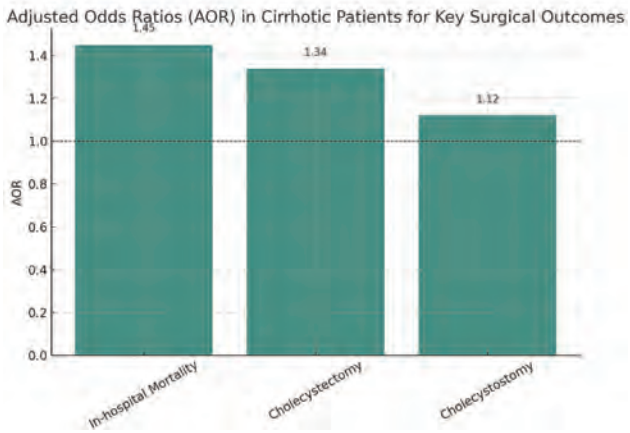
LOS (+1.5 days) and increased sepsis (3.57% vs. 1.78%) though not significant after adjustment. A non-significant trend toward lower use of ERCP was observed in cirrhotic (AOR: 0.79, p = 0.137). **Conclusion:** In this national cohort of adults hospitalized with acute cholecystitis from 2018 to 2022, cirrhotic patients represented a small but clinically significant high risk group with older, predominantly male, white and a greater comorbidity burden. After adjustment, cirrhosis was independently associated with increased odds of in-hospital mortality, and were more likely to undergo surgical interventions, including cholecystectomy and cholecystostomy. While cirrhosis was linked to longer hospital stays and higher rates of sepsis, these associations were not statistically significant after adjustment. Also a decreased incidence of AKI and healthcare costs was found in cirrhotic after adjustment even though it was higher when unadjusted. A non-significant decrease in ERCP may reflect over procedural risk in cirrhotics such as bleeding, infection, or hepatic decompensation. These findings highlight the need for tailored management strategies to optimize outcomes in cirrhotic patients with AC.





Disclosures: Angelin Raju: Nothing to Disclose, Anish Jomy: Nothing to Disclose, Aashish Anunaya: Nothing to Disclose

2415 | SECONDARY SPONTANEOUS BACTERIAL PERITONITIS PROPHYLAXIS IS ASSOCIATED WITH A HIGHER RATE OF SBP RECURRENCE IN NON-CIRRHOTIC PATIENTS: A PROPENSITY-MATCHED ANALYSIS USING A NATIONWIDE EMR DATABASE

Mohammed Aloqaily[1] Pinghsin Hsieh[2] Ahmad Abdulraheem[3] Omar Abureesh[4] Ahmed El Sabagh[3] Rashid Abdel-Razeq[5] Abdulla Massad[6] Alexander Rabadi[7], [1]University of Maryland medical system Midtown Campus, [2]University of Maryland Midtown Campus, [3]MedStar Georgetown Washington Hospital Center, [4]Staten Island University Hospital, [5]Cleveland Clinic Foundation, [6]University of Texas Medical Branch, [7]McLaren Health Care

Background: Spontaneous bacterial peritonitis (SBP) is a life-threatening infection commonly associated with cirrhosis. However, SBP may also occur in non-cirrhotic patients, where its recurrence risk and the role of prophylactic antibiotics remain unclear. We aimed to assess the effectiveness of prophylactic antibiotics in preventing recurrent SBP and improving survival in non-cirrhotic patients using real-world data. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network, a global federated research database comprising de-identified electronic health records and ICD-10-CM coding, encompassing electronic health records from 102 healthcare organizations. Adult patients with no prior diagnosis of cirrhosis who survived their first SBP between October 2015 and October 2022 were identified. Two cohorts were defined: those who started on secondary SBP prophylaxis 1–4 months post-SBP and those who did not. The two cohorts were matched using propensity scores on 16 clinical and demographic variables. Outcomes included SBP recurrence, all-cause mortality, and liver transplantation, assessed over a 2-year follow-up window starting 30 days post-SBP episode. **Results:** We identified 4,169 patients who survived their first SBP episode. And 444 of them (10.7%) were prescribed secondary SBP prophylaxis. After propensity score matching, 440 patients in each cohort were compared. A significantly higher risk of recurrent SBP (OR 2.28; 95% CI: 1.55–3.37; p < 0.001) was observed in those who received prophylactic antibiotics (20.2%) vs those who didn't (10.0%). Kaplan-Meier analysis confirmed significantly worse SBP-free survival in the prophylaxis group (p = 0.001). No significant difference was observed in mortality (33.0% vs 28.9%; p = 0.189) or overall survival (p = 0.720).

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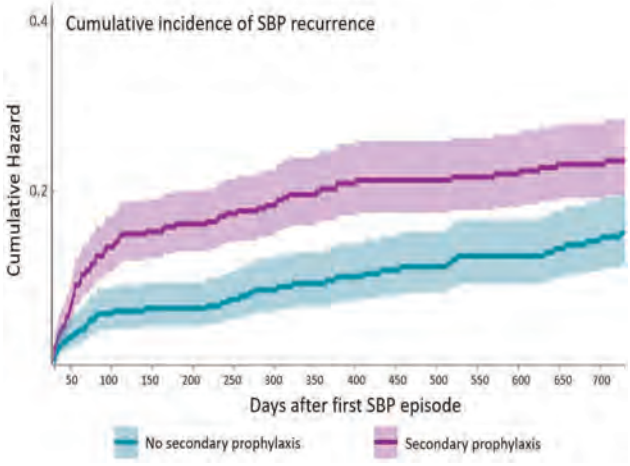
Liver transplantation was rare but occurred only in the prophylaxis group (2.3% vs 0%; p = 0.001). **Conclusion:** In this large, multicenter cohort of non-cirrhotic SBP patients, the use of prophylactic antibiotics was associated with a significantly higher risk of recurrent SBP, with no observed survival benefit. These findings question the utility of prophylactic antibiotics in this population and underscore the need for targeted strategies for SBP management in non-cirrhotic patients rather than extrapolation from cirrhotic SBP paradigms

Table 1. Clinical Outcomes After Propensity Score Matching (N=440 per group)

Outcome	Prophylaxis (%)	No Prophylaxis (%)	OR [95% CI]	p-value
SBP	20.2	10.0	2.28 [1.55–3.37]	<0.001
All-Cause Mortality	33.0	28.9	1.21 [0.91–1.61]	0.189
Liver Transplantation	2.3	0.0	—	0.001



Disclosures: Mohammed Aloqaily: Nothing to Disclose, Pinghsin Hsieh: Nothing to Disclose, Ahmad Abdulraheem: Nothing to Disclose, Omar Abureesh: Nothing to Disclose, Ahmed El Sabagh: Nothing to Disclose, Rashid Abdel-Razeq: Nothing to Disclose, Abdulla Massad: Nothing to Disclose, Alexander Rabadi: Nothing to Disclose

2416 | NON-INVASIVE PREDICTION MODELS OF FIRST HEPATIC DECOMPENSATION IN COMPENSATED ADVANCED CHRONIC LIVER DISEASE – A SYSTEMATIC REVIEW AND META ANALYSIS

Angus Jeffrey[1] James Chen[2] Andrew Chin[1] Emmanuel Tsochatzis[3] Avik Majumdar[4] Luis Calzadilla Bertot[5] Michael Wallace[1] Gary Jeffrey[1] Leon Adams[6], [1]Sir Charles Gairdner Hospital, Perth, Australia, [2]Fiona Stanley Hospital, Perth, Australia, [3]UCL Institute for Liver and Digestive Health and Sheila Sherlock Liver Unit, Royal Free Hospital, [4]Department of Hepatology, The Austin Hospital, Melbourne, [5]The University of Western Australia, Perth, Australia, [6]University of Western Australia

Background: Non-invasive prediction models (NITs) provide an accessible alternative to invasive measures such as hepatic venous pressure gradient in predicting decompensation in cACLD. This review aims to critically appraise available data to determine the accuracy of NITs in identifying patients with cACLD who are at increased risk of decompensation. **Methods:** This systematic review and meta-analysis was conducted from all published articles until February 2025. Studies were included if they evaluated performance of a NIT (defined as two or more individual non-invasive markers that had been combined into a prognostic model). Studies were excluded if analysis was not done on a cACLD population in isolation, such as studies examining only singular prognostic markers (e.g. baseline liver stiffness in isolation). Summary data was extracted from published reports consisting of the c-statistic and/or AUROC and model calibration. This review was registered with PROSPERO (CRD42024608001). **Results:** Of 5,643 articles, 29 were included consisting of 47,469 participants with cACLD. The articles described 38 prognostic models; 12 new prognostic models, and the application of 26 models developed for outcomes other than decompensation in cACLD. Random effects meta-analysis found models developed and validated in cACLD provide the best prediction, including the SAVE score (summary c-statistic 0.87, 95% CI 0.82-0.93) and ABC score (0.85, 0.80-0.89). Of note both of these models had unclear risk of bias and each were studied in only 2 cohorts. Models assessed in a larger number of cohorts (> 10) tended to be validation of existing models of fibrosis or liver-related outcomes, with only ALBI-FIB-4 (c-statistic 0.73, 95% CI 0.71-0.76) being developed in a cohort of cACLD patients with more than 10 validation cohorts, outperforming the other well validated (> 10 cohorts) models with a low risk of bias. Existing models of fibrosis or liver-related outcomes developed in non-cACLD cohorts (e.g. MELD, CPS) are not suitable for use as a prognostic test in cACLD. There was limited validation and calibration of all models. Sensitivity analysis found that method of cACLD diagnosis (invasive vs non-invasive) had a large influence on heterogeneity across all models, improving from high to low/moderate ($< I^2 < 50\%$) when HVPG or liver biopsy was used to define cACLD. Models that incorporated LSM had a higher prognostic performance (c-statistic 0.82, 95% CI 0.79-0.85, $I^2 = 78\%$) compared to those that didn't (0.69, 0.68-0.71, $I^2 = 98\%$, $p < 0.001$). **Conclusion:** cACLD specific NITs offer the best option in predicting decompensation, and future studies should focus on robust validation, calibration and external validation with standardised endpoints to ensure that

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models are reliable for guiding clinical practice in applicable populations. Five scores meet a minimum minimally acceptable diagnostic criteria of 0.8 (SAVE, ABC, LSPS, PH Risk Score, CHESS-ALARM).

Disclosures: Angus Jeffrey: Nothing to Disclose, James Chen: Nothing to Disclose, Andrew Chin: Nothing to Disclose, Emmanuel Tsochatzis: Nothing to Disclose, Avik Majumdar: Nothing to Disclose, Luis Calzadilla Bertot: Nothing to Disclose, Michael Wallace: Nothing to Disclose, Gary Jeffrey: Nothing to Disclose, Leon Adams: Novo Nordisk: Advisor, SCL Behring: Advisor, Dr Falk: Speaking and Teaching, Novo Nordisk: Grant/Research Support, Boehringer Ingelheim: Speaking and Teaching

2417 | EXERCISE AND NUTRITION INTERVENTIONS FOR SARCOPENIA IN CIRRHOSIS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Roongruedee Chaiteerakij[1] Soe Thiha Maung[1] Sirinda Kittiprachakul[1] Solaphat Hemrungrojn[1] Sarissa Rangkla[1], [1]Chulalongkorn University

Background: Sarcopenia is highly prevalent and associated with poor outcomes in cirrhotic patients. We aimed to evaluate the efficacy of exercise, protein supplementation, and branched-chain amino acid (BCAA) supplementation in treating cirrhotic sarcopenia. **Methods:** We conducted systematic review and meta-analysis of randomized controlled trials (RCTs). PubMed, Embase, Scopus and the Cochrane library were searched from the database inception until March 2024 for RCTs of exercise, protein supplementation, and/or BCAA supplementation on improving at least one of the sarcopenia features: muscle mass, muscle strength and physical performance. Differences in post- and pre-intervention changes between intervention and control arms were calculated as a standardized mean difference (SMD), with 95% confidence interval (CI). A network meta-analysis (NMA), component NMA, pairwise meta-analysis (PW-MA) were performed. **Results:** 23 RCTs were included in the meta-analysis. There were 1624 participants, with 977 (60.2%) males and a mean age of 56.4 years (SD: 7.1) The PW-MA, NMA and CNMA revealed that exercise significantly increased muscle mass, while protein or BCAA supplementation alone had no significant effects on muscle mass. Combined exercise with protein and BCAA supplementations had the greatest effect on increasing muscle mass (SMD 2.12; 95%CI: 0.59–3.65). Exercise with BCAA/protein supplementation also significantly increased muscle mass. A subgroup analysis by exercise type, aerobic exercise significantly improved muscle mass ($p < 0.05$), whereas combined aerobic and resistance exercises did not show significant effects compared to the non-exercise groups. By PW-MA, exercise significantly improved physical performance versus control (SMD 1.43; 95%CI: 0.63–2.17; $p < 0.01$; $I^2 = 59\%$) and exercise plus protein supplementation was superior to protein alone (SMD 0.66; 95%CI: 0.26–1.06; $p = 0.001$; $I^2 = 0\%$). By the systematic review, the effects of BCAA supplementation on muscle strength was inconclusive. **Conclusion:** Combining exercise with protein and BCAA supplementation demonstrated the greatest effects on increasing muscle mass, suggesting it is the most effective strategy for treating sarcopenia in cirrhotic patients. Nutritional supplementation alone does not enhance muscle mass. Further well-designed studies are needed to identify the most effective type of exercise.

Disclosures: Roongruedee Chaiteerakij: Nothing to Disclose, Soe Thiha Maung: Nothing to Disclose, Sirinda Kittiprachakul: Nothing to Disclose, Solaphat Hemrungrojn: Nothing to Disclose, Sarissa Rangkla: Nothing to Disclose

2418 | ASCITES PRESSURE ACCOUNTS FOR PATIENT REPORTED MEASURES AND IS A MELD-INDEPENDENT PREDICTOR OF ONE YEAR OUTCOMES AFTER PARACENTESIS

Nikhilesh Mazumder[1] Max Macgregor[2] Elliot Tapper[3] Anna Lok[3], [1]University of Michigan Hospitals and Health Centers, [2]University of Michigan, [3]University of Michigan Medical Center

Background: Therapeutic paracentesis is commonly used for symptom relief in patients with large volume ascites. While this event is known to portend poor 1-year outcomes for patients, it is unclear at the time of paracentesis which patients will ultimately undergo Transjugular Intrahepatic Portosystemic Shunt placement (TIPS), liver transplantation (LT), or die. Earlier recognition of patient trajectory may allow for earlier triage to appropriate treatment course. **Methods:** We prospectively enrolled patients with portal hypertensive ascites (SAAG > 1.1) undergoing therapeutic paracentesis in our ambulatory paracentesis unit. We excluded patients with prior LT, TIPS, or stage 4 or worse chronic kidney disease. We measured patient symptoms and relief using a validated questionnaire (Ascites Symptom Index-7, ASI-7) and directly measured ascites opening pressure (OP) at the start of paracentesis using an open-ended manometer. The primary outcome was time to first event (death, TIPS, or LT) using Fine-Gray competing risk methodology with censoring at one year or study end. Demographic and

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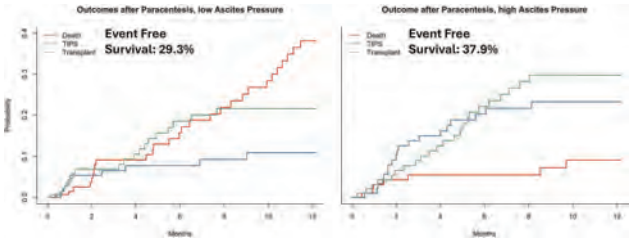
clinical variables on the day of paracentesis were recorded. **Results:** 236 procedures were included in the study among 75 unique patients observed for an average of 143 days for a total of 33,972 patient-days. On the day of procedure, the average age was 60 years, 73 (30.9%) were female, with alcohol (n = 81; 34.3%) and MASLD (n = 98; 41.5%) the most common etiologies of liver disease. The average MELD 3.0 score was 16.4, OP was 14.1 cmH_2O, with 45.3% of patients reaching the primary outcome: 35 (14.8%) died prior to TIPS or transplant, 30 (12.7%) underwent TIPS, and 42 (17.8%) underwent LT without TIPS. Among patients who ultimately underwent TIPS or LT, OPs were higher (16.6 and 15.9 cmH_2O, respectively) compared to patients who died or had no event (12.5 and 13.5 cmH_2O, $p = 0.001$). When adjusted for age and MELD 3.0, patients with greater difficulty moving due to ascites (sHR 1.64, $p = 0.007$), or trouble breathing while walking (sHR 1.60, $p = 0.004$) were more likely to have received TIPS on follow up. In competing risk analyses adjusted for age and MELD 3.0, higher OP but not patient symptoms remained a significant predictor for survival, TIPS, or LT (sHR 0.87, $p = 0.001$ per cm H_2O). **Conclusion:** Pressure measurement was a MELD independent predictor of patient outcomes and can account for symptom assessment in patients undergoing paracentesis. Patients presenting for symptom relief via therapeutic paracentesis without high abdominal pressures may have a worse prognosis. Future analyses would facilitate identification of patients who may benefit from earlier transplant or TIPS referral using this bedside measurement of ascites pressure.



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2419 | SPLENIC STIFFNESS MEASUREMENT AS A NONINVASIVE MARKER FOR MONITORING DOSE OF CARVEDILOL IN CIRRHOTIC PATIENTS WITH HIGH RISK VARICES

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Background: Non-selective beta-blockers (NSBBs), are recommended for prophylaxis of variceal bleeding in patients with cirrhosis and high risk varices (HRV). Recent studies indicate that splenic stiffness measurement (SSM) is a reliable, non-invasive alternative to invasive methods such as hepatic venous pressure gradient (HVPG) and crude methods like blood pressure. SSM effectively assesses hemodynamic response to NSBB therapy used for primary prophylaxis of HRV and reduction in SSM of 10% or more (SSM responders) demonstrates excellent accuracy in identifying HVPG responders. **Methods:** We prospectively studied consecutive patients with cirrhosis, aged 18-60 years, who were candidates for NSBBs for primary variceal bleeding prophylaxis. Patients were evaluated at our department before starting NSBB, then monthly for three months. Patients were started on carvedilol dose 6.25 mg and titrated to 25 mg per day according to tolerability and SSM change. Correlation between delta changes of SSM by using transient elastography with carvedilol dosage was performed. **Results:** Thirty patients were analyzed from the initial group of 65 patients considered for the study (median age 48 years, 80% Males). Patients who were intolerant to carvedilol and having active hepatic insult were excluded. Most common etiology was alcoholic liver disease (80%), followed by Hepatitis C (10%), MASLD (5%), and hepatitis B (5%). Out of the patients who achieved a $\geq$ 10% SSM reduction at 3 months, 14(46.6%) were on a daily dose of 12.5 mg carvedilol, 4(13.33%) on 6.25 mg, and 6(20%) on 25 mg carvedilol daily. Notably, 6 (20%) patients were SSM non responder to carvedilol even at the 25 mg daily dose. Sixty percent of patients were SSM responders even at daily carvedilol doses of $\leq$12.5 mg. This highlights the utility of SSM in effectively monitoring carvedilol treatment, thereby preventing the administration of unnecessary higher dosages and avoiding potential adverse events. **Conclusion:** Splenic stiffness measurement is a non-invasive marker for monitoring the dose of carvedilol

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in cirrhotic patients with high risk varices, and can be used instead of invasive methods like HVPG and crude marker like blood pressure.

Table No: 1 General Characteristics of the included patients and Changes in LSM, SSM and MAP after Follow-up

VARIABLE	PREVALENCE/MEDIAN VALUES
AGE(YRS)	18-60(48)
GENDER(MALE)%	24(80)
(FEMALE)%	6(20)
BMI	26.2(19.7-33.1)
LIVER DISEASE ETILOLOGY	
HCV (%)	3(10)
HBV (%)	1.5(5)
MASLD (%)	1.5(5)
ALD (%)	24(80)
PORTAL HYPERTENSION	
HIGH RISK VARICES (%)	30(100)
GASTRIC VARICES (%)	3(10)
PORTAL HYPERTENSIVE GASTROPATHY (%)	24(80)
ASCITES (%)	1(3.3)
HEPATIC ENCEPHALOPATHY (%)	1(3.3)
BIOCHEMICAL TESTS	
CHILD-PUGH SCORE	6.2(5-9)
MELD-SCORE	11.4(7-27)
TREATMENT	
SYSTOLIC BLOOD PRESSURE	117(102-132)
DIASTOLIC BLOOD PRESSURE	70(60-80)
HEART RATE	77.4(54-88)
MAP	85.5(75.3-94.7)
NSBB CHOICE	
CARVEDILOL (%)	30(100)
DAILY DOSAGE(mg)	15.625(6.25-25)

	LSM BEFORE	LSM AFTER	LSM REDUCTION	LSM% REDUCTIO N	SSM BEFORE	SSM AFTER	SSM REDUCTI ON	SSM% REDUCTION	MAP BEFORE	MAP AFTER
MEAN	51.93	42.76	9.17	18.76	54.02	40.68	13.34	24.62	93.88	85.47
MEDIAN	50.6	40.1	9.55	16.58	57.05	42.45	14	26.54	94	86.67
RANGE(MIN)	14.1	10.5	3.7	11.16	19.1	14.7	4.4	12.95	73.33	75.33
MAX	75	64.6	13.6	33.78	78.4	64.2	21.5	30.75	113.33	94.67
p-value			<0.001				<0.001			

BMI- BODY MASS INDEX, MAP- MEAN ARTERIAL PRESSURE, NSBB- Non selective beta blocker LSM- LIVER STIFFNESS MEASURMENT; SSM-SPLENIC STIFFNESS MEASURMENT; MAP-MEAN ARTERIAL PRESSURE

Disclosures: Virendra Singh: Nothing to Disclose, Nitesh Bassi: Nothing to Disclose, Amandeep Singh: Nothing to Disclose, Jahnvi Dhar: Nothing to Disclose, sandeep kaur toor: Nothing to Disclose, Himanshu Gupta: Nothing to Disclose, Upasna Rajput: Nothing to Disclose, Rashmeet Brar: Nothing to Disclose, Brahmjot Kaur: Nothing to Disclose

2420 | A PANEL OF SYSTEMIC INFLAMMATION BIOMARKERS PREDICTS THE COURSE OF DECOMPENSATED CIRRHOSIS TOWARDS RECOMPENSATION OR FURTHER DECOMPENSATION

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Background: Patients with decompensated cirrhosis are at high risk for further decompensation (FDC) and liver-related death, however, some may achieve recompensation (ReC). Since systemic inflammation (SI) represents a central disease-driving mechanism in cirrhosis, we investigated a broad panel of SI biomarkers and their dynamics across the course of patients with DC. **Methods:** A two-center, prospective cohort of cirrhosis outpatients evaluated between 01/2017 and 12/2023 were stratified at baseline (BL) as compensated (CC), decompensated (DC) and recompensated (ReC) cirrhosis. At baseline and follow-up (FU: minimum of $\geq$ 6-months), surrogates of portal hypertension (PH) and an SI biomarker panel (bead-based immunoassay) were evaluated. In DC, progression was defined as a composite endpoint comprising further decompensation or ACLF, while regression was defined as achieving recompensation. **Results:** A total of 280 cirrhosis patients (median age: 60.1 years; 68.2% men; main etiology: ALD 68.2%) with a median follow-up of 23.0 months were included. At BL, 73 (25.7%) showed CC, 166 (59.2%) DC and 41 (15.1%) ReC. MELD (DC: 12 vs. CC: 9 v ReC: 8; $p < 0.001$), multiple SI biomarkers (IL6, IL8, IL10, IFNy, IL1b, MCP1, IL12p70, IL23 and IL33 pg/mL vs CC/ReC, p-values all < 0.05) and PH surrogates such as VWF (DC: 313 vs. CC: 214 vs ReC: 175%; $p < 0.001$) were significantly higher in DC vs. CC/ReC, respectively. HVPG was significantly lower in recompensated patients (DC: 19 mmHg vs CC:13 vs ReC: 9 mmHg; $p = 0.001$) in comparison to CC and DC. There were no significant differences within SI markers between CC and ReC patients. Among 127 DC patients, $n = 29$

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(22.8%) progressed to FDC with significantly increasing MELD (12 vs. 14; $p = 0.002$) and SI biomarker levels (IL10, IFNa2, IFNy, IL17A, IL8, IL33; paired p-values all < 0.05). There were no significant differences in VWF levels and HVPG. In turn, $n = 27$ (22.3%) of DC patients achieved recompensation with significant decreases in MELD (14 vs 11; $p = 0.05$), in HVPG (18 vs 13 mmHg; $p = 0.006$), VWF (283 vs 217 %; $p = 0.004$) and in SI biomarkers (IL6 and IL8 all $p < 0.05$). **Conclusion:** Patients with DC show not only impaired liver function and PH but also pronounced pro-inflammatory state. Importantly, with progression to further decompensation or regression to recompensation, we found significant dynamics in SI biomarkers paralleling liver disease surrogates (MELD, HVPG). The prognostic value of SI biomarker dynamics seems promising and further validation of their value to define cirrhosis disease states seems warranted.

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2421 | SUBOPTIMAL BETA BLOCKER TITRATION IN PORTAL HYPERTENSION: INSIGHTS FROM THE SVASTA STUDY USING WEARABLE-DERIVED RESTING HEART RATE

Gautham Pranesh[1] Alisha Chaubal[2] HARDIK SHAH[2] Ameet Mandot[3] AMRIK SHAH[4] Ramesh Vangal[4] Shyam Kottilil[5] Mani Subramanian[6] SAMIR SHAH[2], [1]SensEarly, [2]Nanavati Max Super Speciality Hospital, [3]Gleneagles Hospital, [4]Sensearly Inc, [5]University of Maryland, [6]TLC

Background: Non-selective beta blockers (NSBBs) are used to reduce portal hypertension and reduce variceal bleeding in patients with advanced liver disease. However, a significant propotion of patients (~40-60%) do no achie guideline-directed titration targets, defined as $\geq 25\%$ reduction in resting heart rate (RHR) or a RHR target of 55-60 bpm. The further risk of adverse events remains high due to episodic nature of clinical visits and lack of monitoring. **Methods:** The Prospective Observational Study To evaluate Biomarkers of Metabolic Dysfunction Among Patients with Liver Failure (SVASTA study, CTRI/2022/09/045668) was an observational study conducted at a tertiary liver transplant center in western India. Fifty-six patients with advanced liver disease were enrolled, of whom 50 used Garmin Vivosmart wearables for continuous RHR monitoring and attended at least three clinic visits over a 6-month period. NSBB dose titration was assessed retrospectively based on wearable-derived daily RHR trends, blood pressure at clinical visits and chart-reviewed data. **Results:** Beta blockers were prescribed in 28/50 patients (56%) predominantly in the compensated and decompensated cirrhosis cohorts. 17/28 (60.7%) did not meet guideline-defined titration targets throughout the period of observation. Among these, 2/17 had dose-limiting hypotension whereas 15/17 (88.2%) patients had potential for further titration. Missed titration opportunities were primarily due to wide spacing of visits (typically every 2 to 3 months). Event rates over the time of observation were higher in the inadequately titrated group (35.3%) compared to the adequately titrated group (27.3%). **Conclusion:** Despite widespread use, NSBBs are frequently sub-optimally titrated in real-world practice due to limitations in accurate monitoring and reliance on visit-based care. Most patients with inadequate titration had physiological capacity for NSSB dose escalation. Continuous RHR monitoring using wearables may offer a scalable solution for optimizing titration for improving clinical outcomes in patients with portal hypertension.

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2422 | THE PERFORMANCE OF SHEAR WAVE ELASTOGRAPHY-BASED LIVER AND SPLEEN STIFFNESS MEASUREMENT IN PREDICTING HIGH-RISK VARICES AND HEPATIC DECOMPENSATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Kanteera Sriyudthsak[1] Sangdao Boonkaya[1] Chidkamon Pattarawongpaiboon[1] Sirinporn Suksawatamnuay[1] Salisa Wejnaruemarn[1] Panarat Thaimai[1] Nipaporn Siripon[1] Prooksa Ananchuensook[1]

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Background: Liver and spleen stiffness measurement (LSM and SSM) are currently tools for ruling out high-risk varices (HRV) in patients with chronic liver disease. However, their utility has not yet been established in patients with hepatocellular carcinoma (HCC). Moreover, the optimal cut-off values for LSM and SSM using two-dimensional shear wave elastography (2D-SWE) require further investigation. This study aims to evaluate the performance of 2D-SWE-based LSM and SSM in predicting HRV and acute decompensation (AD) in HCC patients, and to validate the Baveno VI and VII criteria in HCC patients. **Methods:** We prospectively enrolled patients with HCC at Chulalongkorn University Hospital, Bangkok, Thailand, from June 2023 to March 2025. Patients underwent EGD, LSM and SSM by TE (Fibroscan, Echosens) and 2D-SWE (Supersonic Imaging). AD, including ascites, spontaneous bacterial peritonitis, variceal bleeding, and hepatic encephalopathy, was recorded during a one-year follow-up period. Optimal cutoffs for predicting HRV were identified by maximizing the negative predictive value (NPV) with a sensitivity $> 90\%$. The Baveno VI and VII criteria were evaluated using LSM by TE and platelet count. **Results:** Overall, 163 patients with HCC were enrolled, with 12 (7.4%) Barcelona-Clinic Liver Cancer (BCLC) 0, 66 (40.5%) BCLC A, 59 (36.2%) BCLC B and 26 (16%) BCLC C, respectively. The most common causes of HCC were HBV (47.9%) and HCV (22.1%). HRV was present in 20.9% ($n = 34$) of patients. LSM and SSM evaluated by TE and 2D-SWE exhibited significant ability to detect HRV (AUROC = 0.68-0.73, $p < 0.05$). Using 2D-SWE, an LSM cutoff of 23.2 kPa yielded 91% sensitivity and a 95% NPV for predicting HRV, avoiding 39.3% unnecessary EGD with an HRV missing rate of 4.7%. An SSM cutoff of 27.5 kPa using 2D-SWE yielded 91% sensitivity and 92% NPV, avoiding 22.1% EGD with an HRV missing rate of 8.3%. The Baveno VI criteria avoided 26.4% EGD with 2.9% missed HRV, while the Baveno VII criteria avoided 55.8% with 14.7% missing rate. After a 1-year follow-up, 16 patients (9.8%) developed AD. Baseline 2D-SWE-based LSM had a good accuracy (AUROC = 0.80, 95%CI: 0.69-0.91, $p \leq 0.001$) in predicting AD. Multivariate analysis revealed that LSM by 2D-SWE (adjusted OR (aOR) = 1.05, 95%CI: 1.00-1.09, $p = 0.05$), portal vein invasion (aOR = 5.49, 95%CI: 1.22-24.76, $p = 0.03$), and albumin-bilirubin (ALBI) score (aOR = 5.89, 95%CI: 1.70-20.38, $p = 0.005$) were independent factors associated with AD. **Conclusion:** LSM by 2D-SWE could safely avoid unnecessary EGD with a low HRV miss rate comparable to that of the Baveno VI criteria in HCC patients. Furthermore, 2D-SWE-based LSM may serve as a useful predictor of AD.

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2423 | LOWER BMI AND SNARE POLYPECTOMY ARE ASSOCIATED WITH A HIGHER RATE OF POSTPOLYPECTOMY BLEEDING IN PATIENTS WITH CIRRHOSIS

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Background: As cirrhosis mortality decreases, more patients with cirrhosis are undergoing screening colonoscopies. Few studies exist on the safety of colonoscopy with polypectomy in patients with cirrhosis. This study aims to investigate the rates of colonoscopy complications in patients with cirrhosis and identify risk factors that may be associated with postpolypectomy bleeding (PPB). **Methods:** We performed a single-center retrospective study of patients with cirrhosis who underwent colonoscopy with polypectomy between 2017 and 2024 at a tertiary care center. Complications including immediate PPB, delayed PPB, perforation, death, need for pressors, intubation, blood transfusion, and hospitalization were recorded to 1-week follow-up. Clinical characteristics of patients with PPB were compared to those who did not have PPB. Polyp characteristics including size, morphology, histology, and removal method were also recorded. Data analysis was conducted using *t* tests and chi-square tests. **Results:** We reviewed 135 colonoscopies with 394 polypectomies. The mean age of the patient population was 63.82 years (SD = 11.29) and consisted of 80 (59.26%) males. Forty-three (31.85%) colonoscopies were complicated by immediate PPB and four (2.96%) by delayed PPB. Six (4.44%) required hospitalization, three (2.22%) blood transfusion, and two (1.48%) pressors and intubation. No cases of perforation or death occurred. Colonoscopies complicated by bleeding ($n = 47$) were compared to those with no bleeding ($n = 88$). Lower BMI, higher INR, and oral anticoagulant use were associated with increased risk of bleeding ($p = 0.03$) [Table 1]. There was no statistically significant difference between bleeders and non-bleeders regarding presence of esophageal varices, antiplatelet use, albumin or platelet levels, MELD 3.0 score, Child-Pugh

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class, or ASA physical status. Of the 394 polyps, 61 (15.48%) bled and 333 (84.52%) did not bleed after removal. Removal by cold or hot snare polypectomy was associated with a higher risk of bleed compared to removal by cold biopsy forceps ($p < 0.01$). Among morphologies, polyps that were flat/semi-sessile or pedunculated were more likely to bleed ($p < 0.01$). Furthermore, adenomatous polyps had an increased risk of bleeding compared to non-adenomatous polyps ($p = 0.04$). The mean size of bleeding polyps was 7.24 mm (SD = 4.08) compared to 4.36 mm (SD = 2.69) for non-bleeding polyps ($p < 0.01$). **Conclusion:** Colonoscopy with polypectomy appears safe in patients with cirrhosis. Immediate PPB was the most common complication. Lower BMI, higher INR, and oral anticoagulant use were associated with higher risk of bleeding. There was no difference in albumin or platelet levels, MELD 3.0 score, Child-Pugh class, or ASA physical status between bleeding and non-bleeding groups. Polyps that bled after removal were often larger in size, adenomatous, flat/semi-sessile or pedunculated, or removed by snare polypectomy.

Table 1: Characteristics of patients and polyps stratified by bleeding status

Patient Characteristic	Non-Bleeding (n=88)	Bleeding (n=47)	*P* value
Age (years)	64.14 ± 10.01	63.23 ± 13.47	0.69
Gender (male)	47 (53.41%)	33 (70.21%)	0.06
BMI (kg/m²)	31.09 ± 8.87	28.35 ± 5.49	**0.03**
ASA			0.20
II	5 (5.68%)	1 (2.13%)	
III	73 (82.95%)	38 (80.85%)	
IV	10 (11.36%)	8 (17.02%)	
Total bilirubin (mg/dL)	1.31 ± 1.82	1.60 ± 1.51	0.32
Albumin (g/dL)	3.39 ± 0.73	3.29 ± 0.68	0.42
Platelets (K/μL)	153.43 ± 64.64	152.55 ± 86.47	0.95
INR	1.19 ± 0.23	1.30 ± 0.33	**0.03**
Creatinine (mg/dL)	1.09 ± 0.92	1.41 ± 1.98	0.29
MELD 3.0	11.72 ± 4.47	13.23 ± 5.18	0.09
Encephalopathy present	4 (4.55%)	6 (12.77%)	0.08
Ascites			0.37
None	64 (72.73%)	30 (63.83%)	
Mild	16 (18.18%)	9 (19.15%)	
Moderate-severe	8 (9.09%)	8 (17.02%)	
Esophageal varices present	30 (34.09%)	17 (36.17%)	0.81
Child-Pugh class			0.16
A	58 (65.91%)	23 (48.94%)	
B	25 (28.41%)	20 (42.55%)	
C	5 (5.68%)	4 (8.51%)	
Antiplatelet use	13 (14.77%)	12 (25.53%)	0.13
Oral anticoagulant use	14 (15.91%)	15 (31.91%)	**0.03**
Polyp Characteristic	**Non-Bleeding (n=333)**	**Bleeding (n=61)**	***P* value**
Size (mm)	4.36 ± 2.69	7.24 ± 4.08	**<0.01**
Morphology			**<0.01**
Flat/semi-sessile	64 (19.22%)	21 (34.43%)	
Sessile	254 (76.28%)	31 (50.82%)	
Semi-pedunculated	10 (3.00%)	3 (4.92%)	
Pedunculated	5 (1.50%)	6 (9.84%)	
Histology			**0.04**
Adenomatous	205 (61.56%)	46 (75.41%)	
Non-adenomatous	128 (38.44%)	15 (24.59%)	
Removal Method			**<0.01**
Cold biopsy	139 (41.74%)	6 (9.84%)	
Cold snare	167 (50.15%)	40 (65.57%)	
Hot snare	27 (8.11%)	14 (22.95%)	
EMR	0 (0.00%)	1 (1.64%)	

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2424 | VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY AS A NON-INVASIVE PREDICTOR OF SARCOPENIA IN CIRRHOSIS: ESTABLISHING A THRESHOLD FOR RISK STRATIFICATION

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Background: Sarcopenia is a significant complication of cirrhosis, associated with poor prognosis and increased morbidity and mortality. Traditional diagnosis involves assessing body composition and muscle strength; however, non-invasive methods for early identification remain limited, particularly when the cut-offs come from different population. Emerging studies suggest that liver stiffness, measured through vibration-controlled transient elastography (VCTE, FibroScan®), may reflect systemic changes, including muscle loss. This study aimed to evaluate the association between liver elastography and sarcopenia in cirrhotic patients and identify optimal cutoff points for risk stratification. **Methods:** Liver stiffness was assessed using VCTE (in kPa). Sarcopenia was defined by muscle mass parameters (Mid-Arm Muscle Circumference and SaRC-CALF score), handgrip strength (by dynamometry), and nutritional assessment (GLIM score). Associations were explored using logistic regression analysis, and ROC curves were constructed to determine optimal elastography cutoff points for sarcopenia and nutritional outcomes, validated through bootstrap analysis. **Results:** A total of 132 cirrhotic patients were analyzed, of whom 16.7% (n = 22) had sarcopenia. Sarcopenic patients exhibited significantly higher liver stiffness values than non-sarcopenic patients (27.1 ± 4.2 kPa vs. 22.8 ± 3.8 kPa, $p < 0.001$). Multivariate analysis confirmed that MELD-Na (OR: 1.20; 95% CI: 1.05–1.38), advanced Child-Pugh classification (Class C vs. A OR: 3.0; 95% CI: 1.50–5.99; Class B vs. A OR: 1.80; 95% CI: 1.10–2.95), and muscle markers (OR: 2.5; 95% CI: 1.30–4.80) were independent predictors of elevated liver stiffness. ROC analysis identified a cutoff of 25.2 kPa as the optimal threshold for discriminating sarcopenia (AUC = 0.81 [0.78–0.84]; sensitivity = 78%; specificity = 74%; $p < 0.001$). Similar cutoffs were

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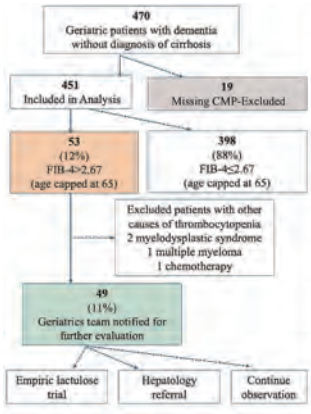
established for handgrip strength (24.0 kPa; AUC = 0.78 [0.75–0.81]; p = 0.002), myopenia (23.5 kPa; AUC = 0.76 [0.73–0.79]; p < 0.001), and severe malnutrition (≥ 24.7 kPa; AUC = 0.79 [0.76–0.82]; p < 0.001). Confidence intervals obtained through bootstrap analysis reinforced the robustness of these findings. **Conclusion:** Liver elastography may serve as a reliable non-invasive marker for sarcopenia, enabling early risk stratification in cirrhotic patients. Liver stiffness values above 25 kPa should be considered indicative of greater muscular and nutritional impairment, potentially aiding clinical decision-making and guiding therapeutic interventions.

Disclosures: Lourianne Nascimento Cavalcante: Nothing to Disclose, Aloma Conceição Campeche-Leão: Nothing to Disclose, Ana Clara Batista: Nothing to Disclose, Rosangela Passos: Nothing to Disclose, Lais Garcez: Nothing to Disclose, Monalisa Reis Arruda: Nothing to Disclose, Helma Cotrim: Nothing to Disclose

2425 | USING FIB-4 TO UNCOVER UNDIAGNOSED CIRRHOSIS IN PATIENTS WITH DEMENTIA: A QUALITY IMPROVEMENT INITIATIVE

Vinay Jahagirdar[1] Michael Weissberger[1] Jawaid Shaw[1] Dan Park[1] Peter Boling[1] Jasmohan Bajaj[1], [1]Virginia Commonwealth University

Background: Dementia and hepatic encephalopathy (HE) can present with overlapping cognitive symptoms, particularly in older adults. Undiagnosed cirrhosis in patients with dementia may result in missed opportunities to identify and treat HE, a reversible contributor to cognitive impairment. National data suggest that 5-10% of patients with dementia may have unrecognized cirrhosis based on elevated Fibrosis-4 (FIB-4) scores. This QI project aimed to identify such patients in a geriatric cohort using FIB-4 as a non-invasive screening tool. **Methods:** We reviewed charts of patients with dementia seen in a geriatric clinic at a quaternary academic medical center. Patients with a known diagnosis of cirrhosis were excluded. FIB-4 scores were calculated using lab values (ALT, AST, platelets) collected near the time of dementia diagnosis. For those over 65, age was capped at 65 in the FIB-4 formula to avoid overestimation. A FIB-4 score > 2.67 was used to flag high risk for advanced fibrosis. Detailed chart reviews were conducted in these patients to identify risk factors and rule out alternative explanations. Kruskal-Wallis test was used for continuous variables and Chi-square test for categorical variables. P-value < 0.5 was considered statistically significant. **Results:** Of 470 charts reviewed, 451 had lab data for FIB-4 calculation. The cohort was predominantly female (70%), with 58% having moderate-to-severe dementia. Alzheimer's dementia was the most common subtype (47%). 53 patients (11.8%) had FIB4 > 2.67, with a median score of 3.3 (IQR 1.1). Compared to those with FIB-4 ≤ 2.67, they had higher rates of severe dementia (40% vs 15%, p < 0.0001), more frequent use of memantine and donepezil, and greater likelihood living in assisted living facilities (47% vs 18%, p < 0.0001). Comorbidities in FIB-4 ≥ 2.67 included diabetes (72%), obesity (23%), alcohol use disorder (9%) and hepatitis C (6%). Imaging findings were suggestive of chronic liver disease in 9.4%. Four patients were excluded due to alternative causes of thrombocytopenia (hematological malignancies, chemotherapy use). The geriatrics team was notified about the remaining 49 patients for further evaluation, with follow up plans individualized to include hepatology consultation, empiric lactulose therapy, or continued observation. **Conclusion:** In this ambulatory geriatric dementia cohort, 11% of patients had elevated FIB-4 scores, suggesting possible undiagnosed cirrhosis. These patients exhibited more severe cognitive decline, higher dependency & other risk factors for chronic liver disease (alcohol, metabolic syndrome, viral hepatitis). Clinicians caring for older adults with dementia should maintain a high index of suspicion for cirrhosis and can consider incorporating FIB-4 screening into dementia care to identify HE as a reversible and treatable cause of cognitive dysfunction.



Disclosures: Vinay Jahagirdar: Nothing to Disclose, Nothing to Disclose, Michael Weissberger: Nothing to Disclose, Jawaid Shaw: Nothing to Disclose, Dan Park: Nothing to Disclose, Peter Boling: Nothing to Disclose, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Genfit: Grant/Research Support, Enterobiotix: Advisor, Boehringer Ingelheim: Advisor

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2426 | REAL WORLD MULTI-CENTER EVALUATION OF THE USE OF TERLIPRESSIN FOR HRS-AKI IN THE UNITED STATES

Prutha Shah[1] Brooklyn Baylis[2] Morgan Elias[1] John Knorr[1] Sarah Yeager[3] Jonathan Fenkel[3] David Sass[3] Rebecca Loh[3] Jamie Schulte[3] Richard Kalman[1], [1]Jefferson Einstein Philadelphia Hospital, Philadelphia PA, [2]Thomas Jefferson University Hospital, Philadelphia, pA, [3]Thomas Jefferson University Hospital, Philadelphia PA

Background: According to various international guidelines, terlipressin, in combination with albumin, is the preferred treatment for Hepatorenal Syndrome-Acute Kidney Injury (HRS-AKI). Although terlipressin has shown benefits in reversing HRS and avoiding renal replacement therapy (RRT), its side effect profile and high financial cost have limited its utilization in the United States since FDA approval in 2022. This study aims to characterize real-world utilization of terlipressin at two tertiary academic medical centers in the U.S. **Methods:** This retrospective evaluation reviewed the efficacy, safety, and cost utilization of terlipressin in adults between the time of formulary addition starting 1/1/23 through 11/30/24. Efficacy and safety outcomes mirrored those of the FDA-approved CONFIRM trial, including verified HRS reversal (two consecutive serum creatinine (SCr) measurements of 1.5 mg/dL or less at least 2 hours apart up to day 14 and survival without RRT for at least an additional 10 days) and safety endpoints. **Results:** A total of 39 patients were included. Patients were male (62%), aged 55 $\pm$ 11.9 years, with alcohol use as the primary cause of cirrhosis (49%). Prior to terlipressin use, midodrine and octreotide were used in 71% of the patients. At the time of terlipressin initiation, median MELD 3.0 was 34 $\pm$ 6, with a baseline SCr of 2.87 $\pm$ 0.7 mg/dL. The average duration of terlipressin was 3.3 $\pm$ 3.3 days. Terlipressin was continued beyond day four in 12 patients (30.7%), 7 of whom had a dose increase. Albumin was continued for an average of 2.5 $\pm$ 3.1 days while on terlipressin, with an average total daily dose of 31 $\pm$ 27g per day. Verified HRS reversal occurred in 7/39 patients (17%), all with a SCr $\leq$ 3mg/dL. Liver transplant occurred in 35% of patients at a mean of 9.8 $\pm$ 10 days after terlipressin initiation. Death within 90 days occurred in 15/39 patients (38%). Adverse events occurred in 19/39 patients (48%), leading to discontinuation of terlipressin in 18/19 patients. Respiratory failure was the most common adverse effect in 14/39 (35%), with a mean time to onset of 2.9 $\pm$ 3.7 days. The average cost per patient for the terlipressin treatment course was $14,084.96 USD. **Conclusion:** In this real-world review of tertiary academic medical centers in the U.S., HRS reversal was similar to the outcomes in the CONFIRM trial (31% compared to 39%); however, verified HRS reversal was lower (17% in the present study vs. 32% in CONFIRM). Adherence to the institutional formulary guidelines was met for this high-cost, newly FDA-approved therapy and should continue to guide appropriate patient selection.

Table 1. Efficacy and safety outcomes

	Terlipressin (n = 39)
Efficacy Endpoints	
Verified reversal of HRS* – no. (%)	7 (17.9)
Competing Event¥	4 (10.3)
HRS Reversal** – no. (%)	12 (30.8)
Competing Event	4 (10.3)
Recurrence of HRS after reversal within 90 days (n=12) – no. (%)	7/12 (58.3)
Requirement of renal replacement therapy within 30 days – no. (%)	15 (38.4)
Underwent liver transplant – no. (%)	14 (35.8)
Death within 90 days – no. (%)	15 (38.4)
Safety Endpoints	
Occurrence of Adverse Event – no. (%)	19 (48.7)

*Verified HRS Reversal - two consecutive serum creatinine measurements of 1.5 mg per deciliter or less at least 2 hours apart and survival without renal-replacement therapy for at least 10 days after the completion of treatment
**HRS Reversal - any serum creatinine level of 1.5 mg per deciliter or less during the first 14 days
¥ Competing Event – liver transplant and/or death before patient could be evaluated for clinical success or failure

Disclosures: Prutha Shah: Nothing to Disclose, Brooklyn Baylis: Nothing to Disclose, Morgan Elias: Nothing to Disclose, John Knorr: Nothing to Disclose, Sarah Yeager: Nothing to Disclose, Jonathan Fenkel: Gilead: Consultant, Abbvie: Research Support to Institution, Alexion: Research Support to Institution, Ipsen: Research Support to Institution, BMS: Consultant, Madrigal: Consultant, David Sass: Gilead: Research support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Rebecca Loh: Nothing to Disclose, Jamie Schulte: Nothing to Disclose, Richard Kalman: Gilead: Speaking and Teaching

2427 | IS TIME LIVER? COMPARING OUTCOMES OF EARLY VERSUS LATE PARACENTESIS IN PATIENTS WITH ADVANCED CHRONIC LIVER DISEASE (ACLD)

Nisha Sanghani[1] Samuel Levine[1] Nishanth Eluri[1] Het Patel[1] Peyton Fair[2] Rana Moawad[2] Vishal Patel[1], [1]St. Luke's University Health Network, [2]Temple/St. Luke's School of Medicine

Background: Patients with advanced chronic liver disease (ACLD) decompensated by ascites are at risk for spontaneous bacterial peritonitis (SBP). Prior studies have shown that early diagnostic paracentesis (within 12 to 24 hours) for SBP detection is associated with lower in-hospital mortality rates, shorter lengths of hospital stay, and a reduced incidence of acute kidney injury (AKI) when compared to that of delayed diagnostic paracentesis. This study aims to investigate the current "time to diagnostic paracentesis" and differences in outcomes based on timing in patients with history of ACLD presenting with ascites at one hospital system. **Methods:** A retrospective chart review was performed on adult patients with history of ACLD, admitted at St. Luke's, Bethlehem Campus between 2021 and 2024 who received a paracentesis during their hospital stay. This study compared outcomes between paracentesis in 12 hours, 12-24 hours, and greater than 24 hours. Encounters for therapeutic paracentesis and paracentesis without subsequent fluid

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analysis were excluded. All statistical analyses were performed with Stata software. **Results:** Of the 317 encounters, 211 met inclusion criteria. 29% had a diagnostic paracentesis within 12 hours, 29% had one between 12-24 hours, and 42% had one greater than 24 hours after ascites detection. Diagnostic paracentesis after 24 hours of ascites detection had the longest length of hospital stay at 8.5 days compared to 6 days in the within 12-hour group and 5 days in the 12-24 hour group (p = 0.025). Diagnostic paracentesis within 12 hours compared with one after 12 hours resulted in a lower incidence of AKI (p-value = 0.032). There was no difference in incidence of ICU stay, 90-day mortality, and 30-day readmission when comparing all three groups. **Conclusion:** This study demonstrates that delaying diagnostic paracentesis in patients with ACLD presenting with ascites leads to an increased length of hospital stay and a higher incidence of AKI. Longer hospital stays are undesirable, as they can lead to increased risk of hospital-acquired infections, higher morbidity, increased in-hospital mortality, and increased healthcare costs. Likewise, AKIs often have long term effects including development of chronic kidney disease and increased risk of cardiovascular events and mortality. This research can be further utilized to create an algorithm at this hospital system for all ACLD patients presenting with ascites to receive a diagnostic paracentesis within 12-24 hours of ascites detection.

Table 1: Demographics and characteristics on presentation compared across time of diagnostic paracentesis start.

Factor	Overall	12 hours of ascites	24 hours of ascites	> 24 hours of ascites	p-value
N	211	62	61	88	
Age in Years, mean	61.05	60.95	60.69	61.36	0.940
Gender					0.160
Male	114 (54.03%)	32 (51.61%)	28 (45.90%)	54 (61.36%)	
Female	97 (45.97%)	30 (48.39%)	33 (54.10%)	34 (38.64%)	
Race					0.740
White or Caucasian	174 (82.46%)	53 (85.48%)	49 (80.33%)	72 (81.82%)	
Other	37 (17.54%)	9 (14.52%)	12 (19.67%)	16 (18.18%)	
Ethnicity					0.640
Non-Hispanic	143 (68.75%)	39 (63.93%)	43 (71.67%)	61 (70.11%)	
Hispanic	65 (31.25%)	22 (36.07%)	17 (28.33%)	26 (29.89%)	
Given antibiotics before paracentesis	108 (51.18%)	26 (41.94%)	38 (62.30%)	44 (50.00%)	0.075
Paracentesis location:					<0.001
Bedside in ED	29 (13.74%)	28 (45.16%)	1 (1.64%)	0 (0.00%)	
Bedside in ICU	16 (7.58%)	3 (4.84%)	7 (11.48%)	6 (6.82%)	
With interventional radiology	166 (78.67%)	31 (50.00%)	53 (86.89%)	82 (93.18%)	

Table 2: Outcomes compared across time of paracentesis start.

Factor	Overall	12 hours of ascites	24 hours of ascites	> 24 hours of ascites	p-value
N	211	62	61	88	
Length of Stay, median (IQR)	7 (4, 13)	6 (3, 12)	5 (3, 10)	8.5 (4.5, 15.5)	0.025
Spontaneous Bacterial Peritonitis positive	22 (10.43%)	7 (11.29%)	8 (13.11%)	7 (7.95%)	0.580
Acute Kidney Injury (AKI)	99 (46.92%)	22 (35.48%)	29 (47.54%)	48 (54.55%)	0.070
90-day mortality	74 (35.07%)	21 (33.87%)	19 (31.15%)	34 (38.64%)	0.620
30-day readmission	88 (41.71%)	24 (38.71%)	25 (40.98%)	39 (44.32%)	0.780
ICU stay	61 (29.05%)	19 (31.15%)	12 (18.67%)	30 (34.09%)	0.150

Table 3: Outcomes compared across time of paracentesis start (binary).

	Paracentesis started within:		
Factor	≤ 12 hours of ascites	> 12 hours of ascites	p-value
N	62	149	
Length of Stay, median (IQR)	6.00 (3.00, 12.00)	8.00 (4.00, 13.00)	0.330
Spontaneous Bacterial Peritonitis positive	7 (11.29%)	15 (10.07%)	0.790
Acute Kidney Injury (AKI)	22 (35.48%)	77 (51.68%)	0.032
90-day mortality	21 (33.87%)	53 (35.57%)	0.810
30-day readmission	24 (38.71%)	64 (42.95%)	0.570
ICU stay	19 (31.15%)	42 (28.19%)	0.670

Disclosures: Nisha Sanghani: Nothing to Disclose, Samuel Levine: Nothing to Disclose, Nishanth Eluri: Nothing to Disclose, Het Patel: Nothing to Disclose, Peyton Fair: Nothing to Disclose, Rana Moawad: Nothing to Disclose, Vishal Patel: Nothing to Disclose

2428 | A LARGE LANGUAGE MODEL (LLM) APPROACH FOR SCREENING LITERATURE AND DRAFTING SYSTEMATIC REVIEWS AND META-ANALYSES USING THE EFFICACY OF CARVEDILOL ON DECOMPENSATION AND MORTALITY COMPENSATED CIRRHOSIS AS A MOTIVATING EXAMPLE

Yuntao Zou[1] Iris Kim[2] Mi-Ok Kim[2] Jin Ge[2], [1]UCSF, [2]University of California, San Francisco

Background: Systematic reviews and meta-analyses entail extensive manual effort for screening articles, constructing analysis and drafting, which LLMs may excel at. This study investigates whether LLMs could emulate a previously written meta-analysis regarding whether carvedilol reduces decompensation and mortality in patients with compensated cirrhosis. **Methods:** We identified 1,077 articles from PubMed, Cochrane, and EMCASE regarding the clinical question. We used protected health information-compliant GPT-4o to filter and screen articles, which was compared with manual screening. We then embedded the filtered articles via retrieval augmented generation into GPT-4o and drafted portions of a systematic review and meta-analysis manuscript. Each section of the manuscript (Introduction, Methods, Results, and Discussion) was independently generated 100 times and evaluated using predefined criteria. **Results:** Of the 1,077 articles, 374 (34.7%) were duplicates across multiple databases. We tested several prompt engineering methods to improve performance: 1) N-shot prompting; 2) Detailed clarifications for inclusion and exclusion criteria; 3) Emphasis on specific details relevant to article selection; 4) Streamlining prompts. Of the 703 unique articles, GPT-4o achieved a sensitivity of 93% (95% CI: 66-100%) and specificity of 96% (95% CI: 94-97%) compared to manual review. LLM screening required 30M tokens (~$82.5) and 2 hrs compared to 62 hrs for manual review. In manuscript drafting: 1. For Introduction and Methods, 100% of drafts met the quality criteria (e.g., generating background, rationale, evidence gap, and study objective). 2. For **Results:** 0% of drafts met quality criteria (e.g., including study selection summary, outcome synthesis, and graphical analyses). Notably, GPT-4o was unable to extract or synthesize numerical and tabular data from constituent articles, resulting in incorrect or incomplete outcome reporting. 3. For Discussion: 89% of drafts included the correct structural components (e.g., principal findings, comparison with

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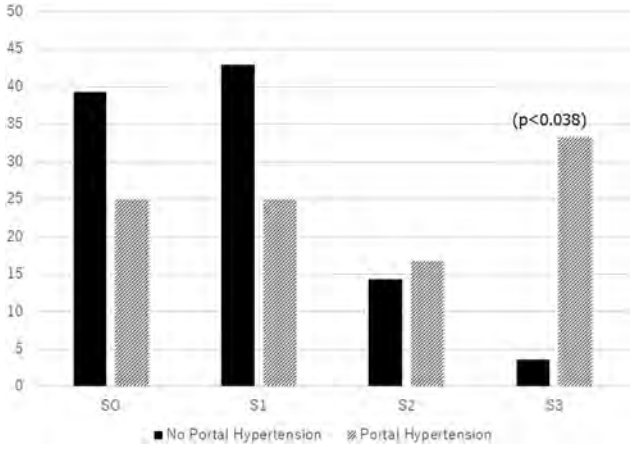
prior literature, limitations, relevance, and future directions). The drafted discussion sections, however, were based on inaccurate results and therefore were unusable. **Conclusion:** LLM shows high utility in automating the early phases of systematic reviews, particularly in screening abstracts and drafting Introduction and Methods sections. LLMs were insufficient for data extraction and result synthesis to draft Results and Discussion sections.

Disclosures: Yuntao Zou: Nothing to Disclose, Iris Kim: Nothing to Disclose, Mi-Ok Kim: Nothing to Disclose, Jin Ge: Merck and Co: Grant/Research Support, Iota Biosciences/Astellas Pharmaceuticals: Consultant, Madrigal Pharamaceuticals: Consultant, Gilead Sciences: Advisor

2429 | ENDOSCOPIC ULTRASOUND (EUS)-GUIDED PORTAL PRESSURE GRADIENT MEASUREMENT: CLINICAL USEFULNESS INCLUDING ASSESSMENT OF ACUTE RESPONSE TO PROPRANOLOL

Rafael Romero-Castro[1] Victoria Jimenez-Garcia[1] Isabel Carmona-Soria[1] Lourdes Grande-Santamaria[1] Paula Fernandez-Alvarez[1] Maria Tous-Romero[1] Enrique Silva Albarellos[1] Patricia Ruiz-Cordero[1] Javier Garcia-Perez[1] Manuel Rodriguez-Tellez[1] Angel Caunedo Alvarez[1], *[1]Virgen Macarena University Hospital*

Background: Portal hypertension is the main driver for complications in liver diseases. Portal pressure gradient can be assessed by Endoscopic Ultrasound (EUS). We report our experience on EUS-guided portal pressure gradient measurement (EUS-PPGm). **Methods:** Prospective study of patients referred for EUS-PPGm using a 25G dedicated needle was used. A 19G FNA needle was used for EUS-guided bilobar liver biopsy (EUS-BLB). Following baseline EUS-PPGm, 0.15 mg/kg of body weight, propranolol was administered intravenously by continuous infusión and the EUS-PPGm repeated 15 minutes later. **Results:** EUS-PPGm was performed in 70 patients. Indications: Assessment of metabolic associated steatotic liver disease in morbid obese patients: 43. Portal hypertension (PH): 20. Evaluation for curative therapy in hepatocellular carcinoma (HCC): 3. Acute response to intravenous propranolol: 4. Additional procedures were also performed in the same endoscopic session: Fifty-one (73%) EUS-BLB, 3 band ligation for esophageal varices and 1 EUS-guided coil therapy for gastric varices. EUS-PPGm was successfully obtained in 63/70 patients (90%). In 12/43 cases of morbid obese patients (28%) the EUS-PPGM was >6 mmHg in patients without varices nor fibrosis on EUS-BLB. In patients with morbid obesity, there was a statistically significant difference in the S3 score of steatosis in the group of portal hypertension (33%) in comparison with the no portal hypertension group (4%) [figure]. Patients were treated accordingly with the results of EUS-PPGm. There was observed a significant reduction of PPG in 2 patients treated with intravenous propranolol [10.5 mmHg to 4.75 mmHg (22%) and 10 mmHg to 2 mmHg (20%), respectively]. In the other two the PPG was normal, avoiding chronic use of beta-blockers. In 7 cases (10%) EUS-PPGm was not obtained. For rapid breathing movements (1 case) and for non-reliable pressure measurements (6 cases). In one case the 25G needle passed in close proximity to the hepatic artery. We experienced difficulty in punction the hepatic and the portal vein in one and two cases, respectively. In one case the 25G needle failed to transverse the liver capsule. Mean time to obtain EUS-PPGm 24 ± 2 minutes for EUS-BLB 17 ± 2 minutes and for combined EUS-PPGm plus EUS-BLB 45 ± 2 minutes. Three adverse events were observed. One mild epigastric pain 2 day after EUS-PPGm combined with EUS-BLB, one self-limited bleeding from the cardias and one atrial fibrillation. **Conclusion:** EUS-PPGm, even combined with EUS-BLB, seems safe, providing relevant clinical information. A notewhorty proportion of morbid obese patients were precociously diagnosed of portal hypertension by EUS-PPGm in early reversible stages without liver fibrosis on EUS-BLB. Acute response to intravenous propranolol can be obtained with EUS-PPGm.



Disclosures: Rafael Romero-Castro: Cook Medical: Consultant, Victoria Jimenez-Garcia: Nothing to Disclose, Isabel Carmona-Soria: Nothing to Disclose, Lourdes Grande-Santamaria: Nothing to Disclose, Paula Fernandez-Alvarez: Nothing to Disclose, Maria Tous-Romero: Nothing to Disclose, Enrique Silva Albarellos: Nothing to Disclose, Patricia Ruiz-Cordero: Nothing to Disclose, Javier Garcia-Perez: Nothing to Disclose, Manuel Rodriguez-Tellez: Nothing to Disclose, Angel Caunedo Alvarez: Nothing to Disclose

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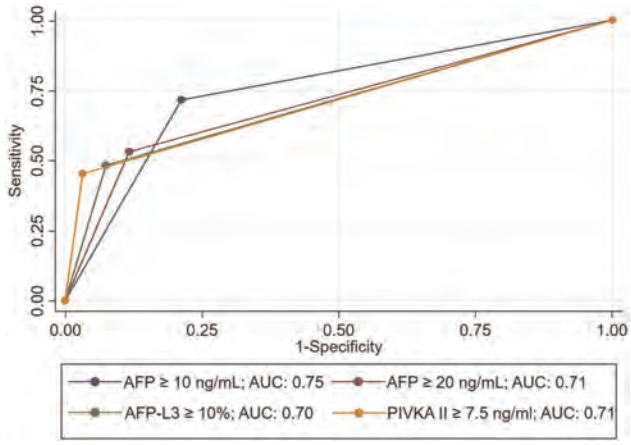
2430 | ENHANCED EARLY DETECTION OF HEPATOCELLULAR CARCINOMA USING THE GALAD SCORE IN VIETNAMESE CIRRHOTIC PATIENTS: A PROSPECTIVE–RETROSPECTIVE COHORT STUDY

Thong Vo[1], [1]University Medical Center Ho Chi Minh City

Background: Hepatocellular carcinoma (HCC) remains a major global health burden and is often diagnosed at advanced stages due to limitations in current surveillance tools. While ultrasound and alpha-fetoprotein (AFP) are widely used, their sensitivity for early-stage HCC remains suboptimal, particularly in high-risk cirrhotic populations. The GALAD score, which integrates gender, age, and three serum biomarkers (AFP, AFP-L3, and PIVKA-II), has emerged as a promising diagnostic tool for early HCC detection. This study aimed to evaluate the diagnostic accuracy of the GALAD score in Vietnamese patients with cirrhosis and to assess its association with tumor characteristics. **Methods:** A combined prospective and retrospective cohort study was conducted at the University Medical Center Ho Chi Minh City from January 2018 to May 2021. We enrolled 196 adult patients with cirrhosis, including 102 with HCC and 94 without. Cirrhosis was confirmed by biopsy or non-invasive criteria (APRI $\geq$2, FibroScan $\geq$12.5 kPa, or MRE $\geq$5.9 kPa). All patients underwent contrast-enhanced CT or MRI and quantitative testing of AFP, AFP-L3, and PIVKA-II within three months of imaging. The GALAD score was calculated using a validated formula. Diagnostic performance was assessed by ROC analysis, and the optimal cutoff was identified by the Youden index. Associations between GALAD score and tumor size, number, and location were evaluated. **Results:** The mean GALAD score was significantly higher in HCC patients (2.5; 95% CI: -2.43–11.09) than in non-HCC patients (-2.46; 95% CI: -6.15–2.04; $p < 0.001$). At the optimal cutoff of -0.518, the GALAD score demonstrated an AUROC of 0.91 (95% CI: 0.86–0.94), with 87.25% sensitivity and 82.98% specificity—outperforming all individual biomarkers (AFP, AFP-L3, and PIVKA-II) with statistically significant differences (all $p < 0.001$). The GALAD score showed a moderate correlation with tumor size ($r = 0.44$; $p < 0.001$), and was significantly higher in patients with multiple tumors compared to those with solitary lesions ($p = 0.0081$). No significant correlation was found between GALAD score and tumor location. **Conclusion:** The GALAD score demonstrates excellent diagnostic performance for HCC detection in Vietnamese patients with cirrhosis and correlates with tumor burden. Its integration into routine surveillance protocols may enhance early detection and risk stratification of HCC, particularly in resource-limited settings where imaging sensitivity is constrained.



Disclosures: Thong Vo: Nothing to Disclose

2431 | PREDICTIVE ACCURACY OF MELD 3.0 AND MELD-NA SCORES FOR MORTALITY AND REBLEEDING AFTER ENDOSCOPIC HEMOSTASIS IN CIRRHOSIS-ASSOCIATED VARICEAL HEMORRHAGE: A MULTICENTER STUDY

Shinya Yokoyama[1] Takashi Honda[1] yoji ishizu[1] Norihiro Imai[2] Takanori Ito[1] Kenta Yamamoto[1] Tomoyuki Tsuzuki[3] Masanao Nakamura[1] Hiroki Kawashima[1], [1]Nagoya University, [2]Nagoya University Graduate School of Medicine, [3]Toyota Kosei Hospital

Background: Acute variceal hemorrhage (AVH) is a life-threatening complication of cirrhosis, carrying substantial risks of mortality and rebleeding. Various scoring systems, including the Model for End-Stage Liver Disease (MELD), MELD-Na, Child-Pugh, and the newly introduced MELD 3.0 scores, have been proposed for outcome prediction in patients with liver diseases including cirrhosis, yet their comparative performance in long-term prognosis following AVH remains to be clarified. We aimed to evaluate which score best predicts mortality and rebleeding in patients with cirrhosis who achieve successful endoscopic hemostasis for AVH. **Methods:** This retrospective, multicenter study included 168 patients with cirrhosis who underwent successful endoscopic treatment including band ligation and glue injection for AVH of the esophagus and stomach between 2013 and 2023. Time-dependent receiver operating characteristic (ROC) analysis was performed to assess each score's predictive accuracy for mortality from day 30 to day 1080 post-AVH. Kaplan–Meier curves with log-rank tests compared survival in high- vs. low-score groups. Cox proportional hazard models identified independent

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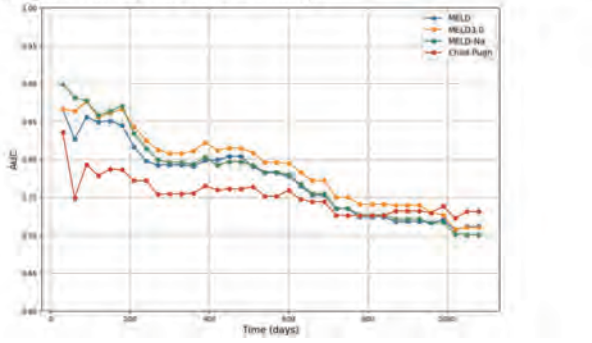
mortality predictors. Rebleeding was analyzed using a competing risk model, with Fine–Gray models incorporating death or variceal retreatment as competing events. **Results:** Median age was 66 years (interquartile range: 53–75), and 117 (69.6%) patients were men. Seventy-nine (47.0%) were classified as Child-Pugh class B and 42 (25.0%) as class C. MELD 3.0 consistently demonstrated the highest time-dependent ROC performance (average area under the curve: 0.789), remaining above 0.8 for up to 18 months after AVH. Patients with MELD 3.0 $\geq$15 had significantly worse survival (median 113 vs. 1750 days; hazard ratio [HR]: 2.71, 95% confidence interval [CI]: 1.68–4.37). Other independent mortality predictors included hepatocellular carcinoma (HR: 3.55, 95% CI: 2.05–6.14) and red blood cell transfusion (HR: 2.04, 95% CI: 1.15–3.62). In contrast, only a high MELD-Na score significantly predicted rebleeding (HR: 1.99, 95% CI: 1.17–3.39), showing a higher cumulative incidence of rebleeding in that group. Neither MELD 3.0, MELD, or Child-Pugh scores effectively stratified rebleeding risk. **Conclusion:** MELD 3.0 and MELD-Na scores are valuable non-invasive tools for predicting long-term mortality and rebleeding, respectively, in patients with cirrhosis after successful AVH hemostasis. These scoring systems can aid clinical decision-making by identifying high-risk individuals for intensive monitoring or intervention. Prospective studies are warranted to validate these findings and optimize post-bleeding management strategies.

Time-dependent receiver-operating characteristic analysis for the MELD, MELD 3.0, MELD-Na, and Child-Pugh scores at the time of initial acute variceal hemorrhage, plotting the area under the curve (AUC) for predicting mortality of every 30 days from 30–1080 days after successful endoscopic hemostasis of acute variceal hemorrhage



Disclosures: Shinya Yokoyama: Nothing to Disclose, Takashi Honda: Nothing to Disclose, yoji ishizu: Nothing to Disclose, Norihiro Imai: Nothing to Disclose, Takanori Ito: Nothing to Disclose, Kenta Yamamoto: Nothing to Disclose, Tomoyuki Tsuzuki: Nothing to Disclose, Masanao Nakamura: Nothing to Disclose, Hiroki Kawashima: Nothing to Disclose

2432 | SAFETY OF TESTOSTERONE SUPPLEMENTATION IN MEN WITH CIRRHOSIS AND HYPOGONADISM: A PROPENSITY SCORE-MATCHED STUDY FROM A MULTINETWORK STUDY

Tinsae Tsegaye Anebo[1] Laith Alomari[1] Karecia Byfield[1] Phuuwadith Wattanachayakul[1] Ghideon Ezaz[1],
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Background: Hypogonadism is a prevalent condition among men with cirrhosis, often leading to significant adverse clinical outcomes such as muscle wasting, decreased bone density, fatigue, sexual dysfunction, and a reduced quality of life. Testosterone supplementation has been explored as a potential therapy to counter these effects, but concerns regarding its safety, particularly about cardiovascular risks, and potential exacerbation of hepatic complications. This study aims to assess the safety and clinical outcomes of testosterone supplementation in men with cirrhosis and hypogonadism, providing insight into its potential benefits and risks. **Methods:** We used the US Collaborative Network-TriNetX database to identify male patients with an index diagnosis of cirrhosis and subsequent hypogonadism with and without testosterone supplementation between 2012 and 2024. Cohort comparability was achieved through 1:1 propensity score matching based on age and ethnicity. We evaluated the following outcomes censored at 12 years: all-cause mortality, hospitalization, anemia, SBP, HCC, variceal bleeding, ascites, hepatic encephalopathy, new-onset type 2 diabetes, sarcopenia, malnutrition, new myocardial infarction, and new stroke. Generalized linear models were used to measure the association, and estimates were presented as risk ratios/hazard ratios and 95% confidence intervals. A p-value of <0.05 was considered significant. **Results:** We used the US Collaborative Network-TriNetX database to identify male patients with an index diagnosis of cirrhosis and subsequent hypogonadism with and without testosterone supplementation between 2012 and 2024. Cohort comparability was achieved through 1:1 propensity score matching based on age and ethnicity. We evaluated the following outcomes censored at 12 years: all-cause mortality, hospitalization, anemia, SBP, HCC, variceal bleeding, ascites, hepatic encephalopathy, new-onset type 2 diabetes, sarcopenia, malnutrition, new myocardial infarction, and new stroke. Generalized linear models were used to measure the association, and estimates were presented as risk ratios/hazard ratios

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and 95% confidence intervals. A p-value of < 0.05 was considered significant. **Conclusion:** These findings suggest that testosterone supplementation in men with cirrhosis appears to be safe, with no increased risk of major adverse events such as myocardial infarction or stroke. While it does not significantly impact overall survival, it may help mitigate certain cirrhosis-related complications, particularly reducing the risk of ascites and potentially alleviating muscle loss. Further research is needed to confirm these findings and evaluate the long-term safety and efficacy of testosterone therapy in this population. The decision to initiate treatment should be carefully individualized, considering potential benefits and risks.

Table 1-Clinical Outcomes

Clinical Outcome	HR	95% CI	P-value
All-Cause Mortality	0.908	(0.795, 1.037)	0.155
Hospitalization	1.079	(0.888, 1.311)	0.445
Spontaneous Bacterial Peritonitis (SBP)	1.139	(0.795, 1.632)	0.478
Anemia	0.941	(0.792, 1.119)	0.491
Hepatocellular Carcinoma (HCC)	0.613	(0.173, 2.172)	0.443
Variceal Bleeding	1.147	(0.764, 1.722)	0.506
Ascites	**0.757**	**(0.620, 0.925)**	**0.006**
Hepatic Encephalopathy	0.902	(0.708, 1.149)	0.402
Sarcopenia	0.478	(0.223, 1.031)	0.054
Acute Myocardial Infarction	0.852	(0.552, 1.114)	0.242
New Stroke/ TIA	0.927	(0.692, 1.243)	0.614
New Type 2 Diabetes Mellitus	1.129	(0.900, 1.417)	0.295
Malnutrition	0.920	(0.753, 1.124)	0.412

Table 2-Baseline patient characteristics after propensity score matching

Characteristic	Cohort 1(Testosterone Group (N = 1,524)	Cohort 2 (N = 1,524)	P-Value	Std Diff.
Age at Index (Mean ± SD)	59.0 ± 11.2	58.8 ± 11.5	0.648	0.015
White (%)	1,517 (72.8%)	1,536 (73.6%)	0.449	0.024
American Indian or Alaska Native (%)	10 (0.5%)	14 (0.5%)	1.000	-0.001
Unknown Race (%)	124 (6.4%)	106 (5.8%)	0.278	0.033
Native Hawaiian or Other Pacific Islander (%)	10 (0.5%)	10 (0.5%)	1.000	-0.001
Unknown Ethnicity (%)	264 (13.2%)	254 (12.2%)	0.617	0.010
Not Hispanic or Latino (%)	1,368 (71.4%)	1,534 (74.1%)	0.122	0.012
Hispanic or Latino (%)	151 (7.8%)	146 (7.1%)	0.597	0.010
Black or African American (%)	176 (8.8%)	171 (8.0%)	0.503	0.032
Male (%)	1,524 (100%)	1,524 (100%)	-	-
Other Race (%)	96 (3.5%)	85 (3.4%)	0.791	0.009
Asian (%)	28 (1.5%)	30 (1.6%)	0.791	0.009

Disclosures: Tinsae Tsegaye Anebo: Nothing to Disclose, Laith Alomari: Nothing to Disclose, Karecia Byfield: Nothing to Disclose, Phuuwadith Wattanachayakul: Nothing to Disclose, Ghideon Ezaz: Nothing to Disclose

2433 | BASELINE CHARACTERISTICS AND IN-HOSPITAL OUTCOMES OF PATIENTS WITH CIRRHOSIS UNDERGOING CORONARY ARTERY BYPASS GRAFTING (CABG): A SEVEN-YEAR ANALYSIS FROM THE NATIONAL INPATIENT SAMPLE

Omar Alkasabrah[1] Abdullah Hafeez[1] Ritu C. Tated[2] Siddharth Agrawal[1] Radhe Shah[3] Kriti Soni[4] Jatin Thukral[1] Mutaz Kalas[5] Ismail Elkhattib[6] Tanuj Sharma[1], [1]NYMC/Landmark Medical Center, [2]New York Medical College, [3]Beth Israel Deaconess Medical Center, [4]SUNY Upstate Medical University, [5]Texas Tech University Health Science Center EL Paso, [6]University of Nebraska

Background: Cirrhosis is associated with multisystem dysfunction that may increase perioperative risk in cardiac surgery patients. Coronary artery bypass grafting (CABG) remains a cornerstone therapy for advanced coronary disease, yet cirrhosis introduces physiological vulnerabilities that may alter procedural outcomes. We aimed to explore how cirrhosis influences postoperative complications and mortality in patients undergoing CABG. **Methods:** We conducted a retrospective cohort study using the National Inpatient Sample (2016–2022). Demographic, clinical, and hospital variables were compared, and multivariable logistic regression was used to assess the adjusted odds of in-hospital complications, controlling for comorbidities and institutional characteristics. The primary outcome was in-hospital mortality. Secondary outcomes included atrial fibrillation, cardiogenic shock, need for mechanical ventilation, and bleeding complications. **Results:** Among 1,296,455 CABG hospitalizations, 10,410 (0.8%) involved patients with cirrhosis. Compared to patients without cirrhosis, the cirrhosis population was younger and more likely to be male (77.7% vs. 75.7%). They had higher rates of diabetes (65.9% vs. 59.7%), anemia (26.5% vs. 16.4%), CKD (23.9% vs. 18.1%), alcohol use (22.5% vs. 3.2%), and coagulopathy (20.3% vs. 6.8%) ($p < 0.001$ for all). Cirrhotics also had longer hospital stays (12.5 vs. 9.8 days, $p < 0.001$) and higher total charges. In adjusted models, cirrhosis was associated with significantly increased in-hospital mortality (5.76% vs. 2.41%; aOR 2.194, 95% CI 2.004–2.401, $p < 0.001$), cardiogenic shock (aOR 1.067, 95% CI 1.023–1.114, $p = 0.002$), need for mechanical ventilation (aOR 1.107, 95% CI 1.038–1.181, $p = 0.002$), atrial fibrillation (aOR 1.047, 95% CI 1.004–1.092, $p = 0.032$), and bleeding complications (aOR 1.257, 95% CI 1.205–1.310, $p < 0.001$). **Conclusion:** Cirrhosis independently doubles the risk of mortality following CABG and significantly increases bleeding and cardiorespiratory complications. Cirrhosis contributes to physiologic fragility that complicates surgical recovery. These results highlight the need for careful risk assessment and multidisciplinary management in patients with chronic liver disease undergoing cardiac surgery.

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Table 1. Baseline and clinical characteristics of patients with and without cirrhosis undergoing CABG in the US

	CABG w/o Cirrhosis	CABG w/ Cirrhosis	P VALUE
Number (n)	n=1286045 (99.20%)	n=10410 (0.80%)	
Age			
35-49y	5.52%	4.95%	
50-64y	34.31%	42.75%	
65-79y	51.85%	48.03%	
Total charges	246000	304644	<0.001
Length of Stay	9.8+/-7.6	12.5+/-10.73	<0.001
Baseline characteristics			
Gender			<0.001
Male	75.66%	77.71%	
§Female	24.34%	22.29%	
Race			<0.001
White	78.30%	75.89%	
Black	6.99%	7.20%	
Hispanic	7.81%	10.85%	
Asian	3.39%	2.16%	
Native American	0.56%	0.82%	
Insurance status			<0.001
Medicare/Medicaid	63.94%	66.71%	
Private including HMO	29.99%	25.46%	
Self-pay/no charge/other	6.06%	7.83%	
Hospital teaching status			<0.001
Rural	2.64%	1.83%	
Urban nonteaching	14.08%	11.38%	
Urban teaching	83.29%	86.79%	
Hospital bed size			0.024
Small	11.52%	10.81%	
Medium	26.55%	26.13%	
Large	61.93%	63.06%	
Hospital Region			<0.001
Northeast	16.85%	15.18%	
Midwest	22.53%	21.57%	
South	43.88%	46.11%	
West	16.74%	17.15%	
Comorbidities			
Hypertension	88.83%	90.01%	0.001
Diabetes Mellitus	59.65%	65.90%	<0.001
Hyperlipidemia	73.75%	65.99%	<0.001
Anemia	16.35%	26.46%	<0.001
COPD	15.19%	22.53%	<0.001
Obesity	31.85%	32.52%	0.144
Coagulation disorders	6.82%	20.27%	<0.001
CKD	18.13%	23.87%	<0.001
Alcohol use	3.25%	22.53%	<0.001
Tobacco use	30.97%	29.73%	0.006
Drug use	19.49%	26.51%	<0.001
Outcomes			
Mortality	2.41%	5.76%	<0.001
Stroke	17.08%	19.74%	<0.001
Atrial Fibrillation	37.12%	38.76%	<0.001
Cardiogenic shock	37.80%	48.03%	<0.001
Mechanical ventilation	8.09%	12.68%	<0.001
Bleeding Complication	51.71%	57.16%	<0.001

Table 2. Adjusted Odds Ratios of mortality and other major complications in patients with and without cirrhosis undergoing CABG in the US

	Odd's Ratio	CI Interval	P value
In hospital mortality			
No Cirrhosis	Reference		
Cirrhosis	2.194	2.004-2.401	<0.001
Stroke			
No Cirrhosis	Reference		
Cirrhosis	0.924	0.878-0.973	0.0025
Atrial Fibrillation			
No Cirrhosis	Reference		
Cirrhosis	1.047	1.004-1.092	0.032
Cardiogenic shock			
No Cirrhosis	Reference		
Cirrhosis	1.067	1.023-1.114	0.002
Mechanical ventilation			
No Cirrhosis	Reference		
Cirrhosis	1.107	1.038-1.181	0.002
Bleeding complications			
No Cirrhosis	Reference		
Cirrhosis	1.257	1.205-1.310	<0.001

Disclosures: Omar Alkasabrah: Nothing to Disclose, Abdullah Hafeez: Nothing to Disclose, Ritu C. Tated: Nothing to Disclose, Siddharth Agrawal: Nothing to Disclose, Radhe Shah: Nothing to Disclose, Kriti Soni: Nothing to Disclose, Jatin Thukral: Nothing to Disclose, Mutaz Kalas: Nothing to Disclose, Ismail Elkhattib: Nothing to Disclose, Tanuj Sharma: Nothing to Disclose

2434 | EFFICACY AND SAFETY OF RECOMBINANT HUMAN THROMBOPIETIN INJECTION IN PATIENTS WITH CHRONIC LIVER DISEASE-RELATED THROMBOCYTOPENIA SCHEDULED FOR INVASIVE SURGERY: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY

Yifan Han[1] Sikui Wang[2] Jinghang Xu[1] Jinglan Jin[3] Jia Shang[4] Yongning Xin[5] Youwen Tan[6] Dazhi Zhang[7] Jinlin Hou[8] Ping An[9] Wen Xie[10] Yujuan Guan[11] Qingfang Xiong[12] Hong Wu[13] Huiguo Ding[14] Yu Chen[14] Rongkuan Li[15] Zhili Wen[16] Mingqin Lu[17] Jinhui Yang[18] Zhongyin Zhou[19] Yongjian Zhou[20] Zujiang Yu[21] Kecan Lin[22] Wei Wang[23] Yan Huang[24] Yuemin Nan[25] Xinhua Luo[26] Rongshu Shi[27] Yi Kang[4] Tao Han[28] Shiyao Chen[29] Kai Wang[16] Yunfeng Shan[17] Jiaping Li[30] Pingguo Liu[31] Zheng Lu[32] Jun Chen[33] Zhen Liu[34] Liaoyun Zhang[35] Li Yang[13] Jifang Sheng[36] Zhan Zeng[1] Ning Lin[1] yanyan yu[1] Xiaoyuan Xu[1], [1]Peking University First Hospital, [2]Liaocheng People's Hospital, [3]The First Hospital of Jilin University, [4]Henan Provincial People's Hospital, [5]Qingdao Municipal Hospital, [6]The Third People's Hospital of Zhenjiang, [7]The Second Affiliated Hospital of Chongqing Medical University, [8]Nanfang Hospital, Southern Medical University, [9]The Sixth People's Hospital of Shenyang, [10]Beijing Ditan Hospital, Capital Medical University, [11]Guangzhou Eighth People's Hospital, Guangzhou Medical University, [12]The Second Hospital of Nanjing, [13]West China Hospital, Sichuan University, [14]Beijing Youan Hospital, Capital Medical University, [15]The Second Hospital of Dalian Medical University, [16]The Second Affiliated Hospital of Nanchang University, [17]The First Affiliated Hospital of Wenzhou Medical University, [18]The Second Affiliated Hospital of Kunming Medical University, [19]Renmin Hospital of Wuhan University, [20]Guangzhou First People's Hospital, [21]The First Affiliated Hospital of Zhengzhou University, [22]Mengchao Hepatobiliary Hospital of Fujian Medical University, [23]The Second Affiliated Hospital of Fujian Medical University, [24]Xiangya Hospital of Central South University, [25]The Third Hospital of Hebei Medical University, [26]Guizhou Provincial People's Hospital, [27]Affiliated Hospital of

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Zunyi Medical University, [28]Tianjin People's Hospital, [29]Zhongshan Hospital, Fudan University, [30]The First Affiliated Hospital, Sun Yat-sen University, [31]Zhongshan Hospital Xiamen University, [32]The First Affiliated Hospital of Bengbu Medical University, [33]Shenzhen Third People's Hospital, [34]Liuzhou People's Hospital, [35]First Hospital of Shanxi Medical University, [36]The First Affiliated Hospital, Zhejiang University School of Medicine

Background: Chronic liver disease (CLD)-related thrombocytopenia limits the feasibility of invasive procedures. Recombinant human thrombopoietin (rhTPO) has demonstrated a favorable safety in clinical application without hepatotoxicity. In this study, we assessed the efficacy and safety of rhTPO in patients with CLD-related thrombocytopenia undergoing elective invasive procedures. **Methods:** This multicenter, randomized(2:1), double-blind, parallel-group, placebo-controlled study was conducted in 41 centers and enrolled adult Chinese patients with CLD-related thrombocytopenia (platelet count $<50\times10^9$/L). Eligible subjects were randomized to receive either rhTPO (15,000 IU) or placebo once daily for a maximum of 5 or 7 days. Treatment was discontinued if platelet counts $>50\times10^9$/L and increased by $>10\times10^9$/L from baseline (Figure 1). The invasive surgery were performed within 1 week after the end of treatment. The primary endpoint was the proportion of subjects with sustained platelet counts $\geq50\times10^9$/L from 24 hours before surgery to 7 days post-surgery, without requiring emergency bleeding management(including whole blood, red blood cells, platelets, plasma, or cryoprecipitate transfusion). **Results:** A total of 120 subjects were randomized, with 80 receiving rhTPO and 40 receiving placebo. By day 7 following surgery, the primary endpoint was met in 85.00% of subjects treated with rhTPO (95%CI: 75.26%–92.00%), compared with 12.50% of placebo-treated subjects (95%CI: 4.19%–26.80%), yielding a statistically significant difference of 72.21% (95%CI: 59.55%–84.86%, stratified Cochran-Mantel-Haenszel test, $p < 0.0001$, Figure 2a). At the preoperative assessment, 92.50% of subjects in the rhTPO group (95% CI: 84.39%-97.20%) achieved platelet counts $\geq50\times10^9$/L compared with 20.00% in the placebo group (95% CI: 9.05%-35.65%), with a statistically significant difference ($p < 0.0001$, Figure 2b). rhTPO markedly reduced the platelet transfusion, with 92.50% of rhTPO-treated patients (95% CI: 84.39%-97.20%) avoiding transfusion, *vs.* only 25.00% in the placebo group (95% CI: 12.69%-41.20%), yielding a significant between-group difference ($p < 0.0001$, Figure 2c). In addition, the median duration of platelet counts $\geq50\times10^9$/L was prolonged to 21 days in the rhTPO group (95% CI: 20–23), *vs.* 3 days in the placebo group (95% CI: 2–4), with a stratified hazard ratio of 0.38 ($p = 0.0007$, Figure 3). Regarding the safety, similar results of treatment-emergence adverse events (TEAEs) were found in rhTPO-treated (81.25%) and placebo-treated subjects (87.50%). Treatment-related TEAEs occurred in 12.5% of subjects in both the rhTPO and placebo groups. No treatment-related serious adverse events were observed. **Conclusion:** rhTPO is effective and well tolerated in the patients enrolled in this study and could be used as a viable therapeutic option for CLD-related thrombocytopenia in patients undergoing elective invasive procedures.

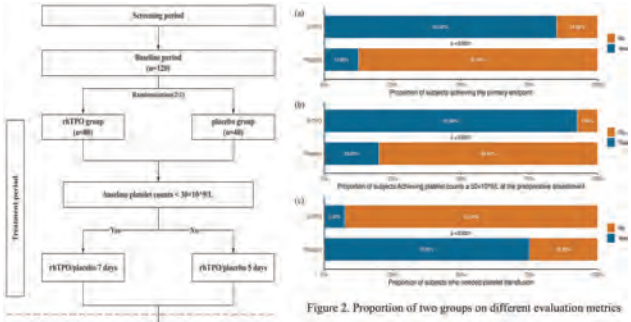

Figure 2. Proportion of two groups on different evaluation metrics

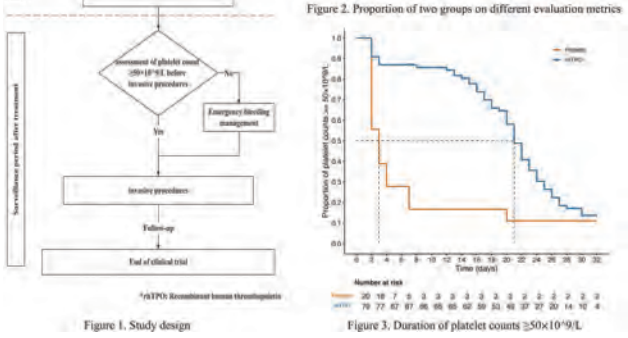

Figure 3. Duration of platelet counts ≥50×10^9/L

Figure 1. Study design

Disclosures: Yifan Han: Nothing to Disclose, Sikui Wang: Nothing to Disclose, Jinghang Xu: Nothing to Disclose, Jinglan Jin: Nothing to Disclose, Jia Shang: Nothing to Disclose, Yongning Xin: Nothing to Disclose, Youwen Tan: Nothing to Disclose, Dazhi Zhang: Nothing to Disclose, Jinlin Hou: Nothing to Disclose, Ping An: Nothing to Disclose, Wen Xie: Nothing to Disclose, Yujuan Guan: Nothing to Disclose, Qingfang Xiong: Nothing to Disclose, Hong Wu: Nothing to Disclose, Huiguo Ding: Nothing to Disclose, Yu Chen: Nothing to Disclose, Rongkuan Li: Nothing to Disclose, Zhili Wen: Nothing to Disclose, Mingqin Lu: Nothing to Disclose, Jinhui Yang: Nothing to Disclose, Zhongyin Zhou: Nothing to Disclose, Yongjian Zhou: Nothing to Disclose, Zujiang Yu: Nothing to Disclose, Kecan Lin: Nothing to Disclose, Wei Wang: Nothing to Disclose, Yan Huang: Nothing to Disclose, Yuemin Nan: Nothing to Disclose, Xinhua Luo: Nothing to Disclose, Rongshu Shi: Nothing to Disclose, Yi Kang: Nothing to Disclose, Tao Han: Nothing to Disclose, Shiyao Chen: Nothing to Disclose, Kai Wang: Nothing to Disclose, Yunfeng Shan: Nothing to Disclose, Jiaping Li: Nothing to Disclose, Pingguo Liu: Nothing to Disclose, Zheng Lu: Nothing to Disclose, Jun Chen: Nothing to Disclose, Zhen Liu: Nothing to Disclose, Liaoyun Zhang: Nothing to Disclose, Li Yang: Nothing to Disclose, Jifang Sheng:

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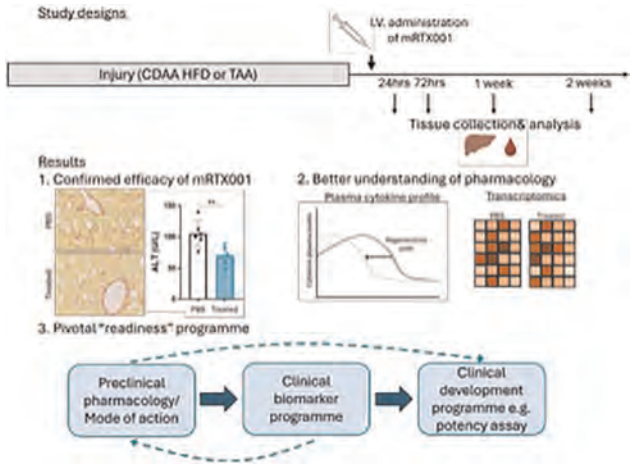
Nothing to Disclose, Zhan Zeng: Nothing to Disclose, Ning Lin: Nothing to Disclose, yanyan yu: Nothing to Disclose, Xiaoyuan Xu: Nothing to Disclose

2435 | EARLY MODULATION OF INR AND MELD AFTER REGENERATIVE MACROPHAGE THERAPY IS ASSOCIATED WITH FAVOURABLE CLINICAL OUTCOMES AT THREE-YEAR FOLLOW-UP

Paul Brennan[1] Jose Meseguer-Ripolles[2] Thomas Manship[3] Alison Glover[4] Debbie Troland[5] Iain MacPherson[1] Catriona Graham[6] Rhona Aird[5] Scott Semple[7] David Morris[8] Alasdair Fraser[4] Chloe Pass[4] Neil McGowan[4] Marc Turner[4] Lynn Manson[4] Neil Lachlan[9] John Dillon[1] Alastair Kilpatrick[5] John Campbell[2] Francesca Moroni[10] Clifford Brass[11] Lara Campana[2] Jonathan Fallowfield[8] Stuart Forbes[8], [1]University of Dundee, [2]Resolution Therapeutics Ltd, [3]Royal Infirmary of Edinburgh, [4]Scottish National blood Transfusion Services, [5]Centre for Regenerative Medicine, University of Edinburgh, [6]Wellcome Trust CRF, University of Edinburgh, [7]Centre for Cardiovascular Science, University of Edinburgh, [8]University of Edinburgh, [9]Glasgow Royal Infirmary, [10]University of Aberdeen, [11]Brass Pharma Consulting LLC

Background: The Phase 2 MATCH study demonstrated that autologous regenerative macrophage cell therapy (RMT) enhanced overall, and transplant-free survival at 3 years in patients with advanced cirrhosis compared to a well-matched standard of care (SoC) control population (SoC: 3 transplant, 8 deaths; vs cell treatment: 2 deaths at 3-year follow-up; Fig.1A). Preclinical models have established a link between regenerative macrophages and anti-inflammatory, and anti-fibrotic functions that facilitate liver regeneration. In patients, improved regeneration should restore the liver's synthetic capacity, ensuring long-term clinical benefits. However, no direct correlation between clinical outcomes and early biomarker measurements of liver function have been established to substantiate the RMT mode of action elucidated in preclinical models. **Methods:** In this study, we investigated the correlation between long-term clinical benefits (transplant-free survival and overall survival) at three years post-treatment and early modulation (90 days post-treatment) of clinical markers of liver synthetic function, such as INR (International Normalised Ratio), and a validated prognostic score associated with overall survival, MELD (Model for End-Stage Liver Disease). **Results:** Directional changes in INR and MELD at 90 days post-therapy were associated with transplant-free survival at three years. For instance, INR exhibited a positive predictive value (PPV) of 0.5, and a strong negative predictive value (NPV) of 0.96 in the cell treatment group, with clinical non-responders (i.e., the two patients who died within the 3-year FU period) not demonstrating any INR improvement at 90 days (Fig.1B). Further, delta MELD at 90 days showed a PPV of 0.29 and a NPV of 1, indicating an increase in MELD score for both clinical non-responders compared to baseline in the cell treatment group (Fig. 1C). **Conclusion:** This is the first dataset to demonstrate that RMT administration is associated with early changes in biomarkers associated with liver function (INR; dMELD), which appear to correlate with better survival in patients with advanced cirrhosis. The primary statistical limitation of this study is the low number of clinical non-responders in the cell treatment group (n = 2). Further follow-up of this cohort will offer additional insights into the relationship between longer-term outcomes of RMT and early modulation of circulating biomarkers.



Disclosures: Paul Brennan: Nothing to Disclose, Jose Meseguer-Ripolles: Resolution Therapeutics LTD: Employee, Thomas Manship: Nothing to Disclose, Alison Glover: Nothing to Disclose, Debbie Troland: Nothing to Disclose, Iain MacPherson: Nothing to Disclose, Catriona Graham: Nothing to Disclose, Rhona Aird: Nothing to Disclose, Scott Semple: Nothing to Disclose, David Morris: Nothing to Disclose, Alasdair Fraser: Nothing to Disclose, Chloe Pass: Nothing to Disclose, Neil McGowan: Nothing to Disclose, Marc Turner: Nothing to Disclose, Lynn Manson: Nothing to Disclose, Neil Lachlan: Nothing to Disclose, John Dillon: Nothing to Disclose, Alastair Kilpatrick: Resolution Therapeutics: Consultant, John Campbell: Nothing to Disclose, Francesca Moroni: Nothing to Disclose, Clifford Brass: Nothing to Disclose, Lara Campana: Resolution Therapeutics: Employee, Jonathan Fallowfield: Stimuliver: Advisor, Ipsen: Advisor, Kynos Therapeutics: Advisor, Resolution Therapeutics: Consultant, River 2 Renal Corp.: Advisor, Global Clinical Trial Partners: Advisor, Guidepoint: Consultant,

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2436 | COMPARATIVE OUTCOMES OF RESPIRATORY SYNCYTIAL VIRUS VACCINATION AND INFECTION IN HOSPITALIZED PATIENTS WITH ADVANCED LIVER DISEASE

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Background: Viral respiratory infections in patients with cirrhosis are associated with increased morbidity and mortality. Vaccinations are a widely used preventative measure aimed at mitigating these negative outcomes. The incidence of RSV infection and real-world outcomes of RSV vaccination is not well explored in chronic liver disease. **Methods:** This retrospective analysis of patients was completed using TriNetX. We created a base population of adults with a healthcare examination from 5/1/2023-10/31/2024. Patients were categorized as either having cirrhosis or not having cirrhosis (controls). We first reported the incidence proportion, or cumulative incidence, and prevalence (%) of RSV infection in patients with cirrhosis, with a focus on differences by sex, ethnicity, obesity, COPD and asthma. Next, to assess the effect of vaccination on the risk of RSV infection, we compared RSV infection from 11/1/2024-5/1/2025 in patients with cirrhosis who received the vaccine from 5/1/2023-10/31/2024 to RSV infection from 11/1/2024-5/1/2025 in patients with cirrhosis who did not receive the RSV vaccine. Incidence proportions were compared using relative risks ratio with 95% confidence intervals. **Results:** A total of 70,671 participants with cirrhosis were identified of which 6,977 received the RSV vaccine and 65,305 did not. The cumulative incidence of RSV infection in patients with cirrhosis was 0.21% and the prevalence was 0.77%, compared to 0.07% and 0.24% in controls, respectively. In the cirrhosis cohort, incidence of RSV was higher in patients who also had obesity (0.24% vs 0.16%, RR 1.50, 95% CI (1.02, 2.20), p = 0.038), COPD (0.31% vs 0.18%, (RR 1.72, 95%CI (1.17, 2.53) p = 0.006) or asthma (0.30% vs 0.18%, RR 1.67, 95% CI (1.12-2.49) p = 0.012) and was trended toward higher in females vs. males (0.22% vs. 0.18%, RR 1.22, 95% CI 0.88-1.69, p = 0.24) and in Hispanics vs. Non-Hispanics (0.30% vs. 0.22%, RR 1.30, 95% CI 0.79-2.12, p = 0.30). The incidence of RSV infection did not differ in cirrhosis participants with and without vaccination (0.19% vs. 0.20%, RR 0.98, 95% CI 0.57-1.68, p = 0.94). Similar findings were observed in patients without liver disease (0.08% vaccinated vs. 0.07% unvaccinated, RR 1.11, 95% CI 0.96-1.28, p = 0.15). **Conclusion:** In this large nationally representative sample, the incidence of RSV infection was elevated in cirrhosis compared to those without liver disease. Within patients with cirrhosis, the incidence was elevated in those who also had COPD, obesity or asthma. Importantly, the incidence did not differ in those with and without the RSV vaccine, however this may be limited by the short term follow up of 1 cold/flu cycle. Additional research and long-term data are needed to further assess the benefit of the RSV vaccine in patients with chronic liver disease.

	Total patients	Incident cases	Incident proportion	Relative risk
Cirrhosis + Obesity	36,853	76	0.24	1.50 (1.02, 2.20) P = 0.038
Cirrhosis without Obesity	30,964	40	0.16	
Cirrhosis + COPD	16,400	40	0.31	1.72 (1.17, 2.53) p=0.006
Cirrhosis without COPD	51,417	72	0.18	
Cirrhosis + Asthma	14,429	35	0.30	1.67 (1.12-2.49) p =0.012
Cirrhosis without Asthma	53,388	77	0.18	
Cirrhosis + RSV vaccine	6,977	12	0.19	0.98, 95% CI 0.57-1.68, p=0.94
Cirrhosis without RSV vaccine	65,305	101	0.20	
Control + RSV vaccine	301,633	209	0.08	1.11, 95% CI 0.96-1.28, p = 0.15
Control without RSV vaccine	4,427,240	2,297	0.07	

Disclosures: Adil Fazir: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Ami Patel: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Avania Medical: Grant/Research Support, Intercept: Grant/Research Support

2437 | ORAL CHOLATE CHALLENGE TEST CHARACTERIZES FUNCTIONAL DIFFERENCES BETWEEN CHILD-PUGH A5 AND A6

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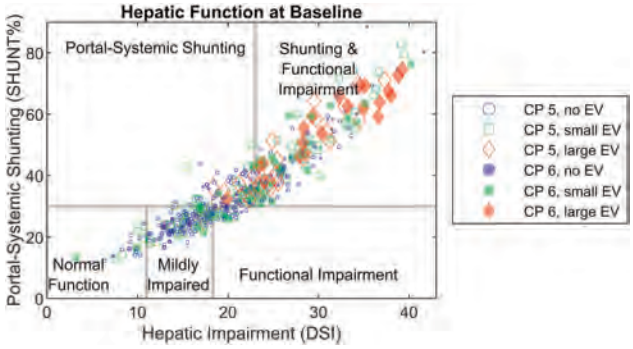
Background: Liver function in patients with Child-Pugh (CP) A cirrhosis may vary from normal to severe functional impairment and shunting. Staging disease severity in patients with CP A cirrhosis is important for clinical decisions regarding further diagnostic testing, treatment, or follow-up interval. We used the oral cholate challenge test results to characterize and compare patients with CP A5 and A6. **Methods:** Subjects were enrolled in two US prospective studies linking the oral cholate challenge test results to endoscopic findings. Test parameters were quantified from 20- and 60-min concentrations of orally administered d4-cholate. Serum was analyzed for cholate concentrations by LC-MS/MS. A disease severity index (DSI) and portal systemic shunting (SHUNT%) were calculated. We combined data from subjects with CP A cirrhosis from two studies: SHUNT-V ($n = 238$) and HALT-C ($n = 216$). Standard laboratory values included albumin, alkaline phosphatase, ALT, AST, bilirubin, INR, and platelet count. **Results:** Subjects were age 56 ± 11 years, BMI 32 ± 7 kg/m^2, 86% overweight, 54% obese, 61% male, 84% White race, and 13% Hispanic ethnicity. Etiologies included hepatitis C (61%), MASLD/MASH (25%), and alcohol-associated liver disease (8%). Out of 454 subjects, 128 (28%) had small esophageal varices (EV), and 48 (11%) had large EV. Demographics were similar between CP A5 and A6; subjects with CP A6 were more likely to have hepatitis C ($p = 0.018$) and less likely to have MASLD/MASH ($p = 0.008$); laboratory values and MELD scores were significantly worse for CP A6 ($p < 0.001$), except ALT ($p = 0.449$); subjects with CP A6 were more likely to have large EV (23%) compared to CP A5 (8%) ($p = 0.0001$). Oral cholate challenge test parameters showed significantly worse function and shunting (Figure 1) in subjects with CP A6 (DSI, 25.2 ± 7.9; SHUNT%, 43.8% ± 16.7%) versus CP A5 (DSI, 19.8 ± 6.4; SHUNT%, 33.0% ± 12.4%) ($p < 0.0001$). For the detection of large EV on endoscopy, AUROCs for DSI (0.82) and SHUNT% (0.83) were significantly higher than CP score (0.63) ($p < 0.0001$). **Conclusion:** Patients with CP A6 cirrhosis have worse hepatic function and more portal-systemic shunting than patients with CP A5 cirrhosis. The oral cholate challenge test allowed characterization of functional differences in CP A5 versus A6 and was more predictive for EV than CP score. Given the heterogeneity within the CP classification, the cholate challenge test may be useful clinically in staging disease severity.



Disclosures: Naga Chalasani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Mitchell Shiffman: Bio89: Grant/Research Support, CymaBay: Advisor, CymaBay: Grant/Research Support, Durect: Grant/Research Support, Galectin: Grant/Research Support, Genentech: Grant/Research Support, Genentech: Speaking and Teaching, Gilead: Grant/Research Support, Gilead: Advisor, Gilead: Speaking and Teaching, HepQuant: Grant/Research Support, HepQuant: Advisor, Hamni: Grant/Research Support, High Tide: Grant/Research Support, Interept: Grant/Research Support, Interecept: Speaking and Teaching, Intercept: Advisor, Intra-Sana: Advisor, Intra-Sana: Speaking and Teaching, Ipsen: Advisor, Ipsen: Grant/Research Support, Ipsen: Speaking and Teaching, Madrigal: Grant/Research Support, Madrigal: Speaking and Teaching, Mirum: Grant/Research Support, Pliant: Grant/Research Support, Salix: Grant/Research Support, Salix: Advisor, Viking: Grant/Research Support, Timothy Morgan: Nothing to Disclose, Michael Leise: Nothing to Disclose, Michael McRae: HepQuant, LLC: Consultant, Joanne Imperial: Nothing to Disclose, Gregory Everson: Nothing to Disclose

2438 | BILE CAST NEPHROPATHY IN CIRRHOSIS: CLINICAL PROFILE, BIOCHEMICAL PATTERNS, AND PROGNOSTIC IMPACT

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Background: Bile Cast Nephropathy (BCN), a bile pigment-induced tubular injury in the setting of hyperbilirubinemia, is increasingly recognized as a distinct cause of acute kidney injury (AKI) in cirrhotic patients. Its pathogenesis is multifactorial, but its clinical impact remains underexplored. This study compared clinical features, liver disease severity, biochemical

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parameters, and short-term mortality in cirrhotic patients with BCN versus those with non-BCN AKI. **Methods:** In this combined retrospective and prospective observational study at a tertiary center, 203 cirrhotic patients with AKI were categorized into Bile AK (n = 102) and Non-Bile AK (n = 101) groups based on clinical and biochemical criteria. A presumptive diagnosis of BCN was made using the presence of bile-stained urinary casts, hyperbilirubinemia, and unexplained renal dysfunction. Data on demographics, liver disease etiology, bilirubin, creatinine, INR, MELD and CTP scores, and 3-month mortality were analyzed. Statistical tests included chi-square and independent t-tests, with $p < 0.05$ as significant. **Results:** Bile AK patients were younger (43.3 ± 9.1 vs. 53.7 ± 11.3 years; $p = 0.001$) and more likely to have alcohol-related liver disease (94.1% vs. 73.3%; $p = 0.003$). ACLF was predominant in Bile AK (39.2% vs. 5.0%), while DCLD was more common in Non-Bile AK (90.1%). Bile AK was associated with significantly higher total bilirubin (25.5 ± 8.3 vs. 7.2 ± 8.9 mg/dL), direct bilirubin (17.2 ± 5.7 vs. 4.6 ± 6.2 mg/dL), creatinine (2.83 ± 1.60 vs. 2.42 ± 1.34 mg/dL), INR (2.56 ± 1.60 vs. 1.92 ± 1.39), and MELD scores (36.0 ± 5.9 vs. 24.2 ± 9.2) (all $p < 0.05$). Three-month mortality was significantly higher in Bile AK (72.5% vs. 33.7%; $p < 0.001$), though time to death was similar (1.28 ± 0.86 vs. 1.40 ± 0.84 months; $p = 0.498$). **Conclusion:** BCN is a severe AKI subtype in cirrhosis, linked to greater hepatic dysfunction, higher bilirubin burden, and significantly worse short-term outcomes. Early recognition is critical for risk stratification and targeted management.

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2439 | FINERENONE IN THE MANAGEMENT OF PORTAL HYPERTENSION AND ASCITES

Butros Fakhoury[1] Leandro Sierra[2] Eyad Abdulrazzak[3], [1]Virginia Commonwealth University, [2]Cleveland Clinic Foundation, [3]Beth Israel Deaconess Medical Center

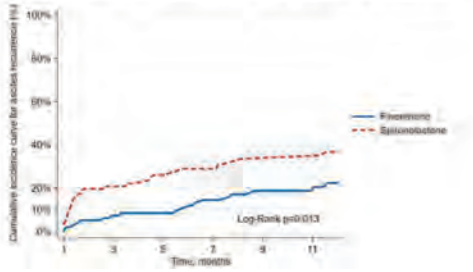
Background: Finerenone, is a selective non-steroidal mineralocorticoid receptor antagonist (MRA), with anti-inflammatory and antifibrotic effects that has demonstrated clinical benefits in chronic kidney disease and heart failure. Compared to spironolactone, Finerenone may offer several advantages in patients with cirrhosis, including greater antifibrotic efficacy, improved potency for ascites management, and fewer hormonal side effects due to its high receptor selectivity. This study evaluates the impact of Finerenone versus spironolactone on recurrent ascites, acute kidney injury (AKI), hyperkalemia, and hormonal adverse effects (gynecomastia and erectile dysfunction) in patients with cirrhosis and ascites. **Methods:** This retrospective cohort study used the TriNetX US Collaborative Network to identify adult patients with cirrhosis and ascites who received either finerenone or spironolactone between January 1, 2021, and January 1, 2025. The index date was defined as the first prescription of MRA prescription. Propensity score matching (PSM) was performed based on demographics, comorbidities, ascites- and portal hypertension–related medications, and baseline MELD laboratory values. Outcomes were evaluated from 1 month to 1 year after the index date. Outcomes included recurrent ascites, acute kidney injury, hyperkalemia, and hyperandrogenic side effects (gynecomastia or erectile dysfunction). **Results:** After PSM, 98 patients were included in each group with a median follow-up of 1 year. Finerenone was associated with a lower risk of recurrent ascites compared to spironolactone (18.6% vs. 30.9%; HR 0.48, 95% CI 0.27–0.87; $p = 0.013$). No significant differences were observed in the risks of AKI (32.0% vs. 28.9%; HR 0.93, 95% CI 0.56–1.55; $p = 0.786$), hyperkalemia (32.0% vs. 30.9%; HR 0.89, 95% CI 0.53–1.45; $p = 0.940$), or hyperandrogenic side effects (10.3% vs. 10.3%; HR 1.61, 95% CI 0.47–5.52; $p = 0.362$). **Conclusion:** In this multi-institutional US cohort, finerenone was infrequently used for ascites management in cirrhotic patients. However, after matching, finerenone was associated with a lower risk of recurrent ascites compared to spironolactone, without increased risk of AKI or hyperkalemia. These findings suggest that finerenone may offer a viable alternative for ascites management in cirrhosis patients. Larger prospective studies are warranted to confirm these findings.

Table.1 Baseline Characteristics Before and after propensity score matching

Variable	Before PSM					After PSM				
	Finerenone N=98		Spironolactone N=51,688		P-value	Finerenone N=97		Spironolactone N=97		P-value
Age, mean (SD)	65.4	11.9	61	13.4	0.001	65.3	12	65.4	13.6	0.982
Sex, Male, N %	64	65.3%	27291	52.8%	0.013	63	64.9%	65	67.0%	0.762
Race, N %										
White	58	59.2%	37011	71.6%	0.006	58	59.8%	60	61.9%	0.769
Asian	20	20.4%	1544	3.0%	<0.001	19	19.6%	18	18.6%	0.855
Black	10	10.2%	6841	13.2%	0.376	10	10.3%	10	10.3%	1.00
Other	10	10.2%	6,292	12.2%	0.691	10	10.3%	9	9.3%	0.815
Heart failure, N %	56	57.1%	22826	44.2%	0.01	56	57.7%	59	60.8%	0.661
Portal hypertension, N %	10	10.2%	22745	44.0%	<0.001	10	10.3%	10	10.3%	1.00
Esophageal varices, N %	10	10.2%	16132	31.2%	<0.001	10	10.3%	10	10.3%	1.00
Furosemide, N %	74	75.5%	43457	84.1%	0.02	74	76.3%	76	78.4%	0.732
ACEi, N %	51	52.0%	18230	35.3%	0.001	51	52.6%	51	52.6%	1.00
Carvedilol, N %	36	36.7%	12996	25.2%	0.008	35	36.1%	36	37.1%	0.882
GFR, mean (SD)	48.9	27.7	74.6	37.6	<0.001	49.3	27.6	55.7	29.3	0.125
Potassium, mean (SD)	4.2	0.5	4	0.6	0.001	4.2	0.5	4.2	0.6	0.503
Total bilirubin, mean (SD)	0.7	0.6	1.2	1.7	0.004	0.7	0.6	0.7	0.4	0.799
INR, mean (SD)	1.2	0.5	1.3	0.5	0.039	1.2	0.5	1.3	0.6	0.239

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; GFR, glomerular filtration rate; HTN, hypertension; INR, international normalized ratio; PSM, propensity score matching; SD, standard deviation; T. bili, total bilirubin.

Figure 1. Cumulative Incidence Curve for recurrent ascites between Finerenone and Spironolactone



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Disclosures: Butros Fakhoury: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Eyad Abdulrazzak: Nothing to Disclose

2440 | FROM PORTAL HYPERTENSION TO DECOMPENSATION: SHIFTING RISK PROFILES AND TIME TO EVENTS ACROSS CIRRHOSIS STAGES IN A US REAL-WORLD OBSERVATIONAL STUDY

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Background: Portal hypertension (PH) is the key determinant of cirrhosis progression to decompensation and liver-related mortality. PH diagnosis is often delayed, limiting effective treatment by non-selective betablockers (NSBBs). Using a real-world data source, we evaluated PH-related event rates across cirrhosis stages. **Methods:** Observational cohort study using the US Optum Market Clarity Database. Three cohorts were identified between January 2016 and May 2021, and followed-up until the earliest of May 2022, liver transplantation, death, or loss to follow-up. Patients with: · Advanced chronic liver disease (cACLD) and PH (cohort 1); · Cirrhosis and a single decompensation event (cohort 2); · Cirrhosis and >1 decompensation event (cohort 3). Patient characteristics are reported. Cumulative incidence rates per 100 person-years (PY) and incidence proportions at 30-days and 1-year were calculated for all-cause mortality, liver transplant, first decompensation, further decompensation ($\geq$ 2 events at least 7 days apart) and hospital admissions. Time to events was calculated. **Results:** 14,344, 26,907 and 31,145 patients were identified in cohorts 1-3, respectively. Comorbidity burden increased with disease severity (Table 1); 94.2% of cohort 3 had a Charlson Comorbidity Index score of 4+. Depression ($>39\%$) and fatigue ($>45\%$) were prevalent. NSBBs were only used in 20.6% of patients in cohort 1. The 1-year all-cause mortality rate was 3.2%, 15.7% and 18.4% in cohorts 1-3, with a median time to death over the study period of 2 years in cohort 1, and <1 year in cohorts 2 and 3. Mortality incidence rates per 100 PY across the study period were 4.0, 12.5 and 15.5 in cohort 1-3. The 1-year first decompensation rate in cohort 1 was 19.6% with a median time to event of 1.2 years. 1-year further decompensation event rate was 73.3% and 77.3% in cohort 2-3, with the median time to event <0.1 years. First and further decompensation incidence rates were 18.5, 125.7 and 163.0 per 100 PY in cohorts 1-3. **Conclusion:** There is a significant disease burden in terms of quality of life indicators, comorbidities, decompensation and mortality in patients with cirrhosis, which is further aggravated in decompensated cirrhosis. Rates of NSBB treatment were alarmingly low. The study highlights the importance of preventing the first decompensation event in patients with cirrhosis and PH.

Table 1 Demographics, clinical characteristics, and outcome rates across cirrhosis cohorts

	Cohort 1: cACLD and PH	Cohort 2: First decompensated	Cohort 3: Further decompensated
N	14,344	26,907	31,145
Sociodemographic variables			
Age,years (median, IQR)	61 (55-68)	60 (53-68)	61 (54-69)
Male (n, %)	7,283 (50.7%)	14,769 (54.9%)	16,992 (54.6%)
% White Ethnicity	9,294 (64.7%)	17,990 (66.9%)	20,378 (65.4%)
Baseline Comorbidities (identified prior to index date)			
CCI, 4+ (n, %)	13,165 (91.9%)	23,409 (87.0%)	29,329 (94.2%)
Myocardial infarction	596 (4.2%)	1,468 (5.5%)	3,663 (11.8%)
Congestive heart failure	2,340 (16.3%)	7,195 (26.7%)	12,693 (40.8%)
Peripheral vascular disease	3,355 (23.4%)	7,174 (26.7%)	11,964 (38.4%)
Cerebrovascular disease	2,368 (16.5%)	5,505 (20.5%)	10,200 (32.8%)
Ischemic heart disease	1,763 (12.3%)	4,745 (17.6%)	7,868 (25.3%)
Hypertension	11,210 (78.2%)	21,324 (79.3%)	27,010 (86.7%)
Hemiplegia or paraplegia	279 (2.0%)	809 (3.0%)	1,856 (6.0%)
Dementia	294 (2.2%)	1,030 (3.8%)	2,511 (8.1%)
Chronic pulmonary disease	6,042 (42.1%)	11,784 (43.8%)	17,308 (55.6%)
Connective tissue disorder	1,389 (9.7%)	2,346 (8.7%)	3,197 (10.3%)
Diabetes with or without chronic complications	7,372 (51.4%)	12,786 (47.5%)	17,337 (55.7%)
Renal disease	2,451 (17.1%)	6,503 (24.2%)	12,045 (38.7%)
Any malignancy including leukaemia and lymphoma	2,442 (17.0%)	4,971 (18.5%)	6,910 (22.2%)
Metastatic solid tumour	473 (3.3%)	1,595 (5.9%)	2,037 (6.5%)
Mild liver disease	14,344 (100%)	25,797 (95.9%)	30,422 (97.7%)
AIDS/HIV	284 (2.0%)	434 (1.6%)	626 (2.0%)
QoL Indicators			
Fatigue	6,731 (46.9%)	14,505 (53.9%)	21,473 (69.0%)
Depression	5,695 (41.1%)	11,773 (43.8%)	17,914 (57.5%)
History of alcohol abuse	3,616 (25.2%)	13,059 (48.5%)	17,719 (56.9%)
Outcomes			
All-cause mortality			
30-days (%)	0.2 (0.2-0.3)	3.0 (2.8-3.2)	3.3 (3.1-3.5)
1-year (%)	3.2 (2.9-3.5)	15.7 (15.2-16.1)	18.4 (18.0-18.8)
Overall study period (per 100 person-years)	4.0 (3.9-4.2)	12.5 (12.2-12.8)	15.6 (15.2- 15.9)
Time to event (years)	2.0 (0.9-3.3)	0.6 (0.2-1.6)	0.7 (0.2-1.9)
Liver Transplant			
30-days (%)	0.02 (0-0.06)	0.2 (0.1-0.2)	0.2 (0.1-0.2)
1-year (%)	0.5 (0.4-0.6)	1.7 (1.6-1.9)	1.8 (1.7-2.0)
Overall study period (per 100 person-years)	1.0 (0.9-1.1)	2.0 (1.9-2.2)	2.1 (2.0-2.2)
Time to event (years)	2.3 (1.3-3.7)	1.2 (0.6-2.2)	1.2 (0.5-2.4)
Decompensation (First in cohort 1, further in cohort 2/3)			
30-days (%)	3.3 (3.0-3.6)	60.0 (50.4-51.6)	49.9 (49.3-50.4)
1-year (%)	19.6 (18.9-20.2)	73.3 (72.7-73.8)	77.4 (77.0-77.8)
Overall study period (per 100 person-years)	18.5 (18.0-18.9)	125.8 (124.1-127.4)	163.0 (161.1-165.0)
Time to event (years)	1.2 (0.4-2.5)	0.04 (0-0.3)	0.05 (0.01-0.3)
All-cause hospital admissions (per 100 person-years)	32.2 (31.6-32.9)	151.2 (149.3-153.1)	130.3 (128.8-131.9)

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2441 | EFFICACY AND SAFETY OF ORAL IBANDRONATE IN PATIENTS OF LIVER CIRRHOSIS WITH HEPATIC OSTEODYSTROPHY: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL [NCT06022237]

Sudhir Verma[1] Chitranshu Vashishtha[2] Manoj Sharma[2] Rajan Vijaraghvan[2] VINOD ARORA[2] Satender Pal Singh[3] Sukriti Baweja[2] Ashok Choudhury[4] Shiv Kumar Sarin[3], [1]Institute of Liver and Biliary Sciences. New Delhi, [2]Institute of Liver and Biliary Sciences, New Delhi, [3]Institute of Liver and Biliary Sciences, [4]ILBS, New Delhi

Background: Hepatic osteodystrophy (HOD) is a metabolic bone disease associated with liver cirrhosis. Despite high prevalence, it is often overlooked. Oral bisphosphonates are a promising option, often discouraged in cirrhosis due to risk of upper gastrointestinal bleeding(UGIB) related to varices and esophagitis. Previous studies on HOD are either non-randomized or open labelled RCT and have focussed mainly in cholestatic liver diseases. **Methods:** Consecutive patients of HOD with low-risk varices between 18 to 70 years of age were included. Patients with high-risk varices, history of UGIB in last 2 months., grade 3 ascites, history of pathological fracture & taking drugs causing bone-loss were excluded. Primary objective was to compare changes in bone mineral density (BMD, ΔT score) at lumbar spine in DEXA scan after 1 year of oral ibandronate 150 mg once monthly (group I) and placebo (group II). The secondary objectives were to compare Δ T score at femur neck and adverse event profile. All patients received calcium 500 mg and Vit D3 500 IU twice daily **Results:** Of 240 patients screened, 173(72.08%) had HOD, and 80 fulfilled the criteria{mean age 51.14 $\pm$ 11.27 yrs, males 64(80%), alcohol 42 (52.5%), baseline MELD 14.9 $\pm$ 6.9, CTP score 8.5 $\pm$ 6.9 & ascites in 51.9%(grade I = 29,1%,gradeII = 22.8%)}. Prior bleeder were 14(17.5%) with low-risk gr II varices in 46.3%, grade I in 23.8%, eradicated varices in 22.5% and no varices in 7.5%. At lumbar spine, T-score improved from -2.46 $\pm$ 0.98 to -1.51 $\pm$ 1.27 (+38.61%, ΔT = -0.95 $\pm$ 0.17) in gr. I and from -2.66 $\pm$ 0.98 to -2.53 $\pm$ 0.96 (+10.54%, Δ T = -0.13 $\pm$ 0.31) in gr II ($p < 0.001$). At femur neck, T-score improved from -1.66 $\pm$ 0.82 to -1.37 $\pm$ 0.85 (+17.57%, ΔT = -0.29 $\pm$ 0.12) in gr I and from -1.653 $\pm$ 0.85 to-1.651 $\pm$ 1.11 (+0.12%, ΔT = -0.002 $\pm$ 0.31) in gr II ($p = 0.03$). Gr I showed significant reduction in bone turnover markers (ng/ml)[Δ osteocalcin = -76.82 $\pm$ 49.2($p = 0.004$), Δ procollagen type 1C propeptide(PICP) = -40.3 $\pm$ 24.2 ($p = 0.001$), Δ c-terminal telopeptide of type I collagen(CTX) = -0.41 $\pm$ 0.3 ($p = 0.021$), Δ amino-terminal telopeptide of type 1 collagen(NTX) = -8.42 $\pm$ 9.48 ($p = 0.020$)]. Liver frailty index significantly improved in gr I with reduction of 0.44 $\pm$ 0.18 and increased by 0.08 $\pm$ 0.04 in gr II ($p = 0.008$). Adverse events included dyspepsia, 3(3.75%) in group I (1 discontinued) and 2(2.5%) in gr II. **Conclusion:** Oral Ibandronate improves BMD both at lumbar spine and femur neck significantly better

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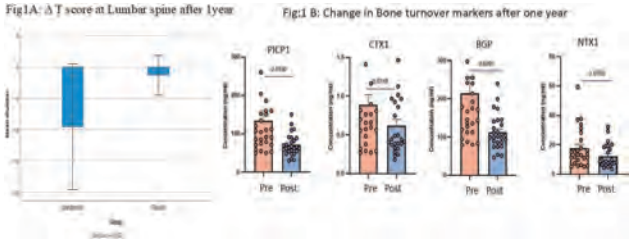
than placebo. It is well tolerated and produces minimal adverse events. It should be recommended for Child A and B cirrhosis patients with osteodystrophy

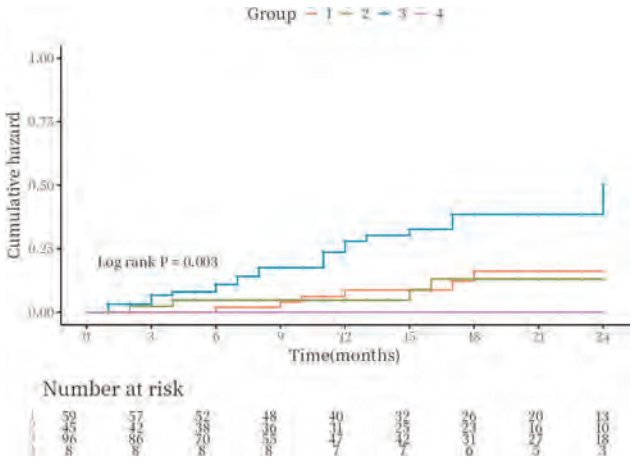


Disclosures: Sudhir Verma: Nothing to Disclose, Chitranshu Vashishtha: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Rajan Vijaraghvan: Nothing to Disclose, VINOD ARORA: Nothing to Disclose, Satender Pal Singh: Nothing to Disclose, Sukriti Baweja: Nothing to Disclose, Ashok Choudhury: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

2442 | VISCERAL ADIPOSITY AREA (VAT)-BASED SARCOPENIC OBESITY SIGNIFICANTLY INCREASES CIRRHOTIC PATIENTS' RISK OF LIVER DISEASE-RELATED MORTALITY

Yi Jiang[1] Guo Feng[2] Hong Yu[3] Jin-hua Jing[4] Wei Sun[5] Yu-yu Li[6] Lei Yang[6] Guzhenur Yiliyar[7] Xin Da[3] Xiao-zhong Wang[2], [1]The Chinese University of Hong Kong (Shenzhen) Affiliated Hospital No. 2 & Longgang District People, [2]Xinjiang Uygur Autonomous Region Hospital of Traditional Chinese Medicine, [3]Xinjiang Karamay Central Hospital, [4]Xinjiang Changji Prefecture Hospital of Traditional Chinese Medicine, [5]Shaanxi University of Traditional Chinese Medicine Hospital, [6]The Fourth Clinical College of Xinjiang Medical University, [7]Affiliated Hospital of Chengdu University of Traditional Chinese Medicine

Background: The prevalence of sarcopenia and obesity is increasing as a result of global urbanization, aging, and changing lifestyles, and has become an important public health problem worldwide.The aim of this study was to investigate the effect of sarcopenic obesity(SO), defined based on visceral adipose area (VAT), on the risk of liver disease-related mortality in cirrhotic patients. **Methods:** This study retrospectively included cirrhotic patients hospitalized in the Department of Hepatology of Xinjiang Autonomous Region Hospital of Traditional Chinese Medicine from January 2020 to December 2022, and CT scan images at the level of the third lumbar vertebrae were selected, and image post-processing was performed using the Slice-O-matic software to compute the skeletal muscle index (SMI) and VAT; based on the third lumbar vertebrae level skeletal muscle index (L3-SMI) <50 cm²/m² (male) or <39 cm²/m² (female) was used to diagnose sarcopenia; VAT >100 cm² was defined as obesity, and SO was defined as obesity by meeting the above criteria at the same time, and the patients were followed up every 3 months, and the time and cause of death were recorded. Survival curves were plotted by Kplan-Meier analysis, and cumulative risk curves were used to assess the survival of cirrhotic patients. **Results:** (1) A total of 258 cases were included in this study, and 208 patients with cirrhosis were finally included, in which the prevalence of SO was 46.15% (96/208). (2) All patients were followed up for 24 months, and death occurred in 36 patients, of which 34 died of liver disease-related deaths, 12 died of rupture and bleeding of esophagogastric fundal varices, 4 died of secondary infections, 7 died of hepatic encephalopathy,9 died of hepatic failure, and 2 died of hepatic malignant tumors; the liver disease-related mortality rates in the myxedematous obesity group and non-myxedematous obesity group were 25.00% (24/96) and 8.93% (96/96), respectively. 96), and 8.93% (10/112), respectively. (3) Survival analysis showed that the cumulative risk of death at 12 and 24 months was higher in the SO group compared with the non-sarcopenic obesity group(NSO) [HR: 4.260 (95% CI: 1.689-10.746), Log rankP <0.001; HR: 3.566 (95% CI: 1.704-7.446), Log rankP <0.001]. 0.001]. Subgroup analysis showed that the cumulative risk of death at 12 and 24 months was higher in the SO group compared with the obesity-only group and sarcopenia-only group [HR: 3.371 (95% CI: 1.140 to 9.969),Log rank P $=0.019$] vs [HR: 4.962 (95% CI: 1.150 to 21.402),Log rank P $=$ 0.016], [HR:3.076(95% CI:1.256~7.532),Log rankP $=0.009$] vs [HR:3.439(95% CI:1.192~9.921),Log rankP $=0.014$]. **Conclusion:** SO is prevalent in cirrhosis; SO based on VAT significantly increases the risk of liver disease-related death in cirrhotic patients; early identification of SO can help improve the prognosis and quality of survival in cirrhotic patients.



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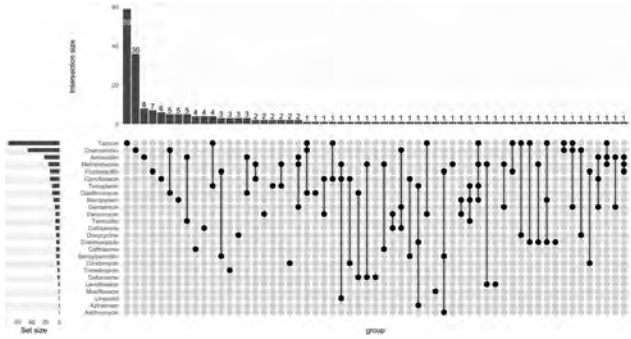
2443 | USE OF PIPERACILLIN-TAZOBACTAM IN PATIENTS HOSPITALISED WITH COMPLICATIONS OF CIRRHOSIS IN ATTIRE WAS ASSOCIATED WITH INCREASED MORTALITY

Gemma Wells[1] Harriett Fuller[2] Louise China[1] Eduard Atanasescu[1] Alastair O'Brien[1], [1]University College London, [2]Fred Hutchinson Cancer Research Center

Background: Infection is common in patients with advanced liver disease, who are often prescribed broad-spectrum antibiotics. These prescriptions are often empirical, chosen prior to microbiology results, and commonly continued if no micro-organism is cultured. However, broad-spectrum antibiotics may be harmful, with piperacillin-tazobactam previously associated with higher mortality in non-cirrhotic patients with sepsis. **Methods:** In the ATTIRE (Albumin to Prevent Infection in Chronic Liver Failure) trial, 777 patients were randomized to daily 20% albumin infusions or standard of care during hospitalization with decompensated cirrhosis across 35 United Kingdom (UK) hospitals (2016-2019). We analysed antibiotic prescribing in patients diagnosed with infection at trial entry reasoning that the antibiotic choice would be empirical i.e. prior to culture availability. We performed adjusted logistic regression modelling adjusted for age, gender, baseline albumin, creatinine, bilirubin, white cell count (WCC) and C-reactive protein (CRP) to evaluate whether use of certain antibiotics was associated with death at 90 days. **Results:** 211 patients were diagnosed with infection and prescribed antibiotics at trial entry, with data available for 205. 279 antibiotics were prescribed for these 205 patients, with the most frequent piperacillin-tazobactam (74). Baseline characteristics for those prescribed piperacillin-tazobactam were similar to the second most frequent antibiotic (co-amoxiclav, 46), with the only significant difference being creatinine levels (75 vs 61 mmol/L, p = 0.03). Patients prescribed piperacillin-tazobactam at baseline were found to be at increased risk of death at 90 days compared to those prescribed other antibiotics (OR = 2.89, 95% CI 1.44-5.91, P = 0.003). This association between piperacillin-tazobactam and death at 90 days remained when considering individuals only prescribed piperacillin-tazobactam at baseline (OR = 2.81, 95% CI 1.31-6.17, P = 0.01). Piperacillin-tazobactam prescription in combination with other empirical antibiotics was not associated with increased risk of death. Age consistently associated with increased risk of death (OR~ 1.06) throughout. The cause for the association between piperacillin-tazobactam and 90-day mortality is not clear. We note that incidence of renal dysfunction was similar to overall and for those prescribed co-amoxiclav, although only 2/14 of the piperacillin-tazobactam patients that developed renal dysfunction received reduced dosing. **Conclusion:** There was substantial variability in empirical antibiotic prescribing in this real-world cohort of patients, with piperacillin-tazobactam most frequently prescribed. However, our data suggest that the use of this antibiotic may cause harm. We encourage clinicians to be judicious in their antibiotic choices and dosing regimens, particularly in patients with renal dysfunction.



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2444 | THE ALBI SCORE, A PROGNOSTIC MARKER IN ADVANCED HEPATIC FIBROSIS: A PROSPECTIVE SINGLE-CENTER STUDY

Maxence de Callataÿ[1] Alix Collard[2] Géraldine Dahlqvist[1] Nicolas Lanthier[1] Peter Starkel[1] Yves Horsmans[1] Bénédicte Delire[1], [1]Hepatology Department, Cliniques Universitaires Saint-Luc, Brussels, belgium, [2]Statistical Unit, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Background: Advanced liver fibrosis (ALF) is associated with significant morbidity and mortality. The ALBI (albumin-bilirubin) score has been validated as a prognostic marker in HCC. Retrospective studies suggest ALBI as a prognostic marker in ALF. This study aims to prospectively evaluate ALBI in ALF. **Methods:** This is a prospective, single-centre study including all patients with ALF (F3-F4 according to Metavir classification) based on elastometry, histology or radiological data, excluding HCC. At inclusion, Child-Pugh,

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MELD and ALBI scores were calculated. The primary objective was to evaluate at 1 year according to ALBI grade the occurrence of: death, hospitalisation for all causes, hospitalisation for hepatic decompensation, admission to ICU and liver transplantation (LT). The secondary objective was to compare the ALBI score with other prognostic scores. **Results:** 106 patients were included: 67 ALBI grade I (63.2%), 32 grade II (30.2%) and 7 grade III (6.6%). Six deaths (5.7%) were observed, with a significant difference according to ALBI grade (I:1.5%, II:12.5%, III:14.3%; $p = 0.0364$). Patients were more likely to be hospitalised according to ALBI grade: for all causes (I:9%, II:56.3%, III:85.7%; $p < 0.001$); for ascitic decompensation (I:1. 5%, II :18.8% and III :42.9%; $p = 0.002$), for hepatic encephalopathy (I :3%, II :21.9% and III :71.4%; $p < 0.001$), for infections (I :0%, II :31.3% and III :57.1%; $p < 0.001$). ICU admissions were more frequent in the grade III group (I:16.7%, II:0% and III:60%; $p = 0.0039$). Three patients were transplanted in the grade III group and none in the other groups ($p = 0.002$). According to Kaplan-Meier method, the probability of survival was lower in the grade II and III group compared with the grade I group ($p = 0.0446$) and the probability of hospitalisation from all causes or associated with liver decompensation was significantly higher in grade II and III groups ($p < 0.0001$ and $p < 0.0001$). The AUROC for overall survival for the ALBI, Child-Pugh and MELD scores was 0.86, 0.83 and 0.74, while the AUROC for the occurrence of hepatic decompensation was 0.85, 0.89 and 0.82. According to the chi-square score, dichotomisation of the ALBI score is the best model for predicting overall survival in this cohort. **Conclusion:** This is the first prospective study showing the prognostic impact of the ALBI score in ALF. In our cohort, the prognostic performance for overall survival was superior with the ALBI score compared with the MELD and Child-Pugh scores. These results encourage the use of the ALBI score in daily clinical practice in ALF patients.

Disclosures: Maxence de Callataÿ: Nothing to Disclose, Alix Collard: Nothing to Disclose, Géraldine Dahlqvist: Nothing to Disclose, Nicolas Lanthier: Nothing to Disclose, Peter Starkel: Nothing to Disclose, Yves Horsmans: Nothing to Disclose, Bénédicte Delire: Nothing to Disclose

2445 | STRUCTURAL AND ENERGETICS-DIRECTED IDENTIFICATION OF NOVEL ALK5-AMPK AXIS AS A MEDIATOR OF HYPERAMMONEMIC STRESS AND SARCOPENIA IN CIRRHOSIS

Srinivasan Dasarathy[1] Sadashiva Karnik[1] Nicole Welch[1] Seshu Vardhan Pothabathula[1] Muaz Alsabbagh Alchirazi[1] Saurabh Mishra[1] Dhanachandra Khuraijam[1] Pugazhendhi Kannan[1] Annette Bellar[1] Dongmei Zhnag[1] Belinda Willard[1], [1]Cleveland Clinic

Background: Hyperammonemic stress response (HASR) causes sarcopenia in cirrhosis via myostatin, a transforming growth factorß (TGFß) superfamily member-dependent AMPKα2 activation. Canonical myostatin signaling occurs via activin IIB receptor-dependent activation of ALK4/5 kinase function, but whether AMPK is a direct target of the myostatin-ALK4/5 axis is unknown. Integrated molecular docking/dynamics and in vitro kinase/mass spectrometry approaches showed that myostatin-ALK5-AMPK axis mediates sarcopenia in HASR. **Methods:** To determine the ALK4-AMPKα2 and ALK5-AMPKα2 complexes, we performed molecular docking using HADDOCK 2.4 with the 3D structures of ALK4, ALK5, and AMPKα2. Clustered conformations are ranked by the HADDOCK score for binding energy. Top ranked conformations of ALK4-AMPKα2 and ALK5-AMPKα2 set for Molecular Dynamics Simulations (MD) using GROMACS tools using AMBER99SB force fileds continued to minimization, NVT/NPT equilibration at 300° K and (1 bar) followed by a 100ns production MD. Principal Component Analysis (PCA) and Free Energy Landscape (FEL) covariance matrix computed to obtain (PC1, PC2) components. Free energy is calculated for total complex and residual energy contribution to overall binding. Experimental validation was done by in vitro kinase assays and LC-MS to identify phosphorylation sites on AMPKα2. **Results:** Molecular docking of ribbon conformations exhibited the minimum binding energy for ALK4-AMPKα2 (-192 kcal/mol) and ALK5–AMPKα2 conformation-1 (–344 kcal/mol). MD simulations showed ALK4 and ALK5 establish stable conformation with AMPKa2 through distinct mechanisms that facilitate phosphorylation. Hydrogen bonds at Thr188, Asp185, and Ser168 on ALK4 orients the active site to AMPKα2. MD analysis showed RMSD equilibrated state at 40-100 ns had significant instability of 2.1 nm for ALK4-AMPKα2. Conversely, the ALK5–AMPKα2 conformation-1, interactions between Ser172, Glu173, and Asp179 on ALK5 with Arg171, Thr172, and Ser173 on AMPKα2, had stable RMSD (2.0 nm) by substrate anchoring. Free energy of ALK5–AMPKα2 exhibited a reduced total free energy ranging from -28.85 to -72.95 kcal/mol, and at stable state the total energy scored -50.90 kcal/mol. The polar solvation penalty 461.99 of ALK5–AMPKα2 had greater structural stability and electrostatic complementarity vs ALK4- AMPKα2. Consistently, in vitro kinase assay showed phosphorylation of AMPKα2 by ALK5, and mass spectrometry showed AMPKα2 phosphorylation at Thr172 with retention time shift and ~80Da increase in net mass. **Conclusion:** ALK5 is an optimal structural and energetic partner for AMPKα2, facilitating a phosphorylation-competent assembly via distinct catalytic interactions and stable conformations. Structural alignment of ALK5 with experimental validation of Thr172 phosphorylation shows ALK5–AMPKα2 as a target for designer

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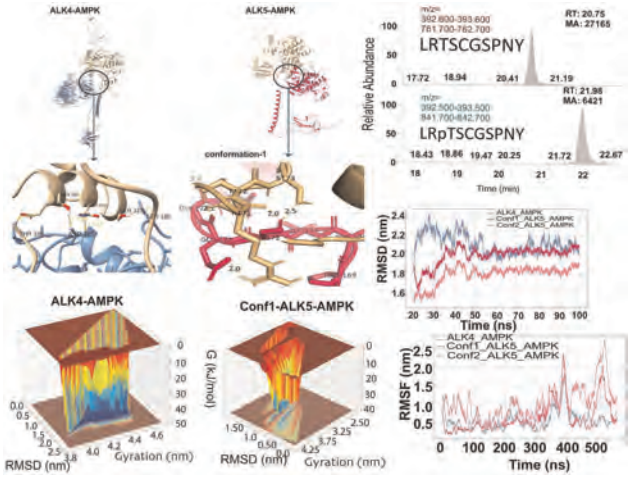
peptide/small molecule based therapeutics for sarcopenia in cirrhosis.



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2446 | SARCOPENIA IS AN INDEPENDENT PREDICTOR OF FURTHER DECOMPENSATION AND MORTALITY AFTER ENDOSCOPIC AND ENDOVASCULAR INTERVENTIONS FOR SECONDARY PROPHYLAXIS OF GASTRIC VARICES IN PATIENTS WITH CIRRHOSIS: A MULTICENTRE, REAL-WORLD STUDY

Sagnik Biswas[1] Souveek Mitra[2] Santhosh Kumar[3] Piyush Aggarwal[4] R G Krishna Kumar[1] Shekhar Swaroop[1] Shubham Mehta[1] Arun Valsan[5] Sanchita Gupta[1] Falguni Hota[2] Goldwin H Cecil[3] Ravi Chaudhary[6] Rajkumar Bayye[1] Samagra Agarwal[1] Umang Arora[7] P Krishna Bharadwaj[3] Shivanand Gamanagatti[1] Ashish Goel[3] Rajesh Puri[8] Anurag Yadav[7] Abhijit Chowdhury[2] Raju Sharma[1] Ankur Goyal[1] . Shalimar[4], [1]All India Institute of Medical Sciences, New Delhi, [2]Indian Institute of Liver and Digestive Sciences, [3]Christian Medical College Vellore, [4]All India Institute of Medical Sciences. New Delhi, [5]Amrita Institute of Medical Sciences, Kochi, [6]Medanta the Medicity, [7]Sir Ganga Ram City Hospital New Delhi, [8]Medanta-The Medicity

Background: Sarcopenia is associated with adverse health-related outcomes and poor survival rates in patients with cirrhosis. However, the impact of sarcopenia on the long-term outcomes of patients with cirrhosis presenting with gastric variceal (GV) hemorrhage is not well known. **Methods:** In this multicentric retrospective analysis, patients with cirrhosis presenting with GV bleeding at 6 tertiary care centres in India from January 2017 to January 2023 were included. Baseline demographics, mortality and further decompensation events- rebleeding, ascites and hepatic encephalopathy (HE) were reviewed. Cross-sectional imaging was used to assess skeletal muscle index (SMI) and intramuscular adipose tissue (IMAT). Gender-specific threshold values of SMI <42 cm^2/m^2 for men and <38 cm^2/m^2 for women were used to identify sarcopenia. Propensity score matched (PSM) analysis (1:1) was performed and the rates of mortality, further decompensation and rebleeding were assessed. Competing risk analysis was done to assess the risk of rebleeding and further decompensation with mortality as a competing event. **Results:** Three hundred and eighteen patients with 214 (67.3%) males were included. The median CTP and MELD scores were 7 (6-9) and 11 (9-15) respectively. Seventy nine (24.8%) patients had sarcopenia. One hundred and sixty seven (52.5%) patients received endoscopic cyanoacrylate glue injection, while 70 (22%) patients underwent EUS guided coil and glue injection. BRTO and TIPS were performed in 61 (19.2%) and 20 (6.3%) patients, respectively. MASLD (49/79, 62%) was the leading cause of cirrhosis in patients with sarcopenia. Sixty (18.9%) patients died over a median follow-up period of 732 (397-1092) days. In the PSM cohort, sarcopenia was associated with higher mortality rates (22 [27.8%] vs 11 [14.1%]; $p=0.04$) and a 1-, 2- and 3-year probability of mortality of 15.3%, 24.9%, 41.1% as compared to 9.1%, 14.9%, 14.9% in non-sarcopenic patients (Fig 1A). Rates of further decompensation were also higher in those with sarcopenia (49 [62%] vs 31 [39.2%]; $p<0.01$) with 1-, 2- and 3-year probability of further decompensation being 41.5%, 57% and 65.1% as compared to 24.8%, 36.1% and 42.8% among non-sarcopenic patients (Fig 1B). Rebleeding rates were similar in both groups (sarcopenia: 27[34.1%] vs no sarcopenia 18[22.8%]; $p=0.113$), while ascites (39 [49.4%] vs 18 [22.8%]; $p<0.01$) and HE (21 [26.6%] vs 6 [7.6%]; $p<0.01$) were significantly higher on follow-up among those with sarcopenia. On multivariate analysis, sarcopenia was an independent predictor of both further decompensation (sHR: 2.45, 95% CI: 1.53-3.89; $p<0.01$) and mortality (HR: 3.32, 95% CI:1.32-8,31; $p=0.01$). **Conclusion:** While endoscopic and endovascular interventions are effective in preventing rebleeding, sarcopenia is a significant determinant of further decompensating events (ascites and encephalopathy) and mortality after GV hemorrhage in patients with cirrhosis.

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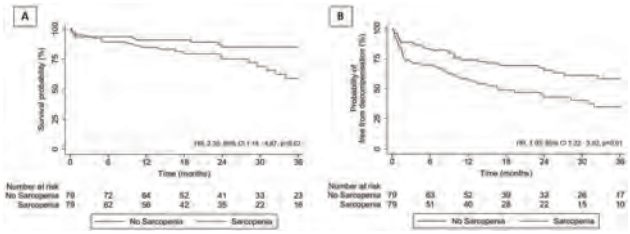

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2447 | CLINICAL PERSPECTIVES ON LONG-TERM ALBUMIN THERAPY IN DECOMPENSATED CIRRHOSIS: A NATIONWIDE DELPHI SURVEY IN SPAIN (THE ALBA STUDY)

Jose Ignacio Fortea[1] Diego Rincon[2] Agustín Albillos[3] Elsa Solà[4] Rafael Bañares[2], [1]Hospital Universitario Marqués de Valdecilla, [2]Hospital General Universitario Gregorio Marañon, [3]Hospital Universitario Ramón y Cajal, [4]Stanford University School of Medicine

Background: Albumin is well established for some acute indications in decompensated cirrhosis, but its long-term use remains controversial. The ALBA study explored clinical views, barriers, and implementation challenges of long-term albumin therapy in Spain. **Methods:** A two-round national Delphi study was conducted with 47 hepatology experts from Spanish hospitals with broad geographic coverage. The survey included 40 Delphi statements and 14 items on opinion, attitude, and behavior across five domains. Consensus was defined as Tastle's coefficient ≥ 0.8. Items with moderate consensus (0.7–0.79) and $<70\%$ agreement, or <0.7, were re-evaluated in round two. **Results:** Most centers used albumin for guideline-endorsed indications, though off-label use was also common. 25.5% reported long-term use in patients with ascites. Panelists agreed on its benefit, particularly to prevent ascites-related complications, and supported its use regardless of transplant eligibility. Use was prioritized in difficult-to-control ascites (89.3%) and renal impairment (55.2%), while acknowledging that the potential benefit may be lower in these late stages. Experts endorsed serum albumin and other biomarkers for monitoring, with day hospitals as the most feasible setting despite strain. Barriers included economic limits, logistical challenges, and protocol requirements. Therapy was viewed as safe overall, with dose-dependent cardiac risk. It was seen to improve quality of life and reduce hospital admissions. Concerns over increased demand underscored the need to optimize use. Cost savings via fewer admissions were expected. Strong support was expressed for a national registry to guide implementation. **Conclusion:** Overall, panelists considered long-term albumin administration to be clinically beneficial, and preferably used in those with advanced disease stages, regardless of transplant candidacy. However, its integration into routine practice remains limited by institutional, logistical, and economic barriers. A national registry and targeted strategies to optimize use and resource allocation were endorsed.

Selected Delphi Statements Included in Results

Item	Consensus Coefficient †	Agreement ‡
Long-term albumin reduces complications and improves survival	0.78	6.4 / 17.0 / 76.6
Long-term albumin treatment reduces the need for paracentesis and ascites-related complications	0.83	2.1 / 8.5 / 89.4
The decision to administer long-term albumin therapy is independent of liver transplant indication	0.83	14 / 6 / 78
Serum albumin levels throughout treatment may be useful to guide long-term therapy	0.87	14 / 6 / 78
Treatment should be supervised by the reference hospital.	0.82	8 / 8 / 84
Implementing this new albumin indication would significantly burden day hospital units	0.75	17.0 / 10.6 / 72.3
Implementing this new albumin indication in my hospital would require protocol approval	0.76	17.0 / 12.8 / 70.2
Long-term albumin treatment is safe and associated with few adverse effects	0.82	2.1 / 6.4 / 91.5
Long-term albumin therapy carries some risk of heart failure that may depend on the dose administered	0.84	11 / 0 / 89
Improves quality of life in cirrhotic patients with ascites	0.75	27.7 / 0 / 72.3
Local strategies should be developed to reduce inappropriate albumin use	0.83	4.3 / 8.5 / 87.2
Costs offset by reduction in complications	0.79	29.8 / 0 / 70.2
A national registry should be promoted	0.90	2.1 / 6.4 / 91.5

† Consensus Coefficient: Calculated using Tastle's method. Values ≥0.8 indicate strong consensus; values between 0.7 and 0.79 indicate moderate consensus.

‡ Agreement: Responses were grouped into three categories based on a 5-point Likert scale: Disagree (1–2), Neutral (3), and Agree (4–5). Items with moderate consensus were re-evaluated in the second round if fewer than 70% of responses clustered at either end of the scale (i.e., Agree or Disagree <70%).

Disclosures: Jose Ignacio Fortea: Grifols: Speaking and Teaching, Diego Rincon: Nothing to Disclose, Agustín Albillos: Nothing to Disclose, Elsa Solà: Nothing to Disclose, Rafael Bañares: Nothing to Disclose

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2448 | SARCOPENIA IS ASSOCIATED WITH WORSE INPATIENT OUTCOMES AND INCREASED PROCEDURE UTILIZATION IN HOSPITALIZED CIRRHOTIC PATIENTS: A NATIONWIDE ANALYSIS

Mohamed Omar[1] David Maundu[2] Sandra Chehayeb[1] Hayder Alamily[3] Joshua Musalia[4] Matthew Stotts[5] Nathan Tofteland[1] William Salyers[1], [1]University of Kansas Medical Center, [2]University of Kansas School Of Medicine- Wichita, [3]University of Colorado, Department of Gastroenterology, [4]University of Cincinnati College of Medicine, [5]University of Kansas Medical Center, AdventHealth Transplant Institution-Porter Hospital, Denver

Background: Patients with chronic liver disease are at an elevated risk of developing sarcopenia due to impaired protein metabolism, among other pathophysiologic mechanisms. Few studies have explored the impact of sarcopenia on inpatient outcomes and healthcare utilization in cirrhotic patients on a national scale. This study aims to evaluate the effect of sarcopenia on inpatient mortality, resource utilization, and procedural burden among hospitalized cirrhotics using the National Inpatient Sample. **Methods:** We conducted a retrospective cohort study utilizing five years of data from the National Inpatient Sample (NIS) spanning from 2018 to 2022. Adults with cirrhosis were identified using validated ICD-10 codes, and those with sarcopenia as a secondary diagnosis were defined using a comprehensive set of diagnostic codes. The outcomes of interest included in-hospital mortality, length of stay, total charges, ICU stay (approximated through the need for mechanical ventilation), and the utilization of specific procedures. These procedures included esophagogastroduodenoscopy (EGD), colonoscopy, Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement, and paracentesis. We performed multivariable logistic regressions adjusted for demographics, hospital characteristics, and comorbidities. The analysis was conducted using STATA 18. **Results:** Among an estimated 3,992,524 weighted hospitalizations for cirrhosis, 118,100 (3.0%) had co-diagnosed sarcopenia. Sarcopenic cirrhotics had higher in-hospital mortality (12.8% vs. 6.0%, $p < 0.001$), longer length of stay (8.35 vs. 6.21 days, $p < 0.001$), and higher total hospital charges ($104,585 vs. $79,733, $p < 0.001$). After adjusting for confounders, sarcopenia remained independently associated with increased odds of mortality [aOR 2.05 (95% CI 1.96–2.15, $p < 0.001$)]. Sarcopenic patients had increased odds of paracentesis [aOR 1.99 (1.93–2.05, $p < 0.001$)] and ICU stay [aOR 1.22 (1.16–1.28, $p < 0.001$)]. No significant differences were found in TIPS [aOR 1.03, $p = 0.72$], EGD [aOR 0.97, $p = 0.265$], or colonoscopy utilization [aOR 1.10, $p = 0.058$]. **Conclusion:** In hospitalized patients with cirrhosis, sarcopenia is associated with increased mortality, greater healthcare resource utilization, and a higher procedural burden. These findings suggest that this population needs more targeted management strategies to improve clinical outcomes and reduce costs

Disclosures: Mohamed Omar: Nothing to Disclose, David Maundu: Nothing to Disclose, Sandra Chehayeb: Nothing to Disclose, Hayder Alamily: Nothing to Disclose, Joshua Musalia: Nothing to Disclose, Matthew Stotts: Nothing to Disclose, Nathan Tofteland: Nothing to Disclose, William Salyers: Nothing to Disclose

2449 | EFFICACY AND SAFETY OF AVATROMBOPAG IN CHRONIC LIVER DISEASE PATIENTS WITH THROMBOCYTOPENIA UNDERGOING ELECTIVE SURGERY

Weihua Cao[1] Yao Xie[1] Minghui Li[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: To evaluate the efficacy and safety of avatrombopag in chronic liver disease (CLD) patients with thrombocytopenia scheduled for elective invasive or minimally invasive procedures, providing clinical guidance for patients requiring platelet count elevation. **Methods:** In this single-center, prospective study, CLD patients with platelet (PLT) counts $< 50\times10^9$/L scheduled for elective invasive/minimally invasive surgery were enrolled as shown in Figure 1. Patients received a 5-day avatrombopag regimen in addition to standard liver disease management. Baseline demographic and biochemical parameters were collected. PLT response, PLT count dynamics, and safety were monitored, with the proportion of patients achieving PLT counts $\geq 50\times10^9$/L on the procedure day recorded. Adverse event rates were assessed. **Results:** A total of 108 CLD patients (mean age: 55.69 $\pm$ 1.26 years; 68.52% male) with baseline PLT counts $< 50\times10^9$/L were enrolled, showing an 83.33% response rate. Responders exhibited significantly higher baseline white blood cell (WBC, $P = 0.009$), neutrophil (NE, $P = 0.016$), hemoglobin (HGB, $P = 0.011$), and PLT ($P = 0.001$) levels compared to non-responders. Baseline PLT correlated positively with age ($P = 0.014$), WBC ($P = 0.046$), HGB ($P = 0.001$), and prothrombin activity (PTA, $P = 0.023$), and negatively with international normalized ratio (INR, $P = 0.020$), as shown in Figure 2. Logistic regression identified baseline PLT as an independent predictor of treatment response ($P = 0.002$). PLT counts began rising by day 5 post-treatment, peaked around day 10, and declined to baseline by day 40 in both the overall cohort and responders. Non-

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responders showed only mild PLT elevation by day 5 (remaining $<50\times10^{9}$/L), with no further increase by day 10 and subsequent decline to baseline, as shown in Figure 3. No adverse events, including bleeding or thrombosis, were observed. **Conclusion:** Avatrombopag demonstrated an 83.33% response rate, with higher baseline PLT predicting better outcomes. PLT counts increased by day 5, peaked around day 10, and were well-tolerated with no safety concerns.

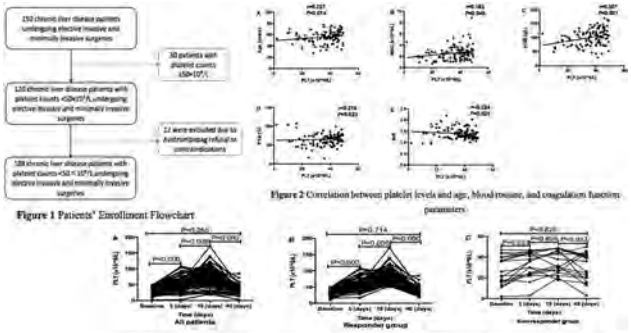


Figure 1 Patients' Enrollment Flowchart

Figure 2 Correlation between platelet levels and age, blood tumor, and coagulation function parameters

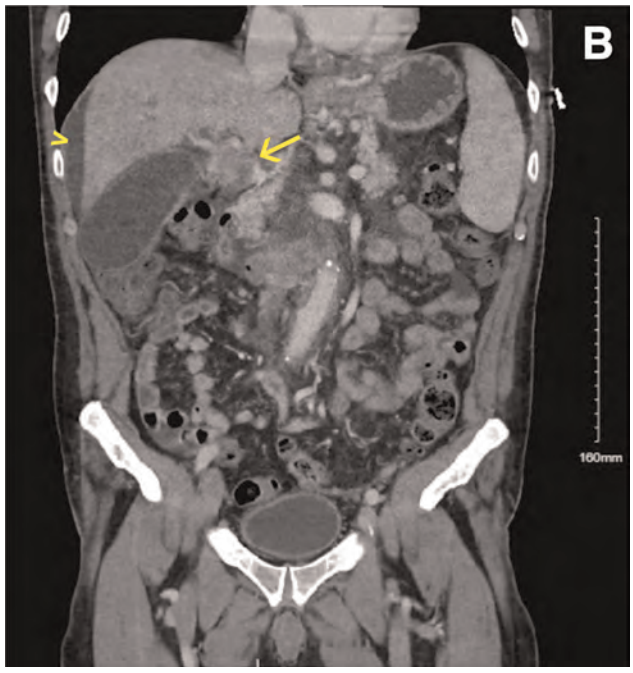
Figure 3 Changes of platelet counts in patients pre- and post-treatment with Avatrombopag.

Disclosures: Weihua Cao: Nothing to Disclose, Yao Xie: Nothing to Disclose, Minghui Li: Nothing to Disclose

2450 | INFLAMMATORY HILAR MASS AND CAVERNOUS TRANSFORMATION IN DISSEMINATED HISTOPLASMOSIS: A RARE CAUSE OF NON-CIRRHOTIC PORTAL HYPERTENSION

Katharine Tippins[1] Elizabeth Townsend[2] Franklyn Wallace[1] Heip Phan[1] Charles Rohrer[1] Adnan Said[2], [1]University of Wisconsin Hospitals and Clinics, [2]University of Wisconsin School of Medicine and Public Health

Background: Disseminated histoplasmosis is a rare but serious fungal infection typically seen in immunocompromised individuals. Hepatic involvement is common, however non-cirrhotic portal hypertension secondary to extrahepatic lymphadenopathy has not been previously reported. We describe a unique case of disseminated histoplasmosis in an immunocompetent host complicated by fibrosing lymphadenitis in the porta hepatis causing portal vein compression and non-cirrhotic portal hypertension. **Methods:** A retrospective review of one patient's clinical course, imaging, histopathology, and treatment response was performed. The patient was followed across multiple hospitalizations for complications related to disseminated histoplasmosis, including cholangitis, spontaneous bacterial peritonitis, and portal hypertension. **Results:** A 68 year old male previously misdiagnosed with sarcoidosis and treated with steroids and methotrexate developed systemic symptoms and pancytopenia. Duodenal biopsy and bone marrow aspirate confirmed disseminated histoplasmosis involving the lungs, GI tract, lymph nodes, and marrow. Despite liposomal amphotericin B and prolonged itraconazole therapy, he developed progressive portal hypertension with ascites, varices, and recurrent spontaneous bacterial peritonitis. Imaging showed a growing porta hepatis mass causing segmental portal vein occlusion, biliary obstruction, and cavernous transformation (see figure). Liver biopsy confirmed non-cirrhotic parenchyma; hilar mass biopsy showed reactive fibrosing lymphadenitis without malignancy or fungal elements. Persistent histoplasma antigenemia and suboptimal antifungal response raised concern for immune reconstitution inflammatory syndrome (IRIS). He was treated with biliary stenting, antifungals, prednisone, diuretics, lactulose, and intermittent paracentesis, with subsequent improvement. This case highlights a rare extrinsic cause of non-cirrhotic portal hypertension due to fibrosing immune response in disseminated histoplasmosis. **Conclusion:** This is the first reported case of disseminated histoplasmosis presenting with non-cirrhotic portal hypertension due to fibrosing lymphadenitis compressing the portal vein. The compressive pathophysiology resembles sclerosing mediastinitis, a known fibrosing complication of histoplasmosis. Clinicians should consider external compression from reactive lymphadenopathy as a rare etiology of portal hypertension, particularly in patients with disseminated fungal infections and no intrinsic hepatic disease. Management requires a multidisciplinary approach including antifungal therapy, supportive care for portal hypertension, and consideration of immunomodulation in suspected IRIS.



Disclosures: Katharine Tippins: Nothing to Disclose, Elizabeth Townsend: Nothing to Disclose, Franklyn Wallace: Nothing to Disclose, Heip Phan: Nothing to Disclose, Charles Rohrer: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching, Madrigal

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Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Advisor

2451 | A SYSTEMATIC REVIEW OF PATIENT AND CAREGIVER REPORTED OUTCOMES IN REFRACTORY ASCITES SECONDARY TO CIRRHOSIS

Yazan Haddadin[1] James Ryley[2] Lucia Macken[1] Sumita Verma[3], [1]University of Sussex, [2]University Hospitals Sussex, [3]Brighton and Sussex Medical School

Background: Refractory ascites (RA) in advanced chronic liver disease (ACLD) is associated with a poor prognosis, especially when a liver transplant is not an option. Developing effective palliative interventions in this cohort requires moving away from traditional clinical endpoints (infection/kidney injury /mortality) toward patient and caregiver reported outcomes (PcROMs). We aimed to examine the existing evidence on PcROMs in ACLD-related RA. **Methods:** A peer-reviewed search strategy was conducted (MEDLINE, Embase, CINAHL, the Cochrane Library, PsychINFO and Web of Science databases) from inception till October 2024. The systematic review was registered onto PROSPERO. Two independent reviewers screened titles/abstracts and full texts, resolving disagreements by consensus. Extracted data included study design/sample size/RA definition/HRQoL instruments/caregiver measures. **Results:** The search yielded 2260 records, 721 being duplicates. 187 full-text articles were assessed and 12 studies met our inclusion criteria. Authors of additional studies that had missing data sets have been contacted. Six were randomised controlled trials (RCT) while the rest were observational studies. The sample size of participants ranged from 13-409, 53-85% were male, the reported mean/median age was 52–72 years with 60%-82% having Child Pugh score B disease. Definition of RA and inclusion/exclusion criteria varied across studies. PcROMs were a primary outcome in only three studies. Tools assessing HRQoL covered both physical and psychological domains and included generic (most commonly SF-36, n = 4), disease-specific (most commonly Chronic Liver Disease Questionnaire, n = 4) and non-validated bespoke questionnaires. Determinants of HRQoL included hospitalisations, leg oedema, confusion, frequency and volume of paracentesis. Six studies looked at symptom burden using a range of instruments (ASI-7 n = 3, ASCITES-Q n = 2, FACIT-AI n = 1, CAS n = 1, IPOS n = 1). Only two studies provided health utility index values for patients with RA (0.56-0.57) and one assessed caregiver burden (using the Zarit Burden Interview), reporting high emotional distress, role strain and unmet support needs. Heterogeneity in the data across studies precluded a meta-analysis. Three studies included controls and showed a significant impact of RA on symptoms burden, physical functioning and role limitations due to physical health when compared to diuretic-controlled ascites. **Conclusion:** Evidence on PcROMs in ACLD-RA is scarce and heterogenous. It is limited by restrictive study designs and inconsistent definitions. The lack of a validated disease-specific instrument is a barrier to both high-quality palliative RCTs and to optimising the complex symptom burden of this cohort. Prioritising PcROMs in ACLD trials could generate the evidence needed to drive equitable, patient-centred palliative care.

Disclosures: Yazan Haddadin: Nothing to Disclose, James Ryley: Nothing to Disclose, Lucia Macken: Nothing to Disclose, Sumita Verma: Beckton Dickinson: Grant/Research Support, Rocket Medical: Grant/Research Support, Gilead Sciences: Grant/Research Support

2452 | CONSTRUCTION OF A RISK PREDICTION MODEL FOR PORTAL VEIN THROMBOSIS IN LIVER CIRRHOSIS BASED ON MACHINE LEARNING

Yaxi Zhang[1], [1]Beijing University of Chinese Medicine

Background: The incidence of portal vein thrombosis (PVT) in patients with cirrhosis is as high as 15% to 25%, which can significantly increase the risk of gastrointestinal bleeding, liver failure, and death. The existing prediction tools rely on a single indicator or traditional scoring, which has the limitations of low sensitivity and insufficient dynamic evaluation ability. The purpose of this study was to apply a variety of machine learning algorithms to construct an accurate PVT risk prediction model, screen the optimal model, and provide a basis for early identification of high-risk groups. **Methods:** A questionnaire on risk factors for the incidence of PVT in liver cirrhosis was developed through literature review and expert consultation. The data of 580 patients with liver cirrhosis who were hospitalized and managed from May 2019 to December 2022 were collected. The Lasso regression method was used to screen the predictors, and the training set (406 cases) and the validation set (174 cases) were randomly divided into a 7:3 ratio. The training set uses multi-layer perception (MLP), support vector machine (SVM), random forest (RF) and adaptive boosting (AdaBoost) to build a prediction model, and evaluates the performance on the validation set. The optimal model was determined according to the area under the receiver operating characteristic curve (AUC) of the validation set. **Results:** A total of 205 patients (35.34%) with cirrhosis developed PVT. Lasso regression

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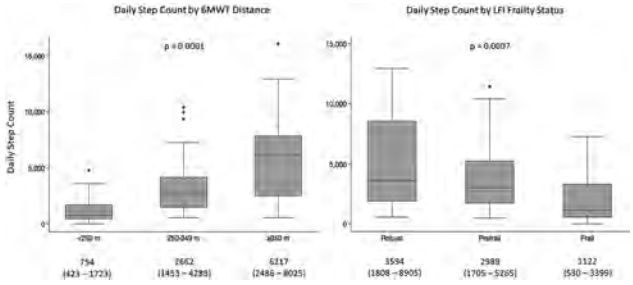
screened seven predictors, including Child-Pugh grade, history of splenectomy, D-dimer level, platelet count, portal vein diameter, ascites, and degree of esophageal varices. The evaluation results of the validation set showed that the random forest model had the best performance (AUC of 0.78 and accuracy of 0.75), which was better than that of other models (MLP: AUC = 0.69; SVM: AUC = 0.72; Adaboost: AUC = 0.74). **Conclusion:** The risk prediction model for PVT in liver cirrhosis based on random forest algorithm has the best overall performance, and can be used for early identification and screening of high-risk groups of PVT in patients with liver cirrhosis.

Disclosures: Yaxi Zhang: Nothing to Disclose

2453 | OPERATIONALIZING A WALKING EXERCISE PRESCRIPTION BASED ON 6-MINUTE WALK TEST RESULTS:

Joshua Sepic[1] Louis Guzman[2] Susanna Miranda[1] Fei-Pi Lin[3] Pamela Bloomer[4] Richard Lieber[5] James Sliwa[5] Andres Duarte-Rojo[1], [1]Northwestern Medicine, [2]Northwestern University, [3]University of Pittsburgh, [4]University of Pittsburgh Medical Center, [5]Shirley Ryan Ability Lab

Background: Providing an exercise prescription to liver transplant (LT) candidates as part of their prehabilitation processing can be challenging. Walking is a proven exercise intervention for improving physical frailty and waitlist mortality in LT candidates, however, access can become a limiting factor for these patients. Physical activity trackers (PAT) provide an opportunity to monitor and prescribe exercise, remotely. In order to operationalize an exercise prescription using walking as the main training strategy, we explored what would be the thresholds we would need to use by cross-referencing 6MWT and PAT data. **Methods:** We did a post-hoc analysis of previously published data. Daily steps from 1-week PAT monitoring data were cross-referenced with baseline 6MWT performance. The latter were categorized in 3 groups: <250 m, 250-349 m, and ≥ 350 m, both due to distribution of data and to align with published literature. The liver frailty index (LFI) was used to categorize patients as frail (≥ 4.5) vs. nonfrail (subcategorized as prefrail [3.2-4.4]; and robust [<3.2]). Kruskal-Wallis was used for comparisons. **Results:** In 107 participants with both PAT-daily steps and 6MWT (age 56 ± 11, male 57%), we found that that 19 (18%), 47 (44%) and 41 (38%) accomplished <250 m, 250-349 m, and ≥ 350 m in their 6MWT, respectively. Participants in the lowest performance category were most likely female (63% vs. 39%), less likely listed for LT (21% vs. 61%), had more ascites (100% vs. 68%) and hepatic encephalopathy (100% vs. 65%), and were most likely frail (79%, vs. 11%). The daily steps per 6WMT category are shown in *Figure 1A*. Grouping daily steps by LFI category produced similar results (*Figure 1B*). **Conclusion:** PAT are a proven, low-cost method of tracking exercise in LT, but have to date seen limited use in exercise prescription. Using these data, appropriate step counts can be prescribed to LT candidates based upon 6MWT performance. Further, these data can be used as a model to appropriately increase daily step counts to levels that correlate with improved 6MWT performance, improved physical frailty, and increased likelihood of listing for LT. We propose a walking prescription of 1500, 3000, and 6000 steps/day for LT candidates doing <250, 250-349, and ≥ 350 m, respectively.



Disclosures: Joshua Sepic: Nothing to Disclose, Louis Guzman: Nothing to Disclose, Susanna Miranda: Nothing to Disclose, Fei-Pi Lin: Nothing to Disclose, Pamela Bloomer: Nothing to Disclose, Richard Lieber: Nothing to Disclose, James Sliwa: Nothing to Disclose, Andres Duarte-Rojo: Echosens: Grant/Research Support

2454 | DYNAMIC LACTATE CLEARANCE PREDICTS MORTALITY IN DECOMPENSATED CIRRHOSIS: A PROSPECTIVE MEXICAN COHORT

Emilio Sandoval-Gonzalez[1] Francisco Bosques-Padilla[2] Miguel Escobedo-Belloc[2] Jorge Zuñiga-Hernandez[2] Hannia Zumaya-Flores[3] Wendy Ruiz-Gallegos[3] Lilia Chavez-García[3] Leonel Castillo-Peña[3] Andres Zapata-Navarro[3], [1]Hospital Universitario Dr. José Eleuterio González, [2]Hospital Universitario Dr. José Eleuterio González, Universidad Autónoma de Nuevo León, Monterrey,Mx, [3]Facultad de Medicina, Universidad Autónoma de Nuevo León, Monterrey, Mexico

Background: Timely identification of high-risk patients during acute decompensation (AD) of cirrhosis remains a key clinical challenge. While hyperlactatemia is frequently observed, its dynamic behavior particularly lactate clearance remains undercharacterized in cirrhotic populations, especially in Latin America.

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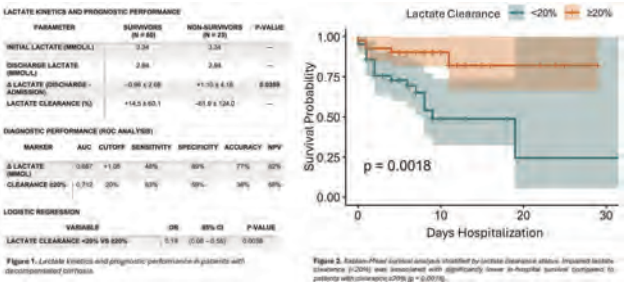
Methods: The prospective study included 83 adults with acute decompensation (AD) of cirrhosis admitted to an academic referral center in Mexico. Serial arterial lactate levels were measured through routine blood gas analysis at admission and at 72 hours, or earlier if new organ failure, discharge, or death occurred first. Although some patients had additional values (e.g., on day 8 ± 2), the primary analysis focused on paired measurements to assess dynamic change. Lactate clearance: [(lactate at admission – follow-up lactate) / lactate at admission] × 100. Impaired clearance was defined as < 20%. The primary outcome was in-hospital mortality. Predictive performance was assessed using ROC analysis and logistic regression. Kaplan–Meier analysis evaluated survival according to lactate clearance. **Results:** Among the 83 patients, in-hospital mortality was 27.7% (n = 23). Survivors showed a significant reduction in lactate (Δ = –0.96 ± 2.68 mmol/L), while non-survivors exhibited a marked increase (Δ = +1.10 ± 4.18 mmol/L; p = 0.0359). Mean clearance was +14.5% in survivors vs. –61.9% in non-survivors (p = 0.0125), reflecting divergent trajectories. Using a 20% threshold, impaired clearance was associated with significantly higher in-hospital mortality. On logistic regression, clearance < 20% remained independently associated with death (OR 0.19; 95% CI: 0.06–0.55; p = 0.0038). Kaplan–Meier curves confirmed worse survival in patients with impaired clearance (log-rank p = 0.0018). **Conclusion:** Lactate clearance is a dynamic, accessible biomarker associated with in-hospital mortality in decompensated cirrhosis. Unlike static values, serial trends reflect clinical deterioration and may guide early triage and care decisions, especially in resource-limited settings, where dynamic monitoring could enhance early recognition and guide timely intervention. This study also represents one of the first prospective Latin American cohorts evaluating lactate kinetics in this population.



Disclosures: Emilio Sandoval-Gonzalez: Nothing to Disclose, Francisco Bosques-Padilla: Nothing to Disclose, Miguel Escobedo-Belloc: Nothing to Disclose, Jorge Zuñiga-Hernandez: Nothing to Disclose, Hannia Zumaya-Flores: Nothing to Disclose, Wendy Ruiz-Gallegos: Nothing to Disclose, Lilia Chavez-García: Nothing to Disclose, Leonel Castillo-Peña: Nothing to Disclose, Andres Zapata-Navarro: Nothing to Disclose

2455 | PRIORITY OUTPATIENT PARACENTESIS PREVENTS UNPLANNED PRESENTATIONS

Janis Fernandes[1] Rohit Gupta[1] James O'Beirne[1],
[1]Sunshine Coast University Hospital

Background: Large volume paracentesis (LVP) for diuretic refractory ascites (RA) often requires regular hospital visits. Typically, this is facilitated through day units shared with other specialities. The unpredictable nature of ascites accumulation and lack of availability of day unit beds can result in unplanned hospital presentations for LVP. This increases clinical demands in the emergency department and skill mix availability may lead to unnecessary hospitalisation and increased patient length of stay (LOS). We implemented a Priority Outpatient Paracentesis (POP) Clinic using dedicated beds on the liver and gastroenterology ward to streamline care for patients requiring regular LVP. The primary outcome was a reduction in unplanned LVP, with secondary outcomes including an increase in planned LVP and a decrease in hospital length of stay (LOS). **Methods:** Single-centre retrospective cohort study analysed data from the 12 months pre implementation of the POP clinic where LVP was performed in the non-specialised Day Unit Investigation and Therapy (DUIT) and compared this to the 12 months following implementation of POP clinic. Across the 24-month study period, LVP was classified as planned or unplanned and LOS was recorded. **Results:** The cohort comprised 114 patients undergoing 373 LVPs, 9 patients overlapped both phases. In DUIT, 62 patients (44 male) underwent 168 paracenteses (52% unplanned, 48% planned). In POP Clinic, 61 patients (44 male) underwent 205 paracenteses (37% unplanned, 63% planned). POP Clinic implementation significantly increased planned LVPs (p = 0.004). Total number of LVPs increased by 22% in the POP clinic phase. Despite an increase in the number of LVPs, the total LOS was significantly reduced (p = 0.04). **Conclusion:** Implementation of POP clinic significantly reduced the number of unplanned admissions for LVP. LOS was significantly reduced reflecting improved access to timely LVP through a dedicated facility.

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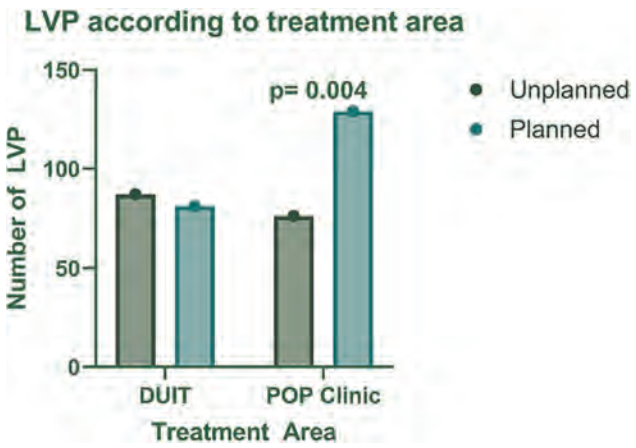

Disclosures: Janis Fernandes: Nothing to Disclose, Rohit Gupta: Nothing to Disclose, James O'Beirne: CSL Behring: Advisor, ROCHE: Advisor, Novo Nordisk: Advisor

2456 | IMPACT OF HELICOBACTER PYLORI ON LIVER OUTCOMES IN CIRRHOTIC PATIENTS: A RETROSPECTIVE COHORT

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Background: Liver cirrhosis is a chronic liver disease that carries a guarded prognosis for affected patients. Helicobacter pylori (H. pylori) infection, while primarily known for causing gastrointestinal disease, has been increasingly reported to affect outcomes in patients with chronic liver disease. This study aims to evaluate whether H. pylori infection worsens clinical outcomes in patients with cirrhosis. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network, utilizing data from 69 healthcare organizations. Two cohorts were identified: Cohort 1 included patients with cirrhosis and H. pylori infection (n = 10,792); Cohort 2 included patients with cirrhosis but without H. pylori infection (n = 643,249). All etiologies of cirrhosis were included in the study using the International Classification of Diseases codes 10 (ICD). Propensity score matching (PSM) was performed between the two cohorts based on demographics, comorbidities, and MELD components (creatinine, bilirubin, INR, Sodium) resulting in 10,674 matched individuals in each cohort. Outcomes assessed included the development of hepatocellular carcinoma (HCC), ascites, spontaneous bacterial peritonitis (SBP), esophageal varices (EV), hepatorenal syndrome (HRS), hepatic encephalopathy (HE), mortality, and combined liver-related events. Comparative analyses used risk ratios and Kaplan-Meier survival estimates over a 10-year follow-up period, excluding patients with pre-existing outcomes. **Results:** Before PSM, remarkable differences were observed between the cohorts in terms of comorbidities and demographics. After PSM, groups were well balanced. As shown in Table 1, patients with H. pylori had significantly higher risks of developing HCC (RR 1.27; $p < 0.001$) compared to liver cirrhosis patients without H. pylori. Interestingly, H. pylori-infected patients had lower all-cause mortality (RR 0.86; $p < 0.001$). No significant differences were found for ascites, SBP, HE, HRS, EV, or combined liver-related events. **Conclusion:** In cirrhotic patients, a higher risk of HCC was observed in those with H. pylori infection compared to those without H. pylori. However, a lower risk of all-cause mortality was seen in patients with H. pylori infection. These findings raise questions for further studies regarding the relationship between H. pylori infection and HCC in cirrhotic patients, and the role of H. pylori eradication therapy.

Outcome	Cohort 1, N (%)	Cohort 2, N (%)	RR 95% CI	p-value
Number of patients in each cohort	10,674	10,674	-	-
Hepatocellular carcinoma (HCC)	629 (6.3%)	503 (5.0%)	1.27 (1.14–1.43)	<0.001
Ascites	1,492 (18.9%)	1,517 (18.0%)	1.05 (0.99–1.12)	0.115
SBP	408 (3.9%)	393 (3.7%)	1.05 (1.04–1.33)	0.496
EV	949 (12.7%)	1,332 (13.7%)	0.93 (0.86, 1.00)	0.060
HRS	464 (4.4%)	417 (4.0%)	1.12 (0.98, 1.27)	0.090
HE	747 (7.4%)	696 (6.7%)	1.09 (0.988, 1.205)	0.086
Mortality	2,254 (21.3%)	2,636 (24.9%)	0.86 (0.81, 0.90)	<0.001
Liver-related events combined	1,584 (21.2%)	1,671 (20.7%)	1.02 (0.96, 1.09)	0.451

Disclosures: Mohammed Al-Aquily: Nothing to Disclose, Abdellatif Ismail: Nothing to Disclose, Kamran Qureshi: Nothing to Disclose, Wing-Kin Syn: Zydus: to University, Merck: Consultant

2457 | PREDICTORS OF HYPOLGYCEMIA IN INDIVIDUALS WITH CIRRHOSIS WITHOUT DIABETES

Alan Hutchison[1] Mary Rinella[1] Celeste Thomas[2], [1]The University of Chicago, [2]University of Chicago

Background: Individuals with cirrhosis are at risk of disruptions in their glucose metabolism. We have reported

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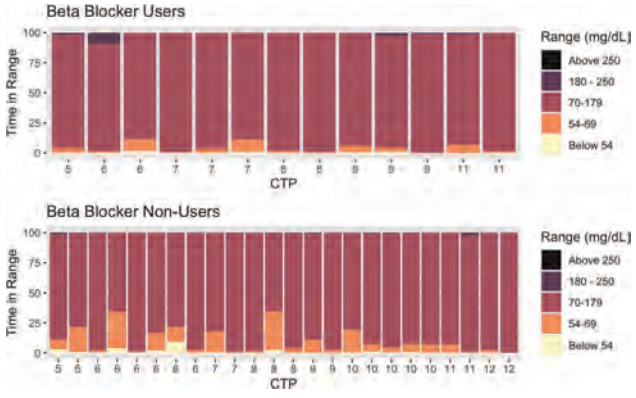
that approximately 50% of individuals with cirrhosis without diabetes have greater than 4% of the time with glucose less than 70 mg/dL in an outpatient setting. Underlying risk factors for ambulatory hypoglycemia in liver disease are unknown. **Methods:** We enrolled patients with cirrhosis without diabetes from pre-liver transplant clinic at the University of Chicago (IRB 23-0691). They were assessed with an Abbott Libre Pro continuous glucose monitor. Subject characteristics of age, BMI, creatinine-based eGFR, beta blocker usage, albumin, INR, TIPS presence, MELD 3.0, and CTP score were compared against the endpoint of time with glucose below 70 mg/dL. We conducted an interim analysis at the point when we had sufficient sample size (37 episodes) to identify a moderate effect size (Cohen's $f^2 = 0.15$) with a power of 0.80 and a significance of 0.05 using 2 variables. **Results:** We had 37 CGM measurement episodes for 28 separate subjects, with repeat measurements separated by at least 3 months. The median age was 51 (Q1–Q3: 45 – 58), the median MELD 3.0 was 15.5 (Q1-Q3: 12.0 – 20.0), and the median CTP score was 8 (Q1–Q3: 6-10) (Figure). 21/37 episodes (16/28 subjects) had greater than 4% time in hypoglycemia (glucose less than 70 mg/dL). 13 subjects were on a beta blocker, while 4 had a TIPS. When controlling for the subject, beta blocker usage was associated with decreased hypoglycemia ($p = 0.04$), but this association was suppressed ($p = 0.06$) when adjusting for CTP score, which itself was not associated with hypoglycemia ($p = 0.84$) (Figure). **Conclusion:** Despite the majority of CGM measurement episodes and subjects having greater than 4% time with glucose less than 70 mg/dL and being powered for a moderate effect size, no variables were predictive of hypoglycemia in this cohort of individuals with cirrhosis without diabetes under evaluation for liver transplant. Further work needs to validate the non-predictive ability of these variables – until then, screening individuals with cirrhosis for hypoglycemia with continuous glucose monitors may be the best modality for identifying dangerous hypoglycemia.



Disclosures: Alan Hutchison: Nothing to Disclose, Mary Rinella: akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, Celeste Thomas: Nothing to Disclose

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2458 | USE OF ENDOHEPATOLOGY TO SAFELY AND EFFECTIVELY STAGE FONTAN-ASSOCIATED LIVER DISEASE

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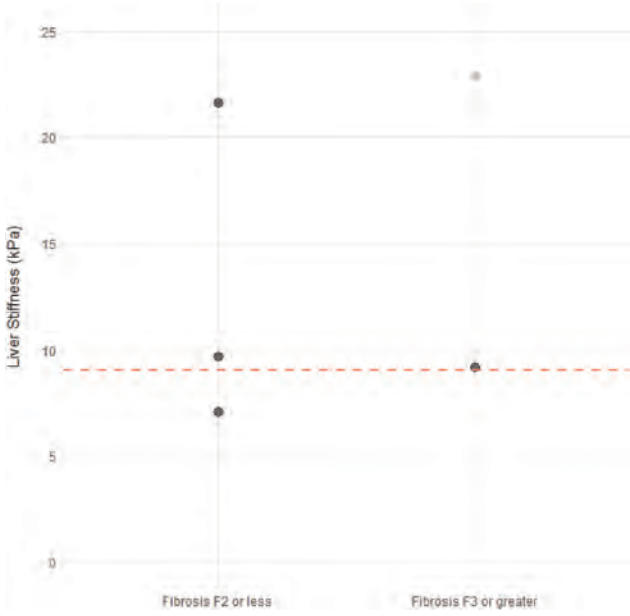
Background: Patients with congenital heart disease (CHD) status post Fontan palliation develop progressive congestive hepatopathy known as Fontan-associated liver disease (FALD) potentially leading to cirrhosis, clinically significant portal hypertension (CSPH), and hepatocellular carcinoma. FALD management including consideration for liver transplant is contingent on accurate disease staging. Yet staging FALD remains challenging for myriad reasons (e.g., limited tissue sampling from transjugular biopsy due to complex anatomy, barriers to noninvasive elastography due to heart failure or indwelling pacemaker). Endohepatology enables simultaneous CSPH assessment and biopsy-determined fibrosis but data on use in FALD patients is lacking. In this pilot study, we sought to determine feasibility and efficacy of endohepatology for FALD staging. **Methods:** This was a single center prospective study composed of patients age $\geq$ 18 years old with history of CHD, Fontan palliation and FALD. All patients completed combined upper endoscopy (EGD) for variceal screening with endoscopic ultrasound (EUS)-guided bilobar liver biopsies and direct portal manometry. Liver fibrosis stage was determined by Metavir score (F0-F4). Biopsy results were compared to noninvasive liver stiffness measurements (LSM) from shear wave elastography (SWE) or transient elastography (TE) within 1 year of endohepatology procedure (EGD-EUS). **Results:** Seven patients completed EGD-EUS. The majority of the cohort was male (86%), mean age was 33 years old (SD 7), mean time since Fontan palliation was 28 years (SD 7), most patients (57%) had clinical heart failure (AHA stage C [N = 1], stage D [N = 3]). Four patients had limited fibrosis (F1-F2) on biopsy. Three patients had advanced fibrosis ($\geq$ F3 [N = 1], F3-F4 [N = 2]). Five patients had LSM 7.1-22.9 kPa (mean 14.1 kPa $\pm$ 7.5). One patient with LSM $<$ 9 kPa had F1-F2 fibrosis on biopsy. Among patients with LSM $>$ 9 kPa, correlation with biopsy-proven fibrosis was variable (see figure). Four patients had esophageal varices on EGD, though only one patient had intrahepatic CSPH per mean hepatic venous pressure gradient $>$ 5 (8). Regarding feasibility, one patient experienced acute hypoxia due to laryngospasm prior to starting endoscopic exam but tolerated the rescheduled procedure without complication. Another patient experienced postprocedural fever. **Conclusion:** Endohepatology provides a well-tolerated, efficient and comprehensive method of FALD staging and determination of CSPH. Our results show some discordance between LSM versus EUS-guided biopsy, especially at more advanced disease stage. This potentially reflects limitations of elastography in heart failure patients, benefits of increased tissue sampling via bilobar EUS-biopsy and/or small cohort size. These results suggest endohepatology may safely provide superior staging in FALD patients though further data is needed.



Disclosures: Michael Dybala: Nothing to Disclose, Abdul Aadam: Nothing to Disclose, Jessica Nguyen: Nothing to Disclose, Amir Borhani: Siemens Healthineers: In-kind research support, Boston Scientific: Consultant, Daniel Ganger: WCG: Consultant, Justin Boike: W. L. Gore and Associates: Grant/Research Support, Eurofins Transplant Genomics: Advisor, Echosens: Consultant, W. L. Gore and Associates, Inc.: Consultant, Dempsey Hughes: Nothing to Disclose

2459 | LIVER-TO-SPLEEN VOLUME RATIO IDENTIFIES HIGH-RISK PATIENTS FOR FURTHER DECOMPENSATION WITHIN 1 YEAR AFTER TIPS AMONG CIRRHOSIS PATIENTS

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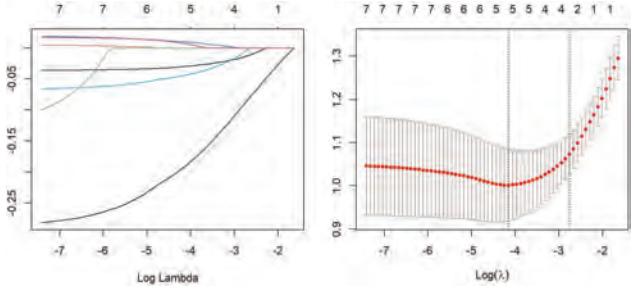
Background: To explore factors influencing further decompensation within 1 year after transjugular intrahepatic portosystemic shunt (TIPS) placement in cirrhosis patients and establish a predictive model for identifying high-risk individuals. **Methods:** In this single-center retrospective study, we enrolled cirrhosis patients who underwent TIPS for decompensation events (ascites, esophagogastric variceal bleeding, or recurrent hepatic encephalopathy) and contrast-enhanced computed tomography (CT) at Tianjin University Central Hospital (China) between January 2018 and January 2024. All patients were followed for at least 1 year post-TIPS, with further decompensation as the primary endpoint. Patients were stratified into clinically stable and further decompensation groups based on 1-year outcomes. Predictors were screened using univariate logistic regression and least absolute shrinkage and selection operator (LASSO) regression, followed by multivariate logistic regression to build the predictive model. **Results:** 152 eligible cirrhosis patients were included. Median age was 57.50 years (IQR 50.00–66.00), with 89 (58.55%) males. Viral and alcoholic etiologies predominated (58.55%). Further decompensation occurred in 52 patients (34.21%) within 1 year post-TIPS. Univariate and LASSO regression identified liver-to-spleen volume ratio (LSVR), serum sodium, and reduction amplitude of portal pressure gradient (PPG) post-TIPS for multivariate analysis. LSVR (OR = 0.761, 95% CI = 0.678–0.853) and PPG reduction amplitude (OR = 0.956, 95% CI = 0.923–0.992) independently predicted further decompensation. The resulting model demonstrated excellent discrimination: AUC = 0.864 (95% CI: 0.804–0.923), sensitivity = 0.846, specificity = 0.790. **Conclusion:** LSVR and PPG reduction amplitude are strongly associated with further decompensation within 1 year post-TIPS. Our clinical prediction model (AUC = 0.864) effectively stratifies post-TIPS risk, informing therapeutic decision-making, postoperative surveillance, and individualized management.



Disclosures: xinyu chen: Nothing to Disclose, Yicheng Lin: Nothing to Disclose, Kefeng Jia: Nothing to Disclose, Jiajun Tian: Nothing to Disclose, Fenghui Li: Nothing to Disclose, Rong Lv: Nothing to Disclose, Chao Yang: Nothing to Disclose, Jiayin Wang: Nothing to Disclose, Huiling Xiang: Nothing to Disclose

2460 | SPLENIC STIFFNESS AND SIZE DIFFERENTIATES NON CIRRHOTIC PORTAL FIBROSIS AND EXTRA HEPATIC PORTAL VEIN OBSTRUCTION IN CHILDREN: PROSPECTIVE OBSERVATION STUDY

Sanjeev Verma[1] Anjali Singh[2] SUMIT RUNGTA[3] Dr Manisha Verma[2] Malti Maurya[4] Saurabh Kumar[5], [1]King George Medical University Lucknow, [2]Department Of Pediatrics, King George Medical University, [3]KGMU, [4]Department Of Pathology, King George Medical University, [5]Department Of Radio diagnosis, King George Medical University

Background: Noncirrhotic Portal Hypertension (NCPF) and Extra Hepatic Portal Vein Obstruction (EHPVO) have clinical presentation of unexplained portal hypertension with or without variceal bleed. At presentation it's difficult to differentiate the two conditions, so this liver and splenic stiffness based study carried out in children with portal hypertension (PHTN) without cirrhosis. **Methods:** This prospective observational study enrolled, 1-14 years old children, presented to tertiary care center of North India, over a period of 1 year, with evidence of unexplained clinical portal hypertension. Clinical, biochemical and radiological data was collected on predesigned format. Liver and splenic elastography done after stabilization. Those without portal cavenoma were subjected to liver biopsy. **Results:** Twenty three children (74% Male) with clinical (PHTN) without cirrhosis were enrolled, 16 were diagnosed as EHPVO and 7 as NCPF. Mean age of enrolled children was 8.43 ± 3.578 years. Seventy four percent children presented with hematemesis, 70% with upper abdominal distension, 22% have transient jaundice, and 87% have splenomegaly. Mean Liver and Splenic stiffness among EHPVO and NCPF were, 3.95 +1.13 vs 3.78+1.07 kpa ($p = 0.736$) and 28.25 +23.77 vs 69.44+62.33 kpa ($p = 0.029$) respectively. While comparing NCPF and EHPVO, NCPF have bigger Spleen size 3.71 ± 2.48 vs 11.93 ± 3.94 cm ($p = 0.001$) below costal margin. NCPF have higher odds (1.2) for Clinically Significant Varices as compared to EHPVO (Table 1). **Conclusion:** EHPVO and NCPF are important cause of PHTN in children without cirrhosis. Liver and splenic stiffness measurement may help to differentiate the two conditions. Higher splenic stiffness and bigger spleen size in absence of portal cavernoma is having good sensitivity to predict NCPF in these children.

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Table 1: Comparison of Clinical, Lab and Elastography findings NCPF & EHPVO in children.

Parameter	EHPVO (n = 16)	NCPF (n = 7)	Significance (non-parametric) p value
Age (years)	8.19±3.56	9.0±3.83	0.628
Gender Male	75%	71.4%	0.865
Jaundice	25%	14.3%	0.587
Hematemesis	81.3%	57.1%	0.313
Liver (BCM) cm	0.938±0.65	1.14±1.7	0.675
Spleen (BCM) cm	3.71±2.48	11.93±3.94	**0.001**
Clinical Significant Varices	4 (25%)	2 (28.6%)	OR 1.2
Hb	7.9±1.8	7.0±2.6	0.378
TLC	6595.50±41	2580.00±813.24	**0.02**
Platelet (10*5/ ml)	1.68±1.4	.68143±.47	**0.026**
Total Bilirubin (mg/dl)	1.16938+1.02	1.76571+1.73	0.422
Conjugated Bilirubin (mg/dl)	.40625+.26	.47143+.27	0.596
INR (Prothrombin Time) at presentation	1.38+.20	1.9071+1.33	0.339
Aspartate aminotransferase (IU/L)	39.43+21.04	41.18+21.03	
Alanine aminotransferase (IU/L)	32.75+17.62	26.66+16.47	0.439
Alkaline phosphatase (IU/L)	348.09+154.15	393.64+147.03	0.513
Total Protein (g/dl)	5.71+.65	5.95+1.03	0.585
Albumin (g/dl)	3.57+.36	3.59+.49	0.942
Liver Stiffness (kpa)	3.95+1.13	3.78+1.07	0.736
Splenic Stiffness (kpa)	28.25+23.77	69.44+62.33	**0.029**
APRI	.73+.39	1.07+.47	0.083
Liver to Spleen stiffness	.23+.14	.07+.022	**0.01**

Clinical significant varices : grade III varices or Grade II Varices with red colour signs of neovascularization.
Abbreviations: BCM Below costal Margin.

Disclosures: Sanjeev Verma: Nothing to Disclose, Anjali Singh: Nothing to Disclose, SUMIT RUNGTA: Nothing to Disclose, Dr Manisha Verma: Nothing to Disclose, Malti Maurya: Nothing to Disclose, Saurabh Kumar: Nothing to Disclose

2461 | WARNING NOTICE FOR A SHORT-TERM ELEVATION OF AMMONIA LEVELS FOLLOWING SPLENIC ARTERY EMBOLIZATION

Tsuyoshi Ishikawa[1] Aika Kirihara[1] Natsuko Nishiyama[1] Daiki Kawamoto[1] Ryo Sasaki[1] Tatsuro Nishimura[1] Taro Takami[1], [1]Yamaguchi University Graduate School of Medicine

Background: Partial splenic embolization (PSE) has attracted considerable attention as a fundamental treatment for portal hypertension-related diseases in terms of portal hemodynamic regulation. However, few studies have demonstrated effects of PSE on hepatic encephalopathy, a portal hypertensive symptom. The present study aimed to investigate ammonia-level changes by PSE and to identify determinants of postprocedural changes in patients with or without portosystemic shunts (PSSs). **Methods:** This retrospective study included 136 patients with hypersplenism undergoing PSE at our hospital. The patients were divided into the PSS (−) group, comprising 90 patients without PSSs with a diameter of ≥ 8 mm, and the PSS (+) group, comprising 46 patients with PSSs with a diameter of ≥ 8 mm. Ammonia levels as well as biochemical and imaging findings were assessed before and at 1 month after PSE. **Results:** Overall, PSE significantly increased ammonia levels (85.3 $\pm$ 41.6 to 99.7 $\pm$ 36.0 μg/dL, $p < 0.01$) despite postprocedural hepatic function amelioration and hepatic venous pressure gradient reduction. Elevated ammonia levels were observed postoperatively in 73.3% and 63.0% patients in PSS (−) and PSS (+) groups, respectively. The procedure significantly increased ammonia levels (74.0 $\pm$ 38.1 to 91.8 $\pm$ 31.6 μg/dL, $p < 0.01$) in the PSS (−) group; in contrast, the post-PSE ammonia-level elevation was not statistically significant (107.4 $\pm$ 39.5 to 115.1 $\pm$ 39.3 μg/dL, $p = 0.21$) in the PSS (+) group. Preprocedural Child-Pugh scores of < 8 and splenic non-infarction volume of ≥ 120.32 cm^3 were significantly and independently associated with postprocedural ammonia-level elevation in the PSS (−) group; the combination of two indicators showed a sensitivity and specificity of 44.6% and 87.0% for elevation prediction, respectively. Preprocedural splenic artery diameter-to-common hepatic artery diameter ratios of < 1.4 and concomitant splenic vein-derived shunt vessels were significant and independent determinants of postprocedural ammonia-level elevation in the PSS (+) group; the combination of two conditions exhibited a sensitivity and specificity of 40.0% and 100.0% for elevation prediction, respectively. **Conclusion:** PSE generally poses a high risk of short-term ammonia-level elevation, particularly in patients without PSSs. Preprocedural therapeutic indications and postprocedural follow-up strategies should be considered according to determinants of post-PSE ammonia-level changes individually.

Disclosures: Tsuyoshi Ishikawa: Nothing to Disclose, Aika Kirihara: Nothing to Disclose, Natsuko Nishiyama: Nothing to Disclose, Daiki Kawamoto: Nothing to Disclose, Ryo Sasaki: Nothing to Disclose, Tatsuro Nishimura: Nothing to Disclose, Taro Takami: Nothing to Disclose

2462 | FLUID IN THE LUNGS: EXPLORING THE ASSOCIATION BETWEEN B-LINE BURDEN ON POINT-OF-CARE ULTRASOUND AND MARKERS OF RIGHT-SIDED PRESSURE OVERLOAD IN HOSPITALIZED PATIENTS WITH CIRRHOSIS

Daniel Alvarez[1] Kelsie Pereyra-Bencosme[1] Suneet Waghmarae[1] Nicholas Samel[2] Ashley Choi[2] Zoe Verzani[3] Paola Mejia[1] Abhilash Koratala[4] Benjamin Galen[1] Brett Fortune[1], [1]Montefiore Medical Center/ Albert Einstein College of Medicine, [2]Albert Einstein College of Medicine, [3]Weill Cornell Medicine, [4]Montefiore Medical Center/Albert Einstein College of Medicine/Medical College of Wisconsin

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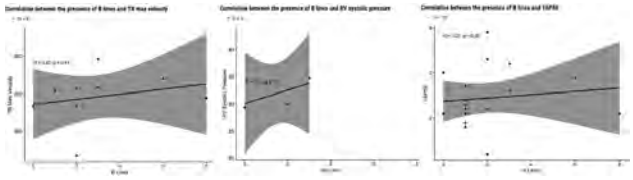
Background: Patients with decompensated cirrhosis frequently experience cardiopulmonary complications, including pulmonary edema. Point-of-care ultrasound (POCUS) has emerged as a rapid, accessible bedside tool for evaluating volume status and pulmonary edema, particularly through the detection of B-lines on lung ultrasound. While B-lines are established markers of pulmonary congestion and elevated left-sided filling pressures in heart failure, their utility in hospitalized patients with cirrhosis is not well described. We aimed to determine whether B-line burden is associated with transthoracic echocardiographic (TTE) parameters of right-sided cardiac pressure overload in hospitalized patients with cirrhosis. **Methods:** We conducted a prospective observational cohort study of 37 hospitalized patients with decompensated cirrhosis, including three readmissions treated as separate encounters (total of 40 observations). Comprehensive POCUS was performed during admission, with 23 observations also having corresponding TTE data, though availability varied by parameter. Lung ultrasound was performed using a phased array probe in four bilateral lung zones: the midclavicular line at the 2nd, 4th, and 6th intercostal spaces, and the midaxillary line at the 8th–9th intercostal space. B-line burden was quantified as the number of zones with ≥ 3 B-lines in a single intercostal space (range: 0–8). We analyzed Spearman's correlation coefficients between B-line burden and TTE parameters, including right ventricular systolic pressure (RVSP), tricuspid regurgitation (TR) max velocity, and tricuspid annular plane systolic excursion (TAPSE). **Results:** The cohort had a median age of 54 years; 63% were male, 68% Hispanic and 68% had alcohol-related liver disease. The median MELD score at admission was 24. The leading reason for hospitalization was refractory ascites. B-lines were present in 82.5% of observations. Among the 23 with complete lung POCUS and TTE data, B-line burden showed a positive correlation with RVSP ($R = 0.8$, $p = 0.33$) and TR max velocity ($R = 0.53$, $p = 0.14$). There was no significant correlation between B-line burden and TAPSE ($R = 0.27$, $p = 0.28$) (Figure). **Conclusion:** In hospitalized patients with decompensated cirrhosis, B-line burden was associated with higher markers of right-sided pressure overload (RVSP and TR max velocity), but not with systolic function (TAPSE). While B-lines should not be interpreted in isolation as markers of venous congestion or right heart dysfunction, their presence should prompt further evaluation of right-sided cardiac parameters and Doppler markers of venous congestion. Ongoing enrollment and larger studies will be critical to validate these findings and determine their prognostic utility for adverse clinical outcomes.



Disclosures: Daniel Alvarez: Nothing to Disclose, Kelsie Pereyra-Bencosme: Nothing to Disclose, Suneet Waghmarae: Nothing to Disclose, Nicholas Samel: Nothing to Disclose, Ashley Choi: Nothing to Disclose, Zoe Verzani: Nothing to Disclose, Paola Mejia: Nothing to Disclose, Abhilash Koratala: Nothing to Disclose, Benjamin Galen: Nothing to Disclose, Brett Fortune: Gilead Sciences: Consultant, Madrigal Pharma: Consultant, WL Gore and Associates: Consultant, BD medical: Consultant

2463 | IS SUBSTITUTING SERUM CREATININE FOR SERUM CYSTATIN C IN CALCULATING MELD SCORES MORE APPROPRIATE FOR ASSESSING THE SEVERITY OF CHRONIC LIVER DISEASE?

Jeff Angelo Taclob[1] Anjana Mary Jacob[1] Satheesh Nair[1], [1]University of Tennessee Health Sciences Center, Memphis

Background: Complications of portal hypertension are represented by renal dysfunction and hyponatremia in the MELD scoring system. However, it is well known that serum creatinine level underestimates renal dysfunction in patients with cirrhosis and sarcopenia. We have been measuring serum Cystatin C in patients undergoing liver transplant evaluation at our center. This study aims to demonstrate that a Cystatin C-based MELD score (MELD Cy) may more accurately reflect renal dysfunction, therefore better represent mortality risk in patients with complications of portal hypertension. **Methods:** A retrospective cohort study was performed on patients who underwent liver transplant evaluation at our institution between October 2024 and March 2025. A total of 96 patients were included in the study. Patient demographics, etiology of cirrhosis, presence of ascites, and pertinent laboratory data were obtained. Student t-test was used to compare the eGFR and MELD scores **Results:** A total of 96 individuals (49 females) were included in the study. 72 (75%) patients had ascites. The most common etiology of cirrhosis was MASH (35%), followed by Alcoholic liver disease (21%). Mean eGFR based on serum creatinine was 81.6 ml/min (CKD-EPI method) and 57.9 ml/min based on Cystatin C. Mean MELD scores with serum creatinine were 18.8 (+/- 6.04), while the mean MELD score obtained using Cystatin C was 22.2 (+/- 6.82) Most patients had a higher MELD Cy compared to MELD 3.0.

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Forty patients (41%) had an increase of 1 to 3 points, 34 (35%) patients had an increase of 4 to 6 points, and 10 (10%) patients had a significant increase of more than 6 points. The differences in MELD 3.0 vs MELD Cy (p value = 0.0005) and eGFR Creatinine vs eGFR Cystatin C (p value = 0.0002) were statistically significant. On further analysis of patients with ascites (n = 72), the disparity between the MELD 3.0 (18.97 (+/- 5.40)) and MELD Cy (22.99 (+/- 5.92)), and eGFR CKD -EPI Creatine (78.8 (+/- 26.94)) and eGFR with Cy (53.99 (+/- 20.84)) persisted (p value < 0.0005 for both variables). **Conclusion:** MELD Cy being higher than MELD 3.0 has the potential to improve accessibility for liver transplantation in patients with complications of portal hypertension.

Total Population (N=96)	
Age in years	Mean 57.4 y/o (28-72) SD 10.58
Gender	Male – 47 (49%) Female – 49 (51%)
Race	Caucasian – 70 (73%) African American – 20 (21%) Hispanic – 5 (5%) Native American/Indian – 1 (1%) Asian – 0 (0%)
BMI	Mean 29.8 (+/- 6.77)
Etiology (Top 4)	MASH – 33 (34.4%) Alcohol – 26 (27.1%) Alcohol and Mash – 8 (8.3%) HCV – 4 (4.2%)
Transplant Eligibility	Yes – 54 No – 42
Presence of Ascites	Yes – 72 (75%) No – 24 (25%)
MELD Increase using Cystatin C	0 Points – 12 (12.5%) 1 to 3 Points – 40 (41.7%) 4 to 6 Points – 34 (35.4%) >6 Points – 10 (10.4%)

Lab Values			
	Creatinine	Cystatin C	P Value
Mean (mg/dL) Median (mg/dL)	1.06 mg/dL (+/- 0.67) 0.87 mg/dL	1.78 mg/dL (+/- 0.71) 1.605 mg/dL	
	w/ Creatinine	w/ Creatinine and Cystatin C	
Mean eGFR (ml/min/1.73m²) CKD-EPI	81.6 ml/min/1.73m² (+/- 27.64)	57.9 ml/min/1.73m² (+/- 22.28)	<0.0005
Median eGFR (ml/min/1.73m²)	91 ml/min/1.73m²	58 ml/min/1.73m²	
Mean MELD 3.0 Median MELD 3.0 Standard Deviation	18.8 (+/- 6.04) 18.5 SD 6.04	22.2 (+/- 6.82) 58 SD 6.82	0.0002

Patients WITH Ascites (n = 72)			
	Creatinine	Cystatin C	
Mean (mg/dL) Median (mg/dL)	1.11 mg/dL (0.55 – 6.14) 0.915 mg/dL	1.87 mg/dL (0.76 – 3.85) 1.71 mg/dL	
	Creatinine	Creatinine and Cystatin C	P Value
CKD-EPI Mean eGFR (ml/min/1.73m²)	78.8 ml/min/1.73m² (+/- 26.94)	53.99 ml/min/1.73m² (+/- 20.84)	
Median eGFR (ml/min/1.73m²)	88.5 ml/min/1.73m²	53 ml/min/1.73m²	<0.0005
Mean MELD 3.0 Median MELD 3.0	18.97 (+/- 5.40) 18	22.99 (+/- 5.92) 22	<0.0005

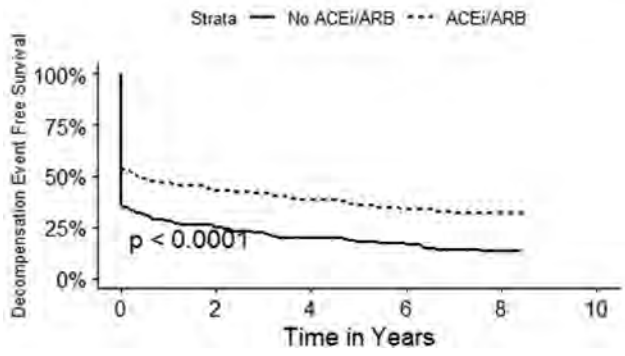
Disclosures: Jeff Angelo Taclob: Nothing to Disclose, Anjana Mary Jacob: Nothing to Disclose, Satheesh Nair: Nothing to Disclose

2464 | THE SAFETY OF ACEI/ARBS IN PATIENTS WITH CIRRHOSIS

Nirmal Desai[1] Christine Son[1] Vineela Appalaneni[1] Irena Helenowski[1] Jonah Rubin[1], [1]Loyola University Medical Center

Background: The AASLD recommends against using ACEi and ARBs in decompensated cirrhosis with ascites. Recently published data suggests that ACEi/ARB use is associated with a lower risk of liver related adverse events in patients with compensated cirrhosis. We aimed to conduct a retrospective cohort study to assess the benefit and harm associated with ACEi/ARB use in both compensated and decompensated cirrhosis. **Methods:** This was a single center retrospective cohort study of the effect of exposure to ACEi/ARB compared to a no exposure cohort. Primary outcomes include transplant free and overall survival. Secondary outcomes include rate of decompensation, renal function and hospitalizations. Demographic and clinical variables were 1:1 propensity score matched to account for confounding. Significant differences were assessed via Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. Kaplan-Meier estimates were used for survival rates. A multivariable Cox regression was performed for a composite outcome of overall survival (OS) and transplant free survival (TFS). **Results:** After propensity score matching, there were 300 patients each in the ACEi/ARB cohort and the control group. Patients in the study group had a significant increase in transplant free survival (p = .003) and fewer decompensation events (p < .001) with univariate analysis. Multivariable Cox regression demonstrated a significant improvement in OS/TFS in the ACEi/ARB group (HR 0.65; 95% CI, 0.49 – 0.87). Subset analysis of compensated cirrhosis patients demonstrated fewer decompensation events (p = .005) for the study group, but the Cox regression analysis showed no difference (HR 0.81; 95% CI, 0.46-1.41). In decompensated cirrhosis patients, there was a significant improvement in OS/TFS in the ACEi/ARB group (HR 0.61; 95% CI, 0.43 – 0.88). Additionally, in patients with ascites, there was no difference in OS/TFS (HR 0.72; 95% CI, 0.48-1.07) with ACEi/ARB exposure. **Conclusion:** ACEi/ARB use was associated with a significant increase in OS/TFS in all cirrhotic patients. In decompensated cirrhosis patients with ascites, ACEi/ARB exposure had no effect on adverse outcomes. Therefore, these medications appear to be safe to administer in all cirrhotic patients and offer a potential benefit.

Figure 1: Kaplan-Meier estimates for decompensation event-free survival rates for the propensity-matched cohort by ACEi/ARB use. The log-rank test indicates significantly lower decompensation event-free survival in the no ACEi/ARB group.



Disclosures: Nirmal Desai: Nothing to Disclose, Christine Son: Nothing to Disclose, Vineela Appalaneni: Nothing to Disclose, Irena Helenowski: Nothing to Disclose, Jonah Rubin: Nothing to Disclose

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2465 | IMPACT OF GUIDELINE-BASED ACUTE KIDNEY INJURY CARE PROCESSES ON OUTCOMES IN HOSPITALIZED PATIENTS WITH DECOMPENSATED CIRRHOSIS

Kavish Patidar[1] Yan Liu[2] George Cholankeril[2] Nagasri Shankar[2] Jennifer Kramer[2] Thomas Taylor[2] Kumar Jalal[2] Avegail Flores[2] Elsa Solà[3] Giuseppe Cullaro[4] Andrew Allegretti[5] Nikhilesh Mazumder[6] Fasiha Kanwal[7] Ruben Hernaez[2], [1]Baylor College of Medicine, Houston Methodist Hospital, [2]Baylor College of Medicine, [3]Standford University, [4]Columbia University, [5]Massachusetts General Hospital, [6]University of Michigan, [7]Michael E. DeBakey VA Medical Center

Background: Acute kidney injury (AKI) is a frequent and severe complication in cirrhosis, associated with high morbidity and mortality. While guidelines recommend specific process measures (PMs) for AKI care in cirrhosis, their impact on outcomes remains understudied. We investigated the association between adherence to PMs and clinical outcomes in hospitalized patients with decompensated cirrhosis and AKI. **Methods:** We conducted a retrospective cohort study of hospitalized adults with decompensated cirrhosis and ascites who developed AKI across 130 VA hospitals between 1/1/2018 and 12/31/2023. AKI was defined using 2015 ICA criteria (increase in serum creatinine (sCr) $\geq$0.3 mg/dl from baseline within 48hrs or $\geq$50% increase in sCr from baseline). PMs evaluated were avoidance of diuretic, non-selective beta blocker (NSBB) and other vasodilators use within 48hrs after AKI onset; volume expansion with albumin or crystalloids within 24hrs after AKI onset; infectious work-up within 48hrs of AKI onset, subspecialty consultation after AKI onset, and outpatient follow-up visit within 15-days of discharge. The primary outcome was in-hospital AKI resolution (return of sCr to within 0.3 mg/dL of baseline) and the secondary outcome was 90-day mortality from the time of discharge. Multivariable logistic and Cox regression analysis were performed to examine independent associations between PMs and outcomes. **Results:** Among 2,221 patients (median age 66yrs; 65% White; 46% alcohol-associated cirrhosis), NSBB, diuretics, and other vasodilators were avoided in 97%, 79%, and 80%, respectively; 21% and 29% received volume expansion with albumin and crystalloids, respectively; 47% had an infectious work-up and 29% had subspecialty consultation. Among patients who survived to hospital discharge (n = 1,811), 24%, 5%, and 1%, had outpatient post-discharge clinic visit with primary care (PC), gastroenterology/hepatology (GI/HEP), and nephrology, respectively. Overall, 53% achieved AKI resolution and 40% died within 90-days. After adjusting for confounders, avoidance of diuretics was associated with increased likelihood of AKI resolution (OR 1.30, 95%CI 1.04–1.64), while volume expansion with crystalloids was associated with lower likelihood (OR 0.81, 95%CI 0.66–0.99). Timely post-discharge outpatient clinic visit with PC (HR 0.53, 95%CI 0.28-0.69) or GI/HEP (HR 0.44, 95%CI 0.28-0.69) were independently associated with reduced 90-day mortality risk (Table). Notably, timely post-discharge clinic visits with all specialties demonstrated the greatest mortality reduction (HR 0.31, 95% CI 0.20-0.48). **Conclusion:** Our study reveals critical gaps in AKI management for hospitalized patients with cirrhosis, with suboptimal rates of albumin administration and timely post-discharge outpatient care. Diuretic avoidance and timely post-discharge outpatient care were associated with significantly improved outcomes. Implementing standardized protocols for medication management and post-discharge care coordination could substantially improve outcomes in this high-risk population.

Process Measures of AKI Care	AKI Resolution* OR (95% CI)	90-Day Mortality** HR (95% CI)
Avoidance of diuretics	1.39 (1.01-1.64)	0.94 (0.75-1.19)
Avoidance of NSBB use	0.97 (0.57-1.64)	1.08 (0.65-1.85)
Avoidance of other vasodilators	1.16 (0.92-1.45)	1.16 (0.91-1.49)
Volume expansion with albumin	0.86 (0.67-1.09)	1.29 (1.03-1.61)
Volume expansion with crystalloids	0.81 (0.66-0.99)	1.18 (0.96-1.44)
Infectious work up	0.89 (0.73-1.07)	1.04 (0.86-1.26)
Subspecialty consultation	1.13 (0.93-1.38)	1.07 (0.88-1.30)
Post-discharge clinic follow-up visit	N/A	
None		Reference
Primary Care		0.53 (0.42-0.67)
GI/HEP		0.44 (0.28-0.69)
Nephrology		0.29 (0.07-1.19)
Primary Care + GI/HEP + Nephrology		0.31 (0.20-0.48)

*adjusted for age, sex, race, etiology of cirrhosis, cirrhosis complications, MELD 3.0, and AKI stage at diagnosis

**adjusted for age, sex, race, etiology of cirrhosis, cirrhosis complications, MELD 3.0, AKI stage at diagnosis, and ICU admission.

Disclosures: Kavish Patidar: Madrigal Pharmaceuticals: Medical Advisory Board, Mallincrodt Pharmaceuticals: Consultant, Yan Liu: Nothing to Disclose, George Cholankeril: Nothing to Disclose, Nagasri Shankar: Nothing to Disclose, Jennifer Kramer: Nothing to Disclose, Thomas Taylor: Nothing to Disclose, Kumar Jalal: Mallinckrodt Pharmaceuticals: Advisor, Avegail Flores: Nothing to Disclose, Elsa Solà: Nothing to Disclose, Giuseppe Cullaro: Nothing to Disclose, Andrew Allegretti: Mallinckrodt: Consultant, Ocelot Bio: Consultant, Bioporto: Consultant, Sequana Medical: Consultant, Motric Bio: Consultant, Acta Pharmaceuticals: Consultant, Nikhilesh Mazumder: Nothing to Disclose, Fasiha Kanwal: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Ruben Hernaez: Nothing to Disclose

2466 | NON-INVASIVE DIAGNOSTIC MODEL FOR HIGH-RISK GASTROESOPHAGEAL VARICES IN CIRRHOTIC PATIENTS USING SPLEEN VOLUME, PLATELET COUNT, AND SERUM ALBUMIN

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Background: High-risk gastroesophageal varices (GEV) in cirrhotic patients pose a significant risk for life-threatening bleeding. While esophagogastroduodenoscopy (EGD) remains the gold standard for GEV

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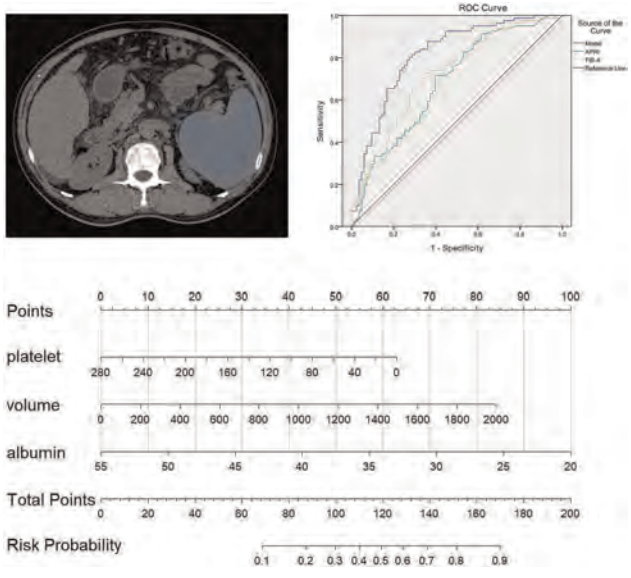
diagnosis, its invasive nature and patient discomfort limit its widespread use. This study aimed to develop a non-invasive model for high-risk GEV in cirrhotic patients. **Methods:** From October 2023 to January 2025, 164 patients with liver cirrhosis consecutively admitted to The Second Affiliated Hospital of Xi'an Jiaotong University were included. GEV was evaluated with EGD. Spleen volume was measured based on noncontrast-enhanced CT imaging. Multivariate logistic regression was performed to identify factors associated with high-risk GEV, and a diagnostic nomogram was constructed based on significant variables. The model's predictive performance was evaluated using the area under the receiver operating characteristic (ROC) curve, with internal validation conducted through 1000 bootstrap resampling iterations. **Results:** Three factors were significantly associated with high-risk GEV: spleen volume (OR = 1.002, 95% CI: 1.000–1.003, P = 0.010), platelet count (OR = 0.987, 95% CI: 0.975–0.998, P = 0.024), and serum albumin level (OR = 0.896, 95% CI: 0.826–0.973, P = 0.009). The diagnostic model incorporating these factors demonstrated excellent discriminative ability, with an area under the ROC curve of 0.814 (95% CI: 0.749–0.880). The model achieved a sensitivity of 81.5% (95% CI:71.0%-88.9%) and a specificity of 71.1% (95% CI:59.9%-80.3%) in identifying high-risk GEV. **Conclusion:** This study establishes a non-invasive model incorporating spleen volume, platelet count, and serum albumin to accurately identify high-risk GEV in patients with cirrhosis.



Disclosures: Wenjun Wang: Nothing to Disclose, Jiaqi Li: Nothing to Disclose, Boyu Chen: Nothing to Disclose, Zhuoran Wang: Nothing to Disclose

2467 | TRENDS IN MORTALITY DUE TO ESOPHAGEAL VARICES IN LIVER DISEASE PATIENTS AGED 65 AND OLDER IN THE UNITED STATES (1999-2024): DISPARITIES BY DEMOGRAPHICS, URBANIZATION, AND REGION

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Background: Esophageal varices represent a significant complication of liver disease with substantial mortality risk, particularly among older adults. This study examined temporal trends in mortality due to esophageal varices among liver disease patients aged 65 years and older, analyzing disparities across demographic groups, urbanization levels, and geographic regions. **Methods:** Using CDC WONDER data (1999-2024), we identified deaths attributed to esophageal varices (I85) in liver disease (K70-K76) in patients aged ≥65 years. Age-adjusted mortality rates (AAMR) were calculated per 100,000 person-years, standardized to the 2000 U.S. standard population. Joinpoint regression analysis was employed to determine trend segments, annual percent changes (APC), and average annual percent changes (AAPC) across demographic, urbanization, and regional strata. **Results:** Among 22,315 deaths recorded across 1.16 billion person-years, overall AAMR showed a U-shaped trend, declining from 2.33 (95% CI: 2.17-2.49) in 1999 to its lowest point around 2008, before increasing to 3.04 (95% CI: 2.90-3.19) by 2024 (AAPC: 1.05%; 95% CI: 0.78-1.35). Three distinct periods were identified: significant decline during 1999-2006 (APC: -8.43%), stabilization during 2006-2013 (APC: 1.53%), and substantial increase during 2013-2024 (APC: 7.26%). Males consistently experienced higher mortality rates than females (2024 AAMR: 4.02 vs. 2.20), though both groups followed similar temporal patterns. Among racial/ethnic groups, Hispanic populations showed the highest mortality rates throughout the study period, increasing from 4.82 to 5.17 (AAPC: 0.46%). White populations experienced the most pronounced relative increase (2.17 to 3.01; AAPC: 1.25%), while Black or African American populations showed a slight overall decline (1.93 to 1.42; AAPC: -0.50%). Regionally, the

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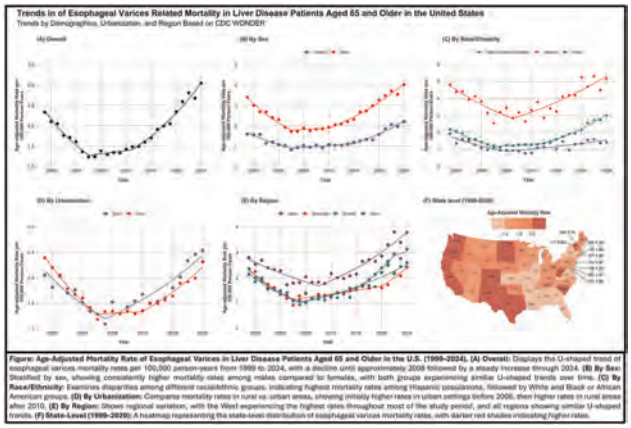
West maintained the highest mortality rates (2.78 to 3.77; AAPC: 1.33%), followed by the South, which demonstrated the steepest overall increase (2.13 to 3.12; AAPC: 1.36%). Rural areas exhibited a consistent increase after 2007 (APC: 5.67%), while urban areas showed a more complex pattern with an overall slight decline (AAPC: -0.41%). **Conclusion:** Mortality due to esophageal varices in older liver disease patients has demonstrated a concerning upward trajectory since 2013, with pronounced disparities across demographic groups and geographic regions. These findings highlight the need for targeted interventions to address rising mortality rates, particularly among Hispanic populations, in Western states, and in rural communities, where the burden is highest or increasing most rapidly.



Disclosures: MOHAMED A ELNAGGAR: Nothing to Disclose, Ibrahim Hassan: Nothing to Disclose, Ayah Obeid: Nothing to Disclose, Hatem Eltaly: Nothing to Disclose, Mohamed Abd El Aziz: Nothing to Disclose, Houman Rezaizadeh: AstraZeneca: Stock - publicly traded company, Bristol Meyers Squibb: Grant/Research Support, CellDex Therapeutics: Grant/Research Support, Celgene: Grant/Research Support, Cryoscope Medical: Grant/Research Support, Regeneron: Grant (PI), consulting, speakers bureau, advisory board, Sanofi: Grant (PI), consulting, speakers bureau, advisory board, Skope Inc: Consultant, patent license, and also hold non-public stocks

2468 | EXPERIENCE AND CONFIDENCE OF GASTROENTEROLOGY FACULTY AND FELLOWS IN PLACEMENT OF BALLOON TAMPONADE DEVICES IN ACUTE VARICEAL HEMORRHAGE

Jessica Vadaketh[1] Farees Saqlain[2] Sarjukumar Panchal[3] Jonathan Nahas[3] Oscar Mitchell[4], [1]Hospital of the University of Pennsylvania, [2]Hospital of the University of Pennsylvania, Department of Internal Medicine, [3]Hospital of the University of Pennsylvania, Division of Gastroenterology and Hepatology, [4]Hospital of the University of Pennsylvania, Department of Pulmonary, Allergy, and Critical Care

Background: Esophageal variceal hemorrhage (AVH) and subsequent hemorrhagic shock remain a substantial cause of morbidity and mortality in patients with decompensated cirrhosis. Current AASLD guidelines indicate that placement of an esophageal balloon tamponade device (BTD) is indicated in acute variceal hemorrhage when endoscopic interventions fail. BTDs are rarely placed, and when they are needed, they must be assembled rapidly, inserted correctly, and maintained appropriately. Due to the high risk/low volume nature of BTD placement, these situations are stressful and error-prone. **Methods:** We sought to describe previous training, current confidence levels, and future training preferences for placement of BTDs in management of AVH within the gastroenterology (GI) division at our large academic center. A survey was created in REDCap with 26 questions and sent to 86 attendings and fellows, including 16 transplant hepatologists within the GI division. The survey questions were built to assess previous experience with BTDs, perceived levels of comfort with placement, and preferences for future educational initiatives. **Results:** Eighty-six participants were sent the survey, and 40% responded (74% were attendings and 26% were fellows). Less than half of the participants (44%) had never placed a BTD as the primary proceduralist (28% of attendings). Almost all respondents (94%) agreed/strongly agreed that they felt confident in knowing when a BTD was indicated, however, only half agreed/strongly agreed that they felt confident in being able to independently place one (similar between attendings and fellows, Figure 1). 36% of participants reported that they had never received prior training on BTD placement (44% of attendings and 22% of fellows). Some participants (42%) were interested in receiving further training on BTDs, with the most widely preferred training modalities being videos and simulation sessions. Additionally, 74% of respondents felt a step-by-step-guide would be very useful for assembly of BTDs. **Conclusion:** Gastroenterology physicians at our large academic center had varying degrees of previous experience in BTD placement. While almost all respondents expressed confidence in knowing when to place a BTD, we observed low levels of confidence in the ability to independently place BTDs across all levels of training and experience. Survey respondents indicated a desire for additional training. Our findings broadly support the need for further educational and practical tools to support clinicians in placing BTDs in treatment of variceal

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bleeding. We have since created and started to use a step-by-step Ikea-like guide given to staff in our Medical Intensive Care Unit and Gastroenterology department and the preliminary feedback from our guide was that the instructions were clear and well developed and overall was well perceived, future directions include specific evaluation for this guide.

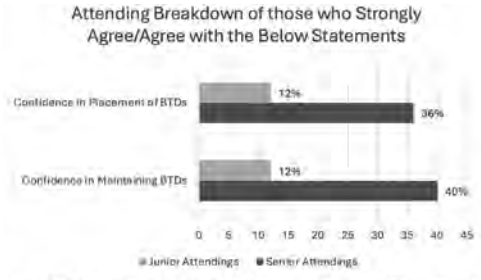

Figure 1: Attending Breakdown of those who Strongly Agree/Agree with the Below Statements. Senior attending is defined as 8 years or more as an attending.

Disclosures: Jessica Vadaketh: Nothing to Disclose, Farees Saqlain: Nothing to Disclose, Sarjukumar Panchal: Nothing to Disclose, Jonathan Nahas: Nothing to Disclose, Oscar Mitchell: Nothing to Disclose

2469 | COMPARATIVE RISKS OF RESPIRATORY SYNCYTIAL VIRUS, COVID-19 AND INFLUENZA A IN IN HOSPITALIZED PATIENTS WITH ADVANCED LIVER DISEASE

Adil Fazir[1] Katherine Cooper[2] Ami Patel[3] Deepika Devuni[2], [1]University of Massachusetts Chan Medical School, [2]University of Massachusetts, [3]Univeristy of Massachusetts

Background: Viral respiratory infections in patients with cirrhosis are associated with increased morbidity and mortality. While COVID and influenza have been well studied, respiratory and liver related outcomes data on respiratory syncytial virus infection (RSV) have been limited. We aimed to assess respiratory and liver-related outcomes in patients with RSV compared to COVID and Flu. **Methods:** This retrospective analysis of patients with cirrhosis hospitalized between 1/1/2022 and 1/1/2025 was completed using TriNetX. Those with a positive test for RSV, COVID, or Influenza A within 5 days of admission were included. Respiratory outcomes included acute hypoxic respiratory failure (AHRF), oxygen saturation $<85\%$ (Spo2 <85), and intubation. Liver outcomes included bilirubin levels $>$ 4mg/dl and hepatic decompensation, which was a composite outcome of ascites, encephalopathy (HE), and variceal bleeding (EVB). Outcomes were assessed at 30-days following hospital admission. Crude risks were reported for each infection (Table 1). For comparisons, propensity score matching (PSM) was used to balance cohorts for age, race, cirrhosis etiology, albumin, bilirubin, and chronic lung disease. Associations were reported as adjusted odds ratios with 95% confidence intervals. **Results:** A total of 6,161 hospitalized patients with cirrhosis who tested positive for RSV ($n=585$, mean age 63.9), COVID ($n=4,450$, mean age 67.1) and Influenza A ($n=1,126$, mean age 64.1) were included. Most participants were white (69-72%) and about one third had baseline lung disease. Compared to Flu-A ($n=542$), RSV ($n=542$) was associated with higher odds of ARHF (1.29, $p=0.04$), SpO2 $<85\%$ (1.80, $p<0.01$), intubation (1.41, $p=0.04$) and bilirubin $>$ 4mg/dl (1.54, $p=0.03$), but similar odds of hepatic decompensation (1.06, $p=0.67$). Compared to COVID ($N=554$), RSV ($N=554$) was associated with higher odds of AHRF (1.94, $p=<0.001$) and SpO2 $<$ 85% (1.65, $p=0.003$) and similar odds of hepatic decompensation (0.96, $p=0.77$). Mortality was 1.62-fold higher in RSV compared to FluA (1.62, $p=0.241$) but did not differ in RSV and COVID (1.04, $p=0.848$). **Conclusion:** In this large nationally representative sample, RSV infection in patients with cirrhosis was associated with increased respiratory related complications, but similar or lower risks of hepatic decompensation compared to COVID and Flu infection, and 1 in 10 patients died within 30 days of admission. Additional research is required to further understand the reasons for which RSV exerts greater respiratory effects and lower hepatic effects relative to COVID and Influenza A.

	RSV	Flu	COVID	RSV vs. Flu A		RSV vs. COVID	
Subject #	584	1,126	4,450	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Death	11.7	9.6	11.6	1.62, (1.08-2.44)	0.241	1.04, (0.71, 1.51)	0.85
Respiratory-related							
AHRF	44.6	40.6	27.5	1.29, (1.01, 1.64)	0.04	1.94, (1.51, 2.49)	<0.01
SpO2<85%	29.8	21.3	21.7	1.80, (1.35, 2.38)	<0.01	1.85, (1.26, 2.17)	<0.01
Intubated	18.2	15.1	12.4	1.41, (1.02, 1.95)	0.04	1.20, (0.88, 1.66)	0.25
Liver-related							
Bilirubin > 4 mg/dl	12.1	7.9	9.9	1.54, (1.03, 2.31)	0.03	1.02, (0.70, 1.47)	0.93
Decompensation	25.3	22.3	24.4	1.06, (0.80, 1.40)	0.67	0.96, (0.74, 1.26)	0.78
Ascites	22.7	17.9	20.3	1.24, (0.92, 1.67)	0.15	0.98, (0.72, 1.27)	0.77
HE	7.2	8.1	9.5	0.93, (0.59, 1.45)	0.73	0.74, (0.48, 1.11)	0.16
EVB	-	1.6	1.5	-	-	0.91, (0.38, 2.14)	0.83

Abbreviations: HRF = hypoxic respiratory failure; HE = hepatic encephalopathy, EVB = esophageal variceal bleeding, SpO2 = oxygen saturation.

Disclosures: Adil Fazir: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Ami Patel: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Avania Medical: Grant/Research Support, Intercept: Grant/Research Support

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2470 | PATIENTS WITH DECOMPENSATED CIRRHOSIS HAVE REDUCED FAT AND MUSCLE VOLUMES COMPARED TO COMPENSATED CIRRHOSIS: A WHOLE-BODY MRI STUDY

Maria Rydfjord[1] Mikael Forsgren[2] Danielle Kirkman[3] Amon Asgharpour[3] Vaishali Patel[3] Geneva Roache[3] Pontus Henriksson[4] Olof Dahlqvist Leinhard[2] Arun Sanyal[3] Mohammad Siddiqui[3], [1]Linköping University; AMRA Medical AB, [2]AMRA Medical AB; Linköping University, [3]Virginia Commonwealth University, [4]Linköping University

Background: Sarcopenia and myosteatosis are common in patients with liver cirrhosis and are associated with adverse outcomes. Magnetic resonance imaging (MRI) can be used to quantify both muscle quantity (volume) and quality (fat infiltration). The MRI-based thigh muscle volume z-score (MVZ), a sex and body size invariant measure of muscle volume, together with muscle fat infiltration (MFI), can be used to identify muscle composition (MC) phenotypes. The adverse MC phenotype (defined as low MVZ and high MFI) has previously been independently linked to all-cause mortality in liver disease and general population. The aim of this study was to compare body fat and muscle composition, and adverse MC prevalence between patients with compensated and decompensated cirrhosis as part of a rapid standardized whole-body MRI and reference-based muscle composition phenotyping. **Methods:** In a cross-sectional analysis of prospectively acquired data, patients with decompensated cirrhosis (n = 46) undergoing liver transplant evaluation and patients with compensated MASLD-related cirrhosis (n = 47) were compared. MRI-based body composition was quantified using AMRA® Researcher, assessing visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue (ASAT), anterior thigh fat-free muscle volume (FFMV), and MFI. MVZ, sex-adjusted MFI, and adverse MC was defined using literature values. Group differences were assessed using t-tests, Chi-square tests, and linear regression analyses adjusted for age, sex, and BMI. **Results:** Patients with decompensated cirrhosis were younger (55.5 ± 10.3 vs. 62.0 ± 9.3 years, p = 0.002) and had lower BMI (29.9 ± 7.1 vs. 33.7 ± 7.0 kg/m², p = 0.007), compared to patients with compensated cirrhosis. They also had lower VAT (4.0 ± 2.7 vs. 6.6 ± 2.9 L, p < 0.001), ASAT (9.5 ± 5.0 vs. 11.9 ± 5.1 L, p = 0.026), FFMV (8.8 ± 2.1 vs. 9.8 ± 2.4 L, p = 0.025), and MVZ (-0.83 ± 1.27 vs. -0.32 ± 1.12 SD, p = 0.045) (Fig). MFI did not differ significantly. After adjusting for age, sex, and BMI, only VAT and MVZ remained significant (p = 0.020 and p = 0.034, respectively). In patients with decompensated cirrhosis 20% presented with adverse MC compared to 15% of patients with compensated cirrhosis. This difference was not statistically significant. **Conclusion:** We found that patients with decompensated cirrhosis had reduced visceral fat and muscle volume compared to those with compensated cirrhosis. It is possible that the loss of visceral adiposity with progression to decompensation is another radiomics marker to predict future risk of hepatic decompensation. Moreover, MRI-based body composition profiling may improve prognostic evaluation and guide targeted interventions aimed at preserving muscle quality and function.

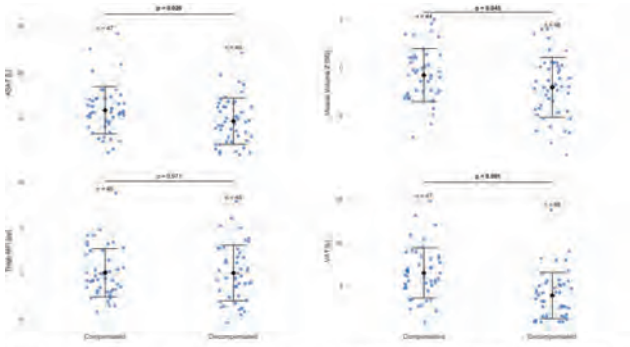

Figure. Group comparisons of adipose and muscle composition measures in patients with compensated and decompensated cirrhosis. Each panel shows individual participant data points (blue dots), group means (black diamonds), and error bars representing ± 1 standard deviation. Sample sizes per group are indicated above each category. P-values are derived from independent t-tests; significant results ($p < 0.05$) are shown in bold. MFI: anterior thigh muscle fat infiltration (sex-adjusted); MVZ: muscle volume z-score; ASAT: abdominal subcutaneous adipose tissue; VAT: visceral adipose tissue.

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★ 2471 | PREDICTORS OF IN-HOSPITAL MORTALITY IN PATIENTS WITH CIRRHOSIS: A MULTICENTER RETROSPECTIVE STUDY FROM ETHIOPIA

Tamrat Petros Elias[1] Abate Bane Shewaye[2] Henok Fisseha Chichaybelu[3] Abdulsemed Mohammed Nur[4], [1]University of Rwanda, [2]Addis Ababa University, Tikur Anbessa Specialized Hospital & Adera Medical Center, [3]St. Paul's Hospital Millennium Medical College, [4]Addis Ababa University, Tikur Anbessa Specialized Hospital

Background: Cirrhosis is a major global health problem and a leading cause of liver-related mortality. In Ethiopia, it ranks as the sixth leading cause of death and contributes significantly to hospitalization and mortality. However, predictors of in-hospital mortality among patients admitted with cirrhosis-related complications remain poorly understood. This study aimed to identify predictors of in-hospital mortality among patients with cirrhosis in Ethiopia. **Methods:** A retrospective cross-sectional study using electronic medical records of patients admitted with cirrhosis-related complications between January 1, 2023, and March 31, 2024, at Adera Medical Center, St. Paul's Hospital Millennium Medical College, and Tikur Anbessa Specialized Hospital. Descriptive statistics were presented using frequencies and cross-tabulations. Variables with a p-value <0.25 in bivariate analysis were included in multivariable logistic regression. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were calculated. A p-value <0.05 was considered statistically significant. **Results:** A total of 299 patients were included in the final analysis, of whom 79.6% were males. The median age of the study participants was 45 (IQR, 36-56) years. Hepatitis B virus (32.1%) was the most common etiology, followed by alcohol-associated liver disease (30.1%) and hepatitis C virus (13.4%). Ascites (69.2%), upper gastrointestinal bleeding (50.5%), and hepatic encephalopathy (44.8%) were the most common forms of presentation. More than half (52.9%) of the patients were in Child-Pugh class C, and 26.1% had other comorbidities. The in-hospital mortality rate was 25.4%. West Haven grade III or IV hepatic encephalopathy (AOR: 12.0; 95% CI 2.33-61.63; P < 0.01), hepatocellular carcinoma (AOR: 9.05; 95% CI 2.18-37.14; P: 0.01), history of previous admission within one year period (AOR: 6.80; 95% CI 2.18-21.18; P < 0.01), acute kidney injury (AOR: 6.47; 95% CI 1.77-23.64; P < 0.01), and model for end-stage liver disease - sodium score (AOR: 1.17; 95% CI 1.05-1.30; P: 0.02), were found to be predictors of in-hospital mortality. **Conclusion:** In-hospital mortality among patients with cirrhosis is high in Ethiopia. West Haven grade III or IV hepatic encephalopathy was the strongest predictor of mortality. Early recognition and treatment of hepatic encephalopathy and its precipitants are essential to improving outcomes.

Disclosures: Tamrat Petros Elias: Nothing to Disclose, Abate Bane Shewaye: Nothing to Disclose, Henok Fisseha Chichaybelu: Nothing to Disclose, Abdulsemed Mohammed Nur: Nothing to Disclose

2472 | THE ASSOCIATION OF LIVER FRAILTY INDEX AND CARDIAC DYSFUNCTION IN PATIENTS UNDERGOING TRANSPLANT EVALUATION

Hannah Laird[1] Jamey Cutts[2] Rebecca Turner[3] Curtis Argo[4], [1]University of Virginia Medical Center, [2]Division of Cardiovascular Medicine, University of Virginia Medical Center, Charlottesville, VA, [3]Division of Transplant Surgery, University of Virginia Medical Center, Charlottesville, VA, [4]University of Virginia

Background: Liver transplant candidates undergo cardiac evaluation with transthoracic echocardiogram (TTE) and assessment of frailty with the Liver Frailty Index (LFI). We aimed to evaluate the relationship between frailty and abnormal TTE findings to identify patients who may benefit from preoperative cardiac rehab. **Methods:** We conducted a retrospective chart review (January 2019-January 2025) of patients undergoing evaluation for liver transplant at a single academic medical center. Patients were included if they had documented LFI at initial evaluation and a comprehensive TTE performed at the transplant center within 6 months of initial LFI. The primary study aim was evaluation of the association of specific TTE parameters and frail status at the initial transplant evaluation visit. Univariate and multivariable statistical analysis were utilized. **Results:** 352 patients underwent TTE and LFI at initial transplant evaluation during the study period. On univariate analysis, female gender was significantly associated with frailty ($p=0.002$). Age ($p=0.02$), MELD ($p<0.0001$), body surface area ($p=0.04$), and tricuspid regurgitation maximum velocity (TR Vmax, $p=0.016$) were all significantly associated with frailty on univariate analysis but LV mass index, E/E', and LV diameter were not. Using multivariate logistic regression, TR Vmax did not remain

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significant, but left ventricular ejection fraction (LVEF; p = 0.031), a criterion for cirrhotic cardiomyopathy (CCM) was significantly associated with frail status by LFI: for every 5% decrease in LVEF, a patient was 8% more likely to be frail (see table). **Conclusion:** Our study showed that for every 5% decrease in a patient's LVEF, a liver transplant evaluation patient is 8% more likely to be frail. This supports that LVEF may be an important predictor of frailty and may be able to estimate the tempo at which a patient is becoming frail over serial TTE exams and at risk of developing CCM. The possibility that cardiac rehab may be a helpful intervention in those who are frail with decreased LVEF warrants further investigation.

Odds Ratios Of Frailty in Liver Transplant Eval Candidates			
Variable	Odds Ratio (OR)	Confidence Interval (CI)	P-value
Age	1.0	1.0-1.0	0.05
Gender	2.7	1.3-5.4	0.008
MELD	1.1	1.04-1.16	0.0004
Body Surface Area	1.4	0.4-5.6	0.61
Tricuspid Velocity	1.005	0.998-1.01	0.15
LVEF	0.92	0.85-0.99	0.031
C-statistic = 0.734			

Disclosures: Hannah Laird: Nothing to Disclose, Jamey Cutts: Nothing to Disclose, Rebecca Turner: Nothing to Disclose, Curtis Argo: Nothing to Disclose

2473 | NOMOGRAM OF CLINICAL PREDICTION MODEL FOR EVALUATING RISK OF PORTAL VEIN THROMBOSIS IN LIVER CIRRHOSIS BASED ON LASSO REGRESSION

Jinglan Jin[1] Zian Wang[1] Feng Jiang[2] Jintao Jiang[1] Yaya Li[1], [1]First Hospital of Jilin University, [2]Meihekou Central Hospital

Background: As one of the complications of liver cirrhosis, portal vein thrombosis (PVT) brings a significant clinical challenge in the treatment. To find the predictive clinical variables which can evaluate the probability of PVT in cirrhosis patients, a series of models were established and a nomogram was built for visualization. **Methods:** This study involved 263 liver cirrhosis patients admitted in First Hospital of Jilin University during July, 1, 2022 to June, 30, 2023. All patients were randomly separated into a training set (211 patients) and a validation set (52 patients) with a ratio of 4:1. Five different methods (Logistic regression, Ridge regression, Lasso regression, Decision tree and Randomforest) were utilized to build predictive models. **Results:** Among all patients, 65 of them had events of portal vein thrombosis within 12 months after their discharge. The C-index of five models in the training set was 0.776, 0.805, 0.783, 0.929 and 0.928, and got 0.816, 0.760, 0.839, 0.608 and 0.739 in the validation set, respectively. The variables selected by Lasso regression were weight, history of drinking, splenectomy, hemoglobin (HGB), platelet (PLT), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), albumin (ALB), fibrinogen (FBG) and portal vein width. History of drinking, ALP and GGT were excluded in the final nomogram for their prediction directions were obviously reverse to clinical experience. **Conclusion:** We finally screened out seven clinical variables predicting the probability of PVT in patients with liver cirrhosis, which can assist clinicians initially identify patients with high risk of thrombosis. Models built by Decision tree and Randomforest performed perfect in training set but performed moderately in validation set, which might be caused by model overfitting. These two machine-learning models also have potential for optimization, we look forward to new prediction models with more accuracy.

Figure.1 ROC Curve of Training Set

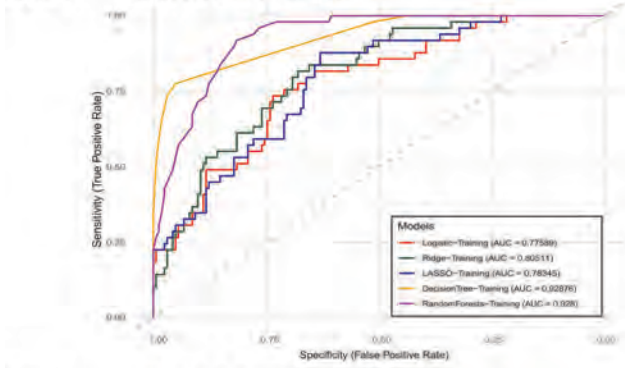


Figure.2 ROC Curve of Validation Set

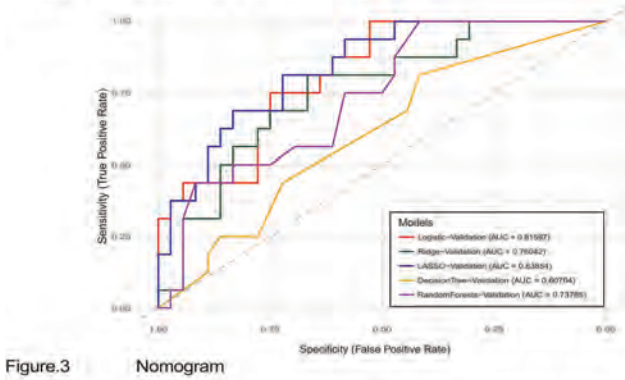
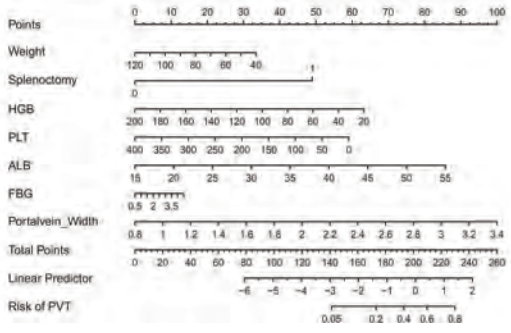


Figure.3 Nomogram



Disclosures: Jinglan Jin: Nothing to Disclose, Zian Wang: Nothing to Disclose, Feng Jiang: Nothing to Disclose, Jintao Jiang: Nothing to Disclose, Yaya Li: Nothing to Disclose

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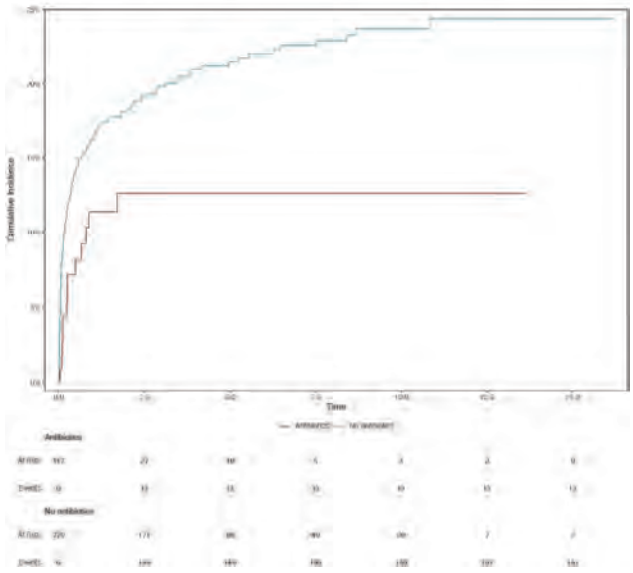
2474 | OUTCOMES ASSOCIATED WITH SECONDARY SPONTANEOUS BACTERIAL PERITONITIS (SBP) PROPHYLAXIS AFTER HOSPITAL DISCHARGE IN A NATION-WIDE SWEDISH COHORT

Max Schechter[1] Linnea Widman[2] Axel Wester[2] Ying Shang[2] Andrea Lindfors[2] Hannes Hagström[2],
[1]University of Pennsylvania, [2]Karolinska Institutet

Background: Secondary spontaneous bacterial peritonitis (SBP) prophylaxis reduces mortality amongst patients with a history of SBP. However, recent evidence suggests that SBP prophylaxis may lead to adverse outcomes such as antibiotic resistant infections. We evaluated proportions of secondary SBP prophylaxis and its impact on readmission with SBP, readmission with other infections, and mortality. **Methods:** We conducted a register-based cohort study identifying hospitalized patients in Sweden diagnosed with a first episode of SBP between 2006 and 2022 from the Swedish National Patient Register utilizing administrative coding. Secondary prophylaxis was defined as dispensing of at least 7 days of treatment with multiple refills within 7 days of discharge. The primary outcome was rates of rehospitalization with repeat SBP, and the secondary outcomes were rehospitalization with sepsis, *Clostridium difficile*, and mortality. Logistic regression was used to assess factors associated with receiving SBP prophylaxis and Cox regression was used to assess the association between secondary prophylaxis and subsequent rehospitalizations and mortality. **Results:** Of 896 patients that met study criteria, 117 (13%) dispensed secondary SBP prophylaxis within 7 days of discharge. There was no impact of year of diagnosis, cirrhosis etiology, or medical comorbidities on likelihood of receiving SBP prophylaxis. There was a trend towards higher SBP prophylaxis amongst patients discharged from a university hospital compared to community hospitals (53 of 117 patients (45%) vs. 287 of 779 patients (37%), p = 0.079). In a multivariable regression model, we found that receiving secondary SBP prophylaxis was associated with lower rates of readmission with SBP compared to patients that did not receive prophylaxis (aHR = 0.49, 95%CI = 0.28–0.87), with no significant increase in readmission with sepsis (aHR = 1.36, 95%CI = 0.28–6.67) or *Clostridium difficile* (aHR = 2.10, 95%CI = 0.71–6.30). No association with mortality was found (aHR = 0.96, 95%CI = 0.74–1.25). **Conclusion:** In this cohort, only 13% of patients hospitalized with a first episode of SBP dispensed secondary antibiotic prophylaxis within 7 days of discharge. These patients may experience lower rates of rehospitalization with SBP, however no effect on mortality was seen. Further investigation into the impact of secondary SBP prophylaxis will help clarify its role given emerging evidence into the potential harms of antibiotic prophylaxis.

Figure 1: Cumulative incidence of rehospitalization with SBP amongst patients that received antibiotic prophylaxis versus patients that do not receive antibiotic prophylaxis within seven days of discharge. X axis represents years after discharge.



Disclosures: Max Schechter: Nothing to Disclose, Linnea Widman: Nothing to Disclose, Axel Wester: Nothing to Disclose, Ying Shang: Nothing to Disclose, Andrea Lindfors: Gilead Sciences: The study was partly financed by Gilead Sciences, Hannes Hagström: Nothing to Disclose

2475 | DYNAMIC RISK MODELING OF HEPATOCELLULAR CARCINOMA FROM MARKOV CHAIN ANALYSIS WITH CURATIVE INTENT

Glenn Ho[1] Zhenning Yu[1] Nicole Shu Ying Tang[2] Anand Kulkarni[3] Ken Liu[4] Karn Wijarnpreecha[5] Beom Kim[6] Sung Won Lee[7] Mark Muthiah[8] Gang Chen[9] Takumi Kawaguchi[10] Hirokazu Takahashi[11] Daniel Huang[12],
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University Hospital, Saga, Japan, [12]National University Hospital, Singapore

Background: Despite advancements in detection and treatment of hepatocellular carcinoma (HCC), prognosis remains poor with a low five-year survival rate (20%). Traditional survival analyses like the Cox model are limited in capturing its dynamic progression across different clinical states. This study aims to address these limitations by employing a Cox semi-Markov model (CSMM) to better inform risk stratification and clinical management strategies for HCC by accounting for transitions between disease states. **Methods:** This cohort study included 934 adult patients with HCC who underwent curative treatment across eight tertiary centers in Australia, China, Japan, Singapore, South Korea, and the United States. The primary objective was to assess the risk of HCC recurrence following curative and to evaluate death rates before and after HCC recurrence using CSMM analysis. **Results:** The median age of the cohort was 65, with overall high male (75.0%) and cirrhosis (72.2%) prevalence. Etiologies included MASLD, HCV, HBV, and ALD. Using CSMM, distinct clinical trajectories were identified: recurrence, death without recurrence, and death after recurrence. Analyses revealed advancing age and HCV increased recurrence risk, while obesity and liver transplantation were protective. RFA and downstaging or neoadjuvant therapies were associated with higher risks of recurrence and post-recurrence death. AFP, tumor size, INR, bilirubin, and advanced BCLC stage were key predictors of poorer outcomes. **Conclusion:** This study highlights the distinct impacts of various predictors on recurrence and survival through a multi-state lens. Our findings emphasize the value of dynamic, state-based modeling in guiding personalized risk stratification and treatment planning for HCC.

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2476 | HERNIA INCARCERATION IS A COMMON COMPLICATION AFTER TIPS: AN ANALYSIS OF INCIDENCE AND ASSOCIATED RISK FACTORS

Anand Vissa[1] Aryana Far[1] Jennifer Lai[1] K. Pallav Kolli[1] Neil Mehta[1] Jin Ge[1], [1]University of California, San Francisco

Background: Transjugular Intrahepatic Portosystemic Shunt (TIPS) is commonly used to treat complications of portal hypertension. Hernia incarceration is a potential complication of TIPS that is poorly understood and not well documented. We examine this complication in a large single-center cohort of TIPS patients. **Methods:** We identified 259 adults who underwent TIPS at the University of California, San Francisco (UCSF) between 2015-2024. We extracted structured variables and unstructured documentation from the UCSF Clinical Data Warehouse. We used OpenAI's GPT-4o large language model (LLM) and manual chart review to identify post-TIPS hernia incarceration and clinical information from unstructured notes. We calculated time to events and used LASSO-Cox regression to identify risk factors associated with incarceration. **Results:** Of 259 patients, 12% (32) developed post-TIPS incarceration with a median time to event of 45.5 days (IQR 11.5-113). Compared to the non-incarcerated group, incarcerated patients were more likely to have existing umbilical hernias (87.5% vs. 29.5%, $p < 0.01$), higher serum creatinine (1.0 vs. 0.9, $p = 0.03$), and higher serum albumin (3.2 vs. 2.9, $p < 0.01$). Multivariate LASSO-Cox regression showed presence of an umbilical hernia pre-TIPS (HR3.08, 95% CI 1.78-5.33, $p < 0.01$), serum creatinine at TIPS (HR1.28, 95%CI 1.03-1.61, $p = 0.03$), serum albumin at TIPS (HR1.69, 95%CI 1.02-2.80, $p = 0.04$) were predictors of post-TIPS incarcerated hernia development. In the incarcerated group, 37.5% underwent hernia repair at a median 0.5 days [IQR 0.0–259.3], 18.8% received liver transplant at 55.5 days [IQR 6.3–152.8], and 25.0% died at 422 days [IQR 261.8–747.0] post-incarceration. In the non-incarcerated group, 6.2% underwent hernia repair, 22.9% received transplant, and 16.3% died post-TIPS. Kaplan-Meier analysis showed no significant difference in mortality between the incarceration and no-incarceration group (2-year probability of 13.8% vs 12.75%, log rank $p = 0.3$). **Conclusion:** Post-TIPS hernia incarceration is a common event with a rate of 12% in this single center cohort and a median event occurrence of 1.5 months post-TIPS. The presence of a known umbilical hernia prior to TIPS had the strongest association with this complication. Serum creatinine and albumin association also suggests ascites severity as a potential contributor. Identifying pre-TIPS risk

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factors could facilitate the development of targeted strategies to mitigate post-TIPS complications.

	Overall	No Post-TIP Hernia Incarceration	Post-TIPS Hernia Incarceration
n	259	227	32
Is Deceased, n (%)	45 (17.4)	37 (16.3)	8 (25.0)
Had Transplant, n (%)	64 (24.7)	58 (25.6)	6 (18.8)
Had Hernia Repair Surgery, n (%)	29 (11.2)	14 (6.2)	12 (37.5)
Gender=Female, n (%)	112 (43.2)	103 (45.4)	9 (28.1)
Age at TIPS, median [Q1,Q3]	58.0 [49.0,64.0]	57.0 [49.0,63.0]	59.5 [50.2,65.0]
Race/Ethnicity: Black/Asian/Pacific Islander/Other, n (%)	38 (14.7)	35 (15.4)	3 (9.4)
Race/Ethnicity: Hispanic, n (%)	92 (35.5)	79 (34.8)	13 (40.6)
Race/Ethnicity: Non-Hispanic White, n (%)	129 (49.8)	113 (49.8)	16 (50.0)
Liver Disease Etiology: Cholestatic/AIH/BCS/Other, n (%)	57 (22.0)	55 (24.2)	2 (6.2)
Liver Disease Etiology: EtOH, n (%)	100 (38.6)	83 (36.6)	17 (53.1)
Liver Disease Etiology: Viral Hepatitis, n (%)	49 (18.9)	43 (18.9)	6 (18.8)
Liver Disease Etiology: NASH/MASH, n (%)	53 (20.5)	46 (20.3)	7 (21.9)
Had Pre-TIPS Hernia, n (%)	148 (57.1)	117 (51.5)	31 (96.9)
Pre-TIPS Hernia Type: Umbilical, n (%)	95 (36.7)	67 (29.5)	28 (87.5)
Pre-TIPS Hernia Type: Ventral, n (%)	47 (18.1)	37 (16.3)	10 (31.2)
Pre-TIPS Hernia Type: Inguinal, n (%)	30 (11.6)	24 (10.6)	6 (18.8)
TIPS Indication: Ascites/HHT, n (%)	176 (68.0)	147 (64.8)	29 (90.6)
TIPS Indication: Variceal Bleeding, n (%)	70 (27.0)	65 (28.6)	5 (15.6)
TIPS Indication: Surgery, n (%)	6 (2.3)	4 (1.8)	2 (6.2)
TIPS Indication: PVT/BCS, n (%)	52 (20.1)	51 (22.5)	1 (3.1)
BMI, median [Q1,Q3]	25.9 [22.8,30.9]	25.9 [22.8,30.9]	26.3 [22.2,30.9]
MELD 3.0, median [Q1,Q3]	18.0 [14.0,21.5]	18.0 [14.0,21.5]	17.0 [14.0,21.2]
Serum Sodium, median [Q1,Q3]	136.0 [134.0,139.0]	136.0 [134.0,139.0]	136.5 [134.0,138.2]
Serum Creatinine, median [Q1,Q3]	0.9 [0.7,1.2]	0.9 [0.7,1.2]	1.0 [0.8,1.3]
Serum Albumin, median [Q1,Q3]	2.9 [2.5,3.2]	2.9 [2.5,3.2]	3.2 [2.7,3.6]
Total Bilirubin, median [Q1,Q3]	2.0 [1.3,3.3]	2.1 [1.3,3.3]	1.9 [1.2,3.0]
INR, median [Q1,Q3]	1.5 [1.4,1.8]	1.5 [1.4,1.8]	1.5 [1.4,1.7]

Disclosures: Anand Vissa: Nothing to Disclose, Aryana Far: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, K. Pallav Kolli: Nothing to Disclose, Neil Mehta: Merck: Consultant, FujiFilm WAKO: Consultant, Jin Ge: Merck and Co: Grant/Research Support, Iota Biosciences/ Astellas Pharmaceuticals: Consultant, Madrigal Pharamaceuticals: Consultant, Gilead Sciences: Advisor

2477 | INVOLVEMENT OF THE ADAMTS13/VON WILLEBRAND FACTOR AXIS IN ACUTE KIDNEY INJURY IN MICE WITH ADVANCED FIBROTIC LIVER

NORIHISA NISHIMURA[1] Kosuke Kaji[1] Shinya Sato[1] Tadashi Namisaki[1] Hitoshi Yoshiji[1], [1]Nara Medical University

Background: Hepatorenal syndrome-induced acute kidney injury (HRS-AKI) is defined by the simultaneous occurrence of acute kidney injury (AKI) and liver cirrhosis (LC), and is a major risk factor for adverse clinical outcomes in LC patients. Recent studies have revealed that the decreased activity of a disintegrin-like metalloproteinase with thrombospondin type 1 motif 13 (ADAMTS13) in tandem with elevated von Willebrand factor (vWF) antigen levels is closely linked to LC progression. We investigated the role of the ADAMTS13/vWF axis in AKI using a mouse model with advanced fibrotic liver. **Methods:** In the primary experimental setup, wild-type (WT) and ADAMTS13-deficient (Adamts13$^{-/-}$) 129^{+Ter}/Sv mice were assigned as controls and experimental groups, respectively. AKI was induced by intraperitoneal administration of carbon tetrachloride (CCl_4), employing a regimen that included a standard CCl_4 protocol, a subsequent single injection of a double CCl_4 dose, and a final challenge with lipopolysaccharide (LPS) to emulate systemic inflammation on a fibrotic background. In a complementary approach, a secondary model using WT and vWF-deficient (vWF$^{-/-}$) C57BL/6J mice was employed to specifically address the role of vWF. The effects of ADAMTS13/vWF alterations on liver and kidney injuries were evaluated, with additional emphasis on the specific role of vWF in the fibrotic mouse model. **Results:** Both WT and Adamts13$^{-/-}$ mice subjected to the AKI protocol showed significant elevations in serum AST, BUN, and creatinine levels; however, these biochemical derangements were markedly exacerbated in the Adamts13$^{-/-}$ group. Doppler flow measurements revealed a significant reduction in hepatic and renal microcirculatory blood flow in Adamts13-/- mice, which was paralleled by pronounced histological evidence of tissue injury including extensive inflammatory cell infiltration, increased F4/80-positive macrophage accumulation, and higher expression of renal injury markers. Oxidative stress, as indicated by elevated malondialdehyde levels and reduced superoxide dismutase activity, was also significantly enhanced in the absence of ADAMTS13. By contrast, vWF-/- mice demonstrated substantial protection from both liver and kidney injury, exhibiting lower levels of serum injury markers, preserved tissue perfusion, attenuated inflammatory responses, and reduced oxidative stress indices. **Conclusion:** An imbalanced ADAMTS13/vWF axis may play a critical role in AKI progression with LC. Reduced ADAMTS13 activity permits the accumulation of prothrombotic and proinflammatory ultra-large vWF multimers, thereby aggravating tissue ischemia, inflammation, and oxidative damage. Conversely, the absence of vWF confers marked tissue protection, highlighting a potential therapeutic target. These results suggest that the regulation of ADAMTS13/vWF axis may be a novel therapeutic option for the progression of AKI in patients with LC.

Disclosures: NORIHISA NISHIMURA: Nothing to Disclose, Kosuke Kaji: Nothing to Disclose, Shinya Sato: Nothing to Disclose, Tadashi Namisaki: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose

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2478 | CLINICAL OUTCOMES OF PATIENTS WITH CLINICALLY SIGNIFICANT PORTAL HYPERTENSION AWAITING ENDOSCOPIC VARICEAL SCREENING IN A METROPOLITAN AUSTRALIAN SETTING

Brandon-Joe Cilia[1] Nicholas Hannah[2] Neeraj Bhala[3] Ashok Raj[2], [1]University of Melbourne, [2]Royal Melbourne Hospital, [3]Royal Melbourne Hospital and Univeristy of Melbourne

Background: The Baveno VII guidelines recommend non-selective β-blockers (NSBBs) for those with chronic liver disease (CLD) and clinically significant portal hypertension (CSPH). Many centres still perform endoscopy in all patients with cirrhosis and little data exist on the potential negative impact of time on the waitlist. We investigated the clinical outcomes of patients with cirrhosis awaiting endoscopic variceal surveillance, between those with and without CSPH. **Methods:** Retrospective cohort study of patients with CLD awaiting endoscopic variceal screening at a large tertiary Australian centre, between July 2020 and March 2024. Primary outcomes were hepatic decompensation, hospitalisation, and liver-related mortality while on the endoscopy waitlist. CSPH was determined non-invasively by ultrasound or elastography prior to waitlisting. Kaplan-Meier curves were compared using the log-rank test with two-tailed P values < 0.05 considered significant. Hazard ratios (HR) with 95% confidence intervals (CI) were also reported using the Mantel-Haenszel method. **Results:** Two hundred and thirty-eight patients (170 (71.4%) with CSPH; 68 (28.6%) without CSPH) were included. Median wait time for endoscopy was 18 (IQR 7–44) weeks. On Kaplan-Meier curves, CSPH was associated with a higher rate of hepatic decompensation (42.4% versus 8.8%, $P < 0.001$), including: increased risk of ascites (HR 3.03, 95% CI 1.73–5.33, $P < 0.001$), hepatic encephalopathy (HR 2.55, 95% CI 1.13–5.76, $P = 0.025$), variceal bleeding (HR 3.21, 95% CI 1.01–10.21, $P = 0.048$), liver-related hospitalisation (HR 2.68, 95% CI 1.46–4.91, $P = 0.001$) and liver-related mortality (HR 3.23, 95% CI 1.12–9.31, $P = 0.03$). Of those with CSPH, 33.8% (23 patients) maintained NSBB use during follow-up, with a 63% reduction in liver-related admissions compared to 133 who did not receive NSBBs (HR 0.37, 95% CI 0.015–0.88, $P = 0.025$). The remaining 14 received NSBB for insufficient length of time. Overall, 167 (70.2%) underwent endoscopy and 46% had oesophageal varices. **Conclusion:** Patients with CLD and CSPH had worse liver-related outcomes while awaiting endoscopy compared to those without CSPH. These data support management guided by Baveno VII guidelines, rather than endoscopy for all, with scope for quality improvement projects to improve liver outcomes.

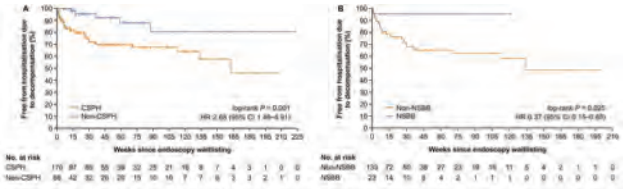

Figure 1: Kaplan-Meier estimates of survival free from hospitalisation for hepatic decompensation in (A) CSPH *versus* non-CSPH, and (B) non-NSBB *versus* NSBB.

Disclosures: Brandon-Joe Cilia: Nothing to Disclose, Nicholas Hannah: Eisai Co., Ltd: Grant/Research Support, Neeraj Bhala: Nothing to Disclose, Ashok Raj: Nothing to Disclose

2479 | RISK FACTORS AND PREDICTION MODEL FOR SARCOPENIA IN PATIENTS WITH CIRRHOSIS UNDERGOING TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

Shuyue Tuo[1] Jia Yuan[1] Ying Liu[1] Zhang Wen[1] Qiuju Ran[1] Yong Li[1] Chan Li[1] Quanxin Yang[1] Jinhai Wang[1] Lu Li[1] Shejiao Dai[1] Xinxing Tantai[1], [1]The Second Affiliated Hospital of Xi'an Jiaotong University

Background: Sarcopenia is highly prevalent and predicts poor outcomes in patients with cirrhosis undergoing transjugular intrahepatic portosystemic shunt (TIPS). However, the risk factors for the development of sarcopenia in this population remain unclear. In addition, validated predictive models based on easily accessible clinical variables have not been developed. This study aimed to address these issues in patients with cirrhosis undergoing TIPS. **Methods:** All patients with cirrhosis undergoing TIPS at the Second Affiliated Hospital of Xi'an Jiaotong University from January 2018 to March 2024 were screened. The risk factors for sarcopenia were identified using Least Absolute Shrinkage and Selection Operator regression and multivariate logistic regression. A new model and nomogram were developed based on the selected variables. The model was evaluated and compared using discrimination, calibration, and decision curve analysis. **Results:** A total of 202 patients with cirrhosis undergoing TIPS were included in the study. Six independent risk factors for sarcopenia were identified: Age (OR = 1.05; 95%CI: 1.01-1.10; p = 0.017); gender (female vs male: OR = 0.03; 95%CI: 0.01-0.11; p < 0.001); body mass index (BMI) (OR = 0.80; 95%CI: 0.70-0.91; p < 0.001); etiology (autoimmune vs viral: OR = 8.22; 95%CI:

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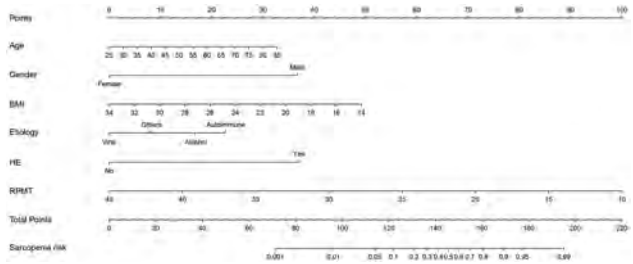
2.26-29.83; p = 0.001), hepatic encephalopathy (HE) (OR = 31.33; 95%CI: 1.98-494.51; p = 0.014); and right psoas muscle thickness (RPMT) (OR = 0.77; 95% CI: 0.69-0.85; p < 0.001). A new model and nomogram for predicting sarcopenia were developed based on these risk factors (Figure 1). The model exhibited good overall performance (Nagelkerke R^2 = 0.473; Brier score = 0.139), discrimination (The area under the receiver operating characteristic curve = 0.857; 95%CI: 0.803-0.910), calibration (Hosmer-Lemeshow p = 0.855), and clinical utility, offering advantages over existing non-dedicated sarcopenia models. Patients were stratified into high-risk and low-risk groups based on the optimal cutoff value of 0.385, with a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for distinguishing sarcopenia of 78.5%, 85.4%, 71.8%, 89.3%, and 83.2%, respectively. **Conclusion:** In patients with cirrhosis undergoing TIPS, age, male sex, BMI, etiology, HE, and RPMT were identified as independent risk factors for sarcopenia. Based on these risk factors, the newly developed sarcopenia model showed good predictive performance and holds potential as a practical screening tool in clinical settings.



Disclosures: Shuyue Tuo: Nothing to Disclose, Jia Yuan: Nothing to Disclose, Ying Liu: Nothing to Disclose, Zhang Wen: Nothing to Disclose, Qiuju Ran: Nothing to Disclose, Yong Li: Nothing to Disclose, Chan Li: Nothing to Disclose, Quanxin Yang: Nothing to Disclose, Jinhai Wang: Nothing to Disclose, Lu Li: Nothing to Disclose, Shejiao Dai: Nothing to Disclose, Xinxing Tantai: Nothing to Disclose

◆ 2480 | LEAN PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE HAVE HIGHER LIVER-RELATED EVENTS AND MORTALITY

Abdellatif Ismail[1] Mohammed Al-Aquily[2] Ahmad Abdulraheem[3] Hanna Blaney[4] Wing-Kin Syn[5],
[1]University of Maryland Medical Center, Midtown Campus, [2]Norwalk Hospital/ Yale university program, [3]MedStar Georgetown Washington Hospital Center, [4]Georgetown University, [5]Saint Louis University School of Medicine

Background: The American Association for The Study of Liver Disease (AASLD) introduced a new definition & diagnostic criteria for metabolic dysfunction associated steatotic liver disease (MASLD) focused on the presence of cardiometabolic risk factors (CMRFs) & hepatic steatosis. A growing body of evidence indicates that patients without obesity may have similar or even worse outcomes compared to those with obesity when diagnosed with MASLD. We aimed to compare liver related events (LRE) & mortality between these two groups. **Methods:** This is a retrospective study using the TriNetX US Collaborative Network. Adult patients with hepatic steatosis (ICD-10 code: K76.0) were included. To minimize confounders, we excluded patients with ICD-10 code for alcohol associated liver disease (K70). *Cohort 1* consisted of patients with hepatic steatosis, BMI ≤24.90 kg/m2 and one or more of the CMRFs per the MASLD criteria by AASLD, 2024. *Cohort 2* consisted of patients with hepatic steatosis, BMI ≥ 25 mg/m2 and one or more of the CMRFs. Propensity score matching (PSM) was performed to balance demographic data and comorbidities resulting in two balanced cohorts. Outcomes were assessed over a 10-year period and included new diagnoses of cirrhosis, endpoint of LRE combined (ascites, hepatic encephalopathy [HE], spontaneous bacterial peritonitis [SBP], esophageal varices [EV] and hepatorenal syndrome [HRS]), hepatocellular carcinoma (HCC), receiving liver transplant (LT), cardiovascular mortality and all-cause mortality. **Results:** Patients in *Cohort 1* (lean or non-obese) had a significantly higher risk of developing cirrhosis (4.4% vs. 3.6%; RR: 1.20; p < 0.001), endpoint of LRE (7.1% vs. 3.7%; RR: 1.92; p < 0.001), HCC (0.9% vs. 0.6%; RR: 1.50; p < 0.001), and undergoing LT (0.5% vs. 0.3%; RR: 1.56; p < 0.001) compared to patients in *Cohort 2* (obese). In addition, patients in *Cohort 1* were found to have higher cardiovascular (1.7% vs 1.0%, RR: 1.64, p < 0.001) and all-cause mortality (14.3% vs. 7.1%; RR: 2.00; p = < 0.001) compared to patients in *Cohort 2*. **Conclusion:** Our findings showed that lean (non-obese) patients with MASLD have worse liver-related events, cardiovascular mortality & all-cause mortality compared to obese patients with MASLD. This is consistent with the notion that lean individuals with MASLD may have more pronounced metabolic dysfunction leading to a higher risk of progression to advanced fibrosis, cirrhosis, and cardiovascular disease compared to their obese counterparts with similar degrees of steatosis. Furthermore, lean patients with MASLD often have a higher prevalence of genetic variants such as PNPLA3 and TM6SF2, which are linked to more severe hepatic injury and fibrosis progression, independent of traditional CMRFs or obesity. Our findings build on the evidence that supports the use of alternative anthropometric indices, such as waist circumference, to identify CMRF.

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Outcome	Hepatic steatosis and BMI ≤24.90	Hepatic steatosis and BMI ≥25	RR (95% CI)	p-value
Number	121,612	818,236	-	-
Cirrhosis, N (%)	4,973 (4.4%)	4,164 (3.6%)	1.20 (1.15, 1.25)	<0.001
LRE (ascites, HE, SBP, EV, HRS), N (%)	7,909 (7.1%)	4,263 (3.7%)	1.92 (1.85, 1.99)	<0.001
Hepatocellular carcinoma, N (%)	1,104 (0.9%)	739 (0.6%)	1.50 (1.37, 1.64)	<0.001
Liver transplant, N (%)	655 (0.5%)	421 (0.3%)	1.56 (1.38, 1.76)	<0.001
Cardiovascular mortality, N (%)	2,173 (1.7%)	1,324 (1.0)	1.46 (1.58-1.76)	<0.001
All-cause mortality, N (%)	12,248 (14.3%)	8,608 (7.1%)	2.00 (1.96, 2.05)	<0.001

Table 1: Comparison of different outcomes between Cohort 1: patients with hepatic steatosis & BMI ≤24.90 kg/m2 and Cohort 2: patients with hepatic steatosis and BMI ≥25 kg/m2.

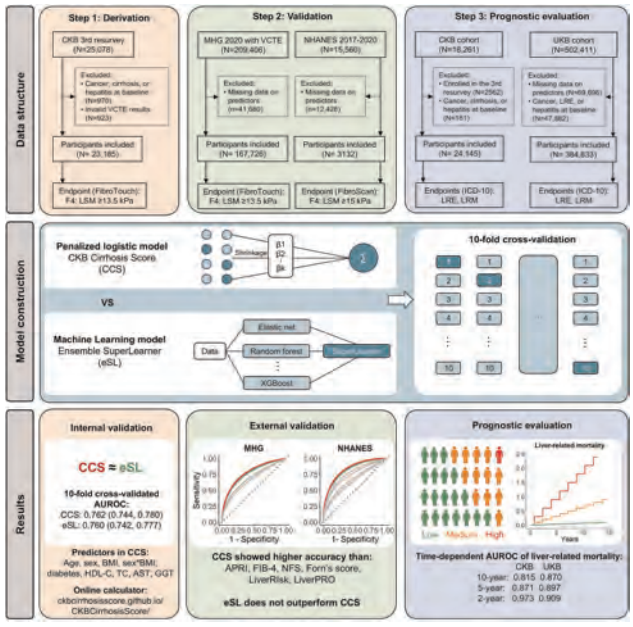
BMI: body mass index, RR: relative risk, CI: confidence interval, LRE: liver related events, HE: hepatic encephalopathy, SBP: spontaneous bacterial peritonitis, EV: esophageal varices, HRS: hepatorenal syndrome

Disclosures: Abdellatif Ismail: Nothing to Disclose, Mohammed Al-Aquily: Nothing to Disclose, Ahmad Abdulraheem: Nothing to Disclose, Hanna Blaney: Nothing to Disclose, Wing-Kin Syn: Zydus: to University, Merck: Consultant

◆ 2481 | PREDICTION AND PROGNOSTIC UTILITY OF A CIRRHOSIS RISK SCORE IN CHINESE ADULTS: DERIVATION AND VALIDATION COHORT STUDY

Xinyu Wang[1] Shuyao Song[2] Shanshan Wu[3] Dianjianyi Sun[2] Canqing Yu[2] Sailimai Man[2] Yining Zu[4] Xiaochen Yang[4] Menglu Liang[5] Zhengming Chen[6] Bo Wang[4] Jun Lv[2] Liming Li[2], [1]Harvard T.H. Chan School of Public Health, [2]School of Public Health, Peking University, [3]Beijing Friendship Hospital, Capital Medical University, [4]Meinian Institute of Health, [5]School of Public Health, University of Maryland, [6]Nuffield Department of Population Health, University of Oxford

Background: Identifying individuals at high risk for cirrhosis could enable timely interventions and reduce the disease burden, but no risk stratification tool has been designed for Chinese. We aimed to develop and validate a novel risk score to facilitate cirrhosis screening in Chinese adults. **Methods:** Based on the China Kadoorie Biobank (CKB), a population-based cohort across 10 regions in China, we developed the CKB Cirrhosis Score (CCS) using a penalized logistic regression. In parallel, an aggregate machine-learning algorithm, the ensemble SuperLearner (eSL), was developed to benchmark the performance of CCS. The scores were then externally validated in the Meinian Health Group (MHG), a nationwide study within China's largest health check-up chain, as well as the National Health and Nutrition Examination Survey (NHANES). The prognostic value of CCS for predicting liver-related events and mortality was assessed in two independent prospective cohorts within CKB and UK Biobank (UKB). **Results:** CCS consists of four clinical risk factors (age, sex, body mass index, and diabetes) and four readily available plasma biomarkers (total cholesterol, high-density lipoprotein cholesterol, aspartate transaminase, and γ-glutamyl transferase). In the CKB derivation cohort (N = 23,185), CCS showed good discrimination, with 10-fold cross-validated area under the receiver-operating characteristics curve (AUROC) of 0.762 (95% confidence interval: 0.744, 0.780). In external validation, the AUROC of CCS was 0.816 (0.799, 0.834) in MHG and 0.859 (0.788, 0.919) in NHANES, comparable to eSL (0.815 [0.796, 0.833] and 0.856 [0.806, 0.904]), and superior to other cirrhosis risk scores (Fibrosis-4 index: 0.684 [0.661, 0.708] and 0.695 [0.619, 0.764]). In prognostic evaluation, accounting for death without liver disease as a competing risk, CCS predicted liver-related mortality with a time-dependent AUROC at 10 years of 0.815 in CKB (N = 24,125) and 0.879 in UKB (N = 384,643). Compared to the low-risk group, the sub-distribution hazard ratios for liver-related mortality were 4.47 (3.83, 5.90) and 66.13 (50.11, 87.27) for the medium- and high-risk groups in UKB. **Conclusion:** CCS is the first cirrhosis risk score developed specifically for the general population of Chinese adults, with transportability to health check-up settings and Western populations. Based on eight easily accessible predictors, CCS could be used for identification of cirrhosis and risk stratification of liver-related mortality.



Disclosures: Xinyu Wang: Nothing to Disclose, Shuyao Song: Nothing to Disclose, Shanshan Wu: Nothing to Disclose, Dianjianyi Sun: Nothing to

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◆ 2482 | FAVORABLE TRENDS IN TRANSIENT ELASTOGRAPHY AND METABOLIC PARAMETERS IN CYSTIC FIBROSIS PATIENTS AFTER TWO YEARS OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR THERAPY

Souhir Hendis[1] Olivia Portolese[2] Marc Bilodeau[2] Helene Castel[2] Bernard WILLEMS[3] Genevieve Huard[4] Annick Lavoie[5] Catherine Vincent[2] Julian Hercun[6], [1]Université de Montréal, Centre hospitalier de l'Université de Montréal, [2]Université de Montréal, Centre hospitalier de l'Université de Montréal, Liver Unit, [3]University of Montreal, [4]Centre De Recherche Du Chum, [5]Université de Montréal, Centre hospitalier de l'Université de Montréal, Pulmonology Unit, [6]National Institutes of Health

Background: Cystic fibrosis (CF) is a genetic disease caused by CFTR mutations. While CFTR modulator therapy with Elexacaftor/tezacaftor/ivacaftor (ETI) improves pulmonary and nutritional outcomes, its long-term hepatic and metabolic effects remain undetermined. This study aims to assess changes in non-invasive tests of fibrosis and metabolic markers in adults with CF after two years of ETI therapy. **Methods:** We conducted a retrospective descriptive cohort study involving adults with CF treated with ETI for a minimum of two years followed at a CF referral center. Pre- and on-treatment serum-based non-invasive markers of fibrosis and transient elastography (TE) were assessed, as well as body mass index (BMI), HbA1c, lipid profile (triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL)), and liver fat content assessed by controlled attenuation parameter (CAP). Analysis was restricted to patients with longitudinal assessment through repeat TE measures. **Results:** A total of 154 patients were included (mean age 37; 64.5% male; 58.1% F508del homozygotes) with 31 having paired TE assessments. Alcohol use was reported in 39% and collected as a binary variable. BMI showed no significant change (median 23 [IQR 5.3] pre- and 23 [IQR 4.9] post-ETI; $p = 0.54$). HbA1c decreased from 6.0% [IQR 1.13] to 5.4% [IQR 1.2] ($p = 0.0084$). LDL was unchanged (1.48 [IQR 1.16] to 1.47 mmol/L [IQR 1.13]; $p = 0.78$). HDL increased from 1.06 [IQR 0.68] to 1.41 mmol/L [IQR 0.79] ($p = 0.002$), and triglycerides from 0.95 [IQR 0.80] to 1.07 mmol/L [IQR 1.0] ($p = 0.23$). CAP did not change significantly (202 to 223 dB/m; $p = 0.41$). Serum based non-invasive markers of fibrosis, FIB-4 (0.58 [IQR 0.36] to 0.81 [IQR 0.60]; $p = 0.30$) and Forns index (3.15 [IQR 2.56] to 3.17 [IQR 1.84]; $p = 0.62$) remained stable. While overall median TE remained stable over three yearly exams was 4.9, 4.9, and 4.6 kPa, paired analysis showed a significant improvement from pre-ETI to year two ($p = 0.02$), particularly in patients with baseline TE > 6.9 kPa, where 8/9 improved (median 9.2 [IQR 1.6] to 8.0 kPa [IQR 2.1]; $p = 0.023$). **Conclusion:** After two years of ETI, patients demonstrated improved glycemic control and HDL levels, with stable BMI, lipid profile, and no significant change in hepatic fat. Notably, liver stiffness decreased significantly, particularly in those with elevated baseline values suggestive of CF-related hepatic involvement, indicating a potential beneficial effect of ETI on liver health.

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◆ 2483 | TYPE 2 DIABETES IS ASSOCIATED WITH HIGHER RISK OF INCIDENT LIVER FIBROSIS AND LOWER LIKELIHOOD OF FIBROSIS REGRESSION IN THE GENERAL POPULATION: LONGITUDINAL RESULTS: FROM THE LIVERSCREEN CONSORTIUM

Jesse Pustjens[1] Katrine Bech[2] Guillem Pera[3] Laurens van Kleef[1] Helle Schnefeld[2] Robert de Knegt[1] Peter Andersen[2] Llorenç Caballeria[3] Carla Chacon[3] Pere Torán[3] Sarwa Darwish Murad[4] Harry Janssen[1] Anita Arslanow[5] Aleksander Krag[6] Isabel Graupera[5] Pere Ginés[5] Maja Thiele[7] Willem Pieter Brouwer[1], [1]Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Centre, Rotterdam, [2]Centre for Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospital, [3]Institut Universitari d'Investigació en Atenció Primària Jordi Gol, Mataró, Barcelona, Spain, [4]Erasmus University Medical Center, [5]Liver Unit, Hospital Clínic, University of Barcelona, Barcelona, Catalonia, Spain, [6]University of Southern Denmark, [7]Odense University Hospital

Background: Type 2 Diabetes Mellitus (T2DM) is associated with an increased prevalence of liver fibrosis. However, fibrosis dynamics and fibrosis

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incidence in the general population with T2DM is still unknown. **Methods:** In this prospective, multicenter cohort study from the European LiverScreen project, we analyzed longitudinal liver stiffness measurement (LSM) data from three population-based cohorts (Barcelona, Rotterdam and Odense). Participants underwent baseline and follow-up screening by vibration-controlled transient elastography (VCTE) with an approximate 4-year interval. T2DM was based on medical history, antidiabetic treatment, HbA1c $\geq$6.5%, or a fasting glucose $\geq$126mg/dL. Incident fibrosis was defined as an LSM increase of $\geq$30% and crossing the 8kPa threshold. Fibrosis regression was defined as a $\geq$30% reduction in LSM and a drop below 8kPa. Logistic regression models were used to assess the associations between T2DM and fibrosis dynamics and adjusted for follow-up duration, baseline LSM, cohort, waist circumference, alcohol consumption, and tobacco use. **Results:** Among 7,884 participants with reliable baseline VCTE, 4,536 had a reliable follow-up VCTE after a median of 4.3 years [IQR: 4.1–8.2]. The follow-up cohort had a median baseline age of 62 years [56–68], 52% were female, 11% had T2DM and 5.5% had prevalent fibrosis (baseline LSM $\geq$8 kPa). During follow-up, incident fibrosis occurred in 2.1% of participants without T2DM versus 5.3% of those with T2DM. Of those without T2DM, 51% achieved fibrosis regression, compared with 33% of those with baseline T2DM. In adjusted regression models, prevalent T2DM (aOR 1.82 95%CI 1.13–2.94) and incident T2DM (aOR 3.10 95% CI 1.74–5.54]) were significantly associated with incident fibrosis. Prevalent T2DM was inversely associated with fibrosis regression (aOR 0.40 95% CI 0.21–0.74). Among participants with both baseline T2DM and fibrosis, 45% (14/31) of those who achieved normal glucose regulation by follow-up experienced fibrosis regression, compared to 26% (17/65) of those who remained hyperglycemic (aOR 2.80, 95% CI: 0.87–9.01). **Conclusion:** Prevalent T2DM is associated with an increased risk of incident fibrosis, and a reduced likelihood of fibrosis regression. Incident T2DM increases risk of incident fibrosis more than three-fold, stressing the importance of fibrosis screening in this population, possibly with a shorter screening interval.In patients with T2DM, achieving normal glucose regulation may contribute to liver fibrosis regression.

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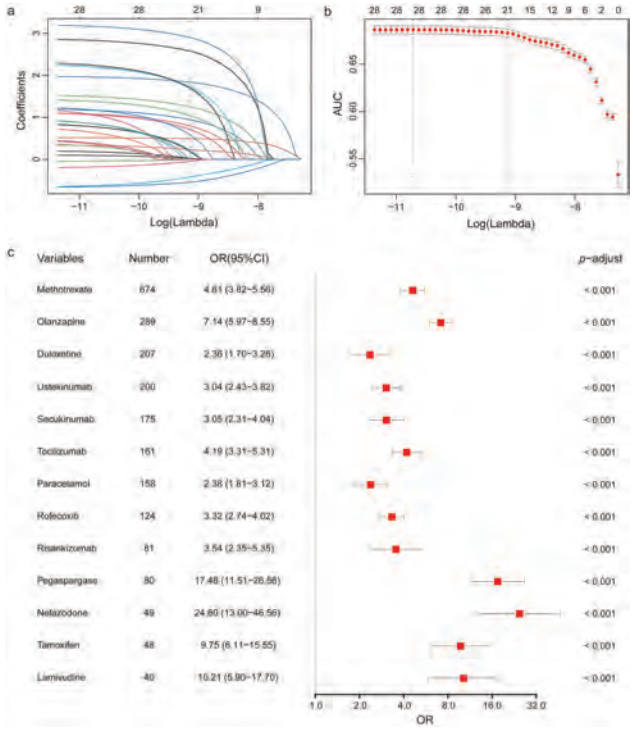
Evido: Co-founder, Willem Pieter Brouwer: Nothing to Disclose

◆ 2484 | RISK FACTORS FOR DRUG-RELATED HEPATIC STEATOSIS: A PHARMACOVIGILANCE STUDY FROM THE FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

Yanjie Lin[1] Chi Zhang[1] Guiqiang Wang[1] Hong Zhao[1], [1]Peking University First Hospital

Background: Drug-induced hepatic steatosis is rare, but it is closely related to the adjustment of the treatment of the underlying disease and the prevention of hepatic steatosis and its inflammation. This study investigates risk factors for drug-induced hepatic steatosis by analyzing a large dataset from the FDA's Adverse Event Reporting System (FAERS). **Methods:** The reporting odds ratio (ROR) and information component (IC) were used to assess the report of hepatic steatosis from Q1 2004 to Q3 2024. Univariate, LASSO, and multivariate regression analyses were used to explore risk factors. In addition, the timing of the onset of hepatic steatosis was assessed. **Results:** Overall, 16,767 cases associated with fatty liver were identified in FAERS. A total of 117 drugs were found to be associated with hepatic steatosis, with antineoplastic drugs (28/117), antiviral drugs (18/117), psychotropic drugs (17/117), and immunomodulatory drugs (12/117) being the most common. Age under 41 years, heavier body weight, and 13 different medications, including 3 antineoplastic agents of interest, namely methotrexate, permenburgase, and tamoxifen, are risk factors for hepatic steatosis. The median time to onset was 123.50 days, while the onset of permenburgase was faster, with a median time of only 19 days ($P < 0.001$). **Conclusion:** With the increasing number of drug types, it is necessary to focus on the treatment of hepatic steatosis and steatohepatitis caused by drugs, and adjust the treatment drugs in time to reduce the incidence of liver fibrosis and liver cirrhosis and prevent the interruption of treatment of the primary disease.



Disclosures: Yanjie Lin: Nothing to Disclose, Chi Zhang: Nothing to Disclose, Guiqiang Wang: Nothing to Disclose, Hong Zhao: Nothing to Disclose

◆ 2485 | OPTIMAL HEMOGLOBIN A_{1C} (HBA_{1C}) TARGET FOR PREVENTING LIVER-RELATED COMPLICATIONS IN INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS (T2DM) WITH AND WITHOUT CIRRHOSIS: A TERRITORY-WIDE RETROSPECTIVE COHORT STUDY FROM 2000 TO 2023 OF 1,130,282 INDIVIDUALS

Mary Yue Wang[1] Sherlot Juan Song[2] Nana Peng[2] Grace Lai-Hung Wong[2] Vincent Wai-Sun Wong[3] Terry Cheuk-Fung Yip[3], [1]The Chinese University of Hong Kong, [2]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, [3]Department of Medicine and Therapeutics, The Chinese University of Hong Kong

Background: Glycemic control in individuals with T2DM and cirrhosis is challenging due to restricted options of anti-diabetic agents and the risk of hypoglycemia. This study aims to determine and compare optimal target HbA_{1c} for preventing liver-related events in individuals with T2DM, with and without cirrhosis. **Methods:** This retrospective study included adult

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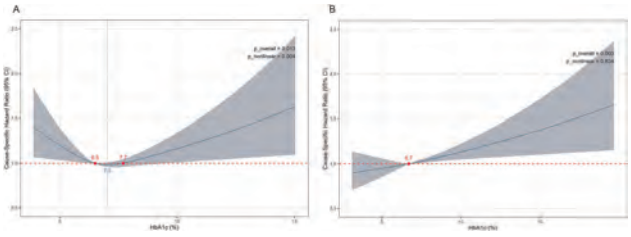
individuals with T2DM, with or without cirrhosis from 2000 to 2023 in Hong Kong after excluding individuals who had missing demographic data, human immunodeficiency virus infection, type 1 diabetes mellitus, and liver-related complications before T2DM diagnosis or within the first 2 years. The primary outcome was liver-related events including hepatic decompensation, hepatocellular carcinoma, liver transplantation, and liver-related death. Non-liver-related death was considered a competing event. Restricted cubic spline analysis was used to assess the nonlinear relationship between HbA_{1c} and liver-related events and to identify optimal HbA_{1c} levels associated with the lowest risk. **Results:** Of 1,130,282 individuals with T2DM, 42,622 (3.8%) had cirrhosis (mean age 70.9 years, 58.2% men). Over a mean follow-up of 9.7 years (IQR 4.9-13.1) in the non-cirrhotic group and 7.3 years (3.5-10.1) in the cirrhotic group, liver-related events developed in 4514 (0.6%) individuals without cirrhosis and 1588 (7.3%) individuals with cirrhosis. After adjustment for possible covariates, a non-linear relationship existed between HbA_{1c} level and risk of liver-related events in cirrhotic group (p for linearity = 0.01, p for cause-specific hazard ratio [CSHR] = 0.004). Individuals with HbA_{1c} between 6.5 and 7.7% had a lower risk of developing liver-related complications. In contrast, a linear relationship between HbA_{1c} level and risk of liver-related events was observed in individuals without cirrhosis (p for CSHR = 0.003), with an increased risk from 6.7% or above (Figure 1). **Conclusion:** A non-linear relationship between HbA_{1c} and the risk of liver-related complications is observed in cirrhotic group, while a linear association was found in those without cirrhosis. Compared to $<6.7\%$ in noncirrhotic group, a higher target HbA_{1c} $<7.7\%$ for cirrhotic group can reduce the risk of liver-related complications. Given the potential impact of extrahepatic complications and medication effects, caution is needed when HbA_{1c} level is excessively low in those with cirrhosis.



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◆ 2486 | HEPATOCELLULAR CARCINOMA RISK STRATIFICATION IN NON-CIRRHOTIC MASLD: A POPULATION-BASED PREDICTION MODEL VALIDATED ACROSS COHORTS

Mei-Hsuan Lee[1] Yi-Ting Chen[1] Loggang Zhao[2] Szu-Ching Yin[1] Xinyuan Zhang[3] Hye Won Lee[4] Xia-Rong Liu[1] Chia-Wei Huang[1] Xuehong Zhang[2] Chien-Jen Chen[5], [1]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, [2]Yale University, [3]Harvard University, [4]Yonsei University, [5]Academia Sinica, Taipei, Taiwan

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects approximately 30% of the global population and is associated with an increased risk of hepatocellular carcinoma (HCC). However, specific risk prediction models tailored to MASLD patients remain limited, hindering efforts to enhance awareness and guide targeted lifestyle modifications. **Methods:** We conducted a large-scale study using two MASLD cohorts: a training cohort of 66,577 individuals enrolled from a private health examination center (1997–2013) and an external validation cohort of 198,453 individuals from a government-led population-based screening program (2012–2013). Participants were followed through computerized data linkage until 2019 and 2021, respectively. The HCC prediction model was developed based on widely available clinical predictors and validated internally and externally. Model performance was assessed using areas under the receiver operating characteristic curves (AUROC) with 95% confidence intervals (CI), Brier scores, and calibration plots. Cumulative HCC risk was stratified by risk score categories and compared using log-rank tests. **Results:** In the training cohort, 44,606 participants (67%) were used for model derivation, and 21,971 (33%) for internal validation. Advanced age, elevated alanine aminotransferase, central obesity, diabetes, and high-density lipoprotein cholesterol were identified as significant predictors of HCC ($p < 0.05$) and incorporated into the risk model. Individual risk scores (range: 0–18) were calculated based on these predictors, demonstrating a direct association with predicted HCC risk. The AUROC for predicting HCC at 3, 5, and

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10 years in the internal validation cohort was 0.786 (95% CI: 0.653-0.918), 0.813 (95% CI: 0.712-0.913), and 0.824 (95% CI: 0.759-0.889), respectively. In the external validation cohort, the corresponding AUROC values were 0.785 (95% CI: 0.738-0.831), 0.805 (95% CI: 0.775-0.836), and 0.784 (95% CI: 0.765-0.804). Stratifying participants by risk scores revealed five distinct risk groups with significantly different cumulative HCC risks ($p < 0.01$). Notably, approximately 40% of HCC cases during follow-up were not preceded by a diagnosis of cirrhosis. The model demonstrated satisfactory predictive performance for non-cirrhotic HCC with AUROC of 0.777 (95% CI: 0.709-0.846), 0.784 (95% CI:0.733-0.836), and 0.766 (95% CI: 0.736-0.796) at 3, 5, and 10 years in the external validation cohort. **Conclusion:** The HCC risk in non-cirrhotic MASLD is low but not negligible. This validated model, integrating common clinical predictors, offers a scalable and practical tool for identifying high-risk groups, supporting targeted precision prevention strategies and public health initiatives.

Disclosures: Mei-Hsuan Lee: Nothing to Disclose, Yi-Ting Chen: Nothing to Disclose, Loggang Zhao: Nothing to Disclose, Szu-Ching Yin: Nothing to Disclose, Xinyuan Zhang: Nothing to Disclose, Hye Won Lee: Nothing to Disclose, Xia-Rong Liu: Nothing to Disclose, Chia-Wei Huang: Nothing to Disclose, Xuehong Zhang: Nothing to Disclose, Chien-Jen Chen: Nothing to Disclose

◆ 2487 | EFFECT OF HYPERTENSION ON LONG-TERM ADVERSE CLINICAL OUTCOMES AND LIVER FIBROSIS PROGRESSION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Ming-Hua Zheng[1] Qin-Fen Chen[1] Liyou Lian[1] Seung Up Kim[2] Terry Cheuk-Fung Yip[3] Salvatore Petta[4] Atsushi Nakajima[5] Emmanuel Tsochatzis[6] Junping Shi[7] Wah Kheong Chan[8] Jerome Boursier[9] Elisabetta Bugianesi[10] Yusuf Yilmaz[11] Hannes Hagström[12] Manuel Romero-Gómez[13] Khalid Alswat[14] Jose Luis Calleja[15] Hirokazu Takahashi[16] Victor de Lédinghen[17] . Shalimar[18] Laurent Castéra[19] Arun Sanyal[20] Boon Bee George Goh[21] Philip N Newsome[22] Jian-Gao Fan[23] Michelle Lai[24] Sandeep Aggarwal[18] Stergios Kechagias[25] Yoichi Hiasa[26] Bheesham Dayal[27] Zhongtao Zhang[28] Jacob George[29] Mohamed El-Kassas[30] Jinjun Chen[31] Hong You[32] Barham K. Abu Dayyeh[33] Huiping Sheng[34] Leon Adams[35] Jing Wang[36] Fangping He[37] Huiqing Liang[38] Yong-Feng Yang[39] Xiaoling Chi[40] Bihui Zhong[41] Yan Bi[42] Yuqiang Mi[43] Yongfen Zhu[44] Rixing Bai[32] Jing Zhang[32] Bingyuan Wang[45] Jinghai Song[46] Hong Deng[47] Qing Xie[48] Lang Bai[49] Yongning Xin[50] Wen Xie[32] Jie Li[42] Celine Fournier[17] Mirko Zoncapè[6] Tianyi Xia[51] Shenghong Ju[51] Chutian Wu[52] Hye Won Lee[2] Grace Lai-Hung Wong[3] Angelo Armandi[10] Ying Shang[12] Grazia Pennisi[4] Elba Llop[15] Masato Yoneda[5] Marc De Saint Loup[53] Clemence Canivet[53] Carmen Lara Romero[13] Rocio Gallego-Durán[13] Paloma Carrillo Fernández[13] Amon Asgharpour[54] Kevin Kim-Jun Teh[21] Sara Mahgoub[22] Mandy Chan[17] Huapeng LIN[55] Wen-Yue Liu[1] Sherlot Juan Song[3] Waleed Al Hamoudi[14] Hiroshi Isoda[56] Teruki Miyake[57] Sanjaya Satapathy[58] Mengyi Li[28] Keshni Sharma[59] Mohammed Emadeldeen[60] Ling Zhou[31] Xiaofei Tong[28] Fateh Bazerbachi[33] Xiaotang Fan[37] Huanming Xiao[61] Junzhao Ye[41] Liang Xu[43] Xiaolin Wang[48] Giovanni Targher[62] Christopher D. Byrne[63] Michael Shapiro[64] Frank Tacke[65] Vincent Wong[3] Ming-Hua Zheng[1], [1]The First Affiliated Hospital of Wenzhou Medical University, [2]Yonsei University College of Medicine, [3]The Chinese University of Hong Kong, [4]University of Palermo, [5]Yokohama City University Graduate School of Medicine, [6]Royal Free Hospital, [7]Hangzhou Normal University Affiliated Hospital, [8]University of Malaya, [9]Angers University, [10]University of Turin, [11]Recep Tayyip Erdoğan University, [12]Karolinska Institutet, [13]Virgen Del Rocío University Hospital, [14]King Saud University/KKUH, [15]Hospital Universitario Puerta de Hierro Majadahonda, [16]Saga University Hospital, [17]Echosens, [18]All India Institute of Medical Sciences, [19]Assistance Publique-Hôpitaux de Paris (AP-HP), [20]Virginia Commonwealth University, [21]Singapore General Hospital, [22]King's College London and King's College Hospital, [23]Shanghai Jiao Tong University, [24]Beth Israel Deaconess Medical Center, [25]University Hospital, [26]Ehime University, [27]Northwell Health, [28]Beijing Friendship Hospital, [29]The University of Sydney, [30]Helwan University, [31]Nanfang Hospital, [32]Capital Medical University, [33]University of Minnesota, [34]General Hospital of Ningxia Medical University, [35]University of Western Australia, [36]The Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University, [37]The First Affiliated Hospital of Xinjiang Medical University, [38]Xiamen Hospital of Traditional Chinese Medicine, [39]the Second Hospital of Nanjing, Affiliated to Nanjing University of Chinese Medicine, [40]The Second Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, [41]Sun Yat-sen University, [42]Drum Tower Hospital Affiliated to Nanjing University Medical School, [43]Tianjin

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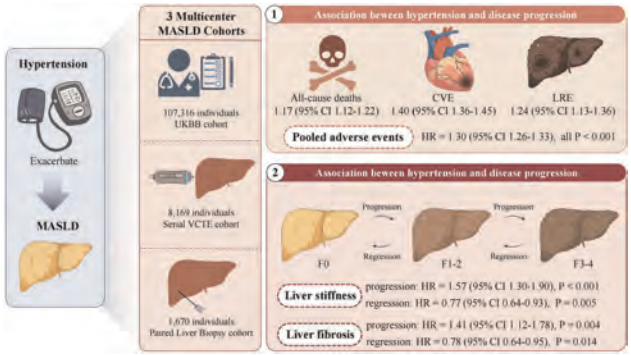
Medical University, [44]Zhejiang University, [45]The First Hospital of China Medical University, [46]Beijing Hospital, National Center of Gerontology, [47]The Third Affiliated Hospital of Sun Yat-Sen University, [48]Ruijin Hospital, [49]Sichuan University, [50]Qingdao University, [51]Southeast University, [52]Guangzhou Medical University, [53]Angers University Hospital, [54]Virginia Commonwealth University School of Medicine, [55]Shanghai Jiao Tong University School of Medicine, [56]Saga Medical School, [57]Ehime University Graduate School of Medicine, [58]North Shore University Hospital/ Northwell Health, [59]University of Sydney, [60]National Hepatology & Tropical Medicine Research Institute (NHTMRI), [61]Guangdong Provincial Hospital of Traditional Chinese Medicine, [62]University of Veron, [63]University Hospital Southampton, [64]Wake Forest University School of Medicine, [65]Charité - Universitätsmedizin Berlin

Background: Hypertension is common in metabolic dysfunction-associated steatotic liver disease (MASLD), but its specific effects on long-term clinical outcomes and disease progression remain unclear. This study examined the association of hypertension with the risk of adverse clinical outcomes and liver stiffness/fibrosis progression in subjects with MASLD. **Methods:** Three multicenter prospective cohorts were analyzed: the UKB cohort to assess the risk of adverse clinical outcomes, the Serial VCTE cohort to assess liver stiffness progression, and the Paired Liver Biopsy cohort to assess histologic liver fibrosis progression. Adverse clinical outcomes were defined as all-cause mortality, cardiovascular events, and/or liver-related events. For MASLD patients with baseline LSM <10 kPa, liver stiffness progression was defined as achieving an LSM ≥ 10 kPa at follow-up.For MASLD patients with baseline LSM ≥ 10 kPa, liver stiffness progression was defined as a $\geq 20\%$ increase in LSM, while regression was defined as LSM <10 kPa or a $\geq 20\%$ decrease at follow-up. Liver fibrosis progression, defined as at least a 1-stage increase in liver fibrosis on histology, while the secondary outcome was fibrosis regression, defined as at least a 1-stage fibrosis decrease. Cox regression and Kaplan-Meier analyses were used to assess the impact of baseline hypertension on the outcomes. **Results:** A total of 107,566 individuals from the UKB, 8,169 from the Serial VCTE cohort, and 1,670 from the Paired Liver Biopsy cohort were included in the final analysis. In the UKB, with a median follow-up of 15.0 years, 23,499 adverse events were documented, including 10,254 deaths, 17,274 major cardiovascular events, and 1,089 LREs. Hypertension was identified as a significant risk factor for long-term adverse outcomes (adjusted HR: 1.30, 95% CI 1.26–1.33, $P<0.001$). In the Serial VCTE cohort, hypertension was associated with an increased risk of liver stiffness progression (adjusted HR: 1.57, 95% CI 1.30–1.90, $P < 0.001$) and a reduced probability of regression (adjusted HR: 0.77, 95% CI 0.64–0.93, $P = 0.005$).In the Paired Liver Biopsy cohort, hypertension was linked to higher liver fibrosis progression (adjusted HR: 1.41, 95% CI 1.12–1.78, $P < 0.001$) and a reduced chance of regression (adjusted HR: 0.78, 95% CI 0.64–0.95, $P = 0.014$). **Conclusion:** Hypertension plays a critical role in MASLD, acting as a significant clinical risk factor for adverse outcomes and the progression of liver fibrosis. However, its impact is frequently underappreciated in clinical practice, with management efforts often focusing more on diabetes and obesity. This lack of recognition highlights the need to prioritize hypertension as a key risk factor in the progression of MASLD and its associated major clinical complications.



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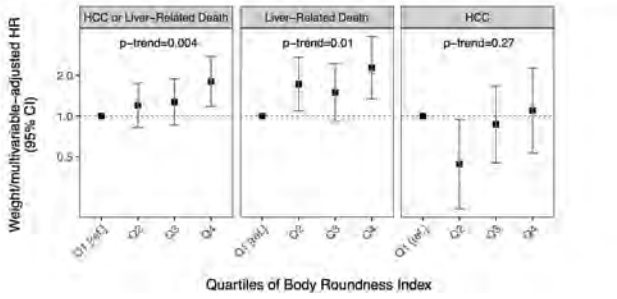
◆ 2488 | BODY ROUNDNESS INDEX AND RISK OF LIVER-RELATED MORTALITY AND HEPATOCELLULAR CARCINOMA

Daniel Sikavi[1] Hanseul Kim[1] Prooksa Ananchuensook[1] Jiaxian Shen[1] Etienne Nzabarushimana[1] Amrisha Bhosle[1] Longgang Zhao[2] Xuehong Zhang[2] Tracey Simon[1] Wenjie Ma[1] Andrew Chan[1] Long Nguyen[3], [1]Massachusetts General Hospital, [2]Yale University School of Nursing, [3]Harvard University Medical School

Background: The body roundness index (BRI) is a novel, easy-to-calculate anthropometric measure that estimates visceral and total body adiposity. BRI uses an elliptical model that combines waist circumference and height (compared to height/weight for body mass index [BMI]) and has been associated with higher risk of metabolic dysfunction-associated steatotic liver disease (MASLD), cardiometabolic disease, and all-cause mortality. However, its association with risk and complications of chronic liver disease, including hepatocellular carcinoma (HCC), remains unclear. **Methods:** We conducted a prospective cohort study among 30,336 men (Health Professionals Follow-up Study) and 46,300 women (Nurses' Health Study) from 1986-2018, free of advanced liver disease at baseline and followed with biennial questionnaires querying anthropometrics, lifestyle, medical history, and disease outcomes with $>90\%$ follow-up. Deaths were reported by next-of-kin, postal authorities, or National Death Index, and cause of death was identified by review of death certificates and medical records. HCC cases were identified by medical records review. BRI was cumulatively averaged over the study period to capture long-term exposures and classified into quartiles. Time-varying multivariable Cox proportional hazards models were used to estimate hazard ratios (HR) for liver-related death or incident HCC by BRI. **Results:** We identified 225 liver-related deaths and 92 cases of incident HCC over 2,140,289 person-years of follow-up. As expected, BRI and BMI were correlated at baseline (Spearman $\rho = 0.78$, $p < 0.001$). Compared to participants at the lowest quartile, the HR for liver-related mortality or HCC was 1.18 (95% CI: 0.81-1.71) for Q2, 1.21 (95% CI: 0.83-1.74) for Q3, and 1.68 (95% CI: 1.17-2.41) for Q4 (P-trend = 0.003, Fig. 1). In secondary analyses, we did not adjust for BMI given collinearity with BRI (each use height in its calculation), but HRs remained robust and only slightly attenuated after additionally adjusting for weight (Fig. 1), suggesting that BRI may be an independent risk factor for complications of liver disease, regardless of weight (and BMI by proxy). When evaluating outcomes independently, the association was strongest for liver-related death (P-trend = 0.01) **Conclusion:** In a large prospective cohort free of advanced liver disease at baseline, higher BRI was strongly associated with a greater risk of a composite outcome inclusive of liver-related death and/or HCC, largely driven by liver-related mortality. BRI, independently of weight, predicted adverse hepatic outcomes beyond traditional anthropometric measures and may serve as a complementary adjunct for predicting liver disease risk at the population level.

Outcome	Cases/ Person-Years	Age/Sex-Adjusted HR* (95% CI)	MV-Adjusted HR* (95% CI)	Weight/MV-Adjusted HR* (95% CI)
HCC or Liver-Related Death				
Quartiles of BRI				
Q1	51/582,982	1 [reference]	1 [reference]	1 [reference]
Q2	69/567,252	1.27 (0.88, 1.83)	1.18 (0.81, 1.71)	1.20 (0.82, 1.76)
Q3	80/540,920	1.46 (1.02, 2.05)	1.21 (0.83, 1.74)	1.27 (0.85, 1.88)
Q4	116/449,134	2.53 (1.80, 3.55)	1.68 (1.17, 2.41)	1.81 (1.18, 2.77)
P-trend		<0.001	0.003	0.004
Liver-Related Death				
Quartiles of BRI				
Q1	31/582,994	1 [reference]	1 [reference]	1 [reference]
Q2	58/567,257	1.76 (1.14, 2.77)	1.64 (1.05, 2.56)	1.72 (1.09, 2.72)
Q3	54/540,930	1.66 (1.06, 2.60)	1.36 (0.86, 2.15)	1.49 (0.91, 2.45)
Q4	82/449,151	3.01 (1.97, 4.61)	2.07 (1.32, 3.25)	2.28 (1.34, 3.87)
P-trend		<0.001	0.005	0.01
HCC				
Quartiles of BRI				
Q1	20/582,982	1 [reference]	1 [reference]	1 [reference]
Q2	11/567,252	0.50 (0.24, 1.05)	0.46 (0.22, 0.98)	0.44 (0.21, 0.94)
Q3	26/540,920	1.12 (0.62, 2.04)	0.93 (0.50, 1.71)	0.87 (0.45, 1.68)
Q4	35/449,134	1.82 (1.03, 3.20)	1.12 (0.60, 2.06)	1.10 (0.53, 2.27)
P-trend		0.001	0.21	0.27

* All models were stratified by age, cycle year, and sex. Multivariable-adjusted models were additionally adjusted by physical activity (categories), Alternate Healthy Eating Index 2010 score (quartiles), alcohol consumption (categories), smoking (categories), race (white/non-white), regular aspirin use (yes/no), presence of viral hepatitis (yes/no), diabetes (yes/no), and hyperlipidemia (yes/no). Weight/multivariable-adjusted models were further adjusted by weight in quartiles.



Disclosures: Daniel Sikavi: Nothing to Disclose, Hanseul Kim: Nothing to Disclose, Prooksa Ananchuensook: Nothing to Disclose, Jiaxian Shen: Nothing to Disclose, Etienne Nzabarushimana: Nothing to Disclose, Amrisha Bhosle: Nothing to Disclose, Longgang Zhao: Nothing to Disclose, Xuehong Zhang: Nothing to Disclose, Tracey Simon: Nothing to Disclose, Wenjie Ma: Nothing to Disclose, Andrew Chan: Nothing to Disclose, Long Nguyen: Nothing to Disclose

◆ 2489 | EVALUATING THE ASSOCIATION OF PATIENT CHARACTERISTICS ON HOSPITALIZATIONS AMONG A COHORT OF CANADIAN MASLD PATIENTS IN PRIMARY CARE

Elizabeth Baguley[1] Juan Abraldes[2] Seungwon Lee[1] Abdel-Aziz Shaheen[1], [1]University of Calgary, [2]University of Alberta

Background: The impact of implementing a Canadian primary care pathway to risk-stratify patients with metabolic-associated steatotic liver disease (MASLD) on

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hospitalizations is unknown. We evaluated patient characteristics associated with hospitalizations post-pathway enrollment. **Methods:** Adult patients enrolled in the Calgary MASLD risk-stratification pathway from March 2017-June 2022 were included (n = 12,070). The Discharge Abstract Database was linked to the Calgary MASLD pathway database to capture hospitalizations from pathway entry to March 31st, 2023. Primary cause for hospitalization was defined by the first diagnostic code. Multivariable negative binomial models were used to calculate the estimated adjusted incidence rate ratio (aIRR) of overall, liver- and cardiovascular-related hospitalizations, with a time offset function. Model covariates included age (> = 54 vs. < 54 years), sex (male vs. female), diabetes status (yes vs. no), rural status (rural vs. urban), body mass index (BMI) (> = 30 vs. < 30 kg/m^2), Charlson Comorbidity Index (CCI) (> = 3 vs. < 3), and liver stiffness measurements (LSM) by shear wave elastography (> = 8 vs. < 8 kPa). **Results:** Cohort mean age was 53.1 ± 13.3 years, and 51.9% were female. After adjusting for relevant covariates, several factors were significantly associated with overall hospitalizations including age > = 54 (aIRR: 1.36 [95% CI: 1.21-1.53], p < 0.001), male sex (0.82 [0.74-0.92], p = 0.001), diabetes (1.32 [1.17-1.48], p < 0.001), rural residence (1.32 [1.08-1.61], p = 0.006), BMI > = 30 kg/m^2 (1.24 [1.10-1.39], p < 0.001), CCI > = 3 (1.24 [1.20-1.27], p < 0.001), and LSM > = 8kPa (1.55 [1.32-1.82], p < 0.001), Figure 1. For liver-related hospitalizations, age > = 54 (aIRR: 6.93 [95% CI: 1.47-32.66], p = 0.014) and LSM > = 8kPa (7.45 [2.62-21.16, p < 0.001) were independently associated with use. Cardiovascular-related hospitalizations were significantly associated with age > = 54 (aIRR: 2.75, 95% CI: 1.97-3.84, p < 0.001), male sex (1.70 [1.29-2.25], p < 0.001), diabetes (2.14 [1.61-2.84], p < 0.001), CCI > = 3 (1.27 [1.20-1.34], p < 0.001), and LSM > = 8kPa (2.19 [1.58-3.05], p < 0.001). **Conclusion:** Among MASLD patients in primary care, patient age and LSM were associated with all types of hospital admissions. Patient sex, diabetes status, and CCI were associated with both overall and cardiovascular-related hospitalizations, while rural status and BMI were associated only with overall hospitalizations.

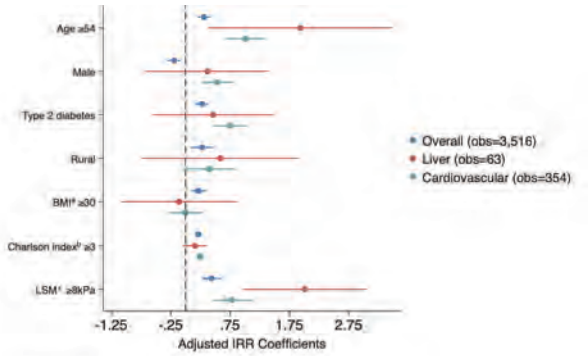

Figure 1. Adjusted Incidence Rate Ratio (aIRR) Coefficients for Hospitalization Admission Type

a. Body mass index
b. Charlson index excluded liver-related points (mild liver disease [+1], moderate to severe liver disease [+3]) and diabetes-related points (diabetes without complications [+1], diabetes with end organ damage [+2])
c. Liver stiffness measurement

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◆ 2490 | ELEVATED RISK OF GASTROINTESTINAL CANCERS IN LEAN MASLD: A PROPENSITY-MATCHED COHORT STUDY

Omar Al Ta'ani[1] Yahya Alhalalmeh[2] Marissa Gorvet[1] Pojsakorn Danpanichkul[3] Nabeeha Mohy-ud-din[1], [1]Allegheny Health Network, [2]New York Medical College-Saint Michael's Medical Center, [3]Texas Tech University Health Sciences Center

Background: Metabolic dysfunction associated steatotic liver disease (MASLD) is increasingly recognized as a risk factor for gastrointestinal cancers. However, cancer risk among individuals with lean MASLD remains poorly defined. Because these patients often lack traditional metabolic risk factors, clarifying their cancer risk is critical for improving risk stratification, guiding surveillance, and informing clinical care. **Methods:** We conducted a retrospective cohort study using the TriNetX research network, which aggregates electronic health records from multiple healthcare organizations. Adults with MASLD (ICD codes K76.0 or K75.81) were identified between January 1, 2005, and December 31, 2015. Lean MASLD was defined as body mass index (BMI) < 25 kg/m². Patients were grouped by BMI category and matched 1:1 using propensity scores to balance demographics, comorbidities, laboratory values, and medication use. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident gastrointestinal cancers with lifelong follow up. **Results:** Among 242,835 MASLD patients identified, 47,317 were lean and 195,518 were non-lean. After 1:1 matching, the final cohort included 47,317 individuals in each group with well-balanced baseline characteristics. Lean MASLD was associated with significantly elevated risks of both intestinal and extraintestinal gastrointestinal cancers compared to non-lean MASLD (Figure 1). For intestinal cancers, patients with lean MASLD had a higher risk for colorectal cancer (HR 1.47, 95% CI 1.35–1.61, p < 0.001) and small bowel cancer (HR 1.66, 95% CI 1.28–2.16, p < 0.001). For extraintestinal cancers, lean MASLD patients had increased risk of liver cancer (HR 1.82, 95% CI 1.54–2.14, p < 0.0001), pancreatic cancer (HR 1.96, 95% CI 1.76–2.19, p < 0.001), esophageal cancer (HR 1.76, 95% CI 1.40–2.21, p < 0.001), gastric

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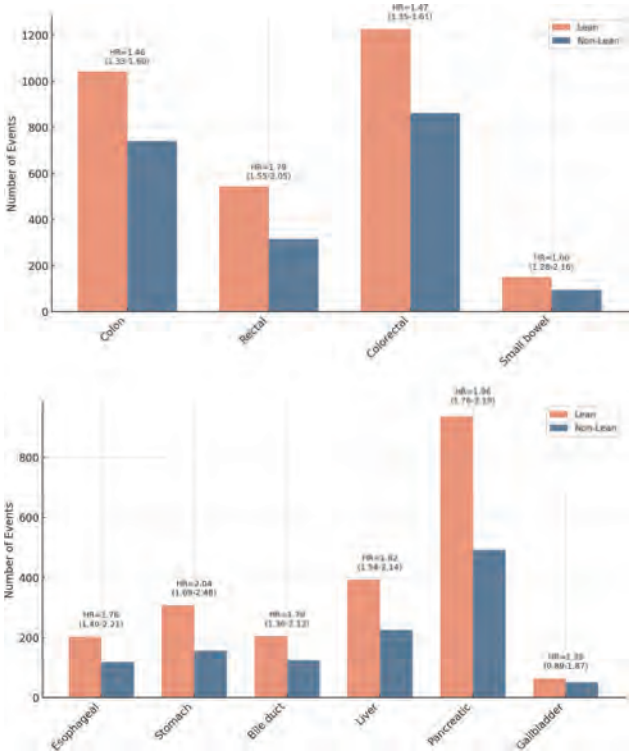
cancer (HR 2.04, 95% CI 1.69–2.48, p < 0.001), and biliary cancer (HR 1.70, 95% CI 1.36–2.12, p < 0.001). **Conclusion:** Lean individuals with MASLD face significantly elevated risks of gastrointestinal cancers compared to their non-lean counterparts. These findings suggest that mechanisms beyond traditional metabolic dysfunction, such as visceral adiposity not captured by BMI, immune dysregulation, gut-liver axis alterations, and possible genetic susceptibility, may contribute to cancer development in this population. Our results underscore the importance of tailored surveillance strategies and highlight the need for further prospective and mechanistic research to better characterize cancer risk in lean MASLD.



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◆ 2491 | RISK FACTORS AND DEFINITION OF EARLY ONSET METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) CIRRHOSIS

Veeral Ajmera[1] Tae-Hwi Schwantes-An[2] Luis Díaz[1] Callie Zaborenko[2] Egbert Madamba[1] Katherine Yates[3] Naga Chalasani[4] Rohit Loomba[1], [1]University of California, San Diego, [2]Indiana University, [3]Johns Hopkins University, [4]Indiana University Medical Center

Background: Older age is associated with an increased risk for cirrhosis; however, a subset of patients presents with cirrhosis at an earlier age. We examined the association between genetic and modifiable factors with early-onset cirrhosis due to metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** This prospective study included adults with biopsy proven MASLD enrolled in the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN). DNA was genotyped in duplicate for risk alleles in PNPLA3, TM6SF2, and the protective variant in HSD17B13. A genetic risk score (GRS) was estimated as the sum of risk alleles in PNPLA3, TM6SF2 plus the wild-type allele in HSD17B13 and dichotomized at the median to low and high-risk groups. The primary analyses evaluated factors associated with early-onset cirrhosis defined as the lowest quartile of age among participants with cirrhosis in the NASH CRN. **Results:** Of 234 included patients with cirrhosis, the mean (SD) age and BMI were 56.9 (9.7) years and 35.6 (± 6.8) kg/m^2, respectively and 66% had type 2 diabetes (T2DM). Early-onset cirrhosis was defined as the lowest quartile, which was age < 50 years old. Participants with early-onset cirrhosis were more likely to be male and less likely to have hypertension or hyperlipidemia than those with non-early cirrhosis (P < 0.05). Early-onset cirrhosis vs non-early onset cirrhosis was not associated with significant differences in ALT, AST or platelet count, however it was associated with higher mean (SD) steatosis grade on liver histology, 1.5 (0.9) vs 1.2 (0.8) P = 0.009. Early-onset cirrhosis vs non-early onset cirrhosis was associated with a lower prevalence of the protective variant in HSD17B13 (T/TA or TA/TA) (24% vs 34%, P = 0.004) but no significant difference in PNPLA3 or TM6SF2 risk variants. When comparing characteristics of participants under age 50 with cirrhosis vs non-cirrhotic MASLD (N = 999), early presentation with cirrhosis vs non-cirrhotic MASLD was associated with T2DM, BMI ≥ 35 kg/m^2, higher alkaline phosphatase and lower ALT. In multivariable analysis adjusted for sex, Hispanic ethnicity, GRS, obesity, T2DM, HTN and alcohol intake only high GRS, aOR 2.30 (95% CI:1.24-4.19, P = 0.007) and T2DM, aOR 3.38 (95% CI: 1.88-6.16, P < 0.001) remained associated with cirrhosis in participants under 50 with an additive increase in the prevalence of cirrhosis (Figure). **Conclusion:** One-quarter of patients with MASLD cirrhosis present before age 50 years and have distinct features including elevated alkaline phosphatase, higher genetic risk and a greater prevalence of T2DM.

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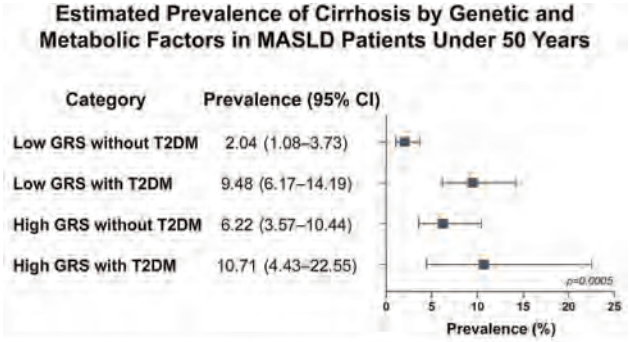

Prevalence of cirrhosis and 95% confidence interval by type 2 diabetes (T2DM) and dichotomized genetic risk score (GRS) including *PNPLA3*, *TM6SF2* and *HSD17B13* status in MASLD participants under 50 years (N=1,052). P-value calculated by Pearson's Chi-squared test for the prevalence of cirrhosis between groups.

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◆ 2492 | TAMOXIFEN IS ASSOCIATED MASLD PROGRESSION IN WOMEN WITH ER+ BREAST CANCER: A MULTICENTER RETROSPECTIVE COHORT STUDY

Emma Leipsner[1] Kate Johnson[1] Priyanka Gaur[1] Scarlet Yang[1] Tatyana Kushner[1], [1]Weill Cornell Medical College

Background: Tamoxifen, a Selective Estrogen Receptor Modulator (SERM), functions as an estrogen antagonist in breast tissue for estrogen receptor-positive (ER+) breast cancer. Its effect on liver outcomes in women with pre-existing Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) remains unclear. We evaluated whether tamoxifen influences MASLD progression in women with concurrent ER+ breast cancer compared to untreated controls. **Methods:** Using the TriNetX Research Network, we conducted a retrospective cohort study comparing liver disease outcomes in women with ER+ breast cancer and MASLD who received tamoxifen versus those who did not. Patients with prior decompensating events were excluded. Propensity score matching was conducted on 16 characteristics, including demographics and comorbidities. A composite decompensation outcome was defined as the presence of hepatic encephalopathy, variceal bleeding, portal hypertension, ascites, or hepatocellular carcinoma (HCC). **Results:** We identified 3,001 women with MASLD and ER+ breast cancer who had received tamoxifen (mean age 57.1 +/- 11.9) and 15,198 untreated controls (mean age 64.1 +/- 10.7) from 2005 to 2025. Most women were white (72% vs. 78%, $p < 0.001$), followed by Black (9.5% vs. 10.5%, $p = 0.0899$), Asian (8.7% vs. 5.3%, $p < 0.001$), and other races (3.7% vs. 2.4%, $p < 0.001$). After propensity score matching, 3000 women remained in each group, with median follow-up times of 1,220 and 1,098 days, respectively. Tamoxifen users had significantly higher rates of liver disease progression (Figure 1), including occurrence of MASH (RR 1.91), hepatic fibrosis (RR 1.99), and cirrhosis (RR 2.04). Composite liver decompensation was over twice as likely in tamoxifen users compared to non-users, with significantly increased risks of individual decompensation markers: portal hypertension (RR 3.98), jaundice (RR 3.33), and ascites (RR 2.36). Hepatic encephalopathy, HCC, esophageal variceal bleeding, and liver transplant sample sizes were too small to calculate. **Conclusion:** Tamoxifen-treated women with MASLD and ER+ breast cancer experience increased liver disease progression

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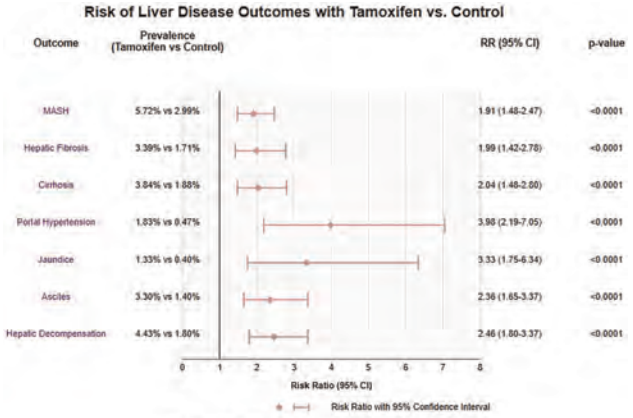
compared to those not receiving tamoxifen. These findings highlight tamoxifen's important influence on liver disease progression. Interdisciplinary care between hepatology and oncology is necessary to optimize both oncologic and hepatic outcomes for this particular group. Duration of tamoxifen exposure and baseline MASLD disease status are likely important influencers of our observed association and warrant further investigation.



Disclosures: Emma Leipsner: Nothing to Disclose, Kate Johnson: Nothing to Disclose, Priyanka Gaur: Nothing to Disclose, Scarlet Yang: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support

◆ 2493 | HYPOTHYROIDISM AND RISK OF LIVER-RELATED EVENTS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Xinrui Jin[1] Sherlot Juan Song[1] Vincent Wong[1] Jimmy Che-To Lai[1] Grace Lai-Hung Wong[1] Alice Pik-Shan Kong[1] Terry Cheuk-Fung Yip[1], [1]The Chinese University of Hong Kong

Background: Hypothyroidism is associated with an increased risk of MASLD and possibly its histologic severity. However, its effects on the development of liver-related events (LREs) remain uncertain. We aimed to assess the association between hypothyroidism and LREs in patients with MASLD. **Methods:** A territory-wide retrospective cohort study was conducted between 2000 and 2024 in Hong Kong, including adult patients with MASLD who had thyroid function tests. Baseline thyroid status was identified using ICD-9-CM diagnosis codes and thyroid function tests (thyroid stimulating hormone [TSH] and free thyroxine [T4]), and thyroxine replacement treatment; time-varying thyroid status was determined by thyroid function tests. LREs, the primary outcome, were defined as a composite of hepatocellular carcinoma (HCC), hepatic decompensation, liver transplantation, and liver-related death. The association between baseline and time-varying thyroid status and incident LREs was assessed using Fine-Gray model and time-dependent cause-specific hazard model, respectively. **Results:** The study included 20478 patients, with 179 LREs over a median follow-up of 4.8 years. In univariate model, baseline hypothyroidism (subdistribution hazard ratio [SHR] 1.59, 95% CI 1.04-2.43, $p = 0.032$), but not hyperthyroidism (SHR 1.11, 95% CI 0.49-2.51, $p = 0.80$), was associated with LREs. Baseline TSH and free T4 levels, whether analyzed as continuous or categorical variables, were not linked to LREs. In contrast, time-varying TSH levels (adjusted cause-specific hazard ratio [aCSHR] 1.01, 95% CI 1.004-1.036, $p = 0.016$) and TSH groups (4-10 mIU/L: aCSHR 2.36, 95% CI 1.42-3.92, $p < 0.001$; >10 mIU/L: aCSHR 4.73, 95% CI 1.50-14.88, $p = 0.008$) were significantly linked to higher risk of LREs. The cumulative incidence of LREs differed significantly by thyroid status over time (Figure 1). Compared with patients who were euthyroid, time-varying hypothyroidism was also associated with a higher LRE rate (aCSHR 3.01, 95% CI 1.94-4.67, $p < 0.001$). The aCSHR was 2.60 (95% CI 1.56-4.31, $p < 0.001$) in patients with subclinical hypothyroidism and 6.31 (95% CI 2.92-13.63, $p < 0.001$) in those with overt hypothyroidism, while time-varying hyperthyroidism showed no association. **Conclusion:** Both subclinical and overt hypothyroidism are linked to increased LRE risk in patients with MASLD. As thyroid function can change over time and be modified with treatment, dynamic thyroid function assessment has a stronger correlation with LREs than a one-off assessment.

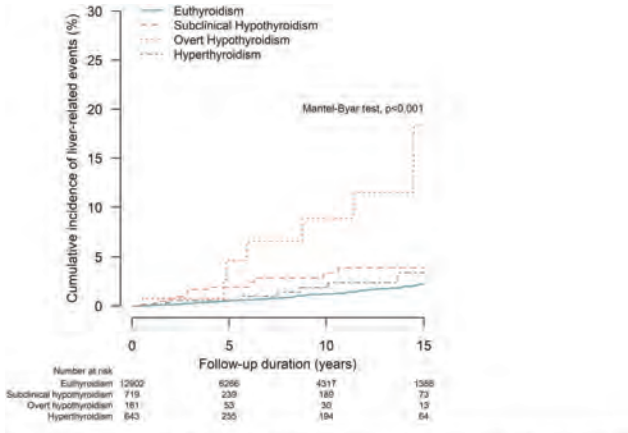


Figure 1. Cumulative risk of incident LRE in accordance with thyroid status during follow-up

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◆ 2494 | IMPACT OF FIRST AND FURTHER DECOMPENSATION IN METABOLIC-DYSFUNCTION ASSOCIATED COMPENSATED ADVANCED CHRONIC LIVER DISEASE

Grazia Pennisi[1] Gabriele Di Maria[2] Vincent Wong[3] Victor de Ledinghen[4] Giada Sebastiani[5] Mauro Viganò[6] Anna Ludovica Fracanzani[7] Luca Miele[8] Elisabetta Bugianesi[9] Mattias Ekstedt[10] Roberta D'Ambrosio[11] Federico Ravaioli[12] filippo schepis[13] Fabio Marra[14] Alessio Aghemo[15] Gianluca Svegliati-Baroni[16] Marcello Persico[17] Luca Valenti[18] Annalisa Berzigotti[19] Jacob George[20] Angelo Armandi[9] Patrik Nasr[21] Stergios Kechagias[22] Antonio Liguori[8] Dario Saltini[13] Yuli Paulin Mendoza[19] Vincenza Calvaruso[23] Marco Enea[23] Huapeng LIN[3] Giuseppe Infantino[23] Mario Masarone[16] Nicola Pugliese[24] Adele Tulone[23] Vito Di Marco[23] Calogero Cammà[23] Salvatore Petta[23], [1]Section of Gastroenterology and Hepatology, Dipartimento Di, [2]Dipartimento Di Promozione Della Salute, Materno Infantile, Medicina Interna e Specialistica Di Ecce, [3]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, [4]Centre d'Investigation de la Fibrose Hépatique, INSERM U1053, Hôpital Haut-Lévêque, Bordeaux Univers, [5]Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal QC, Canada, [6]Hepatology Unit, Ospedale San Giuseppe, University of Milan, Milan, Italy, [7]University of Milan, [8]DiSMeC-Department of Scienze Mediche e Chirurgiche, Fondazione Policlinico Gemelli IRCCS, 00168 Rome, [9]Division of Gastroenterology, Department of Medical Sciences, University of Torino, Torino, Italy, [10]Division of Diagnostics and Specialist Medicine, Department of Health, Medicine and Caring Sciences, [11]Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlini, [12]Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, IRCCS Azienda Ospedaliero-, [13]Severe Liver Lisease Unit, Azienda Ospedaliero-Universitaria di Modena and University of Modena and, [14]University of Florence, [15]Department of Biomedical Sciences, Humanitas University, Milan, Italy, [16]Liver Injury and Transplant Unit, Università Politecnica delle Marche, 60121 Ancona, Italy, [17]Department of Medicine and Surgery, "Scuola Medica Salernitana", Internal Medicine and Hepatology Un, [18]Fondazione Ca' Granda OMP Milano, [19]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Be, [20]The University of Sydney, [21]Division of Diagnostics and Specialist Medicine, Department of Health, Medicine and Caring Science, [22]Sweden, [23]University of Palermo, [24]Division of Internal Medicine and Hepatology, Department of Gastroenterology, IRCCS Humanitas Resear

Background: The first and further decompensation mark the natural history and the risk of mortality in patients with cirrhosis. We assessed the cumulative incidence of first and further (acute and non-acute) decompensation and evaluated their impact on both liver-related death (LR-D) in patients with compensated advanced chronic liver disease (cACLD) due to metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** International multicenter retrospective study (17 centers) on 6,061 consecutive patients with clinical (LSM > 10 kPa) or biopsy-proven (F3-F4 fibrosis) diagnosis of cACLD due to MASLD. First and further decompensation were defined according to Baveno VII criteria. Competing risk analysis by cumulative incidence functions and Cause-specific Cox models with baseline and time-dependent variables were performed. A multistate model was built to better assess the clinical course of cACLD due to MASLD. **Results:** The cumulative incidence of the first decompensation was 3.5% at 5 years, increasing 19-fold the risk of LR-D using Cox analysis; the cumulative incidence of further decompensation was 43.9% (95% C.I 37.2-50.2) at 5 years among patients with first decompensation, additionally increasing 1.5-times the risk of LR-D. Ascites, followed by variceal bleeding, were the most common events in both first and further decompensation. Hepatocellular carcinoma (HCC) further independently increased the risk of LR-D by 3- and 1.4-fold in the whole cohort of cACLD due to MASLD

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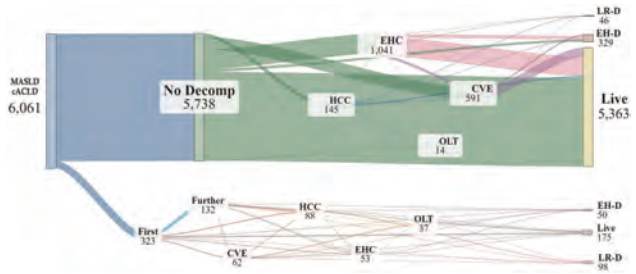
and in those who experienced first decompensation, respectively. **Conclusion:** The first and further decompensations represent tipping points in the clinical course of patients with cACLD due to MASLD, increasing 19-times and additionally 1.5-times the risk of LR-D. HCC is an independent predictor of LR-D in patients with cACLD due to MASLD, resulting in an additional risk of LR-D when associated with both first and further decompensation.



Disclosures: Grazia Pennisi: Nothing to Disclose, Gabriele Di Maria: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Consultant, Boehringer Ingelheim: Consultant, Echosens: Speaking and Teaching, Eli Lilly: Consultant, Gilead: Consultant, Gilead: Grant/Research Support, Intercept: Consultant, Inventiva: Consultant, Illuminatio Medical Technology: Stock – privately held company, Merck: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet: Consultant, TARGET PharmaSolutions: Consultant, Unilab: Speaking and Teaching, Visirna: Consultant, AstraZeneca: Consultant, Victor de Ledinghen: Nothing to Disclose, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Theratechnologies Inc.: Grant/Research Support, Eli Lilly: Consultant, Mauro Viganò: Nothing to Disclose, Anna Ludovica Fracanzani: Nothing to Disclose, Luca Miele: Nothing to Disclose, Elisabetta Bugianesi: Nothing to Disclose, Mattias Ekstedt: Nothing to Disclose, Roberta D'Ambrosio: Nothing to Disclose, Federico Ravaioli: Nothing to Disclose, filippo schepis: Nothing to Disclose, Fabio Marra: Nothing to Disclose, Alessio Aghemo: Nothing to Disclose, Gianluca Svegliati-Baroni: Nothing to Disclose, Marcello Persico: Nothing to Disclose, Luca Valenti: Nothing to Disclose, Annalisa Berzigotti: Nothing to Disclose, Jacob George: Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, novo Nordisk: Advisor, Boehringer Ingleheim: Advisor, Boehringer Ingleheim: Speaking and Teaching, Roche: Advisor, Astra Zeneca: Advisor, Gilead: Advisor, Eisai: Advisor, Angelo Armandi: Nothing to Disclose, Patrik Nasr: Boehringer Ingelheim: Advisor, Stergios Kechagias: Nothing to Disclose, Antonio Liguori: Nothing to Disclose, Dario Saltini: Nothing to Disclose, Yuli Paulin Mendoza: Nothing to Disclose, Vincenza Calvaruso: Nothing to Disclose, Marco Enea: Nothing to Disclose, Huapeng LIN: Nothing to Disclose, Giuseppe Infantino: Nothing to Disclose, Mario Masarone: Nothing to Disclose, Nicola Pugliese: Nothing to Disclose, Adele Tulone: Nothing to Disclose, Vito Di Marco: Nothing to Disclose, Calogero Cammà: Nothing to Disclose, Salvatore Petta: Nothing to Disclose

◆ 2495 | LONGITUDINAL CHANGES IN STEATOTIC LIVER DISEASE SUBTYPE CLASSIFICATION AND SUBSEQUENT RISK OF MAJOR ADVERSE LIVER OUTCOMES: A LANDMARK ANALYSIS

Pedro Ochoa-Allemant[1] Douglas Schaubel[1] Nadim Mahmud[1] David Kaplan[1] Marina Serper[1], [1]University of Pennsylvania

Background: Steatotic liver disease (SLD) includes metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-associated liver disease (ALD), and their intersection (MetALD). Patient classification by SLD subtype may change over time; however, the impact of these transitions on major adverse liver outcomes (MALO) is unknown. **Methods:** We conducted a retrospective cohort study of adults receiving outpatient care in the Veterans Health Administration (2010-2021) with imaging-confirmed hepatic steatosis identified using natural language processing. We excluded those with baseline cirrhosis, cirrhosis-related complications, or coexisting liver disease etiologies. The primary exposure was the change in SLD subtype classification between cohort entry (first imaging indicating steatosis) and a 2-year landmark. The primary outcome was incident MALO (cirrhosis, decompensation, HCC, liver transplant, or liver-related death). Follow-up started at the 2-year landmark and continued until the occurrence of MALO, non-liver-related death, loss to follow-up, or study end (December 31, 2021). We restricted analyses to patients alive and uncensored at the landmark. We calculated incidence rates per 100 person-years (PY). To examine the magnitude of the association between changes in SLD subtype classification with subsequent risk of MALO, we used cause-specific Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% CIs, treating non-liver-related death as a censoring event. We identified confounders a priori and final models included age, sex, smoking status, social deprivation index, and index year. **Results:** Of 270,302 adults (mean age, 59.7 years; 7.8% female; 68.0% non-Hispanic White), 211,916 (78.4%) had MASLD, 46,545 (17.2%) had MetALD, and 11,841

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(4.4%) had ALD at baseline. At the 2-year landmark, 17,281 (8.2%) of those with baseline MASLD were reclassified to MetALD or ALD, 15,922 (34.2%) of those with baseline MetALD were reclassified to MASLD or ALD, and 7,581 (64.0%) of those with baseline ALD were reclassified to MASLD or MetALD. Among patients with baseline MASLD, the risk of MALO was higher for those reclassified to MetALD (0.68 per 100 PY; HR 1.55, 95% CI 1.40-1.71) or ALD (0.95 per 100 PY; HR 2.13, 95% CI 1.66-2.74) compared with those who remained MASLD (0.43 per 100 PY). Among patients with baseline MetALD, the risk of MALO was lower for those reclassified to MASLD (0.47 per 100 PY; HR 0.55, 95% CI 0.48-0.64) and higher for those reclassified to ALD (1.64 per 100 PY; HR 1.80, 95% CI 1.58-2.06) compared with those who remained MetALD (0.88 per 100 PY). Among patients with baseline ALD, the risk of MALO was lower for those reclassified to MASLD (0.49 per 100 PY; HR 0.31, 95% CI 0.21-0.46) or MetALD (1.32 per 100 PY; HR 0.82, 95% CI 0.70-0.96) compared with those who remained ALD (1.63 per 100 PY). **Conclusion:** Changes in SLD subtype classification within 2 years are associated with distinct risks of MALO.

Table. Association of changes in steatotic liver disease subtype classification with major adverse liver outcomes

Baseline	2-Year Landmark	No. (%)	Events	Person-Years	IR per 100 PY (95% CI)	Hazard Ratio (95% CI)[a]
MASLD	MASLD	194,635 (91.8)	3,418	799,771	0.43 (0.41-0.44)	1 [Reference]
	MetALD	15,720 (7.4)	431	63,561	0.68 (0.62-0.75)	1.55 (1.40-1.71)
	ALD	1,561 (0.7)	62	6,515	0.95 (0.74-1.22)	2.13 (1.66-2.74)
MetALD	MetALD	30,623 (65.8)	1,125	127,571	0.88 (0.83-0.93)	1 [Reference]
	MASLD	11,688 (25.1)	229	48,907	0.47 (0.41-0.53)	0.55 (0.48-0.64)
	ALD	4,236 (9.1)	279	16,976	1.64 (1.46-1.85)	1.80 (1.58-2.06)
ALD	ALD	4,260 (36.0)	272	16,639	1.63 (1.45-1.84)	1 [Reference]
	MASLD	1,325 (11.2)	28	5,692	0.49 (0.34-0.71)	0.31 (0.21-0.46)
	MetALD	6,256 (52.8)	335	25,391	1.32 (1.19-1.47)	0.82 (0.70-0.96)

ALD, alcohol-associated liver disease; CI, confidence interval; IR, incidence rate; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; No, number; PY, person-years.

Note: Percentages have been rounded and may not total 100.

[a] Major adverse liver outcome was defined as the first occurrence of cirrhosis, decompensation, hepatocellular carcinoma, liver transplant, and liver-related death. Hazard ratios were estimated using cause-specific Cox proportional hazards regression models, adjusted for age, sex, smoking status, social deprivation index, and index year.

Disclosures: Pedro Ochoa-Allemant: Nothing to Disclose, Douglas Schaubel: Nothing to Disclose, Nadim Mahmud: Grifols: Grant/Research Support, David Kaplan: AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Sirtex: Advisor, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research Support, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Eurofins: Grant/Research Support

◆ 2496 | ASSOCIATION OF END-STAGE LIVER DISEASE WITH STEATOTIC LIVER DISEASE AMONG PEOPLE WITH AND WITHOUT HIV INFECTION

Jessie Torgersen[1] Craig Newcomb[1] Janet Tate[2] Melissa Skanderson[2] Farah Kidwai-Khan[2] Dean Carbonari[1] Catherine Mezzacappa[2] Jennifer Price[3] Tamar Taddei[4] Joseph Lim[2] Debika Bhattacharya[5] Amy Justice[6] Vincent Lo Re, III[1], [1]University of Pennsylvania Perelman School of Medicine, [2]Yale University School of Medicine; VA Connecticut Healthcare System, [3]University of California, San Francisco School of Medicine, [4]Yale University, [5]David Geffen School of Medicine at UCLA; VA Greater Los Angeles Healthcare System, [6]Yale University School of Medicine; VA Connecticut Healthcare System; Yale School of Public Health

Background: Despite the high prevalence of steatotic liver disease (SLD), its association with end-stage liver disease (ESLD) remains unclear, particularly among people with HIV (PWH). HIV modifies the association between chronic viral hepatitis and ESLD; however, it is unknown if the association between SLD and ESLD differs by HIV status. **Methods:** We identified patients from the Veterans Aging Cohort-HIV (includes 1:2 matching to people without HIV [PWoH]) who underwent an abdominal ultrasound, CT, or MRI inclusive of the liver between 2001-2017. Patients with diagnosed cirrhosis or chronic viral hepatitis at baseline were excluded to more clearly identify effects associated with SLD. SLD was defined by a natural language processing (NLP) algorithm previously validated against manual clinician review of radiology reports. ESLD was defined as a composite outcome of hepatocellular carcinoma (defined by the VA Cancer Registry or ICD-9/-10) or hepatic decompensation (defined by validated ICD-9/-10 criteria). Follow-up began on the date of the imaging study and continued until first ESLD event, death, or December 31, 2021. Multivariable Cox regression was used to determine hazard ratios (HR, 95% confidence interval [CI]) of ESLD associated with SLD, by HIV status. **Results:** Among 19,545 patients with imaging inclusive of the liver (mean age: 55 years; 97.0% male; 28.7% PWH), 13,617 (69.7%) had an imaging report with SLD as determined by NLP. A total of 228 ESLD events were observed among PWH, and 513 events were observed in PWoH (incidence rates: 36.5 and 30.2/10,000 person-years, respectively; $p = 0.02$). In the overall multivariable model, there was a significant interaction between SLD and HIV on risk of ESLD (p for interaction < 0.001); thus, models were stratified by HIV status. Among PWH, SLD was associated with increased risk of ESLD (HR:1.66, 95% CI:1.19-2.33), independent of alcohol and metabolic comorbidities. Among PWoH, SLD was associated with an even greater risk of incident ESLD (HR:2.43, 95% CI:1.86-3.18) (Table 1). **Conclusion:** In PWH and PWoH, without known cirrhosis or chronic viral hepatitis, radiographic findings of SLD were associated with increased risk of ESLD independent of alcohol or metabolic comorbidities. Although PWH had higher incidence of ESLD compared with PWoH, the effect of SLD on risk of ESLD differs in the setting of HIV, suggesting HIV-specific factors may impact this risk. Future work is needed to understand how modifiable factors, such as HIV viremia or antiretroviral drugs, affect the association between SLD and ESLD in PWH.

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Table 1. Adjusted Cox Proportional Hazards Ratios of End-Stage Liver Disease Among Patients with Clinical Liver Imaging Reports Without Baseline Cirrhosis or Viral Hepatitis, By HIV Status.

Baseline Characteristics	HIV Monoinfection (n=5,584)		No HIV or Viral Hepatitis (n=13,961)	
	N	Adjusted HR* (95% CI)	N	Adjusted HR* (95% CI)
Steatotic liver disease†	3752	1.66 (1.19-2.33)	9865	2.43 (1.86-3.18)
Age, years				
<40 years	838	Ref	1482	Ref
40-49 years	1452	1.86 (1.08-3.19)	3456	1.42 (0.95-2.12)
50-59 years	1782	2.03 (1.18-3.50)	5172	1.53 (1.03-2.26)
≥60 years	1512	2.61 (1.48-4.60)	3851	1.94 (1.28-2.93)
Female sex	185	0.82 (0.36-1.86)	471	0.62 (0.32-1.21)
Race/Ethnicity				
Non-Hispanic White	2564	Ref	5943	Ref
Non-Hispanic Black	2128	0.64 (0.46-0.88)	5560	0.69 (0.56-0.84)
Hispanic	434	0.63 (0.37-1.09)	1143	0.67 (0.47-0.96)
Other‡	272	1.22 (0.73-2.04)	925	0.85 (0.60-1.20)
Unknown	186	1.72 (0.94-3.13)	390	0.93 (0.51-1.70)
Body mass index, kg/m²				
<18.5	122	0.28 (0.04-2.05)	136	1.02 (0.37-2.78)
18.5-24.9	1828	Ref	2205	Ref
25.0-29.9	2016	0.87 (0.63-1.19)	4418	0.84 (0.64-1.10)
30.0-39.9	1020	0.63 (0.42-0.95)	3898	0.68 (0.50-0.91)
≥40.0	481	0.61 (0.35-1.06)	2910	1.01 (0.75-1.36)
Missing	117	2.33 (1.20-4.53)	394	1.32 (0.79-2.20)
Tobacco use, ever§	3706	0.87 (0.66-1.14)	9341	1.09 (0.89-1.33)
Diabetes¶	805	2.33 (1.67-3.26)	3465	1.72 (1.41-2.10)
Hypertension¶	2940	1.20 (0.89-1.62)	9532	1.41 (1.13-1.78)
Hyperlipidemia¶	2815	0.82 (0.61-1.09)	8982	1.00 (0.81-1.22)
Alcohol use disorder¶	1125	1.26 (0.90-1.78)	3102	2.09 (1.72-2.55)
AUDIT-C Score‖				
0	1375	Ref	3452	Ref
Low	1363	0.68 (0.43-1.07)	2777	1.01 (0.73-1.40)
Moderate	342	0.62 (0.28-1.38)	851	1.84 (1.26-2.68)
High	117	2.87 (1.46-5.63)	341	2.53 (1.62-3.94)
Missing	2387	1.11 (0.79-1.57)	6540	1.22 (0.94-1.57)

*Models adjusted for all variables presented in table
†Defined by radiographic text reports including the terms "fatty" and "liver" or "hepat", "steatosis", "steatotic", and "steatohepatitis"
‡Other includes Asian, American Indian/Pacific Islander
§Tobacco use was determined from the VA's Health Factors Dataset
¶Defined by one inpatient or two outpatient diagnostic codes
‖Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) categories defined as abstinent (0), low risk (1-2 [women] or 1-3 [men]), moderate risk (3-7 [women] or 4-7 [men]), and high risk (≥8 [women and men])

Disclosures: Jessie Torgersen: Nothing to Disclose, Craig Newcomb: Nothing to Disclose, Janet Tate: Nothing to Disclose, Melissa Skanderson: Nothing to Disclose, Farah Kidwai-Khan: Nothing to Disclose, Dean Carbonari: Nothing to Disclose, Catherine Mezzacappa: Nothing to Disclose, Jennifer Price: AbbVie: Grant/Research Support, Gilead: Grant/Research Support, Genentech: Grant/Research Support, VIR: Grant/Research Support, Cepheid: Grant/Research Support, Aligos: Grant/Research Support, Tamar Taddei: Nothing to Disclose, Joseph Lim: Nothing to Disclose, Debika Bhattacharya: Nothing to Disclose, Amy Justice: Nothing to Disclose, Vincent Lo Re, III: Nothing to Disclose

◆ 2497 | REFINED INDICATORS FOR MASLD-INDUCED FIBROSIS DETECTION SAFELY REDUCE THE NEED FOR SCREENING BY MORE THAN 50% IN CLINICAL CARE PATHWAYS

Laurens van Kleef[1] Jesse Pustjens[1] Maja Thiele[2] Maurice Michel[3] Adriaan Holleboom[4] Manuel Castro Cabezas[5] Maarten Tushuizen[6] Harry Janssen[1] Jörn Schattenberg[7] Pere Ginés[8] Sven Francque[9] Zobair Younossi[10] Aleksander Krag[11] Willem Pieter Brouwer[1], [1]Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, [2]Odense University Hospital, [3]Department of Internal Medicine II, University Medical Center Saarland, [4]Amsterdam UMC, [5]Sint Franciscus Gasthuis, [6]Department of Gastroenterology and Hepatology, Leids Universitair Medisch Centrum, [7]Department of Internal Medicine II, Saarland University Medical Center, [8]Liver Unit, Hospital Clinic of Barcelona, University of Barcelona, [9]Department of Gastroenterology and Hepatology, Antwerp University Hospital, [10]The Global NASH Council, Washington DC, [11]University of Southern Denmark

Background: Diabetes, obesity, and elevated ALT are commonly used indicators to screen for (advanced) liver fibrosis. However, current guidelines differ in their recommendations on who to screen. In light of the increasing prevalence of metabolic comorbidities, we sought to refine screening criteria using population-based data aiming to reduce the need for screening in the general population **Methods:** We analyzed participants without excessive alcohol consumption, aged 18-80 from NHANES 2017-2020, with data on indicators for screening and BMI ≥18.5 kg/m2. We estimated the weighted proportion of the population meeting screening criteria based on various international guidelines. Additionally, we assessed the prevalence of liver stiffness measurement (LSM) ≥8 kPa across the full spectrum of screening indicators through stratified analysis. All estimates were adjusted using NHANES-provided sampling weights. **Results:** We included 5,904 individuals (mean age 47 yr, 49% male) of whom 8.9% had LSM ≥ 8 kPa. Current screening guidelines identified 60–76% of the general population as target for screening, with a positive predictive value (PPV) of 11.1–13.5% for LSM ≥8 kPa. In contrast, among the 24–40% who did not meet any screening criteria, the prevalence of LSM ≥8 kPa was only 2.0–2.2%. Some subgroups were not at increased risk of LSM ≥8 kPa such as individuals with diabetes and normal ALT levels without obesity, or individuals with obesity class I and II without diabetes and normal ALT. Based on these findings, a refined screening strategy identified only 22% of the population as needing screening, while maintaining a high negative predictive value (NPV) of 96.3% and improving the PPV to 27.7% for LSM ≥ 8 kPa and an NPV of 98.9% with PPV of 10.0% for LSM ≥ 12 kPa. Similar results were obtained across age categories. **Conclusion:** Current guideline-based strategies classifies 60–76% of the U.S. population as eligible for liver fibrosis screening. Our findings suggest that refining these criteria could safely reduce the target

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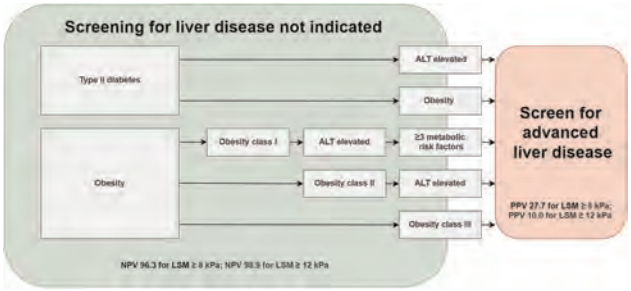
screening population by more than half to 22%, as certain metabolic risk subgroups, particularly in the absence of diabetes or class III obesity, do not exhibit substantially increased risk for (advanced) liver fibrosis.



Disclosures: Laurens van Kleef: Nothing to Disclose, Jesse Pustjens: Nothing to Disclose, Maja Thiele: Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, GSK: Advisor, GSK: Advisor, GSK: Advisor, Novo Nordisk: Speaking and Teaching, GSK: Grant/Research Support, Evido: Co-founder, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, GSK: Advisor, GSK: Advisor, GSK: Advisor, Novo Nordisk: Speaking and Teaching, GSK: Grant/Research Support, Evido: Co-founder, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, GSK: Advisor, GSK: Advisor, GSK: Advisor, Novo Nordisk: Speaking and Teaching, GSK: Grant/Research Support, Evido: Co-founder, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, GSK: Advisor, GSK: Advisor, GSK: Advisor, Novo Nordisk: Speaking and Teaching, GSK: Grant/Research Support, Evido: Co-founder, Maurice Michel: Nothing to Disclose, Adriaan Holleboom: Nothing to Disclose, Manuel Castro Cabezas: Nothing to Disclose, Maarten Tushuizen: Nothing to Disclose, Harry Janssen: Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Academic Medical Education: Consultant, H.C. 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◆ 2498 | MACHINE LEARNING MODELS ACCURATELY PREDICT CHANGES IN FIB-4 CATEGORY FOR PATIENTS WITH DIABETES MANAGED IN PRIMARY CARE – AN ANALYSIS OF 59,872 CASES

Chloe Yitian Guo[1] Christen Ong[1] Daniel Lim[2] Yiying Pei[2] Bochao Jiang[2] Chanda Ho[2] Kevin Kim Jun Teh[3] Yong Mong Bee[4] Hairil Rizal[5] Chee-Kiat Tan[2] George Boon-Bee Goh[2], [1]Yong Loo Lin School of Medicine, National University of Singapore, [2]Dept of Gastroenterology and Hepatology, Singapore General Hospital, [3]SingHealth, [4]Dept of Endocrinology, Singapore General Hospital, [5]Dept of Anaesthesiology, Singapore General Hospital

Background: The Fibrosis-4 (FIB-4) score is a non-invasive test that assesses the risk of liver fibrosis in patients with metabolic-associated steatotic liver disease (MASLD). Based on age-dependent FIB-4 score cut-offs, there are 3 risk categories for fibrosis: low, indeterminate and high. Patients in primary care are recommended for specialist referral when the FIB-4 is indeterminate or high. However, it is known that medications such as SGLT2 inhibitors (SGLT2is) and GLP-1 receptor agonists (GLP1RAs) may cause regression of liver fibrosis in MASLD. We sought to develop a risk model using demographic, laboratory and medication factors to predict risk of FIB-4 progression or regression, in patients with diabetes managed in primary care. **Methods:** Data from 59,872 patients in the SingHealth Diabetes Registry (SDR) was analyzed. Median age is 68 (IQR = 59, 77) with 54% male. Multivariable logistic regression was used to assess the effect size of the following predictor variables: gender, ethnicity, smoking status, current FIB-4 score, body mass index, lab values (HBA1C, selected liver and lipid panel results) and medications (oral glucose lowering drugs, insulins, antihypertensives, antiplatelets, lipid-lowering drugs). Four different machine learning (ML) models (logistic regression (LR), random forest (RF), gradient boosting (GB) and multilayer perceptron (MLP)) were used to predict whether the FIB-4 category is low (negative class) or not low (i.e. indeterminate or high, positive class) after 1 year, using the predictor variables. **Results:** Multivariable logistic regression showed that some antihypertensives and diabetes medications are independently associated with a low FIB-4 category after 1 year, such as angiotensin receptor blockers (ARBs) (OR = 0.949, CI = 0.905, 0.996, p = 0.033) and metformin (OR = 0.824, CI = 0.79, 0.86, $p < 0.001$). SGLT2is and GLP1RAs are not statistically significantly associated with low FIB-4 category. All 4 ML models could predict the 1-year FIB-4 category with high area under the receiving operator curve (AUROC) scores. GB performed best (AUROC = 84.2% ± 0.3%) followed by LR (AUROC = 82.4% ± 0.3%), MLP (AUROC = 82.0% ± 0.5%), and RF (AUROC = 80.8% ± 0.4%). **Conclusion:** Antihypertensives and diabetes medications are beneficial in improving FIB-4 category to low after 1 year. ML models are also able to accurately predict the FIB-4 category after 1 year. Optimisation of medications rather than upfront specialist referral may be a viable strategy for patients with indeterminate or high FIB-4.

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Table of Multivariable Logistic Regression Results

Variable	Adjusted Odds Ratio* (95% Confidence Interval)	p-value
Demographics		
Male gender	1.134 (1.091, 1.178)	<0.001
Indian ethnicity	0.943 (0.887, 1.001)	0.056
Malay ethnicity	0.953 (0.902, 1.006)	0.079
Other ethnicities	0.953 (0.876, 1.036)	0.258
Current smoker	0.919 (0.862, 0.980)	0.010
Body Mass Index	0.989 (0.985, 0.992)	<0.001
Laboratory Values		
Current FIB-4 Score	2.165 (2.121, 2.209)	<0.001
Albumin	0.990 (0.987, 0.993)	<0.001
GGT	1.001 (1.001, 1.001)	<0.001
HBA1C	0.959 (0.947, 0.970)	<0.001
LDL	0.970 (0.952, 0.989)	0.002
Triglycerides	0.966 (0.948, 0.984)	<0.001
Current Medications		
Single Antiplatelet[1]	1.031 (0.986, 1.079)	0.184
Dual Antiplatelet[2]	0.983 (0.912, 1.059)	0.646
GLP-1 Receptor Agonist	1.203 (0.961, 1.506)	0.106
Insulins[3]	0.909 (0.869, 0.950)	<0.001
ACE Inhibitor	0.959 (0.913, 1.008)	0.102
Angiotensin Receptor Blocker	0.949 (0.905, 0.996)	0.033
Calcium Channel Blocker	0.887 (0.852, 0.923)	<0.001
Diuretics[4]	1.273 (1.217, 1.331)	<0.001
Beta Blocker, Alpha Blocker, Hydralazine	1.164 (1.115, 1.214)	<0.001
Ezetimibe	1.050 (0.934, 1.180)	0.412
Fibrate	1.003 (0.926, 1.087)	0.936
Statin	0.967 (0.923, 1.013)	0.160
Other Lipid-Lowering Agents[5]	1.110 (0.699, 1.763)	0.658
Metformin	0.824 (0.790, 0.860)	<0.001
SGLT2 Inhibitor	0.972 (0.919, 1.028)	0.318
Sulphonylurea	0.955 (0.914, 0.997)	0.036
Thiazolidinedione	1.478 (0.746, 2.929)	0.263
Other Oral Glucose Lowering Drugs[6]	1.061 (1.005, 1.121)	0.034

*Adjusted for all the variables in the Variables column
[1]Aspirin or P2Y12 Receptor Antagonist
[2]Both Aspirin and P2Y12 Receptor Antagonist
[3]Regular Human Insulin, Long Acting Insulin Analogue, Premixed Insulin Analogue, Premixed Human Insulin, NPH Human Insulin, Rapid Acting Insulin Analogue
[4]Loop Diuretic, Thiazide, Aldosterone Antagonist, Amiloride, Renin Inhibitor
[5]Bile Acid Sequestrant, Niacin, PCSK9 Inhibitor
[6]Meglitinide, DPP-4 Inhibitor, Acarbose

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◆ 2499 | SEMAGLUTIDE DISCONTINUATION AMONG PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Samantha Clark[1] Dominic Nunag[1] Matthew Davis[1] Arushi Chadha[1] Nipun Atreja[2] Blake Thomas[2] Francis Lobo[2], [1]Medicus Economics, LLC, [2]Madrigal Pharmaceuticals, Inc.

Background: MASLD and its more progressive subtype, MASH, are chronic liver conditions, with progression to the latter underdiagnosed in clinical practice. Subcutaneous (SC) semaglutide is currently being investigated for use in MASH in the ongoing ESSENCE clinical trial (NCT0482218). Interim trial results indicate that over 89% of participants remained persistent at 72-weeks of follow-up. In this study, we aim to assess alignment between real-world medication compliance and that observed in the ESSENCE trial among MASLD patients starting SC semaglutide for an approved indication. **Methods:** A retrospective cohort study including MASLD patients initiating SC semaglutide (both Ozempic® and Wegovy®) from 2017-2024 was conducted in Optum Market Clarity data. The 12-month period prior to the first SC semaglutide prescription claim (index date) was used for sample selection and covariate measurement. Patients with other liver diseases (e.g., viral hepatitis) or severe complications from MASH (e.g., cirrhosis) were excluded. Discontinuation was defined as a gap in medication coverage of $\geq$45 days. Patients were followed from their index date until death, dropout, or end of data availability. Kaplan-Meier (KM) curves illustrating persistence probability and time-to-discontinuation were constructed for the overall sample. **Results:** Of the 36,531 adults included in the final sample, 69.5% (n = 25,371) presented with type 2 diabetes. Mean (standard deviation) age was 52.6 (12.0) years old and 63.0% (n = 23,021) were female. Overall, 64.3% (n = 23,473) of patients discontinued SC semaglutide, with 56.3% (n = 20,566) doing so within a year and 60.1% (n = 21,966) doing so within 72 weeks. Mean time-to-discontinuation was 24.7 weeks (28.6) weeks and mean follow-up time was 77.9 weeks (57.6). Accounting for censoring, 64% of patients (95% confidence interval (CI): 63%-64%) discontinued by 1 year and 72% (95% CI: 71%-72%) discontinued by 72 weeks. **Conclusion:** The majority of MASLD patients discontinued SC semaglutide, with 72% doing so within 72 weeks of initiation. Results are consistent with findings from similar observational studies and highlight the importance of monitoring SC semaglutide use patterns in a real-world setting, especially with respect to the resultant impact on liver outcomes as well as BMI and glycemic goals.

Disclosures: Samantha Clark: Madrigal Pharmaceuticals Inc: Consultant, Dominic Nunag: Nothing to Disclose, Matthew Davis: Medicus Economics, LLC: Employee, Arushi Chadha: Nothing to Disclose, Nipun Atreja: Madrigal Pharmaceuticals: Employee, Immunovant: Employee, Bristol Myers Squibb: Employee, Blake Thomas: Madrigal Pharmaceuticals: Employee, Francis Lobo: Madrigal Pharmaceuticals: Employee

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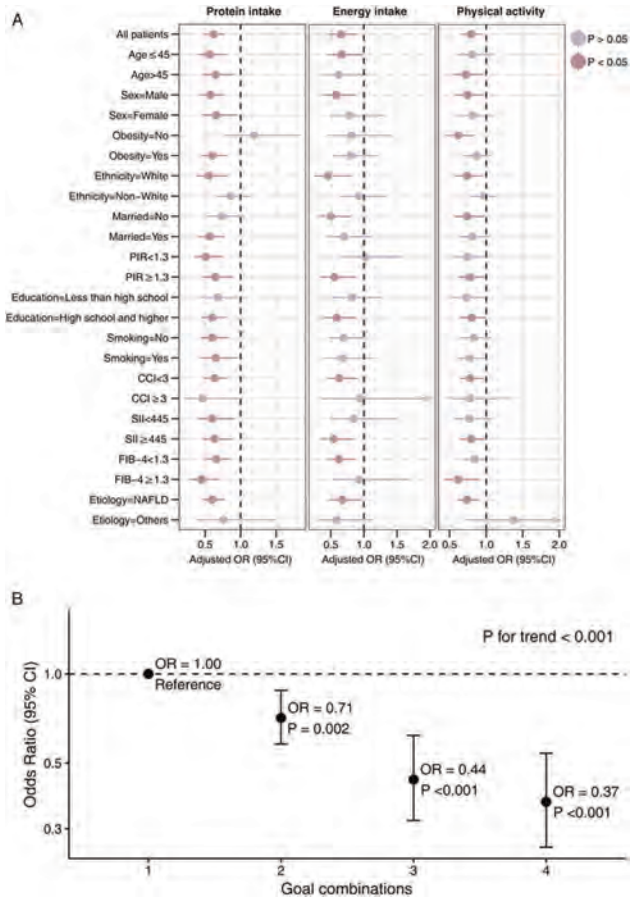
◆ 2500 | IMPACT OF PROTEIN AND ENERGY INTAKE AND PHYSICAL ACTIVITY ON SARCOPENIA IN CHRONIC LIVER DISEASE: A POPULATION-BASED STUDY

Ying Liu[1] Qiuju Ran[1] Shuyue Tuo[1] Zhang Wen[1] Jinhai Wang[1] Shejiao Dai[1] Lu Li[1] Xinxing Tantai[2], [1]The Second Affiliated Hospital of Xi'an Jiaotong University, [2]The Second Affiliated Hospital of Xi'an Jiaotong University

Background: The impact of protein and energy intake and physical activity on sarcopenia among patients with chronic liver disease (CLD) has not been determined. Additionally, the recommended amounts of protein, energy, and physical activity to effectively reduce the risk of sarcopenia in patients with CLD is unknown. A protein intake of ≥ 1.2 g/kg/day, an energy intake of ≥35 kcal/kg/day, and engagement in moderate-intensity physical activities (MPA) for≥150 minutes per week are recommended as goals for managing sarcopenia in patients with cirrhosis. Whether these goals are equally applicable to patients with less advanced CLD remains to be validated. **Methods:** This study selected data from the National Health and Nutrition Examination Survey (1999-2020). Weighted multivariate logistic regression models were used to estimate the associations between sarcopenia and quantitative measures of daily protein and energy intake, weekly moderate-intensity physical activity (MPA) time, their respective qualitative goals, and various combinations of these goals. **Results:** A total of 8298 participants with CLD were included. The highest tertile of daily protein intake [odds ratio (OR) = 0.71, 95% confidence interval (CI): 0.54-0.92), daily energy intake (OR = 0.63, 95%CI: 0.47-0.87), and weekly MPA time (OR = 0.77, 95%CI: 0.62-0.96) was significantly associated with a lower risk of sarcopenia compared with the lowest tertile group. Restricted cubic spline analyses and trend tests indicated that these associations were linear. Maintaining a daily protein intake of ≥ 1.2 g/kg, a daily energy intake of ≥ 35 kcal/kg, and a weekly MPA time totaling ≥ 150 min was associated with a 38%, 35%, and 21% reduction in the risk of sarcopenia, respectively (Figure 1A). The majority of subgroup analyses (Figure 1A) and various sensitivity analyses demonstrated consistent results. Four combinations of meeting the goals for protein intake, energy intake, and MPA were analyzed: (1) None of the goals were met; (2) One of the three goals was met; (3) Two of the three goals were met; (4) All goals were met. The risk of sarcopenia decreased progressively as the number of achieved goals increased (Figure 1B). Meeting all three goals was associated with the lowest risk of sarcopenia in individuals with CLD (Figure 1B). **Conclusion:** Increased daily protein and energy intake as well as higher weekly MPA levels were significantly associated with a reduced risk of sarcopenia among individuals with CLD. The established goals for these three measures were applicable, and achieving more of these goals was associated with a lower risk of sarcopenia.



Disclosures: Ying Liu: Nothing to Disclose, Qiuju Ran: Nothing to Disclose, Shuyue Tuo: Nothing to Disclose, Zhang Wen: Nothing to Disclose, Jinhai Wang: Nothing to Disclose, Shejiao Dai: Nothing to Disclose, Lu Li: Nothing to Disclose, Xinxing Tantai: Nothing to Disclose

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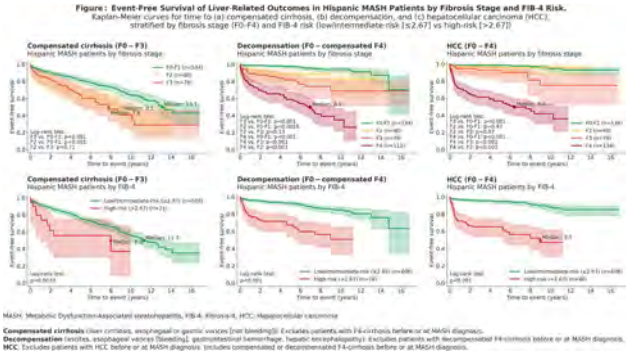
2501 | NATURAL HISTORY OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) IN HISPANIC PATIENTS: A REAL-WORLD COHORT STUDY STRATIFIED BY FIBROSIS SEVERITY

Robert Matson[1] Subash C[1] Steven Perrault[1] Jason Maron[1] Xiao Zhang[2] Gail Fernandes[2] Samuel Engel[2] Matthew Melaragno[2] Yuzhi Xi[2] Precious Ejelonu[2], [1]nference, Inc., Cambridge, MA, USA, [2]Merck & Co., Inc., Rahway, NJ, USA

Background: The Hispanic population is disproportionately affected by metabolic dysfunction-associated steatohepatitis (MASH), yet few disaggregated studies describe the clinical characteristics and progression to outcomes in Hispanic patients stratified by fibrosis severity at MASH diagnosis. **Methods:** A retrospective cohort study was conducted in Hispanic adults diagnosed with MASH between 1/1/2006–12/31/2023, using electronic health record (EHR) data from Mayo Clinic sites and affiliated healthcare systems in Minnesota, Arizona, Florida, Wisconsin, and Iowa. Fibrosis stage and risk of advanced fibrosis defined by fibrosis-4 (FIB-4) were used to describe fibrosis severity. Fibrosis stage (F0–F4) was assessed using diagnostic codes and liver biopsy results when available, or estimated from non-invasive tests based on published criteria from analogous liver diseases. FIB-4 of 2.67 was used to differentiate low/intermediate risk (≤ 2.67) and high-risk (> 2.67) of advanced fibrosis. Patient characteristics were assessed by fibrosis stage and FIB-4. Kaplan-Meier (K-M) analysis was performed to evaluate time to compensated cirrhosis, decompensation, and hepatocellular carcinoma (HCC) by fibrosis stage and FIB-4. **Results:** Among 892 Hispanic patients with MASH and fibrosis stage data (mean age 50.1 years, 56.3% female, median BMI 32.0 kg/m²), 59.8% had F0–F1, 9.0% had F2, 8.9% had F3, and 22.3% had F4; among 759 Hispanic patients with MASH and FIB-4 data, 79.8% had low/intermediate-risk and 20.2% had high-risk FIB-4. Increasing fibrosis stage was correlated with older age, higher AST, and lower platelet count. F4 and high-risk FIB-4 groups had higher prevalence of type 2 diabetes and chronic kidney disease than F0-F3 and low/intermediate-risk FIB-4, respectively. K-M estimates showed that patients with more advanced fibrosis stages and higher risk of advanced fibrosis had worse prognosis. Median time to compensated cirrhosis was 13.1, 9.1, and 7.8 years for F0–F1, F2, and F3, respectively; and 11.3 vs 8.0 years for low/intermediate- vs high-risk FIB-4. Compensated F4 and high-risk FIB-4 groups had significantly higher rates of decompensation and HCC compared to F0–F3 and low/intermediate-risk FIB-4, respectively. **Conclusion:** Hispanic MASH patients with more advanced fibrosis stages and higher risk of advanced fibrosis at diagnosis had more comorbidities and faster progression to liver-related endpoints. These findings underscore the need for early risk stratification and targeted interventions.



Disclosures: Robert Matson: Nothing to Disclose, Subash C: Nothing to Disclose, Steven Perrault: Nothing to Disclose, Jason Maron: Nothing to Disclose, Xiao Zhang: Merck: Employee, Gail Fernandes: Merck & Co., Inc: Employee, Merck & Co., Inc: Stock - publicly traded company, Samuel Engel: Merck Sharp Dohme: Employee, Matthew Melaragno: Merck & Co., Inc.: Employee, Merck & Co., Inc.: Stock - publicly traded company, Yuzhi Xi: Nothing to Disclose, Precious Ejelonu: Nothing to Disclose

2502 | DYNAMICS OF LIVERRISK SCORE AND MAF-5 PREDICT PERSISTENT LIVER STIFFNESS ELEVATION AND NORMALIZATION IN THE GENERAL POPULATION: LONGITUDINAL RESULTS: FROM THE EUROPEAN LIVERSCREEN PROJECT

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Background: Serum-based non-invasive tests (NITs) form the cornerstone for referral strategies aimed to detect liver disease in the general population. However, the associations between changes in NITs and progression of liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) remain unclear. **Methods:** In this multicenter cohort study, embedded within the European LiverScreen project, longitudinal data from three population-based cohorts (Barcelona, Rotterdam and Odense) were analyzed. Participants underwent baseline and follow-up screening by VCTE over an approximate four-year interval, alongside anthropometric and laboratory assessments. In participants with baseline LSM <8 kPa, incident fibrosis was defined as a $\geq 30\%$ increase crossing the 8 kPa threshold. In those with baseline LSM ≥ 8 kPa, fibrosis regression was defined as a $\geq 30\%$ reduction and falling below 8 kPa, while persistent fibrosis was defined as an LSM that remained ≥ 8 kPa. NIT-specific cut-offs were: APRI ≥ 0.5, FIB-4 ≥ 1.3, FORNS ≥ 4.2, LiverRisk Score (LRS) ≥ 6, and MAF-5 ≥ 1.0. **Results:** Among 7,884 participants with reliable baseline VCTE, 4,536 had a valid follow-up VCTE after a median of 4.3 years [IQR: 4.1–8.2]. The follow-up cohort had a median age of 62 years [56–68], and 52% were female. At baseline, 5.5% (251/4,536) had an LSM ≥ 8 kPa, of which 56% (141/251) had persistent fibrosis after follow-up. Of those with baseline LSM <8 kPa (4,285/4,536), 2.6% (112/4,285) developed incident fibrosis. The best performing scores predicting persistent fibrosis were the baseline MAF-5 (AUC: 0.875), and LRS (0.852), followed by FORNS (0.792), APRI (0.785) and FIB-4 (0.700). A baseline NIT score below the risk cut-off was associated with an increased likelihood of LSM regression compared to those with a concurrent high NIT and high LSM: LRS (OR 4.45, 95%CI 1.41–4.25), MAF-5 (OR 2.29, 95%CI 1.34–3.92), FIB-4 (OR 2.34, 95%CI 1.38–3.98), APRI (OR 2.24, 95% CI 1.18–4.27), except for the FORNS (OR 1.75, 95%CI 0.92–3.37). Among those with LSM <8 kPa at baseline, the proportion who changed from a low to a high NIT risk category was: MAF-5: 6.8%, LRS: 12%, FORNS: 21%, APRI: 2.9%, and FIB-4: 16%. For all tests, this was significantly associated with incident fibrosis: LRS (OR 5.12, 95%CI 3.02–8.69), MAF-5 (OR 4.83, 95%CI 2.46–8.80), FIB-4 (OR 1.95, 95% CI 1.05–3.63), APRI (OR 7.78, 95%CI 4.37–13.8) and FORNS (OR 1.27, 95%CI 1.50–6.95). **Conclusion:** Baseline MAF-5 and LRS best predicted persistent LSM elevation, potentially distinguishing true at-risk fibrosis from false positive LSM elevations. Transitions from low to high NIT risk-category identified individuals at-risk of incident fibrosis, while a low baseline NIT was associated with LSM normalization over time.

Disclosures: Jesse Pustjens: Nothing to Disclose, Katrine Bech: Nothing to Disclose, Guillem Pera: Nothing to Disclose, Laurens van Kleef: Nothing to Disclose, Helle Schnefeld: Nothing to Disclose, Robert Knegt: Nothing to Disclose, Peter Andersen: Nothing to Disclose, Johanne Hansen: Nothing to Disclose, Llorenç Caballeria: Nothing to Disclose, Carla Chacon: Nothing to Disclose, Pere Torán: Nothing to Disclose, Sarwa Darwish Murad: Nothing to Disclose, Harry Janssen: Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Academic Medical Education: Consultant, H.C. Wainwright & Co: Consultant, Aleksander Krag: Novo Nordisk: Advisor, Boehringer Ingelheim: Advisor, Norgine: Speaking and Teaching, Siemens: Independent Contractor, Nordic Bioscience: Speaking and Teaching, GSK: Advisor, Anita Arslanow: Nothing to Disclose, Isabel Graupera: Nothing to Disclose, Pere Ginés: Gilead & Grifols: Grant/Research Support, SeaBeLife, Merck, Sharp and Dohme (MSD), Ocelot Bio, Roche Diagnostics Intern, Boehringer Ingelheim: Advisor, Gilead, RallyBio, Behring: Advisor, Pfizer: Speaking and Teaching, Astra Zeneca: Advisor, Maja Thiele: Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, GSK: Advisor, GSK: Advisor, GSK: Advisor, Novo Nordisk: Speaking and Teaching, GSK: Grant/Research Support, Evido: Co-founder, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, GSK: Advisor, GSK: Advisor, GSK: Advisor, Novo Nordisk: Speaking and Teaching, GSK: Grant/Research Support, Evido: Co-founder, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and

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2503 | REAL-WORLD USE OF PETH IN A MASLD CLINIC

Timothy Daugherty[1] Erik Roepke[1] Dalton Caviness[1] Fernando Bril[1] Meagan Gray[1], [1]The University of Alabama at Birmingham

Background: In 2023, the term MetALD (metabolic dysfunction- and alcohol-associated liver disease) was introduced to identify patients with dual disease etiology. The diagnosis of these patients remains imprecise due to multiple factors, an important one being the reliance on self-reported alcohol consumption. Phosphatidylethanol (PEth) is a highly sensitive and specific serum biomarker to detect moderate to heavy alcohol consumption at levels 25 ng/mL. Therefore, we aimed to characterize alcohol consumption using PEth testing among patients referred to a MASLD clinic, and compare results with patient-reported alcohol intake. **Methods:** We retrospectively collected data on consecutive patients evaluated at the University of Alabama at Birmingham's MASLD clinic between February 2022 and January 2024. PEth testing was performed as part of standard clinical care on new and return patients. Patients were excluded if PEth testing was not performed or if decompensated cirrhosis was present. **Results:** We retrospectively collected data on consecutive patients evaluated at the University of Alabama at Birmingham's MASLD clinic between February 2022 and January 2024. PEth testing was performed as part of standard clinical care on new and return patients. Patients were excluded if PEth testing was not performed or if decompensated cirrhosis was present. **Conclusion:** A substantial proportion (10.9%) of patients referred to a tertiary MASLD clinic had evidence of significant alcohol use based on PEth testing, despite being presumed to have non-alcohol-associated liver disease. This suggests that alcohol use is frequently underestimated when relying solely on patient self-report. Objective alcohol biomarkers such as PEth may enhance diagnostic accuracy and facilitate more appropriate classification of liver disease, including the identification of patients who may meet criteria for MetALD.

Table 1. Clinical characteristics of patients with PETh-defined MetALD versus MASLD

	MASLD (n = 367)	MetALD (n = 45)	p-value
Age (years)	53±1	55±2	0.25
Male (%)	34	64	<0.001
Race			0.23
Non-Hispanic White (%)	78%	76%	
Non-Hispanic Black (%)	12%	20%	
Other	10%	4%	
Presence of diabetes (%)	42%	33%	0.28
BMI (kg/m^2)	34.7±0.3	32.5±1.1	0.035
HbA1C (%)	6.3±0.1	5.9±0.1	0.087
AST (U/L)	35±1	50±6	<0.001
ALT (U/L)	47±2	56±6	0.103
GGT (U/L)	57±4	188±44	<0.001
Triglycerides (mg/dL)	170±6	220±47	0.035
HDL-C (mg/dL)	44±1	55±4	<0.001
LDL-C (mg/dL)	111±2	118±7	0.32
FIB-4	1.43±0.07	1.72±0.19	0.158

Disclosures: Timothy Daugherty: Nothing to Disclose, Erik Roepke: Nothing to Disclose, Dalton Caviness: Nothing to Disclose, Fernando Bril: NovoNordisk: Consultant, NovoNordisk: Speaking and Teaching, Boehringer Ingelheim: Speaking and Teaching, Boehringer Ingelheim: Consultant, Madrigal: Consultant, Meagan Gray: NovoNordisk: Consultant, Madrigal Pharmaceuticals: Consultant, Intercept Pharmaceuticals: Consultant

2504 | NATIONWIDE ASSESSMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) PREVALENCE IN SAUDI ARABIA: INSIGHTS FROM THE GENESIS POPULATION-BASED COHORT STUDY

Saleh Alqahtani[1] Faisal Sanai[2] Haifa Alotaibi[3] Shadan AlMuhaidib[1] Duna Barakeh[1] Faisal Abaalkhail[1] Saleh Alessy[1] Waleed Alomaim[1] Samar Alqussayer[3] Ahmad Alshehri[4] Abdulraheem Bayameen[5] Basmah Khoja[1] Tagreed Mazi[6] Hani Tamim[7] Habeeb Razack[6] Mohammed Alghamdi[4] Mariam Seria[4] Fahad Alharbi[8] Saad Alghamdi[1] Bandar Aljudaibi[1] Waleed Al-Hamoudi[1] Waleed Alhazzani[3], [1]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [2]King Abdulaziz Medical City, KAIMRC, Jeddah, Saudi Arabia, [3]Ministry of Defense Health Services, Riyadh, Saudi Arabia, [4]King Fahad Military Medical Complex, Dhahran, Saudi Arabia, [5]King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia, [6]King Saud University, Riyadh, Saudi Arabia, [7]Alfaisal University, Riyadh, Saudi Arabia, [8]Prince Sultan Military Medical City, Riyadh, Saudi Arabia

Background: MASLD is a common global cause of chronic liver disease. It is closely associated with obesity and type 2 diabetes (T2D), both of which are

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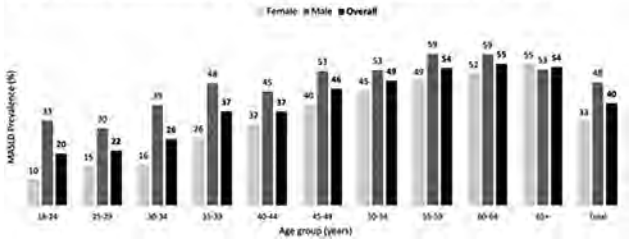
rising rapidly in Saudi Arabia; yet national MASLD data remain limited. To address this gap, we aimed to estimate MASLD prevalence among Saudi adults in the first large-scale, population-based study using clinical, biochemical, and imaging data. **Methods:** GENESIS is a prospective, population-based cohort study assessing MASLD prevalence and severity. Adults with no history of liver disease, except for MASLD, were recruited between March 2024 and April 2025 from primary healthcare centers in three populous regions. Clinical assessments, blood tests, and liver elastography (FibroScan®) were performed. MASLD was defined as a controlled attenuation parameter (CAP) $\geq$268 dB/m and $\geq$1 cardiometabolic risk factor (CMRF) (e.g., BMI $\geq$25 kg/m², elevated HbA1c, hypertension, or dyslipidemia). Alternative definitions (CAP $\geq$220 dB/m; MASLD liver fat score [MASLD-LFS]) were used in sensitivity analyses. Significant fibrosis (F2–F4) was defined as liver stiffness $>$7.0 kPa. **Results:** Of the 2,073 participants, MASLD was found in 829 (40.0%; female: 32.9%, male: 48.2%), with prevalence increasing with age and consistently higher in males than females (Figure 1). Hepatic steatosis was present in 70.2%, with 22.5% showing severe steatosis (CAP $\geq$300 dB/m). Prevalence using CAP $\geq$220 dB/m and MASLD-LFS was 68.1% and 62.2%, respectively. Significant fibrosis was observed in 3.1%. The proportion of males was higher among those with MASLD (55.9% vs. 40.0%, $p<0.001$); they were older (48.0 vs. 41.6 years, $p<0.001$), and fewer had higher education (39.9% vs. 54.3%, $p<0.001$). No significant differences were seen in smoking or coffee intake. Participants with MASLD had higher BMI (31.6 vs. 27.3 kg/m²), waist-to-hip ratio (0.91 vs. 0.87), and more comorbidities (T2D: 37.8% vs. 16.2%; hypertension: 26.5% vs. 12.5%; dyslipidemia: 39.1% vs. 24.0%) (all $p<0.001$). Despite similar liver enzyme levels, participants with MASLD had higher insulin (14.2 vs. 8.8 μU/mL) and CRP (3.2 vs. 2.2 mg/L), and lower HDL cholesterol (1.2 vs. 1.4 mmol/L) (all $p<0.001$). **Conclusion:** Screening a segment of the general Saudi adult population revealed that MASLD was present in 4 out of 10 participants, with steatosis in 70%. Participants with MASLD were more often male, older, and more likely to have CMRFs. These concerning trends, highlighted by this first-of-its-kind national study, support the need for targeted public health strategies in Saudi Arabia.

Figure 1. MASLD prevalence by age group and gender in Saudi Arabia (N = 2,073).



Disclosures: Saleh Alqahtani: Nothing to Disclose, Faisal Sanai: Nothing to Disclose, Haifa Alotaibi: Nothing to Disclose, Shadan AlMuhaidib: Nothing to Disclose, Duna Barakeh: Nothing to Disclose, Faisal Abaalkhail: Nothing to Disclose, Saleh Alessy: Nothing to Disclose, Waleed Alomaim: Nothing to Disclose, Samar Alqussayer: Nothing to Disclose, Ahmad Alshehri: Nothing to Disclose, Abdulraheem Bayameen: Nothing to Disclose, Basmah Khoja: Nothing to Disclose, Tagreed Mazi: Nothing to Disclose, Hani Tamim: Nothing to Disclose, Habeeb Razack: Nothing to Disclose, Mohammed Alghamdi: Nothing to Disclose, Mariam Seria: Nothing to Disclose, Fahad Alharbi: Nothing to Disclose, Saad Alghamdi: Nothing to Disclose, Bandar Aljudaibi: Nothing to Disclose, Waleed Al-Hamoudi: Nothing to Disclose, Waleed Alhazzani: Nothing to Disclose

2505 | CORRECTED T1 VALUE IN LIVER MRI IS ASSOCIATED WITH ALL-CAUSE, CARDIOVASCULAR-RELATED MORTALITY AND LIVER-RELATED OUTCOME WITH LOWER CUT-OFF VALUE OF 700MS

Ju Dong Yang[1] Min-Sun Kwak[2] Shelly Lu[1] Abdelrahman Attia[1] Hyunseok Kim[3] Mohammad Saeid Rezaee-Zavareh[4] Yufeng Wang[1] Lixia Wang[1] Walid Ayoub[1] Alexander Kuo[1] Hirsh Trivedi[1] Aarshi Vipani[1] Yun Wang[1] Martin Paul[1] Stephen Pandol[1] Debiao Li[1], [1]Cedars-Sinai Medical Center, [2]Seoul National University Hospital, [3]Cedars Sinai Medical Center, [4]Middle East Liver Diseases (MELD) center, Tehran, Iran

Background: Liver MRI-based corrected T1 (cT1) is an emerging non-invasive biomarker of hepatic fibro-inflammation. A threshold of 800ms has been associated with at-risk metabolic dysfunction-associated steatohepatitis and adverse outcomes; however, only ~5% of individuals exceed this level, limiting broader applicability. The prognostic significance of lower cT1 values is unclear. This study aimed to investigate the relationship between cT1 values and all-cause, cause-specific mortality, and liver-related outcomes in UK biobank cohort. **Methods:** Participants with MRI-derived cT1 were included. Cut-off values for outcome associations were determined based on P-spline curve taking into consideration on Harrell's C index. Participants were stratified by cT1 $<$700 vs. $\geq$700ms and $<$800 vs. $\geq$800ms. Outcomes included all-cause, cardiovascular, and cancer mortality, and liver-related events (cirrhosis, liver transplant, hepatocellular carcinoma, or liver-related death). Cox proportional hazard models were adjusted for age, sex, cardiometabolic risk factors, smoking, and alcohol. **Results:** Among 33,988 participants, 45% had cT1 $\geq$700ms. Over a median

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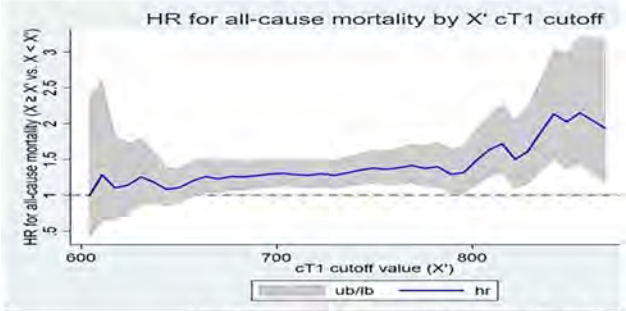
follow-up of 5.3 years, those with cT1 ≥700ms had increased risks of all-cause mortality (adjusted hazard ratio [95% CI], 1.25 [1.08–1.45]), cardiovascular mortality (1.52 [1.08–2.13]), and liver-related events (2.28 [1.25–4.13]) vs. <700ms. Effect modification for all-cause mortality was noted by alcohol and smoking; increased mortality risk was confined to non-drinkers (1.97 [1.31-2.96] vs. 1.16 (0.99-1.36) in drinkers, *P* for interaction <0.01) or ever-smokers (1.42 [1.14-1.76] vs. 1.11 (0.90-1.36) in never-smokers, *P* for interaction < 0.05). cT1 ≥800ms was associated with higher all-cause mortality (1.40 [1.08–1.81]) and liver-related events (3.01 [1.56–5.83]) <800ms. Again, risk was elevated in non-drinkers (2.30 [1.49–3.55] vs. 1.12 [0.81–1.55] in drinkers; P for interaction <0.01). For cardiovascular mortality, significant association was observed only in females (4.99 [2.07–12.01] vs. 1.03 [0.53–1.99] in males; *P* for interaction = 0.01). **Conclusion:** Elevated liver cT1 values, even below the conventional high-risk threshold of 800ms, were independently associated with increased risks of mortality and liver-related outcomes. These associations were influenced by modifiable lifestyle factors. Broader application of cT1 thresholds may improve risk stratification and early identification of high-risk individuals.

Figure 1. P-spline curve for all-cause mortality and multivariate analysis for all-cause mortality, cause-specific mortality and liver-related outcomes in participants, according to different cT1 cut-off values, after adjusting for age, sex, cardiometabolic risk factors, smoking and alcohol.



	cT1≥700ms vs. cT1 <700ms	cT1≥800ms vs. cT1 <800ms
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
All-cause mortality	**1.25 (1.08-1.45)**	**1.40 (1.08-1.81)**
Cardiovascular mortality	**1.52 (1.08-2.13)**	1.55 (0.93-2.61)
Cancer mortality	1.22 (1.00-1.48)	1.33 (0.92-1.91)
Liver-related outcome*	**2.28 (1.25-4.13)**	**3.01 (1.56-5.83)**

Disclosures: Ju Dong Yang: Exact Sciences: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Exelixis: Consultant, Fujifilm Medical Sciences: Consultant, Min-Sun Kwak: Nothing to Disclose, Shelly Lu: Nothing to Disclose, Abdelrahman Attia: Nothing to Disclose, Hyunseok Kim: Nothing to Disclose, Mohammad Saeid Rezaee-Zavareh: Nothing to Disclose, Yufeng Wang: Nothing to Disclose, Lixia Wang: Nothing to Disclose, Walid Ayoub: Intercept: Speaking and Teaching, Mirum: Grant/Research Support, GSK: Grant/Research Support, Madrigal: Grant/Research Support, Cymabay: Consultant, Ipsen: Grant/Research Support, Zydus: Grant/Research Support, Gilead: Grant Research Support, Alexander Kuo: Nothing to Disclose, Hirsh Trivedi: Nothing to Disclose, Aarshi Vipani: Nothing to Disclose, Yun Wang: Nothing to Disclose, Martin Paul: Nothing to Disclose, Stephen Pandol: Nothing to Disclose, Debiao Li: Nothing to Disclose

2506 | FREQUENCY AND SIGNIFICANCE OF VARIANTS IN LYSOSOMAL ACID LIPASE (LAL) GENE IN A LARGE COHORT OF INDIVIDUALS WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Background: Lysosomal acid lipase deficiency (LAL-D) is as a rare autosomal recessive disorder caused by mutations in the *LAL* gene. LAL-D is a rare cause of steatotic liver disease but the frequency of LAL-D as a cause for MASLD or its severity is not well understood. We examined the prevalence of *LAL* genetic variants in a large cohort of patients with well-characterized MASLD and their relationship to histological severity. **Methods:** Children and adults with biopsy-proven MASLD enrolled into Non-Alcoholic Steatohepatitis Research Network studies were analyzed. Advanced fibrosis defined as fibrosis stage ≥ 3 and metabolic dysfunction-associated steatohepatitis (MASH) defined as NAFLD Activity Score ≥ 4. From the published literature, we curated a list of rare pathogenic or likely pathogenic variants in *LAL* gene, and subsequently searched for their presence in the whole exome sequencing (WES) and GWAS data of the NASH CRN cohort. WES and GWAS were performed by the Regeneron Genetics Center. Individuals carrying one or more of the *LAL* variants were defined as *LAL* carriers. For each *LAL* carrier, we identified ≥ 1control without *LAL* variants matched for age, sex, and 3-SNP candidate gene score (CGS). CGS was calculated by adding the number of risk alleles in *PNPLA3* (rs738409), *HSD17B13* ((rs72613567), and *TM6SF2* (rs58542926). **Results:** Our study cohort (N = 3,358) consisted of 2,553

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non-Hispanic White and 961 Hispanic indviduals. The following seven *LAL* variants were present in the study cohort: rs143793106, rs201242614, rs756396844, rs116928232, rs147426329, rs746967258, and rs377251678. At least 1of the *LAL* variants was present in 22 individuals (22 carriers, 0.65%). 18 were adults and 4 children. The prevalence of MASH and advanced fibrosis in *LAL* carriers was 64% and 23%, respectively. There were no significant differences in anthropometry, co-morbidities, liver biochemistries, or lipid profile between 2 groups (Table). Grades of steatosis, portal and lobular inflammation, and ballooning, fibrosis stage, and proportion of advanced fibrosis and MASH were comparable between 2 groups (Table). No carriers showed histological changes of LAL deficiency. **Conclusion:** The frequency of pathogenic or likely pathogenic *LAL* variants in MASLD is less than 1% and they were present in both children and adults. Presence of LAL variants was not associated with biochemical or histological severity in MASLD. LAL carriers showed no evidence of LAL deficiency on histology.

Table: Baselines charactertistic between children and adults with MASLD without and with *LAL* genetic variant carriage

Variable	*LAL* Carriers (N=22)	Matched controls (N=82)	Non-*LAL* carriers (N=3,336)	P value for *LAL* carries vs. matched controls
Age at enrollment, mean (SD)	43.9 (17.4)	44.2 (17.7)	39.9(19.8)	0.93
Male (%)	46%	48%	48%	1.0
Self-reporting White (%)	64%	79%	76%	0.16
Children (%)	18%	20%	28%	1
BMI (kg/m^2, mean±sd)	34.7 (8.6)	34 (6.3)	33.7(6.5)	0.73
Type2 Diabetes (%)	22.7%	34.1%	27.8%	0.44
Hyperlipidemia (%)	40.9%	50%	42.2%	0.48
CVD (%)	0%	3.7%	3.8%	1.0
ALT (U/L, mean±sd)	75.8 (44.6)	76.5 (53.1)	79(65.1)	0.95
AST (U/L, mean±sd)	48.4 (22.3)	49.9 (26.8)	53.6(38.8)	0.79
AlkPhos (U/L, mean±sd)	95.5 (61)	117.8 (73.5)	124.2(88.2)	0.15
HDL (mg/dL, mean±sd)	43.1 (13.3)	42.3 (11.7)	42.8(11.9)	0.79
LDL (mg/dL, mean±sd)	104.9 (42.5)	112.2 (39.8)	108.3(35.9)	0.48
Total Cholesterol (mg/dL, mean±sd)	181 (54.5)	188.6 (46.8)	182.5(43.4)	0.55
Serum Triglyceride (mg/dL, mean±sd))	178.4 (98.1)	173.6 (109.1)	167.7(129.7)	0.84
Steatosis grade (mean±sd)	1.6 (1.1)	1.6 (0.9)	1.9(0.9)	0.96
Lobular Inflammation (mean±sd)	1.5 (0.5)	1.6 (0.6)	1.5(0.7)	0.24
Portal Inflammation (mean±sd)	1 (0.4)	1.1 (0.5)	1.1 (0.6)	0.051
Ballooning (mean±sd)	0.9 (0.9)	0.9 (0.9)	0.8 (0.8)	0.9
Fibrosis stage (mean±sd)	1.4 (1.3)	1.5 (1.2)	1.5(1.3)	0.75
NAS (mean±sd)	4 (1.7)	4.1 (1.7)	4.2(1.7)	0.64
MASH	64%	59%	66%	0.80
Advanced Fibrosis(%)	23%	24%	25%	1.0

Disclosures: Chaowapong Jarasvaraparn: Nothing to Disclose, Marco Antonio Abreu: Nothing to Disclose, Tae-Hwi Schwantes-An: Nothing to Disclose, David Kleiner: Nothing to Disclose, Miriam Vos: Boehringer Ingelheim: Consultant, Madrigal: Consultant, Eli Lilly: Consultant, Inventiva: Consultant, Alberio: Consultant, Target Real World Evidence: Advisor, Thiogenesis: Advisor, Tern Pharmaceuticals: Stock - publicly traded company, Dexcom: Grant/Research Support, Sonic Incytes Medical Corp: Grant/Research Support, Prosciento: Advisor, Katherine Yates: Nothing to Disclose, Callie Zabarenko: Nothing to Disclose, Jingyi Tan: Nothing to Disclose, Xiuqing Guo: Nothing to Disclose, Jerome I Rotter: Nothing to Disclose, Jean Molleston: Gillead: Grant/Research Support, Albireo: Grant/Research Support, Abbvie: Grant/Research Support, Mirum/Shire: Grant/Research Support, Naga Chalasani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose

2507 | METABOLIC DYSFUNCTION IS ASSOCIATED WITH THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA, HEPATIC DECOMPENSATION, AND REDUCED SURVIVAL, INDEPENDENT OF LIVER DISEASE ETIOLOGY

Ming-Lun Yeh[1] Chung-Feng Huang[2] Jee-Fu Huang[2] Chia-Yen Dai[2] Wan Long Chuang[2] Ming-Lung Yu[3], [1]National Sun Yat-sen University, [2]Kaohsiung Medical University, [3]Kaohsiung Medical University/ Kaohsiung Medical University Hospital

Background: The importance of cardiometabolic risk factors (CMRFs) in influencing disease severity and long-term outcomes has been well established in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). However, the impact of CMRFs in patients with other etiologies of liver disease remains underexplored. This study aimed to investigate the influence of CMRFs on patients across different liver disease etiologies. **Methods:** We analyzed data from a nationwide cohort in Taiwan. Subjects with available assessments for liver fibrosis and CMRFs were included. SLD was diagnosed via abdominal ultrasound or blood-based indices, including the Hepatic Steatosis Index and Fatty Liver Index. Alcohol consumption was categorized as moderate or heavy according to the diagnostic criteria for alcoholic liver disease (ALD) and MetALD. We linked participants data with the national health insurance database, and cancer/death registry database of Taiwan for long-term outcomes. The primary outcome was the associations between metabolic dysfunction and long-term risks of hepatocellular carcinoma (HCC), hepatic decompensation, and survival. **Results:** A total of 612,051 subjects (mean age 39.9 years; 47.7% male) were included in the analysis. Among them, 13.3%, 1.8%, 3.1%, and 2.0% had hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, moderate alcohol consumption, and heavy alcohol consumption, respectively. SLD was diagnosed in 33.1% of subjects, while advanced liver fibrosis (FIB-4 > 2.67) was present in 1.3%. At least one CMRF was identified in 442,917 subjects (72.4%), with overweight/obesity being the most prevalent (47.5%), followed by pre-diabetes/diabetes (32.9%).

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Subjects with CMRFs had significantly higher long-term risks of HCC, hepatic decompensation, and all-cause, acute myocardial infarction (AMI), and stroke-related mortality. After adjusting for factors including SLD and liver disease etiologies, the presence of CMRFs remained significantly associated with these outcomes. In stratified analyses of subjects with HBV, HCV, moderate, and heavy alcohol consumption, CMRFs were significantly associated with increased risks of HCC, all-cause mortality, AMI, and stroke-related mortality. Notably, the association between CMRFs and hepatic decompensation was observed only in HBV-infected subjects. Furthermore, the long-term risks of HCC, hepatic decompensation, all-cause mortality, AMI, and stroke-related mortality increased progressively with the number of CMRFs present. **Conclusion:** The presence and cumulative number of CMRFs were associated with poorer long-term outcomes, regardless of liver disease etiology.

Disclosures: Ming-Lun Yeh: Nothing to Disclose, Chung-Feng Huang: Nothing to Disclose, Jee-Fu Huang: Roche: Consultant, Gilead: Consultant, Sysmex: Consultant, Aligos: Consultant, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, Merck: Speaking and Teaching, Sysmex: Speaking and Teaching, Novo Nordisk: Consultant, Berlinger-Ingelheim: Consultant, Chia-Yen Dai: Nothing to Disclose, Wan Long Chuang: Nothing to Disclose, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching

2508 | DIFFERENT CARDIOVASCULAR RISK IDENTIFIED BY THE KASL/EASL TWO-STEP PATHWAY ACCORDING TO DIABETES STATUS IN INDIVIDUALS WITH MASLD

Jaehong Jeong[1] Jung Pyo Hong[1] Jae Seung Lee[1] Mi Na Kim[1] Beom Kyung Kim[1] Do Young Kim[1] Sang Hoon Ahn[1] Hye Won Lee[1] Seung Up Kim[1], [1]Yonsei University College of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is an increasingly common risk factor for atherosclerotic cardiovascular disease (ASCVD). The Korean and European Associations for the Study of the Liver (KASL and EASL) include a two-step, non-invasive pathway in their guidelines for assessing advanced liver fibrosis in MASLD, based on the Fibrosis-4 index (FIB-4) and vibration-controlled transient elastography (VCTE). Given the overlap in risk factors between MASLD and ASCVD, we evaluated whether this pathway can also stratify ASCVD risk in MASLD, and whether stratification patterns differ according to diabetes mellitus (DM) status. **Methods:** Among 12,738 health check-up participants from 2012 to 2020, 6,519 individuals with MASLD were retrospectively analyzed. Participants were stratified into four risk groups (low, intermediate-low, intermediate-high, and high) based on the KASL/EASL pathway. Due to relatively small sample sizes in the intermediate-high-risk group and high-risk group (n = 35 and 114, respectively), these were combined into a single intermediate-high– and high-risk group to ensure statistical robustness. ASCVD risk was assessed using the 2025 ACC/AHA Pooled Cohort Equations. Group comparisons were performed using two-way ANOVA. **Results:** Among individuals with MASLD, the proportion of low-risk subjects was significantly higher in the non-DM group (n = 4,366 [74.1%] in low-risk; n = 1,419 [24.1%] in intermediate-low-risk; n = 107 [1.8%] in intermediate-high– and high-risk), whereas that of high-risk subjects was significantly higher in the DM group (n = 392 [62.5%] in low-risk; n = 193 [30.8%] in intermediate-low-risk; n = 42 [6.7%] in intermediate-high– and high-risk) ($P < 0.001$). ASCVD risk was consistently higher in diabetic than in non-diabetic individuals across all liver fibrosis risk groups (mean 14.5 vs. 4.3 in low-risk groups, mean 15.0 vs. 6.8 in intermediate-low-risk groups, mean 20.3 vs. 14.7 in intermediate-high– and high-risk groups), with a statistically significant interaction between liver fibrosis risk and diabetes status ($P < 0.001$). The proportion of individuals with high-risk ASCVD (≥ 20%) increased with fibrosis risk among non-diabetic individuals (2.9%, 4.7%, and 28.0%). In diabetic individuals, the highest proportion was observed in the intermediate-high– and high-risk group (38.1%), although the trend across lower-risk groups was non-linear. **Conclusion:** The KASL/EASL liver fibrosis risk stratification pathway correlates with ASCVD risk in individuals with MASLD, particularly among those without diabetes. However, in diabetic patients, ASCVD risk remained elevated regardless of fibrosis risk category, suggesting that additional risk assessment tools may be necessary for more accurate cardiovascular risk stratification in this population.

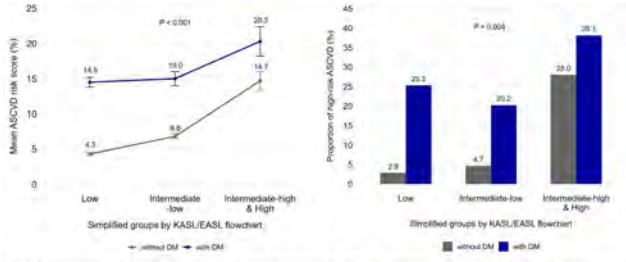

Figure 1. Comparison of ASCVD risk scores by diabetes status and KASL/EASL flowchart-based liver fibrosis risk groups. (A) Mean ASCVD risk scores. (B) Proportion of high-risk ASCVD (≥ 20%). ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus; KASL, the Korean Association for the study of the Liver; EASL, the European Association for the Study of the Liver.

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2509 | HEPATIC FIBROSIS IS ASSOCIATED WITH DIASTOLIC DYSFUNCTION IN THE ABSENCE OF OVERT HEART FAILURE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Rabab Ali[1] Alejandra Paredes-Marin[1] Vikram Sivakumar[1] Kim Le[1] Parth Trivedi[1] Maryfe Coronel Novoa[1] Julia Napoli[1] Asher Leviton[1] Xiaotao Zhang[1] Anuradha Lala[1] Meena Bansal[1], [1]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: The independent association of metabolic dysfunction-associated steatotic liver disease (MASLD) and heart failure with preserved ejection fraction (HFpEF) due to perturbed metabolic pathophysiology is often underrecognized. A hallmark finding in HFpEF is left ventricular diastolic dysfunction (LVDD), yet how subclinical echocardiographic (TTE) markers of LVDD track with hepatic fibrosis in MASLD remains understudied. **Methods:** Ambulatory MASLD patients enrolled in a longitudinal registry between 2021-2024 with ejection fraction (EF) > 40% on TTE and no prior HFpEF diagnosis were included. TTE parameters included EF and strain as markers of systolic function, while left atrial volume index (LAVi), wall thickness, E/A ratio, deceleration time, and E/e' represented LVDD. Relevant laboratory values and non-invasive fibrosis scores (FIB4, SAFE, NFS) were assessed. Fibrosis and steatosis were assessed using liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) from vibration-controlled transient elastography (VCTE). Spearman R and ANOVA were performed using fibrosis (LSM < 8 kPa or F0-1, n = 117 vs. LSM 8-12 kPa or F2-3, n = 33, vs. LSM > 12 kPa or F4, n = 32) and steatosis (CAP < 288 dB/m, n = 77 vs. > 288, n = 102). **Results:** 189 MASLD patients (60% female, mean age 57 years, mean BMI 32.2 kg/m^2) had a TTE and VCTE. There was no difference in LV systolic function when stratified by fibrosis or steatosis. Two LVDD parameters (LAVi and E/e') were elevated in F4 fibrosis (LSM p = 0.003, p = 0.035); but not in steatosis (CAP p = 0.63, p = 0.728). Association of LAVi and E/e' with F4 fibrosis remained significant when adjusted for age, gender, smoking, DM, HTN, CKD, BMI, lipid profile, CAP, and cardiac medications (Table 1). LAVi and E/e' were inversely associated with platelets and albumin; positively with FIB4, SAFE, NFS; and only LAVi positively with IgG and INR (Table 1). Change in LAVi with F4 fibrosis was only significant in the presence of obesity, DM, or HTN (p = 0.039, p = 0.014, p = 0.017). **Conclusion:** LVDD markers LAVi and E/e' are linked to advanced liver fibrosis independent of demographic and cardiometabolic covariates. They also correlate with serological markers of liver injury, hepatic dysfunction, and non-invasive fibrosis scores. These findings highlight a link between subclinical markers of HFpEF amongst patients with MASLD and fibrosis, potentially suggesting a lower threshold for HFpEF screening to mitigate cardiac-related adverse events in MASLD.

Multivariable Linear Regression Analysis

	LAVi		E/e'	
Coefficients	Estimate	Pr(>|t|)	Estimate	Pr(>|t|)
(Intercept)	7.93	0.33630	10.52	0.00027
F2-F3 Fibrosis (kPa)	2.45	0.19730	0.54	0.37480
F4 Fibrosis (kPa)	**4.90**	**0.02610**	**2.14**	**0.00240**
CAP (dB/m)	0.01	0.47780	0.00	0.75442
Age (years)	0.11	0.11340	0.03	0.17337
Gender (male)	0.20	0.90570	-0.76	0.17424
Former Smoker	-2.51	0.36840	-1.26	0.20135
Never Smoker	-0.02	0.99440	-1.74	0.07297
BMI (kg/m^2)	0.01	0.93130	-0.03	0.57183
DM (yes)	-0.77	0.69220	-1.12	0.08693
HTN (yes)	-1.22	0.51980	1.14	0.06243
CKD (yes)	-2.27	0.43390	1.28	0.16369
HDL (mg/dL)	0.02	0.75710	0.00	0.97187
LDL (mg/dL)	0.03	0.12070	-0.01	0.29504
TG (mg/dL)	0.00	0.74230	0.00	0.98633
Statin (yes)	0.84	0.60680	-1.47	0.00787
Mineralocorticoid RA (yes)	4.49	0.43420	1.41	0.45189
Metformin (yes)	0.83	0.65910	0.49	0.42308
GLP1 RA (yes)	-3.06	0.13470	1.35	0.04188
SGLT2i (yes)	-2.84	0.20120	-0.92	0.21279
ACEi/ARB (yes)	3.57	0.04510	0.21	0.71729
CSBB (yes)	1.61	0.41390	-0.16	0.80846
NSBB (yes)	4.74	0.08250	1.00	0.27961
CCB (yes)	1.04	0.57700	-0.20	0.73582

Spearman Correlation With Liver Disease Parameters

	LAVi		E/e'	
Variables	p-value	Spearman r	p-value	Spearman r
FIB4	**0.00471**	**0.23**	**0.00065**	**0.28**
SAFE	**0.00290**	**0.25**	**0.00116**	**0.27**
NFS	**0.00091**	**0.26**	**0.00052**	**0.27**
ALT (IU/L)	0.55398	-0.05	0.32398	-0.08
AST (IU/L)	0.71842	-0.03	0.77466	0.02
GGT (IU/L)	0.86617	0.02	0.18830	0.13
ALP (IU/L)	0.15430	0.11	0.10510	0.13
IgG (mg/dL)	**0.01095**	**0.33**	0.67086	0.06
Total Bilirubin (mg/dL)	0.38489	0.07	0.99325	0.00
Direct Bilirubin (mg/dL)	0.25725	0.09	0.16937	0.11
INR	**0.04234**	**0.16**	0.36928	0.07
Platelets (x10^9/L)	**0.00148**	**-0.25**	**0.00226**	**-0.25**
Albumin (g/dL)	**0.01300**	**-0.20**	**0.01889**	**-0.19**

Disclosures: Rabab Ali: Nothing to Disclose, Alejandra Paredes-Marin: Nothing to Disclose, Vikram Sivakumar: Nothing to Disclose, Kim Le: Nothing to Disclose, Parth Trivedi: Nothing to Disclose, Maryfe Coronel Novoa: Nothing to Disclose, Julia Napoli: Nothing to Disclose, Asher Leviton: Nothing to Disclose, Xiaotao Zhang: Nothing to Disclose, Anuradha Lala: Nothing to Disclose, Meena Bansal: Madrigal: Advisor, Fibronostics: Advisor, NOVO Nordisk: Advisor, GSK: Advisor, Merck: Advisor, Boeheringer-Ingelheim: Advisor, Boston Pharma: Advisor, The Kinetix Group: Advisor

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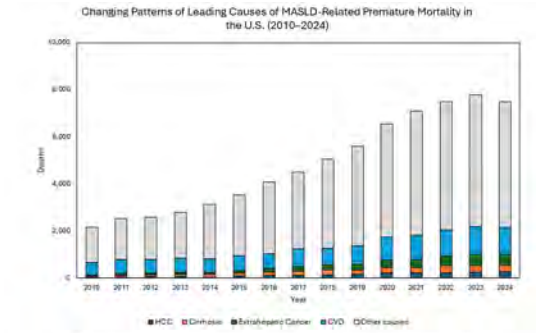
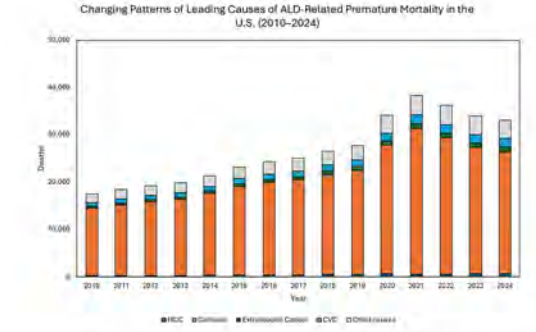
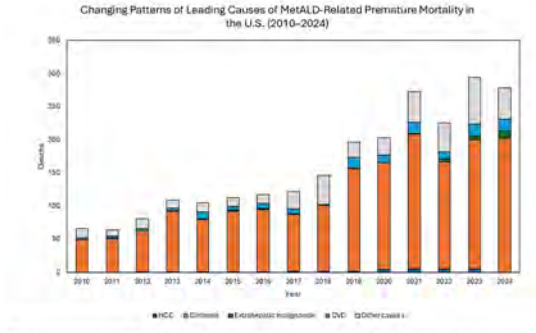
2510 | TRENDS IN PREMATURE MORTALITY AND LEADING CAUSES OF DEATH IN THE SPECTRUM OF STEATOTIC LIVER DISEASE (SLD) INCLUDING METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD), ALCOHOL-RELATED LIVER DISEASE (ALD), AND METABOLIC DYSFUNCTION AND ALCOHOL-RELATED LIVER DISEASE (METALD): A U.S. NATIONWIDE ANALYSIS (2010-2024)

Dana Ivancovsky Wajcman[1] James Paik[2] Shira Zelber-Sagi[3] Linda Henry[1] Saleh Alqahtani[4] Zobair Younossi[1], [1]The Global NASH Council, [2]Beatty Liver and Obesity Research Center, [3]Tel-Aviv Sourasky Medical Center, [4]Liver, Digestive, and Lifestyle Health Research Section, and Organ Transplant Center of Excellenc

Background: MASLD and ALD are growing causes of liver mortality in the U.S. MetALD, an increasingly recognized subtype of SLD, may be difficult to distinguish from misclassified MASLD or ALD due to overlapping clinical and coding features. We aimed to examine trends in premature mortality and leading causes of death from MASLD, ALD, and misclassified MASLD, presumed to represent MetALD. **Methods:** A cross-sectional analysis was conducted utilizing U.S. National Vital Statistics System data (2010–2024) for decedents aged ≤75 (men) and ≤80 (women). Decedents were classified as: (1) MASLD (ICD-10: K75.8, K76.0) without concurrent liver diseases (e.g., ALD, viral, autoimmune, toxic) or alcohol use disorder (AUD); (2) ALD: ALD-related codes without other liver diseases; (3) Misclassified MASLD: MASLD codes co-occurring with AUD codes, presumed to represent MetALD. Leading causes of death were categorized as cirrhosis (K70, K74), hepatocellular carcinoma (HCC, C22.0), cardiovascular disease (CVD, I00–I78), and extrahepatic cancers (C00–C97, excluding C22.0). COVID-19 (U07.1) deaths were excluded. Trends in age-adjusted premature mortality rates and proportional causes of death were evaluated using annual percent change (APC) from Joinpoint regression. **Results:** During the study period, MASLD-related premature mortality rate tripled from 1.01 (n = 2,151) to 3.12 per 100,000 (n = 7,490; APC = 9.01%). ALD-related mortality rose from 8.20 (n = 17,541) to 13.79 (n = 33,112; APC = 4.46%). MetALD mortality increased from 0.03 (n = 66) to 0.12 (n = 278; APC = 10.87%). In MASLD, CVD remained the leading cause but declined (24.2% to 15.5%; APC = -3.54%), while deaths from HCC (1.63% to 3.47%; APC = 4.51%) and extrahepatic cancers (2.14% to 6.11%; APC = 8.30%) increased, and cirrhosis remained stable (2.32% to 3.93%; APC = 3.14%, p = 0.312). In ALD, cirrhosis remained the leading cause but declined modestly (81.4% to 78.0%; APC = -0.23%), while deaths from HCC (1.23% to 1.87%; APC = 1.84%), extrahepatic cancers (2.23% to 2.98%; APC = 1.43%), and CVD (4.64% to 5.65%; APC = 0.94%) increased (Figure). **Conclusion:** Premature mortality from MASLD increased more rapidly than ALD. While cirrhosis remained the leading cause in ALD, MASLD saw a shift from CVD to malignancies, including HCC and extrahepatic cancers. The rise in presumed MetALD mortality highlights challenges in applying updated diagnostic definitions and underscores the need for clearer classification and coding guidelines across the SLD spectrum.







The "Other causes" category includes all non-specified causes of death beyond hepatocellular carcinoma (HCC), cirrhosis, extrahepatic cancers, and cardiovascular disease (CVD).

Disclosures: Dana Ivancovsky Wajcman: Nothing to Disclose, James Paik: Nothing to Disclose, Shira Zelber-Sagi: Nothing to Disclose, Nothing to Disclose, Linda Henry: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant

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2511 | SEX DISPARITIES AND EPIDEMIOLOGY OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) GLOBALLY IN 2021 WITH FORECASTING TO 2050

Charles Levesley Xinrong Zhang[1] Scott Barnett[1] Linda Henry[1] Ramsey Cheung[1] Mindie Nguyen[1], [1]Stanford University Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is now the most common metabolic liver disease worldwide. Although its burden is rising globally, there remains a lack of literature investigating sex-specific trends in the disease. Understanding disparities in age-standardized prevalence, incidence, mortality and disability-adjusted life-year (DALY) rates, as well as forecasting future trends, is critical in shaping prevention and policy efforts. **Methods:** We analyzed MASLD-related age-standardized prevalence (ASP), incidence (ASIR), mortality (ASMR) and DALY rates from 1990 to 2021 using data from the Global Burden of Disease (GBD) 2021 database. Our analyses were stratified by sex, age, geographical region, country, and socio-demographic index (SDI). Joinpoint regression calculated annual percentage change (APC) values in each subgroup. Forecasts through 2050 were generated using Prophet, a time-series model suitable for long-term global health projections. To validate our findings, we performed sensitivity analyses using linear regression models. **Results:** From 1990 to 2021, ASP and ASIR increased more rapidly in females (APC +0.77%, +0.75%) than males (APC +0.65%, +0.70%), while ASMR and DALY rates rose more in males (APC +0.35%, +0.34%) than females (APC +0.07%, +0.05%). Across regions, the greatest increase in age-standardized prevalence (ASP) was observed in males from the Eastern Mediterranean (APC +0.72%) and females from the Western Pacific region (APC +0.80%). The Americas showed the steepest rise in age-standardized mortality rates (ASMR) for both sexes (APC +1.20% in males vs. +0.90% in females). For age-standardized incidence rates (ASIR), the highest APCs occurred among individuals in high SDI regions (APC +0.82% in males vs. +0.96% in females), as well as those aged less than or equal to 20 years (APC +0.92% in males vs. +1.02% in females). ASP and ASIR are projected to be highest by 2050 in the Eastern Mediterranean region, while ASMR and DALY rates are expected to increase most in the Americas overall and among males, however in the Eastern Mediterranean region for females. **Conclusion:** Our study demonstrates the growing burden of MASLD as prevalence and incidence rates rise globally from 1990 to 2021, with males demonstrating consistently higher prevalence and incidence rates compared to females. ASP of MASLD is estimated to increase to 19.03% in males and 17.64% in females by 2050. The Middle East and North Africa (MENA) region is particularly affected, demonstrating the highest ASP and ASIR, especially in countries such as Saudi Arabia and Egypt. Our findings highlight significant disparities in MASLD burden by sex and region, particularly in younger populations and areas with high MASLD burden due to increasing rates of metabolic diseases, including diabetes and obesity. Our study aims to inform effective global health strategies.

Disclosures: Charles Levesley: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Scott Barnett: Nothing to Disclose, Linda Henry: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

2512 | THE GENETIC ARCHITECTURE OF METABOLIC SYNDROME SUGGESTS COMMON UNDERLYING BIOLOGY AND GENETIC PREDISPOSITION WITH MASLD: INSIGHTS FROM ENHANCED POLYGENIC RISK SCORES

Carlos Pirola[1] Luis Diambra[2] Silvia Sookoian[1], [1]CONICET. CENITRES Maimónides University, [2]CONICET.

Background: Evidence indicates that the relationship between metabolic syndrome (MetS) and MASLD is bidirectional. MASLD can trigger MetS, while MetS can worsen MASLD or raise the risk of MASLD. MetS and MASLD share common lifestyle and environmental risk factors, creating a reciprocal causality between them. Nevertheless, the common genetic susceptibility of MASLD, the disease severity, and MetS is poorly understood. Enhanced polygenic risk scores (EPRSs) are powerful tools for assessing genetic predisposition to complex traits and clinical risks by integrating genetic data from the entire genome. Here, we used EPRSs linked to major MetS phenotypes to explore the mediation effects on MASLD and fibrosis. **Methods:** We used longitudinal data from the UK Biobank (application #485675), which included genetic and phenotypic information from 488,377 participants aged 40 to 69 years. MASLD and the disease severity (liver fibrosis) were identified using MRI-derived PDFF ($>5.5\%$) and iron corrected T1 (cT1) measurements (cutoff >800 ms), and ICD10 classifications. EPRS were generated using a Bayesian approach applied to meta-analysed summary statistics GWAS data, obtained from a combination of external and internal UK Biobank data. Explored EPRSs covered 148,835 participants of which 9520 have comprehensive

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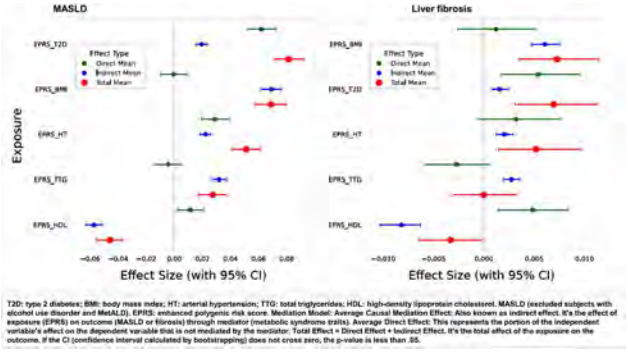
characterization of the liver phenotype: arterial hypertension (HT); type 2 diabetes (T2D); BMI; total triglycerides TTG) and high-density lipoprotein cholesterol (HDL-C). Causal mediation effects of EPRSs through corresponding phenotypes on MASLD and fibrosis, adjusted for age and sex, were examined using Statsmodels 0.14.4. **Results:** Mediation analysis suggests significant effects of EPRSs for traits of the MetS on MASLD and liver fibrosis (Figure). HT-EPRS has an indirect effect of 43.1% on MASLD and 39% on liver fibrosis; T2D-EPRS has an indirect effect of 24% on MASLD and 23% on fibrosis. HDL-EPRS directly affects MASLD and fibrosis, and protects indirectly through HDL-C. **Conclusion:** Consistent with the clinical and epidemiological evidence, our findings suggest a substantial degree of shared genetic risk between MASLD, the disease severity, and MetS. Furthermore, MetS-EPRSs may exhibit considerable pleiotropic effects. This underscores the potential for modulating the same pathways and targets as a viable therapeutic strategy when treating MASLD and traits of the MetS concurrently.



T2D: type 2 diabetes; BMI: body mass index; HT: arterial hypertension; TTG: total triglycerides; HDL: high-density lipoprotein cholesterol. MASLD (excluded subjects with alcohol use disorder and MetALD). EPRS: enhanced polygenic risk score. Mediation Model: Average Causal Mediation Effect: Also known as indirect effect. It's the effect of exposure (EPRS) on outcome (MASLD or fibrosis) through mediator (metabolic syndrome traits). Average Direct Effect: This represents the portion of the independent variable's effect on the dependent variable that is not mediated by the mediator. Total Effect = Direct Effect + Indirect Effect. It's the total effect of the exposure on the outcome. If the CI (confidence interval calculated by bootstrapping) does not cross zero, the p-value is less than .05.

Disclosures: Carlos Pirola: Nothing to Disclose, Luis Diambra: Nothing to Disclose, Silvia Sookoian: Nothing to Disclose

2513 | RATE OF INCREASE IN APOLIPOPROTEIN B (APOB) DURING EARLY ADULTHOOD AND PREVALENT MASLD IN MID-LIFE: THE CORONARY ARTERY RISK DEVELOPMENT IN YOUNG ADULTS (CARDIA) STUDY

Seong Park[1] Hongyan Ning[1] Dempsey Hughes[1] John Wilkins[1] SeJong Bae[2] Ankeet Bhatt[3] Lisa VanWagner[4], [1]Northwestern University Feinberg School of Medicine, [2]Augusta University, [3]Kaiser Permanente San Francisco Medical Center, [4]University of Texas Southwestern Medical Center

Background: Optimizing cardiometabolic health at an earlier age is associated with lower prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) in midlife. Higher rates of triglyceride (TG) increase in early adulthood are positively associated with prevalent MASLD in midlife. Apolipoprotein B (apoB) concentration reflects the total number of atherogenic lipoproteins and can vary substantially across a given TG and cholesterol concentration. To date, no studies have examined how differences in apoB progression throughout young adulthood are linked with prevalent MASLD in midlife. **Methods:** We used data from participants (20-32 years at Year 2, 1987-88) of the Coronary Artery Risk Development in Young Adults (CARDIA) study who had liver fat assessed by non-contrast computed tomography at Year 25 (Y25, 2010-11) and apoB measured at $\geq$ 1 exam at Year 2, 7, 15, 20 or 25 using nuclear magnetic resonance. MASLD was defined as liver attenuation of $<$ 51 Hounsfield units after exclusions for other causes of liver fat. Random-effects mixed linear regression modeling was used to estimate slope of apoB from Y2 to Y25. Participants were stratified into groups based on quartile of slope estimates for apoB from Y2 to Y25 (Figure). Logistic regression models were used to assess the odds of Y25 MASLD prevalence across apoB quartiles. **Results:** Of 2641 study participants, Y25 MASLD prevalence was 23.5% (n = 620). Average annual change in apoB from Y2 to Y25 for all participants ranged from 0.21 (-0.39-0.37) mg/dL/year in the stable increase group to 0.96 (0.76-2.28) mg/dL/year in the major increase group. Participants with major increase in apoB were more likely to be male (47.6% vs. 37.0%) and current smoker at Y25 (18.0% vs. 12.6%) compared to those with stable apoB increase. These individuals also had higher absolute apoB, low-density lipoprotein, and total cholesterol levels at Y2 and Y25 as well as prevalent MASLD at Y25 (33.0% vs. 18.2%), compared to those with stable increase in apoB. The major increase group had the highest odds of Y25 MASLD prevalence when compared to the stable increase group (Figure). The odds of Y25 prevalent MASLD increased in those with moderate (aOR = 1.57, 95% CI: 1.03-2.40) and major (aOR = 2.45, 95% CI: 1.54-3.92) apoB increases throughout early adulthood, compared to the stable (reference) increase group. The associations between moderate and major apoB increase with MASLD remained strong even after adjusting for the baseline apoB value, suggesting that rapid increases in apoB blood levels are associated with higher risk of MASLD in midlife even if the absolute apoB level is low at younger age. **Conclusion:** Rates of increase in apoB ($>$ 0.5mg/dL/year) during early adulthood are positively associated

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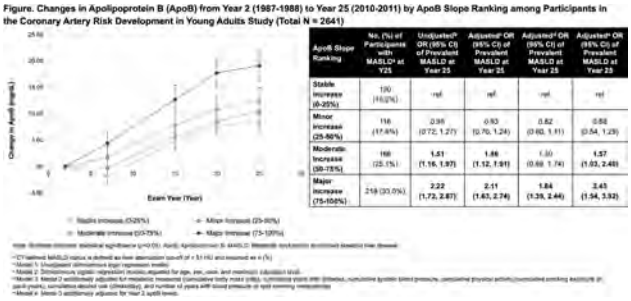
with higher odds of MASLD in midlife. Monitoring apoB levels throughout early adulthood may aid in detection of individuals at risk of developing MASLD in midlife and bolster early prevention strategies for MASLD.



Disclosures: Seong Park: Nothing to Disclose, Hongyan Ning: Nothing to Disclose, Dempsey Hughes: Nothing to Disclose, John Wilkins: Nothing to Disclose, SeJong Bae: Nothing to Disclose, Ankeet Bhatt: Nothing to Disclose, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support

2514 | WOMEN'S HEALTH AND MASLD: THE CRITICAL ROLE OF HDL CHOLESTEROL IN BOTH OBESE AND NON-OBESE WOMEN

Tsubasa Tsutsumi[1] Takumi Kawaguchi[2] Mary Rinella[3] Michael Charlton[4] Yoshihiro Kamada[5] Hideki Fujii[6] Yuichiro Suzuki[7] Koji Sawada[8] Miwa Tatsuta[9] Tatsuji Maeshiro[10] Hiroshi Tobita[11] Takemi Akahane[12] Chitomi Hasebe[13] Miwa Kawanaka[14] Takaomi Kessoku[15] Yuichiro Eguchi[16] Hayashi Syokita[17] Tomoari Kamada[18] Hiroshi Sakugawa[19] Asahiro Morishita[20] Tsutomu Masaki[20] Takumi Ohmura[21] Toshio Watanabe[5] Yoshioki Yoda[22] Nobuyuki Enomoto[23] Masafumi Ono[20] Kanako Fuyama[24] Kazufumi Okada[24] Naoki Nishimoto[24] Yoichi Ito[24] Hirokazu Takahashi[25] Yoshio Sumida[26] Hitoshi Yoshiji[27] Atsushi Nakajima[28],
[1]University of Chicago, [2]Kurume University School of Medicine, [3]The University of Chicago, [4]Madrigal Pharmaceuticals, [5]Osaka University Graduate School of Medicine, [6]Osaka Metropolitan University, [7]University of Yamanashi, [8]Asahikawa Medical University, [9]KKR Takamatsu Hospital, [10]University of the Ryukyus Hospital, [11]Shimane University Hospital, [12]Uda City Hospital, [13]Japanese Red Cross Asahikawa Hospital, [14]Okayama University, [15]International University Health and Welfare Narita Hospital, [16]Loco Medical General Institute, [17]Northern OKINAWA Medical Center, [18]Kawasaki Medical School, [19]Heartlife Hospital, [20]Kagawa University, [21]Asahikawa-Kosei General Hospital, [22]JA Yamanashi Koseiren Health Care Center, [23]University of Yamanahsi, [24]Hokkaido University Hospital, [25]Saga University Hospital, [26]International University of Healthcare and Welfare, [27]Nara Medical University, [28]IUHW ATAMI HOSPITAL

Background: Women with metabolic-associated steatotic liver disease (MASLD) exhibit distinct clinical characteristics different from men. Postmenopausal women undergo a decline in estrogen secretion, which subsequently leads to a reduction in HDL cholesterol levels. This study aimed to investigate the impact of cardiometabolic risk factors (CMRFs), including low HDL cholesterol, on MASLD onset in individuals without pre-existing steatotic liver disease (SLD). **Methods:** This is a registry-based, multicenter cohort study that used a health checkup database (n = 410,061). SLD was diagnosed by ultrasonography, and non-SLD individuals were followed for 65,657 person-years. The incidence rates of MASLD were assessed using Kaplan-Meier analysis. Independent risk factors for MASLD development were identified using Cox regression analysis, stratified by four groups: obese women, non-obese women, obese men, and non-obese men. Partial correlation analysis was performed to identify independent associations between metabolic parameters and MASLD development, stratified by obesity status. **Results:** The overall incidence rate of MASLD was 39.3/1,000 person-years, with a higher incidence in obese women than in non-obese men (13.7% vs. 7.2%). Women developed MASLD at an older age compared to men (non-obese: 58 vs. 54 years; obese: 56 vs. 55 years). Low HDL cholesterol was the most potent independent risk factor for MASLD in women, regardless of obesity status (HR [95% CI]: non-obese women 1.9 [1.5—2.4], obese women 1.4 [1.1—1.8]), while hypertriglyceridemia was the primary risk factor in men. Additionally, a partial correlation analysis demonstrated distinct patterns of risk among women. In non-obese women, low HDL cholesterol levels emerged as a central factor associated with MASLD development. In obese women, low HDL cholesterol also demonstrated a strong association with MASLD, acting as a key component within a cluster of other metabolic factors. **Conclusion:** The metabolic risk factors contributing to MASLD development differed by sex, with low HDL cholesterol being the most potent predictor in women. These findings suggest that MASLD prevention in women should consider not only the presence of obesity but also the potential impact of low HDL cholesterol levels, even in non-obese individuals. Furthermore, a greater emphasis on reproductive health, including menopausal status, may be necessary for a more comprehensive risk assessment.

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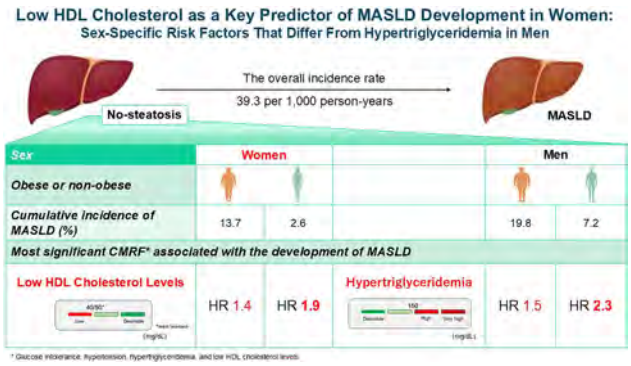

Disclosures: Tsubasa Tsutsumi: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching, Mary Rinella: akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, Michael Charlton: Nothing to Disclose, Yoshihiro Kamada: Nothing to Disclose, Hideki Fujii: Nothing to Disclose, Yuichiro Suzuki: Nothing to Disclose, Koji Sawada: Nothing to Disclose, Miwa Tatsuta: Nothing to Disclose, Tatsuji Maeshiro: Nothing to Disclose, Hiroshi Tobita: Nothing to Disclose, Takemi Akahane: Nothing to Disclose, Chitomi Hasebe: Nothing to Disclose, Miwa Kawanaka: Nothing to Disclose, Takaomi Kessoku: Nothing to Disclose, Yuichiro Eguchi: Nothing to Disclose, Hayashi Syokita: Nothing to Disclose, Tomoari Kamada: Nothing to Disclose, Hiroshi Sakugawa: Nothing to Disclose, Asahiro Morishita: Nothing to Disclose, Tsutomu Masaki: Nothing to Disclose, Takumi Ohmura: Nothing to Disclose, Toshio Watanabe: Nothing to Disclose, Yoshioki Yoda: Nothing to Disclose, Nobuyuki Enomoto: Nothing to Disclose, Masafumi Ono: Nothing to Disclose, Kanako Fuyama: Nothing to Disclose, Kazufumi Okada: Nothing to Disclose, Naoki Nishimoto: Nothing to Disclose, Yoichi Ito: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Yoshio Sumida: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose, Atsushi Nakajima: Nothing to Disclose

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2515 | A SYSTEMATIC REVIEW AND META-ANALYSIS: DOES LIVER DISEASE REPRESENT AN INDEPENDENT RISK FACTOR FOR CARDIOVASCULAR DISEASE IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE?

Alexander Hung[1] Ida Katharina Ziegler Spedtsberg[2] David Etoori[3] Maja Thiele[2] William Rosenberg[3], [1]Department of Hepatology, Royal Free Hospital, London, UK, [2]Odense University Hospital, [3]Institute for Liver and Digestive Health, UCL Division of Medicine, London, UK

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with elevated risk of incident cardiovascular disease (CVD), the leading cause of death in people with MASLD. However, it is unclear whether liver disease is an independent risk factor (RF) for CVD or whether cardiometabolic RFs common to MASLD and CVD fully explain this risk. Equipoise exists in the literature, with studies conducted in liver centres suggesting MASLD confers higher CVD risk regardless of metabolic RFs, but large epidemiological studies suggesting the converse. Mendelian epidemiology cannot resolve this question. A systematic review and meta-analysis was conducted to delineate the relationship between MASLD and CVD. **Methods:** Medline, Embase, and Cochrane databases were interrogated from database inception to December 2024. Exclusion criteria incorporated: method of MASLD diagnosis (imaging, elastography or biopsy), alcohol intake (<30g/20g daily for males/females), pre-existing CVD, and follow-up period. Cross-sectional studies were excluded. The primary outcome was overall incident CVD. Secondary endpoints were fatal/non-fatal CVD events (CVEs), atrial fibrillation (AF), acute coronary syndrome (ACS), CVD mortality, and stroke. Raw outcome data were extracted from studies and meta-regression analyses performed using random-effects models to derive pooled odds ratios (ORs) with 95% confidence intervals (CIs). **Results:** Nineteen longitudinal cohort studies with various cardiovascular endpoints were identified, with aggregate data on 1,250,661 individuals (median follow-up 8.4 years [IQR 5.7-10.0]). MASLD was associated with an increased risk of any incident CVD (OR 1.90 [1.27–2.84]; $p=0.004$). After adjustment for age, sex and cardiometabolic RFs, this association remained but with CIs spanning 1.0 (OR 1.62 [0.06–3.18]; $p=0.043$). Further adjustment for follow-up duration yielded similar results (OR 1.83 [0.03–3.63; $p=0.048$). MASLD was associated with CVEs (OR 1.52 [0.12–2.91]; $p=0.037$) and CVD mortality (OR 1.51 [0.03–2.99]; $p=0.049$) in covariate-adjusted models, but CIs again spanned 1.0. MASLD was associated with elevated risk of incident ACS, AF, and stroke, but eligible study numbers precluded full adjustment for all cardiometabolic RFs. **Conclusion:** MASLD is associated with a nearly twofold increase in the risk of incident CVD. After adjusting for common cardiometabolic RFs, this association is equivocal due to the relatively wide CIs for ORs calculated in fully adjusted models. Thus, these data demonstrate no irrefutable evidence that there exists an association between MASLD and CVD independent of common cardiometabolic RFs. As such, further high-quality studies are needed to resolve the discrepancy between hepatological and epidemiological studies. Regardless, the association between MASLD and CVD highlights the importance of effective CVD risk management for people with MASLD.

Figure 1. Forest plot depicting the risk of overall incident CVD in the MASLD vs. non-MASLD groups for each of the included studies.

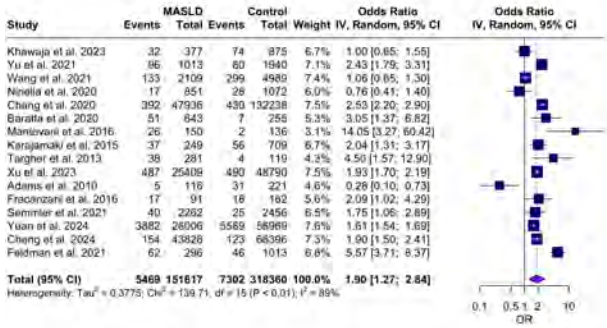

Figure 1. Forest plot depicting the risk of any incident CVD in the MASLD group as compared to non-MASLD controls. Unadjusted odds ratios (ORs) are given for each of the individual studies (*dark blue squares*) included in the meta-analysis ($n=16$), with the pooled OR presented at the base of the plot (*purple diamond*) alongside heterogeneity statistics.

Disclosures: Alexander Hung: Nothing to Disclose, Ida Katharina Ziegler Spedtsberg: Nothing to Disclose, David Etoori: Nothing to Disclose, Maja Thiele: Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Boehringer Ingelheim: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, Astra Zeneca: Advisor, GSK: Advisor, GSK: Advisor, GSK: Advisor, Novo Nordisk: Speaking and Teaching, GSK: Grant/Research Support, Evido: Co-founder, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Echosens: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Madrigal: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Takeda: Speaking and Teaching, Tillotts pharma: Speaking and Teaching, Tillotts pharma: Speaking and

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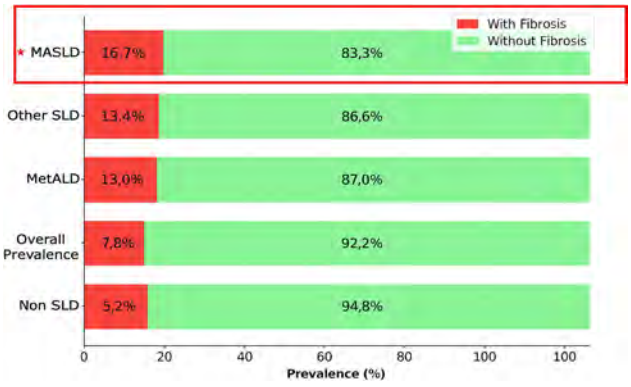
2516 | STEATOTIC LIVER DISEASE PHENOTYPES IN INFLAMMATORY BOWEL DISEASE: A SCREENING STUDY IDENTIFYING MASLD AS THE PRIMARY DRIVER OF LIVER FIBROSIS

Dana Kablawi[1] Solomon Sasson[2] Roy Nitulescu[1] Raman Agnihotram[3] Faisal Aljohani[4] Riccardo Righetti[4] Gary Wild[1] Alain Bitton[1] Chiara Saroli Palumbo[1] Waqqas Afif[1] Peter Lakatos[1] Talat Bessissow[1] Giada Sebastiani[1], [1]McGill University Health Center, [2]University of British Columbia, [3]Research Institute, McGill University Health Center, Montreal, Canada, [4]McGill University Health Centre

Background: Steatotic liver disease (SLD) seems common in people living with inflammatory bowel disease (IBD). The newly proposed definition of metabolic dysfunction-associated steatotic liver disease (MASLD) highlights metabolic drivers of hepatic steatosis while recognizing its frequent coexistence with other chronic liver diseases, including alcohol and drug-induced liver injury. We aimed to characterize the distribution of SLD phenotypes in people with IBD and evaluate the association of coexisting MASLD and IBD with liver fibrosis. **Methods:** As part of a routine MASLD screening program, transient elastography was performed in consecutive people with IBD from a prospective cohort in Montreal, Canada. SLD was defined as hepatic steatosis with a controlled attenuation parameter ≥275 dB/m. MASLD was determined by the presence of steatosis with at least 1 cardiometabolic risk factor: elevated body mass index, prediabetes or diabetes, hypertension, or dyslipidemia. Significant liver fibrosis was defined as liver stiffness measurement ≥8 kPa. Factors associated with fibrosis were assessed using logistic regression models. Associations between clinical and demographic factors and the presence of significant fibrosis were evaluated using multivariable logistic regression models, with results reported as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). **Results:** A total of 495 patients (mean age 45, 54% male, 64% Crohn's disease, mean IBD duration 14 years, mean BMI 25, diabetes prevalence 32%). SLD was identified in 35% of patients, of which 57% met the criteria for MASLD, 5% had alcohol-related SLD, and 38% had other forms. The overall prevalence of significant liver fibrosis was 8%, increasing to 13% and 22% in patients with 1-2 or 3-4 cardiometabolic risk factors, respectively. The prevalence of liver fibrosis was higher in patients with MASLD versus those without SLD (see Figure). In an exploratory analysis, methotrexate exposure was more frequent among patients with liver fibrosis (8%) compared to those without (2%). After adjusting for IBD subtype, biological sex, and disease duration, MASLD remained independently associated with a significantly increased likelihood of liver fibrosis aOR 3.1; 95%CI:(1.5–6.1). In contrast, no significant association was observed for non-MASLD steatotic liver disease (SLD) phenotypes. Notably, 3.5% of patients with IBD exhibited significant fibrosis despite the absence of detectable SLD. **Conclusion:** MASLD is the most frequent phenotype of SLD in people with IBD and it is strongly associated with liver fibrosis. A proportion of patients also exhibit SLD and liver fibrosis without metabolic comorbidities, suggesting a potential role for chronic medication exposure. Clinicians should prioritize the identification and management of cardiometabolic risk factors in IBD care to mitigate liver-related complications.



Disclosures: Dana Kablawi: Nothing to Disclose, Solomon Sasson: Nothing to Disclose, Roy Nitulescu: Nothing to Disclose, Raman Agnihotram: Nothing to

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2517 | INFLUENCE OF CARDIOMETABOLIC RISK FACTORS AND ALCOHOL CONSUMPTION ON LIVER STIFFNESS IN PATIENTS WITH MASLD: A MULTICENTER STUDY IN COLOMBIA INFLUENCE OF CARDIOMETABOLIC RISK FACTORS AND ALCOHOL CONSUMPTION ON LIVER STIFFNESS IN PATIENTS WITH MASLD: A MULTICENTER STUDY IN COLOMBIA

ISMAEL YEPES[1] Juan Carlos Restrepo[2] Clara Milena Caez[3] Yohana Poveda[4] NICOLE CHAMORRO[5] Guillermo Donado[6] Jorge Ortiz[7] Pablo Osorio[8] Santiago Pino[9] Juan Ignacio Marin Zuluaga[10], [1]Universidad de Cartagena. Asociacion Colombiana de Hepatologia., [2]Hospital Pablo Tobon Uribe. Asociacion Colombiana de Hepatologia., [3]Asociacion Colombiana de Hepatologia., [4]Gastropack SAS. Asociacion Colombiana de Hepatologia., [5]Universidad de Cartagena. Gastropack SAS, [6]Universidad de Cartagena. Gastropack SAS, [7]Clinica IMAT. Asociacion Colombiana de Hepatologia, [8]Universidad de Cartagena., [9]Universidad de Antioquia., [10]Hospital Pablo Tobon Uribe. Asociacion Colombiana de Hepatologia

Background: A new nomenclature has been proposed to better classify steatotic liver disease based on etiology. The term *Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD)* includes all patients with steatosis and at least one cardiometabolic risk factor (CMRF). However, CMRFs differ in their impact on disease progression. Additionally, the alcohol thresholds in MASLD criteria are arbitrary, despite evidence suggesting liver risk may increase even below these cutoffs. Alcohol might interact with CMRFs—or CMRFs among themselves—promoting liver damage. This study aimed to explore how CMRFs and alcohol intake, independently and in interaction, relate to liver stiffness in MASLD patients. **Methods:** Patients with MASLD from four Colombian cities were included. All underwent transient elastography and other causes of liver disease were excluded. Significant alcohol intake ($\geq$30 g/day in men, $\geq$20 g/day in women) was an exclusion criterion. CMRFs were defined using ATP III criteria, and alcohol use was measured in standard drink units per week. A multivariate linear regression, including interaction terms between CMRFs and alcohol, was performed. Significance was set at $p \leq 0.05$. **Results:** A total of 354 patients were analyzed (39.3% male; mean age: 54 years). Regarding CMRFs, 30.2%, 31.9%, 29.4%, and 8.5% had 1, 2, 3, and 4 factors, respectively. Mean alcohol intake was 14.5 g/week, and 5% exceeded 100 g/week. Prevalence of ATP III criteria: glucose metabolism impairment (50.6%), hypertension (54.2%), dyslipidemia (68.6%), and increased waist circumference (42.7%). In univariate analysis, liver stiffness was associated with age, BMI, number of CMRFs, and impaired glucose metabolism. In multivariate analysis, only BMI (β = 0.14; 95% CI: 0.03–0.27; p = 0.012) and impaired glucose metabolism (β = 0.11; 95% CI: 0.08–2.6; p = 0.03) remained significant. Alcohol intake and its interactions showed no significant association. However, interactions between diabetes and waist circumference, hypertension and diabetes, and the three combined were linked to higher liver stiffness. Only the diabetes–waist circumference interaction remained significant. **Conclusion:** MASLD represents a heterogeneous condition. Diabetes, especially when combined with increased waist circumference, appears to be a key driver of liver stiffness. These findings warrant further validation.

Table 1. Factors associated with elastographic values. Univariate linear regression.

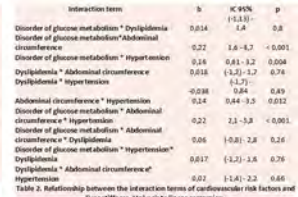

Table 2. Relationship between the interaction terms of cardiovascular risk factors and liver stiffness, Univariate linear regression.

Variable	b	p
Disorder of glucose metabolism*Abdominal circumference	0,19	< 0,01
BMI (Kgs/m2)	0,14	0,012
Disorder of glucose metabolism	0,11	0,03

Table 3. Factors associated with liver stiffness. Multivariate linear regression analysis

Disclosures: ISMAEL YEPES: Nothing to Disclose, Juan Carlos Restrepo: Nothing to Disclose, Clara Milena Caez: Nothing to Disclose, Yohana Poveda: Nothing to Disclose, NICOLE CHAMORRO: Nothing to Disclose, Guillermo Donado: Nothing to Disclose, Jorge Ortiz: Nothing to Disclose, Pablo Osorio: Nothing to Disclose, Santiago Pino: Nothing to Disclose, Juan Ignacio Marin Zuluaga: Nothing to Disclose

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2518 | INFLAMMATORY BURDEN VARIES BY DIET QUALITY IN A SUSPECTED MASLD POPULATION

Sindhuja Battula[1] Adnan Said[1], [1]University of Wisconsin School of Medicine and Public Health

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease world-wide. Chronic inflammation plays a central role in the pathogenesis and progression of MASLD to advanced liver disease. Dietary composition is a modifiable factor that may influence systemic inflammation, but the relationship between diet quality and inflammatory biomarkers in individuals with MASLD remains unclear. **Methods:** We conducted a cross-sectional analysis of data from the 2017–2018 National Health and Nutrition Examination Survey (NHANES). MASLD was defined by the presence of hepatic steatosis (CAP $\geq$285 dB/m), low alcohol intake, and at least one cardiometabolic risk factor: elevated body mass index (BMI), impaired glucose metabolism, elevated blood pressure, hypertriglyceridemia, or reduced high-density lipoprotein (HDL) cholesterol. Participants under 18 years of age or with hepatitis B, hepatitis C, or hemochromatosis were excluded. Diet quality was assessed using the Healthy Eating Index (HEI-2015) and the Dietary Inflammatory Index (DII), both derived from Day 1 24-hour dietary recall data. Inflammatory biomarkers, including high-sensitivity C-reactive protein (hs-CRP) and serum ferritin, were analyzed as primary outcomes. Sample survey-weighted univariate analyses were performed to evaluate associations between diet quality and inflammatory markers in the MASLD population. **Results:** Among adults with MASLD (n = 881), higher Dietary Inflammatory Index (DII) scores were significantly associated with elevated hs-CRP levels (β = 0.61, SE = 0.17, p = 0.002) and lower serum ferritin levels (β = –10.39, SE = 2.46, p < 0.001). Conversely, higher Healthy Eating Index (HEI-2015) scores were significantly associated with lower hs-CRP levels (β = –0.063, SE = 0.021, p = 0.009), but not with ferritin levels (β = 0.60, SE = 0.39, p = 0.15). **Conclusion:** Our findings indicate that a pro-inflammatory diet is significantly associated with increased systemic inflammation, while better overall diet quality correlates with reduced inflammation in adults with MASLD. These results highlight diet as a modifiable risk factor in managing inflammation and suggest that anti-inflammatory dietary strategies could play an important role in the clinical care of MASLD. Following a pro-inflammatory diet, lower ferritin likely reflects impaired iron storage or absorption driven by poor nutritional quality and impaired iron homeostasis in the MASLD population. Moreover, hs-CRP may serve as a useful and accessible biomarker to help patients and clinicians better understand the impact of dietary habits on inflammation and motivate healthier lifestyle changes.

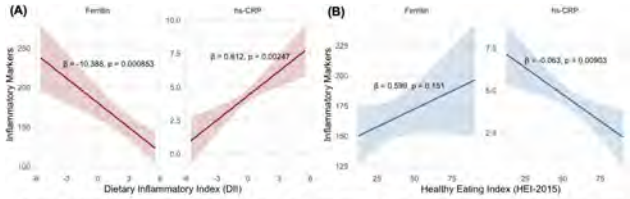

Figure 1: Survey-weighted univariate analyses showing associations between diet quality and inflammation in MASLD: **(A)** Dietary Inflammatory Index and **(B)** Healthy Eating Index (HEI-2015), each evaluated against serum ferritin and hs-CRP.

Disclosures: Sindhuja Battula: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Advisor

2519 | INDEPENDENT ASSOCIATION BETWEEN VITAMIN D INSUFFICIENCY AND LIVER FIBROSIS IN PEOPLE WITH HIV, REGARDLESS OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE OR HEPATITIS C COINFECTION

FRANCESCA FARINA[1,2], AURGHO DATTA[1], JOVANA MILIC[3], FELICE CINQUE[1], GIOVANNI GUARALDI[3], GIADA SEBASTIANI[1], [1]DEPARMENT OF MEDICINE, MCGILL UNIVERSITY HEALTH CENTRE, MONTREAL, CANADA, [2]SAN RAFFAELE HOSPITAL, MILAN, ITALY, [3]MODENA HIV METABOLIC CLINIC, UNIVERSITY OF MODENA AND REGGIO EMILIA, MODENA, ITALY, Francesca Farina[1] Aurgho Datta[1] Felice Cinque[1] Giovanni Guaraldi[2] Giada Sebastiani[1] Jovana Milic[2], [1]McGill University Health Centre, Montreal, Canada, [2]University of Modena and Reggio Emilia, Modena, Italy

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disease in people with HIV (PWH), who are also at high risk of liver fibrosis. Vitamin D insufficiency is prevalent in PWH and frequently observed in individuals with MASLD, yet its role in liver fibrosis progression in this population remains unclear. **Methods:** We conducted a multicenter cohort study involving PWH screened for hepatic steatosis and fibrosis using transient elastography. Hepatic steatosis was defined as controlled attenuation parameter $\geq$275 dB/m, and significant liver fibrosis as liver stiffness measurement $\geq$8 kPa. Vitamin D insufficiency was defined as serum 25-hydroxyvitamin D levels <50 nmol/L. Incidence of significant liver fibrosis was assessed by survival analysis, and independent predictors were identified through logistic regression and generalized estimating equations

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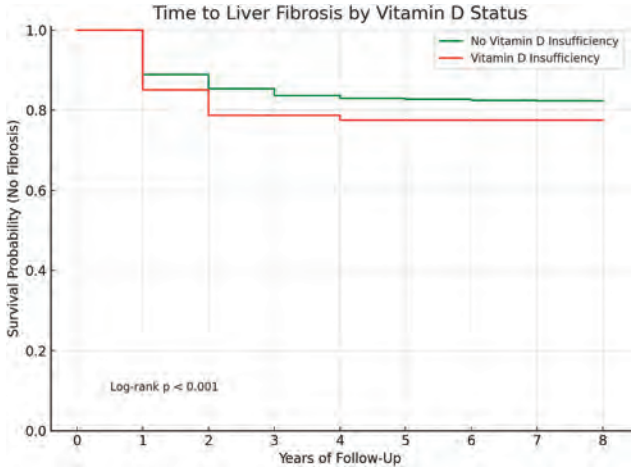
modelling. **Results:** A total of 4,746 PWH were included (mean age 60.2 years, 72% men, mean BMI 25 Kg/m^2, 11% with diabetes, 23% with hepatitis C coinfection, 5% with hepatitis B coinfection, all on antiretroviral therapy) between 2014-2024. Vitamin D insufficiency was observed in 42% of participants, hepatic steatosis in 19% and significant fibrosis in 14%. At baseline, independent cofactors of vitamin D insufficiency included hepatitis C coinfection (adjusted odds ratio [aOR] 1.15, 95% CI 1.02-1.31), BMI (aOR 1.1, 95% CI 1.03-1.08), and hepatic steatosis (aOR 1.71, 95% CI 1.35-2.18) after adjusting for HIV duration, diabetes, CD4 cell count, parathormone levels, sex, and ethnicity. Over a median 7-year follow-up, the cumulative incidence of significant liver fibrosis was 17%, and significantly higher among PWH with vitamin D insufficiency (see Figure). On multivariable generalized estimating equations models, vitamin D insufficiency was independently associated with development of liver fibrosis (aOR 1.44, 95% CI 1.14-1.80), adjusting for hepatic steatosis, diabetes, obesity, parathormone, CD4 cell count and HIV duration. **Conclusion:** Vitamin D insufficiency is common in PWH, particularly in those with MASLD and hepatitis C coinfection. It is independently associated with the development of liver fibrosis, beyond traditional metabolic risk factors. These findings suggest a potential role for vitamin D supplementation in MASLD prevention strategies in PWH, possibly through anti-inflammatory and insulin-sensitizing mechanisms.

Figure. Survival curves for incidence of significant liver fibrosis by category of vitamin D insufficiency.



Disclosures: Francesca Farina: Nothing to Disclose, Aurgho Datta: Nothing to Disclose, Felice Cinque: Nothing to Disclose, Giovanni Guaraldi: Nothing to Disclose, Giada Sebastiani: Novo Nordisk: Consultant, Abbvie: Speaking and Teaching, Merck: Consultant, Gilead: Speaking and Teaching, Theratechnologies Inc.: Grant/Research Support, Eli Lilly: Consultant, Jovana Milic: Nothing to Disclose

2520 | STEATOSIS-ASSOCIATED FIBROSIS ESTIMATOR (SAFE) OUTPERFORMS OTHER BLOOD-BASED BIOMARKERS FOR PREDICTING MAJOR ADVERSE LIVER OUTCOMES IN THE COMMUNITY

Vincent Chen[1] Chinmay Raut[2] Antonino Oliveri[2] Yousif Alyousifi[2] Yanhua Chen[2] Elizabeth Speliotes[1], [1]University of Michigan Medical Center, [2]University of Michigan

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects >30% of adults in the US and is a leading cause of major adverse liver outcomes (MALO). Blood-based non-invasive tests (NITs) are recommended for risk stratification but may miss a significant proportion of incident MALO. Here we assess the performance of non-proprietary NITs for predicting risk of MALO. **Methods:** We utilized UK Biobank, a community-based cohort of >500,000 adults in the United Kingdom. We included all participants with non-missing values of all primary predictors; at least one MASLD cardiometabolic risk factor; and no diagnosis of non-MASLD chronic liver diseases or report of excess alcohol intake. The primary predictors were the blood-based NITs FIB4, APRI, NFS, and SAFE. The primary outcome was MALO, defined as hospitalization for cirrhosis or hepatocellular carcinoma, or liver-related death. We utilized a time-dependent area under the curve (tAUC) approach where cases were those with MALO in <= 2-10 years of follow-up and controls were those with no MALO in > 2-10 years of follow-up respectively. **Results:** We included 238,657 participants with non-missing data, of whom 375 developed MALO within <10 years. The 10-year tAUC for identifying MALO was highest for SAFE (0.840 [95% CI 0.816-0.864]), then APRI (0.820 [0.793-0.846]), FIB4 (0.780 [0.753-0.808]), and NFS (0.771 [0.744-0.798]); $p < 0.05$ for all vs. SAFE. SAFE remained superior to the other NITs in individuals with elevated alanine aminotransferase or who met criteria for screening based on AASLD guidance. We next assessed patients who developed MALO and determined what proportion of patients had high, intermediate, or low NIT values at baseline based on previously-reported cutoffs. High SAFE identified 23/28 (82.1%) of patients who went on to develop MALO within 2 years of measurement, vs. 16/28 (57.1%), 14/28 (50.0%), and 10/28 (35.7%) for high FIB4, NFS, and APRI, respectively. At 5 years, the corresponding values were 101/153 (66.0%), 75/153 (49.0%), 57/153 (37.7%), and 30/153 (19.6%) for SAFE, FIB4, NFS, and APRI,

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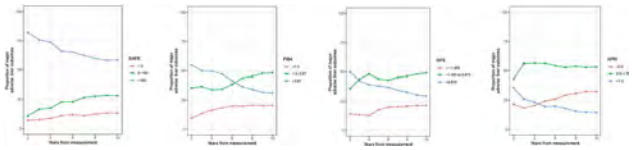
respectively. This performance was primarily driven by very low incidence of MALO in the low and intermediate SAFE categories. **Conclusion:** SAFE more accurately identified risk of MALO in a community cohort than other non-proprietary NITs. High SAFE category (>100) identified nearly all MALO occurring within 2-3 years after measurement, suggesting that it may be more efficient of a screening cutoff to identify at-risk participants.



Disclosures: Vincent Chen: AstraZeneca: site PI on industry-sponsored trial, Ipsen: site co-I on industry-sponsored trial, Kowa: site co-I on industry-sponsored trial, Chinmay Raut: Nothing to Disclose, Antonino Oliveri: Nothing to Disclose, Yousif Alyousifi: Nothing to Disclose, Yanhua Chen: Nothing to Disclose, Elizabeth Speliotes: University of Michigan: Pending patent on use systems for MASLD/insulin resistance

2521 | SPLEEN, LIVER, MUSCLE, AND FAT TRAITS ARE ASSOCIATED WITH MAJOR ADVERSE LIVER OUTCOMES AND LIVER-RELATED MORTALITY IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Vincent Chen[1] Brian Derstine[2] Brian Ross[2] June Sullivan[2] Peng Zhang[2] Grace Su[1], [1]University of Michigan Medical Center, [2]University of Michigan

Background: Muscle and fat quantity and density associate with disease severity in metabolic dysfunction-associated steatotic liver disease (MASLD), and data are emerging on importance of liver and spleen properties. However, data are limited on whether these factors are associated with major adverse liver outcomes (MALO). **Methods:** We included patients with MASLD diagnosed on computed tomography (CT) at Michigan Medicine between 2001-2024, with at least one cardiometabolic risk factor and no excess alcohol intake or alternative chronic liver diseases. CT scans were processed using Analytic Morphomics Platform (Matlab version 2024a) for axial predictors and TotalSegmenter version 2.4.0 for liver/spleen predictors. Predictors included axial L3 body composition measures (visceral fat, subcutaneous fat, and skeletal muscle area and attenuation, aortic calcification) and liver/spleen traits. Outcomes were MALO, liver-related death (LRD), and overall mortality. We deduplicated highly-correlated traits (r>0.8) and assessed the remaining features with a Cox proportional hazards model with a 12 month landmark. Models were adjusted for slice thickness and contrast phase (model 1), or model 1 plus age, sex, diabetes, and body mass index (model 2). Effects were reported per standard deviation (SD) in the predictor. Predictors were considered significant if p value in either model 1 or 2 met a Bonferroni corrected p value cutoff. **Results:** The cohort included 6,886 patients. Median age was 52 years and 55% were female. Median body mass index was 32.8 kg/m^2 and prevalence of diabetes, hypertension, and dyslipidemia were 40%, 67%, and 57% respectively. MALO, LRD, and death occurred in 112, 24, and 555 participants, respectively. 15, 16, and 37 features associated with MALO, LRD, and death, respectively. Factors associated with increased MALO or LRD included greater heterogeneity or asymmetry in liver or spleen attenuation, peak liver or spleen attenuation, greater spleen volume (Table). Greater muscle density and area were associated with lower risk of MALO and LRD, and greater subcutaneous and visceral fat density with LRD. Overall mortality-associated features were overall similar. Associations remained significant after stratification by contrast phase and Fibrosis-4 score. **Conclusion:** Subtle liver and spleen traits such as peak intensity and heterogeneity, along with muscle, subcutaneous fat, and visceral fat area/density, are associated with prognosis in MASLD. Automated quantitative image analysis of CT scans may serve to provide predictive biomarkers at the time of MASLD diagnosis.

Major adverse liver outcomes				
Predictor	Model 1		Model 2	
	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Liver attenuation variability	1.12 (1.08-1.17)	<0.001	1.13 (1.08-1.18)	<0.001
Expected muscle attenuation	0.59 (0.49-0.71)	<0.001	0.58 (0.46-0.73)	<0.001
Spleen attenuation variable	1.21 (1.11-1.31)	<0.001	1.20 (1.10-1.31)	<0.001
Low-dependence emphasis (higher = less homogeneous texture)	0.74 (0.62-0.89)	<0.001	0.67 (0.55-0.82)	<0.001
Peak spleen attenuation	1.14 (1.05-1.24)	<0.001	1.16 (1.08-1.26)	<0.001
Peak liver attenuation	1.17 (1.03-1.34)	<0.001	1.24 (1.11-1.38)	<0.001
Spleen coarseness	1.25 (1.10-1.41)	<0.001	1.28 (1.13-1.46)	<0.001
Asymmetry of spleen intensity distribution	1.31 (1.10-1.54)	0.0018	1.38 (1.17-1.63)	<0.001
Spleen volume	1.23 (1.10-1.37)	<0.001	1.25 (1.11-1.41)	<0.001
Volume of spleen at 10th percentile of spleen attenuation	1.34 (1.09-1.65)	0.0050	1.49 (1.20-1.85)	<0.001
Average spleen attenuation	1.30 (1.13-1.49)	<0.001	1.32 (1.14-1.53)	<0.001
Volume of spleen at 90th vs. 10th percentile of spleen attenuation	1.59 (1.16-2.18)	0.0037	1.82 (1.31-2.54)	<0.001
Peak spleen intensity	1.12 (1.02-1.21)	0.013	1.15 (1.06-1.24)	<0.001
Area with uniform attenuation	0.82 (0.74-0.91)	<0.001	0.82 (0.74-0.92)	<0.001
Normal-density muscle area	0.65 (0.53-0.79)	<0.001	0.70 (0.55-0.89)	0.0030
Liver-related death				
Predictor	Model 1		Model 2	
	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Subcutaneous fat attenuation	2.07 (1.58-2.71)	<0.001	2.34 (1.72-3.18)	<0.001
Spleen volume	1.43 (1.16-1.77)	<0.001	1.89 (1.50-2.38)	<0.001
Low-dependence emphasis (higher = less homogeneous texture)	0.44 (0.29-0.67)	<0.001	0.26 (0.16-0.44)	<0.001
High-dependence emphasis (higher = more patchy attenuation)	1.27 (1.13-1.42)	<0.001	1.40 (1.23-1.60)	<0.001
Asymmetry of spleen intensity distribution	1.50 (1.17-1.91)	<0.001	1.73 (1.37-2.19)	<0.001
Average spleen attenuation	1.52 (1.18-1.95)	<0.001	1.79 (1.39-2.31)	<0.001
Surface area-volume ratio of spleen	0.08 (0.02-0.33)	<0.001	0.02 (0.00-0.12)	<0.001
Boundaries between differ	0.67 (0.54-0.84)	<0.001	0.60 (0.47-0.75)	<0.001
Large zones in spleen	1.37 (1.16-1.63)	<0.001	1.44 (1.22-1.71)	<0.001
Visceral fat attenuation	1.98 (1.31-3.00)	0.0013	2.50 (1.60-3.89)	<0.001
Volume of liver the at 90th percentile of liver attenuation	0.65 (0.52-0.82)	<0.001	0.56 (0.43-0.75)	<0.001
Spleen intensity kurtosis	0.27 (0.11-0.66)	0.0040	0.16 (0.06-0.41)	<0.001
Intensity coefficient of variation in liver	1.40 (1.16-1.70)	<0.001	1.55 (1.22-1.97)	<0.001
Low-dependence emphasis (higher = less homogeneous texture)	1.64 (1.10-2.45)	0.015	1.99 (1.36-2.90)	<0.001
Expected muscle attenuation	0.41 (0.26-0.64)	<0.001	0.46 (0.26-0.81)	0.0070
Normal-density muscle area	0.41 (0.26-0.66)	<0.001	0.48 (0.27-0.86)	0.014

Disclosures: Vincent Chen: AstraZeneca: site PI on industry-sponsored trial, Ipsen: site co-I on industry-

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sponsored trial, Kowa: site co-I on industry-sponsored trial, Brian Derstine: Nothing to Disclose, Brian Ross: Nothing to Disclose, June Sullivan: Nothing to Disclose, Peng Zhang: Nothing to Disclose, Grace Su: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose

2522 | SCREENING FOR FIBROTIC MASH IN SUBJECTS WITH DIABETES IN THE POPULATION: OPTIMIZING THE STRATEGY USING IMPERFECT TOOLS

Thuy-Duyen Nguyen[1] Alina Allen[2] Ajitha Mannalithara[3] W. Ray Kim[1], [1]Mayo Clinic Arizona, [2]Mayo Clinic Rochester, [3]Stanford University School of Medicine

Background: Type 2 diabetes is a strong risk factor for metabolic dysfunction-associated steatohepatitis (MASH). Guidelines have been developed to recommend proactive screening for fibrotic MASH, typically consisting of two steps, first using a laboratory-based risk stratification score, commonly the FIB4 score, followed by elastography (such as vibration controlled transient elastography, VCTE) for liver stiffness measurement (LSM). The Steatosis-Associated Fibrosis Estimator (SAFE) score was developed to enhance the performance of FIB4 by incorporating additional variables relevant for MASH, e.g., diabetes and body mass index. We investigate the extent to which the SAFE score may improve the detection of fibrotic MASH in subjects with diabetes in the US population. **Methods:** We interrogated the National Health and Nutrition Examination Survey data, 2017-2020, in which a sample of subjects, representative of the US civilian population, underwent a comprehensive medical examination including VCTE. The FIB4 and SAFE scores were calculated in all adult examinees with a diabetes diagnosis. The current recommendation using FIB4 ≥ 1.3 as the initial risk stratification modality was compared to using SAFE at the rule-out and rule-in thresholds (a score of 0 and 100, respectively), in identifying (1) the number of subjects correctly diagnosed with fibrotic MASH (defined by a median controlled attenuation parameter [CAP] ≥ 274 dB/m and LSM ≥ 8 kPa) and (2) the number of VCTEs to be performed. **Results:** The survey data projected that 75.8 million US adults had steatosis (CAP ≥ 274 dB/m), of whom 41.6 million had diabetes. The prevalence of fibrotic MASH was high in this group, with 21.8% of subjects with diabetes and steatosis having VCTE ≥ 8 kPa. Of those, only 35.5% had FIB4 ≥ 1.3, leaving 64.5% of those with fibrotic MASH uncaptured when guideline recommendations are followed to use FIB4 < 1.3 to avoid LSM evaluation. When utilizing SAFE, a SAFE ≥ 0 threshold would capture 87.4% of fibrotic MASH and SAFE ≥ 100 would detect 51.8%. In the Table, when compared to FIB4 ≥ 1.3, using SAFE ≥ 100 would diagnose 1.5 million more fibrotic MASH while utilizing fewer VCTE examinations. However, this strategy still misses nearly 50% of fibrotic MASH. With SAFE ≥ 0, much fewer (12.6%) fibrotic MASH would be missed, but it would require 16.4 million more VCTEs. **Conclusion:** These data support society guidelines recommending screening for fibrotic MASH in subjects with diabetes, given the high prevalence and available liver-diirected therapy. However, as the initial screening test, FIB4 has unacceptably high false negative rates, missing more cases than diagnosed. Using SAFE ≥ 100 is superior to FIB4, detecting more fibrotic MASH while utilizing fewer VCTEs. However, to maximize the sensitivity of the strategy, the detection threshold would need to be lowered, which would require systematic investment to deploy large numbers of elastography on the population level.

Stratification Test	Number of VCTEs	Fibrotic MASH	
		Diagnosed	Missed
FIB4 ≥1.3	13.1M	3.2M	5.8M
SAFE ≥100	12.3M	4.7M	4.4M
SAFE ≥0	29.5M	7.9M	1.1M

Disclosures: Thuy-Duyen Nguyen: Nothing to Disclose, Alina Allen: Novo Nordisk: Grant/Research Support, Novo Nordisk: Advisor, Target Pharma: Grant/Research Support, Pfizer: Grant/Research Support, Boehringer Ingelheim: Advisor, Madrigal: Advisor, GSK: Advisor, Oncoustics: Grant/Research Support, Escopics: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Madrigal: Grant/Research Support, Siemens: Grant/Research Support, Ajitha Mannalithara: Nothing to Disclose, W. Ray Kim: Nothing to Disclose, Nothing to Disclose

2523 | KEY DIAGNOSTIC FACTORS IN STEATOTIC LIVER DISEASE AND THEIR LONGITUDINAL IMPACT ON OVERALL MORTALITY

Do Han Kim[1] Ethan Kai Jun Tham[2] Pojsakorn Danpanichkul[3] Donghyun Ko[4] Faith Xin Ning Tan[2] Glenn Ho[2] Shyna Zhuoying Gunalan[2] N. Apoorva Sasikumar[2] Karn Wijarnpreecha[5] Daniel Huang[6]

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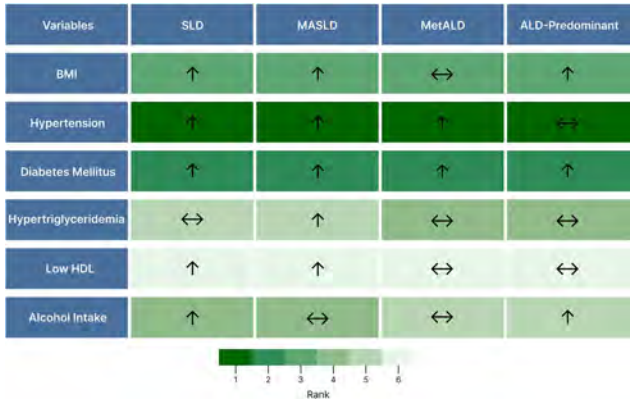
Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects up to 37% of individuals and is anticipated to rise alongside obesity and diabetes mellitus (DM) rates. Limited data exists on the impact of key diagnostic factors on mortality across steatotic liver disease (SLD) spectrum. This study evaluates the effect of diagnostic criteria on overall mortality across the SLD spectrum. **Methods:** A retrospective cohort study using the National Health and Nutrition Examination Survey registries from 1999-2018. All patients with hepatic steatosis were classified as SLD. Multivariate Cox-regression and Shapley value analysis assessed associations and relative contribution respectively on each diagnostic criterion influence on mortality. **Results:** A total of 20,510 individuals with SLD were included, with a median follow-up time of 113 months. DM increased mortality across the SLD spectrum, with a 63% increase (aHR: 1.63, 95%CI: 1.51-1.75, $P < 0.01$) in SLD, 61% (aHR: 1.61, 95%CI: 1.48-1.74, $P < 0.01$) in MASLD, 62% (aHR: 1.62, 95% CI: 1.29-2.03, $P < 0.01$) in MetALD, and 112% (aHR: 2.12, 95%CI: 1.58-2.85, $P < 0.01$) in ALD-predominant. Hypertension increased mortality by 37% (aHR: 1.37, 95%CI: 1.25-1.51, $P < 0.01$) in SLD, 38% (aHR: 1.38, 95%CI: 1.24-1.54, $P < 0.01$) in MASLD, and 48% (aHR: 1.48, 95%CI: 1.12-1.97, $P < 0.01$) in MetALD. Dominance analysis revealed hypertension as the strongest predictor of mortality across the SLD spectrum (52.83-69.16%), followed by DM (19.62-43.39%). **Conclusion:** This study highlights the association and relative contributions of key diagnostic factors to mortality across the SLD spectrum. DM and hypertension not only consistently increase mortality across SLD and its subtypes but also represent the predominant relative contributors to mortality risk. Alcohol intake most significantly affects MASLD and less on MetALD and ALD-predominant.



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2524 | COMPREHENSIVE RISK ASSESSMENT OF GASTROINTESTINAL CANCER IN PATIENTS WITH MASLD, METALD, AND ALD

Nobuharu Tamaki[1] Takefumi Kimura[2] Shun-Ichi Wakabayashi[2] Naoki Tanaka[2] Namiki Izumi[1] Rohit Loomba[3] Masayuki Kurosaki[1], [1]Musashino Red Cross Hospital, [2]Shinshu University School of Medicine, [3]University of California, San Diego

Background: Steatotic liver disease (SLD), which includes metabolic dysfunction-associated SLD (MASLD), MASLD with increased alcohol intake (MetALD), and alcohol-associated liver disease (ALD), is recognized as a risk factor for gastrointestinal cancers. However, the comparative risk of gastrointestinal cancers among MASLD, MetALD, and ALD remains unclear. **Methods:** We conducted a nationwide, population-based cohort study involving 978,607 patients with MASLD, 366,152 with MetALD, 152,721 with ALD, and 4,884,398 control individuals. The primary outcome was the incidence of gastrointestinal cancers, including hepatocellular carcinoma (HCC), biliary tract cancer, esophageal cancer, gastric cancer, colorectal cancer, and pancreatic cancer. **Results:** Compared to controls, the adjusted hazard ratios (aHRs) for HCC were 4.47 (95% confidence interval [CI], 3.54–5.64) for MASLD, 3.55 (95% CI, 2.69–4.68) for MetALD, and 5.39 (95% CI, 3.96–7.35) for ALD. For biliary tract cancer, the aHRs were 1.66 (95% CI, 1.39–2.00) for MASLD, 1.45 (95% CI, 1.16–1.82) for MetALD, and 1.58 (95% CI, 1.17–2.12) for ALD. The risks of both HCC and biliary tract cancer were significantly elevated across all SLD subgroups compared to controls. For esophageal cancer, the aHRs were 0.75 (95% CI, 0.66–0.85) for MASLD, 1.28 (95% CI, 1.13–1.45) for MetALD, and 2.48 (95% CI, 2.18–2.83) for ALD. For gastric cancer, the aHRs were 1.00 (95% CI, 0.94–1.06) for MASLD, 1.09 (95% CI, 1.02–1.16) for MetALD, and 1.13 (95% CI, 1.03–1.24) for ALD. The aHRs for colorectal cancer were 1.26 (95% CI, 1.19–1.32) for MASLD, 1.44 (95% CI, 1.36–1.54) for MetALD, and 1.84 (95% CI, 1.70–1.99) for ALD. The risk of gastrointestinal cancers increased with higher levels of alcohol consumption, with the highest risk observed in the ALD group, followed by the MetALD group. The risk of pancreatic cancer was similar to that of controls in both the MetALD and ALD groups. **Conclusion:** Patients with SLD—including MASLD, MetALD, and ALD—have a significantly elevated risk of gastrointestinal cancers compared to controls. The degree of risk varies depending on the underlying liver disease subtype, particularly in relation to alcohol consumption. These findings underscore the need for risk-stratified cancer screening strategies in individuals with SLD.

Disclosures: Nobuharu Tamaki: Nothing to Disclose, Takefumi Kimura: Nothing to Disclose, Shun-Ichi Wakabayashi: Nothing to Disclose, Naoki Tanaka: Nothing to Disclose, Namiki Izumi: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals:

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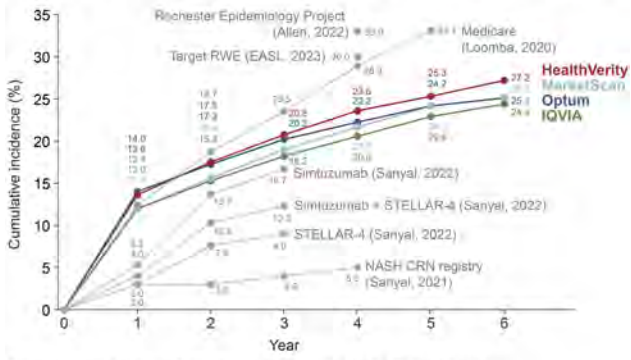
2525 | REAL-WORLD INCIDENCE OF LIVER DECOMPENSATION OR TRANSPLANTATION EVENTS IN PATIENTS WITH COMPENSATED METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS IN THE UNITED STATES

Steve Gao[1] Colin Anderson-Smits[1] Catherine Frenette[1] Lulu Wang[1] Fang Xia[1] Chunmay Fu[1], [1]Gilead Sciences, Inc., Foster City, CA, USA

Background: Patients with compensated cirrhosis (CC) due to metabolic dysfunction-associated steatohepatitis (MASH) or metabolic dysfunction-associated steatotic liver disease (MASLD) are at risk of decompensated cirrhosis. Decompensation events, liver transplantation (LT) and death are considered level-1 clinical endpoints for MASH/MASLD. This study used real-world data (RWD) to evaluate the incidence of and time to decompensated liver disease or LT in patients with CC in the US. **Methods:** This was a descriptive analysis of four databases (2007–2022): MarketScan (MS, n = 21,678), HealthVerity (HV, n = 42,472), Optum Clinformatics DataMart (OCDM, n = 23,267) and IQVIA PharMetrics (PM, n = 52,649). Eligibility criteria: 18–80 years old, MASH/MASLD, CC diagnosis $\leq$ 90 days before or after MASH/MASLD diagnosis, and $\geq$ 1 year of continuous enrollment before CC. Exclusion criteria: history of decompensated cirrhosis, alcohol-related liver disease, viral hepatitis, LT, hepatocellular carcinoma or other chronic liver disease causes. Primary outcome was the cumulative incidence of a composite of decompensated liver disease (variceal hemorrhage, hepatic encephalopathy, ascites or jaundice) or LT, by year 6. **Results:** The participants' median age (IQR) was 58 (13), 59 (14), 66 (16), and 57 (12) years in the MS, HV, OCDM, and PM databases, respectively. The proportion of males was 43%, 39%, 44%, and 49%, respectively. The proportion of patients with type 2 diabetes, portal hypertension, and non-bleeding esophageal varices were similar in MS (57%/12%/15%), HV (58%/12%/13%), and OCDM (57%/13%/14%) databases, but lower in the PM database (44%/6%/5%). There were 3066, 6695, 3564, and 9033 patients who experienced decompensated liver disease or LT in the four databases, respectively, with a mean follow-up duration of 1.4–2.5 years. The cumulative incidences by year 6 were 25.2% (MS), 27.2% (HV), 25.1% (OCDM) and 24.4% (PM) (Figure). **Conclusion:** Our estimates of decompensation events were higher than those reported in clinical trials, likely owing to differences in patient populations and outcome assessments. While our data are useful for informing future study design, limitations inherent to claims-based data (misclassifications, nonstandardized outcome definitions) should be considered. Prospective observational studies with defined sampling and clinical validation may yield more accurate incidence estimates.

Figure. Cumulative incidence of decompensated liver disease or LT over time in patients with CC in the MarketScan, HealthVerity, Optum ClinFormatics DataMart and IQVIA PharMetrics databases, compared with published studies.



CC, compensated cirrhosis; EASL, European Association for the Study of the Liver; LT, liver transplantation; NASH CRN, Clinical Research Network in Nonalcoholic Steatohepatitis; RWE, real-world evidence.

References for comparator studies:

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Sanyal AJ *et al. N Engl J Med.* 2021;385(17):1559–69.

Disclosures: Steve Gao: Nothing to Disclose, Colin Anderson-Smits: Nothing to Disclose, Catherine Frenette: Gilead Sciences: Employee, Lulu Wang: Nothing to Disclose, Fang Xia: Gilead Sciences: Employee, Chunmay Fu: Nothing to Disclose

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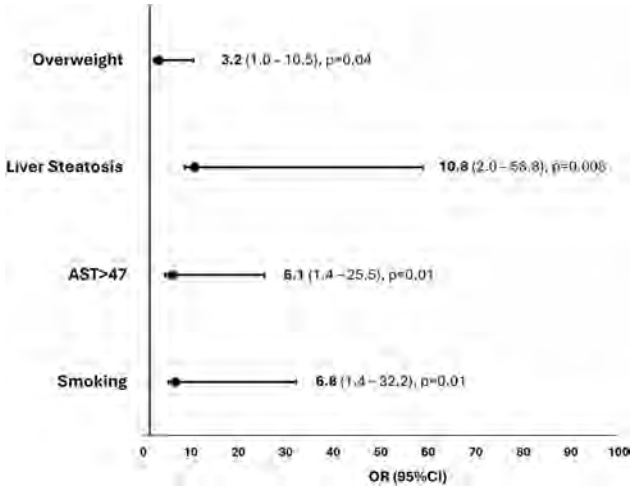
2526 | PREVALENCE AND ASSOCIATION OF LIVER STEATOSIS AND NON-ALCOHOLIC PANCREATIC STEATOSIS IN PATIENTS WITH HIGH CARDIOVASCULAR RISK

Eva Juárez-Hernández[1] Raúl Gómez-Mendoz[2] Vicente Toledo-Coronado[2] Javier Sánchez-Zavala[2] Graciela Castro-Narro[2] Iván López-Méndez[2], [1]Medica Sur Clinic and Foundation, [2]Medica Sur Clinic & Foundation

Background: In the last decade, the prevalence of metabolic-associated fatty liver disease (17-46%) and nonalcoholic fatty pancreas disease (NAFPD) (16-33%) has increased. The prevalence of obesity significantly affects the presence of liver and pancreatic steatosis in patients without excessive alcohol consumption and those with a high cardiovascular risk. Specific risk factors for pancreatic steatosis have not been fully described; thus, evaluating populations with a high cardiovascular risk, such as patients in coronary care units, could provide evidence regarding the prevalence of this condition and its relationship with cardiovascular risk. The aim of this study is to describe the prevalence and association of NAFPD and liver steatosis in patients with high cardiovascular risk. **Methods:** A retrospective review was conducted on the medical records of adult patients ($>$ 18 years) diagnosed with acute coronary syndromes who underwent a Computed Tomography (CT) scan at the Coronary Care Unit of a tertiary care private hospital in Mexico City. NAFPD was determined by the difference in pancreatic and splenic attenuation (-1.9), while hepatic steatosis was identified by hepatic attenuation $<$40 Hounsfield units. A logistic regression model was performed to estimate the odds ratio and 95% CI of factors associated with NAPFD in patients with high cardiovascular risk. **Results:** 106 medical records were collected, 69.8% (n = 74) were men, with a median age of 71 [IQR 65-85] years and 25.7 [IQR 22.9 – 28.2] kg/m2 of body mass index. According to the CT scans, 75.5% (n = 80) presented NAFPD, 35.8% (n = 38) had hepatic steatosis, and 34% (n = 36) had both. In the univariate analysis, dyslipidemia (OR 1.2 CI95% (1.0-1.5), p = 0.04), elevated levels of aspartate aminotransferase (AST) (OR 2.4 CI 95% (1.2-4.7), p = 0.02) and presence of liver steatosis (OR 6.5 CI95% (1.6-26.1), p = 0.001), shown association with NAPFD. Meanwhile, in multivariate analysis, hepatic steatosis, smoking, increased AST, and being overweight were independent factors associated with NAFPD (Figure 1). **Conclusion:** In a high cardiovascular-risk population, the prevalence of NAFPD is high, and it is independently associated with the presence of liver steatosis.



Disclosures: Eva Juárez-Hernández: Nothing to Disclose, Raúl Gómez-Mendoz: Nothing to Disclose, Vicente Toledo-Coronado: Nothing to Disclose, Javier Sánchez-Zavala: Nothing to Disclose, Graciela Castro-Narro: Nothing to Disclose, Iván López-Méndez: Nothing to Disclose

2527 | SEMAGLUTIDE TITRATION PATTERNS AMONG PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Samantha Clark[1] Dominic Nunag[1] Matthew Davis[1] Arushi Chadha[1] Nipun Atreja[2] Blake Thomas[2] Francis Lobo[2], [1]Medicus Economics, LLC, [2]Madrigal Pharmaceuticals, Inc.

Background: MASLD and its more progressive subtype, MASH, are chronic liver conditions. Progression to MASH is underdiagnosed in clinical practice. Subcutaneous (SC) semaglutide is being investigated for MASH in the ongoing ESSENCE clinical trial. Interim results indicate that 88% of participants followed the 16-week dose-escalation schedule and maintained a 2.4 mg target dose at 72-weeks of follow-up. We aim to assess alignment between real-world titration patterns and those observed in the ESSENCE trial among MASLD patients starting SC semaglutide for a currently approved indication. **Methods:** A retrospective cohort study including MASLD patients initiating SC semaglutide 2.4 mg (Wegovy®) from 2021-2024 was conducted in Optum Market Clarity data. The 12 months prior to the first SC semaglutide prescription claim (index date) served as the baseline period. Patients with other liver diseases (e.g., viral hepatitis) or severe complications from MASH (e.g., cirrhosis) were excluded. Patients

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were followed for titration to a 2.4 mg SC semaglutide dose from their index date until death, dropout, or end of data availability. Kaplan-Meier (KM) curves illustrating titration probability and time-to-titration were constructed. **Results:** Of the 4,871 adults included in the final sample, 10.5% (n = 511) presented with type 2 diabetes. Mean (standard deviation) age was 47.2 (11.0) years and 68.0% (n = 3,313) were female, with a mean follow-up time of 59.3 weeks (33.1). Overall, 39.6% (n = 1,930) of patients titrated to 2.4 mg, with 17.5% (n = 852) doing so within 16 weeks, 39.0% (n = 1,902) doing so within 72 weeks, and a mean time-to-titration of 20.1 (15.6) weeks. Accounting for censoring, 17% (95% confidence interval (CI): 16%-19%) titrated by 16 weeks, 45% (95% CI: 43%-46%) titrated by 72 weeks, and 78% (95% CI: 77%-80%) discontinued within 72 weeks. Among the 1,930 patients who titrated, 34.4% (n = 663) subsequently discontinued and 16.8% (n = 325) subsequently reduced their dose. **Conclusion:** Less than 40% of MASLD patients titrated to a 2.4 mg SC semaglutide dose over the follow-up period, with only 17% doing so within 16 weeks and 78% discontinuing treatment within 72 weeks. Results are consistent with findings from similar observational studies and highlight the importance of monitoring SC semaglutide use patterns in a real-world setting. Further research is needed to assess the relationship between non-persistence and liver-related outcomes among patients prescribed GLP-1s.

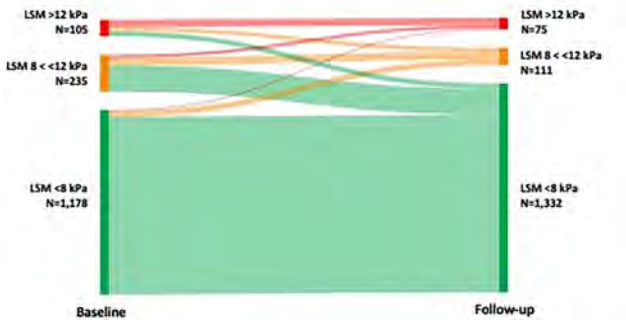
Disclosures: Samantha Clark: Madrigal Pharmaceuticals Inc: Consultant, Dominic Nunag: Nothing to Disclose, Matthew Davis: Medicus Economics, LLC: Employee, Arushi Chadha: Nothing to Disclose, Nipun Atreja: Madrigal Pharmaceuticals: Employee, Immunovant: Employee, Bristol Myers Squibb: Employee, Blake Thomas: Madrigal Pharmaceuticals: Employee, Francis Lobo: Madrigal Pharmaceuticals: Employee

2528 | MONITORING LIVER DISEASE PROGRESSION USING SERIAL TRANSIENT ELASTOGRAPHY ASSESSMENTS IN A LARGE REAL-WORLD COHORT OF PATIENTS WITH TYPE 2 DIABETES AND MASLD

Tiphaine Vidal-Trécan[1] Jean-Baptiste Julla[2] Yelena Schwartz[2] Helene Fontaine[3] Dominique Valla[3] Jean-Pierre Riveline[1] Jean-Francois Gautier[1] Laurent Castera[3], [1]Dept of Diabetology, Hopital Lariboisière, Paris, France, [2]Dept of Diabetology, Hopital Lariboisière, AP-HP, Paris, France, [3]Dept of Hepatology, Hopital Beaujon, AP-HP, Clichy, France

Background: Despite the recommendation to screen for MASLD and fibrosis in patients with type 2 diabetes mellitus (T2D), follow-up data is scarce. We examined the use of vibration-controlled transient elastography (VCTE) to monitor liver disease progression in a large real-world cohort of T2D outpatients with MASLD. **Methods:** A total of 1,518 patients with T2D and MASLD (steatosis and/or elevated ALT), who were seen at a tertiary diabetes clinic and underwent serial liver stiffness measurements (LSM) by VCTE between 2019 and 2024, were evaluated. The primary endpoint was the change in liver disease severity risk categories at follow-up: low (LSM < 8 kPa), intermediate (LSM 8-12 kPa), or high (LSM ≥ 12 kPa). The secondary endpoint was an increase in LSM of at least 30% at follow-up. A multivariate analysis was performed to identify factors independently associated with this increase. **Results:** The characteristics of the 1,518 patients were as follows: men 60.3%; median age 61 years [IQR 15]; diabetes duration 13 years [14]; BMI 28.9 kg/m² [6.9]; WC 103 cm [16]; HbA1c 7.5% [1.7]; LSM 5.6 kPa [3], and CAP 290 dB/m [78]). The median interval between two VCTE was 2.4 years [1.9]. The absolute median change during follow-up was -0.5 kPa [2.2] for LSM and -0.73 kg/m² [2.1] for BMI. At baseline, 1,178 patients (78%) were considered low risk, 235 (15%) intermediate risk, and 105 (7%) high risk. Changes in risk categories over time are shown in the Figure. At follow-up, 1,332 patients (88%) were in the low-risk category, while 111 (7%) in the intermediate risk, and 75 (5%) in the high risk. At follow-up, 1228 (81%) remained in the same risk group while 224 (15%) move to a lower risk category and 66 (4%) to a higher risk category. Of the 1,518 patients, 144 patients (9.5%) experienced an increase in LSM ≥ 30%, 1,046 (68.9%) had stable LSM, and 328 (21.6%) experienced a decrease in LSM ≥ 30%. Baseline age, diabetes duration, BMI, HbA1c and GGT levels were independently associated with an increase in LSM ≥ 30%. **Conclusion:** After 2.4 years of follow-up, most patients with T2D and MASLD remained in the same risk category according to LSM. Only a few patients (< 10%) displayed disease progression, which was associated with age, diabetes duration, BMI, HbA1c, and GGT levels.

Figure. LSM changes according to the 3 risk categories for advanced fibrosis (low (<8 kPa); intermediate (8 < < 12kPa); and high (>12 kPa) between baseline and follow-up (n=1,518).



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2529 | IMPLICATIONS OF EXPANDED ADVANCED FIBROSIS SCREENING STRATEGIES FOR MASLD IN PRIMARY CARE

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Background: Advanced fibrosis is associated with cirrhosis, cancer, and mortality in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). Since MASLD is underdiagnosed in primary care, and diabetes mellitus type 2 (T2DM) is strongly associated with MASLD, the 2024 American Diabetes Association (ADA) guidelines recommend screening for advanced fibrosis in patients with T2DM and prediabetes using the Fibrosis-4 Index (FIB-4). We aimed to determine the proportion of primary care patients with T2DM and prediabetes who had FIB-4s at-risk for advanced fibrosis and required confirmatory testing. **Methods:** This cross-sectional study evaluated primary care patients with T2DM or prediabetes and a FIB-4 score between 2022 and 2024. The outcome of interest was a FIB-4 score in need of confirmatory fibrosis risk assessment. Univariate analyses were used to describe the cohort. Logistic regression models evaluated the association between T2DM and a FIB-4 score at indeterminate-risk or greater for advanced fibrosis. **Results:** Of 8,366 patients with T2DM and prediabetes, 2,064 (25%) had FIB-4s in need of confirmatory risk assessment. The expanded FIB-4 fibrosis screening for T2DM and prediabetes increased the number of patients needing confirmatory fibrosis risk assessment 9-fold compared to those with diagnoses of MASLD. Further, patients with T2DM were not more likely to have an indeterminate-risk or greater FIB-4 (OR: 0.86; 95% CI: 0.77-0.96) compared to those with prediabetes in the fully adjusted model. **Conclusion:** Expanded screening for advanced liver fibrosis would substantially increase the number of patients who need confirmatory testing for liver fibrosis, increasing cost and straining access.

Table 2. Cohort characteristics by FIB-4 advanced fibrosis risk (indeterminate-risk or greater) in need of confirmatory advanced fibrosis risk assessment (column percents).

Characteristics	Overall	FIB-4 Advanced Fibrosis Risk		p-value
		Indeterminate- or High-Risk	Low-Risk	
		n=2,064	n=6,302	
T2DM Diagnosis, % (n)	60.3% (5,045)	60.9% (1,257)	60.1% (3,788)	0.523†
Demographic variables				
Age, mean (SD)	60.1 (15.4)	66.6 (13.2)	58.0 (15.5)	< 0.001‡
Sex, % (n)				< 0.001†
Female	63.3% (5,293)	50.8% (1,049)	67.3% (4,244)	
Male	36.7% (3,073)	49.2% (1,015)	32.7% (2,058)	
Race, % (n)				0.410†
Black	56.7% (4,746)	57.5% (1,187)	56.5% (3,559)	
Non-Black	43.3% (3,620)	42.5% (877)	43.5% (2,743)	
Marital status, % (n)				0.979†
Married	40.9% (3,419)	40.8% (843)	40.9% (2,576)	
Unmarried	59.1% (4,947)	59.2% (1,221)	59.1% (3,726)	
Smoking status				0.001†
Current	11.2% (934)	13.1% (270)	10.5% (664)	
Never or Quit	88.8% (7,432)	86.9% (1,794)	89.5% (5,638)	
Clinical Variables				
BMI, mean (SD)	32.3 (8.4)	29.8 (7.3)	33.1 (8.5)	< 0.001‡
Comorbidities, % (n)				
Hypertension	84.3% (7,050)	90.9% (1,876)	82.1% (5,174)	< 0.001†
Hyperlipidemia	77.5% (6,480)	83.6% (1,726)	75.4% (4,754)	< 0.001†
CVD	40.5% (3,384)	50.6% (1,044)	37.1% (2,340)	< 0.001†
Hypothyroidism	19.0% (1,588)	18.7% (385)	19.1% (1,203)	0.661†
CKD	25.0% (2,095)	36.5% (753)	21.3% (1,342)	< 0.001†
MASLD Diagnosis	8.2% (684)	11.1% (228)	7.2% (456)	< 0.001†
MASLD by Imaging and CMRF	13.5% (1,133)	15.3% (315)	13.0% (818)	0.009†

‡Two sample t test. †Chi square test. BMI=body mass index. CMRF=cardiometabolic risk factor. CKD=chronic kidney disease. CVD=cardiovascular disease. MASLD=metabolic dysfunction-associated steatotic liver disease. SD=standard deviation. T2DM=type 2 diabetes mellitus.

Disclosures: Kush Patel: Nothing to Disclose, Cecil Jnawali: Nothing to Disclose, Jingwen Zhang: Nothing to Disclose, Justin Marsden: Nothing to Disclose, Chloe Bays: Nothing to Disclose, Andrew Schreiner: Nothing to Disclose

2530 | IMPROVING ADVANCED FIBROSIS SCREENING AND REFERRALS FOR MASLD IN PRIMARY CARE

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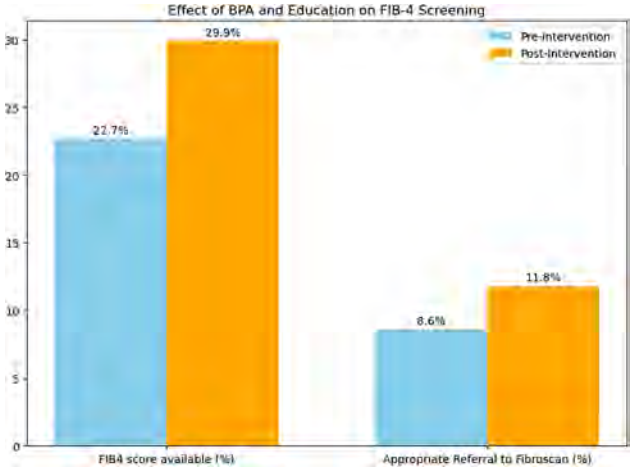
Background: Patients with metabolic dysfunction-associated steatotic liver disease (MASLD) who develop advanced fibrosis are at increased risk for liver-related complications and mortality. [1] As new therapies emerge, screening at-risk patients and linking them to care is critical [2, 3] Liver, GI and Endocrine societies recommend screening for advanced liver fibrosis in patients living with Type 2 Diabetes (PWD) using the FIB-4 score. [4, 5] Primary care providers (PCPs) are uniquely positioned to have the greatest reach, but face multiple competing priorities. Clinical decision support (CDS) tools embedded into the electronic health record (EHR) can help streamline care and aid providers. This study aimed to identify barriers to screening and develop an intervention to increase screening and referrals for MASLD in PWD in the primary care setting. **Methods:** This single-site quality improvement evaluation included adult PWD seen by PCPs at Mount Sinai Internal Medicine Associates from April 2023 to April 2025. We conducted an anonymous survey to understand provider preferences and implemented a two-part intervention: (1) didactics on MASLD delivered to faculty and residents and (2) two EHR best practice advisories (BPAs). The first BPA prompted providers to order labs to calculate the FIB-4 score if unavailable. The second BPA was triggered when a patient was screened as intermediate or high risk by FIB-4, prompting referral to FibroScan. The BPAs were non-interruptive and visible only to providers during the primary care visit. We compared rates of FIB-4 score availability and appropriate referrals before and after the intervention using the Chi-Square test. **Results:** A total of 35 providers completed the survey. Common barriers were forgetting to screen and not knowing their PWD needed screening. Almost all providers (80%) agreed or strongly agreed that the EHR can help them screen better. Following implementation of didactics and BPAs, FIB-4 score availability increased by 32% (22.7% pre-intervention vs 29.9% post-intervention, $p < 0.0001$). Of the patients screened as intermediate and high risk, appropriate FibroScan referrals increased by 37% (8.6% pre vs 11.8% post, $p = 0.43$). **Conclusion:** Among PCPs, barriers to screening patients with T2DM for advanced liver fibrosis include forgetting to screen and not knowing that their patient was indicated for screening. An intervention combining education and CDS tools increased FIB-4 screening and appropriate FibroScan referrals.



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2531 | TRENDS IN MORTALITY FROM METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE, CHRONIC KIDNEY DISEASE, AND DIABETES MELLITUS IN THE UNITED STATES, 1999-2020

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Background: The incidence of metabolic dysfunction-associated steatotic liver disease (MASLD), chronic kidney disease (CKD), and diabetes mellitus (DM) has risen significantly in recent decades. This study aimed to investigate temporal trends in mortality from MASLD, CKD, and DM in the US from 1999-2020, and to identify demographic groups at higher risk. **Methods:** We analyzed deidentified data from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research (CDC WONDER) database on underlying causes of death in the United States from 1999 to 2020. Mortality attributable to MASLD, CKD,

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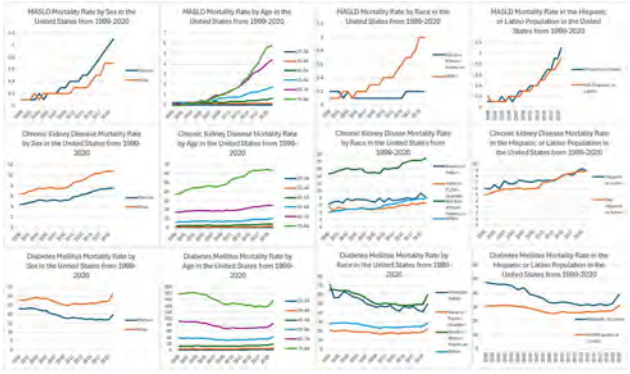
and DM was determined using ICD-10 codes. Age adjusted mortality rates (AAMRs) per 100,000 population were calculated by race and sex, while crude mortality rates were used for age group comparisons. Temporal trends in mortality rates for MASLD, CKD, and DM were evaluated using linear regression. **Results:** From 1999-2020, MASLD and CKD related mortality rates increased, while DM related mortality declined. In 2020 men had higher AAMRs than women for CKD (10.8 vs 7.5) and DM (31.2 vs. 19.5), whereas women had higher MASLD related mortality (1.1 vs 0.7). The 75-84 age group had the highest crude mortality rates for MASLD (5.8), CKD (63.3), and DM (154.7). Hispanic individuals had higher AAMRs for MASLD (1.1 vs 0.9) and DM (39.1 vs 31.2) than non-Hispanic individuals. CKD mortality was similar across Hispanic and non-Hispanic groups (8.9). Black or African American individuals had the highest AAMRs for CKD (19.0) and DM (59.7), followed by American Indian, White and Asian or Pacific Islander (Figure 1). **Conclusion:** Mortality from MASLD and CKD has increased from 1999-2020, while DM related mortality declined. Notable disparities in mortality rates exist by sex, age, and race. These trends reflect the interconnected pathophysiology and shared risk factors among MASLD, CKD, and DM. The rising burden of MASLD, in particular, underscores its emerging role as both a consequence and driver of metabolic dysfunction, highlighting the urgent need for integrated strategies targeting liver and kidney health.



Disclosures: Yash Hegde: Nothing to Disclose, Adnan Said: Mallinckrodt: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Advisor

2532 | MULTIOMICS SIGNATURES OF ADIPOSITY AND ADVERSE LIVER OUTCOMES: A PROSPECTIVE COHORT STUDY

Longgang Zhao[1] Yun Chen[1] Jun Li[2] Tamar Taddei[3] Xiaomei Ma[4] Shuangge Ma[5] Deirdre Tobias[6] Edward Giovannucci[7] Howard Sesso[6] JoAnn Manson[6] Frank Hu[2] Xuehong Zhang[1], [1]Yale School of Nursing, [2]Harvard T.H. Chan School of Public Health, [3]Yale University, [4]Yale School of Medicine, [5]Yale School of Public Health, [6]Brigham and Women's Hospital and Harvard Medical School, [7]Harvard University Medical School

Background: Excess adiposity is a key risk factor for chronic liver disease (CLD), but the underlying metabolomic and proteomic mechanisms are unclear. We evaluated the association of excess adiposity and related metabolomic and proteomic signatures with the risk of adverse liver outcomes. **Methods:** We analyzed data from 450,412 UK Biobank participants (40-69 years at baseline). Adiposity was assessed by body mass index (BMI) and waist circumference (WC). CLD outcomes (metabolic dysfunction-associated steatotic liver disease [MASLD], cirrhosis, liver cancer, severe liver diseases [SLD, including hepatocellular carcinoma and other severe liver diseases], and CLD mortality) were ascertained from in-hospital records, cancer and death registries. We derived a novel metabolomic (NMR platform, 168 metabolites) and proteomic scores (Olink platform, 1459 proteins) related to BMI or WC using elastic net regression. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals for the associations of the omic signatures with liver outcomes, adjusting for age, sex, ethnicity, Townsend deprivation index, alcohol drinking, smoking, physical activity, aspirin use, and history of diabetes. **Results:** After a median follow-up of 8.9 years, there were 4,077 cases of MASLD, 3,550 of cirrhosis, 755 of liver cancer, 2,253 of SLD, and 331 CLD deaths. Compared to participants with normal BMI (18.5-23.9 kg/m^2), obesity (BMI $\geq$ 30 kg/m^2) was positively associated with risk of all adverse liver disease outcomes. Central obesity showed similar magnitude. The BMI-related metabolomic (107 metabolites) and proteomic (116 proteins) scores were associated with higher risks of MASLD, cirrhosis, liver cancer, and SLD with HRs ranged from 1.18 to 2.26. The WC-related metabolomic (92 metabolites) and proteomic (116 proteins) scores were associated with higher risks of MASLD, liver cancer, and SLD with HRs ranged from 1.06 to 2.69. **Conclusion:** General and central obesity and their omic signatures were positively associated with long-term risk of liver diseases, revealing the molecular perturbations in metabolites and proteins associated with adiposity and liver health, which may inform the etiology and prevention of liver disease.

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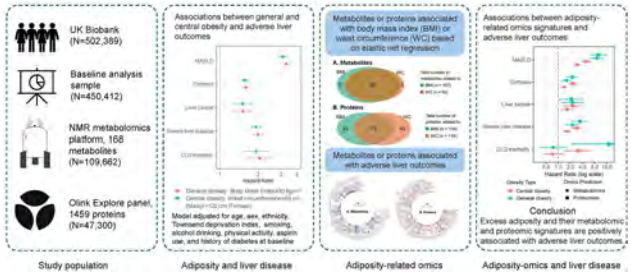

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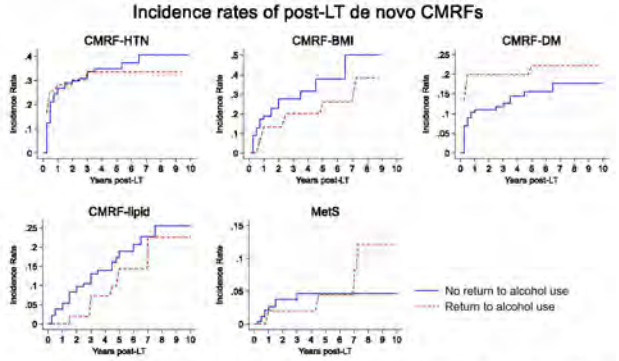
2533 | CARDIOMETABOLIC RISK FACTORS BEFORE AND AFTER EARLY LIVER TRANSPLANTATION FOR SEVERE ALCOHOL-ASSOCIATED HEPATITIS: AN ACCELERATE-AH STUDY

Matthew Dukewich[1] Neha Jakhete[2] Sheila Eswaran[3] Mohamed Shoreibah[4] Christine Hsu[5] George Therapondos[6] Ethan Weinberg[7] Manotri Chaubal[8] Adam Khalaf[8] Amol Rangnekar[9] Kirti Shetty[10] Cerise Kleb[2] Sevda Aghayeva[7] Ruona Ebial[6] Sameera Shuaibi[6] Chandler Shapiro[3] John Rice[11] Jessica Musto[11] R. Mark Ghobrial[12] Ashton Connor[13] Michael Lucey[11] Norah Terrault[14] Brian Lee[15], [1]University of Southern California- Keck Medicine, [2]University of Maryland, [3]Rush University Medical Center, [4]University of Alabama at Birmingham, [5]National Institute of Diabetes, Digestive, [6]Ochsner Medical Center, [7]University of Pennsylvania, [8]Georgetown University, [9]Georgetown University Hospital, [10]University of Maryland, Baltimore, [11]University of Wisconsin, [12]Houston Methodist JC Walter Transplant Center, [13]Houston Methodist, [14]University of Southern California, [15]Keck School of Medicine

Background: Early liver transplantation (ELT) for severe alcohol-associated hepatitis (AH) has increased significantly across the US. Data regarding cardiometabolic risk factors (CMRFs) in this population is a critical knowledge gap, representing a potentially important and intervenable driver of graft outcomes, given the synergistic effect of CMRFs with alcohol in the development and progression of steatotic liver disease. **Methods:** In this retrospective multi-center (9 US LT centers) cohort, we included consecutive LT recipients for clinically diagnosed severe AH between 2006-2021 and excluded those who did not survive to post-LT hospital discharge. *De novo* CMRFs during post-LT follow-up were defined according to the consensus SLD definition: 1) hypertension, if new diagnosis or new prescription of antihypertensives; 2) elevated BMI: if BMI $\geq$ 25 kg/m^2; 3) glucose intolerance, if new diagnosis of type II diabetes, new prescription of antidiabetic medications, or new A1c $\geq$ 5.7%; or 4) hyperlipidemia, if new diagnosis of hyperlipidemia or hypertriglyceridemia or new prescription of lipid-lowering therapy. Metabolic syndrome was defined as $\geq$ 3 CMRFs. Return to alcohol use was defined by first detection of any alcohol use post-LT. Multivariable Cox regression adjusted for age, sex, and MELD at LT was used to assess risk factors for development of *de novo* post-LT metabolic syndrome. **Results:** Among 310 included LT recipients (67% male, median age 43 years, median MELD-Na at LT of 37) with median post-LT follow-up of 4.4 years (IQR 1.5-7.0 years), 65 (20.6%) had pre-LT hypertension, 216 (68.4%) had elevated BMI, 27 (8.5%) had glucose intolerance, and 20 (6.3%) had hyperlipidemia. There was high post-LT incidence of *de novo* HTN (1 year: 26.2% [95%CI 21.1-32.5%]; 5 year: 32.2% [95%CI 26.0-39.3%]), BMI (1 year: 18.8% [95%CI 12.1-28.6%], 5 year: 33.8% [95%CI 23.5-47.0%]), glucose intolerance (1 year: 11.4% [95%CI 8.1-15.8%], 5 year: 15.4% [95%CI 11.2-21.0%]) and hyperlipidemia (1 year: 4.8% [95%CI 2.8-8.1%], 5 year: 18.2% [95%CI 13.1-24.8%]), while incidence of *de novo* metabolic syndrome was low (5 year: 4.9% [95%CI 2.7-8.8%]). These incidence rates differed by presence of return to any alcohol use post-LT (Figure). In multivariable analysis, active smoking at time of LT hospitalization (aHR 2.84, 95%CI 1.70-4.73) and African American race (vs. white race) (aHR 5.93, 95%CI 1.67-21.0) were associated with development of *de novo* post-LT metabolic syndrome. **Conclusion:** CMRFs (except being overweight) are relatively uncommon before ELT for AH, but development of *de novo* CMRFs after ELT is common and is influenced by return to alcohol use. Our findings highlight the importance of smoking cessation at time of LT and post-LT close monitoring and personalized interventions to prevent, identify, and treat CMRFs among ELT for AH recipients.

Figure. Incidence rates of post-LT *de novo* cardiometabolic comorbidities



BMI: body mass index; DM: diabetes mellitus; HLD: hyperlipidemia; HTN: hypertension; MetS: metabolic syndrome

Disclosures: Matthew Dukewich: GlaxoSmithKline: Stock - publicly traded company, Neha Jakhete: Proctor & Gamble: Stock - publicly traded company, Sheila

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2534 | EVALUATING THE ASSOCIATION OF PATIENT CHARACTERISTICS ON EMERGENCY DEPARTMENT USE AMONG A COHORT OF CANADIAN MASLD PATIENTS IN PRIMARY CARE

Elizabeth Baguley[1] *Juan Abraldes*[2] *Seungwon Lee*[1] *Abdel-Aziz Shaheen*[1], [1]*University of Calgary,* [2]*University of Alberta*

Background: Limited literature exists when examining emergency department (ED) use among Canadian primary care patients enrolled in a metabolic-associated steatotic liver disease (MASLD) risk-stratification pathway. We aimed to identify patient characteristics associated with ED use post-pathway enrollment. **Methods:** Adult patients enrolled in the Calgary MASLD risk-stratification pathway from March 2017-June 2022 were included (n = 12,070). The National Ambulatory Care Reporting System database was linked to the Calgary MASLD pathway database to capture ED visits from pathway entry to March 31st, 2023. Primary ED cause was defined by the first diagnostic code. Multivariable negative binomial models were used to calculate the estimated adjusted incidence rate ratio (aIRR) of overall, liver- and cardiovascular-related ED visits, with a time offset function. Model covariates included age (> = 54 vs. < 54 years), sex (male vs. female), diabetes status (yes vs. no), rural status (rural vs. urban), body mass index (BMI) (> = 30 vs. < 30 kg/m^2), Charlson Comorbidity Index (CCI) (> = 3 vs. < 3), and liver stiffness measurements (LSM) by shear wave elastography (> = 8 vs. < 8 kPa). **Results:** Patients mean age was 53.1 ± 13.3 years, and 51.9% were female. After covariate adjustment, age > = 54 (aIRR: 0.87 [95% CI: 0.81-0.94], p < 0.001), male sex (0.81 [0.76-0.87], p < 0.001), diabetes (1.17 [1.08-1.27], p < 0.001), rural residence (2.04 [1.80-2.32], p < 0.001), BMI > = 30 kg/m^2 (1.22 [1.14-1.32], p < 0.001), CCI > = 3 (1.17 [1.14-1.19], p < 0.001), and LSM > = 8kPa (1.25 [1.12-1.41], p < 0.001) were significantly associated with overall ED use, Figure 1. For liver-related ED use, LSM > = 8kPa (aIRR: 14.62, 95% CI: 5.34-40.08, p < 0.001) was the only variable significantly associated with use. However, cardiovascular-related ED use was significantly associated with age > = 54 (aIRR: 1.82, 95% CI: 1.47-2.26, p < 0.001), male sex (1.23 [1.00-1.51], p = 0.046), diabetes (1.66 [1.35-2.05], p < 0.001), rural residence (1.49 [1.06-2.09], p = 0.023), CCI > = 3 (1.21 [1.16-1.27], p < 0.001), and LSM > = 8kPa (1.58 [1.19-2.10], p = 0.002). **Conclusion:** Demographic and clinical characteristics of MASLD patients in primary care were significantly associated with both overall and condition-specific ED use. This highlights the importance of managing metabolic risk factors and improving access to care in patients with MASLD within the primary care setting.

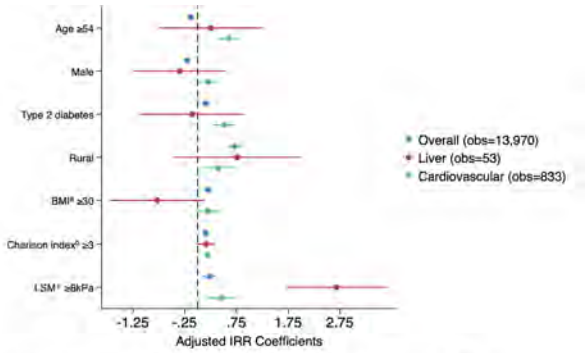

Figure 1. Adjusted Incidence Rate Ratio (aIRR) Coefficients for Emergency Department Admission Type

a. Body mass index
b. Charlson index excluded liver-related points (mild liver disease [+1], moderate to severe liver disease [+3]) and diabetes-related points (diabetes without complications [+1], diabetes with end organ damage [+2])
c. Liver stiffness measurement

Disclosures: Elizabeth Baguley: Nothing to Disclose, Juan Abraldes: Gilead: Grant/Research Support, 89bio: Consultant, Boston Pharmaceuticals: Consultant, Novo Nordisk: Consultant, Boehringer Ingelheim: Consultant, Astra Zeneca: Consultant, Agomab: Consultant, Terumo: Speaking and Teaching, Cook: Grant/Research

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2535 | AN INNOVATIVE SCREENING AND TREATMENT PATHWAY FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: THE UK-CURES APPROACH

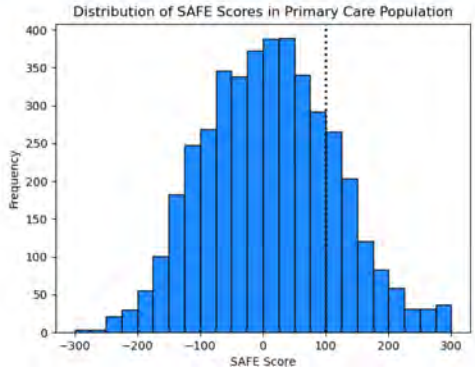
Lindsey Sheehan[1] Christian Rhudy[1] Francis Lobo[2] Doug Welch[2], [1]UK HealthCare, [2]Madrigal Pharmaceuticals

Background: Metabolic-associated steatotic liver disease (MASLD) and its subtype metabolic-associated steatohepatitis (MASH) are the most common liver diseases in the United States, affecting an estimated 75-100 million people. There are few routinized screening and treatment pathway models for MASLD/MASH, leading to underdiagnosis and undertreatment. The Steatosis-Associated Fibrosis Estimator (SAFE) score could be used to identify high risk individuals in need of intervention. This project will characterize SAFE scores of a University of Kentucky HealthCare (UKHC) primary care patient population and how they are used to inform development of a screening and treatment pathway. **Methods:** This is an observational, single center, cross-sectional study including patients between 18 and 80 years of age with primary care encounters at an eligible UKHC clinic between 1/1/2024 and 5/22/2024. Patients with a history of hepatitis B or C; alcohol use disorder (AUD); conditions that may falsely elevate a SAFE score (e.g. chronic idiopathic thrombocytopenia, leukemias, other hepatic disease); or insufficient data to calculate a SAFE score are excluded. Eligible patients are classified as having a SAFE ≥ 100, and differences in demographics, medical history and laboratory study data were compared between groups. Categorical data has been analyzed using Chi-square test or Fisher exact test, while numeric variables have been assessed using Mann-Whitney U test as appropriate. **Results:** Of 10,550 patients eligible for inclusion, 6,339 are excluded (hepatitis B/C n = 254; AUD n = 496; false elevation n = 120; missing data n = 5,469). In 4,211 included patients, 831 (19.7%) have a SAFE ≥ 100. In this analysis, patients with SAFE ≥ 100 are more frequently male (n = 377, 45.4%; SAFE < 100 n = 1,319, 39%; $p < 0.0001$), Black or African American (n = 206, 24.8%; SAFE < 100 n = 539, 16%; $p < 0.0001$) with Medicare insurance (n = 465, 56%; SAFE < 100 n = 762, 22.5%; $p < 0.0001$). Comorbid cardiovascular disease are more common in SAFE ≥ 100 patients (n = 317, 38.2%; SAFE < 100 n = 536, 15.9%; $p < 0.0001$). 242 (29.1%) of patients with SAFE ≥ 100 have current or historic orders for glucagon-like peptide-1 receptor agonists. **Conclusion:** Significant differences in demographics and clinical attributes are observed between patients with SAFE ≥ 100 and SAFE < 100. Patients with SAFE ≥ 100 are eligible for further workup to identify and link to treatment for MASLD/MASH, highlighting an opportunity to improve screening and initiate appropriate therapy.

Table 1. Baseline attributes by SAFE ≥ 100

Attribute		SAFE < 100 or missing (n = 3,380)	SAFE ≥ 100 (n = 831)	p-value
Age				
	Mean (SD)	48.4 (16.3)	64.6 (10.4)	
	Median (IQR)	48 (28)	66 (15)	<0.0001
	Range	18, 80	20, 80	
Sex				
	Male	1,319 (39%)	377 (45.4%)	0.0007
	Female	2061 (61%)	454 (54.6%)	
Gender				
	Female	1,889 (55.9%)	452 (54.4%)	<0.0001
	Male	1,238 (36.6%)	373 (44.9%)	
	Non-Binary	61 (1.8%)	1 (0.1%)	
	Queer/Other	9 (0.3%)	0 (0%)	
	Transgender Female	77 (2.3%)	1 (0.1%)	
	Transgender Male	106 (3.1%)	4 (0.5%)	
Race				
	American Indian or Alaskan Native	12 (0.4%)	3 (0.4%)	<0.0001
	Asian	209 (6.2%)	34 (4.1%)	
	Black or African American	539 (16%)	206 (24.8%)	
	Native Hawaiian or Other Pacific Islander	8 (0.2%)	2 (0.2%)	
	Other/Unknown	70 (2.1%)	17 (2.1%)	
	White	2,542 (75.2%)	569 (68.5%)	
Ethnicity				
	Hispanic, Latino/a, or Spanish origin	201 (6%)	38 (4.6%)	0.0005
	Not Hispanic, Latino/a, or Spanish origin	3080 (91.1%)	777 (93.5%)	
	Unknown	99 (2.9%)	16 (1.9%)	
Payor				
	Commercial	1,856 (54.9%)	247 (29.7%)	<0.0001
	Medicaid	619 (18.3%)	91 (11%)	
	Medicare	762 (22.5%)	465 (56%)	
	Self-Pay/Other	143 (4.2%)	28 (3.4%)	
BMI (kg/m^2)				
	< 18.5	47 (1.4%)	2 (0.2%)	<0.0001
	18.5 - 24.9	744 (22.9%)	79 (9.5%)	
	25 - 29.9	1,110 (32.5%)	189 (22.7%)	
	30 - 34.9	685 (20.3%)	225 (27.1%)	
	35 - 39.9	422 (12.5%)	161 (19.4%)	
	≥ 40	352 (10.4%)	175 (21.1%)	
Comorbid diagnoses				
	Type 2 diabetes mellitus	574 (17%)	561 (67.5%)	<0.0001
	Cardiovascular disease	536 (15.9%)	317 (38.2%)	<0.0001
Medication history				
	GLP-1RA Exposure	415 (12.3%)	242 (29.1%)	<0.0001

BMI = body mass index; GLP-1RA = glucagon-like peptide-1 receptor agonist; IQR = interquartile range; kg = kilogram; m = meter; SAFE = steatosis-associated fibrosis estimator; SD = standard deviation. Categorical variable assessed for significance with Pearson's chi-square test or Fisher's exact test as appropriate. Numeric variables assessed for significance with Mann-Whitney U test.



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Pharmaceuticals: Grant/Research Support, Francis Lobo: Madrigal Pharmaceuticals: Employee, Doug Welch: Nothing to Disclose

2536 | GLP-1 RECEPTOR AGONISTS USE IS ASSOCIATED WITH LOWER LIVER- AND CARDIAC-RELATED EVENTS IN PATIENTS WITH MASH CIRRHOSIS WITH TYPE 2 DIABETES: A MULTINATIONAL ANALYSIS

Do Han Kim[1] Donghyun Ko[2] Christina Lee[3] Paul Kroner[4] Frank Lukens[5] Donghee Kim[6] Vincent Chen[7] Karn Wijarnpreecha[8] Meena Bansal[9] Raffi Karagozian[3], [1]Department of Medicine, Mount Sinai Morningside and West, Icahn School of Medicine at Mount Sinai, [2]Department of Medicine, Bridgeport Hospital, Yale New Haven Health, Bridgeport, CT, USA, [3]Division of Gastroenterology and Hepatology, Tufts University School of Medicine, Boston, MA, [4]Department of Gastroenterology, Riverside Health System, Newport News, VA, USA, [5]Division of Gastroenterology and Hepatology, Mayo Clinic Florida, Jacksonville, FL, USA, [6]Stanford University Medical Center, [7]University of Michigan Medical Center, [8]University of Arizona College of Medicine-Phoenix, [9]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: The therapeutic landscape for metabolic dysfunction-associated steatohepatitis (MASH) and cirrhosis is evolving with the emergence of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors. Both classes have independently demonstrated survival and organ-specific benefits, including favorable cardiovascular and hepatic outcomes. However, comparative data in patients with MASH cirrhosis are limited. This study evaluates clinical outcomes in patients with MASH cirrhosis and type 2 diabetes (T2D) treated with either GLP-1RAs or SGLT2 inhibitors. **Methods:** We conducted a retrospective cohort study using the TriNetX global federated health research network. Adult patients with MASH cirrhosis and concurrent T2D were identified and stratified based on GLP-1RA or SGLT2 inhibitor use. Propensity score matching (1:1) was performed, balancing for demographics, comorbidities, and concomitant medications. Outcomes included all-cause mortality, hepatic decompensation, major adverse liver outcomes (MALO) and its components (ascites, hepatic encephalopathy, variceal bleeding, and liver transplant), major adverse cardiovascular events (MACE), as well as renal and cancer-related outcomes. Hazard ratio (HR) and 95% confidence intervals (95%CI) were calculated to quantify the associations between variables. **Results:** A total of 12,206 adult patients with MASH cirrhosis and concurrent T2D were identified, of whom 6,586 (54.0%) were on GLP-1 RA. After matching, 4,610 patients on GLP-1 RA (mean age 62.6 years, 56.9% female) were compared to 4,610 on SGLT2 inhibitors (mean age 62.7 years, 56.8% female). GLP-1 RA therapy was associated with significantly lower risk of hepatic decompensation (HR:0.86, 95%CI: 0.79-0.93), MALO (HR:0.87, 95%CI: 0.81-0.94), ascites (HR:0.85, 95%CI: 0.78-0.93), hepatic encephalopathy (HR:0.91, 95%CI: 0.82-0.99), and MACE (HR:0.86, 95%CI: 0.79-0.93). No significant differences were observed in all-cause mortality, kidney- and cancer-related outcomes. **Conclusion:** In patients with MASH cirrhosis and T2D, GLP-1 receptor agonists are associated with superior hepatic and cardiovascular outcomes compared to SGLT2 inhibitors. These findings support the potential of GLP-1RAs as a preferred therapeutic option in this high-risk population. Nonetheless, clinical decision-making should remain individualized, as tolerability and side effect profiles must be carefully considered.

Outcomes of GLP-1 RA versus SGLT2 Inhibitor Use in Patients with MASH Cirrhosis and Type 2 Diabetes

	GLP-1 RA		SGLT2 Inhibitor		HR (95% CI)
Outcomes	Included	Events	Included	Events	
Mortality	4,584	506	4,588	527	0.92 (0.81, 1.03)
Hepatic decompensation	4,610	1,198	4,610	1,309	**0.86 (0.79, 0.93)**
MALO	4,610	1,360	4,610	1,461	**0.87 (0.81, 0.94)**
Ascites	4,610	868	4,610	963	**0.85 (0.78, 0.93)**
Encephalopathy	4,610	780	4,610	814	**0.91 (0.82, 0.99)**
Variceal bleeding	4,610	213	4,610	240	0.85 (0.70, 1.02)
SBP	4,610	64	4,610	75	0.82 (0.59, 1.14)
HCC	4,610	342	4,610	366	0.90 (0.78, 1.04)
HRS	4,610	87	4,610	103	0.81 (0.61, 1.07)
MACE	4,610	1,228	4,610	1,355	**0.86 (0.79, 0.93)**
AKI	3,623	459	3,619	499	0.91 (0.80, 1.03)
CKD	2,812	471	2,854	526	0.91 (0.80, 1.03)
Liver cancer	4,315	148	4,320	165	0.86 (0.69, 1.07)
Non-liver cancer	3,947	162	3,947	156	1.00 (0.80, 1.24)
Obesity related cancer	3,891	242	3,909	241	0.97 (0.81, 1.16)

Abbreviations: GLP-1 RA, Glucagon-like peptide-1 receptor agonists; SGLT2, Sodium-Glucose Co-Transporter 2; MASH, Metabolic Dysfunction-Associated Steatotic Hepatitis; MALO, Major Adverse Liver Outcomes; SBP, Spontaneous Bacterial Peritonitis; HCC, Hepatocellular Carcinoma; HRS, Hepatorenal Syndrome; MACE, Major Adverse Cardiovascular Events; AKI, Acute Kidney Injury; CKD, Chronic Kidney Disease; HR, Hazard Ratio; CI, Confidence Interval.

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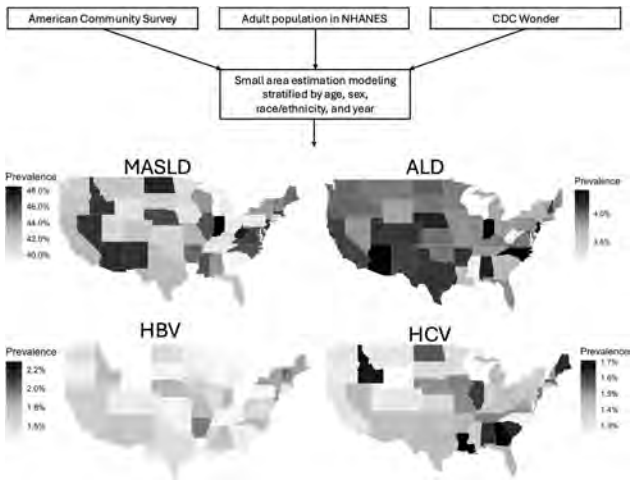
2537 | INCREASING PREVALENCE OF CHRONIC LIVER DISEASE IN THE U.S.: A STATE-LEVEL AND LIVER DISEASE ETIOLOGY-SPECIFIC MODELING STUDY

Michael Le[1] Sovann Linden[1] Etienne Lefranc[1] David Le[1] Thomas Baez[2] Isaac Le[1] Mindie Nguyen[1], [1]Stanford University Medical Center, [2]William Beaumont Army Medical Center

Background: The prevalence of chronic liver disease in the United States (USA) has evolved over the last two decades. With ongoing public health funding cuts in the U.S., granular state-level data are necessary for informing resource allocation and public policy at the local and national level. This current study aimed to estimate the state-level prevalence of chronic liver disease (CLD) in the U.S. using small area estimation techniques. **Methods:** We utilized data from three sources: the National Health and Nutrition Examination Survey (NHANES), CDC Wide-ranging Online Data for Epidemiologic Research (WONDER), and the American Community Survey (ACS). In short, age, sex, ethnicity, and Hispanic-origin specific prevalence, cause-specific mortality, and population data were gathered from each dataset and synthesized in a small area estimation model (Figure 1). The Fay-Herriot technique was applied, using NHANES-based direct prevalence estimates and mortality-based auxiliary data to generate yearly state-level CLD prevalence estimates. **Results:** From 1999 to 2020, national CLD prevalence increased from 28.6% to 36.6% ($p < 0.001$) primarily driven by a rise in metabolic dysfunction-associated steatotic liver disease (MASLD) from 23.1% to 32.7% ($p < 0.001$). Chronic hepatitis C (CHC) decreased sharply from 1.8% to 0.9% ($p = 0.01$). Chronic hepatitis B (CHB) and alcohol-associated liver disease (ALD) remained stable at 0.2-0.4% and 3-4% respectively ($p > 0.05$). Small area estimates in 2020 revealed highest burden of MASLD was in Indiana, West Virginia, and the Western states especially Idaho, Nevada, Arizona, and New Mexico. Meanwhile, the prevalence of ALD was concentrated mostly in the South and Southwest, with highest prevalence in Arizona, Indiana, North Carolina, and Alabama. The prevalence of CHB was low across the United States with no notable geographic pattern. The prevalence of CHC was concentrated in the Southern region, with the highest prevalence in Louisiana, Alabama, Georgia, and South Carolina (Figure 1). **Conclusion:** Using data from multiple population-based databases, this study provides updated granular, state-level insights into the evolving epidemiology of CLD in the U.S. These findings offer valuable insights to guide policy makers in making evidence-based decisions regarding resource allocation and public health policy to combat the growing burden of CLD.



Disclosures: Michael Le: Nothing to Disclose, Sovann Linden: Nothing to Disclose, Etienne Lefranc: Nothing to Disclose, David Le: Nothing to Disclose, Thomas Baez: Nothing to Disclose, Isaac Le: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

2538 | ASSOCIATION OF CARDIOMETABOLIC RISK FACTORS WITH CLINICAL OUTCOMES IN PATIENTS WITH ALD- A RETROSPECTIVE STUDY

Ravi Nishad[1] Babu Meena[1] Ravinder Singh[1] Shasthry SM[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences

Background: Alcoholic hepatitis and cirrhosis are leading causes of liver-related morbidity and mortality, with cardiometabolic risk factors (CMRFs) playing a crucial role in disease progression and outcomes. In this retrospective study, we reviewed the electronic data of patients presented between 2018-2023. We aimed to evaluate the prevalence and association and impact of CMRFs in patients diagnosed with alcoholic hepatitis and cirrhosis. **Methods:** A total of 1,951 patients (1,906 males) were enrolled. Out of these 482 patients had alcoholic hepatitis and 1,469 with cirrhosis. The presence of CMRFs, including obesity, type 2 diabetes mellitus (T2DM), hypertension (HTN), hypertriglyceridemia, and low high-density lipoprotein (HDL), was assessed. **Results:** CMRFs were present in 71% of patients. Among those with alcoholic hepatitis, 71.25% had ≥ 1 CMRF, most commonly obesity (67.4%) and diabetes (46.1%). Mortality was high: 39% died during initial admission, and 24.5% during follow-up. While 18.3% were readmitted but survived, another 18.3% had no readmission. Non-survivors had significantly worse liver function: total bilirubin (20.5 $\pm$ 10.3 mg/dL), and INR (2.62 $\pm$ 1.08) (p

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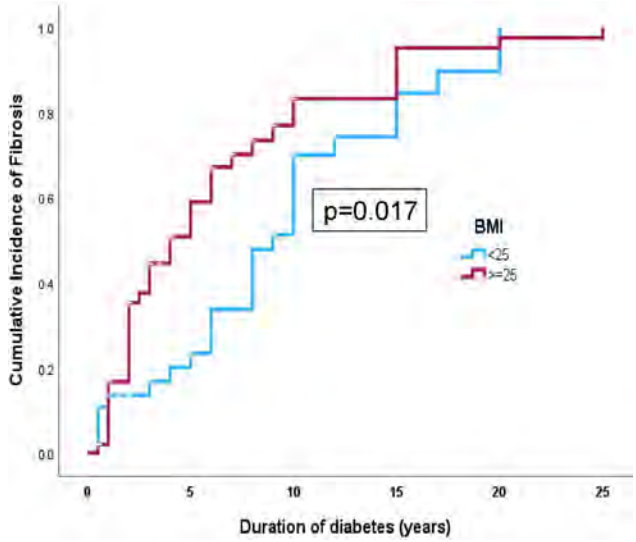
< 0.001). Renal dysfunction markers-urea (64.1 ± 51.3 mg/dL) was strongly associated with mortality (p < 0.001). Kaplan-Meier analysis showed significantly lower survival in those with CMRFs versus without CMRF (81% vs 58%, p < 0.001), particularly obesity, hypertension, and hypertriglyceridemia (p < 0.001). Among patients with alcohol associated liver cirrhosis, 70.7% had ≥ 1 CMRF, again most commonly obesity (62.3%) and diabetes (44.4%). Index admission mortality was 15.6%, with 27.5% dying during follow-up. Of the remainder, 27.6% required readmission and survived, while 29.3% had no further admission. Multivariate Cox regression showed CMRFs were independent predictors of mortality (HR 3.84, CI- 2.56 - 5.75, p < 0.001), with hypertension (HR1.56, CI 1.14 - 2.12, p = 0.005) and hypertriglyceridemia (HR 2.00, CI 1.336 - 3.001, p = 0.001) further increasing risk. Kaplan-Meier analysis confirmed significantly poorer survival with multiple CMRFs (p < 0.001). **Conclusion:** CMRFs significantly worsen outcomes in alcoholic hepatitis and alcohol-associated liver cirrhosis, increasing mortality and readmissions. Obesity, T2DM, hypertension, hypertriglyceridemia, and low HDL are key risk factors. Patients of ALD with CMRFs need closer monitoring and triage for improving outcomes.

Disclosures: Ravi Nishad: Nothing to Disclose, Babu Meena: Nothing to Disclose, Ravinder Singh: Nothing to Disclose, Shasthry SM: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

2539 | DURATION OF TYPE 2 DIABETES MELLITUS IMPACTS DEVELOPMENT OF FIBROSIS IN LEAN VS OBESE METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

Rajan Vijayaraghavan[1] Archana Rastogi[1] GURESH KUMAR[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences, New Delhi

Background: Metabolic dysfunction associated steatotic liver disease (MASLD) and diabetes mellitus (T2DM) are increasingly prevalent, with differing progression in obese MASLD vis-à-vis lean MASLD. Duration of T2DM and development of liver related events is known, however impact of T2DM duration in fibrosis development across different BMI categories is unknown. We aim to determine the association of duration of T2DM and development of fibrosis in obese and lean or overweight MASLD. **Methods:** Patients of T2DM and suspected liver disease and who underwent liver biopsy were prospectively enrolled. T2DM was defined as patients on anti-diabetic medication or HbA1c > 6.5%. All baseline parameters including BMI, biochemical parameters and liver stiffness by transient elastography (LSM) and controlled attenuation parameter (CAP) were assessed. Patients were categorized into BMI > = 25 (grA, obese MASLD) and BMI < 25 (grB, Lean/ overweight MASLD). Duration of T2DM was noted for each patient. Primary objective was to assess the association of 'diabetes duration' with grade of fibrosis in the groups. **Results:** A total of 162 patients (grA, n = 120, 74.1%; grB, n = 42, 25.9%) were enrolled with comparable baseline parameters (grA vs grB, age-49.5 ± 10.9 vs 49.4 ± 3.3; LSM-22.8 ± 16.3 vs 20.4 ± 14.3, p = 0.44; CAP-295 ± 42.6 vs 277 ± 46.2, p = 0.08), and Fib-4-2.85 ± 1.59 vs 2.35 ± 1.19, p = 0.18). The mean BMI was 29.7 ± 3.58 (grA) vs. 23.5 ± 1.33 (grB), p < 0.001) and serum triglycerides were high in non-obese patients (141 ± 63.3 vs 190 ± 56.6, p = 0.09). The histological spectrum was comparable for grade of inflammation (NAS > = 4, 56.7% vs 42.8%, p = 0.23) and stage of fibrosis (p = 0.89). The median T2DM duration was longer for development of advanced fibrosis (F3 fibrosis) in lean patients compared to obese patients [F3 fibrosis, grA median (IQR) 2.75 (2-5.0 yrs) vs grB 6.0 (5.5-11 yrs), p = 0.005; for F4 fibrosis, grA- 3.0 (2-7.75 yrs) vs grB-8.5 (2.5-11.5 yrs), p = 0.09]. On KM analysis, the cumulative development of significant fibrosis and advanced fibrosis was significantly higher in obese MASLD (> = F2 fibrosis, at 5-year, 62% vs 34%, at 10-year, 79% vs 62%, p = 0.014; > = F3 fibrosis, at 5-year, 59% vs 24%, at 10-year, 84% vs 70%, p = 0.017, fig1). **Conclusion:** Obese MASLD patients with T2DM develop fibrosis with a shorter diabetes duration compared to lean MASLD patients. More robust screening in obese MASLD patients with T2DM is required as they are metabolically different compared to lean or overweight MASLD patient.



Disclosures: Rajan Vijayaraghavan: Nothing to Disclose, Archana Rastogi: Nothing to Disclose, GURESH KUMAR: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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2540 | ASSOCIATIONS BETWEEN PER- AND POLYFLUOROALKYL SUBSTANCES (PFAS) AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN CHILDREN AND YOUNG ADULTS

Shiwen Li[1], [1]University of Southern California

Background: Longitudinal studies on associations between per- and polyfluoroalkyl substances (PFAS) exposure and metabolic dysfunction-associated steatotic liver disease (MASLD) are limited, particularly among children and young adults. **Methods:** We evaluated two cohorts spanning distinct age ranges. In the Study of Latino Adolescents at Risk of Type 2 Diabetes (SOLAR), we followed children aged 8–13 years for 8 years (n = 74 at baseline; n = 88 at follow-up). In the Metabolic and Asthma Incidence Research (Meta-AIR) study, we assessed young adults aged 17–23 years (n = 122 at baseline). MASLD was defined as hepatic fat fraction > 5% on MRI plus ≥ 1 cardiometabolic risk factor. Eight PFAS were quantified in plasma by liquid chromatography–high-resolution mass spectrometry. Logistic regression models estimated associations between baseline PFAS levels and MASLD, incorporating an interaction term for PFAS and baseline age. **Results:** In SOLAR, cross-sectional analyses demonstrated that age modified the association of PFOA and PFNA with MASLD (p-interaction < 0.05). Longitudinally, one ng/mL increase in baseline PFOA was associated with 49% higher odds of MASLD (OR 1.49; 95% CI 1.00-2.23). No significant PFAS–MASLD associations were observed in Meta-AIR. **Conclusion:** Baseline PFOA exposure was linked to increased MASLD risk in children, both cross-sectionally and over time, with evidence that age amplifies susceptibility to PFOA and PFNA.

Disclosures: Shiwen Li: Nothing to Disclose

2541 | COST-EFFECTIVENESS OF SEMIANNUAL HEPATOCELLULAR CARCINOMA SURVEILLANCE (HCC) IN PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) WITHOUT CIRRHOSIS: A MARKOV MODELING STUDY

Joanne Liu[1] Sovann Linden[1] Malvyn Lai[1] Xinrong Zhang[1] Ramsey Cheung[2] Rui Huang[1] Taotao Yan[1] Mindie Nguyen[1], [1]Stanford University Medical Center, Stanford, California, USA, [2]Palo Alto Veterans Affairs Health Care System, Palo Alto, CA, USA

Background: HCC is a leading cause of mortality in people with MASLD. HCC risk in people with MASLD and cirrhosis is well established, and routine HCC surveillance is recommended. A substantial proportion of MASLD-related HCC also occurs in MASLD patients without cirrhosis, but routine HCC surveillance is currently not recommended for this group. Cirrhosis is also often unrecognized (up to 40% in prior real-world studies), adding further challenges. HCC surveillance for the overall population with MASLD without cirrhosis is not cost-effective, but cost-effectiveness data based on other established risk factors such as age and sex are limited. Therefore, we aimed to fill in this gap. **Methods:** Based on a surveillance strategy of semiannual ultrasound and AFP test, a Markov model simulating a cohort of 100,000 patients with non-cirrhotic MASLD was constructed, with a 1-year cycle length. The primary study outcome was incremental cost-effectiveness ratio (ICER), with a willingness-to-pay (WTP) threshold of $100,000 per quality-adjusted life years (QALY) gained. Model inputs included age-dependent transition rates between health states, surveillance adherence, and HCC stage distribution that determined the percentage of patients assigned to early, intermediate and late-stage HCC upon diagnosis, as per published data, expert opinion, and/or large national databases. The rate of undiagnosed cirrhosis among people with MASLD of 25% was used for main analyses with sensitivity analyses performed for rates of 20% and 30%. Both costs and QALYs were discounted at an annual rate of 3%. **Results:** HCC surveillance was not cost-effective in the overall MASLD cohort (ICER: $131,598) or for either the overall male (ICER: $110,732) or female (ICER: $192,764) (Table). However, HCC surveillance was cost-effective among males aged ≥60 years (ICER: $78,488) in main as well as sensitivity analyses with undiagnosed cirrhosis rate of 20%. For females ≥60 years, ICER was above WTP threshold at $105,287 but below threshold at $95,827 in sensitivity analyses using undiagnosed cirrhosis rate of 30%. **Conclusion:** Semiannual HCC surveillance using ultrasound and AFP test is cost-effective in males 60 years or older and near WTP threshold for females 60 years or older.

Table 1: ICERs for the overall cohort and subgroups by sex and age, stratified by percent undiagnosed cirrhosis.

Percent Undiagnosed Cirrhosis	Overall	All Male	All Female	Male ≥60 years	Male <60 years	Female ≥60 years	Female <60 years
20%	162,658	126,868	274,058	84,556	296,161	124,965	117,017,011
25%	**131,598**	**110,732**	**192,764**	**78,488**	**200,859**	**105,287**	**573,331**
30%	115,118	100,713	157,931	73,996	162,932	95,827	333,289

Disclosures: Joanne Liu: Nothing to Disclose, Sovann Linden: Nothing to Disclose, Malvyn Lai: Nothing to

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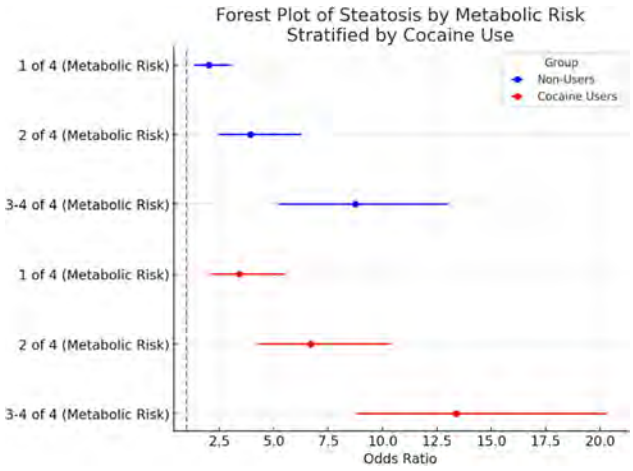
Disclose, Xinrong Zhang: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Rui Huang: Nothing to Disclose, Taotao Yan: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

2542 | DETERMINANTS OF HEPATIC STEATOSIS AMONG BALTIMORE PWID

Redeat Assefa[1] Jacquie Astemborski[1] Jacqueline Rudolph[1] David Thomas[1] Shurti Mehta[1] Gregory Kirk[1], [1]Johns Hopkins University

Background: Hepatic steatosis is an increasingly important comorbidity with a prevalence of 24% in the USA. However, the prevalence, associations and its interplay with substance use patterns is unclear among people who inject drugs (PWID). We investigated among PWID hepatic steatosis determinants and whether they are influenced by cocaine use. **Methods:** The study included 1,267 adults enrolled in the ALIVE (AIDS Linked to the Intravenous Experience) study with validated liver elastography measurements between January 2017 and February 2020. Hepatic steatosis was assessed using vibration-controlled transient elastography (VCTE) with controlled attenuation parameter (CAP) measured by the FibroScan device, with CAP $\geq$248 dB/m indicating significant (>5%) steatosis. Covariates examined included age, sex, race, current injection drug use, HCV RNA levels, liver stiffness, metabolic risk factors (waist circumference, blood pressure, diabetes, and serum cholesterol), HIV viral load, CD4 count, and ART regimen. Statistical analyses were performed using Generalized Estimating Equation (GEE) logistic regression, stratified by recent cocaine use. **Results:** Among 1267 people at baseline, the median age was 55 years. Most were Black (77%), male (68%), and HIV-negative (72%). 431(34%) had CAP $\geq$248. Measures of adiposity and metabolic risk factors were major determinants of hepatic steatosis, with a strong dose-response relationship that appeared to be enhanced by cocaine use. Among recent cocaine users, steatosis risk increased with 1 (aOR = 3.41, 95% CI: 2.13, 5.46), 2 (aOR = 6.68, 95% CI: 4.11, 10.85), and $\geq$3 (aOR = 13.50, 95% CI: 7.99, 22.80) metabolic risk factors versus none. Smaller associations were observed among PWID not using cocaine: 1 (aOR = 2.01, 95% CI: 1.35, 2.99), 2 (aOR = 3.91, 95% CI: 2.60, 5.89), and $\geq$3 (aOR = 8.73, 95% CI: 5.65, 13.50) risk factors. Current IV drug use (aOR = 0.68; 95% CI: 0.54-0.84) and detectable HCV RNA (aOR = 0.65; 95% CI: 0.50-0.85) were inversely associated with hepatic steatosis. No strong association was detected with alcohol use (aOR = 0.96; 95% CI:0.77-1.19) or HIV with viral load undetected (aOR = 0.84; 95% CI: 0.67-1.05). Neither did we detect significant changes in median CAP scores (dB/m) in PWID with changes in HIV viral load detectability: 211 (179–241) for consistently detectable, 213 (172–263) for undetectable-to-detectable, 224 (193–259) for detectable-to-undetectable, and 227 (193–274) for consistently undetectable viral loads across paired visits. **Conclusion:** A high prevalence of hepatic steatosis was observed among PWID, despite the protective effect of ongoing HCV infection. Metabolic factors chiefly contributed, with a clear dose-response relationship that may be exacerbated by cocaine use.



Disclosures: Redeat Assefa: Nothing to Disclose, Jacquie Astemborski: Nothing to Disclose, Jacqueline Rudolph: Nothing to Disclose, David Thomas: Nothing to Disclose, Shurti Mehta: Nothing to Disclose, Gregory Kirk: Nothing to Disclose

2543 | RACIAL DISPARITIES IN MAESTRO-NAFLD-1: A GEOGRAPHIC AND DEMOGRAPHIC ANALYSIS OF A PHASE 3 TRIAL FOR RESMETIROM

Rahul Thakkar[1] Neel Shah[1] Erik Rahimi[1], [1]Baylor Scott & White Health

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly non-alcoholic fatty liver disease (NAFLD), is a leading cause of chronic liver disease in the United States, with disproportionate prevalence and outcomes across racial and ethnic groups. While Hispanic Americans have the highest rates of NAFLD, Black and Asian populations are at increased risk for advanced liver disease and underdiagnosis. Ensuring that clinical trials reflect these affected populations is essential to equitable and generalizable therapeutic development. **Methods:** We evaluated demographic

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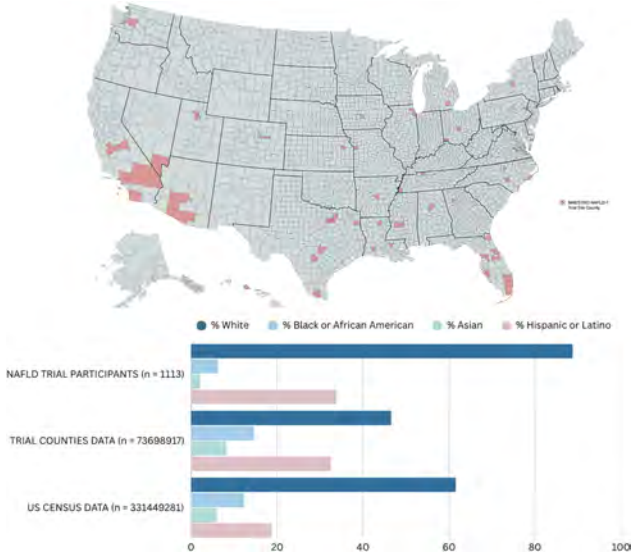
representation in MAESTRO-NAFLD-1 (NCT04197479), a completed Phase 3 trial of resmetirom, using ClinicalTrials.gov site data and U.S. Census 2020 demographics. Trial site ZIP codes were matched to corresponding counties, and racial and ethnic participant distributions were compared to aggregated trial county and national data. **Results:** Among 1,113 participants at 77 U.S. trial sites, 88.8% identified as White, compared to 46.6% in trial counties and 61.6% nationally. Black participants comprised only 6.3% of the cohort, despite representing 14.7% of trial county populations and 12.4% nationally. Asian participants made up 2.1% of the trial but 8.3% of trial counties. Hispanic participation was 33.9%, closely aligned with trial counties (32.5%) and notably exceeding the national average (18.7%), reflecting commendable outreach to this high-burden group. **Conclusion:** MAESTRO-NAFLD-1 demonstrates meaningful inclusion of Hispanic individuals, a population disproportionately affected by MASLD. However, the underrepresentation of Black and Asian participants relative to trial site communities highlights ongoing gaps in equitable enrollment. Building on the success of Hispanic engagement, future MASLD trials should adopt broader equity-focused recruitment strategies to ensure trial populations reflect the full racial and ethnic diversity of those affected—thereby improving the generalizability and fairness of therapeutic development.



Disclosures: Rahul Thakkar: Nothing to Disclose, Neel Shah: Nothing to Disclose, Erik Rahimi: Nothing to Disclose

2544 | IMPACT OF CIRRHOSIS ETIOLOGY ON OUTCOMES AFTER TIPS: A NATIONAL COHORT STUDY

Gurmehr Brar[1] Brian Lee[2], [1]University of Southern California, [2]Keck School of Medicine

Background: Transjugular intrahepatic portosystemic shunt (TIPS) is an effective intervention for portal hypertension, but whether its benefits in alcohol and viral-associated cirrhosis differ in metabolic-dysfunction associated steatotic liver disease (MASLD) has been identified as a knowledge gap. We aimed to (i) characterize outcomes by cirrhosis etiology at 90 days and 1 year following TIPS and (ii) identify demographic and clinical features associated with post-TIPS outcomes. **Methods:** Using a national health system database between 2008-2023, we performed multivariable competing risk analysis by cirrhosis etiology with a primary outcome of overall mortality and competing risk of transplant. Competing risk regression was done using the Fine Gray model. **Results:** 2,846 patients with cirrhosis underwent TIPS (median age 63 [IQR 56-71], 61% male, 74% non-Hispanic White). Probability of transplant-free survival post-TIPS was 84.3% (95%CI 80.3-88.3) at 90 days and 72.1% (95%CI 67.2-77.0) at 1 year with MASLD, versus ALD (78.5% [95%CI 76.7-80.3] at 90 days, 68.7% [95%CI 66.7-70.8] at 1 year), viral hepatitis (78.5% [95%CI 75.6-81.4] at 90 days, 69.1% [95%CI 62.8-75.5] at 1 year), and other etiologies (76.4% [95%CI 73.5-79.4] at 90 days, 62.7% [95%CI 57.7-67.8] at 1 year). In multivariable competing risk analysis, MASLD (vs ALD) was associated with decreased mortality at 90 days (sHR 0.59[95CI 0.42-0.83]) and 1 year (sHR 0.76[95CI 0.60, 0.97]) post-TIPS, and similar to viral hepatitis and other etiologies. Younger age and more recent year undergoing TIPS were associated with decreased survival, whereas pre-TIPS ascites, hepatic encephalopathy, and increasing Charlson Comorbidity Index score were associated with increased mortality at 90 days and 1 year post-TIPS. **Conclusion:** TIPS is associated with excellent survival rates in MASLD cirrhosis and we identified risk factors that should be utilized to refine patient selection. Together these findings affirm that TIPS can be an effective intervention in reducing morbidity and mortality in MASLD cirrhosis, and provide areas for future research to improve patient selection and outcomes.

Disclosures: Gurmehr Brar: Nothing to Disclose, Brian Lee: NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, DURECT: Advisor, HepaTx: Advisor, CymaBay: Consultant, Ipsen: Consultant, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor, Assertio: Consultant

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2545 | RISK OF MICROVASCULAR AND MACROVASCULAR COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES AND CIRRHOTIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: A RETROSPECTIVE COHORT STUDY

Semiu Gbadamosi[1] David Shi[1] Abdalla Aly[1] Caichen Zhong[1] Husam Albarmawi[1] Aidan McGovern[1] Anthony Hoovler[1] Carlos Campos[2], [1]Novo Nordisk Inc, [2]University of Texas Health Science Center

Background: Metabolic dysfunction-associated steatohepatitis (MASH) in patients with type 2 diabetes (T2D) is associated with increased risk of T2D complications. As MASH progresses to cirrhosis, it further alters hepatic function, impairs glucose regulation and exacerbates systemic inflammation. However, real-world data on the burden of T2D complications in patients with T2D and cirrhotic MASH are limited. This study compared risks of micro- and macrovascular complications between cirrhotic and noncirrhotic MASH in a T2D population. **Methods:** This retrospective cohort study identified patients (≥18 years) with T2D and MASH from 2016 to 2024 using Optum's Clinformatics® Data Mart Database – a large, national, de-identified, adjudicated claims database of medically insured patients in the US. Patients were required to have 12 months' continuous enrollment pre-index (baseline) and ≥1 month of follow-up through June 2024. Eligible patients were categorized into cirrhotic or noncirrhotic groups based on presence of cirrhosis or its complications. Propensity score matching was used to balance baseline characteristics between groups. Composite outcomes assessed were new onset of micro- and macrovascular complications of T2D. Cumulative incidences of T2D complications were calculated using the Aalen-Johansen estimator. Subdistribution hazard ratios (SHRs) and 95% confidence intervals (CIs) were computed using a Fine-Gray model, accounting for death as competing risk. Stratified analyses by age group (<65 vs ≥65 years) were also performed. **Results:** The analyses included 1197 and 966 matched pairs in the micro- and macrovascular complications cohorts, respectively. Over a 2-year follow-up period, incidence of microvascular complications was similar in the cirrhotic and noncirrhotic groups (36.7% vs 31.8%; risk ratio [RR] = 1.15, 95% CI: 0.99;1.33). Higher risks of macrovascular complications were observed in the cirrhotic vs noncirrhotic group (RR = 1.48, 95% CI: 1.24;1.78). Overall, patients in the cirrhotic group had significantly increased hazards of microvascular (SHR: 1.22, 95% CI: 1.08;1.38) and macrovascular complications (SHR:1.36, 95% CI: 1.19;1.57) vs the noncirrhotic group. A stronger effect was seen in patients <65 years for microvascular (SHR: 1.44, 95% CI: 1.17;1.79) and macrovascular complications (SHR: 1.62, 95% CI: 1.27;2.05) (Table). **Conclusion:** Patients with T2D and cirrhotic MASH face higher risks of T2D complications than those with T2D and noncirrhotic MASH, especially in younger populations.

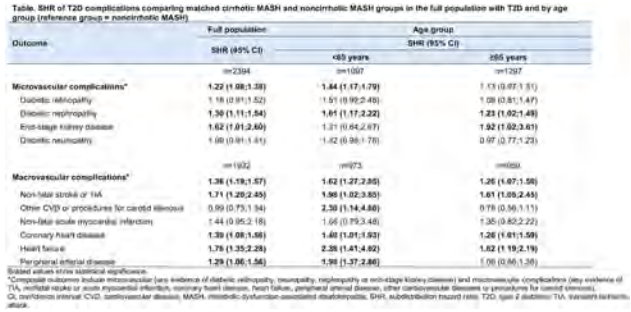

Table. SHR of T2D complications comparing matched cirrhotic MASH and noncirrhotic MASH groups in the full population with T2D and by age group (reference group = noncirrhotic MASH)

Outcome	Full population	Age group	
	SHR (95% CI)	SHR (95% CI)	
		<65 years	≥65 years
	n=2394	n=1097	n=1297
Microvascular complications*	1.22 (1.08;1.38)	1.44 (1.17;1.79)	1.13 (0.97;1.31)
Diabetic retinopathy	1.18 (0.97;1.52)	1.51 (0.99;2.48)	1.08 (0.81;1.47)
Diabetic nephropathy	1.30 (1.11;1.54)	1.61 (1.17;2.22)	1.23 (1.02;1.48)
End-stage kidney disease	1.62 (1.01;2.60)	1.31 (0.64;2.67)	1.92 (1.02;3.61)
Diabetic neuropathy	1.09 (0.91;1.41)	1.52 (0.98;1.78)	0.97 (0.77;1.23)
	n=1932	n=973	n=959
Macrovascular complications*	1.36 (1.19;1.57)	1.62 (1.27;2.05)	1.26 (1.07;1.50)
Non-fatal stroke or TIA	1.71 (1.20;2.45)	1.98 (1.02;3.85)	1.61 (1.09;2.45)
Other CVD or procedures for carotid stenosis	0.99 (0.73;1.34)	2.30 (1.14;4.60)	0.78 (0.56;1.11)
Non-fatal acute myocardial infarction	1.44 (0.95;2.18)	1.66 (0.79;3.46)	1.35 (0.82;2.22)
Coronary heart disease	1.39 (1.08;1.80)	1.40 (1.01;1.93)	1.26 (1.01;1.59)
Heart failure	1.76 (1.35;2.28)	2.38 (1.41;4.02)	1.62 (1.19;2.19)
Peripheral arterial disease	1.29 (1.00;1.66)	1.98 (1.37;2.86)	1.06 (0.86;1.30)

Bolded values show statistical significance.
*Composite outcome include microvascular (any evidence of diabetic retinopathy, neuropathy, nephropathy or end-stage kidney disease) and macrovascular complications (any evidence of TIA, nonfatal stroke or acute myocardial infarction, coronary heart disease, heart failure, peripheral arterial disease, other cerebrovascular diseases or procedures for carotid stenosis).
CI, confidence interval; CVD, cardiovascular disease; MASH, metabolic dysfunction-associated steatohepatitis; SHR, subdistribution hazard ratio; T2D, type 2 diabetes; TIA, transient ischemic attack.

Disclosures: Semiu Gbadamosi: Novo Nordisk Inc: Employee, Novo Nordisk A/S: Stock - publicly traded company, David Shi: Novo Nordisk: Employee, Abdalla Aly: Novo Nordisk Incorporated: Employee, Novo Nordisk Incorporated: Stock - publicly traded company, Caichen Zhong: Nothing to Disclose, Husam Albarmawi: Novo Nordisk Inc.: Employee, Novo Nordisk Inc.: Stock - publicly traded company, Genentech Inc.: Employee, Genentech Inc.: Stock - publicly traded company, Aidan McGovern: Novo Nordisk: Employee, Anthony Hoovler: Novo Nordisk Inc: Employee, Carlos Campos: Novo Nordisk: and Consultant, Lilly USA: and Consultant, Boeringer Inglelheim: Consultant

2546 | FATTY LIVER INDEX (FLI) SHOULD NOT BE USED TO STUDY STEATOTIC LIVER DISEASE IN LEAN INDIVIDUALS

Mohammed Rifat Shaik[1] Nishat Anjum Shaik[2] Yaron Rotman[3], [1]National Institute of Health, [2]SSM Health/ Saint Louis University School of Medicine, [3]National Institutes of Health

Background: The Fatty Liver Index (FLI) is a widely used and validated serological tool for detection of steatotic liver disease (SLD) in population studies. While it has been used to study unique features of SLD in lean individuals, its performance in this subgroup has not been directly validated. We hypothesized that FLI would not identify lean SLD accurately due to its dependence on body size measures. **Methods:** Data from the National Health and Nutrition Examination Survey (NHANES) 2017-20 database

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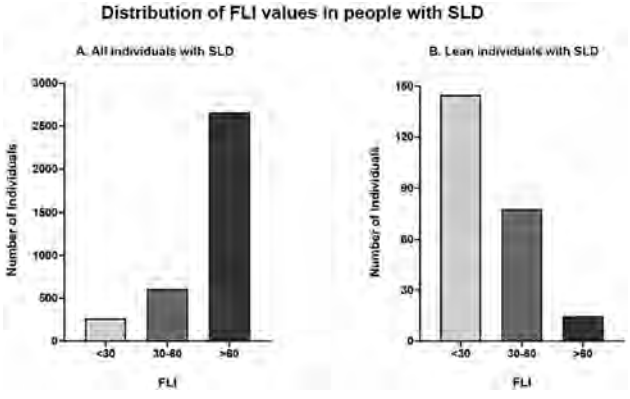
was utilized. Adult participants with available vibration-controlled transient elastography data and complete variables for FLI calculation were included. SLD was defined by a controlled attenuation parameter (CAP) ≥263 dB/m. Lean status was determined using ethnicity-adjusted BMI cutoffs. The diagnostic performance of FLI was assessed overall and in lean participants using standard rule-in (≥60) and rule-out (<30) thresholds, with additional subgroup analyses across BMI categories. **Results:** The study population included 7191 individuals, of whom 3602 (50%) had SLD. There were 1739 lean individuals, 238 of whom (13.7%) had SLD. In the overall population, FLI had adequate performance. SLD was detected by FLI ≥60 with a sensitivity of 73.8% and a specificity of 75.7%, with a positive predictive value (PPV) of 75.3%. FLI <30 had a negative predictive value of 86.9%. In contrast, among lean participants, FLI ≥60 detected only 15 of 238 SLD cases (sensitivity 6.3%, Figure) with PPV of only 45.5% with only modest improvement using the rule-out threshold. Lean individuals predicted to have SLD by FLI markedly differed from those with imaging-confirmed lean SLD. They were older, had higher body mass index(BMI), waist circumference, gamma-glutamyl transferase, and triglyceride levels, and had a greater burden of cardiometabolic comorbidities. **Conclusion:** Due to its inherent dependence on body size measures, FLI is not accurate in identifying lean participants with SLD. Moreover, using FLI in lean individuals tends to capture a distinct subgroup at the upper end of the lean BMI range with more pronounced metabolic abnormalities. The biases introduced by the inaccuracy and misrepresentation of true lean SLD phenotype imply that FLI should not be used in population-based studies focusing on lean SLD.



Disclosures: Mohammed Rifat Shaik: Nothing to Disclose, Nishat Anjum Shaik: Nothing to Disclose, Yaron Rotman: Astra Zeneca: My spouse is an employee

2547 | HISPANIC OR LATINO PATIENTS WITH COMPENSATED MASH CIRRHOSIS HAVE A HIGHER RATE OF ADVERSE OUTCOMES COMPARED TO NON-HISPANICS OR NON-LATINO

Aryan Ayati[1] Alexandre Watanabe[2] Shadera Azzam[1] Xiao Zhang[2] Eirum Chaudhri[2] Gail Fernandes[2] Melissa Vendetti[2] Vivek Rudrapatna[1] Jin Ge[3], [1]University of California San Francisco, [2]Merck & Co., Inc., Rahway, NJ, USA, [3]University of California, San Francisco

Background: Prior literature has indicated that Hispanic and Latino patients have a higher disease burden related to MASH compared to non-Hispanic and non-Latino patients. However, it is unclear whether this difference extends to clinical outcomes in compensated cirrhosis. This study characterizes the real-world trajectory of compensated MASH cirrhosis at a large academic medical center with a large population of Hispanic and Latino patients. **Methods:** We used a previously validated natural language processing algorithm for detecting MASH from clinical notes ("NASH Detection") to identify patients with compensated MASH cirrhosis at UCSF from 2012-2022. The cohort was stratified by race/ethnicity and characterized using clinical variables and residential-level measures of social determinants of health (SDOH). Outcomes of interest were defined as mortality, hepatic decompensations, and liver disease progression. We evaluated differences between subgroups using Chi^2, T-, and Mann-Whitney tests and Kaplan-Meier and Cox regressions for time-to-event analyses. **Results:** We identified 493 patients with compensated MASH cirrhosis with a median follow-up time of 3.4 years, of which 34% were Hispanic or Latino. Hispanic or Latino patients were younger, more likely female, lived further away from UCSF and in areas with higher Area Deprivation Indices, and had higher baseline MELDs compared to non-Hispanic or non-Latino patients (Table 1). In terms of outcomes, Hispanic or Latino patients had higher annual incidences of mortality and ascites compared to non-Hispanic or non-Latino patients (Table 1). Associations with outcomes were attenuated when adjusted for SDOH measures and clinical variables. Time-to-event analyses for Hispanic or Latino patients showed higher baseline FIB-4 (HR 1.4, $P < 0.01$), being male (HR 2.1, $P = 0.03$), and abnormal alkaline phosphatase (HR 2.6, $P = 0.01$) as predictors for hepatic decompensation. **Conclusion:** Hispanic or Latino

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patients with compensated MASH cirrhosis are at greater risk for mortality and hepatic decompensation events compared to non-Hispanic or non-Latino patients. These differences may be partially explained by disparities in socioeconomic status and healthcare access. This study provides insights on the clinical burden of compensated MASH cirrhosis among Hispanic and Latino patients in a real-world setting, highlighting the need of strategies to mitigate socio-economic barriers and effective treatments to improve patient outcomes.

Table 1: Comparison of Baseline Characteristics and Outcomes Between Hispanic or Latino and non-Hispanic or non-Latino Patients with MASH Cirrhosis

	Overall (n=493)	Not Hispanic or Latino (n=326)	Hispanic or Latino (n=167)
Baseline Characteristics			
Demographics			
Age, mean (SD)	56.1 (13.2)	57.1 (12.3)	54.3 (14.6)
Sex (Female), n (%)	303 (61.5)	177 (54.3)	126 (75.4)
Driving Distance (km), median [IQR]	130.9 [30.8,251.7]	96.4 [24.6,238.8]	142.0 [48.4,271.3]
ADI (Mean State), median [IQR]	5.8 [2.4,8.8]	4.9 [2.3,8.4]	7.7 [4.5,9.2]
Insurance Type, n (%)			
Commercial	207 (42.0)	160 (49.1)	47 (28.1)
Medicaid	117 (23.7)	52 (16.0)	65 (38.9)
Medicare	164 (33.3)	111 (34.0)	53 (31.7)
Self-Pay	5 (1.0)	3 (0.9)	2 (1.2)
Comorbidities, n (%)			
Hypertension	320 (64.9)	210 (64.4)	110 (65.9)
Hyperlipidemia	257 (52.1)	173 (53.1)	84 (50.3)
Diabetes	226 (45.8)	140 (42.9)	86 (51.5)
Chronic Kidney Disease	25 (5.1)	15 (4.6)	10 (6.0)
Prediabetes	114 (22.9)	79 (23.9)	35 (21.0)
Obesity	367 (74.4)	243 (74.5)	124 (74.3)
Charlson Comorbidity Index, median [IQR]	5.0 [4.0,6.0]	5.0 [4.0,6.0]	5.0 [4.0,5.0]
Laboratory Values, median [IQR]			
MELD Score	8.0 [6.4,9.9]	7.9 [6.3,9.5]	8.5 [6.9,10.1]
FIB-4 Index	2.3 [1.5,2.8]	2.1 [1.5,2.7]	2.2 [1.4,3.2]
Alkaline phosphatase (U/L)	100.9 [76.0,100.9]	100.9 [72.0,100.9]	100.9 [89.5,120.5]
Alanine aminotransferase (U/L)	55.5 [35.0,55.5]	55.5 [39.0,55.5]	55.5 [30.5,55.5]
Aspartate aminotransferase (U/L)	47.4 [33.0,47.4]	47.4 [33.0,47.4]	47.4 [34.0,47.4]
HbA1c (%)	6.4 (1.4)	6.3 (1.4)	6.5 (1.3)
eGFR (mL/min)	93.7 (17.9)	93.0 (17.2)	95.0 (19.1)
Triglycerides (mg/dL)	176.8 (53.9)	176.7 (53.5)	177.1 (54.8)
Medication use, n (%)			
Anti-hyperglycemic medications			
Oral Diabetic Medication	103 (30.8)	54 (32.3)	49 (29.3)
Insulin	85 (17.2)	47 (14.4)	38 (22.8)
GLP-1 receptor agonists	22 (6.6)	12 (7.2)	10 (6.0)
Statins	83 (24.3)	42 (25.1)	41 (24.6)
Vitamin E	72 (14.6)	56 (17.2)	16 (9.6)
Outcomes			
All-cause Mortality, n (%, Annual Incidence[1])	70 (14.2%, AI=1.4%)	39 (12.0%, AI=2.3%)	31 (18.6%, AI=4.6%)
Ascites, n (%, Annual Incidence)	69 (14.0%, AI=3.3%)	38 (11.7%, AI=3.0%)	31 (18.6%, AI=5.2%)
MELD-3 score ≥ 15, n (%, Annual Incidence)	48 (9.7%, AI=2.3%)	21 (6.4%, AI=1.6%)	27 (16.2%, AI=4.5%)
eCPT Score ≥ 7, n (%, Annual Incidence)	81 (16.4%, AI=4.1%)	44 (13.5%, AI=3.6%)	37 (22.2%, AI=6.5%)
Decompensation symptoms[2], n (%, Annual Incidence)	98 (19.9%, AI=5.00%)	60 (18.4%, AI=4.9%)	38 (22.8%, AI=6.8%)
Composite outcome[3], n (%, Annual Incidence)	160 (32.5%, AI=9.6%)	98 (30.1%, AI=8.8%)	62 (37.1%, AI=11.7%)

[1] Annual incidence calculated as the number of events divided by the person year of follow-up

[2] Defined as the earliest occurrence of any of the following: Ascites, Esophageal varices, SBP, Encephalopathy

[3] Defined as the earliest occurrence of any follow-up outcome (Decompensation symptoms, Hepatocellular Carcinoma, Liver transplant, MELD-3 ≥ 15 , eCPT ≥ 7)

Disclosures: Aryan Ayati: Nothing to Disclose, Alexandre Watanabe: Merck & Co., Inc.: Employee, Shadera Azzam: Nothing to Disclose, Xiao Zhang: Merck: Employee, Eirum Chaudhri: Merck: Employee, Gail Fernandes: Merck & Co., Inc: Employee, Merck & Co., Inc: Stock - publicly traded company, Melissa Vendetti: Merck Sharpe and Dohme LLC: Employee, Vivek Rudrapatna: Nothing to Disclose, Jin Ge: Merck and Co: Grant/Research Support, Iota Biosciences/Astellas Pharmaceuticals: Consultant, Madrigal Pharamaceuticals: Consultant, Gilead Sciences: Advisor

2548 | METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN INDIVIDUALS WITH OBSTRUCTIVE SLEEP APNEA (OSA): A META-ANALYSIS

Sarva Patel[1] Tanya Gupta[2] Eric Huang[1], [1]Kaiser Permanente SCAL, [2]Cornell University

Background: Obstructive sleep apnea (OSA) is a condition known for its recurrent episodes of upper airway obstruction resulting in periods of apnea. Metabolic dysfunction–associated steatotic liver disease (MASLD) is known for the excessive accumulation of lipids in the hepatic parenchyma with the potential of progressing to cirrhosis or hepatocellular carcinoma. While the relationship between both OSA and MASLD was explored in primary studies, a comprehensive meta-analysis is needed for quantifying this association and the possible role of OSA on liver enzymes. **Methods:** A systematic search process was conducted across PubMed, Web of Sciences and Scopus to identify observational studies exploring the co-occurrence of MASLD in OSA compared to controls for calculation of the pooled odds ratio (OR) of MASLD in OSA. Additionally, weighted mean differences (WMD) for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) between OSA and non-OSA groups were calculated. **Results:** A statistically significant increase in the risk for MALD in individuals with OSA compared to controls was observed with an OR of 2.41 [95% CI: 1.857-3.127]. Individuals with severe OSA had higher pooled OR of MASLD compared with less severe OSA, OR = 2.68 [95% CI: 1.732-4.145] and 2.096 [95% CI: 1.511-2.907] respectively. A statistically significant WMD was found for both ALT and AST in OSA compared to controls, WMD = 4.006 [95% CI: 1.561-6.45] and 1.624 [95% CI: 0.855-2.393], respectively. No significant differences were found regarding study region, exclusion of individuals with prior OSA diagnosis, population type and method of MASLD detection. **Conclusion:** OSA is associated with an increased risk for MASLD, and the risk increases by increasing OSA severity. Those with OSA had higher liver enzymes compared to controls. These findings highlight the need for routine screening for MASLD in individuals with OSA

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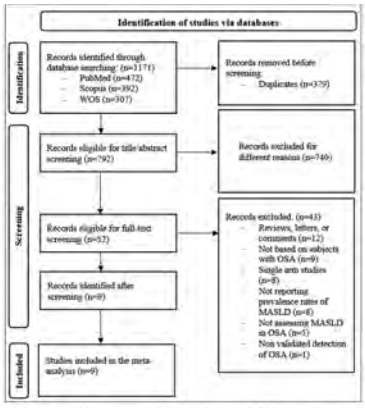

Figure 1: Graphical representation of the detailed results of database searching process

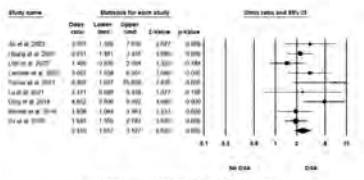

Figure 2: Odds ratio for MASLD in individuals with OSA

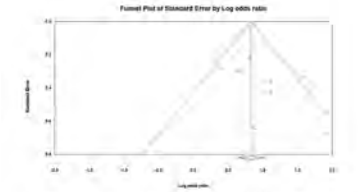

Figure 3: The funnel plot for the pooled odds ratio of MASLD in OSA compared to controls

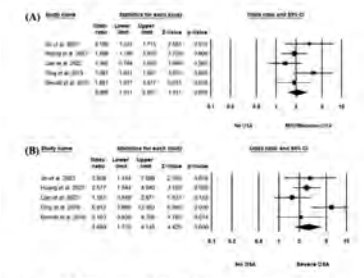

Figure (4) Pooled OR estimates for MASLD in (A) mild/moderate OSA, (B) Severe OSA

Table 2: Subgroup analysis for different study categories

Categorical variables	Included groups	Studies (n)	I² (%)	Pooled OR	Lower limit	Upper limit	p-value: (within)	p-value: (across)
Region	Asia	7	47.01	2.46	1.79	3.39	<0.001	0.91
	Europe/ America	2	0	2.57	1.32	5.27	0.004	
MASLD diagnosis	US or biopsy	6	53.33	2.53	1.78	3.59	<0.001	0.76
	Others	3	0	2.29	1.4	3.76	0.001	
population	General	6	43.62	2.35	1.7	3.23	<0.001	0.644
	Special	3	36.42	2.73	1.56	4.78	<0.001	
Exclusion of previous OSA diagnosis	No	5	32.21	2.09	1.52	2.89	<0.001	0.497
	Yes	4	21.07	2.93	1.97	4.35	<0.001	

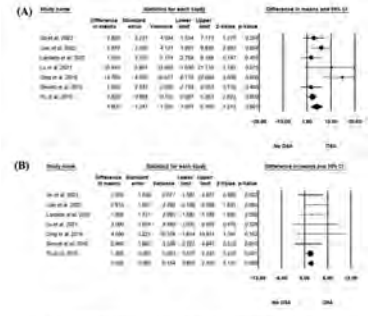

Figure (5) WMD between OSA and non-OSA subjects for (A) ALT, (B) AST

Disclosures: Sarva Patel: Nothing to Disclose, Tanya Gupta: Nothing to Disclose, Eric Huang: Nothing to Disclose

2549 | UNVEILING THE PROGNOSTIC BURDEN OF METALD: A MULTICENTER BIOPSY-BASED STUDY: A NATIONWIDE BIOPSY-BASED STUDY OF 2,131 PATIENTS

Takuma Nakatsuka[1] Takeshi Okanoue[2] Makiko Taniai[3] Rie Irie[4] Hanako Tsujikawa[4] Eisuke Murakami[5] yuya seko[6] Kanji Yamaguchi[7] Hirokazu Takahashi[8] Norio Akuta[9] Takumi Kawaguchi[10] Jun Arai[11] Kiyoaki Ito[11] Michiie Sakamoto[4] Mitsuhiro Fujishiro[1] Kazuhiko Koike[1] Ryosuke Tateishi[1], [1]The University of Tokyo, [2]Osaka Saiseikai Suita Hospital, [3]Tokyo Women's Medical University, [4]Keio University School of Medicine, [5]Hiroshima University, [6]Kyoto Prefectural University of Medicine, [7]Kyoto Prefectural University of Medicine Graduate School of Medical Science, [8]Saga University Hospital, [9]Toranomon Hospital and Okinaka Memorial Institute for Medical Research, [10]Kurume University School of Medicine, [11]Aichi Medical University

Background: Metabolic dysfunction-associated alcohol-related liver disease (MetALD), a recently defined subtype of steatotic liver disease (SLD), is characterized by excessive alcohol intake and cardiometabolic risk factors. Its prognosis remains unclear compared to metabolic dysfunction–associated steatotic liver disease (MASLD). **Methods:** We analyzed 2,131 patients with biopsy-proven SLD (2,014 MASLD; 117 MetALD) from a nationwide multicenter registry. Survival and clinical event incidence, including hepatocellular carcinoma (HCC), liver decompensation (LD), cardiovascular disease (CVD), and extrahepatic cancer (EHC), were assessed. Risks were estimated using multivariable Cox and Fine–Gray models. **Results:** Compared to MASLD, the MetALD group had more males (74.4% *vs.* 47.9%), diabetes (65.8% *vs.* 51.2%), and current smokers (24.8% *vs.* 10.4%), with no significant differences in liver histology. During a median follow-up of 8.3-years (17,627 person-years), 149 patients died. Overall mortality was significantly higher in MetALD (1.80 *vs.* 0.79 per 100 person-years; $P < .001$), primarily driven by nonliver-related causes ($P < .001$), whereas liver-related mortality was comparable ($P = .95$). Multivariate analysis identified older age (adjusted hazard ratio [aHR] 1.09; 95% CI, 1.07–1.11), higher BMI (aHR 1.05; 95% CI, 1.01–1.10), and MetALD (aHR 1.87; 95% CI, 1.06–3.30) as independent predictors of mortality, while dyslipidemia was protective (aHR 0.69; 95% CI, 0.48–1.00). Histologic features, including cirrhosis (aHR 1.85; 95% CI, 1.09–3.13), steatosis $< 33\%$ (aHR 1.68; 95% CI, 1.16–2.44), and moderate-

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to-severe portal inflammation (aHR 1.64; 95% CI, 1.07–2.50), were also independently associated with mortality. During follow-up, 87 developed HCC, 77 LD, 112 CVD, and 130 EHC. Annual rates of liver-related events were comparable between groups (HCC: 0.59 *vs.* 0.50; LD: 0.56 *vs.* 0.43 per 100 person-years), whereas CVD (1.33 *vs.* 0.66; $P = .04$) and EHC (2.25 *vs.* 0.72; $P < .001$) were more frequent in MetALD. In multivariate analysis, MetALD was independently associated with EHC (aHR 2.58; 95% CI, 1.52–4.39), but not with HCC or LD. **Conclusion:** MetALD is associated with poorer overall survival than MASLD, primarily due to excess CVD and EHC. In contrast, liver-specific outcomes were comparable. Histologic features beyond fibrosis, particularly low-grade steatosis and portal inflammation, were independent predictors of worse survival. These findings underscore the need for comprehensive risk assessment in SLD, incorporating individual alcohol consumption, metabolic status, and the risk of extrahepatic complications.

Disclosures: Takuma Nakatsuka: Nothing to Disclose, Takeshi Okanoue: Nothing to Disclose, Makiko Taniai: Nothing to Disclose, Rie Irie: Nothing to Disclose, Hanako Tsujikawa: Nothing to Disclose, Eisuke Murakami: Nothing to Disclose, yuya seko: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Kanji Yamaguchi: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Norio Akuta: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching, Jun Arai: Nothing to Disclose, Kiyoaki Ito: Nothing to Disclose, Michiie Sakamoto: Nothing to Disclose, Mitsuhiro Fujishiro: Nothing to Disclose, Kazuhiko Koike: Nothing to Disclose, Ryosuke Tateishi: EA Pharma: Speaking and Teaching, MSD: Speaking and Teaching, Aska Pharma: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Abbvie: Speaking and Teaching, Eisai: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Covidien: Speaking and Teaching, Bayer: Speaking and Teaching, Century Medical: Speaking and Teaching, Canon Medical: Speaking and Teaching, Asahikasei Pharma: Speaking and Teaching, Terumo: Speaking and Teaching, TechsoMed: Speaking and Teaching, Sumitomo Pharma: Speaking and Teaching, Taisho Pharmaceutical: Speaking and Teaching, Daiichi-Sankyo: Speaking and Teaching, Chugai: Speaking and Teaching, Fujifilm: Speaking and Teaching

2550 | PREVALENCE OF LIVER FIBROSIS IN RELATIVES OF PATIENTS WITH MASLD-RELATED CIRRHOSIS: A STUDY ON DEGREE OF KINSHIP

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Background: First-degree relatives of patients with MASLD-related cirrhosis are recommended to undergo systematic liver fibrosis screening, based on high prevalence rates reported in Europe and the U.S. Growing evidence supports a strong hereditary component in the development and progression of fatty liver disease, including genetic polymorphisms associated with fibrosis. However, it remains unclear whether the risk extends beyond first-degree relatives or if a family history of MASLD-related cirrhosis is a relevant risk factor in Latin American populations. This study aimed to determine the prevalence of liver fibrosis and associated factors in first-, second-, and third-degree relatives of patients with MASLD-related cirrhosis. **Methods:** Patients with confirmed MASLD-related cirrhosis were identified from a liver disease outpatient clinic in Cartagena, Colombia. Their first-, second-, and third-degree relatives were offered transient elastography (Echosens) and body composition analysis using bioelectrical impedance (InBody 270) after a 6-hour fast. Only elastography results with an interquartile range $\leq$30% of the median and success rate $\geq$60% were included. All participants underwent physical examination and a detailed interview on medical history and alcohol use. Those with abnormal elastography ($\geq$7.2 kPa) were referred to hepatology for follow-up. Written informed consent was obtained from all participants. Numeric and categorical variables were expressed as means (SD) and percentages (n), respectively. The chi-square test was used to compare fibrosis prevalence across kinship degrees. A univariate logistic regression identified predictors of liver fibrosis, with statistical significance set at $p \leq 0.05$. **Results:** A total of 99 relatives were included: 56 first-degree, 13 second-degree, and 30 third-degree. Mean age was 44 years (SD 14), and 32.3% were male. Mean CAP was 247 dB/m (SD 64), visceral fat 12.7% (SD 5.3), body fat 26.7% (SD 9.6), and skeletal muscle mass 27 kg (SD 7). Hypertension, diabetes, dyslipidemia, and overweight/obesity were found in 17.2%, 4%, 14.1%, and 74% of the sample, respectively. Overall liver fibrosis prevalence was 15.2%, and by kinship degree: 21.4% (first), 7.7% (second), and 6.7% (third), with no

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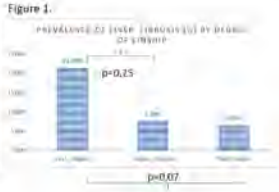
significant differences (Figure 1). Five individuals had advanced but compensated liver disease (≥10 kPa). BMI, visceral fat, body fat percentage, and waist circumference were predictors of fibrosis (Table 1). **Conclusion:** Liver fibrosis prevalence is high in first-degree relatives of patients with MASLD-related cirrhosis. Although not statistically significant, a decreasing trend in prevalence was observed with increasing kinship degree. BMI, abdominal circumference, and fat distribution may help identify individuals at greater risk.

Variable	OR	95% CI	p-value
Male sex	1,05	0.32 – 3.3	0,92
Age	1,02	0.98 – 1.06	0,32
BMI	1,14	1.02 – 1.28	0,019
Second-degree kinship	0,48	0.22 – 1.06	0,07
Third-degree kinship	0,26	0.05 – 1.25	0,09
Arterial hypertension	3	0.87 – 10.3	0,08
Diabetes mellitus	1,9	0.18 – 19.8	0,58
Dyslipidemia	1,65	0.40 – 6.8	0,48
Weekly alcohol intake (g)	0,99	0.98 – 1.00	0,64
Abdominal circumference (cm)	1,08	1.02 – 1.14	0,003
CAP (dB/m)	1	0.99 – 1.01	0,54
Visceral fat (%)	1,13	1.02 – 1.26	0,018
Muscle mass (kg)	1,02	0.94 – 1.10	0,59
Body fat percentage (%)	1,07	1.009 – 1.10	0,023

Table 1. Factors Associated with Liver Fibrosis in Relatives of Patients with MASLD-Related Cirrhosis. Univariate Logistic Regression Analysis



Disclosures: ISMAEL YEPES: Nothing to Disclose, NICOLE CHAMORRO: Nothing to Disclose, Juan Ignacio Marin Zuluaga: Nothing to Disclose, GUILLERMO DONADO: Nothing to Disclose

2551 | INCIDENCE OF HEPATOCELLULAR CARCINOMA IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A RECONSTRUCTED INDIVIDUAL PATIENT DATA META-ANALYSIS

Faith Tan[1] Glenn Jun Kit Ho[1] Ryan YanZhe Lim[1] Alfred Kow[2] Karn Wijarnpreecha[3] Vincent Chen[4] Hirokazu Takahashi[5] Cheng Han Ng[6] Mark Muthiah[7] Daniel Huang[7], [1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [2]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, National University Hospita, [3]University of Arizona College of Medicine-Phoenix, [4]University of Michigan Medical Center, [5]Division of Metabolism and Endocrinology, Faculty of Medicine, Saga University, Saga, Japan, [6]"1) Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospita, [7](1)Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; (2) Divi

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the fastest-rising etiology of hepatocellular carcinoma (HCC). The time-dependent incidence of HCC in people with MASLD has not been reported. We performed a pooled analysis of time-to-event data to provide robust estimates for the incidence of HCC in MASLD. **Methods:** Medline and Embase were searched from inception to November 2024. Individual participant data were reconstructed from published Kaplan–Meier curves, and a pooled analysis of cumulative HCC incidence was performed using a random-effects model. **Results:** We screened 4,951 articles and included 26 studies (3,995,728 individuals). The 1-, 3-, 5-, and 10-year cumulative incidence of HCC in people with MASLD and known advanced fibrosis was 0.8%, 2.4%, 3.9%, and 8.8%, respectively in administrative database studies, and 3.9%, 11.7%, 21.0% and 48.5%, respectively in hospital/clinic-based studies. The cumulative incidence of HCC in people with MASLD but without advanced fibrosis was 0.1%, 0.5%, 0.7%, and 1.3%, respectively, inadministrative database studies, and 1.6%, 4.7%, 8.2%, and 18.3%, respectively, in hospital/clinic-based studies. The risk of HCC in patients with advanced fibrosis was significantly higher compared to those without advanced fibrosis in both administrative database (HR: 11.09 [95% CI: 2.68 – 45.89], $p < 0.001$) and hospital/clinic-based studies (HR: 10.50 [95% CI: 3.19 – 34.51], $p < 0.001$). **Conclusion:** This reconstructed individual participant data meta-analysis provides updated, robust estimates for the incidence of HCC in people with MASLD. The incidence of HCC is elevated in people with MASLD and advanced fibrosis. These data may have implications for further research in HCC surveillance and the future development of surveillance algorithms.

Disclosures: Faith Tan: Nothing to Disclose, Glenn Jun Kit Ho: Nothing to Disclose, Ryan YanZhe Lim: Nothing to Disclose, Alfred Kow: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose, Vincent Chen: AstraZeneca: site PI on industry-sponsored trial, Ipsen: site co-I on industry-sponsored trial, Kowa: site co-I on industry-sponsored trial, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Cheng Han Ng: Nothing to Disclose, Mark Muthiah: Nothing to Disclose, Daniel Huang: Nothing to Disclose

2552 | LEGACY REFERRAL BIAS: REFLEXIVE REFERRAL BEHAVIOR LIMITS THE EFFECTIVENESS OF FIB-4 SMART TOOLS IN MASLD TRIAGE

Ruona Ebiai[1] Sameera Shuaibi[1] Jasmine McNair[1] Adil Memon[1] Anshuman Desai[1] George Therapondos[1] Nigel Girgrah[1] Erin Biggs[1], [1]Ochsner Clinic Foundation

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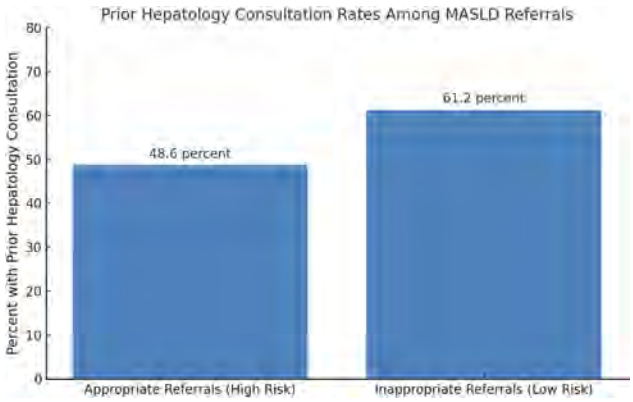
Background: Accurate MASLD risk stratification ensures high-risk patients receive specialty care while low-risk patients are managed in primary care. We evaluated whether implementing a FIB-4 Smart Tool—with an embedded score calculator and automated risk grouping—would improve adherence to MASLD referral guidelines or influence referral decision-making. Preliminary analysis revealed that many referrals involved patients with prior hepatology consultation, seemingly irrespective of current fibrosis risk. This prompted further examination of how consultation history may influence provider behavior and referral patterns. **Methods:** In 2024, our tertiary referral center's primary care clinic implemented a FIB-4 smartphrase calculator and risk categorizer in the EMR using age-adjusted thresholds. Forty-three primary care providers received education on its use and MASLD risk stratification. We retrospectively reviewed hepatology referrals made by these providers from January–July (pre) and July–December (post). We evaluated changes in inappropriate (low risk) referrals and associations between prior hepatology consultation and fibrosis risk at current referral. **Results:** A total of 125 hepatology referrals were analyzed—64 prior to and 61 following implementation of the FIB-4 smart phrase. The rate of inappropriate referrals did not significantly change following the intervention (76.6% pre vs. 73.8% post; $p = 0.72$), suggesting availability of FIB-4 tool did not meaningfully improve referral appropriateness. Prior hepatology consultation was present in 56.0% of all referred patients, and 61.25% of inappropriately referred (low-risk) patients. In contrast, among appropriate referrals (high-risk), prior hepatology contact was present in 48.65% of cases. Logistic regression showed no significant association between prior consultation and inappropriate referral (OR 1.22, 95% CI 0.57–2.62, $p = 0.616$). However, the higher frequency of prior consultation in inappropriate referrals suggests a reflexive referral pattern that may not take current fibrosis risk into account. **Conclusion:** Despite deployment of a FIB-4 smart phrase intended to improve MASLD triage, inappropriate referral rates remained high and unchanged—suggesting either limited tool utilization or a decision-making strategy that ignores current fibrosis risk. While repeat hepatology consultation is expected in high-risk patients, the even higher rate among low-risk, inappropriately referred patients suggests a referral pattern not grounded in current fibrosis severity. We term this behavioral phenomenon 'Legacy Referral Bias'—the reflexive tendency to refer based on historical specialist contact rather than present clinical need. We are assembling a larger real-world dataset including both referred and non-referred patients to better characterize the impact of reflexive referral behavior on MASLD care pathways.



Disclosures: Ruona Ebiai: Nothing to Disclose, Sameera Shuaibi: Nothing to Disclose, Jasmine McNair: Nothing to Disclose, Adil Memon: Nothing to Disclose, Nothing to Disclose, Anshuman Desai: Nothing to Disclose, George Therapondos: Novo Nordisk: Consultant, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Ipsen: Speaking and Teaching, Gilead: Speaking and Teaching, Nigel Girgrah: Gilead Sciences: Speaking and Teaching, Novo Nordisk: Consultant, Erin Biggs: Nothing to Disclose

2553 | PREDICTORS OF INCIDENT HEPATIC FIBROSIS AND STEATOTIC LIVER DISEASE–ASSOCIATED FIBROSIS AMONG WOMEN WITH AND WITHOUT HIV

Maria Duarte[1] Phyllis Tien[1] Yifei Ma[1] Mark Kuniholm[2] Michelle Floris-Moore[3] Margaret Fischl[4] Audrey French[5] Elizabeth Topper[6] Deborah Konkle-Parker[7] Howard Minkoff[8] Ighovwerha Ofotokun[9] Michael Plankey[10] Anjali Sharma[11] Jennifer Price[1], [1]University of California, San Francisco, [2]College of Integrated Health Sciences at the University at Albany, [3]University of North Carolina, Chapel Hill School of Medicine, [4]University of Miami Miller School of Medicine, [5]Stroger Hospital of Cook County, [6]Johns Hopkins Bloomberg School of Public Health, [7]University of Mississippi Medical Center, [8]SUNY Downstate Health Sciences University, [9]Emory University Rollins School of Public Health, [10]Georgetown University Hospital, [11]Albert Einstein College of Medicine

Background: Steatotic liver disease (SLD) is highly prevalent among women living with HIV (WWH). However, predictors of fibrosis and SLD-associated fibrosis in this population are not well established. **Methods:** We included participants from the MACS/WIHS Combined

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Cohort Study (MWCCS), who underwent vibration controlled transient elastography between 2013–2018 and had at least one additional scan. Fibrosis was defined as liver stiffness ≥7.1 kPa and SLD-associated fibrosis (SLD-fibrosis) as fibrosis with concurrent hepatic steatosis (controlled attenuation parameter, or CAP ≥248 dB/m). Women with chronic viral hepatitis or baseline fibrosis were excluded. Poisson regression with robust standard errors clustered by participant was used to estimate incidence rate ratios (IRRs) for fibrosis incidence. Models included time-varying covariates and the log of follow-up interval as an offset to account for varying person-time between visits. Interaction terms were tested to assess differential effects by HIV status. **Results:** A total of 1,036 women were included: 709 WWH and 327 women living without HIV (WWOH). Median age was 49, median BMI was 32 and 14% were Hispanic. During follow-up (mean 24.5 months), 19% developed fibrosis, and 8% developed advanced fibrosis; 74% of all fibrosis cases were SLD-fibrosis. In models examining and adjusting for age, BMI, Hispanic ethnicity, alcohol use and tobacco use, only HIV infection and CAP score were independently associated with higher incidence rates of fibrosis (Table 1). The association of higher CAP with fibrosis differed by HIV status: among WWOH, each 10 dB/m increase in CAP was associated with an 11% increase in incident rate of fibrosis (IRR 1.11, 1.04–1.18), compared to a 1% increase in WLWH (IRR 1.01, (0.96–1.06) (interaction p = 0.02, 95% CI 0.84–0.98). In a separate model examining SLD-fibrosis, HIV was associated with higher rate of SLD-fibrosis (IRR 1.91, 1.10–3.31), and the effect of CAP appeared attenuated in WWH, however this did not achieve significance (Table 1, interaction p = 0.13, 95% CI 0.86–1.02). **Conclusion:** In a large cohort of women living with and without HIV, the amount of hepatic steatosis was associated with higher rates incident fibrosis and SLD-fibrosis. However, HIV infection modified and attenuated the impact of steatosis on fibrosis risk, suggesting that fibrosis in women with HIV may result from both steatotic and non-steatotic pathways.

Table 1: Multivariable predictors of incident fibrosis and SLD- fibrosis in women with and without HIV

Predictor	Model 1 Incidence Rate Ratio Fibrosis (95% CI)	p-value	Model 2 Incidence Rate Ratio SLD-Fibrosis (95% CI)	p-value
HIV infection (main effect)	1.74 (1.13–2.68)	0.01	1.91 (1.10–3.31)	0.02
CAP score (per 10 dB/m, main effect)	1.04 (1.00–1.08)	0.05	1.18 (1.14–1.23)	<0.001
CAP*HIV interaction	0.91 (0.84–0.98)	0.02	0.94 (0.86–1.02)	0.13
CAP (per 10 dB/m) in WWOH	1.11 (1.04–1.18)	0.001	1.23 (1.15–1.32)	<0.001
CAP (per 10 dB/m) in WWH	1.01 (0.96–1.06)	0.76	1.15 (1.10–1.20)	<0.001

*SLD-Fibrosis was defined as incident fibrosis (liver stiffness ≥7.1 kPa) with concurrent hepatic steatosis (CAP ≥248 dB/m). All models adjusted for age, BMI, Hispanic ethnicity, alcohol, and smoking.

Disclosures: Maria Duarte: Nothing to Disclose, Phyllis Tien: Nothing to Disclose, Yifei Ma: Nothing to Disclose, Mark Kuniholm: Nothing to Disclose, Michelle Floris-Moore: Nothing to Disclose, Margaret Fischl: Nothing to Disclose, Audrey French: Nothing to Disclose, Elizabeth Topper: Nothing to Disclose, Deborah Konkle-Parker: Nothing to Disclose, Howard Minkoff: Nothing to Disclose, Ighovwerha Ofotokun: Nothing to Disclose, Michael Plankey: Nothing to Disclose, Anjali Sharma: Nothing to Disclose, Jennifer Price: AbbVie: Grant/Research Support, Gilead: Grant/Research Support, Genentech: Grant/Research Support, VIR: Grant/Research Support, Cepheid: Grant/Research Support, Aligos: Grant/Research Support

2554 | EVOLVING EPIDEMIOLOGY OF MASLD AND ALCOHOLIC LIVER DISEASE IN SOUTH KOREA: A 13-YEAR NATIONWIDE ANALYSIS BASED ON PHYSICIAN DIAGNOSES

Son Gue[1], [1]Daejeon University

Background: Alcohol overuse and metabolic dysfunction are the primary contributors to steatotic liver disease (SLD), encompassing both metabolic dysfunction–associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD). This study aimed to investigate the epidemiologic trends in the prevalence of MASLD and ALD among the Korean population from 2010 to 2022. **Methods:** We analyzed data from the Korean Health Insurance Review and Assessment Service (HIRA), a nationwide claims database based on physician-recorded diagnoses and treatments. Annual prevalence rates of MASLD and ALD-related fatty liver and hepatitis were calculated and stratified by year, age, and sex across the entire Korean population. **Results:** From 2010 to 2022, the annual prevalence of MASLD-related fatty liver increased from 15.6 to 34.3 per 1,000 persons (2.2-fold increase), while metabolic-associated steatohepatitis (MASH) rose nearly 20-fold (from 0.49 to 9.79 per 1,000 persons). In contrast, the prevalence of alcoholic fatty liver (AFL) remained stable (approximately 2.8 per 1,000), and alcoholic (steato)hepatitis (ASH) slightly declined (from 2.4 to 2.1 per 1,000). The mean MASLD-to-AFL ratio was approximately 10:1, and the MASH-to-ASH ratio was about 2:1, reflecting relatively faster progression to hepatitis among ALD patients. Unlike the persistent male predominance in AFL and ASH, MASLD and MASH showed a sex-dimorphic pattern: male predominance under age 50, but female predominance in individuals aged 50 and older. **Conclusion:** The prevalence of MASLD and MASH has increased rapidly in clinical practice over the past decade, while ALD prevalence has remained stable or declined slightly. These trends reflect a shifting burden of liver disease in South Korea and offer a valuable reference for future research and healthcare planning.

Disclosures: Son Gue: Nothing to Disclose

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2555 | NATURAL HISTORY AND RISK FACTORS OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOSIS LIVER DISEASE IN CHINESE COHORTS: A SCOPING REVIEW

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Background: Metabolic dysfunction-associated steatosis liver disease (MASLD) has rapidly become the predominant chronic liver disorder in China. However, evidence on its natural history and determinants of progression remains fragmented. We conducted a scoping review to synthesize evidence from Chinese cohorts on disease trajectories from steatosis through fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), and to identify key risk factors driving progression. **Methods:** Following PRISMA-ScR guidelines, we searched PubMed, EMBASE, Cochrane Library, CNKI, Wanfang, and VIP databases from January 2012 to January 2024. Eligible studies included Chinese MASLD cohorts reporting natural history outcomes or multivariate-adjusted risk factors for progression. We mapped outcomes: Metabolic dysfunction-associated steatohepatitis (MASH), fibrosis progression, cirrhosis, HCC, liver-related events, cardiovascular events, mortality, and tabulated risk factors evaluated across studies. **Results:** 41 articles (36 natural history; 21 risk factor) met the inclusion criteria, involving 247,502 participants for disease-course analyses (Figure 1) and 66,143 for risk modelling. For MASLD patients, in 5 years or less, fibrosis advanced in 27.5-38.4%, and cirrhosis developed in up to 1% (0.9%). Over longer follow-up (>5 years), 0-2.1% transitioned to cirrhosis and 0-2.7% to HCC (annual incidence 0.3-2%). Hepatic decompensation (ascites, encephalopathy, variceal bleeding) occurred in 0.1-1.1% by 11 years. Within 5 years, cardiovascular mortality (2.1-7.0%) and all-cause mortality (2.2-6.8%) outpaced liver-related mortality (0.3-0.6%). Key independent predictors of progression included older age, male sex, hypertension, and overweight/obesity, especially type 2 diabetes, each reported in ≥ 3 studies across endpoints. Additional risk factors variably linked to adverse outcomes were dyslipidemia, sarcopenia, elevated transaminases, viral hepatitis coinfection, and low albumin. Heterogeneity in study populations, endpoint definitions, and reporting of demographic covariates limited comparability. **Conclusion:** MASLD in China trends similarly to the global pattern but may exhibit notably rapid progression in specific populations or stages. Multiple risk factors contribute to disease advancement. Further large-scale prospective cohort studies are warranted to elucidate the associations between risk factors and MASLD, and to better inform early intervention strategies for this condition.

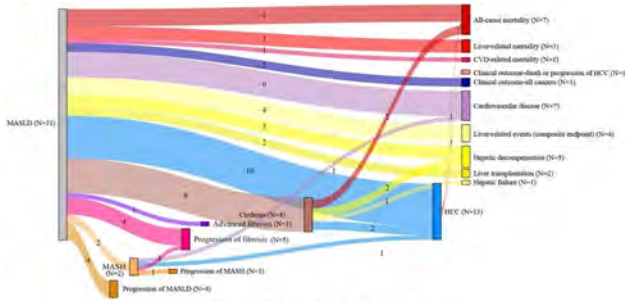

Figure 1. Overview of MASLD Progression

Notes: CVD, Cardiovascular disease; HCC, hepatocellular carcinoma; MASH, Metabolic dysfunction-associated steatohepatitis; MASLD, Metabolic dysfunction-associated steatotic liver disease.

Disclosures: Jing Zhang: Nothing to Disclose, Ruixi Zhan: Novo Nordisk: Employee, Ying Wang: Nothing to Disclose, Yuemin Nan: Nothing to Disclose

2556 | ANY AMOUNT OF ALCOHOL INTAKE INCREASES THE RISK OF SIGNIFICANT FIBROSIS AND FIBROTIC MASH IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) - INSIGHTS FROM 7189 PATIENTS FROM INDIAN CONSORTIUM ON MASLD (ICOM-D).

Ajay Duseja[1] Nipun Verma[2] Arka De[2] Manu Mehta[2] Shivaram Singh[3] Prajna Anirvan[3] Shrikant Mukewar[4] Saurabh Mukewar[5] Dr Shalimar[6] Sanjib Kar[7] Omesh Goyal[8] Rakhi Maiwall[9] Jayanthi Venkataraman[10] Krishnadas Devadas[11] Vk Dixit[12] Varun Mehta[13] Piyush Ranjan[14] Aabha Nagral[15] Narendra Choudhary[16] Anil Arora[14] Arun Valsan[17] Sunil Dadhich[18] Brij Sharma[19] Rohit Gupta[20] Sandeep Nijhawan[21] Akash Roy[22] Dibyalochan Praharaj[23] Padaki Nagaraja Rao[24] Akash Shukla[25] Rajiv Mehta[26] Pankaj Asati[27] Sanjiv Saigal[28] Naryansamy Krishnasamy[29] Mallika Bhattacharyya[30] V. G.Mohan Prasad[31] Abraham Koshy[32] Mukul Rastogi[33] Seema Alam[9] Arun Sanyal[34], [1]Postgraduate Institute of Medical Education & Research, [2]Postgraduate Institute of Medical Education and Research, Chandigarh, India, [3]Kalinga Gastroenterology Foundation, Cuttack, India, [4]MIDAS Multspeciality Hospital, Nagpur, India, [5]Mayo Clinic Rochester, [6]All India Institute of Medical Science. New Delhi, India, [7]Gastro Liver Care, Cuttack, India, [8]D. M.C. and Hospital, [9]Institute of Liver and Biliary Sciences, [10]Institute of HepatoBiliary Sciences and Liver Transplant, Gleneagles Hospital, Chennai, India, [11]Government Medical College, Thiruvananthapuram, [12]Institute of Medical Sciences, Banaras Hindu

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Background: The recent classification of fatty liver disease under the Steatotic Liver Disease (SLD) spectrum, encompassing MASLD and MetALD, highlights the role of alcohol and metabolic dysfunction in liver injury. However, the impact of low-dose alcohol consumption (0–20 g/day), particularly within MASLD spectrum, remains underexplored. This study aimed to evaluate differences in disease severity and fibrosis risk across MASLD patients stratified by alcohol intake: abstinent MASLD, MASLD with 0–20 g/day alcohol use, and MetALD (30–60 g/day). **Methods:** Data were analyzed from 7,189 patients with SLD (median-age: 45 years, 66.9% males, 38.9% with metabolic syndrome, 29.7% with significant fibrosis) enrolled in 32 centers of the Indian Consortium on MASLD (ICOM-D) with information on alcohol consumption. Participants were stratified by alcohol intake. Liver fibrosis severity was assessed using non-invasive scores (FIB-4, APRI, NFS, FAST), and liver stiffness measurement (LSM) on elastography. Outcomes were compared across alcohol categories, and multivariable logistic regression models identified predictors of significant ($\geq$F2: 8.2Kpa) and advanced fibrosis ($\geq$F3: 9.7Kpa) as defined with LSM **Results:** Compared to abstinent MASLD (N = 6729), both low alcohol (0–20 g/day, N = 403) and MetALD (30–60 g/day, N = 57, all males) groups exhibited higher fibrosis scores (Mean FIB-4: 1.1 vs 1.2 and 1.4; Mean LSM: 6.4 vs 6.8 and 8.4 kPa; all $p < 0.01$). Prevalence of significant fibrosis ($\geq$F2) and fibrotic-MASH (FAST > 0.67) was 29.2% and 12.4% in MASLD, 33.5% and 15.9% in low alcohol group, and 54.4% and 22.8% in MetALD ($p < 0.001$). Metabolic risk factors adjusted models confirmed that even low-level alcohol use was independently associated with increased odds of significant fibrosis (aOR: 1.25, 1.01-1.56, $p = 0.041$), while MetALD conferred a threefold higher risk (aOR: 3.04, 1.79-5.17, $p < 0.001$). **Conclusion:** Among patients with MASLD, any alcohol intake increases the risk of significant fibrosis and fibrotic MASH. These findings underscore the need to refine risk stratification and counselling practices in MASLD.

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2557 | PROGNOSTIC NUTRITIONAL INDEX (PNI) AS A PROGNOSTIC FACTOR FOR HCC PATIENTS STRATIFIED BY STATUS OF MASLD

Chun-Ting Ho[1] Wei-Yu Kao[2] Yi-Hsiang Huang[3] Ming-Chih Hou[3] Jaw-Ching Wu[4] Chien-Wei Su[3], [1]Taipei Veterans General Hospital/NYCU, [2]Taipei Medical University Hospital, [3]Taipei Veterans General Hospital, [4]National Yang Ming Chiao Tung University

Background: The impact of concurrent metabolic dysfunction-associated steatotic liver disease (MASLD) on patients with hepatocellular carcinoma (HCC) is still under debate. While the protective effect of concurrent MASLD was proposed in previous studies, the mechanisms of action and further subgroup analysis were lacking. Prognostic Nutritional Index (PNI), calculated by serum albumin level and lymphocyte count, demonstrated the ability to reflect the nutritional and inflammatory status of patients in different studies. Our research aimed to evaluate and compare the prognostic role of PNI in HCC patients stratified by their disease status of MASLD. **Methods:** This retrospective study included 991 consecutive treatment-naïve HCC patients from 2016 to 2023 with baseline serum biochemistry, image, and pathological data. Patients were categorized into MASLD and non-MASLD groups according to their pathology specimens, serum biochemistry data, and medication records. The two groups were then divided into four subgroups according to their PNI levels. COX proportional hazard models (COX PH) were performed to identify independent factors affecting overall survival (OS) and recurrence-free survival (RFS). Kaplan-Meier survival analysis was performed to compare the prognosis between different subgroups. **Results:** After a median follow-up of 38.0 months (interquartile range 10.0–68.0 months), 207 patients had died, and the 5-year OS was 71.4%. The four subgroups demonstrated significant differences in baseline characteristics, including age, tumor characteristics (size, stage, numbers, vascular invasions, distant metastasis), serum biochemistry profile (platelet, albumin, ALT, AST, ALK-P, AFP), and liver function reserve. COX PH identified high PNI as an independent protective factor against poor OS for all patients. In the KM analysis, while comparing the four groups, the MASLD with high-PNI group had the best OS, and the non-MASLD with low-PNI group had the worst OS. The OS of the MASLD with low-PNI and the non-MASLD with high-PNI was comparable. Regarding RFS, the non-MASLD with low-PNI group had the worst RFS, while the three other groups had better RFS, but no difference between groups. Subgroup COX PH analysis identified high-PNI as an independent protective factor for OS in the non-MASLD group but not for the MASLD group. **Conclusion:** PNI can serve as an important factor to differentiate HCC patients into different risk groups and can even serve as an independent protective factor against poor outcomes, especially in patients without concurrent MASLD.

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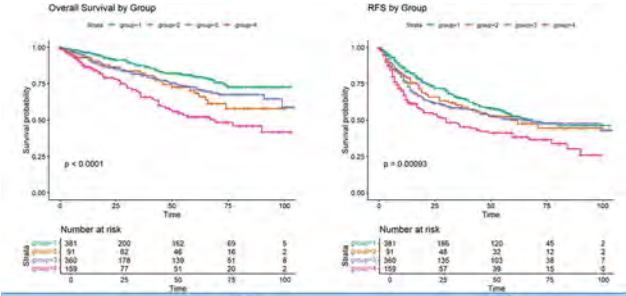

	OS		RFS	
PNI>45	HR	P-value	HR	P-value
All patients	0.67 (0.5-0.89)	0.006	0.84 (0.67-1.04)	0.112
MASLD				
Non-MASLD	0.63 (0.44-0.9)	0.011	0.78 (0.59-1.04)	0.089

- **PNI** can **stratify the prognosis** of HCC patients along with their **MASLD status** and **performs better in the non-MASLD group.**

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2558 | CARDIOVASCULAR RISK OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE AND FATTY LIVER DISEASE: RESULTS: FROM TWO NATIONWIDE COHORT

Juhee Ahn[1] Moon Haeng Hur[2] Hyunjae Shin[2] Min Kyung Park[3] Sungho Won[4] Jeayeon Park[2] Yunmi Ko[2] Yun Bin Lee[5] Eun Ju Cho[3] Jeong-Hoon Lee[3] Su Jong Yu[3] Jung-Hwan Yoon[2] Yoon Jun Kim[2], [1]Division of Data Science, College of Intelligent Software Convergence, University of Suwon, [2]Seoul National University College of Medicine, [3]Seoul National University Hospital, [4]Institute of Health and Environment, Seoul National University, [5]Seoul National University

Background: There is a lack of evidence on whether metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with an increased risk of cardiovascular disease (CVD) or whether it outperforms metabolic dysfunction-associated fatty liver disease (MAFLD) in predicting CVD risk. This study aimed to compare the incidence of CVD according to MASLD and/or MAFLD status using two independent nationwide cohorts. **Methods:** A population-based cohort was established using data from the general health screening program provided by the National Health Insurance Service (NHIS) of Korea in 2009. In parallel, we also utilized UK Biobank phenotype data, which is a population-based prospective cohort consisting of UK residents enrolled between 2006 and 2010. Hepatic steatosis was identified using a fatty liver index greater than 30. The primary outcome was the incidence of composite CVD events, which included myocardial infarction, ischemic stroke, heart failure, and CVD-related death. **Results:** A total of 7,198,643 patients were included in the Korean NHIS, and they were categorized as MASLD ($n = 2,056,609$) or MAFLD ($n = 2,388,436$). Patients with MASLD or MAFLD had a higher risk of CVD compared to the control group (MASLD: subdistribution hazard ratio [SHR] = 1.43, 95% confidence interval [95% CI] = 1.42–1.44, $P < 0.001$; MAFLD: SHR = 1.42, 95% CI = 1.40–1.43, $P < 0.001$). Patients satisfying both MASLD and MAFLD criteria showed a significantly higher risk of CVD (SHR = 1.79, 95% CI = 1.75–1.82, $P < 0.001$), followed by those with MAFLD only (SHR = 1.31, 95% CI = 1.18–1.46, $P < 0.001$). Similar results were reproduced in the UK Biobank cohort ($n = 485,895$), where both MASLD (SHR = 1.65, 95% CI = 1.60–1.71, $P < 0.001$) and MAFLD (SHR = 1.61, 95% CI = 1.55–1.66, $P < 0.001$) were associated with a greater risk of CVD compared to the control group. **Conclusion:** Patients with MASLD had a significantly higher risk of CVD compared to those without steatotic liver disease. MASLD criteria are comparable to MAFLD criteria in reflecting CVD outcome risk.

Disclosures: Juhee Ahn: Nothing to Disclose, Moon Haeng Hur: Nothing to Disclose, Hyunjae Shin: Nothing to Disclose, Min Kyung Park: Nothing to Disclose, Sungho Won: Nothing to Disclose, Jeayeon Park: Nothing to Disclose, Yunmi Ko: Nothing to Disclose, Yun Bin Lee: Eisai: Consultant, Gilead Sciences: Consultant, Roche: Consultant, Chong Kun Dang Pharmaceutical Corporation: Grant/Research Support, Samil Pharmaceutical: Grant/Research Support, Eun Ju Cho: Nothing to Disclose, Jeong-Hoon Lee: Nothing to Disclose, Su Jong Yu: Nothing to Disclose, Jung-Hwan Yoon: Bayer: Grant/Research Support, Daewoong Pharmaceutical: Grant/Research Support, Bukwang Pharmaceutical: Grant/Research Support, Yoon Jun Kim: AstraZeneca: Grant/Research Support, Celltrion: Grant/Research Support, Samil: Grant/Research Support, Yuhan: Grant/Research Support, Daewoong: Grant/Research Support

2559 | INTERACTING EFFECT OF ALCOHOL, ADIPOSITY AND GENETIC RISK ON STEATOTIC LIVER DISEASE IN YOUNG ADULTS

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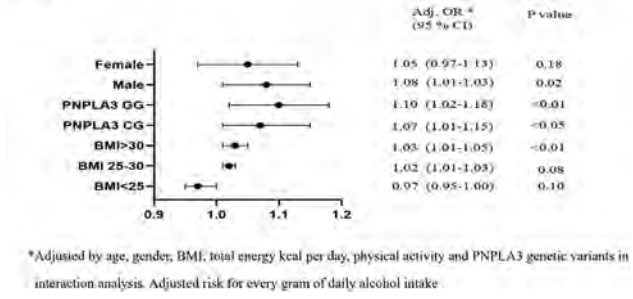
Background: Steatotic liver disease (SLD) maybe due to excessive alcohol consumption, excess adiposity or genetic effects. The independent or modifying effects of these risk factors for SLD are unclear. We examined the association between alcohol, adiposity and PNPLA3 genetic variants on the risk of SLD in a population-based cohort of young adults **Methods:** Participants of the Raine Study Gen2 27-year-old cohort (n = 710) underwent assessments including, questionnaires, anthropometry, magnetic resonance imaging (MRI) and genotyping. SLD was determined by MRI volumetric liver fat fraction (HepaFat). Associations and interactions between BMI, PNPLA3 variants, sex and alcohol were assessed using logistic regression and restricted cubic spline analysis with adjustment for physical activity and total kilocalories per day. **Results:** SLD was detected in 111(16%) participants (55% male). On multivariable analysis, BMI (OR: 1.40, P < 0.001), PNPLA3 variants (OR: 1.65, P < 0.05) and alcohol/grams per day (OR: 1.08, P = 0.02), were associated with increased risk of SLD. Restricted cubic spline analysis showed a nonlinear increase in the risk of SLD for every gram of daily alcohol intake (p = 0.04). Significant interactions between alcohol and BMI, PNPLA3 variants and sex were observed (see Figure). The risk of SLD per daily gram of alcohol consumed was incrementally higher in participants who were overweight (BMI 25-30 kg/m2) and obese (BMI > 30kg/m2) but not among those with a normal BMI (< 25 kg/m2). Similarly, the impact of alcohol was greater in people with increasing number at-risk PNPLA3 alleles (CG variant, Adj. OR: 1.07, p < 0.05, GG variant Adj. OR 1.10, P < 0.01). The risk of SLD with alcohol consumption was also greater in male participants (Adj. OR: 1.08, P = 0.02). **Conclusion:** In young adults, the risk of SLD related to alcohol is greater in male participants, in the presence of obesity and in those with at-risk PNPLA3 variants.

Joint effects between alcohol and sex, PNPLA3 variants and BMI categories on the risk of steatotic liver disease.



*Adjusted by age, gender, BMI, total energy kcal per day, physical activity and PNPLA3 genetic variants in interaction analysis. Adjusted risk for every gram of daily alcohol intake

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2560 | PREVALENCE OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST USE AMONG PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS AND COMPENSATED CIRRHOSIS IN USUAL CLINICAL CARE IN THE USA

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive phenotype of metabolic dysfunction-associated steatotic liver disease (MASLD), which includes simple liver steatosis, chronic liver inflammation with/without fibrosis, and cirrhosis. Several glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are approved to treat type 2 diabetes mellitus (T2D) and/or obesity, which are common comorbidities of MASH. Since 2021, the approval of three new GLP-1 RAs has rapidly changed the treatment landscape for patients (pts) with compensated cirrhosis due to MASH. Understanding GLP-1 RA use is crucial to inform trial design and to evaluate their therapeutic benefit in MASH and its comorbidities. **Methods:** This was a retrospective, cross-sectional analysis of the HealthVerity closed claims database in the USA. Pts aged 18–80 years who had a diagnosis of MASH/MASLD and compensated cirrhosis within 90 days before or after a MASH/MASLD diagnosis from Jan 1, 2015 to Oct 30, 2024 were included. One year of continuous enrollment before a diagnosis of compensated cirrhosis was required for excluding any pts with other causes of chronic liver disease. GLP-1 RA users were defined as those who had a pharmacy claim for any approved GLP-1 RA in the USA. The prevalence of GLP-1 RA use was calculated as the proportion of GLP-1 RA users among pts with compensated cirrhosis due to MASH enrolled during the observation period. Descriptive statistics were used for demographics and comorbidities. **Results:** Overall, 91,837 pts with compensated cirrhosis due to MASH were identified. The median (IQR) age was 59 (15) years; 54,845 (59.7%) pts were women; 54,848 (59.7%) had T2D; and 56,659 (61.7%) had obesity. In total,

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17,754 (19.3%) pts were GLP-1 RA users; of which, 15,991 (90.1%) had T2D and 13,711 (77.2%) had obesity. Since 2018, the prevalence of GLP-1 RA use has increased. Since the last 3 years of the observation period, the prevalence increased from 11.2% in Q1 2022 to 15.0% in Q1 2023, and further to 18.3% in Q1 2024. **Conclusion:** The prevalence of GLP-1 RA use for underlying comorbidities has increased over time in pts with MASH and compensated cirrhosis under usual clinical care. Monitoring GLP-1 RA use is crucial to inform future trial design, such as enrollment strategy and eligibility criteria related to GLP-1 RA use.
Disclosures: Steve Gao: Nothing to Disclose, Eva Flahavan: Gilead Sciences: Employee, Roche: Employee, Grace Chee: Nothing to Disclose, Lisa Albert: Nothing to Disclose, Fang Xia: Gilead Sciences: Employee

2561 | ASSOCIATIONS OF DEVICE-MEASURED SEDENTARY BEHAVIOR WITH HEALTH-RELATED QUALITY OF LIFE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE PATIENTS

Hadeel Saad[1] Khalid Alswat[2] Sulaiman Aljaloud[1] Maram Alkhammash[2] Amani Alsadoon[2] Abdullah Alansare[3], [1]Department of exercise physiology,College of sports sciences and physical activity,KSU, [2]Liver Disease Research Center, College of Medicine, King Saud University,Riyadh, Saudi Arabia, [3]College of sports sciences and physical activity,King Saud University,Riyadh,Saudi Arabia

Background: Robust evidence suggests that sedentary behavior (SB), such as prolonged sitting, is associated with low quality of life among the general population. Of clinical significance, SB is also a significant risk factor for metabolic dysfunction-associated steatotic liver disease (MASLD), independent of physical inactivity. Both excessive SB and low health-related quality of life (HRQol) are prevalent among MASLD patients. However, the relationship between device-measured SB and HRQoL in this population remains unexplored.Objectives: To examine the association between device-measured SB and both overall and domain-specific HRQoL in patients with MASLD. **Methods:** We conducted a cross-sectional analysis of 101 (50.0 years old; 57% males) MASLD patients, who routinely visited hepatology clinic. Participants wore the wActiSleep-BT accelerometer on their non-dominant wrist for 7 days to measure their total SB (hours/day). The Chronic Liver Disease Questionnaire for Non-Alcoholic Fatty Liver Disease (CLDQ-NAFLD) was utilized to assess the overall and domain-specific (i.e., abdominal symptoms, fatigue, systemic symptoms, emotion, worry, and activity) HRQol. Associations between SB and HRQoL were analyzed using multiple and multivariable linear regression, adjusting for relevant covariates. **Results:** Participants spent on average 12.8 hours/day in total SB, with 97% exceeding the high-risk SB threshold ($>$ 8 hours/day). The mean overall HRQoL score was 4.14 out of 7. Each additional hour of SB was independently associated with lower overall HRQol (ß = -0.056; p = 0.017), greater fatigue (ß = -0.120; p = 0.004), and more systemic symptoms (ß = -0.089; p = 0.016). **Conclusion:** This study is the first to demonstrate that higher levels of device-measured SB are independently associated with poorer overall and domain-specific HRQoL in MASLD patients, particularly in fatigue and systemic symptoms. These findings underscore the need to consider SB reduction intervention as a potential target to improve patient-centered outcomes. Longitudinal and interventional studies are warranted to confirm the associations and explore causality.
Disclosures: Hadeel Saad: Nothing to Disclose, Khalid Alswat: Nothing to Disclose, Sulaiman Aljaloud: Nothing to Disclose, Maram Alkhammash: Nothing to Disclose, Amani Alsadoon: Nothing to Disclose, Abdullah Alansare: Nothing to Disclose

2562 | GENETIC RISK OF STEATOTIC LIVER DISEASE AND ITS SEVERITY AMONG PEOPLE LIVING WITH HIV

Eduardo Vilar-Gomez[1] Samer Gawrieh[1] Tiebing Liang[1] Jordan Lake[2] Susanna Naggie[3] Tinsay Woreta[4] Jennifer Price[5] Richard Sterling[6] Sonya Heath[7] Kathleen Corey[8] Laura Wilson[9] Rohit Loomba[10] Mark Sulkowski[11] Naga Chalasani[12], [1]Indiana University School of Medicine, [2]University of Texas - Houston, [3]Duke Clinical Research Institute, [4]Johns Hopkins University School of Medicine, [5]University of California, San Francisco, [6]Virginia Commonwealth University, [7]University of Alabama, [8]Massachusetts General Hospital, [9]Johns Hopkins University, [10]University of California, San Diego, [11]Johns Hopkins Medicine, [12]Indiana University Medical Center

Background: The role of genetic risk variants in modulating steatotic liver disease (SLD) has been extensively studied in general populations but not in persons with HIV (PWH). We investigated the associations between candidate gene variants and the risk of SLD and clinically significant fibrosis (CSF) in PWH. **Methods:** Adult PWH prospectively enrolled in US multicenter studies underwent detailed phenotyping including VCTE for controlled attenuation parameter (CAP) and liver stiffness measurement (LSM). CAP $\geq$ 263 dB/m and LSM $\geq$ 8 kPa were used to define SLD and CSF, respectively. PWH with a history of excessive alcohol use or other liver diseases were excluded.

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PNPLA3 rs738409, *TM6SF2* rs58542926, *HSD17B13* rs72613567, *MBOAT7-TMC4* rs641738, *GCKR* rs1260326, were genotyped by TaqMan assay. Associations between SLD and CSF and genetic variants were analyzed under an additive genetic model with logistic regression models. **Results:** 1089 PWH were enrolled, median age 52 years, male 74%, White 27%, Black 46%, Hispanic 23%, median BMI 30 kg/m^2, 48% SLD (37%, MASLD; 11%, MetALD), and 18% of SLD with CSF. Minor allelic frequencies were as follows: *PNPLA3*-G, 27.1%; *TM6SF2*-T, 4.8%; *HSD17B13*-A, 14.5%; *TMC4-MBOAT7*-T, 36.8%, and *GCKR*-T, 28.7%. Compared to non-SLD PWH, those with SLD, were more likely to be White/Hispanic and older, had diabetes and abdominal obesity, higher triglycerides, ALT, and higher frequency of *PNPLA3-G (*48% vs 41%), and *GCKR*-T (50% vs 45%) alleles, $p < 0.05$ for all. HIV-related factors such as HIV duration, viral load, and ART were not significantly different between the two groups. Variants in *PNPLA3*, *TM6SF2, MBOAT7-TMC4, and GCKR,* but not *HSD17B13* were independently associated with higher odds of SLD (Figure). Among PWH and SLD, those with CSF vs. without CSF had a higher frequency of *PNPLA3-G (59% vs* 45%), *MBOAT7-TMC4*-T (68% vs 61%), and GCKR-T (61% vs 47%) alleles, $p < 0.05$ for all. On multivariable analysis, variants in *PNPLA3, MBOAT7-TMC4, and* GCKR but not HSD17B13 were associated with higher odds of CSF (Figure). Among PWH, an unweighted polygenic risk score (PRS) that sums the total number of risk alleles for *PNPLA3*, *TM6SF2, MBOAT7-TMC4, and GCKR* was strongly independently associated with SLD and CSF. **Conclusion:** Several genetic variants influence the risk of SLD and CSF in PWH. An unweighted PRS comprising *PNPLA3, TM6SF2, MBOAT7-TMC4*, and *GCKR* predicts HIV-SLD disease risk and severity.

Figure. Association of genetic variants (additive genetic model) with SLD, MASLD, MetALD, or CSF. Results based on multivariable[a] analyses.

	SLD[b]		MASLD		MetALD		CSF[c]	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
PNPLA3 rs738409	1.4 (1.1-1.8)	<0.01*	1.4 (1.1-1.8)	<0.01*	1.7 (1.2-2.5)	<0.01*	2.0 (1.4-2.9)	<0.01*
TM6SF2 rs58542926	1.7 (1.1-2.6)	0.01*	1.6 (1.02-2.6)	0.04*	1.5 (0.7-3.0)	0.29	1.3 (0.6-2.7)	0.48
MBOAT7 rs641738	1.3 (1.04-1.6)	0.02*	1.2 (1.01-1.5	0.048	1.5 (1.04-2.1)	0.02*	1.4 (1.01-2.0)	0.047
GCKR rs1260326	1.3 (1.04-1.6)	0.02*	1.3 (1.01-1.6)	0.046	1.3 (0.9-1.8)	0.16	1.4 (1.04-2.0	0.03*
GRS (0-8)[d]	1.3 (1.2-1.5)	<0.01*	1.3 (1.2-1.5)	<0.01*	1.6 (1.2-1.8)	<0.01*	1.4 (1.3-1.9)	<0.01*

[a] Covariate-adjusted analysis included age, sex, race/ethnicity, diabetes, BMI (kg/m^2), and alcohol intake. All genetic variants were simultaneously included in the multivariable analysis. [b] It includes participants with MASLD and MetALD. [c] It includes participants with SLD. [d] It comprises the unweighted summed count of the 4 SNPs. * Benjamini-Hochberg adjusted p-values <0.05.

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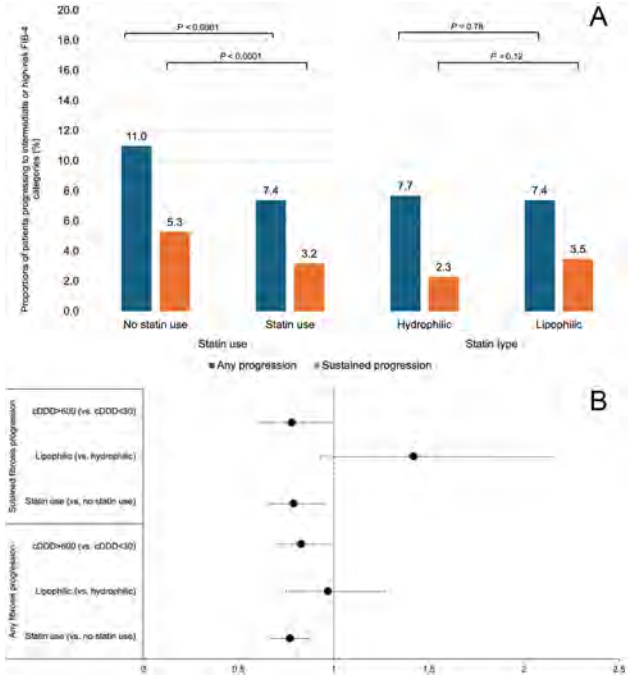
2563 | STATIN USE REDUCES LIVER FIBROSIS PROGRESSION IN PATIENTS WITH LOW-RISK CHRONIC LIVER DISEASE

Vy Nguyen[1] Jonggi Choi[2] Eric Przybyszewski[3] Jiunn Song[4] Allison Carroll[5] Megan Michta[4] Erik Almazan[6] Raymond Chung[4], [1]Harvard Medical School, [2]Department of Gastroenterology, Liver Center, Asan Medical Center, [3]Massachusetts General Hospital, [4]Liver Center, Gastroenterology Division, Massachusetts General Hospital, Boston, MA, USA, [5]Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, [6]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Background: Previous studies have demonstrated that statin use is associated with slower hepatic fibrosis progression. However, their preventative benefit in low-risk chronic liver disease (CLD) remains uncertain. We therefore aimed to characterize whether early statin use in CLD patients with minimal fibrosis attenuates fibrosis progression and adverse liver-related outcomes. **Methods:** We performed a retrospective cohort study of adult patients with CLD and a baseline Fibrosis-4 index (FIB-4) of 1.3 or lower. Patients were categorized into statin users (cumulative defined daily dose [cDDD] ≥ 30) and nonusers (cDDD < 30). We used inverse probability of treatment weighting (IPTW) to minimize potential confounding. **Results:** Among 16,360 patients with low-risk CLD (4256 statin users and 12,104 nonusers), statin users were older and had higher rates of hypertension (75.4% vs 42.3%), diabetes (42.7% vs. 20.1%), and hyperlipidemia (79.6% vs. 35.0%). After IPTW adjustment, statin use was associated with significantly fewer upward transitions in FIB-4 risk categories over a median of 42.5 months of follow-up (7.4% vs 11.0%, $P < 0.0001$, Figure). This finding held in a sensitivity analysis requiring ³ 2 higher risk FIB-4 measurements (3.2% vs. 5.3%, $P < 0.0001$). Fibrosis progression rates were similar between hydrophilic and lipophilic statin users (7.7% and 7.4%, $P = 0.12$), whereas patients with cDDD > 600 had significantly lower odds of fibrosis progression compared to those with cDDD <30 (OR: 0.83, $P = 0.03$). In a 10-year follow-up, statin users and nonusers had similar cumulative incidence of cirrhosis (7.9% vs. 6.3%, respectively, $P = 0.49$), hepatic decompensation (4.9% for both, $P = 0.66$), and HCC (0.6% for both, $P = 0.81$). After additionally adjusting for age, hyperlipidemia, diabetes mellitus, GLP-1, metformin, and SGLT-2 use in a multivariable Cox regression model, statin use was not associated with significant risk reductions for incident cirrhosis (HR: 0.95, $P = 0.67$), hepatic decompensation (HR: 0.82, $P = 0.14$), or HCC (HR: 0.81, $P = 0.53$). **Conclusion:** In patients with low-risk CLD, statin use was associated with reduced fibrosis progression with a clear dose-response effect but did not demonstrate significant effects on incident cirrhosis, hepatic decompensation, or HCC, though likely due to the early-stage disease profile of this group. These findings suggest anti-fibrotic activity of statins even in early, low-risk patients with CLD and warrant further prospective trials to validate these effects.



Disclosures: Vy Nguyen: Nothing to Disclose, Jonggi Choi: Gilead Sciences: Grant/Research Support, Eric Przybyszewski: Nothing to Disclose, Jiunn Song: Nothing to Disclose, Allison Carroll: Nothing to Disclose, Megan Michta: Nothing to Disclose, Erik Almazan: Nothing to Disclose, Raymond Chung: Nothing to Disclose

2564 | LEAN MASLD: RECLASSIFICATION DISCREPANCIES, CHARACTERISTICS, AND ADVERSE LIVER OUTCOMES ACROSS DIVERSE POPULATIONS

Sherlot Juan Song[1] Eileen Yoon[2] Vincent Wong[1] Aejeong Jo[3] Grace Lai-Hung Wong[4] Jimmy Che-To Lai[1] Dae Won Jun[2] Terry Cheuk-Fung Yip[1], [1]The Chinese University of Hong Kong, [2]Department of Internal Medicine, Hanyang

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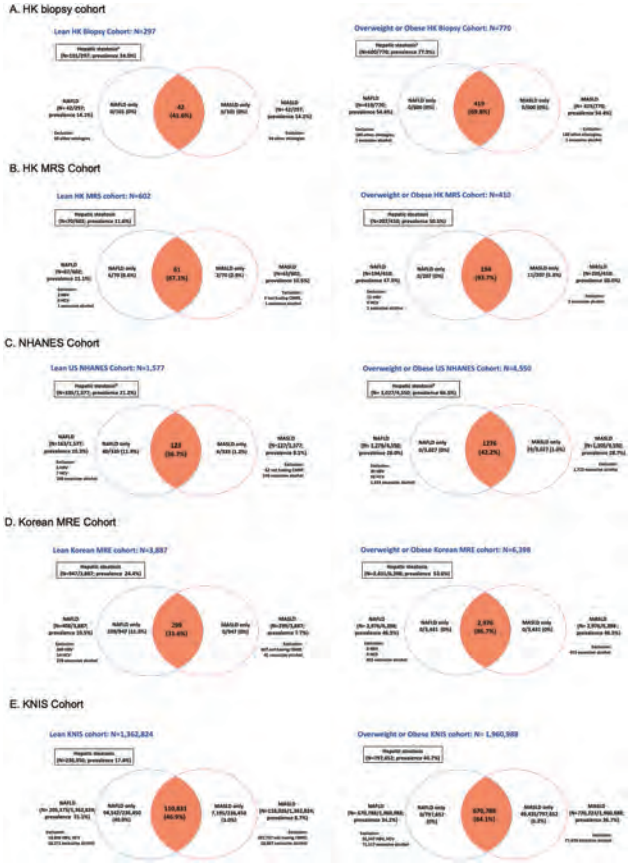
Background: Previous studies suggested a high degree of overlap in the non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD) population, but the same may not apply to lean patients with a lower degree of cardiometabolic risk factor (CMRF) burden. This study aims to investigate the overlap between NAFLD and MASLD in lean patients with normal body mass index (BMI), and to compare the risk of fibrosis and liver-related events (LRE) in patients with lean vs. non-lean MASLD. **Methods:** This study included participants with SLD from six cohorts in Hong Kong (HK), South Korea and the United States (US). The participants were recruited from hospital, community, or health check-up settings. Individuals meeting the definitions of MASLD were classified into lean vs. overweight or obese group. Follow-up data were captured in two cohorts for longitudinal analyses, where the primary outcome was LRE. LRE were defined as the occurrence of clinical events, including hepatic decompensation, hepatocellular carcinoma, liver transplantation and liver-related deaths. Patients were categorized into lean, overweight and obese groups based on their BMI levels to examine clinical outcomes. **Results:** This study included 1,058,175 participants with SLD from six cohorts, of whom 858,950 patients met the diagnosis of MASLD. In hospital-based cohorts, 0-2.1% of lean patients with NAFLD did not fulfil the definition of MASLD. (Figure) In contrast, 8.6%-11.9% of lean patients with NAFLD in community and health check-up settings did not have MASLD, and the proportion was up to 40% in the Korean national health insurance cohort (KNHIS cohort). The lean MASLD group shared a similar prevalence of CMRF2-5 but a less total amount of CMRFs compared with overweight/obese MASLD. Lean MASLD was significantly associated with a reduced risk of LRE in the KNHIS cohort (Gray's test $p < 0.001$), but not in the Hong Kong CDARS cohort (Gray's test $p = 0.54$). **Conclusion:** The shift from NAFLD to MASLD results in a discrepancy of around 10% in the general lean population. Caution is warranted when applying the findings from previous studies based on lean NAFLD to the current lean MASLD definitions.



Disclosures: Sherlot Juan Song: Nothing to Disclose, Eileen Yoon: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept: Advisor, Inventiva: Advisor, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Pfizer: Advisor, Sagimet: Advisor, TARGET PharmaSolutions: Advisor, Unilab: Speaking and Teaching, Visirna: Consultant, Illuminatio Medical Technology: Stock – privately held company, Eli Lilly: Consultant, Merck: Consultant, Aejeong Jo: Nothing to Disclose, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Jimmy Che-To Lai: Nothing to Disclose, Dae Won Jun: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead

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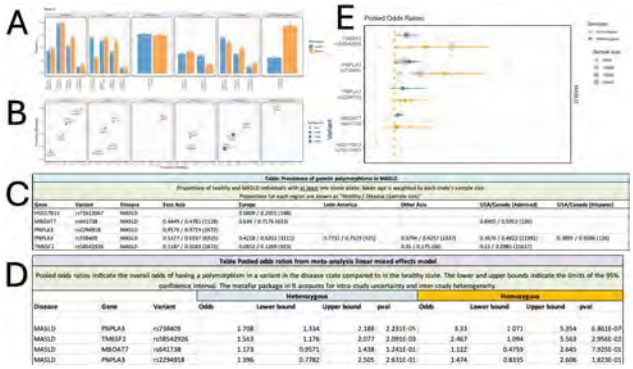
Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support

2565 | GLOBAL PREVALENCE AND RISK OF HIGH-RISK GENETIC POLYMORPHISMS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): A SYSTEMATIC REVIEW AND META-ANALYSIS

Kaanthi Rama[1] Vinay Jahagirdar[1] Ronnie Li[2] Natalia Baeza Radmilovic[3] Anas Aljabi[1] Ambuja Banerjee[1] John Cyrus[1] Stephen Hoang[1] Anand Kulkarni[4] Luis Antonio Diaz[5] Juan Pablo Arab[1], [1]Virginia Commonwealth University, [2]Virginia Commonwealth University Health, [3]Pontificia Universidad Católica de Chile, Virginia Commonwealth University, [4]Asian Institute of Gastroenterology, [5]University of California San Diego

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading global cause of chronic liver disease, with notable variation in prevalence and progression across populations. Genetic susceptibility plays a key role, particularly with variants *PNPLA3* (rs738409, rs2294918), *TM6SF2* (rs58542926), *MBOAT7* (rs641738), and *HSD17B13* (rs72613567). We aimed to determine the global prevalence of these high-risk polymorphisms in MASLD and quantify their disease association using pooled effect estimates. **Methods:** MEDLINE, EMBASE, and CENTRAL were systematically searched from inception to 9/2024, to identify case-control studies evaluating the presence of high-risk variants in individuals with MASLD compared to healthy controls. Regional prevalence of each polymorphism was calculated using weighted proportions for healthy and MASLD cohorts, defined as the proportion of individuals with at least one copy of the minor allele. To evaluate the association between polymorphisms and MASLD, pooled odds ratios were generated using a linear mixed effects model in R (metafor package) to account for intra-study variance and inter-study heterogeneity. For external benchmarking, prevalence rates were compared against corresponding allele frequencies from the Genome Aggregation Database (gnomAD v4), which is a population-level reference for global variant prevalence. **Results:** From 2,370 abstracts screened, 39 studies comprising 63,435 individuals were included. The PNPLA3 rs738409 variant showed the higher enrichment among MASLD individuals compared to healthy (Fig A, C): Europe (62% vs 42%), USA/Canada (48% vs 37% in Admixed, 93% vs 31% in Hispanic), and East Asia (69% vs 54%). The MBOAT7 rs641738 allele also showed high prevalence in MASLD cases in Europe (72%) and East Asia (48%). In Latin America, the PNPLA3 rs738409 allele was highly prevalent in both healthy (77%) and MASLD (75%) individuals. In contrast, the protective HSD17B13 variant demonstrated a lower prevalence in MASLD adults compared to healthy in Europe (30% vs. 68%). Meta-analysis showed increased MASLD risk with: 1. PNPLA3 rs738409: OR 1.7 (95% CI: 1.3-2.2, $p < 0.0001$) for heterozygotes and OR 3.3 (2.0-5.4, $p < 0.0001$)for homozygotes; 2. TM6SF2 (heterozygous OR 1.6, 95% CI 1.2-2, $p = 0.002$; homozygous OR 2.5, 95% CI 1.1-5.6, $p = 0.030$); 3. MBOAT7 (heterozygous OR 1.17, $p = 0.24$) (Fig C, E). TM6SF2 estimates in Europe aligned closely with gnomAD. Deviations were observed in few variants across regions, likely reflecting sampling bias (Fig B). **Conclusion:** This global synthesis demonstrates substantial variation in the prevalence of high-risk polymorphisms associated with MASLD, particularly for PNPLA3, which shows the strongest and most consistent association with disease across all regions. These findings underscore the need for ancestry-informed genetic screening approaches and region-specific risk models in liver disease management.



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2566 | BMI AND DIETARY INTAKE AS MODIFIABLE PREDICTORS OF POSTPARTUM STEATOTIC LIVER DISEASE: RESULTS: FROM THE PROSPECTIVE FATTY LIVER IN PREGNANCY (FLIP) COHORT

Cecilia Katzenstein Nina Rodriguez[1] Keith Sigel[1] Rhoda Sperling[1] Norah Terrault[2] Tatyana Kushner[3] Xiaotao Zhang[1] [1]Icahn School of Medicine at Mount

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Background: Steatotic liver disease (SLD) affects an estimated 14% of women in pregnancy and may persist or develop de novo in the postpartum period. While elevated BMI and poor diet are suspected contributors, data on modifiable risk factors remain limited. We aimed to evaluate the influence of these factors on postpartum SLD. **Methods:** We leveraged the prospective Fatty Liver in Pregnancy (FLIP) cohort to evaluate the prevalence of SLD during pregnancy and postpartum using vibration-controlled transient elastography (VCTE), defining SLD as a CAP score ≥ 248 dB/m. Pre-pregnancy BMI and BMI at delivery were obtained from the medical record, and postpartum weight at the time of follow-up VCTE. Participants also completed the NIH Dietary Screener Questionnaire in the postpartum period. Adequate nutrition intake was defined per USDA guidelines. Chi-squared tests were used to compare SLD prevalence by diet, paired t-tests evaluated changes in CAP scores over time, and age adjusted logistic regression identified predictors of postpartum SLD. **Results:** Among participants with intrapartum and postpartum assessment ($n = 28$), the mean age was 29, 54% identified as Hispanic, 14% had persistent SLD, and 32% developed new postpartum SLD. Mean CAP scores significantly increased from pregnancy to postpartum, with a mean difference of 35.64 (95% CI: 16.62-54.67; $p < 0.001$). Higher BMI at delivery was the strongest predictor of postpartum SLD (aOR 1.35, 95% CI: 1.06-1.72; $p = 0.01$). Pre-pregnancy BMI was also significantly associated with postpartum SLD (aOR 1.25, 95% CI: 1.04-1.51; $p = 0.02$). While postpartum weight was higher among those with SLD than those without (89.8 kg vs 72.6 kg; $p = 0.028$), inadequate weight loss postpartum based on pregnancy weight gain was not significantly associated. Among patients with postpartum SLD, mean daily intake of fiber, calcium, whole grains, dairy, fruits, and vegetables were significantly below recommended levels, while added sugar intake exceeded guidelines. Adequate fiber intake and adequate calcium intake were associated with a significantly lower prevalence of postpartum SLD (0% vs 68%, $p < 0.001$; 20% vs 68%; $p = 0.01$). **Conclusion:** In this cohort, CAP scores increased significantly after pregnancy, with over one-third of participants developing new SLD in the postpartum period. Elevated BMI—particularly at delivery—was the strongest predictor, highlighting the role of gestational weight trajectory. Poor dietary quality, especially inadequate fiber and calcium intake, was common among those with SLD and may represent modifiable risk factors.

Table 1. Participant Characteristics and Dietary Intake by Postpartum SLD Status

	No Postpartum SLD (n=15)	Postpartum SLD (n=13)	*p* value
Demographic features			
Mean age (years)	29.3 (5.0)	29.3 (5.2)	0.983
Hispanic ethnicity (%)	53%	54%	0.978
BMI, Weight, and SLD Features			
SLD in pregnancy (%)	7%	31%	0.097
Pre-pregnancy BMI (kg/m²)	24.3 (5.7)	31.8 (7.0)	0.005*
BMI at delivery (kg/m²)	30.0 (4.2)	36.1 (6.0)	0.006*
Weight postpartum (kg)	72.6 (17)	89.8 (21.5)	0.028*
Dietary features			
Adequate fiber intake (%)	47%	0%	0.004*
Adequate calcium intake (%)	53%	15%	0.037*
Excess added sugar (%)	87%	62%	0.126
Daily vegetable intake (cups)	2.3	2.2	0.82
Daily fruit intake (cups)	0.86	0.86	0.98
Daily beans intake (cups)	0.23	0.15	0.31
Daily pizza intake (cups)	0.06	0.14	0.05
Daily candy intake (cups)	0.15	0.28	0.21
Daily cereal intake (cups)	0.15	0.18	0.78

* Denotes significant *p* values < 0.05.

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2567 | PERSISTENT BINGE DRINKING IS ASSOCIATED WITH ADVANCED LIVER FIBROSIS AND ALL-CAUSE MORTALITY IN METALD

Ru-Tao Lin[1] Zhe-Kun Xiong[2] Bi-Wei Chen[2] Xin Xin[1] Tao-Ying Deng[2] Qin-Mei Sun[1] Li-Ming Gan[2] Yiyang Hu[1] qin feng[1], [1]Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, [2]Department of Spleen, Stomach and Hepatobiliary, Zhongshan Hospital of Traditional Chinese Medicine

Background: Metabolic and alcohol related/associated liver disease (MetALD) is characterized by the coexistence of metabolic dysfunction and moderate alcohol intake. In this population, the impact of specific drinking patterns, particularly persistent binge drinking (PBD), on disease severity and prognosis remains unclear. The study aimed to evaluate the association between a history of PBD and the risks of advanced liver fibrosis and all-cause mortality in individuals

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with MetALD. **Methods:** We analyzed data from NHANES 1999–2016, including adults with MetALD. PBD is defined as having had a history of drinking ≥ 5 alcoholic beverages almost every day, based on ALQ150/151 questionnaires. Advanced fibrosis was defined as FIB-4 >2.67, and mortality outcomes were obtained from the National Death Index. Multivariable logistic and Cox regression models were used to examine the associations between PBD and both liver fibrosis and all-cause mortality, adjusting for alcohol intake and other confounders. Survival analyses excluded individuals who died within the first two years of follow-up. **Results:** Among 896 individuals with MetALD, 344 (38.4%) reported a history of PBD. Compared to those without PBD, participants with PBD had a higher risk of advanced fibrosis (adjusted OR = 3.23, 95% CI: 1.34–7.76, $p < 0.01$) (Table 1). PBD was also associated with increased all-cause mortality (adjusted HR = 1.62, 95% CI: 1.14–2.32, $p < 0.01$). These associations were more pronounced in individuals with elevated liver enzymes. Sensitivity analyses supported the robustness of the findings. When participants aged <35 or >65 years were excluded, the association between PBD and advanced fibrosis remained significant (adjusted OR = 3.05, 95% CI: 1.20–7.77, p = 0.02). When individuals who died within the first two years of follow-up were re-included, PBD was still associated with increased all-cause mortality (adjusted HR = 1.88, 95% CI: 1.22–2.91, p < 0.01). **Conclusion:** Persistent binge drinking is associated with increased risks of advanced fibrosis and mortality in MetALD, especially among individuals with elevated liver enzymes. In clinical assessment, attention should be paid to drinking patterns, particularly the presence of a persistent binge drinking history.

Table 1. Multivariable logistic regression models for advanced liver fibrosis (FIB-4 > 2.67) by persistent binge drinking, and Cox regression models for all-cause mortality stratified by persistent binge drinking.

	Crude model		Model 1		Model 2	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Advanced liver fibrosis (FIB-4 > 2.67)						
Never persistent binge drinking	Reference	-	Reference	-	Reference	-
Persistent binge drinking	1.97 (1.13, 3.43)	0.016	2.04 (1.11, 3.72)	0.021	3.23 (1.34, 7.76)	0.009

	Crude model		Model 1		Model 2	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
All-cause mortality						
Never persistent binge drinking	Reference	-	Reference	-	Reference	-
Persistent binge drinking	1.50 (1.08, 2.09)	0.016	1.62 (1.14, 2.30)	0.007	1.62 (1.14, 2.32)	0.008

Model 1 was adjusted for age, sex, race, education level, and body mass index.

Model 2 was further adjusted for ALT > 40 U/L, AST > 40 U/L, and GGT > 40 U/L, HbA1c, triglycerides, uric acid, and average daily alcohol intake.

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2568 | THE OBESITY EPIDEMIC AND ITS IMPACT ON ADULT LIVING LIVER DONATION: A DECLINING DONOR POOL

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Background: The global obesity epidemic increasingly impedes living donor liver transplantation (LDLT). Obesity-associated comorbidities, especially MASLD, frequently lead to donor exclusion. This study characterized donor attrition patterns related to obesity at a single center and evaluated national graft outcomes for recipients of grafts from living donors with obesity. **Methods:** A retrospective cohort study analyzed adult LDLT referrals at a single academic center (2018–2024). Donor outcomes were categorized: (1) declined pre-evaluation, (2) evaluated and declined, or (3) donated. Reasons for exclusion were documented. Institutional policy favored BMI <30 kg/m2; BMI 30.0−34.9 kg/m2 (Class I obesity) was considered case-by-case, while BMI ≥35.0 kg/m2 (Class II/III obesity) generally resulted in exclusion due to steatosis concerns. National LDLT recipient graft survival data (SRTR, 2013–2024) were analyzed, stratified by donor obesity, using Kaplan-Meier and log-rank tests. A sensitivity analysis excluded pediatric recipients/donors, multiorgan/re-transplants, and missing data. Statistical significance was p < 0.05. **Results:** Of 844 adult referrals, 166 underwent LDLT. 296 (35.1%) had Class I/II obesity. 345 (40.9%) potential donors completed evaluation. Individuals with obesity were less likely to complete evaluation (31% [91/296] vs. 46% [254/548]). Two hundred and five of them (69.3%) were declined pre-evaluation (81% due to obesity). An additional 49 (16.6%) were evaluated but declined (53% had MASLD). Only 42 (14.2%) potential donors with obesity proceeded to donation (28.6% had MASLD), following a mandated median weight loss of 2.4 kg (IQR 0–5.4 kg). [Fig 1A] The median BMI of accepted donors declined, while that of declined donors increased (p < 0.001), reflecting heightened selection pressure. [Fig 1B] At our center, recipients of grafts from carefully selected donors with obesity showed similar graft survival to donors without obesity (log-rank p = 0.154). However, national SRTR data revealed reduced recipient survival for LDLT from Class II/

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III obesity donors (BMI ≥35 kg/m2) (log-rank p<0.001). [Fig 1C]. **Conclusion:** Obesity is a barrier to adult LDLT, causing significant donor attrition. While selected donors with obesity yield acceptable single-center outcomes, national data indicate increased graft risk with higher donor BMI. Proactive donor metabolic optimization strategies are crucial to safely expand the living donor pool.

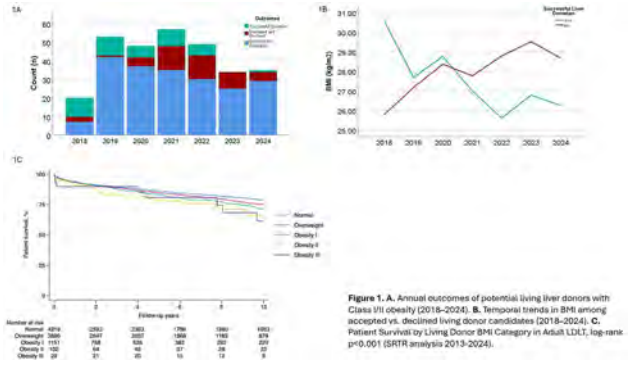

Figure 1. A. Annual outcomes of potential living liver donors with Class I/II obesity (2018–2024). **B.** Temporal trends in BMI among accepted vs. declined living donor candidates (2018–2024). **C.** Patient Survival by Living Donor BMI Category in Adult LDLT, log-rank p<0.001 (SRTR analysis 2013-2024).

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2569 | SEX-BASED DIFFERENCES IN LIVER FIBROSIS PROGRESSION AMONG ADULTS AGED 55 AND OLDER WITH MASLD: AN ANALYSIS OF A NATIONAL DATABASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) progression may differ by sex, but the impact of post-menopausal estrogen decline on these patterns relative to men remains unclear. Previous research in older adults has often been hampered by limitations such as small cohorts, cross-sectional designs, and insufficient control for metabolic confounders. This study used a large, propensity-matched national database to determine if women aged 55 and older with MASLD exhibit distinct liver fibrosis progression compared to age-matched men with similar metabolic risk. **Methods:** We queried the TriNetX Research Network (100 healthcare organizations) for adults ≥55 years old with an incident diagnosis of MASLD and ≥5 years of follow-up. Patients with competing liver diseases or women on hormone-replacement therapy were excluded. A 1:1 propensity-score match (nearest-neighbor, caliper 0.1) balanced sex cohorts on age, race/ethnicity, obesity, diabetes, hypertension, dyslipidemia, alcohol use, and tobacco use. Outcomes included new-onset fibrosis, cirrhosis, liver-enzyme elevations, individual features of hepatic decompensation, liver transplantation, and hepatocellular carcinoma. Adjusted relative risks and hazard ratios are reported with 95 % confidence intervals. **Results:** The analysis included 27,204 women (≥55 years) and 27,204 men (≥55 years). The population was 76.9% White, 10.3% Hispanic, 101% Black or African American, and 6.0% Asian. Women demonstrated significantly lower risk of hepatic fibrosis compared to men (RR 0.830, 95% CI 0.705–0.976, p=0.024) (Table 1). Women with MASLD also had lower rates of ascites (RR 0.774, 95% CI 0.638–0.939, p=0.008), jaundice (RR 0.426, 95% CI 0.331–0.548, p<0.001), liver transplantation (RR 0.341, 95% CI 0.189–0.614, p<0.001), and hepatocellular carcinoma (RR 0.556, 95% CI 0.325–0.951, p=0.029). Women demonstrated a 22.1% lower hazard of developing any hepatic decompensation (HR 0.779, 95% CI 0.647–0.939, p=0.008) and an 11.1% lower hazard of cirrhosis (HR 0.889, 95% CI 0.791–0.998, p=0.045) (Table 1). **Conclusion:** Despite post-menopausal estrogen decline, women aged 55+ with MASLD demonstrated significantly lower fibrosis progression and decompensation than age-matched men with similar metabolic risks. This finding suggests a persistent female protective advantage not solely reliant on estrogen, potentially driven by other intrinsic sex-specific biological factors like genetic or immune differences. This challenges simpler estrogen-centric views and highlights the need to explore these non-estrogenic mechanisms.

Outcome	Female Events	Male Events	Risk Ratio (95% CI)	Hazard Ratio (95% CI)	*p*-value
Fibrosis	264 (1.0%)	318 (1.2%)	0.83 (0.71–0.98)	0.83 (0.71–0.98)	0.027
Cirrhosis	522 (1.9%)	590 (2.2%)	0.89 (0.79–0.99)	0.89 (0.79–1.00)	0.043
Decompensation (composite)	190 (0.7%)	244 (0.9%)	0.78 (0.65–0.94)	0.78 (0.65–0.94)	0.010
Ascites	187 (0.7%)	242 (0.9%)	0.77 (0.64–0.94)	0.77 (0.65–0.94)	0.008
Jaundice	92 (0.3%)	216 (0.8%)	0.43 (0.33–0.54)	0.43 (0.33–0.54)	<0.001
Esophageal varices	56 (0.2%)	64 (0.2%)	0.88 (0.61–1.25)	0.87 (0.61–1.25)	0.447
ALT ≥2x ULN	2,944 (10.8%)	4,559 (16.8%)	0.65 (0.62–0.67)	0.62 (0.59–0.65)	<0.001
AST ≥2x ULN	610 (2.2%)	773 (2.8%)	0.79 (0.71–0.88)	0.79 (0.71–0.88)	<0.001
Liver Transplant	15 (0.1%)	44 (0.2%)	0.34 (0.19–0.61)	0.34 (0.19–0.61)	<0.001
Hepatocellular Carcinoma	22 (0.08%)	39 (0.14%)	0.56 (0.34–0.95)	0.56 (0.33–0.95)	0.029

Disclosures: Kate Solpari: Nothing to Disclose, Emma Leipsner: Nothing to Disclose, Priyanka Gaur: Nothing to Disclose, Scarlet Yang: Nothing to Disclose, Jessica Siguencia: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support

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2570 | COMPARING THE RISK OF MAJOR ADVERSE CARDIOVASCULAR AND LIVER OUTCOMES IN PATIENTS WITH PROBABLE MASH TO THOSE WITH DIAGNOSED MASH AND WITHOUT MASH

Caichen Zhong[1] Nana Boame[2] Semiu Gbadamosi[3] Maximilian Kurt Jara[1] Rakesh Luthra[3] Yu Hong[2] Bret Zeldow[2] Abdalla Aly[4] Mary Rinella[5], [1]Novo Nordisk Inc., [2]Genesis Research Group, [3]Novo Nordisk Inc, [4]Novo Nordisk, [5]The University of Chicago

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is associated with adverse outcomes, particularly major adverse cardiovascular events (MACE) and major adverse liver outcomes (MALO). MASH is highly underdiagnosed, and the clinical burden of probable MASH remains unclear. The study aimed to assess the clinical burden experienced by patients with probable MASH, evaluating the risk of MACE, heart failure (HF) hospitalization, and MALO, and comparing these risks to those in patients with diagnosed MASH and those without MASH. **Methods:** This retrospective study used Komodo Healthcare Map™ data from 2017 to 2022. Probable MASH was defined by an adapted metabolic dysfunction-associated steatotic liver disease Decision Tree: hepatic steatosis index >36 or ICD-10-CM code K76.0, plus ≥ 1 cardiometabolic risk factor, during a 12-month baseline period. Patients with diagnosed MASH had an ICD-10-CM code K75.81: ≥ 1 primary inpatient code or ≥ 2 outpatient codes ≥ 30 days apart. Patients without MASH met none of these criteria. Propensity score weighting was applied to balance baseline characteristics. Hazard ratios and 95% confidence intervals estimated the risk of 2-point MACE (non-fatal acute myocardial infarction [AMI] or stroke), expanded MACE (AMI, stroke, coronary revascularization, HF hospitalization, or all-cause mortality), HF hospitalization, and MALO. MACE and MALO outcomes were evaluated in patients without previous events, respectively. **Results:** The study comprised patients with probable MASH (n = 1,893,764), diagnosed MASH (n = 18,252), and without MASH (n = 647,652). Patients with probable MASH compared to those without MASH were more likely to develop 2-point MACE (1.08 [1.05, 1.10]), expanded MACE (1.07 [1.05, 1.08]), and HF hospitalization (1.40 [1.37, 1.44]). The hazard of MALO was not significantly different (1.00 [0.99, 1.01]). Patients with probable MASH had a similar hazard of 2-point MACE compared to patients with diagnosed MASH, (0.99 [0.86, 1.14]) but a lower hazard of expanded MACE (0.90 [0.82, 0.99]), HF hospitalization (0.79 [0.69, 0.90]), and MALO (0.43 [0.41, 0.45]). **Conclusion:** Patients with probable MASH had a higher rate of cardiovascular events compared to those without MASH, but a lower rate of MACE and MALO events than those with diagnosed MASH. These findings show that probable MASH adds to clinical burden, which is higher than patients without MASH, and closer to patients with diagnosed MASH, emphasizing the importance of early screening and management of patients.

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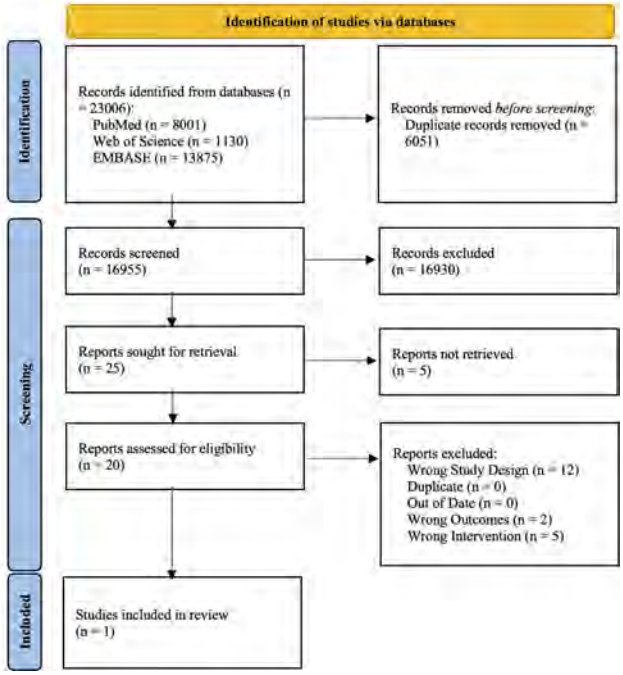
2571 | THE IMPACT OF HIGH FRUCTOSE CORN SYRUP ON LIVER INJURY AND GLUCOSE METABOLISM: A SYSTEMATIC REVIEW

Maimuna Marenah[1] Zane Yu[2] Sneha Varahala[1] Sean Lim[1] Julia Wattacheril[3], [1]Mailman School of Public Health, Columbia University, [2]Warren Alpert Medical School, Brown University, [3]Columbia University

Background: High fructose corn syrup (HFCS) is a popular dietary sweetener that is used in a substantial portion of food and beverages. Recent evidence has cited dietary HFCS as a risk factor in the development of obesity, metabolic syndrome and liver disease. In particular, HFCS has been implicated in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Preclinical studies suggest that HFCS induces cellular damage, oxidative stress, impairs molecular signaling, and causes dysfunction in metabolic pathways. This systematic review provides a new evaluation of the potential hepatic and metabolic risks posed by HFCS to inform both clinical practice and public health policy. **Methods:** We conducted a systematic review of English-language, human studies of adults ($\geq$ 18 years) with low to no alcohol intake using the most recent version of Covidence. Only quantitative studies that specified a link supported by direct evidence between HFCS and markers of liver injury or glucose metabolism in the setting of MASLD or NAFLD were included in this review. **Results:** The literature search yielded 23,006 studies. After removing duplicates, 16,955 studies were screened and 16,930 were excluded after abstract screening. 20 texts were reviewed in full; 5 texts were not found, and 19 were excluded. 1 study was included after study selection. **Conclusion:** This review identifies and critically appraises the methodological strengths and limitations of the sole study meeting eligibility criteria for the systematic review. The 2022 study by Sigala et al. involved a non-randomized, controlled dietary intervention examining the dose-response effects of high-fructose corn syrup (HFCS) on hepatic lipid accumulation and insulin sensitivity in healthy adults. The identification of only a single eligible study – despite an exhaustive search strategy – emphasizes a stark absence of focused investigations in this area. Given the increasingly widespread consumption of HFCS and its prevalence in the modern food supply, this scarcity of research is concerning. Further research in this area should focus on clinical studies of longer duration, comparative studies of HFCS and other sugars, and incorporate greater demographic and geographic diversity.

Figure 1: PRISMA Flow Diagram



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2572 | ENHANCING METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE SCREENING AND DOCUMENTATION: THE IMPACT OF AN EDUCATIONAL INTERVENTION IN A PRIMARY CARE CLINIC

Nadera Altork[1] Ahmad Abdulraheem[1] Bara Abujaber[1] Boniface Mensah[2] Deeptha Bejugam[3] Keerthana

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) has a global prevalence of approximately 25% and is expected to increase parallel with rising rates of obesity and type 2 diabetes mellitus. In 2023, AASLD guidelines emphasized the role of primary care providers (PCPs) in screening for MASLD and ruling out advanced fibrosis using the Fibrosis-4 (FIB-4) index, which has a high negative predictive value. A survey conducted in our primary care clinic found that although 15% of internal medicine residents screened for MASLD, only 7% felt comfortable using the FIB-4 index, and 15.4% routinely counseled patients about the condition. This study aims to enhance awareness, screening practices, and risk assessment for MASLD within our primary care clinic. **Methods:** We included patients aged $\geq$ 18 years who were seen in the primary care clinic and had type 2 diabetes mellitus (HbA1c $\geq$ 7%) or morbid obesity (BMI $\geq$ 35 with hypertension or hyperlipidemia) during the pre-intervention period (Oct 2023 – Mar 2024) and the post-intervention period (Jun – Nov 2024). Exclusions were chronic liver disease or alcohol use disorder. The intervention (Apr–May 2024) included didactic sessions, clinic huddles, reminder emails, and the addition of MASLD screening to the general screening dot phrase bundle in the Electronic Health Record (EHR). Outcomes included MASLD documentation, FIB-4 use, and referrals. Data were analyzed using t-tests and chi-square/Fisher's exact tests. A p-value <0.05 was considered statistically significant. **Results:** A total of 557 patients were included (296 pre-intervention and 261 post-intervention). The demographics and comorbidities were similar between the two groups, as shown in Table 1. Most patients were African American (86.3% vs. 84.9%, p-value = 0.97) and non-Hispanic (95.7% vs. 94.8%, p-value = 0.61). Documentation of MASLD increased significantly after the intervention, from 0% to 16.0% (p-value < 0.001). Medical management, including counseling about lifestyle modifications and hepatology referrals, increased significantly post-intervention, from 7.1% to 16.5% (p-value < 0.001) **Conclusion:** Our study underscores the positive impact of a targeted educational intervention on improving MASLD documentation and increasing awareness among internal medicine residents. These findings highlight the critical role of PCPs in the early detection and risk stratification of MASLD, reinforcing the importance of integrating focused training and EHR-based tools into routine primary care practice to enhance long-term patient outcomes

		Pre-Intervention	Post-Intervention	p-value
		N=296	N=261	
Sex n (%)	Female	210 (70.9%)	179 (68.6%)	0.54
	Male	86 (29.1%)	82 (31.4%)	
Age (Mean/SD)		62.1 (13.1)	62.0 (12.8)	0.90
Race n (%)	White	13 (4.4%)	15 (5.8%)	0.97
	African American	253 (86.3%)	220 (84.9%)	
	Asian	2 (0.7%)	2 (0.8%)	
	Multi/Bi-racial	1 (0.3%)	1 (0.4%)	
	Other	24 (8.2%)	21 (8.1%)	
Ethnicity n (%)	Non-Hispanic	270 (95.7%)	238 (94.8%)	0.61
	Hispanic	12 (4.3%)	13 (5.2%)	
Provider	Attending	134 (46.7%)	112 (44.3%)	0.57
	Resident	153 (53.3%)	141 (55.7%)	
GLP-1 Agonist use n (%)		40 (13.5%)	39 (14.9%)	0.62
Metabolic Conditions				
Diabetes Mellitus n (%)		295 (99.7%)	259 (99.2%)	0.49
Obesity n (%)		220 (74.3%)	198 (75.9%)	0.68
Hypertension n (%)		279 (94.3%)	246 (94.3%)	1.00
Hyperlipidemia n (%)		272 (91.9%)	236 (90.4%)	0.54
Other Comorbidities				
Congestive Heart Failure n (%)		126 (42.6%)	115 (44.1%)	0.72
Vascular Disease n (%)		96 (32.4%)	96 (36.8%)	0.28
Chronic Kidney Disease n (%)		114 (38.5%)	109 (41.8%)	0.43
Obstructive Sleep Apnea n (%)		150 (50.7%)	137 (52.5%)	0.67
Hypothyroidism n (%)		60 (20.8%)	51 (19.5%)	0.91
Social History				
Alcohol use n (%)		44 (14.9%)	43 (16.5%)	0.60
Smoking n (%)		107 (36.1%)	93 (35.6%)	0.90

Table 1: Demographics of Study Participants

Disclosures: Nadera Altork: Nothing to Disclose, Ahmad Abdulraheem: Nothing to Disclose, Bara Abujaber: Nothing to Disclose, Boniface Mensah: Nothing to Disclose, Deeptha Bejugam: Nothing to Disclose, Keerthana Chintalapati: Nothing to Disclose, Aishwarya Yannamani: Nothing to Disclose, Qusai Al Zureikat: Nothing to Disclose, Ujjwala Narang: Nothing to Disclose, Isha Isha: Nothing to Disclose, Sahana Karkera: Nothing to Disclose, Arul Thomas: Nothing to Disclose

2573 | TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT YIELDS SIMILAR CLINICAL OUTCOMES IN MASH AND ALCOHOLIC CIRRHOSIS: A MULTINATIONAL ANALYSIS

Donghyun Ko[1] Do Han Kim[2] Christina Lee[3] Pojsakorn Danpanichkul[4] Frank Lukens[5] Paul Kroner[6] Raffi Karagozian[3], [1]Bridgeport Hospital, Yale New Haven Health, Connecticut, USA, [2]Department of Medicine, Mount Sinai Morningside and West, Icahn School of Medicine at Mount Sinai, [3]Department of Medicine, Tufts Medical Center, Boston, Massachusetts, [4]Texas Tech University Health Sciences Center, [5]Division of Gastroenterology and Hepatology, Mayo Clinic Jacksonville, Florida, [6]Department of Gastroenterology, Riverside Regional Medical Center, Newport News, VA, USA

Background: Current evidence on safety regarding the placement of transjugular intrahepatic portosystemic

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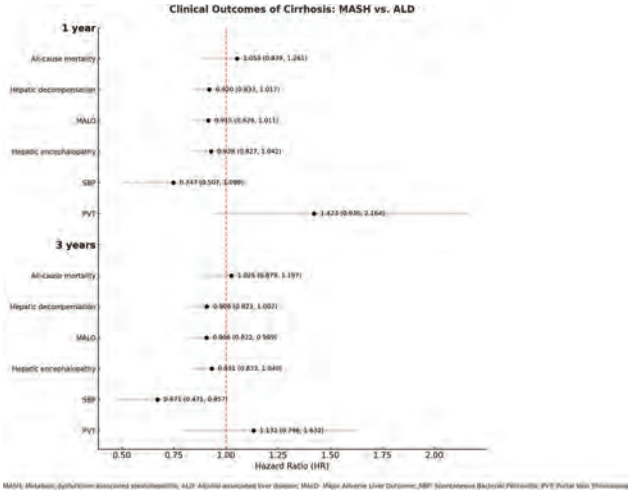
shunt (TIPS) is limited to retrospective observational studies. This leads to the question of whether the clinical outcomes of TIPS among the different etiologies of cirrhosis are similar. Given that no decisive Conclusion: can be drawn from the current evidence regarding TIPS placement among different etiologies, this study aims to explore the outcomes of TIPS placement between cirrhosis by MASH vs. ALD. **Methods:** A retrospective cohort study was performed using TriNetX. Patients with cirrhosis who underwent TIPS were identified and stratified by etiology into two groups: MASH cirrhosis and alcoholic cirrhosis. The cohorts were matched using propensity score matching (1:1) based on gender, demographics, comorbidities, and medications. Outcomes assessed included all-cause mortality, hepatic decompensation, major adverse liver outcomes (MALO), hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), and portal vein thrombosis (PVT). These outcomes were analyzed at 1- and 3-year follow-up following the index event. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to evaluate associations between variables. **Results:** A total of 5,096 adult patients with cirrhosis who underwent TIPS were identified, of which 1,326 had MASH cirrhosis. 1,035 patients with MASH cirrhosis (mean age 62.1 years, 46.6% female) were matched with 1,035 patients with alcoholic cirrhosis (mean age 62.3 years, 45.2% female). No differences were observed in all-cause mortality, hepatic decompensation, MALO, HE, SBP, and PVT. **Conclusion:** Discussion: Our study demonstrated that there is no significant clinical difference following TIPS placement between MASH and ALD cirrhosis. This finding suggests that decompensated cirrhosis necessitating TIPS has a similar progression of the disease regardless of the inciting event. Although our study is limited to the available data in the database, it gives rise to the hypothesis that such behavior might be expected in cirrhosis arising from other causes. Further longitudinal studies are warranted to validate this hypothesis.



Disclosures: Donghyun Ko: Nothing to Disclose, Do Han Kim: Nothing to Disclose, Christina Lee: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Frank Lukens: Nothing to Disclose, Paul Kroner: Nothing to Disclose, Raffi Karagozian: Nothing to Disclose

2574 | ASSESSING MASLD AND LIVER FIBROSIS WITH TRANSIENT ELASTOGRAPHY: FINDINGS FROM A MULTICENTER POPULATION-BASED STUDY IN MEXICO

Luis Enrique Gutiérrez Rosas[1] Carlos Martinez-Cabrera[1] Berenice Roman-Calleja[2] Victor Montoya Guzman[1] Marcela Castillo-Medina[1] Alma Ladron-De-Guevara-Cetina[1], [1]Centro de Investigación y Gastroenterología, [2]Universidad Nacional Autónoma de México

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects up to 30% of the global population and over 44% in Latin America. In Mexico, prevalence is estimated between 41–52%, mostly based on ultrasound or clinical indices. The Mexican population is of particular interest due to its genetic predisposition, high burden of metabolic diseases, and frequent use of potentially hepatotoxic herbal supplements. We aimed to describe the prevalence and clinical characteristics of liver health in a general population using transient elastography. **Methods:** We conducted a cross-sectional study including 981 participants from the general population between September 2024 and May 2025, recruited from different states of Mexico, at two clinical sites belonging to the "Centro de Investigación y Gastroenterología, Mexico City", a facility with experience in clinical trials. All participants underwent the FibroScan® Compact 530 model to assess hepatic steatosis (CAP $\geq$288 dB/m) and liver fibrosis (LSM $\geq$8.2 kPa). Clinical and metabolic data were collected to explore associations with MASLD. **Results:** A total of 981 adults from the general population were included with a median of 54 (41-63) years and 64.2% were female. MASLD was present in 33.4 % (n = 328),of which 59 (18.0%) had significant fibrosis. From the whole sample, we identified significant fibrosis in 16.3% (n = 161). Among those with significant fibrosis, 31 (19.2%) had F2, 37 (23.0%) had F3, and 93 (57.8%) had F4. When stratified by fibrosis stage, CAP values tended to decrease with advancing fibrosis, from a median of 294 dB/m in F2 to 238 dB/m in F3 and 217 dB/m in F4 ($p = 0.021$). Participants with advanced fibrosis (F2–F4) also had higher BMI ($p = 0.002$), with values up to 30.5 kg/m², and a higher prevalence of diabetes or prediabetes, reaching 50.5% in F4 ($p < 0.001$). Hypertension was more frequent in advanced fibrosis (up to 45.2% in F2,

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$p < 0.001$). **Conclusion:** MASLD and significant liver fibrosis are common in the general Mexican population. CAP values decreased with advancing fibrosis, likely reflecting the replacement of steatotic hepatocytes by fibrotic tissue. The presence of fibrosis at a young age raises concern for disease progression and highlights the need for early identification and targeted interventions.

Table 1. Characteristics of the study population according to presence or absence of MASLD and liver fibrosis.

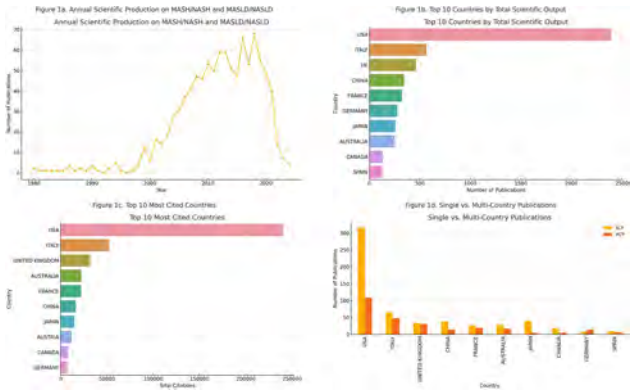
	MASLD (N=328)	Non-MASLD (N=653)	P value	F0-F1 (n=820)	F2 (N=31)	F3 (N=37)	F4 (N=93)	P value
Sex (Female) n(%)	183 (55.7)	446 (68.3)	<0.001	514 (62.7)	24 (77.4)	27 (72.9)	64 (68.8)	0.163
Age (years)	52 (41-61)	55 (41-64)	0.039	52 (38-62)	56 (51-65)	59 (53-63)	60 (54-67)	<0.001
CAP	315 (301-335)	241 (214-266)	<0.001	266 (230-303)	294 (266-316)	261 (238-309)	257 (217-297)	0.021
KPA	5.7 (4.5-7.2)	4.9 (3.9-6.6)	<0.001	4.8 (3.9-5.9)	8.8 (8.6-9.2)	11.1 (10.0-12.0)	19.8 (15.7-28.6)	<0.001
BMI (Kg/m2)	31.2 (28.0-35.1)	27.1 (24.1-30.5)	<0.001	28.1 (25.3-31.9)	30.5 (27.9-38.4)	30.1 (27.0-32.9)	29.7 (25.8-33.2)	0.002
DM2 or Prediabetes n(%)	118 (36.0)	161 (24.7)	<0.001	203 (24.8)	12 (38.7)	13 (35.1)	47 (50.5)	<0.001
Hypertension n(%)	105 (32.0)	141 (21.6)	<0.001	184 (22.4)	14 (45.2)	13 (35.1)	35 (37.6)	<0.001
Dyslipidemia n(%)	143 (43.6)	185 (28.3)	0.001	278 (33.9)	10 (32.3)	15 (40.5)	25 (26.9)	0.461

Disclosures: Luis Enrique Gutiérrez Rosas: Nothing to Disclose, Carlos Martinez-Cabrera: Nothing to Disclose, Berenice Roman-Calleja: Nothing to Disclose, Victor Montoya Guzman: Nothing to Disclose, Marcela Castillo-Medina: Nothing to Disclose, Alma Ladron-De-Guevara-Cetina: Nothing to Disclose

2575 | FROM HOTSPOTS TO BLINDSPOTS: A GLOBAL VIEW OF MASH RESEARCH DISPARITIES OVER TIME

Renan Prado[1] Melissa Lou Silva[2], [1]Cleveland Clinic Foundation, [2]University of California San Diego

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH, formerly NASH), represent a major cause of chronic liver disease worldwide. MASLD is now recognized as a systemic metabolic disorder with significant cardiovascular and malignant complications. With evolving nomenclature and rising global prevalence, publication trends and research impact across regions warrant evaluation. **Methods:** A bibliometric analysis was performed using the Web of Science Core Collection. All articles and reviews published between 1980 and 2024 containing the terms “NASH”, “MASH”, “NAFLD”, or “MASLD” were included. Bibliometric indicators were analyzed using the Bibliometrix package in R, including annual productivity, citation impact, authorship, and international collaboration. **Results:** A total of 51,619 relevant publications were identified, with 15,351 with Meeting Abstract. The total percentage of publications from the most recent 10 years (January 2016– May 2025) accounts for approximately 70.3% of all records. This highlights the interest the interest of MASH/MASLD in the most recent years. We evaluated the 1,000 most cited articles, among the 36,268 evaluated. The United States led with 425 publications, followed by Italy (113), China (96), Japan (81), and the UK (70). Low- and middle-income countries collectively accounted for approximately 18% of the total output. *Hepatology*(169 articles), *Journal of Hepatology* (105), and *Gastroenterology* (74) were the top 3 journals with most prolific sources. The most cited paper, published in *Hepatology* (Kleiner et al., 2005), accrued 8,489 citations. The USA, Italy, and Japan ranked highest in total citations. While the USA dominated both single-country and multi-country collaborations, international engagement varied by region. **Conclusion:** Global research output on MASH/NASH and MASLD/NASLD continues to grow rapidly, yet significant disparities persist. High-income countries dominate authorship and citation impact, emphasizing the need for more inclusive and collaborative research efforts involving underrepresented regions.



Disclosures: Renan Prado: Nothing to Disclose, Melissa Lou Silva: Nothing to Disclose

2576 | HORMONE REPLACEMENT THERAPY AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Garvita Singhal[1] Shahid Habib[2] Elias Shamieh[3], [1]Tucson Medical Center, [2]Liver Institute PLLC, Tucson, [3]University of Cincinnati

Background: MASLD is increasingly recognized in postmenopausal women, likely due to estrogen deficiency. While estrogen influences metabolic and hepatic function, the impact of hormone replacement therapy (HRT) on MASLD progression remains unclear. This

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study evaluated associations between estrogen therapy and clinical, metabolic, and hepatic parameters related to MASLD in women. **Methods:** We conducted a retrospective analysis of IRB-approved, prospectively collected liver registry data (July 2015–Dec 2020). Inclusion required ≥6 months of estrogen use and complete exposure data. Of 684 women, 400 (58.5%) had estrogen exposure (via contraception, HRT, or both), and 284 (41.5%) did not. Clinical, metabolic, liver, and immunologic parameters were compared. Multivariable logistic regression (adjusted for age, alcohol, comorbidities) assessed associations with cirrhosis (by biopsy/imaging) and metabolic syndrome (≥3 criteria). Spearman's correlation examined estrogen duration and insulin resistance (HOMA-IR). Stratified analyses used Mantel-Haenszel method. **Results:** Among estrogen users, indications were contraception (n = 123), HRT (n = 232), or both (n = 46). Mean age was 57.3 years; mean estrogen duration 5.2 years. Estrogen duration (combined contraception and/or HRT) negatively correlated with HOMA-IR ($r = -0.149$, $p = 0.001$), suggesting reduced insulin resistance. This correlation was lost when subgroups were analyzed separately. Estrogen use (HRT or combined) was not independently associated with metabolic syndrome or cirrhosis in adjusted models. On unadjusted analysis, contraception-only users had lower cirrhosis risk vs. nonusers (OR 0.57, $p = 0.003$), but this lost significance after adjustment. Predictors of metabolic syndrome included hypertension, NAFLD/NASH, diabetes/prediabetes, hypertriglyceridemia, low HDL, high NAFLD fibrosis score, and low Fib-4 (all $p < 0.05$). Independent cirrhosis predictors included autoimmune disease (OR ~5.4–5.8), elevated Fib-4 and NFS, AST/ALT ratio, alcohol use, hypertension, ANA positivity, and BMI ≥29. **Conclusion:** Lifetime estrogen use was not independently associated with cirrhosis or metabolic syndrome but was linked to improved insulin sensitivity, a key MASLD factor. Findings underscore MASLD's multifactorial nature in women and the need for prospective studies to clarify HRT's impact on liver outcomes.

Disclosures: Garvita Singhal: Nothing to Disclose, Shahid Habib: Nothing to Disclose, Elias Shamieh: Nothing to Disclose

2577 | PNPLA3 P.I148M POLYMORPHISM IS ASSOCIATED WITH THE RISK OF LIVER FIBROSIS IN PATIENTS WITH BREAST CANCER RECEIVING LONG-TERM TAMOXIFEN THERAPY

Wonseok Kang[1] Sangdeok Shin[1] Myung Ji Goh[1] Byeong Geun Song[1] Dong Hyun Sinn[1] Geum-Youn Gwak[1] Yong-Han Paik[1] Moonseok Choi[1] Joon Hyeok Lee[1] Jonghan Yu[1], [1]Samsung Medical Center

Background: Estrogen upregulates PNPLA3 gene expression and activates energy-consuming hepatic metabolism. Recent studies suggest that estrogen may induce metabolic dysfunction-associated steatotic liver disease (MASLD) in women carrying the PNPLA3 p.I148M variant. Tamoxifen, a selective estrogen receptor modulator, is widely used for the prevention and treatment of estrogen receptor-positive breast cancer but is associated with steatotic liver disease (SLD). However, the relationship between PNPLA3 genotypes and tamoxifen-associated SLD remains unexplored. We aimed to investigate the prevalence and progression of MASLD in breast cancer patients receiving tamoxifen therapy, stratified by PNPLA3 genotype, to identify high-risk populations who may benefit from enhanced monitoring and personalized treatment strategies. **Methods:** This retrospective analysis utilized a prospective cohort of breast cancer patients from Samsung Medical Center between January 2015 and May 2020. Of 909 women screened, 548 breast cancer patients treated with tamoxifen for ≥2 years were included in the final analysis. PNPLA3 genotyping was performed using the TaqMan SNP Genotype Assay. Patients were classified into low-risk (CC/CG types, n = 467) and high-risk (GG type, n = 81) groups. Data were analyzed over five years using FIB-4 scores to detect fibrosis progression, with patients stratified by baseline liver fibrosis status. **Results:** In multivariable analysis, the PNPLA3 GG genotype had a significantly increased risk of fibrosis progression (HR 2.69, 95% CI 1.18-6.11; p = 0.018) compared to CC/CG genotype. In patients with low baseline fibrosis risk (FIB-4 <1.3), the GG genotype was associated with a 5.08-fold increased risk (HR 5.08, 95% CI 1.85-14.0; p = 0.002) compared to CC/CG genotypes, with cumulative incidence curves diverging after 24 months of treatment. In patients with moderate baseline fibrosis risk, no significant association was found (HR: 0.60; 95% CI: 0.07-4.94; P = 0.600). Subgroup analysis revealed significantly elevated fibrosis risk associated with GG genotype in patients aged ≥65 years (HR 3.73, 95% CI 1.25-11.20), those without diabetes mellitus (HR 3.27, 95% CI 1.18-9.07), patients with pre-existing MASLD (HR 2.53, 95% CI 1.01-6.35), and postmenopausal status (HR: 3.10; 95% CI: 1.26-7.61). **Conclusion:** The PNPLA3 GG genotype is associated with accelerated liver fibrosis in breast cancer patients undergoing tamoxifen therapy, particularly in those with low baseline fibrosis risk. Our findings suggest that PNPLA3 genotyping could serve as a valuable risk stratification tool, especially for older, postmenopausal women with pre-existing MASLD, who may benefit from enhanced liver monitoring during tamoxifen therapy.

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Disclose, Joon Hyeok Lee: Nothing to Disclose, Jonghan Yu: Nothing to Disclose

2578 | INTEGRATING FIB-4 SCORING INTO PRIMARY CARE TO DETECT ADVANCED FIBROSIS IN PATIENTS WITH METABOLIC RISK: A MULTICENTER PILOT IMPLEMENTATION STUDY

Noor Albusta[1] Ammar Kheyami[2], [1]Lahey Hospital and Medical Center, [2]Bahrain Government Hospitals

Background: The global burden of metabolic dysfunction-associated steatotic liver disease (MASLD) underscores the need for early identification of advanced fibrosis, particularly in primary care settings where liver disease is often overlooked. The Fibrosis-4 (FIB-4) index, calculated from age, AST, ALT, and platelet count, is a validated, low-cost, non-invasive fibrosis risk tool using routine labs. Despite its simplicity, FIB-4 remains underutilized in primary care workflows. This study evaluated the feasibility, diagnostic yield, and real-world challenges of implementing FIB-4 screening across a network of public primary care clinics in a high-risk population. **Methods:** We conducted a 12-month prospective pilot across 10 government-affiliated primary care centers in Bahrain. Adults aged $\geq$35 years with at least one metabolic risk factor (type 2 diabetes, obesity, hypertension, or dyslipidemia) and recent laboratory tests were included. FIB-4 scores were calculated and stratified into low ($<$1.3), indeterminate (1.3–2.66), and high ($\geq$2.67) risk. High-risk patients were referred for hepatology review, with transient elastography performed where available. Outcomes included FIB-4 completion rate, referral follow-through, fibrosis detection, and provider-reported barriers. **Results:** Of 2,450 eligible patients, FIB-4 was successfully calculated in 2,136 (87.2%). High-risk scores were found in 262 patients (12.3%), of whom 188 (71.8%) were referred. Among 113 who completed elastography, 34.5% had advanced fibrosis ($\geq$F3), and 6.2% had cirrhosis. The number needed to screen (NNS) to detect one case of advanced fibrosis was 55. The positive predictive value (PPV) of a high FIB-4 score for advanced fibrosis was 34.5%, with a 95% confidence interval of 25.5%–43.5%. Referral efficiency (confirmed fibrosis per referral) was 20.7%. Referral adherence was high (89%). Providers reported moderate ease of implementation. Common barriers included inconsistent lab ordering (38%), limited familiarity with interpreting FIB-4 scores (31%), patient reluctance to attend hepatology (16%), and lack of automated FIB-4 calculators within the EMR (15%). **Conclusion:** This multicenter pilot confirms that FIB-4–based screening in primary care is feasible and effective in detecting undiagnosed advanced fibrosis in patients with metabolic risk. These findings support integrating simple non-invasive tools into frontline workflows, with potential for national-level scale-up to reduce MASLD-related liver disease burden.

Disclosures: Noor Albusta: Nothing to Disclose, Ammar Kheyami: Nothing to Disclose

2579 | DISPARITIES IN OUTCOMES AND COMPLICATIONS OF ALCOHOL-RELATED AND NASH-RELATED CIRRHOSIS: A NATIONWIDE PERSPECTIVE

Abdelhaleem Sideeg Fatima Elmustafa[1] Mohammad Adam[2] Ali Osman[3] Miqdad Dafaallah[4] Blaire Burman[5] Asma Siddique[5] Richard Kozarek[5], [1]Henry Ford Hospital, [2]University of Missouri - Kansas City, [3]Washington University School of Medicine in St. Louis, [4]Mercyone Des Moines Medical Center, [5]Virginia Mason Medical Center

Background: Liver cirrhosis caused 1.48 million deaths globally in 2019. While cases of hepatitis B and C are declining, those linked to heavy alcohol consumption and nonalcoholic steatohepatitis (NASH), recently renamed metabolic-associated steatohepatitis (MASH), are increasing. The current literature offers limited comparison data on the outcomes and complications associated with these etiologies. This nationwide study aimed to fill this knowledge gap and enhance the quality of patient care. **Methods:** This cohort study analyzed 419,144 adult patients ($\geq$18 years) hospitalized for alcohol-related cirrhosis (n = 336,829) or NASH-related cirrhosis (n = 82,315) between 2017 and 2021, using the National Inpatient Sample database. ICD-10 codes were used to identify patient groups, and multivariate logistic regression was adjusted for demographic, socioeconomic, and hospital factors. Patients with concurrent alcohol-related and NASH-related cirrhosis were excluded. The primary outcome was in-hospital mortality. Secondary outcomes included total charges, length of stay (LOS), and cirrhosis complications, including hepatocellular carcinoma (HCC), portal hypertension, variceal bleeding, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), coagulopathy, and liver failure. **Results:** Patients with alcohol-related cirrhosis were younger (mean age 56 years; 69.4% male) than those with NASH-related cirrhosis (mean age 64 years; 60.6% female, $p < 0.001$). Crude median charges were higher for NASH-related cirrhosis ($43,777, IQR $24,388–$83,794) than for alcohol-related cirrhosis ($41,792, IQR $23,623–$78,045, $p < 0.001$). Adjusted analysis showed that alcohol-related cirrhosis was associated with longer hospital stays by 0.78 days (95% CI 0.72–0.85, $p < 0.001$), higher odds of HCC (OR 1.36, 95% CI 1.29–1.43; $p < 0.001$), in-hospital mortality (OR 1.95, 95% CI 1.88–2.04, $p < 0.001$), ascites (OR 1.86, 95% CI 1.82–1.89, $p < 0.001$), hepatic encephalopathy (OR 1.41, 95% CI 1.37–1.45, $p <$

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0.001), and coagulopathy (OR 1.82, 95% CI 1.76–1.88, p < 0.001). **Conclusion:** Our study revealed notable differences in the outcomes of alcohol consumption and NASH -related cirrhosis. Alcohol-related cirrhosis leads to extended hospital stays, more complications, and higher rates of mortality during hospitalization. These findings highlight the considerable impact of alcohol consumption on both the healthcare system and patient outcomes. Additional studies are needed to investigate the underlying causes of these disparities and assess management strategies tailored to specific etiologies.

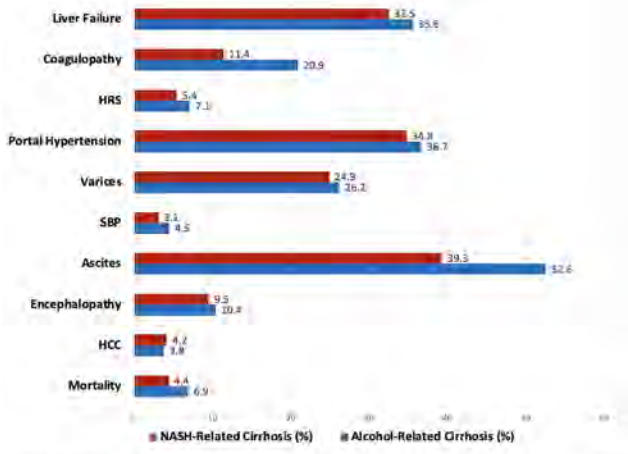

Fig 1: Comparison of Crude Complications Rates Between Alcohol-Related and NASH-Related Cirrhosis

In- Hospital variable	OR (95% CI)	p-value
Mortality	1.95 (1.88–2.04)	<0.001
Hepatocellular carcinoma (HCC)	1.36 (1.29–1.43)	<0.001
Hepatic encephalopathy	1.41 (1.37–1.45)	<0.001
Esophageal or gastric Varices	1.03 (1.01–1.05)	0.012
Ascites	1.86 (1.82–1.89)	<0.001
Spontaneous bacterial peritonitis (SBP)	1.4 (1.33–1.47)	<0.001
Portal hypertension (PHT)	1.29 (1.26–1.32)	<0.001
Hepatorenal syndrome (HRS)	1.61 (1.55–1.68)	<0.001
Coagulopathy	1.82 (1.76–1.88)	<0.001
Liver Failure	1.45 (1.42–1.48)	<0.001

Table 1: Adjusted Odd ratio for Alcohol-related Cirrhosis compared to NASH- related cirrhosis

Disclosures: Abdelhaleem Sideeg: Nothing to Disclose, Fatima Elmustafa: Nothing to Disclose, Mohammad Adam: Nothing to Disclose, Ali Osman: Nothing to Disclose, Miqdad Dafaallah: Nothing to Disclose, Blaire Burman: Nothing to Disclose, Asma Siddique: Nothing to Disclose, Richard Kozarek: Nothing to Disclose

2580 | ASSOCIATIONS OF CARDIOVASCULAR HEALTH WITH HEPATIC FIBROSIS, MASLD AND METALD IN THE FRAMINGHAM HEART STUDY

Alejandro Campos[1] Tianyu Liu[2] Brenton Prescott[3] Jiantao Ma[4] Maura Walker[5] Vanessa Xanthakis[6] Arpan Mohanty[1], [1]Boston University Chobanian & Avedisian School of Medicine - Boston Medical Center, [2]Boston University School of Public Health, [3]Boston University Chobanian & Avedisian School of Medicine, [4]Friedman School of Nutrition Science and Policy, Tufts University, [5]Sargent College of Health and Rehabilitation, Boston University, [6]Boston University and National Heart, Lung, and Blood Institute's Framingham Heart Study

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD), metabolic and alcohol-associated liver disease (MetALD), and hepatic fibrosis are increasingly common with shared cardiometabolic risk factors. The American Heart Association's (AHA) Life's Essential 8 (LE8) score assesses cardiovascular health (CVH) using four health behaviors (diet, physical activity [PA)], nicotine exposure, sleep) and four risk factors (Body Mass Index [BMI], blood glucose, blood pressure [BP], and non-HDL cholesterol). The associations of LE8 and its behavioral subset (LE4), with MASLD, MetALD, and hepatic fibrosis remain understudied. **Methods:** We evaluated the association of LE4 with MASLD and MetALD, and of LE8 with hepatic fibrosis among Framingham Heart Study participants with valid and complete CVH and transient elastography data (n = 2,968). Steatosis was defined as controlled attenuation parameter ≥274 dB/m; significant fibrosis as liver stiffness ≥8.2 kPa. MASLD and MetALD were defined as steatosis plus ≥1 cardiometabolic risk factor with mild alcohol use (women < 140g/wk; men < 210g/wk) and moderate alcohol use (women 141–350g/wk; men 211–420g/wk), respectively. The LE8-Fibrosis analysis was performed in participants with complete LE8 data (n = 2,884). We used multivariable logistic mixed-effects models adjusted for age, sex, education, and familial relatedness to estimate odds ratios (ORs) per 10-point increase in LE4 or LE8. **Results:** Among 2,968 participants (57% women; mean age 58.6 years), 2,703 reported mild and 265 moderate alcohol use. MASLD was present in 33.7% of the mild group and MetALD in 39.2% of the moderate group. Significant fibrosis was present in 8% of all participants. Median LE8 and LE4 scores were 70 and 76.9 in the fibrosis group, 68.4 and 77.5 in mild, and 67 and 73.1 in moderate alcohol use groups. Higher LE8 scores were associated with a 17% lower odds of fibrosis (OR 0.83; 95% CI:0.78–0.88; p < 0.0001), primarily driven by BMI, glucose, BP, sleep, and PA. Higher LE4 scores were associated with 14% lower odds of MASLD (OR 0.86; 95% CI:0.81–0.91; p < 0.001), driven by diet, PA, and nicotine exposure. There was no association between LE4 and MetALD. **Conclusion:** Better CVH was associated with lower odds of fibrosis and MASLD. Among individual CVH components, physical activity showed the strongest inverse association with both outcomes, while healthier BMI, blood glucose, and

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blood pressure were associated with lower odds of fibrosis.

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2581 | MUSCLE FUNCTION CORRELATES WITH DISEASE SEVERITY IN PATIENTS WITH MASLD. A PROSPECTIVE STUDY

Mary Olayiwola[1] Pinelopi Manousou[1] Michael Yee[1] Maria Kalafateli[1] Roberta Forlano[1] Benjamin Mullish[1] Mark Thursz[1], [1]Imperial College London

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects over 30% of adults globally, yet non-invasive predictors of disease progression remain suboptimal. Muscle function assessments remain underutilised in clinical practice, despite growing evidence that sarcopenia contributes to MASLD progression and adverse outcomes. **Methods:** We conducted a prospective cross-sectional study of 382 MASLD patients at a UK tertiary centre (2023-2025). Liver stiffness measurement (LSM) via transient elastography (TE), FIB-4, Mediterranean Diet Score (MDS), International Physical Activity Questionnaire (IPAQ), Short Form-36 (SF36), and muscle function assessments (Handgrip Strength [HGS], Five Times Sit-to-Stand Test [FTSST]) were collected. Advanced fibrosis was defined as LSM $\geq$8 kPa. **Results:** The median age was 58 years, 56% male, median BMI 32.6 kg/m², and 64.9% had Type 2 Diabetes. Advanced fibrosis (LSM $\geq$8 kPa) was present in 57.3% of patients. Patients with advanced fibrosis had significantly lower emotional well-being scores (61.6 vs 68.9, $p = 0.028$), lower physical activity (median MET 1614 vs 2338 min/week, $p = 0.024$), and impaired lower limb muscle function (FTSST 13.3 vs 11.2 sec, $p = 0.004$). FTSST times were significantly longer in patients with advanced fibrosis ($r = 0.164$, $p = 0.001$), indicating a positive correlation between slower lower limb performance and fibrosis severity. Also, FTSST times negatively correlated with all SF36 domains ($p < 0.05$), with the strongest association seen for physical functioning ($r = -0.453$, $p = 0.001$). Higher HGS values were positively correlated with improved QoL across all SF36 domains. Overall, greater muscle function—reflected by higher HGS and faster FTSST performance—was strongly associated with better QoL. **Conclusion:** This study demonstrates the critical associations between muscle function, physical activity, QoL, and MASLD severity. Impaired muscle strength, particularly lower limb function assessed via the Five Times Sit-to-Stand Test (FTSST), was significantly associated with advanced fibrosis and lower QoL, outperforming FIB-4 as a marker of disease severity. These findings underscore the need to incorporate routine muscle function assessments—especially FTSST—into MASLD care.

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2582 | MASLD VS METALD: DISTINCT CLINICAL PHENOTYPES IN A CENTRAL EUROPEAN COHORT

Jerzy Jaroszewicz[1] Karol Zmudka[1] Marlena Dubatówka[2] Małgorzata Chlabicz[2] Damian Piotrowski[1] Karol Kaminski[2], [1]Department of Infectious Diseases and Hepatology, Medical University of Silesia in Katowice, Poland, [2]Department of Population Medicine and Lifestyle Diseases Prevention, Medical University of Bialystok

Background: There is a lack of data regarding the prevalence and clinical characteristics of metabolic dysfunction-associated steatotic liver disease (MASLD), as well as the role of alcohol consumption as a cofactor in disease progression in Central and Eastern Europe. This study aims to address this gap. **Methods:** This analysis is part of the Bialystok PLUS (Polish Longitudinal University Study), an ongoing prospective, population-based epidemiological study. We assessed the prevalence of MASLD and MetALD in a random sample of adult residents of Bialystok, Poland. Additionally, we analyzed anthropometric, epidemiological, clinical, and lifestyle data from 2,456 participants, comparing individuals with MASLD and MetALD to a control group without liver steatosis. **Results:** In the studied cohort, 22.72% of participants met the diagnostic criteria for MASLD, and 2.08% for MetALD. Age-adjusted for standard population prevalence per 1,000 inhabitants was 126.48 [95% CI: 96.32–170.84] for MASLD and 20.77 [95% CI: 15.83–27.20] for MetALD. Distinct cardiometabolic patterns were observed: MASLD was associated with a higher prevalence of obesity and type 2 diabetes, whereas MetALD was more frequently linked to hypertension and dyslipidemia. Significant liver fibrosis (LSM $\geq$ F2) was more prevalent in the MetALD group (17.78%) compared to MASLD (15.64%) and controls (5.12%, $P < 0.001$). Similarly, cirrhosis was more common in MetALD (4.44%) than in MASLD (0.58%) and controls (0.12%). Additional analyses of anthropometric, clinical, epidemiological, and lifestyle characteristics were conducted,

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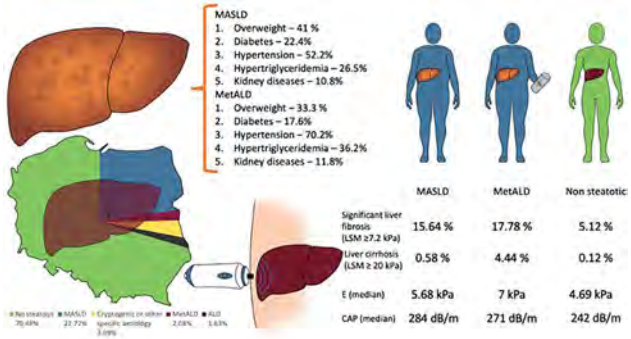
and risk factors for significant fibrosis in MASLD and MetALD were evaluated. **Conclusion:** Both MASLD and MetALD represent significant public health challenges, yet they exhibit distinct clinical phenotypes. Understanding the interplay between metabolic dysfunction and alcohol consumption is crucial for improving diagnosis, treatment, and prevention strategies.

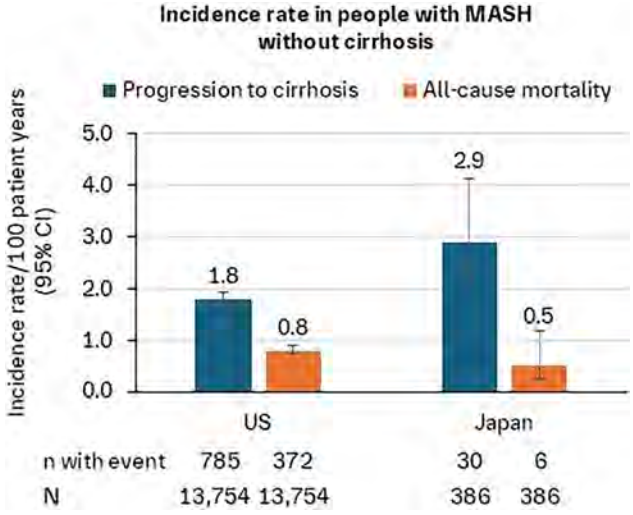


Disclosures: Jerzy Jaroszewicz: AbbVie: Advisor, Roche: Grant/Research Support, Gilead Sciences: Advisor, Grifols: Speaking and Teaching, GSK: Advisor, MSD: Advisor, Novo Nordisk: Advisor, Novartis: Consultant, Karol Zmudka: Nothing to Disclose, Marlena Dubatówka: Nothing to Disclose, Małgorzata Chlabicz: Nothing to Disclose, Damian Piotrowski: Nothing to Disclose, Karol Kaminski: Nothing to Disclose

2583 | PROGRESSION TO CIRRHOSIS IN PEOPLE WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) IN REAL-WORLD COHORTS IN THE US AND JAPAN

Jörn Schattenberg Zuleika Aponte-Torres[1] Ronald Herrera[2] Mireia Raluy[3] Mark Yates[3] Ramy Younes[2] Claudio Sartini[2] [1]Boehringer Ingelheim Pharmaceuticals, Inc., [2]Boehringer Ingelheim International GmbH, [3]Evidera, Data Analytics

Background: MASH, formerly called non-alcoholic steatohepatitis (NASH), can progress to cirrhosis and increase mortality risks. As real-world evidence on MASH progression in different countries is limited, we estimated progression to cirrhosis, mortality, and associated risk factors in MASH real-world patient cohorts from the United States (US) and Japan to inform clinical decision-making. **Methods:** This was a retrospective observational study using electronic health records and claims data from two databases: Optum® Market Clarity (OMC) in the US and Medical Data Vision (MDV) hospital data in Japan. Eligibility criteria included ≥1 claim or medical encounter with a diagnosis code for MASH (ICD-10-CM: K75.81) during the identification period (OMC: January 2016–May 2021; MDV: January 2016–June 2021), age ≥18 years at the diagnosis date, and laboratory values for aspartate aminotransferase (AST), alanine aminotransferase, and platelets in the 3 months before or after diagnosis (to calculate Fibrosis-4 score [FIB-4]). Individuals with a diagnosis code or medical claim for other liver diseases were excluded, as were those with evidence of cirrhosis (claim or medical encounter with a diagnosis code for cirrhotic conditions in the 3 months before or after diagnosis date). Patients were followed from the MASH diagnosis date to the earliest of liver transplant, death, loss to follow-up, or end of study (OMC: May 2022; MDV: June 2022). **Results:** Out of 18,710 patients with MASH in OMC, 13,754 (73.5%) did not have cirrhosis (mean age 42.1 years, 7,181 [52.2%] female, 10,796 [78.5%] non-Hispanic White, 10,028 [72.9%] FIB-4 <1.3). Of 452 patients with MASH in MDV, 386 (85.4%) did not have cirrhosis (mean age 46.8 years, 228 [59.1%] female, 251 [65.0%] FIB-4 <1.3). At a median follow-up of 1,169 days in OMC and 941 in MDV, the cumulative incidence of progression to cirrhosis was 5.7% and 7.8% in OMC and MDV, respectively. The respective incidence rates per 100 patient-years in OMC and MDV were 1.8 and 2.9 for progression to cirrhosis and 0.8 and 0.5 for all-cause mortality (Figure). Risk factors for elevated all-cause mortality in OMC included age, comorbidities, increased AST and glycated hemoglobin, and FIB-4 >1.3. **Conclusion:** Prevention of cirrhosis is key to avoiding further progression to mortality in MASH patients. Rates of progression to cirrhosis may vary depending on data source and patient population (claims vs hospital data or younger vs older patients).



Disclosures: Jörn Schattenberg: Apollo Endoscopy, Boehringer Ingelheim, Gilead Sciences: Consultant, Intercept Pharmaceuticals: Consultant, Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals: Consultant, MSD, Northsea Therapeutics, Novartis, Novo Nordisk: Consultant, Pfizer, Roche, Sanofi, and Siemens Healthineers: Consultant, Boehringer Ingelheim, Siemens Healthcare GmbH: Grant/Research Support, Alentis, Alexion, Altimmune, Astra Zeneca, 89Bio,Bionorica,:

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2584 | LONGITUDINAL ASSOCIATION BETWEEN CHANGE IN CARDIOVASCULAR HEALTH AND INCIDENT HEPATIC STEATOSIS

Alejandro Campos[1] Tianyu Liu[2] Brenton Prescott[3] Jiantao Ma[4] Vanessa Xanthakis[5] Maura Walker[6] Arpan Mohanty[1], [1]Boston University Chobanian & Avedisian School of Medicine - Boston Medical Center, [2]Boston University School of Public Health, [3]Boston University Chobanian & Avedisian School of Medicine, [4]Friedman School of Nutrition Science and Policy, Tufts University, [5]Boston University and National Heart, Lung, and Blood Institute's Framingham Heart Study, [6]Sargent College of Health and Rehabilitation, Boston University

Background: The American Heart Association's Life's Essential 8 (LE8) quantifies cardiovascular health (CVH) using four health behaviors (diet, physical activity, nicotine exposure, sleep) and four health factors (body mass index, blood pressure, blood glucose, non-HDL cholesterol). Adherence to LE8 metrics or higher LE8, has been associated with lower odds of hepatic steatosis in cross-sectional studies. However, the longitudinal association of changes in LE8 (ΔLE8) with incident hepatic steatosis remains understudied. **Methods:** We evaluated participants from the Second and Third Generation cohorts of the Framingham Heart Study who underwent two abdominal multidetector computed tomography scans between 2002–2005 and 2008–2011, with corresponding complete LE8 and covariate data. Participants with prevalent steatosis or cardiovascular disease (CVD), or heavy alcohol use ($>350/>420$ g/week for women/men) were excluded. Binary steatosis was defined as a liver-to-phantom attenuation ratio (LPR) ≤ 0.33. Baseline and follow-up LE8 were dichotomized at the sample median. Participants were categorized as high-high (LE8 > median at both exams; referent), low-high, high-low, or low-low. Multivariable logistic and linear mixed-effects models assessed associations of ΔLE8 categories with steatosis at follow-up exam and change in LPR (ΔLPR), adjusting for age, sex, baseline LE8, education, alcohol intake, familial relatedness, cohort and interim CVD. **Results:** Among 1,250 participants (mean age 50 ± 9 years; 53% women), 222 (18%) developed steatosis over a mean follow up of 6.3 years. Median LE8 was 71.9 at both baseline (IQR: 63.1–80.0) and follow-up (IQR: 63.8–80.6). There were 455 participants (38%) in the high-high group, 148 (12%) in the low-high, 166 (13%) in the high-low, and 481 (38%) in the low-low group. Compared to the high-high group, the high-low (OR 1.84, 95% CI: 1.04–3.23) and low-low (OR 2.23, 95% CI: 1.19–4.19) groups had higher odds of steatosis; there was no association between the low-high and the referent group. ΔLPR was lower in the high-low (−0.010, 95% CI: -0.018– -0.002, $p = 0.02$) and low-low (−0.011, 95% CI: -0.021– -0.001, $p = 0.03$) groups compared to referent, but not in the low-high group. **Conclusion:** Compared to participants maintaining high CVH, declining or persistently low LE8 scores conferred significantly higher odds of developing steatosis and increase in hepatic fat over 6 years. These findings emphasize the need for early intervention and sustained CVH to prevent hepatic steatosis.

Disclosures: Alejandro Campos: Nothing to Disclose, Tianyu Liu: Nothing to Disclose, Brenton Prescott: Nothing to Disclose, Jiantao Ma: Nothing to Disclose, Vanessa Xanthakis: Nothing to Disclose, Maura

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2585 | METABOLIC MATCHUP: COMPARING SGLT2, GLP-1, AND DUAL AGONISTS IN NASH/MASLD RISK AMONG DIABETICS

Muhammad Ali Ibrahim Kazi Qetevan Gvazava MD[1] Zurabi Lominadze[2] Maia Tavadze[1] [1]Anne Arundel Medical Center, [2]Baltimore VA Medical Center

Background: Nonalcoholic steatohepatitis (NASH) is a progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD), characterized by hepatic inflammation and fibrosis, often leading to cirrhosis, hepatocellular carcinoma, and increased cardiovascular mortality. Type 2 diabetes mellitus (T2DM) is a major risk factor for NASH/MASLD, contributing to its development through insulin resistance, chronic inflammation, and dyslipidemia. Recent studies have suggested that certain antidiabetic medications, including GLP-1 RAs, SGLT2 inhibitors, and dual GLP-1/GIP, may have differential effects on hepatic steatosis and fibrosis. However, comparative real-world data on their impact on NASH incidence remain limited.

This study aims to evaluate whether GLP-1 RAs, Tirzepatide, or SGLT2 inhibitors increase or decrease the risk of developing NASH after at least one year of continuous therapy in patients with diabetes. **Methods:** A retrospective cohort study was conducted using the TriNetX Global Health Research Network. The study population included adults ($\geq$18 years) with type 2 diabetes mellitus (T2DM) who initiated treatment with GLP-1 RAs, Tirzepatide, or SGLT2 inhibitors. To ensure comparability among the treatment groups, propensity score matching (PSM) was performed, balancing cohorts based on demographics, clinical characteristics, and medication use of antidiabetic agents such as metformin, sulfonylureas, DPP-4 inhibitors, and insulin, as well as antilipidemic drugs including statins and fibrates.

Patients were followed for a minimum of 12 months from the date of drug initiation. The primary outcome was the incidence of newly diagnosed nonalcoholic steatohepatitis (NASH). Statistical analyses included risk difference and risk ratio, each reported with 95% confidence intervals to assess the association between medications and the development of NASH. **Results:** Results:

1. GLP-1 RAs vs. Tirzepatide (50,522 patients each)

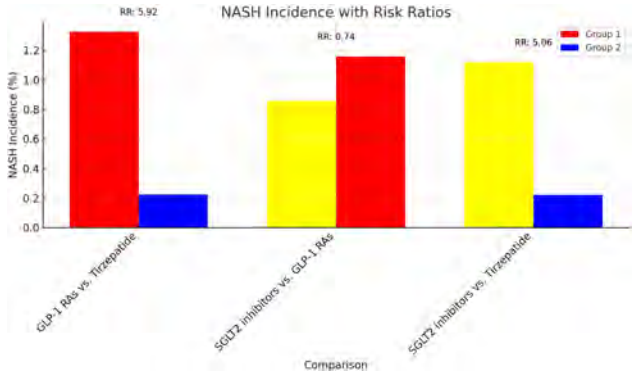
   NASH incidence: 1.324% (GLP-1) vs. 0.224% (Tirzepatide)
   RD: 1.101% (95% CI: 0.993%–1.208%), p < 0.0001
   RR: 5.92 (95% CI: 4.852–7.224)

2. SGLT2 inhibitors vs. GLP-1 RAs (384,228 patients each)

   NASH incidence: 0.857% (SGLT2 inhibitors) vs. 1.158% (GLP-1)
   RD: -0.301% (95% CI: -0.346% to -0.256%), p < 0.0001
   RR: 0.74 (95% CI: 0.708–0.774)

3. SGLT2 inhibitors vs. Tirzepatide (49,379 patients each)

   NASH incidence: 1.118% (SGLT2 inhibitors) vs. 0.221% (Tirzepatide)
   RD: 0.897% (95% CI: 0.796%–0.999%), p < 0.0001
   RR: 5.064 (95% CI: 4.125–6.217). **Conclusion:** Tirzepatide demonstrated the most significant reduction in NASH incidence among diabetic patients, followed by SGLT2 inhibitors, while GLP-1 receptor agonists were associated with a higher risk. These findings highlight the potential of newer antidiabetic agents in mitigating NASH risk and emphasize the need for prospective trials to confirm these associations and explore underlying mechanisms.



Disclosures: Muhammad Ali Ibrahim Kazi: Nothing to Disclose, Qetevan Gvazava MD: Nothing to Disclose, Zurabi Lominadze: Nothing to Disclose, Maia Tavadze: Nothing to Disclose

2586 | ACCULTURATION IS ASSOCIATED WITH IMPROVED LIVER MEASUREMENTS AMONG MEXICAN AMERICANS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Sharan Poonja[1] Rithvik Vutukuri[2] Molly Delk[1] Wei-Ting Lin[1] Hui-Yi Lin[3] Tung-Sung Tseng[3] Po-Hung (Victor) Chen[4] Peng-Sheng Ting[1], [1]Tulane University, [2]Tulane University School of Medicine, [3]Louisiana State

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Background: Latin America holds the highest global prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), affecting up to 44.4% of the population. The growing Hispanic population in the U.S. makes understanding MASLD in this population increasingly relevant. Acculturation, or the process by which immigrants adopt host country behaviors and norms, influences disease patterns through shifts in socioeconomic and lifestyle factors. This study examines the prevalence of MASLD, metabolic dysfunction-associated steatohepatitis (MASH), and fibrosis in different levels of acculturation among Mexican Americans and other Hispanic adults in a nationally representative sample. **Methods:** NHANES 2017–2020 pre-pandemic data was analyzed for Hispanic adults ≥20 years without non-steatotic liver disease and significant alcohol use (>20g for females and >30g for males daily). An acculturation index (scored 0–5) was adapted from prior literature using the sum of scores assigned for US born or foreign born and years in the U.S., and language spoken at home, and categorized as low (0–1), medium (2–3), and high (4–5); see Table 1 note. MASLD was defined as ≥1 cardiometabolic risk factor with CAP ≥294 dB/m, MASH as MASLD with elevated ALT (>25 U/L in females, >33 U/L in males), and fibrosis measured by fibroscan as liver stiffness measurement (LSM). All analyses were conducted using survey weights adjusted. **Results:** Among Mexican Americans, higher acculturation to the US was significantly associated with a lower prevalence of MASLD and MASH. MASLD prevalence declined from 53.3% in those classified as low acculturation to 30.9% in those with high acculturation ($p = 0.035$), while MASH declined from 18.7% to 8.2% ($p = 0.024$). In other Hispanics, there were no differences in prevalence of MASLD, MASH or fibrosis by acculturation level, but more acculturated individuals had a lower diet quality by HEI-2020 (p = 0.021). **Conclusion:** Among Mexican Americans, a lower prevalence of MASLD and MASH was found in those with increasing acculturation, contrasting with prior literature linking Westernization to increased metabolic risk. In contrast, these patterns were not observed in the non-Mexican Hispanic subgroup, suggesting the link between acculturation and liver health is distinct between these two Hispanic subgroups. Mexican Americans with low acculturation may benefit from additional screening and early counseling, as they appear to be an at-risk group for MASLD.

Table 1 Demographic, Lifestyle Patterns, and Metabolic Liver Disease Among Mexican Americans and other Hispanics Stratified by Level of Acculturation to the United States

	Acculturation level (0–5 score, 5 = most acculturated)							
	Mexican Americans (n=627)				Other Hispanics (n=560)			
	0-1	2-3	4-5	P value	0-1	2-3	4-5	P value
Survey weights-adjusted	8.6%	42.5%	49.0%		14.5%	46.6%	38.9%	
Demographic factors								
Age (years), mean±se	34.2±0.2	43.5±1.4	37.3±1.1	**0.013**	41.4±1.3	48.5±0.7	39.0±1.8	0.216
Sex				0.501				0.589
male	56.2%	42.1%	44.5%		48.8%	45.4%	48.5%	
female	43.8%	57.9%	55.5%		51.2%	54.6%	51.5%	
Poverty income ratio				0.106				**0.034**
below poverty	32.6%	27.4%	8.4%		46.9%	30.4%	18.3%	
1-2.99	49.5%	51.9%	36.6%		47.2%	41.0%	27.8%	
≥3	17.9%	20.8%	54.9%		5.9%	28.6%	54.0%	
Status of alcohol use				0.139				**0.019**
none	27.3%	23.3%	14.6%		33.2%	30.9%	11.1%	
light	72.7%	76.7%	85.4%		66.8%	69.1%	88.9%	
Low physical activity	67.0%	61.5%	47.5%	0.253	62.2%	64.8%	57.9%	0.569
Medical conditions (yes)	22.7%	43.8%	39.0%	0.452	52.4%	58.0%	45.5%	0.323
Daily dietary intake, mean±se								
Total energy, kcal	2354±249	2098±79	2074±140	**0.037**	1815±82	1833±62	2100±97	0.642
Total protein, g	100.4±4.1	85.7±4.1	87.6±4.0	**0.011**	82.5±1.5	75.3±1.0	80.6±1.3	0.397
Total sugar, g	115.0±19.1	99.4±1.4	83.7±6.6	**0.004**	91.0±6.0	95.7±1.8	100.1±9.1	0.639
Total fat, g	87.3±11.6	83.5±3.3	89.3±7.6	**0.046**	65.3±5.9	66.4±2.3	86.2±4.2	0.249
Total saturated fatty acids, g	29.8±5.1	25.6±0.5	28.9±2.0	0.068	21.3±2.3	21.4±0.7	27.8±1.0	0.107
Total caffeine, mg	82.7±8.5	89.8±10.1	104.7±7.1	0.081	91.7±8.1	119.6±6.0	140.4±23.7	**0.003**
Total alcohol g	5.2±0.6	4.2±1.3	8.2±0.1	0.091	3.6±0.9	5.0±1.7	6.2±1.0	0.065
Total HEI-2020 score (0-100)	47.1±0.6	51.8±0.5	48.2±0.6	**0.039**	53.2±1.0	54.8±0.8	47.7±0.1	**0.021**
Metabolic syndrome components								
Large waist circumference	45.7%	59.0%	63.1%	0.346	45.8%	56.7%	52.2%	0.315
Elevated blood pressure	11.4%	30.4%	32.4%	0.174	44.2%	40.1%	34.8%	0.493
Elevated triglycerides	61.0%	44.3%	28.2%	**0.012**	38.5%	37.8%	26.6%	0.230
Low HDL-C	46.3%	43.1%	28.3%	0.145	40.3%	35.4%	31.0%	0.444
Elevated glucose	4.4%	14.3%	6.1%	0.266	3.3%	11.8%	5.2%	0.051
Body mass index				0.558				0.235
normal weight	15.2%	18.0%	15.4%		25.5%	17.1%	22.9%	
overweight	38.3%	36.8%	32.4%		48.7%	45.4%	31.7%	
obese	46.5%	45.2%	52.1%		25.8%	39.6%	45.4%	
Liver outcomes								
MASLD (yes)	53.3%	48.1%	30.9%	**0.035**	22.7%	36.2%	35.9%	0.172
MASH (yes)	18.7%	22.0%	8.2%	**0.024**	1.8%	13.3%	11.7%	0.175
Fibrosis MASLD (yes)	4.7%	5.4%	4.7%	0.883	3.8%	4.0%	7.0%	0.490
LSM (kPa)	5.5±0.2	5.6±0.4	5.2±0.2	0.131	5.0±0.2	5.2±0.1	5.6±0.1	0.150

Acculturation scoring: foreign born and lived in the U.S. < 5 years (0), foreign born and lived in the U.S. 5- 15 years (1), foreign born and lived in the U.S. ≥ 15 years (2), U.S. born (3); only non-English spoken at home (0), more non-English than English spoken at home or both another language and English equally or more English than non-English (1), only English spoken at home (2)

Disclosures: Sharan Poonja: Nothing to Disclose, Rithvik Vutukuri: Nothing to Disclose, Molly Delk: Nothing to Disclose, Wei-Ting Lin: Nothing to Disclose, Hui-Yi Lin: Nothing to Disclose, Tung-Sung Tseng: Nothing to Disclose, Po-Hung (Victor) Chen: Gilead Sciences Research Scholars Program: Grant/Research Support, Peng-Sheng Ting: Nothing to Disclose

2587 | DISTINCT PHENOTYPIC AND COMORBIDITY PROFILES OF LEAN VERSUS NON-LEAN YOUNG ADULTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): A STUDY FROM "ALL OF US" RESEARCH PROGRAM

Thanathip Suenghataiphorn[1] Vitchapong Prasitsumrit[2] Pojsakorn Danpanichkul[3] Narathorn Kulthamrongsri[4], [1]Yale/Griffin Hospital, [2]Texas Tech Lubbock Health Science Center, [3]Texas Tech University Health Sciences Center, [4]Univesity of Hawaii

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly prevalent in adolescents and young adults (AYAs), but the

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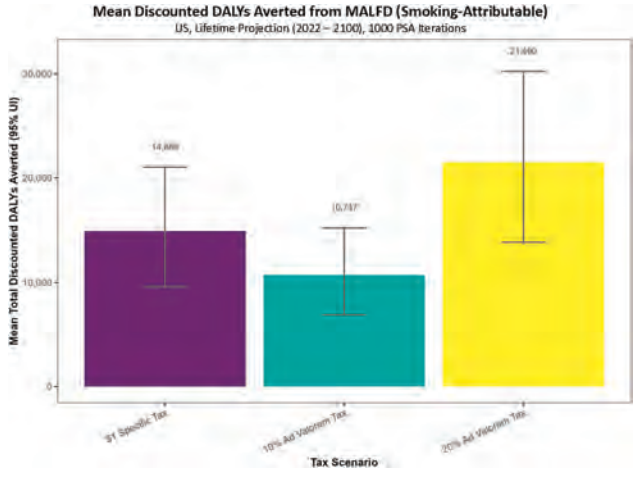
characteristics of MASLD in lean AYAs (BMI <25 kg/m ^{2}) remain poorly understood. We aimed to compare the demographic, metabolic, and comorbidity profiles of lean versus non-lean AYAs with MASLD in a large, diverse national cohort. **Methods:** We identified AYA (18-39 years) participants with MASLD (from the "All of Us" Research Program. AYAs were stratified into lean (BMI <25 kg/m ^{2}) and non-lean (BMI ≥ 25 kg/m ^{2}) groups. Demographics, prevalence of MASLD-defining, and 19 predefined comorbidity groups were compared. **Results:** Of 2,097 AYAs with MASLD (mean age 31.7 yrs), 85 (4.1%) were lean. Lean AYA MASLD patients were more likely to be male (41.2% vs. 26.5%, $p=0.009$) and of Black or African American (22.4% vs. 8.6%) or Asian (8.2% vs. 3.4%) race ($p<0.001$ vs. non-lean). Lean AYAs more frequently met blood pressure criteria (62.4% vs. 34.8%, $p<0.001$) and glucose dysregulation criteria (12.9% vs. 6.0%, $p=0.018$) for their MASLD diagnosis. Compared to non-lean AYAs, lean AYAs had a significantly higher prevalence of chronic kidney disease (7.1% vs. 2.3%, $p=0.016$), thyroid disorders (8.2% vs. 2.2%, $p=0.002$), and heart failure (5.9% vs. 1.6%, $p=0.014$), despite a lower overall comorbidity count (mean 1.1 vs. 1.6, $p=0.003$). Conversely, obesity-related comorbidities like obstructive sleep apnea and polycystic ovary syndrome were less common in lean AYAs. **Conclusion:** Lean AYA MASLD represents a distinct phenotype characterized by specific demographic features, a greater reliance on non-obesity metabolic drivers like hypertension and glucose dysregulation, and a unique, concerning pattern of non-obesity-related comorbidities including heart failure. These findings underscore the need for heightened awareness and tailored management strategies for this underrecognized MASLD subgroup.

Disclosures: Thanathip Suenghataiphorn: Nothing to Disclose, Vitchapong Prasitsumrit: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Narathorn Kulthamrongsri: Nothing to Disclose

2588 | LONG-TERM HEALTH AND ECONOMIC IMPACT OF CIGARETTE TAXATION ON SMOKING-ATTRIBUTABLE BURDEN OF METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE (MAFLD) IN THE UNITED STATES: A GBD LIFETIME SIMULATION STUDY

Thanathip Suenghataiphorn[1] Kanachai Boonpiraks[2] Vitchapong Prasitsumrit[3] Pojsakorn Danpanichkul[4] Narathorn Kulthamrongsri[5], [1]Yale/Griffin Hospital, [2]University of Kansas Medical Center · Kansas City, USA, [3]Texas Tech Lubbock Health Science Center, [4]Texas Tech University Health Sciences Center, [5]University of Hawaii

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a growing public health concern in the U.S. While metabolic factors are primary drivers, smoking is a modifiable co-factor. We projected the long-term impact of cigarette taxation on DALYs and healthcare costs associated with the smoking-attributable component of MAFLD. **Methods:** An age-sex stratified dynamic population cohort model simulated the U.S. population from 2022-2100. Baseline smoking prevalence (SEV) and smoking-attributable MAFLD DALY rates were from GBD 2021, with future trends projected via ARIMA. Three tax scenarios ($1 specific, 10% & 20% ad valorem) reduced smoking prevalence based on U.S. price elasticity. Health benefits accrued over a 10-year distributed lag. Discounted (3%) DALYs averted and healthcare cost savings (2021 USD) were estimated from a healthcare perspective. Probabilistic sensitivity analysis (PSA, 1000 iterations) assessed uncertainty. **Results:** Over a lifetime (2022-2100), a $1 specific cigarette tax was projected to avert a mean of 14,889 (95% UI: 9,552–21,031) discounted DALYs from smoking-attributable NAFLD burden and save $6.18 billion (95% UI: 3.06B–10.32B) in healthcare costs. A 20% ad valorem tax averted ~21,490 DALYs and saved ~$8.93 billion. All tax scenarios were consistently cost-saving (probability $>99\%$). **Conclusion:** Implementing or increasing cigarette taxes is a robustly cost-saving strategy projected to yield substantial long-term reductions in DALYs and healthcare expenditures related to the smoking-attributable burden of MAFLD in the U.S., supporting tobacco control as a component of liver health promotion.



Disclosures: Thanathip Suenghataiphorn: Nothing to Disclose, Kanachai Boonpiraks: Nothing to Disclose, Vitchapong Prasitsumrit: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Narathorn Kulthamrongsri: Nothing to Disclose

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2589 | STEATOTIC LIVER DISEASE SUBTYPES AND COLORECTAL CANCER: A LARGE-SCALE RISK ANALYSIS INCLUDING FIBROSIS

takefumi kimura[1] Shun-Ichi Wakabayashi[1] Nobuharu Tamaki[2], [1]Shinshu University School of Medicine, [2]musashino red cross

Background: The recently proposed subtypes of steatotic liver disease (SLD), MASLD, MetALD, and ALD, may differ in their risk for extrahepatic cancers. However, colorectal cancer (CRC) risk stratification in these subgroups remains unclear. This study aimed to evaluate CRC incidence across SLD subtypes and assess the impact of advanced fibrosis. **Methods:** We analyzed data from 6.3 million individuals in a nationwide Japanese claims and health check-up database. Among these, 1,497,813 patients had MASLD, MetALD, or ALD; 4,885,536 served as controls without liver disease. CRC was defined using ICD-10 and treatment codes. Multivariable Cox regression adjusted for age, sex, smoking, diabetes, dyslipidemia, hypertension, colonoscopy frequency, aspirin/metformin use, and advanced fibrosis. Advanced fibrosis ($\geq$F3) was included as an independent covariate and defined using a validated algorithm (PMID: 40191781). **Results:** During a median follow-up of 4.5 years, 12,065 individuals developed CRC. The 10-year cumulative incidence was highest in ALD (0.97%), followed by MetALD (0.73%), MASLD (0.48%), and controls (0.32%) (all $p < 0.001$). Adjusted hazard ratios (95% CI) for CRC were 1.28 (1.20–1.33) for MASLD, 1.35 (1.26–1.44) for MetALD, and 1.70 (1.57–1.84) for ALD. Advanced fibrosis was independently associated with CRC risk (HR 1.08, 95% CI 1.03–1.15, $p = 0.003$). **Conclusion:** SLD is associated with an increased risk of CRC, with the highest risk observed in ALD, followed by MetALD and MASLD. The presence of advanced fibrosis further elevates CRC risk, highlighting the need for tailored surveillance strategies based on liver disease subtype and fibrosis severity.

Disclosures: takefumi kimura: Nothing to Disclose, Shun-Ichi Wakabayashi: Nothing to Disclose, Nobuharu Tamaki: Nothing to Disclose

2590 | MILD ALKALINE PHOSPHATASE ELEVATION ASSOCIATES WITH INCREASED MORTALITY AND MAJOR ADVERSE LIVER OUTCOMES IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Jingyi Hu[1] Blake Czapla[1] Kira Zhao[1] Christopher Okarski[1] Karn Wijarnpreecha[2] Vincent Chen[3], [1]University of Michigan, [2]University of Arizona College of Medicine-Phoenix, [3]University of Michigan Medical Center

Background: Alkaline phosphatase (ALP) elevation is commonly observed in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), but its clinical implications in this context remain unclear. We aimed to evaluate the impact of mild ALP elevation (1-1.5x upper limit normal [ULN]) on clinical outcomes in MASLD. **Methods:** We conducted a retrospective cohort study of patients at Michigan Medicine. We included patients with MASLD defined as hepatic steatosis on imaging and at least one cardiometabolic comorbidity, with at least 1 ALP measurement within 1 year of the index date (date of imaging). Patients were excluded if they had excessive alcohol use, other chronic liver diseases, or chronic bone disease at any time, or malignancy, fracture, or pregnancy within 1 year of the index date. Elevated ALP was defined as >1-≤ 1.5x ULN (115 IU/L at our center). Outcomes were overall mortality, major adverse liver outcomes (MALO), and major adverse cardiovascular events (MACE). Mortality was modeled as a Cox proportional hazards model and non-mortality outcomes as Fine-Gray competing risk models. **Results:** We included 13,046 MASLD patients. 11,085 (85.0%) had persistently normal ALP, 615 (4.7%) had transiently elevated ALP, and 1,346 (10.3%) had persistently elevated ALP. In total, 779 deaths, 129 MALO, and 3,110 MACE occurred. We manually reviewed the medical records of all patients with MALO and found no patient with other chronic liver diseases. Persistently elevated ALP was associated with higher risks of mortality (adjusted hazard ratio [aHR], 1.48; 95% CI, 1.19–1.86; $p < 0.001$) and MALO (aHR, 2.40; 95% CI, 1.54–3.74; $p < 0.001$) compared to persistently normal ALP. These associations remained significant in sensitivity analyses excluding patients with baseline cirrhosis: mortality (aHR, 1.53; 95% CI, 1.21–1.95; $p < 0.001$) and MALO (aHR, 2.10; 95% CI, 1.01–4.35; $p = 0.046$). Stratification by FIB-4 scores showed elevated ALP was significantly associated with mortality among patients with FIB-4 <1.3 and FIB-4 1.3–2.67. The risk of MALO associated with elevated ALP was significant in patients with FIB-4 1.3–2.67. In contrast, no significant associations were observed with FIB-4 >2.67, nor for the risk of MALO with FIB-4 <1.3. ALP elevations were not significantly associated with MACE. **Conclusion:** Even mild (1-1.5x ULN) ALP elevations were associated with increased risk of mortality and MALO in MASLD, particularly among patients with low-intermediate FIB-4 scores. These findings suggest that ALP may serve as a clinically meaningful biomarker for risk stratification in early MASLD and warrants further prospective validation.

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Outcome		Unadjusted		Adjusted	
		Hazard/Subhazard Ratio (95% CI)	P value	Hazard/Subhazard Ratio (95% CI)	P value
Primary analysis					
Mortality		1.61 (1.33-1.96)	<0.0001	1.48 (1.19-1.86)	0.00055
MALO		2.87 (1.82-4.51)	<0.0001	2.40 (1.54-3.74)	0.00012
Excluding cirrhosis					
Mortality		1.64 (1.33-2.02)	<0.0001	1.53 (1.21-1.95)	0.000416
MALO		2.19 (1.06-4.54)	0.035	2.10 (1.01-4.35)	0.046
FIB-4 stratification					
Mortality	<1.3	1.64 (1.19-2.28)	0.00291	1.53 (1.05-2.23)	0.0258
	1.3-2.67	1.62 (1.18-2.23)	0.0031	1.64 (1.15-2.35)	0.00674
	>2.67	1.34 (0.71-2.53)	0.367	1.66 (0.74-3.75)	0.221
MALO	<1.3	2.43 (1.06-5.58)	0.036	2.24 (0.97-5.15)	0.059
	1.3-2.67	4.03 (1.93-8.43)	0.00021	3.26 (1.62-6.54)	0.00089
	>2.67	2.32 (0.94-5.68)	0.066	1.56 (0.58-4.18)	0.38

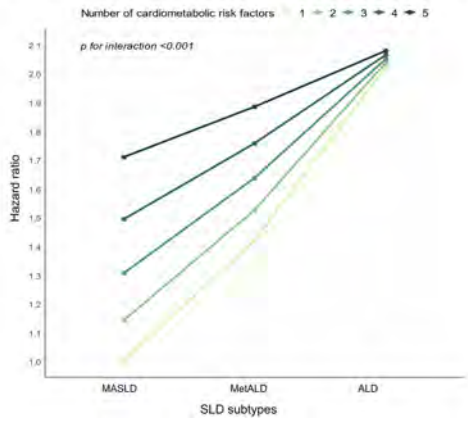
Disclosures: Jingyi Hu: Nothing to Disclose, Blake Czapla: Nothing to Disclose, Kira Zhao: Nothing to Disclose, Christopher Okarski: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose, Vincent Chen: AstraZeneca: site PI on industry-sponsored trial, Ipsen: site co-I on industry-sponsored trial, Kowa: site co-I on industry-sponsored trial

2591 | MORTALITY BY CARDIOMETABOLIC RISK FACTOR AND ALCOHOL CONSUMPTION IN STEATOTIC LIVER DISEASE: A NATIONWIDE COHORT STUDY

Yewan Park[1] Gi-Ae Kim[1], [1]Kyung Hee University Hospital

Background: Steatotic liver disease (SLD) emerged as a nomenclature encompassing metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver diseases (ALD). We aimed to investigate the all-cause and cause-specific mortality risk across SLD subtypes by cardiometabolic risk factors (CMRFs) and alcohol consumption. **Methods:** Health checkup results of 2,049,641 Korean individuals were analyzed. SLD was defined as a fatty liver index $\geq$30. Multivariable Cox proportional hazard models were used to calculate the adjusted hazard ratios (HR) for mortality in MASLD, metabolic dysfunction and alcohol-related liver disease (MetALD), and ALD. **Results:** Compared to no SLD, MASLD (HR, 1.27; 95% confidence interval [CI], 1.24−1.30), MetALD (HR, 1.40; 95% CI, 1.36−1.44), and ALD (HR, 1.71; 95% CI, 1.66−1.77) showed higher risks of all-cause mortality. All SLD subtypes had an increased cause-specific mortality risk from liver-related disease, extrahepatic cancer, and cardiovascular disease with liver-related mortality being the most prominent (HR, 2.57 for MALSD; HR, 4.35; 95% CI, 3.94−4.80 for MetALD; HR, 6.32; 95% CI, 5.72−7.00 for ALD). The cumulative incidence of all-cause mortality increased as the number of CMRF increased in all SLD subtypes. The impact of CMRF numbers on the mortality risk was the most pronounced in MASLD but the least pronounced in ALD. **Conclusion:** This study demonstrated that MASLD, MetALD, and ALD had an increased risk of all-cause and cause-specific mortality and the impact of CMRF numbers on the mortality risk was the most pronounced in MASLD. A profound insight into the mortality risk by CMRF and alcohol consumption was provided, ushering in more customized management strategies.

Risk of all-cause mortality by the number of cardiometabolic risk factors and SLD subtypes



Disclosures: Yewan Park: Nothing to Disclose, Gi-Ae Kim: Nothing to Disclose

2592 | SHIFTING TRENDS IN U.S. STEATOTIC LIVER DISEASE CARE: PATIENT-REPORTED INSIGHTS FROM THE 2022-2025 SLD CARE SURVEY

Neeraj Mistry[1] Tiffany Mensah[1] Jennifer Jones[2] Henry Chang[1] Wayne Eskridge[1], [1]Fatty Liver Foundation, [2]Sober Livers

Background: The State of Steatotic (Fatty) Liver Care in America (SLD Care) survey is an annual, patient-facing survey tracking the social and medical experiences of people living with steatotic liver disease (SLD) in the United States. This analysis includes data from 2022 to 2025. Capturing patient-reported experiences is essential to identifying care gaps and informing targeted interventions and policies. **Methods:** Data from survey years 2022 to 2025 were analyzed and compared to identify trends. The survey included U.S. adults diagnosed with SLD and consisted of 49 items across four domains: diagnosis and staging, medical management and physical impact, psycho-social and

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environmental impact, and current health. Items were developed in collaboration with the patient community, Fatty Liver Foundation Medical Advisory Group, and the SLD Care Survey Analysis Group. **Results:** Respondents across all years were mostly white women with undergraduate degrees. Among those living with metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic dysfunction-associated steatohepatitis (MASH), the majority reported a diagnosis staging of MASLD or Stage 4 MASH. A sizable portion reported they were unaware of their disease stage at diagnosis. Starting in 2023, referrals to hepatologists and gastroenterologists after diagnosis have increased. An emerging downward trend was observed in the proportion of respondents who reported being told there was "nothing to worry about" after diagnosis. Respondents continue to report that dietitians and fitness professionals are not integrated into their care teams. Preliminary 2025 data reveal increased use of medications including resmetirom and GLP-1 receptor agonists such as semaglutide and tirzepatide compared to previous years. **Conclusion:** Analysis of shifting trends revealed two primary patterns. On the patient side, while general awareness of MASLD has increased, understanding of disease staging and nuanced diagnosis remains limited. Involving patients more actively in their care may help close persistent gaps in education and engagement. On the provider side, a shift towards more proactive disease management is reflected in rising specialist referrals and a decline in the persistent "nothing to worry about" reassurance. However, gaps remain in multidisciplinary care, particularly in integrating dieticians and fitness professionals. Additionally, increased off-label use of medications suggests a growing interest in pharmacologic approaches to disease management.

Disclosures: Neeraj Mistry: Nothing to Disclose, Tiffany Mensah: Madrigal Pharmaceuticals: Consultant, Jennifer Jones: Boehringer Ingelheim: Independent Contractor, GlaxoSmithKline: Patient Council, Boehringer Ingelheim: Advisor, GSK: Advisor, Henry Chang: Nothing to Disclose, Wayne Eskridge: Madrigal Pharmaceuticals: Consultant, Regeneron: Consultant, PathAI: Consultant, Novo Nordisk: Consultant

2593 | SIGNIFICANT DIFFERENCES IN DIETARY PATTERNS BETWEEN RURAL VERSUS URBAN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A PROSPECTIVE STUDY

Swetha Tummala[1] *Trevor Dean*[1] *Renwei Wang*[1] *Jessica Izenas*[1] *Olivia Popovich*[1] *Oscar Shaver*[1] *Olivia Hansol Lee*[1] *Jian-Min Yuan*[1] *Jaideep Behari*[1], [1]*University of Pittsburgh*

Background: Unhealthy dietary patterns are associated with metabolic dysfunction-associated steatotic liver disease (MASLD). Rural communities in the U.S. have a higher burden of MASLD-associated chronic conditions, such as obesity, compared to urban populations. We aimed to study the differences in dietary patterns associated with MASLD across urban-rural populations in a mid-Atlantic region-based healthcare system. **Methods:** We prospectively enrolled adult patients with MASLD referred to a subspecialty clinic between 2021 and 2025. Demographic and clinical characteristics were recorded at enrollment. Dietary patterns were assessed at the baseline visit using two validated dietary questionnaires, the Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24), for 24-hour dietary recall, and Diet History Questionnaire III (DHQ III) for dietary intake over the past year. The Healthy Eating Index (HEI-2015) was calculated to determine the adherence to the Dietary Guidelines for Americans. Rural versus urban status was determined using Rural-Urban Commuting Area (RUCA) codes matched to ZIP code of primary residence. **Results:** Among the 729 subjects, 81 were from rural and 648 from urban areas. Age, sex, ethnicity, smoking status, and Type 2 diabetes prevalence were similar between the two groups, with a higher proportion of Whites in the rural group (98.8% vs 88.7%, $p = .02$). There was a trend towards higher body mass index in the rural group (36.4 vs 34.8 kg/m^2, $p = .06$) but no difference in physical activity level. There was no difference among the groups in Transient Elastography-determined CAP score (302 vs 292 dB/m, $p = .14$), a measure of steatosis, and liver stiffness score (9.1 vs 9.2 kPa, $p = .78$), a measure of liver fibrosis, or in Fibrosis-4 index (1.4 vs 1.3, $p = .85$). No differences were found between the two groups in dietary patterns on the ASA24 survey and in the HEI-2015 scores. When evaluating the past year's nutrient intake via DHQ III, the rural cohort had similar total energy intake but significantly higher carbohydrate (230 vs 196 g/day, $p = .03$), total sugar (122 vs 96 g/day, $p < .01$), and added sugar (84 vs 62 g/day, $p = .05$). Both groups had low, but similar, intake of fiber (17.4 vs 16.2 g/day, $p = .28$). **Conclusion:** Rural and urban patients with MASLD have significant dietary differences. Nutritional interventions targeting MASLD at the health system-wide level may require distinct strategies for rural vs urban communities.

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	MASLD		
	Rural (N=81)	Urban (N=648)	P-value
Age (years)			0.1071[1]
Mean (SD)	51.6 (14.49)	54.4 (13.81)	
Sex, n (%)			0.8767[2]
Female	50 (61.7%)	413 (63.7%)	
Race, n (%)			0.0174[2]
White	80 (98.8%)	575 (88.7%)	
Ethnicity, n (%)			0.7881[2]
Hispanic/latino	2 (2.5%)	13 (2.0%)	
T2DM, n (%)			0.6649[2]
Mean (SD)	32 (39.5%)	240 (37.0%)	
BMI (kg/m2)			0.0562[1]
Mean (SD)	36.4 (7.86)	34.8 (8.21)	
Physical activity (minutes/week)			0.3578[1]
Mean (SD)	108.7 (164.53)	124.3 (188.90)	
CAP score (dB/m)			0.1380[1]
Mean (SD)	301.9 (47.11)	292.1 (49.21)	
Liver stiffness measurement (kPa)			0.7762[1]
Mean (SD)	9.1 (7.05)	9.2 (8.22)	
Fibrosis-4 index			0.8530[1]
N (Missing)	68 (13)	556 (92)	
Mean (SD)	1.4 (1.27)	1.3 (1.12)	
Energy intake (kcal/day)			0.2847[1]
Mean (SD)	1774.5 (1022.89)	1607.4 (904.12)	
Carbohydrate intake (grams/day)			0.0316[1]
Mean (SD)	229.6 (135.65)	196.2 (122.21)	
Total sugar intake (grams/day)			0.0063[1]
Mean (SD)	121.8 (88.87)	96.3 (78.15)	
Added sugar intake (grams/day)			0.0504[1]
Mean (SD)	84.1 (69.49)	62.2 (71.51)	
Fiber intake (grams/day)			0.2776[1]
Mean (SD)	17.4 (9.98)	16.2 (10.02)	

[1]Kruskal-Wallis p-value; [2]Chi-Square p-value;

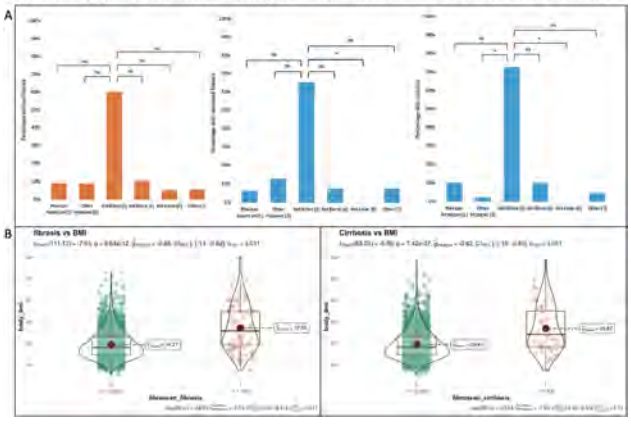
Disclosures: Swetha Tummala: Nothing to Disclose, Trevor Dean: Nothing to Disclose, Renwei Wang: Nothing to Disclose, Jessica Izenas: Nothing to Disclose, Olivia Popovich: Nothing to Disclose, Oscar Shaver: Nothing to Disclose, Olivia Hansol Lee: Nothing to Disclose, Jian-Min Yuan: Nothing to Disclose, Jaideep Behari: Pfizer: Grant/Research Support, Endra Life Sciences: Grant/Research Support, AstraZeneca: Grant/Research Support, Gilead: Grant/Research Support, Pfizer: Institutional research contract, Intercept: Institutional research contract, Madrigal: Institutional research contract, Inventiva: Institutional research contract, Rhythm: Institutional research contract, Galectin: Institutional research contract, Akero: Institutional research contract

2594 | DEMOGRAPHIC AND METABOLIC DISPARITIES IN STEATOTIC LIVER DISEASE PROGRESSION DURING COVID USING THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) 2021–2023

Kimberly Ho[1] Samiran Mukherjee[2] Paige McLean Diaz[3], [1]Brown University, [2]University of Pennsylvania, [3]Brown Medicine/Brown University Health

Background: Before COVID, metabolic-dysfunction associated steatotic liver disease (MASLD) affected 25-30%, and recent estimates show an increase to 38%. MASLD's burden may have worsened in the pandemic, intensifying barriers to care and widened existing healthcare disparities. In this study, we aimed to characterize demographic and clinical patterns associated with MASLD and progression to fibrosis and cirrhosis, using the 2021–2023 NHANES database. **Methods:** We analyzed 6,337 adults from NHANES 2021–2023 in a cross-sectional study. MASLD severity was defined using FibroScan thresholds: steatosis (CAP >288), advanced fibrosis (LSM >13.5 kPa), and cirrhosis (LSM >20 kPa). Multivariate logistic regression identified factors associated with each phenotype. We compared MASLD without fibrosis, with fibrosis, and with cirrhosis using race/ethnicity, BMI, alcohol use, diabetes, age, and sex. **Results:** 26% of participants had MASLD in NHANES 2021-2023. Among Non-Hispanic (NH) Whites, 73% had cirrhosis and 65% had advanced fibrosis. MASLD with advanced stages of fibrosis showed disproportionately higher representation among NH White individuals compared to Asian ($p = 0.01$ for cirrhosis; $p = 0.04$ for advanced fibrosis) and non-Mexican Hispanic individuals ($p = 0.01$ for cirrhosis). No significant differences were observed between NH White and other groups including Mexican American, NH Black, or other racial/ethnic groups. (Figure 1A). Results from multivariate regression reveal BMI to be strongly associated with both steatosis and cirrhosis ($p<0.001$). It was also associated with disease progression, with differences noted in the overweight and obese categories in fibrosis, and across all BMI classes in cirrhosis particularly obesity classes I, II, and III ($\chi^2 = 13.2$, $p < 0.001$; $\chi^2 = 4.74$, $p = 0.03$; $\chi^2 = 69.7$, $p < 0.001$, respectively) (Figure 1B). Alcohol use also differed among the various groups. Patients with fibrosis or cirrhosis had significantly higher rates of frequent alcohol consumption in a dose dependent manner ($p < 0001$). Comorbid diabetes was associated with disease severity compared to those with prediabetes ($\chi^2 = 3.71$ for fibrosis; $\chi^2 = 10.0$ for cirrhosis; all $p < 0.001$). **Conclusion:** NH White individuals were overrepresented in MASLD with fibrosis and cirrhosis, potentially reflecting disparities in access to care and retention in follow-up among minority populations post-COVID. Obesity, diabetes, and alcohol use emerged as key modifiable factors associated with disease severity.

Figure 1. **Widening Demographic and Metabolic Disparities with Increasing MASLD Severity Among US Adults.** (A) Bar plots of demographic trends specifically in race/ethnicity. *Non-Hispanic Whites were overrepresented in steatotic liver disease, advanced fibrosis, and cirrhosis compared to other racial/ethnic groups, indicating potential disparities in MASLD screening and outcomes captured in NHANES 2021-2023.* (B) Violin plots of advance fibrosis and cirrhosis vs BMI. *Participants with cirrhosis and advanced fibrosis had significantly higher BMI compared to subjects without MASLD complications (mean 36.87 and 37.06, respectively).*



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Disclosures: Kimberly Ho: Nothing to Disclose, Samiran Mukherjee: Nothing to Disclose, Paige McLean Diaz: Nothing to Disclose

2595 | HIGH BURDEN OF MASLD AND RISK OF FIBROSIS IN TYPE 1 DIABETES: PRELIMINARY RESULTS: FROM FIBROSCAN-BASED SCREENING

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Background: The burden and and clinical significance of metabolic dysfunction–associated steatotic liver disease (MASLD) is well-established in type 2 diabetes, yet remains remain poorly characterized in type 1 diabetes mellitus (T1DM). Emerging data suggest that individuals with T1DM may also be at considerable risk, independent of traditional metabolic risk factors.Aims:To evaluate the prevalence of MASLD and its clinical and metabolic predictors, as well as disease severity, in individuals with type 1 diabetes mellitus (T1DM) using FibroScan. **Methods:** This ongoing cross-sectional study includes individuals aged ≥14 years with ≥1-year T1DM. Data collected include demographics, BMI, comorbidities, insulin regimen, HbA1c, CGM-derived time-in-range (TIR), and liver biochemistry. Imaging involves ultrasound and FibroScan (CAP for steatosis, LSM for fibrosis). MASLD is defined as CAP ≥248 dB/m with ≥1 metabolic risk factor; advanced fibrosis as LSM ≥8.2 kPa. **Results:** Among the first 92 participants (mean age 27.8 ± 11.4 years), 30.4% met MASLD criteria. The mean CAP was 235 ± 45.3 dB/m and liver stiffness was 4.67 ± 1.1 kPa. MASLD prevalence peaked in the 40–49 age group (50%) and was slightly higher among those using multiple daily injections (36.1%) compared to insulin pump users (33.3%). Notably, 8.7% had LSM ≥8.2 kPa, indicating a meaningful subset at high risk for significant fibrosis despite young age and absence of clinical liver disease. Liver stiffness showed weak correlations with HbA1c ($r = -0.17$), time-in-range ($r = 0.19$), and diabetes duration ($r = 0.11$), suggesting that traditional glycemic markers may not reliably predict liver involvement. FibroScan and ultrasound demonstrated poor agreement ($\kappa = -0.047$), with FibroScan detecting more cases of steatosis, highlighting the potential underdiagnosis associated with ultrasound. **Conclusion:** Preliminary findings reveal a substantial prevalence of MASLD in individuals with T1DM, including a notable proportion at high risk for significant fibrosis despite young age and lack of overt liver disease. FibroScan outperformed ultrasound in detecting steatosis, reinforcing its utility in early liver assessment. These results challenge the assumption that MASLD is exclusive to type 2 diabetes and underscore the need for routine, non-invasive liver screening in the T1DM population.
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2596 | PRIMARY CARE PERSPECTIVES ON DIAGNOSIS AND MANAGEMENT OF MASLD: IDENTIFYING GAPS AND OPPORTUNITIES IN THE DALLAS-FORT WORTH AREA

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing global health concern. As MASLD becomes increasingly endemic, primary care physicians (PCPs) often serve as first-line identifiers and managers. However, many PCPs underestimate its prevalence and report low confidence in managing it. This study aims to evaluate current knowledge gaps, comfort levels, and perceived barriers in MASLD diagnosis and management among PCPs, as well as explore trends across racial and ethnic groups in the Dallas-Fort Worth area. **Methods:** This was a cross-sectional survey study of primary care physicians (PCPs) in North Texas, primarily in the Dallas-Fort Worth area. A link to a survey was distributed via email to PCPs in the Methodist Medical Group (MMG) network. The survey assessed PCPs' confidence in diagnosing MASLD, comfort with management, use of non-invasive tools, and referral criteria to hepatology. Additional questions addressed frequency of Fib-4 score use, management approaches, nutritional counseling, use of GLP-1 agonists and statins, and referrals to weight loss programs. Perceptions of local trends among racial and ethnic groups was also evaluated. **Results:** Among 56 PCPs surveyed, 75% rated their confidence in diagnosing MASLD as "more or less," "not very," or "not at all" confident; 86% selected similar

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categories regarding MASLD management. The most commonly used tools were abnormal LFTs (85.5%), ultrasound findings (83.6%), and history of metabolic syndrome (52.7%). Imaging suggestive of cirrhosis (37.5%), abnormal LFTs (17.9%), and Fib-4 >1.3 (16.1%) were top reasons for hepatology referral. Over half (57.1%) never calculated Fib-4 scores for at-risk patients. PCPs referred 32.3% of MASLD patients to weight management (median 20%, IQR 60%). Most PCPs (57.1%) did not observe racial/ethnic disparities in MASLD prevalence; among those who did, Hispanic/Latino (83%) and South Asian (25%) populations were most cited. Nearly all PCPs (96.4%) reported specialists were "very" or "moderately" accessible. **Conclusion:** This study reveals that the majority of PCPs rely primarily on incidental imaging and abnormal liver function tests to diagnose MASLD, with limited use of non-invasive fibrosis tests such as Fib-4. PCPs also report low confidence in both diagnosis and management, underscoring gaps in education and clinical practice. Given that PCPs are the frontline providers facing the growing MASLD burden, establishing standardized clinical pathways is essential to improve early detection, risk stratification, and appropriate referral. Encouragingly, nearly all PCPs in our network reported moderate to high access to hepatology specialists, providing a strong foundation for multidisciplinary care coordination.

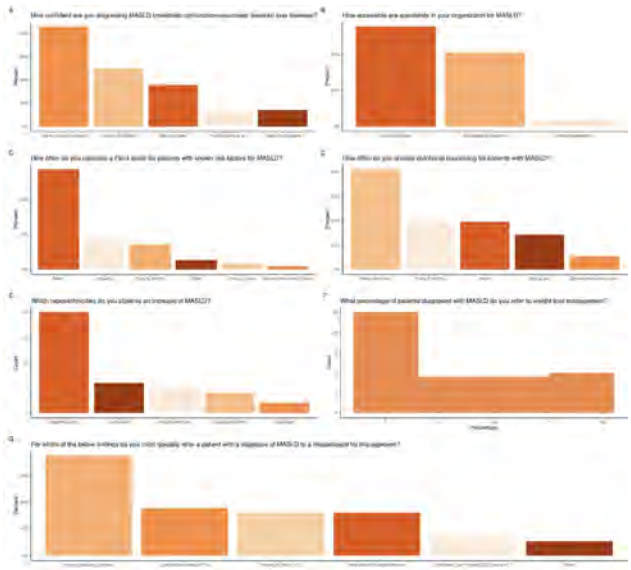

Figure 1: Summary of primary care provider responses on MASLD diagnosis, management practices, and referral patterns within a North Texas health network.

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2597 | HIGH PREVALENCE OF PORTOSINUSOIDAL VASCULAR DISEASE IN EARLY STAGE METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease worldwide. Liver stiffness measurement (LSM) is routinely to assess the stage of fibrosis, but results are often discordant. Another phenomenon of MASLD is the occurrence of portal hypertension-related complications such as ascites or variceal bleeding in the absence of cirrhosis. This might be explained by fibrotic features not assessed in the currently used Brunt staging system or by features of portosinusoidal vascular disease (PSVD). Therefore, we aimed to assess the presence of PSVD in early stage MASLD and its correlation with markers of portal hypertension (PH). **Methods:** We conducted a cohort study in patients with MASLD who underwent liver biopsy between 2015 and 2022. All biopsies with early-stage disease, defined as F0-F2 according to NASH/MASH CRN staging, were revised by two expert liver pathologists in tandem-read for histological features of PSVD. Clinical

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data was collected from the patient medical files. Primary endpoint was the presence of PSVD. Secondary endpoint was the correlation of histology with LSM (Fibroscan®) and other signs of PH. **Results:** We included 136 patients, 60% male, median age 50y, median BMI 30 kg/m^2, 15% F1 and 85% F2. Median LSM was 8.2 kPa [IQR 6.2-11.2]. Clinical signs of PH were present in 11 patients (8%) One patient had esophageal varices, 10 out of 11 patients had splenomegaly, 3 patients had thrombocytopenia, and 2 patients had ascites. In total 74% of patients fulfilled the VALDIG criteria for the diagnosis of PSVD. Portal vein stenosis as a specific histological sign of PH was the most relevant finding in our cohort, occurring in 74% of biopsies. However, portal vein stenosis did not correlate with LSM or platelet count at time of biopsy. Perisinusoidal fibrosis (grade 0-3) was present in 97% of biopsies, with 62% grade 1, and 32% grade 2. We observed a correlation between the LSM value and the grade of perisinusoidal fibrosis ($r = .25$, $p = 0.03$), but not with platelet count. **Conclusion:** PSVD is a frequent finding in early stage MASLD, with portal vein stenosis as the most frequent PSVD-specific histological lesion and perisinusoidal fibrosis as the most frequent PSVD non-specific lesion. PSVD can possibly explaining the presence of portal hypertension in early, non-cirrhotic MASLD and its presence should trigger further investigation for clinical signs of portal hypertension.

Disclosures: Diederick van Doorn: Nothing to Disclose, Lotte Schoenmakers: Nothing to Disclose, Sebastiaan de Jager: Nothing to Disclose, Marten Alexander Lantinga: Nothing to Disclose, Adriaan Holleboom: Nothing to Disclose, Joost Drenth: Nothing to Disclose, Sven Francque: Nothing to Disclose, Bart Takkenberg: Nothing to Disclose, Ann driessen: Nothing to Disclose, Joanne Verheij: Nothing to Disclose

2598 | THE IMPACT OF STATIN THERAPY ON MASLD PREVALENCE AND SEVERITY: ANALYSIS OF A COMMUNITY-BASED, PROSPECTIVE COHORT OF 717 ADULTS WITH OVERWEIGHT AND OBESITY

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[1]University of California, San Diego, [2]UCSD

Background: Given anti-inflammatory and antioxidant properties, it is posited that statins may reduce prevalence and severity of metabolic dysfunction-associated steatotic liver disease (MASLD), though available data is conflicting. The aim of this study was to determine the prevalence and severity of MASLD by statin use using advanced MRI biomarkers in a prospective, well-phenotyped cohort of community-dwelling adults with overweight and obesity. **Methods:** This is a cross-sectional analysis of prospectively enrolled adults with overweight [body mass index (BMI) >25 kg/m^2] and obesity, aged 40-75 from primary care and community-based settings. Participants underwent a standardized clinical research visit with magnetic resonance imaging proton-density-fat-fraction (MRI-PDFF) and MR Elastography (MRE) liver stiffness measurement (LSM). Individuals with other causes of chronic liver disease, secondary causes of hepatic steatosis, and those meeting AASLD definition for alcohol-associated liver disease (ALD) and MetALD were excluded. MASLD was defined as MRI-PDFF of $\geq 5\%$, at-risk metabolic dysfunction-associated steatohepatitis (MASH) by histology, significant and advanced fibrosis by LSM on MRE as ≥ 3.14 and ≥ 3.63 kPa respectively. Linear and logistic regression were used to assess the association of statin use with outcomes of interest. **Results:** The cohort included 717 adults with mean ($\pm$SD) age 51.3 (13.2) years, BMI 32.5 (6) kg/m^2, with 45% male sex, 41% Hispanic ethnicity and 26% with type II diabetes (T2DM). In the overall cohort, 246 (34.3%) participants were on a statin, 19.5% of which were lipophilic. Those on a statin were older (58 vs 47), had lower BMI (31.7 vs 32.9), had higher prevalence of T2DM (48 vs 14.7%), hypertension (54.5 vs 26.5%), incretin therapy (13.8 vs 5.9%) and less physical activity. The only significant difference in disease prevalence and severity was higher prevalence of at-risk MASH among those on statins (Table 1a). On multivariate analysis accounting for differences in baseline characteristics, statin use was not significantly associated with risk of MASLD nor MASLD severity (Table 1b). **Conclusion:** Using advanced MRI methods in a prospective cohort of adults with overweight and obesity, statin use was not associated with statistically significant differences in risk of MASLD nor MASLD severity after adjusting for differences in baseline characteristics. Higher unadjusted prevalence of at-risk MASH among those on statins highlights the importance of screening and liver-directed pharmacotherapy for these individuals.

Table 1a. Prevalence and Severity of MASLD by Statin Use

	N	Statin	No Statin	p-value
Overall Cohort				
	N=717	N=246	N=471	
MASLD	717	168 (68.3%)	341 (72.4%)	0.25
At-risk MASH	83	19 (63.3%)	18 (34.0%)	**0.009**
Significant Fibrosis	717	34 (13.8%)	46 (9.8%)	0.10
Advanced Fibrosis	717	25 (10.2%)	35 (7.4%)	0.20
MASLD Cohort				
	N=509	N=168	N=341	
At-risk MASH	76	18 (69.2%)	18 (36%)	**0.005**
Significant Fibrosis	509	32 (19.1%)	43 (12.6%)	0.05
Advanced Fibrosis	509	25 (14.9%)	35 (10.3%)	0.12
MASLD Cohort- Lipophilic Statin				
	N=389	N=48	N=341	
At-risk MASH	55	4 (80%)	18 (36%)	0.14
Significant Fibrosis	389	7 (14.6%)	43 (12.6%)	0.70
Advanced Fibrosis	389	5 (10.4%)	35 (10.3%)	1.00

Table 1b. Association of Statin Use with Liver Disease Severity among those with MASLD

	Unadjusted OR	Model 1	Model 2	Model 3
MRI PDFF	0.99 (0.97-1.01)	1.00 (0.97-1.02)	1.00 (0.97-1.02)	1.00 (0.98-1.04)
FAST score	1.88 (0.81-4.36)	2.08 (0.79-5.46)	1.12 (0.39-3.18)	1.09 (0.32-3.69)
High FAST	1.25 (0.52-2.50)	1.27 (0.58-2.76)	0.95 (0.41-2.21)	1.03 (0.40-2.65)
High MEFIB	1.95 (0.81-4.69)	0.90 (0.35-2.33)	0.47 (0.17-1.29)	0.51 (0.16-1.56)
MRE kPa	1.04 (1.00-1.08)	1.03 (0.98-1.08)	1.00 (0.95-1.05)	1.01 (0.95-1.07)
Significant Fibrosis	1.63 (0.98-2.69)	1.36 (0.77-2.39)	0.99 (0.54-1.82)	1.20 (0.59-2.42)
Advanced Fibrosis	1.52 (0.88-2.65)	1.38 (0.74-2.57)	0.93 (0.47-1.82)	1.15 (0.52-2.53)

Model 1: age, gender, Hispanic ethnicity, BMI
Model 2: age, gender, Hispanic ethnicity, BMI, DM
Model 3: age, gender, BMI, DM, HTN, GLP-1 use, physical activity, hyperlipidemia, LDL
FAST: fibroscan AST score; MEFIB:MRE FIB-4 score; High FAST: ≥0.67; High MEFIB: MRE ≥3.3 kPa + FIB 4 ≥1.6; significant fibrosis ≥3.14 kPa MRE; advanced fibrosis ≥3.63 kPa MRE

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2599 | TYPE 2 DIABETES MELLITUS IS ASSOCIATED WITH ACCELERATED PROGRESSION TO CIRRHOSIS AND CHRONIC KIDNEY DISEASE IN PATIENTS WITH MASLD: A REAL-WORLD MULTI-CENTER COHORT STUDY

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing public health concern with known hepatic and extrahepatic complications. Type 2 diabetes mellitus (T2DM) is a well-established risk factor, but data on its impact across organ systems in real-world longitudinal cohorts remain limited. We aimed to quantify the association between T2DM and progression to cirrhosis, portal hypertension, and chronic kidney disease (CKD) among MASLD patients using a large multi-institutional electronic health record (EHR) network. **Methods:** We conducted a retrospective cohort study using TriNetX's US Collaborative Network. Adults ($\geq$ 18 years) with MASLD (ICD-10 K76.0 or K75.81) were stratified into two cohorts: MASLD with T2DM (E11.x) and MASLD without diabetes. Patients with baseline cirrhosis, portal hypertension, varices, CKD, ESRD, or other chronic liver diseases were excluded. Propensity score matching (1:1) was performed across 16 covariates, including age, sex, BMI, comorbidities, and medication use. Kaplan-Meier curves and Cox proportional hazards models were used to evaluate time-to-event outcomes. **Results:** After 1:1 propensity score matching, 341,177 patients were included in each cohort. The median follow-up duration was 861 days for the MASLD+T2DM cohort and 770 days for the MASLD-only group. Patients with T2DM exhibited significantly greater risk and faster progression to both hepatic and renal complications. The incidence of cirrhosis was higher among MASLD+T2DM patients (1.0% vs 0.4%), with a hazard ratio (HR) of 2.11 (95% CI: 2.00–2.23; $p < 0.0001$). At five years, cirrhosis-free survival declined from 98.0% in MASLD-only to 94.3% in MASLD+T2DM. Similar trends were observed for portal hypertension (0.3% vs 0.1%; HR: 2.39; 95% CI: 2.16–2.64) and esophageal varices (0.2% vs 0.1%; HR: 2.64; 95% CI: 2.30–3.04), confirming an accelerated hepatic disease course in the diabetic cohort.

Renal outcomes demonstrated even greater disparities. CKD was diagnosed in 44.8% of MASLD+T2DM patients versus 23.2% of MASLD-only, corresponding to an HR of 1.68 (95% CI: 1.64–1.72; $p < 0.0001$). CKD-free survival at five years dropped from 76.8% in non-diabetic patients to 55.2% in those with T2DM. Furthermore, the incidence of ESRD was nearly fivefold higher in the diabetic group (0.2% vs 0.05%; HR: 4.45; 95% CI: 3.86–5.11). The association remained consistent across CKD stages 1 through 5, with stage-specific hazard ratios ranging from 1.67 to 4.87. Kaplan-Meier survival curves demonstrated significantly steeper declines in event-free survival for all outcomes in the T2DM cohort, reinforcing the finding of accelerated progression. **Conclusion:** T2DM is linked to increased risk and faster progression to cirrhosis, portal hypertension, and CKD in MASLD. These findings highlight the need for proactive multi-organ surveillance and metabolic control.

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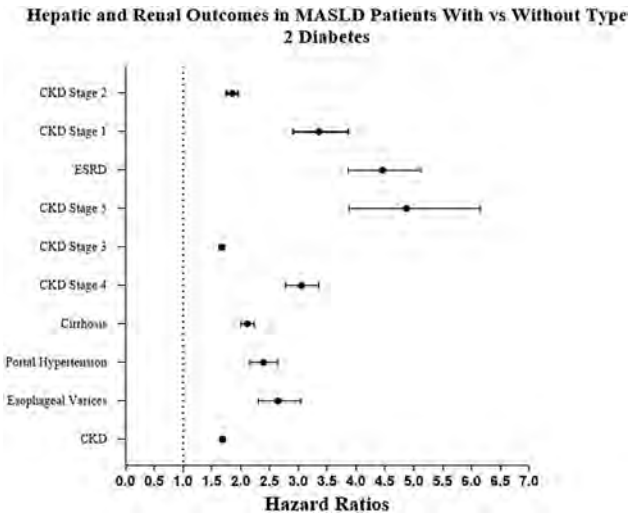

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2600 | CARDIOMETABOLIC BURDEN INCREASES THE RISK OF KIDNEY FAILURE IN A DOSE-DEPENDENT MANNER AMONG PATIENTS WITH STEATOTIC LIVER DISEASE

Han-Tse Cheng[1] Hsin-Yun Wu[2] Tung-Hung Su[3] Kai-Chun Chang[3] Shang-Chin Huang[1] Tai-Shuan Lai[3] Tai-Chung Tseng[3] Chun-Ming Hong[1] Chen-Hua Liu[3] Hung-Chih Yang[3] Chun Jen Liu[3] Jia-Horng Kao[3], [1]National Taiwan University, [2]National Taiwan University Hospital, Jinshan Branch, Taipei, Taiwan, [3]National Taiwan University Hospital

Background: Emerging evidence links metabolic dysfunction–associated steatotic liver disease (MASLD) with renal outcomes. However, few studies have assessed how cumulative cardiometabolic risk factors (CMRFs) influence kidney failure in MASLD patients. We aimed to examine the impact of metabolic burden on the incidence of kidney failure among individuals with steatotic liver disease (SLD). **Methods:** We conducted a retrospective cohort study using the National Taiwan University Hospital Integrated Medical Database from 2006 to 2019. A total of 14,343 patients with persistent steatosis confirmed by abdominal ultrasound were included. MASLD was defined by hepatic steatosis with at least 1 CMRF, based on the 2023 multisociety consensus. Patients were classified as "MASLD" (n = 12,296), "SLD with later MASLD" (n = 1,442), and "SLD without later MASLD" (n = 605) groups. The primary outcome was kidney failure, defined by chronic kidney disease (CKD) stage 5 or receiving renal replacement therapy. The Fine–Gray subdistribution hazard model was used to adjust for competing mortality. **Results:** MASLD patients were older and had more comorbidities than other groups. After adjusting for age, sex, estimated Glomerular filtration rate (eGFR), malignancy, HBV, HCV, cirrhosis, and rheumatologic disease, MASLD was significantly associated with kidney failure (Sub-distribution Hazard Ratio [SHR] 3.415; 95% CI: 1.092–10.678; P = 0.035) compared with the SLD without later MASLD group. There is also a trend of increased kidney failure risks in patients with SLD who later developed MASLD (SHR: 1.270, 95% CI: 0.380–4.244).

When analyzing CMRFs separately, there was a significant dose-dependent association with kidney failure risk. Compared to individuals with no CMRFs, the risk for kidney failure increased with each additional risk factor, with the SHR: 2.01 (95% CI: 1.28–3.15, P = 0.002), 1.85 (95% CI: 1.17–2.91, P = 0.008), 2.93 (95% CI: 1.91–4.50, P < 0.0001), 3.85 (95% CI: 2.50–5.93, P < 0.0001), and 5.84 (95% CI: 3.68–9.26, P < 0.0001) in patients with 1, 2, 3, 4 and 5 CMRFs, respectively. Diabetes mellitus and hypertension were the most significant contributors (SHR 2.17 and 1.76, respectively; both P < 0.0001). In contrast, dyslipidemia and BMI ≥23 kg/m² were not associated with kidney failure development. **Conclusion:** There is a dose-dependent relationship between metabolic burden and kidney failure risks in patients with SLD. The cumulative number of CMRFs—particularly diabetes and hypertension—strongly predicts kidney failure. These findings highlight the need for early identification and management of metabolic risks in MASLD to prevent kidney-related complications.

Table. The univariate and multivariable analyses for the risks of kidney failure in patients with steatotic liver disease

N= 14343	Univariate analysis		Multivariable analysis	
	SHR (95%CI)	P value	SHR (95%CI)	P value
Age	1.048 (1.041 , 1.056)	<.0001	1.006 (0.998 , 1.015)	0.137
Sex	1.778 (1.486 , 2.128)	<.0001	2.065 (1.713 , 2.489)	<.0001
Baseline_eGFR	0.949 (0.944 , 0.953)	<.0001	0.953 (0.947 , 0.959)	0.000
Malignancy	1.086 (0.856 , 1.378)	0.496	1.150 (0.894 , 1.479)	0.276
Rheumatologic disease	1.064 (0.673 , 1.683)	0.79	1.175 (0.708 , 1.950)	0.533
HBV	0.646 (0.515 , 0.811)	<.0001	0.831 (0.655 , 1.054)	0.127
HCV	1.044 (0.730 , 1.492)	0.814	1.021 (0.695 , 1.499)	0.916
Cirrhosis	0.772 (0.319 , 1.868)	0.566	0.610 (0.238 , 1.562)	0.303
CMRF (1 Vs 0)	2.337 (1.488 , 3.671)	<.0001	2.006 (1.279 , 3.147)	0.002
CMRF (2 Vs 0)	2.495 (1.589 , 3.916)	<.0001	1.848 (1.173 , 2.912)	0.008
CMRF (3 Vs 0)	4.413 (2.885 , 6.749)	<.0001	2.930 (1.906 , 4.504)	<.0001
CMRF (4 Vs 0)	6.150 (4.029 , 9.390)	<.0001	3.849 (2.498 , 5.931)	<.0001
CMRF (5 Vs 0)	9.277 (5.915 , 14.549)	<.0001	5.836 (3.677 , 9.264)	<.0001

SHR: Subdistribution Hazard Ratio, eGFR: estimated Glomerular filtration rate.
CMRF: Cardiometabolic risk factor.

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2601 | UNRECOGNIZED FIBROSIS RISK IN MASLD: A REAL-WORLD ANALYSIS AND THE CASE FOR AI-AUGMENTED STRATIFICATION

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease globally, affecting nearly one in four adults. While non-invasive fibrosis risk stratification tools such as the FIB-4 index are guideline-recommended, real-world implementation is inconsistent. We aimed to quantify care gaps in MASLD risk stratification and evaluate the potential role of artificial intelligence (AI) in addressing them. **Methods:** We performed a retrospective analysis of all abdominal ultrasounds conducted from January 1, 2023, to December 31, 2024, across all South Shore campuses of our academic health system. Studies were included if the liver was visualized, regardless of indication (n = 34,926). Using natural language processing (NLP) string-matching, we identified patients with ≥5% hepatic steatosis (n = 5,399; 15.5%). MASLD was defined by ≥1 cardiometabolic risk factor documented in the structured problem list. FIB-4 scores were calculated and stratified by standard age-adjusted thresholds. Referral patterns and primary care continuity were assessed via EMR review. **Results:** Among 5,399 patients with ≥5% hepatic steatosis on imaging, 4,395 (81.4%) met MASLD criteria based on ≥1 cardiometabolic risk factor documented in the EMR. However, FIB-4 stratification was performed on all-comers with steatosis (n = 5,399) to reflect real-world imaging-based identification. Of these, 574 (10.6%) were high-risk and lacked hepatology referral, while only 257 (4.8%) were appropriately referred. Among indeterminate-risk patients, 662 (12.3%) had a primary care provider (PCP) but no referral, compared to 346 (6.4%) who were referred—highlighting missed triage opportunities. At our institution, hepatologists—not PCPs—typically initiate secondary risk assessment (e.g., FibroScan, ELF), underscoring the importance of referral in this group. Additionally, 189 (3.5%) low-risk patients had no documented PCP, suggesting missed opportunities for longitudinal re-evaluation. **Conclusion:** Despite validated tools, MASLD care remains fragmented. Most high-risk patients are not referred to hepatology, and many indeterminate-risk cases lack appropriate follow-up—even when a primary care provider is involved. These gaps highlight systemic shortcomings in risk recognition and adherence to guideline-based care. AI-powered solutions that automate FIB-4 calculation, flag high-risk and indeterminate cases, and trigger referrals or highlight care gaps may represent the only scalable path to closing these implementation failures and improving MASLD outcomes.

Risk Stratification Table

Group	Category	Criteria	Count (%)
A	High Risk, Unmanaged	FIB-4 > 2.67; no hepatology referral	574 (10.6%)
B	High Risk, Managed	FIB-4 > 2.67; hepatology referral present	257 (4.8%)
C	Indeterminate, No PCP	FIB-4 1.3–2.67 (<65) or 2.0–2.67 (≥65); no PCP or referral	15 (0.3%)
D	Indeterminate, Managed	Indeterminate FIB-4; hepatology referral present	346 (6.4%)
E	Indeterminate, Unmanaged	Indeterminate FIB-4; has PCP but no referral	662 (12.3%)
F	Missing FIB-4	No sufficient labs to calculate FIB-4	78 (1.4%)
G	Low Risk, No PCP	FIB-4 below threshold; no documented PCP	189 (3.5%)
H	Low Risk, With PCP	FIB-4 below threshold; PCP documented	3,219 (59.6%)

Legend

FIB-4 thresholds:

- Under 65 years: Low <1.3, Indeterminate 1.3–2.67, High >2.67
- 65 years and older: Low <2.0, Indeterminate 2.0–2.67, High >2.67

Definitions:

- Managed: Documented hepatology referral in EMR.
- Unmanaged: No referral documented.
- PCP: Presence of a named primary care provider in the EMR field.
- Missing FIB-4: Lacking labs (AST, ALT, or platelets) to compute FIB-4.

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2602 | ASSOCIATION OF PULMONARY HYPERTENSION WITH HEPATIC OUTCOMES IN PATIENTS UNDERGOING RIGHT HEART CATHETERIZATION: A PROPENSITY-MATCHED COHORT STUDY

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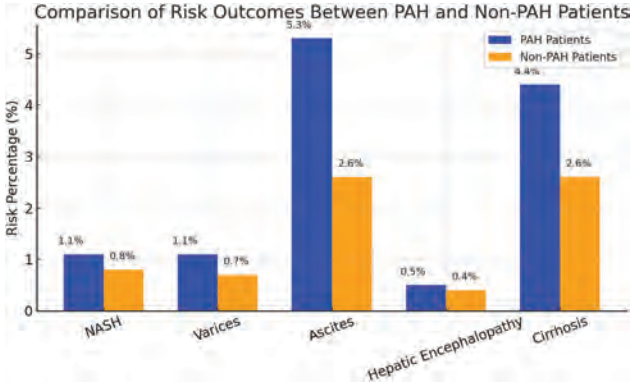
Background: Pulmonary hypertension (PH) is a progressive condition characterized by elevated pulmonary arterial pressure, often diagnosed through right heart catheterization (RHC) or bilateral heart catheterization (BHC). PH affects systemic circulation and may alter liver hemodynamics, increasing the risk of hepatic complications. Despite its known impact on portal pressure and hepatic perfusion, the PH–liver disease link remains underexplored. Patients with PH often exhibit increased systemic inflammation, endothelial dysfunction, and altered blood flow, which are risk factors for developing liver pathologies such as non-alcoholic steatohepatitis (NASH), cirrhosis, and other hepatobiliary conditions. Given the potential for these complications to contribute to adverse clinical outcomes, it is imperative to explore this association further. This study investigates the association between PH and hepatic outcomes—NASH, varices, ascites, hepatic encephalopathy (HE), and cirrhosis—using a propensity-matched cohort design, which may inform early screening strategies and guide preventive interventions in high-risk populations. **Methods:** This retrospective cohort study utilized the TriNetX database. Patients who underwent RHC or BHC were identified and divided into two cohorts: with PH and without PH. Propensity score matching was performed to balance baseline characteristics. Outcomes measured included NASH, varices, ascites, HE, cirrhosis. Risk ratios (RR) with 95% confidence intervals (CI) calculated. **Results:** A total of 158,096 patients were included, with 79,048 in each cohort. The PH group demonstrated significantly higher risks for the following outcomes compared to the non-PH group:

- NASH: PH 1.1% vs. Non-PH 0.8% (RR: 1.316, CI: 1.187- 1.459)
- Varices: PH 1.1% vs. Non-PH 0.7% (RR: 1.528, CI: 1.374- 1.698)
- Ascites: PH 5.3% vs. Non-PH 2.6% (RR: 2, CI: 1.900- 2.107)
- Hepatic Encephalopathy: PH 0.5% vs. Non-PH 0.4% (RR: 1.299, CI: 1.125- 1.501)
- Cirrhosis: PH 4.4% vs. Non-PH 2.6% (RR: 1.697, CI: 1.608- 1.791) **Conclusion:** Patients diagnosed with PH following RHC or BHC had a significantly higher risk of developing hepatic complications, including NASH, varices, ascites, HE, and cirrhosis, compared to matched controls without PH. These findings highlight the need for heightened surveillance and multidisciplinary care in this vulnerable population. Given the substantial burden of hepatic complications observed, routine screening for liver dysfunction may improve early diagnosis and timely interventions in patients with PH. Future research should investigate the underlying mechanisms linking PH and hepatic disease progression, with a focus on potential therapeutic strategies to reduce liver-related morbidity and mortality in this patient population. Expanding the understanding of these interactions may guide clinical decisions and improve outcomes for individuals with PH at risk of liver disease.



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2603 | LOW FAT AND LOW CARBOHYDRATE DIETS ARE ASSOCIATED WITH WORSE SURVIVAL IN SUBJECTS WITH METABOLIC DYSFUNCTION AND ALCOHOL ASSOCIATED STEATOTIC LIVER DISEASES.

Nicholas Dunn[1] Abdelhaleem Sideeg[2] Fatima Elmustafa[3] Sheel Patel[4] Naim Alkhouri[5] Luis Antonio Diaz[6] Robert Wong[7] Juan Pablo Arab[8] Shira Zelber-Sagi[9] Aleksander Krag[10] Zobair Younossi[11] Ashwani Singal[12], [1]Pembroke Hill School, [2]Virginia Mason University, [3]Henry Ford Hospital, [4]University of Louisville School of Medicine, [5]Summit Clinical Research, [6]Pontificia Universidad Católica de Chile, [7]VA Palo Alto Healthcare System, [8]Virginia Commonwealth University, [9]Tel-Aviv Medical Center,

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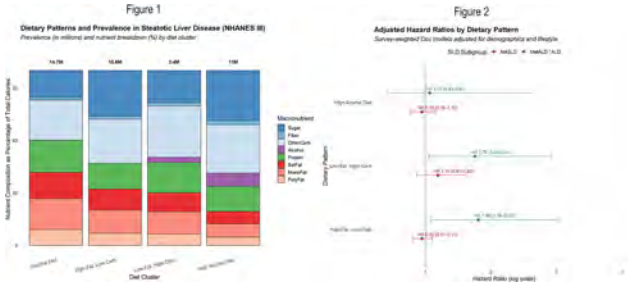
Background: Limited data exist regarding the association of diet and survival in subjects with steatotic liver disease (SLD). In another abstract, we showed the association of dietary patterns with liver fibrosis in SLD. In this analysis, we examined the association of dietary patterns with overall survival in subjects with SLD. **Methods:** We performed an unsupervised clustering analysis using NHANES III (1988-94) adult participants. Dietary patterns were derived using unsupervised clustering of % calories from protein, carbohydrates, sugar, fiber, alcohol, saturated, and polyunsaturated fats. We performed survival analysis on adult participants with ultrasound-defined hepatic steatosis and ≥ 1 cardiometabolic risk factor (CMRF) who were stratified based on self-reported alcohol use to metabolic dysfunction-associated SLD (MASLD, n = 3,657; 37.4 million U.S. adults), metabolic dysfunction and alcohol associated liver disease (MetALD, n = 217; 2.5 M), or alcohol-associated liver disease (ALD, n = 84; 0.8 M). Cox regression models examined the association between dietary clusters and all-cause mortality, adjusting for demographics, income, urban/rural residence, number of CMRFs, smoking, leisure-time physical activity, and caffeine intake. **Results:** Four dietary patterns were identified in SLD subjects: general diet (14.7M $\pm$1.1M), high-fat low-carb diet (18.6M $\pm$1.3M), low-fat high-carb diet (3.4M $\pm$0.4M), and high-alcohol diet (11.0M $\pm$0.7M) (Fig. 1A). Prevalence estimates represent US adults with SLD 1988-94. NHANES III SLD cohort (n = 4538) median (IQR) follow-up was 313 (229-336) mo., with 1882 deaths. Diet patterns were not associated with survival in MASLD subjects. However, in those with MetALD/ALD, high-fat low-carb and low-fat high-carb diets were associated with mortality with HR (95% CI) of 1.80 (1.08–3.03) and 1.75 (1.06–2.91), respectively (Fig.1B). **Conclusion:** Specialized dietary patterns characterized by either very high or very low carbohydrate content are associated with higher mortality in subjects with MetALD/ALD. These findings reinforce the potential risks of restrictive dietary strategies in patients with alcohol-associated liver disease, emphasizing the need for cautious dietary guidance in this population. Further prospective studies are needed to validate these findings, examine dietary fat (saturated vs. unsaturated) and carbohydrates (sugar vs. non-sugar), and explore mechanistic insights to help tailor diet recommendations for subjects with SLD.



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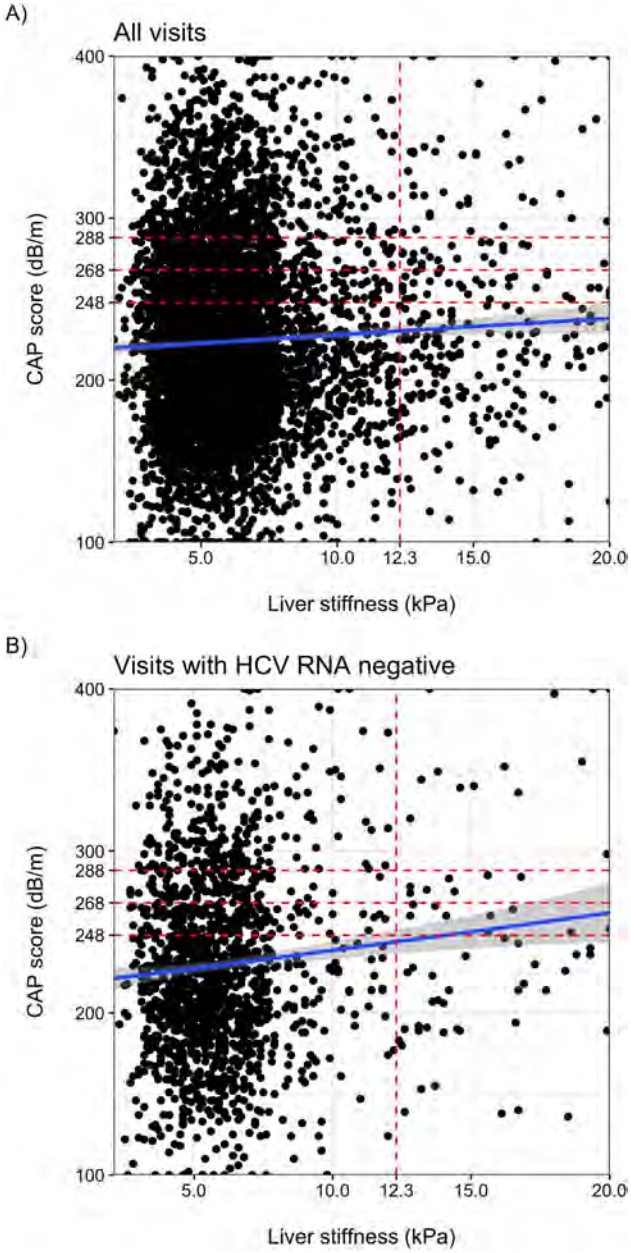
2604 | DECOUPLING OF HEPATIC STEATOSIS AND LIVER DISEASE AMONG BALTIMORE PWID

Jacqueline Rudolph Jacquie Astemborski[1] Redeat Assefa[1] Gregory Kirk[1] Shruti Mehta[1] David Thomas[2], [1]Johns Hopkins Bloomberg School of Public Health, [2]Johns Hopkins School of Medicine

Background: Steatotic liver disease (SLD) is a growing concern in the general population and may be particularly significant among people who inject drugs (PWID) in whom there is a high burden of cirrhosis from hepatitis C virus (HCV), alcohol, and HIV. **Methods:** Between 2017 and 2024, we performed binannual vibration controlled transient elastography (TE) with controlled attenuation parameter (CAP) on 6172 visits contributed by 1664 participants from the AIDS Linked to the IntraVenous Experience cohort. FIB-4 was calculated annually. Another analysis focused on the initial tests for 1,267 participants and the risk factors for SLD. Here, we considered the association between steatosis and liver disease, overall and by HCV status. SLD was characterized as CAP scores (dB/m) $\geq$248 and $\geq$268, corresponding to S1 and S2 steatosis, and $\geq$288, corresponding to Rinella et al. Cirrhosis was defined as TE measures $\geq$12.3 kPa. We considered data (FIB-4, demographics, current substance use, and comorbidities) nearest to the TE visit. **Results:** There was no correlation between CAP and TE scores (correlation coefficient, r = 0.05) or FIB-4 (r = -0.03) (Figure 1). SLD was detected at 1867 (30%), 1296 (21%), and 871 (14%) participant visits, using the 248, 268, and 288 dB/m cutpoints, respectively. Cirrhosis was detected at 437 (7%) visits. SLD and cirrhosis were concurrently detected at 3% (248 dB/m), 2% (268 dB/m), and 1% of visits (288 dB/m); the prevalence of cirrhosis was higher at visits with SLD (288 dB/min) than at visits without SLD (11% vs. 6%). Once persons with ongoing HCV were removed, over 90% of those with CAP scores $\geq$288 dB/m did not have cirrhosis, and the prevalence was only marginally higher than persons with scores $<$288 dB/m. At visits with SLD ($\geq$288 dB/m) and concurrent cirrhosis, compared to visits with SLD but without cirrhosis, participants were more likely to be HCV RNA positive and report heavy alcohol use. At visits with cirrhosis and concurrent SLD, compared to visits with cirrhosis but without SLD, participants were more likely to be female, have BMI $\geq$30, have $\geq$2 chronic conditions, and report heavy alcohol use and less likely to be HCV RNA positive and report active injection, heroin use, and cocaine use. Age, race, and HIV status were similar across groups. **Conclusion:** In a community-based cohort of PWID with routine measurement of SLD and liver fibrosis, the two forms of liver disease were not correlated, suggesting that in most persons there was steatosis but not concurrent liver disease.



Disclosures: Jacqueline Rudolph: Nothing to Disclose, Jacquie Astemborski: Nothing to Disclose, Redeat Assefa: Nothing to Disclose, Gregory Kirk: Nothing to

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Disclose, Shruti Mehta: Nothing to Disclose, David Thomas: Nothing to Disclose

2605 | SEDENTARY LIFESTYLE IS ASSOCIATED WITH STEATOTIC LIVER DISEASE (SLD): RESULTS: FROM THREE LARGE US PROSPECTIVE COHORTS.

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Continuing Medical Education

Background: The prevalence of steatotic liver disease (SLD), including metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic and alcohol-associated liver disease (MetALD), is rising globally. Sedentary behavior has been linked to MASLD in cross-sectional studies, which are limited by concerns about reverse causation. Given their established links to other metabolic disorders, we investigated the relationship between sedentary times, specifically TV watching and total sitting time, and SLD in large prospective cohorts. **Methods:** We analyzed data from three US prospective cohorts - Nurses' Health Study (NHS) I, II and Health Professionals Follow-up Study (HPFS) which included participants with ≥1 metabolic risk factor and alcohol intake <60 g/day for males and <50 g/day for females. Sedentary lifestyle was assessed using biennial (HPFS) or quadrennial (NHSI, II) questionnaires and represented by the cumulative average total sitting time and TV watching time (hours/week). Self-reported SLD (PPV >88% vs. medical records review) and the year of diagnosis were recorded. Hazard ratios (HR) for sedentary lifestyle and SLD incidence were assessed using time-varying Cox proportional hazard models to estimate relative risk (RR), adjusting for demographics, comorbidities, and lifestyle factors, including moderate-vigorous physical activities.

Results: A total of 7,517 SLD cases among 196,604 participants were identified across three cohorts: NHS I (1,241 cases/1,527,657 person-years [p-y]), NHS II (6,044 cases/1,645,345 p-y and HPFS (232 cases/770,976 p-y). Compared to <28, total sitting time of 28-56 hours/week and >56 hours/week significantly increased risk of SLD with a pooled multivariable RR of 1.10 (95% CI 1.04-1.16) and 1.20 (1.05-1.37), respectively (P-trend, 0.002; Table 1A) Compared to < 14, watching TV ≥14 hours/week was linked to SLD (RR 1.09 [95% CI 1.05-1.14], Table 1A) Subgroup analyses demonstrated a significant association between sedentary behaviors and SLD in participants with alcohol intake <30 g/day for males or <20 g/day for females, BMI ≥25 kg/m², and physical activity <15 MET-hours/day (Fig. 1B). **Conclusion:** Prolonged sitting and excess TV viewing were significantly associated with SLD incidence, particularly in individuals with low alcohol intake, non-lean and physically inactive individuals. Limiting time spent sitting or TV viewing may help prevent SLD independently of other risk factors or measures of physical expenditure.

Table 1A. Sedentary total sitting and TV watching time and risk of steatotic liver disease from three cohorts.

Cohort		Total sitting time				TV viewing time		
		< 28 hrs/wk	28-56 hrs/wk	>56 hrs/wk	P trend*	< 14 hrs/wk	≥ 14 hrs/wk	
NHS I	Univariate RR (95%CI)	1 (ref.)	1.12 (0.99-1.27)	1.51 (1.28-1.77)	<0.001	1 (ref.)	1.25 (1.11-1.40)	
	Multivariable RR (95%CI)†	1 (ref.)	1.05 (0.92-1.19)	1.28 (1.09-1.51)	0.004	1 (ref.)	1.11 (0.99-1.25)	
NHS II	Univariate RR (95%CI)	1 (ref.)	1.23 (1.17-1.30)	1.43 (1.31-1.55)	<0.001	1 (ref.)	1.30 (1.23-1.39)	
	Multivariable RR (95%CI)†	1 (ref.)	1.10 (1.04-1.16)	1.11 (1.02-1.21)	0.002	1 (ref.)	1.06 (1.02-1.15)	
HPFS	Univariate RR (95%CI)	1 (ref.)	1.33 (0.99-1.80)	1.33 (0.98-1.81)	0.03	1 (ref.)	1.00 (0.80-1.49)	
	Multivariable RR (95%CI)†	1 (ref.)	1.60 (0.98-2.62)	1.54 (0.94-2.52)	0.08	1 (ref.)	1.01 (0.74-1.39)	
Combined	Univariable RR (95%CI)‡	1 (ref.)	1.21 (1.14-1.29)	1.44 (1.34-1.54)	<0.001	1 (ref.)	1.19 (1.13-1.25)	
	Multivariable RR (95%CI)‡	1 (ref.)	1.10 (1.04-1.16)	1.20 (1.05-1.37)	0.002	1 (ref.)	1.09 (1.03-1.14)	

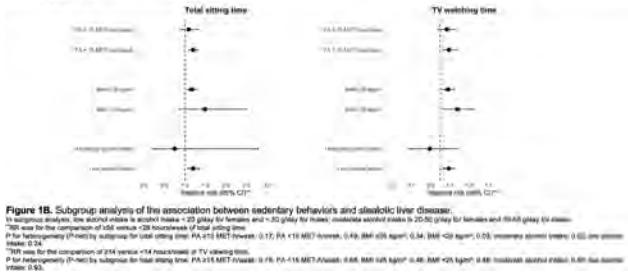

Figure 1B. Subgroup analysis of the association between sedentary behaviors and steatotic liver disease.

Disclosures: Prooksa Ananchuensook: Nothing to Disclose, Hanseul Kim: Nothing to Disclose, Daniel Sikavi: Nothing to Disclose, Jiaxian Shen: Nothing to Disclose, Etienne Nzabarushimana: Nothing to Disclose, Xuehong Zhang: Nothing to Disclose, Edward Giovannucci: Nothing to Disclose, Amrisha Bhosle: Nothing to Disclose, Yin Cao: Nothing to Disclose, Tracey Simon: Nothing to Disclose, Andrew Chan: Nothing to Disclose, Long Nguyen: Nothing to Disclose

2606 | GCKR POLYMORPHISMS INCREASE THE RISKS OF LOW BONE MINERAL DENSITY IN YOUNG AND NON-OBESE PATIENTS WITH MASLD AND HYPERURICEMIA

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Background: Metabolic-associated steatotic liver disease (MASLD) encompasses common comorbidities

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including low bone mineral density (BMD) and hyperuricemia (HU), yet relevant genetic analyses are limited. This study aimed to investigate the genetic effects of risk single nucleotide polymorphisms (SNPs) on the occurrence of low BMD in patients with MASLD and HU, particularly focusing on relatively young or non-obese populations. **Methods:** We conducted a cross-sectional study utilizing data from the Taiwan Biobank, screening a total of 150,709 participants who were prospectively enrolled over a period of 13 years. The risk SNPs of MASLD were identified. Genotype analyses of HU and its effects on the occurrence of low BMD in the general population were evaluated, with further analyses of common SNPs focusing on patients with MASLD, including subgroup analyses on relatively young and non-obese populations. **Results:** A total of 20,496 participants were eligible for analysis, including 7,526 patients with MASLD. Several risk SNPs for MASLD were identified. Furthermore, MASLD patients carrying the PNPLA3-rs738409 C_C, PNPLA3-rs2896019 T_T, GCKR-rs780094 T_T, and GCKR-rs1260326 T_T genotypes exhibited an increased risk of comorbidity with HU. Trend analysis revealed that the T alleles in GCKR-rs780094 and GCKR-rs1260326 were associated with the occurrence of low BMD in MASLD individuals comorbid with HU, particularly among relatively young or non-obese populations. In relatively young, non-obese patients with MASLD and HU, genetic effects significantly increase the risk of occurrence of low BMD. **Conclusion:** Although the risk of BMD loss may seem ostensibly low due to age and anthropometric characteristics, genetic effects are still significant in this subgroup. Therefore, heightened awareness and close follow-up are recommended.

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2607 | REAL-WORLD OBSERVATIONAL DATA ON MASLD IN A DIVERSE COHORT FROM A SINGLE HEPATOLOGY CLINIC IN SOUTHERN CALIFORNIA: RACIAL AND ETHNIC DISPARITIES AND IMPACT OF THE METABOLIC SYNDROME ON FIBROSIS

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Background: MASLD is a common progressive condition influenced by socioeconomic, lifestyle, and metabolic syndrome (MS) factors. This study aimed to characterize racial and ethnic disparities in MASLD within a diverse, non-academic hepatology clinic in Los Angeles County (LAC). **Methods:** Retrospective cohort study of patients with MASLD diagnosed by accepted AASLD criteria including only non-invasive testing (NIT). Demographic, socioeconomic, metabolic, biochemical data and degree of disease (FibroScan® CAP and stiffness) were compared by univariate and multivariate analysis. **Results:** 333 patients seen between 2009 and 2023 met inclusion criteria. 210/333 self-identified as White (51.9%) or Non-White (11.9% Asian, 1.4% African American, 34.8% Other). 249/333 self-identified as Hispanic/Latino (HL, 65.8%) or Non-Hispanic/Latino (NHL, 34.1%). Median age was 55y (17-88), 65.4% were female. 63.3% of patients were married. 177 had either blue-collar (19.7%) or white-collar (80.3%) jobs. Versus NHL, HL had a higher rate of blue-collar jobs (27.7% vs. 12.2%, $p = 0.0321$) and a higher Area Deprivation Index score [(ADI, 1-10, least to most disadvantaged) 1-3: 20.7% vs. 48.2%; 4-6: 53.5% vs. 38.8%; 7-10: 26.2% vs. 12.9%; $p < 0.0001$]. 14.4% drank minimal to moderate amounts of alcohol. 36.0% had DMT2, 33.9% had dyslipidemia, and 45.7% had HTN. Median BMI was 32(20-59.9): of 275/333, 5.5% were lean, 28.8% overweight and 65.7% obese. Of 274/333, 0.7% had 0, 35.0% had 1, 30.3% had 2, 23.7% had 3 and 10.2% had 4 components of the MS. Versus NHL, HL were more obese (Lean: 4.9% vs. 6.8%; Overweight: 26.1% vs. 41.9%; Obese: 69.0% vs. 51.4%; $p = 0.0389$). 10.5% of patients had clinical cirrhosis. 182/333 had a Fibroscan® [median stiffness kPa 6.7(3.2-61.2)], IQR 12(2.4-29), CAP 315(157-400)]: 53.8% stage F0/F1, 23.1% F2, 10.4% F3, 12.6% F4; and 3.3% grade S0 (steatosis confirmed on other imaging), 9.3% S1, 20.9% S2, 66.5% S3. Median HbA1c was 6.1(4.4-13.4), platelets 239K(50-528)], and AST/ALT ratio 0.80(0.22-2.8)]. 277 patients had a Fib-4 calculated (< 1.45: 62.8%; 1.45-3.25: 27.4%; > 3.25: 9.7%). The number of MS components was positively associated with a higher marriage rate ($p = 0.0042$), HbA1c levels ($p < 0.0001$), fibrosis stage ($p = 0.0017$), and Fib-4 ($p = 0.0140$). By multivariate analysis, BMI [OR: 1.17(1.07-1.32), $p = 0.0003$], platelet levels [OR: 0.98(0.97-0.99), $p < 0.0001$], and blue-collar work [OR: 7.99(1.47-67.3), $p = 0.0142$] were independently associated with stage F2-4. **Conclusion:** This real-world study from a diverse MASLD population in LAC suggests that HLs had higher rates of obesity, metabolic risk, and fibrosis. More MS components were linked to marriage, unmanaged diabetes, and fibrosis. Increasing BMI, lower platelet counts, and blue-collar employment were independently associated with F2-4.

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2608 | METABOLIC-DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE IN INFLAMMATORY BOWEL DISEASE: PREVALENCE AND PROGRESSION

Grazia Pennisi Emanuele Bracciamà[1] Miriam Iacono[1] Francesca Maria Di Giorgio[1] Piera Melatti[1] Livia Maria Amato[1] Ivan Alberto Salerno[1] Roberto Ajovalasit[1] Lavinia Di Prima[1] Simone Scalia[1] Domenico Gambadauro[1] Salvatore Petta[1] Calogero Camma[1] Maria Cappello[1], [1]University of Palermo

Background: Prevalence of MASLD in patients with Inflammatory Bowel Disease (IBD) has been reported 24.4% in a recent metaanalysis and 21.6% in a previous cross-sectional study from our center. However, data on the progression of MASLD in IBD patients are scanty. We aimed to investigate the prevalence and the progression of MASLD, diagnosed by non-invasive tools, in a homogeneous cohort of patients with IBD followed in our referral center. **Methods:** Consecutive IBD patients without known chronic liver disease were retrospectively enrolled and prospectively followed between 2020 and 2024. MASLD was defined as Controlled Attenuation Parameter (CAP) $\geq$275 dB/m according to EASL criteria. Significant fibrosis was defined as Liver Stiffness (LSM) $\geq$8 kPa by FibroScan©. Demographic, metabolic and biochemical data were collected at baseline and at the last follow-up visit. All patients were genotyped for PNPLA3 rs738409 C > G by Taqman assay. Univariate logistic regression analysis was performed to identify risk factors associated with the prevalence of MASLD and its progression. **Results:** 230 patients (mean age was 46.1 $\pm$ 13.4 years, 49.2% were males, 50.8% had Crohn's disease, mean disease duration was 9.4 $\pm$ 7.5 years) were recruited. 14.8% of them were obese (BMI > 30 kg/m^2), 9.8% diabetic. 49.2% were PNPLA3 rs738409 CG/GG. 62 out of 230 patients had complete metabolic and biochemical assessment at follow-up. Mean follow-up time was 4 years. At baseline, according to EASL criteria, 31.1% (19/62) had MASLD. 19.1% (8/42) of patients without steatosis at baseline, developed steatosis at follow-up; while 42.1% of those having steatosis at baseline, did not show steatosis at follow-up. Two patients without fibrosis assessed by LSM at baseline developed significant fibrosis, while two patients with fibrosis at baseline experienced fibrosis regression. 13.5% developed obesity. Obesity was significantly associated with the prevalence of MASLD both at baseline (p = 0.01) and on follow-up (p = 0.01) and was a predictor of steatosis progression (p = 0.01); no association was found in relation to sex, PNPLA3 polymorphism, disease characteristics and the use of biologics. Diabetes was not significantly associated with MASLD in our cohort, but the number of patients was low. **Conclusion:** One third of IBD patients had MASLD and obesity was the main predictor of its prevalence and progression, highlighting the relevance of active surveillance of MASLD and appropriate nutritional and lifestyle counselling especially in obese IBD patients. The use of biologics to control inflammation seems to have no influence on MASLD progression but data need further confirm in larger cohorts.

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2609 | THE OBESITY-MASH-SARCOPENIA CASCADE: METABOLIC PARADOX IN ADVANCED LIVER DISEASE

ATSUSHI NAKAMURA[1] Takeshi Ichikawa[2], [1]Nippon koukan hospital, [2]Nippon koukan hospital

Background: Obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) are increasing in chronic liver disease (CLD), emphasizing the need for weight management. Meanwhile, sarcopenia (SP) is a key prognostic factor in liver cirrhosis (LC), and the coexistence of obesity and SP complicates treatment. We investigated the prognostic impact of obesity and SP using liver stiffness (LS) by MR elastography, liver fat by proton density fat fraction (PDFF), and muscle mass by MRI. **Methods:** We enrolled 865 patients (mean age: 61 years; mean BMI: 25 kg/m²; 60% male; HCC: 32 patients). Etiologies: MASLD (M, n = 276), non-MASLD (n-M, n = 589; viral 349, alcohol 128, others 112). Disease staging was determined by LS (F0–1, F2–3, F4), with F4 further divided into compensated (cLC) and decompensated (dLC) cirrhosis. SP was diagnosed based on low paraspinal muscle area by MRI. Obesity was defined as BMI $\geq$ 25, and the combination defined as sarcopenic obesity (SO). Prognostic analysis was conducted using Cox hazards modeling. **Results:** 1) Nutritional status: Obesity was present in 35% (M group / n-M group: 74% / 27%), SP in 28% (12% / 36%, both P < 0.01), and SO in 7% (8% / 6%, P = 0.47).
2) By stage (F0–1/F2–3/cLC/dLC): (a) M group (n = 184 / 45 / 33 / 14): Obesity: 68 / 89 / 82 / 93 %, SP: 8 / 11 / 18 / 50%, SO: 3 / 11 / 12 / 50%, (P < 0.01 for all). (b) n-M group (n = 246 / 197 / 81 / 65): Obesity: 19 / 29 / 43 / 27%, SP: 24 / 33 / 43 / 78%, SO: 3 / 5 / 10 / 16%, (P <

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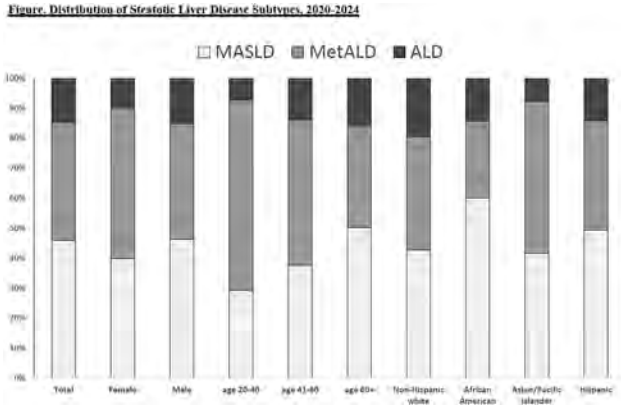
0.01 for all). (c) LS and ALBI scores correlated with stage progression, and median PDFF showed a decrease in dLC in both groups, suggesting a *"burnout"* (M group: 10.8 / 15.0 / 12.5 / 3.3%, n-M group: 3.3 / 3.7 / 4.3 / 2.7%, both $P < 0.01$).
3) Analysis of SO: In obese patients ($n = 363$), multivariate analysis showed age, CRP, and ALBI score were positively associated with SP, while BMI and PDFF were negatively associated (all $P < 0.05$). ALBI ≥ -2.36 emerged as the root node in the decision-tree analysis for predicting SP.
4) Prognosis (33 ± 22 months, 57 liver-related deaths): Kaplan-Meier analysis of 328 ACLD patients (LS $\geq$ 3kPa) divided into 4 groups (no obesity / SP: 75, obesity only: 110, SP only: 100, and SO: 43) showed that SO had as poor prognosis as SP ($P < 0.01$), with no difference in the presence/absence of obesity. In the Cox model, HCC (HR: 3.20), MELD score (1.10), and SP (2.57) were independent poor prognostic factors (all $P < 0.01$). **Conclusion:** The increase in MASLD drives SO, worsening prognosis. We propose a novel pathophysiological model, the "Obesity–MASH–Sarcopenia Cascade," where obesity-induced liver injury induces SP, identifying ALBI ≥ -2.36 as a phenotype switch in energy metabolism (anabolic to catabolic). Improvement of liver fibrosis may prevent this switch, highlighting the need for a shift in nutritional therapy in obese ACLD patients—from weight loss to muscle preservation and appropriate energy supplementation.
Disclosures: ATSUSHI NAKAMURA: Nothing to Disclose, Takeshi Ichikawa: Nothing to Disclose

2610 | GREATER CONTRIBUTION OF ALCOHOL TO STEATOTIC LIVER DISEASE EPIDEMIOLOGY THAN PREVIOUSLY ESTIMATED AMONG VETERANS IN THE UNITED STATES

Robert Wong[1] Mandana Khalili[2] Meimei Liao[3] Michael Ostacher[4] Steven Batki[5] Derek Satre[5] Ramsey Cheung[6], [1]VA Palo Alto Healthcare System, [2]University of California, San Francisco, [3]VA Palo Alto Health Care System, [4]Stanford University School of Medicine, [5]University of California San Francisco, [6]Stanford University Medical Center

Background: Steatotic liver disease (SLD) is the leading cause of chronic liver disease, with studies reporting that SLD is predominated by metabolic dysfunction-associated SLD (MASLD). However, the contribution of alcohol to SLD epidemiology is likely underestimated due to underreporting and limited alcohol use data from existing datasets. We aim to accurately characterize the impact of alcohol use on SLD epidemiology among U.S. Veterans, a population where alcohol use is routinely assessed in primary care settings. **Methods:** Consecutive adults seen in hepatology clinic from 1/1/2020 to 12/31/2024 with evidence of hepatic steatosis (HS) on transient elastography (TE) (controlled attenuation parameter $\geq$ 263 dB/m) were identified. Alcohol use was assessed via manual chart review and categorized based on documented AUDIT-C score within 6 months of TE: no alcohol (AUDIT-C = 0), low-risk alcohol (AUDIT-C = 1-2 for women, 1-3 for men), high-risk alcohol (AUDIT-C $\geq$3 for women, $\geq$4 for men). SLD subtypes were defined as: MASLD = HS + no alcohol; MetALD = HS + low-risk alcohol; alcohol-associated liver disease (ALD) = HS + high-risk alcohol. Proportion of SLD patients with MASLD vs. MetALD vs. ALD were stratified by sex, age, and race/ethnicity, and compared using chi-square tests. **Results:** Among 798 adults with HS, 695 (87.1%) had AUDIT-C documented within 6 months of TE, among whom 46.0% had MASLD, 39.1% MetALD, and 14.8% ALD (Figure). Across the three groups, majority were men (92-96%) and median age was 64-68yr. Median body mass index (BMI) and proportion with diabetes was significantly higher in MASLD and MetALD vs. ALD (median BMI: 31.6 and 32.3 vs. 30.0, $p < 0.01$; diabetes: 58.1% and 51.5% vs. 35.9%, $p < 0.01$). The proportion with advanced fibrosis (AF) (liver stiffness measurement (LSM) $\geq$12kPa) or cirrhosis (LSM $\geq$20kPa) was higher in ALD (33.0%, 24.3%) vs. MetALD (22.8%, 10.3%) or MASLD (21.6%, 8.1%), $p = 0.05$ for AF, $p < 0.01$ for cirrhosis. The proportion with MetALD or ALD was higher in women (60% vs. 53.6% in men), higher in younger patients (70.7% in age 20-40y vs. 49.7% in age $\geq$60yr, $p < 0.01$), and highest in non-Hispanic whites (57.2%) and Asians (58.3%) and lowest in African Americans (40.0%). **Conclusion:** Among consecutively identified Veterans with SLD and documented alcohol assessment, the proportion with MetALD and ALD is much higher than existing reports, suggesting that the impact of alcohol use on SLD epidemiology may be significantly under-estimated.



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2611 | FEMALE SEX HORMONES ARE NEGATIVELY ASSOCIATED WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN CHILDREN WITH OVERWEIGHT AND OBESITY

Judith Lubrecht[1] Robert Kleemann[2] Bjorn Winkens[3] Eveline Gart[4] Annemieke Heijboer[5] Anita Vreugdenhil[1], [1]Maastricht University Medical Centre+, [2]The Netherlands Organization for Applied Scientific Research (TNO), [3]Maastricht University, [4]The Netherlands Organisation for Applied Scientific Research, [5]Amsterdam University Medical Centre

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause for chronic liver disease in children and adolescents. Studies in adults demonstrate that MASLD is more prevalent in males compared to females of reproductive age, implicating sex hormones in the pathogenesis of MASLD. Currently, there is a lack of pediatric research examining the relationship between sex hormones and MASLD. This study investigates the associations between sex hormones and MASLD in children with overweight and obesity. **Methods:** A cross-sectional study was performed at Maastricht UMC+. A comprehensive sex hormone panel was quantified via liquid chromatography-tandem mass spectrometry (LC-MS/MS) in 290 participants. Additionally, serum alanine aminotransferase (ALT) and hepatic steatosis on ultrasound (HS) were assessed. Continuous Attenuation Parameter (CAP, Fibroscan©) data were available for 75 participants. The relationships between sex hormones and MASLD parameters (ALT, HS, and CAP) were analyzed using linear and logistic regression models. **Results:** Estradiol, anti-mullerian hormone (AMH) and sex hormone-binding globulin (SHBG) inversely associated with ALT, whereas dehydroepiandrosterone sulfate (DHEAS) positively associated, independent of BMI z-score, sex and age. Total, free and bioavailable testosterone (TT, FT and BioT) also positively associated with ALT, independent of BMI z-score and sex. AMH and SHBG inversely associated with HS, independent of BMI z-score and sex, while FT, BioT and DHEAS positively associated with HS, independent of sex. AMH and SHBG inversely associated with CAP, while follicle stimulating hormone, TT, androstenedione and DHEAS positively associated, independent of sex and BMI z-score. FT and BioT also positively correlated with CAP, independent of BMI z-score. **Conclusion:** This pioneering study reveals that estradiol, AMH and SHGB inversely associate with MASLD parameters, while androgens, including TT, FT, BioT, and DHEAS, positively associate with MASLD parameters in children with overweight and obesity. Our findings support the hypothesis that sex hormones contribute to MASLD development

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2612 | CLINICAL AND GENETIC PREDICTORS OF CRYPTOGENIC STEATOTIC LIVER DISEASE AS COMPARED TO METABOLIC-ASSOCIATED STEATOTIC LIVER DISEASE IN LEAN INDIVIDUALS

Angela Sato Espinoza[1] Robert Vierkant[2] Perapa Chotiprasidhi[1] Filippo Pinto e Vairo[3] Shulan Tian[4] Jun Ma[5] Konstantinos Lazaridis[1] Alina Allen[6] Kirk Wangensteen[1], [1]Mayo Clinic, [2]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, [3]Department of Clinical Genomics, Mayo Clinic, Rochester, [4]Division of Computational Biology, Mayo Clinic, [5]Division of Computational Biology, Mayo Clinic, Rochester, [6]Mayo Clinic Rochester

Background: Steatotic liver disease (SLD) is characterized by liver fat accumulation exceeding 5%. Lean individuals (BMI $\leq$ 25 kg/m2) with SLD can be classified into lean metabolic-associated liver disease (MASLD)—characterized by comorbid diabetes, hypertension, or hyperlipidemia—and cryptogenic SLD, with no metabolic disorders or other known cause of SLD. This study aimed to identify clinical and genetic predictors distinguishing cryptogenic SLD from lean MASLD. **Methods:** We conducted a retrospective cohort analysis using the Mayo Clinic Biobank and Tapestry databases. Lean individuals with SLD were identified using International Classification of Diseases (ICD) codes, radiological assessments, and pathology reports. Patients were subcategorized into lean MASLD or cryptogenic SLD based on thorough clinical review of comorbidities, imaging findings, and biochemical data. Exome sequencing data were analyzed for germline variants in PNPLA3 (rs738409), GCKR (rs1260326), MBOAT7 (rs641738), and TM6SF2 (rs58542926). Advanced fibrosis (F3-F4) was classified using FibroScan, imaging evidence of cirrhosis on CT, or advanced fibrosis

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indicated by magnetic resonance elastography (MRE) or biopsy. **Results:** Among 177 patients with lean SLD, 47 had cryptogenic SLD, and 130 had lean MASLD. The MASLD group predominantly exhibited hyperlipidemia (88%), followed by hypertension (62%), and diabetes (25%). Compared to lean MASLD, cryptogenic SLD was associated with younger mean age (58 vs 65 years, $p = 0.001$), lower rates of coronary artery disease (10.6% vs 33.8%, $p = 0.002$), and chronic kidney disease (4.3% vs. 23.1%, $p = 0.003$). Gender distribution and BMI did not differ significantly between groups.

Additionally, lean MASLD was associated with homozygosity for the risk allele T of *GCKR* (20% vs. 9%, $p = 0.04$), which was attenuated in multivariable analysis that included diabetes. However, there was no difference between the groups in *PNPLA3* ($p = 0.257$), *TM6SF2* ($p = 0.766$), or *MBOAT7* ($p = 0.824$).

Advanced fibrosis was present in 4 out of 47 (8.5%) cases of cryptogenic SLD and 12 out of 114 (10.5%) cases of lean MASLD, which was not significantly different. **Conclusion:** Individuals with cryptogenic SLD tend to be younger and healthier than those with MASLD, exhibiting more favorable metabolic profiles. Additionally, the homozygosity for the risk allele in GCKR was associated with lean MASLD, which may reflect a link between diabetes and SLD in lean people. Advanced fibrosis is present in 8-10% of patients with lean SLD.

Table 1. Lean cryptogenic SLD vs lean MASLD

Variables	Lean cryptogenic SLD (N=47)	Lean MASLD (N=130)	p-value
Gender, n (%)			0.711
Male	11 (23.4%)	34 (26.2%)	
Female	36 (76.6%)	96 (73.8%)	
Age, Mean (SD)	57.9 (14.1)	65.1 (12.4)	0.001
BMI, Mean (SD)	22.9 (2)	23.1 (1.6)	0.512
CAD, n (%)	5 (10.6%)	44 (33.8%)	0.002
CKD, n (%)	2 (4.3%)	30 (23.1%)	0.003
Hyperlipidemia, n (%)	0 (0%)	114 (87.7%)	<0.001
Hypertension, n (%)	0 (0%)	81 (62.3%)	<0.001
T2DM, n (%)	0 (0%)	32 (24.6%)	<0.001
HDL, Mean (SD)	70.2 (22)	60.2 (21.7)	0.036
Total Cholesterol, Mean (SD)	160.1 (38)	174.2 (50)	0.130
Triglyceride, Mean (SD)	95.9 (60)	165.4 (190)	0.040
Glucose, Mean (SD)	98.3 (16.4)	106.9 (21)	0.018
AST, Mean (SD)	32.3 (16.8)	36.7 (28)	0.334
ALT, Mean (SD)	33.5 (22)	36.5 (36.2)	0.611
Common variants			
PNPLA3, n (%)			0.257
CC	22 (46.8%)	67 (51.5%)	
CG	19 (40.4%)	56 (43.1%)	
GG	6 (12.8%)	7 (5.4%)	
TM6SF2, n (%)			0.766
CC	41 (87.2%)	109 (83.8%)	
CT	5 (10.6%)	20 (15.4%)	
TT	1 (2.1%)	1 (0.8%)	
GCKR, n (%)			0.044
CC	19 (40.4%)	37 (28.5%)	
CT	24 (51.1%)	67 (51.5%)	
TT	4 (8.5%)	26 (20%)	
MBOAT7, n (%)			0.824
CC	15 (31.9%)	42 (32.3%)	
CT	23 (48.9%)	66 (50.8%)	
TT	9 (19.1%)	22 (16.9%)	
Advanced fibrosis (F3-F4)	**Lean cryptogenic SLD (N=4)**	**Lean MASLD (N=12)**	
PNPLA3, n (%)			1.000
CC	2 (50%)	6 (50%)	
CG	2 (50%)	6 (50%)	
GG	0 (0%)	0 (0%)	
TM6SF2, n (%)			0.599
CC	3 (75%)	10 (83.3%)	
CT	1 (25%)	1 (8.3%)	
TT	0 (0%)	1 (8.3%)	
GCKR, n (%)			0.379
CC	2 (50%)	2 (16.7%)	
CT	2 (50%)	9 (75%)	
TT	0 (0%)	1 (8.3%)	
MBOAT7, n (%)			0.449
CC	2 (50%)	3 (25%)	
CT	2 (50%)	6 (50%)	
TT	0 (0%)	3 (25%)	

Disclosures: Angela Sato Espinoza: Nothing to Disclose, Robert Vierkant: Nothing to Disclose, Perapa Chotiprasidhi: Nothing to Disclose, Filippo Pinto e Vairo: Nothing to Disclose, Shulan Tian: Nothing to Disclose, Jun Ma: Nothing to Disclose, Konstantinos Lazaridis: Nothing to Disclose, Alina Allen: Novo Nordisk: Grant/Research Support, Novo Nordisk: Advisor, Target Pharma: Grant/Research Support, Pfizer: Grant/Research Support, Boehringer Ingelheim: Advisor, Madrigal: Advisor, GSK: Advisor, Oncoustics: Grant/Research Support, Escopics: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Madrigal: Grant/Research Support, Siemens: Grant/Research Support, Kirk Wangensteen: Nothing to Disclose

2613 | SEMAGLUTIDE USE AMONG INDIVIDUALS DIAGNOSED WITH METABOLIC-DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE IN A MEDICARE ADVANTAGE POPULATION.

Francis Lobo[1] Rich Sheer[2] Brandon Suehs[2] Nipun Atreja[1] Scott Farris[1], [1]Madrigal Pharmaceuticals, Inc., [2]Humana Healthcare Research, Inc.

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a condition that is associated with fat build up in the liver. Risk factors for MASLD include obesity and type 2 diabetes. Semaglutide is a glucagon-like peptide-1 receptor agonist medication approved for the treatment of diabetes and weight loss and has been studied as a treatment for MASLD that has progressed to steatohepatitis (metabolic dysfunction-associated steatohepatitis; MASH). In this study, we describe patient characteristics and real-world treatment patterns among patients with MASLD or MASH receiving treatment with semaglutide. **Methods:** Individuals ≥ 18 years with a diagnosis of MASLD or MASH and initiated on semaglutide SC weekly (sema SC) between July 1, 2018 and June 30, 2023 were identified from the Humana Research Database. All Individuals were enrolled in a Medicare Advantage (MA) plan and the index date was the first dispensing of sema SC. Twelve months pre-index and 72 weeks post-index enrollment was required. Patients with other causes of liver disease or advanced liver disease were excluded. Patient demographics, baseline clinical characteristics, and sema SC treatment patterns were summarized. Treatment discontinuation was defined as gap in therapy of ≥ 45 days (sensitivity analyses conducted using 60- and 90-day gap threshold). **Results:** A total of 8,432 individuals with MASLD or MASH initiating sema SC were identified. Mean (SD) age in this MA

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population was 64.8 (9.6) years, with 39.5% being under the age of 65, 68.0% were female, and 77.1% classified as white race. Diagnoses of diabetes (87.6%), hyperlipidemia (84.0%), and obesity (73.1%) were common. Discontinuation rate during 72 weeks of follow-up was 77.5% (range including sensitivity analyses from 66.8%-77.5%), and mean time to discontinuation was 139.4 (±107.3) days. Among N = 6,538 individuals that discontinued treatment, 42.7% reinitiated sema SC with mean (SD) days to reinitiation 127.4 (90.5). Among individuals with both baseline and follow-up observations, HbA1c reduced from 7.8% to 7.0%, and only 24.8% had a reduction in BMI classification observed during follow-up. **Conclusion:** Semaglutide treatment discontinuation rates were high among individuals with metabolic conditions and MASLD enrolled in MA plans. Given this observation, future research should be directed at assessing the relationship between treatment persistence and outcomes in patients receiving treatment for hepatic disease.

TABLE 1. Semaglutide Discontinuation Rates Among Individuals with Diagnosis of MASH/MAFLD.

	Patients with MASH/MAFLD N=11,432					
Discontinuation Gap Threshold	45-day Gap		60-day Gap		90-day Gap	
Discontinued semaglutide, n %	6,538	77.5%	6,169	73.2%	5,634	66.8%
Time to discontinuation, mean SD	139.4	107.3	141.2	105.4	141.1	100.8
Time to discontinuation, med IQR	102	56 - 190	108	56 - 196	111	59 - 200
Restarted semaglutide after d/c, n %	2,794	42.7%	2,274	36.90%	1,608	28.5%
Time to restart of semaglutide, mean SD	127.4	90.5	149.4	90.2	185.1	86.7
Time to restart of semaglutide, med IQR	91	61 - 166	117	79 - 196	157	115 - 236

Abbreviations: d/c, discontinuation; MASH, metabolic dysfunction-associated steatohepatitis; MAFLD, metabolic dysfunction-associated fatty liver disease; med, median; SD, standard deviation.

Disclosures: Francis Lobo: Madrigal Pharmaceuticals: Employee, Rich Sheer: Nothing to Disclose, Brandon Suehs: Nothing to Disclose, Nipun Atreja: Madrigal Pharmaceuticals: Employee, Immunovant: Employee, Bristol Myers Squibb: Employee, Scott Farris: Madrigal Pharmaceuticals: Employee

2614 | DEMOGRAPHIC AND METABOLIC PREDICTORS OF MASLD PROGRESSION IN SAUDI ARABIA: A RETROSPECTIVE CROSS-SECTIONAL ANALYSIS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a significant public health concern in Saudi Arabia and globally. However, data on population-specific risk factors for progression to advanced disease stages, namely metabolic dysfunction-associated steatohepatitis (MASH) and cirrhosis, remain underexplored in Middle Eastern populations. Aim:
To identify the demographic and metabolic predictors associated with MASLD severity, specifically MASH and cirrhosis, in a Saudi clinical sample. **Methods:** This retrospective cross-sectional study analyzed anonymized data from 780 adult patients diagnosed with MASLD at the Liver Disease Research Center, King Saud University. MASH and cirrhosis were diagnosed based on Fibroscan stiffness values (≥7.9 kPa and ≥13.0 kPa, respectively) and elevated liver enzymes. Multivariable logistic regression was performed to identify independent predictors, including age, sex, body mass index (BMI), type 2 diabetes mellitus (DM), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, and hypertension. Discriminative ability was evaluated using receiver operating characteristic (ROC) curves. **Results:** Among 780 MASLD patients, 6.5% had cirrhosis and 5.8% met criteria for MASH based on liver stiffness and enzyme thresholds. Multivariable logistic regression identified male sex as a consistent and robust predictor for both outcomes. Male patients had a 2.8-fold higher odds of cirrhosis (OR = 2.82; 95% CI: 1.36–5.59; $p = 0.003$) and were 2.4 times more likely to have MASH (OR = 2.38; 95% CI: 1.24–4.53; $p = 0.009$) compared to females. Age was significantly associated with MASH progression (OR = 1.04 per year; 95% CI: 1.01–1.08; $p = 0.012$), but not with cirrhosis after adjusting for metabolic confounders. Paradoxically, type 2 diabetes mellitus was inversely associated with cirrhosis risk (OR = 0.31; 95% CI: 0.16–0.65; $p = 0.002$), suggesting earlier diagnosis or referral bias in diabetic patients. Traditional risk indicators such as BMI, triglycerides, HDL cholesterol, and hypertension were not statistically significant in predicting either outcome. Model performance demonstrated moderate to strong discriminatory power, with an area under the ROC curve (AUC) of 0.77 for cirrhosis and 0.69 for MASH, supporting the validity of the predictive models. **Conclusion:** Age and sex are key demographic predictors of MASLD severity in this Saudi clinical population. The unexplained inverse relationship of diabetes with cirrhosis may suggest some early clinical diagnosis or selection bias. These findings underscore the need for demographic-specific screening strategies, which align with the goals of Vision 2030 for Saudi Arabia regarding the prevention of non-communicable diseases (NCDs) and the promotion of liver health.

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2615 | THE USEFULNESS OF NON-INVASIVE SCORING SYSTEMS FOR HEPATOCARCINOGENESIS, EXTRAHEPATIC MALIGNANCIES AND CEREBROCARDIOVASCULAR DISEASE IN MASLD PATIENTS

Takashi Nishimura[1] Yukihisa Yuri[1] Tomoyuki Takashima[1] Nobuhiro Aizawa[1] Naoto Ikeda[1] Hiroko Iijima[1] Hirayuki Enomoto[1], [1]Hyogo Medical University

Background: In MASLD patients, to estimate the risk of hepatocarcinogenesis, extrahepatic malignancies and cerebrocardiovascular events is crucial. The aim of this study is to clarify the usefulness of non-invasive scoring systems including FAST score, Agile 3+ and Agile 4 for hepatocarcinogenesis, extrahepatic malignancies, and cerebrocardiovascular disease in MASLD patiens. **Methods:** We retrospectively analyzed 922 MASLD patients (female/male: 446/476; median age: 57 years [IQR: 46–68]) who underwent vibration controlled transient elastography (VCTE) and controlled attenuation parameter (CAP) between October 2014 and March 2024. Inclusion criterias were as follows. 1) no history of HCC 2) followed more than at least 180 days. VCTE/CAP measurements were expressed as the median of 10 valid measurements. FAST score, Agile 3+, and Agile 4 was investigated and each cutoff value was adopted from previously manuscript. **Results:** HCC developed in 12 of 922 patients (1.30%), with cumulative incidence rates of 0.33%, 1.00%, and 1.25% at 1, 3, and 5 years, respectively. The predictive performance of each non-invasive scoring system for HCC was as follows:

- FAST score (cutoff 0.67): HR 4.821 (95% CI: 1.449–16.04, $p = 0.010$), C-index 0.587
- Agile 3+ (cutoff 0.679): HR 8.366 (95% CI: 1.829–38.25, $p = 0.006$), C-index 0.689
- Agile 4: (cutoff 0.251): HR 8.623 (95% CI: 1.887–39.41, $p = 0.005$),C-index 0.695 (cutoff 0.565): HR 9.277 (95% CI: 2.785–30.90, $p < 0.001$), C-index 0.680

No MASLD patients with less than each cutoff value for Agile 3+ in 0.679 and Agile 4 in 0.251 or 0.565 had HCC development at more than 3 years later from baseline. In contrast, extrahepatic malignancies occurred in 30 patients (3.25%) and cerebrocardiovascular disease in 11 patients (1.19%), but none of the non-invasive scoring systems demonstrated sufficient discriminatory ability for these outcomes. **Conclusion:** Non-invasive scoring systems were useful markers for the prediction of HCC development in MASLD patients. Follow-up strategies for MASLD patients using these non-invasive scoring systems should be needed. On the other hands, the developments of extrahepatic malignancies and cardiovascular disease should be investigated furthermore.

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2616 | STEATOTIC LIVER DISEASE: A KEY UPSTREAM RISK FACTOR IN THE EMERGENCE OF METABOLIC SYNDROME-RELATED DISORDER

Yoshihiro Kamada[1] Hitoshi Nishizawa[1] Makoto Fujii[1] Shiro Fukuda[1] Iichiro Shimomura[1] Eiji Miyoshi[1], [1]Graduate School of Medicine, The University of Osaka

Background: Steatotic liver disease (SLD) is the most common chronic liver disease, strongly linked to obesity and metabolic risk factors. SLD is thought to be one of the metabolic syndrome (MetS), and often coexists with conditions like type 2 diabetes (T2D), hypertension (HT), and dyslipidemia (DL), and may accelerate disease progression. While SLD is considered a hepatic manifestation of MetS, its role as a risk factor for the development of individual MetS-related diseases is not fully understood. This study examines whether SLD is an upstream risk factor for the development of MetS-related diseases using longitudinal health checkup data. **Methods:** A total of 2,167 individuals who underwent a health examination at a health check-up center from 2009–2011 (baseline) were initially recruited into the study, and 806 of these subjects received a follow-up health examination after 7 years (follow-up after 7 years. In this study, the subjects were the same individuals (n = 714 (521 men, 193 women)) who underwent health checkups and abdominal ultrasound examinations one year and seven years later. All data obtained during a health checkup: Age, sex, physical findings, blood pressure, and blood data collected during health checkups, interview data (medication, lifestyle etc.). Logistic regression analysis was used to estimate odds ratios and quantify the impact of steatotic liver on the development of metabolic syndrome-related diseases. **Results:** At baseline, 60.9% were diagnosed with SLD, and 59.1% at follow-up. SLD was more common in males and those with higher BMI, as well as elevated levels of liver enzymes, triglycerides, LDL cholesterol, uric acid, and fasting blood glucose, while HDL cholesterol was lower in SLD subjects. The SLD group had higher rates of obesity, T2D, HT, and DL both at baseline and after seven

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years. Logistic regression analyses revealed that baseline SLD was an independent risk factor for developing T2D, HT, and DL, while obesity was not. Conversely, obesity and DL at baseline independently predicted new SLD cases after seven years, but T2D and HT did not. Notably, improvement in SLD status was linked to a reduced risk of developing metabolic syndrome-related diseases, suggesting that targeting SLD may help prevent these conditions. **Conclusion:** This study revealed that SLD is an important upstream risk factor for the development of MetS-related diseases. The findings of this study highlight the strong association between SLD and metabolic disorders and highlight the importance of early detection and intervention of SLD.

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2617 | RAMADAN FASTING ENHANCES HEPATIC AND CARDIOMETABOLIC PROFILES IN MASLD: A PROSPECTIVE REAL-WORLD STUDY

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Background: Lifestyle modification is central to managing metabolic dysfunction-associated steatotic liver disease (MASLD). Ramadan, a lunar month observed by most Muslims through dry, diurnal fasting, represents a natural model of time-restricted eating. However, the hepatic and metabolic impacts of Ramadan diurnal intermittent fasting (RDIF) in MASLD remain understudied. Objective: To evaluate the effects of RDIF on liver health and cardiometabolic parameters among MASLD patients, with additional assessment of dietary and physical activity changes. **Methods:** This prospective observational study enrolled 79 adults with MASLD (median age: 47 years; 58.2% male) who fasted for ≥ 21 consecutive days during Ramadan. Assessments were conducted within 7 days before and at the end of Ramadan, and included anthropometric measurements, liver biochemistry, transient elastography (liver stiffness and controlled attenuation parameter [CAP]), lipid and glycemic profiles, 24-hour dietary recall, and physical activity using the IPAQ-Short Form. Data were analyzed using multivariable regression and linear mixed-effects models, adjusting for demographic and clinical covariates. **Results:** Despite a 6% increase in caloric intake (+178 kcal/day, $p = 0.016$), RDIF was associated with significant reductions in AST (−11.5 U/L, $p = 0.001$), liver stiffness (−0.5 kPa, $p = 0.003$), LDL cholesterol (−6.8 mg/dL, $p = 0.002$), and total cholesterol (−12.8 mg/dL, $p = 0.016$). CAP declined non-significantly (−16 dB/m, $p = 0.086$). Fasting glucose rose modestly (+1.0 mmol/L, $p = 0.048$), while HbA1c remained stable ($p = 0.056$). Light-intensity physical activity increased substantially (+180 min/day, $p < 0.001$). Sedentary behavior duration, however, remained unchanged ($p = 0.573$). Higher Physical Activity and Sedentary Time (PAST index) correlated with lower ALT ($\beta = -3.56$, $p = 0.005$) and LDL ($\beta = -3.68$, $p = 0.012$). Carbohydrates increased (+2.2 g/day, $p < 0.001$), protein decreased (−2.1 g/day, $p = 0.007$), and fat declined (−12.6 g/day, $p = 0.19$). Changes in micronutrient intake (e.g., vitamin A, C, fiber) were observed but not significantly linked to hepatic outcomes. **Conclusion:** RDIF was associated with favorable hepatic and cardiometabolic changes in MASLD patients, independent of increased energy intake. These findings highlight RDIF as a potential lifestyle intervention warranting validation in larger, multiethnic cohorts.

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to Disclose, Faisal Sanai: Nothing to Disclose, Mohamed El-Kassas: Nothing to Disclose

2618 | CLINICAL CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH PRESUMED MASLD WHO MEET METALD CRITERIA IN THE TARGET-NASH COHORT

Alfred Barritt IV[1] Ellen Green[1] Andrea Mospan[2] Breda Munoz[2] Heather Morris[2] Rohit Loomba[3] Vincent Wong[4] Brent Neuschwander-Tetri[5] Arun Sanyal[6], [1]University of North Carolina, [2]Target RWE, [3]University of California, San Diego, [4]The Chinese University of Hong Kong, [5]Saint Louis University, [6]Virginia Commonwealth University

Background: Many patients with hepatic steatosis are presumed to have metabolic dysfunction associated steatotic liver disease (MASLD) due to comorbid cardiovascular (CV) risk factors. However, alcohol use may not be accurately quantified by providers or fully disclosed by some patients. The characteristics and outcomes of patients with MASLD and increased alcohol intake (MetALD) are unknown. We sought to describe these patients in the TARGET-NASH cohort. **Methods:** Study participants were enrolled in the US TARGET NASH cohort which did not exclude moderate alcohol use from 2016 through 2024. Patients with MetALD were defined as those with an Alcohol Use Disorders Identification Test (AUDIT) score >7. Baseline demographic and clinical data were compared between the MetALD and MASLD groups. Hazard ratios were calculated for time to event analyses. Major adverse cardiovascular events (MACE), decompensation events, and cancer were the longitudinal outcomes of interest. **Results:** Overall, 4714 patients with ≥ 1 year follow-up were included in the analysis. The MetALD group had 124 (2.6%) patients with an AUDIT score >7. 4590 patients were included in the MASLD group. MetALD patients were younger (median 55 vs 59 years $p=0.05$), male (67% vs 39% $p<0.01$), and non-Hispanic white (82% vs 73%). Clinical characteristics and outcomes are reported in Table 1. A smaller proportion of MetALD patients had diabetes, obesity, and prevalent CV disease (all $p<0.05$). MetALD patients were more likely to be current tobacco and alcohol users ($p<0.01$). Five patients denied alcohol use yet had AUDIT scores >7. There were no differences in incident MACE between MetALD (4.8.%) and MASLD (6.9%) patients, however, MetALD patients experienced these events sooner than MASLD patients (median time to event 71 months vs 79 months, $p=0.02$). A smaller proportion of patients with MetALD had cirrhosis at index. The Hazard Ratios for decompensation events and incident cancers were not statistically significant when controlling for liver disease severity. **Conclusion:** Among patients presumed to have MASLD, 124 (2.6%) had AUDIT scores >7 and were reclassified at MetALD for this analysis. Despite younger age and fewer metabolic risk factors, MetALD patients suffered a similar number of incident MACE events on a faster timeframe compared with traditional MASLD patients. It is critical for providers to address alcohol use among patents with presumed MASLD to accurately risk stratify adverse events.

Table 1. Clinical and behavioral characteristics at enrollment and incident outcomes

Patient characteristic	MetALD (N=124)	MASLD (N=4590)	p-value
Disease severity			
Hepatic steatosis	39 (31.5%)	1155 (25.2%)	<0.01
Steatohepatitis	77 (62.1%)	2199 (47.9%)	
Cirrhosis	8 (6.5%)	1236 (26.9%)	
Male sex, n (%)	83 (67%)	1790 (39%)	<0.01
Age (years)	55.0	59.0	0.05
Type 2 Diabetes, n (%)	38 (30.6%)	2603 (56.7%)	<0.01
Hypertension, n (%)	117 (94.4%)	4494 (97.9%)	<0.01
Obesity, n (%)	68 (54.8%)	3287 (71.6%)	<0.01
Hyperlipidemia/dyslipidemia, n (%)	72 (58.1%)	2999 (65.3%)	0.09
Depression, n (%)	44 (35.5%)	1907 (41.5%)	0.18
Cardiovascular disease, n (%)	65 (52.4%)	2965 (64.6%)	<0.01
Tobacco use at enrollment, n (%)			
Former	44 (35.5%)	1151 (25.1%)	<0.01
Current	22 (17.7%)	315 (6.9%)	
Never	43 (34.7%)	2435 (53.1%)	
Not reported	15 (12.1%)	689 (15.0%)	
Alcohol use at enrollment, n (%)			
Former	9 (7.3%)	326 (7.1%)	<0.01
Current	92 (74.2%)	1405 (30.6%)	
Never	5 (4.0%)	1871 (40.8%)	
Not reported	18 (14.5%)	988 (21.5%)	
MACE: Number of events (Incidence Proportion)	6 (4.8%)	319 (6.9%)	0.36
Time to first MACE event[2] (months)			
Median	71.3	78.5	0.02
Decompensation: Number of events	21 (16.9%)	1808 (39.4%)	<0.01
Hazard ratio for decompensation (95% CI)			
MASLD vs MetALD disease severity=Cirrhosis	1.339 (0.319, 5.619)		
MASLD vs MetALD disease severity=MASH	1.523 (0.856, 2.712)		
MASLD vs MetALD disease severity=MASL	1.815 (0.817, 4.03)		
Any cancer excluding skin cancer: Number of events	17 (13.7%)	995 (21.7%)	0.03
Hazard ratio for cancer (95% CI)			
MASLD vs MetALD disease severity=Cirrhosis	2.088 (0.259, 16.849)		
MASLD vs MetALD disease severity=MASH	1.71 (0.85, 3.439)		
MASLD vs MetALD disease severity=MASL	0.714 (0.345, 1.479)		

Chi-square or Fisher exact test p-values comparing categorical variables reported
Index date was defined as the first date one of the cardio-metabolic criteria was met
[1]Time to event was calculated as the time from index date to the time to first event, time to death or time to last data available
[2] N of events too small for multivariable analysis

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2619 | PATIENT EXPERIENCE OF COMPENSATED AND DECOMPENSATED LIVER CIRRHOSIS: A PATIENT INTERVIEW STUDY

Elin Gruffydd[1] Rebekah Hall[1] Ginny Shand[1] Villum Wittrup-Jensen[2] Preety Gautam[2] Andrew Lloyd[1] Jeff McIntyre[3] Norah Crossnohere[4], [1]Acaster Lloyd, [2]Boehringer Ingelheim International GmbH, [3]Global Liver Institute, [4]The Ohio State University College of Medicine

Background: Liver cirrhosis is a growing cause of morbidity and mortality in the United States (US). It is a progressive disease, categorized as compensated liver cirrhosis (CLC) (i.e., liver is scarred but functioning) or decompensated liver cirrhosis (DLC) (i.e., impaired liver function), with high burden on health-related quality of life (HRQL), particularly at the DLC stage. CLC has historically been considered a "silent" condition. The symptoms and impacts of CLC on patients' daily activities are not well understood. This study aimed to explore patient-reported symptoms and impacts of CLC and DLC using qualitative methods. **Methods:** Qualitative semi-structured interviews were conducted between February–April 2023 with US adults, with confirmed diagnosis of CLC or DLC who provided informed consent. Interviews covered symptoms and impacts of CLC/DLC, summarized using content analysis. Diagnosis, symptoms and HRQL impacts were explored using thematic analysis. **Results:** In total, 10 CLC and 10 DLC patients were interviewed (80% female, mean age 58 years, mean 2.3 years since diagnosis). Patients with CLC and DLC, respectively, described experiencing fatigue (n = 8; n = 10), bloating (n = 3; n = 10), cognitive problems (n = 6; n = 5), weight loss (n = 5; n = 8), appetite loss (n = 4; n = 5), and nausea (n = 1; n = 7). Patients attributed some symptoms directly to cirrhosis, but other problems (e.g., sleeping difficulties [n = 5; n = 8]), were sometimes attributed to anxiety, skin itch or pain. Nearly all patients experienced psychological impacts, most frequently anxiety relating to uncertainty about disease progression. Patients described how their symptoms affected day-to-day functioning. Daily activities (e.g., housework, work) required more effort and planning due to fatigue. Additionally, CLC patients in particular reported making lifestyle changes (e.g., diet, exercise, alcohol abstinence) to manage their condition. Some patients reported reduced time spent socializing and perceived stigma, whilst others reported some improvements in their relationships since their diagnosis. **Conclusion:** Patients described various impacts associated with CLC, as well as DLC, despite CLC being previously described as a silent condition. These findings show the complexity of liver cirrhosis, with symptoms often linked to both the disease and the psychological impacts it causes. Symptoms and impacts in CLC and DLC all influence patients' HRQL and

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should be considered to fully understand the HRQL burden and inform treatment management.

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2620 | LIVER FIBROSIS IS MORE PREVALENT IN MASLD PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND SIGNIFICANT CORONARY HEART DISEASE

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Background: The stage of Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD)-related liver fibrosis has previously been identified as a risk factor for cardiac mortality. The prevalence and characteristics of MASLD in people with an acute myocardial infarction (AMI) are not fully elucidated. Therefore, we compared the prevalence and the characteristics of liver steatosis and fibrosis in patients presenting with an AMI to those without. **Methods:** In this Belgian, multicentric, prospective, cohort study (n = 1,274; included from March 2018 till May 2024) patients who had significant coronary stenosis (>70%) on angiography at the occasion of an AMI (group A, n = 191) were compared to patients without an AMI (group B, n = 1083; recruited both in primary and secondary care, of whom 33% had type 2 diabetes). The occurrence of steatosis and fibrosis was assessed with Controlled Attenuation Parameter (CAP^{TM}), Liver Stiffness Measurement (LSM) (FibroScan®) and non-invasive tests (NITs) (hepatic steatosis index (HSI), fibrosis 4 (FIB4), NAFLD Fibrosis Score (NFS) and AST-to-platelet ratio index (APRI). **Results:** MASLD patients (CAP^{TM} >215 dB/m) in the two groups were compared after correction for age, gender, Body Mass Index (BMI) and presence of type 2 diabetes. Group A had a higher odds of metabolic syndrome, showed significantly less steatosis (both as a continuous variable, CAP^{TM} 282 ± 48 vs 299 ± 50 dB/m (p = 0.022), or as a dichotomous diagnosis of steatosis yes/no) and had more fibrosis measured with LSM and NITs. (Table) Fibrotic (LSM > 8 kPa) MASLD patients with AMI were on average 6 years older than MASLD patients without AMI (p < 0.001), more often male (85% vs. 56%; p < 0.001) and more frequently current smokers (41% vs. 15%; p < 0.001). They also had a lower prevalence of type 2 diabetes (24% vs. 60%; p < 0.001). Among AMI patients with liver fibrosis, a positive relationship was observed between the severity of fibrosis and the number of coronary arteries affected. Among patients with LSM values between 8–10 kPa, 79% had single-vessel disease; in those with LSM between 10–15 kPa 33% had single-vessel, 44% two-vessel and 22% three-vessel disease; in LSM ≥ 15 kPa 86% had three-vessel disease (Chi-square p = 0.003; Fisher's Exact p = 0.0005). Conversely, mean LSM values increased with the number of affected arteries (p = 0.0049). **Conclusion:** AMI MASLD patients were diagnosed with significantly lower steatosis and increased fibrosis compared to non-AMI MASLD patients. There was a positive relationship observed between the severity of fibrosis and the number of coronary arteries affected. Fibrotic MASLD AMI patients were older, more often male and current smokers. Larger population studies are warranted to distinguish those MASLD patients who are at a high risk of developing the extrahepatic CVD manifestations.

Table: Comparison of MASLD AMI patients versus MASLD control patients. The table presents the number of patients with indications for steatosis or fibrosis (n), the total number of patients (ntot), and their corresponding proportions (%). Formal comparisons of the MASLD AMI and MASLD control groups are made using a logistic regression model adjusted for age, gender, BMI, and type II diabetes. The adjusted odds ratios (OR) and p-values are derived from this logistic regression model, with no correction for multiple testing applied.

	AMI with CAP >215	Control with CAP >215		
	n/ntot (%)	n/ntot (%)	OR (95%CI)	p value
Steatosis				
HSI > 36	76/154 (49.35%)	692/859 (80.56%)	0.31 (0.18;0.56)	< 0.001
Fibrosis				
LSM > 8.0 kPa	29/131 (22.14%)	116/655 (17.71%)	1.74 (1.02;2.95)	0.042
FIB-4 > 1.3	107/154 (69.48%)	289/833 (34.69%)	2.37 (1.55;3.66)	<0.001
FIB-4 > 3.25	57/154 (37.01%)	153/833 (18.37%)	2.13 (1.42;3.19)	<0.001
NFS > 0.676	21/116 (18.10%)	36/527 (6.83%)	4.38 (1.93;9.97)	<0.001
APRI > 0.5	36/154 (23.38%)	101/841 (12.01%)	2.91 (1.79;4.71)	<0.001
Metabolic syndrome	79/149 (53.02%)	442/871 (50.75%)	1.63 (1.08;2.44)	0.020

Abbreviations: Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD), Acute Myocardial Infarction (AMI); Controlled Attenuation Parameter (CAP^{TM}), Liver Stiffness Measurement (LSM) (FibroScan®); hepatic steatosis index (HSI); fibrosis 4 (FIB4); NAFLD Fibrosis Score (NFS); AST-to-platelet ratio index (APRI).

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2621 | HEALTH-RELATED QUALITY OF LIFE (HRQOL) IN ADULTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): FINDINGS FROM THE GENESIS STUDY IN SAUDI ARABIA

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Background: MASLD is a leading cause of chronic liver disease worldwide. While research interest in MASLD is increasing in Saudi Arabia, representative data on its population-level burden and impact on HRQoL remain limited. The GENESIS study, a prospective, population-based cohort, was established to address this gap by generating the first comprehensive national data on MASLD prevalence and outcomes. In this analysis, we aimed to evaluate and compare HRQoL in adults with and without MASLD using the RAND 36-Item Health Survey (SF-36) to understand MASLD's broader impact. **Methods:** Adults aged ≥ 18 years were recruited between March 2024 and April 2025 from three populous regions in Saudi Arabia using a multistage stratified sampling approach. MASLD was defined by transient elastography (FibroScan®) with a controlled attenuation parameter (CAP) ≥ 268 dB/m plus ≥ 1 cardiometabolic risk factor. HRQoL was assessed using the SF-36, which comprises eight domains: physical functioning, role limitations due to physical health (role-physical), role limitations due to emotional problems (role-emotional), energy/fatigue, emotional well-being, social functioning, bodily pain, and general health. Composite scores for physical component summary (PCS), mental component summary (MCS), and overall SF-36 were calculated. Mean scores were compared between MASLD and non-MASLD groups using t-tests. **Results:** Of 2,073 participants, 829 (40.0%) had MASLD. Participants with MASLD reported significantly lower mean scores in physical functioning (79.8 ± 25.2 vs. 86.5 ± 21.0, $p < 0.001$), role-physical (83.4 ± 23.0 vs. 87.0 ± 21.0, $p < 0.001$), bodily pain (82.1 ± 19.0 vs. 85.4 ± 17.6, $p < 0.001$), and general health (70.0 ± 19.2 vs. 72.1 ± 18.0, $p = 0.01$) compared to those without MASLD. Emotional well-being scores were slightly higher (81.3 ± 17.9 vs. 79.1 ± 19.1, $p = 0.008$) in the MASLD group. No significant differences were seen in role-emotional, energy/fatigue, or social functioning. PCS scores were lower in the MASLD group (78.8 ± 17.3 vs. 82.7 ± 15.0, $p < 0.001$), while MCS scores were similar (81.1 ± 15.3 vs. 81.0 ± 16.4, $p = 0.89$). Overall, the SF-36 score was modestly lower in those with MASLD (80.0 ± 14.6 vs. 81.9 ± 14.1, $p = 0.003$) (Table 1). **Conclusion:** In this nationally representative cohort, adults with MASLD reported lower HRQoL, particularly in physical and general health domains. These findings underscore the impact of MASLD on HRQoL and highlight the need for integrated, patient-centered care, aligning with Saudi Vision 2030's goals to improve population health.

Table 1: SF-36 health-related quality of life scores by MASLD status in the GENESIS study cohort.

Variable	Full cohort (n = 2073)	MASLD (n = 829)	No MASLD (n = 1244)	P-value
Physical functioning	83.8 ± 23.0	79.8 ± 25.2	86.5 ± 21.0	<0.001
Role-physical	85.5 ± 21.9	83.4 ± 23.0	87.0 ± 21.0	<0.001
Role-emotional	84.9 ± 22.6	84.5 ± 22.7	85.2 ± 22.5	0.51
Vitality energy/fatigue	69.9 ± 21.4	69.2 ± 20.4	70.4 ± 22.0	0.20
Mental health emotional well-being	80.0 ± 18.7	81.3 ± 17.9	79.1 ± 19.1	0.008
Social functioning	89.5 ± 18.5	89.6 ± 18.1	89.4 ± 18.8	0.90
Bodily pain	84.1 ± 18.3	82.1 ± 19.0	85.4 ± 17.6	<0.001
General health	71.3 ± 18.5	70.0 ± 19.2	72.1 ± 18.0	0.01
Physical component summary (PCS)	81.2 ± 16.1	78.8 ± 17.3	82.7 ± 15.0	<0.001
Mental component summary (MCS)	81.1 ± 15.9	81.1 ± 15.3	81.0 ± 16.4	0.89
Quality of life SF-36 overall score	81.1 ± 14.3	80.0 ± 14.6	81.9 ± 14.1	0.003

Note: Values are reported as mean ± standard deviation. MASLD was defined as CAP ≥268 dB/m plus ≥1 metabolic risk factor. Scores range from 0 (worst) to 100 (best). P-values are from independent t-tests comparing MASLD vs. non-MASLD participants.

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2622 | EVALUATING THE IMPACT OF CARDIOMETABOLIC RISK FACTORS ON NON-INVASIVE TESTING AND HISTOLOGICAL FINDINGS IN MASH: A TERTIARY CENTER EXPERIENCE IN NORTH TEXAS

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a leading cause of chronic liver disease and liver transplantation in the U.S. Accurate non-invasive evaluation is critical for risk stratification and monitoring. While non-invasive tests (NITs) like FIB-4, liver stiffness measurement (LSM), and controlled attenuation parameter (CAP) from vibration-controlled transient elastography (VCTE) are widely used to assess fibrosis and steatosis, liver biopsy remains the diagnostic gold standard. Real-world data comparing NITs and biopsy findings across varying cardiometabolic (CM) risk burdens are limited. This study evaluates correlations between NITs, liver biopsy, and CM risk factors in patients at a tertiary liver and transplant center in North Texas and the Dallas-Fort Worth Metropolitan Area. **Methods:** We performed a retrospective analysis of 450 ICD confirmed MASH patients who underwent VCTE, Liver Biopsy and various NITs at our tertiary liver center. Demographic and clinical data, including the presence of CM risk factors (type 2 diabetes, obesity, hypertension, dyslipidemia, and coronary artery disease), were collected. Non-invasive tests (FIB-4, LSM, CAP) and Liver Biopsy were analyzed and compared across subgroups defined by the number of CM risk factors present. Patients were grouped with either having less than or greater than 3 CM factors. Continuous outcomes (CAP, LSM, and Fib-4 Scores) were compared using Welch's t-Tests. The categorical outcome (Brunt Scoring System) was evaluated through a Pearson-Chi Square test. **Results:** Patients with 3+ CM risk factors had a significantly higher FIB-4 score (Mean ± SD: 2.7 ± 3.6; P-value: 0.030) than those with less than 3 CM risk factors (Mean ± SD: 2.0 ± 3.1). The Chi Square test also revealed a significant association between the Brunt Scoring system for severity of NASH with the amount of CM risk factors present (P-value: 0.006). Both outcomes for the Fibroscan, liver stiffness (kPa) and liver steatosis (CAP scores), did not differ between patients with 3+ CM risk factors and those with less than 3 CM risk factors. **Conclusion:** Patients with ≥3 cardiometabolic risk factors had significantly higher FIB-4 scores and histologic findings were significantly associated with the presence of CM risk factors, highlighting the impact of metabolic burden on MASH severity. In contrast, LSM and CAP values did not significantly differ between groups, suggesting limitations of VCTE parameters in this setting, potentially via user variability and BMI limitations. These findings support the utility of FIB-4 and biopsy in risk stratification and underscore the need for improved non-invasive tools in high-risk, tertiary care populations.

	<3 Comorbidities	3+ Comorbidities	P-Val
Fib-4 Index, *N*	199	216	
Mean (SD)	2.0 (3.1)	2.7 (3.6)	0.030
Fibroscan – Cap Score, *N*	87	96	
Mean (SD)	307.8 (51.0)	315.12 (68.1)	0.409
Fibroscan – LSM, *N*	93	100	
Mean (SD)	9.2 (8.1)	11.2 (10.0)	0.121
Liver Biopsy – Brunt Scoring System, N	124	123	0.006
Grade 1, N	49	34	
Grade 1-2, N	17	23	
Grade 2, N	9	25	
Grade 2-3, N	17	20	
Grade 3, N	11	12	
Grade 3-4, N	21	9	

Table 1: Comparison of non-invasive test scores (FIB-4, LSM, CAP) and histologic severity (Brunt Score) between patients with fewer than 3 versus ≥ 3 cardiometabolic risk factors.

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2623 | SEX-BASED DISPARITIES IN ADVANCED LIVER DISEASE OUTCOMES AMONG METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) PATIENTS: A 5-YEAR REAL-WORLD MULTICENTER ANALYSIS

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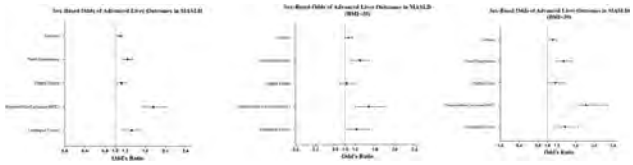
Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease and its complications. Hormonal, immunologic, and metabolic differences may underlie sex-based variation in disease progression. This study aimed to evaluate disparities in liver-related outcomes between male and female MASLD patients over a 5-year period using a large, real-world EHR dataset. **Methods:** We performed a retrospective cohort study using TriNetX, a federated EHR network encompassing 69 U.S. healthcare organizations. Adults ($\geq$18 years) diagnosed with MASLD or NASH (ICD-10: K76.0, K75.81) were included, excluding those with alcohol-related, viral, or other chronic liver diseases. Male and female cohorts (n = 604,256 each) were matched 1:1 using propensity scores for age, race/ethnicity, BMI, diabetes, hypertension, hyperlipidemia, atrial fibrillation, and nicotine use. Outcomes assessed over 5 years included cirrhosis, portal hypertension, hepatic failure, hepatocellular carcinoma (HCC), and esophageal varices. Odds ratios (ORs) with 95% confidence intervals (CIs) and Kaplan-Meier survival analyses were used for comparisons. **Results:** Males demonstrated significantly increased odds of developing all adverse liver outcomes. Compared to females, males had 9.6% higher odds of cirrhosis (OR 1.096; 95% CI: 1.046–1.147; $p < 0.001$), 24.8% higher odds of portal hypertension (OR 1.248; 95% CI: 1.151–1.352; $p < 0.001$), 12.3% higher odds of hepatic failure (OR 1.123; 95% CI: 1.027–1.229; $p = 0.012$), 75.9% higher odds of HCC (OR 1.759; 95% CI: 1.526–2.028; $p < 0.001$), and 32.7% higher odds of esophageal varices (OR 1.327; 95% CI: 1.173–1.502; $p < 0.001$). Kaplan-Meier survival curves showed significantly lower event-free survival among males for all outcomes (*log-rank* $p < 0.001$), although median survival was not reached within 5 years.
Among MASLD patients with BMI <30, male sex remained associated with higher odds of portal hypertension (OR 1.295), HCC (OR 1.473), and esophageal varices (OR 1.226), while differences in cirrhosis and hepatic failure were not statistically significant. In the BMI ≥ 30 group, males had increased odds for all outcomes, including cirrhosis (OR 1.115), HCC (OR 1.824), and portal hypertension (OR 1.346), with statistical significance across the board. **Conclusion:** In this large multicenter matched cohort of MASLD patients, males were at significantly higher risk of developing cirrhosis, portal hypertension, hepatic failure, HCC, and esophageal varices within 5 years. These findings highlight the need for sex-specific surveillance and management strategies in MASLD and warrant further investigation into the biological mechanisms underlying these disparities.



Disclosures: Rishi Chowdhary: Nothing to Disclose, Kirti Arora: Nothing to Disclose, Dhruvi Shah: Nothing to Disclose, Rohit Goyal: Nothing to Disclose, Simran Joshi: Nothing to Disclose, Prachi Dawar: Nothing to Disclose

2624 | RISK FACTORS FOR SEVERE HEPATIC STEATOSIS (SS) AND RENAL RISK: LESSONS FROM NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY 2017-2020 (NHANES)

Juliana Pava De Los Rios[1] Franklyn Vega Batista[1] Maria Jose Lorenzo Capps[1] Song Ang[1] Riddhi Machchhar[2] Eunseuk Lee[1] Jose Iglesias[1], [1]Rutgers Health/Community Medical Center, [2]Hackensack Meridian Ocean University Medical Center

Background: In Western developed nations the most common cause of severe hepatic steatosis is non-alcoholic fatty liver disease (NAFLD). This can lead to progressive liver inflammation and cirrhosis. NAFLD is associated with obesity, metabolic syndrome, insulin resistance, and diabetes. These clinical conditions are also linked to chronic kidney disease (CKD) and inflammation. In the current study employing the NHANES 2017-database we sought to investigate if there is an association with severe hepatic steatosis, CKD, renal risk and systemic inflammation. **Methods:**

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In order to determine which variables were associated with severe steatosis (SS) defined as a controlled attenuation parameter of >289 dB/m, we performed a univariate and multivariate complex samples analysis choosing variables that were clinically relevant variables and included them in a multivariate logistic regression model. **Results:** There was an inverse relationship between age and SS suggesting a protective role (OR = 0.955, p = 0.018). Both hemoglobin A1C and BMI emerged as major contributors to SS (OR = 1.428, p = 0.028, OR = 1.204, p < 0.001). Additionally, the neutrophil-to-lymphocyte ratio (nlratio) is associated with increased odds of SS (OR = 1.591, p = 0.002), indicating a possible inflammatory component in the severity of steatosis. Neither estimated GFR, the degree of albuminuria or renal risk were associated with SS. **Conclusion:** This study highlights the intricate relationship between obesity, insulin resistance, and inflammation in the pathogenesis of SS. The lack of association between parameters of renal dysfunction and SS suggest that the relationship is complex and nonlinear in nature. In comparison to the risks of renal dysfunction associated with the metabolic syndrome, it is possible that the liver maybe more sensitive to the detrimental effects of the metabolic syndrome.

Disclosures: Juliana Pava De Los Rios: Nothing to Disclose, Franklyn Vega Batista: Nothing to Disclose, Maria Jose Lorenzo Capps: Nothing to Disclose, Song Ang: Nothing to Disclose, Riddhi Machchhar: Nothing to Disclose, Eunseuk Lee: Nothing to Disclose, Jose Iglesias: Nothing to Disclose

2625 | REAL-WORLD PREVALENCE OF DIAGNOSED METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS AMONG MEDICARE BENEFICIARIES

Husam Albarmawi[1] Abdalla Aly[1] Anthony Hoovler[1] Caichen Zhong[1] Anran Tan[2] Jamieson Vaccaro[2] Joanna Harton[2] Parvez Mantry[3], [1]Novo Nordisk Inc., [2]Genesis Research Group, [3]Methodist Dallas Medical Center

Background: The prevalence of metabolic dysfunction-associated steatohepatitis (MASH) among older adults is under documented. Accurate assessment of MASH prevalence is crucial for understanding disease burden and population health, and guiding screening, diagnosis, and treatment. This study sought to estimate prevalence of diagnosed MASH in the Medicare Fee-for-Service (FFS) population. **Methods:** This observational study used 100% Medicare FFS data to assess the prevalence of diagnosed MASH among beneficiaries ≥ 65 years of age from Jan. 1, 2016 to Dec. 31, 2022. The MASH cohort included patients with ≥ 1 ICD-10-CM diagnosis code for MASH (K75.81). Annual prevalence of MASH was estimated as the number of patients with continuous enrollment in Medicare FFS for the entire year (or until death) who were diagnosed with MASH in that year, or any prior year in the study period, out of the number of patients with continuous enrollment for that entire year (or until death). To account for changes in age distribution over time, age-standardized prevalences were estimated using direct standardization to the 2022 US Census Bureau age distribution. MASH annual prevalence was stratified by age, sex, race, region and state of domicile. **Results:** From 2016 through 2022, between 22.2 and 23.5 million beneficiaries were assessed per year. Annual prevalence of MASH was: 0.22% (n = 50,997) in 2016, 0.35% in 2017, 0.47% in 2018, 0.59% in 2019, 0.69% in 2020, 0.80% in 2021, and 0.91% (n = 202,455) in 2022. Age-standardized estimates were similar. Across time, lower prevalence was observed in those who were older, male, Black, and from the West. In 2022, the highest prevalence was observed in those aged 70-74 (1.16%) and lowest in those aged 85+ (0.36%). Prevalence was greater in females vs males (2022: 0.99% vs 0.81%). By race/ethnicity, prevalence in 2022 was lowest for Black patients (0.53%) and highest for Native American patients (1.67%). By region and state, 2022 prevalence was lowest for the West (0.77%) and Montana (0.53%), respectively, and highest for the South (1.04%) and Mississippi (1.31%), respectively. **Conclusion:** Prevalence of diagnosed MASH increased from 2016 to 2022 with more than 200,000 patients living with MASH in the Medicare FFS population in 2022. However, the reported prevalence of MASH is likely to be underestimated due to underdiagnosis and undercoding in clinical practice.

Disclosures: Husam Albarmawi: Novo Nordisk Inc.: Employee, Novo Nordisk Inc.: Stock - publicly traded company, Genentech Inc.: Employee, Genentech Inc.: Stock - publicly traded company, Abdalla Aly: Novo Nordisk Incorporated: Employee, Novo Nordisk Incorporated: Stock - publicly traded company, Anthony Hoovler: Novo Nordisk Inc: Employee, Caichen Zhong: Nothing to Disclose, Anran Tan: Nothing to Disclose, Jamieson Vaccaro: Nothing to Disclose, Joanna Harton: Novo Nordisk: Independent Contractor, Parvez Mantry: Akero: Grant/Research Support, Abbvie: Speaker and Advisory Board, BMS: Research Grants & Speaker, Boston Scientific: Advisory Board and Speaker, Chemomab: Grant/Research Support, Cymabay: Research Grants & Advisory Board, Care Dx: Grant/Research Support, Eisai: Speaker and Advisory Board, Genfit: Grant/Research Support, Gilead: Speaker, Advisory Board, & Research Grants, GSK: Grant/Research Support, Gore: Speaking and Teaching, Genentech: Grant/Research Support, Intercept: Speaker, Advisory Board, & Research Grants, Ipsen: Speaker and Advisory Board, Inventiva: Grant/

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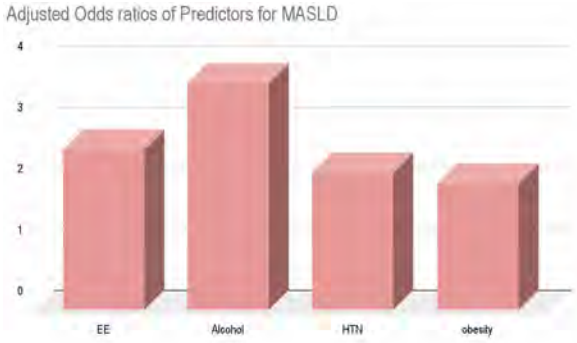
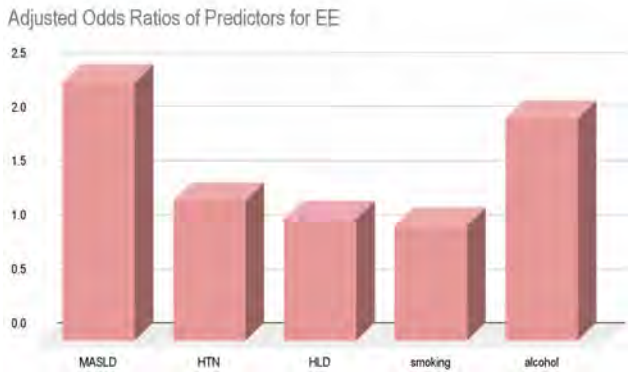
Research Support, Fibronostics: Grant/Research Support, Hanmi: Grant/Research Support, Hepquant: Research Grants & Advisory Board, Lipocine: Grant/Research Support, Madrigal: Speaker, Advisory Board, & Research Grants, Mallinckrodt: Advisor, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Novo Nordick: Pipeline Advisor, Speaker, Consulting & Research Grants, Regneron: Grant/Research Support, Sirtex: Speaker, Advisory Board, & Research Grants, Salix: Speaker, Advisory Board, & Research Grants, Taiho: Grant/Research Support, Transthera Sciences: Grant/Research Support, Transthera Sciences: Grant/Research Support, Viking: Grant/Research Support, Aldeyra Sciences: Grant/Research Support, Tempest Therapeutics: Grant/Research Support, Amgen: Consulting & Speaker, Helio: Advisor

2626 | EROSIVE ESOPHAGITIS AND MASLD: A NATIONWIDE CROSS-SECTIONAL ANALYSIS OF HOSPITALIZED ADULTS IN THE UNITED STATES

Hima Varsha Voruganti[1] Rohit Sekandlapuram[2] Yeongjin Kim[3] Rahul Karna[4] Manasa Ginjupalli[2], [1]North Alabama Medial Center, [2]The Brooklyn Hospital Center, [3]North Albama Medical Center, [4]University of Minnesota Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and erosive esophagitis (EE) are common conditions linked to obesity and metabolic syndrome. While both share overlapping risk factors, the population-level association between MASLD and EE remains unclear. Understanding this relationship is essential to guide screening and management strategies in at-risk populations. **Methods:** We conducted a cross-sectional analysis of the National Inpatient Sample (2018–2020) to examine the association between MASLD and EE. Adults aged ≥18 years were included. Survey-weighted logistic regression was used, adjusting for demographics, hospital characteristics, Charlson Comorbidity Index, diabetes, hypertension (HTN), hyperlipidemia (HLD), obesity, smoking, alcohol use, and obstructive sleep apnea. **Results:** The survey estimated approximately 953,705 hospitalizations with EE and 1,864,820 cases of MASLD between 2018 and 2020. Among hospitalizations with MASLD, mean age did not differ significantly between those with and without EE (53.5 vs. 53.8 years).Females comprised 51% of MASLD patients with EE vs. 52% without ($p = 0.055$), and White race was more prevalent in the EE group (72% vs. 66%, $p < 0.001$). Multivariable survey-weighted logistic regression showed that EE was independently associated with MASLD (OR 2.63, 95% CI 2.55–2.70). Alcohol use (OR 3.71), HTN (OR 2.25), and obesity (OR 2.08) also showed strong associations. MASLD was strongly associated with higher odds of EE (OR 2.39, 95% CI 2.32–2.46; $p < 0.001$). Other independent predictors included HTN (OR 1.30), HLD (OR 1.13), smoking (OR 1.07), and alcohol use (OR 2.06), all with $p < 0.001$. **Conclusion:** MASLD and EE are strongly associated at the population level, with each condition significantly increasing the odds of the other. Shared metabolic risk factors—including obesity, hypertension, and alcohol use—likely contribute to this bidirectional relationship. These findings highlight the need for integrated screening and management strategies targeting metabolic risk factors to prevent and mitigate both conditions.





Disclosures: Hima Varsha Voruganti: Nothing to Disclose, Rohit Sekandlapuram: Nothing to Disclose, Yeongjin Kim: Nothing to Disclose, Rahul Karna: Nothing to Disclose, Manasa Ginjupalli: Nothing to Disclose

2627 | MASLD: SCREENING FOR CARDIOVASCULAR DISEASE

Sindhu Chadalawada[1] Katherine Jones[2] Jeffrey Liu[2] Charizza Besmanos[2] Marina Roytman[2], [1]University of California San Francisco, [2]UCSF Fresno

Background: Metabolic associated steatotic liver disease (MASLD) or steatohepatitis (MASH) has been

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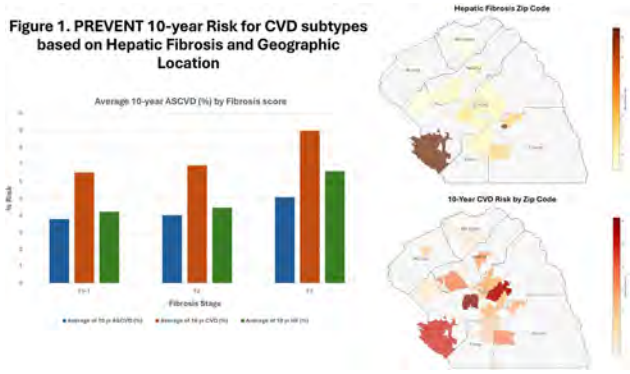
associated with increased risk of cardiovascular disease (CVD). At present, there are no cardiovascular screening guidelines for patients with MASLD. **Methods:** A single center retrospective cohort study in Fresno, California aimed to assess CVD risk in patients ages > 18 years with biopsy or transient elastography proven MASLD or MASH between January 2015 - May 2025. Those with preexisting CVD at the time of their initial hepatology encounter were excluded from the study. The American Heart Association's Predicting Risk of Cardiovascular Disease Events (PREVENT) score was used to determine the 10-year risks of CVD, atherosclerotic cardiovascular disease (ASCVD), and heart failure (HF) for the entire cohort. Thirty-year risk estimates were calculated for patients ages 30-59 years. Secondary outcomes, including progression of liver disease, liver transplantation, and major cardiovascular events were also studied. Descriptive statistics were reported for continuous variables including mean, median interquartile range (IQR), and standard deviation. **Results:** In total, 290 cases were reviewed, of which 96 patients met inclusion criteria. Of these, 74% were female, 46% non-Hispanic whites, 90% English speaking, and 80% married. Mean age was 53 years (median 56 [IQR 46-64] SD 12), body mass index (BMI) 32.5 kg/m2 (median 33 [IQR 28.4 - 37.3] SD 6.9), and HbA1c of 6% (median 5.8% [IQR 5.5-6.4] SD 1.1). Patients with advanced fibrosis (F3) had a 10-year CVD risk of 9%, ASCVD risk of 5.1%, and HF risk of 6.6%. PREVENT 30-year estimates for individuals ages 30-59 demonstrated a mean CVD risk of 16.6% (median 18.3 [IQR 10.4-29.2] SD 12.8), ASCVD risk of 9.9% (median 10.2 [IQR 6.2-16.7] SD 7.9), and HF risk of 10.3% (median 11.2 [IQR 6.1-18] SD 10.3). When examined geographically by zip code, elevated CVD risk profiles correlated with lower socioeconomic strata, as identified by the United States Department of Agriculture (USDA). **Conclusion:** In this single center study, a clear trend of increased CVD, ASCVD, and HF risk is demonstrated with advancing fibrosis, particularly among younger and middle-aged adults. These high-risk profiles were concentrated in underserved regions defined by limited access to nutritious, unprocessed food, contributing to the development of obesity and its downstream effects. Therefore, noninvasive cardiovascular disease screening should be considered in MASLD patients 30 years and older in the presence of fibrosis.



Disclosures: Sindhu Chadalawada: Nothing to Disclose, Katherine Jones: Nothing to Disclose, Jeffrey Liu: Nothing to Disclose, Charizza Besmanos: Nothing to Disclose, Marina Roytman: Gilead: Speaking and Teaching, Salix: Speaking and Teaching, Madrigal: Speaking and Teaching

2628 | EXPLORING THE LINK BETWEEN EOSINOPHILIC ESOPHAGITIS AND MASLD IN U.S. HOSPITALIZED ADULTS

Hima Varsha Voruganti[1] Rohit Sekandlapuram[2] Yeongjin Kim[3] Pratiksha Moliya[4] Rahul Karna[5], [1]North Alabama Medial Center, [2]Brooklyn Hospital Center, [3]North Alabama Medical Center, [4]University of Nebraska Medical Center, [5]University of Minnesota Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly linked to components of metabolic syndrome, while eosinophilic esophagitis (EoE) has traditionally been viewed through an allergic or inflammatory lens. Although both conditions have individually seen rising prevalence, their potential intersection has not been thoroughly investigated. Using a large, nationally representative database, we sought to explore this potential association in hospitalized adults. **Methods:** We analyzed adult hospitalizations (≥ 18 years) from the National Inpatient Sample (2018–2020). MASLD and EoE were identified using ICD-10-CM diagnosis codes. A multivariable survey-weighted logistic regression was performed to evaluate the association between EoE and MASLD, adjusting for demographics, hospital characteristics, Charlson Comorbidity Index, obesity, obstructive sleep apnea (OSA), diabetes, hypertension (HTN), hyperlipidemia (HLD), asthma, Crohn's disease (CrD),

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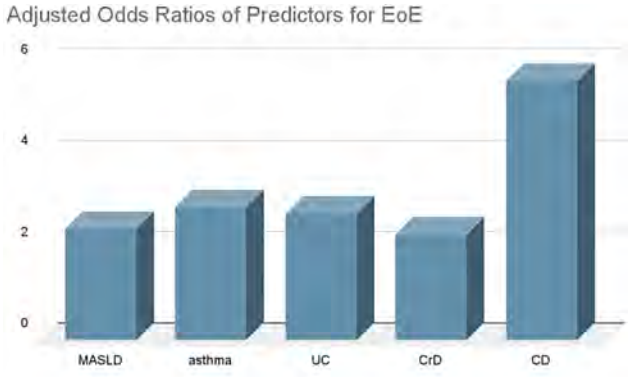
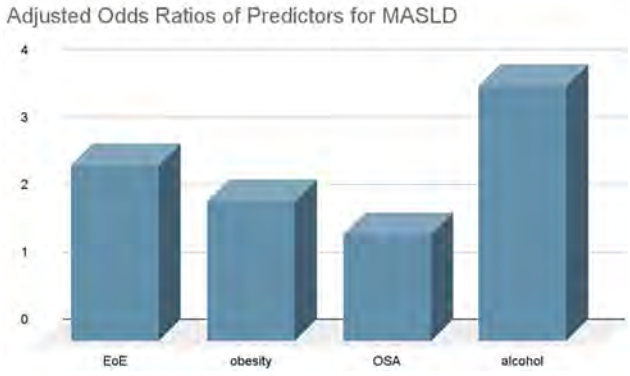
ulcerative colitis (UC), celiac disease (CD), smoking, and alcohol use. **Results:** Among 174,776,205 adult hospitalizations, an estimated 1,864,820 had MASLD and 31,550 had EoE. Among MASLD patients, those with EoE were younger (mean age 43.3 vs. 53.8 years) and had a similar sex distribution (female: 48.8% with EoE vs. 51.9% without; $p = 0.42$); however, racial distribution differed significantly ($p = 0.0498$), with a higher proportion of White individuals among those with EoE (77.9% vs. 65.8%). EoE was independently associated with higher odds of MASLD (OR 2.61; 95% CI: 2.21–3.08; $p < 0.001$). Other significant predictors included obesity (OR 2.07), OSA (OR 1.58), and alcohol use (OR 3.78). MASLD was significantly associated with increased odds of EoE (OR 2.45; 95% CI: 2.07–2.90; $p < 0.001$). Other conditions with strong positive associations included asthma (OR 2.91), UC (OR 2.78), CrD (OR 2.33), and CD (OR 5.68). **Conclusion:** Our study demonstrates a significant association between MASLD and EoE in hospitalized adults. These findings highlight the importance of considering comorbid conditions in patients with either diagnosis. Further investigation is needed to better understand the clinical relevance of this relationship.





Disclosures: Hima Varsha Voruganti: Nothing to Disclose, Rohit Sekandlapuram: Nothing to Disclose, Yeongjin Kim: Nothing to Disclose, Pratiksha Moliya: Nothing to Disclose, Rahul Karna: Nothing to Disclose

2629 | PREVALENCE AND CHARACTERISTICS OF STEATOTIC LIVER DISEASE ACCORDING TO THE NEW NOMENCLATURE IN A JAPANESE HEALTH CHECKUP POPULATION

Satoko Tajirika[1] Takao Miwa[2] Tatsunori Hanai[2] Masahito Shimizu[2] Mayumi Yamamoto[1], [1]Gifu University, Gifu, Japan, [2]Graduate School of Medicine, Gifu University, Gifu, Japan.

Background: The recently introduced nomenclature for steatotic liver disease (SLD) aims to better classify patients based on metabolic dysfunction and alcohol intake. However, the prevalence of SLD based on recently introduced nomenclature in the Japanese population is yet to be explored. This study examined the prevalence and characteristics of SLD and its subclasses in Japanese individuals. **Methods:** This cross-sectional study included 694 participants who underwent health checkups. SLD was evaluated using liver ultrasonography, and participants were categorized into metabolic dysfunction-associated steatotic liver disease (MASLD), MetALD, alcohol-associated/related liver disease (ALD), and cryptogenic SLD groups using consensus nomenclature. The prevalence and characteristics of the SLD subclasses were assessed, and subgroup analyses were conducted for the non-obese (body mass index [BMI] $\leq$ 25 kg/m^2) and lean (BMI $\leq$ 23 kg/m^2) populations. **Results:** Among participants with a median age of 47 years and 54% males, the prevalence of MASLD, MetALD, ALD, and cryptogenic SLD in the total population was 26%, 2%, 1%, and 2%, respectively. A remarkable difference was observed in the prevalence of SLD subclasses according to age, sex, and BMI (Figure) . Subgroup analyses revealed heterogeneous demographic, clinical, and biochemical parameters between the SLD categories. Notably, individuals with MetALD had higher gamma-glutamyl transferase levels, lower platelet counts, and higher fibrosis-4 index than those with MASLD. Furthermore, the prevalence of non-obese and lean MASLD was 13% and 6%, respectively. **Conclusion:** This study provides information on the prevalence of SLD based on a new nomenclature in the Japanese population. The findings of our study highlight potential areas for further research, particularly in relation to different BMI categories and SLD subclasses.

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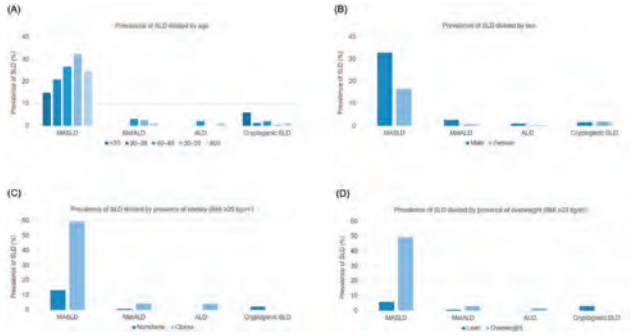

Disclosures: Satoko Tajirika: Nothing to Disclose, Takao Miwa: Nothing to Disclose, Tatsunori Hanai: Nothing to Disclose, Masahito Shimizu: Nothing to Disclose, Mayumi Yamamoto: Nothing to Disclose

2630 | MASLD ETIOLOGY INDEPENDENTLY PREDICTS 3-MONTH HOSPITAL READMISSION IN DECOMPENSATED CIRRHOSIS – A SINGLE-CENTER STUDY

Rohit Mehtani[1] Ananya Nanda[1] Prerna Agarwal[1] Shankey Garg[1] Akash Roy[2] Mahendra Rajput[1] Suraj Bhagat[1] Bhaskar Nandi[1], [1]Amrita Institute of Medical Sciences and Research Center, Faridabad, Haryana, India, [2]Apollo Multispeciality Hospital, Kolkata

Background: Readmission in patients with decompensated cirrhosis is common and leads to significant morbidity and healthcare costs. The role of underlying etiology in predicting readmission risk, particularly metabolic dysfunction associated steatotic liver disease (MASLD) remains unexplored. The study was done to assess 3-month readmission risk and identify predictors of readmission in patients with decompensated cirrhosis, focusing on the impact of disease etiology. **Methods:** A retrospective analysis of admitted patients with decompensated cirrhosis in a tertiary care center in North India was done. Data on demographic parameters, etiology & severity of liver disease, comorbidities, laboratory parameters, decompensations and complications of liver cirrhosis (ascites, Hepatic encephalopathy [HE], gastrointestinal [GI] bleeding, acute kidney injury [AKI], jaundice, hepatocellular carcinoma [HCC], hepatopulmonary syndrome [HPS], portal vein thrombosis [PVT], sarcopenia), survival, 3-month readmissions and reasons for readmission was collected. Primary outcome was hospital readmission within 3 months of discharge. Logistic regression analysis was performed to identify independent predictors of readmission, adjusted for baseline age and MELD-Na score. **Results:** Of 124 patients, 57 (46%) required hospital readmission within 3 months. Baseline parameters including disease severity scores – CTP (10 [9–11.5] vs 10 [8-12]; p = 0.384) and MELD-Na (19.5 [13.5-25.5] vs 20 [14-24]; p = 0.726) were similar irrespective of readmission status. MASLD was the most common etiology of liver disease (29%) in our cohort. Patients with MASLD were older, more often females, had more comorbidities and lower liver disease severity scores (CTP and MELD-Na) as compared to patients without MASLD (Table 1). Readmission rate was high in patients with MASLD related cirrhosis (61.11% vs 39.77%; p = 0.030). On logistic regression analysis, MASLD etiology was the only significant predictor of readmission (Odds ratio [OR] 2.40, 95% CI 1.01 – 5.74; p = 0.048) even after adjusting for baseline age and MELD-Na score. Symptomatic ascites recurrence (n = 25, 43.86%) was the most common reason for hospital readmission followed by HE (n = 8, 14%). Readmission due to hepatic hydrothorax was more common in MASLD group (13% vs 0%; p = 0.025). **Conclusion:** MASLD etiology is a significant independent predictor of 3-month hospital readmission in patients with decompensated cirrhosis. Our study highlights the need for targeted post-discharge monitoring and interventions in patients with MASLD to reduce readmission rates.

Table 1 – Baseline and follow-up data of patients with cirrhosis stratified by MASLD as etiology of liver disease

Variable	Non-MASLD (n=88)	MASLD (n=38)	p-value
Age (years)*	48 [41 – 61]	65.5 [58.5 – 69.5]	***<0.001***
Male Gender (n, %)	81 (92.05%)	28 (77.78%)	***0.027***
Duration of Cirrhosis (years)*	2 [1.1 – 2.5]	2 [1 – 3]	0.906
Comorbidities (n, %)			
Diabetes Mellitus	19 (21.59%)	26 (72.22%)	***<0.001***
Hypertension	12 (13.64%)	11 (30.56%)	***0.028***
CAD	2 (2.3%)	3 (8.33%)	0.149
Complications (n, %)			
Ascites	69 (78.41%)	25 (69.44%)	0.290
GI bleed	23 (26.14%)	12 (33.33%)	0.419
Hepatic encephalopathy	22 (25%)	8 (22.22%)	0.743
AKI	27 (30.68%)	8 (22.22%)	0.342
Jaundice	72 (81.82%)	21 (58.33%)	***0.006***
HCC	13 (14.94%)	6 (6.67%)	0.810
Infections	36 (40.91%)	10 (27.78%)	0.169
Sarcopenia	15 (17.05%)	5 (13.89%)	0.792
PVT	5 (5.68%)	2 (5.56%)	0.978
HPS	5 (5.68%)	1 (2.78%)	0.671
Lab parameters			
Hemoglobin (g/dL)*	9.45 [8.5 – 10.55]	9.5 [8.35 – 11.15]	0.787
Total Leukocyte count (per cu. Mm.)*	7350 [5150 – 10900]	4550 [3500 – 7600]	***0.002***
Platelet count (per cu. Mm)*	88500 [60000 – 148000]	75500 [51500 – 132000]	0.407
Total Bilirubin (mg/dL)*	3.35 [1.55 – 7.88]	1.54 [0.88 – 3.085]	***<0.001***
Direct bilirubin (mg/dL)*	2.02 [0.96 – 4.75]	0.69 [0.45 – 1.88]	***<0.001***
AST (IU/L)*	78.5 [39 – 136]	44 [33.5 – 60]	***<0.001***
ALT (IU/L)*	35 [21 – 56]	29 [21 – 37]	0.148
ALP (IU/L)*	130.5 [95.5 – 192.5]	112 [92.5 – 151]	0.094
GGT*	64.5 [33 – 110.27]	52.8 [24 – 99]	0.191
Protein (g/dL)*	6.56 [5.96 – 7.01]	6.59 [6.135 – 7.08]	0.793
Albumin (g/dL)*	2.69 [2.32 – 3.09]	3.02 [2.64 – 3.45]	0.004
Prothrombin time (seconds)*	20 [16.5 – 24.8]	16.2 [14.1 – 19.4]	***<0.001***
INR*	1.74 [1.46 – 2.18]	1.41 [1.24 – 1.17]	***<0.001***
Sodium (mEq/L)*	134 [130.5 – 137]	136 [134 – 139]	***0.01***
Potassium (mEq/L)*	4.2 [3.72 – 4.5]	4.3 [3.9 – 4.55]	0.423
Urea (mg/dL)*	33 [22 – 58.5]	35.5 [23.5 – 58.5]	0.914
Creatinine (mg/dL)*	0.9 [0.7 – 1.465]	0.98 [0.68 – 1.21]	0.778
AFP (ng/mL)*	5.6 [1.7 – 181]	3.75 [1.85 – 9.75]	0.654
Liver Disease Severity scores			
CTP*	10 [9 – 12]	9 [8 – 10]	***0.002***
MELD-Na*	22 [16 – 26]	14 [11.5 – 20.5]	***<0.001***
Outcome measures			
3-month Readmission (n, %)	35 (39.77%)	22 (61.11%)	***0.030***
90-day survival (n, %)	51 (76.12%)	28 (87.5%)	0.187
Reason for Readmission			
Ascites (n, %)	17 (48.57%)	8 (36.36%)	0.366
AKI (n, %)	4 (11.43%)	3 (13.64%)	0.805
GI bleed (n, %)	4 (11.43%)	3 (13.64%)	0.805
HE (n, %)	3 (8.57%)	5 (22.73%)	0.239
Hydrothorax (n, %)	0	3 (13.6%)	***0.025***

* - Median [IQR]

Disclosures: Rohit Mehtani: Nothing to Disclose, Ananya Nanda: Nothing to Disclose, Prerna Agarwal:

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Nothing to Disclose, Shankey Garg: Nothing to Disclose, Akash Roy: Nothing to Disclose, Mahendra Rajput: Nothing to Disclose, Suraj Bhagat: Nothing to Disclose, Bhaskar Nandi: Nothing to Disclose

2631 | MIND THE GAP: THE DISCONNECT BETWEEN PERCEIVED AND ACTUAL LIFESTYLE IN MASLD

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Background: Metabolic-associated steatotic liver disease (MASLD) affects nearly 30% of the global population and can progress to steatohepatitis, advanced fibrosis, and hepatocellular carcinoma, posing a growing burden on healthcare systems. Its pathogenesis is strongly associated with modifiable factors such as obesity, physical inactivity, and insulin resistance. As lifestyle modification remains the cornerstone of treatment, this study aims to evaluate the discrepancy between self-reported lifestyle behaviors and objective clinical indicators, focusing on diet and physical activity. **Methods:** This cross-sectional observational study includes individuals with MASLD followed at the outpatient clinic of San Raffaele Hospital (Milan) between June 2024 and April 2025. Participants complete two validated lifestyle questionnaires: the Mediterranean Diet Scoring Tool (MDS) and the International Physical Activity Questionnaire (IPAQ). Clinical data collected include abdominal circumference, BMI, HOMA-IR, liver ultrasound, liver elastography, and Doppler ultrasound of supra-aortic trunks. **Results:** 148 participants are enrolled (108 male, 73%), with a median age of 63 years (range 20–92) and a median BMI of 27 kg/m² (range 16–42). Major comorbidities include type 2 diabetes [38 (26%)], hypertension [78 (53%)], and dyslipidemia [80 (54%)]. Significant alcohol consumption is reported in 52 individuals (35%), with a mean intake of 92 g/week. Steatosis is mild in 57 (40%), moderate in 62 (43%), and severe in 24 (17%). Median liver stiffness is 6.4 kPa (range 4–35), and 70 participants (42%) show signs of atheromasia. MDS scores show low adherence to the Mediterranean diet in 8%, moderate in 44%, and high in 48%. According to IPAQ, 11% are inactive, 30% have low activity, 50% moderate, and 9% high. **Conclusion:** Despite 48% of participants reporting high adherence to the Mediterranean diet and around 60% engaging in at least moderate physical activity, a substantial proportion presents with clinically relevant steatosis, increased liver stiffness, and signs of vascular disease. These findings suggest that self-reported lifestyle questionnaires may not adequately guide interventions, as individuals often overestimate their adherence due to a misperception of healthy behaviors. Addressing this gap may require moving beyond questionnaires alone, incorporating direct clinical assessment to better identify and address lifestyle misperceptions. **Disclosures:** Lorenzo Ciocca: Nothing to Disclose, Francesco Mignone: Nothing to Disclose, Alessia Siribelli: Nothing to Disclose, Sara Menchi: Nothing to Disclose, Federica Invernizzi: Nothing to Disclose

2632 | SPONTANEOUS PROGRESSION AND REGRESSION OF FIBROSIS IN METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS (MASH)

Zobair Younossi[1] Maria Stepanova[1] Brian Lam[2] Daisong Tan[3] Andrei Racila[1] Manirath Shirshord[3] Linda Henry[1] Fatema Nader[4], [1]The Global NASH Council, [2]INOVA Fairfax Hospital, [3]Beatty Liver and Obesity Research Program, Inova Health System, Falls Church, VA, [4]Center for Outcomes Research in Liver Diseases, CORLD

Background: In patients with MASH, fibrosis may increase or spontaneously decrease. The aim was to assess factors associated with progression or regression of fibrosis in patients with MASH. **Methods:** Patients with MASH (N = 1,060; F1: 9%, F2: 20%, F3: 49%, F4: 22%) with two liver biopsies (9-24 months apart) who did not receive specific MASH treatment were included. Fibrosis regression and progression were defined as a decrease or increase of ≥ 1 fibrosis stage or hepatic decompensation in cirrhosis. Clinical and laboratory parameters associated with regression and progression of fibrosis were assessed. **Results:** Over a follow-up of 1.14 ± 0.22 years, 20% of MASH patients experienced fibrosis regression, 62% did not have changes in fibrosis, 18% had progression. Patients with fibrosis regression were younger (54 ± 12 years vs. 57 ± 10 years in unchanged fibrosis, 56 ± 10 years in progressed fibrosis), less likely to have type 2 diabetes (T2D) (54% vs. 65% and 67%, respectively) ($p < 0.05$). Patients with fibrosis regression had lower noninvasive test (NIT) scores at baseline: mean FIB-4 = 1.40 (improved) vs. 2.03 (unchanged) vs. 2.14 (progressed); mean ELF = 9.45 vs. 9.94 vs. 10.0; mean liver stiffness (LS) by transient elastography = 13.2 kPa vs. 16.2 kPa vs. 15.4 kPa (all $p < 0.01$). Patients with fibrosis improvement had the greatest reductions in BMI (mean -0.63 vs. -0.31 vs. -0.10), ALT (-15.3 U/L vs. -8.0 U/L vs. -8.5 U/L), AST (-9.8 U/L vs. -5.7 U/L vs. -3.7 U/L), ALP (-3.4 U/L vs. -1.5 U/L vs. +1.5 U/L), and GGT (-12.2 U/L vs. -7.8 U/L vs. -2.5 U/L) ($p < 0.05$). In multivariate analysis, factors associated with regression of fibrosis were younger age, lower baseline AST and GGT levels, higher baseline platelet count, decreases in AST and ALP, increase in platelet count ($p \leq 0.05$) (Table). Association of fibrosis regression with a decrease in BMI or HbA1c showed a positive trend (OR (95% CI) = 1.08 (0.98-1.18) per -1 kg/

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m^2 and 1.18 (0.93-1.49) per -1%%). In contrast, factors associated with fibrosis progression in F1-F3 were higher baseline AST and HbA1c, an increase in AST from baseline ($p < 0.05$) (Table). Only older age, higher baseline BMI and lower baseline platelet count were associated with decompensation in patients with MASH-F4 (Table). **Conclusion:** Patients with MASH may experience spontaneous regression or progression of fibrosis. Lower baseline or decreasing liver enzymes and possibly a reduction in BMI and HbA1c could explain fibrosis regression in MASH.

Table

Predictor / outcome	OR (95% CI)	p
Fibrosis regression		
Age, per year	0.984 (0.968 - 1.000)	0.0508
Baseline AST, per 1 U/L	0.983 (0.973 - 0.993)	0.0009
Baseline platelet count, per 1 unit	1.006 (1.003 - 1.008)	<.0001
Baseline GGT, per 1 U/L	0.997 (0.994 - 0.999)	0.0153
Change in AST, per 1 U/L	0.982 (0.972 - 0.992)	0.0007
Change in platelet count, per 1 unit	1.006 (1.001 - 1.010)	0.0188
Change in ALP, per 1 U/L	0.987 (0.976 - 0.999)	0.0340
Fibrosis progression (in F1-F3)		
Baseline AST, per 1 U/L	1.013 (1.006 - 1.020)	0.0003
Baseline HBA1C, per 1 %%	1.151 (1.001 - 1.323)	0.0490
Change in AST, per 1 U/L	1.013 (1.006 - 1.021)	0.0002
Decompensation (in F4)		
Age, per year	1.114 (1.019 - 1.219)	0.0182
Baseline BMI, per 1 kg/m^2	1.087 (1.010 - 1.171)	0.0263
Baseline platelet count, per 1 unit	0.970 (0.956 - 0.985)	<.0001

Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, Maria Stepanova: Nothing to Disclose, Brian Lam: Madrigal: Speaking and Teaching, Daisong Tan: Nothing to Disclose, Andrei Racila: Nothing to Disclose, Manirath Shirshord: Nothing to Disclose, Linda Henry: Nothing to Disclose, Fatema Nader: Nothing to Disclose

2633 | ASSESSMENT OF PRIMARY CARE PHYSICIAN MANAGEMENT OF PATIENTS WITH MASLD SINCE THE 2023 DELPHI CONSENSUS STATEMENT

Ariana Stuart[1] Ashley Dotson[1] Katya Swarts[1] Marion Granich[1] Jessica Yeung[1] Arthi Thirumalai[1] Manish Dhyani[1] James Perkins[1] Rotonya Carr[2], [1]University of Washington, [2]University of Washington Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects ~30% of US adults. Despite AASLD management guidelines, confusion remains regarding diagnosis and management. We developed an Artificial Intelligence (AI) algorithm identifying patients meeting MASLD criteria within electronic health records. Our algorithm found only half of these patients had a MASLD-associated ICD diagnosis, with <5% receiving appropriate risk stratification. We aim to increase primary care physician (PCP) comfort and competency of MASLD management with an educational quality improvement (QI) intervention. **Methods:** Our AI algorithm identified 1869 patients meeting MASLD criteria (between January 1, 2022 and December 31, 2023) without associated MASLD-related ICD codes. These patients had 259 unique PCPs within our medical system. We sent PCPs a one-page infosheet on AASLD-based MASLD management guidelines, including risk stratification by FIB-4 and referral for elastography or specialty care. A survey was then sent to assess PCP comfort with, perceived importance of, and effectiveness of the material. Data on baseline fibrosis risk assessment methods used by PCPs were collected. **Results:** 58 PCPs who completed the survey and their 58 patients were included in the study. Risk Stratification: Automatic FIB-4 calculation was able to be performed in 53 patients. 15.1% (n = 8) were intermediate risk for significant fibrosis (FIB-4 $\geq$ 1.3) and 3.8% (n = 2) were high risk (FIB-4 $\geq$2.67). Yet only 5.2% (n = 3) of patients had FIB-4 documented by PCPs. No patients had elastography; one high risk patient was referred to hepatology. Survey Assessment: 7.4% of PCPs felt the information was "completely new", and 33.3% felt it was "somewhat new". 67.3% rated their comfort with risk stratification for MASLD patients as 3/5 or less. Based on ratings of 4/5 or greater, 88.3% were eager to use the educational material and 87.5% felt they would have opportunity to use it; 84.5% felt the material was both effective and would be easy to integrate into practice. **Conclusion:** MASLD is underrecognized in our population, with significant gaps in risk stratification and referral to specialty care. Many PCPs are not familiar with or comfortable implementing guideline-based management, but the majority are motivated to do so and feel it would be easy to integrate into practice.

Disclosures: Ariana Stuart: Nothing to Disclose, Ashley Dotson: Nothing to Disclose, Katya Swarts: Nothing to Disclose, Marion Granich: Nothing to Disclose, Jessica Yeung: Nothing to Disclose, Arthi Thirumalai: Fractyl Health: Grant/Research Support, Novo Nordisk Inc: Grant/Research Support, Novo Nordisk: Consultant, Manish Dhyani: Nothing to Disclose, James Perkins: Nothing to Disclose, Rotonya Carr: Nothing to Disclose

2634 | TEMPORAL TRENDS IN HEPATIC STEATOSIS AND ITS RISK FACTORS AMONG YOUNG ADULTS: A COMPARATIVE COHORT STUDY

Abdullah Alsaeed[1] Khalid Alswat[1] Maram Alkhammash[2] Khaled Alsulaim[1] Ajeed Alrashoud[3] Badr Alhumayyd[1] Rakan Aldoghmani[1] Noura Alkathiri[1] Yazeed Alsulaim[1], [1]Department of Medicine, College of Medicine, King Saud University, [2]Liver Disease Research Center,KSU, [3]Department of Medicine, King Fahad Medical City

Background: The burden of metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly

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shifting to younger populations. However, early-phase data, particularly from low-risk, health-literate groups, remain limited. This study evaluates the temporal changes in hepatic steatosis prevalence and associated risk factors across two independent cohorts of medical students, six years apart. **Methods:** A total of 489 students from King Saud University were enrolled in two cross-sectional cohorts 301 in 2017 and 188 in 2023. All participants underwent non-invasive hepatic assessment via vibration-controlled transient elastography (FibroScan®). Steatosis was defined as CAP $\geq$248 dB/m. Anthropometric indices and lifestyle parameters were collected through standardized protocols and questionnaires. Univariable and multivariable logistic regression models were constructed to identify independent predictors of steatosis. **Results:** The overall prevalence of hepatic steatosis was 21.1%, increasing from 18.6% in 2017 to 25.0% in 2023 ($p = 0.092$). Students with steatosis had significantly higher BMI, waist circumference, and obesity prevalence (all $p < 0.01$). Advanced fibrosis ($\geq$F2) was rare (1.6%). Male sex and central adiposity were strongly associated with steatosis. Strength training showed a protective effect in 2023 cohort (34.8% vs. 69.4%, $p = 0.002$). Fast-food consumption and reduced intake of antioxidant-rich foods were associated with steatosis in univariable analysis but lost significance in adjusted models. On multivariable analysis, a prior self-reported fatty liver diagnosis remained the only independent predictor (aOR = 6.28, 95% CI: 1.14–47.8; $p = 0.042$). **Conclusion:** This dual-cohort analysis reveals a rising burden of hepatic steatosis among young, apparently healthy adults, many of whom exhibited anthropometric features suggestive of metabolic dysfunction. Although advanced fibrosis was rare and MASLD could not be fully diagnosed in all individuals with steatosis due to the absence of laboratory data, these findings underscore the importance of early identification and targeted lifestyle interventions to mitigate long-term MASLD risk.

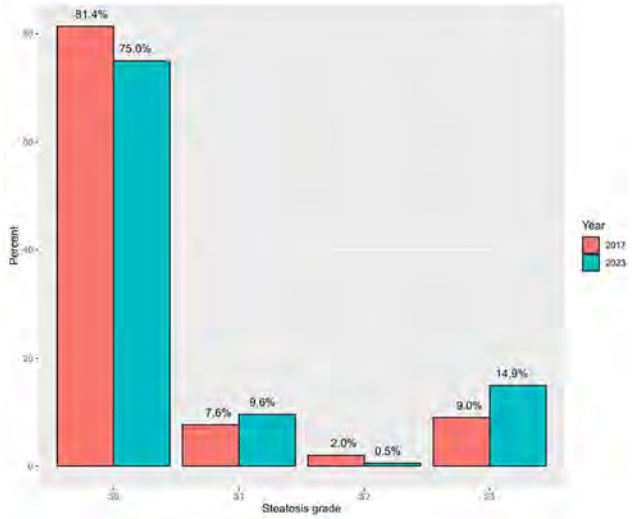

Figure 1: The proportions of steatosis grades based on CAP

Disclosures: Abdullah Alsaeed: Nothing to Disclose, Khalid Alswat: Nothing to Disclose, Maram Alkhammash: Nothing to Disclose, Khaled Alsulaim: Nothing to Disclose, Ajeed Alrashoud: Nothing to Disclose, Badr Alhumayyd: Nothing to Disclose, Rakan Aldoghmani: Nothing to Disclose, Noura Alkathiri: Nothing to Disclose, Yazeed Alsulaim: Nothing to Disclose

2635 | HYPERTENSION ASSOCIATED WITH THE RISK OF FEMALE REPRODUCTIVE SYSTEM CANCERS IN MASLD POPULATION

Xinyue Zhao[1] Yuchao Lu[1] Feng Xue[1] Shanshan Wang[2] Haiyun Ding[2] Shuangqing Gao[2] Ming Yang[1] Lai Wei[1], [1]Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, [2]Beijing North Medical & Health Economic Research Center

Background: Female reproductive system cancers have been confirmed that associated with metabolic dysfunction-associated steatosis liver disease (MASLD). We aimed to investigate the association of five cardiometabolic risk factors, as well as liver fibrosis, and female reproductive system cancers in the MASLD population. **Methods:** The MASLD population and those with comorbid female reproductive system cancers-including ovarian cancer, cervical cancer, endometrial cancer-were derived from a hospital-based database across 11 canters in Chinese nationwide, according to MASLD and female reproductive system cancers diagnostic criteria based on keywords and ICD-10 codes. Logistic regression was used to estimate odds ratio (OR) and 95% confidence interval (CI) between risk factors and female reproductive system cancers. **Results:** Totally 36,231 female MASLD individuals were identified with 631 cases diagnosed female reproductive system cancers. The primary outcome showed that diagnosed hypertension (OR 1.35, 95%CI:1.12,1.63) and its combination with hyperglycemia (OR 1.93, 95%CI 1.53,2.43) significantly associated with female reproductive system cancers in MASLD population. Diagnosed type 2 diabetes (OR 1.50, 95%CI: 1.25,1.81), fasting glucose 5.6-6.9mmol/L (OR 1.28,95%CI:1.00,1.63) and menopause (OR 1.92,95%CI:1.38,2.68) associated with the risk of the cancers respectively as well. MASLD population aged 35 to 65, FIB-4 over 1.3, between 1.3-2.67, over 2.67, over 3.48 were associated with approximately 1.5-fold,1.96-fold, 1.62-fold risky possibilities of the cancers compared with FIB-4 less than 1.3, which was consistent with aged over 65 whose FIB-4 over 2 5-fold associated with the risk in MASLD population. **Conclusion:** Hypertension and its combination with hyperglycemia, menopause and elevated FIB-4

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associated with female reproductive system cancers in MASLD population.

Disclosures: Xinyue Zhao: Nothing to Disclose, Yuchao Lu: Nothing to Disclose, Feng Xue: Nothing to Disclose, Shanshan Wang: Nothing to Disclose, Haiyun Ding: Nothing to Disclose, Shuangqing Gao: Nothing to Disclose, Ming Yang: Nothing to Disclose, Lai Wei: Nothing to Disclose

★ 2636 | PHENOTYPIC AND METABOLIC FEATURES OF MASLD IN CENTRAL ASIAN POPULATIONS LIVING IN MODERATE-ALTITUDE HYPOXIA

Nurgul Toktogulova[1], [1]Kyrgyz State Medical Academy

Background: Metabolic dysfunction-associated fatty liver disease (MASLD) is one of the leading causes of chronic liver disease globally. Its clinical manifestations vary widely depending on ethnicity, lifestyle, and environmental conditions. Among ethnic residents of Central Asia living at moderate altitudes, the effects of hypobaric hypoxia on metabolic processes remain understudied. **Methods:** The study included 733 individuals living at low altitudes (750–800 m above sea level; n = 319: control = 36, with MASLD = 283) and moderate altitudes (2046–2300 m; n = 414: control = 24, with MASLD = 392) in Kyrgyzstan. Clinical assessments included BMI, waist circumference, body composition via bioimpedance analysis, lipid and glucose metabolism markers, cytokine profile (IL-6, TNF-α), and cytosolic ATP levels. Liver fibrosis stage was determined using elastography. **Results:** Among Kyrgyz patients with MASLD, 25% exhibited the so-called "lean phenotype," with BMI < 23 kg/m² (Asian criteria), but pronounced visceral adiposity. This group showed notable insulin resistance, hypertriglyceridemia, and decreased HDL levels. Hypobaric hypoxia modulated transaminase levels and reduced cytolytic activity in patients without T2DM. However, in individuals with coexisting MASLD and T2DM, fibrosis progression (≥F2 METAVIR) was significantly accelerated. Levels of IL-6 and TNF-α positively correlated with the degree of steatosis and fibrosis. The results indicate that MASLD in ethnic Central Asians living in moderate-altitude hypoxia displays phenotypic variability and dissociation between body weight and metabolic abnormalities. Hypoxia appears to reduce biochemical markers of cytolysis, potentially masking active disease. When combined with T2DM, this effect is overridden, necessitating distinct clinical strategies. The use of inflammatory markers and functional tests alongside elastography is recommended for more accurate assessment of liver damage. **Conclusion:** • MASLD in Central Asian populations frequently presents with a normal-weight phenotype yet marked metabolic dysfunction. • Hypobaric hypoxia modulates cytolytic activity but does not prevent fibrosis in the presence of T2DM. • Comprehensive diagnostics that consider ethnic and geographic context can help identify subclinical forms of MASLD.

Disclosures: Nurgul Toktogulova: Nothing to Disclose

2637 | PREVALENCE OF AT-RISK MASLD IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Martin Kluge[1] Gregor Wilken[1] Jakob Weglage[1] Jana Knorr-Klocke[1] Frank Tacke[1] Münevver Demir[2], [1]Charité - Universitätsmedizin Berlin, [2]Charité - Universitätsmedizin

Background: Globally, the prevalence of MASLD is high and likely to continue to rise. A key challenge for healthcare providers is to identify those patients with at-risk MASLD (fibrosis grade F ≥ 2) to provide them with specialized care. The European and American guidelines do not recommend the comprehensive screening of the general population but recommend the case-finding in individuals with risk factors, such as type 2 diabetes (T2D). The aim of this study is to evaluate the prevalence of at-risk MASLD in T2D patients without previously known MASLD. **Methods:** Between March 2023 and February 2025, 1008 patients were referred from primary care and/or diabetology practices to our hepatology outpatient clinic to test for MASLD. For n = 432 patients with T2D lab values and medical history were available. To identify at-risk MASLD (F ≥ 2) in T2D we used vibration controlled transient elastography (VCTE, Fibroscan®) for liver stiffness measurement (LSM), FIB-4 and FAST score, as independent non-invasive tests (NITs). Patients were ruled-in for the assumption of at-risk MASLD when LSM indicated significant fibrosis (LSM ≥ 8.0 kPa), FIB-4 ≥ 1.3 for age ≤ 65 and FIB-4 ≥ 2.0 for age > 65, as well as FAST ≥ 0.67. **Results:** In the cohort of T2D patients 30.32% (n = 131) were ruled out by each NIT. 69.68% (n = 301) of the study population were ruled in by at least one of the NITs (LSM: 54,86%, n = 237; FIB-4 48.61%, n = 210; FAST 28.70%, n = 131). Among these patients, 15.51% (n = 67) were ruled in only by LSM, 14.12% (n = 61) were ruled in only by FIB-4 and only 0.69% (n = 3) were ruled in by FAST alone. 4.86% (n = 21) were ruled in by a combination of FAST and LSM, whereas 11.34% (n = 49) were ruled in by a combination of FIB-4 and LSM. A large proportion of patients were classified by all 3 tests as at-risk MALSD (23.15%; n = 100). Those patients have the highest likelihood of being at risk with MASLD and a fibrosis stage F ≥ 2. **Conclusion:** Using a combination of NITs the prevalence of at-risk MASLD in T2D is estimated to be 23.15%. The high prevalence in T2D emphasizes the need for routine case-finding for at-risk MASLD in individuals with cardiometabolic risk factors.

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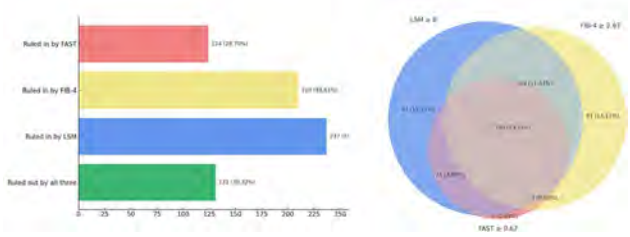
Figure 1: Estimation of at-risk MASLD in T2D patients by LSM, FIB-4 and FAST

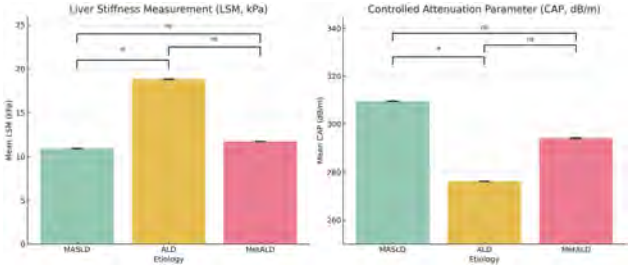


Disclosures: Martin Kluge: Nothing to Disclose, Gregor Wilken: Nothing to Disclose, Jakob Weglage: Nothing to Disclose, Jana Knorr-Klocke: Nothing to Disclose, Frank Tacke: Nothing to Disclose, Münevver Demir: Echosens: Grant/Research Support

2638 | PHENOTYPIC DIFFERENCES BETWEEN ALD AND MASLD: INSIGHTS FROM A VETERAN COHORT USING REVISED SLD CRITERIA- A RETROSPECTIVE STUDY

Thanita Thongtan[1] Navila Sharif[1] Anand Shah[2] Thuy-Van Hang[1], [1]Emory University School of Medicine, [2]Joseph Maxwell Cleland Atlanta VA Medical Center

Background: Steatotic liver disease (SLD) remains a major global health issue. In December 2023, a multi-society Delphi consensus redefined SLD categories, introducing Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), Alcohol-Associated Liver Disease (ALD), and a new overlapping subtype, MetALD (MASLD with increased alcohol intake). This shift enables better phenotyping of liver disease, but comparative data on ALD, MetALD, and MASLD under this new framework remain limited. **Methods:** We retrospectively analyzed adult patients with non-viral SLD who had abnormal FibroScan at the our Vetarans Affairs Medical Center between November 2017 and February 2024. Liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) were compared among ALD, MASLD, and MetALD groups using one-way analysis of variance (ANOVA). **Results:** Out of 262 patients (mean age 62.5 years; 87.8% male), ALD patients had significantly higher LSM values than MASLD patients (18.82 vs 10.95 kPa, $p = 0.003$). In contrast, MASLD patients had significantly higher CAP values than ALD (309.6 vs 276.3 dB/m, $p < 0.001$) [Figure1]. There was no significant different with LSM or CPAP when comparing MetALD to MASLD or ALD groups. **Conclusion:** Our study revealed distinct phenotypic differences between ALD and MASLD. ALD patients demonstrated significantly higher liver stiffness measurements (LSM), consistent with a greater fibrosis burden, while MASLD patients had higher controlled attenuation parameter (CAP) values, indicating more pronounced steatosis. These differences may reflect underlying pathophysiology—alcohol-related steatohepatitis and inflammation in ALD, versus insulin resistance and chronic metabolic stress in MASLD. Prior studies support these findings, noting transient elastography (TE) overestimates fibrosis in ALD due to inflammatory activity, and artificial intelligence-powered histologic analysis has identified structural differences in fibrosis architecture between the two. Additional histologic comparisons show steatosis is more severe and centrally distributed in MASLD, aligning with our CAP results. Together, these data highlight the value of noninvasive tools in distinguishing SLD subtypes under the revised nomenclature.



Disclosures: Thanita Thongtan: Nothing to Disclose, Navila Sharif: Nothing to Disclose, Anand Shah: Nothing to Disclose, Thuy-Van Hang: Nothing to Disclose

2639 | ROLE OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) AS A RISK FACTOR FOR HEPATOCELLULAR CARCINOMA (HCC) DEVELOPMENT

Samantha Clark[1] Yestle Kim[2] Erik Zuk[1] Arushi Chadha[1] Robert Gish[3], [1]Medicus Economics, LLC, [2]Madrigal Pharmaceuticals Inc, [3]Robert G Gish Consultants LLC

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide. Metabolic dysfunction-associated steatohepatitis (MASH), has become one of the fastest growing risk factors of HCC in the US. While clinical evidence indicates that MASH predisposes an individual to HCC development, the strength and relative impact of this relationship with respect to other underlying etiologies is less well understood. **Methods:** A matched case-control study was conducted using SEER-Medicare linked data from October 2015 through December 2020. Eligible controls (non-HCC cases) were matched to cases using k:1 exact matching without replacement based on birth year, race/ethnicity, and sex. Control

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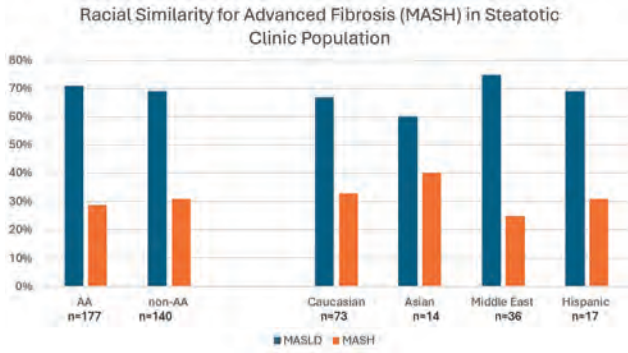
index date was assigned as the HCC diagnosis date of their matched case. MASH was defined using the K75.81 ICD-10 code, with exposure status ascertained during the 36-months prior to a patient's index date. This interval additionally served as the washout and baseline period for covariate measurement and application of inclusion/exclusion criteria. Logistic regression with robust standard errors was used to calculate adjusted odds ratios (OR) and 95% confidence intervals (CI) controlling for matching factors (race/ethnicity, sex, birth year) and obesity, diabetes, cirrhosis, and index year. **Results:** A total of 4,875 HCC cases were matched to 5,030 controls from a 5% random subsample of non-cancer Medicare beneficiaries. Exposure status was heavily skewed, with MASH identified in 5% of HCC cases and only 0.1% of non-cancer controls. MASH was found to be significantly associated with a 4.88-fold (95% CI: 1.36 - 17.5, $p < 0.001$) increase in the odds of HCC development relative to non-MASH patients over the study period. **Conclusion:** In this analysis, clinically rich SEER-Medicare data were used to generate additional insight into the relationship between MASH and HCC development. Results suggesting that MASH patients are at a higher risk of HCC relative to patients with other precipitating liver conditions highlight the importance of expanded surveillance and effective treatment in reducing the clinical burden of HCC in the MASH population.

Disclosures: Samantha Clark: Madrigal Pharmaceuticals Inc: Consultant, Yestle Kim: Nothing to Disclose, Erik Zuk: Nothing to Disclose, Arushi Chadha: Nothing to Disclose, Robert Gish: please see full disclosures document: Consultant

2640 | RACIAL DISPARITY IN MASLD/MASH USING A PREDOMINANTLY AFRICAN AMERICAN ACADEMIC MEDICAL CENTER

Sriraj Atluri[1] Michael Mello[1] Reema Smadi[1] Abigail Limary[1] Cyra Kharas[1] Izabel Thomas[1] Astha Saini-Goeman[2] Paul Naylor[1] Milton Mutchnick[1], [1]Wayne State University School of Medicine, [2]Wayne Statw University School of Medicine

Background: African Americans (AA) are reported to have a lower MASLD (Metabolic dysfunction Associated Steatotic Liver Disease) incidence as compared to non-AA individuals, but two recent meta-analysis studies suggest only moderate overall differences (Cau = 12-14% vs AA = 11-13%). Due to the variability in data and under representation of AA in the literature, evidence with respect to severity of disease manifestation and racial disparity remain elusive. This study evaluates racial disparity using a predominant AA clinic population and defined MASLD/MASH criteria. **Methods:** ICD-10 codes K76.0 and K75.8 identified MASLD/MASH patients seen between 2017 and 2023. Imaging defined steatosis was available for 85% of the 317 patients with the remaining having documented cardiometabolic risk factors, such as obesity, diabetes and lipidemia. Only 61% had a GI visit and 15% had missing laboratory information. Patients were defined as MASH (Metabolic disfunction Associated Steatohepatitis) if significant fibrosis (F2-4) was present as defined by at least one laboratory result (NAFLD Fibrosis Score (NFS), Fib-4 or APRI, FibroSure) or FibroScan (kPa > 14). **Results:** MASLD/MASH patients were racially similar between AA (56%) and non-AA (44%) with 64% being female. The majority were MASLD (60%; n = 187), with 25% MASH (n = 79). As shown in Figure 1, for the 266 patients with Fibrosis evaluation, there was no difference in the proportion of MASH patients in AA vs non-AA. When evaluated by racial sub-categories there was also no variation. With respect to the issue of defining MASH, NAFLD Fibrosis Score yielded higher levels of advanced fibrosis (14%) as compared to FIB-4 (5%) and APRI (8%). While FibroScan (50% Advanced Fibrosis) and FibroSure (55% Advanced Fibrosis) scored higher, only 31 patients were evaluated (31/317 = 10%) as compared to NFS patients where the results were available for the most patients (255/317 = 80%). **Conclusion:** Consistent with the literature, although the clinic's population was 80% AA, MASLD/MASH rates among AA were only slightly higher compared to non-AA. The primary observation of this study is that if AA patients are diagnosed with MASLD (liver steatosis on imaging or metabolic disease) they are at similar risk for developing advanced fibrosis (MASH) as non-AA individuals (30%). Given the similar risk of MASH regardless of race, the importance of referral to GI for evaluation of advanced fibrosis needs to be emphasized.



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2641 | HIGH RISK OF OBSTRUCTIVE SLEEP APNEA (OSA) AMONG ADULTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD): INSIGHTS FROM THE GENESIS STUDY USING THE BERLIN QUESTIONNAIRE

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Background: MASLD is closely associated with obesity, diabetes, and metabolic syndrome. Sleep disturbances, especially OSA, have been increasingly implicated in the pathogenesis and progression of metabolic diseases, including MASLD. This study aimed to assess and compare the prevalence of high OSA risk among adults with and without MASLD in a large, population-based cohort from Saudi Arabia using the Berlin Questionnaire, a validated screening tool for identifying individuals at risk of OSA. **Methods:** Data were drawn from the GENESIS study, a prospective, population-based cohort conducted in three major regions of Saudi Arabia. MASLD was defined by transient elastography (FibroScan®) with a controlled attenuation parameter (CAP) $\geq$268 dB/m plus $\geq$1 cardiometabolic risk factor. Between March 2024 and April 2025, participants underwent clinical assessment for MASLD and completed the Berlin Questionnaire, which categorizes OSA risk into three symptom domains: snoring/apnea (Category 1), fatigue/sleepiness (Category 2), and body mass index (BMI) $>$30 kg/m² or hypertension (Category 3). BMI was assessed through direct clinical measurements; all other responses were self-reported, in accordance with the questionnaire structure. High OSA risk was defined as positive scores in $\geq$2 categories. Differences between MASLD and non-MASLD groups were analyzed using chi-square and t-tests. **Results:** Of 2,073 adults, 829 had MASLD and 1,244 did not. High OSA risk was significantly more prevalent among participants with MASLD than those without (35.6% vs. 16.7%, $p<0.001$). Category 1 (snoring/apnea) was positive in 29.4% of participants with MASLD compared to 16.4% in the non-MASLD group ($p<0.001$), and Category 3 (BMI/hypertension) was positive in 73.1% vs. 39.7%, respectively ($p<0.001$). No significant difference was observed in Category 2 (fatigue/sleepiness) (21.8% vs. 19.4%, $p=0.19$). Self-reported OSA diagnosis was low and similar in both groups (3.1% vs. 2.5%, $p=0.46$) (Table 1). **Conclusion:** Adults with MASLD exhibited a significantly higher prevalence of Berlin Questionnaire–defined OSA risk, primarily driven by increased rates of elevated BMI/hypertension and snoring/apnea symptoms. The low rate of self-reported OSA diagnosis suggests potential under-recognition in this population. These findings support the integration of sleep disorder screening into MASLD management. Early identification of OSA risk may offer critical opportunities for intervention to prevent disease progression.

Table 1: Sleep habits and Berlin questionnaire scores by MASLD status in the GENESIS cohort.

Variable	MASLD (n=829)	No MASLD (n=1244)	P-value
Sleeping hours (weekdays), mean ± SD	6.5 ± 1.3	6.5 ± 1.3	0.99
Sleeping Hours (weekend), mean ± SD	6.7 ± 1.3	6.8 ± 1.3	0.09
Sleep apnea (OSA), n (%)	26 (3.1%)	31 (2.5%)	0.46
Berlin Category 1, n (%)	244 (29.4%)	204 (16.4%)	<0.001
Berlin Category 2, n (%)	181 (21.8%)	241 (19.4%)	0.19
Berlin Category 3, n (%)	606 (73.1%)	494 (39.7%)	<0.001
High OSA risk (≥2 positive Berlin categories), n (%)	295 (35.6%)	208 (16.7%)	<0.001

Note: Berlin Questionnaire categories—Category 1: snoring/apnea; Category 2: fatigue/sleepiness; Category 3: BMI >30 kg/m² or hypertension. High risk for OSA is defined as a positive score in two or more categories.
Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; OSA, obstructive sleep apnea; SD, standard deviation; BMI, body mass index.

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2642 | MUSCLE QUALITY, DEFINED BY LOW MUSCLE VOLUME AND MUSCLE FAT INDEX ON MRI, IS WORSE IN DECOMPENSATED NASH CIRRHOSIS, BUT NOT IN COMPENSATED MASH CIRRHOSIS

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Background: Muscle health is often stated to be poor in patients with MASH cirrhosis; however, rigorous interrogation of muscle quality in MASH cirrhosis is lacking. We investigated skeletal muscle characteristics via MRI and their relation to health-related quality of life (HR-QoL) and frailty in MASH cirrhosis. **Methods:** 75 Individuals with MASH cirrhosis were prospectively investigated for their muscle quality, HR-QOL, and frailty. Muscle quality was determined by muscle volume index (MVI) which captures fat-free muscle mass and muscle fat index (MFI) which encompasses T2-corrected fat by AMRA® MAsS, a specialized neck-to-knee rapid MRI protocol. Myosteatosis was defined as thigh MFI >1.25 pp in males and >1.31 pp in females. Low muscle volume (LMV) was defined as thigh MVI <-0.67SD in males and <-0.68SD in females. Frailty was determined using Liver Frailty Index (LFI) and HR-QoL by CLDQ. Muscle quality of this cohort (stratified by decompensation status) was compared to two control groups: 39,804 general population and 160 non-cirrhotic MALD. Further, we also examined the frequency of sarcopenia in our cohort via DEXA based on European Working Group on Sarcopenia in Older people 2 (EWGSOP2) criteria. **Results:** Of 75 individuals with MASH cirrhosis, 45% were decompensated, 59% female, mean age 62 $\pm$ 7 years, mean BMI 35 $\pm$ 6 kg/m^2, and mean MELD3.0 of 11.5 $\pm$ 4.7. LMV was seen in 45%, myosteatosis in 36% and frailty in 32% (Table1 Panel A). A higher proportion of decompensated cirrhotics had LMV (59% vs 34%, $p=0.03$), lower HR-QoL (38% vs 15%, $p=0.02$), and frailty (53% vs 15%, $p=0.002$). Compared to general population and MASLD controls, MVI and MFI were significantly different in decompensated cirrhosis, but not in those with compensated cirrhosis (Table1, Panel B). Interestingly, no one in our cohort met the EWGSOP2 definition for sarcopenia (appendicular lean mass/height^2 cutoffs <7Kg/m^2 (males) or <5.5Kg/m^2 (females)). Low muscle volume was associated with poor HR-QoL ($b=0.65$, 95% CI:0.43 – 0.98, $p=0.04$) and LFI ($b=1.99$, 95% CI:1.03 - 3.87, $p=0.04$), after adjusting for age, sex and MELD3.0. **Conclusion:** Muscle quality, defined by low muscle volume and muscle fat index on MRI, is worse in decompensated MASH cirrhosis, but is relatively preserved in compensated MASH cirrhosis. Low muscle volume is significantly associated with poor quality of life and greater frailty. DXA underestimates sarcopenia in MASH cirrhosis.

Panel A: Baseline characteristics of MASH Cirrhosis cohort stratified by decompensation

	Entire Cohort N=75 N (%) or Mean ± SD	Decompensated N=34 N (%) or Mean ± SD	Compensated N=41 N (%) or Mean ± SD	P-value
MELD 3.0	11.5 ± 4.7	15 ± 5	9 ± 3	<0.001
Muscle Volume Index by MRI	-0.75 ± 1.17	-1.3 ± 1.14	-0.4 ± 1.05	0.002
Muscle Fat Index by MRI	1.03 ± 2.98	2.2 ± 2.3	0.2 ± 2.3	0.008
Low Muscle Volume, n(%)*	36 (48%)	20 (59%)	14 (34%)	0.03
Myosteatosis, n(%)*	27 (36%)	16 (47%)	11 (27%)	0.07
Adverse Muscle Composition, n(%)*	19 (25%)	13 (38%)	6 (15%)	0.02
Liver Frailty Index	4.3 ± 0.9	4.6 ± 0.9	4.0 ± 0.7	0.002
Frailty (LFI ≥ 4.5)	24 (32%)	18 (53%)	6 (15%)	0.002
CLDQ total score	4.8 ± 1.3	4.2 ± 1.3	5.2 ± 1.2	<0.001

Panel B: Muscle Volume Index and Muscle Fat Index in compensated and decompensated cirrhosis, compared to general population and non-cirrhotic MASLD

	General Population (n=39,804)	MASLD non-cirrhotic (N=160)	MASLD with compensated cirrhosis (N=41)	MASLD with decompensated cirrhosis (N=34)
Muscle Volume Index	0.1 ± 0.98	0.2 ± 1.02 p=NS vs. gen population	-0.4 ± 1.1 p=NS vs. gen population or non-cirrhotic MASLD	-1.3 ± 1.14 p<0.01 vs all other groups
Muscle Fat Index	0.27 ± 1.81	-0.21 ± 1.96 p=0.04 vs. gen population	0.2 ± 2.3 p=NS vs. gen population or non-cirrhotic MASLD	2.2 ± 2.3 p<0.01 vs all other groups

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◆ 2643 | IMPLEMENTATION OF A WECHAT MINI-PROGRAM-DRIVEN LIFESTYLE INTERVENTION AMONG OVERWEIGHT OR OBESE INDIVIDUALS WITH METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE

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Background: Weight loss is the standard recommendation for patients with metabolic dysfunction-associated fatty liver disease (MAFLD), but its successful implementation is difficult in practice. Digital lifestyle interventions may provide an efficient and scalable solution to enhance patient self-management. This study aimed to assess the effects of a WeChat mini-program-delivered lifestyle intervention on weight loss and hepatic steatosis among overweight or obese individuals with MAFLD. **Methods:** Overweight or obese adults with clinically diagnosed MAFLD with transient elastography examination were enrolled in this prospective randomized controlled trial. Patients were randomly assigned to receive either WeChat mini-

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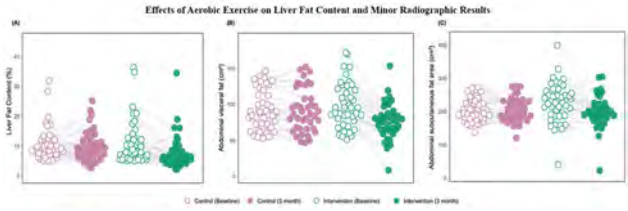
program management (intervention group) or standard care (control group) at a 1:1 ratio. Body weight and clinical parameters were assessed at baseline and then at 6 months. **Results:** Among the 89 included MAFLD patients, 60.0% achieved ≥5% weight loss, and 24.4% had ≥10% weight loss in the intervention group, which were greater than those in the control group ($P < 0.05$). Importantly, patients receiving the intervention were significantly more likely to achieve a ≥10% controlled attenuation parameter (CAP)reduction or CAP normalization than those in the control group were (57.8% vs. 31.8%, $P < 0.05$). In parallel, the intervention group presented greater reductions in liver enzymes (ALT, AST, and GGT) and metabolic parameters (fasting insulin, HbA1c, TG, and HDL-C) than the control group ($P < 0.05$). According to the fibrosis assessment, only the FibroScan-aspartate aminotransferase (FAST) score decreased more in the intervention group than in the control group ($P < 0.05$). No significant difference was found in the liver stiffness measurement (LSM) values or noninvasive scores (APRI, FIB-4, NFS, and Agile 3+) between the groups ($P > 0.05$). **Conclusion:** Digital lifestyle coaching via a WeChat mini-program demonstrates efficacy in enhancing weight reduction, improving hepatic steatosis, and ameliorating metabolic disorders, offering novel perspectives regarding the practicality and therapeutic value of digital tools in managing MAFLD through behavioral interventions.
Disclosures: CHAO SUN: Nothing to Disclose

2644 | EFFECTS OF AEROBIC EXERCISE ON LEAN NON-ALCOHOLIC FATTY LIVER DISEASE: A RANDOMIZED CLINICAL TRIAL

Ci Song[1] Chengxiao Yu[2] Pei Qin[2] Wentao Yao[1] Siyu Wang[1] Xuanyu Chen[1], [1]Nanjing Medical University, [2]The First Affiliated Hospital of Nanjing Medical University

Background: Exercise represents a remarkably cost-effective lifestyle intervention for preventing and treating non-alcoholic fatty liver disease (NAFLD). However, the benefits of exercise in lean NAFLD patients remains incompletely understood. In this study, we conducted a 3 months aerobic exercise to assess the multifaceted effects of exercise on lean NAFLD. **Methods:** 100 participants of lean NAFLD (BMI < 24) were randomly assigned to either the aerobic exercise (n = 50) or control group (n = 50). The aerobic exercise group underwent high-intensity exercise training three times per week (60 minutes per session), while the control group maintained their usual physical activity levels. The primary outcome was the difference between the two groups in the change from baseline in liver fat content (LFC) at 3 months. The secondary outcomes included changes in body weight, waist circumference, body fat, body lean mass, metabolic risk factors, blood pressure, lipids, glucose levels, insulin resistance, and beta cell function. The trial is registered at ClinicalTrials.gov (NCT0148027). **Results:** By intention-to-treat analysis, the mean LFC change from baseline to 3 months was -2.71% (95% confidence interval [CI], -4.23% to -1.19%; P = 0.001) in the intervention group and -0.59% (95 CI, -2.32% to 1.14%; P = 0.505) in the control group, with a mean between-group difference (of intervention vs control) of -2.11 (95% CI -3.14 to -1.10; P < 0.001). Among the secondary outcomes, there were greater reductions in Abdominal visceral fat and Abdominal subcutaneous fat area in the exercise group compared with controls, with significant between-group differences of -14.22 (95% CI -20.01 to -8.42; P < 0.001), and -22.82 (95% CI -32.32 to -13.33; P < 0.001), respectively. No adverse events were noted in either study group. **Conclusion:** Over 3 months, aerobic exercise alleviates LFC and other relevant clinical phenotypes among lean-NAFLD patients. Our study identifies the benefits of aerobic exercise in patients with lean NAFLD.



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2645 | IMPACT OF LIVER HISTOLOGY AND MASLD-ASSOCIATED GENETIC VARIANTS ON INSUFFICIENT WEIGHT LOSS AFTER BARIATRIC SURGERY

Felice Cinque[1] Sara Badiali[2] Marica Meroni[1] Miriam Longo[1] Erika Paolini[1] Elisa Galfrascoli[2] Giovanna Oberti[1] Giuseppina Pisano[1] Emma Calzavara[1] Annalisa Cespiati[1] Luigi Boni[2] Anna Ludovica Fracanzani[3] Paola Dongiovanni[4] Rosa Lombardi[5], [1]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy, [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [3]University of Milan, [4]SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, [5]University of the Study of Milan

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is now the leading global

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cause of liver disease, closely linked to rising rates of obesity and diabetes. In Europe, no pharmacological treatment is approved; thus, weight loss remains the only effective option, with bariatric metabolic surgery (BMS) being the most durable intervention. However, a substantial proportion of patients experience insufficient weight loss (IWL), limiting liver-related benefits. While IWL is associated with demographic, metabolic, and psychological factors, the role of MASLD and genetics remains poorly defined. **Methods:** We retrospectively analyzed patients undergoing BMS (2008–2023) at Policlinico Hospital of Milan with intraoperative liver biopsy and 12–18 month weight follow-up. IWL was defined according to Reinhold criteria: $<50\%$ excess weight loss or BMI >35 kg/m² at 12–18 months. MASLD ($>5\%$ steatosis), MASH (NAFLD Activity Score ≥ 3), and significant fibrosis (stage ≥ 2) were histologically diagnosed. Genotyping for MASLD-related variants (PNPLA3, TM6SF2, GCKR, HSD17B13) and insulin resistance (IRS1) was performed. **Results:** Among 308 patients (77.9% female; median BMI 42.1 kg/m²), MASLD was present in 84.7%, MASH in 50.1%, and significant fibrosis in 7.5%. IWL occurred in 29.5%, and was more frequent in patients undergoing gastric banding (75.8% vs 24.2%) and with higher preoperative BMI (46.3 vs 40.9 kg/m², $p < 0.001$) and higher prevalence of hypertension (54.1% vs 29.5%, $p = 0.008$). Notably, IWL occurred most frequently in patients with baseline significant fibrosis (12.1% vs 5.6%, $p = 0.048$). In 109 genotyped patients, IWL was less frequent in carriers of the IRS1 rs2972146 T allele (78% vs 95%, $p = 0.009$), while other variants showed no significant association. On multivariable analysis, higher preoperative BMI and gastric banding remained independently associated with IWL, while the IRS1 T allele was protective (Table). **Conclusion:** In this well-characterized bariatric cohort with integrated liver histology and genetic profiling the prevalence of MASLD, MASH, and significant fibrosis was notably high. IWL affected nearly one-third of patients and was independently associated withgastric banding and higher baseline BMI, but not with underlying liver comorbidities. Notably, the IRS1 genetic variant—implicated in insulin signalling and adiposity regulation—was found to be protective against IWL, highlighting the potential influence of insulin pathways on post-BMS outcomes. Given the central role of weight reduction in the management of MASLD, particularly in individuals with obesity, identifying predictors of suboptimal response to bariatric surgery is critical to improving long-term hepatic and metabolic outcomes.

Table: Multivariable logistic regression analysis of factors associated with IWL

Variable	Odds Ratio	95% CI	p-value
Male Sex	1.46	0.31–6.98	0.63
Age	1.01	0.96–1.06	0.80
Hypertension	1.31	0.45–3.84	0.62
Significant fibrosis (≥F2)	0.71	0.13–3.91	0.70
Preoperative BMI	**1.22**	**1.11–1.34**	**<0.001**
Gastric banding	**16.61**	**3.79–72.87**	**<0.001**
IRS1 rs2972146 T allele	**0.18**	**0.04–0.81**	**0.03**

Disclosures: Felice Cinque: Nothing to Disclose, Sara Badiali: Nothing to Disclose, Marica Meroni: Nothing to Disclose, Miriam Longo: Nothing to Disclose, Erika Paolini: Nothing to Disclose, Elisa Galfrascoli: Nothing to Disclose, Giovanna Oberti: Nothing to Disclose, Giuseppina Pisano: Nothing to Disclose, Emma Calzavara: Nothing to Disclose, Annalisa Cespiati: Nothing to Disclose, Luigi Boni: Nothing to Disclose, Anna Ludovica Fracanzani: Nothing to Disclose, Paola Dongiovanni: Nothing to Disclose, Rosa Lombardi: Nothing to Disclose

2646 | A SYSTEMATIC REVIEW OF THE EFFECTIVENESS OF LIFESTYLE INTERVENTIONS IN IMPROVING LIVER HEALTH FOR PATIENTS WITH STEATOTIC LIVER DISEASE

Laura Temperley[1] Stephanie Landi[2] Fanyi Su[2] Tonia Momoh[2] Varinder Athwal[2] Gabriel Rogers[2], [1]Barts Health Trust, UK, [2]University of Manchester, UK

Background: Steatotic liver disease (SLD), which includes alcohol-related liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD), and metabolic and alcohol-related steatotic liver disease (MetALD), is a widespread condition with few treatment options. Although global guidelines recommend lifestyle interventions, the definitive evidence supporting their effectiveness in improving liver outcomes is limited. This systematic review aims to evaluate the impact of lifestyle interventions on clinical outcomes in patients with SLD, while identifying key areas for future research. **Methods:** A systematic review was conducted, including randomized controlled trials (RCTs) for MASLD and MetALD populations and both RCTs and cohort studies for ALD populations. A protocol was registered with PROSPERO (CRD42024516755). We searched MEDLINE and Embase to identify studies comparing lifestyle interventions with usual care in SLD populations, with two reviewers performing the screening. The risk of bias was assessed using RoB-2 and ROBINS-I tools.

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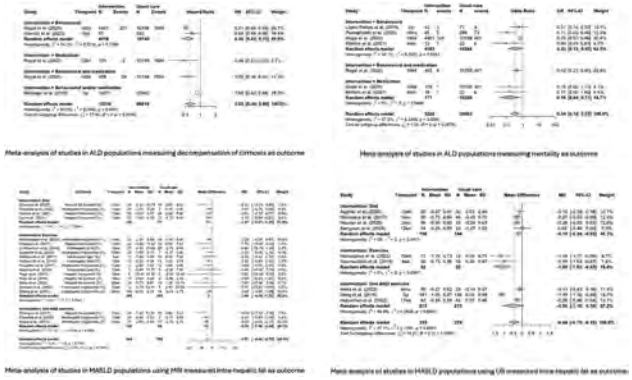
Random-effects meta-analyses were performed for various outcomes, stratified by intervention type. Findings were summarized using the GRADE approach. **Results:** 47 studies were included, with 38 focusing on MASLD populations, eight on ALD populations, and one in a MetALD population, comprising 3,696 participants in MASLD groups and 103,127 participants in ALD groups. Meta-analyses showed statistically significant pooled effects favouring interventions for MRI/1H-MRS, ultrasound, and histology-measured outcomes in MASLD populations, as well as cirrhotic decompensation and mortality outcomes in ALD populations. Only the meta-analysis of MRI/1H-MRS showed low heterogeneity, with a mean difference of −3.37 percentage points [95% CI −4.44 to −2.70] in favour of the intervention groups ($p < 0.01$). The quality of evidence for all outcomes was rated as low or very low. **Conclusion:** This review is the first to evaluate the impact of lifestyle interventions on liver outcomes in ALD and MetALD populations and serves as an up-to-date assessment for MASLD populations. The evidence is insufficient to draw conclusions about the effectiveness of lifestyle interventions in improving liver outcomes in SLD due to the low quality of included studies. This was driven by high risk of bias, heterogeneity, and indirectness in the studies. The review highlights the urgent need for well designed RCTs focusing on patient-important outcomes, such as progression to cirrhosis and mortality, with longer follow up periods to better inform clinical practice. Additionally, further research in MetALD populations is necessary, given the growing evidence of its high prevalence. Finally, exploring the role of newly developed pharmacological interventions alongside lifestyle changes is crucial, as a combined approach could significantly influence future treatment strategies.



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2647 | MARS: A SIMPLE, READILY AVAILABLE, NON-INVASIVE SCORE TO ASSESS TREATMENT RESPONSE IN PATIENTS WITH MASH

Jérôme Boursier Adele Delamarre[1] Christophe Bureau[2] Yasmina Chouik[3] Lucia Parlati[4] Stephanie Faure[5] Cyrielle Caussy[3] Vincent Leroy[6] Vlad Ratziu[7] Laurent Castéra[8], [1]Bordeaux University Hospital, [2]Toulouse University Hospital, [3]Lyon University Hospital, [4]APHP Cochin Hospital, [5]Montpellier University Hospital, [6]APHP Mondor Hospital, [7]APHP La Pitie Salpetriere Hospital, [8]APHP Beaujon Hospital

Background: With the recent approval of pharmacologic treatments, the non-invasive assessment of treatment response in MASH is a crucial unmet need. Although recent data suggest that regression of liver steatosis, as measured by MRI-PDFF, is a promising surrogate for MASH resolution, MRI is expensive and has limited availability. Controlled Attenuation Parameter (CAP) is a point-of-care ultrasound technology developed to assess and quantify liver steatosis. We aimed to evaluate CAP and to develop a new score for the non-invasive assessment of MASH resolution. **Methods:** A total of 205 adult patients with MASH who had undergone paired liver biopsies and contemporaneous CAP examinations were retrospectively included from ten tertiary centers. The study endpoint was MASH resolution, defined as no or mild inflammation (NASH CRN grade 0-1), no hepatocyte ballooning (NASH CRN grade 0), and no worsening of fibrosis on the second liver biopsy. The relative deltas of biomarkers (relΔ, %) were calculated as follows: [follow-up - baseline] / baseline results. **Results:** The median age of the patients included was 60 years (IQR: 54-66), 50% were female, median BMI was 33 kg/m^2 (IQR: 30-36), and 65% had type 2 diabetes. The median interval between the baseline and the second liver biopsy was 18 months (IQR: 15-22). MASH resolution occurred in 29 patients (14%). CAP decreased was -55 dB/m (IQR: -87; -25) in patients with MASH resolution, compared to -9 dB/m (IQR: -47; +22) in those without resolution ($p < 0.001$). The AUROC of relΔCAP was 0.708 ± 0.054. Multivariate analysis showed that relΔCAP, relΔgammaGT, baseline AST, and baseline CAP were independent predictors of MASH resolution. Combining these four parameters in the MASH Resolution Score (MARS, ranging from 0 to 1) increased the AUROC for MASH resolution to 0.854 ± 0.037. The 90% sensitivity threshold (< 0.07) provided an excellent negative predictive value (NPV: 97%). As expected in this population with a low prevalence of MASH resolution, the 90% specificity threshold (> 0.30) provided moderate positive predictive value (PPV: 48%). Simulations showed that the PPV reached 90% at a prevalence rate of 60%, which corresponds to the MASH resolution rate in the ESSENCE Phase 3 Trial (Sanyal et al. NEJM 2025). **Conclusion:** MARS enables an accurate evaluation of MASH resolution. This new score, which is based on simple routine parameters and the results

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of a point-of-care device, can easily be calculated in an outpatient clinic. It will facilitate the assessment of treatment response in patients with MASH.

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2648 | IN TREATMENT OF METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD), PATIENT&RSQUO;S CHOICE MATTERS

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Background: For MASLD, weight loss is an effective strategy to reduce hepatic steatosis and fibrosis. However, among the various weight loss strategies, the impact of *patient's choice* of intervention on outcomes and their sustainability remains unclear. To address this gap, we performed a prospective pilot study. **Methods:** We screened 198 patients, 64 consented to participate, 11 withdrew, and 53 completed the study. Patients were offered five choices of intervention. We assessed their weights, liver function tests, elastography, CK18 levels, body composition analysis via bioimpedance, and quality of life (QOL) using SF36 and CLDQ at baseline, 6 and 12 months. **Results:** Mean age was 49.6 years, 60% were females. Patients chose: Group exercise + RDN (n = 40), RDN (n = 6), Medication + RDN (n = 4), Bariatric surgery (n = 2), and Medication + RDN + Group exercise (n = 1). The RDN protocol involved bi-weekly phone calls focusing on motivational interviewing, goal setting, nutritional education, Fitbit tracking, and diet reviews. This cohort demonstrated significant weight loss at 6 and 12 months, averaging 4.6% and 4.7% respectively ($p < 0.0001$). Reductions in ALT, AST, CK-18, and CAP scores were observed at both 6 and 12 months ($p < 0.05$ *for all*), though reduction in liver stiffness was not significant. Thirty percent achieved ≥ 7% wight loss. Patients achieving ≥7% weight loss at 12 months showed greater improvements in outcomes, particularly in CK-18 levels (p = 0.0007). Significant reductions in HbA1c, ferritin, and iron binding capacity were also noted ($p < 0.05$ *for all*). SECA analysis indicated a non-significant decrease in body fat, with significant reductions in fat mass index z-score and visceral adipose at 6 months, and fat-free mass index z-score at 12 months ($p < 0.05$ *for all*). Quality of life improved at 6 and 12 months, with those achieving ≥7% weight loss at 12 months showing higher improvements in SF-36 and CLDQ scores. Activity level was not associated with study outcomes.Greater adherence was associated with improved ALT and CLDQ scores.The sub-group analysis results for the largest group (Group exercise+ RDN) were consistent with the overall analysis. **Conclusion:** In MASLD, patient's choice of weight loss strategy improves compliance, effectiveness, and QOL. Strategies involving intensive interactive dietitian engagement increase weight loss that is sustained up to 12 months. This approach shows promise and warrants further investigation in controlled trials, particularly in conjunction with emerging pharmacological therapies for weight loss.

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2649 | THE IMPORTANCE OF WEIGHT REDUCTION IN MASH MANAGEMENT

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) and associated cardiometabolic conditions are major causes of morbidity and mortality. A prevalent comorbidity of MASH patients is obesity, underscoring the critical role of effective weight management in mitigating the disease's progression and impacts. **Methods:** Data are from the Ipsos Syndicated MASH Therapy Monitor, an online medical chart review and physician perceptual study including 663 physicians in the US (205), Germany (158), Japan (100), China (100) and Brazil (100) treating MASH patients, collected between Oct 2024-Jan 2025. Participants consisted of primary care physicians (PCPs), diabetologists/endocrinologists and gastroenterologists/hepatologists and were screened for caseload. Physicians reported on 2536 MASH patients in the US (735), Germany (541), Japan (420), China (500) and Brazil (340) seen in the last 3 months. **Results:** When aggregating regional data, 87% of all reported MASH patients are also obese/overweight (US/DE/BR BMI ≥ 27; CN/JP BMI ≥ 24) and weight gain is one of the most common symptoms MASH patients presented with; an average of 34% patients. Consequently, weight reduction is a leading treatment goal for 44% of the reported

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patients, with over two-thirds engaging in exercise and/or nutritional programs, predominantly alongside drug treatment. Among patients on exercise and nutrition therapy, physicians reported control over their MASH in 66% and 62% of cases, respectively. However, when choosing a treatment for this condition, 'reduces weight' falls outside of the top 3 attributes important to physicians; it is also less likely to be cited by them as an expectation of future treatments compared to several efficacy and safety attributes. **Conclusion:** The study findings reiterate the pivotal role of weight management in MASH treatment, particularly given the high rate of obesity/overweight among this population. Nutrition and exercise therapies, often used alongside medication, provide substantial control over the disease and help towards weight reduction as a key treatment goal. However, more may need to be done to join up the continued importance of weight loss in physicians' minds with unmet efficacy needs when deciding on pharmacotherapy for their MASH patients. It will be interesting to see if these attitudes shift as more treatments become available for MASH which also demonstrate weight reduction potential.

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2650 | ASSOCIATION BETWEEN CHANGE IN RELATIVE FAT MASS (RFM), BODY MASS INDEX (BMI) WITH NON-INVASIVE MARKERS OF MASH

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Background: Lifestyle intervention remains crucial in the treatment of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction associated steatohepatitis (MASH). Body mass index (BMI) is a well-established independent risk factor for MASLD, however, BMI is unable to differentiate fat mass from lean mass and can misclassify body fat defined obesity. Relative fat mass (RFM) has been proposed as a superior estimator of whole-body fat percentage. Whether RFM is more sensitive to lifestyle intervention than BMI remains unknown in individuals living with MASLD. **Methods:** A post-hoc analysis of the NASHFit trial was performed to compare improvement in RFM vs. BMI and in particular, their association with improvement in non-invasive biomarkers of MASH activity and metabolic risk. The NASHFit trial investigated the efficacy of 20 weeks of moderate-intensity aerobic exercise in adults with histologically confirmed MASH. In total, 24 patients completed the trial and paired data was available for analysis for 23 patients [exercise = 16, standard of care (SOC) = 7]. **Results:** The mean RFM pre-intervention was 41.5 and 37.8 in the exercise arm and SOC arm respectively. There was no statistically significant difference in mean RFM pre and post intervention, although an increase in RFM was observed in the SOC post intervention (38.1) which trended toward significance ($p = 0.066$). Greater than or equal to 5% reduction in RFM, the clinically significant threshold of response that is predictive of patient outcomes, was seen in 13% ($n = 2$) and 0% ($n = 0$) in the exercise arm and SOC arm respectively. Change in RFM and BMI were both positively correlated in most noninvasive markers of MASH (Table 1), with RFM more strongly correlated with visceral adipose tissue. Change in RFM and BMI were equivocal in their correlation with change in both total body fat and subcutaneous adipose tissue. **Conclusion:** Changes in RFM and BMI both correlate with change in noninvasive biomarkers of MASH and metabolic risk. While either RFM or BMI can be used as tools to guide clinicians in their monitoring of treatment response to lifestyle intervention, RFM appears more sensitive to change in visceral adipose tissue. This is of particular importance as RFM can be readily performed in clinic, thus making it a cost effective and time-efficient tool not requiring formal body composition testing with either bioelectric impedance or dual x-ray absorptiometry (DXA) scans.

Table 1: Correlation between RFM, BMI and noninvasive biomarkers of MASH

Change	RFM (r)	BMI (r)
Body Mass Index (BMI)	+0.43	—
Relative Fat Mass (RFM)	—	+0.43
Abdominal skin fold	+0.30	+0.54
Body fat	+0.37	+0.41
Visceral adipose tissue (VAT)	+0.58	+0.45
Subcutaneous adipose tissue (SAT)	+0.44	+0.46
Homeostatic model assessment of insulin resistance (HOMA-IR)	+0.36	+0.47
Hemoglobin A1c	+0.45	+0.02
Triglyceride	+0.55	+0.22
MRI proton density fat fraction (MRI-PDFF)	+0.36	+0.41
Maximal oxygen uptake (VO2peak)	-0.33	-0.40

R = Pearson Correlation Coefficient

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2651 | EFFECT OF BARIATRIC SURGERY ON MAJOR ADVERSE CARDIOVASCULAR AND CEREBROVASCULAR EVENTS IN MASLD PATIENTS: INSIGHTS FROM THE NATIONAL INPATIENT SAMPLE DATA (2016–2022)

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Background: The prevalence of MASLD continues to rise, affecting approximately 25% of the global population, with strong associations to obesity and cardiometabolic diseases. Bariatric surgery has shown metabolic benefits in MASLD, but its long-term impact on cardiovascular and cerebrovascular outcomes remains unclear. This study aims to evaluate the trends and effect of bariatric surgery on major adverse cardiovascular and cerebrovascular events (MACCE), as well as inpatient outcomes, among MASLD patients using national data. **Methods:** National Inpatient Sample (NIS) from 2016 to 2022 were utilized to identify adults >18 years with a diagnosis of MASLD using ICD-10 codes. Patients were stratified by the history of bariatric surgery. Multivariable logistic regression was used to assess associations with outcomes, adjusting for potential confounders. **Results:** Among MASLD patients, 394,535 underwent bariatric surgery. These patients demonstrated a significant reduction in inpatient mortality (aOR 0.33, 95% CI 0.317–0.344, $P<0.001$), LOS (–1.54 days, 95% CI –1.59 to –1.49, $P<0.001$), and THC (–$4,495.74, 95% CI –$5,365.01 to –$3,626.46, $P<0.001$). Moreover, there was a notable decrease in the risk of myocardial infarction (aOR 0.377, 95% CI 0.364–0.391), stroke (aOR 0.872, 95% CI 0.863–0.881), atrial fibrillation (aOR 0.729, 95% CI 0.718–0.739), arrhythmias (aOR 0.779, 95% CI 0.753–0.805), AKI (aOR 0.500, 95% CI 0.494–0.506), respiratory failure (aOR 0.362, 95% CI 0.352–0.372), liver failure (aOR 0.508, 95% CI 0.499–0.517), deep vein thrombosis (aOR 0.594, 95% CI 0.577–0.611), and sepsis (aOR 0.500, 95% CI 0.339–0.737); all $P<0.001$. However, the risk of bleeding was higher (aOR 1.277, 95% CI 1.262–1.293, $P<0.001$) which may be related to altered coagulation profiles, micronutrient deficiencies, or perioperative anticoagulant use in this population. **Conclusion:** Bariatric surgery significantly lowers the risk of MACCE, mortality, and resource utilization in the MASLD population, though it is associated with a higher risk of bleeding. With the increasing burden of MASLD and advancements in endo-bariatric techniques, these findings support bariatric surgery as a promising therapeutic option for MASLD.

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Table 1. Baseline Characteristics and Comorbidities in MASLD Patients With and Without Bariatric Surgery

	Bariatric Surgery		
	NO	YES	P VALUE
N. of patients (n)	n=3273779	n=394535	
Age			<0.001
18-34y	10.20%	15.53%	
35-49y	20.88%	34.88%	
50-64y	34.96%	33.42%	
65-79y	28.00%	14.43%	
Baseline Characteristics			
Sex			<0.001
Male	48.44%	27.83%	
Female	51.56%	72.17%	
Race			<0.001
White	67.85%	64.13%	
Black	9.41%	13.37%	
Hispanic	16.36%	16.91%	
Asian or Pacific Islander	2.43%	1.37%	
Native American	0.99%	0.71%	
Insurance Status			<0.001
Medicare/Medicaid	60%	46.93%	
Private insurance	30.11%	45.72%	
Self-pay	9.69%	7.34%	
Hospital teaching status			<0.001
Rural Non-Teaching	6.71%	3.58%	
Urban Non-teaching	19.12%	19.55%	
Urban Teaching	74.17%	76.87%	
Hospital Region			<0.001
Northeast	16.24%	22.32%	
Midwest	21.78%	19%	
South	39.95%	37.44%	
West	22.00%	21%	
Comorbidities			
Hypertension	85.40%	68.62%	<0.001
Diabetes Mellitus	43.36%	34.83%	<0.001
Hyperlipidemia	40.87%	37.34%	<0.001
CAD	18.29%	9.15%	<0.001
Anemia	24.52%	20.84%	<0.001
COPD	23.00%	21.81%	<0.001
OSA	13.17%	28%	<0.001
Obesity	40.44%	71.90%	<0.001
Coagulation disorders	24.87%	33.57%	<0.001
CKD	15.46%	7.30%	<0.001
Alcohol use	18%	11.41%	<0.001
Tobacco use	20.54%	21.72%	<0.001
Charlson Comorbidity Index			<0.001
Mild	40	44.97	
Moderate	26.56	16.83	
Severe	33.43	38.2	
Length of Stay (LOS)	5.5+/-0.008	3.79+/-0.019	<0.001
Total Health Charges (THC)	72012.542	67378.8992	<0.001

Table 2. Adjusted Odds for Adverse Cardiovascular, Cerebrovascular, and Inpatient Outcomes in MASLD Patients Undergoing Bariatric Surgery

	OR	95% CI	P value
Death			
No Bariatric surgery		Ref	
Bariatric Surgery	0.33	0.317-0.344	<0.001
Myocardial Infarction			
No Bariatric surgery		Ref	
Bariatric Surgery	0.377	0.364-0.391	<0.001
Stroke			
No Bariatric surgery		Ref	
Bariatric Surgery	0.872	0.863-0.881	<0.001
Atrial Fibrillation			
No Bariatric surgery		Ref	
Bariatric Surgery	0.729	0.718-0.739	<0.001
Arrhythmias			
No Bariatric surgery		Ref	
Bariatric Surgery	0.779	0.753-0.805	<0.001
Heart Failure			
No Bariatric surgery		Ref	
Bariatric Surgery	0.523	0.516-0.530	<0.001
Respiratory failure			
No Bariatric surgery		Ref	
Bariatric Surgery	0.362	0.352-0.372	<0.001
Bleeding complication			
No Bariatric surgery		Ref	
Bariatric Surgery	1.277	1.262-1.293	<0.001
AKI			
No Bariatric surgery		Ref	
Bariatric Surgery	0.5	0.494-0.506	<0.001
Liver Failure			
No Bariatric surgery		Ref	
Bariatric Surgery	0.508	0.499-0.517	<0.001
DVT			
No Bariatric surgery		Ref	
Bariatric Surgery	0.594	0.577-0.611	<0.001
	Coefficient	CI	P value
LOS			
No Bariatric surgery		Ref	
Bariatric Surgery	-1.54	-1.59 to -1.49	<0.001
THC (In US dollars)			
No Bariatric surgery		Ref	
Bariatric Surgery	-4,495.74	-5365.01 to -3626.46	<0.001

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2652 | IMPACT OF BODY WEIGHT CHANGES ON NEW-ONSET DIABETES IN INDIVIDUALS WITH NON-DIABETIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with an increased risk of diabetes. While weight reduction is the primary recommended intervention for MASLD and is known to improve hepatic steatosis and fibrosis, its effect on the development of diabetes remains unclear. This study aimed to investigate the association between body weight changes and the risk of new-onset diabetes in individuals with non-diabetic MASLD. **Methods:** This study included 14,126 adults with MASLD and no diabetes at baseline, all of whom underwent at least two health examinations between 2003 and 2021. MASLD was diagnosed by ultrasonography. Changes in body weight were calculated as the percentage change from baseline to the last available measurement. **Results:** Over a follow-up of 75,496 person-years (mean duration, 5.3 years), 2,258 individuals with non-diabetic MASLD developed diabetes. Compared to participants with no significant body weight change ($>-5.0\%$ to $<5.0\%$), the adjusted hazard ratios (aHRs) for incident diabetes were 1.16 (95% CI, 1.00–1.33) and 1.33 (95% CI, 1.00–1.76) for weight gains of 5.0–9.9% and $\geq 10.0\%$, respectively. Conversely, the aHRs were 0.52 (95% CI, 0.44–0.60) and 0.48 (95% CI, 0.37–0.63) for weight reductions of 5.0–9.9% and $\geq 10.0\%$, respectively. In spline regression models, body weight change showed a dose–response relationship with incident diabetes risk, with increasing weight gain associated with an elevated risk, while greater weight loss associated with a reduced risk. Notably, the association between body weight reduction and reduced diabetes risk was consistently observed in all subgroups analyzed. **Conclusion:** In individuals with MASLD without diabetes, changes in body weight were significantly associated with the risk of new-onset diabetes in a dose-dependent manner. Weight loss was strongly associated with a lower risk of

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developing diabetes, with greater reductions conferring greater benefit, while weight gain increased the risk. These findings emphasize the critical role of weight reduction in diabetes prevention and underscore the importance of avoiding weight gain in participants with MASLD.

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2653 | INTERMITTENT CALORIE RESTRICTION MODULATES GUT MICROBIOTA IN PATIENTS WITH MASLD: A DIFFERENTIAL IMPACT ON MEGAMONAS, LACHNOSPIRA, AND ENTEROBACTER IN OBESE AND NON-OBESE PATIENTS

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Background: In our previous randomized controlled trial (RCT), we demonstrated that a 12-week intermittent calorie restriction (ICR) diet effectively reduced liver fat content (LFC) compared to the standard of care (SOC) diet, particularly in patients with obesity. This study aims to investigate the changes in gut microbiome composition following a 12-week dietary intervention in patients with MASLD to identify the underlying mechanisms of this effect. **Methods:** Patients with MRI-proton density fat fraction (PDFF) $\geq 8\%$ were randomly assigned to either the ICR group (5:2 diet) or the SOC group (80% of recommended calorie intake). The primary outcome was the proportion of patients achieving a $\geq 30\%$ reduction in LFC measured by MRI-PDFF. **Results:** ICR increased microbiome diversity and was associated with a reduction in Megamonas (linear discriminant analysis [LEfSe] = 4.14; $P < 0.001$) and Enterobacter (LEfSe = 2.71; $P = 0.01$), while promoting an increase in beneficial bacteria, including Alistipes (LEfSe = 3.87; $P < 0.001$), Clostridium (LEfSe = 3.51; $P = 0.03$), Romboutsia (LEfSe = 3.67; $P = 0.04$), and Lachnospira (LEfSe = 3.16; $P = 0.02$), compared to the SOC group. In patients with obesity, Enterobacter significantly decreased in the ICR group, whereas it increased in the SOC group. Megamonas showed no significant change in the ICR group, whereas it significantly decreased in the SOC group. In patients without obesity, Megamonas significantly decreased in both groups, but the reduction was significantly greater in the ICR group compared to the SOC group. Ruminococcus, Lachnospira, and Parabacteroides increased in the ICR group, whereas no significant changes were observed in the SOC group. In the group with relative LFC reduction $\geq 30\%$, Megamonas and Enterobacter decreased, while Bacteroides and Alistipes increased. However, in the group with LFC reduction $< 30\%$, Megamonas and Enterobacter increased and Lachnospira decreased. **Conclusion:** Changes in gut microbiome could be one of the mechanisms through which ICR contributes to LFC improvement in MASLD patients.

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2654 | YOGA IS NON INFERIOR TO EXERCISE IN IMPROVING HEPATIC STEATOSIS IN MASLD - AN OPEN LABEL, NON-INFERIORITY, RANDOMISED CONTROLLED TRIAL

Sunil Taneja[1] Balaraja S[1] Akshay Anand[1] Nancy Sahni[1] Naveen Kalra[1] Vikram Kumar[1] Sweta Rose[1] Arpit Shastri[1] Ganesh CP[1] Dr. Ashwin Vinod[1] Muhammad Uwais Ashraf[1] Kannupriya .[1] Arka De[1] Nipun Verma[1] Madhumita Premkumar[2] Ajay Duseja[1], [1]Postgraduate Institute of Medical Education & Research, [2]Postgraduate Institute of Medical Education & Research,

Background: There is lack of data on efficacy of yoga in improving steatosis in patients with metabolic dysfunction associated steatotic liver disease(MASLD). This study aimed to compare effectiveness of Yoga combined with dietary calorie restriction with Exercise and dietary calorie restriction in reducing hepatic steatosis in MASLD. **Methods:** 110 overweight/obese patients with MASLD with hepatic steatosis(CAP > 248 on transient elastography) were randomized(1:1) into Yoga and Exercise group. Patients were advised Obesity yoga protocol. Duration of yoga session was 1 hour daily for 6 days per week. All the patients were assessed by a dietician and advised dietary calorie restriction of 500-1000 kcal/day using a diet chart according to local dietary practices and culinary tastes. 20 patients in each group underwent MRI PDFF pre and post intervention. Primary outcome was improvement in hepatic steatosis at six months. **Results:** There was a significant reduction in hepatic steatosis 325(305.5-343.5) to 278(268-298), ($p < 0.001$) in yoga group vs 332(307.5-367.5) to 300(277-328.5),($p < 0.001$) in exercise group with higher delta change improvement seen in yoga group compared to control group -47(-65 to-19) versus -27(-55to-9),(p-0.025) at six months. There was significant reduction in MRIPDFF 16.4(12.9-21.23) to 14.4(9.45-17.88,($p < 0.014$) in yoga group vs 17.3 (13.25-22.67) to 15(12.65-22.1),(p-0.065) in exercise group. On logistic regression analysis, delta weight reduction(OR2.36,95%CI 1.49–3.73;p < 0.001) and

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weight loss ≥ 10%(OR1.1,95%CI 1.01- 1.7;p-0.03) were independent predictors of improvement in steatosis. There was significant improvement in weight 80 (74-84.35) to 75(70-79), ($p < 0.001$) in yoga group vs 80 (71-85.5) to 75(67.5-82.25), ($P < 0.001$) in exercise group, BMI 28.09(26.93-30.14) to 26.3(25.25-28.24), ($p < 0.001$) vs 28.273(27-31.54) to 27.7(25.71-29.60), ($p < 0.001$) in exercise group and waist circumference 100(96.5-104.5) to 95(91.5-101), ($p < 0.001$) in yoga group vs 102(96-108) to 99(93-106.5), ($p < 0.001$) in exercise group. There was significant reduction in ALT and delta ALT reduction was more in yoga group-16 (-53.1to -0.5)vs-5(-34 to 3.3) in exercise group(p-0.042). There was significant improvement in fasting insulin, HbA1c, triglycerides, HDL and insulin resistance as measured by HOMA-IR in both groups with no inter-group differences. There was a significant improvement in frailty and sarcopenic obesity seen in yoga group[22 (40%) to 11(20%)](p-0.02) as compared to control group. **Conclusion:** Yoga with dietary calorie restriction, is non-inferior to exercise with dietary calorie restriction in improving hepatic steatosis, liver inflammation, and fibrosis. Additionally, yoga demonstrates significant benefits in improving metabolic parameters, reducing body weight and sarcopenic obesity.

Table-2. Improvement in Hepatic steatosis at six months of follow-up.

Parameters	Diet + Yoga			Diet + Exercise			P value between the groups at six months
	Baseline (n=55)	Six months (n=55)	P value within the group	Baseline (n=55)	Six months (n=55)	P value within the group	
CAP	325.00 (305.50 - 343.50)	278.00 (268.00 - 298.00)	<0.001	332.00 (307.50 - 367.50)	300.00 (277.00 - 328.50)	<0.001	0.022
Δ CAP		-47.00 (-65.00 - -19.00)			-27.00 (-55.00 - -9.00)		0.025
Improvement of steatosis by ≥1 category		32 (58.2%)			15 (27.3%)		0.001
Improvement from severe to moderate steatosis		19(34.5%)			10(18.2%)		0.083
Improvement from severe to mild steatosis		9(16.4%)			4(7.3%)		0.184
Resolution of steatosis (CAP <248dB/m)		4(7.3%)			2(3.6%)		0.401
MR PDFF (20 patients in each group)	16.4(12.9-21.23)	14.4(9.45-17.88)	0.014	17.3(13.25-22.67)	15(12.65-22.10)	0.065	0.632
Δ MR PDFF		-4.2(-6.60 - -1.75)			-1.80(-3.13 - -0.78)		0.099
≥30% reduction in MRI PDFF		8(40%)			2(10%)		0.028

Disclosures: Sunil Taneja: Nothing to Disclose, Balaraja S: Nothing to Disclose, Akshay Anand: Nothing to Disclose, Nancy Sahni: Nothing to Disclose, Naveen Kalra: Nothing to Disclose, Vikram Kumar: Nothing to Disclose, Sweta Rose: Nothing to Disclose, Arpit Shastri: Nothing to Disclose, Ganesh CP: Nothing to Disclose, Dr. Ashwin Vinod: Nothing to Disclose, Muhammad Uwais Ashraf: Nothing to Disclose, Kannupriya.: Nothing to Disclose, Arka De: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, Ajay Duseja: Nothing to Disclose

2655 | A TRADITIONAL MEXICAN DIET AGAINST VIRAL HEPATITIS B AND C, AND MASLD: AN INTEGRATIVE BIOINFORMATIC ANALYSIS

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Background: Viral hepatitis B (HBV), hepatitis C (HCV), and metabolic dysfunction-associated steatotic liver disease (MASLD) are significant causes of cirrhosis and hepatocellular carcinoma (HCC) worldwide. Despite their clinical impact, there is a lack of specific nutritional guidelines for the management of viral hepatitis. Regional diets have been shown to influence liver health positively. In this context, the traditional Mexican diet is rich in bioactive compounds with potential antiviral and hepatoprotective effects. This study aimed to find and examine nutrients from traditional Mexican foods that might affect important biological processes related to HBV, HCV, and MASLD. **Methods:** A comprehensive review of existing research (from PubMed and Google Scholar, 2000–2024) was done to find studies on nutrients from traditional Mexican foods that have antiviral and anti-MASLD effects, including experimental (in silico, in vitro, in vivo) and clinical studies. Next, a detailed analysis using bioinformatics tools like CTD, STRING, DAVID, and Enrichr was performed to see how genes work with these nutrients, how they connect to KEGG pathways, and their links to liver diseases. Data analysis and visualization were done using RStudio. **Results:** Five key foods (maize, beans, chili, tomato, and avocado) were found to influence genes that are important for immune response (*TNF, IL6*), dealing with oxidative stress (*NFE2L2, CAT*), fat metabolism (*PPARA, FASN*), cell death (*BAX, CASP3*), and cancer growth (*TP53*). The functional enrichment analysis indicated that the beneficial compounds in these foods have various effects on important processes like metabolism, antioxidant activity, immune function, tissue formation, and cancer. The network analysis indicated that all five foods were linked to viral hepatitis, MASLD, and HCC, influenced by different beneficial nutrients. The network analysis revealed that distinct bioactive nutrients interconnected all five ingredients with viral hepatitis, MASLD, and HCC. Both viral hepatitis and HCC shared vitamin E as a modulator, and both viral hepatitis and MASLD shared potassium. Lycopene and anthocyanins were associated with both MASLD and HCC. In contrast, folate, monounsaturated fatty acids, and phytosterols were associated with MASLD.

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Conclusion: Bioactive compounds in traditional Mexican foods modulate critical pathways in the pathogenesis of HBV, HCV, MASLD, and HCC. These findings support culturally and genome-based nutrition strategies to prevent liver diseases in populations facing limited access to antiviral therapy and high prevalence of metabolic dysfunction diseases.
Disclosures: Leonardo Leal-Mercado: Nothing to Disclose, Arturo Panduro: Nothing to Disclose, Sonia Roman: Nothing to Disclose

◆ 3001 | A VALUE-BASED HEALTHCARE DELIVERY MODEL FOR MASH-RELATED COMPENSATED CIRRHOSIS AND OBESITY: INTEGRATED SHARED MEDICAL APPOINTMENTS

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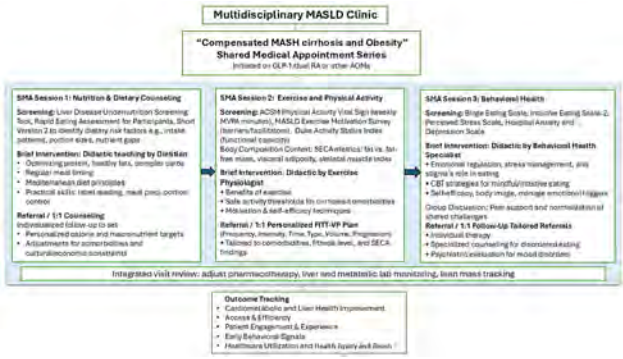
Background: MASH-related compensated cirrhosis with obesity is a complex, high-burden disease. Current care often lacks the necessary comprehensive, accessible, and multidisciplinary structure to optimize outcomes and manage costs. Value-based healthcare models are vital for delivering efficient, high-quality care to this vulnerable population. **Methods:** A novel three-part monthly Shared Medical Appointment (SMA) series was developed and piloted within a Multidisciplinary MASLD Clinic (MMC) for patients with MASH-related compensated cirrhosis and obesity. The series integrated structured lifestyle interventions with ongoing anti-obesity medication (AOM) management. Each 90-minute SMA session accommodated up to 8 patients and was led by a physician and a facilitator (registered dietician, exercise physiologist, or behavioral psychologist, varying by theme). Session themes were: 1) Nutrition and Dietary Counseling, 2) Exercise and Physical Activity, and 3) Behavioral Health, utilizing Screening, Brief Intervention, and Referral to Treatment (SBIRT) principles. Regular physician oversight and individual check-ins facilitated AOM titration and adjustment, with comprehensive laboratory and lean mass tracking (via SECA DEXA). [Fig 1]This pragmatic approach aimed to integrate with existing care, minimize patient burden, and foster peer support. **Results:** Early pilot data reveal promising initial findings across key tracked areas. Process and efficiency outcomes included rapid patient enrollment (within 4 weeks of MMC referral) and high session utility, with a 94% attendance rate. Patient engagement outcomes were strong, evidenced by high attendance and the formation of a vital peer support group. Early clinical outcomes tracked over the three-month SMA period showed an average of 14% total body weight loss (%TBWL), alongside systematic monitoring of body composition and liver frailty index. Additionally, AOM management outcomes were positive: 91.6% of patients were successfully initiated on AOMs, with 100% adherence among those initiated. The model also effectively facilitated safe, individualized AOM and cardiometabolic disease pharmacotherapy titration and adjustments. **Conclusion:** This innovative and scalable SMA model enhances access to integrated MASH cirrhosis and obesity care by optimizing resources, patient engagement, and clinical oversight, offering a sustainable route to improved clinical outcomes and quality of life for this complex disease.



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◆ 3002 | BASELINE SYMPTOM BURDEN AND NETWORK ANALYSIS IN ADULTS WITH PSC, PBC, AND CIRRHOSIS ENROLLED IN THE EMPOWER RCT

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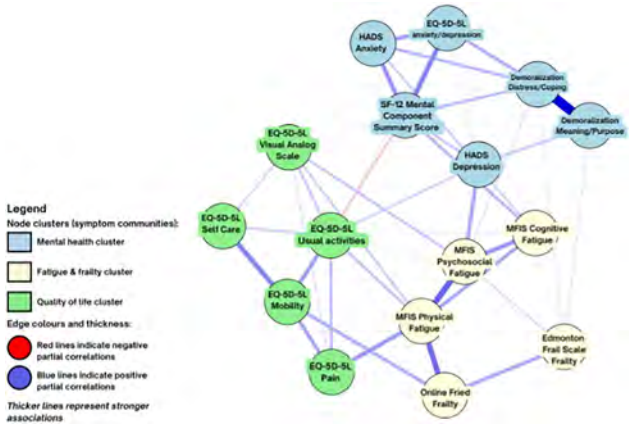
Background: Fatigue is among the most debilitating and under-treated symptoms in chronic liver disease, significantly affecting quality of life. In Primary Biliary Cholangitis (PBC), Primary Sclerosing Cholangitis (PSC), and cirrhosis, fatigue is common, multidimensional, and closely linked to mental health and frailty. Anxiety and depression are also common yet remain underrecognized and undertreated in hepatology care. However, few studies have examined how these symptoms co-occur or interact across chronic liver disease populations. **Methods:** This is a prespecified subgroup analysis of liver participants (n = 255) enrolled in the 3-arm eMPower RCT (NCT05786482). The eMPower RCT evaluated a 12-week online mind-body wellness intervention combining acceptance and commitment therapy informed strategies, breathwork, meditation, mindful movement, and disease-specific education. Validated baseline surveys assessed fatigue (Modified Fatigue Impact Scale [MFIS]), mental health (Hospital Anxiety and Depression Scale [HADS]), demoralization (Demoralization-II), frailty (online Fried Frailty Phenotype, Edmonton Frail Scale), sleep disturbance (PROMIS Sleep SF-8a), and quality of life (EQ-5D-5L, Short Form-12 (SF-12)). Symptom networks were constructed using LASSO-regularized partial correlations. **Results:** Of 255 participants (PBC: 72.2%; cirrhosis: 20.0%; PSC: 7.8%), mean age was 59 ± 11.1 years, and 88% were female. At baseline, fatigue was moderate to severe (MFIS: 46.7 ± 15.1), with physical fatigue most affected. Mental health symptoms were common, with mean HADS-Anxiety scores of 7.6 ± 3.7 and HADS-Depression scores of 4.9 ± 3.0., Demoralization scores averaged 9.7 ± 6.6, indicating moderate existential distress in the overall sample. Frailty was prevalent, with a mean Fried Frailty score of 2.7 ± 1.4 and EFS score of 6.3 ± 1.8, indicating that many participants were in the pre-frail to mildly frail range, with increased vulnerability to physical and functional decline. Symptom network analysis (Figure 1) revealed three interconnected clusters: 1) mental health, 2) fatigue/frailty, and 3) quality of life. Physical fatigue was the most central node in the network, followed by demoralization-II and SF-12 Mental Component Summary score. **Conclusion:** Baseline data highlight a substantial and overlapping symptom burden among individuals with chronic liver disease, with physical fatigue emerging as the most central and interconnected symptom. These findings support the need for targeted interventions that address fatigue alongside mental health and frailty in liver care.



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◆ 3003 | EXPLORE B POST HOC ANALYSIS OF CHRONIC SYMPTOMS IN PATIENTS WITH ACUTE HEPATIC PORPHYRIA

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Background: Acute hepatic porphyria (AHP) is a group of rare disorders with acute attacks of pain, and neurological symptoms, which can lead to altered mental status. Patients have chronic symptoms with significant disease burden, as reported in part B of the observational EXPLORE study, which included patients aged $\geq$12 years with symptomatic AHP ($\geq$1 acute attack in the past 12 months) and/or receiving hemin or gonadotrophin-releasing hormone (GnRH) treatment to prevent attacks. The International Porphyria Network (IPNET) has categorized two profiles of what is referred to as symptomatic AHP, as per their assessments, by attack frequency ($\geq$4 or 1-3 attacks/year [a/y]). **Methods:** This cross-sectional, *post hoc* analysis of baseline EXPLORE B data evaluated chronic disease burden and health-related quality of life (HRQoL) in patients with $\geq$4 a/y or hemin/GnRH use or with $<$4 a/y without hemin/GnRH use. Chronic symptoms (those not necessarily associated with an AHP attack) were self-reported by patients. Pain and its impact were assessed with the Brief Pain Inventory short form (BPI-SF), and HRQoL with the EQ-5D-5L. Results are descriptive, and *p* values are nominal. **Results:** Among 136 patients (mean [SD] age 41.0 [12.6] years; 90.4% female), 100 had $\geq$4 a/y, and 36 had $<$4 a/y. Demographics were similar, and patients with $\geq$4 a/y were older with more years since diagnosis (Table). Most patients in both groups reported chronic symptoms; other than 'trouble sleeping' (higher with $<$4 a/y: odds ratio, 3.52; 95% CI [1.10-11.24]; $p = 0.0276$), no notable between-group differences were observed.

No differences in pain intensity were found in BPI-SF scores, and in 4 of 7 items the impact of pain interfering with daily activities was higher in patients with $\geq$4 a/y than with $<$4 a/y (Table). Pain values were in the mild range, and the mean difference did not exceed the minimal clinically-important difference of 2 points for any item.

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EQ-5D-5L index scores were slightly worse in patients with ≥4 a/y (p = 0.0253, Table). However, visual analog scale scores and the odds of having moderate or worse problems in any EQ-5D-5L dimension did not differ significantly between groups (all $p > 0.05$, Table). **Conclusion:** Patients in EXPLORE B had chronic symptoms irrespective of which profile of AHP they met. While a greater burden was reported for some outcomes in patients with ≥4 a/y, many were similar between groups. The results suggest a considerable chronic impact of AHP in both patient groups.

Table: Disease Burden and Health-Related Quality of Life

Parameter, mean (SD)*	<4 attacks/year and no hemin/GnRH (n=56)	≥4 attacks/year or hemin/GnRH (n=100)	Mean difference (95% CI) p value
Age, years	37.5 (13.9)	42.2 (12.6)	—
Female, n (%)	51 (91.1)	91 (91.0)	—
Years since diagnosis	8.37 (11.69)	12.92 (11.42)	—
Race, n (%)			
White	29 (69.6)	86 (86.0)	
Asian	3 (4.3)	6 (6.0)	
Black/African American	3 (4.3)	5 (5.0)	
American Indian/Alaska Native	0	1 (1.0)	
Other	1 (1.8)	0 (0.0)	
Not stated	0	2 (1.9)	
Geographic region, n (%)			
Europe	23 (69.9)	47 (47.0)	
North America	8 (22.2)	48 (48.0)	
Other (Africa, Asia, Australia)	5 (13.9)	5 (5.0)	
Porphyria type, n (%)			
AIP	51 (88.9)	93 (93.0)	
HCP	1 (1.8)	1 (1.0)	
VP	3 (5.3)	6 (6.0)	
ADP	0	0	
BPI-SF	n=56	n=97	
Pain at its worst in the past 24 hours	3.5 (2.8)	4.6 (3.1)	−1.13 (−2.09, −0.04); p=0.0420
Pain at its least in the past 24 hours	1.8 (2.2)	2.1 (2.2)	−0.18 (−0.87, 0.51); p=0.6064
Pain on average	3.2 (2.4)	3.8 (2.4)	−0.63 (−1.34, 0.19); p=0.1772
Pain right now	2.4 (2.6)	2.9 (3.4)	−0.53 (−1.52, 0.49); p=0.3243
Pain interference in the past 24 hours with:	n=25	n=47	
General activity	2.9 (2.9)	5.8 (3.3)	−1.95 (−3.13, −0.73); p=0.0016
Mood	2.9 (2.9)	4.1 (3.3)	−1.06 (−2.02, −0.42); p=0.0089
Walking ability	2.1 (2.9)	2.9 (3.7)	−0.82 (−1.90, 0.29); p=0.1498
Normal work	2.9 (2.7)	4.1 (3.7)*	−1.45 (−2.78, −0.12); p=0.325
Relations	1.4 (2.2)	3.8 (3.4)	−1.95 (−3.18, −0.72); p=0.0019
Sleep	3.8 (3.3)	4.1 (4.4)	−4.14 (−2.80, 0.51); p=0.0978
Enjoyment of life	2.7 (2.9)	4.3 (3.5)	−1.84 (−3.14, −0.54); p=0.0058
Baseline EQ-5D-5L, n	n=38	n=67	
Index score	0.91 (0.14)	0.75 (0.19)	0.07 (0.01, 0.13); p=0.0253
VAS	89.9 (19.0)	82.7 (20.1)	7.29 (−0.45, 14.99); p=0.0664
Moderate or worse problems in EQ-5D-5L dimension (EQ-5D-5L score ≥2), n (%)	n=38	n=100	OR(95 CI)(95% CI) p value
Mobility	15 (41.7)	38 (38.0)	1.58 (0.90, 4.28); p=0.1617
Self-care	4 (11.1)	22 (22.0)	0.90 (0.28, 3.94); p=0.9250
Usual activities	16 (44.4)	66 (66.0)	0.41 (0.18, 1.03); p=0.0535
Pain/discomfort	12 (31.1)	78 (78.0)	0.80 (0.37, 1.93); p=0.1860
Anxiety/depression	15 (41.7)	61 (61.0)	0.91 (0.32, 2.92); p=0.1575

95% CI and p value were calculated from two sample t-test for BPI-SF, EQ-5D-5L index and VAS scores, and from a Mantel-Haenszel chi-square test for EQ-5D-5L dimensions.

Significant p values (p<0.05) are in bold. Pain ranges in the BPI-SF are mild (1-5), moderate (5-6), and severe (7-10). EQ-5D-5L score is derived using the US reference value given for that particular set of responses in the 5 domains. The US reference values are provided in the Crosswalk value dataset associated with this instrument. All EQ-5D-5L scores presented are asymptomatic scores.

*Unless stated otherwise, *n=98

ADP, delta-aminolevulinic acid dehydratase-deficiency porphyria; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; BPI-SF, Brief Pain Inventory short form; CI, confidence interval; GnRH, gonadotrophin-releasing hormone; HCP, hereditary coproporphyria; SD, standard deviation; VAS, visual analog scale; VP, variegate porphyria.

Disclosures: Susana Monroy: ALNYLAM PHARMACEUTICALS: Speaking and Teaching, ASTRA ZENECA: Speaking and Teaching, Manish Thapar: Alnylam Pharmaceuticals: Consultant, Disc Medicine: Consultant, Mitsubishi Tanabe: Consultant, Recordati Rare Diseases: Consultant, Raili Kauppinen: Nothing to Disclose, Encarna Guillén-Navarro: Nothing to Disclose, Desmond Murphy: Alnylam Pharmaceuticals: Employee, Alnylam Pharmaceuticals: Stock - publicly traded company, Teresa Kauf: Alnylam, Inc: Employee, Mural Oncology: Stock - publicly traded company, Alkermes, Inc: Stock - publicly traded company, Weiming Du: Alnylam Pharmaceuticals: Employee, David Cassiman: Alnylam: Speaking and teaching

◆ 3004 | ASSESSING THE ENVIRONMENTAL IMPACT OF PATIENT TRAVEL TO A LIVER TRANSPLANT CLINIC: CAN WE MAKE THE LIVER TRANSPLANT OUTPATIENT SERVICE MORE SUSTAINABLE?

Mhairi Donnelly[1] Lisa Norman[2] Katherine Connor[2] Zareena Khan-Orakzai[2] Ben Stutchfield[2], [1]Royal Infirmary of Edinburgh, [2]Edinburgh Transplant Centre

Background: The Scottish Liver Transplant Unit (SLTU) is the single referral centre in Scotland for liver transplantation. Patients travel long distances to attend the transplant clinic. Our specialty is increasingly aware of the need to reduce our carbon footprint. This study aimed to assess the carbon footprint of patient travel to the SLTU clinic (a suspected carbon hotspot), and the potential carbon savings offered by virtual consultations and outreach services. **Methods:** A one year period was studied, 09/06/2022-08/06/2023. A travel questionnaire was distributed to patients attending one in-person SLTU clinic to provide an accurate snapshot of travel-related emissions. A carbon footprint calculator for (avoided) patient travel produced by the Centre for Sustainable Healthcare was used for virtual and outreach consultations. **Results:** The carbon footprint of patient travel to one SLTU clinic (calculated using questionnaire data) was 753kg CO2e. Extrapolated to 102 clinics per year, patient-related travel created 76,806kg CO2e (equivalent to 22 economy class return flights from London to Hong Kong).

218 virtual consultations were delivered via SLTU over this year, saving 7080kg CO2e and 29,762 miles travelled.

Patients seen in outreach clinics do not travel to SLTU; outreach appointments resulted in 164,761 avoided miles, and 43,965kg CO2e saved compared with travel to SLTU. These patients still travelled to their outreach centre however, so overall the total saving was 130,670 avoided miles and 34,634kg CO2e.

Patients seen in outreach clinics are well and may be suitable for virtual consultations. If all outreach appointments were delivered virtually, instead of patients attending their local centre, this would avoid 34,091 patient miles travelled and save 9331kg CO2e. **Conclusion:** Delivery of an in-person clinic in the transplanting centre is associated with a significant carbon footprint through patient travel. Patient travel is a carbon hotspot, which could be addressed by using novel technology to deliver more virtual appointments.

Disclosures: Mhairi Donnelly: Nothing to Disclose, Lisa Norman: Nothing to Disclose, Katherine Connor:

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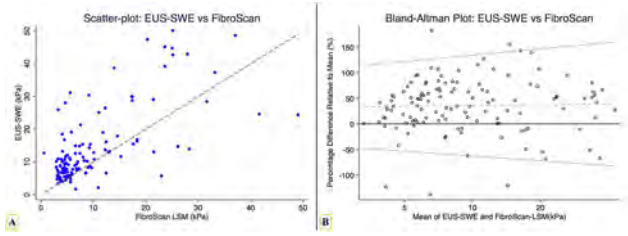
Nothing to Disclose, Zareena Khan-Orakzai: Nothing to Disclose, Ben Stutchfield: Nothing to Disclose

◆ 3005 | EUS-SHEAR WAVE ELASTOGRAPHY EFFECTIVELY EXCLUDES ADVANCED CHRONIC LIVER DISEASE DURING ROUTINE EUS PROCEDURES

Umang Arora[1] SHIVAM KHARE[1] Shrihari Anikhindi[1] Ashiesh Khandelwal[1] Ashish Kumar[1] Praveen Sharma[1] Naresh Bansal[1] Anil Arora[1], [1]Sir Ganga Ram Hospital

Background: Noninvasive assessment of liver stiffness is essential for evaluating hepatic fibrosis. While transient elastography (TE, FibroScan®) is widely established, endoscopic ultrasound shear wave elastography (EUS-SWE) offers potential advantages, particularly in patients already undergoing EUS for other indications. This study aimed to assess the agreement between EUS-SWE and FibroScan liver stiffness measurements (LSM), and to evaluate the diagnostic accuracy of EUS-SWE for identifying advanced chronic liver disease (ACLD). **Methods:** In this cross-sectional study, consecutive patients undergoing EUS evaluation between Jan-May 2025 for any indication (liver biopsy, lymph node sampling, pancreatitis evaluation) in the absence of biliary obstruction were included. Liver stiffness was measured in the right hepatic lobe using EUS-SWE with the Olympus ME3 system, and by FibroScan (Echosens) using the standard M or XL probe at the right midaxillary line. The median of ten valid measurements was used for each modality. Correlation analysis was performed using Spearman's method. Agreement between the two modalities was assessed using Bland-Altman analysis. For assessing clinical utility, we categorized patients as having high likelihood of advanced chronic liver disease (ACLD) based on LSM values >15 kPa (Baveno criteria). The ability of EUS-SWE to predict ACLD was evaluated using area under the receiver operating characteristic curve (AUROC) analysis and Liu's method to identify optimum threshold. **Results:** Among 139 patients identified in the cohort, 128 patients with complete LSM and EUS-SWE data were analyzed. The mean age was 45 ± 14 (range 14 – 83) years, and 30% were female. The median LSM by TE was 5.8 kPa (range: 3–49 kPa), with 48 and 32 patients fulfilling criteria for advanced fibrosis (LSM ≥ 8 kPa) and cirrhosis (LSM ≥ 12 kPa), respectively. Spearman's correlation analysis demonstrated a moderate positive correlation between EUS-SWE and FibroScan LSM measurements ($\rho = 0.61$, $P < 0.001$). Bland-Altman analysis demonstrated a mean percentage difference of 35.4%, with 95% limits of agreement from –67.34% to 138.3% (Figure 1). Diagnostic accuracy for EUS-SWE in predicting ACLD was 0.90, indicating excellent diagnostic performance, at an optimum threshold of 15.5 kPa. Visual inspection of the Bland-Altman plot, as well as a positive regression slope of 0.15 for the difference against the mean, indicated the presence of proportional bias, with greater differences observed at higher liver stiffness values. **Conclusion:** EUS-Shear Wave Elastography (EUS-SWE) tends to overestimate liver stiffness compared to FibroScan and demonstrates only moderate agreement, suggesting the two modalities are not interchangeable. Nevertheless, incorporating EUS-SWE into routine EUS procedures may offer clinical value in excluding advanced chronic liver disease in patients undergoing EUS for unrelated indications.



Disclosures: Umang Arora: Nothing to Disclose, SHIVAM KHARE: Nothing to Disclose, Shrihari Anikhindi: Nothing to Disclose, Ashiesh Khandelwal: Nothing to Disclose, Ashish Kumar: Roche: Consultant, Viatris: Consultant, Praveen Sharma: Nothing to Disclose, Naresh Bansal: Nothing to Disclose, Anil Arora: Nothing to Disclose

◆ 3006 | THE NATIONAL UNDER-UTILIZATION OF HEPATOCELLULAR CARCINOMA ADHERENCE AND ITS PREDICTORS IN THE UNITED STATES

Dominic Vitello[1] Mitchell Paukner[2] Laura Kulik[3] Saad Hussain[1] Bima Hasjim[4] Aditya Jain[5] Andres Duarte-Rojo[6] Filip Obradovic[5] Joy Obayemi[7] Federico Crippa[5] Michael Gmeiner[8] Therese Banea[5] Oriana Dentici[5] Lihui Zhao[5] Charles Manski[5] Daniela Ladner[5], [1]Northwestern University Feinberg School of Medicine, [2]Wake Forest University School of Medicine, [3]Northwestern Medical Faculty Foundation, [4]University of California, Irvine, [5]Northwestern University, [6]Northwestern Medicine, [7]University of Michigan / Northwestern University, [8]London School of Economics and Political Science

Background: National guidelines recommend hepatocellular carcinoma (HCC) surveillance every 6 to 8 months for patients with cirrhosis. However, rates of adherence are estimated to be extremely low. This study aimed to determine the rate of HCC surveillance adherence and identify its predictors. **Methods:** Validated ICD-9/-10 codes were used to identify patients with cirrhosis between 2011-2020 within a large, national, insurance, claims database. Clinicodemographic factors were also identified including cirrhosis

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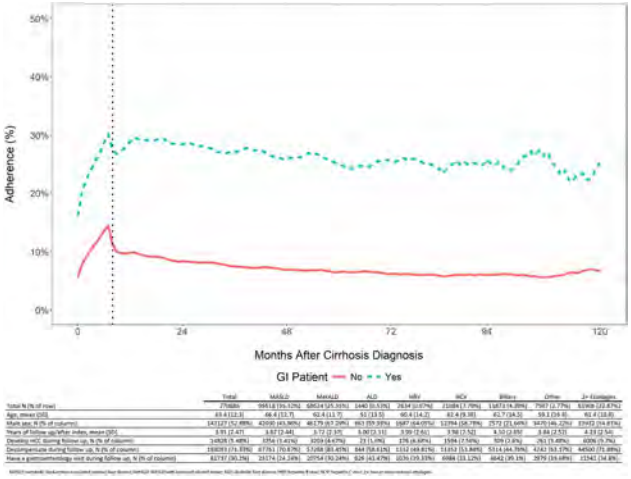
etiologies and decompensation. CPT-identified surveillance exams included serum alpha fetoprotein level with an abdominal ultrasound (AFP with US) or contrast-enhanced CT or MRI. Patients were considered adherent for 8 months following any surveillance exam. A multivariable generalized linear mixed-effects model was used to identify predictors of HCC surveillance adherence. **Results:** 270,686 patients were included in the analysis. Among other etiologies, 95,618 (35.3%) had metabolic dysfunction-associated steatotic liver disease (MASLD) and 21,084 (7.8%) had hepatitis C-associated (HCV) cirrhosis. Patients were followed for a mean (SD) of 3.9 (2.5) years. During follow up, 81,737 (30.2%) had a gastroenterology visit and 14,828 (5.5%) developed HCC. Within the 12 months following cirrhosis identification, 26,825 (9.9%) had an AFP with US, 24,406 (9.9%) had an MRI, and 14,635 (5.4%) had a CT. Only 97,102 (35.9%) patients ever received any surveillance over the entire course of follow-up. Figure 1 shows the longitudinal rate of adherence. Following with gastroenterology (OR 7.1 CI 7.0-7.2), having HCV cirrhosis (OR 3.0 CI 2.9-3.1), and decompensation (OR 1.4 CI 1.3-1.5) were significant predictors of better HCC surveillance adherence. MRI was the costliest mode of surveillance at $486.00 on average per exam, followed by CT ($278.70) and US ($114.90). Fewer than 2% of claims were denied. **Conclusion:** Despite its reported benefits, in this study of a large, national, insured cohort of patients with cirrhosis, HCC surveillance adherence was estimated to be low. Following with a gastroenterologist was a significant predictor of higher adherence. Further involvement of gastroenterologists and heightened incentives for patients are needed to maximize the population-level benefits of HCC surveillance.



Disclosures: Dominic Vitello: Nothing to Disclose, Mitchell Paukner: Nothing to Disclose, Laura Kulik: astrazeneca: Advisor, astrazeneca: steering committee, genetech: Advisor, genetech: steering committee, Fujifilm: Consultant, AstraZeneca: Speaking and Teaching, astrazeneca: Advisor, astrazeneca: steering committee, genetech: Advisor, genetech: steering committee, Fujifilm: Consultant, AstraZeneca: Speaking and Teaching, astrazeneca: Advisor, astrazeneca: steering committee, genetech: Advisor, genetech: steering committee, Fujifilm: Consultant, AstraZeneca: Speaking and Teaching, Saad Hussain: Nothing to Disclose, Bima Hasjim: Nothing to Disclose, Aditya Jain: Nothing to Disclose, Andres Duarte-Rojo: Echosens: Grant/Research Support, Filip Obradovic: Nothing to Disclose, Joy Obayemi: Nothing to Disclose, Federico Crippa: Nothing to Disclose, Michael Gmeiner: Nothing to Disclose, Therese Banea: Nothing to Disclose, Oriana Dentici: Nothing to Disclose, Lihui Zhao: Nothing to Disclose, Charles Manski: Nothing to Disclose, Daniela Ladner: Nothing to Disclose

◆ 3007 | DEVELOPMENT AND FEASIBILITY OF A PATIENT-REPORTED EXPERIENCE SURVEY FOR OUTPATIENTS WITH LIVER DISEASE

Oliver Tavabie[1] Amy Johnson[2] Felicity Williams[3] Vanessa Hebditch[4] Safa Al-Shamma[5] Dina Mansour[6], [1]Leeds Liver Unit, [2]Northumbria Healthcare NHS Foundation Trust, [3]University of Birmingham, [4]British Liver Trust, [5]University Hospitals Dorset, [6]Gateshead Health NHS Foundation Trust

Background: In the United Kingdom, regional variations in care provision and outcomes for patients with liver disease have been repeatedly highlighted. Whilst initiatives, such as Improving Quality in Liver services, as well as care bundles have been developed to address variation, there is currently no standardised patient-reported experience tool for outpatient services. This presents a challenge when comparing service provision. We aimed to develop a patient-reported experience survey (PRES) and undertake a feasibility study to understand the challenges in delivering it in the outpatient setting. **Methods:** A PRES working group was developed with healthcare professionals (HCP) from specialist and non-specialist centres, trainee, allied health professional and patient charity representatives. A survey was developed utilising existing literature. Patient feedback was provided from the British Liver Trust and HCP feedback was provided from the British Society of Gastroenterology Liver Section and Quality Standards working group. The PRES was then trialled for one month at Leeds Teaching Hospitals (LTH),

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University Hospitals Dorset (UHD) and Gateshead Health NHS Foundation Trust (GH). Projected margin of error was calculated with a target of $<10\%$ to demonstrate adequate power. **Results:** 122/1182 surveys were completed (65/848 LTH, 27/146 UHD, 30/188 GH). Margin of error for the entire sample was 8.4% meaning commonalities across sites were likely true. However, individual site margin of error was greater than 10% (LTH 11.7%, UHD 17.1%, GH 16.5%) which prevented comparison between sites. Most PRES responses were online with 22.1% completed through written format. Responses were predominately from patients with face-to-face appointments with 12.3% of respondents from telephone appointments. Appointments were mostly with Consultants (61.5%) although a broad range of HCPs were represented. 9.8% of respondents saw an HCP that they were not expecting to see.

Most respondents were happy with their overall care. All patients felt like they were treated with respect and knew why they were being seen and why tests were taken. 1.6% were unsure if they were involved with decisions around their care. 6.6% did not know how to raise questions following the appointment. 9.0% were dissatisfied with frequency of appointments. Free-text comments highlighted the challenges in seeing their team frequently enough (particularly face-to-face appointments) and with communication of appointments and tests. **Conclusion:** We have developed a PRES which can be utilised to understand patient experience of outpatient encounters. Further work is required to improve engagement with surveys to allow for this tool to be used to benchmark services.

Disclosures: Oliver Tavabie: Chiesi: Consultancy, Amy Johnson: Nothing to Disclose, Felicity Williams: Nothing to Disclose, Vanessa Hebditch: Nothing to Disclose, Safa Al-Shamma: Nothing to Disclose, Dina Mansour: Nothing to Disclose

◆ 3008 | HEPATITIS C DETECTION TO PREVENT LIVER DISEASE: IMPLEMENTATION OF OPT-OUT SCREENING WITHIN A SOUTH TEXAS EMERGENCY DEPARTMENT

Makayla Tey[1] Racquel Owino[1] Serena Gaultier-Soliz[1] Dianita Gamino[1] Delana Gonzales[1] Ralph Riviello[2] Tatiana Emanuel[2] Anna Taranova[1], [1]University Health, [2]University Health Science Center San Antonio

Background: Hepatitis C virus (HCV) remains a significant public health challenge with 40% of individuals unaware of their status until late stage liver disease. Emergency departments (ED) often serve as a primary point of care for underserved populations, providing a critical opportunity for early identification and linkage to care. Opt-out HCV testing in the ED is a strategy to increase detection rates among high risk and underdiagnosed groups. University Health (UH) is the only Level I trauma center in South Texas providing the highest level of care in the San Antonio community. **Methods:** UH implemented an opt-out HCV screening program in the ED. Providers notified of eligible patients via silent Best Practice Advisory via the electronic medical record (EMR). All patients aged 18 years and older were screened for HCV antibody with reflex to RNA testing to identify an active infection. EMR data was used to identify positive individuals and collect diagnosis data. Patients with confirmed RNA-positive results were notified of their diagnosis and referred to a patient navigator to facilitate linkage to care. **Results:** From March 2024 to March 2025, 20,637 individuals were tested for HCV in the ED. Among those screened, 17.3% (n = 1190) were antibody positive and 2.9% (n = 594) were RNA confirmed positive. Of confirmed positives 41.4% (n = 246) is a new diagnosis, 55.4% (n = 329) have a history of HCV and 3.2% (n = 19) have an unknown history of HCV. Of these, 22.6% (n = 134) were linked to care and 77.4% (n = 460) were either unreachable, incarcerated, pending diagnosis notification or deceased. **Conclusion:** Opt-out HCV testing in the ED significantly increased case identification, highlighting the ED's role as a key access point for HCV screening. There is a need for improved linkage to care among the vulnerable and transient populations however substantial barriers remain in linking patients to care to prevent liver disease.

Disclosures: Makayla Tey: Nothing to Disclose, Racquel Owino: Nothing to Disclose, Serena Gaultier-Soliz: Nothing to Disclose, Dianita Gamino: Nothing to Disclose, Delana Gonzales: Nothing to Disclose, Ralph Riviello: Nothing to Disclose, Tatiana Emanuel: Nothing to Disclose, Anna Taranova: Nothing to Disclose

◆ 3009 | LARGE-LANGUAGE-MODEL-ASSISTED VALIDATION OF ICD-10-CM CODES FOR LIVER DISEASE IN 865,079 DOCUMENTATIONS

Yichen Wang[1] Yan Yan[1] Yuting Huang[2], [1]Mayo Clinic, [2]Mayo Clinic Florida

Background: Robust health-services and population studies increasingly depend on administrative datasets,

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yet the fidelity of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes remains uncertain and manual chart review is impractical at scale. Ensuring that coded diagnoses truly mirror what was documented is critical for accurate disease surveillance, reimbursement, quality benchmarking, and resource planning in hepatology and public-health programs. **Methods:** We applied a GPT-4o-based text-analysis pipeline – built with iterative prompt optimization and majority-vote aggregation – to MIMIC-IV, a de-identified database containing full clinical text and corresponding ICD-10-CM assignments. For each code we calculated the positive predictive value (PPV), defined as the proportion of assigned codes whose target condition was explicitly documented in the source note. Performance metrics were benchmarked against physician adjudication in a 971-record validation set. **Results:** GPT-4o accurately confirmed or rejected codes (overall accuracy 97.8%, sensitivity 98.5%, specificity 94.5%). Among 865,079 total codes, 15,614 (1.8%) were liver-related. Etiology distribution was: alcohol-associated liver disease (ALD) 2,343 (15.0%), metabolic dysfunction-associated fatty liver disease or steatotic hepatitis (MAFLD/MASH) 1,448 (9.3%), hepatitis C 615 (3.9%). Stage distribution was: acute liver failure 392 (2.5%), compensated cirrhosis 1,751 (11.2%), decompensated cirrhosis 3,861 (24.7%), hepatocellular carcinoma 726 (4.7%) (Table 1). Liver codes showed higher PPV than non-liver codes at any diagnostic position (90.2 % vs 84.5 %; OR 1.69, 95 % CI 1.60-1.78; $p < 0.001$) but similar PPV when listed as the principal diagnosis (94.0 % vs 93.9 %; OR 1.01, 95 % CI 0.81-1.27; $p = 0.903$). Within liver codes, PPV varied by condition: ALD 92.7 %, hepatitis C 95.3 %, MAFLD/MASH 84.5 %, toxic/drug-induced liver injury 78.7 %, and acute liver failure 66.8 % (Table 2). Detailed PPVs for every individual ICD-10-CM code are available at https://huggingface.co/datasets/wangyichen25/ICD-10-CM_Validation_Results.

Conclusion: Most liver-related ICD-10-CM codes faithfully captured the underlying clinical conditions and out-performed non-liver codes, supporting their use in large-scale health-services research and public-health monitoring. Nevertheless, the lower reliability observed for emerging metabolic entities, toxic/drug-induced injury, and acute liver failure highlights priority areas for coder education and refinement of coding guidelines, reinforcing the need for ongoing validation to maintain data quality across administrative datasets.

Table 1. Distribution of liver-related ICD-10-CM codes (N = 15 614)

Category	ICD-10-CM group(s)	n	% of liver codes
Etiology			
Alcohol-related	K70.*	2 343	15
MAFLD / MASH	K75.81, K76.0	1 448	9.3
Hepatitis C	B17.1, B18.2	615	3.9
Hepatitis B	B16.*, B18.0, B18.1	371	2.4
Cholestatic (PBC/PSC)	K74.3, K83.01	131	0.8
Autoimmune hepatitis	K75.4	171	1.1
Metabolic (HH, Wilson, A1AT)	E83.11, E83.01, E88.01	218	1.4
Malignancy (HCC, ICC)	C22.*	726	4.6
Toxic / drug-induced	K71.*	141	0.9
Congenital (biliary atresia)	Q44.2*	2	< 0.1
Other / unspecified	Various‡	9 448	45.7
Total		15 614	100
Stage			
Acute liver failure	K72.0*	392	2.5
Compensated cirrhosis	K74.3–K74.6	1 751	11.2
Decompensated cirrhosis / PHT	I85., K72.1, K76.6, R18*	3 861	24.7
Hepatocellular carcinoma	C22.0	726	4.6
Other liver disease (non-cirrhotic)	K70., K73., K75.*, etc.	8 884	56.9
All liver codes		15 614	100

† Liver-specific codes that did not map neatly to an etiology category (e.g., K76.2, K76.8).
‡ Includes broad descriptors such as "unspecified chronic liver disease."
Abbreviations: ALD, alcohol-associated liver disease; A1AT, alpha-1 antitrypsin; CI, confidence interval; HCC, hepatocellular carcinoma; HH, hereditary haemochromatosis; ICC, intrahepatic cholangiocarcinoma; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; MAFLD, metabolic dysfunction-associated fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PHT, portal hypertension

Table 2. Positive-predictive value (PPV) of liver-related ICD-10-CM codes

	n	Correct	PPV %	95 % CI
Etiology				
Hepatitis C	615	584	95.0	92.9 – 96.4
Hepatitis B	371	346	93.3	90.2 – 95.4
Alcohol-related	2 343	2 107	89.9	88.6 – 91.1
MAFLD / MASH	1 448	1 224	84.5	82.6 – 86.3
Cholestatic (PBC / PSC)	131	116	88.6	82.0 – 93.0
Autoimmune hepatitis	171	162	94.7	90.3 – 97.2
Metabolic (HH, Wilson, A1AT)	218	181	83.0	77.5 – 87.4
Malignancy (HCC, ICC)	726	699	96.3	94.6 – 97.4
Toxic / drug-induced	141	111	78.7	71.3 – 84.7
Congenital (biliary atresia)	2	2	100.0	34.2 – 100.0
Other / unspecified	9 448	8 550	90.5	89.9 – 91.1
All liver codes	15 614	14 082	90.2	89.6 – 90.8
Stage				
Acute liver failure	392	262	66.8	62.03 – 71.31
Compensated cirrhosis	1 751	1 636	93.4	92.17 – 94.50
Decompensated cirrhosis / PHT	3 861	3 648	94.5	93.72 – 95.16
Hepatocellular carcinoma	726	699	96.3	94.64 – 97.43
Other liver disease (non-cirrhotic)	8 884	7 837	88.2	87.53 – 88.87
All liver codes	15 614	14 082	90.2	89.60 – 90.76

PPV = positive predictive value (true-positive codes ÷ total codes).
Abbreviations: ALD, alcohol-associated liver disease; A1AT, alpha-1 antitrypsin; CI, confidence interval; HCC, hepatocellular carcinoma; HH, hereditary haemochromatosis; ICC, intrahepatic cholangiocarcinoma; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; MAFLD, metabolic dysfunction-associated fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PHT, portal hypertension

Disclosures: Yichen Wang: Nothing to Disclose, Yan Yan: Nothing to Disclose, Yuting Huang: Nothing to Disclose

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◆ 3010 | REDUCING ROUTINE CONSULTATION WAIT TIMES AT A LARGE TERTIARY CARE OUTPATIENT HEPATOLOGY CLINIC

Ofodile Joe-Uzuegbu[1] Stephen Congly[1] Peter Wang[2] Alexandra Frolkis[1] Meredith Borman[1] Matthew Sadler[2] Kelly Burak[2] Laura Stinton[1] Carla Coffin[1] Mark Swain[2] Henry Nguyen[2] Abdel-Aziz Shaheen[1] Mayur Brahmania[1] Alex Aspinall[2], [1]University of Calgary Cumming School of Medicine, Calgary, AB, [2]University of Calgary

Background: Prolonged wait times for outpatient hepatology consultations can negatively affect patient outcomes and healthcare system efficiency. This quality improvement (QI) project aimed to reduce the median wait time for routine referrals from 79 weeks to 39 weeks (a 50% reduction). **Methods:** The QI project took place at Foothills Medical Centre Hepatology Clinic in Calgary, Alberta, which serves a catchment population of over 1.5 million residents. Between October 2023 and April 2025, five Plan-Do-Study-Act (PDSA) cycles were implemented: (1) re-coding and reorganization of referral diagnoses using ICD-10 classifications; (2) establishment of a dedicated hepatitis B virus (HBV) clinic to address high referral volume in this subgroup; (3) development of optimized triage guidelines for the Central Access and Triage (CAT) system to eliminate redundancies and ensure acuity-aligned prioritization; (4) structured waitlist management processes, including new protocols to fairly remove long-standing inactive referrals while ensuring equitable access to care; and (5) re-triaging benign liver neoplasm cases back to primary care with management guidelines. **Results:** Routine wait times decreased steadily over the study period, with special cause variation first observed in June 2024 and sustained improvement from February to April 2025. By April 2025, the median wait time for routine cases decreased from 78.4 to 32.9 weeks (Figure 1). Notably, although the intervention was designed to address routine wait times, its system-wide effects contributed to significant reductions in urgent wait times (from 28.3 to 4.9 weeks), while preserving access for emergent cases (stable at 2.1 weeks). Overall, the waitlist size declined from 1,426 to 252 patients, a reduction of over 80%. Statistical process control (SPC) charts were used throughout to monitor variation and system stability (Figure 1). **Conclusion:** A multi-pronged, data-driven, and clinically aligned QI project supported by leadership and embedded within clinic workflows can significantly reduce wait times without compromising timely access for higher-priority patients.

Figure 1: Statistical process chart showing sustained reduction in wait times for routine cases.

Disclosures: Ofodile Joe-Uzuegbu: Gilead Sciences Incorporated: Grant/Research Support, Stephen Congly: Axcella Health, Inc.: Grant/Research Support, AstraZenica: Grant/Research Support, Merck: Grant/Research Support, Ipsen: Grant/Research Support, Bausch Health: Grant/Research Support, Gilead Sciences Canada: Grant/Research Support, AstraZeneca: Consultant, GSK: Consultant, Oncoustics: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Boehringer Ingelheim: Consultant, Peter Wang: Nothing to Disclose, Alexandra Frolkis: Nothing to Disclose, Meredith Borman: Nothing to Disclose, Matthew Sadler: Nothing to Disclose, Kelly Burak: Nothing to Disclose, Laura Stinton: Nothing to Disclose, Carla Coffin: Gilead: Grant/Research Support, Janssen Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, Altimmune Pharmaceuticals: Fund paid to the University of Calgary, Riche Pharmaceuticals: Grant/Research Support, GSK: Funds paid to the University of Calgary, GSK: unknown, Gilead Sciences: Funds Paid to the University of Calgary, Janssen: Grant/Research Support, Gilead: Consultant, GSK: Consultant, Gilead: Sponsored lecturer (national or International), GSK: Sponsored lecturer (national or International), Roche: Consultant, Gilead (paid to the University of Calgary): Consultant, Roche (paid to the University of Calgary): Consultant, GSK (paid to the University of Calgary): Consultant, Gilead (paid to the University of Calgary): Speaking and Teaching, GSK (paid to the University of Calgary): Speaking and Teaching, Mark Swain: Nothing to Disclose, Henry Nguyen: Nothing to Disclose, Abdel-Aziz Shaheen: Nothing to Disclose, Mayur Brahmania: Nothing to Disclose, Alex Aspinall: Nothing to Disclose

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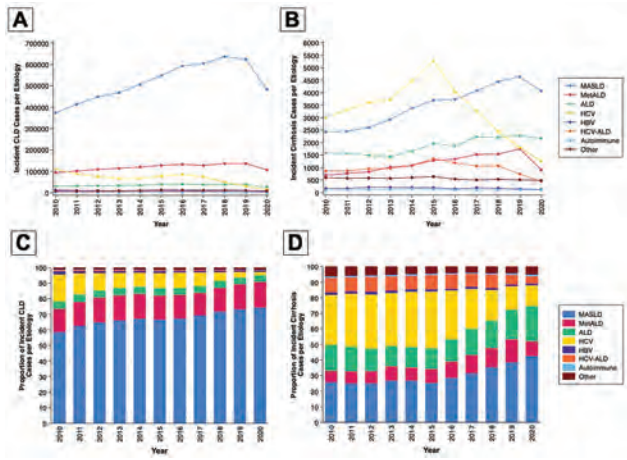
◆ 3011 | BURDEN OF CHRONIC LIVER DISEASE AND CIRRHOSIS BY ETIOLOGY IN U.S. VETERANS

Akshatha Kiran[1] Pedro Ochoa-Allemant[2] Catherine Mezzacappa[3] David Kaplan[2] Nadim Mahmud[4], [1]Hospital at the University of Pennsylvania, [2]University of Pennsylvania, [3]Yale University, [4]Hospital of the University of Pennsylvania

Background: Steatotic liver disease, encompassing metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-associated liver disease (ALD), and metabolic and alcohol-associated liver disease (MetALD), is the leading cause of liver disease worldwide. The epidemiology of chronic liver disease and cirrhosis according to the revised nomenclature is incompletely characterized. This study aimed to determine temporal trends and distribution of underlying etiologies of chronic liver disease and cirrhosis over the past decade in the Veterans Health Administration (VHA). **Methods:** We conducted a retrospective cohort study of adults with newly diagnosed chronic liver disease (imaging-confirmed steatosis or primary liver disease) and cirrhosis (at least 1 inpatient or 2 outpatient ICD codes) receiving care in the national VHA between 2010 and 2020. Etiology of liver disease was determined using a previously validated hierarchical approach incorporating laboratory values, vital signs, anthropometric measurements, diagnosis codes, and validated alcohol use assessments. We quantified annual incident cases of chronic liver disease and cirrhosis and examined changes in distribution of underlying liver disease etiologies over time. **Results:** Between 2010 and 2020, incident chronic liver disease due to MASLD increased by 70%, rising from 374,020 to 623,520 cases (absolute increase, 20,994 per year; 95% CI, 8,345 to 33,644; $P = 0.005$). In contrast, the number of incident cases of chronic liver disease due to hepatitis C virus (HCV) infection gradually declined, from 110,180 to 14,520 cases (absolute decrease, 6,868 per year; 95% CI, -10,212 to -3,523; $P = 0.001$). By 2020, MASLD accounted for over 70% of all newly diagnosed cases of chronic liver disease. In comparison, the number of incident cases of cirrhosis due to HCV infection progressively increased through 2015, followed by a drastic decline thereafter, from 5,292 to 1,258 cases (absolute decrease, 791 per year; 95% CI, -947 to -635; $P < 0.001$). Since 2017, MASLD has become the leading cause of newly diagnosed cases of cirrhosis. There were no substantial changes in the number of incident cases of chronic liver disease or cirrhosis due to other liver disease etiologies over the study period. **Conclusion:** The burden of chronic liver disease and cirrhosis have changed over the past decade in the VHA. MASLD has emerged as the main cause of both chronic liver disease and cirrhosis. Cirrhosis due to HCV infection has notably declined since 2015. These epidemiological shifts reflect the success of the highly effective direct-acting antiviral therapies and underscores the importance of early identification and treatment of MASLD to prevent progression of disease.



Disclosures: Akshatha Kiran: Nothing to Disclose, Pedro Ochoa-Allemant: Nothing to Disclose, Catherine Mezzacappa: Nothing to Disclose, David Kaplan: AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Sirtex: Advisor, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research Support, Nadim Mahmud: Grifols: Grant/Research Support

◆ 3012 | SOCIAL RISK PHENOTYPES PREDICT STAGE, TREATMENT, AND MORTALITY IN HEPATOCELLULAR CARCINOMA: A LATENT CLASS ANALYSIS

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Background: Disparities in hepatocellular carcinoma (HCC) outcomes are shaped by intersecting social determinants of health (SDOH), but most studies assess individual risk factors in isolation. We hypothesized that patients cluster based on SDOH into distinct social risk phenotypes associated with differences in cancer stage at diagnosis, treatment receipt, and mortality. **Methods:** We analyzed data from 4,117 adults diagnosed with HCC in the Indiana State Cancer Registry (2009–2020). Latent class analysis (LCA) was used to empirically identify social risk profiles using sex, race, insurance, marital status, occupation, neighborhood Social Deprivation Index (SDI), and geographic access to care. Outcomes included early-stage diagnosis, curative therapy receipt, and two-year mortality. Associations were assessed using logistic regression. **Results:** Among 4,117 patients, 74% were men, 26% women, and15.8% non-White. Most were publicly insured

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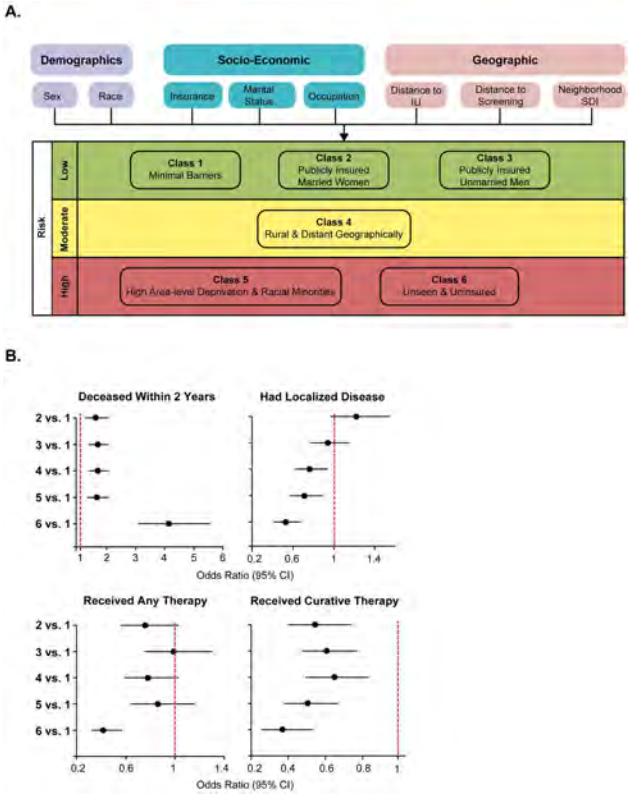
(67.6%), and 54.9% were unemployed, retired, or disabled. Just over half had localized disease (51.1%), 16.2% received curative therapy, and 67.4% died within two years. LCA identified six distinct social risk classes with variation in structural and geographic characteristics (Figure 1A). Class 1 ("Minimal Barriers") had the best outcomes while Class 6 ("Unseen and Uninsured") had the worst with 55.4% vs. 39.7% early diagnosis, 24.4% vs. 10.5% curative therapy, and 55.4% vs. 83.6% mortality. The OR for 2-year mortality for Class 6 vs. Class 1 was 4.12, (95% CI 3.06–5.54). Rural patients (Class 4) and racially marginalized, publicly insured patients (Class 5) also had lower odds of early detection and treatment. When grouped into three tiers, outcomes declined progressively: Tier 1 (Classes 1–3) had 60.2% early-stage diagnosis, compared to 47.6% in Tier 2 (Class 4) and 39.7% in Tier 3 (Classes 5–6) (Figure 1B).

Figure 1 Legend

Panel A illustrates the distribution of demographic, socioeconomic, and geographic variables that informed an empirically derived latent class analysis. This analysis identified six distinct social risk phenotypes.

Panel B presents odds ratios for key clinical outcomes (e.g., early-stage diagnosis, treatment receipt, mortality) by class, demonstrating clear gradients in disease burden and care access. **Conclusion:** Social risk phenotypes were strongly associated with stage, treatment, and mortality in HCC. These findings support the use of risk-based stratification to guide tailored, scalable strategies to improve early detection and outcomes.



Disclosures: Lauren Nephew: NovoNordisk: Consultant, Allie Carter: Nothing to Disclose, Katherine Ross-Driscoll: Nothing to Disclose, Dipika Gupta: Nothing to Disclose

◆ 3013 | A NOVEL CLINICAL TOOL FOR DECOMPENSATION PREDICTION AND RISK STRATIFICATION IN CIRRHOSIS

Dominic Vitello[1] Federico Crippa[2] Saad Hussain[1] Saad Hussain[1] Bima Hasjim[3] Filip Obradovic[2] Joy Obayemi[4] Gil Peled[2] Melvin Adams[2] Paola Barrios Martinez[1] Aditya Jain[2] Kelly Bates[1] Michael Gmeiner[5] Andres Duarte-Rojo[6] Laura Kulik[7] Therese Banea[2] Oriana Dentici[2] Lihui Zhao[2] Lisa VanWagner[8] Charles Manski[2] Daniela Ladner[1], [1]Northwestern University Feinberg School of Medicine, [2]Northwestern University, [3]University of California, Irvine, [4]University of Michigan / Northwestern University, [5]London School of Economics and Political Science, [6]Northwestern Medicine, [7]Northwestern Medical Faculty Foundation, [8]University of Texas Southwestern Medical Center

Background: Care for patients with cirrhosis is chronic, complex, and costly. There are no tools available to stratify decompensation risk in a generalizable cirrhosis population. The aim was to develop a model for decompensation risk that can be used as a clinical decision support tool. **Methods:** Validated ICD-9, -10, and CPT codes were used identify patients with baseline compensated cirrhosis between 2012-2023 within a large, national, insurance, claims database. Demographics, cirrhosis etiology, and laboratory values were also identified. Multivariable logistic regression was used to predict 6- and 12-month decompensation risk. The model was internally temporally cross-validated. **Results:** 188,526 patients were included. 50.8% were male with a median age of 63. Among other etiologies, 47.1% had metabolic dysfunction-associated liver disease (MASLD), 14.2% had hepatitis C-associated liver disease (HCV) 12.2% had MASLD with increased alcohol intake (MetALD), 8.3% had biliary cirrhosis, and 2.1% had alcohol-associated liver disease (ALD). 9,841 (5.2%) and 18,907 (11.3%) decompensated by 6 and 12 months respectively. The model had excellent calibration in derivation and validation sets, with predicted risks within 0.8% of true risk, on average (Figure 1a). The 12-month decompensation risk was highest for those with ALD (OR 1.9 95% CI 1.6-2.3) and MetALD (OR 1.3 95% CI 1.1-1.5), but lowest for those with biliary cirrhosis (OR 0.5 95% CI 0.4-0.6). The presence of hepatocellular carcinoma (OR 1.9 95% CI 1.6-2.2) or chronic kidney disease requiring dialysis (OR 1.4 95% CI 1.1-1.7) conferred substantial increases in risk (Figure 1b). **Conclusion:** The risk of decompensated

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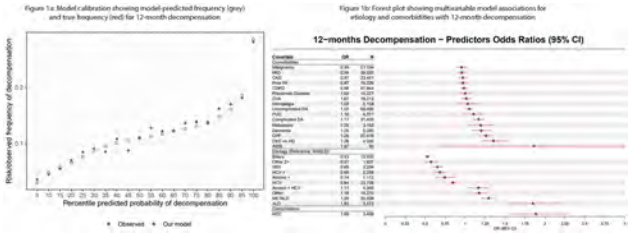
cirrhosis is higher in this general cohort of patients than patients receiving specialty care. The associated risk calculator may be used by clinicians to identify patients in need of escalated care, including transplant.



Disclosures: Dominic Vitello: Nothing to Disclose, Federico Crippa: Nothing to Disclose, Saad Hussain: Nothing to Disclose, Nothing to Disclose, Saad Hussain: Nothing to Disclose, Nothing to Disclose, Bima Hasjim: Nothing to Disclose, Filip Obradovic: Nothing to Disclose, Joy Obayemi: Nothing to Disclose, Gil Peled: Nothing to Disclose, Melvin Adams: Nothing to Disclose, Paola Barrios Martinez: Nothing to Disclose, Aditya Jain: Nothing to Disclose, Kelly Bates: Nothing to Disclose, Michael Gmeiner: Nothing to Disclose, Andres Duarte-Rojo: Echosens: Grant/Research Support, Laura Kulik: astrazeneca: Advisor, astrazeneca: steering committee, genetech: Advisor, genetech: steering committee, Fujifilm: Consultant, AstraZeneca: Speaking and Teaching, astrazeneca: Advisor, astrazeneca: steering committee, genetech: Advisor, genetech: steering committee, Fujifilm: Consultant, AstraZeneca: Speaking and Teaching, astrazeneca: Advisor, astrazeneca: steering committee, genetech: Advisor, genetech: steering committee, Fujifilm: Consultant, AstraZeneca: Speaking and Teaching, Therese Banea: Nothing to Disclose, Oriana Dentici: Nothing to Disclose, Lihui Zhao: Nothing to Disclose, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, Charles Manski: Nothing to Disclose, Daniela Ladner: Nothing to Disclose

◆ 3014 | PERSISTENT USE OF MEDICATIONS FOR ALCOHOL USE DISORDER IN ALL OF US PARTICIPANTS

Phuc Le[1] Yihua Yue[1] Michael Rothberg[1] Daniel Jonas[2] Hamlet Gasoyan[1] Sudie Back[3] Ha Tran[1] Olajide Adekunle[1] Katharine Bradley[4], [1]Cleveland Clinic, [2]Ohio State University College of Medicine, [3]Medical University of South Carolina, [4]Kaiser Permanente Washington Health Research Institute

Background: Pharmacotherapy for alcohol use disorder (AUD) is effective yet underutilized. While the initiation of medications has been studied, less is known about the persistence of AUD medication use. **Methods:** We conducted a retrospective cohort study using the All of Us nationwide database (N = 633,540 participants with data up to September 2023) to assess AUD medication persistence. Adults (aged ≥ 18 years) with any AUD diagnosis who received ≥ 1 prescription for FDA-approved medications (naltrexone, acamprosate, or disulfiram) were included. Persistent AUD medication treatment was defined as orders for AUD medication(s) covering ≥ 180 continuous days (with < 20% or 36 days total gap, i.e. days without medication). Descriptive analyses compared characteristics between patients with ≥ 1 persistent episode and those without. Multivariable mixed-effects logistic regression was used to examine factors associated with persistence, adjusting for demographic, socioeconomic, and clinical characteristics, with a random intercept to account for patient-level clustering. Analyses were restricted to treatment episodes that began in 2010 or later and were shorter than three times the standard deviation of the overall mean episode length. **Results:** Among 26,211 patients with AUD identified from the database, 3,457 patients were treated with 46,121 episodes (median 2 per patient ever treated). Over one-third of patients (N = 1,236) had ≥ 1 treatment episode lasting ≥ 180 days ("persistent treatment"), but most episodes (N = 44,354; 96.2%) were < 180 days. Compared to those without persistent treatment, patients with ≥ 1 persistent episode were more likely to be non-Hispanic White, employed, married, have a college degree or higher, annual income > $100k, and private insurance, and reside in the least deprived areas (1st quintile of the Area Deprivation Index—ADI). In the multivariable model, factors associated with decreased odds of persistent treatment included having a substance use disorder (OR = 0.72; 95% CI: 0.61-0.85), annual income < $10k (OR = 0.66; 95% CI: 0.45-0.96), living in 2nd-4th ADI areas, and having VA (OR = 0.41; 95% CI: 0.30-0.56) or no insurance (OR = 0.56; 95% CI: 0.38-0.83). In contrast, receipt of individual psychotherapy sessions was associated with higher odds of persistence (OR = 1.51; 95% CI: 1.23-1.86). **Conclusion:** Persistent treatment with AUD medications remains uncommon, with < 4% of episodes lasting ≥ 180 days. People with low income, living in more deprived areas, having VA or no insurance, and substance use disorder were less likely to be persistent, while individual psychotherapy sessions were positively associated with persistence. These findings emphasize the need to address barriers to sustained pharmacotherapy for AUD.

Disclosures: Phuc Le: Nothing to Disclose, Yihua Yue: Nothing to Disclose, Michael Rothberg: Nothing to Disclose, Daniel Jonas: Nothing to Disclose, Hamlet

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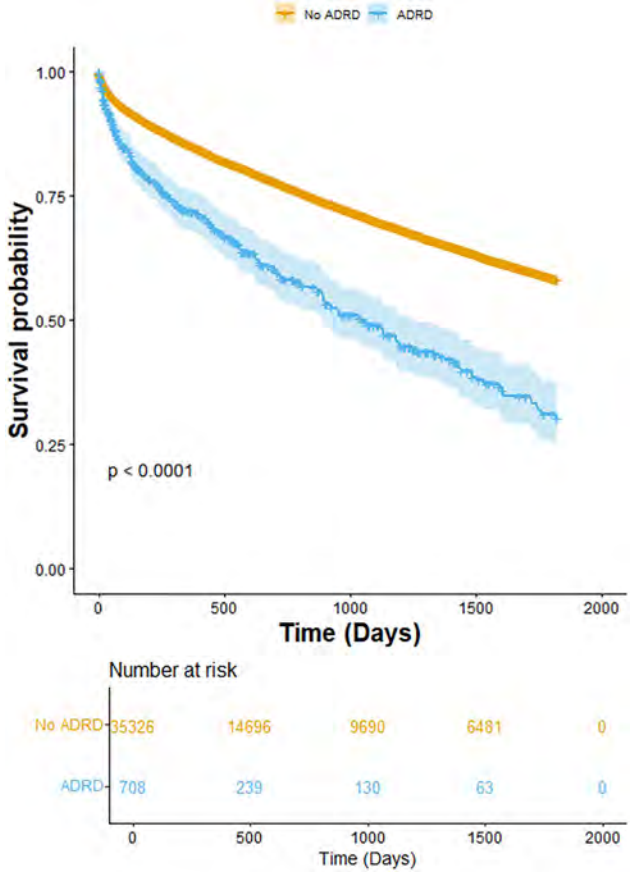
Gasoyan: Nothing to Disclose, Sudie Back: Nothing to Disclose, Ha Tran: Nothing to Disclose, Olajide Adekunle: Nothing to Disclose, Katharine Bradley: Nothing to Disclose

◆ 3015 | THE PREVALENCE AND IMPACT OF ALZHEIMER'S AND RELATED DEMENTIA ON CIRRHOSIS: A RETROSPECTIVE STUDY USING REAL-WORLD DATA

Sijia Wei[1] Suyangpeng Zhang[2] Saad Hussain[3] Salva Balbale[4] Oriana Dentici[3] Alona Furmanchuck[4] Nikhilesh Mazumder[5] Lisa VanWagner[6] Liui Zhao[4] Andres Duarte-Rojo[7] Sanjay Mehrotra[2] Daniela Ladner[1] CAPriCORN Consortium[8], [1]Department of Surgery, Northwestern University Feinberg School of Medicine, [2]McCormick School of Engineering and Applied Science, Northwestern University, [3]Northwestern University Transplant Outcomes Research Collaborative, [4]Northwestern University Feinberg School of Medicine, [5]Department of Gastroenterology, University of Michigan, [6]Department of Medicine, University of Texas Southwestern Medical Center, [7]Northwestern Medicine, [8]CAPriCORN Consortium

Background: Alzheimer's and related dementia (ADRD) complicate cirrhosis management; particularly, its symptoms overlap with hepatic encephalopathy. However, ADRD prevalence and impact on cirrhosis remain unclear. This study examined ADRD prevalence and its association with mortality and 1-year hospitalization in cirrhosis after ascertaining ADRD diagnostic certainty. **Methods:** We retrospectively analyzed 36,971 patients diagnosed with cirrhosis between 2011 and 2021 at seven health systems in a US metropolitan area using electronic health records data. ADRD diagnosis and diagnostic certainty were determined using ICD-9/10 codes, medications, specialist involvement, and diagnostic timing. Multivariable logistic regressions and the Cox proportional hazards models assessed ADRD risk factors and ADRD influence on mortality and hospitalization. **Results:** The cohort had a mean age of 59.6 years, with 41.9% female, 43.0% White, 21.8% Black, and 20.6% Hispanic. Common etiologies included MASLD (24.0%), MetALD (20.4%), HCV (13.9%), and ALD (10.3%), with a mean MELD score of 15.5 and Charlson Comorbidity Index of 6.8. At initial cirrhosis diagnosis, 2.0% (n = 727) had an ADRD diagnosis. After adjusting for covariates, having ADRD was associated with increased risk of mortality (HR = 1.81, $p < 0.001$) and likelihood of 1-year hospitalization (OR = 2.60, $p < 0.001$) in compensated, but not in decompensated cirrhosis (HR = 0.89, $p = 0.44$; OR = 1.44, $p = 0.12$). Key factors associated with ADRD diagnosis and outcomes included age, MetALD, ALD, and Area Deprivation Index. **Conclusion:** Early detection and management of ADRD and developing tailored interventions based on the underlying mechanisms of cognitive decline may improve cirrhosis outcomes. Further development of new psychometric tools to better differentiate ADRD from HE in routine care is needed.



Disclosures: Sijia Wei: Nothing to Disclose, Suyangpeng Zhang: Nothing to Disclose, Saad Hussain: Nothing to Disclose, Salva Balbale: Nothing to Disclose, Oriana Dentici: Nothing to Disclose, Alona Furmanchuck: Nothing to Disclose, Nikhilesh Mazumder: Nothing to Disclose, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, Liui Zhao: Nothing to Disclose, Andres Duarte-Rojo: Echosens: Grant/Research Support, Sanjay Mehrotra: Nothing to Disclose, Daniela Ladner: Nothing to Disclose, CAPriCORN Consortium: Nothing to Disclose

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◆ 3016 | SARCOPENIA, OBESITY, AND THEIR ASSOCIATIONS WITH INCIDENT CIRRHOSIS, HEPATOCELLULAR CARCINOMA, AND LIVER-RELATED MORTALITY: SYNERGISTIC RISK OF SARCOPENIA AND ALCOHOL IN A METABOLICALLY AT-RISK POPULATION: A PROSPECTIVE COHORT STUDY

Hyunseok Kim[1] Abdelrahman Attia[2] Minsun Kwak[2] Derin Celtik[2] Beza Mengistu[3] Kelsy Larios[3] Walid Ayoub[2] Alexander Kuo[2] Paul Martin[2] Hirsh Trivedi[2] Aarshi Vipani[2] Yun Wang[2] Suthat Liangpunsakul[4] Stephen Pandol[2] Debiao Li[2] Shelly Lu[2] Ju Dong Yang[2], [1]Cedars Sinai Medical Center, [2]Cedars-Sinai Medical Center, [3]UCLA, [4]Indiana University Medical Center

Background: Sarcopenia and obesity are each associated with adverse liver outcomes, but their combined effects—and potential interaction with alcohol use—in populations at risk for metabolic dysfunction-associated steatotic liver disease (MASLD) or Metabolic dysfunction–Associated Alcohol-Related Liver Disease (MetALD) are not well understood. We evaluated the associations of sarcopenia, obesity, and sarcopenic obesity with incident cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality, and assessed effect modification by excessive alcohol intake. **Methods:** We included UK Biobank participants with ≥1 metabolic risk factor (diabetes, hypertension, dyslipidemia, or obesity) at baseline to define a metabolically at-risk population. Sarcopenia was defined using sex- and age-specific 20th percentile cutoffs for handgrip strength and appendicular lean mass index; obesity was defined as body fat percentage ≥25% in men and ≥35% in women by bioimpedance. Outcomes were identified through linked national health records. Cox proportional hazards models estimated adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs), adjusting for demographic, lifestyle, and metabolic factors, as well as PNPLA3 genotype. Interaction with excessive alcohol use was also evaluated. **Results:** Among 354,495 participants (mean age 56 years; 54% women), 2.1% had sarcopenia alone, 54.5% obesity alone, and 0.8% sarcopenic obesity. Over a median follow-up of 13 years, all phenotypes were associated with significantly increased risk of incident cirrhosis compared to those without either condition: sarcopenia alone (aHR 1.65 [1.27–2.15]), obesity alone (1.77 [1.60–1.95]), and sarcopenic obesity (1.87 [1.23–2.83]). Sarcopenic obesity was also associated with the highest observed hazard ratios for liver-related mortality (2.53 [1.38–4.65]) and comparably elevated risk for HCC (2.51 [1.12–8.03]). The association between sarcopenia and cirrhosis was significantly stronger among individuals with excessive alcohol use (aHR 2.34 [1.00–3.45]) compared to non-excessive drinkers (aHR 1.55 [1.17–2.06]; p-interaction <0.01). **Conclusion:** In this large metabolically at-risk cohort, sarcopenia and obesity were independently associated with increased risks of cirrhosis, HCC, and liver-related mortality. Sarcopenic obesity conferred the highest overall risk, highlighting the importance of evaluating both muscle and fat composition. Sarcopenia was particularly prognostic in the context of excessive alcohol use, identifying a potentially high-risk subgroup relevant to MetALD.

Table. Associations Between Sarcopenia-Obesity Phenotype and Liver Outcomes

Phenotype	Incident Cirrhosis HR (95% CI)	Incident HCC HR (95% CI)	Liver-related Mortality HR (95% CI)
Neither sarcopenia nor obesity	Reference	Reference	Reference
Sarcopenia only	1.65 (1.27-2.15)	2.96 (1.56-5.63)	2.21 (1.54-3.19)
Obesity only	1.77 (1.60-1.95)	2.85 (2.14-3.79)	2.01 (1.71-2.37)
Sarcopenic obesity	1.87 (1.23-2.83)	2.51 (1.12–8.03)	2.53 (1.38-4.65)

Adjusted for age, sex, race/ethnicity, smoking status, socioeconomic deprivation, alcohol use, diabetes, hypertension, dyslipidemia, and *PNPLA3* genotype

Disclosures: Hyunseok Kim: Nothing to Disclose, Abdelrahman Attia: Nothing to Disclose, Minsun Kwak: Nothing to Disclose, Derin Celtik: Nothing to Disclose, Beza Mengistu: Nothing to Disclose, Kelsy Larios: Nothing to Disclose, Walid Ayoub: Intercept: Speaking and Teaching, Mirum: Grant/Research Support, GSK: Grant/Research Support, Madrigal: Grant/Research Support, Cymabay: Consultant, Ipsen: Grant/Research Support, Zydus: Grant/Research Support, Gilead: Grant Research Support, Alexander Kuo: Nothing to Disclose, Paul Martin: Nothing to Disclose, Hirsh Trivedi: Nothing to Disclose, Aarshi Vipani: Nothing to Disclose, Yun Wang: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Stephen Pandol: Nothing to Disclose, Debiao Li: Nothing to Disclose, Shelly Lu: Nothing to Disclose, Ju Dong Yang: Exact Sciences: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Exelixis: Consultant, Fujifilm Medical Sciences: Consultant

◆ 3017 | AUTOMATED SCREENING OF BLOODBORNE VIRUSES IN HEALTH SYSTEMS: REGIONAL MODEL FOR SYNDEMIC TESTING

Su Wang[1] Ruth Brogden[2] Jaymie Yango[2] Nandanie Budhoo[2] Eric Handler[2] Stephen O'Mahony[3], [1]RWJBarnabas Health, Barnabas Health Medical Group, [2]Cooperman Barnabas Medical Center, [3]RWJBarnabas Health

Background: Hepatitis B and C surveillance in the US is at risk due to public health funding cuts. In April 2025

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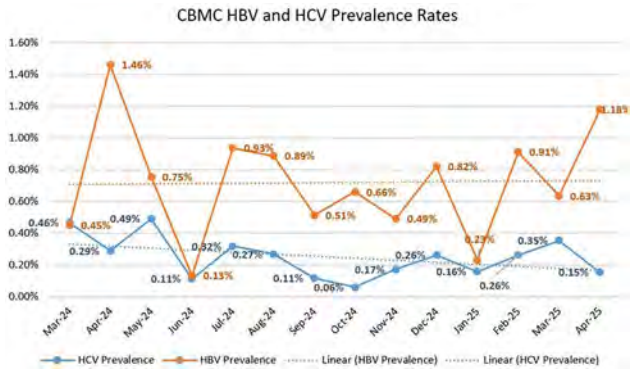
the CDC viral hepatitis reference laboratory was shut down which conducts hepatitis testing for the NHANES national survey and is essential for surveillance and monitoring of viral hepatitis (VH). Thus, regional testing efforts in health care systems will be important to assess local prevalence and detect rises in VH cases. Integrated testing of blood borne viruses (BBV) to include hepatitis and HIV will be critical to elimination efforts of syndemics. Electronic medical record (EMR) based automated screening at hospitals can be a streamlined approach for syndemic BBV testing. In a 597-bed community hospital with an Emergency Department (ED) of 100,000 yearly visits, an algorithm was implemented to scale up HCV, HBV, HDV and HIV screening and linkage to care (LTC). **Methods:** In 2018, the EMR was modified at Cooperman Barnabas Medical Center (CBMC) to implement automated HCV (HCVAb reflex to HCV RNA) and HBV (HBsAg) screening, in 2020 screening criteria was expanded to meet CDC recommendations (universal HCV screening) and to increase identifying undiagnosed (urine/serum toxicology and peer recovery specialist orders added), in 2021 at-risk automated HIV screening was included in ED, and in 2022 automated hepatitis delta (HDV Ab) reflex testing (HBsAg+ reflex HDV Ab) was implemented. Positive results are sent to patient navigators (PN) in real-time who initiate individualized linkage-to-care for evaluation and treatment.
Results: A total 140,064 HCV screenings were conducted with 504 (0.36%) current HCV infection and 432 (86%) LTC. Since 2021, ED at-risk HIV screenings totalled 7,892 with 121 (1.5%) infected and 117 (97%) LTC. Patients screened for HBV totalled 61,730 with 511 (0.83%) infected and 437 (86%) LTC. Since August 2022, when HDV Ab reflex testing began, there were 115 HBsAg+ and in those,100 HDV Ab tests were reflexively tested. There were 3 (3.0%) HDV Ab+ and only one had HDV RNA tested with was negative. One patient followed up with provider and HDV RNA was negative. One patient was lost to follow up. **Conclusion:** Automated EMR based screening in a community hospital was able to scale up population level hepatitis and HIV screening and found about 1,000 individuals with VH, a prevalence rate of 0.8% for HBV and 0.4% for HCV and more than 80% were LTC. The program successfully piloted HBsAg reflex to HDV Ab testing, though no cases were found. With risk based HIV testing, more than 100 HIV infected individuals were found with a prevalence of 1.5% and 97% were linked to care. This emphasizes the need to continue scaled-up system-based screening and LTC to combat the VH and HIV epidemics. This screening program was partially funded by the NJ Department of Health, and such private-public partnerships are important with federal public health funding challenges.



Disclosures: Su Wang: Gilead Sciences: Grant/Research Support, Ruth Brogden: Nothing to Disclose, Jaymie Yango: Nothing to Disclose, Nandanie Budhoo: Nothing to Disclose, Eric Handler: Nothing to Disclose, Stephen O'Mahony: Nothing to Disclose

◆ 3018 | IMPACT OF PRIOR AWARENESS OF CHRONIC LIVER DISEASE ON THE RISK OF FURTHER DECOMPENSATION IN PATIENTS WITH HEPATIC DECOMPENSATION

Junlong DAI[1] Jan Catherine Carrera[2] Terry Cheuk-Fung Yip[1] Grace Lai-Hung Wong[1] Vincent Wai-Sun Wong[1] Jimmy Che-To Lai[1], [1]The Chinese University of Hong Kong, [2]Chong Hua Hospital, Republic of the Philippines

Background: Chronic liver disease often begins insidiously and lacks specific clinical symptoms, leading the diagnosis only be made at the first hepatic decompensation event in some patients. This study aimed to evaluate the proportion of patients with decompensated cirrhosis who were aware of the diagnosis at initial decompensation and whether that affected clinical outcomes and the risk of further decompensation. **Methods:** We conducted a territory-wide cohort study of 9,748 patients with confirmed chronic liver disease who developed hepatic decompensation between 2000 and 2020. Decompensation and further decompensation were defined by Baveno VII criteria. Patients were categorized as "aware" or "unaware" group based on the presence of ICD-9-CM diagnosis codes for chronic liver disease or relevant laboratory results < 1 month versus ≥ 1 month, respectively, before their first decompensation. We compared baseline characteristics, initial decompensation patterns and further decompensation. Fine-Gray regression was used to assess the association between prior awareness and further decompensation, accounting for death and liver transplantation. **Results:** Overall, 44.7% of patients were unaware of their liver disease at the time of first

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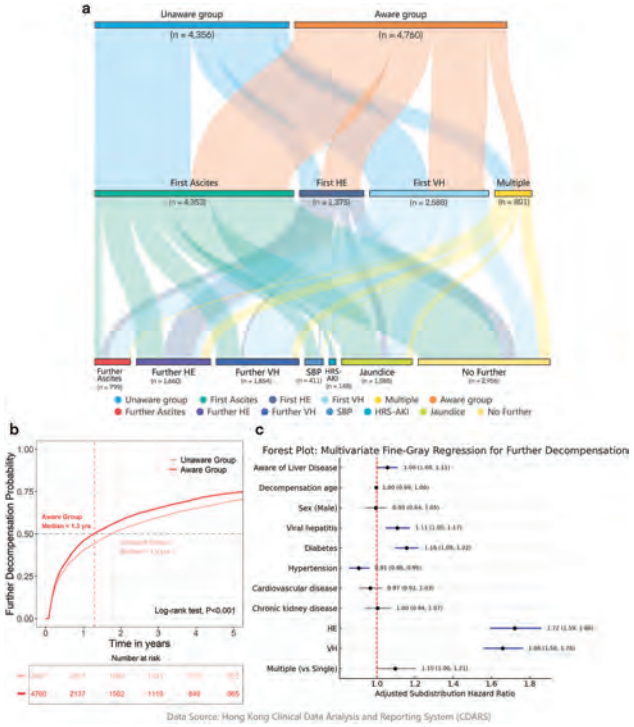
decompensation (Unaware group: 4,357 vs. Aware group: 4,760). The two groups were comparable in age (62.9 ± 13.4 vs. 62.6 ± 13.0 years, p = 0.259) and sex (male: 72.7% vs. 73.4%, p = 0.486). The unaware group had lower Model for End-stage Liver Disease score) but higher rates of variceal hemorrhage (30.3% vs. 26.7%, p < 0.001) and ascites (49.5% vs. 46.2%, p < 0.001) at the index decompensation. However, the unaware group had a lower crude incidence of further decompensation (13.6 vs. 17.1 per 100 person-years, p <0.001). In multivariable analysis, prior awareness (adjusted sHR 1.06, 95% CI 1.01-1.11), viral hepatitis, and diabetes were independently associated with further decompensation. **Conclusion:** A high proportion of patients are unaware of their liver disease at the time of the first decompensation. However, patients who still develop decompensation despite being under medical care have worse liver function and a higher risk of further decompensation.



Disclosures: Junlong DAI: Nothing to Disclose, Jan Catherine Carrera: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Vincent Wai-Sun Wong: Nothing to Disclose, Jimmy Che-To Lai: Nothing to Disclose

◆ 3019 | CHINESE PHYSICIANS&RSQUO; PERSPECTIVES ON HUMAN ALBUMIN FOR THE TREATMENT OF CIRRHOSIS COMPLICATIONS: INSIGHTS FROM A NATIONWIDE QUESTIONNAIRE STUDY

Zhan Zeng[1] Jinghang Xu[1] Yifan Han[1] Ning Lin[1] yanyan yu[2] Xiaoyuan Xu[1], [1]Peking university first hospital, [2]Peking universtiy first hospital

Background: Previous studies in Europe and the United States have investigated the use of human albumin (HA) in patients with liver disease, but no such research has been conducted in China. This study investigated patterns of HA use among Chinese physicians. **Methods:** A questionnaire-based survey was conducted among physicians across 29 provinces in China. The primary objectives of this study were to assess the use of HA for indications and other complications. Additionally, we compared HA use between different hospital levels and between physicians with different job titles. **Results:** A total of 531 valid responses were collected from physicians. Among them, 19.8% were chief physicians, 29.5% were associate chief physicians, 34.5% were attending physicians, and 16.2% were residents. Among all the physicians, 80.0% worked in tertiary hospitals, whereas 20.0% worked in secondary hospitals. The physicians were from various specialties: infectious disease (37.3%), gastroenterology (23.5%), hepatology (17.1%), general internal medicine (8.7%), and other departments (13.4%). The primary reasons for initiating HA therapy were ascites (44.4%) and hypoalbuminemia (28.4%). The main concerns regarding HA use, as cited by 56.7% of the physicians, were medical insurance restrictions, followed by cost concerns (20.0%).

HA was used to treat ascites, spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome (HRS) by 95.7%, 75.3%, and 87.4% of the physicians, respectively. An initial dosage of 10–20 g/day was used for ascites, SBP, and HRS by 82.5%, 82.6%, and 79.6% of the physicians, respectively. The median durations of HA use to treat ascites, SBP, and HRS were 7, 5, and 7 days, respectively.

The use of HA for other complications varied by condition, with 50.0% of the physicians using HA to treat shock and pleural effusion (PE), 30.0% using HA to treat gastrointestinal bleeding and non-SBP infections, and 27.0% using HA to treat primary liver cancer. Compared with those in secondary hospitals, physicians in tertiary hospitals were more likely to prescribe an initial dose of 10–20 g/day ($P < 0.001$) and more likely to use HA to treat shock ($P < 0.001$). For other complications, such as hepatic encephalopathy, hyponatremia, portal vein thrombosis (PVT), sarcopenia in cirrhosis, and non-SBP infections, chief physicians were

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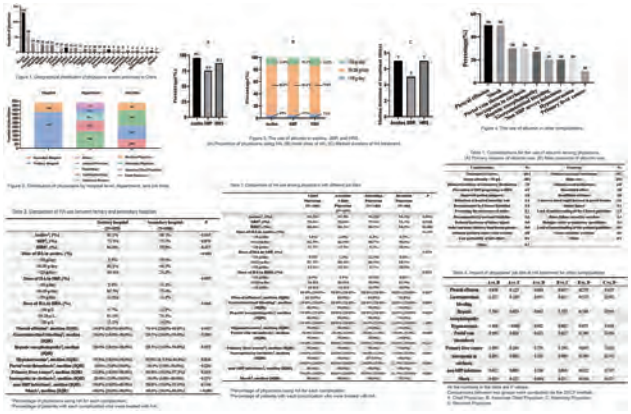
more likely than attending physicians to use HA ($P < 0.05$). Additionally, chief physicians used HA more often than residents to treat PE, hyponatremia, and shock ($P < 0.05$). Associate chief physicians prescribed HA more frequently than attending physicians to treat hyponatremia, PVT, and sarcopenia ($P < 0.05$). **Conclusion:** HA is primarily used in China for treating ascites and hypoalbuminemia, with insurance restrictions being a major concern. While HA is used in accordance with clinical guidelines, notable variations exist on the basis of hospital level and physician job title.



Disclosures: Zhan Zeng: Nothing to Disclose, Jinghang Xu: Nothing to Disclose, Yifan Han: Nothing to Disclose, Ning Lin: Nothing to Disclose, yanyan yu: Nothing to Disclose, Xiaoyuan Xu: Nothing to Disclose

◆ 3020 | A POCKET OF UNTAPPED POTENTIAL: A NOVEL APPROACH TO ENSURING TIMELY PARACENTESIS

Joseph Abraham[1] Frank Nelson[1] Vasundhara Singh[1] Lance Maresky[2], [1]Mount Sinai Morningside-West, [2]Mount Sinai West

Background: The imperative to perform diagnostic paracentesis as proximal to admission as possible has been firmly established, but a simple, cost-effective, and consistently reliable solution to ensuring timely performance has proven elusive to date. With increasing subspecialization in the field of Internal Medicine, the role of the hospitalist has metamorphosed, and the expectation for certification in specialized procedures, such as paracentesis, has diminished. Many hospitals have traditionally relied on procedure services to manage specialized procedures. As a result, the majority of clinicians are uncertified to perform these procedures, which were previously squarely in their scope of practice. This gap in certification poses challenges for procedural safety and operational efficiency. **Methods:** The pilot project involved several key components: 1) secure chat integration, 2) certification program, 3) rigorous training modules, and 4) strict guidelines and protocols. A secure Epic chat group was established, containing members who are either already certified in performing paracenteses or those who are seeking certification. As soon as the need for a paracentesis is identified, a chat is started with this Paracentesis Team. Once suitable clinicians are identified to perform the paracentesis, the trainee is encouraged to review our proprietary online modules which provide comprehensive insight into the procedure. A high bar is set for the minimum requirement of procedures successfully completed before becoming independently certified. **Results:** Prior to implementation of the intervention, only 16 out of 256 Internal Medicine residents (6.3%) in our residency program were certified to independently perform abdominal paracentesis. Between November 19, 2024, and March 10, 2025: • 68 chats in 111 days (~4.5/week). • Mean pairing time: 1.4 minutes. • 71 procedures logged vs. 39 prior year → 55% increase. • 18 new certifications vs. 16 pre-existing prior to our intervention. **Conclusion:** Preliminary results from this pilot strongly suggests that real-time secure chat enables rapid performance and supervision of paracenteses. The decentralized model improves access and scalability and has led to significant gains in volume and certification. The skill building loop inherent in the program means that increased access of trainees to procedures leads to more certified supervisors in a positive feedback cycle. Ultimately, this initiative has proven so far to be a sustainable, low-burden alternative to traditional services. Further investigation is ongoing into the effects of this initiative on metrics like length of stay, mortality, and antibiotic use.

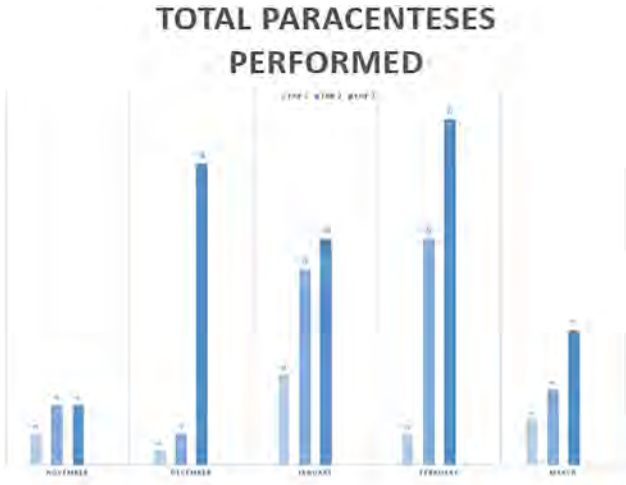


Table 1: Total number of procedures 1 and 2 years prior to our intervention, as well as during the intervention period (Year 3).

Disclosures: Joseph Abraham: Nothing to Disclose, Frank Nelson: Nothing to Disclose, Vasundhara Singh:

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Nothing to Disclose, Lance Maresky: Nothing to Disclose

◆ 3021 | COMPREHENSIVE HEPATITIS B PERINATAL PREVENTION INTERVENTIONS IN DELTA STATE, NIGERIA

Catherine Freeland[1] Prince Okinedo[2] Gregsonil Idibofu[2] Anita Abifade[2] Dafe Akokotu[3] Kevin Igweh[4] Sandra Igah[4] Linda Peter-Enyi[4] Ossai Theresa[5] Aki-Famous Betty[5] Ubiri Obaherhekre[6] Idanesi Stella[7] Kelechi Okorie[8] Kiyem wamari[9], [1]Hepatitis B Foundation, [2]Hepatitis Advocacy Foundation, [3]Central Hospital Agbor, [4]State Ministry of Health, [5]General Hospital Ozoro, [6]Central Hospital Sapele, [7]Central Hospital Warri, [8]Asaba Specialist Hospital, [9]Central Hopsital Agbor

Background: Chronic hepatitis B remains a global health challenge, with 250 million people infected. Perinatal transmission is the primary route, preventable through WHO-recommended interventions: antiviral prophylaxis (second trimester), timely birth dose (within 24 hours), and the pentavalent vaccine (6, 10, 14 weeks). In Africa, uptake of these measures is low due to limited screening, treatment access, and knowledge. Nigeria has offered the birth dose since 2004, but coverage remains inconsistent. In Delta State, where HBV prevalence is ~8%, a pilot found just 5.7% coverage within facilities. This study evaluated the impact of a community-driven perinatal prevention program in five public hospitals. **Methods:** The program, implemented across five state-run hospitals, involved routine hepatitis B screening for pregnant women, free antiviral prophylaxis for those testing positive, and timely birth dose vaccination for newborns. Healthcare workers received training, and logistical support was provided to ensure vaccine cold storage and delivery. Qualitative and quantitative data were collected to assess uptake and implementation barriers. **Results:** Of 1,623 pregnant women screened, 35 (2.5%) tested positive for HBV; none were HCV positive. Birth dose was administered to 100% of exposed infants—73% within 3 hours. Prophylaxis uptake was limited (2/35) due to late ANC booking. Key barriers included low provider awareness, vaccine misconceptions, and concerns about wastage. Post-training, provider knowledge and timely birth dose coverage significantly improved. **Conclusion:** This intervention improved screening, timely vaccination, and provider capacity. Sustained progress requires continued investment in healthcare training, public awareness, and policy support for integrated, cost-covered perinatal hepatitis B prevention.

Disclosures: Catherine Freeland: Nothing to Disclose, Prince Okinedo: Nothing to Disclose, Gregsonil Idibofu: Nothing to Disclose, Anita Abifade: Nothing to Disclose, Dafe Akokotu: Nothing to Disclose, Kevin Igweh: Nothing to Disclose, Sandra Igah: Nothing to Disclose, Linda Peter-Enyi: Nothing to Disclose, Ossai Theresa: Nothing to Disclose, Aki-Famous Betty: Nothing to Disclose, Ubiri Obaherhekre: Nothing to Disclose, Idanesi Stella: Nothing to Disclose, Kelechi Okorie: Nothing to Disclose, Kiyem wamari: Nothing to Disclose

◆ 3022 | HEALTH-RELATED QUALITY OF LIFE (HRQOL) OF PATIENTS WITH LIVER DISEASE: A CROSS-SECTIONAL ANALYSIS BY DISEASE SEVERITY AND AETIOLOGY

Stephanie Landi[1] Christopher Mysko[1] Huw Purssell[1] Karen Piper Hanley[2] Neil Hanley[3] Varinder Athwal[1], [1]Manchester NHS Foundation Trust / University of Manchester, [2]University of Manchester, [3]University of Birmingham / University Hospitals Birmingham NHS Foundation Trust

Background: Liver disease is a major cause of premature mortality and working lives lost, which has significant personal and national consequences. Understanding the impact of Health-Related Quality of Life (HRQoL) in patients with chronic liver disease, across a spectrum of aetiology and fibrosis, can help assess the burden of disease on the individual and inform clinical management, public health policies and resource allocation to help address these consequences. **Methods:** 1914 EQ5D5L (EuroQol, Netherlands) questionnaires were analysed from two prospective studies to assess the association between HRQoL, aetiology and fibrosis. Participants were divided into four groups based on liver stiffness measurement (LSM) or pre-existing chronic liver disease: Group 1: <8kPa ($n=1171$); Group 2: 8.1-15 kPa ($n=210$); Group 3: >15 kPa ($n=89$); and Group 4: pre-existing cirrhosis/chronic liver disease ($n=444$). 1108 (57.9%) had Metabolic Dysfunction Associated Liver Disease (MASLD), 212 (11.1%) Metabolic and Alcohol Associated Liver Disease (MetALD), 335 (17.5%) Alcohol-Related Liver Disease (ALD) ($n=335$), 92 (4.8%) viral hepatitis, 10 (0.5%) auto-immune liver disease, 12 (0.6%) hereditary haemochromatosis, 76 (4.0%) other liver-related aetiology and 62 (3.2%) no identifiable liver disease. Along with the surmised EQ5D5L value, the five dimensions of EQ5D5L were individually assessed: "mobility", "usual activities", "self-care", "pain" and "anxiety and depression". Statistical analysis was adjusted for age, gender, weekly alcohol consumption (units/week), Body Mass Index (BMI) and Charlson Comorbidity Index. **Results:** There was a progressive decrease in mean EQ5D5L value, indicating a poorer

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HRQoL, with an increasing fibrosis: 0.83 (SD: 0.23), 0.75 (SD: 0.27), 0.70 (SD: 0.29) and 0.66 (SD: 0.31) for groups 1-4 respectively ($P < 0.0001$) (Figure 1). However, there was no significant difference between HRQoL between individuals with MASLD, MetALD and ALD in each group: Group 1 ($p = 0.07$), 2 ($p = 0.25$), 3 ($p = 0.95$) and 4 ($p = 0.26$). Across the five dimensions each aetiology demonstrated different significant associations in multivariate regression analysis with fibrosis group. For participants with MASLD a significant association was observed between fibrosis group and "mobility" (ß = 0.12; 95% CI, 0.05-0.19; $p = 0.001$), "self-care" (ß = 0.06; 95% CI, 0.01-0.12; $p = 0.02$) and "usual activities" (ß = 0.11; 95% CI, 0.04-0.19; $p = 0.004$). However in participants with MetALD and ALD this was "usual activities" (ß = 0.27; 95% CI, 0.11-0.43; $p = 0.001$) and "anxiety and depression" (ß = 0.16; 95% CI, 0.02-0.29; $p = 0.02$), respectively. **Conclusion:** Across a spectrum of steatotic liver disease, HRQoL declines with increased fibrosis. This is driven by different dimensions of HRQoL dependent upon the underlying chronic liver disease aetiology.

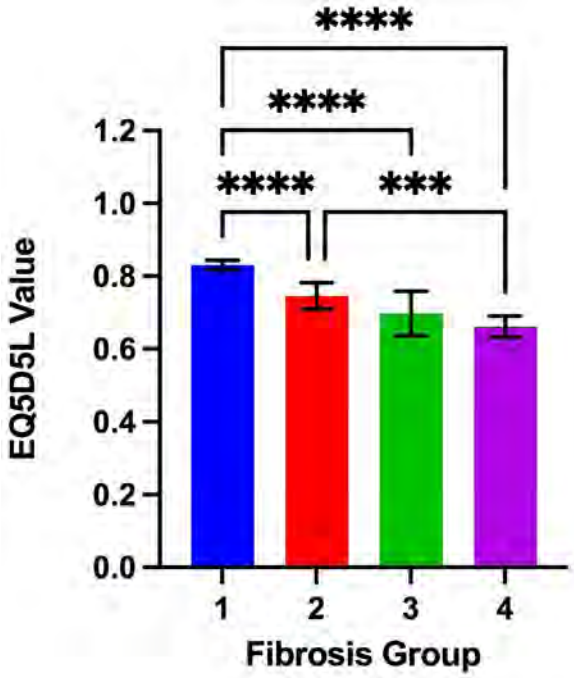

Figure 1: Bar chart showing the mean EQ5D5L value for each liver fibrosis group. Error bars represent the 95% confidence intervals and brackets show comparisons between groups statistically analysed with ANOVA and Tukey's Multiple Comparison test with **** representing P<0.0001 and ***, P<0.001.

Disclosures: Stephanie Landi: Nothing to Disclose, Christopher Mysko: Nothing to Disclose, Huw Purssell: Nothing to Disclose, Karen Piper Hanley: Nothing to Disclose, Neil Hanley: Nothing to Disclose, Varinder Athwal: Nothing to Disclose

◆ 3023 | A HOSPITAL-BASED HCV ELIMINATION MODEL BASED ON MULTIDISCIPLINARY COLLABORATION.

Xuehua Yan[1] Haiyan Wang[1], [1]The No.2 People's Hospital of Lanzhou

Background: The incomplete referral system of HCV in hospitals, and the lack of understanding of the diagnostic process and therapeutic advances of hepatitis C by doctors in non-infectiou disease(NID)/hepatology departments have seriously affected the diagnosis rate and the treatment rate of the patients. In this context, HCV elimination programs in hospitals are particularly important. To improve the diagnosis and treatment rate of HCV patients by establishing a standardized and efficient in-hospital HCV management model. **Methods:** From April 1, 2021, multidisciplinary collaboration was carried out in the No.2 people's hospital of Lanzhou, including various clinical departments, laboratory departments(LD), hospital infection control departments, and hospital information technology departments. Hospital-wide education and training on the importance of HCV screening and treatment were conducted, a hepatitis C management working group was established, and a mechanism for professional supervision and inspection was developed. After detecting anti-HCV positivity or HCV RNA positivity, the LD will immediately notify the relavant supervising physician and medical staff of the Infectious Diseases (ID)/hepatology department to follow up the patient's medical consultation, at the same time, the test report form will indicate the need for further medical diagnosis and treatment as well as a pop-up window reminder for hospitalized patients were also set up. **Results:** A total of 71,696 patients were screened from the database of the infection control department, of which 8,604 patients were screened from March 31, 2019, to March 31, 2021, and 1,291 patients were HCV antibody-positive. 399 HCV antibody-positive patients were from the ID department, accounting for 30.9%, and 892 HCV antibody-positive patients were from the NID department, accounting for 69.1%. Among them, 456 HCV antibody-positive patients underwent HCV RNA testing, 436 patients were HCV RNA positive, 79.8% of ID department HCV RNA testing, and 20.2% of NID department HCV RNA testing. The number of patients receiving DAA treatment was 212, with a treatment rate of 48.6%. From April 1, 2021 to April 1, 2024, a total of

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63,092 patients were screened since the start of the hospital HCV elimination program, with 1,201 HCV antibody-positive patients, 322 patients in the ID department were HCV antibody-positive, accounting for 26.8% of the patients, and the proportion of HCV antibody-positive patients in the NID department was 73.2%. Of these, 675 antibody-positive patients underwent HCV RNA testing, and there were 640 HCV RNA positive patients. The number of patients treated was 398, with a treatment rate of 62.2%. **Conclusion:** Since the implementation of the hospital-based HCV elimination program, the number of HCV patients screened, the diagnosis rate of HCV patients, and the treatment rate have increased significantly compared to the previous rates.

Disclosures: Xuehua Yan: Nothing to Disclose, Haiyan Wang: Nothing to Disclose

◆ 3024 | HOW CAN GEN AI EMPOWER LIVER PATIENTS?

Mustafa Behan[1] Jutta Kurz[1] Valeriia Aksakovska[1] Richard Jaenisch[2] Michael Tunkelrott[3] Lorrinda Gray-Davis[2] David Jaenisch[2] Karen Hoyt[2] Emmanuel Gorospe[4] Tarek Hassanein[5], [1]Amsety, [2]None, [3]Amsety LLC, [4]Burrell College of Osteopathic Medicine, [5]Southern California Liver Centers

Background: Over 67 million people use ChatGPT/week in the US. Among post-liver transplant patients (pts), 37% rely mainly on online tools for health information versus physicians (30%) or support groups (23%). With growing usage of digital tools, we need to understand the implications on the liver health field in general and the diagnosis and treatment context for liver pts. The aim is to develop strategies for pt communication with the help of Gen AI and identify benefits for pt management. **Methods:** The Amsety database consists of 650,000 individuals in the US. These individuals are mainly connected to Amsety through online educational tools. 3 additional surveys were conducted with 177 respondents with cirrhosis, post-transplant status, or recent liver diagnoses. The surveys assessed awareness and use of Gen AI, perceived quality, and comparisons to medical professionals. **Results:** The average age was 42 years old; 70% had metabolic liver. 58% used Gen AI tools in the previous 6 months. Top use cases were for nutrition/meal planning (72%), understanding their pattern of disease (62%) and diagnosis (56%). 58% rated AI responses as good or excellent. Pts perceived advantages of Gen AI over medical providers as constant availability (66%), cost-effectiveness (58%), unlimited question handling (50%). However, their concerns were no access to personal health history (48%), generic advice (34%) and lack of emotional support and privacy concerns (28%). The advantages of medical professionals over Gen AI are viewed as better qualification of providers (66%), access to their full medical history (60%) and legal accountability (52%). The disadvantages of information from a medical professional over Gen AI are viewed as inconsistent availability at the time of need (70%), unclear/difficult-to-understand information (44%) in some occasions, discomfort or time pressure during appointments (44%) and difficulties in getting appointments (42%). Pts sought Gen AI to answer liver-specific questions (68%), suggest medical tests (42%), use medical history for personalized advice (42%) and link to latest research (40%). **Conclusion:** Digital tools are widely accepted by liver patients and serve as key resources for health information, often convinced with the answers they receive. Gen AI has strong potential to support education, lifestyle guidance, and early intervention but must evolve to provide personalized, curated support while deferring critical decisions to physicians.

Disclosures: Mustafa Behan: Amsety GmbH: Founder and Co-Owner, Jutta Kurz: Nothing to Disclose, Valeriia Aksakovska: Amsety GmbH: Employee, Richard Jaenisch: Nothing to Disclose, Michael Tunkelrott: amsety: non-compensated advisor, Lorrinda Gray-Davis: Nothing to Disclose, David Jaenisch: Nothing to Disclose, Karen Hoyt: Nothing to Disclose, Emmanuel Gorospe: Nothing to Disclose, Tarek Hassanein: AbbVie: Speaker and Research Support, Gilead: Speaker and Research Support, HepQuant Shunt: Advisor, Madrigal: Advisor and Research Support, Amgen: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer- Ingelheim: Grant/Research Support, COUR: Grant/Research Support, Escient: Grant/Research Support, Galectin: Grant/Research Support, Grifols: Grant/Research Support, Intercept: Grant/Research Support, Janssen: Grant/Research Support, Merck: Grant/Research Support, Mirum: Grant/Research Support, NeuroBo: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pfizer: Grant/Research Support, Regeneron: Grant/Research Support, Salix Pharmaceuticals: Grant/Research Support, Takeda: Grant/Research Support, Akero: Grant/Research Support, Ipsen: Grant/Research Support, Kowa: Grant/Research Support, Bristol-Myers Squibb: Grant/Research Support, DURECT: Grant/Research Support, HepQuant: Grant/Research Support, Terns Pharmaceutical: Grant/Research Support, Mallinckrodt: Speaker and Research Support, Eli Lilly: Grant/Research Support, PharmaIn: Grant/Research Support, Sonic incytes: Grant/Research Support, Tensor Bio: Grant/Research Support, 89Bio: Grant/Research Support, Terns Pharmaceuticals: Grant/Research Support, Nterica: Consultant

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3025 | CLINICIAN ADHERENCE TO AN ELECTROCARDIOGRAM-ENABLED ARTIFICIAL INTELLIGENCE MODEL FOR DETECTION OF LIVER DISEASE IN PRIMARY CARE: INSIGHTS FROM THE DULCE TRIAL

Alberto Calleri[1] David Rushlow[2] Blake Kassmeyer[3] Kan Liu[4] Ryan Lennon[3] Puru Rattan[1] Matthew Bernard[2] Gagandeep Singh[5] Mark Deyo-Svendsen[2] Graham King[2] Stephen Stacey[2] Amy Olofson[1] Alina Allen[1] Joseph Ahn[1] Paul Friedman[4] Patrick Kamath[1] Zacchi Attia[4] Peter Noseworthy[4] Vijay Shah[1] Douglas Simonetto[1], [1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, [2]Department of Family Medicine, Mayo Clinic Health System, [3]Division of Clinical Trials and Biostatistics, Mayo Clinic, Rochester, Minnesota, [4]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, [5]Department of Family Medicine, Mayo Clinic Health

Background: The expanding use of artificial intelligence (AI) raises questions about clinician trust in AI-generated results, particularly in community settings. The Detection of Undiagnosed Liver Cirrhosis via Electrocardiogram (DULCE) was a pragmatic, randomized clinical trial demonstrating that a machine learning (ML) model applied to routine electrocardiograms (ECG) improves the detection of advanced chronic liver disease in primary care. In this post-hoc analysis, we examine clinician characteristics and adherence to follow-up recommendations prompted by positive ECG-ML results. **Methods:** Ninety-eight Primary Care Teams in Minnesota and Wisconsin were cluster-randomized to either the intervention arm (access to ECG-ML results) or standard care. Adults without known liver disease undergoing ECG between April and October 2023 were included. Clinician demographics were collected via REDCap survey. In the intervention arm, adherence was defined as the proportion of ECG-ML positive results followed by clinical action, such as ordering follow-up diagnostic tests or documenting a reason for not proceeding with further testing. High adopters were defined as providers in the upper quartile of adherence. **Results:** Of 126 clinicians randomized to the intervention arm, 110 were assessed for adherence, as had at least one patient with positive ECG-ML result. Mean age was 45 years; 67% physicians; 55% female; mean 14 years in practice. Most (85%) reported low confidence in managing cirrhosis at baseline. In the intervention arm, 8,034 patients had an ECG of whom 1,385 (17.2%) tested positive. Adherence to the AI alerts ranged from 19.5 to 49% across geographic regions. An adherence rate above 66.7% identified high adopters in our cohort. No differences in adherence were found by age, sex, degree type, or years in practice. The rate of follow-up diagnostic tests ordered was higher among high adopters compared to low adopters (55.1% vs. 9.1%, $p = 0.0001$). Among ECG-ML positive patients, any liver fibrosis was diagnosed in 65/274 cases (23.7%) in the high-adherence group compared to 73/1,111 (6.6%) in the low-adherence group ($p < 0.001$). High adopters were more likely to detect advanced fibrosis (F3–F4; OR 2.12, 95% CI 1.36–3.30, $p = 0.001$) and mild fibrosis (F1–F2; OR 2.08, 95% CI 1.88–4.72, $p < 0.001$) when compared to low adopters. **Conclusion:** In the DULCE trial, overall adherence to AI-based recommendations was moderate. However, providers with high adherence were significantly more likely to diagnose both early and advanced liver disease. Adherence was not linked to clinician demographics, suggesting a broader acceptance of AI across provider groups. Strategies to support clinician engagement may further enhance the real-world impact of AI in primary care.

Disclosures: Alberto Calleri: Nothing to Disclose, David Rushlow: Anumana: Advisor, Blake Kassmeyer: Nothing to Disclose, Kan Liu: Nothing to Disclose, Ryan Lennon: Nothing to Disclose, Puru Rattan: Nothing to Disclose, Matthew Bernard: Nothing to Disclose, Gagandeep Singh: Nothing to Disclose, Mark Deyo-Svendsen: Nothing to Disclose, Graham King: Nothing to Disclose, Stephen Stacey: Nothing to Disclose, Amy Olofson: Nothing to Disclose, Alina Allen: Novo Nordisk: Grant/Research Support, Novo Nordisk: Advisor, Target Pharma: Grant/Research Support, Pfizer: Grant/Research Support, Boehringer Ingelheim: Advisor, Madrigal: Advisor, GSK: Advisor, Oncoustics: Grant/Research Support, Escopics: Grant/Research Support, Astra Zeneca: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Madrigal: Grant/Research Support, Siemens: Grant/Research Support, Joseph Ahn: AITRICS: Consultant, Paul Friedman: AliveCor: Licensed AI ECG algorithms, Anumana: Licenses AI-ECG Algorithms, Eko Health: Licenses AI-ECG Algorithms, Patrick Kamath: Sequana: Advisor, NovoNordisk: Advisor, GSK: Advisor, GSK: Advisor, Zacchi Attia: Nothing to Disclose, Peter Noseworthy: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Douglas Simonetto: Mallinckrodt: Consultant, BioVie: Consultant, Resolution Therapeutics: Consultant, Evive: Consultant, Iota: Consultant

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3026 | HEPATITIS C TREATMENT EXPOSURE IN PREGNANCY: THREE-YEAR EXPERIENCE FROM THE &LDQUO;TIP-HEPC&RDQUO; CLINICAL CASE REGISTRY

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Background: About one-fifth of HCV infections worldwide are among women of childbearing age. In countries such as the US, policies for antenatal screening have led to greater identification of pregnant persons with HCV. However, due of a lack of safety data, pregnant persons are not universally recommended to receive antiviral therapy. AASLD-IDSA recommends case-by-case collaborative decision making for considerations of HCV treatment in pregnancy. The TiP-HepC registry was launched in June 2022 to capture, analyze, and routinely publish data regarding safety of HCV antiviral treatment in pregnancy. **Methods:** Standard data elements from cases of exposure to HCV antiviral therapy during pregnancy were reported to the registry through a web-based secure portal. Primary adverse pregnancy outcomes were defined as preterm delivery (< 37 weeks gestational age), stillbirth or fetal demise, and maternal death. Primary adverse birth outcomes were defined as low birth weight (LBW < 2500g), small for gestational age (SGA), neonatal intensive care unit (NICU) admission, and congenital anomalies. Descriptive analysis was conducted for cases submitted from June 1, 2022, to May 29, 2025. **Results:** A total of 37 eligible cases were reported in the registry (see table). Cases were from the US (n = 30), Canada (n = 3), Mexico (n = 2) and Australia (n = 2); 21 cases had been previously published in clinical trials or case series. There was a high prevalence of co-morbid substance use. There was one maternal death attributed to acute respiratory infection. Primary adverse birth outcomes included 10 NICU admissions, one LBW, and one SGA. Among cases with infant follow-up data, there were no infant deaths or congenital anomalies reported. **Conclusion:** The TiP-HepC registry provides valuable real-world data on HCV treatment exposure in pregnancy. To date, the registry has accrued substantial data, including 16 previously unreported cases. Although completeness of case reporting remains a limitation, current data from the registry has not revealed major safety concerns in terms of primary adverse pregnancy outcomes, infant deaths, or congenital anomalies. The Tip-HepC registry continues to solicit case reports to better inform collaborative decision-making, treatment and follow-up of pregnant persons and their newborns.

Table 1. Maternal-Infant characteristics and outcomes of TiP-HepC Registry cases (June 1, 2022 – May 29, 2025)

Exposures during first trimester (≤13 weeks gestation):	
Cumulative registry cases	8
Median age, years (range)	30 (22-35)
Baseline co-morbidities or substance use	IVDU=3, opioid use=3, tobacco=2, marijuana=4, cocaine=1, mental/behavioral disorders related to opioid use disorder=6, methamphetamine=2
Treatment regimen	G/P=3, SOF/VEL=5
Treatment completed	Yes=6, No=2
Median number of days of treatment exposure in pregnancy (range)	56 (32-79)
Maternal HCV outcomes	Cured = 2, No data = 6
Primary adverse pregnancy outcomes	None = 3, Maternal death = 1, No data = 4
Primary adverse birth outcomes	None = 3, NICU admission = 1, No data = 4
Congenital anomaly	Yes = 0, No = 3, No data = 5
Infant HCV outcome	No data = 8
Exposures after first trimester (>13 weeks gestation)	
Cumulative registry cases	29
Median age (range)	30 (18-44)
Baseline co-morbidities or substance use	IVDU=12, opioid use=7, tobacco=7, marijuana=4, cocaine=4, mental/behavioral disorders related to opioid use disorder=6, methamphetamine=2
Treatment regimen	SOF/LDV = 20, SOF/VEL = 9
Treatment completed	Completed=23, Not Completed=0, No data=6
Median number of days of treatment exposure in pregnancy (range)	83 (42-92)
Maternal HCV outcomes	Cured=17, not cured = 2, No data = 10
Primary adverse pregnancy outcomes	No adverse pregnancy outcomes =17, preterm delivery = 6, no data = 6
Primary adverse birth outcomes	NICU admission = 9, low birth weight = 1, small for gestational age = 1, no data = 2
Congenital anomaly	Yes = 0, No = 22, No data = 7
Infant HCV outcome	Positive = 0, Negative = 13, No data = 16

Abbreviations: G/P = glecaprevir/pibrentasvir, SOF/VEL = sofosbuvir/velpatasvir, SOF/LDV = sofosbuvir/ledipasvir, NICU = neonatal intensive care unit, IVDU = intravenous drug use

Disclosures: Neil Gupta: Nothing to Disclose, Lindsey Hiebert: Nothing to Disclose, Jana Manning: Nothing to Disclose, Saeed Hamid: Nothing to Disclose, Manal El-Sayed: Nothing to Disclose, Ravi Jhaveri: AstraZeneca: Consultant, Sanofi: Consultant, Seqirus: Consultant, Gilead: Advisor, GSK: Grant/Research Support, Ali Judd: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Mia Biondi: Gilead Sciences: Grant/Research Support, Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, AbbVie: Grant/Research Support, Cepheid: Grant/Research Support, Catherine Chappell: Gilead Sciences: Grant/Research Support, Gilead Sciences: Advisor, Organon: Grant/Research Support, Merck: Grant/Research Support, John Ward: Abb Vie, Abbott, Gilead, Siemens, Roche,

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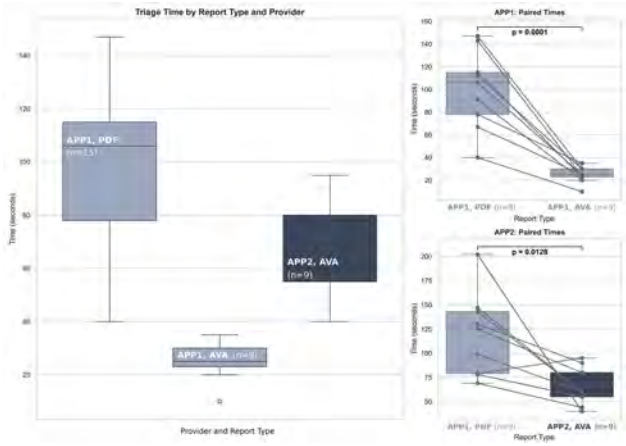
Pharco, Virion,: Grant/Research Support, Dynavax, Merck, Cepheid,: Grant/Research Support

3027 | AVATAR: AI VIRTUAL ASSISTANT FOR TRIAGE AND REFERRALS IN AN ACADEMIC HEPATOLOGY PRACTICE

Anubhav Shankar[1] Hersh Shroff[2] Oren Fix[3], [1]University of North Carolina, [2]UNC Chapel Hill, [3]University of North Carolina at Chapel Hill

Background: In tertiary hepatology care settings, efficient and accurate triage of new outpatient referrals is an important yet burdensome process due to patient complexity, antiquated processes involving faxed paper records from external institutions, and lacking interoperability standards for electronic health records. Artificial intelligence (AI) tools provide an opportunity to improve the review and triage of patient referral records. **Methods:** We used our institution's HIPAA-secure, GPT-4o-powered large language model (LLM), known as AI Virtual Assistant (AVA), to read and extract data from scanned PDF records of new referrals to our academic hepatology practice. In the *development* phase, we analyzed dictated audio recordings made by an advanced practice provider (APP1) while triaging new patient referrals and extracted a comprehensive list of data elements required for triage. An AVA prompt was created using the final list of data elements and iteratively tested on unique patient records to maximize accuracy. In the *testing* phase, structured summaries of 15 unique referral records were generated in AVA using the final prompt. APP1 reviewed all 15 records for triage. After a 3-month delay, APP1 re-reviewed a subset of the AVA summaries, and a second APP (APP2) reviewed a different subset. Outcomes measured included *time to triage* (original records and AVA summaries), *accuracy of data extraction* compared to human review, and *appropriateness of resulting triage decision* judged by a member of our study team. Statistics were conducted using Python 3.11.8. **Results:** In the development phase, we identified 48 unique data elements used for triage (e.g., reason for referral, urgency, demographics including address and insurance, and various clinical details). Upon completion of the development phase, average AVA accuracy in data element extraction was 94.1%. In the testing phase, we observed a significant reduction in average time to triage per referral: *within-provider (APP1)*: 100s with full records vs 25s with AVA summaries, $p = 0.0001$; *between-providers:* 119s for APP1 with full records vs 65s for APP2 with AVA summaries, $p = 0.0128$. Mean $\pm$ SD lengths of AVA summaries were 2 ± 1 pages vs. 30 ± 34 pages with original records. Both APPs reached an appropriate triage decision in 89% ($n = 16/18$) of patients with AVA. The two instances of inappropriate triage decisions occurred due to an inability of AVA to read lab values in the referral records. In both cases, the APPs recognized the need to refer to the original records to verify missing or incorrect information. **Conclusion:** In this pilot study, a HIPAA-secure LLM extracted data from scanned patient records with high accuracy, significantly reducing triage times with minimal compromise of the appropriateness of triage. With further refinement, our model has the potential to significantly reduce the burden on providers of record review, triage, and other administrative tasks.



Disclosures: Anubhav Shankar: Nothing to Disclose, Hersh Shroff: Nothing to Disclose, Oren Fix: Nothing to Disclose

3028 | INTEGRATING EVIDENCE-BASED STRATEGIES FOR HBSAG TESTING UPTAKE IN VIET NAM: A HYBRID EFFECTIVENESS-IMPLEMENTATION TRIAL ★

Thanh Kim[1] Diem Dao[2] Trang Ngoc Doan Pham[3] Loc Phan[2] Thuy Tran[4] Trang Nguyen[4] Anh Le[2] Khanh Tran[4] Doan Dao[5] Vu Dang[4] Toan Le[6] Cong Ly[4] Hung Vo[4] Tung Do[4], [1]Pham Ngoc Thach University of Medicine, [2]Vietnam Viral Hepatitis Alliance, Reston, VA, USA, [3]University of Illinois at Chicago, Chicago, IL, USA, [4]Le Van Thinh Hospital, Thu Duc City, Ho Chi Minh City, Viet Nam, [5]Johns Hopkins School of Medicine, [6]University of Medicine and Pharmacy at Ho Chi Minh City, Viet Nam

Background: Despite WHO guidelines, hepatitis B surface antigen (HBsAg) screening remains $< 10\%$ in low- and middle-income countries (LMICs), including Viet Nam (HBV prevalence $> 8\%$; baseline HBsAg testing ~0.35%). Our systematic review of 25 trials ($n = 130{,}598$) confirmed that healthcare provider (HCP)-led education combined with point-of-care (POC) rapid testing increases HBsAg uptake (risk difference 62.5%, 95% CI: 53.1–71.9) [1]. Yet, no trials have tested these strategies in LMICs or under a hybrid implementation framework. **Methods:** We conducted a hybrid

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effectiveness-implementation trial (06/2024–03/2025) in the outpatient department of a general hospital in Ho Chi Minh City. The sequential interventions included: 1) continuous medical education (CME, 06/2024) for providers focused on HBV epidemiology, screening guidelines, and testing procedures, reinforced with quarterly refreshers; (2) best practice alerts (BPAs, 10/2024); and (3) POC HBsAg rapid testing (02/2025). BPAs were real-time EHR prompts alerting providers to order HBsAg testing for eligible patients. The primary outcome: HBsAg testing uptake; secondary outcomes: downstream care linkage and implementation fidelity. We analyzed 201,851 outpatient visits (including preimplementation phase from 01/2023- 05/2024 serving as control) using seasonal ARIMA modeling. ARIMA was chosen to account for significant seasonality and autocorrelation detected in weekly testing rates to evaluate the incremental and combined impact of the bundle on HBsAg testing (interventions 1,2, and 3), with anti-HCV, cholesterol, and glucose screening serving as negative controls. **Results:** Baseline HBsAg testing was 3.41 tests/1000 visits/week. CME alone showed no significant effect on HBsAg testing (immediate: −2 tests/1,000 visits/week, 95% CI: −8.2 to +4.1; gradual: +1.1/1,000/week, 95% CI: −0.2 to +2.6). Adding the BPAs demonstrated modest ramp-up effects (+1.7/1,000/week, 95% CI: +0.04 to +3.4). Notably, the final addition of free POC testing drove dramatic increases (immediate: +9.9/1,000, 95% CI: +5.1 to +14.7; gradual: +8.4/1,000/week, 95% CI: +7.2 to +9.5), translating to a 28-fold testing rate improvement compared to pre-implementation. Qualitative analyses to evaluate for implementation fidelity and downstream metrics (anti-HBs, HBV DNA, referrals, treatment) are underway. **Conclusion:** This trial offers the first LMIC evidence demonstrating that provider education and digital BPAs alone are insufficient, but when combined with free POC-HBsAg, they catalyze transformative increases in HBsAg testing uptake. Our findings present an innovative, scalable, and evidence-backed model for advancing hepatitis B elimination goals.

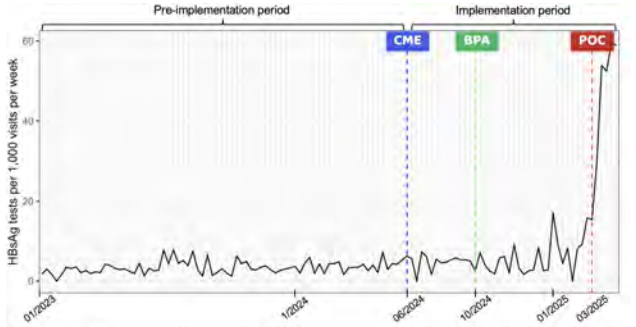

Figure 1. Weekly HBsAg testing rates during the study period. The timing of each intervention is indicated by dashed vertical lines: blue for the introduction of CME (June 2024), green for EHR best practice alerts (October 2024), and red for point-of-care (POC) testing (February 2025).

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

3029 | EFFECT OF THE COVID-19 PANDEMIC ON OVERALL SURVIVAL AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA IN THE UNITED STATES

Yi-Te Lee[1] Jasmine Wang[2] Pojsakorn Danpanichkul[3] Hyunseok Kim[4] Alexander Kuo[1] Walid Ayoub[1] Hirsh Trivedi[1] Yun Wang[1] Aarshi Vipani[1] Paul Martin[1] Amit Singal[5] Ju Dong Yang[1], [1]Cedars-Sinai Medical Center, [2]University of Washington, [3]Texas Tech University Health Sciences Center, [4]Cedars Sinai Medical Center, [5]University of Texas Southwestern Medical Center

Background: The COVID-19 pandemic affected diagnosis and management of hepatocellular carcinoma (HCC). However, its impact on survival remains unknown. **Methods:** We conducted a retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER) Program among patients diagnosed with HCC between 2000 and 2022. Kaplan–Meier analysis was performed to estimate 1-, 2-, and 3-year overall survival (OS) rates. Multivariable Cox regression, adjusting for demographic and clinical factors, was used to identify factors associated with OS, including a comparison of the COVID-19 era (2020-2022) vs. the pre-COVID-19 era (2016-2019). **Results:** Among 107,911 eligible HCC patients with survival data, 16,838 were diagnosed during the COVID-19 pandemic (2020-2022) and 25,131 during the pre-COVID era. The 1- and 2-year OS for patients during the COVID-19 era and pre-COVID-19 era were 57.3% (95% CI: 56.5-58.1%) and 41.9% (95% CI: 40.9-42.8%), compared to 58.6% (95% CI: 58.0-59.2%) and 43.7% (95% CI: 43.1-44.4%), respectively (log-rank test, $p < 0.001$) (Figure 1a). However, in multivariable analysis, the COVID-19 era was not significantly associated with worse survival compared to the pre-COVID era (HR: 1.01, 95% CI: 0.98-1.03, $p = 0.3$). In subgroup analyses, the COVID-19 era was significantly associated with better survival in patients < 50 years old (HR: 0.84, 95% CI: 0.71-0.98, $p = 0.035$, Figure 1b). Conversely, the COVID-19 era was significantly associated

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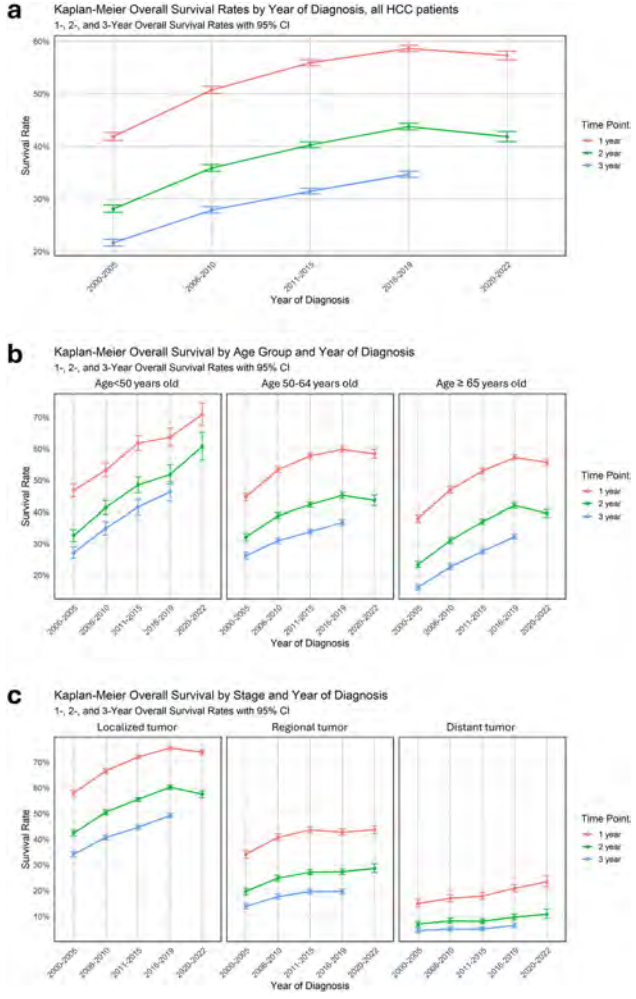
with worse survival in patients with localized tumors (HR: 1.06, 95% CI: 1.01-1.11, p = 0.01, Figure 1c).
A smaller proportion of HCC patients diagnosed during the COVID-19 era received curative-intent therapies (local ablation, liver resection, liver transplantation) compared to the pre-COVID era (21.7% vs. 23.9%, p < 0.001). This difference in curative treatments was also observed in patients with localized tumors (35.5% vs. 37.5%, p < 0.001), although a higher proportion of younger patients < 50 years old received curative-intent therapies during the COVID era (36.6% vs. 29.9%, p = 0.003). **Conclusion:** The COVID-19 pandemic was associated with worse survival in patients with HCC overall, including subgroup with early-stage HCC, although better survival was observed in younger patients. These differences in survival may reflect variations in access to curative-intent therapies.



Disclosures: Yi-Te Lee: Nothing to Disclose, Jasmine Wang: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Hyunseok Kim: Nothing to Disclose, Alexander Kuo: Nothing to Disclose, Walid Ayoub: Intercept: Speaking and Teaching, Mirum: Grant/Research Support, GSK: Grant/Research Support, Madrigal: Grant/Research Support, Cymabay: Consultant, Ipsen: Grant/Research Support, Zydus: Grant/Research Support, Gilead: Grant Research Support, Hirsh Trivedi: Nothing to Disclose, Yun Wang: Nothing to Disclose, Aarshi Vipani: Nothing to Disclose, Paul Martin: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Ju Dong Yang: Exact Sciences: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Exelixis: Consultant, Fujifilm Medical Sciences: Consultant

3030 | REAL-WORLD ASCITES TREATMENT PATTERNS DIVERGE FROM AASLD RECOMMENDATIONS: AN ANALYSIS OF OVER 200,000 PATIENTS WITH CIRRHOSIS AND ASCITES

Kate Solpari[1] Dominique Gay[1] Emma Leipsner[1] Scarlet Yang[1] Jessica Siguencia[1] Tatyana Kushner[1], [1]Weill Cornell Medical College

Background: The 2021 American Association for the Study of Liver Diseases (AASLD) guidelines recommend a stepwise approach to ascites management beginning with sodium restriction and spironolactone, adding furosemide as needed for refractory ascites, the guidelines advise escalation to large-volume paracentesis (LVP), transjugular intrahepatic portosystemic shunt (TIPS), and ultimately liver transplantation. We sought to evaluate national real-world practices in adherence with these recommendations for ascites management. **Methods:** Patients with cirrhosis and associated ascites were identified using ICD-10 diagnosis codes from 99 healthcare organizations in the TriNetX Research Network. We tracked ascites-related treatments over time, defining a new line of therapy (LOT) when a new medication or procedure was initiated or substituted. We quantified therapy use and identified common treatment sequences across up to six LOTs. **Results:** Of 257,245 adults with cirrhosis-related ascites treated between 2005 and 2025 (68% White, 10% Black or African American, 5% Asian; median follow-up 371 days, IQR 1,140), treatment pathways were reconstructed for 185,128. Across all therapy lines, dual diuretics (furosemide plus spironolactone) were prescribed to 58% of patients, furosemide alone to 56%, and large-volume paracentesis to 36% (see Figure). First-line practice diverged from

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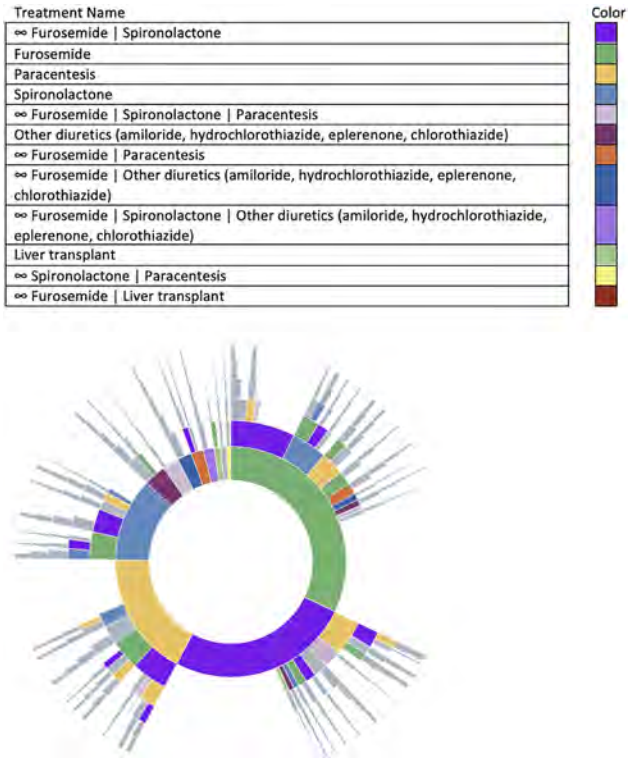
guidelines: furosemide monotherapy was used in 37% of patients—nearly three times as often as spironolactone alone (14%, $p < 0.001$). The most common escalation sequence was furosemide followed by combination diuretics, seen in 14% of those who started on furosemide. Paracentesis use increased with treatment progression, reaching 21% among patients receiving a sixth line of therapy. Other diuretics appeared in 7.5% of treatment pathways (3% at first line). Advanced interventions were rare: TIPS was used in 0.002% of patients, and liver transplantation in 2.8%. **Conclusion:** Real-world ascites management frequently diverges from AASLD guidelines, with many patients starting treatment on furosemide monotherapy rather than spironolactone. Escalation to guideline-recommended rescue therapies such as TIPS and transplantation was rare. These patterns suggest that clinical decision-making may be influenced by provider preference, institutional norms, or patient factors not captured in guidelines. Findings should be validated in prospective cohorts due to potential misclassification bias inherent in administrative coding data. Efforts to promote guideline-concordant care and address barriers to appropriate escalation are warranted.



Disclosures: Kate Solpari: Nothing to Disclose, Dominique Gay: Nothing to Disclose, Emma Leipsner: Nothing to Disclose, Scarlet Yang: Nothing to Disclose, Jessica Siguencia: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support

3031 | HOSPITAL AT HOME FOR ACUTE CARE PATIENTS WITH DECOMPENSATED CIRRHOSIS PROVIDES COMPARABLE CLINICAL OUTCOMES TO HOSPITAL-BASED CARE WHILE IMPROVING PATIENT-CENTEREDNESS: A PROSPECTIVE STUDY

Miranda Stovall[1] Haleigh Rodgers[2] Qing Tang[1] Bridget Hawryluk[3] Courtney Moore[3] Andrea Kiser[3] Nanditha Kolur[1] Elyse Thorne[2] Blaine Takesue[2] Raj Vuppalanchi[1] Eric Orman[3] Naga Chalasani[4] Archita Desai[1], [1]Indiana University School of Medicine, [2]Indiana University Health, [3]Indiana University, [4]Indiana University Medical Center

Background: Hospital at Home (HaH) is a patient-centered program that delivers hospital-level care at home using telemedicine. This model has been shown to reduce adverse events, readmissions, and costs while improving patient satisfaction. In liver disease, many hospital days after initial stabilization are spent on lower acuity needs like IV medications or lab monitoring, representing an opportunity for HaH to reduce hospital-related adverse events and healthcare utilization. We aim to prospectively explore the clinical and patient-reported outcomes of HaH services. **Methods:** Thirty-four hospitalized liver disease patients received HaH care from 6/2023-4/2025. 17 consented to participate in pre-post qualitative interviews and to complete the Telemedicine Satisfactory Survey (TSQ) after HaH care. Using interactive activities, patients and caregivers were asked to (1) identify perceived risks, benefits, barriers of HaH care, (2) provide expectations of HaH, (3) explore how expectations aligned with experienced outcomes, and (4) provide revisions of the program. Control participants were propensity score matched in a 1:3 ratio using a greedy nearest-neighbor algorithm from a prospective inpatient cirrhosis cohort (7/2020–4/2025), based on age, gender, active alcohol use, liver disease etiology, admission reason, Child-Pugh (CP) class, primary service team, ED visits in the past 30 days, and hospitalizations in the past 6 months. Clinical outcomes were compared between study participants to matched controls using regression models. **Results:** The study cohort ($n = 17$) and matched controls ($n = 51$) are described in Figure. Among HaH participants, 96% were classified as CP class B/C with a median MELD 3.0 score of 22.5 (IQR: 17.0, 28.5). The primary reasons for admission were ascites (41%), hepatic encephalopathy (18%), and AKI (15%). The mean inpatient stay was shorter in the HaH

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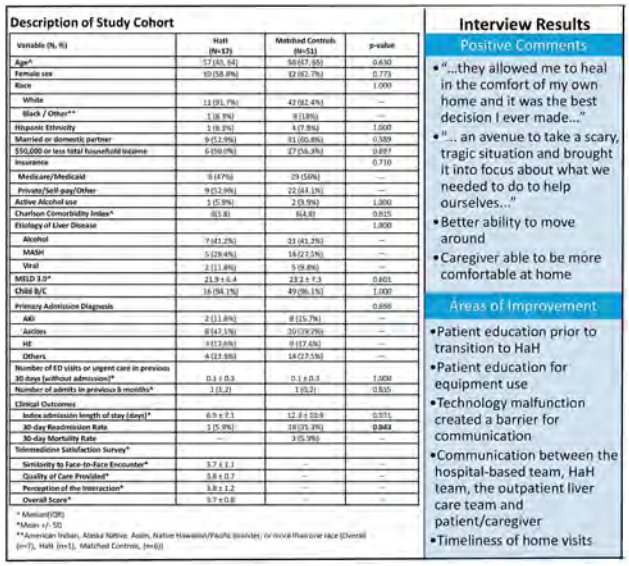
group compared to the control (6.9 ± 7.1 days vs 12.3 ± 10.9 days; p = 0.071). 30-day readmissions were less frequent in the HaH group (6%, n = 1) than in the control group (35%, n = 18; p = 0.043). There were no 30-day deaths in the HaH group vs. 6% (n = 3) in the control group. All TSQ mean scores in HaH exceeded 3, indicating agreement that care was comparable to in person care (Table). In qualitative interview activities (e.g., participants wrote love/breakup letters), participants noted many strengths of the program (Figure). Indications for improvement noted vague discharge instructions, issues with technology, and timeliness of home visits. **Conclusion:** HaH is an emerging model of acute care for patients with decompensated cirrhosis. Our experience indicates similar clinical outcomes to hospital-based care while improving patient-centered care. Future studies are needed to analyze the impact of HaH-based cirrhosis care on inpatient complications, cost of care, and patient/caregiver reported outcomes.



Disclosures: Miranda Stovall: Nothing to Disclose, Haleigh Rodgers: Nothing to Disclose, Qing Tang: Nothing to Disclose, Bridget Hawryluk: Nothing to Disclose, Courtney Moore: Nothing to Disclose, Andrea Kiser: Nothing to Disclose, Nanditha Kolur: Nothing to Disclose, Elyse Thorne: Nothing to Disclose, Blaine Takesue: Nothing to Disclose, Raj Vuppalanchi: Eli LIlly: Grant/Research Support, GSK: Consultant, Madrigal: Consultant, Zydus Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Kowa: Grant/Research Support, Takeda: Grant/Research Support, GSK: Consultant, UBC: Consultant, Gilead: Grant/Research Support, GSK: Grant/Research Support, 89 Bio: Consultant, Eric Orman: Sitero: Consultant, Biovie: Advisor, Naga Chalasani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Archita Desai: Nothing to Disclose

3032 | DIMENSION ANALYSIS OF ENVISION STUDY EQ-5D DATA TO ASSESS RELATIONSHIP BETWEEN ANNUALIZED ATTACK RATE AND CHRONIC SYMPTOMS IN PATIENTS WITH ACUTE HEPATIC PORPHYRIA

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Background: Acute hepatic porphyria (AHP) is a group of rare disorders with acute attacks of pain and neurological symptoms, which may lead to altered mental status. While attack frequency is often used to categorize AHP, data from the phase 3 ENVISION study of givosiran suggest patients may have chronic symptoms that are not necessarily related to acute attacks. Here, we further investigate the relationship between annualized attack rate (AAR) and chronic symptom burden, using a broader classification of attacks than used in ENVISION. **Methods:** ENVISION enrolled patients with AHP aged ≥ 12 years with ≥ 2 attacks requiring hospitalization, urgent care, or intravenous hemin at home in the 6 months before randomization.

In this *post hoc* analysis, patients from the givosiran and placebo groups were categorized into quartiles by an expanded measure of historical AAR (eAAR), also including attacks requiring healthcare facility visit, and attacks without hemin use at home, to account for less severe attacks that may contribute to disease burden. Patients completed the EQ-5D survey at baseline (BL), rating mobility, self-care, usual activities, pain/discomfort, and anxiety/depression on that day. BL EQ-5D scores were thought to reflect chronic disease burden, as patients were not in an acute attack during assessment. The relationship between historical eAAR and BL EQ-5D dimension scores was tested by Spearman correlation coefficients (ρ) and logistic regression. **Results:** Among 94 patients (mean [SD] age 38.8 [11.4] years; 89.4% female), the median (range) historical eAAR was 8 (4-50); 52% of patients reported prior chronic symptoms between attacks. Patients most frequently reported problems in the pain/discomfort dimension (75.5%) and least frequently in the self-care dimension (17.2%). The proportions of patients reporting problems in each dimension were

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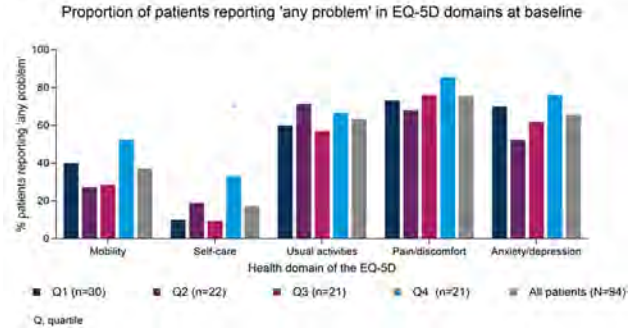
generally similar across eAAR quartiles (Figure). Aside from self-care (weak correlation of $\rho = 0.2$; odds ratio 1.06), no correlations were found between eAAR and individual EQ-5D dimension scores, and odds of reporting a problem in other EQ-5D dimensions did not significantly increase with increased historical eAAR. **Conclusion:** Patients with AHP may experience chronic symptoms not necessarily predicted by historical AAR, including pain/discomfort and anxiety/depression. Broadening the AAR criteria did not meaningfully affect the results. The chronic burden of AHP on health-related quality of life should be assessed regularly to help guide disease management.

Figure



Disclosures: Manisha Balwani: Alnylam Pharmaceuticals: Consulting/Advisory Board/Speaker's Bureau, Astra Zeneca: Consulting/Advisory Board/Speaker's Bureau, Recordati Rare Diseases: Consulting/Speaker's Bureau, Ultragenyx Pharmaceutical: Speaker's Bureau, Stendhal Pharma: Consulting/Speaker's Bureau, Mitsubishi Tanabe: Grant/Research Support, Disc Medicine: Grant support/ Advisory board fees, Genzyme/Sanofi: Advisor, CRISPR Therapeutics: Advisor, Mount Sinai: Royalties or patent beneficiary, Manish Thapar: Alnylam Pharmaceuticals: Consultant, Disc Medicine: Consultant, Mitsubishi Tanabe: Consultant, Recordati Rare Diseases: Consultant, Susana Monroy: ALNYLAM PHARMACEUTICALS: Speaking and Teaching, ASTRA ZENECA: Speaking and Teaching, Weiming Du: Alnylam Pharmaceuticals: Employee, Teresa Kauf: Alnylam, Inc: Employee, Mural Oncology: Stock - publicly traded company, Alkermes, Inc: Stock - publicly traded company, Marianne Sweetser: Alnylam Pharmaceuticals, Inc: Former employee of Alnylam, and own stock and stock options, Jamie Weiss: Nothing to Disclose, Paolo Ventura: Nothing to Disclose, Bruce Wang: Alnylam Pharmaceuticals: Consultant, Recordati Rare Diseases: Consultant, Disc Medicine: Consultant, Mitsubishi Tanabe Pharma: Consultant, Mitsubishi Tanabe Pharma: Grant/Research Support, CRISPR Therapeutics: Consultant

3033 | ADOLESCENT LIVED EXPERIENCES WITH HEPATITIS B

Catherine Freeland Suzanne Block[1] Vincent DiLorenz[2] Prutha Tailor[2] Djeneba Fofana[3] Samuel Etien[4] Patricia Brazille[5] Agathe Beauquesne[5] Chari Cohen[1] Manal El-Sayed[6], [1]Hepatitis B Foundation, [2]Thomas Jefferson University, [3]Université des Sciences, des Téchniques et des Téchnologies de Bamako (USTTB), Mali, [4]Youth Health Center (Espace Santé Jeunes), Diagnostic and Therapeutic Center, Hôtel-Dieu Hospital, G, [5]Youth Health Center (Espace Santé Jeunes), Diagnostic and Therapeutic Center, Hôtel-Dieu Hospital, [6]Ain Shams University

Background: Hepatitis B affects over 250 million people globally, yet research rarely considers the lived experiences and treatment preferences of those infected, especially young adults and adolescents. To address this gap, qualitative interviews were conducted with individuals with hepatitis B under the age of 30 to better understand their management experiences, challenges and treatment preferences. **Methods:** The study includes qualitative interviews focused on individuals aged 18–30 living with hepatitis B. Interviews assessed lived experiences, treatment preferences, stigma, and quality of life. Interviews were conducted virtually and in-person, utilizing a semi-structured interview guide with five sections and 26 questions, lasting approximately 30–50 minutes. Data were analyzed using grounded theory and Nvivo software, with interviews transcribed and translated verbatim and double coded by at least two trained researchers. A codebook guided analysis, ensuring intercoder reliability and agreement. **Results:** Participants represented global perspectives from various international settings (including Nigeria, Mali, Egypt, the United States and France). Qualitative interviews of young people with hepatitis B highlight overarching themes such as common experiences of discrimination and stigma, challenges associated with accessing care and affording medication to manage their condition, low knowledge within the community, and fear to disclose their hepatitis B status to others. Experience differences related to accessing treatment and care were commonly reported in upper income countries (France and the United States), while medication access and provider challenges were less reported. Despite varying experiences associated with hepatitis B, young people remain hopeful towards a cure for hepatitis B and are optimistic in the outlook of their health. **Conclusion:** While young people with hepatitis B experience challenges associated with their diagnosis, they maintain an optimistic outlook on current and future developments towards a hepatitis B cure and treatment. Efforts should continue to understand young person's perspectives associated with hepatitis B so interventions can be effectively designed to

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address their specific needs, challenges and concerns related to care.

Disclosures: Catherine Freeland: Nothing to Disclose, Suzanne Block: Nothing to Disclose, Vincent DiLorenz: Nothing to Disclose, Prutha Tailor: Nothing to Disclose, Djeneba Fofana: Nothing to Disclose, Samuel Etien: Nothing to Disclose, Patricia Brazille: Nothing to Disclose, Agathe Beauquesne: Nothing to Disclose, Chari Cohen: Gilead Sciences: Grant/Research Support, VBI Vaccines: Grant/Research Support, GSK: Grant/Research Support, Roche: Grant/Research Support, Vio Biotechnology: grant funds renumerated to Hepatitis B Foundation, Dynavax Technologies: grant funds renumerated to Hepatitis B Foundation, Gilead Sciences: grant funds renumerated to Hepatitis B Foundation, GSK: grant funds renumerated to Hepatitis B Foundation, Roche: grant funds renumerated to Hepatitis B Foundation, Gilead Sciences: funds renumerated to Hepatitis B Foundation, GSK: funds renumerated to Hepatitis B Foundation, Manal El-Sayed: Nothing to Disclose

3034 | PROSPECTIVE IMPLEMENTATION AND EVALUATION OF A REAL-WORLD FIB-4 SCREENING PATHWAY FOR MASLD WITH SIGNIFICANT FIBROSIS IN PRIMARY CARE PATIENTS WITH DIABETES, OBESITY, OR BOTH

Mohsen Merati[1] Max Goldman[2] Janet Chu[1] Bilal Hameed[1] Nghiem Ha[1] Mandana Khalili[1] Gabrielle Winer[3] Rena Fox[1], [1]University of California, San Francisco, [2]Kaiser Permanente, Northern California, [3]Stanford University

Background: AASLD recommends primary care providers (PCPs) perform FIB-4 screening for MASLD with significant fibrosis (F2-4) in patients with one or more risk factors. However, awareness and adoption of this pathway among PCPs remains low, and few studies have evaluated its real-world implementation. We prospectively assessed a FIB-4-based MASLD screening pathway in primary care (PC) patients with type 2 diabetes mellitus (DM), obesity, or both, focusing on the detection of significant fibrosis, referral drop-offs, and opportunities for education or system improvement. **Methods:** We identified adult patients from a large urban primary care practice using EMR data from 2019-2023. Annual FIB-4 scores were calculated, and the most recent score was categorized by age-based thresholds into low-, indeterminate-, or high-risk for advanced fibrosis. For patients with indeterminate- or high-risk FIB-4, PCPs received an EMR prompt recommending Fibroscan referral. All steps took place within routine care: PCPs chose whether to refer or not, and scheduling followed usual processes. Fibroscan results were classified as significant fibrosis (F2-F4) if median liver stiffness was $\geq$8kPa. **Results:** Among 22,806 PC patients, 7,027 (31%) had DM, obesity, or both. Of these, 5,055 (72%) had at least one FIB-4, and 1,158 (23%) were categorized as indeterminate- or high-risk. To date, the PCPs of 430 indeterminate- and high-risk FIB-4 patients received a prompt recommending Fibroscan. The PCPs referred 223 (52%) thus far, of whom 162 (73%) scheduled Fibroscans. The majority (80%) are completed or pending. Significant fibrosis was detected in 26 of 104 patients (25%) to date (Figure 1). **Conclusion:** We report interim results from our prospective FIB-4 screening in PC patients in three risk-factor cohorts, including real-world uptake by PCPs and Fibroscan results. In over half the patients, PCPs opted to refer for Fibroscan, and most referred patients completed a Fibroscan. Previously unrecognized $\geq$F2 fibrosis was found in 25% of scanned patients with elevated FIB-4. The most significant drop-off in the pathway was the PCP decision to refer for Fibroscan; 48% of patients were not referred, revealing a critical point for improved PCP education. Given the emergence of therapies to treat MASLD fibrosis, optimizing the uptake of the screening pathway will improve delivery of high-quality MASLD care to the large population of patients with unrecognized fibrosis.

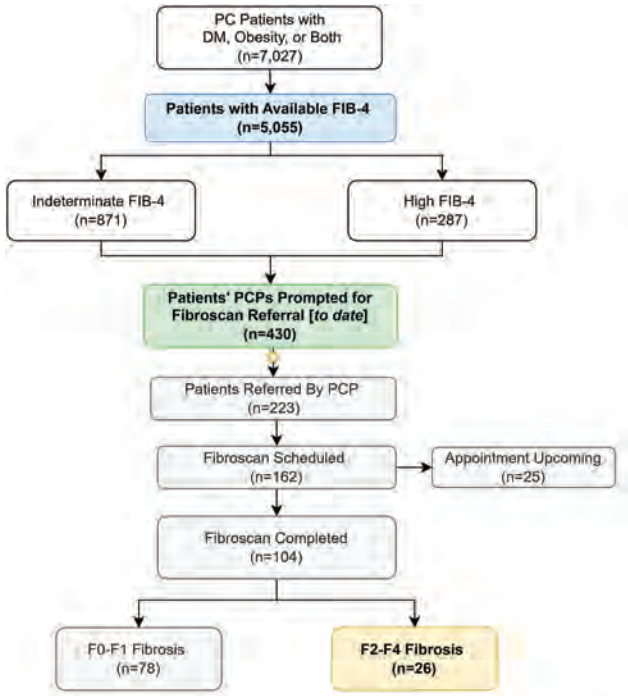

Figure 1 Implementation and interim evaluation of a real-world referral algorithm in primary care for identifying significant fibrosis (F2-4) in MASLD among patients with type 2 diabetes, obesity, or both. The most significant drop off point is indicated by a "*". *Abbreviations: DM, type 2 diabetes mellitus; FIB-4, fibrosis-4 index score; PC, primary care; PCP, primary care provider*

Disclosures: Mohsen Merati: Nothing to Disclose, Max Goldman: Eli Lilly: Stock - publicly traded company, Novo Nordisk: Stock - publicly traded company, Eli Lilly:

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3035 | EPIDEMIOLOGY OF AT-RISK CLINICALLY SIGNIFICANT PORTAL HYPERTENSION IN THE UNITED STATES

Ritik Mahaveer Goyal[1] Apoorva Doshi[2] Sameer Rao[3] Rohan Karkra[3] Imran Qureshi[4] Paul Gaglio[3], [1]Rutgers New Jersey Medical School, [2]University of Alabama at Birmingham, [3]Rutgers NJMS, [4]RUTGERS THE STATE UNIVERSITY OF NEW JERSEY

Background: Clinically significant portal hypertension (CSPH) represents a pivotal stage in the progression of chronic liver disease. According to the Baveno VII guidelines, CSPH can be ruled out in individuals with liver stiffness measurement (LSM) <15 kPa and platelet count $>150{,}000/\mu l^3$. However, patients with compensated advanced chronic liver disease (cACLD) who do not meet these criteria require further evaluation, as they are considered at risk for CSPH. This study aimed to characterize the prevalence and demographic features of individuals at risk for CSPH in the United States. **Methods:** We analyzed data from adults who underwent complete transient elastography (TE) using the National Health and Nutrition Examination Survey (NHANES) from 2017 - March 2020. Patients meeting Baveno VII rule-out criteria (LSM <15 kPa and platelets $>150{,}000/\mu l^3$) were categorized as "rule-out CSPH," while all others (LSM ≥ 15 kPa or LSM <15 kPa with platelets $<150{,}000/\mu l^3$) were defined as "at-risk CSPH." We applied NHANES-recommended sample weights to account for the complex sampling design. Chi-square tests were used for categorical variables and ANOVA for continuous variables. **Results:** A total of 7,847 adult participants had complete TE data, of which 7,479 met criteria for rule-out CSPH, while 368 were classified as at-risk CSPH. The weighted prevalence of at-risk CSPH was 5.78% (95% CI: 4.9%–6.8%). Compared to the rule-out group, at-risk CSPH patients were older (mean age 54.9 vs. 46.9 years, $p<0.001$), had a lower proportion of males (32.2% vs. 52.2%, $p<0.05$), higher mean BMI (33.4 vs. 29.4, $p<0.001$), and waist circumference (110.1 vs. 99.5 cm, $p<0.001$). The at-risk group had a significantly higher prevalence of hypertension (66.2% vs. 45%, $p<0.001$), diabetes mellitus (30.1% vs. 13.8%, $p<0.001$), MASLD (33.8% vs. 23.5%, $p<0.05$), and chronic hepatitis C (6.5% vs. 1.8%, $p<0.001$). No significant differences were observed in the prevalence of chronic hepatitis B, excessive alcohol use, or current smoking. Notably, 88% of those in the at-risk group were unaware of their liver disease. **Conclusion:** In this nationally representative sample, nearly 6% of U.S. adults undergoing transient elastography were at risk for CSPH. This group demonstrated a distinct clinical profile marked by older age, higher BMI, and greater metabolic and viral liver disease burden. Alarmingly, most remained unaware of their liver condition, underscoring the need for enhanced screening and early detection strategies.

Table: Demographic, comorbidity and etiological profile of patients with CSPH ruled out and at-risk CSPH

Participant Factors	LSM<15kPa and Platelet count >150,000/uL (CSPH ruled out) (N=7,479)	LSM>15kPa OR LSM < 15kPa + Platelet count ≤150,000/uL (at-risk CSPH) (N=368)	p-value
Weighted Prevalence	94.2% (93.2%-95.1%)	5.78% (4.9%-6.82%)	
Mean Age in years (SE)	46.91 (± 0.55)	54.91 (±1.04)	<0.001
Males, % (95% CI)	52.2% (50.4-53.9)	32.2% (26.5-38.5)	<0.05
Race, prevalence % (95% CI)			0.72
White	62.8% (57.9-67.4)	63.3% (52.2-73.1)	
Black	10.77% (8.28-13.89)	12.13% (8.37-17.26)	
Asian	5.76% (4.14-7.98)	3.4% (3.34-8.54)	
Mexican American	8.85% (6.64-11.67)	7.6% (4.47-12.86)	
Other Hispanic	7.77% (6.34-9.48)	6.52% (4.29-9.8)	
Multiracial	4.05% (3.39-4.84)	4.97% (2.67-9.09)	
Have been told that they have liver disease, % (95% CI)	4.23% (3.46-5.15)	11.97% (8.01-17.51)	<0.001
Mean BMI (SE)	29.4 (±0.17)	33.43 (±0.71)	<0.001
Waist Circumference (±SE) (in cm)	99.5 (±0.48)	110.14 (±1.41)	<.001
Current Smoker, % (95% CI)	16.67% (14.65-18.92)	15.54% (9.46-24.46)	0.77
Diabetes Mellitus, % (95% CI)	13.8% (12.8-14.7)	30.1% (25.4-35.3)	<0.001
Hypertension, % (95% CI)	45% (42.1-47.8)	66.2% (58.8-73)	<0.001
MASLD, % (95% CI)	23.48% (21.52-25.56)	33.79% (26.25-42.26)	<0.05
Excess Alcohol Intake, % (95% CI)	9.74% (8.44-11.22)	9.24% (5.27-15.7)	0.84
Active Hepatitis B_s % (95% CI)	0.87% (0.56-1.33)	1.14% (0.24-5.16)	0.71
Chronic hepatitis C, % (95% CI)	1.84% (1.13-2.97)	6.32% (4.94-8.58)	<0.001

Disclosures: Ritik Mahaveer Goyal: Nothing to Disclose, Apoorva Doshi: Nothing to Disclose, Sameer Rao: Nothing to Disclose, Rohan Karkra: Nothing to Disclose, Imran Qureshi: Nothing to Disclose, Paul Gaglio: Nothing to Disclose, Nothing to Disclose

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3036 | TREATMENT DELAYS AND SURVIVAL IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: A MULTICENTER COHORT STUDY

Mohammad Jarrah[1] Mohammed Al-Hasan[1] Gloria Figueroa[2] Stephanie Garces[2] Sruthi Yekkaluri[1] Lisa Quirk[1] Suaiba Syeda[1] Patricia Jones[2] Adam Yopp[1] Nicole Rich[1] Amit Singal[1], [1]University of Texas Southwestern Medical Center, [2]University of Miami

Background: Interruptions in the cancer care continuum, such as treatment delays, can impact survival in patients with hepatocellular carcinoma (HCC). While the impact of such delays have been described in other cancers, data are limited on the prevalence of these delays what factors predict delays, and the impact of delays on survival among patients with HCC. **Methods:** We conducted a retrospective cohort study of patients diagnosed with HCC between 2010 and 2018 across 4 U.S. health systems. Treatment delay was defined as receiving the first treatment >90 days after HCC diagnosis. Patients who remained untreated and those with BCLC stage D were excluded from analyses given limited options for HCC-directed treatment outside of liver transplantation. Univariable and multivariable logistic regression models were performed to identify factors associated with treatment delays. The association between treatment delay and overall survival was evaluated using multivariable Cox regression model; to account for immortal time bias, we established a 6-month landmark in which patients who died before 6 months were excluded. **Results:** Of the 1561 eligible patients (median age 61.7 [IQR 56.7 – 67.7], 75.0% men, 48.0% BCLC stage 0/A), treatment delays occurred in 357 (22.9%) patients. Treatment delays were observed in 31.1% of patients with BCLC stage 0, 24.3% of BCLC stage A, 22.6% of BCLC stage B, and 13.6% of BCLC stage C, including 28.1% of patient within Milan criteria. Men (OR 0.68, 95%CI 0.49 – 0.96) and patients with BCLC stage C HCC (vs BCLC A: OR 0.40, 95%CI 0.25 – 0.63) were less likely to experience delays, while those with BCLC stage 0 (vs BCLC A: OR 1.56, 95%CI 1.06 – 2.29) were more likely to experience delays. Using a 6-month landmark analysis, median overall survival was 19.0 months (IQR: 7.9 – 40.6) in patients who received timely treatment compared to 18.7 months (IQR: 8.5 – 39.6) in those with delayed treatment. Based on this landmark, there was no significant difference in survival between delayed vs. timely treatment (HR 0.94, 95%CI 0.76 – 1.18). **Conclusion:** Treatment delays beyond 90 days occur in nearly one-fourth of patients, with significant associations with sex and tumor burden. Treatment delays did not significantly impact overall survival, suggesting that modest delays may not compromise survival outcomes. Additional studies are needed to better understand the impact of treatment delays.

Disclosures: Mohammad Jarrah: Nothing to Disclose, Mohammed Al-Hasan: Nothing to Disclose, Gloria Figueroa: Nothing to Disclose, Stephanie Garces: Nothing to Disclose, Sruthi Yekkaluri: Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Suaiba Syeda: Nothing to Disclose, Patricia Jones: Nothing to Disclose, Adam Yopp: Nothing to Disclose, Nicole Rich: AstraZeneca: Advisor, Genentech: Consulting, Exelixis: Advisor, Eisai: Advisor, Madrigal: Advisor, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant

3037 | SURVEILLANCE FOR HEPATOCELLULAR CARCINOMA IN ALASKA NATIVE PEOPLES WITH CHRONIC HEPATITIS B

LESLEIGH KOWALSKI FRANK, BRIAN J MCMAHON, CHRISS HOMAN, MARY SNOWBALL, LISA TOWNSHEND-BULSON*, Lesleigh Kowalski Frank[1] Brian McMahon[2] Lisa Townshend-Bulson[1] Chriss Homan[1] mary snowball[1]*

[1]Alaska Native Tribal Health Consortium, [2]Alaska Native Medical Center

Background: Hepatitis B virus (HBV) causes the most common acute and chronic serious viral infections globally. Chronic hepatitis B (CHB) is a leading risk factor for developing hepatocellular carcinoma (HCC). HBV is endemic in Western Alaska and Alaska Native (AN) peoples have high prevalence rates of HBV infection, acquired primarily at birth or early in life, and have a higher incidence of HCC compared to other communities. AASLD recommends people at a higher risk for HCC receive bi-annual liver function (LFT)/HBV tests, AFP tests, and liver ultrasound (US). In this study, we aimed to identify the proportion of people who did/did not meet AASLD HCC surveillance guidelines. **Methods:** We established a clinical registry for all HBsAg-positive AN peoples in the 1980s during a HBV screening and vaccination campaign. We send letters to all AN persons with CHB and their providers every 6 months to remind them to obtain liver blood tests and HCC screening with US. For this analysis, we used registry data from a 5-year period from 2017 through 2021 of AN peoples who consented to participle in a long-term hepatitis B cohort study to determine receipt of these surveillance tests. **Results:** Of the 913 AN peoples with CHB, 689 (75.5%) were considered high risk for HCC based on: cirrhosis, a family

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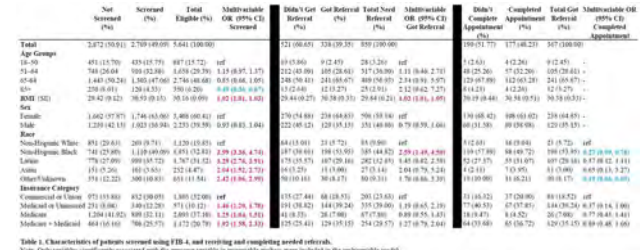
history of HCC, age ≥40 years men and ≥50 year women, or HBV genotype F at any age. Of these persons, an average of 38.4% had LFT/HBV and 21.4% had AFP tests at least twice/year; 67.4% obtained LFT/HBV and 54.8% had AFP tests at least once/year. During the pandemic (years 2020-2021), 8.7% had at least two US tests/year while 40.6% had at least one, compared to 9.7% and 41.6% before the pandemic (2017-2019), respectively. US frequency was significantly higher ($p < 0.001$) in all years in urban and hub communities with access to US compared to more rural communities where air travel is required to access US. **Conclusion:** We were one of the first organizations to initiate an HCC surveillance program for those with chronic HBV infection in an endemic region. This study shows that encouraging people with CHB with no symptoms to complete screening tests every 6 months is challenging, especially if they live in remote Alaskan communities. HCC US screening rates lag behind other cancer screening rates among AN peoples, such as colorectal (56.2%) and breast (61.3%), with the exception of lung (9.3%). Further targeted risk stratification may help to prioritize patients at the highest risk of HCC to increase surveillance rates.
Disclosures: Lesleigh Kowalski Frank: Nothing to Disclose, Brian McMahon: Nothing to Disclose, Lisa Townshend-Bulson: Gilead Sciences: Grant/Research Support, Chriss Homan: Nothing to Disclose, mary snowball: Nothing to Disclose

3038 | MASLD/MASH CARE PATHWAY ADHERENCE IDENTIFIES PATIENTS WITH ADVANCED FIBROSIS

Anna Mageras[1] Jake DeBroff[2] Jihae Jeon[3] Rama Hussein[4] Tracey Rosa[5] Ilana Ramer Bass[3] Christopher Gold[6] Stephanie Wang[7] Theresa Mack[7] Desiree Chow[3] Nina Priven[3] Heather Viola[3] Xiaotao Zhang[3] Fernando Carnavali[3] Meena Bansal[8], [1]Liver Diseases, Icahn School of Medicine at Mount Sinai, [2]Mount Sinai Beth Israel, [3]Icahn School of Medicine at Mount Sinai, [4]Mount Sinai Morningside-West Hospital, Icahn School of Medicine at Mount Sinai New York, NY, United, [5]Icahn School of Medicine at Mount Sinai New York, [6]Mount Sinai West, New York, NY, [7]Mount Sinai Morningside, New York, NY, [8]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: At baseline in our large, urban healthcare system, <10% of patients with diabetes (PWD) were screened for metabolic dysfunction-associated steatotic liver disease (MASLD) with FIB-4 score per American Association for the Study of Liver Diseases (AASLD) recommendation. Nevertheless, ambulatory leaders were reluctant to add a screening prompt to our electronic medical record (EMR), citing provider alert fatigue. To generate supporting data, a group of primary care providers (PCPs) and endocrinology fellows piloted improved adherence to the care pathway. We evaluated different methods, barriers to care, and health disparities. **Methods:** In two primary care and one endocrinology clinics, providers used a SmartPhrase typed into their encounter note to calculate FIB-4 from existing AST, ALT, and Platelet lab results. The SmartPhrase provided age-adjusted recommendations for VCTE (FIB-4 1.3-2.67 for ages 18-64; 2.0-2.67 for 65+) or hepatology referral (> 2.67). In two additional clinics, backend FIB-4s were calculated from existing labs, and PCPs were given lists of PWD needing referrals. For analysis, we removed PWD seen by oncology or liver and lacking requisite labs. We used chi-square tests to compare arms and univariable and multivariable logistic regression to assess health disparities through the care pathway. **Results:** Among 5,641 PWD eligible for FIB-4 screening, 45% were under age 65; 60% female; 33% Black, and 31% Latino. Of 2,769 (49%) screened, 859 (31%) needed a referral, 367 (13%) received one, and 177 (6%) completed VCTE, identifying 13% F2 (8-10kPa), 6% F3 (10-14kPa), and 7% F4 (>14kPa) cases. Of 190 PWD who received but did not complete referrals, 22 had upcoming appointments, 69 needed outreach, 7 no-showed, 5 declined, 1 was unable to complete, and 72 were pending provider signature in the EMR. Backend FIB-4 calculation resulted in a 100% screening rate, versus a 16% rate via provider-driven screening. But significantly higher rates of referrals were given and completed among PWD screened by providers ($p < .0001$). PWD with higher BMI, non-white, and Medicare- and/or Medicaid-insured had higher odds of being screened; PWD with higher BMI and identifying as Black had higher odds of getting a referral; but Black PWD and those of unknown race had lower odds of completing VCTE (Table 1). **Conclusion:** Forty-nine percent of eligible patients were screened, and 26% of VCTE-evaluated patients had F2-F4, demonstrating the care pathway's utility. Our quality intervention improved adherence to the care pathway, but gaps remain. Placing referrals and engaging patients is labor intensive. Patient navigators would support providers and patients and reduce disparities. Patient anxiety about out-of-pocket expenses was a barrier; VCTE-only appointments may streamline referrals. A provider dashboard that auto-calculates FIB-4 and allows bundled referrals may be a more effective, equitable, and less burdensome implementation.



Disclosures: Anna Mageras: The Kinetix Group: Advisor, Novo Nordisk: Advisor, Gilead Sciences: Grant/Research

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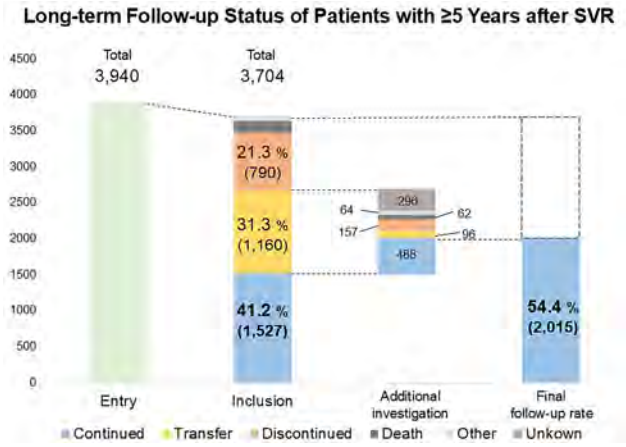
3039 | LONG-TERM FOLLOW-UP AND FACTORS INFLUENCING FOLLOW-UP ADHERENCE AFTER DAAS THERAPY: A MULTICENTER STUDY OF SVR 3,704 PATIENTS IN NATIONWIDE SURVEY

Masatsugu Ohara[1] Ritsuzo Kozuka[2] Yoshihito Uchida[3] Chikara Iino[4] Ryo Sasaki[5] Hiroki Tojima[6] Satoru Kakizaki[7] Yoshio Tokumoto[8] Hirokazu Takahashi[9] Akira Asai[10] Jun Inoue[11] Mizuki Endo[12] Kazuhito Kawata[13] Kenji Nagata[14] Koji Ogawa[15] Tetsuro Shimakami[16] Masaru Enomoto[2] Tadashi Ikegami[17] Tatsuya Ide[18] Naoya Sakamoto[19] Masaaki Korenaga[20], [1]Hokkaido University Hospital, [2]Osaka Metropolitan University, [3]Saitama Medical University, [4]Hirosaki University, [5]Yamaguchi University, [6]Gunma university, [7]NHO Takasaki General Medical Center, [8]Ehime university, [9]Saga university, [10]Osaka Medical and Pharmaceutical University Hospital, [11]Tohoku university, [12]Oita university, [13]Hamamatsu University School of Medicine, [14]University of Miyazaki, [15]NTT Medical Center Sapporo, [16]Kanazawa university, [17]Tokyo Medical University Ibaraki Medical Center, [18]Kurume university Medical center, [19]Graduate School of Medicine Hokkaido University, [20]Japan Institute for Health Security (JIHS)

Background: Achieving sustained virologic response (SVR) after direct-acting antiviral (DAA) therapy significantly improves the prognosis of hepatitis C virus (HCV) patients. However, the long-term follow-up status for SVR patients, particularly regarding the continuation of care and risk factors for discontinuation, remains underexplored. This study aims to address this gap by evaluating the follow-up outcomes of SVR patients at regional core centers across Japan. To evaluate the long-term follow-up outcomes of patients who achieved SVR after DAA therapy and analyze factors influencing follow-up adherence, transfer, and discontinuation. **Methods:** A retrospective, multicenter study was conducted at 16 regional core centers, analyzing data from 3,704 patients who achieved SVR between 2015 and 2018. We assessed patient demographics, follow-up status, and clinical outcomes, including hepatocellular carcinoma (HCC). Multivariate analyses identified factors associated with discontinuation, transfer, and follow-up continuation. **Results:** At the time of analysis, 41.2% of patients remained under follow-up at regional core centers, 31.3% transferred to other institutions, and 21.3% discontinued follow-up. Serotype 2 (OR 1.61, 95% CI 1.34–1.93, $p < 0.001$) was significantly associated with a higher likelihood of discontinuation. Furthermore, a higher FIB-4 index, HCC, and other malignancies were all significantly associated with a reduced likelihood of discontinuation (FIB-4 index between 1.3 and 3.25: OR 0.628, 95% CI 0.497–0.793; FIB-4 index $\geq$ 3.25: OR 0.701, 95% CI 0.526–0.934; HCC: OR 0.209, 95% CI 0.121–0.362, $p < 0.001$; other malignancies: OR 0.61, 95% CI 0.386–0.963, $p = 0.0338$). In contrast, age $\geq$65 years, serotype 2, and hypertension were significantly associated with a higher likelihood of transfer to other institutions (age: OR 1.59, 95% CI 1.33–1.89, $p < 0.001$; hypertension: OR 1.24, 95% CI 1.04–1.49, $p = 0.0188$). Patients with a higher FIB-4 index (OR 0.755 for 1.3-3.25, OR 0.709 for $\geq$3.25) and HCC (OR 0.27, 95% CI 0.18–0.405, $p < 0.001$) were less likely to transfer. **Conclusion:** This study highlights that serotype 2, higher FIB-4 index, and HCC are key factors related to follow-up adherence. Patients with higher FIB-4 indices and HCC were more likely to remain under follow-up at regional core centers, indicating these centers effectively manage high-risk cases.



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3040 | OPTIMIZING WORKFLOWS FOR PROVIDERS USING LARGE LANGUAGE MODELS TO RESPOND TO PATIENT MESSAGES IN THE ELECTRONIC PORTAL

Hersh Shroff[1] Oren Fix[2], [1]UNC Chapel Hill, [2]University of North Carolina at Chapel Hill

Background: Healthcare providers (HCPs) who care for patients with complex, chronic liver disease spend significant time outside of clinic on electronic health record (EHR) tasks. An increasing volume of patient medical advice requests (PMARs) has been linked to clinician burnout. Artificial intelligence (AI) tools offer opportunities to reduce EHR burden on HCPs. We assessed two methods for using a large language model (LLM) to assist HCPs in responding to PMARs. **Methods:** We enrolled a convenience sample of HCPs at an academic center to test two LLM workflows (Models 1 and 2). Model 1 uses Epic's *Automated Response Technology (ART)*, where an EHR-integrated LLM is given a standard prompt and reads the text of a patient message to generate a draft reply. Model 2 uses our institution's HIPAA-secure LLM, accessed separately from the EHR. In this workflow, HCPs provide the LLM with a standard prompt written by the study investigators followed by a shorthand description of the provider's desired response, and the LLM generates a reply. Both models use OpenAI's GPT 4o. HCPs tested 40 unique PMARs (20 per model) and used an online survey (Qualtrics, Provo, UT) to rate AI-generated drafts on quality of information content, communication style, provider's preference of using model vs. self, and cognitive burden. Ratings were compared using the Mann-Whitney U test. All statistics were performed in R (version 4.5.0). **Results:** Of 13 currently-enrolled HCPs, 8 are gastroenterologists and hepatologists, 10 are physicians, and 3 are advanced practice providers. Thus far, 5 HCPs have completed testing of 90 Model 1 and 95 Model 2 messages. On a 5-point Likert scale (0 = significantly disagree; 4 = significant agree), HCPs were significantly more likely to agree that messages from Model 2 (as compared to Model 1) provided high information quality (median [IQR]: 4 [3-4] vs. 1 [0-3], $p < 0.001$) and appropriate communication style (4 [3-4] vs. 2 [1.25-3], $p < 0.001$). HCPs reported lower cognitive burden to use Model 2 (1 [0-2] vs. 2 [1-2.75], $p < 0.001$). When asked if they preferred to use the AI response versus writing the message on their own, HCPs agreed for Model 2 responses (3 [1-4]) but not for Model 1 (1 [0-3]). **Conclusion:** With increasing integration of AI tools into clinical practice, it is important for HCPs and health systems to continuously re-evaluate optimal workflows. In our study, a model allowing HCPs to engage with and instruct an LLM was significantly preferred over an alternative model where providers had little input or control.

Table 1: Example of a top-rated draft message by Model 2 workflow

Patient's Original Message	Thank you! I will continue with the nifedipine and that Miralax bowel prep. I will also add that I was only taking Miralax twice a day for a week before that scan - and I know that likely isn't long enough to move things along. I will continue with the Miralax! I will also add that yesterday evening I had another significant bowel movement (half diarrhea, half solid) yesterday evening - but for a couple seconds I blacked out from the pain during that bowel movement. I wasnt straining, but there was likely a ton of pain within my colon as things were passing through. I felt fine after that. And I feel relatively normal today. Thank you,
Provider Input to Large Language Model (LLM)	[Copied and pasted text of patient's initial message into LLM] * discuss vagal response and constipation, advise to continue to monitor symptoms
LLM Draft Response	Hi XXXX, Thank you for your message. I'm glad to hear that you will continue with the nifedipine and the Miralax bowel prep. It's important to give Miralax some time to work, so continuing it is a good plan. Regarding your recent experience, it sounds like you might have had a vagal response during your bowel movement. This can happen when the vagus nerve is stimulated, leading to a temporary drop in heart rate and blood pressure, causing you to feel faint or briefly black out. This response can sometimes occur during bowel movements, especially if there is significant pain or strain. Constipation can contribute to this issue, as the discomfort and effort to pass stool can trigger the vagal response. It's good to hear you felt fine afterward and feel relatively normal today. Please monitor your symptoms closely and let us know if you experience any more severe pain or other concerning symptoms. If you have any questions or need further assistance, please let us know. Best regards, XXX

Disclosures: Hersh Shroff: Nothing to Disclose, Oren Fix: Nothing to Disclose

3041 | DETERMINANTS OF HEALTH-RELATED QUALITY OF LIFE AMONG CHRONIC HEPATITIS B PATIENTS IN FRANCE

Clotilde Lepers[1] Clovis Lusivika-Nzinga[2] Samuel Nilusmas[2] Jonathan Bellet[2] Paul Burgat[2] Marc Bourliere[3] Maria Patrizia Carrieri[4] Fabrice Carrat[5] Sylvie Deuffic-Burban[6], [1]Université Paris Cité, Inserm, IAME, Hôpital Bichat, AP-HP Nord, Paris, France, [2]Sorbonne Université, Inserm, iPLesp, Paris, France, [3]Aix Marseille Univ, Inserm, IRD, SESSTIM, ISSPAM, Hospital Saint Joseph, Marseille, France, [4]Aix Marseille Univ, Inserm, IRD, SESSTIM, ISSPAM, Marseille, France, [5]Sorbonne Université, Inserm, iPLesp, Hôpital Saint-Antoine, AP-

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Background: Health-related quality of life (HRQoL) has been shown to be impaired in patients with chronic hepatitis B (CHB). Beyond the level of disease severity, HRQoL may be affected by socio-demographic and economic conditions. The objective was to evaluate the HRQoL and their determinants among CHB patients included in the French ANRS CO22 HEPATHER cohort. **Methods:** A cross-sectional study was conducted within the prospective multicenter ANRS CO22 HEPATHER cohort between 2012 and 2019. All patients with CHB were invited to complete a questionnaire on HRQoL, at enrolment and at clinical visits. HRQoL was assessed using EQ-5D-5L collected at the first questionnaire, and utility scores were derived using the French value set. Sociodemographic, behavioral, and clinical data were obtained from HEPATHER database. Utility scores were rescaled to the (0,1) interval and modeled using a Beta-inflated GAMLSS approach. Variables were first tested in univariable analyses; those with $p < 0.05$ or clinical relevance (e.g., sex) were included in the multivariable model after multiple imputation. Average association (mean odd-ratios and their 95% confidence interval (95%CI)) was obtained using Rubin's methods. **Results:** A total of 1,715 patients completed at least one questionnaire. Among respondents, 64.4% were men, the median age was 46 years, 63.6% were under current or past treatment, 11.7% had compensated cirrhosis, 5.2% had complications (0.9% < 1 year; 4.3% > 1 year). The mean utility score was 0.94, and the median 0.98. In univariable analyses, mean utility score decreased with older age, female sex, non-sub-Saharan African origin, separated/divorced/widowed status, lower education, unemployment and at-risk alcohol consumption (current or former), and the presence of cirrhosis, complication, hypertension, diabetes and obesity. However, only unemployment and separated/divorced/widowed status decreased significantly HRQoL in the final model (Table). **Conclusion:** In this large cohort of CHB patients, HRQoL was mainly influenced by sociodemographic and behavioral factors rather than CHB-related clinical parameters. Among CHB patients, unemployment and separated/divorced/widowed status significantly alter HRQoL. These results suggest that future therapies to achieve functional cure will not necessarily improve HRQoL in these patients, underlying the importance of considering sociodemographic determinants in CHB patients' healthcare.

Table: Determinants of HRQoL (mean odd-ratios and their 95% confidence interval (95%CI)): Multivariate analysis

Variable	Odd ratio	95% CI Low	95% CI High	p-value
Women	0.93	0.82	1.04	0.23
Age superior or equal to median (46years)	0.95	0.83	1.08	0.45
Sub-Saharan origin	1.08	0.94	1.24	0.3
Lower education	0.96	0.86	1.08	0.52
Separated/divorced/widowed status	**0.82**	**0.7**	**0.96**	**0.04**
Unemployment	**0.82**	**0.73**	**0.92**	**0.01**
Current or former excessive alcohol consumption	0.88	0.71	1.08	0.24
Diabetes	0.92	0.76	1.12	0.41
Hypertension	0.86	0.75	0.99	0.06
Obesity	0.86	0.74	0.99	0.06
Cirrhosis	0.97	0.79	1.19	0.8
Ancient complication	0.96	0.74	1.26	0.78
Recent complication	0.63	0.39	1.02	0.09

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3042 | PREDICTORS OF SPECIALTY REFERRAL AMONG RESETTLED REFUGEES LIVING WITH HEPATITIS B

Erin Mann[1] Darin Erickson[1] Jose Debes[1], [1]University of Minnesota

Background: Most refugees resettling to the United States (US) are from regions with intermediate to high hepatitis B virus (HBV) endemicity. Linkage to care is critical to establish proper care and reduce HBV-related complications. However, studies show gaps in chronic HBV management and care linkage after refugee arrival. The domestic medical examination (DME), the initial medical screening for refugees, often marks their first interaction with US healthcare. **Methods:** We conducted a cross-sectional analysis of DME screening data for refugees living with hepatitis B who arrived between 2003–2023, using data from the Colorado Center of Excellence in Newcomer Health, a national surveillance network spanning seven states. We summarized referrals and used multivariate regression to estimate risk ratios (RR) for associations between referral and age, sex, region of origin, hepatitis C, and HIV. Two definitions of specialty referral were used: "hepatitis B" only compared to "hepatitis B" or "gastrointestinal," based on coding review. **Results:** Among 2,449 refugees who tested positive for HBV (median age 29, IQR 21- 39; 62.0% male), most were from Asia (50.0%), the Eastern Mediterranean (27.1%), and Africa

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(21.2%). Co-infection rates were low (1.6% for HCV; 1.1% for HIV). During the DME, 16.4% were referred based on “hepatitis B” codes alone, and 23.0% when including both "hepatitis B" or “gastrointestinal.” The broader definition had a higher area under the ROC curve (0.67 vs. 0.59). In this model, adult age (RR 1.44, 95% CI 1.14–1.82) and male gender (RR 1.17, 95% CI 1.03–1.32) were associated with higher referral probability. HCV and HIV were not associated with referral, though analyses may have been underpowered. Predicted referral probabilities were highest for refugees from Asia (26.8%), the Eastern Mediterranean (25.5%), and Africa (22.8%), and lowest for Europe (15.1%) and the Americas (8.0%). **Conclusion:** In this national sample of refugees with HBV (largest to date on this topic), 16.4% were referred to specialty care based on “hepatitis B” coding alone and 23.0% when including both “hepatitis B” and “gastrointestinal” codes. Adult age and male gender were associated with a higher probability of referral. Referral probabilities were highest among refugees from Asia, the Eastern Mediterranean, and Africa. Strengthening early referral pathways may help reduce long-term HBV-related health disparities.
Disclosures: Erin Mann: Nothing to Disclose, Darin Erickson: Nothing to Disclose, Jose Debes: Nothing to Disclose

3043 | EARLY DETECTION OF HEPATIC FIBROSIS AND HEPATOCELLULAR CANCER IN VULNERABLE ADULTS IN COMMUNITY SETTINGS: A PILOT SERVICE EVALUATION PROJECT IN SE ENGLAND

James Ryley[1] Vikki Charles[1] Margaret O'Sullivan[1] Jason Howell[1] Duncan Cresswell[1] Jeremy Tibble[1], [1]University Hospitals Sussex

Background: Many patients with chronic liver disease (CLD) present with cirrhosis and its complications including hepatocellular cancer (HCC). Early detection of CLD is the key to prevent liver related morbidity/mortality. CLD screening in the community to enable timely HCC surveillance was commissioned by NHS England as a service evaluation pilot and Sussex (SE England) selected as one of the pilot sites. In addition, screening of the public (without known risk factors) was done as part of a British Liver Trust (BLT) event. **Methods:** The setting was multiple community centres/ events, targeted populations included alcohol and substance misusers, metabolic dysfunction-associated steatotic liver disease, viral hepatitis, people experiencing homelessness (at risk group) and general public (not known risk group). At drop-in and booked clinics, transient elastography (TE) performed and routine clinical data collected. After consultant clinical review, most with liver stiffness measurement of > 11.5 kPa were offered HCC surveillance with ultrasound. Multivariate analysis was performed to determine predictors of advanced hepatic fibrosis. Data were collected between 2022 and 2025. **Results:** Total number of individuals undergoing TE were n = 3054, n = 1783 (58%) being male, majority white British, mean age 54 +/- 12 years. Average weekly alcohol consumption was 44 units. Distribution of hepatic fibrosis was none/mild (< 8.5kPa, n = 2446 (80%)), moderate (8.5 - 11.5 kPa, n = 294 (10%)) and advanced (> 11.5kPa, n = 293 (10%)).[SV1] Of the n = 293 with advanced fibrosis, n = 184/189 (97%) offered, attended for HCC surveillance ultrasound, mean time to surveillance being 87 days +/- 126. Three individuals were diagnosed with HCC (BCLC stages 0/A).
Using a multivariate logistic regression model predictors of advanced fibrosis were, alcohol units per week and at-risk vs BLT group. Each additional unit of alcohol consumed per week, increased odds of advanced fibrosis by 0.6% (OR = 1.006, 95% CI: 1.005–1.008, $p < 0.001$). Those screened at the BLT event (not known risk group) had 86% reduced odds of having advanced fibrosis (OR = 0.139, 95% CI: 0.03-0.37, $p < 0.001$). **Conclusion:** Community screening of at-risk individuals identifies a 20% prevalence of moderate to advanced hepatic fibrosis. Despite the vulnerable nature of the cohort, nearly all patients offered, accepted HCC surveillance which allowed for detection of HCC at early BCLC stage.
Disclosures: James Ryley: Nothing to Disclose, Vikki Charles: Nothing to Disclose, Margaret O'Sullivan: Nothing to Disclose, Jason Howell: Nothing to Disclose, Duncan Cresswell: Nothing to Disclose, Jeremy Tibble: Nothing to Disclose

3044 | LIVER DISEASE-SPECIFIC LARGE LANGUAGE MODELS (LLMS) DRAFTED HEPATOLOGY "E-CONSULT" RESPONSES ARE NOT EQUIVALENT TO HUMAN RESPONSES

Debra Yen[1] Michelle Li[1] Gabrielle Jutras[1] Lisa Deng[1] Mark Pletcher[1] Jennifer Lai[1] Bilal Hameed[1] Jin Ge[1], [1]University of California, San Francisco

Background: We developed LiVersa, a protected health information (PHI)-compliant liver disease LLM customized with Retrieval Augmented Generation (RAG) on OpenAI’s GPT-4o. Specialty-specific LLMs like LiVersa may be able to address “e-consults,” which answer limited clinical questions without a patient visit using only electronic health record (EHR) data. In this study, we evaluated LiVersa-generated e-consult drafts versus actual human responses. **Methods:** We queried hepatology e-consults answered at UCSF between April-June 2024. We used LiVersa to draft responses

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using only the question contained in the e-consult request and no additional information to the chart. Three hepatologists who did not write the original responses compared LiVersa drafts with human responses using 12 Likert scale and free-text questions. These questions were specifically developed within UCSF to grade clinical LLMs by clinical equivalence, specificity, accuracy, and safety. We used correlation heatmap analyses to determine associations in responses. **Results:** We evaluated 52 e-consults. Compared to human responses, only 25% of drafts contained all components of human responses without missing information, and 28% of drafts were considered clinically equivalent. 29% of drafts had content with potential for mild or moderate harm, and 3.8% had potential for severe or life-threatening harm. However, 74% of LiVersa-generated drafts were considered "helpful starting points," 69% had no misleading or incorrect information, and 96% were sufficiently specific to the clinical scenario. Correlation heatmaps showed that lack of clinical equivalence in the LiVersa draft had moderate associations with being incorrect (0.46) and potentially harmful (0.5). Of note, evaluators thought most (61%) e-consult requests, as written, did not contain sufficient information. In these cases, the actual human responses contained data from further chart review that was not available to LiVersa. **Conclusion:** While LLMs, in their current form, are unlikely to replace human expertise, this study concerning e-consults showed that disease-specific LLMs like LiVersa have potential to augment human hepatologists. Further work is needed to improve the quality of clinically relevant EHR data passed to LiVersa, as our study suggests LLM drafts were more clinically equivalent and more accurate when the relevant data was available to the LLM.

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3045 | HARNESSING THE PATIENT PERSPECTIVES TO IMPROVE EMERGENCY DEPARTMENT UTILIZATION IN CIRRHOSIS

Swetha Parvataneni[1] Nicholas Harrison[1] Bridget Hawryluk[1] Courtney Moore[1] Anurag Harishchandrakar[1] William Bennett[1] Raj Vuppalanchi[1] Eric Orman[1] Naga Chalasani[2] Archita Desai[1], [1]Indiana University, [2]Indiana University Medical Center

Background: Individuals with cirrhosis often visit emergency department (ED) with 20% experiencing high ED use (HEDU) $\geq$2 ED visits within 90-days. We aimed to understand patient and caregiver perspectives on the reasons that contribute to HEDU and identify potential opportunities for reducing unnecessary visits. **Methods:** At a large tertiary care center, we retrospectively identified adult patients with diagnosis of cirrhosis who were HEDU patients in 2024. Eligible patients were invited to participate in a 3-hour semi-structured group-based interactive session facilitated by human-centered design experts. A custom board game modeled on the children's game "Chutes and Ladders" was used to facilitate engagement. This interactive game included questions exploring decision making prior to ED utilization and patient perspective after ED visit (Figure 1). **Results:** Seven participants (three dyads of patients and caregiver, and one patient without a caregiver) attended the session. At baseline, three patient participants had decompensated cirrhosis (2 with ascites, 1 with encephalopathy). Affinity mapping during analysis generated key drivers of HEDU. Some participants described needing to present to the ED because they did not monitor their symptoms until they were severe. Participants valued receiving effective and immediate relief for symptoms in the ED and reported that it reduced patient and caregiver stress. Participants also expressed a lack of trust in available online resources regarding cirrhosis management. Participants typically informed their outpatient doctors only after the ED visit because their prior written instructions directed them to ED for worsening symptoms. Patients believed that correctly taking their medications and monitoring their symptoms play a major role in improving their condition but are also burdensome for patients and caregivers. Conceptual modes were created to explore and explain the relationship between these drivers and relationships between patient, caregiver and provider. **Conclusion:** Our study highlights that uncontrolled symptoms, lack of access to on-demand advice from the outpatient team, and the daily stress of living with cirrhosis as drivers for frequent ED use. Patients viewed the ED as a reliable and quick source of care. These findings reveal the need for improved outpatient support, medication management, symptom monitoring, and trusted educational resources in cirrhosis care. Digital health technologies partnered with

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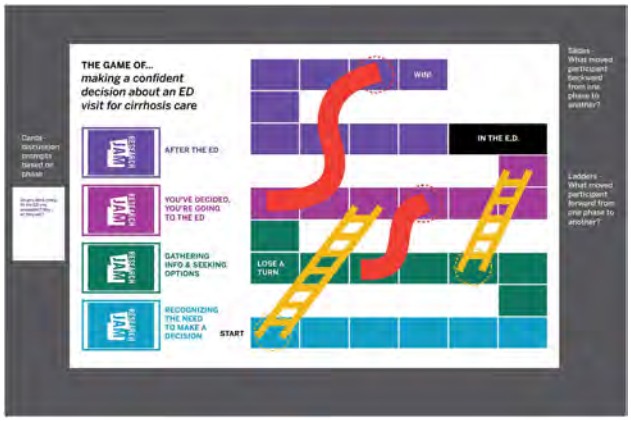
multidisciplinary patient-centered models may help reduce repeated ED visits and caregiver burden.



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3046 | HEPATOLOGY-LED PATIENT EDUCATION ON ALCOHOL-RELATED LIVER DISEASE DURING CHEMICAL DEPENDENCY TREATMENT: PATIENT PERSPECTIVES

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Background: Alcohol use disorder (AUD) treatment is traditionally led by licensed alcohol counselors with limited education on medical complications of heavy alcohol use. Patients often only learn about medical consequences of alcohol use after the development of alcohol-related liver disease (ARLD). An earlier multidisciplinary approach would be ideal, but needs to be scalable given the number of people with AUD. To help foster this approach, our institution's inpatient alcohol treatment program added a group session led by hepatology providers to educate patients about ARLD. In this retrospective survey-based study, we aimed to understand patient perspectives on this educational intervention. **Methods:** Residents at an inpatient alcohol treatment program completed a voluntary and anonymous survey after attending a physician-led lecture on medical complications of ARLD. The survey included 14 multiple choice questions and 4 open-ended questions. Data was collected on resident demographics, knowledge of ARLD before and after the lecture, likelihood of following up with a health provider, and likelihood of maintaining sobriety after attending the lecture. Descriptive statistics were used to analyze the data. **Results:** Questionnaires were completed by 83 residents over six sessions (Table 1). The response rate was estimated to be 46% (estimated 180 attendees). Most commonly residents were male (68.7%), who identified as white (68.7%), and were between the ages of 31 and 60 (30.1% aged 31-40 years, 22.9% aged 41-50 years, 24.1% aged 51-60 years). Residents' highest educational level was some college for 33.7% followed by 21.7% with a high school degree. 85.6% of residents were interested in the lecture topic. Most residents (75.9%) had previously engaged in conversation with a health care provider about alcohol impacting their health. Residents reported that their knowledge of ARLD improved after attending the lecture. Furthermore, 74.7% of residents were more likely to follow-up with their health care provider after the lecture, and 83.1% of residents believed that the presentation was helpful in maintaining sobriety from alcohol. **Conclusion:** Overall, the majority of residents reported that the lecture enhanced their understanding of ARLD, positively impacted their sobriety and increased their willingness to follow-up with a health care provider. These results suggest that a group educational lecture on ARLD is an effective intervention to encourage abstinence and potentially reduce alcohol-related morbidity and mortality in patients with AUD.

Table 1. Survey Results	Total N = 83	
This topic was interesting to me		
Strongly agree	44.6 (37)	
Agree	41.0 (34)	
Neutral	4.8 (4)	
Disagree	1.2 (1)	
Strongly disagree	6.0 (5)	
This topic was presented in a non-stigmatizing manner		
Strongly agree	57.8 (48)	
Agree	24.1 (20)	
Neutral	3.6 (3)	
Disagree	1.2 (1)	
Strongly disagree	9.6 (8)	
Knowledge about ARLD	**Before Presentation**	**After Presentation**
Extremely knowledgeable (5)	8.4 (7)	22.9 (19)
Very knowledgeable (4)	21.7 (18)	44.6 (37)
Moderately knowledgeable (3)	36.1 (30)	24.1 (20)
Slightly knowledgeable (2)	24.1 (20)	2.4 (2)
Not knowledgeable (1)	7.2 (6)	1.2 (1)
Average (Standard Deviation)	3.0 +/- 1.05	3.90 +/- 0.84
A health care provider has talked to me about alcohol affecting my health in the past?		
Yes	75.9 (63)	
No	21.7 (18)	
This presentation made me more likely to talk to a health care provider about my liver		
Strongly agree	37.3 (31)	
Agree	37.3 (31)	
Neutral	16.9 (14)	
Disagree	3.6 (3)	
Strongly disagree	2.4 (2)	
This presentation will be helpful in maintaining sobriety from alcohol	42.2 (35)	
Strongly agree	41.0 (34)	
Agree	9.6 (8)	
Neutral	0 (0)	
Disagree	3.6 (3)	
Strongly disagree		

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Disclosures: Taylor Bowler: Nothing to Disclose, Elizabeth Aby: United Health Care Group: Stock - publicly traded company, Medtronic: Stock - publicly traded company, Lisa Vollmer: Nothing to Disclose, Mary Thomson: Nothing to Disclose

3047 | HEPATOLOGY CLINICIAN PERCEPTIONS OF ADDICTION TREATMENT IMPORTANCE FOR PATIENTS WITH LIVER DISEASE ACROSS THE CONTINUUM OF TRANSPLANT CARE

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Background: Alcohol (AUD), opioid (OUD), and tobacco use disorder (TUD) are common in patients with liver disease, yet few receive treatment. Patients receive care along a transplant spectrum: non-transplant (NT), listed for transplant (LT), and post-transplant (PT). It is unclear how addiction treatment is prioritized for these groups. We assessed hepatology clinicians' views on the importance of treating AUD, OUD, and TUD for NT, LT, and PT patients. **Methods:** From July-September 2022, we conducted a mixed-methods study of hepatology clinicians at six sites within an academic center as part of a formative evaluation of attitudes toward treating addiction in liver clinics. Clinicians rated the importance of treating AUD, OUD, and TUD for NT, LT, and PT patients on a 5-point Likert scale. To compare perceived treatment importance across patient groups, we used generalized linear mixed-effects models while accounting for repeated measures from the same clinician. Type III test of fixed effects assessed whether transplant status predicted perceived treatment importance. Among a subset of clinicians, we also conducted semi-structured interviews and used thematic analysis to explore clinician views on addiction treatment for NT, LT, and PT patients. **Results:** Of 50 survey respondents (94% response rate; median age 41; 56% female), 35 completed interviews. Most clinicians rated AUD treatment as very important for NT (86%), LT (92%), and PT patients (90%), with no significant differences between groups. For OUD, treatment was rated very important less often for NT vs PT patients (52% vs 80%; $p = 0.002$), but similarly for LT vs PT patients (84% vs 80%; $p = 0.42$). For TUD, treatment was rated very important less often for NT vs PT patients (42% vs 78%; $p < 0.001$) and similarly for LT vs PT patients (86% vs 78%; $p = 0.17$). Overall, transplant status predicted perceived importance of treating OUD ($p = 0.0003$) and TUD ($p < 0.001$), but not AUD ($p = 0.51$). Emergent themes showed that clinicians deemed treatment more crucial for LT and PT patients due to transplant requirements and care investment. Fragmentation of care was a barrier to integrating hepatology and addiction care (Table 1). **Conclusion:** Hepatology clinicians believe AUD treatment is important for all patients, while OUD and TUD treatment is more crucial for LT and PT patients, underscoring varying attitudes toward addiction treatment for different patient groups. Interventions are needed to overcome barriers to integrated addiction treatment across the transplant spectrum.

Table 1: Major Themes and Representative Quotes from Qualitative Interviews Describing Perceived Importance of Addiction Treatment Across Non-Transplant, Listed, and Post-Transplant Patients in Liver Clinics

Theme	Quotes
Due to limited resources, addiction care may be prioritized for patients being considered for liver transplantation.	• "But I think that maybe at least for the ones that are really struggling, decompensated, having alcoholic hepatitis, you're trying to get them maybe potential transplant and they're having multiple readmissions, it might be worthwhile like having a separate clinic for those really high-risk patients so that you have that option. But yeah, I mean you have to prioritize, I don't think it's a very realistic goal that every single patient with alcohol use disorder and cirrhosis gets a mental health visit or addiction care at the same time when they come to your clinic." – Gastroenterology/Hepatology Fellow • "It becomes very, you know, difficult, because we obviously all want patients to get a transplant, but you know our job on the psychosocial team is really to point out the risks of those patients, because obviously we don't have enough livers to go around. So I mean just yeah I mean it's you know a huge issues, because I feel like the bottom line is it is often a life or death situation. Sometimes, you know, we get people very early or very late, you know, in terms of referrals and, you know, we do our best to try and beat the clock so people can be able to get the treatment." – Behavioral Health Provider
Pre-transplant candidates are viewed as more motivated to engage with addiction treatment due to transplant requirements, whereas engaging non-transplant patients can be more challenging.	• "I would land on the side of you know, like incorporating services to treat addiction to reduce the risk of recidivism, and I think that, like part of the opportunity with a transplant-based approach to treating this is that is that patients sort of number one are firsthand already like what alcohol has done, like they're sort of a captive audience, but then also a highly motivated audience in some ways." – Hepatology Attending • "I mean I think that sometimes like the advantage of the transplant hepatologist who says, you just have to do this or else you're not going to be able to get listed." – Hepatology Attending • "Yeah, I mean, I think we definitely hold our pre-transplant, and post, but especially pre-transplant patients to very high standards in terms of them achieving sobriety or cessation." – Gastroenterology/Hepatology Fellow • "And the thing is a little bit different when you're seeing transplant versus non-transplant patients because with transplant patients it's almost easier because you can say this is a prerequisite for your transplant. When it's a non-transplant patient, the person has to be, you know, ready to commit and I think a lot of the people you meet who are non-transplant are like pre-contemplative, like they're not even at that stage. So I don't have as much success with the non-transplant patients." – Hepatology Attending
Post-transplant patients may have greater access to addiction treatment resources due to significant investment in their care.	• "I mean we invested enough to transplant them, we should invest to someone being there, you know, and say well look, now you've seen the surgeon and now you can see your addiction specialist." – Hepatology Attending • "It is a post-transplant setting where everything is available to them to help them stop, because we want our outcomes and everything to be great, and those patients are just supported like probably too much." – Gastroenterology/Hepatology Fellow • "Yeah to me this if you invested all this money to get somebody successfully through transplant, it's kind of silly not to give them ways to succeed long-term, and even, you know, you can make the argument that maybe post-transplant alcohol relapse is not such a big deal from the liver perspective, the liver can take a lot and only a small minority of patients will actually lose the graft because of alcohol, you know. But from a psychological perspective of the medical team, you really feel let down if somebody has alcohol relapse." – Hepatology Attending
Limited time, lack of training, and fragmentation of care are barriers to robust integration of addiction care into hepatology visits.	• "There are both time constraints, and also I think there needs to be a lot of more deeper diving into why that's the problem, and what to do, and that definitely is not going to happen in a hepatology clinic, so it ends up being a referral when someone is in a bad place." – Gastroenterology/Hepatology Fellow • "Well, I have to say, I admit that I completely fell in tobacco addiction, like I don't, unfortunately, I just don't have the bandwidth to address that, but that's like a whole separate thing that I probably don't even address at all like, I would say, because there's so many other things on the table." – Advanced Practice Provider • "There is something that I actually feel probably fairly inadequate in. The current process – I think it's fair to say that there is no formal process at the present – but it's really geared towards the individual patients and existing resources that a patient may have engaged with already, either relapse prevention programs or other addiction services with other community organizations, rather than those that are initiated within our liver clinic." – Hepatology Attending • "I think, part of this challenge has been another one really fragmented access to specialty services that have expertise in the management and potential pharmacotherapy of these addiction disorders, and number two, a relative lack of knowledge and training in the management, specifically in the context of liver disease, and so that has led to a general sense of inadequacy and that we are not meeting the needs to this area for patients and a clear desire for something better." – Hepatology Attending • "So I think even the separation, you know hepatology/transplant hepatology, seems kind of artificial, you know, we basically we work in silos because this is how the health system is created." – Hepatology Attending
Integrating addiction treatment into hepatology care settings may facilitate addiction treatment for patients with liver disease	• "I would love to be able to refer a patient as part of the multi-disciplinary team for alcohol cessation and tobacco cessation and if that provider is also integrated into our system that would make sense." – Advanced Practice Provider • "I see patients who have alcohol use disorder have a concomitant tobacco use disorder and so I would like to have a provider that I know is available for that support ... pretty much all of those patients who are coming in with alcohol use disorder and have been admitted or have issues with their liver, they need that support, they need a formal pathway to assess them and help them achieve abstinence, in knowing that, as a provider my focus would be on that liver, and then the other providers' focus would be on trying to help eliminate those risks in terms of alcohol use and tobacco use that are detrimental to the liver so it would be sort of a collaboration, you know, very close, hands off, and you know those providers also would be familiar with working with patients with liver disease, because not all mental health providers are comfortable familiar doing that." – Hepatology Attending • "But maybe there could be a system where there are two physicians in this clinic, and they take turns taking on the sort of more liver-oriented stuff, and then the other more alcohol, tobacco, or opioid and treatment-related things. I think it's just a time issue." – Trainee

Disclosures: Dylan Balter: Nothing to Disclose, Hye Young Choi: Nothing to Disclose, Marissa Justen: Nothing to Disclose, Yanhong Deng: Nothing to Disclose, E. Jennifer Edelman: Nothing to Disclose, David Fiellin: Nothing to Disclose, Lamia Haque: Nothing to Disclose, Nothing to Disclose

3048 | PATIENT AND PHYSICIAN PREFERENCES FOR SYSTEMIC TREATMENT IN UNRESECTABLE HEPATOCELLULAR CARCINOMA (UHCC): FORMATIVE QUALITATIVE RESEARCH FINDINGS

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Background: Several immuno-oncology regimens are approved or under consideration for uHCC. With the evolving treatment landscape, understanding how patients' and physicians' make trade-offs among the differing benefit-risk profiles is increasingly important. As part of the AMBER preference study, qualitative research was conducted to explore decision-making, identify attributes of treatment, and understand the outcomes that are important to patients with uHCC and physicians making treatment recommendations in this setting. **Methods:** In-depth semistructured interviews (n = 29) were conducted with 15 physicians (3 hepatologists, 12 oncologists) who treat patients with uHCC and 14 patients diagnosed with uHCC who have received systemic treatment. Interviews were audio-recorded, transcribed, and analyzed to identify themes related to treatment perceptions, preferences, and decision-making. Key agreements and disagreements between patients and physicians also were identified. **Results:** Both patients and physicians prioritized survival while balancing side effects. However, physicians considered conventional clinical trial endpoints (e.g., median overall survival), whereas patients tended to focus on survival in the context of concrete landmarks (i.e., how much extension to their lives they could obtain while maintaining independence and daily functioning). Physicians factored in patient characteristics, including bleeding risk and liver function, and emphasized the need to limit severe adverse events (AEs) to preserve patients' quality of life and avoid hospitalization. Patients tended to assess AEs, such as nausea and fatigue, by the impact these had on their daily functioning. Patients reported not being offered treatment options and consequently physicians reported needing to make treatment decisions on behalf of their patients. **Conclusion:** Despite a shared priority of survival, patients and physicians viewed the outcome through different lenses. The absence of shared decision-making may mean these divergences are not apparent during consultations about treatment. These findings will be used to inform discrete choice experiment survey, which forms part of the wider AMBER preference study.

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3049 | ANXIETY AND WORRY AFTER REVIEW OF ABNORMAL HEPATOCELLULAR CARCINOMA IMAGING RESULTS

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Background: Disclosure of abnormal hepatocellular carcinoma (HCC) imaging results via the patient portal is discordant with delivering bad news protocols. We have demonstrated that patients review their HCC imaging results rapidly and well before result-related patient-provider communication (PPC); however, reactions to receipt of these results on the portal before PPC remain unknown. Herein, we report preliminary survey data measuring anxiety and worry in patients reviewing their abnormal HCC imaging results before PPC. **Methods:** We identified patients with cirrhosis enrolled in the patient portal who had a new LI-RADS (LR) liver lesion seen on ambulatory US or multiphasic CT/MRI. Patients who reviewed the result prior to documented PPC were eligible for inclusion and were contacted to participate in the survey study within 2-4 weeks of result review. Survey scales included 1) PROMIS Anxiety 7a (anxiety): raw scores converted to T-scores with a population mean of 50, 2) Worry: one-item Likert question measuring result-related worry, and 3) Perceived Severity: Likert question with responses ranging from 1 (not severe) to 10 (highly severe). We calculated the mean (SD) anxiety scores between patients reviewing US and CT/MRI results and for patients with low (scores 1-5) and high (score 6-10) perceived severity scores. We also determined the proportion of patients with increased worry after reviewing the result. **Results:** A total of 25 patients were surveyed, with median age 55 years, 52% female, and 68% non-Hispanic White. Imaging results included 5 US-2, 10 US-3, 4 LR-3, 2 LR-4, 3 LR-5, and 1 LR-M. Mean Anxiety score was 52.3 (SD 13.8), and scores ranged from 36.3 to 82.7. Mean anxiety scores were higher in patients reviewing CT/MRI versus US results showing a new liver mass (55.0 [SD 14.5] vs 50.5 [SD 13.5]). Patients who perceived the severity of the result as high (32%) had a mean anxiety score of 61.2 (SD 14.7) compared to 48.1 (SD 11.5) in those who perceived the severity as low. Over one-fourth (28%) of patients reported feeling more or much more worry after result review. For patients with an LR-4 lesion or higher, 50% reported increased worry compared to 21% in patients with lower risk lesions. However, only one patient regretted the decision to view their results before PPC. **Conclusion:** These preliminary findings suggest patients with abnormal HCC surveillance results may experience high anxiety/worry related to imaging type, finding, and perceived severity that require future study.

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3050 | MEANINGFUL ENGAGEMENT OF PATIENTS WITH CIRRHOSIS AND THEIR CARE PARTNERS: STRATEGIES FROM THE LIVE-SMART STUDY

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Background: The LIVE-SMART trial (NCT#05794555) is a PCORI (Patient-Centered Outcomes Research Institute)-funded multi-center randomized trial aimed at reducing the risk of injurious falls in people with cirrhosis. The investigative team collaborates with a Cirrhosis Patient Engagement Group (CPEG) consistent with PCORI's foundational expectations for patient engagement. We report how the investigative team engaged with the CPEG throughout the design and implementation of the study. **Methods:** During the grant writing phase, we convened a group of seven CPEG members to contribute to the study: 5 patients with cirrhosis and 2 care partners. During the project, CPEG meetings were held every 3-6 months to solicit CPEG feedback on various elements of the study. The CPEG was kept informed through bi-monthly study update emails. Satisfaction with patient engagement is evaluated bi-annually using a brief Qualtrics survey. Engagement was guided by community engagement principles, a detailed patient engagement plan, and specific engagement goals that were approved by the CPEG within the first six months of the project. The investigative team engaged with the CPEG members on information, consultation, and collaboration during LIVE-SMART. **Results:** From 2021 to 2025, 10 meetings were held with CPEG members in which they provided feedback on study measures, patient remuneration, development of a participant newsletter, retention strategies, informed consent form, tailoring patient-facing materials, and suggestions on meaningful outcomes and presentation of study results. CPEG members helped the study team make specific and impactful adjustments to the study, such as shifting from the term "caregivers" to "care partners" to utilize more sensitive language and emphasize the partnership that is needed to manage cirrhosis. The CPEG played a collaborative role in designing quarterly participant e-newsletters to share study updates. Suggestions included using a reader rather than writer focus and limiting the use of cartoons that might downplay the seriousness of cirrhosis. The principal investigators held a special informational session on self-management of cirrhosis to address this pre-specified goal of several members. Meeting attendance has been $>80\%$. Through engagement satisfaction surveys, CPEG members express appreciation for the study team, gaining knowledge about cirrhosis care, and being involved in LIVE-SMART.

Conclusion: The CPEG was engaged primarily as consultants during the LIVE SMART study from design to completion of the primary trial. CPEG engagement led to several meaningful changes to patient-facing materials and how to communicate study updates to study participants. We will continue to engage with the CPEG during the data analysis and dissemination phase of LIVE-SMART to ensure the study findings are patient-centered and meaningful for people living with cirrhosis and their loved ones.

Disclosures: Jacqueline Theroux: Nothing to Disclose, Anvi Sonarikar: Nothing to Disclose, Tasnuva

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Tarannum: Nothing to Disclose, Oma Anaenugwu: Nothing to Disclose, Mark Alber: Nothing to Disclose, Geraldine Hynes: Nothing to Disclose, James Hynes: Nothing to Disclose, Beanna Martinez: Nothing to Disclose, Samantha Nikirk: Nothing to Disclose, Richard Mason: Nothing to Disclose, Sumeet Asrani: Nothing to Disclose, Elliot Tapper: Madrigal: Grant/Research Support, Marina Serper: Nothing to Disclose, Donna Evon: Nothing to Disclose

3051 | USING THE INTEGRATED PALLIATIVE CARE OUTCOME SCALE (IPOS) FOR SYMPTOM ASSESSMENT: A PROSPECTIVE STUDY IN A LIVER SUPPORTIVE CARE PROGRAM IN SINGAPORE

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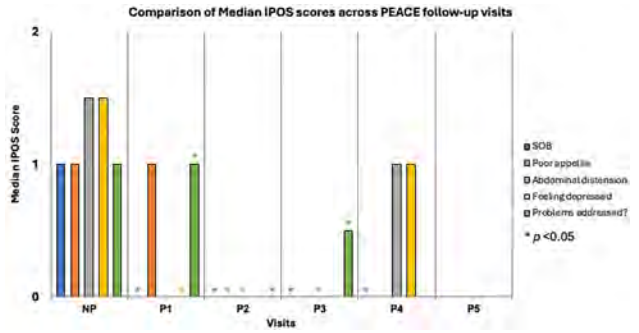
Background: Patients with decompensated cirrhosis experience a high burden of physical and psychosocial symptoms, yet structured symptom assessment is not routinely integrated into hepatology care. There are currently no dedicated programs in Singapore to streamline multidisciplinary care for this vulnerable population. The Integrated Palliative Care Outcome Scale (IPOS) is a validated patient-reported outcome measure (PROM) widely used in palliative care. This study evaluates the feasibility and utility of IPOS—supplemented with liver-specific symptoms—within PEACE (Palliate End-stage and Advanced Cirrhotics Early), a multidisciplinary liver supportive care program. **Methods:** Patients with decompensated cirrhosis were prospectively recruited from a tertiary public hospital in Singapore. IPOS was administered at enrollment, follow-up visits, during decompensation, and post-intervention. Additional questions on pruritus, abdominal distension, and sleep disturbance were included. Scores were graded on a Likert scale from 0 (not at all) to 4 (overwhelmingly) based on the extent to which symptoms affected patients. Patients seen in hepatology clinics or inpatient wards but not enrolled in PEACE served as the comparison group. **Results:** Fifty patients were recruited, of whom 23 were enrolled in PEACE. When comparing the PEACE to non-PEACE group, mean age was higher in PEACE (73.9 vs 66.1 years); males comprised 47.8% and 58.3% respectively. Most participants were Chinese (87.0% vs 70.8%). The PEACE group had significantly better mean IPOS scores at second and third follow-up visits compared to non-PEACE (0.91 and 0.70 vs 0.92; $p = 0.029$ and $p = 0.01$). Dyspnea scores improved across all PEACE follow-ups ($p < 0.05$). Appetite scores improved at the second follow-up visit, but this was not sustained subsequently. Abdominal distension scores were better in PEACE (median 0 vs 1.5 at first and second follow-ups; $p < 0.05$). PEACE patients also reported better outcomes on addressing practical problems related to illness from second to fourth follow-ups (all $p < 0.05$). **Conclusion:** IPOS, supplemented with liver-specific symptoms, is a feasible and practical PROM for holistic symptom assessment in patients with advanced liver disease. It requires minimal training, can be implemented at pre-clinic nursing triage, and supports longitudinal tracking of symptom burden. PEACE participants demonstrated significantly better patient-reported outcomes, highlighting the value of integrating early palliative care into hepatology.



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3052 | DEFEAT MASLD - METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE: A PRECISION DIGITAL THERAPEUTICS PILOT FEASIBILITY RANDOMIZED CONTROLLED TRIAL

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Background: MASLD afflicts ~100 million Americans. Resource constraints limit access to a structured diet and lifestyle intervention, key to managing MASLD. In a randomized controlled pilot feasibility trial (RCT), we studied Aim 1: the acceptance, engagement and adherence of digital therapeutics (DT), and Aim 2: the impact on liver and metabolic health. **Methods:** 38 MASLD subjects (White: 60%, 89.5% males; average age 51 years) were enrolled between 3/2024 to 7/2024

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and randomized to 3 groups: ***Grp1*** DT using *Livvy*® app (n = 13), ***Grp 2*** DT + home delivered planned Mediterranean diet (n = 12), and ***Grp 3*** DT + self-hypnosis eat well *Reveri*® app (n = 13). For Aim 1, number of Bluetooth enabled weight measurements, steps goal, *Livvy*® app related daily logins, % assessments completed, app and device activity were tracked for 1-21 weeks till access to DT license expired. For Aim 2, changes in ALT levels, *Fibroscan*® CAP, weight and visceral fat area up to 24-weeks were evaluated. **Results:** For ***Aim 1*** at 12-weeks (average/week, whole group and Grp 1 vs. Grp 2 vs. Grp 3): number of weight measurements were 6.1/week (6.4 vs. 6.7 vs. 5.5), daily step goals were met 96%/week (113% vs. 75% vs. 102%). Subjects logged in every 2nd day in *Livvy*® app, which was comparable for all groups. Average educational articles read 40% (10-82%) (51.6% vs. 30% vs. 25%). 100% of *Livvy*® app assessments were completed. Only 5.5% had low *Livvy*® app activity (not logged in 10 days) and device activity (not weighed in 7 days). In ***Grp 2***, 92% adhered to ordering 100% of free meals offered as part of study. In ***Grp 3***, 33% opted out of *Reveri*® app with low Eat Well weekly usage averaging 1 day/week compared to 3-4 days/week for *Livvy*® app, which was similar in other groups. The secondary end points assessed for ***Aim 2*** are summarized in the table. **Conclusion:** This *DEFEAT MASLD* RCT demonstrates excellent acceptance and patient engagement. Disease specific educational content, reminders, goal-setting features, ready access to and communication with healthcare providers likely improved patient knowledge, motivation, and long-term adherence. This remote treatment with periodic in person visits also improved liver and metabolic health. Notably, the effects of intervention persisted beyond intervention at 24-weeks. Future studies in larger MASLD population are needed. This can be a transformative, scalable and data-driven management approach of chronic diseases such as MASLD.

% Change at 12-weeks from baseline				
	ALT level	CAP Score	Body Weight	Visceral Fat Area
Whole Group	-10.6%	-3.9%	-1.8%	-6.6%
Group 1: DT using Livvy® app	-25.7%	-7.4%	-1.2%	-4.3%
Group 2: DT + Mediterranean diet	-26.0%	-3.7%	-1.7%	-6.6%
Group 3: DT + Reveri® self-pnosis app	-8.5%	-3.2%	-2.4%	-8.6%
% Change at 24-weeks from baseline				
	ALT level	CAP Score	Body Weight	Visceral Fat Area
Whole Group	-8.0%	-4.2%	-2.4%	-7.4%
Group 1: DT using Livvy® app	-14.8%	-8.3%	-1.5%	-3.6%
Group 2: DT + Mediterranean diet	8.9%	-1.1%	-1.7%	-7.9%
Group 3: DT + Reveri® self-pnosis app	-15.7%	-3.2%	-3.8%	-10.6%

Disclosures: Puneet Puri: Nothing to Disclose, Thuyduyen Vu: Nothing to Disclose, Maribeth Capuno: Nothing to Disclose, Joelle Lemmons: Nothing to Disclose, HoChong Gilles: Madrigal: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, Mallinckrodt: Advisor, Michael Fuchs: Nothing to Disclose

3053 | OUTREACH CLINICS IMPROVE ACCESS AND REDUCE MORTALITY IN LIVER TRANSPLANT CANDIDATES

Sanad Dawod[1] Mei Lu[1] Qiong Zhang[1] Yichu Wang[1] Kimberly Ann Brown[1], [1]Henry Ford Health System

Background: Geographic disparities in liver transplant access and outcomes persist, especially for rural and underserved patients. Limited proximity to transplant centers reduces rates of evaluation, waitlisting, and transplantation, and increases cirrhosis-related mortality. This study evaluates the impact of outreach clinics on evaluation, waitlisting, pre-transplant mortality, transplantation, and post-transplant outcomes, within 12 months of first evaluation for transplant. **Methods:** We conducted a retrospective cohort study of adults evaluated for liver transplant at Henry Ford Health (2007–2022). This analysis focused on LT evaluations and their outcomes within 12 months of the first evaluation (index date). Distances to transplant and outreach clinics were mapped. Three outcomes were assessed: time to waitlisting, transplant, and pre-transplant mortality, using Fine and Gray competing risks models adjusted for age, race, MELD, albumin, and distance. Patients without transplant indication were excluded. **Results:** Among 3,572 adults evaluated, 804 (22.5%) were waitlisted, 320 (9.1%) received a transplant, and 2,086 (59.4%) died before transplant within 12 months of evaluation. Compared to 2018–2022, patients in 2007–2012 and 2013–2017 had lower waitlisting (aHR 0.58, 0.41) and transplant (aHR 0.028, 0.061) rates, and higher pre-transplant mortality (aHR 1.85, 1.875; all $p < 0.0001$). Black patients had lower odds of waitlisting (aHR 0.615) and transplant (aHR 0.492). Distance to outreach clinics was protective: patients within 14 miles had lower mortality compared to those ≥ 31 miles away (aHR 0.852 for < 7.5 mi; 0.836 for 7.5–14 mi), while proximity to the main center was linked to lower waitlisting. MELD ≥ 30 was linked to reduced waitlisting (aHR 0.577) and a fivefold higher risk of mortality (aHR 5.07). MELD 9–17 and MELD > 17–30 were linked to higher transplant rates (aHR 1.487, 1.836). Age ≥ 60 (aHR 2.694), albumin ≤ 3.5 (aHR 0.734, 0.577), and ALT levels also influenced mortality. Key predictors of outcomes are summarized in figure 1. **Conclusion:** Outreach clinics were associated with improved transplant outcomes and lower pre-transplant mortality within 12 months of evaluation. Proximity to outreach clinics, rather than the main center, conferred a protective effect, suggesting that decentralized care can reduce spatial barriers to transplantation. However, Black patients continued to

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experience disparities, highlighting the need for targeted, equity-focused interventions beyond geographic outreach.

Variable	Outcome A (Waitlist)	Outcome B (Transplant)	Outcome C (Pre-LT Mortality)
Age 40–49 vs <40	1.396 (1.008–1.934)*	–	1.517 (1.152–1.997)*
Age 50–59 vs <40	–	–	2.198 (1.684–2.851)*
Age ≥60 vs <40	–	–	2.694 (2.07–3.506)*
Black vs White	0.615 (0.475–0.797)*	0.492 (0.314–0.770)*	–
MELD ≥30 vs <9	0.577 (0.406–0.819)*	–	5.07 (3.978–6.462)*
2007–2012 vs 2018–2022	0.580 (0.49–0.687)*	0.028 (0.013–0.059)*	1.85 (1.628–2.102)*
2013–2017 vs 2018–2022	0.412 (0.344–0.493)*	0.061 (0.038–0.098)*	1.875 (1.655–2.125)*
Distance <12.5 vs ≥92.7	0.776 (0.622–0.969)*	–	–
Distance 12.5–31 vs ≥92.7	0.704 (0.569–0.871)*	–	–

Figure 1. Adjusted hazard ratios (aHR) and 95% confidence intervals for key predictors of waitlisting, transplant, and pre-liver transplant mortality. ***MELD**: Model For End-stage Liver Disease*

* Statistically *significant* ($p < 0.05$).
– indicates *non-significant* or not evaluated for that outcome.

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3054 | EXPLORING FACTORS ASSOCIATED WITH BEING &LDQUO; TOO EARLY&RDQUO; FOR LIVER TRANSPLANTATION: A CALIFORNIA LIVER NETWORK STUDY

Jasleen Singh[1] Mignote Yilma[2] Kabir Rahal[1] Julia Valenzuela[1] Fatima Zahoui[1] Michaela Evans[1] Hannah Choi[1] Allison Kwong[3] Steven Wisel[4] Hirsh Trivedi[4] Justin Steggerda[4] Alexander Kuo[5] Aarshi Vipani[4] Tiffany Lim[4] Michie Adjei[4] Lana Bridi[6] Veeral Ajmera[6] Monica Tincopa[7] Irine Vodkin[7] Hillary Braun[2] Chris Freise[2] Ryutaro Hirose[8] Neil Mehta[8] Shayana Seneviratne[9] Kali Zhou[10] Arpan Patel[11], [1]UCLA, [2]UCSF, [3]Stanford University Medical Center, [4]Cedars Sinai Medical Center, [5]Cedars-Sinai Medical Center, [6]UCSD, [7]University of California, San Diego, [8]University of California, San Francisco, [9]University of Southern California, [10]USC, [11]University of California, Los Angeles

Background: Optimizing efficiency and value of liver transplant (LT) assessments is an important consideration for centers. Understanding the clinical and demographic factors associated with being “too early for transplant” may help quality improvement efforts to streamline referrals for LT evaluation. **Methods:** The California Liver Network (CLN) is a retrospective cohort of adults referred to six transplant centers for LT between 2018-2020. Demographic, psychosocial, and clinical factors were obtained for evaluated patients. Reasons for denial were assessed by chart review. We used descriptive statistics to assess clinical factors of patients deemed “too early”. We then conducted Pearson’s χ^2 tests to assess differences in socio-demographic factors between patients deemed “too early” and those waitlisted. For this second analysis, we limited comparisons to adults with alcohol-related liver disease (ALD) to reduce heterogeneity. **Results:** Among 6,630 patients evaluated for LT, 3,148 (47.4%) were declined for listing and 3,482 (52.5%) were waitlisted. Among those declined, “too early” (N = 575, 18.3%) was the most commonly cited reason, though the reported rate across centers varied significantly (range: 3.5%-26.0%, median: 16.4%). The most commonly referred conditions were: 1) decompensated cirrhosis, MELD < 15 (N = 165, 28.7%); 2) compensated cirrhosis (N = 136, 23.7%); and 3) decompensated cirrhosis, MELD³15 (N = 101, 17.6%). ALD comprised 40.4% of all evaluations. Compared to patients who were waitlisted, patients deemed “too early” with ALD were more likely to be female, non-Hispanic/Latino, English-speaking, Medicaid-insured, and non-foreign born. A significantly larger portion of patients who were deemed “too early” were reported to have “no social support” at time of initial evaluation, compared to those waitlisted (29.0 vs. 4.3%, $p < 0.001$) (Table). **Conclusion:** Nearly a quarter of adults declined for being “too early” were referred for compensated cirrhosis only, indicating potential over-utilization of transplant resources. Center-level variation in denials for early candidates may reflect differences in the LT referral intake process across institutions. Social support at initial visit may influence determination of being “too early” and should be explored further. Greater efforts to improve screening of referrals and promote education of referring providers are needed.

Sociodemographic Factors Associated with Being Deemed “Too Early” Among Patients with ALD Evaluated for Liver Transplantation.

Variable	Waitlisted, ALD (N=1,303)	“Too Early”, ALD (N=193)	p-value
Socio-demographics			
Age (mean, SD)	54.7 (26.8)	53.7 (10.5)	0.61
Sex (N, %)[a]			
Female	328 (25.2%)	67 (34.7%)	0.005
Male	975 (74.8%)	126 (65.3%)	
Race (N, %)			
AA	27 (2.1%)	7 (3.6%)	
AI/AN	20 (1.5%)	1 (0.5%)	
Asian/Pacific Islander	52 (4.0%)	3 (1.6%)	0.10
Caucasian	831 (63.8%)	121 (62.7%)	
Other/multi-racial	297 (22.8%)	46 (23.8%)	
Missing/unknown	66 (5.1%)	15 (7.8%)	
Ethnicity (N, %)[a]			
Hispanic/Latino	616 (47.3%)	58 (30.1%)	
Non-Hispanic/Latino	658 (50.5%)	119 (61.6%)	<0.001
Missing/Unknown	29 (2.2%)	16 (8.3%)	
Social support (N, %)[a,b]			
No	56 (4.3%)	56 (29.0%)	<0.001
Yes	1,212 (93.0%)	117 (60.6%)	
Missing/unknown	35 (2.7%)	20 (10.3%)	
Insurance (N, %)[a]			
Medicaid	415 (31.9%)	96 (49.7%)	
Medicare	326 (25.0%)	30 (15.5%)	<0.001
Other	10 (0.8%)	2 (1.0%)	
Private	533 (40.9%)	65 (33.7%)	
Missing/Unknown	19 (1.5%)	0 (0.0%)	
Primary language English (N, %)[a]			
Yes	1,004 (77.1%)	168 (87.1%)	
No	297 (22.8%)	25 (13.0%)	0.01
Unknown	1 (0.1%)	0 (0.0%)	
Foreign born (N, %)[a]			
Yes	426 (33.7%)	35 (24.3%)	0.02
No	840 (66.4%)	109 (75.7%)	

[b] Indicates presence of social support at time of first social work evaluation.

Disclosures: Jasleen Singh: Madrigal: Speaking and Teaching, Mignote Yilma: Nothing to Disclose, Kabir

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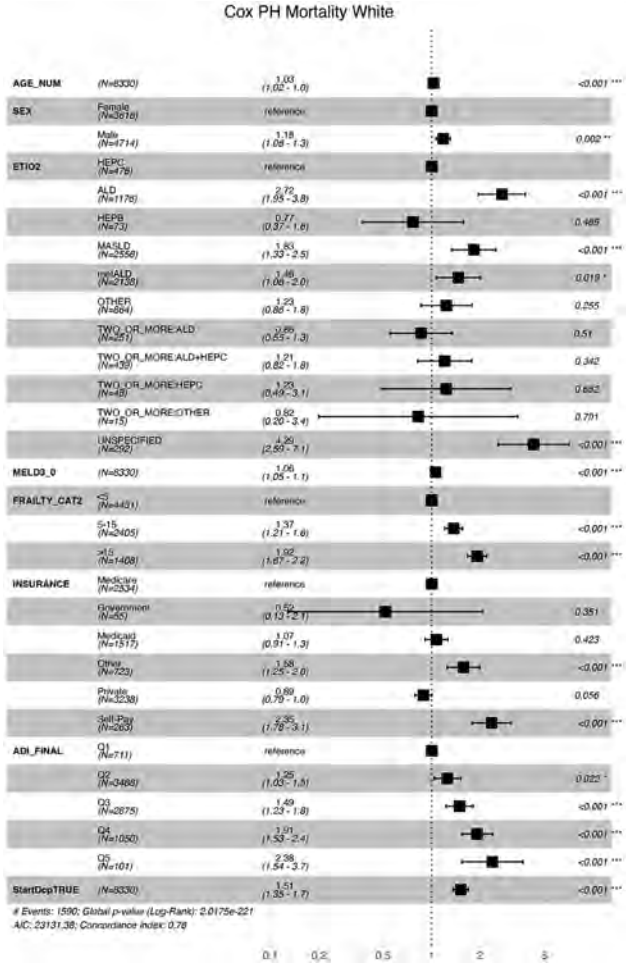
Rahal: Nothing to Disclose, Julia Valenzuela: Nothing to Disclose, Fatima Zahoui: Nothing to Disclose, Michaela Evans: Nothing to Disclose, Hannah Choi: Nothing to Disclose, Allison Kwong: Nothing to Disclose, Steven Wisel: Nothing to Disclose, Hirsh Trivedi: Nothing to Disclose, Justin Steggerda: Nothing to Disclose, Alexander Kuo: Nothing to Disclose, Aarshi Vipani: Nothing to Disclose, Tiffany Lim: Nothing to Disclose, Michie Adjei: Nothing to Disclose, Lana Bridi: Nothing to Disclose, Veeral Ajmera: Nothing to Disclose, Monica Tincopa: Nothing to Disclose, Irine Vodkin: Nothing to Disclose, Hillary Braun: Nothing to Disclose, Chris Freise: Nothing to Disclose, Ryutaro Hirose: Nothing to Disclose, Neil Mehta: Merck: Consultant, FujiFilm WAKO: Consultant, Shayana Seneviratne: Nothing to Disclose, Kali Zhou: Gilead Sciences Inc: Grant/Research Support, Merck: Grant/Research Support, Arpan Patel: Nothing to Disclose

3055 | MORTALITY AND HOSPITALIZATION ASSOCIATED WITH HIGH NEIGHBORHOOD DEPRIVATION ONLY AMONG WHITE PATIENTS WITH CIRRHOSIS

Saad Hussain[1] Paola Barrios[1] Suyanpeng Zhang[1] Dominic Vitello[1] Sijia Wei[1] Salva Balbale[1] Oriana Dentici[1] Al'ona Furmanchuck[1] Nikhilesh Mazumder[2] Lisa VanWagner[3] Lihui Zhao[1] Andres Duarte-Rojo[4] Sanjay Mehrotra[1] Daniela Ladner[1], [1]Northwestern University, Chicago, IL, [2]University of Michigan Hospitals and Health Centers, [3]University of Texas Southwestern Medical Center, [4]Northwestern Medicine

Background: Neighborhood deprivation, as measured by the Area Deprivation Index (ADI), has been associated with higher mortality and hospitalizations in cirrhosis. We evaluated the clinical outcomes for patients from different ADIs by race/ethnicity. **Methods:** CAPriCORN, a large EHR data repository across 7 health care systems in a large US metropolitan area, was used to identify adult patients with cirrhosis from 2016-2021. Demographics and clinical factors were collected including age, sex, race/ethnicity, urban/rural, etiology, insurance type, Area Deprivation Index (ADI) [Q1: high resourced, Q5: low resourced), MELD 3.0, Charlson comorbidity index (CCI), decompensation and frailty (HFRS); [Low: HFRS <5, severe: HFRS >15]. The primary outcomes of interest were all-cause mortality and hospitalization. Rates are reported per 100 patient-years (PY). Multivariable Cox proportional hazard models were used to assess mortality and multivariable logistic regression assessed hospitalization within 1 year. Significance $= P<0.05$. **Results:** 18,718 patients with cirrhosis were included. Mean age was 59.8, 43.1% were women, 45% were white, 19% black, 21% Hispanic, and 97% lived in urban areas. Most common etiologies were MASLD (28.6%), MetALD (23.1%), ALD (12.8%). 29.5% had Medicare, 27.8% Private, 22.3% Medicaid, 14.3% other insurance, 6.2% uninsured. ADI (Q1: 5.7%, Q2: 30.8%, Q3: 36.4%, Q4: 23.6%, Q5: 2.4%). Mean MELD was 16.3, CCI 6.79 and 29.7% were decompensated at inclusion. The overall, unadjusted mortality rate was 13.3 deaths per 100 patient-years. This was 16.1, 9.1, and 8.9 for white, black, and Hispanic patients respectively. Among the cohort, there were 57.9 hospitalizations per 100 patient-years. This was 66.28, 66.63, and 46.83 for white, black, and Hispanic patients respectively. On adjusted analyses, among white patients, higher ADI was associated with stepwise increases in mortality (Q5 vs Q1: HR 2.38, 95% CI 1.54–3.70) and hospitalization (Q5 vs Q1: OR 2.80, 95% CI 1.52-5.24). (Figure) This effect was not observed in other racial groups (black: $p=0.686$, Hispanic $=0.561$). **Conclusion:** In white patients with cirrhosis, neighborhood deprivation was associated with higher mortality and hospitalization rates, an effect not observed in any other race/ethnicity. Non-white patients might have mediating factors that make neighborhood deprivation less pertinent.



Disclosures: Saad Hussain: Nothing to Disclose, Paola Barrios: Nothing to Disclose, Suyanpeng Zhang:

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Nothing to Disclose, Dominic Vitello: Nothing to Disclose, Sijia Wei: Nothing to Disclose, Salva Balbale: Nothing to Disclose, Oriana Dentici: Nothing to Disclose, Al'ona Furmanchuck: Nothing to Disclose, Nikhilesh Mazumder: Nothing to Disclose, Lisa Van-Wagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, Lihui Zhao: Nothing to Disclose, Andres Duarte-Rojo: Echosens: Grant/Research Support, Sanjay Mehrotra: Nothing to Disclose, Daniela Ladner: Nothing to Disclose

3056 | PALLIATIVE CARE INVOLVEMENT IN INPATIENT LIVER TRANSPLANT EVALUATIONS: AN OPPORTUNITY FOR GROWTH

Kathy Nguyen[1] Katherine Cooper[1] Navine Nasser-Ghodsi[2] Mary Flynn[2], [1]University of Massachusetts School of Medicine, [2]University of Massachusetts Memorial Health Care

Background: Expedited liver transplant evaluation (eLTE) is a resource intensive process reserved for critically ill patients with advanced liver disease. Palliative care (PC) consultation has been studied in the context of cirrhosis and LT, but the role of PC consult during eLTE remains underexplored. **Methods:** This is a retrospective analysis of eLTEs at our center from 2019-2021. Patients with acute liver failure were excluded. eLTE outcomes were categorized as Favorable (index admission LT, listed at discharge) or Unfavorable (declined, no decision, or deceased). Length of stay (LOS), intensive medical interventions, advanced care planning (ACP) and discharge location were compared in those with and without a PC consult. **Results:** A total of 165 patients were included. Patients with Unfavorable outcomes ($n = 54$) were more likely to be women ($p < 0.01$) and age over 50 years ($p = 0.08$) than those with Favorable outcomes ($n = 111$). Only 15% ($n = 24$) received a PC consult, without differences between groups ($p = 0.59$), most of which occurred at an outside hospital prior to transfer for eLTE ($n = 13$, 54%), and the remainder were for medical decision-making during eLTE ($n = 5$, 21%) or after patient was declined for LT ($n = 6$, 35%). Those who received a PC consult prior to decision ($n = 18$) tended to be White ($p = 0.09$) and to have graduated high school ($p = 0.05$) compared to no PC consult. Receipt of a PC consult prior to hospital transfer or declined for LT was not associated with fewer intensive medical interventions (p-values 0.2-0.9) or reduced length of stay ($p = 0.54$). However, PC consult recipients were more likely to have goals of care conversations (GOCC), though this association was observed in those with Favorable outcomes ($p < 0.01$) but not in the Unfavorable outcomes ($p = 0.90$) on stratified analysis. Of those not listed for LT, PC consult was associated with more intensive interventions following decision. **Conclusion:** In this single center study, PC consultation during eLTE was not associated with reduced care utilization. There were more GOCC for listed patients who had a PC consult than no consult. However, many patients who were not listed had a GOCC regardless of a PC consult or not. Most PC consults occurred prior to transfer for eLTE, potentially indicating patient preference/commitment toward treatment course, and/or the provider's concern the patient might not be an LT candidate. Future steps will assess these relationships in subsequent years of LTEs to assess if the role of PC has changed over time in the context of eLTE.

	PC Consult (n=18)	No PC Consult (n=147)	P-value
Age > 50	10 (55.6)	100 (68.0)	0.29
Sex, Female	8 (44.4)	67 (45.6)	0.93
Race, White	17 (94.4)	122 (83.0)	0.21
Highschool graduate	18 (100.0)	120 (81.6)	0.05
MELD-Na >35	6 (33.3)	40 (27.2)	0.56
Activated decision maker	6 (33.3)	49 (33.3)	1.00
Length of stay	49 (33.3)	5 (27.8)	0.54
Outcome Group			
Favorable, LT	4 (22.2)	38 (25.9)	0.76
Favorable, Discharged	9 (50.0)	60 (40.8)	
Unfavorable, All	5 (27.8)	49 (33.3)	
Interventions			
Intensive care stay	7 (38.9)	67 (45.9)	0.57
Mechanical ventilation	6 (33.3)	34 (23.3)	0.35
Feeding Tube	4 (22.2)	35 (23.8)	0.88
Dialysis	8 (44.4)	43 (29.5)	0.20
CPR	2 (11.1)	15 (10.2)	0.91
Palliative Outcomes			
Goals of Care Conversation	26 (17.8)	11 (61.1)	<0.01
MOLST form on File	16 (11.0)	3 (16.7)	0.48
Large volume paracentesis	78 (53.4)	8 (44.0)	0.47
Discharge to Hospice	2 (2.3)	0 (0.0)	0.80
Code Status Change	6 (33.3)	26 (17.7)	0.11

***Outcomes reported as n (%).** *PC= Palliative Care; MELD= Model for End Stage Liver Disease; CPR = cardiopulmonary resuscitation; MOLST= Massachusetts Medical Orders for Life-Sustaining Treatment*

Disclosures: Kathy Nguyen: Nothing to Disclose, Katherine Cooper: Nothing to Disclose, Navine Nasser-Ghodsi: Boston Scientific: Consultant, Mary Flynn: Nothing to Disclose

3057 | TECHNOLOGY UTILIZATION AND (HEALTH) LITERACY ASSESSMENT FOR PATIENTS WITH CHRONIC LIVER DISEASE (TULAP-CLD)

Jonathan Day[1] Zoe Post[2] Ashley Cawthon[2] Sierra Anderson[2] Ana Maria Davila Morales[2] Sujit Janardhan[2], [1]Rush Medical College, [2]Rush University Medical Center

Background: Chronic liver diseases (CLD) affect a considerable part of the population in the United States. Chronic Disease Management (CDM) models allow patients to actively monitor their disease using mobile technology and can improve patient outcomes. For mobile CDM models to be successful, we need to understand CLD patients' health literacy and ability to use technology. Therefore, we aimed to assess technology utilization and health literacy in CLD patients. **Methods:** Single tertiary center prospective study

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including adult, English-speaking CLD patients. Informed consent was obtained. Demographics such as age, sex, race/ethnicity, level of education, and CLD characteristics were obtained. Health literacy was assessed using the Rapid Estimate of Adult Literacy in Medicine Short Form (REALM-SF). We developed a technology utilization measuring instrument, including device and internet access questions based on Health Survey by Pew Research Centers' Internet and American Life project. **Results:** 100 patients were included. 58% were female. 33% were Caucasian, 29% Hispanic and 27% Black. Highest education level is high school for 23% and bachelor's degree or higher for 40%. Most have metabolic (38%) or alcohol (19%) associated CLD; 44% have cirrhosis, 30% of which have complications. Average REALM-SF score was 6.34, with 24% at 7-8th grade level or less. 95% use the internet, of which 98% through smartphone and 97% report daily internet use. Text messaging, video calling, checking weather/traffic and finding product information online are activities most engaged in ($>90\%$), whereas posting online (e.g. blog or photos) is done by $<60\%$ of patients. 86% of patients use the internet for health-related activities, most commonly looking up personal health information, accessing online chart and learning about medical conditions (both $>85\%$). 71% of patients engage in e-visits with providers. However, sending personal medical information to providers and communicating with support groups is less frequently used (53% and 25% respectively). **Conclusion:** Reassuringly, the majority of CLD patients use the internet and engage in relatively simple activities. However, CDM models often include more advanced tasks, such as posting online or sending medical information, which are not commonly performed by CLD patients. Furthermore, our REALM-SF data suggests that a quarter of patients may not understand provided patient education materials, affecting usability of available and future CDM models.

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3058 | REAL-WORLD IMPLICATIONS OF THE NEW AASLD/IDSA HCV "TEST AND TREAT" ALGORITHM: FOCUS ON CARDIOVASCULAR COMEDICATIONS IN HEPATITIS C VIRUS (HCV) PATIENTS RECEIVING DIRECT-ACTING ANTIVIRALS (DAAS)

DILIP MAKHIJA[1] Thomas Debray[2] Candido Hernandez[3], [1]GILEAD SCIENCES, INC., [2]Smart Data Analysis and Statistics, [3]Gilead Sciences Ltd.

Background: The new AASLD/IDSA algorithm for Hepatitis C point-of-care (POC) testing and treatment recommend medication reconciliation via the Liverpool DDI tracker (https://www.hep-druginteractions.org/) to assess drug-drug interaction (DDI) risk. If DDIs exists, specialist consultation is advised, potentially adding complexity to this expedited pathway. We aimed to assess the real-world applicability of this algorithm by evaluating the impact of cardiovascular comedications on DDI risk among US HCV patients receiving pangenotypic direct-acting antivirals (pDAAs). **Methods:** We leveraged the IQVIA PharMetrics Plus claims database (July 2015-June 2023) to evaluate the co-administration of statins and antihypertensive drugs with pDAAs, specifically sofosbuvir/velpatasvir (SOF/VEL) or glecaprevir/pibrentasvir (GLE/PIB), in US patients. DDI risk was assessed using the Liverpool DDI tracker; and reconciled with the AASLD/IDSA algorithm's guidance regarding specialist consultation. We used 1:1 propensity score (PS) matching without replacement to create matched SOF/VEL and GLE/PIB cohorts for comparative analysis. **Results:** Among 11,324 HCV patients receiving pDAAs, 11.6% ($n=1,317$) were on statins and 2.5% ($n=280$) were on antihypertensives. Of those on statins, 867 received SOF/VEL and 450 received GLE/PIB. For anti-hypertensives, 174 received SOF/VEL and 106 received GLE/PIB. After PS matching, cohorts comprised 431 statin patients and 91 antihypertensive patients, with similar baseline characteristics. Based on Liverpool DDI tracker risk assessment, 14.6% (63/431) of SOF/VEL-treated patients on statins and 78.0% (71/91) on antihypertensives could follow the AASLD/IDSA algorithm without requiring specialist consultation. In contrast, all GLE/PIB-treated patients on concomitant statins ($n=431$) or antihypertensives ($n=91$) would require specialist consultation. All 321 contraindications among statin users were associated with GLE/PIB, specifically involving atorvastatin, lovastatin, and simvastatin. For antihypertensives, olmesartan, prazosin, and enalapril were the most common comedications posing a clinically significant DDI risk. **Conclusion:** Applying the new AASLD/IDSA algorithm, especially when statins or antihypertensives are co-administered with pDAAs, would necessitate specialist consultation for a significant number of patients due to DDI risk. This potential barrier to rapid "test and treat" implementation could be substantially reduced by carefully selecting the DAA regimen based on individual patient DDI risk profiles.

Disclosures: DILIP MAKHIJA: Gilead Lifesciences: Employee, Thomas Debray: Nothing to Disclose, Candido Hernandez: Nothing to Disclose

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3059 | IMPACT OF LIVER-RELATED CLINICAL COMPLICATIONS AT FIRST HOSPITALIZATION ON THE OUTCOME OF PATIENTS WITH LIVER CIRRHOSIS AND HEPATOCELLULAR CARCINOMA: A 13-YEAR NATIONAL STUDY

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Background: In cirrhotic and/or hepatocellular carcinoma patients (HCC), liver-related deaths are mainly HCC-related in viral and metabolic liver disease and liver failure-related in alcohol. Yet the impact of the presence of these complications at 1st hospitalization on outcome remains to be assessed. **Methods:** Data of patients hospitalized between 2011 and 2023 with ≥ 1 ICD-10 code of cirrhosis and/or HCC were extracted from the French national medicalized information system program. Probabilities of death over the study period and during the 1st hospitalization were estimated according to presence of liver complications (HCC or liver failure) and etiology of liver disease (viral [VIR], alcohol [ALC], metabolic syndrome [MS], others). **Results:** Over 2011-2023, deaths occurred in 219,587/543,208 (40.4%) cirrhotic/HCC patients and were 64.2%-liver-related. At 1st hospitalization, 101,419 (18.7%) patients were admitted with liver-related complications. The probability of being admitted with liver complications was 1.7-1.8 higher in VIR (21.3%) and ALC (20.0%) than in MS (11.8%). Liver-related deaths were more frequent for patients admitted with liver complications at 1st hospitalization (80% vs 60% in absence, $p < 0.01$).

At 1st hospitalization, liver-failure was more frequent than HCC (13.5% vs. 5.2%). Of the 28,144 patients with HCC, 7,767 (27.6%) also had liver failure, more often in ALC patients (34.7% vs 23.5% in VIR and 17.5% in MS, $p = 0.02$). The probability of death during the 1st hospitalization was 2.3% and 17-times higher when admitted for liver complications (10.0% vs. 0.6% in absence, $p < 0.01$), regardless of etiology ($p = 0.81$). Probabilities of death during the 1st hospitalization were 5.6% for HCC patients without liver failure, 9.8% for liver-failure patients and 22.4% for those with HCC and liver failure ($p < 0.01$), regardless of etiology ($p = 0.92$). **Conclusion:** Of the 543,208 patients with cirrhosis and/or HCC, 40% died during the 13-year period, of which 64% were liver-related deaths. At 1st hospitalization, liver event as a cause of hospitalization was around 2-times lower in MS than in VIR and ALC patients. First hospitalization for liver complications was associated with 10%-probability of death after admission, with the highest risk observed in those with liver failure and HCC (23%). Changes in the management pathway of cirrhotic and/or HCC patients are required to improve their outcomes.

Disclosures: Claire DELACOTE: Nothing to Disclose, Xavier Lenne: Nothing to Disclose, Line-Carolle Ntandja-Wandji: Nothing to Disclose, Alexandre Louvet: Glaxo-Smith-Kline: Consultant, AbbVie: Speaking and Teaching, Gilead: Speaking and Teaching, Ipsen: Consultant, Astra-Zeneca: Speaking and Teaching, Amélie Bruandet: Nothing to Disclose, Sylvie Deuffic-Burban: Nothing to Disclose, Philippe Mathurin: Nothing to Disclose

3060 | THE IMPACT OF EARLY EVALUATION AFTER REFERRAL FOR LIVER TRANSPLANT ON PATIENT OUTCOMES

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Background: Time from referral to liver transplant (LT) evaluation is a proposed AASLD quality measure, though no benchmark exists for the optimal time window. In the Veterans Affairs (VA) system, early LT evaluation within 30 days of referral is associated with lower pretransplant mortality. Whether this applies outside the VA system is not known. We aimed to examine the impact of time from referral to LT evaluation on patient outcomes at a large-volume transplant center. **Methods:** We identified all adult patients referred and evaluated for first-time, single-organ LT at our center from 1/1/2016 to 12/31/2023, with follow up data through 12/31/2024. Patients referred for urgent inpatient LT evaluation were excluded. Patients were categorized as early evaluation (EE, evaluation within 30 days of referral), and late evaluation (LE, >30 days). The Charlson Comorbidity Index was calculated to account for comorbidities outside of liver disease. Logistic regression was performed to evaluate the association between EE and waitlisting. Competing risk analysis was used to examine the relationship between EE and pretransplant mortality, accounting for the competing outcome of transplant. **Results:** A total of 1369 patients met inclusion criteria: 452 underwent EE (33.0%) and 917 LE (67.0%). Median time from referral to evaluation for

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EE was 21 days (interquartile range [IQR] 17-26), compared to 48 days (IQR 39-73) for LE. The proportion of EE declined over time (40.6% in 2016 vs. 27.6% in 2023, $p_{trend} = 0.01$). EE patients were more likely to be male, have higher MELD-Na scores, and live closer to the transplant center (Table 1). Overall, 709 (51.8%) patients were waitlisted, and 594 (43.3%) underwent LT. EE patients were more likely to be waitlisted (57.7% vs 42.3%, p = 0.002) and transplanted (49.3% vs 40.5%, p = 0.002). The relationship between EE and waitlisting persisted after adjusting for confounders (adjusted odds ratio 1.32, 95% confidence interval [CI] 1.04-1.68). The median time from referral to waitlisting and LT was shorter in the EE group (78 vs. 116 days, p < 0.001;188 vs. 220 days, p = 0.01, respectively). There were 429 pretransplant deaths, 140 (31.0%) in the EE group and 289 (31.5%) in the LE group (p = 0.84). In competing risk analysis, EE was not associated with pretransplant mortality (subhazard ratio 0.99, 95% CI 0.81-1.21). **Conclusion:** At our center, EE for liver transplant was associated with higher rates of waitlisting and transplantation, as well as shorter time to listing and transplant. However, despite these associations, it was not associated with differences in pretransplant mortality. These findings suggest that while timely evaluation improves access and progression through the transplant process, it may not impact pre-transplant survival. Further multicenter studies are needed to define optimal evaluation timelines and assess whether these findings generalize across diverse healthcare settings.

Table 1. **Baseline Characteristics of Referred Patients for Liver Transplant by Time to Evaluation**

	Cohort (n=1369)	Early Evaluation (n=452)	Late Evaluation (n=917)	p-value
Age at referral, years	59 (51–65)	60 (51–65)	59 (51–65)	0.45
Sex				0.01
Female	37.2% (509)	32.5% (147)	39.5% (362)	
Male	62.8% (860)	67.5% (305)	60.5% (555)	
Etiology				0.48
Alcohol-associated liver disease	26.2% (359)	23.9% (108)	27.4% (251)	
Autoimmune	9.9% (135)	11.7% (53)	8.9% (82)	
Hepatocellular carcinoma	17.2% (236)	17.7% (80)	17.0% (156)	
MASH	26.4% (362)	25.4% (115)	26.9% (247)	
Viral hepatitis	9.5% (130)	10.2% (46)	9.2% (84)	
Other	10.7% (147)	11.1% (50)	10.6% (97)	
Insurance				0.12
Commercial	48.4% (661)	52.3% (236)	46.4% (425)	
Medicaid	7.7% (105)	6.0% (27)	8.5% (78)	
Medicare	38.8% (530)	36.4% (164)	40.0% (366)	
Other	5.2% (71)	5.3% (24)	5.1% (47)	
MELD-Na	18 (13–22)	18 (12–24)	18 (13–21)	0.04
Charlson Comorbidity Index	7 (5–8)	6 (5–8)	7 (5–8)	0.24
Distance from center, miles	101.5 (52.9–158.5)	86.8 (44.8–154.0)	106.0 (56.7–160.3)	0.01

Data displayed as median (interquartile range) or % (n).

Disclosures: Kaushik Puranam: Nothing to Disclose, Lindsay King: Nothing to Disclose, April Wall: Nothing to Disclose, Andrew Muir: Gilead: Grant/Research Support, Cymabay: Grant/Research Support, Ultragenyx: Grant/Research Support, Regcell: Consultant, Jacqueline Henson: Nothing to Disclose

3061 | IMPROVING CIRRHOSIS IDENTIFICATION: EVALUATION OF ICD-10 CODES AND DEVELOPMENT OF A HYBRID ALGORITHM FOR ENHANCED ACCURACY IN ALBERTA&RSQUO;S HEALTHCARE SYSTEM

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Background: Cirrhosis is a global health issue contributing to high morbidity, mortality, and repeated hospitalizations. The Cirrhosis Care Alberta initiative aims to standardize cirrhosis management through order sets and Our Practice Advisories (OPAs) integrated into the Connect Care (CC) electronic medical record system (EMR). However, inconsistent documentation and underutilization of EMR problem lists hinders accurate identification of cirrhosis, leading to missed opportunities for clinical decision support. This study aimed to evaluate published consensus ICD-10 codes and develop an enhanced algorithm integrating administrative and EMR data for improved cirrhosis identification. **Methods:** Firstly, the consensus ICD-10 codes (Shearer et al 2022) were evaluated in a cohort of 719 patients with chart-review confirmed cirrhosis patients based on clinical, biochemical, and imaging criteria. The positive predictive value (PPV) of each ICD-10 code was determined and confirmed to be greater than 90%. Subsequently, a novel cirrhosis identification algorithm was developed using ICD-codes from the consensus code set recorded either in the administrative data (Discharge Abstract Database, DAD) or EMR problem lists (Connect Care) or if a patient was noted to have “cirrhosis” in their Connect care diagnosis. Patients with a history of liver transplant were excluded using transplant-specific codes. Lastly, the algorithm’s performance was evaluated in a cohort of 913 patients admitted to gastroenterology or internal medicine services at four healthcare sites in Alberta over a 12 week period. This included two tertiary centres and two smaller centres. Chart reviews served as the reference standard to assess sensitivity and specificity. **Results:** The validation of consensus codes yielded positive predictive values consistent with previous studies. Sensitivity and specificity of cirrhosis identification using

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administrative data alone (DAD) were 76.2% and 97.7%, respectively (Table 1). Using EMR data (Connect Care) alone, sensitivity was 85.3%% and specificity was 97.5%. When combining DAD and EMR data, the algorithm achieved sensitivity of 86.2% and specificity of 97%. Site variability was observed, with lower sensitivity at rural sites (70% and 78.6) likely due to differences in coding practices. **Conclusion:** A combined administrative and EMR-based algorithm provides a robust algorithm for identifying cirrhosis patients across diverse healthcare settings. This algorithm holds promise to support more accurate OPA activation, facilitate clinician use of cirrhosis order sets, and enable the development of a comprehensive cirrhosis registry for quality improvement and research. Further optimization, particularly in rural settings, may improve specificity and overall performance.

Population	Algorithm	Specificity (%)	Sensitivity (%)
Overall (n=913)	DAD	97.74	76.15
	CC	97.49	85.32
	DAD or CC	97	86.24
University of Alberta Hospital (n=172)	DAD	97.71	77.14
	CC	99.24	88.57
	DAD or CC	97.71	91.43
Foothills Medical Centre (n=371)	DAD	97.9	88.89
	CC	96.11	91.67
	DAD or CC	96.11	91.67
High River Health Centre (n=171)	DAD	98.14	60
	CC	99.38	70
	DAD or CC	98.14	70
Red Deer Regional Hospital (n=199)	DAD	97.08	64.29
	CC	97.08	78.57
	DAD or CC	97.08	78.57

Disclosures: Kinjal Patel: Nothing to Disclose, Mayur Brahmania: Nothing to Disclose, Grace Wang: Nothing to Disclose, Mathew Daniel: Nothing to Disclose, Samina Khan: Nothing to Disclose, Mohamed Abdalla: Nothing to Disclose, Puneeta Tandon: Nothing to Disclose

3062 | ASSESSING NEED FOR HEPATITIS B VACCINATION IN ADULTS AGED 18-59 ACROSS HEALTH SYSTEM ENTERPRISE

Jayati Anand[1] Beatriz Torre[2] Jonathan Fenkel[2], [1]Beth Israel Deaconess Medical Center, [2]Thomas Jefferson University Hospital

Background: In March 2023, the CDC recommended Hepatitis B virus (HBV) triple-screening for all adults, testing surface antigen (sAg), surface antibody (sAb), and total core antibody (cAb), regardless of perceived risk. We designed a quality improvement (QI) project using an EMR-based tool called a Care Gap, a "hard-stop" mechanism of QI, within our academic health system's EPIC-based EMR to increase HBV triple-screening. This intervention aimed to improved triple-screening rates and permitted an opportunity to examine HBV immunity at an enterprise level. We sought to understand the need for HBV vaccination in adults aged 18-59, as this population is recommended to be vaccinated against HBV. **Methods:** The HBV screening Care Gap was enacted from 2/13/24 - 5/2/24 for adult patients at a large non-profit, metropolitan health system encompassing 10 EPIC-based hospitals surrounding an academic tertiary care center. HBV test results were collected at an enterprise level pre-intervention (6 weeks prior) and post-intervention (14 weeks through 5/23/24 to permit completion of tests ordered during intervention period). The pre- and post-intervention groups were compared using descriptive statistics. **Results:** In the pre-Care Gap period, 3,192 patients had some form of HBV testing. Of these patients, only 622 (19.5%) were triple-screened, per CDC guidelines. Of the triple-screened patients, 39.4% were vaccine-immune (sAb+, sAg-, cAb-), and 50.8% were triple-negative. When cohorted by age, 33.3% of the triple-screened patients were 18-59 years old and non-immune, non-exposed to HBV, making them eligible for vaccination. In the post-Care Gap period, 34,519 patients had some form of HBV testing. Of these patients, 28,641 (83%) were triple-screened, a robust increase from the pre-Care Gap period ($p < 0.0001$). Of the triple-screened patients, 33.1% were vaccine-immune (sAb+, sAg-, cAb-), and 61.5% were triple negative (sAb-, sAg-, cAb-) to HBV. When cohorted by age, 41.1% of the of the triple-screened patients were 18-59 years old and non-immune, non-exposed to HBV, making them eligible for vaccination. **Conclusion:** The EMR-based HBV screening Care Gap resulted in a significant increase in HBV triple-screening. The results support CDC guidance on screening and vaccination, as approximately 2 in 5 triple-screened adults in our enterprise are candidates for HBV vaccination. This data supports further use of EMR-based QI tools such as the hard-stop Care Gap to enhance screening and vaccination for HBV.

Table 1: Triple-Screening and Immunity Status in Pre and Post Care Gap Populations

	Triple Screened	Vaccine Immune (sAb+, sAg-, cAb-)	Non-immune, Non-exposed (sAb-, sAg-, cAb-)	Non-immune, Non-exposed AND 18-59 years old
Pre-Care Gap	622	245 (39.4%)	316 (50.8%)	207 (33.3%)
Post-Care Gap	28641	9480 (33.1%)	17625 (61.5%)	11768 (41.1%)

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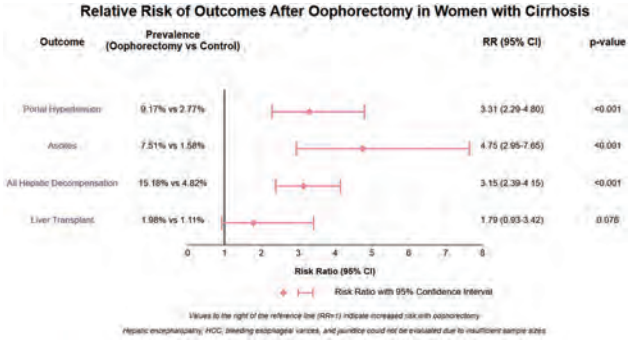
3063 | OOPHORECTOMY IS ASSOCIATED WITH HEPATIC DECOMPENSATION IN WOMEN WITH PRE-EXISTING CIRRHOSIS: A MULTICENTER RETROSPECTIVE COHORT STUDY

Emma Leipsner[1] Kate Johnson[2] Priyanka Gaur[2] Scarlet Yang[2] Tatyana Kushner[2], [1]Weill Cornell Medicine, [2]Weill Cornell Medical College

Background: Estrogen is thought to play a protective role in chronic liver disease progression, but the impact of estrogen withdrawal after oophorectomy in women with pre-existing cirrhosis is less understood. We evaluated whether surgical menopause independently contributes to hepatic decompensation in patients undergoing oophorectomy. **Methods:** This retrospective cohort study used the TriNetX Research Network compared women with cirrhosis who underwent an oophorectomy to those who had not, excluding those with prior decompensation. Propensity score matching was conducted on 22 characteristics, including demographics, comorbidities, and history of hysterectomy. A composite decompensation outcome was defined as the presence of hepatic encephalopathy, variceal bleeding, portal hypertension, ascites, and/or hepatocellular carcinoma (HCC). Kaplan-Meier analysis was used to determine time to decompensation events. **Results:** We identified 1,275 women with cirrhosis who had undergone oophorectomy (mean age at index 62.7 +/- 12.4) and 65,299 female controls with cirrhosis only (mean age at index 61.5 +/- 13.6) from 2005 to 2025. Oophorectomy indications included ovarian cysts (19.2%), ovarian cancer (7.8%), and endometriosis (8.3%). Hormone replacement therapy (HRT) was used more frequently in the oophorectomy group (12.1% vs. 3.8%, $p < 0.001$). After propensity score matching, 1265 women remained in each group with a median follow up time of 843 and 829 days, respectively. Women with cirrhosis who underwent oophorectomy had significantly higher rates of all hepatic decompensation compared to controls (RR 3.15, $p < 0.001$) (Figure 1). Specifically, portal hypertension (RR 3.31, $p < 0.001$) and ascites (RR 4.75, $p < 0.001$) were more common in the oophorectomy group. There was a significantly shorter time to onset of the composite hepatic decompensation outcome post-oophorectomy (HR 3.66, $p < 0.001$). **Conclusion:** Women with cirrhosis who undergo oophorectomy have a significantly higher and accelerated risk of hepatic decompensation, especially ascites and portal hypertension, highlighting the role of endogenous estrogen withdrawal and surgical risk in liver disease progression. These findings highlight the importance of supporting HRT and interdisciplinary care between hepatology and gynecology to optimize management post-oophorectomy.



Disclosures: Emma Leipsner: Nothing to Disclose, Kate Johnson: Nothing to Disclose, Priyanka Gaur: Nothing to Disclose, Scarlet Yang: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support

3064 | EVALUATING SHORT-TERM AND LONG-TERM PATIENT REPORTED SYMPTOMS FOLLOWING COVID-19 EXPOSURE IN CIRRHOSIS: IMPLICATIONS FOR QUALITY PATIENT CARE MANAGEMENT

Dhweeja Dasarathy[1] Jeremy Luk[2] Robert Wong[3] Ramsey Cheung[4] Alexander Monto[5] Amy Shui[6] Michael Ostacher[7] Steven Batki[8] Hannah Snyder[9] Taylor Fakadej[10] Christina Haight[8] Meimei Liao[11] Derek Satre[12] Mandana Khalili[13], [1]Department of Medicine, Stanford University, [2]National Institute on Alcohol Abuse and Alcoholism, [3]VA Palo Alto Healthcare System, [4]Stanford University Medical Center, [5]Veterans Affairs Greater Los Angeles Health Care System, [6]Department of Epidemiology and Biostatistics, University of California, San Francisco, [7]Stanford University School of Medicine, [8]Veterans Affairs San Francisco Health Care System, [9]University of California, San Francisco, CA, [10]Zuckerberg San Francisco General, [11]Veterans Affairs Palo Alto Health Care System, [12]Weill Institute for Neurosciences, University of California, San Francisco, [13]University of California, San Francisco

Background: Patient-reported symptoms can adversely impact quality of life (QOL) in patients with cirrhosis and are an important component of cirrhosis management. To date, a significant proportion of patients have been exposed to coronavirus disease (COVID-19), which may result in both acute or chronic symptoms but data on type and severity of symptoms or impact on QOL has not been assessed in patients with cirrhosis. In this analysis, we

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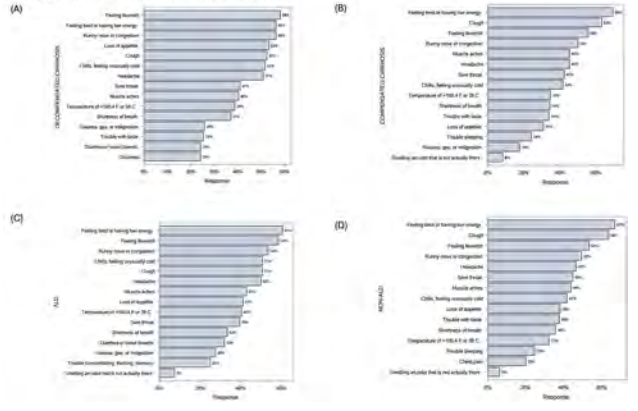
evaluated how the severity and number of symptoms post-exposure to COVID-19 affects QOL in patients with cirrhosis. **Methods:** Participants with cirrhosis and a prior COVID-19 diagnosis were identified from hepatology clinic records and administered telephone-based surveys (208 surveys in 156 participants) about COVID-19 diagnosis, symptoms following COVID-19 exposure (a total of 31 symptoms were evaluated), and Liver Disease QOL (LDQoL) instruments. Liver disease etiology and severity were extracted from electronic health records. Multivariable regression models assessed the relationship between QOL and total number of COVID-19 symptoms and symptom severity. **Results:** The study sample had a mean age of 64.5 years, 19% female, 39% had alcohol-related liver disease (ALD), and 39% decompensated cirrhosis. Overall, similar to the general population, the most common symptoms post-COVID-19 were fatigue, cough, and fever. The mean (SD) number of COVID-19 symptoms reported was 7.4 (6.4), with 66% proportion reporting at least one severe/very severe symptom. 16% of patients had long COVID-19 ($\geq$ 3 months of symptoms). When stratified by cirrhosis etiology (ALD versus no-ALD) and severity (decompensation versus compensation), patients had a similar distribution of symptoms reported (Figure 1) and did not have significant differences in severity of symptoms. However, among those with at least one severe symptom, the total number of severe symptoms was inversely associated with QOL. For each additional severe symptom reported, QOL decreased by 1.3 points (95% CI -1.83 to -0.78, $p < 0.001$). This was true even as we controlled for age, sex, decompensation, MELD-Na, and ALD, with QOL decreasing by 1.1 point for each additional severe symptom (95% CI -1.70 to -0.53, $p = 0.001$). **Conclusion:** In patients living with cirrhosis, assessing severity and chronicity of post-COVID-19 exposure symptoms can help clinicians address patient reported QOL concerns in order to improve cirrhosis management.

Figure 1. Most frequently encountered symptoms among patients with a history of COVID-19 and (A) Decompensated cirrhosis; (B) Compensated cirrhosis; (C) Alcoholic liver disease; (D) Non-Alcoholic Liver Disease



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3065 | PROSPECTIVE EVALUATION OF A FAST-TRACK TREATMENT PATHWAY FOR INDIVIDUALS WITH CHRONIC HEPATITIS B UNDER PRIMARY CARE

Jimmy Che-To Lai[1] Tiffany Ying-Tung Joeng[1] Vincent Wong[1] Vicki Wing-Ki Hui[1] Yee-Kit Tse[1] Terry Cheuk-Fung Yip[1] Grace Lai-Hung Wong[1], [1]The Chinese University of Hong Kong

Background: Linkage-to-care has been an issue leading to suboptimal engagement of individuals with chronic hepatitis B (CHB) into the hepatology care pathway. We developed a novel fast-track treatment pathway for individuals with CHB under primary care and evaluate its effect on linkage-to-care. **Methods:** From 2021 to 2024, individuals with CHB under two primary care clinics were offered access to transient elastography examination, serum hepatitis B virus (HBV) DNA and liver biochemistry tests at baseline and 3 years later, with an additional HBV DNA and liver biochemistry tests in between. Participants who fulfilled the antiviral treatment criteria (HBV DNA $>$2,000 IU/mL with serum alanine transaminase [ALT] $>$1-2 times upper limit of normal or liver stiffness measurement $>$9.0 kPa) were referred to hepatology specialist clinic by the fast-track treatment pathway, while those not fulfilling the antiviral treatment criteria continued their care at the primary care clinics. The linkage-to-care, including referral and antiviral treatment uptake rate, were analyzed and compared to participants under primary care over 3 years before the commencement of this treatment pathway (i.e., prospective and retrospective groups, respectively). **Results:** 466 and 2,703 participants were recruited in the prospective and retrospective groups, respectively. The mean age was 61.9 vs 59.9 years and female (60.5% vs 71.0%) were predominant, respectively (both $p<0.001$). The mean HBV DNA level was 2.8 ± 1.3 vs 3.5 ± 2.0 $\log_{10}$ IU/mL and serum ALT was 24.0 (18.0-33.0) vs 27.0 (19.0-42.0) IU/L, respectively (all $p<0.001$). In the

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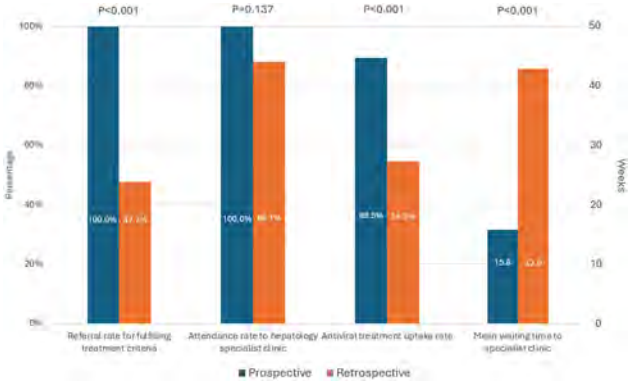
prospective group, 384 participants (82.4%) underwent at least one scheduled assessment and 19.6% out of those who remained in primary care attended all three assessments. Overall, 4.4% and 6.2% of the participants in prospective and retrospective groups, respectively, fulfilled the antiviral treatment criteria ($p = 0.194$). All participants in the prospective group who fulfilled the treatment criteria were referred through the fast-track treatment pathway, while 47.7% in the retrospective group were referred ($p < 0.001$). The mean waiting time to the hepatology specialist clinic was 15.8 vs 42.9 weeks ($p < 0.001$) and the attendance rate to the specialist clinic was 100% vs 88.1% ($p = 0.137$), respectively. Among those who fulfilled antiviral treatment criteria, the treatment uptake rate was 89.5% vs 54.5% ($p < 0.001$), respectively (Figure). **Conclusion:** A fast-track treatment pathway enhances timely referral and antiviral treatment uptake rates for individuals with CHB indicated for antiviral treatment.



Disclosures: Jimmy Che-To Lai: Nothing to Disclose, Tiffany Ying-Tung Joeng: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Consultant, Boehringer Ingelheim: Consultant, Echosens: Speaking and Teaching, Eli Lilly: Consultant, Gilead: Consultant, Gilead: Grant/Research Support, Intercept: Consultant, Inventiva: Consultant, Illuminatio Medical Technology: Stock – privately held company, Merck: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet: Consultant, TARGET PharmaSolutions: Consultant, Unilab: Speaking and Teaching, Visirna: Consultant, AstraZeneca: Consultant, Vicki Wing-Ki Hui: Nothing to Disclose, Yee-Kit Tse: Nothing to Disclose, Terry Cheuk-Fung Yip: Gilead Sciences: Consultant, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Grace Lai-Hung Wong: Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Fe: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline, Janssen and V: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens: Speaking and Teaching, Ferring, Gilead Sciences, GlaxoSmithKline, Janssen, RochE: Speaking and Teaching, Gilead Sciences: Grant/Research Support

3066 | "FIB-4 MORE": IMPROVING MASLD SCREENING AND MANAGEMENT IN PATIENTS WITH TYPE 2 DIABETES IN AN URBAN DIVERSE ENDOCRINOLOGY CLINIC

Melina Manolas[1] Lorena Rasquin Leon[2] Zoe Verzani[3] Brett Fortune[2], [1]Montefiore Medical Center, Weill Cornell Medicine, [2]Montefiore Medical Center, [3]Weill Cornell Medicine

Background: Metabolic dysfunction-associated steatotic liver diseaes (MASLD) affects 65–70% of adults with type 2 diabetes (T2D). Despite major endocrinology society guidelines to screen adults with T2D using Fibrosis-4 (FIB-4) index, screening in endocrinology practices remains low. Before this project, our electronic health record (EHR) lacked standardized screening tools, leading to missed opportunities for early detection and risk stratification. **Methods:** We conducted a pre/post-intervention quality improvement project at a single-center tertiary system for an urban diverse population aimed at increasing MASLD screening in patients with T2D by 15% over six months. Two *Epic* SmartPhrases (".FIB4" and ".FIB4MORE") were developed and implemented to calculate and interpret FIB-4 and initiate appropriate labs, imaging, and referrals (Fig 1). The SmartPhrase was shared with all endocrinology providers, who also received an in-person educational session and email. Data were collected for three months pre- and four months post-intervention. Clinical encounters for adults with T2D were included; those with T1D or pre-existing hepatology care were excluded. **Results:** Primary outcome was the percentage of patients with T2D who received documented MASLD screening using FIB-4. Baseline median MASLD screening rate was 4% in the 3 months pre-intervention (Weeks 1–12). Median screening rates increased to 47% and ultimately 59% in the 4-months post-intervention (Weeks 13–29) and tracked with SmartPhrase use, which was adopted into note templates by 44% of providers. Among patients with intermediate/high FIB-4, a composite of downstream clinical actions (hepatology referral, labs, and imaging orders) increased significantly from 17% to 43% post-intervention ($p = 0.019$), though overall volume of referrals and imaging orders placed were low and follow-through actions were inconsistent across providers. **Conclusion:** EHR-based decision support tools make for a feasible and scalable strategy to improve MASLD screening in patients with T2D. In our endocrinology clinic, these tools led to a 14-fold increase in MASLD screening rates with FIB-4 and improved downstream clinical actions, particularly among patients with intermediate/high-risk scores. SmartPhrase note template integration and provider buy-in were key drivers of adoption. However, follow-through actions

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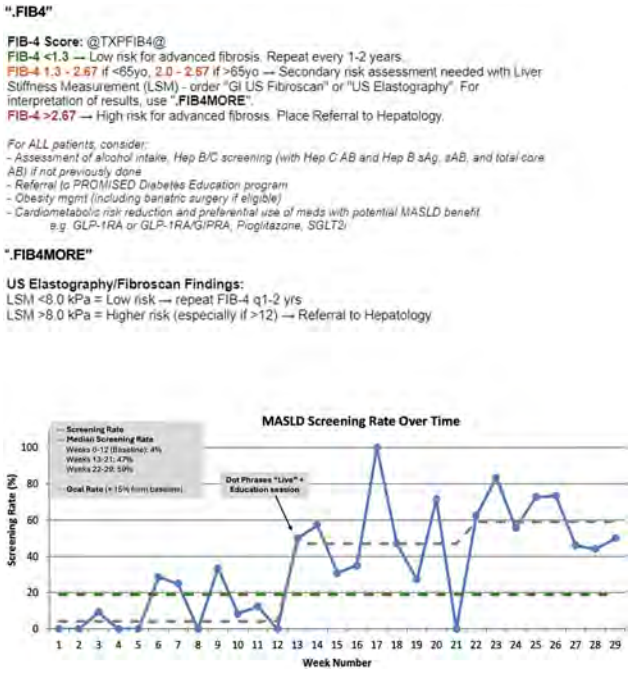
such as imaging and referrals were inconsistently applied, underscoring the need to strengthen structured screening pathways that bridge recognition with timely, coordinated management. Future directions include enhanced automation (e.g., lab prompts) and incorporation of the ELF (enhanced liver fibrosis) test.



Disclosures: Melina Manolas: Nothing to Disclose, Lorena Rasquin Leon: Nothing to Disclose, Zoe Verzani: Nothing to Disclose, Brett Fortune: Gilead Sciences: Consultant, Madrigal Pharma: Consultant, WL Gore and Associates: Consultant, BD medical: Consultant

3067 | USING COMMUNITY PARTNERSHIPS TO ACHIEVE HCV MICRO-ELIMINATION IN VANCOUVER'S INNER-CITY

Christina Wiesmann[1] Shana Yi[1] David Truong[1] Brian Conway[1], [1]Vancouver Infectious Diseases Centre

Background: The individuals living in Vancouver's inner city have some of the highest rates of hepatitis C virus (HCV) Canda, and the Vancouver Infectious Diseases Centre (VIDC) is working towards eliminating HCV in this population. The VIDC does this using an approach involving regular community pop-up clinics, or CPCs, at various inner-city locations. At each event, point-of-care HCV antibody testing is offered to up to 30 individuals. Individuals testing positive for HCV antibodies often have their blood drawn on site and those confirmed to be viremic are followed up with by outreach individuals and engaged in treatment under a multi-disciplinary model of care. We aimed to determine whether VIDC is achieving a reduction in the prevalence of HCV viremia in Vancouver's inner-city through a CPC approach to diagnosis and treatment. **Methods:** As part of a partnership with Atira housing society, since 2022 CPCs have regularly been held in the common spaces of Atira inner-city buildings with the goal of achieving elimination of HCV infection among the individuals living in these spaces. As a preliminary analysis, we determined the proportion of individuals testing positive for HCV antibodies, and those viremic, at CPC events held at 4 different Atira buildings in 2022 and in 2024. We then averaged the proportion of individuals testing positive at each location in 2022 and in 2024. Using these data, we were able to determine if there was a significant reduction in the proportion of individuals residing in these four buildings living with HCV in 2024 relative to 2022. **Results:** We saw that Indigenous ancestry, incarceration history, and history of injection drug use were all significantly associated with HCV seropositivity among the residents of these four buildings who were tested for HCV. We saw a clear reduction in the proportion of viremic individuals tested over time at all four locations. We performed a more detailed analysis of the individuals testing positive at pop-up events at the Luugat and saw that the reduction in viremic individuals over time largely due to the previous treatment of viremic individuals living in that building. Overall, we did not see a reduction in the proportion of individuals with HCV antibodies in these four buildings (32% in 2022 vs. 26% in 2024). However, we saw a clear reduction in the proportion of individuals residing in these residences who were viremic for HCV (14% in 2022 vs. 4% in 2024; $p = 0.1$). **Conclusion:** This study has demonstrated that while PWID may be a particularly difficult demographic to target for HCV treatment, with the help of community partnerships, a multidisciplinary approach to care, and continued testing and follow-up, we are on our way to achieving micro-elimination of HCV among the residents of Vancouver's inner city. By decreasing barriers to care and meeting people where they are at, we can achieve high rates of HCV cure even among unstable and traditionally difficult-to-treat populations.

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3068 | APPROPRIATE INTERVENTIONS HELP TO REDUCE 30-DAY HOSPITAL READMISSIONS FOR CIRRHOSIS: A SCOPING REVIEW

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Background: Hospital readmissions (RA) for cirrhosis impose burdensome clinical, psychological and financial implications for the patients (pts), caregivers and the healthcare systems. The aim of our scoping review was to ascertain the burden of 30-day RA, predictors of such readmission and to see if any strategies work in reducing RA. **Methods:** A scoping literature search from 2015-2025 was performed. Studies reporting 30-day RA in cirrhosis pts hospitalized for non-elective reasons were included. Two reviewers independently reviewed and agreed upon a particular study to be included for extraction of detailed data including demographics, admission and predictors of RA. **Results:** We identified 98 studies, out of which 26 (8 retrospective/8 prospective) were selected after applying inclusion and exclusion criteria consisting of 700,764 patients, from heterogenous sources and design. The sample size ranged from 134 to 303,346 (Table 1). The mean age of patients was 60 years (ranged 52-73 years) with MELD Na 13-21. The 30-day RA rates were 10% to 50% with the pooled readmission rate being 25.8% (95% CI 23.8-30.2). Most of the studies had higher rates with 12 studies between 20% to 29.9%; 10 between 30% to 39.9%;3 between 10%-15%; and only 1 study at 50%. Only 6 studies reported 90-day RA, and this ranged from 21% to 41%. Predictors of higher RA found were: broadly grouped as follows, concomitant medical illnesses (COPD, in-patient dialysis use, CVA, etc.), presence of complications of cirrhosis (liver failure, ACLF, HE, Ascites, EVB, HRS, etc.), lab values at index admission (increased MELD Na Score, WBC, CRP >10, etc.), patient characteristic (advanced age, higher BMI, lower patient education, etc.), others (Medicaid or Medicare coverage, early outpatient follow up in <7days, GI attending service). Predictors of decreased RA were: Female sex, Age $\geq$ 45, cancer, infections, interventions (Attendance in transitional liver clinic, application of interruptive alerts for medication adherence, electronic decision support), others (being on hospitalist service, EGD during index admission, DC to SNF & attendance at alcohol rehab facility).

Conclusion: On our updated review the 30-day hospital RA for cirrhosis continues to be high despite focus on this problem from last many decades. While most of the predictors for increased RA are non-modifiable, interventions shown to decrease RA include attendance in transitional liver clinic and using the electronic health record (EHR)interventions.

Table 1. Showing details of the included studies along with 30-Day Readmission Rate

S no.	Reference. PMID#, (year)	Single/Multi-center/Database	Sample size (n=700,764)	Age (Mean/ Median*) in Yrs	MELD-Na (Mean/Median*)	30 -Day RA (%)
		Retrospective Studies/Data				
1	Ifrah, et al. 39685484, (2024)	Single	230	58*	18*	26.5
2	Aryan, et al. 38179671, (2023)	Single	1017	56.8	NA	26.8
3	Bhave-Sarkar, et al. 35971218, (2022)	Single	467	56.7	16.9	20.1
4	Dishiya, et al. 35865917, (2022)	NRD	5787	58.5	NA	30
5	Yoder, et al. 34655589, (2022)	Single	498	52	18.9	20
6	Gonzalez, et al. 34144013, (2021)	Single	268	53.2	18.45	32.6
7	Garg, et al. 34422964, (2021)	NRD	303,346	NA	NA	31.4
8	Khan, et al. 32710679, (2021)	NRD	28,021	56.9	NA	27.8
9	Patel, et al. 32093164, (2020)	Single	392	58.9	17.85	26.5
10	Gasper, et al. 31113738, (2019)	Single	177	59	NA	31.2
11	Rosenblatt, et al. 31180921, (2019)	SID	8,964	73	NA	29.3
12	Mumtaz, et al. 30218583, (2019)	NRD	123,011	59.5	NA	27
13	Shaheen, et al. 30688401, (2019)	NRD	58,954	NA	NA	15
14	Seraj, et al. 29085229, (2017)	RPDR	222	56.7	13	20.7
15	Scaglione, et al. 28383303, (2017)	PHIC	16,107	56.6	NA	50
16	Tapper, et al. 27085758, (2016)	SID	119,722	60.9	NA	12.9
17	Kanwal, et al. 26991920, (2016)	VA data base	25,217	62	NA	20
18	Agrawal, et al. 26539850, (2015)	Single VA	134	59	13.8*	27.1
		Prospective Studies				
19	Orman, et al. 37543729, (2024)	Single	654	57.5	21.4	37.6
20	Orman, et al. 35207230, (2023)	Single	679	57.4	20.5	36.5
21	Orman, et al. 34311111, (2022)	Single	654	57.5	18.9	38
22	Louissant, et al. 35520619, (2022)	Single	2,787	NA	NA	9.8
23	Deng, et al. 34348942, (2022)	Single	233	61*	15*	32
24	Hu, et al. 33038189, (2021)	Multicenter	2170	57	18	28
25	Piano, et al. 28853729, (2017)	Single	139	61	15	30
26	Tapper, et al. 28407750, (2016)	Single	824	56.9	17.6	32

Legends: SID, Multiple Inpatient State Database; RPDR, Internal Research Patient Registry; PHIC, Private Health Insurance Claims Data

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3069 | DESIGNING FOR ADOPTION: A QUALITATIVE STUDY OF CLINICIAN PERSPECTIVES ON RISK PREDICTION TOOLS IN CIRRHOSIS

Kinza Khan[1] Mackenzie Bolas[2] Nadim Mahmud[3], [1]University of Pennsylvania Health System, [2]PSOM School of Medicine, [3]Hospital of University of Pennsylvania

Background: Although medical risk prediction tools are widely developed and published, few achieve sustained clinical adoption. In hepatology, surgical risk calculators are particularly underutilized in the care of patients with cirrhosis. In this study, we sought to identify key design and implementation factors that influence provider uptake of such tools, using the VOCAL-Penn Score (VPS) as a case example. **Methods:** We conducted a qualitative study of diverse clinicians who care for patients with cirrhosis. Semi-structured interviews were guided by the Consolidated Framework for Implementation Research (CFIR) to explore factors influencing the adoption of medical risk prediction tools, including the VPS. Interviews were transcribed and analyzed using a combined grounded theory and deductive approach. Emergent themes were synthesized into a conceptual framework for future implementation efforts. **Results:** We interviewed 22 clinicians (median age 38 years; 64% male; 45% White) representing a range of specialties and career stages (Table). Five recurrent themes emerged as central to the adoption of risk prediction tools: efficiency, accessibility, transparency, accuracy, and generalizability. Clinicians emphasized the need for tools that are intuitive, require minimal inputs, and integrate seamlessly into existing workflows (e.g., EMRs, web tools, UpToDate). Face validity of input variables — ensuring they were clinically meaningful and readily available — was cited as critical to encouraging use. Transparency in model development, validation, and limitations was essential to building trust. Participants stressed the importance of comparative performance data relative to existing clinical standards, as well as published external validations, to support the tool's credibility in real-world settings. Finally, generalizability was emphasized as key to equitable application across diverse patient populations. **Conclusion:** Using the VPS as a grounding example relevant to hepatology, our findings reveal how clinicians evaluate the utility of risk prediction tools in practice, emphasizing the importance of face-valid inputs, seamless workflow integration, and transparent communication of model performance and limitations. The five domains identified — efficiency, accessibility, transparency, accuracy, and generalizability — provide a practical framework to inform the development and dissemination of future tools. By aligning tool design with real-world clinical needs, this framework may support broader adoption and more equitable implementation of medical risk prediction tools across hepatology and other fields.

Table – Cohort Characteristics

Variable and Category	N=22
Age (years), median (IQR)	38 (33–53)
Sex	
Male	14 (64%)
Female	8 (36%)
Race/Ethnicity	
White	10 (45%)
Asian	9 (41%)
Black	2 (9%)
Hispanic	1 (5%)
Practice Setting	
Academic Center	16 (73%)
Academic Center/VA	3 (14%)
Private Practice	1 (5%)
Health System	1 (5%)
Hybrid - Academic / Health System	1 (5%)
Medical Specialty	
Hepatology	15 (68%)
Gastroenterology	4 (18%)
Surgery	2 (9%)
Internal Medicine	1 (5%)
Title	
Resident	1 (5%)
Fellow	2 (9%)
Instructor	1 (5%)
Assistant Professor	7 (32%)
Associate Professor	3 (14%)
Professor	5 (23%)
Non-Academic Physician	3 (14%)
Years in Practice, median (IQR)	10 (7–22)

Disclosures: Kinza Khan: Nothing to Disclose, Mackenzie Bolas: Nothing to Disclose, Nadim Mahmud: Grifols: Grant/Research Support

3070 | RACE AND ETHNICITY INFLUENCE PREGNANCY OUTCOMES IN WOMEN WITH CHRONIC LIVER DISEASE AND CIRRHOSIS

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Background: Pregnancies with chronic liver disease (CLD) have increased maternal and fetal risks. Racial

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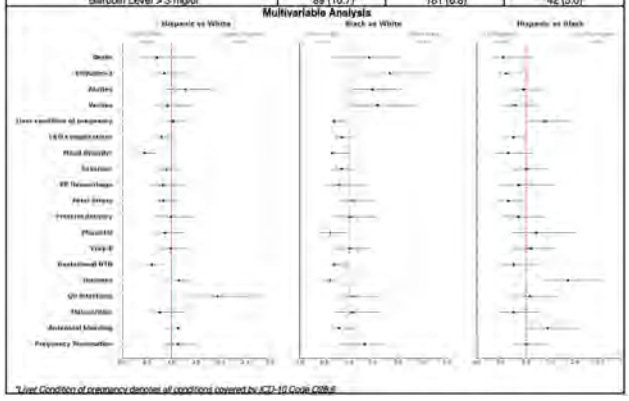
disparities contribute to pregnancy risks in the general population, though differences in the context of CLD are not known, which is essential to informing equitable care. **Methods:** This study evaluated the association between race/ethnicity and pregnancy outcomes between 2010-2024 in those with pre-pregnancy CLD using the TriNetX Research Network. Racial/ethnic groups included: White, Black, and Hispanic. Pregnancy outcomes were reported as percentages for each group. MELD-3.0 was calculated using mean laboratory values nearest index pregnancy event. Multivariable analyses were performed after 1:1 propensity score matching (PSM) to balance cohorts by age, body mass index (BMI), bilirubin, baseline varices, type 2 diabetes (T2DM) and CLD etiology: alcohol associated (ALD) or metabolic dysfunction-associated steatotic liver disease (MASLD). **Results:** Among 4,380 pregnancies (mean age 33.8 years), 2,672 were White, 833 Black, and 875 Hispanic. The most common CLD etiology was MASLD (26- 52%). Prior to matching, rates of antenatal bleeding (12% vs. 8%), genitourinary infections (GUI, 9% vs. 6%), DM (22% vs. 10-15%), and liver conditions of pregnancy (18% vs. 12-15%) were higher in Hispanic patients compared to White and Black patients. In contrast, liver complications, including bilirubin $\geq$ 3 (11%), ascites (11%), varices (8%) and mortality (3%), were highest in Black patients. After matching, 59% of each group had pre-pregnancy cirrhosis. Compared to Black patients, Hispanic patients had increased adjusted odds of GUI (OR 1.93, 95% CI 1.30-2.87, $p < 0.01$), and antenatal bleeding (OR 1.44, 95% CI 1.00-2.11, $p = 0.05$) and T2DM (OR 1.85, 95% CI 1.33-2.57). Compared to Hispanic patients, White patients had increased adjusted odds of gestational hypertension (OR 1.67, 95% CI 1.14-2.44, $p < 0.01$) and perinatal mood disorders (OR 95% CI 2.17, 95% CI 1.41-3.23, $p < 0.,01$), with similar point estimates when compared to Black patients. Black patients had increased odds of ascites (OR 1.47, 95% CI 1.04-2.08, $p = 0.03$), varices (OR 1.58, 95% CI 1.05-2.40, $p = 0.03$) and bilirubin $\geq$ 3 (OR 1.83, 95% CI 1.27-2.63, $p < 0.01$) as compared to White patients but no increased odds of adverse pregnancy outcomes. However, compared to Hispanics, Black patients had increased odds of labor complications (OR 1.33, 95 CI 1.02-1.75, $p = 0.04$) and fetal stress during labor (OR 1.65, 95% CI 1.04-2.22, $p = 0.03$). **Conclusion:** In this diverse, nationally represented cohort, pregnancy-related risks in CLD differed by race/ethnicity. Many differences were eliminated when adjusted for CLD etiology. However, infection and bleeding risk persisted in Hispanic females and liver-related events remained more common in those of Black race. These patterns underscore the need for individually tailored care to optimize pregnancy outcomes in the growing population with CLD.

	Black (n=833)	White (n=2,672)	Hispanic (n=875)
Age, mean years (SD)	34.0 (8)	34.1 (8)	32.8 (8)
BMI, mean kg/m² (SD)	32.5 (10)	32.6 (9)	33.3 (9)
Albumin, mean mg/dL (SD)	3.7 (0.7)	3.9 (0.7)	3.8 (0.7)
History of ascites, n (%)	170 (21.9)	457 (16.8)	123 (14.5)
Etiology: ALD, n (%)	72 (9.3)	384 (14.2)	49 (5.8)
Etiology: MASLD, n (%)	201 (25.9)	1081 (39.6)	440 (51.9)
Pregnancy Outcomes, n (%)			
Abortive Outcome of Pregnancy	105 (12.7)	264 (9.9)	108 (12.8)
Early Pregnancy Bleeding	69 (8.3)	234 (8.8)	102 (12.1)
Malnutrition in Pregnancy	45 (5.4)	119 (4.5)	27 (3.2)
Genitourinary (GU) Infection	58 (7.0)	142 (5.3)	75 (8.9)
Diabetes Mellitus (Diabetes)	82 (9.9)	401 (15.0)	187 (22.1)
Hyperemesis (Vomiting)	52 (6.3)	141 (5.3)	47 (5.5)
Gestational Hypertension (HTN)	48 (5.8)	204 (7.6)	44 (5.2)
Preeclampsia/Eclampsia (PreE-E)	268 (10.0)	78 (9.4)	90 (10.6)
Placental Conditions	37 (4.5)	198 (7.4)	56 (6.6)
Preterm Delivery	47 (5.7)	153 (5.7)	49 (5.8)
Fetal Stress During Labor	99 (11.9)	313 (11.7)	84 (9.9)
Postpartum Hemorrhage (PPH)	25 (3.0)	101 (3.8)	35 (4.1)
Cesarean Delivery	94 (11.4)	362 (13.5)	108 (12.8)
Perinatal Mood Disorder (PMAD)	41(4.9)	204 (7.6)	221 (8.1)
Postpartum Complications	95 (11.5)	292 (10.9)	98 (11.6)
Liver Outcomes n (%)			
Mortality (all cause)	27 (3.3)	69 (2.6)	12 (1.4)
Liver Condition of Pregnancy	96 (11.6)	410 (15.3)	150 (17.7)
Ascites	88 (10.6)	205 (7.7)	63 (7.4)
Esophageal Varices	63 (7.6)	201 (7.6)	36 (4.3)
Variceal Bleed	-	45 (1.7)	10 (1.2)
Bilirubin Level > 3 mg/dl	89 (10.7)	181 (6.8)	42 (5.0)



Liver Condition of pregnancy denotes all conditions covered by ICD-10 Code O26.6

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3071 | STRATEGIES FOR REDUCING THE TIME FROM HCV DIAGNOSIS TO TREATMENT INITIATION: LESSONS FROM VANCOUVER, BC, CANADA

Christina Wiesmann[1] Shana Yi[1] David Truong[1] Brian Conway[1], [1]Vancouver Infectious Diseases Centre

Background: The eradication of HCV infection as a public health concern requires targeted initiatives. In Canada, approximately 35% of people who use drugs are infected with HCV, representing more than 60,000 individuals. The Vancouver Infectious Diseases Centre (VIDC) runs weekly or twice-weekly pop-up clinics in Vancouver's inner-city to test for HCV antibodies. Anecdotally, we identify numerous individuals who have

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documented HCV viremia and who state they have never been offered treatment. There is an urgent need to meaningfully re-engage these indivdiuals in an accessible and timely manner. Reducing the time from HCV antibody diagnosis to treatment initiation is thought to be a key strategy for increasing HCV treatment uptake. **Methods:** Between August of 2023 and June of 2024, many measures were put in place to help reduce the time from point-of-care testing to initiation of treatment. These included on-site medical records look-up and phlebotomy if required, immediate special authority (SA) application, physician appointment with telehealth assistance and/or an appointment at our Downtown East-side (DTES) inner-city clinic, and a partnership with a pharmacy with a ready supply of HCV medication and daily delivery services. We measured the effect of these measures on time from initial contact to treatment initiation. **Results:** The median time from initial contact to treatment initiation was reduced from 6 weeks to approximately 3.5 weeks, with a range from 4 days to 57 days. The time median from initial patient contact to SA application being sent was 2 days (range from 0 to 33 days), and the median number of days for SA approval was 1 day (range from 1 to 22 days). The median number of days from SA approval to prescription being written was 5 days (range from 0 to 40 days), and the median number of days from the prescription being written to the patient receiving their first dose of medication was 7 days (range from 0 to 25 days).
We identified a number of facilitators and barriers to timely treatment initiation. Facilitators included on-site phlebotomy, telehealth assistance for appointments, pharmaceutical delivery, and dispensation with other medications. Barriers included follow-up with individuals without a fixed address, lengthy SA approval times for complex cases, requirement for a fibroscan in some cases, and wait times for HCV medication or pharmaceutical delivery services. **Conclusion:** We have identified many different interventions which have helped to decrease the time between initial contact and treatment start date. We believe that many of these interventions can be implemented in similar communities around the world. Follow-up analysis will investigate whether or not these measure helped to increase the numer of individuals initiating treatment, and reduce rates of loss to follow-up.
Disclosures: Christina Wiesmann: Nothing to Disclose, Shana Yi: Nothing to Disclose, David Truong: ABBVIE: Advisor, MERCK: Advisor, Brian Conway: AbbVie: Grant/Research Support, AbbVie: Advisor, Astra Zeneca: Grant/Research Support, Gilead Sciences: Grant/Research Support, GSK: Grant/Research Support, Indivior Canada: Grant/Research Support, Merck: Grant/Research Support, Vir Biotechnology: Grant/Research Support, Moderna: Grant/Research Support, Sanofi Pasteur: Grant/Research Support, Seqirus: Grant/Research Support, Atea Pharmaceuticals: Grant/Research Support, Pfizer: Grant/Research Support, AbbVie: Speaking and Teaching, Astra Zeneca: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, GSK: Speaking and Teaching, Indivior Canada: Speaking and Teaching, Merck: Speaking and Teaching, Moderna: Speaking and Teaching, Pfizer Canada: Speaking and Teaching, Sanofi Pasteur: Speaking and Teaching, Seqirus: Speaking and Teaching, ViiV Healthcare: Speaking and Teaching, AbbVie: Consultant, Astra Zeneca: Consultant, Gilead Sciences: Consultant, GSK: Consultant, Indivior Canada: Consultant, Merck: Consultant, Moderna: Consultant, Sanofi Pasteur: Consultant, Seqirus: Consultant, ViiV Healthcare: Consultant

3072 | BARRIERS AND PROPOSED INTERVENTIONS TO IMPROVE HEPATOCELLULAR CARCINOMA SURVEILLANCE ADHERENCE IN PATIENTS WITH HEPATITIS C VIRUS POST-SUSTAINED VIROLOGIC RESPONSE: A QUALITATIVE SURVEY ASSESSMENT OF HEPATOLOGY EXPERTS

Seren Gedallovich[1] Sudharshan Achalu[1] Tatyana Kushner[2] Ashwani Singal[3] Robert Brown[2] Neehar Parikh[4] Nancy Reau[5] T.Tara Ghaziani[1] Douglas Dieterich[6] K Rajender Reddy[7] Amit Singal[8] Mindie Nguyen[1] Paul Pockros[9] Stuart Gordon[10] Renumathy Dhanasekaran[1] Paul Kwo[1], [1]Stanford University Medical Center, [2]Weill Cornell Medicine, [3]University of Louisville, [4]University of Michigan Medical Center, [5]Rush University Medical Center, [6]Icahn School of Medicine at Mount Sinai, [7]University of Pennsylvania, [8]University of Texas Southwestern Medical Center, [9]Scripps Clinic and Scripps Translational Science Institute, [10]Henry Ford Health System

Background: Hepatitis C virus (HCV) therapy significantly reduces hepatocellular carcinoma (HCC) risk in patients who achieve sustained virologic response (SVR). However, patients remain at risk of HCC due to persistent oncogenic inflammation and fibrosis, coupled with host genetic susceptibility. HCC surveillance after SVR is widely underused, highlighting need for quality improvement. We aimed to gather expert perspectives on barriers to surveillance adherence and inform strategies for improving uptake through a qualitative analysis. **Methods:** Semi-structured interviews were conducted by teleconferencing with 13 nationwide hepatologists, experienced in managing patients with post-SVR HCV. Interviews focused on perceived barriers to HCC surveillance adherence and strategies for long-term follow-up. Transcripts were coded, and reflexive thematic analysis was completed to identify recurrent patterns and challenges. **Results:** In interviews, four major themes emerged (Figure):
1. Variation in Surveillance Practices:

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Surveillance protocols varied, especially for patients with advanced fibrosis without cirrhosis. For patients with cirrhosis, surveillance was uniformly recommended every 6 months, whereas practices for those with F2-F3 fibrosis were dependent on patient risk factors and provider discretion.

2. Patient-Related Barriers:

Patients may mistakenly believe that achieving SVR eliminates HCC risk. Factors such as asymptomatic status, low health literacy, limited financial resources, and competing life priorities hinder routine follow-up.

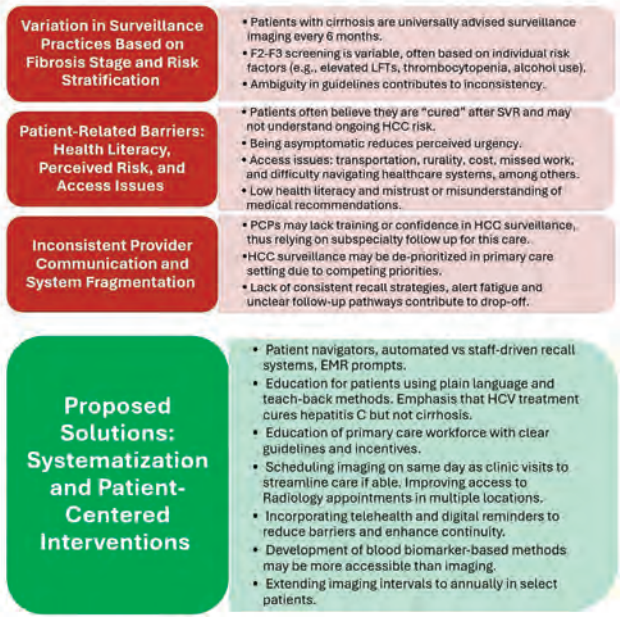
3. Provider and System Fragmentation:

Inconsistent recall strategies, unclear messaging, and lack of shared responsibilities between hepatologists and primary care providers (PCPs) result in lapses in care. Many patients are followed by PCPs after SVR, but PCPs may prioritize other health issues over HCC surveillance due to educational gaps and competing concerns.

4. Proposed Solutions and Innovations:

Suggested interventions included embedding patient navigators, establishing digital tracking systems, streamlining EMR prompts, and improving coordination with Radiology for easier access. Enhanced patient and provider education using simple language and teach-back techniques, along with longer imaging intervals and the development of blood biomarker-based surveillance strategies, were also recommended. **Conclusion:** HCC surveillance in post-SVR HCV patients faces challenges due to inconsistent protocols and multiple barriers. Targeted interventions to improve adherence are necessary.

Figure. Overview of barriers to HCC surveillance and proposed solutions.



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3073 | THE RISING GLOBAL CLINICAL AND ECONOMIC BURDEN OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOHEPATITIS (MASH) DRIVEN BY TYPE 2 DIABETES (T2D): A 20-YEAR MODELING STUDY ACROSS NINE COUNTRIES

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Background: T2D is an important risk for MASH. To inform long-term planning and intervention strategies, we projected the clinical and economic burden of MASH among adults with and without T2D across 9 countries (United States [US], Germany [DE], Spain [ESP], France [FR], Italy [IT], United Kingdom [UK], Japan [JPN], Brazil [BR], and Saudi Arabia [SA]) over 2 decades. **Methods:** Country-specific Markov models were developed to estimate 20-year (2021–2040) burden of MASH, stratified by T2D status across 9 health states: MASH without fibrosis (F0), fibrosis stages 1–3 (F1–F3), compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplantation (LT) year 1, and post-LT survival. Competing mortality risks (liver-related, cardiovascular, and other) were incorporated. Transition probabilities were derived from literature and calibrated using country-level data on T2D, obesity, and advanced liver disease. Direct medical costs, work productivity (WP) losses, and health-related quality-of-life (HRQL) impairments were estimated annually by disease stage and T2D status. All costs were expressed in 2020 USD and adjusted using International Monetary Fund inflation forecasts. **Results:** From 2021 to 2040, MASH prevalence in the general population is projected to rise in all countries: US (6.71% to 7.41%), DE (4.43% to 4.97%), ESP (4.50% to 5.38%), JPN (3.67% to 5.02%), BR (7.19% to 7.52%), SA (7.39% to 7.50%), FR (4.04% to 4.26%), IT (4.57% to 4.92%), and UK (4.74% to 4.86%). Among MASH patients, proportion of MASH with T2D is expected to rise: US (43.6% to 51.7%), DE (31.1% to 37.3%), ESP (49.8% to 60.3%), JPN (68.8% to 84.9%), BR (25.3% to 30.8%), SA (47.0% to 53.2%), FR (27.6% to 33.0%), IT (33.3% to 40.8%), and UK (41.6% to 48.5%). Cirrhosis cases among MASH patients with T2D are estimated to increase in every country (Figure 1A). Direct annual MASH-related medical costs will more than double, with the share attributable to T2D increasing: JPN (79.5% to 93.0%), ESP (67.8% to 79.4%), US (63.5% to 72.4%), FR (56.0% to 67.6%), UK (57.7% to 67.9%), IT (59.2% to 71.0%), DE (44.1% to 54.8%), SA (54.5% to 64.5%), and BR (30.7% to 40.1%,) (Figure 1B). WP losses and HRQL impairments among MASH patients with T2D are also projected to worsen. **Conclusion:** T2D is a major and growing driver of the clinical and economic burden of MASH in most regions. Targeting T2D patients to identify and treat MASH could help reduce future clinical and economic burden.

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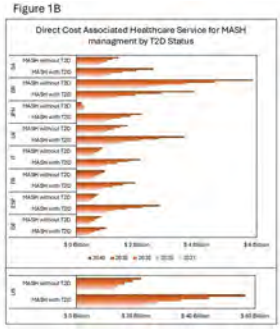
Figure 1B



Disclosures: Zobair Younossi: Zobair M. Younossi is a consultant or has received research: Consultant, James Paik: Nothing to Disclose, Cyrielle Caussy: Nothing to Disclose, Amalia Gastaldelli: Nothing to Disclose, Michael Roden: Astra Zeneca: Speaking and Teaching, Echosens: Advisor, Boehringer Ingelheim: Grant/Research Support, Madrigal: Speaking and Teaching, MSD: Speaking and Teaching, Lilly: Advisor, Novo Nordisk: Advisor, Synlab: Speaking and Teaching, Scott Isaacs: Nothing to Disclose, Cristiane Villela-Nogueira: Nothing to Disclose, Jeremy Tomlinson: Nothing to Disclose, Hussain Abdulrahman Al-Omar: Nothing to Disclose, Patrizia Burra: Nothing to Disclose, Yuichiro Eguchi: Nothing to Disclose, Javier Crespo: Nothing to Disclose, Elisabetta Bugianesi: Nothing to Disclose, Jerome Boursier: Nothing to Disclose, Mario Pessoa: Nothing to Disclose, Frank Tacke: Nothing to Disclose, Manuel Romero-Gómez: Nothing to Disclose, Hirokazu Takahashi: Nothing to Disclose, Claudia Pinto Oliveira: Nothing to Disclose, Paul Brennan: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching, Faisal Abaalkhail: Nothing to Disclose, Vincent Wai-Sun Wong: Nothing to Disclose, Philip Newsome: Nothing to Disclose, Fatema Nader: Nothing to Disclose, Linda Henry: Nothing to Disclose, Shira Zelber-Sagi: Nothing to Disclose, Nothing to Disclose, Laurent Castera: Boerhinger Ingelheim: Consultant, AstraZeneca: Speaking and Teaching, Boston Pharmaceutical: Consultant, Echosens: Speaking and Teaching, Gilead: Consultant, Inventiva: Speaking and Teaching, GSK: Consultant, Madrigal: Consultant, Madrigal: Speaking and Teaching, MSD: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Speaking and Teaching, Pfizer: Consultant, Sagimet: Consultant, Siemens Healthineers: Consultant, Boerhinger Ingelheim: Speaking and Teaching, Siemens Healthineers: Speaking and Teaching, Saleh Alqahtani: Nothing to Disclose

3074 | RURAL-URBAN TRENDS IN LIVER-RELATED MORTALITY POST-PANDEMIC DIFFER BY ETIOLOGY AND AGE

Tiange Zhang[1] Brian Lee[2] Jennifer Dodge[1] Norah Terrault[1], [1]University of Southern California, [2]Keck School of Medicine

Background: Before the COVID-19 pandemic, liver-related mortality increased in both rural and urban areas with a widening rural-urban disparity. During the pandemic, liver-related deaths surged but trends post-pandemic have been less studied. **Methods:** Using CDC WONDER mortality data for adults aged ≥25 from 2005 to 2023, overall liver-related deaths were identified using validated ICD-10 codes for cirrhosis, ALD, MASLD, viral hepatitis, autoimmune/cholestatic, and hereditary/genetic disorders. Rural-urban status was defined by established definitions (rural: micropolitan/noncore; urban: large central metro/large fringe metro/medium/small metro). We calculated age-adjusted mortality rates (AAMR) overall and by etiology (ALD, MASLD, others), sex, and age. Trends were assessed using Joinpoint regression to estimate annual percentage change (APC) across detected trend segments, comparing rural and urban areas. **Results:** In both rural and urban areas, overall AAMR for liver-related etiologies peaked in 2021 before declining through 2023 (Fig. 1A). Rural areas had a positive APC of +11.38% (95%CI: +6.6 to +16.3) in 2018-2021, followed by a negative APC of −5.76% (-9.6 to -1.8) in 2021-2023. Urban areas had similar trends (2018-2021: +8.1% [+4.9 to +11.3]; 2021-2023: -3.9% [-6.6 to -1.2]). Between 2021-2023, AAMR remained above pre-pandemic levels and higher in rural vs. urban areas. ALD (Fig. 1B), but not MASLD (Fig. 1C), mirrored overall trends with a peak in 2021 followed by a decline in 2021-2023. When ALD and MASLD were excluded, the 2021-2023 segment had a stable APC in rural areas (-2.44% [-7.6 to +3.0]), and no distinct 2021-2023 segment was detected by trend analysis in urban areas. Within the ALD group, the 2021-2023 segment had an APC that declined in both rural and urban areas for females, males, adults age 25-44, and adults age 45-64 but not among adults age ≥65 with ALD, where the 2021-2023 segment had a stable APC in rural areas (+0.35% [-10.7 to +12.8]), and no distinct 2021-2023 segment in urban areas. No trend differences by sex or age were observed for MASLD. **Conclusion:** Overall liver-related mortality remains above pre-pandemic levels, with rural rates consistently exceeding urban rates. ALD clearly drove pandemic increases but has had variable declines across age groups from 2021-2023, with older adults in both rural and urban areas remaining particularly vulnerable. Strategies to curtail liver-related mortality in the post-pandemic era are an

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urgent priority, with rural populations and older adults with ALD among the highest risk groups.

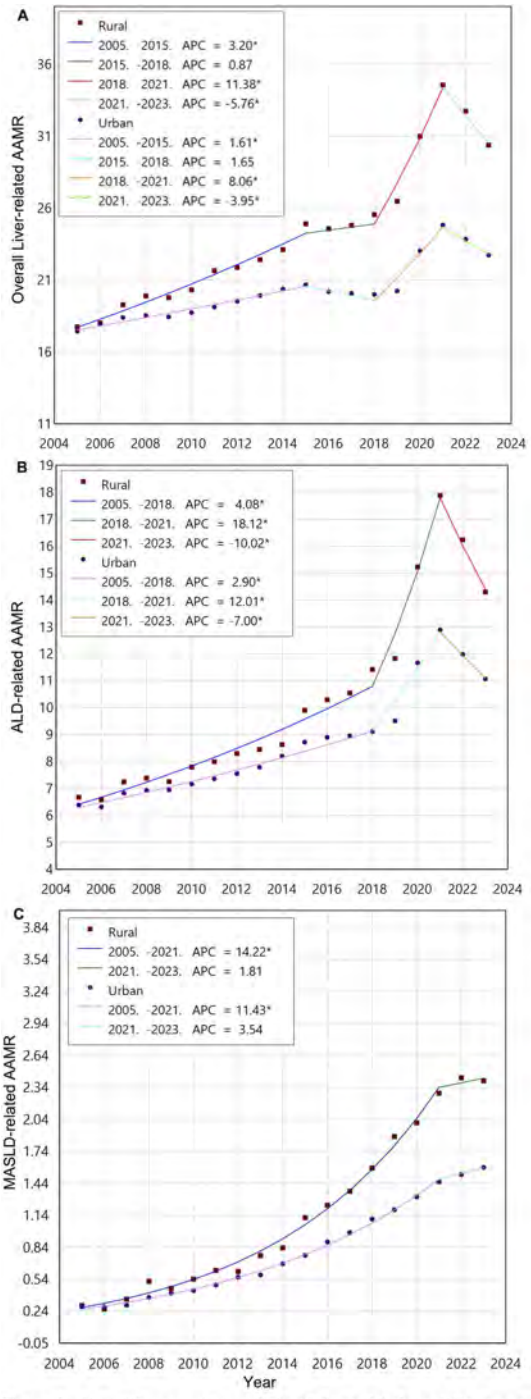

Figure 1. Joinpoint regression analysis of liver-related mortality among adults in rural vs. urban areas, 2005-2023. (A) Overall liver-related mortality. (B) Mortality from ALD. (C) Mortality from MASLD. *Indicates that the Annual Percentage Change (APC) is significantly different from zero at alpha of 0.05. AAMR: age-adjusted mortality rate.

Disclosures: Tiange Zhang: Nothing to Disclose, Brian Lee: NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, DURECT: Advisor, HepaTx: Advisor, CymaBay: Consultant, Ipsen: Consultant, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor, Assertio: Consultant, Jennifer Dodge: Nothing to Disclose, Norah Terrault: Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, ImmunoCore: Grant/Research Support, HBV Foundation: Board member, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role

3075 | MATERNAL AND PERINATAL OUTCOMES IN PREGNANT PATIENTS WITH COMORBID INFLAMMATORY BOWEL DISEASE AND CHRONIC LIVER DISEASE: A NATIONAL INPATIENT SAMPLE STUDY

Jessica Lee[1] Konstantinos Papamichael[2] Lauren Grinspan[3] Adam Cheifetz[2] Melissa Spiel[4] Tatyana Kushner[5] Loren Rabinowitz[2], [1]Department of Medicine, Beth Israel Deaconess Medical Center, [2]Division of Gastroenterology, Department of Medicine, Beth Israel Deaconess Medical Center, [3]Division of Liver Diseases, RMTI, Icahn School of Medicine at Mount Sinai, [4]Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, [5]Division of Gastroenterology and Hepatology, Department of Medicine, Weill Cornell Medical College

Background: Chronic liver disease (CLD) and inflammatory bowel disease (IBD) are each associated with adverse pregnancy outcomes. IBD also increases the risk of liver diseases such as primary sclerosing cholangitis, but the impact of coexisting IBD and CLD on pregnancy is unknown. We compared maternal and perinatal outcomes among patients with both IBD and CLD to those with IBD only, CLD only, or neither. **Methods:** We conducted a retrospective cohort study using the National Inpatient Sample from 2016-2022 to identify delivery hospitalizations among pregnant women aged ≥18 years, excluding nonviable pregnancies and abortions. Deliveries were classified into mutually exclusive groups using ICD-10-CM codes: IBD+CLD, IBD only, CLD only, or neither. CLD etiologies included alcohol, autoimmune, viral hepatitis, metabolic dysfunction-associated steatotic liver disease, alpha-1 antitrypsin deficiency, Budd-Chiari syndrome, Wilson's disease, hemochromatosis, and toxic liver disease. NIS survey discharge weights were applied to generate national estimates. Multivariable logistic regression was adjusted for age, race, insurance status, multiple gestation, obesity, diabetes, hyperlipidemia, hypertension, and cirrhosis. **Results:** Among 21,304,600 weighted deliveries, 680 (0.003%) had IBD+CLD, 47,555 (0.22%) had IBD only, and 178,025 (0.84%) had CLD only. IBD+CLD patients had

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higher rates of preexisting hypertension and hyperlipidemia compared to all groups and steroid use and autoimmune liver disease compared to CLD only. Regarding maternal outcomes, IBD+CLD had higher odds ($p < 0.001$ for most) of hypertensive complications, perinatal mood disorders, cesarean delivery, postpartum hemorrhage, and severe maternal morbidity (Table 1). In terms of perinatal outcomes, IBD+CLD had increased odds ($p \leq 0.01$ for most) of preterm premature rupture of membranes (PPROM) and PROM, preterm birth, fetal growth restriction and fetal death. IBD and CLD only were each associated with increased adverse outcomes compared to controls, with IBD+CLD showing even higher odds than either condition alone. **Conclusion:** Individuals with coexisting IBD and CLD face substantially higher risk of multiple maternal and perinatal complications than those with either condition alone. These findings suggest a compounding effect of IBD and CLD and support risk-based liver disease screening in prenatal care for patients with IBD to improve pregnancy outcomes.

Table 1. Adjusted multivariable logistic regression analyzing the association of an inflammatory bowel disease and/or chronic liver disease status in pregnancy with each adverse maternal and perinatal outcome.

Characteristic	IBD+CLD vs IBD		IBD+CLD vs CLD		IBD+CLD vs Control		IBD vs Control		CLD vs Control	
	AOR (95% CI)†	p-value	AOR (95% CI)†	p-value	AOR (95% CI)†	p-value	AOR (95% CI)†	p-value	AOR (95% CI)†	p-value
Maternal Outcomes										
Gestational diabetes	0.36 (0.23, 0.56)	<0.001	0.35 (0.24, 0.53)	<0.001	0.31 (0.20, 0.48)	<0.001	0.89 (0.85, 0.92)	<0.001	1.25 (1.03, 1.06)	<0.001
Gestational hypertension	1.29 (0.98, 1.69)	0.07	1.28 (0.98, 1.66)	0.07	1.49 (1.14, 1.95)	0.003	1.09 (1.05, 1.13)	<0.001	1.04 (1.02, 1.06)	<0.001
Hypertensive complication‡	1.96 (1.57, 2.46)	<0.001	1.60 (1.29, 1.98)	<0.001	2.66 (2.13, 3.33)	<0.001	1.33 (1.29, 1.38)	<0.001	1.42 (1.40, 1.44)	<0.001
Perinatal mood disorder	1.75 (1.48, 2.08)	<0.001	1.45 (1.23, 1.72)	<0.001	4.01 (3.39, 4.76)	<0.001	2.10 (2.05, 2.15)	<0.001	2.57 (2.54, 2.60)	<0.001
Cesarean section	1.92 (1.22, 3.03)	0.005	1.61 (1.03, 2.52)	0.04	2.28 (1.46, 3.55)	<0.001	1.10 (1.10, 1.27)	<0.001	1.17 (1.13, 1.21)	<0.001
Perineal laceration	0.95 (0.70, 1.13)	0.53	1.22 (1.03, 1.44)	0.02	0.82 (0.69, 0.97)	0.02	0.88 (0.85, 0.89)	<0.001	0.76 (0.75, 0.77)	<0.001
Postpartum hemorrhage	1.55 (1.15, 2.13)	0.005	1.20 (0.90, 1.60)	0.22	1.89 (1.38, 2.53)	<0.001	1.23 (1.18, 1.28)	<0.001	1.47 (1.44, 1.49)	<0.001
Chorioamnionitis	0.69 (0.35, 1.23)	0.19	0.71 (0.38, 1.32)	0.28	0.92 (0.48, 1.72)	0.80	1.38 (1.31, 1.46)	<0.001	1.16 (1.12, 1.19)	<0.001
Severe maternal morbidity§	1.76 (1.24, 2.50)	0.002	1.17 (0.85, 1.61)	0.33	3.33 (2.36, 4.70)	<0.001	1.75 (1.66, 1.85)	<0.001	2.23 (2.18, 2.28)	<0.001
Perinatal Outcomes										
Fetal growth restriction	1.58 (1.18, 2.13)	0.002	1.31 (0.83, 1.46)	0.49	2.49 (1.79, 3.21)	<0.001	1.56 (1.50, 1.63)	<0.001	1.69 (1.65, 1.72)	<0.001
Large for gestational age	0.50 (0.27, 0.84)	0.03	0.84 (0.34, 1.21)	0.17	0.49 (0.26, 0.91)	0.02	1.00 (0.95, 1.06)	0.88	0.80 (0.78, 0.83)	<0.001
PPROM/PROM	1.35 (1.06, 1.71)	0.01	1.39 (1.10, 1.74)	0.005	1.64 (1.30, 2.07)	<0.001	1.17 (1.13, 1.20)	<0.001	1.16 (1.14, 1.18)	<0.001
Preterm birth	2.50 (1.85, 3.21)	<0.001	1.89 (1.34, 2.13)	<0.001	3.29 (2.57, 4.20)	<0.001	1.25 (1.21, 1.32)	<0.001	1.75 (1.72, 1.78)	<0.001
Fetal death	1.70 (0.90, 3.21)	0.10	1.97 (1.17, 3.31)	0.01	2.24 (1.20, 4.20)	0.01	1.30 (1.27, 1.53)	<0.001	1.17 (1.12, 1.23)	<0.001

IBD, inflammatory bowel disease; CLD, chronic liver disease; AOR, adjusted odds ratio; CI, confidence interval; PPROM/PROM, preterm premature rupture of membranes/premature rupture of membranes.
† = AORs and CIs were adjusted for age, race, insurance, multiple gestation, preexisting comorbidities (obesity, diabetes, dyslipidemia, and hypertension), and cirrhosis
‡ = preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelets [HELLP] syndrome
§ = defined per CDC criteria, including any of 21 indicators: acute myocardial infarction, aneurysm, acute renal failure, acute respiratory distress syndrome, amniotic fluid embolism, cardiac arrest/ventricular fibrillation, conversion of cardiac rhythm, disseminated intravascular coagulation, blood transfusion, eclampsia, heart failure/arrest during surgery or procedure, puerperal cerebrovascular disorders, pulmonary edema/acute heart failure, severe anesthesia complications, sepsis, shock, sickle cell disease with crisis, air and thrombotic embolism, hysterectomy, temporary tracheostomy, and ventilation

Disclosures: Jessica Lee: Nothing to Disclose, Konstantinos Papamichael: Prometheus Laboratories Inc: Consultant, Celltrion Inc: Advisor, ProciseDx Inc: Advisor, Scipher Medicine Corporation: Advisor, Physicians Education Resource LLC: Speaking and Teaching, Grifols: Speaking and Teaching, Prometheus Laboratories Inc: Speaking and Teaching, Lauren Grinspan: Nothing to Disclose, Adam Cheifetz: Nothing to Disclose, Melissa Spiel: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Loren Rabinowitz: Nothing to Disclose

3076 | TIMING IS EVERYTHING: ECONOMIC IMPLICATIONS OF IMMEDIATE VERSUS DELAYED HEPATITIS C CARE

Mark Sulkowski[1] Nancy Reau[2] Natasha Martin[3] Zach Baldwin[4] Yuri Sanchez Gonzalez[4] Barbra Cave[4] Hélène Parisé[5] Tianzhou Yu[5] Warren Stevens[5], [1]Johns Hopkins Medicine, [2]Rush University Medical Center, [3]University of California, San Diego, [4]AbbVie Inc., North Chicago, IL, USA, [5]Medicus Economics, Boston, MA, USA

Background: Immediate care for hepatitis C virus (HCV) infection by treating at time of diagnosis could reduce the risk of disease progression and onward viral transmission. A recent study demonstrated the efficacy of 8-week glecaprevir/pibrentasvir (G/P) therapy in acute HCV. We evaluated the cost-effectiveness of treating newly diagnosed HCV patients with G/P vs waiting to determine chronicity to treat with sofosbuvir/velpatasvir (SOF/VEL). **Methods:** A health state transition model of HCV natural history and disease progression was developed from the healthcare system perspective over a lifetime horizon. In the strategy to treat at time of diagnosis, all patients were treated with 8-week G/P regardless of chronicity. In the strategy to wait for chronicity, only those who remained viremic after 6 months were treated with 12-week SOF/VEL and assumed to infect an average of 0.4 persons while untreated. Costs included were related to treatment, direct hepatic medical costs, and extra-hepatic manifestations. Re-infection and re-treatment were not considered. Efficacy of G/P was obtained from NCT04903626 and efficacy of SOF/VEL was sourced from its US product insert. Other parameters including drug acquisition costs were derived from published literature. All costs were inflated to 2025 Q1 US dollars. Key outcomes were total healthcare costs, total quality-adjusted life-years (QALYs), and net monetary benefit (NMB) calculated using a willingness-to-pay threshold of $100,000/QALY. To assess the impact of uncertainty in model parameters and structural assumptions, sensitivity analyses were performed. **Results:** In the base case analysis, treatment at time of first diagnosis with G/P regardless of chronicity was a dominant strategy compared to waiting for chronicity to treat with SOF/VEL, providing greater incremental QALYs (difference: 3.456), lower costs (difference: $32,121), and a NMB of $377,699. In the probabilistic sensitivity analyses, immediate treatment with G/P was a dominant strategy in 99.22% of the 10,000 simulations and cost-effective in 99.96% of the simulations. **Conclusion:** Treating HCV at first diagnosis with 8-week G/P therapy regardless of chronicity is projected to be a QALY- and cost-saving strategy compared to delaying treatment with SOF/VEL until confirmed HCV chronicity. This highlights the importance of therapies effective in treating HCV at the time of diagnosis, as it enables a more efficient use of finite healthcare resources, and lowers the transmission risk and time to cure.

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Figure 1. Cost-effectiveness results of immediate treatment with G/P vs. waiting for chronicity to treat with SOF/VEL

Outcome	Immediate treatment with G/P [A]	Waiting for chronicity to treat with SOF/VEL [B]	Difference [A] - [B]
Total Costs ($)	28,361	60,482	-32,121
Drug costs	26,400	57,713	-31,313
Testing/monitoring costs	574	929	-354
Direct medical costs	1,386	1,625	-238
Extra-hepatic manifestations costs	0	215	-215
Total QALYs	21.807	18.351	3.456
NMB at $100,000/QALY			377,699 (i.e., cost-effective)

NMB, net monetary benefit; QALY, quality-adjusted-life-years

Disclosures: Mark Sulkowski: Nothing to Disclose, Nancy Reau: Gilead: Grant/Research Support, eiger: Grant/Research Support, abbott: Consultant, Arbutus: Consultant, Gilead: Consultant, VIR: Consultant, Salix: Consultant, Salix: Grant/Research Support, AbbVie: Grant/Research Support, VIR: Grant/Research Support, Natasha Martin: Gilead: Grant/Research Support, Abbvie: Grant/Research Support, Zach Baldwin: Nothing to Disclose, Yuri Sanchez Gonzalez: Nothing to Disclose, Barbra Cave: AbbVie: Employee, Hélène Parisé: AbbVie, Inc: Consultant, Tianzhou Yu: AbbVie: Employee, AbbVie: Consultant, Warren Stevens: Nothing to Disclose

3077 | OPTIMIZING TRANSITIONS OF CARE FOR LIVER CIRRHOSIS PATIENTS: A RETROSPECTIVE ANALYSIS OF INPATIENT ENCOUNTER DATA ON 30- DAY READMISSIONS

Sai Patel[1] Ayush Kaushish[1] Michael Moseley[1] Alexis Kim[1] Allison Ladetto[2] Hannah Lee[3] Carolyn Marcelo[1], [1]Virginia Commonwealth University Health System, [2]Virginia Commonwealth University School of Medicine, [3]Virginia Commonwealth University

Background: Liver cirrhosis is a major cause of morbidity and mortality and is associated with high hospital readmission rates. Reducing readmissions, particularly for cirrhosis patients, is a priority at Virginia Commonwealth University Health System (VCUHS). According to FY 2024 Vizient data, VCUHS's General Medicine-Hepatobiliary Sub-Service Line, which includes all patients with a cirrhosis diagnosis-related group, had a readmission rate of 25.3%, compared to a median of 21.7% among academic medical centers. This retrospective cohort study identifies gaps in discharge care coordination by evaluating 30-day readmission data among cirrhosis patients. **Methods:** Cirrhosis patients admitted to a medicine service at VCUHS between January and June 2024 were identified. Data was collected on readmission timing, chief complaints, discharge planning, and follow-up care. Cirrhosis etiology, Model for End-Stage Liver Disease (MELD) 3.0 scores, and transplant status were also analyzed. **Results:** 78 cirrhosis patients who were readmitted within 30 days of discharge were identified. Alcohol-associated (47.4%) and metabolic dysfunction-associated (30.8%) were the most common cirrhosis etiologies. The mean MELD 3.0 score was 23. Hepatic encephalopathy (HE) (43.6%) and hypervolemia (29.4%) were the most common admission symptoms. 41% were listed for transplant during or prior to hospitalization. Only 26.9% had primary care follow-up scheduled within 30 days; of these, 57.1% were scheduled within 7 days. Hepatology follow-up was arranged for 55.1% of patients, with only 32.6% occurring within 7 days. 84.6% received new prescriptions, 63.7% of which were filled at the VCUHS discharge pharmacy. 65.3% of patients received free text written instructions, 28.2% received standard patient education materials, and 25.6% received no cirrhosis- related instructions. 38.4% received home health services, 10.3% received remote patient monitoring services, and 8.9% received a care coordination follow-up call. HE (35.9%) and hypervolemia (17.9%) were the most frequent reasons for readmission. **Conclusion:** Our findings highlight substantial gaps in discharge coordination for cirrhosis patients. Low rates of early follow-up, underutilization of monitoring services, and inconsistent discharge education were prevalent. Enhanced transitional care strategies, including timely follow-up scheduling, standardized patient education, and increased use of remote monitoring, may reduce avoidable readmissions and improve patient outcomes.

Disclosures: Sai Patel: Nothing to Disclose, Ayush Kaushish: Nothing to Disclose, Michael Moseley: Nothing to Disclose, Alexis Kim: Nothing to Disclose, Allison Ladetto: Nothing to Disclose, Hannah Lee: Nothing to Disclose, Carolyn Marcelo: Nothing to Disclose

3078 | HOSPITALIZATION PATTERNS AND RESOURCE UTILIZATION IN LIVER CIRRHOSIS

Paola Barrios[1] Gil Peled[2] Aditya Jain[3] Saad Hussain[1] Oriana Dentici[1] Lisa VanWagner[4] Andres Duarte-Rojo[5] Laura Kulik[6] Nikhilesh Mazumder[2] Charles Manski[2] Daniela Ladner[1], [1]Northwestern University Comprehensive Transplant Center, [2]Northwestern University, [3]Northwestern Univeristy, [4]University of Texas Southwestern Medical Center, [5]Northwestern Medicine, [6]Northwestern Medical Faculty Foundation

Background: Liver cirrhosis affects 2-5 million adults and is associated with high morbidity, mortality and a reduced quality of life. Patients with chronic diseases in high resourced areas have been found to have better outcomes. We examine hospitalizations, in-hospital resource utilization and cost in a large longitudinal

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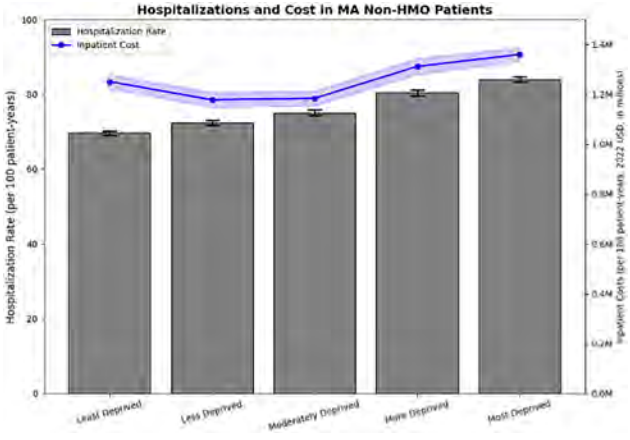
national dataset and compare patients in low vs high-resourced environments using Area Deprivation Index (ADI). **Methods:** This is a retrospective cohort study of privately insured adults with cirrhosis using a large national insurer claims database from 7/2011-12/2022. Hospitalization rates, in-hospital resource utilization and cost were analyzed. ADI categories are reported (D1: least deprived; D5: most deprived). Multivariate analyses were adjusted for age, gender, insurance type, Charleston Comorbidity Index (CCI), and etiology. **Results:** In 393,745 patients (mean age 63.9 years; 45.5% female; Medicare 57.6%), the most common etiology was ALD (38.8%). Average CCI is 5.7, and mean MELD 3.0 is 14.1. Mean hospitalization rate is 65 hospitalizations/100 patient years. Patients in D5 vs DI 1 had 11.1% higher hospitalization rates, lower outpatient-to-inpatient visit ratio by 13.5%, and an increase in acute care visits by 50.8%. D5 patients experienced 2.1% higher LOS. D5 patients were 10.3% more likely to be discharged to hospice and 28% more likely to leave the hospital against medical advice. D5 patients underwent 17.8% fewer cirrhosis related procedures while inpatient. D1 had a higher cost per single hospitalization at $18,251.74 vs $16,194.69 in D5 but overall cost of care/100-patient years was 5.1% higher in D5 vs D1 ($1,332,500 vs $1,268,478) (Figure). All results reached statistical significance ($p < 0.05$). **Conclusion:** Hospitalization rates are high for patients with cirrhosis. Patients living in the most deprived geographic areas have lower cost of hospitalizations, but likely because of higher hospitalization rates and fewer outpatient relative to inpatient visits, patients in more deprived areas incur higher overall costs of inpatient care.



Disclosures: Paola Barrios: Nothing to Disclose, Gil Peled: Nothing to Disclose, Aditya Jain: Nothing to Disclose, Saad Hussain: Nothing to Disclose, Oriana Dentici: Nothing to Disclose, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, Andres Duarte-Rojo: Echosens: Grant/Research Support, Laura Kulik: astrazeneca: Advisor, astrazeneca: steering committee, genetech: Advisor, genetech: steering committee, Fujifilm: Consultant, AstraZeneca: Speaking and Teaching, astrazeneca: Advisor, astrazeneca: steering committee, genetech: Advisor, genetech: steering committee, Fujifilm: Consultant, AstraZeneca: Speaking and Teaching, astrazeneca: Advisor, astrazeneca: steering committee, genetech: Advisor, genetech: steering committee, Fujifilm: Consultant, AstraZeneca: Speaking and Teaching, Nikhilesh Mazumder: Nothing to Disclose, Charles Manski: Nothing to Disclose, Daniela Ladner: Nothing to Disclose

3079 | FRAILTY AND DECOMPENSATED CIRRHOSIS ARE ASSOCIATED WITH SIGNIFICANTLY HIGHER MORTALITY INDEPENDENT OF RACE AND ETHNICITY

Saad Hussain[1] Paola Barrios[1] Suyanpeng Zhang[1] Dominic Vitello[1] Sijia Wei[1] Salva Balbale[1] Oriana Dentici[1] Al'ona Furmanchuck[1] Nikhilesh Mazumder[2] Lisa VanWagner[3] Lihui Zhao[1] Andres Duarte-Rojo[4] Sanjay Mehrotra[1] Daniela Ladner[1], [1]Northwestern University, Chicago, IL, [2]University of Michigan Hospitals and Health Centers, [3]University of Texas Southwestern Medical Center, [4]Northwestern Medicine

Background: Mortality is very high in patients with cirrhosis. We examine if mortality varies across different racial and ethnic groups. **Methods:** A retrospective cohort study was performed to identify adult patients with cirrhosis using CAPriCORN, a large EHR data repository across 7 health care systems in a large US metropolitan area from 2016-2021. Demographics and clinical covariates examined including age, sex, race/ethnicity, urban/rural, etiology, insurance type, Area Deprivation Index (ADI) [Q1: high resourced, Q5: low resourced), MELD 3.0, Charlson comorbidity index (CCI), decompensation and frailty (HFRS); [Low: HFRS < 5, severe: HFRS > 15]. The primary outcome of interest was all-cause mortality rates reported per 100 patient-years (PY). Univariate and multivariate analyses were performed. Significance = $P < 0.05$. **Results:** 18,718 patients with cirrhosis were included. The mean age was 59.8, 43.1% were women, 45% were white, 19% black, 21% Hispanic, and 97% lived in urban areas. Most common etiologies were MASLD (28.6%), MetALD (23.1%), ALD (12.8%). 29.5% had Medicare,

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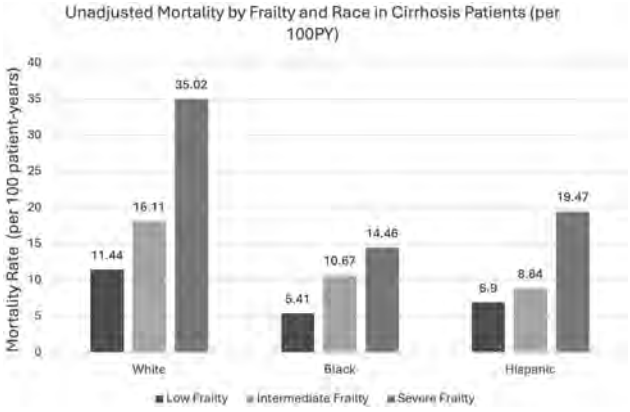
27.8% Private, 22.3% Medicaid, 14.3% other insurance, 6.2% uninsured. ADI (Q1: 5.7%, Q2: 30.8%, Q3: 36.4%, Q4: 23.6%, Q5: 2.4%). Mean MELD was 16.3, CCI 6.79 and 29.7% were decompensated at inclusion. 54.1% patients had low frailty, 28.1% intermediate and 15.7% severe frailty. (Table) Mean mortality per 100 PY was 13.26 (white: 16.13, black: 9.08, Hispanic: 8.86 per 100PY). Severe vs low frailty was associated with increased mortality (25.48 vs 10.22 per 100PY) and was consistently associated with >2.8x higher mortality across races/ethnicity (white: 306%, black: 367%, hispanic: 289% increase, respectively). (Figure) Decompensated vs compensated cirrhosis was associated with increased mortality (21.35 vs 10.35 per 100PY) and decompensation was consistently associated with >1.8x higher mortality across races/ethnicity (white: 233%, black: 251%, Hispanic: 183% increase, respectively). **Conclusion:** Severe frailty and decompensation is race-agnostic, as patients with cirrhosis of any race/ethnicity had 3-fold and 2-fold increase in mortality respectively, independent of race and ethnicity.



Disclosures: Saad Hussain: Nothing to Disclose, Paola Barrios: Nothing to Disclose, Suyanpeng Zhang: Nothing to Disclose, Dominic Vitello: Nothing to Disclose, Sijia Wei: Nothing to Disclose, Salva Balbale: Nothing to Disclose, Oriana Dentici: Nothing to Disclose, Al'ona Furmanchuck: Nothing to Disclose, Nikhilesh Mazumder: Nothing to Disclose, Lisa Van-Wagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, Lihui Zhao: Nothing to Disclose, Andres Duarte-Rojo: Echosens: Grant/Research Support, Sanjay Mehrotra: Nothing to Disclose, Daniela Ladner: Nothing to Disclose

3080 | CHARACTERIZING HEALTHCARE COSTS IN MEDICARE BENEFICIARIES WITH A NEW DIAGNOSIS OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) WITH COMPENSATED CIRRHOSIS

Nipun Atreja[1] Francis Lobo[1] Yestle Kim[1] Dominic Nunag[2] Andrew Epstein[2], [1]Madrigal Pharmaceuticals, [2]Medicus Economics

Background: Current studies on the economic burden of MASH with compensated cirrhosis are limited by focusing on short-term (annual) costs and only reporting average costs, without examining heterogeneity across the cost distribution. **Methods:** We conducted a cohort study using a full sample of Medicare FFS beneficiaries aged ≥ 65, continuously enrolled for any 4-year span between 01/01/2016 to 12/31/2023 (1-year baseline, 3-year follow-up). Compensated cirrhosis was defined by ≥ 1 inpatient or ≥ 2 outpatient claims (any position) for cirrhosis (ICD-10-CM: K74.4–K74.6, I85.00, I85.10, I85.9, I98.2) and MASH (K75.81), occurring ≤ 90 days apart in either order. Mean total healthcare costs per beneficiary were calculated over the 3-year follow-up and adjusted to 2023 dollars. Beneficiaries were stratified into quartiles (Q) based on total costs. Baseline characteristics were compared using chi-square (categorical) and ANOVA (continuous) tests. **Results:** Among 3,726 beneficiaries (mean age, 72.1 years) with a new diagnosis of compensated cirrhosis, mean (standard deviation [SD]) total 3-year healthcare costs were $95,891 ($108,188) and were highly skewed (mean [SD], Q1: $19,950 [$7,658]; Q2: $47,703 [$9,118]; Q3: $90,025 [$16,707]; Q4: $225,973 [$146,228]; Figure). Beneficiaries in the highest-spending quartile (Q4) were responsible for 59% of total spending, while those in the lowest-spending quartile (Q1) contributed 5%. Beneficiaries in the highest-spending quartile (Q4) were more likely to be dual eligible for Medicare/Medicaid coverage compared to those in the lower-spending quartiles ($P<0.001$). Compared to those in the lower-spending quartiles (Q1–Q3), beneficiaries in the highest-spending quartile (Q4) also had more unique medications, greater prevalence of hospitalization, greater comorbidity, and greater diabetes complications severity index, all measured in the baseline period ($P<0.001$ for all). **Conclusion:** In Medicare FFS, total healthcare costs in the 3 years after a new diagnosis of MASH with compensated cirrhosis are high overall and highly

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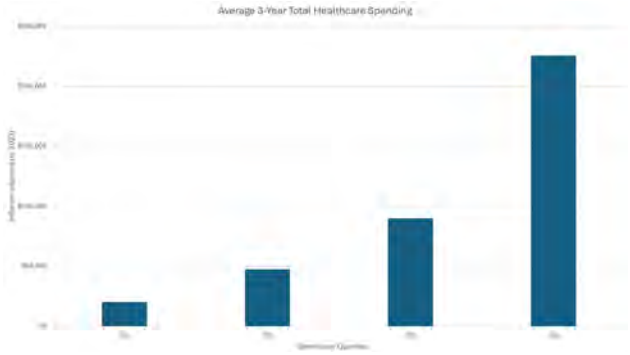
concentrated, with a quarter of beneficiaries accounting for 59% of total spending. Targeting early identification and treatment for compensated cirrhosis in the costliest patients may translate into meaningful savings for payers.

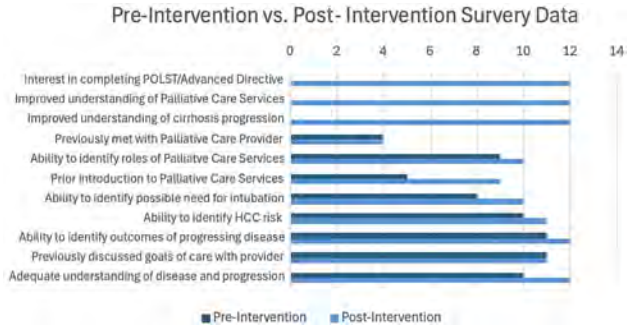


Disclosures: Nipun Atreja: Madrigal Pharmaceuticals: Employee, Immunovant: Employee, Bristol Myers Squibb: Employee, Francis Lobo: Madrigal Pharmaceuticals: Employee, Yestle Kim: Nothing to Disclose, Dominic Nunag: Nothing to Disclose, Andrew Epstein: Nothing to Disclose

3081 | IMPACT OF A BRIEF VIDEO INTERVENTION ON DISEASE UNDERSTANDING AND ADVANCED CARE PLANNING IN HOSPITALIZED PATIENTS WITH DECOMPENSATED CIRRHOSIS

Helene Bloom[1] Nabeeha Mohy-ud-din[1] Dheera Grover[1], [1]Allegheny Health Network

Background: Cirrhosis has an increasing incidence with over 54,000 new diagnoses/year and is currently the tenth leading cause of death in the US [1]. Despite this, patients historically have limited understanding of disease progression and it's impact on their health and prognosis. This pilot project aimed to increase education regarding progression of cirrhosis and to introduce patients to advanced care planning with the goal of limiting invasive medical interventions at the end of their lives. **Methods:** Inpatients aged 18-89 years with Child-Pugh Class B and C cirrhosis who are not deemed transplant candidates with two prior hospitalizations within 6 months at our tertiary care hospital were included in the study. Participants completed a questionnaire assessing their pre-existing knowledge and were shown a 5-minute informative video designed by our team on progression of cirrhosis and introduction to palliative care services, followed by a post-intervention survey. **Results:** 14 patients were included in the study with one unable to complete the survey due to fatigue. The mean age of patients was 63.4 and 84.6% were male. Pre-intervention, 76.9% (n = 10) patients reported understanding of their liver disease and its progression, with improvement to 92.3% (n = 12) post intervention. Pre-intervention, 69.2% (n = 9) noted an understanding of palliative care services, with an improvement to 76.9% (n = 10) post-intervention. Only 5 patients had been introduced to the term palliative care and 4 had met a palliative care provider previously. 53.8% (n = 7) patients were 'full code' prior to the intervention, and one patient was interested in changing the code status to DNR/okay to intubate from full code. 92.3% (n = 12) patients either agreed or strongly agreed to have a better understanding of cirrhosis and goals of palliative care services/advanced care planning post-intervention and 92.3% (n = 12) were interested in completing a POLST or advanced care directive at the conclusion of the study. **Conclusion:** A brief educational video regarding disease progression and advanced care planning can be beneficial in improving patients' knowledge and aid with decisions regarding end-of-life care.



Disclosures: Helene Bloom: Nothing to Disclose, Nabeeha Mohy-ud-din: Nothing to Disclose, Dheera Grover: Nothing to Disclose

3082 | MISSED OPPORTUNITIES IN HCV ELIMINATION: INSIGHTS FROM ITALY&RSQUO;S NATIONAL SCREENING AND EQUITY GAPS

Loreta Kondili[1] Maria Giovanna Quaranta[1] Benedetta Mattioli[1], [1]Istituto Superiore Di Sanita (ISS)

Background: IItaly bears one of the highest HCV burdens in Europe, with prevalence and liver-related mortality nearly three times the EU average. Unlike other countries where infection is limited to high-risk groups, Italy's epidemic significantly affects the general population, particularly adults over 55. Italy leads Europe in HCV treatment and remains the only country to fund a national screening program via its Ministry of Health. Launched in 2022, this feasibility project targeted individuals born 1969–1989, people in addiction services (SerD), and inmnates. **Methods:** Ongoing

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HCV free of charge screening is delivered in Italy via proactive and opportunistic approaches. Screening indicators are validated by the Istituto Superiore di Sanità. Interim evaluations of screening coverage, test uptake, antibody and RNA positivity, and linkage to care, are reported across the three populations' settings. **Results:** A total of 2,605,054 individuals were screened within this nationwide program, identifying 16.866 active infections:

- General population: 2, 384.024 screened; 3,302 infections (0.14%)
- SerD: 135,469 screened; 10.551 infections (7.8%)
- Prisons: 85, 561 screened; 3.013 infections (3.5%)
- Linkage to care is still a challenge variying from 49.5% in SerD to 67% in prisons.

Among SerD invitees, 33% were PWID, with 474 reinfections.The lower prevalence in SerD and prison settings, compared to historical data, likely reflects the positive impact of DAA scale-up. Prisons achieved the highest HCV screening coverage (92.6%) and adherence (82.8%) in Europe, demonstrating success in structured environments.
In contrast, the general population showed low antibody (0.8%) and RNA positivity rates, likely due to participation by previously treated individuals and a poor risk perception of individuals who did not undergo HCV screening. The explanation of a lower chronicity rate in infections acquired via non-classical routes (non-injection exposures), is currently under investigation. Comparative studies show that HCV prevalence in marginalized populations can significantly exceed that of the general population (2,9% vs 0.4%), indicating the national program failed to sufficiently reach those at highest risk, limiting its effectiveness in driving HCV elimination. **Conclusion:** Italy's free of charge screening of over 2.6 million people, mainly from general population,and from people who use drugs and inmates, offers a rare glimpse into population-scale HCV elimination strategies in a European Union country. Successes in SerD and prisons contrast with general population's low engagement and unsustained efforts.The program's closure with unused funds risks political misinterpretation that no further action is needed. Without renewed investment, outreach programs, and effective testing and linkage-to-care strategies for older adults, Italy risks an ongoing disease burden and failure to meet the elimination goals.

Disclosures: Loreta Kondili: Gilead Science: Grant/Research Support, Maria Giovanna Quaranta: Gilead: Grant/Research Support, Benedetta Mattioli: Nothing to Disclose

3083 | LIVER AND SPLENIC STIFFNESS IN CLINICALLY SIGNIFICANT PORTAL HYPERTENSION.

Sandeep Kaur Toor[1] Himanshu Gupta[1] Amandeep Singh[2] Jahnvi Dhar[1] Nitesh Bassi[1], KABIR KANG[1] Rashmeet Brar[1] MANJYOT[1] Virendra Singh[1] [1]Punjab institute of liver and biliary sciences, [2]PUNJAB INSTITUTE OF LIVER AND BILIARY SCIENES

Background: Non-invasive strategies to determine portal hypertension are crucial to stratify patient care . Elastography in clinical practice has enabled the early identification of patients with clinically significant portal hypertension (CSPH) and consequently, risk of decompensation and liver-related death. The aim of the present study was to reach the highest predictive accuracy using liver stiffness measurement (LSM), and splenic stiffness measurement (SSM) as different parameters for predicting the development of CSPH, without the need for doing invasive procedures such as endoscopy. Endoscopy was taken as a gold standard for the development of CSPH. We evaluated patients who presented to our institute between March, 2024 and April, 2025 with clinical features of chronic liver disease. These patients underwent elastography for measurement of both liver and splenic stiffness; and endoscopy . We calculated the cut off values of LSM and SSM; beyond which diagnosis of CSPH can be reliably made. **Methods:** It is a cross sectional study . 86 selected patients had undergone both endoscopy and had liver and splenic stiffness measurements; **Methods:** The eligibilty criteria included- all adult patients; age more than 18 years; who underwent endoscopy and fibroscan (for hepatic and splenic stiffness within an interval of maximum 15 days. The data was collected irrespective of the aetiology of the cirrhosis, laboratory parameters or clinical presentation of the patient. Patients with IQR more than 30% were excluded. **Results:** Analysis: The presence of the endoscopy findings were categorized into binary variables 0 and 1; depending upon whether portal hypertensive gastropathy(PHG) was present or absent; irrespective of the grading of the PHG and varices .The LSM and SSM were taken as continous variables. **Results:** Binary logistic regression reveals a positive coeffficient of variables (both liver stiffness and splenic stiffness) with the endoscopy findings. P values are less than .01 implying a stastically significant correlation between increasing stiffness measurements(both liver and splenic) and evidence of portal hypertension. This was also corroborated with odd's ratio which is more

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than 1 in analysing both the variables. Further analysis of the liver stiffness measurement in patients with positive endoscopy findings reveals a median measurement of 42, with 95% confidence interval of liver stiffness varying between 38.08-48.54. The splenic stiffness in these patients had a median value of 50.56 with 95% confidence interval between 43.86-57.26. **Conclusion:** LSM and SSM can be used as independent predictors of CSPH, With increasing LSM and SSM values, the possiblity of portal hypertension increases. Cut off values of 42 KPa and 52 KPa for LSM and SSM can suggest definte portal hypertension; without needing endoscopic correlation. However further studies with larger patient groups would be needed for confirming these findings.

	LIVER STIFFNESS	SPLENIC STIFFNESS
Mean	43.31	50.56
Median	42	52
Mode	75	27.2
Std. Deviation	22.1	25.24
Variance	488.57	637.23
Minimum	4.7	5.7
Maximum	75	98.4
Quartile 1	27.35	28.6
Quartile 2	42	52
Median absolute deviation	16.7	21.1
95% Confidence interval for mean	38.08 - 48.54	43.86 - 57.26
Mean ± Std.	43.31 ± 22.1	50.56 ± 25.24

Disclosures: sandeep kaur toor: Nothing to Disclose, Himanshu Gupta: Nothing to Disclose, Amandeep Singh: Nothing to Disclose, Jahnvi Dhar: Nothing to Disclose, Nitesh Bassi: Nothing to Disclose, KABIR KANG: Nothing to Disclose, Rashmeet Brar: Nothing to Disclose, MANJYOT -: Nothing to Disclose, Virendra Singh: Nothing to Disclose

3084 | LONG TERM ANTIBODY RESPONSE FOLLOWING CHADOX1–NCOV (COVISHIELD) VACCINE IN PATIENTS WITH CIRRHOSIS: A CROSS-SECTIONAL OBSERVATIONAL STUDY

Amandeep Singh[1] Rishav Aggarwal[2] Arka De[3] Mini P Singh[4] Rashmeet Kaur Brar[5] Virendra Singh[5] Simrat Kaur Parmar[5] Tanu kundal[6], [1]Punjab Institute of Liver and biliary sciences, SAS Nagar, [2]Department of Medicine, PGIMER, Chandigarh, [3]Department of Hepatology, PGIMER Chandigarh, [4]Department of Virology, PGIMER, Chandigarh, [5]Punjab Institute of Liver and biliary sciences, SAS Nagar, Punjab, India, [6]Adesh Institute of Medical Sciences, Ambala

Background: Patients with cirrhosis have a higher risk of severe COVID-19 and mortality. WHO recommended booster doses of vaccination in view of Global uncertainties around COVID-19 pandemic, waning of Antibody response and variants of concerns. However, data on long term antibody response and timing of vaccination in patients with cirrhosis is scarce. Hence, we aimed to assess the long-term antibody response following ChAdOx1–nCOV (Covishield) vaccine in patients with cirrhosis. **Methods:** Patients with cirrhosis who attended the Liver clinic at our institute in May to June 2022 were screened using a pre-specified questionnaire. Patients who had completed 2 doses of ChAdOx1-nCOV (with the 2nd dose administered at least 6 months back) and without history of documented COVID-19 infection (pre- or post-vaccination) were tested for antibodies against the spike protein. Seropositive patients were divided into high, moderate, and low antibody responses based on the signal/cut-off. **Results:** Total of 139 patients of cirrhosis who were completely vaccinated with COVID-19 vaccines were screened and 86 patients were enrolled in the study as per the inclusion and exclusion criteria with at least 6 months duration between the 2nd dose of ChAdOx1-nCOV vaccine and the date of sampling. Breakthrough infections were seen in 4.4% patients. Local and systemic adverse events were reported by 25 % and 9% patients with first and second dose respectively. None developed serious adverse events requiring hospitalization. Seroconversion was documented in 83 (96.5%) out of 86 patients. Sub-optimal antibody response was seen in 12(13.9%). No difference was observed in level of antibody response between patients with compensated and decompensated cirrhosis. Antibody titre comparison of 35 patients at 40 days and 6 months of receipt of 2nd dose of ChAdOx1-nCOV vaccine showed that titres after 6 months were on lower side but there was no statistical significance ($p = 0.09$). **Conclusion:** The present study concludes that cirrhosis patients have good long term seropositivity with Covishield vaccine, irrespective of age, gender, aetiology of cirrhosis, comorbidities and severity scores, indicating a good vaccine immunogenicity in this population. However, suboptimal antibody titres in a small subgroup, may indicate the need of an early Covishield booster requirement in cirrhosis patients.

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Table 1. Comparison of patients with suboptimal antibody response and optimal antibody response who were completely vaccinated with Covishield vaccine(N=86)

Characteristics			P-Value#
Demographic characteristics	Suboptimal antibody response (n= 12)	Optimal antibody response (n=74)	
Age (years)*	54.00 ± 10.49	54.26 ± 10.70	0.9385
Sex			
Male– n (%)	11 (91.7)	61 (82.4)	0.6809
Female – n (%)	1 (8.3)	13 (17.6)	
Clinical Characteristics			
Comorbidities present–n (%)	5 (41.7)	30 (40.5)	1.0000
DM – n (%)	4 (33.3)	20 (27.0)	0.7315
HTN – n (%)	0 (0.00)	12 (16.2)	-
Hypothyroidism – n (%)	1 (8.3)	2 (2.7)	0.3666
HCC – n (%)	1 (8.3)	6 (8.1)	1.0000
Etiology of cirrhosis			
Alcohol – n (%)	7 (58.3)	40 (54.0)	0.7824
NASH – n (%)	2 (16.7)	31 (41.9)	0.1189
HCV – n (%)	1 (8.3)	15 (20.3)	0.4505
HBV – n (%)	3 (25.0)	5 (6.8)	0.0785
AIH – n (%	0 (0.0)	3 (4.1)	-
Decompensation present – n (%)	11 (91.7)	56 (75.7)	0.2863
CTP score *			
Pre-vaccination-n (%)	6.08 ± 1.00	5.85 ± 1.13	0.5053
Post- vaccination-n (%)	8.00 ± 1.41	7.12 ± 1.63	0.0820
MELD score*			
Pre-vaccination -	10.25 ± 2.67	9.80 ± 2.65	0.5846
Post- vaccination -	15.92 ± 4.23	13.31 ± 5.51	0.1223
Antibody signal/Cut-off ratio	2.28 ± 1.49	15.83 ± 3.77	<0.001

*Mean ± SD; #p- value calculated using independent sample t-test; DM- Diabetes Mellitus; HTN – Hypertension; HCC – Hepatocellular carcinoma; NASH – Nonalcoholic steatohepatitis; HCV – Hepatitis C Virus; HBV – Hepatitis B Virus; AIH – Autoimmune hepatitis; UGI – Upper Gastro-intestinal; CTP – Child Turcotte Pugh; MELD – Model for end stage liver disease. Antibody signal/Cut-off ratios were estimated by detection IgG antibodies by automated chemiluminescent assay (Orthoclinical Diagnostics) available in the Department of Virology, PGIMER, Chandigarh. Depending upon the signal/cut off ratio, antibody response in seropositive patients was further subcategorized into low (signal/cut-off: 1 to ≤4.62), moderate (signal/cut-off: >4.62 to ≤18.45) and high (signal/cut-off > 18.45). Suboptimal response- Patients with no antibody response and low antibody response. Optimal response will include patients with medium and high antibody response.

Table 2. Comparison of antibody signal/cut off ratios of follow up COVID-19 naïve patients with previous titers (n=35) who were completely vaccinated with Covishield

	Mean titers - present study (n=35)	Mean Titers - previous study (n =35)	P-value#
Antibody signal/Cut-off ratio*	10.3 ± 3.9	14.7 ± 4.9	0.09

*P-value calculated using paired *t*-test; Antibody signal/Cut-off ratios were estimated by detection IgG antibodies by automated chemiluminescent assay (Orthoclinical Diagnostics) available in the Department of Virology, PGIMER, Chandigarh. Depending upon the signal/cut off ratio, antibody response in seropositive patients was further subcategorized into low (signal/cut-off: 1 to ≤4.62), moderate (signal/cut-off: >4.62 to ≤18.45) and high (signal/cut-off > 18.45).

Disclosures: Amandeep Singh: Nothing to Disclose, Rishav Aggarwal: Nothing to Disclose, Arka De: Nothing to Disclose, Mini P Singh: Nothing to Disclose, Rashmeet Kaur Brar: Nothing to Disclose, Virendra Singh: Nothing to Disclose, Simrat Kaur Parmar: Nothing to Disclose, Tanu kundal: Nothing to Disclose

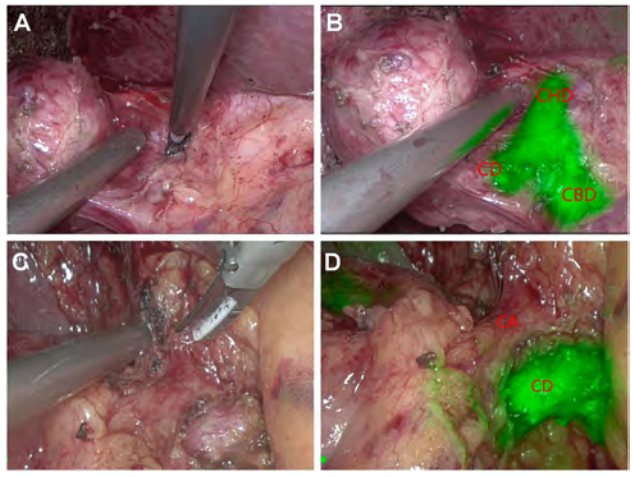
3085 | BALANCING QUALITY TRAINING FOR PRIMARY SURGEONS AND IMPROVED PATIENT OUTCOMES: THE ART OF FLUORESCENCE NAVIGATION IN DIFFICULT LAPAROSCOPIC CHOLECYSTECTOMY – RESULTS: FROM AN ONGOING OPEN-LABEL RANDOMIZED CLINICAL TRIAL

Baojia Zou[1] Luyao Zhang[1] Peiping Li[1] Jiafan Chen[1] Jianzhong He[1] Xialei Liu[1] Zhouying Zheng[1] Xiaopeng Hong[1] Genglong Zhu[1] Jian Li[1] Chaonong Cai[1], [1]The Fifth Affiliated Hospital of Sun Yat-sen University

Background: Difficult laparoscopic cholecystectomy (LC) increases the risk of bile duct injury (BDI), especially in patients with obscured biliary anatomy. This presents a dual challenge: safeguarding patient safety while providing meaningful training opportunities for junior surgeons. Near-infrared fluorescence (NIRF) imaging with indocyanine green (ICG) enables real-time visualization of key biliary structures, offering a unique solution that bridges these two needs. **Methods:** As part of a prospective clinical trial (ChiCTR2400088163), 80 patients undergoing complex LC at the Department of Hepatobiliary Surgery, the Fifth Affiliated Hospital of Sun Yat-sen University were analyzed. Patients were grouped based on whether NIRF (ICG-guided) or standard white-light (WL) imaging was used. The study evaluated the rate and time of intraoperative visualization of the cystic duct (CD), common bile duct (CBD), and common hepatic duct (CHD), along with implications for surgical training. **Results:** NIRF significantly enhanced intraoperative biliary visualization compared to WL:

- CD–CBD junction: 98% vs. 73%, $P = 0.003$
- CHD: 88% vs. 63%, $P = 0.010$
- CD visualization time: 2.0 vs. 7.0 min, $P < 0.001$
- CHD visualization time: 5.0 vs. 8.0 min, $P = 0.009$
- CD–CBD junction visualization time: 4.0 vs. 9.0 min, $P < 0.001$

These improvements not only supported more accurate and confident dissections but also created safer conditions for supervised training of primary surgeons. **Conclusion:** NIRF-guided LC facilitates safer navigation of complex biliary anatomy, significantly reducing operation time and enhancing surgical confidence. Importantly, this approach supports high-quality, real-time training for junior surgeons without compromising patient safety. These interim results from our ongoing clinical trial demonstrate NIRF as a promising strategy to balance surgical education and clinical excellence in hepatobiliary surgery.



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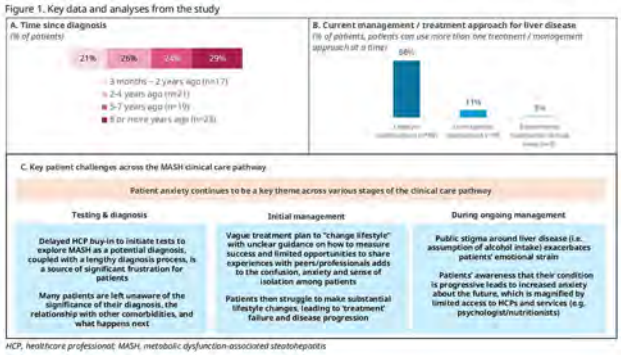
3086 | A QUALITATIVE STUDY EXPLORING THE EXPERIENCES AND UNMET NEEDS OF PATIENTS LIVING WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Ahsan Shoeb[1] Jannie Laursen[1] Nathalie Marcela Eklöf[1], [1]Novo Nordisk A/S

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a chronic, progressive metabolic disease affecting the liver. This study explored the lived experiences of patients with MASH, identifying unmet needs and focusing on understanding their perspectives regarding their clinical care pathway (CCPs). **Methods:** Qualitative data were collected Oct–Nov 2024. Patients with a MASH diagnosis (n = 80 [US (n = 25), France (n = 11), Italy (n = 12), Germany (n = 15), Canada (n = 8), Japan (n = 9]) were enrolled via social media/healthcare professional (HCP) or patient advocacy group referral. The web-assisted telephone interviews were moderated using a semi-structured discussion guide, utilizing open-ended questions. Thematic analysis was used to analyse the data. **Results:** Clinical patient characteristics are shown in Figures 1A–B, with 56% of patients aged 50–69 years, and 60% identifying as female.

MASH diagnoses are delayed, in part, due to low awareness and misattribution of symptoms (abdominal pain, bloating, fatigue, nausea etc.) to other comorbidities. Delayed diagnosis of a progressive condition was associated with increased levels of anxiety amongst patients. Regardless of severity, few patients associated their symptoms with MASH. Patient interactions with HCPs are negatively impacted by perceived stigma and incorrect assumptions of alcohol intake. Delayed access/HCP buy-in to initiate tests exploring potential diagnoses is a source of frustration for patients. Following diagnosis, patients struggle with unclear treatment options and poor communication about the consequences of MASH, resulting in concern, worry and anxiety; few patients feel satisfied when moving into the initial management stage. A lack of psychological support for managing multiple chronic conditions also contributes to high patient anxiety throughout the CCP (Figure 1C). **Conclusion:** This research demonstrates significant unmet needs across MASH CCPs from a patient perspective, including a need for improved patient information, and guidance and support mechanisms from HCPs and the healthcare system. Engaging HCPs with customised education on presentation, diagnosis and management of MASH to support dialogue with patients is essential to drive clarity and reduce patient anxiety.



Disclosures: Ahsan Shoeb: Novo Nordisk: Employee, Novo Nordisk: Stock - publicly traded company, Jannie Laursen: Novo Nordisk: Employee, Nathalie Marcela Eklöf: novo Nordisk: Share holder

3087 | FIB-4 RISK STRATIFICATION MODEL CAN PREDICT LIVER-RELATED OUTCOMES OF MASLD PATIENTS RECEIVING CARE IN NON-SPECIALTY/PRIMARY CARE SETTINGS

Jay Bae[1] Mark Hartman[2] Yuanyuan Tang[1] Arti Mansharamani[3] Belle van Rosmalen[1] Arun Sanyal[4], [1]Eli Lilly and Company, [2]Eli Lilly & Co, [3]Eli Lilly and Company, Indianapolis, IN, USA, [4]Virginia Commonwealth University

Background: The MASLD clinical risk stratification model (Sanyal et al, 2023) represents a simple yet high performing clinical risk stratification tool developed from the TARGET-NASH registry, conducted at hepatology, gastroenterology and endocrinology sites. This study aimed to validate the model in non-specialty/primary care settings. **Methods:** A large electronic health record database linked to claims (Optum Market Clarity, 2003-2020) from all non-long-term care providers was analyzed. MASLD/MASH index diagnosis, overweight/obesity, and liver enzyme tests were required at baseline for inclusion. Patients with a diagnosis of alcoholic liver disease at any time were excluded. Fibrosis-4 (FIB-4) score was calculated using the closest laboratory test results to the index diagnosis, and patients were classified into Class A (FIB-4 < 1.3), Class B (FIB-4 1.3 - 2.6), and Class C (FIB-4 > 2.6).

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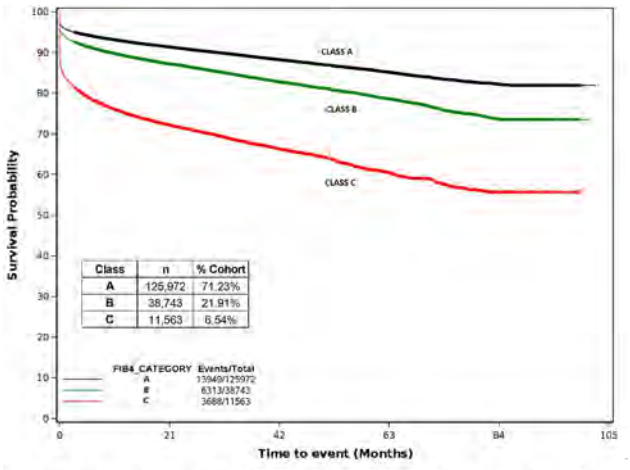
The composite endpoint MASLD progression (defined as occurrence of cirrhosis, hepatic decompensation or liver transplantation by ICD-10 diagnoses) was examined both descriptively and with a Cox proportional hazard model using baseline characteristics (i.e., FIB-4 classes, age, sex, race, body mass index, smoking status, diabetes status, statin use, chronic kidney disease, hypertension, etc.). **Results:** The validation cohort consisted of 176,856 patients with mean follow-up of 3.07 years (total 543,524 patient-years). Mean age was 51.5 years (SD: 14.9), 57% were female, 78% White, 9% African American, 2% Asian, and 10% others/unknown. Distribution of FIB-4 class was A:71.2%; B:21.9%; C:6.5%. Overall, 13.7% experienced one or more liver-related clinical events. The most frequent outcomes were compensated cirrhosis (10.5%) and decompensated cirrhosis (4.7%) with mean times to first occurrence of 18.8 months and 19.7 months, respectively. MASLD progression rate was 11.1% for A, 16.3% for B, and 31.9% for C. The risk of liver outcomes was significantly ($p < 0.001$) increased for both Class B (HR: 1.44, 95% CI: 1.39-1.49) and Class C (HR: 3.16, 95% CI: 3.02-3.30) versus Class A (figure). **Conclusion:** In this non-specialty/primary care database, the FIB-4 based risk classification was a highly significant predictor of progression to liver-related clinical events among patients with MASLD. The model demonstrated consistent performance. The non-invasive risk stratification system is a practical and useful tool for assessing MASLD progression risk in the non-specialty/primary care setting.



Kaplan-Meier curves demonstrating MASLD progression events (occurrence of cirrhosis, hepatic decompensation, or liver transplantation) for patients classified as Class A (FIB-4 <1.3), Class B (FIB-4 1.3 - 2.6), and Class C (FIB-4 >2.6) at index diagnosis.

Disclosures: Jay Bae: Eli Lilly and Company: Employee, Mark Hartman: Eli Lilly and Company: Employee, Eli Lilly and Company: Stock - publicly traded company, Yuanyuan Tang: Nothing to Disclose, Arti Mansharamani: Nothing to Disclose, Belle van Rosmalen: Eli Lilly: Employee, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor

3088 | TRENDS IN HEPATITIS C VIRUS (HCV) ANTIBODY SCREENING AND POSITIVITY RATES, 2020-2024: ANALYSIS OF >35 MILLION US ADULTS USING REAL-WORLD DATA

Isabelle Winer[1] Monica Silver[1] Alina Bogdanov[1] Natalia Coenen[1] Maryam Ajose[1] Janna Manjelievskaia[1],
[1]Veradigm

Background: With HCV prevalence on the rise in the US, clinical practice guidelines were updated in March 2020 to recommend universal screening, thus marking a change from the former risk-based and birth-cohort screening approaches. Despite updated guidelines, HCV screening rates in the US remain low. We sought to understand the real-world trends in HCV antibody screening in a general US population born on or after 1966 (post 'Baby Boomer' generation) between 2020-2024. **Methods:** Adults (18+), born on or after 01/01/1966, with at least 1 preventive healthcare visit between March 2, 2020-December 31, 2024 were identified in the Veradigm Network EHR database linked to healthcare claims from Komodo Health. Presence of HCV antibody screening and proportion of positive/reactive antibody HCV tests were evaluated by year (2020-2024), overall and by birth cohort (Gen X (1966-1979), Millennials (1980-1996), Gen Z (1997-2012)). Demographic characteristics, including social determinants of health (SDOH), were evaluated during patient history or as of earliest visit date. **Results:** A total of 35,975,646 adult patients were identified as having a preventive healthcare visit. Among them, 1,850,836 had evidence

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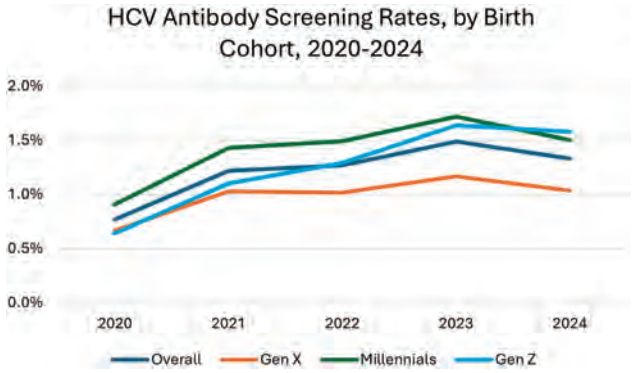
of HCV antibody screening, reflecting an HCV screening rate of 5.1%. The majority of those screened were female (69%). Among 258,461 patients with documented access to care issues, the HCV screening rate was 20.3%. The proportion of adults with HCV screening generally increased from 2020-2024 (Figure 1). Among those screened, a majority were in the Millennial birth cohort (51%), followed by Gen X (32%), and Gen Z (17%). Among HCV tests containing a valid result, 2.6% were positive/reactive overall, with the highest proportion among Millennials (2.9%), followed by Gen X (2.8%), and Gen Z (0.9%). Positivity rates remained fairly stable from 2020-2023 (2.7%-3.0%) with a minor decrease in 2024 (1.5%). **Conclusion:** Our real-world study of adults in a large ambulatory EHR database linked to claims found an overall HCV screening rate of 5.1%. The substantially higher screening rate (20.3%) among those with access to care issues may be reflective of patients perceived to be at higher risk for HCV, or potential confounding between documentation of SDOH factors and likelihood of HCV screening. Continued surveillance of HCV among the general adult population is important in understanding the prevalence of disease over time.



Disclosures: Isabelle Winer: Nothing to Disclose, Monica Silver: Nothing to Disclose, Alina Bogdanov: Nothing to Disclose, Natalia Coenen: Nothing to Disclose, Maryam Ajose: Nothing to Disclose, Janna Manjelievskaia: Nothing to Disclose

3089 | LIVER DISEASE ELIMINATION: WUWEI MEDICAL CONSORTIUM OF LIVER DISEASE SPECIALISTS MODEL

Fengmei Wang[1] Wenhua Zhang[1] Haitao Tang[1] Wenling Jia[1] Chunhui Liang[1], [1]Wuwei Academy of Medical Sciences

Background: To study the impact of the medical consortium on the level of prevention and treatment of liver disease in Wuwei City and surrounding areas of Gansu Province. **Methods:** Since 2018, the Hepatobiliary Disease Center of Wuwei Academy of Medical Sciences started to establish a medical consortium of liver disease specialists in Wuwei City and surrounding areas of Gansu province and formed a management model for liver disease patients: 1. We helped county-level hospitals to establish hepatology departments and we appointed a liver disease specialist from a tertiary hospital as the director of the hepatology department for these hospitals. 2. Liaison specialists were selected by the rural health centers to conduct follow-up work for chronic liver disease patients. 3. A network platform for remote consultation has been established. 4. Hepatology department of tertiary hospitals organized academic activities, training, and patient education activities every year. 5. Established a green referral channel for two-way communication and referral between superior and subordinate medical institutions. **Results:** Through the medical consortia, we have set up hepatology departments in 9 county-level hospitals in Wuwei and surrounding areas. We have also trained 27 liver disease specialists and 54 liver disease specialist nurses to provide specialized diagnosis and treatment for liver disease patients. At the same time, 14 rural health centers were included in the medical consortium. In the past 5 years, a total of 10 academic meetings and training sessions on liver disease were held with 2,324 participants. A total of 22,280 chronic liver disease patients have been followed up. The number of outpatients at the Hepatobiliary Disease Center,Wuwei Academy of Medical Sciences has increased from 11,544 in 2017 to 21,373 in 2023, and the number of hospitalized patients has increased from 1,987 in 2017 to 3,337 in 2023. **Conclusion:** The medical consortium of liver disease specialists was first established and operated in Wuwei City, Gansu Province. The management mode of liver disease patients has been gradually formed under the situation of the medical consortium.The prevention and treatment network of liver disease specialists has been gradually formed there, laying the foundation for achieving the goal of eliminating viral hepatitis by 2030.

Disclosures: Fengmei Wang: Nothing to Disclose, Wenhua Zhang: Nothing to Disclose, Haitao Tang: Nothing to Disclose, Wenling Jia: Nothing to Disclose, Chunhui Liang: Nothing to Disclose

3090 | ACCESSIBILITY AND EFFECTIVENESS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR (PPAR) AGONISTS FOR PRIMARY BILIARY CHOLANGITIS (PBC): A REAL-WORLD EXPERIENCE AT A TERTIARY ACADEMIC MEDICAL CENTER HEPATOLOGY CLINIC

Jane Giang[1] Alison Baron[2] Alfred Barritt IV[3] Sasha Deutsch-Link[4] Oren Fix[5] Vikki Metheny[5] Andrew Moon[2]

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Neil Shah[5] Lindsay Yoxheimer[3] Hersh Shroff[4], [1]UNC Healthcare, [2]University of North Carolina, [3]University of North Carolina Health, [4]UNC Chapel Hill, [5]University of North Carolina at Chapel Hill

Background: Peroxisome proliferator-activated receptor (PPAR) agonists, elafibranor and seladelpar, were recently approved as second-line agents for primary biliary cholangitis (PBC) in ursodeoxycholic acid (UDCA) non-responders. This study provides real-world data on medication accessibility and efficacy at a tertiary academic medical center hepatology clinic. **Methods:** A 10-month, single-center retrospective chart review was conducted for patients with PBC who were prescribed elafibranor or seladelpar from 6/2024-3/2025. We defined access as successful initiation of treatment, and we assessed the steps required to attain access, including insurance prior authorizations (PAs), denials and appeals. Effectiveness was measured by changes in relevant biochemical markers. **Results:** A total of 37 patients were prescribed elafibranor (n = 14) or seladelpar (n = 23). 89% were female and the median age was 61 years. Payor types included commercial (n = 14), Medicare (n = 16), Medicaid (n = 3), and manufacturer patient assistance program (n = 4). All 37 patients were on UDCA. 30% of patients (n = 11) were on other second-line PBC therapies at the time PPAR agonist therapy was considered. A majority of these (n = 8) discontinued the second-line agent upon starting the PPAR agonist. Treatment was approved in 90% (n = 33) of patients, of whom 27 (73%) required PA, 5 (14%) did not require PA, and 1 (3%) was denied but successfully overturned after appeal. Among the four patients who did not access treatment, two were denied for not being on UDCA for ≥ 1 year and two had insurance plans where PPAR agonists were excluded from coverage. At the time of chart review, 32 patients (86.5%) had started PPAR agonist treatment, with a median time from prescription date to treatment initiation of 16 days. Median (IQR) baseline lab values included: AST 37 (27-43) U/L, ALT 27 (17-57) U/L, total bilirubin (TB) 0.6 (0.4-1.1) mg/dL, and alkaline phosphatase (ALP) 229 (193-296) U/L. In 25 patients with follow-up labs (obtained an average of 71 days after treatment initiation), median (IQR) follow-up ALP was 149 (120-183) U/L. The median change in ALP per 30 days of PPAR agonist treatment was –42.6 U/L. **Conclusion:** In our cohort, despite their novelty and specialty medication status, PPAR agonists were highly accessible with relatively low administrative burden. Consistent with clinical trials, treatment was associated with rapid improvements in relevant biochemical markers.

Table 1. Baseline characteristics and follow-up results

	Total (n=37)
Age, median (IQR) – years	61 (54 –67)
Gender, # (%)	
Female	33 (89%)
Prescriptions, # (%)	
Elafibranor	14 (38%)
Seladelpar	23 (62%)
Patients on UDCA, # (%)	37 (100%)
Second-line treatments*	11 (30%)
Obeticholic acid (OCA)†	7 (n=5 discontinued)
Fenofibrate†	5 (n=4 discontinued)
Insurance, # (%)	
Commercial	14 (38%)
Medicare	16 (43%)
Medicaid	3 (8%)
Manufacturer	4 (11%)
Fibrosis stage, # (%)	
F0-1	12 (32%)
F2	9 (24%)
F3	11 (30%)
F4	5 (14%)
Approval Status, # (%)	
Approved with PA	27 (73%)
Approved without PA	5 (14%)
Approved after Appeal	1 (3%)
Denied	2 (5%)
Not Covered	2 (5%)
Time from Rx to Start, median (IQR) – days	16 (12 – 27)
Baseline Labs, median (IQR)	
AST (U/L)	37 (27 – 43)
ALT (U/L)	27 (17 – 57)
T. Bili (mg/dL)	0.6 (0.4 - 1.1)
ALP (U/L)	229 (193 – 296)
Follow-up Labs^, median (IQR)	
AST (U/L)	33 (25 – 37)
ALT (U/L)	21 (15 – 41)
T. Bili (mg/dL)	0.5 (0.4 - 0.8)
ALP (U/L)	149 (120 – 183)
Change in labs per 30 days of PPAR agonist treatment, median (IQR)	
Δ AST	-2.1 (-6.0 to +2.1)
Δ ALT	-1.9 (-10.8 to +0.6)
Δ T. Bili	0.0 (-0.1 to 0.0)
Δ ALP	-42.6 (-61.7 to -22.9)

* At time of decision to initiate PPAR-agonist
† One patient was on both OCA and fenofibrate and discontinued both
^ Obtained an average of 71 days after treatment initiation

Disclosures: Jane Giang: Nothing to Disclose, Alison Baron: Nothing to Disclose, Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant, Target-RWE: Consultant, Madrigal Pharmaceuticals: Consultant, Merck (Any division): Consultant, Boehringer Ingleheim: Consultant, Sasha Deutsch-Link: Nothing to Disclose, Oren Fix: Nothing to Disclose, Vikki Metheny: Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant, Neil Shah: GSK: Advisor, Ipsen: Advisor, GSK: Consultant, Ipsen: Consultant, Lindsay Yoxheimer: Nothing to Disclose, Hersh Shroff: Nothing to Disclose

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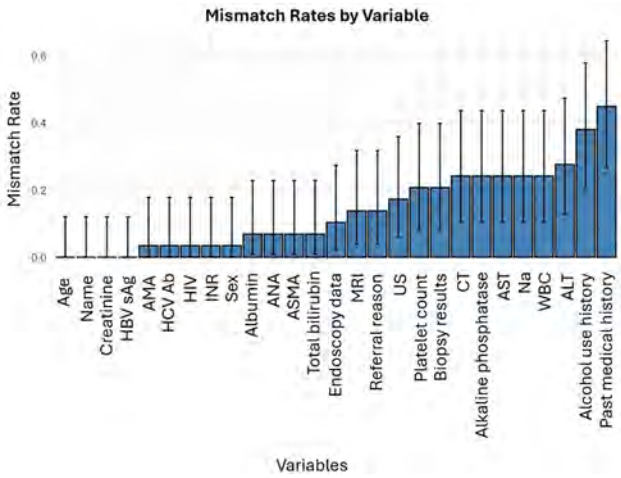
3091 | CHATGPT FOR CLINICAL DATA EXTRACTION: A COMPARISON WITH MANUAL REVIEW OF HEPATOLOGY REFERRAL PACKETS

Vinathi Polamraju[1] Jason Pan[2], [1]Washington University School of Medicine, [2]Washington University in St. Louis

Background: Large language models (LLMs) such as ChatGPT are increasingly being evaluated for their potential to automate clinical data extraction. This retrospective study from a high-volume hepatology referral center aimed to compare manual versus institutional ChatGPT-based extraction across structured and unstructured clinical fields in referral packets. **Methods:** Twenty-nine consecutive referral packets were reviewed. Manual data extraction was performed and compared to ChatGPT-based extraction using a uniform prompt. All extractions were conducted using a secured sandbox version of ChatGPT-4o that is HIPAA-compliant. Variables included numeric fields (e.g., age, sex, lab values) and string fields (e.g., past medical history, alcohol use history, imaging findings). A mismatch was defined as a significant discrepancy between manual and ChatGPT-extracted data. For numeric values, mismatches were defined as deviations >0.5 units. String fields were first preprocessed via lowercasing, punctuation/stopword removal, de-duplication, and alphabetic sorting. A tuning experiment identified 0.25 as the optimal threshold. As such, for string fields, a normalized Levenshtein distance >0.25 indicated mismatch. Mismatch rates were calculated per variable as mismatches divided by total entries (29). **Results:** Referral packets ranged 6–242 pages (mean = 63.86). Mismatch rates ranged 0–0.482 (mean = 0.150). Structured fields (e.g., age, name, Cr) showed near-perfect agreement. Highest mismatch rates were in semi-structured fields: past medical history (0.448), alcohol use history (0.379), ALT (0.276) (Figure 1). When ChatGPT was asked to extract only these variables individually, mismatch rates dropped: past medical history (0.207), alcohol use (0.138), ALT (0.138), indicating improved accuracy with focused prompts. Referral packet length correlated with mismatch rate ($r = 0.673$, $p < 0.001$). Linear regression revealed each 1-page increase in referral length was associated with a 0.0016 increase in mismatch rate ($R^2 = 0.453$). Formatting inconsistencies, data redundancy, and fragmented information contributed to mismatches. **Conclusion:** ChatGPT performs well with structured data and improves on unstructured fields when queried individually. Longer, more complex documents are associated with higher mismatch rates. Hybrid methods combining targeted LLM queries with preprocessing may enhance automation in clinical data workflows.



Disclosures: Vinathi Polamraju: Nothing to Disclose, Jason Pan: Nothing to Disclose

3092 | CHARACTERIZING HEALTHCARE COSTS IN MEDICARE BENEFICIARIES WITH A NEW DIAGNOSIS OF NON-CIRRHOTIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Nipun Atreja[1] Francis Lobo[1] Yestle Kim[1] Dominic Nunag[2] Andrew Epstein[2] Zachary Marcum[2], [1]Madrigal Pharmaceuticals, [2]Medicus Economics

Background: Current studies on the economic burden of non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) are limited by reporting average costs, without examining variation across the cost distribution, and have focused on short-term (annual) costs. **Methods:** We conducted a retrospective cohort study using a full sample of Medicare FFS beneficiaries aged ≥ 65, continuously enrolled for any 4-year period between 01/01/2016–12/31/2023 (1-year baseline, 3-year follow-up). MASH (ICD-10-CM: K75.81) was identified by ≥ 1 inpatient or ≥ 2 outpatient claims (any position); those with cirrhosis codes 360 days before or 90 days after the index date were excluded. Mean total healthcare costs per beneficiary were calculated over the 3-year follow-up and adjusted to 2023 dollars. Beneficiaries were stratified into quartiles (Q) based on total costs. Baseline characteristics were compared across quartiles using chi-square tests for categorical variables and ANOVA tests for continuous variables. **Results:** Among 26,927 beneficiaries (mean age, 71.8 years) with a new diagnosis of non-cirrhotic MASH, mean (standard deviation [SD]) total 3-year healthcare costs were $67,094 ($88,775) and were highly skewed (mean [SD], Q1: $10,951 [$4,410]; Q2:

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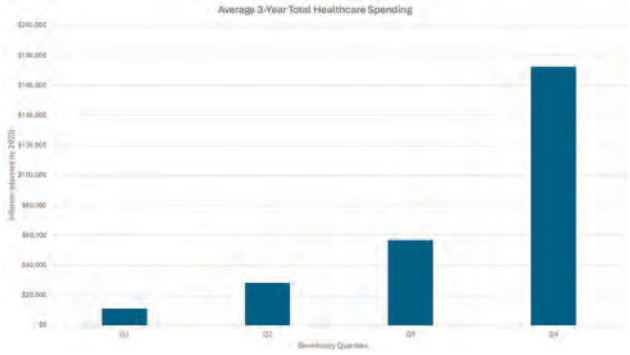
$28,275 [$5,891]; Q3: $56,730 [$11,559]; Q4: $172,437 [$124,406]; Figure). Beneficiaries in the highest-spending quartile (Q4) were responsible for 64% of total spending, while those in the lowest-spending quartile (Q1) contributed 4%. Beneficiaries in the highest-spending quartile (Q4) were more likely to be dual eligible for Medicare/Medicaid coverage compared to those in the lower-spending quartiles ($P < 0.001$). Compared to those in the lower-spending quartiles (Q1–Q3), beneficiaries in the highest-spending quartile (Q4) also had more medications, more GLP-1 agonist use (Q4: 11.2% vs. Q1: 0.5%), greater prevalence of hospitalization, and greater comorbidity, all measured in the baseline period ($P < 0.001$ for all). **Conclusion:** In Medicare FFS, total healthcare costs in the 3 years after a new diagnosis of non-cirrhotic MASH are high overall and highly concentrated, with a quarter of beneficiaries accounting for 64% of total spending. Baseline characteristics, including dual-eligibility status and comorbidity, differed across cost quartiles. Early identification and treatment of MASH in the highest-cost patients stand to generate substantial cost savings for healthcare payers.



Disclosures: Nipun Atreja: Madrigal Pharmaceuticals: Employee, Immunovant: Employee, Bristol Myers Squibb: Employee, Francis Lobo: Madrigal Pharmaceuticals: Employee, Yestle Kim: Nothing to Disclose, Dominic Nunag: Nothing to Disclose, Andrew Epstein: Nothing to Disclose, Zachary Marcum: Nothing to Disclose

3093 | SHIFTING PATTERNS IN LIVER BIOPSY INDICATIONS AND DIAGNOSES: A RETROSPECTIVE COMPARISON BETWEEN TWO TIME PERIODS

Fani Karapanagiotidi[1] Emmanouil Sinakos[1] Anastasia Fotiadou[2] Spiros Papadopoulos[3] Evangelos Akriviadis[1] Ioannis Goulis[1] Prodromos Hytiroglou[2], [1]Aristotle University of Thessaloniki, Hippokratio General Hospital, [2]Aristotle University of Thessaloniki, [3]Hippokratio General Hospital

Background: The role of liver biopsy is perceived to have lost part of its central role in the diagnostic evaluation of liver diseases. Advances in antiviral treatments, the increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), and the widespread use of non-invasive fibrosis assessment tools may have contributed to this shift. This study aimed to assess potential changes in the use of liver biopsy across two distinct time periods. **Methods:** This was an observational, single-center, retrospective study. We reviewed liver biopsy indications and outcomes in patients, who underwent a liver biopsy during two 5-year periods: 2010–2014 (Group A) and 2020–2024 (Group B). Patients with malignant neoplasms were excluded. Data recorded included age (> 16 years), sex, liver enzyme levels, prior liver transplant, referral indication, histological diagnosis and fibrosis stage. Statistical analysis was performed using R software, with Mann-Whitney U, Student's t-test, chi-square, and logistic regression applied as appropriate. **Results:** A total of 725 liver biopsies were analyzed—465 in Group A (50.5% male, median age 51 years) and 260 in Group B (48.5% male, median age 54 years). A prior biopsy was noted in 150 cases (127 in Group A vs. 23 in Group B, $p < 0.05$), while liver transplantation was reported in 51 patients (35 vs. 16, $p > 0.05$). A significant decrease in the mean annual number of biopsies was observed in Group B (93 vs. 52, $p < 0.05$), especially for biopsies performed solely for disease staging (204 vs. 30, $p < 0.05$). Histological diagnoses in Group A included: chronic hepatitis B (25.2%), MASLD (17.4%), non-specific histological changes (11%), primary biliary cholangitis (10.7%), chronic hepatitis C (8.8%), autoimmune hepatitis (5.4%), drug-induced liver injury (4.7%), chronic cholangiopathies (4.3%) and others (12.3%). In Group B: MASLD (32.4%), non-specific histological changes (15.9%), autoimmune hepatitis (13.1%), chronic cholangiopathies (6.6%), drug-induced liver injury (5.4%), primary biliary cholangitis (5.4%), and others (21.2%). A significant reduction in biopsies for viral hepatitis was observed in Group B ($OR = 0.06$, 95% CI: 0.03–0.12, $p < 0.001$), alongside an increase in MASLD-related biopsies ($OR = 1.91$, 95% CI: 1.35–2.70, $p < 0.001$). Advanced fibrosis (F3–F4) was more common in Group B ($OR = 1.48$, 95% CI: 1.07–2.06, $p = 0.019$), although significance was lost after adjustment for age, sex, and diagnosis ($p = 0.10$). **Conclusion:** This study highlights a significant reduction in the total number of liver biopsies between the two time periods, with a marked decline in biopsies for viral hepatitis and a notable increase in those related to MASLD in the more recent period. Biopsies conducted solely for fibrosis staging also significantly decreased. The role of liver biopsy seems to gradually change mainly due to shifts in disease epidemiology and advances in non-invasive diagnostics.

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3094 | AVOIDING THE IMPACT OF INACTION: HOW TO MAXIMIZE PROGRESS TO HCV ELIMINATION IN THE UNITED STATES

Nancy Reau[1] Zach Baldwin[2] Barbra Cave[2] Yuri Sanchez-Gonzalez[2] Mark Sulkowski[3], [1]Rush University Medical Center, [2]AbbVie Inc., North Chicago, IL, USA, [3]Johns Hopkins Medicine

Background: Only twelve countries — ten of them high-income — are on track toward the World Health Organization (WHO) global targets for eliminating hepatitis C virus (HCV). With the current diagnosis and treatment levels, the U.S. is not expected to achieve elimination targets before 2050. We explore clinical, economic, and societal benefits associated with alternative strategies for HCV elimination in the U.S. using a model populated with real-life data. **Methods:** A previously published disease burden and economic impact model was populated with data from published literature. Clinical outcomes included end-stage liver disease (ESLD) and deaths; economic outcomes included healthcare costs from HCV screening, treatment, and liver-related and extrahepatic complications; societal outcomes included new infections, net present value (value of quality-adjusted life-years gained net of screening and treatment costs), and return on investment (ROI, incremental medical savings over screening and treatment costs). Three scenarios were projected over 2025-2034: (1) Base Case following the status quo of current treatment and diagnosis levels in the U.S., (2) Elimination scenario defined by the minimum level of annually diagnosed and treated chronic viremic cases needed to reach the WHO's 2030 elimination goals (starting in 2026), and (3) Optimized Elimination scenario augmenting the latter Elimination scenario by diagnosing 90% of incident acute cases of HCV and treating 80% of those diagnosed. **Results:** The Base Case scenario would incur $160.6 billion in total costs and lead to 1.2 million new infections and 9,735 deaths over 2025–2034. The Elimination scenario would require annually diagnosing 557,000 and treating 593,000 chronic cases starting in 2026 to save $41.3 billion in total costs compared to the Base Case. This would avoid 668,000 new infections and 6,924 deaths for a net present value of $27 billion. The Optimized Elimination scenario would achieve the highest total cost savings of $46 billion and lead to the greatest reduction in new infections (704,000) and deaths (6,991) for a net present value of $29.5 billion. **Conclusion:** An optimized HCV elimination strategy requiring treatment at first diagnosis regardless of HCV chronicity can maximize clinical, economic, and societal benefits. The implementation of test-and-treat models of care is needed to achieve these required levels of diagnosis and treatment and meet 2030 elimination goals.

Table 1. Clinical, Economic, and Societal Outcomes of HCV Elimination Scenarios

	Base case	Elimination	Optimized Elimination
Cumulative new cases (2025–2034)			
Decompensated cirrhosis	6,861	1,879	1,835
HCC	13,074	3,778	3,686
Liver transplant	1,141	363	359
Total ESLD averted (vs. base case)	*Comparator*	*15,055*	*15,196*
Deaths	9,735	2,811	2,744
Total deaths averted (vs. base case)	*Comparator*	*6,924*	*6,991*
Cumulative incident cases (2025–2034)			
Incident cases of acute HCV	1,188,239	520,060	483,902
Incident cases averted (vs. base case)	*Comparator*	*668,179*	*704,337*
Treatment of acute HCV infections (2025–2034)			
Acute HCV infections treated	0	0	252,776
Acute HCV infections not treated	1,188,239	520,060	230,916
Cumulative costs - $ (2025–2034)			
Total spending on liver-related complications	7,250,945,050	2,789,036,412	2,574,970,931
Total spending on extra-hepatic complications	121,596,508,885	44,268,273,866	40,374,940,180
Total spending on HCV treatment	30,099,219,147	67,625,568,823	62,885,128,964
Total spending on HCV screening	1,627,897,970	4,578,908,295	4,501,987,879
Additional cost to reach acute HCV screening target	–	–	4,527,814,421
Total spending on HCV	160,574,571,053	119,261,487,396	114,554,822,378
Total costs saved (vs. base case)	*Comparator*	*41,292,083,657*	*46,019,748,675*
Societal cost (2025–2034)			
Cumulative QALYs gained	*Comparator*	325,344	356,502
Incremental cost-effectiveness ratio - $/QALY	*Comparator*	-126,532	-129,087
Net present value of HCV care - $	*Comparator*	27,011,195,308	29,507,336,652
Return on investment	*Comparator*	111.2%	120.0%

ESLD, End-stage liver disease; QALY, Quality-adjusted-life-years

Disclosures: Nancy Reau: Gilead: Grant/Research Support, eiger: Grant/Research Support, abbott: Consultant, Arbutus: Consultant, Gilead: Consultant, VIR: Consultant, Salix: Consultant, Salix: Grant/Research Support, AbbVie: Grant/Research Support, VIR: Grant/Research Support, Zach Baldwin: Nothing to Disclose, Barbra Cave: AbbVie: Employee, Yuri Sanchez-Gonzalez: Nothing to Disclose, Mark Sulkowski: Nothing to Disclose

3095 | INSIGHTS FROM THE ELPA EUROPEAN LIVER SCREENING WEEK 2024

Beatrice Credi[1] Richard Hall[2] Veronika Vsetickova[1] Marko Korenjak[3] Milan Mishkovikj[4] Jacques Schuurman[5] Lydie Moreaux[5] Julie Odienne[5], [1]European Liver Patients' Association - ELPA, [2]European Liver Patients' Association - ELPA, Liver4Life, [3]European Liver Patients' Association - ELPA, Slovenija Hep, [4]European Liver Patients' Association - ELPA, Hepar Centar Bitola, [5]European Liver Patients' Association - ELPA, SOS Hépatites Champagne-Ardennes

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Background: The European Union faces a growing rise in MASLD and MASH, conditions characterised by the accumulation of excess fat in liver cells. They are at a heightened risk of liver cancer. This project aimed to raise awareness of early liver disease detection using portable transient elastography (TE) in community settings. **Methods:** In October 2024, ELPA Members Liver4Life and SOS Hépatite testing vans offered TE scans to European Parliament staff and the public over 5 days. ELPA representatives engaged MEPs and sent invitations to promote the event. The vans were outside the main entrance with specific messaging placed on the vans. The TE devices were managed by trained operators, including some Belgian HCPs. A brief intervention on lifestyle was used when a high Controlled Attenuation Parameter (CAP) reading was identified. The same was used if a high stiffness reading was identified paired with a self-referral letter for medical follow-up. Participants also completed an anonymous questionnaire assessing iver health. **Results:** The total number of completed and recorded TE examinations over the 5 days was 309 paired with the same number of questionnaires. These were all adults: 165 men and 144 women. Of the total examinations, 30 people (9.7%) had stiffness readings in excess of 7.1Kpa, and these people were given self-referral letters after brief intervention advice. The highest stiffness reading over the 5 days was 12.4 Kpa. The study also identified 67 people (22%) with a CAP reading of 275 or higher (UK criteria) and 181 people (59%) with a CAP reading of 225 or higher (Belgium criteria). Everyone with a CAP score of 225 or greater was given brief intervention lifestyle advice.The average age of people who completed the examinations was 44.8 years old. The average weight was 74.8 kg, height was 169.2 cm, and BMI was 26.1. 40 people had a BMI higher than 30 (9.7%).99 people (32%) stated that they were worried their liver could be damaged, and the main reasons given were: 55 (17.7%)overweight, 50 (16.1%) thought they drank too much, and 23 (7.4%) thought they may have an auto-immune condition. There was no option to select more than a single primary reason.38 people (12.3%) stated that they drank alcohol on 4 or more days per week, 47 people (15.2%) reported high bloodpressure, and 75 people (24.2%) reported a stress level of 7 out of 10 or higher, and 77 people (24.9%) had relied onsubstances (alcohol, caffeine or medication) to manage their stress level. **Conclusion:** This year's larger cohort showed similar results to last year, with more people than expected having raised CAP readings under both criteria. The lack of agreement on criteria may lead to differing care for similar patients. Most with high CAP readings were unaware they had fat in the liver, though many suspected it due to their lifestyles but hesitated to see the results. These findings highlight the urgent need for public health action to raise awareness.

Disclosures: Beatrice Credi: Nothing to Disclose, Richard Hall: Nothing to Disclose, Veronika Vsetickova: Nothing to Disclose, Marko Korenjak: Nothing to Disclose, Milan Mishkovikj: Nothing to Disclose, Jacques Schuurman: Nothing to Disclose, Lydie Moreaux: Nothing to Disclose, Julie Odienne: Nothing to Disclose

3096 | ASSOCIATION BETWEEN PRURITUS AND HEALTHCARE UTILIZATION AND COSTS AMONG INDIVIDUALS WITH PRIMARY BILIARY CHOLANGITIS IN THE UNITED STATES

Robert Gish[1] Michel Mendler[2] Edward Mena[3] Chong Hoon Kim[4] C. Fiorella Murillo Perez[4] Yi Pan[5] Mihail Samnaliev[5] Diane Ito[5] Maria Agapova[4], [1]Robert G Gish Consultants LLC, [2]California Liver Research Institute, [3]California Liver Reasearch Institiute, [4]Gilead Sciences, [5]Stratevi

Background: Pruritus is a prevalent, debilitating but under-prioritized symptom of primary biliary cholangitis (PBC). This study assessed the impact of pruritus on healthcare resource utilization (HCRU) and costs among individuals with PBC in the US. **Methods:** A retrospective cohort study was conducted using US claims and laboratory data from Komodo's Healthcare Map between September 1, 2017 and September 30, 2023. Cases (PBC with pruritus) were indexed on a random medical encounter with a pruritus diagnosis code; controls (PBC only) were indexed on a random encounter without pruritus. Subgroup analyses required pruritus treatment (sertraline, naltrexone, cholestyramine, cholestipol, rifampin, colesevelam, hydroxyzine or diphenhydramine) within ± 90 days of the index date. Eligibility included age $>=18$, continuous enrollment for $>=12$ months pre- and post-index date, excluding patients receiving obeticholic acid during baseline. Negative binomial models estimated HCRU rate ratios, and linear regression models estimated incremental all-cause total costs (2024 USD) associated with pruritus over the 12-month post-index period, adjusting for baseline demographics and clinical characteristics. **Results:** 10,077 patients with PBC and pruritus and 41,957 controls (PBC only) were identified. Most were female (85.9%), over 65 years old (54.3%) and enrolled in Medicare (57.2%). At baseline, 16.0% had depression, 8.6% had sleep disorders and 2.3% had dementia. Adjusted HCRU rates were significantly higher in the pruritus compared to the control group, with rate ratios of 1.69 (inpatient), 1.36 (outpatient), 1.65 (emergency room), and 1.44 (prescription counts), all $p < 0.001$. Total regression-adjusted average 1-year healthcare costs were $39,949 and $25,695 in the pruritus and control group, respectively with an incremental cost of

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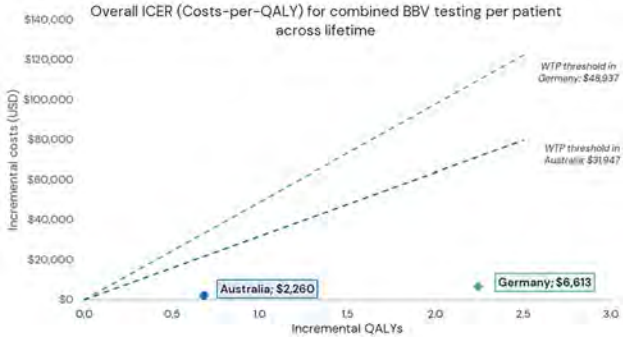
$14,254 ($p < 0.001$) associated with pruritus. In the subgroup analysis, 3,043 cases and 21,957 controls were identified. Estimates associated with pruritus were more pronounced in the subgroup analysis, with rate ratios of 2.38 (inpatient), 1.50 (outpatient), 2.06 (emergency room), and 2.04 (prescription counts), and incremental regression-adjusted costs of $27,669 (all $p < 0.001$). **Conclusion:** In a real-world study of patients with PBC, pruritus was a significant contributor to HCRU and costs. These findings highlight the need for effective management and novel therapies to alleviate pruritus and reduce its associated clinical burden and costs.

Disclosures: Robert Gish: please see full disclosures document: Consultant, Michel Mendler: Nothing to Disclose, Edward Mena: Nothing to Disclose, Chong Hoon Kim: Gilead Sciences, Inc.: Employee, C. Fiorella Murillo Perez: Nothing to Disclose, Yi Pan: Nothing to Disclose, Mihail Samnaliev: Nothing to Disclose, Diane Ito: CymaBay: Consultant, Gilead Sciences: Consultant, Maria Agapova: Nothing to Disclose

3097 | COST-EFFECTIVENESS OF EMERGENCY DEPARTMENT OPT-OUT BBV TESTING TO ADVANCE ELIMINATION TARGETS FOR VIRAL HEPATITIS AND HIV TRANSMISSION: TALES FROM OPPOSITE CORNERS OF THE WORLD

Joseph Doyle[1] Jürgen Rockstroh[2] Phillip Keen[3] Valerie Delpech[4] Louise Evans[5] Hartmut Stocker[6] Laurel Bates[7] Yixuan Ma[7] Andrea Polokaova[7] Elisabeth Adams[7] James Jarrett[8] Murad Ruf[9], [1]Department of Infectious Diseases, Alfred Health and Monash University, Australia, [2]Department of Internal Medicine, University Hospital Bonn, Bonn, Germany, [3]The Kirby Institute, UNSW Sydney, Australia, [4]North Coast Population and Public Health Directorate, Coffs Harbour, New South Wales, Australia, [5]Department of Clinical Immunology, Liverpool Hospital, NSW and the University of New South Wales, [6]Department of Infectious Diseases, St. Joseph Krankenhaus, Berlin, Germany, [7]Aquarius Population Health, London, United Kingdom, [8]Global Health Economics and Outcomes Research, Gilead Sciences Europe, London, United Kingdom, [9]Public Health, Medical Affairs, Gilead Sciences Europe, London, United Kingdom

Background: In Germany and Australia, despite advances in meeting national viral hepatitis elimination targets, an estimated 80% and 31% of Hepatitis B (HBV) and 63% and 16% of Hepatitis C (HCV) infections, respectively, remain undiagnosed. Additionally, 10% and 8% of HIV infections are undiagnosed. European and US study results demonstrate the impact of opt-out blood-borne virus (BBV) testing in emergency departments (ED) in high-prevalence areas. While Australia has piloted testing in EDs, the approach has not been widely adopted. In Germany, there is no systematic BBV testing in EDs. Our study assessed the potential health and economic value of opt-out combined BBV (HBV, HCV, HIV) testing in high-prevalence areas. **Methods:** We developed a hybrid cost-effectiveness model based on defined published clinical pathways to compare projected outcomes of opt-out BBV testing with current testing in ED as standard of care (SoC). A decision tree simulated testing and linkage to care (LTC) for ED attendees requiring blood tests who do not opt out; a Markov model estimated long-term outcomes. Publicly available country-specific parameters informed the model and were supplemented with international literature and national expert opinion. We used a national health service perspective over a lifetime. Primary outcomes were the number of new diagnoses, LTC, quality-adjusted life years (QALYs) and healthcare costs, converted to USD. **Results:** ED opt-out testing resulted in 82 incremental new BBV diagnoses per 10,000 attendees in Germany and 32 in Australia compared to SoC, of which over 85% were active chronic viral hepatitis cases. Additionally, an incremental 39 (Germany) and 17 (Australia) BBV patients per 10,000 were linked to care. Combined testing for all three BBVs was highly cost-effective over a lifetime, with an incremental cost per QALY gained of $6,613 in Germany and $2,260 in Australia (Figure 1). While individual cost-effectiveness varied by virus, HCV testing was estimated to be cost-saving in both countries, driven by disease progression when left undiagnosed and the high effectiveness of treatment among those linked to care. **Conclusion:** Our findings suggest targeted high-prevalence area opt-out BBV ED testing could prove highly cost-effective, enhance earlier viral hepatitis and HIV infection diagnosis, and facilitate engagement in care in both countries.



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3098 | TRENDS IN 1-YEAR POST-LIVER TRANSPLANT OVER TWO DECADES: A NATIONAL COHORT STUDY USING THE UNOS REGISTRY

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Background: Employment is a key indicator of recovery and quality of life after liver transplant (LT), reflecting not only medical stability, but also functional and social integration. Prior studies have shown persistently low post-LT employment rates (17-24%), but the transplant landscape has changed significantly over the past two decades. Whether these clinical advances have improved return-to-work outcomes remains unknown. **Methods:** We conducted a retrospective cohort study of adult LT recipients (age 18-60 years) in the United States using the UNOS/OPTN registry (2002-2022). Included patients survived 1 year post-LT without re-transplant or death. The transplant year was examined as a categorical (2002-2012 vs. 2013-2022) and a continuous variable. Employment status at 1 year was modelled using Poisson regression with robust standard errors. The multivariable model was adjusted for sex, race/ethnicity, education, insurance, pre-LT employment, diabetes, liver disease etiology, post-LT functional status and hospitalization. **Results:** Among 65,692 event-free 1-year survivors, employment rose from 32.2% in the first decade (2002-2012) to 34.2% in the second (2013-2022), while event-free survival improved from 71.2% to 84.4%. Over time, the transplant population included more patients with private insurance, higher education, and etiology of ALD or MASH vs. fewer HCV. Transplant year was associated with a 0.8% annual employment increase (RR: 1.008, 95% CI: 1.006-1.010); this remained significant after adjustment (aRR: 1.003, 95% CI: 1.001-1.005), confirming a modest but consistent upward trend. Strong positive predictors of employment included private insurance (aRR: 2.34), pre-LT employment (aRR: 2.25), male sex, college education, and autoimmune/cholestatic liver disease. Negative predictors included post-LT mobility limitations (aRR: 0.47), hospitalization (aRR: 0.87), hepatitis C virus, diabetes, and Hispanic ethnicity. **Conclusion:** Employment at 1-year post-LT has modestly improved alongside greater post-transplant survival. Yet, most recipients remain unemployed, revealing a persistent gap between clinical success and functional reintegration. These findings suggest that transplant programs should go beyond medical care and proactively address social and functional recovery. Integrating employment-focused rehabilitation and navigation into multidisciplinary care could help more patients reclaim their independence and quality of life after transplant.
Disclosures: Sangmin Lee: Nothing to Disclose, Mohammad Qasim Khan: Nothing to Disclose

3099 | ASSESSING GOALS OF CARE PRACTICES AMONG INTERNAL MEDICINE RESIDENTS DURING A DEDICATED INPATIENT LIVER SERVICE ROTATION

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Background: Inpatient liver teaching services care for medically complex patients with advanced liver disease and high mortality. These rotations provide internal medicine residents with a key opportunity to engage in goals of care (GOC) communication. However, the frequency of these discussions, the extent of resident leadership, and alignment with palliative care (PC) practices remain poorly understood. **Methods:** Internal medicine residents who completed an inpatient liver teaching service rotation between June 2023 and March 2025 completed a 10-question survey assessing their experiences delivering care in this setting. The survey included items on training year, participation and leadership in GOC conversations, alignment with attendings on treatment planning, follow-through on palliative care (PC) consultations when indicated, and the perceived impact of knowing patients' baseline functional status. Responses were summarized descriptively. **Results:** Twenty-seven residents who had rotated on inpatient liver service completed the survey. Most respondents (22, 81%) completed the rotation during PGY-1. Nearly half (11 of 25, 44%) reported participating in goals of care conversations

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less than once per week. Only 4 residents (16%) participated in GOC conversations more than weekly. When goals of care conversations occurred, most residents (20 of 25, 80%) reported that they led them only sometimes, rarely, or never.
Over half of respondents (13 of 25, 52%) reported that their treatment plans differed from those of their attendings either "sometimes" or "often," while the remaining 12 (48%) reported disagreement "rarely" or "never." When a PC consult was clinically indicated, only 12 residents (48%) reported it was obtained often or always; 13 residents (52%) reported follow-through occurred "sometimes," "rarely," or "never." Among 23 respondents, 14 residents (61%) reported that a better understanding of patients' baseline functional status would have improved care "quite a bit" or "a great deal." **Conclusion:** Despite frequent exposure to seriously ill patients, residents reported infrequent GOC participation and rarely led discussions on the inpatient liver teaching service. Discrepancies with attendings and inconsistent PC consultation suggest missed opportunities for goal-concordant care. Most felt that understanding baseline functional status would improve decision-making. These findings highlight the need for educational and systems-level changes to support serious illness communication.

Disclosures: Charles Marvil: Nothing to Disclose, Ramya Sampath: Nothing to Disclose, Stephen Possick: Nothing to Disclose, Vandana Khungar: Nothing to Disclose, Alex Choi: Nothing to Disclose, Laura Morrison: Nothing to Disclose

3100 | RE-LIVE STUDY (RE-LINKAGE TO PAN-VIRAL HEPATITIS): INTERIM RESULTS: FROM A MULTICENTER OBSERVATIONAL STUDY ON CARE ENGAGEMENT IN CHRONIC VIRAL HEPATITIS

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Background: Despite the availability of effective antiviral therapies, linkage to care remains a key barrier to the global elimination of viral hepatitis. A considerable proportion of individuals with chronic hepatitis B, C, and D remain undiagnosed, untreated, or lost to follow-up, sustaining the burden of disease and transmission. In Korea, reimbursement criteria for HBV treatment were expanded in 2023; however, a substantial number of eligible patients remain untreated. This study aimed to evaluate systematic re-linkage strategies to re-engage these individuals in the continuum of care, with the goal of improving clinical outcomes and contributing to public health objectives. **Methods:** A retrospective chart review was conducted at four tertiary hospitals in Korea. HBV treatment eligibility included: (i) non-cirrhotic patients with HBV DNA $>2{,}000$ IU/mL and fibrosis stage ≥ 2, and (ii) cirrhotic patients with any detectable HBV DNA. For HCV, partially diagnosed-but-untreated (DBU) cases were defined as anti-HCV positive without HCV RNA data; completely DBU cases were HCV RNA positive without prior antiviral therapy. Eligible HBV patients were screened for HDV via RT-PCR. Identified patients were re-contacted via phone or text for evaluation and potential linkage to care. **Results:** Among 2,192 patient charts reviewed, 33 HBV and 127 HCV patients were enrolled in the call-back program. Among HBV patients, 21.2% (7) responded and agreed to further evaluation; 6.1% (2) initiated antiviral therapy, while 78.8% (26) did not respond to call-back. Of 92 partial HCV DBU cases, 13.0% (12) agreed to evaluation, 3.3% (3) had prior treatment, 3.3% (3) sought care elsewhere, 2.2% (2) refused, and 78.3% (72) did not respond. Among them, 2.2% (2) initiated treatment. Among 35 complete DBU cases, 2.9% (1) agreed to evaluation, 2.9% (1) sought care elsewhere, 5.7% (2) refused, and 88.6% (31) did not respond; only 2.9% (1) initiated treatment. HDV RT-PCR was performed in 618 chronic HBV patients; 0.1% (1) tested positive but declined further management. In total, 3.1% (5) of 160 patients identified through the call-back program initiated antiviral therapy. **Conclusion:** Although effective antiviral treatments and expanded eligibility criteria are now available, many patients with viral hepatitis remain disconnected from care. Our re-linkage efforts showed limited success in bringing patients back into the treatment pathway. These findings emphasize the need for continued, practical strategies to improve access to care and support national and global goals for viral hepatitis elimination.

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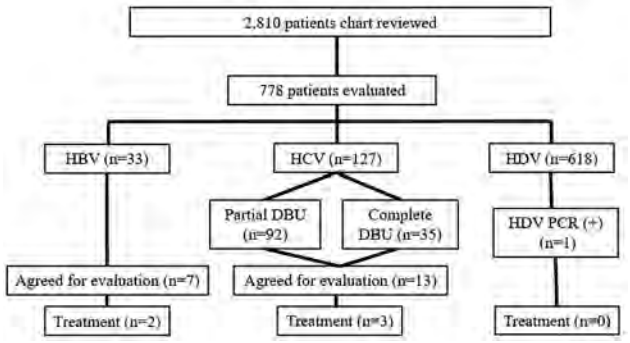

Disclosures: Jae hyun Yoon: Nothing to Disclose, Young-Sun Lee: Nothing to Disclose, Yang Jae Yoo: Nothing to Disclose, Yu Rim Lee: Nothing to Disclose, Seul Ki Han: Nothing to Disclose

3101 | EVALUATING THE AGREEMENT BETWEEN PATIENT SELF-ADMINISTERED QUESTIONNAIRES VS. TRANSPLANT TEAM PSYCHOSOCIAL ASSESSMENTS IN LIVER TRANSPLANT CANDIDACY SCREENING

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Background: Psychosocial evaluations are a key part of determining liver transplant candidacy. These assessments can be supported by self-administered, web-based questionnaires, which offer scalable and standardized data collection that may be less susceptible to social desirability bias. However, it remains unclear how closely such self-reported data align with clinical assessments conducted by transplant clinicians. We hypothesized that discrepancies would be more common for variables perceived as stigmatizing, due to differences in disclosure behaviors between private, web-based questionnaires and real-time, face-to-face clinical interviews. **Methods:** In this single-center, observational study, we compared data from liver transplant candidates who finished a web-based psychosocial questionnaire with corresponding clinical assessments conducted by social workers and documented in electronic medical records (EMR). We evaluated categorical variables using kappa statistics to assess agreement. For continuous variables, Lin's concordance correlation coefficients (CCC) and Bland-Altman plots were used to assess agreement and visualize systematic biases. Demographic and socioeconomic factors associated with discordant responses were also identified. **Results:** Among the 140 participants, the median age was 55.8 $\pm$ 8.6 years, with 56.4% male and 84.2% identifying as White. Alcohol-associated liver disease was the most common diagnosis (34.3%). Agreement between the questionnaire and EMR data varied across domains (Table). Very good or good agreement was observed for smoking history, education level, and marriage/partnered living status. Moderate agreement was found for psychiatric history and employment status, while drug use history showed fair agreement. Discordance in drug use history was significantly associated with younger age, marriage/partnered living status, increased proximity of support, and cohabitation. For continuous variables, abstinence duration showed high concordance (CCC = 0.969), whereas age at first drink showed low concordance (CCC = 0.235). **Conclusion:** This study highlights the potential for discrepancies between self-administered questionnaires and clinical interview data in psychosocial assessment. While certain variables showed higher concordance, variables perceived as potentially stigmatizing, like drug use history, were more prone to discordance. These findings underscore the complexity of psychosocial evaluation and suggest that data source and reporting context can influence the information obtained. Further investigation is needed to understand how specific characteristics of assessment modalities or settings may influence reporting behaviors in transplant evaluations.

Table: Agreement Level Between Self-Administered Questionnaire and Electronic Medical Record Data Across Psychosocial Binary and Categorical Variables

Variable	Kappa (95% CI)	Agreement Level*
Binary Variables		
Psychiatric History	0.573 (0.426 – 0.708)	Moderate
Smoking History	0.885 (0.786 – 0.995)	Very good
Drug Use History	0.344 (0.179 – 0.488)	Fair
Employment Status	0.553 (0.388 – 0.678)	Moderate
Categorical Variables**		
Marriage/Partnered Living Status	0.786 (0.678 – 0.872)	Good
Education Level	0.803 (0.730 – 0.877)	Good

Agreement Level*
0.00-0.20: Poor agreement
0.21-0.40: Fair agreement
0.41-0.60: Moderate agreement
0.61-0.80: Good agreement
0.81-1.00: Very good agreement

Levels for Categorical Variables**
Marriage/Partnered Living Status: Married or living with partner; Widowed; Divorced; Separated or single. In cases with mixed information (e.g., "divorced/cohabitate"), partnered living status was prioritized over legal marital status to better reflect the individual's social support structure. Education Level: No high school or some high school (no diploma); High school diploma or equivalent; Some college, no degree; Associate's degree; Bachelor's degree; Master's or doctorate or post-graduate.

Disclosures: Hyundam (Dami) Gu: Nothing to Disclose, Marie Diener-West: Nothing to Disclose, FNU Baimaji: Nothing to Disclose, Jason Wheatley: Nothing to Disclose, Andrew Cameron: Nothing to Disclose, Ahmet Gurakar: DURECT: Grant/Research Support, Orphalan: Advisor, Po-Hung (Victor) Chen: Gilead Sciences Research Scholars Program: Grant/Research Support

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3102 | IMPACT OF COVID-19 INFECTION ON OUTCOMES IN HOSPITALIZED PATIENTS WITH LIVER CIRRHOSIS: A NATIONWIDE ANALYSIS

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Background: Liver cirrhosis is a major public health concern and is associated with high morbidity and mortality. Currently, a significant number of cirrhotic patients are found to have a COVID-19 infection in clinical settings. Given the immune dysfunction and hepatic reserve limitations in cirrhosis, concurrent COVID-19 infection may significantly worsen outcomes. This study aimed to evaluate the impact of COVID-19 on clinical outcomes in hospitalized patients with liver cirrhosis. **Methods:** We utilized the 2020 National Inpatient Sample (NIS) to identify adult hospitalizations with a diagnosis of liver cirrhosis. Patients were stratified based on the co-diagnosis of COVID-19 infection. We assessed differences in in-hospital mortality, major adverse liver outcomes (MALOs), length of stay (LOS), and total hospital charges between the two groups. Multivariable logistic and linear regression analyses were conducted, adjusting for age, sex, race, income, insurance status, and comorbidities. Statistical analyses were performed using SPSS, with $p < 0.05$ considered statistically significant. **Results:** A total of 842,625 hospitalizations with liver cirrhosis were identified, of which 29,305 (3.5%) had concurrent COVID-19 infection. Compared to cirrhosis patients without COVID-19, those with COVID-19 had significantly higher in-hospital mortality (OR 3.57; 95% CI: 3.46–3.69; $p < 0.001$), higher total hospital charges (β = \$5,496.04; 95% CI: \$3,980–\$7,012; $p < 0.001$), and longer LOS (β = 0.777; 95% CI: 0.690–0.864; $p < 0.001$). They had lower odds of MALOs including ascites (OR 0.48; $p < 0.001$), hepatic encephalopathy (OR 0.53; $p < 0.001$), variceal bleeding (OR 0.47; $p < 0.001$), portal hypertension (OR 0.45; $p < 0.001$), hepatorenal syndrome (OR 0.36; $p < 0.001$), spontaneous bacterial peritonitis (OR 0.39; $p < 0.001$), and liver transplantation (OR 0.13; $p < 0.001$). There was no significant difference in rates of septic shock (OR 0.98; $p = 0.24$). Patients with COVID-19 had higher odds of requiring mechanical ventilation (OR 1.22; $p < 0.001$) but lower odds of acute kidney injury (OR 0.64; $p < 0.001$). **Conclusion:** Hospitalized cirrhosis patients with COVID-19 infection experienced significantly higher mortality and hospital charges, despite lower rates of MALOs. These findings highlight the profound systemic impact of COVID-19 and the need for targeted preventive and management strategies in this vulnerable population.

Table: Impact of COVID-19 on Clinical Outcomes in Hospitalized Cirrhosis Patients: Multivariable Regression Analysis Adjusted for Demographics and Illness Severity

	Adjusted Odds	95% CI	p-value
Marginal Values			
Length of Stay	0.777	0.690 to 0.864	<0.001
Hospitalization Charges	5,496.04	3980 to 7012	<0.001
Odds Ratios			
Mortality	3.569	3.457 to 3.686	<0.001
Ascites	0.483	0.465 to 0.501	<0.001
Hepatic Encephalopathy	0.528	0.450 to 0.619	<0.001
Variceal Bleeding	0.467	0.450 to 0.484	<0.001
Portal HTN	0.447	0.434 to 0.461	<0.001
Hepatorenal syndrome	0.359	0.336 to 0.384	<0.001
SBP	0.386	0.354 to 0.422	<0.001
Intubation	1.215	1.166 to 1.267	<0.001
Septic Shock	0.976	0.936 to 1.017	0.244
AKI	0.641	0.624 to 0.659	<0.001
Liver Transplant	0.125	0.094 to 0.165	<0.001

Disclosures: Ritik Mahaveer Goyal: Nothing to Disclose, Vraj Shah: Nothing to Disclose, Sameer Rao: Nothing to Disclose, Rohan Karkra: Nothing to Disclose, Imran Qureshi: Nothing to Disclose, Paul Gaglio: Nothing to Disclose, Nothing to Disclose

3103 | PREVENTIVE HEPATOLOGY TO TACKLE THE GROWING BURDEN OF LIVER DISEASE AND HEPATOCELLULAR CARCINOMA IN AUSTRALIA.

Neeraj Bhala[1] Nicholas Hannah[2] James Haridy[2] Aparna Morgan[2] Ashok Raj[2], [1]Melbourne Digestive Diseases Centre, University of Melbourne, [2]Royal Melbourne Hospital

Background: Liver disease is a rising cause of premature mortality in Australia, with increasing burden driven by alcohol-related liver disease (ALD), metabolic-associated steatotic liver disease (MASLD), chronic hepatitis B virus (HBV) and hepatocellular carcinoma (HCC). Liver disease remains under-recognized in the National Prevention Health Strategy, prompting our evaluation of critical gaps in preventive hepatology. **Methods:** We analyzed data from the Australian Institute of Health and Welfare (AIHW), national hospital admissions, mortality data, and burden of disease estimates (DALYs) from 2013 to 2023. Subgroup analyses were performed by liver disease etiology, age, sex, Aboriginal and Torres Strait Islander peoples (ATSI), and geography (urban vs rural/remote). We reviewed national preventive strategies related to alcohol use, obesity, and viral hepatitis control. **Results:** Liver disease is now the 5th leading cause of death in Australia when combined with HCC mortality. There was a 41% increase in cirrhosis mortality over the past decade. MASLD accounts for

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over 30% of all liver-related hospital admissions, while ALD-related cirrhosis rose by 38%, particularly among younger adults aged 25–44. Indigenous Australian face liver disease mortality rates up to 3-4 times higher than non-Indigenous populations, with lower access to liver health services. Despite available treatments, only ~20% of people with HBV are engaged in care.
HCC incidence increased by 38% over the past decade, with mortality rising in parallel. Over 60% of cases were diagnosed at late stage, with only 20–30% of patients receiving curative-intent therapy. The leading underlying etiologies were HBV (30%), MASLD (28%), and ALD (22%). **Conclusion:** Adverse liver disease and HCC outcomes in Australia continue to increase yet national strategies have not adequately addressed these preventive chronic hepatology conditions. Emphasising early detection, risk factor modification, and equitable access to care for ALD, MASLD, viral hepatitis and HCC is urgently needed in Australia by embedding liver health in national non-communicable disease and cancer strategies.
Disclosures: Neeraj Bhala: Nothing to Disclose, Nicholas Hannah: Nothing to Disclose, James Haridy: Nothing to Disclose, Aparna Morgan: Nothing to Disclose, Ashok Raj: Nothing to Disclose

3104 | ESTABLISHING BASELINE QUALITY METRICS FOR PARACENTESIS IN PATIENTS WITH CIRRHOSIS IN ALBERTA, CANADA

Leona Chan[1] Swapan Mahal[2] Christopher Fung[1] Puneeta Tandon[1] Mayur Brahmania[3], [1]University of Alberta, [2]Alberta Health Services, [3]University of Calgary

Background: Decompensated cirrhosis is associated with high health care utilization, with ascites recognized as the most common complication requiring frequent therapeutic paracentesis. Given the high volumes of paracenteses performed and its vital role in reducing admissions and emergency department (ED) visits, it is important to ensure that best practices are met. Connect Care (CC) is Alberta's province-wide clinical information system, containing electronic medical records for inpatient and outpatient encounters. In this project, we aim to quantify paracentesis volume and burden across the province, identify quality gaps, and inform targeted quality improvement initiatives to optimize patient care. **Methods:** This is a retrospective population study examining adult patients with cirrhosis who underwent paracentesis in Alberta, Canada between January 1, 2020 and December 31, 2024. In collaboration with the Strategic Clinical Network (DHSCN), patients were identified using CC grouper codes (123346, 34674, 110482) corresponding to procedures performed under Interventional Radiology. Paracenteses performed using point-of-care ultrasound (POCUS) were excluded in this study. To ensure data quality, chart audits were conducted to validate the accuracy of ICD coding for cirrhosis and ascites. **Results:** A total of 25,172 paracenteses were performed in Alberta between 2020 and 2024, with an average year-to-year increase of 9.9%. Among the procedures with documented output volumes (60%), the average volume removed was 5.53L; 54.2% were large-volume paracenteses ($\geq$5L drained) with albumin administered in 89% of cases. Overall, there has been a steady increase in the number of paracenteses performed across all care settings (outpatient, inpatient, ED), with a growing proportion conducted in the inpatient setting and a relatively stable proportion performed in the ED with subsequent discharge. Specifically, despite a 373% increase in ED presentations over the study period, the percentage of ED patients discharged after paracentesis has steadily declined from 19% in 2020 to 7% in 2024. **Conclusion:** In this large retrospective population-based study, we have observed increasing provincial demands for paracentesis alongside rising hospital presentations. Notably, a substantial proportion of patients underwent small-volume paracentesis, many of whom received albumin replacement. These findings highlight opportunities for targeted interventions, especially if small-volume paracenteses were performed for therapeutic purposes. Ongoing work will focus on further data validation and inclusion of additional quality metrics, such as wait times and appropriateness of referrals for Transjugular Intrahepatic Portosystemic Shunt (TIPS) or liver transplant among patients requiring frequent paracentesis.

Variable	2020	2021	2022	2023	2024
Age (years), Median (IQR)	60 (53-67)	59 (50-67)	60 (50-69)	61 (51-69)	62 (51-70)
Sex (Male %)	62	63	61	59	59
Number of Paracenteses Performed, n	3,303	3,848	5,349	6,596	6,097
Small Volume, n (%)	411 (39)	469 (46)	502 (41)	1,634 (48)	2,255 (55)
Albumin Given, n (%)	289 (70)	372 (79)	340 (68)	772 (47)	943 (42)
Large Volume, n (%)	632 (61)	561 (54)	718 (59)	1,756 (52)	1,873 (45)
Albumin Given, n (%)	596 (94)	525 (94)	640 (89)	1471 (84)	1541 (82)
Number of Paracenteses per Patient, Median (IQR)	2.0 (1-7)	2.0 (1-6)	3.0 (1-7)	3.0 (1-7)	2.0 (1-6)
Paracenteses by Encounter Type, n (%)					
Outpatient	2,808 (85)	3,188 (83)	4,215 (79)	4,616 (70)	3,894 (64)
Inpatient	414 (13)	583 (15)	995 (19)	1,784 (27)	2,034 (33)
Emergency Department	81 (2)	77 (2)	139 (3)	196 (3)	148 (2)
Volume Drained (mL), Median (IQR)					
All Paracenteses	4,455 (2,950-6,223)	4,365 (2,903-6,000)	4,613 (2,700-6,200)	4,045 (2,310-5,781)	3,600 (2,000-5,203)
Small Volume	3,060 (2,050-3,788)	3,050 (1,804-3,852)	2,650 (1,600-3,615)	2,850 (1,800-3,700)	2,700 (1,590-3,600)
Large Volume	6,917 (6,004-7,973)	6,691 (5,765-8,006)	6,850 (5,900-8,100)	6,999 (5,996-8,177)	6,567 (5,771-7,700)

Disclosures: Leona Chan: Nothing to Disclose, Swapan Mahal: Nothing to Disclose, Christopher Fung: Nothing to Disclose, Puneeta Tandon: Nothing to Disclose, Mayur Brahmania: Nothing to Disclose

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3105 | IMPROVING TOBACCO CESSATION IN LIVER TRANSPLANT CANDIDATES THROUGH A MULTIDISCIPLINARY QUALITY IMPROVEMENT INITIATIVE

BRANDON SHORE, SUSAN TROUT, KIM SHOENBILL, HERSH SHROFF, Brandon Shore[1] Susan Trout[1] Kimberly Shoenbill[2] Hersh Shroff[1] [1]UNC Chapel Hill, [2]Moffitt Cancer Center

Background: Nicotine use is prevalent among liver transplant (LT) candidates and negatively impacts post-LT outcomes. Though nicotine policies vary by LT center, there is opportunity for cross-institutional multidisciplinary partnerships to improve smoking cessation In LT candidates. **Methods:** We conducted a multifaceted QI intervention to improve diagnosis and treatment of nicotine use in LT candidates, including an educational session for our LT team, a standardized note template for documenting smoking status during LT evaluation (LTE), and a streamlined pathway for early referral to our institution's Tobacco Treatment Program (TTP). Eligible patients included those who began LTE and had active or "recent" (quit within previous 6 months) nicotine use. We surveyed our LT team via Qualtrics (Provo, UT) to assess baseline level of comfort with smoking cessation practices. We collected the following data on pre- and post-intervention cohorts: baseline demographics, clinical characteristics, and process and outcome metrics that occurred between 6 months before LTE start until LTE completion. **Results:** Over 24 months pre-intervention, 371 patients were referred for LTE. 17% were active or recent ($n = 62$) smokers, of whom 63% quit during the defined time period. 4 patients were referred to the TTP and 18 were prescribed pharmacotherapy. We surveyed 24 multidisciplinary LT team members (5 physicians or advanced practice providers, 10 nurses, 3 pharmacists, and 6 social workers/psychologists/dieticians). A majority reported *always* or *often* asking about nicotine use (75%), assessing readiness to quit (75%), counseling patients (83%), and providing resources (58%). Top barriers to screening for nicotine use were competing health concerns, low patient motivation, and other clinical priorities. Treatment barriers included patient refusal, limited educational materials, time constraints, and competing priorities. Over 10 months post-intervention, 184 patients were referred for LT and 15% ($n = 28$) were active/recent smokers. We excluded 8 who either never started LTE or underwent fully inpatient LTEs. Of the remaining 20 patients, 12 had smoking status appropriately documented by a nurse coordinator at LTE start, 12 were referred to TTP, and 10 attended ≥ 1 visit. Nine patients received smoking cessation medications. At the 3-month follow-up with the TTP, 4 out of 6 patients had either reduced, quit, or maintained abstinence from tobacco use. **Conclusion:** Active smoking remains common among LT candidates, yet referral to tobacco cessation programs is low despite available resources. Early identification, improved patient education, and streamlined referral pathways may improve quit rates and post-transplant outcomes.

Disclosures: Brandon Shore: Nothing to Disclose, Susan Trout: Nothing to Disclose, Kimberly Shoenbill: Nothing to Disclose, Hersh Shroff: Nothing to Disclose

3106 | CAN CHANGING LIVER TRANSPLANT SURGICAL LEADERSHIP INCREASE TRANSPLANT VOLUME?

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Background: Liver transplant centers, like professional sports teams, change leadership in hopes of improving production (i.e., increasing transplant volume). There is however little empirical data to determine whether leadership change is associated with increases in transplant volumes. **Methods:** We used publicly available OPTN transplant data to quantify annual liver transplant volume from 2010-2019 to evaluate the association between leadership change and change in transplant volume. We only included centers that performed an average of at least 50 liver transplants per year during this period to focus on higher-volume centers and to reduce bias in relative annual changes due to small sample sizes. Surgical leadership data were collected by identifying each center's primary liver transplant surgeon from another OPTN database. Data on the surgeon's start date were found from various sources, including transplant center websites and publicly available profiles such as LinkedIn. We fit mixed effect linear regression models to evaluate the interaction of leadership change and calendar year. **Results:** Independent of leadership changes, the average transplant center volume increased annually. There was a significant interaction between transplant volume, calendar year, and leadership change ($p < 0.001$), signifying an overall relationship between leadership change and increases in transplant volume. However, when compared on a year-to-year basis, there were only two years where there was a significant increase from one year to the next, and both occurred in the absence of a leadership change (Table). Yet when centers were compared over a longer period of time, the changes became more apparent. For example, when

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2010 was the reference for all comparisons, centers in 2015 with the same leadership as 2010 performed an average of 12 more liver transplants than they did in 2010, while centers in the first or second year of a leadership change performed an average of 29 more transplants ($p = 0.003$). **Conclusion:** Our study demonstrates that there is an overall association between leadership change and increase in transplant volume among liver transplant centers. However, this association was not uniform and did not occur with all leadership changes, suggesting that changing leadership does not guarantee improvement. Future work needs to investigate practices associated with growth in transplant volume with new leadership.

Year + Status	Beta Coefficient	P-Value
2010 no leadership change	Reference	Reference
2010 honeymoon	31.6 (-5.8, 69.1)	0.10
2011 no leadership change	2.1 (-5.1, 9.3)	0.57
2011 no leadership change	Reference	Reference
2011 honeymoon	3.6 (-19.2, 26.4)	0.76
2012 no leadership change	0.97 (-6.4, 8.3)	0.80
2012 no leadership change	Reference	Reference
2012 honeymoon	-11.1 (-31.1, 8.9)	0.23
2012 post-honeymoon	-0.46 (-38.0, 37.1)	0.98
2013 no leadership change	1.3 (-6.2, 8.7)	0.74
2013 no leadership change	Reference	Reference
2013 honeymoon	-5.7 (-32.4, 21.1)	0.68
2013 post-honeymoon	4.7 (-18.2, 27.6)	0.69
2014 no leadership change	4.6 (-2.9, 12.1)	0.23
2014 no leadership change	Reference	Reference
2014 honeymoon	8.5 (-28.1, 45.1)	0.65
2014 post-honeymoon	-2.6 (-21.2, 15.9)	0.78
2015 no leadership change	3.5 (-4.2, 11.2)	0.37
2015 no leadership change	Reference	Reference
2015 honeymoon	16.4 (-2.8, 35.6)	0.09
2015 post-honeymoon	-10.2 (-28.8, 8.5)	0.29
2016 no leadership change	9.6 (1.7, 17.6)	0.02
2016 no leadership change	Reference	Reference
2016 honeymoon	7.5 (-9.9, 24.9)	0.40
2016 post-honeymoon	-5.8 (-23.1, 11.5)	0.51
2017 no leadership change	1.4 (-6.8, 9.5)	0.74
2017 no leadership change	Reference	Reference
2017 honeymoon	6.3 (-12.8, 25.4)	0.52
2017 post-honeymoon	2.2 (-12.4, 16.8)	0.77
2018 no leadership change	0.5 (-8.3, 18.5)	0.90
2018 no leadership change	Reference	Reference
2018 honeymoon	2.0 (-14.1, 18.1)	0.81
2018 post-honeymoon	4.5 (-9.1, 18.1)	0.51
2019 no leadership change	9.6 (0.8, 18.4)	0.03
2019 no leadership change	Reference	Reference
2019 honeymoon	9.492 (-9.7, 28.6)	0.33
2019 post-honeymoon	-1.3 (-13.9, 11.4)	0.85

Disclosures: Jonah Ladetsky: Nothing to Disclose, David Goldberg: Nothing to Disclose

3107 | ENHANCING THE PRESCRIPTION FREQUENCY OF COST-EFFECTIVE PHARMACOTHERAPY IN METABOLIC ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) AND OBESITY: A QUALITY IMPROVEMENT INITIATIVE

Chusila Lee[1] Cody Ashcroft[1] Christina Awad[1] Raphael John Sabado[1], [1]Brooke Army Medical Center

Background: Metabolic associated steatotic liver disease (MASLD) affects over 30% of US adults and is the most common chronic liver disease in Western nations. Obesity, a significant comorbidity, drives MASLD progression to cirrhosis, ultimately drastically increasing healthcare costs. Modeling studies suggest that effective therapies for MASLD, particularly those halting fibrosis progression, could avert $7.6 billion in healthcare costs. Glucagon-like peptide-1 receptor agonists and glucose-dependent insulinotropic polypeptide receptor agonists (GLP1) have demonstrated efficacy in MASLD reversal. Data gathered from 1108 patients seen in the gastroenterology clinic over the past two years showed a baseline GLP1 prescription rate of 22.9% in patients with comorbid obesity and MASLD/MASH. Based on this data, we conducted a preliminary quality improvement (QI) project to increase GLP1 prescription rates to reduce MASLD cirrhosis-related financial healthcare burden. **Methods:** An online provider survey (35% response from 150 internal medicine and GI providers) identified the prior authorization (PA) as the primary barrier to prescription. In response, we delivered an educational lecture to Gastroenterology and Internal Medicine trainees and staff that included a flowchart on the qualifying criteria for a GLP1. Prescription rate was reassessed after 2 months in 100 patients. As a process measure, the rate of GLP1 prescription in the Hepatology clinic was also assessed during this time. While the sample size and time frame are limited, this was intended as an initial gap analysis and test of intervention impact. **Results:** After the intervention, the prescription rate increased to 29%. Though still below our goal of $>75\%$, this early improvement supports expanding the project. However, amongst patients seen in the Hepatology clinic, only 5% of eligible patients evaluated during this time frame were prescribed a GLP1. **Conclusion:** This preliminary study suggests that education alone is insufficient to substantially improve GLP1 prescription rates. A multi-faceted approach addressing broader systemic issues, such as policy change or system-level interventions, is necessary to enhance prescription rates and ultimately make an impact on the cost associated with the complications of progression to cirrhosis. Our future efforts will involve larger sample

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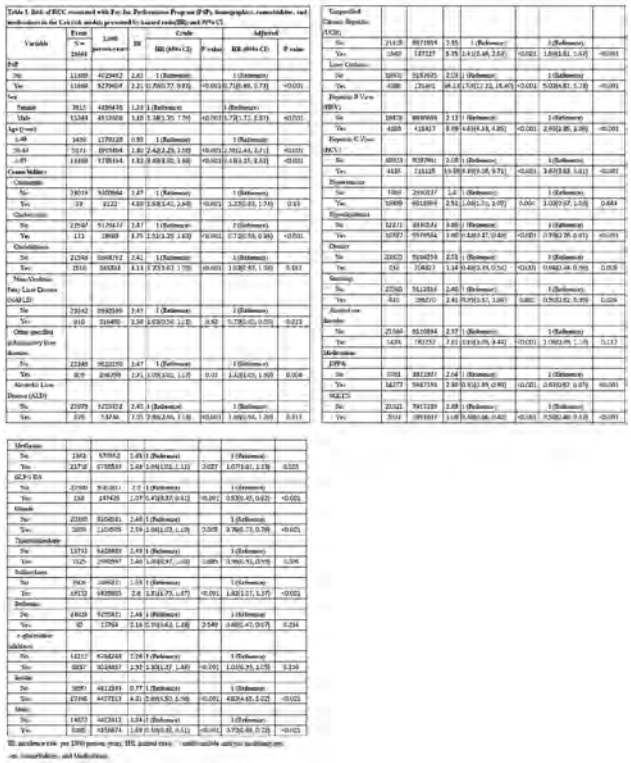
sizes, longer interval follow-up, and multiple cycles to test and refine interventions.

Disclosures: Chusila Lee: Nothing to Disclose, Cody Ashcroft: Nothing to Disclose, Christina Awad: Nothing to Disclose, Raphael John Sabado: Nothing to Disclose

3108 | DOES THE PAY-FOR-PERFORMANCE PROGRAM (P4P) FOR TYPE 2 DIABETES PATIENTS REDUCE THE INCIDENCE OF PRIMARY LIVER CANCER?

Chao-Yi Lai[1] CHENG-LI LIN[1] Hsueh-Chou Lai[1], [1]China Medical University Hospital, Taichung, Taiwan

Background: Patients with type 2 diabetes mellitus (T2DM) face an elevated risk of developing primary liver cancer, particularly hepatocellular carcinoma (HCC). Improved glycemic control, has been linked to reduced cancer risk. To improve diabetes outcomes, Taiwan's National Health Insurance Administration launched the Pay-for-Performance (P4P) program in 2001. However, its impact on HCC incidence remains uncertain. **Methods:** We conducted a retrospective cohort study using National Health Insurance Research Database (NHIRD) from 2008 to 2021. A total of 1,952,586 T2DM patients were included, with 976,293 enrolled in the P4P program and 976,293 matched controls. The risk of HCC was evaluated using Cox proportional hazards models, Fine and Gray competing risk regression, and inverse probability of treatment weighting (IPTW) based on propensity scores. All models were adjusted for age, sex, liver-related comorbidities (e.g., HBV, HCV, cirrhosis), and use of antidiabetic and lipid-lowering medications. **Results:** P4P participation was significantly associated with a reduced risk of HCC. The adjusted hazard ratio (aHR) was 0.71 (95% CI: 0.69–0.73, $p < 0.001$) in Cox proportional hazards model, and the adjusted subhazard ratio (aSHR) was 0.72 (95% CI: 0.70–0.74, $p < 0.001$) in Fine and Gray competing risk regression. Inverse probability of treatment weighting (IPTW) based on propensity scores further confirmed this protective effect (aHR = 0.71). The benefit was consistent across all age groups, both sexes, and patients with high-risk comorbidities. Use of SGLT2 inhibitors (aHR = 0.50), GLP-1 receptor agonists (aHR = 0.53), and statins (aHR = 0.70) were independently associated with lower HCC risk. Conversely, insulin (aHR = 4.83) and sulfonylureas (aHR = 1.32) were associated with increased HCC risk. Although among non-P4P participants, metformin users had a borderline significant risk of HCC compared to non-users, P4P participants using metformin showed a reduced risk of HCC. Regardless of metformin use, P4P enrollment consistently conferred protection. Subgroup analyses confirmed the benefits of P4P, even in patients with hepatitis B, hepatitis C, or liver cirrhosis. **Conclusion:** This large nationwide cohort study demonstrates that participation in Taiwan's diabetes P4P program significantly lowers the risk of HCC in patients with T2DM. The protective effect remains robust across subgroups and after adjustment for key clinical variables. These findings support structured, performance-based diabetes care as an effective strategy for reducing cancer risk.



Disclosures: Chao-Yi Lai: Nothing to Disclose, CHENG-LI LIN: Nothing to Disclose, Hsueh-Chou Lai: Nothing to Disclose

3109 | EARLY LIFE BODY SIZE AND RISK OF DEVELOPING BILIARY TRACT CANCERS

Prema Bhattacharjee[1], [1]National Cancer Institute

Background: Biliary tract cancers (BTCs) are rare, aggressive, and vary by sex and subsite. Early-life body size may play a role in BTC risk. We investigated childhood body mass index (BMI) trajectories, BMI and height at individual ages and birthweight in relation to BTC risk, including subsites, in a large Danish cohort. **Methods:** The study included 172,113 males and 168,503 females born from 1930-1996 from the Copenhagen School Health Records Register. Heights and weights were measured at ages 6-15 years. Five sex-specific trajectories were identified using latent

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class trajectory models. At individual ages, BMI was categorized as normal weight or overweight using Centers for Disease Control age- and sex-specific criteria. BMI and height were further analyzed continuously as z-scores based upon an internal reference. We estimated hazard ratios using sex- and birth-cohort-stratified Cox regressions. **Results:** During a median follow-up of 34.5 years, 635 individuals developed BTCs (314 males, 321 females). The overweight (HR: 1.58; 95% confidence interval [CI]: 1.06–2.34) and obesity (HR: 3.22; 95% CI: 1.61–6.44) trajectories in males and the obesity trajectory in females (HR: 2.88; 95% CI: 1.62–5.15) were associated with increased BTC risk. Childhood overweight/obese at age 7 was strongly associated with intrahepatic bile duct cancer risk in males (HR: 2.66; 95% CI: 1.48–4.75) and extrahepatic bile duct cancer risk in females (HR: 3.83; 95% CI: 1.94–7.56). Taller childhood height was linked to higher BTC risk in males only; birthweight showed no associations. We found no sex interaction. **Conclusion:** Our study provides evidence that being overweight or obese in childhood increases BTC risk in adulthood.

Disclosures: Prema Bhattacharjee: Nothing to Disclose

3110 | DEVELOPMENT OF THE PALLIATE END-STAGE AND ADVANCED CIRRHOTICS EARLY (PEACE) LIVER SUPPORTIVE CARE PROGRAMME: LESSONS AND EARLY OUTCOMES FROM A MULTIDISCIPLINARY APPROACH TO PROVIDING PALLIATION FOR LIVER CIRRHOSIS PATIENTS IN SINGAPORE

Marianne De Roza[1] Danielle Ho[1] Qiqi Su[2] Charlene Tan[1] Aiden Lin Yuda[1] Guan Hong Koh[1] Jolyn Tan[1] Kee Yon Lionel See[1], [1]Sengkang General Hospital, [2]Sengkang Genral Hospital

Background: Liver cirrhosis patients have a high symptom burden with frequent hospitalizations and reduced quality of life. There is an unmet need for these patients to receive palliative care but this is often provided late in their disease. **Methods:** PEACE is a multidisciplinary team led by hepatologists with palliative care training and comprises nurses, physiotherapists, social workers, pharmacists, dietitians, and palliative medicine doctors. PEACE holistically delivers specialty liver disease management together with physical symptom control, addressing caregiver and psychosocial needs, advanced care planning, preventive health through vaccinations and frailty screenings, anticipatory planning with patient and family, direct support hotline service, seamless transitions to community and hospice teams and bereavement support. The programme referral criteria used was adapted from SPICT (*Supportive and Palliative Care Indicators Tool)* and includes decompensated liver cirrhosis with any of the following: >1 complication in the past year for refractory ascites, hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, recurrent variceal bleed, inoperable hepatocellular carcinoma and/or indicators of deteriorating health or frailty: >2 unplanned admissions in 1 year, deteriorating performance status with limited reversibility, progressive weight loss/sarcopenia, frequent falls, recurrent infections or complex psychosocial issues not fitting clinical criteria. **Results:** Patients were enrolled prospectively at a tertiary public hospital in Singapore from September 2024 to current. Despite an estimated 100 patients who fulfilled criteria from an internal audit (between jul-dec 2024), only 30 were referred and 25 enrolled, the remaining 5 passed away within a week of referral. 52% were female and 87% of patients were Chinese with mean age of 74. Serious illness conversations were conducted for all patients with attending caregivers and advanced care planning (ACP) completed for 44%. Barriers to ACP discussions were lack of readiness, denial and family-centredness. 29 hospital admissions were prevented via the hotline service. Physical and psychosocial symptom assessment scores were tracked using the Integrated Palliative care Outcome Scale. PEACE patients had better outcomes for both physical and psychosocial symptoms ($p<0.05$) compared to a control group of liver cirrhosis patients. **Conclusion:** Earlier integration of palliation through a structured programme improves quality of life and fosters better communication to help align shared preferences and values. More support is needed to expand and further develop similar programmes.

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3111 | CONFLICTING EXPERT OPINIONS ON HOSPITAL READMISSION PREVENTION IN ADVANCED LIVER DISEASE

Eric Orman[1] Elliot Tapper[2] Richard Kalman[3] Mary Rinella[4] Nicole Bendin[4] Jake McCarty[1] Francis Pike[1] Pavani Jyothi Kavuri[1] Lindsay Yoder[1], [1]Indiana University, [2]University of Michigan Medical Center, [3]Jefferson Einstein Philadelphia Hospital, [4]University of Chicago

Background: Following hospital discharge, patients with cirrhosis frequently experience early readmission, but preventability of these readmissions has been understudied, and methods to reliably define

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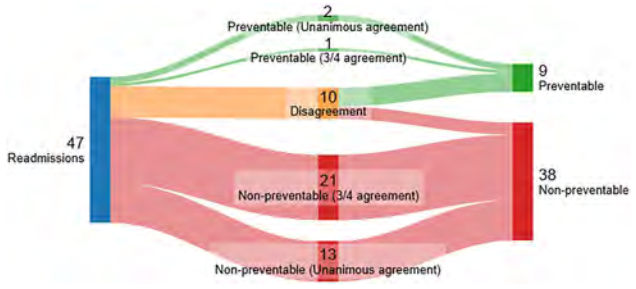
preventability are lacking. **Methods:** We performed a multicenter prospective observational study of patients with decompensated cirrhosis or alcohol associated hepatitis enrolled in the "usual care" control arm of an ongoing clinical trial at 4 centers. We included 47 readmissions (within 30 days), up to the first 12 patients who were enrolled during their index hospitalization at each center. 4 hepatologists (1 from each center) independently reviewed preventability of all readmissions using a 5-point Likert scale ranging from "unlikely ($<25\%$ likelihood)" to "definite ($>95\%$)." Those with $\geq 50\%$ likelihood of preventability were considered preventable. We assessed inter-reviewer agreement using Gwet's AC2 and compared preventable to non-preventable readmissions. **Results:** The 4 reviewers assessed the following proportions of events as preventable: 11%, 15%, 40%, 45%. All 4 agreed on "unlikely" preventability ($<25\%$ likelihood) for 7 events (15%). No other preventability rating had unanimity. 3/4 reviewers agreed on "unlikely" for 8 events and "possible" preventability (25-49%) for 1 event. When scores were collapsed into preventable ($\geq 50\%$ likelihood) vs. non-preventable, reviewers had unanimous agreement on 15 cases (2 preventable, 13 non-preventable), and 3/4 agreed in 22 cases (1 preventable, 21 non-preventable), leaving 10 cases with disagreement (21%) (Figure). Overall, agreement was moderate (0.46, 95% CI 0.28-0.63). All 4 reviewers discussed the 10 with disagreement, and the consensus was that 6 of these were preventable, for a total of 9 preventable readmissions (19%). In those with preventable readmission, the index hospitalization was most often for hepatic encephalopathy (33%), and in those with non-preventable, the index hospitalization was most often for ascites (34%). Non-preventable readmissions were most often for laboratory abnormalities (24%), abdominal pain (16%), and GI bleeding (16%); and preventable readmissions were most often for dyspnea (22%) and abdominal distention (22%). **Conclusion:** In a multicenter prospective study of patients with advanced liver disease, agreement between expert reviewers on readmission preventability was moderate, and most readmissions were not preventable. Harmonization of preventability criteria may enhance the reliability of this outcome and facilitate interventions to prevent readmission.



Disclosures: Eric Orman: Sitero: Consultant, Biovie: Advisor, Elliot Tapper: Madrigal: Grant/Research Support, Richard Kalman: Gilead: Speaking and Teaching, Mary Rinella: akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, Nicole Bendin: Nothing to Disclose, Jake McCarty: Nothing to Disclose, Francis Pike: Nothing to Disclose, Pavani

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Jyothi Kavuri: Nothing to Disclose, Lindsay Yoder: Nothing to Disclose

3112 | LONGITUDINAL MONITORING WITH COMMERCIAL WEARABLE TECHNOLOGY IS FEASIBLE ACROSS SOCIODEMOGRAPHIC AND DISEASE SEVERITY SPECTRUM IN CIRRHOSIS

Adam Buckholz[1] Kamaryn Tanner[2] Avesh Thuluvath[3] Olivia Blocker[4] Jessica Siguencia[4] Brian McSteen[4] Ziyu Liu[4] Jialin Gao[4] Elizabeth Verna[5] Alan Cohen[2] Robert Brown[6], [1]New York Presbyterian Hospital Program, [2]NewYork-Presbyterian/Columbia University Medical Center, [3]Columbia University Irving Medical Center, [4]NewYork-Presbyterian/Weill Cornell Medical Center, [5]Columbia University Medical Center, [6]Weill Cornell Medicine

Background: Cirrhosis is a highly morbid, progressive condition. Commercial wearable technology could enable development of digital biomarkers which would enable novel monitoring and intervention strategies, to improve clinical outcomes. While most research in wearable technology has been conducted in healthy volunteers, people with cirrhosis may experience more healthcare barriers. Thus, the feasibility of longitudinal monitoring in this population is unclear. **Methods:** We enrolled a large pragmatic cohort of patients with cirrhosis from 8/2023-5/2025 at two academic medical centers. English- or Spanish-speaking patients with a smart phone were eligible. Clinical, cognitive and survey data was collected at baseline and participants were given an Oura fitness tracker, which they were instructed to wear continuously for 6 months. Participants received assistance with downloading the app, connecting the ring, and troubleshooting. Wear time (% of possible) of the ring was used to assess adherence. Our primary endpoint was percentage of days with full adherence, defined as at least 90% data available (< 10% non-wear time). The final day of "possible wear" was the first of 180 days after enrollment or 5/11/25. Beta regression was used to estimate the association between proportion of days with full adherence and hepatic encephalopathy [HE], impaired cognition (by PHES), Child-Turcotte-Pugh Score [CTP], decompensation, and history of ascites. We hypothesized that adherence would be higher in younger patients with earlier, compensated cirrhosis, but that all groups would have significant overall usage. **Results:** Of 117 participants who provided consent, 6 were lost to follow up without collecting any sleep data. In total, 11,788/13,949 (84.5%) potential days had non-zero data collection, with a median 115 days of collection (92% of potential) per participant, and 9484 (68%) and 8453 (61%) of the potential days had 80 or 90% "wear time," respectively. Demographic factors (gender, education, race/ethnicity) were not significantly associated with adherence, but power was limited and age > 60 trended to lower adherence (OR 0.76, 95%CI: 0.51, 1.14). Adjusted for age and other demographics, participants with higher CTP [OR = 0.66, 95% CI: 0.43, 1.0], HE [OR = 0.63, 95% CI: 0.41, 0.96] and impaired cognition [OR = 0.60, 95% CI: 0.38, 0.94] had lower odds of having a higher proportion of fully adherent days. Prior decompensation status was not associated with lower adherence. **Conclusion:** Results from a large diverse cohort provide the strongest evidence to date for the feasibility of commercial wearables for longitudinal monitoring in cirrhosis, with high frequency of days with both non-zero (84.5%) and > 90% (61%) data collection, and all examined groups had more than half of days with full (> 90%) wear. Though more advanced disease, especially HE, had lower adherence, wearables can still be used in these groups for digital biomarker development.

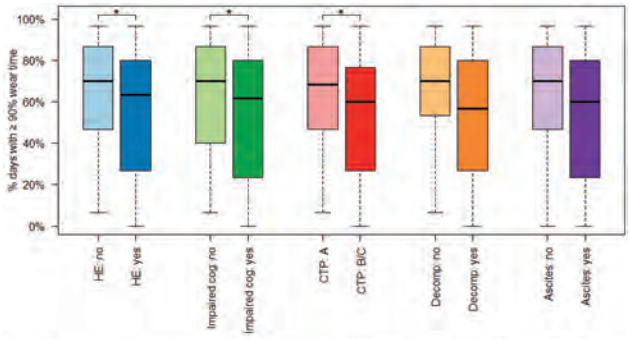

Figure. Bar plots of the percentage of days with at least 90% wear time, stratified by severity of liver disease. * Indicates a significant association in a beta regression adjusted for age, gender, years of education and race/ethnicity at $p<0.01$.

Disclosures: Adam Buckholz: Nothing to Disclose, Kamaryn Tanner: Nothing to Disclose, Avesh Thuluvath: Nothing to Disclose, Olivia Blocker: Nothing to Disclose, Jessica Siguencia: Nothing to Disclose, Brian McSteen: Nothing to Disclose, Ziyu Liu: Nothing to Disclose, Jialin Gao: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose, Alan Cohen: Nothing to Disclose, Robert Brown: Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant

3113 | GLOBAL BURDEN OF LIVER CANCER FROM 1990 TO 2021 AND 20-YEAR PROJECTIONS: FINDINGS FROM THE GLOBAL BURDEN OF DISEASE STUDY 2021

Yikai Wang Yaping Li[1] Liu Yang[1] Meng Zhang[1] Zihan Liu[1] Juanjuan Shi[1] Shuangsuo Dang[1], [1]The Second Affiliated Hospital of Xi 'an Jiaotong University

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Background: Liver cancer poses a significant global health burden, characterized by substantial regional disparities. We analyzed liver cancer incidence and mortality across 204 countries and territories from 1990 to 2021 and projected trends from 2021 to 2041. **Methods:** Data from the Global Burden of Disease (GBD) Study 2021 were used to calculate age-standardized rates (ASRs), average annual percentage change (AAPC), and estimated annual percentage change (EAPC). Risk factors, human development index (HDI), and sociodemographic index (SDI) were evaluated. The Nordpred and BAPC models projected future trends. **Results:** Globally, the ASR of liver cancer incidence rose by 0.03% annually, while mortality ASR declined by 0.21%. Viral hepatitis B and C remained primary causes, but non-alcoholic steatohepatitis (NASH) contributions increased. Drug-use-associated liver cancer rose by 12%, notably in North America. High-HDI/SDI countries exhibited higher ASRs due to aging and metabolic diseases. Projections indicated rising cases but declining ASRs by 2041. **Conclusion:** Tailored prevention strategies are needed to address region-specific risk factors and mitigate the growing burden of liver cancer.

Disclosures: Yikai Wang: Nothing to Disclose, Yaping Li: Nothing to Disclose, Liu Yang: Nothing to Disclose, Meng Zhang: Nothing to Disclose, Zihan Liu: Nothing to Disclose, Juanjuan Shi: Nothing to Disclose, Shuangsuo Dang: Nothing to Disclose

3114 | A MODIFIED NOMINAL GROUP TECHNIQUE CONSENSUS TO DEFINE IMPLEMENTATION PRIORITIES FOR A CHRONIC HEPATITIS B FUNCTIONAL CURE TREATMENT PATHWAY

Carla Coffin[1] Kosh Agarwal[2] Tarik Asselah[3] Chari Cohen[4] Markus Cornberg[5] Sabela Lens Garcia[6] Robert Gish[7] Cary James[8] Patrick Kennedy[9] Pietro Lampertico[10] Jeffrey Lazarus[11] Mark Sulkowski[12] Yasuhito Tanaka[13] Thomas Tu[14] Grace Lai-Hung Wong[15] Hong Yu[16] Norah Terrault[17] Harry L.A. Janssen[18], [1]Cumming School of Medicine, The University of Calgary, Calgary, AB, Canada, [2]Institute of Liver Studies, King's College Hospital, London, UK, [3]Beaujon Hospital APHP, Service d'hépatologie, INSERM UMR1149, Université de Paris-Cité, France, [4]Baruch S. Blumberg Institute, Hepatitis B Foundation, Doylestown, PA, USA, [5]Hannover Medical School, Hannover, Germany, [6]Hospital Clinic Barcelona, Barcelona, Spain, [7]Hepatitis B Foundation, Doylestown, PA, USA, [8]World Hepatitis Alliance, London, UK, [9]Barts Health NHS Trust, London, UK, [10]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [11]Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain, [12]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [13]Kumamoto University, Kumamoto, Japan, [14]Westmead Institute for Medical Research, The University of Sydney, Sydney, Australia, [15]Medical Data Analytics Centre (MDAC), The Chinese University of Hong Kong, Hong Kong, China, [16]Beijing Friendship Hospital, Capital Medical University, Beijing, China, [17]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA, [18]Erasmus MC, University Medical Center, Rotterdam, Netherlands

Background: Novel therapies and treatment strategies that aim to achieve a functional cure (FC) for chronic hepatitis B (CHB) are in development. Such strategies are likely to require changes to treatment and care pathways. This study evaluated the level of consensus within an expert panel regarding the recommended clinical pathway for CHB FC, and implementation priorities. **Methods:** A modified nominal group technique (NGT) meeting took place in May 2025. The panel included members from Europe, North America, and the Asia-Pacific region, and included patient advocates, hepatologists, gastroenterologists, infectious disease specialists, and public health specialists. NGT was modified to support participation from panelists who could not attend in person (allowing advance comments and conducting final voting online). Voting used a 7-point Likert scale. Clinical pathway steps were subject to a $\geq$75% agree/strongly agree consensus threshold. Implementation priorities were ranked by mean score. **Results:** In total, 18 panelists participated (3 participated remotely). After round-robin idea sharing and follow-up discussion, the clinical pathway put forward for voting included nine steps: 1) Screening, diagnosis, and preparing the person with CHB for FC; 2) Supporting people receiving nucleos(t)ide analogs (NA) across settings; 3) Discussing the use of FC treatments with individuals living with CHB; 4) Shared decision to attempt FC treatment based on eligibility, risk / benefit profile, patient preference and predictors for treatment response; 5) Initiation of FC treatment; 6) Management and response-guided milestones, and patient support during FC treatment; 7) Treatment completion; 8) Follow-up after FC treatment; and 9) Rescue therapy and retreatment (if applicable). Steps 1, 2, 4, 5, 7, and 9 reached the consensus threshold, while steps 3, 6, and 8 did not. Comments indicated that lack of consensus was due to regional and national variations in care systems. In total, 19 implementation areas were identified and prioritised during the NGT process (Table). **Conclusion:** Care pathways for CHB FC will vary between regions and countries, but should be evidence-based and patient-centered. This study identifies themes and priorities that regional and national healthcare stakeholders should consider in CHB care and planning to implement functional cure strategies.

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Table: Mean priority scores for priority implementation areas identified by panellists. Higher scores indicate higher priority.

Implementation area	Mean priority score (0–7)
Access to and use of quantitative hepatitis B surface antigen testing	6.78
Simple, evidence-based, algorithmic pathway design	6.67
Effective screening and diagnosis	6.56
Access to treatment targeting functional cure	6.56
Education tools for healthcare professionals, particularly on functional cure and alanine aminotransferase flares (e.g. extension for community healthcare outcomes [ECHO])	6.50
Risk / benefit analysis (including assessment of co-morbidities and predicting individual response to treatment)	6.50
Education tools for people with chronic hepatitis B	6.44
Engagement with policymakers	6.39
Early specialist involvement	6.17
Support tools/systems – patient adherence	6.11
Implementation of digital management / telehealth / remote support	5.94
Increase the number of patients eligible for treatment (via expanded and simple guidelines)	5.94
Understanding patient experience using patient-reported experience measures / patient-reported outcome measures	5.89
Incentives for HCPs to target functional cure	5.83
Provision of peer engagement / peer navigators	5.78
Support tools/systems – patient information networks	5.67
Learning from care models in other therapy areas	5.50
Prioritising care at home	5.44
Support tools/systems – mental health support	5.33

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3115 | US HEALTH CARE SPENDING ON CIRRHOSIS AND OTHER CHRONIC LIVER DISEASES

Xiaomeng Cui[1] Wenjun Wang[1] Yan Tian[2] Ting Li[1] Shuangsuo Dang[1] Xiaoli Jia[1], [1]Second Affiliated Hospital of Xi'an Jiaotong University, [2]Second Affiliated Hospital of Xi'an Jiaotong University

Background: Chronic liver diseases (CLD), including cirrhosis, represent a significant burden on the US health care system. This study aims to quantify health care spending on CLD from 2010 to 2019, examining variation by sex, age, type of care, and geographic

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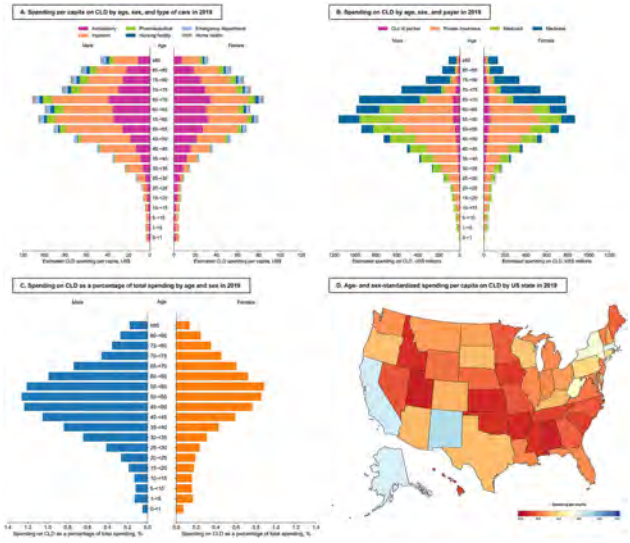
location to inform policy and resource allocation. **Methods:** Using data from a comprehensive analysis of US health care spending by health condition, we extracted spending estimates for CLD. Spending was stratified by sex, age group, type of care, and state. All estimates were adjusted for inflation (2019 USD). **Results:** Health care spending on CLD increased from $9.8 billion in 2010 (95% CI, $9.6 billion-$10.0 billion) to $13.6 billion (95% CI, $13.3 billion-$13.9 billion) in 2019. The proportion of health care spending attributed to CLD increased from 0.51% (95% CI, 0.50%-0.52%) in 2010 to 0.57% (95% CI, 0.56%-0.58%) in 2019. Males accounted for $7.5 billion (95% CI, $7.3 billion-$7.7 billion), while female accounted for $6.1 billion (95% CI, $5.9 billion-$6.2 billion). By age group, individuals aged 45-64 years had the highest spending (49.3%), followed by those aged ≥65 years (30.1%), 20-44 years (17.6%), and <20 years (3.0%). Hospital inpatient care accounted for the largest share of spending (49.8%), followed by ambulatory care (35.8%), prescribed retail pharmaceuticals (6.4%), emergency department care (3.8%), nursing facility care (2.2%), and home health care (2.1%). At the state level, age- and sex-standardized spending per capita ranged from $29.2 (95% CI, $27.2-$37.1) in Utah, to $55.2 (95% CI, $50.7-$57.9) in New Mexico. **Conclusion:** Health care spending on CLD has increased significantly from 2010 to 2019, with substantial variation by sex, age, type of care, and geographic location. These findings highlight the growing economic burden of CLD and underscore the need for targeted interventions to reduce disparities and improve the efficiency of care delivery.



Disclosures: Xiaomeng Cui: Nothing to Disclose, Wenjun Wang: Nothing to Disclose, Yan Tian: Nothing to Disclose, Ting Li: Nothing to Disclose, Shuangsuo Dang: Nothing to Disclose, Xiaoli Jia: Nothing to Disclose

3116 | TEMPORAL CHANGES IN SCREENING FOR ESOPHAGEAL VARICES IN PATIENTS WITH CIRRHOSIS

Ethan Weinberg[1] *Tanvi Goyal*[1] *Hemza Tarawneh*[1], [1]*University of Pennsylvania*

Background: Endoscopic screening for esophageal varices (EV) in patients with cirrhosis is invasive, costly, and can usually be avoided in patients who meet the low-risk Baveno criteria (Vibration-controlled transient elastography (VCTE) liver stiffness < 20 kPa and platelets > 150×10^9/L). Our goal was to evaluate the temporal trends in EV screening in the context of evolving portal hypertension guidelines at a large American liver clinic. **Methods:** We performed a single-center retrospective cohort study of adults with compensated advanced chronic liver disease seen in January to March of the following years: 2014, 2018, and 2022. We used descriptive statistics to characterize the study population. We calculated the proportion of patients who were low risk for portal hypertension yet still underwent screening endoscopy, patients that received primary treatment with non-selective beta-blocker (NSBB, patients that met criteria for treatment with non-selective beta-blocker, but did not receive one, and patients that underwent endoscopy despite being on a non-selective beta-blocker. Secondary analyses examined compliance by NSBB status, as well as excess procedures and complications. **Results:** We found no difference in endoscopy screening and NSBB prescription practices across the three time points evaluated (ANOVA). We found that about 50%, 64%, and 46% of the endoscopies done in 2014, 2018, and 2022 respectively were unnecessary based on low risk for large varices. There was little change in referral pattern for upper endoscopy across these three time-points despite the recommendations in 2016 from Baveno VI conference that patients withVCTE liver stiffness of <20 kPa and platelet >150,000 do not warrant varices screening. However, some individual providers cited the Baveno criteria, patient preference for non-invasive management and platelets >150,000 as reasons for deferring endoscopies. Baveno VII, published in 2022, recommended initiation of NSBB if patients met criteria for clinically significant portal hypertension. We did not find a change in NSBB prescribing patterns in our early 2022 cohort. **Conclusion:** We assessed practice gaps and their clinical consequences to show that our health system can benefit from improved targeted implementation strategies to reduce unnecessary endoscopies. This study will inform resource utilization and beta blocker use for patients with cirrhosis to improve outcomes.

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	2014	2018	2022
N	46	39	39
Average age (years)	59.6	61.4	63.7
% Males	71.7	64.1	59
On NSBB (%)	5 (10.9)	5 (12.8)	7 (17.9)
Inapp. Decision (%)	50	64	46
Unnecessary EGD (%)	43.4	54.8	39.5
EGD ordered or completed with NSBB	3/5 (0.6)	2/5 (0.4)	2/7 (0.29)
Met criteria for NSBB, not prescribed (%)	83.3	88.9	77.8

Table 1. Demographics and Unnecessary Screening Results

Disclosures: Ethan Weinberg: PharmaIN: Consultant, BioVie: Consultant, Sequana: Consultant, Novo Nordisk: Advisor, Amgen: Consultant, Astra Zeneca: Consultant, Kezar: Consultant, Tanvi Goyal: Nothing to Disclose, Hemza Tarawneh: Nothing to Disclose

3117 | HBV SCREENING AND LINKAGE TO CARE PROJECT IN THE FIRST AFFILIATED HOSPITAL OF XINJIANG MEDICAL UNIVERSITY

Ziyi Zhang[1] tongtong shao[1] Rongjiong Zheng[1] Rongjiong Zheng[1] Xiaobo Lu[1], [1]The First Affiliated Hospital of Xinjiang Medical University

Background: China has the world's heaviest burden of HBV infection and is crucial to achieving the WHO's goal of eliminating hepatitis worldwide by 2030. Previous studies have shown that the effective screening and referral strategies can improve the diagnosis and treatment rates of HBV in the hospital and optimize the management of HBV in the hospital. This study is to explore an optimized HBV screening and linkage to care model to improve HBV diagnosis and treatment rates in the hospital setting. **Methods:** This HBV screening and linkage to care project in the First Affiliated Hospital of Xinjiang Medical University was initiated by the Center for Infectious Disease and Hepatology(CIDH) in February 2024, in collaboration with the Information Department (ID), Clinical Laboratory Department, Internal Medicine Departments and Surgery Departments. HBsAg testing is recommended for all patients visiting the hospital. It is recommended that HBsAg-positive patients be referred to the CIDH clinics or be seen by an infectious disease and hepatology specialist for further examination and treatment. Additionally, the ID collects data and sends message reminders to the doctors overseeing patients to prevent missed follow-ups. Interdisciplinary academic exchanges are actively carried out within the hospital to raise awareness among HCPs of non-infectious and liver diseases regarding the diagnosis and treatment of HBV. We incorporate relevant work into the assessment of the Xinjiang Center for Quality Control of Infectious Diseases, and periodically have assessment and feedback exchange. **Results:** From February 2024 to February 2025, a total of 17,005 HBsAg positive patients were identified in the hospital compared to 16,912 from 2023 to 2024, the rate of HBV DNA testing increased from 91.0% (15,405/16,912) to 92.2%(15,685/17,005), and the antiviral treatment rate according to the 2022 China HBV guideline increased from 77.1% to 82.5% respectively before and after the project started. The top ten departments with HBsAg positive rate were 2nd CIDH (13.2%, 2,244/17,005), 1st CIDH(9.5%, 1,615/17,005), 3rd CIDH(7.2%, 1,224/17,005), Interventional Radiology department(5.7%, 969/17,005), 2nd Gastroenterology department(5.3%, 901/17,005), Hepatobiliary surgery department(3.4%, 578/17,005), Hepatobiliary Echinococcosis surgery department(2.7%, 459/17,005), 1st Coronary Heart Disease department(2.6%, 442/17,005), Hypertension department(2.5%, 425/17,005) and 2nd Coronary Heart Disease department(2.4%, 408/17,005). **Conclusion:** This project can be replicated because it effectively improved the screening, diagnosis, and treatment rates for HBV patients in the hospital, as well as supporting the optimization of HBV management.

Disclosures: Ziyi Zhang: Nothing to Disclose, tongtong shao: Nothing to Disclose, Rongjiong Zheng: Nothing to Disclose, Nothing to Disclose, Rongjiong Zheng: Nothing to Disclose, Nothing to Disclose, Xiaobo Lu: Nothing to Disclose

◆ 3118 | AI DRIVEN CT DECIPHERING OF INTRATUMORAL HETEROGENEITY TO PREDICT RESPONSE TO TACE PLUS IMMUNOTHERAPY AND MOLECULAR TARGETED THERAPY IN HCC ★

Zhi-Cheng Jin[1] Jian-Jian Chen[1] Hai-Dong Zhu[1] Gao-Jun Teng[1], [1]Zhongda Hospital, Southeast University

Background: The efficacy of combining transarterial chemoembolization (TACE) with immune checkpoint inhibitors (ICIs) and molecular targeted therapies (TACE-ICI-MTT) has been validated by two prospective randomized controlled trials—EMERALD-1 and LEAP-012—as well as several real-world studies. However, the ability to identify HCC patients who could benefit from combination therapy is an important unmet clinical need. This study aims to quantify intratumor heterogeneity (ITH) and identify prognostic imaging biomarkers in patients with HCC treated with TACE-ICI-MTT. **Methods:** This multicenter cohort study included 742 patients with unresectable HCC who received first-line TACE-ICI-MTT from Jan. 2018 to Dec. 2022 (323 patients in the training set, 139 in internal validation set, 228 in external test set, and 52 in TCIA-TCGA set). Primary endpoint was objective response rate. Three-dimensional tumoral regions of interest (ROIs) were delineated on pretreatment computed tomography (CT) scans using deep learning method, followed by manual calibration. A simple linear iterative clustering algorithm was used to segment super-pixel regions. Radiomics features were extracted

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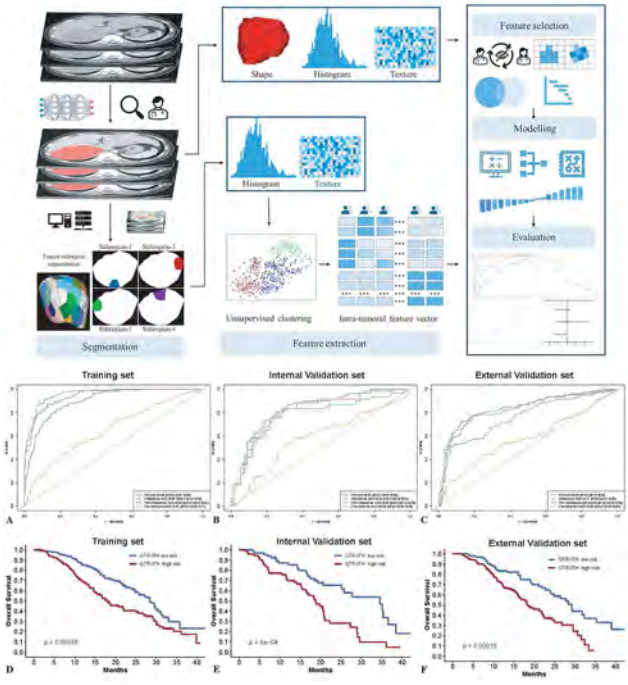
from global tumor region (GTR) and intratumoral subregions. Unsupervised clustering was applied to subregions using a Gaussian mixture model to identify similar features, and an ITH feature vector was established. Ensemble learning was employed to integrate multiple machine learning algorithms for predicting patient outcomes. The principal component analysis was used to generate a unified composite (GTR-ITH) score. Model discrimination was evaluated using receiver operating characteristic curves with area under the curve (AUC) values. Bulk RNA-seq from TCGA-LIHC set explored immune-infiltration patterns. **Results:** After feature dimension reduction, 27 ITH features and 17 GTR radiomics features were retained for model construction. For predicting treatment response, the GTR-ITH model achieved AUC values of 0.94 (95%CI: 0.92−0.97) in the training set, 0.82 (95%CI: 0.74-0.89) in the internal validation set, and 0.83 (95%CI: 0.78-0.88) in the test set. After adjustment, the GTR-ITH score strongly associated with treatment response (OR 34.39; $P < 0.001$) and independently associated with overall survival (HR 0.63; $P = 0.004$). The GTR-ITH low-risk group consistently demonstrated longer median OS across all datasets. In the TCIA cohort, GTR-ITH low-risk patients showed higher effector cell infiltration (plasma cells, M1 macrophages), elevated ESTIMATE immune/stromal scores, and lower tumor purity, whereas high-risk patients were characterized by increased suppressive populations (M2 macrophages). **Conclusion:** A CT-based imaging biomarker that integrates global tumor features and intratumoral heterogeneity accurately predicts response to TACE-ICI-MTT in HCC and correlates with immune microenvironment status.



Disclosures: Zhi-Cheng Jin: Nothing to Disclose, Jian-Jian Chen: Nothing to Disclose, Hai-Dong Zhu: Nothing to Disclose, Gao-Jun Teng: Nothing to Disclose

◆ 3119 | GLOBAL BURDEN OF PRIMARY LIVER CANCER: A POPULATION-BASED ANALYSIS FROM 1990 TO 2021 WITH PROJECTIONS TO 2050

Xinrong Zhang[1] Charles Levesley[1] Sovann Linden[1] Tyler Wong[1] Scott Barnett[1] Ramsey Cheung[2] Fanpu Ji[3], [1]Division of Gastroenterology and Hepatology, School of Medicine, Stanford University Medical Center, [2]Stanford University Medical Center, [3]Xi'an Jiaotong University

Background: The etiologies of primary liver cancer (PLC) have changed in recent years, but its impact on the global PLC burden and future forecast data are limited. We presented temporal trends between 1990 and 2021 and future forecasted to 2050 for PLC-related incidence, mortality, and disability-adjusted life-years (DALYs) by age, sex, regions and etiologies. **Methods:** We analyzed data from the Global Burden of Disease study between 1990 and 2021 to assess the age-standardized incidence rates (ASIRs), mortality rates (ASMRs), and disability-adjusted life years (ASDALYs) of PLC by age, sex, regions and etiologies. DALYs were calculated as the sum of years of life lost and years lived with disability. The estimated frequency of incidences, deaths, and DALYs are accompanied by 95% uncertainty intervals (UIs). Trends were evaluated by annual percentage change (APC) with 95% confidence intervals (CIs) using joinpoint regression analysis and forecasted to 2050 using prediction models. **Results:** Globally in 2021, there were 529,202 incident cases, 483,875 deaths, and 12.9 million DALYs related to PLC. The estimated ASIR, ASMR, and ASDALYs of PLC were 6.15 (95% UI 5.58-6.90), 5.65 (95% UI 5.13-6.30), and 149.29 (95% UI 135.24-167.48) per 100,000 population, respectively. During the forecasted period between 2021 and 2050 (Table 1), there was a predicted global decline in PLC-related ASIR (APC: -1.12%, 95% CI -1.13 to -1.12), ASMR (APC: -0.91%, 95% CI -0.92 to -0.89) and ASDALYs (APC: -1.05%, 95% CI -1.08 to -1.03). The ASIRs, ASMRs and ASDALYs of PLC were higher among males and the elderly. The greatest decrease of ASIR and ASMR were observed in the Western Pacific (APC: -1.60% and -1.65%) and the Africa regions (APC: -1.25% and -1.60%), whereas the greatest increase were observed in the Americas (APC: 0.67% and 0.77%) and Southeast Asia (APC: 0.62% and 0.61%), respectively. For etiologies, the ASIRs, ASMRs and ASDALYs showed the largest decrease for hepatitis B and C-related PLC, remained stable for alcohol-related PLC, and increased for metabolic dysfunction-associated steatotic liver disease (MASLD)-related PLC. **Conclusion:** The global burden of PLC was predicted to decrease over the next three decades, mostly in the

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Western Pacific and Africa regions and in hepatitis B or C-related PLC, while the burden increased for MASLD-related PLC and for other regions including the Americas. Future targeted prevention measures and region-specific interventions are needed.

Table 1. Forecast age-standardized incidence and mortality rates from 2021 to 2050 of primary liver cancer stratified by age, sex, regions and etiologies

	Age-standardized incidence rate, per 100,000 (95% UI)		APC of incidence rate (95% CI)	Age-standardized mortality rate, per 100,000 (95% UI)		APC of mortality rate (95% CI)
	2021	2050		2021	2050	
Overall	6.15 (5.58-6.90)	4.42 (0.97-8.10)	-1.12* (-1.13 to -1.12)	5.65 (5.13-6.30)	4.35 (1.81-7.01)	-0.91* (-0.92 to -0.89)
Age (years)						
20-54	3.26 (2.84-3.81)	3.21 (2.80-3.63)	-0.08* (-0.11 to -0.06)	2.57 (2.25-2.99)	2.05 (1.63-2.47)	-0.79* (-0.80 to -0.77)
55-59	15.10 (13.37-17.42)	10.92 (8.43-13.47)	-1.08* (-1.11 to -1.03)	12.87 (11.39-14.84)	7.73 (6.52-9.09)	-1.69* (-1.73 to -1.63)
60-64	20.84 (18.95-23.36)	20.40 (19.06-21.80)	-0.10* (-0.15 to -0.07)	18.24 (16.55-20.48)	15.61 (14.39-16.82)	-0.54* (-0.57 to -0.51)
65-69	27.77 (25.37-30.80)	27.97 (18.51-36.82)	0.002 (-0.03 to 0.02)	25.57 (23.34-28.35)	21.38 (17.89-24.49)	-0.61* (-0.63 to -0.59)
≥70	40.07 (35.56-43.75)	32.55 (16.32-48.36)	-0.70* (-0.71 to -0.68)	41.17 (36.55-44.93)	33.82 (23.00-45.51)	-0.67* (-0.68 to -0.66)
Sex						
Female	3.60 (3.24-3.96)	2.71 (1.27-4.39)	-1.15* (-1.16 to -1.15)	3.46 (3.11-3.80)	2.82 (1.79-3.91)	-0.97* (-0.98 to -0.95)
Male	8.98 (7.96-10.37)	6.39 (0.66-11.56)	-0.97* (-0.98 to -0.97)	8.10 (7.24-9.37)	6.12 (2.13-10.62)	-0.72* (-0.73 to -0.71)
Region						
Africa	6.57 (5.53-7.90)	4.54 (3.20-6.48)	-1.25* (-1.26 to -1.22)	7.05 (5.94-8.50)	4.39 (1.32-7.59)	-1.60* (-1.62 to -1.58)
Eastern Mediterranean	5.49 (4.73-6.27)	4.69 (3.36-6.62)	-0.53* (-0.54 to -0.52)	5.79 (4.98-6.60)	6.37 (6.17-6.57)	0.31* (0.29-0.34)
Europe	4.20 (3.94-4.41)	3.77 (1.91-7.04)	-0.36* (-0.37 to -0.34)	3.90 (3.64-4.09)	3.62 (2.11-5.16)	-0.25* (-0.26 to -0.24)
Americas	3.76 (3.52-3.92)	4.57 (3.10-6.71)	0.67* (0.67-0.68)	3.28 (3.06-3.43)	4.10 (3.53-4.73)	0.77* (0.76-0.78)
Southeast Asia	3.38 (2.98-3.88)	4.06 (3.17-5.22)	0.62* (0.62-0.63)	3.54 (3.12-4.05)	4.22 (3.52-4.93)	0.61* (0.60-0.62)
Western Pacific	10.16 (8.68-11.97)	6.36 (2.67-15.91)	-1.60* (-1.61 to -1.60)	8.75 (7.47-10.31)	5.43 (1.99-8.67)	-1.65* (-1.69 to -1.61)
Etiology						
Hepatitis B	2.37 (1.95-2.89)	2.11 (1.74-2.49)	-0.43* (-0.46 to -0.41)	2.09 (1.72-2.55)	1.62 (0.86-2.44)	-0.90* (-0.93 to -0.86)
Hepatitis C	1.82 (1.56-2.08)	1.19 (0.40-1.97)	-1.41* (-1.43 to -1.38)	1.74 (1.49-1.99)	1.32 (0.90-1.76)	-0.93* (-0.95 to -0.92)
Alcohol	1.14 (0.93-1.38)	1.07 (0.48-1.60)	-0.211* (-0.213 to -0.209)	1.06 (0.86-1.29)	1.03 (0.62-1.42)	-0.13* (-0.14 to -0.11)
MASLD	0.49 (0.40-0.60)	0.51 (0.27-0.75)	0.11* (0.11-0.12)	0.48 (0.39-0.58)	0.53 (0.34-0.72)	0.29* (0.25-0.32)
Other causes	0.27 (0.21-0.32)	0.21 (0.08-0.34)	-0.75* (-0.76 to -0.74)	0.24 (0.19-0.29)	0.21 (0.12-0.29)	-0.52* (-0.59 to -0.45)

*P value<0.001. APC, annual percentage change; MASLD, metabolic dysfunction–associated steatotic liver disease; UI, uncertainty interval; CI, confidence interval

Disclosures: Xinrong Zhang: Nothing to Disclose, Charles Levesley: Nothing to Disclose, Sovann Linden: Nothing to Disclose, Tyler Wong: Nothing to Disclose, Scott Barnett: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Fanpu Ji: Gilead Sciences: Speaking and Teaching, Gilead Sciences: Consultant, MSD: Consultant, MSD: Speaking and Teaching

◆ 3120 | VISUALIZATION QUALITY AND EFFECTIVENESS OF NONCONTRAST-ABBREVIATED MAGNETIC RESONANCE IMAGING FOR HEPATOCELLULAR CARCINOMA SURVEILLANCE IN CIRRHOTIC PATIENTS WITH PRIOR ULTRASOUND VISUALIZATION SCORE C

Sunyoung Lee[1] Hyun Kyung Yang[1] Min Young Lee[2], [1]Severance Hospital, Yonsei University College of Medicine, [2]Yonsei University

Background: The recently updated Liver Imaging Reporting and Data System (LI-RADS) version 2024 surveillance ultrasound (US) algorithm introduced alternative strategies, including abbreviated magnetic resonance imaging (AMRI), for patients with repeat or at high risk for repeat US visualization score C (VIS-C) examinations. We investigated the adequacy of the liver visualization and effectiveness of noncontrast-abbreviated magnetic resonance imaging (NC-AMRI) for hepatocellular carcinoma (HCC) surveillance in cirrhotic patients with VIS-C on prior US. **Methods:** This retrospective study included Child–Pugh class A or B cirrhotic patients with prior US VIS-C and underwent NC-AMRI for HCC surveillance between December 2018 and August 2022. Two radiologists reviewed the visualization quality of the NC-AMRI, assessing three parameters: the degree of liver parenchymal heterogeneity (1 = homogeneous or mildly heterogeneous; 2 = moderate parenchymal heterogeneity; or 3 = severely heterogeneous), artifacts (1 = no or minimal; 2 = moderate; or 3 = severe), and liver visualization (1 = liver visualized in near entirety; 2 = some portions of the liver or diaphragm not visualized; or 3 = majority of the right or left lobe or diaphragm not visualized) on each T2-weighted image (T2WI) and diffusion-weighted image (DWI). Early- and very early-stage detection, receipt of curative treatment, and false referral were evaluated. **Results:** A total of 264 patients (mean age, 60.1 years; 169 men) were included. On 264 prior VIS-C, the frequencies of severely heterogeneous liver parenchyma, severe beam attenuation or shadowing, and majority (> 50%) of right or left lobe or diaphragm not visualized were 51.5% (136/264), 19.3% (51/264), and 41.7% (110/264), respectively, according to the LI-RADS surveillance US algorithm. On NC-AMRI, the mean values for the degree of liver parenchymal heterogeneity, artifacts, and liver visualization were 1.23, 1.02, and 1.03 on T2WI, respectively, and 1.36, 1.08, and 1.07 on DWI, respectively. Among the 264 patients, 23 HCCs developed in 18 (18/264, 6.8%) patients. The proportions of early- and very early-stage detection were 94.4% (17/18) and 55.6% (10/18); receipt of curative treatment, 55.6% (10/18); and proportion of false referral, 22.2% (4/18). **Conclusion:** NC-AMRI provided adequate visualization of the liver in cirrhotic patients with prior US VIS-C. NC-AMRI may be an effective surveillance modality for early-stage HCC detection and may serve as an alternative surveillance strategy for cirrhotic patients following US VIS-C.

Disclosures: Sunyoung Lee: Nothing to Disclose, Hyun Kyung Yang: Nothing to Disclose, Min Young Lee: Nothing to Disclose

◆ 3121 | THE EFFICACY OF DEXAMETHASONE VERSUS N-ACETYLCYSTEINE IN PREVENTION OF POST-EMBOLIZATION SYNDROME IN HEPATOCELLULAR CARCINOMA PATIENTS: A MULTICENTER RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, NON-INFERIORITY TRIAL ★

Padungkeat Karasin[1] Sakkarin Chirapongsathorn[2], [1]Phramongkutklao hospital, Bangkok, Thailand, [2]Phramongkutklao Hospital

Background: Postembolization syndrome (PES) is a frequent complication after hepatocellular carcinoma (HCC) treatment but lacks standardized treatment guidelines. We compared dexamethasone versus

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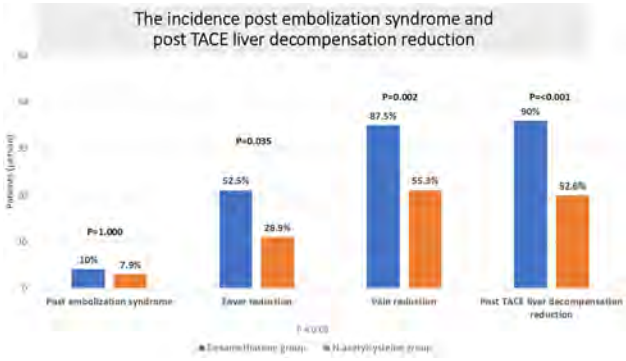
N-acetylcysteine for efficacy and safety in preventing PES after transcatheter arterial chemoembolisation (TACE).

This study primary aimed to evaluate an outcome was a negative result of PES at 48 h after TACE, which was defined as temperature ≥ 38.5 °C and 3-fold higher alanine transaminase level from baseline to evaluated. The secondary outcome included liver decompensation at 48 hours, duration of admission, and safety outcomes (e.g., blood sugar changes and adverse reactions). Additionally, progression-free survival at one month was evaluated in both the DEX and NAC groups. **Methods:** In this phase 3, randomized (1:1), double-blind, double-dummy, parallel-group, non-inferiority study, patients with early to intermediate stage HCC (BCLC stage A-B) without macrovascular invasion who had eligible indication for TACE were randomly assigned to either an intravenous single dose of dexamethasone 8 mg (DEX) or N-acetylcysteine - initial dose 150 mg/kg IV 1 hour, followed by 12.5 mg/kg IV 4 hours then 6.25 mg/kg IV up to 48 hours after TACE (NAC). **Results:** A total of 90 patients were initially enrolled in the study. However, outcome analysis was conducted on 85 patients, seventy-five patients (88%) were male, mean age over 60 years in both groups. HBV cirrhosis was the most common cause, found 46 participants (55%). Most participants had liver cirrhosis, Child-Pugh A, and BCLC stage B, approximately 70% and 87%, respectively. PES incidence was non-inferior between groups (difference proportion DEX-NAC 0.02, (95%CI: -0.13-0.17), $p = 0.002$). However, subgroup symptoms analysis showed significantly greater reduction in abdominal pain (87.5% vs. 55.3%, $p = 0.002$) and fever (52.5% vs. 28.9%, $p = 0.035$) in DEX group compared to NAC group. Liver decompensation was significantly greater reduction in DEX group than NAC group (90% vs. 52.6%, $p = < 0.001$). Anaphylactoid reactions, presenting as dermatologic manifestations (18.4%), and other adverse events (10.4%) were observed exclusively in the NAC group. There was no significant difference in the incidence of hyperglycemia between the two groups. The median length of hospital stay was 4 days in both groups. Additionally, a one-month follow-up for progression-free survival revealed no significant difference between the groups in terms of disease progression or stable disease. **Conclusion:** PES incidence was non-inferior between groups. However, at 48 hours post-TACE, the DEX regimen was associated with a significant reduction in fever, pain, and liver decompensation. Additionally, anaphylactoid reactions and other adverse events occurred exclusively in the NAC group, while the median length of hospital stay did not differ significantly between the groups.



Disclosures: Padungkeat Karasin: Nothing to Disclose, Sakkarin Chirapongsathorn: Nothing to Disclose

◆ 3122 | ADVANCING HCC DIAGNOSTICS: OUTPERFORMANCE OF NOVEL BIOMARKER LC-SPIK IN DETECTION OF HCC IN EARLY-STAGE, AFP-NEGATIVE AND NON-VIRAL CIRRHOSIS CASES

karteek kadimisetty[1] Felix Lu[1] Connor Ott[1] Prabha Bista[1] Lanla Conteh[2] Anne Noonan[3] Daryl Lau[4] Xuanyong Lu[1], [1]ImCare Biotech, [2]Ohio State University, Wexner Medical Center, [3]The Ohio State University, Comprehensive Cancer Center, [4]Beth Israel Deaconess Medical Center

Background: Hepatocellular carcinoma (HCC) is the most prevalent and lethal form of liver cancer with an estimated 905,677 new cases in 2020 worldwide. Unfortunately, most cases are diagnosed late, where curative options are limited with a 5-year survival rate below 15%. Early detection of HCC significantly improves clinical outcomes, yet existing screening tests like ultrasound and α-fetoprotein (AFP) fall short in accuracy, especially in early-stage disease. Ultrasound is operator-dependent, considered suboptimal in patients with obesity and MASLD. AFP shows poor sensitivity ($< 40\%$) for detecting HCC in early stage and cirrhosis patients, particularly in non-viral cirrhosis. **Methods:** ***Novel Biomarker.*** ImCare Biotech discovered and developed liver cancer-secreted serine protease inhibitor Kazal (LC-SPIK), a protein that is uniquely secreted by liver cancer cells but not by normal hepatocytes or inflamed tissues. LC-SPIK retains an extra 23-amino-acid N-terminal fragment which is usually removed during protein secretion. We have developed proprietary monoclonal antibodies that specifically detects LC-SPIK and built a robust ELISA platform *Seravue*® that enables sensitive and specific detection of HCC across diverse population,

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including those with AFP-negative disease cases or complex cirrhotic etiologies. **Results:** In one case-control study, which included 164 HCC patients and 324 controls, LC-SPIK had an AUC of 0.87 compared to only 0.70 for AFP in distinguishing HCC from other liver disease (cirrhosis, HBV/HCV). LC-SPIK also performed significantly better than AFP for the 81 patients with early-stage HCC (BCLC stage 0 and A), with an AUC of 0.85 compared to only 0.61 for AFP. Notably, LC-SPIK identified HCC in over 70% of patients both with early and late HCC who were AFP-negative. LC-SPIK's clinical performance was also studied in HCC patients with cirrhosis, which is the major risk factor for HCC, including viral and non-viral cirrhosis caused by MASLD and ALD. In total 163 viral cirrhosis patients with 93 HCC patients (50 early-stage), LC-SPIK had an AUC of 0.85, while AFP had an AUC of 0.70. For 120 patients with nonviral cirrhosis, including 62 HCC (23 early-stage) patients, LC-SPIK had an AUC of 0.84, while AFP had an AUC of only 0.72. **Conclusion:** Serum levels of LC-SPIK have shown significant improvement in HCC detection, especially in early-stage and AFP-negative HCC cases as well as in patients with viral and non-viral cirrhosis. All these results suggest its potential for disease stratification and monitoring the development of HCC.

Disclosures: karteek kadimisetty: Nothing to Disclose, Felix Lu: Nothing to Disclose, Connor Ott: Nothing to Disclose, Prabha Bista: Nothing to Disclose, Lanla Conteh: Nothing to Disclose, Anne Noonan: Nothing to Disclose, Daryl Lau: Gilead: Grant/Research Support, GSK: Consultant, Abbott Laboratories: Consultant, Xuanyong Lu: Nothing to Disclose

◆ 3123 | DIAGNOSTIC PERFORMANCE OF GALAD AND GAAD VS. ULTRASOUND FOR HCC DETECTION IN PATIENTS WITH NON-VIRAL LIVER DISEASE

Mohammad Jarrah[1] Sneha Deodhar[1] Lisa Quirk[1] Mohammed Al-Hasan[1] Eunice Amador[1] Hannah Pitts[1] Nicole Rich[1] Neehar Parikh[2] Jorge Marrero[3] Fasiha Kanwal[4] Amit Singal[1], [1]University of Texas Southwestern Medical Center, [2]University of Michigan Medical Center, [3]University of Pennsylvania, [4]Michael E. DeBakey VA Medical Center

Background: Ultrasound (US) is operator dependent and is prone to hepatocellular carcinoma (HCC) surveillance failure, particularly in metabolic dysfunction–associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD). As the predominant etiology of HCC shifts from viral to non-viral, there is growing interest in blood-based biomarkers. **Methods:** We conducted a case-control study evaluating the performance of blood-based biomarkers GALAD and GAAD vs. US for detection of early-stage HCC (BCLC stage 0 or A) in patients with MASLD or ALD cirrhosis. Blood specimens were collected within 6 months following HCC diagnosis (cases) and during routine visits for cirrhosis (controls). GALAD and GAAD scores were measured using the Roche Elecsys platform and established cutoffs of 2.47 and 2.57, respectively. A positive US was defined as a liver lesion ≥ 1 cm within 6 months of blood collection. Diagnostic accuracy, using AUROC, was compared using DeLong's test, and sensitivity and specificity were compared using Wald test. **Results:** Among 152 patients (56.6% men), 46.7% had HCC (54.9% BCLC 0/A) and 53.3% had cirrhosis. Liver disease etiologies were MASLD (53.5%) and ALD (46.5%). For any-stage HCC, US had 67.5% sensitivity and 89.9% specificity (AUROC 0.79); GALAD 91.5% sensitivity and 67.9% specificity (AUROC 0.92); GAAD 91.5% sensitivity and 69.1% specificity (AUROC 0.92). Compared to US, GALAD and GAAD had higher sensitivity (both $p = 0.01$), lower specificity (both $p < 0.001$), and higher AUROC (both $p = 0.01$); they had comparable performance to each other ($p = 0.96$). For early-stage HCC, US had a sensitivity of 57.1% and specificity of 89.9% (AUROC 0.73). GALAD sensitivity of 87.2% and specificity of 67.9% (AUROC 0.90), GAAD sensitivity of 88.0% and specificity of 69.1% (AUROC 0.90). Compared to US, GALAD and GAAD had higher sensitivity (both $p = 0.12$), lower specificity (both $p < 0.001$), and higher AUROC (both $p = 0.01$); they had comparable performance to each other ($p = 0.39$). Combining GALAD and GAAD with US improved sensitivity for early-stage HCC to 90.5% for both, albeit with lower specificities (63.8% and 65.2%, respectively). **Conclusion:** In a pilot study, blood-based biomarkers had high performance, competitive to ultrasound, in patients with non-viral cirrhosis. These results support ongoing prospective studies validating biomarkers for HCC surveillance in patients with cirrhosis.

Disclosures: Mohammad Jarrah: Nothing to Disclose, Sneha Deodhar: Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Mohammed Al-Hasan: Nothing to Disclose, Eunice Amador: Nothing to Disclose, Hannah Pitts: Nothing to Disclose, Nicole Rich: AstraZeneca: Advisor, Genentech: Consulting, Exelixis: Advisor, Eisai: Advisor, Madrigal: Advisor, Neehar Parikh: Genentech: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Consultant, AstraZeneca: Consultant, Exact Sciences: Grant/Research Support, Exact Sciences: Consultant, Fujifilm Medical: Advisor, Jorge Marrero: Nothing to Disclose, Fasiha Kanwal: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant

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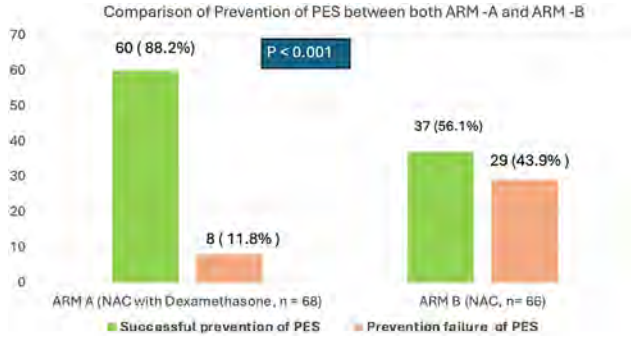
◆ 3124 | "COMPARISON OF DEXAMETHASONE AND N-ACETYLCYSTEINE VERSUS N-ACETYLCYSTEINE ALONE IN PREVENTION OF POST-EMBOLIZATION SYNDROME IN PATIENTS WITH HEPATOCELLULAR CARCINOMA FOLLOWING TRANSARTERIAL CHEMOEMBOLIZATION – RANDOMIZED CONTROLLED TRIAL."

Phool Chand[1] VINOD ARORA[1] Rakhi Maiwall[2] Amar Mukund[1] YASHWANT PATIDAR[1] Nirupma Trehanpati[3] Sukriti Baweja[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences (ILBS), New Delhi, [2]Institute of Liver and Biliary Sciences, New Delhi, [3]Institute of Liver and Biliary Sciences (ILBS),New Delhi

Background: Post-embolization syndrome (PES), characterized by fever, nausea vomiting and abdominal pain, is a frequent complication following transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC), contributing to increased morbidity and hospitalization. While N-acetylcysteine (NAC) and corticosteroids have shown individual benefit, no randomized controlled trial (RCT) has evaluated their combined efficacy. This study addresses this clinical gap by assessing whether adjunctive dexamethasone with NAC reduces the incidence of PES more effectively than NAC alone. **Methods:** Adults (18–75 years) TACE eligible patients for unresectable HCC were enrolled and randomized 12 hours prior to TACE into two arms: Arm A (NAC + dexamethasone) and Arm B (NAC alone). Patients with Child-Pugh C, curative intent therapies, uncontrolled diabetes or hypertension, recent surgery, or viral activity (HBV DNA >100 IU/mL, detectable HCV RNA) were excluded. The primary endpoint was incidence of PES within 72 hours, defined by SWOG toxicity score ≥ 2. Secondary endpoints included post-TACE hepatic decompensation at 4 weeks, hospital stay duration, and adverse events (CTCAE 5.0). **Results:** Of 208 screened, 134 patients were randomized (Arm A: $n=68$; Arm B: $n=66$). PES at day 3 was noted in 11.8% (8/68) in Arm A vs 43.9% (29/66) in Arm B ($p<0.001$). PES prevention was achieved in 88.2% (60/68) of patients in Arm A compared to 56.1% (37/66) in Arm B ($p<0.001$).Mean hospital stay was shorter in Arm A (3.13 ± 0.38 days) vs Arm B (3.58 ± 1.07; $p<0.001$). Post-TACE decompensation was observed in 4.6% (Arm A) vs 7.8% (Arm B) ($p=0.452$). Adverse events were similar (9 vs 8 patients), with no serious events requiring discontinuation. On multivariate analysis, higher baseline AST (OR 1.035, CI 1.013–1.057, $p=0.001$), baseline serum creatinine (OR 17.82, CI 2.072–153.25, $p=0.008$), and baseline CRP (OR 1.066, CI 1.004–1.131, $p=0.039$) independently predicted PES. **Conclusion:** Dexamethasone plus NAC significantly reduced PES incidence and hospitalization following TACE in HCC patients, with a favourable safety profile. These findings support combined prophylaxis as an effective strategy to improve post-TACE outcomes.



Disclosures: Phool Chand: Nothing to Disclose, VINOD ARORA: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, Amar Mukund: Nothing to Disclose, YASHWANT PATIDAR: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose, Sukriti Baweja: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

◆ 3125 | OUTCOMES OF US LI-RADS VISUALIZATION SCORE B IN HEPATOCELLULAR CARCINOMA SURVEILLANCE

Sanjna Shelukar[1] Caroline Conlon[1] Jashanveer Johal[1] Shuchi Rodgers[2] Andrej Lyshchik[1] Jesse Civan[1], [1]Thomas Jefferson University Hospital, [2]University of Pennsylvania, Perelman School of Medicine

Background: Surveillance for hepatocellular carcinoma (HCC) with 6-monthly ultrasound (US) and alpha fetoprotein (AFP) is recommended for high-risk individuals. The US LI-RADS system was created to standardize reporting of liver lesions detected on US (US-1: negative, US-2: subthreshold [lesion <10mm], US-3: positive [lesion >10mm]) and the US quality (VIS-A [no or minimal limitations], VIS-B [moderate limitations], VIS-C [severe limitations]). There is a paucity of literature on the expected false negative and false positive rates for VIS-B US. There is no specific guideline regarding optimal recall strategy for the VIS-B cohort. This study aims to assess the patient factors and clinical outcomes associated with US LI-RADS VIS-B. **Methods:** A retrospective chart review of electronic health records at our institution was conducted. Patients aged 18 years and older at high-risk for HCC with an US with a VIS-B score between March 2020 and August 2022 were included in the study. Descriptive analysis of patient demographics and disease characteristics was performed. **Results:** 384 patients with an index US result of VIS-B were identified. 63% were male. The median age at index scan was 59 years. The main etiologies of liver disease were chronic hepatitis B (HBV) (60%), MASLD (20%) and

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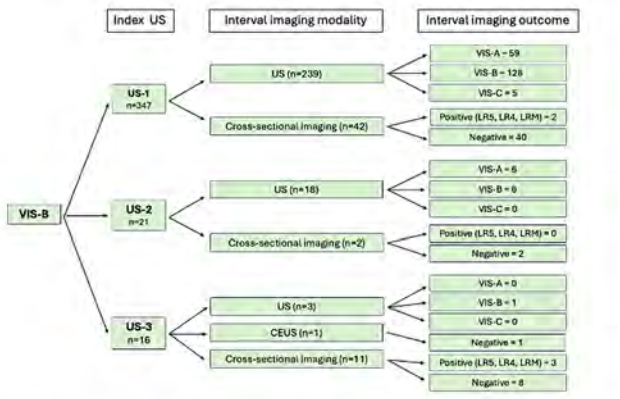
chronic hepatitis C (13%). 60% were non-cirrhotic, of which 91% had chronic HBV. At index scan, the median BMI was 28.7, median AFP was 2.70ng/mL and median MELD 3.0 for patients with cirrhosis was 8. The results of the index scans were as follows; 90% US-1, 5.5% US-2 and 4.5% US-3.
316 patients proceeded to further imaging: 260 US (VIS-A = 65, VIS-B = 135, VIS-C = 5), 46 multiphase MRI, 9 multiphase CT and 1 contrast-enhanced US. The median time to interval scan was 7 months. The incidence of HCC on interval imaging was 0.9% (n = 3). Graph 1 outlines the interval imaging modalities and outcomes per index scan results. **Conclusion:** Our data shows that patients with negative or sub-threshold findings on HCC surveillance US, even with US LI-RADS VIS-B score, are unlikely to have HCC identified on subsequent imaging. For our cohort with US-1 and VIS-B findings on index US, about one quarter improved to VIS-A on subsequent US. Our findings suggest that following US-1 VIS-B surveillance US with multiphase, contrast-enhanced CT or MRI is unlikely to have higher yield than repeating the US. One limitation of our study was the high proportion of non-cirrhotic patients, which may limit generalizability of our findings.



Graph 1. Interval imaging modalities and outcomes per index scan US LI-RADS result. Cross-sectional imaging included multiphase, contrast-enhanced CT or MRI. Visualization score was not recorded in 55 interval ultrasounds. CEUS = contrast-enhanced ultrasound; CT = computed tomography; LR5 = LI-RADS 5 lesion (HCC); LR4 = LI-RADS 4 lesion (probable HCC); LRM = LI-RADS M lesion (likely malignant, but not definite HCC); MRI = magnetic resonance imaging; US = ultrasound; VIS-B = visualization score B.

Disclosures: Sanjna Shelukar: Nothing to Disclose, Caroline Conlon: Nothing to Disclose, Jashanveer Johal: Nothing to Disclose, Shuchi Rodgers: Nothing to Disclose, Andrej Lyshchik: Nothing to Disclose, Jesse Civan: Nothing to Disclose

◆ 3126 | GLYCOLYTIC REWIRING OF MONOCYTE-DERIVED MACROPHAGES PROMOTES IMMUNOSUPPRESSION IN HEPATOCELLULAR CARCINOMA

Hengdong Qu[1] Di Zhang[1] Junli Liu[1] Peixin Zhao[1] Yihui Yu[1] Ziwei Kang[1] Yiming Cui[1] Jinyu Lv[1] Hao Bai[1] Ping Tao[1] Nan Yao[1] Wencai Ye[1] Jian Hong[1], [1]State Key Laboratory of Bioactive Molecules and Druggability Assessment, Jinan University

Background: While glycolysis is generally considered to fuel pro-inflammatory activation and anti-tumoral immunity of macrophages, emerging evidence highlights its paradoxical role in tumor-associated macrophages (TAMs) through upregulation of immune checkpoints, including programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1). This study is aimed at deciphering the role of glycolysis in TAMs and at investigating its impact on tumor immunity of hepatocellular carcinoma (HCC). **Methods:** Glycolytic landscape and immunomodulatory signatures of hepatic TAMs, including Kupffer cells and monocytes-derived macrophages (MDMs), were assessed by multi-dimensional approaches. To interrogate the function and mechanism of glycolytic MDMs in HCC progression, we established diethylnitrosamine/carbon tetrachloride (DEN/CCl_4)-induced and orthotopically implanted HCC models using mice with myeloid-specific deletion of pyruvate kinase M2 (PKM2), the rate-limiting enzyme of glycolysis. **Results:** Bioinformatic screening and flow cytometry analysis identified that $PKM2^+$ MDMs, which constructively represent the major cellular source of glycolytic macrophages in HCC tumors, displayed an immunosuppressive phenotype. Macrophage-specific PKM2 knockout profoundly mitigated tumor progression (24-week: number of surface tumor, $P < 0.001$; largest tumor diameter, $P < 0.001$) but not tumor formation (19-week: number of surface tumor, $P = 0.977$; largest tumor diameter, $P = 0.940$) in DEN/CCl_4-induced spontaneous HCC model. The protective effect of macrophage PKM2 ablation was verified in orthotopic HCC model. Functional studies illustrated that macrophage PKM2 deficiency reduced conventional M1 macrophages but enhanced the anti-tumoral activities of $CD8^+$T cells through downregulation of macrophage PD-L1 expression. Furthermore, PKM2-dependent glycolysis promotes histone lactylation and the transcription of immunosuppressive molecules (PD-L1, IL-10, TGF-β, etc.) in macrophages, which thereby facilitates $CD8^+$T cell exhaustion and HCC progression. Interestingly, compared to non-steatotic liver conditions, the abundance of $PKM2^+$ MDMs was markedly enriched in metabolic dysfunction-associated steatotic liver disease (MASLD), whilst depletion of macrophage PKM2 efficiently reversed immunosuppression and boosted the efficacy of anti-PD-1 therapy in MASLD-HCC mice. **Conclusion:** This study demonstrates that PKM2-dependent glycolytic reprogramming of MDMs promotes immunosuppression and HCC progression. Targeting PKM2/glycolysis/lactylation axis in macrophage may potentiate the therapeutic effect of immune checkpoint blockades in MASLD-HCC.

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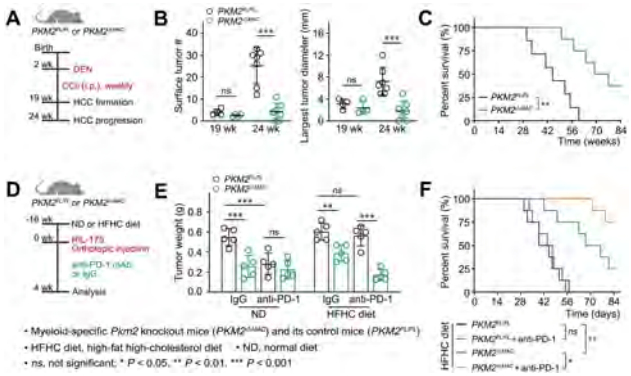


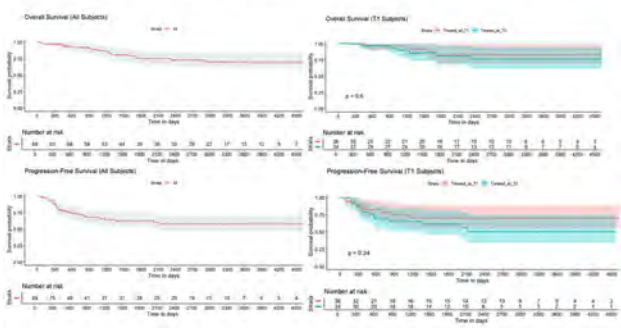
Disclosures: Hengdong Qu: Nothing to Disclose, Di Zhang: Nothing to Disclose, Junli Liu: Nothing to Disclose, Peixin Zhao: Nothing to Disclose, Yihui Yu: Nothing to Disclose, Ziwei Kang: Nothing to Disclose, Yiming Cui: Nothing to Disclose, Jinyu Lv: Nothing to Disclose, Hao Bai: Nothing to Disclose, Ping Tao: Nothing to Disclose, Nan Yao: Nothing to Disclose, Wencai Ye: Nothing to Disclose, Jian Hong: Nothing to Disclose

◆ 3127 | WATCH OR TREAT? OUTCOMES FOLLOWING MANAGEMENT OF VERY SMALL HEPATOCELLULAR CARCINOMA (LESS THAN 2 CM)

Varun Rohatgi[1] Andrea Kierans[1] Jeffrey Sung[1] Robert Brown[1] Resmi Charalel[1], [1]Weill Cornell Medicine

Background: Current OPTN liver transplant guidelines provide HCC exception points for stage T2 disease (single HCC $\geq$2 cm or multifocal HCC). For patients with T1 disease ($<$ 2 cm), clinicians may consider deferring treatment until T2 progression to gain exception points and potentially expedite transplant. However, the risks/benefits and resultant outcomes of this strategy are poorly understood. With the recent alignment of OPTN guidelines with LI-RADS, there is a growing need to understand the progression of these smaller lesions to inform decision-making. **Methods:** Retrospective, single-center cohort study of treatment-naïve patients presenting with LR-4 or LR-5 lesions less than 2 cm on triple-phasic liver protocol CT or MR between January 2010-June 2024. Patient records were evaluated for demographics, treatment history, staging, transplant outcomes (wait-time, evaluation/listing metrics, receipt/timing of exception points, MELDs) and pathology correlation. Subjects presenting with T1 disease were compared based on cancer stage (T1 or T2) at time of treatment. Separate analysis was performed for patients who presented with pre-2023 criteria OPTN 5a lesions vs those presenting with T1-compatible LR-4 or LR-5 disease. Overall survival (OS) and post-therapeutic progression free survival (PFS) were evaluated via Kaplan-Meier. **Results:** Eighty-eight subjects with 110 lesions (40 LR-4 and 70 LR-5) met inclusion criteria. Of these, 70 subjects presented with T1-stage LR-4/LR-5 lesions (34 treated at stage T2 vs 36 treated at T1) with 47 classified as pre-2023 OPTN 5a. Reviewing the pooled LR-4/LR-5 group, the median delay associated with deferring treatment to T2 was 105 days (169 days T2-treated vs 64 days T1-treated, p = 0.001). Median wait-time between presentation and transplant was greater for T2-treated subjects (416 vs 204.5 days, p = 0.0461). While T2-treated subjects more often underwent transplant evaluation (79.4% vs 55.6%, p = 0.0434), they weren't more likely to be listed (61.8% vs 41.7%, p = 0.102) nor receive transplant (52.9% vs 38.9%, p = 0.337). Among those with available pathology, all 17 T2-treated subjects demonstrated malignancy compared to 18/23 T1-treated subjects (p = 0.060). OS was 70.25% and PFS was 57.8%, with no significant difference between T2-treated and T1-treated patients (OS 76.5% T2-treated vs 82.8% T1-treated, p = 0.60; PFS 50.3% T2-treated vs 70.2% T1-treated, p = 0.24). **Conclusion:** For patients presenting with single LR-4 and LR-5 lesions less than 2 cm, while those with T2 progression were more likely to undergo transplant evaluation, they experienced similar transplant rates and slower total wait-times than those treated at T1. There was no impact on survival outcomes. Therefore, despite delays in transplant receipt, this study suggests no negative long-term impact of delaying treatment decision, which already minimizes the risk of potential transplant for non-malignant disease.

Figure: OS and PFS Curves (Left: All Subjects; Right: Subjects Presenting at Stage T1)



Disclosures: Varun Rohatgi: Nothing to Disclose, Andrea Kierans: Nothing to Disclose, Jeffrey Sung: Nothing to Disclose, Robert Brown: Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant, Resmi Charalel: Nothing to Disclose

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◆ 3128 | MORPHOLOGICAL SIGNATURES AND SPATIAL BIOLOGY IN HCC: FOCUS ON MACROTRABECULAR AND VESSELS-ENCAPSULATING TUMOR CLUSTERS PATTERNS

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Background: Hepatocellular carcinoma (HCC) is a histologically heterogeneous tumor, with macrotrabecular massive (MTM) and vessels-encapsulating tumor clusters (VETC) types recognized as aggressive subtypes associated with poor prognosis. Our previous studies demonstrated that even a 5% presence of MT or VETC pattern is a poor prognostic factor, and these patterns often coexist within the same nodule. To elucidate the spatial diversity and biological significance of these patterns, we conducted a spatial transcriptomic analysis using surgical specimens and performed a detailed histopathological investigation using autopsy cases. **Methods:** Two surgically resected HCC cases exhibiting MT and/or VETC components within the same tumor nodule were analyzed. Formalin-fixed paraffin-embedded (FFPE) tissues were processed using the tissue microarray method to selectively sample characteristic regions. Spatial transcriptomics was performed using the Visium HD platform (10X Genomics). In parallel, 254 autopsy-confirmed HCC cases were histologically reviewed to evaluate the frequency of MT and VETC patterns in both primary tumors and metastatic lesions. A 5% cut-off was used to define pattern positivity. **Results:** Spatial transcriptomic analysis revealed that conventional HCC and VETC-HCC from the same tumor had relatively similar gene expression profiles; however, endothelial cell–dominant clusters were observed specifically in VETC-HCC. MT-HCC exhibited clearly distinct expression patterns. In another case, AFP expression was confined to MT-HCC, and multiple transcriptionally distinct clusters were identified among AFP-positive cells. Clusters characterized by tumor cells with large nuclei also exhibited unique gene signatures, distinct from surrounding populations.
Histological analysis of autopsy cases showed significantly higher frequencies of MT-HCC (44.2%) and VETC-HCC (38.5%) compared to surgically resected cases (24.6% and 23.8%, respectively). Cases with MT or VETC patterns had significantly higher rates of distant metastasis, especially pulmonary, but lymph node involvement was unaffected. Macroscopically, these subtypes were more likely to present as diffuse or massive forms and less frequently as nodular types. No consistent pattern concordance was found between primary and metastatic lesions. **Conclusion:** MT and VETC subtypes display distinct spatial transcriptomic profiles, even within a single tumor, reflecting the intratumoral heterogeneity of HCC. These patterns were more frequently observed in autopsy cases and were associated with aggressive metastatic behavior. Ongoing bioinformatic analyses and case expansion aim to further clarify their roles in HCC progression and tumor evolution.
Disclosures: Jun Akiba: Nothing to Disclose, Reiichiro Kondo: Nothing to Disclose, Hironori Kusano: Nothing to Disclose, Masamichi Nakayama: Nothing to Disclose, Taro Shioga: Nothing to Disclose

◆ 3129 | ARID1A IS DECISIVE FOR INITIATING HEPATOCYTE-DERIVED INTRAHEPATIC CHOLANGIOCARCINOMA VIA NOTCH PATHWAY ACTIVATION

Jinqiang Zhang[1] Weina Chen[2] Tong Wu[3], [1]Tulane University, [2]Tulane, [3]Tulane Medical Center

Background: ARID1A, a DNA-binding subunit of the SWI/SNF chromatin remodeling complex, has context-dependent roles in cancer as both a tumor suppressor and oncogene. In intrahepatic cholangiocarcinoma (iCCA), high-throughput sequencing studies have identified ARID1A mutations as among the most common genetic alterations. However, the functional relevance of ARID1A in iCCA initiation and progression remains unclear. **Methods:** We analyzed ARID1A mutations and expression across multiple iCCA patient cohorts. To investigate ARID1A's functional role, we employed two genetically engineered mouse models of hepatocyte-derived iCCA: TAZ^S89A/myr-AKT and NICD/myr-AKT. We evaluated tumor burden following ARID1A deletion and performed chromatin accessibility (ATAC-seq) and transcriptomic (RNA-seq) analyses to explore downstream molecular effects. **Results:** Patient cohort analyses showed that ARID1A mutations were frequent and marginally correlated with better survival, whereas high ARID1A expression was associated with poorer prognosis. In both mouse models, ARID1A deletion significantly reduced liver tumor burden in mice iCCA induced by hydrodynamic tail vein injection, suggesting its oncogenic role in hepatocyte-derived iCCA. Mechanistically, ARID1A loss reduced chromatin accessibility at Notch target loci, leading to suppression of Notch pathway gene expression essential for cholangiocyte differentiation and iCCA development. We identified that RBP-J, a core Notch transcription factor, recruits ARID1A-containing SWI/SNF complexes to activate target genes. These findings were corroborated by similar tumor suppression upon ARID1A loss in the NICD/myr-AKT model. Additional analyses indicated ARID1A mutations are rare in hepatocyte-origin human iCCA, consistent with its tumor-promoting function in this context. Moreover, patients with intact ARID1A showed gene expression profiles suggestive of greater responsiveness to immunotherapy. While the functional loss of ARID1A is associated with poor prognosis in numerous types of cancers, our data suggest

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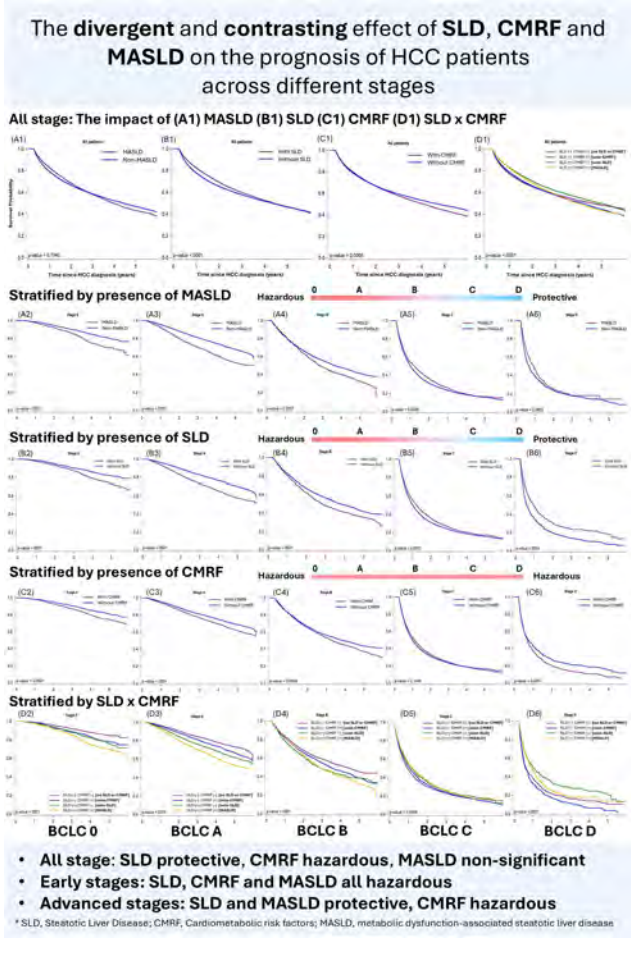
that its loss in iCCA inhibits tumorigenesis, highlighting the complex and context-dependent role of ARID1A across different tissues. **Conclusion:** Our study identifies ARID1A as a key oncogenic driver in hepatocyte-derived iCCA by maintaining chromatin accessibility and Notch signaling. These findings highlight its context-specific function and suggest that targeting ARID1A or its downstream pathways may represent a novel therapeutic approach for iCCA, a cancer with few effective treatment options.

Disclosures: Jinqiang Zhang: Nothing to Disclose, Weina Chen: Nothing to Disclose, Tong Wu: Nothing to Disclose

◆ 3130 | THE STAGE-DEPENDENT, DIVERGENT, AND CONTRASTING EFFECT OF CONCURRENT MASLD ON THE PROGNOSIS OF PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC): A NATIONWIDE COHORT STUDY

Chun-Ting Ho[1] Elise Chia-Hui Tan[2] Wei-Yu Kao[3] Yi-Hsiang Huang[4] Ming-Chih Hou[4] Jaw-Ching Wu[5] Chien-Wei Su[4], [1]Taipei Veterans General Hospital/NYCU, [2]China Medical University, [3]Taipei Medical University, [4]Taipei Veterans General Hospital, [5]National Yang Ming Chiao Tung University

Background: The prognostic impact of cardiometabolic risk factors (CMRF), steatotic liver disease (SLD), and Metabolic dysfunction-associated steatotic liver disease (MASLD) on patients with hepatocellular carcinoma (HCC) remains inconclusive. Besides, further risk stratification and subgroup analysis across stages are still lacking. This study aims to evaluate the prognostic influence of SLD, CMRF, and MASLD on HCC patients across different stages. **Methods:** This retrospective study included 30,857 treatment-naïve patients diagnosed with HCC in Taiwan between 2017 and 2021 from the National Health Research Database in Taiwan. Patients were classified into MASLD and non-MASLD groups utilizing ICD-10 codes and demographic data. Further stratification divided patients into four subgroups: patients without SLD or CMRF, patients with SLD but without CMRF, patients with CMRF but without SLD, and MASLD. The primary outcome was overall survival (OS). Cox proportional hazards models (COX PH) and Fine and Gray's sub-distribution hazard model were used to evaluate the prognostic impact of SLD, CMRF, and MASLD on OS. Kaplan-Meier (KM) survival analyses were performed to compare the outcomes between subgroups. **Results:** Among all patients, 4747 (15.4%) HCC patients have concurrent MASLD. Patients with MASLD are older, more female, have smaller tumor sizes, early tumor stages, and lower serum alpha-fetoprotein. After a median follow-up of 26.3 months, 13460 patients died. 5-year OS of MASLD and non-MASLD groups were 43.5% and 47.1%, respectively. The OS in the two groups was comparable. COX PH model identified MASLD as an independent risk factor for poor OS, while the sole presence of SLD or CMRF was not prognostically significant. Further analysis revealed a stage-dependent effect of SLD, CMRF, and MASLD: In earlier stages, the presence of SLD, CMRF, or MASLD was all associated with poor OS, while in advanced stages, the presence of SLD or MASLD became protective, and CMRF remained hazardous. Stage-stratified COX PH models also identified SLD and MASLD as independent risk factors in early stages. While stratified into four groups, patients without SLD and CMRF had the best OS in early stages, and patients with SLD but without CMRF had the best OS in advanced stages. **Conclusion:** The prognostic effects of SLD, CMRF, and MASLD on HCC patients are divergent and contrasting across different stages. SLD and MASLD were hazardous in early stages but became protective in advanced stages, while CMRF remains hazardous across all stages.



Disclosures: Chun-Ting Ho: Nothing to Disclose, Elise Chia-Hui Tan: Nothing to Disclose, Wei-Yu Kao: Nothing to Disclose, Yi-Hsiang Huang: Nothing to Disclose, Ming-Chih Hou: Nothing to Disclose, Jaw-Ching Wu: Nothing to Disclose, Chien-Wei Su: Nothing to Disclose

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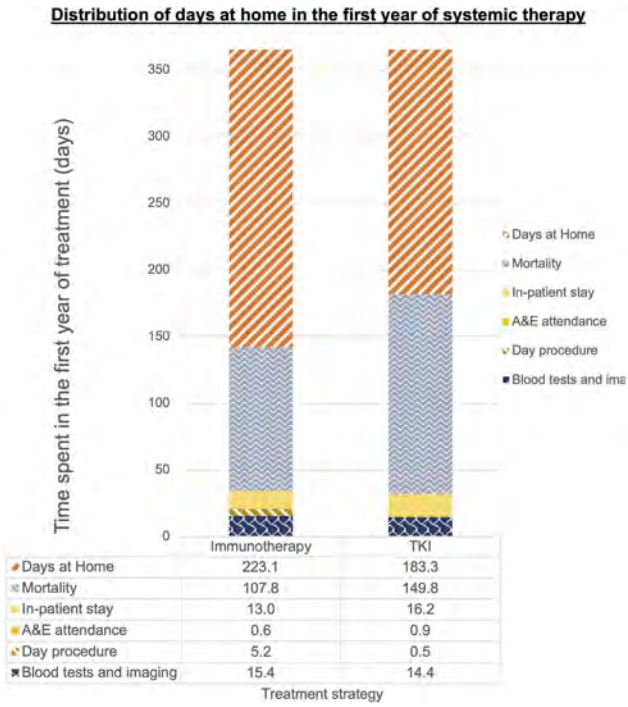
◆ 3131 | HEALTHCARE UTILITY AND DISEASE BURDEN IN ADVANCED HEPATOCELLULAR CARCINOMA PATIENTS RECEIVING SYSTEMIC THERAPY

Rex Wan-Hin Hui[1] Matthew Shing Hin Chung[1] Lu Li[1] Xianhua Mao[1] Chi-Leung Chiang[2] Carlos King-Ho Wong[3] Ian Chi-Kei Wong[3] Ka-Shing Cheung[1] Man-Fung Yuen[1] Wai-Kay Seto[1] Lung-Yi Mak[1], [1]Department of Medicine, The University of Hong Kong, [2]Department of Clinical Oncology, The University of Hong Kong, [3]Department of Pharmacology and Pharmacy, The University of Hong Kong

Background: While cancer survivorship for hepatocellular carcinoma (HCC) improves, associated disease time burden in HCC patients on systemic therapies has not been well studied. We utilized days at home (DAH), a patient-centered metric, to compare the disease time burden between patients on immunotherapies and tyrosine kinase inhibitors (TKIs). **Methods:** Advanced HCC patients receiving systemic therapy from 2008 – 2023 were identified from a population-based cohort in Hong Kong. Patients were classified based on the use of immunotherapy (nivolumab, pembrolizumab, atezolizumab, durvalumab, tremelimumab, and ipilimumab; including monotherapies or combinations) or TKI (lenvatinib, sorafenib, cabozantinib, and regorafenib). The primary outcome was DAH – defined as days alive and not requiring healthcare utilization within the first year of systemic therapy. **Results:** This study included 3,988 patients (578 on immunotherapy and 3,410 on TKI), with the immunotherapy group having significantly higher 1-year overall survival (58.1% vs 34.2% respectively, $p < 0.001$). Mean DAH was significantly higher in the immunotherapy group than in the TKI group (223.1 +/- 134.7 vs 183.3 +/- 129.4 days respectively, $p < 0.001$), and these results remained robust in multivariate and subgroup analyses. Immunotherapy was associated with fewer days spent on inpatient stay and emergency department attendance, but was associated with more days spent on day procedures and investigations (all $p < 0.01$). Immune-related adverse events (irAEs) occurred in 12.3% of immunotherapy patients, and had a negative impact on DAH (32.5 fewer days, $p = 0.056$). Immunotherapy patients with irAEs had comparable DAH with TKI patients ($p = 0.469$). **Conclusion:** Immunotherapy, when compared with TKI, was associated with significantly reduced disease time burden in advanced HCC patients in this real-world cohort. However, this difference was mitigated with the occurrence of irAEs. Our data has important quality of life implications, and may influence patients' decisions for therapy.



Disclosures: Rex Wan-Hin Hui: Nothing to Disclose, Matthew Shing Hin Chung: Nothing to Disclose, Lu Li: Nothing to Disclose, Xianhua Mao: Nothing to Disclose, Chi-Leung Chiang: Nothing to Disclose, Carlos King-Ho Wong: Nothing to Disclose, Ian Chi-Kei Wong: Nothing to Disclose, Ka-Shing Cheung: Nothing to Disclose, Man-Fung Yuen: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose, Lung-Yi Mak: Nothing to Disclose

◆ 3132 | A MARKOV MODEL FOR COST-EFFECTIVENESS ANALYSIS COMPARING THE NOVEL BLOOD-BASED HELIOLIVER® TEST VS LIVER ULTRASOUND SEMIANNUALLY FOR EARLY DETECTION OF HEPATOCELLULAR CARCINOMA

Jim C. Huang[1] Xinrong Zhang[2] Guan-Wei Huang[1] Chieh-Ying Chang[1] Rui Huang[2] Taotao Yan[2] Sovann Linden[2] Ramsey Cheung[2] Mindie Nguyen[2], [1]National Sun-Yat Sen University, Kaohsiung, Taiwan, [2]Stanford University Medical Center, Stanford, California, USA

Background: While significant progress has been made in detecting hepatocellular carcinoma (HCC) at earlier stages using serum biomarkers, the economic value of such strategies remains insufficiently evaluated. **Methods:** This study assessed the cost-effectiveness of semiannual HCC surveillance using the HelioLiver Test compared to

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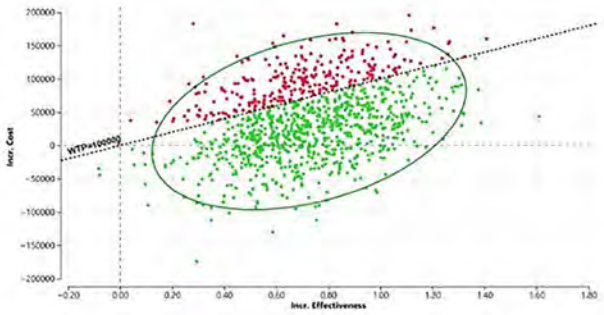
conventional abdominal ultrasound in patients with compensated cirrhosis. A Markov model with 9 health states and a 6-month cycle length was constructed. The model incorporated surveillance sensitivity, specificity, compliance rates, and costs associated with surveillance and treatment across liver disease stages, from a payer's perspective. Health outcomes were measured in quality-adjusted life years (QALYs). Model parameters were informed by data from published literature and expert opinions. Both costs and QALYs were discounted at an annual rate of 3% over a lifetime horizon. The primary outcome was the incremental cost-effectiveness ratio (ICER), with a willingness-to-pay threshold set at $100,000 per QALY gained. A microsimulation with 100,000 iterations was conducted for the base-case analysis. Deterministic and probabilistic sensitivity analyses were performed to evaluate the robustness of the results against parameter uncertainty. All costs were reported in 2024 US dollars. **Results:** The HelioLiver Test strategy demonstrated an incremental cost of $39, 154 with an incremental effectiveness of 0.705 QALYs compared to the ultrasound-based surveillance strategy, yielding an ICER of $55,574 per QALY gained. The one-way sensitivity analysis identified the utility, treatment cost, and mortality rate associated with decompensated cirrhosis as the most influential parameters for the estimated ICER. The conclusion remains robust even when the market price of the HelioLiver Test is set as high as $1,000, where the ICER is $67,502 per QALY gained. Probabilistic sensitivity analysis with 1,000 trials of 1,000 resamples using Monte Carlo simulation further indicated that 75.1% of simulations favored the HelioLiver Test as the more cost-effective option (Figure). **Conclusion:** Semiannual HCC surveillance using the HelioLiver Test is more cost-effective than the ultrasound-based surveillance strategy for patients with compensated cirrhosis. This study addresses a critical knowledge gap in the economic evaluation of blood-based biomarker screening and provides valuable insights for healthcare policy and reimbursement decisions.



Scatterplot of Incremental Effectiveness (QALYs) and Incremental Cost (in 2024 USD) based on Probabilistic Sensitivity Analysis

Note: The dots in the scatter plot indicate the result of incremental cost and effectiveness for each simulation run from the probabilistic sensitivity analysis, where green dots are the runs indicating a more cost-effective option for semiannual HelioLiver Test and red ones indicate the runs preferring regular sonography screening.

Disclosures: Jim C. Huang: Nothing to Disclose, Xinrong Zhang: Nothing to Disclose, Guan-Wei Huang: Nothing to Disclose, Chieh-Ying Chang: Nothing to Disclose, Rui Huang: Nothing to Disclose, Taotao Yan: Nothing to Disclose, Sovann Linden: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

◆ 3133 | SOCIAL DETERMINANTS OF HEALTH ARE ASSOCIATED WITH TREATMENT RECEIPT AND SURVIVAL IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Mohammed Al-Hasan[1] Nicole Rich[1] Gloria Figueroa[2] Stephanie Garces[2] Sruthi Yekkaluri[1] Lisa Quirk[1] Mohammad Jarrah[1] Gi Giamarqo[1] Mariadelcarmen Yanez[1] Adam Yopp[1] Amit Singal[1] Patricia Jones[3], [1]University of Texas Southwestern Medical Center, [2]University of Miami, [3]University of North Carolina at Chapel Hill

Background: The association between social determinants of health and hepatocellular carcinoma (HCC) remains unclear. **Methods:** We leveraged the Multi-Ethnic HCC (ME-HCC) Cohort comprised of adults diagnosed with HCC between September 2018 and July 2023 across four U.S. health systems. Patients completed baseline and follow-up surveys assessing various domains, including health literacy, medical mistrust, experienced discrimination, patient-provider communication, and barriers to treatment. We used multivariable logistic regression models to identify factors associated with treatment receipt, and Fine-Gray subdistribution hazard models to identify factors associated with risk of death, with liver transplantation as a competing event. **Results:** Among 1,245 eligible patients, 833 (66.9%) completed the baseline survey and 495 (59.4%) completed the follow-up survey. Median age was 64.2 years, 75.8% were men, and 55.4% had Child Pugh A cirrhosis. HCC-directed treatment was completed in 69.9% of patients, of whom 45.5% received curative therapy. Median survival was 29.0 months (IQR 9.0–57.6). In multivariable analysis excluding BCLC stage D patients, ALD etiology (OR 0.52, 95%CI 0.28–0.98), Child Pugh class B (OR 0.45, 95%CI 0.27–0.75), higher medical mistrust (OR 0.61, 95%CI 0.38–0.98), and higher experienced discrimination (OR 0.80, 95%CI 0.76–0.83) were negatively associated with treatment receipt. Among patients who completed the follow-up survey, barriers to treatment were also negatively associated with treatment receipt (OR 0.79, 95%CI 0.65–0.93). In multivariable analysis adjusting for tumor stage and type of HCC treatment, patients with Child Pugh class B had a higher risk of death (sHR 1.44, 95%CI 1.08–1.91), while patients with higher experienced discrimination had lower risk of death (sHR 0.96, 95%CI 0.93–0.98). Among patients who completed the follow-up survey,

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patients with better patient-provider communication had lower risk of death (sHR 0.95, 95% CI 0.92–0.98). **Conclusion:** Medical mistrust, experienced discrimination, and barriers to treatment are inversely associated with treatment receipt, while better patient-provider communication is associated with improved survival. These findings underscore the importance of addressing social determinants of health and health beliefs and enhancing patient-provider communication to improve equitable treatment delivery and HCC survival.

Disclosures: Mohammed Al-Hasan: Nothing to Disclose, Nicole Rich: AstraZeneca: Advisor, Genentech: Consulting, Exelixis: Advisor, Eisai: Advisor, Madrigal: Advisor, Gloria Figueroa: Nothing to Disclose, Stephanie Garces: Nothing to Disclose, Sruthi Yekkaluri: Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Mohammad Jarrah: Nothing to Disclose, Gi Giamarqo: Nothing to Disclose, Mariadelcarmen Yanez: Nothing to Disclose, Adam Yopp: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Patricia Jones: Nothing to Disclose

◆ 3134 | DISPARITIES IN OUTCOMES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA TREATED WITH LIVER TRANSPLANTATION

Imran Qureshi[1] Muhammad Ali Ibrahim Kazi[2] Muhammad Hassaan Arif Maan[3] Rohan Karkra[3] Ritik Mahaveer Goyal[4] Wajiha Khan[3] Siddharth Verma[5] Ahmed Al-Khazraji[3] Paul Gaglio[3], [1]RUTGERS THE STATE UNIVERSITY OF NEW JERSEY, [2]Luminis Health Anne Arundel Medical Centre, Annapolis, Maryland, United States, [3]Rutgers New Jersey Medical School, Newark, New Jersey, United States, [4]Rutgers New Jersey Medical School, [5]Veterans Affairs Medical Center, East Orange, USA

Background: Hepatocellular carcinoma (HCC) is on the rise globally and is the fastest-growing cause of cancer deaths in the U.S. In select patients with HCC, Liver transplant (LT) offers a potentially curative modality. However, there is data to suggest racial and socioeconomic disparities related to receipt of LT. In this study, we look at disparities in outcomes in patients who have received LT. **Methods:** We queried the National Cancer Database from 2004 to 2022 for patients with HCC who had received LT. We fit a multivariate Cox proportional hazards model using sociodemographic factors as predictors of overall survival (OS) in patients. We reported adjusted hazard ratios (HR) of OS, along with their 95% confidence intervals (CI) and p-values. **Results:** We identified 16,893 patients with HCC who received LT between 2004 and 2022. Compared to males, females had a lower risk of mortality after LT (HR: 0.92, 95% CI 0.86–0.99, $p = 0.02$). In terms of race, Black patients had a higher mortality after LT compared to White patients (HR: 1.11, 95% CI 1.01–1.23, $p = 0.03$), while Asian patients had a lower mortality (HR: 0.73, 95% CI 0.63–0.84, $p < 0.01$). Hispanics had higher OS than non-Hispanic patients (HR: 0.82, 95% CI 0.74–0.91, $p < 0.01$). Patients with public insurance (HR: 1.28, 95% CI 1.20–1.36, $p < 0.01$) and those uninsured (HR: 1.30, 95% CI 1.01–1.67, $p = 0.04$) had higher mortality than those with private insurance. Interestingly, higher Charlson-Deyo Comorbidity scores were associated with lower odds of mortality compared to a score of 0: score 1 (HR: 0.89, 95% CI 0.82–0.96, $p < 0.01$), score 2 (HR: 0.90, 95% CI 0.81–0.99, $p = 0.04$), and score ≥ 3 (HR: 0.87, 95% CI 0.81–0.94, $p < 0.01$). Median household income between $46,277 and $57,856 was also associated with lower OS (HR: 1.10, 95% CI 1.00–1.21, $p = 0.04$). Compared to the Northeast region, residing in the West was associated with lower mortality (HR: 0.84, 95% CI 0.76–0.93, $p < 0.01$). Finally, patients aged under 50 years had a higher OS compared to those over 50 years (HR: 0.80, 95% CI 0.72–0.89, $p < 0.01$). No significant disparities were noted in terms of the education status of the area, hospital type, or region (Table 1). **Conclusion:** Our study demonstrated significant socioeconomic disparities related to mortality in patients who receive LT for HCC. This may be due to multiple factors, including disparities in post-transplant care or differences in tumor biology associated with higher recurrence rates or poor response to therapy. This underscores the need for studies to further assess the cause of these poor outcomes and targeted public health interventions to address them.

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	Frequency (n=16,893)	Adjusted Hazard Ratio	P-value	95% Confidence Interval
Sex				
Male	12,999	Reference	-	-
Female*	3,894	0.92	0.02	0.86 - 0.99
Race				
White	13,717	Reference	-	-
Black*	1,484	1.31	0.03	1.01 - 1.23
American Indian/Alaska Native	124	0.82	0.33	0.55 - 1.22
Asian*	982	0.73	<0.01	0.63 - 0.84
Pacific Islander	27	1.09	0.81	0.54 - 2.18
Other	373	0.83	0.14	0.65 - 1.06
Ethnicity				
Non-Hispanic	14,177	Reference	-	-
Hispanic*	2,229	0.82	<0.01	0.74 - 0.91
Insurance				
Private Insurance	8,644	Reference	-	-
Public Insurance*	7,821	1.28	<0.01	1.20 - 1.36
Uninsured*	186	1.3	0.04	1.01 - 1.67
Setting				
Metropolitan	12,884	Reference	-	-
Urban	1,957	1	0.96	0.91 - 1.09
Rural	236	1	0.98	0.79 - 1.28
Charlson-Deyo Comorbidity score				
CDCC 0	5,796	Reference	-	-
CDCC 1*	3,993	0.89	<0.01	0.82 - 0.96
CDCC 2*	1,760	0.9	0.04	0.81 - 0.99
CDCC >=3*	5,344	0.87	<0.01	0.81 - 0.94
Highschool non-graduates in area				
<=5%	2,647	Reference	-	-
>=15.3%	3,594	1.01	0.86	0.90 - 1.13
9.1%-15.2%	4,113	1.04	0.40	0.94 - 1.15
5.0%-9.0%	3,846	1.02	0.61	0.93 - 1.12
Median income in area				
>$74,062	5,227	Reference	-	-
< $46,277	2,488	1.08	0.19	0.96 - 1.20
$46,277 - $57,856*	3,063	1.1	0.04	1.00 - 1.21
$57,857 - $74,062	3,386	1.05	0.06	1.00 - 1.18
Hospital type				
Academic	13,807	Reference	-	-
Community	2,735	1.05	0.18	0.98 - 1.14
Region				
Northeast	2,863	Reference	-	-
South	6,940	1.02	0.71	0.94 - 1.10
Midwest	3,936	0.95	0.26	0.86 - 1.04
West*	2,803	0.84	<0.01	0.76 - 0.93
Age				
>50 years	15,127	Reference	-	-
<50 years*	1,766	0.8	<0.01	0.72 - 0.89

Disclosures: Imran Qureshi: Nothing to Disclose, Muhammad Ali Ibrahim Kazi: Nothing to Disclose, Muhammad Hassaan Arif Maan: Nothing to Disclose, Rohan Karkra: Nothing to Disclose, Ritik Mahaveer Goyal: Nothing to Disclose, Wajiha Khan: Nothing to Disclose, Siddharth Verma: Nothing to Disclose, Ahmed Al-Khazraji: Nothing to Disclose, Paul Gaglio: Nothing to Disclose, Nothing to Disclose

◆ 3135 | A REAL-WORLD STUDY OF HEPATOCELLULAR CARCINOMA SURVEILLANCE OVER 4 DECADES – IS THE CURRENT SURVEILLANCE STRATEGY ADEQUATE?

Wei-Lun Liou[1] Yi-Xuan Lee[1] Kaina Chen[2] George Boon-Bee Goh[1] Jason Pik Eu Chang[1] Chee-Kiat Tan[1], *[1]Singapore General Hospital, [2]SingHealth*

Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality worldwide and in Singapore. The poor prognosis is partly due to barriers to effective HCC surveillance, leading to HCC presenting at advanced stages. HCC surveillance was first recommended by major liver societies in 2000, with further refinement of the recommendations in 2011. The aim of the current study is to examine the trend of HCC surveillance and its impact on HCC characteristics in Singapore over the last 4 decades. **Methods:** Study cohort comprised HCC patients seen in the Department of Gastroenterology and Hepatology, Singapore General Hospital between 1990 and 2024. Baseline demographics and HCC clinical characteristics were compared across 4 decades (1990-1999, 2000-2009, 2010-2019, 2020-2024). **Results:** There were 1,963 patients of which 79.1% were males. The median age was 64.6 (IQR 15.9) years. The most common etiologies of HCC were hepatitis B (HBV), with 1,236 (63%) cases, followed by metabolic dysfunction-associated steatotic liver disease (MASLD), with 445 (22.6%) cases. Overall, 697 (35.5%) were diagnosed via surveillance. The number of HCC diagnosed by surveillance improved from 221 (18.7%) cases in pre-2010, to 476 (61%) cases in post-2010 ($p < 0.001$). In line with the increase in HCC surveillance post-2010, more patients presented with early-stage HCC (BCLC stage 0/A), 460 (59%), compared with pre-2010, 226 (19.1%) ($p < 0.001$). The proportion of HCC diagnosed by surveillance stagnated after the initial rise in 2010-2019, 60.2% versus 62.2% in 2020-2024. This may be due to increasing prevalence of MASLD contributing to cases of HCC in patients who were not identified for surveillance, as evidenced by lower proportion of HCC diagnosed on surveillance in MASLD patients post-2010 in comparison to HBV (53.9% versus 66.8%, $p < 0.001$). In patients on surveillance, there was still a proportion of HCC who presented with intermediate or advanced stage (BCLC stages B/C/D) - 72 (26.1%) cases in 2010-2019 and 44 (21.9%) in 2020-2024 period. This suggests that our current surveillance strategy is inadequate in patients with higher risk of HCC development and progression. **Conclusion:** Current HCC surveillance strategy may have reached its maximum capability in diagnosing early-stage HCC in our population. This study highlights the need for better identification algorithms and personalised surveillance strategy in particular for patients with MASLD, as well as validated risk stratification HCC biomarkers to improve detection of early stage HCC.

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Table showing HCC characteristics over the last 4 decades.

	1990-1999 (n=666)	2000-2009 (n=517)	2010-2019 (n=457)	2020-2024 (n=323)
Age, median (IQR) years	61.4 (16.8)	63.7 (15.2)	65.7 (13.5)	69.2 (13.7)
Gender, male (%)	562 (84.4%)	415 (80.3%)	347 (75.9%)	228 (70.6%)
Etiology				
HBV	500 (75.1%)	368 (71.2%)	250 (54.7%)	118 (36.5%)
HCV	18 (2.7%)	26 (5.0%)	30 (6.6%)	19 (5.9%)
HBV/HCV	40 (6.0%)	11 (2.1%)	4 (0.9%)	1 (0.3%)
MASLD	97 (14.6%)	81 (15.7%)	132 (28.9%)	137 (42.4%)
Alcohol	10 (1.5%)	30 (5.8%)	34 (7.4%)	39 (12.1%)
Autoimmune	1 (0.2%)	1 (0.2%)	7 (1.5%)	9 (2.8%)
HCC diagnosed via surveillance (%)	63 (9.5%)	158 (30.6%)	275 (60.2%)	201 (62.2%)
HCC diagnosed via surveillance by etiology				
HBV	55 (11.0%)	122 (33.2%)	161 (64.4%)	85 (72.0%)
MASLD	1 (1.0%)	19 (23.5%)	66 (50.0%)	79 (57.7%)
Staging (all-comers HCC)				
BCLC 0	10 (1.5%)	45 (8.7%)	89 (19.5%)	65 (20.1%)
BCLC A	47 (7.1%)	124 (24.0%)	168 (36.8%)	138 (42.7%)
BCLC B	51 (7.7%)	103 (19.9%)	100 (21.9%)	62 (19.2%)
BCLC C	437 (65.6%)	171 (33.1%)	73 (16.0%)	37 (11.5%)
BCLC D	80 (12.0%)	68 (13.2%)	26 (5.7%)	15 (4.6%)
Staging (HCC diagnosed via surveillance)				
BCLC 0/A	31 (49.2%)	99 (62.7%)	203 (73.8%)	154 (76.6%)
BCLC B	13 (20.6%)	30 (19.0%)	54 (19.6%)	32 (15.9%)
BCLC C/D	13 (20.6%)	28 (17.7%)	18 (6.5%)	12 (6.0%)

Disclosures: Wei-Lun Liou: Nothing to Disclose, Yi-Xuan Lee: Nothing to Disclose, Kaina Chen: Nothing to Disclose, George Boon-Bee Goh: Nothing to Disclose, Jason Pik Eu Chang: Nothing to Disclose, Chee-Kiat Tan: Eisai: Advisor, Abbott Laboratories: Advisor, Gilead Sciences: Advisor, Roche Diagnostics: Advisor, FUJIFILM: Advisor

◆ 3136 | ASSOCIATION OF CONCOMITANT MASLD AND HEPATITIS B VIRUS WITH CLINICAL OUTCOMES IN HEPATOCELLULAR CARCINOMA FOLLOWING CURATIVE RESECTION

Chih Wen Lin[1] Yaw-Sen Chen[1] Yao-Chun Hsu[1] Wen-Lung Wang[1] Chih-Jan Ko[2] Shang-Chen Tseng[1] Ming-Lung Yu[3], [1]E-Da Hospital, I-Shou University, [2]China Medical University Hsinchu Hospital, [3]Kaohsiung Medical University

Background: In 2023, a multisociety Delphi consensus redefined that the term "metabolic dysfunction–associated steatotic liver disease" (MASLD) was introduced to replace the term "nonalcoholic fatty liver disease." The prevalence of MASLD is increasing worldwide. The prevalence of concomitant MASLD and hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) is also increasing. In Taiwan, where HBV is endemic, the prevalence of concurrent MASLD in HBV-related HCC is expected to increase. Only one study has explored the effect of MASLD on the clinical prognosis of HBV-related HCC after curative hepatectomy. The new definitions emphasize MASLD as a critical condition that can coexist with HBV, highlighting the need for further research in this area. Accordingly, the present study investigated the effect of MASLD and HBV coexistence on the clinicopathological features and long-term clinical outcomes of MASLD and/or HBV-related HCC after curative hepatectomy. The study focused on HBV-endemic countries with a high prevalence of HCC. **Methods:** The study retrospectively collected the data of 653 patients with HCC who had undergone curative hepatectomy between 2011 and 2022 from E-Da health group. Patients were included if they were diagnosed as having HBV infection, were diagnosed as having MASLD, underwent curative hepatectomy between 2011 and 2022, and had a pathology report of liver steatosis. Patients were excluded if they lacked a report of liver steatosis, were diagnosed as having HCV infection, consumed a substantial amount of alcohol (>210 g/week for men, >140 g/week for women), or had less than 6 months of follow-up data. We assessed the association of histologically confirmed MASLD with HCC recurrence and mortality. **Results:** Of 653 patients, 320 (49.0%), 103 (15.8%), and 230 (35.2%) had concomitant MASLD and HBV, MASLD only, andHBV only, respectively. The median follow-up period was 5.1 years. Patients with concomitant MASLD and HBV were at a significantly increased risk of HCC recurrence ($P = 0.013$ and $P = 0.041$) and mortality ($P = 0.044$ and $P = 0.026$) than those with MASLD or HBV alone in Figure 1. Multivariable analysis results indicated that male sex (hazard ratio [HR]: 1.66; 95% confidence interval [CI]: 1.15–2.42, $P = 0.008$), tumor size ≥ 5 cm (HR: 1.35; 95% CI, 1.06–1.72, $P = 0.022$), and concomitant MASLD and HBV (HR: 1.62; 95% CI, 1.13–2.33, $P = 0.007$) were also significant risk factors for HCC recurrence. However, BMI ≥ 23 (HR: 0.56; 95% CI, 0.41–0.76, $P < 0.001$) and antiviral therapy (HR: 0.74; 95% CI, 0.56–0.95, $P = 0.021$) were significantly associated with lower HCC recurrence rates. Furthermore, multivariable analysis results revealed that male sex (HR: 1.66; 95% CI: 1.09–2.52, $P = 0.019$), type 2 diabetes mellitus (HR: 1.54; 95% CI, 1.13–2.09, $P = 0.006$), serum aspartate aminotransferase ≥ 40 U/L (HR: 1.34; 95% CI, 1.02–1.76, $P = 0.033$), tumor size ≥ 5 cm (HR: 1.56; 95% CI, 1.19–2.05, $P < 0.001$), tumor cell differentiation II–III (HR: 3.63; 95% CI, 1.89–6.95, $P < 0.001$), microvascular invasion (HR: 1.51; 95% CI, 1.21–2.05, $P = 0.007$), lymph node invasion (HR: 2.29; 95% CI, 1.28–4.09, $P = 0.005$), tumor recurrence (HR: 2.79; 95% CI, 2.14–3.66, $P < 0.001$), and concomitant MASLD and HBV (HR: 1.45; 95% CI, 1.01–2.08, $P = 0.046$) were significant risk factors for mortality. **Conclusion:** Patients with concomitant MASLD and HBV are at a significantly greater risk of HCC recurrence and mortality after curative hepatectomy than those with MASLD or HBV alone.

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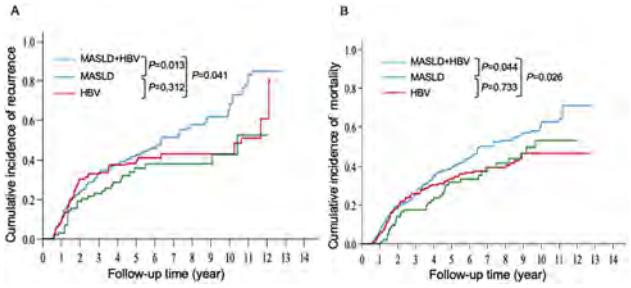
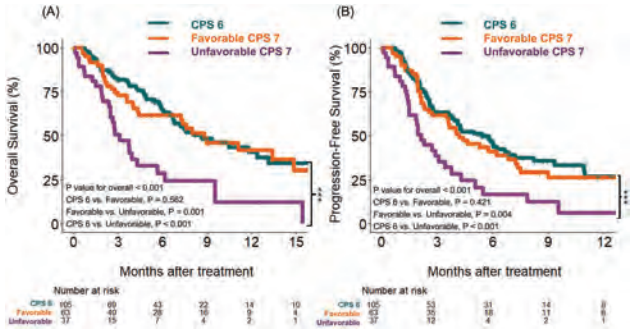


Disclosures: Chih Wen Lin: Nothing to Disclose, Yaw-Sen Chen: Nothing to Disclose, Yao-Chun Hsu: Nothing to Disclose, Wen-Lung Wang: Nothing to Disclose, Chih-Jan Ko: Nothing to Disclose, Shang-Chen Tseng: Nothing to Disclose, Ming-Lung Yu: Abbvie, Gilead and Roche diagnostics.: Grant/Research Support, Abbott, Abbvie, Gilead, Roche and Roche diagnostics: Consultant, Abbvie, BMS, Gilead, Roche and Roche diagnostics: Speaking and Teaching

◆ 3137 | CHILD-PUGH SCORE 7 WITH MILD ASCITES AND HYPOALBUMINEMIA DEMONSTRATES COMPARABLE OUTCOMES TO CHILD-PUGH SCORE 6 IN HCC PATIENTS TREATED WITH ATEZOLIZUMAB/BEVACIZUMAB

Soon Kyu Lee[1] Jaejun Lee[1] Keungmo Yang[1] Ji Won Han[1] Pil Soo Sung[1] Jeong Won Jang[1] Hee Sun Cho[1] Hyun Yang[2] SI HYUN BAE[1] Heechul Nam[1] Chang Wook Kim[3] Hae Lim Lee[1] Hee Yeon Kim[1] Sung Won Lee[1] Ahlim Lee[1] Do Seon Song[1] Myeong Jun Song[1] SOON WOO NAM[1] Jung Hyun Kwon[4], [1]College of Medicine, The Catholic University of Korea, [2]Seoul St. Mary's Hospital, [3]Uijeongbu St. Mary's Hospital, [4]The Catholic University of Korea

Background: Atezolizumab plus bevacizumab (Ate/Bev) has demonstrated remarkable outcomes and is now approved as a first-line treatment for patients with advanced hepatocellular carcinoma (HCC), particularly those with a Child-Pugh score (CPS) of 5 or 6. However, as limited data exist regarding its efficacy in patients with CPS 7, this study aims to evaluate the effectiveness of Ate/Bev in CPS 7 patients and to identify specific subgroups within CPS 7 that may benefit from this treatment. **Methods:** This study included patients with advanced HCC who received Ate/Bev as first-line therapy between September 2020 and December 2023 at six university hospitals. The primary outcome was overall survival (OS), while secondary outcomes included progression-free survival (PFS) and treatment response. Within the CPS 7 group, patients were further subdivided into two groups based on the survival risk distribution of CPS variables. **Results:** Among the 374 included patients, those with CPS 5 (n = 169) demonstrated the highest OS and PFS, followed by patients with CPS 6 (n = 105) and CPS 7 (n = 100) ($P < 0.05$). For the variables comprising CPS, the hazard ratio (HR) for OS increased with elevated total bilirubin (TB) levels and was lower in patients with moderate or severe ascites ($P < 0.05$). Regarding albumin levels, the HR for OS tended to decrease as albumin levels dropped to 2.8 g/dL. Based on these findings, CPS 7 patients were further classified into two subgroups: favorable (TB < 2 mg/dL, $3.5 >$ Alb ≥ 2.8 g/dL, mild ascites, and absence of hepatic encephalopathy) and unfavorable (other CPS 7). Compared to patients with CPS 6, those in the favorable CPS 7 group exhibited similar OS and PFS, while unfavorable CPS 7 patients had significantly lower OS and PFS ($P < 0.05$, Figure A and B). Moreover, the favorable CPS7 group demonstrated higher treatment response compared to the unfavorable CPS7 group. Multivariate analysis identified unfavorable CPS 7 as a significant risk factor for both OS and PFS ($P < 0.01$). **Conclusion:** This study suggests that Ate/Bev treatment can be effective in favorable CPS 7 patients, highlighting the potential to broaden treatment eligibility for this population.



Disclosures: Soon Kyu Lee: Nothing to Disclose, Jaejun Lee: Nothing to Disclose, Keungmo Yang: Nothing to Disclose, Ji Won Han: Nothing to Disclose, Pil Soo Sung: Nothing to Disclose, Jeong Won Jang: Nothing to Disclose, Hee Sun Cho: Nothing to Disclose, Hyun Yang: Nothing to Disclose, SI HYUN BAE: Nothing to Disclose, Heechul Nam: Nothing to Disclose, Chang Wook Kim: Nothing to Disclose, Hae Lim Lee: Nothing to Disclose, Hee Yeon Kim: Nothing to Disclose, Sung Won Lee: Nothing to Disclose, Ahlim Lee: Nothing to Disclose, Do Seon Song: Nothing to Disclose, Myeong Jun Song: Nothing to Disclose, SOON WOO NAM: Nothing to Disclose, Jung Hyun Kwon: Nothing to Disclose

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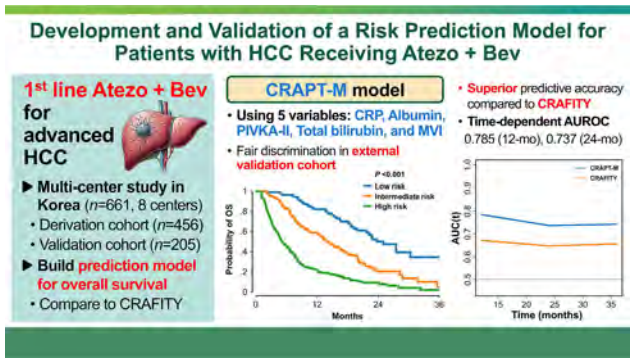
3138 | DEVELOPMENT AND VALIDATION OF A RISK PREDICTION MODEL FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA RECEIVING ATEZOLIZUMAB-BEVACIZUMAB

Heechul Nam[1] Dong Yun Kim[2] Sung Won Lee[1] Do Young Kim[3] Jeong Won Jang[1], [1]The Catholic University of Korea, [2]Yonsei University, [3]Yonsei University College of Medicine

Background: Atezolizumab plus bevacizumab (AB) has become the standard first-line treatment for advanced hepatocellular carcinoma (HCC). However, identifying reliable prognostic biomarkers remains a critical challenge. We aimed to develop a comprehensive scoring system to predict overall survival (OS) in advanced HCC patients receiving first-line AB. **Methods:** We established inception cohorts consisting of consecutive HCC patients who were undergoing AB treatment. The derivation cohort was constructed in a retrospective multicenter manner, including patients from seven academic hospitals of the Catholic University of Korea between September 2020 and July 2024. For validation, we used a retrospective single-center cohort from Severance Hospital, Korea, spanning October 2020 to December 2023. **Results:** We included patients with advanced HCC receiving first-line (AB) from multiple centers in Korea, forming a derivation cohort (n = 456) and a validation cohort (n = 205). Multivariable analysis identified five independent prognostic factors: C-reactive protein ≥ 1.0 mg/dL (hazard ratio [HR] 2.06; p < 0.001), albumin < 3.5 g/dL (HR 1.60; p = 0.002), protein induced by vitamin K absence or antagonist-II ≥ 1,500 mAU/mL (HR 1.60; p = 0.002), total bilirubin ≥ 1.0 mg/dL (HR 1.50; p = 0.006), and macrovascular invasion (HR 1.48; p = 0.009). We developed the CRAPT-M model named after these factors' initial letters. Patients were categorized into low (≤ 4), intermediate (5-12), and high (≥ 13) risk groups by CRAPT-M score. Median OS differed significantly: 22.4 (95% CI, 18.6-25.0), 12.9 (95% CI, 8.7–14.8), and 6.7 (95% CI, 5.1–7.7) months for low-, intermediate-, and high-risk groups, respectively (p < 0.001). Time-dependent area under the receiver operating characteristic for CRAPT-M demonstrated consistently higher predictive accuracy than the CRAFITY model, with values of 0.785, 0.737, and 0.742 at 12, 24, and 36 months, respectively. The model demonstrated robust predictive performance in external validation cohort, with excellent calibration and consistent discrimination across sensitivity analyses. **Conclusion:** The CRAPT-M model demonstrated robust OS prediction, offering a valuable tool for prognosis estimation and clinical decision-making in advanced HCC patients receiving AB.



Disclosures: Heechul Nam: Nothing to Disclose, Dong Yun Kim: Nothing to Disclose, Sung Won Lee: Nothing to Disclose, Do Young Kim: Nothing to Disclose, Jeong Won Jang: Nothing to Disclose

3139 | POLY(I:C) COULD BE AN EFFICIENT CANCER ADJUVANT FOR IMMUNOTHERAPY IN HEPATOCELLULAR CARCINOMA BY ACTIVATING CYTOTOXIC CD8+ T CELLS

yichun ji[1] Yanting Wang[2] Nicholas Webster[3] Gensheng Feng[3], [1]Department of Medicine, University of California San Diego, [2]the Second Affiliated Hospital of Zhejiang University School of Medicine, [3]University of California, San Diego

Background: Immune checkpoint inhibitors combined with antiangiogenic therapy has become the standard of care for advanced hepatocellular carcinoma, albeit with limited therapeutic benefit. Our previous studies demonstrated the immunomodulatory and antitumor effects of polyIC, a synthetic double-stranded RNA. Here, we compared the efficacy of anti-programmed death ligand 1 (αPD-L1) plus polyIC versus αPD-L1 plus anti-vascular endothelial growth factor (αVEGF) in primary and metastasized liver tumor models. **Methods:** We established a primary liver tumor model using hydrodynamic tail vein injection of Ras/Myc oncogenes and metastasized model via intrasplenic injection of colon cancer cells. Flow cytometry and gene expression analysis were performed to assess immune profiles across treatment groups. Key factors contributing to

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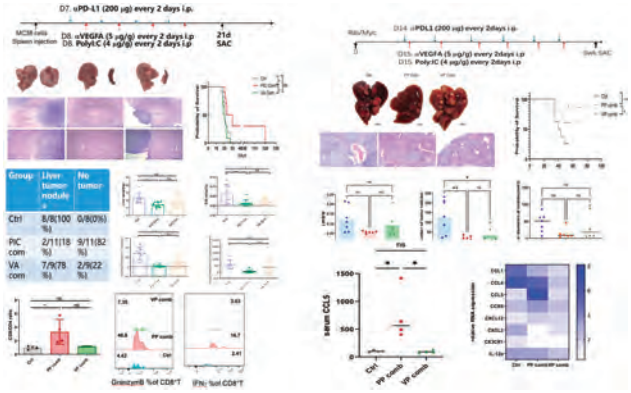
antitumor efficacy were explored. **Results:** In both models, αPD-L1 plus polyIC demonstrated superior antitumor effects relative to αPD-L1 plus αVEGF. Unlike αVEGF, polyIC enhanced the immune response to αPD-L1 by increasing T cell infiltration, T effector memory CD8+ T cells, CD8+ to CD4+ T cell ratios, and CD8+ T cell function. This combination also promoted apoptosis in tumors and accumulation of conventional dendritic cells and invariant Natural Killer T cells. Additionally, αPD-L1 plus polyIC treatment led to upregulation of cytokines and chemokines, with CCL5 blockade partially reducing CD8+ to CD4+ T cell ratios and attenuating polyIC-driven antitumor effects. **Conclusion:** This preclinical study identifies polyIC as a better enhancer of αPD-L1 efficacy than αVEGF in liver cancer, providing a novel strategy for improving immunotherapy outcomes. Further clinical investigation is warranted.



Disclosures: yichun ji: Nothing to Disclose, Yanting Wang: Nothing to Disclose, Nicholas Webster: Nothing to Disclose, Gensheng Feng: Nothing to Disclose

3140 | NON-ADHERENCE TO SURVEILLANCE PROTOCOL OF HEPATOCELLULAR CANCER IN PATIENTS WITH LIVER CIRRHOSIS: PREVALENCE AND REASONS

Vaibhav Padole[1] Arun Vaidya[1] Akash Shukla[1], [1]Seth GS Medical College & KEM Hospital

Background: Surveillance for hepatocellular carcinoma (HCC) in cirrhosis is recommended. There is paucity of data regarding adherence to the surveillance protocols. We conducted this study to assess the adherence to HCC surveillance protocol (6monthly alfa-feta protein [AFP] and ultrasound [USG]) and determine factors responsible for non-adherence. **Methods:** We collected data of 3 year follow-up of consecutive adult patients with liver cirrhosis from a prospectively maintained database with regards to adherence to the HCC . Patients with pre-existing liver lesions and incomplete medical records were excluded. Factors leading to non-adherence were enquired during each visit. **Results:** Out of 945 patients screened, 800 patients (649 males; mean age 47.7 years) were included. The etiology of cirrhosis was alcohol- related liver disease[380(47.6 %)], chronic hepatitis B seen [139(17.4%)], metabolic dysfunction associated steatotic liver disease [98 (12.3%)] and chronic hepatitis C [92(11.5%)] . Only 73/800(9.1%) patients were completely adherent to protocol. Additionally, 346 (47.5%) patients were compliant to six- monthly ultrasound abdomen but not with serum AFP testing. The factors leading to non-adherence are enumerated in Table 1. Lack of advice by the treating doctor was the commonest cause for non-adherence to HCC surveillance (almost one-fourth of patients). **Conclusion:** Only a small minority adhere to the HCC surveillance protocol. The most common cause for non-adherence to HCC surveillance was lack of advice by treating doctor for surveillance, followed by lack of access to surveillance tools.

Table 1: Factors leading to non-adherence to HCC surveillance protocol

Factors	Number and proportion of patients with non-adherence (total 727 patients)
Serum AFP or ultrasound not advised by treating doctor	189 (26%)
Living in remote area with no nearby access	115 (15.8%)
Was unwell at the time of visit for the HCC surveillance	70 (9.6%)
Financial constraints	128 (17.6%)
Felt that they were better and need not follow-up	90 (12.3 %)
Radiology appointment delay	56 (7.7%)
Could not specify the reason	42 (5.7%)
More than one risk factor	37 (5.1%)

Disclosures: Vaibhav Padole: Nothing to Disclose, Arun Vaidya: Nothing to Disclose, Akash Shukla: Nothing to Disclose

3141 | COMBINED TEAD AND RAS INHIBITOR THERAPY ACHIEVES LONG-TERM SURVIVAL IN KRAS-MUTANT CHOLANGIOCARCINOMA

Qiuyan Sun[1] Dhruv Goyal[1] Sheila Gonzalez Ramos[1] Robert Schwabe[1], [1]Columbia University

Background: Despite an expanding arsenal of FDA-approved therapies for the treatment of cholangiocarcinoma (CCA), including chemotherapy +/- immunotherapy and targeted therapies, 5-year survival remains below 7-20%. Here, we sought to uncover novel therapeutic vulnerabilities in CCA and synergistic

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combination treatments. **Methods:** Expression of transcriptional regulators and druggable targets was analyzed by bulk RNA-seq in mouse models of CCA and the TCGA and Fu-iCCA cohorts, and validated by scRNA-seq in 14 patients. *In vivo* CRISPR interference (CRISPRi) and pharmacologic panTEAD inhibitors (panTEADi) VT104 and IAG933 were used to functionally study the role of TEADs in CCA growth in the $KRAS^{G12D}$+$p19^{CRISPR}$, FBXW7delF+AKT and NICD +AKT models. RAS inhibition (RASi) was achieved using $KRAS^{G12D}$ inhibitor MRTX1133 and panRAS inhibitors RMC-7977 and RMC-6236. Drug synergies were evaluated in primary CCA cell lines and in $KRAS^{G12D}$+$p19^{CRISPR}$ model. **Results:** Bulk and scRNA-seq analysis in mouse CCA models, the TCGA and Fu-iCCA cohorts and human scRNA-seq data revealed a consistent upregulation of YAP/TAZ/TEAD pathway members. Tumor cell-specific CRISPRi of each of the four TEAD paralogs significantly reduced tumor burden and extended survival in mouse models of CCA, suggesting YAP/TAZ/TEAD as a novel therapeutic target. Pharmacologic panTEADi suppressed YAP target gene expression, altered tumor transcriptomic profiles, impaired proliferation, and improved survival across three distinct mouse models, including KRAS-driven CCA. Based on the high prevalence of KRAS mutations in CCA, we next evaluated the therapeutic potential of combined panTEADi and RASi treatment. VT104 or IAG933 plus $KRAS^{G12D}$-specific inhibitor MTRX1133 or panRAS inhibitors RMC-7977 and RMC-6236 blocked compensatory YAP/TAZ pathway activation, achieved strong synergies *in vitro* and extended median survival from 2.3 weeks to 9.7 weeks (VT104 + MRTX1133, $p < 0.0001$) and 14.4 weeks (VT104 + RMC7977, $p < 0.0001$) in $KRAS^{G12D}$-driven CCA. However, prolonged dual therapy induced resistance and the emergence of drug-tolerant persister cells, stromal remodeling, and treatment failure. Mechanistic analysis implicated the contribution of epithelial-mesenchymal transition (EMT) in tumor cells and enhanced fibroblast activation and extracellular matrix deposition in the TME in the development of resistance, which can be partially reversed by targeting cancer-associated fibroblasts (CAFs). **Conclusion:** Collectively, our study identified TEAD and RAS signaling as convergent and druggable vulnerabilities that can be targeted to prolong CCA survival and delay the development of resistance.

Disclosures: Qiuyan Sun: Nothing to Disclose, Dhruv Goyal: Nothing to Disclose, Sheila Gonzalez Ramos: Nothing to Disclose, Robert Schwabe: Nothing to Disclose

3142 | HORMONE-REPLACEMENT THERAPY REDUCES THE RISK OF HEPATOCELLULAR CARCINOMA AND SLOWS CHRONIC LIVER-DISEASE PROGRESSION IN POST-MENOPAUSAL WOMEN: A PROPENSITY-MATCHED TRINETX ANALYSIS

Prabhat Kumar[1] Archana Kharel[2] Michael Eiswerth[1] Vinay Jahagirdar[1] Hasan Alroobi[1] umesh bhagat[2] Gowthami Kanagalingam[1] Scott Matherly[1], [1]Virginia Commonwealth University, [2]Cleveland Clinic Foundation

Background: Estrogen has antifibrotic and antitumor properties in experimental liver models, yet population-level data on its clinical impact remain limited. We assessed whether hormone-replacement therapy (HRT) has a role in reducing the risk of development of hepatocellular carcinoma (HCC) and the development of chronic liver disease (CLD) in women without pre-existing liver disorders. **Methods:** We queried the cloud-based TriNetX Research Network (> 100 U.S. and international health-care systems) for women ≥ 50 years without chronic liver disease ICD-10 codes K70–K76 (database inception–May 2025). Exposure was systemic hormone-replacement therapy (HRT: estradiol or conjugated estrogens). Women with prior hepatocellular carcinoma (HCC; C22.0), liver transplantation (Z94.4), or unspecified primary malignancy (C80.1) before index were excluded. Greedy 1:1 propensity-score matching (caliper 0.01) balanced age, race, body-mass index, digestive-system disorders, and endocrine/metabolic comorbidities, yielding two cohorts of 203,726 each (standardized differences < 0.01). Follow-up began one day post-index and continued until outcome, death, or end of data. Primary outcomes were (i) incident HCC and (ii) incident/progressive chronic liver disease (fatty liver, NASH, or cirrhosis newly coded). Absolute risk, risk difference (RD), risk ratio (RR), Kaplan–Meier curves, and Cox hazard ratios (HR) were calculated. **Results:** After matching, the median age was 63 years with identical racial and BMI distributions. HCC developed in 2,632 non-HRT women (1.29 %) versus 1,853 HRT users (0.91 %), yielding an RD = -0.38 %, RR 1.42 (non-HRT vs. HRT; 95 % CI 1.34-1.51), and HR 1.48 (1.40-1.57; log-rank $p < 0.001$). Chronic liver disease progression occurred in 68,796 non-HRT patients (33.8 %) vs. 62,570 HRT patients (30.7 %): RD = -3.1 %, RR 1.10 (1.09-1.11), and HR 1.19 (1.18-1.20; log-rank $p < 0.001$). Median time to CLD was delayed by > 2,500 days with HRT (6,646 vs. 4,114). Survival

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probabilities at study end were consistently higher among estrogen users for both endpoints. **Conclusion:** In a large real-world cohort of women without underlying liver disease, estrogen therapy was associated with a 40 % relative reduction in HCC incidence and a 10 % relative reduction—and marked delay—in CLD progression after rigorous confounder adjustment. These findings suggest a hepatoprotective role for HRT and support prospective trials to clarify causality and inform clinical decision-making for post-menopausal women at risk for liver malignancy and fibrosis.

Table 1. Outcomes for incidence of hepatocellular carcinoma (HCC) in post-menopausal women after 1:1 propensity-score matching.

Cohort	Patients in Cohort	Patients with Outcome	Risk	
Without HRT	203,726	2,632	0.013	
With HRT	203,726	1,853	0.009	
Statistical Analysis:				
Measure	Value	95% Confidence Interval	z-value	p-value
Risk Difference	0.004	(0.003, 0.004)	11.697	<0.001
Risk Ratio	1.42	(1.339, 1.507)	N/A	N/A
Odds Ratio	1.426	(1.343, 1.514)	N/A	N/A

Table 2. Survival analysis for incidence of chronic liver disease (CLD) in post-menopausal women after 1:1 propensity-score matching.

Cohort	Patients in Cohort	Patients with Outcome	Median Survival (days)	Survival Probability (%)	
Without HRT	203,726	68,796	4,114	42.71%	
With HRT	203,726	62,570	6,646	49.70%	
Statistical Analysis:					
Test	HR	CI	Chi-square (χ^2)	df	p-value
Log-Rank Test			968.913	1	<0.001
Hazard Ratio	1.187	95% CI (1.175 - 1.200)	χ^2 = 12.401	1	<0.001

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3143 | EXTRATUMORAL HSC-DERIVED CXCL12 PROMOTES LIVER METASTASIS IN MASLD THROUGH THE CXCR4/YAP AXIS AND IMMUNE-FIBROTIC REMODELING

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Background: Liver metastasis is a major determinant of poor prognosis in patients with colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC). MASLD significantly increases the risk of liver metastasis, yet the underlying mechanisms are not fully understood. We previously showed that intratumoral hepatic stellate cells (HSCs) or cancer-associated fibroblasts (CAFs) in steatotic livers promote metastasis in metabolic dysfunction-associated steatotic liver disease (MASLD) by mediating intercellular communication within the tumor microenvironment (TME). However, the role of extratumoral HSCs in MASLD-related liver metastasis remains unclear. Here, we hypothesized that CXCL12 secreted by extratumoral HSCs recruits and activates cancer cells, CAFs, and immune cells through the CXCL12/CXCR4/YAP axis, establishing a pro-metastatic niche. **Methods:** To model MASLD-associated liver metastasis, mice were fed either a low-fat or high-fat diet (HFD) for 6 weeks, followed by splenic injection of MC38 CRC or Pan02 PDAC cells, and monitored for two additional weeks. **Results:** HFD-fed mice developed more liver metastases and higher CXCL12 expression in HSCs. CXCL12+ HSCs were primarily found in extratumoral, non-tumor liver areas and did not produce collagen, whereas intratumoral HSCs produced collagen but expressed little CXCL12. This spatial distinction suggests that extratumoral HSCs initiate a chemotactic niche via CXCL12, while intratumoral HSCs contribute to fibrosis. In HSC-specific CXCL12-deleted mice, metastatic tumor growth, CAF activation, and collagen deposition were reduced. Mechanistically, we identified HIF-1α as a transcriptional regulator of CXCL12 in HSCs. Deleting HIF-1α in HSCs downregulated CXCL12 and suppressed metastasis in MASLD. Steatotic liver also enhanced collagen deposition and CXCR4, YAP, CD44, and osteopontin (OPN) expression in tumor areas. In 3D spheroid cultures, collagen-rich matrices induced CXCR4 and YAP expression in cancer cells, but this effect was abolished by CXCR4 deletion, indicating that CXCR4/YAP axis is critical for tumor growth in the fibrotic TME. Our scRNA-seq analysis further revealed that M2 macrophages in steatotic livers highly express CXCR4, CD44, and PD-L1, and interact with PD1+ exhausted CD8 T cells. In addition, activated CAFs express OPN and interact with CD44+ M2 macrophages and cancer cells in the fibrotic TME. These interactions are enriched in steatotic livers and contribute to an immunosuppressive TME in steatotic livers. **Conclusion:** In conclusion, CXCL12 from extratumoral HSCs orchestrates the recruitment and activation of cancer cells, CAFs, and immune cells, thereby reshaping the TME through CXCR4/YAP axis in MASLD-associated liver metastasis.

Disclosures: Jieun Kim: Nothing to Disclose, So Yeon Kim: Nothing to Disclose, Mustafa Karabicici: Nothing to

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Disclose, Ekihiro Seki: Nippon Zoki: Research Grant Support, Novonordisc: Consultant

3144 | ACCURATE DIAGNOSIS OF HEPATOCELLULAR CARCINOMA WITH A HIGH-THROUGHPUT TEST FOR PLASMA DNA METHYLATION SIGNATURES

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Background: Early diagnosis of hepatocellular carcinoma (HCC) is often challenging due to the limited accuracy of current biomarkers. DNA methylation signatures may enable differentiation of HCC and non-HCC DNA in plasma, which in turn facilitates noninvasive and accurate HCC detection. **Methods:** Consecutive patients with HCC referred to a tertiary surgical unit for management were prospectively recruited. Healthy controls were also recruited for comparison. Plasma samples were taken from all subjects and analyzed with the epiLiver test, which is a validated high-throughput test for detection of DNA methylation signatures. The epiLiver test assesses four CpG markers in cg02012576, cg03768777, cg05739190, and cg24804544 of the CHFR, VASH2, CCNJ, and GRID2IP gene respectively. **Results:** This exploratory analysis included 86 patients (61 HCC patients and 25 healthy controls, mean age 57.5 +/- 17.9, 72.1% male). Among the HCC patients, 56 patients (91.8%) had chronic hepatitis B and 32 patients (52.5%) had cirrhosis. The Barcelona Clinic Liver Cancer (BCLC) staging was BCLC-0, BCLC-A, BCLC-B, and BCLC-C in 15 (24.6%), 39 (63.9%), 3 (4.9%), and 4 (6.6%) of patients respectively. The epiLiver test achieved area under curve of 0.861 for diagnosing HCC (Specificity 100%, sensitivity 72.1%, positive predictive value 100%, negative predictive value 59.5%). All healthy controls had negative results. The epiLiver test had excellent performance in patients with higher HCC and liver disease burden, as it accurately identified HCC in 87.5% of patients with cirrhosis, 85.7% of patients with BCLC-B or BCLC-C staging, 84.2% of patients with alpha fetoprotein $\geq$ 20 ng/ml, and 80.6% of patients with dominant HCC lesion $\geq$ 3 cm respectively. **Conclusion:** Our high-throughput test for plasma DNA methylation signatures accurately diagnosed HCC with high specificity. This technology has potential as a confirmatory test, and its role in HCC prognostication should be further explored.

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3145 | UNDER-UTILIZATION OF ANTIVIRAL THERAPIES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC) AND VIRAL HEPATITIS B (HBV) OR C (HCV): A MULTINATIONAL REAL-WORLD STUDY

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Background: Antiviral treatment is associated with improved survival and cancer recurrence in viral HCC patients, but treatment rate data is limited. We aimed to assess the utilization rates of antiviral treatment in HBV patients with either HBV or HCV. **Methods:** We conducted a multicenter real-world study of adult HCC patients with either HBV or HCV from 16 centers across

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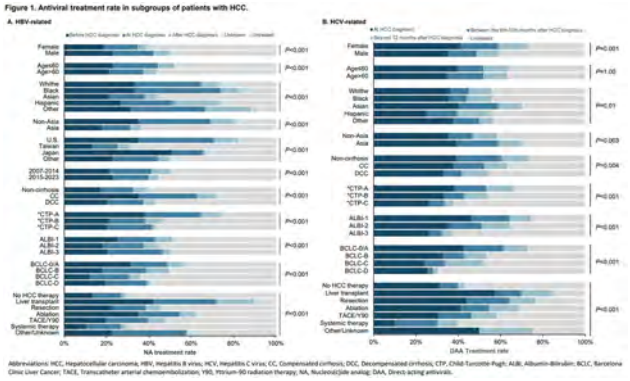
7 countries/regions. The primary study outcomes were the treatment rates with either nucleos(t)ide analogs (NAs) at any time in HBV-HCC patients or direct acting antivirals (DAAs) at/or after HCC diagnosis in HCV-HCC patients. **Results:** We analyzed 3883 HCC patients: 3186 with HBV and 647 with HCV. Overall, half (49.7%) of HCC patients with HBV and two-third (63.2%) of those with HCV received antiviral treatment, with marked variations among the subgroups for both the HBV and HCV groups **(Figure 1)**. For HBV patients, NA treatment rates were lower in those who were female (41.7 vs. 51.8%), older than 60 (45.3 vs. 54.5%), without cirrhosis (41.2 vs. 56.8%) and from Asia (37.9 vs. 85.0%), all $P < 0.001$, while among HCV patients, DAA treatment rates were lower in patients who were male (59.0 vs. 72.4%), without cirrhosis (60.5 vs. 73.2%) and from non-Asia regions (58.2 vs. 69.9%), all $P < 0.005$. Child C (vs. A and B) cirrhosis also patients had lower antiviral treatment rates for both NA (78.6 vs. 48.3 vs. 43.8%) and DAA (68.2 vs. 53.3 vs. 38.6%), while early BCLC stage (0/A vs. B vs. C vs. D) patients had higher rates for both NA (59.9 vs. 50.9 vs. 36.7 vs. 41.0%) and DAA (72.5 vs. 53.3 vs. 51.9 vs. 30.2%), respectively, all $P < 0.001$. In multivariable regressions, factors associated with lower NA treatment rate were female sex [adjusted odds ratio (aOR) = 1.59 for male vs. female], age > 60 (aOR = 0.63), Asia (vs the U.S) such as Taiwan (aOR 0.11) and Japan (aOR 0.49), and noncirrhosis (aOR = 1.62 for Child A and 1.36 for Child B vs. noncirrhosis) for HBV (all $P < 0.05$), and included male sex (aOR 0.62), age > 65 (aOR 0.65), and Child B (aOR = 0.46) or C (aOR 0.35) for HCV (all $P < 0.05$). BCLC stage B or C (vs. 0/A) were associated with lower treatment rate in both HBV (aOR = 0.76, 0.58) and HCV (aOR = 0.57, 0.53), respectively (all $P < 0.05$). **Conclusion:** In this global study of HCC patients, only 50% of HBV and 60% of HCV patients received antiviral treatment, with multiple age, sex, and region-specific disparities, often in opposite directions between HBV and HCV patients. Treatment rates were especially poor in those who may benefit the most such as those with more advanced liver disease or HCC stage.



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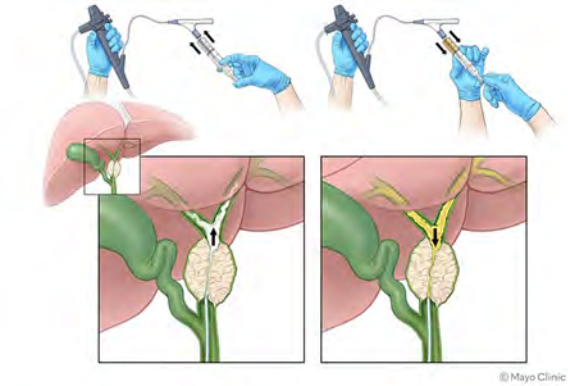
3146 | A PROSPECTIVE STUDY OF CYTOLOGY, FISH, AND METHYLATED DNA MARKERS IN BILE AND BILIARY LAVAGE FOR PANCREATOBILIARY CANCER DETECTION

Shuji Mitsuhashi[1] Chinmay Guralwar[1] Qiliang Ding[1] Emily Barr Fritcher[1] Manik Aggarwal[1] Khushboo Gala[1] Rishad Khan[1] Eric Vargas[1] Ryan Law[1] John Martin[1] Bret Petersen[1] Samuel Han[1] Jad AbiMansour[1] Andrew Storm[1] Gregory Gores[1] Lewis Roberts[1] Benjamin Kipp[1] Vinay Chandrasekhara[1], [1]Mayo Clinic Rochester

Background: Early diagnosis of pancreatobiliary (PB) malignancies remains challenging due to the limited sensitivity of current methods. While ERCP-based brush cytology and fluorescence *in situ* hybridization (FISH) improve diagnostic yield in biliary strictures, overall performance remains suboptimal. Post-brushing biliary lavage may enhance detection by capturing residual tumor material dislodged during diagnostic maneuvers. This study evaluated whether methylated DNA markers (MDMs) in bile and/or post-brushing lavage fluid improve diagnostic accuracy. **Methods:** This prospective single-center study included patients undergoing ERCP-guided sampling for biliary strictures between 2023 and 2024. Samples were obtained via bile aspiration before brushing (Bile-MDMs), brush cytology with FISH, and post-brushing biliary lavage and aspiration (Lavage-MDMs) (Figure 1). Positive cytology was defined as “suspicious” or “malignancy”. Previously identified MDM panel (TWIST1, HOXA1, CLEC11A, VSTM2B) was analyzed using methylation-specific droplet digital PCR. Malignancy was defined by histopathology or by meeting institutional clinical criteria. Benign cases were confirmed by negative surgical pathology and $\geq$6 months of follow-up. **Results:** Of 51 patients, 16 (31.0%) were diagnosed with malignancy: 10 cholangiocarcinoma (CCA), 2 pancreatic adenocarcinoma, 3 periampullary adenocarcinoma, and 1 gallbladder adenocarcinoma. 22 (43.1%) had primary sclerosing cholangitis, of whom 19 had benign disease and 3 were diagnosed with CCA. The diagnostic sensitivities of individual tests were as follows: brush cytology 50.0%, polysomy FISH 68.8%, Bile-MDMs 46.7%, and Lavage-MDMs 66.7%. Combining brush cytology and/or polysomy FISH improved sensitivity to 81.3%. While Lavage-MDMs demonstrated higher standalone sensitivity compared to Bile-MDMs, both assays provided comparable additive diagnostic value when used alongside cytology and FISH. The highest diagnostic performance was achieved when all modalities were combined, yielding a sensitivity 93.8%, specificity 77.1%, positive predictive value 65.2%, and negative predictive value 96.6%. Sample acquisition was successful in all patients, and no adverse events were observed. **Conclusion:** Post-brushing biliary lavage enhances MDM sensitivity compared to pre-brushing bile samples. When combined with cytology and FISH, both contribute similarly to a safe, and high-yield strategy for enhancing the diagnosis of PB malignancy during ERCP.



	Sensitivity	(95% CI)	Specificity	(95% CI)	PPV (95% CI)		NPV (95% CI)	
Cytology	50.0%	(36.3-63.7%)	100.0%	(100.0-100.0%)	100.0%	(100.0-100.0%)	81.4%	(70.7-92.1%)
Polysomy FISH	68.8%	(56.0-81.5%)	97.1%	(92.6-101.7%)	91.7%	(84.1-99.3%)	87.2%	(78.9-95.4%)
Bile-MDMs	46.7%	(32.7-60.6%)	85.3%	(75.4-95.2%)	58.3%	(44.9-72.1%)	78.4%	(66.9-89.9%)
Lavage-MDMs	66.7%	(53.2-80.1%)	81.3%	(70.1-92.4%)	62.5%	(48.7-76.3%)	83.9%	(73.4-94.4%)
Cytology and/or FISH	81.3%	(70.5-92.0%)	97.1%	(92.6-101.7%)	92.9%	(85.8-99.9%)	91.9%	(84.4-99.4%)
Bile-MDMs and/or Lavage-MDMs	66.8%	(56.0-81.5%)	80.9%	(69.0-91.0%)	61.1%	(47.7-74.5%)	84.9%	(75.0-94.7%)
Cytology and/or FISH and/or Bile-MDMs	87.5%	(78.4-96.6%)	82.9%	(72.5-93.2%)	70.0%	(57.4-82.6%)	93.6%	(86.8-100.3%)
Cytology and/or FISH and/or Lavage-MDMs	87.5%	(78.4-96.6%)	80.9%	(69.0-91.0%)	68.7%	(53.7-79.9%)	93.3%	(86.5-100.2%)
Cytology and/or FISH and/or Bile-MDMs and/or Lavage-MDMs	93.8%	(87.1-100.4%)	77.1%	(65.6-88.7%)	65.2%	(52.2-78.3%)	96.4%	(91.3-101.5%)

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3147 | REAL-WORLD INSIGHTS INTO THE TREATMENT LANDSCAPE OF HEPATOCELLULAR CARCINOMA AND ITS ADHERENCE WITH GUIDELINE RECOMMENDATIONS: A 5-YEAR NATIONWIDE PROSPECTIVE STUDY IN THE NETHERLANDS

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Background: Dutch guidelines for hepatocellular carcinoma (HCC) are based on the European Association for the Study of the Liver (EASL) guidelines, with the version of 2018 as the leading reference during this study period. As new treatment options have emerged, the therapeutic landscape has evolved. This study aimed to assess the extent to which first-line treatments aligned with the EASL guidelines in a real-world national patient cohort. Secondary aim was to provide insight into underlying liver diseases. **Methods:** This prospective nationwide cohort study enrolled treatment-naïve HCC patients ($\geq$18 years) from 2019–2024 across six Dutch tertiary centers, with a 12-month follow-up. Staging was in accordance to the Barcelona Clinic Liver Cancer (BCLC) classification system. Data on patient demographics, tumor stage, presence of cirrhosis, treatments provided and outcome were systematically collected. **Results:** 621 patients (79.0% male, median age 71 years) received 775 oncological treatments. BCLC stage distribution at diagnosis was: 11.3% BCLC-0, 51.7% BCLC-A, 13.7% BCLC-B, 18.4% BCLC-C, 3.9% BCLC-D, and 1.1% missing data. 59.4% received a single treatment, 28.3% two treatments, and 12.5% underwent more than two treatments. First line treatment guidelines adherence was 44.1%, with the greatest treatment heterogeneity in BCLC-C patients. The highest therapeutic stage migration rate was in BCLC-D patients, with 45.8% treated according to left-sided stage migration. For comparative analysis, adherence was also assessed based on the updated 2025 EASL guidelines. An increase in adherence and a concurrent decline in the use of treatment techniques not endorsed by the guidelines were observed across all stages, except for BCLC-D. In this context, the average guideline adherence rate would have been 63.9%. Cirrhosis was present in 65% of the patients, alcoholic liver disease was the main etiology for this (31.1%). Among patients without cirrhosis, metabolic dysfunction-associated steatotic liver disease was the main etiology (37.9%). One-year transplantation-free overall survival rates were 95.6% (BCLC-0), 91.2% (BCLC-A), 81.6% (BCLC-B), 70.1% (BCLC-C), and 66.8% (BCLC-D). Sensitivity analysis, accounting for patients censored due to best supportive care, showed one-year overall survival rates of 94.8% (BCLC-0), 84.5% (BCLC-A), 72.5% (BCLC-B), 43.9% (BCLC-C), and 31.9% (BCLC-D). **Conclusion:** In this real-world national cohort, first line treatment adhered to guidelines in less than half of the newly diagnosed patients with HCC, with particularly low adherence in patients with BCLC-C HCC. The wide range of therapies across all BCLC stages at initial and subsequent treatment sessions, resulted in favorable short-term outcomes, highlighting a shift towards personalized treatment strategies. Over half of the patients was diagnosed at an early disease stage, indicating a shift towards earlier diagnosis.

Disclosures: Coosje Verhagen: Nothing to Disclose, Jochem Grossouw: Nothing to Disclose, Danny van der Helm: Nothing to Disclose, Jose Willemse: Nothing to Disclose, Jeffrey Braak: Nothing to Disclose, Sorina de Jonge: Nothing to Disclose, M. Kater: Nothing to Disclose, Simeon Ruiter: Nothing to Disclose, F van Vilsteren: Nothing to Disclose, Judith de Vos-Geelen: Nothing to Disclose, Matthijs Kramer: Nothing to Disclose, Christiaan van der Leij: Nothing to Disclose, Ijsbrand Zijlstra: Nothing to Disclose, Otto van Delden: Nothing to Disclose, Bart Takkenberg: Nothing to Disclose, Dewkoemar Ramsoekh: Nothing to Disclose, Heinz Josef Klumpen: Nothing to Disclose, J de Bruijne: Nothing to Disclose, Maarten Smits: Nothing to Disclose, Merve Rousian: Nothing to Disclose, Pam van der Meeren: Nothing to Disclose, Kevin Wiese: Nothing to Disclose, Dave Sprengers: Nothing to Disclose, Bas Groot Koerkamp: Nothing to Disclose, Roeland de Wilde: Nothing to Disclose, Mark Burgmans: Nothing to Disclose, Minneke Coenraad: Nothing to Disclose

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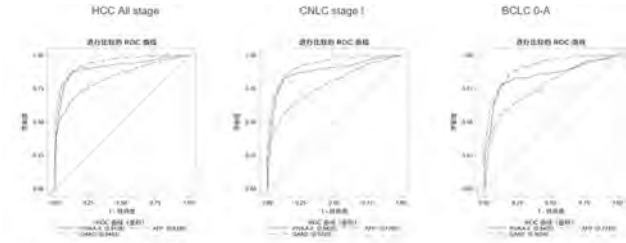
3148 | MULTI-CENTER VALIDATION OF ELECSYS GAAD DIGITAL ALGORITHM PERFORMANCE IN CHINESE POPULATION

Yujuan Guan[1] Ao Zhang[2] Changmin Wang[3] Yifan Han[4] Qi Zhang[5] Yihua Sun[6] Aiqi Lu[1] Shuli Guo[3] Cheng Chen[3] Yuemeng Li[5] Danni Mu[5] Song Gao[7] Wanli Liu[2] Xiaoyuan Xu[4], [1]Guangzhou Eighth People's Hospital, Guangzhou Medical University, Guangzho, [2]Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, [3]People's Hospital of Xinjiang Uygur Autonomous Region, China, [4]Peking University First Hospital, Beijing, China, [5]Peking Union Medical College Hospital, Peking Union Medical College, [6]Affiliated Cancer Hospital of Harbin Medical University, China, [7]Affiliated Cancer Hospital of Harbin Medical University, Harbin, China

Background: The Elecsys GAAD algorithm digitally integrates age, gender, AFP, and DCP to yield a semi-quantitative result for hepatocellular carcinoma (HCC) diagnosis. While the performance of GAAD has been documented in Caucasian and Asian populations, its effectiveness in the Chinese population is yet to be determined. This study intends to assess the Elecsys GAAD algorithm's performance specifically within the Chinese population. **Methods:** This retrospective study included patients with clinically confirmed chronic liver disease (CLD) or hepatocellular carcinoma (HCC) who underwent the Elecsys AFP/PIVKA-II test across research sites. Data collected for all participants included their Child-Pugh level. For HCC patients, the number and size of tumors were recorded to confirm their Barcelona Clinic Liver Cancer (BCLC) and China Liver Cancer (CNLC) stages. The Elecsys GAAD score was calculated using patients' baseline data. The study aims to validate the diagnostic performance of AFP/PIVKA-II and the Elecsys GAAD algorithm for HCC. **Results:** A multi-center study from June 2023 to March 2025 involving 1616 patients (779 with hepatocellular carcinoma [HCC] and 837 with chronic liver disease [CLD], of whom 76.05% were HBV-positive and 7.12% were HCV-positive, 4.27% ALD, 7.12% MAFLD and 11.94% other cause of CLD/HCC validated the performance of the Elecsys GAAD digital algorithm in a Chinese population. Using a cut-off of 2.57, the GAAD test achieved 82.93% sensitivity, 90.32% specificity, and 86.76% accuracy, with an area under the curve (AUC) of 94.43%. In comparison, AFP (at a 20ng/ml cut-off) showed 57.51% sensitivity, 92.23% specificity, 75.50% accuracy, and an AUC of 83.36%. PIVKA-II (at a 21.29ng/ml cut-off) demonstrated 88.45% sensitivity, 82.08% specificity, 85.15% accuracy, and an AUC of 91.08%. The Delong test indicated that GAAD had a statistically significant performance advantage ($p < 0.001$) of 3.35% over PIVKA-II and 11.08% over AFP. In CNLC HCC stage I and BCLC 0-A populations, GAAD achieved AUCs of 92.59% and 90.56%, respectively, also showing statistically significant performance advantages over individual tumor markers. **Conclusion:** This study indicates that Elecsys GAAD demonstrates superior analytical performance compared to using tumor markers independently.



AUCs comparison Delong test

	Estimate	Error	P
All HCC			
PIVKA-II - AFP	0.0772	0.01200	<.0001
GAAD - AFP	0.1108	0.00849	<.0001
GAAD - PIVKA-II	0.0335	0.00662	<.0001
BCLC Stage 0-A			
PIVKA-II - AFP	0.0665	0.0221	0.0026
GAAD - AFP	0.1317	0.0139	<.0001
GAAD - PIVKA-II	0.0652	0.0136	<.0001
CNLC Stage I			
PIVKA-II - AFP	0.1036	0.0179	<.0001
GAAD - AFP	0.1469	0.0128	<.0001
GAAD - PIVKA-II	0.0433	0.0098	<.0001

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3149 | PATIENTS WITH CIRRHOSIS LIVING IN RURAL AREAS ARE LESS LIKELY TO RECEIVE HEPATOCELLULAR CARCINOMA SURVEILLANCE: A POPULATION-BASED STUDY INVOLVING 43,207 PATIENTS WITH CIRRHOSIS

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Background: Cirrhosis is the leading risk factor for hepatocellular carcinoma (HCC), and semi-annual

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surveillance improves stage at diagnosis and overall survival. HCC mortality rates are increasing at a higher rate for rural populations, suggesting disparities in screening access and utilization. **Methods:** We conducted a retrospective cohort study of patients with cirrhosis using claims data from NC Medicare, NC Medicaid, and private insurers. Patients were included if they were >17 years of age, had 12 months of continuous insurance coverage prior to diagnosis, and had at least two corresponding cirrhosis ICD-9/10 codes between 2004 and 2017. Rural versus urban residence was based on county-level Rural-Urban Continuum Codes. Our primary outcome was HCC surveillance (abdominal ultrasound, CT, or MRI) after cirrhosis diagnosis. Index date was defined as date of first cirrhosis diagnosis. We calculated the 2-year cumulative incidence of first HCC surveillance, with HCC diagnosis, liver transplant, and death as competing events, and stratified by level of rurality. We estimated unadjusted and adjusted subdistribution hazard ratios (sdHRs) using the Fine and Gray competing risks regression model. **Results:** Baseline characteristics for the patients included in this study are provided in Table 1. Among 43,207 patients with cirrhosis eligible for screening, 70% of patients lived in urban areas, 26% in rural adjacent to urban (RAU), and 4% in rural non-adjacent to urban (RNAU). The overall 2-year cumulative incidence of HCC surveillance was 54.7% (95% CI: 54.3-55.1%). When stratified by rurality level, the 2-year cumulative incidence was 55.2% (95% CI: 54.7-55.7%) for patients in urban areas, 54.0% (95% CI: 53.2-54.7%) for those in RAU, and 52.5% (95% CI: 50.6-54.4%) for those in RNAU. Univariable Fine and Gray regression results also showed that patients residing in rural areas were less likely to receive HCC surveillance within 2 years of cirrhosis diagnosis compared to their urban counterparts (sdHR: 0.97, 95% CI 0.94-0.99 for RAU; sdHR: 0.93, 95% CI 0.87-0.98 for RNAU). Moreover, rural patients remain less likely to receiving appropriate HCC surveillance compared to their urban counterparts after adjusting for age group, sex, etiology of liver disease, decompensated status, and Charlson Comorbidity Score (sdHR: 0.97, 95% CI 0.95-0.99 for RAU; sdHR: 0.94, 95% CI 0.88-0.99 for RNAU). **Conclusion:** In this statewide, population-based study, patients with cirrhosis living in rural areas were less likely to receive guideline-concordant HCC surveillance compared to those in urban areas. Disparities in surveillance access, in addition to other rural-health barriers, could be contributing to disproportionately increasing HCC mortality rates. Further research is necessary to elucidate which contributors most significantly impact rising mortality in rural populations.

Table 1: Baseline patient characteristics

	Overall	Urban	Rural Adjacent to Urban	Rural Non-Adjacent to Urban
Age (mean, std)	64.1 (13.44)	63.95 (13.33)	64.28 (13.2)	65.27 (13.33)
Primary Etiology				
Alcohol	9,701 (21.1)	6,216 (20.6)	2,444 (21.9)	426 (22.2)
Hepatitis B	543 (1.2)	369 (1.2)	124 (1.1)	26 (1.4)
Hepatitis C	8,731 (19)	5,917 (19.7)	1,879 (16.8)	263 (13.7)
NAFLD	7,378 (16)	4,824 (16)	1,778 (15.9)	331 (17.2)
Other	19,699 (42.8)	12,802 (42.5)	4,955 (44.3)	873 (45.5)
Age Category				
18-39	2,001 (4.3)	1,305 (4.3)	421 (3.8)	71 (3.7)
40-64	20,882 (45.3)	13,424 (44.6)	4,900 (43.8)	777 (40.5)
65+	23,169 (50.3)	15,379 (51.1)	5,859 (52.4)	1,071 (55.8)
Race/Ethnicity				
Missing	6,445 (14)	3,778 (12.6)	1,077 (9.6)	165 (8.6)
White NH	28,779 (62.5)	19,101 (63.4)	7,241 (64.8)	1,399 (72.9)
Black NH	9,164 (19.9)	6,264 (20.8)	2,309 (20.7)	299 (15.6)
Hispanic	364 (0.8)	272 (0.9)	54 (0.5)	7 (0.4)
Other	1,300 (2.8)	683 (2.3)	499 (4.5)	49 (4.5)
Sex				
Missing	349 (0.8)	222 (0.7)	85 (0.4)	10 (0.5)
Male	24,655 (53.5)	16,032 (53.2)	6,038 (54)	1,070 (55.8)
Female	21,048 (45.7)	13,854 (46)	5,097 (45.6)	839 (43.7)
Primary Insurance				
Private Insurance	6,532 (14.2)	3,847 (12.8)	1,102 (9.9)	168 (8.8)
MDCD	6,788 (14.7)	4,709 (15.6)	1,608 (14.4)	241 (12.6)
MDCR	32,732 (71.1)	21,532 (71.6)	8,470 (75.8)	1,510 (78.7)
Charlson Comorbidity Score				
0	17,779 (38.6)	11,734 (39)	4,206 (37.6)	667 (34.8)
1	11,179 (24.3)	7,256 (24)	2,754 (24.6)	448 (25.4)
2+	17,094 (37.1)	11,138 (37)	4,220 (37.7)	764 (39.8)
CCI not including liver disease				
0	21,736 (47.2)	14,323 (47.6)	5,120 (45.8)	818 (42.6)
1	11,417 (24.8)	7,349 (24.4)	2,829 (25.3)	520 (27.1)
2+	12,899 (28)	8,436 (28)	3,231 (28.9)	581 (30.3)
Provider Specialty				
Missing	90 (0.2)	36 (0.1)	15 (0.1)	3 (0.2)
GI/Hep	19,653 (42.7)	14,701 (46.7)	4,393 (39.3)	624 (32.5)
Primary care	24,426 (53)	15,594 (51.8)	6,587 (58.9)	1,226 (63.9)
Other	1,883 (4.1)	407 (1.4)	195 (1.7)	66 (3.4)
Decompensated Cirrhosis at Index				
Not decomp	27,097 (58.8)	17,818 (59.2)	6,427 (57.5)	1,116 (58.2)
Decomp	18,955 (41.2)	12,290 (40.8)	4,753 (42.5)	803 (41.8)
Overall SVI				
Missing	2,685 (5.8)	0 (0)	0 (0)	0 (0)
Quartile 1	11,103 (24.1)	8,949 (29.7)	1,382 (12.4)	612 (31.9)
Quartile 2	11,015 (23.9)	9,293 (30.9)	1,197 (10.7)	525 (27.4)
Quartile 3	10,744 (23.3)	7,965 (26.5)	2,779 (24.9)	0 (0)
Quartile 4	10,505 (22.8)	3,901 (13)	5,822 (52.1)	782 (40.8)
All	46,052 (100)*	30,108 (100)	11,180 (100)	1,919 (100)

*This table includes all patients with cirrhosis meeting inclusion and exclusion criteria (N=46,052)

Disclosures: Paul Karre: Nothing to Disclose, Christine Hsu: Nothing to Disclose, Louise Henderson: Nothing to Disclose, Bradford Jackson: Nothing to Disclose, Christopher Baggett: Nothing to Disclose, Michele Jonsson-Funk: Nothing to Disclose, Andrew Olshan: Nothing to Disclose, Parul Gupta: Nothing to Disclose, A. Sidney Barritt: Nothing to Disclose, Hanna Sanoff: Nothing to Disclose, Stephanie Wheeler: Nothing to Disclose, Jennifer Lund: Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant

3150 | CA9 FUNCTIONS BOTH AS A BIOMARKER OF RESISTANCE TO ATEZ/BEV THERAPY IN HEPATOCELLULAR CARCINOMA AND AS A PROMISING THERAPEUTIC TARGET

Yu Sato[1] Takahiro Kodama[1] Machiko Kai[1] Kazuki Maesaka[1] Yuta Myojin[1] Kazuhiro Murai[1] Yuki Tahata[1] Yoshinobu Saito[2] Hayato Hikita[2] Tomohide Tatsumi[1]

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Background: Combination therapy with atezolizumab and bevacizumab (Atez/Bev) has improved outcomes in unresectable hepatocellular carcinoma (uHCC), but significant responses are limited to a subset of patients. This study aimed to identify predictive biomarkers for Atez/Bev efficacy and explore the novel therapeutic targets, focusing on carbonic anhydrase 9 (CA9). **Methods:** Pre-treatment plasma samples were collected from 167 uHCC patients receiving Atez/Bev and divided into discovery (n = 78) and validation (n = 89) cohorts. In the discovery cohort, 92 cancer immunity-related proteins were profiled using high-sensitivity proteomics. Proteins significantly elevated in non-responders were identified as candidate markers. In the validation cohort, patients were stratified by candidate protein levels and evaluated for clinical outcomes. A CA9-overexpressing mouse HCC cell line was established and subcutaneously implanted in immunocompetent mice to assess the tumor immune microenvironment (TIME) using single-cell RNA sequencing. Functional assays using CA9 inhibitors were performed in vitro and in vivo. **Results:** Proteomic analysis revealed elevated CA9, IL-6, and IL-8 in non-responders. High CA9 levels were associated with significantly shorter progression-free survival (PFS) and overall survival (OS), supporting CA9 as a predictive biomarker. In the validation cohort, using a CA9 cutoff of 187.7 pg/mL from ROC curve, the high CA9 group showed a lower response rate (47.8% vs 74.4%, $p < 0.05$), shorter median PFS (3.0 vs 8.2 months, $p < 0.05$), and OS (11.3 vs 25.0 months, $p < 0.05$) compared to the low CA9 group. In the TIME analysis, CA9-overexpressing tumors displayed enhanced angiogenesis, increased M2 macrophages, and reduced cytotoxic T cells, indicating an immune-excluded phenotype. These tumors were less responsive to PD-L1 and VEGF antibodies. CA9 expression was induced under hypoxia in vitro, and CA9 inhibition suppressed tumor cell proliferation. In vivo, combining CA9 inhibition with PD-L1/VEGF therapy improved anti-tumor efficacy. **Conclusion:** CA9 is a predictive biomarker for Atez/Bev resistance in HCC and a potential therapeutic target contributing to an immune-suppressive tumor microenvironment.

Disclosures: Yu Sato: Nothing to Disclose, Takahiro Kodama: Nothing to Disclose, Machiko Kai: Nothing to Disclose, Kazuki Maesaka: Nothing to Disclose, Yuta Myojin: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Tomohide Tatsumi: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

3151 | BILE-DERIVED EXOSOMAL MIR-196A/-196B AS DIAGNOSTIC BIOMARKERS ASSOCIATED WITH TUMOR PROGRESSION IN BILIARY TRACT CANCE

Naotaka Kugiyama[1] Katsuya Nagaoka[1] Yasuhito Tanaka[1], [1]Kumamoto University

Background: Bile-based liquid biopsy presents a promising approach for identifying novel biomarkers for biliary tract cancer (BTC) given its proximity to tumor sites. The aim of this study was to identify bile-derived exosomal microRNAs (miRNAs) with diagnostic potential for BTC. **Methods:** Exosomal RNA was extracted from the bile samples of 10 BTC patients and 10 controls. The candidate miRNAs were screened by RNA sequencing, and validated in an independent cohort of 50 BTC patients and 53 controls using TaqMan PCR. The serum levels of miRNAs were analyzed in 64 BTC patients and 79 controls. Functional assays were performed to determine the effects of the miRNAs on cholangiocarcinoma cells. **Results:** MiR-196a, miR-196b, and miR-424 were identified as candidate biomarkers of BTC. Validation assays confirmed that miR-196a and miR-196b were significantly elevated in the bile samples of BTC patients, and miR-196a was also elevated in early-stage BTC patients. MiR-196a achieved an area under the receiver operating characteristic curve (AUROC) of 0.79 for the diagnosis of BTC. The combination of miR-196a and CA19-9 increased the AUROC to 0.86, and further improvement to 0.88 was observed upon the addition of CEA. Furthermore, serum miR-196a levels were significantly elevated in patients with metastatic BTC (3.0E-6 vs. limit of detection (LOD), $p = 0.02$). Functional assays demonstrated that miR-196a/-196b promoted the proliferation and invasion of cholangiocarcinoma cells ($p < 0.05$). **Conclusion:** Bile-derived exosomal miR-196a/-196b are novel BTC-specific biomarkers. MiR-196a may contribute to early BTC detection, enhance diagnostic accuracy in combination with serum markers, and detect metastasis.

Disclosures: Naotaka Kugiyama: Nothing to Disclose, Katsuya Nagaoka: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

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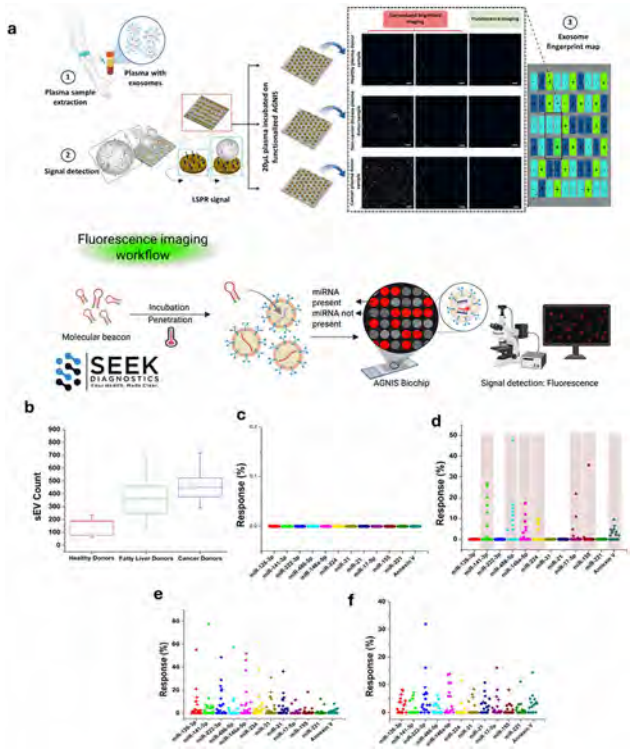
3152 | NEXT-GENERATION PLASMONIC IMAGING PLATFORM FOR HEPATOCELLULAR CARCINOMA DETECTION

Mohammad Sadman Mallick[1] Kshipra Kapoor[1] Giovanni Duca[1] Guadalupe Cisneros[1] Saswat Mohapatra[2] Prasun Jalal[3] Matthew Clayton[1] Steven Lin[4] Wei-Chuan Shih[5], [1]Seek Diagnostics Inc., [2]University of Houston, [3]Baylor College of Medicine, [4]The University of Texas MD Anderson Cancer Center, [5]Seek Diagnostics Inc. & University of Houston

Background: Hepatocellular carcinoma (HCC), the most common primary liver cancer, remains a major health burden due to late diagnosis and limited screening tools. Current methods like ultrasound and Alpha-Fetoprotein (AFP) testing suffer from poor sensitivity and specificity, while advanced imaging and biopsies are invasive, costly, and prone to false negatives. This has led to growing interest in small extracellular vesicles (sEVs) as blood-based biomarkers. sEVs carry molecular cargo reflective of disease states, making them valuable for early cancer detection. However, their clinical utility is limited by challenges in detecting and characterizing them at the single-particle level. To address this, we developed PANORAMA (PlAsmonic NanO-apeRture lAbel-free iMAging), a label-free plasmonic imaging system using antibody-functionalized arrayed gold nanodisks on invisible substrate (AGNIS). The platform quantifies and sizes individual sEVs from just 20 μL of plasma. Previously, PANORAMA achieved 99.5% sensitivity and 97.3% specificity in distinguishing cancer patients (n = 205) from healthy controls (n = 106). In this study, we further enhanced the system with a molecular profiling module using 11 fluorescently labeled molecular beacons (MBs) and a protein probe for multiplexed detection of miRNAs and surface markers. **Methods:** PANORAMA is built on an Olympus IX83 inverted microscope with bandpass-filtered illumination. The AGNIS surface is functionalized with biotin-PEG-thiol, neutravidin, and antibodies (CD9, CD63, CD81) to capture sEVs. Fluorescence imaging detects target miRNAs via hybridization with MBs, triggering a conformational change that emits fluorescence. The overview of our technology is shown in Figure 1a. **Results:** Plasma from 76 participants (13 healthy, 21 liver disease, 42 cancer) was analyzed. PANORAMA sEV counts varied: healthy (156 ± 55), liver disease (370 ± 130), and cancer (458 ± 100) (Figure 1b). Using a 280 sEV cutoff, PANORAMA achieved 100% sensitivity but only 55% specificity due to elevated sEVs in non-cancer liver disease. To improve specificity, we profiled sEVs using 11 MBs and 1 surface protein, Annexin V. A five-miRNA panel (miR-126-3p, miR-222-3p, miR-31, miR-21, miR-221) showed no signal in healthy samples and selected liver disease cases, but positive in cancer samples with 90.8% sensitivity and 100% specificity (Figure 1c-f). Validation in 10 additional plasma samples showed 100% sensitivity and 83% specificity. A larger prospectively collected set of samples will be evaluated blinded, and these results will be reported at the meeting. **Conclusion:** In conclusion, our plasmonic imaging platform enables sensitive, specific, and minimally invasive molecular profiling of sEVs, supporting its potential as a clinical tool for early HCC detection.



Disclosures: Mohammad Sadman Mallick: Nothing to Disclose, Kshipra Kapoor: Nothing to Disclose, Giovanni Duca: Nothing to Disclose, Guadalupe Cisneros: Seek Diagnostics Inc.: Employee, Saswat Mohapatra: Nothing to Disclose, Prasun Jalal: Nothing to Disclose, Matthew Clayton: Nothing to Disclose, Steven Lin: Seek Diagnostics: Co-founder, stock options, Beyond Spring Pharmaceuticals, Inc: Grant/Research Support, Nektar Therapeutics: Grant/Research Support, STCube Pharmaceuticals: Grant/Research Support, Wei-Chuan Shih: Nothing to Disclose

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3153 | IMPACT OF SOCIAL DETERMINANTS OF HEALTH ON HEPATOCELLULAR CARCINOMA SURVEILLANCE RECEIPT AND EARLY DETECTION

Mohammed Al-Hasan[1] Nicole Rich[1] Gloria Figueroa[2] Stephanie Garces[2] Lisa Quirk[3] Sruthi Yekkaluri[3] Thomas Kerr[1] Patricia Jones[4] Adam Yopp[5] Amit Singal[3], [1]University of Texas Southwestern Medical Center, [2]Division of Digestive Health and Liver Diseases, Department of Internal Medicine, U Miami, Miami, FL, [3]Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, [4]University of North Carolina at Chapel Hill, [5]Department of Surgery, UT Southwestern Medical Center, Dallas, TX

Background: The association between social determinants of health (SDOH) and hepatocellular carcinoma (HCC) surveillance receipt and early tumor detection remains unclear. **Methods:** We leveraged the Multi-Ethnic HCC (ME-HCC) Cohort comprised of adults diagnosed with HCC between September 2018 and July 2023 across four U.S. health systems in Texas and Florida. Patients completed surveys assessing demographics, health literacy (using Chew health literacy assessment), medical mistrust (using the group-based medical mistrust score), experienced discrimination (using the shortened everyday discrimination scale), patient-doctor communication, health locus of control, and barriers to treatment. We used multivariable logistic regression models to identify factors associated with surveillance imaging in the 3-9 months prior to HCC diagnosis and early-stage detection, defined as BCLC stage 0/A or tumor within Milan criteria. **Results:** Among 1,245 eligible patients, 833 (66.9%) completed the baseline survey and 495 (59.4%) completed the follow-up survey. Median age was 64.2 years, 75.8% were men, and 55.4% had Child Pugh A cirrhosis. Surveillance was only completed in 40.5% of patients, and HCC was detected at an early stage in 50.9% of patients per BCLC and in 47.8% per Milan criteria. Surveillance receipt was positively associated with ALD etiology (vs: hepatitis C: OR 1.61, 95% CI 1.04-2.61) and negatively associated with lack of insurance (vs: Medicare: OR 0.36, 95% CI 0.14-0.94). Early-stage HCC detection per BCLC was positively associated with surveillance receipt (OR 2.70, 95% CI 1.87-3.91) and Hispanic ethnicity (OR 1.87, 95% CI 1.20-2.94), while it was negatively associated with male gender (OR 0.54, 95% CI 0.35-0.84) and Child Pugh class B (OR 0.45, 95% CI 0.31-0.66). Survey measures failed to have a significant association with surveillance receipt nor BCLC early-stage detection. Detection within Milan Criteria was positively associated with surveillance receipt (OR 3.13, 95% CI 2.23-4.39), while it was negatively associated with Black race (OR 0.50, 95% CI 0.28-0.91), Child Pugh Class B (OR 0.63, 95% CI 0.43-0.92), and age > 65 years (OR 0.65, 95% CI 0.42-0.98). Among patients who completed the follow-up survey, better patient-doctor communication was associated with detection within Milan (OR 1.08, 95% CI 1.02-1.13). **Conclusion:** HCC surveillance receipt is the strongest correlate of early-stage tumor detection but remains underused in clinical practice.

Disclosures: Mohammed Al-Hasan: Nothing to Disclose, Nicole Rich: AstraZeneca: Advisor, Genentech: Consulting, Exelixis: Advisor, Eisai: Advisor, Madrigal: Advisor, Gloria Figueroa: Nothing to Disclose, Stephanie Garces: Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Sruthi Yekkaluri: Nothing to Disclose, Thomas Kerr: Madrigal: Consultant, GSK: Grant/Research Support, Patricia Jones: Nothing to Disclose, Adam Yopp: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant

3154 | A SIMPLE LIVER-STIFFNESS AND FIB-4 ALGORITHM IDENTIFIES PATIENTS WITH NON-CIRRHOTIC MASLD WHO ARE AT HIGHER RISK FOR HCC

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Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a rising cause of hepatocellular carcinoma (HCC). HCC surveillance focuses almost exclusively on patients with established cirrhosis (> 1% per year risk of HCC). However, up to one-third of MASLD-related HCC cases occur without a diagnosis of cirrhosis. Simple methods of identifying patients with non-cirrhotic MASLD who have sufficiently high risk of HCC to merit screening are lacking. To bridge this gap, we sought to develop a pragmatic, two-parameter classification that leverages two widely available non-invasive tests—FibroScan-derived liver stiffness (LS) and the serum fibrosis-4 (FIB-4) index—to identify non-cirrhotic MASLD patients at high enough HCC risk to merit HCC surveillance, using a risk threshold of > 0.2 per 100 person-years (P-Ys).

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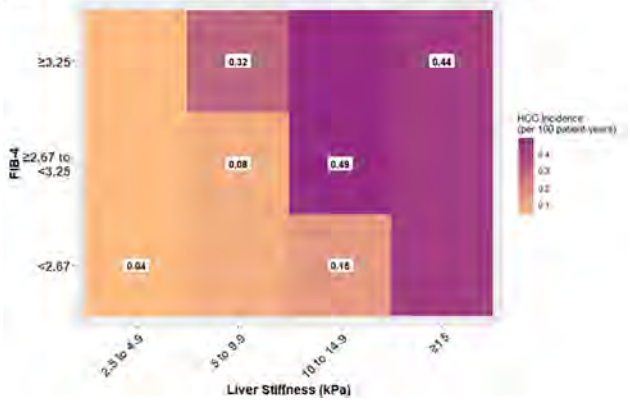
Methods: We identified 21,747 patients with MASLD who underwent a valid LS measurement between 5/2014 to 5/2023. Patients were required to have a FIB-4 score within 6 months of LS, and no HCC or cirrhosis diagnosis prior to or within 90 days after LS. Patients were followed from the LS date until the earliest of death, HCC, or last follow-up. We created risk categories according to incremental LS cut-offs: 5, 10, 15, 20, 25 kPa, and FIB-4 cut-offs of either 2.67 or 3.25. We calculated HCC incidence rates per 100 P-Ys. **Results:** In this cohort of patients with non-cirrhotic MASLD, 90.8% were male and the mean age was 58.2 ± 13.2 years. Over a median follow-up of 3.25 years, 91 patients were diagnosed with incident HCC. HCC incidence was very low (0.04 per 100 P-Ys) for those with LS <5 kPa (Table, Figure). HCC incidence was substantial when LS was ≥ 15 kPa (0.44 per 100 P-Ys), when LS 5-9.9 kPa & FIB-4 ≥ 3.25 (0.32 per 100 P-Ys), and LS 10-14.9 kPa & FIB-4 ≥ 2.67 (0.49 per 100 P-Ys). **Conclusion:** In this national non-cirrhotic MASLD cohort, a simple algorithm consisting of LS and FIB-4 scores identified patients at high enough HCC risk to warrant HCC surveillance. These data suggest HCC surveillance should be considered in individuals with LS ≥ 15 kPa, LS 5-9.9 kPa with FIB-4 ≥ 3.25 and LS 10-14.9 kPa and FIB-4 ≥ 2.67.

Table. HCC incidence for U.S. veterans with non-cirrhotic MASLD according to LS and FIB-4 risk category

LS and FIB-4 risk categories	Number of patients	Follow-up time (Years)	Number with HCC (%)	HCC incidence (per 100 patient-years)
LS 2.5-4.9 kPa	4997	18,514	8 (0.2%)	0.04
LS 5-9.9 kPa & FIB-4 <3.25	11,984	45,030	34 (0.3%)	0.08
LS 10-14.9 kPa & FIB-4 <2.67	2373	8802	13 (0.5%)	0.15
LS 5-9.9 kPa & FIB-4 ≥3.25	526	1848	6 (1.1%)	0.32
LS 10-14.9 kPa & FIB-4 ≥2.67	411	1433	7 (1.7%)	0.49
LS ≥15 kPa	1456	5210	23 (1.6%)	0.44

Figure. Heatmap demonstrating HCC incidence according to LS and FIB-4 categories



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3155 | SMYD2 INHIBITION REDUCES TUMOR GROWTH AND SYNERGIZES WITH ANTI-PD1 THERAPY IN MURINE HCC ★

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Background: Immune checkpoint inhibitors have improved treatment options for advanced hepatocellular carcinoma (HCC), yet outcomes and response rates remain limited. Epigenetic alterations in HCC highlight epigenetic modifiers as potential therapeutic targets. Among them, the methyltransferase SMYD2 has emerged as an oncogenic factor overexpressed in several tumors, targeting histones and various non-epigenetic substrates mutated in HCC, such as p53, β-catenin and PTEN. However, its role in hepatocarcinogenesis remains poorly understood. Our goal was to study the effect of SMYD2 inhibition in HCC and assess its therapeutic potential. **Methods:** SMYD2 expression was analyzed in public and spatial transcriptomic datasets from HCC patients. Its correlation with key pathways was assessed by Gene Ontology analysis and immune deconvolution. RNA-seq was performed on HuH7 cells after SMYD2 inhibition. To study the effect of the SMYD2 inhibitor AZ505 on Wnt signaling, we used PM299L cells, which harbor hyperactive β-catenin. In vitro assays with Wnt pathway modulators were performed in J774 macrophages to assess tumor–macrophage interactions. In vivo, AZ505 was tested in orthotopic Hepa129 and PM299L murine HCC models, as well as in combination with anti-PD-1 in PM299L tumors. Immune infiltrate was assessed by flow cytometry and gene expression by qPCR. **Results:** SMYD2 is upregulated in HCC and linked to oncogenic transcriptional programs. RNA-seq showed that its inhibition in HCC cells normalizes these programs. AZ505 selectively reduced HCC cell viability without affecting primary hepatocytes. In vivo, AZ505 reduced Hepa129 tumor growth, while shifting gene expression toward an inflammatory profile. Immune deconvolution revealed a negative correlation between SMYD2 and immune effector infiltration in patients, supporting a role in immune exclusion. Mechanistically, SMYD2 inhibition downregulated Wnt/β-catenin signaling targets in vivo and in vitro, accompanied by a reduction of Wnt ligand expression in PM299L cells. Conditioned media from AZ505-treated tumor cells induced lower TGF-β expression in J774 cells, indicating impaired tumor-driven immunosuppressive signaling. Finally, AZ505 synergized with anti-PD-1 to reduce PM299L tumor growth and enhance immune response, increasing

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$CD8^+CD107a^+$ activated T cells. **Conclusion:** SMYD2 inhibition disrupts oncogenic transcriptional programs and macrophage-mediated immunosuppression, leading to improved response to anti-PD-1. These findings highlight SMYD2 as a promising therapeutic target in HCC, especially in Wnt/β-catenin -active tumors.

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3156 | PRE-DIAGNOSTIC PLASMA METABOLITES AND RISK OF HEPATOCELLULAR CARCINOMA IN A MULTIETHNIC COHORT

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Background: Hepatocellular Carcinoma (HCC) is the most common liver cancer and closely associated with cirrhosis, which accounts for 80-90% of HCC cases. Metabolomics emerges as a promising tool in cancer research and may offer insights into disease mechanisms. While prior studies have explored associations between metabolites profiles and HCC, gaps remain in our understanding of metabolic alterations specific to disease progression, particularly from cirrhosis to HCC. This study aimed to identify key metabolic biomarkers and pathways and to develop a metabolite-based prediction model for early HCC detection. **Methods:** This study included 151 cirrhosis and 240 incident HCC cases from the Multiethnic Cohort Study, individually matched to controls on sex, race/ethnicity, study area, birth year, blood draw date, and fasting status. Pre-diagnostic plasma metabolites were measured using an untargeted high-resolution approach^6 . Metabolome-wide association study (MWAS) and pathway enrichment analysis were performed to identify metabolites and pathways associated with HCC risk. In the cirrhosis samples, least absolute shrinkage and selection operator (LASSO) regression with 5,000 iterations was used to identify robust predictive metabolites. The prediction model was developed in cirrhosis patients and predictive performance of known HCC risk factors (age, sex, race/ethnicity, study area, BMI, smoking, alcohol intake, diabetes), metabolites, and polygenic risk score (PRS) was evaluated in the HCC cases using logistic regression. **Results:** 53 of 294 annotated metabolites were significantly associated with HCC risk, most of which were involved in lipid and amino acid metabolism. Glutamate and glycochenodeoxycholate, selected from the cirrhosis samples, were identified as key predictors of HCC risk. Using coefficients from the cirrhosis cohort to test prediction in the HCC cohort, the model including metabolites and risk factors showed the highest area under the receiver operator characteristics curve (AUC) of 0.73 (95%CI 0.68–0.78), outperforming the model with risk factors alone (AUC = 0.64, 95%CI 0.59–0.69) and with risk factors and PRS (AUC = 0.65, 95%CI 0.60-0.70). A similar improvement was observed using coefficients from the HCC samples, where the model including metabolites and risk factors achieved an AUC of 0.76 (95%CI 0.71–0.80). **Conclusion:** Our findings highlight the potential of metabolomics to enhance early detection of HCC. Higher pre-diagnostic levels of glutamate and glycochenodeoxycholate were significantly associated with increased HCC risk, supporting their potential role as early biomarkers of disease progression. When combined with established risk factors, these metabolites notably improved predictive accuracy. These results underscore the value of metabolite profiling as a complementary tool for conventional and genetic risk assessment strategies in liver cancer prevention.

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3157 | EFFICACY AND SAFETY OF SBRT COMBINED WITH ATEZOLIZUMAB PLUS BEVACIZUMAB VS ATEZOLIZUMAB PLUS BEVACIZUMAB IN TREATING UNRESECTABLE ADVANCED HEPATOCELLULAR CARCINOMA (SAB –AN OBSERVATIONAL STUDY)

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Background: Hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) is associated with poor prognosis and limited treatment options. Although atezolizumab combined with bevacizumab (AB) is the current first-line standard of care, real-world outcomes remain suboptimal. Stereotactic body radiotherapy (SBRT) has been proposed to enhance immunogenicity and synergize with immunotherapy and may also help in recanalizing PVT. However, clinical data comparing

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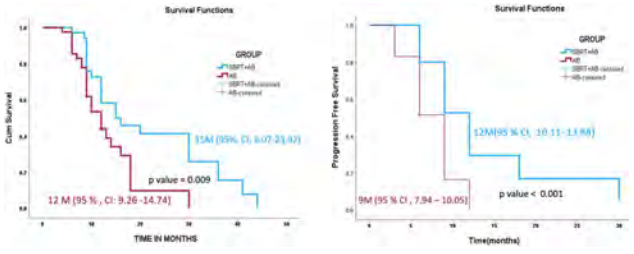
SBRT+AB with AB alone are scarce. **Methods:** We conducted an ambi-spective, single-centre observational study between November 2023- November 2024. 388 patients with cirrhosis with unresectable advanced HCC and PVTT were screened, and patients with CTP score > B7, prior systemic therapy, high-risk varices, or fewer than two cycles of AB were excluded. 76 (68 males and 8 females) patients met inclusion criteria. 35 received SBRT+AB and 41 AB alone. The primary endpoint was objective response rate (ORR) at 6 months per mRECIST. Secondary endpoints included overall survival (OS), progression-free survival (PFS), disease control rate (DCR), biomarker trends (AFP, PIVKA-II), and treatment-related adverse events (TRAEs). **Results:** Despite significantly more aggressive tumor biology in the SBRT+AB group, including higher median AFP {1230.4 () vs 96.1 () ng/mL; $P = 0.013$}, higher tumor volume (320.5 vs 105.1 cm³; $p = 0.015$), and largest tumor diameter (8.3 ± 2.55 vs 6.48 ± 2.08 cm; $P = 0.001$), outcomes were notably superior. ORR at 3, 6, and 12 months was 88.6%, 74.3%, and 66.7% in the SBRT+AB group, compared to 61%, 40%, and 29.4% in the AB group ($p = 0.006$, 0.003, 0.03, respectively). DCR at 6 and 12 months was also higher in the SBRT+AB group (80% and 66.7% vs 55% and 29.4%; $p = 0.022$ and 0.027). Median overall survival was 15 {95% CI: (6.07-23.92) } months in the SBRT+AB group versus 12 {95%CI: (9.26 -14.74) } months with AB alone (p = 0.01), while median progression-free survival was 12 vs 9 months (p = 0.001) (Figure). Grade ≥3 treatment-related adverse events (TRAEs) were infrequent and comparable between groups (8.6% in the SBRT+AB group vs 9.7% in the AB group). The most frequent adverse events were hypertension and fatigue, with no treatment-related deaths reported. **Conclusion:** SBRT in combination with atezolizumab and bevacizumab significantly improved tumor response, disease control and survival, and in patients with unresectable advanced HCC and PVTT, even in the presence of more aggressive disease features. These findings support the incorporation of SBRT into systemic treatment strategies in unresectable advanced HCC and PVTT.



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3158 | HEPATOCELLULAR CARCINOMA RISK IN METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE WITH INCREASED ALCOHOL INTAKE (METALD)

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Background: Limited data exist on HCC risk in patients with MetALD (Metabolic Dysfunction Associated Steatotic Liver Disease [MASLD] with increased alcohol consumption) and how it compares to other steatotic liver diseases. The primary aim of this study was to examine annual incidence rates of HCC in patients with MetALD, with and without cirrhosis. The secondary aim was to compare HCC rates in patients with MetALD with those in MASLD, Alcohol-associated liver disease (ALD), and non-SLD controls. **Methods:** We conducted a retrospective cohort study of veterans with MetALD, MASLD, ALD, or no SLD. We identified patients with SLD using natural language processing that has been validated to identify steatosis from abdominal imaging reports with a high degree of accuracy. The baseline was defined as the date of imaging documenting the presence (SLD) or absence (controls) of steatosis. We used Poisson regression to estimate incidence rates within stratifications of patient characteristics and a multivariable time-updated Fine and Gray competing risk model with death as a competing risk to examine HCC risks, adjusted for sex, race, age, cirrhosis, diabetes, BMI, tobacco use, ALT and AST levels, and platelet counts.

Results: We included 666,428 participants (392,286 MASLD, 104,065 MetALD, 40,230 ALD, and 129,847 controls) between 1/1/2011 and 12/31/2022, with a follow-up period to 5/31/2023. In patients without cirrhosis, adjusted HCC rates per 100,000 person-years (PY) were lowest for MASLD (71.64, 95% CI 68.14-75.32), higher for MetALD (80.24, 73.23-87.94), and highest for ALD (104.83, 91.59-119.98). The cumulative incidence of HCC per 100,000 at 5 years was highest with ALD (663.79, 581.77-754.83), followed by MASLD (450.71, 428.46-473.89), and MetALD (449.89, 407.56-495.74) vs. controls (76.03, 61.47-93.46). Similarly, the cumulative rates of HCC per 100,000 at 10 years was highest with ALD (1176.65, 1033.78-1334.36), followed by MetALD (814.16, 739.33-894.10), and MASLD (762.86, 725.86-801.35) vs. controls (89.67, 72.67-110.06).

The rates of HCC were significantly higher in patients with cirrhosis. HCC rates per 100,000 PY in cirrhosis were highest with MetALD (1078.13, 95% CI 950.05-1223.48) and MASLD (1061.91, 95% CI 992.76-

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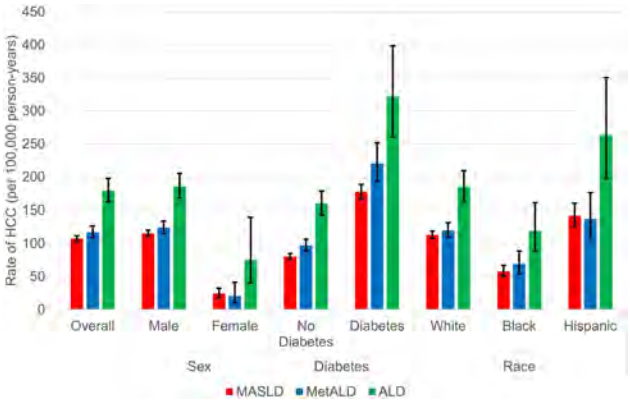
1135.88), followed by ALD (887.92, 95% CI 769.66-1024.34, p = 0.03 vs. MASLD).
Compared to the non-SLD groups (reference), the hazard of HCC increased 2.9-fold in patients with MetALD (aHR 2.90, 95% CI 2.71-3.10). The above HCC risk among MetALD was intermediate between that of MASLD (aHR vs. controls 2.64, 95% CI 2.46-2.82) and ALD (aHR 3.11, 95% CI 2.91-3.33).
Conclusion: The risk of HCC associated with MetALD is higher than MASLD and significantly lower than ALD. These differences may be attributable to the carcinogenic potential of alcohol. This data is useful for counselling patients with MetALD.



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3159 | PIVKA-II MONITORING TO PREDICT RESPONSE OF THE FIRST TRANSARTERIAL CHEMOEMBOLIZATION (TACE) IN INTERMEDIATE STAGE OF HEPATOCELLULAR CARCINOMA ★

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Background: Hepatocellular carcinoma (HCC) is a major cause of cancer-related mortality, with transarterial chemoembolization (TACE) being the standard treatment for intermediate-stage disease. Early prediction of treatment response is crucial for optimizing patient management and critically guiding therapeutic decisions. Protein induced by vitamin K absence-II (PIVKA-II) has emerged as a potential biomarker for monitoring HCC treatment. However, the utility of PIVKA-II in predicting a complete radiologic response (CR) after the first TACE is not well established. This study aims to determine the optimal cutoff and diagnostic performance of the percentage reduction in PIVKA-II levels (PIVKA-II response) at 2 weeks post-TACE in predicting CR at 8 weeks as assessed by imaging. Additionally, the study evaluates the predictive accuracy of the PIVKA-II response at both 2 and 8 weeks following the initial TACE. **Methods:** We performed a prospective diagnostic accuracy study involving 57 patients with intermediate-stage HCC undergoing their first TACE at Srinagarind Hospital, Khon Kaen University, Thailand. Serum levels of PIVKA-II were measured at baseline and subsequently at 2 and 8 weeks following TACE. The radiologic response at 8 weeks was evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST). The predictive value of changes in PIVKA-II levels at 2 and 8 weeks post-TACE was assessed using the area under the receiver operating characteristic (AUROC) curve. **Results:** At 8 weeks following TACE, 26% of patients achieved a complete radiological response. The median reduction in PIVKA-II levels at 2 weeks was not significantly different in the CR group (97.8%) compared to those with partial response (PR) (79.3%), stable disease (SD) (70.6%), and progressive disease (PD) (64.7%) (p = 0.40). The area under the AUROC curve for PIVKA-II response at 2 weeks was 0.74 for predicting CR, 0.65 for the objective response rate (ORR), and 0.63 for the disease control rate (DCR). At 8 weeks, the AUROC curve improved slightly, with values of 0.79 for CR, 0.72 for ORR, and 0.71 for DCR. AUROC analysis revealed that a reduction in PIVKA-II of ≥83.8% at 2 weeks predicted CR with 80.0% sensitivity, 64.3% specificity, a positive predictive value of 44.4%, a negative predictive value of 90.0%, and an overall accuracy of 68.4%. At 8 weeks, a reduction of ≥87.7% in PIVKA-II predicted CR with an accuracy of 75.4%. **Conclusion:** An early reduction in serum PIVKA-II levels following the first TACE is associated with radiologic responses, notably CR. This suggests its potential as a valuable biomarker for treatment monitoring. With an AUROC of 0.74 for predicting CR, the PIVKA-II response at 2 weeks offers promise as an early surrogate marker. This may facilitate timely therapeutic decisions and improve clinical outcomes.

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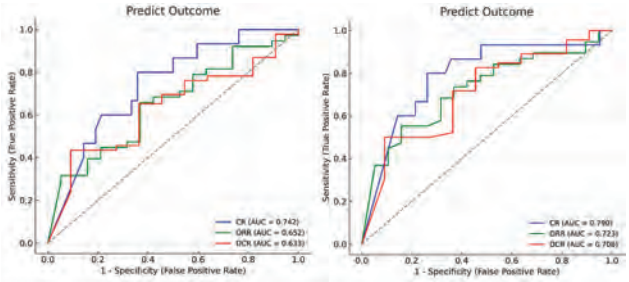

Figure 1. AUROC curves of % reduction of the PIVKA-II levels at 2 weeks (left) and 8 weeks (right) after first TACE to predict radiological response

CR, complete response; DCR, disease control rate; ORR, objective response rate

Disclosures: Napapong Nitiwaranggoon: Nothing to Disclose, Anucha Ahooja: Nothing to Disclose, Tanita Suttichaimongkol: Nothing to Disclose, Chitchai Rattanankukrom: Nothing to Disclose

3160 | RISK FACTORS FOR INCIDENTAL HEPATOCELLULAR CARCINOMA AT TIME OF LIVER TRANSPLANTATION

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Background: Despite routine hepatocellular carcinoma (HCC) screening for patients listed for liver transplant (LT), incidental hepatocellular carcinoma (iHCC) on explant is a persistent phenomenon. Rates of iHCC and risk factors for iHCC remain poorly characterized. The purpose of this investigation is to elucidate differences in pre-LT patient characteristics and imaging patterns between known HCC (kHCC) and iHCC cases to identify risk factors for iHCC and avenues for improving pre-LT HCC screening. **Methods:** This was a retrospective study of LT patients with HCC from 1998-2025 at a large academic medical center. iHCC cases were defined by the absence of HCC identification on pre-LT imaging. Patient characteristics, pre-LT imaging, tumor characteristics on explant, and post-LT outcomes were extracted via manual chart review. **Results:** Among 746 LT patients with HCC on explant, there were 673 kHCC cases and 73 iHCC cases. There were no significant differences in age, sex, race/ethnicity, BMI, or liver disease etiology between groups. In univariable analysis, as compared to kHCC cases, iHCC cases exhibited significantly higher laboratory model for end-stage liver disease (MELD) at time of LT but significantly lower pre-LT maximum alpha-fetoprotein (AFP) and days on the waitlist (all $p < 0.01$). iHCC cases had smaller maximum tumor size ($p < 0.01$) and lower rates of moderate and poor differentiation ($p < 0.01$). There were no iHCC cases with macrovascular invasion; however, 11 had microvascular invasion and 21 were multifocal. In multivariable analysis controlling for patient and tumor characteristics, laboratory MELD at LT, presence of ascites, number of tumors, and maximum tumor size were associated with iHCC. Notably, overall survival (OS) was longer in iHCC cases as compared to kHCC cases (93.3 months v. 70 months, $p < 0.01$). Pre-LT imaging patterns also differed significantly between groups, with magnetic resonance imaging (MRI) performed in 83% of kHCC cases versus 65% of iHCC cases ($p < 0.01$). **Conclusion:** In this large cohort of LT patients spanning >25 years, 9.8% of HCC cases were incidentally identified on explant. Though iHCC cases overall exhibited less aggressive disease, 29% were multifocal and 15% had microvascular invasion. kHCC patients had significantly less ascites and higher rates of pre-LT MRI, suggesting suboptimal performance of non-MRI based imaging, especially in patients with ascites. Despite higher MELD at LT, patients with iHCC had better OS than their kHCC counterparts.

Differences in patient characteristics, pre-liver transplant (pre-LT) imaging, and tumor characteristics between known HCC (kHCC) and incidental HCC (iHCC) cases

		Univariable Analysis		Multivariable Analysis
	kHCC N = 673	iHCC N = 73	p-value	p-value
Patient Characteristics				
Laboratory MELD at LT	15.4 ± 7.9	24.2 ± 7.4	***<0.01***	***<0.01***
Pre-LT maximum AFP	420.2 ± 2801.5	35.5 ± 105.9	***<0.01***	0.09
Days on LT waitlist	344.2 ± 478.7	191.7 ± 264.6	***<0.01***	0.27
Last Pre-LT Imaging Study Characteristics				
Type of study CT MRI US	 16.4 83.1 0.5	 24.3 64.9 10.8	***<0.01***	*Not included*
Ascites present (%)	39.3	81.8	***<0.01***	***<0.01***
Tumor Characteristics				
Number of tumors	2.6 ± 4.8	2.1 ± 3.8	0.39	***0.03***
Maximum tumor size (cm)	3.1 ± 2.0	1.5 ± 0.8	***<0.01***	***<0.01***
Tumor differentiation Well Moderate Poor	 25.3 60.2 14.5	 49.0 49.0 2.0	***<0.01***	*Not included*
Microvascular invasion (%)	24.3	15.5	0.10	0.95

Abbreviations: MELD (model for end-stage liver disease), AFP (alpha-fetoprotein), CT (computed tomography), MRI (magnetic resonance imaging), US (ultrasound)

Disclosures: Mahip Grewal: Nothing to Disclose, Yuan Zhang: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose, Meaghan Phipps: AstraZeneca: Advisor

3161 | TYROSINE KINASE INHIBITORS/ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR ANTIBODY AND IMMUNE CHECKPOINT INHIBITORS WITH OR WITHOUT TRANSARTERIAL CHEMOEMBOLIZATION FOR ADVANCED HEPATOCELLULAR CARCINOMA WITH HEPATIC VEIN AND/OR INFERIOR VENA CAVA TUMOR THROMBUS : A MULTICENTER PROPENSITY SCORE MATCHING STUDY

long-wang lin[1], [1]Center of Interventional Radiology & Vascular Surgery

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Background: Due to the infrequent occurrence of HCC-HVTT/IVCTT, comprehensive studies on its clinical outcomes are lacking, with existing data limited to small case series. There still is no evidence to support a standardized first-line therapy for these patients. Therefore, this study aimed to evaluate the effectiveness and safety of tyrosine kinase inhibitors (TKIs)/anti-vascular endothelial growth factor (anti-VEGF) antibody plus immune checkpoint inhibitors (ICIs) with or without transarterial chemoembolization (TACE) as first-line therapy for hepatocellular carcinoma (HCC) with hepatic vein and/or inferior vena cava tumor thrombus (HCC-HVTT/IVCTT). **Methods:** This multi-center retrospective cohort study included HCC-HVTT/IVCTT treated with either TKIs/anti-VEGF antibody with ICIs plus TACE (TKIs/VEGF-ICIs-TACE) or TKIs/anti-VEGF antibody plus ICIs (TKIs/VEGF-ICIs) between June 2018 and March 2024. Propensity score matching (PSM) was utilized to balance baseline characteristics. The primary outcomes were OS and PFS. The second outcomes were objective response rate (ORR), disease control rate (DCR) and treatment-related adverse events (TRAEs). **Results:** Among 746 patients with HCC-HVTT/IVCTT included: 479 in TKIs/VEGF-ICIs-TACE group and 267 in TKIs/VEGF-ICIs group. The median follow-up time was 32.1 months. TKIs/VEGF-ICIs-TACE group demonstrated a significantly longer median OS compared to TKIs/VEGF-ICIs group (20.9, 95% CI: 19.1–22.4 months vs. 14.3, 95% CI: 12.0–16.8 months; HR = 0.65, 95% CI: 0.54–0.77, $p < 0.0001$). According to RECIST v1.1, TKIs/VEGF-ICIs-TACE group achieved a significantly longer median PFS compared to TKIs/VEGF-ICIs group (10.7, 95% CI: 9.8–11.7 months vs. 7.3 95% CI: 6.4–8.5 months; HR = 0.67, 95% CI: 0.57–0.79, $p < 0.0001$); TKIs/VEGF-ICIs-TACE group exhibited a significantly higher ORR and DCR using either RECIST v1.1 (ORR: 45.3% vs. 28.8%, $p < 0.001$; DCR: 81.2% vs. 64.8%, $p < 0.001$) or mRECIST criteria (ORR: 53.6% vs. 36.3%, $p < 0.001$; DCR: 81.6% vs. 64.4%, $p < 0.001$). 238 patients (34.2%) in TKIs/VEGF-ICIs-TACE group and 87 patients (31.5%) in TKIs/VEGF-ICIs group experienced grade ≥ 3 TRAEs. **Conclusion:** TKIs/VEGF-ICIs-TACE has shown improved survival benefit as first-line therapy for HCC-HVTT/IVCTT, with manageable safety profiles.

Disclosures: long-wang lin: Nothing to Disclose

3162 | DISTINCT MOLECULAR PATHWAYS REGULATED BY ACTIVATED AKT AND YAP SIGNALING DURING INTRAHEPATIC CHOLANGIOCARCINOMA PROGRESSION

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Background: Activated AKT and YAP signaling cascades have key roles in intrahepatic cholangiocarcinoma (iCCA) pathogenesis. However, how these pathways modulate iCCA progression, especially how they regulate tumor microenvironment remains unclear. **Methods:** We engineered two doxycycline (doxy) conditional iCCA murine models using hydrodynamic injection to deliver transposon plasmids encoding inducible activated *YAP* or *Akt* into the mouse liver, *Akt/TRE-YAP* or *TRE-Akt/YAP*, respectively. *YAP* or *Akt* was inhibited in established *Akt/YAP* iCCA tumor cells by withdrawing doxycycline. Histological and molecular analyses were used to investigate the phenotypes, especially tumor microenvironment, as well as genes and pathways that are regulated by *Akt* and/or *YAP* during iCCA progression. **Results:** We found that suppression of YAP in *Akt/TRE-Yap* iCCA model led to tumor regression initially. However, livers eventually progress in the liver, leading to HCC-like lesions in mice due to the activated AKT signaling. In contrast, suppression of AKT in *TRE-Akt/Yap* iCCA model lead to a more profound regression of iCCA lesions with limited tumor burden over long term AKT suppression. Histologically, we found that YAP inhibition led to the elimination of the neutrophils in iCCAs with the infiltration of CD4+ and CD8+ T cells, whereas AKT suppression has limited impacts on immune cells. The data suggest that YAP, but not AKT, is the major driver of tumor immune microenvironment in iCCA. The activation of YAP/TAZ and the immune suppressive phenotypes were consistently observed in human iCCAs. Using gene expression analysis, we discovered that AKT and YAP largely modulated distinct pathways during iCCA pathogenesis with limited overlapping genes. Furthermore, we identified RNF125 as a tumor suppressor whose expression is inhibited by YAP in iCCA cells. Overexpression of RNF125 inhibited iCCA tumor and cell growth both *in vivo* and *in vitro*. Finally, while YAP-OFF leads to increased T-cell infiltration, these T cells express PD1. Combined YAP-OFF with anti-PDL1 treatment resulted in increased tumor regression. **Conclusion:** Our studies systematically analyzed the molecular signatures of AKT and YAP during iCCA progression. We identified novel YAP targets and revealed activated YAP as a key regulator of the suppressive tumor immune microenvironment in iCCA. The data support the therapeutic potential of combining YAP inhibitors with immune checkpoint inhibitors for iCCA treatment.

Disclosures: Jinqiu Zhao: Nothing to Disclose, xin chen: Nothing to Disclose

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

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3163 | UBE2D3 FUNCTIONS AS A NOVEL TUMOR SUPPRESSOR IN HEPATOCARCINOGENESIS BY MODULATING THE P62–SHP2–STAT3 SIGNALING AXIS

Hideharu Nagasawa[1], [1]Department of Gastroenterology and hepatol, Osaka University

Background: Pharmacological treatment for hepatocellular carcinoma (HCC) has advanced significantly in recent years, with an increasing number of therapeutic agents becoming available. However, the prognosis for HCC remains poor, underscoring the need for a deeper understanding of the mechanisms underlying hepatocarcinogenesis. Through a cancer gene screen using transposon insertional mutagenesis, we identified UBE2D3 as a candidate tumor suppressor gene in the liver. This study aimed to elucidate the role of UBE2D3 in HCC.
. **Methods:** We assessed the clinical significance of UBE2D3 alterations in human HCC across multiple patient cohorts. Functional studies were conducted by either silencing or overexpressing UBE2D3 using shRNA transfection in murine immortalized liver progenitor cells (LPCs) or cDNA transfection in the human HCC cell line SNU-387. Effects on cell proliferation, apoptosis (Caspase-3/7 activity), sphere formation, and tumorigenicity were evaluated, alongside analyses of associated signaling pathways. To assess in vivo relevance, we generated liver-specific Ube2d3 knockout mice and examined hepatocarcinogenesis in models of steatohepatitis induced by a CDAA-HFD diet or liver-specific Pten deletion. **Results:** Human HCC samples exhibited significant copy number loss at the UBE2D3 locus, accompanied by markedly reduced UBE2D3 mRNA expression compared to adjacent nontumorous liver tissues. Lower UBE2D3 expression levels were significantly associated with poorer patient survival. UBE2D3 suppression in LPCs inhibited apoptosis, promoted cell proliferation and sphere formation, and significantly increased allograft tumor formation. Conversely, forced expression of UBE2D3 in SNU-387 cells enhanced apoptosis, reduced proliferation and sphere formation, and suppressed xenograft tumor growth. Mechanistically, UBE2D3 negatively regulated STAT3 phosphorylation, and pharmacological inhibition of STAT3 attenuated the oncogenic phenotypes induced by UBE2D3 knockdown in LPCs. UBE2D3-deficient cells also showed increased levels of p62 and SHP2 proteins, and STAT3 hyperactivation induced by UBE2D3 knockdown was reversed upon SHP2 co-silencing. In vivo, hepatic deletion of Ube2d3 promoted liver tumorigenesis by increasing hepatic levels of p62, SHP2, and phosphorylated STAT3, accompanied by activation of downstream effectors NRF2 and mTOR. **Conclusion:** UBE2D3 functions as a novel tumor suppressor in hepatocarcinogenesis by modulating the p62–SHP2–STAT3 signaling axis.
Disclosures: Hideharu Nagasawa: Nothing to Disclose

3164 | HEPATOCELLULAR CARCINOMA (HCC): GANKYRIN AND MIRNA EXPRESSION PROFILING AS POTENTIAL MARKERS FOR DIAGNOSIS AND MONITORING

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Background: Early diagnosis of (HCC) and detection of disease recurrence are vital for improving patient survival. This study investigated plasma gankyrin/PSMD10 mRNA expression and tissue microRNA profiles as potential biomarkers for HCC diagnosis and monitoring, particularly focusing on their utility in differentiating HCC from cirrhotic liver. **Methods:** The study included 64 participants: HCC ($n = 32$), metastatic HCC ($n = 5$), cirrhosis ($n = 7$), HCV+ ($n = 5$), and healthy individuals ($n = 5$). Blood plasma was evaluated for gankyrin expression, while gankyrin/PSMD10 mRNA and key microRNAs (miR-122, miR-152, miR-200A, miR-200B, miR-21, miR-15, miR-130, miR-9) were analyzed in tissue samples from HCC tumors, adjacent tissues, cirrhotic liver, and normal liver using RT-qPCR. Expression levels were calculated using the 2^-ΔΔCq method with 18S rRNA as reference for gankyrin and miR-26 as reference for microRNAs. **Results:** Importantly, gankyrin mRNA was undetectable in plasma of patients with cirrhosis, HCV+, or healthy individuals, but present in all HCC patients (mean ΔCq: 11.69 ± 1.6 in HCC vs. 10.16 ± 0.4 in metastatic HCC, $p < 0.0002$). Tissue analysis showed significant gankyrin upregulation in HCC (418.5 ± 220.6) compared to adjacent tissue (78.68 ± 49.40), cirrhosis (20.62 ± 11.32), and normal liver (1.02 ± 0.23) ($p < 0.001$). MicroRNA analysis revealed upregulation of miR-200A, miR-200B, miR-21, miR-15, miR-130, and miR-9 in HCC tissues. Most notably, we identified a distinctive pattern of miR-122 and miR-152: miR-122 showed decreased expression in HCC (0.598-fold) and adjacent tissues but increased in cirrhotic liver (1.093-fold), while miR-152 exhibited an opposite pattern with upregulation (1.508-fold) in HCC tissues but downregulation in adjacent (0.471-fold) and cirrhotic tissues (0.258-fold). These miR-122/miR-152 signatures create distinct tissue-specific phenotypes for diagnostic use. **Conclusion:** This study demonstrates that gankyrin RNA is significantly increased in HCC tissues and, crucially, is detectable in plasma of HCC patients but completely

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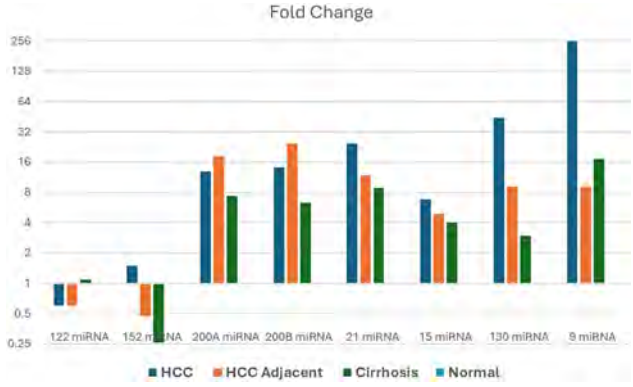
absent in all non-HCC individuals. The discovery of distinct miR-122/miR-152 expression signatures enables differential diagnosis between HCC, adjacent tissue, and cirrhotic liver through unique molecular phenotypes: miR-122↓/miR-152↓ in adjacent tissue, miR-122↓/miR-152↑ in HCC, and miR-122↑/miR-152↓ in cirrhosis without HCC. These findings could have particular clinical value for patients with LiRads-3 lesions, where conventional imaging cannot definitively diagnose malignancy. Combining gankyrin RNA detection in liquid biopsy with tissue microRNA profiling presents a promising approach for early detection, differential diagnosis, and monitoring of HCC in high-risk patients, potentially enabling earlier intervention and improved clinical outcomes.



Disclosures: Levan Gogichaishvili: Nothing to Disclose, Mikheil Jangavadze: Nothing to Disclose, Zanda Bedinashvili: Nothing to Disclose

3165 | RE-EVALUATION OF SERUM AMYLOID A-POSITIVE HEPATOCELLULAR NEOPLASM/ INFLAMMATORY HEPATOCELLULAR ADENOMA (HCA) BY EXPRESSION PATTERN OF GLUTAMINE SYNTHETASE FOR DETECTION OF ASSOCIATED β-CATENIN ACTIVATED HCA

Motoko Sasaki[1], [1]Kanazawa University

Background: Serum amyloid A-positive hepatocellular neoplasm (SAA-HN) is a unique hypervascular hepatocellular lesion resembling hepatocellular carcinoma on the image in patients with alcoholic cirrhosis and shares genetic and histological features with inflammatory hepatocellular adenoma (IHCA). SAA-HN is now regarded as a specific type of IHCA associated with advanced liver disease in metabolic dysfunction–associated steatotic liver disease (MASLD). Recent studies reported that the immunostaining for glutamine synthetase (GS), which is useful for a diagnosis of beta-catenin activated HCA (b-HCA), shows various patterns (pattern 1 [P1], diffuse homogeneous pattern suggesting exon 3-non-S45 mutation; P2, diffuse-heterogeneous, suggesting exon 3-S45 mutation; P3, rim and focal heterogeneous, suggesting exon 7/8 mutations). Previous evaluation of the immunostaining for GS may overlook b-HCA other than P1. The aim of this study is to examine a frequency and clinicopathological features of SAA-HN/b-IHCA by re-evaluating the expression pattern of GS. **Methods:** Twenty-three patients with SAA-HN/IHCA (31 tumors, 4 women and 19 men, mean age, 50yrs) and 14 patients (15 tumors, 2 women and 12 men, mean age, 45yrs) were retrieved from our pathological files (1997-2025). An immunostaining for GS was performed and the expression patterns were classified into P1-P3 and P4 (negative). In addition, hotspot genetic mutations in βcatenin/*CTNNB1*, exon3 and exon7/8 were examined by direct sequencing. **Results:** Expression pattern of GS was classified into 2 of P1, one P2, one P3 and 27 P4 in 31 SAA-HN/IHCAs and 2 of P1, 2 P2, 3 P3 and 8 P4 in 15 IHCAs, suggesting 3 SAA-HN/b-IHCAs, exon3-mutated (10%) and one SAA-HN/b-IHCA, exon7/8-mutated (5%). Furthermore, four IHCAs (27%) may be b-IHCA, exon3-mutated and 3 (20%) may be b-IHCA, exon7/8-mutated. Genetic analysis disclosed one SAA-HN/b-IHCA, exon7-mutated (4%) and 2 SAA-HN/b-IHCAs, exon8-mutated (9%). The SAA-HN/b-IHCA, exon 7-mutated, showed P3 in GS immunostaining, whereas the immunostaining for GS in the rim of tumor nodule was obscure in 2 SAA-HN/b-IHCA, exon 8-mutated (both needle biopsied specimen). **Conclusion:** A part of SAA-HN/IHCA and IHCA may be b-IHCAs, exon3-mutated or exon7/8-mutated. Since a risk of malignant transformation is higher in b-IHCA, exon 3-mutated, than usual IHCA, careful evaluation of immunoreactivity for GS and genetic analysis is mandatory to detect SAA-HN/b-IHCA arising in advanced MASLD.

Disclosures: Motoko Sasaki: Nothing to Disclose

3166 | ADVANCED BLOOD PLASMA SPECTROSCOPY IMPROVES DIAGNOSTIC ACCURACY FOR LIVER CANCER ACCORDING TO BCLC STAGE

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Background: The overall survival of hepatocellular carcinoma (HCC) significantly declines with delayed diagnosis making early detection essential for improving therapeutic outcomes. In at-risk populations, surveillance is typically performed using liver

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ultrasonography (USG), which has limited sensitivity of 60% in early stages (BCLC 0+A). Currently, alpha-fetoprotein is the only widely used biomarker for screening, although its clinical utility remains controversial. We hypothesized that a combination of spectroscopic techniques could reveal distinct plasma spectral patterns identifying patients with and without HCC, offering superior diagnostic accuracy – even in early stages – compared to current standards. **Methods:** We employed a combination of conventional and chiroptical spectroscopic techniques – infrared (IR) and Raman spectroscopy (RS), electronic circular dichroism (ECD), and Raman optical activity (ROA) – to differentiate between cirrhotic patients with and without HCC. We enrolled a total of 152 patients with liver cirhosis, including 64 subjects with HCC and 88 subjects without HCC. The BCLC stage distribution among HCC patients was stage 0+A (n = 24; 37%), stage B (n = 19; 30%), and stage C (n = 21; 33%). Spectral data from each technique were analyzed using partial least squares discriminant analysis (PLS-DA) with 10-times repeated 5-fold cross-validation to calculate the area under the receiver operating characteristic curve (AUROC) in distinguishing between HCC and non-HCC samples. **Results:** Conformational changes in plasma proteins were observed, particularly in the infrared and Raman spectra within the amide I, II, and III regions (bands at 1648, 1637, 1546, 1285, and 1270 cm^{-1}). Additional spectral changes were noted in the intensity of signals corresponding to aliphatic lipid chains (~1450 cm^{-1}) and aromatic amino acids (1192 and 1006 cm^{-1}). The most significant difference between spectra of patients with hepatocellular carcinoma (HCC) and healthy controls was found in the intensity of carotenoid signals (1519, 1158, and 1006 cm^{-1}).

Diagnostic performance by BCLC stage was as follows (sensitivity, specificity, and AUROC):

Stage 0+A: IR 0.735, 0.696, and 0.776; ECD 0.589, 0.704, and 0.706; RS 0.745, 0.483, and 0.690; ROA 0.655, 0.700, and 0.752; combination 0.744, 0.743, and 0.814

Stage B: IR 0.712, 0.769, and 0.815,; ECD 0.602, 0.771, and 0.755; RS 0.758, 0.568, and 0.740; ROA 0.735, 0.670, and 0.779; combination 0.745, 0.792, and 0.852

Stage C: IR 0.756, 0.799, and 0.857; ECD 0.780, 0.845, and 0.876; RS 0.954, 0.695, and 0.878; ROA 0.788, 0. 786, and 0.872; combination 0.819, 0.917, and 0.913

Conclusion: Our findings suggest that spectroscopic methods are capable of distinguishing liver cancer even at early stages with promising accuracy, particularly when combined. These techniques could potentially enhance current screening strategies in at-risk populations.

Disclosures: Petr Hříbek: Eisai: Speaking and Teaching, Roche: Speaking and Teaching, Medison: Speaking and Teaching, Ondřej Vrtělka: Nothing to Disclose, Lucie Habartová: Nothing to Disclose, Vladimír Setni? ka: Nothing to Disclose, Petr Urbánek: Nothing to Disclose

3167 | US HEALTH CARE SPENDING ON LIVER CANCER

Yan Tian[1] Wenjun Wang[1] Xiaomeng Cui[1] Ting Li[1] Shuangsuo Dang[1] Xiaoli Jia[1], [1]Second Affiliated Hospital of Xi'an Jiaotong University

Background: Liver cancer imposes a substantial and growing burden on the US health care system. This study aims to quantify health care spending on liver cancer from 2010 to 2019, examining variation by sex, age, type of care, and geographic location to inform policy and resource allocation. **Methods:** Using data from the US Health Care Spending by Condition database, we analyzed inflation-adjusted (2019 USD) spending estimates for liver cancer. Spendings were stratified by sex, age groups, care categories, and state-level distribution. **Results:** Health care spending on liver cancer increased from $3.5 billion in 2010 (95% CI, $3.4 billion–$3.6 billion) to $5.6 billion (95% CI, $5.4 billion-$5.8 billion) in 2019. The proportion of health care spending attributed to liver cancer increased from 0.18% (95% CI, 0.17%–0.19%) in 2010 to 0.23% (95% CI, 0.22%–0.24%) in 2019. In 2019, males accounted for $3.3 billion (95% CI, $3.1 billion-$3.4 billion), while female accounted for $2.4 billion (95% CI, $2.3 billion–$2.5 billion). By age group, individuals aged $\geq$65 years had the highest spending (54.3%), followed by those aged 45–64 years (37.2%), 20–44 years (6.7%), and $<$20 years (1.8%). Ambulatory care accounted for the largest share of spending (56.3%), followed by hospital inpatient care (25.9%), prescribed retail pharmaceuticals (14.6%), home health care (1.4%), nursing facility care (0.8%), and emergency department care (0.7%). At the state level, age- and sex-standardized spending per capita ranged from $9.9 (95% CI, $8.6–$11.3) in Wyoming, to $23.5 (95% CI, $22.0–$24.8) in California. **Conclusion:** Health care spending on liver cancer has increased significantly from 2010 to 2019, with substantial variation by sex, age, type of care, and geographic location. These findings highlight the growing economic burden of liver cancer and underscore the need for targeted interventions to reduce disparities and improve the efficiency of care delivery.

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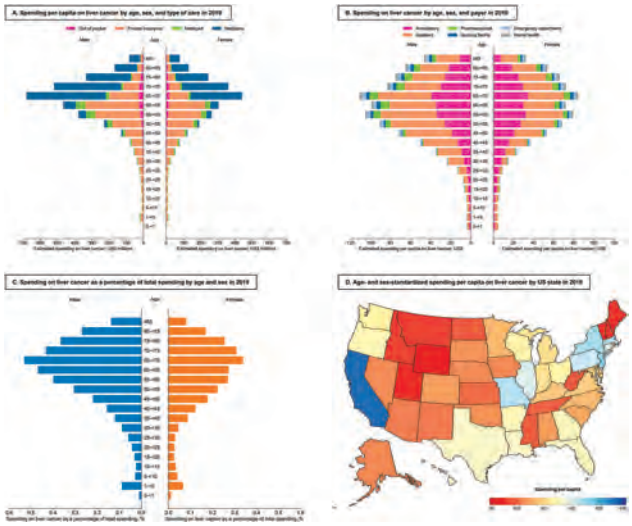
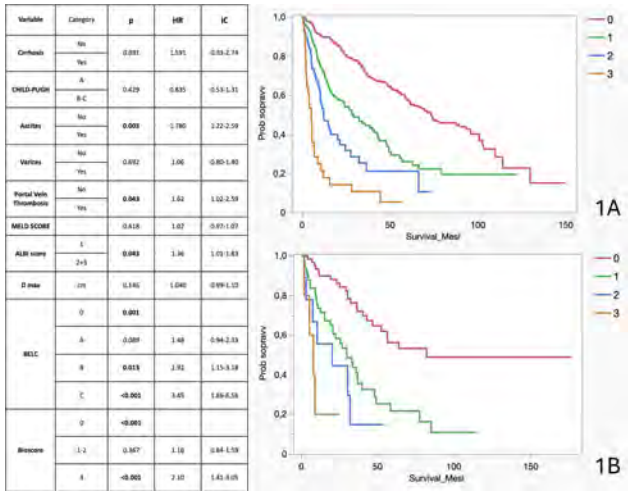


Disclosures: Yan Tian: Nothing to Disclose, Wenjun Wang: Nothing to Disclose, Xiaomeng Cui: Nothing to Disclose, Ting Li: Nothing to Disclose, Shuangsuo Dang: Nothing to Disclose, Xiaoli Jia: Nothing to Disclose

3168 | TUMOR BIOMARKERS ADDED TO BCLC SCORE AMELIORATE SIGNIFICANTLY HEPATOCELLULAR CARCINOMA STAGING

Francesco Damone[1] Gian Paolo Caviglia[2] Piero Colombatto[1] Filippo Oliveri[1] Gabriele Ricco[1] Silvia Gaia[3] Veronica Romagnoli[1] Daniela Cavallone[1] Marta Guariglia[4] Emanuela Rolle[3] Patrizia Carucci[3] Francesco Faita[5] Ferruccio Bonino[5] Maurizia Rossana Brunetto[1], [1]Hepatology Unit, Pisa University Hospital, Italy, [2]Department of Medical Sciences, University of Turin, Turin, Italy, [3]Unit of Gastroenterology, Città della Salute e della Scienza - Molinette Hospital, Turin, Italy, [4]Department of Medical Sciences, University of Turin, Turin, Italy;, [5]Biostructure and Bio-imaging Institute of National Research Council of Italy

Background: The promising results of new combinations of hepatocellular carcinoma (HCC) targeted therapies prompt the improvement of treatment decision based only on tumor and liver function burdens without staging of tumor biology. The combined prognostic value of Alpha-fetoprotein (AFP), Prothrombin Induced by Vitamin K Absence-II (PIVKA-II), and Glypican-3 (GPC-3) for overall survival (OS) remains unclear. **Methods:** We retrospectively analyzed 605 consecutive HCC patients (pts) from two tertiary centers (Pisa n = 279 and Turin n = 326). The cohort was split in training (n = 483) and validation (n = 122) subsets by stratified random sampling based on key clinical and tumor features. In the training set, univariate Cox regression identified variables associated with OS. Statistically significant variables ($p < 0.05$) were included in a multivariate Cox regression model to determine independent prognostic factors. AFP, PIVKA-II, and GPC-3 were combined in a bio-score: 0 = none > cut-off; 1 = one/two > cut-off; 2 = all > cut-off (cut-offs: AFP = 10ng/ml, PIVKA-II = 200mAu/ml, GPC-3 = 100pg/ml). Statistically significant variables in multivariate analysis ($p < 0.05$) were used to build a prognostic score, weighted by their hazard ratios (HR). The score prognostic ability was tested in the validation cohort and compared with the BCLC score by log-rank test. **Results:** Multivariate analysis (Table1) of the training set showed that bio-score, BCLC stage, and ascites were independently associated with OS. Final HRs weighted scores (range 0–7) were: BCLC (0 = 0, A = 1, B = 2, C = 3), ascites (no = 0, yes = 2), and bioscore (0–2). Pts were classified into four groups based on survival distribution: low (0–1), intermediate (2–3), high (4–5), and very high risk (6–7). Median OS significantly decreased across groups ($p < 0.001$): 40.8, 19.3, 12.2, and 5.2 months, respectively. Kaplan–Meier curves confirmed a clear separation between groups, highlighting the reproducibility and prognostic utility of the model, both in training and validation sets (Figure1A-B). The new prognostic score showed a significant stratification of OS (log-rank $p < 0.001$, $\chi^2 = 153.7$), outperforming BCLC staging alone (log-rank $p < 0.001$, $\chi^2 = 108.1$). **Conclusion:** A new prognostic score combining HCC biomarkers, BCLC stage, and ascites offers a simple and effective tool for risk stratification in HCC outperforming BCLC staging alone



Disclosures: Francesco Damone: Nothing to Disclose, Gian Paolo Caviglia: Nothing to Disclose, Piero Colombatto: Nothing to Disclose, Filippo Oliveri: Nothing to Disclose, Gabriele Ricco: Nothing to Disclose, Silvia Gaia: Nothing to Disclose, Veronica Romagnoli:

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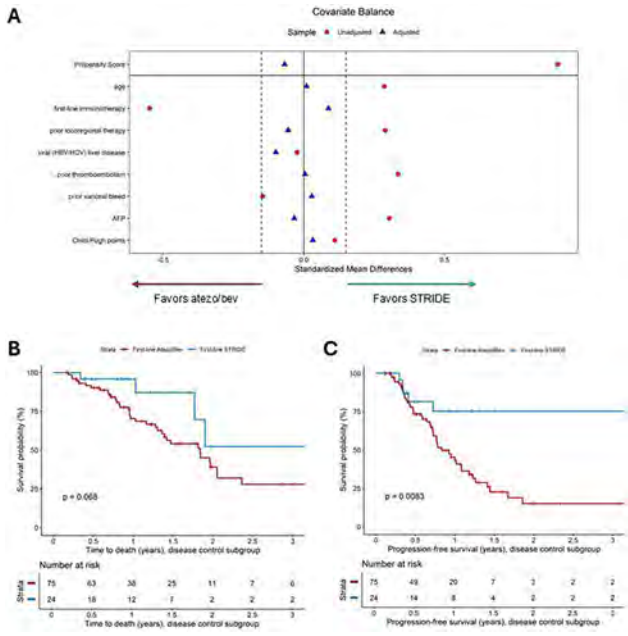
Nothing to Disclose, Daniela Cavallone: Nothing to Disclose, Marta Guariglia: Nothing to Disclose, Emanuela Rolle: Nothing to Disclose, Patrizia Carucci: Nothing to Disclose, Francesco Faita: Nothing to Disclose, Ferruccio Bonino: Nothing to Disclose, Maurizia Rossana Brunetto: Nothing to Disclose

3169 | CLINICAL OUTCOMES IN PATIENTS WITH ADVANCED/ UNRESECTABLE HEPATOCELLULAR CARCINOMA TREATED WITH STRIDE VERSUS ATEZOLIZUMAB-BEVACIZUMAB

Michael Li[1] Huat Lim[1] John Gordan[1] Jocelin Chen[1] Quincy Harris[1] Jennifer Lai[1] Lawrence Fong[2] Robin Kelley[1], [1]University of California, San Francisco, [2]Fred Hutchinson Cancer Center

Background: Single tremelimumab regular interval durvalumab (STRIDE) and atezolizumab-bevacizumab (atezo/bev) are first-line systemic therapy options which improve survival in advanced hepatocellular carcinoma (HCC) but have not been directly compared. We sought to evaluate the impact of regimen on outcomes. **Methods:** We performed a single-center retrospective cohort study of HCC patients who received STRIDE or atezo/bev. Primary outcomes were overall survival (OS) and real-world progression-free survival (rwPFS), defined as clinically-assessed PFS. The secondary outcome was time on treatment (TOT) as a surrogate measure of PFS. To account for confounding by indication, a propensity score model predicting STRIDE treatment (vs atezo/bev) was developed and then used in inverse probability of treatment weighting (IPTW) to create balanced groups for Cox regression. Sensitivity analyses were performed using standard Cox regression adjusting for the same confounders included in the propensity score. **Results:** Of 203 patients, 76 (37%) received STRIDE and 127 (63%) received atezo/bev. There were no differences in liver function, HCC stage, liver disease etiology, or bleeding history between the two groups. STRIDE patients were less likely to be receiving first-line systemic therapy (67% vs 89%, $p < 0.001$) and more likely to have prior extrahepatic thromboembolism (12% vs 3%, $p = 0.014$). STRIDE was associated with a lower disease control rate (56% vs 72%, $p = 0.051$) compared to atezo/bev. After IPTW, key baseline characteristics were balanced, including line of therapy and prior thromboembolism (Love plot, Fig A). On IPTW-Cox regression, there were no differences in OS (HR 0.7, $p = 0.147$) or rwPFS (HR 0.9, $p = 0.662$) when comparing STRIDE vs atezo/bev. However, in the subgroup of patients who achieved disease control ($n = 122$, 60%), STRIDE was associated with longer OS (HR 0.5, 95% CI 0.2-0.9, $p = 0.034$), rwPFS (HR 0.4, 95% CI 0.2-0.9, $p = 0.018$), and TOT (HR 0.4, 95% CI 0.2-0.8, $p = 0.013$ compared to atezo/bev. Sensitivity analyses in the disease control subgroup using standard Cox regression resulted in similar hazard ratios, with STRIDE remaining associated with longer OS (aHR 0.4, 95% CI 0.2-0.8, $p = 0.011$), rwPFS (aHR 0.3, 95% CI 0.2-0.7, $p = 0.004$), and TOT (aHR 0.3, 95% CI 0.2-0.7, $p = 0.002$). In the first-line subgroup of patients with disease control, unadjusted OS (median not reached vs 1.8 years, Fig B) and rwPFS (median not reached vs 0.8 years; Fig C) favored STRIDE. **Conclusion:** STRIDE may be associated with a lower disease control rate compared to atezo/bev, which could reflect that some atezo/bev-treated patients respond to the antiangiogenic component (bev). However, in patients who do achieve disease control, STRIDE treatment was associated with longer OS, rwPFS, and TOT. Our findings support the hypothesis that dual checkpoint inhibition may be associated with more durable immune response.



Disclosures: Michael Li: Nothing to Disclose, Huat Lim: Boston Scientific: Grant/Research Support, John Gordan: Nothing to Disclose, Jocelin Chen: Nothing to Disclose, Quincy Harris: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Lawrence Fong: Roche/Genentech: Grant/Research Support, Merck: Grant/Research Support, BMS: Grant/Research Support, Robin Kelley: Nothing to Disclose

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3170 | ARTIFICIAL INTELLIGENCE FOR HCC RISK PREDICTION IN MASLD: DEVELOPMENT AND VALIDATION OF A PREDICTIVE MODEL IN 306 PATIENTS

Giovane Viola Carvalho[1] Rodolfo Viola Carvalho[1] Regiane Alencar[1] Claudia Tani[1] Mario Pessoa[1] Lisa Saud[1] Aline Chagas[1] Renato Altikes[1] Claudia Oliveira[1], [1]HCFMUSP

Background: The global incidence of hepatocellular carcinoma (HCC) associated with Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) is increasing.
However, there are no specific, accurate, and validated tools to predict HCC risk in this population. **Methods:** We conducted a retrospective cohort study including 306 patients with MASLD. Clinical and laboratory variables were used to train a machine learning
model (XGBoost) to predict the development of HCC, confirmed by imaging or histology. The model's performance was evaluated using the area under the
ROC curve (AUC), sensitivity, and specificity. Results were compared with existing scores such as AFP, GALAD, and aMAP. **Results:** The MASLD-HCC Score achieved an AUC-ROC of 0.90, with sensitivity of 90.9% and specificity of 84.3%. Compared to other tools, GALAD had an AUC
of 0.92 (sens. 82%, spec. 89%), aMAP had an AUC of 0.85 (sens. 96%, spec. 64%), and AFP alone performed worse (AUC 0.83; sens. 61%, spec. 86%). Our
model showed superior overall balance between discrimination and clinical utility, especially in MASLD patients without cirrhosis. The most relevant
features included FIB-4, neutrophil-to-lymphocyte ratio (NLR), AST, ALT, albumin, platelets, and age. The model was deployed into an interactive digital
interface for clinical use. **Conclusion:** We developed and validated an artificial intelligence–based model to predict HCC risk in MASLD. The MASLD-HCC Score outperformed existing tools and
may support individualized surveillance strategies in the growing MASLD population.

Model	AUC-ROC	Sensitivity (%)	Specificity (%)
MASLD-HCC Score (Our Model)	0.9	90.9	84.3
GALAD	0.92	82.0	89.0
AFP	0.83	61.0	86.0
Ultrasound (US)	0.81	63.0	97.0
AFP + US	0.83	69.0	95.0
HCC Risk Score	0.89	89.4	71.4
aMAP	0.85	96.0	64.0

Disclosures: Giovane Viola Carvalho: Nothing to Disclose, Rodolfo Viola Carvalho: Nothing to Disclose, Regiane Alencar: Nothing to Disclose, Claudia Tani: Nothing to Disclose, Mario Pessoa: Nothing to Disclose, Lisa Saud: Nothing to Disclose, Aline Chagas: Nothing to Disclose, Renato Altikes: Nothing to Disclose, Claudia Oliveira: Nothing to Disclose

3171 | INDUCTION OF CUPROPTOSIS AND IMMUNOGENIC CELL DEATH BY A NOVEL COPPER CARRIER A3 IN HEPATOCELLULAR CARCINOMA: SYNERGISTIC ENHANCEMENT WITH PX-478

yuntao bao[1] Yu-Lan Li[1] wei gao[1], [1]The First Affiliated Hospital of Guangxi Medical University

Background: Cuproptosis is a copper-dependent form of programmed cell death driven by copper binding to mitochondrial lipoylated proteins, leading to protein aggregation and mitochondrial dysfunction. We synthesized a quinoline-derived thiosemicarbazone compound (A3) as a copper ionophore and investigated its ability, alone and with the HIF-1α inhibitor PX-478, to induce cuproptosis and immunogenic cell death (ICD) in hepatocellular carcinoma. **Methods:** Huh-7 cells were treated with A3/Cu (IC_{50} = 1.3 μM) ± PX-478. We measured intracellular copper, FDX1 and DLAT (Western blot), ROS, autophagy markers (LC3-II, p62), and mitochondrial ultrastructure (TEM). ICD was assessed via CRT exposure, HMGB1 release, and ATP secretion. Specificity for cuproptosis was tested using TTM, Ferrostatin-1, Necrostatin-1, and Z-VAD-FMK. In vivo, C57BL/6 mice bearing H22 xenografts received A3/Cu ± PX-478 for 21 days; tumor growth, histology (H&E, Ki-67), DLAT/FDX1 immunofluorescence, and organ toxicity (H&E, serum biochemistry) were evaluated. **Results:** A3/Cu inhibited Huh-7 proliferation, elevated intracellular copper, upregulated FDX1, and altered DLAT; only TTM reversed cytotoxicity, confirming cuproptosis. Treatment increased ROS, autophagy, and mitochondrial damage. ICD markers rose and were further enhanced by PX-478. In vivo, A3/Cu reduced tumor growth, with greater suppression upon PX-478 co-treatment; tumors exhibited necrosis, reduced Ki-67, and DLAT/FDX1 changes consistent with cuproptosis. No organ toxicity was observed. **Conclusion:** A3 induces cuproptosis and ICD in liver cancer cells. Combined with PX-478, it enhances antitumor efficacy with minimal toxicity, offering a promising immunotherapeutic strategy.
Disclosures: yuntao bao: Nothing to Disclose, Yu-Lan Li: Nothing to Disclose, wei gao: Nothing to Disclose

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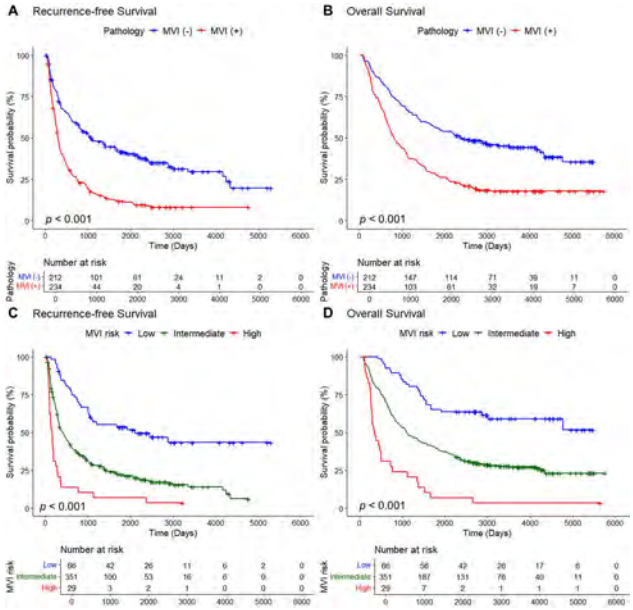
3172 | PREOPERATIVE PREDICTION OF MICROVASCULAR INVASION IN INTRAHEPATIC CHOLANGIOCARCINOMA AND ITS PROGNOSTIC IMPLICATIONS: A MULTICENTER STUDY

Dong Hwan Kim[1] Sang Hyun Choi[1], [1]Asan Medical Center

Background: Microvascular invasion (MVI) is a well-established adverse prognostic factor in intrahepatic cholangiocarcinoma (ICCA). However, previous studies on preoperative predictors of MVI in ICCA have yielded inconsistent results. This study aimed to identify preoperative clinical and magnetic resonance imaging (MRI) factors that can predict MVI in ICCA and to evaluate their prognostic utility using a multicenter cohort. **Methods:** A multicenter cohort of 446 patients who underwent preoperative MRI and curative-intent resection for ICCA at six tertiary referral centers between 2009 and 2018 was analyzed. Clinical, pathological, and MRI features were evaluated. Univariable and multivariable logistic regression analyses were performed to identify significant predictors of pathologically confirmed MVI, which were subsequently used to stratify patients into low-, intermediate-, and high-risk groups based on the number of predictors identified. Kaplan–Meier survival analysis and log-rank tests were performed to assess overall survival and early recurrence (defined as recurrence within one year postoperatively) across risk groups. **Results:** Among the 446 patients (mean age, 63.0 ± 9.9 years; 277 men), 234 (52.5%) had MVI on pathology. Independent predictors of MVI included serum carbohydrate antigen 19-9 levels (≥ 80 U/mL; odds ratio [OR]: 2.68, 95% confidence interval [CI]: 1.64–4.37, $p < 0.001$), tumor size (≥ 4 cm; OR: 1.60, 95% CI: 1.01–2.54, $p = 0.046$), tumor multiplicity (OR: 2.84, 95% CI: 1.58–5.12, $p < 0.001$), and arterial-phase peritumoral enhancement (OR: 2.83, 95% CI: 1.81–4.42, $p < 0.001$). Stratifying patients by MVI risk—low (no predictors), intermediate (1–3 predictors), and high (4 predictors)— revealed a significant decrease in both recurrence-free and overall survival rates ($p < 0.001$), along with a corresponding increase in early recurrence rates ($p < 0.001$) as the risk level increased. **Conclusion:** Risk stratification utilizing four key predictors can effectively assess the risk of MVI in ICCA and is associated with postoperative outcomes.



Disclosures: Dong Hwan Kim: Nothing to Disclose, Sang Hyun Choi: Nothing to Disclose

3173 | INVESTIGATION OF TUMOR HETEROGENEITY IN LIVER USING HISTOLOGICAL ANALYSIS AND SPATIAL LIPIDOMICS IN MYRISTOYLATED AKT-TAZ (MYRAKT-TAZ S89A)-DRIVEN MURINE MODEL

Jee Won Jennifer Shin[1] Seul Kee Byeon[1] Olajide Olaleye[1] Chady Meroueh[1] Pandey Akhilesh[1] Kirk Wangensteen[1], [1]Mayo Clinic

Background: While TAZ overexpression alone is insufficient to drive tumorigenesis (leading to cancer only in a minority of cells after prolonged latency), co-expression of AKT and TAZ significantly accelerates liver tumor development, effectively recapitulating human intrahepatic cholangiocarcinoma (iCCA) more effectively. We have used the myristoylated AKT-TAZ (myrAKT-TAZ S89A) driven murine model that recapitulates human iCCA and have studied its histological spatial distribution of lipids using imaging mass spectrometry(IMS) to study tumor heterogeneity. This study can help correlate specific oncogenic pathways with unique lipid and metabolic fingerprints, which can help

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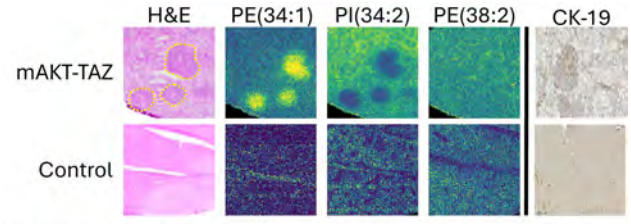
identify and validate biomarkers for early detection of liver cancer. **Methods:** 5 Mice were hydrodynamically injected with plasmids co-expressing myrAKT and TAZ S89A. We monitored tumor development and confirmed tumor formation by histological analysis. After 7 weeks, livers were cryosectioned, and spatial lipidomics was performed to map lipid distributions within the tumor environment. We also performed immunohistochemical staining for cytokeratin 19 (CK19) as an aid for tumor morphological assessment. **Results:** All mice (n = 5) receiving the oncogenic plasmids (myrAKT-TAZ S89A) developed liver tumors. Histological analysis of mouse liver sections showed tumors that exhibited cholangiocarcinoma-like features, such as marked nuclear pleomorphism, glandular formation, dense fibrotic stroma, and a tendency to grow near portal tracts. We examined the spatial distribution of various specific lipids. Control liver tissue demonstrated uniform distribution of lipids, reflecting normal liver histology. The myrAKT-TAZ S89A-treated mouse livers had spatially distinguished phosphatidylinositol (PI)-enriched tumors that were spatially distinguished from the tumors that were enriched with ceramide phosphate. Within the ceramide phosphate-enriched tumors, PE(34:1) was enriched, PI(34:2) was depleted, and phosphatidylethanolamine PE(38:2) was unchanged in tumors. CK19 staining was positive but was not uniform, with high nuclear pleomorphism and some gland formation. Some of the neoplastic cells show some eosinophilic cytoplasm, which might represent mixed hepatocellular carcinoma (HCC)- CCA components. We are applying additional markers (e.g., MOC31, arginase1, glypican3) to further characterize the HCC and CCA components of these tumors. **Conclusion:** myrAKT-TAZ S89A -driven murine liver tumors display marked histological and lipidomic heterogeneity reminiscent of human HCC and CCA. Distinct spatial lipid signatures correlate with tumor subtypes, offering insights into tumor biology and pointing to potential metabolic vulnerabilities. Ongoing work is examining the mechanisms underlying these lipidomic differences and aims to identify novel therapeutic targets associated with dysregulated lipid metabolism.



3D Lipidomics: Tumors in mouse livers repopulated with oncogenic plasmids (mAKT-TAZ) showed spatial distribution in which PE(34:1) is enriched, PI(34:2) is depleted, and PE(38:2) is unchanged compared to the control. CK-19 staining shown on the left for both oncogenic liver and control.

Disclosures: Jee Won Jennifer Shin: Nothing to Disclose, Seul Kee Byeon: Nothing to Disclose, Olajide Olaleye: Nothing to Disclose, Chady Meroueh: Nothing to Disclose, Pandey Akhilesh: Nothing to Disclose, Kirk Wangensteen: Nothing to Disclose

3174 | INTERIM SHORT-TERM FEASIBILITY AND SAFETY ANALYSIS OF SINGLE-SESSION YTTRIUM-90 TRANSARTERIAL RADIOEMBOLIZATION FOR SMALL HEPATOCELLULAR CARCINOMA: ONE & DONE TRIAL

Nima Kokabi[1] Sandra Gad[1] Andrew Moon[1] Hanna Sanoff[1] Jingquan jia[2] Neil Shah[3] Michael Mohnasky[1] David Mauro[2] Alex Villalobos[1] Hyeon Yu[1], [1]University of North Carolina, [2]Univeristy of North Carolina, [3]University of North Carolina at Chapel Hill

Background: The One and Done prospective single-arm phase II clinical trial [NCT06618300] aims to evaluate the efficacy and safety of a streamlined single-session treatment protocol in patients with small hepatocellular carcinoma (HCC) receiving resin-based Yttrium-90 (Y90) transarterial radioembolization (TARE). **Methods:** This prospective, currently ongoing study enrolls patients with small HCC lesions with no evidence of macrovascular invasion (Organ Procurement and Transplantation Network (OPTN) Stage T2). The study is designed to enroll a total of 30 patients, and this analysis represents the preplanned interim safety assessment at the halfway point. Enrolled patients have a focal HCC (a single lesion $\leq$5 cm or $\leq$ 3 nodules, $\leq$ 3 cm) confined to one or two anatomical liver segments. Additional inclusion criteria include total serum bilirubin $<$3.0 mg/dL, serum albumin $>$2.5 g/dL, and an Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2. Patients undergo a single-session Y90 TARE. During angiography, 3D Cone Beam Computed Tomography (3D-CBCT) is used to confirm complete tumor perfusion. Personalized curative Y90 dose is calculated intraprocedurally, and the corresponding prescribed activity of Y90 microspheres is administered during the same session. Post-procedural imaging includes a single photon emission computed tomography (SPECT)/CT scan to confirm adequate dose delivery and retrospectively calculate lung shunt fraction (LSF). Follow-up includes clinical and biochemical toxicity assessments at 1, 3, 6, and 12 months and imaging to assess response according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) at 3, 6, and 12 months. The study's primary endpoint is time to treatment, with secondary endpoints assessing safety and efficacy. **Results:** Thus far, among recruited patients (n = 15), 14 patients have successfully undergone streamlined single-session Y90 TARE with at least 1 month of postprocedural follow-ups. In one

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patient, the treatment was aborted due to visualization of early enhancement of hepatic veins on 3D-CBCT, which suggested high LSF. The cohort was predominantly male (86%), with an average age of 66.4+ 7.5 years old. The most common underlying etiologies for HCC were viral hepatitis. Most patients had Child-Pugh Class A liver function (86%). Overall, 15 tumors were treated in the 14 patients with a median tumor size of 2.2 cm (IQR-2). The median time to treatment was 28 days (IQR-18). Mean LSF was 6.7% (SD: 2.6%). The mean delivered dose to the tumor was 465 Gy (SD: 363 Gy). No patients developed $\geq$ Grade 3 AEs post-TARE. Specifically, no patient developed any signs of radiation pneumonitis. Of these patients, 7 had follow-up imaging at 3 months, with all (100%) demonstrating objective response in the treated tumors. **Conclusion:** The interim analysis of this study suggests that streamlined single-session resin-based Y90-TARE in patients with small HCC is feasible and safe

Disclosures: Nima Kokabi: Sirtex: Consultant, Okami: Consultant, Boston Scientific: Consultant, Sandra Gad: Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant, Hanna Sanoff: Nothing to Disclose, Jingquan jia: Nothing to Disclose, Neil Shah: GSK: Advisor, Ipsen: Advisor, GSK: Consultant, Ipsen: Consultant, Michael Mohnasky: Nothing to Disclose, David Mauro: Nothing to Disclose, Alex Villalobos: Nothing to Disclose, Hyeon Yu: Nothing to Disclose

3175 | COMBINED TEAD AND TYROSINE KINASE INHIBITOR THERAPY STRONGLY EXTENDS SURVIVAL IN HEPATOCELLULAR CARCINOMA

Marcella Steffani[1] Yoshinobu Saito[2] Vera Garcia-Outeiral[3] Qiuyan Sun[3] Kirk Wangensteen[4] Robert Schwabe[5], [1]Department of Medicine, Columbia University, [2]The University of Osaka, Graduate School of Medicine, Osaka, Japan, [3]Department of Medicine, Columbia University, New York, NY, USA, [4]Mayo Clinic, [5]Columbia University

Background: Despite recent therapeutic advances such as the combination of immune checkpoint inhibitors with anti-VEGF, the majority of patients with advanced hepatocellular carcinoma (HCC) die within 2 years. Current combination therapies selectively target the tumor microenvironment (TME), leaving tumor cell-targeted therapies a therapeutic gap. Here, we used tumor-selective CRISPR interference (CRISPRi), followed by pharmacologic inhibition of candidates, to uncover novel tumor cell-intrinsic vulnerabilities and extend survival in HCC. **Methods:** Druggable targets were identified using tumor cell-specific *in vivo* CRISPRi screens in models of TAZ-, MET+CCNTB1- or AKT+NRas-driven HCC, induced by hydrodynamic tail vein injection in dCas9 transgenic mice. The impact on tumor growth and survival was evaluated by single-gene CRISPRi and pharmacologic inhibitors, followed by mechanistic evaluation. Synergies between candidates were assessed by high-throughput drug screens. **Results:** CRISPRi screens identified TEAD family members as druggable therapeutic vulnerabilities in HCC. *In vitro* silencing revealed unique transcriptional targets in tumor cells for each of the 4 TEAD members. Accordingly, tumor cell-specific *in vivo* CRISPRi significantly prolonged the median overall survival (OS) in mouse models of HCC for each TEAD. Notably, pharmacological panTEAD inhibitors (panTEADi) recently entered trials for various tumor entities but not for HCC. panTEADi VT104 and IAG933 exerted strong anti-tumor effects in 3 mouse models of HCC, with nearly doubled median OS in MET +CCNTB1-driven HCC (11.9 vs. 5.3 wks, $p = 0.0015$). A complementary high-throughput synergy screen of 372 anti-cancer drugs uncovered strong and significant ($p < 0.001$) synergies between panTEADi and four tyrosine kinase inhibitors (TKI) in murine and human HCC. The combination of TKI lenvatinib and panTEADi IAG933 significantly extended median OS ($>$ 18 wks/ ongoing IAG933+lenvatinib vs 10.5 wks IAG933, 9.9 wks lenvatinib, 5.9 wks vehicle) in MET+CCNTB1-driven HCC. Mechanistically, panTEADi+TKI therapy led to a strong induction of tumor cell death *in vitro* and *in vivo*. **Conclusion:** The unique HCC-promoting functions of each TEAD family member provide the basis for potent anti-tumor effects of panTEADi in HCC. Owing to strong synergies, the combination of panTEADi and TKI may represent a potent and clinically applicable tumor cell-targeted therapy for HCC that could be combined with current TME-directed therapies.

Disclosures: Marcella Steffani: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Vera Garcia-Outeiral: Nothing to Disclose, Qiuyan Sun: Nothing to Disclose, Kirk Wangensteen: Nothing to Disclose, Robert Schwabe: Nothing to Disclose

3176 | UNRAVELLING STEMNESS DYNAMICS IN INTRAHEPATIC CHOLANGIOCARCINOMA: INSIGHTS INTO PRIMARY AND METASTATIC STEM-LIKE CELL EVOLUTION

Margherita Correnti[1] Marco Erreni[2] Marina Sironi[3] Matteo Ramazzotti[4] Chiara Raggi[5] Jesper Andersen[5] Colm O'Rourke[5] Cedric Coulouarn[6] Fabio Pagni[7] Mario Urso[7] Diego Calvisi[8] LUCA DI TOMMASO[9] Stefania

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Background: The aggressiveness of intrahepatic cholangiocarcinoma (iCCA) relies on key tumor features such as cellular plasticity, self-renewal capacity, and metastatic potential, collectively described as tumor stemness. Molecular mechanisms driving the maintenance and evolution of stemness features during iCCA progression remain poorly understood. This study aims to characterize the dynamics of stemness-related traits in primary and metastatic iCCA, identify key molecular pathways that sustain tumor cell plasticity, and explore their role in disease dissemination. By elucidating these features in vivo, we seek to uncover novel targets to disrupt tumor stemness and hinder disease progression. **Methods:** Taking advantage of a 3D sphere culture system (SPH) as a model for cancer stem cells, an orthotopic mouse model was developed through intrahepatic injection of Luciferase-GFP-transfected SPH cells obtained by both established and primary iCCA cells. Disseminated GFP+ tumor cells in target organs (lungs, spleen, peritoneum, mesenteric lymph nodes) and blood were analyzed via FACS. GFP+ cells from primary and metastatic lung tumors were isolated by FACS for molecular profiling using pathway-focused qRT-PCR arrays. These findings were validated in human metastatic and non-metastatic iCCA samples through immunohistochemistry and correlated with clinical and pathological data. **Results:** SPH cells were responsible for a great tumor spread in all secondary organs analyzed, especially those derived from MTCHC-01 primary cells. The absence of CD45-/GFP + tumor cells in the blood of animals suggested that lymphatic circle is the preferential via to iCCA dissemination. Notably, lung SPH-disseminated cells showed up-regulation of many tested stem-like, epithelial-to-mesenchymal transition, angiogenesis and drug resistance related genes compared to SPH-primary tumor cells. A panel of 34 genes commonly up-regulated was found in all SPH-disseminated cells. High expression of some of these genes were correlated with a significantly lower 5-years and disease-free survival of 289 iCCA patients. Among these, *TSPAN13* and *WNT5A* are of particular importance. Expression levels of these 2 genes-derived proteins were significantly up-regulated metastatic CCA specimens compared to non-metastatic ones. **Conclusion:** Our data indicate that a core stemness program is maintained during iCCA progression, with *TSPAN13* and *WNT5A* emerging as key markers of stemness and metastasis.

Disclosures: Margherita Correnti: Nothing to Disclose, Marco Erreni: Nothing to Disclose, Marina Sironi: Nothing to Disclose, Matteo Ramazzotti: Nothing to Disclose, Monika Lewinska: Nothing to Disclose, Jesper Andersen: Nothing to Disclose, Colm O'Rourke: Nothing to Disclose, Cedric Coulouarn: Nothing to Disclose, Fabio Pagni: Nothing to Disclose, Mario Urso: Nothing to Disclose, Nothing to Disclose, Diego Calvisi: Nothing to Disclose, LUCA DI TOMMASO: Nothing to Disclose, Stefania Recalcati: Nothing to Disclose, Fabio Marra: Nothing to Disclose, Monika Lewinska: Nothing to Disclose

3177 | OUTCOME PREDICTION IN HCC AFTER LIVER TRANSPLANT: HOW MUCH CAN WE TRUST IMAGING?

Natalia Marcos Carrasco[1] Cristina Martinez Cuevas[1] Alicia San Jose Crespo[1] Elena Velasco Martinez[1] Carolina Almohalla Alvarez[1] FELIX GARCIA PAJARES[1] Maria Jordan de la Fuente[1] Laura Jimenez Gonzalez[2] Gloria Sanchez Antolín[1], [1]Hepatology and Liver Transplant Unit. Hospital Universitario Rio Hortega, [2]Hepatology and Liver Transplant Unit. Hospital Universitaria Rio Hortega

Background: Hepatocellular carcinoma (HCC) accounts for 35% of liver transplant (LT) indications. Its diagnosis primarily relies on imaging studies, which often underestimate tumor size. Additionally, vascular invasion in the explant is a significant risk factor for post-transplant recurrence.

The aim of this study was to evaluate the correlation between radiological and pathological findings of HCC in liver explants and their influence on post-transplant survival and recurrence. **Methods:** A retrospective, observational, single-center study was conducted at Hospital Universitario Río Hortega, including patients transplanted for HCC between 2010 and 2022. Radiological findings were compared with histopathological data from liver explants. Survival and associated risk factors were analyzed. **Results:** A total of 147 liver transplant recipients were included, 85.03% male, with

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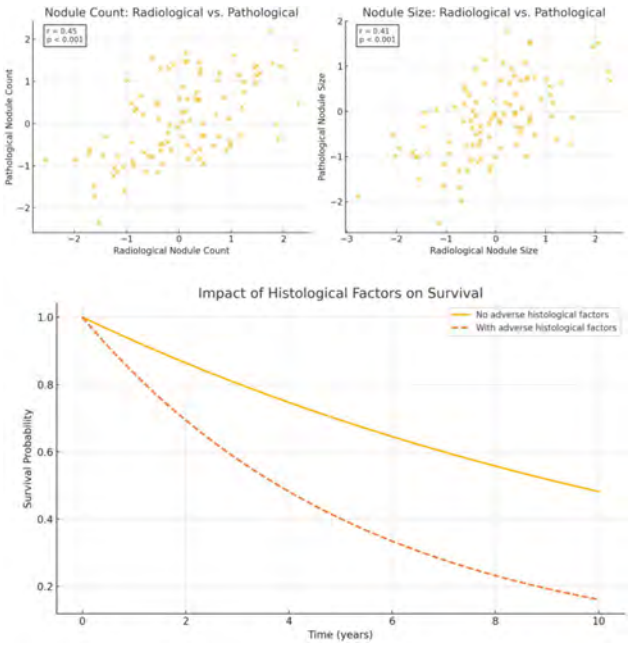
a median age of 60 years (55-64). The most common etiologies were alcohol-related liver disease (52.4%), hepatitis C virus (19%), and combined etiologies (15.6%). Pre-transplant assessments showed that 66% of patients were Child-Pugh A, with a median MELD score of 10 (8-13). Imaging revealed that 88.4% met Milan criteria, while the remainder met expanded criteria.

In imaging studies, 51% of patients had 1 nodule, 27.2% had 2, 14.3% had 3, and the remainder had ≥ 4 nodules, with a median size of 2.5 cm (1.8-3 cm). Pathological findings revealed that 70.75% of patients met Milan criteria, with 46.2% showing 1 nodule, 21.1% showing 2, 12.9% showing 3, and the remainder ≥ 4 nodules, with a median size of 2.5 cm (1.7-3.5 cm). The correlation between radiological and pathological findings was moderate, 0.45 for nodule number ($p < 0.001$) and 0.41 for size ($p < 0.001$). Median survival was 8.6 years (3,155 days), with 42.2% mortality at the end of follow-up. Neither nodule count nor adherence to Milan criteria (radiological) significantly influenced mortality. However, histological factors associated with poor prognosis were significantly linked to survival ($p < 0.001$). **Conclusion:** Pre-transplant radiological evaluation of HCC is crucial for staging and achieving high post-transplant survival rates. However, survival is not influenced by adherence to Milan or expanded criteria but rather by the presence of histopathological poor prognostic factors, which significantly impact recurrence and post-transplant survival. Strategies to enhance pre-transplant evaluation and address adverse histological features may improve outcomes.



Disclosures: Natalia Marcos Carrasco: Nothing to Disclose, Cristina Martinez Cuevas: Nothing to Disclose, Alicia San Jose Crespo: Nothing to Disclose, Elena Velasco Martinez: Nothing to Disclose, Carolina Almohalla Alvarez: Nothing to Disclose, FELIX GARCIA PAJARES: Nothing to Disclose, Maria Jordan de la Fuente: Nothing to Disclose, Laura Jimenez Gonzalez: Nothing to Disclose, Gloria Sanchez Antolín: Nothing to Disclose

3178 | ADDITION OF COMPUTED-TOMOGRAPHY-DERIVED RADIOMICS FEATURES DID NOT IMPROVE MORTALITY PREDICTION AFTER TRANSARTERIAL CHEMOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA

Philip Vutien[1] George Ioannou[1] Amilcare Gentili[2] Chunnan Hsu[2], [1]University of Washington Medical Center, [2]Veterans Affairs San Diego Healthcare System

Background: Prior work has shown that a model that includes abdominal computer-tomography (CT)-based radiomics features can predict progression-free survival following transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC). We examined whether the addition of CT-based radiomics adds predictive value to a clinical model for 1-year mortality after TACE. **Methods:** From the WAW-TACE dataset, we analyzed 229 patients with hepatocellular carcinoma (HCC) with multiphase CT imaging ≤ 90 days before initial TACE, excluding those with metastatic disease, vascular invasion, or Child-Pugh class C. Data were split into 80/20 training/testing sets. Radiomics features were extracted previously using PyRadiomics, which yielded selected features based on abdominal structures that were clinically associated with portal hypertension and liver function (e.g. liver, liver vessels, spleen, and tumor characteristics). From this pool of 53 radiomics features, rank-sum testing ($p < 0.05$) was used to select 7 features associated with 1-year mortality and for eventual model development. Three XGBoost models were built to predict 1-year mortality after initial TACE: 1) Clinical model – liver disease etiology, BCLC stage, Child-Pugh score, INR, AFP, bilirubin, creatinine, albumin, age, sex, and largest tumor characteristics (size, number, location); 2) Radiomics model – 7 features derived from liver, liver vessels, spleen, and tumor characteristics; 3) Combined clinical and radiomics model. Model performance was evaluated on the test dataset and the DeLong test was used to compare differences in C-statistic (e.g. discrimination) between models. **Results:** Among 229 patients, median age was 66 years, 21% were women, 48% had viral hepatitis, and 89% had Child-Pugh A cirrhosis, and 62 died within 1 year following TACE. 63% had unifocal HCC, and median tumor size was 4.5 cm (IQR 3 to 6.2 cm). Model discrimination (Table, Figure) was highest for the

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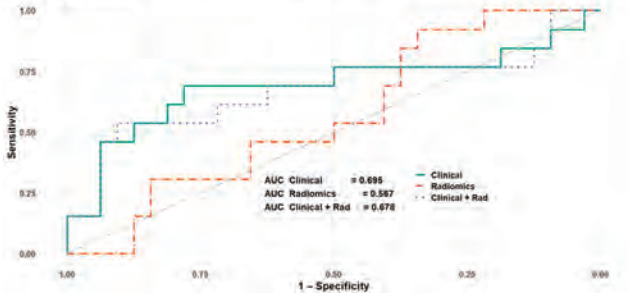
clinical model (AUC 0.70), lower for the clinical + radiomics model (AUC 0.68), and lowest for the radiomics-only model (AUC 0.57). The performance of the clinical + radiomics model was not significantly different from that for the clinical model (DeLong *p:* 0.72). **Conclusion:** In this cohort with relatively few deaths, adding liver- and spleen-focused radiomics did not improve 1-year mortality prediction over clinical variables, alone. Larger studies and optimized feature extraction are warranted.

Table. Model characteristics ascertained on the test set.

	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV
Clinical*-only Model	0.70	0.76	0.62	0.81	0.57	0.84
Radiomics**-only Model	0.57	0.67	0.15	0.88	0.33	0.72
Clinical + radiomics model	0.68	0.71	0.54	0.78	0.50	0.81

*Clinical model predictors included: etiology of liver disease, BCLC class, Child Pugh score, INR, AFP, biltrubin, creatinine, albumin, age, sex, largest lesion diameter, number of lesions, location (right or left lobe) of the largest lesion. **Radiomics model includes features derived from CT imaging of the spleen, liver, and liver vessels.

Figure. AUC of the three models developed using (1) clinical, (2) radiomics predictors, and (3) clinical + radiomics predictors.

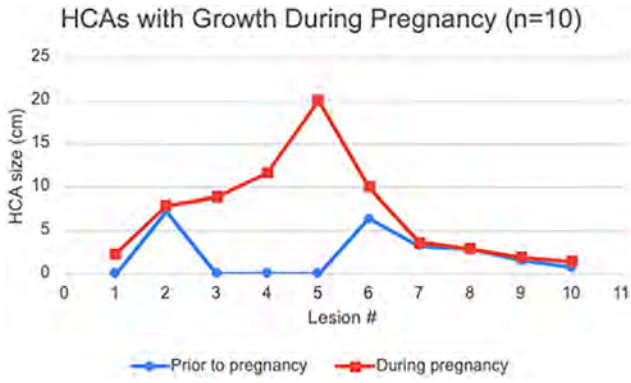


Disclosures: Philip Vutien: Nothing to Disclose, George Ioannou: Nothing to Disclose, Amilcare Gentili: Nothing to Disclose, Chunnan Hsu: Nothing to Disclose

3179 | HEPATOCELLULAR ADENOMA (HCA): GROWTH AND OUTCOMES IN PREGNANCY

Gowthami Kanagalingam[1] Mallika John[2] Jasmine Gamez[3] Liina Poder[4] Richard Sterling[1] Monika Sarkar[5], [1]Virginia Commonwealth University, [2]Wellesley College, [3]UCSF Hepatology/Liver Transplant, [4]UCSF Radiology, [5]University of California, San Francisco

Background: HCAs are typically estrogen-responsive benign liver lesions with risk for growth and rupture during pregnancy. However, granular data on HCA behavior during pregnancy, particularly for lesions larger than 5 cm, are limited. **Methods:** This two-center retrospective study utilized chart-validation and imaging review to evaluate growth and clinical outcomes of HCAs (abdominal pain, hemorrhage, rupture, and/or HCA interventions). HCAs identified prior to or during pregnancy from 2013 to 2024 were included. A change in size from pre-conception to postpartum was reported. **Results:** The cohort included 29 patients, with 37 pregnancies reflecting 20 and 17 pregnancies at each tertiary care center. Median age was 34.5 years and median pre-pregnancy BMI was 27.3kg/??2; 59.3% (16/27) used prior combined hormonal contraception. Median gestation was 38 weeks with 6/37 (16.2%) pre-term births and 13/37 (35%) c-sections. There were 3 (8%) abortions, two induced and one spontaneous. The largest hepatic adenoma lesion pre-pregnancy measured 16.4 cm and the largest lesion during pregnancy was 20 cm. Twenty one percent (4/19) of the hepatic adenomas prior to pregnancy were > 5 cm in size and during pregnancy 6/17 (35.3%) were > 5 cm in size. Among patients with pre-conception and/or multiple gestational scans (n = 18), 55.5% had growth, 16.6% stability, and 27.7% regression during pregnancy. Among patients with post-partum scans (n = 22), the median size was 2.3 cm (IQR 4.9) with 11.8% growth, 23.5% stability, and 64.7% regression at 7 median months postpartum. Abdominal pain was reported in 59.4% (22/37). 5.4% (2/37) had hemorrhage, 5.4% (2/37) had embolization and 2.7% (1/37) resection during pregnancy for lesions with a median size of 9.9 cm (IQR 2.95). **Conclusion:** In this cohort of well-characterized HCA outcomes in pregnancy, growth was observed in over 50% of cases, with the majority showing regression postpartum. Hemorrhage occurred only in lesions > 5.9 cm, with no maternal or neonatal mortality.



Disclosures: Gowthami Kanagalingam: Nothing to Disclose, Mallika John: Nothing to Disclose, Jasmine Gamez: Nothing to Disclose, Liina Poder: Nothing to Disclose, Richard Sterling: ABIM: GI Specialty Board, Abott: Grant/Research Support, AbbVie: Grant/Research Support, Roche: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research Support, Monika Sarkar: GSK: Grant/Research Support, Zydus Pharmaceuticals: Grant/Research Support, Gilead Sciences: Grant/Research Support

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3180 | RURAL RESIDENCE IS ASSOCIATED WITH HIGHER ODDS OF ABSENT OR INCOMPLETE LI-RADS CLASSIFICATION ON CROSS-SECTIONAL IMAGING IN PATIENTS REFERRED TO A MULTIDISCIPLINARY HEPATOCELLULAR CARCINOMA CLINIC

Parsa Pazooki[1] Gabriel Lupu[1] Lauren Burke[1] A. Sidney Barritt[1] Sasha Deutsch-Link[2] Oren Fix[1] Neil Shah[1] Hersh Shroff[2] Andrew Moon[3], [1]University of North Carolina at Chapel Hill, [2]UNC Chapel Hill, [3]University of North Carolina

Background: Hepatocellular carcinoma (HCC) prognosis is closely tied to timely diagnosis, and HCC mortality is increasing disproportionately in rural populations. The Liver Imaging Reporting and Data System (LI-RADS) aims to standardize radiologic reporting and diagnosis of HCC for patients with cirrhosis. Rural residence may be associated with barriers to care, delayed diagnosis, and distance from liver transplant centers with expert radiologists. This study evaluated whether rural residence is associated with the absence of proper LI-RADS classification on referral imaging among patients with cirrhosis referred to a multidisciplinary HCC clinic. **Methods:** We performed a single-center, retrospective analysis of patients with cirrhosis who were referred for evaluation of liver masses between 9/30/2016 and 12/6/2024 with CT or MRI imaging. Rural-urban classification was determined using the North Carolina Department of Health and Human Services designations. The primary outcome was incomplete LI-RADS classification on referral imaging. A multivariable logistic regression model was used to assess the association between rurality and incomplete or absent LI-RADS classification, adjusting for serum alpha-fetoprotein (AFP) levels, BMI, imaging modality, and liver disease etiology. **Results:** Of the 89 identified patients, 76 had cirrhosis with CT or MRI imaging, and most referrals (99%) occurred after 2019. 96.3% of rural patients and 85.7% of urban patients were referred from gastroenterology or other subspecialty clinics. Missing LI-RADS was noted in 44.4% of patients with rural residence as compared to 34.7% of urban patients (Table 1). After adjustment for potential confounders, rural residence was associated with increased odds of incomplete LI-RADS classification (OR 2.31; 95% CI: 0.77–6.91). Higher serum AFP levels were associated with incomplete or absent LI-RADS classification, although this finding was not statistically significant. **Conclusion:** Among rural patients with cirrhosis referred for evaluation of liver masses there were increased odds of incomplete LI-RADS classification on initial referral imaging in both unadjusted and adjusted models, although this was not statistically significant. These findings highlight a potential disparity in diagnostic imaging quality or reporting that may impact the timely management of HCC among rural residents. Further work is needed to develop solutions to address this potential contributor to rural–urban disparities.

Table 1. Patient characteristics and multivariable logistic regression analysis of the association between rural residence and the application of LI-RADS criteria on initial CT/MRI imaging among patients with cirrhosis referred to an HCC clinic

	LI-RADS Present on Referral Imaging	
	No	Yes
N = 76	29 (38.2%)	47 (61.8%)
Age (SD)	69.83 (7.81)	66.23 (9.52)
Urban/Rural		
Urban	17 (58.6%)	32 (68.1%)
Rural	12 (41.4%)	15 (31.9%)
Sex		
Male	23 (79.3%)	32 (68.1%)
Female	6 (20.7%)	15 (31.9%)
Serum AFP (ng/mL)		
Normal (<10) or Borderline (11-19)	17 (58.6%)	35 (74.5%)
Elevated (20-199)	5 (17.2%)	6 (12.8%)
Very High (>/= 200)	7 (24.1%)	6 (12.8%)
BMI	30.39 (8.04)	28.93 (6.48)
Referral Imaging Type		
CT Abdomen	6 (20.7%)	1 (2.1%)
MRI Abdomen	23 (79.3%)	46 (97.9%)
Referral Setting		
External GI or Other		
Subspecialty	28 (96.6%)	40 (85.1%)
Primary Care or Urgent Care	1 (3.4%)	5 (10.6%)
Emergency Room or Admission	0 (0.0%)	2 (4.3%)
Liver Disease Etiology		
HCV post SVR/Viremic HCV/HBV-related	12 (41.4%)	10 (21.3%)
Alcohol-Associated	4 (13.8%)	15 (31.9%)
MASLD	12 (41.4%)	19 (40.4%)
Other*	1 (3.4%)	3 (6.4%)
MELD 3.0 Score	10.21 (4.22)	9.49 (2.75)

Logistic Regression Analysis†		
Absent or incomplete LI-RADS classification on referral	Unadjusted OR (95% CI)	Adjusted OR (95% CI)**
Urban/Rural		
Urban	Reference	Reference
Rural	1.51 (0.51, 4.36)	2.31 (0.77, 6.91)

* Other liver disease etiologies included autoimmune hepatitis, 3; hereditary hemochromatosis, 2; unknown, 1
†α = 0.05; p < 0.05 considered statistically significant
**Adjusted for serum AFP, BMI, Referral Imaging Type, Liver Disease Etiology
Hepatocellular Carcinoma (HCC); Liver Imaging Diagnostics and Reporting System (LI-RADS) Body Mass Index (BMI); Hepatitis C Virus (HCV); Sustained Virologic Response (SVR); Hepatitis B Virus (HBV); Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD); Model for End Stage Liver Disease (MELD); Alpha-fetoprotein (AFP); Odds Ratio (OR)

Disclosures: Parsa Pazooki: Nothing to Disclose, Gabriel Lupu: Nothing to Disclose, Lauren Burke: Nothing to Disclose, A. Sidney Barritt: Nothing to Disclose, Sasha Deutsch-Link: Nothing to Disclose, Oren Fix: Nothing to Disclose, Neil Shah: GSK: Advisor, Ipsen: Advisor, GSK: Consultant, Ipsen: Consultant, Hersh Shroff: Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant

3181 | A PHASE II STUDY OF DUAL VEGF/PD-L1 BLOCKADE IN THE NEOADJUVANT SETTING IN PATIENTS WITH RESECTABLE HCC

Joe Eid[1] Hop Tran Cao[1] Jean-Nicolas Vauthey[1] Ching-Wei Tzeng[1] Timothy Newhook[1] Yun Shin Chun[1] Manal Hassan[1] Joshua Kuban[1] Ryan Sun[1] Sakara McGrew[1] Sunyoung Lee[1] Zishuo Ian Hu[1] Mahesh Kumar Kannan[1] James Yao[1] Asif Rashid[1] Hesham Amin[1]

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Ahmed Kaseb[1], [1]The University of Texas MD Anderson Cancer Center

Background: Hepatocellular carcinoma (HCC) has a high recurrence rate after resection, 70% at 5 years. However, no effective adjuvant or neoadjuvant therapies currently exist. Given the efficacy of anti-VEGF (bevacizumab (Bev)) and anti-PD-L1 (atezolizumab (Atezo)) against HCC, we initiated a pilot trial of pre-operative dual VEGF/PD-L1 blockade in patients with resectable HCC. **Methods:** Patients enrolled in this trial during 2021-2024 received atezolizumab 1200 mg IV and bevacizumab 15 mg/kg IV on day 1 of a 21-day cycle. Patients received 3 cycles before undergoing curative-intent resection during week 12. Co-primary endpoints were safety and tolerability of the Atezo/Bev combination in the pre-operative setting and the rate of major pathologic response (MPR) or pathologic complete response (pCR), identified as occurrence of $\geq$ 70% and 100% necrosis, respectively. Secondary endpoints included overall response rate (ORR) at time of surgery per RECIST 1.1 criteria, duration of response, and overall survival. **Results:** Sixteen patients were enrolled. Median (IQR) age was 72 (67-76) years, and 75% of patients were male. Out of 16 patients enrolled, 13 completed therapy and resection, one patient received all 3 cycles of Atezo/Bev but was not resected due to advanced cirrhosis, and 2 patients dropped out before treatment began. At the time of surgery, pCR was observed in 1/13 patients (7.7% pCR). Another patient had 50% necrosis, and the rest $<$50%. Per RECIST 1.1, 2/13 (15.4%) patients, including the patient who achieved pCR, had partial response ($>$30% radiologic response). No grade 4 or higher toxicity were observed. Immunohistochemical staining of the resection specimens exhibited upregulation of the expression of the growth hormone receptor (GHR) and its downstream oncogenic targets including pERK, pSTAT3, and pIGF-IR, specifically in the viable tumor areas in the patients who did not achieve pCR. After a median follow-up of 23 months, all the patients are alive, and of the 13 patients who received Atezo/Bev and were resected, 2 patients had recurrence. **Conclusion:** Despite the low pCR rate, our study remains significant as it allows to assess resistance biomarkers and identify druggable targets. Further analysis of the GHR pathway and downstream cascade will be our next focus, which may lead to a clinical study to investigate the effects of Atezo/Bev with or without GHR inhibitors in HCC patients.

Disclosures: Joe Eid: Nothing to Disclose, Nothing to Disclose, Hop Tran Cao: Merck: Grant/Research Support, Intuitive Foundation: Grant/Research Support, Jean-Nicolas Vauthey: Nothing to Disclose, Ching-Wei Tzeng: Panther: Consultant, Timothy Newhook: Nothing to Disclose, Yun Shin Chun: Nothing to Disclose, Manal Hassan: Nothing to Disclose, Joshua Kuban: Boston Scientific: Advisor, Ethicon: Advisor, Bayou Surgical: Stock – privately held company, Radioclash: Advisor, Ethicon: Grant/Research Support, Elekta: Grant/Research Support, Lunglife AI: Grant/Research Support, Ryan Sun: Nothing to Disclose, Sakara McGrew: Nothing to Disclose, Sunyoung Lee: Nothing to Disclose, Zishuo Ian Hu: Nothing to Disclose, Mahesh Kumar Kannan: Nothing to Disclose, James Yao: Nothing to Disclose, Asif Rashid: Nothing to Disclose, Hesham Amin: Nothing to Disclose, Ahmed Kaseb: Nothing to Disclose

3182 | PATIENT CHARACTERISTICS AND TREATMENT PATTERNS AMONG PATIENTS WITH INTRAHEPATIC CHOLANGIOCARCINOMA WITH AND WITHOUT AUTOIMMUNE COMORBIDITIES: A RETROSPECTIVE STUDY

Sumera Ilyas[1] Nilofer Azad[2] Shishir Maithel[3] Rachna Shroff[4] Milind Javle[5] Mitesh Borad[6] Nehemiah Kebede[7] Young Jung[8] Sheena Dupuy[9] Stephen Valerio[10] Juan Valle[11], [1]Division of Gastroenterology and Hepatology, Mayo Clinic; Department of Immunology, Mayo Clinic, [2]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, [3]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, [4]Division of Hematology and Oncology, University of Arizona Cancer Center, [5]Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, [6]Division of Hematology and Oncology, Department of Medicine, Mayo Clinic, [7]Oncology Data and Statistics, AstraZeneca, [8]AstraZeneca Canada, [9]GI Oncology, AstraZeneca, [10]US Medical Affairs, AstraZeneca, [11]Cholangiocarcinoma Foundation; Division of Cancer Sciences, University of Manchester

Background: Findings from TOPAZ-1 support durvalumab and gemcitabine + cisplatin (GemCis) as a standard-of-care treatment for advanced biliary tract cancer. However, patients (pts) with intrahepatic cholangiocarcinoma (iCCA) often have autoimmune comorbidities that could restrict immunotherapy use. Treatment patterns in pts with iCCA with and without autoimmune comorbidities are reported. **Methods:** This study is a retrospective observational analysis of adult pts diagnosed with iCCA in the United States who were enrolled in registries between 2019 and 2023, with datasets enriched for pts treated with durvalumab. The study used data from the International Cholangiocarcinoma Patient Registry, a collaboration between The Cholangiocarcinoma Foundation and Citizen Health®. The registry contains de-identified data from medical records obtained directly from consenting pts and

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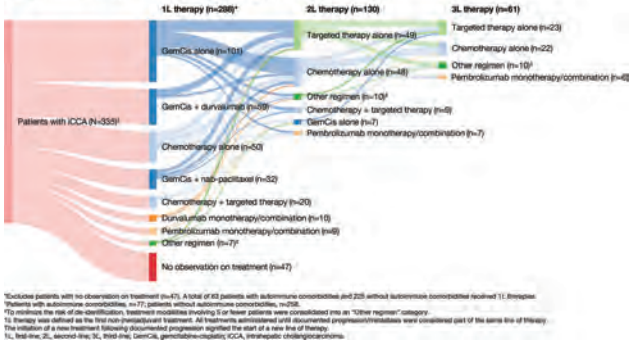
caregivers. Pts were followed from the index date (initial date of CCA diagnosis) until the last activity in the database or death, whichever occurred first. We report pt demographics, clinical characteristics, biomarkers, and treatment patterns (line of therapy) for pts with iCCA with and without autoimmune comorbidities. **Results:** The median (quartile [Q]1–Q3) age of pts with iCCA (N = 335) was 59.0 (48.0–66.0) years, 66.6% were female, and pts had a mean of 9.9 comorbidities. The most common genetic alterations occurring in pts with iCCA were in *FGFR2* (20.3%), *IDH1* (20.3%), *PD-L1* (15.8%), and *HER2* (any method, 5.7%). Autoimmune comorbidities were present in 77 (23.0%) pts with iCCA; colitis (26.0%), rheumatoid arthritis (18.2%), and ulcerative colitis (16.9%) were the most common autoimmune comorbidities recorded. Durvalumab + GemCis was received by 20.5% (60.8% [n/N = 45/74] post-March 2022) and GemCis alone by 35.1% (13.5% [n/N = 10/74] post-March 2022) of pts with iCCA at first-line (1L) (Figure). In pts with iCCA, durvalumab + GemCis was received by 19.0% (60.0% [n/N = 9/15] post-March 2022) of pts with autoimmune comorbidities, and 20.9% (61.0% [n/N = 36/59] post-March 2022) without, at 1L. The use of other immunotherapy regimens at 1L was generally similar across both populations. **Conclusion:** Treatment patterns for immunotherapy regimens were generally similar for the iCCA cohort with and without autoimmune comorbidities, suggesting that autoimmune comorbidities do not restrict durvalumab use. Future research will focus on clinical outcomes and toxicities in these populations, which could inform clinical decision-making.

Figure. Treatment modalities in each line of therapy among patients diagnosed with iCCA



Disclosures: Sumera Ilyas: Astrazeneca: Consultant, Nilofer Azad: Nothing to Disclose, Shishir Maithel: AstraZeneca: Advisor, Genentech: Advisor, Rachna Shroff: Nothing to Disclose, Milind Javle: Nothing to Disclose, Mitesh Borad: Nothing to Disclose, Nehemiah Kebede: AstraZeneca Pharmaceuticals LP: Employee and hold stock, Young Jung: Nothing to Disclose, Sheena Dupuy: Nothing to Disclose, Stephen Valerio: Nothing to Disclose, Juan Valle: Nothing to Disclose

3183 | HEAD-TO-HEAD COMPARISON OF SCORING SYSTEMS TO ASSESS LIVER FUNCTION IN HEPATOCELLULAR CARCINOMA: A MULTICENTRE STUDY

Kai Yi Benjamin Nah[1] N Apoorva Sasikumar[2] Beom Kyung Kim[3] Mark Muthiah[4] Daniel Huang[4] Karn Wijarnpreecha[5] Sung Won Lee[6] Ken Liu[7] Takumi Kawaguchi[8] Gang Chen[9] Hirokazu Takahashi[10], [1]National University Hospital, [2]National University Singapore, [3]Yonsei University College of Medicine, [4]National University Hospital, Singapore, [5]University of Arizona College of Medicine-Phoenix, [6]The Catholic University of Korea, [7]University of Sydney, [8]Kurume University School of Medicine, [9]The First Affiliated Hospital of Wenzhou Medical University, [10]Saga University

Background: Hepatocellular carcinoma (HCC) remains the third leading cause of cancer-related deaths globally, with a 5-year survival rate of less than 20%. Liver function is a key determinant of treatment eligibility and prognosis in HCC. Several scoring systems, including Child-Turcotte-Pugh (CTP), MELD, APRI, FIB-4, and the ALBI grade, are used to assess liver function, but their effectiveness in predicting outcomes specifically in HCC patients is unclear. This study aims to compare the clinical utility of these scores in predicting survival in HCC. **Methods:** This retrospective, multicentre cohort study analysed data from 2,685 adults diagnosed with HCC across seven international centres from January 2003 to July 2021. We compared the prognostic performance of five liver function scores: ALBI grade, CTP score, APRI, MELD, and FIB-4. Discrimination and calibration were assessed using statistical methods such as Harrell's C-index, Brier score, and Kaplan-Meier survival analysis. **Results:** The ALBI grade showed superior discrimination with the highest Harrell's C statistic (0.6724) and AUC values (0.663–0.716), outperforming CTP, MELD, APRI, and FIB-4. Calibration analysis demonstrated that the ALBI grade had the closest alignment to observed survival outcomes, as shown by calibration curves and residual plots. All scoring systems displayed satisfactory calibration, but ALBI consistently showed the best fit. **Conclusion:** The ALBI grade is the most reliable score for assessing liver function in HCC patients, offering superior prognostic accuracy compared to other commonly used scores. While all scores demonstrated acceptable calibration, the ALBI grade's consistent performance suggests it should be prioritized in clinical

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practice. Future studies should focus on integrating liver function scores with other biomarkers and clinical parameters to further enhance prognostic accuracy in HCC.

Disclosures: Kai Yi Benjamin Nah: Nothing to Disclose, N Apoorva Sasikumar: Nothing to Disclose, Beom Kyung Kim: Nothing to Disclose, Mark Muthiah: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Daniel Huang: Gilead: Consultant, Roche: Speaking and Teaching, Karn Wijarnpreecha: Nothing to Disclose, Sung Won Lee: Nothing to Disclose, Ken Liu: Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching, Gang Chen: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support

3184 | PROGNOSTIC IMPACT OF DIABETES AND HYPERTENSION ON HEPATOCELLULAR CARCINOMA SURVIVAL: A 15-YEAR REGISTRY-BASED ANALYSIS

Jonggi Choi[1] Ji won Yang[2] Hyeyeon Hong[2] Songgyung Kim[2] Jina Park[2] Chaeyeon Lim[2] Won-Mook Choi[2] Danbi Lee[2] Ju Hyun Shim[2] Kang Mo Kim[2] YOUNG-SUK LIM[2] Han Chu Lee[2], [1]University of Ulsan, Asan Medical Center, [2]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: In Korea, hepatocellular carcinoma (HCC) is a major cause of cancer-related mortality, and its incidence is rising in the elderly population. Given this trend, the influence of comorbidities, such as diabetes mellitus (DM) and hypertension (HTN), on survival warrants further investigation. This study investigated the prognostic implications of these comorbidities using a 15-year, large-scale registry. **Methods:** A total of 21,699 treatment-naïve HCC patients from the Asan Medical Center HCC registry (2009–2023) were analyzed. The influence of DM and HTN on overall survival (OS) was assessed according to the Barcelona Clinic Liver Cancer (BCLC) staging system. Patients were stratified into four groups based on comorbidity status: none, HTN only, DM only, and both HTN and DM. OS was estimated using the Kaplan–Meier method, with comparisons via log-rank tests. Cox proportional hazards models were used to evaluate the association between comorbidities and survival, with hazard ratios (HRs) calculated for each group. **Results:** The median age of the cohort was 59 years, 80.6% were male, and hepatitis B virus infection was the most common etiology of HCC. Among all patients, 5,476 (26.5%) had DM, and 7,541 (34.8%) had HTN. When stratified by comorbidity status, the median OS was 6.0 years in patients with no comorbidities, 6.8 years in those with HTN only, 5.6 years in those with DM only, and 4.9 years in those with both DM and HTN. Patients with both DM and HTN had significantly worse survival compared to those without comorbidities (HR 1.12, $p < 0.001$).

In patients with BCLC stage 0, OS was significantly lower in those with comorbidities. The HR for OS was 1.20 in patients with HTN, 2.02 in those with DM, and 2.17 in those with both DM and HTN (all $p < 0.001$). A similar pattern was observed in BCLC stage A, where the HR for OS was 1.09 in patients with HTN, 1.33 in those with DM, and 1.49 in those with both comorbidities (all $p < 0.001$). However, in BCLC stages B, C, and D, OS did not show significant differences based on comorbidity status. **Conclusion:** Our findings suggest that DM is associated with poorer prognosis in HCC patients, and the presence of both DM and HTN further worsens survival outcomes, particularly in very early (BCLC 0) and early-stage (BCLC A) disease. These results highlight the need for tailored surveillance and management strategies for HCC patients with metabolic comorbidities.

Disclosures: Jonggi Choi: GILEAD SCIENCE: Grant/Research Support, Ji won Yang: Nothing to Disclose, Hyeyeon Hong: Nothing to Disclose, Songgyung Kim: Nothing to Disclose, Jina Park: Nothing to Disclose, Chaeyeon Lim: Nothing to Disclose, Won-Mook Choi: Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, Roche: Consultant, Danbi Lee: Nothing to Disclose, Ju Hyun Shim: Nothing to Disclose, Kang Mo Kim: Nothing to Disclose, YOUNG-SUK LIM: Nothing to Disclose, Han Chu Lee: Roche: Grant/Research Support, BMS: Grant/Research Support, Astrazeneca: Grant/Research Support, Merck: Grant/Research Support

3185 | GERANYLGERANYL PYROPHOSPHATE REGULATES HUMAN HEPATIC STELLATE CELL FUNCTION VIA YES-ASSOCIATED PROTEIN AND RHO GTPASES.

Courtney Labrecque[1] Bo Qiao[1] Arthur Ko[2] Renu Nandakumar[3] Kushan Chowdhury[1] Calvin Pan[1]

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Namrata Venkatesan[1] Matteo Pellegrini[1] Samuel French[1] Joseph Pisegna[4] Vatche Agopian[5] Enrique Rozengurt[1] Rajat Singh[1] Jihane Benhammou[1], [1]University of California, Los Angeles, [2]Chidren's National Research Institute, Washington DC, [3]Columbia University, [4]University of California, Los Angles, [5]David Geffen School of Medicine at UCLA

Background: Hepatic stellate cells (HSC) are central to cirrhosis and hepatocellular carcinoma (HCC) development. Statin use is associated with decreased incidence of cirrhosis and HCC; however, the mechanisms for their chemoprotective effects remains elusive. We aimed to identify novel pathways in MASLD-related HCC as part of our hypothesis that statins regulate HSC function by lowering the levels of the mevalonate pathway metabolite geranylgeranyl pyrophosphate (GGPP). **Methods:** We integrated single nucleus RNA sequencing (snRNA-seq) of 13 MASLD-HCC patients (n = 12 adj non-tumor, 12 HCC) and spatial transcriptomics of human MASLD-HCC livers (n = 6) using CosMx to identify novel pathways of interest. We used bulk RNA sequencing of statin-treated primary human HSCs (pHSCs) (n = 4) to examine the effects of statins. pHSCs and LX2 cells were used to validate proteins and genes of interest. To investigate the role of GGPP, we used pharmacogenetic inhibition of key pathway targets and reciprocal exogenous GGPP repletion to assess YAP protein localization and effector gene regulation. Intracellular GGPP levels were then assessed via LC-MS/MS. **Results:** Reference cell-types and their proportions were generated from snRNAseq (334,803 cells). We identified 762,287 cells in our spatial transcriptomic analyses and observed cell-type heterogeneity across cell-types including HSCs. Spatial imaging revealed HSCs are predominantly localized with immune cells in HCCs. We identified that statin-treated pHSCs have a significant downregulation of Yes-associated protein (YAP) genes and Rho-dependent pathways ($p < 0.001$). We showed that pHSCs exposed to statin led to cytoplasmic retention of YAP, reduced expression of YAP effector genes, and cytoskeleton restructuring. These effects were restored to baseline with GGPP repletion. Knockdown of GGPP synthase 1, inhibition of GGTAse I (GGPP transferase), and inhibition of Rho each recapitulated the statin effects in HSCs. LC-MS/MS measurements revealed a 10-fold reduction in intracellular GGPP levels in response to statins, confirming our findings that statins downregulate HSC function by lowering GGPP levels. **Conclusion:** We present the largest integrated transcriptomic studies of MASLD-HCCs revealing subsets of HSCs that are spatially localized with immune cells. Our data are the first to directly measure GGPP levels, confirming statins regulate YAP and Rho GTPases in HSCs via GGPP. Further studies will investigate the HSC-immune cross-talk in MASLD/MASH and its relevance to HCC.

Disclosures: Courtney Labrecque: Nothing to Disclose, Bo Qiao: Nothing to Disclose, Arthur Ko: Nothing to Disclose, Renu Nandakumar: Nothing to Disclose, Kushan Chowdhury: Nothing to Disclose, Calvin Pan: Nothing to Disclose, Namrata Venkatesan: Nothing to Disclose, Matteo Pellegrini: Nothing to Disclose, Samuel French: Nothing to Disclose, Joseph Pisegna: Nothing to Disclose, Vatche Agopian: Nothing to Disclose, Enrique Rozengurt: Nothing to Disclose, Rajat Singh: Nothing to Disclose, Jihane Benhammou: Nothing to Disclose

3186 | TARGET-SPECIFIC LOCKED NUCLEIC ACID GAPMER DECREASES GROWTH OF HEPATOCELLULAR CARCINOMA

Keyue ZHANG[1] Hong Cao[1] Wenqiang Chen[1] Jill Smith[1], [1]Georgetown University

Background: Hepatocellular carcinoma (HCC) is the fastest growing cause of cancer-related deaths worldwide. The CCK-B receptor (CCKBR) is absent in normal liver tissue but is upregulated with inflammation, cirrhosis, and in HCC. Gastrin promotes tumor cell growth via autocrine signaling at the CCKBR. LNA Gapmers are antisense oligonucleotides that are 16-20 nucleotides in length. They contain a central stretch ("gap") of DNA monomers flanked by 'locked nucleic acid, i.e., (LNA)" modified nucleotides. **Methods:** In this study, we developed a specific LNA Gapmer (Gapmer-90) targeting gastrin. This Gapmer was modified by click chemistry to conjugate an amino acid ligand for selective binding to CCKBR, aiming to disrupt the CCKBR-Gastrin signaling axis. In vitro, human HepG2 and Hep3B HCC cells were characterized for CCKBRs and gastrin expression by qRT-PCR and flow cytometry. In vitro HCC cells were transfected with Gapmer-90 and gastrin expression was evaluated by PCR and immunohistochemistry. Effects on growth were evaluated by MTT assay and viable cell counting assays. Hep3B tumors were developed in Athymic nude mice subcutaneously and mice were treated with PBS (control), untargeted Gapmer-90 (120μM), and targeted Gapmer-90 (120μM). Survival analysis was performed. **Results:** Hep3B cells expressed more gastrin and had more CCKBRs than HepG2 cells by qRT-PCR. Flow cytometry revealed Hep3B expressed more CCK-BRs than HepG2 cells. HCC cells transfected in vitro with Gapmer-90 revealed a significant reduction of gastrin mRNA expression by PCR in Hep3B cells only ($P < 0.01$). Gapmer-90-treated Hep3B cells showed decreased growth by MTT and trypan blue assays by 74% compared to controls ($P < 0.0001$).

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Immunocytochemistry showed decreased gastrin peptide in Gapmer#90-treated HCC cells compared to controls. In vivo, mice bearing Hep3B tumors treated with the targeted Gapmer-90 had a 50% greater survival than PBS-controls and also 50% greater survival than mice treated with the untargeted Gapmer-90. **Conclusion:** Gastrin peptide is expressed in human HCC and regulates growth via the CCK-BR in an autocrine fashion. CCK-BR targeted Gapmer-90 effectively down regulates gastrin to inhibit growth of HCC in vitro and improve survival of HCC-tumor bearing mice in vivo. Selective targeting of the CCK-BR- gastrin axis by LNA Gapmers offers a novel strategy for precision medicine by inhibiting growth of HCC and improving survival.
Disclosures: Keyue ZHANG: Nothing to Disclose, Hong Cao: Nothing to Disclose, Wenqiang Chen: Nothing to Disclose, Jill Smith: Nothing to Disclose

3187 | PLASMA TWEAK LEVELS AS A PREDICTIVE BIOMARKER FOR TREMELIMUMAB PLUS DURVALUMAB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

Takeru Hirao[1] Takahiro Kodama[1] Yu Sato[1] Yuta Myojin[1] Kazuma Daiku[1] Ryo Takahashi[1] Shuhei Yamamoto[1] Kazuki Maesaka[1] Kumiko Shirai[1] Kazuhiro Murai[1] Yuki Tahata[1] Yuki Makino[1] Yoshinobu Saito[1] Hayato Hikita[1] Tomohide Tatsumi[1] Tetsuo Takehara[2], [1]The University of Osaka, [2]Kansai Rosai Hospital

Background: Immunotherapy has transformed the therapeutic landscape of hepatocellular carcinoma (HCC). However, survival benefits for patients are still limited. This study aimed to identify novel blood-based biomarkers predictive of treatment response to tremelimumab plus durvalumab (Dur/Tre) in advanced HCC patients. **Methods:** We used Proximity Extension Assay (PEA) technology from Olink® to simultaneously profile 92 plasma proteins in pre-treatment samples from 50 patients with unresectable HCC who received Dur/Tre therapy, aiming to identify proteins predictive of progression-free survival (PFS), over-all survival (OS) and response rate. Next, pre-treatment plasma protein levels of tumor necrosis factor-like weak inducer of apoptosis (TWEAK) were evaluated by Enzyme-Linked Immunosorbent Assay (ELISA) in 64 patients with unresectable HCC who received Dur/Tre, and their association with clinical outcomes was investigated. Similarly, plasma TWEAK levels were also measured by ELISA in 66 patients treated with atezolizmab plus bevacizumab (Atez/Bev). **Results:** Using Normalized Protein eXpression (NPX) values generated by Olink®, patients were divided into high and low groups for each circulating protein. Stratification by TWEAK levels enabled clear separation of both PFS and OS. Comparison between NPX values and concentrations measured by ELISA for TWEAK showed a Pearson correlation coefficient greater than 0.85, indicating a strong positive correlation. In 45 patients with unresectable HCC treated with Dur/Tre, high TWEAK levels were associated with a significantly higher overall response rate (ORR: 30.4% vs. 4.8%, $p = 0.0481$) compared to low TWEAK levels. Both PFS (109 days vs. 55 days, $p < 0.05$) and OS (578 days vs. 313 days, $p < 0.05$) were significantly longer in the high TWEAK group. In the validation cohort of 19 HCC patients, similar findings to those in the initial 45 patient cohort were observed. Multivariate Cox proportional hazard analysis identified a high plasma TWEAK level as an independent predictor of prolonged OS. Comparison between the Dur/Tre group ($n = 64$) and the Atez/Bev group ($n = 66$) revealed no significant differences in pre-treatment plasma TWEAK concentrations or OS. Among patients with high plasma TWEAK levels, those treated with Dur/Tre tended to have better OS compared to those who received Atez/Bev. Conversely, among patients with low plasma TWEAK levels, OS was significantly longer in those treated with Atez/Bev than in those who received Dur/Tre. **Conclusion:** Plasma TWEAK levels predicted clinical outcomes in advanced HCC patients treated with Dur/Tre therapy. Furthermore, pre-treatment plasma TWEAK concentrations may serve as a decision-making biomarker for choosing between Dur/Tre and Atez/Bev therapies.
Disclosures: Takeru Hirao: Nothing to Disclose, Takahiro Kodama: Nothing to Disclose, Yu Sato: Nothing to Disclose, Yuta Myojin: Nothing to Disclose, Kazuma Daiku: Nothing to Disclose, Ryo Takahashi: Nothing to Disclose, Shuhei Yamamoto: Nothing to Disclose, Kazuki Maesaka: Nothing to Disclose, Kumiko Shirai: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Yuki Makino: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Tomohide Tatsumi: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

3188 | SYNERGISTIC TUMOR IMMUNOTHERAPY VIA CUPROPTOSIS, APOPTOSIS AND CHEMODYNAMIC THERAPY: FUNCTIONAL COPPER(II) COMPLEXES COMBINED WITH HIF-1α INHIBITION

Yu-Lan Li[1] yuntao bao[1] Songqing He[1], [1]The First Affiliated Hospital of Guangxi Medical University

Background: Hepatocellular carcinoma (HCC) is a highly malignant tumor with limited treatment efficacy

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due to the immunosuppressive tumor microenvironment (TME). Although immunotherapy has made significant progress, overcoming this barrier remains a major challenge. Cuproptosis, a novel mitochondria-dependent form of regulated cell death driven by protein lipoylation, can synergize with apoptosis and chemodynamic therapy to induce immunogenic cell death (ICD) and promote antitumor immune responses. **Methods:** MTT assay, western blotting, electron paramagnetic resonance (EPR) spectroscopy, flow cytometry, ELISA and transmission electron microscopy (TEM) . **Results:** A series of copper(II) complexes based on pyridine hydrazone ligands were synthesized and evaluated. Among them, Cu4B exhibited the most potent cytotoxicity against Huh-7 cells, with an IC_{50} of 0.46 $\pm$ 0.07 μM. Western blot analysis revealed that Cu4B upregulated DLAT while downregulating LISA, and FDX1, indicating activation of the cuproptosis pathway. EPR results demonstrated that these copper complexes could deplete intracellular glutathione (GSH) and catalyze the conversion of hydrogen peroxide (H_2O_2) into hydroxyl radicals (•OH). This led to decreased GSH levels, increased oxidized glutathione (GSSG), and elevated reactive oxygen species (ROS), suggesting a Fenton-like reaction and resulting in oxidative stress. TEM revealed mitochondrial damage, and apoptosis assays confirmed that Cu4B significantly increased apoptotic cell rates (28.8%) compared to control (2.84%) and cisplatin-treated groups (3.93%), indicating mitochondrial pathway–mediated apoptosis. Furthermore, Cu4B treatment triggered the release of damage-associated molecular patterns (DAMPs) such as calreticulin (CRT), HMGB1, and ATP, demonstrating ICD induction. In a subcutaneous HCC mouse model, Cu4B elicited a potent antitumor immune response, as demonstrated by dendritic cell maturation and T cell proliferation. Cu4B treatment significantly inhibited tumor growth in both single and bilateral HCC-bearing mouse models. Notably, the combination of Cu4B with the HIF-1α inhibitor PX-478 significantly enhanced therapeutic efficacy by promoting cuproptosis, apoptosis, chemodynamic therapy, and immune activation, leading to marked tumor growth inhibition. **Conclusion:** Cu4B induces ICD in HCC by simultaneously activating cuproptosis, apoptosis, and chemodynamic therapy. Co-administration of PX-478 further amplifies these effects. This work providing a promising strategy for enhancing the efficacy of HCC immunotherapy.

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3189 | DIAGNOSTIC ACCURACY OF THE GAAD SCORE IN NON-CIRRHOTIC PATIENTS WITH FOCAL LIVER LESIONS

Mohamed Moussa[1] Dave Sprengers[1] Vera Ketting[1] Christian Ramakers[1] Robert De Man[1] Roy Dwarkasing[1] Harry Janssen[2] Antonius van Herwaarden[3] Eric Tjwa[4] Milan Sonneveld[5], [1]Erasmus University Medical Center, Rotterdam, The Netherlands., [2]Erasmus University Medical Centre, Toronto Centre for Liver Disease, Toronto General Hospital, [3]Radboud University Medical Center, Nijmegen, The Netherlands, [4]Radboud University Medical Center, Nijmegen, Netherlands., [5]Erasmus University Medical Center, Rotterdam, The Netehrlands

Background: Focal liver lesions are frequently encountered, often as incidentalomas, in patients without cirrhosis. There is an urgent unmet need for non-invasive tests to distinguish hepatocellular carcinoma (HCC) from other lesions. We studied the diagnostic accuracy of the GAAD score, which is based on patient age, sex and serum values of AFP and PIVKA-II, in non-cirrhotic patients with focal liver lesions. **Methods:** In a multi-center prospective study, all consecutive patients presenting with focal liver lesions in a non-cirrhotic liver were enrolled from two tertiary referral clinics in the Netherlands. The diagnostic accuracy of the GAAD score was assessed at its predefined cutoff score of 2.57 and compared to AFP and PIVKA-II alone in the overall study population and after stratification by lesions size and presence of underlying liver disease. **Results:** A total of 583 patients were included. The median age was 50 years (IQR: 39–65), with 69% females, and the majority were Caucasian (84%). Liver disease was present in 37% of this cohort, with SLD as the most common etiology (28%), followed by viral hepatitis (10%). HCC was diagnosed in 74 (12.7%) cases. Patients with HCC were significantly older (median age 72 vs. 48, $p < 0.001$), and more often male (77% vs. 24%, $p < 0.001$). The GAAD score offered superior discrimination over AFP (AUC 0.96 vs 0.75, $p < 0.001$) and PIVKA-II (AUC 0.96 vs 0.91, $p < 0.011$). At a GAAD cut-off of 2.57, the sensitivity, specificity, PPV and NPV were 85%, 96%, 76% and 98%, with GAAD offering superior specificity over PIVKA-II and superior sensitivity over AFP. The performance of GAAD was consistent regardless of the presence of an underlying chronic liver disease (AUC 0.93 vs 0.97, $p = 0.228$), and regardless of the presence of viral hepatitis (AUC 0.99 vs 0.96, $p = 0.048$) or steatotic liver disease (AUC 0.92 vs 0.98, $p =$

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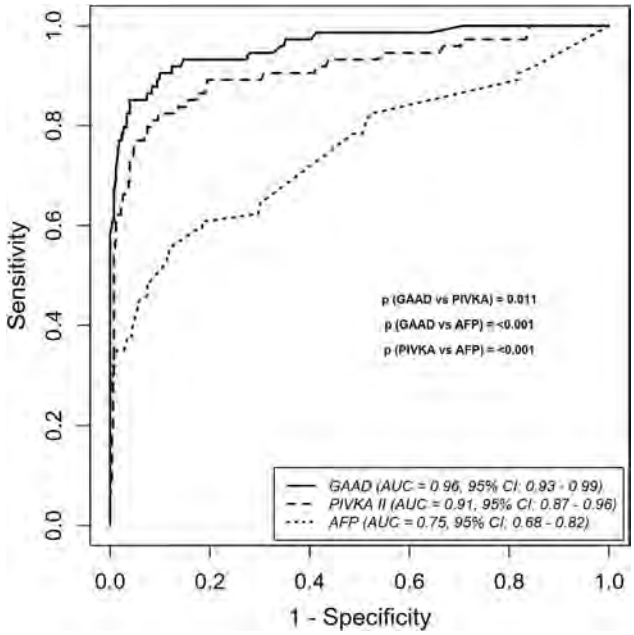
0.189). The GAAD score had superior discriminatory performance over AFP in small (AUC; 0.92 vs 0.67, $p = 0.030$), intermediate (AUC; 0.93 vs 0.61, $p < 0.001$) and large (AUC; 0.98 vs 0.80, $p < 0.001$) lesions. GAAD also outperformed PIVKA-II in small (AUC; 0.92 vs 0.81, $p = 0.331$), intermediate (AUC; 0.93 vs 0.89, $p = 0.219$), and large (0.98 vs 0.93, $p = 0.011$) lesions and offered NPVs $> 95\%$ regardless of lesion size. **Conclusion:** In this cohort of non-cirrhotic patients with focal liver lesions, the GAAD score was highly predictive of HCC and offered superior diagnostic accuracy over AFP and PIVKA-II alone. These findings support the use of the GAAD score to guide management decisions in these patients.



Disclosures: Mohamed Moussa: Nothing to Disclose, Dave Sprengers: Nothing to Disclose, Vera Ketting: Nothing to Disclose, Christian Ramakers: Nothing to Disclose, Robert De Man: Nothing to Disclose, Roy Dwarkasing: Nothing to Disclose, Harry Janssen: Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Academic Medical Education: Consultant, H.C. Wainwright & Co: Consultant, Antonius van Herwaarden: Nothing to Disclose, Eric Tjwa: Nothing to Disclose, Milan Sonneveld: Roche: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Consultant, ViR: Advisor, GSK: Grant/Research Support, Fujirebio: Grant/Research Support

3190 | DYNAMICS OF ALPHA-FETOPROTEIN LEVELS DURING TREATMENT WITH ATEZOLIZUMAB COMBINED WITH BEVACIZUMAB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

Rania Lithy[1] Bavly Daoud[2] Hany William[3] Yasser Elesnawy[3] Nouran Roby[3] Marwa Abdelghany[3] Mohamed Abdelwahed[3] Ashraf Omar[4] Ahmed Abdelmaksoud[5] Tamer Elbaz[6], [1]Faculty of Medicine, Cairo University, ESLC member, Cairo, Egypt, [2]Faculty of Medicine, Cairo University, [3]Ahmed Maher teaching hospital, Cairo, Egypt, [4]Faculty of Medicine, Cairo University, Egypt, ESLC founder, [5]Faculty of Medicine, Cairo University, Egypt, [6]Faculty of Medicine, Cairo University, Egypt, New giza University

Background: Atezolizumab plus bevacizumab is the current first-line standard for advanced unresectable hepatocellular carcinoma (HCC), with improved survival outcomes. However, the biological mechanisms underlying these outcomes, particularly the role of AFP dynamics, remain unclear. This study evaluates changes in Alpha-Fetoprotein (AFP) levels in advanced HCC patients treated with this regimen to assess AFP as a potential biomarker for treatment response and prognosis. **Methods:** This longitudinal study included 34 patients with advanced HCC treated with Atezolizumab and Bevacizumab every three weeks. Baseline characteristics, AFP levels, liver biochemical profile, tumor characteristics, and treatment response by the modified RECIST were assessed at three-month intervals over one year. Additionally, changes in AFP levels were analyzed in relation to total tumor volume (TTV). **Results:** Among the 34 patients, male were predominant (82.4%) with a mean age of 63 years, and 94% had chronic hepatitis C. All patients had an ECOG score of 0 and Child-Pugh class A; 33 were classified as BCLC stage C and one as stage B. The median baseline AFP level was 209.5 ng/mL (range: 6.9–5617.0 ng/mL), which declined significantly to 6.7 ng/mL after one year of treatment. Elevated AFP levels (> 10 ng/mL) were observed in 23 patients, of whom 78% showed an early AFP response ($\geq 30\%$ reduction within 3–6 months) and 21.7% showed a delayed response (6–12 months). Overall, 55.9% were AFP responders, 17.6% were non-responders, and 26.5% had stable AFP levels. Multivariate analysis identified baseline AFP and treatment-related side effects as potential predictors of AFP response. According to mRECIST, 11.7% achieved complete response, 47% partial response, and 8.8% had

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progressive disease (P = 0.021). Progression-free survival was 58%, and overall survival reached 100%. A significant correlation was observed between reduced total tumor volume (TTV) and decreased AFP levels, with AFP declining from a mean of 11,741 ng/mL at baseline to 62 ng/mL at one year in patients exhibiting a favorable TTV response (p = 0.042). **Conclusion:** AFP dynamics can serve as a promising biomarker for evaluating treatment response in advanced HCC, especially in patients receiving Atezolizumab and Bevacizumab. These findings suggest that AFP monitoring could aid in predicting clinical outcomes and adjusting therapeutic strategies

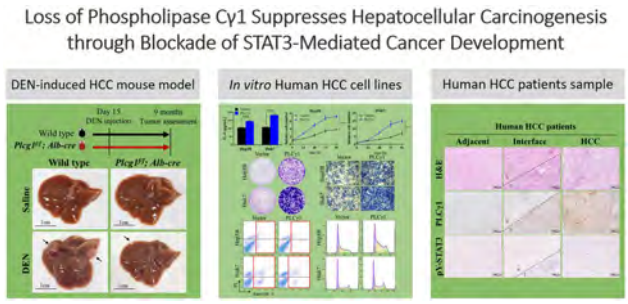
Response by TTV 2 Groups	Time point	Mean AFP Level	Standard Error	95% C.I.for OR	
				Lower	Upper
Favorable (Same or Decrease)	Baseline	11741	3854	3890	19591
	3 Months	226	83	57	396
	6 Months	57	343	-643	756
	1 Year	62	767	-1501	1625
Increased	Baseline	945	5971	-11217	13107
	3 Months	145	129	-118	408
	6 Months	1089	532	6	2172
	1 Year	2498	1189	76	4919

Disclosures: Rania Lithy: Nothing to Disclose, Bavly Daoud: Nothing to Disclose, Hany William: Nothing to Disclose, Yasser Elesnawy: Nothing to Disclose, Nouran Roby: Nothing to Disclose, Marwa Abdelghany: Nothing to Disclose, Mohamed Abdelwahed: Nothing to Disclose, Nothing to Disclose, Ashraf Omar: Nothing to Disclose, Ahmed Abdelmaksoud: Nothing to Disclose, Tamer Elbaz: Nothing to Disclose

3191 | LOSS OF PHOSPHOLIPASE CΓ1 SUPPRESSES HEPATOCELLULAR CARCINOGENESIS THROUGH BLOCKADE OF STAT3-MEDIATED CANCER DEVELOPMENT

Eun-Bi Seo[1], [1]Seoul National University College of Medicine

Background: Phospholipase C gamma 1 (PLCγ1) plays an oncogenic role in several cancers, alongside its usual physiological roles. Despite studies aimed at identifying the effect of PLCγ1 on tumors, the pathogenic role of PLCγ1 in the tumorigenesis and development of hepatocellular carcinoma (HCC) remains unknown. **Methods:** To investigate the function of PLCγ1 in HCC, we generated hepatocyte-specific PLCγ1 conditional knockout ($PLC\gamma1^{f/f}$; Alb-Cre) mice and induced HCC with diethylnitrosamine (DEN). **Results:** Here, we identified that hepatocyte-specific PLCγ1 deletion effectively prevented DEN-induced HCC in mice. $PLC\gamma1^{f/f}$; Alb-Cre mice showed reduced tumor burden and tumor progression, as well as a decreased incidence of HCC and less marked proliferative and inflammatory responses. We also showed that oncogenic phenotypes such as repressed apoptosis, and promoted proliferation, cell cycle progression and migration, were induced by PLCγ1. In terms of molecular mechanism, PLCγ1 regulated the activation of signal transducer and activator of transcription 3 (STAT3) signaling. Moreover, PLCγ1 expression is elevated in human HCC and correlates with a poor prognosis in patients with HCC. **Conclusion:** Our results suggest that PLCγ1 promotes the pathogenic progression of HCC, and PLCγ1/STAT3 axis was identified as a potential therapeutic target pathway for HCC.



Disclosures: Eun-Bi Seo: Nothing to Disclose

3192 | PROGNOSTIC AND FUNCTIONAL STUDY OF SLC27A2 IN HEPATOCELLULAR CARCINOMA

Zhan Zeng Yifan Han[1] Ning Lin[1] yanyan yu[1] Xiaoyuan Xu[1], [1]Peking university first hospital

Background: Hepatocellular carcinoma (HCC) is a severe disease with poor prognosis. Solute carrier family 27 member 2 (SLC27A2), a fatty acid transport protein, has been reported to suppress tumor progression in renal cell carcinoma, lung cancer, and ovarian cancer. However, its role in HCC remains unclear. **Methods:** mRNA expression profiles and clinical data were extracted from the TCGA-LIHC cohort. Kaplan-Meier curves were generated to compare the survival difference in two groups. Plasmid-mediated overexpression of SLC27A2 was established in Huh7 hepatoma cells, with transfection efficiency confirmed by quantitative PCR (qPCR) and western blotting (WB). Functional assays, including Transwell migration, wound healing, Cell Counting Kit-8 (CCK-8) proliferation, and Annexin V-APC/PI apoptosis assays by flow cytometry, were conducted to assess phenotypic alterations following SLC27A2 overexpression. Differences between groups were compared by unpaired t-tests. **Results:** Analysis results of TCGA-LIHC dataset showed that SLC27A2 expression was significantly

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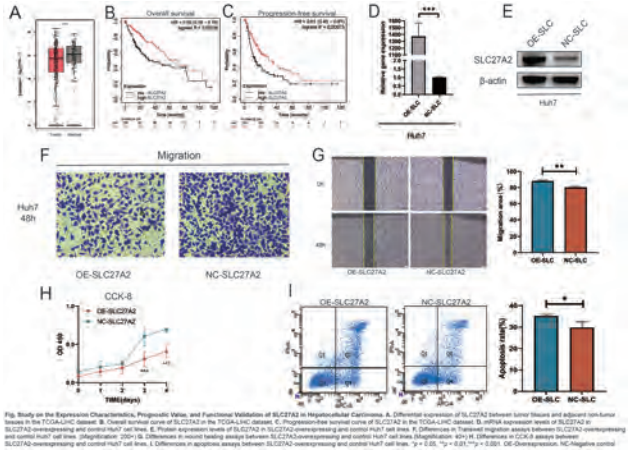
decreased in HCC tissues compared to adjacent tissues ($p < 0.001$). And higher SLC27A2 expression correlated with improved overall survival and progression-free survival ($p < 0.001$). In vitro, SLC27A2 overexpression was successfully validated by qPCR ($p < 0.001$) and WB. Functionally, overexpression of SLC27A2 led to: (1) reduced cell migration in Transwell assays at 48 hours; (2) delayed wound closure in wound healing assays ($p = 0.001$); (3) suppressed proliferation, evidenced by lower CCK-8 optical density values from day 3 onward (($p < 0.001$); and (4) increased apoptosis rates compared to control cells ($p = 0.031$). **Conclusion:** SLC27A2 is downregulated in HCC and may associated with worse prognosis. Its overexpression suppresses proliferation and migration while promoting apoptosis in hepatoma cells, indicating a potential tumor-suppressive role in HCC pathogenesis.

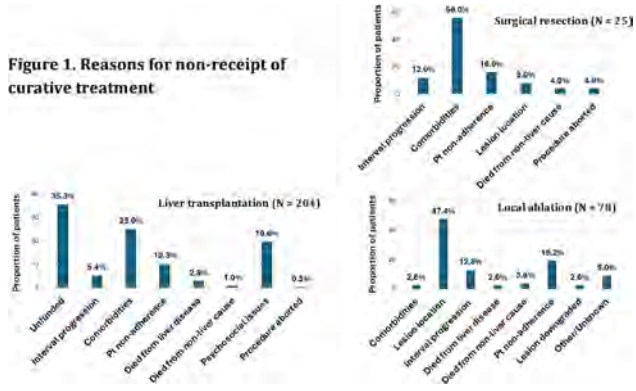


Disclosures: Zhan Zeng: Nothing to Disclose, Yifan Han: Nothing to Disclose, Ning Lin: Nothing to Disclose, yanyan yu: Nothing to Disclose, Xiaoyuan Xu: Nothing to Disclose

3193 | PREDICTORS OF CURATIVE TREATMENT IN PATIENTS WITH EARLY-STAGE HEPATOCELLULAR CARCINOMA

Ashwini Arvind[1] Samuel Phen[2] Sneha Deodhar[1] Lisa Quirk[1] Gi Giamarqo[1] Amit Singal[1] Nicole Rich[3], [1]UT Southwestern Medical Center, [2]University of California, Riverside, [3]University of Texas Southwestern Medical Center

Background: Curative treatments are available for patients with early-stage hepatocellular carcinoma (HCC) but is underutilized in clinical practice. We aimed to identify predictors of curative treatment receipt and describe reasons for non-receipt in patients with early-stage HCC. **Methods:** We conducted a retrospective cohort study of patients with treatment-naïve, early-stage HCC (within Milan Criteria) seen between 2010 and 2021 at two US medical centers. Curative treatment included liver transplantation, surgical resection and ablation. Recommended primary treatment was determined per AASLD guidelines, and we recorded any barriers to treatment per clinical notes. We also used multivariable logistic regression analysis to identify predictors of curative treatment receipt. **Results:** Of 629 eligible patients, 396 (63.0%) received curative treatment (median age 60 years, 72.3% male). The cohort was racially and ethnically diverse (39.3% White, 25.8% Black, 28.8% Hispanic, 6.2% other). Per AASLD guidelines, liver transplant, surgical resection, and ablation were recommended in 204 (87.6%), 25 (10.7%), and 78 (33.5%) patients, respectively. The most common barriers to liver transplant were lack of funding (35.3%), comorbidities (25.0%) and psychosocial issues (19.6%). The most common barrier to resection was medical comorbidities (56.0%), whereas the most common barrier to ablation was proximity to major vessels or other technical challenges to a percutaneous approach (47.4%). Aggressive tumor biology and patient non-adherence were uncommon barriers to curative treatment (Figure 1). In multivariable analyses, curative treatment receipt was associated with care at the tertiary care transplant center (vs. safety-net system: OR 3.0, 95%CI 2.0-4.5), multifocal disease (OR 0.5, 95%CI 0.3-0.8), tumor size (continuous) (OR 0.7, 95%CI 0.6-0.9) and liver dysfunction (Child Pugh B vs. A: OR 0.3, 95%CI 0.2-0.4; Child Pugh C vs. A: OR 0.1, 95%CI 0.1-0.2). Compared to private insurance, those with Medicaid (OR 0.3, 95%CI 0.1-0.5), county-based financial assistance (OR 0.3, 95%CI 0.2-0.6) or no insurance (OR 0.2, 95%CI 0.1-0.5) were also less likely to receive curative treatment. **Conclusion:** Curative treatment is underused in early-stage HCC due to clinical, tumor-related and health system factors. Targeted strategies are needed to address specific barriers to improve overall treatment receipt.



Disclosures: Ashwini Arvind: Nothing to Disclose, Samuel Phen: Nothing to Disclose, Sneha Deodhar: Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Gi

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Giamarqo: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Nicole Rich: AstraZeneca: Advisor, Genentech: Consulting, Exelixis: Advisor, Eisai: Advisor, Madrigal: Advisor

3194 | ASSOCIATION OF TGF-β MOLECULES IN CIRCULATING TUMOR CELLS WITH DRUG RESISTANCE IN SYSTEMIC THERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

Yosuke Murata[1] Takuto Nosaka[1] Yu Akazawa[1] Tomoko Tanaka[1] Tatsushi Naito[1] Kazuto Takahashi[1] Masahiro Ohtani[1] Yasunari Nakamoto[1], [1]University of Fukui

Background: Systemic therapy for patients with advanced, unresectable hepatocellular carcinoma (HCC) has significantly changed with the introduction of combined immunotherapy. However, the mechanisms of drug resistance remain unclear, and there is no reliable biomarker for predicting disease progression. Circulating tumor cells (CTCs) derived from peripheral blood offer a noninvasive, real-time approach to assess tumor biology and treatment response, and have attracted attentions to reveal mechanisms of disease progression. In this study, CTCs were serially collected from patients with HCC undergoing systemic therapy: Atezolizumab plus Bevacizumab (Atezo+Bev), Tremelimumab plus Durvalumab (STRIDE) and Lenvatinib (LEN). Changes in molecular profiles of CTCs were analyzed to elucidate the mechanisms of drug resistance. **Methods:** We obtained 5mL of peripheral blood from 48 patients with HCC treated by systemic therapy (Atezo+Bev/STRIDE/LEN:29/8/11). Treatment response was assessed by RECIST ver.1.1. CTCs were isolated with RosetteSep Human CD45 Depletion Cocktail and enriched cells were stained with monoclonal antibodies targeting the cell surface antigens including Pan-CK and CD45. CD45 negative and Pan-CK positive cells were defined as CTCs by flow cytometry using a FACSAria II. CTC-derived RNA of patients with HCC (Atezo+Bev/STRIDE/LEN:14/5/9) underwent targeted RNA sequencing of 373 genes with next-generation sequencing (NGS) on Illumina Miseq. Gene set enrichment analysis (GSEA) was also performed. **Results:** CTC counts significantly increased correlating with Barcelona clinic liver cancer stages. In PR/SD group, CTC counts decreased at response evaluation, compared to baseline (Atezo+Bev, 193 ± 21 vs. 120 ± 16; STRIDE, 291 ± 91 vs. 85 ± 52; LEN, 185 ± 23 vs. 111 ± 16, $p < 0.05$, respectively) and increased at PD responses, reflecting changes in tumor burden. In NGS analysis, unsupervised hierarchical clustering classified into two clusters, A: responder group and B: non-responder group, in all three treatment groups. Notably, in Atezo+Bev and LEN, the median PFS was significantly longer in cluster A than in cluster B, with a tendency for improved OS in cluster A. GSEA in Atezo+Bev group revealed significant enrichment of TGF-β and MET signaling molecules such as ITGB1 and TGF-β1 in cluster B, and immune-related signaling pathways were enriched in cluster A in clinical course ($p < 0.05$). Furthermore, in LEN group, TGF-β signaling pathway was also elevated in cluster B ($p < 0.05$). **Conclusion:** In systemic therapy for HCC, CTC counts accurately reflect changes in tumor burden during clinical course. NGS analysis revealed that patients with elevated expression of TGF-β molecules in CTCs showed poorer responses to Atezo+Bev and LEN. This suggests TGF-β molecules may promote drug resistance and molecular profiling of CTCs may offer an effective biomarker to elucidate mechanisms of drug resistance in systemic therapy for HCC.
Disclosures: Yosuke Murata: Nothing to Disclose, Takuto Nosaka: Nothing to Disclose, Yu Akazawa: Nothing to Disclose, Tomoko Tanaka: Nothing to Disclose, Tatsushi Naito: Nothing to Disclose, Kazuto Takahashi: Nothing to Disclose, Masahiro Ohtani: Nothing to Disclose, Yasunari Nakamoto: Nothing to Disclose

3195 | IMPACT OF PRIOR ONCOLOGICAL TREATMENT ON IMMUNOTHERAPY RESPONSES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

SHING HIN CHUNG[1] Rex Wan-Hin Hui[1] Lu Li[1] Xianhua Mao[1] Chi Leung Chiang[1] Carlos King-Ho Wong[1] Ian Chi-Kei Wong[1] Man-Fung Yuen[1] Wai-Kay Seto[1] Lung Yi Mak[1], [1]The University of Hong Kong

Background: In recent years, immunotherapy has revolutionized the treatment of hepatocellular carcinoma (HCC). Our study aimed to investigate whether prior oncological treatment impacts HCC immunotherapy response. **Methods:** Patients with HCC treated with immunotherapy (nivolumab, pembrolizumab, atezolizumab, durvalumab, tremelimumab, ipilimumab) in January 2008 – June 2024 were identified from an electronic database in Hong Kong. Patients with other types of cancer diagnosis were excluded. Primary outcomes were overall survival (OS) and hospitalization

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stratified by prior oncological treatment (curative: surgical resection, liver transplant, radiofrequency ablation, microwave ablation; non-curative: tyrosine kinase inhibitors (TKIs), transcatheter arterial chemoembolization and radiotherapy). Secondary outcomes included OS and hospitalization stratified by age (>60 vs ≤ 60 years), sex, virus-related HCC (hepatitis B virus or hepatitis C virus infection vs non-viral HCC), type 2 diabetes, cirrhosis, albumin-bilirubin (ALBI) grades (grades 2 & 3 vs grade 1), Model for End-Stage Liver Disease (MELD) scores (≥ 10 vs <10), and AFP levels (≥ 400 vs <400 ng/mL). Sensitivity analysis of excluding patients who received TKIs were also performed. The OS was evaluated using Kaplan–Meier method and hazard ratios (HRs) were calculated using Cox regression models. **Results:** We identified 1363 patients who received immunotherapy (15.1% with atezolizumab +bevacizumab, 37.8% with nivolumab monotherapy, 2.2% with durvalumab+tremelimumab). Among them, 314 (23.0%) received curative therapy and 470 (34.5%) received non-curative therapy prior to immunotherapy. The median time from curative and non-curative therapies to immunotherapy were 22.8 (IQR 7.3 – 77.2) and 13.5 (IQR 4.7 – 33.7) months, respectively. Kaplan-Meier analysis showed that patients with prior curative treatment had better OS [median 10.3 vs 7.5 months; HR 1.24 (95%CI 1.05-1.46), $p=0.011$], compared to those without. Conversely, patients with prior non-curative treatment were associated with worse OS [median 7.9 vs 8.1 months; HR 0.61 (95%CI 0.52-0.71), $p<0.001$] and higher risk of hospitalization [43.6% vs 29.5%; HR 1.63 (95%CI 1.37-1.94), $p<0.001$], compared to those without. Cirrhosis, higher ALBI grades, and higher AFP were associated with worse OS (all $p<0.001$) and higher risks of hospitalization (cirrhosis: $p=0.024$; ALBI: $p=0.044$; AFP: $p=0.026$), respectively. Higher MELD score was associated with worse OS ($p<0.001$). The results remained robust in sensitivity and subgroup analyses. **Conclusion:** HCC patients with history of curative therapy had better OS after immunotherapy treatment. Conversely, history of non-curative therapy was associated with poorer outcomes. Treatment history, HCC disease burden, and baseline liver function are important factors that influence the prognosis of HCC patients on immunotherapy.

	Overall survival			Hospitalization		
	HR	95% CI	P-value	HR	95% CI	P-value
Viral-HCC	1.16	(0.94, 1.42)	0.169	1.10	(0.85, 1.44)	0.459
Age (>60 vs ≤60 years)	1.09	(0.94, 1.27)	0.238	1.00	(0.84, 1.19)	0.979
Sex	1.02	(0.85, 1.23)	0.812	0.96	(0.76, 1.21)	0.725
T2D	1.00	(0.87, 1.16)	0.957	0.88	(0.73, 1.05)	0.156
Cirrhosis	0.70	(0.59, 0.85)	<0.001	1.27	(1.03, 1.56)	0.024
Curative therapy	1.24	(1.05, 1.46)	0.011	1.17	(0.96, 1.42)	0.115
Non-curative therapy	0.61	(0.52, 0.71)	<0.001	1.63	(1.37, 1.94)	<0.001
ALBI grades (Grades 2 & 3 vs grade 1)	0.59	(0.50, 0.69)	<0.001	1.22	(1.00, 1.48)	0.044
MELD scores (≥10 vs <10)	0.62	(0.51, 0.77)	<0.001	1.16	(0.91, 1.49)	0.234
AFP levels (≥400 vs <400 ng/mL)	0.56	(0.47, 0.67)	<0.001	1.24	(1.03, 1.49)	0.026

Disclosures: SHING HIN CHUNG: Nothing to Disclose, Rex Wan-Hin Hui: Nothing to Disclose, Lu Li: Nothing to Disclose, Xianhua Mao: Nothing to Disclose, Chi Leung Chiang: Nothing to Disclose, Carlos King-Ho Wong: Nothing to Disclose, Ian Chi-Kei Wong: Nothing to Disclose, Man-Fung Yuen: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose, Lung Yi Mak: Nothing to Disclose

3196 | IMMUNE CHECKPOINT INHIBITOR-INDUCED RAPID DECLINE IN HBV MARKERS IMPROVES THE PROGNOSIS OF HBV-RELATED HEPATOCELLULAR CARCINOMA PATIENTS

Yujie Ran[1] Minghui Zhu[1] Kunyuan Wang[1] Ying Xia[1] Yun Zhu[1] Mengya Zang[1] Shuai Kang[1] Qi Li[1] Xiaoyun Hu[1] Ying Wang[1] Fang Liu[1] Xiaowei Chen[1] Qian Zhao[1] Hongyan Liu[1] Dingli Liu[1] Huaiyu Chen[1] Jinzhang Chen[1] Yabing Guo[1] Rong Fan[1], [1]Nanfang Hospital, Southern Medical University, China

Background: There has been limited investigation regarding the antiviral efficacy of immune checkpoint inhibitors (ICIs) in HBV-related hepatocellular carcinoma (HCC) patients. We aimed to determine the antiviral effects of ICIs in patients with HBV-related HCC and investigate the correlation between declines in HBV markers and HCC prognosis. **Methods:** A retrospective cohort study was performed on 318 HBV-related HCC patients, including 268 who received ICIs (with or without targeted therapy; ICI group) and 50 who received targeted therapy alone (non-ICI group). During follow-up, the levels of quantitative HBsAg (qHBsAg), HBV DNA, HBV RNA, and HBcrAg were measured. Tumor response was evaluated according to RECIST 1.1. **Results:** Patients in the ICI group exhibited greater declines in the levels of qHBsAg, HBV DNA, HBV RNA, and HBcrAg than those in the non-ICI group after multiple imputation (Figure 1). At week 96, patients receiving ICIs demonstrated significantly higher cumulative incidences of HBsAg loss or decline ≥ 0.5 Log_{10} IU/mL (41.6% vs. 14.9%; HR: 5.74, 95% CI: 1.40-23.60, $p = 0.006$), HBV RNA negativity or decline ≥ 0.5 Log_{10} copies/mL (94.1% vs. 100%; HR: 1.80, 95% CI: 1.08-2.99, $p = 0.021$), and HBcrAg negativity or decline ≥ 1 Log_{10} U/mL (46.3% vs. 18.1%; HR: 4.29, 95% CI: 1.34-13.72, $p = 0.007$) compared with those receiving targeted therapy alone. Notably, lower baseline levels of HBV markers were significantly associated with improved overall survival (OS). Multivariate Cox analysis identified baseline HBcrAg levels as an independent prognostic factor for OS (HR: 2.75, 95% CI: 1.26-6.02, $p = 0.011$). Additionally, patients achieving HBsAg loss or a ≥ 0.5 Log_{10} decline, HBV DNA negativity, or HBV RNA negativity or a ≥ 0.5 Log_{10} decline had significantly improved OS than non-responders (HBsAg: 77.8% vs. 61.9%, $p = 0.046$; HBV DNA: 78.2% vs. 26.7%, $p < 0.001$; HBV RNA:

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70.3% vs. 46.0%, p = 0.001), while HBcrAg negativity or a ≥1 Log_{10} decline trended toward improved OS (74.5% vs. 59.5%, p = 0.137). These virological responders also showed significantly improved progression-free survival (HBsAg: 44.0% vs. 24.2%, p = 0.023; HBV DNA: 43.0% vs. 13.2%, p < 0.001; HBV RNA: 34.9% vs. 12.3%, p < 0.001; HBcrAg: 35.1% vs. 24.0%, p = 0.032) and better objective response rate and disease control rate. **Conclusion:** ICIs may serve as an effective strategy for managing or eliminating HBV infection. The effective suppression of HBV markers is crucial for improving the prognosis of HCC patients.

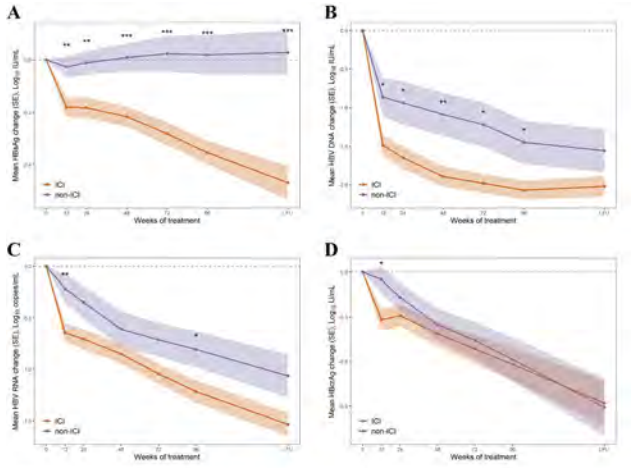

Figure. 1. The decline in the levels of qHBsAg (A), HBV DNA (B), HBV RNA (C) and HBcrAg (D) among the ICI and non-ICI groups after multiple imputation. Statistical significance between groups at each time point is indicated (*p<0.05, **p<0.01, ***p<0.001). qHBsAg, quantitative hepatitis B surface antigen; HBV, hepatitis B virus; HBcrAg, hepatitis B virus core-related antigen.

Disclosures: Yujie Ran: Nothing to Disclose, Minghui Zhu: Nothing to Disclose, Kunyuan Wang: Nothing to Disclose, Ying Xia: Nothing to Disclose, Yun Zhu: Nothing to Disclose, Mengya Zang: Nothing to Disclose, Shuai Kang: Nothing to Disclose, Qi Li: Nothing to Disclose, Xiaoyun Hu: Nothing to Disclose, Ying Wang: Nothing to Disclose, Fang Liu: Nothing to Disclose, Xiaowei Chen: Nothing to Disclose, Qian Zhao: Nothing to Disclose, Hongyan Liu: Nothing to Disclose, Dingli Liu: Nothing to Disclose, Huaiyu Chen: Nothing to Disclose, Jinzhang Chen: Nothing to Disclose, Yabing Guo: Nothing to Disclose, Rong Fan: Nothing to Disclose

3197 | TUMOR RESPONSE PATTERNS OF SECOND-LINE TYROSINE KINASE INHIBITORS FOLLOWING ATEZOLIZUMAB/BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA: A PROPORTIONAL META-ANALYSIS

Nehemias Guevara Rodriguez[1] Ronald Blanco Montecino[2] Noemy Coreas[3] Yassine Kilani[4] Syeda Fatima Kamal[5] Daniel Mendoza Quispe[2] Iqra Arshad[4] Kamran Qureshi[6] John Richart[1], [1]Division of Hematology-Oncology and BMT, Saint Louis University, St. Louis, MO, [2]Department of Internal Medicine, St Barnabas Hospital, Bronx, NY., [3]National University of El Salvador, Social Security System, Division of OBGYN-Oncology, [4]Division of General Internal Medicine, Saint Louis University School of Medicine, St. Louis, MO, [5]Division of Hospice and Palliative Medicine, Saint Louis University School of Medicine, St. Louis, MO, [6]Division of Gastroenterology and Hepatology, Saint Louis University School of Medicine, St. Louis,MO

Background: The introduction of Atezolizumab/Bevacizumab has redefined first-line therapy for advanced hepatocellular carcinoma (HCC). However, the optimal second-line strategy remains unclear, especially regarding expected tumor responses. While survival outcomes have been reported, tumor control metrics such as objective response rate (ORR) and disease control rate (DCR) have not been comprehensively evaluated across second-line tyrosine kinase inhibitors (TKIs). This proportional meta-analysis aimed to define radiologic tumor response patterns with TKIs following immune checkpoint inhibitor (ICI) failure. **Methods:** We conducted a systematic proportional meta-analysis of studies reporting RECIST 1.1-based tumor responses to second-line TKIs—including Lenvatinib, Regorafenib, Sorafenib, and Cabozantinib—following progression on Atezolizumab/Bevacizumab. Outcomes of interest included absolute CR, PR, SD, ORR, DCR. Extracted data from 9 retrospective studies were pooled using a random-effects model and TKI-stratified proportions. All statistical analyses, including pooled proportions and heterogeneity estimates, were performed using Stata version 18 (StataCorp, College Station, TX). **Results:** Across 907 patients, ORR remained modest overall, with a pooled rate of 7%. Stratified analysis demonstrated an ORR of 12% for Lenvatinib, 11% for Regorafenib, 5% for Cabozantinib, and 4% for Sorafenib. DCR was notably higher, with a pooled estimate of 53%, mainly driven by stable disease. Regorafenib had the highest DCR at 67%, followed by Lenvatinib (50%), Cabozantinib (66%), and Sorafenib (35%). Complete responses were exceedingly rare (< 1%). Study heterogeneity was moderate to high (I^2 ranging from 41% to 85%), which could be attributed to differences in sample size, patient populations, and study design across the included retrospective studies. **Conclusion:** Although objective responses to second-line TKIs are limited, their ability to achieve substantial disease stabilization underscores their continued clinical utility following immune checkpoint inhibitor (ICI) failure in advanced HCC. This study found that while the overall objective response rate (ORR) remained modest at 7%, disease control rates (DCR) were notably higher, with Regorafenib and Lenvatinib showing the most favorable

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profiles. The findings emphasize the importance of TKIs as second-line agents for HCC, particularly in the evolving post-immunotherapy landscape where DCR may be a relevant surrogate for clinical benefit. Notably, moderate to high heterogeneity (I^2 ranging from 41% to 85%) was observed, likely due to differences in sample size, patient populations, and study designs. Despite these limitations, the ability of second-line TKIs to stabilize disease in over half of patients progressing on Atezolizumab/Bevacizumab highlights their potential as viable second-line options.

Table 1. Summary of all included studies.

Author (Year)	Intervention(s)	Study Design	Study Period	Sample Size (N)	Location	Placebo-Controlled
Eun Chon (2023)	Lenvatinib	Retrospective	40 months	36	Asia (South Korea)	No
Muto (2023)	Lenvatinib	Retrospective	27 months	20	Asia (Japan)	No
Falette-Puisieux (2023)	Regorafenib, Sorafenib, Cabozantinib	Retrospective	N/A	29 / 41 / 4 / 8	Western (France)	No
Hiraoka (2023)	Lenvatinib	Retrospective	24 months	101	Asia (Japan)	No
Kimura (2024)	Lenvatinib	Retrospective	65 months	13	Asia (Japan)	No
Persano (2024)	Lenvatinib	Retrospective	42 months	86	Western (Italy)	No
Kuzuya (2023)	Cabozantinib	Retrospective	20 months	19	Asia (Japan)	No
Yano (2023)	Lenvatinib	Retrospective	23 months	24	Asia (Japan)	No
Kun-Lee (2024)	Lenvatinib, Regorafenib, Sorafenib, Cabozantinib	Retrospective	83 months	154 / 36 / 324 / 12	Asia (South Korea)	No

Disclosures: Nehemias Guevara Rodriguez: Nothing to Disclose, Ronald Blanco Montecino: Nothing to Disclose, Noemy Coreas: Nothing to Disclose, Yassine Kilani: Nothing to Disclose, Syeda Fatima Kamal: Nothing to Disclose, Daniel Mendoza Quispe: Nothing to Disclose, Iqra Arshad: Nothing to Disclose, Kamran Qureshi: Nothing to Disclose, John Richart: Sanofi: Stock - publicly traded company

3198 | PHARMACOLOGICAL ACTIVATION OF PPARα REVERSES ANTI-PD-1 RESISTANCE IN HCC BY RESTORING GSDME-MEDIATED PYROPTOSIS WITHIN FIBROINFLAMMATORY LIVER MICROENVIRONMENT

peng chen[1] Zheyu Dong[1] Kai Xiong[2] Zhili Wen[2] Huajin Pang[1] Yuchuan Jiang[2], [1]Nanfang Hospital Southern Medical University, [2]The Second Affiliated Hospital of Nanchang University

Background: Resistance to anti-Programmed cell death protein 1 (anti-PD-1) remains a major clinical obstacle in hepatocellular carcinoma (HCC). The fibroinflammatory liver microenvironment (FILM), characterized by excessive extracellular matrix deposition and immunosuppressive inflammatory cell infiltration, has been implicated in anti–PD-1 resistance; however, the underlying mechanisms remain poorly understood. **Methods:** Clinical HCC cohorts and syngeneic HCC mouse models were used to investigate the role of FILM in reducing immune activation and attenuating the efficacy of anti–PD-1 therapy through pyroptosis suppression. Multi-omic analyses and in vivo assays were conducted to determine the role of peroxisome proliferator-activated receptor alpha (PPARα) in FILM mediated inhibition of pyroptosis. Mechanistic studies were conducted using ChIP-PCR, flow cytometer, co-culture assays. The therapeutic synergy between PPARα activation and anti–PD-1 therapy was evaluated in murine models and a retrospective HCC patient cohort. **Results:** Clinically, we stratified HCC patients based on the degree of inflammation and fibrosis in para-tumor liver tissues using the METAVIR scoring system. Patients characterized by significant inflammation and advanced fibrosis—referred to as the representative FILM group—exhibited the poorest prognosis compared to other subgroups and demonstrated resistance to anti-PD-1 therapy. Functionally, FILM suppressed GSDME-dependent pyroptosis in HCC cells, leading to reduced infiltration immune cells and anti-PD-1 resistance. Mechanistically, with in the FILM, cancer-associated fibroblasts recruited $NOS2^+$ macrophages, which down-regulated PPARα transcription and activation in HCC via nitric oxide signaling. This reduced PPARα binding to the PDK4 promoter, decreased mitochondrial ROS production, and ultimately impaired the canonical ROS/Caspase-3/GSDME pyroptotic pathway. Therapeutically, pharmacological activation of PPARα using the agonist GW7647 promoted GSDME-mediated pyroptosis and reprogrammed the immunosuppressive microenvironment, suppressing tumor growth. Notably, combination therapy with PPARα agonists (GW7647 or the clinically approved fenofibrate) and anti-PD-1 achieved superior anti-tumor effects compared to monotherapy in both mouse models and retrospective patient analyses. **Conclusion:** This study identifies PPARα activation as a promising strategy to overcome FILM-induced anti-PD-1 resistance in HCC by restoring GSDME-mediated pyroptosis. Combining PPARα agonists with immune checkpoint inhibitors represents a potential therapeutic approach for HCC patients, particularly those with FILM.

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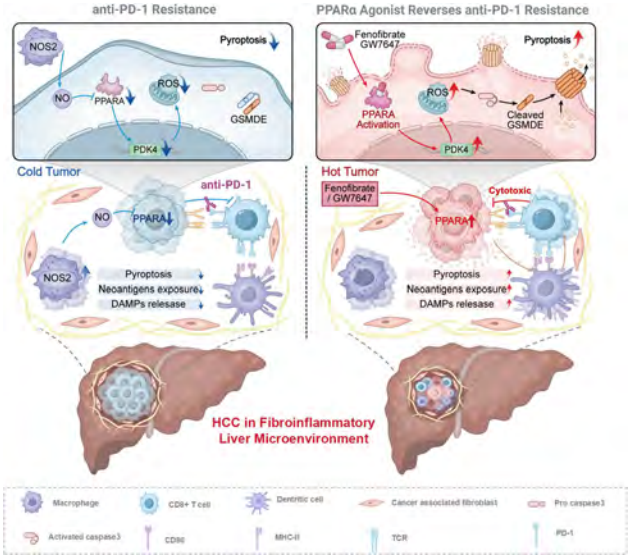

Disclosures: peng chen: Nothing to Disclose, Zheyu Dong: Nothing to Disclose, Kai Xiong: Nothing to Disclose, Zhili Wen: Nothing to Disclose, Huajin Pang: Nothing to Disclose, Yuchuan Jiang: Nothing to Disclose

3199 | AGE-DEPENDENT DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN LIVER-SPECIFIC BETAINE HOMOCYSTEINE METHYLTRANSFERASE (BHMT) KNOCKOUT MICE

Sathish kumar Perumal[1] Ramachandran Rajamanickam[1] Ramesh Bellamkonda[2] Sundararajan Mahalingam[2] Natalia Osna[3] Kurt Fisher[3] Benita McVicker[3] Karuna Rasineni[3] Kusum Kharbanda[1], [1]Research Service, Veterans Affairs Nebraska-Western Iowa Health Care System, Omaha, Nebraska, USA, [2]University of Nebraska Medical Center, Omaha, Nebraska, USA, [3]University of Nebraska Medical Center, Omaha, NE, USA

Background: Hepatocellular carcinoma (HCC) is a major form of liver cancer, often associated with chronic liver diseases and genetic predispositions. Betaine homocysteine methyltransferase (BHMT) is an enzyme critical for one-carbon metabolism and liver health. There is a loss of BHMT in liver cancer cell lines. To understand whether this loss is a cause or a consequence of HCC development, we investigated the role of liver-specific deletion of BHMT in hepatocarcinogenesis development. **Methods:** We generated liver-specific BHMT knockout (BHMT LKO) mice using Cre-loxP recombination under the control of the albumin promoter. Both male and female mice were monitored and aged up to 2 years. Liver tissues were harvested at various time points for histopathological examination, immunohistochemistry, and gene expression analyses. **Results:** Liver-specific BHMT deletion resulted in progressive liver pathology in aging mice. Starting at 6 months of age, BHMT LKO mice began to develop steatosis, which progressed to severe steatohepatitis and fibrosis with aging. At 2 years of age, a 3-fold increase in the liver to body weight ratio and HCC development identified by reticulin staining in all BHMT LKO mice compared to the floxed mice. Further analysis revealed increase in IL-6 with a concomitant decrease in PTEN that correlated with the severity of liver damage and tumor burden in BHMT LKO mice compared with age-matched floxed mice. **Conclusion:** Liver-specific deletion of BHMT in mice results in an age-dependent progression of liver disease, ranging from steatosis to steatohepatitis and fibrosis, ultimately leading to HCC development in 100% of BHMT LKO mice. These findings highlight the critical role of BHMT in preserving liver homeostasis and suggests that individuals carrying loss-of-function BHMT polymorphisms may be at increased risk for developing advanced liver disease with age. The BHMT LKO mouse model could serve as a valuable tool for investigating the molecular mechanisms that connect one-carbon metabolism to HCC development.

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3200 | Q-HCC: DEVELOPMENT OF A HIGH-QUALITY DATASET TO ENABLE AI-SUPPORTED DIAGNOSIS AND PRECISION TREATMENT IN HEPATOCELLULAR CARCINOMA

Isaac Israel Rodriguez Salazar[1] Timo Itzel[1] Dennis Grimm[2] Fabian Tollens[3] Wenzhao Zhao[4] Marcus Buchwald[4] Catharina Gerhards[5] Nathally Espinosa Montagut[1] Xiaoyun Xiong[1] Michael Neumaier[5] Christoph Reissfelder[6] Matthias Ebert[7] Stefan Schoenberg[3] Martin Lablans[2] Fabian Siegel[8] Juergen Hesser[2] Matthias Froelich[3] Andreas Teufel[1], [1]Div. of Hepatology, Dep. of Medicine II, Medical Faculty Mannheim of Heidelberg University, Germany, [2]Division of Federated Information Systems, German Cancer Research Center, Heidelberg, Germany, [3]Dep. of Radiology and Nuclear Medicine, Medical Faculty

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Background: Hepatocellular carcinoma (HCC) is a leading cause of tumor-related mortality worldwide, with increasing incidence in Europe and the United States. Early diagnosis remains a major challenge but is critical for improving patient outcomes. Artificial intelligence (AI) applications, particularly radiomics, offer new opportunities for enhanced imaging-based detection. However, high-quality standardized datasets for AI training are lacking. **Methods:** All patient data were extracted from the Mannheim University Hospital´s clinical information system and securely stored in a REDCap database. The project was reported to the Ethics Committee II of the University of Heidelberg (application number 2023-873). Data quality was ensured through rigorous validation processes, including SOPs and structured data flow mappings. Imaging data were fully segmented and radiomics features were extracted. **Results:** Clinical, imaging, and laboratory data from 100 HCC patients were systematically collected, annotated, and integrated into a secure Digital Research Environment (DRE). Validation demonstrated high data consistency and integrity. A use case applying multi-modal classification for TNM staging achieved a prediction accuracy of 0.89 $\pm$ 0.05 and an AUC of 0.93 $\pm$ 0.03 using an XGBoost classifier. Data packages were made publicly available via the heiDATA platform (https://doi.org/10.11588/DATA/IKFTTQ), accompanied by the development of a user-friendly access interface. A synthetic data generation approach based on diffusion models was also developed to enhance patient data privacy. **Conclusion:** Q-HCC successfully established a high-quality, privacy-compliant dataset for HCC, demonstrating the critical value of combining clinical, imaging, and laboratory data for AI applications. This initiative provides a strong foundation for future research in precision oncology and AI-supported diagnostics. Free Online access: https://doi.org/10.11588/DATA/IKFTTQ

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3201 | PHYSIOLOGIC AND SOCIAL STRESS PREDICT MORTALITY IN HEPATOCELLULAR CARCINOMA: INDEPENDENT CONTRIBUTIONS OF ALLOSTATIC LOAD AND HEALTH LITERACY

Sebastian Abad[1] Allie Carter[2] Nicole Garcia[3] Lauren Nephew[4], [1]Indiana University School of Medicine, [2]Department of Biostatistics & Health Data Science, IUSM, [3]Division of Hepatology and Gastroenterology, Indiana University School of Medicine, [4]Indiana University

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death, disproportionately affecting socially vulnerable populations. Chronic social adversity may influence outcomes through physiologic stress pathways. Allostatic load (AL), a composite biomarker of stress-related physiologic dysregulation, has not been well studied in liver cancer. **Methods:** We conducted a retrospective cohort study of 139 adults with HCC from two hospitals in Indianapolis. AL was calculated using six biomarkers (blood pressure, BMI, glucose, albumin, creatinine/eGFR, and heart rate); scores ≥ 3 indicated high AL. Relationships between AL and 14 social determinants of health (SDOH) indicators were examined using correlation and regression. Cox proportional hazards models assessed associations with mortality, adjusting for clinical variables. **Results:** The cohort was 73% male, 83% White, with a median age of 64. AL was not significantly correlated with individual or cumulative SDOH indicators ($r = -0.11$; $p = 0.21$). High AL was associated with increased mortality (HR 1.25; 95% CI 1.01–1.55; $p = 0.045$). Low health literacy was also associated with mortality (HR 1.83; 95% CI 1.10–3.05; $p = 0.021$). When both were modeled together, the hazard ratio for AL was attenuated. In stratified models, AL predicted mortality only among patients with high health literacy (HR 1.29; 95% CI 1.03–1.61; $p = 0.028$), but not among those with low literacy (HR 1.11; 95% CI 0.71–1.72; $p = 0.65$). The interaction term in combined models was not statistically significant ($p = 0.727$). **Conclusion:** Physiologic stress (AL) and low health literacy are each associated with mortality in HCC. The effect of AL may be attenuated in patients with low health literacy, suggesting that social and biological risks interact in complex ways. Future studies should

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examine whether interventions that address both biologic stress and communication barriers can improve liver cancer outcomes.

Table 1. Associations Between Allostatic Load, Health Literacy, and Mortality

Model Description	HR (95% CI)	p-value
Allostatic Load (univariable)	1.27 (1.05–1.55)	0.016
Health Literacy (univariable)	1.83 (1.10–3.05)	0.021
Allostatic Load + Health Literacy (multivariable)*	1.20 (0.96–1.50); 1.84 (1.09–3.12)	0.107; 0.023
Allostatic Load: High Health Literacy (stratified)	1.29 (1.03–1.61)	0.028
Allostatic Load: Low Health Literacy (stratified)	1.11 (0.71–1.72)	0.650
Interaction Term (AL × Health Literacy)	—	0.727

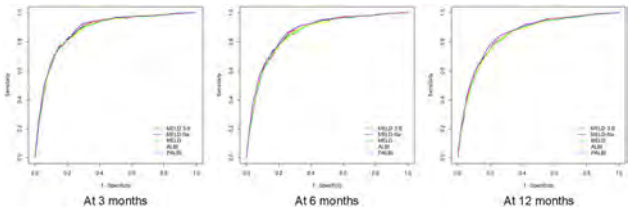
*Models adjusted for age, MELD-Na, BCLC stage, and Charlson comorbidity index.

Disclosures: Sebastian Abad: Nothing to Disclose, Allie Carter: Nothing to Disclose, Nicole Garcia: Nothing to Disclose, Lauren Nephew: NovoNordisk: Consultant

3202 | PREDICTING MORTALITY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: INSIGHTS FROM A MULTICENTER COHORT

JIHYE LIM[1] Seok-Hwan Kim[2] Myeong Jun Song[3], [1]Yeouido St. Mary's Hospital, [2]Daejeon St. Mary's Hospital, The Catholic University of Korea, [3]The Catholic University of Korea

Background: Renal function is a known prognostic factor in patients with end-stage liver disease, yet its impact in hepatocellular carcinoma (HCC) remains underexplored. This study aimed to evaluate the effect of renal function on overall survival in patients with HCC and to compare the prognostic performance of commonly used liver-specific risk models stratified by renal function. **Methods:** We analyzed a nationwide, multicenter cohort comprising 12,665 treatment-naïve patients newly diagnosed with HCC, including 11,464 with preserved renal function and 1,201 with reduced renal function. Overall survival was compared between the two groups. Prognostic performance of the Child–Pugh score, MELD, MELD-Na, MELD 3.0, ALBI, and PALBI grades was assessed using Cox proportional hazards models and time-dependent area under the receiver operating characteristic curve (AUROC) analysis. **Results:** The mean age of the cohort was 61.5 ± 11.7 years, and 78.9% were male. Over a mean follow-up of 51.0 ± 46.9 months, 7,766 deaths occurred in the preserved renal function group and 1,017 in the reduced renal function group. Reduced renal function was independently associated with increased mortality (hazard ratio: 1.58; 95% CI: 1.48–1.69). Despite lacking renal parameters, the PALBI grade consistently demonstrated the highest prognostic accuracy across both renal function strata (time-dependent AUROC at 1 years: 0.828 in reduced renal function group, 0.866 in preserved group), outperforming other models (Figure). **Conclusion:** Renal function significantly impacts survival in patients with HCC and should be routinely monitored and managed. PALBI grade, though lacking direct renal parameters, serves as a reliable risk stratification. Combined use of PALBI and renal function assessments may enhance prognostication and guide clinical management in HCC.



Disclosures: JIHYE LIM: Nothing to Disclose, Seok-Hwan Kim: Nothing to Disclose, Myeong Jun Song: Nothing to Disclose

3203 | SETDB1 PROMOTES INTRAHEPATIC CHOLANGIOCARCINOMA PROGRESSION THROUGH METABOLIC REPROGRAMMING AND IMMUNOSUPPRESSIVE MICROENVIRONMENT REMODELING

Xiuqin Huang[1] Xinhua Song[1] Jiabo Wang[1] Zherui Liu[2] Qidi Cui[1] Enxiang Zhang[1], [1]School of Traditional Chinese Medicine, Capital Medical University, Beijing 100069, China, [2]Peking University 302 Clinical Medical School, Beijing, China

Background: Intrahepatic cholangiocarcinoma (ICC), the second most prevalent primary liver malignancy with limited therapeutic options. SETDB1 has been reported to promote the development of multiple tumors. However, the role of SETDB1 in ICC remains unclear. **Methods:** Immunohistochemical staining was performed to detect SETDB1 expression in ICC tumor tissues. SETDB1-knockout sgp19-KRas-induced and AKT-YAP-induced orthotopic ICC models were established using hydrodynamic tail vein transfection. Seahorse glycolysis rate assays were used to determine the glycolytic levels of ICC cells. Flow cytometry and immunohistochemical staining were used to detect the infiltration of immune cells in the ICC tumor microenvironment. ATAC-seq and RNA-seq were used to identify potential functional targets of SETDB1 in ICC, while CUT-RUN assays were employed to validate the interaction pattern and binding regions between SETDB1 and P53. **Results:** Immunohistochemical staining revealed high expression of SETDB1 in ICC tumor tissues, and its expression was correlated with patient prognosis. The deficiency of SETDB1 can inhibit the progression of intrahepatic cholangiocarcinoma and prolong the survival time of model mice. SETDB1-

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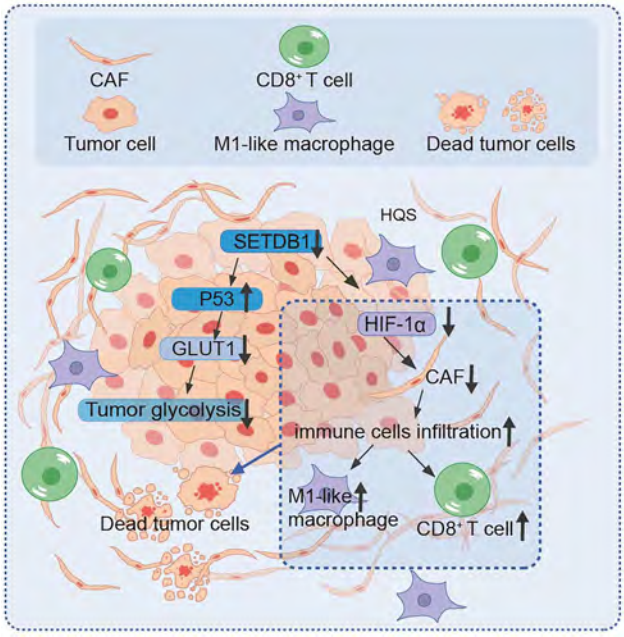
deficient tumor cells exhibited significantly reduced glycolytic activity. Furthermore, flow cytometry and immunohistochemical analysis showed that SETDB1 depletion inhibited the distribution of vimentin$^+$ cancer-associated fibroblasts, and promoted the infiltration of CD8$^+$ T cells and M1-type macrophages in the ICC tumor microenvironment. Mechanistically, SETDB1 deficiency relieved transcriptional repression of the TP53 promoter, upregulated P53 expression, suppressed GLUT1 expression in the glycolytic pathway, and consequently inhibited tumor glycolysis. **Conclusion:** This study highlights the role of SETDB1 in tumor glycolysis and tumor microenvironment in ICC. As an oncogenic factor, SETDB1 promotes ICC progression through dual mechanisms: 1. Enhancing tumor glycolysis via the SETDB1-P53-GLUT1 axis; 2. Regulating the tumor microenvironment to facilitate immune evasion. Targeting SETDB1 may represent a promising therapeutic strategy for ICC.



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3204 | NRF2–COX2–PGE$_2$ AXIS DRIVES IMMUNE COLD TUMORS AND PREDICTS RESISTANCE TO ATEZOLIZUMAB AND BEVACIZUMAB THERAPY IN HEPATOCELLULAR CARCINOMA

Shuhei Yamamoto[1] Takahiro Kodama[1] Kazuki Maesaka[1] Akifumi Kuwano[2] Kenta Motomura[2] Tomomi Yoshida-Hashidate[3] Hideo Shindo[4] Haruhiko Takeda[5] Kumiko Shirai[1] Yuta Myojin[1] Kazuhiro Murai[1] Yuki Makino[1] Yuki Tahata[1] Yoshinobu Saito[1] Hayato Hikita[1] Tomohide Tatsumi[1] Tetsuo Takehara[6], [1]Osaka University Graduate School of Medicine, [2]Iizuka Hospital, [3]Japan Institute for Health Security, National Center for Global Health and Medicine, [4]Japan Institute for Health Security, National Institute of Global Health and Medicine, [5]Kyoto University Graduate School of Medicine, [6]Kansai Rosai Hospital

Background: Atezolizumab plus bevacizumab (Atez/Bev) is a first-line therapy for advanced hepatocellular carcinoma (HCC), but many patients show limited or no response. To elucidate resistance mechanisms, we analyzed the tumor immune microenvironment (TIME) in mouse models and human HCC tissues. **Methods:** Two immunocompetent mouse HCC models were used: a genetically heterogeneous model generated by hydrodynamic tail vein injection (HTVi) of 10 oncogenes, and a syngeneic model using Hep55.1c cells. TIME was assessed using RNA sequencing and spatial transcriptomics (ST). Human samples included 199 resected HCC tissues, 33 pre-treatment biopsies from Atez/Bev-treated patients, and 247 biopsies from the IMbrave150 clinical trial. ST was also performed on paired pre- and post-progression biopsies from two patients. Outcomes related to COX2 inhibitor use were analyzed in 220 Atez/Bev-treated HCC patients. **Results:** In mice, Atez/Bev therapy inhibited angiogenesis, increased tumor-infiltrating lymphocytes (TILs), and prolonged survival. Responding tumors were enriched for effector CD8$^+$ and cytotoxic CD4$^+$ T cells with active antigen presentation via CCL5 and MHC signaling. Resistant tumors exhibited Treg accumulation, exhausted CD8$^+$ T cells, reduced MHC expression, and NRF2 pathway activation. In human HCC tissues, an immune “HOT” TIME with partial exhaustion and close spatial proximity between tumor and immune cells correlated with favorable responses. Non-responders and tumors at progression showed immune “COLD” features, TIL reduction, and NRF2 activation. NRF2-overexpressing tumors also showed increased COX2 expression and an immunosuppressive TIME. In the syngeneic model, NRF2 overexpression induced COX2/PGE2 signaling and conferred resistance to Atez/Bev. Inhibition of NRF2 or COX2 restored therapeutic response. In human samples, NRF2-high tumors showed TIL exclusion and high COX2 expression. Patients treated with COX2 inhibitors had prolonged progression-free survival during Atez/Bev therapy. Notably, in the IMbrave150 trial cohort, patients with poor response also exhibited immune COLD TIME with elevated NRF2 and COX2 signatures. Additionally, plasma PGE2 levels stratified patients according to treatment response. **Conclusion:** NRF2/COX2-driven immune COLD TIME underlies resistance to Atez/Bev

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therapy in HCC. Therapeutic targeting of this pathway and stratification using plasma PGE2 may improve outcomes through biomarker-guided treatment strategies.

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3205 | COMPARATIVE EVALUATION OF FIRST-LINE IMMUNOTHERAPY REGIMENS IN ADVANCED HCC: A NNT- (NUMBER NEEDED TO TREAT) AND NNH- (NUMBER NEEDED TO HARM) BASED ANALYSIS

Luca Galbato Muscio[1] Giorgia Pezzola[1] Emanuela Di Giacomo[1] Andrea Falcomatà[2] Claudia Fulgenzi[3] Giovanni Galati[4] Paolo Gallo[4] Giuseppina Pacella[5] Gianluca Mascianà[6] Rebecca Casati[5] Gabriele D'Ercole[7] Michele Fiore[7] Giuseppe Tonini[1] Antonio Picardi[4] Rosario Francesco Grasso[5] Marianna Silletta[1], *[1]Medical Oncology, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy, [2]Hepatology, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy, [3]Department of Surgery and Cancer, Imperial College London, London, UK, [4]Hepatology, Department of Medicine and Surgery, Università Campus Bio-Medico, Rome, Italy, [5]Interventional Radiology, Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italy, [6]Colorectal Surgery, Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italy, [7]Radiation Oncology, Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italy*

Background: In the past decade, the treatment landscape of advanced hepatocellular carcinoma (HCC) has evolved significantly with the introduction of several effective immunotherapy-based regimens. However, no direct head-to-head comparisons exist between these therapies. In this context, network meta-analyses have been employed to indirectly compare six immune checkpoint inhibitor (ICI) combinations. **Methods:** The aim of our study is to assess and compare the selected regimens using two clinically relevant parameters: Number Needed to Treat (NNT) and Number Needed to Harm (NNH); which reflect the risk reduction in mortality and the increase in treatment-related toxicities, respectively. We included first-line positive phase III clinical trials that reported or allowed extraction of 18- and 24-month overall survival (OS) rates. The trials analyzed were: REFLECT, IMbrave150 (including updates), HIMALAYA, CAREs-310, RATIONALE-301, and CheckMate 9DW. NNT and NNH were calculated using the following formulas: NNT = 1 / (Risk in control arm – Risk in experimental arm) and NNH = 1 / (Risk in experimental arm – Risk in control arm). A lower NNT indicates a more effective treatment, while a higher NNH indicates better safety. Negative NNH values, due to the comparison with an active treatment instead of placebo, suggest that ICI-based therapies appear less toxic. OS rates were taken from published data or extracted from Kaplan–Meier curves using WebPlotDigitizer v10 when not directly reported. For NNH, we analyzed rates of grade 3–4 treatment-related adverse events (TRAEs). **Results:** At 18 and 24 months, the most favorable regimens in terms of NNT were: camrelizumab/rivoceranib: NNT = 6.4 (18 months), 8.1 (24 months); atezolizumab/bevacizumab: NNT = 8.3 (18 months), 9.0 (24 months) and durvalumab/tremelimumab: NNT = 13.9 (18 months), 12.7 (24 months). Based on NNH, the regimens with the most favorable safety profiles were: tislelizumab: NNH = –3.21; durvalumab/tremelimumab: NNH = –9.1 and atezolizumab/bevacizumab: NNH = –33.3. These findings highlight both efficacy and differential safety profiles among the first-line immunotherapy options for advanced HCC. **Conclusion:** In the absence of direct comparisons between first-line treatments for unresectable HCC, NNT and NNH offer valuable quantitative tools to support clinical decision-making. According to the selected metrics, Atezolizumab/Bevacizumab and Durvalumab/Tremelimumab appeared to have the best risk/benefit ratio.

STUDY	OS 18MO ICK	OS 18MO EXP	OS 24MO CR	OS 24MO EXP	NNT 18MO	NNT 24MO	NNH
REFLECT	36,60%	40,70%	25,10%	29,70%	24,4	21,7	12,5
IMBRAVE 150	40,00%	52,4%	30,70%	41,80%	8,3	9	-33,3
HIMALAYA	41,5%	48,70%	32,60%	40,50%	13,9	12,7	-9,1
CARES 310	45,2%	60,9%	34,5%	46,9%	6,4	8,1	3,45
RATIONALE 301	47,20%	50,30%	31,8%	39,00%	32,3	13,9	-3,21
CHECKMATE 9DW	54,9%	58,1%	49%	49%	19,4	10	-50

Disclosures: Luca Galbato Muscio: Nothing to Disclose, Giorgia Pezzola: Nothing to Disclose, Emanuela Di Giacomo: Nothing to Disclose, Andrea Falcomatà: Nothing to Disclose, Claudia Fulgenzi: Nothing to Disclose, Giovanni Galati: Nothing to Disclose, Paolo Gallo: Nothing to Disclose, Giuseppina Pacella: Nothing to Disclose, Gianluca Mascianà: Nothing to Disclose, Rebecca Casati: Nothing to Disclose, Gabriele D'Ercole: Nothing to Disclose, Michele Fiore: Nothing

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to Disclose, Giuseppe Tonini: Nothing to Disclose, Antonio Picardi: Nothing to Disclose, Rosario Francesco Grasso: Nothing to Disclose, Marianna Silletta: Nothing to Disclose

3206 | A NOVEL ROLE OF SECRETED METHIONINE ADESNOSYLTRANSFERASE α2 IN THE DEVELOPMENT OF COLORECTAL LIVER METASTASES

Monica Justo[1] Heping Yang[1] Andrea Floris[1] Youngyi Lim[1] Swati Chandla[1] Manisha Dagar[1] Alexandra Gangi[1] Maria Lauda Tomasi[1] Shelly Lu[1], [1]Cedars Sinai Medical Center

Background: Colorectal liver metastasis (CRLM) occurs in 50% of patients with colorectal cancer (CRC). Methionine adenosyltransferase (MAT) catalyzes the formation of S-adenosylmethionine (SAMe), the principal methyl donor. *MAT1A* (encodes MATα1) is expressed mainly in normal adult liver, whereas *MAT2A* (encodes MATα2) is expressed in all extrahepatic tissues. We reported MAT1A is a major defense against CRLM as loss of *Mat1a* sensitizes the liver to CRLM. In contrast, MAT2A is overexpressed in CRC and promotes oncogenicity. We found that human hepatocytes co-cultured with RKO (human CRC) cells, had lower MAT1A expression. Here, we sought to determine if MATα2 is secreted and if it affects hepatocytes' MAT1A expression.

. **Methods:** Our study included human hepatocytes, RKO cells, extracellular vesicle (EV) isolation, chromatin immunoprecipitation (ChIP), ChIP-seq, promoter activity assays, proliferation, migration, and invasion assays, western blotting, immunohistochemistry and immunofluorescence. We confirmed some of the findings using human CRLM and normal liver tissue array and human plasma. **Results:** CRCs secrete MATα2 in free but truncated form (MATα2-t) and intact within EVs. EV-MATα2 can be internalized by human hepatocytes and found within the nucleus, which then binds to *MAT1A* and *MAT2A* promoters on ChIP to lower and increase *MAT1A* and *MAT2A* promoter activities, respectively. In human CRLM samples, hepatocytes in nontumor regions express lower MATα1 but higher MATα2 as compared to normal liver. Treating RKO cells with EVs released from RKO cells overexpressing MAT2A promoted cell proliferation, migration, and invasion. MATα2-t was detected at a higher level in media from colon, pancreatic, and prostate cancer cell lines than corresponding normal epithelial cells as well as CRC patients' plasma than healthy controls. RKO cells treated with MATα2-t activated focal adhesion kinase (FAK), an important kinase for cancer cell evasion of apoptosis. Conversely, treatment with MATα2 neutralizing antibody inhibited FAK and induced apoptosis. **Conclusion:** CRC cells secrete both MATα2 within EVs and free MATα2-t. EV-MATα2 can be internalized and act as a transcription factor to lower hepatocytes' MAT1A, the major defense against CRLM, while promoting CRC oncogenicity. Freely released MATα2-t acts as a ligand in an autocrine fashion to activate FAK, which is essential for CRC survival. Taken together, secreted MATα2 plays an essential role in promoting CRLM.

Disclosures: Monica Justo: Nothing to Disclose, Heping Yang: Nothing to Disclose, Andrea Floris: Nothing to Disclose, Youngyi Lim: Nothing to Disclose, Swati Chandla: Nothing to Disclose, Manisha Dagar: Nothing to Disclose, Alexandra Gangi: Nothing to Disclose, Maria Lauda Tomasi: Nothing to Disclose, Shelly Lu: Nothing to Disclose

3207 | RECENT TRENDS IN SURVEILLANCE-DETECTED HCC IN THE UNITED STATES

Naomy Kim[1] Abdelrahman Attia[1] Emily Truong[1] Hasmik Adetyan[1] Rami Hemadeh[1] Manaf Alsudaney[1] Jaeho Park[2] Aarshi Vipani[1] Hirsh Trivedi[1] Yun Wang[1] Walid Ayoub[1] Alexander Kuo[1] Paul Martin[1] Hyunseok Kim[1] Ju Dong Yang[1], [1]Cedars-Sinai Medical Center, [2]University of Arkansas Medical Sciences

Background: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality. Surveillance programs aim to detect HCC at an early stage, potentially improving survival through curative treatments. Despite increased public awareness, recent trends in surveillance-detected HCC and its associated outcomes require further investigation. **Methods:** We analyzed data from 1,801 HCC patients diagnosed between 2009 and 2025 at a tertiary referral center in the U.S., categorized by detection method: symptomatic ($n = 486$), incidental ($n = 614$), and surveillance ($n = 701$). Tumor characteristics (size and number of lesions) and staging (BCLC) were compared across groups. Survival was assessed using Cox regression, with median overall survival (OS) and hazard ratios (HR) calculated. **Results:** Surveillance-detected HCC rates have not increased recently, with detection rates remaining stable at 23.4% (2021–2025), comparable to 23.0% (2009–2012) and 22.7% (2017–2020. Surveillance-detected cases were associated with smaller tumors (≤ 2 cm: 36.2% vs. 4.0% symptomatic, 19.4% incidental and > 5 cm: 11.1% vs. 70.1% symptomatic, 30.5% incidental, $p < 0.001$) and earlier BCLC stages (0–A: 78.8% vs. 24.0% symptomatic, 64.2% incidental, $p < 0.001$). Single lesions were more common in surveillance cases (70.3% vs. 49.5% symptomatic, 62.4% incidental, $p < 0.001$). Surveillance cases had a

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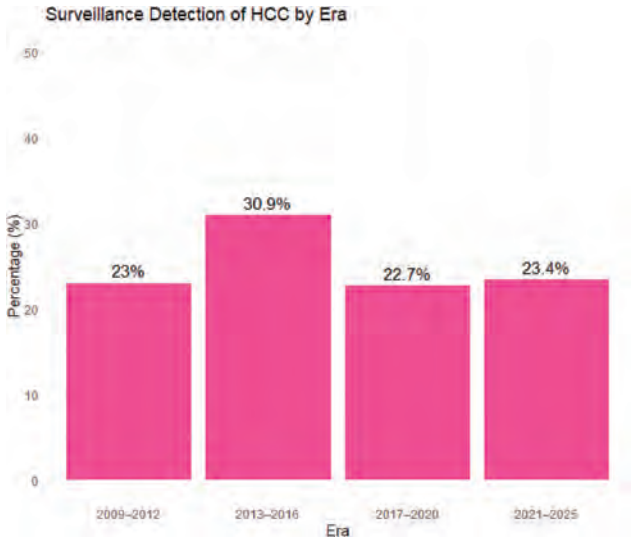
higher chance of curative treatment (52.2% vs. 17.2% symptomatic, 43.3% incidental, $p < 0.001$). Median OS was significantly higher for surveillance (75 months) and incidental (65 months) cases compared to symptomatic (21 months, $p < 0.001$) cases. Cox regression analysis adjusted for maximum tumor diameter, number of lesions, age, gender, and race showed improved survival for incidental (HR 0.73, 95% CI 0.60–0.88, $p < 0.001$) and surveillance (HR 0.76, 95% CI 0.62–0.93, $p = 0.007$) versus symptomatic cases, with no significant survival difference between incidental and surveillance groups. **Conclusion:** Despite increased awareness, surveillance-detected HCC has not risen recently, suggesting potential gaps in implementation, which could be in part attributable to COVID 19 pandemic in the most recent years. Surveillance is strongly associated with early-stage disease, smaller tumors, and fewer lesions, offering a higher chance of curative treatment and improved survival compared to symptomatic detection, though outcomes are similar to incidental cases. Enhanced surveillance strategies are needed to improve early detection rates.



Disclosures: Naomy Kim: Nothing to Disclose, Abdelrahman Attia: Nothing to Disclose, Emily Truong: Nothing to Disclose, Hasmik Adetyan: Nothing to Disclose, Rami Hemadeh: Nothing to Disclose, Manaf Alsudaney: Nothing to Disclose, Jaeho Park: Nothing to Disclose, Aarshi Vipani: Nothing to Disclose, Hirsh Trivedi: Nothing to Disclose, Yun Wang: Nothing to Disclose, Walid Ayoub: Intercept: Speaking and Teaching, Mirum: Grant/Research Support, GSK: Grant/Research Support, Madrigal: Grant/Research Support, Cymabay: Consultant, Ipsen: Grant/Research Support, Zydus: Grant/Research Support, Gilead: Grant Research Support, Alexander Kuo: Nothing to Disclose, Paul Martin: Nothing to Disclose, Hyunseok Kim: Nothing to Disclose, Ju Dong Yang: Exact Sciences: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Exelixis: Consultant, Fujifilm Medical Sciences: Consultant

3208 | QUALITY OF LIFE AND BEHAVIORAL RISK PROFILES IN PATIENTS WITH CHOLANGIOCARCINOMA AND HEPATOCELLULAR CARCINOMA

Fowsiyo Ahmed[1] Joseph Larson[1] Qian Shi[1] Lewis Roberts[1], [1]Mayo Clinic Rochester

Background: Cholangiocarcinoma (CCA) and hepatocellular carcinoma (HCC) are distinct liver cancers with limited comparative data on quality of life (QoL) and behavioral risk factors. We analyzed baseline QoL and self-reported smoking and alcohol use at diagnosis using self-administered FACT-Hep and lifestyle questionnaires to identify factors influencing patient well-being and guide personalized supportive care strategies. **Methods:** We identified 6,332 patients with CCA or HCC from a single-institution prospective registry who were consented from 2000-2025. The cohort represented patients with diverse demographics and clinical backgrounds. Only those who completed the FACT-Hep and lifestyle questionnaires within one year of diagnosis ($n = 609$) were included. Patients were excluded if key data were missing, or surveys were completed beyond one year. Descriptive statistics summarized patient responses. **Results:** Of the 609 patients included, 320 had CCA and 289 had HCC. Among them, 477 (CCA $n = 264$; HCC $n = 213$) completed smoking and alcohol surveys. The cohort was predominantly male (69%) and Caucasian decent (87%). Median FACT-Hep total scores, where higher values indicate better overall quality of life, were similar between CCA and HCC patients (135.0 vs. 136.0; $p = 0.47$). CCA patients reported significantly lower physical well-being scores (21.0 vs. 23.0; $p = 0.04$), while emotional (17.0 vs. 18.0; $p = 0.18$), functional (18.0 vs. 18.0; $p = 0.65$), and hepatobiliary cancer subscale scores (54.0 vs. 55.0; $p = 0.35$) were not significantly different. Fatigue and lack of energy were the most reported symptoms in both groups: fatigue was reported by 88.3% of CCA and 83.3% of HCC patients, and lack of energy by 87.9% vs. 85.2%, respectively. Other frequent symptoms included pain (63% vs. 62%), feeling ill (56% vs. 45%), and difficulty meeting family needs (52% vs. 46%). HCC patients more often reported a history of smoking (65% vs. 41%), while current alcohol use was higher among CCA patients (44% vs. 23%), who more frequently described social or occasional drinking patterns. **Conclusion:** Despite similar overall QoL scores, CCA patients reported lower physical well-being, and a slightly higher symptom burden compared to those with HCC. Differences in

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behavioral risk profiles, such as smoking and alcohol use, highlight the importance of incorporating lifestyle assessments into baseline evaluations. These findings support the importance of tailored supportive care strategies based on tumor type and individual patient factors.

Disclosures: Fowsiyo Ahmed: Nothing to Disclose, Joseph Larson: Nothing to Disclose, Qian Shi: Yiviva Inc.: Consultant, Regeneron Pharmaceuticals, Inc.: Consultant, Hoosier Cancer Research Network: Consultant, Kronos Bio: Consultant, Mirati Therapeutics Inc.: DSMB, Yiviva Inc: DSMB, Hoosier Cancer Research Network: DSMB, Genmab US, Inc.: DSMB, HopeAI, Inc: Advisor, BMS: DSMB, AbbVie: Consultant, BeOne Medicines USA, Inc: DSMB, Exelixis: DSMB, Regeneron: Grant/Research Support, BMS: Grant/Research Support, Roche/Genentech: Grant/Research Support, Janssen: Grant/Research Support, Novartis: Grant/Research Support, MPAACT: Grant/Research Support, Lewis Roberts: Astra Zeneca: Advisor, Astra Zeneca: Grant/Research Support, Bayer: Advisor, Bayer: Grant/Research Support, Boston Scientific: Grant/Research Support, Eisai: Advisor, Exact Sciences: Advisor, Exact Sciences: Grant/Research Support, Focal Medical Communications: Speaking and Teaching, Fujifilm Medical Systems: Grant/Research Support, Genentech: Grant/Research Support, Gilead Sciences: Advisor, Gilead Sciences: Grant/Research Support, Glycotest: Grant/Research Support, GRAIL: Advisor, HERMES: Grant/Research Support, Hepion Pharmaceuticals: Consultant, Innovo Bioanalysis: Grant/Research Support, Medscape: Speaking and Teaching, AiCME: Speaking and Teaching, Novartis Venture Fund: Consultant, Olympus: Grant/Research Support, Pontifax: Consultant, Prometrika - Surface Oncology: Consultant, RedHill Biopharma: Grant/Research Support, Regeneron Genetics Center: Grant/Research Support, TARGET RWE: Grant/Research Support

3209 | FRAILTY IS ASSOCIATED WITH ADVERSE INPATIENT OUTCOMES IN HEPATOCELLULAR CARCINOMA: A NATIONWIDE STUDY FROM 2018 TO 2022

Daniel Gonzalez Mosquera[1] Maria Mateo Chavez[2] Mariana Nunes Ferreira[1] Sakina Paracha[1] Juan Martinez-Ortega[1] Carolina Gonzalez Mosquera[3] Yassine Kilani[4] Victor Victor-Prophete[1], [1]New York Health + Hospitals | Lincoln–Weill Cornell Medical College Affiliate, New York, USA, [2]Knowledge and Research Evaluation Unit, Mayo Clinic, Rochester, Minnesota, USA, [3]Universidad Catolica Santiago de Guayaquil, [4]Washington University in St. Louis, Saint Louis, Missouri, USA

Background: Frailty has emerged as a critical determinant of adverse outcomes in chronic liver disease, yet its impact on hepatocellular carcinoma (HCC)-related hospitalizations remains insufficiently explored in recent large-scale datasets. This study aimed to assess the relationship between frailty and clinical outcomes in HCC hospitalizations using the National Inpatient Sample (NIS). **Methods:** We performed a retrospective cohort study identifying adult hospitalizations with diagnosis of HCC from the NIS database (2018–2022). Frailty was measured using the Hospital Frailty Risk Score (HFRS) and categorized as low (<5), intermediate (5–15), and high (>15) for descriptive analyses. Due to a small sample size in the high frailty group, multivariable regression models were constructed using a binary frailty variable (no frailty: HFRS <5 vs. frailty: HFRS ≥ 5). Descriptive statistics were used to report unadjusted incidence of mortality, ICU admission, length of stay (LOS), charges, organ dysfunction, vascular events, and procedures. Adjusted odds ratios (aOR) were estimated through logistic regression controlling for age, race, comorbidity index, and hospital characteristics. **Results:** We identified 59,345 HCC hospitalizations, with 66.8% classified as low frailty, 32.5% intermediate, and 0.6% high frailty. Descriptive analysis showed a consistent increase in adverse outcomes with higher frailty. Mortality rose from 5.1% in the low frailty group to 8.1% in the high frailty group. ICU admission rates increased from 1.9% to 13.2%, and sepsis-related complications from 0.4% to 7.9%. Additionally, mean LOS rose from 4.8 to 14.5 days, and total hospital charges were higher in patients with greater frailty.

In adjusted regression analysis comparing patients with frailty (HFRS ≥ 5) to those without (HFRS <5), frailty was independently associated with higher odds of mortality (aOR: 3.12 [2.68–3.63], $p<0.001$), ICU admission (aOR: 4.29 [3.45–5.35], $p<0.001$), respiratory failure (aOR: 5.52 [3.67–5.56], $p<0.001$), and sepsis-related complications (aOR: 12.06 [8.06–18.03], $p<0.001$). Frailty was also significantly associated with increased risk of cerebrovascular events, acute renal failure, and thrombotic complications. Notably, frail patients were less likely to undergo locoregional therapies including TACE (aOR: 0.71 [0.59–0.87], $p=0.001$) and ablation (aOR: 0.31 [0.20–0.47], $p<0.001$). **Conclusion:** Our study reveals a strong association between frailty and adverse outcomes in HCC hospitalizations. Even after adjustment, frailty correlated with significantly higher mortality, organ dysfunction, and reduced use of TACE and ablation. These findings highlight the need for routine frailty assessment and targeted interventions to improve outcomes and optimize resource use. Incorporating frailty into clinical pathways may enhance risk stratification and guide management in this vulnerable population.

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Table 1. Descriptive and Adjusted Inpatient Outcomes Among Hospitalizations for Hepatocellular Carcinoma (N = 59,345) by Frailty Risk Categories and Presence of Frailty (HFRS)

Outcomes	INCIDENCE N (%)				REGRESSION ANALYSIS aOR* [95% CI]			
	Low Frailty score (HFRS <5)	Intermediate Frailty score (HFRS 5-15)	High Frailty score (HFRS >15)	p value	No Frailty (HFRS <5)	p value	With Frailty (HFRS >5)	p value
Total primary Hepatorenal hospitalizations	100% (39,675)	100% (19290)	100% (380)	N/A	N/A	N/A	N/A	N/A
Mortality	5.1% (2,025)	14.2% (2,735)	8.1% (55)	<0.001	0.32 [0.27 - 0.37]	<0.001	3.12 [2.68 - 3.63]	<0.001
ICU Admission	1.9% (740)	7.2% (1,384)	13.2% (50)	<0.001	0.23 [0.18 - 0.29]	<0.001	4.29 [3.43 - 5.35]	<0.001
LOS (Mean/Days)	4.8	8.1	14.5	<0.001	0.03 [0.02 - 0.04]	<0.001	3.46 [3.15 - 3.76]	<0.001
Total Charge (Mean/$)	105310	55515	1200	<0.001	N/A	N/A	N/A	N/A
Sepsis related complications	0.4% (160)	4.3% (819)	7.9% (30)	<0.001	0.08 [0.05 - 0.12]	<0.001	12.06 [8.06 - 18.03]	<0.001
End Organ dysfunction								
Acute heart failure	0.5% (200)	1.2% (233)	0% (0)	<0.001	0.31 [0.33 - 0.82]	0.006	1.92 [1.20 - 3.06]	0.006
Respiratory failure	2.0% (800)	8.2% (1,595)	11.8% (45)	<0.001	0.22 [0.18 - 0.27]	<0.001	5.52 [3.67 - 3.56]	<0.001
Vascular events								
Cerebrovascular accident	0.1% (40)	0.5% (95)	5.2% (20)	<0.001	0.18 [0.08 - 0.45]	<0.001	5.30 [2.23 - 12.61]	<0.001
Acute Renal Failure	17.0% (6,733)	45.9% (8,860)	31.3% (195)	<0.001	0.25 [0.23 - 0.28]	<0.001	3.98 [3.62 - 4.37]	<0.001
Acute coronary syndrome	2.8% (110)	6.5% (125)	0% (0)	0.009	0.48 [0.27 - 0.83]	0.009	2.09 [1.20 - 3.65]	0.009
Deep vein thrombosis	2.1% (825)	4.4% (845)	5.3% (20)	<0.001	0.43 [0.35 - 0.55]	<0.001	2.29 [1.82 - 2.88]	<0.001
Pulmonary embolism	1.6% (625)	2.3% (565)	0% (0)	<0.001	0.55 [0.41 - 0.73]	<0.001	1.82 [1.36 - 2.42]	<0.001
Portal vein thrombosis	17.3% (6,783)	20.% (3,865)	11.8% (45)	<0.001	0.86 [0.78 - 0.96]	0.007	1.16 [1.04 - 1.28]	0.007
Procedure								
TACE	7.6% (3,015)	5.6% (1,070)	2.6% (10)	<0.001	1.39 [1.15 - 1.69]	0.001	0.71 [0.59 - 0.87]	0.001
Ablation	6.5% (2,604)	2.2% (430)	0% (0)	<0.001	3.30 [2.57 - 4.25]	<0.001	0.30 [0.24 - 0.39]	0.001
Liver Transplant	4.1% (1,640)	4.1% (835)	0% (0)	0.223	0.88 [0.70 - 1.10]	0.272	1.13 [0.90 - 1.41]	0.272

*adjusted for age, race, comorbidity index, income, insurance status, and hospital characteristics.

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*adjusted for age, race, comorbidity index, income, insurance status, and hospital characteristics.

Disclosures: Daniel Gonzalez Mosquera: Nothing to Disclose, Maria Mateo Chavez: Nothing to Disclose, Mariana Nunes Ferreira: Nothing to Disclose, Sakina Paracha: Nothing to Disclose, Juan Martinez-Ortega: Nothing to Disclose, Carolina Gonzalez Mosquera: Nothing to Disclose, Yassine Kilani: Nothing to Disclose, Victor Victor-Prophete: Nothing to Disclose

3210 | ASSOCIATION BETWEEN STATIN USE AND HEPATOCELLULAR CARCINOMA RECURRENCE AFTER CURATIVE TREATMENT: A META-ANALYSIS OF ADJUSTED HAZARD RATIOS

Madia Ahad[1] Anwar Uddin[1] Aisha Elamin[1] Rahat Uddin[1], [1]Suny Downstate Medical Center

Background: Hepatocellular carcinoma (HCC) remains a major cause of cancer-related death worldwide. Although curative treatments such as surgical resection and ablation have improved outcomes, recurrence rates remain high, often surpassing 50% within five years. Statins, widely used for cardiovascular disease, have demonstrated potential anticancer effects, including antiproliferative and immunomodulatory properties. However, their impact on recurrence-free survival (RFS) after curative treatment for HCC remains unclear. This meta-analysis assessed whether statin use is associated with reduced recurrence following definitive HCC therapy. **Methods:** We conducted a meta-analysis of observational studies reporting multivariable-adjusted hazard ratios (HRs) for HCC recurrence after curative therapy (resection or ablation). PubMed, EMBASE, and Scopus were searched through April 2025. Studies included adult HCC patients, compared recurrence between statin users and non-users, and reported adjusted HRs with 95% CIs. Eight studies (n = 3,625) met inclusion. Extracted data included study design, statin type, treatment, follow-up, adjustment covariates, and HRs. A DerSimonian–Laird random-effects model pooled log-transformed HRs. Heterogeneity was assessed via I^2 and τ^2; publication bias via funnel plot and Egger's test. **Results:** Eight observational studies involving 3,625 patients with HCC were included. All reported multivariable adjusted hazard ratios for recurrence free survival following curative treatment, comparing statin users to nonusers. Covariates commonly included tumor size, liver function (Child Pugh or MELD), antiviral therapy, age, and comorbid conditions. Pooled analysis using a random effects model showed statin use was associated with a significantly lower risk of recurrence. The pooled adjusted HR was 0.61 (95% CI 0.54 to 0.70), reflecting a 39% relative reduction. Individual adjusted HRs ranged from 0.48 to 0.70, consistently favoring statin use. The direction and magnitude of association were similar across studies despite variation in statin class, treatment modality, and patient population. No statistical heterogeneity was observed ($I^2 = 0\%$ $\tau^2 = 0$ Q = 3.55 df = 7), though clinical differences such as follow up duration, statin intensity, and cointerventions may exist. Funnel plot inspection revealed no asymmetry, and Egger's test (p = 0.58) indicated no evidence of publication bias, although the limited number of included studies may reduce power to detect subtle bias. **Conclusion:** Statin use was associated with a significantly lower risk of hepatocellular carcinoma recurrence after curative treatment. The results were consistent across studies with no statistical heterogeneity observed. Future studies, preferably prospective in design and stratified by statin class and dose, are needed to confirm these findings and evaluate causality.

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Table 1. Characteristics of Included Studies in Meta-Analysis on Statin Use and HCC Recurrence

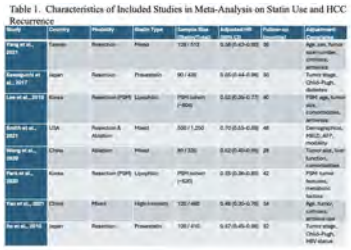


Figure 1: Forest Plot Statin Use and HCC Recurrence

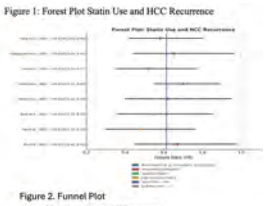
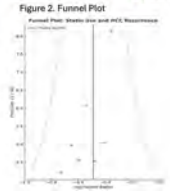


Figure 2. Funnel Plot



Disclosures: Madia Ahad: Nothing to Disclose, Anwar Uddin: Nothing to Disclose, Aisha Elamin: Nothing to Disclose, Rahat Uddin: Nothing to Disclose

3211 | COMPARATIVE OUTCOMES OF TRANSRADIAL (TRA) VERSUS TRANSFEMORAL (TFA) ACCESS IN LOCOREGIONAL THERAPIES FOR HEPATOCELLULAR CARCINOMA: SYSTEMATIC REVIEW AND META-ANALYSIS IN TARE, TACE, AND HAIC

Renan Prado[1] Julia TIrelli Rocha[2] Gustavo Jose Silva Sanchez[3] Maria Julia Godoy Siqueira[4] Milena Zadra Prestes[5] Mariana Leticia de Bastos Maximiano[6] Melissa Lou Silva[7], [1]Cleveland Clinic Foundation, [2]Jundiai Medical School, Brazil, [3]University of Connecticut, [4]Anhembi Morumbi University, Brazil, [5]State University of Ponta Grossa, [6]Federal Fluminense University, Brazil, [7]University of California San Diego

Background: Transradial access (TRA) is increasingly adopted as an alternative to the conventional transfemoral approach (TFA) in various endovascular procedures. In hepatocellular carcinoma (HCC), locoregional therapies such as transarterial radioembolization (TARE), transarterial chemoembolization (TACE), and hepatic arterial infusion chemotherapy (HAIC) rely heavily on arterial access. Emerging evidence suggests potential advantages of TRA in terms of safety, efficiency, and patient satisfaction. However, comparative data across modalities have not been systematically evaluated. **Methods:** We conducted a systematic meta-analysis of studies comparing outcomes of TRA versus TFA in TARE, TACE, and HAIC for HCC. PubMed, Embase, and the Cochrane Library were searched through December 31, 2024, yielding 358 records. After removing screening, 19 studies (2 for HAIC, 6 for TARE, and 11 for TACE) were included. Key outcomes analyzed included access failure, arterial occlusion, hematoma, bruising, procedural metrics, radiation exposure, pain scores, and patient preference. Pooled risk ratios (RRs), mean differences (MDs), and standardized mean differences (SMDs) were calculated with 95% confidence intervals (CIs). (PROSPERO ID: CRD420251013220). **Results:** In HAIC procedures, TRA was associated with a significantly lower risk of hematoma (RR 0.16; 95% CI: 0.04–0.58) and arterial occlusion (RR 0.10; 95% CI: 0.02–0.47), with comparable procedural success (RR 1.00; 95% CI: 0.99–1.01). Procedure time was significantly reduced in the TRA group (SMD −0.87; 95% CI: −1.17 to −0.58).

In TARE procedures, TRA led to shorter fluoroscopy (MD −6.59 min; 95% CI: −9.20 to −3.99), procedure time (MD −12.13 min; 95% CI: −16.49 to −7.77), and radiation time (MD −5.17 min; 95% CI: −6.94 to −3.40). Pain was significantly lower both during the procedure (MD −1.01; 95% CI: −1.41 to −0.60) and in the recovery room (MD −1.20; 95% CI: −1.63 to −0.76). Conversion from TRA to TFA was uncommon.

In TACE interventions, TRA was associated with fewer access site complications, including a lower rate of access failure (RR 0.41; 95% CI: 0.22–0.78), hematoma (RR 0.55; 95% CI: 0.33–0.92), and bruising/ecchymosis (RR 0.58; 95% CI: 0.34–0.99). Moreover, 84% of patients preferred TRA over TFA, citing less discomfort and improved mobility post-procedure. **Conclusion:** TRA demonstrates a superior safety and efficiency profile compared to TFA across locoregional therapies for HCC. TRA offers reduced complication rates, shorter procedure and fluoroscopy times, lower radiation exposure, and greater patient comfort and preference. These findings support wider adoption of TRA in interventional oncology for HCC, particularly in appropriately selected patients. Further high-quality randomized trials are warranted to validate these benefits.

Table 1 Study characteristics. Details the year of each study included in the meta-analysis along with the study type, design, oncologic procedure, and number of patients in each cohort.

Study, year	Study design	Procedure	TRA (n)	TFA (n)
Kis et al., 2016	Retrospective	TARE	33	31
Loewenstein et al., 2018	Retrospective	TARE	302	302
Liu et al., 2019	Crossover trial	TARE	30	30
Ghosh et al., 2022	Retrospective	TARE	188	63
Pedersoli et al., 2023,	Retrospective	TARE	10	12
Yakupoğlu et al., 2023	Retrospective	TARE	75	147
Li et al., 2024	Randomized controlled trial	HAIC	60	60
Wan et al., 2022	Crossover trial	HAIC	36	84
Shiozawa et al., 2003	Retrospective	TACE	177	150
Toyoda et al., 2021	Retrospective	TACE	206	240
Jiang et al., 2022	Randomized controlled trial	TACE	90	30
Du et al., 2019	Retrospective	TACE	112	107
Ghosh et al., 2022	Retrospective	TACE	90	56
You et al., 2023	Retrospective	TACE	131	145
Iezzi et al., 2017	Prospective	TACE	42	42
Yamada et al., 2017	Randomized controlled trial	TACE	18	18
Minici et al., 2023	Retrospective	TACE	42	40
Zhang et al., 2022	Randomized controlled trial	TACE	65	65
Wu et al., 2015	Retrospective	TACE	126	158

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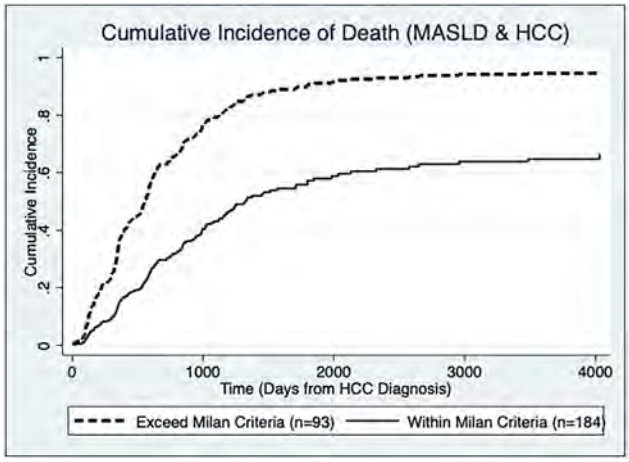
Disclosures: Renan Prado: Nothing to Disclose, Julia TIrelli Rocha: Nothing to Disclose, Gustavo Jose Silva Sanchez: Nothing to Disclose, Maria Julia Godoy Siqueira: Nothing to Disclose, Milena Zadra Prestes: Nothing to Disclose, Mariana Leticia de Bastos Maximiano: Nothing to Disclose, Melissa Lou Silva: Nothing to Disclose

3212 | RISK FACTORS AND OUTCOMES ASSOCIATED WITH HEPATOCELLULAR CARCINOMA IN NONCIRRHOTIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Claudio Salinas[1] Jacob Lizak[1] Craig Rosenstengle[2] Shivang Mehta[2] Saleh Elwir[3] Niluka Wickramaratne[2] Marc Najjar[2], [1]Burnett School of Medicine at TCU, [2]Baylor Scott and White All Saints Medical Center Fort Worth, [3]Baylor University Medical Center

Background: Individuals with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and cirrhosis are at increased risk of hepatocellular carcinoma (HCC) and require surveillance. Although HCC can occur with MASLD in the absence of cirrhosis, this is infrequent and risk factors for HCC in this population are poorly defined. **Methods:** Retrospective review of consecutive patients with HCC and a diagnosis of MASLD or cryptogenic liver disease with coexisting metabolic comorbidities who presented to a multidisciplinary liver tumor clinic between 2007 and 2023. Patients with a history of alcohol use or other liver disease were excluded. Noncirrhotic patients were identified by liver biopsy review or a combination of imaging, laboratory, and clinical parameters indicating absence of cirrhosis or portal hypertension. Multivariate logistic regression and competing risks survival regression were performed to evaluate risk factors and cumulative incidence of death, respectively. **Results:** Among 277 patients identified with MASLD and HCC, 28 (10%) were found to be noncirrhotic. Patient characteristics included median age 68 (range 32-91), BMI 31.5 kg/m^2 (16.7-65.7), 62% obese, 70% diabetes, 74% hypertension, and 47% hyperlipidemia. Overall, the majority (75%) had a solitary tumor at time of presentation, 96% received treatment for HCC, and 27% were listed for liver transplantation (LT). Median follow up was 1.5 years (range 3 days to 9.5 years). All 28 noncirrhotic patients received HCC treatment. Compared with cirrhotics, noncirrhotic patients were more likely to have hyperlipidemia (64% vs. 45%; $p = 0.05$) and less likely to have diabetes (50% vs. 72%; $p = 0.02$). Hyperlipidemia was an independent predictor of noncirrhotic HCC (OR 2.98, 95% CI 1.22-7.24) vs. other metabolic syndrome risk factors, while diabetes predicted HCC with cirrhosis (OR 3.39, 1.46-7.88). None of the noncirrhotic patients underwent HCC surveillance prior to presentation, at which time tumor size was greater in noncirrhotics with median size 7.5 cm (2.5-21.2) vs. 2.8 cm (1.0-22.1; $p < 0.001$) and noncirrhotic patients were more likely to exceed Milan Criteria; only 4/28 (14%) of noncirrhotics presented within Milan criteria vs. 180/249 (72%) of cirrhotics ($p < 0.001$). Exceeding Milan criteria was strongly associated with decreased survival overall (SHR 2.80, 2.03-3.85) and noncirrhotic status predicted LT ineligibility (OR 0.02, 0.001-0.28) independent of increasing age and obesity class. **Conclusion:** HCC may occur in a small but significant proportion of noncirrhotic patients with MASLD. In the absence of surveillance, HCC presented at an advanced stage among our noncirrhotic cohort, leading to LT ineligibility and poor survival. Identifying factors associated with an increased risk of noncirrhotic HCC among those with MASLD may guide surveillance strategies in selected patients.



Disclosures: Claudio Salinas: Nothing to Disclose, Jacob Lizak: Nothing to Disclose, Craig Rosenstengle: Nothing to Disclose, Shivang Mehta: Nothing to Disclose, Saleh Elwir: Nothing to Disclose, Niluka Wickramaratne: Nothing to Disclose, Marc Najjar: Nothing to Disclose

3213 | HEPATIC FIBROSIS AS PREDICTOR OF CANCER-ASSOCIATED THROMBOSIS IN PATIENTS WITH INTRAHEPATIC CHOLANGIOCARCINOMA

***NEW SUBMISSION**, Luca Fabris[1] Yahima Frion-Herrera[2] Camilla Venturin[2] Massimiliano Cadamuro[3] Jessica Gasparello[4] Claudia Maria Radu[2] Matteo Fassan[5] Claudia Mescoli[6] Umberto Cillo[7] Enrico Gringeri[7] Giacomo Zanus[7] Mario Strazzabosco[8] Paolo*

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Background: Cholangiocarcinoma (CCA) is an aggressive malignancy with a steadily increasing incidence worldwide, particularly of the intrahepatic variant (iCCA). Consequently, identifying factors that may modify the natural history of this disease has become the focus of interest in multiple studies. While the relationship between hepatic fibrosis and the development of CCA has been previously explored, the contribution of fibrosis-induced coagulation imbalance to disease progression remains unclear. This study aimed at investigating the relationship between advanced liver fibrosis, hemostasis activation, and occurrence of cancer-associated thrombosis (CAT) in patients with iCCA. **Methods:** Fifty iCCA patients who underwent curative liver surgery were studied. Graft wedge biopsies served as controls (n = 10). Histological evaluation was performed on archival formalin-fixed, paraffin-embedded samples using the Ishak Fibrosis Score (IFS, 0-6). Immunohistochemical staining was performed to assess tissue factor (TF), FX, fibrinogen and von Willebrand factor (vWF). Portal vein microthrombosis highlighted by fibrin deposition within the vessel lumen was quantified using Martius Scarlet Blue (MSB) staining. Immunofluorescence (IF) analysis for TF and FX was performed on patient-derived organoids (PDOs, n = 10). Extracellular vesicles (EVs) isolated from iCCA-PDO media were analyzed by flow cytometry (FACS) using Calcein-AM, EpCAM-PE, and Annexin V markers. EV-induced platelet activation was evaluated by FACS using CD41, CD62P, and Annexin V markers. **Results:** iCCA patients showed a procoagulant profile with increased coagulation activation and impaired fibrinolysis compared to controls. In iCCA, patients with advanced fibrosis (IFS 4–5, n = 16) showed a more prominent expression of TF, FX, vWF, and fibrinogen than patients with fibrosis stages ≤ 3 (n = 34). Furthermore, the degree of fibrosis correlated with either TF expression by malignant bile ducts or the number of portal vein microthrombosis ($p < 0.05$). IF analysis in iCCA-PDOs confirmed a marked TF and FX upregulation, whereas EVs from iCCA-PDO media promoted platelet activation. **Conclusion:** Hepatic fibrosis is closely linked to CAT occurrence in iCCA patients, and associated with increased expression of TF and platelet activation by malignant cholangiocytes. This fibrosis-coagulation interplay underscores the need to unravel the mechanisms promoting CAT development in CCA progression.

Disclosures: Luca Fabris: Nothing to Disclose, Yahima Frion-Herrera: Nothing to Disclose, Camilla Venturin: Nothing to Disclose, Massimiliano Cadamuro: Nothing to Disclose, Jessica Gasparello: Nothing to Disclose, Claudia Maria Radu: Nothing to Disclose, Matteo Fassan: Astellas: Speaking and Teaching, roche: Grant/Research Support, Thermofisher: Grant/Research Support, Sanofi: Speaking and Teaching, Pfizerr: Speaking and Teaching, Novartis: Advisor, Servier: Speaking and Teaching, MSD: Speaking and Teaching, GSK: Speaking and Teaching, Beone: Consultant, BMS: Speaking and Teaching, Amgen: Speaking and Teaching, Incyte: Speaking and Teaching, Pierre Fabre: Speaking and Teaching, Claudia Mescoli: Nothing to Disclose, Umberto Cillo: Nothing to Disclose, Enrico Gringeri: Nothing to Disclose, Giacomo Zanus: Nothing to Disclose, Mario Strazzabosco: Nothing to Disclose, Paolo Simioni: Nothing to Disclose

3214 | PREDICTORS OF OUTCOMES FOLLOWING TRANSARTERIAL EMBOLIZATION THERAPIES IN UNRESECTABLE HEPATOCELLULAR CARCINOMA: A MULTICENTER ANALYSIS

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Background: Transarterial radioembolization (TARE) with Yttrium-90 resin microspheres and transarterial chemoembolization (TACE) are widely recognized locoregional treatments for patients with unresectable hepatocellular carcinoma (uHCC). However, uHCC is a heterogeneous group of patients, with varying safety and efficacy outcomes influenced by both tumor burden and host-related factors. In this study, we aimed to identify clinical and biochemical predictors of response and survival outcomes in patients with uHCC undergoing TACE and TARE. **Methods:** We retrospectively analyzed consecutive, unselected patients treated with TARE or TACE at four academic institutions. Exclusion

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criteria included extrahepatic metastases, Child-Pugh (CP) class C disease, or receipt of non-selective TARE or TACE. Baseline demographics, liver function parameters, and treatment-related variables were collected; adverse events, median overall survival (mOS), and objective response (per mRECIST) were assessed using multivariable modeling to determine independent predictors of efficacy and prognosis. Median follow-up was 24 (interquartile range 11-42) months. **Results:** The cohort comprised 312 patients, predominantly male (73.9%), with a mean age of 66.8 ± 10.5 years. Most patients had intermediate-stage disease (BCLC 'B', 54.5%), followed by early-stage (BCLC '0/A' 34.0%) and locally advanced-stage disease (BCLC 'C', 11.5%). Of the total cohort, 177 patients received TACE (56.7%) and 135 received TARE (43.3%). The mOS of the overall cohort was 32 months (95% CI: 27.0-37.0), and was significantly longer in patients with BCLC stage '0/A' (47 months [95% CI: 33.0-67.0]) than BCLC stage 'B' (30 months [HR, 1.58; 95% CI: 1.17-2.13]) and BCLC stage 'C' (22 months [HR, 2.63; 95% CI: 1.46-4.73]). Multivariable analyses revealed ECOG '0' (OR 2.61, 95% CI: 1.05-6.46), AFP < 400 ng/mL (OR 2.24, 95% CI: 1.31-3.82), complete tumoral response (OR 4.40, 95% CI: 1.99-9.71) and lower ALBI scores (OR 1.69, 95% CI: 1.14-2.51) as independent predictors of survival. The TACE group showed higher complete response rates (33.5%) compared to TARE (23.2%; P = 0.049). Independent predictors of disease control included alkaline phosphatase (OR 0.99, 95% CI: 0.993-0.999), AFP < 400 ng/mL (OR 0.31, 95% CI: 0.16-0.63), and BCLC stage '0/A' (OR 4.92, 95% CI: 1.88-12.92). **Conclusion:** Despite enhanced complete response rates, TACE did not confer a survival advantage over TARE in patients with uHCC. Patient-related factors, rather than the type of intervention, were the primary determinants of treatment outcomes. Given their prognostic significance, a thorough evaluation of these factors is crucial for optimal patient selection for embolization therapies.

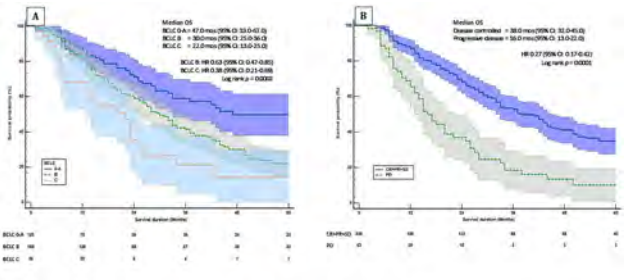

Figure 1: Survival analysis of patients undergoing transarterial chemoembolization and radioembolization in **A)** early-advanced BCLC stages and **B)** in relation to disease control and progressive disease

Disclosures: Faisal Sanai: Nothing to Disclose, Saad Aldosari: Nothing to Disclose, Adnan Alzanbagi: Nothing to Disclose, Mohammed Arabi: Nothing to Disclose, Khalid Bzeizi: Nothing to Disclose, Jameel Bardesi: Nothing to Disclose, Sarah Alfawaz: Nothing to Disclose, Fatimah Albenmousa: Nothing to Disclose, Mohamed Shawkat: Nothing to Disclose, Ali Albenmousa: Nothing to Disclose, Hamdan Alghamdi: Nothing to Disclose, Majed Almaghrabi: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose

3215 | CHARACTERISTICS AND POTENTIAL ROLES OF PROLIFERATIVE CD8$^+$ T CELLS IN HBV-RELATED HCC PATIENTS

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Background: While different CD8$^+$ T cell subsets within the hepatocellular carcinoma (HCC) tumor microenvironment (TME) are critically important and extensively studied, research on proliferative CD8$^+$ T cells (Tpro) remains limited. We aimed to characterize Tpro cells and elucidate their potential roles in hepatitis B virus (HBV)-related HCC patients. **Methods:** We integrated 114,539 liver tissue-derived immune cells from 26 patients across three GEO datasets, including 8 with HBV infection, 6 with HBV and liver fibrosis, and 12 with HBV-related HCC. Bulk RNA-seq data from GEO and TCGA were analyzed using deconvolution, survival analysis, and ssGSEA to investigate Tpro cells. **Results:** We identified Tpro cells exhibiting hyperproliferative capacity (overexpression of 18 cell cycle genes), tissue-resident properties (CD69$^+$ ITGAEhigh), an exhausted state (LAG3$^+$ CTLA4$^+$), cytotoxicity (GZMBhigh IFNG$^+$), and distinct from TCF7-high precursor exhausted T cells (Tpex) (TCF7low). The proportion of Tpro cells significantly increased in HBV-related HCC and demonstrated inter-patient heterogeneity. Tpro enrichment correlated with advanced BCLC and TNM stages and elevated AFP levels. Furthermore, Tpro cells were subdivided into PDCD1$^+$Tpro and PDCD1-Tpro subsets, with PDCD1$^+$Tpro predominating in HBV-related HCC. Patients with higher PDCD1$^+$Tpro proportions exhibited significantly shorter overall survival (OS) and progression-free survival (PFS). HCC TMEs enriched for PDCD1$^+$Tpro displayed increased immunosuppressive CD4$^+$ T cell subsets (Th2, Treg) and decreased immunostimulatory subsets (Th1, Th17). Moreover, patients responding to anti-PD1 therapy showed an upregulated PDCD1$^+$Tpro to PDCD1-Tpro ratio. **Conclusion:** PDCD1$^+$Tpro cells are increased in HBV-related HCC and are strongly associated with disease progression and poor prognosis. They may also serve as predictive biomarkers for immune checkpoint blockade therapy response.

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Disclosures: Ruoyu Gao: Nothing to Disclose, Hong Li: Nothing to Disclose, Wen Zhang: Nothing to Disclose, Wenyue Wu: Nothing to Disclose, Ziyan Pan: Nothing to Disclose, Haodong Ma: Nothing to Disclose, Caihong Wang: Nothing to Disclose, Hong You: Nothing to Disclose, Wei Chen: Nothing to Disclose

3216 | ENHANCED ANTITUMOR ACTIVITY OF PROGRAMMED CELL DEATH-1 ANTIBODY/REGORAFENIB COMBINED WITH DIPEPTIDYL PEPTIDASE-4 INHIBITION IN HEPATOCELLULAR CARCINOMA ORGANOID MODEL

Heejoon Jang[1] Yookyoung Lim[2] Su Jong Yu[3] Jung-Hwan Yoon[4], [1]SMG-SNU Boramae Medical Center, [2]Boramae Medical Center, [3]Seoul National University Hospital, [4]Seoul National University

Background: Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer mortality globally. While immune checkpoint inhibitors show promise in HCC treatment, their efficacy remains limited. Dipeptidyl peptidase-4 (DPP4) inhibitors are known to enhance immune cell chemotaxis through CXCL10 preservation. This study investigates the potential synergistic effects of combining programmed cell death-1 antibody/regorafenib with DPP4 inhibition using murine-derived organotypic tumor spheroids, which better simulate the tumor microenvironment than conventional models,. **Methods:** Tumor tissues were harvested from mice bearing RIL-175 hepatocellular carcinoma, mechanically minced, and filtered through 70-100 μm cell strainers. The resulting cell suspensions were embedded in collagen hydrogel and cultured in 3D microfluidic devices to generate murine-derived organotypic tumor spheroids (MDOTS). During MDOTS formation, specimens were divided into four treatment groups: control (IgG + DMSO), anti- programmed cell death-1 (PD-1) antibody plus regorafenib, sitagliptin, and anti-PD-1 antibody/regorafenib plus sitagliptin. After MDOTS formation, cultures were maintained for 4-6 days with respective treatments. The proportion of live/dead cells was assessed using confocal microscopy, while DPP-4 activity and CXCL10 concentrations were measured in culture supernatants. **Results:** Confocal microscopy findings of cell viability revealed varying proportions of dead cells across treatment groups: control (14.5%), anti-PD-1 antibody plus regorafenib (25%), sitagliptin (25%), and triple combination therapy (36%). Notably, only the triple combination therapy group (anti-PD-1 antibody/regorafenib plus sitagliptin) demonstrated a significantly higher proportion of dead cells compared to the control group. Furthermore, CXCL10 concentrations in culture supernatants were significantly elevated in the triple therapy group compared to other treatment groups, suggesting enhanced immune cell recruitment potential. **Conclusion:** In this MDOTS platform, triple combination therapy with anti-PD-1 antibody/regorafenib and DPP4 inhibition demonstrated superior cytotoxic effects compared to anti-PD-1 antibody/regorafenib therapy. This improved antitumor activity may be mediated through enhanced immune cell recruitment via CXCL10 preservation, suggesting a potential mechanism for improved therapeutic efficacy in hepatocellular carcinoma.

Figure 1. Anti-tumor response of combined anti-PD-1 antibody, regoraferlib, and sitagliptin treatment in murine-derived organotypic tumor spheroids using RIL-175 tumor cells. (A) Representative confocal microscopy images of live and dead cells. (B) Quantitative analysis of live and dead cell areas.

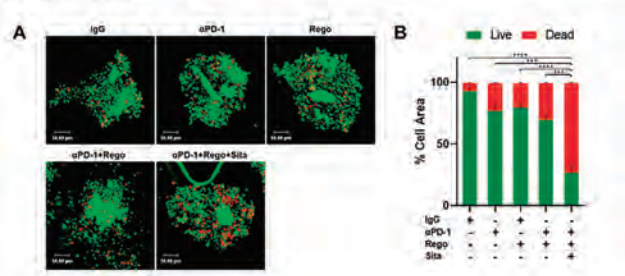
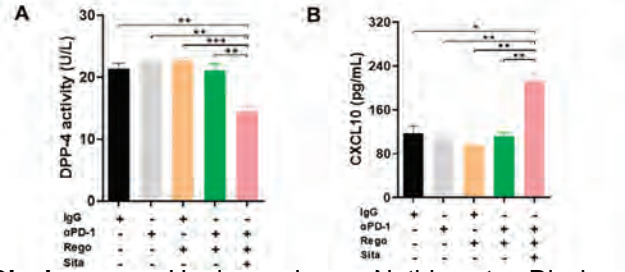


Figure 2. Effects of combined anti-PD-1 antibody, regorafenib, and sitagliptin treatment on murine-derived organotypic tumor spheroids using RIL-175 tumor cells. (A) DPP-4 activity. (B) CXCL10 concentration.



Disclosures: Heejoon Jang: Nothing to Disclose, Yookyoung Lim: Nothing to Disclose, Su Jong Yu: Nothing to Disclose, Jung-Hwan Yoon: Bayer: Grant/Research Support, Daewoong Pharmaceutical: Grant/Research Support, Bukwang Pharmaceutical: Grant/Research Support

3217 | THE EFFECT OF CIRCULATING INFLAMMATORY BIOMARKERS ON THE RISK OF NON-VIRAL RELATED HEPATOCELLULAR CARCINOMA DEVELOPMENT

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Background: Inflammatory pathway is a complex biological process triggered by several factors associated with chronic liver diseases. Independent of chronic viral infection, alcohol abuse and chronic metabolic disorders are the major causes of nonviral related hepatocellular carcinoma (NVRHCC). However, there is a paucity in data examining the role of inflammatory-related biomarkers on the risk of NVRHCC. We aimed to assess the associations of blood-based biomarkers involved in the inflammatory pathway and HCC diagnosis in the absence of viral hepatitis. **Methods:** Between 2001 and 2014, all newly diagnosed HCC patients were enrolled in an IRB-approved study at The University of Texas MD Anderson Cancer Center. Controls were healthy spouses of patients who were diagnosed with non-liver/GI cancers. Only cases and controls who were negative for hepatitis B and C markers were included in this study. Blood samples collected at diagnosis/enrollment were tested for 28 inflammatory biomarkers by Myriad RBM, Inc. Using the tertiles of the biomarkers among the controls as a cutoff point, all participants were categorized into subjects with low, moderate, and high levels of the biomarkers. Odds ratio (OR) and 95% confidence interval (CI) values were estimated using multivariable unconditional logistic regression analysis adjusted for relevant confounders. The *P* value is adjusted for multiple testing using the Benjamini-Hochberg with the false discovery rate at 0.25. **Results:** The study analyzed 378 NVR HCC cases and 200 healthy controls, with mean ages of 64.96 ± 12.78 and 60.17 ± 9.53 years, respectively; 76.8% were white. Table 1 shows adjusted ORs and 95% CIs for the top significant five inflammatory biomarkers most strongly linked to NVRHCC risk. Comparing moderate and high levels (2nd and 3rd tertiles) to low levels (1st tertile), Tissue Inhibitor of Metalloproteinases-1 (TIMP-1) showed the strongest HCC risk link (OR = 38.45, *P* = 0.01, highest vs. lowest tertile), followed by Vascular Cell Adhesion Molecule (VCAM-1) (OR = 15.06, *P* = 0.02). Interleukin 8 (IL-8) (OR = 6.16) and Intercellular Adhesion Molecule-1 (ICAM-1) (OR = 4.42) also had positive associations. In contrast, Interleukin 18 (OR = 0.17) and Interleukin 23 (OR = 0.24) were inversely linked to risk. **Conclusion:** TIMP-1, VCAM, IL-8 and ICAM-1 showed significant and independent associations with increased risk of HCC. These observations suggest a potential value of these plasma biomarkers in predicting the risk of HCC in the absence of viral hepatitis infection. This should enhance our knowledge about the role of these markers in the diagnosis of NVRHCC and their potential implication in identifying high risk population for early detection.

Table 1: ORs and 95% Confidence Interval (CI) for the association of each inflammatory-related biomarker with the risk of hepatocellular carcinoma in 378 non-viral HCC cases and 200 controls

	Tertile 1		Tertile 2		Tertile 3		P_{trend}
Inflammatory Biomarker	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)	
Tissue Inhibitor of Metalloproteinases-1	5/66	1	20/73	5.78(1.22- 27.52)	347/61	38.45 (9.48- 228.03)	0.01
Vascular Cell Adhesion Molecule	14/66	1	33/65	5.84(1.36- 23.33)	331/66	15.06 (3.20- 70.81)	0.02
Interleukin 18	80/66	1	91/68	0.39 (0.13- 1.18)	207/66	0.17 (.051- 0.54)	0.03
Interleukin 8	18/69	1	14/65	0.79 (0.21- 2.91)	348/66	6.16 (1.75- 21.70)	0.04
Intercellular Adhesion Molecule-1	23/66	1	32/67	0.95 (0.26- 3.49)	323/67	4.42 (1.36- 14.51)	0.04
Interleukin 23	200/71	1	88/65	0.45 (0.15- 1.36)	73/64	0.24 (0.07- 0.83)	0.05

Model adjusted for age, sex, race, viral hepatitis, smoking, alcohol consumption, history of diabetes, family history of cancer. P is adjusted for multiple testing using the Benjamini-Hochberg with the false discovery rate at 0.25.

Disclosures: Mazen Elsheikh: Nothing to Disclose, Rikita Hatia: Nothing to Disclose, Sherry Fares: Nothing to Disclose, Mohamad Ali Ibrahim: Nothing to Disclose, Karim Adhem: Nothing to Disclose, Megha Bhongade: Nothing to Disclose, Donghui Li: Nothing to Disclose, Ximena Ramirez-Morales: Nothing to Disclose, Ping Chang: Nothing to Disclose, Yun Shin Chun: Nothing to Disclose, Asif Rashid: Nothing to Disclose, Ahmed Kaseb: Nothing to Disclose, Prasun Jalal: Nothing to Disclose, Manal Hassan: Nothing to Disclose

3218 | NOVEL APPROACHES FOR THE EARLY DETECTION OF HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW OF DIAGNOSTIC ACCURACY STUDIES

Melissa Barlow[1] Sarah Bailey[1] Badr Albawardy[2] Sadeem Aldarwesh[2] Rowaedh Bawaked[3] Ahmed Allehebi[4] Heba Alharith[2] Asrar Alaklabi[2] Aldanah Althwanay[5] Nora Althumiri[6] Saleh Alabbad[2] Mohamed Mawardi[4] Khalid Bzeizi[2] Saleh Alessy[2] Bandar Aljudaibi[2] Saleh Alqahtani[2], [1]University of Exeter, Exeter, United Kingdom, [2]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [3]Saudi Electronic University, Riyadh, Saudi Arabia, [4]King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia, [5]Washington University in St. Louis, St. Louis, MO, USA, [6]Informed Decision Making, Riyadh, Saudi Arabia

Background: Hepatocellular carcinoma (HCC) remains a major global health burden, with rising incidence and mortality. Novel diagnostic approaches may improve early detection and streamline diagnostic pathways, crucial for improving survival. We aimed to systematically review novel HCC detection approaches reporting diagnostic accuracy measures. **Methods:** A systematic review was conducted using PRISMA guidelines by searching PubMed, EMBASE, Scopus, and the Cochrane Library on Dec 11, 2024. Eligible studies were cohort or randomized controlled trials in design, in English or Arabic, reported a novel diagnostic approach for

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HCC in any clinical setting, enrolled ≥300 participants, and reported diagnostic accuracy measures. Studies identifying incident HCC were included. Two reviewers independently screened studies and assessed risk of bias using the QUADAS-2 tool. Due to heterogeneity in index tests, populations, and outcome measures, meta-analysis was not performed. **Results:** Four studies (n = 50,363) met the inclusion criteria, each evaluating a distinct approach (Table). Three studies focused on patients with existing liver conditions (hepatitis B and cirrhosis); two studies in hepatitis B cohorts reported predictive algorithms aimed at improving HCC detection above usual care. The methylation, mutation, and protein-HCC (M2P-HCC) clinical prediction model for patients with hepatitis B had an AUC of 0.88 (95% CI 0.81-0.95), outperforming standard care (0.76 [0.69-0.84]), with low risk of bias. Another model for patients with hepatitis B that included circulating tumor DNA had an AUC of 0.93 (0.90-0.97); however, CIs overlapped with those of standard care, limiting the strength of the comparative claim. The ALARM model, based on radiomics and deep learning techniques, achieved an AUC of 0.92 (0.90-0.96) in a cohort of patients with cirrhosis. The fourth study identified novel hepatitis B-specific AFP cut-off for screening in a high-prevalence area, reporting an AUC of 0.999 at a pre-specified cut-off of ≥8.1ng/ml, though concerns remain about overfitting and generalizability. **Conclusion:** This review highlights four novel approaches to HCC diagnosis, encouraging diagnostic performance, particularly in the M2P-HCC and ALARM models. Prospective validation in broader populations is crucial to assess clinical and health economic impacts, alongside regulatory, interpretability, and implementation challenges. The limited number of eligible studies highlights the need for further high-quality, real-world evaluations.

Disclosures: Melissa Barlow: Nothing to Disclose, Sarah Bailey: Nothing to Disclose, Badr Albawardy: Nothing to Disclose, Sadeem Aldarwesh: Nothing to Disclose, Rowaedh Bawaked: Nothing to Disclose, Ahmed Allehebi: Nothing to Disclose, Heba Alharith: Nothing to Disclose, Asrar Alaklabi: Nothing to Disclose, Aldanah Althwanay: Nothing to Disclose, Nora Althumiri: Nothing to Disclose, Saleh Alabbad: Nothing to Disclose, Mohamed Mawardi: Nothing to Disclose, Khalid Bzeizi: Nothing to Disclose, Saleh Alessy: Nothing to Disclose, Bandar Aljudaibi: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose

3219 | SERUM TYROSINE LEVEL IS AN INDEPENDENT FACTOR FOR HEPATOCELLULAR CARCINOMA DEVELOPMENT AND MORTALITY IN PATIENTS WITH CHRONIC LIVER DISEASE

Mikita Oi[1] Takao Miwa[1] Yuki Utakata[2] Masashi Aiba[1] Shinji Unome[1] Tatsunori Hanai[1] Makoto Shiraki[2] Naoki Katsumura[2] Yasuhiro Kawashima[3] Masahito Shimizu[1],
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Background: Amino acid imbalance, with decreased branched-chain amino acids (BCAAs) and increased aromatic amino acids (AAAs) is observed in approximately 30–50% of patients with CLD. Independent contributions of serum BCAA and AAA levels to complications of chronic liver disease (CLD) have been noticed. However, very few studies have focused on their impact on hepatocellular carcinoma (HCC) development. The primary aim of this study is to investigate the effect of amino acid imbalance, including decreased BCAAs and increased AAAs, on HCC development in patients with CLD. The secondary aim is to elucidate the effect of both aspects of amino acid imbalance on mortality in these patients. **Methods:** This multicenter retrospective study included patients with CLD at two institutions in Japan. Amino acid imbalance was assessed by serum BCAA and tyrosine levels. Factors associated with HCC development was analyzed using the Fine–Gray competing risk regression model. Given HCC and overt hepatic encephalopathy as time-dependent covariates, independent determinants of mortality was evaluated using Cox proportional hazards regression model. **Results:** Among 563 patients without HCC at baseline, the median age was 67 years and 51% were male. The median Child–Pugh and MELD scores were 6 and 8, respectively. The underlying etiology of CLD was viral hepatitis (40%), followed by alcohol-associated/related liver disease (24%), metabolic dysfunction-associated steatotic liver disease (10%), and other causes (26%). During a median follow-up period of 3.5 years, 14% (n = 80) developed HCC and 23% (n = 130) died. The cumulative incidence of HCC at 1, 3, and 5 years was 4%, 11%, and 15%, respectively. Patients with high tyrosine levels (>99 μmol/L) had a significantly higher incidence of HCC than those within normal levels (1, 3, and 5 years: 4%, 16%, and 20% vs. 3%, 8%, and 11%; p = 0.002). Given mortality as a competing risk, multivariable analysis showed that serum tyrosine level (subdistribution hazard ratio [HR] 1.01; 95% CI [confidence interval] 1.00–1.02; p = 0.002) was an independent factor for HCC development. Similarly, using HCC development as a time-dependent covariate, serum tyrosine level (HR 1.01; 95% CI 1.01–1.02; p < 0.001) and HCC development (HR 2.84; 95% CI 1.72–4.69; p < 0.001) were independent factors for mortality. **Conclusion:** Serum tyrosine level is an independent factor for HCC development and mortality in patients with CLD. As HCC development affects mortality, amino acid imbalance, especially serum tyrosine levels, should be evaluated to identify high-risk populations and to improve outcomes.

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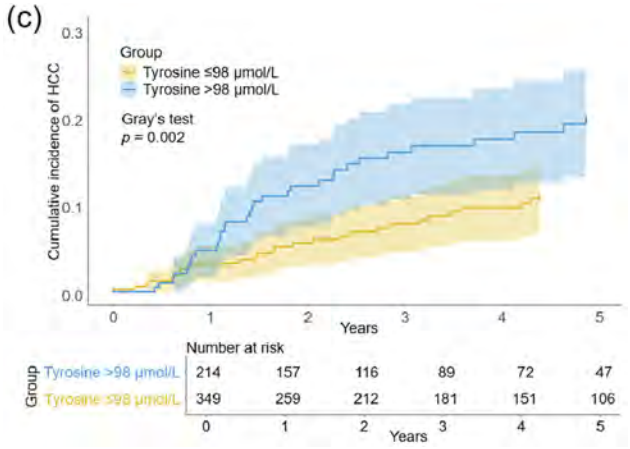

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3220 | NOVEL RISK PREDICTION SCORE FOR ACUTE CARE UTILIZATION AFTER LOCOREGIONAL THERAPY FOR HEPATOCELLULAR CARCINOMA

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Background: Locoregional therapies (LRTs) for hepatocellular carcinoma (HCC) slow tumor growth and improve survival but may cause post-treatment symptoms and decompensation events, resulting in emergency room (ER) visits and hospitalizations. Remote monitoring systems reduce acute care utilization for patients with cancer but it is unclear which HCC patients would benefit most from such resource-intensive interventions. To identify HCC patients most likely to benefit, we aimed to develop a predictive model of post-treatment acute care utilization within 90 days of LRT. **Methods:** We identified all patients with HCC treated with LRT from 4/4/2014 to 12/31/2021 in a large health system including academic and community hospitals. We extracted pre-LRT baseline characteristics and ER visits or hospitalizations (excluding planned post-LRT observation) within 90 days after LRT. We randomly divided the analytic cohort into derivation (80%) and validation (20%) cohorts. In the derivation cohort, group logistic LASSO was used to select variables for a reduced model, with the penalty term identified as that which maximized concordance (AUROC) in 5-fold cross-validation. Adjusted odds ratios are provided for (non-regularized) multivariable logistic regression models containing all predictors and those selected by the group logistic LASSO in the validation set. We compared the AUROC of our model to Child Pugh (CP), Albumin-Bilirubin (ALBI) grade (1,2, 3), and ALBI score (continuous). **Results:** This study included 819 unique patients with 1,412 separate procedures (42% bland- or chemoembolization, 35% laparoscopic or percutaneous thermal ablation, 13% radioembolization, 9% external beam radiotherapy and 1% combination/other). On a procedure-level basis, 7% of procedures were performed in patients with BCLC-0 stage HCC, 30% BCLC-A, 14% BCLC-B, 42% BCLC-C (81% based on ECOG ≥ 1 alone), 7% BCLC-D. ER visits or hospitalizations occurred within 90 days for 18% of procedures. Results of the bivariate analyses are shown in Table 1. The variables selected by the group logistic LASSO were ER visit in the prior year, hospitalization in the prior year, Charlson Comorbidity Index (based on ICD codes from the EMR), and CP Score. The multivariable logistic regression model using only these variables had an AUROC of 0.706 in the validation set compared to 0.694 using the full model, which was superior to CP score (0.611), ALBI grade (0.598) or ALBI score (0.628) only. **Conclusion:** In our cohort, acute care utilization with 90 days occurred after nearly one-fifth of LRTs. This novel predictive model of post-LRT acute care utilization had fair accuracy and outperformed CP score, ALBI grade and ALBI score. This model could help identify patients at greatest risk of post-LRT acute care utilization who may benefit from remote monitoring or enhanced patient navigation, which have been shown to reduce acute care utilization in patients with cancer.

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Table 1. Characteristics among all locoregional therapy procedures for HCC (N = 1,412)

		Acute care utilization within 90 days (n = 255)	No acute care utilization within 90 days (n = 1157)	p-value
Age (median, Q1-Q3)		63.4 (56.4 – 68.6)	65.0 (60.1 – 71.1)	**0.001**
Sex	Male	190 (75%)	901 (78%)	0.281
	Female	65 (25%)	256 (22%)	
Race	White	164 (64%)	787 (68%)	0.673
	Black	57 (22%)	235 (20%)	
	American Indian/Alaskan Native/Asian	15 (6%)	54 (5%)	
	Other/Unknown	19 (7%)	81 (7%)	
Ethnicity	Hispanic	17 (7%)	61 (5%)	0.485
	Non-Hispanic/ Unknown	238 (93%)	1096 (95%)	
Marital status	Single	63 (25%)	294 (25%)	0.702
	Married/partnered	140 (55%)	604 (52%)	
	Separated/divorced/ widowed/unknown	52 (20%)	259 (22%)	
ER visit within prior 12 months (%)		114 (45%)	231 (20%)	**<0.001**
Hospitalization within prior 12 months (%)		94 (37%)	203 (18%)	**<0.001**
Charlson comorbidity score (median, Q1-Q3)		9 (7 – 12)	7 (6 – 11)	**<0.001**
Etiology of liver disease	MASLD	50 (20%)	205 (18%)	0.548
	ALD	28 (11%)	125 (11%)	
	HCV	79 (31%)	432 (37%)	
	HBV	9 (4%)	41 (4%)	
	Other	66 (26%)	260 (22%)	
	Multiple	23 (9%)	94 (8%)	
Cirrhosis	No	39 (15%)	176 (15%)	>0.999
	Yes	216 (85%)	981 (85%)	
Child Pugh score	A	134 (53%)	746 (64%)	**<0.001**
	B7	26 (10%)	191 (17%)	
	B8	29 (11%)	111 (10%)	
	B9	28 (11%)	66 (6%)	
	C	38 (15%)	43 (4%)	
ECOG PS	0	135 (53%)	649 (56%)	0.251
	1	80 (31%)	347 (30%)	
	2	30 (12%)	140 (12%)	
	3	9 (4%)	19 (2%)	
	4	1 (0%)	2 (0%)	
BCLC stage	0	14 (5%)	90 (8%)	**<0.001**
	A	65 (25%)	357 (31%)	
	B	30 (12%)	171 (15%)	
	C	110 (43%)	480 (41%)	
	D	36 (14%)	59 (5%)	
Prior LRTs	0	151 (59%)	617 (53%)	0.231
	1	56 (22%)	294 (25%)	
	>2	48 (19%)	296 (26%)	

Disclosures: Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant, Chidi Iloabachie: Nothing to Disclose, Merete Lund: Nothing to Disclose, Arjun Juneja: Nothing to Disclose, Patrick Hazelrigg: Nothing to Disclose, Parsa Pazooki: Nothing to Disclose, Sydney Power: Nothing to Disclose, Gabriel Lupu: Nothing to Disclose, Joyce Badal: Nothing to Disclose, Yue Jiang: Nothing to Disclose, David Seligson: Nothing to Disclose, Hanna Sanoff: Nothing to Disclose, David Mauro: Nothing to Disclose, David Gerber: BMI OrganBank: CMO, Theodore Yanagihara: Nothing to Disclose, Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant, Target-RWE: Consultant, Madrigal Pharmaceuticals: Consultant, Merck (Any division): Consultant, Boehringer Ingleheim: Consultant

3221 | THE MECHANISM OF M5C METHYLATION REGULATED ENERGY METABOLIC REPROGRAMMING OF HEPATOCELLULAR CARCINOMA MEDIATED BY ALYREF/UGP2 SIGNALING AXIS INVOLVED IN TUMOR PROGRESSION

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Background: The molecular mechanism of hepatocellular carcinoma (HCC) development has been the focus of research, due to the low early diagnosis rate of HCC and poor clinical prognosis. RNA methylation modification plays an important regulatory role in tumor progression, whereas, the mechanism of m5C methylation "reader" protein ALYREF in HCC progression has not been reported.We found that ALYREF was highly expressed in HCC tissues and correlated with clinical prognosis.ALYREF can affect the proliferation of tumor cells by targeting UGP2 expression in the m5C methylation-dependent manner. **Methods:** Based on public database, we explored the expression level of ALYREF in pan-tumor and, liver cancer tissues and liver cancer cell lines, separately, furthering searching for the influence of ALYREF expression on the prognosis of HCC and the characteristics of the mutation sites of ALYREF. We explored the effect of knockdown ALYREF on the biological behavior of tumor cells through lentivirus transfection technique, screened ALYREF targets by m5C methylated RNA immunoprecipitation sequencing (m5C MeRIP-seq). The binding effect of UGP2 and ALYREF protein through RNA pulldown technology. **Results:** The results showed that the expression of ALYREF was significantly increased in HCC tissues, and the up-regulated ALYREF was closely related to the poor prognosis of HCC patients based on public database. The proliferation ability of HCC cells was significantly inhibited after the expression of knockdown ALYREF, and the proportion of apoptosis was significantly increased. Further in vivo experiments confirmed that knockdown ALYREF expression could significantly reduce the tumor size and tumor weight of subcutaneous liver cancer in nude mice. The results of m5C MeRIP-seq revealed the change of m5C modification level in cells of the knockout ALYREF group, and screened a number of genes with decreased m5C methylation level after

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knockout ALYREF. The binding effect of UGP2 and ALYREF protein through RNA pulldown technology, confirmed that UGP2 is the downstream target of ALYREF. The change of m5C methylation level of UGP2 after the knockout of ALYREF, confirmed that ALYREF regulated UGP2 expression by m5C methylation mode. The differentially expressed genes were screened in the knockdown ALYREF cells group. GSEA enrichment analysis was performed on differential genes, found that more than 20 genes that play key roles in the WNT pathway are significantly enriched. **Conclusion:** We found that WNT pathway regulates the m5C methylation modification level of UGP2 by mediating ALYREF, and is involved in the process of cellular glycolysis metabolism to affect the progression of HCC, which has certain theoretical significance and application value and can provide potentially effective drug targets for the treatment of HCC.

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3222 | SERUM METABOLOMIC SIGNATURES PREDICT TUMOR RECURRENCE AFTER RESECTION OR ABLATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Ashwini Arvind[1] Hiroaki Kanzaki[1] Sneha Deodhar[1] Kevin Bass[1] Julia Terrell[1] Courtney Katz[1] Naoto Kubota[2] Naoto Fujiwara[3] Yujin Hoshida[4] Amit Singal[1], [1]UT Southwestern Medical Center, [2]Keio University, [3]Mie University, [4]University of Texas Southwestern Medical Center

Background: Hepatocellular carcinoma (HCC) recurrence occurs in over half of patients who achieve complete response to treatment, potentially reflecting aggressive tumor biology. Serum metabolites reflect cellular metabolic activity and may serve as noninvasive surrogates of tumor behavior. Prior studies have suggested fatty acid-related and microbial-derived metabolites may be linked to poor prognosis. Herein, we aimed to conduct external validation of previously reported metabolite signatures[1,2] for association with HCC recurrence after resection or local ablation. **Methods:** We collected serum samples from patients diagnosed with HCC between 2015 and 2023 at UT Southwestern Medical Center and Parkland Health. All eligible patients had Barcelona Clinic Liver Cancer stage 0/A disease and achieved complete response on imaging after resection or local ablation. Serum metabolite concentrations were quantified by Metabolon, Inc. using liquid chromatography and untargeted mass spectrometry, and data were normalized to the sample median. We applied previously reported 6- and 13-metabolite signatures to stratify the patients into prognostic risk groups. We used univariable and multivariable Cox regression to evaluate the association between the metabolite signatures and overall recurrence, early recurrence (i.e. within two years of treatment), late recurrence, and overall death. **Results:** Of 78 eligible patients, recurrence occurred in 40 (51.3%). Early recurrence occurred in 35 (44.9%) patients, and 32 (41.0%) patients died during a median follow-up of 5.0 years. Median age at diagnosis was 62 years, and 70.5% of the cohort was male. The most common liver disease etiologies were hepatitis C (61.5%) and alcohol (12.8%). In multivariable models, the 13-metabolite signature was associated with overall recurrence (HR: 2.3, 95%CI 1.0-5.4) after adjusting for tumor-related factors. The 6-metabolite signature was associated with early recurrence (HR: 2.1, 95%CI 1.0-4.5) but not late recurrence (HR 0.5, 95%CI 0.1-2.2) after adjusting for tumor-related factors, age, and sex. **Conclusion:** Fatty acid- and microbial-derived metabolite signatures are associated with early and overall recurrence in patients with early-stage HCC and may aid prognostication.

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3223 | TEMPORAL TRENDS AND REGIONAL VARIATIONS IN HEPATOCELLULAR CARCINOMA ETIOLOGY AND ASSOCIATED CLINICAL FEATURES: A MULTINATIONAL-APASL HEPATOLOGY/ONCOLOGY CONSORTIUM (A-HOC)- STUDY ACROSS ASIA

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Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death in Asia, where over 70% of global cases occur. While recent advances in hepatitis B vaccination and antiviral therapy have reduced the burden of viral hepatitis, lifestyle-related liver diseases are increasingly recognized. This study investigated regional and temporal changes in HCC etiology and associated clinical features across Asia. **Methods:** This multinational, retrospective study included 6,261 patients with newly diagnosed HCC from 19 institutions across seven Asian countries and regions, between 2013 and 2023, as part of the APASL Hepatology/Oncology Consortium (A-HOC). Data on demographics, tumor characteristics, underlying liver disease, and initial treatments for HCC were analyzed. HCC etiologies included hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease (ALD), metabolic dysfunction-associated fatty liver disease (MAFLD), MAFLD with excess alcoholic (a daily alcohol consumption of $\geq$30 g and $<$60 g for men, and $\geq$20 g and $<$60 g for women) intake (MAFLD+AL), autoimmune disease, and cryptogenic causes. **Results:** Tumor size and Barcelona Clinic Liver Cancer (BCLC) stage varied by etiology and region. HBV remained dominant (43.3%–69.5%) and stable in most countries and regions. While HCV was the leading cause of HCC in Japan (33.1%) with a marked decline over time probably due to the anti-HCV therapy ($p < 0.01$). The prevalence of MAFLD-related HCC increased in Japan and Turkey, whereas ALD-related HCC rose in South Korea. The tumor size at presentation is smaller in Japan and Taiwan, in contrast, China and Indonesia exhibited more advanced-stage presentations and larger tumors, reflecting the timing of the detection. Treatment patterns reflected these differences; curative treatments were more common in Japan and Taiwan, while systemic therapy and no treatment were more frequent in Indonesia. **Conclusion:** This large-scale study highlights clear regional disparities and evolving etiological trends of HCC in Asia. While viral hepatitis remains the major cause overall, the rising impact of MAFLD and ALD requires region-specific surveillance and prevention strategies. Moreover, differences in tumor burden and treatment selection may contribute to regional variations in prognosis. Strengthening early detection programs and addressing gaps in access to care—particularly for viral hepatitis and metabolic liver disease—are essential to improve outcomes in Asia.

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3224 | HEPATOCELLULAR CARCINOMA SCREENING ADHERENCE IS ASSOCIATED WITH HIGHER CURATIVE INTENT SURGICAL RESECTION RATE

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Background: Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer worldwide. Surgical resection is an effective local-regional therapy for early-stage HCC. International guidelines recommend HCC screening be performed every 6 months for at-risk populations, though screening remains underutilized and there is limited data on whether adherence to screening guidelines affect surgical resection candidacy. Our study aims to determine if HCC screening adherence impacts the likelihood of receiving curative intent surgical resection. **Methods:** A retrospective study of adults with cirrhosis was performed, including only those with at least two visits with a hepatologist at our institution between 2018-2022. HCC screening compliance was defined as completion of abdominal imaging within one year of their first hepatology appointment and second abdominal imaging within one year after their second appointment. A sub-group of patients who had undergone resection of primary intrahepatic malignancy at our institution was also identified. Statistical analysis was performed using Wilcoxon rank sum, Pearson's Chi-squared, Mann-Whitney U and Fisher's exact tests. **Results:** There were 1,992 patients with at least 2 visits with a hepatologist in our institution during our study period. Of those, 625 patients were compliant with screening and 1,367 patients were non-compliant. In total, 14 patients had undergone resection of primary intrahepatic malignancy; 9 (1.4%) patients were in the screening compliant group and 5 (0.4%) patients were in the non-compliant group ($p = 0.016$). Subgroup analysis demonstrated 33% 5-year transplant free survival rate after surgical resection in the screening compliant group, as compared to 0% in the non-compliant group ($p = 0.417$). There were no statistically significant differences in tumor burden, BCLC or TNM staging, cirrhosis etiology, MELD or age at diagnosis between the screening compliant and non-compliant patients with surgical resection. **Conclusion:** Compliance with HCC screening is associated with a higher rate of curative intent surgical resection in our retrospective study. The likelihood of surgical resection is not associated with other patient or disease characteristics, which further demonstrates the importance of screening at-risk individuals. Early diagnosis of HCC through screening may improve the candidacy for curative intent surgical resection.

Characteristics	Overall	Non-Adherent	Adherent	p-value
	N = 1,992	N = 1,367	N = 625	
Sex				0.043
Male	1,017 (51%)	677 (50%)	340 (54%)	
Female	975 (49%)	690 (50%)	285 (46%)	
Age	64 (54.7, 71)	64 (55, 71)	63 (53, 70)	0.02
Race				0.17
White	1,690 (85%)	1,169 (86%)	521 (83%)	
Black	166 (8.3%)	103 (7.5%)	63 (10%)	
Other/Multiracial	76 (3.8%)	50 (3.7%)	26 (4.2%)	
Unavailable/Declined	60 (3.0%)	45 (3.3%)	15 (2.4%)	
Ethnicity				0.13
Not Hispanic	1,847 (93%)	1,264 (93%)	583 (93%)	
Hispanic	81 (4.1%)	52 (3.8%)	29 (4.6%)	
Unavailable/Declined	63 (3.2%)	50 (3.7%)	13 (2.1%)	
Language				0.36
English	1,934 (97%)	1,324 (97%)	610 (98%)	
Others	58 (2.9%)	43 (3.1%)	15 (2.4%)	
Marital status				0.78
Single	492 (25%)	329 (24%)	163 (26%)	
Married	1,104 (55%)	769 (56%)	335 (54%)	
Divorced	209 (10%)	142 (10%)	67 (11%)	
Widowed	125 (6.3%)	83 (6.1%)	42 (6.7%)	
Others/Unknown	62 (3.1%)	44 (3.2%)	18 (2.9%)	
Employment status				0.003
Employed	460 (23%)	334 (24%)	126 (20%)	
Not Employed	938 (47%)	625 (46%)	313 (50%)	
Retired	524 (26%)	349 (26%)	175 (28%)	
Other/Unknown	70 (3.5%)	59 (4.3%)	11 (1.8%)	
BMI	28.7 (24.8, 34.0)	28.8 (24.9, 34.4)	28.3 (24.7, 33.1)	0.031
Ascites	1,019 (51%)	636 (47%)	383 (61%)	< 0.001
Hepatic Encephalopathy	812 (41%)	480 (35%)	332 (53%)	< 0.001
Varices	785 (39%)	462 (34%)	323 (52%)	< 0.001
MELD3	15.5 (10.8, 22.3)	15.5 (10.7, 22.6)	15.3 (11.0, 21.7)	0.85
kPa	14.95 (8.60, 30.40)	14.10 (8.25, 27.00)	19.40 (9.60, 35.20)	0.005
CAP	274 (217, 324)	272 (217, 324)	278 (218, 324)	0.54
Resection	14 (0.7%)	5 (0.4%)	9 (1.4%)	**0.016**

Disclosures: Rachel McNulty: Nothing to Disclose, Ayushi Jain: Nothing to Disclose, Jessica Zangmeister:

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Nothing to Disclose, Huijin Xiao: Nothing to Disclose, Omar Sims: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Dian Chiang: Ipsen: Advisor

3225 | CLINICO-PATHOLOGICAL DIFFERENCES AND KEY GENOMIC ALTERATIONS IN MASLD-RELATED HEPATOCELLULAR CARCINOMA WITH AND WITHOUT CIRRHOSIS: INTEGRATING WHOLE-EXOME AND SANGER SEQUENCING

Ajay Duseja[1] Priya Singh[2] Muhammad Uwais Ashraf[2] Suvradeep Mitra[2] Amanjit Bal[2] Arka De[2] Divya Khosla[2] Sunil Taneja[2] Harish Bhujade[2] Naveen Kalra[2], [1]Postgraduate Institute of Medical Education & Research, [2]POST GRADUATE INSTITUTE OF MEDICAL EDUCATION AND RESEARCH

Background: In addition to clinico-pathological differences, genetic alterations may influence the occurrence of HCC in the presence or absence of cirrhosis in metabolic dysfunction-associated steatotic liver disease (MASLD). Aim of the present study was to analyse the clinico-pathological-radiological differences and compare and validate the genomic alterations identified by whole exome sequencing (WES) by next-generation sequencing (NGS) and Sanger sequencing in patients with MASLD-HCC with and without cirrhosis. **Methods:** Of 400 patients screened during the study period (January 2022 to March 2025), 322 HCC patients were enrolled, and clinicopathological and radiological differences were studied in 68 MASLD-HCC patients (53 with and 15 without cirrhosis). Fourteen gene variants identified on WES/NGS in 10 patients with MASLD-HCC (with and without cirrhosis) were further validated by Sanger sequencing in a new cohort of 10 MASLD-HCC patients and 10 patients each with Hepatitis B and C related HCC and MASLD patients without cirrhosis and HCC. **Results:** MASLD-HCC patients without cirrhosis were younger, presented with larger tumors, single lesions, less portal vein thrombosis, and more extrahepatic spread. MASLD-HCC without cirrhosis exhibited greater poorly differentiated and macrotrabecular-massive patterns on histopathology; more disease progression on treatment with no survival difference from the cirrhotic group. On WES/NGS, MASLD-HCC patients with cirrhosis had more frequent USF3, CCDC150, HNF1A, BAP1, NBN, CTNNB1, MAPK1, and MED15 gene alterations. In contrast, GNAS, TSC2 and TBP mutations were seen exclusively in non-cirrhotic MASLD-HCC. MED15 was present in 8.3% of cirrhosis vs. 1.6% in those without cirrhosis amongst the MASLD HCC. Shared mutations across both groups included UBXN11, MUC4, MAP2K3, MADCAM1, and DSPP. Sanger sequencing confirmed MED15 mutation as the most frequently altered gene, seen in (60%) MASLD-HCC, (30%) CHB-HCC, (50%) CHC-HCC, and (50%) MASLD samples. **Conclusion:** In addition to clinico-pathological-radiological differences, there are distinct differences in gene alterations among MASLD-HCC patients with and without cirrhosis demonstrated both on whole exome sequencing by NGS and Sanger sequencing. MED15 emerged as the most frequently altered gene across MASLD-HCC and demonstrated a higher frequency in HCC patients with cirrhosis.

Disclosures: Ajay Duseja: Nothing to Disclose, Priya Singh: Nothing to Disclose, Muhammad Uwais Ashraf: Nothing to Disclose, Suvradeep Mitra: Nothing to Disclose, Amanjit Bal: Nothing to Disclose, Arka De: Nothing to Disclose, Divya Khosla: Nothing to Disclose, Sunil Taneja: Nothing to Disclose, Harish Bhujade: Nothing to Disclose, Naveen Kalra: Nothing to Disclose

3226 | THE PROGNOSTIC METAL SCORE IN HEPATOCELLULAR CARCINOMA TREATED WITH TRANSARTERIAL CHEMOEMBOLIZATION PLUS MOLECULAR TARGETED AGENTS AND IMMUNOTHERAPY

Qian Chen[1] long-wang lin[1] Zhi-Cheng Jin[1] Hai-Dong Zhu[1] Gao-Jun Teng[1], [1]Zhongda Hospital, Medical School, Southeast University

Background: Transarterial chemoembolization combined with molecular targeted agents and immunotherapy represents a promising treatment strategy for unresectable hepatocellular carcinoma (uHCC). However, concerns remain regarding the increased hepatic toxicity associated with this combination regimen, which may counterbalance its survival benefit. We aimed to develop a prognostic tool to identify ideal candidates for this triple therapy. **Methods:** We retrospectively included uHCC patients with preserved liver function (Child-Pugh A/B7) who received first-line triple therapy across 13 tertiary hospitals. A prognostic score was developed in a derivation cohort (n = 378) using multivariable Cox regression and validated in an external cohort (n = 148). Restricted cubic spline analyses were used to determine optimal cut-offs for stratification of survival and radiological response. Survival outcomes across risk strata were assessed using the Kaplan-Meier curves and compared via log-rank test. Score applicability was further evaluated in a separate cohort treated with systemic therapy alone (n = 149). **Results:** A three-variable score incorporating metastatic burden, alpha-fetoprotein, and albumin-bilirubin grade (METAL score) was constructed and showed a linear association with mortality risk (overall $p < 0.001$; nonlinear $p = 0.556$). Median overall survival

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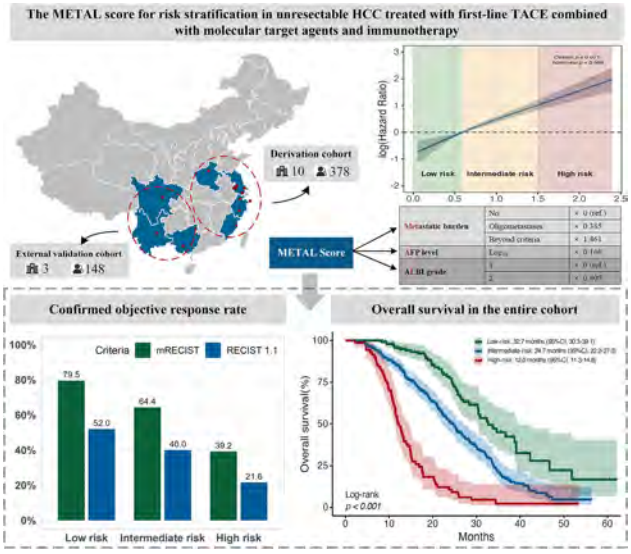
for low- (≤0.5 points), intermediate- (0.5-1.5 points), and high-risk (>1.5 points) patients was 30.8 (95% confidence interval, 27.1—42.3), 25.2 (22.5—28.8), and 11.6 (10.7—13.3) months in the derivation cohort, and 34.6 (30.5—NE), 23.0 (21.1—27.9), 14.8 (11.4—21.0) months in the external validation cohort, respectively (all log-rank $p < 0.001$). Additionally, according to either the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or the modified RECIST criteria, confirmed objective response rates decreased progressively across risk groups in both cohorts (all $p < 0.001$). Among high-risk (>1.5 points) patients, receiving systemic therapy alone yielded longer survival than triple therapy (15.6 *vs.* 12.0 months; $p = 0.024$). **Conclusion:** The proposed METAL score allows for early prediction of survival and radiological response, and may help optimize participant selection strategy for triple therapy in future clinical trials.



Disclosures: Qian Chen: Nothing to Disclose, longwang lin: Nothing to Disclose, Zhi-Cheng Jin: Nothing to Disclose, Hai-Dong Zhu: Nothing to Disclose, Gao-Jun Teng: Nothing to Disclose

3227 | PRESERVING LIVER FUNCTION: IMMUNE-CHECKPOINT INHIBITORS VS. TYROSINE KINASE INHIBITORS FOR ADVANCED HEPATOCELLULAR CARCINOMA

Avi Toiv[1] Allison Malick[1] Hayley Justus[1] Hope O'Brien[2] Gokturk Tepe[2] Hwasoo Shin[1] Sunita Ghosh[1] Reena Salgia[1], [1]Henry Ford Hospital, [2]Wayne State University School of Medicine

Background: In the era of improved systemic therapy for hepatocellular carcinoma (HCC), progressive hepatic decompensation often drive mortality rather than tumor burden alone. Over the past 5 years, immune-checkpoint inhibitors (ICI) have been supplanting tyrosine-kinase inhibitors (TKI) as first-line systemic therapy; however, studies comparing the impact of these 2 drugs on liver reserve and overall survival (OS) are limited. We examined OS and longitudinal changes in Model for End-Stage Liver Disease-3.0 (MELD-3), Child-Pugh score (CPS), and Albumin–Bilirubin (ALBI) grade in patients treated with ICI versus TKI. **Methods:** Retrospective comparative cohort study of patients with HCC initiated on ICI or TKI therapy from January 2018 to March 2025. Liver function test results at baseline and at 1, 3, 6, and 12 months of treatment were compared. OS was evaluated with Kaplan-Meier analysis. **Results:** Of 339 patients with HCC, 136 (40%) were in the ICI group; 203 (60%) were in the TKI group. Initially, TKI use was higher than ICI use. Since 2021, ICI use surpassed that of TKI (Figure 1A). No significant differences between the ICI and TKI groups were seen in age (66.7 ± 9.1 vs 64.8 ± 8.7 y), sex, or medical comorbidities, including cirrhosis. A significantly higher number of patients with BCLC stage C HCC were treated with TKI (97 vs 38; $p = 0.01$), other BCLC stages were not significantly different. At baseline, the ICI group had significantly higher median liver function scores (MELD-3.0 median: 10 vs 11; CPS: 5 vs 6; ALBI: –2.5 vs –2; $p < 0.01$). At 3 months, the ICI group continued to have superior hepatic preservation (MELD-3.0: 11 vs 13, $p = 0.02$; CPS: 6 vs 7, $p < 0.01$; ALBI: –2.2 vs –1.8; $p < 0.01$). By 6 months, significant differences between groups in all indices diminished numerically (MELD-3.0: 11 vs 12; CPS 6 vs 7; and ALBI –2.3 vs –2.0; $p > 0.05$), which persisted at 1 year. Median OS did not differ significantly between ICI and TKI groups (14.2 vs 10.5 months; Figure 1B). **Conclusion:** Patients with HCC treated with ICI showed superior preservation of liver function across all metrics during the initial 3 months of therapy compared to those treated with TKI; but this advantage was diminished by 6 months. The early improved hepatic function stability from ICI was not accompanied by a significant benefit in OS. However, this early hepatic stability suggests that ICI may have a benefit for patients at the highest risk of rapid decompensation due to aggressive tumor burden.

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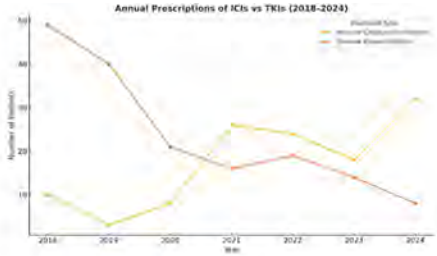


Figure 1A: Number of patients prescribed Immune-Checkpoint Inhibitors (ICIs) and Tyrosine Kinase Inhibitors (TKIs) each year from 2018 to 2024. ICIs show a rising trajectory over time, surpassing TKI use in 2021 and continuing to increase thereafter, indicating a shift in treatment patterns favoring immunotherapy.

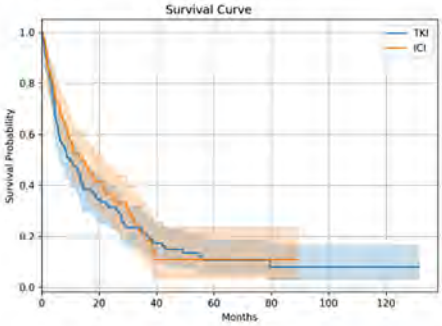


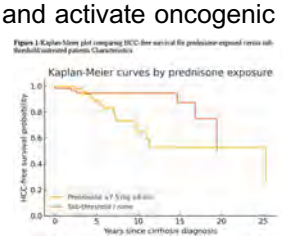
Figure 1B: Kaplan-Meier survival analysis of patients treated with immune checkpoint inhibitors (ICIs) versus tyrosine kinase inhibitors (TKIs). Median overall survival was 14.2 months in the ICI group and 10.5 months in the TKI group. There was no statistically significant difference in survival between groups (log-rank p = 0.30).

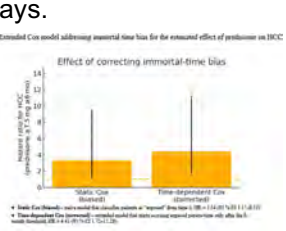
Disclosures: Avi Toiv: Nothing to Disclose, Allison Malick: Nothing to Disclose, Hayley Justus: Nothing to Disclose, Hope O'Brien: Nothing to Disclose, Gokturk Tepe: Nothing to Disclose, Hwasoo Shin: Nothing to Disclose, Sunita Ghosh: Nothing to Disclose, Reena Salgia: Eisai: Speaking and Teaching, AstraZeneca: Advisor

3228 | THE IMPACT OF LONG-TERM PREDNISONE USE ON HEPATOCELLULAR CARCINOMA RISK IN AUTOIMMUNE HEPATITIS AND CIRRHOSIS: A RETROSPECTIVE COHORT STUDY WITH LITERATURE REVIEW

Jessica Liu[1] Rami Hemadeh[2] Abdelrahman Attia[2] Pojsakorn Danpanichkul[3] Hasmik Adetyan[2] Naomy Kim[2] Tamar Yalda[2] Manaf Alsudaney[2] Walid Ayoub[2] Ju Dong Yang[2], [1]Chicago Medical School at Rosalind Franklin University of Medicine and Science, [2]Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, [3]Department of Internal Medicine, Texas Tech University Health Sciences Center

Background: Autoimmune hepatitis (AIH) is an immune-mediated liver condition marked by progressive inflammation, piecemeal necrosis, and eventual cirrhosis. Prednisone has long served as a foundational therapy for AIH. However, its prolonged use warrants closer evaluation regarding long-term outcomes. Among cirrhotic patients, the combination of chronic inflammatory and tumor-promoting changes may synergize to compromise immune surveillance and increase susceptibility to hepatocellular carcinoma (HCC). In this context, the additional immunosuppressive burden of corticosteroids may influence cancer risk in ways not yet well investigated. We evaluated whether sustained, dose-defined prednisone use after cirrhosis onset increases HCC incidence in AIH-cirrhosis, aiming to refine risk stratification and inform future therapeutic strategies while recognizing prednisone's essential role in disease control. **Methods:** We conducted a retrospective cohort analysis of 121 adults with AIH-cirrhosis evaluated at Cedars-Sinai between 2001 and 2023. Patients were categorized based on prednisone exposure: those exposed ($\geq$7.5 mg/day for $\geq$6 months following cirrhosis diagnosis) vs. subthreshold exposure (with prednisone $<$7.5 mg/d or without alternative therapies). The primary outcome was HCC incidence and annual incidence rates and hazard ratios derived from Cox proportional hazards models. Secondary outcomes included estimation of HCC incidence by treatment group and evaluation of risk factors using multivariable models adjusted per demographics and liver disease severity. **Results:** In unadjusted time-to-event analysis, prednisone use shortened HCC-free survival. HCC developed in 25.4 % of the prednisone group vs. 9.7 % of controls (p = 0.030). The annual HCC incidence was higher in the prednisone group 3.31% vs. 0.90% (p 0.0182; HR 3.31; 95% CI 1.22-8.96; p = 0.0180). Multivariable analysis adjusted per age, gender, race/ethnicity, Child-Turcotte-Pugh, and alpha-fetoprotein confirmed prednisone as an independent risk factor (adjusted HR 3.36; CI 1.06-10.66; p = 0.040). **Conclusion:** Our cohort study findings suggest that prolonged prednisone exposure in patients with established AIH-cirrhosis may independently contribute to HCC development. This association appears to be supported by mechanistic pathways, driven by prednisone's dose-dependent immunosuppressive and metabolic effects, which disrupt immune surveillance, promote hepatic fibrosis, and activate oncogenic pathways.





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3229 | INCREASED LIVER-RELATED MORBIDITY IN AUTOIMMUNE HEPATITIS–PRIMARY SCLEROSING CHOLANGITIS OVERLAP SYNDROME COMPARED TO AUTOIMMUNE HEPATITIS ALONE: A RETROSPECTIVE MULTICENTER ANALYSIS

Muhammad Hassaan Arif Maan[1] Soban Maan[2] Muhammad Mursaleen Ahmad[3] Ritik Mahaveer Goyal[4] Imran Qureshi[5] Menna-Allah Elaskandrany[6] Rohan Karkra[1] Ethan Shamsian[1] Sunnia Khan[7] Ahmed Al-Khazraji[1], [1]Rutgers-New Jersey Medical School, [2]West Virginia University, [3]Pakistan Institute of Medical Sciences, [4]Rutgers New Jersey Medical School, [5]RUTGERS THE STATE UNIVERSITY OF NEW JERSEY, [6]Lennox Hill Hospital, [7]Punjab Medical College

Background: Autoimmune Hepatitis (AIH) is a chronic inflammatory disease driven by immune-mediated hepatocyte injury. Primary Sclerosing Cholangitis (PSC) is a progressive cholestatic disorder characterized by intra- and extrahepatic biliary fibrosis. AIH-PSC overlap syndrome is a rare condition combining features of both diseases. While prior studies have compared AIH-PSC to PSC, data directly comparing AIH-PSC to AIH alone remains limited. **Methods:** We conducted a retrospective cohort study using TriNetX, a multicenter electronic health record network. Patients from January 2000 to December 2024 were categorized into two cohorts: AIH-PSC and AIH. Individuals with a prior history of cirrhosis, hepatocellular carcinoma (HCC), cholangiocarcinoma, or liver transplant were excluded. Propensity score matching (1:1) was employed to balance demographics and comorbidities, including tobacco use, alcohol-related disorders, primary biliary cholangitis, chronic kidney disease, inflammatory bowel disease, obesity, hemochromatosis, Wilson's disease, and viral hepatitis [Table 1]. Primary outcomes included incidence of cirrhosis and HCC; secondary outcomes included cholangiocarcinoma, liver transplant, hospitalization, viral hepatitis, and steroid use. **Results:** Before matching, AIH-PSC patients had significantly higher risks of cirrhosis, HCC, cholangiocarcinoma, liver transplant, viral hepatitis, and steroid use ($p < 0.05$). No difference was observed in hospitalizations. After matching, follow-up durations were comparable (1919 vs. 1715 days). Adequate balancing of all confounding covariates was achieved. Cirrhosis occurred in 53.7% of the AIH-PSC cohort vs. 33.2% in AIH (RR: 1.62, 95% CI: 1.45–1.81). HCC incidence was 2.4% vs. 1.1% (RR: 2.18, 95% CI: 1.08–4.43). Cholangiocarcinoma was seen in 1.0% of both cohorts (RR: 1.00, 95% CI: 0.42–2.39). Liver transplant occurred in 11.2% vs. 5.8% (RR: 1.95, 95% CI: 1.43–2.66). Hospitalization occurred in 34.7% vs. 29.5% (RR: 1.18, 95% CI: 1.04–1.34). Viral hepatitis was similar (6.7% vs. 6.0%, RR: 1.12, 95% CI: 0.80–1.59). Steroid use was higher in AIH-PSC (20.4% vs. 13.8%, RR: 1.48, 95% CI: 1.20–1.82). **Conclusion:** In this novel multicenter cohort study, patients with AIH-PSC overlap syndrome demonstrated a significantly higher risk of several liver-related outcomes, including cirrhosis and HCC, highlighting its more aggressive nature and greater clinical burden.

	Before Propensity Matching			After Propensity Matching		
Confounding Variable	AIH-PSC Cohort n=993	AIH Cohort n=33,494	Std Mean Diff	AIH-PSC Cohort n=990	AIH Cohort n=990	Std Diff
Demographics						
Age at Index (Mean ± SD)	37.5 ± 17.7	52.5 ± 17.4	0.856	37.5 ± 17.7	37.5 ± 17.7	<0.001
Female	517 (52.2%)	24,879 (74.3%)	0.470	517 (52.2%)	517 (52.2%)	<0.001
Male	463 (46.8%)	7,915 (23.6%)	0.499	463 (46.8%)	463 (46.8%)	<0.001
White	704 (71.1%)	21,630 (64.6%)	0.140	704 (71.1%)	704 (71.1%)	<0.001
American Indian or Alaska Native	10 (1.0%)	159 (0.5%)	0.062	10 (1.0%)	10 (1.0%)	<0.001
Native Hawaiian or Pacific Islander	10 (1.0%)	172 (0.5%)	0.057	10 (1.0%)	10 (1.0%)	<0.001
Hispanic or Latino	54 (5.5%)	2,811 (8.4%)	0.116	54 (5.5%)	54 (5.5%)	<0.001
Black or African American	157 (15.9%)	4,411 (13.2%)	0.076	157 (15.9%)	157 (15.9%)	<0.001
Asian	22 (2.2%)	1,999 (6.0%)	0.190	22 (2.2%)	22 (2.2%)	<0.001
Co-morbid Conditions						
Alcohol Related Disorders	10 (1.0%)	775 (2.3%)	0.102	10 (1.0%)	10 (1.0%)	<0.001
Tobacco Use Disorder	37 (3.7%)	2,517 (7.5%)	0.164	37 (3.7%)	37 (3.7%)	<0.001
Chronic Kidney Disease	30 (3.0%)	2,041 (6.1%)	0.147	30 (3.0%)	30 (3.0%)	<0.001
Crohn's Disease	136 (13.7%)	677 (2.0%)	0.446	136 (13.7%)	136 (13.7%)	<0.001
Ulcerative Colitis	270 (27.3%)	884 (2.6%)	0.736	270 (27.3%)	270 (27.3%)	<0.001
Primary Biliary Cholangitis	10 (1.0%)	21 (0.1%)	0.130	10 (1.0%)	10 (1.0%)	<0.001
Hemochromatosis	10 (1.0%)	230 (0.7%)	0.035	10 (1.0%)	10 (1.0%)	<0.001
Wilson's Disease	10 (1.0%)	68 (0.2%)	0.104	10 (1.0%)	10 (1.0%)	<0.001
Overweight/Obesity	84 (8.5%)	4,922 (14.7%)	0.195	84 (8.5%)	84 (8.5%)	<0.001
Viral Hepatitis	38 (3.8%)	2,558 (7.6%)	0.164	38 (3.8%)	38 (3.8%)	<0.001

SMD=Standard Mean Difference
AIH=Autoimmune Hepatitis
PSC=Primary Sclerosing Cholangitis

Table 1: Baseline Characteristics of AIH-PSC Cohort and AIH Cohort Before and After Propensity Score Matching

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3230 | TRENDS IN HEPATOCELLULAR CARCINOMA INCIDENCE BY UNDERLYING ETIOLOGY: A RETROSPECTIVE TRINETX ANALYSIS, 2010–2024

Abdallah Hussein[1] Nyan Latt[2] Islam Rajab[3] Ahmed Salem[4] Abdallatif Hussein[5], [1]Virtua Our Lady Of Lourdes Hopspital, Camden, NJ, [2]Virtua our Lady of Lourdes Hospital, [3]St Joseph University medical center hospital, Paterosn, NJ, [4]Maimonides Medical Center Brooklyn, NY, [5]Al-Najah Universirty

Background: Hepatocellular carcinoma (HCC) incidence is rising worldwide, driven by shifts in underlying liver disease etiologies. We sought to characterize temporal trends in HCC incidence attributable to nonalcoholic fatty liver disease (NAFLD), hepatitis B virus (HBV), and hepatitis C virus (HCV) from 2010 through 2024, and to examine demographic patterns across sex, race, ethnicity, and age. **Methods:** We performed a retrospective cohort study using data from the TriNetX US database between January 1, 2010, and December 31, 2024. Annual trends in HCC incidence attributable to NAFLD, HBV, and HCV were extracted and reported as incidence proportions among the corresponding at-risk populations. Stratified analyses by sex, race (American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, White, Other, Unknown), ethnicity (Hispanic/Latino vs. non-Hispanic), and 10-year age bands were conducted to evaluate demographic patterns. **Results:** A total of 42,144 new HCC cases were identified between 2010 and 2024—21,914 (52.0%) NAFLD-related, 3,129 (7.4%) HBV-related, and 17,101 (40.6%) HCV-related. NAFLD-related HCC incidence rose from 0.072% in 2010 to 0.197% in 2024 ($p < 0.01$), HBV-related from 0.122% to 0.645% ($p < 0.01$), and HCV-related from 0.139% to 0.631% ($p < 0.01$). Incidence was higher in males than females for all etiologies (NAFLD 1.568% vs 0.841%; HBV 4.255% vs 1.402%; HCV 4.842% vs 1.823%; all $p < 0.01$). By race, Asian patients had the highest etiology-specific rates (NAFLD 1.066%; HBV 4.547%; HCV 8.738%), whereas White patients had intermediate rates (NAFLD 1.210%; HBV 1.696%; HCV 3.239%). Hispanic/Latino individuals experienced higher HCC incidence for HCV (5.192% vs 3.704% non-Hispanic; $p < 0.01$). Incidence increased with age, peaking in the 75–79 year group (NAFLD 3.223%; HBV 4.377%; HCV 8.166%). **Conclusion:** From 2010 to 2024, HCC incidence increased markedly across all major etiologies, with the greatest relative rise in HBV-related cases, while HCV-related HCC remained the most common. Male sex, Asian race, Hispanic ethnicity, and older age were consistently associated with higher incidence. These findings highlight evolving epidemiology and underscore the need for tailored surveillance and preventive interventions in high-risk subgroups.

	NAFLD (%)	HBV (%)	HCV (%)
Overall incidence	1.133% (21914)	2.827% (3129)	3.569% (17101)
2010	0.072%	0.122%	0.139%
2024	0.197%	0.645%	0.631%
Female	0.841%	1.402%	1.823%
Male	1.568%	4.255%	4.842%
Race			
American Indian or Alaska Native	0.249%	3.323%	3.029%
Asian	1.066%	4.547%	8.738%
Black or African American	0.653%	1.985%	4.075%
Native Hawaiian or Other Pacific Islander	0.94%	3.917%	6.646%
Unknown Race	1.219%	2.327%	3.049%
White	1.21%	1.696%	3.239%
Other Race	1.316%	3.718%	6.32%
Ethnicity			
Hispanic or Latino	1.234%	2.271%	5.192%
Not Hispanic or Latino	1.219%	3.304%	3.704%
Unknown Ethnicity	0.998%	1.68%	2.746%
Age			
25 - 29	0.262%	1.154%	0.201%
30 - 34	0.309%	1.632%	0.386%
35 - 39	0.472%	2.291%	0.985%
40 - 44	0.647%	3.142%	2.213%
45 - 49	1.03%	3.827%	4.067%
50 - 54	1.52%	4.402%	6.253%
55 - 59	2.189%	4.358%	7.717%
60 - 64	2.729%	4.844%	7.788%
65 - 69	3.124%	4.998%	7.493%
70 - 74	3.333%	4.85%	7.726%
75 - 79	3.223%	4.377%	8.166%
80 - 84	1.842%	3.414%	5.733%
85 and older	2.23%	5.618%	3.205%

Disclosures: Abdallah Hussein: Nothing to Disclose, Nyan Latt: Nothing to Disclose, Islam Rajab: Nothing to Disclose, Ahmed Salem: Nothing to Disclose, Abdallatif Hussein: Nothing to Disclose

3231 | PLATELETS FROM PATIENTS WITH HEPATOCELLULAR CARCINOMA PROMOTE DISEASE PROGRESSION BY ENHANCING TUMOR CELL MIGRATION AND INVASION

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Background: The regulatory role of platelets in the tumor microenvironment has garnered increasing

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attention, yet their functional differences and mechanisms in hepatocellular carcinoma (HCC) progression remain unclear. We aimed to investigate platelet activation in HCC patients and examines how platelets influence HCC cell proliferation, migration, and invasion. **Methods:** Peripheral blood samples were collected from 30 HCC patients and 30 healthy volunteers. Platelets were labeled using APC anti-human CD62P (P-Selectin) and PE anti-human CD41 antibodies, and their activation levels were assessed via flow cytometry. Additionally, peripheral blood was collected from three primary HCC patients and three healthy volunteers, from which platelets were isolated and co-cultured with HepG2 and Hep3B HCC cells at a ratio of 100:1. The interactions between platelets and tumor cells were traced using CellTracker CM-DiI fluorescence labeling. After 48 hours of co-culture, platelets were removed, and HCC cell proliferation was evaluated using the CCK-8 assay. Transwell assays (with or without Matrigel coating) were performed to quantitatively assess tumor cell migration and invasion. **Results:** Flow cytometry analysis revealed that the platelet activation marker (CD62P%) was significantly elevated in HCC patients compared to healthy controls (16.39 ± 1.07 vs. 3.21 ± 0.52, $p < 0.001$). Confocal laser microscopy demonstrated prominent fusion and internalization of platelets by tumor cells in HCC patients. The CCK-8 assay indicated that tumor cells co-cultured with either HCC patient-derived or healthy donor-derived platelets exhibited significantly higher proliferation rates compared to the non-co-cultured group ($p < 0.01$), though no significant difference was observed between the HCC and healthy control platelet groups. Transwell migration assays demonstrated that tumor cells co-cultured with healthy donor platelets (359.00 ± 11.53 vs. 246.67 ± 15.04, $p < 0.001$) or HCC patient platelets (519.00 ± 31.51 vs. 246.67 ± 15.04, $p < 0.001$) exhibited significantly enhanced migration compared to non-co-cultured tumor cells. Notably, HCC patient-derived platelets exhibited a stronger promotive effect on tumor cell migration than healthy donor-derived platelets ($p = 0.001$). Similarly, invasion assays revealed that both healthy donor platelets (107.00 ± 9.17 vs. 76.47 ± 18.45, $p = 0.05$) and HCC patient platelets (152.33 ± 19.14 vs. 74.67 ± 18.45, $p = 0.007$) significantly enhanced tumor cell invasion, with HCC patient-derived platelets exhibiting a more pronounced effect ($p = 0.021$). **Conclusion:** Platelet activation levels were significantly elevated in HCC patients compared to healthy individuals. Furthermore, HCC patient-derived platelets exerted a greater promotive effect on tumor cell migration and invasion than healthy donor-derived platelets, suggesting that platelets may play a crucial role in HCC metastasis.

Disclosures: Meng Zhang: Nothing to Disclose, Muqi Wang: Nothing to Disclose, Yikai Wang: Nothing to Disclose, Chenrui Liu: Nothing to Disclose, Wenhao Wang: Nothing to Disclose, Guoe Gou: Nothing to Disclose, Yaping Li: Nothing to Disclose, Shuangsuo Dang: Nothing to Disclose

3232 | PROGNOSTIC VALUE OF TERT PROMOTER–MUTATED CFDNA AFTER CURATIVE ABLATION IN EARLY-STAGE HEPATOCELLULAR CARCINOMA

Masaru Muraoka[1] Shinya Maekawa[1] Leona Osawa[1] Shuya Matsuda[1] Yuichiro Suzuki[1] Mitsuaki Sato[1] Atsunori Tsuchiya[1], [1]University of Yamanashi

Background: *TERT* promoter mutations are frequently observed not only in advanced hepatocellular carcinoma (HCC) but also in early-stage disease. Although cell-free DNA (cfDNA) harboring this mutation is a potential target for liquid biopsy, its detection in serum remains challenging. We developed an ultra-sensitive detection method combining PNA clamping and digital PCR (referred to as the MGB-PNA clamp method), and investigated its utility in detecting *TERT* promoter–mutated cfDNA after curative treatment of HCC and its association with early recurrence. **Methods:** We enrolled 41 patients with BCLC stage 0 or A HCC who underwent curative treatment with radiofrequency ablation (RFA) or microwave ablation (MWA) in 2023. Serum samples were collected before treatment and 2 to 3 weeks after treatment. cfDNA was extracted and quantified for *TERT* promoter mutations using the MGB-PNA clamp method. The association between post-treatment mutant DNA detection and recurrence within six months was assessed. **Results:** *TERT* promoter mutations were detected in 20 of 41 patients (48.8%). Among these mutation-positive cases, the median mutant DNA concentration was 9.6 (6.5–17.0) copies/ml serum before treatment and 6.5 (0–12.0) copies/ml serum 2–3 weeks after treatment. Early recurrence within six months occurred in 10 patients overall, including 6 among the 20 mutation-positive cases. In this subgroup, we compared recurrence and non-recurrence groups. Median pre-treatment AFP levels were 4.1 (2.3–19.6) ng/ml in the recurrence group and 4.3 (2.6–5.5) ng/ml in the non-recurrence group ($P = 0.97$). A $\geq 20\%$ decrease in AFP was observed in 50% of the recurrence group and 46.2% of the non-recurrence group ($P = 1.00$), showing no significant association with early recurrence. In contrast, mutant DNA was detectable 2–3 weeks post-treatment in 100% of the recurrence group and 41.7% of the non-recurrence group ($P = 0.038$), suggesting that persistent post-ablation mutant DNA may be associated with early recurrence. **Conclusion:** Persistent detection of *TERT* promoter–mutated cfDNA after curative ablation for

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HCC may be associated with early recurrence. Further studies are warranted to validate these findings.
Disclosures: Masaru Muraoka: Nothing to Disclose, Shinya Maekawa: Nothing to Disclose, Leona Osawa: Nothing to Disclose, Shuya Matsuda: Nothing to Disclose, Yuichiro Suzuki: Nothing to Disclose, Mitsuaki Sato: Nothing to Disclose, Atsunori Tsuchiya: Nothing to Disclose

3233 | RADIATION AS AN IMMUNOLOGIC PRIMER: SCOPING THE EMERGING LANDSCAPE OF MULTIMODAL STRATEGIES IN HEPATOCELLULAR CARCINOMA

Eric Welwin[1] Viren Sehgal[1] Ibrahim Qadri[1] Samin Faiaz[1] Taseen Tanzil[1] Colin Hill[2] Brock Hewitt[2], [1]CUNY School of Medicine, [2]The NYU Grossman School of Medicine and NYU Langone Health

Background: Advanced hepatocellular carcinoma (HCC) carries a dismal prognosis, with many patients ineligible for curative resection or transplantation. While radiotherapy has historically been limited by toxicity concerns, advances in techniques like stereotactic body radiation therapy (SBRT), volumetric modulated arc therapy (VMAT), and non-ionizing modalities (such as histotripsy) have renewed interest as a means to overcome treatment resistance. Importantly, emerging data suggest that combining radiotherapy with systemic therapies (immunotherapy, targeted agents, gene modulation) can yield synergistic antitumor effects exceeding monotherapy. This review synthesizes the evolving landscape of radiation-based combination therapies in HCC, exploring mechanisms of synergy, outcomes, and persistent challenges. **Methods:** A scoping review was conducted across clinical trials, preclinical studies, and translational research. Eligible studies involved combinations of SBRT or other radiotherapy modalities with immune checkpoint inhibitors, anti-angiogenic therapies, gene-modulating agents (e.g., microRNAs), or physical techniques such as VMAT or histotripsy. Data was extracted and organized to characterize efficacy outcomes, mechanistic interactions, and toxicity profiles. **Results:** We found that multiple combination strategies demonstrated consistent therapeutic synergy. SBRT combined with PD-1 inhibitors (e.g., sintilimab) showed objective response rates up to 96% and favorable safety in second-line settings. SABR-ipilimumab regimens elicited systemic immune responses, including potential abscopal effects. Triplet therapies with SBRT, lenvatinib, and PD-1 blockade extended median overall survival beyond 30 months. Co-therapies with miR-22-3p and miR-29a-3p sensitized tumors to sorafenib by downregulating pathways such as STK26 and AKT3. VMAT improved precision in treating tumors near radiosensitive structures, while histotripsy combined with local heat enhanced cytotoxicity and immune priming in preclinical models. **Conclusion:** Radiation-based combination strategies are reshaping the therapeutic landscape of hepatocellular carcinoma, offering synergistic gains in both locoregional control and systemic antitumor response. The integration of immunotherapy, anti-angiogenic agents, and gene-targeting modalities with precision radiotherapy holds substantial promise for patients with limited treatment options. However, optimizing therapeutic sequencing, identifying precise biomarkers, and addressing disparities in access to radiation platforms remain critical challenges. These findings strongly advocate for a paradigm shift in HCC treatment, with radiation-based combination therapies poised to become a cornerstone of future clinical practice. Large-scale trials are imperative to validate these results and define optimal implementation strategies.

Reference	Treatment Type	Clinical Scenario	Outcome	Year Published
Chen et al.	SBRT + sintilimab	Oligometastatic HCC	68% and 45.3% mPFS, 91.5% and 83.2% mOS, at 12 and 24 mo, respectively. 1 and 2 year LCR were 100% and 90.9%, respectively. 96% ORR and 96% DCR	2023
He et al.	SABR + Ipilimumab	Liver or lung metastases from non-melanoma cancers	61%, 23%, and 15% mOS for 12, 36, and 60 months, respectively. 2.93 months mPFS	2023
Wang et al.	SBRT + Lenvatinib + PD-1	Unresectable HCC	31.2 months mOS and 15.6 months mPFS. 63% ORR	2024
O'Kane et al.	SBRT + Pembrolizumab	Advanced HCC	41% ORR, 5.4 months mPFS and 12.6 months mOS	2025
Cantaloube et al.	VMAT + SBRT	Inoperable HCC	1 year OS and DSF 83.9% and 46.7%, respectively	2021
Li et al.	miR-22-3p + sorafenib	HCC	Inhibition by upregulation of STK26, ATG4B, and p-ATG4B	2024
Wang et al.	miR-22-3p + miR-29a-3p	Liver fibrosis	Proliferation, migration and activation of LX-2 cells were inhibited	2022
Dai et al.	Histotripsy + Heating	In Vitro VX2 cancer cells	Reduction of normalized concentration of living cells and proliferation rate of residual cells	2025

Disclosures: Eric Welwin: Nothing to Disclose, Viren Sehgal: Nothing to Disclose, Ibrahim Qadri: Nothing to Disclose, Samin Faiaz: Nothing to Disclose, Taseen Tanzil: Nothing to Disclose, Colin Hill: Nothing to Disclose, Brock Hewitt: Nothing to Disclose

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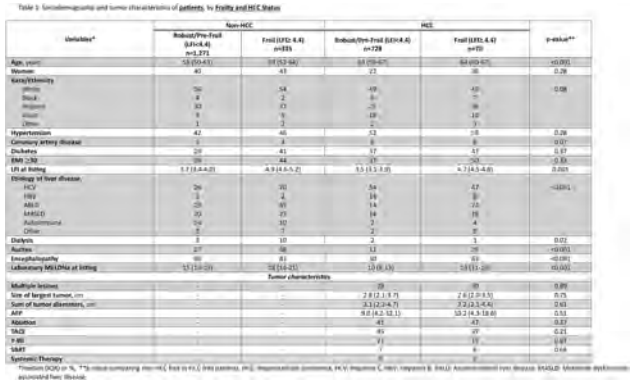
3234 | ASSOCIATION BETWEEN TUMOR BURDEN AND FRAILTY IN LIVER TRANSPLANT CANDIDATES WITH HEPATOCELLULAR CARCINOMA

Gabrielle Jutras[1] Melinda Wang[2] Aryana Far[1] Michael Li[1] Jin Ge[1] Jennifer Lai[1], [1]University of California, San Francisco, [2]Yale University

Background: Frailty studies in liver transplantation (LT) candidates have largely focused on patients with cirrhosis *without* hepatocellular carcinoma (HCC). However, HCC patients represent a distinct subgroup of LT candidates who are older with better compensated liver disease and more non-hepatic comorbidities. These factors, in addition to HCC tumor burden may influence both the prevalence and underlying contributors to frailty. We aimed to characterize and compare frailty in HCC versus non-HCC LT candidates. **Methods:** We included adults with cirrhosis listed for LT at a single U.S. transplant center (2012-2024) who underwent ambulatory frailty assessment using the Liver Frailty Index (LFI; "frail" = LFI $\geq$ 4.4). HCC tumor characteristics at diagnosis—including number of lesions, tumor size, AFP levels, and initial treatment—were extracted using validated automated data capture. Logistic regression was used to evaluate associations between tumor characteristics and frailty. **Results:** Of 2,420 LT candidates, 801 (33%) had HCC. Frailty was observed in only 9% of HCC candidates, compared to 21% of non-HCC candidates. Among those who were frail, HCC candidates were older, had lower laboratory MELDNa scores, and lower rates of ascites, hepatic encephalopathy and dialysis compared to non-HCC candidates (Table). Rates of hypertension and diabetes were similar between groups, though HCC candidates trended toward more coronary artery disease. Among frail vs. non-frail HCC LT candidates, tumor burden, total tumor diameter, and AFP were comparable ($p > 0.21$). These tumor characteristics were not associated with frailty in uni- and multi-variable analyses. **Conclusion:** In this large cohort of HCC LT candidates, frailty was associated with established hepatic (e.g., MELD, ascites, HE) and non-hepatic (e.g., gender, comorbidities) factors but not associated with tumor characteristics. This differs from patients with non-HCC malignancy, in whom cancer-related frailty is common. In LT candidates with HCC, who generally have well-compensated liver disease, the presence of frailty more likely reflects advanced non-hepatic co-morbidities that are less likely to resolve with LT. This highlights the need for studies specifically investigating the contributors to frailty unique to patients with HCC.



Disclosures: Gabrielle Jutras: Nothing to Disclose, Melinda Wang: Nothing to Disclose, Aryana Far: Nothing to Disclose, Michael Li: Nothing to Disclose, Jin Ge: Merck and Co: Grant/Research Support, Iota Biosciences/Astellas Pharmaceuticals: Consultant, Madrigal Pharamaceuticals: Consultant, Gilead Sciences: Advisor, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI

3235 | EVALUATION OF FACTORS AFFECTING ALPHA FETOPROTEIN LEVELS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA IN A LARGE MULTICENTRE COHORT

Ethan Kai Jun Tham[1] Cheng Han Ng[2] Nicole Shu Ying Tang[3] Nicholas Syn[4] Ken Liu[5] Gang Chen[6] Beom Kyung Kim[7] Mark Muthiah[8] Takumi Kawaguchi[9] Asahiro Morishita[10] Sung Won Lee[11] Karn Wijarnpreecha[12] Hirokazu Takahashi[13] Daniel Huang[14], [1]Yong Loo Lin School of Medicine, [2]Division of Gastroenterology and Hepatology, National University Hospital, Singapore, Singapore, [3]Yong Loo Ling School of Medicine, National University of Singapore, Singapore, [4]National University of Singapore, Department of Biomedical Informatics, Yong Loo Lin School of Medic, [5]Royal Prince Alfred Hospital, [6]Wenzhou Medical University, [7]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [8]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [9]Kurume University School of Medicine, [10]Department of Gastroenterology, Kagawa University Graduate School of Medicine, Kagawa, Japan, [11]Division of Hepatology, Department of Internal Medicine, Catholic University of Korea, Seoul, Republ, [12]University of Arizona College of Medicine-Phoenix, [13]Division of Metabolism and

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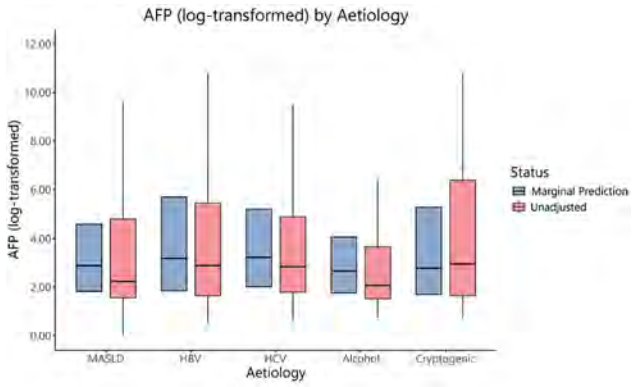
Background: Alpha-fetoprotein (AFP) remains the most widely used biomarker for hepatocellular carcinoma (HCC), yet its clinical utility is hindered by wide inter-individual variability. Traditional linear regression methods may oversimplify these complex patterns, masking important insights. To address this, we employed quantile regression—a powerful technique that captures differential predictor effects across the AFP distribution—to better elucidate the nuanced influence of demographic and clinical factors. **Methods:** This international multicentre retrospective cohort study analysed data from adult HCC patients across nine tertiary institutions between 1 January 2003 and 27 December 2021. Quantile regression was applied at the 0.10, 0.50, and 0.90 quantiles of AFP to characterise how predictor effects vary across its distribution. Logistic regression was also performed, stratifying AFP into <20 ng/mL and ≥ 20 ng/mL groups, to enable direct comparison with conventional analytical approaches. **Results:** A total of 2,298 HCC patients were included, with a median AFP of 13.70 ng/mL (IQR: 4.10–182.85). Multivariable quantile regression revealed striking heterogeneity: Asian ethnicity, elevated AST/ALT, advancing BCLC stage, and HBV or HCV aetiologies were associated with higher AFP levels, particularly in upper quantiles. In contrast, male sex, older age, and elevated creatinine predicted lower AFP levels. Compared to MASLD, HBV ($\beta = 0.44$, 95% CI: 0.05–0.83) and HCV ($\beta = 0.30$ at Q10; $\beta = 0.40$ at Q50) were consistently associated with higher AFP. Logistic regression identified similar predictors but failed to detect the distribution-specific effects captured by quantile regression. **Conclusion:** This study highlights the substantial heterogeneity in how clinical factors shape AFP levels across its distribution. These findings challenge the oversimplified reliance on fixed AFP thresholds and advocate for a more nuanced, distribution-aware interpretation of this widely used biomarker in HCC.



Disclosures: Ethan Kai Jun Tham: Nothing to Disclose, Cheng Han Ng: Nothing to Disclose, Nicole Shu Ying Tang: Nothing to Disclose, Nicholas Syn: Nothing to Disclose, Ken Liu: Nothing to Disclose, Gang Chen: Nothing to Disclose, Beom Kyung Kim: Nothing to Disclose, Mark Muthiah: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching, Asahiro Morishita: Nothing to Disclose, Sung Won Lee: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Daniel Huang: Gilead: Consultant, Roche: Speaking and Teaching

3236 | TRANSARTERIAL CHEMOEMBOLIZATION COMBINED WITH SORAFENIB VERSUS MONOTHERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA: AN UMBRELLA REVIEW OF META-ANALYSES

Ruchir Paladiya[1] Vikash Karmani[2] Krishan Joshi[3] Vikash Kumar[4] Aalam Sohal[4] Neil Parikh[5], [1]University of Connecticut health center, [2]Jinnah Sindh Medical University, [3]California Health Sciences University, College of Osteopathic Medicine, [4]Creighton University, [5]Hartford Hospital

Background: This umbrella review aimed to synthesize evidence from previously conducted meta-analyses and review articles to compare transarterial chemoembolization combined with sorafenib versus monotherapy for unresectable hepatocellular carcinoma. **Methods:** While adhering to the PRIOR guidelines, PubMed, Google Scholar, Web of Science, and Scopus were searched from database inception to December 2024 to identify relevant articles. The outcomes of interest included (1) Overall, (2) Time to Progression, (3) Disease Control Rate, and (4) Objective Response Rate. A Corrected Covered Area (CCA) assessment was performed to determine the overlap between reviews. The quality and rigor of each included review were assessed using the AMSTAR-2 tool. **Results:**

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Nine meta-analyses were included from the 13,821 articles identified during the literature search; 9 meta-analyses were included. A significant overlap was noted across studies, with a corrected coverage area of 49%. Eight reviews assessed overall survival, with five reporting a significant survival benefit (HR range: 0.62–0.74, $P < 0.001$), while two found no significant effect (HR range: 0.75–0.97, $P > 0.05$). Similarly, eight reviews examined the time to progression, with six showing a significant risk reduction (HR range: 0.61–0.75, $P < 0.05$), whereas two reported non-significant findings (HR: 0.74–0.77, $P > 0.05$). Four reviews evaluated the disease control rate, with two reporting a significant benefit (OR range: 0.52–4.72, $P < 0.01$), one showing a non-significant trend (OR: 1.57, $P = 0.059$), and one finding no effect (RR: 1.04, $P = 0.568$). Six reviews assessed the objective response rate, with three reporting a significant increase in risk (OR range: 2.19–3.59, $P < 0.01$) and one showing a potential reduction in risk (OR: 0.85, $P = 0.0006$). One review found no significant effect (RR: 1.20, $P = 0.257$), while another reported a protective effect (OR: 0.39, $P = 0.008$). **Conclusion:** This umbrella review highlights the efficacy of TACE plus sorafenib in improving the time to progression, objective response rate, and overall survival in patients with unresectable HCC. This underscores the need for personalized treatment and further research to refine protocols.

Figure 2: Forest plots from nine meta-analyses (four to eight studies in each category) assessing overall survival, time to progression, disease control rate, and objective response rate.

Disclosures: Ruchir Paladiya: Nothing to Disclose, Vikash Karmani: Nothing to Disclose, Krishan Joshi: Nothing to Disclose, Vikash Kumar: Nothing to Disclose, Aalam Sohal: Nothing to Disclose, Neil Parikh: Nothing to Disclose

3237 | PROTEINURIA AND ITS CLINICAL IMPLICATIONS IN HCC PATIENTS TREATED WITH ATEZOLIZUMAB/BEVACIZUMAB: A MULTICENTER REAL-WORLD STUDY

Yu Rim Lee[1] Sung Bum Cho[2] Hyun Young Woo[3] Jae Hyun Yoon[4] Jun Sik Yoon[5] yeowool kang[6] Jeong Eun Song[7] Young Mi Hong[8] Sang Youn Hwang[9] Joonho Jeong[10] Jeong Heo[3] Young Oh Kweon[11] Yang Hyun Baek[6] Soo Young Park[11] Won Young Tak[12], [1]Kyungpook National University, Kyungpook National University Chilgok Hospital, [2]Chonnam National University Hwasun Hospital and Chonnam National University Medical School, [3]Pusan National University and Medical Research Institute, Pusan National University Hospital, [4]Chonnam National University Hospital, [5]Busan Paik Hospital, Inje University College of Medicine, [6]Dong-A University Hospital, [7]Daegu Catholic University School of Medicine, [8]Pusan National University School of Medicine, Pusan National University Yangsan Hospital, [9]Dongnam Institute of Radiologic & Medical Sciences, [10]University of Ulsan College of Medicine, Ulsan University Hospital, [11]Kyungpook National University, Kyungpook National University Hospital, [12]School of Medicine, Kyungpook National University

Background: Atezolizumab/bevacizumab (atezo/bev) has been demonstrated as an effective first-line treatment for hepatocellular carcinoma (HCC). Proteinuria is one of the common adverse events of atezo/bev therapy. Therefore, we evaluated the Prevalance and risk factors for proteinuria in patients treated with atezo/bev for unresectable HCC in a large, multicenter real-world population. **Methods:** From July 2020 to October 2024, this retrospective cohort study included 869 patients with HCC from 9 tertiary hospitals who were treated with atezo/bev. The level of proteinuria was evaluated based on the Common Terminology Criteria for Adverse Events version 5.0. **Results:** After excluding 242 patients due to unavailable baseline urinalysis results or confirmed proteinuria, a total of 627 patients were included in the analysis. During a median follow-up of 8.1 months, 127 (20.3%) patients developed proteinuria at a median of 3.6 months. Three patients permanently discontinued atezo/bev due to proteinuria, and 12 patients temporarily discontinued or reduced the dose of atezo/bev. Treatment duration of atezo/bev was not significantly different between the proteinuria and non- proteinuria groups.

However, both overall survival and progression-free survival were significantly higher in patients with proteinuria compared with patients without proteinuria (log-rank test: $P < 0.001$, $P < 0.001$, respectively). In the multivariate analysis, proteinuria was significantly associated with the presence of hypertension and serum creatinine level (all $P < 0.05$). **Conclusion:** The occurrence of proteinuria during atezo/bev treatment in patients with advanced HCC is not associated with a poor prognosis if treated appropriately.

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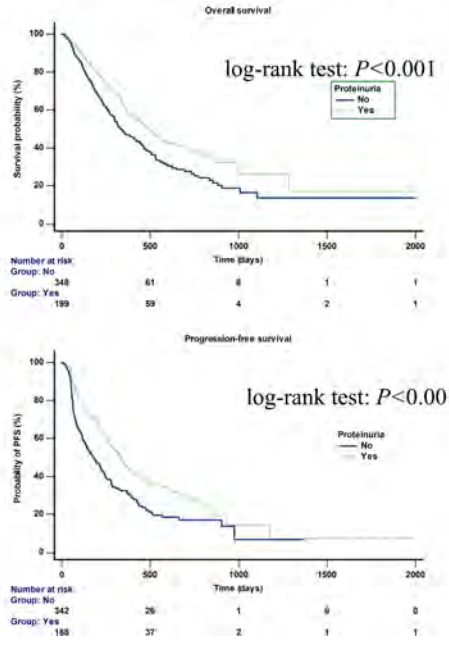
Fig. 1. (A) Overall survival (OS) and (B) progression-free survival (PFS) according to proteinuria in patients receiving atezo/bev.



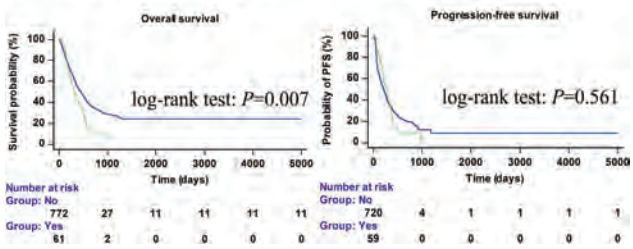
Disclosures: Yu Rim Lee: Nothing to Disclose, Sung Bum Cho: Nothing to Disclose, Hyun Young Woo: Nothing to Disclose, Jae Hyun Yoon: Nothing to Disclose, Jun Sik Yoon: Nothing to Disclose, yeowool kang: Nothing to Disclose, Jeong Eun Song: Nothing to Disclose, Young Mi Hong: Nothing to Disclose, Sang Youn Hwang: Nothing to Disclose, Joonho Jeong: Nothing to Disclose, Jeong Heo: Gilead: Grant/Research Support, Roche: Speaking and Teaching, Yuhan: Speaking and Teaching, Abbvie: Speaking and Teaching, AstraZeneca: Advisor, Oncolys Japan: Grant/Research Support, Surrozen: Advisor, MedVir: Advisor, Young Oh Kweon: Nothing to Disclose, Yang Hyun Baek: Nothing to Disclose, Soo Young Park: Nothing to Disclose, Won Young Tak: Nothing to Disclose

3238 | BLEEDING COMPLICATIONS AND SURVIVAL OUTCOMES IN HCC PATIENTS TREATED WITH ATEZOLIZUMAB/BEVACIZUMAB: MULTICENTER REAL-WORLD STUDY

Yu Rim Lee[1] Sung Bum Cho[2] Hyun Young Woo[3] Jae Hyun Yoon[4] Jun Sik Yoon[5] yeowool kang[6] Jeong Eun Song[7] Young Mi Hong[8] Sang Youn Hwang[9] Joonho Jeong[10] Jeong Heo[3] Young Oh Kweon[11] Yang Hyun Baek[6] Soo Young Park[11] Won Young Tak[11], [1]Kyungpook National University, [2]Chonnam National University Hwasun Hospital and Chonnam National University Medical School, [3]Pusan National University and Medical Research Institute, Pusan National University Hospital, [4]Chonnam National University Hospital, [5]Busan Paik Hospital, Inje University College of Medicine, [6]Dong-A University Hospital, [7]Daegu Catholic University School of Medicine, [8]Pusan National University School of Medicine, Pusan National University Yangsan Hospital, [9]Dongnam Institute of Radiologic & Medical Sciences, [10]University of Ulsan College of Medicine, Ulsan University Hospital, [11]Kyungpook National University, Kyungpook National University Hospital

Background: Atezolizumab/bevacizumab (atezo/bev) have been demonstrated as an effective first-line treatment for hepatocellular carcinoma (HCC). However, the risk of bleeding complications is a major concern in atezo/bev treatment. Therefore, we evaluated the efficacy and safety with a focus on bleeding events of atezo/bev in a large, multicenter real-world population. **Methods:** From July 2020 to October 2024, this retrospective cohort study included 869 patients with HCC from 9 tertiary hospitals who were treated with atezo/bev. **Results:** During a median follow-up of 8.4 months, 112 (12.9%) patients developed bleeding episodes at a median of 3.9 months. Of these, variceal hemorrhage occurred in 62 (7.1%) patients treated with atezo/bev at a median of 5.5 months (8 cycle). Grade III or IV bleeding occurred in 35 (5.1%) patients of patients, with grade V bleeding observed in 4 (0.6%) patients. At the time of variceal bleeding, 72.9% of the patients were receiving atezo/bev. Progression-free survival was not significantly different between the variceal hemorrhage and non-variceal hemorrhage groups. However, overall survival was significantly lower in patients with variceal hemorrhage (log-rank test: $P = 0.007$). In the multivariate analysis, variceal hemorrhage was significantly associated with the presence of varices, history of variceal bleeding, and macrovascular invasion (all $P < 0.05$). **Conclusion:** Patients with advanced HCC who develop variceal bleeding during atezo/bev treatment may have a poor prognosis. It is necessary to identify high-risk group of variceal bleeding and monitor them carefully.

Fig. 1. (A) Overall survival (OS) and (B) progression-free survival (PFS) according to variceal bleeding in patients receiving atezo/bev.



Disclosures: Yu Rim Lee: Nothing to Disclose, Sung Bum Cho: Nothing to Disclose, Hyun Young Woo: Nothing to Disclose, Jae Hyun Yoon: Nothing to

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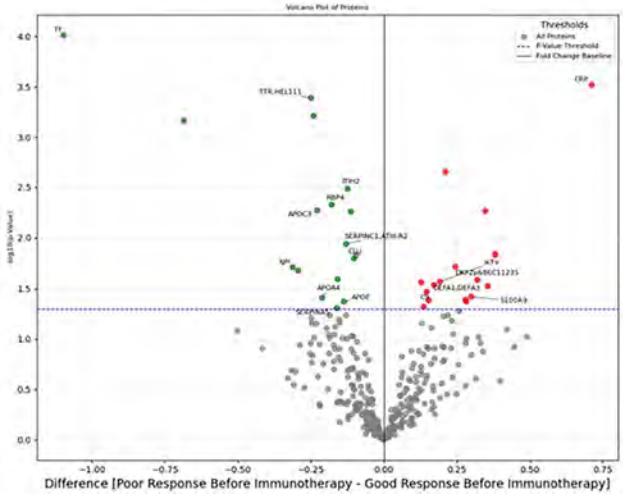
3239 | CIRCULATING SERUM PROTEINS AS PREDICTIVE BIOMARKERS FOR IMMUNOTHERAPY EFFICACY IN ADVANCED HC

Young-Sun Lee[1] Eunho Choi[1] IN HEE KIM[2] Jin Woo Lee[3] Jung Hwan Yu[3] Sung Bum Cho[4] Ha Seok Lee[1] Youngwoo Lee[1] Yang Jae Yoo[1] Seong Hee Kang[1] Taehyung Kim[1] Yim Sun Young[1] Young Kul Jung[1] Ji Hoon Kim[1] Yeon Seok Seo[1] Hyung Joon Yim[1] Jong eun Yeon[1] Kwan Soo Byun[1], [1]Korea University College of Medicine, [2]Jeonbuk National University Hospital, [3]Inha University School of Medicine, [4]Chonnam National University Hwasun Hospital

Background: Combination immunotherapies like atezolizumab with bevacizumab and durvalumab with tremelimumab are first-line standards for advanced hepatocellular carcinoma (HCC). However, predicting which patients will respond remains challenging due to the absence of validated biomarkers. This study investigates circulating serum proteins to identify predictive biomarkers for immunotherapy efficacy in advanced HCC. **Methods:** Pre-treatment serum samples from advanced HCC patients receiving atezolizumab-bevacizumab were collected across 4 academic centers. Participants were stratified into responders (stable disease, partial/complete response) and non-responders (progressive disease after three cycles). Differential protein expression between groups was analyzed via mass spectrometry-based proteomics. **Results:** The study analyzed samples from a total of 44 patients, of whom 32 were classified as responders and 12 as non-responders. The results showed that non-responders had higher serum levels of C-reactive protein (CRP) and protein S100-A9 (S100A9). In contrast, non-responders had lower levels of several other proteins, including transferrin (TF), transthyretin (TTR), apolipoprotein C-III (APOC3), clusterin (CLU), retinol-binding protein 4 (RBP4), inter-alpha-trypsin inhibitor heavy chain H2 (ITIH2), insulin-like growth factor-binding protein complex acid labile subunit (IGFALS), and antithrombin-III (SERPINC1). The analysis also revealed that proteins such as APOC3 and CLU were highly interconnected within the serum protein interaction network, indicating that they may play important roles as central hubs related to treatment response. **Conclusion:** The findings suggest that circulating serum proteins could serve as useful biomarkers for predicting how patients with advanced HCC will respond to atezolizumab and bevacizumab therapy. Identifying such biomarkers may help guide treatment decisions and improve outcomes for these patients.



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3240 | SINGLE-CELL ANALYSIS REVEALS DISTINCT IMMUNE CHARACTERISTICS OF TWO INTERACTING T CELL SUBSETS IN IMMUNOTHERAPY-RESPONSIVE HBV-ASSOCIATED HEPATOCELLULAR CARCINOMA

Wenli Xu[1] Tingfeng Xu[1] Jie Zhang[1] Mingjiang Liu[1] Pengzhan Deng[1] Qiuli Xie[1] Lijuan Liao[1] Songqing He[1], [1]The First Affiliated Hospital of Guangxi Medical University

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Background: The prognosis for hepatocellular carcinoma (HCC) remains poor, with 55%-80% of cases linked to hepatitis B virus (HBV) infection. While immunotherapy has demonstrated potential in improving clinical outcomes, its benefits are limited to a small subset of patients. By systematically analyzing the tumor immune microenvironment in responders to immunotherapy, we can obtain critical insights into the underlying immune response mechanisms. **Methods:** To identify cell subsets involved in the immune response to immunotherapy in HBV-HCC, we collected tumor and adjacent liver tissues and PBMCs from two responding HBV-HCC patients. We used scRNA-seq and scTCR-seq to characterize cell clusters with distinct functions. These clusters were analyzed using univariate, multivariate, and survival analyses based on TCGA and GSE14520 data. Differences between responders and non-responders were validated using GSE206325. Spatial distribution was elucidated using skrxzf279n. Finally, findings were confirmed in an independent cohort of 28 HBV-HCC patients. **Results:** Here, we identified two interacting T cell subsets using scRNA-seq. CD8-Pro-T cells, characterized by high expression of proliferation-associated markers such as MKI67, exhibit dysregulated cell cycle control. The other subset, CD8-CXCL13-T cells, displays elevated expression levels of the chemokine CXCL13 and co-expression of PD-1. This subset demonstrates strong exhaustion scores and represents the predominant localization of high-frequency clones within tumor tissues. Furthermore, a robust correlation and interaction were observed between these two T cell subsets. By integrating our single-cell data with external datasets, we found that these cells are predominantly localized in tumor tissues and closely distributed at the tumor periphery, which is associated with poor prognosis. Notably, CD8-Pro-T cells constitute a smaller proportion in responders compared to non-responders. Finally, we validated the expression of CXCL13, PD-1, MKI67, and other markers primarily in tumor tissues from an independent cohort of 28 HBV-HCC patients. **Conclusion:** This study identified and validated two distinct interacting T-cell subsets that exhibit responsiveness to immunotherapy in HBV-HCC, providing a novel therapeutic strategy for the management of HCC.

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3241 | PROGNOSIS OF LOW FIB-4 IN A MULTINATIONAL LONGITUDINAL HEPATOCELLULAR CARCINOMA COHORT

Yong Chuan Tan[1] Zhenning Yu[2] Nicole Shu Ying Tang[2] Ken Liu[3] Karn Wijarnpreecha[4] Beom Kyung Kim[3] Sung Won Lee[3] Gang Chen[3] Takumi Kawaguchi[5] Hirokazu Takahashi[6] Daniel Q Huang[1] Mark Muthiah[1], [1]Division of Gastroenterology and Hepatology, National University Hospital, Singapore, [2]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, [3]., [4]University of Arizona College of Medicine-Phoenix, [5]Kurume University School of Medicine, [6]Saga University

Background: The fibrosis-4 index (FIB-4) is recommended as one method to risk stratify people with chronic liver disease. However, it is unclear what proportion of people with hepatocellular carcinoma (HCC) have a low FIB-4. We aimed to assess the proportion of people with HCC of various etiologies who have a low FIB-4. **Methods:** This multicenter, multinational cohort study included 1,778 adults (26% female) with hepatocellular carcinoma (HCC) from seven international centers in Australia, India, Japan, South Korea, Singapore, and the United States. The primary objective was to determine the proportion of patients with a low FIB-4 for each etiology, defined according to established standards for each etiology. **Results:** The median (IQR) age and body mass index were 73 (66-82) and 25.6 (22.3 – 28.0) kg/m^2 with 55% having known cirrhosis. The median FIB-4 was 5.09 (2.60 – 9.96) with a total of 138 patients (8%) who had a low FIB-4. However, the proportion of patients with a low FIB-4 varied by etiology: 11% in HBV, 2% in HCV, 3% in ALD, and 11% in MASLD. Low FIB-4 group presented with fewer tumor nodules (1.22 vs 1.65, $p < 0.001$), lower AFP levels (5.3 vs 13.3 ng/mL, $p < 0.001$), and was associated with better survival outcomes (adjusted HR: 0.54, 95% CI: 0.38–0.76, $p < 0.001$). The odds of receiving curative treatment were significantly higher in those with a low FIB-4 (70% vs 52%, $p < 0.001$). Male sex, HBV, and MASLD were associated with a low FIB-4 (adjusted OR: 5.03, 95% CI: 2.00–15.44), while cirrhosis and advanced BCLC stage were inversely associated (adjusted OR: 0.34, 95% CI: 0.19–0.58, $p < 0.001$). **Conclusion:** Most people with alcohol- and HCV-related HCC have an elevated FIB-4, however, one in ten with HBV- and MASLD-related HCC have a low FIB-4. Hence, while FIB-4 is commonly used in risk stratification for HCC, its ability to accurately predict prognosis may be limited. The reliance on FIB-4 as a stratification tool could potentially misclassify certain patients, particularly those with HBV

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and MASLD-related HCC, warranting further investigation into more reliable markers for risk stratification.

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3242 | SMART-HCC OUTPERFORMS PLEASE SCORE IN STRATIFYING HCC AND LIVER-RELATED EVENTS RISK IN ADVANCED CHRONIC LIVER DISEASE PATIENTS

Kessarin Thanapirom[1] Kanteera Sriyudthsak[1] Sirinporn Suksawatamnuay[1] Panarat Thaimai[1] Nipaporn Siripon[1] Wanwisar Makhasen[1] Tassanan Jaihan[1] Sombat Treeprasertsuk[2] Piyawat Komolmit[1], [1]Division of Gastroenterology and Hepatology, Chulalongkorn University, [2]Chulalongkorn University

Background: Patients with advanced chronic liver disease (ACLD) are at increased risk of hepatocellular carcinoma (HCC). Effective risk stratification is essential to enhance surveillance and facilitate early detection. The PLEASE and SMART-HCC scores, both based on liver stiffness measurement (LSM), have been developed to identify high-risk individuals. However, comparative data between both scores remained limited. This study aims to compare the performance of both scores in identifying high-risk patients for HCC development and in predicting liver-related events (LRE). **Methods:** This retrospective cohort study included 703 patients with ACLD due to MASLD and HBV infection receiving anti-viral therapy, who underwent LSM using transient elastography (TE) at Chulalongkorn University Hospital between 2017 and 2022, were screened. ACLD was defined as TE $\geq$ 10 kilopascals. Based on the original study, PLEASE score $\geq$ 4 and SMART-HCC score $\geq$ 0.08 were used to identify patients at a high risk for HCC. LRE was defined as the development of one of the following complications: ascites, hepatic encephalopathy and variceal bleeding. **Results:** A total of 461 patients with ACLD (296 with MASLD and 165 with HBV) met inclusion criteria. During the 5-year follow-up, HCC developed in 46 (10%) patients. Among those identified as high-risk, HCC occurred in 19 patients (22.6%) by the PLEASE score and in 31 (27.0%) by the SMART-HCC score. The SMART-HCC score demonstrated superior performance in predicting HCC than the PLEASE score (AUC 0.74 vs 0.63, $p = 0.03$). PLEASE score had a sensitivity of 41.4% and a negative predictive value (NPV) of 92.8%, whereas the SMART-HCC score showed a sensitivity of 67.4% and an NPV of 95.7%. Seventeen patients (3.7%) developed LRE during the follow-up. Those who experienced LRE had significantly higher baseline SMART-HCC scores than those who did not. SMART-HCC score demonstrated fair predictive ability for LRE (AUC = 0.69, 95%CI 0.59-0.80), whereas PLEASE score did not (AUC = 0.54, 95%CI: 0.39-0.68). A SMART-HCC cut-off $\geq$ 0.033 was identified as optimal for predicting LRE risk. In multivariate analysis, a SMART-HCC $\geq$ 0.033 (AUC = 3.81, 95%CI: 1.18-12.17, $p = 0.03$) was independently associated with LRE development. **Conclusion:** The SMART-HCC score outperformed the PLEASE score in identifying high-risk patients for HCC development and predicting LRE in ACLD. These findings support its utility as a risk stratification tool. Future studies are warranted to validate its role in optimizing HCC surveillance strategies.

Disclosures: Kessarin Thanapirom: Nothing to Disclose, Kanteera Sriyudthsak: Nothing to Disclose, Sirinporn Suksawatamnuay: Nothing to Disclose, Panarat Thaimai: Nothing to Disclose, Nipaporn Siripon: Nothing to Disclose, Wanwisar Makhasen: Nothing to Disclose, Tassanan Jaihan: Nothing to Disclose, Sombat Treeprasertsuk: Nothing to Disclose, Piyawat Komolmit: Nothing to Disclose

3243 | UTILITY OF TYROSINE KINASE INHIBITORS AFTER ATEZOLIZUMAB/BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Ronald Blanco Montecino[1] Nehemias Guevara Rodriguez[2] Iqra Arshad[3] Daniel Mendoza Quispe[1] Noemy Coreas[4] Yassine, Kilani[3] Syeda Fatima Kamal[3] Kamran Qureshi[5] John Richart[2], [1]Department of Internal Medicine, St Barnabas Hospital, Bronx, NY., [2]Division of Hematology-Oncology and BMT, Saint

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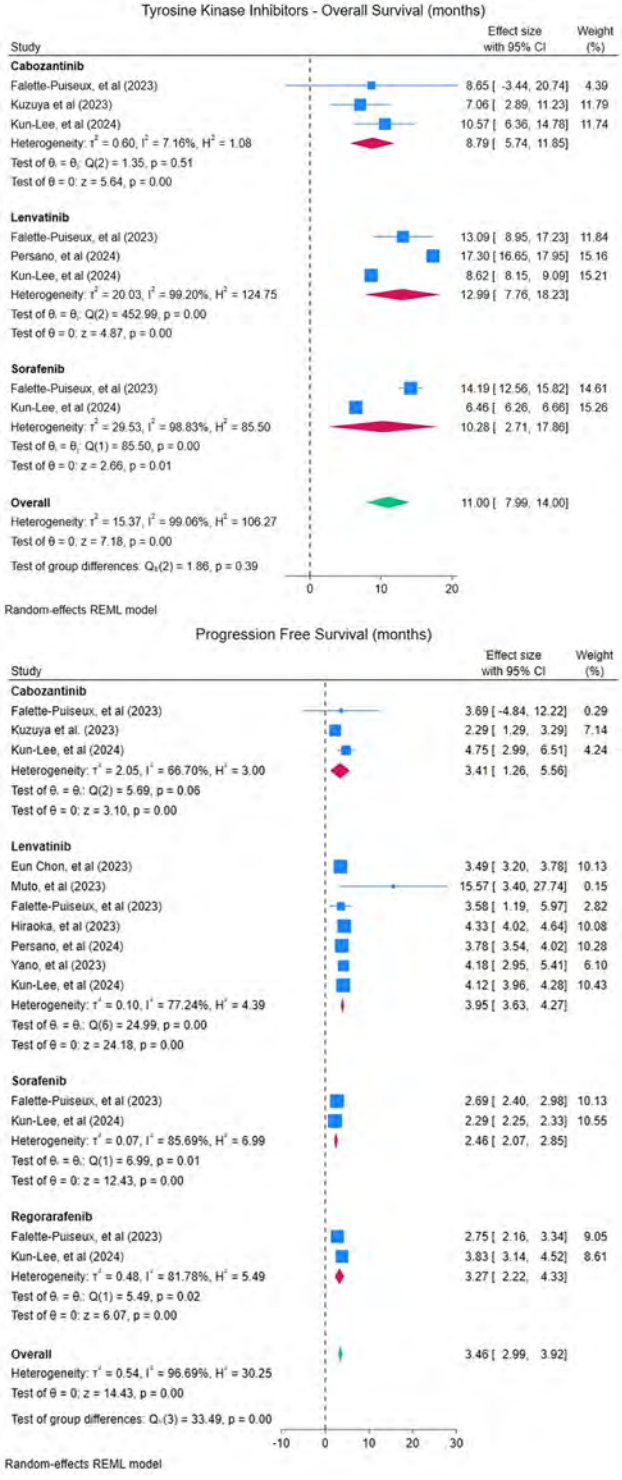
Background: Atezolizumab, in combination with Bevacizumab, is currently established as one of the standard first-line regimens for patients with advanced hepatocellular carcinoma (HCC). However, the therapeutic landscape following the progression of this regimen is evolving, particularly regarding the role and relative efficacy of various second-line tyrosine kinase inhibitors (TKIs). To clarify the optimal second-line option, we conducted a systematic review and meta-analysis to evaluate the experience with various TKIs as second-line therapy in patients with advanced HCC who experienced disease progression on Atezolizumab/Bevacizumab. **Methods:** A systematic search of PubMed, Scopus, Embase, and the Cochrane Central Register of Controlled Trials was performed from inception to October 2024. Eligible studies reported median overall survival (OS) and/or progression-free survival (PFS) for patients receiving second-line TKIs. Mean and standard deviation estimates were derived from medians and interquartile ranges using an Excel-based tool for estimating sample mean and standard deviation (SD) (Data Estimation and Conversion for Meta-Analysis [DECoMA]). A random-effects model was applied to pool median OS and PFS across studies. Statistical analyses were conducted using Stata version 18. **Results:** Nine retrospective studies were included, with 907 patients with advanced HCC who progressed on Atezolizumab/Bevacizumab. All patients received a TKI as second-line therapy: Lenvatinib (n = 442), Sorafenib (n = 365), Regorafenib (n = 65), or Cabozantinib (n = 35). Across all studies, overall survival (OS) was 11.0 months (95% CI: 7.99–14.00). When stratified by treatment, the median OS was 12.99 months with Lenvatinib (95% CI: 7.76–18.23), 10.28 months with Sorafenib (95% CI: 2.71–17.86), and 8.79 months with Cabozantinib (95% CI: 5.74–11.85), and data were limited for Regorafenib. No statistically significant differences in OS were observed between the agents. The pooled mean progression-free survival (PFS) was 3.46 months (95% CI: 2.99–3.92). Among the evaluated TKIs, Lenvatinib showed the longest PFS at 3.95 months (95% CI: 3.63–4.27). Sorafenib had a PFS of 2.46 months (95% CI: 2.07–2.85). Cabozantinib and Regorafenib demonstrated mean PFS of 3.41 months (95% CI: 1.26–5.56) and 3.27 months (95% CI: 2.22–4.33), respectively. No statistically significant differences in PFS were observed among Cabozantinib, Sorafenib, and Regorafenib. **Conclusion:** Tyrosine kinase inhibitors showed modest clinical benefits as second-line options for advanced HCC after progression on Atezolizumab/Bevacizumab. While overall survival did not differ significantly among agents, Lenvatinib showed a longer PFS, with no significant differences seen with Cabozantinib or Regorafenib. Further large-scale prospective studies are needed to validate these findings and refine treatment sequencing in this setting.



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3244 | N-ACETYLCYSTEINE SLOWS DOWN LIVER CARCINOGENESIS: MECHANISTIC INSIGHTS FROM A PRECLINICAL HEPATOCELLULAR CARCINOMA MODEL

Fernando Caloca-Camarena[1] Scarlet Arceo-Orozco[2] Alondra Martinez-Lara[2] Jorge Salto-Sevilla[3] Roberto Flores-Peña[2] Hugo Monroy-Ramírez[2] Marina Galicia-Moreno[2] Juan Armendariz-Borunda[4], [1]IBMMyTG, CUCS, Universidad de Guadalajara, México., [2]IBMMyTG, CUCS, Universidad de Guadalajara, México, [3]IBMMyTG, CUCS, Universidad de Guadalajara, Méxic, [4]IBMMyTG, CUCS, Universidad de Guadalajara, México/ Tecnologico de Monterrey, EMCS, México.

Background: Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the third leading cause of cancer-related deaths. Its development involves the dysregulation of cellular processes, such as fibrosis, proliferation, and oxidative stress. Given limited treatment options, preventive strategies and a better understanding of their molecular basis are crucial. N-acetylcysteine (NAC), widely used for acetaminophen overdose and as a mucolytic, remains understudied in HCC. This study aims to investigate the effects and mechanisms of NAC in HCC models. **Methods:** Male Fischer-344 rats (180–200 g) were randomly assigned to three groups (n = 4): 1) Control (carboxymethylcellulose), 2) Damage (diethylnitrosamine [50 mg/kg/week, i.p.] + 2-acetylaminofluorene [25 mg/kg/week, p.o.]), and 3) Treatment (Damage + NAC [300 mg/kg/day, p.o.]). Interventions lasted 16 weeks. Serum and liver samples were collected to assess liver injury, oxidative stress, fibrosis, and proliferation. Biochemical, molecular, histological, and immunostaining analyses were performed. Data were analyzed using one-way ANOVA with Tukey's post hoc test. All procedures were approved by the institutional committee (CI-01723). **Results:** NAC prevented weight loss and reduced serum markers of liver injury. The HCC group showed neoplastic changes and dysplastic nodules, which NAC attenuated. Furthermore, fibrosis was reduced, with lower extracellular matrix and collagen deposition, supported by decreased α-SMA and TGF-β expression. Tumor proliferation was also limited, as indicated by low levels of Ki-67, PCNA, and Glypican-3. NAC modulated the Nrf2/Keap1 pathway, enhancing antioxidant enzymes such as catalase, superoxide dismutase, heme oxygenase, and glutathione reductase. Additionally, NAC protected against oxidative DNA damage by upregulating the enzyme OGG1 and decreasing 8-oxoguanine. **Conclusion:** NAC's efficacy in preventing HCC appears to stem from its modulation of oxidative stress, fibrogenesis, cellular proliferation, and tumor progression. Our findings underscore the potential of this approach as an adjuvant therapy in HCC. However, further preclinical and clinical studies are crucial to fully elucidate its mechanisms, confirm its therapeutic benefits, and establish its safety before clinical repositioning in this setting.

Disclosures: Fernando Caloca-Camarena: Nothing to Disclose, Scarlet Arceo-Orozco: Nothing to Disclose, Alondra Martinez-Lara: Nothing to Disclose, Jorge Salto-Sevilla: Nothing to Disclose, Roberto Flores-Peña: Nothing to Disclose, Hugo Monroy-Ramírez: Nothing to Disclose, Nothing to Disclose, Marina Galicia-Moreno: Nothing to Disclose, Juan Armendariz-Borunda: Nothing to Disclose

3245 | N6-METHYLADENOSINE–MEDIATED UP-REGULATION OF ARRB2 REGULATES INTRAHEPATIC CHOLANGIOCARCINOMA MALIGNANT PROGRESSION AND PEMIGATINIB RESISTANCE THROUGH MAPK AND HIPPO SIGNALING PATHWAYS

qiwei yang[1] Haoqi Chen[2] Genshu Wang[1], [1]Guangdong Provincial Hospital of Traditional Chinese Medicine, [2]The Third Affiliated Hospital of Sun Yat-Sen University

Background: Intrahepatic cholangiocarcinoma (ICC) is a major contributor to cancer-related mortality on a global scale, yet it suffers from a lack of reliable early diagnostic biomarkers and effective therapeutic targets. Pemigatinib has been identified as a therapeutic option for advanced ICC; however, its long-term clinical efficacy is significantly hindered by the development of drug resistance. **Methods:** Pemigatinib resistant ICC cells were established by culturing with increasing drug treatment. 98 pairs of ICC tissue samples were collected and analyzed to assess the association between β-arrestin 2 (ARRB2) and ICC progression. The role and mechanism of ARRB2 in the malignant progression of ICC and resistance to pemigatinib were explored *in vitro* and *in vivo* experiments. **Results:** ARRB2 expression is markedly upregulated in pemigatinib-resistant ICC cells compared to their parental counterparts. Suppression of ARRB2 expression markedly attenuated ICC chemoresistance to pemigatinib. Clinical data further verified that ARRB2 is correlated with poorer pathological classification and prognosis in ICC patients. Mechanistic studies revealed that ARRB2

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activation in ICC is mediated by METTL3-dependent m6A methylation. Functional analyses demonstrated that ARRB2 promotes the malignant progression of ICC by facilitating YAP1 nuclear translocation while also modulates the sensitivity of ICC to pemigatinib through the Raf-MEK-ERK signaling axis. **Conclusion:** This study identifies the tumor-suppressing activities of ABBR2 and elucidates the regulatory mechanism of the METTL3-ARRB2-YAP1/Raf axis in ICC, which may provide novel prognostic biomarker and potential therapeutic target for human ICC.

Disclosures: qiwei yang: Nothing to Disclose, Haoqi Chen: Nothing to Disclose, Genshu Wang: Nothing to Disclose

3246 | INTRATUMORAL FIBROSIS AND AGGRESSIVE FEATURES IN TREATMENT-NAÏVE ADVANCED HEPATOCELLULAR CARCINOMA

Makoto Fujiya[1] Sadahisa Ogasawara[1] Haruka Anzai[1] Kazuo Tsubura[1] Taro Watabe[1] Midori Sawada[1] Takahiro Tsuchiya[1] Ryohei Yoshino[1] Teppei Akatsuka[1] Ryo Izai[1] Keiichi Katayama[1] Chihiro Miwa[1] Takuya Yonemoto[1] Sae Yumita[1] Kanzaki Hiroaki[1] Keisuke Koroki[1] Masanori Inoue[1] Masato Nakamura[1] Naoya Kanogawa[1] Shingo Nakamoto[1] Jun Kato[1] Mina Komuta[2], [1]Department of Gastroenterology, Graduate School of Medicine, Chiba University, [2]Department of Pathology, International University of Health and Welfare, School of Medicine

Background: Hepatocellular carcinoma (HCC) undergoes continuous morphological transformation during progression. While early-stage, resectable HCC is well characterized, the histology of advanced HCC remains poorly defined. Intratumoral fibrosis is common in advanced cases, but its timing and associations with tumor size, vascular invasion, metastasis, and histological subtypes such as macrotrabecular-massive (MTM) and vessels encapsulating tumor clusters (VETC), which are linked to poor prognosis in early-stage disease, remain unclear. We previously found that spatial patterns of $CD8^+$ T cells, such as parenchymal localization and diffuse distribution, were associated with response to immune checkpoint inhibitors in advanced HCC. This study aimed to clarify when and how intratumoral fibrosis and immune architecture develop in advanced HCC and how they relate to histological subtypes and clinical features. **Methods:** We analyzed 104 biopsy-confirmed, treatment-naive advanced HCC cases ineligible for locoregional therapy. MTM, VETC, and fibrosis were assessed and correlated with imaging-based necrosis, tumor size, MVI, and EHM. **Results:** All patients had intrahepatic lesions confirmed by imaging and biopsy. MVI and EHM were present in 47.1% and 29.8% of cases, respectively; 38.5% had neither. Histologically, 26.9% of tumors were moderately and 64.4% poorly differentiated. Intratumoral fibrosis was seen in 62.5%, more frequent than in early-stage HCC. It was also found in 65.0% of patients without MVI or EHM, showed no association with tumor size, and occurred independently of MTM or VETC. Among 51 patients evaluated for immune features, $CD8^+$ T cells localized mainly within the parenchyma in 78.0%, with diffuse distribution in 58.0%. These patterns were unrelated to MTM/VETC, tumor size, or MVI/EHM, suggesting early establishment. MTM was identified in 50.0%, significantly associated with necrosis ($p < 0.05$) and showed a trend with larger size ($p = 0.078$). VETC was found in 29.9% and showed a non-significant trend toward necrosis ($p = 0.096$). Neither correlated with MVI or EHM, indicating a localized histological role. **Conclusion:** Intratumoral fibrosis and $CD8^+$ T-cell spatial patterns appear to emerge before established morphological and clinical features of tumor progression. MTM and VETC were linked to necrosis and tumor size but not to dissemination. Fibrosis and immune architecture may represent preceding histological changes and warrant further investigation.

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3247 | CHEMOPREVENTIVE EFFECT OF FIBRATE AS AN ADD-ON TO STATIN ON THE RISK OF HEPATOCELLULAR CARCINOMA: A NATIONWIDE-POPULATION BASED STUDY

Won Sohn[1] Hyun Woo Oh[2] Cheol-Young Park[2] Kyoung A Ko[3], [1]Kangbuk Samsung Hospital, Sungkyunkwan University School of, [2]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, [3]Kangbuk Samsung Hospital

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Background: This study aimed to investigate the chemopreventive effects of fibrates as an add-on to statins on the risk of hepatocellular carcinoma (HCC). **Methods:** This population-based cohort study was conducted from the Korean National Health Insurance Service from 2010 to 2019 in Korea. We compared the incidence of HCC between the users of statin and those with fibrate and statin for dyslipidemia, matched using age, sex, and hypertriglyceridemia. **Results:** We analyzed 789,958 individuals, including 394,979 statin users and 394,979 matched fibrate-statin users. During the 1,644,037.6 person-years of follow-up, 791 HCC cases were observed in the statin group, whereas 703 HCC cases were observed in the fibrate-statin group during 1,646,939.6 person-years of follow-up. The HCC incidence rates per 1,000 person-years were 0.48 and 0.43 in the statin and fibrate-statin groups, respectively. The risk of HCC development was lower in the fibrate-statin group compared to the statin group in the unadjusted and adjusted models (hazard ratio [HR] 0.89 with 95% confidence interval [CI]: 0.80–0.98 and adjusted HR [aHR] 0.74 with 95% CI: 0.67–0.83). The chemopreventive effects of fibrate-statin on HCC development increased as the duration of fibrate administration lengthened (aHR 0.76 with 95% CI: 0.68–0.86 in statin and fibrate use for <1 year; and aHR 0.71 with 95% CI: 0.61–0.82 for >1 year). **Conclusion:** The fibrate as an add-on to statin was associated with a reduced risk of HCC compared to statin. The findings of this study may suggest the chemopreventive role of fibrate on HCC.

Disclosures: Won Sohn: Nothing to Disclose, Hyun Woo Oh: Nothing to Disclose, Cheol-Young Park: Nothing to Disclose, Kyoung A Ko: Nothing to Disclose

3248 | EFFICACY OF SYSTEMIC THERAPY FOR PATIENTS WITH INFILTRATIVE TYPE UNRESECTABLE HEPATOCELLULAR CARCINOM

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Background: Infiltrative hepatocellular carcinoma (HCC) is a radiologically aggressive subtype frequently associated with vascular invasion and poor prognosis. However, data on its efficacy on treatment outcomes with contemporary first-line systemic therapies, including Lenvatinib and immunotherapy-based regimens, remain unclear. This study aimed to compare clinical characteristics, treatment response, and survival outcomes between infiltrative and non-infiltrative HCC. **Methods:** We retrospectively analyzed 270 patients with unresectable HCC who received first-line systemic therapy (Lenvatinib: $n=103$; immunotherapy: $n=167$) at Taipei Veterans General Hospital between May 2017 and October 2023. Infiltrative HCC was defined by radiologic pattern assessed by two radiologists. Baseline demographics, tumor burden, and liver function parameters were recorded. Treatment response was evaluated using RECIST 1.1 criteria. Multivariate Cox regression analyses were performed to identify factors associated with progression-free survival (PFS) and overall survival (OS). **Results:** Among the 270 patients, 39 (14.4%) had infiltrative HCC. These patients showed significantly higher rates of portal vein invasion (Lenvatinib: 76.9%; Immunotherapy: 92.3%) compared to non-infiltrative HCC (47.8% and 49.6%, respectively; $p<0.001$). Infiltrative HCC was also associated with poorer ALBI grades, elevated ALT levels, and more advanced tumor burden (Up-to-11 criteria). Although the treatment results show that the objective response rate (ORR) of infiltrative HCC is lower than that of non-infiltrative HCC (17.9% vs. 29.9%, $p=0.126$), the disease control rates (DCR) were similar (58.9% vs. 67.1%, $p=0.322$). Infiltrative HCC was associated with significantly shorter median OS (10.9 vs. 24.1 months, $p=0.04$). In the subgroup of infiltrative HCC, no significant difference in survival was observed between patients receiving Lenvatinib versus immunotherapy (median OS: 6.1 vs. 10.8 months, $p=0.492$; median PFS: 5.0 vs. 8.3 months, $p=0.827$). Independent predictors of OS included ALBI grade 2–3 (HR: 1.822), elevated AST (HR: 2.202), and viral etiology (HR: 0.588, protective). Independent factors associated with shorter PFS included ALBI grade 2–3 (HR: 1.551), AFP >100 ng/mL (HR: 1.338), and BMI >27.5 kg/m² (HR: 0.657, protective). **Conclusion:** Infiltrative HCC responds similarly to systemic treatment with lenvatinib or immunotherapy but has poorer survival than non-infiltrative HCC. Lenvatinib or immunotherapy did not result in significant differences in OS or PFS in infiltrative HCC.

Disclosures: Ming Chieh Hsieh: Nothing to Disclose, Yi-Hsiang Huang: Nothing to Disclose

3249 | PROGNOSTIC IMPACT OF ETIOLOGIES ON INTRAHEPATIC CHOLANGIOCARCINOMA: AN ANALYSIS OF A NATIONWIDE REGISTRY IN JAPAN

Kazuya Okushin[1] Ryosuke Tateishi[1] Koji Uchino[1] Ryo Nakagomi[1] Yuki Matsushita[1] Tomoharu Yamada[1]

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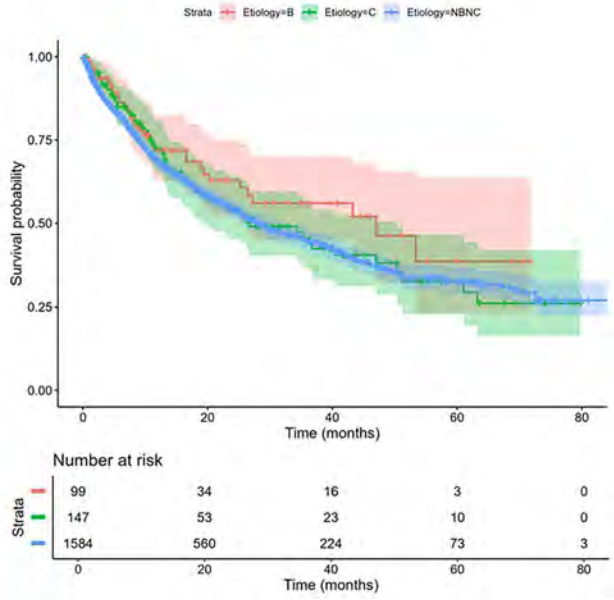
Background: Chronic viral hepatitis is considered a risk factor for intrahepatic cholangiocarcinoma (ICC), but its impact on prognosis remains controversial. **Methods:** Patients initially diagnosed with ICC between 2018 and 2023 were enrolled from a nationwide registry in Japan. Patients were classified as HBV-related, HCV-related, or non-B, non-C based on the presence of hepatitis B surface antigen or hepatitis C antibody. The primary endpoint was overall survival. Inverse probability of treatment weighting (IPTW) was applied to generate adjusted Kaplan–Meier survival curves. **Results:** Among 1,906 eligible patients (62.7% male), 99 (5.2%), 147 (7.7%), and 1,584 (83.1%) were classified as HBV-related, HCV-related, or non-B, non-C, respectively. Patients with HBV were younger with median age of 73.0 years (interquartile range [IQR], 61.0–73.0) in HBV, than HCV (74.0 years [68.0–79.0]) in HCV and non-B, non-C (73.0 years [67.0–79.0]) in non-B, non-C). A solitary tumor was more frequently observed in HCV patients (80.3%) compared to HBV (73.7%) and non-B, non-C (74.5%). Tumor size was significantly smaller in HCV cases (median 3.50 cm [2.50–5.00]) than in HBV (4.30 cm [3.00–6.00]) and non-B, non-C (4.30 cm [2.95–6.60]). Bile duct invasion was more common in the non-B, non-C group (34.1%) than in HBV (18.2%) and HCV (25.9%). Distant metastases were less frequent in HCV patients (23.8%) than in HBV (26.3%) and non-B, non-C (27.0%). The distribution of Child–Pugh class was similar across all etiologies (Child–Pugh A: 77.6% in HBV, 73.7% in HCV, and 74.0% in non-B, non-C). Surgical resection was performed at comparable rates (61.6% for HBV, 61.2% for HCV, and 59.1% for non-B, non-C). The overall median survival time was 13.0 months (IQR: 4.8–26.5). Unadjusted survival curves did not significantly differ by etiology ($p = 0.11$ for HBV vs. non-B, non-C; $p = 0.74$ for HCV vs. non-B, non-C). IPTW-adjusted analyses confirmed no significant difference in overall survival ($p = 0.90$ for HBV vs. non-B, non-C; $p = 0.30$ for HCV vs. non-B, non-C). **Conclusion:** Although HBV patients tended to be younger and HCV patients were more likely to be diagnosed at earlier stages due to surveillance, the prognosis of ICC patients was similar across etiologies after adjusting for confounding factors including tumor stage and liver function.

Figure 1



Disclosures: Kazuya Okushin: Nothing to Disclose, Ryosuke Tateishi: EA Pharma: Speaking and Teaching, MSD: Speaking and Teaching, Aska Pharma: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Abbvie: Speaking and Teaching, Eisai: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, Covidien: Speaking and Teaching, Bayer: Speaking and Teaching, Century Medical: Speaking and Teaching, Canon Medical: Speaking and Teaching, Asahikasei Pharma: Speaking and Teaching, Terumo: Speaking and Teaching, TechsoMed: Speaking and Teaching, Sumitomo Pharma: Speaking and Teaching, Taisho Pharmaceutical: Speaking and Teaching, Daiichi-Sankyo: Speaking and Teaching, Chugai: Speaking and Teaching, Fujifilm: Speaking and Teaching, Koji Uchino: Nothing to Disclose, Ryo Nakagomi: Nothing to Disclose, Yuki Matsushita: Nothing to Disclose, Tomoharu Yamada: Eisai: Speaking and Teaching, Chugai Pharmaceutical: Speaking and Teaching, astrazeneca: Speaking and Teaching, Takuma Nakatsuka: Nothing to Disclose, Tatsuya Minami: Asahi Kasei Pharma Corporation: Speaking and Teaching, AstraZeneca K. K.: Speaking and Teaching, Masaya Sato: Nothing to Disclose, Yotaro Kudo: Nothing to Disclose, Yoshinari Asaoka: Eisai Co., Ltd.: Advisor, Mitsuhiro Fujishiro: Nothing to Disclose, Yuichiro Eguchi: Nothing to Disclose, Kiyoshi Hasegawa: Eisai: Speaking and Teaching, Chugai: Speaking and Teaching, Astellas: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Mochida: Grant/Research Support, Fujifilm Medical: Grant/Research Support, Johnson&Johnson: Speaking and Teaching, Ohtsuka: Speaking and Teaching, Miyarisan: Speaking and Teaching,

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3250 | PREDICTING AND MANAGING HEPATOCELLULAR CARCINOMA RECURRENCE AFTER LIVER TRANSPLANT: A SINGLE CENTER EXPERIENCE 2012-2024

Jesse Civan[1] Madison Force[1] Adam Bodzin[1] Daniel Lin[1], [1]Thomas Jefferson University Hospital

Background: Although orthotopic liver transplantation (OLT) is a curative option for selected patients with hepatocellular carcinoma (HCC), post-transplant recurrence can occur. Despite advances in therapy for HCC, management of post-transplant recurrence remains challenging. **Methods:** This single-center retrospective study included all patients undergoing OLT at our center from 1/1/12 to 12/31/24. Clinical data were manually extracted. Patients transplanted for HCC underwent a 5-year protocol of surveillance for recurrence, with mean radiographic follow-up of 40 months. Explant pathology, as well as other clinical data, was reviewed and RETREAT scores were calculated. Statistical analyses were performed using IBM SPSS Version 29. Survival analysis was conducted by Meier-Kaplan log-rank method. **Results:** A total of 923 patients underwent OLT with mean follow-up of 58 months. Of these, 329 (35.6%) underwent OLT for HCC. Overall survival (OS) was similar for patients with HCC (89% 1-year, 82% 3-year) compared to those without HCC (87% 1-year, 82% 3-year). Post-OLT HCC recurred in 36 patients (11%). Mean time from transplant to recurrence was 22 months (range 0 to 55 months). Sites of recurrence were liver (22%), lung (17%), bone (11%), other abdominal/pelvic site (25%), or multiple (25%). Post-OLT OS was worse for patients with recurrence (1-year 78%, 3-year 29%) compared with those without recurrence (1-year 94%, 3-year 89%). Recurrence was more likely in patients with viable tumor beyond Milan on explant, microvascular invasion on explant, and with higher RETREAT scores. Treatment of post-OLT recurrence included sorafenib (36%), lenvatinib (33%), cabozantinib (17%), cytotoxic chemotherapy (8%), locoregional therapy (33%), surgery (14%), and external radiation (47%), with some patients undergoing multiple modalities of treatment. For those with post-OLT HCC recurrence, median survival from transplant was 46 months, and median survival time from diagnosis of recurrence was 9 months. **Conclusion:** In our dataset post-OLT HCC recurrence rate was 11%. Our experience validates previously reported risk factors for post-OLT recurrence including viable tumor beyond Milan Criteria, presence of microvascular invasion, and RETREAT score. However, fully a third of patients who recurred post-OLT were “low risk” by these criteria. Further investigation is needed to identify other criteria to guide post-OLT surveillance.

RETREAT Score	Patients without Recurrence N = 290	Patients with Recurrence N = 36
0	110 (37.8%)	6 (16.7%)
1	114 (39.3%)	6 (16.7%)
2	38 (13.1%)	10 (27.8%)
3	18 (6.2%)	4 (11.1%)
4	4 (1.4%)	3 (8.3%)
5	4 (1.4%)	7 (19.4%)
6	2 (0.7%)	0 (0%)

Disclosures: Jesse Civan: Nothing to Disclose, Madison Force: Nothing to Disclose, Adam Bodzin: Nothing to Disclose, Daniel Lin: Agenus: Consultant, Astra Zeneca: Consultant

3251 | INCIDENCE AND SURVIVAL OUTCOMES OF LIVER CANCER: ANALYSIS OF THE SEER DATABASE

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Background: The global incidence of adult primary liver cancer is declining, although recent GBD study showed continued increases in North America. We aim to investigate trends, clinical features, and survival outcomes of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). **Methods:** The National Cancer Institute Surveillance Epidemiology and End Results (SEER) Program, including the SEER-21 and SEER-17 registries, was used to extract data on adult (aged 20 years or older) patients with HCC and iCCA. Using the SEER-21 registry, we calculated age-standardized incidence rates (ASIRs), age-standardized mortality rates (ASMRs), and annual percentage changes (APCs) from 2004 to 2022 with SEER*Stat and Joinpoint. Using the SEER-17 registry, we compared demographic and clinical features between patients with HCC and iCCA. We calculated overall survival (OS) using Stata. Multivariable Cox proportional hazard regression models were performed to examine differences in OS between the two groups. **Results:** Of 269,835 adult patients in SEER-21, there

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were 232,212 HCCs and 37,623 iCCAs. In 2022, HCC had higher ASIR (9.7 vs. 2.7 per 100,000 population) and ASMR (6.3 vs. 2.8 per 100,000 population) than iCCA. From 2004 to 2022, ASIRs increased for HCC (APC: 0.58, 95%CI 0.27 – 0.92) and iCCA (APC: 6.65, 95%CI 6.34 – 7.14); however, we noted variation over the study period. Between 2015-2022, there were declines in ASIR (APC: -2.53, 95%CI -3.22 to -1.58) and ASMR (APC: -1.38, 95%CI -1.68 to -1.20). for HCC. Conversely over this same period, continued increases were noted for ASIR (APC: 5.36, 95% CI 4.64 – 5.96) and ASMR (APC: 2.72, 95%CI 1.88 – 3.36) for iCCA. Of 114,281 patients in SEER-17, 99,898 had HCC and 14,383 had iCCA. Median (IQR) age was 65 (58–73) years, 72.3% were men, and 51.2% were White. The baseline characteristics of the HCC and iCCA groups are compared in Table 1. Median overall survival in patients with HCC and iCCA was 13 vs. 8 months, with 1-, 3-, and 5-year OS survival rates of 54.9%, 31.2%, and 22.1%, vs. 43.2%, 17.3%, and 11.0%, respectively. In multivariable analysis, survival was higher in patients with HCC than those with iCCA (adjusted HR = 0.82, 95%CI 0.79 – 0.84). **Conclusion:** In this large cohort study, the ASIR and ASMR of adult primary liver cancer increased over the last 2 decades, with a recent decline noted for HCC but not for iCCA. Patients with HCC were more likely to be younger, male, Black/Asian/Pacific Islander, not married, and have a lower median household income compared to patients with iCCA. Although HCC continues to have higher incidence and mortality rates, iCCA is associated with worse overall survival.

Variables	HCC (n = 99,898)	CCA (n = 14,383)	P value
Age, median, IQR	64 (58 – 72)	68 (59 – 76)	<0.001
Male, (%)	75,434 (75.5)	7,181 (49.9)	<0.001
Race, (%)			<0.001
White	49,670 (49.7)	8,897 (61.8)	
Black	11,814 (11.8)	1,129 (7.8)	
Asian or Pacific Islander	15,741 (15.7)	1,870 (13.0)	
American Indian/Alaska Native	1,319 (1.3)	115 (0.8)	
Hispanic	21,138 (21.1)	2,343 (16.2)	
Year of diagnosis, (%)			<0.001
2004 – 2009	23,048 (23.0)	1,977 (13.7)	
2010 – 2017	46,661 (46.7)	6,122 (42.5)	
2018 – 2022	30,189 (30.2)	6,284 (43.6)	
SEER registry, (%)			<0.001
Northeast	13,722 (13.7)	2,373 (16.5)	
Midwest	2,766 (2.7)	578 (4.0)	
South	20,445 (20.4)	3,169 (22.0)	
West	62,965 (63.0)	8,263 (57.4)	
Marital status, (%)			<0.001
Married	51,058 (51.1)	8,382 (58.2)	
Not married	48,840 (48.8)	6,001 (41.7)	
Median household income, (%)			<0.001
<$45,000	1,839 (1.8)	266 (1.8)	
$45,000 - $75,000	32,239 (32.2)	4,002 (27.8)	
$75,000 - $120,000	58,884 (58.9)	8,640 (60.0)	
>$120,000	6,922 (6.9)	1,474 (10.2)	
Cirrhosis, (%)			<0.001
Yes	15,033 (80.3)	526 (38.5)	
No	3,665 (19.6)	838 (61.4)	
Tumor size, (%)			<0.001
< 2 cm	9,737 (11.5)	554 (5.8)	
2 – 3 cm	18,534 (22.0)	1,144 (12.0)	
> 3 cm	55,819 (66.3)	7,821 (82.1)	
Tumor grade, (%)			<0.001
Well differentiated	10,783 (30.3)	581 (9.4)	
Moderately differentiated	16,918 (47.6)	2,930 (47.5)	
Poorly differentiated	7,325 (20.6)	2,606 (42.3)	
Undifferentiated	467 (1.3)	42 (0.6)	
Metastatic disease, (%)			<0.001
Yes	11,960 (12.5)	5,535 (39.8)	
No	83,793 (87.5)	8,372 (60.2)	
Surgical treatment, (%)			<0.001
Tumor ablation	12,344 (45.6)	269 (8.5)	
Liver resection	9,391 (34.7)	2,247 (71.3)	
Liver transplantation	5,303 (19.6)	634 (20.1)	
Chemotherapy, (%)			<0.001
Yes	39,012 (39.0)	8,133 (56.5)	
No/Unknown	60,886 (60.9)	6,250 (43.4)	
Radiation, (%)			<0.001
Yes	13,519 (13.5)	2,203 (15.3)	
No/Unknown	87,379 (86.4)	12,180 (84.6)	

Disclosures: Chawin Lopimpisuth: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Ju Dong Yang: Exact Sciences: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Exelixis: Consultant, Fujifilm Medical Sciences: Consultant

3252 | PREDICTIVE VALUE OF PERIPHERAL BLOOD FOLLICULAR HELPER T CELLS FOR SHORT-TERM PROGNOSIS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA TREATED WITH IMMUNE CHECKPOINT INHIBITORS

yuhai hu[1], [1]First Affiliated Hospital of Fujian Medical University

Background: Immune checkpoint inhibitors (ICIs), as an emerging immunotherapy, have shown great potential in improving the prognosis of patients. Peripheral blood follicular helper T cells (Tfh), As a specialized T cell subset, Tfh cells play a pivotal role in humoral immunity. In the context of ICIs therapy, Tfh cells may have an important impact on the short-term prognosis of HCC patients by affecting the function of B cells and then regulating humoral immune response. However, the specific role of Tfh cells in predicting the efficacy of ICIs in HCC patients remains to be fully elucidated. **Methods:** This study aims to assess the prognostic potential of peripheral Tfh cells in HCC patients undergoing ICIs treatment.200 patients treated with ICIs for HCC in The First Affiliated Hospital of Fujian Medical University from Jan 2020 to 2023 were retrospectively selected as the study subjects. This study used flow cytometry to analyze peripheral blood lymphocyte subsets and cytokines.All treatment protocols in this study were conducted in accordance with the “Chinese Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition)”. In clinical trials, the research team used lenvatinib and triplimumab targets specific diseases. Patients were followed up regularly every three months after starting treatment. During each follow-up visit, physical examinations, blood tests (including liver function, tumor markers, etc.), and imaging examinations (such as ultrasound, CT, or MRI) were performed to assess treatment response, disease progression, and any treatment-related

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adverse events. **Results:** Patients were retrospectively analyzed, and those with improved conditions within six months post-treatment were classified as having a favorable prognosis (n = 86), while those with no remission, worsening, or death were grouped as having a poor prognosis (n = 114). C-reactive protein (CRP), interleukin-6 (IL-6), Tfh cell counts, and combination therapy were significantly associated with prognosis ($P < .05$). Multivariate analysis confirmed CRP, IL-6, Tfh cells, and combination therapy as independent predictors of short-term prognosis ($P < .05$), explaining 78.3% of the variation. The area under the curve (AUC) for Tfh cells in predicting prognosis was 0.902 (95% CI: 0.8567-0.9477), with 100% sensitivity and 80.70% specificity at an optimal cut-off of 1.995. Patients with high Tfh cell levels (≥ 1.995, n = 93) had a median overall survival (OS) of 5 months, significantly better than those with low levels (< 1.995, n = 107) whose median OS was not reached ($P < .05$). **Conclusion:** Tfh cells are an independent predictor of short-term prognosis in HCC patients receiving ICIs. High Tfh cell levels indicate a better short-term prognosis, offering valuable insights for clinical decision-making.
Disclosures: yuhai hu: Nothing to Disclose

3253 | CHARACTERISTICS AND CLINICAL COURSE OF FONTAN-ASSOCIATED LIVER DISEASE (FALD)

Sumire Takano[1] Tomomi Kogiso[1] Motoyuki Otsuka[2] Makiko Taniai[1] Yousuke Nakai[1], [1]Tokyo Women's Medical University, [2]Okayama University Hospital

Background: In Fontan-associated liver disease (FALD), fibrosis progression and hepatocellular carcinoma (HCC) development in young patients are major concerns. Connective tissue growth factor (CTGF), produced by endothelial cells and platelets, plays a key role in fibrosis across various organs. We retrospectively analyzed the clinical features and progression of FALD and FALD-HCC, as well as the significance of CTGF in FALD. **Methods:** 1) Among FALD patients who visited our department between 2003 and 2025, 282 cases (140 males, 49.6%) were analyzed. Of these, 27 (9.6%) developed FALD-HCC (14 males, 51.9%). We examined their characteristics and clinical course. 2) Serum levels of full-length CTGF and its N-terminal fragment were measured using two detection antibodies targeting the N- and C-terminal regions. We assessed CTGF levels (via enzyme-linked immunosorbent assay) and liver fibrosis stage in 38 FALD patients. **Results:** 1) The median age at Fontan surgery was 4.7 years (range: 0.0–37.4), and at referral, 27.0 years (range: 6.4–61.4). HCC developed at a median age of 32.6 years, occurring 26.1 years postoperatively. The median laboratory values for FALD-HCC were: albumin 4.3 g/dL, total bilirubin 1.4 mg/dL, ALT 21 U/L, GGT 73 U/L, platelet count 13.8 $\times 10^4$/μL, AFP 39 ng/mL, and MELD-XI 11.51. Tumors were located in the left/right/caudate lobe (n = 8/12/1), and both lobes (n = 6), predominantly in the liver periphery. Tumor counts were single (n = 19), two (n = 3), and multiple (≥ 3, n = 5). Staging included stage I (n = 11), II (n = 9), III (n = 2), and IV (n = 5). HCC differentiation was well/moderate/poor in 3/1/4 cases, and fibrosis in non-cancerous liver tissue was F1/2/3/4 in 0/1/1/2 cases. Treatment included liver resection (n = 4), transarterial embolization (n = 6), radiotherapy (n = 6), proton beam therapy (n = 6), and systemic therapy (n = 2). Three patients received only palliative care due to liver failure. The 5-year survival rate for FALD-HCC was 55%, with six of seven deaths attributed to liver-related causes. 2) Full-length CTGF was significantly inversely correlated with liver fibrosis in FALD, while the N-terminal fragment increased with fibrosis progression. **Conclusion:** CTGF may be involved in fibrosis progression in FALD. FALD-HCC develops approximately 26 years after Fontan surgery and is associated with poor survival. HCC significantly affects prognosis, underscoring the need for surveillance strategies and preventive measures.
Disclosures: Sumire Takano: Nothing to Disclose, Tomomi Kogiso: Nothing to Disclose, Motoyuki Otsuka: Nothing to Disclose, Makiko Taniai: Nothing to Disclose, Yousuke Nakai: Nothing to Disclose

3254 | HISTOTRIPSY TO ACHIEVE LOCAL TUMOR CONTROL FOR LIVER TUMORS: A NATIONAL MULTI-CENTER STUDY

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Background: Histotripsy is a non-invasive, non-ionizing, non-thermal, ultrasound-based modality for treatment of liver tumors that received FDA clearance in October 2023. National studies have demonstrated favorable safety profiles, yet only isolated case reports have been published regarding oncologic outcomes after treatment. We aim to describe the ability of histotripsy to achieve local tumor control (LTC) for primary and secondary liver tumors. **Methods:** All patients receiving histotripsy since FDA clearance (Edison system, HistoSonics Inc) four institutions (two academic; two private practice) performing histotripsy who achieved at least 30 days active-follow-up were

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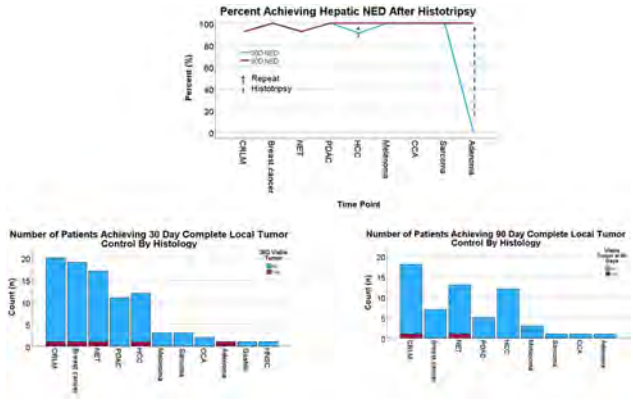
included. Cases were divided into palliative-intent and complete control, in which the treatment was intended to yield no-evidence of disease (NED) on radiographic imaging. 30- and 90-day follow-up are reported. Outcomes are reported according to the standardized imaging-guided tumor ablation criteria. **Results:** In total, 161 patients received treatment to 285 individual liver tumors. The most common treated tumor types were colorectal metastasis (CRLM, n = 84), cholangiocarcinoma (CCA, n = 52), neuroendocrine (NET, n = 48), breast (n = 34), pancreatic (PDAC, n = 32), and hepatocellular (HCC, n = 21). Treatment intent by liver tumor was palliative (n = 194, 68%) or complete (n = 91, 32%) intent.

Patients (n = 47) and tumors (n = 91) intended for complete treatment were assessed for complete tumor response, or radiologic non-viability. At 30-days, 95% (n = 86/91) of treated liver tumors were radiographically non-viable. Two patients received repeat treatment between POD30 and POD90, both converted to complete response after the second treatment. Thirty-two patients receiving treatment for 62 tumors achieved 90-day follow-up. Of these, 30 patients (94%) and 60 tumors (97%) achieved complete tumor response in the liver. The two patients with viable disease had NET (n = 1) and CRLM (n = 1) respectively. We thus report a primary efficacy rate of 94% and a secondary efficacy rate of 97% at 90-days with no serious safety events reported. **Conclusion:** This preliminary data suggests histotripsy can achieve local control of liver tumors. Longer-term follow-up is needed to evaluate treatment durability.



Disclosures: Chase Wehrle: HistoSonics: Above, Kevin Burns: Nothing to Disclose, Tarub Mabud: Nothing to Disclose, Ahmed Sayed Ahmed: Nothing to Disclose, Nothing to Disclose, Ahmed Sayed Ahmed: Nothing to Disclose, Nothing to Disclose, Mohamed Alassas: Nothing to Disclose, Tiffany Juarez: Nothing to Disclose, Jimmy Ton: Nothing to Disclose, Andrea Schlegel: Nothing to Disclose, Jaekeun Kim: Nothing to Disclose, Federico Aucejo: Nothing to Disclose, Evan Ong: Nothing to Disclose, Mikhail Silk: Nothing to Disclose, Brock Hewitt: Nothing to Disclose, David Kwon: Medtronics: Consultant, GE medical: Consultant, Histosonics: Consultant

3255 | CLINICALLY SIGNIFICANT PORTAL HYPERTENSION AS A PROGNOSTIC FACTOR IN CHOLANGIOCARCINOMA: A COHORT STUDY

Yingfan Chen[1] Yu-Jen Chen[1], [1]Division of Gastroenterology and Hepatology, Taipei Veterans General Hospital, Taiwan

Background: The clinical significance of cholangiocarcinoma (CCA) has grown in recent decades due to a notable rise in global incidence and mortality, especially for iCCA. While survival is influenced by various factors such as tumor stage and location, the prognostic impact of clinically significant portal hypertension (CSPH) remains under investigation. CSPH is associated with an elevated risk of cirrhosis-related complications, but its impact on cancer prognosis remains inconclusive. This study seeks to determine whether CSPH functions as an independent prognostic factor in patients with CCA. **Methods:** We conducted a retrospective cohort study of 841 patients with histologically confirmed CCA at Taipei Veteran General Hospital, Taiwan, from 2013 to 2024. CSPH was defined by the presence of at least one of the following: moderate ascites, esophageal varices, or splenomegaly with thrombocytopenia. Overall survival (OS) was analyzed using Kaplan-Meier curves and Cox proportional hazards models. Subgroup analyses were performed based on surgical treatment, tumor stage, and tumor location. **Results:** Among 841 patients, 194 (23%) met criteria for CSPH. Compared to patients without CSPH, those with CSPH were more likely to be male (64.9% vs. 57.0%, $p = 0.049$) and had significantly worse platelet counts (184000 vs. 224000/uL, $p < 0.001$), INR(1.14 vs. 1.08, $p < 0.001$), albumin (3.65 vs. 3.8g/dL, $p = 0.001$), total bilirubin (1.04 vs. 0.75mg/dL, $p = 0.001$), and higher FIB-4 scores (3.08 vs. 2.08, $p < 0.001$). Fewer patients with CSPH underwent surgery (26.8% vs. 38.3%, $p = 0.03$). After a median follow-up of 374 days, 293 patients died. Median OS was significantly shorter in the CSPH group (260 vs. 412 days, $p < 0.001$). Subgroup analysis revealed that CSPH predicted worse survival in both iCCA and non-surgical patients. **Conclusion:** CSPH is an independent predictor of poor survival in patients with CCA. It reflects compromised hepatic reserve and correlates with decreased likelihood of curative surgery. Incorporating CSPH into routine prognostic assessment may improve treatment planning. Further prospective studies are needed to validate these findings and explore therapeutic strategies targeting this high-risk subgroup.

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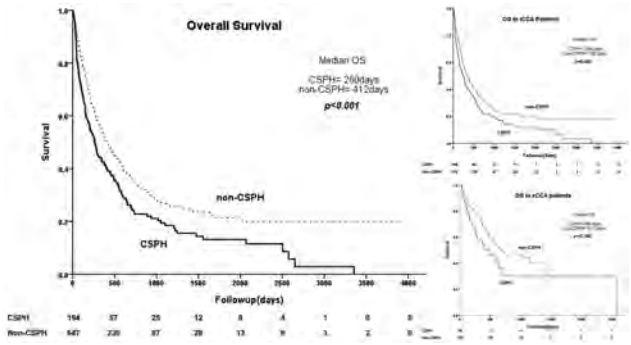

Disclosures: Yingfan Chen: Nothing to Disclose, Yu-Jen Chen: Nothing to Disclose

3256 | BARRIERS AND FACILITATORS TO HEPATOCELLULAR CARCINOMA CARE COORDINATION AMONG HISPANIC PATIENTS AT A MULTIDISCIPLINARY CLINIC

JANAN LEPPO[2], MD; MARYAM ZAFER[1], MD; KELLI LIU[2], MD; EDMUNDO ESPARZA, MD[2]; JESSE NODORA[3], DRPH; ADAM BURGOYNE[4], MD, PHD; ZACHARY BERMAN[5], MD; YUKO KONO, MD, PHD[1], [1]UC SAN DIEGO DEPARTMENT OF HEPATOLOGY, [2]DEPARTMENT OF INTERNAL MEDICINE, [3]DEPARTMENT OF FAMILY MEDICINE AND PUBLIC HEALTH, [4]DEPARTMENT OF HEMATOLOGY AND ONCOLOGY, AND [5]DEPARTMENT OF INTERVENTIONAL RADIOLOGY. Janan Leppo[1] Maryam Zafer[1] Kelli Liu[1] Edmundo Esparza[1] Jesse Nodora[1] Adam Burgoyne[1] Zachary Berman[1] Yuko Kono[1] [1]UCSD

Background: Hepatocellular carcinoma (HCC) is among the fastest rising causes of cancer-related death in the U.S., with Hispanic patients disproportionately affected by late-stage diagnosis, fragmented care, and referral delays. A retrospective study at UC San Diego (UCSD) found that multidisciplinary clinic care improved treatment timelines, but Hispanic patients still entered care late and often with advanced disease. This study underpinned future efforts to explore barriers to and facilitators of cancer care coordination, particularly as they apply to timely referrals to specialty cancer care. To date, no qualitative study has explored experiences with cancer care coordination among Hispanic patients with HCC. **Methods:** We conducted 19 interviews with 14 Hispanic patients with imaging-or-biopsy confirmed HCC and 5 key informants. Participants also completed a brief survey in which questions were crafted to discuss barriers and facilitators in the referral process. Four additional key informants completed surveys only. All patients were seen at UCSD's Moores Cancer Center. Interviews explored referral experiences and systemic, cultural, and linguistic barriers. Certified interpreters supported interviews. Transcripts were coded line-by-line in Taguette, and themes and subthemes were developed using an inductive approach informed by grounded theory. Clinical and demographic data were collected by chart review. **Results:** The median age of patients was 69.5 years. Ten were referred from providers outside of UCSD. BCLC stages were as follows: 0 (n = 1), A (n = 7), B (n = 1), C (n = 5, D (n = 0). Five had decompensated cirrhosis. Twelve patients were treatment naive. Referral-to-appointment time averaged 35 days. Eleven patients primarily spoke Spanish. Ten had public insurance. From patient interviews, analysis revealed key themes including logistical barriers (transport, insurance), communication gaps (language, literacy), emotional responses (guilt, anxiety), and trust. From provider interviews, themes included system inefficiencies, administrative delays, provider-level knowledge gaps about when to refer, and patient disengagement linked to unclear communication. **Conclusion:** Patient and provider perspectives highlight key breakdowns in care coordination, ranging from incomplete referrals and missing imaging to limited comprehension and logistical barriers like language and transportation. Interventions should include standardized electronic medical record referral templates, streamlined record retrieval, bilingual navigation from the point of referral, and targeted outreach to enhance provider awareness of when and how to refer patients. Culturally responsive education and interpreter-supported scheduling should also be expanded upon. These strategies are critical to improving care coordination and referral efficiency, ultimately advancing equity in HCC care for Hispanic patients.

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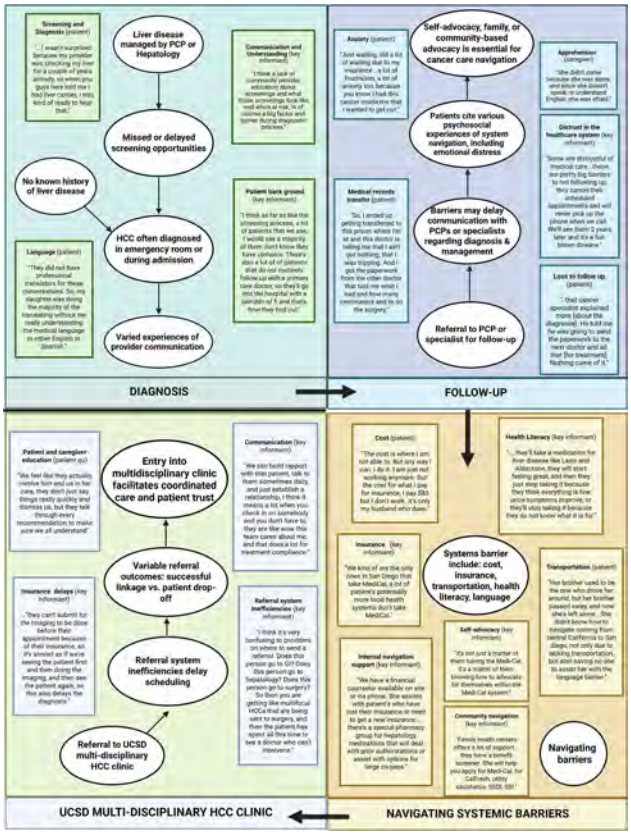

Disclosures: Janan Leppo: Nothing to Disclose, Maryam Zafer: Nothing to Disclose, Kelli Liu: Nothing to Disclose, Edmundo Esparza: Nothing to Disclose, Jesse Nodora: Nothing to Disclose, Adam Burgoyne: Nothing to Disclose, Zachary Berman: Boston Scientific: Consultant, Sirtex: Consultant, Trisalus Life Sciences: Consultant, AstraZenica: Consultant, Geurbet: Speaking and Teaching, Yuko Kono: Bracco Diagnostics. Inc: Grant/Research Support, Cannon Medical systems co: Independent Contractor

3257 | EFFICACY AND SAFETY OF BINTRAFUSP ALFA IN BILIARY TRACT CANCER: A REVIEW OF THE CLINICAL TRIALS

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Background: Biliary tract cancers (BTCs) are rare and aggressive with limited treatment options. Bintrafusp alfa (BA), a bifunctional fusion protein targeting Programmed Cell Death Ligand 1 (PD-L1) and Transforming Growth Factor-β (TGF-β), has been investigated in clinical trials. **Methods:** A detailed search was done on Pubmed, Scopus and Embase for the articles, using the search terms ("bintrafusp alfa" OR "M7824") AND ("biliary tract cancer" OR "biliary tract neoplasm*" OR "cholangiocarcinoma" OR "gallbladder cancer" OR "extrahepatic cholangiocarcinoma" OR "intrahepatic cholangiocarcinoma") AND ("locally advanced" OR "metastatic" OR "advanced stage" OR "unresectable"). Upon analysis, descriptive synthesis was conducted from two trials: a randomized phase 2/3 trial assessing BA plus GemCis versus GemCis alone in first-line BTC, and a phase 2 single-arm trial evaluating BA monotherapy in chemorefractory BTC.

We reviewed findings from two multinational clinical trials:

(1) An open-label, single-arm Phase 2 trial (n = 159) assessing BA monotherapy, and

(2) A randomized, double-blind, placebo-controlled Phase 2/3 trial (n = 297) evaluating BA + Gemcitabine and Cisplatin (GemCis) versus placebo + GemCis.

Key endpoints were objective response rate (ORR), progression-free survival (PFS), overall survival (OS) and safety. **Results:** In the single-arm phase 2 trial (N = 159), BA monotherapy showed a modest ORR of 10.7% with a median OS of 7.6 months and a manageable safety profile. In the phase 2/3 trial (N = 297), BA+GemCis did not show improvement of OS compared to GemCis alone (11.5 vs 11.5 months; HR: 1.23; p = 0.7394), with higher early death and bleeding rates.

In the monotherapy trial, BA showed an ORR of 10.7%, including 3 complete responses, 10.0 months median duration of response. Response was present irrespective of PD-L1 expression. Of note, ORR was higher in those who had low tumor mutational burden (15.5%) and Isocitrate Dehydrogenase 1 (IDH1) mutations (21.4%). Immune-related adverse events (irAEs) occurred in 28.9%, with steroid management required in the majority of the cases.

In the Phase 2/3 trial, bintrafusp alfa + GemCis did not improve OS (11.5 vs 11.5 months; HR 1.23) or PFS (5.5 vs 5.6 months) compared to GemCis alone. Though ORR was higher (31.5% vs 19.5%) in numbers, the combination arm patients showed a higher incidence of irAEs (20.5%), bleeding events (28.8% vs 7.4%), and early deaths. Biomarker analyses got limited due to early trial termination but there was no suggestion of strong benefit. **Conclusion:** Comparatively, BA monotherapy showed a bit better response than combination therapy, as the latter had more toxicity without clear additional benefits. BA is not effective for unselected patient population, with limited Results: in only certain molecular subgroups.

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Author, year	Study design	Objective	Sample	Primary efficacy	Durability of response	Safety profile	Interpretation
Yoo et al, 2022	Open label, single arm phase 2 trial	Evaluate the antitumor activity, safety and immune biomarkers	159 patients with advanced/ metastatic BTC (IHCC, EHCC, gallbladder)	Objective response rate(ORR), 10.7%(17/159 responded)	Median duration of response(DOR):1 0 months, durable response rate(>6 months):6.3% of all patients, Median progression-free survival(PFS) 1.6 months	Treatment related AEs(all grades):92.3%, grade>3 treatment related AEs:29.4%, Immune related AEs:28.9%	Good single-agent activity with durable responses in subset, manageable safety profile
Oh et al, 2024	Multinational multicenter phase III trial	Evaluate safety and efficacy in combination with standard chemotherapy Gemcitabine + Cisplatin	297 randomized patientsto orally advanced/ metastatic BTC)	ORR 31.5% in drug group, and 19.5% in placebo group.	Median DOR in the drug group 7 months, while in placebo group it was 12.6 months, Median PFS of 5.5 months in drug group vs 5.6 months in placebo	More treatment related AEs in bintrafusp alfa groupIesp immune related), higher rate of bleeding events(28.8% vs 7.4%) and immune related AEs(20.5% in bintrafusp group), more early treatment discontinuations and deaths in the bintrafusp alfa group(within 60 days)	No added OS/PFS benefit observed, increased side effects caused early termination

Figure 1: Table showing the overview of efficacy and safety of the clinical trials of Bintrafusp alfa on biliary tract cancer

Disclosures: MANASA SINDHURA NAGINENI: Nothing to Disclose, Sunil Bogati: Nothing to Disclose, Bheshraj Karki: Nothing to Disclose, Qi Yu: Nothing to Disclose

3258 | TARGETING PAK1 ON TUMOUR-ASSOCIATED MACROPHAGES ENHANCES THE EFFICACY OF IMMUNOTHERAPY IN HEPATOCELLULAR CARCINOMA

Tongguo Miao[1] ying zhang[2] Yuemin Nan[2], [1]Tianjin First Central Hospital, [2]Hebei Medical University Third Hospital

Background: The tumour microenvironment (TME) is an important mediator of tumour immunotherapy resistance. Unfortunately, hepatocellular carcinoma (HCC) does not respond to immunotherapy due to a lack of enhancing inflammation in tumor microenvironment (TME), a contributing factor is P21 (RAC1) Activated Kinase 1 (PAK1). PAK1 is selectively highly expressed in tumour-associated macrophages (TAMs). How PAK1 impacts the TME remains understudy. **Methods:** We investigated the role of the PAK1/mTORC1/TFEB pathway in HCC development by conducting metabolomic analysis, gene expression profiling and immunohistochemistry analyses in RAW264.7 cells, oncogene-induced HCC mouse models and human HCC samples, and further explored the molecular mechanism by which PAK1 promoted macrophages M2 polarization. **Results:** PAK1 is selectively expressed in different types of tumours, and was associated with adverse clinical outcome in patients with cancer. We show that targeting PAK1 is a novel and tolerable approach to significantly reverse M2 transition to inhibit tumor development in vitro experiment. This approach reshaped the tumour immune microenvironment, reduced IL-10 and TGF-β expression of macrophages, together with increasing expression and nuclear localization of TFEB. Mechanistically, PAK1 promoted M2 polarisation of macrophages by activating mTORC1/TFEB pathway. **Conclusion:** The PAK1/mTORC1/TFEB pathway plays an important role in HCC, targeting PAK1 represents a potential strategy to enhance the efficacy of immunotherapy in HCC patients.

Disclosures: Tongguo Miao: Nothing to Disclose, ying zhang: Nothing to Disclose, Yuemin Nan: Nothing to Disclose

3259 | BASELINE VON WILLEBRAND FACTOR AS A PREDICTIVE BIOMARKER FOR RESPONSE TO ATEZOLIZUMAB PLUS BEVACIZUMAB IN ADVANCED HEPATOCELLULAR CARCINOMA

Tadashi Namisaki Shinya Sato[1] NORIHISA NISHIMURA[2] Kosuke Kaji[2] Hiroaki Takaya[2] Naoki Nishimura[2] Hitoshi Yoshiji[1], [1]Nara Medical University, [2]奈良医大　消化器代謝・内科

Background: We have previously reported that von Willebrand factor antigen (VWF), a blood coagulation factor, is a potential predictor of response to molecularly targeted drugs and hepatic infusion chemotherapy in patients with advanced hepatocellular carcinoma (HCC). In this study, we investigated the usefulness of VWF as a predictor of response to atezolizumab plus bevacizumab (AB) therapy for HCC. **Methods:** This study included 58 patients with advanced HCC treated with AB therapy. Serum vWF levels were measured by ELISA prior to treatment. Treatment response was assessed using RECIST v1.1 and modified RECIST (mRECIST). Multivariate logistic regression was performed to identify independent predictors of response. Associations between vWF and progression-free survival (PFS), overall survival (OS), liver function, and tumor characteristics were also analyzed. **Results:** Median age: 74 years, HBV/HCV/alcohol/MASLD/PBC/other: 11/13/13/12/1/8, median maximum tumor diameter: 3.7 cm, median number of tumors: 4. VWF was positively correlated with Child-Pugh score, ALBI score, PIVKA2, and number of tumors, and negatively correlated with Alb. VWF, ALBI score, and Child-Pugh score were significantly lower in the response group [CR/PR] than in the non-response group [SD/PD] in the RECIST study. In multivariate analysis, only low VWF (<135) was identified as a predictor of therapeutic response based on RECIST. Progression-free survival (PFS) was prolonged in the low VWF group (<135) compared to the high VWF group ($135\leq$). mRECIST showed that VWF was significantly lower in the response group than in the non-response group. Only

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low VWF (< 135) was also identified as a predictor of therapeutic response based on mRECIST in multivariate analyses. PFS in the low VWF group was prolonged compared to the high VWF group. The area under the ROC curve (AUC) was 0.807 (RECIST v1.1) and 0.760 (mRECIST). vWF levels correlated positively with T-Bil, AST, ALT, tumor number, and VEGF, and negatively with albumin. Positive correlations were also observed with Child-Pugh and ALBI scores. **Conclusion:** Low baseline vWF levels are associated with favorable response and prognosis in AB therapy for advanced HCC. vWF may serve as a useful non-invasive biomarker to guide treatment selection in clinical practice.

Disclosures: Tadashi Namisaki: Nothing to Disclose, Shinya Sato: Nothing to Disclose, NORIHISA NISHIMURA: Nothing to Disclose, Kosuke Kaji: Nothing to Disclose, Hiroaki Takaya: Nothing to Disclose, Naoki Nishimura: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose

3260 | THERAPEUTIC EFFICACY AND SAFETY OF LENVATINIB AS A SECOND-LINE THERAPY AFTER FIRST-LINE THERAPY OF ATEZOLIZUMAB PLUS BEVACIZUMAB IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA

Chinatsu Nishioka[1] Kazuki Maesaka[1] Machiko Kai[1] Kumiko Shirai[1] Kazuhiro Murai[1] Yuki Makino[1] Yuki Tahata[1] Kazuyoshi Ohkawa[2] Masanori Miyazaki[3] Nobuyuki Tatsumi[4] Kengo Matsumoto[5] Yasutoshi Nozaki[6] Takayuki Yakushijin[7] Ryotaro Sakamori[8] Takahiro Kodama[1] Hayato Hikita[1] Tetsuo Takehara[6], [1]The University of Osaka, [2]Osaka International Cancer Institute, [3]Osaka Police Hospital, [4]Japan Community Health Care Organization Osaka Hospital, [5]Toyonaka Municipal Hospital, [6]Kansai Rosai Hospital, [7]Osaka General Medical Center, [8]Osaka National Hospital

Background: Atezolizumab plus bevacizumab is approved as a first-line treatment for unresectable hepatocellular carcinoma (uHCC). Most patients experience disease progression during this therapy, but optimal subsequent therapies remain unclear. In Japan, re-administration of immune checkpoint inhibitors is permitted for uHCC, and durvalumab plus tremelimumab or lenvatinib is often used as second-line therapy following first-line treatment with atezolizumab plus bevacizumab. This study aimed to compare the therapeutic efficacy and safety in patients who received durvalumab plus tremelimumab or lenvatinib as a second-line therapy, all following prior first-line therapy of atezolizumab plus bevacizumab. **Methods:** We retrospectively analyzed the therapeutic efficacy and safety in 85 patients with unresectable HCC who received durvalumab plus tremelimumab (18) or lenvatinib (67) as a second-line therapy after first-line therapy of atezolizumab plus bevacizumab using a prospectively registered cohort. Tumor response was assessed using RECIST version 1.1. Progression-free survival (PFS), overall survival (OS), and adverse events (AEs) were compared. **Results:** In the durvalumab plus tremelimumab group, the background etiology was viral/non-viral in 6/12 patients, modified ALBI (mALBI) grade 1–2a/2b–3 in 9/9, and BCLC stage A/B or C in 8/10. In the lenvatinib group, etiology was viral/non-viral in 32/35, mALBI grade 1–2a/2b–3 in 38/29, and BCLC stage A/B or C in 24/43. Following atezolizumab plus bevacizumab, the ORRs were 11.1% in the durvalumab plus tremelimumab group and 20.9% in the lenvatinib group ($p = 0.616$); the DCRs were 33.3% and 68.7%, respectively ($p = 0.005$). The median PFS was 1.9 months vs. 4.2 months, favoring lenvatinib ($p < 0.001$), and median OS was 10.6 vs. 14.0 months ($p = 0.323$). In the analysis of PFS, the treatment regimen (durvalumab plus tremelimumab) was a significant factor ($p = 0.002$). For OS, BCLC stage C ($p = 0.015$) and neutrophil-to-lymphocyte ratio ≥ 3 ($p = 0.020$) were significant; treatment regimen was not ($p = 0.137$). **Conclusion:** Following first-line therapy with atezolizumab plus bevacizumab, lenvatinib showed better PFS than durvalumab plus tremelimumab and may be considered an effective second-line treatment option.

Disclosures: Chinatsu Nishioka: Nothing to Disclose, Kazuki Maesaka: Nothing to Disclose, Machiko Kai: Nothing to Disclose, Kumiko Shirai: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Yuki Makino: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Kazuyoshi Ohkawa: Nothing to Disclose, Masanori Miyazaki: Nothing to Disclose, Nobuyuki Tatsumi: Nothing to Disclose, Kengo Matsumoto: Nothing to Disclose, Yasutoshi Nozaki: Nothing to Disclose, Takayuki Yakushijin: Nothing to Disclose, Ryotaro Sakamori: Nothing to Disclose, Takahiro Kodama: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

3261 | GENETIC PREDISPOSITION IN METABOLIC-DRIVEN HEPATOCELLULAR CARCINOMA: PNPLA3/GCKR POLYMORPHISMS AND THEIR DIFFERENTIAL ASSOCIATION PATTERNS COMPARED TO VIRAL ETIOLOGY

Tao Liu[1] yali Liu[1] Hongqin Xu[1] jingyuan zhou[1] Jia Zhou[1] Junqi Niu[1] Yanhang Gao[1], [1]The First Hospital of Jilin University

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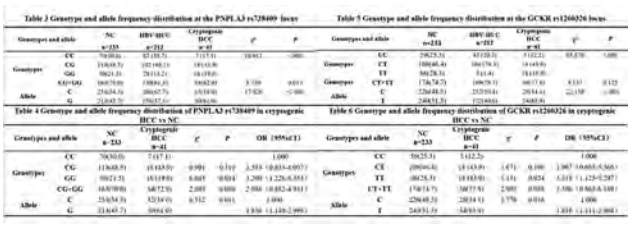
Background: A subset of primary liver cancer patients lacks identifiable etiologies at diagnosis, termed cryptogenic hepatocellular carcinoma (HCC). Increasing evidence suggests metabolic dysfunction-associated steatotic liver disease (MASLD) as a key contributor to cryptogenic HCC. Genetic factors play a critical role in MASLD-associated HCC pathogenesis. This study aims to compare the clinical and genetic profiles of cryptogenic HCC and hepatitis B virus (HBV)-related HCC (HBV-HCC), providing novel insights for early diagnosis and targeted treatment. **Methods:** From January 2017 to December 2023, 41 cryptogenic HCC patients diagnosed at the Department of Hepatology, First Hospital of Jilin University, were enrolled. 212 patients with HBV-HCC diagnosed during the same period were randomly selected. 233 healthy controls (NC group) from the health examination center were included. Demographic characteristics, laboratory parameters, and genetic polymorphisms (PNPLA3 rs738409, TM6SF2 rs58542926, GCKR rs1260326, MBOAT7 rs641738, HSD17B13 rs72613567, ALDH2 rs671) were analyzed to compare NC, cryptogenic HCC and HBV-HCC groups and explore disease-specific features. **Results:** Among 4,545 HCC patients, 85 (1.87%) met cryptogenic HCC criteria. Compared to HBV-HCC patients, cryptogenic HCC patients exhibited older age at diagnosis, higher BMI, increased female predominance, higher rates of non-cirrhotic background and diabetes, and elevated GGT, ALP, and TG levels (all $P < 0.05$). Statistic analysis revealed significant differences in genotype and allele frequencies of PNPLA3 rs738409 and GCKR rs1260326 among cryptogenic HCC, HBV-HCC, and NC groups (all P **Conclusion:** Patients with cryptogenic HCC exhibit older age at diagnosis, higher BMI, and a higher prevalence of female, diabetes, non-cirrhotic background, distant/lymph node metastasis. Notably, this group demonstrated lower rates of AFP elevation but significantly elevated serum levels of GGT, ALP, and TG compared to HBV-HCC patients. PNPLA3 rs738409 (GG genotype and G allele) and GCKR rs1260326 (TT genotype and T allele) polymorphisms may serve as genetic risk factors for cryptogenic HCC, highlighting their potential involvement in disease development.



Disclosures: Tao Liu: Nothing to Disclose, yali Liu: Nothing to Disclose, Hongqin Xu: Nothing to Disclose, jingyuan zhou: Nothing to Disclose, Jia Zhou: Nothing to Disclose, Junqi Niu: Nothing to Disclose, Yanhang Gao: Nothing to Disclose

3262 | PERFORMANCE OF HCC RISK SCORES IN PATIENTS WITH ADVANCED CHRONIC LIVER DISEASE IN THE NETHERLANDS

Mohamed Moussa[1] Koos de Wit[2] Bert Baak[3] Dave Sprengers[1] Stan van Wijk[1] Emma Kleij[1] Roy Dwarkasing[4] Willem Pieter Brouwer[4] Femme Dirksmeier-Harinck[5] Jordan Feld[6] Harry Janssen[7] Bart Takkenberg[8] Milan Sonneveld[9], [1]Erasmus University Medical Centre, Rotterdam, The Netherlands, [2]Amsterdam University medical center, Amsterdam, The Netherlands., [3]OLVG Hospital, Amsterdam, The Netherlands., [4]Erasmus University Medical Center, Rotterdam, The Netherlands., [5]St. Franciscus hospital, Rotterdam, Netherlands., [6]Toronto Centre for Liver Disease, University Health Network, University of Toronto, Toronto, Ontario, [7]Erasmus University Medical Centre, Toronto Centre for Liver Disease, Toronto General Hospital, [8]Amsterdam University Medical Centers, location AMC, Amsterdam, The Netherlands, [9]Erasmus University Medical Center, Rotterdam, The Netherlands

Background: Patients with advanced chronic liver disease (ACLD) are at high risk of developing HCC and are therefore recommended to undergo bi-annual HCC surveillance. Given the increasing prevalence of ACLD, individualised risk prediction would be helpful to identify patients in whom surveillance could be safely deferred. This study aimed to assess the performance of three HCC risk scores—PAGE-B, THRI, and aMAP in patients with ACLD in the Netherlands. **Methods:** In this retrospective multicentre study, adults (≥ 18 years) with ACLD (diagnosed by liver stiffness ≥ 10 kPa, liver biopsy, or compatible imaging findings) were included. Exclusion criteria were follow-up < 6 months, missing data for any of the three risk scores, prior HCC, other baseline malignancies, or other life-limiting conditions (e.g. heart or kidney failure). PAGE-B (age, gender, platelet count), THRI (age, gender, platelet count, etiology) and aMAP (age, male, albumin-bilirubin and platelets) scores were calculated as previously reported, and patients were allocated to low, intermediate and high-risk groups according to established cut-offs (PAGE-B: 0-9, 10-18, > 18; THRI < 120, 120-240, > 240; aMAP < 50, 50-60, > 60). Kaplan–Meier analysis was used to estimate cumulative HCC incidence according to risk score categories. **Results:** A total of 1,698 patients were included in this cohort, with the most common etiologies being steatotic liver disease 494 (29%), HCV 307 (18%), and HBV 294 (18%). The majority were male (64%), and the median age was

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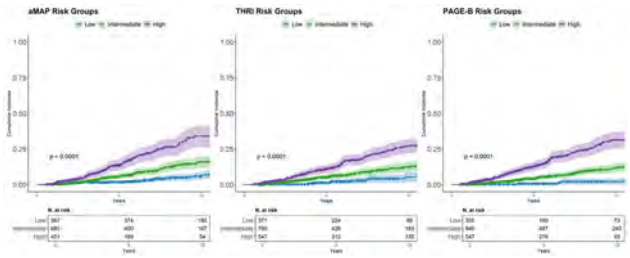
52 years (IQR: 43–60). Median baseline CTP was 5 (IQR: 5–6), and 316 (19%) had a history of decompensation. A total of 201 (11.8%) patients developed HCC during a median follow-up time of 5.7 years (IQR: 3.3–9.7 years). The 5-year and 10-year cumulative HCC incidence was 6.34% (95% CI: 5.02–7.64) and 16.20% (95% CI: 13.63–18.68), respectively. For PAGE-B, the numbers of patients identified as low/intermediate/high risk were 305 (18%)/ 846 (50%)/ 547 (32%). The 5-year cumulative incidences of HCC in the low, intermediate, and high-risk groups were 0.78%, 4.26%, and 12.97%, respectively. For THRI, the numbers of patients identified as low, intermediate, and high risk were 371 (22%), 780 (46%), and 547 (32%). The 5-year cumulative incidences of HCC in the low, intermediate, and high-risk groups were 1.40%, 5.19%, and 11.30%, respectively. For aMAP, the numbers of patients identified as low, intermediate, and high risk were 567 (33%), 680 (40%), and 451 (27%). The 5-year cumulative incidences of HCC in the low, intermediate, and high-risk groups were 1.92%, 5.96%, and 13.71%, respectively. **Conclusion:** Patients with ACLD at low predicted risk of HCC according to PAGE-B, THRI and/or aMAP scores had a very limited 5-year risk of HCC. Application of these scores could allow for safe deferral of HCC surveillance in 20-30% of patients with ACLD.



Disclosures: Mohamed Moussa: Nothing to Disclose, Koos de Wit: W. L. Gore & Associates: Speaking and Teaching, Bert Baak: Nothing to Disclose, Dave Sprengers: Nothing to Disclose, Stan van Wijk: Nothing to Disclose, Emma Kleij: Nothing to Disclose, Roy Dwarkasing: Nothing to Disclose, Willem Pieter Brouwer: Nothing to Disclose, Femme Dirksmeier-Harinck: Nothing to Disclose, Jordan Feld: AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/ Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/ Research Support, Vir: Grant/Research Support, AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/ Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/ Research Support, Vir: Grant/Research Support, Harry Janssen: Gilead Sciences: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Janssen: Grant/Research Support, Roche: Grant/Research Support, Vir Biotechnology Inc.: Grant/Research Support, Aligos: Consultant, Gilead Sciences: Consultant, GlaxoSmithKline: Consultant, Grifols: Consultant, Roche: Consultant, Vir Biotechnology Inc: Consultant, Precision Biosciences: Consultant, Academic Medical Education: Consultant, H.C. Wainwright & Co: Consultant, Bart Takkenberg: Nothing to Disclose, Milan Sonneveld: Roche: Grant/Research Support, Gilead: Grant/ Research Support, Gilead: Consultant, ViR: Advisor, GSK: Grant/Research Support, Fujirebio: Grant/ Research Support

3263 | UTILITY OF CONTRAST-ENHANCED ULTRASOUND IN HCC SURVEILLANCE IN FONTAN ASSOCIATED LIVER DISEASE

Rachel Orbuch[1] Amanda Pirola[1] Daniel Ganger[2] Amir Borhani[2] Maryam Haghshomar[2] Camila Lopes Vendrami[2] Frank Miller[2] Helena Gabriel[2],
[1]Northwestern McGaw Medical Center, [2]Northwestern Memorial Hospital

Background: The Fontan procedure for patients with congenital heart disease and univentricular physiology involves diversion of systemic venous return to the pulmonary artery. This results in chronic hepatic venous congestion and decreased cardiac output, leading to progressive hepatic fibrosis known as Fontan-associated liver disease (FALD). FALD is associated with an increased risk of hepatocellular carcinoma (HCC). Additionally, these patients may have lesions associated with Fontan physiology, such as nodular regenerative hyperplasia (NRH) and focal nodular hyperplasia (FNH). These benign focal lesions can erroneously demonstrate suspicious features on CT and MR imaging. Society guidelines recommend HCC surveillance and screening. No universal guidelines exist as to the correct screening method or interval in Fontan

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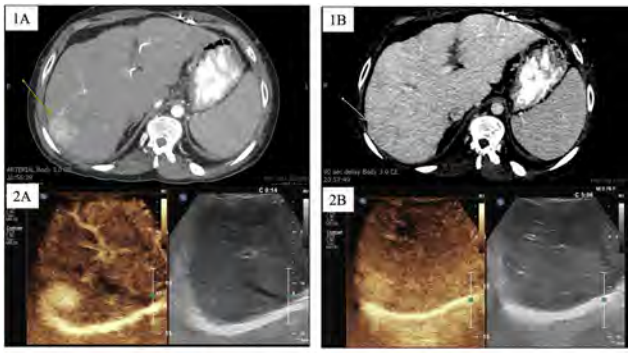
patients. CT and MR are problematic in this patient population due to the cumulative radiation risk and difficulty with MRI due to pacemakers and postsurgical changes. Ultrasound is often used as the surveillance method; however, gray scale ultrasound may not visualize focal lesions seen with FALD. Contrast-enhanced ultrasound (CEUS) is typically used as a diagnostic tool once a focal lesion is identified, however, in this specific patient population it may also be helpful as a screening/surveillance tool. This is a novel use of CEUS. The purpose of this study is to introduce CEUS as a means of screening, surveillance, and diagnostic characterization of focal lesions in FALD. **Methods:** We conducted a retrospective case series of 10 post-Fontan patients receiving care at a tertiary academic medical center. Patients who underwent both non-contrast liver ultrasound and CEUS between 2020 and 2024 were identified. We gathered the data from previous imaging studies, including MRI and CT scans. The stability at 2 years was utilized as a reference standard for benign lesions in accordance with AASLD criteria. We assessed the impact and accuracy of CEUS on lesion characterization and clinical decision-making. **Results:** 10 post-Fontan patients underwent HCC surveillance with both standard US and CEUS to screen for HCC. The median age of the Fontan procedure for patients was 3 years old. Patients were aged between 22 to 38 years old at the time of CEUS scan (mean age: 29.8). CEUS classified hepatic lesions as benign in 8 of 10 patients (6 FNH and 2 NRH). In one patient case, CEUS was unable to localize the lesion, and in another, lesion characterization was incomplete. In all 8 visualized cases, the lesions were stable on subsequent imaging. **Conclusion:** CEUS is a novel diagnostic imaging method that can problem-solve and confirm benign lesions with suspicious characteristics. CEUS can potentially be used as a surveillance method in FALD patients in whom CT and MR imaging is limitated. Although small in scope, this study introduces a method that can have utility in surveillance and management of post-Fontan patients.



Surveillance imaging of post-Fontan patient comparing CT triple-phase imaging demonstrating enhancing lobulated mass in the right hepatic lobe (1A). The mass is hyperdense on 60 second image and is isodense to slightly hypodense on CT washout image (1B). Contrast-enhanced ultrasound (CEUS) performed demonstrating arterially hyperenhancing lesion (2A) without washout at 4 minutes (2B). CEUS is able to further classify the lesion as a benign Fontan-related FNH-like lesion.

Disclosures: Rachel Orbuch: Nothing to Disclose, Amanda Pirola: Nothing to Disclose, Daniel Ganger: WCG: Consultant, Amir Borhani: Siemens Healthineers: In-kind research support, Boston Scientific: Consultant, Maryam Haghshomar: Nothing to Disclose, Camila Lopes Vendrami: Nothing to Disclose, Frank Miller: Nothing to Disclose, Helena Gabriel: Nothing to Disclose

3264 | TP53 ALTERATIONS PREDICT POOR RESPONSE TO IMMUNE CHECKPOINT INHIBITOR-BASED CHEMOTHERAPY IN INTRAHEPATIC CHOLANGIOCARCINOMA.

Hiroki Inada[1] Satoshi Narahara[1] Daiki Maeda[1] Hideaki Miyamoto[1] Katsuya Nagaoka[1] Hiromitsu Hayashi[1] Yasuhito Tanaka[1], [1]Kumamoto University

Background: Comprehensive genome profile (CGP) has shown promise in improving outcomes for biliary tract cancer, particularly intrahepatic cholangiocarcinoma (ICC). However, there are no reports linking genetic mutations identified through CGP to the efficacy of immune checkpoint inhibitors (ICIs) for ICC. This study aimed to clarify the association between genetic alterations and clinical outcomes of ICI-combined chemotherapy. **Methods:** We retrospectively analyzed 25 patients with ICC who initiated Gemcitabine + Cisplatin + Durvalumab (GCD) therapy between December 2022 and August 2024 at our institution and affiliated facilities. **Results:** The median patient age was 73 years (range: 47–81), with 18 males (72%). Disease stage distribution was I/II/III/IV (2/3/0/20), and distant metastases were present in 14 patients (56%). GCD was used as first-line therapy in 16 patients (64%), and CGP was performed in 19 patients (76%). The best overall response included partial response in 6 (24%), stable disease in 13 (52%), and progressive disease in 2 (8%); one patient underwent conversion surgery. Median overall survival (OS) was 11.1 months (95% CI: 6.9–not reached), and median progression-free survival (PFS) was 7.8 months (95% CI: 3.6–10.6). Actionable gene mutations were identified in 16 of 19 patients (84%) who underwent CGP, and 6 of 8 patients whose GCD therapy was discontinued due to progression received genomically matched therapies. Multivariate analysis identified TP53 mutation as a significant factor associated with shorter PFS ($P = 0.036$, HR: 4.2, 95% CI: 1.10–16.1). The disease control rate (DCR) was significantly higher in the TP53 wild-type group (100%, 11/11) compared to the TP53-mutant group (62.5%, 5/8) ($P = 0.047$). Median PFS was also significantly shorter in the TP53-mutant group (4.0 months, 95% CI: 1.8–5.2) than in the TP53 wild-type group (9.6 months, 95% CI: 3.4–14.0) ($P = 0.011$). Spatial transcriptomic analysis further revealed a reduced density of CD8+ T cells at the tumor–non-tumor interface in TP53-

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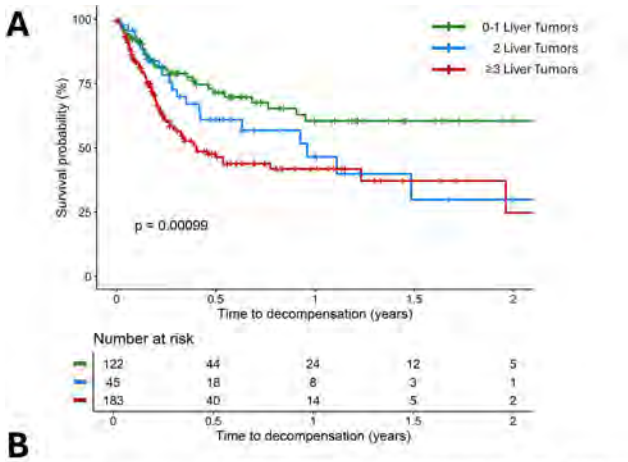
mutated ICC, suggesting a potential immune evasion mechanism. **Conclusion:** Our findings indicate that TP53-mutated ICC is characterized by an immune-cold tumor microenvironment, potentially contributing to resistance to immune checkpoint inhibitors. CGP may play a critical role in identifying predictive biomarkers and guiding personalized treatment strategies for ICC.

Disclosures: Hiroki Inada: Nothing to Disclose, Satoshi Narahara: Nothing to Disclose, Daiki Maeda: Nothing to Disclose, Hideaki Miyamoto: Nothing to Disclose, Katsuya Nagaoka: Nothing to Disclose, Hiromitsu Hayashi: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

3265 | LIVER TUMOR BURDEN INDEPENDENTLY PREDICTS RISK OF HEPATIC DECOMPENSATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA RECEIVING IMMUNOTHERAPY.

Erica Storm[1] Yoo Jin Lee[1] Willis Tang[1] Francis Yao[1] Neil Mehta[1] Robin Kelley[1] Jennifer Lai[1] Michael Li[1], [1]University of California, San Francisco

Background: Hepatic decompensation is a major driver of mortality in patients with advanced hepatocellular carcinoma (HCC). We hypothesized that liver tumor burden contributes to decompensation risk. **Methods:** We conducted a single center retrospective cohort study of all patients who received immune checkpoint inhibitors (ICI) for HCC from 2016-2024. The primary outcome was time to first decompensation or further decompensation. First decompensation was defined as new ascites, hepatic encephalopathy (HE), and/or variceal bleeding (VB). In patients with decompensated liver disease, further decompensation was defined as per Baveno VII criteria. Competing risks regression was utilized to investigate the impact of number of liver tumors (as a surrogate for hepatic tumor burden) on time to hepatic decompensation, with mortality as a competing risk. **Results:** Of 350 study patients with a median follow-up of 288 days, 134 (38%) decompensated after starting ICI therapy. The median time to decompensation was 63 days (IQR 27-199); ascites (29%) was the most common event followed by HE (15%) and VB (5%). Patients with 3+ liver tumors had significantly shorter time to decompensation compared to those with 2 tumors and to those with 0-1 tumors (median 0.4 vs 1.0 vs 2.4 years, $p < 0.001$; Figure 1A). On competing risks regression, number of hepatic tumors was significantly associated with hepatic decompensation (HR: 1.28 for each additional tumor up to 4, 95% CI 1.11-1.48, $p < 0.001$) after adjusting for key confounders including MELD 3.0, ICI regimen, prior locoregional therapy, line of systemic therapy, macrovascular invasion, extrahepatic metastases, and alpha-fetoprotein (Figure 1B). This effect was maintained in subgroup analyses of patients without cirrhosis ($n = 79$) (HR 1.89 per tumor, $p = 0.008$) and previously compensated cirrhosis ($n = 245$) (HR 1.43 per tumor, $p < 0.001$). However, in patients with prior decompensation ($n = 105$), liver tumor number was not associated with further decompensation (HR 1.07, $p = 0.541$). Patients who decompensated ≤ 90 days of ICI initiation had shorter overall survival compared to those who remained compensated (median 0.2 vs 1.7 years, $p < 0.001$). **Conclusion:** Number of liver tumors is positively associated with time to hepatic decompensation, even after adjusting for liver function and cancer stage. Compensated patients with high tumor burden may be at higher risk for decompensation than their MELD score would suggest and may benefit from co-management with hepatology.



B

Parameter	Hazard Ratio (HR)	95% Confidence Interval	P-Value
# Hepatic Tumors	1.280	1.107-1.480	0.0009
Atezolizumab plus Bevacizumab	1.050	0.642-1.718	0.8461
STRIDE†	0.907	0.547-1.504	0.7045
Prior Systemic therapy	0.898	0.557-1.447	0.6585
Prior Locoregional Therapy	1.282	0.859-1.913	0.2248
Macrovascular Invasion	1.367	0.922-2.027	0.1201
Distant metastasis	1.014	0.680-1.512	0.9461
AFP	1.065	0.954-1.188	0.2607
MELD3.0	1.155	1.112-1.199	<0.0001

Figure 1A: Kaplan-Meier analysis of time to decompensation based on number of hepatic tumors. Patients were censored at time of death. **Figure 1B:** Competing risks regression comparing rate of hepatic decompensation across several baseline parameters (with death as a competing risk). Number of hepatic tumors was an ordinal variable consisting of 0, 1, 2, 3, and ≥4 tumors. Each therapy parameter was compared to non-Atezolizumab plus Bevacizumab and non-STRIDE regimens. AFP was an ordinal variable consisting of <20, 20-200, 200-400, 400-1000 and >1000.
† Single Tremelimumab Regular Interval Durvalumab

Disclosures: Erica Storm: Nothing to Disclose, Yoo Jin Lee: Nothing to Disclose, Willis Tang: Nothing to Disclose, Francis Yao: Nothing to Disclose, Neil Mehta: Merck: Consultant, FujiFilm WAKO: Consultant, Robin Kelley: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Michael Li: Nothing to Disclose

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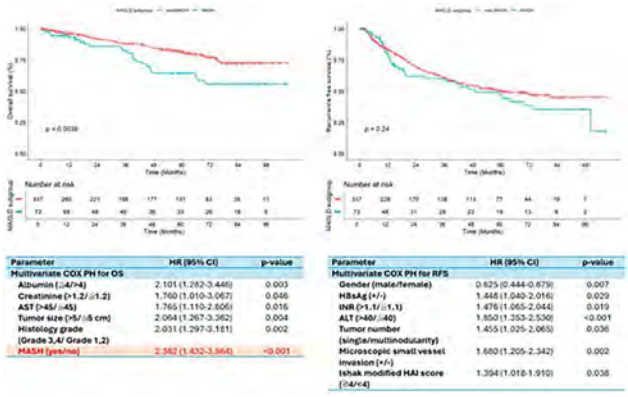
3266 | METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS PREDICTED POOR PROGNOSIS IN HEPATOCELLULAR CARCINOMA PATIENTS WITH CONCURRENT MASLD

Chien-Wei Su[1] Chun-Ting Ho[1] Chia-Jung Ho[1] Wei-Yu Kao[2] Ying-Ying Yang[1] Yi-Hsiang Huang[1] Ming-Chih Hou[1] Jaw-Ching Wu[3], [1]Taipei Veterans General Hospital, [2]Taipei Medical University Hospital, [3]National Yang Ming Chiao Tung University, Taipei, Taiwan

Background: The prognostic significance of metabolic dysfunction-associated steatotic liver disease (MASLD) in patients with hepatocellular carcinoma (HCC) remains unclear. Furthermore, the impact of metabolic dysfunction-associated steatohepatitis (MASH), on clinical outcomes in patients with MASLD-related HCC has not been well defined. This study aimed to evaluate the prognostic role of MASH in HCC patients with concurrent MASLD and to identify risk factors associated with poor overall survival (OS) and recurrence-free survival (RFS). **Methods:** We retrospectively analyzed 410 HCC patients with histologically confirmed MASLD who underwent curative surgical resection at Taipei Veterans General Hospital between 2016 and 2022. MASLD was defined as $>5\%$ steatosis in non-tumor liver tissue with at least one cardiometabolic risk factor. Patients with histopathological features of steatohepatitis were categorized as MASH. The primary and secondary endpoints were OS and RFS, respectively. Clinical, laboratory, imaging, and histopathological data were collected. Survival outcomes were estimated using the Kaplan–Meier method and compared by the log-rank test. Independent prognostic factors were identified through Cox proportional hazards models. **Results:** Among the 410 MASLD-HCC patients, 73 were classified as MASH and 337 as non-MASH. Compared to the non-MASH group, MASH patients were older, had smaller tumors, higher serum aspartate aminotransferase (AST) and fibrosis-4 (FIB-4) scores, and lower platelet counts (all $p < 0.05$). After a median follow-up of 59.2 months, 79 patients died and 168 experienced HCC recurrence. The 5-year OS rate was significantly lower in the MASH group (64.4%) than in the non-MASH group (81.7%; $p = 0.006$), while RFS was comparable between the two groups. Multivariate analysis identified lower serum albumin, higher serum creatinine and AST levels, larger tumor size, higher histological grade, and presence of MASH as independent predictors of poor OS. **Conclusion:** MASH was associated with poor OS in HCC patients with concurrent MASLD following surgical resection.



Parameter	HR (95% CI)	p-value
Multivariate COX PH for OS		
Albumin (≦4/>4)	2.101 (1.282-3.446)	0.003
Creatinine (>1.2/≦1.2)	1.760 (1.010-3.067)	0.046
AST (>45/≦45)	1.765 (1.110-2.806)	0.016
Tumor size (>5/≦5 cm)	2.064 (1.267-3.362)	0.004
Histology grade (Grade 3,4/ Grade 1,2)	2.031 (1.297-3.181)	0.002
MASH (yes/no)	2.582 (1.432-3.864)	<0.001

Parameter	HR (95% CI)	p-value
Multivariate COX PH for RFS		
Gender (male/female)	0.625 (0.444-0.879)	0.007
HBsAg (+/-)	1.446 (1.040-2.016)	0.029
INR (>1.1/≦1.1)	1.476 (1.065-2.044)	0.019
ALT (>40/≦40)	1.850 (1.353-2.530)	<0.001
Tumor number (single/multinodularity)	1.455 (1.025-2.065)	0.036
Microscopic small vessel invasion (+/-)	1.680 (1.205-2.342)	0.002
Ishak modified HAI score (≧4/<4)	1.394 (1.018-1.910)	0.038

Disclosures: Chien-Wei Su: Nothing to Disclose, Chun-Ting Ho: Nothing to Disclose, Chia-Jung Ho: Nothing to Disclose, Wei-Yu Kao: Nothing to Disclose, Ying-Ying Yang: Nothing to Disclose, Yi-Hsiang Huang: Nothing to Disclose, Ming-Chih Hou: Nothing to Disclose, Jaw-Ching Wu: Nothing to Disclose

3267 | A NOVEL MOUSE MODEL OF INTRAHEPATIC CHOLANGIOCARCINOMA AND EFFECTS OF SGLT2 INHIBITORS ON THE MALIGNANCY

Yohei Shirakami[1] Masahito Shimizu[1] Hiroyasu Sakai[1], [1]Gifu University

Background: Cholangiocarcinoma (CCA) is the second most common primary cancer of the liver and has a poor prognosis. Although animal models for various human cancers have been established, an appropriate model for CCA has not been established yet. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been reported to possess anti-tumor effects against several types of cancers; however, studies examining their potential impact on CCA are lacking. This study was conducted to establish a novel mouse model for CCA induced by administration of a carcinogen to obese mice. This study also investigated anti-tumor effects of SGLT2 inhibitors on CCA. **Methods:** C57BLKS/J-db/db (db/db) mice, which displayed obesity and steatohepatitis, and a colonic carcinogen azoxymethane (AOM) were used. CCA cell lines were also used to investigate the mechanism of action of an SGLT2 inhibitor canagliflozin (CANA) on CCA, evaluating cell proliferation, cell cycle, and epithelial-mesenchymal transition (EMT). **Results:** Histopathological analysis revealed that biliary tract lesions in the liver appeared to be intrahepatic CCA with higher tumor incidence, shorter experimental duration, and a markedly increased incidence in obese mice. Molecular markers analyzed by microarray and qPCR indicated that cancerous lesions originated from cholangiocytes and developed in inflamed livers. These findings indicated that

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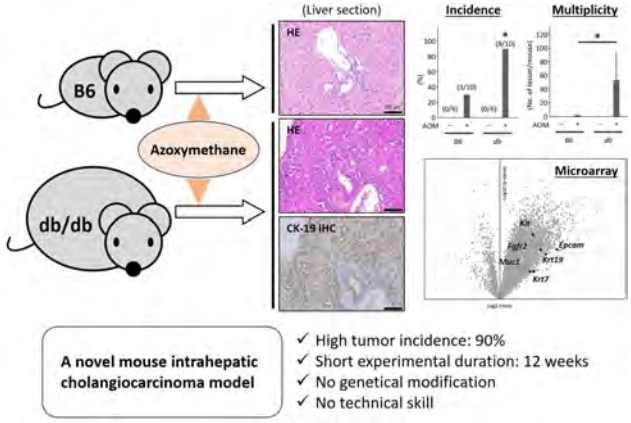
this might be a novel mouse model of intrahepatic CCA in the context of steatohepatitis. SGLT2 gene expression was confirmed in human CCA tissue and cell lines. CANA treatment decreased CCA cell viability, while growth promotion was also observed in a relatively low dose treatment. CANA treatment arrested the cell cycle and suppressed EMT in CCA cells. CANA reduced the expressions of histone deacetylase 6 (HDAC6), increased NAMPT and SIRT1, and activated the NAD+ salvage pathway. Combination of CANA with an NAMPT inhibitor significantly decreased cell viability. In addition, administration of an SGLT2 inhibitor suppressed the development of bile duct lesions in a novel mouse CCA model. **Conclusion:** We established a novel mouse model of intrahepatic CCA using obese db/db mice administered AOM. This novel CCA model may provide insights into the pathogenesis of intrahepatic CCA and contribute to the establishment of new therapies for this disease. An SGLT2 inhibitor CANA inhibited cell proliferation and EMT by inducing cell cycle arrest in CCA cells, while CANA may also have tumor-promoting effects. Further studies are required to investigate the dual effects of CANA on CCA.



Disclosures: Yohei Shirakami: Nothing to Disclose, Masahito Shimizu: Nothing to Disclose, Hiroyasu Sakai: Nothing to Disclose

3268 | DIFFERENTIAL IMPACT OF ANTIBIOTICS ON ANTI-PD-1 VERSUS ANTI-PD-L1 THERAPY IN HEPATOCELLULAR CARCINOMA

Cheng-Hao Kuo[1] Chun-Ying Wu[1], [1]National Yang MIng Chiao Tung University, Taiwan

Background: Immune check point inhibitors (ICIs) targeting the PD-1/PD-L1 axis have improved clinical outcomes in advanced hepatocellular carcinoma (HCC), yet response rates remain suboptimal. Recent findings have demonstrated an association between ICI responsiveness and the gut microbiota, suggesting that the microbiome may modulate ICI efficacy. Mechanistic distinctions between anti-PD-1 and anti-PD-L1 antibodies imply that the microbiome and its perturbations may differentially affect treatment outcomes. We therefore evaluated the impact of antibiotic-induced dysbiosis on anti-PD-1/PD-L1 therapy in real-world HCC patients. **Methods:** We conducted a multicenter, retrospective cohort study using the TriNetX Global Collaborative Network. HCC patients initiating anti-PD-1 or anti-PD-L1 therapy between 2006 and 2023 were identified. Antibiotic (ABX) exposure was defined as ≥ 1 ABX prescription within 3 months before to 3 months after ICI initiation, with a 3-month wash-out to minimize confounding by active infection. Propensity score matching (PSM) was performed to adjust for 78 covariates, including demographics, liver function and decompensation status, etiology, tumor burden, comorbidities, and concurrent medications. The primary outcome was 1-year overall mortality; secondary outcomes included liver decompensation and metastasis. Exploratory analyses extended follow-ups for all outcomes up to 3 years. Cox proportional hazard regression was performed, and all outcomes were assessed using landmark analysis at 6, 12, and 36 months. **Results:** After PSM, the anti-PD-1 cohort comprised 698 matched pairs of ABX-exposed and non-exposed patients, and the anti-PD-L1 cohort 627 pairs. In patients initiating anti-PD-L1, ABX exposure was associated with a higher 1-year mortality risk (HR, 1.47; 95% CI, 1.13-1.91), with survival curves diverging through 36 months. In contrast, the anti-PD-1 cohort showed no significant difference in overall mortality between ABX-exposed and non-exposed patients. Both ICI classes exhibited an increased risk of liver decompensation with ABX use, while metastasis risk did not differ by ABX exposure in either cohort. **Conclusion:** Recent ABX exposure significantly impairs 1-year survival in HCC patients receiving anti-PD-L1 therapy, but not in anti-PD-1 therapy. These findings highlight a microbiome-dependent modulation of the PD-L1 axis, whereas PD-1 blockade appears less sensitive to antibiotic-induced dysbiosis.

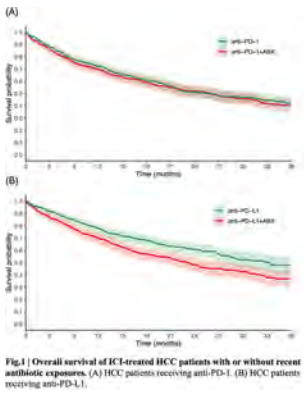


Fig.1 | Overall survival of ICI-treated HCC patients with or without recent antibiotic exposures. (A) HCC patients receiving anti-PD-1. (B) HCC patients receiving anti-PD-L1.

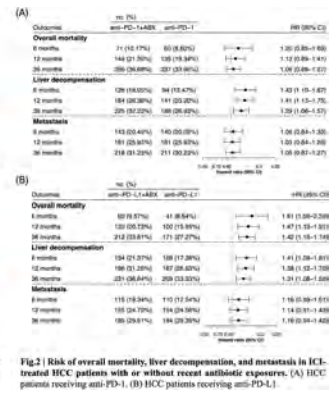


Fig.2 | Risk of overall mortality, liver decompensation, and metastasis in ICI-treated HCC patients with or without recent antibiotic exposures. (A) HCC patients receiving anti-PD-1. (B) HCC patients receiving anti-PD-L1.

Disclosures: Cheng-Hao Kuo: Nothing to Disclose, Chun-Ying Wu: Nothing to Disclose

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3269 | ASSESSMENT OF QUALITY OF LIFE IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA RECEIVING ATEZOLIZUMAB PLUS BEVACIZUMAB

Rania Lithy[1] Mohamed Samy[2] Menna Rashwan[2] Tamer Elbaz[3] Ashraf Omar[4] Hend Shousha[2] Yasser Hamada[2] Yasser Elesnawy[5] Marwa Abdelghany[5] Mohamed Abdelwahed[5] Hany William[5] Nouran Roby[5] Ahmed Abdelmaksoud[2] Moahmed Nabil[2], [1]Faculty of Medicine, Cairo University, ESLC member, Cairo, Egypt, [2]faculty of medicine, Cairo University, Cairo, Egypt, [3]Faculty of medicine, Cairo Univeristy, NGU, Cairo, Egypt, [4]Faculty of medicine, Cairo university, ESLC founder, Cairo, Egypt, [5]Ahmed Maher teaching hospital, Cairo, Egypt

Background: Patients with hepatocellular carcinoma (HCC) experience significantly lower health-related quality of life (HRQOL) compared to the general population. This study aimed to evaluate changes in HRQOL and its correlation with treatment response and overall survival in patients with advanced HCC receiving Atezolizumab plus Bevacizumab. **Methods:** This prospective study included 25 patients with advanced HCC treated with Atezolizumab and Bevacizumab. HRQOL was assessed every three months using the FACT-G, EORTC HCC-18, and EORTC QLQ-C15-PAL questionnaires. Over a 12-month period, we evaluated the association between HRQOL, and tumor characteristics, and treatment response according to modified RECIST. Overall survival was determined at the end of the study. **Results:** Among 25 participants (88% male, median age 63), all had ECOG 0 and Child-Pugh A. 24 of the patients were BCLC stage C; one was stage B. Overall survival was 92%. Per mRECIST, 8% achieved complete response, 44% partial response, 21.7% stable disease, and 22.7% progression. At 12 months, QOL was assessed based on mRECIST-defined treatment response (regression, stable disease, progression). The regression group reported the highest overall FACT-G score (59.38 ± 8.26), followed by the stable disease group (56.80 ± 1.10) and the progression group (55.80 ± 0.45), although these differences were not statistically significant. Notably, the regression group also had the highest scores in both emotional and physical well-being domains. The EORTC HCC-18 scores suggested a tendency toward a higher symptom burden in the regression group across several domains, including nutrition (5.38 ± 0.87) and fatigue (3.85 ± 1.77). Similar patterns were noted in the subscales for body image, jaundice, fever, and pain, all showing numerically elevated scores in the regression group. Similarly, EORTC QLQ-C15-PAL scores showed a slightly higher symptom burden in the regression group (22.85 ± 6.14). Tumor size negatively correlated with FACT-G pain ($r = –0.476$, $p = 0.025$) and physical well-being ($r = –0.409$, $p = 0.059$), and was significantly linked to greater symptom burden on the HCC-18 physical subscale ($r = –0.425$, $p = 0.049$). **Conclusion:** HRQOL was not significantly compromised in patients who completed a one-year course of Atezolizumab plus Bevacizumab. This suggests HRQOL may be a useful prognostic marker in advanced hepatocellular carcinoma, with potential importance comparable to survival. **Disclosures:** Rania Lithy: Nothing to Disclose, Mohamed Samy: Nothing to Disclose, Menna Rashwan: Nothing to Disclose, Tamer Elbaz: Nothing to Disclose, Ashraf Omar: Nothing to Disclose, Hend Shousha: Nothing to Disclose, Yasser Hamada: Nothing to Disclose, Yasser Elesnawy: Nothing to Disclose, Marwa Abdelghany: Nothing to Disclose, Mohamed Abdelwahed: Nothing to Disclose, Nothing to Disclose, Hany William: Nothing to Disclose, Nouran Roby: Nothing to Disclose, Ahmed Abdelmaksoud: Nothing to Disclose, Moahmed Nabil: Nothing to Disclose

3270 | MALIGNANT LIVER NEOPLASM RELATED MORTALITY TRENDS DUE TO INFECTIVE VS NON-INFECTIVE ASSOCIATION: CDC WONDER ANALYSIS (1999–2020)

Jay Kakadiya[1] Jayasree Rajapandian[2] Kush Varsadiya[3] Areeba Fatima[4] [1]Kansas University Medical Center, [2]University of Alabama Birmingham, Montgomery, [3]Shri MP Shah Government Medical College, Jamnagar, India., [4]Civil Hospital Karachi

Background: Hepatocellular carcinoma (HCC), including intrahepatic bile duct cancer, remains the sixth leading cause of cancer-related mortality in the United States. Despite an overall decline in cancer mortality, deaths from liver cancer continue to rise. Recent surge in metabolic abnormalities plays a significant role in developing liver disorders. This study evaluates trends in age-adjusted mortality rates (AAMRs) for malignant liver cancers, distinguishing between infective causes (hepatitis B and C) and non-infective causes. These insights can guide future public health strategies and policy interventions. **Methods:** We conducted a cross-sectional analysis using CDC WONDER data from 1999 to 2020, focusing on malignant liver neoplasms, including intrahepatic bile duct cancer. Data were extracted using ICD-10 codes and stratified by age, sex, race, and region. Mortality trends were categorized by infective (hepatitis B or C) and non-infective (e.g., alcohol-related or metabolic liver disease) causes. Joinpoint regression was utilized to determine annual percent changes (APCs) and to identify trend inflection points across all the groups. **Results:** As shown in Figure 1A, AAMR from non-infective causes of liver

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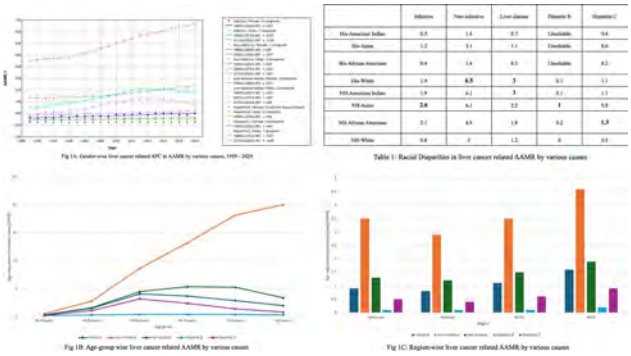
cancer significantly increased from 2.8 in 1999 to 4.5 in 2020, with APCs were 3.26% for males and 2.97% for females. In contrast, infective causes showed a more modest rise in AAMR—from 0.6 to 1.2 during the same period. Non-infective cause is associated with 80% of total death count attributable to liver cancer. Table 1 highlights racial disparities: Non-Hispanic (NH) Asians had the highest AAMR among the infective cohort (2.6), driven primarily by hepatitis B (1.0). NH African Americans showed the highest hepatitis C-related AAMR (1.3). Among non-infective causes, Hispanic Whites had the highest AAMR (6.5). Age-group wise disparities: non-infective AAMR rose steadily with age, peaking in those 85+, while infective AAMRs peaked in the 55–64 age group. Regional variation is depicted in Figure 1C, with the Western U.S. consistently showing the highest AAMRs across all groups. Detailed result is shown in Figure 1. **Conclusion:** With advances in viral hepatitis management, the mortality burden from HCC has shifted toward non-infective etiologies, likely driven by alcohol use, obesity, and metabolic syndrome. Targeted public health interventions addressing these modifiable risk factors are essential to curb the rising trend of liver cancer mortality in the U.S.



Disclosures: Jay Kakadiya: Nothing to Disclose, Jayasree Rajapandian: Nothing to Disclose, Kush Varsadiya: Nothing to Disclose, Areeba Fatima: Nothing to Disclose

3271 | IDENTIFICATION OF URIC ACID-RELATED GENES AS POTENTIAL BIOMARKERS IN HEPATOCELLULAR CARCINOMA

Yuqin Xie[1] Fengsheng Dai[1] sheng wang[1] Cheng Zhang[1] MaoYun Liu[1] Yi Wang[1] Jiale Lu[1] Hui Li[1] DeWei Li[1], [1]Chongqing University Cancer Hospital

Background: The potential role of abnormal uric acid metabolism in the pathogenesis and progression of hepatocellular carcinoma (HCC) has attracted increasing attention. Recent studies have shown that serum uric acid levels are closely related to the development of HCC. However, the role of uric acid in the occurrence and recurrence of HCC remains unclear. In this study, our goal was to explore the role of uric acid-related genes in HCC comprehensively. **Methods:** We analyzed RNA sequencing and clinical data from 374 HCC patients to develop a prognostic model of UARGs via 10 machine learning algorithms and 117 unique combinations. Survival and time-dependent receiver operating characteristic (ROC) analyses were performed to assess the efficacy of the model. Differences in clinical characteristics, the tumor immune microenvironment and drug sensitivity between the high- and low-risk groups were also analyzed. The function of the target gene PSRC1 was evaluated through in vitro and in vivo experiments, including CCK-8, colony formation, flow cytometry, Transwell assays, and xenograft mouse models. **Results:** UARGs have strong predictive performance for the prognosis and predictive performance of HCC patients. In addition, prediction models based on UARGs can effectively predict the outcomes of HCC immunotherapy and chemotherapy and are related to the immune characteristics of different risk groups. PSRC1 is a key gene whose high expression is associated with poor prognosis in HCC patients. Knockdown of PSRC1 significantly inhibits HCC cell proliferation, induces apoptosis, promotes cell cycle arrest, and inhibits HCC cell migration and invasion. **Conclusion:** This integrative strategy not only bridges the gap between uric acid metabolism and HCC pathobiology but also paves the way for identifying novel diagnostic biomarkers and therapeutic targets. Our work is anticipated to contribute to a deeper understanding of the molecular mechanisms linking metabolic dysregulation to HCC, ultimately guiding the development of more effective precision medicine approaches for HCC patients.

Disclosures: Yuqin Xie: Nothing to Disclose, Fengsheng Dai: Nothing to Disclose, sheng wang: Nothing to Disclose, Cheng Zhang: Nothing to Disclose, MaoYun Liu: Nothing to Disclose, Yi Wang: Nothing to Disclose, Jiale Lu: Nothing to Disclose, Hui Li: Nothing to Disclose, DeWei Li: Nothing to Disclose

3272 | RETENTION OF LYMPHATIC OUTFLOW HINDERS NANOPARTICLE BIODISTRIBUTION IN HEPATOCELLULAR CARCINOMA

Jin-Kyu Park[1] Tae-Un Kim[1] Su-Min Baek[1] Jae-Hyuk Yim[1] Woo Jun Kim[1], [1]Kyungpook National University

Background: Nanotechnology has long been studied as therapeutics for chronic liver disease, and various nanoparticles (NPs) including PLGA, silica, gold nanoparticles and liposomes had been used in attempt to establish strategies for efficient drug delivery. NPs hold

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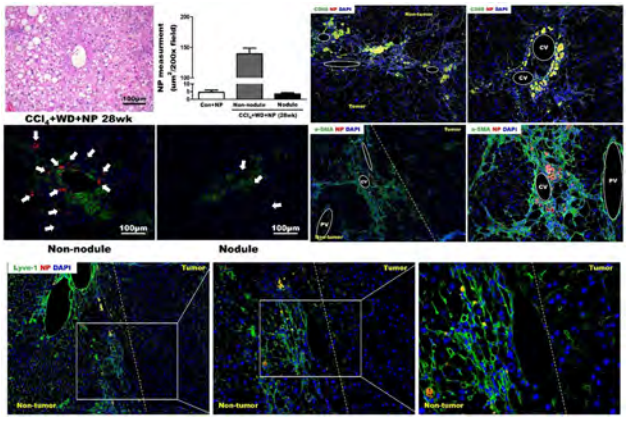
great promises for hepatocellular carcinoma (HCC) treatment, but several factors limit the delivery of NPs: tumor microenvironment, vasculature, reticulo-endothelial clearance, and immune responses. This study aims to investigate the specific vasculature and angiogenesis of HCC which hinders the NP distribution. **Methods:** HCC was induced with western diet and high-sugar water in combination with CCl_4 injection for 28 weeks. 200nm-sized NPs were injected 24hrs before sacrifice. Gross examination and histopathological analysis, serum biochemistry, immunofluorescence (IF), and immunohistochemistry (IHC) were performed to assess the microenvironment and vasculature of the disease related to NP distribution. **Results:** In tumor-induced mouse livers, hepatic NPs showed excess distribution in the pericentral areas of cirrhotic liver and fibrotic capsule surrounding the tumor. Majority of NPs were co-localized with CD68-positive Kupffer cells surrounded by collagen matrix. Also, nanoparticles were mainly distributed in the borderline of tumor region, showing limited entrance into the tumor tissue. In contrast to high distribution in cirrhotic tissue, NPs were significantly decreased in tumor tissues. Lyve-1 expression was significantly diminished in tumor tissues, and dilated lymphatic vessels were observed in the borderline of tumor region. **Conclusion:** Previously, the studies on limitations for nanoparticle therapy were focused on the penetration of nanoparticles into the tumor region. However, nanoparticle distribution in the tumor region was extensively low despite the nanoparticle influx through arterial blood supply. Absence of Lyve-1 expression in the tumor region suggests the loss of LSEC fenestration and dilated lymphatic vessels in the borderline of tumor showed retention of lymphatic outflow. Conclusively, the defenestration of LSEC and elevated blood pressure in the tumor region explains the absence of nanoparticles, suggesting the need for extensive study on tumor microvasculature for efficient delivery of therapeutic nanoparticles.



Disclosures: Jin-Kyu Park: Nothing to Disclose, Tae-Un Kim: Nothing to Disclose, Su-Min Baek: Nothing to Disclose, Jae-Hyuk Yim: Nothing to Disclose, Woo Jun Kim: Nothing to Disclose

3273 | IMPACT OF CARDIOMETABOLIC RISK ON HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HEPATITIS B: A RETROSPECTIVE STUDY

Chanavee Toh[1] Kedsiree Sanit[2] Pimsiri Sripongpun[2] Naichaya Chamroonkul[2] Suthat Liangpunsakul[3] Teerha Piratvisuth[4] Apichat Kaewdech[2], [1]Faculty of Medicine, Prince of Songkla University, Thailand, [2]Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Thailand, [3]Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA, [4]NKC Institute of Gastroenterology and Hepatology, Faculty of Medicine, Prince of Songkla University

Background: Chronic hepatitis B virus (HBV) infection remains a major global health concern and a leading cause of hepatocellular carcinoma (HCC). While cirrhosis is a well-established risk factor for HCC, the role of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and cardiometabolic risk (CMR) factors —such as obesity, diabetes mellitus, hypertension, and dyslipidemia—remains unclear. This study aimed to evaluate the impact of MASLD and CMR factors on HCC risk in patients with chronic hepatitis B (CHB). **Methods:** We conducted a retrospective cohort study at Songklanagarind Hospital from January 2011 to December 2021. Adults with CHB and no evidence of HCC within six months of diagnosis were included. Data collected included demographics, liver biochemistry, metabolic comorbidities, HBV viral load, antiviral treatment, and imaging findings. HCC diagnoses were confirmed through the hospital cancer registry. Cumulative HCC incidence was estimated using Nelson-Aalen plots, and multivariable Cox proportional hazards models identified predictors of HCC. The aMAP score was assessed in subgroups with obesity, CMR factors, and MASLD. **Results:** Among 4,944 patients with CHB, 151 (3.1%) developed HCC. HCC occurred more frequently in older, male patients. Cirrhosis was the strongest predictor (adjusted hazard ratio [aHR] = 7.22; 95% CI: 4.46–11.70), followed by obesity (aHR = 1.85; 95% CI: 1.28–2.67) and male sex (aHR = 1.78; 95% CI: 1.25–2.53). Hypertension (aHR = 1.34; 95% CI: 0.91–1.97) and diabetes (aHR = 1.08; 95% CI: 0.70–1.65) showed nonsignificant trends toward increased risk. Statin use (aHR = 0.43; 95% CI: 0.22–0.85), higher platelet count (aHR = 0.62; 95% CI: 0.47–0.82), and higher serum albumin (aHR = 0.64; 95% CI: 0.48–0.86) were associated with lower HCC risk. Dyslipidemia without statin therapy (aHR = 1.10; 95% CI: 0.70–1.72) and hepatic steatosis (aHR = 0.85; 95% CI: 0.49–1.48) were not significantly associated with HCC. HCC incidence increased with the number of

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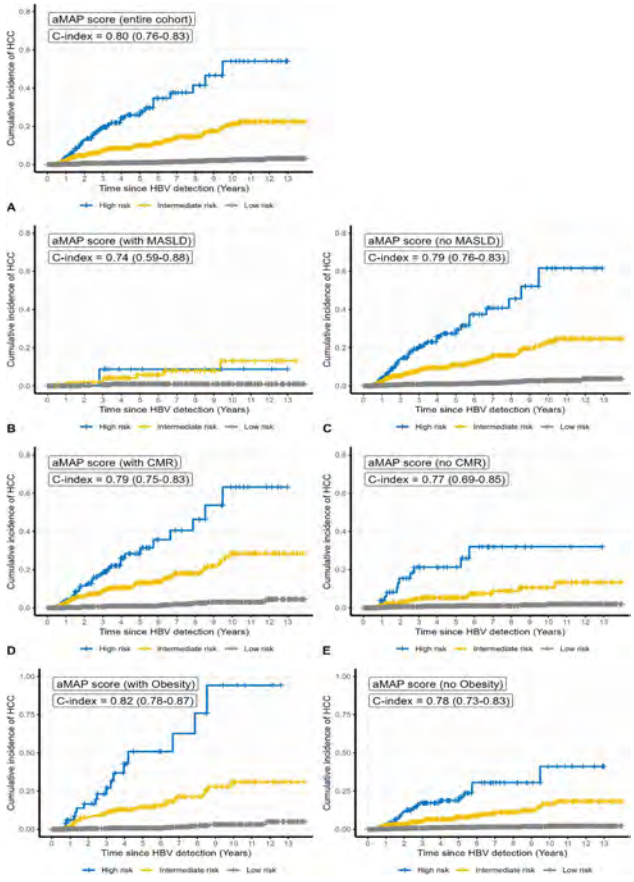
CMR factors. The aMAP score demonstrated good discriminatory performance in patients with obesity (C-index = 0.82), CMR factors (0.79), and MASLD (0.74). **Conclusion:** In this CHB cohort, cirrhosis, male sex, and obesity independently increased the risk of HCC, while statin use, higher platelet count, and higher albumin were protective. An increasing number of CMR factors was associated with higher HCC risk. The aMAP score effectively stratified HCC risk among patients with obesity, CMR, and MASLD.



Disclosures: Chanavee Toh: Nothing to Disclose, Kedsiree Sanit: Nothing to Disclose, Pimsiri Sripongpun: Nothing to Disclose, Naichaya Chamroonkul: Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Teerha Piratvisuth: Nothing to Disclose, Apichat Kaewdech: Nothing to Disclose

3274 | PUS7-MEDIATED RNA PSEUDOURIDYLATION DRIVES PROLIFERATION AND METASTASIS IN INTRAHEPATIC CHOLANGIOCARCINOMA

liu maoyun[1] Fengsheng Dai[1] sheng wang[1] Yi wang[1] Jiale Lu[1] YuQin Xie[2] Ai Shen[1] DeWei Li[1] Hui Li[1],

[1]Chongqing University Cancer Hospital, [2]Chongqing university cancer h

Background: Intrahepatic cholangiocarcinoma (ICC), the second most common subtype of primary liver cancer, is a highly aggressive and metastatic malignancy with limited therapeutic options. Despite progress in surgical and systemic treatments, clinical outcomes for ICC remain dismal. Post-transcriptional RNA modifications have emerged as key regulators of tumor biology. Among these, pseudouridine (Ψ) is one of the most abundant RNA modifications, broadly distributed across RNA species and implicated in various pathological processes. This study aims to investigate the biological role and mechanistic contribution of PUS7-mediated pseudouridylation in ICC progression. **Methods:** Three pairs of matched primary and recurrent ICC tissues were collected. RNA modification levels were quantified using LC-MS/MS and dot blot analysis, and differentially expressed genes were identified by RNA sequencing. Immunohistochemistry (IHC) was performed on a tissue microarray containing 136 ICC samples to evaluate PUS7 expression and its association with clinicopathological features and patient prognosis. Pus7 knockout ($Pus7^{-/-}$) mice and a hydrodynamic tail vein injection–induced ICC model was used to investigate the role of PUS7 in ICC development. Functional assays were conducted to assess the proliferative, migratory, and invasive capacities of ICC cells. Nascent protein synthesis was measured using the SUnSET assay and HPG pulse-labeling assay. **Results:** LC-MS/MS analysis revealed that the Ψ modification level was significantly elevated in recurrent ICC tissues compared to primary tumors. This increase in Ψ modification was primarily mediated by PUS7, a pseudouridine synthase which was also found to be highly expressed in recurrent tumors. High PUS7 expression was significantly associated with vascular invasion, lymph node metastasis, and poor patient prognosis. In vitro functional assays demonstrated that PUS7 promotes ICC cell proliferation, migration, and invasion. In vivo, hydrodynamic tail vein injection–based ICC models showed that Pus7 knockout markedly suppressed tumor initiation and progression, whereas PUS7 overexpression significantly enhanced tumor development. Mechanistically, PUS7 was shown to regulate nascent protein synthesis in ICC cells, suggesting a critical role of PUS7-mediated pseudouridylation in driving ICC progression. **Conclusion:** Our study revealed that PUS7-mediated pseudouridylation plays a critical regulatory role in the progression of ICC, providing a theoretical foundation for the development of novel PUS7-targeted therapeutic strategies.

Disclosures: liu maoyun: Nothing to Disclose, Fengsheng Dai: Nothing to Disclose, sheng wang: Nothing to Disclose, Yi wang: Nothing to Disclose, Jiale Lu: Nothing to Disclose, YuQin Xie: Nothing to Disclose,

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Ai Shen: Nothing to Disclose, DeWei Li: Nothing to Disclose, Hui Li: Nothing to Disclose

3275 | ADVERSE EVENT PROFILE OF SECOND-LINE TYROSINE KINASE INHIBITORS AFTER ATEZOLIZUMAB/BEVACIZUMAB IN ADVANCED HCC: A META-ANALYSIS OF TREATMENT-RELATED TOXICITY

Ronald Blanco Montecino[1] Nehemias Guevara Rodriguez[2] Noemy Coreas[3] Yassine Kilani[4] Syeda Fatima Kamal[5] Daniel Mendoza Quispe[1] Iqra Arshad[4] Kamran Qureshi[6] John Richart[2], [1]Department of Internal Medicine, St Barnabas Hospital, Bronx, NY., [2]Division of Hematology-Oncology and BMT, Saint Louis University, St. Louis, MO, [3]National University of El Salvador, Social Security System, Division of OBGYN-Oncology, [4]Division of General Internal Medicine, Saint Louis University School of Medicine, St. Louis, MO, [5]Division of Hospice and Palliative Medicine, Saint Louis University School of Medicine, [6]Division of Gastroenterology and Hepatology, Saint Louis University School of Medicine, St. Louis,MO

Background: The tolerability of tyrosine kinase inhibitors (TKIs) in the post-immunotherapy setting has gained increasing relevance as treatment sequencing in HCC evolves. Comparative safety data are critical for optimizing therapeutic decisions with multiple agents available as second-line options after Atezolizumab/Bevacizumab failure. We conducted a proportional meta-analysis to quantify the incidence of treatment-related adverse events (AEs) associated with second-line TKIs in advanced HCC. **Methods:** We reviewed retrospective studies reporting any-grade and grade ≥ 3 AEs in patients receiving Lenvatinib, Regorafenib, Sorafenib, or Cabozantinib as second-line therapy following progression on first-line treatment. Data on nausea, vomiting, hypothyroidism, and other key toxicities were extracted. Pooled proportions were calculated using a random-effects model, and heterogeneity was assessed using I² statistics. All statistical analyses, including pooled proportions and heterogeneity estimates, were performed using Stata version 18 (Stata Corp, College Station, TX). **Results:** We included 9 studies comprising 907 patients treated with second-line tyrosine kinase inhibitors (TKIs) for advanced hepatocellular carcinoma (HCC). The overall safety profile was favorable, with most adverse events (AEs) being low grade. Pooled incidence rates for any-grade vomiting, and hypothyroidism were 4%, and 29%, respectively. Hypothyroidism was common with cabozantinib (32%) and lenvatinib (28%). Grade ≥ 3 AEs were infrequently reported due to inconsistent data across studies.

In lenvatinib-treated patients, elevated liver enzymes (AST/ALT) were the most frequent AE (any-grade: 61%; grade ≥ 3: 11%), followed by thrombocytopenia (33%/3%), bilirubin elevation (43%/5%), and hypothyroidism (28%/2%). Other notable AEs included proteinuria (37%/18%), fatigue (43%/5%), and hypertension (27%/3%).

Across TKIs, fatigue was the most common AE overall (48%, 95% CI: 34–61%), followed by hand-foot syndrome (30%, 95% CI: 17–43%), diarrhea (14–30%), and hypertension (21%, 95% CI: 10–33%). Severe events such as liver failure (overall: 6%/1%) and rash, vomiting, or elevated bilirubin $\geq$ G3 were rare. Anorexia and proteinuria were reported with similar frequency in lenvatinib and cabozantinib, with anorexia reaching up to 53% in cabozantinib-treated patients.

Heterogeneity was moderate (I² 43–70%) for most endpoints, reflecting variability in reporting and patient populations. **Conclusion:** Overall, our findings suggest that second-line TKIs exhibit a manageable safety profile, with low rates of high-grade toxicity. These results support their continued use in appropriately selected patients and highlight the need for uniform AE reporting in future head-to-head trials.

Table 1. Adverse events

Adverse Event	Lenvatinib (Any/ ≥G3)	Cabozantinib (Any / ≥G3)	Regorafenib(Any/ ≥G3)	Sorafenib (Any/ ≥G3)	Overall (Any/≥G3)
Nausea	0.18/0.02	—/—	—/—	—/—	—/—
Vomiting	0.03/0.02	0.10/0.10	0.03/0.02	0.07/0.02	0.04/0.02
AST/ALT elevation	0.61/ 0.11	—/—	—/—	—/—	—/—
Bilirubin elevation	0.43/ 0.05	—/—	—/—	—/—	—/—
Thrombocytopenia	0.33/ 0.03	—/—	—/—	—/—	—/—
Hypothyroidism	0.28 / 0.02	0.32 / 0.02	—/—	—/—	0.29/0.02
Proteinuria	0.37 / 0.18	0.42 / 0.32	—/—	—/—	0.38/0.20
Fatigue	0.43 / 0.05	0.43 / 0.12	0.55 / 0.03	0.73 / 0.05	0.48/0.05
Diarrhea	0.25 / 0.02	0.30 / 0.06	0.14 / 0.03	0.24 / 0.05	0.24/0.02
Hypertension	0.27 / 0.03	0.17 / 0.03	0.03 / 0.02	0.17 / 0.02	0.21/0.03
Hand-foot syndrome	0.23 / 0.02	0.34 / 0.06	0.45 / 0.07	0.54 / 0.07	0.30/0.03
Anorexia	0.37 / 0.06	0.53 / 0.05	—/—	—/—	0.39/0.06
Liver failure	0.08 / 0.01	0.10 /—	0.07 /—	0.12 /—	0.06/0.01

Disclosures: Ronald Blanco Montecino: Nothing to Disclose, Nehemias Guevara Rodriguez: Nothing to Disclose, Noemy Coreas: Nothing to Disclose, Yassine Kilani: Nothing to Disclose, Syeda Fatima Kamal: Nothing to Disclose, Daniel Mendoza Quispe: Nothing to Disclose, Iqra Arshad: Nothing to Disclose, Kamran Qureshi: Nothing to Disclose, John Richart: Sanofi: Stock - publicly traded company

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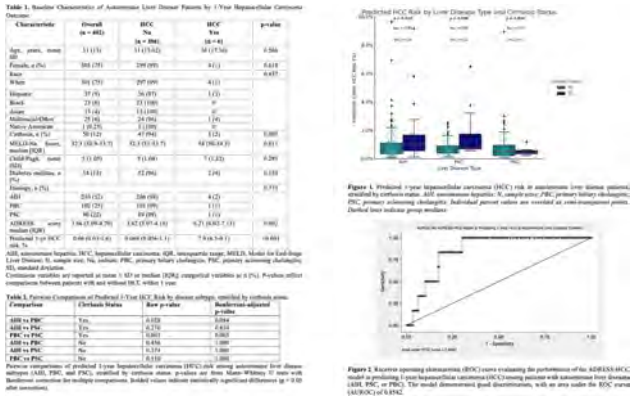
3276 | RISK STRATIFICATION FOR HEPATOCELLULAR CARCINOMA IN AUTOIMMUNE LIVER DISEASES USING THE ADRESS-HCC MODEL: U.S. SINGLE-CENTER VALIDATION

Ana Marenco-Flores[1] Ximena Parraga[2] Esteban Garita[3] Natalia Rojas-Amaris[2] Kim Ruiz-Arellanos[1] Romelia Barba[4] Vilas Patwardhan[1] Behnam Saberi[2] Alan Bonder[2], [1]Beth Israel Deaconess Medical Center, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, [3]Montefiore Medical Center, Albert Einstein College of Medicine, [4]Texas Tech University

Background: Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is typically fatal without early detection, with >90% of cases occurring in patients with cirrhosis. The incidence of autoimmune liver diseases, including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), is rising, though reported 1-year HCC risk varies widely. Risk is further shaped by age, sex, cirrhosis, comorbidities, and lifestyle factors. The ADRESS-HCC model provides personalized HCC risk estimates based on these variables. This study aims to externally validate the ADRESS-HCC score in autoimmune liver disease to estimate 1-year HCC risk and guide surveillance strategies. **Methods:** We conducted a prospective cohort study of adults with autoimmune liver disease (AIH, PBC, or PSC) evaluated at a U.S. tertiary care center between January 2018 and May 2025. Patients with complete data for ADRESS-HCC scoring and at least 12 months of follow-up or a 1-year HCC event were included. Exclusion criteria included prior HCC, liver transplantation, viral hepatitis, non-hepatic malignancy, or insufficient baseline data. The primary outcome was 1-year HCC. Predicted risk was compared by outcome and subtype using Mann–Whitney U tests with Bonferroni correction. Analyses were conducted in Stata; visualizations in Python. **Results:** Among 402 patients with autoimmune liver disease, 1.5% developed HCC within 1 year. Predicted 1-year HCC risk varied by disease subtype and cirrhosis status. Cirrhosis was more frequent among those who developed HCC compared to those who did not (50% vs. 12%, $p = 0.005$). The median predicted risk was higher in patients who developed HCC (7.9%) than in those who did not (0.069%; $p < 0.001$). Among patients with cirrhosis, predicted risk was significantly higher in AIH and PBC ($p = 0.015$ and $p = 0.006$, respectively), but not in PSC ($p = 0.826$). In pairwise comparisons, risk was significantly greater in PBC than PSC ($p = 0.003$, Bonferroni-adjusted), while no significant differences were observed among patients without cirrhosis. The ADRESS-HCC model demonstrated strong discriminatory performance, with an AUROC of 0.858 for predicting 1-year HCC. **Conclusion:** The ADRESS-HCC model accurately stratified 1-year HCC risk in patients with autoimmune liver disease, particularly those with cirrhosis. These findings support its use to guide individualized HCC surveillance strategies in this population.



Disclosures: Ana Marenco-Flores: Nothing to Disclose, Ximena Parraga: Nothing to Disclose, Esteban Garita: Nothing to Disclose, Natalia Rojas-Amaris: Nothing to Disclose, Kim Ruiz-Arellanos: Nothing to Disclose, Romelia Barba: Nothing to Disclose, Vilas Patwardhan: Nothing to Disclose, Behnam Saberi: Nothing to Disclose, Alan Bonder: GSK: Grant/Research Support, Mirium: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Cymabay: Grant/Research Support, Intercept: Grant/Research Support, Intercept: Consultant, GSK: Consultant, Ipsen: Consultant, Chemobab: Grant/Research Support, Alnylam: Consultant, Thirammune: Consultant

3277 | TUMOR-DERIVED CXCL2 SUPPRESSES HEPATOCELLULAR CARCINOMA THROUGH PROMOTING NEUTROPHIL N1 POLARIZATION VIA THE YBX1/SREBP2 AXIS

Xin Liu[1] Danli Yang[1] Ting Zhang[1] Lin Wang[1] Fengmin Lu[1] Xiangmei Chen[1], [1]Peking University Health Science Center

Background: While anti-tumor neutrophils (N1) play pivotal roles in immune regulation and tumor control, hepatocellular carcinoma (HCC) frequently reprograms them into a pro-tumor (N2) phenotypes to facilitate tumor immune escape. Identifying key modulators of neutrophil polarization toward the anti-tumor state is thus critically needed. **Methods:** We integrated comparative genomic hybridization and the RNA expression profile to identify pivotal neutrophil associated genes with copy number variations in HCC. Clinical specimens and *in vitro* and *in vivo* experiments, including gain-function assays, flow cytometry and subcutaneous

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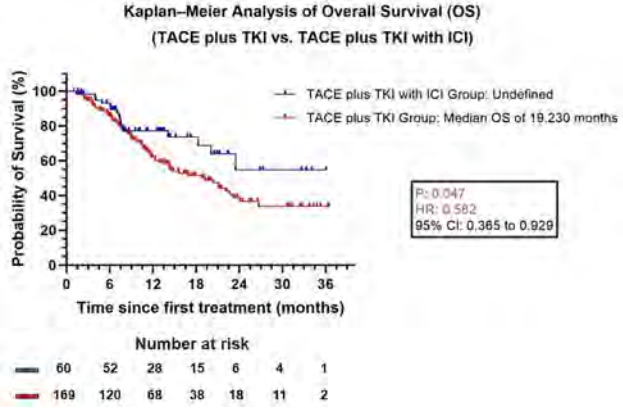
tumor xenograft model, were conducted to validate the roles and molecular mechanisms by which C-X-C Motif ligand 2 (CXCL2) modulating HCC immune microenvironment and its synergistic therapeutic efficacy of anti-PD-1 antibody. **Results:** CXCL2, a well-documented chemokine for neutrophil recruitment, was significantly downregulated in HCC tissues. Low CXCL2 expression was associated with poor prognosis and increased pro-tumor neutrophils. Surprisingly, subsequent experiments results identified that the overexpression of CXCL2 not only recruited neutrophils but also polarized them toward the N1 phenotype, thereby inhibiting HCC progression. Mechanistically, deviating from its canonical extracellular role, intracellular CXCL2 could bind to YBX1 and block its nuclear translocation. This reduced SREBP2-mediated transcriptional activation of the genes in regulating cholesterol biosynthesis, thereby remodeling the tumor microenvironment and impeding HCC development. More importantly, the combination of CXCL2 overexpression with anti-PD1 therapy synergistically suppressed HCC progression. **Conclusion:** We demonstrate an unconventional, tumor-suppressive role of CXCL2 in driving neutrophil N1 polarization and anti-tumor immune responses in HCC, positioning it as a promising therapeutic target for HCC.

Disclosures: Xin Liu: Nothing to Disclose, Danli Yang: Nothing to Disclose, Ting Zhang: Nothing to Disclose, Lin Wang: Nothing to Disclose, Fengmin Lu: Nothing to Disclose, Xiangmei Chen: Nothing to Disclose

3278 | EFFICACY OF TACE WITH TKIS ALONE VERSUS TACE COMBINED WITH TKIS AND ICIS IN UNRESECTABLE HEPATOCELLULAR CARCINOMA: A RETROSPECTIVE COHORT STUDY

ABOUBACAR HAROUNA ABOUBACAR[1] Xin Zheng[2] Yujing Zhang[1] Yuhan Zhou[1] Haonan Liu[1] Tianli Liu[1], [1]Xi'an Jiaotong University, [2]First Affiliated Hospital of Xi'an Jiaotong University

Background: Unresectable hepatocellular carcinoma (uHCC) remains a major treatment challenge worldwide. Trans-arterial chemoembolization (TACE) combined with tyrosine kinase inhibitors (TKIs) is commonly used as first-line treatment for uHHC patients. However, survival outcomes remain limited, with overall survival (OS) of 13-20 months. Recent interest has focused on whether adding immune checkpoint inhibitors (ICIs) to this combination can improve outcomes. This study aimed to compare OS, progression-free survival (PFS), tumor response, and safety between TACE plus TKIs and TACE plus TKIs with ICIs in uHCC patients, and to identify subgroups that derive the greatest benefit. **Methods:** This retrospective cohort study included 229 uHCC patients treated at the First Affiliated Hospital of Xi'an Jiaotong University between 2019 and 2022. The patients received either TACE plus TKIs (n = 169) or TACE plus TKIs with ICIs (n = 60). The primary endpoint was OS, while the secondary endpoints included PFS, tumor response (ORR, DCR), and adverse events (AEs). Kaplan-Meier and Cox regression were used for survival analysis. Tumor response was evaluated using modified RECIST. AEs were classified using NCI-CTCAE version 5.0. **Results:** The TACE plus TKI with ICI group showed improved OS, which was not reached at the final follow-up cut-off date, compared to 19.23 months in the TACE plus TKI group (HR: 0.582; 95% CI: 0.365–0.929; P = 0.047). Subgroup analysis showed significant OS benefit in patients with BCLC 0&A (HR: 0.336, P = 0.016), AFP > 400 ng/mL (HR: 0.422, P = 0.028), Child-Pugh A (HR: 0.541, P = 0.035), and tumors > 3 cm (HR: 0.451, P = 0.013). Objective Response Rate (ORR) and Disease Control Rate (DCR) were higher in the TACE plus TKI with ICI group (56.1% vs. 30.4%, P < 0.001; 96.5% vs. 86.9%, P = 0.044). Median PFS was similar between the two groups (7.23 vs. 7.37 months; HR: 0.981, P = 0.423). Most AEs were mild to moderate, with more vomiting (P = 0.006) and elevated ALT (P = 0.047) in the TACE plus TKI with ICI group, but fewer serious complications overall. **Conclusion:** TACE combined with TKIs and ICIs significantly improved survival and tumor response in patients with uHCC while maintaining an acceptable safety profile. These findings support further investigation of TACE plus TKIs with ICIs therapy as a potential new standard of care for patients with uHCC.



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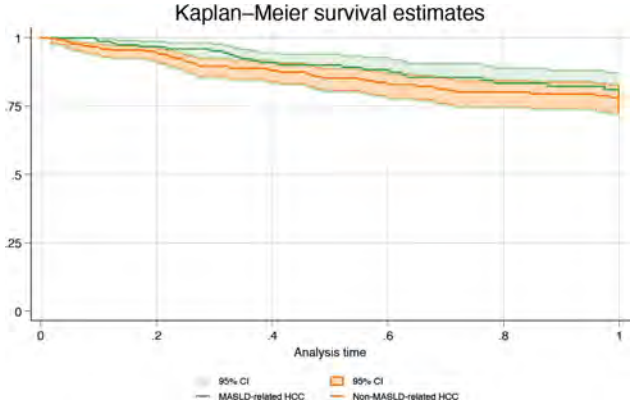
3279 | CLINICAL CHARACTERISTICS AND ONE-YEAR SURVIVAL OF PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)-RELATED HEPATOCELLULAR CARCINOMA (HCC): INSIGHTS FROM A LARGE INSTITUTIONAL REGISTRY

Saleh Alqahtani[1] Saleh Alessy[1] Faisal Abaalkhail[1] Waleed Al-Hamoudi[1] Abeer Alabdullah[1] Amwaj Alanazi[1] Heba Alharith[1] Mussadique Ali Jhatial[1] Mehwish Shahzadi Sajjad Hussain[1] Fahad AlMugbel[1] Ali Alqahtani[1] Ali Albenmousa[1] Dimitri Raptis[1] Dieter Broering[1] Waleed Alomaim[1] Bandar Aljudaibi[1] Saad Alghamdi[1], [1]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

Background: HCC, the most common type of primary liver cancer globally, remains a leading cause of cancer-related mortality in Saudi Arabia. With the declining prevalence of viral hepatitis, there is a global shift in HCC etiology toward MASLD. Data on the clinical presentation and outcomes of MASLD-related HCC in Saudi Arabia are still evolving. We aimed to assess and compare patient characteristics, disease presentation, and clinical outcomes between individuals with MASLD-related HCC and those with HCC of other etiologies (non-MASLD-related HCC). **Methods:** We retrospectively analyzed a prospectively maintained HCC registry at King Faisal Specialist Hospital and Research Center, Riyadh, which included patients diagnosed with HCC (histologically or radiologically) between August 2020 and May 2025. Demographic, clinical, and tumor characteristics, as well as treatment modalities, were assessed and compared between patients with MASLD-related and non-MASLD-related HCC. One-year survival was estimated using Kaplan-Meier analysis, with censoring at the date of last follow-up for patients who did not die within the first year. All patients, including those with less than one year of follow-up, were included in the analysis. **Results:** Of the 427 patients with HCC, 152 (35.6%) had MASLD-related HCC. Most patients were male (69.5%), with no significant difference in sex distribution between MASLD-related and non-MASLD-related HCC groups ($p = 0.971$). Patients with MASLD were older at diagnosis (median age 66 vs. 63 years, $p < 0.001$) and more likely to have diabetes (67.8% vs. 46.9%, $p < 0.001$). There were no significant differences between the groups in ECOG performance status, BCLC stage, Milan criteria, or Child-Pugh class at the time of diagnosis. Locoregional therapies were the most common first-line treatments in both groups (53.3% in MASLD vs. 57.1% in others, $p = 0.913$). One-year survival was similar across groups (log-rank $p = 0.44$), with comparable Kaplan-Meier survival estimates. **Conclusion:** MASLD has become the predominant etiology of HCC in Saudi Arabia, accounting for over one-third of the cases. Despite presenting at an older age and having a higher diabetes prevalence, patients with MASLD-related HCC had similar tumor burden, treatment approaches, and one-year survival outcomes compared to non-MASLD-related HCC. The findings underscore the need for increased surveillance efforts and earlier risk stratification for MASLD. Future research should focus on long-term outcomes and tailoring therapies to the distinct metabolic profile of MASLD-related HCC.



Disclosures: Saleh Alqahtani: Nothing to Disclose, Saleh Alessy: Nothing to Disclose, Faisal Abaalkhail: Nothing to Disclose, Waleed Al-Hamoudi: Nothing to Disclose, Abeer Alabdullah: Nothing to Disclose, Amwaj Alanazi: Nothing to Disclose, Heba Alharith: Nothing to Disclose, Mussadique Ali Jhatial: Nothing to Disclose, Mehwish Shahzadi Sajjad Hussain: Nothing to Disclose, Fahad AlMugbel: Nothing to Disclose, Ali Alqahtani: Nothing to Disclose, Ali Albenmousa: Nothing to Disclose, Dimitri Raptis: Nothing to Disclose, Dieter Broering: Nothing to Disclose, Waleed Alomaim: Nothing to Disclose, Bandar Aljudaibi: Nothing to Disclose, Saad Alghamdi: Nothing to Disclose

3280 | A NOVEL INDEX TO PREDICT TREATMENT RESPONSE TO ATEZOLIZUMAB AND BEVACIZUMAB THERAPY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Satoshi Narahara[1] Takahiro Mizuta[1] Toshinori Toyota[1] Daiki Maeda[1] Kentaro Tanaka[1] Hiroki Inada[1] Sotaro Kurano[1] Estuko Iio[1] Yoko Yoshimaru[1] Takehisa Watanabe[1] Katsuya Nagaoka[1] Hiroko Setoyama[1] Masaya Onishi[2] Yasuhito Tanaka[1], [1]Department of Gastroenterology and Hepatology, Faculty of Life

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Background: Atezolizumab plus bevacizumab therapy (Atezo+Bev) is widely used for the treatment of advanced hepatocellular carcinoma (HCC); however, no reliable biomarker is currently available to predict treatment response before or in the early phase of therapy. Previously, we reported that elevated AGRP1 (tentatively named) levels were associated with poor response to lenvatinib (AASLD The Liver Meeting 2023). Furthermore, using VISIUM, a spatial transcriptome analysis of HCC tissue and serum, we identified cytokine X as a contributor to resistance against Atezo+Bev (AASLD The Liver Meeting 2024). In this study, we aimed to develop a novel composite index by combining these two serum proteins to predict resistance to Atezo+Bev therapy. **Methods:** We retrospectively analyzed 155 patients who started Atezo +Bev therapy between November 2018 and December 2024. Inclusion criteria included availability of stored serum samples collected before treatment and at week 3, and sufficient clinical follow-up to assess response. Tumor response was evaluated using mRECIST. Serum AGRP1 and Cytokine X levels were measured by ELISA, and cutoff values were established via ROC analysis. **Results:** Median age was 67 years (range: 41-87), 30 men and 4 women, 28 in primary treatment and 6 in secondary or later treatment. Pretreatment AGRP1 and cytokine X were 351.3 (177.9-736.4) pg/mL and 138.9 (31.3-900.2) pg/mL, respectively; second course AGRP1 and cytokine X were 308.2 (93.1-643.7) pg/mL and 90.4 (14.0-547.7) pg/mL. Dichotomized by median value, high AGRP level at 3 weeks and high cytokine X level before treatment had significantly shorter PFS ($p = 0.046$ and 0.036, respectively). Next, using ROC analysis to set cutoff values, high AGRP level at 3 weeks and high cytokine X level before treatment were identified as contributing to PD significantly ($p = 0.049$ and 0.041, respectively). Finally, we developed a novel index, the Atezo+Bev Resistance Index (ABRI), calculated by assigning +1 point for each parameter exceeding the defined cutoff. A total score of 2 points was significantly associated with progressive disease ($p = 0.042$), demonstrating a high AUC of 0.826 and significantly shorter progression-free survival (PFS) ($p = 0.002$). **Conclusion:** We developed a novel predictive index, the ABRI, based on serum AGRP1 and cytokine X levels before and early after initiation of therapy. ABRI may serve as a useful index for predicting resistance to Atezo+Bev in patients with HCC.

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3281 | INVESTIGATION INTO THE DIFFERENCES BETWEEN HBV-RELATED HCC AND MAFLD-RELATED HCC BASED ON SINGLE-CELL SEQUENCING

Jiashuo Li[1] Ying Cao[1] Wen Xie[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: Hepatocellular carcinoma (HCC) remains a critical global public health issue, posing persistent challenges in management and treatment. The etiology of HCC is diverse, primarily involving hepatitis B virus (HBV) infection, and metabolic dysfunction-associated fatty liver disease (MAFLD). HCC patients exhibit distinct characteristics depending on its underlying etiology. Unlike virus-related HCC, MAFLD-associated HCC is diagnosed at later stages constantly, as well as exhibits distinct immunological features and treatment responses. Therefore, a deeper understanding of the tumor microenvironment differences under varying etiological backgrounds has become a crucial research direction for improving therapeutic precision, optimizing immunotherapy efficacy, and enhancing patient survival. **Methods:** This study enrolled patients who were treated at Beijing Ditan Hospital between June 2023 and June 2024. Based on etiology, patients were divided into two groups, with 5 patients per group, and one tumor tissue sample was collected from each patient. Additionally, 2 paired adjacent tissues from MAFLD-related HCC patients and 1 adjacent tissue from a HBV-related HCC patient were included as controls. Firstly, differentially expressed genes (DEGs) between the two groups were identified following dimensionality reduction, and cell annotation. Subsequently, functional enrichment analysis was performed to annotate the biological processes and signaling pathways associated with the DEGs. Finally, ligand-receptor interaction analysis was conducted to investigate intercellular communication networks among different cell types. **Results:** The results of this study revealed significant disparities in the proportions of macrophage, T cell, and NK cell subsets between HBV-related HCC and MAFLD-related HCC. Specifically, $GZMK^+CD8^+$ T cells were markedly enriched in MAFLD-associated HCC, whereas $ACP5^+$ macrophage subsets were more prevalent in HBV-related HCC. Additionally, the study identified distinct signaling pathway enrichment patterns and immune checkpoint

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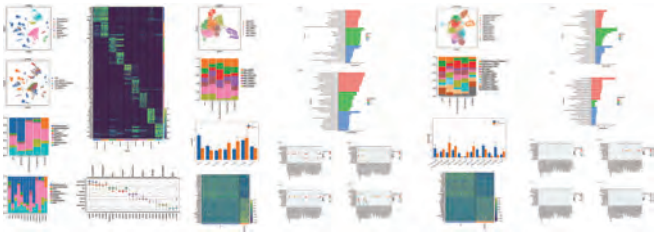
interaction networks. **Conclusion:** The results of single-cell RNA sequencing revealed distinct immune microenvironment between HBV-related HCC and MAFLD-related HCC, indicating potential immunological heterogeneity.



Disclosures: Jiashuo Li: Nothing to Disclose, Ying Cao: Nothing to Disclose, Wen Xie: Nothing to Disclose

3282 | TEAD INHIBITION BY IAG933 AS A NOVEL THERAPEUTIC STRATEGY FOR CHOLANGIOCARCINOMA

Hidemi Nishi[1] Erik Jessen[1] Enis Hikmet Ozmert[1] Danielle Carlson[1] Jack Sample[1] Amro Abdelrahman[1] Nathan Werneburg[1] Rory Smoot[1], [1]Mayo Clinic Rochester

Background: Cholangiocarcinoma (CCA) is an aggressive and heterogeneous malignancy of the biliary epithelium and remains one of the most challenging hepatobiliary cancers, with limited systemic treatment options and poor prognosis. Dysregulation of the Hippo signaling pathway, particularly hyperactivation of YAP/TAZ and their interaction with TEAD transcription factors, is increasingly recognized as a key driver of CCA progression, proliferation, and treatment resistance. Targeting the YAP/TAZ–TEAD axis represents a promising strategy to overcome these limitations. IAG933 is a novel oral pan-TEAD inhibitor specifically designed to disrupt YAP/TAZ–TEAD interactions and suppress oncogenic transcriptional programs in CCA. **Methods:** We investigated the effects of IAG933 in human (HuCCT1, RBE) and murine (SB1, FAC) CCA cell lines. Cells were treated with IAG933 alone or in combination with either standard chemotherapy (gemcitabine/cisplatin; GemCis) or a pan-KRAS inhibitor (RMC-6236). Cell viability assays were performed to determine IC_{50} values and calculate combination indices (CI) for synergy. TEAD transcriptional activity was quantified using luciferase reporter assays and qRT-PCR of target genes (CTGF, CYR61, NUAK2). RNA sequencing was performed to assess transcriptomic changes. In vivo efficacy was evaluated using a syngeneic orthotopic liver tumor model. **Results:** IAG933 significantly suppressed TEAD-dependent transcription ($IC_{50} \approx 500$ nM) and downregulated key TEAD target genes. Combination with GemCis or RMC-6236 showed synergistic anti-tumor effects (CI < 1) in all tested cell lines. In vivo, IAG933 reduced tumor growth to a similar extent as GemCis. qRT-PCR confirmed downregulation of CYR61 and NUAK2. Transcriptomic analysis revealed upregulation of oxidative stress response genes, most notably SOD2. MitoSOX staining demonstrated increased mitochondrial ROS levels 8 hours post-treatment, suggesting a compensatory transcriptional stress response associated with TEAD inhibition. **Conclusion:** IAG933 robustly inhibits TEAD-driven transcription and suppresses CCA growth in vitro and in vivo. Its synergy with GemCis and RMC-6236 supports its potential as a therapeutic candidate for CCA, including KRAS-mutated subtypes. Notably, SOD2 upregulation as a response to TEAD inhibition may represent a general resistance mechanism in CCA. These findings support further translational development of IAG933 and highlight the Hippo–TEAD axis as a targetable vulnerability in aggressive hepatobiliary cancers.

Disclosures: Hidemi Nishi: Nothing to Disclose, Erik Jessen: Nothing to Disclose, Enis Hikmet Ozmert: Nothing to Disclose, Danielle Carlson: Nothing to Disclose, Jack Sample: Nothing to Disclose, Amro Abdelrahman: Nothing to Disclose, Nathan Werneburg: Nothing to Disclose, Rory Smoot: Nothing to Disclose

3283 | THE PROGNOSTIC SIGNIFICANCE OF AAA SCORING SYSTEM IN BCLC STAGE 0/A RUPTURED HEPATOCELLULAR CARCINOMA

Chao Wang[1] Zhiyuan Huang[1] Peng Zhu[1] Hongping Luo[1] Yifa Chen[1], [1]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Background: Ruptured hepatocellular carcinoma (rHCC) is a rare yet life-threatening disease with a poor prognosis. Accurate evaluation of liver function and survival outcomes is critical in managing patients with rHCC. Traditional methods including the Child-Pugh classification have limitations due to subjective parameters. The Albumin-Bilirubin (ALBI) grade offers a more objective assessment, while the AAA (ALBI + AST + AFP) scoring system has emerged as a comprehensive prognostic tool. This study evaluates the predictive performance of various prognostic systems, including ALBI, Child-Pugh, AFP, AST, and AAA scoring, among BCLC Stage 0/A rHCC patients. **Methods:** A total of 249 patients with rHCC were retrospectively analyzed. Kaplan-Meier survival analysis assessed overall survival (OS) differences based on AFP (>100 ng/ml vs. ≤ 100 ng/ml) and AST (>45 U/L vs. ≤ 45 U/L).

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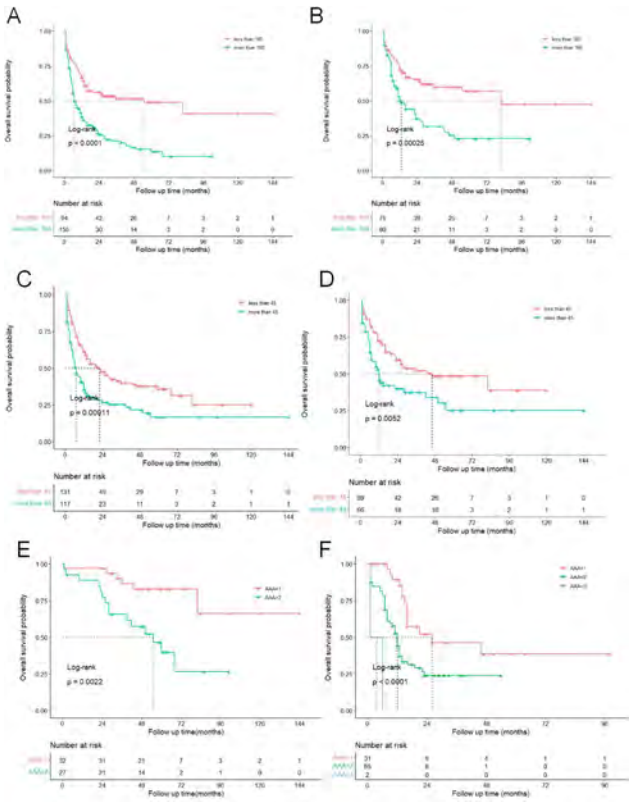
Predictive accuracy of ALBI grade, AAA score, Child-Pugh class, AFP, and AST levels was compared using time-dependent ROC curve analysis for 1-, 3-, and 5-year OS. Subgroup analysis was conducted to evaluate gender-specific predictive capacities of the AAA score. Statistical significance was set at $P < 0.05$. **Results:** Elevated AFP and AST levels were significantly associated with reduced OS ($P < 0.001$ and $P < 0.01$, respectively). The AAA scoring system showed superior predictive performance for 1-, 3-, and 5-year OS (AUCs: 0.672, 0.705, and 0.739, respectively) compared to other indicators. Subgroup analysis revealed that AAA scoring had strong prognostic significance in male patients ($P < 0.001$), whereas the association was not statistically significant in females ($P = 0.230$). AAA scoring demonstrated consistent stratification of survival outcomes and outperformed single-parameter models. **Conclusion:** The AAA scoring system offers superior prognostic accuracy over conventional methods for predicting survival in BCLC Stage 0/A rHCC patients, particularly in males. Its integrative approach makes it a valuable tool for individualized prognosis and therapeutic planning. Further investigation is warranted to clarify observed gender disparities in predictive performance.



Disclosures: Chao Wang: Nothing to Disclose, Zhiyuan Huang: Nothing to Disclose, Peng Zhu: Nothing to Disclose, Hongping Luo: Nothing to Disclose, Yifa Chen: Nothing to Disclose

3284 | SEX DISPARITIES IN HEPATOCELLULAR CARCINOMA: AGE, ETIOLOGY, AND TREATMENT GAPS IN A KOREAN NATIONWIDE COHORT

Do Seon Song Su Jong Yu[1] Ji Won Han[2] Gwang Hyeon Choi[3], [1]Seoul National University Hospital, [2]The Catholic University of Korea, [3]Seoul University

Background: Hepatocellular carcinoma (HCC) is a malignancy with a well-established male predominance, with incidence rates two to three times higher in men than in women. However, sex-related disparities in HCC have not been well characterized in Asian populations. **Methods:** This study included patients newly diagnosed with HCC between 2008 and 2020 from the Korea Central Cancer Registry. Exclusion criteria were age < 18 years, missing data, and combined HCC and cholangiocarcinoma. Tumor stage was classified according to the modified Union for International Cancer Control (mUICC) staging system. **Results:** A total of 19,729 patients with HCC were included, of whom 15,595 (79.0%) were men. HCC in men peaked in their 50s and declined thereafter, whereas in women, the number of cases increased with age. The male-to-female (M:F) ratio was highest in patients aged 40–59 years (6.0:1), followed by 60s (3.7:1) and ≥ 70 years (2.4:1), indicating a decreasing male predominance with age.

By etiology, the M:F ratio was 2.7 for HBV, 1.4 for HCV, 22.0 for alcohol-related HCC, and 2.2 for other causes, with the most pronounced male predominance in alcohol-related cases. From 2008 to 2020, the proportion of women with alcohol-related HCC increased from 3.6% to 5.6% ($P < 0.05$), while no significant sex-based changes were observed in other etiologies ($P > 0.05$).

At diagnosis, the proportion of women decreased with advancing stage: 28.2% in stage I, 23.2% in stage II, 18.2% in stage III, and 14.9% in stage IV ($P < 0.001$), suggesting later-stage diagnosis in men.

In stage I, treatment patterns did not differ by sex. However, in stage II, men were more likely to undergo surgical resection (35.2% vs. 28.2%). In stage IVa, systemic therapy was more common in men (17.4% vs. 12.6%), whereas more women remained untreated (43.2% vs. 36.1%). In stage IVb, men more frequently received transarterial therapy (24.4% vs. 17.7%) and systemic therapy (26.4% vs. 22.6%), while untreated rates were higher among women (50.9% vs. 41.0%). These findings indicate that men were more likely to receive active treatment, especially in advanced stages. **Conclusion:** The incidence of HCC differs by sex across age groups and underlying etiologies, with the most pronounced disparity observed in alcohol-related liver disease. Notably, the proportion of women developing alcohol-related HCC has been gradually

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increasing. Following diagnosis, men tend to receive more active treatment compared to women. Recognizing these sex-based differences in HCC is essential to guide strategies aimed at improving outcomes
Disclosures: Do Seon Song: Nothing to Disclose, Su Jong Yu: Nothing to Disclose, Ji Won Han: Nothing to Disclose, Gwang Hyeon Choi: Nothing to Disclose

3285 | ONCOLOGIC OUTCOMES FOLLOWING LIVER TRANSPLANTATION FOR CHOLANGIOCARCINOMA: A NATIONAL COHORT ANALYSIS (2009–2022)

Andrew Caddell[1] Minzhi Xing[1] Andrew Moon[1] Neil Shah[1] Jinquan Jia[1] Hanna Sanoff[1] Sandra Gad[1] Jonathan Sorah[1] Ted Yanagihara[1] David Mauro[1] Alexander Villalobos[1] Nima Kokabi[1], [1]University of North Carolina at Chapel Hill

Background: Purpose: To evaluate oncologic outcomes of adult patients undergoing liver transplantation (LT) for the indication of Cholangiocarcinoma (CCA) since its adoption as a structured, protocol-driven treatment in 2009. **Methods:** Materials and Methods: Using the United Network for organ Sharing (UNOS) database, adult patients undergoing whole-organ LT for CCA between 2009 and 2022 were identified. Exclusion criteria included prior LT, prior hepatocellular carcinoma diagnosis, retransplantaion, and follow up less than 1 year. Kaplan-Meier analysis was used to estimate post-transplant recurrence and survival at 1,2,3 and 5 years. Waitlist time difference by recurrence status was evaluated using the Wilcoxon test. Multivariable Cox proportional hazards models were used to assess predictors of recurrence and survival, adjusted for sex, MELD at listing, and MELD prior to transplant. Association comparing additional tranplantation indictations and recurrence were evaluated using Fisher's Exact test. **Results:** Results: A total of 402 patients met inclusion criteria. The cumulative recurrence rates were 7.7%, 16.3%, 21.2% and 24.8% at 1, 2, 3 and 5-years post LT. Corresponding overall survival rates were 90.3%, 78.7%, 69.7%, and 61.1%. Median waitlist time did not differ significantly by recurrence status ($p = 0.92$). Multivariable analysis showed MELD at listing (HR 0.98; $p = 0.50$) and MELD prior to LT (HR 1.01; $p = 0.54$) were not associated with recurrence. Female sex showed a non-significant trend toward increased recurrence (HR 1.45; $p = 0.13$). The recurrence model did not reach significance ($p = 0.25$).
During follow up, 165 patients (41.0%) died. MELD at listing (HR 1.01; $p = 0.49$) and MELD prior to LT (HR 1.07; $p = 0.10$) were not predictive of survival. MELD categorized into three groups (< 15, 15-24, ≥ 25) also showed no significant association (HR 1.47; $p = 0.19$). There was a non-significant trend toward worse survival in female patients (HR 1.37; $p = 0.07$). The survival model did not reach statistical significance ($p = 0.14$). CCA recurrence was more common in patients listed with transplantation diagnosis of cirrhosis compared to primary sclerosing cholangitis (33.3% vs 9.2%; $p = 0.0014$). **Conclusion:** Conclusions: LT for CCA is associated with encouraging long-term survival outcomes, with a 5-year survival rate exceeding 61% and recurrence in approximately 25% of patients. No clinical variable evaluated significantly predicted outcomes. Further prospective national cohort studies are needed to refine selection criteria and improve prediction of patient prognosis.

Variable	All Patients (n = 402)	With Recurrence (n = 84)	Without Recurrence (n = 318)
Age (y), median (IQR)	56 (47-63)	55 (44.5-61)	56 (47-63)
Sex			
Female	101 (25.12)	25 (29.76)	76 (23.90)
Male	301 (74.88)	59 (70.24)	242 (76.10)
Wait Time (days), median (IQR)	140 (63-291)	157 (65.50-286)	138 (61-293)
MELD at listing, median (IQR)	9 (7-13)	8.5 (7-13.5)	9 (6-13)
MELD at Transplant, median (IQR)	10 (7-18)	11 (8-18)	10 (7-18)
Donor Type			
Deceased	397 (98.7)	82 (97.6)	315 (78.4)
Living	5 (1.2)	2 (2.4)	3 (0.94)
Cirrhosis	24 (5.97)	8 (9.5)	16 (5.0)
PSC	120 (29.6)	11 (13.1)	109 (34.3)
Neoadjuvant Therapy			
Yes	104 (25.9)	12 (14.3)	116 (36.5)
No	49 (12.2)	7 (8.3)	42 (13.2)
Not Reported	237 (59.0)	65 (7.7)	172 (54.1)
Recurrence Rate			
1-year	7.67		
2-year	16.27		
3- year	21.17		
5-year	24.76		
Survival Rate			
1-year	90.3		
2-year	78.71		
3- year	69.66		
5-year	61.11		

Disclosures: Andrew Caddell: Nothing to Disclose, Minzhi Xing: Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant, Neil Shah: GSK: Advisor, Ipsen: Advisor, GSK: Consultant, Ipsen: Consultant, Jinquan Jia: Nothing to Disclose, Hanna Sanoff: Nothing to Disclose, Sandra Gad: Nothing to Disclose, Jonathan Sorah: Nothing to Disclose, Ted Yanagihara: Nothing to Disclose, David Mauro: Nothing to Disclose, Alexander Villalobos: Nothing to Disclose, Nima Kokabi: Sirtex: Consultant, Okami: Consultant, Boston Scientific: Consultant

3286 | NON-INVASIVE HISTOTRIPSY FOR LIVER TUMORS: LINKS TO CTDNA TUMOR MUTATIONAL BURDEN, TUMOR VIABILITY, AND RADIOLOGIC OUTCOME.

Ahmed Sayed Ahmed[1] Chase Wehrle[1] MUHAMMAD AHMAD NADEEM[1] Eren Berber[1] Federico Aucejo[1] Jaekeun Kim[1] David Kwon[1], [1]Cleveland Clinic, Section

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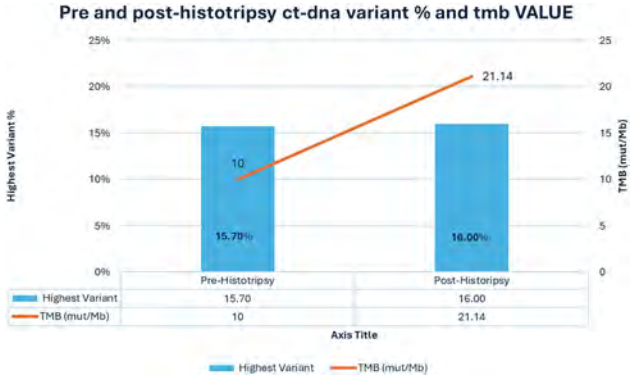
Background: Histotripsy, a non-invasive and non-thermal focused ultrasound method, is being studied for its potential in treating liver tumors. This research examines the radiologic and molecular impacts of histotripsy, with a focus on circulating tumor DNA (ctDNA) positivity, tumor mutational burden (TMB), and the viability of lesions. **Methods:** A retrospective study was conducted on 16 patients with liver tumors who underwent histotripsy. ctDNA and TMB (mut/Mb) were evaluated at a median of 91 days before and 50 days after the treatment (average interval: 141 days). Changes in ctDNA were classified as stable, cleared, or newly positive. Associations with diagnosis, systemic therapy, number of treatments, tumor viability on post-operative day (POD) 1 and 30, and off-target effects were analyzed using Chi-square and Fisher's exact tests. **Results:** The study included patients with colorectal cancer (37.5%), neuroendocrine tumors (12.5%), breast cancer (19%), and other cancer types (31%). They had a total of 25 liver lesions, averaging 3.27 cm in size, primarily located in segments III and IV. Most treatments (97%) were palliative, and 62.5% of the patients received systemic chemotherapy. The average TMB was 10 mut/Mb before treatment and 21.14 mut/Mb after treatment. The highest variant allele fraction recorded was 15.71% before treatment and 16% after. TMB was categorized into low, intermediate, and high levels, with 7 patients having pre-treatment TMB of 29%, 57%, and 14%, and post-treatment, 13 patients had TMB of 38.5%, 38.5%, and 23%, respectively. Eleven patients experienced an increase in TMB after treatment, most of whom had prior disease progression and systemic therapy. Among these, 6 out of 15 lesions were non-viable on POD-1, and 4 remained non-viable by POD-30. Off-target effects were noted in 4 lesions. Only one patient showed a decrease in TMB, who had not undergone primary tumor resections and had progressive disease before histotripsy. This patient had 2 lesions treated twice with histotripsy, and the lesions were viable on POD-1 and POD-30, with off-target effects observed. Of the remaining four patients, 2 out of 4 had negative ct-DNA tests, and 2/4 patients lacked pre-histotripsy TMB data, with one of these 2 patients having a positive intermediate TMB post-histotripsy; their lesions were viable on POD-1 and POD-30, with off-target effects seen in the patient with intermediate TMB post-histotripsy. Trends in ctDNA positivity, although not statistically significant, were associated with disease burden ($p = 0.079$) and tumor viability at POD-1 ($p = 0.079$) and POD-30 ($p = 0.098$). **Conclusion:** Histotripsy appears promising in inducing local tumor non-viability, particularly in smaller, palliatively treated lesions. ctDNA dynamics and TMB changes seem to reflect prior disease progression and treatment context. Further prospective studies are needed to clarify their predictive roles in histotripsy outcomes.



Disclosures: Ahmed Sayed Ahmed: Nothing to Disclose, Chase Wehrle: HistoSonics: Above, MUHAMMAD AHMAD NADEEM: Nothing to Disclose, Eren Berber: Medtronic: Consultant, Ethicon: Consultant, fluoptics: Consultant, Federico Aucejo: Nothing to Disclose, Jaekeun Kim: Nothing to Disclose, David Kwon: Medtronics: Consultant, GE medical: Consultant, Histosonics: Consultant

3287 | DEEP LEARNING AND MACHINE LEARNING DERIVED MRI RADIOMICS OUTPERFORMS CLINICAL BIOMARKERS IN PREDICTING RECURRENCE IN HEPATOCELLULAR CARCINOMA PATIENTS UNDERGOING RADIOFREQUENCY ABLATION.

Mathew Vithayathil[1] Yuki Agarwala[1] Amar Rai[1] Osman Ocal[2] Matthias Fabritius[2] Maciej Pech[3] Thomas Berg[4] Christian Loewe[5] Heinz-Josef Klümpen[6] Paul Tait[1] Rafael Duran[7] Antonia Digklia[8] Isabelle PACHE[9] Pierre Deltenre[9] Jean-François Knebel[10] Alban Denys[7] Naik Vietti-Violi[7] Max Seidensticker[11] Eric Aboagye[1] Jens Ricke[11] Rohini Sharma[1], [1]Imperial College London, [2]Department of Radiology, University Hospital, LMU Munich, Munich, Germany, [3]Department of Radiology and Nuclear Medicine, University of Magdeburg, [4]Klinik und Poliklinik für Gastroenterologie, Sektion Hepatologie, Universitätsklinikum Leipzig AöR, [5]Department of Bioimaging and Image-Guided Therapy, Medical University of Vienna, [6]Department of Medical Oncology, Amsterdam University Medical Centers, University of Amsterdam, [7]Department of Radiology and Interventional Radiology, Lausanne University Hospital, [8]Department of Oncology, Lausanne University Hospital and University of Lausanne, [9]Department of Gastroenterology, Lausanne University Hospital and University of Lausanne, [10]Department of

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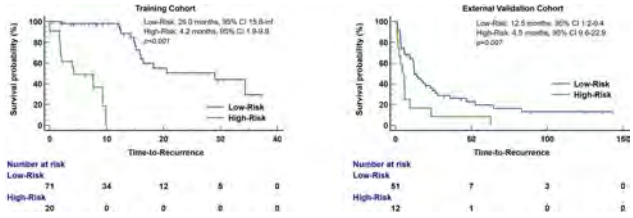
Background: Recurrence after curative radiofrequency ablation (RFA) in hepatocellular carcinoma (HCC) patients is high. Currently there are limited predictive biomarkers. This study combined deep learning with machine learning to develop radiomic models predicting time-to-recurrence (TTR) and disease-free survival (DFS) after RFA. **Methods:** 156 consecutive HCC patients from two prospective randomised control clinical trials were included in the study. Patients undergoing RFA from the SORAMIC trial (n = 93) were used for training. A deep learning U-Net model automatically segmented tumour lesions from pre-treatment dynamic contrast-enhanced MRI, with subsequent radiologist verification. A total of 12,393 radiomic features were extracted from arterial, portal venous and delayed phases. Radiomic models predicting 12-month recurrence were trained using seven supervised machine learning algorithms with thirteen feature selection techniques for each phase. Ensemble learning selected the best performing machine learning and feature selection combinations. Radiomic models were benchmarked against established clinical predictors. Using unsupervised K-means clustering and threshold optimisation, high- and low-risk radiomic risk groups were identified. The model performance was evaluated on an external independent patient cohort from a prospective randomised control trial (CHUV, n = 63). **Results:** The arterial phase based radiomic model had the highest AUC when predicting 12-month post-RFA recurrence in the training (AUC: 0.90, 95% CI 0.80-0.98) cohort, significantly outperforming Barcelona Clinic Liver Cancer (BCLC) stage (AUC: 0.58, 95% CI 0.39-0.77, $p = 0.003$) and Child-Pugh (CP) class (AUC: 0.47, 95% CI 0.30-0.65, $p < 0.001$). The arterial phase radiomic model maintained predictive performed in the independent external validation cohort (AUC: 0.74, 95% CI 0.61-0.87) cohorts, significantly outperforming BCLC (AUC: 0.58, 95% CI 0.51-0.67, $p = 0.03$) and CP class (AUC: 0.45, 95% CI 0.34-0.56, $p < 0.001$). Threshold optimisation identified a high-risk arterial-phase radiomic group, with a significantly shorter TTR compared to the low-risk radiomic group in both the training (median TTR: 4.2 months, 95% CI 1.9-9.9 vs. 29.0 months, 95% CI 15.8-inf; $p < 0.001$) and external validation (4.5 months, 95% CI 9.6-22.9 vs. 12.5 months, 95% CI 1.2-9.4, $p = 0.007$) cohorts. The high-risk group had significantly shorter DFS compared to the low-risk group in both training and validation (4.5 months, 95% CI 1.2-9.4 vs. 12.2 months, 95% CI 5.9-19.7, $p = 0.023$). In a multivariable Cox regression model with BCLC stage, CP class, tumour size and multinodularity, radiomic risk group was the strongest predictor of TTR and DFS. **Conclusion:** Arterial phase radiomic-based models predicts TTR and DFS after RFA in HCC patients. Deep learning combined with machine learning model can stratify patients to allow for precision treatment strategies.



Disclosures: Mathew Vithayathil: Nothing to Disclose, Yuki Agarwala: Nothing to Disclose, Amar Rai: Nothing to Disclose, Osman Ocal: Nothing to Disclose, Matthias Fabritius: Nothing to Disclose, Maciej Pech: Nothing to Disclose, Thomas Berg: Nothing to Disclose, Christian Loewe: Nothing to Disclose, Heinz-Josef Klümpen: Nothing to Disclose, Paul Tait: Nothing to Disclose, Rafael Duran: Nothing to Disclose, Antonia Digklia: Nothing to Disclose, Isabelle PACHE: Nothing to Disclose, Pierre Deltenre: Nothing to Disclose, Jean-François Knebel: Nothing to Disclose, Alban Denys: Nothing to Disclose, Naik Vietti-Violi: Nothing to Disclose, Max Seidensticker: Nothing to Disclose, Eric Aboagye: Nothing to Disclose, Jens Ricke: Nothing to Disclose, Rohini Sharma: Nothing to Disclose

3288 | DEVELOPMENT OF A NOVEL PROGNOSTIC SCORE FOR 1-YEAR SURVIVAL IN IMMUNOTHERAPY-TREATED PATIENTS WITH UNRESECTABLE HCC

Spyridon Pantzios[1] Iakovos Vlachos[2] Antonia Syriha[1] Orestis Sidiropoulos[1] Maria-Stella Malatesta[1] Despoina Gyriki[1] Vaios Mosialos[1] Dina Tiniakos[2] Ioannis Elefsiniotis[1], [1]School of Health Sciences, National and Kapodistrian University of Athens, Greece, [2]Medical School, National and Kapodistrian University of Athens, Greece

Background: There is a lack in reliable and widely used prognostic scores to predict survival in patients with hepatocellular carcinoma (HCC) receiving immunotherapy. Possible biomarkers include ALBI grade and intratumoral lymphocyte infiltration, while disease burden possibly correlates with overall survival (OS). The aim of our study was to develop a prognostic score that could predict 1-year OS in patients with HCC receiving immunotherapy. **Methods:** We studied 100 patients who received 1st line immunotherapy in our center. Intrahepatic disease burden was evaluated with up-to-7 criteria. We did a univariate cox regression analysis to

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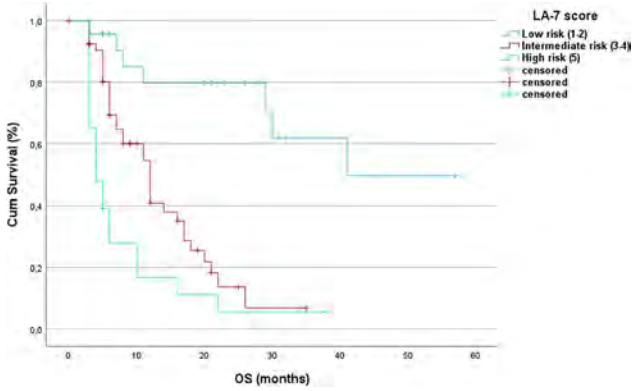
assess which of the parameters is associated with OS. Factors strongly associated with OS were used in the multivariate model. We used the B coefficients from the multivariate model to produce a normalized score (LA-7 score) that could predict 1-year OS. Internal validation was done using ROC analysis and 10-fold cross-validation. Then, we separated our patients in three risk groups (low, intermediate, high) based on the new score and studied them for their baseline characteristics, response to immunotherapy and OS. **Results:** In univariate analysis, significant correlation with OS was found for ALBI grade ($p < 0.001$, HR = 2.725), BCLC stage ($p = 0.031$, HR = 1.809), MVI ($p < 0.001$, HR = 2.587), up-to-7 criteria ($p < 0.001$, HR = 0.218) and lymphocyte infiltration ($p = 0.005$, HR = 0.485). In the multivariate analysis we found that three factors were significantly correlated with OS; ALBI grade (grade II vs. grade I, $p = 0.025$, HR = 1.946), up-to-7 criteria (beyond vs. within, $p = 0.001$, HR = 3.506) and lymphocyte infiltration (no vs. yes, $p = 0.016$, HR = 1.889). The LA-7 score was calculated with the contribution of 1 point for ALBI grade II, 2 points for exceeding up-to-7 criteria and 1 point for absence of lymphocyte infiltration. The score had an AUROC of 0.755 for 1-year OS, with 75% sensitivity and 65.4% specificity. We established three risk groups; low (LA-7: 1-2), intermediate (LA-7: 3-4) and high (LA-7: 5). Objective response was reported in 34.8% of patients in the low risk group, compared to 18.5% in intermediate risk patients and 4.3% in high risk patients ($p = 0.031$). The median OS of the three groups was 41, 12 and 3 months, respectively ($p < 0.001$). The 1-year OS was 80%, 41% and 16%, the 2-year OS was 80%, 14% and 6%, and the 3-year OS was 62%, 7% and 6%, respectively. **Conclusion:** The LA-7 score is a promising tool for predicting 1-year OS in HCC patients undergoing immunotherapy. Further research should focus on its integration with other biomarkers, particularly in immunotherapy settings, to optimize patient management.



Disclosures: Spyridon Pantzios: Nothing to Disclose, Iakovos Vlachos: Nothing to Disclose, Antonia Syriha: Nothing to Disclose, Orestis Sidiropoulos: Nothing to Disclose, Maria-Stella Malatesta: Nothing to Disclose, Despoina Gyriki: Nothing to Disclose, Vaios Mosialos: Nothing to Disclose, Dina Tiniakos: Inventiva: Consultant, ICON: Consultant, CymaBay: Consultant, Ioannis Elefsiniotis: Nothing to Disclose

3289 | HEPATOCELLULAR CARCINOMA (HCC) IS MORE FREQUENT IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

Nicole Welch[1] Ana Ostojic[1] Annette Bellar[1] Amy Attaway[1] Lars Deutz[1] Ryan Musich[1] John McMichael[1] Lopa Mishra[2] Srinivasan Dasarathy[1], [1]Cleveland Clinic, [2]Feinstein Institutes for Medical Research & Cold Spring Harbor Laboratory

Background: HCC is a significant complication of cirrhosis with variable incidence across liver disease etiologies. Less is known about disease compensation status and the incidence of HCC. Identifying the clinical characteristics of patients with/without HCC and with/without decompensation can inform targeted surveillance and prognostication. We aimed to compare demographics, etiology distribution, clinical status, and outcomes in cirrhosis patients with and without HCC. **Methods:** Using an electronic database of patients evaluated in the hepatology department at a large tertiary care center between January 2000 and December 2024, we identified patients with cirrhosis using ICD9 and ICD10 codes. Patients were further stratified by those who ether had compensated disease or had decompensation without recompensation to reduce disease course variability and by presence or absence of HCC diagnosis. Decompensation was defined by gastrointestinal bleeding, encephalopathy, ascites event. HCC was defined by biopsy, imaging, or physician documentation. Disease etiologies included metabolic-associated (MASLD), alcohol-related (ALD), combined metabolic and alcohol-related (MetALD), viral hepatitis-related (VHLD) liver disese, and other causes. Demographic, clinical, and laboratory variables were compared between those with/without HCC and/or decompensation using chi-square tests for categorical and Student's t-test for continuous variables. **Results:** Of 29,999 patients with cirhosis, 2,276 (7.6%) had confirmed HCC. 16,368[54.6%] had compensated disease (n = 15,325[93.6%] without HCC/13,631 [6.37%] with HCC) and 13,631[45.4%] had decompensated disease (n = 12,174 without HCC/1457 [10.7%] with HCC). The majority of patients were male (n = 9335[56.9%] compensated/ n = 7873[57.8%] decompensated, $p < 0.001$). The percent of patients with HCC in the decompensated group was higher than that of the compensated group (n = 58.3% vs 41.7%, $p < 0.001$). Patients with HCC were older (mean 63.1 vs 58.0 years, $p < 0.001$), more frequently male (74.6% vs 57.4%, $p < 0.001$), and more likely to have underlying

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viral hepatitis (25.2% vs 9.6%, $p < 0.001$). The most frequent cause of initial decompensation was ascites (n = 7966[58.4%]), followed by hepatic encephalopathy (n = 5646[41.4%]]. Among those patients with cirrhosis prescribed statins, there was a higher percentage of decompensated patients (Compensated n = 5255 [48.9%] vs Decompensated n = 5493[51.1%], $p < 0.001$). Of those patients on Medicaid, there was a higher percentage with cirrhosis that was decompensated (n = 335[61.5%] vs. 210[38.5%]), while those with private insurance had a higher ($p < 0.001$) percentage with compensated disease (5928[54.3%] vs 4988 [45.7%]). **Conclusion:** HCC is more frequent in patients with decompensated cirrhosis who are older, have diabetes, and MetALD while statin use despite decompensation was associated less with HCC.

Table 1. Multivariate analysis

Model		Unstandardized Coefficients B	Std. Error	Standardized Coefficients Beta	t	Sig.
1	(Constant)	1.055	.012		91.222	<.001
	Sex	-.065	.003	-.116	-20.266	<.001
	Statin	-.017	.004	-.030	-4.908	<.001
	Diabetes	.021	.004	.036	5.944	<.001
	Etiology	.008	.001	.040	6.853	<.001
	Decomp. group	.054	.003	.097	16.487	<.001
	MELD at LDDx	-.004	.000	-.086	-14.427	<.001

a. Dependent Variable: HCC.
Decomp.: Decompensation, LDDx: Liver disease diagnosis, MELD: Model for end stage liver

Disclosures: Nicole Welch: Nothing to Disclose, Ana Ostojic: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Lars Deutz: Nothing to Disclose, Ryan Musich: Nothing to Disclose, John McMichael: Nothing to Disclose, Lopa Mishra: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

3290 | "HOT" IMMUNE MICROENVIRONMENT OF AFP^{LOW} HEPATOCELLULAR CARCINOMA PATIENTS HARBOURS PROLIFERATIVE NATURAL KILLER CELLS

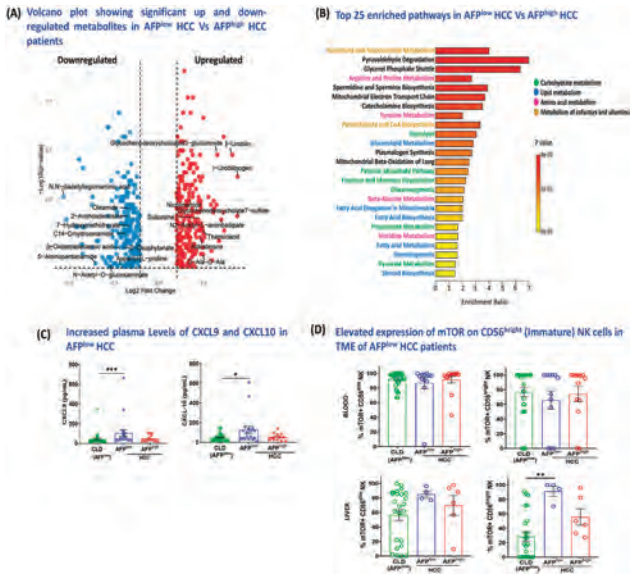
Pushpa Yadav[1] Viniyendra Pamecha[1] Sherin Thomas[1] Gayatri Ramakrishna[1] Shiv Kumar Sarin[1] Nirupma Trehanpati[1], [1]Institute of Liver and Biliary Sciences

Background: Hepatocellular carcinoma (HCC) exhibits a heterogeneous tumor microenvironment (TME) characterized by immunologically "hot" versus "cold" phenotypes, significantly impacting therapeutic outcomes. Alpha-fetoprotein (AFP), a traditional HCC diagnostic marker, correlates with immunosuppressive mechanisms that influence TME classification. Our aim was to identify immunometabolic differences in AFP^{low} and AFP^{high} HCC patients. **Methods:** Total of ninety-eight patients (median age = 50 (30-78), M/F = 11/98), including HCC (n = 38) with serum AFP ≤15ng/mL {AFP^{low} HCC (n = 21)} and >15ng/mL {AFP^{high} HCC (n = 17)} and AFP^{low} chronic liver disease (CLD, n = 60) were analysed for plasma metabolomics using liquid chromatographic-mass spectrometry (LC-MS), plasma CXCL-9 and CXCL-10 levels by ELISA and immune-metabolic phenotyping in both PBMCs and tumor-infiltrated lymphocytes (TILs) by flow metabolic panels. **Results:** AFP^{low} HCC patients' plasma metabolomics profile revealed enriched nicotinate and nicotinamide synthesis along with carbohydrate metabolism pathways such as glycolysis, pentose phosphate, gluconeogenesis and mitochondrial electron transport chain pathway compared to AFP^{high} HCC patients (Figure 1A-B).

In AFP^{low} HCC patients, CXCL-9 [p value = 0.0002] and CXCL-10 [p value = 0.0158] chemokine levels were increased compared to AFP^{low} CLD patients, (Figure 1C).

Further, AFP^{low} patients also had significantly increased mTOR expression in tumor-infiltrated CD56 bright (immature) NK cells [p value = 0.0063] (Figure 1D). No significant difference was observed in the mTOR expression of CD56 dim (mature) NK cells isolated from either peripheral blood or liver tumor. **Conclusion:** Upregulation of the energy metabolism pathways is suggestive of increased immune activation and proliferation in AFP^{low} HCC patients. Resultant elevated levels of CXCL-9 and CXCL-10 promoting immune infiltration and proliferation in AFP^{low} HCC patients. Increased expression of mTOR which is linked to cell growth and division observed in immature NK cells in the tumor-microenvironment of AFP^{low} HCC may also be linked to the significantly upregulated energy metabolism.

In conclusion, in AFP^{low} HCC patients, proliferating immune cells show upregulated energy metabolism pathways, with CXCL-9 and CXCL-10 facilitating immune cell trafficking.



Disclosures: Pushpa Yadav: Nothing to Disclose, Viniyendra Pamecha: Nothing to Disclose, Sherin Thomas: Nothing to Disclose, Gayatri Ramakrishna: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Nirupma Trehanpati: Nothing to Disclose

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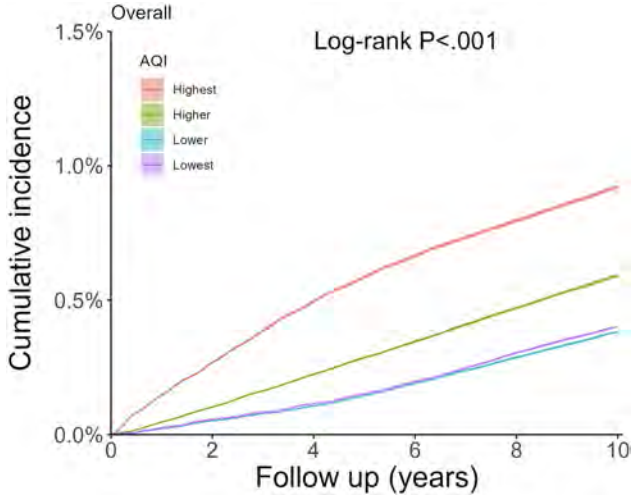
3291 | ASSOCIATION BETWEEN AIR QUALITY INDEX AND RISK OF HEPATOCELLULAR CARCINOMA: A NATIONWIDE POPULATION-BASED STUDY

Chun-Ying Wu[1] Kuei-Mao Wang[1] Chia-Da Wu[2], [1]National Yang MIng Chiao Tung University, Taiwan, [2]National Cheng Kung University, Taiwan

Background: Epidemiological evidence indicates association between air pollution and an increased risk of hepatocellular carcinoma (HCC). However, the results are controversial. **Methods:** We conducted a nationwide cohort study to investigate the association between air pollution and HCC based on the Taiwan National Health Insurance Laboratory Database (NHILD) and the Air Quality Monitoring System Database (AQMSD) between 1 January 2009 and 31 December 2020. Ten-year cumulative incidences of HCC and the Fine-Gray competing risk model was used to determine the association between air pollution and the subsequent HCC risk. **Results:** Among the 18,998,172 participants with a mean age of 41.2 years and equally distributed sex, we found the 10-year cumulative incidence of HCC increased progressively across AQI quartiles. The highest AQI group (Q4) exhibited the greatest 10-year HCC incidence at 0.92%, followed by Q3 at 0.59%, Q2 at 0.38%, and the lowest AQI group (Q1) at 0.40%. In the multivariate analysis, participants in the highest AQI quartile (Q4) had a significantly higher risk of HCC compared to those in the lowest quartile (Q1), with a hazard ratio (HR) of 1.86 (95% CI: 1.54–2.25). Each unit increase in AQI was associated with a 2% increase in HCC risk (HR: 1.02; 95% CI: 1.02–1.02). In the stratified analysis, the positive associations between higher AQI levels and HCC risk were observed across most subgroups. **Conclusion:** Higher air pollution associated with higher subsequent HCC risk was found in our nationwide cohort study.



Disclosures: Chun-Ying Wu: Nothing to Disclose, Kuei-Mao Wang: Nothing to Disclose, Chia-Da Wu: Nothing to Disclose

3292 | CANCER-RELATED DEATH IN INDIVIDUALS WITH ALCOHOL-ASSOCIATED LIVER DISEASE

Pojsakorn Danpanichkul[1] Thanathip Suenghataiphorn[2] Do Han Kim[3] Donghyun Ko[4] Karecia Byfield[5] Romelia Barba[6] Ahmed Shukri[6] Chawin Lopimpisuth[7] Ornpailin Wanichthanaolan[8], [1]Texas Tech University Health Sciences Center, [2]Griffin hospital, [3]Mount Sinai Hospital, [4]Bridgeport hospital, [5]Thomas Jefferson Hospital, [6]texas tech university, [7]University of Miami, [8]Chiang Mai University

Background: Alcohol-associated liver disease (ALD) is a leading cause of liver cancer. While mortality from liver cancer in ALD has improved, little is known about trends in extrahepatic cancer-related deaths in this population. This study aimed to characterize national trends in liver and extrahepatic cancer-related mortality among individuals with ALD in the U.S. **Methods:** We used the National Vital Statistics System Multiple Cause of Death database (2011–2020) to identify decedents with ALD (ICD-10: K70) listed as a contributing cause and cancer (C*) as the primary cause of death. Cancers were categorized as liver or extrahepatic. Age-adjusted mortality rates (AAMRs) per 100,000 population were calculated using 2000 U.S. standard population weights and stratified by sex, race/ethnicity, census region, and urbanization level. Trends were analyzed using Joinpoint regression to estimate annual percent change (APC) with 95% confidence intervals (CI). **Results:** From 2011 to 2020, 14,566 cancer-related deaths listed ALD as a contributing cause. AAMRs per 100,000 for liver and extrahepatic cancer among ALD patients were 0.25 and 0.17, respectively, in 2020. Over the decade, AAMRs increased significantly for liver cancer (APC: 4.66%; 95% CI: 2.95–6.39) and extrahepatic cancer (APC: 5.73%; 95% CI: 3.99–7.49). In contrast, extrahepatic cancer-related mortality declined in the general population. Increases were more pronounced among males, non-Hispanic Whites, and residents of non-metropolitan areas. **Conclusion:** Despite national declines in extrahepatic cancer mortality, individuals with ALD experienced a significant rise in both liver and extrahepatic cancer deaths. These findings highlight the growing extrahepatic cancer burden in ALD and the need for expanded surveillance strategies.

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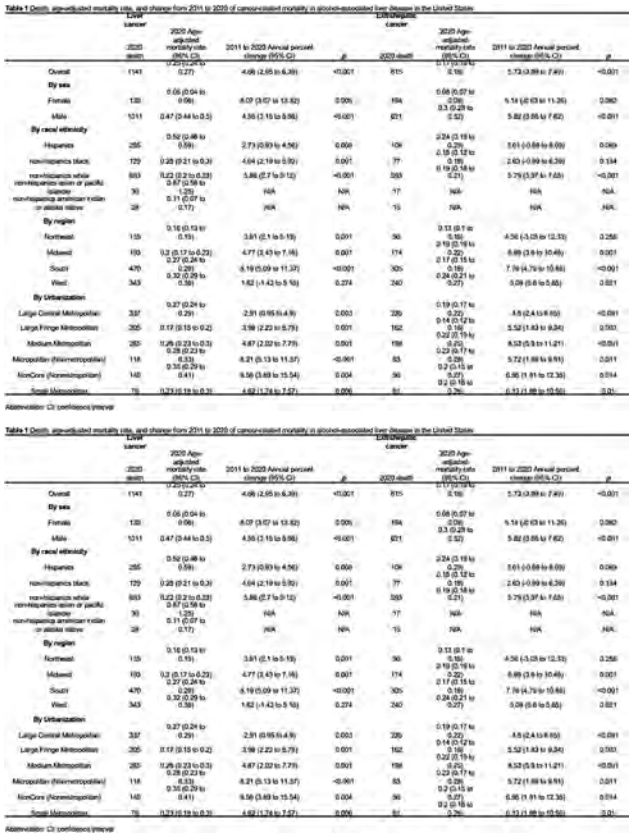

Disclosures: Pojsakorn Danpanichkul: Nothing to Disclose, Thanathip Suenghataiphorn: Nothing to Disclose, Do Han Kim: Nothing to Disclose, Donghyun Ko: Nothing to Disclose, Karecia Byfield: Nothing to Disclose, Romelia Barba: Nothing to Disclose, Ahmed Shukri: Nothing to Disclose, Chawin Lopimpisuth: Nothing to Disclose, Ornpailin Wanichthanaolan: Nothing to Disclose

3293 | MECHANISTIC INSIGHTS INTO PROGLUMIDE&RSQUO;S ROLE IN IMMUNE CELL EFFICACY AND RESISTANCE TO IMMUNE CHECKPOINT INHIBITOR THERAPY FOR HEPATOCELLULAR CARCINOMA

Priyanka Doneparthi[1] Hong Cao[1] Wenqiang Chen[1] Wenyu Dou[1] Hong-Bin Fang[1], [1]Georgetown University

Background: Hepatocellular carcinoma (HCC) is the fastest growing cause of cancer-related deaths worldwide. Treatment with immune checkpoint inhibitors (ICIs) has shown promise in HCC, but the response is still low at about 15%-20%. One reason for the low efficacy is the fibrosis in most livers that harbor HCC that prevent penetration of anti-cancer agents and also the penetration of tumoral CD8+ T-cells. Our laboratory discovered that the cholecystokinin-B receptor (CCK-BR) is overexpressed in HCC tumors. A prior study showed that the survival of mice bearing HCC xenografts was significantly improved when mice were treated with a CCK-BR receptor antagonist, proglumide, and PD-1 ICI. This study's primary objective is to understand the mechanisms by which the CCK-BR antagonist, proglumide, enhances the efficacy of immune checkpoint PD-1Ab therapy. **Methods:** Three significant areas of investigation were explored: changes to the tumor microenvironment (TME), the activity of the host T-cells, and the gut microbiome. C57BL/6 mice were injected subcutaneously in each flank with RIL-175 HCC cells (100,000). Once the mice had palpable tumors, they were divided into four groups of equal tumor size ($N = 10$ per group). Treatment included: PBS-control, proglumide (0.1mg/ml) in drinking water, PD-1Ab (50μg, ip, days 0, 7, and 14), and combination therapy with the PD-1Ab and proglumide. After 4 weeks of treatment, the tumors were excised and TME examined histologically. T-cells were isolated from the spleens and analyzed, and the microbiome was analyzed by whole genome 16s sequencing and compared to baseline. **Results:** Histologic analysis of the TME showed a 4.5-fold influx of CD8 T-cells, decreased M2-polarized macrophages ($P < 0.0001$), and >5-fold less fibrosis with the tumors of mice treated with the combined therapy. Combination treatment decreased the host T-cell exhaustion markers (TIM3, LAG3, and CD-279-PD-1) and proglumide increased T-cell cytokine release (TNFα, INFγ). The microbiome showed increased diversity and beneficial bacteria in the combination-treated groups. *Prevotella* genus decreased, and *Lactobacillus* species, known to promote T cell and immune cell activation significantly increased. *Eubacterium,* a beneficial bacterium that improves response to ICI, increased with the combined therapy. **Conclusion:** Co-administration of proglumide with ICIs appears to enhance the efficacy of PD-1 antibody therapy by remodeling the TME, changing a relatively “cold” tumor to a “hot” immune-responsive tumor, activating T-cells, and rendering the host microbiome to a population of bacteria that are beneficial.

Disclosures: Priyanka Doneparthi: Nothing to Disclose, Hong Cao: Nothing to Disclose, Wenqiang Chen: Nothing to Disclose, Wenyu Dou: Nothing to Disclose, Hong-Bin Fang: Nothing to Disclose

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3294 | SINTILIMAB PLUS BEVACIZUMAB AS SYSTEMIC THERAPY IN PATIENTS WITH CHILD-PUGH A AND CHILD-PUGH B ADVANCED HEPATOCELLULAR CARCINOMA: A MULTI-INSTITUTIONAL COHORT STUDY

Yuanxu Zhang[1] Weifeng Zhao[1] Youhan Miao[2] Wei Sun[1] Yang Li[3] XiuCheng Pan[4], [1]The First Affiliated Hospital of Soochow University, [2]Nantong Third People's Hospital, [3]The Affiliated Taizhou people's Hospital of Nanjing Medical University, [4]The Affiliated Hospital of Xuzhou Medical University

Background: Sintilimab plus bevacizumab is an approved first-line regimen for unresectable hepatocellular carcinoma (uHCC) in China. However, data on its safety and efficacy in patients with impaired liver function remain limited. We assessed the clinical outcomes of this combination therapy in HCC patients with Child-Pugh class A (CP-A) and class B (CP-B) liver function. **Methods:** In this multicentre retrospective cohort study, 99 patients with advanced uHCC (73 CP-A; 26 CP-B) who received first-line sintilimab and bevacizumab were included. Tumor response was assessed using modified RECIST criteria, and adverse events (AEs) were graded per CTCAE v5.0. Survival outcomes, including overall survival (OS), progression-free survival (PFS), and time to hepatic decompensation (TTD), were analyzed via Kaplan-Meier estimates and Cox proportional hazards models. **Results:** The objective response rates (ORR) of patients with Child-Pugh A and Child-Pugh B treated with Sintilimab plus bevacizumab were 50.7% and 57.7%, respectively, and both could achieve good anti-tumor efficacy. CP-B had inferior survival: median OS (15 vs 22 months, $p = 0.044$), PFS (8 vs 14 months, $p = 0.014$), and TTD (7 vs 15 months, $p < 0.001$) shown in the Figure. The Child-Pugh B cohort demonstrated comparable incidence rates of grade 3-4 adverse events (AEs) to the CP-A group (34.6% vs 34.2%). Hemorrhagic events and thrombocytopenia emerged as predominant grade 3-4 AEs in CP-B patients (15.4% for both). In multivariate analysis for OS, CP-B status remained an independent predictor of reduced survival (HR 2.744, 95% CI 1.152-6.537; $p = 0.023$). Deterioration in ALBI grade after 6 months of treatment was also an independent predictor of worse OS (HR 3.661, 95% CI 1.331-10.064; $p = 0.012$). For PFS, ALBI grade deterioration after 6 months remained a significant negative prognostic factor (HR 3.353, 95% CI 1.083–10.384; $p = 0.036$). **Conclusion:** Sintilimab plus bevacizumab demonstrated encouraging short-term anti-tumor activity in unresectable hepatocellular carcinoma across CP-A and CP-B, while survival outcomes were affected by differences in hepatic function reserve. Although the regimen was generally well tolerated, patients with impaired liver reserve require vigilant monitoring and comprehensive supportive strategies to maximize therapeutic outcomes.

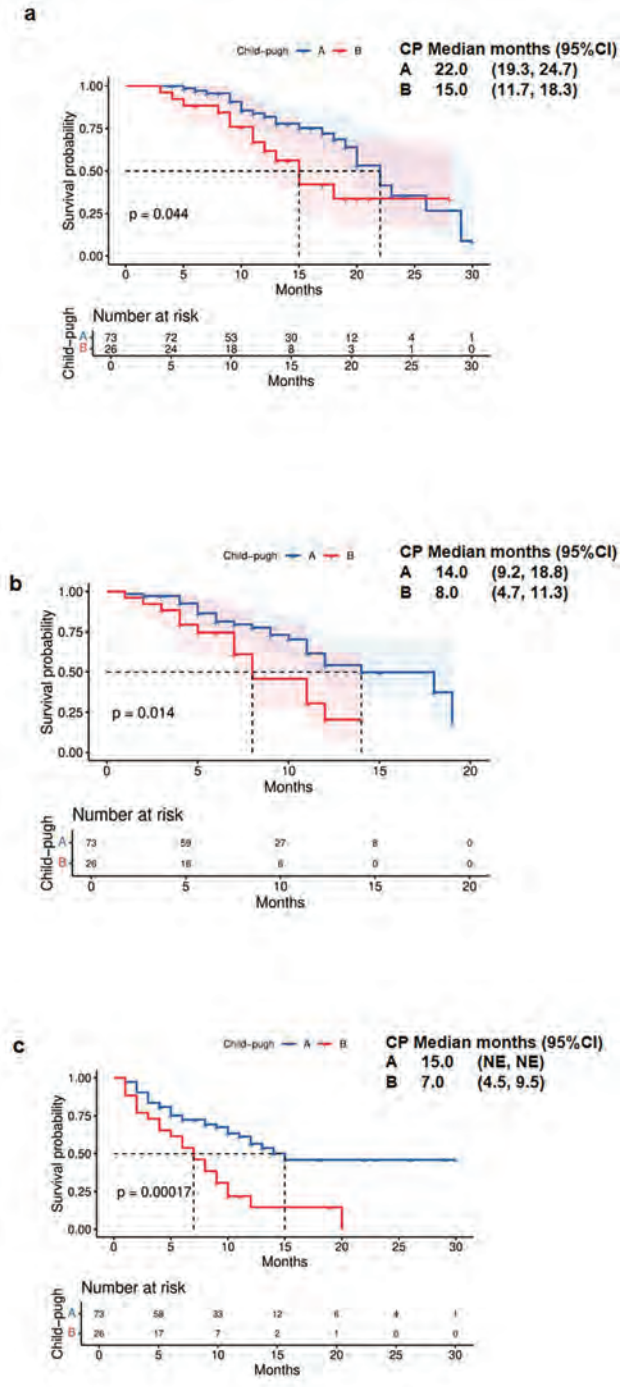

Figure. Overall survival (OS) by (a) Child-Pugh liver status (A vs B). Progression-free survival (PFS) by (b) Child-Pugh liver status (A vs B). Time to decompensation (TTD) by (c) Child-Pugh liver status (A vs B).

Disclosures: Yuanxu Zhang: Nothing to Disclose, Weifeng Zhao: Nothing to Disclose, Youhan Miao:

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Nothing to Disclose, Wei Sun: Nothing to Disclose, Yang Li: Nothing to Disclose, XiuCheng Pan: Nothing to Disclose

3295 | INTEGRATIVE SCRNA AND CLINICAL PROFILING UNCOVERS SDC2 AS A FUNCTIONAL BIOMARKER IN HEPATOCELLULAR CARCINOMA

yuhai hu

Background: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide. Identifying tumor-specific surface receptors involved in intercellular communication is essential for understanding tumor progression and developing targeted therapies. **Methods:** We analyzed publicly available scRNA datasets of HCC and applied NicheNet to explore ligand-receptor interactions within the tumor microenvironment. Syndecan-2 (SDC2) was identified as a highly expressed receptor in malignant hepatocytes. To validate its clinical relevance, we analyzed transcriptomic data from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) datasets to assess SDC2 expression. Additionally, we performed immunohistochemistry on liver tissue samples from 95 HCC patients and assessed the correlation between SDC2 expression and clinicopathological features. **Results:** scRNA analysis revealed that SDC2 was highly expressed in malignant hepatocytes and involved in multiple ligand-receptor interactions. SDC2 was involved in multiple ligand-receptor interactions, with its ligands originating from both malignant hepatocytes and hepatic stellate cells, including ANGPTL4, MDK, and PTN. To explore the role of SDC2 in HCC, we first analyzed its expression using data from the TCGA and GEO databases, We found that SDC2 expression was significantly upregulated in HCC tissues compared to adjacent non-tumorous liver tissues. At the protein level, we performed a tissue microarray (HLivH180Su31, Shanghai ChipScreen Biosciences Co., Ltd., Shanghai, China). A total of 95 HCC tissues and 81 adjacent non-tumorous tissues were successfully subjected to immunohistochemical staining and scoring. Similarly, compared with adjacent non-tumorous liver tissues, SDC2 expression was significantly upregulated in hepatocellular carcinoma. Higher SDC2 expression was associated with poor prognosis, advanced TNM stage, age, and survival status in HCC patients. **Conclusion:** SDC2 is a tumor-enriched receptor in HCC associated with disease progression and unfavorable prognosis. Both scRNA and clinical data suggest that SDC2 plays an important role in mediating intercellular communication within the tumor microenvironment and represents a promising biomarker and potential therapeutic target. Further studies are warranted to investigate its downstream signaling pathways and functional roles in HCC.
Disclosures: yuhai hu: Nothing to Disclose

3296 | SIGNIFICANCE OF MEASURING INTERFERON-Γ-INDUCED PROTEIN-10 LEVELS IN PATIENTS RECEIVING SYSTEMIC THERAPIES FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

Hitomi Takada[1] Shinya Maekawa[1] Atsunori Tsuchiya[1] Nobuyuki Enomoto[2], [1]University of Yamanashi, [2]University of Yamanahsi

Background: Atezolizumab-bevacizumab (AB) and durvalumab-tremelimumab (DT) combination therapies are widely used for unresectable hepatocellular carcinoma (uHCC). However, the optimal predictors of therapeutic response remain unclear. Interferon-γ-induced protein-10 (IP-10) levels are considered potential biomarkers in immunotherapy for uHCC and other cancers. This study investigates the relationship between blood IP-10 levels and treatment response in patients with uHCC receiving AB or DT. **Methods:** This retrospective cohort included 106 patients who initiated immunotherapy for uHCC at our institution between November 2020 and September 2024. Inclusion criteria encompassed advanced-stage HCC (Barcelona Clinic Liver Cancer [BCLC] stage C) or intermediate-stage HCC (BCLC stage B), with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, and Child-Pugh grade A or B. In these patients, IP-10 levels were measured at baseline and 1, 3, 6, and 12 weeks after induction in the AB group, and at baseline and 1, 2, 4, 8, and 12 weeks in the DT group. The association between IP-10 levels and treatment response was analyzed. IP-10 levels were measured via ELISA using stored plasma samples, and the ratio of post-induction to baseline IP-10 levels was calculated. **Results:** Of the 106 patients, 84 received AB and 22 received DT. The median age was 72 years (range 44–88), with 90 men (85%). Forty-four patients (42%) received as late-line therapy. The distribution of BCLC stages was 50 (47%) stage B and 56 (53%) stage C. The initial therapeutic responses were PR/SD/PD in 44/30/32 patients, corresponding to 42%, 28%, and 30%. The best responses were CR/PR/SD/PD in 3/45/28/30 patients, corresponding to 3%, 43%, 26%, and 28%, respectively.
Baseline IP-10 levels in the PR group as the initial therapeutic response were significantly higher than in the SD/PD group ($p = 0.0067$). Using ROC curve analysis, a baseline IP-10 level > 150 pg/mL predicted PR as the initial therapeutic response, and patients with high baseline IP-10 levels showed a higher response

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rate compared to those with not-high levels (62 vs. 26%, $p < 0.001$).

Moreover, the non-PD group as the best response exhibited a lower IP-10 ratio (post-induction/baseline) before response evaluation compared to the PD group ($p = 0.015$). Progression-free survival (PFS) was longer in patients achieving an IP-10 ratio < 1—defined as a predictor of non-PD via ROC analysis—compared to those who did not ($p = 0.012$). Achieving an IP-10 ratio < 1 was the only factor independently associated with longer PFS (hazard ratio 2.0, $p = 0.006$). **Conclusion:** Patients with high baseline IP-10 levels are likely to have high therapeutic effects from the point of the initial assessment. Patients achieving IP-10 ratio < 1 are likely to show non-PD as best response. These findings suggest that IP-10 levels may be useful predictors of therapeutic response in patients receiving AB or DT for uHCC.

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3297 | PERFORMANCE OF GALAD, GAAD, AND ASAP FOR EARLY HCC DETECTION IN CHRONIC LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Mohammad Jarrah[1] Ashwini Arvind[1] Purva Gopal[1] Sneha Deodhar[1] Ju Dong Yang[2] Neehar Parikh[3] Amit Singal[1], [1]UT Southwestern Medical Center, [2]Cedars-Sinai Medical Center, [3]University of Michigan Medical Center

Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality worldwide, with a 5-year survival below 20%, primarily due to late-stage diagnoses. Blood-based multi-biomarker panels have shown promise to improve HCC surveillance in patients with cirrhosis, but we lack comparative data on their performance for early-stage HCC detection. **Methods:** We conducted a systematic review of PubMed, Ovid MEDLINE, and EMBASE databases from January 2010 to November 2024 to identify studies evaluating the performance of three commercially available biomarker panels (GALAD, GAAD, and ASAP) for HCC screening. Pooled estimates were calculated using the DerSimonian and Laird method for a random effects model. The study was conducted per Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. **Results:** We identified 44 studies ($n = 33{,}100$ patients), with 37 studies evaluating GALAD, 12 evaluating GAAD, and 11 evaluating ASAP for HCC screening. Nine studies were cohort studies, while the remainder were case-control studies. Pooled sensitivity and specificity estimates for early-stage HCC were: 70.2% (95%CI 66.5 – 73.7) and 87.2% (95%CI 84.4 – 89.6) for GALAD, 74.1% (95%CI 59.3 – 84.9) and 85.7% (95%CI 66.3 – 94.8) for GAAD, and 72.1% (95% CI 43.8 – 89.5) and 83.3% (95%CI 61.3 – 94.0) for ASAP. Among studies directly comparing biomarker panels in the same patients, there was no significant difference in sensitivity for early stage-HCC between GALAD and GAAD (RR 0.96, 95%CI 0.80 – 1.15) or between GALAD and ASAP (RR 1.12, 95%CI 0.79 – 1.60). The pooled sensitivity of GALAD for early-stage HCC was higher than that of ultrasound among studies directly comparing the two (79.0% (95%CI 62.2 – 89.6) versus 73.3% (95%CI 45.4 – 90.1), respectively); however, this difference was not statistically significant (RR 1.09, 95%CI 0.78 – 1.51). When combined with ultrasound, GALAD showed a pooled c-statistic of 0.89 (95%CI 0.73 – 1.00), compared to 0.84 (95%CI 0.80 – 0.88) for ultrasound alone. Studies were limited by inclusion of patients with non-cirrhotic liver disease, variability in biomarker panel cutoffs across studies, and substantial statistical heterogeneity ($I^2 > 50\%$). **Conclusion:** Multi-biomarker panels including GALAD, GAAD, and ASAP demonstrate promising performance for the early detection of HCC, supporting their further prospective validation as potential alternatives to ultrasound-based screening.

Disclosures: Mohammad Jarrah: Nothing to Disclose, Ashwini Arvind: Nothing to Disclose, Purva Gopal: Nothing to Disclose, Sneha Deodhar: Nothing to Disclose, Ju Dong Yang: Exact Sciences: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Exelixis: Consultant, Fujifilm Medical Sciences: Consultant, Neehar Parikh: Genentech: Grant/Research Support, Exelixis: Grant/Research Support, Exelixis: Consultant, AstraZeneca: Consultant, Exact Sciences: Grant/Research Support, Exact Sciences: Consultant, Fujifilm Medical: Advisor, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant

3298 | IL-1β INDUCED BY ER STRESS IN HEPATIC STELLATE CELLS FACILITATES THE PROGRESSION OF HEPATOCELLULAR CARCINOMA

Makoto Morita[1] Yoshio Tokumoto[1] Takao Watanabe[1] Yusuke Imai[1] Atsushi Yukimoto[1] Toyoki Shimamoto[1] Ryo Yano[1] Yuki Okazaki[1] Yoshiko Nakamura[1] Osamu

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Yoshida[1] Teruki Miyake[1] Masashi Hirooka[1] Masanori Abe[1] Yoichi Hiasa[1] [1]Ehime University Graduate School of Medicine

Background: In metabolic dysfunction-associated steatohepatitis (MASH), palmitic acid (PA) absorbed from the intestine is increased. PA induces endoplasmic reticulum (ER) stress and interleukin-1 beta (IL-1β) production in hepatic stellate cells (HSCs). Protein kinase R-like endoplasmic reticulum kinase (PERK), an ER stress sensor, has been reported to regulate IL-1β. The aim of this study is to elucidate the mechanism of ER stress-induced IL-1β production in HSCs and to clarify the role of IL-1β in the progression of MASH-associated hepatocellular carcinoma (HCC). **Methods:** The human HSC cell line LX-2 cell was treated with PA. Reverse transcription polymerase chain reaction and western blotting were used to measure PERK and IL-1β expression. LX-2 cells were transfected with PERK siRNA or PERK plasmid, and IL-1β expression was measured. In addition, PERK knockdown cells were treated with PA, and the change in IL-1β was examined. The human HCC cell line HepG2 cell was treated with recombinant human IL-1β (rhIL-1β) or with an IL-1β neutralizing antibody (IL-1β NAb) in the conditioned medium (CM) from PA-treated LX-2 cells, and their proliferation was assessed by MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) assay. Enzyme-linked immunosorbent assay was used to measure the IL-1β concentration in CM from LX-2 cells under different conditions. HepG2 cells were cultured in CM from LX-2 cells under different conditions, and their proliferation, migration, and invasion were assessed by MTS, scratch, and Transwell assays. RNA-sequencing (RNA-seq) analysis was performed on PA-treated LX-2 cells with or without PERK knockdown to identify the intermediate molecule in the PERK-mediated IL-1β production pathway. The change in IL-1β expression was examined following modulation of the identified molecule expression. **Results:** PA increased PERK and IL-1β expression in LX-2 cells. IL-1β was decreased by PERK siRNA transfection and increased by PERK plasmid transfection. The increase in IL-1β induced by PA treatment was suppressed in PERK knockdown cells. rhIL-1β promoted the proliferation of HepG2 cells, whereas IL-1β NAb suppressed the proliferation of HepG2 cells cultured in the CM from PA-treated LX-2 cells. The IL-1β concentration in the CM from PA-treated LX-2 cells was increased. The CM from PA-treated LX-2 cells enhanced the proliferation, migration, and invasion of HepG2 cells; however, these effects were suppressed by PERK knockdown. RNA-seq analysis identified p38δ mitogen-activated protein kinase (MAPK) as an intermediate molecule between PERK and IL-1β. The modulation of p38δ MAPK expression changed IL-1β expression. **Conclusion:** ER stress-induced IL-1β secretion via PERK/p38δ MAPK axis in HSCs facilitates MASH-HCC progression.

Disclosures: Makoto Morita: Nothing to Disclose, Yoshio Tokumoto: Nothing to Disclose, Takao Watanabe: Nothing to Disclose, Yusuke Imai: Nothing to Disclose, Atsushi Yukimoto: Nothing to Disclose, Toyoki Shimamoto: Nothing to Disclose, Ryo Yano: Nothing to Disclose, Yuki Okazaki: Nothing to Disclose, Yoshiko Nakamura: Nothing to Disclose, Osamu Yoshida: Nothing to Disclose, Teruki Miyake: Nothing to Disclose, Masashi Hirooka: Nothing to Disclose, Masanori Abe: Nothing to Disclose, Yoichi Hiasa: Nothing to Disclose

3299 | ASSESSING POST-TACE LIVER DECOMPENSATION RISK IN HCC: A COMPARATIVE ANALYSIS OF MELD 3.0, MELD-NA, CHILD-PUGH, AND ALBI SCORES"

Hasan Bualbanat[1] David Hudson[2], [1]Western University/ Transplant Hepatology Program, [2]Western University/ Department of Gastroenterology

Background: Background: & Aim: Patients with hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE) are at risk of hepatic decompensation. Accurate pre-procedural prediction of such events is crucial for patient selection and optimization of outcomes. This study aims to evaluate and compare the predictive accuracy of MELD 3.0, MELD-Na, Child-Pugh, and Albumin-Bilirubin (ALBI) scoring systems in forecasting hepatic decompensation following TACE in patients with HCC. **Methods:** Methods:: This retrospective cohort study included 280 patients diagnosed with HCC who underwent TACE at our institution. We calculated MELD 3.0, MELD-Na, Child-Pugh, and ALBI scores for each patient immediately prior to TACE treatment. The primary endpoint was the occurrence of hepatic decompensation post-TACE, recorded as a binary outcome (yes/no). Receiver Operating Characteristic (ROC) curve analysis was performed to determine and compare the predictive accuracy of each scoring system, with the Area Under the Receiver Operating Characteristic Curve (AUROC) as the primary measure. Optimal cutoff values for MELD 3.0 and MELD-Na scores were identified using Youden's index. **Results:** Results:: Among the evaluated scoring systems, MELD 3.0 demonstrated the highest predictive accuracy with an AUROC of 0.81. MELD-Na showed slightly lower accuracy (AUROC 0.79), followed closely by Child-Pugh (AUROC 0.78), and ALBI scores (AUROC 0.75). The optimal cutoff scores identified for predicting hepatic decompensation were ≥ 16 for MELD 3.0 (sensitivity 69.0%, specificity 87.2%) and ≥ 14 for MELD-Na (sensitivity 66.7%, specificity 85.7%). **Conclusion:** Conclusion:: Our findings suggest that MELD 3.0 score provides superior predictive accuracy for

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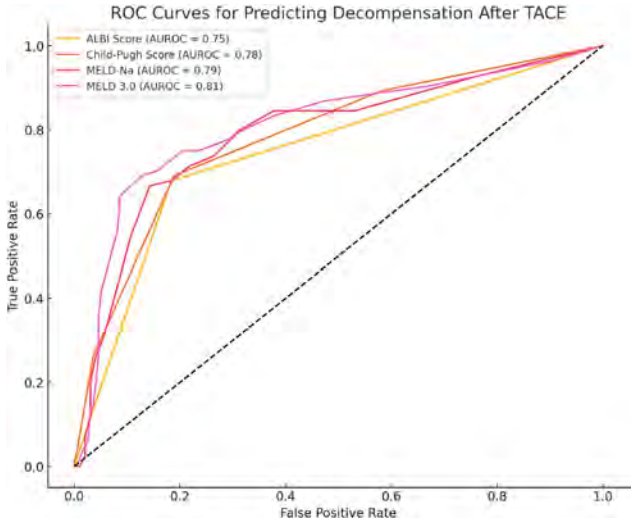
hepatic decompensation in patients with HCC undergoing TACE, compared to MELD-Na, Child-Pugh, and ALBI scores. A MELD 3.0 score of 16 or higher effectively identifies patients at increased risk, aiding clinicians in decision-making and targeted patient management to minimize post-procedural complications.

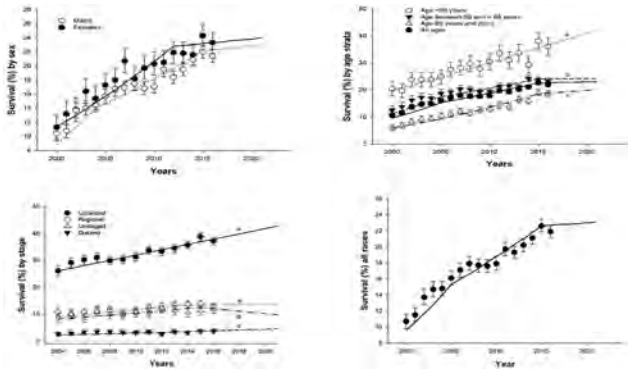


Disclosures: Hasan Bualbanat: Nothing to Disclose, David Hudson: Nothing to Disclose

3300 | TWO DECADES OF INTRAHEPATIC CHOLANGIOCARCINOMA: A MIXED-EFFECTS ANALYSIS OF AGE, SEX, TUMOR STAGE AND DEMOGRAPHICS

Ivan Mogollon[1] Aura Calderon[1] Julian Galindo-Ramirez[1] Juan Lopez-Alvarenga[1] Everardo Cobos[1], [1]The University of Texas Rio Grande Valley

Background: Intrahepatic cholangiocarcinoma (ICC), a subtype of cholangiocarcinoma arising from the bile ducts within the liver, is a rare but increasingly prevalent malignancy with poor prognosis. Due to vague clinical symptoms, ICC is often diagnosed at an advanced stage, limiting curative treatment options such as surgical resection. While systemic therapies are available, their efficacy remains modest, and survival outcomes vary widely. Understanding how survival has evolved over time and how demographic and clinical factors influence prognosis is essential to guide future interventions and improve patient care. This study aims to evaluate long-term survival trends in ICC and assess how factors such as age, sex, race, and tumor stage at diagnosis impact survival outcomes. **Methods:** We analyzed longitudinal survival data for intrahepatic cholangiocarcinoma patients diagnosed between 2000 and 2020 using relative survival statistics from the JPSurv program. Annual survival rates, tracked for up to 10 years post-diagnosis, were evaluated to assess trends over time and across patient subgroups. A mixed-effects panel regression model with a random intercept for year was applied to account for within-group correlations and the temporal dependency of survival. Fixed effects included sex, age group, and tumor stage, with interaction terms to test for differential trends. Joinpoint analysis identified time segments with changing survival trends, and the average absolute change in survival was used to quantify survival improvement between joinpoints. Post hoc comparisons were conducted using Fisher's notation to identify statistically homogeneous groups. **Results:** Survival rates demonstrated a consistent upward trend from 2000 to 2020. Females showed slightly higher survival than males, though this difference was not statistically significant. A significant survival advantage was observed among younger patients, with those aged $\geq$65 years showing the lowest survival and minimal improvement over time. Patients with localized tumors had the highest survival and greatest gains over time, while those with regional or unstaged lesions exhibited intermediate outcomes. Patients with distant metastases had persistently poor survival, underscoring the poor prognosis of late-stage disease. Survival improved across all racial groups, particularly in the early 2000s; however, disparities between racial groups remain evident. **Conclusion:** Despite incremental progress in ICC survival, substantial disparities remain by age and tumor stage. Early detection and timely, accessible treatment are critical to improving patient outcomes. Future strategies should prioritize the development of more effective therapies for advanced-stage disease and implement targeted interventions for older adults and underserved populations to reduce survival inequities.



Disclosures: Ivan Mogollon: Nothing to Disclose, Aura Calderon: Nothing to Disclose, Julian Galindo-Ramirez: Nothing to Disclose, Juan Lopez-Alvarenga: Nothing to Disclose, Everardo Cobos: Nothing to Disclose

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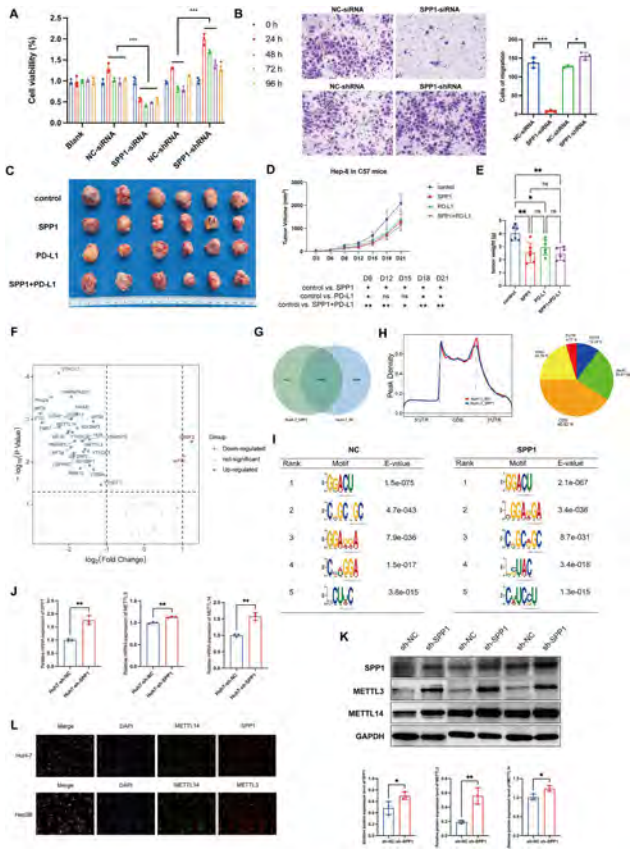
3301 | SPP1 PROMOTES HEPATOCELLULAR CARCINOMA PROGRESSION THROUGH REGULATION OF M6A METHYLTRANSFERASES METTL3 AND METTL14

Yanqiu Li[1] Yao Liu[1] Xianbo Wang[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world. Secretory phosphoprotein 1 (SPP1) plays an important role in a variety of tumors, and RNA N6-methyladenosine (m6A) modification is involved in the occurrence and development of tumors. However, the interaction mechanism between SPP1 and m6A methylation in HCC is still unclear. **Methods:** This study used a combination of in vitro and vivo experiments. SPP1 knockdown and overexpression cell lines were constructed in HuH7 cells, and the effect of SPP1 on the biological behavior of HuH7 cells was evaluated by cell viability detection and Transwell migration assay. The HCC subcutaneous tumor mouse model was established using Hepa 1-6 cells and treated with SPP1 and PD-L1 monoclonal antibody by intraperitoneal injection. Methylation sequencing technology was used to analyze the changes in the m6A modification spectrum of SPP1-knockdown HuH 7cells and control cells. qRT-PCR and Western blot were used to detect the expression levels of key genes and proteins. Immunofluorescence staining was used to observe the localization and distribution of proteins in cells. **Results:** SPP1 knockdown significantly inhibited HuH7 cell viability ($P < 0.001$) and reduced cell migration ability, while SPP1 overexpression promoted cell proliferation and migration. In the mouse HCC model, tumor growth was significantly inhibited in the SPP1 monoclonal antibody treatment group ($P < 0.01$), and combined PD-L1 treatment further enhanced the anti-tumor effect, and tumor weight was reduced. Methylation sequencing analysis found that SPP1 regulates the expression of multiple m6A methylases, especially METTL3 and METTL14. The gene and protein levels of METTL3 and METTL14 were significantly upregulated in the SPP1 overexpression group. Immunofluorescence staining showed that METTL3, METTL14 and SPP1 were expressed in HuHh7 and Hep3B cells, and there was a co-localization phenomenon. **Conclusion:** SPP1 participates in the proliferation and migration of HuH7 cells by regulating the expression of m6A methylases, especially METTL3 and METTL14. Inhibition of SPP1 can effectively inhibit the progression of HCC and has a synergistic anti-tumor effect when combined with PD-L1 therapy. The important role of the SPP1-m6A methylation axis in the development of HCC provides a new theoretical basis and potential therapeutic strategy for the targeted treatment of liver cancer.



Disclosures: Yanqiu Li: Nothing to Disclose, Yao Liu: Nothing to Disclose, Xianbo Wang: Nothing to Disclose

3302 | LYMPHOCYTE-TO-MONOCYTE RATIO (LMR) AS A PROGNOSTIC INDICATOR IN PATIENTS WITH CHOLANGIOCARCINOMA

Chung-Hao Hsu[1] Chun-Ting Ho[2] Chien-Wei Su[2] Wei-Yu Kao[3] Yi-Hsiang Huang[2] Ming-Chih Hou[2] Jaw-Ching Wu[2], [1]School of Medicine, National Yang Ming Chiao Tung University, [2]Taipei Veterans General Hospital, [3]Taipei Medical University Hospital

Background: Cholangiocarcinoma (CCA) is a highly aggressive malignancy, often diagnosed at advanced stages, with a five-year survival rate below 25%. The lymphocyte-to-monocyte ratio (LMR), a marker reflecting systemic inflammatory response, has been associated with prognosis in several cancers. However, its role in CCA is not fully elucidated. This study aimed to evaluate the prognostic significance of LMR in patients with CCA. **Methods:** We retrospectively analyzed 912 patients diagnosed with CCA at Taipei Veterans General Hospital between 2014 and 2024. Baseline clinical characteristics, imaging data, and laboratory results were collected at diagnosis. The primary

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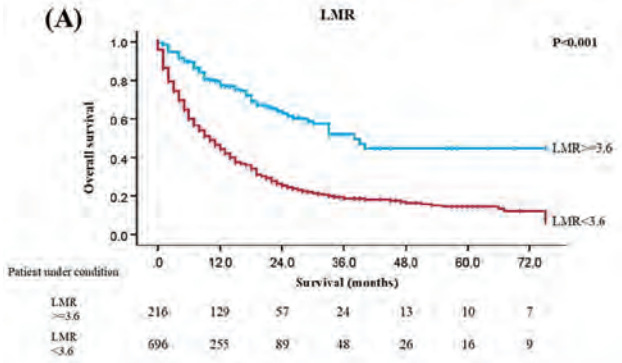
endpoint was overall survival (OS). Cox proportional hazards models were used for multivariate analysis to identify independent prognostic factors. Non-invasive serum markers including LMR, Prognostic Nutritional Index (PNI), AST-to-Platelet Ratio Index (APRI), Fibrosis-4 (FIB-4), Albumin-Bilirubin (ALBI) score, and Child-Pugh score—were evaluated for prognostic accuracy using the Akaike Information Criterion (AIC) and area under the ROC curve (AUROC). Cutoff values were defined by established clinical thresholds or the Youden index. Kaplan-Meier survival analyses were performed to compare OS across subgroups. **Results:** After a median follow-up of 9.0 months (IQR 4.0–18.0), 440 patients had died, with a 5-year OS rate of 20.2%. Multivariate analysis identified age, tumor stage and location, serum bilirubin, aspartate aminotransferase (AST), prothrombin time international normalized ratio (PT INR), carbohydrate antigen 19-9 (CA19-9) levels, treatment modality, surgery, LMR, and PNI as independent predictors of OS. Among all serum biomarker scores, LMR demonstrated the best prognostic performance (highest AUROC and lowest AIC). Patients with high LMR had significantly better OS (median 15.0 months, IQR 7.0–24.0) compared to those with low LMR (median 7.0 months, IQR 3.0–16.0; $p < 0.001$). High LMR was associated with favorable clinical features including earlier tumor stage, higher albumin, lower bilirubin and liver enzyme levels, greater likelihood of receiving treatment and surgery, and lower ALBI, APRI, PNI, FIB-4, the model for end-stage liver disease (MELD) scores, and Child-Pugh scores. **Conclusion:** LMR is an independent prognostic biomarker in CCA and may serve as a simple, non-invasive tool to stratify patients by survival risk.

Figure 1. Kaplan-Meier survival analysis and COX proportional hazardous models (COX PH) showed LMR can serve as an prognostic factor in CCA.
(A) Kaplan-Meier survival analysis in subgroup of LMR.
(B) COX proportional hazardous models (COX PH) of multiple serum index.



(B)

	AUROC	AIC	P value
PNI	0.645	6672.174	<0.001
ALBI	0.627	6689.847	<0.001
APRI	0.588	6735.800	0.003
FIB-4	0.589	6723.377	<0.001
LMR	0.727	6652.411	<0.001
Child-Pugh Grade	0.638	6689.458	<0.001

Disclosures: Chung-Hao Hsu: Nothing to Disclose, Chun-Ting Ho: Nothing to Disclose, Chien-Wei Su: Nothing to Disclose, Wei-Yu Kao: Nothing to Disclose, Yi-Hsiang Huang: Nothing to Disclose, Ming-Chih Hou: Nothing to Disclose, Jaw-Ching Wu: Nothing to Disclose

3303 | INFLUENCE OF HISTOTRIPSY ON PATIENT-REPORTED QUALITY OF LIFE: A RETROSPECTIVE COHORT STUDY

Ahmed Sayed Ahmed[1] Chase Wehrle[1] Eren Berber[1] Federico Aucejo[1] Jaekeun Kim[1] David Kwon[1], [1]Cleveland Clinic, Section of Hepato-Pancreato-Biliary (HPB) Surgery, Cleveland, OH

Background: Histotripsy is a noninvasive, non-thermal focused ultrasound method used for the ablation of tumors, particularly in liver lesions. Although its effectiveness is under investigation, there is limited data on its effects on patient-reported quality of life (QoL). This study aimed to evaluate changes in QoL and functional health following histotripsy. **Methods:** This retrospective cohort study involved 14 patients who underwent histotripsy for liver tumors at a single center. Eligible patients had completed at least one patient-reported outcome measure (PROM) before and after treatment. PROMs were collected at a median of 27.5 days before treatment (range, 1–100) and 88.5 days after treatment (range, 5–264). Tools included the PROMIS-10 (used by 7 patients) and both PROMIS-10 and NCCN Distress Thermometer V2 (used by 7 patients). These instruments assessed general health, QoL, physical and mental health, social satisfaction, emotional well-being, fatigue, pain, and physical activity. PROMIS T-scores were analyzed. Descriptive statistics summarized changes between assessments. **Results:** Among the 14 patients included in the study, the primary cancer types were colorectal carcinoma (CRC) in 5 (36%), neuroendocrine tumors (NETs) in 3 (21%), breast cancer in 2 (14%), and other tumor types in 4 (29%). A total of 29 liver lesions were treated, with the highest concentration found in liver segment 3 (III). The treatment intent was palliative in 19 lesions (86%) and curative in 3 lesions (14%). The percentage of patients reporting “poor” general health dropped by 50% (from 14% to 7%), while those reporting “good” general health rose from 29% to 43%. The percentage of “poor” overall QoL ratings decreased from 14% to 0%, with increases in “fair” and “good” responses. Physical health saw a decline in “poor” ratings (14% to 7%) and an increase in “fair” responses (50% to 64%). Mental health remained mostly stable, with a slight rise in “good” ratings (7% to 14%). Social satisfaction improved, with “very good”

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responses increasing from 7% to 21%, although "good" ratings decreased. Physical activity levels rose, with no patients reporting inactivity post-treatment, and more patients reporting being "a little" or "completely" active. Emotional distress showed mixed changes, with "sometimes" responses decreasing from 64% to 50%, but increases in both "rarely" and "often" categories. Fatigue severity shifted toward moderate levels (50% to 71%), and no patient reported severe fatigue post-treatment. The mean pain scores slightly decreased (3.21 to 3.00). The PROMIS physical health scores improved from 40.8 to 42.2, while the PROMIS mental health scores remained stable (44.4 to 44.2). Patients' perceived physical and mental changes also improved (from 2.07 to 2.36 and from 2.00 to 2.50, respectively). **Conclusion:** Histotripsy improved health, activity, and well-being in 14 patients; QoL benefits need further study.

Disclosures: Ahmed Sayed Ahmed: Nothing to Disclose, Chase Wehrle: HistoSonics: Above, Eren Berber: Medtronic: Consultant, Ethicon: Consultant, fluoptics: Consultant, Federico Aucejo: Nothing to Disclose, Jaekeun Kim: Nothing to Disclose, David Kwon: Medtronics: Consultant, GE medical: Consultant, Histosonics: Consultant

3304 | ★ MACHINE LEARNING BASED OUTCOMES IN GALLBLADDER ADENOCARCINOMA (GBA) WITH LIVER METASTASIS

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Background: GBA with liver metastasis is a rare and aggressive malignancy with a poor prognosis and limited treatment guidance. Due to its late presentation and varied clinical behavior, its management remains challenging. This study is the first to apply machine learning (ML) to identify key prognostic factors and improve survival prediction, specifically in GBA patients with liver metastasis. **Methods:** Data were obtained from the SEER database (2004-2021). Patients who met any of the following criteria were excluded: diagnosis not confirmed by histology; previous history of cancer or other concurrent malignancies; or unknown data. To identify prognostic variables, we conducted Cox regression analysis and constructed prognostic models using ML algorithms to predict the 5-year survival. Patient records were randomly divided into training (70 %) and validation (30 %) sets. A validation method incorporating the area under the curve (AUC) of the receiver operating characteristic curve was used to validate the accuracy and reliability of the ML models. We also investigated the role of multiple therapeutic options using Kaplan-Meier survival analysis. **Results:** A total of 1,189 patients were included. Most patients (57.0%) were younger than 70 years, and the majority were female (72.6%). The racial distribution showed that 72.5% were white, followed by black (16.3%) and Asian or Pacific Islander (11.2%). T3 stage was the most common (60.1%), and nodal involvement was observed in 41.4% of the patients (N1,32.7%; N2,8.7%). Cancer-directed surgery was performed in 60.6% of patients, while 54.8% received chemotherapy. Additionally, 68.2% of the tumors measured ≥ 3 cm.

At 5 years, patients aged < 70 years had higher survival rates (OS: 5.5%, CSS: 5.9%) than those aged ≥ 70 years (OS: 2.7%, CSS: 3.1%). White patients had a 5-year CSS of 7.5%, followed by Asian or Pacific Islanders (6.0%), and Black patients (1.4%). Patients who underwent cancer-directed surgery had better outcomes (OS, 9.5%; CSS, 10.8%) than those who did not (OS, 0.3%; CSS, 0.3%). Chemotherapy was associated with improved survival (OS: 6.2%, CSS: 6.9%) compared to no chemotherapy (OS: 1.8%, CSS: 1.9%).

Multivariate Cox regression analysis identified older age and male sex as poor prognostic factors, while surgery and chemotherapy were good prognostic factors. Gradient boosting and Random Forest were the most accurate models. The ML models identified the T-category as the most significant prognostic factor, followed by age. **Conclusion:** ML enhances personalized medicine by identifying key prognostic factors in GBA with liver metastasis, which may guide treatment decisions for better patient management.

Disclosures: Sakhr Alshwayyat: Nothing to Disclose, Salsabeel Aljawabrah: Nothing to Disclose, Kholoud Alqasem: Nothing to Disclose, Yamen Alshwaiyat: Nothing to Disclose

3305 | GROWTH HORMONE (GH) PATHWAY AS A PROGNOSTIC AND THERAPEUTIC BIOMARKER IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA TREATED WITH RADIOTHERAPY

Joe Eid[1] Safa Kaseb[2] Lianchun Xiao[1] Ryan Sun[1] Mahesh Kumar Kannan[1] Manal Hassan[3] Asif Rashid[1] Hop Tran Cao[1] Sunyoung Lee[2] Emad Singer[1] Hesham Amin[1] Ahmed Kaseb[3] Eugene Koay[3], [1]The University

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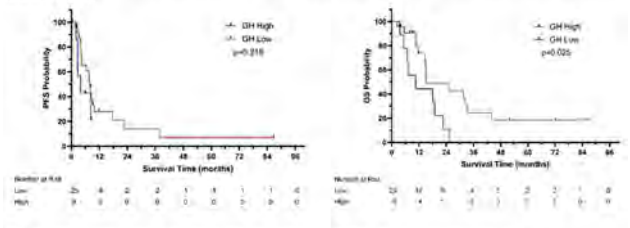
Background: Radiation therapy (RT) has emerged as an effective local therapy option for patients with unresectable HCC and is associated with improved OS. However, some patients still have poor outcomes after RT and biomarkers are needed to stratify prognostic groups. High circulating GH levels promote HCC proliferation and survival and associate with aggressive disease. In this study, we evaluated whether pre-treatment GH levels associate with overall survival (OS) and progression-free survival (PFS) in patients who underwent RT for unresectable HCC. **Methods:** Patients undergoing RT for HCC during 2017-2023 were identified from a prospectively maintained database. Pre-treatment blood samples were obtained, and patients without GH levels within 8 weeks of radiotherapy were excluded. A cutoff of 3.7 ng/mL for women and 0.9 ng/mL for men was used to categorize high vs low GH levels, as set by the Endocrine and Pituitary societies based on population studies and clinical trial data. The primary endpoint was OS and secondary endpoint was PFS, both measured from the time of RT. Kaplan-Meier method was used to estimate OS and PFS. Cox proportional hazards models were used to evaluate the association of OS or PFS with covariates. **Results:** Thirty-four patients were included. Median age was 67 years, 73.5% of patients were male, and 26.5% had high GH levels. Both groups were balanced regarding how many prior lines of therapy patients had received ($p = 0.999$). Median (IQR) follow-up time was 10 (4-25) months. The median PFS for the GH-low group was 7.9 months versus 3.9 months in the GH-high group ($p = 0.219$). The median OS was significantly higher for the GH-low group (15.2 months) compared with the GH-high group (10.6 months, $p = 0.025$). On multivariate analysis, high GH was significantly associated with an increased risk of death (HR: 2.66, 95% CI: 1.07-6.61; $p = 0.036$). **Conclusion:** High pre-treatment GH level associated with worse prognoses for patients with unresectable HCC undergoing RT. These results warrant further validation and potential integration of anti-GH therapy into personalized therapeutic management based on GH levels in HCC patients undergoing HCC.

Figure 1. Kaplan-Meier curves representing OS and PFS among GH-High and GH-Low patients who underwent radiation therapy



Abbreviations: GH, Growth Hormone; OS, Overall Survival; PFS, Progression-free Survival

Disclosures: Joe Eid: Nothing to Disclose, Nothing to Disclose, Safa Kaseb: Nothing to Disclose, Lianchun Xiao: Nothing to Disclose, Ryan Sun: Nothing to Disclose, Mahesh Kumar Kannan: Nothing to Disclose, Manal Hassan: Nothing to Disclose, Asif Rashid: Nothing to Disclose, Hop Tran Cao: Merck: Grant/Research Support, Intuitive Foundation: Grant/Research Support, Sunyoung Lee: Nothing to Disclose, Emad Singer: Nothing to Disclose, Hesham Amin: Nothing to Disclose, Ahmed Kaseb: Nothing to Disclose, Eugene Koay: Nothing to Disclose

3306 | PRESENTATION AND CLINICAL OUTCOMES OF PATIENTS WITH HEPATOCELLULAR CARCINOMA DIFFER BY TYPE OF STEATOTIC LIVER DISEASE

Ashwini Arvind[1] Megha Sheth[1] Mohammed Al-Hasan[2] Mohammad Jarrah[1] Dariel Solis[1] Celina Li[1] Pojsakorn Danpanichkul[3] Jordan Mayberry[2] Thomas Kerr[2] Thomas Cotter[1] Lisa Quirk[1] Sneha Deodhar[1] Nicole Rich[2] Amit Singal[1], [1]UT Southwestern Medical Center, [2]University of Texas Southwestern Medical Center, [3]Texas Tech University Health Sciences Center

Background: The updated AASLD nomenclature for steatotic liver disease (SLD) encompasses alcohol-related liver disease (ALD), metabolic dysfunction and alcohol-related liver disease (MetALD) and metabolic dysfunction-related steatotic liver disease (MASLD). We aimed to assess differences in hepatocellular carcinoma (HCC) presentation and outcomes between these groups. **Methods:** We studied a retrospective cohort of patients with cirrhosis and underlying SLD diagnosed with HCC between January 2010 and December 2024 at two US medical centers. We classified liver disease etiology according to alcohol use and cardiometabolic risk factors (CMRF) using the 2023 AASLD SLD criteria, independent of other chronic liver diseases. CMRF included BMI ≥ 25 (23 in Asians), type 2 diabetes, hypertension and dyslipidemia. We categorized patients with current or prior heavy alcohol use and no CMRF as ALD, current or prior heavy alcohol use and ≥ 1 CMRF as MetALD, and ≥ 1 CMRF without heavy alcohol use as MASLD. Surveillance receipt was defined as ultrasound, contrast-enhanced MRI or multiphase CT within 7 months before HCC diagnosis. We used multivariable logistic and Cox regression analyses to evaluate associations between SLD subtype and clinical outcomes. Multivariable models were adjusted for age, sex, race and Child-Pugh class. **Results:** Of 1124 eligible patients, 467 (41.5%) had MASLD, 583 (51.9%) had MetALD and 74 (6.6%) had ALD. Over 70% of patients across the three groups had concurrent viral liver disease. Compared to those with ALD and

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MetALD, patients with MASLD were older (median 55.7 and 57.6 vs. 61.7), a higher proportion were women (5.4% and 10.5% vs. 39.6%) and fewer were non-Hispanic White (48.6% and 36.5% vs. 26.8%) ($p < 0.001$ for all comparisons). Only 40.8% of patients had surveillance imaging. Patients with ALD were less likely to undergo surveillance than those with MetALD (aOR 0.41, 95%CI 0.23–0.70) or MASLD (aOR 0.46, 95%CI 0.25–0.81). A smaller proportion of ALD patients were diagnosed with early-stage HCC (BCLC 0/A) compared to MetALD and MASLD (29.8% vs. 38.6% and 44.4%, $p = 0.003$) but this was not significant in multivariable analysis (ALD vs. MetALD: aOR 0.70, 95%CI 0.42-1.17; ALD vs. MASLD: aOR 0.59, 95%CI 0.34–1.01). Only 30.8% underwent curative treatment, including 62.8% of those with early-stage HCC. Patients with ALD were less likely to receive curative treatment than those with MASLD (aOR 0.26, 95%CI 0.11–0.52) and MetALD (aOR 0.35, 95%CI 0.16–0.71) with similar differences in the subgroup with early-stage HCC (ALD vs. MASLD: aOR 0.33, 95%CI 0.11–0.94; ALD vs. MetALD aOR 0.54, 95%CI 0.20–1.43). Finally, ALD was associated with worse survival compared to MetALD (aHR 1.32, 95% CI 1.01–1.73) and MASLD (aHR 1.34, 95% CI 1.01–1.79). **Conclusion:** Patients with ALD-HCC have worse survival than those with MetALD-HCC and MASLD-HCC, partly related to differences in surveillance receipt, early-stage detection and curative treatment.

Disclosures: Ashwini Arvind: Nothing to Disclose, Megha Sheth: Nothing to Disclose, Mohammed Al-Hasan: Nothing to Disclose, Mohammad Jarrah: Nothing to Disclose, Dariel Solis: Nothing to Disclose, Celina Li: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Jordan Mayberry: Nothing to Disclose, Thomas Kerr: Madrigal: Consultant, GSK: Grant/Research Support, Thomas Cotter: Nothing to Disclose, Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Sneha Deodhar: Nothing to Disclose, Nicole Rich: AstraZeneca: Advisor, Genentech: Consulting, Exelixis: Advisor, Eisai: Advisor, Madrigal: Advisor, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant

3307 | HCC IN THE RIO GRANDE VALLEY: UPDATED DATA ON LATINO POPULATION DISPARITIES AND TREATMENT

Rishika Trivedi[1] Sergio Hernandez-Llamas[1] Laura Reyes-Uribe[1] Yasitha Kakarlapudi[1] Andrea Morales-Acosta[1] Maria Pinzon-Torres[2] Edgar Lopez[1] Fernando Membreno[3] Jose Cruz[4], [1]DHR Health, Edinburg, Texas, [2]University of Monterrey, San Pedro Garza Garcia, Mexico, [3]DHR Health Liver Transplantation, Hepatobiliary Services, Mcallen, Texas, [4]DHR Health Hematology/Oncology, Edinburg, Texas

Background: Hepatocellular carcinoma (HCC) has steadily increased in the U.S. In recent years, with higher incidence among racial and ethnic minorities, particularly Latinos. This retrospective study examines the different etiologies, presentation of diagnosis, management, and outcomes in the Rio Grande Valley, home of 1.3 million Latinos. **Methods:** A retrospective chart review was conducted on patients with HCC diagnosis who were presented at the Liver Tumor Board of our institute between 2017 and 2023. This analysis includes updated data extracted from the electronic health records (EHR), such as medical history, laboratory results, and radiological studies required for each patient's staging and transplant eligibility assessment. Data on patients' clinical characteristics and treatment were also collected. **Results:** A total of 537 cases were reviewed, and 138 patients with complete clinical data were included in the analysis. 95% were identified as White/ Hispanic. The median age at diagnosis was 65.5 $\pm$ 9.6 years, with 69% male and 11.6% uninsured. The average BMI was 30.6, metabolic-associated steatotic liver disease (MASLD) was present in 48.5% of patients and 48.5% were alcohol-related.The longest average interval between initial imaging and diagnosis was seen in Viral Hepatitis (415.8 days). The highest rate of multifocal tumor involvement (54.5%) and the greatest proportion of patients who underwent liver transplant (18.2%) were observed in the MASLD and Alcohol-related group. The peak MELD-Na at diagnosis was found in Alcohol-related and Hemochromatosis (18.0). Vascular invasion was most frequent in the Viral Hepatitis and Alcohol-related group (35.0%). Complete survival (100%) was noted in the Autoimmune, Other, and Alcohol-related with Hemochromatosis cohorts (Table 1a). Ablative therapy was used in 93 (67.4%) of the patients. The number of patients sent for liver transplant evaluation was 59 (42.8%), and only 6

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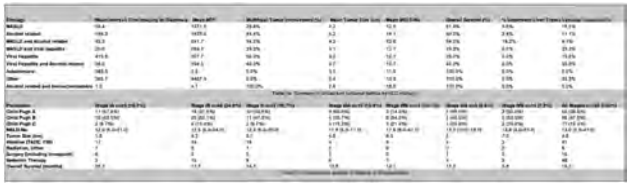
(10.2%) patients received liver transplants. Of the total, 80 (58.0%) had disease progression, while the others faced challenges such as lack of transportation, inadequate family support, or insurance issues (Table 1b). **Conclusion:** In this predominantly Latino cohort with HCC, MASLD and alcohol were the most common underlying liver diseases. Social determinants of health, including access, support, and insurance, were key contributors to disease progression. Our data by staging is in concordance with the distribution of SEER incidence cases from 2012–2021. Despite multidisciplinary evaluation, the rate of transplantation at our institution is below the national average, highlighting the need to bridge this disparity in the Latino community.

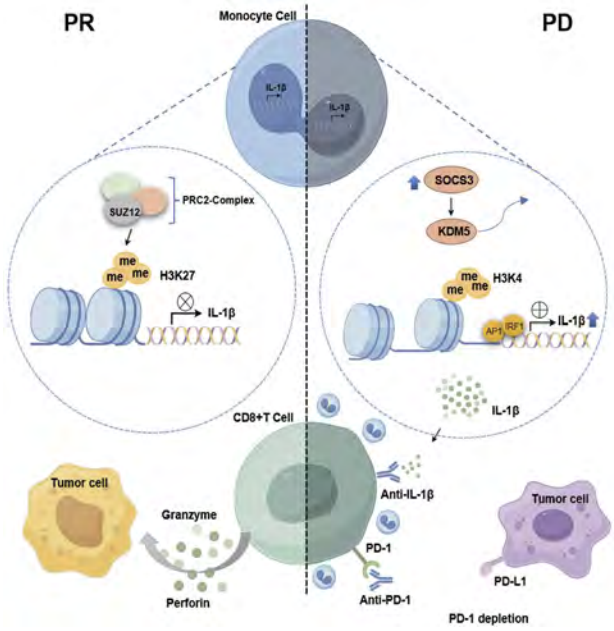


Disclosures: Rishika Trivedi: Nothing to Disclose, Sergio Hernandez-Llamas: Nothing to Disclose, Laura Reyes-Uribe: Nothing to Disclose, Yasitha Kakarlapudi: Nothing to Disclose, Andrea Morales-Acosta: Nothing to Disclose, Maria Pinzon-Torres: Nothing to Disclose, Edgar Lopez: Nothing to Disclose, Fernando Membreno: Nothing to Disclose, Jose Cruz: Nothing to Disclose

3308 | KDM5A-DRIVEN REPROGRAMMING OF IL-1γ⁺ CD14+ MONOCYTES MEDIATES RESISTANCE TO ANTI-PD-1 THERAPY IN ADVANCED HEPATOCELLULAR CARCINOMA BY SUPPRESSING T CELL-MEDIATED ANTITUMOR IMMUNITY

Ronghua Jin[1] Wenying Qiao[1] Xuefeng Huang[1] Ziyi Li[1] Yang Wang[1] Xiaoxue Yuan[1] Xi Wang[1] Xiaoyan Ding[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality globally, with anti-PD-1 immunotherapy emerging as a promising therapeutic strategy. However, the clinical efficacy of immune checkpoint blockade remains limited, primarily due to complex and poorly understood immune evasion mechanisms. This study aims to characterize circulating immune signatures in HCC patients treated with anti-PD-1 immunotherapy, elucidate the role and mechanisms of IL-1β⁺ CD14⁺ monocytes in tumor immune evasion, and identify novel targets to improve HCC immunotherapy outcomes. **Methods:** Peripheral blood from 10 HCC patients undergoing anti-PD-1 treatment was analyzed via single-cell RNA sequencing (scRNA-seq). Paired tumor tissue samples from 4 patients receiving targeted immunotherapy were examined using multiplex immunofluorescence staining and spatial transcriptomics. To explore mechanisms, we integrated ATAC-seq analysis, in vitro monocyte-T cell co-culture experiments, and murine tumor models, combining single-cell and spatial omics with functional validation to comprehensively assess systemic immune responses to therapy. **Results:** Responders exhibited a higher abundance of CD8⁺ T cells and fewer CD14⁺ monocytes compared to non-responders. The accumulation of IL-1β⁺ CD14⁺ monocytes suppressed CD8⁺ T cell function and contributed to resistance. Spatial transcriptomics revealed increased infiltration of IL-1β⁺ CD14⁺ macrophages in non-responders, which interacted with T cells to inhibit antitumor activity—a pattern confirmed by multiplex immunofluorescence. Mechanistically, in non-responders, CD14⁺ monocytes showed synergistic upregulation of the immunosuppressive SOCS3 and pro-inflammatory IL-1β, leading to M1 macrophage reduction and CD8⁺ T cell dysfunction. These gene expression patterns were epigenetically regulated by KDM5A. In murine HCC models, combined IL-1β blockade and anti-PD-1 therapy decreased immunosuppressive factors, enhanced T cell infiltration, and significantly suppressed tumor progression and improved therapeutic efficacy. **Conclusion:** IL-1β⁺ monocytes play a key role in suppressing CD8⁺ T cell–mediated antitumor immunity. Targeting these monocytes enhances T cell responses and synergizes with anti-PD-1 therapy, offering a promising strategy to improve HCC immunotherapy outcomes.



Disclosures: Ronghua Jin: Nothing to Disclose, Wenying Qiao: Nothing to Disclose, Xuefeng Huang: Nothing

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to Disclose, Ziyi Li: Nothing to Disclose, Yang Wang: Nothing to Disclose, Xiaoxue Yuan: Nothing to Disclose, Xi Wang: Nothing to Disclose, Xiaoyan Ding: Nothing to Disclose

3309 | LONG SHORT-TERM MEMORY–BASED PROJECTION OF HEPATOBILIARY CARCINOMA MORTALITY TRENDS USING CDC WONDER DATA.

Sri Harsha Boppana[1] Manaswitha Thota[2] Gautam Maddineni[3] Sachin Sravan Kumar Komati[4] Sai Lakshmi Prasanna Komati[5] C. David Mintz MD PhD[6], [1]Nassau University Medical Center / Johns Hopkins University, [2]Virginia Commonwealth University, [3]Creighton university school of medicine, [4]Florida International University, [5]Government Medical College, Ongole, [6]Johns Hopkins University

Background: Hepatobiliary malignancies persist among the top causes of cancer-related death worldwide, even as biomarker discovery and imaging techniques have advanced. Accurate projections of future mortality patterns are essential for public health planning and resource allocation. We therefore examined national mortality data and built a deep-learning model capable of forecasting upcoming trends in hepatobiliary cancer deaths based on demographic information. **Methods:** We retrieved annual death counts for hepatobiliary carcinoma from the CDC's WONDER database covering 1999 through 2020. After normalizing rates per 100 000 population, we converted age, sex, race and ethnicity classifications into numeric encodings. Trend analysis and visualization were performed in R. To predict future mortality, we designed a Long Short-Term Memory (LSTM) network with an input sequence window of 20 years and trained it to forecast the subsequent year's rate. The model underwent 80/10/10 split for training, validation and testing, respectively. We optimized parameters using the Adam algorithm (learning rate $3\times10_{50}$, batch size 32) and halted training when validation loss plateaued. Model performance was quantified by mean squared error (MSE) on both training and independent test sets. **Results:** Age-stratified analysis demonstrated steeply rising mortality among individuals over 65, with men and non-Hispanic populations exhibiting the highest rates. The LSTM network achieved a training MSE of 0.0061 and a validation MSE of 0.0020, indicating strong fidelity between predicted and observed values. Overlay plots of recorded versus projected mortality revealed tight alignment across the test interval, with residuals uniformly small and without systematic bias. **Conclusion:** Our findings confirm distinct demographic disparities in hepatobiliary cancer death rates and validate the LSTM approach for reliable near-term forecasting. Although the model leverages only publicly available demographic inputs—and thus omits clinical details such as tumor stage or comorbidity profiles—it provides a scalable tool for epidemiologic surveillance. Incorporating patient-level variables and extending the prediction horizon represent logical next steps toward personalized prognostic modeling and strategic health policy development.

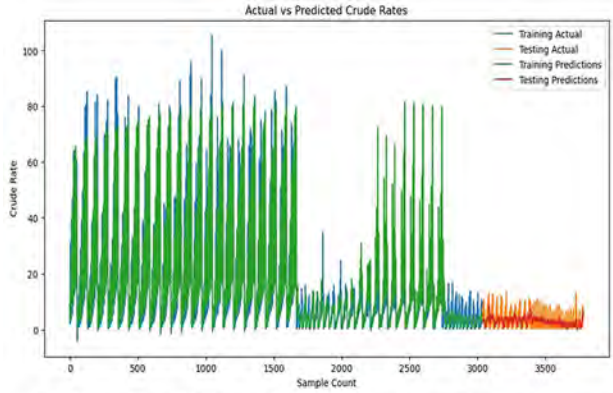

Figure 1. Actual versus LSTM-Predicted Hepatobiliary Cancer Mortality Rates: This plot compares observed crude death rates (per 100 000 population) from the CDC WONDER database (1999–2020) with values forecast by the LSTM network. Solid blue curves represent recorded rates, while the overlaid orange curves depict model predictions. Both training and test intervals are shown to emphasize the model's ability to replicate historical trends accurately.

Disclosures: Sri Harsha Boppana: Nothing to Disclose, Manaswitha Thota: Nothing to Disclose, Gautam Maddineni: Nothing to Disclose, Sachin Sravan Kumar Komati: Nothing to Disclose, Sai Lakshmi Prasanna Komati: Nothing to Disclose, C. David Mintz MD PhD: Nothing to Disclose

3310 | ASSOCIATIONS BETWEEN DEPRIVATION INDEX AND POST-LOCOREGIONAL THERAPY MORTALITY AND ACUTE CARE UTILIZATION AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA

Merete Lund[1] Yue Jiang[2] Chidi Iloabachie[1] Arjun Juneja[1] Patrick Hazelrigg[1] Parsa Pazooki[1] Sydney Power[1] Gabe Lupu[1] Joyce Badal[1] David Seligson[1] Hanna Sanoff[1] David Mauro[1] David Gerber[3] Theodore Yanagihara[1] Sidney Barritt[1] Andrew Moon[4], [1]University of North Carolina - Chapel Hill, [2]Department of Statistical Science Duke University, Durham, NC, [3]University of North Carolina at Chapel Hill, [4]University of North Carolina

Background: Area Deprivation Index (ADI) scores are compiled block group percentiles based on the socioeconomic disadvantage in a region of interest and have been associated with health outcomes in many chronic diseases. The relationship between ADI and outcomes

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among patients with hepatocellular carcinoma (HCC) receiving locoregional therapies (LRTs) is unclear. ADI may impact multiple steps in the pathway to diagnosis and treatment of HCC including disease etiology, initial diagnosis of HCC, access to care, treatment choices, and care utilization after treatment. This project sought to examine potential associations between ADI and outcomes in HCC patients receiving LRTs. **Methods:** We performed a retrospective analysis of patients with HCC who received LRTs within a single health system between 2014 and 2021. For patients with multiple treatments, we used only information from their initial treatment. We pulled ADI data from the Center for Health Disparities Research database for each patient based on their home address and categorized them into quartiles (e.g., 4th quartile, scores 76-100, greatest deprivation) and extracted other baseline sociodemographic and clinical characteristics. Outcomes of interest included post-treatment mortality and acute care utilization (ER visits or unplanned hospitalizations). A log-rank test was used to examine associations between ADI and outcomes, and a Cox proportional hazards model was used for the same analysis, adjusting for demographic and clinical characteristics. **Results:** There were 790 patients with HCC who received LRT in in our cohort. There were 146 procedures among 85 patients in quartile 1 (scores 1-25), 345 procedures among 190 patients in quartile 2 (scores 26 – 50), 432 procedures among 259 patients in quartile 3 (Scores 51-75), and 425 procedures among 256 patients in the top quartile (Scores 76-100). Median age for quartiles 2-4 was 64.4, 64.2, and 64.1 years, while median age for quartile 1 was statistically significantly higher at 68.3 years. Other demographic and clinical characteristics were similar across quartiles- 75% of patients were male, the most frequent treatment was TACE, and most patients were BCLC C. We did not identify a statistically significant association between ADI quartile and mortality in the unadjusted or multivariable models. 13% of procedures were associated with acute care utilization within 90 days for both the lowest and highest quartiles compared with 21% of procedures in both the 2nd and 3rd quartiles, a statistically significant difference. **Conclusion:** In this analysis, we did not identify statistically significant associations between ADI quartile and mortality, although there was sufficient evidence to suggest an association between ADI quartile and acute care utilization within 90 days. Procedures among patients in the lowest and highest ADI quartiles had lower unplanned ER visits or hospitalizations within 90 days of their procedures.

Patient-level characteristics (N = 790)						
		ADI Quartile 1 (N = 85)	ADI Quartile 2 (N = 190)	ADI Quartile 3 (N = 259)	ADI Quartile 4 (N = 256)	p-value
Age (median, Q1-Q3)		68.3 (61.3 – 75.8)	64.4 (59.5 – 70.9)	64.2 (59.2 – 69.2)	64.1 (57.7 – 68.3)	<0.001
Sex	Male	64 (75%)	148 (78%)	187 (72%)	199 (78%)	0.431
	Female	21 (25%)	42 (22%)	72 (28%)	57 (22%)	
Charlson comorbidity score (median, Q1-Q3)		8 (6 – 11)	8 (6 – 11)	8 (6 – 11)	7 (6 – 10)	0.417
Child Pugh score	A	65 (76%)	116 (61%)	159 (61%)	145 (57%)	0.172
	B7	8 (9%)	24 (13%)	41 (16%)	44 (17%)	
	B8	6 (7%)	25 (13%)	22 (8%)	34 (13%)	
	B9	3 (4%)	12 (6%)	23 (9%)	17 (7%)	
	C	3 (4%)	13 (7%)	14 (5%)	16 (6%)	
ECOG PS	0	60 (71%)	114 (60%)	152 (59%)	156 (61%)	0.697
	1	17 (20%)	57 (30%)	74 (29%)	66 (26%)	
	2	7 (8%)	15 (8%)	26 (10%)	29 (11%)	
	>2	1 (1%)	4 (2%)	7 (3%)	5 (2%)	
BCLC stage	0	15 (18%)	16 (8%)	16 (6%)	21 (8%)	0.236
	A	28 (33%)	60 (32%)	87 (34%)	80 (31%)	
	B	11 (13%)	21 (11%)	38 (15%)	40 (16%)	
	C	28 (33%)	77 (41%)	101 (39%)	96 (38%)	
	D	3 (4%)	16 (8%)	17 (7%)	19 (7%)	
Etiology	MASLD	10 (12%)	32 (17%)	59 (23%)	48 (19%)	0.003
	Alcoholic	16 (19%)	25 (13%)	20 (8%)	25 (10%)	
	HCV	26 (31%)	63 (33%)	93 (36%)	95 (37%)	
	HBV	8 (9%)	5 (3%)	8 (3%)	3 (1%)	
	Other/Multiple	25 (29%)	65 (34%)	79 (31%)	85 (33%)	
Treatment-level characteristics (N = 1,348)						
		ADI Quartile 1 (N = 146)	ADI Quartile 2 (N = 345)	ADI Quartile 3 (N = 432)	ADI Quartile 4 (N = 425)	p-value
Treatment Type	Laparoscopic Ablation	29 (20%)	81 (23%)	83 (19%)	94 (22%)	0.452
	Percutaneous Ablation	21 (14%)	46 (13%)	67 (16%)	68 (16%)	
	Bland Embolization	1 (1%)	6 (2%)	10 (2%)	8 (2%)	
	TACE	58 (40%)	137 (40%)	160 (37%)	180 (42%)	
	TARE/Y90	19 (13%)	41 (12%)	67 (16%)	46 (11%)	
	SBRT	18 (12%)	34 (10%)	45 (10%)	29 (7%)	
Acute care utilization within 90 days (ER visit or hospitalization)		19 (13%)	72 (21%)	91 (21%)	56 (13%)	0.003

Disclosures: Merete Lund: Nothing to Disclose, Yue Jiang: Nothing to Disclose, Chidi Iloabachie: Nothing to Disclose, Arjun Juneja: Nothing to Disclose, Patrick Hazelrigg: Nothing to Disclose, Parsa Pazooki: Nothing to Disclose, Sydney Power: Nothing to Disclose, Gabe Lupu: Nothing to Disclose, Joyce Badal: Nothing to Disclose, David Seligson: Nothing to Disclose, Hanna Sanoff: Nothing to Disclose, David Mauro: Nothing to Disclose, David Gerber: BMI Organ Bank: CMO, Theodore Yanagihara: Nothing to Disclose, Sidney Barritt: Nothing to Disclose, Andrew Moon: TARGET RWE: Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant

3311 | EXPRESSION AND FUNCTION OF MIR-1297 AND ITS TARGET THYMOSIN-Β10 IN HYPOXIA-INDUCED LENVATINIB RESISTANCE IN HEPATOCELLULAR CARCINOMA

Takayuki Kogure[1] *MARI SATOH*[1] *Kennichi Satoh*[1], [1]*Tohoku Medical and Pharmaceutical University*

Background: Lenvatinib has shown a superior response rate in hepatocellular carcinoma (HCC), although its overall survival remains comparable to sorafenib, suggesting potential drug resistance. Hypoxia in the tumor microenvironment is a pivotal factor in

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resistance acquisition. Tyrosine kinase inhibitors that inhibit VGEF suppress angiogenesis, leading to significant hypoxia in the tumor microenvironment. This study investigates the mechanisms underlying lenvatinib resistance and the role of microRNAs (miRNAs) under hypoxic conditions in HCC. **Methods:** The human HCC cell lines PLC/PRF/5, HepG2, and Huh7 were cultured under normoxia (95% air and 5% CO_2) or hypoxia (94% N_2 with 1% O_2 and 5% CO_2). Anchorage-dependent proliferation was assessed using a metabolic assay, and induction of apoptosis was evaluated morphologically and activation of caspase-3/7. Genome-wide miRNA profiling was performed to identify resistance-related miRNA alterations. An argonaute2-based RIP assay followed by mRNA profiling was used to identify miRNA targets. **Results:** Lenvatinib inhibited cell proliferation in a concentration-dependent manner; however, its IC_{50} increased significantly under hypoxia, indicating the acquisition of resistance. Hypoxia reduced lenvatinib-induced apoptosis by 22.4% and 19.6% in PLC/PRF/5 and HepG2 cells, respectively, and also suppressed caspase-3/7 activation. Genome-wide profiling revealed 42 upregulated miRNAs in PLC/PRF/5 cells treated with lenvatinib under normoxia, and 28 of these downregulated under hypoxia. Further investigation was focused on miR-1297, which showed the most significant change. Forced expression of miR-1297 significantly reduced cell viability under hypoxia (PLC/PRF/5: 76.6%, HepG2: 67.1%) compared to negative controls (88.3%, 75.3%). RIP assays identified 88 significantly upregulated mRNAs under the miR-1297 overexpression, and TargetScan analysis identified TMSB10 mRNA as a direct target. Forced expression of miR-1297 reduced thymosin-β10 protein expression by 46.3% and 33.4% in PLC/PRF/5 and HepG2 cells, respectively. Silencing TMSB10 mRNA partially restored lenvatinib cytotoxicity, reducing viability by 14.7% and 13.5% under hypoxia. **Conclusion:** miR-1297 may play a role in hypoxia-induced lenvatinib resistance by targeting thymosin-β10, a protein associated with cell survival and proliferation. These observations suggest that miRNAs could be a potential target for overcoming lenvatinib resistance.

Disclosures: Takayuki Kogure: Nothing to Disclose, MARI SATOH: Nothing to Disclose, Kennichi Satoh: Nothing to Disclose

3312 | GERMLINE VARIANTS DO NOT INFLUENCE THE RATE OF SOMATIC MUTATIONS IN TERT IN HEPATOCELLULAR CARCINOMA

Chunmiao Cai[1] Salah Adlat[2] Dingzi Yin[1] Markcus Lee[1] Kirk Wangensteen[1], [1]Mayo Clinic, [2]Mayo Clinic, Rochester

Background: TERT promoter mutations and amplifications represent the most prevalent somatic genomic events in hepatocellular carcinoma (HCC). Also, germline Single Nucleotide Polymorphisms (SNPs) at the TERT locus have been found to be protective or risk factor for HCC. However, the relationship between the somatic events and inherited germline variants in TERT remains poorly understood. Here, we investigated the association between TERT somatic alterations and germline variations. **Methods:** Whole genome sequencing (WGS) data from The Cancer Genome Atlas Liver Hepatocellular Carcinoma (TCGA-LIHC) cohort were analyzed. TERT promoter mutations were detected using MuTect2, copy number variations were identified using ModelSegments, and germline variations were called using HaplotypeCaller. Four SNPs were selected for analysis, including rs2242652 and rs10069690, which are two protective loci in alcohol-related HCC, and rs2736098 and rs2736100, associated with increased risk. Somatic alterations, germline genotypes, and clinical metadata were integrated. Different genetic models were used to assess whether risk is driven by heterozygosity, homozygosity, or both. Stratified analyses were performed according to etiologic subgroups. Statistical significance was evaluated using chi-square or Fisher's exact tests with Benjamini-Hochberg correction. **Results:** Among 324 patients with available WGS data from TCGA-LIHC cohort, TERT promoter mutations were identified in 138 cases (42.6%), and TERT amplification was detected in 44 cases (13.6%), demonstrating high consistency with previously reported frequencies. Genotypes for the selected SNPs were successfully assigned to all patients. There was no statistically significant association between TERT promoter mutation status and any of the selected SNPs. For TERT amplification, a significantly lower frequency was observed in patients with the reference homozygous genotype (CC) at rs2736100 (4.7%) compared to those carrying CA or AA genotypes (15.8% for CA or AA; 17.8% for CA; 17.8% for AA; adjusted $P = 0.023$), when P-values were corrected within this single locus. However, these associations lost statistical significance after adjusting across all four tested loci (adjusted $P = 0.092$). Stratified analyses based on etiological subgroups did not show any differences, but the sample sizes might have limited analysis. The lack of significant associations between the two risk SNPs and TERT promoter mutations contrasts with findings from a previous study in a Chinese Han population, potentially due to differences in HCC etiology. **Conclusion:** Our findings suggest no clear association between four germline SNPs and either TERT promoter mutation or amplification, indicating that these germline variants are unlikely to serve as clinical predictors of TERT somatic alterations in HCC. Future research should examine the mechanism of the polymorphisms in altering HCC risk.

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Figure 1. *TERT* somatic alterations and germline SNPs in the TCGA-LIHC cohort. Oncoplot summarizing all identified *TERT* somatic alterations, including promoter mutations and amplifications, and germline SNP genotypes. Data were derived from 324 patients with available WGS data in the TCGA-LIHC cohort

Table 1. Frequency of *TERT* promoter mutations and amplifications by genotype at four SNP loci in the TCGA-LIHC cohort (n = 324).

	Pro_WT	Pro_MUT	*P*-value (per SNP[a])	*P*-value (all 4 SNPs[b])	Amp⁻	Amp⁺	*P*-value (per SNP[a])	*P*-value (all 4 SNPs[b])
non.rs2242652 (GG)	135	68			191	32		
rs2242652 (GA + AA)	51	50	0.136	0.271	89	12	0.861	0.983
rs2242652 (GA)	46	46	0.136	0.271	81	11	0.861	0.983
rs2242652 (AA)	5	4	0.743	0.811	8	1	1.000	1.000
non.rs10069690 (CC)	119	80			169	30		
rs10069690 (CT + TT)	67	58	0.408	0.395	111	14	0.598	0.954
rs10069690 (CT)	55	49	0.408	0.395	92	12	0.598	0.954
rs10069690 (TT)	12	9	0.814	0.814	19	2	0.746	0.995
non.rs2736098 (CC)	78	74			132	20		
rs2736098 (CT + TT)	108	64	0.066	0.264	148	24	1.000	1.000
rs2736098 (CT)	90	53	0.066	0.264	122	21	1.000	0.995
rs2736098 (TT)	18	11	0.288	0.395	26	3	1.000	1.000
non.rs2736100 (CC)	33	31			61	3		
rs2736100 (CA + AA)	153	107	0.398	0.395	219	41	*	0.093
rs2736100 (CA)	93	64	0.398	0.395	129	28	*	0.093
rs2736100 (AA)	60	43	0.398	0.477	85	18	*	0.093

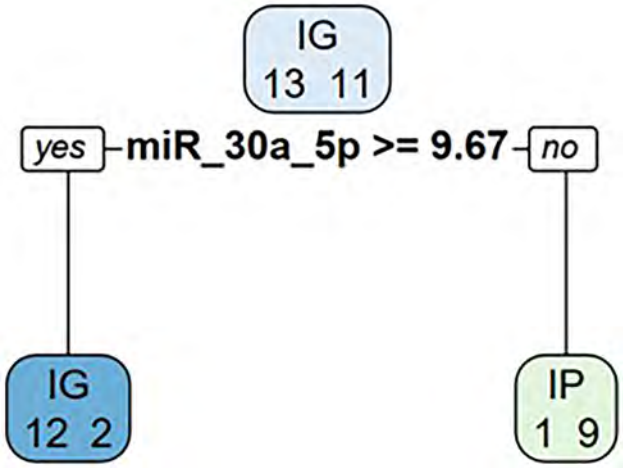
Note: Pro_WT, no *TERT* promoter mutation; Pro_MUT, *TERT* promoter mutation; Amp⁻, no *TERT* amplification; Amp⁺, *TERT* amplification; a, *P*-value corrected by Benjamini-Hochberg method for three genotypes within each individual SNP; b, *P*-value corrected across all four SNPs (12 genotypes in total). *, $P < 0.05$

Disclosures: Chunmiao Cai: Nothing to Disclose, Salah Adlat: Nothing to Disclose, Dingzi Yin: Nothing to Disclose, Markcus Lee: Nothing to Disclose, Kirk Wangensteen: Nothing to Disclose

3313 | EXOSOMAL MIR-30A-5P DECISION TREE DISTINGUISHES RESPONDERS TO ATEZOLIZUMAB-BEVACIZUMAB THERAPY IN ADVANCED HEPATOCELLULAR CARCINOMA

Young-Sun Lee[1] Eunho Choi[1] Ha Seok Lee[1] Youngwoo Lee[1] Yang Jae Yoo[1] Taehyung Kim[1] Seong Hee Kang[1] Yim Sun Young[1] Young Kul Jung[1] Ji Hoon Kim[1] Yeon Seok Seo[1] Hyung Joon Yim[1] Jong eun Yeon[1] Kwan Soo Byun[1], [1]Korea University College of Medicine

Background: Atezolizumab in combination with bevacizumab is currently recognized as the standard initial treatment for patients with advanced hepatocellular carcinoma (HCC). Nevertheless, there is still no established biomarker that can reliably predict how patients will respond to this therapy. Previous research by our group suggested that miR-30a-5p could serve as a potential predictive biomarker. The objective of this study was to validate the clinical relevance of this exosomal microRNA in a larger group of patients. **Methods:** Blood samples were collected from patients with advanced HCC before they began treatment with atezolizumab and bevacizumab. After three cycles of therapy, patients were categorized as responders if they exhibited stable disease, partial response, or complete response, and as non-responders if their disease progressed. Extracellular vesicles were isolated from the serum, and exosomal RNA was analyzed using next-generation small RNA sequencing. The researchers used decision tree analysis to pinpoint microRNAs that could distinguish between responders and non-responders. **Results:** The study analyzed samples from 13 responders and 11 non-responders. Next-generation sequencing detected a total of 1,076 microRNAs, among which let-7c-5p, miR-30a-5p, and miR-192-5p were found at significantly higher levels in responders. In agreement with earlier studies, miR-30a-5p was notably elevated in responders, with a statistically significant difference ($p = 0.0039$). Decision tree analysis revealed that miR-30a-5p levels of 9.67 or higher could effectively separate responders from non-responders. Additionally, random forest modeling identified miR-30a-5p as the most important factor for classifying patients by treatment response. **Conclusion:** miR-30a-5p appears to be a promising exosomal biomarker for predicting which patients with advanced HCC are likely to benefit from atezolizumab and bevacizumab therapy.



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3314 | CLINICAL INSIGHTS INTO MUCINOUS CYSTIC NEOPLASM OF THE LIVER: A SINGLE-CENTER CASE SERIES

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Background: Mucinous cystic neoplasm of the liver (MCN-L) is a rare, slow-growing cyst-forming epithelial tumor characterized by mucin-producing epithelium and ovarian-like stroma (OS). Due to its indolent nature and overlapping imaging features, it is frequently misdiagnosed as a simple hepatic cyst. This study aimed to describe the clinical, radiologic, and pathological characteristics of MCN-L and review outcomes following surgical resection. **Methods:** We retrospectively analyzed 17 patients diagnosed with MCN-L at a single tertiary referral center from 1994 to 2018. Demographics, imaging findings, serum and intracystic CA 19-9 levels, surgical outcomes, and pathological features were reviewed. **Results:** Among the 17 patients (15 females, 2 males; mean age: 57.5 years), all underwent complete surgical resection. Abdominal fullness was the most common presenting symptom. The mean tumor size was 10.4 cm, predominantly located in the left hepatic lobe. Preoperative sonography detected internal septation in 10 patients and mural nodules in a few. Serum CA 19-9 was elevated in 6 patients, and intracystic CA 19-9 levels were markedly elevated in all 4 aspirated cases (range: 1246.4–38705 U/mL). Only one patient had focal in situ adenocarcinoma. No recurrence was observed during a mean follow-up of 65.6 months. **Conclusion:** MCN-L is a rare hepatic cystic tumor with a strong female predominance and left lobe predilection. Internal septation and mural nodules on sonography should prompt suspicion. Despite its benign course, early surgical resection is critical to avoid malignant transformation and ensure excellent prognosis.

Table 1. Characteristic of patients and tumors; Serum and Intra-cystic tumor markers

No.	Age	Gender	Symptoms	Tumor location	Tumor size (cm)	Serum CA19-9 (U/mL)	Serum CEA (ng/mL)	Intra-cystic CA19-9 (U/mL)	Intra-cystic CEA (ng/mL)
1	73	M	NR	R	2.7	11.0	2.23	ND	ND
2	57	F	Abdominal fullness	L	5	15.9	1.43	ND	ND
3	44	M	Epigastralgia, RUQ pain Poor appetite Abdominal fullness	R	0.7	15.6	3.27	ND	ND
4*	64	F	NR	L	8.6	>18.1	7.28	ND	ND
5	59	F	Abdominal fullness	L	10	ND	ND	ND	ND
6	82	F	Epigastralgia Poor appetite Abdominal fullness	L	10	<0.8	2.20	1246.4	3229.96
7	73	F	Epigastralgia	R	0.7	69.9	1.53	ND	ND
8*	53	F	NR	R	0.5	ND	3.26	ND	ND
9	48	F	Poor appetite Abdominal fullness Palpable mass	R	10	230	1.57	ND	ND
10	73	F	Epigastralgia	R	2.3	ND	1.11	ND	ND
11	42	F	Epigastralgia Abdominal fullness Palpable mass	L	13.6	763	1.39	ND	ND
12	41	F	RUQ pain Abdominal fullness Palpable mass	L	11	1.5	2.2	38705	141.1
13	50	F	Poor appetite Abdominal fullness Palpable mass	L	11	4.16	0.9	ND	ND
14	51	F	Epigastralgia Abdominal fullness	L	18	ND	ND	ND	ND
15	40	F	NR	L	10	9.63	1.5	10421	70.1
16	64	F	Epigastralgia Palpable mass	L	10	168	0.67	7430	576
17*	63	F	Epigastralgia Abdominal fullness Palpable mass	R	21	34	0.8	ND	ND

M = Male; F = Female; RUQ = Right Upper Quadrant; R = Right lobe; L = left lobe; ND = not done; *Patient with invasive MCN-L; *Patient with hepatic failure.

Disclosures: Cong-Tian Wang: Nothing to Disclose, Chia-Sheng Chu: Nothing to Disclose, I-Ping Chiang: Nothing to Disclose, Hsueh-Chou Lai: Nothing to Disclose

3315 | MEDICAL SPECIALTY TREATMENT PATTERNS IN THE MULTIDISCIPLINARY MANAGEMENT OF HEPATOCELLULAR CARCINOMA: THE MAYO CLINIC EXPERIENCE

Fatima Islam[1] Robert Lewandowski[2] Beau Toskich[1], [1]Mayo Clinic Florida, [2]Northwestern University Feinberg School of Medicine

Background: Hepatocellular carcinoma (HCC) is a heterogeneous disease process which requires the involvement of multiple medical specialties in its management. The patterns of medical specialty treatment utilization within a large health system are not well characterized. The aim of this study is to describe the frequency and sequence of medical specialty involvement in HCC management within a large, tertiary care health system. **Methods:** A retrospective review was conducted at the Mayo Clinic using the Mayo Data Explorer (MDE). HCC patients were identified by ICD code (C22.0) and comprehensive CPT codes for Interventional Radiology (IR), Surgery, Radiation Oncology, and Medical Oncology. Treatments were collected after May 2020, the FDA approval date of atezolizumab-bevacizumab, keeping in line with the current standard of therapy. Treatment sequence and specialty involvement were assessed descriptively. **Results:** A total of 2,965 HCC patients with 4,953 treatments across specialties were identified. For all treatments (N = 4,953), IR accounted for 39%, medical oncology 30%, surgery 23%, and radiation 8%. For procedural or infusion treatments (N = 2,643), 42% of patients saw IR as their first HCC provider, followed by surgery (29%), medical oncology (21%), and radiation oncology (8%). Among second treatments (N = 998), 48% were with IR, followed by surgery (25%), medical oncology (15%), and radiation oncology (12%). For third or further treatments (N = 633), most were with IR (57%), followed by surgery (19%), medical oncology (14%), and radiation oncology (10%). HCC patients averaged 13 sessions with medical oncology, 7.6 with radiation oncology, 1.6 with IR, and 1 with surgery. For patients with recorded BCLC stage, stage 0 (N = 43) had 51% treated by IR, stage A (N = 265) had 54% by IR, and stage B (N = 302) had 48% by medical oncology and 38% by IR. Stage C (N = 270) and D (N = 26) were mostly treated by medical oncology (73% and 77%, respectively). For patients having surgery first (N = 778), 6% had subsequent IR treatments, 4% second surgery,

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4% subsequent medical therapies, and 3% subsequent radiation. **Conclusion:** This data highlights the evolving landscape of HCC care, with IR providing the largest proportion of overall therapy while medical oncology serves a predominant role in both intermediate and advanced stage HCC. Understanding medical specialty involvement patterns for the treatment of HCC may better inform both programmatic and multidisciplinary care strategies.

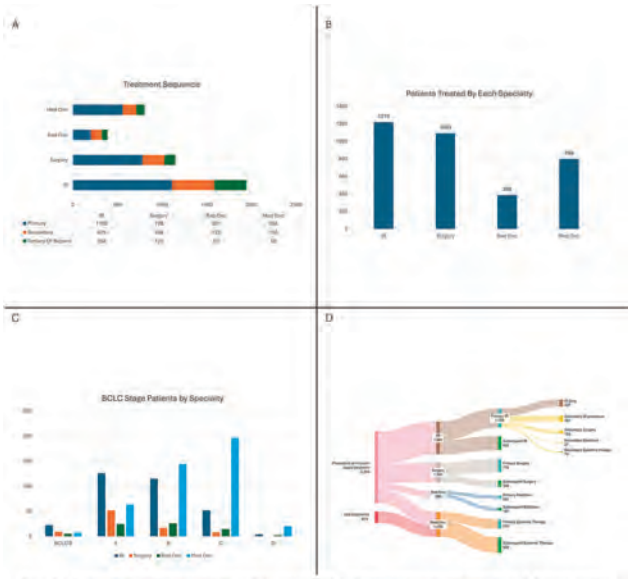

Figure 1 A. Treatment breakdown by specialty for first, second, and third or beyond treatments per patient, B. Patients treated by medical specialty, C. BCLC Stage breakdown by treatment specialty, D. Sequence of specialty treatments for all patients

Disclosures: Fatima Islam: Nothing to Disclose, Robert Lewandowski: Boston Scientific: Consultant, Boston Scientific: Consultant, BD: Advisor, AstraZeneca: Advisor, Eisai: Advisor, Genentech: Advisor, ABK: Consultant, Beau Toskich: Nothing to Disclose

3316 | CHARACTERISTICS AND TREATMENT OF PRIMARY HEPATIC PERIVASCULAR EPITHELIOID CELL TUMOR (PECOMA) IN ADULTS: A SYSTEMATIC REVIEW

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Background: Perivascular epithelioid cell tumors (PEComas) are a rare group of mesenchymal neoplasms with distinctive histological and immunohistochemical features. Due to their infrequent occurrence, primary hepatic PEComas present challenges in establishing evidence-based clinical guidelines and optimal management strategies. This systematic review aims to characterize the clinical presentation, diagnostic approach, treatment, and outcomes of adult patients with hepatic PEComa. **Methods:** We performed a systematic literature search in PubMed, Scopus and Cochrane libraries for English-language articles regarding hepatic PEComas using the terms: (perivascular epithelioid cell tumor) OR (PEComa) AND (liver) OR (hepatic), up to May 25, 2025. We included case series and case reports of adult patients diagnosed with primary hepatic PEComa after the age of 18. Included studies reported individual patient history, symptoms at presentation and a follow-up of at least two months. **Results:** A total of 145 studies encompassing 281 patients were included in the analysis. Most studies originated from Asia. The mean age at diagnosis was 46 years (IQR: 35,25–53,75) with a female predominance (74%). The underlying comorbidities were uncommon among the reported cases, and more than half were asymptomatic at presentation. Commonly reported symptoms were abdominal pain, abdominal discomfort, fever, weight loss, fatigue, vomiting, and nausea. During the diagnostic workup, 152 patients (54,1%) underwent ultrasound, 221 (78,6%) CT, 156 (55,5%) MRI, and 31 (11%) PET-CT. The tumor presented as a single liver lesion in almost 9 out of 10 patients. Tumors were most frequently positive for HMB-45, MELAN-A, smooth muscle actin (SMA) and vimentin, while they were commonly negative for S-100 and epithelial markers. Surgical excision was the primary treatment, and 74% of diagnoses were confirmed postoperatively. . A malignant phenotype was reported in 30 cases. The median follow-up duration was 24 months (IQR: 12–48); recurrence occurred in 17 patients (6%), and disease-related mortality in 8 patients 2.85%. **Conclusion:** Primary hepatic PEComa is a rare liver tumor with mostly benign clinical behavior and nonspecific presentation. Although surgical resection remains the cornerstone of management, prospective studies examining optimal patient treatment and surveillance strategies are currently lacking. Future studies are needed to support clinician decisions regarding this entity and improve patient care.

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Parameter	Value
Study origin	
Asia	97 studies (66,6%)
Europe	35 studies (24,1%)
North America	8 studies (5,5%)
South America	3 studies (2,1%)
Africa	1 study (0,7%)
Australia	1 study (0,7%)
Age	46 years (IQR: 35,25–53,75)
Females	208 patients (74%)
Comorbidities	
Hepatitis B	23 patients (8,2%)
Hepatitis C	5 patients (1,8%)
History of Extrahepatic malignancy	30 patients (10,7%)
Tuberous sclerosis	9 patients (3,2%)
Li-Fraumeni syndrome	6 patients (2,1%)
Presentation	
Asymptomatic	157 patients (55,9%)
Abdominal pain	84 patients (29,9%)
Abdominal discomfort	24 patients (8,5%)
Fever	15 patients (5,3%)
Weight loss	10 patients (3,6%)
Fatigue	7 patients (2,5%)
Vomiting	5 patients (1,8%)
Nausea	5 patients (1,8%)
Diagnostic work up	
U/S	152 patients (54,1%)
CT	221 patients (78,6%)
MRI	156 patients (55,5%)
PET-CT	31 patients (11%)
Tumor size	5,15 cm (IQR: 3–9,3)
Tumor location	
Right lobe	149 cases (53%)
Left lobe	101 cases (34%)
Caudate lobe	12 cases (4,3%)
Tumor nodules	
Single liver lesion	249 patients (88,6%)
Multiple nodules	22 patients (7,8%)
Positive Immunohistochemical markers	
HMB-45	261/264 (98,9%)
MELAN-A	124/132 (93,2%)
SMA	179/200 (89,5%)
Vimentin	62/79 (78,5%)
Negative Immunohistochemical markers	
S-100	85/126 (67,5%)
Desmin	45/83 (54,2%)
Cytokeratins	123/125 (98,1%)
EMA	26/28 (92,9%)
HepPar-1	43/44 (97,7%)
Final diagnosis	
Radiology	29 cases (10,3%)
Biopsy	44 cases (15,7%)
Post-surgical analysis	208 cases (74%)
PEComa type	
AML	197 patients (70,1%)
PEComa-NOS	74 patients (26,3%)
CCMMT of the falciform ligament	7 patients (2,5%)
Clear cell sugar tumor	3 (1,1%)
Malignancy	30 cases (10,7%)
Surgery	251 patients (89,3%)
Follow up duration (months)	24 months (IQR: 12–48)
Recurrence	17 patients (6%)
Death due to PEComa	8 patients (2,85%)

Disclosures: Christos Triantos: Nothing to Disclose, Konstantinos Papantoniou: Nothing to Disclose, Ioanna Aggeletopoulou: Nothing to Disclose

3317 | TREATMENT PATTERNS FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA IN A NATIONAL MEDICAID COHORT

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Background: Treatment for hepatocellular carcinoma (HCC) remains underused in practice, particularly in patients of low socioeconomic status. We evaluated treatment patterns, correlates of treatment receipt, and risk of hepatic decompensation following treatment in a cohort of patients with Medicaid insurance coverage. **Methods:** We analyzed Medicaid registry data, including patients diagnosed with HCC between January 2016 and December 2019. We used multivariable logistic regression to assess associations between treatment receipt and patient characteristics, including age, sex, race/ethnicity, ascites and hepatic encephalopathy. Multivariable analyses adjusted for age, sex, race/ethnicity, liver disease etiology and underlying cirrhosis. Associations between treatment receipt and incident ascites and hepatic encephalopathy were also adjusted for baseline hepatic decompensation. **Results:** We identified 21339 eligible patients (66.1% male). Median age was 57 years, and 38.6% were White, 16.9% Black, 15.8% Hispanic, and 8.5% Asian/Pacific Islander (AAPI). HCC treatment was received by 43.5% of patients. Curative treatment, defined as liver transplantation, resection and local ablation, was received by 2.8%, 3.3% and 9.9% of patients, respectively. Locoregional treatment, including transarterial chemoembolization, transarterial radioembolization, and external beam radiation was received by 25.5%, 7.0% and 16.9%, respectively.

Receipt of any HCC treatment did not significantly differ by patient age, sex or race/ethnicity; however, those with ascites were less likely to undergo treatment (aOR 0.46, 95%CI 0.43-0.50). In univariable analyses, women (OR 0.75, 95%CI 0.69-0.81) and Black patients (vs. White: OR 0.89, 95%CI 0.79-0.99) were less likely to receive curative treatment; however, neither remained significant in adjusted analysis. In multivariable analysis, AAPI patients were more likely to receive curative treatment (vs White: aOR 1.22, 95%CI 1.10-1.37) and those with ascites were less likely to undergo curative treatment (aOR 0.67, 95%CI 0.60-0.74).

Receipt of treatment was associated with increased incident ascites (aOR 1.16, 95%CI 1.09-1.23) and HE (aOR 1.40, 95%CI 1.30-1.50). **Conclusion:** Demographic and clinical factors are associated with HCC

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treatment receipt. HCC treatment is associated with increased risk of incident hepatic decompensation, highlighting the importance of careful patient selection. **Disclosures:** Ashwini Arvind: Nothing to Disclose, Gi Giamarqo: Nothing to Disclose, Dyanna Gregory: Nothing to Disclose, Karim Seif El Dahan: Nothing to Disclose, Lisa Quirk: Nothing to Disclose, Anna Tavakkoli: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant

3318 | ASSOCIATIONS BETWEEN LIVER DISEASE ETIOLOGY AND MORTALITY AFTER LIVER-DIRECTED THERAPY IN HCC

Chidi Iloabachie[1] Yue Jiang[2] Merete Lund[1] Arjun Juneja[1] Patrick Hazelrigg[1] Parsa Pazooki[1] Sydney Power[1] Gabe Lupu[1] Joyce Badal[1] David Seligson[1] Hanna Sanoff[1] David Mauro[1] David Gerber[1] Ted Yanaighara[1] A. Sidney Barritt IV[1] Andrew Moon[1], [1]UNC School of Medicine, [2]Duke University

Background: Hepatocellular carcinoma (HCC) is the most common cancer in patients with chronic liver disease and cirrhosis. Most patients with HCC receive one or more locoregional therapies (e.g., thermal ablation, transarterial chemo- or radioembolization, external beam radiation). The underlying liver diseases leading to HCC are changing rapidly. The degree to which liver disease etiology influences outcomes after locoregional therapies for HCC is uncertain. This study aimed to assess if the etiology of HCC is associated with mortality after liver-directed therapy. **Methods:** We performed a retrospective analysis of adults with non-metastatic HCC treated with liver-directed locoregional therapies from 4/4/2014 to 12/31/2021 at a large academic health system. Baseline sociodemographic and clinical characteristics were extracted. The primary outcome was time to death after initial treatment. Etiologies of HCC were categorized as alcohol-associated (ALD), metabolic dysfunction-associated (MASLD), HBV, HCV, and other (e.g., Wilson's disease, autoimmune hepatitis)/multiple. Mortality was determined via linkage to the state death database with confirmation by chart review. We performed unadjusted and multivariable proportional hazards regression to assess potential associations between etiology and mortality, adjusting for potential confounders. **Results:** This study included 808 patients with HCC with the following initial treatments: 207 laparoscopic thermal ablations, 130 percutaneous thermal ablations, 20 bland embolizations, 296 TACE, 91 TARE, and 64 SBRT. The most common etiologies among patients with only a single etiology were HCV (N = 288; 36%) and MASLD (N = 151; 19%). 259 patients had multiple etiologies (32%). In the multivariable model adjusting for age, year of therapy, sex, Charlson comorbidity index, Child-Pugh score, ECOG performance status, BCLC stage, and treatment type, patients with HCV-only etiology had a significantly lower hazard of death compared to those with MASLD-only (aHR 0.722; 95% CI 0.538–0.970). **Conclusion:** In this retrospective study, liver disease etiology was independently associated with mortality after liver-directed therapy for HCC. This suggests that liver disease etiology may have utility in risk stratification and prognostication for non-metastatic HCC.

Table 1. Adjusted Hazard Ratios (aHR) and 95% Confidence Intervals for All-Cause Mortality Following Liver-Directed Therapy for HCC

		aHR	95% CI
Age		1.010	(0.998, 1.023)
Year	2014	Ref.	Ref.
	2015	0.981	(0.644, 1.496)
	2016	1.066	(0.692, 1.644)
	2017	1.048	(0.699, 1.570)
	2018	0.899	(0.591, 1.390)
	2019	0.944	(0.612, 1.455)
	2020	0.695	(0.436, 1.107)
	2021	0.810	(0.507, 1.296)
Sex	Male	Ref.	Ref.
	Female	0.864	(0.677, 1.103)
Charlson comorbidity score		1.022	(0.993, 1.053)
Child Pugh score	A	Ref.	Ref.
	B7	1.260	(0.934, 1.700)
	B8	**1.985**	**(1.448, 2.721)**
	B9	1.336	(0.872, 2.046)
	C	1.602	(0.786, 3.264)
ECOG PS	0	Ref.	Ref.
	1	0.829	(0.553, 1.242)
	2	1.150	(0.719, 1.841)
	3	0.756	(0.269, 2.124)
BCLC stage	0	Ref.	Ref.
	A	0.904	(0.589, 1.389)
	B	1.504	(0.922, 2.453)
	C	1.519	(0.883, 2.612)
	D	1.557	(0.654, 3.708)
Treatment type	Laparoscopic ablation	Ref.	Ref.

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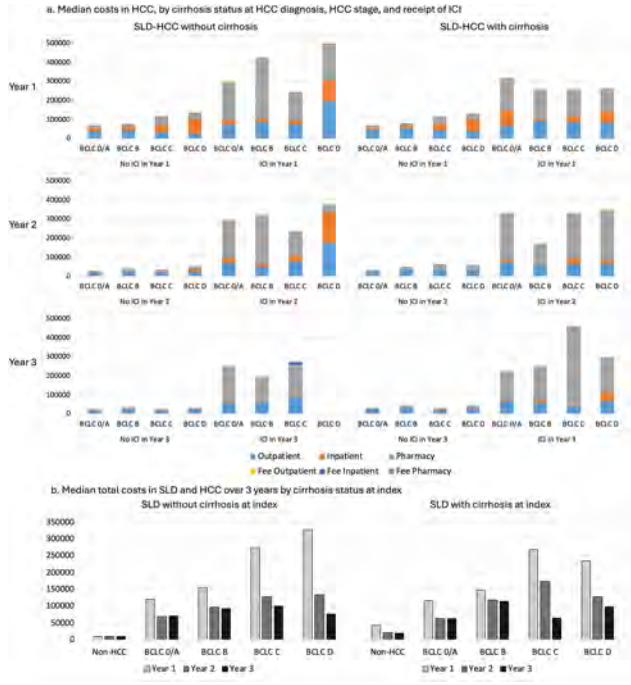
Consultant, DCN Diagnostics: Grant/Research Support, Intercept Pharmaceuticals: DSMB, IDEOlogy: Consultant, Eisai: Consultant, AstraZeneca: Consultant

3319 | HEALTHCARE COSTS OF STEATOTIC LIVER DISEASE-ASSOCIATED HEPATOCELLULAR CARCINOMA

Catherine Mezzacappa[1] Tamar Taddei[1] Pedro Ochoa-Allemant[2] David Kaplan[2] Amy Justice[1] Ronald Braithwaite[3], [1]Yale University, [2]University of Pennsylvania, [3]New York University

Background: The cost-effectiveness of screening for hepatocellular carcinoma (HCC) in steatotic liver disease (SLD) without cirrhosis is unknown. While the costs of HCC in cirrhosis have been measured, they are unknown in SLD without cirrhosis, a critical knowledge gap for evaluating the cost-effectiveness of HCC screening strategies in this population. **Methods:** Using Veterans Health Administration (VA) data between 2012-2024, we assessed outpatient, inpatient, pharmacy, and purchased care costs for adults with two elevated ALT levels $\geq$180 days apart and imaging-confirmed steatosis with no history of viral hepatitis or primary liver disease. We defined index date as date of first abnormal ALT in the SLD group and date of HCC diagnosis in the HCC group. Costs were measured for 3 years from index date and follow-up ended at death or 90 days after last VA contact. We adjusted for inflation and pro-rated costs to the proportion of each year that an individual remained in follow-up. We estimated the marginal costs of HCC using linear models with a gamma distribution adjusted for age, sex, and smoking. We stratified analyses by presence of known cirrhosis at index (diagnosis of cirrhosis or decompensation before or within 180 days after index) and, in HCC, receipt of an immune checkpoint inhibitor (ICI). **Results:** Of 336,657 Veterans with SLD (4,525 with cirrhosis) and 10,176 with HCC (6,243 with cirrhosis), over 99% accrued healthcare costs in all groups, suggesting high use of VA care. Median total cost per year differed by cirrhosis status. For example, those without cirrhosis had a median cost of $11,085 in year 1 compared to $43,514 in those with cirrhosis. Median costs were highest in year 1 for all stages of HCC across cirrhosis groups. The adjusted marginal cost of HCC was higher in Veterans with cirrhosis than those without cirrhosis each year. For example, in year 1, the marginal cost of BCLC 0/A HCC was $26,782 in Veterans without cirrhosis compared to $66,632 in those with cirrhosis. The largest contributors to HCC costs were outpatient care and ICI treatment. For example, median pharmacy costs in Veterans with BCLC C HCC without cirrhosis were $149,679 in recipients of ICIs compared to $49,049 in those not treated with ICIs. **Conclusion:** Receipt of ICIs and presence of cirrhosis dramatically alter the costs of HCC care. These differences should be considered when assessing the cost-effectiveness of potential HCC screening strategies in the population with SLD without cirrhosis. Observed cost differences may be attributable to treatment eligibility and synergistic effects of advanced liver disease with HCC.



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3320 | THE RELATIONSHIP BETWEEN M6A MODIFICATION OF CHARACTERISTIC GENES OF DIFFERENT CELL SUBPOPULATIONS AND DISEASE PROGRESS IN THE WHOLE PROCESS OF HEPATITIS-CIRRHOSIS-LIVER CANCER: A COMBINED MULTI-OMICS STUDY BASED ON SINGLE-CELL RNA-SEQ DATA

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Background: The m6A modification, as an important epigenetic mechanism, plays a pivotal role in chronic liver diseases and hepatocellular carcinoma (HCC). It is involved in processes such as hepatocyte injury, inflammatory cell recruitment, and activation of hepatic stellate cells (HSCs) during fibrogenesis. Therefore, this study aimed to investigate the effect of m6 A gene modification on the immune microenvironment during the progression of chronic liver disease. **Methods:** This study integrated multi-omics approaches to investigate the genetic and cellular mechanisms of m6A in liver diseases. First, we identified m6A-related single nucleotide polymorphisms (SNPs) associated with liver diseases using genome-wide association studies (GWAS) summary data. We performed functional annotation of these SNPs by integrating them with single-cell RNA sequencing (scRNA-seq) datasets. Macrophage/microglia cells were further clustered into distinct subpopulations based on transcriptomic profiles. We analyzed intercellular communication patterns among these cell subsets using ligand-receptor interaction mapping and identified key pathways involved in disease pathogenesis. **Results:** Based on the results of GWAS analysis, 100, 75, and 70 m6A-associated SNPs were screened from CHB, cirrhosis, and HCC samples. Single-cell transcriptomic profiling revealed distinct cellular compositions across different liver disease states: B-cells and T-cells were more prevalent in CHB patients; NKT cells increased in cirrhotic livers; while epithelial cells and fibroblasts were enriched in HCC samples. Analysis of cell-specific gene modules highlighted significant enrichment of macrophage/monocyte genes in pathways related to myeloid leukocyte activation and cytokine production regulation. Unsupervised clustering of macrophage/microglia cells identified eight distinct subpopulations, with Mac. Mono_SEPP1 shows unique communication patterns indicative of its role in disease pathogenesis. Finally, we identified a significant causal relationship between the m6A-related gene HLA-DPA1 and HCC development. **Conclusion:** Our results reveal that genes related to Mac.Mono_SEPP1 macrophage subpopulation plays a key role in liver disease progression through m6A modification. Among them, m6A modification of LA-DPA1 is a protective factor for HCC.

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3321 | OBSERVATION ADMISSION FOLLOWING LOCOREGIONAL THERAPY FOR HEPATOCELLULAR CARCINOMA IS ASSOCIATED WITH SUBSEQUENT EMERGENCY ROOM VISITS AND HOSPITALIZATIONS

Gabriel Lupu[1] Yue Jiang[2] Chidi Iloabachie[1] Merete Lund[1] Arjun Juneja[1] Patrick Hazelrigg[1] Parsa Pazooki[1] Sydney Power[1] Joyce Badal[1] David Seligson[1] Hanna Sanoff[1] David Mauro[1] Nima Kokabi[1] Theodore Yanagihara[1] A. Sidney Barritt[1] Andrew Moon[3], [1]University of North Carolina at Chapel Hill, [2]Duke University, [3]University of North Carolina

Background: Hepatocellular carcinoma (HCC) has one of the lowest 5-year survival rates. Treatment varies by stage and includes locoregional therapy (LRT) such as thermal ablation, transarterial chemoembolization/radioembolization (TACE/TARE), or stereotactic body radiation therapy (SBRT). While post-LRT observation admissions are common, their association with subsequent emergency room (ER) visits and hospitalizations is unclear. This study examined the relationship between post-LRT observation admissions and later ER visits or hospitalizations. **Methods:** We performed a single-center retrospective analysis of adults with diagnosed HCC who underwent LRT from 4/4/2014 to 12/31/2021. The primary outcome was an ER visit or hospitalization within 90 days post-LRT. The main exposure was an observation admission immediately post-LRT. We collected data on demographics, liver disease etiology and severity, HCC stage, and LRT type. Unadjusted and adjusted multivariable logistic regression analyses were used to assess the association between observation admissions and subsequent ER visits or hospitalizations. **Results:** Among 763 patients, 1,266 LRT procedures were identified. Of these, 585 (46.2%) were TACE or bland embolization, 178 (14.1%) were TARE, and 503 (39.7%) were ablation therapies. An unplanned ER visit or inpatient admission occurred within 90 days in 234 (18.5%) procedures. Observation admission occurred in 328 procedures (25.9%). In unadjusted analysis, post-LRT observation admission was associated with higher odds of subsequent ER visit or hospitalization (OR 1.81; 95% CI: 1.33–2.44). After adjusting for potential confounders, observation admission remained associated with higher odds of subsequent ER visit or hospitalization (OR 1.73; 95% CI: 1.19–2.50). **Conclusion:** Our findings show a significant association between post-LRT observation admission and subsequent ER visits

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or hospitalizations, even after adjustment for confounders such as severity of hepatic dysfunction, type of LRT, and year of procedure. Higher Charlson Comorbidity Index and Child-Pugh scores were also independently associated with 90-day ER visits and hospitalizations. Future work will investigate the relationship between these factors as potential predictors of decompensation. These findings may help guide risk stratification and post-LRT care planning.

Table 1. Unadjusted and adjusted logistic regression analysis of post-LRT observation admission and ER visit or hospitalization within 90 days*

ER Visit or Hospital admission within 90 days		Odds Ratio (95% CI)
Post-LRT Observation Admission		
	Unadjusted	1.81 (1.33, 2.44)†
	Adjusted	1.73 (1.19, 2.50)†
Age		0.99 (0.97, 1.00)
Sex		
	Male	Reference
	Female	1.28 (0.89, 1.81)
Charlson Comorbidity Score		1.09 (1.05, 1.14)†
ECOG Performance Status		
	0-1	Reference
	2	0.92 (0.55, 1.51)
	>2	1.25 (0.43, 3.46)
BCLC Stage		
	0	Reference
	A	1.23 (0.63, 2.55)
	B	1.22 (0.57, 2.74)
	C	1.49 (0.76, 3.11)
	D	1.81 (0.68, 4.95)
Child-Pugh Score		
	A	Reference
	B7	0.81 (0.50, 1.28)
	B8	1.10 (0.65, 1.81)
	B9	1.90 (1.11, 3.20)†
	C	3.41 (1.66, 7.03)†
Treatment Type		
	TACE/Bland Embolization	Reference
	TARE	1.49 (0.91, 2.41)
	Ablation	1.13 (0.79, 1.63)
Year of Treatment		
	2014	Reference
	2015	0.88 (0.47, 1.66)
	2016	0.73 (0.38, 1.42)
	2017	0.94 (0.51, 1.74)
	2018	0.40 (0.20, 0.79)†
	2019	0.80 (0.42, 1.53)
	2020	0.57 (0.28, 1.17)
	2021	1.02 (0.53, 1.98)

*Adjusted for age, sex, Charlson comorbidity score, Child-Pugh score, ECOG performance status, BCLC stage, year and treatment type
†α = 0.05; p < 0.05 considered statistically significant
Locoregional Therapy (LRT), Emergency Room (ER), Eastern Cooperative Oncology Group (ECOG), Barcelona Clinic Liver Cancer (BCLC), Transarterial Chemoembolization (TACE), Transarterial Radioembolization (TARE)

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3322 | TBX15 REGULATES SORAFENIB RESISTANCE IN HEPATOCELLULAR CARCINOMA THROUGH CGAS/STING PATHWAY

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Background: In recent years, targeted therapy and immunotherapy have provided a new approach for the clinical treatment of patients with advanced hepatocellular carcinoma (HCC). However, as targeted therapies advance, drug resistance also increases. Therefore, in order to overcome drug resistance and develop effective targeted therapies, further exploration of HCC related molecular signaling pathways and corresponding targeted therapies is important. **Methods:** Differential genes were screened through TCGA and GEO databases. RNA sequencing was performed to uncover the downstream factor of TBX15 in HCC cells. The luciferase and co-ip assays were used to verify whether TBX15 acted as a transcription factor of HERC5 in HCC cells. **Results:** Compared with HCC patients' paracancer tissues, immunohistochemical and WB results indicated that TBX15 was lower in HCC tissues. IC50 results suggested that TBX15 could enhance the sensitivity of HCC cells to sorafenib. RNA-seq results showed that ferroptosis-related genes were significantly increased in TBX15-overexpressing HCC cells. We demonstrated that TBX15 increased ferroptosis in sorafenib resistant HCC cells (HCC-SR) in vitro. We further found that TBX15 could activate the cGAS/STING pathway in HCC-SR. Ferroptosis was inhibited after treatment of HCC-SR with cGAS inhibitors. We subsequently treated HCC-SR with cycloheximide and found that TBX15 enhanced the stability of cGAS in HCC-SR. Co-IP results indicated that TBX15 does not bind directly to cGAS. The above RNA-seq results suggested that HERC5, a key enzyme involved in ISG, was significantly increased in TBX15-overexpressing HCC cells. Then we found that the ISGylation level of cGAS increased significantly with the increase of TBX15 expression. We further constructed wild type and mutant HERC5 plasmids targeting the binding site between TBX15 and HERC5. The results showed that the co-mutations of 1452-1459 and 1623-1630 sites on HERC5 mRNA inhibited the transcriptional activity of TBX15. Finally, we found that compared with sorafenib alone, the tumor volume and weight of TBX15 combined with sorafenib group were reduced from 0.68 cm3 to 0.20 cm3 and 0.56 g to 0.14 g. **Conclusion:** TBX15 promotes ferroptosis by regulating

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HERC5-mediated ISGylation of cGAS to improve sorafenib resistance in HCC cells. TBX15 may be a novel therapeutic target for improving sorafenib resistance in HCC patients.
Disclosures: Hui Yuan: Nothing to Disclose, Mengfan Jiao: Nothing to Disclose, Chuanlong Zhu: Nothing to Disclose

3323 | DISTINCT RECURRENCE PATTERNS AND INFERIOR POSTOPERATIVE OUTCOMES OF COMBINED HEPATOCELLULAR-CHOLANGIOCARCINOMA COMPARED WITH HEPATOCELLULAR CARCINOMA

Yeongseok Hwang[1] Subin Heo[2] In Hye Song[3] Young-In Yoon[4] SUNG WON CHUNG[5] Jonggi Choi[6] Danbi Lee[7] Ju Hyun Shim[7] Kang Mo Kim[7] YOUNG-SUK LIM[7] Lee Han-chu[7] Won-Mook Choi[7], [1]Asan medical center, [2]Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicin, [3]Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea, [4]Department of Surgery, Asan Medical Center, [5]Department of Gastroenterology, Asan Medical Center, [6]University of Ulsan, Asan Medical Center, [7]Department of Gastroenterology, Liver Center, Asan Medical Center

Background: Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare liver malignancy that shares clinical and radiologic features with hepatocellular carcinoma (HCC), making preoperative diagnosis difficult. This study aimed to compare postoperative outcomes between cHCC-CCA and HCC in patients with very early or early-stage tumors. **Methods:** A retrospective cohort of 3,637 HCC and 148 cHCC-CCA patients, all pathologically diagnosed at BCLC stage 0 or A and treated with surgical resection between 2010 and 2018, was analyzed from a high-volume tertiary center in Korea. Overall survival (OS) and recurrence-free survival (RFS) were compared using multivariable Cox regression. Prognostic differences were further assessed via 1:4 propensity score (PS) matching and subgroup analyses. **Results:** Compared to HCC, cHCC-CCA patients were older (56.9 vs. 54.8 years; $p = 0.009$), had lower rates of diabetes (15.5% vs. 23.3%; $p = 0.04$) and hepatitis B infection (65.5% vs. 75.4%; $p = 0.004$), and showed higher rates of microvascular (35.1% vs. 26.2%; $p = 0.02$) and capsular invasion (18.2% vs. 8.2%; $p < 0.001$). The 5-year RFS and OS were significantly lower in cHCC-CCA (RFS: 47.9% vs. 58.5%; adjusted hazrd ratio [HR], 1.51; 95% confidence interval [CI], 1.22–1.88; $p < 0.001$; OS: 70.9% vs. 87.8%; adjusted HR, 2.48; 95% CI, 1.88–3.26; $p < 0.001$). These findings remained robust in the PS-matched cohort and across all clinical subgroups. Among patients with recurrence, those with cHCC-CCA had significantly worse OS (adjusted HR, 2.17; 95% CI, 1.56–3.03; $p < 0.001$)[WC1] and a higher rate of extrahepatic recurrence (23.0% vs. 7.7%; $p < 0.001$), particularly to the lungs and lymph nodes, whereas OS was comparable between groups in those without recurrence. **Conclusion:** cHCC-CCA is associated with significantly poorer postoperative outcomes than HCC, particularly in the setting of recurrence. Intensified surveillance for extrahepatic recurrence may be warranted in this population.
Disclosures: Yeongseok Hwang: Nothing to Disclose, Subin Heo: Nothing to Disclose, In Hye Song: Nothing to Disclose, Young-In Yoon: Nothing to Disclose, SUNG WON CHUNG: Nothing to Disclose, Jonggi Choi: GILEAD SCIENCE: Grant/Research Support, Danbi Lee: Nothing to Disclose, Ju Hyun Shim: Nothing to Disclose, Kang Mo Kim: Nothing to Disclose, YOUNG-SUK LIM: Nothing to Disclose, Lee Han-chu: Nothing to Disclose, Won-Mook Choi: Gilead Sciences: Speaking and Teaching, AbbVie: Speaking and Teaching, Roche: Consultant

3324 | BREAKING RESISTANCE AND REWRITING THE SYSTEMIC PLAYBOOK: A SCOPING REVIEW OF COMBINATION TARGETED THERAPIES IN ADVANCED HEPATOCELLULAR CARCINOMA

Taseen Tanzil[1] Eric Welwin[1] Ibrahim Qadri[1] Samin Faiaz[1], [1]CUNY School of Medicine

Background: Hepatocellular carcinoma (HCC) is a highly aggressive liver cancer with limited options in advanced stages. In unresectable cases, targeted therapies have modestly improved outcomes but are limited in long-term effectiveness due to resistance, heterogeneity, and toxicity. Recent research has explored alternative modalities that overcome such barriers by combining tyrosine kinase inhibitors (TKIs) with immune checkpoint inhibitors (ICIs), or pairing targeted agents with cellular or anti-angiogenic therapies. This scoping review addresses the latest combination regimens with drugs such as sorafenib, lenvatinib, cabozantinib, regorafenib, and ramucirumab concerning their clinical impact and immunologic rationale. **Methods:** A review of preclinical and clinical studies on targeted combination therapies in HCC was conducted. Regimens combining TKIs with ICIs, VEGFR inhibitors, EGFR inhibitors, and immunomodulatory cell therapies were emphasized. Included studies were analyzed based on treatment setting (first-line vs. second-line), mechanism of synergy, objective response rate (ORR), progression-free survival (PFS),

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and safety. Selected trials were contrasted with each other to identify trends in efficacy, toxicity, and molecular targeting. **Results:** Several key findings emerged. Lenvatinib plus envafolimab and cabozantinib plus atezolizumab as front-line treatments demonstrated increased PFS and disease control, but with inconsistent OS benefit, compared to monotherapies. In resistant or second-line populations, regorafenib-based regimens enhanced immune activation, response durability, and early biomarker signals of T-cell and myeloid reprogramming. Additionally, preclinical pairing of sorafenib with NK cells or targeting VEGFR-2 (ramucirumab) blockade demonstrated synergy with angiogenesis, fibrosis, and apoptosis, providing opportunities to re-sensitize the tumor and reduce dose requirements. The limitations included small cohort sizes, incomplete OS data, and the need for validated predictive biomarkers, while toxicity was generally manageable across the board. **Conclusion:** This review illustrates an important shift in research towards combined immunotherapeutic HCC therapies that aim to avoid resistance and extend patient eligibility. The preliminary results from the observed clinical trials suggest moving towards these regimens, guided by known drivers and immune signatures. Future directions should focus on biomarker-based tumor selection, dose optimization, and combination with locoregional or cell-based modalities to offer a clear roadmap to enhance systemic impact.

Reference	Treatment Type	Clinical Scenario	Outcome	Year Published
Zhang et al.	Sorafenib + IL-12/IL-18-activated NK cells	Preclinical model of HCC	Increased tumor cell density, reduced angiogenesis and fibrosis, synergistic antitumor effect	2025
Zheng et al.	Camrelizumab (PD-1) + Apatinib (VEGFR2 inhibitor)	First-line for unresectable HCC	Better outcomes than sorafenib alone in CARES-310; approved in China	2025
Jiang et al.	Lenvatinib + Envafolimab (PD-L1 inhibitor)	Unresectable HCC, first-line	18.5 mo mOS, 9.4 mo mPFS, 40% ORR, 80% DCR, well tolerated	2024
Shi et al.	Lenvatinib + Gefitinib (EGFR inhibitor)	Lenvatinib-resistant HCC with EGFR↑	13.7 mo mOS, 4.4 mo mPFS, 30% ORR, 76.7% DCR; common toxicities (fatigue, rash, diarrhea)	2024
Kelley et al. / Yau et al.	Cabozantinib (VEGFR/MET/AXL) + Atezolizumab (PD-L1 inhibitor)	First-line for advanced HCC	6.9 mo mPFS vs. 4.3 (sorafenib); 16.5 mo mOS (not significant); higher grade 3/4 AEs	2022
Kim et al.	Regorafenib + Nivolumab	Front-line treatment of unresectable HCC	7.38 mo mPFS, 31% ORR, 80.5% 1-yr OS; favorable safety profile	2024
Galle et al.	Regorafenib + Pembrolizumab	Intermediate HCC (outside up-to-7)	Phase III trial ongoing (REPLACE); testing against TACE/TARE	2024
Taha et al.	Sorafenib + Ramucirumab (VEGFR-2 inhibitor)	Preclinical (HepG2 liver tumor cells)	Synergistic apoptosis, cell cycle arrest, ↓ VEGFR2/MMP-9/pSTAT 3, enhanced sorafenib cytotoxicity	2022

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3325 | EVOLVING TRENDS IN THERAPY FOR HEPATOCELLULAR CARCINOMA AND THE IMPACT OF MULTIDISCIPLINARY MANAGEMENT – A REAL-WORLD STUDY OF 1,627 CASES OVER 5 DECADES

Chee-Kiat Tan[1] Kaina Chen[1] Boon Bee George Goh[1] Jason Chang[1] Wei-Lun Liou[1], [1]Singapore General Hospital

Background: There are many recent developments in locoregional and systemic therapies for hepatocellular carcinoma (HCC). There is also a growing advocate for multidisciplinary involvement in the management of HCC. Our weekly multidisciplinary HCC tumor board with the participation of hepatobiliary surgeons, hepatologists, medical and radiation oncologists, diagnostic and therapeutic radiologists and nuclear medicine physicians started in early 2021. The aim of our study is to examine the evolving trends of HCC therapy and the impact of multidisciplinary tumor board on HCC cases seen in our department over the past 5 decades. **Methods:** HCC patients seen in the Singapore General Hospital Department of Gastroenterology and Hepatology from 1980-2024 with documentation available were included in the study. The therapy received by the patient was categorised as curative (including local ablation), locoregional, systemic or best supportive care. This was analysed by successive decades starting from 1980, according to BCLC stage. **Results:** There were 1,627 patients with an overall median age of 64.3 years. 79% were males and the majority were hepatitis B related (63.4%). The median age in the 5 decades were 59.0, 61.4, 62.9, 65.6 and 69.4 years respectively. As seen in the table, there was a dearth of HCC therapy available in the early decade of 1980-1989. With the advancement of locoregional therapy (LRT), increasing more patients in BCLC B received LRT from 1990 with a significant increase in 2010-2019. Several systemic agents were available from the beginning of 2020, with a correspondingly significant increase in BCLC C patients receiving systemic therapy in 2020-2024. Curative therapy remained the main modality for BCLC 0 and BCLC A without any significant change over 5 decades. For BCLC D, although best supportive care (BSC) is prevalent, other active therapies such as LRT were also given in the earlier 4 decades. However, with the introduction of multidisciplinary tumor board in the current decade, no active therapies were given for BCLC D except for a small minority on systemic therapy. In this decade of

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multidisciplinary tumor board, the most frequent therapies given were also appropriate to the BCLC stage. **Conclusion:** HCC therapy for our patients over the decades was in line with the advances globally. The multidisciplinary tumor board advocated for patients to receive appropriate therapy which included BSC for patients with advanced BCLC D disease unlike deviations in the previous decades.

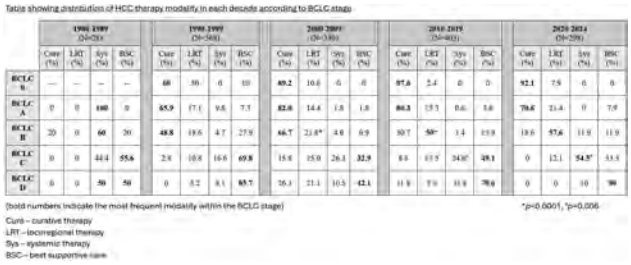

Table showing distribution of HCC therapy modality in each decade according to BCLC stage

	1980-1989 (N=20)				1990-1999 (N=308)				2000-2009* (N=530)				2010-2019 (N=402)				2020-2024 (N=299)			
	Cure (%)	LRT (%)	Sys (%)	BSC (%)	Cure (%)	LRT (%)	Sys (%)	BSC (%)	Cure (%)	LRT (%)	Sys (%)	BSC (%)	Cure (%)	LRT (%)	Sys (%)	BSC (%)	Cure (%)	LRT (%)	Sys (%)	BSC (%)
BCLC 0	–	–	–	–	60	30	0	10	80.2	10.8	6	4	87.6	5.4	0	7	92.1	7.9	0	0
BCLC A	0	0	100	0	65.9	17.1	9.8	7.3	82.0	14.4	1.8	1.8	86.3	13.7	0.6	3.6	78.6	21.4	0	7.9
BCLC B	20	0	60	20	48.8	19.6	4.7	27.9	66.7	21.8*	4.6	6.9	80.7	50*	1.4	13.9	19.6	57.6	11.9	11.9
BCLC C	0	0	44.4	55.6	2.9	10.8	16.6	69.8	15.6	15.0	26.1	32.9	8.8	13.5	24.0*	49.1	0	12.1	54.5*	33.3
BCLC D	0	0	50	50	0	5.2	8.1	85.7	26.1	21.1	10.3	42.1	11.9	7.9	11.9	78.6	0	0	10	90

(bold numbers indicate the most frequent modality within the BCLC stage) *p<0.0001, *p=0.006

Cure – curative therapy
LRT – locoregional therapy
Sys – systemic therapy
BSC – best supportive care

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3326 | TRENDS AND FACTORS ASSOCIATED WITH HEPATOCELLULAR CARCINOMA DIAGNOSIS, STAGE, TREATMENT AND SURVIVAL

George Ioannou[1] vera yakovchenko[2] Tamar Taddei[3] Alexander Monto[4] Heather Patton[5] Monica Merante[2] Patrick Spoutz[6] Linda Chia[6] Jennifer Yudkevich[7] Ayse Aytaman[8] Atoosa Rabiee[9] Binu John[10] Boris Blechacz[11] Cincy Cai[12] HoChong Gilles[13] Anand Shah[14] Heather McCurdy[15] Puneet Puri[16] Janice Jou[17] Khurram Mazhar[18] Cesar Taborda-Vidarte[19] Sujan Ravi[20] Alpna Limaye[21] Amar Mandalia[22] Karlyn Rupert[23] Jason Dominitz[24] Jennifer Anwar[25] Timothy Morgan[26] Shari Rogal[27], [1]University of Washington Medical Center, [2]VA Pittsburgh Health Care System, [3]Yale University, [4]University of California, San Francisco, [5]VA San Diego Health Care System, [6]Pharmacy Benefits Management, Veterans Integrated Service Network 20, Vancouver, WA, [7]VA New York Harbor Healthcare System, Brooklyn, NY, [8]VA NY Harbor Healthcare System Brooklyn Campus, [9]Washington DC VA Medical Center, [10]University of Miami and Miami VA, [11]VA South Texas Health Care System, San Antonio, TX, [12]VA Loma Linda, [13]McGuire Veterans Affairs Medical Center, [14]VA Atlanta, [15]VA Ann Arbor, [16]VA Richmond, [17]OHSU, [18]VA North Texas Health Care System, Dallas, TX, [19]VA Tampa, [20]Birmingham VA Medical Center, Birmingham, AL, [21]Gainesville VA, [22]Orlando VA Medical Center, Orlando, FL, [23]VA Martinsburg Health Care System, [24]VA Puget Sound, [25]VA Long Beach, [26]VA Long Beach Healthcare System, [27]University of Pittsburgh

Background: The National Gastroenterology and Hepatology Program of the US Veterans Health Administration (VHA) established an ongoing program of biennial assessment of hepatocellular carcinoma (HCC) diagnosis, stage, HCC-directed treatment (type and timeliness), and survival. **Methods:** Out of >2000 patients with a new diagnosis of HCC in 2023 in VHA, a random sub-sample of 194 confirmed HCC cases were selected for a structured medical record review by expert hepatologists. Factors associated with stage at diagnosis, receipt of treatment and survival were assessed and compared to our prior extraction of HCC cases diagnosed in VHA in 2021. **Results:** Among 194 confirmed HCC cases in 2023 (42.8% cured HCV, 24.2% MASLD, 13.9% ALD, 5.2% active HCV, 4.1% MetALD), mean age was 73 years, 56.7% had cirrhosis diagnosed before HCC, 12.9% had cirrhosis diagnosed after HCC and 22.2% did not have cirrhosis. Stage at diagnosis was T1 in 17.5%, T2 in 42.3% and beyond T2 in 40.2%. Early-stage diagnosis (T1 or T2) was more common in the following groups: cirrhosis diagnosed before HCC (70.9%), HCC diagnosed by screening (86.3%), high performance status (73.0%), receipt of VA primary care (63.3%) or VA liver care (72.6%). Among 147 out of 194 patients (75.8%) who received HCC-directed treatments after a median of 68 days (IQR 39-107) from diagnosis, the most common, first-line treatment was Y-90 radioembolization (28.6%), followed by ablation (21.1%), transarterial chemoembolization (20.4%), systemic therapy (17.0%), surgical resection (7.5%) and external beam radiation (5.4%). Potentially curative treatments (overall 21.6%) were more common in the following groups: early-stage diagnosis (35.8%), diagnosed by screening (35.3%), pre-diagnosis liver care (28.2%). During a mean follow-up of 481 days, 84 (43.2%) died. Factors associated with lower all-cause mortality were: early-stage diagnosis, diagnosis via screening, CTP class A, MELD ≤10, absence of cirrhosis, cured HCV, receipt of curative treatments, VA primary or liver care and good performance status. Compared to the VHA HCC cases that were diagnosed in 2021, the cases in 2023 were more likely to have MASLD/MetALD (28.3% vs. 15.6%), to be diagnosed at stage T1/T2 (59.8% vs. 53.8%), and to receive Y90 (28.6% vs. 17.0%) and systemic therapy (17.0% vs. 10.9%) as first-line treatment and less likely to have active or cured HCV (48.0% vs. 62.8%). **Conclusion:** These results highlight the importance of HCC screening and engagement in care for HCC diagnosis, treatment, and survival while demonstrating the feasibility of developing a national quality improvement agenda for addressing persistent gaps in the HCC care continuum.

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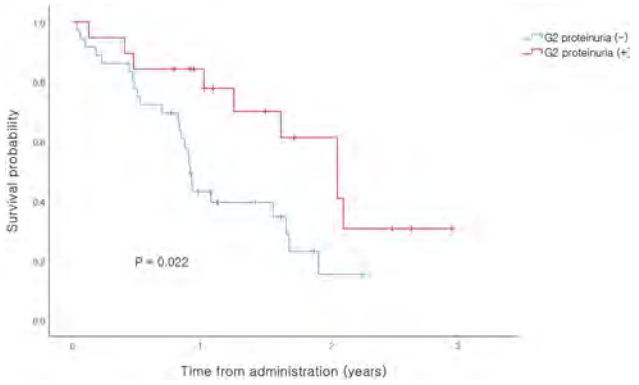
3327 | PROGNOSTIC IMPACT OF PROTEINURIA IN PATIENTS WITH ADVANCED HCC TREATED WITH ATEZOLIZUMAB PLUS BEVACIZUMAB

Young Mi Hong[1] Hyung Myung Cho[2], [1]Pusan National University School of Medicine, [2]Pusan National University Yangsan Hospital

Background: Proteinuria is a common adverse event associated with atezolizumab plus bevacizumab combination therapy. However, its prognostic implications in hepatocellular carcinoma (HCC) remain unclear. This study aimed to evaluate the clinical relevance of proteinuria and identify predictive factors for its development in HCC patients treated with atezolizumab plus bevacizumab. **Methods:** We conductive a retrospective observational study to investigate the development of proteinuria following atezolizumab plus bevacizumab treatment in patients with advanced HCC. Patients with low level of proteinuria (1+ or less on a dipstick test) at the initiation of therapy were included in the analysis. Overall survival (OS) was evaluated using Cox proportional hazards models and Kaplan–Meier analysis. Baseline clinical variables were analyzed to identify potential predictors of proteinuria development. **Results:** A total of fifty-five patients with advanced HCC treated with atezolizumab plus bevacizumab were enrolled. Grade 2 proteinuria developed during treatment in 19 patients (34.5%). Patients who developed grade 2 proteinuria had significantly longer OS compared to those who did not ($P = 0.022$). Additionally, OS differed significantly according to the severity of proteinuria developed during treatment ($P = 0.013$). In univariate analysis, a history of prior transarterial chemoembolization was the only predictive factor associated with the development of grade 2 proteinuria ($P = 0.044$). **Conclusion:** The development of proteinuria was associated with longer OS in patients with advanced HCC treated with atezolizumab plus bevacizumab. These findings suggest that proteinuria could serve as a potential predictive marker of treatment efficacy and should not be regarded solely as an adverse event.



Disclosures: Young Mi Hong: Nothing to Disclose, Hyung Myung Cho: Nothing to Disclose

3328 | ACCEPTABILITY OF BLOOD BIOMARKERS FOR LIVER CANCER SURVEILLANCE: CONSUMERS AND CLINICIANS' PERSPECTIVE

Lucinda Vaux[1] Angela Carberry[2] Rhian Jones[2] Brooke Gaggin[1] Mikaela Daniells[1] James O'Beirne[1], [1]Sunshine Coast University Hospital, [2]Sunshine Coast Health Institute

Background: Hepatocellular carcinoma (HCC) mortality is rising faster than any other cancer in Australia. Current HCC surveillance—ultrasound and alpha-fetoprotein—are suboptimal and challenged by poor sensitivity and limited access. Blood-based biomarkers represent a potential strategy to overcome these

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barriers. There is limited data on clinician and patient perspectives in Australia.
Aim; To assess patient and clinician attitudes toward current HCC surveillance and the potential future role of blood-based biomarkers. **Methods:** Anonymous online surveys were distributed in December 2024 to patients undergoing HCC surveillance at a single health service in Queensland, Australia, and clinicians involved in HCC monitoring across Australia. The patient and clinician surveys contained 19 and 23 items, respectively. Descriptive analysis was performed to summarise responses. **Results:** A total of 105 patients (response rate: 32%) and 48 clinicians (response rate 55%) completed the survey. Summary of selected survey responses in Table 1.
Patient results: Most patients were male (52%) and 65 years or older (58%). Patients reported high levels of comfort with current surveillance methods – 92% *comfortable* with ultrasound and 93% with blood test. Most patients *agreed* or *strongly agreed* that blood tests (79%) and ultrasounds (80%) contribute to improved liver cancer surveillance. The effort required for attending appointments was perceived as low, with 89% of patients reporting *little* to *no effort* for blood tests, and 80% for ultrasounds. When given a choice, 70% preferred combined surveillance, 25% blood tests only, and 3% ultrasound only.
Clinician results: The majority of clinicians were hepatologists (83%), practising in metropolitan areas (83%). In evaluating current HCC surveillance practices, 88% of clinicians reported using both ultrasound and AFP. Regarding the effectiveness of ultrasound and AFP, 77% agreed that ultrasound contributes to effective surveillance, and 69% agreed for AFP. If accuracy were equal, 81% would prefer blood-based biomarkers over ultrasound and AFP. Overall, 92% *agreed* or *strongly agreed* that blood-based biomarkers could improve HCC surveillance, and 73% reported feeling *comfortable* using the test. However, clinicians remained cautious about eliminating ultrasound, only 29% *comfortable*, 48% *uncomfortable*, and 6% *very uncomfortable,* with this approach. Additionally, 27% believe there are moral or ethical consequences associated with only using blood-based biomarkers. **Conclusion:** Patients reported high levels of comfort and confidence with current HCC surveillance methods. Clinicians expressed comfort with the use of blood-based biomarkers and recognised their potential to enhance surveillance. Future research should focus on strategies for implementing blood-based biomarkers in clinical practice, with particular attention to patient acceptability and feasibility.

Summary of patient survey responses: 5 of 13 questions	Patient N=105
Comfort with blood test for surveillance	
Very comfortable / Comfortable	98
Very uncomfortable	4
No opinion/ response	3
Comfort with ultrasound for surveillance	
Very comfortable /Comfortable	97
Uncomfortable	5
No opinion/ response	3
A blood test helps to improve my surveillance	
Strongly agree/ Agree	83
Strongly disagree/ Disagree	7
No opinion/ response	15
Ultrasounds helps to improve my surveillance	
Strongly agree/ Agree	84
Strongly disagree/ Disagree	6
No opinion/ response	15
Summary of clinician survey responses: 4 of 23 questions	**Clinician N=48**
Blood based biomarkers could improve surveillance	
Strongly agree / agree	44
No opinion/ no response	4
Comfort level using blood-based biomarkers	
Very comfortable / comfortable	35
Very uncomfortable/ uncomfortable	4
No opinion/ response	9
Comfort level not using ultrasound for surveillance	
Comfortable	14
Very uncomfortable / Uncomfortable	26
No opinion / response	8
Moral/ ethical concerns with only using blood-based biomarkers	
Strongly agree / agree	13
Strongly disagree / disagree	25
No opinion/ no response	10

Disclosures: Lucinda Vaux: Nothing to Disclose, Angela Carberry: Nothing to Disclose, Rhian Jones: Nothing to Disclose, Brooke Gaggin: Nothing to Disclose, Mikaela Daniells: Nothing to Disclose, James O'Beirne: CSL Behring: Advisor, ROCHE: Advisor, Novo Nordisk: Advisor

3329 | CLINICAL OUTCOMES OF IMMUNOTHERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA IN PATIENTS WITH COEXISTING MALIGNANCIES

Haruhiko Takeda[1] Hiroki Morimura[1] Masayuki Ueno[1] Masako Mishima[1] Tadashi Inuzuka[1] Atsushi Takai[1] Ken

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Takahashi[2] Hiroshi Seno[1], [1]Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, [2]Center for Cancer Immunotherapy and Immunobiology, Graduate School of Medicine, Kyoto University

Background: The efficacy and safety of immunotherapy for hepatocellular carcinoma (HCC) in patients with coexisting malignancies remain unclear, as such cases are typically excluded from clinical trials. This study aimed to assess the clinical outcomes of immune checkpoint inhibitor (ICI) therapy in HCC patients with other cancer types. **Methods:** We retrospectively analyzed 126 unresectable HCC patients treated with atezolizumab plus bevacizumab (AB) or durvalumab plus tremelimumab (DT) at our institution between September 2020 and February 2025. We extracted the patients who contracted any cancers other than HCCs before and after the initiation of ICI treatment. We compared treatment efficacy and safety profiles between patients with and without coexisting cancers. All the statistical analyses were conducted with R. **Results:** The cohort included 74 patients with BCLC stage C, and 10 with Child-Pugh class B. Thirty five patients (28%) had a history of or concurrent other malignancies, and 28 (22%) had received anti-cancer treatment including surgery, chemotherapy or radiation therapy within 5 years before initiating ICIs. The most frequent coexisting cancer types were lung, genitourinary, gastric, esophageal and colorectal (n = 9, 9, 7, 4 and 3, respectively). Baseline HCC stage and liver function did not significantly differ between those with comorbid cancers and those without. The overall survival and progression-free survival were not significantly different between those with or without comorbid cancers. The objective response rate (evaluated with modified RECIST) was 36% with coexisting cancers vs. 34% without; disease control rate was 63% vs. 73%, respectively. Complex cases included patients with liver metastases from lung cancer under anti-PD-1 therapy and those whose general condition worsened due to oral cancer therapy despite initial remission with AB. Noteworthy cases included dual tumor regression after DT in patients with early-stage lung or gastric cancer and HCC, suggesting cross-cancer immunotherapy effects. In contrast, five patients developed new or progressive comorbid malignancies including lung, colon or gastric origin. One patient with early gastric cancer showed hyperprogressive disease resulting in mortal outcome, despite favorable HCC response. No increased incidence of immune-related adverse events was observed in patients with comorbid malignancies. **Conclusion:** While coexisting malignancies do not significantly affect the overall efficacy or safety of immunotherapy for HCC, individual cancer biology may influence outcomes. Cross-cancer predictive biomarkers are needed to optimize treatment in patients with multiple primary malignancies.

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3330 | PERFORMANCE OF A MULTI-TARGET DNA-BASED BLOOD TEST FOR HEPATOCELLULAR CARCINOMA DETECTION IN A PREDOMINANTLY HISPANIC POPULATION IN SOUTH TEXAS

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Background: Hepatocellular carcinoma (HCC) disproportionately affects Hispanic populations, particularly in South Texas, where MASH, obesity, and healthcare disparities are prevalent. A novel multi-target blood-based test, combining three methylated DNA markers (HOXA1, TSPYL5, B3GALT6), AFP, and sex in a logistic regression model, has shown promise for early HCC detection. However, prior validation studies lacked Hispanic representation. This study assessed its performance in a real-world, predominantly Hispanic cohort. **Methods:** A retrospective chart review was conducted at a tertiary care center in South Texas from January 2023 to May 2025. All patients who underwent the multi-target blood-based test as part of HCC evaluation were included. Clinical, laboratory, and imaging data, including LI-RADS classification, liver biopsy results, and tumor board adjudications, were extracted from the electronic health record. MELD scores and liver disease etiology were analyzed to assess test performance across clinical strata. **Results:** A total of 43 patients were included in the analysis (mean age 64.4 years; range 33–86), with 65% male and 90% identifying as Hispanic/Latino. Obesity was present in 46.5% of the cohort. Thirty-three patients tested positive using a multi-target DNA-based blood test. Among these, 11 underwent liver biopsy, with 8 cases confirmed as HCC (biopsy-confirmed PPV: 72.7%). An additional 14 were diagnosed by multidisciplinary tumor board review, yielding 22 total confirmed HCC cases (overall PPV: 66.7%; sensitivity: 84.6%). MASH was the most common etiology among test-positive patients. Biopsy-confirmed HCC was observed in 80% of MASH cases, and in 100% of

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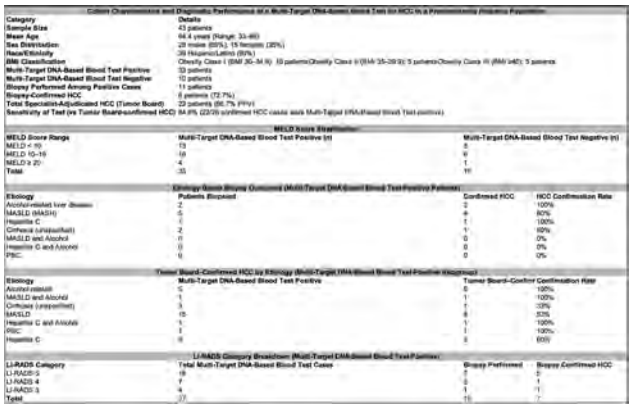
those with alcohol-related or hepatitis C associated cirrhosis. Tumor board confirmed HCC was also seen in 100% of patients with alcohol-related, MASH, hepatitis C and alcohol overlap, and PBC-related cirrhosis. Most test-positive patients had MELD scores between 10–19, while those with MELD $\geq$20 were more likely to test negative. Among test-positive cases with available imaging, 16 had LI-RADS 5 lesions, 7 had LI-RADS 4, and 4 had LI-RADS 3. Of the LI-RADS 5 lesions that were biopsied, 5 of 7 were confirmed as HCC (71%). **Conclusion:** These findings demonstrate that the multi-target DNA-based blood test performs well in detecting HCC among a predominantly Hispanic cohort, including those with indeterminate LI-RADS lesions and lower MELD scores. With 84.6% sensitivity and 66.7% PPV by tumor board adjudication, the test shows promise as a noninvasive diagnostic adjunct in real-world settings. Despite the limited sample size, this study reinforces the test's potential role in expanding early HCC detection in underserved, high-risk populations, where traditional surveillance strategies often fall short.



Category	Details
Sample Size	43 patients
Mean Age	64.4 years (Range: 33–86)
Sex Distribution	28 males (65%), 15 females (35%)
Race/Ethnicity	39 Hispanic/Latino (91%)
BMI Classification	Obesity Class I (BMI 30–34.9): 10 patients/Obesity Class II (BMI 35–39.9): 5 patients/Obesity Class III (BMI ≥40): 3 patients
Multi-Target DNA-Based Blood Test Positive	33 patients
Multi-Target DNA-Based Blood Test Negative	10 patients
Biopsy Performed Among Positive Cases	11 patients
Biopsy-Confirmed HCC	8 patients (72.7%)
Total Specialist-Adjudicated HCC (Tumor Board)	22 patients (66.7% PPV)
Sensitivity of Test (vs Tumor Board–confirmed HCC)	84.6% (22/26 confirmed HCC cases were Multi-Target DNA-Based Blood Test positive)

MELD Score Range	Multi-Target DNA-Based Blood Test Positive (n)	Multi-Target DNA-Based Blood Test Negative (n)
MELD < 10	13	5
MELD 10–19	18	4
MELD ≥ 20	4	1
Total	35	10

Etiology	Patients Biopsied	Confirmed HCC	HCC Confirmation Rate
Alcohol-related liver disease	2	2	100%
MASLD (MASH)	5	4	80%
Hepatitis C	1	1	100%
Cirrhosis (unspecified)	2	1	50%
MASLD and Alcohol	0	0	0%
Hepatitis C and Alcohol	0	0	0%
PBC	0	0	0%

Etiology	Multi-Target DNA-Based Blood Test Positive	Tumor Board–Confirmed HCC	Confirmation Rate
Alcohol-related	5	5	100%
MASLD and Alcohol	1	1	100%
Cirrhosis (unspecified)	3	1	33%
MASLD	15	8	53%
Hepatitis C and Alcohol	1	1	100%
PBC	1	1	100%
Hepatitis C	6	5	83%

LI-RADS Category	Total Multi-Target DNA-Based Blood Test Cases	Biopsy Performed	Biopsy-Confirmed HCC
LI-RADS 5	16	7	5
LI-RADS 4	9	3	1
LI-RADS 3	4	1	1
Total	27	11	7

Disclosures: Rishika Trivedi: Nothing to Disclose, Prince Shah-Riar: Nothing to Disclose, Sergio Hernandez-Llamas: Nothing to Disclose, Laura Reyes-Uribe: Nothing to Disclose, Fernando Membreno: Nothing to Disclose, Jose Cruz: Nothing to Disclose

3331 | TYROSINE KINASE INHIBITOR SEQUENCING IN UNRESECTABLE HEPATOCELLULAR CARCINOMA: A REAL-WORLD DUAL-CENTER RETROSPECTIVE ANALYSIS

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Background: The treatment landscape of unresectable hepatocellular carcinoma (HCC) has evolved with first-line immunotherapy (IO) combinations, yet most patients progress within 12 months. Tyrosine kinase inhibitors (TKIs) remain foundational, particularly in second- and third-line therapy, though data beyond second line are limited, and access remains restricted in several Canadian provinces. **Methods:** We conducted a retrospective cohort study of 20 patients with unresectable HCC treated at two tertiary care centers (MUHC and JGH) between January 2021 and March 2025. Patients who received $\geq$1 TKI were included. Demographics, ECOG status, presence of cirrhosis, treatment duration per line, and overall survival (from first oncology visit to death or March 1, 2025) were collected. **Results:** The median age at oncology consultation was 66.9 years. Most patients (90%) had an ECOG of 0–1, and half had underlying cirrhosis. The overall median survival was 21.9 months. Survival varied significantly by clinical features: non-cirrhotic patients lived longer than cirrhotic ones (26.2 vs 13.0 months), and patients with ECOG 0–1 outlived those with ECOG 2 (28.9 vs 12.2 months). Access to treatment intensity was a strong prognostic factor—patients receiving three or more lines of therapy had markedly better survival than those receiving two or fewer lines (29.9 vs 4.8 months), highlighting the importance of longitudinal access to systemic therapy.
Median treatment durations were 4.3 months in the first-line setting, 6.1 months in second line, and 1.9 months in third line. The drop in third-line duration likely reflects worsening performance status, treatment-limiting toxicity, or resistant disease biology. Nonetheless, several patients maintained therapy beyond three months in later lines, suggesting continued benefit in selected cases.
Compared to benchmarks from pivotal trials such as IMbrave150 (OS 19.2 months), REFLECT (13.6 months), RESORCE (10.6 months), and CELESTIAL (10.2 months), real-world outcomes in our cohort —particularly among patients with preserved function and access to multiple therapies—were comparable or superior. **Conclusion:** This real-world study reinforces the value of TKIs across treatment lines in unresectable HCC. Outcomes were strongest in patients with ECOG 0–1, no cirrhosis, and access to multiple therapies. While third-line therapy was shorter in duration, it still offered benefit in selected cases. These findings support flexible sequencing strategies and underscore the need for broader TKI access and prospective validation in the IO era.

Disclosures: Khalid Abumelha: Nothing to Disclose, Belinda Jiao: Nothing to Disclose, Jamil Asselah:

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Nothing to Disclose, Daphnee Lamoussenery: Nothing to Disclose, Jonathan Cools-Lartigue: Nothing to Disclose, Rhythm Sharma: Nothing to Disclose, Kim Ma: Nothing to Disclose

3332 | USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS, ASPIRIN, IBUPROFEN, AND ACETAMINOPHEN IN RELATION TO BILIARY TRACT CANCERS IN THE BILIARY TRACT CANCERS POOLING PROJECT (BITCAPP)

Ilona Argirion[1] Crystal Najib[2] Katherine McGlynn[3] Peter Campbell[4] Jill Koshiol[3], [1]Georgetown University, [2]University of Maryland, [3]National Cancer Institute, [4]Albert Einstein College of Medicine

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to reduce the risk of several cancers, leading to their proposed use as chemopreventive agents; nevertheless, their relationship with biliary tract cancers (BTCs) remains to be fully elucidated. **Methods:** Data from thirteen prospective studies in the Biliary Tract Cancers Pooling Project (BiTCaPP) were harmonized to investigate the association between NSAIDs, aspirin, ibuprofen, acetaminophen and BTCs. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression after adjustment for sex, race, education, smoking, alcohol use, body mass index, and cardiovascular disease. Sensitivity analyses were conducted to assess the role of duration and intensity of use, presence of gallstones, and cholecystectomy on the observed associations. **Results:** During 19,036,644 person-years of follow up, 494 gallbladder cancer (GBC), 339 intrahepatic bile duct cancer (IHBDC), 499 extrahepatic bile duct cancer (EHBDC), and 291 ampulla of Vater cancer (AVC) cases occurred. NSAIDs were inversely associated with IHBDC (HR = 0.57 [95%CI: 0.44-0.73]) and EHBDC (HR = 0.76 [95% CI: 0.62-0.94]); similar results were found for aspirin ($HR_{IHBDC} = 0.58$ [95%CI: 0.45-0.75]; $HR_{EHBDC} = 0.80$ [95%CI: 0.64-0.98]). Ibuprofen use was inversely associated with IHBDC (HR = 0.71 [95%CI: 0.52-0.97]) and AVC (HR = 0.61 [95%CI: 0.43-0.86]). Increasing intensity of NSAID use was associated with decreased EHBDC risk ($p_{trend} = 0.04$), and increased intensity of aspirin use was associated with decreased IHBDC risk ($p_{trend} = 0.02$), while increasing intensity of acetaminophen use was associated with increased IHBDC and EHBDC risk ($p_{trend} = 0.003$ and 0.02, respectively). Results did not vary by cholecystectomy or gallstone status. **Conclusion:** NSAIDs mitigate chronic inflammation and could protect against IHBDC and EHBDC. Conversely, acetaminophen use may increase the risk of IHBDC and EHBDC.

Disclosures: Ilona Argirion: Nothing to Disclose, Crystal Najib: Nothing to Disclose, Katherine McGlynn: Nothing to Disclose, Peter Campbell: Nothing to Disclose, Jill Koshiol: Nothing to Disclose

3333 | INFLUENCE OF METABOLIC SYNDROME ON POST-ABLATION OUTCOMES IN EARLY-STAGE HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) is the most common cause of primary liver cancer, with increasing incidence noted in Western countries due to concomittent rise in metabolic dysfunction-associated steatohepatitis (MASH) cirrhosis. Thermal ablation has evolved to become standard of care in non-surgical candidates in early-stage HCC. There has been increased interest in characterizing the pro-tumorigenic pathways in HCC with relation to metabolic syndrome (MetS), a cluster of metabolic disorders that includes high BMI, diabetes, dyslipidemia, and elevated blood pressure. These factors have been linked to the development of HCC and potentially contributes to poor outcomes after locoregional therapy. The goal of this study was to evaluate the association between metabolic syndrome and clinical outcomes after thermal ablation - specifically local tumor progression, intrahepatic distant tumor progression, progression free survival, and overall survival. **Methods:** A total of 126 patients with early-stage HCC who were treated with thermal ablation between 2005 and 2022 in this IRB-approved single-institution retrospective cohort study. Patients were divided into two groups based on presence or absence of MetS (n = 65 versus n = 61, respectively). MetS was defined by the presence of at least three of the following criteria adapted from the NCEP ATP III guidelines: BMI >30 kg/m² (used as a surrogate for central obesity), elevated triglycerides (≥ 150 mg/dL or on lipid-lowering therapy), reduced HDL cholesterol (<40 mg/dL in men, <50 mg/dL in women or on therapy), hypertension ($\geq 130/85$ mmHg or on antihypertensives), and fasting glucose ≥ 100 mg/dL or diabetes diagnosis. Progression-free survival (PFS) were compared between the two groups, including local, distant intrahepatic, and overall PFS, as well as overall survival using using Kaplan-Meier curves with log-rank test. **Results:** Local PFS after thermal ablation was decreased in the MetS group compared to the non-MetS group (98 vs 184 months;

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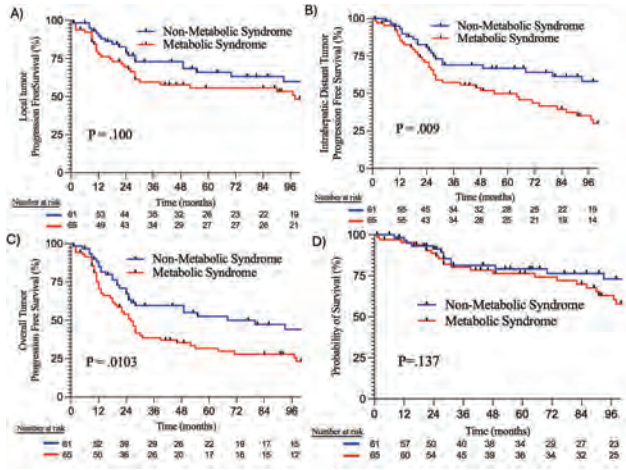
p = 0.10), although the difference was not found to be significant (Figure 1A). Intrahepatic distant PFS after thermal ablation was significantly reduced in the MetS group compared to non-MetS group (median time: 54 months versus 184 months; p = 0.009) (Figure 1B). Overall PFS rate was significantly reduced in MetS patients (26 versus 68 months; p = 0.01) (Figure 1C). Median overall survival showed a downward trend in the MetS group, (median time 126 vs 184 p = 0.14), although the difference was not significant (Figure 1D). **Conclusion:** Metabolic syndrome significantly correlates with increased recurrence risk, both local and intrahepatic distant among early-stage HCC patients after going standard of care thermal ablation. Interventions that target metabolic syndrome may potentially reduce the risk of progression after thermal ablation and or used as a strategy to keep early-stage HCC patients on the transplant list.



Disclosures: Zahra Mohammadigoldar: Nothing to Disclose, Pedram Keshavarz: Nothing to Disclose, David Lu: Nothing to Disclose, Steven Raman: Nothing to Disclose, Jihane Benhammou: Nothing to Disclose, Rajat Singh: Nothing to Disclose, Vatche Agopian: Nothing to Disclose, Jason Chiang: Nothing to Disclose

3334 | HYPOXIA-INDUCIBLE FACTOR 1A KNOCKOUT ENHANCES THE ANTITUMOR EFFICACY OF TYROSINE KINASE INHIBITORS IN AN ORTHOTOPIC HEPATOCELLULAR CARCINOMA MOUSE MODEL

Tania Payo-Serafín[1] Jennifer Martínez-Geijo[1] Carolina Méndez Blanco[1] Inés Martínez-Herráez[1] Daira Valencia-Sánchez[1] Beatriz San-Miguel[1] Andrés García-Palomo[2] Juan José Ortiz-de-Urbina[2] Francisco Jorquera[3] José Mauriz[1], [1]1. IBIOMED ULE, [2]1. IBIOMED ULE, 2. CAULE, [3]1. IBIOMED ULE, 2. CAULE, 3. CIBERehd ISCIII

Background: Hepatocellular carcinoma (HCC) is one of the deadliest cancers worldwide, largely due to late-stage diagnosis and limited therapeutic options. A hallmark of HCC is the hypoxic tumor microenvironment, which contributes to resistance to systemic therapies. Hypoxia-inducible factor 1α (HIF-1α) plays a pivotal role in the cellular adaptation to hypoxia, promoting survival and treatment resistance. For this, we investigated the effect of HIF1A knockout (KO) on the efficacy of the tyrosine kinase inhibitors (TKIs) sorafenib and regorafenib in an orthotopic mouse model of HCC. **Methods:** Huh-7 wild-type (WT) and HIF1A KO cells stably expressing luciferase activity were orthotopically injected into the liver of immunodeficient nude mice via ventral mid-laparotomy. Mice were randomized into six groups: WT control, KO control, WT + sorafenib, KO + sorafenib, WT + regorafenib, and KO + regorafenib. After five weeks of tumor development (confirmed via *in vivo* bioluminescence imaging using IVIS SpectrumCT Imaging System), mice received daily oral administration of the corresponding TKI or vehicle for three weeks and were sacrificed at the endpoint for tissue collection and analysis. Tumor progression was assessed by bioluminescence signal (total flux; photons/s), and pathophysiological parameters such as liver tumor burden index (LTBI; tumor-to-liver weight ratio), tumor burden index (TBI; tumor-to-body weight ratio) and hepatosomatic index (HSI; liver-to-body weight ratio) were assessed. **Results:** KO control mice showed a significant reduction in bioluminescence signal compared to WT control, indicating impaired tumor growth in the absence of HIF-1α. In both TKI treatment groups, HIF1A KO further enhanced the antitumor response: KO-treated groups exhibited markedly lower bioluminescence signal, LBTI, TBI and HSI compared to their respective WT-treated groups. **Conclusion:** Overall, our data suggest that HIF-1α plays a crucial role in tumor cell survival under hypoxic conditions in HCC. Its inhibition substantially improved the therapeutic efficacy of sorafenib and regorafenib in an orthotopic mouse model. Targeting hypoxia-driven mechanisms, such as HIF-1α activity, may represent a promising strategy to overcome resistance to TKIs in HCC.

Disclosures: Tania Payo-Serafín: Nothing to Disclose, Jennifer Martínez-Geijo: Nothing to Disclose, Carolina Méndez Blanco: Nothing to Disclose, Inés Martínez-Herráez: Nothing to Disclose, Daira Valencia-Sánchez: Nothing to Disclose, Beatriz San-Miguel: Nothing to Disclose, Andrés García-Palomo: Nothing to Disclose, Juan José Ortiz-de-Urbina: seagen spain: Speaker at a clinical session sponsored by Seagen Spain, janssen cilag: Speaker at a clinical session sponsored by Janssen Cilag Spa, Francisco Jorquera: Abbvie: Speaking and Teaching, Roche: Speaking and Teaching, Astra: Speaking and Teaching, José Mauriz: Nothing to Disclose, Nothing to Disclose

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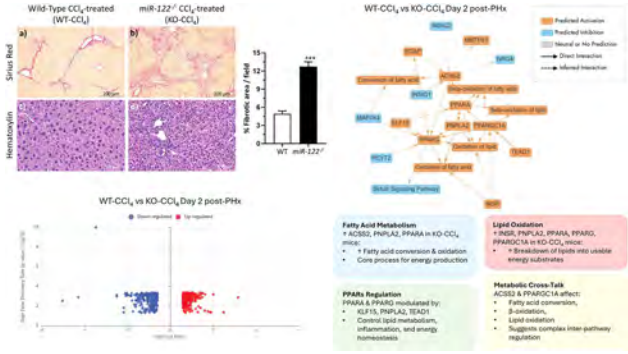
◆ 3335 | ABSENCE OF MIR-122 IN MICE TRIGGERS PATHOLOGICAL REGENERATION AND LIVER FAILURE IN FIBROTIC CONDITIONS

Anna Cardona-Simó[1] Jordi Ribera[2] Irene Portolés[3] Aleix Fabregat Bolufer[4] Pedro Melgar-Lesmes[5] Gregori Casals[6] Wladimiro Jimenez[6] Manuel Morales-Ruiz[6], [1]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [2]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Spain, [3]Centre de Recherche des Cordeliers, Sorbonne Université, INSERM, Université de Paris, France, [4]Biochemistry and Molecular Genetics Department, Hospital Clinic of Barcelona, Spain, [5]University of Barcelona, IDIBAPS, CIBERehd, Spain, [6]Hospital Clinic of Barcelona, IDIBAPS, University of Barcelona, CIBERehd, Spain

Background: miR-122 is the most abundant microRNA in the liver, playing a key role in hepatic physiology. While miR-122 has been extensively studied for its role as a tumor suppressor in hepatocellular carcinoma, its involvement in liver regeneration and in the hepatic fibrotic process remains unexplored. Our previous work showed that miR-122 expression is decreased in liver fibrosis in both patient samples and mouse models, and that its suppression in healthy livers leads to increased regeneration following partial hepatectomy. This study aims to determine whether miR-122 suppression can promote liver regeneration in fibrotic livers. **Methods:** We generated mice with miR-122 gene deficiency by CRISPR/Cas9. Fibrosis was induced by intraperitoneal injection of CCl_4 three times a week for four weeks. We performed partial hepatectomy (PHx) by resection of median and left lateral lobes (n = 20). A proteome analysis was carried out by mass spectrometry (LC-MS/MS). **Results:** At baseline, miR-122 knockout mice treated with CCl_4 (KO-CCl_4) exhibited a threefold increase in collagen fiber content compared to their wild-type CCl_4-treated counterparts. At day 2 post-PHx, KO-CCl_4 mice showed increased Ki67 expression and a trend toward elevated cyclin D1, suggesting increased proliferative activity. Nonetheless, this did not translate into functional regeneration and by day 7 post-PHx, 90% of the KO-CCl_4 mice had died. Proteomic analysis revealed that fibrotic KO livers had exaggerated metabolic activation, with increased protein synthesis and mitochondrial respiration, as a compensatory response to chronic injury. The absence of miR-122 also intensified a persistent inflammation and enhanced hepatic stellate cell activation, resulting in worsened fibrosis. The bioinformatic functional analysis of the proteomic results also showed that KO-CCl_4 mice post-PHx developed a severe inflammatory response marked by a cytokine storm, oxidative stress, extensive hepatocyte apoptosis, microcirculatory collapse, and features consistent with systemic inflammatory response syndrome, ultimately preventing effective regeneration. **Conclusion:** The absence of miR-122 disrupts the regenerative process by exacerbating inflammation, fibrosis and metabolic stress. Although miR-122 suppression transiently enhances hepatocyte proliferation, the resulting imbalance leads to hepatocellular damage and liver failure. These findings highlight the essential role of miR-122 in orchestrating effective regeneration under chronic injury.



Disclosures: Anna Cardona-Simó: Nothing to Disclose, Jordi Ribera: Nothing to Disclose, Irene Portolés: Nothing to Disclose, Aleix Fabregat Bolufer: Nothing to Disclose, Pedro Melgar-Lesmes: Nothing to Disclose, Gregori Casals: Nothing to Disclose, Wladimiro Jimenez: Nothing to Disclose, Manuel Morales-Ruiz: Nothing to Disclose

◆ 3336 | INHIBITION OF NEUTROPHIL EXTRACELLULAR TRAP FORMATION BY ANTICOAGULATION ATTENUATES LIVER FIBROSIS AND IDENTIFIES CYSTATIN B AS A POTENTIAL TARGET FOR ANTIFIBROTIC THERAPIES

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Background: Neutrophil extracellular traps (NETs) play an important role in the progression of liver fibrosis by sustaining inflammation and activating hepatic stellate cells. Anticoagulants have shown antifibrotic potential in preclinical models, but the underlying mechanisms are incompletely understood. As coagulation factors are known to influence neutrophil activation and NETs release, it is hypothesized that anticoagulation may indirectly suppress NETs formation and thereby attenuate fibrosis. Cystatin B (CSTB) is a cysteine protease inhibitor involved in immune regulation and the control of proteolytic activity during inflammation, but its role in liver fibrosis and relation with NETs remains underexplored. This study aimed to investigate whether anticoagulant therapy mitigates liver fibrosis through modulation of NETs and CSTB to explore the feasibility

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of combination therapy. **Methods:** Advanced liver fibrosis was induced in mice via intraperitoneal injection of thioacetamide (TAA, 150 mg/kg), three times per week for 12 weeks. Mice were then randomly divided into a treatment group (the factor X antagonist Edoxaban, Edo) and a control group (Ctr) (each n = 6). Edo was given as a suspension by gavage (30 mg/kg in 0.2 ml) daily for 3 weeks, while controls received the same volume of saline, from week 10-12 of TAA administration. Liver fibrosis was evaluated by collagen morphometry, RT-qPCR and WB. NETs formation and CSTB expression was assessed via RNA sequencing, WB and IHC. **Results:** Masson's trichrome and Sirius Red morphometry demonstrated significantly decreased hepatic collagen deposition in the Edo group. RT-qPCR and WB also showed significant downregulation of fibrosis-related transcripts and proteins including Col1a1, Fn and Acta2 in the Edo group. HE staining of the Edo group showed a significantly reduced neutrophil infiltration and IHC showed lower expression of NETs markers including Myeloperoxidase (MPO) and Neutrophil elastase (NE), and WB showed decreased levels of citrullinated histone H3 (CitH3), another marker of NETs formation, in the Edo vs the control group. Except for down-regulation of fibrogenesis and inflammation related genes, differential gene expression analysis revealed enrichment in the NETs formation pathway. Further correlation analysis of 68 NETs pathway genes identified CSTB to be positively correlated with 67 genes. CSTB was significantly downregulated in the Edo group (logFC = –2.89, p = 0.0016). WB and IHC validated a corresponding reduction at the protein level. **Conclusion:** CSTB is strongly associated with NETs-related gene expression and is significantly suppressed by anticoagulant therapy. Anticoagulation may prominently alleviate liver fibrosis through inhibition of NETs formation, suggesting a previously unrecognized regulatory role. Ongoing work will investigate CSTB's functional contribution to NETs formation and antifibrotic therapy.

Disclosures: Yingjie Ai: Nothing to Disclose, Detlef Schuppan: Nothing to Disclose, Shiyao Chen: Nothing to Disclose

◆ 3337 | MACHINE LEARNING IDENTIFIES PROTEO-TRANSCRIPTOMICS MODULES ASSOCIATED WITH FIBROGENESIS IN ADVANCE FIBROSIS IN A JAPANESE MASH COHORT

Ali Ebrahimi[1] Maria Paraskevopoulou[1] Banishree Saha[1] Ruixue Hou[1] Jen-Chieh Chuang[1] Saman Farahmand[1] Zoltan Derdak[1] Vandana Gupta[1] Hiroaki Yashiro[1] Paresh Thakker[1] Bernard Allan[1] Shinichi Aishima[2] Hideyuki Hyogo[3] Yuichiro Eguchi[3] Eisuke Murakami[4] Hirokazu Takahashi[3] Atsushi Nakajima[5] Masato Yoneda[6], [1]Takeda Development Center Americas, Inc., Cambridge, MA, United States, [2]Department of Scientific Pathology, Kyushu University, Japan, [3]Department of Hepatology, Division of Metabolism, Faculty of Medicine, Saga University, Saga, Japan, [4]Department of Gastroenterology and Metabolism, Hiroshima University, Hiroshima, Japan, [5]International University of Health and Welfare Department of Gastroenterology & Hepatology, Japan, [6]Department of Gastroenterology and Hepatology, Yokohama City University, Kanagawa, Japan

Background: Novel non-invasive biomarkers associated with active metabolic-associated steatohepatitis (MASH) and advanced fibrosis remain a huge unmet need. Machine learning (ML)-based multi-omics analysis provides a unique opportunity for biomarker discovery. The study conducts paired tissue/serum proteo-transcriptomic analysis from a Japanese MASH cohort to identify biomarker modules linked to active fibrogenesis in advanced fibrosis. **Methods:** 11K protein Somascan platform and bulk RNA-seq for a serum/tissue paired omics were performed across MAFLD to MASH (F0/F2: N = 78, F3/F4: N = 47) in a large Japanese cohort.

An ML model was applied to predict proteo-transcriptomic modules for advanced fibrosis. Modules were functionally characterized via pathway enrichment, assessed for their liver cellular origin in single-nuclei (Snuc) RNA-Seq, and associated with Nordic biomarkers of fibrogenesis and fibrolysis (Pro-C3/C4/C5/C6, CTX-III, C4M).

Proteomics signatures were cross-validated in a European cohort (LITMUS) to detect conserved and population-specific biomarkers. **Results:** Differential gene/protein analysis identified 338 serum proteins and tissue genes consistently upregulated in advanced fibrosis (F4-F3), including CHI3L1, CLSTN2, ADAMTSL2, MFAP4, ENPP2, and AKR1B10. Pathway analysis highlighted processes linked to extracellular matrix remodeling, immune responses, angiogenesis, glycosylation, and integrin activity.

The ML model identified 7 proteo-transcriptomic modules predicting advanced fibrosis with AUROC > 0.9 in this cohort.

A MASH liver Snuc-Seq dataset revealed hepatocytes and scar-associated non-parenchymal cells as the cellular sources of these biomarkers. Modules were found to be highly correlated with fibrogenesis biomarkers such as Pro-C3, Pro-C4, Pro-C5, and fibrolysis biomarkers (e.g., C4M).

Proteomics findings validated fibrosis-associated proteins from the LITMUS cohort with high correlation (~0.87), while identifying 550 new proteins for advanced

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fibrosis. Over 50% of these proteins were regulated in tissue transcriptomics, with 36 being uniquely identified in our ML model. **Conclusion:** This is a first of a kind proteo-transcriptomics study of a Japanese MASH cohort powered by AI/ML that integrates histological features, tissue transcriptomics, and serum proteomics, identifying unique modules that are highly associated with advanced fibrosis and active fibrogenesis. The potential of these as non-invasive biomarkers and therapeutic targets is being actively evaluated.

Disclosures: Ali Ebrahimi: Takeda: Employee, GSK: Employee, Maria Paraskevopoulou: Nothing to Disclose, Banishree Saha: Nothing to Disclose, Ruixue Hou: Takeda Pharmaceuticals: Employee, Jen-Chieh Chuang: Takeda: Employee, Takeda: Employee, Saman Farahmand: Nothing to Disclose, Zoltan Derdak: Nothing to Disclose, Vandana Gupta: Takeda Pharmaceuticals: Employee, Hiroaki Yashiro: Takeda Pharmaceuticals: Employee, Paresh Thakker: Nothing to Disclose, Bernard Allan: Nothing to Disclose, Shinichi Aishima: Nothing to Disclose, Hideyuki Hyogo: Nothing to Disclose, Yuichiro Eguchi: Nothing to Disclose, Eisuke Murakami: Nothing to Disclose, Hirokazu Takahashi: Sysmex: Grant/Research Support, Novo Nordisk: Speaking and Teaching, Kowa: Speaking and Teaching, Taisho: Speaking and Teaching, Takeda: Grant/Research Support, Atsushi Nakajima: Nothing to Disclose, Masato Yoneda: Nothing to Disclose

◆ 3338 | NON-INVASIVE ESTIMATION OF PORTAL PRESSURE USING MACHINE LEARNING: DEVELOPMENT AND VALIDATION IN 670 CIRRHOTIC PATIENTS

Seul Ki Han[1] Moon Young Kim[1] Taesic Lee[1] Myung Jae Seo[1] Eui Young Oh[2], [1]Yonsei wonju severance christian hospital, [2]Yonsei University Wonju College of Medicine

Background: Clinically significant portal hypertension (CSPH), defined as hepatic venous pressure gradient (HVPG) $\geq$10 mmHg, is a key determinant of decompensation and mortality in cirrhosis. However, HVPG measurement remains invasive and is not widely applied in clinical practice. Although non-invasive fibrosis markers such as FIB-4 or transient elastography are widely used, they have limited correlation with portal pressure itself. This study aimed to develop and validate a non-invasive model to estimate portal pressure and predict CSPH using machine learning based on clinical parameters from a large real-world cirrhotic cohort. **Methods:** We retrospectively analyzed 670 patients with liver cirrhosis who underwent HVPG measurement. Clinical and laboratory variables were collected on the day of HVPG. After rigorous data cleaning and outlier exclusion using PCA and Mahalanobis distance, 618 patients were used for model construction. Feature selection was conducted via univariate linear regression and 250×4-fold cross-validation. Seven most predictive features (INR, albumin, platelets, ascites, hemoglobin, spleen size, and sodium) were used to develop HVPG estimation and CSPH prediction models using multivariate regression and logistic regression, respectively. Models were externally validated using independent datasets from another institution. **Results:** HVPG showed significant correlation with CTP and MELD scores. The final HVPG estimation model demonstrated acceptable performance (bias –0.011, RMSE 4.257, PCC 0.579). INR and albumin were the strongest predictors. The CSPH prediction model achieved an AUC of 0.82 in internal validation, with similar results in the external cohort. Model performance improved as more variables were added, and was comparable or superior to conventional prognostic indices. Blood pressure, sex, and alcohol intake also contributed to model performance. The model maintained predictive accuracy for CSPH without including imaging or endoscopic data. **Conclusion:** We present a machine learning–based model to estimate HVPG and predict CSPH using easily accessible clinical parameters. This model offers a non-invasive tool to stratify portal hypertension severity, potentially guiding endoscopic screening and risk-based medical therapy in cirrhosis. Further prospective validation in larger, diverse populations is warranted.

Disclosures: Seul Ki Han: Nothing to Disclose, Moon Young Kim: Nothing to Disclose, Taesic Lee: Nothing to Disclose, Myung Jae Seo: Nothing to Disclose, Eui Young Oh: Nothing to Disclose

◆ 3339 | FIBROBLASTIC ACTIVITY IS PROGNOSTIC FOR FURTHER DECOMPENSATION AFTER TIPS IN PATIENTS WITH LIVER CIRRHOSIS

Alejandro Mayorca Guiliani[1] Simon Gairing[2] Eva Schleicher[2] Myriam Meineck[2] Michael Pitton[3] Julia Weinmann-Menke[2] Peter Galle[4] Diana Leeming[5] Morten Karsdal[5] Christian Labenz[2], [1]Nordic Bioscience, [2]Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg-University Ma, [3]Department of Radiology, University Medical Center of the Johannes Gutenberg-University Main. Mainz, [4]Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg-University, [5]Nordic Bioscience A/S

Background: Background:: Severe liver disease engages mechanisms regulating immune function, ECM protein synthesis and degradation that result in

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abnormal ECM formation. Circulating by-products of these mechanisms, or ECM biomarkers, provide information about disease activity and therapeutic efficacy. Here, we hypothesize that ECM biomarkers predict the risk of further decompensation in cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) insertion. **Methods:** Methods:: 63 patients with cirrhosis and TIPS-insertion for refractory ascites or secondary prophylaxis after variceal bleeding were included and followed for 90 days. Serum samples from the right atrium and portal vein were taken during TIPS, then during outpatient visits. We measured white blood cell count, IL-6, IL-8, ammonia, C reactive protein, the propeptide of collagen type III (NordicPRO-C3 ™), the cleavage product of collagen type VI (NordicPRO-C6 ™), Calprotectin-Human Neutrophil Elastase (CPa9-HNE) a marker of neutrophil activation, Citrullinated Vimentin (VICM), a marker of macrophage activity and MMP-cleaved fragments of collagens type III (C3M) and IV (C4M). We clustered patients according to baseline values using silhouette and k-means clustering. Missing values were imputed using multivariate imputation by chained equations. **Results:** Results:: Ascites was the indication for TIPS insertion in 86% of patients. Median MELD was 12. 63% of patients had a further decompensation event within 90 days. Biomarkers in portal and central serum did not differ significantly. We identified 3 clusters (1 = 17 patients, 2 = 28 patients, 3 = 20 patients). 47% of patients in cluster 1 and 57% of patients in cluster 2 had a decompensation event within 90 days, while 90% of patients in cluster 3 did ($p = 0.013$). Cluster 1 was characterized by neutrophil (CPa9-HNE, $p < 0.001$), macrophage activation (VICM $p < 0.001$) and ECM degradation (C4M $p < 0.001$). Cluster 2 had lower ECM biomarkers, whilst cluster 3 had higher fibroblastic activity (PRO-C3 $p < 0.001$ and PRO-C6 $p < 0.001$). After 90 days, 53.8% of cluster 1 patients and 20% of cluster 2 patients transitioned to cluster 3. **Conclusion:** Conclusion:: ECM biomarkers identified inflammatory (cluster 1), quiescent (cluster 2) and pro-fibrotic (cluster 3) endotypes. Pro-fibrotic patients have significantly higher risk of further decompensation. ECM biomarkers show potential to dissect patient heterogeneity during severe liver disease and therapeutic effect, as well as prognosticate post-TIPS decompensation.

Disclosures: Alejandro Mayorca Guiliani: Nothing to Disclose, Simon Gairing: Nothing to Disclose, Eva Schleicher: Nothing to Disclose, Myriam Meineck: Nothing to Disclose, Michael Pitton: Nothing to Disclose, Julia Weinmann-Menke: Boehringer Ingelheim: Speaker, AstraZeneca: Speaking and Teaching, GSK: Speaking and Teaching, Lilly: Speaking and Teaching, Otsuka: Speaking and Teaching, Novartis: Speaking and Teaching, Peter Galle: Nothing to Disclose, Diana Leeming: Nothing to Disclose, Morten Karsdal: Nothing to Disclose, Christian Labenz: Nothing to Disclose

◆ 3340 | RAP1A MODULATES LSEC CAPILLARIZATION TO DRIVE HEPATIC FIBROSIS PROGRESSION

Guangwen Chen[1] Junjun Wang[1] Weiming Dai[2] Zhenyang Shen[1] Jianxiang Wang[1] Zhuqiong Lu[1] Hanjing Zhangdi[1] Yuecheng Guo[1] Qingqing Zhang[1] Qichao Ge[1] Yufei Yang[1] Lungen Lu[1] Hui Dong[1] Xiaobo Cai[1], [1]Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, [2]Peking University People's Hospital

Background: Liver sinusoidal endothelial cell (LSEC) capillarization has been demonstrated to exacerbate the progression of hepatic fibrosis. This study reveals the role of *Rap1a* in LSEC capillarization and hepatic fibrosis, uncovering mechanisms driving endothelial phenotypic switching. **Methods:** RAP1A expression was assessed in chronic liver samples from mice by immunofluorescence (IF). Single-cell RNA sequencing (scRNA-seq) data from GEO were analyzed via KEGG/GO enrichment. Scanning electron microscopy (SEM) was used to evaluate the fenestrae of LSEC in vitro and vivo. EC-specific *Rap1a* deficiency knockout mice ($Rap1a^{\Delta EC}$) was generated by breeding $Rap1a^{fl/fl}$ with the Cdh5-Cre mice. Histology, western blot (WB), immunohistochemistry (IHC), and RT-qPCR were used to assess the severity of capillarization and fibrosis in CCl4-induced hepatic fibrosis models. The RAP1A activity agonist 8-CPT-2ME-cAMP was administered at graded concentrations and evaluated its effects on LSEC capillarization and fibrosis progression in CCl_4-induced hepatic fibrosis models. **Results:** KEGG/GO analyses identified significant Rap1 signaling pathway enrichment in LSEC from metabolic dysfunction-associated steatohepatitis (MASH) mice compared to controls. RAP1A was primarily expressed in LSEC and its expression was downregulated during chronic liver injury. EC-specific *Rap1a* deficiency significantly decreased the fenestrae of LSEC in vitro and vivo and aggravated hepatic fibrosis. RNA-seq shows upregulation of Notch signaling in *Rap1a*-deficient LSEC. Mechanistically, RAF1 interacted with both RAP1A and Notch intracellular domain (NICD). The absence of RAP1A reduced RAF1 levels, impaired the formation of RAF1-NICD complex and enhanced NICD nuclear translocation to activate Notch signaling. Restoration of RAP1A activity attenuated capillarization and fibrosis in the CCl_4 model. **Conclusion:** *Rap1a* deficiency in LSECs promotes NICD nuclear translocation via the RAP1A -RAF1-NICD axis, activating the Notch signaling pathway and exacerbating capillarization with subsequent fibrosis. Restoration of RAP1A activity ameliorates both capillarization and hepatic fibrosis progression. These findings highlight *Rap1a* as a therapeutic target for attenuating LSEC-driven fibrosis.

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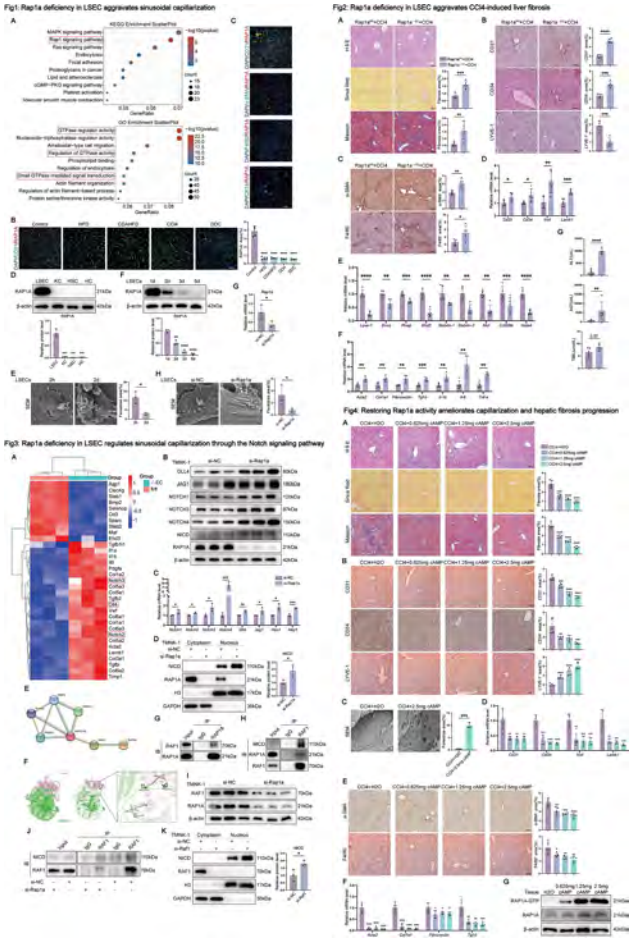

Disclosures: Guangwen Chen: Nothing to Disclose, Junjun Wang: Nothing to Disclose, Weiming Dai: Nothing to Disclose, Zhenyang Shen: Nothing to Disclose, Jianxiang Wang: Nothing to Disclose, Zhuqiong Lu: Nothing to Disclose, Hanjing Zhangdi: Nothing to Disclose, Yuecheng Guo: Nothing to Disclose, Qingqing Zhang: Nothing to Disclose, Qichao Ge: Nothing to Disclose, Yufei Yang: Nothing to Disclose, Lungen Lu: Nothing to Disclose, Hui Dong: Nothing to Disclose, Xiaobo Cai: Nothing to Disclose

◆ 3341 | SINGLE CELL FIXED RNA-SEQUENCING ANALYSIS REVEALED HSCS^{LMCD1+} IS A DRIVER OF LIVER FIBROSIS BY MODULATING AKT-PRAS40-4EBP1

Thi Thanh Thuy Le[1] Duc Pham[1] Hoang Hai[1] Tuan Anh Pham[1] Thi Ha Nguyen[1] Norifumi Kawada[1], [1]Osaka Metropolitan University

Background: Background and Aims: Single Cell Fixed RNA Profiling (FLEX) is a novel technology that captures RNA expression in single cells from frozen tissues. Herein, we applied FLEX in the murine model of cirrhosis progression and regression to discover novel targets for anti-fibrotic therapy. **Methods:** Methods: Thioacetamide (TAA) was administered intraperitoneally to mice at escalating doses ranging from 50 to 400 mg/kg over a 10-week period to induce liver fibrosis, while control mice received saline. Regression of liver fibrosis was assessed two weeks after TAA cessation. Frozen liver tissues from both mice and human samples were fixed, dissociated into single cells, and analyzed via single-cell RNA sequencing (scRNA-seq) following the 10X Genomics protocol. Multiplex flow cytometry, immunoblotting, immunohistochemistry, proteome cytokine array, and pharmacological inhibitors were used for molecular analysis. **Results:** Results:: Using FLEX technology, whole liver cells were preserved and analyzed at single cell resolution and classified into 10 major cell types under the transcriptome of 38,136 cells. Disease progression showed expansion of inflammatory and fibrogenic populations (macrophages, cholangiocytes, HSCs), while regression restored hepatocytes and LSECs. We identified 9 disctint HSCs subclusters with distinct signature genes and enrichment pathways in healthy control, fibrosis progression and regression. Notably, LIM-domain-related genes, including LIMA1, LIMK2, PDLIM2, PDLIM5, PDLIM7, FHL2, FHL3, and LMCD1, were significantly upregulated in cirrhotic HSCs from both mouse and human samples but were downregulated during fibrosis regression. Functional studies demonstrated that silencing LMCD1 attenuated HSC activation, whereas overexpression of LMCD1 strongly enhanced HSC activation via the AKT-PRAS40-4EBP1 pathway. Specific pathways inhibition using AZD8055 mitigated HSCs activation, both spontaneously and under TGF-β stimulation, and significantly reduced the phosphorylation of 16/39 proteins implicated in HSC activation, including CREB, c-JUN, TP53, WNK1, GSK3B, ERK1/2, P70S6K, and RSK1/2/3. Interestingly, treatment of AZD8055 attenuated TAA-induced liver fibrosis. LMCD1 highly expressed in fibrotic region and strongly correlated with fibrosis severity, with an area under the receiver operating characteristic (AUROC) curve of 0.92 (95% CI: 0.76–1; $p = 0.006$) for predicting MASLD-related fibrosis. **Conclusion:** Our single-cell transcriptomic atlas reveals the cellular and molecular reprogramming underpinning fibrosis progression and regression in the liver. HSC subclustering revealed novel activation marker LMCD1, upregulated during fibrosis and reduced in regression via LMCD1-AKT-PRAS40-4EBP1 axis. These findings provide a foundation for the development of targeted therapies aimed at mitigating liver fibrosis and its progression.

Disclosures: Thi Thanh Thuy Le: Nothing to Disclose, Duc Pham: Nothing to Disclose, Hoang Hai: Nothing to Disclose, Tuan Anh Pham: Nothing to Disclose, Thi Ha

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Nguyen: Nothing to Disclose, Norifumi Kawada: Nothing to Disclose

◆ 3342 | CONTINUOUS DIGITAL PATHOLOGY SCORING REVEALS FIBROSIS REVERSAL AND TREATMENT BENEFIT OF LANIFIBRANOR: INSIGHTS FROM A PRECLINICAL RODENT MODEL.

Guillaume Wettstein[1] reethika Chokkakula[2] Mathieu Petitjean[2] Arun Sanyal[3] Scott Friedman[4] Michael Cooreman[1] Pierre Broqua[1], [1]Inventiva, [2]PHARMANEST, [3]Virginia Commonwealth University, [4]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Lanifibranor is a pan-PPAR agonist targeting PPARα, PPARδ, and PPARγ—nuclear receptors that regulate metabolism, inflammation, and fibrosis. Its antifibrotic effects have been established in preclinical fibrosis models using conventional histological and biochemical assays and in the NATIVE Phase 2b trial (NCT03008070) using the NASH CRN histological grading and staging. Here, we apply FibroNest™, a high-resolution single-fiber digital pathology platform, to extract continuous phenotypic biomarkers and gain deeper insight into lanifibranor's treatment potential. **Methods:** The study used a therapeutic design in a CCl-induced mouse fibrosis model (N = 48) with escalating doses of lanifibranor (Table 1). Mouse liver were harvested and sections were stained with Picrosirius Red (PSR), scanned at 40X and assessed using three modalities: (1) hydroxyproline content (µg/mg wet liver), (2) conventional image analysis to determine PSR area %, and (3) the FibroNest™ platform, which provides high-resolution, continuous, phenotypic scores of fibrosis severity (Ph-FCS [1–10]) and ~100 quantitative histological features (qFT) as described in DOI: 10.1126/scitranslmed.add3949. **Results:** Ph-FCS tracked fibrosis progression and treatment response with greater sensitivity and precision than conventional assays, as evidenced by means, standard deviations, and with a high degree of statistical significance p-values (Tables 1–2) in the CCL4 study. Ph-FCS detected significant differences in fibrosis severity between weeks 3 and 6 of fibrosis induction, illustrating sensitivity to changes in fibrosis architecture beyond mere just collagen content. Ph-FCS showed significant fibrosis reduction at both 10 and 30 mg/kg lanifibranor doses. In contrast, hydroxyproline content and PSR area % detected significant effects only at 30 mg/kg, with 10 mg/kg showing a non-significant trend. qFT that most describe the progression and regression of fibrosis and individually assessed to provide insights to mechanism of action. **Conclusion:** Lanifibranor demonstrated antifibrotic activity in preclinical therapeutic models. High-resolution single-fiber digital pathology (Ph-FCS) offers a more sensitive and continuous assessment of fibrosis regression than traditional methods. These findings support Ph-FCS as a translational biomarker and further support lanifibranor's efficacy as an antifibrotic agent.

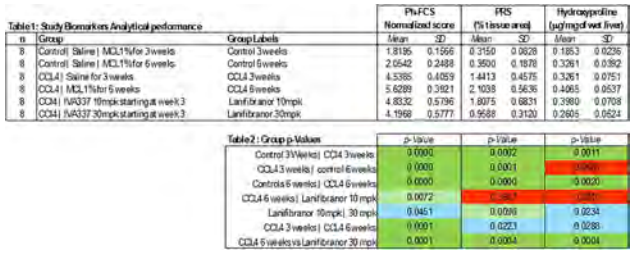

Table1: Study Biomarkers Analytical performance		Ph-FCS Normalized score		PRS (% tissue area)		Hydroxyproline (µg/mg of wet liver)	
n	Group	Mean	SD	Mean	SD	Mean	SD
8	Control| Saline | MCL1%for 3 weeks	Control 3 weeks	1.8195	0.1566	0.3150	0.0628	0.1853	0.0236
8	Control| Saline | MCL1%for 6 weeks	Control 6 weeks	2.0542	0.2488	0.3500	0.1878	0.3261	0.0392
8	CCL4| Saline for 3 weeks	CCL4 3 weeks	4.5385	0.4059	1.4413	0.4575	0.3261	0.0751
8	CCL4| MCL1%for 6 weeks	CCL4 6 weeks	5.6289	0.3921	2.1038	0.5636	0.4065	0.0537
8	CCl4| IVA337 10mpk starting at week 3	Lanifibranor 10mpk	4.8332	0.5796	1.8075	0.6831	0.3980	0.0708
8	CCl4| IVA337 30mpk starting at week 3	Lanifibranor 30mpk	4.1968	0.5777	0.9588	0.3120	0.2605	0.0624

Table2 : Group p-Values	p-Value	p-Value	p-Value
Control 3Weeks| CCl4 3weeks	0.0000	0.0002	0.0011
CCL4 3 weeks| control 6weeks	0.0000	0.0001	0.0000
Controls 6 weeks| CCL4 6weeks	0.0000	0.0000	0.0020
CCL4 6 weeks| Lanifibranor 10 mpk	0.0072	0.3887	0.3887
Lanifibranor 10mpk| 30 mpk	0.0451	0.0098	0.0234
CCL4 3 weeks| CCL4 6weeks	0.0001	0.0223	0.0288
CCL4 6 weeks vs Lanifibranor 30 mpk	0.0001	0.0004	0.0004

Disclosures: Guillaume Wettstein: Nothing to Disclose, reethika Chokkakula: Nothing to Disclose, Mathieu Petitjean: PHARMANEST INC: Employee, PHARMANEST INC: Stock – privately held company, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (< 5K), Terns (< 5K), Merck (< 5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (< 5K),: Consultant, Novo Nordisk: Consultant, Regeneron (< 5K), Alnylam (< 5K), Akero (< 5K),: Consultant, Tern (< 5K), Histoindex (< 5K), Corcept (< 5K),: Consultant, Path AI (< 5K), Genfit (< 5K), Mediar (< 5K),: Consultant, Satellite Bio (< 5K), Echosens (< 5K), Abbott (< 5K),: Consultant, Promed (< 5K), Glaxo Smith Kline (~11K), Arrowhead (< 5K): Consultant, Zydus (> 60K), Boston Pharmaceutical (< 5K), Myovent (< 5K),: Consultant, Variant (< 5K), Cascade (< 5K), Northsea (< 5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Scott Friedman: Nothing to Disclose, Michael Cooreman: Nothing to Disclose, Pierre Broqua: Nothing to Disclose

◆ 3343 | REGULATION OF COL1A1 BY BRD4 CONDENSATES IN HEPATIC STELLATE CELLS

Luke Doskey[1] Dawood Al Dawood[1] Maria Hernandez-Tejero[1] Sofia Jerez[2] Sheng Cao[3] Vijay Shah[3], [1]Mayo Clinic, [2]Mayol Clinic, [3]Mayo Clinic Rochester

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Background: Liver fibrosis is progressive condition that may lead to cirrhosis, which presents excessive extracellular matrix and the dysregulation of collagen (COL) deposition and turnover. Hepatic stellate cells (HSCs) are the major depositors of COL in response to TGFβ, a key fibrosis regulator. Transcriptional condensates are phase separations of transcriptional machinery and nucleic acids, that create favorable biochemical environments to regulate gene transcription. The increased COL expression in fibrosis resembles the expression of genes regulated by transcriptional condensates. However, their role in liver disease is unknown. Thus, we aim to analyze the role of transcriptional condensates in pathological COL expression in liver fibrosis. **Methods:** Publicly available chromatin immunoprecipitation-sequencing data were mined to determine histone modifications and transcriptional regulator occupancy near the COL1A1 gene using Integrated Genomics Viewer and computeMatrix. Immortalized HSCSs (LX-2) were treated with I-BET151, a bromo and extra-terminal (BET) family of transcriptional regulators inhibitor before stimulation with TGFβ. COL1A1 expression was assessed using qPCR. BRD4 condensate dynamics were measured by fluorescence recovery after photobleaching (FRAP) in LX-2 cells expressing GFP-tagged BRD4. BRD4 condensate formation was analyzed by immunofluorescence imaging employing super-resolution microscopy. **Results:** Data mining showed that in response to TGFβ treatment, the COL1A1 locus is significantly modified by H3K27AC and occupied by the BET protein BRD4. This suggests the presence of super enhancers, which are clusters of positive gene regulatory elements that control the expression of multiple genes and recruit condensate-forming transcriptional regulators (e.g. BRD4). This observation implies condensate regulate *COL1A1* expression. TGFβ stimulation induced the formation of BRD4 condensates and concurrently increased the *COL1A1* expression 4.8-fold in LX-2 cells, which was decreased by 92% with BET inhibition. This demonstrates that COL1A1 expression is regulated by BRD4. FRAP further showed active diffusion of GFP-BRD4 into condensates in LX2 cells (79% recovery in 338 seconds). **Conclusion:** These findings propose a novel model of pathological COL expression, whereby BRD4 transcriptional condensates are formed in response to TGFβ stimulation to modulate the expression of pathological *COL1A1.* Thus, specific condensate targeting may be a therapeutic approach for treating liver fibrosis.

Disclosures: Luke Doskey: Nothing to Disclose, Dawood Al Dawood: Nothing to Disclose, Maria Hernandez-Tejero: Nothing to Disclose, Sofia Jerez: Nothing to Disclose, Sheng Cao: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant

◆ 3344 | A NOVEL PROTEOMICS STRATEGY TO IDENTIFY NATURAL SUBSTRATES OF AMINOPEPTIDASES IN HUMAN CIRRHOSIS

Yiqun Qu[1] Mujia Li[2] Badwi Boumelhem[1] Miguel Cosenza-Contreras[2] Nelanka Halgamuge[3] Fiona Guan[4] Chuanmin Wang[4] Avik Majumdar[5] William Bachovchin[6] Jack Lai[6] Geoffrey McCaughan[4] Ken Liu[4] Oliver Schilling[2] Mark Gorrell[7], [1]Centenary Institute, [2]University of Freiburg, [3]University of Sydney, [4]Royal Prince Alfred Hospital, [5]Austin Health, [6]Tufts University, [7]The Centenary Institute, The University of Sydney, Sydney, Australia

Background: Fibroblast activation protein (FAP) and the similar aminopeptidase DPP4 are upregulated in cirrhosis, with myofibroblasts making FAP while DPP4 is ubiquitous. We report a novel approach to identify extracellular proteins that are digested by FAP/DPP4 in injured liver. **Methods:** Fibroblast activation protein (FAP) and the similar aminopeptidase DPP4 are upregulated in cirrhosis, with myofibroblasts making FAP while DPP4 is ubiquitous. We report a novel approach to identify extracellular proteins that are digested by FAP/DPP4 in injured liver.

Methods

Suspensions of fresh human liver cells from cirrhotic explants were incubated up to 72 h in supplemented William's E medium (Figure). Portions of each mixed liver cell culture were incubated with a selective inhibitor of either FAP or DPP4 for the final 24 hours before collecting cell culture supernatant (CCM). N-termini of peptides in CCM were labelled by Tandem Mass Tag (TMT) and then analyzed by high-resolution liquid chromatography–tandem mass spectrometry (LC-MS/MS; Q-Exactive Orbitrap) using data-dependent acquisition (DDA) and FragPipe, then statistically analyzed in RStudio to derive a proteome and DPP4- and FAP-degraded degradomes. **Results:** The cultivated liver cells were about 40-50% fibroblasts (FAP+SMA+), 40% hepatocytes (albumin+) and 10% macrophages (CD68+). The 23 CCM were subdivided into 4 groupings of etiologies (biliary, metabolic, viral and alcoholic). The CCM proteome contained 2,008-4,164 identifiable proteins of which 11-42 were differentially abundant after exposure to FAP inhibitor. In FAP degradomics,

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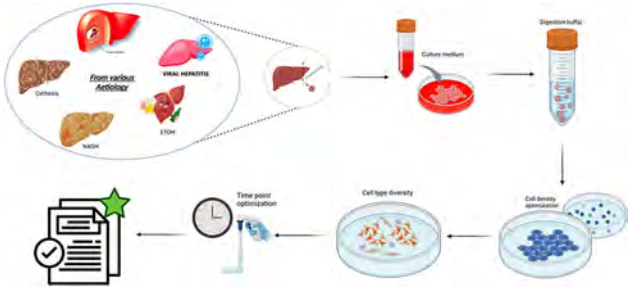
3,231-7,256 TMT-labelled peptides were identified and 42 neo-N-termini derived from 18 human proteins were cleaved post-proline, which is the preferred site of hydrolysis by FAP. Proteins associated with matrix, TGF-beta, MMPs and innate immunity were prominent in both proteomics and degradomics datasets. Degradome analyses are ongoing. Novel N-termini, indicating potential aminopeptidase substrates, included known substrates and proteins associated with fibrosis, metabolism, inflammation, cell proliferation and matrix remodelling that were not previously known to be FAP substrates. **Conclusion:** This study aligns with our previous FAP degradomics[1] and is expanding the knowledge of the human liver proteome, and suggests roles of DPP4 and FAP in fibrosis and metabolism.

Reference-1. *Molecular Cellular Proteomics* (2019) 18:65-85.



Disclosures: Yiqun Qu: Nothing to Disclose, Mujia Li: Nothing to Disclose, Badwi Boumelhem: Nothing to Disclose, Miguel Cosenza-Contreras: Nothing to Disclose, Nelanka Halgamuge: Nothing to Disclose, Fiona Guan: Nothing to Disclose, Chuanmin Wang: Nothing to Disclose, Avik Majumdar: Nothing to Disclose, William Bachovchin: Nothing to Disclose, Jack Lai: Nothing to Disclose, Geoffrey McCaughan: Nothing to Disclose, Ken Liu: Nothing to Disclose, Oliver Schilling: Nothing to Disclose, Mark Gorrell: Nothing to Disclose

3345 | FIBROSIS MICROENVIRONMENT AFTER HBSAG CLEARANCE IS ASSOCIATED WITH HCC RECURRENCE IN HBV PATIENTS.

Michitaka Matsuda[1] Shinji Kondo[2] Tatsuya Kanto[1], [1]JIHS, National Institute for Global Health and Medicine, [2]JIHS, National Institute of Global Health and Medicine

Background: Hepatocellular carcinoma (HCC) pathogenesis is regulated by the microenvironment of the background fibrotic liver. We used spatial and single-cell transcriptome analysis for resolving the cellular microenvironment associated with HCC recurrence in patients with chronic HBV infection. **Methods:** We used surgically resected HCC specimens from the patients with chronic hepatitis B. For the GeoMx spatial transcriptome, liver tissue sections containing HCC and adjacent liver tissue were prepared. HBsAg and HBV-DNA were histologically detected by immunofluorescent staining and in situ hybridization. Under microscopy, ROIs were selectedfrom mild and advanced fibrosis areas based on the morphological information obtained by collagen staining. Each ROI was further divided into fibrosis and parenchymal areas by type1 collagen staining positivity, and area-specific transcriptomes were acquired using the masking method. Finally, HbsAg+/- early and advanced fibrosis transcriptomes were obtained and comparatively analyzed. Single-cell RNA sequencing (scRNA-seq) from the matched patients was used for spatial deconvolution analysis. HCC recurrence risk genes were defined from the liver transcriptome data of HBV patients. **Results:** Spatial deconvolution revealed that the fibrosis area consists of immune, vascular, and mesenchymal populations, while parenchyma dominantly consists of hepatocytes. Amongst early fibrosis, HBV-DNA was located in the cytosol at the HBsAg-positive area but not the HBsAg-negative area, indicating active viral replication at the HBsAg-positive area. Spatial deconvolution anlysis revealed that HBsAg-positive area has more macrophage and gdT than the HBsAg-negative area, suggesting an active innate response to the infected cells. Advanced fibrosis enriches more activated HSCs and lymphocytes, including immunosuppressive T cells, than early fibrosis. HBsAg was sparsely observed near the advanced fibrosis, suggesting fibrosis develops with HBsAg disappearance. Interestingly, HBV-DNA was located in hepatocyte nuclei at HBsAg-sparse area, suggesting cccDNA of HBV at the site. The recurrence risk gene signature was enriched at the HBsAg-sparse area surrounded by bridging firbosis, suggesting HBsAg clearance is associated with developing a precancerous microenvironment. **Conclusion:** Depending on the HBV infection status, the fibrosis microenvironment is heterogeneous across the tissue. Immunosuppressive microenvironment after HBsAg clearance was associated with early recurrence of HCC after surgical resection in chronic HBV patients.

Disclosures: Michitaka Matsuda: Nothing to Disclose, Shinji Kondo: Nothing to Disclose, Tatsuya Kanto: Nothing to Disclose

3346 | DYNAMIC CELLULAR CHANGES IN A PRECISION CUT LIVER SLICE MODEL

Denisse Rubio Cruz[1] Sofía Izunza Barba[2] Hua Xu[3] Shanshan Su[3] Sehrish Naz[4] Susmita Bhattarai[4] Xing Liu[3] Sizhe Wan[3] Imad Nasser[3] Gyongyi Szabo[5] Gordon

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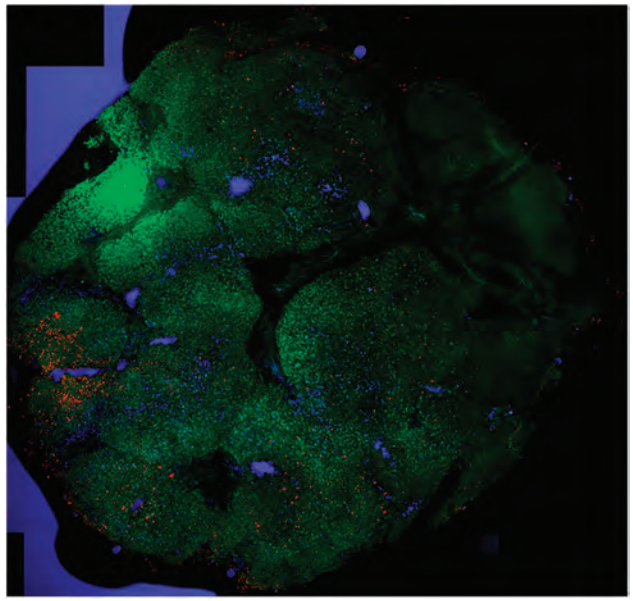
Background: Precision Cut Liver Slice (PCLS) is a human tissue-derived 3D culture that preserves native liver microarchitecture and all resident cell types. As an ex vivo model, PCLS offers a promising alternative to animal studies, aligning with the recent NIH and FDA initiatives to reduce animal use. Through iterative refinement, we have extended PCLS viability in culture to 14 days. However, the cellular viability, function, and dynamic changes over time remain incompletely characterized. **Methods:** We procured liver tissue from healthy and diseased patients enrolled in the End-Stage Liver Disease Patient Registry and developed a protocol to generate PCLS capable of sustained culture for 14 days. We evaluated structural and functional changes through serial histology, gene expression profiling, whole-tissue viability assay, extracellular matrix (ECM) staining, and metabolic analysis using Seahorse assay. **Results:** PCLS from both normal and diseased liver maintained largely intact morphology throughout the 14-day culture period. Immunohistochemistry confirmed the preservation of all liver parenchymal and nonparenchymal liver cells. An innovative whole tissue imaging using live/dead differential staining showed $>85\%$ of viability at day 7 and $>65\%$ at day 14, with cell death initiating preferentially at the tissue periphery (Fig 1). Serial histological analysis revealed progressive portal fibrosis in normal liver derived PCLS, reaching bridging fibrosis by day 7, indicating active mesenchymal cell remodeling. Reticulin staining confirmed the integrity of lobular ECM throughout culture. Notably, focal hepatocellular regeneration is present, leading to the formation of nascent hepatocyte clusters, emerging after day 7. Finally, functional Seahorse assays corroborated the vitality of PCLS with robust oxygen consumption measured at days 3, 6 and 9 in both healthy and cirrhotic PCLS, supporting sustained metabolic activity. **Conclusion:** Using a refined protocol, we demonstrate that PCLS from both healthy and cirrhotic livers remain viable for up to 14 days, exhibiting dynamic, reproducible changes that reflect the inherent plasticity of liver tissue in an ex vivo environment. This platform offers a robust model for studying human liver biology and diseases outside the body.



Disclosures: Denisse Rubio Cruz: Nothing to Disclose, Sofía Izunza Barba: Nothing to Disclose, Hua Xu: Nothing to Disclose, Shanshan Su: Nothing to Disclose, Sehrish Naz: Nothing to Disclose, Susmita Bhattarai: Nothing to Disclose, Xing Liu: Nothing to Disclose, Sizhe Wan: Nothing to Disclose, Imad Nasser: Nothing to Disclose, Gyongyi Szabo: CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria,

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3347 | COMBINING DIGITAL PATHOLOGY AND BIOMARKERS OFFER A TRANSLATIONAL FRAMEWORK TO QUANTIFY FIBROSIS AND LANIFIBRANOR TREATMENT RESPONSE IN A TAA-INDUCED CIRRHOSIS MODEL.

reethika Chokkakula[1] Guillaume Wettstein[2] Mathieu Petitjean[1] Arun Sanyal[3] Scott Friedman[4] Michael Cooreman[2] Pierre Broqua[2], [1]PHARMANEST, [2]Inventiva, [3]Virginia Commonwealth University, [4]Icahn School of Medicine at Mount Sinai (ISMMS)

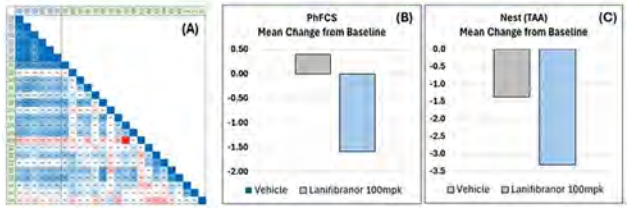
Background: Lanifibranor is a pan-PPAR agonist regulating metabolism, inflammation, and fibrosis. Its antifibrotic activity has been demonstrated in patients with noncirrhotic MASH in the NATIVE Phase 2b trial (NCT03008070). While Biomarkers are increasingly favored over histology in clinical settings, they may not fully capture tissue-level responses. We explored the benefits of combining Biomarkers with digital histological biomarkers to construct a holistic metric of lanifibranor treatment response in a TAA-induced rodent cirrhosis model. **Methods:** Rats (N = 33) received TAA for 12 weeks to induce cirrhosis, followed by a 4-day washout and 2-week treatment with vehicle (n = 12) or lanifibranor 100 mg/kg (n = 13). Nineteen biomarkers (BM) were measured using immunohistochemistry (IHC), western blot, and qPCR to capture fibrosis biology, hepatic stellate cell activity, and liver tests (AST, ALT, albumin). Livers were stained with Picrosirius Red and H&E, scanned at 40X, and analyzed using the FibroNest platform to generate continuous phenotypic fibrosis scores (Ph-FCS, 1–10), fiber morphometry scores (fine, assembled, all fibers), collagen remodeling scores, and fibrosis architecture. Spearman correlation coefficients (ρ) were measured for these 25 continuous biomarkers. The FibroNest scores and BMs that exhibited most correlation (top 2) were normalized and assembled into an equi-weighed score (NEST(TAA)) whose performance is compared to the Ph-FCS alone. **Results:** Spearman correlations coefficient (r) ranged from -0.0266 to 0.788 (Panel A). Highest correlations were found for a-SMA % area (IHC), and col1a1 mRNA (qPCR). Each biomarker performance is compared by means, standard deviations, and p-values (Tables 1-2). BMs were more sensitive to spontaneous changes during the washout, which influenced the NEST score, integrating with tissue, protein, and gene expression data. Independently from these effects, the mean change from baseline (Lani100mpk vs Vehicle) of the Ph-FCS and the NEST(TAA) were the same (-1.98; -1.94, Panel B-C)) and superior to col1a1 and s-SMA% changes alone (-0.49; -2.22). **Conclusion:** Continuous quantitative digital pathology biomarkers can be integrated with complementary molecular or functional biomarkers to provide a multifaceted view of treatment response. While this study demonstrates feasibility, further validation is needed. Differences in response kinetics and biological variability may affect the sensitivity of each modality.

Table 1: Study Biomarkers Analytical performance

		Ph-FCS		col1a1 mRNA(qPCR)		a-SMA% Positive Area (IHC)		NEST(TAA)	
n	Group	Mean	STD	Mean	STD	Mean	STD	Mean	STD
8	Baseline	4.36	1.29	2.01	0.70	9.74	3.84	5.79	0.71
12	Vehicle	4.76	0.93	1.00	0.42	5.23	2.35	4.42	0.96
13	Lanifibranor 100mg/kg	2.78	0.96	0.50	0.21	3.00	1.23	2.48	0.83

Table 2 : Group p-Values

	p-Value	p-Value	p-Value	p-Value
Baseline | Vehicle	0.466	0.008	0.006	0.004
Vehicle | Lanifibranor 100mpk	0.000	0.005	0.026	0.000



Disclosures: reethika Chokkakula: Nothing to Disclose, Guillaume Wettstein: Nothing to Disclose, Mathieu Petitjean: PHARMANEST INC: Employee, PHARMANEST INC: Stock – privately held company, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (< 5K), Terns (< 5K), Merck (< 5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (< 5K),: Consultant, Novo Nordisk: Consultant, Regeneron (< 5K), Alnylam (< 5K), Akero (< 5K),: Consultant, Tern (< 5K), Histoindex (< 5K), Corcept (< 5K),: Consultant, Path AI (< 5K), Genfit (< 5K), Mediar (< 5K),: Consultant, Satellite Bio (< 5K), Echosens (< 5K), Abbott (< 5K),: Consultant, Promed (< 5K), Glaxo Smith Kline (~11K), Arrowhead (< 5K): Consultant, Zydus (> 60K), Boston Pharmaceutical (< 5K), Myovent (< 5K),: Consultant, Variant (< 5K), Cascade (< 5K), Northsea (< 5K): Consultant, Gilead,

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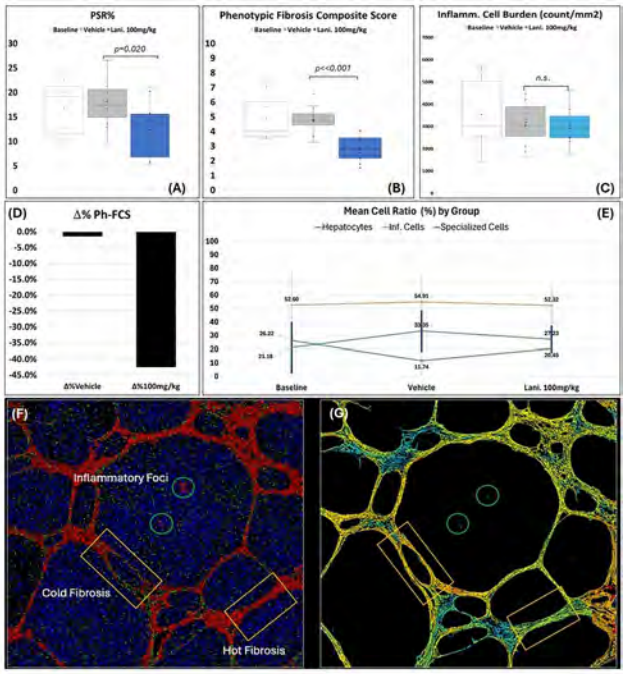
Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Scott Friedman: Nothing to Disclose, Michael Cooreman: Nothing to Disclose, Pierre Broqua: Nothing to Disclose

3348 | HIGH-RESOLUTION DIGITAL PATHOLOGY DEMONSTRATES ANTIFIBROTIC AND ANTI-INFLAMMATORY EFFECTS OF LANIFIBRANOR IN THERAPEUTIC INTERVENTIONS USING TAA-INDUCED CIRRHOTIC RODENT MODELS.

Guillaume Wettstein[1] reethika Chokkakula[2] Louis Petitjean[2] Arun Sanyal[3] Scott Friedman[4] Michael Cooreman[1] Pierre Broqua[1], [1]Inventiva, [2]Pharmanest, [3]Virginia Commonwealth University, [4]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Histological staging in MASH is semi-quantitative categorical and limited by observer variability. To address this limitation continuous digital pathology biomarkers were applied to assess the antifibrotic and anti-inflammatory effects of lanifibranor, a pan-PPAR agonist (PPARα, δ, γ), in a therapeutic rat model of advanced liver cirrhosis due to thioacetamide (TAA). **Methods:** TAA-induced cirrhosis was established over 12 weeks in rats (N = 33), followed by a 4-day washout and 2-week treatment with either vehicle (n = 12) or lanifibranor 100 mg/kg (n = 13). Liver tissues were stained with Picrosirius Red (PSR) and H&E, scanned at 40X, and analyzed by: (1) conventional PSR % image quantification; (2) FibroNest™ platform for high-resolution phenotypic fibrosis scores (Ph-FCS, scale 1–10) and ~100 histological features (qFTs); and (3) quantitative tissue panels measuring healthy hepatocytes, immune and specialized cells via burden (count/mm²) and proportion (% of total cells), based on published methods (DOI: 10.1126/scitranslmed.add3949; 10.3390/ijms24108494). **Results:** Ph-FCS showed greater sensitivity than PSR% in tracking fibrosis severity and treatment response, with lower susceptibility to spontaneous regression during washout (Panels A,B). At 100 mg/kg, vehicle-corrected Ph-FCS showed significant fibrosis reduction (−41.8%, Panel D). The AI classifier used for feature extraction achieved 85–89% accuracy against > 15k annotated cells. Cell burden and percentage ratios are only marginally affected (panels C and E). Notably, the digital layering of fibrosis and inflammation (panels F–G) enabled the identification of faint, low-stoichiometry fibers associated with inflammatory foci, as well as distinct “hot” zones (areas of high immune- cells burden with partially established fibrosis) and “cold” zones (regions of low immune cells burden with established fibrosis). These spatial features add meaningful context to the interpretation of therapeutic effects. **Conclusion:** Lanifibranor showed strong antifibrotic and anti-inflammatory activity in a therapeutic cirrhosis model. Digital pathology biomarkers, including Ph-FCS and cellular panels, provided continuous, high-resolution metrics that outperform traditional readouts. These findings position digital pathology as a powerful translational tool to quantify therapeutic response and advance antifibrotic drug development.



Disclosures: Guillaume Wettstein: Nothing to Disclose, reethika Chokkakula: Nothing to Disclose, Louis Petitjean: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (< 5K), Terns (< 5K), Merck (< 5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (< 5K),: Consultant, Novo Nordisk: Consultant, Regeneron (< 5K), Alnylam (< 5K), Akero (< 5K),: Consultant, Tern (< 5K), Histoindex (< 5K), Corcept (< 5K),: Consultant, Path AI (< 5K), Genfit (< 5K), Mediar (< 5K),: Consultant, Satellite Bio (< 5K), Echosens (< 5K), Abbott (< 5K),: Consultant, Promed (< 5K), Glaxo Smith Kline (~11K), Arrowhead (< 5K): Consultant, Zydus (> 60K), Boston Pharmaceutical (< 5K), Myovent (< 5K),: Consultant, Variant (< 5K), Cascade (< 5K), Northsea

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3349 | LABORATORY AND ELASTOGRAPHY CHARACTERISTICS OF AT-RISK CLINICALLY SIGNIFICANT PORTAL HYPERTENSION (CSPH) IN THE UNITED STATES

Ritik Mahaveer Goyal[1] Apoorva Doshi[2] Sameer Rao[3] Komal Arora[4] Muhammed Maan[3] Paul Gaglio[3], [1]Rutgers New Jersey Medical School, [2]University of Alabama at Birmingham, [3]Rutgers NJMS, [4]NYMC/St Clare & St Mary's Hospital

Background: Clinically significant portal hypertension (CSPH) marks a critical transition in the course of chronic liver disease. Per Baveno VII criteria, CSPH can be reliably ruled out in individuals with liver stiffness measurement (LSM) <15 kPa and platelet count >150,000/μL. However, patients with compensated advanced chronic liver disease (cACLD) who fall outside these parameters are considered at increased risk and warrant further evaluation. This study aimed to describe the laboratory and elastographic profiles of individuals at risk for CSPH using a nationally representative U.S. sample. **Methods:** We utilized data from adults who underwent complete transient elastography (TE) as part of the National Health and Nutrition Examination Survey (NHANES) between 2017 and March 2020. Based on Baveno VII criteria, participants were categorized into two groups: "rule-out CSPH" (LSM <15 kPa and platelet count >150,000/μL) and "at-risk CSPH" (LSM ≥15 kPa or LSM <15 kPa with platelets <150,000/μL). Categorical and continuous variables were compared using chi-square and ANOVA tests, respectively. **Results:** Among 7,847 adults with complete TE data, 7,479 (95.3%) were classified as rule-out CSPH, while 368 (4.7%) were considered at-risk CSPH. Compared to the rule-out group, the at-risk CSPH group had significantly lower mean levels of total cholesterol (179.6 vs. 187.1 mg/dL, $p<0.05$), LDL (100.1 vs. 109.9 mg/dL, $p<0.05$), and HDL (50.7 vs. 53.7 mg/dL, $p<0.05$). No significant difference was noted in triglyceride levels ($p=0.83$). The at-risk group had significantly lower platelet counts (169.9 vs. 251.8 $\times10^3$/μL, $p<0.001$), higher ALT (29.97 vs. 22.38 IU/L, $p<0.001$), AST (30.02 vs. 21.39 IU/L, $p<0.001$), ALP (79.5 vs. 75.0 IU/L, $p<0.05$), and total bilirubin levels (0.56 vs. 0.47 mg/dL, $p<0.001$). Serum creatinine was higher (0.97 vs. 0.87 mg/dL, $p<0.05$), though serum sodium levels were not significantly different. CAP scores were elevated (294.6 vs. 261.7 dB/m, $p<0.001$), and mean LSM was significantly higher (15.98 vs. 5.26 kPa, $p<0.001$) in the at-risk group. **Conclusion:** Individuals at risk for CSPH demonstrated distinct biochemical and elastographic abnormalities, including elevated liver enzymes, higher CAP and LSM values, and significantly lower platelet counts. These findings support the need for closer monitoring and potential early intervention in this subgroup, many of whom may be undiagnosed or under-recognized in clinical practice.

Table: Laboratory and Elastography characteristics of patients with CSPH ruled out and at-risk CSPH

Laboratory Values	LSM<15kPa and Platelet count >150,000/uL (CSPH ruled out) (N=7,479)	LSM>15kPa and LSM < 15kPa + Platelet count ≤150,000/uL (at-risk CSPH) (N=368)	p-value
Total Cholesterol (±SE) (in mg/dL)	187.12(±1.13)	179.64 (±3.38)	<0.05
LDL (±SE) (in mg/dL)	109.85 (±1.03)	100.1 (±4.1)	<0.05
HDL (±SE) (in mg/dL)	53.75 (±0.43)	50.73 (±0.87)	<.05
TG (±SE) (in mg/dL)	109.86 (±2.64)	111.34 (±6.71)	0.83
Hemoglobin (±SE) (in g/dL)	14.22 (±0.05)	14.31 (±0.12)	0.45
Platelet Count (±SE) (x 1000/uL)	251.76 (±1.64)	169.92 (±3.91)	<.001
Serum ALT (±SE) (in IU/L)	22.38 (±0.3)	29.97 (±1.55)	<.001
Serum AST (±SE) (in IU/L)	21.39 (±0.2)	30.02 (±1.59)	<.001
Serum ALP (±SE) (in IU/L)	75.07 (±0.51)	79.51 (±1.22)	<.05
Serum Total Bilirubin(±SE) (in mg/dL)	0.47(±0.01)	0.56 (±0.02)	<.001
Serum Sodium(±SE) (in mmol/dL)	140.5(±0.3)	140.21 (±0.27)	0.13
Serum Creatinine (±SE) (in mg/dL)	0.87 (±0.01)	0.97 (±0.02)	<.05
CAP (±SE)	261.67 (± 1.4)	294.69 (±5.7)	<.001
LSM (±SE)	5.26 (± 0.05)	15.98 (±1.18)	<.001

Abbreviations: LDL: low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglycerides; ALT: Alanine aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline phosphatase; CAP: Controlled attenuation parameter; LSM: Liver stiffness measurement

Disclosures: Ritik Mahaveer Goyal: Nothing to Disclose, Apoorva Doshi: Nothing to Disclose, Sameer Rao: Nothing to Disclose, Komal Arora: Nothing to Disclose, Muhammed Maan: Nothing to Disclose, Paul Gaglio: Nothing to Disclose, Nothing to Disclose

3350 | FGF-21 AGONISM BLOCKS THE ABILITY OF HUMAN PALMITATE STIMULATED HEPATOCYTES TO ACTIVATE HUMAN HSC IN A KLOTHO DEPENDENT MANNER

Suyavaran Arumugam[1] Xinshou Ouyang[2] Wajahat Mehal[2], [1]Yale University, [2]Section for Digestive diseases, Yale School of Medicine

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Background: Fibroblast growth factor 21 (FGF-21) is a hepatokine with pleotropic biological effects and strong evidence for anti-fibrotic effects in clinical trials of subjects with MASH with F2-F3 and F4 fibrosis. FGF-21 agonism is likely having anti-fibrotic effects due to metabolic effects on hepatocytes, but direct anti-fibrotic effects of FGF-21 on primary human HSC in the context of MASH have not been established. Our goal was to test if FGF-21 agonism can directly block activation of primary human HSC in a MASH relevant model. **Methods:** We used a primary human hepatocyte and HSC sandwich culture in which the hepatocytes were plated on to collagen coated cover slips (20mm) in 12 well culture plates, treated with palmitate (200uM) for 16hrs to induce steatosis. Fresh primary HSC in collagen (0.01% in DMEM pH 7.4) suspension were layered on top and allowed to set for 2 hrs. The co-culture sandwich was treated with human FGF-21 (hFGF-21) at 400ng/ml. Post 24hrs, HSC activation in co-culture was examined by immuno-staining for a-SMA. To ascertain the specificity of the FGF-21 effect, the HSC were knocked down for the co-receptor β-klotho which is essential for FGF signaling (24 hrs). Knockdown was achieved by KLB silencer select siRNA for 24 hrs and confirmed by qPCR. The knocked down HSC in collagen suspension were then layered onto hepatocytes in collagen sandwich with prior palmitate (200uM) exposure. Following 24 hrs in co-culture the coverslips were immuno-stained for a-SMA. **Results:** Exposure of hepatocytes to palmitate resulted in activation of primary human HSC in co-culture, and this was significantly reduced by treatment with hFGF-21 (5 fold decrease; ****$P < 0.0001$) (Fig 1A). Knockdown on of β-klotho on HSC alone prior to co-culture resulted in a loss of the ability of FGF-21 to block HSC activation in co-culture with steatotic hepatocytes. **Conclusion:** hFGF-21 can block activation of primary human HSC stimulated by steatotic hepatocytes in a FGF – β-klotho receptor dependent manner. This provides experimental support for the premise that FGF-21 has a direct anti-fibrotic effect on human HSC, and supports the strong anti-fibrotic effects seen in MASH clinical trials.

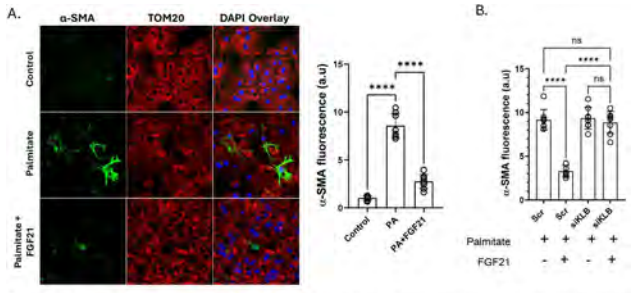

Figure 1. A. Primary human hepatocyte – HSC collagen sandwich culture, subjected to palmitate (200μM) with or without FGF21 (400ng/ml) for 24 hrs and immunostained for α-SMA and TOM20 (N=3) (****P<0.001) **B.** Quantification of α-SMA in the hepatocyte-HSC coculture in which the HSC are either siRNA knocked down for β-klotho (siKLB) or scramble (Scr) control and exposed to palmitate (200μM) with or without FGF21 (400ng/ml) for 24 hrs and immunostained for α-SMA and TOM20 (N=3) (****P<0.001).

Disclosures: Suyavaran Arumugam: Nothing to Disclose, Xinshou Ouyang: Nothing to Disclose, Wajahat Mehal: Nothing to Disclose, Nothing to Disclose

3351 | THE DEUBIQUITINASE MYSM1 STABILIZES GSN TO EXACERBATE LIVER FIBROSIS BY INHIBITING HEPATOCYTE AUTOPHAGY

Han Ding[1] Le Wang[1] Songbo Zhao[1] Wanhua Ren[1] Qiang Zhu[1], [1]Shandong Provincial Hospital Affiliated to Shandong First Medical University

Background: Hepatocyte autophagy provides resistance to liver fibrosis. Deubiquitinases contribute to autophagy through modulation of the ubiquitination status of autophagy-related proteins. Myb-like SWIRM and MPN domains 1 (MYSM1), a histone H2A deubiquitinase, is upregulated in hepatocellular carcinoma (HCC); however, its impact on liver fibrosis remains unclear. Gelsolin (GSN) inhibits autophagosome formation by regulating actin depolymerization and has been demonstrated to interact with MYSM1 via CoIP mass spectrometry. This study investigates whether MYSM1 could promote the progression of liver fibrosis by regulating GSN to affect autophagy. **Methods:** Normal and fibrotic human liver samples were obtained. Mice primary hepatocytes were isolated. This study evaluated the relationship between MYSM1, GSN, hepatocyte autophagy, and liver fibrosis through immunohistochemistry, qRT-PCR, flow cytometry, immunofluorescence staining, Co-IP, transmission electron microscopy, and WB techniques. The study used MYSM1 hepatocyte knockout mice to investigate the function of MYSM1 in liver fibrosis. Additionally, mouse models with hepatocyte-specific MYSM1 overexpression and GSN knockdown were generated through the injection of AAV8-TBG-MYSM1 and AAV8-TBG-sh-GSN viruses, respectively. Liver fibrosis induced by carbon tetrachloride and nonalcoholic steatohepatitis induced by methionine-choline deficiency models were established. HEK293T cells underwent transfection with MYSM1 and ubiquitin mutant plasmids to examine the effect of MYSM1 on GSN deubiquitination. **Results:** Single-cell transcriptomic analysis revealed that MYSM1 is predominantly expressed in hepatocytes within the liver. During liver fibrosis, the expression of MYSM1 in hepatocytes significantly increased, correlating with both the severity of fibrosis and the degree of autophagy impairment. In vivo studies demonstrated that the deletion of MYSM1 reduced the accumulation of extracellular matrix and enhanced autophagy. Moreover, MYSM1 deletion resulted in decreased GSN expression. In contrast, overexpression of GSN ameliorated these effects. Co-IP mass spectrometry

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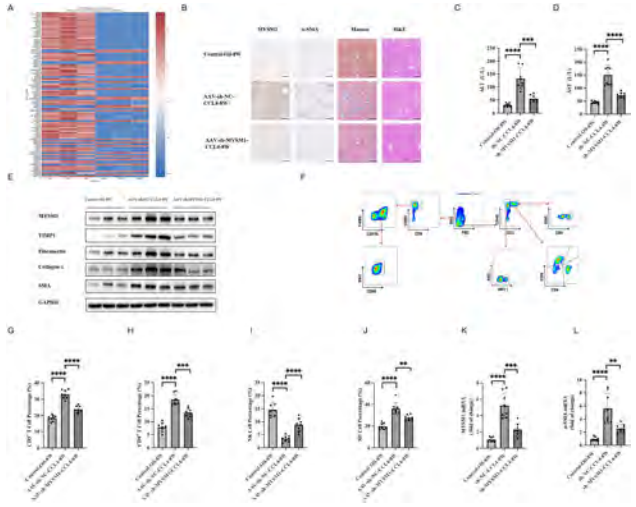
confirmed an interaction between MYSM1 and GSN, indicating that MYSM1 stabilizes GSN by inhibiting its ubiquitination. Overexpression of MYSM1 notably decreased the levels of K29-linked ubiquitination on GSN. Additionally, GSN was found to hinder autophagy progression by blocking autophagosome formation and disrupting the autophagic flux in hepatocytes. **Conclusion:** MYSM1 promotes liver fibrosis by inhibiting the ubiquitination of GSN and the associated autophagy in hepatocytes. This study elucidates the mechanism and function of MYSM1 in the progression of liver fibrosis, providing a theoretical basis for the development of potential early interventions.



Disclosures: Han Ding: Nothing to Disclose, Le Wang: Nothing to Disclose, Songbo Zhao: Nothing to Disclose, Wanhua Ren: Nothing to Disclose, Qiang Zhu: Nothing to Disclose

3352 | SELECTIVELY TARGETING HEPATIC STELLATE CELLS-DERIVED MICROFIBRIL-ASSOCIATED GLYCOPROTEIN 4 RETARDS LIVER FIBROSIS

Wenyue Wu[1] Wen Zhang[1] Hong Li[1] Haodong Ma[1] Ziyan Pan[1] Caihong Wang[1] Yameng Sun[1] Xuzhen Yan[1] Aiting Yang[1] Wei Chen[1] Hong You[2], [1]Beijing Friendship Hospital, Capital Medical University, [2]Capital Medical University

Background: Microfibril-associated glycoprotein 4 (MFAP-4) belongs to the fibrinogen-related protein superfamily and is a vital extracellular matrix (ECM) protein. However, the role of MFAP-4 in the pathogenesis of liver fibrosis has yet to be elucidated. **Methods:** Liver biopsies from cirrhotic patients with diverse etiologies and multiple murine models of liver fibrosis were used to investigate the expression pattern and cellular source of MFAP-4. The *in vivo* effects of silencing *Mfap4* in hepatic stellate cells (HSCs) were examined using adeno-associated virus vector (serotype 6) containing short-hairpin RNAs targeting *Mfap4*, under the regulatory control of either U6 ($U6^{siMfap4}$) or glial fibrillary acidic protein (GFAP; $GFAP^{siMfap4}$) promoter, in mouse models of carbon tetrachloride (CCl_4) or bile duct ligation (BDL)-induced liver fibrosis. The function of $MFAP4^+$ HSCs was assessed in Mfap4-Linker-tdTomato-P2A-DTR ($Mfap4^{DTR}$) mice by diphtheria toxin (DT)-mediated cell ablation, following CCl_4 or BDL. Histological staining, serum biochemistry, bulk RNA sequencing, and *in vitro* analyses were conducted to elucidate the roles of MFAP-4 in liver fibrogenesis. **Results:** MFAP-4 was predominantly enriched in activated HSCs and significantly upregulated in advanced liver fibrosis in both humans and mice. HSC-specific suppression of *Mfap4* in $U6^{siMfap4}$ and $GFAP^{siMfap4}$ mice markedly attenuated fibrosis and intrahepatic inflammation subjected to CCl_4 treatment or BDL operation, as indicated by downregulation of α-SMA, COL-1 and elastin, along with reduced serum ALT and AST levels. Mechanistically, transcriptomic profiling revealed that Mfap4 deficiency resulted in decreased expression of fibrosis-specific matrisome genes (LFMGs). Kyoto Encyclopedia of Genes and Genomes analysis identified notable downregulation of pathways related to ECM remodeling and focal adhesion in both $U6^{siMfap4}$ and $GFAP^{siMfap4}$ mice. Additionally, $Mfap4^{DTR}$ mice treated with low-dose DT exhibited marked ablation of $MFAP4^+$ HSCs, significant suppression of LFMGs, and attenuation of liver fibrosis. In vitro results demonstrated that *MFAP4* overexpression in human HSCs promoted the aggregation of elastin globules in two-dimensional culture conditions and significantly enhanced collagen gel contraction in three-dimensional environments. **Conclusion:** Selectively targeting HSC-derived MFAP4 significantly attenuates liver fibrosis, representing a promising therapeutic strategy for liver fibrosis.

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3353 | THE ROLES OF THBS2-SPP1 AXIS IN HEPATIC STELLATE CELLS ACTIVATION AND LIVER FIBROGENESIS

Hong Li[1] Ning Zhang[1] Weng Zhang[1] Wenyue Wu[1] Ziyan Pan[1] Haodong Ma[1] Caihong Wang[1] Qi Han[1] Xuzhen Yan[1] Aiting Yang[1] Hong You[1] Wei Chen[1], [1]Beijing Friendship Hospital, Capital Medical University

Background: Thrombospondin-2 (THBS2) is markedly upregulated in fibrotic livers and correlates with fibrosis

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stage, independent of etiology. This study aimed to elucidate the role and underlying mechanisms of hepatic stellate cell (HSC)-derived THBS2 in HSC activation and the progression of liver fibrosis. **Methods:** We generated HSC-specific *Thbs2* knockout mice (*Thbs2*$^{\Delta HSC}$) and HSC-specific human *THBS2* knock-in mice (h*THBS2*$^{KI\ HSC}$), subjecting them to intraperitoneal carbon tetrachloride (CCl_4) injection and bile duct ligation (BDL) to induce liver fibrosis. The involvement of the THBS2-SPP1 axis in fibrogenesis was interrogated using dual targeting strategies: extracellular SPP1 neutralization via intraperitoneal administration of inVivoMAb anti-mouse SPP1 antibody, and intracellular SPP1 suppression using AAV6-GFAP-sh*Spp1*, with parallel in vitro validation. **Results:** *Thbs2*$^{\Delta HSC}$ mice exhibited significantly reduced hepatic inflammation and fibrosis in both CCl_4- and BDL-induced models. Conversely, h*THBS2*$^{KI\ HSC}$ mice displayed markedly aggravated hepatic inflammation and fibrotic progression. Mechanistic studies revealed that *Thbs2* knockdown in HSCs substantially suppressed the expression of the pro-fibrotic effector Spp1, while *THBS2* overexpression robustly enhanced both SPP1 expression and its secretion—findings consistently validated in vitro. Notably, molecular interaction assays confirmed that THBS2 directly interacts with SPP1 in a dimeric configuration. Furthermore, we found intraperitoneal administration of inVivoMAb anti-mouse SPP1 neutralizing antibody and AAV6-GFAP-shSPP1-mediated *Spp1* silencing significantly attenuated fibrotic progression in CCl_4-treated h*THBS2*$^{KI\ HSC}$ mice, demonstrating distinct anti-fibrotic efficacy through coordinated blockade of extracellular SPP1 signaling and intracellular SPP1 biosynthesis. Additionally, we identified a novel THBS2 inhibitor through integrated virtual drug screening and surface plasmon resonance (SPR) validation. Pharmacodynamic evaluations confirmed the compound's potent anti-fibrotic effects in both CCl_4- and 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC)-induced liver fibrosis mouse models, with significant improvements in histopathological features. **Conclusion:** HSC-derived THBS2 promotes liver fibrogenesis by regulating SPP1 expression and secretion. Targeting HSC-derived THBS2 can mitigate liver fibrosis. Further studies are warranted to investigate the specific mechanisms by which THBS2 regulates SPP1 in HSCs. **Disclosures:** Hong Li: Nothing to Disclose, Ning Zhang: Nothing to Disclose, Weng Zhang: Nothing to Disclose, Wenyue Wu: Nothing to Disclose, Ziyan Pan: Nothing to Disclose, Haodong Ma: Nothing to Disclose, Caihong Wang: Nothing to Disclose, Qi Han: Nothing to Disclose, Xuzhen Yan: Nothing to Disclose, Aiting Yang: Nothing to Disclose, Hong You: Nothing to Disclose, Wei Chen: Nothing to Disclose

3354 | HETEROZYGOUS G153D MUTATION OF LYSYL OXIDASE LIKE-1 GENE IS ASSOCIATED WITH LIVER FIBROSIS NON-REGRESSION

Wen Zhang[1] Wenyue Wu[2] Hong Li[2] Ning Zhang[2] Ziyan Pan[2] Haodong Ma[2] Caihong Wang[2] Xuzhen Yan[2] Aiting Yang[2] Wei Chen[2] Hong You[3], [1]Beijing Friendship Hospital, Capital Medical Univerity, [2]Beijing Friendship Hospital, Capital Medical University, [3]Capital Medical University

Background: Lysyl oxidase like-1 (LOXL1) is a copper-dependent enzyme crucial for extracellular matrix (ECM) cross-linking, thereby influencing tissue remodeling and fibrosis. While LOXL1 mutations are known to enhance ECM cross-linking in glaucoma, their role in liver fibrosis remains unclear. **Methods:** Genomic DNA from 168 patients with chronic hepatitis B virus (CHB)-related liver fibrosis was analyzed for LOXL1 single nucleotide polymorphisms (SNPs). Clinical characteristics and Ishak scores were compared between patients with and without LOXL1 mutations, both before and after antiviral treatment (AVT). In vivo, heterozygous Loxl1 G153D mutant mice were subjected to CCl_4-induced liver fibrosis. Transcriptome sequencing was performed during both the progression and regression phases to elucidate underlying mechanisms. In vitro experiments were conducted to investigate the biological effects of the LOXL1 G153D mutation. **Results:** Patients carrying the heterozygous LOXL1 G153D mutation exhibited significantly reduced fibrosis regression after 78 weeks of AVT (reversal rates: 26.3% in mutants ***vs***. 52.4% in non-mutants, $\boldsymbol{p} = 0.025$). Compared to non-mutant patients post-AVT, those with the mutation showed higher serum ALT and GGT levels, increased liver stiffness measurements (LSM), and elevated Ishak scores. In vivo, Loxl1 G153D mutant mice displayed more severe hepatic inflammatory infiltration, lipid accumulation, and pronounced perisinusoidal fibrosis during the spontaneous regression phase of CCl_4-induced liver fibrosis. Mechanistically, metabolism-related pathways were predominantly activated during fibrosis progression, while inflammation-related pathways were enriched during regression. In hepatic stellate cells (HSCs) harboring the LOXL1 G153D mutation, LOXL1 protein was significantly translocated to the cell membrane and extracellular space, markedly enhancing HSC migration and contractility. These findings suggest that the LOXL1 G153D mutation promotes extracellular secretion of LOXL1, facilitates intercellular communication, and increases ECM protein cross-linking and deposition, thereby impairing fibrosis regression. **Conclusion:** Our study demonstrates that the heterozygous LOXL1 G153D mutation is associated with impaired liver fibrosis regression following AVT in CHB patients. Furthermore,

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we elucidate the underlying mechanisms, highlighting a potential genetic basis for suboptimal treatment response in this population.

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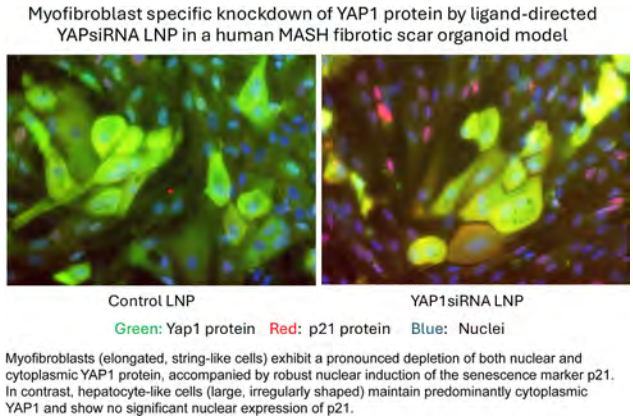
3355 | A MASH PATIENT LIVER–DERIVED 3D FIBROSIS MODEL FOR THE DESIGN AND VALIDATION OF CANDIDATE THERAPEUTIC LIPID NANOPARTICLES

Tobias Raabe[1] Dylan Haseman[1] Andy Liu[1] Khushal Bantu[1] Vladimir Muzykantov[1] Drew Weissman[1] Jilian Melamed[1] Jia Nong[1], [1]University of Pennsylvania

Background: There is an urgent need for physiologically relevant human *in vitro* models of MASH (Metabolic Dysfunction-Associated Steatohepatitis) that capture the full complexity of liver fibrosis, especially as MASH is highly prevalent and deadly, yet without effective therapies. Key pathological features—such as hepatocyte senescence, hepatocyte ballooning, bridging fibrosis, and pro-fibrotic TREM2$^+$ scar-associated macrophages—are poorly recapitulated in current rodent models and even in some non-human primate systems. Moreover, the development of cell-type-specific therapeutic strategies is hindered by the lack of platforms suitable for efficient delivery and validation of targeted therapies within fibrotic tissue. **Methods:** We established a human 3D MASH fibrotic scar model by co-culturing hepatic organoids derived from explant MASH liver tissue of a 53-year-old male undergoing liver transplantation (McCarron et al., Hepatology, 2021) with primary human hepatic stellate cells/myofibroblasts and peripheral blood–derived macrophages. This triple co-culture system reconstructs key fibrotic components of human MASH. We then performed a targeted lipid nanoparticle (LNP) screen to identify formulations capable of selectively delivering mRNAs or siRNAs to hepatocytes, myofibroblasts, and macrophages within the organoid model. **Results:** In our 3D MASH fibrotic scar organoid model, hepatic organoids derived from MASH patient liver—but not from healthy donor liver—displayed epigenetically preserved hallmark features of human MASH: Immunofluorescence microscopy shows hepatocyte ballooning, >3-fold upregulation of nuclear p21 (a marker of senescence), strong myofibroblast proliferation, and extensive accumulation of scar-associated TREM2$^+$ macrophages localized to activated myofibroblasts. Further, single cell RNA sequencing confirms this and additionally reveals unprecedented transcriptome similarity to the fibrotic niche in human MASH livers. Our LNP screen identified cell-type-specific delivery vehicles for all three cell types. A lead formulation targeting myofibroblasts, when loaded with anti-YAP1 siRNA, achieved $>95\%$ knockdown of nuclear YAP1, suppressed myofibroblast proliferation, and induced senescence—without observable off-target effects on hepatocytes or macrophages. **Conclusion:** We present a robust human MASH liver derived 3D fibrotic scar organoid model that enables high-efficiency, cell-type-selective genome editing using LNPs. This system provides a powerful platform for screening and validating targeted therapeutics, supporting the development of precision interventions that modulate hepatocyte, myofibroblast, or macrophage function while minimizing off-target effects. This approach has broad potential to accelerate translational research in MASH and other fibrotic liver diseases.



Disclosures: Tobias Raabe: Nothing to Disclose, Dylan Haseman: Nothing to Disclose, Andy Liu: Nothing to Disclose, Khushal Bantu: Nothing to Disclose, Vladimir Muzykantov: Nothing to Disclose, Drew Weissman: Nothing to Disclose, Jilian Melamed: Nothing to Disclose, Jia Nong: Nothing to Disclose

3356 | MACHINE LEARNING-BASED FUSION OF CONTRAST-ENHANCED UPPER ABDOMINAL MRI SIGNATURES AND CLINICAL SCORES IMPROVES PREDICTION OF 1-YEAR MORTALITY IN ACUTELY DECOMPENSATED CIRRHOSIS

Qingren Cao[1] Lan Zhu[1] Chenxi Zhang[1] Juhua Li[2] Baoyan An[1] Dandan Weng[3] Minghao Cai[1] Zhuping Qian[1] Ziqiang Li[1] Ruokun Li[1] Haiguang Xin[1] Zhujun Cao[1] Qing Xie[1], [1]Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, [2]Wuwei People's Hospital, [3]Yuyao People's Hospital

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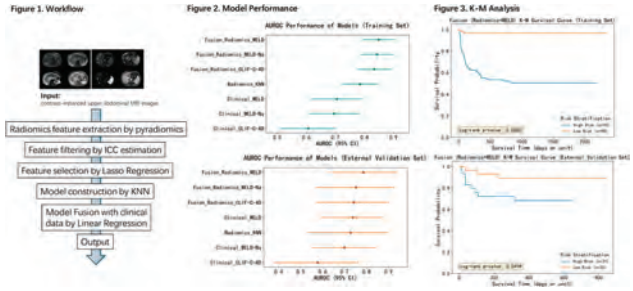
Background: Patients with acutely decompensated cirrhosis (ADC) have poor outcome with 1-year mortality ranging from 20% to 63%. Traditional prognostic tools (CLIF-C AD, MELD-Na, MELD) demonstrate limited accuracy in predicting long-term mortality. Radiomics from contrast-enhanced upper abdominal MRI provides novel quantitative biomarkers. This study developed and validated a machine learning-based fusion model, combining liver and spleen radiomics with clinical prognostic scores, to enhance the predictive accuracy of 1-year mortality in patients with ADC. **Methods:** The current study was an imaging investigation of the RJH (Ruijin Hospital) cohort of adult patients with cirrhosis non-electively admitted for ADC between 2016 and 2023 (RJH-radiomics). Patients who were free of acute-on-chronic liver failure at the time of admission and underwent contrast-enhanced upper abdominal MRI (Philips) during the index admission were included for analysis. In addition to baseline clinical and lab data, sequences from T1, T2, diffusion weighted imaging, and portal phases were collected for features extraction. Patients were randomly divided in a ratio of 8:2 to train and test a machine-learning MRI radiomics model (termed RJH-ADC-MRI score) for predicting 1-year mortality. After training the radiomics model using KNN, the commonly used clinical models (MELD, MELD-Na, CLIF-C AD) were fused with the radiomics model using logistic regression (Figure 1). Furthermore, Kaplan-Meier survival analysis was performed for the fused model. An independent cohort was used for validating the performance of RJH-ADC-MRI score. **Results:** A total of 318 patients were included for this analysis (mean age 57 ± 10.3, 67% male, 45% HBV, median CLIF-C AD 45.77 [39.57, 51.32]). By 1-year follow-up, 75 patients died or received liver transplantation (LT), and the remaining 243 survived without LT. RJH-ADC-MRI score was developed based on four identified MRI features (three derived from the liver and one from the spleen) in the training set with 197 patients.

The Area Under the Curve (AUC) in predicting 1-year mortality of RJH-ADC-MRI score was 0.78, higher than that of CLIF-C AD (0.61), MELD (0.70) or MELD-Na (0.70) (P all < 0.05). Incorporating the RJH-ADC-MRI score into the commonly used models led to a further improvement in the model's predictive capabilities and reached a highest AUC of 0.85 (Figure 2). The RJH-ADC-MRI based MELD score could stratify patients into two risk groups with significantly different 1-year survival probability ($p < 0.001$) (Figure 3). These findings were successfully validated on both a test set and an independent external validation cohort ($n = 61$). **Conclusion:** Machine learning-based fusion of contrast-enhanced upper abdominal MRI signatures and clinical scores demonstrated higher accuracy in predicting 1-year mortality of patients with ADC compared to the traditional scores.



Disclosures: Qingren Cao: Nothing to Disclose, Lan Zhu: Nothing to Disclose, Chenxi Zhang: Nothing to Disclose, Juhua Li: Nothing to Disclose, Baoyan An: Nothing to Disclose, Dandan Weng: Nothing to Disclose, Minghao Cai: Nothing to Disclose, Zhuping Qian: Nothing to Disclose, Ziqiang Li: Nothing to Disclose, Ruokun Li: Nothing to Disclose, Haiguang Xin: Nothing to Disclose, Zhujun Cao: Nothing to Disclose, Qing Xie: Nothing to Disclose

3357 | CLINICAL UTILITY OF A 50% RELATIVE DECLINE IN MRI-PDFF IN PREDICTING FIBROSIS IMPROVEMENT IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Daniel Huang[1] Rohit Loomba[2] Peter Daniel[3] Ricki Bettencourt[4] Egbert Madamba[5] Harris Siddiqi[5] Lisa Richards[2] Mildred Gottwald[6] Shibao Feng[6] Maya Margalit[6], [1]National University Hospital, Singapore, [2]University of California, San Diego, [3]National University Hospital, [4]University of California San Diego, [5]MASLD Research Center, University of California San Diego, [6]89Bio

Background: MRI-proton-density-fat fraction (MRI-PDFF) response (defined as $\geq$ 30% relative decline in liver fat content on MRI-PDFF) can help to detect resolution of metabolic dysfunction-associated steatohepatitis (MASH) resolution but there are limited data on whether it can reliably predict fibrosis improvement. The association of MRI-PDFF super-response (defined as $\geq$ 50% decline in liver fat content on MRI-PDFF) with the likelihood of fibrosis regression and MASH resolution has not been systematically assessed and quantified. We examined the association between MRI-PDFF super-response and fibrosis regression and MASH resolution in a multi-center randomized placebo-controlled trial. **Methods:** This is a secondary analysis of a large, multi-center, randomized, placebo-controlled trial study that included 163 participants (64% female) with biopsy-confirmed MASH with stage 2 or 3 fibrosis who were treated for 24 weeks with either pegozafermin or placebo and underwent

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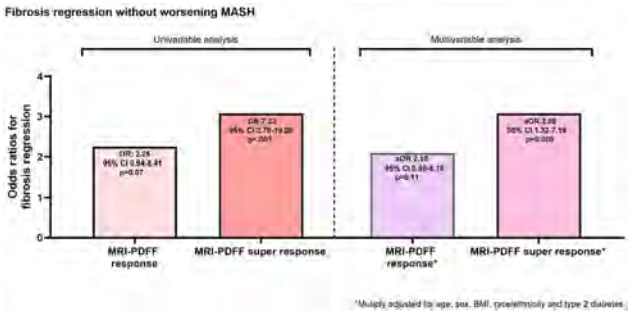
contemporaneous laboratory testing, MRI-PDFF, and liver biopsy at two time points (Loomba et al. NEJM 2024). The two *primary outcomes* were fibrosis improvement without worsening of MASH and MASH resolution with no worsening of fibrosis. We evaluated the outcomes among those with MRI-PDFF super-response and those with MRI-PDFF response. **Results:** The median (IQR) age and BMI of participants were 56.0 (48.0-62.0) years and 36.5 (32.2-40.2) kg/m^2. The proportion of patients who achieved super-response was significantly higher in participants treated with pegozafermin (pooled 15 mg, 30 mg, and 44 mg arms) versus placebo (57.8% versus 11.1%, $p < .0001$). After multivariable adjustment for age, sex, BMI, race/ethnicity, and type 2 diabetes, MRI-PDFF super response (adjusted OR 3.08, 95% CI 1.32-7.19, $p = 0.009$) remained an independent predictor of fibrosis regression without worsening MASH, but not MRI-PDFF response (adjusted OR 2.10, 95% CI 0.85-5.16, $p = 0.11$). Both MRI-PDFF response (adjusted OR 5.22, 95% CI 1.68-16.10, $p = 0.004$) and MRI-PDFF super-response (adjusted OR 7.29, 95% CI 2.68-19.78, $p < .001$) were statistically significant predictors of MASH resolution without worsening fibrosis. **Conclusion:** MRI-PDFF super-response predicts fibrosis regression without worsening MASH, and a greater likelihood of MASH resolution without worsening fibrosis than MRI-PDFF response. These data have important implications for clinical trial design in MASH and assessing dose response and dose selection for Phase 3.



Disclosures: Daniel Huang: Gilead: Consultant, Roche: Speaking and Teaching, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Peter Daniel: Nothing to Disclose, Ricki Bettencourt: Nothing to Disclose, Egbert Madamba: Nothing to Disclose, Harris Siddiqi: Nothing to Disclose, Lisa Richards: Novo Nordisk: Advisor, Madrigal: Advisor, Mildred Gottwald: 89bio: Employee, 89bio: Stock - publicly traded company, Shibao Feng: 89bio: Employee, 89bio: Stock - publicly traded company, Maya Margalit: 89bio Inc.: Stock and options holder, 89bio Inc.: Stock and options holder, 89bio Inc.: Employee, 89bio Inc.: Stock - publicly traded company

3358 | SPATIAL TRANSCRIPTOMICS REVEALS GPNMB-POSITIVE MACROPHAGES AS DRIVERS OF FIBROTIC NICHES AND PROGNOSTIC INDICATORS IN CHRONIC LIVER DISEASE

Kenji Fukumoto[1] Kazumasa Soma[1] Seiya Kato[1] Yoichi Sasaki[1] Kazuhiro Murai[1] Yuki Makino[1] Yuki Tahata[1] Yoshinobu Saito[1] Takahiro Kodama[1] Hayato Hikita[1], [1]Osaka University Graduate School of Medicine

Background: Glycoprotein non-metastatic melanoma protein B (GPNMB) is upregulated in senescence-related conditions such as obesity and aging. This study explored its role in the hepatic microenvironment of chronic liver disease and its potential as a biomarker of disease progression. **Methods:** Single-cell RNA sequencing (scRNA-seq) was conducted in two chronic liver disease mouse models— hepatocyte-specific Mcl-1 knockout (hepatocyte apoptosis-driven) and Western diet–fed (MASH) mice—as well as in liver specimens from patients with MASH, chronic hepatitis B, alcoholic hepatitis, and Fontan-associated liver disease. In vitro studies used THP-1 and HepG2 cell lines. CosMx spatial transcriptomics was performed on MASH and HCV patient tissues. Serum GPNMB levels were

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measured in 936 patients with MASLD/MASH or HCV-related liver disease to assess cancer risk, and prognostic value was analyzed in an additional 290 HCV-cirrhosis patients. **Results:** scRNA-seq analysis of liver tissues from patients with chronic hepatitis revealed that CD68-positive hepatic macrophages showed high GPNMB expression across all chronic liver disease etiologies. Spatial transcriptomics in non-tumor regions from MASH and HCV patients revealed that GPNMB-positive macrophages highly expressed genes related to lipid metabolism, phagocytosis, and the senescence-associated secretory phenotype (SASP). Hepatic stellate cells within 20 μm of these macrophages showed elevated fibrosis-related gene expression, while nearby hepatocytes expressed apoptosis-related genes. In tumor areas, GPNMB-positive macrophages upregulated genes linked to tumor progression.

In mouse models of chronic liver disease, including apoptosis-driven chronic hepatitis and diet-induced MASH, hepatic macrophages showed increased GPNMB expression versus controls. Lysosomal stress from fatty acid loading or bafilomycin enhanced GPNMB and cytokine secretion (e.g., IL-6, TNF-α) in THP-1-derived macrophages. These findings were further supported by in vitro experiments, where phagocytosis of apoptotic bodies from HepG2 cells induced GPNMB expression in THP-1-derived macrophages.

Serum GPNMB levels were an independent risk factor for liver carcinogenesis in both MASLD and HCV cohorts, with 15.4 ng/mL as an effective cutoff for risk stratification. In a separate cohort of 290 HCV-related cirrhosis patients, GPNMB levels were significantly higher in those with decompensated cirrhosis than in those with compensated cirrhosis, and levels $\geq$ 18.8 ng/mL were associated with significantly shorter overall survival without liver transplantation. **Conclusion:** GPNMB is upregulated in hepatic macrophages under lysosomal stress induced by efferocytosis and lipid accumulation, contributing to hepatic fibrosis and hepatocyte death. Serum GPNMB may serve as a novel biomarker for assessing hepatocarcinogenesis risk and prognosis in patients with chronic liver disease. **Disclosures:** Kenji Fukumoto: Nothing to Disclose, Kazumasa Soma: Nothing to Disclose, Seiya Kato: Nothing to Disclose, Yoichi Sasaki: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Yuki Makino: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Takahiro Kodama: Nothing to Disclose, Hayato Hikita: Nothing to Disclose

3359 | REGULATION OF DDX5 BY FL118 AND ITS ASSOCIATION WITH CELLULAR SENESCENCE DURING HEPATIC STELLATE CELL ACTIVATION

Thi Nga Ha[1] Hyon-Seung Yi[1], [1]Chungnam National University School of Medicine

Background: DDX5 (p68) is a DEAD-box RNA helicase that regulates transcription, RNA processing, and cell proliferation. Emerging evidence suggests that DDX5 plays a critical role in hepatic stellate cell (HSCs) activation, a key event in liver fibrosis progression. Our findings indicate that DDX5 contributes to HSCs activation via translational regulation and cellular senescence. **Methods:** We analyzed total and phosphorylated DDX5 (pDDX5) levels using antibody arrays in primary mouse HSCs (pHSCs) cultured for 1 and 4 days and in the human HSC line LX-2 following TGF-β treatment. To functionally assess DDX5, we used FL118, a small-molecule compound that binds to DDX5 and promotes its proteasome-mediated degradation. We evaluated its effects on α-SMA expression (a marker of HSCs activation) and global protein translation. **Results:** Antibody array analysis revealed an increase in total DDX5 and a reduction in pDDX5 during HSCs activation, observed both in day 4 pHSCs and TGF-β-treated LX-2 cells. TGF-β stimulation induced DDX5 expression in LX-2 cells, while in pHSCs, DDX5 expression increased initially but declined by day 7, suggesting stage-dependent regulation during activation. Public RNA-seq data confirmed DDX5 upregulation alongside ribosome biogenesis genes in LX-2 cells after TGF-β exposure, implicating DDX5 in translational enhancement during HSCs activation. Treatment with FL118 led to a marked reduction in total and phosphorylated DDX5, decreased α-SMA expression, and impaired global protein translation, supporting its antifibrotic potential via DDX5 degradation. In senescent HSCs, total DDX5 levels were reduced while pDDX5 remained unchanged, correlating with diminished protein synthesis and suggesting that DDX5 downregulation in senescence occurs independently of its phosphorylation status. **Conclusion:** DDX5 plays a pro-fibrotic role by promoting HSCs activation, likely through modulation of translation and cellular state. Its expression is dynamically regulated via post-translational mechanisms. Pharmacological targeting of DDX5 with FL118, which induces DDX5 degradation, may serve as a promising antifibrotic strategy by suppressing HSCs activation and global translation.

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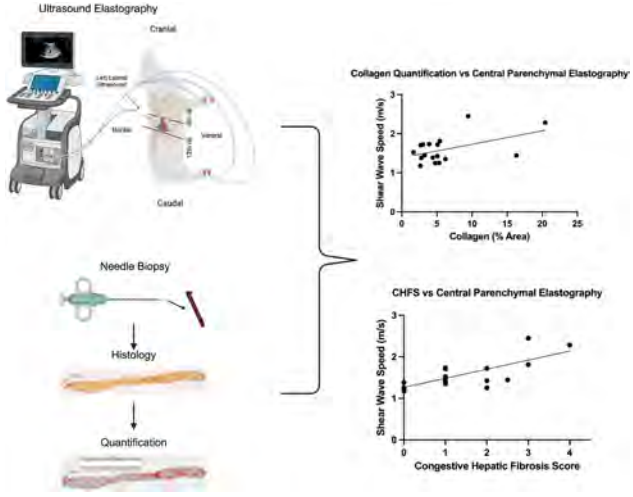
Disclosures: Thi Nga Ha: Nothing to Disclose, Hyon-Seung Yi: Nothing to Disclose

3360 | MULTIMODAL ASSESSMENT OF FONTAN-ASSOCIATED LIVER DISEASE IN A NOVEL OVINE MODEL USING ULTRASOUND AND HISTOLOGICAL QUANTIFICATION

Jennifer Kievert[1] Cameron DeShetler[1] Tatsuya Watanabe[1] Junya Matsuda[1] Fahd Taha[1] Joshua Spiess[1] Satoshi Yuhara[1] Joseph Leland[1] Syed Faizullah Hussaini[1] Jocelyhnn Zucco[1] Jingru Che[1] Rajesh Krishnamurthy[2] Aymen Naguib[3] Christopher McKee[3] Andrew Yates[3] David Brigstock[2] Sergio Carrillo[3] Christopher Breuer[1] John Kelly[1], [1]The Abigail Wexner Research Institute at Nationwide Children's Hospital, [2]Nationwide Children's Hospital, [3]Nationwide Children's Hospital

Background: Fontan Associated Liver Disease (FALD) is a universal and progressive disease in single ventricle heart patients that have undergone Fontan palliation; however, the natural history of the disease is poorly understood. This is primarily due to the inability of ultrasound elastography to distinguish between fibrosis and congestion, the infeasibility of performing longitudinal liver biopsy samples clinically, and the lack of relevant animal models. We developed a novel chronic ovine model of Fontan palliation and found significant liver fibrosis 1-year post-operation. Herein, we investigate FALD progression in the first 6 months following surgery using ultrasound elastography/doppler and liver biopsies. **Methods:** Six sheep were divided into 2 groups: complete Fontan (C-F) with both the inferior vena cava (IVC) and superior vena cava (SVC) connected to the main pulmonary artery (MPA) ($n = 3$) or incomplete Fontan (IC-F) with only the IVC to MPA connection ($n = 3$). Over 6 months, progression of liver disease was tracked through monthly ultrasound doppler/elastography, and bimonthly right liver biopsies. The biopsies were formalin fixed and histologically stained with picrosirius red for a blinded assessment of congestive hepatic fibrosis score (CHFS) and percent area of collagen. These results were compared to ultrasound elastography measurements to determine if increased stiffness accurately correlates with the degree of fibrosis. **Results:** The data reported spanned from pre-operation to 6 months post operation. There were significant increases in hepatic vein (HV) diameter (1.06 ± 0.15 cm to 1.78 ± 0.21 cm, $p < 0.001$) and IVC area (0.77 ± 0.38 cm^2 to 1.84 ± 0.65 cm^2, $p < 0.001$) for both cohorts. There was no statistical difference between cohorts for HV diameter ($p = 0.458$), however the C-F animals' IVC area increased significantly slower than the IC-F animals (0.24 cm^2/month vs 0.07 cm^2/month, $p = 0.003$). Ultrasound elastography around the central parenchymal area showed a non-significant ($p = 0.172$) increased tissue stiffness for both surgical groups (C-F:1.52 ± 0.25 m/s to 1.82 ± 0.43 m/s, IC-F: 1.3 ± 0.11 m/s to 1.68 ± 0.79 m/s). There was a nonsignificant increase in collagen quantification (3.689% to 8.89%, $p = 0.15$) and a significant increase in CHFS (0 to 1, $p = 0.018$) for both cohorts. Increases in central parenchymal stiffness had a significant positive correlation with the biopsy CHFS score (slope = 0.22, $R^2 = 0.51$, $p = 0.001$). There was a significant weakly positive trend between collagen quantification compared to central elastography (slope = 0.03, $R^2 = 0.25$, $p = 0.04$). **Conclusion:** An increase in liver stiffness was observed in both surgical cohorts; however, liver histology confirms only a mild degree of liver fibrosis. Liver elastography accurately follows FALD development in the sheep model when compared to CHFS and % area. Ongoing follow-up of these animals will lead to insights into the later period of FALD progression.



Disclosures: Jennifer Kievert: Nothing to Disclose, Cameron DeShetler: Nothing to Disclose, Tatsuya Watanabe: Nothing to Disclose, Junya Matsuda: Nothing to Disclose, Fahd Taha: Nothing to Disclose, Joshua Spiess: Nothing to Disclose, Satoshi Yuhara: Nothing to Disclose, Joseph Leland: Nothing to Disclose, Syed Faizullah Hussaini: Nothing to Disclose, Jocelyhnn Zucco: Nothing to Disclose, Jingru Che: Nothing to Disclose, Rajesh Krishnamurthy: Nothing to Disclose, Aymen Naguib: Nothing to Disclose, Christopher McKee: Nothing to Disclose, Andrew Yates: Nothing to Disclose, David Brigstock: Nothing to Disclose, Sergio Carrillo: Nothing to Disclose, Christopher Breuer: Gunze Limited: Grant/Research Support, IQVIA: DSMB member, Cytiva: Grant/Research Support, University of Zurich: Grant/Research Support, John Kelly: Nothing to Disclose

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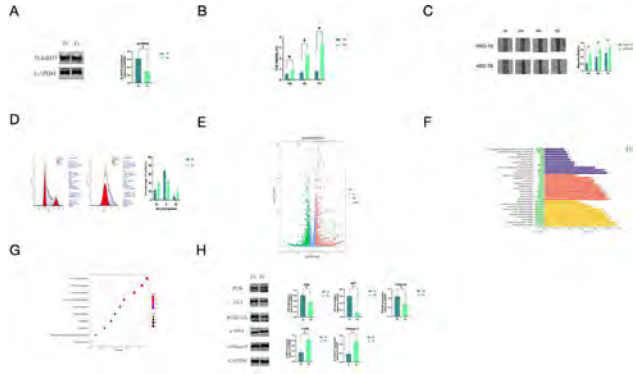
3361 | ALKBH5 AMELIORATES HEPATIC FIBROSIS BY REGULATING THE PI3K-AKT-FOXO3A SIGNALING AXIS

lingyu kong[1] Hongxin Piao[2], [1]Yanbian University, [2]Yanbian University Hospital

Background: Liver fibrosis is characterized by disruption of the liver's self-repair process, leading to excessive deposition of extracellular matrix (ECM). Abnormal activation of hepatic stellate cells (HSC) is a key factor in liver fibrosis.ALKBH5, a key protein for m6A demethylation modification, has been found to play an important regulatory role in the fibrotic process of various tissues, including pulmonary fibrosis, myocardial fibrosis, and renal fibrosis. However, its role in liver fibrosis is unclear.PI3K/AKT/FOXO3A is an important signaling axis involved in multiple biological processes, including cell growth, proliferation, differentiation, and apoptosis, and is closely related to liver fibrosis.The complex relationship between ALKBH5 and PI3K/AKT/FOXO3A and liver fibrosis needs further research. **Methods:** 1. Silencing of ALKBH5 gene in HSC cells by recombinant lentiviral transfection and determination of the transfection effect by protein imprinting assay. 2. Silencing of ALKBH5 gene in HSC cell lines, dividing the cells into HSC-T0 and HSC-T6 groups, and detection of cell proliferation by CCK8 assay, comparison of the migration ability of the cells by scratch assay, and detection of cell cycle by attrition cytometry. 3. 3. Use transcriptome sequencing to explore the differential gene expression before and after ALKBH5 gene silencing and Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis to investigate the gene changes in the downstream signaling pathway after knocking down ALKBH5 gene, so as to reveal the mechanism of action.4. Apply WB to explore the differences in the expression of key proteins in the PI3K/AKT/FOXO3A signaling axis between HSC-T0 and HSC-T6 cells. **Results:** The success of ALKBH5 knockdown in HSC-T6 group was verified by WB assay. The results of CCK8 and scratch assay showed that the cells in HSC-T6 group had accelerated cell proliferation and migration compared with the cells in HSC-T0 group; the results of attrition cytometry showed that the cells in HSC-T6 group were in G0/G1 phase. The results of high-throughput sequencing of the transcriptome showed that the differential gene was significantly enriched in the PI3K/AKT/FOXO3A signaling axis after silencing ALKBH5; after silencing ALKBH5, the results of the WB assay showed that in the HSC cells, the expression of PI3K, AKT, and FOXO3A proteins was down-regulated in the HSC-T6 group, and the expression of Collagen I and α-SMA proteins were up-regulated in the HSC-T6 group. **Conclusion:** ALKBH5 inhibits the proliferation and migration ability of HSC cells.
ALKBH5 affects HSC cells by regulating the PI3K/AKT/FOXO3A signaling axis.



Disclosures: lingyu kong: Nothing to Disclose, Hongxin Piao: Nothing to Disclose

3362 | BAICALEIN INDUCES HEPATIC STELLATE CELL SENESCENCE VIA INHIBITING GLYCOLYSIS BY CEBPZ/P53/HK2 SIGNALING PATHWAY TO INHIBIT LIVER FIBROSIS

Shuling Chen[1] Ruiqi Li[2] Dawei Yong[3] Jun Guo[1] Anyin Yang[4] Hongli Liu[2] Hao Ren[1] Jing Fan[5] Qingfang Xiong[1] Caiyun Zhang[5] Dandan Yin[1] Xixuan Wang[2] YongFeng Yang[1], [1]The Second Hospital of Nanjing, Affiliated to Nanjing University of Chinese Medicine, [2]The Second Hospital of Nanjing, Southeast University, [3]David_young1994@outlook.com, [4]Gaochun Hospital Affiliated to Jiangsu University, [5]Nanjing University of Chinese Medicine

Background: Liver fibrosis is a condition in which abnormal proliferation of connective tissue occurs in the liver. Baicalein (BA) is a flavonoid compound extracted from the dried root of *Scutellaria baicalensis*, which can inhibit the mechanisms of cancer development such as metastasis, angiogenesis, and inflammation without harming healthy cells. However, there has been little research on its effects in liver fibrosis. This study aimed to investigate the protective effect of BA on liver fibrosis and elucidate its potential mechanisms. **Methods:** Serum markers for liver injury, liver tissue histochemical staining, tissue immunofluorescence tissue immunohistochemistry, Western blotting analysis, real-time quantitative polymerase chain reaction(qRT-PCR), β-galactosidase staining, cell cycle detection, enzyme-linked immunosorbent assay (ELISA), Cellular Thermal Shift Assay (CETSA), Cleavage Under Targets and Tagmentation (CUT&Tag), Small Molecule pull-down

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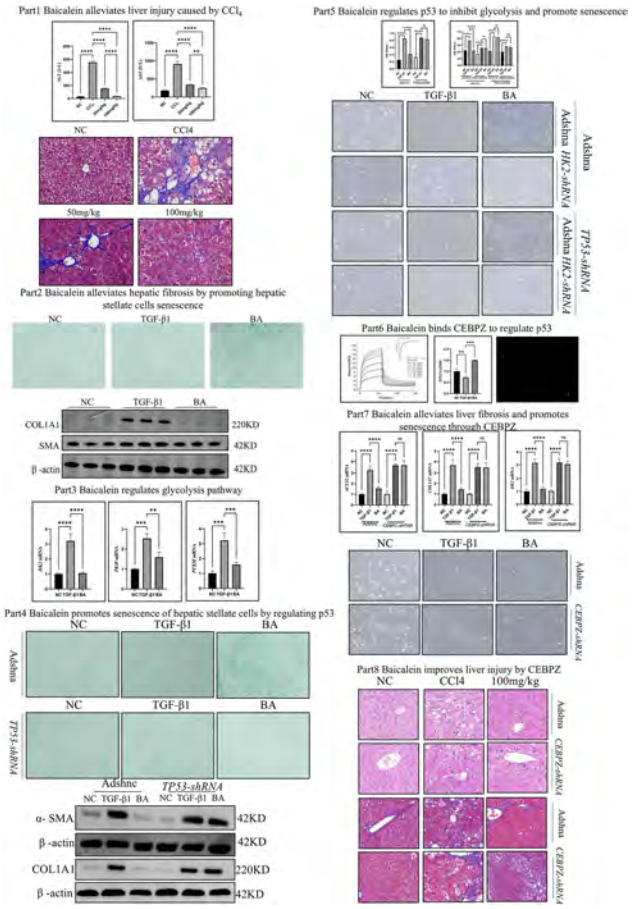
(SM pull-down) and Surface Plasmon Resonance (SPR) were utilized to identify the targets of BA, as well as to detect the expression of proteins associated with cellular senescence, fibrosis markers, and signaling pathways. **Results:** Serum liver injury indicators, fibrosis markers, and histochemical staining results indicated that BA treatment significantly ameliorated liver injury, inflammation, and fibrosis in vivo. Concurrently, BA markedly inhibited the activation of human hepatic stellate cell (HSC) line (LX2 cell line). The results further suggested that BA significantly promoted the senescence of activated HSCs, with cell cycle arresting at the G1 phase. BA could promote cellular senescence by inhibiting glycolysis in activated HSCs. Mechanistic studies demonstrated that BA could directly bind to CEBPZ, and regulate p53/HK2 signaling pathway at the transcriptional level. The pharmacological inhibitor of p53, pifithrin-a hydrobromide, significantly suppressed the anti-fibrotic effects of BA. **Conclusion:** Our findings suggested that BA had a protective effect on liver fibrosis, and the underlying mechanism might be related to the CEBPZ/p53/HK2 signaling pathway.



Disclosures: Shuling Chen: Nothing to Disclose, Ruiqi Li: Nothing to Disclose, Dawei Yong: Nothing to Disclose, Jun Guo: Nothing to Disclose, Anyin Yang: Nothing to Disclose, Hongli Liu: Nothing to Disclose, Hao Ren: Nothing to Disclose, Jing Fan: Nothing to Disclose, Qingfang Xiong: Nothing to Disclose, Caiyun Zhang: Nothing to Disclose, Dandan Yin: Nothing to Disclose, Xixuan Wang: Nothing to Disclose, YongFeng Yang: Nothing to Disclose

3363 | SINGLE-CELL ANALYSIS OF HETEROGENEITY IN REVERTED HUMAN HEPATIC STELLATE CELLS

Xinjia Wang[1], [1]THE CLEVELAND CLINIC FOUNDATION

Background: Hepatic stellate cells (HSCs) are central mediators of liver fibrosis. While activated HSCs are known to drive fibrogenesis, their fate following removal of the causative insult remains unclear. We aimed to investigate whether human activated HSCs can revert to a less activated state, and to characterize the cellular and molecular features of such reversion using a human induced pluripotent stem cell (hiPSC)-derived multicellular liver model. **Methods:** We employed a hiPSC-derived liver culture system containing hepatocytes, HSCs, and macrophages. HSCs were activated by hepatitis C virus (HCV) infection and then subjected to antiviral treatment to induce HCV clearance. Reverted HSCs (rHSCs) were characterized via gene expression profiling, vitamin A quantification, functional assays, and single-cell RNA sequencing (scRNA-seq). The role of macrophage- derived IL-10 in HSC reversion was investigated through receptor knockdown and cytokine treatment experiments. **Results:** When HSCs are activated by a hepatitis C virus (HCV) infection and subsequently cured, they transition to a less active state. These are termed reverted HSCs (rHSCs). Comprehensive characterization revealed that rHSCs re-express some markers typical of naïve quiescent HSCs that had never been activated, including regaining lipid droplets and vitamin A storage; additionally, they display functions similar to quiescent HSCs. Notably, single-cell RNA sequencing of rHSCs uncovered considerable heterogeneity amongst the population; it identified subpopulations that express markers indicative of apoptotic and senescent pathways, as well as HSCs in a less activated state. Further analysis of the less activated cells revealed a subpopulation of rHSCs closely resembling quiescent HSCs. Functional characterization demonstrated that these cells maintained features similar to naïve quiescent HSCs. Subsequent comparative analyses revealed that rHSCs exhibit heightened sensitivity to re-stimulation, whether exposed to the same stimulus or new stimuli. To further elucidate the mechanisms driving HSC reversion, we investigated the roles of macrophages within the liver culture. **Conclusion:** Activated HSCs demonstrate plasticity, with the capacity to revert to a quiescent-like

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state following removal of activating stimuli, though they retain increased sensitivity to re-stimulation. Macrophage-derived IL-10 plays a critical role in driving this reversion by regulating vitamin A metabolism. These findings provide insights into HSC dynamics and suggest potential therapeutic avenues for liver fibrosis by targeting HSC reversion.

Disclosures: Xinjia Wang: Nothing to Disclose

3364 | FUNCTIONAL ROLE OF NICOTINAMIDE N-METHYLTRANSFERASE IN HEPATIC STELLATE CELL ACTIVATION AND LIVER FIBROSIS

Ji Hyun LEE[1] Jae Min KIM[2] Ji Hye YANG[2] Sung Hwan KI[1], [1]College of Pharmacy, Chosun University, [2]College of Korean Medicine, Dongshin University

Background: Hepatic stellate cells (HSCs) activation is important in the progression of liver fibrosis. Nicotinamide *N*-methyltransferase (NNMT), a nicotinamide metabolizing enzyme, regulates both NAD^+ and methionine metabolism. Recently, the expression of nicotinamide methyl metabolites has increased in patients with cirrhosis and the role of NNMT in various liver diseases has been investigated, but there is no study on the expression and its regulatory mechanism of NNMT on liver fibrosis. **Methods:** In this study, we explored the molecular mechanisms regulating NNMT expression and its functional role in hepatic stellate cell activation *in vitro* and *in vivo*. **Results:** We compared NNMT expression with that of glycine N-methyltransferase (GNMT), another hepatic methyltransferase, during HSC activation. Using GEO transcriptional data, we confirmed that NNMT expression specifically increases during HSC activation. Moreover, treatment of LX-2 cells (a human HSC line) with TGF-β resulted in transcription-dependent upregulation of NNMT. We further demonstrated that modulation of NNMT, through either inhibition or overexpression, affected TGF-β-induced HSC activation. Moreover, liver fibrosis induced by chemical was significantly improved in NNMT KO mice. **Conclusion:** NNMT plays a significant role in hepatic stellate cell activation and may serve as a novel therapeutic target for the prevention and treatment of liver fibrosis.

Disclosures: Ji Hyun LEE: Nothing to Disclose, Jae Min KIM: Nothing to Disclose, Ji Hye YANG: Nothing to Disclose, Sung Hwan KI: Nothing to Disclose

3365 | MACROPHAGE NRF1-FOXO1-KLF6 AXIS DRIVES MITOCHONDRIAL DYSFUNCTION AND INFLAMMATORY PROGRESSION IN LIVER FIBROSIS

Qiong Wu[1] Mingwei Sheng[2] Fengmei Wang[2], [1]Nankai University, [2]Tianjin First Central Hospital

Background: Liver fibrosis is a progressive condition driven by chronic injury, ultimately leading to cirrhosis. Immune dysregulation, particularly macrophage polarization, plays a crucial role in fibrosis progression. Pro-inflammatory M1 macrophages worsen inflammation and fibrosis, with their polarization influenced by metabolic shifts between glycolysis and oxidative phosphorylation. Nuclear factor erythroid 2- related factor 1 (Nrf1), a key redox-sensitive factor essential for mitochondrial homeostasis, has been extensively studied in hepatocytes but remains largely unexplored in macrophages in the context of liver fibrosis. This study aims to elucidate the immunoregulatory role of macrophage Nrf1 in liver fibrosis, potentially identifying novel therapeutic targets to mitigate or reverse fibrosis progression. **Methods:** Myeloid-specific Nrf1-knockout ($Nrf1^{M\text{-}KO}$) mice and Foxo1 knockout ($Foxo1^{M\text{-}KO}$) mice were developed to investigate the role and underlying mechanisms of macrophage Nrf1-Foxo1 axis across three murine models of liver fibrosis induced by a high-fat diet, carbon tetrachloride injection or bile duct ligation. Bone marrow-derived macrophages (BMDMs) were isolated from conditional mice, then stimulated with lipopolysaccharide (LPS, 100 ng/mL, 6 hours). CRISPR/Cas9 and siRNA approaches were used to assess downstream targets. **Results:** Nrf1 expression was significantly reduced in macrophages from fibrotic liver tissues, as confirmed by qRT-PCR and immunofluorescence staining in both human and murine models. $Nrf1^{M\text{-}KO}$ mice exhibited exacerbated liver fibrosis, characterized by elevated serum ALT/AST levels, increased collagen deposition, and upregulated fibrotic markers (TGF-β, Col1a1, TIMP1). Loss of Nrf1 promoted M1 macrophage polarization, enhanced inflammatory responses (elevated TNF-α, IL-1β, iNOS), and impaired mitochondrial function (reduced ATP production and increased mitochondrial ROS). In contrast, $Foxo1^{M\text{-}KO}$ mice exhibited attenuated fibrosis, reduced inflammation, and improved mitochondrial integrity. Mechanistically, Nrf1 directly interacted with Foxo1 to regulate the transcription of KLF6, a key mediator of mitochondrial function and macrophage polarization. These findings underscore the pivotal role of the Nrf1-Foxo1-KLF6 axis in macrophage-driven

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inflammation and fibrosis, highlighting potential therapeutic targets for liver fibrosis. **Conclusion:** Our study highlights the functional properties of macrophage Nrf1-Foxo1 axis in controlling mitocondrial reprogramming and liver fibrosis progression.

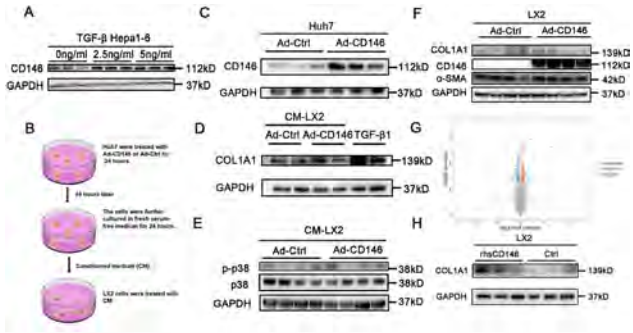
Disclosures: Qiong Wu: Nothing to Disclose, Mingwei Sheng: Nothing to Disclose, Fengmei Wang: Nothing to Disclose

3366 | TGF-β PROMOTES SCD146-MEDIATED HSC ACTIVATION BY UPREGULATING CD146 EXPRESSION IN HEPATOCYTES

Bingqing Yang[1] Chenxue Hou[1] Qi Wang[1] Yue Li[1], [1]Beijing Ditan Hospital, Capital Medical University, Beijing, China.

Background: Hepatic fibrosis represents a critical intermediate stage in the progression to cirrhosis. A cellular network composed of hepatocytes, macrophages, and hepatic stellate cells (HSCs) plays a central role in its pathogenesis. However, the interactions between HSCs and other hepatic cell types remain incompletely understood. This study aims to elucidate the mechanisms by which hepatocyte-derived CD146 regulates intercellular interactions and promotes hepatic fibrosis. **Methods:** Hepa1-6 cells were stimulated with TGF-β, and CD146 expression was assessed via Western blotting. CD146-overexpressing Huh7 cells were constructed and compared with control cells. Conditioned media (CM) from these cells were collected for proteomic analysis and used to treat the HSC cell line LX2 to assess the expression of fibrosis-related proteins. Additionally, recombinant CD146 protein(rhsCD146) was applied to LX2 cells to evaluate its direct effect on HSC activation. **Results:** TGF-β significantly upregulated CD146 expression in the Hepa1-6 cell in a time- and dose-dependent manner, suggesting a potential role in shaping the early fibrotic microenvironment via hepatocyte-derived CD146. To further investigate the mechanism of hepatocyte-mediated HSC activation, CD146-overexpressing Huh7 cells were generated, and their CM were used to treat LX2. Proteomic analysis of the CM identified the top 50 significantly differentially expressed proteins (fold change >1.5, $p < 0.05$), with soluble CD146 (sCD146) emerging as one of the most markedly upregulated factors.

Treatment of LX2 cells with either CM from CD146-overexpressing hepatocytes or rhsCD146 robustly activated the p38-MAPK pathway and induced collagen I (COL1A1) expression. In contrast, direct overexpression of CD146 in LX2 cells did not significantly alter fibrosis-associated gene or protein levels, indicating that sCD146—rather than intracellular CD146—plays a critical role in HSC activation. **Conclusion:** This study reveals that TGF-β induces CD146 expression in hepatocytes, promoting the shedding and secretion of sCD146, which in turn activates the p38-MAPK signaling pathway in hepatic stellate cells and enhances COL1A1 expression. These findings highlight a novel mechanism by which hepatocyte-derived sCD146 facilitates HSC activation and drives the progression of hepatic fibrosis.



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3367 | FUT8-MEDIATED CORE FUCOSYLATION OF SPARC DRIVES HEPATIC FIBROSIS VIA COLLAGEN CROSSLINKING AND TGF-B SIGNALING

Hanjie Yu[1] Junhong Wang[2] Han Lin[3] Mengmeng Liu[4] Xue Li[4] Zhenghaoyu Huang[3] Xijuan Wei[4] Zheng Li[5] YONGHONG GUO[4], [1]The Third Hospital of Xi'an, [2]Department of Endocrine, Shanghai Pudong New Area Gongli Hospital, [3]School of Gongli hospital Medical Technology,University of Shanghai for Science and Techonology, [4]Department of Infectious Disease, Shanghai Pudong New Area Gongli Hospital, [5]Laboratory for Functional Glycomics, College of Life Sciences, Northwest University

Background: Hepatic fibrosis is characterized by a self-perpetuating cycle involving the activation of hepatic stellate cells (HSCs) and the pathological stiffening of the extracellular matrix (ECM). The specific role of glycosylation in this process remains to be elucidated. **Methods:** Bioinformatic analysis of enzyme fucosyltransferase 8(Fut8)expression patterns was conducted utilizing data from the TCGA and GEO databases. Fut8 knockdown was achieved via siRNA transfection in LX-2 cells. Lectin affinity glycoproteomics, principal component analysis, and hierarchical clustering were employed to identify core fucosylation-modified proteins. The expression of SPARC was

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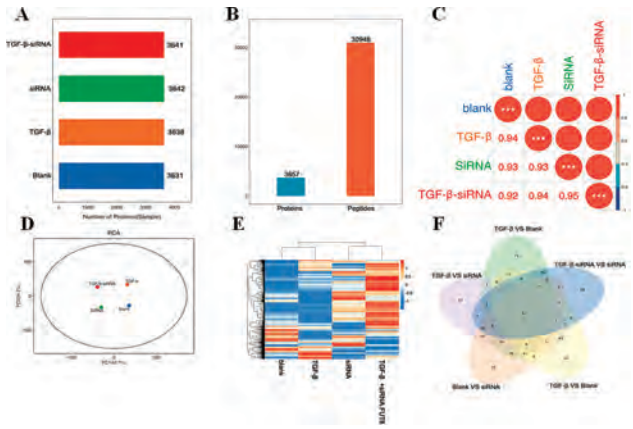
validated by Western blotting, and the core fucosylation levels of SPARC were quantified through LCA immunoprecipitation. Fut8 overexpression was induced through adenoviral infection, while competitive inhibition of Fut8 was performed using 2-deoxy-2-fluoro-L-fucose (2FF) at a concentration of 100 μM, with a 48-hour pretreatment period. Control groups included normal HSCs and a group treated with TGF-β at 10 ng/mL as a positive control. Phenotypic and pathway analyses were conducted by assessing fibrotic markers collagens and α-Smooth Muscle Actin(α-SMA) via quantitative PCR and Western blotting.The interaction between SPARC and COL I was analyzed using AutoDock software to examine the impact of glycosylation on their binding interaction. Statistical analysis was conducted on data from three biological replicates using ANOVA followed by Tukey's test (GraphPad Prism 9.0; $p < 0.05$). **Results:** The results demonstrated a significant upregulation of Fut8 expression in fibrotic liver tissues, which was correlated with HSCs activation. Knockdown of Fut8 resulted in the downregulation of TGF-β/Smad2/3, Wnt/β-catenin, and integrin signaling pathways. Lectin affinity glycoproteomics identified 92 upregulated and 118 downregulated proteins following Fut8 inhibition, including SPARC-interacting type I collagen(COL I)and fibronectin (FN). Additionally, Fut8 knockdown led to reduced core fucosylation of SPARC and mitigated the pathological accumulation of COL I and FN. Overexpression of Fut8 led to increased levels of COL I, FN, and α-SMA ($p < 0.05$ compared to control). Molecular docking analysis reveals that core fucosylation of SPARC enhances its binding affinity to type I collagen via hydrogen bonding, with a binding energy of -5.53 kcal/mol, whereas non-core fucosylated SPARC does not bind. This interaction facilitates pathological crosslinking and stiffening of the ECM. **Conclusion:** These findings underscore that Fut8-mediated core fucosylation of SPARC augments its binding to COL I through conformational remodeling, thereby promoting ECM crosslinking and stiffness. Inhibition of core fucosylation by targeting Fut8 mitigates these fibrogenic pathways and alleviates hepatic fibrosis.



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3368 | LIVER STIFFNESS RESPONSE AND HETEROGENEITY ASSESSED VIA MAGNETIC RESONANCE ELASTOGRAPHY IN ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE: RESULTS: FROM PHASE 2 STUDIES OF FAZIRSIRAN

Chien-Lin Yeh[1] Talakad Lohith[1] Ozlem Yardibi[1] Jen-Chieh Chuang[1] Vandana Gupta[1] Chantal Beauchemin[1] Abeer Zeitone[1] Susana Gonzalez[1] Nirav Desai[1] Thomas Schluep[2] James Hamilton[2] Virginia Clark[3] Pavel Strnad[4] Rohit Loomba[5], [1]Takeda Development Center Americas, Inc., Cambridge, MA, USA, [2]Arrowhead Pharmaceuticals, Inc., Pasadena, CA, USA, [3]University of Florida, Gainesville, FL, USA, [4]University Hospital RWTH Aachen, Aachen, Germany, [5]University of California San Diego, San Diego, CA, USA

Background: Liver stiffness measurement (LSM) via magnetic resonance elastography (MRE) offers an alternative to liver biopsy for the detection and monitoring of fibrosis in patients (pts) with alpha-1 antitrypsin deficiency-associated liver disease (AATD-LD). Spatial heterogeneity of LSM via MRE has been characterized in pts with MASLD, viral hepatitis and PSC, but not AATD-LD. We evaluated spatial heterogeneity of LSM via MRE in pts with AATD-LD after fazirsiran treatment (an investigational siRNA therapy) and concordance between MRE- and biopsy-based liver fibrosis assessments. **Methods:** Baseline (BL) and post-treatment MRE and histology data from pts with AATD-LD who received fazirsiran or placebo in AROAAT-2001/-2002 (NCT03945292/NCT03946449) were included. LSM via MRE was an exploratory endpoint in both studies. MRE data were collected at BL and at one of the Week (Wk) 24/48/72/96 visits. Histograms were used to map LSM distribution within the tissue region of interest from BL to end of study and Kullback-Leibler divergence (K-L distance) was used to calculate the magnitude of shift. MRE heterogeneity metrics (entropy, variability, coefficient of variation [CoV]) were calculated, with significance of change determined by repeated measures ANOVA. **Results:** Overall, 20 pts enrolled in AROAAT-2001/-2002 treated with fazirsiran (n = 17) or placebo (n = 3) had BL and ≥ 1 follow-up MRE assessment. Both MRE imaging (Figure) and histograms showed a change in LSM after

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fazirsiran treatment. Mean peak LSM across imaging slices was 7.8 kPa at BL and 4.6 kPa at Wk 48 after fazirsiran treatment (not significant); values remained similar in pts treated with placebo from BL to Wk 48 (5.8 vs 5.6 kPa). Based on MRE histograms, mean K-L distance from BL to Wk 48 after fazirsiran treatment was 3,000 across BL fibrosis stages defined by MRE (F1–3; n = 11) and 1,776 across BL fibrosis stages defined by biopsy-based METAVIR (F1–4; n = 11; differences not significant); no shift was observed for placebo or in pts with a BL F0 fibrosis stage. A larger shift was observed at higher BL MRE fibrosis stages, while treatment response was similar regardless of BL METAVIR stage. From BL to Wk 48 after fazirsiran treatment, heterogeneity assessed by mean entropy significantly decreased (5.2 vs 4.7 nats; $p < 0.05$); mean variability (81.7% vs 76.7%) and CoV (27.4% vs 25.3%) declined after treatment, although changes were not statistically significant. **Conclusion:** MRE imaging in AATD-LD using histogram-based spatial LSM distribution and heterogeneity metrics offer additional granularity relative to biopsy. After fazirsiran treatment, heterogeneity metrics indicated a trend towards improved liver stiffness uniformity across fibrotic regions. Further MRE image analyses using radiomics from larger cohorts of pts with AATD-LD may yield robust features for monitoring and predicting treatment response.

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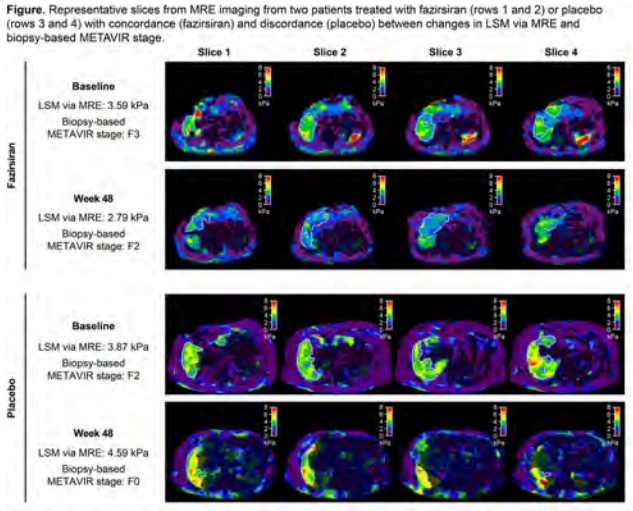

Figure. Representative slices from MRE imaging from two patients treated with fazirsiran (rows 1 and 2) or placebo (rows 3 and 4) with concordance (fazirsiran) and discordance (placebo) between changes in LSM via MRE and biopsy-based METAVIR stage.

Concordance between LSM via MRE and biopsy-based METAVIR stage was shown for patients treated with fazirsiran, while discordance between LSM via MRE and biopsy-based METAVIR stage was shown for patients treated with placebo.
LSM, liver stiffness measurement; METAVIR, meta-analysis of histological data in viral hepatitis; MRE, magnetic resonance elastography.

Disclosures: Chien-Lin Yeh: Takeda Phamaceutical Company: Employee, Talakad Lohith: Takeda Pharmaceutical Company Limited: Employee, Ozlem Yardibi: Nothing to Disclose, Jen-Chieh Chuang: Takeda: Employee, Vandana Gupta: Takeda Pharmaceuticals: Employee, Chantal Beauchemin: Nothing to Disclose, Abeer Zeitone: Nothing to Disclose, Susana Gonzalez: Nothing to Disclose, Nirav Desai: Nothing to Disclose, Thomas Schluep: Nothing to Disclose, James Hamilton: Nothing to Disclose, Virginia Clark: Novo Nordisk: Research support, Takeda: Research support, Vertex: Research support, Takeda: Consulting fees, Vertex: Research support, Takeda: Consulting fees, Vertex: Consulting fees, 89 Bio: Grant/Research Support, hamni pharmaceuticals: Grant/Research Support, Novo Nordisk: Research support, Takeda: Research support, Vertex: Research support, Takeda: Consulting fees, Vertex: Research support, Takeda: Consulting fees, Vertex: Consulting fees, 89 Bio: Grant/Research Support, hamni pharmaceuticals: Grant/Research Support, Pavel Strnad: Arrowhead Pharmaceuticals: Grant/Research Support, CSL Behring: Grant/Research Support, CSL Behring: Speaking and Teaching, BioMarin Pharmaceutical: Consultant, GSK: Consultant, Intellia: Consultant, Takeda Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Swedish Orphan Biovitrum: Consultant, Swedish Orphan Biovitrum: Speaking and Teaching, IPSEN: Consultant, Albireo: Consultant, AiRNA: Consultant, BioMarin: Consultant, Korro Bio: Consultant, Wave: Consultant, AiRNA: Consultant, Tessera: Consultant, Vertex: Material transfer, IQVIA: Material transfer, Arrowhead: Grant/Research Support, Takeda: Consultant, GSK: Consultant, BioMarin: Consultant, IPSEN: Consultant, Korro Bio: Consultant, CSL Behring: Grant/Research Support, CSL Behring: Speaking and Teaching, CSL Behring: Consultant, Sobi: Speaking and Teaching, Sobi: Advisor, Sanofi: Grant/Research Support, Rohit Loomba: Nothing to Disclose

3369 | DEVELOPMENT OF A FIBROSIS INDEX USING MACHINE LEARNING TO PREDICT LIVER FIBROSIS PROGRESSION IN CHRONIC LIVER DISEASE

David Zhang[1] Alexandra Greb[1], [1]David Geffen School of Medicine at UCLA

Background: Timely identification of liver fibrosis progression is critical in chronic liver disease management. While several noninvasive modalities assess fibrosis stage, tools that predict fibrosis progression over time remain limited. We aimed to develop a predictive model using routinely available laboratory data and validate a fibrosis index for progression risk stratification. **Methods:** We conducted a retrospective chart review of adult patients ($\geq$ 18 years) at UCLA from January 2015 to December 2024 with chronic liver disease who underwent two or more liver fibrosis assessments (via Fibroscan, ultrasound elastography, MR elastography, or liver biopsy) at least one year apart. The primary outcome was fibrosis progression, defined as an increase of $\geq$1 fibrosis stage from baseline. Demographics, liver disease etiology, and

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laboratory values were extracted. Generalized linear models (GLM) identified univariate and multivariate predictors. A random forest classifier was trained using the most significant variables to generate a probability score ("Fibrosis Index"). Model performance was evaluated using accuracy, positive predictive value (PPV), and negative predictive value (NPV). A web-based calculator was developed for clinical use. **Results:** A total of 230 patients were included. The cohort had a mean age of 58.6 years, with 59% female and diverse etiologies including MASLD/MetALD (52%), HBV (11%), and autoimmune liver disease (9%). On univariate and multivariate GLM, lower CO2 and higher AST and INR were independently associated with fibrosis progression ($p < 0.05$). These variables were used to train a random forest model, which achieved an accuracy of 0.84. The model's PPV was 85.7%, and NPV was 89.7%. The Fibrosis Index score, derived from model probabilities, was significantly associated with fibrosis progression ($p = 0.009$). A 40% threshold of the Fibrosis Index score demonstrated a PPV of 96% and an NPV of 97.6%. An online tool was developed to support clinical use (https://fibrosis-index.shinyapps.io/fibrosis_index/). **Conclusion:** We developed and validated a machine learning–based Fibrosis Index using routine labs to predict fibrosis progression in chronic liver disease. The index demonstrates strong predictive accuracy and may assist clinicians in identifying patients at higher risk for disease advancement.

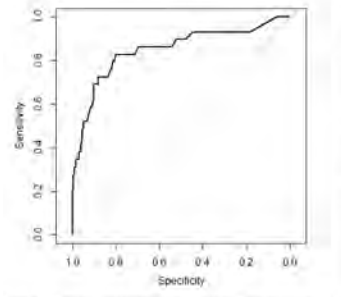

Figure 1: ROC plot of the random forest classifier to predict fibrosis progression. AUC: 0.643

Characteristic	All (n=230)
Age (Mean)	58 (25.2%)
Sex	
Male	94 (40.9%)
Female	136 (59.1%)
Race	
White	106 (46.7%)
Black or African American	13 (5.7%)
Asian	40 (17.4%)
Native Hawaiian or Other Pacific Islander	1 (0.4%)
American Indian or Alaska Native	3 (1.3%)
Other/Unknown	66 (28.6%)
Ethnicity	
Hispanic or Latino	46 (20.0%)
Not Hispanic	171 (74.3%)
Unknown	13 (5.7%)
Etiology of Liver Disease	
MASLD/MetALD	120 (52%)
EtOH	15 (6.5%)
HCV	15 (6.5%)
HBV	25 (10.8%)
Autoimmune	20 (8.7%)
DILI	15 (6.5%)
PBC	8 (3.5%)
Hemochromatosis	3 (1.3%)
PSC	2 (0.9%)
Other/Unknown	16 (7%)

Table 1: Patient demographics

Disclosures: David Zhang: Nothing to Disclose, Alexandra Greb: Nothing to Disclose

3370 | EARLY TISSUE DAMAGE–DERIVED CELLS ORCHESTRATE THE FORMATION OF AGE-RELATED SENESCENT MICROENVIRONMENTS

Kwon Yong Tak[1] Seoyeong Lee[2] Juyeon Kim[3] Chuna Kim[3] Jong-Eun Park[2] Yongjun Koh[2], [1]Seoul St. Mary's Hospital, [2]KAIST, [3]KRIBB

Background: Recent findings suggest that senescent cells organize into spatially restricted niches, evolving from localized early aging environments into widespread aged regions. Using the Fibrotic Niche (FiNi)-seq technique, we previously enriched and profiled age-associated niches within fibrotic liver microenvironments. In this study, we extend FiNi-seq to early liver injury models to uncover the origin and trajectory of senescent niches and to track their maturation into aged microenvironments via transcriptional profiling of senescent cell populations. **Methods:** We collected liver cells from young (3 months) and old (22 months) mice using both control and FiNi-seq approaches and were evaluated using in-vitro culture and single-cell RNA sequencing (scRNA-seq) to elucidate the age driver populations. Their spatial context were validated using Visium spatial transcriptomics (GSE192742), in-house Stereo-seq, RNA-scope, and immunohistochemistry. To examine whether early liver injury initiates senescent microenvironments, we applied FiNi-seq and snFiNi-ATAC-seq to early damage models of DDC-diet and CCl4. **Results:** FiNi-seq identified specific cell types driving the formation of age-associated fibrotic niches within defined spatial regions (Figure 1).

When applied to early liver injury models, FiNi-seq revealed an increase in mesenchymal cell populations and a shift in myeloid cells marking the onset of fibrosis. We also observed expansion of Fibrotic EC as early as 7 days after DDC exposure (Figure 2).

FiNi-seq and FiNi-ATAC-seq of livers at 1 week, 3 weeks, and post-recovery stages showed progressive expansion of Fibrotic_ECs, even persisting post-recovery. Profiling chromatin accessibility revealed differential activity in acute damage versus aging and post-recovery (Figure 3).

Fibrotic_ECs in DDC injury exhibited transcriptional signatures of early inflammation, while aged counterparts displayed DNA damage–associated patterns. Although both promoted angiogenic transcription factor (TF) activity, the specific TF usage varied with the degree of inflammation and tissue context (Figure 3). **Conclusion:** This study reveals that early, mild tissue injury can initiate the formation of senescent microenvironments, using FiNi-seq and chromatin accessibility profiling. Fibrotic_ECs emerge early in liver damage and persist even after apparent tissue recovery, suggesting a durable reprogramming event. These cells display distinct transcriptional and epigenetic traits shaped by inflammation, hypoxia, and angiogenic cues, differing by context of age versus injury. This framework provides a new perspective on how cellular responses to damage can act as a central driver of aging phenotypes and opens the door for targeting early microenvironmental changes to delay or modulate age-related tissue decline.

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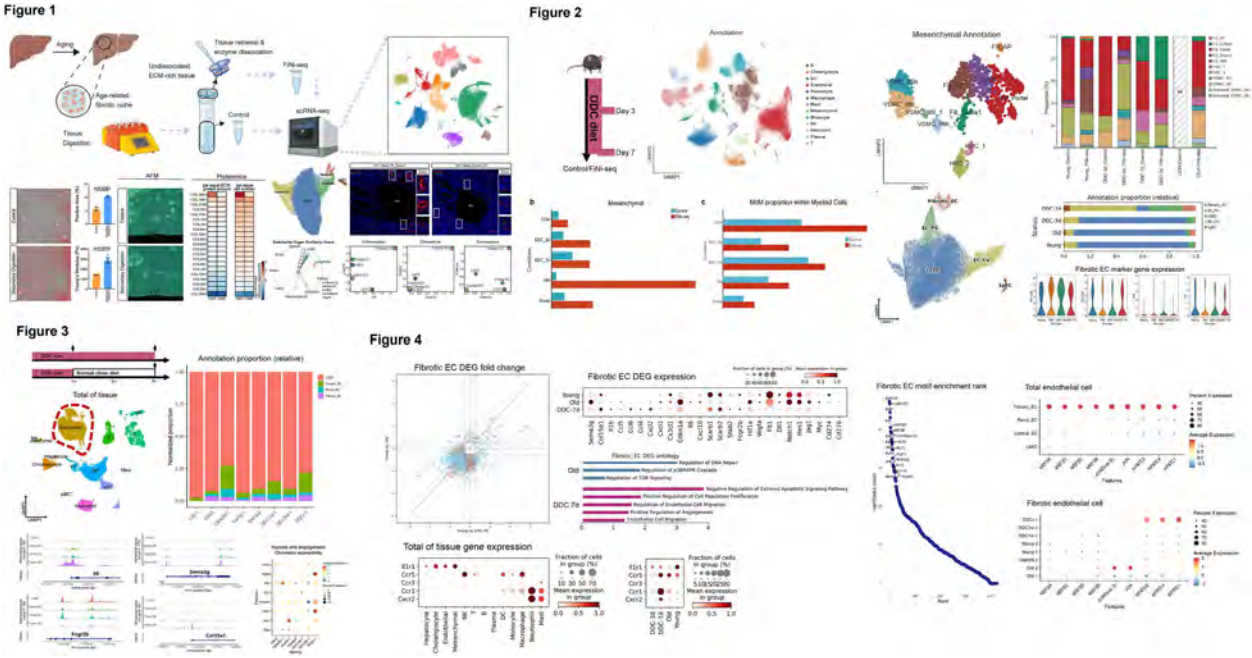

Disclosures: Kwon Yong Tak: Nothing to Disclose, Seoyeong Lee: Nothing to Disclose, Juyeon Kim: Nothing to Disclose, Chuna Kim: Nothing to Disclose, Jong-Eun Park: Nothing to Disclose, Yongjun Koh: Nothing to Disclose

3371 | POTENT ANTIFIBROTIC EFFECTS OF ONCOLYTIC REOVIRUS ON LIVER FIBROSIS VIA RESTORATION OF ACTIVATED HEPATIC STELLATE CELLS TO QUIESCENT STATUS FOLLOWING INTRAVENOUS ADMINISTRATION

Ikuho Ishigami[1] Kanako Nakagawa[1] Yuki Kibe[1] Shunsuke Inoue[1] Takuya Yamashita[2] Kazuya Nagano[2] Kazuo Ohashi[3] Hiroyuki Mizuguchi[1] Fuminori Sakurai[4], [1]Osaka University, [2]Wakayama Medical University, [3]Ohashi General Internal Medicine and Surgery Clinic, [4]Kindai University

Background: Liver fibrosis is often caused by chronic inflammation which is induced by various factors, including hepatitis virus infection and excessive alcohol consumption. Although many patients suffer from liver fibrosis, there are few curative medicines. A curative agent that not only suppresses the progression of fibrosis but also reverses fibrotic tissue to a healthy one is urgently needed. We previously revealed that mammalian orthoreovirus type 3 Dearing (reovirus), which has been actively studied as an oncolytic virus in clinical trials, significantly reduced the extracellular matrices (ECMs) in the tumors of subcutaneous tumor-bearing mice. These findings let us hypothesize that reovirus could show efficient anti-fibrotic effects on liver fibrosis. **Methods:** Liver fibrosis levels were evaluated by measuring fibrosis marker gene expression and ECM disposition 1 week after intravenous administration of reovirus in CCl4-induced liver fibrosis mice. Next, we examined which type of cells in the liver took up reovirus following intravenous administration. Furthermore, fibrosis marker gene expression in LX-2 cells (a human hepatic stellate cell line) was evaluated after reovirus treatment. Furthermore, we investigated the lipid storage and migration activity in LX-2 cells following reovirus treatment. **Results:** After intravenous administration, reovirus efficiently reduced the fibrosis marker gene expressions, including ACTA2 and COL1A, and the ECMs deposition in the liver to 1/10-1/3 without apparent hepatotoxicity or virus replication. Reovirus was mainly taken up by activated hepatic stellate cells. Fibrosis marker gene expressions were also apparently reduced in LX-2 cells by reovirus without apparent cell death or virus replication. Furthermore, PCA analysis of LX-2 cells indicated that reovirus treatment led to a transcriptome shift of activated status to quiescent one. Lipid storage and migration activity of LX-2 cells was significantly restored by reovirus treatment. **Conclusion:** Viruses have been generally considered to cause tissue fibrosis by chronic inflammation. Here, we demonstrated that reovirus showed significant anti-fibrotic effects on liver fibrosis mice and activated HSCs. Furthermore, reovirus not only suppressed fibrotic marker gene expressions, but also restored the properties of myofibroblast-like activated HSCs to quiescent HSCs. Together, this study showed

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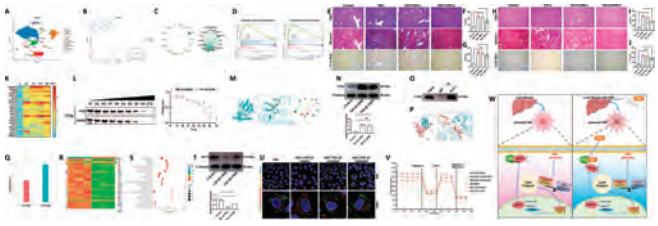
the potential of oncolytic reovirus of drug repurposing for the treatment of tissue fibrosis.

Disclosures: Ikuho Ishigami: Nothing to Disclose, Kanako Nakagawa: Nothing to Disclose, Yuki Kibe: Nothing to Disclose, Shunsuke Inoue: Nothing to Disclose, Takuya Yamashita: Nothing to Disclose, Kazuya Nagano: Nothing to Disclose, Kazuo Ohashi: Nothing to Disclose, Hiroyuki Mizuguchi: Nothing to Disclose, Fuminori Sakurai: Nothing to Disclose

3372 | THE MECHANISM OF HYDROXYNIDONE IN THE TREATMENT OF LIVER FIBROSIS BY TARGETING CTSL-SIRT1 TO REGULATE LIPID METABOLISM REPROGRAMMING OF HEPATIC STELLATE CELLS.

hanjing zhangdi[1] Qichao Ge[2] Hui Huang[3] Yuecheng Guo[2] Yufei Yang[2] Qingqing Zhang[2] Junjun Wang[4] Zhenyang Shen[2] Yanping Ye[5] Ling Zhang[5] Ying Luo[5] Xiaobo Cai[2] Hui Dong[2] Hu Zhou[3] Lungen Lu[2], [1]Department of Gastroenterology, Shanghai General Hospital, S, [2]Department of Gastroenterology, Shanghai General Hospital, [3]Department of Analytical Chemistry, State Key Laboratory of Drug Research, [4]Department of Gastroenterology, Shanghai General Hospital., [5]Continent Pharmaceuticals Co.,Ltd., Beijing, China

Background: The imbalance of lipid metabolism homeostasis in hepatic stellate cells (HSC) can trigger its activation and lead to liver fibrosis. Our team confirmed that hydronidone(HDD) can reverse liver fibrosis in clinical patients through clinical phase II (54.8% improvement) and phase III trials (52.85% improvement). Accordingly, we will further explore the mechanism and therapeutic targets of HDD in reversing liver fibrosis. **Methods:** We constructed a mouse liver fibrosis model by intraperitoneal injection of CCL4 and DDC diet, and established a mouse liver fibrosis treatment model by oral administration of hydronidone. The activated and quiescent HSCs of mice before and after hydronidone treatment were screened by single cell sequencing. The therapeutic target of hydronidone was screened as CTSL protein by DARTS-MS analysis in mouse HSC. SPR, CETSA, fluorescence co-localization experiments, molecular docking and other experiments confirmed that CTSL was the target of hydronidone in HSC. The changes of RNA level, protein level and enzyme activity of CTSL before and after hydronidone treatment were detected by PCR, WB and specific fluorescence substrate consumption experiment. The changes of lipid metabolism in HSC before and after hydronidone treatment were detected by immunofluorescence, lipid fluorescence probe staining, mitochondrial fluorescence probe staining and lysosomal fluorescence probe staining. Through in-depth analysis of lipid metabolomics technology and IP-MS, the downstream protein of CTSL enzyme was screened as SirT1. The changes of lipid metabolism in HSC before and after treatment were detected by Seahorse test. To regulate the expression of CTSL and SirT1 in mouse hepatic stellate cells by constructing lentivirus. **Results:** Hydronidone was found to partially reverse liver fibrosis in both CCL4 and DDC treatment models. DARTS-MS screening showed that CTSL protein was the target protein of hydronidone in HSC, and hydronidone in HSC was detected to bind to CTSL protein stably. In addition, we found that hydronidone treatment did not change the RNA and protein levels of CTSL in HSC, but changed the enzyme activity of CTSL. CO-IP experiments confirmed the interaction between CTSL and SirT1, and overexpression of CTSL reduced the degradation expression of SirT1. When hydronidone treats TGF-β1-induced activated HSC, the endogenous lipid droplets of HSC will be partially restored, reducing the occurrence of β-oxidation in HSC and inhibiting HSC activation. Knockdown of SirT1 inhibited the therapeutic effect of hydronidone on activated HSC, increased lipid metabolism in HSC and reversed the therapeutic effect of hydronidone on activated HSC. **Conclusion:** By targeting the CTSL enzyme active site in HSC, hydronidone inhibits the degradation of SirT1 by CTSL, thereby protecting the intrinsic endogenous lipid droplets of HSC and inhibiting HSC activation, thereby reversing liver fibrosis.



Disclosures: hanjing zhangdi: Nothing to Disclose, Qichao Ge: Nothing to Disclose, Hui Huang: Nothing to Disclose, Yuecheng Guo: Nothing to Disclose, Yufei Yang: Nothing to Disclose, Qingqing Zhang: Nothing to Disclose, Junjun Wang: Nothing to Disclose, Zhenyang Shen: Nothing to Disclose, Yanping Ye: Nothing to Disclose, Ling Zhang: Nothing to Disclose, Ying Luo: Nothing to Disclose, Xiaobo Cai: Nothing to Disclose, Hui Dong: Nothing to Disclose, Hu Zhou: Nothing to Disclose, Lungen Lu: Nothing to Disclose

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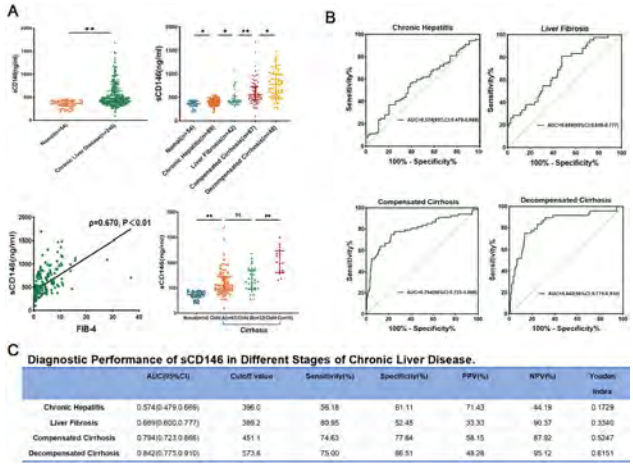
3373 | DIAGNOSTIC VALUE OF SERUM SOLUBLE CD146 IN THE PROGRESSION OF CHRONIC LIVER DISEASE

Bingqing Yang[1] Yue Li[1] Xinhua Ren[1] Jingya Yin[1] Chenxue Hou[1] Qi Wang[1], [1]Beijing Ditan Hospital, Capital Medical University, Beijing, China.

Background: Chronic liver disease (CLD) has a high global prevalence and often progresses to hepatic fibrosis and cirrhosis, which, in severe cases, may lead to liver failure or hepatocellular carcinoma. Thus, there is an urgent need for more sensitive, specific, and cost-effective non-invasive biomarkers. This study aimed to investigate the expression pattern of serum soluble CD146 (sCD146) in chronic liver disease and evaluate its potential as a diagnostic marker. **Methods:** Serum samples were collected from 300 individuals at Beijing Ditan Hospital, Capital Medical University, including healthy controls undergoing routine physical examinations (n = 54) and patients at various stages of chronic liver disease (n = 246). Serum sCD146 levels were measured using enzyme-linked immunosorbent assay (ELISA). Differences in sCD146 expression across disease stages were analyzed, and correlations with FIB-4 scores were assessed. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of sCD146, including calculation of area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and optimal cutoff values. **Results:** Serum sCD146 levels were significantly higher in CLD patients than in healthy controls (466.28 ng/mL vs. 370.07 ng/mL, $P < 0.01$). sCD146 levels increased progressively with disease severity: chronic hepatitis (405.88 ng/mL), liver fibrosis (428.43 ng/mL), compensated cirrhosis (549.14 ng/mL), and decompensated cirrhosis (776.93 ng/mL), with statistically significant differences among groups ($P < 0.05$). A strong positive correlation was observed between sCD146 levels and FIB-4 scores ($\rho = 0.670$, $P < 0.01$). In cirrhotic patients, sCD146 levels rose with advancing Child-Pugh classification, with significantly higher levels in class C than class B (999.74 ng/mL vs. 623.08 ng/mL, $P < 0.05$).

ROC analysis showed increasing diagnostic performance of sCD146 across disease stages, with AUCs of 0.574 for chronic hepatitis, 0.689 for hepatic fibrosis, 0.794 for compensated cirrhosis, and 0.842 for decompensated cirrhosis. Notably, sCD146 showed the highest diagnostic efficacy in decompensated cirrhosis, with a Youden index of 0.6151, sensitivity of 75.00%, and specificity of 86.51%. These findings suggest that sCD146 may serve as a non-invasive serum biomarker for assessing CLD progression, particularly for identifying decompensated cirrhosis. **Conclusion:** This study demonstrates that serum sCD146 is significantly associated with the progression of chronic liver disease. sCD146 exhibits diagnostic value across various stages of CLD, with particularly high sensitivity and specificity in detecting decompensated cirrhosis, underscoring its potential as a non-invasive biomarker for disease monitoring and risk stratification.



	AUC(95%CI)	Cutoff value	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)	Youden Index
Chronic Hepatitis	0.574(0.479,0.669)	396.0	56.18	61.11	71.43	44.19	0.1729
Liver Fibrosis	0.689(0.600,0.777)	389.2	69.95	52.45	33.33	90.37	0.3340
Compensated Cirrhosis	0.794(0.723,0.866)	451.1	74.63	77.64	58.15	87.92	0.5247
Decompensated Cirrhosis	0.842(0.775,0.910)	573.6	75.00	86.51	48.28	95.12	0.6151

Disclosures: Bingqing Yang: Nothing to Disclose, Yue Li: Nothing to Disclose, Xinhua Ren: Nothing to Disclose, Jingya Yin: Nothing to Disclose, Chenxue Hou: Nothing to Disclose, Qi Wang: Nothing to Disclose

3374 | A GENE EXPRESSION SIGNATURE CORRELATES WITH FIBROSIS SEVERITY IN PATIENTS WITH MASH, ALCOHOL-ASSOCIATED LIVER DISEASE, AND VIRAL HEPATITIS

Jennifer Chen[1] Srilaxmi Nerella[1] Carson Cable[1] Vijaya Prathigudupu[1] Mandana Khalili[1] Stephanie Christenson[1], [1]University of California, San Francisco

Background: Liver fibrosis is characterized by an accumulation of extracellular matrix proteins and leads to progressive organ dysfunction. While there have been advances in noninvasive diagnostic tests that detect advanced fibrosis, there is a paucity of tools that capture the heterogenous pathways that drive fibrogenesis. To develop a precision approach towards hepatic fibrogenesis, clinical biomarkers that measure dysregulated pathways among patients are needed, which will facilitate development of targeted therapies. We previously developed a gene signature score, the ceramide-YAP score, based on our preclinical studies in human hepatic stellate cells. Here, we aimed to elucidate the association between the ceramide-YAP score, fibrosis severity, and disease progression among patients with different etiologies of chronic liver disease. **Methods:** To explore the correlation between the

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ceramide-YAP score and fibrosis severity among patients with different etiologies of chronic liver disease, we reviewed datasets in Gene Expression Omnibus of liver tissue samples that included fibrosis stage by histologic scoring from 2000-2023. This identified a total of 6 datasets. Raw genome profiling data were downloaded from GEO and normalized using previously validated methods. The ceramide-YAP score was generated on a per-subject basis by combining the log2 gene expression of the genes in the ceramide-YAP using the GSVA algorithm as previously performed. We utilized Mann-Whitney U tests to measure the association between the signature and histologic staging. **Results:** The Ceramide-YAP signature score significantly increased with fibrosis severity among patients with chronic hepatitis B, chronic hepatitis C, alcohol-associated liver disease, and MASH. Among patients with HCV cirrhosis, we did not observe an association between the ceramide-YAP score and progression to Child-Pugh B or C, death, or HCC. **Conclusion:** Our studies demonstrate that the ceramide-YAP score correlates with fibrosis severity among patients with alcohol-associated liver disease, MASH, HBV, and HCV infection. This work suggests that the ceramide and YAP pathways are dysregulated with fibrogenesis and may serve as biomarkers to identify patients whom may benefit from targeted therapies.

Disclosures: Jennifer Chen: Nothing to Disclose, Srilaxmi Nerella: Nothing to Disclose, Carson Cable: Nothing to Disclose, Vijaya Prathigudupu: Nothing to Disclose, Mandana Khalili: gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant, Stephanie Christenson: Nothing to Disclose

3375 | RESOLVING FIBROSIS BY STIMULATING HSC-DEPENDENT EXTRACELLULAR MATRIX REMODELING

Sachin Sharma[1] Vijaya Prathigudupu[1] Carson Cable[1] Alina Chen[1] Srilaxmi Nerella[1] Carlos Lizama Valenzuela[1] Tatsuya Tsukui[1] Jaejun Kim[1] Holger Willenbring[1] Aras Mattis[1] Balyn Zaro[1] Lia Serrano[2] Josh Coon[2] Richard Beresis[1] William DeGrado[1] Hyunil Jo[1] Stephanie Christenson[1] Jennifer Chen[1], [1]University of California, San Francisco, [2]University of Wisconsin-Madison

Background: Tissue fibrosis arises from a critical imbalance between the production and breakdown of extracellular matrix (ECM) components. While current strategies predominantly focus on curbing ECM production, the possibility of promoting ECM degradation to resolve fibrosis remains largely untapped. The role of hepatic stellate cells (HSCs) in ECM degradation is an intriguing area for investigation. We previously identified that inhibiting acid ceramidase (aCDase) increases ceramide to ameliorate liver fibrosis. Here, we describe mechanistic studies aimed at clarifying how targeting aCDase reduces tissue collagen, focusing on the role of HSC-mediated matrix degradation. **Methods:** Ceramide-treated HSCs were profiled by RNA sequencing, proteomics, and phosphoproteomics. Liver fibrosis induced by carbon tetrachloride (CCl_4) and fructose, palmitate, cholesterol, and *trans* fat (FPC) models was inhibited using a newly developed aCDase inhibitor compound 5A, and results were compared to those observed using an inducible HSC-specific deletion of aCDase. Mouse HSCs were isolated using flow cytometry and cell sorting. ECM remodeling was analyzed by immunostaining with an antibody that recognizes degraded type 1 collagen; collagen hybridizing peptide; Sirius red staining; and second harmonic generation microscopy following liver decellularization. We conducted gene set enrichment analysis on liver tissue samples from individuals with metabolic dysfunction-associated steatotic liver disease (MASLD) and stratified by fibrosis severity. **Results:** RNA sequencing and proteomics demonstrated that ceramide increased levels of matrix metalloproteinases (MMPs), including MMP1, to promote pericellular collagen degradation. Through phosphoproteomic analysis, we identified that the effects of ceramide on MMP1-mediated collagen degradation were dependent on PRKCα, ERK1/2, and AP-1 signaling since pharmacologic inhibition or siRNA depletion of each mitigated the effect of ceramide. Inducible deletion of aCDase in CCl_4-treated mice increased *Mmp1a* and *Mmp1b* expression in HSCs, increased collagen degradation, and promoted fibrosis regression. Inhibition of aCDase with compound 5A recapitulated these findings in the FPC model of fibrosis. Among MASLD patients, pathway analysis revealed that ceramide signaling is highly associated with ECM remodeling. **Conclusion:** These findings underscore the critical role of HSCs in ECM degradation. We identified a novel signaling axis in HSCs whereby ceramide promotes PRKCα-ERK1/2-AP1-MMP1 to increase collagen degradation. This work reveals potential targets to promote regression in patients with tissue fibrosis.

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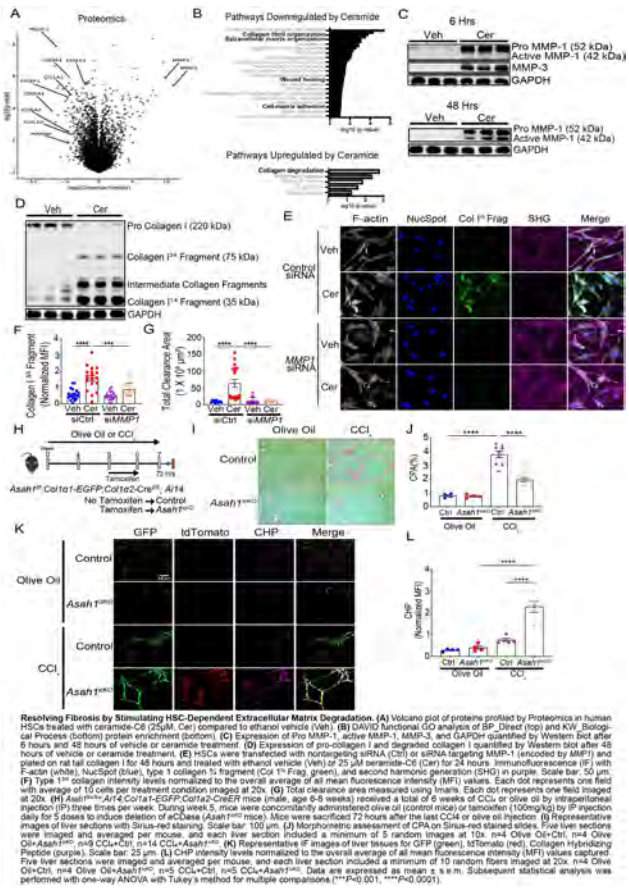

Resolving Fibrosis by Stimulating HSC-Dependent Extracellular Matrix Degradation. **(A)** Volcano plot of proteins profiled by Proteomics in human HSCs treated with ceramide-C6 (25μM, Cer) compared to ethanol vehicle (Veh). **(B)** DAVID functional GO analysis of BP_Direct (top) and KW_Biological Process (bottom) protein enrichment (bottom). **(C)** Expression of Pro MMP-1, active MMP-1, MMP-3, and GAPDH quantified by Western blot after 6 hours and 48 hours of vehicle or ceramide treatment. **(D)** Expression of pro-collagen I and degraded collagen I quantified by Western blot after 48 hours of vehicle or ceramide treatment. **(E)** HSCs were transfected with nontargeting siRNA (Ctrl) or siRNA targeting MMP-1 (encoded by *MMP1*) and plated on rat tail collagen I for 48 hours and treated with ethanol vehicle (Veh) or 25 μM ceramide-C6 (Cer) for 24 hours. Immunofluorescence (IF) with F-actin (white), NucSpot (blue), type 1 collagen ¾ fragment (Col 1^{¾} Frag, green), and second harmonic generation (SHG) in purple. Scale bar: 50 μm. **(F)** Type 1^{¾} collagen intensity levels normalized to the overall average of all mean fluorescence intensity (MFI) values. Each dot represents one field with average of 10 cells per treatment condition imaged at 20x. **(G)** Total clearance area measured using ImarIs. Each dot represents one field imaged at 20x. **(H)** *Asah1*$^{fl/fl}$*-Ai14;Col1a1-EGFP;Col1a2-CreER* mice (male, age 6-8 weeks) received a total of 6 weeks of CCl_4 or olive oil by intraperitoneal injection (IP) three times per week. During week 5, mice were concomitantly administered olive oil (control mice) or tamoxifen (100mg/kg) by IP injection daily for 5 doses to induce deletion of aCDase (*Asah1*^{cko} mice). Mice were sacrificed 72 hours after the last CCl_4 or olive oil injection. **(I)** Representative images of liver sections with Sirius-red staining. Scale bar: 100 μm. **(J)** Morphometric assessment of CPA on Sirius-red stained slides. Five liver sections were imaged and averaged per mouse, and each liver section included a minimum of 5 random images at 10x. n=4 Olive Oil+Ctrl, n=4 Olive Oil+*Asah1*^{cko}, n=9 CCl_4+Ctrl, n=14 CCl_4+*Asah1*^{cko}. **(K)** Representative IF images of liver tissues for GFP (green), tdTomato (red), Collagen Hybridizing Peptide (purple). Scale bar: 25 μm. **(L)** CHP intensity levels normalized to the overall average of all mean fluorescence intensity (MFI) values captured. Five liver sections were imaged and averaged per mouse, and each liver section included a minimum of 10 random fibers imaged at 20x. n=4 Olive Oil+Ctrl, n=4 Olive Oil+*Asah1*^{cko}, n=5 CCl_4+Ctrl, n=5 CCl_4+*Asah1*^{cko}. Data are expressed as mean ± s.e.m. Subsequent statistical analysis was performed with one-way ANOVA with Tukey's method for multiple comparisons.(***P<0.001, ****P<0.0001)

Disclosures: Sachin Sharma: Nothing to Disclose, Vijaya Prathigudupu: Nothing to Disclose, Carson Cable: Nothing to Disclose, Alina Chen: Nothing to Disclose, Srilaxmi Nerella: Nothing to Disclose, Carlos Lizama Valenzuela: Nothing to Disclose, Tatsuya Tsukui: Nothing to Disclose, Jaejun Kim: Nothing to Disclose, Holger Willenbring: Nothing to Disclose, Aras Mattis: BioMarin Pharmaceuticals: Consultant, Pliant Therapeutics: Consultant, Regeneron Phamaceuticals: Consultant, HepaTx: Consultant, Pharmanest: Consultant, Balyn Zaro: Nothing to Disclose, Lia Serrano: Nothing to Disclose, Josh Coon: Nothing to Disclose, Richard Beresis: Nothing to Disclose, William DeGrado: Nothing to Disclose, Hyunil Jo: Nothing to Disclose, Stephanie Christenson: Nothing to Disclose, Jennifer Chen: Nothing to Disclose

3376 | MEDICATION ADHERENCE IN WILSON DISEASE PATIENTS TREATED WITH TRIENTINE TETRAHYDROCHLORIDE SUPPLIED BY A SINGLE SOURCE SPECIALTY PHARMACY

jamie Heise[1] Veronica Tomor[1] Christina Dockery[1] Nick Manamley[2] Michael Heifets[1] Maria DiVito[3] Frances Youschak[3] Joshua Sherback[3] Frederick Askari[4], [1]Orphalan Inc, [2]Orphalan UK Ltd, [3]PANTHERx Rare Pharmacy, [4]University of Michigan Medical Center

Background: Wilson disease (WD) is a rare inherited disorder characterized by copper accumulation, which can be fatal if untreated. Prognosis improves significantly with early diagnosis, effective copper control, and sustained lifelong therapy. Adherence to treatment is essential for achieving optimal clinical outcomes; however, it remains a significant challenge for patients, and poor adherence is associated with disease progression. Trientine tetrahydrochloride (TETA-4HCl, Cuvrior®) received FDA approval in 2022 and became commercially available in April 2023. In the USA, TETA-4HCl tablets are dispensed to patients through a single-source rare disease specialty pharmacy.
Aim/Objective: Retrospective analysis to characterize the patient population and evaluate treatment adherence of TETA-4HCl. **Methods:** A pharmacy database of patients prescribed and having received at least one shipment of TETA-4HCl between May 2023 and December 2024 was evaluated. The following variables were collected and defined: Proportion of Days Covered (PDC): the proportion of days where patients actively have medication on hand over a given time (minimum time for calculation is 180 days); Gap days: defined as the number of days a patient does not have medication on hand based on shipment history (patients included if therapy > 4 months); treatment discontinuation with reasons, demographics and prescriber data. Gap days and PDC were calculated on eligible patients to assess adherence through April 30, 2025. **Results:** During the study period 142 patients were identified and included in the demographics: 78 (55%) males and 64 (45%) females with an overall mean (SD) age of 39 (15.7) years were prescribed TETA-4HCl. Forty-five patients (32%) traveled out of state to consult with their prescriber. Patient payer segmentation was 72% commercial, 15% Medicare, 10% Medicaid, and 3% uninsured. Prescribers were predominantly hepatologists and gastroenterologists at 64% and 23% respectively. Forty-six percent of patients indicated a history of treatment with more than one therapy. Most frequently reported were trientine hydrochloride capsules, zinc salts and penicillamine in that order. Twenty-four patients discontinued therapy; four of those were due to an adverse event. Ninety-three patients met the 180-day threshold for PDC calculation, and 126 were included in the gap day calculation. The mean (SD) PDC was 84 (24) %, with an average gap of 2.7 days per shipment. **Conclusion:** In this real-world analysis of patients with WD receiving TETA-4HCl through a single-source specialty pharmacy, adherence was consistently high with minimal interruption in therapy as described with a gap of 2.7 days per shipment and a low overall discontinuation rate of 17%. The extent to

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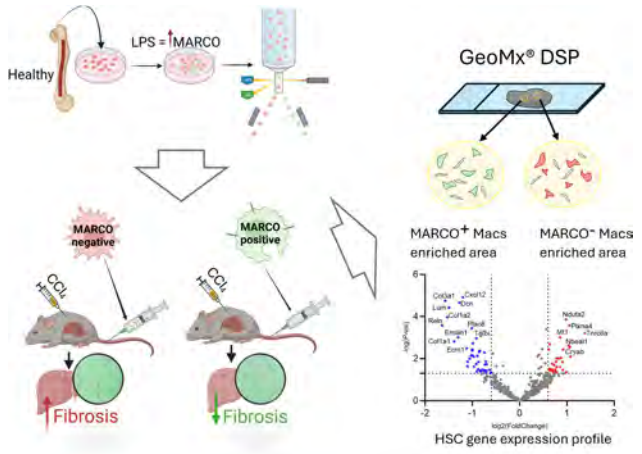
which single-source pharmacy distribution mitigates barriers to access, reduces treatment burden, and facilitates adherence warrants further investigation.
Disclosures: Jamie Heise: Orphalan Inc: Employee, Veronica Tomor: Nothing to Disclose, Christina Dockery: Nothing to Disclose, Nick Manamley: Mundipharma: Employee, Orphalan: Employee, Michael Heifets: Orphalan Inc: Employee, Maria DiVito: Nothing to Disclose, Frances Youschak: Nothing to Disclose, Joshua Sherback: Nothing to Disclose, Frederick Askari: Alexion: Advisor, Ultragenyx Pharmaceutical, Inc.: Advisor, Vivet: Advisor, Deep Genomics: Advisor, Intercept: Advisor

3377 | ADOPTIVE TRANSFER OF MARCO⁺ MACROPHAGES ATTENUATE LIVER FIBROSIS AND SUPPRESS ECM GENE EXPRESSION IN HEPATIC STELLATE CELLS

Sofia Jerez[1] Shawna Cooper[1] Usman Yaqoob[1] Maria Hernandez-Tejero[1] Luke Doskey[1] Nidhi Jalan-Sakrikar[2] Sheng Cao[2] Vijay Shah[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Macrophages (Macs) play a dual role in liver injury, acting as promoters or suppressors of fibrosis depending on their phenotype and the environment. Macs expressing the scavenger receptor MARCO (Macrophage Receptor with Collagenous Structure) increase during fibrosis and have been associated with tissue repair, but their role in the liver remains unclear. Previous findings from our group, using scRNA-seq of fibrotic livers and bone marrow-derived macs (BMDMs), suggest that MARCO⁺ macs exhibit a pro-restorative phenotype. These results prompted us to investigate whether the adoptive transfer of MARCO⁺ BMDMs could attenuate fibrosis and modulate hepatic stellate cells (HSCs), which are the main secretors of extracellular matrix (ECM), in a carbon-tetrachloride (CCl_4)-induced mouse model of liver injury. **Methods:** MARCO expression was induced in BMDMs by LPS stimulus. Next, these cells were FACS-sorted into MARCO⁺ and MARCO- populations and were transferred via the tail vein into recipient mice undergoing CCl_4-induced liver fibrosis. Homing of BMDMs to the liver was confirmed via immunofluorescence, immunoblotting, and flow cytometry. Fibrosis was assessed by Picrosirius red staining. GeoMx DSP was utilized to spatially analyze the transcription profile of HSCs within regions enriched in MARCO⁺ versus MARCO- macrophages, in response to cell transfer. **Results:** Marco⁺ BMDMs successfully homed to the liver and reached injured areas as assessed by immunostaining. Adoptive transfer of MARCO⁺ BMDMs significantly reduced collagen deposition and bridging fibrosis (FC = 0.5, P < 0.05) compared to MARCO⁻ or no cell transfer. Spatial transcriptomic analysis revealed that HSCs from mice that received MARCO⁺ BMDMs (17 Regions of Interest [ROIs] analyzed) presented downregulation of ECM genes, including collagens *Col1a1* and *Col3a1* (FC = 0.3, P < 0.01) and modulatory components such as *Dcn* and *Ecm1* (FC = 0.4, P < 0.01). These transcriptional changes were not observed in fibrotic livers without cell transplantation (16 ROIs analyzed), indicating that the observed gene modulation was specific to the transferred MARCO⁺ BMDMs. Pathway analysis confirmed suppression of key fibrotic pathways, including collagen biosynthesis, collagen trimerization, and fibril assembly. **Conclusion:** Adoptive transfer of MARCO⁺ macs reduces liver fibrosis in vivo and exerts anti-fibrotic effects by downregulating the expression of ECM-related genes in HSCs. These findings highlight the therapeutic potential of MARCO⁺ macs as a cell-based strategy for treating liver fibrosis.



Disclosures: Sofia Jerez: Nothing to Disclose, Shawna Cooper: Nothing to Disclose, Usman Yaqoob: Nothing to Disclose, Maria Hernandez-Tejero: Nothing to Disclose, Luke Doskey: Nothing to Disclose, Nidhi Jalan-Sakrikar: Nothing to Disclose, Sheng Cao: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant

3378 | THE DSRNA-TLR3-IRF3 PATHWAY MEDIATES FIBROTIC RESPONSES OF HEPATIC STELLATE CELLS

Jared Travers[1] Yingting Zhang[1] Megan McMullen[1] Christina Cajigas-Du Ross[1] Emily Huang[2] Jianguo Wu[3] Laura Nagy[3], [1]Cleveland Clinic, [2]Cleveland Clininc, [3]Cleveland Clinic Foundation

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Background: Nucleic acid-induced activation of the anti-viral transcription factor interferon regulatory factor 3 (IRF3) mediates hepatic fibrogenesis in multiple experimental murine models. IRF3 promotes transforming growth factor-beta (TGFβ)-induced fibrotic responses of cultured hepatic stellate cells (HSCs). **Methods:** Short interfering RNA (siRNA)-mediated gene silencing was performed in human LX2 HSCs, and primary HSCs were isolated from wild-type (WT) and Toll-like receptor 3 knock-out (*Tlr3*$^{-/-}$) mice. Fibrogenic gene expression and accumulation of extracellular matrix proteins were determined by quantitative real-time polymerase chain reaction and Western blot analysis of conditioned media, respectively. The presence of cytoplasmic double-stranded RNA (dsRNA) was assessed by immunofluorescence. HSC-specific *Tlr3* knock-out (*Lrat-Cre;Tlr3*$^{fl/fl}$) and control *Tlr3*$^{fl/fl}$ mice were subjected to the chronic carbon tetrachloride (CCl_4) hepatic fibrosis model. **Results:** *IRF3* gene-silencing decreased TGFβ-induced collagen 1A1 (*COL1A1*) mRNA expression and extracellular accumulation in LX2 cells. In order to identify proximal recognition molecules critical to IRF3 activation in TGFβ-induced fibrotic responses, we utilized siRNA technology to assess the contributions of upstream receptors and convergent common adaptors. In addition to stimulator of interferon genes (*STING*), gene-silencing of *TLR3* decreased TGFβ-stimulated *COL1A1* mRNA expression and extracellular accumulation. *Tlr3*$^{-/-}$ primary murine HSCs exhibited decreased *Col1a1* mRNA expression as compared to HSCs isolated from WT mice. Cytoplasmic accumulation of dsRNA was observed both during differentiation of WT primary murine HSCs and upon TGFβ stimulation in LX2 cells. Finally, *Lrat-Cre;Tlr3*$^{fl/fl}$ mice exhibited decreased CCl_4-induced hepatic *Col1a1* mRNA expression as compared to control *Tlr3*$^{fl/fl}$ mice. **Conclusion:** Collectively, these findings identify a cell-intrinsic contribution for TLR3-dependent activation of IRF3 in fibrotic responses of HSCs, which is likely mediated by sensing of accumulated endogenous dsRNA by TLR3. **Disclosures:** Jared Travers: Nothing to Disclose, Yingting Zhang: Nothing to Disclose, Megan McMullen: Nothing to Disclose, Christina Cajigas-Du Ross: Nothing to Disclose, Emily Huang: Nothing to Disclose, Jianguo Wu: Nothing to Disclose, Laura Nagy: Nothing to Disclose

3379 | IDENTIFICATION OF TBX20 AS A MEDIATOR OF HEPATIC STELLATE CELL MEMORY AND PLASTICITY

Alvaro Gonzalez Dominguez[1] *Twinkle Bapuji Vhatkar*[1] *Maylene Yu*[1] *Xuedi Wang*[1] *Deniz Demircioglu*[1] *Saul Carcamo*[1] *Dan Hasson*[1] *Scott Friedman*[2] *Shuang Wang*[1], [1]*Icahn School of Medicine,* [2]*Icahn School of Medicine at Mount Sinai (ISMMS)*

Background: Following acute liver injury hepatic stellate cells (HSCs) are activated to repair the liver but without scarring; however, recurrent liver injury disrupts this balance generating a fibrotic organ. Thus, following repeated injury, HSCs can undergo cycles of activation/deactivation, with deactivated HSCs showing a sensitized response characterized by an intensified expression of fibrogenic genes (Kisseleva 2012, Troeger 2012). Our goal is to understand this maladaptive response of HSCs to repeated injury. **Methods:** In our murine model of fibrogenic memory, animals with or without previous fibrosis regression were exposed to acute carbon tetrachloride-induced liver injury. Single nucleus RNA and ATAC sequencing (snRNAsesq/ATACseq) were carried out at critical timepoints to characterize the transcriptomic and epigenomic changes in HSCs using R/Python packages. HSCs-specific *Tbx20* knockout mice were generated by crossing *Tg(Lrat:Cre)* mice with *Tbx20* floxed mice. **Results:** Following fibrosis regression, the transcriptome of HSCs returned to baseline but epigenomic changes remained as depicted by a drastically altered chromatin accessibility landscape. This "epigenetic memory" in HSCs from regressed mice leads to an increase in HSC plasticity following repeated injury, with novel subsets of HSCs taking up alternative cell identities, such as epithelial, endothelial, or immune. Computational pipelines to predict gene regulatory networks (GRNs) enriched in HSCs across different conditions identified dynamic changes in the TBX20 GRN with repeated injuries, pointing to Tbx20 as a mediator of cell memory and plasticity in HSCs. In line with this finding, knocking out *Tbx20* in HSCs did not affect HSC's response to initial injury but only affected their response to repeated injury. **Conclusion:** We describe for the first time how HSCs retain an epigenetic memory of previous insults, and how this memory leads to increased cell plasticity following repeated injuries to the liver. Furthermore we identify the *Tbx20* GRN as a key mediator of HSC's memory and plasticity.

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3380 | ACTIVATION OF THE INTEGRIN αV-YAP-CTGF AXIS IN LSECS PROMOTES LIVER FIBROGENESIS IN CONGESTIVE HEPATOPATHY

Seiya Kato[1] Yoichi Sasaki[1] Kenji Fukumoto[1] Yuta Myojin[1] Kazuhiro Murai[1] Yuki Tahata[2] Yuki Makino[1] Yoshinobu Saito[1] Takahiro Kodama[2] Hayato Hikita[1], [1]Osaka University Graduate School of Medicine, [2]Osaka University

Background: Congestive hepatopathy (CH), such as right-sided heart failure, post-Fontan surgery and Budd-Chiari syndrome, progresses to liver fibrosis, eventually leading to cirrhosis and cancer despite an absence of significant inflammation. Liver sinusoidal endothelial cells (LSECs) play a key role in liver diseases through angiocrine signaling, which contribute to liver pathogenesis. This study aimed to elucidate the mechanism of CH, focusing on LSECs. **Methods:** Partial IVC ligation (pIVCL) was performed to induce hepatic congestion in mice. Single-cell RNA sequencing (scRNA-seq) was performed using murine livers after pIVCL. As in vitro experiments, primary murine LSECs or TMNK-1 cells, human liver endothelial cell line, were subjected to hydrostatic pressure stimulation (HPS). scRNA-seq and spatial transcriptomics were performed using human livers from patients with Fontan-associated liver disease (FALD). **Results:** The scRNA-seq analysis showed that the integrin signaling pathway and YAP were activated in pericentral LSECs after pIVCL. The most upregulated gene in pericentral LSECs was connective tissue growth factor (CTGF). HPS activated YAP through integrin αV, leading to the upregulation of CTGF and type IV collagen (COL4) expression in LSECs. HPS-induced CTGF upregulation in TMNK-1 cells was suppressed by siRNA-induced YAP silencing, a YAP inhibitor, or an integrin αV inhibitor. LSEC-derived CTGF upregulated the type I collagen (COL1) and COL4 expression in hepatic stellate cells (HSCs). We generated tamoxifen-inducible endothelial cell-specific CTGF knockout mice (Cdh5-CreERT2; $CTGF^{fl/fl}$), followed by pIVCL. CTGF knockout in LSECs suppressed pIVCL-induced liver fibrosis and portal hypertension, and even liver tumorigenesis. Treatment with an integrin αV inhibitor also improved pIVCL-induced liver fibrosis and portal hypertension with the decreased expression of CTGF, COL4 and COL1. The scRNA-seq analysis of clinical FALD samples showed YAP activation and CTGF upregulation in LSECs. Spatial transcriptomics revealed CTGF upregulation in pericentral LSECs from the perisinusoidal fibrosis, and increased COL4 expression in LSECs and increased COL1 expression in HSCs as fibrosis progressed to bridging fibrosis. **Conclusion:** The activation of the integrin αV–YAP–CTGF axis in LSECs plays a crucial role in CH pathology, and therefore, this axis could be a potential therapeutic target for CH.

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3381 | THERAPEUTIC POTENTIAL OF EXERCISED EXTRACELLULAR VESICLES IN IMPROVING SARCOPENIA IN CHRONIC LIVER DISEASE

Sukriti Baweja[1] Preeti Negi[2] Anupama Parasar[2] Chhagan Bihari[2] Shiv Kumar Sarin[2], [1]Institute of Liver and Biliary Sciences, New Delhi, [2]Institute of Liver and Biliary Sciences

Background: Sarcopenia worsens outcomes in chronic liver disease patients, increasing morbidity and mortality. Exercise presents a promising intervention for sarcopenia. Recently, exercised extracellular vesicles (ExEVs), gained attention in muscle-liver crosstalk. This study aims to evaluate the therapeutic effects of ExEVs in sarcopenia-CLD model. **Methods:** ExEVs were isolated at baseline and immediately after 60 mins of hamster wheel running of C57/BL6J mice plasma, characterized using nanoparticle tracking assay and transmission electron microscopy. The ExEVs proteomic cargoes were assessed by mass spectrometry. Sarcopenia was developed in carbon tetrachloride (CCl_4)-CLD mice. After sarcopenia was developed, alongwith CCL4, the 1×10^8 ExEVs or resting EVs were administered intramuscularly on every alternate day and compared with CCl_4 alone (disease control) and vehicle control. Frailty, Grip strength, muscle size, Liver functions test (LFTs) and histology was measured. The gene expression for muscle atrophy (MYOD, Myogenin, MRF4) and myogenesis, myokines, hepatokines, and senescence associated genes were assessed in liver and muscle tissue using qRT-PCR. All parameters were evaluated at 8, 12 and 14 weeks of CCL_4 administration. **Results:** A significant >10-fold increase in total ExEV count post exercise ($p=0.02$) was found than the resting EVs. The ExEV size ranged between 80nm-280nm, with concentration of, $2.65\text{x}10^8 \pm 0.65$particles/ml with zeta potential -17.7 ± 2.4mV. ExEVs cargo proteins were enriched with >7 fold high levels of follistatin, FGF 21, fetuin-B, IGF-1, ApoE, retinol-binding protein-4 than resting EVs. The gait speed, liver frailty index were significantly low by week 8 ($p<0.001$) in CCl_4 mice along with significant increase in liver and muscle fibrosis ($p<0.0003$). By 12 and 14 week of

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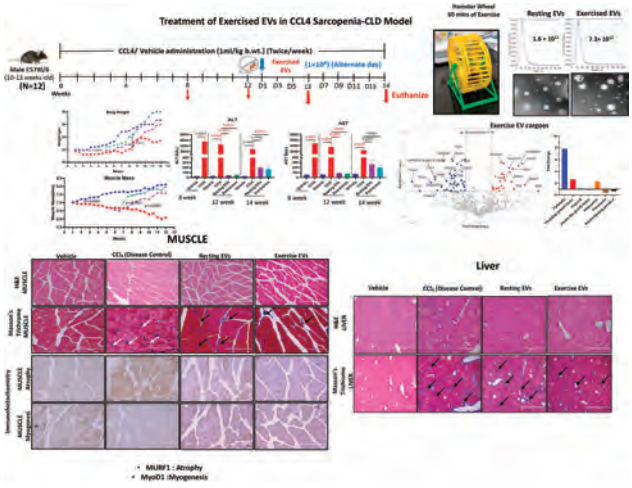
treatment with ExEVs+CCL4, a significant increase in body weight, muscle mass, muscle strength was found ($p < 0.0001$), while muscle fibrosis ($p = 0.05$), AST ($p = 0.03$), and ALT ($p = 0.05$) levels significantly declined compared to resting EVs+CCL4 and disease controls. The expression of muscle atrophy markers (MuRF1 and Atrogin-1) decreased ($p < 0.0001$), while markers of muscle myogenesis (MYOD, Myogenin, MRF4) increased ($p < 0.0001$) significantly in animals receiving ExEVs than resting EVs. Myostatin levels decreased ($p = 0.004$), while Myonectin ($p = 0.05$), IGF ($p = 0.002$), and IL-6 ($p = 0.01$) increased in muscle tissue while Hepatokines including Follistatin ($p < 0.0001$) and Lect2 ($p < 0.0001$) increased significantly in the liver. **Conclusion:** ExEVs are enriched with myokines and hepatokines. Treatment with ExEVs significantly improved muscle mass, strength, and liver function and modulated muscle regeneration and reduced atrophy. Thus, ExEVs possess potent therapeutic effects in mitigating sarcopenia in a CLD model and can serve as promising living drugs mediating beneficial muscle-liver crosstalk.



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3382 | IDENTIFICATION OF NOVEL DRIVERS OF HSC ACTIVATION AND FIBROGENESIS THROUGH LEVERAGING COMPLEMENTARY PROTEOMIC ANALYSIS

Ian Green[1] James Rooney[2] Chunna Guo[2] Reese Baxter[2] Emely Bibian[1] Whitney Smith-Kinnaman[2] Samer Gawrieh[2] Amber Mosley[2] Jessica Maiers[3], [1]Indiana University Indianapolis, [2]Indiana University School of Medicine, [3]Indianapolis School of Medicine

Background: Liver fibrosis is driven by persistent liver injury, characterized by deposition of scar tissue. The major fibrogenic liver cells are Hepatic Stellate Cells (HSCs), which transdifferentiate into myofibroblasts, proliferate, migrate, and secrete matrix proteins. Targeting HSCs is an ideal therapeutic strategy to limit or reverse fibrosis, but has not been successfully achieved in the clinic. While numerous studies have utilized transcriptomics to gain insight into HSC pathophysiology, recent advancements in proteomic analyses have increased the depth of data obtained from approaches such as Mass Spectrometry (MS) and Olink; assessing both global abundance and protein thermal stability. We sought to leverage recently established proteomic techniques and analyses to identify novel drivers of HSC activation and fibrogenesis. **Methods:** Primary hHSCs (ScienCell) were treated with 2ng/mL TGFβ or vehicle for 8 or 24h. Cell lysates were processed directly for proteomic analysis, or incubated along a temperature gradient prior to removal of insoluble proteins to identify changes in protein stability. Soluble proteins were analyzed by TMT-Mass Spectrometry or the Olink Explore 3084 panel (cut off p-value < 0.05). Top targets were validated in patient samples and immortalized HSCs (LX-2 cells), and deleted from LX-2 cells using shRNA to determine their impact on HSC activation. **Results:** MS analysis identified 19 and 131 differently abundant proteins at 8 and 24h TGFβ treatment, while stability of 49 and 140 proteins were changed at 8 and 24h. Olink identified 66 and 150 differentially abundant proteins, and 73 and 196 differentially stabilized proteins at 8 and 24h respectively. Pathway analysis revealed enrichment of proteins involved in matrix organization and fibrogenesis, while changes in protein stability associated with translation initiation and elongation, and protein sorting and trafficking. We validated 5 proteins for investigation: TGFBI, PALLD, SERPINA1, STT3B, and DNAJB11. TGFBI, PALLD, SERPINA1, and DNAJB11 increased in response to TGFβ in LX-2 cells, and TGFBI increased in MASLD patients with F3/F4 fibrosis compared to F0/1. Knockdown of TGFBI, SERPINA1, or STT3B significantly blocked TGFβ-induction of HSC activation markers, highlighting potential fibrogenic roles for these proteins in fibrogenesis. **Conclusion:** Leveraging advanced proteomic techniques and analyses, we identified several novel drivers of HSC activation which could provide essential insight into therapeutic targeting of liver fibrosis.

Disclosures: Ian Green: Nothing to Disclose, James Rooney: Nothing to Disclose, Chunna Guo: Nothing to Disclose, Reese Baxter: Nothing to Disclose, Emely Bibian: Nothing to Disclose, Whitney Smith-Kinnaman: Nothing to Disclose, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research

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3383 | ATP-CITRATE LYASE IN HEPATIC STELLATE CELLS PROMOTES LIVER FIBROSIS IN RESPONSE TO CHEMICAL INJURY

Shi Su[1] Lei Zhao[2] Ray Mastriani[3] Stephen Pinkosky[3] David Cohen[1], [1]Brigham and Women's Hospital/ Harvard Medical School, [2]Brigham and Women's Hospital, [3]Esperion Therapeutics, Inc.

Background: Activated hepatic stellate cells (HSCs) are a main driver of liver fibrosis. ATP-citrate lyase (ACLY) converts citrate to acetyl-CoA, which is a substrate for both lipogenesis and lysine acetylation reactions. Using the LX-2 human HSC line, we previously demonstrated that TGFβ-mediated activation increases ACLY expression. Knock down of ACLY reduced mitochondrial respiration and glycolytic activity of LX-2 cells at baseline and in response to activation. The aim of this study was to evaluate whether ACLY expression in HSCs promotes liver fibrosis in response to chemical injury. **Methods:** HSC-specific ACLY knockout (*HSC-Acly*$^{-/-}$) mice were generated by crossing *Acly*$^{f/f}$ with *Lrat*^{cre} mice. Mouse primary HSCs were isolated and cultured from both control (*Acly*$^{f/f}$) and *HSC-Acly*$^{-/-}$ mice for baseline characterization. Immunoblotting was used to assess the expression of key glycolytic enzymes associated with HSC activation and acetylation of lysine residues as an indicator of transcriptional activation. Age-matched chow fed *HSC-Acly*$^{-/-}$ and control mice were subjected to 4 weeks of carbon tetrachloride (CCl_4)-induced liver injury. ACLY expression in the liver post injury was measured using immunoblotting. Plasma hydroxyproline concentrations were measured using enzymatic assays. Liver sections were stained with Hematoxylin and Eosin for hepatocyte necrosis assessment and with trichrome for fibrosis. **Results:** Primary HSCs from *HSC-Acly*$^{-/-}$ mice exhibited lower glycolytic enzyme expression (20% reduction for Hexokinase 2, 62% reduction for Pyruvate kinase), in addition to distinct protein acetylation, versus controls. After CCl_4 treatment, ACLY expression was increased 2.3-fold in control livers, an effect that was markedly attenuated in *HSC-Acly*$^{-/-}$ mice (60% reduction compared to CCl_4 treated controls). In both *HSC-Acly*$^{-/-}$ and control livers, CCl_4 treatment induced substantial hepatocyte necrosis. However, plasma hydroxyproline concentrations in *HSC-Acly*$^{-/-}$ mice were 43% lower than control mice, in keeping with reduced fibrosis observed in livers of *HSC-Acly*$^{-/-}$ mice. **Conclusion:** Upregulation of ACLY in HSCs promotes liver fibrosis in response to chemical injury. We speculate that increased acetyl-CoA levels due to ACLY upregulation promotes histone acetylation, which in turn upregulates expression of glycolytic enzymes required for HSC activation. These findings suggest that ACLY inhibition may be of therapeutic value in the management of fibrotic liver diseases.

Disclosures: Shi Su: Nothing to Disclose, Lei Zhao: Nothing to Disclose, Ray Mastriani: Esperion Therapeutics: Employee, Stephen Pinkosky: Nothing to Disclose, David Cohen: Pfizer: Data monitoring committee, Astra Zenica: Data monitoring committee, Ipsen: Data monitoring committee, Amryt: Data monitoring committee, Spruce Biosciences: Data monitoring committee, Esperion: And grant support; Investigator initiated basic research, Novo Nordkisk: Advisor

3384 | EFFECT OF MESENCHYMAL STROMAL CELL-DERIVED EXTRACELLULAR VESICLES PURIFIED BY PHOSPHATIDYLSERINE AFFINITY METHOD ON A MURINE MODEL OF LIVER FIBROSIS

Ryo Jimbo[1] Hiroyuki Abe[1] Masayuki Yamane[2] Tomoaki Yoshida[1] Naruhiro Kimura[1] Reina Sasaki-Tanaka[1] Takeshi Yokoo[1] Akira Sakamaki[1] Hiroteru Kamimura[1] Tatsuo Kanda[3] Atsunori Tsuchiya[4] Shuji Terai[1], [1]Graduate School of Medical and Dental Sciences, Niigata University, [2]Bio Science & Engineering Laboratory, FUJIFILM Corporation, [3]Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, [4]Faculty of Medicine, University of Yamanashi

Background: Mesenchymal stromal cells (MSCs) and extracellular vesicles (EVs) derived from MSCs have been shown to suppress liver fibrosis and chronic inflammation in cirrhosis, raising expectations for their clinical application. Although there are various extraction methods for EVs, the phosphatidylserine (PS) affinity method, an affinity purification technique targeting PS on the surface of EVs, is expected to extract EVs with higher purity by targeting PS. In this study, we aimed to evaluate the therapeutic efficacy of EVs purified by the PS affinity method against liver cirrhosis. **Methods:** 7- to 10-week-old female mice ($n = 10$) were treated with intraperitoneal injection of carbon tetrachloride twice weekly for 12 weeks to create a liver fibrosis model, and administered MSC-derived EVs purified by PS affinity (PS group), tangential flow filtration (TFF group), and size-exclusion chromatography (SEC group) at 8th weeks. Samples were collected 4 weeks after EVs administration and analyzed by serum biochemistry and liver tissue. **Results:** In serum biochemistry, AST was significantly decreased to

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148.0 ± 181.3 IU/L in PS group compared to 454.1 ± 325.6 IU/L in the control group ($p < 0.05$), while it was 251.4 ± 178.7 IU/L in TFF group, and 252.2 ± 162.0 IU/L in SEC group, which were not significantly different from the control group. Changes in ALT were similar to those in AST. Sirius-Red staining of liver tissue showed a significant decrease in the positive area ratio of 3.4 ± 2.2% in PS group, 3.2 ± 2.1% in TFF group, and 3.3 ± 2.0% in SEC group, compared to 5.1 ± 2.9% in the control group ($p < 0.001$). Real-time PCR assay in liver tissue showed a significant decrease in mRNA expression of Timp1 in PS group compared to the control group ($p = 0.0397$), while no significant difference was observed in TFF and SEC groups ($p = 0.74$, $p = 0.42$). Similarly, the mRNA expression of Col1a1 was significantly decreased in PS group ($p = 0.018$) and not significantly different in TFF and SEC groups ($p = 0.71$, $p = 0.19$). **Conclusion:** The PS affinity-purified MSC-derived EVs showed comparable or better efficacy in improving fibrosis and liver injury compared with EVs purified by other methods, suggesting their usefulness for clinical application in the treatment of liver cirrhosis in the future.

Disclosures: Ryo Jimbo: Nothing to Disclose, Hiroyuki Abe: Nothing to Disclose, Masayuki Yamane: Nothing to Disclose, Tomoaki Yoshida: Nothing to Disclose, Naruhiro Kimura: Nothing to Disclose, Reina Sasaki-Tanaka: Nothing to Disclose, Takeshi Yokoo: Nothing to Disclose, Akira Sakamaki: Nothing to Disclose, Hiroteru Kamimura: Nothing to Disclose, Tatsuo Kanda: Nothing to Disclose, Atsunori Tsuchiya: Nothing to Disclose, Shuji Terai: Nothing to Disclose

3385 | CT-BASED LIVER MORPHOLOGY SCORING AS A TOOL FOR STRATIFYING AGE-RELATED LIVER DISEASE RISK

Nobuyuki Matsumoto[1] Hideaki Takahashi[1] Takuya Ehira[1] Hironori Aoki[1] Yoshihide Morikawa[1] Jun Ishida[1] Minoru Kanazawa[1] Yuki Mihara[1] Kazuma Terashi[1] Keisuke Tateishi[2], [1]St. Marianna University Yokohama City Seibu Hospital, [2]St. Marianna University School of Medicine

Background: Aging leads to both morphological and functional changes in various organs. While the relationship between age, organ morphology, and organ function has been suggested, research on liver morphology using imaging modalities remains limited. Although recent studies have focused on age-related decline in liver function and fibrosis, quantitative evaluation of morphological changes using CT imaging is scarce. This study aimed to evaluate age-related morphological changes of the liver in a population of generally healthy adults using non-contrast-enhanced CT, and to investigate the potential of such changes as non-invasive markers of aging and liver disease risk. **Methods:** We retrospectively analyzed adult cases who underwent non-contrast-enhanced abdominal CT at our institution between September 1, 2022, and March 31, 2024. Cases were included if they met the following criteria:

1) No abnormal findings requiring treatment or further evaluation, as determined by board-certified radiologists.

2) Results of routine blood tests (hematology and biochemistry) performed within 3 months before or after the CT scan were within 0.5 to 2.0 times the normal reference range.

Thirteen CT-based morphological parameters of the liver (e.g., left lobe hypertrophy, right lobe atrophy, surface irregularity) were each scored on a 0–4 scale. The sum of these scores was defined as the Liver Morphology Score (LMS). **Results:** Among 444 cases meeting the first criterion, 301 also satisfied the second and were included in the final analysis (145 males, 156 females; age range: 16–96 years; mean: 64.5, median: 68). The LMS ranged from 1 to 30 and tended to increase with age. Fatty liver was observed in 127 cases (42.2%). Adjusting the score by subtracting points for fatty liver improved its correlation with age. Although LMS showed a positive correlation with age, the values varied widely among elderly individuals (≥ 80 years), ranging from 3 to 30. LMS was also significantly correlated with the Fib-4 index, which itself had a stronger correlation with age than LMS. **Conclusion:** The Liver Morphology Score (LMS) showed a significant correlation with the Fib-4 index, suggesting its potential as an indicator of age-related hepatic fibrosis progression. Notably, considerable variation in morphology scores was observed even among individuals with similar Fib-4 indices, indicating that structural evaluation may contribute to risk stratification of liver disease in older adults and serve as a useful non-invasive screening tool. In the future, integration with AI-based imaging analysis may further enhance the objectivity and reproducibility of this modality. However, even at present, the liver morphology score holds promise as a cost-effective method for identifying high-risk individuals in clinical practice.

Disclosures: Nobuyuki Matsumoto: Nothing to Disclose, Hideaki Takahashi: Nothing to Disclose, Takuya Ehira: Nothing to Disclose, Hironori Aoki: Nothing to Disclose, Yoshihide Morikawa: Nothing to Disclose, Jun Ishida: Nothing to Disclose, Minoru Kanazawa: Nothing to Disclose, Yuki Mihara: Nothing to Disclose, Kazuma Terashi: Nothing to Disclose, Keisuke Tateishi: Nothing to Disclose

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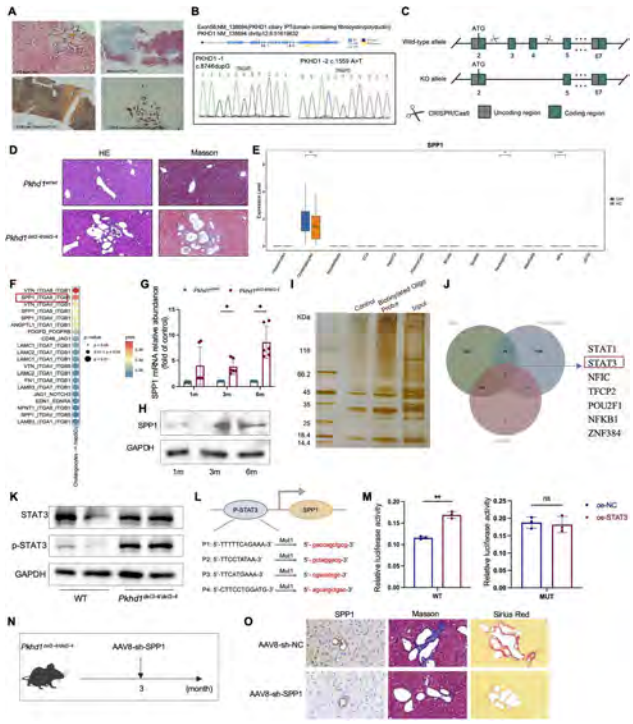
3386 | PKHD1 MUTATION PROMOTE HEPATIC STELLATE CELL ACTIVATE VIA SPP1 IN BILE DUCT CELL

Mengfan Jiao[1] *Chuanlong Zhu*[1], [1]*Nanjing medical university*

Background: Autosomal recessive polycystic kidney and hepatic disease (ARPKD) is a rare hereditary liver disorder, with polycystic kidney and hepatic disease 1 gene (PKHD1) being the most frequently mutated gene. The hallmark features of ARPKD encompass abnormal dilation of cholangiocytes, progressive hepatic fibrosis, and polycystic liver and kidneys as commonly observed clinical manifestations. **Methods:** Whole-exome sequencing revealed the presence of PKHD1 mutations in patients with congenital hepatic fibrosis (CHF). To explore the underlying mechanisms, single-cell RNA sequencing was performed on liver tissue samples. A *PKHD1*-deficient mouse model was established by deleting exons 3–4 of the *PKHD1* gene using CRISPR-Cas9 technology. DNA pull-down assays combined with mass spectrometry (MS) were employed to identify transcription factors upstream of differentially expressed genes. Dual-luciferase reporter assays were conducted to confirm the regulatory interactions between candidate transcription factors and their target genes. **Results:** Whole-exome sequencing identified a compound heterozygous mutation in PKHD1 in a patient with liver histology consistent with CHF (Figure1A, B). A *PKHD1*-deficient mouse model ($Pkhd1^{del3-4/del3-4}$) was generated and showed marked peribiliary fibrosis (Figure1C, D).

Single-cell RNA sequencing of liver tissues from CHF patients and controls revealed enhanced interaction between cholangiocytes and hepatic stellate cells, primarily driven by the secreted protein SPP1 from cholangiocytes and the integrin $\alpha 8\beta 1$ on hepatic stellate cells(Figure1E, F). SPP1 expression was significantly upregulated in mutant cholangiocytes and increased with age in $Pkhd1^{del3-4/del3-4}$ mouse livers (Figure1G, H). To explore the mechanism of SPP1 upregulation, DNA pull-down and MS identified candidate SPP1-binding proteins (Figure1I). Seven potential transcription factors were found, with p-STAT3 notably elevated in $Pkhd1^{del3-4/del3-4}$(Figure1J, K). Luciferase assays confirmed that p-STAT3 binds to and activates the SPP1 promoter, and mutation of the STAT3-binding site abolished this effect (Figure1L, M). AAV8-sh-SPP1 delivered via tail vein effectively reduced SPP1 expression in the liver and attenuated fibrosis in CHF mice (Figure1N, O). These findings suggest that targeting SPP1 may help limit fibrosis progression in CHF.

Conclusion: STAT3-mediated upregulation of SPP1 in PKHD1-deficient cholangiocytes contributes to fibrosis progression, and its inhibition alleviates liver fibrosis. This mechanism reveals a novel, disease-specific antifibrotic target for the treatment of CHF.



Disclosures: Mengfan Jiao: Nothing to Disclose, Chuanlong Zhu: Nothing to Disclose

3387 | DIAGNOSTIC AND PROGNOSTIC PERFORMANCE OF MAGNETIC RESONANCE ELASTOGRAPHY AND MAGNETIC RESONANCE IMAGING-PROTON DENSITY FAT FRACTION IN PATIENTS UNDERGOING LIVER TRANSPLANTATION

Eun-Ki Min[1] *Seung Up Kim*[2] *Jae Geun Lee*[3], [1]*Departement of Surgery, Yonsei University College of Medicine, Seoul, Korea,* [2]*Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea.,* [3]*Department of Surgery, Yonsei University College of Medicine, Seoul, Korea*

Background: Accurate assessment of advanced fibrosis and steatosis is essential for prognostication in chronic liver disease. This study aimed to evaluate the diagnostic performance of magnetic resonance imaging (MRI) in assessing liver fibrosis and steatosis in patients undergoing liver transplantation (LT). **Methods:** Patients who underwent LT between January 2019 and December 2023 with pretransplant magnetic resonance elastography (MRE) and MRI-based proton density fat fraction (MRI-PDFF) examinations were included. Explanted livers were assessed for fibrosis

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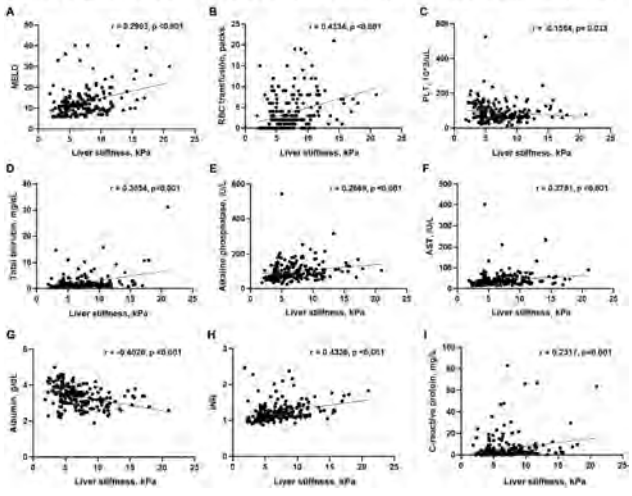
and steatosis, with cirrhosis subclassified using the Laennec system. Diagnostic performance was evaluated using area under the receiver operating characteristic curve (AUC) analysis. **Results:** Among 187 patients (median age, 57 years), 72.2% were male. Hepatitis B virus (55%) and alcoholic liver disease (21.4%) were the most common aetiologies. The median Model for End-Stage Liver Disease (MELD) score was 11. MRE detected cirrhosis (F4) with an AUC of 0.92 (95% confidence interval [CI], 0.87–0.97) and severe cirrhosis (F4c) with an AUC of 0.85 (95% CI, 0.79–0.91), at threshold values of 4.76 and 6.43 kPa, respectively. MRI-PDFF identified steatosis with an AUC of 0.83 (95% CI, 0.76–0.89) at a threshold of 2.80%. Comparisons of patients stratified by the threshold values for cirrhosis and severe cirrhosis revealed significant differences in MELD scores, history of portal hypertension-related complications, liver function parameters, and intraoperative transfusion requirements (all $p < 0.05$). **Conclusion:** MRI demonstrated high diagnostic accuracy for cirrhosis and steatosis in patients undergoing LT. MRE further stratified cirrhosis severity, correlating with liver function, prior decompensation, and transfusion requirements.

Figure 3. Association between clinical variables and liver stiffness by MRE



Disclosures: Eun-Ki Min: Nothing to Disclose, Seung Up Kim: Nothing to Disclose, Jae Geun Lee: Nothing to Disclose

3388 | LIVER MESENCHYMAL STROMAL CELLS (LMSCS) REDUCE HEPATIC STELLATE CELL (HSC) MIGRATION AND EX VIVO HUMAN LIVER FIBROSIS

Alexander Washington[1] Esma Kesik[1] Patrick Starlinger[1] Timucin Taner[2] Enis Kostallari[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Platelet-derived growth factor (PDGF)-mediated activation of hepatic stellate cells (HSCs) is a key driver of liver fibrosis. Liver mesenchymal stromal cells (LMSCs) regulate liver homeostasis through a paracrine mechanism. Nevertheless, the effect of LMSCs signaling on HSC activation and liver fibrosis is unknown and is the aim of this study. **Methods:** In vitro, primary human HSC migration was studied using a transwell assay. In vivo liver fibrosis was induced in C57Bl/6J mice by carbon tetrachloride (CCl_4). Livers were analyzed by spatial transcriptomics (GSE259363) to plot co-expression of HSC markers (Acta2, Des, Pdgfrb) to LMSC markers (Cd44, Thy1, Vim, Nes). Ex vivo, human precision cut liver slices (hPCLS) were obtained using a Precisionary vibratome and analyzed by Western blot. PDGF treatment was used to activate HSCs in vitro and induce collagen deposition ex vivo. **Results:** To understand how spatial proximity between HSCs and LMSCs evolves during liver fibrosis, we analyzed our deposited spatial transcriptomics dataset. CCl_4-mediated liver fibrosis presented a reduced co-expression of HSC and LMSC markers compared to olive oil control (adj.$p < 0.05$), suggesting a role for HSC and LMSC crosstalk during liver homeostasis. To determine whether LMSCs affect HSC migration, a hallmark of HSC activation, we utilized a transwell assay, where HSCs were seeded in the upper chamber and no cells, HSCs as controls or LMSCs were seeded in the lower chamber in the presence of vehicle or PDGF. PDGF only or HSCs+PDGF increased HSC migration by 3-fold compared to vehicle or HSCs+vehicle ($n = 3$, $p < 0.05$). However, the presence of LMSCs (LMSCs+vehicle or LMSCs+PDGF) significantly abrogated HSC migration by 4.96-fold and 4-fold, respectively (transwell, $n = 3$, $p < 0.05$), suggesting that LMSCs reduce HSC activation. Finally, our findings prompted us to assess the role of LMSCs during ex vivo human liver fibrosis utilizing hPCLS from patient liver resections. PDGF treatment increased COL1 protein expression compared to vehicle by 2-fold, which was abrogated 2.4-fold by the presence of LMSCs ($n = 5$, $p < 0.05$), suggesting that LMSC are beneficial to human *ex vivo* liver fibrosis. **Conclusion:** Our results suggest that LMSCs inhibit HSC migration and reduce human ex vivo liver fibrosis.

Disclosures: Alexander Washington: Nothing to Disclose, Esma Kesik: Nothing to Disclose, Patrick Starlinger: Nothing to Disclose, Timucin Taner: Nothing to Disclose, Enis Kostallari: Nothing to Disclose

3389 | GLYCOLYSIS-DERIVED CARBONS ACETYLATE HISTONES TO PROMOTE HEPATIC STELLATE CELL ACTIVATION AND SUBSEQUENT MURINE AND HUMAN LIVER FIBROSIS.

Alexander Washington[1] Zeba Firdaus[1] Patrick Starlinger[1] Petra Hirsova[2] Taro Hitosugi[1] Enis Kostallari[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

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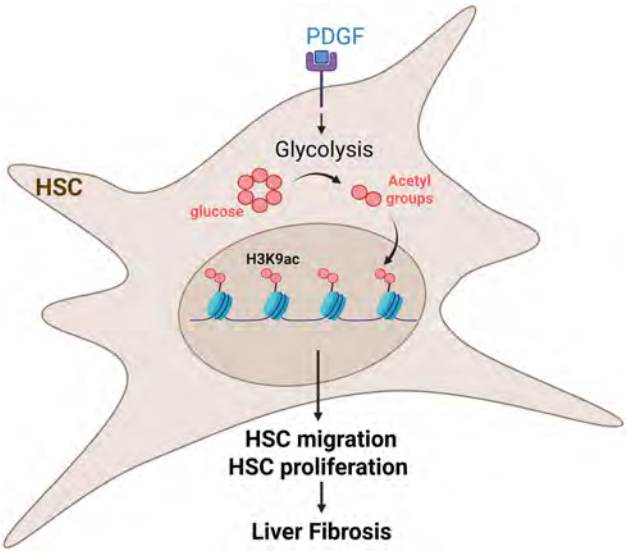
Background: Activated hepatic stellate cells (HSCs), key drivers of liver fibrosis, utilize glycolysis, a metabolic process that generates acetyl groups for protein acetylation. Histone acetylation is an epigenetic process that promotes gene transcription. Nevertheless, how glycolysis directly affects the epigenetic regulation of HSC activation and subsequent liver fibrosis remains unknown and is the focus of this study. **Methods:** In vitro, cells were analyzed by western blot (WB), transwell, 5-ethynyl-2′-deoxyuridine (EdU) uptake, and liquid chromatography mass spectroscopy. In vivo, C57Bl/6J mice were fed choline-deficient high-fat diet (CDHFD) and treated with lysine acetyltransferase (KAT) inhibitor CPTH6. Livers were analyzed by immunofluorescence (IF) and Sirius red. Ex vivo, human precision cut liver slices (PCLS) from liver resections were analyzed by WB. PDGF was used to activate HSCs in vitro and fibrosis in PCLS. **Results:** To understand how histone acetylation is directly dependent on glycolysis, glucose carbons were ^{13}C-traced. PDGF-activated LX2 cells presented an increased percentage of glucose-derived carbons on the acetyl group of H3K9ac, gene promoter acetylation mark, compared to vehicle (incorporation of 1 or 2 heavier isotopes: 5.5-fold for M+1, 7.7-fold for M+2, $n = 5$, $p < 0.05$). However, acetate, another source of acetyl groups, did not participate in H3K9ac ($n = 3$), suggesting that activated HSCs utilize glycolysis for histone acetylation. To understand the importance of H3K9ac in HSC activation, we performed a pharmacological screen of epigenetic marks on primary human HSCs. CPTH6, a selective H3K9ac inhibitor, was the top molecule to reduce PDGF-mediated HSC proliferation by 1.8-fold (EdU, $n = 6$, $p < 0.05$) and migration by 1.6-fold compared to vehicle (transwell, $n = 6$, $p < 0.05$). Knocking down KAT2B, the enzyme leading to H3K9ac, confirmed these effects on proliferation (EdU, 1.9-fold decrease, $n = 6$, $p < 0.05$) and migration (transwell, 1.7-fold decrease, $n = 6$, $p < 0.05$), suggesting that H3K9ac promotes HSC activation. In vivo, in a MASH model of liver fibrosis, CDHFD-induced collagen deposition (19.1-fold by Sirius Red, 20.1-fold by IF, $p < 0.05$) was reduced by CPTH6 treatment (2.1-fold by Sirius Red, 3.2-fold by IF, $p < 0.05$, 10 mice/group). Finally, ex vivo human PCLS model demonstrated that CPTH6 abrogated PDGF-mediated collagen expression (4.5-fold, WB, $n = 5$, $p < 0.05$). **Conclusion:** Our results suggest that H3K9ac in HSCs is directly dependent on glycolysis and promotes HSC activation to amplify liver fibrosis.



Disclosures: Alexander Washington: Nothing to Disclose, Zeba Firdaus: Nothing to Disclose, Patrick Starlinger: Nothing to Disclose, Petra Hirsova: Nothing to Disclose, Taro Hitosugi: Nothing to Disclose, Enis Kostallari: Nothing to Disclose

3390 | POLYSTYRENE NANOPLASTICS PROMOTE HEPATIC STELLATE CELL ACTIVATION BY INDUCING STRETCH-INDUCED MECHANICAL STRESS

Jin-Kyu Park[1] Jae-Hyuk Yim[1] Su-Min Baek[1] Tae-Un Kim[1] Woo Jun Kim[1], [1]Kyungpook National University

Background: Global plastic pollution has led to increased risks of nanoplastics (NPs) ingestion and subsequent accumulation in the liver. However, there is a significant lack of toxicological studies evaluating the long-term effects of NPs on liver physiology, particularly regarding their impact on specific liver cell types. In our previous study, we demonstrated that polystyrene nanoparticles (PS-NPs) exacerbate liver fibrosis. In the present study, we aimed to investigate the direct effects of PS-NPs on hepatic stellate cells (HSCs), which play a central role in liver fibrogenesis. **Methods:** HSC activation was assessed by treating LX-2 cells, a human HSC line, with fluorescently labeled PS-NPs (200μg/mL, 200nm in diameter). Primary HSCs were isolated using an Optiprep density gradient, and after

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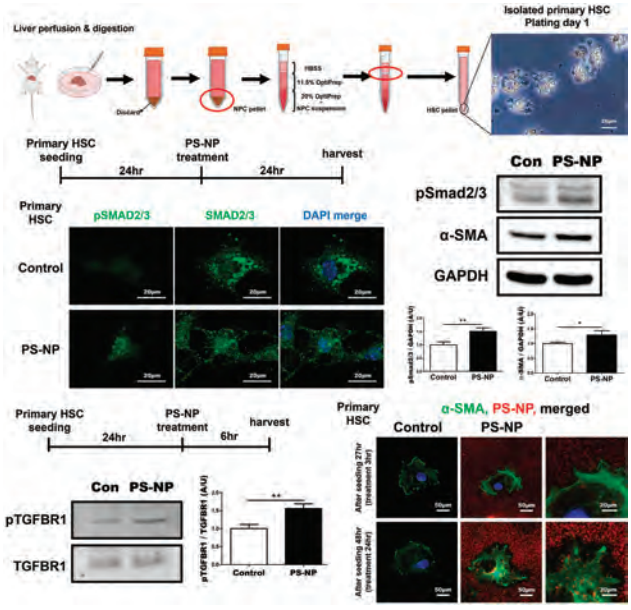
PS-NP treatment, the protein expression levels of α-SMA, phosphorylated Smad2/3 (pSmad2/3), and pTGF-β receptor1(pTGFBR1) were compared through immunofluorescence(IF) and western blot(WB). Time-dependent cytoplasmic changes in HSCs were also examined. Furthermore, confocal microscopy was employed to assess the spatial relationship between PS-NPs and pTGFBR1. **Results:** After 6 hours of PS-NPs exposure, PS-NPs were engulfed by LX-2 cells, resulting in elevated expression of α-SMA and pSmad2/3. In primary HSCs, 24-hour PS-NP treatment induced nuclear translocation of Smad2/3 and significantly elevated pSmad2/3 levels, indicating direct activation of HSCs. PS-NPs also increased pTGFBR1 expression, but confocal analysis revealed no co-localization between PS-NPs and pTGFBR1. Notably, as the treatment time progressed, the pericellular PS-NPs were removed, revealing an empty space between the PS-NPs and the HSCs. During this process, HSCs extended cytoplasmic protrusions toward the PS-NPs, generating mechanical tension which enhanced α-SMA expression. **Conclusion:** This study provides the first evidence of direct HSC activation by PS-NPs via a mechanical stress-mediated mechanism. HSCs actively attempted to remove pericellular PS-NPs, recognized as xenobiotic materials, by stretching their cytoplasm. This mechanical stress contributed to HSC activation, suggesting that PS-NP accumulation in the liver may increase the risk of fibrosis by directly stimulating HSCs.



Disclosures: Jin-Kyu Park: Nothing to Disclose, Jae-Hyuk Yim: Nothing to Disclose, Su-Min Baek: Nothing to Disclose, Tae-Un Kim: Nothing to Disclose, Woo Jun Kim: Nothing to Disclose

3391 | ASSESSMENT OF REGENERATIVE MACROPHAGE THERAPY PHARMACOLOGY SUPPORTS ANTI-INFLAMMATORY AND ANTI-FIBROTIC EFFECTS IN PRECLINICAL MODELS OF LIVER FIBROSIS

Joanna Sweetman[1] Jessica Llewellyn[1] Kayleigh Thirlwell[1] Anna Hoy[1] Olivia Matthews[1] Philip Starkey Lewis[1] Cecilia Rocchi[1] Keith Sutton[1] Lara Campana[1], [1]Resolution Therapeutics Ltd

Background: Resolution Therapeutics is developing a regenerative macrophage cell therapy (RMT), for end stage liver disease. Our lead asset, RTX001, was engineered to possess anti-inflammatory and anti-fibrotic properties. Safety, biodistribution and proof of concept of RTX001 were assessed in uninjured and CCl_4-treated NSG mice to support a successful Clinical Trial Application (CTA) filing. However, due to its immunodeficiency, the NSG strain has limited use in assessing the full pharmacology of RMT. In preparedness for the pivotal clinical trial we have:

1. Assessed the utility of liver fibrosis models (CCl_4, TAA, & CDAA HFD) to determine the pharmacology of RMT
2. Determined the mode of action (MoA) of the murine surrogate (mRTX001) of our product
3. Built a preclinical pharmacodynamic (PD) biomarker program to support and inform our clinical development programme (PD biomarker & potency strategies).

Methods: Liver fibrosis was induced in C57BL/6J WT mice by either CCl_4 IP dosing (4-12 weeks), TAA dosing in drinking water (6-12 weeks), or feeding with CDAA HFD (8-12 weeks). In intervention groups, mRTX001 (murine surrogate) was administered after establishment of disease. Injury, inflammation and fibrosis were assessed by measurement of liver function, collagen deposition, cytokine profile (MSD), proteomics (O-link) and transcriptomics (nCounter®). **Results:** Each model showed distinct inflammatory and fibrotic signatures. Importantly, CDAA HFD and TAA models were found to have an appropriate therapeutic window, with stable fibrosis after removal of insult. Here, we use the CDAA HFD to illustrate our findings. Efficacy of mRTX001 was confirmed by a reduction in collagen deposition (-30% picrosirius red staining) and improvement in liver function (-26% AST & -33% ALT). mRTX001 treatment led to an increase in liver macrophage numbers (F4/80 staining) at 24hrs, followed by a reduction at 72hrs, and a shift towards an anti-inflammatory, pro-regenerative chemokine and cytokine profile, affecting both the innate and

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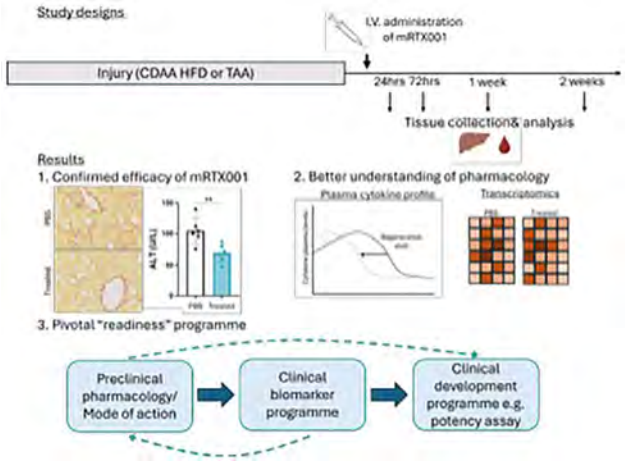
adaptive immunity responses. **Conclusion:** We assessed the pharmacology of a mRTX001 using a combination of models to reflect the broad spectrum of intended patient population. Our data shows that recruitment of macrophages, modulation of inflammation and collagen breakdown form the basis of the MoA of our product. The preclinical datasets provided direction for the development of our clinical biomarker and potency strategy. RTX001 has progressed to clinical testing in UK and Spain (EMERALD Phase 1/2 study).

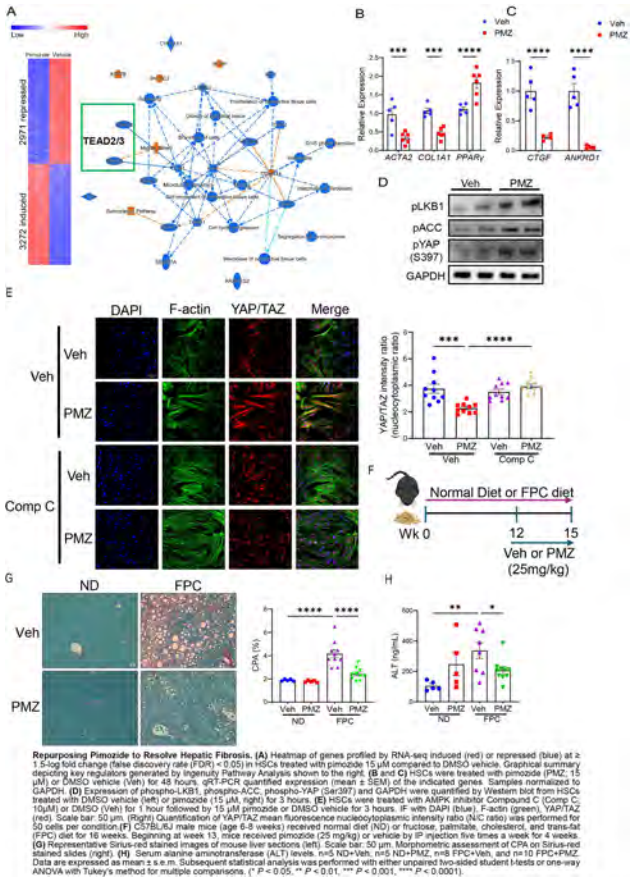


Disclosures: Joanna Sweetman: Nothing to Disclose, Jessica Llewellyn: Nothing to Disclose, Kayleigh Thirlwell: Nothing to Disclose, Anna Hoy: Resolution Therapeutics: Employee, Resolution Therapeutics: Stock – privately held company, Olivia Matthews: Nothing to Disclose, Philip Starkey Lewis: Nothing to Disclose, Cecilia Rocchi: Nothing to Disclose, Keith Sutton: Nothing to Disclose, Lara Campana: Resolution Therapeutics: Employee

3392 | REPURPOSING PIMOZIDE TO REVERSE HEPATIC FIBROSIS VIA AMPK-YAP/TAZ SIGNALING IN HEPATIC STELLATE CELLS

Vijaya Prathigudupu[1] Nidhi Nautiyal[1] Amy Yu[1] Sachin Sharma[1] Aras Mattis[1] Jennifer Chen[1], [1]University of California, San Francisco

Background: Activation of hepatic stellate cells (HSCs) plays a pivotal role in hepatic fibrosis. Targeting their activation offers a promising approach for antifibrotic therapy, which currently lacks FDA-approved drugs. We previously performed a high-throughput small molecule screen, which identified pimozide, an antipsychotic drug in clinical use, as a potential inducer of HSC inactivation. Here, we aimed to validate this finding and discover the molecular mechanisms by which pimozide promotes HSC inactivation. **Methods:** RNA sequencing and Ingenuity Pathway Analysis (IPA) were performed on pimozide- or vehicle-treated primary human HSCs. We modeled HSC activation in vitro by culture on plastic. Hepatic fibrosis was induced in vivo using CCl_4 treatment for 6 weeks or the FPC (fructose, palmitate, cholesterol, trans fats) diet for 16 weeks. Pimozide was administered by intraperitoneal injection for 6 weeks in the CCl_4 model and 4 weeks in the FPC model. Fibrosis was assessed by hydroxyproline and Sirius red staining, and a blinded pathologist performed histological analysis. We performed qPCR, western blotting, and immunofluorescence on mouse liver tissues. **Results:** IPA analysis identified the YAP/TAZ pathway as a downstream pathway of pimozide. We observed that pimozide promotes YAP phosphorylation, inhibits YAP/TAZ nuclear localization, and decreases expression of their transcriptional targets. Furthermore, pimozide activated LKB1-AMPK signaling to inhibit YAP/TAZ. Notably, the inhibition of AMPK rescued YAP/TAZ activation, suggesting that pimozide is mediating YAP/TAZ signaling via AMPK. In the CCl_4 and FPC models of fibrosis, treatment with pimozide ameliorated fibrosis. In the FPC model, pimozide did not alter parameters of MASH such as steatosis, lobular inflammation, or ballooning, but was associated with decreased food intake and improved insulin sensitivity. **Conclusion:** Through a small molecule screen, we discovered that pimozide promotes HSC inactivation and ameliorates hepatic fibrosis. Mechanistically, our findings identify a novel cascade by which pimozide activates LKB1-AMPK to inhibit YAP/TAZ signaling in HSCs. These findings suggest that pimozide may be repurposed for the treatment of hepatic fibrosis.



Repurposing Pimozide to Resolve Hepatic Fibrosis. (A) Heatmap of genes profiled by RNA-seq induced (red) or repressed (blue) at ≥ 1.5-log fold change (false discovery rate (FDR) < 0.05) in HSCs treated with pimozide 15 μM compared to DMSO vehicle. Graphical summary depicting key regulators generated by Ingenuity Pathway Analysis shown to the right. **(B** and **C)** HSCs were treated with pimozide (PMZ; 15 μM) or DMSO vehicle (Veh) for 48 hours. qRT-PCR quantified expression (mean ± SEM) of the indicated genes. Samples normalized to GAPDH. **(D)** Expression of phospho-LKB1, phospho-ACC, phospho-YAP (Ser397) and GAPDH were quantified by Western blot from HSCs treated with DMSO vehicle (left) or pimozide (15 μM, right) for 3 hours. **(E)** HSCs were treated with AMPK inhibitor Compound C (Comp C; 10μM) or DMSO (Veh) for 1 hour followed by 15 μM pimozide or DMSO vehicle for 3 hours. IF with DAPI (blue), F-actin (green), YAP/TAZ (red). Scale bar: 50 μm. (Right) Quantification of YAP/TAZ mean fluorescence nucleocytoplasmic intensity ratio (N/C ratio) was performed for 50 cells per condition.**(F)** C57BL/6J male mice (age 6-8 weeks) received normal diet (ND) or fructose, palmitate, cholesterol, and trans-fat (FPC) diet for 16 weeks. Beginning at week 13, mice received pimozide (25 mg/kg) or vehicle by IP injection five times a week for 4 weeks. **(G)** Representative Sirius-red stained images of mouse liver sections (left). Scale bar: 50 μm. Morphometric assessment of CPA on Sirius-red stained slides (right). **(H)** Serum alanine aminotransferase (ALT) levels. n=5 ND+Veh, n=5 ND+PMZ, n=8 FPC+Veh, and n=10 FPC+PMZ. Data are expressed as mean ± s.e.m. Subsequent statistical analysis was performed with either unpaired two-sided student t-tests or one-way ANOVA with Tukey's method for multiple comparisons. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$).

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3393 | DIGITAL PATHOLOGY QUANTIFICATION REVEALS FIBROTIC SIGNATURES LINKED TO EARLY RECURRENCE IN PATIENTS WITH HEPATITIS B VIRUS-ASSOCIATED HEPATOCELLULAR CARCINOMA

Li Chen Michitaka Matsuda[1] Tatsuya Kanto[1], [1]Japan Institute for Health Security

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality, with early and late recurrence posing significant challenges. Chronic hepatitis B virus (HBV) infection, a dominant HCC etiology, drives fibrogenesis that may influence tumor recurrence by altering the extracellular matrix and immune microenvironment. This study used high-resolution FibroNest™ digital pathology to identify phenotypic fibrosis features linked to recurrence timing and examine the role of HBsAg localization in modulating fibrosis. **Methods:** Liver tissues stained with PSR from HBV-infected HCC patients with early (N = 5) and late (N = 5) recurrence were analyzed using the AI-powered FibroNest™ platform. Fibrosis was quantified across four tissue regions—tumor border, intratumoral area, peritumoral area, and entire tissue—using composite scores for collagen deposition, morphometric traits (fine and assembled fibers), architectural features, and an integrated phenotypic fibrosis composite score (Ph-FCS), a continuous measure of fibrosis severity. Fibrosis scores were also compared between dense and sparse HBsAg+ localized regions within the early and late recurrence samples. **Results:** In analysis for entire tissue, the morphometric score for assembled fibers (early: 5.15 vs. late: 3.86, $p = 0.044$) and the Ph-FCS (early: 5.10 vs. late: 3.90, $p = 0.049$) were significantly elevated in patients with early recurrence. The Ph-FCS demonstrated strong discriminatory power between early and late recurrence, with an AUROC of 0.88, underscoring its potential as a reliable biomarker. No significant differences were observed within specific regional compartments. In the HBsAg+ localized analysis, Ph-FCS was significantly higher in antigen-dense regions (3.98 vs. 2.82, $p = 0.012$). Other fibrosis metrics exhibited non-significant trends toward higher values in dense areas. **Conclusion:** Full-tissue fibrotic burden and structural complexity are more strongly associated with early HCC recurrence than regional fibrotic patterns. Dense HBsAg+ microenvironments may drive localized fibrosis, linking antigen distribution to fibrotic remodeling. These findings highlight spatially resolved digital pathology's potential for recurrence risk stratification and suggest antifibrotic strategies targeting the tissue microenvironment in HBV-related HCC.

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3394 | CONSTITUTIVE MAS1 G PROTEIN-COUPLED RECEPTOR PARTICIPATES IN THE PATHOGENESIS OF LIVER FIBROSIS

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Background: The activation of the renin-angiotensin system (RAS) in experimental and human liver cirrhosis, leads to increased levels of angiotensin-II (Ang-II) and angiotensin type 1 receptor (AT1R) stimulation, thus contributing to liver fibrosis and portal hypertension (PTH). Mas-related G protein-coupled receptor (MAS1) is increased in the cirrhotic liver, representing an alternate mechanism that opposes the effects of the Ang-II/AT1R axis. Thus, we investigated the protective role of MAS1 as a potential antifibrotic receptor constitutively activated in liver fibrosis. **Methods:** Human blood samples were measured for Angiotensin levels. Gene and protein expressions were investigated in human donors and recipients. Wildtype (wt) and Mas-receptor knock out mice ($Mas1^{-/-}$) received CCl_4, MCD, WD or a bile-duct ligation (BDL) to induce liver fibrosis. BDL mice were treated with Ang(1-7) or AVE0991. To assess PHT, the portal pressure (PP) was measured. Murine livers were histologically analyzed and gene and protein expressions were measured. Hepatic stellate cells (HSC) were isolated from mice and cell lines were transfected with Mas1 plasmid. **Results:** MAS1 deficiency stimulates Ang-II/AT1R signaling and thereby aggravates fibrosis and PTH in BDL and CCl_4-mice. *In vivo* studies showed that Ang-(1-7) and AVE0991 lowered portal pressure (PP) in MAS1 deficient mice after BDL, suggesting another receptor different than MAS1 involved in vasoconstriction. *In vitro*, Ang-(1-7) did not attenuate expression of fibrotic markers and

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contraction in MAS1 transfected HSC cells, suggesting that constitute activation of MAS1 is sufficient to relax HSC. **Conclusion:** Constitutive activation of MAS1 in HSC reduces liver fibrosis and PTH.

Disclosures: Sabine Klein: Nothing to Disclose, Fernando Magdaleno Verduzco: Nothing to Disclose, Robert Schierwagen: Nothing to Disclose, Frank Erhard Uschner: Nothing to Disclose, Maximilian Joseph Brol: AbbVie: Consultant, Gilead: Speaking and Teaching, Falk Foundation: Speaking and Teaching, Thomas Walther: Nothing to Disclose, Jonel Trebicka: Nothing to Disclose

3395 | DOES IQR/MEDIAN OF LIVER STIFFNESS MEASUREMENT IMPACT THE ACCURACY OF PREDICTING OF ADVANCED FIBROSIS IN MASLD?

Michael Eiswerth[1] Laura Wilson[2] Samer Gawrieh[3] Raj Vuppalanchi[3] Bryce Hatfield[1] Arun Sanyal[1] Richard Sterling[1], [1]Virginia Commonwealth University, [2]Johns Hopkins University, [3]Indiana University

Background: Liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) is used to estimate fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD). A reliable LSM requires at least 10 valid measurements with the ratio of interquartile range to the median (IQR/M) $\leq$30%. However, for those with a reliable LSM, the impact of IQR/M across the range (1-30%) on the accuracy of LSM is not well defined. We hypothesized that a lower IQR/M within that range would improve the diagnostic performance of LSM by VCTE in predicting biopsy-proven advanced fibrosis (AF), F3-4. **Methods:** This was a prospective analysis of adult participants (pts) with MASLD in the NASH CRN who underwent liver biopsy within 6 months of LSM by VCTE evaluation. Pts were excluded if they had an IQR/M > 30% or less than 10 valid measurements. The degree of fibrosis was determined by central pathology review. Our objective was to evaluate the performance of LSM (analyzed as a continuous variable) across the IQR/M by tertile (1-10, 11-20, 21-30%) to identify AF by histology. Performance characteristics were calculated across tertiles at maximum Youden Index adjusted for age, race, sex, BMI, and type 2 diabetes (T2DM). **Results:** The cohort consisted of 1406 pts: mean (SD) age 52 (12), 39% male, 78% White/9% Asian/3% Black, 13% Hispanic, BMI 34.6 (6.6), 53% with T2DM, and 36% with AF by biopsy. The mean LSM was 12 (10.5) kPa and CAP 323 (51.5) dB/m. The mean days between biopsy and LSM was 52 (35). The mean IQR/M was 15.7 (6.9)%. The performance characteristics of LSM for predicting advanced fibrosis are shown in Table 1 for the entire cohort and each IQR/M tertile (1-10%, 11-20%, 21-30%). The sensitivity (Sn) was highest 1-10% IQR/M group while the specificity (Sp) and PPV was highest in the 21-30% IQR/M group with similar NPV across the groups. The AUROC was 0.88 for the entire cohort and comparable across the IQR/M groups (P = 0.09). **Conclusion:** In patients with IQR/M $\leq$30%, the IQR/M reliability metric did not significantly affect the accuracy of LSM in the diagnosis of AF among MASLD pts. LSM had high diagnostic accuracy for AF. Our results confirm that in patients with IQR/M $\leq$30%, LSM by VCTE demonstrate very good diagnostic accuracy. While LSM by VCTE performed well across all measured tertiles and was not better in the low (<10%) compared to high (21-30%) IQR/M, the performance by IQR/M varied when prioritizing Sn, Sp, or overall performance.

Table 1. Performance characteristics of LSM* to predict advanced fibrosis (F3-4) on biopsy by IQR/med%

			Model fixed at maximum Youden Index†				
IQR/M %¶	N (%)	Prevalence of advanced fibrosis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUROC (95% CI)
Overall	1406 (100%)	36%	0.83	0.73	0.63	0.88	0.85 (0.83-0.87)
1-10%	360 (26%)	32%	0.68	0.84	0.67	0.85	0.84 (0.80-0.89)
11-20%	683 (49%)	36%	0.85	0.69	0.61	0.89	0.84 (0.81-0.87)
21-30%	363 (26%)	39%	0.75	0.86	0.77	0.85	0.87 (0.83-0.91)

* LSM as a continuous measure

† Maximum Youden Index: Overall: 0.55, 1-10%: 0.53, 11-20%: 0.53, 21-30%: 0.61

¶ IQR/M = interquartile range/median; PPV = positive predictive value; NPV = negative predictive value

Models adjusted for age, race, sex, BMI, and diabetes. P=0.09 across the three groups (1-10, 11-20, 21-30 IQR/med%)

Disclosures: Michael Eiswerth: Nothing to Disclose, Laura Wilson: Nothing to Disclose, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant, Raj Vuppalanchi: Eli Lilly: Grant/Research Support, GSK: Consultant, Madrigal: Consultant, Zydus Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Kowa: Grant/Research Support, Takeda: Grant/Research Support, GSK: Consultant, UBC: Consultant, Gilead: Grant/Research Support, GSK: Grant/Research Support, 89 Bio: Consultant, Bryce Hatfield: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,.

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3396 | GENE EXPRESSION PROFILING REVEALS THBS2 AS A CANDIDATE MEDIATOR OF PERIDUCTAL FIBROSIS IN PRIMARY SCLEROSING CHOLANGITIS

Tomohiro Katsumi[1] Keita Maki[1] Fumi Uchiyama[1] Fumiya Suzuki[1] Kyoko Hoshikawa[1] Hiroaki Haga[1] Yoshiyuki Ueno[1], [1]Yamagata University Faculty of Medicine

Background: Primary sclerosing cholangitis (PSC) is pathologically characterized by periductal concentric ("onion-skin") fibrosis. Previous studies have investigated the relationship between injured bile ducts and surrounding inflammatory and fibrotic responses. Spatial transcriptomics has recently enabled gene expression profiling based on morphological context, revealing distinct gene expression patterns in regions of bile duct injury and fibrosis. This study aimed to evaluate the involvement of highly expressed genes identified in specific spatial clusters in the pathogenesis of PSC. **Methods:** We analyzed gene groups that were highly expressed in clusters corresponding to bile duct injury and fibrotic regions in previous spatial transcriptomic analyses. Among these, we focused on genes related to inflammation and fibrosis. Protein levels of candidate genes were measured in serum samples by ELISA and compared between PSC patients and healthy controls. In addition, protein expression in liver tissues was evaluated by immunohistochemistry. **Results:** A total of 556 Visium spots were analyzed from PSC liver tissues, with an average of 3,336 genes detected per spot. In the cluster corresponding to bile duct injury with inflammatory cell infiltration, genes encoding chemokines such as CCL19, CXCL1, and CXCL6, as well as immune modulators such as SPP1, were highly expressed in addition to extracellular matrix markers such as COL and ACTA family members. Among these, Thrombospondin 2 (THBS2) exhibited particularly high expression. Serum THBS2 protein levels were significantly elevated in PSC patients (mean: 58.3 ng/mL) compared to healthy controls (mean: 31.0 ng/mL). Furthermore, THBS2 expression in liver tissue correlated with the degree of fibrosis severity. **Conclusion:** THBS2 was highly expressed in bile duct injury regions of PSC liver tissues. THBS2 is known to promote liver fibrosis via TLR4-FAK/TGF-β signaling pathways. The elevated serum levels of THBS2 in PSC patients further support its involvement in periductal fibrogenesis. Our findings suggest that THBS2 may serve as a potential marker and therapeutic target in PSC-related liver fibrosis.

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3397 | PLATELET INDICES ARE ASSOCIATED WITH CHANGES IN LIVER STIFFNESS MEASUREMENT IN CHRONIC LIVER DISEASE

Robert Pecha[1] James Vu[1] Jordan Hollliday[1] Vikrant Rachakonda[2], [1]University of California Davis Medical Center, [2]Northern California VA Healthcare System

Background: Platelets are key drivers of fibrosis and inflammation in chronic liver diseases. The aim of the current study was to assess predictive relationships between platelet indices, non-invasive fibrosis markers, and fibrosis progression in chronic liver diseases. **Methods:** This retrospective study included 234 patients seen at the Northern California Veterans Affairs Hepatology Clinic (Sacramento, CA) between January 2018-March 2024. Inclusion criteria included chronic liver disease assessment with two vibration controlled transient elastography (VCTE) examinations; each examination was accompanied by laboratory testing. **Results:** Median age was 65 (IQR 53 – 73) years; 160 (68.4%) patients were male, and 150 (64.1%) were Caucasian. Fifty-four patients (23.1%) had chronic HCV, 6 (2.6%) had chronic HBV, and 202 (86.3%) had steatotic liver disease, defined as controlled attenuation parameter > 238 dB/m. Median interval between examinations was 24.1 (14.9 – 39.5) months. Ninety-three (40.1%) patients had compensated advanced liver disease (cALD) defined as liver stiffness measurement (LSM) > 10 kPA on index VCTE, and 71 patients (31.0%) had cALD on follow-up examination. Median platelet count (PC) was lower [201 (156 – 241) $x10^9/mm^3$ vs. 222 (177 – 270)$10^9/mm^3$, $p < 0.001$ by rank sum test], while mean platelet volume-to-platelet ratio (MPVR) was higher [0.052 (0.042 – 0.066) a.u. vs.

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0.047 (0.037 – 0.060) a.u., $p = 0.033$] in cALD patients. MPVR exhibited significant correlation with LSM (spearman rho = 0.0451, $p = 0.001$]. Overall, 106 (45.3%) patients experienced 20% or greater decline in LSM on second VCTE (LSM improvement). On multivariate logistic regression, only change in MPVR (Δ-MPVR) [OR 2.200 (95% CI 1.243 – 3.896. $p = 0.004$], change in AST (Δ-AST) [OR 0.996 (95% CI 0.992 – 0.999), $p = 0.032$], and change in CAP (Δ-CAP) [OR 0.994 (95% CI 0.990 – 0.997), $p = 0.001$] were associated with LSM improvement. Among patients with cALD, 43 experienced reductions in LSM to < 10 kPA (cALD regression), and these subjects exhibited greater decline in MPVR compared to cALD non-regressors [0.052 (0.043 – 0.067) vs. 0.434 (0.037 – 0.058), $p = 0.025$]. **Conclusion:** Platelet indices including PC and MPVR are correlated with LSM in ambulatory patients with chronic liver disease. Δ-MPVR, Δ-AST, and Δ-CAP are independently associated with 20% or greater improvement in LSM. Future studies are planned to prospectively validate platelet indices for outcome prediction in chronic liver disease.

Disclosures: Robert Pecha: Nothing to Disclose, James Vu: Nothing to Disclose, Jordan Hollliday: Nothing to Disclose, Vikrant Rachakonda: Nothing to Disclose

3398 | COMPARING NON-INVASIVE FIBROSIS ASSESSMENT TO BIOPSY: EVALUATING A CONTEMPORARY COHORT

Muhammad Saad Faisal[1] Ammad Chaudhary[1] Mustafa Saadi[1] Kevin Harris[1] Yara Dababneh[1] Abdulmalik Saleem[1] Muhammad Qureshi[1] Reena Salgia[1] Andrew Watson[1], [1]Henry Ford Hospital, Detroit

Background: Accurate staging of liver fibrosis is essential for clinical decision-making in patients with chronic liver disease. While established non-invasive tests (NIT) such as Fibrosis-4 (FIB-4) score and Transient Elastography (TE) are widely used, recent advances introduce a need to evaluate diagnostic precision. Among these, Endoscopic Ultrasound-guided Shear Wave Elastography (EUS-SWE) and Endoscopic Ultrasound-guided Liver Biopsy (EUS-LB) represent promising advancements, offering both real-time imaging and histologic assessment in a single session. However, data on the comparative performance of EUS-SWE remains limited. We aim to evaluate the diagnostic accuracy of specific NITs using EUS-LB as the reference standard. **Methods:** This is a retrospective study conducted after IRB approval, reviewing all patients at a quaternary health care system who underwent EUS-LB from 2022–2024. Histological fibrosis staging from EUS-LB, based on the METAVIR score, served as the reference standard. Performance of TE, EUS-SWE, and FIB-4 was evaluated by comparative fibrosis staging across F0–F4 stages. TE and EUS-SWE were also assessed by sensitivity, specificity, accuracy and comparing mean values for F4 versus F0–F3. Secondary endpoints included procedural safety and biopsy adequacy. **Results:** 75 patients met our inclusion criteria. Mean age was 60.75 ± 10.57, predominantly male(66.7%). EUS-LB yielded a mean biopsy length of 23.61 ± 14.76 mm with 26.05 ± 14.87 complete portal tracts (CPT). 72 (96%) of the biopsy specimens were adequate with > 11 CPT. EUS-SWE was performed in 51(68%) patients, TE was performed in 32(42.7%) patients, and FIB- 4 score was calculated for all patients. EUS-SWE had a sensitivity of 75%, specificity of 57.1%, and accuracy of 62.7%. TE had a sensitivity of 55.6%, specificity of 69.6%, and accuracy of 65.6%. Among 23 patients who underwent both EUS-SWE and TE, Cohen's kappa coefficient for agreement on cirrhosis diagnosis was 0.34 (95% CI: –0.06 to 0.74), indicating fair but statistically uncertain agreement. Mean EUS-SWE and TE values progressively increased from F0–F4, however the difference of means between F4 versus F0-F3 was not significant (p = 0.072 for SWE and p = 0.065 for TE). Adverse events were noted in 1 patient (1.3%) with minor self-resolving bleeding from the biopsy site one day after EUS-LB. **Conclusion:** FIB-4, EUS-SWE and TE, while widely used, demonstrate moderate diagnostic accuracy in staging liver fibrosis, with increased precision in identifying advanced fibrosis/cirrhosis; F4. EUS-LB has emerged as an accurate and safe method for staging hepatic fibrosis while concomitantly assessing for portal hypertension. Importantly, this data challenges the accuracy of NITs which can have an important role in clinical decision making at the patient level including surgical risk stratification, indication for MASH therapies, cancer surveillance, and monitoring protocols.

Biopsy Score	N (%)	EUS- SWE (kPa) Mean ± SD	TE (kPa) Mean ± SD	Fib-4 score (n, %)
F0-F1	16 (21.33)	12.7 ± 4.22	12.3 ± 7.6	>2.67= 6 (37.5), 1.3-2.67= 1 (6) <1.3= 4 (25)
F2	12 (16)	11.8 ± 6.58	12.1 ± 6.36	>2.67= 2 (16.7), 1.3-2.67= 5 (41.7), <1.3= 5 (41.7)
F3	20 (26.67)	16.6 ± 7.75	11.8 ± 8.4	>2.67= 8 (40), 1.3-2.67= 9 (45) <1.3= 1 (5)
F4	27 (36)	18.2 ± 8.31	27 ± 26	>2.67= 13 (48.1), 1.3-2.67= 10 (37) <1.3= 4 (14.8)
Diagnostic Analysis*		**EUS-SWE**	**TE**	**P- Value**
Sensitivity (%)		75	55.6	0.5
Specificity (%)		57.1	69.6	0.69
Accuracy (%)		62.7	65.6	1.0
Statistical Significance of Mean Difference, F4 versus F0-F3 (p-value)		0.072	0.065	

Table 1. Comparison of mean values of EUS-SWE, TE and FIB-4 scores across different fibrosis stages along with data for diagnostic precision *Since diagnostic cut offs are not standardized for EUS-SWE, diagnostic evaluation was based on standardized cutoff values for TE.

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Disclosures: Muhammad Saad Faisal: Nothing to Disclose, Ammad Chaudhary: Nothing to Disclose, Mustafa Saadi: Nothing to Disclose, Kevin Harris: Nothing to Disclose, Yara Dababneh: Nothing to Disclose, Abdulmalik Saleem: Nothing to Disclose, Muhammad Qureshi: Nothing to Disclose, Reena Salgia: Eisai: Speaking and Teaching, AstraZeneca: Advisor, Andrew Watson: Nothing to Disclose

3399 | THE ROLE OF IRON IN HEPATIC FIBROSIS SEVERITY IN BLACK AND WHITE PATIENTS

Michael Attanasi[1] Mathew Gregoski[2] Don Rockey[2], [1]Northwell Health, [2]Medical University of South Carolina

Background: The epidemiology of iron deposition in the liver and its impact on the development of fibrosis is understudied. The purpose of our study was to evaluate the epidemiology and association of iron with cirrhosis. We hypothesized that Black patients would have more iron deposition, but iron deposition would not be associated with cirrhosis. **Methods:** All adults who had a liver biopsy at our institution from January 1, 2013 through July 1, 2021 were identified. Histologic and complete clinical data were abstracted via the medical record. Iron grading was based on the presence of iron granules in hepatocytes, with grade 0 being absent granules at 400x field, grade 1 as granules seen at 250x field (trace), grade 2 with granules seen at 100x field (mild), grade 3 with granules seen at 25x field (moderate, present), and grade 4 with granules seen at 10x field (severe) as per standard histological assessment. Patients with liver lesions, hemochromatosis (determined through genetic testing), or who had undergone liver transplantation were excluded. Chi squared and Pearson correlation analysis were used to determine statistical significance using XLSTAT. **Results:** Of 3,572 patients having a liver biopsy, 839 met inclusion criteria; 189 patients were Black and 650 were White. Etiologies of the liver disease were significantly different between races, where Black patients were more likely to have viral and autoimmune hepatitis (based on serology/histology) and White patients were more likely to have ALD (based on history) and MASLD (based on history and clinical features). Black patients were more likely to have iron on biopsy than White patients (68/189 (36%) vs 179/839 (28%), $p < 0.01$) (Table 1). Pearson correlation demonstrated that the presence of iron was significantly correlated with cirrhosis ($r = 0.156$, $p < 0.0001$); this trend persisted for both Black and White races. Iron was not significantly associated with inflammation, but inflammation was associated with cirrhosis ($r = 0.207$, $p < 0.0001$) and race ($r = 0.077$, $p < 0.05$). The prevalence of cirrhosis was more prevalent in White patients than in Black patients (284 (44%) vs 65 (34%), $p < 0.05$). **Conclusion:** Although Black patients had a greater degree and prevalence of intrahepatic iron than white patients and iron was significantly associated with fibrosis, Black patients had a lower prevalence of cirrhosis than White patients.

Table 1. Population Description

Demographics	White	Black	Total	p
Total	650	189	839	-
Male	314 (48%)	92 (49%)	406	NS
Female	336 (52%)	97 (51%)	433	NS
Histology				
Cirrhosis	284 (44%)	65 (34%)	418	< 0.05
Iron	165 (28%)	63 (36%)	775	< 0.05
Grade 0	471 (74%)	121 (66%)	592	< 0.05
Grade 1	129 (20%)	40 (22%)	169	NS
Grade 2	27 (4%)	16 (9%)	43	< 0.05
Grade 3	8 (1%)	7 (4%)	115	NS
Grade 4	1 (0%)	0 (0%)	1	NS
Etiology				
HBV	18 (3%)	17 (9%)	35	< 0.001
HCV	184 (28%)	79 (42%)	263	< 0.001
AIH	57 (9%)	38 (20%)	95	< 0.0001
ALD	191 (29%)	35 (19%)	226	< 0.01
MASLD	200 (31%)	20 (11%)	220	< 0.0001

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3400 | STUDY ON THE DEGREE OF LIVER FIBROSIS BY FIB-4 INDEX AND ARFI TECHNIQUE IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND NON-DIABETES

Trung Huynh[1], [1]Tam Anh Hospital

Background: Non-alcoholic fatty liver disease (NAFLD) is rising at an alarming rate and has become the most common cause of chronic liver disease worldwide.

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While the interplay between NAFLD and type 2 diabetes mellitus in terms of prevalence and disease progression risks has been extensively studied, the relationship between NAFLD and patients without diabetes has been less investigated. The FIB-4 index and ARFI (Acoustic Radiation Force Impulse) are two non-invasive, accurate, and cost-effective methods for diagnosing liver fibrosis, providing quick results suitable for Vietnam's healthcare context. However, studies on NAFLD in patients without diabetes in Vietnam remain limited. *Objective:* To evaluate the FIB-4 index and shear wave velocity (SWV) measured by the ARFI technique in non-diabetic patients with NAFLD. Additionally, to investigate factors related to liver fibrosis severity in these patients. **Methods:** A cross-sectional descriptive study was conducted on 107 patients diagnosed with NAFLD and without diabetes. **Results:** The mean age of study participants was 50.9 ± 15.2 years, with the youngest being 20 years old and the oldest 78 years old. Females accounted for a higher proportion than males (67.3% vs. 32.7%). All participants (100%) had dyslipidemia; 71% had insulin resistance; 67.3% had metabolic syndrome; 53.3% were obese; 47.7% had prediabetes; 30.8% had hypertension; and 3.7% had other comorbidities. Moderate fatty liver was the most common form, accounting for 63.5%, followed by severe fatty liver (20.6%), while mild fatty liver was the least common (15.9%).The mean FIB-4 value was 1.45 ± 1.83, ranging from 0.1 to a maximum of 13. The mean shear wave velocity (SWV) was 1.29 ± 0.44 m/s, with values ranging from 0.82 m/s to 3.43 m/s. There was a moderate positive correlation between FIB-4 and liver fibrosis stage (Spearman's $r = 0.438$; $p < 0.001$). A statistically significant correlation was found between age, platelet count, AST, GGT, and the degree of liver fibrosis ($p < 0.05$). Additionally, age, AST, and total cholesterol were significantly associated with advanced liver fibrosis ($p < 0.05$). **Conclusion:** There is a moderate positive correlation between the FIB-4 index and liver fibrosis stages assessed by ARFI. In non-diabetic patients with NAFLD, factors associated with significant liver fibrosis ($F \geq 2$) include age, platelet count, AST, and GGT levels. Factors associated with advanced liver fibrosis ($F \geq 3$) in this population are age, AST, and total cholesterol

Factor		OR	95% CI	p
Age		1,19	1,01-1,42	**0,047**
Hb	Decreased	0,11	0,00-10,59	0,342
	Normal	1	-	-
Platelets (10⁹/L)		0,98	0,96-1,00	0,088
AST (U/L)		1,05	1,01-1,09	**0,031**
GGT (U/L)		1,02	0,99-1,06	0,155
Albumin (g/dl)		0,01	0,00-2,61	0,097
Total Cholesterol (mg/dl)		0,96	0,93-0,99	**0,045**

Disclosures: Trung Huynh: Nothing to Disclose

3401 | HIV COINFECTION EXACERBATES HBV-INDUCED LIVER FIBROGENESIS VIA AN EXOSOMAL MIR-103A-3P DEPENDENT PATHWAY

Min Xu[1] Olivia Mezzetti[1] Thien Nguyen[1] Sreya Biswas[2] Cecilie S. Bach-Nielsen[1] Charlotte Warner[1] Xiaoqiong Duan[3] Shasha Li[4] Yongtao Wang[1] Volney Spalding[1] Zeinab Heidariyan[1] Shadi Salloum[1] Xu Yu[5] Benjamin Burwitz[2] Raymond Chung[1] Wenyu Lin[1], [1]Liver Center and GI Division, Massachusetts General Hospital and Harvard Medical School, [2]Oregon National Primate Research Center, Oregon Health and Science University, [3]Institute of Blood Transfusion, Chinese Academy of Medical Sciences and Peking Union Medical College, [4]The Second People's Hospital of Fuyang City, [5]The Ragon Institute of Massachusetts General Hospital, MIT, and Harvard University

Background: HIV coinfection accelerates chronic hepatitis B virus (CHB)-induced cirrhosis compared to monoinfection. Exosomes in cell culture supernatants and patient serum can facilitate intercellular communication by transferring functional molecules such as miRNAs and proteins. Notably, HIV infection has been shown to upregulate miR-103a-3p expression. We sought to investigate the mechanisms by which HIV-induced miR-103a-3p in macrophages contribute to HBV-induced liver fibrogenesis. **Methods:** Exosomes were isolated from the supernatants of HIV-infected (HIVexo), uninfected (U937exo) U937 macrophages and patient plasma. HepG2-NTCP cells, human hepatic stellate (HSC) LX2 cells, primary human hepatocytes (PHHs), and primary HSCs (PHSCs), as well as 3D co-culture models and precision-cut liver slice (PCLS) models, were directly exposed to HIVexo or U937exo in both mono- and coculture with or without treatment with synthetic miR-103a-3p mimics, inhibitors, or siRNA-mediated knockdown of inhibitor of DNA-binding protein 2 (ID2) (target of miR-103a-3p). Rhesus macaque (RM) models of HBV mono- and SHIV/HBV coinfection were employed to confirm the *in vivo* effects of miR-103a-3p on liver fibrogenesis. **Results:** We found that miR-103a-3p is significantly upregulated in exosomes from HIV-infected U937 supernatants and plasma of HIV-positive patients. miR-103a-3p mimics promote HBV-induced liver fibrogenesis in NTCP-HepG2 and LX2 cell lines, a finding validated in PHHs and PHSCs. Furthermore, we found that SHIV/HBV co-infection led to a more pronounced upregulation of miR-103a-3p and profibrogenic gene expression in RM liver tissue compared to baseline levels. These effects were reversed following treatment with combination antiretroviral therapy (cART). We found that miR-103a-3p mimics exacerbate HBV-induced fibrogenesis, while miR-103a-3p inhibitors attenuate this effect. miR-103a-3p's effects are

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mediated by downregulation of ID2 expression, which in turn is associated with increased expression of HIF1A, TGF-b1, and liver fibrosis related gene expression in HBV monoinfected and HIV/HBV coinfected single-cell culture and 3D triple-cell coculture models. **Conclusion:** HIV coinfection exacerbates HBV-induced liver fibrogenesis through upregulation of miR-103a-3p, which suppresses ID2 and consequently leads to overactivation of the HIF-1α and TGF-β1 signaling pathways. miR-103a-3p is a potential biomarker and therapeutic target for liver fibrosis in individuals coinfected with HIV and HBV.

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3402 | TETRACHLOROETHYLENE IS ASSOCIATED WITH SIGNIFICANT LIVER FIBROSIS: A NATIONAL CROSS-SECTIONAL STUDY

Yinan Su[1] Jennifer Dodge[2] Brian Lee[2], [1]Keck School of Medicine of USC, [2]University of Southern California

Background: Tetrachloroethylene (PCE) is a volatile organic compound (VOC) used in dry-cleaning and the textile industry. Pre-clinical studies have linked PCE to hepatotoxicity via oxidative stress and activation of PPAR-α, a regulator of fatty acid metabolism in the liver, but clinical data represent a critical knowledge gap. In this national study, we studied association between PCE levels and liver fibrosis among US adults. **Methods:** We performed a cross-sectional study using the National Health and Nutrition Examination Survey between 2017-2020. Adults aged ≥20 were included and those with hepatitis B or C, current or former smoking, or missing data on PCE levels, alcohol intake, metabolic syndrome, or transient elastography (TE) were excluded. Significant liver fibrosis was defined as TE liver stiffness measurement > 8.2kPA. Detectability of blood PCE levels (ng/mL) was based on lower limits of detection. Associations between liver fibrosis and PCE were analyzed via multivariate logistic regression, adjusted for age, sex, race/ethnicity, poverty, education level, and metabolic syndrome. To strengthen causality of our findings, we performed a negative control analysis using VOC N-Acetyl-S-(2-hydroxyethyl)-l-cysteine (HEMA) as the exposure variable, given co-exposure between precursor substrates to HEMA and PCE. **Results:** Among 1,614 adults, 116 (7.4%) had detectable PCE. Individuals with detectable (vs. undetectable) PCE had higher prevalence of significant liver fibrosis: 12.6% (95%CI 5.9-24.8%) vs. 7.1% (4.8-10.3%). Participants with detectable (vs. undetectable) PCE were similar in age, sex, race/ethnicity, education status, but were less likely to have public health insurance and metabolic syndrome (Table). Detectable (vs. undetectable) PCE (aOR 3.17 [1.23-8.20]) and PCE concentration (aOR per 1 ng/mL increase 5.13 [1.09-24.26]) were associated with higher odds of significant liver fibrosis. In our negative control analysis, 35% of participants with detectable PCE had detectable HEMA. HEMA concentration (aOR per 1 ng/mL increase 0.86 [0.47-1.58]) was not associated with significant liver fibrosis. **Conclusion:** In this national study, PCE was associated with significant liver fibrosis, with a negative control analysis suggesting that this association is distinct to PCE. Our results should encourage prospective studies to confirm PCE as a contributor in liver disease progression to inform screening strategies and environmental policies.

Table. Demographics, socioeconomic and clinical characteristics of group with detectable vs undetectable PCE and HEMA

	PCE		HEMA	
	Detectable (n= 116)	Undetectable (n=1498)	Detectable (n=380)	Undetectable (n=707)
Characteristic	Weighted %, (95% CI)	Weighted %, (95% CI)	Weighted %, (95% CI)	Weighted %, (95% CI)
Age ≥45	57.8 (42.8-71.5)	55.9 (50.0-61.7)	45.9 (36.0-56.2)	64.2 (54.8-72.7)
Male sex	55.8 (43.7-67.3)	45.5 (41.6-49.3)	46.9 (37.9-56.1)	45.1 (38.6-51.7)
Race-ethnicity				
Non-Hispanic white	54.8 (46.0-63.3)	59.9 (53.7-65.8)	50.0 (40.0-60.0)	64.9 (59.0-70.4)
Non-Hispanic black	16.4 (9.1-28.0)	11.5 (9.0-14.7)	18.3 (14.0-23.5)	8.7 (6.8-10.9)
Hispanic	21.1 (14.9-29.2)	18.3 (14.6-22.7)	21.4 (14.8-29.9)	16.8 (13.3-20.9)
Other	7.6 (3.2-17.0)	10.2 (7.7-13.5)	10.4 (7.8-13.8)	9.6 (6.5-13.9)
Below poverty income threshold	5.5 (2.3-12.4)	10.5 (8.5-12.9)	15.3 (11.8-19.7)	7.3 (5.2-10.2)
Insurance status				
None	11.8 (8.4-16.4)	11.6 (9.8-13.7)	14.3 (10.2-19.8)	9.8 (7.4-12.7)
Publicly insured	12.2 (7.6-19.0)	22.3 (18.8-26.2)	23.6 (18.5-29.7)	19.8 (15.1-25.5)
Privately insured	76.0 (68.8-82.1)	66.1 (61.9-70.0)	62.1 (55.0-68.6)	70.4 (64.2-76.0)
Education				
Less than high school	6.4 (2.6-15.0)	8.2 (6.6-10.1)	9.5 (6.6-13.5)	7.8 (5.4-11.1)
High school graduate/GED or equivalent	22.5 (13.4-35.4)	24.8 (21.9-28.0)	25.2 (17.3-35.1)	24.5 (19.7-30.0)
Some college or college graduate	71.0 (55.8-82.6)	67.0 (63.3-70.5)	65.3 (54.9-74.5)	67.7 (62.3-72.8)
Employed	72.5 (62.8-80.5)	69.5 (65.7-73.2)	72.3 (65.9-78.0)	67.8 (62.2-73.0)
Heavy alcohol use[a]	6.8 (1.7-23.8)	5.5 (4.2-7.1)	5.5 (2.4-12.3)	6.6 (4.9-8.8)
Metabolic syndrome	18.5 (11.8-28.2)	31.4 (26.5-36.7)	30.5 (21.7-41.0)	29.2 (21.9-37.7)
Elevated triglycerides	21.7 (13.1-33.8)	28.2 (24.0-32.7)	24.9 (17.6-34.0)	29.6 (23.9-35.9)
High waist circumference	52.3 (40.6-63.9)	59.3 (55.7-62.7)	60.9 (54.6-66.8)	57.9 (52.4-63.3)
Hypertension or taking anti-hypertensive medication	43.2 (29.3-58.2)	41.1 (36.4-45.9)	33.4 (24.0-44.3)	44.7 (38.8-52.7)
Diabetes or taking diabetes medication	35.5 (27.6-44.4)	36.2 (31.3-41.4)	36.8 (27.9-46.6)	35.9 (28.2-39.7)
Low HDL	17.9 (11.3-27.1)	25.8 (22.2-29.9)	70.5 (65.4-75.1)	79.1 (74.3-83.2)
Liver fibrosis (LSM > 8.2kPA)	12.6 (5.9-24.8)	7.1 (4.8-10.3)	7.4 (4.1-13.3)	8.7 (5.3-14.0)
Detectable HEMA	35.0 (25.1-46.4)	29.8 (25.7-34.2)	—	—
Detectable PCE	—	—	9.0 (5.1-15.4)	7.2 (5.2-10.0)

PCE, tetrachloroethylene; HEMA, N-Acetyl-S-(2-hydroxyethyl)-L-cysteine; CI, confidence interval; HDL, high-density lipoprotein; LSM, liver stiffness measurement; kPA, kilopascals; NHANES, National Health and Nutrition Examination Survey; NIAAA, National Institute on Alcohol Abuse and Alcoholism.

[a]Heavy alcohol use was set according to NIAAA definition: ≥ 8 and ≥ 15 drinks per week for women and men, respectively.

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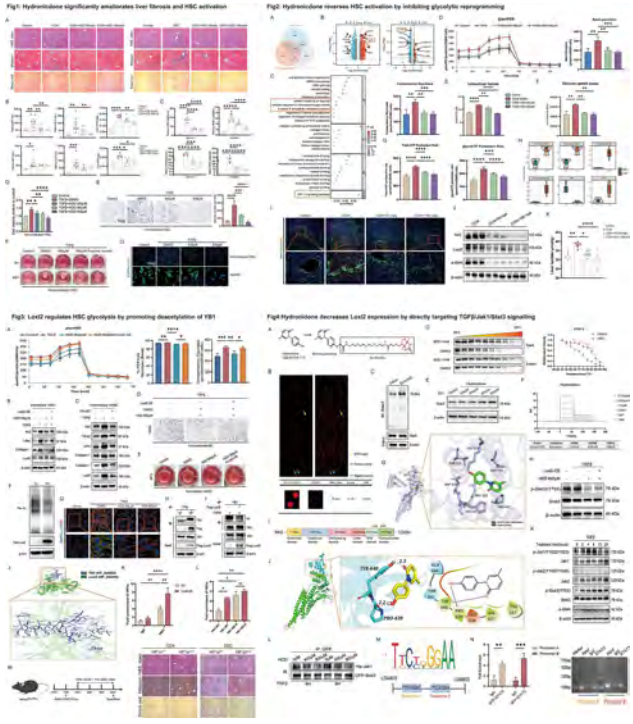
3403 | FROM TRIALS TO TARGETS: HYDRONIDONE'S MECHANISTIC ROLE IN REVERSING HEPATIC FIBROSIS

Qichao Ge[1] Zhangdi Hanjing[1] Hui Huang[2] Yuecheng Guo[1] Yufei Yang[1] Xin Luo[1] Qingqing Zhang[1] Junjun Wang[1] Zhenyang Shen[1] Mingwang Wang[1] Guangwen Chen[1] Yanping Ye[3] Ling Zhang[3] Ying Luo[3] Xiaobo Cai[1] Hui Dong[1] Hu Zhou[2] Lungen Lu[1], [1]Department of Gastroenterology, Shanghai General Hospital, [2]State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, [3]Continent Pharmaceuticals Co., Ltd., Beijing, China

Background: Hydronidone (HDD) has been demonstrated to have beneficial effects on alleviating liver fibrosis in phase II and phase III clinical trials conducted by our group. However, the direct targets of HDD remain unclear. **Methods:** Proteomics, 20K Human Proteome Microarray (20K HuProt), Pull Down/LC-MS/MS, Surface Plasmon Resonance (SPR) and Cellular Thermal Shift Assay (CETSA) were used to detect and validate target proteins of HDD in HSCs. Molecular docking technology was used to explore the HDD binding domain in the target protein. Histology, western blot (WB), immunofluorescence (IF) staining, and RT-qPCR were used to detect the antifibrotic effect of HDD on 3, 5-diethoxycarbonyl-1, 4-dihydropyridine (DDC) and carbon tetrachloride (CCl_4) mouse hepatic fibrosis models. The CCK8, WB, IF staining, cell-contraction assay and transwell assay were used to examine the activation of HSC. Seahorse assay was used to detect the metabolic changes of HSC. CHIP assay was used to investigate the transcriptional regulation. HSC-specific *Hif1a* knockout (*Hif1a*-KO^{HSC}) mice were generated by injecting LRAT-Cre-AAV9 into the *Hif1a*$^{flox/flox}$ mice. **Results:** In DDC and CCl_4-induced hepatic fibrosis mouse models, HDD alleviated liver damage and collagen accumulation(Figure 1A-C). Besides, HDD significantly inhibited the proliferation, migration and contraction in immortalized mouse-HSC(Figure 1D-G). Among all the proteins reversed by HDD, LOXL2 was one of the top-ranked proteins(Figure 2A-B). Furthermore, HDD significantly reversed the glycolytic reprogramming during HSC activation(Figure 2C-G). HDD also inhibited glycolytic metabolism in primary HSCs of mice and reduced liver lactate content(Figure 2H-K). Subsequently, our findings revealed that LOXL2 mediated glycolysis by deacetylating YBX1(K81) which could stabilize the *Hif1a* mRNA and promote its translation(Figure 3A-L). In *Hif1a*-KO^{HSC} mice, DDC and CCl_4-induced liver fibrosis were significantly reduced compared with *Hif1a*$^{flox/flox}$ mice(Figure 3M). As detected by 20K HuProt Microarray, Pull-down/LC-MS/MS and SPR, HDD targeted STAT3 in HSC (Figure 4A-C, 4F). CETSA and WB were used to validate that HDD could influence the thermal stability of STAT3(Figure 4D-E). Further molecular docking revealed that HDD directly bound to the conservative SH2 domain of STAT3, inhibiting the interaction of JAK1 and STAT3 and preventing subsequent dimerization and phosphorylation of STAT3(Figure 4G-L). Furthermore, we also validated that STAT3 directly regulated the transcription of *Loxl2* by the CHIP assay(Figure 4M-N). **Conclusion:** HDD reversed the glycolytic reprogramming mediated by LOXL2/YBX1/HIF1a axis during HSC activation. HDD alleviated liver fibrosis by directly targeting STAT3 which regulated *Loxl2* at transcriptional level in HSCs.



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Disclose, Hui Dong: Nothing to Disclose, Hu Zhou: Nothing to Disclose, Lungen Lu: Nothing to Disclose

3404 | FIVE ANTI-FIBROTIC MICRORNAS ENRICHED IN EXTRACELLULAR VESICLES DERIVED FROM MESENCHYMAL STEM CELLS SUPPRESS HEPATIC STELLATE CELL FIBROGENESIS VIA DOWNREGULATION OF RHOA SIGNALING

Daiki Kawamoto[1] Toshihiko Matsumoto[2] Tsuyoshi Fujioka[1] Naoki Yamamoto[1] Taro Takami[1], [1]Yamaguchi University Graduate School of Medicine, [2]Yamaguchi University Graduate School of Medicine

Background: We have developed a liver regeneration therapy for decompensated liver cirrhosis (DLC) using cultured autologous bone marrow-derived mesenchymal stem cells (BMSCs). A clinical trial (jRCT2063200014) is currently underway, in which hepatic arterial infusion of these cells has improved liver function and fibrosis in patients with DLC. However, the precise anti-fibrotic mechanisms of BMSCs remain unclear. Therefore, we identified anti-fibrotic microRNAs (miRNAs) enriched in MSC-derived extracellular vesicles (MSC-EVs) and investigated the mechanisms by which they suppress fibrogenesis of hepatic stellate cells (HSCs). **Methods:** We compared the miRNA expression profiles in MSC-EVs from DLC patients with those in HSCs using microarray analysis. To identify anti-fibrotic miRNAs enriched in MSC-EVs, we transfected HSCs with miRNA mimics that were highly expressed in MSC-EVs but lowly expressed in HSCs and assessed the expression of fibrosis-related genes. We performed pathway analysis using RNA sequencing data from HSCs transfected with a cocktail of anti-fibrotic miRNAs. RhoA activity and cell motility of HSCs were evaluated using G-LISA assay and time-lapse cell migration assay, respectively. Furthermore, the anti-fibrotic miRNA cocktail was administered to CCl4-induced LC model mice and the resulting histological changes were evaluated. **Results:** We identified 11 miRNAs with normalized intensities $>1{,}000$ in MSC-EVs from DLC patients, with expression levels 100-fold higher than in HSCs. Transfection of these miRNA mimics into HSCs revealed five miRNAs that suppressed the expression of fibrosis-related genes (*ACTA2, COL1A1, COL1A2, COL3A1, and ELN*). Notably, transfection of a cocktail of these five miRNAs led to downregulation of all fibrosis-related genes. KEGG pathway analysis revealed downregulation of RhoA signaling pathway in the HSCs transfected with the miRNA cocktail, which was confirmed by G-LISA as reduced RhoA activity. Time-lapse cell migration assays showed that the miRNA cocktail treatment inhibited HSC migration. Moreover, administering the miRNA cocktail significantly reduced fibrotic areas in the livers of LC model mice. **Conclusion:** This study identified five anti-fibrotic miRNAs in MSC-EVs and elucidated a mechanism of action in suppressing fibrosis via downregulation of RhoA signaling in HSCs. These findings could lead to the development of novel therapeutic strategies for liver fibrosis.

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3405 | WITH NO LYSINE KINASE 1 (WNK1) SIGNALING IN HEPATIC STELLATE CELLS PROMOTES GLUCOSE TRANSPORTER 1 (GLUT1) TRANSLOCATION TO THE PLASMA MEMBRANE AND EX VIVO HUMAN LIVER FIBROSIS.

Zeba Firdaus[1] Shalil Khanal[1] Alexander Washington[1] Jasmin Farmakes[1] Vijay Shah[2] Patrick Starlinger[1] Gina Razidlo[1] Matthew Schellenberg[1] Enis Kostallari[2], [1]Mayo Clinic, [2]Mayo Clinic Rochester

Background: Hepatic stellate cell (HSC) activation in response to platelet-derived growth factor B (PDGF) and transforming growth factor beta 1 (TGF) is a hallmark of liver fibrosis. HSC activation is characterized by increased glucose uptake and glycolysis to meet high energy demands. However, the signaling leading to this metabolic shift, subsequent HSC activation, and liver fibrosis remain unknown and are the aim of this study. **Methods:** In vitro, primary human HSCs or LX2 cells (HSC line) were analyzed by Western blot (WB) and immunofluorescence (IF). Chemical genetics consisted in generating a $WNK1^{T301G}$ mutant that utilizes bulky N6-substituted ATP-γ-S analog. Thiophosphorylated proteins were immunoprecipitated and analyzed by WB. Ex vivo, human precision cut liver slices (PCLS) were obtained utilizing a vibratome and analyzed by WB. **Results:** Our lab has previously identified WNK1 as a novel kinase in HSC activation that promotes glucose uptake (TLM 2024). Public RNA sequencing (GSE119606) demonstrated that HSCs expressed higher levels of WNK1 compared to WNK2, WNK3 and WNK4 (23971-fold, 104-fold, 25-fold, respectively, $n=3$, $p<0.05$). In addition, PDGF, but not TGF, increased WNK1 expression in HSCs (1.4-fold, $n=3$, $FDR<0.05$). More strikingly, PDGF, but not TGF, increased WNK1 phosphorylation, and thus activation by 3-fold (WB, $n=4$, $p<0.05$). Next, we assessed the effect of WNK1 on glucose transporter 1 (GLUT1) translocation to the

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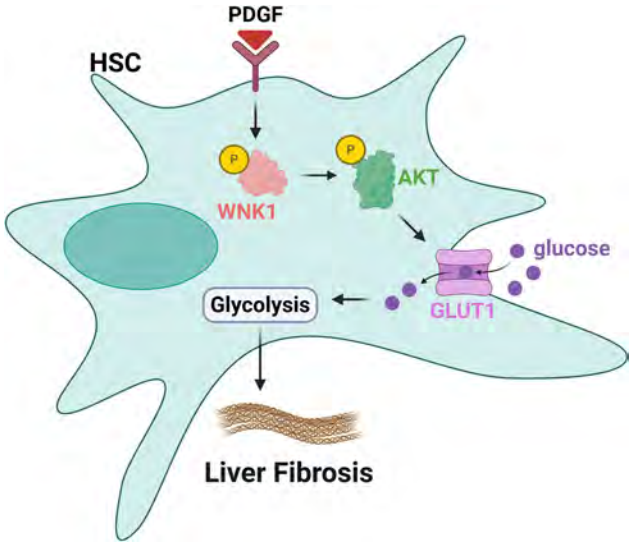
plasma membrane, a crucial step for glucose uptake. PDGF increased GLUT1 translocation to the plasma membrane by 1.5-fold compared to vehicle, which was abrogated by WNK1 selective inhibitor WNK-IN-11 (IF, $n = 3$, $p < 0.05$). To explore the widely unknown WNK1 downstream signaling, we employed chemical genetics. PDGF treatment of mutant WNK1^{T301G}-transfected LX2 cells increased thio-phosphorylation of several proteins compared to controls. PDGF stimulation led to increased AKT phosphorylation in HSCs by 8.5-fold, which was significantly reduced 3-fold by WNK-IN-11 ($n = 3$, $p < 0.05$), indicating that WNK1 activates downstream AKT. Functionally, we utilized our ex vivo 3D culture of human liver sections from consented patients to assess the effect of WNK1 on human liver fibrosis. We found that PDGF-mediated collagen 1 deposition in hPCLS was 2-fold abrogated by WNK-IN-11 ($n = 5$, $p < 0.05$). **Conclusion:** Together, these results identify WNK1 as a PDGF-activated kinase that promotes GLUT1 translocation to the plasma membrane and ex vivo human liver fibrosis.



Disclosures: Zeba Firdaus: Nothing to Disclose, Shalil Khanal: Nothing to Disclose, Alexander Washington: Nothing to Disclose, Jasmin Farmakes: Nothing to Disclose, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Mallinckrodt Pharmaceuticals: Advisor, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant, Patrick Starlinger: Nothing to Disclose, Gina Razidlo: Nothing to Disclose, Matthew Schellenberg: Nothing to Disclose, Enis Kostallari: Nothing to Disclose

3406 | MECHANISTIC AND CLINICAL APPLICATION STUDY ON GSTM3 KNOCKOUT PROMOTING REVERSAL OF LIVER FIBROSIS VIA INHIBITION OF HEPATIC STELLATE CELL ACTIVATION

Chenxue Hou[1] Yuanying Zhao[1] Lei Sun[1] Qi Wang[1] Yue Li[1], [1]Beijing Ditan Hospital, Capital Medical University, Beijing, China.

Background: Liver fibrosis, a key pathological step in chronic liver disease progression to cirrhosis, features dynamic reversibility that offers a critical therapeutic window. However, unclear reversal mechanisms and lacking precise diagnostic markers hinder effective efficacy assessment. Glutathione S-transferase Mu3 (GSTM3), a GST superfamily member involved in detoxification, metabolism, oxidative stress, and carcinogen handling, is upregulated in murine fibrosis models. Yet its role in fibrosis reversal and underlying mechanisms—given distinct progression/regression pathways—remain undefined. This study explores GSTM3's regulatory function in hepatic stellate cell (HSC) activation during fibrosis reversal and its molecular basis, aiming to establish GSTM3 as a novel therapeutic target and noninvasive biomarker. **Methods:** CCL4-induced fibrotic mice were allowed 4- or 12-week withdrawal to model spontaneous regression. Western blot and immunohistochemistry analyzed hepatic GSTM3 protein expression. LX-2 cells with GSTM3 overexpression/silencing were stimulated with TGF-β to assess fibrosis markers (elastin, COL1A1, fibronectin). RNA-seq identified differential pathways in GSTM3-silenced, TGF-β-activated LX-2 cells. Plasma GSTM3 levels in patients were measured via ELISA and correlated with severity. **Results:** ELISA showed higher plasma GSTM3 in fibrosis patients vs. controls, correlating with severity. Hepatic GSTM3 increased in CCL4 mice but decreased in regression models, correlating with resolution degree. TGF-β upregulated GSTM3 in LX-2 cells. GSTM3 silencing reduced elastin, COL1A1, and fibronectin; overexpression increased α-SMA, TIMP-1, and COL1A1. Transcriptomics revealed GSTM3 knockdown inhibited PI3K-Akt and PPAR pathways, blocking HSC activation. **Conclusion:** GSTM3 knockdown promotes fibrosis reversal by inhibiting HSC activation and collagen deposition. With dual tissue/serum expression, GSTM3 offers translational potential as both therapeutic target and noninvasive biomarker, providing a molecular strategy for precision management of liver fibrosis.

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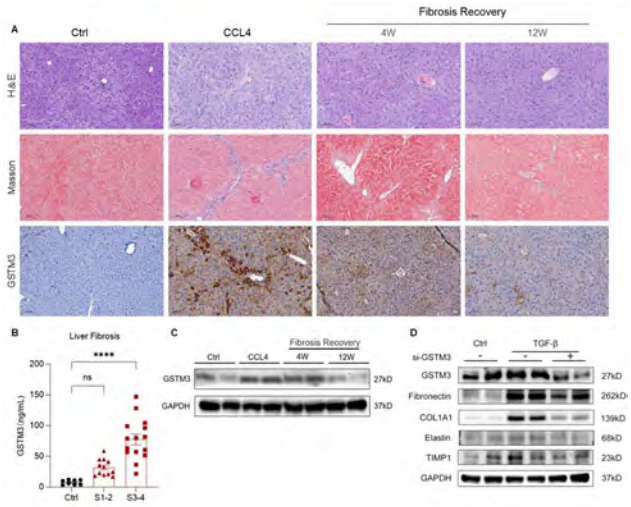

Disclosures: Chenxue Hou: Nothing to Disclose, Yuanying Zhao: Nothing to Disclose, Lei Sun: Nothing to Disclose, Qi Wang: Nothing to Disclose, Yue Li: Nothing to Disclose

3407 | CAN YOU REASON YOUR WAY OUT OF CIRRHOSIS? EVALUATING THE IMPACT OF REASONING ON LARGE TRANSFORMER-BASED PRETRAINED MODELS FOR LIVER CIRRHOSIS MANAGEMENT

Ernest Saenz[1] Jose A. Benitez, M.D.[1] Manuel Linares[1] Andres Gomez Aldana[1], [1]Texas Liver Institute, University of Texas Health Science Center, San Antonio, United States

Background: Liver cirrhosis remains a major global health challenge, accounting for approximately 1.47 million deaths in 2021 (95% UI 1.37–1.58 million), equivalent to 2.4% of all global deaths that year. Rising prevalence of non-alcoholic fatty liver disease further amplifies this burden, driving both morbidity and healthcare costs worldwide. Large language models (LLMs) have emerged as promising aids, capable of extracting key clinical data and automating score calculations, but their effectiveness in hepatology may depend on explicit reasoning capabilities from the latest reasoning architectures implemented on their training. **Methods:** We conducted a three-phase evaluation of twelve state-of-the-art LLMs, six engineered for explicit chain-of-thought reasoning and six using standard next-token prediction, First, two hepatologist selected 58 MedQA multiple-choice items (A–D) and 41 PubMedQA yes/no/maybe questions, and we measured each model's accuracy. Next, one board-certified hepatologist crafted five clinical vignettes containing all required lab values to compute FIB-4 and MELD-Na scores, prompted each model to calculate directly from free text, and analyzed absolute error, signed error, and MAPE. **Results:** Across tasks, reasoning-enabled LLMs consistently outperformed non-reasoning models, while open-source status had no significant effect. In the MedQA benchmark, reasoning conferred a significant accuracy advantage ($F = 11.86$, $p = 0.0006$), with no main effect of open-source status ($p = 0.171$) or interaction ($p = 0.149$). In the PubMedQA task, all model categories achieved similar accuracy ($F = 0.435$, $p = 0.734$). For FIB-4 calculation, reasoning models reduced median MAE by 54.7% compared to non-reasoning counterparts (5.10 vs. 11.27; Mann–Whitney $U = 118$, $p \approx 7 \times 10^{-5}$), despite a mean bias of –7.66 and overall MAPE of 37.3%. MELD-Na predictions proved most challenging: only 12% of outputs fell within ± 5 points of the reference score, and 12% deviated by > 10 points, with no significant influence of reasoning ($p = 0.42$) or open-source status ($p = 0.38$). **Conclusion:** Reasoning-enabled LLMs significantly outperform their non-reasoning counterparts in numeric score calculation (FIB-4: 5.10 vs. 11.27 MAE, $p < 0.0001$) and contribute a robust main effect in multiple-choice hepatology Q&A (MedQA: $F = 11.86$, $p = 0.0006$). Open-source status does not substantially affect performance across tasks. Despite persistent challenges in MELD-Na accuracy and prediction outliers, our findings demonstrate that integrating explicit reasoning chains into LLM architectures yields a marked improvement over "original" non-reasoning models for liver cirrhosis management. We recommend prioritizing reasoning-capable LLMs when developing AI-driven clinical decision support tools in hepatology.

Disclosures: Ernest Saenz: Nothing to Disclose, Jose A. Benitez, M.D.: Nothing to Disclose, Manuel Linares: Nothing to Disclose, Andres Gomez Aldana: Nothing to Disclose

3408 | DISCOVERY OF A NOVEL ACID CERAMIDASE INHIBITOR TO REVERSE HEPATIC FIBROSIS

Vijaya Prathigudupu[1] Richard Beresis[1] Carson Cable[1] Amy Yu[1] Marc Adler[2] Roopa Ramamoorthi[1] Sachin Sharma[1] William DeGrado[1] Hyunil Jo[1] Jennifer Chen[1], [1]University of California, San Francisco, [2]Chemparter

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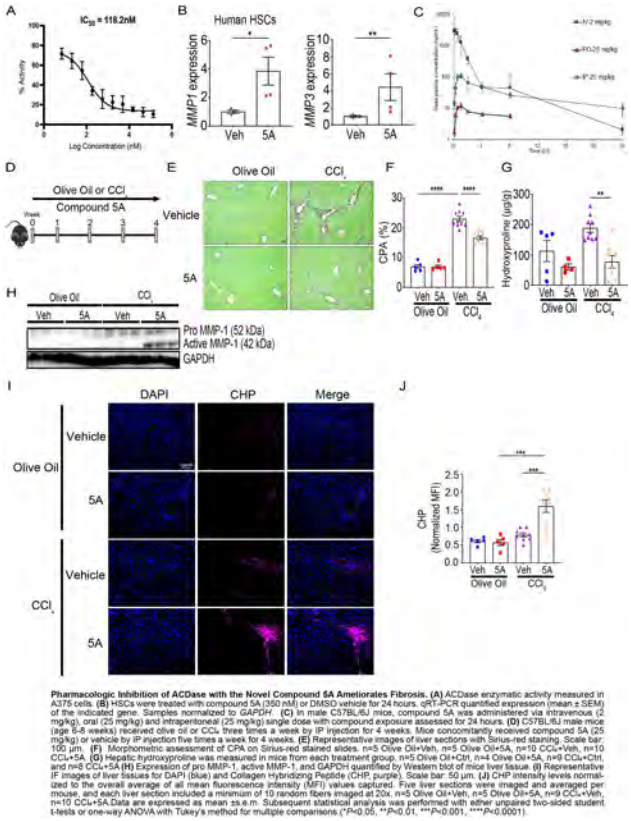
Background: Acid ceramidase (aCDase) is a key enzyme in sphingolipid metabolism and is upregulated in several diseases including cancer and fibrosis. Our previous studies demonstrated that aCDase inhibition or deletion in hepatic stellate cells (HSCs) ameliorated hepatic fibrosis in mouse models and *ex vivo* human precision cut liver slices. There are no FDA-approved therapies to inhibit aCDase, and current tool compounds often lack potency and metabolic stability. Thus, we aimed to develop novel aCDase inhibitors for the treatment of fibrotic diseases. **Methods:** Using structure-based drug design and systematic SAR cataloging, we identified covalent inhibitors of acid ceramidase (aCDase) through enzymatic assays on purified protein and primary hepatic stellate cell (HSC) lysates. HSC activation and collagen degradation were evaluated by qPCR, Western blotting, and immunofluorescence staining with a collagen hybridizing peptide. Cell viability was assessed in primary HSCs and HepG2 cells. Pharmacokinetic profiling of compound 5A was conducted following intravenous (IV), oral (PO), and intraperitoneal (IP) administration to determine its plasma concentration. Hepatic fibrosis was induced using the carbon tetrachloride (CCl_4) model, and compound 5A was delivered via IP injection. Fibrosis and collagen remodeling were assessed by hydroxyproline quantification, Sirius Red staining, collagen hybridizing peptide staining, and second harmonic generation (SHG) microscopy. **Results:** We screened over 50 compounds with various warhead groups, and discovered aryl-substituted heterocyclic urea as a new scaffold. We enhanced potency and metabolic stability through targeted modifications, which led to the discovery of compound 5A. Compared to tool compounds, compound 5A exhibited higher potency and metabolic stability. Furthermore, compound 5A promoted HSC inactivation and induced the production of collagenases to degrade collagen. Among CCl_4-treated mice, compound 5A significantly increased collagen degradation and ameliorated fibrosis. **Conclusion:** Through structure-based drug design, we discovered a novel aCDase inhibitor, compound 5A. Our findings identify compound 5A as a potent and metabolically stable aCDase inhibitor that effectively promotes hepatic stellate cell inactivation, enhances collagen degradation, and reduces liver fibrosis in vivo. These results support further development of compound 5A as a promising therapeutic candidate for the treatment of fibrotic liver disease.



Pharmacologic Inhibition of ACDase with the Novel Compound 5A Ameliorates Fibrosis. (A) ACDase enzymatic activity measured in A375 cells. **(B)** HSCs were treated with compound 5A (350 nM) or DMSO vehicle for 24 hours. qRT-PCR quantified expression (mean ± SEM) of the indicated gene. Samples normalized to *GAPDH*. **(C)** In male C57BL/6J mice, compound 5A was administered via intravenous (2 mg/kg), oral (25 mg/kg) and intraperitoneal (25 mg/kg) single dose with compound exposure assessed for 24 hours. **(D)** C57BL/6J male mice (age 6-8 weeks) received olive oil or CCl_4 three times a week by IP injection for 4 weeks. Mice concomitantly received compound 5A (25 mg/kg) or vehicle by IP injection five times a week for 4 weeks. **(E)** Representative images of liver sections with Sirius-red staining. Scale bar: 100 μm. **(F)** Morphometric assessment of CPA on Sirius-red stained slides. n=5 Olive Oil+Veh, n=5 Olive Oil+5A, n=10 CCl_4+Veh, n=10 CCl_4+5A. **(G)** Hepatic hydroxyproline was measured in mice from each treatment group. n=5 Olive Oil+Ctrl, n=4 Olive Oil+5A, n=9 CCl_4+Ctrl, and n=8 CCl_4+5A **(H)** Expression of pro MMP-1, active MMP-1, and GAPDH quantified by Western blot of mice liver tissue. **(I)** Representative IF images of liver tissues for DAPI (blue) and Collagen Hybridizing Peptide (CHP, purple). Scale bar: 50 μm. **(J)** CHP intensity levels normalized to the overall average of all mean fluorescence intensity (MFI) values captured. Five liver sections were imaged and averaged per mouse, and each liver section included a minimum of 10 random fibers imaged at 20x. n=5 Olive Oil+Veh, n=5 Olive Oil+5A, n=9 CCl_4+Veh, n=10 CCl_4+5A.Data are expressed as mean ±s.e.m. Subsequent statistical analysis was performed with either unpaired two-sided student t-tests or one-way ANOVA with Tukey's method for multiple comparisons.(*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001).

Disclosures: Vijaya Prathigudupu: Nothing to Disclose, Richard Beresis: Nothing to Disclose, Carson Cable: Nothing to Disclose, Amy Yu: Nothing to Disclose, Marc Adler: Nothing to Disclose, Roopa Ramamoorthi: Nothing to Disclose, Sachin Sharma: Nothing to Disclose, William DeGrado: Nothing to Disclose, Hyunil Jo: Nothing to Disclose, Jennifer Chen: Nothing to Disclose

3409 | IMPACT OF EXTRACELLULAR MATRIX STIFFNESS ON TEMPORAL DYNAMICS OF HEPATIC STELLATE CELL ACTIVATION IN VITRO

Kento Inada[1] Masato Miyoshi[1] Sei Kakinuma[1] Tomohiro Mochida[1] Taro Shimizu[1] Jun Tsuchiya[1] Tsubasa Nobusawa[1] Shun Kaneko[1] Fukiko Kawai-Kitahata[1] Miyako Murakawa[1] Sayuri Nitta[1] Mina Nakagawa[1] Yasuhiro Asahina[1] Ryuichi Okamoto[1], [1]Institute of Science Tokyo

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Background: Activation of hepatic stellate cells (HSCs) is the main cause of liver fibrosis, which leads to cirrhosis, liver failure, and hepatocellular carcinoma. Understanding the mechanisms underlying HSC activation is essential, as there is currently no effective treatment for liver fibrosis. However, a major challenge in studying HSCs is that they spontaneously activate and transdifferentiate into myofibroblasts over time when cultured on plastic plates. Although recent studies have reported that the stiffness of the extracellular matrix (ECM) contributes to HSC activation, the details of the mechanism remain unclear. The aim of this study is to clarify the dynamics of HSC activation influenced by ECM stiffness with temporal progression. **Methods:** After perfusion of livers of BALB/c mice with pronase and collagenase, HSCs were isolated by density gradient centrifugation and seeded onto soft polydimethylsiloxane (PDMS) plates (0.2 kPa) as well as standard polystyrene plastic plates ($>$ 1 GPa). Single cell RNA-sequencing (scRNA-seq) was performed on six HSC samples: day 0 (immediately after isolation), days 1 and 3 for PDMS plates, and days 1, 3, and 8 for plastic plates. **Results:** Morphologically, day 1 HSCs on PDMS plates were rounded, while those on plastic plates exhibited characteristic protrusions. Integrated scRNA-seq data from six samples were clustered and annotated, identifying thirteen distinct HSC clusters. Gene set enrichment analysis demonstrated that the cluster which was predominantly composed of day 1 HSCs on PDMS plates highly expressed hallmark genes of unfolded protein response. Moreover, violin plots revealed that quiescent markers such as *Reln* and *Rgs5* were significantly higher in day 0 HSCs and remained elevated in HSCs of days 1 and 3 on PDMS plates compared to the plastic conditions on the same day. Myofibroblastic markers such as *Acta2* and *Col1a1* were most highly expressed in day 8 HSCs on plastic plates. Notably, inflammatory markers such as *Ccl2* and *Ccl7*, which are suggested to be expressed in the early period of HSC activation, were high and increased with ECM stiffness on day 1 and persisted at high level in day 3 HSCs on PDMS plates, whereas their expression declined in day 3 HSCs on plastic plates. **Conclusion:** ECM stiffness is one plausible factor contributing HSC activation. Since the initiatory phase of HSCs rapidly diminishes, culturing on softer matrices is more suitable for research in initiation of HSC activation.

Disclosures: Kento Inada: Nothing to Disclose, Masato Miyoshi: Nothing to Disclose, Sei Kakinuma: Nothing to Disclose, Tomohiro Mochida: Nothing to Disclose, Taro Shimizu: Nothing to Disclose, Jun Tsuchiya: Nothing to Disclose, Tsubasa Nobusawa: Nothing to Disclose, Shun Kaneko: Nothing to Disclose, Fukiko Kawai-Kitahata: Nothing to Disclose, Miyako Murakawa: Nothing to Disclose, Sayuri Nitta: Nothing to Disclose, Mina Nakagawa: Nothing to Disclose, Yasuhiro Asahina: Nothing to Disclose, Ryuichi Okamoto: Nothing to Disclose

3410 | PET-BASED MOLECULAR IMAGING OF INTEGRIN αVβ6 ENABLES NONINVASIVE ASSESSMENT OF LIVER FIBROSIS

TUO SHAO Yanzhang Tian[1] Xiaoyi Wang[2] Xin Gao[1] Huanhuan Song[2] Mengqi Wang[2] Xunchen Zhao[1] Congzhong Hu[1] Raymond Chung[3] Zhifang Wu[4], [1]Shanxi Bethune Hospital, [2]Soochow University, [3]Massachusetts General Hospital, [4]Shanxi Medical University

Background: The activation of latent transforming growth factor beta 1 (TGFβ1) on epithelial surfaces, accompanied by the upregulation of integrin αvβ6, plays a critical role in liver fibrogenesis. Molecular imaging targeting the integrin αvβ6 offers a potential noninvasive approach to assess its expression and function in the activation of TGFβ1 in the injured liver. This could provide valuable prognostic insights into chronic liver disease. The radiotracer ^{68}Ga-DOTA-R01-MG, a cystine knot peptide specifically targeting integrin αvβ6, has shown promise as a PET tracer. In this study, we aimed to compare the uptake of ^{68}Ga-DOTA-R01-MG between normal and fibrotic livers to evaluate its utility in assessing liver fibrogenesis. **Methods:** We utilized PET/CT to assess changes in integrin αvβ6 binding of ^{68}Ga- DOTA-R01-MG in the livers of mice with bile duct ligation (BDL)- and carbon-tetrachloride (CCl_4)-induced liver fibrosis compared with controls. We performed Sirius red staining to assess liver fibrosis, immunofluorescence to identify the location of integrin αvβ6 expressed in fibrotic liver. Additionally, we measured the expression levels of integrin αvβ6, CK19, F4/80 and alpha smooth muscle actin (α-SMA) at both the protein and mRNA levels in control and fibrotic livers. Autoradiography was also conducted to assess tracer uptake in liver sections from both animal models. *Ex vivo* analysis of frozen liver tissue from patients with fibrosis and cirrhosis verified the animal findings. **Results:** Fibrotic mouse livers exhibited significantly increased uptake and retention of ^{68}Ga- DOTA-R01-MG. The radiotracer demonstrated specific binding to integrin αvβ6, primarily expressed on activated bile duct epithelial cells. Hepatic tracer uptake at 30 minutes post-injection was notably higher in fibrotic livers compared to controls. Autoradiography and histopathological analysis corroborated the PET imaging findings, further supporting the specificity of the tracer. Additionally, mRNA and protein levels of integrin αvβ6 and its signaling complex were elevated in both fibrosis models compared to controls. Autoradiography further confirmed the PET imaging finding of high radioactivity

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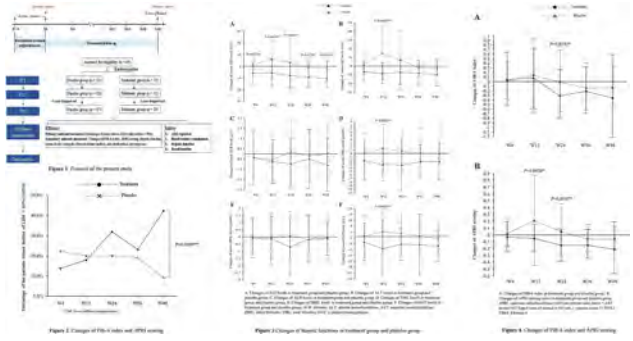
binding in fibrotic liver. The results obtained from analyses on human fibrotic liver sections supported the animal findings. **Conclusion:** Imaging hepatic integrin αvβ6 with PET and ^{68}Ga-DOTA-R01-MG offers a potential noninvasive method for monitoring the progression of liver fibrosis.

Disclosures: TUO SHAO: Nothing to Disclose, Yanzhang Tian: Nothing to Disclose, Xiaoyi Wang: Nothing to Disclose, Xin Gao: Nothing to Disclose, Huanhuan Song: Nothing to Disclose, Mengqi Wang: Nothing to Disclose, Xunchen Zhao: Nothing to Disclose, Congzhong Hu: Nothing to Disclose, Raymond Chung: GSK: Grant/Research Support, Salix: Grant/Research Support, GSK: Consultant, Precision Biosciences: Consultant, Boehringer: Grant/Research Support, BMS: Grant/Research Support, Zhifang Wu: Nothing to Disclose

3411 | VERIFICATION OF THE EFFICACY AND SAFETY OF KEHUANG CAPSULE IN TREATING THE HEPATIC FIBROSIS INDUCED BY CHRONIC HEPATITIS B, A MULTICENTRIC, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Yifan Han[1] Jinghang Xu[1] yanyan yu[1] Yu Chen[2] Sikui Wang[3] Yong Pan[4] Mingqin Lu[5] Shuangsuo Dang[6] Jingbao Hu[7] Wei Li[8] Qingxian Cai[9] Qinshou Chen[10] Xiong Li[10] Guangming Li[11] Ming He[12] Zhan Zeng[13] Ning Lin[13] Xiaoyuan Xu[13], [1]Peking University Fisrt Hospital, [2]BEIJING YOUAN HOSPITAL,CAPITAL MEDICAL UNIVERSITY, [3]Liaocheng People's Hospital, [4]Xuzhou Infectious Disease Hospital, [5]The First Affiliated Hospital of Wenzhou Medical University, [6]The Second Affiliated Hospital of Xi'an Jiaotong University(Xibei Hospital), [7]Shenzhen Bao'an Traditional Chinese Medicine Hospital Group, [8]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, [9]Shenzhen Third People's Hospital, [10]GaoZhou people's hospital, [11]The Sixth People's Hospital of Zhengzhou, [12]The First Affiliated Hospital of Nanyang Medical college, [13]Peking University First Hospital

Background: Infection with hepatitis B virus can cause chronic hepatitis B (CHB) with sustained inflammation of liver, which may cause hepatic fibrosis. Kehuang capsule (KHC) is an herbal medicine traditionally used to treat hepatic diseases and many components of KHC were reported to have anti-inflammatory effects. In this study, we evaluated the efficacy and safety of KHC treating CHB-induced hepatic fibrosis. **Methods:** This multicentric, randomized (1:1), double-blind, placebo-controlled study was conducted in 12 centers and enrolled adult Chinese patients with hepatic fibrosis induced by CHB. This study adopted the protocol of "C + T vs C + P" (C = conventional treatment = antiviral treatment, T = treatment = KHC 4# tid for 48 weeks Z P = placebo, Figure 1). The primary outcome measure was set as the percentage of cases whose liver stiffness measurement (LSM) value reduced ≥ 30%. The second outcome measures were set as fibrosis (FIB)-4 index, AST-to-platelet ratio index (APRI) scores, indices of hepatic function, indices of hepatic fibrosis, and hepatic fibrosis-related symptoms. **Results:** A total of 56 subjects finished the follow-up and were analyzed. Figure 2 shows the primary outcome measure, percentage of the patients whose LSM declined > 30% in treatment group was significantly higher than that of placebo group after treatment for 48 weeks (42.31% vs 9.09, P = 0.0099). In terms of the secondary outcome measures, the indices of hepatic functions (aspartate aminotransferase, alanine aminotransferase, total bilirubin, and β-glutamyltranspeptidase) and aspartate aminotransferase-to-platelet ratio index significantly ameliorated in treatment group after 12 weeks (Figure 3). The indices of fibrosis-4 ameliorate after 24 weeks, and pain in the right upper abdomen significantly ameliorated in treatment group after 48 weeks (Figure 4). In terms of safety, KHC did not add the incidence of adverse events. No drug-related ADE, ADE inducing drug withdrawal, ADE inducing reduction of dose, and ADE causing death were reported. **Conclusion:** KHC is a useful adjuvant with satisfactory efficacy and safety for the mainstream antiviral therapy in treating CHB-induced hepatic fibrosis.



Disclosures: Yifan Han: Nothing to Disclose, Jinghang Xu: Nothing to Disclose, yanyan yu: Nothing to Disclose, Yu Chen: Nothing to Disclose, Sikui Wang: Nothing to Disclose, Yong Pan: Nothing to Disclose, Mingqin Lu: Nothing to Disclose, Shuangsuo Dang: Nothing to Disclose, Jingbao Hu: Nothing to Disclose, Wei Li: Nothing to Disclose, Qingxian Cai: Nothing to Disclose, Qinshou Chen: Nothing to Disclose, Xiong Li: Nothing to Disclose, Guangming Li: Nothing to Disclose, Ming He: Nothing to Disclose, Zhan Zeng: Nothing to Disclose, Ning Lin: Nothing to Disclose, Xiaoyuan Xu: Nothing to Disclose

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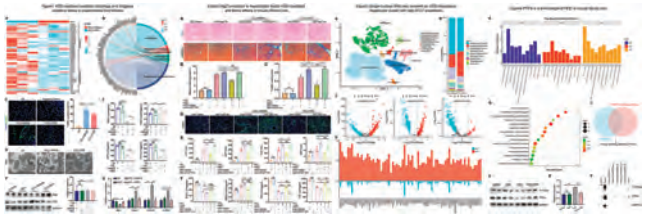
3412 | HYDRONIDONE ACTIVATES THE PTEN–ATG7 AXIS TO RESTORE MITOPHAGY AND CURB OXIDATIVE STRESS IN HEPATOCYTES DURING EXPERIMENTAL LIVER FIBROSIS

Yuecheng Guo[1] Qichao Ge[1] Hanjing Zhangdi[1] Yufei Yang[1] Junjun Wang[1] Qingqing Zhang[1] Yanping Ye[2] Ling Zhang[2] Ying Luo[2] Xiaobo Cai[1] Hui Dong[1] Lungen Lu[1], [1]Shanghai general hospital, [2]Continent Pharmaceuticals Co.

Background: Chronic liver injury drives extracellular-matrix accumulation and hepatocyte damage, culminating in fibrosis. Hydronidone (HDD) is a newly identified anti-fibrotic compound. We aimed to investigate whether HDD protects hepatocytes during fibrogenesis and delineate the underlying mechanism. **Methods:** C57BL/6 mice received carbon tetrachloride (CCl_4, 6 weeks) to induce fibrosis; HDD (100 mg kg^{-1} day^{-1}, oral) was administered throughout. Hepatocyte apoptosis and oxidative stress were assessed by TUNEL staining and antioxidant-enzyme assays. Mitophagy and mitochondrial damage were monitored under a transmission electron microscope. Bulk RNA-seq, single-nucleus RNA-seq and protein microarrays, combined with drug-affinity-responsive-target-stability (DARTS) assays, were used to identify HDD targets. Hepatocyte-specific ATG7 knock-down was achieved with AAV8-TBG-shAtg7. **Results:** HDD down-regulated inflammatory and fibrogenic gene sets. ATG7 may be the core gene regulating mitophagy, oxidative stress and cell death in injured livers. HDD significantly up-regulated ATG7, accelerated mitophagic flux, reduced reactive-oxygen-species levels and decreased TUNEL-positive hepatocytes during liver fibrogenesis. Silencing ATG7 abolished HDD-mediated anti-fibrotic effects. Single-nucleus RNA-seq revealed an HDD-responsive hepatocyte cluster with high ATG7 expression. Proteomic screening and DARTS identified phosphatase-and-tensin homologue (PTEN) as a direct HDD target. HDD increased total PTEN and decreased its inhibitory phosphorylation. **Conclusion:** HDD mitigates hepatocyte injury in fibrotic liver by binding to PTEN and activating the PTEN–ATG7 pathway, which restores mitophagy and limits oxidative stress. These findings position HDD as a promising therapeutic candidate for liver fibrosis.



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3413 | MITOCHONDRIAL UNCOUPLER PROMOTES HEPATIC STELLATE CELL ACTIVATION AND LIVER FIBROSIS BY IMPAIRING MITOCHONDRIA AND LYSOSOME FUNCTION

Ji Hyun LEE[1] Jae Min KIM[2] Ji Hye YANG[2] Sung Hwan KI[1], [1]College of Pharmacy, Chosun University, [2]College of Korean Medicine, Dongshin University

Background: Hepatic stellate cells (HSCs) play a central role in liver fibrosis. Mitophagy, the lysosome-dependent degradation of mitochondria, can be induced by carbonyl cyanide m-chlorophenyl hydrazone (CCCP). However, the role of CCCP-mediated mitophagy in HSC activation and liver fibrogenesis remains poorly understood. **Methods:** The effects of CCCP on mitochondrial function, mitophagy, and liver fibrogenesis in relation to lysosomal dysfunction were evaluated both *in vitro* and *in vivo*. Moreover, the antifibrotic effect of 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), which is representative AMPK activator, was also investigated. **Results:** CCCP treatment in HSCs led to mitochondrial dysfunction, evidenced by reduced mitochondrial membrane potential, mitochondrial DNA content, and ATP production, along with increased mitochondrial reactive oxygen species (mROS). CCCP also induced mitophagy but impaired mitophagic flux due to lysosomal dysfunction. Furthermore, CCCP upregulated plasminogen activator inhibitor-1 (PAI-1), an effect that was mitigated by mitochondrial division inhibitor 1 (Mdivi-1). This CCCP-induced increase in PAI-1 was attributed to lysosomal impairment. *In vivo*, CCCP administration in mice induced both mitophagy and liver fibrogenesis. Liver tissues from CCCP-injected mice showed elevated markers of hepatic fibrosis and mitophagy. Importantly, AICAR treatment reversed CCCP-induced mitophagy and the subsequent activation of HSCs, which is not dependent on AMPK activation. **Conclusion:** CCCP promotes hepatic fibrogenesis through mitochondrial dysfunction and lysosomal impairment, suggesting that CCCP-associated pathways may serve as potential therapeutic targets for liver fibrosis.

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Disclosures: Ji Hyun LEE: Nothing to Disclose, Jae Min KIM: Nothing to Disclose, Ji Hye YANG: Nothing to Disclose, Sung Hwan KI: Nothing to Disclose

3414 | FUNCTIONAL EVALUATION OF BM-MSC–EVS ON LSEC NORMALIZATION AND HEPATIC PROGENITOR CELL INDUCTION

Seul Ki Han[1] Mi Ra Lee[2] Jin Suk Lee[2] Moon Young Kim[2] Soon Koo Baik[2], [1]Yonsei wonju severance christian hospital, [2]Yonsei University Wonju College of Medicine

Background: Liver sinusoidal endothelial cell (LSEC) normalization (deactivation) is important for suppressing the progression of liver fibrosis and cirrhosis by improving the liver's microenvironment and stabilizing various cells involved in liver fibrosis through cross-talk. Recent studies have revealed that the normalization (deactivation) of damaged (activated) LSECs enhances Wnt-β-catenin signaling in LSECs, which, in turn, promotes the activation of hepatic progenitor cells (HPCs) and strengthens regeneration. Therefore, LSEC normalization can serve as a critical and useful target for the treatment of liver fibrosis and liver regeneration. In this context, we aim to confirm LSEC normalization using LSEC-targeting extracellular vesicle (EVs). **Methods:** The cytotoxicity of exosomes at different concentrations was assessed using the CCK-8 assay in mouse primary LSECs. The non-cytotoxic concentration of exosomes (50 μg/ml) was then treated on LSECs, and changes in the expression of factors involved in the Wnt-β-catenin signaling pathway were analyzed using qPCR and Western blot. Additionally, the expression changes of markers related to proliferation and activation in HPCs induced by exosomes were examined using molecular biological techniques. **Results:** After treating LSECs with exosomes, the expression of relevant factors was analyzed 24 hours later. Gene expression of markers associated with the Wnt-β-catenin signaling pathway (eNOS, Wnt2, Wnt9b, β-catenin, caveolin1) was found to increase. Additionally, the expression of HGF and VEGF also showed an increase. Regarding protein expression changes, levels of eNOS, Wnt2, Wnt9b, and β-catenin were elevated. When HPCs were treated with exosomes, an increase in cell number was observed. Furthermore, in markers related to differentiation, the expression of Krt19, Sox9, and Epcam decreased, while the expression of CD133 and Alb increased. **Conclusion:** Using BM-MSC-derived EVs, we observed an increase in factors related to normalization in LSECs. Additionally, it appears that EVs can promote both proliferation and differentiation in HPCs.

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3415 | LY6C^{LOW} MACROPHAGES MITIGATE LIVER FIBROSIS VIA GALECTIN-9-MEDIATED TIM-3 ACTIVATION

Eunmi Lee[1] Kyurae KIM[1] Sung Eun Choi[2] Min Jeong Kim[1] Katherine Po Sin Chung[2] Kwang Woo LEE[1] Jihyo Byun[1] Jaewoo Oh[1] Seungryong Choo[1] WON-IL JEONG[1], [1]KAIST, [2]Korea Advanced Institute of Science and Technology

Background: Despite the global prevalence of liver fibrosis, effective treatments remain unavailable to date. As an immune checkpoint molecule, T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) plays a role in regulating both adaptive and innate immune cells, including macrophages, and is deeply involved in chronic liver disease. Here, we investigate how TIM-3 expression changes in macrophages in a spatio-temporal manner during liver fibrosis. **Methods:** Liver fibrosis was induced in wild-type (WT) and TIM-3 whole knockout (KO) mice using carbon tetrachloride (CCl_4). Single-cell RNA sequencing (scRNA-seq) analysis was performed in CCl_4-treated mouse livers. To explore the expression changes of TIM-3, macrophages of bone marrow, blood and liver were subjected to flow cytometry analysis. Other biochemistry, qRT-PCR, and immunostaining were performed. For *in vitro* mechanistic studies, bone marrow-derived macrophages (BMDMs) were stimulated with a specific recombinant galectin-9 (Gal-9) to evaluate its role. **Results:** In scRNA-seq analysis, Gal-9 was expressed in multiple cell types but TIM-3 expression was mainly observed in Ly6C^{low} macrophages. In normal mice, flow cytometry analysis revealed that TIM-3 expression was detected in most macrophages of blood and bone marrow, whereas its expression significantly increased in Ly6C^{low} macrophages but decreased in Ly6C^{high} macrophages of liver. Similarly, in liver fibrosis, TIM-3 expression was predominantly expressed in Ly6C^{low} macrophages, and these cells were observed near activated hepatic stellate cells. Interestingly, liver fibrosis was more aggravated in TIM-3 KO mice than WT mice although CCl_4-mediated liver injury was similar in both mice. Moreover, the expression of fibrosis-related genes such as *Col1a1* and *Tnf* was significantly elevated in TIM-3 KO mice. *In vitro*, Gal-9 treatment suppressed LPS-induced activation of WT BMDM but not in TIM-3 KO BMDM. **Conclusion:** Ly6C^{low} macrophages specifically express TIM-3, and its activation inhibits liver fibrosis. Therefore, our

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findings may provide novel insights into therapeutic strategy for liver fibrosis through the Gal-9/TIM-3 axis in Ly6C^{low} macrophages.

Disclosures: Eunmi Lee: Nothing to Disclose, Kyurae KIM: Nothing to Disclose, Sung Eun Choi: Nothing to Disclose, Min Jeong Kim: Nothing to Disclose, Katherine Po Sin Chung: Nothing to Disclose, Kwang Woo LEE: Nothing to Disclose, Jihyo Byun: Nothing to Disclose, Jaewoo Oh: Nothing to Disclose, Seungryong Choo: Nothing to Disclose, WON-IL JEONG: Nothing to Disclose

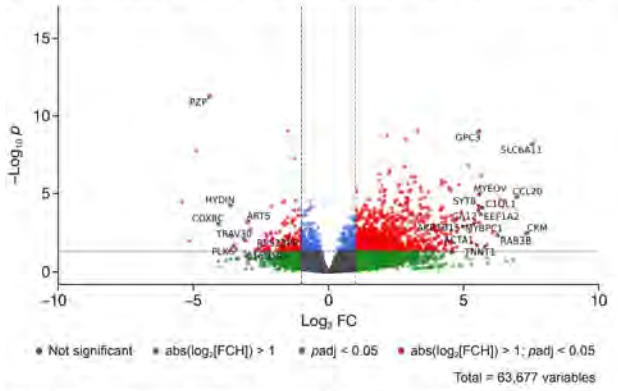
3416 | LIVER TRANSCRIPTOMIC SIGNATURES IN PATIENTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE WITH A PI*ZZ GENOTYPE ARE SIMILAR TO THOSE IN OTHER FIBROTIC LIVER DISEASES

Malin Fromme[1] Maria Paraskevopoulou[2] Ruixue Hou[2] Jen-Chieh Chuang[2] Nirav Desai[2] Susana Gonzalez[2] Tami Nussbaum[2] Abeer Zeitone[2] Pavel Strnad[1], [1]University Hospital RWTH Aachen, Aachen, Germany, [2]Takeda Development Center Americas, Inc., Cambridge, MA, USA

Background: Alpha-1 antitrypsin deficiency-associated liver disease (AATD-LD), caused by the protease inhibitor (Pi)*ZZ genotype, arises owing to accumulation of hepatic misfolded alpha-1 antitrypsin leading to cell stress, inflammation and cell damage, and subsequent liver fibrosis/cirrhosis. The underlying molecular mechanisms associated with fibrosis in patients (pts) with AATD-LD and a Pi*ZZ genotype are not fully understood. We aimed to identify and map differentially expressed genes (DEGs) associated with liver fibrosis in pts with AATD-LD with fibrosis and a Pi*ZZ genotype versus a healthy reference (Pi*MM) and compare Pi*ZZ transcriptomic signatures with those of other fibrotic liver diseases. **Methods:** Samples from pts with AATD-LD with fibrosis and a Pi*ZZ genotype were analyzed versus the Pi*MM reference. Bulk RNA sequencing and logistic regression were used to identify DEGs. DEGs were integrated with single nucleus RNA-sequencing (sNuc-seq) data consisting of pts with metabolic dysfunction-associated steatohepatitis (MASH) to map potential source cells in the liver. Functional characterization of DEGs was performed to link changes in gene expression to pathways using over-representation analysis (ORA) and ingenuity pathway analysis (IPA). Pathway analyses were extended to MASH and primary sclerosing cholangitis (PSC) data to enable cross-disease comparisons. **Results:** Bulk RNA sequencing data from 13 pts with AATD-LD and fibrosis with a Pi*ZZ genotype and 6 healthy individuals with a Pi*MM genotype were analyzed. Comparison of the Pi*ZZ and Pi*MM genotypes identified 1645 DEGs ($p < 0.05$), including 1277 upregulated and 368 downregulated DEGs (Figure). Of the upregulated DEGs in Pi*ZZ, 69% mapped to non-parenchymal cells (mesenchymal, immunocytes, cholangiocytes and endothelial) while 63% of downregulated DEGs were enriched in hepatocytes. ORA and IPA linked DEGs to pathways involved in cell stress, inflammation and extracellular matrix and collagen production; upstream regulators (e.g., *IL-1B, TNF* and *TGFB1*) of these pathways were enriched in the Pi*ZZ genotype. Canonical pathways associated with hepatic stellate cell activation and liver fibrosis were activated in the Pi*ZZ versus Pi*MM genotype and overlapped with pathways associated with fibrosis in MASH and PSC. **Conclusion:** This is the first known liver transcriptomics study including the Pi*ZZ genotype. In pts with AATD-LD and fibrosis with a Pi*ZZ genotype, transcriptomic profiles were similar to those identified in MASH and PSC. Findings from this study advance the understanding of AATD-LD pathophysiology and highlight potential non-invasive biomarkers with utility in the diagnosis and management of AATD-LD. Future research to further evaluate the importance of these biomarkers in AATD-LD pathophysiology and response to emerging therapy is currently under investigation.

Writing support provided by R Tooze, Oxford PharmaGenesis.

Figure. Volcano plot of DEGs in patients with AATD-LD and fibrosis with a Pi*ZZ genotype versus healthy individuals with a Pi*MM genotype.



DEGs with a significant change in expression were defined as abs(log$_2$[FCH]) > 1 and *p*adj < 0.05. The top 1% of upregulated and downregulated genes that adhered to the FCH and *p*adj criteria are annotated.
AATD-LD, alpha-1 antitrypsin deficiency-associated liver disease; abs, absolute; DEG, differentially expressed gene; FCH, fold change; NS, not significant; *p*adj, adjusted *p* value; Pi, protease inhibitor.

Disclosures: Malin Fromme: Takeda Pharmaceuticals: Consultant, CSL Behring: Speaking and Teaching, Grifols Inc: Speaking and Teaching, Takeda Pharmaceuticals: Speaking and Teaching, Maria Paraskevopoulou: Nothing to Disclose, Ruixue Hou: Takeda Pharmaceuticals: Employee, Jen-Chieh Chuang: Takeda: Employee, Nirav Desai: Nothing to Disclose, Susana Gonzalez: Nothing to Disclose, Tami

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Nussbaum: Nothing to Disclose, Abeer Zeitone: Nothing to Disclose, Pavel Strnad: Arrowhead Pharmaceuticals: Grant/Research Support, CSL Behring: Grant/Research Support, CSL Behring: Speaking and Teaching, BioMarin Pharmaceutical: Consultant, GSK: Consultant, Intellia: Consultant, Takeda Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Swedish Orphan Biovitrum: Consultant, Swedish Orphan Biovitrum: Speaking and Teaching, IPSEN: Consultant, Albireo: Consultant, AiRNA: Consultant, BioMarin: Consultant, Korro Bio: Consultant, Wave: Consultant, AiRNA: Consultant, Tessera: Consultant, Vertex: Material transfer, IQVIA: Material transfer, Arrowhead: Grant/Research Support, Takeda: Consultant, GSK: Consultant, BioMarin: Consultant, IPSEN: Consultant, Korro Bio: Consultant, CSL Behring: Grant/Research Support, CSL Behring: Speaking and Teaching, CSL Behring: Consultant, Sobi: Speaking and Teaching, Sobi: Advisor, Sanofi: Grant/Research Support

3417 | EPIDERMAL GROWTH FACTOR RECEPTOR MEDIATES HIV-RELATED LIVER INFLAMMATION AND FIBROSIS

Yongtao Wang[1] Shadi Salloum[1] Wenyu Lin[1] Min Xu[1] Ben Leaker[1] Eliana Epstein[1] Ava Brookshier[1] Zeinab Heidariyan[1] Tanvi Patel[1] Nadia Alatrakchi[1] Kenneth Tanabe[1] Georg Lauer[1] Raymond Chung[1],
[1]Massachusetts General Hospital and Harvard Medical School

Background: Although HIV is not directly hepatotropic, chronic liver disease has become a major cause of mortality in individuals infected with HIV, even under conditions of effective antiretroviral therapy (ART) suppression. Therefore, new strategies to slow HIV-induced liver fibrosis and the development of suitable are urgently needed. Our previous study supports the notion that epidermal growth factor receptor (EGFR) plays a significant role in liver disease, particularly in liver regeneration, fibrosis, and hepatocellular carcinoma (HCC). **Methods:** Bioinformatics analysis of single-cell RNA sequencing (scRNA-seq) data from peripheral blood mononuclear cells (PBMCs) and microarray data from primary Kupffer cells (pKCs, liver-resident macrophages) infected with HIV, were conducted. Livers from HIV gp120 protein-exposed mice were also investigated. Precision-cut liver slices (PCLS) were prepared from human livers and subsequently infected with HIV virus, along with supplementary treatment. Molecular assessments were further performed. **Results:** scRNA-seq data revealed that, compared with healthy donor, HIV infection was associated with upregulation of EGFR and its downstream genes in PBMCs, along with increased inflammation. Similarly, microarray data from pKCs showed that HIV infection resulted in the upregulation of EGFR and its downstream genes, while liver function signatures decreased and inflammatory and profibrogenic markers were induced. A prognostic liver signature (PLS) panel analysis also indicated that signatures predicting good prognosis or lower risk of progressive liver disease were significantly inhibited, whereas signatures (including EGF, a ligand that binds to EGFR) associated with poor prognosis or higher risk of liver disease progression were increased. More importantly, increased phosphorylation of EGFR was observed in the livers from HIV gp120 protein-exposed mice, accompanied by heightened inflammatory and fibrogenic gene expression. Using the *ex vivo* precision-cut liver slices (PCLS) model, HIV infection induced upregulation of EGFR expression, HIV gag mRNA, and inflammatory and profibrogenic gene expression. Additionally, treatment with erlotinib, an EGFR inhibitor, effectively mitigated HIV-induced EGFR expression and the associated inflammatory and profibrogenic responses in PCLS. **Conclusion:** HIV infection enhances hepatic EGFR signaling, leading to increased inflammation and profibrogenic activity in the liver. The findings suggest that targeting EGFR with inhibitors such as erlotinib may offer a potential therapeutic strategy to mitigate HIV-associated liver inflammation and fibrosis.

Disclosures: Yongtao Wang: Nothing to Disclose, Shadi Salloum: Nothing to Disclose, Wenyu Lin: Nothing to Disclose, Min Xu: Nothing to Disclose, Ben Leaker: Nothing to Disclose, Eliana Epstein: Nothing to Disclose, Ava Brookshier: Nothing to Disclose, Zeinab Heidariyan: Nothing to Disclose, Tanvi Patel: Nothing to Disclose, Nadia Alatrakchi: Nothing to Disclose, Kenneth Tanabe: Nothing to Disclose, Georg Lauer: Pfizer: Consultant, Raymond Chung: Nothing to Disclose

3418 | ANALYSIS OF CLINICAL CHARACTERISTICS AND LONG-TERM PROGNOSIS IN YOUNG HEPATITIS B CIRRHOSIS: A PROPENSITY SCORE MATCHING STUDY

Zhenhua Zhang[1] Pengyue Zhang[1] Xiaodan Hong[1],
[1]Second Affiliated Hospital of Anhui Medical University

Background: Cirrhosis is rare in young individuals, and clinical differences between young and elderly patients remain unclear. This study aimed to evaluate the clinical characteristics and prognosis of HBV-related cirrhosis in young patients. **Methods:** A hospital-based retrospective cohort of young cirrhosis patients was analyzed. Multivariable analysis identified risk factors for

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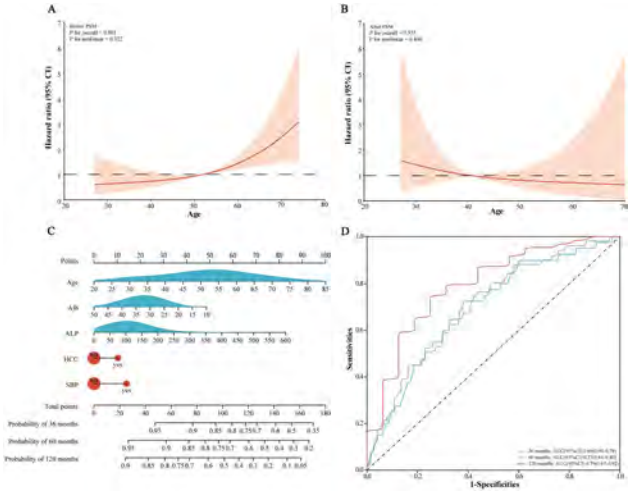
severe complications during follow-up, while the Cox proportional-hazards model assessed the prognosis of young and adult patients with HBV-related cirrhosis. Prognostic analysis was conducted using propensity score matching (PSM) to adjust for baseline differences between the groups. **Results:** The study included 545 patients with cirrhosis, including 119 in the younger group. Young patients with HBV-related cirrhosis exhibited significant differences from adult patients in gender, Alb, ALT, AST, and HBV titer. Kaplan-Meier analysis indicated a higher survival rate in the young group (log-rank test, $P = 0.04$); however, no significant difference remained after PSM. Youth was identified as an independent risk factor for gastrointestinal bleeding during follow-up (OR = 3.61, 95% CI: 1.62–8.00, $P = 0.002$). Additionally, age and elevated ALP levels were independent risk factors for survival. A Cox-based prediction model demonstrated good prognostic performance (C-index = 0.69). **Conclusion:** The prognosis of young patients with HBV-related cirrhosis was not superior to that of elderly after PSM. Special attention should be given to severe complications, particularly gastrointestinal bleeding, during follow-up. These findings may inform targeted interventions to reduce the burden of early-onset cirrhosis.



Disclosures: Zhenhua Zhang: Nothing to Disclose, Pengyue Zhang: Nothing to Disclose, Xiaodan Hong: Nothing to Disclose

3419 | THYROID DYSFUNCTION REFLECTS DISEASE SEVERITY AND IS ASSOCIATED WITH SHORT-TERM MORTALITY IN HOSPITALIZED CIRRHOTIC PATIENTS

Christos Triantos[1] Konstantinos Papantoniou[1] Efthymios Tsounis[1] Evdoxia Avramopoulou[1] Pinelopi Filippopoulou[2] Ioanna Aggeletopoulou[1] Georgios Geramoutsos[1] Odyssefs Ampazis[1] Markos Marangos[2] Spilios Manolakopoulos[3] Konstantinos Thomopoulos[1] Marina Michalaki[4], [1]Division of Gastroenterology, Department of Internal Medicine, University of Patras, Patras, Greece, [2]Department of Internal Medicine, University of Patras, Patras, Greece, [3]Hippocrates General Hospital of Athens, [4]Division of Endocrinology, Department of Internal Medicine, University of Patras, Patras, Greece

Background: Non-Tyroidal Illness Syndrome (NTIS) refers to thyroid hormone abnormalities in critically ill patients despite an intact hypothalamic-pituitary-thyroid axis. This study investigates thyroid hormone alterations in hospitalized cirrhotic patients and their potential prognostic significance. **Methods:** We prospectively enrolled patients with cirrhosis of any etiology who were hospitalized at our center. Blood samples were collected upon admission and at discharge for survivors. Thyroid function tests—including T3, free T3 (fT3), T4, free T4 (fT4), and TSH—were measured alongside routine laboratory parameters. **Results:** A total of 72 patients were included (M/F: 56/16; median age: 63 years) Cirrhosis etiologies included ALD (n = 44), viral hepatitis (n = 10), ALD + viral (n = 6), MASH (n = 2), PBC (n = 3), and unknown (n = 7). Significant negative correlations were found between T3 and MELD (r = -0.266, $p = 0.026$), and CLIF-C/ACLF (r = -0.409, $p < 0.001$). fT3 was also negatively associated with MELD (r = -0.245, $p = 0.041$) and CLIF-C/ACLF (r = -0.334, $p = 0.005$). T4 inversely correlated with MELD (r = -0.406, $p < 0.001$) and Child-Pugh (r = -0.268, $p = 0.025$). TSH positively correlated with MELD (r = 0.364, $p = 0.002$) and Child-Pugh (r = 0.398, $p = 0.001$).

Patients with decompensated cirrhosis had significantly lower T3 (median 0.75 vs. 0.90 ng/mL, p = 0.039), lower fT3 (3.29 vs. 3.72 pmol/L, p = 0.014), and higher TSH (1.82 vs. 1.11 mIU/L, p = 0.038) compared to those with compensated disease. Among patients with paired samples at discharge, further thyroid dysfunction was noted, with a median decline in fT3 of 0.62 pmol/L (IQR: 0.05–1.13, p = 0.001) and T4 of 0.78 µg/dL (IQR: 0.16–1.75, p = 0.002). Eight patients died during hospitalization, and twelve more died within two months post-discharge due to liver-related complications. Those who died had significantly higher baseline TSH [median 2.36 mIU/L (IQR: 1.35–3.66) vs. 1.20 (0.83–2.78); p = 0.048] and lower fT3 [3.19 pmol/L (2.35–3.51) vs. 3.42 (3.10–4.12); p = 0.048] compared to longer-term survivors. **Conclusion:** Hospitalized patients with cirrhosis exhibit abnormal thyroid hormone profiles suggestive of NTIS, which correlate with liver disease severity and are associated with short-term mortality. Thyroid function testing at admission may provide valuable prognostic information in this vulnerable patient population.

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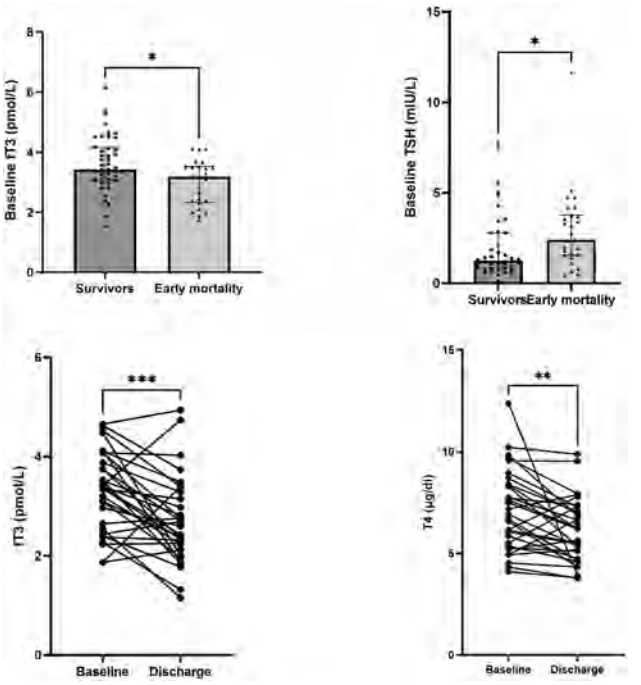

Disclosures: Christos Triantos: Nothing to Disclose, Konstantinos Papantoniou: Nothing to Disclose, Efthymios Tsounis: Nothing to Disclose, Evdoxia Avramopoulou: Nothing to Disclose, Pinelopi Filippopoulou: Nothing to Disclose, Ioanna Aggeletopoulou: Nothing to Disclose, Georgios Geramoutsos: Nothing to Disclose, Odyssefs Ampazis: Nothing to Disclose, Markos Marangos: Nothing to Disclose, Spilios Manolakopoulos: Nothing to Disclose, Konstantinos Thomopoulos: Nothing to Disclose, Marina Michalaki: Nothing to Disclose

3420 | CD146 PROMOTES THE PROGRESSION OF HEPATIC FIBROSIS VIA ACTIVATION OF THE P38-MAPK SIGNALING PATHWAY

Bingqing Yang[1] Chenxue Hou[1] Yixue Shu[2] Quan Sun[2] Qi Wang[1], [1]Beijing Ditan Hospital, Capital Medical University, Beijing, China., [2]Capital Medical University, Beijing, China.

Background: Hepatic fibrosis represents a common terminal pathway of various chronic liver diseases and may progress to cirrhosis or hepatocellular carcinoma. It is characterized by excessive deposition and insufficient degradation of the extracellular matrix (ECM). Currently, our understanding of the regulatory mechanisms underlying hepatic fibrosis remains limited, and effective therapeutic strategies are lacking. This study aims to investigate the role of CD146 in hepatic fibrosis and elucidate its potential molecular mechanisms. **Methods:** Mouse models of hepatic fibrosis were established using carbon tetrachloride (CCl_4) administration and a methionine-choline-deficient (MCD) diet. CD146 expression in hepatic tissues was assessed. To examine the role of CD146 in hepatocytes, mice overexpressing CD146 specifically in the liver (AAV8-CD146) and control mice (AAV8-GFP) were generated and subjected to a high-fat diet (HFD). Hepatic inflammation and fibrosis were evaluated, and transcriptomic analysis of liver tissues was performed. Additionally, hepatocyte-specific CD146 knockout mice ($CD146^{Alb\text{-}Cre}$) and their littermate controls ($CD146^{flox/flox}$) were constructed under CCl_4-induced fibrotic conditions to further validate the function of CD146. **Results:** Western blot and RT-qPCR analyses demonstrated that both CCl_4- and MCD-induced hepatic fibrosis significantly upregulated CD146 mRNA and protein levels in liver tissues. Under HFD conditions, AAV8-CD146 mice exhibited more pronounced hepatic inflammation and fibrosis compared to control mice, as evidenced by increased macrophage infiltration (F4/80 immunohistochemistry) and enhanced collagen deposition (Masson's trichrome staining). These findings suggest that CD146 overexpression exacerbates hepatic inflammatory responses and fibrotic progression. Conversely, in CCl_4-$CD146^{Alb\text{-}Cre}$ mice, macrophage infiltration and collagen deposition were markedly reduced, indicating that CD146 deficiency mitigates hepatic inflammation and fibrosis.

Mechanistic studies further revealed that CD146 overexpression significantly upregulated various pro-inflammatory genes (Il6, Il1β, Tnfα, Mcp1) and pro-fibrotic genes (Tgfβ, Col1a1, Col3a1), accompanied by activation of the p38-MAPK signaling pathway. In contrast, CD146 deletion suppressed the expression of these genes and their corresponding proteins. Taken together, these findings suggest that CD146 may promote hepatic inflammation and fibrosis by activating the p38-MAPK signaling pathway, thereby enhancing the expression of inflammatory and fibrogenic mediators. **Conclusion:** This study demonstrates that CD146 expression is upregulated during hepatic fibrosis. Its overexpression aggravates liver inflammation and fibrosis, whereas CD146 deletion exerts a protective effect. Mechanistically, CD146 may promote disease progression by activating the p38-MAPK signaling pathway.

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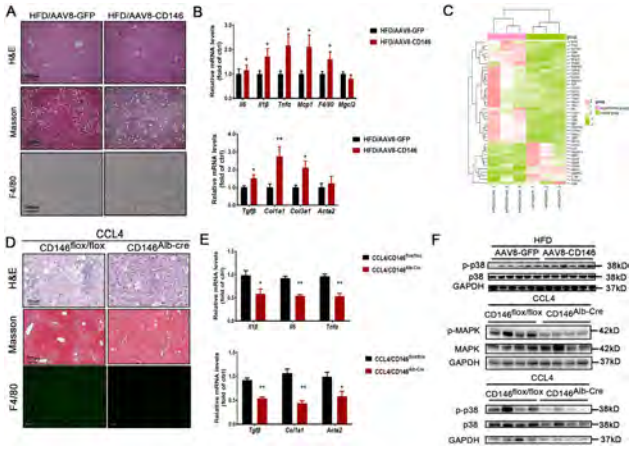

Disclosures: Bingqing Yang: Nothing to Disclose, Chenxue Hou: Nothing to Disclose, Yixue Shu: Nothing to Disclose, Quan Sun: Nothing to Disclose, Qi Wang: Nothing to Disclose, Nothing to Disclose

◆ 3421 | INTERLEUKIN-22 PROMOTES LIVER REGENERATION BY REPROGRAMMING GLYCOLYTIC METABOLISM IN A MOUSE ALPPS MODEL

sheng wang[1] Jiale Lu[1] Fengsheng Dai[1] Cheng Zhang[1] MaoYun Liu[1] Yi Wang[1] YuQin Xie[1] Genshu Wang[2] DeWei Li[1] Hui Li[1], [1]Chongqing University Cancer Hospital, [2]The Second Affiliated Hospital of Guangzhou University of Chinese Medicine

Background: Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) enables curative resection in patients with previously unresectable liver cancer by rapidly inducing liver regeneration. However, the underlying molecular mechanisms remain unclear. Interleukin-22 (IL-22), a cytokine involved in tissue repair, may promote hepatocyte proliferation, but its role in ALPPS-induced regeneration and metabolic regulation is unknown. This study explores the contribution of IL-22 to liver regeneration in a mouse ALPPS model, with a focus on glycolytic metabolic reprogramming. **Methods:** Liver regeneration was induced using the ALPPS procedure in 8-week-old C57BL/6J mice. Global *Il22* knockout ($Il22^{-/-}$) mice were generated in-house using CRISPR/Cas9 gene editing technology. IL-22 signaling was inhibited in vivo via hydrodynamic injection of IL-22 binding protein (IL-22BP). Cytokine arrays were used to screen for differentially expressed cytokines in liver tissues. Single-cell RNA sequencing was performed to identify distinct cell clusters and analyze cell–cell interactions. AML12 cells were treated with recombinant IL-22 (rmIL-22) in vitro, and cell proliferation was assessed using EdU, CCK-8 and cell cycle analysis. RNA-seq was performed to identify differentially expressed genes following IL-22 stimulation, followed by enrichment analysis. Metabolic assays, including ^{13}C-glucose tracing, glucose uptake, lactate production assays, and Seahorse extracellular flux analysis, were performed to assess glycolytic flux. **Results:** Cytokine array profiling revealed IL-22 as the most significantly upregulated cytokine in liver tissues after ALPPS. IL-22 knockout or inhibition with IL-22BP significantly suppressed liver regeneration. RNA-seq and enrichment analyses revealed that ALPPS significantly promoted cell cycle progression and cytokine-receptor interactions. Single-cell RNA sequencing analysis showed a pronounced post-ALPPS accumulation of monocytes and natural killer T (NKT) cells in the regenerating liver. In vitro, rmIL-22 stimulation markedly enhanced the proliferative capacity of AML12 cells. Integrated transcriptomic and metabolic flux analyses further demonstrated that IL-22 regulates glycolytic metabolism during liver regeneration. **Conclusion:** This study identifies IL-22 as a key cytokine upregulated during ALPPS-induced liver regeneration, with NKT cells as a potential primary source. These findings support a model in which NKT cell–derived IL-22 promotes liver regeneration by driving glycolytic metabolic reprogramming.

Disclosures: sheng wang: Nothing to Disclose, Jiale Lu: Nothing to Disclose, Fengsheng Dai: Nothing to Disclose, Cheng Zhang: Nothing to Disclose, MaoYun Liu: Nothing to Disclose, Yi Wang: Nothing to Disclose, YuQin Xie: Nothing to Disclose, Genshu Wang: Nothing to Disclose, DeWei Li: Nothing to Disclose, Hui Li: Nothing to Disclose

◆ 3422 | HCV NAT+ CONSENT IS ASSOCIATED WITH INCREASED LIVER TRANSPLANTATION AND REDUCED WAITLIST MORTALITY IN PATIENTS LISTED WITH A MELD EXCEPTION FOR HCC

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Background: The supply-demand mismatch in liver transplantation remains significant. In the last decade, direct-acting antiviral agents for the Hepatitis C virus (HCV) have expanded the donor pool by allowing HCV nucleic acid testing-positive (NAT+) organs to be safely transplanted. However, to receive HCV NAT+ organs, waitlist registrants must provide specific consent. We have shown that this HCV NAT+ consent reduces time to transplantation and waitlist mortality in the overall waitlisted population. It is unclear if this benefit extends to the unique population of registrants with hepatocellular carcinoma (HCC) who are listed with low Model for End-stage Liver Disease (MELD) scores and a

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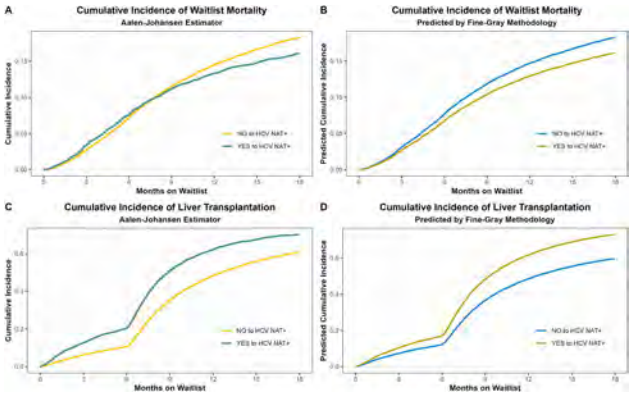
MELD exception. **Methods:** A retrospective cohort study using United Network for Organ Sharing (UNOS) data was conducted. All adult patients listed between 1/2016 and 10/2023 with an application for MELD exception for HCC were included. The primary exposure was the HCV NAT+ consent status at the time of registration. Two primary outcomes were considered: (1) time to transplantation and (2) time to waitlist mortality. All covariates were collected at time of registration. A time-dependent covariate to indicate active exception status was also created to occur 6 months after the first accepted MELD exception application. Time-to-event analyses were performed to evaluate the association between HCV NAT+ consent and the two outcomes accounting for competing risks. Both Fine-Gray subdistribution hazard ratios (sHR) and cause-specific hazard ratio (csHR) with 95% confidence intervals were calculated. **Results:** There were 15,852 patients in the analytical cohort with 4,954 (31.3%) having consented to receive HCV NAT+ organs. Those consenting were over-represented by registrants with HCV-related CLD and a higher MELD. The proportion of registrants consenting increased from 21% to 56% over the study length with an average increase of 6% per year. Overall, HCV NAT+ consent was associated with a significantly higher rate of transplantation (sHR 1.46, 95% CI: 1.33-1.61) and a marginally lower rate of waitlist mortality (sHR 0.82, 95% CI: 0.68-0.99). **Conclusion:** The proportion of liver transplant waitlist registrants, specifically those listed with a MELD exception for HCC, consenting for HCV NAT+ organs is increasing over time. This pattern is similar to the overall waitlist population but substantial center-level variation is more apparent. The benefit of HCV NAT+ consent in the form of increased likelihood of receiving a transplant and decrease waitlist mortality is clearly shown here. These findings provide evidence to support broadening the donor pool to HCV NAT+ organs to improve transplant access and reduce waitlist mortality even among the patients listed with a MELD exception for HCC. Furthermore, efforts to improve HCV NAT+ consent across all centers is needed.



Disclosures: Puru Rattan: Nothing to Disclose, Farinaz Ghodrati: Nothing to Disclose, Nadim Mahmud: Grifols: Grant/Research Support

◆ 3423 | IS MACHINE PERFUSION REPLACING LIVING DONATION FOR LIVER TRANSPLANTATION?

Vladislav Fomin Russell Rosenblatt[1] Robert Brown[1],
[1]Weill Cornell Medicine

Background: In order to increase the supply of organs in the face of ever-increasing demand, liver transplant (LT) centers have been utilizing living donation (LD) and, more recently, machine perfusion (MP). MP is a technique of preserving organs with circulating perfusate during the organ procurement process to increase access to previously marginal organs. LD provides increased access and superior outcomes, but does require a healthy donor to have surgery. Therefore, we aimed to study whether the increased use and comfort with MP is associated with a decrease in LD utilization. **Methods:** We analyzed 70,450 adult LTs from UNOS STAR file from 2016-2024. We focused on 27,685 low-MELD (<20) recipients, who typically have poor access to high-quality deceased donor organs but would be most likely benefit from MP or LD. Centers were categorized by annual LT volume (<25, 25-50, 51-100, >100 /year) and MP adoption patterns. We calculated pre- and post-adoption rates for both MP and LD programs, examined temporal trends, and assessed correlations between MP and LD program changes using chi-square tests, t-tests, and Pearson correlation coefficients. Centers were stratified by MP adoption intensity into terciles (low: $<6\%$, moderate: 6-28%, high: $>28\%$ increase) to examine differential LD response patterns through ANOVA. **Results:** During this period, there were 5,240 MP and 3,688 LD transplants. There was widespread adaptation of MP starting in 2022, accounting for 30% (2,875/9,498) of transplants by 2024 by 86 centers. LD experienced steady growth from 4.4% (283) to 6.5% (516) of transplants until 2022, after which there was a decline to 4.9% (493) of transplants. The mean MELD at transplant for MP patients was 21.2 and 16 for LD patients. Living donor rates increased significantly with center volume (3.0% vs 12.9%, $p<0.001$), while machine perfusion adoption peaked with medium-volume centers (12.0% vs 9.9% high-volume, $p<0.05$), surpassing the early advantage of high-volume centers. Use of LD predicted use of MP (+9.3%/year, $p < 0.001$) while MP did not predict LD (0.3%/year, $p = 0.58$). There was a non-statistically significant negative correlation (-0.42, $P = 0.082$) between an increase in MP and LD use. The 23 centers that had the largest year-to-year adaptation rate of MP

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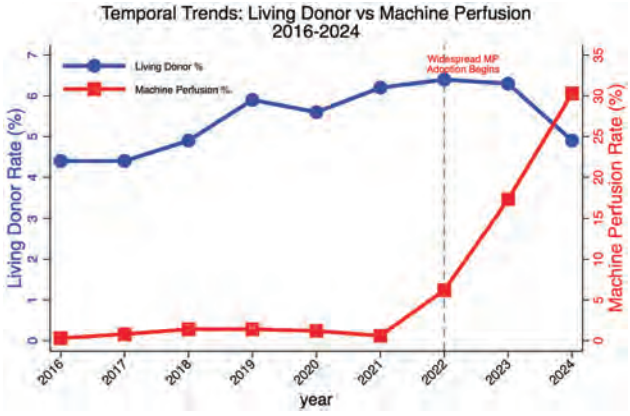
(42%) had a decrease in LD use -1.6%, the following year, suggesting substitution. While low (2.5%) and moderate (15.3%) rate of MP adaptation had a gradual increase in LD use 1.2% and 0.8%, respectively. **Conclusion:** As MP use increased over time, LD has had a decrease peaking in 2022 and declining every year since. This possible substitution was most prominent only among centers with aggressive MP adoption (>28% increase). While conservative and moderate MP adopters (86% of centers) maintained or increased their LD programs, demonstrating a complementary strategy. Ultimately, both strategies are needed to meet the increasing demand.



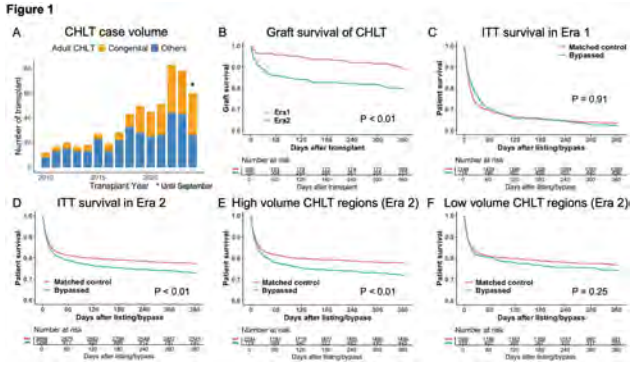
Disclosures: Vladislav Fomin: Nothing to Disclose, Russell Rosenblatt: Nothing to Disclose, Robert Brown: Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant

◆ 3424 | THE IMPACT OF COMBINED HEART-LIVER ALLOCATION ON HIGH-ACUITY LIVER TRANSPLANT CANDIDATES IN THE UNITED STATES: INTENTION-TO-TREAT ANALYSIS

Toshihiro Nakayama[1] Antony Attia[1] Marc Melcher[1] Tami Daugherty[2] Kazunari Sasaki[1], [1]Stanford University, [2]Stanford University Medical Center

Background: In the United States, high-acuity adult liver transplant candidates are bypassed by candidates for combined heart-liver transplant (CHLT) who accepted the heart. After the heart allocation policy change in 2018, access to CHLT has increased, raising concerns that a growing CHLT volume may disadvantage high-acuity liver candidates. The OPTN Ad Hoc Multi-Organ Transplantation Committee is currently debating standardized multi-organ allocation to ensure equitable access, making it essential to assess whether bypassed liver candidates are disadvantaged today. **Methods:** We analyzed OPTN match run data from January 2010 to September 2024, identifying 568 adult CHLT and 2,014 high acuity (MELD ≥ 35) adult candidates bypassed on the match run by CHLT candidates. The bypass cohort included only high-acuity candidates, as these patients are at increased risk for waitlist dropout and are more likely than lower MELD candidates to receive livers allocated to CHLT candidates. One-year graft survival of CHLT was compared between before (Era 1) and after the heart policy change on October 18, 2018 (Era 2). One-year intention-to-treat (ITT) survival of bypassed candidates —from the time of bypass until any death (waitlist dropout or post-transplant death)— were compared to a control cohort (three matched listings per bypassed candidate) matched by age at offer, gender, laboratory MELD score, blood type, and UNOS region. In Era 2 only, we conducted subgroup analyses of one-year ITT survival within UNOS regions stratified by CHLT volume, defining high-volume regions (UNOS 4, 5, 7, 9, 11; ≥ 30 CHLT cases in Era 2) and low-volume regions (all others; < 30 cases). **Results:** The number of CHLT has gradually increased, with 73 cases conducted in 2023. One-year graft survival worsened from 88.9% in Era 1 to 79.8% in Era 2 ($p < 0.01$), driven by early graft loss. In Era 1, one-year ITT survival was similar between bypassed candidates and matched controls (62.3% vs. 63.5%, $p = 0.91$). In Era 2, bypassed candidates exhibited inferior one-year ITT survival (72.8% vs. 77.3%, $p < 0.01$). This impact was particularly observed in high-volume regions (71.9% vs. 77.6%, $p < 0.01$), while no significant difference was observed in low-volume regions (74.2% vs. 76.9%, $p = 0.25$). **Conclusion:** CHLT volume has increased after the heart policy change, and the short-term outcomes are worsening. In the current era, adult candidates bypassed by CHLT candidates exhibited inferior ITT survival, especially in UNOS regions with high CHLT volume. Future simulation analyses are warranted to establish evidence-based allocation strategies that do not disadvantage either heart-liver or high-acuity liver candidates.

Figure 1



Disclosures: Toshihiro Nakayama: Nothing to Disclose, Antony Attia: Nothing to Disclose, Marc Melcher:

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Nothing to Disclose, Tami Daugherty: Nothing to Disclose, Kazunari Sasaki: Nothing to Disclose

◆ 3425 | CLEVER-LG: A MULTIMODAL MACHINE LEARNING BIOMARKER FOR NON-INVASIVE DIAGNOSIS OF LIVER GRAFT INJURY

Soumita Ghosh[1] Cristina Baciu[1] Maryam Naghibzadeh[1] Amirhossein Azhie[1] Muhammad Enrizky Brilian[1] Sara Naimimohasses[1] Sandra Fischer[2] Sandra Holdsworth[1] Arya Rahmani[1] Elisa Pasini[1] Bima Hasjim[3] Michael Brudno[2] Daniel Decarvalho[1] Bastian Engel[4] Elmar Jaeckel[1] Richard Taubert[5] Mamatha Bhat[6], [1]University Health Network, [2]University of Toronto, [3]University of California, Irvine, [4]Medizinische Hochschule Hannover/ Hannover Medical School, Hannover, Germany, [5]Medizinische Hochschule Hannover/Hannover Medical School, Hannover, [6]Toronto General Hospital

Background: Graft injury affects over 30% of liver transplant recipients (LTRs), and its etiology—such as T cell–mediated rejection (TCMR) and metabolic dysfunction–associated steatohepatitis post-transplant (MASH-LT)—can currently only be confirmed through invasive liver biopsy. A non-invasive diagnostic tool is urgently needed to guide treatment and improve patient outcomes. This study aimed to develop CleVER-LG (Cell-free DNA Methylation with Clinical Variables for Early Recognition of Liver Graft Injury), a multimodal machine learning (MML) model that integrates clinical variables with circulating cell-free DNA methylation signatures to classify graft pathology. **Methods:** We analyzed plasma-derived methylation profiles from 135 LTRs (40 MASH-LT, 50 TCMR, and 45 Control-LT) and integrated these with clinical variables to develop CleVER-LG. Differential methylation analysis and pathway enrichment were performed to identify subtype-specific signatures. Feature selection was conducted using the Boruta algorithm, and multiple MMLs—including random forest (RF) and support vector classifier (SVC)—were evaluated using 5-fold cross-validation. **Results:** Distinct methylation signatures associated with graft injury subtypes were identified, revealing enrichment of lipid metabolism and mTORC1 signaling in MASH-LT, and immune response and platelet activation in TCMR. The RF-based CleVER-LG model achieved the highest performance, with a mean weighted AUROC of 0.8005 ± 0.0603. In comparison, unimodal models using only clinical variables or only methylation data showed relatively lower performance (AUROC 0.6016 ± 0.0497 and 0.7987 ± 0.0586, respectively). SHAP analysis of the combined model identified key genes—GPR35, SH3PXD2A, and LDLRAD4—as major contributors to model predictions, consistent with their known roles in hepatic inflammation, extracellular matrix remodeling, and fibrogenic signaling. **Conclusion:** CleVER-LG is a promising non-invasive diagnostic tool for liver graft pathology. By combining clinical and methylation data, it improves the classification of graft injury subtypes, potentially reducing reliance on biopsy and enabling more precise post-transplant monitoring.

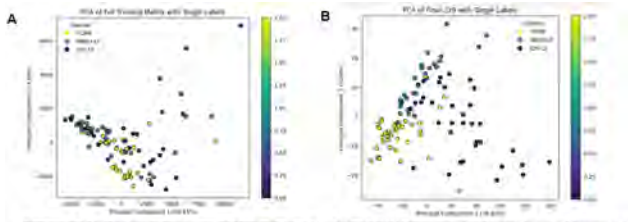

Figure 1 (A) Principal Component Analysis (PCA) of the FPKM (Fragments Per Kilobase of transcript per Million mapped reads)-normalized methylation data for > 5 million sites (full matrix after low reads removal but before feature selection). Each point represents a sample, and the first two principal components show distinct clustering. All the sites together show limited separation among the three graft pathology classes (indicated by color)—TCMR, MASH-LT, and Control-LT (Ctrl-LT)—indicating noise and redundancy in the high-dimensional data. **(B)** PCA of the FPKM - normalized methylation data for the 239 sites after feature selection. Here also, each point represents a sample, and the first two principal components are shown. The selected features reveal improved class separation, with clearer clustering of TCMR and MASH-LT groups. This highlights the effectiveness of Boruta-based feature selection in capturing biologically relevant variance in methylation signatures.

Disclosures: Soumita Ghosh: Nothing to Disclose, Cristina Baciu: Nothing to Disclose, Maryam Naghibzadeh: Nothing to Disclose, Amirhossein Azhie: Nothing to Disclose, Muhammad Enrizky Brilian: Nothing to Disclose, Sara Naimimohasses: Nothing to Disclose, Sandra Fischer: Nothing to Disclose, Sandra Holdsworth: Nothing to Disclose, Arya Rahmani: Nothing to Disclose, Elisa Pasini: Nothing to Disclose, Bima Hasjim: Nothing to Disclose, Michael Brudno: Nothing to Disclose, Daniel Decarvalho: Nothing to Disclose, Bastian Engel: Nothing to Disclose, Elmar Jaeckel: Nothing to Disclose, Richard Taubert: Nothing to Disclose, Mamatha Bhat: Transplant Genomics: Grant/Research Support, Novo Nordisk: Grant/Research Support, Roche: Grant/Research Support, Natera: Grant/Research Support, Oncoustics: Grant/Research Support, Paladin: Grant/Research Support, Astra Zeneca: Consultant, Merck: Grant/Research Support

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◆ 3427 | OLDER RECIPIENTS TRANSPLANTED WITH HEPATOCELLULAR CARCINOMA HAVE WORSE SURVIVAL DESPITE LOWER SEVERITY OF ILLNESS AND FEWER POST-TRANSPLANT COMPLICATIONS

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Background: Over the past two decades, the proportion of liver transplants (LTs) performed among patients aged ≥65 years has nearly doubled, with this group now representing one-fifth of the national volume. Hepatocellular carcinoma (HCC) is known to account for a substantial proportion of LTs in older individuals. The impact of HCC status and older age on post-transplant outcomes beyond mortality are poorly understood. **Methods:** This was a retrospective cohort study using a data linkage between inpatient and outpatient Medicare claims and the Organ Procurement and Transplantation Network and. All patients aged ≥65 years undergoing first LT alone between 1/1/2007-12/31/2019 with active Medicare coverage at LT were included. Patients were stratified by HCC status and age group (65-69, 70-72 and ≥73 years). Non-liver chronic conditions and rehospitalizations were captured using Medicare claims. Factors associated with post-transplant mortality were evaluated using Cox regression among patients alive with their native allograft at 1-year. **Results:** The cohort included 11,046 Medicare LT recipients with median follow-up time 4.6 years (IQR: 2.6-7.5). This Medicare cohort accounted for 76.8% of all LT recipients ≥65 years nationally during the study period. HCC prior to LT increased from 44.0% in patients 65-69 years to 51.4% in those ≥73 years ($p < 0.001$). Relative to non-HCC recipients, HCC recipients had less advanced liver disease at LT: median Model for End-stage Liver Disease 11 vs 22 ($p < 0.001$) and 20.0% vs 62.1% Child-Pugh class C ($p < 0.001$). Overall non-liver chronic condition burden post-LT was high, with differences being more apparent by HCC status than by age (Table). While most post-LT chronic conditions were more prevalent among non-HCC recipients, non-liver cancers were more common in HCC recipients (14.3% vs 10.4%; $p < 0.001$). Rehospitalizations at 30-, 90- and 365-days were also lower in the HCC group: 17.4% vs 19.1% non-HCC ($p = 0.025$), 33.8% vs 40.2% ($p < 0.001$), 51.9% vs 61.1% ($p < 0.001$), respectively. Yet, unadjusted long-term survival was not different by HCC status ($p = 0.259$). Adjusting for pre-transplant severity of illness, early non-liver chronic conditions and readmissions during the first post-LT year, the HCC group had greater all-cause mortality aHR 1.26 vs non-HCC ($p < 0.001$). **Conclusion:** In this highly representative cohort, older HCC recipients had less advanced liver disease at LT, fewer non-liver chronic conditions and fewer rehospitalizations after LT. The higher prevalence of non-liver cancers, known risk of HCC recurrence, and possibly other unmeasured markers of transplant fitness, may explain the worse post-transplant survival seen in older HCC recipients. Whether older HCC recipients derive survival benefit from LT requires further study, particularly in an era of expanding treatment alternatives.

Table – Prevalence of non-liver chronic conditions post-LT identified during follow-up by HCC status and age at LT (N=11,046)

	HCC at LT (N=4,966)	Non-HCC LT (N=6,080)	p-value
Diabetes	58.4%	61.4%	0.002
CAD	47.2%	45.0%	0.022
Heart failure	21.2%	37.5%	<0.001
Stroke, N(%)	17.2%	19.9%	<0.001
COPD, N(%)	20.0%	19.9%	0.957
CKD without ESRD, N(%)	53.1%	67.0%	<0.001
ESRD on dialysis, N(%)	10.0%	19.1%	<0.001
Keratinocyte carcinoma N(%)	19.1%	23.0%	<0.001
Non-liver solid cancer, N(%)	14.3%	10.4%	<0.001
Hematologic cancer, N(%)	3.8%	4.1%	0.337
	Age 65-69 (N=8,557)	Age 70-72 (N=1,872)	Age ≥73 (N=617)	p-value
Diabetes, N(%)	60.2%	59.7%	58.7%	0.708
CAD, N(%)	55.0%	51.7%	47.8%	<0.001
Heart failure, N(%)	32.6%	33.3%	35.0%	0.401
Stroke, N(%)	18.3%	19.9%	19.9%	0.182
COPD, N(%)	19.9%	19.7%	21.9%	0.462
CKD without ESRD, N(%)	59.8%	61.2%	62.6%	0.251
ESRD on dialysis, N(%)	15.2%	14.4%	14.6%	0.643
Keratinocyte carcinoma N(%)	20.9%	21.7%	25.1%	0.042
Non-liver solid cancer, N(%)	12.1%	12.3%	12.5%	0.942
Hematologic cancer, N(%)	3.8%	4.4%	5.0%	0.212

Note: Blue shading indicates p<0.001 across categories
Abbreviations: CAD – coronary artery disease; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; ESRD – end-stage liver disease

Disclosures: Therese Bittermann: Nothing to Disclose, David Goldberg: Nothing to Disclose, David Kaplan: AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Sirtex: Advisor, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research Support, Douglas Schaubel: Nothing to Disclose

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◆ 3428 | SURVIVAL OUTCOMES IN DCD AND DBD LIVER TRANSPLANTATION ARE EQUIVALENT IN THE ERA OF NORMOTHERMIC MACHINE PERFUSION

Michelle Nguyen[1] Michele Barnhill[1] Stephanie Ohara[1] Bashar Aqel[1] Blanca Lizaola-Mayo[1] Caroline Jadlowiec[1] Adyr Moss[1] Kunam Reddy[1] Amit Mathur[1], [1]Mayo Clinic Arizona

Background: Liver transplantation using donation after circulatory death (DCD) grafts has historically been associated with worse outcomes than donation after brain death (DBD), primarily due to ischemic complications from static cold storage (SCS). Normothermic machine perfusion (NMP) is now widely used to mitigate ischemia-reperfusion injury and improve graft viability, particularly in DCD transplantation. Its impact relative to contemporary DBD outcomes remains under investigation. **Methods:** We conducted a retrospective, single-center cohort study of adult liver transplants from the post-NMP era between 2022–2024, comparing DCD livers preserved with NMP (DCD-NMP) to all DBD livers including DBD-NMP and DBD-SCS. Primary outcomes were 1-year graft and patient survival. Secondary outcomes included early allograft dysfunction (EAD), ischemic cholangiopathy (IC), primary nonfunction (PNF), and hepatic artery thrombosis (HAT). Associations between donor type and outcomes were assessed using univariate and multivariable Cox models. **Results:** Among 780 liver transplant recipients, 458 received DCD-NMP grafts and 322 received DBD grafts (DBD-NMP n = 127, 39.4%; DBD-SCS n = 195, 60.6%). Donor age was higher in the DCD-NMP group (median 54.0 vs. 47.5 years; $p = 0.012$), and DRI scores were significantly higher (median 2.6 vs. 1.6; $p < 0.001$). DCD-NMP recipients were slightly older (median 62.0 vs. 59.0 years; $p = 0.022$) and had lower MELD scores at transplant (median 17.0 vs. 21.0; $p < 0.001$). Re-transplantation was less frequent in the DCD-NMP group (3.7% vs. 11.2%; $p < 0.001$) (Table 1). EAD occurred in 22.1% of DCD-NMP and 18.9% of DBD recipients ($p = 0.29$); adjusted odds showed no significant difference (aOR 0.77; 95% CI, 0.47–1.27; $p = 0.305$). Biliary anastomotic stricture was more common in DCD-NMP (17.7% vs. 2.8%; $p < 0.001$). Ischemic cholangiopathy was more frequent in DCD-NMP (6.1% vs. 1.2%; $p < 0.001$), with DBD recipients having lower odds (aOR 0.25; 95% CI, 0.08–0.79; $p = 0.018$). Rates of hepatic artery thrombosis (early 0.7% vs. 1.2%, $p = 0.39$; late 2.2% vs. 1.2%, $p = 0.33$) and primary nonfunction (0.9% vs. 0.6%, $p = 1.00$) were low and similar. One-year graft survival was 94.3% for DCD-NMP and 93.7% for DBD ($p = 0.77$); patient survival was 95.5% and 95.6%, respectively ($p = 0.99$). In multivariable analysis, overall (aHR 2.04; 95% CI, 0.65–6.44; $p = 0.223$) and graft survival (aHR 1.47; 95% CI, 0.61–3.54; $p = 0.394$) were comparable between groups. **Conclusion:** In the NMP era, LT using DCD grafts achieves graft and patient survival equivalent to that of DBD transplants, despite higher-risk donor profiles. These findings challenge longstanding biases against DCD use and support the broader adoption of DCD-NMP to safely expand the donor pool and reduce transplant waitlist mortality.

Table 1. Donor and recipient characteristics in DCD-NMP, and DBD (DBD-SCS and DBD-NMP) cases

	DCD-NMP (n=458)	DBD-SCS (n=195)	DBD-NMP (n=127)	P value
Donor Characteristics				
Age, median (IQR), years	54 (42.0, 61.0)	47 (34.5, 60.0)	48 (35.0, 62.5)	0.012
BMI, median (IQR)	29.4 (24.9, 35.5)	27.2 (23.7, 31.6)	28 (24.2, 32.7)	<0.001
dWIT, median (IQR), min	25 (21.0, 29.0)	N/A	N/A	
Distance to recipient hospital, median (IQR), miles	301.5 (68.2, 759.0)	261.0 (22.5, 348.5)	278.0 (133.5, 427.0)	<0.001
Share Type, No. (%)				.001
Local	150 (32.8%)	75 (38.5%)	33 (26.0%)	
Regional	133 (29.0%)	80 (41.0%)	61 (48.0%)	
National	175 (38.2%)	40 (20.5%)	33 (26.0%)	
Preservation time, median (IQR), hours	10.7 (13.4, 20.8)	5.9 (5.0, 7.1)	15.2 (12.0, 19.2)	<0.001
Perfusion time, median (IQR), hours	13.2 (9.5, 17.0)	N/A	11.8 (8.3, 15.9)	0.067
DRI score, median (IQR)	2.6 (2.1, 3.1)	1.6 (1.3, 1.9)	1.6 (1.3, 2.0)	
Recipient Characteristics				
Age, median (IQR)	62.0 (52.2, 66.0)	60.0 (50.5, 66.0)	58.0 (48.0, 66.0)	0.022
Sex, No. (%)				0.279
Female	165 (36.2%)	85 (43.6%)	44 (34.6%)	
Male	292 (63.8%)	110 (56.4%)	83 (65.4%)	
BMI, median (IQR)	28.1 (24.8, 32.5)	27.2 (23.9, 33.0)	27.0 (23.4, 32.0)	0.107
Allocation MELD, median (IQR)	17.0 (12.0, 22.0)	21.0 (14.0, 28.0)	20.0 (13.0, 26.5)	<0.001
Etiology of Liver Disease, No (%):				<0.001
Alcoholic Liver Disease	92 (20.1%)	66 (33.8%)	36 (27.5%)	
Hepatocellular Carcinoma	154 (33.6%)	42 (21.5%)	28 (22.0%)	
Metabolic	93 (20.3%)	38 (19.5%)	21 (16.5%)	
Autoimmune	42 (9.2%)	15 (7.7%)	4 (3.1%)	
Other*	77 (16.8%)	34 (17.4%)	36 (30.7%)	
Portal Vein Thrombus	94 (20.5%)	47 (24.1%)	22 (18.1%)	0.082
ICU Status at Time of Transplant	17 (3.7%)	26 (13.3%)	9 (7.1%)	<0.001
Retransplant, No. (%)	17 (3.7%)	9 (4.6%)	27 (21.3%)	<0.001

Disclosures: Michelle Nguyen: Nothing to Disclose, Michele Barnhill: Nothing to Disclose, Stephanie Ohara: Nothing to Disclose, Bashar Aqel: Nothing to Disclose, Blanca Lizaola-Mayo: Nothing to Disclose, Caroline Jadlowiec: Nothing to Disclose, Adyr Moss: Nothing to Disclose, Kunam Reddy: Nothing to Disclose, Amit Mathur: Nothing to Disclose

◆ 3429 | DYNAMELD: A DYNAMIC MODEL OF END-STAGE LIVER DISEASE FOR PERSONALIZED AND EQUITABLE WAITLIST PRIORITIZATION

Michael Cooper[1] Dariia Khoroshchuk[2] Xiang Gao[3] Xun Zhao[4] Yingke Wang[5] Xinle Wang[6] Peter Maksymowsky[2] Peregrina Peralta[2] Katie Bain[7] Amirhossein Azhie[2] Maryam Naghibzadeh[2] Sandra Holdsworth[7] Jed Gross[2] Bo Wang[2] Jordan Feld[2] Elmar

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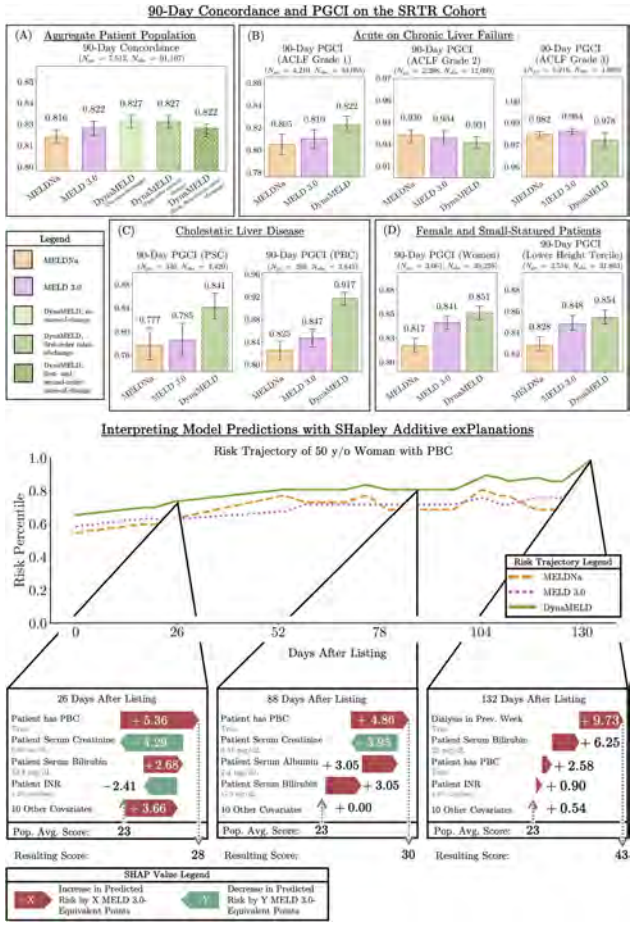
Background: Liver transplantation (LT) is a life-saving intervention for patients with end-stage liver disease (ESLD). However, between 12% and 20% of patients on the LT waitlist die before receiving an LT in the United States, and patient subgroups such as women and those with primary biliary cholangitis (PBC) remain disadvantaged in allocation. Our study objective was to enable more equitable prioritization by individualizing risk prediction with a more expressive class of statistical models. **Methods:** We created DynaMELD, a deep learning-based model of dynamic waitlist prioritization. DynaMELD uses a neural network to model complex interactions between covariates and leverages the rate-of-change (velocity) of time-varying biomarkers to predict risk of mortality or dropout. Our primary cohort comprised 53,046 patients with ESLD listed for LT from 2016 to 2023 from the U.S. Scientific Registry of Transplant Recipients (SRTR), and our external validation cohort comprised 466 patients waitlisted for LT at University Health Network (UHN) in Canada.

DynaMELD was integrated into the electronic health record system at UHN via a dashboard. We then conducted a silent trial of 380 patients waitlisted for LT at UHN, simulating real-time usage without influencing clinical decisions. The dashboard provides patient risk estimates and uses SHapley Additive exPlanations to visualize and interpret the individualized model predictions. **Results:** DynaMELD achieved a 90-day concordance that was 0.5% higher than MELD 3.0 ($p < 0.001$) on the SRTR cohort. Using pooled group concordance (PGCI) as a measure of fairness, DynaMELD achieves a PGCI 1.2% higher for women ($p < 0.001$), 8.3% higher for patients with PBC ($p < 0.001$), 7.2% higher for patients with primary sclerosing cholangitis (PSC; $p < 0.001$), and 1.5% higher for patients with acute-on-chronic liver failure Grade 1 ($p < 0.001$) compared to MELD 3.0. On the UHN cohort, DynaMELD achieves comparable 90-day concordance to MELD 3.0 while improving PGCI in the aforementioned subpopulations. In the silent trial, patients allocated under DynaMELD have a higher probability of receiving a transplant in the following 29 days than under MELD 3.0 ($p < 0.001$). DynaMELD effectively identified higher-risk patients, assigning increased priority to 6.7% more patients who subsequently died on the waitlist, with notable improvements for disadvantaged groups: 2.7% more women, 25.0% more PSC patients, and 56.3% more PBC patients were assigned increased priority, suggesting it would improve these patients' access to organ offers. **Conclusion:** DynaMELD provides more accurate, individualized predictions of waitlist mortality, potentially enabling more fair LT waitlist prioritization. Our study demonstrates the feasibility of deploying a deep learning-based risk scoring tool in the clinic to provide real-time, individualized risk prediction for patients on the LT waitlist.



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Yingke Wang: Nothing to Disclose, Xinle Wang: Nothing to Disclose, Peter Maksymowsky: Nothing to Disclose, Peregrina Peralta: Nothing to Disclose, Katie Bain: Nothing to Disclose, Amirhossein Azhie: Nothing to Disclose, Maryam Naghibzadeh: Nothing to Disclose, Sandra Holdsworth: Nothing to Disclose, Jed Gross: Nothing to Disclose, Bo Wang: Nothing to Disclose, Jordan Feld: AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support, AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support, Elmar Jaeckel: Nothing to Disclose, Michael Brudno: Nothing to Disclose, Gideon Hirschfield: Intercept: Consultant, Intercept: Consultant, GSK: Consultant, GSK: Consultant, CymaBay: Consultant, CymaBay: Consultant, Ipsen: Consultant, Ipsen: Consultant, Falk: Consultant, Falk: Consultant, Pliant: Consultant, Pliant: Consultant, Mirum: Consultant, Mirum: Consultant, Advanz: Consultant, Advanz: Consultant, Chemomab: Consultant, Chemomab: Consultant, Gilead: Consultant, Gilead: Consultant, Kowa: Consultant, Kowa: Consultant, Kezar: Consultant, Intercept: Consultant, Intercept: Consultant, GSK: Consultant, GSK: Consultant, CymaBay: Consultant, CymaBay: Consultant, Ipsen: Consultant, Ipsen: Consultant, Falk: Consultant, Falk: Consultant, Pliant: Consultant, Pliant: Consultant, Mirum: Consultant, Mirum: Consultant, Advanz: Consultant, Advanz: Consultant, Chemomab: Consultant, Chemomab: Consultant, Gilead: Consultant, Gilead: Consultant, Kowa: Consultant, Kowa: Consultant, Kezar: Consultant, Rahul Krishnan: Nothing to Disclose, Mamatha Bhat: Transplant Genomics: Grant/Research Support, Novo Nordisk: Grant/Research Support, Roche: Grant/Research Support, Natera: Grant/Research Support, Oncoustics: Grant/Research Support, Paladin: Grant/Research Support, Astra Zeneca: Consultant, Merck: Grant/Research Support

◆ 3430 | FINITE HUMAN HEPATOCYTE EXPANSION IN CHIMERIC MOUSE LIVERS IS NOT OVERCOME BY TERT OVEREXPRESSION

Viktoriia Iakovleva[1] Eleftherios Michailidis[2] William Schneider[3] Catherine Freije[3] Alireza Ramandi[4] Chenhui Zou[4] Yingpu Yu[3] Corrine Quirk[3] Yichen Zhou[4] Briana Zeck[5] Alison Ashbrook[3] Tomoe Shiomi[5] Markus Grompe[6] John Poirier[7] Luis Chiriboga[5] Charles Rice[3] Ype De Jong[4], [1]Weill Cornell Medicine, [2]Department of Pediatrics, School of Medicine, Emory University, Atlanta, Georgia, [3]Laboratory of Virology and Infectious Disease, The Rockefeller University, New York, NY, [4]Division of Gastroenterology and Hepatology, Weill Cornell Medicine, New York, NY, [5]Department of Pathology, New York University Langone Health, New York, NY, [6]Papé Family Pediatric Research Institute, Oregon Health & Science University, Portland, OR, [7]Laura and Isaac Perlmutter Cancer Center, New York University Langone Health, New York, NY

Background: Human hepatocyte transplantation remains under investigation as a therapeutic modality for liver disease. However, the capacity of transplanted primary human hepatocytes (PHH) to divide and the cellular factors that affect engraftment remains undefined. While murine hepatocytes can divide extensively, the cell division limit for PHH may be governed by replicative aging. Here, we aimed to quantify PHH proliferative constraints and assess strategies to alleviate these constraints. **Methods:** PHH were serially transplanted into immunodeficient liver injury (FNRG) mice and serum human albumin (hAlb) was used to monitor humanization. To quantify productive seeding and expansion, PHH were transduced with lentiviruses encoding multiple fluorophores (Confetti) or encoding unique sequence barcodes. Confetti-labeled liver sections were imaged and barcodes were sequenced to quantify PHH engraftment and expansion. To assess whether telomere attrition limits expansion, PHH at various stages of serial passage were transduced with human telomerase reverse transcriptase (hTERT) before re-transplantation. **Results:** PHH effectively humanized FNRG livers through three rounds of serial transplantation, after which humanization sharply decreased with subsequent passages (Figure 1). Confetti labeling revealed that individual PHH gave rise to spatially distinct, monochromatic islands, supporting their clonal origin. Using image segmentation and a mathematical model, we estimated that islands had a

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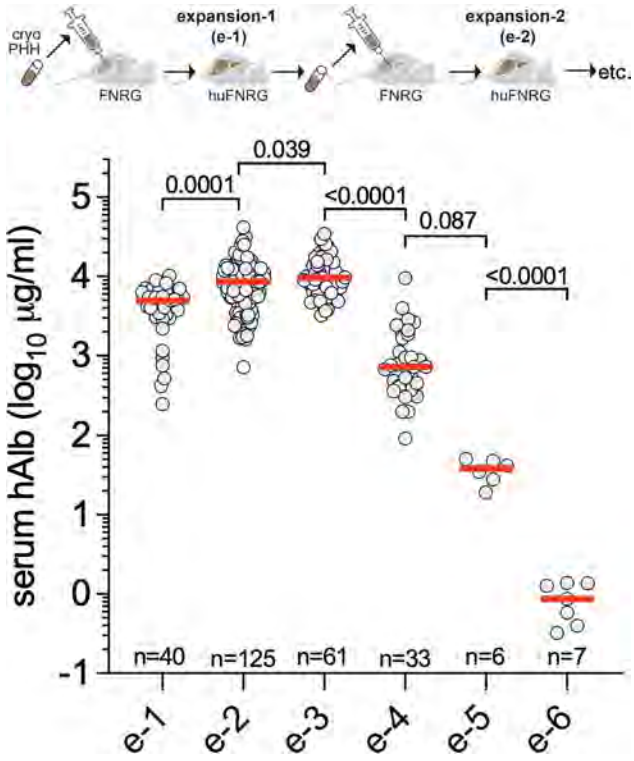
median diameter of 510.2 μm, corresponding to 16,423 hepatocytes per island, or ~14 cell divisions from a single founder cell. In parallel, high-complexity barcoding provided quantitative clonal resolution at scale. Barcode sequencing showed approximately ~10^4 unique PHH clones engrafted per liver and expanded to ~10^8 cells during each transplantation cycle. This ~10^4-fold increase equates to ~13.3 cell divisions, in close agreement with Confetti-based estimates. To assess whether replicative exhaustion limited expansion, we overexpressed wild-type hTERT in PHH prior to retransplantation. While hTERT did not significantly enhance engraftment or expansion as measured by hAlb levels in third or fourth transplant rounds, it did improve survival in fourth-round-transplanted mice compared to LVAA (catalytically dead) hTERT controls. **Conclusion:** In total, PHHs can expand efficiently for approximately 40 cell divisions during serial passaging, after which their ability to humanize chimeric livers diminishes. hTERT overexpression had no major impact on PHH humanization kinetics, as measured by hAlb levels, during the first four rounds of expansion. This suggests that alternative strategies are needed to extend their proliferative lifespan. These findings highlight the clonal limitations of human hepatocyte therapy and emphasize the need to overcome replicative barriers for sustained liver repopulation.



Disclosures: Viktoriia Iakovleva: Nothing to Disclose, Eleftherios Michailidis: Nothing to Disclose, William Schneider: Nothing to Disclose, Catherine Freije: Nothing to Disclose, Alireza Ramandi: Nothing to Disclose, Chenhui Zou: Nothing to Disclose, Yingpu Yu: Nothing to Disclose, Corrine Quirk: Nothing to Disclose, Yichen Zhou: Nothing to Disclose, Briana Zeck: Nothing to Disclose, Alison Ashbrook: Nothing to Disclose, Tomoe Shiomi: Nothing to Disclose, Markus Grompe: Nothing to Disclose, John Poirier: Nothing to Disclose, Luis Chiriboga: Nothing to Disclose, Charles Rice: Nothing to Disclose, Ype De Jong: Nothing to Disclose

◆ 3431 | PREOPERATIVE EXERCISE THERAPY ALLEVIATES SURGICAL STRESS-PROMOTED COLORECTAL CANCER LIVER METASTASES BY SHIFTING KUPFFER CELLS TO AN ANTI-TUMOR PHENOTYPE

Janice Oh[1] Carolyn Tsung[1] Arad Jain[1] Yiyu Zhang[1] Hongji Zhang[1], [1]University of Virginia

Background: Colorectal cancer (CRC) is the second leading cause of cancer death in the US, with the majority of patients dying of hepatic metastasis. Surgical resection is the standard of care for hepatic metastasis of colorectal cancer. However, surgery-induced immunologic disturbances can evoke alterations in the host tumor environment to promote disease recurrence. Indeed, systemic and local inflammation and their sustained responses after surgery directly correlate with cancer outcomes for colorectal cancer. To date, strategies to mitigate the negative outcomes of surgical stress have only been shown to be minimally effective. However, preoperative exercise therapy (PEx) has emerged as a promising protective strategy against post-surgical inflammation and recurrence. Our recent findings demonstrate that PEx significantly attenuates liver surgery-induced hepatic inflammatory response. Based on novel data, we hypothesize that PEx ameliorates surgical stress-induced protumorigenic inflammatory responses and sustains an anti-tumor immune microenvironment in the liver. **Methods:** 8-week-old male wild-type mice were randomly divided into PEx and sedentary (Sed) groups, in which the PEx mice ran on a motorized treadmill one hour per day for four weeks. MC38 CRC cells were injected into the mice through the portal vein and surgical stress was induced using a partial hepatic ischemia and reperfusion model. Tumor growth was determined weekly by bioluminescence imaging. The CD45+ immune cells in the liver from Sed and PEx mice 3 weeks after tumor injection were submitted for single-cell RNA sequencing (scRNA-seq). Immune cell populations, Kupffer cells (KCs) and CD8 T cells function were quantified by flow cytometry. KCs from both Sed and PEx mice were isolated for metabolomics. **Results:** We found that 4 weeks of PEx significantly reduces hepatic metastatic tumor growth compared to the sedentary controls. Transcriptomic

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analysis using scRNA-seq demonstrated substantial changes in the immune profiles, particularly that PEx shifts pro-tumor Kupffer cells (KC) towards an anti-tumor immunity phenotype. PEx KCs also promote recruitment of CD8+ T cells through the CXCL9-CXCR3+ axis. Furthermore, CXCL9 enhances the anti-tumor activity of CXCR3+ CD8+ T cells. Mechanistically, PEx-induced butyrate accumulation in KCs inhibits histone deacetylase 3, thereby promoting the transcription of CXCL9. **Conclusion:** These results demonstrate PEx remodels the liver microenvironment and enhances anti-tumor immune responses, primarily through CXCL9-CXCR3 axis-mediated interactions between Kupffer cells and CD8+ T cells. These findings provide a strong rationale for incorporating PEx into the treatment strategy for colorectal liver metastasis patients undergoing hepatic surgery, with the potential to reduce post-operative recurrence.

Disclosures: Janice Oh: Nothing to Disclose, Carolyn Tsung: Nothing to Disclose, Arad Jain: Nothing to Disclose, Yiyu Zhang: Nothing to Disclose, Hongji Zhang: Nothing to Disclose

◆ 3432 | PREDICTING RECOMPENSATION AMONG LIVER TRANSPLANT CANDIDATES USING MACHINE LEARNING: INSIGHTS FROM THE UNOS REGISTRY

Damien Chua[1] Yang Hee Seung[2] Ming-Yao Pierre Lim[3] Nicole Shu Ying Tang[4] Donghyun Ko[5] Eunice Xiang-Xuan Tan[2] Mohammad Shadab Siddiqui[6] Margaret Teng[2] Mark Muthiah[2], [1]Lee Kong Chian School of Medicine, Nanyang Technological University Singapore, [2]Division of Gastroenterology and Hepatology, National University Hospital Singapore, [3]Chemical Technology, Ngee Ann Polytechnic, [4]Yong Loo Lin School of Medicine, National University of Singapore, [5]Mount Sinai Morningside and West, Icahn School of Medicine at Mount Sinai, [6]Division of Gastroenterology & Hepatology, Virginia Commonwealth University

Background: Recompensation, or the clinical recovery of liver function in patients initially deemed transplant candidates, remains poorly characterized in large populations. We aimed to identify predictors and develop a predictive model of recompensation among individuals listed for liver transplantation using data from the United Network for Organ Sharing (UNOS). **Methods:** We conducted a retrospective cohort study including adults listed for liver transplantation in the UNOS database between January 1, 2000, and December 31, 2024. Recompensation was defined as delisting due to clinical improvement. Extreme Gradient Boosting (XGBoost) was employed to develop a predictive model, using an 80:20 train-test split. Model performance was assessed via the area under the precision-recall curve (AUC-PR). Univariable logistic regression was performed to quantify the association between clinical features and recompensation. **Results:** Among 178,620 listed individuals, 11,753 (6.6%) were delisted due to improvement. Recompensated individuals had lower MELD scores (median 13 vs. 18), higher albumin levels (3.3 vs. 3.0 g/dL), and lower prevalence of diabetes, ascites, and hepatic encephalopathy (all $p < 0.001$). The XGBoost model achieved an AUC-PR of 0.950, accuracy of 89.8%, and specificity of 95.0%. Key predictors included MELD score, bilirubin, albumin, creatinine, and INR. Alcohol-associated liver disease and HCV were positively associated with recompensation, whereas MASLD and diabetes were negatively associated ($p < 0.001$). **Conclusion:** Recompensation occurs in a clinically distinct subset of liver transplant candidates and can be accurately predicted using machine learning. These findings have implications for refining transplant candidacy assessment and optimizing organ allocation policies.

Disclosures: Damien Chua: Nothing to Disclose, Yang Hee Seung: Nothing to Disclose, Ming-Yao Pierre Lim: Nothing to Disclose, Nicole Shu Ying Tang: Nothing to Disclose, Donghyun Ko: Nothing to Disclose, Eunice Xiang-Xuan Tan: Nothing to Disclose, Mohammad Shadab Siddiqui: Sagimet Bio: Consultant, AMRA: Consultant, 89 Bio: Consultant, Novo Nordisk: Grant/Research Support, Margaret Teng: Nothing to Disclose, Mark Muthiah: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose

◆ 3433 | DIGITAL TWIN TRAJECTORY MATCHING REVEALS EQUIPOISE BETWEEN SIMULTANEOUS LIVER-KIDNEY TRANSPLANTATION AND LIVER TRANSPLANT ALONE: A DEEP LEARNING ANALYSIS OF 11,152 UNOS REGISTRY PATIENTS

Eytan Palte[1] Elizabeth Verna[2] Giuseppe Cullaro[1], [1]Columbia University Irving Medical Center, [2]Columbia University Medical Center

Background: Simultaneous liver-kidney transplantation (SLKT) has become standard for patients with combined organ failure. Comparative effectiveness studies have been limited by methodologies that inadequately match by the dynamic decline in pre-transplant kidney function. We employed a novel digital twin approach using deep learning trajectory matching to compare 3-year event-free survival between SLKT and liver transplant alone (LTA). **Methods:** We identified 11,152 liver transplant recipients (UNOS, 2017-2025) with pre-transplant kidney function trajectories. We calculated longitudinal eGFR (2021 CKD-EPI) and extracted eGFR data including final eGFR, rate of late

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decline, percentage of time below thresholds, and time to reach critical values. Deep learning autoencoders with 32-dimensional embeddings processed these patterns in 256-patient batches to create high-dimensional representations. Digital twins were generated by matching each SLKT patient to the most similar LTA patient using cosine similarity distance. Primary outcome was 3-year event-free survival (composite of death, liver graft failure). Cox proportional hazards models adjusted for Liver Donor Risk Index (LDRI), MELD at transplant, and Karnofsky Performance Scale (KPS). **Results:** After digital twin matching, 10,840 patients were analyzed (5,446 SLKT, 5,394 LTA) with median follow-up of 2.6 years. The deep learning matching achieved excellent balance with median cosine similarity distance of 0.3 between matched pairs. Trajectory analysis revealed successfully balanced pre-transplant eGFR decline patterns, with mean final eGFR of 7.9 ± 14.0 vs 8.5 ± 14.7 mL/min/1.73m² ($p = 0.04$) for SLKT vs LTA, respectively. SLKT patients had significantly lower LDRI (1.5 ± 0.3 vs 1.6 ± 0.4, $p < 0.001$) and better KPS (51.7% vs 73.5% with grade $< 50\%$, $p < 0.001$). The primary endpoint occurred in 2,067 patients(19.1% event rate). Three-year unadjusted event-free survival was 81.7% vs 80.1% (log-rank $p = 0.04$). After adjusting for LDRI, MELD at transplant, and KPS, this survival advantage was not statistically significant (adjusted HR 0.9, 95% CI 0.9-1.0, $p = 0.3$). **Conclusion:** Using innovative digital twin methodology with trajectory-based matching, we found no significant difference in 3-year event-free survival between SLKT and LTA after adjustment for donor quality and recipient factors. These findings demonstrate equipoise between treatment strategies and support decisions based on individual factors rather than presumed survival benefit. **Disclosures:** Eytan Palte: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose, Giuseppe Cullaro: Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant

◆ 3434 | RISK STRATIFICATION FOR WAITLIST DROPOUT IN HCC PATIENTS BEYOND UCSF CRITERIA: A COMPETING-RISKS ANALYSIS

Butros Fakhoury[1] Ximena Parraga[2] Eyad Abdulrazzak[2] Behnam Saberi[2], [1]Virginia Commonwealth University, [2]Beth Israel Deaconess Medical Center

Background: Patients with hepatocellular carcinoma (HCC) listed for liver transplantation (LT) beyond the University of California, San Francisco (UCSF) criteria face a high risk of waitlist dropout due to tumor progression or death. Identifying predictors of dropout in this population is essential for optimizing candidate selection and management. We aimed to evaluate predictors of waitlist dropout using a competing-risks framework, accounting for liver transplantation as a competing event. **Methods:** This retrospective cohort study included HCC patients listed beyond UCSF criteria who received bridging locoregional therapy (LRT) between 2003 and 2023, using data from the OPTN/UNOS database Dropout was defined as waitlist removal due to death or clinical deterioration. Liver transplantation was treated as a competing event, while other reasons for removal were censored. Fine-Gray competing-risks regression was used to evaluate predictors of dropout, including interaction terms for Child-Pugh (CP) class and LRT modality (TACE, TARE, ablation, or combination therapy), age, Eastern Cooperative Oncology Group (ECOG) performance status, alpha-fetoprotein, tumor diameter, and tumor multinodularity. Subhazard ratios (sHR) with 95% confidence intervals (CIs) were reported. **Results:** A total of 1,347 patients were included: CP class A ($n = 538$), B ($n = 471$), and C ($n = 338$). TACE was the most common LRT ($n = 613$), followed by combination therapy ($n = 467$), TARE ($n = 147$), and ablation therapies ($n = 120$). The median follow up time was 7 months. Patients with CP class C receiving either TACE or combination LRT had significantly higher dropout risk (sHR 2.8, 95% CI 1.9–4.1; $p < 0.001$ and sHR 2.4, 95% CI 1.6–3.7; $p < 0.001$, respectively). Neither TARE nor ablation was associated with increased dropout risk across CP classes. No significant differences in dropout were observed between LRT modalities among CP class A or B patients. Elevated AFP (≥ 20 ng/mL) independently predicted higher dropout risk, regardless of tumor size or multinodularity. **Conclusion:** Among HCC patients listed beyond UCSF criteria, advanced liver dysfunction (CP class C) and recepients of TACE or combination LRT were associated with a two- to threefold increased risk of waitlist dropout. AFP ≥ 20 ng/mL was a strong, independent predictor of dropout irrespective of tumor burden. These findings highlight the need for individualized risk stratification and tailored

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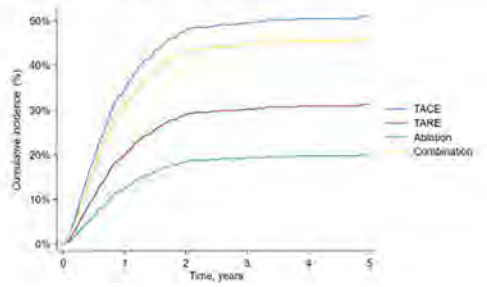
treatment approaches in this high-risk LT population.

Table 1. Subhazard Ratios for Waitlist Dropout in HCC Patients by CPT Class and Locoregional Therapy, with liver transplant considered as competing risk.

Variable	sHR	95% CI	p-value
CP Class A (Reference: TACE)			
TARE	1.3	0.7-2.4	0.38
Ablation	0.9	0.4-2.0	0.754
Combination	0.9	0.6-1.4	0.674
CP Class B			
TACE	1	0.6-1.5	0.871
TARE	0.8	0.3-1.7	0.525
Ablation	0.9	0.4-1.9	0.812
Combination	1.3	0.9-2.1	0.181
CP Class C			
TACE	2.8	1.9-4.1	**<0.001**
TARE	1.5	0.7-3.0	0.303
Ablation	0.9	0.4-2.0	0.747
Combination	2.4	1.6-3.7	**<0.001**
Covariates			
Elderly (Age>60)	1.2	0.9-1.5	0.147
Poor functional status (ECOG ≥2)	1	0.8-1.2	0.921
Tumor burden (Ref: AFP<20, single lesion, total diameter <8 cm)			
AFP>20, single lesion, total diameter <8 cm	3.5	1.3-9.6	**0.013**
AFP>20, single lesion, total diameter >8 cm	2	1.1-3.7	**0.02**
AFP>20, multinodular, total diameter <8 cm	2.7	1.1-7.9	**0.042**
AFP>20, multinodular, total diameter >8 cm	1.9	1.1-3.5	**0.033**

AFP, alpha-fetoprotein; CP, Child-Pugh; ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

Figure 1. Cumulative Incidence of Dropout by LRT Across CP Class C.



Disclosures: Butros Fakhoury: Nothing to Disclose, Ximena Parraga: Nothing to Disclose, Eyad Abdulrazzak: Nothing to Disclose, Behnam Saberi: Nothing to Disclose

◆ 3435 | PLATELET-RICH PLASMA PERFUSION DURING STATIC COLD STORAGE REDUCES ISCHEMIA-REPERFUSION INJURY IN LIVER TRANSPLANTATION

Boris Yaremin[1] Catherine Anosova[1] Bakhtiyar Kazymov[1] Kamran Alekperov[1] Murad Novruzbekov[1], [1]Sklifosovsky Emergency Medicine Institute

Background: Ischemia-reperfusion injury contributes to primary graft dysfunction in 5-25% of liver transplants, limiting transplant success. Platelet-rich plasma contains concentrated growth factors (PDGF, TGF-β, VEGF) and anti-inflammatory mediators that promote tissue repair. We hypothesized that PRP perfusion during cold storage could protect against IRI without increasing thrombotic complications. **Methods:** Ten liver grafts received PRP perfusion between January-October 2024 with IRB approval. Autologous PRP was prepared by double-centrifugation, achieving 4.2 × 10^5 platelets/μL (3.1-fold increase over baseline). Following procurement, grafts were perfused via portal vein with 500 mL PRP diluted 1:4 in UW solution at 4°C, then stored in standard UW solution for 8.4 ± 2.1 hours. Thrombotic risk was assessed by thromboelastography, D-dimer, fibrinogen levels, and histological examination for microthrombi. IRI evaluation included serum transaminases, bilirubin, INR, histological Suzuki scoring, TUNEL staining for apoptosis, and oxidative stress markers (malondialdehyde, glutathione). **Results:** Recipients averaged 54.2 ± 11.8 years (60% male) with hepatitis C cirrhosis (40%), alcoholic liver disease (30%), PSC (20%), and HCC (10%). No thrombotic risk increase was observed: TEG parameters, D-dimer (245 vs 251 ng/mL, $p = 0.85$), and fibrinogen (312 vs 318 mg/dL, $p = 0.71$) remained unchanged post-perfusion. Histological examination revealed no microthrombi. Significant IRI protection was demonstrated at 24 hours post-reperfusion compared to historical controls: peak AST 1,248 ± 342 vs 2,156 ± 678 U/L ($p < 0.001$), peak ALT 986 ± 298 vs 1,742 ± 521 U/L ($p < 0.001$), total bilirubin 3.2 ± 1.1 vs 5.8 ± 2.3 mg/dL ($p = 0.003$), and INR 1.8 ± 0.3 vs 2.4 ± 0.6 ($p = 0.012$). Histological assessment showed improved Suzuki IRI scores (4.1 ± 1.2 vs 6.8 ± 1.8, $p < 0.001$), reduced TUNEL-positive hepatocytes (12.3 ± 3.8% vs 28.7 ± 7.2%, $p < 0.001$), and decreased oxidative stress markers. Clinical outcomes included 100% primary graft function vs 82% historical rate, reduced hospital stay (12.4 vs 16.2 days, $p = 0.04$), and no thrombotic complications. This pilot study demonstrates that PRP perfusion during static cold storage provides significant hepatoprotection without increasing thrombotic risk. The 42% reduction in peak transaminases and 60% decrease in hepatocyte apoptosis suggest substantial cytoprotective effects, likely mediated by growth factor release, anti-inflammatory mechanisms, and antioxidant properties of PRP components. **Conclusion:** PRP perfusion during static cold storage appears safe and effective in reducing ischemia-reperfusion injury in liver transplantation. This novel preservation enhancement technique warrants further investigation through randomized controlled trials to potentially establish its role in standard organ preservation protocols.

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Disclosures: Boris Yaremin: Nothing to Disclose, Catherine Anosova: Nothing to Disclose, Bakhtiyar Kazymov: Nothing to Disclose, Kamran Alekperov: Nothing to Disclose, Murad Novruzbekov: Nothing to Disclose

◆ 3436 | LOW BILE OUTPUT DURING NORMOTHERMIC MACHINE PERFUSION IS NOT PREDICTIVE OF POOR GRAFT OUTCOMES

Stephanie Ohara[1] Victoria Stevens[1] Kunam Reddy[1] Amit Mathur[1] Michelle Nguyen[1], [1]Mayo Clinic Arizona

Background: Bile production during normothermic machine perfusion (NMP) is often used as a surrogate for hepatobiliary function and liver graft viability, with thresholds such as ≥4 cc/hr proposed to guide acceptance. However, the predictive value of bile volume remains uncertain, particularly when other perfusion parameters are reassuring. This study evaluates whether low bile output during NMP is associated with adverse graft outcomes. **Methods:** We performed a single-center retrospective cohort study of adult liver transplants preserved using the TransMedics Organ Care System (OCS) between 2022 and 2024. Grafts were categorized by bile production rate during perfusion: low bile output (<4 cc/hr) and high bile output (≥4 cc/hr). The primary outcomes were early allograft dysfunction (EAD), primary nonfunction (PNF), ischemic cholangiopathy, and 1-year graft survival. **Results:** Of 579 NMP-preserved liver transplants, 347 had high bile output (≥4 cc/hr) and 232 had low bile output (<4 cc/hr). Donor and recipient characteristics are summarized in Table 1. Donor age was similar between groups (median 53.0 vs. 53.5 years; p = 0.79), as was the proportion of DCD donors (77.2% vs. 76.3%; p = 0.79). Pump time was longer in the low bile output group (median 14.1 vs. 12.2 hours; p < 0.001). Recipient age (median 62.0 vs. 61.0 years; p = 0.32) and MELD score (median 17.5 vs. 18.0; p = 0.17) were comparable. Perfusion characteristics are summarized in Table 2. End-perfusion lactate was slightly higher in the low bile group (median 0.690[IQR 0.37–1.16] vs. 0.54 [IQR 0.30–0.98] mmol/L; p = 0.005), though both groups demonstrated adequate lactate clearance. Rates of EAD (25.4% vs. 18.7%; p = 0.06), IC (6.9% vs. 3.5%; p = 0.07), and PNF (1.3% vs. 0.6%; p = 0.39) were comparable. One-year graft survival was equivalent between groups, both exceeding 95% (p = 0.8). **Conclusion:** Low bile output during NMP is not associated with inferior post-transplant outcomes and should not be used as a sole criterion for graft discard. These findings support a more nuanced, multiparametric approach to viability assessment, potentially expanding the use of NMP, particularly in marginal grafts.

Table 1: Donor and Recipient Characteristics Between ≥4 cc/hour vs < 4 cc/hour Groups

Variable	≥4 cc/hr	<4 cc/hr	Total (N=579)	p-value
Donor Age, median [IQR], years	53.0 [38.5, 61.0]	53.5 [40.0, 61.0]	53.0 [39.0, 61.0]	0.75
Donor BMI, median [IQR], kg/m²	28.6 [23.7, 33.2]	30.2 [26.1, 36.2]	29.0 [24.6, 34.8]	<0.001
Distance to Recipient Hospital, median [IQR], miles	274.0 [22.0, 593.0]	420.0 [102.8, 783.2]	278.0 [76.5, 765.0]	<0.001
Preservation Time, median [IQR], hours	16.1 [12.4, 20.2]	17.9 [14.3, 22.2]	16.7 [13.4, 20.8]	<0.001
Pump Time, median [IQR], hours	12.2 [8.6, 16.7]	14.1 [10.6, 18.6]	13.3 [9.4, 17.2]	<0.001
Donor WIT, median [IQR], minutes	25.0 [21.0, 30.0]	25.0 [21.0, 30.0]	25.0 [21.0, 30.0]	0.92
ORI Score	2.3 [1.9, 2.8]	2.5 [1.9, 3.0]	2.4 [1.9, 2.8]	0.12
UK DCD score				0.45
Low Risk	51 (19.0%)	28 (15.8%)	79 (17.8%)	
High Risk	161 (60.1%)	104 (58.8%)	265 (59.6%)	
Futile	56 (20.9%)	45 (25.4%)	101 (22.7%)	
Recipient Age, median [IQR], years	61.0 [51.0, 67.0]	62.0 [52.0, 67.0]	61.0 [51.0, 67.0]	0.33
Recipient BMI, median [IQR], kg/m²	28.2 [24.5, 32.8]	27.7 [24.3, 31.8]	28.0 [24.5, 32.5]	0.50
MELD/PELD Score	18.0 [13.0, 23.0]	17.5 [12.0, 22.0]	18.0 [12.0, 23.0]	0.17

BMI, body mass index; WIT, warm ischemia time (extubation to crossclamp

Table 2. Pump Characteristics Comparisons Between ≥4 cc/hour vs < 4 cc/hour Groups

Variable	≥ 4 cc/hour (N=347)	< 4 cc/hour (N=232)	Total (N=579)	p value
Final HA Flow, median [IQR], L/min	0.58 [0.51, 0.61]	0.59 [0.55, 0.64]	0.58 [0.52, 0.62]	< 0.001
Final HA Pressure, median [IQR], mmHg	47.0 [43.0, 51.0]	46.0 [41.8, 50.0]	47.0 [43.0, 51.0]	0.01
Final PV Flow, median [IQR], L/min	1.37 [1.32, 1.43]	1.37 [1.32, 1.43]	1.37 [1.32, 1.43]	0.58
Final PV Pressure, median [IQR], mmHg	3.00 [3.00, 4.00]	4.00 [3.00, 4.00]	4.0 [3.00, 4.00]	0.55
Final Perfusate pH	7.4 [7.36, 7.44]	7.40 [7.35, 7.43]	7.4 [7.36, 7.44]	0.08
Starting Perfusate Lactate, median [IQR], mmol/L	7.31 [5.10, 9.69]	7.75 [5.67, 9.58]	7.47 [5.26, 9.65]	0.25
Terminal Perfusate Lactate, median [IQR], mmol/L	0.54 [0.30, 0.98]	0.69 [0.37, 1.16]	0.61 [0.30, 1.06]	0.01

HA, hepatic artery, PV, portal vein

Disclosures: Stephanie Ohara: Nothing to Disclose, Victoria Stevens: Nothing to Disclose, Kunam Reddy: Nothing to Disclose, Amit Mathur: Nothing to Disclose, Michelle Nguyen: Nothing to Disclose

◆ 3437 | PRE-TRANSPLANT FRAILTY IS NOT ASSOCIATED WITH CARDIOVASCULAR EVENTS WITHIN 1 YEAR OF LIVER TRANSPLANTATION

Avesh Thuluvath[1] Fawzy Barry[2] Brendan Blackburn[1] Reeti Gulati[3] Angel Wilson[4] Grace Johnson[5] Avery Longdon[5] Anjana Rajan[5] Yuan Zhang[6] Robert Rahimi[4] Andres Duarte-Rojo[7] Matthew Kappus[3] Jennifer Lai[2] Elizabeth Verna[1], [1]Division of Digestive and Liver

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Background: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality after liver transplantation (LT). Frailty independently predicts post-LT mortality but it's specific impact on CVD after LT has not been well-described. The purpose of this study was to investigate the association between frailty and the risk of post-LT cardiovascular events. **Methods:** We performed a retrospective chart review of adult patients who were enrolled in the prospective FrAILT cohort study and underwent LT between 1/1/2019-12/31/2022 at five LT centers. Pre-transplant frailty was assessed with the most recent Liver Frailty Index (LFI: grip, chair stands, balance testing) measured in an ambulatory setting prior to LT. The primary outcomes were major adverse cardiovascular events (MACE: acute coronary syndrome, coronary revascularization, congestive heart failure and cerebrovascular events) and composite cardiac events (CCE: MACE, atrial fibrillation and cardiac arrest). A time-to-event analysis was performed, with death as a competing risk. **Results:** 771 patients were included in the study (Table); 64% were male, the mean age was 57.3 ($\pm$10.9) years and mean MELD 3.0 score of 21.6 ($\pm$10.1). The mean ambulatory LFI was 3.86 ($\pm$0.73), with 21% classified as frail, 61% as pre-frail and 18% as robust using previously established LFI cut-offs. Twenty-two (3%) patients experienced a MACE, 57 (7%) experienced a CCE and 32 (4%) died within 1 year of LT. Pre-LT LFI was not associated with MACE on univariable (HR 1.71, 95% CI 0.84-3.49, $p = 0.14$, per 1.0 LFI) or multivariable analysis (HR 1.38, 95% CI 0.74-2.58, $p = 0.32$) adjusted for age, history of type II diabetes mellitus (DMII), coronary artery disease (CAD) and congestive heart failure (CHF). A history of CHF was significantly associated with MACE (HR 9.76, HR 3.53-27.01, $p < 0.01$); 27 (4%) patients had CHF, 25 of whom had CHF due to diastolic dysfunction. Pre-LT LFI was associated with CCE on univariable (HR 1.56, 95% CI 1.03-2.37, $p = 0.04$), but not multivariable (HR 1.25, 95% CI 0.82-1.91, $p = 0.30$) analysis adjusted for age, history of DMII, CAD, CHF or atrial fibrillation/flutter. A history of atrial fibrillation/flutter (HR 4.80, HR 2.36-9.78, $p < 0.01$) was associated with CCE. **Conclusion:** In this retrospective multi-center study, only 3% of LT recipients experienced a MACE and 7% a CCE within 1 year of LT. Pre-transplant frailty was not associated with MACE or CCE. Though CVD contributes to substantial morbidity and mortality in LT recipients, our findings suggest that pre-LT frailty does not significantly impact the overall cardiovascular risk profile of LT recipients.

Table: Baseline Clinical Characteristics

	Total	With MACE	Without MACE	P-value
N	771	22	748	
Sex, male (%)	490 (64%)	13 (59%)	477 (62%)	p=0.48
Age, mean (±SD)	57.3 (±10.9)	56.1 (±11.8)	57.3 ((±10.8)	p=0.61
Etiology of ESLD (%)				
MASLD	204 (26%)	9 (41%)	195 (26%)	p=0.16
ALD	197 (26%)	6 (27%)	191 (26%)	p=0.95
HBV	36 (5%)	2 (9%)	34 (5%)	p=0.35
HCV	118 (15%)	1 (5%)	117 (15%)	p=0.14
AIH	33 (4%)	0 (0%)	33 (4%)	p=0.30
PBC/PSC	93 (12%)	2 (9%)	91 (12%)	p=0.61
Others	90 (12%)	2 (9%)	88 (12%)	p=0.65
Comorbidities				
HTN	365 (47%)	10 (45%)	355 (47%)	p=0.71
HLD	233 (30%)	7 (32%)	226 (30%)	p=0.91
DMII	318 (41%)	12 (55%)	306 (41%)	p=0.31
CAD	114 (15%)	4 (18%)	110 (15%)	p=0.72
CHF	27 (4%)	6 (27%)	21 (3%)	**p<0.01**
Atrial Fibrillation/Flutter	60 (8%)	4 (18%)	52 (7%)	p=0.06
LFI, mean (±SD)	3.86 (±0.73)	4.14 3 (±1.01)	3.85 (±0.72)	**p=0.02**

Disclosures: Avesh Thuluvath: Nothing to Disclose, Fawzy Barry: Nothing to Disclose, Brendan Blackburn: Nothing to Disclose, Reeti Gulati: Nothing to Disclose, Angel Wilson: Nothing to Disclose, Grace Johnson: Nothing to Disclose, Avery Longdon: Nothing to Disclose, Anjana Rajan: Nothing to Disclose, Yuan Zhang: Nothing to Disclose, Robert Rahimi: Nothing to Disclose, Andres Duarte-Rojo: Echosens: Grant/Research Support, Matthew Kappus: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Elizabeth Verna: Nothing to Disclose

◆ 3438 | THE ROLE OF IGF-1 AND GDF-8 IN RESTORATION OF MUSCLE HEALTH ASSESSED BY ^{31}P MR SPECTROSCOPY AFTER LIVER TRANSPLANTATION.

Pavel Trunecka[1] Denisa Kyselova[1] Irena Mikova[2] Petr Sedivy[1] Monika Dezortova[1] Mariia Lunova[1] Dana Kautznerova[1] Milan Hajek[1], [1]Institute for Clinical and

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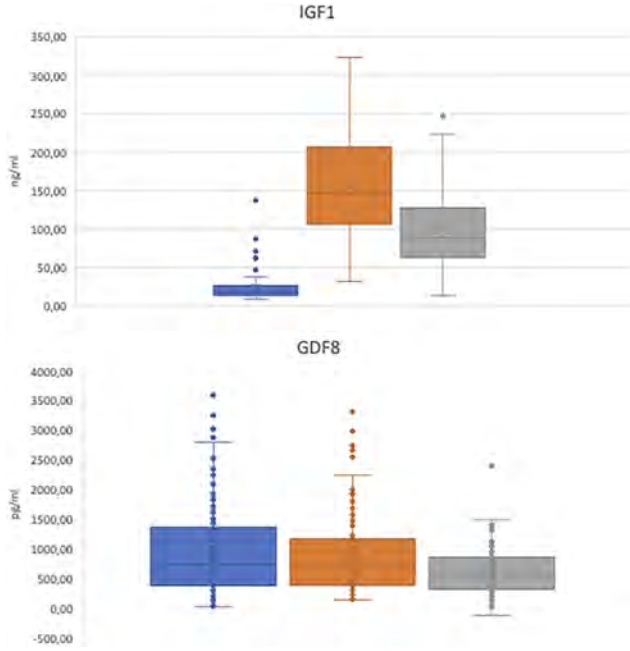
Experimental Medicine, [2]Institute for Clilnical and Experimental Medicine

Background: Skeletal muscle is subject of deterioration during chronic liver disease contributing to frailty and impaired patient survival on transplant waiting list or after liver transplantation (LT). Besides assessment of sarcopenia and myosteatosis by pretransplant abdominal CT scan, there is possibility to assess a quality skeletal muscle using ^{31}P MR spectroscopy (MRS) by measuring concentration of macroergic phosphates. In contrast to CT, MRS can be performed repeatedly after liver transplantation and is more predictive of outcome than sarcopenia or myosteatosis [1)]. Insulin-like growth factor-1 (IGF-1) and myostatin (GDF-8) are well known moderators of skeletal muscle growth. Goals of our study was to determine relationship between pre-LT skeletal muscle characteristics and course of its metabolic state up to 12 months after LT. **Methods:** Presence of sarcopenia was assessed using skeletal muscle index and myosteatosis by measuring radiation attenuation of psoas muscle on pretransplant CT scan. Additionally, patients underwent resting ^{31}P MRS of the calf muscle before LT, and 6 and 12 months after. Area of M. gastrocnemius were calculated, and strength of plantar flexes were measured during each MRS session by dedicated ergometr. Plasma concentration of IGF-1 and GDF-8 were measured using commercially available Quantikine ELISA kits (R&D Systems) according to manufacturer's protocols. GDF-8 samples underwent an activation step to convert GDF-8 into its immunoreactive form. **Results:** 83 liver transplant recipients surviving at least 2 years from Tx (33 F, 50M) median age 59 (range 34 - 71) years were evaluated. We have found highly significant differences in concentration of GDF-8 and IGF-1 during the study period corresponding with significant increase in concentration of ATP in skeletal muscle despite very small changes in muscle volume and strength. We have found highly significant differences in concentrations of GDF-8 and IGF-1 measured during pre- and post-LT visits from patients, who presented with ATP muscle concentration bellow 50th percentile in comparison to recipients with "healthy" muscles ($p < 0.001$). **Conclusion:** We have found strong association between the content of ATP measured by ^{31}P MRS in skeletal muscle and concentrations of cytokines involved in skeletal muscle regulation during the first year after LT. Only very weak correlations between pre-LT presence of sarcopenia and myosteatosis and these cytokines concentrations after LT was found supporting our notion of superiority of ^{31}P MRS as a tool for precise skeletal muscle evaluation.

1. Kyselova D. J Cachexia, Sarcopenia, Muscle 2025; 16(1): e13635.



Disclosures: Pavel Trunecka: Nothing to Disclose, Denisa Kyselova: Nothing to Disclose, Irena Mikova: Nothing to Disclose, Petr Sedivy: Nothing to Disclose, Monika Dezortova: Nothing to Disclose, Mariia Lunova: Nothing to Disclose, Dana Kautznerova: Nothing to Disclose, Milan Hajek: Nothing to Disclose

◆ 3439 | IMPACT OF ACUITY CIRCLES POLICY ON MULTIPLE LISTING IN LIVER TRANSPLANTATION

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Background: Multiple listing (ML) is a practice that allows liver transplant candidates to register at multiple centers, historically providing advantages to patients with higher socioeconomic status. The 2020 Acuity Circles (AC) policy aimed to improve geographic equity in liver allocation by replacing donation service areas with broader distribution zones; however, the unintended consequences of this policy remain underexplored. We examined how this policy change affected ML patterns and waiting times across MELD scores. **Methods:** We analyzed UNOS liver transplant data (2016-2023) for adult candidates, comparing pre-AC (2016-2019) and post-AC (2020-2023) eras. ML was defined as a single patient registered at multiple centers on different dates. Our primary outcome was the change in ML rates between AC eras. For our secondary outcome, we analyzed changes in ML by

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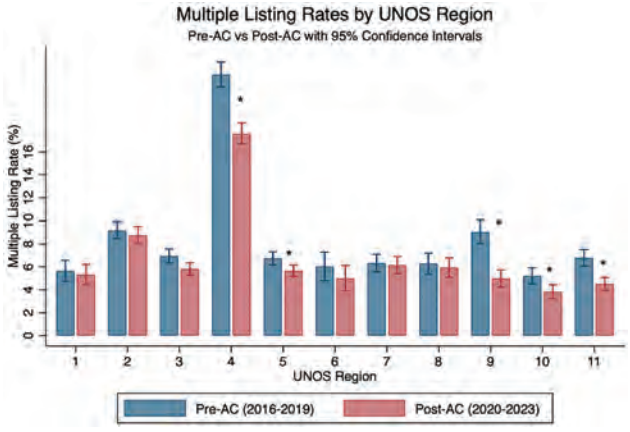
patient demographics and UNOS region, waitlist dynamics, and using difference-in-differences analysis and chi-square tests with Bonferroni correction for multiple comparisons. **Results:** Among 94,940 adult liver transplant candidates, ML rates declined significantly from 5.1% pre-AC to 3.1% post-AC (39% relative reduction, $p < 0.001$). White males remained overrepresented among ML patients and ML patients increased in age 53.9 to 54.8 years ($p = 0.017$). 5 of 11 UNOS regions (4, 5, 9, 10, 11) demonstrated significant decreases in ML after Bonferroni correction ($p < 0.0045$), with reductions ranging from 16% to 45% (mean 29%). The proportion of all transplanted patients who were ML declined from 1.6% (443 of 28,378) to 1.1% (346 of 32,884) ($p < 0.001$). ML patients had consistently lower MELD scores compared to single-listed (-2.9 points, $p < 0.001$). Multiple-listed patients had their MELD score increase from 17.2 to 17.8 ($p < 0.05$), and wait times decreased from 170 to 100 days ($p < 0.01$). For ML patients, the transplant rate increased significantly from 18.8% (443 of 2,361) in the pre-AC era to 22.5% (346 of 1,536) in the post-AC era ($p < 0.01$). Among ML patients, private insurance remained stable (66%), while the number of patients with college degrees increased (33.7% to 41.5% $p < 0.001$), suggesting increased concentration among higher socioeconomic status (SES) patients. **Conclusion:** The AC policy achieved substantial reductions in ML overall and across 6 UNOS regions. However, ML continues to be utilized by lower MELD patients to secure shorter wait times and higher transplant rates. While geographic disparities have improved, SES inequities in ML persist.



Disclosures: Vladislav Fomin: Nothing to Disclose, Russell Rosenblatt: Nothing to Disclose, Robert Brown: Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant

◆ 3440 | IMPACT OF COVID-19 VACCINATION ON THROMBOSIS RISK IN LIVER TRANSPLANT RECIPIENTS- A MULTICENTER PROPENSITY-MATCHED STUDY

Islam Mohamed[1] Basil Jalamneh[2] Hazem Nasser[3] Jonathan Ghobrial[4] Mirella Youssef[5] Archana Kharel[6] Ahmed Abdelwahab[7], [1]The Cleveland Clinic Foundation-Fairview hospital, [2]Cleveland Clinic Foundation-Internal Medicine, [3]Internal Medicine, University of Wisconsin-Madison, Madison, WI, United States, [4]Alleghany Health Network, [5]The Ohio State University, Columbus, OH, United States., [6]Cleveland Clinic Foundation, [7]The University of Toledo College of Medicine and Life Sciences, Toledo, OH, United States

Background: Covid-19 has significant impact on liver transplant recipients (LTR) including higher rates of hospitalization, ICU admission and mortality. Reports of increased thrombosis attributed to covid vaccine increased uncertainty about the vaccine in solid organ transplant recipients. Despite the plethora of data on positive covid vaccine outcomes on LTR, multiple case records reported increased Portal vein thrombosis (PVT) in vaccinated LTR. This study evaluates the effect of COVID-19 vaccination on thrombosis risk in LTR. **Methods:** Using data from the TriNetX US Collaborative Network, a propensity-matched cohort analysis was conducted. Cohort 1 (vaccinated) included 6,741 patients with liver transplant status who received at least one COVID-19 vaccine dose. Cohort 2 (unvaccinated) comprised 6,741 matched patients who did not receive vaccination. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for mortality, transplant-specific outcomes, mechanical ventilation, and thrombosis, using Kaplan-Meier survival analysis. **Results:** Of 919 vaccinated LTR; the mean age was 54.0 years ($\pm$14.6), predominantly male, with 62.8% (577/919) identifying as male and 37.2% (342/919) as female, and White individuals represented the majority: 70.4% (647/919). The median follow-up duration in the 1,245 days (IQR: 718 days). COVID-19 vaccination significantly reduced the risk of all measured outcomes. Vaccinated patients demonstrated a 16% reduction in liver transplant complications (HR: 0.84, 95% CI: 0.69–1.0, p0.004), a 23% reduction in post-transplant hospitalizations (HR: 0.77,95% CI: 0.52;1.15, p 0.35), a 36% reduction in ICU admission (HR: 0.64, 95% CI: 0.48–0.85, p 0.05), and a 29 % reduction in thrombosis risk (HR: 0.71, 95% CI: 0.48;1.047, p.2). However, there was increased risk of portal vein thrombosis (HR: 1.22, 95% CI: 0.70;2.13, p.05). **Conclusion:** COVID-19 vaccination was associated with a significant reduction in overall liver transplant complications, ICU admissions, and thrombotic events in liver transplant

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recipients. While the vaccine demonstrated a favorable safety profile and protective benefit across most outcomes, a non-significant trend toward increased risk of portal vein thrombosis was observed. These findings support the overall benefit of COVID-19 vaccination in the liver transplant population, while highlighting the need for further investigation into post-vaccination portal vein thrombosis.

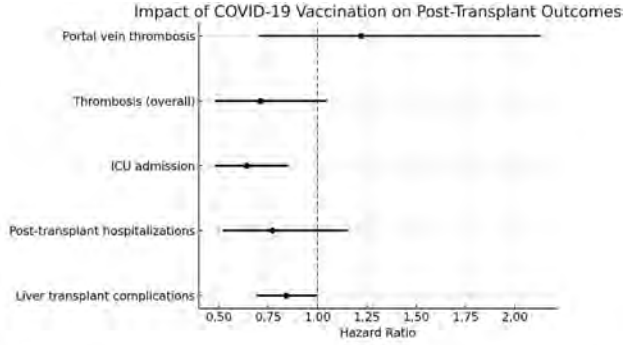

Figure.

Forest plot showing the impact of COVID-19 vaccination on clinical outcomes in liver transplant recipients. Vaccinated patients had a reduced risk of liver transplant complications, ICU admissions, and overall thrombosis compared to unvaccinated counterparts. Hazard ratios (HR) and 95% confidence intervals (CI) are displayed for each outcome. A non-significant increase in portal vein thrombosis was noted. The dashed vertical line indicates the reference value (HR = 1.0).

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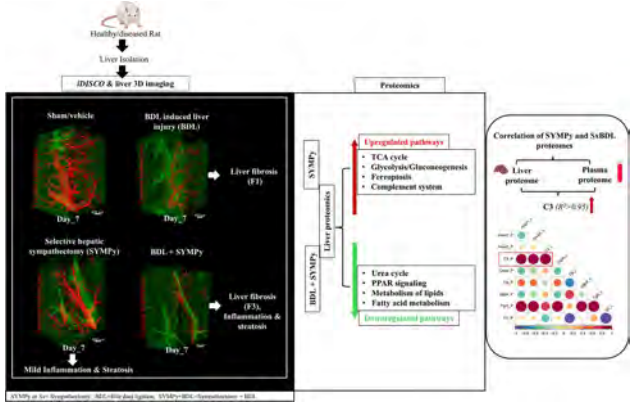
◆ 3441 | LOSS OF LIVER SYMPATHETIC INNERVATION EXACERBATES HEPATIC INJURY AND METABOLIC DYSREGULATION

Sadam Bhat[1] NUPUR SHARMA[1] Csaba Adori[2] Anupama Parasar[1] Ravinder Singh[1] Babu Mathew[1] Tore Bengtsson[3] Roshan Koul[1] Savneet Kaur[4] Manoj Sharma[1] Jaswinder Singh[5] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences, [2]Karolinsika Institute, Sweden, [3]Department of Molecular Biosciences, The Wenner-Gren Institute (MBW), Stockholm University, Stockh, [4]Institute of Live rand Biliary Sciences, [5]jassi2param@gmail.com

Background: Hepatic innervation has had little attention in hepatology research so far, largely because liver functions do not seem to be significantly affected after orthotopic liver transplantation (OLT). Nevertheless, long-term studies have shown the development of dyslipidemia, postprandial hyperglycemia, insulin resistance, and changes in intrahepatic blood flow after OLT. Whether the denervated and newly implanted liver can perform functions akin to those of a normally innervated liver remains an area worth investigating. However, the pattern of hepatic innervations and their functional role in the liver has not been well studied. Moreover, the effect of injury to these neuronal innervations in healthy and diseased states has remained obscure. We undertook to study the neuroanatomical pattern of innervations in an animal model of sympathectomy (SYMPy). **Methods:** Animals were categorized into four groups: control rats with intact hepatic sympathetic innervation (HSI), sympathectomized rats (SYMPy), rats subjected to bile duct ligation (BDL) with intact HSI, and SYMPy rats with BDL (BDL+ SYMPy). The anatomical distribution and characteristics of neuronal innervations were performed by using Immunolabeling-Enabled 3D Imaging of Solvent-Cleared Organs (iDISCO) methodology. The functional aspects were performed by the LC-MS-based proteomics of hepatic tissue under physiological and pathophysiological conditions. **Results:** We identified that the neural connections within the liver are predominantly sympathetic. After selective hepatic disruption of these sympathetic nerves (Sx) in healthy rats, this led to mild fat accumulation and inflammation in the liver. When Sx was combined with a liver disease model (SxBDL), an expedited onset of liver damage with metabolic dysfunction and increased fibrosis was observed in comparison to the control. The hepatic proteome of SxBDL showed increased inflammatory (NLRP3, MAPK, and PDGF), fibrogenic (TNFR2, Wnt, and FGF) pathways ($p < 0.05$, $FC > 1.5$) and metabolic dysregulation [increase in the tricarboxylic acid cycle and a decrease in the urea cycle ($p < 0.05$, $FC > 1.5$) and C3 ($FC > 2$, $FDR < 0.01$, $p < 0.05$, $R^2 > 0.95$) as a key driver of accelerated injury in SxBDL. **Conclusion:** We demonstrated the development of a neuropathic phenomenon following reduction in the sympathetic drive in the liver, with implications for both pathological and metabolic aspects of liver health, with an increased level of C3.



Disclosures: Sadam Bhat: Nothing to Disclose, NUPUR SHARMA: Nothing to Disclose, Csaba Adori: Nothing to Disclose, Anupama Parasar: Nothing to

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◆ 3442 | THE IMPACT OF GLP-1 AGONIST UTILIZATION ON POST LIVER TRANSPLANT OUTCOMES: A RETROSPECTIVE REVIEW

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Background: Patients with metabolic dysfunction-associated steatohepatitis (MASH) have underlying cardiometabolic risk factors which persist following liver transplantation (LT) and can lead to recurrent MASH and cardiometabolic events. The rate of recurrent MASH after LT has been reported in up to 25% of patients with up to 20% of patients developing recurrent fibrosis within 2 years of LT. Given the emergence and demonstrated efficacy of GLP-1 agonists for type 2 diabetes (T2DM) and obesity, these therapies likely have benefit in the post-LT setting. This study was designed to analyze the potential clinical benefit associated with GLP-1 agonist use in patients with high risk cardiometabolic profiles after LT. **Methods:** We collected data from a global de-identified database (TriNetX) over a 5-year period and identified patients with an ICD label of T2DM and obesity as defined by a BMI $\geq$ 30 prior to LT. We then compared a cohort with GLP-1 agonist exposure (semaglutide, tirzepatide, liraglutide, dulaglutide) post-LT to a cohort without GLP-1 agonist exposure post-LT. GLP-1 agonist exposure was defined as at least one occurrence within 90 days post-LT. We then used propensity score matching to control for age, sex, INR, total bilirubin, creatine and albumin prior to LT in an attempt to match severity of liver disease prior to LT. Cohorts consisted of 2244 patients following matching. We assessed the primary outcome of mortality and secondary outcomes of graft rejection, hospital readmission, and myocardial infarction at 90-day and 1-year intervals post-LT. **Results:** GLP-1 agonist use was associated with decreased mortality at both 90-day (odds ratio [OR]: 0.28, P = 0.001) and 1-year ([OR]: 0.39, P = 0.0001) intervals post-LT. Rates of graft rejection in the GLP-1 agonist cohort were reduced at both 90-day ([OR]: 0.44, P = 0.001) and 1-year ([OR]: 0.69, P = 0.03) intervals post-LT. Rates of hospital readmission were significantly reduced at both 90-day ([OR]: 0.44, P = 0.0001) and 1-year ([OR]: 0.57, P = 0.0001) intervals post-LT. The rate of acute MI was not significantly different between cohorts at both 90-day ([OR]: 0.75, P = 0.25) and 1 year ([OR]: 0.86, P = 0.39) intervals post-LT. **Conclusion:** Our study showed that GLP-1 agonist use in the post-LT setting is associated with an increased survival benefit at both the 90-day and 1-year intervals. Additionally, there were significantly reduced rates of graft rejection and hospital readmission in the GLP-1 agonist cohort. This study highlights the potential need for earlier and increased utilization of cardiometabolic medications, particularly GLP-1 agonists after LT in a population at high risk for recurrent MASH and cardiometabolic events that could potentially impact outcomes beyond cardiometabolic events.

Disclosures: Taylor Seacor: Nothing to Disclose, Garrick Gu: Nothing to Disclose, Anita Krishnarao: Nothing to Disclose

◆ 3443 | DIFFERENTIAL MACHINE PERFUSION ADOPTION RESHAPES ORGAN UTILIZATION PATTERNS IN LIVER TRANSPLANTATION

Vladislav Fomin Robert Brown[1] *Russell Rosenblatt*[1], [1]*Weill Cornell Medicine*

Background: Machine perfusion (MP) is a technique of preserving organs with circulating perfusate during the organ procurement process in liver transplantation (LT). Although there has been an increase in the utilization of MP, it has not been equally distributed among different-sized transplant centers. We hypothesized that MP changed the transplant landscape, and unequal adoption fundamentally alters organ utilization patterns. **Methods:** We analyzed 71,600 adult liver transplants (2010-2024) from UNOS data across 150 centers with MP data. We evaluated adult (age $\geq$18, single-organ, deceased donor transplantation. Centers were stratified by annual transplant volume into very low ($<$25), low (25-50), medium (51-100), and high ($>$100 LT/year) categories. We employed structural break analysis to identify technology tipping points, cross-correlation analysis with temporal lags to establish causal sequences, and examined donor quality sorting patterns. The primary outcomes were differences in MP adoption by center type. Secondary outcomes were transplant donor type utilization patterns with regard to MP utilization and center type. **Results:** MP was used in 5,240 transplantations with volume-dependent adoption: 95% of high-volume vs 17.6% of very low-volume centers utilized MP ($p<0.001$). Among 93 MP-adopting centers, 30 (32%) were early adopters (2016-2019), dominated by high (16) and medium (13) volume centers. 2022 was identified as the year in which there was a critical transplant volume inflection point for low, medium, and high-volume centers ($p<0.001$). 2022 was identified as the tipping point for MP use, growing

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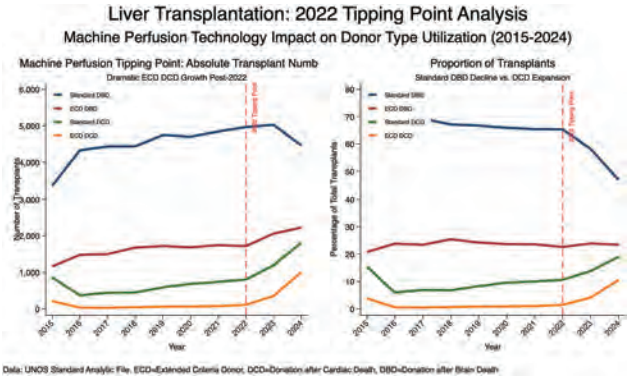
by 250%. Post-2022 total annual transplants increased by 28% (7,399 to 9,498), however, standard DBD declined from 65% to 47%, while DCD increased from 11% to 19% and ECD DCD increased from 1.4% to 10.6% (all $p < 0.001$). Center donor portfolio transformation patterns were volume-dependent: high-volume centers showed the largest standard DBD decline (-13%) and greatest DCD adoption (14%), while very low-volume centers increased their standard DBD usage (0.7%) and increased DCD usage (3.4%). **Conclusion:** MP adoption creates systematic differences in organ utilization patterns based on center volume. High-volume centers were the first to utilize MP, resulting in an early increase in their transplant volumes. This early adoption has culminated in increased utilization of ECD and DCD donors by high-volume centers at the expense of DBD organs, compared to low-volume centers. Overall, DBD volume has declined with a greater proportion of transplants now involving DCD and ECD donors.



Disclosures: Vladislav Fomin: Nothing to Disclose, Robert Brown: Gilead: Consultant, Intercept: Consultant, Abbvie: Consultant, Madrigal: Consultant, GSK: Consultant, eGenesis: Consultant, mirum: Consultant, mallinckrodt: Consultant, Russell Rosenblatt: Nothing to Disclose

◆ 3444 | QUANTITATIVE MRCP ACCURATELY DETECTS THE PRESENCE OF NON-ANASTOMOTIC STRICTURES IN PATIENTS AFTER LIVER TRANSPLANTATION

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Background: Advances in normothermic machine perfusion (NMP) have improved post-transplant liver function, but biliary complications, such as anastomotic (AS) and non-anastomotic (NAS) strictures, remain a common cause of morbidity and mortality after liver transplantation (LT). Quantitative magnetic resonance cholangiopancreatography (MRCP+) has shown utility in monitoring patients with biliary diseases, and here we assess MRCP+ metrics for identification of NAS after liver transplantation. **Methods:** Participants in the normothermic liver preservation trial by the Consortium for Organ Preservation in Europe (COPE) that underwent an MRCP within 6 months of LT were included in this study. The MRCPs were read by three radiologists (consensus) for AS and NAS, and analysed with MRCP + (Perspectum Ltd, Oxford) for quantitative assessment of biliary metrics. Principal component analysis (PCA) was performed, the levels of the key MRCP+ metric from the PCA was compared in LT recipients with or without NAS (Wilcoxon tests) and diagnostic accuracy assessed with area under the receiver operator curve (AUC). **Results:** In the total N = 83 LT recipients with MRCP (male sex = 71%, donation after circulatory death = 33%, NMP = 54%), 7 cases of NAS, 42 cases of AS and 3 with both were determined. PCA demonstrated two main components: one quantifying localised strictures and dilatations and a second quantifying the biliary tree's dimensions. The total length of strictures and dilatations was the single metric most representative of both components and was higher in patients with NAS compared to those without (150 mm [110-246] vs 42 mm [19-99], $p = 0.03$). When assessing the length of strictures and dilatations separately, only the latter was higher in patients with NAS compared to those without (95 mm [81-168] vs 28 mm [8-58], $p = 0.02$). Additionally, the number of dilatations was higher in those with NAS (16 [13-23] vs 2 [1-5]). The total length of strictures and dilatations identified LT recipients with NAS with a diagnostic accuracy of AUC = 0.75 (0.50-0.92), while number of dilatations had an AUC of 0.76 (0.51-0.94) for NAS. **Conclusion:** This study shows that the total length of strictures and dilatations, as well as number of dilatations, could identify LT recipients with NAS. This suggests that MRCP+ may have utility in effectively monitoring biliary complications after LT and further research should assess the ability to predict clinical outcomes and resulting patient management improvements.

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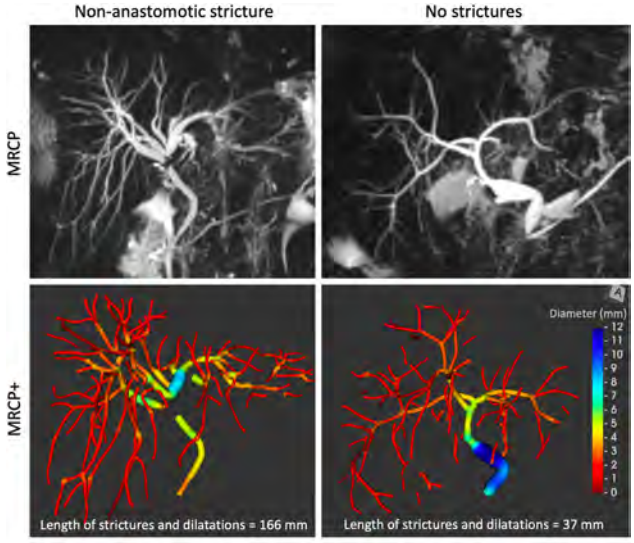

Figure 1: Example maximum intensity projections of 3D MRCP and corresponding MRCP+ derived biliary tree models for patients with and without non-anastomotic strictures.

Disclosures: Andrea Dennis: Nothing to Disclose, Emmanuel Selvaraj: Nothing to Disclose, David Nasralla: Nothing to Disclose, Carlos Ferreira: Perspectum: Employee, John Karani: Nothing to Disclose, Arvind Pallan: Nothing to Disclose, Rutger Ploeg: Nothing to Disclose, Sara Upponi: Nothing to Disclose, Peter Friend: Nothing to Disclose

◆ 3445 | LIVER FRAILTY INDEX PREDICTS POOR PHYSICAL ACTIVITY VOLUME AND INTENSITY (GENEACTIV® ACCELEROMETER) IN ADVANCED CHRONIC LIVER DISEASE: UK PROSPECTIVE CASE-CONTROL STUDY

Felicity Williams[1] Jonathan Quinlan[1] Amritpal Dhaliwal[2] Leigh Breen[1] Carolyn Greig[1] Ahmed Elsharkawy[2] Thomas Marjot[3] Janet Lord[1] Alex Rowlands[4] Matthew Armstrong[2], [1]University of Birmingham, [2]University Hospitals Birmingham, [3]University of Oxford, [4]University of Leicester

Background: Physical frailty leads to poor clinical outcomes in advanced chronic liver disease (AdvCLD). However, the volume and intensity of physical activity in AdvCLD remains unknown limiting the ability to tailor interventions for frailty. This study investigated (a) physical activity profiles in AdvCLD vs healthy controls (HC), (b) predictors of physical activity volume/intensity and their association with frailty, and (c) the physical activity volume and intensity achievable in AdvCLD. **Methods:** Outpatients with AdvCLD awaiting liver transplant were recruited, alongside age/sex matched controls (Birmingham, UK). Participants wore a GENEActivâ wrist-accelerometer for 14-days to measure physical activity volume and intensity, including most active continuous periods of the day. Measures of physical frailty included liver frailty index (LFI), gait speed, quadriceps strength, and thigh muscle ultrasound measures. **Results:** 42 AdvCLD (65% male, mean age 56, UKELD 52, 53% ArLD, 12% MASLD, 31% Autoimmune) and 17 HC (59% male, age 47) were recruited. Participants with ArLD had significantly lower volume of physical activity (mean[SD] acceleration 13.4 [4.6] vs 29.2[8.9]m*g*, $p < 0.01$) and spent proportionately more time at low physical activity intensities than HC (Intensity gradient -2.9 vs -2.4, $p < 0.01$). Older age and refractory ascites independently predicted both lower volume ($B = -0.24$, $p = 0.02$; $B = -7.6$, $p < 0.01$, respectively) and intensity ($B = -0.001$, $p = 0.02$; $B = -0.15$, $p = 0.04$, respectively). Lower LFI (less frail) and higher quadriceps strength were associated with higher physical activity volume ($B = -4.68$, $p = 0.03$; $B = 0.11$, $p < 0.01$, respectively) and intensity ($B = -0.21$, $p < 0.01$; $B = 0.004$, $p < 001$, respectively); but not chair stands. Physical activity volume and intensity across quartiles of LFI revealed a non-significant downward trend in volume as frailty worsened (Fig. 1A). Physical activity intensity differed significantly by LFI quartile ($p = 0.002$, Fig. 1B), with higher intensity in the 1st (most robust) and 2nd quartile than the 4th quartile (most frail) (-2.7 [0.2] vs 3.1[0.1], $p = 0.004$; -2.8[0.2] vs -3.1[0.1], $p = 0.02$, respectively). The most active continuous one-minute of the day was at a vigorous intensity in the most robust LFI quartile (red line, Fig. 1C), but only a slow walk for the most frail LFI quartile (purple line, Fig. 1C). **Conclusion:** Physical activity (especially intensity) is significantly reduced in patients with AdvCLD, being more pronounced in the most frail. Older age, refractory ascites and ArLD are associated with lower physical activity. The LFI is a valuable predictor of physical activity and could be used to prioritise and tailor exercise interventions. This study highlights realistic exercise targets in patients with AdvCLD (i.e. short bursts (i.e. < 5mins) of brisk walking) rather than those for the general population.

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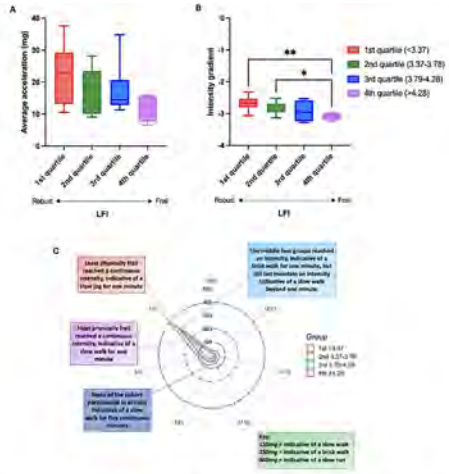


Fig 1. Physical activity (PA) profile of patients with advanced liver disease.

A: PA volume (mg) by quartile of liver frailty index (LFI);

B: PA intensity distribution (intensity gradient) by quartile of liver frailty index;

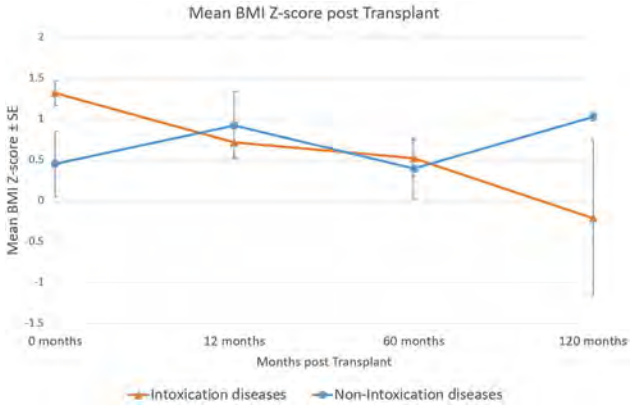
C: Intensity (mg) of the most active continuous 1 (M1) to 60 (M60) minutes of the day by LFI quartile. (Note: intensity of a slow walk = 100 mg, brisk walk 250 mg, vigorous PA 400 mg).

Disclosures: Felicity Williams: Nothing to Disclose, Jonathan Quinlan: Nothing to Disclose, Amritpal Dhaliwal: Nothing to Disclose, Leigh Breen: Nothing to Disclose, Carolyn Greig: Nothing to Disclose, Ahmed Elsharkawy: Gilead: Advisor, GSK: Advisor, Ipsen: Advisor, Alfasigma: Advisor, Thomas Marjot: Nothing to Disclose, Janet Lord: Nothing to Disclose, Alex Rowlands: Nothing to Disclose, Matthew Armstrong: Nothing to Disclose

◆ 3446 | LONG-TERM LINEAR GROWTH OUTCOMES FOR PEDIATRIC LIVER TRANSPLANT RECIPIENTS WITH INBORN ERRORS OF METABOLISM

Srinidhi Mereddy[1] Leila Mahdavi[1] Nada Yazigi[2] Gabriel Gondolesi[2] Kimberly Chapman[3] Udeme Ekong[2] Khalid Khan[2], [1]Georgetown University School of Medicine, [2]Georgetown University Hospital, [3]Children's Hospital Los Angeles

Background: The second-leading indication of liver transplantation (LT) in pediatric patients has recently evolved to be treatment of inborn errors of metabolism, such as urea cycle disorders, MSUD, organic acidemias, etc.[1] While liver transplantation is often able to stabilize the primary metabolic disorder in children, the long-term implications of improved growth are not well characterized. This study investigates the linear growth in pediatric LT recipients over a 10-year period at MedStar Georgetown University Hospital. **Methods:** A retrospective chart review was conducted of pediatric patients who underwent LT as treatment for their metabolic disease at The Transplant Center for Children at MedStar Georgetown University Hospital between 2005 and 2020. Data extraction at key clinical time-points post-transplant (1 year, 5 years, 10 years) included the following parameters: body mass index (BMI) Z-score, weight Z-score, and height Z-score, diagnosis, and steroid use. Inclusion criteria required: 1) a diagnosis of inborn error of metabolism including Intoxication diseases such as Urea Cycle Disorder, Maple Syrup Urine Disease, Organic Acidemia, or Non-Intoxication diseases and 2) patients that only underwent one LT. **Results:** An unpaired sample t-test was performed in Microsoft Excel to compare BMI Z-score, Height Z-score, and Weight Z-score in patients with Intoxication diseases and Non-Intoxication diseases. Significantly abnormal BMIs, Weights, and Heights compared to age were noted at the time of transplant ($p = 0.0181$, $p = 0.0001$, $p = 0.0021$) and at 1 year post-transplant for only Weight and Height ($p = 0.0427$, $p = 0.01$), but not at 5 years and 10 years. None of the patients were found to be taking steroid immunosuppression past 6 months post-transplant, thus the relationship between steroid use and linear growth impact could not be assessed. **Conclusion:** Patients with both Intoxication and Non-intoxication diseases had abnormal Weight and Height up to 1 year post-transplant and abnormal BMI at the time of transplant, but after these time points these metrics were normalized. These findings indicate that liver transplant improved growth for patients and normalized linear growth long-term compared to solely medication management of metabolic disorders.[2,3]



Disclosures: Srinidhi Mereddy: Nothing to Disclose, Leila Mahdavi: Nothing to Disclose, Nada Yazigi: Nothing to Disclose, Gabriel Gondolesi: Nothing to Disclose, Kimberly Chapman: Nothing to Disclose, Udeme Ekong: Nothing to Disclose, Khalid Khan: Nothing to Disclose

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◆ 3447 | LONGER DRIVING DISTANCE AND TIME TO TRANSPLANT CENTER ARE ASSOCIATED WITH INCREASED WAITLIST REMOVAL AND LOWER TRANSPLANT PROBABILITY IN PATIENTS WITH LOW MELD AT LISTING

John Esli Medina Morales[1] Mahinaz Mohsen[2] Vraj Shah[2] Margaret Carrel[3] Qianyi Shi[3] Tomohiro Tanaka[3], [1]Rutgers New Jersey Medical School; Washington University in St Louis, [2]Rutgers New Jersey Medical School, [3]University of Iowa School of Medicine

Background: Although longer travel time and traffic congestion have been associated with higher waitlist mortality among adult liver transplant (LT) candidates, their impact on patients listed with low initial MELD scores remains poorly understood. Rural disparities are also understudied in this population. Using travel distance to the listing transplant center (LTC) and time as proxies for access to high-volume centers, we evaluated their association with waitlist outcomes among LT candidates with low MELD at listing. **Methods:** We identified adult LT candidates in the United States listed between 2013 and 2023 with an initial MELD score ≤ 18 using data from nationwide transplant registry. Candidates with MELD exception points and listed with Status 1 were excluded. Travel distance and driving time from the patient's residence to the LTC were calculated and stratified into tertiles. Rurality was categorized as urban or rural using Rural-Urban Commuting Area (RUCA) codes. The primary outcome was waitlist removal due to death or clinical deterioration; the secondary outcome was receipt of LT. Competing risk regression was used to assess the association of travel burden and rurality with waitlist outcomes. **Results:** A total of 34,541 LT candidates with initial MELD ≤ 18 were included. The median age was 58 years (IQR 51–64), and the median MELD at listing was 14 (IQR 10–16). The most common etiologies were alcohol-associated liver disease (27%), metabolic dysfunction-associated steatohepatitis (26%), and hepatitis C (20%). Compared to those in the shortest travel group, candidates in the longest tertile of travel distance and driving time had a higher rate of waitlist removal due to death or clinical deterioration (travel distance: 21.5% vs. 24.3%; travel time: 30.3% vs. 35.5%; both $p = < 0.001$). On multivariable competing risk analysis, both longer driving distance and longer driving time were independently associated with increased risk of waitlist removal (adjusted subdistribution hazard ratio [aSHR] 1.20, 95% CI 1.05–1.18; and aSHR 1.20, 95% CI 1.14–1.28, respectively) and decreased probability of transplantation (aSHR 1.15, 95% CI 1.08–1.21; and aSHR 1.23, 95% CI 1.16–1.30, respectively). No differences were found on RUCA classification (Table 1). **Conclusion:** Among LT candidates with low MELD scores at listing, greater driving distance and travel time to the LT center, used as proxies for access to a higher level of care, were independently associated with a higher risk of waitlist removal and decreased probability of LT.

Table 1. Competing risk regression analysis for waitlist removal due to death or clinical deterioration or incidence of transplantation

	Waitlist removal		Transplantation	
	aSHR (95% CI)	p-value	aSHR (95% CI)	p-value
Driving distance[a]				
Shortest	Ref		Ref	
Medium	1.11 (1.05–1.18)	<0.001	0.93 (0.89–0.97)	<0.001
Longest	1.20 (1.14–1.28)	<0.001	0.92 (0.88–0.96)	<0.001
Driving time[b]				
Shortest	Ref		Ref	
Medium	1.15 (1.08–1.21)	<0.001	0.91 (0.87–0.95)	<0.001
Longest	1.23 (1.16–1.30)	<0.001	0.90 (0.86–0.94)	<0.001
RUCA				
Urban (1-3)	Ref		Ref	
Non-Urban (4-10)	0.97 (0.92–1.04)	0.45	0.98 (0.94–1.02)	0.44

aHR, adjusted subdistribution hazard ratio; BMI, body mass index RUCA, rural-urban commuting area.
[a] Driving distance in kilometers
[b] Driving time in minutes
Model adjusted for age at listing, sex, race/ethnicity, diabetes, BMI, insurance, liver disease and Child-Pugh score.

Disclosures: John Esli Medina Morales: Nothing to Disclose, Mahinaz Mohsen: Nothing to Disclose, Vraj Shah: Nothing to Disclose, Margaret Carrel: Nothing to Disclose, Qianyi Shi: Nothing to Disclose, Tomohiro Tanaka: Nothing to Disclose

◆ 3448 | CREATINE METABOLISM DURING LIVER REGENERATION

Thi Linh Nguyen[1] Thi Nga Ha[1] Hyon-Seung Yi[1], [1]Department of Medical Science, Chungnam National University School of Medicine

Background: The liver has a remarkable regenerative capacity following to injury, a process that is critical for recovery in patients with liver disease. While various metabolic pathways have been implicated in liver regeneration, the role of creatine metabolism remains poorly understood. This study aimed to elucidate the impact of creatine deficiency on liver regeneration. **Methods:** A two-thirds partial hepatectomy (PH) model in mice was used to evaluate the role of creatine in hepatic regeneration. Creatine deficiency was induced by administering beta-guanidinopropionic acid (ß-GPA), a creatine analogue, while controls received standard drinking water. Liver regeneration was assessed by measuring the expression of proliferation markers and metabolic genes. Additionally, single-cell RNA sequencing was performed to identify key cells types involve in creatine transport. A reduced-size liver transplantation model in Sprague-Dawley rats was also employed to evaluate the effect of ß-GPA on liver regeneration in a clinically relevant context. **Results:** Expression of the creatine transporter gene *Slc6a8* increased during the

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early phase of liver regeneration, paralleling the induction of proliferative markers such as PCNA and Ki67. ßGPA treatment significantly reduced hepatocyte proliferation, as evidenced by decreased PCNA and Ki67 expression. Single cell RNA sequencing revealed that Slc6a8 is predominantly expressed in hepatic stellate cells (HSCs) and upregulated upon activation. Furthermore, ß-GPA administration led to the upregulation of oxidative phosphorylation genes, indicating a shift in energy metabolism under creatine-deficient conditions. Moreover, ß-GPA treatment markedly delayed liver regeneration in reduced-size rat liver transplantation model, supporting its inhibitory effect in a clinically relevant setting. **Conclusion:** Creatine deficiency impairs liver regeneration and alters hepatic energy metabolism. These findings highlight creatine metabolism as a previously underappreciated contributor to liver regenerative capacity and a potential therapeutic target for improving recovery following liver injury.

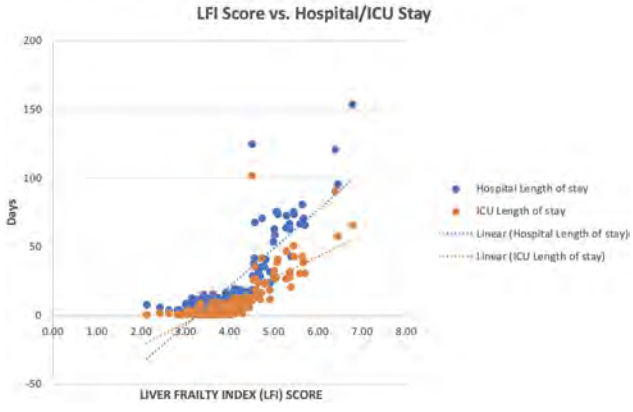
Disclosures: Thi Linh Nguyen: Nothing to Disclose, Thi Nga Ha: Nothing to Disclose, Hyon-Seung Yi: Nothing to Disclose

◆ 3449 | EVALUATING THE ROLE OF FRAILTY IN EXTUBATION TIMING AND RECOVERY FOLLOWING LIVER TRANSPLANTATION

Ishan Antony[1] Noor Albusta[1] Ryan Nazemian[2] Bartholomew Kane[1] Ming Lin[1], [1]Lahey Hospital and Medical Center, [2]Lahey Clinic Medical Center

Background: Frailty is a clinical state of decreased physiologic reserve and increased vulnerability to health stressors. Frailty in cirrhotic patients is measured by the Liver Frailty Index (LFI) which is a simple, reliable, low-cost method that encompasses grip strength, chair stands, and balance. Early extubation (EE) has been associated with improved short-term outcomes in post-liver transplant (LT) patients. Little is known about the association between frailty, EE, and hospital outcomes. **Methods:** We conducted a multidisciplinary, retrospective, single-center cohort study to assess the effect of frailty on the rate of early extubation (EE, defined as the removal of the endotracheal tube post-LT surgery in the operating room) and the associations with the hospital and ICU length of stay (LOS) in cirrhotic patients undergoing LT. Statistical analysis included Chi-square tests to compare rates between groups, independent t-tests for mean comparisons, and linear regression analysis to evaluate the relationship between LFI scores and LOS. **Results:** A total of 360 cirrhotic LT patients between 01/2019 and 07/2023 were assessed, and 158 patients (44%) had LFI scores. Of the 158 patients, 111 patients were male (70%), 142 patients were white (90%), the mean age was 57 years (range 20–74 years), the mean BMI was 29.2 (range 17.7-43.7) and median MELD score was 21 at the time of LT (range 6 to 41). Alcohol (46%) was the most common cause of liver disease. Out of 158 patients, 38 patients (24.1%) were frail (LFI ≥ 4.5), and 120 patients (75.9%) were non-frail (LFI < 4.5). There were no statistical differences in the EE rates between frail and non-frail patients (76.32% vs. 79.17%, $P = 0.709$). Hospital and ICU LOS were significantly longer in frail patients compared to non-frail patients (33.18 vs. 4.23 days for ICU stay, $P < 0.001$; and 59.53 vs. 10.08 days for hospital stay, $P < 0.001$). However, amongst the frail patients with EE, hospital and ICU LOS were shorter compared to those with delayed extubation (26.79 vs. 53.78 days for ICU stay, $P = 0.012$; and 52.00 vs. 83.78 days for hospital stay, $P = 0.003$). Similarly, in the non-frail patients with EE, LOS was shorter compared to those with delayed extubation (2.93 vs. 9.16 days for ICU stay, $P < 0.001$; and 8.88 vs.14.60 days for hospital stay, $P < 0.001$). **Conclusion:** Frailty is associated with worse post-transplant outcomes. Frail patients had significantly prolonged ICU and hospital stays. Our study demonstrated that frailty does not affect the rate of EE in cirrhotic patients undergoing LT. However, in those patients who are frail, EE was associated with a significant reduction in the hospital and ICU LOS post-liver transplant. Based on our findings, we encourage EE in frail cirrhotic patients undergoing LT whenever possible. Our findings show the importance of factoring frailty into perioperative and post-LT care.

Fig. 1: Relationship between Liver Frailty Index (LFI) Score and Hospital/ICU Length of Stay



Disclosures: Ishan Antony: Nothing to Disclose, Noor Albusta: Nothing to Disclose, Ryan Nazemian: Nothing to Disclose, Bartholomew Kane: Nothing to Disclose, Ming Lin: Nothing to Disclose

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◆ 3450 | IMPACT OF CHANGING LIVER TRANSPLANT EXCEPTION POLICIES TO ADDRESS BLOOD TYPE DISPARITIES IN ACCESS TO TRANSPLANTATION

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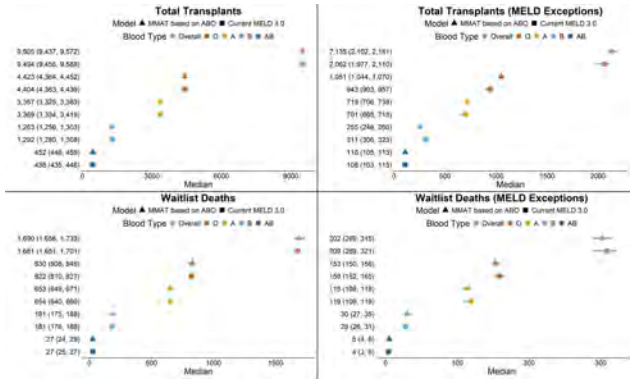
Background: When the Acuity Circles (AC) liver allocation policy was implemented in the US in 2/2020, MELD exception policy changed to award MELD exceptions to patients based on the median MELD score at transplant -3 points (MMAT-3) for transplant recipients within 250 nautical miles (NM) of the transplant centers. In 6/2022, the policy was updated to award exceptions based on MMAT-3 for recipients within 150NM of donor hospital, thereby changing based on the location of the deceased donor. Concerns have been raised because patients receive the same MELD exception, regardless of blood type, despite vast differences in the MMAT based on blood type. We sought to simulate the impact of changing liver allocation to award MELD exceptions based on a blood-type specific MMAT. **Methods:** We conducted a simulation study using the Liver Simulated Allocation Model (LSAM) from the Scientific Registry of Transplant Recipients (SRTR). We simulated two scenarios: 1) current allocation using the MELD 3.0 score; and 2) MELD exception scores based on a blood type-specific MMAT. Because the current system awards MELD exceptions based on transplants within 150NM of the donor hospital, which varies for every donor, we instead used the blood type-specific MMAT for all transplants within each DSA from 1/1/2024-6/30/2024 using OPTN data. All simulations were iterated 10 times (standard LSAM procedure). **Results:** Awarding MELD exceptions using a blood-type specific MMAT was not simulated to change the overall number of liver transplants, with only small differences by blood type (Figure). However, the median number of transplants for patients with MELD exceptions was simulated to increase by 73 transplants overall, with increases of 108 and 18 for patients with blood type O and A, respectively, with a decrease in 56 transplants for exception patients with blood type B (Figure). Despite these changes, the overall and blood type-specific number of waitlist deaths did not change for the waitlist population, or the subset with MELD exceptions (Figure). **Conclusion:** Despite well-established differences in the median MELD score at transplant by blood type, current allocation policy awards the same MELD exceptions to all patients, thereby disadvantaging MELD exception patients with blood type A or O who should have equal access to transplant for those with blood type B or AB. Our simulations demonstrate that changing the allocation policy to a blood type-specific MMAT could mitigate this disparity, without impacting waitlist mortality. While these data are based on LSAM simulations, this remains the gold standard in the US for assessing the impact of policy changes. These data underscore the need to update MELD exception policies to account for the differences in MMAT based on blood type.



Disclosures: David Goldberg: Nothing to Disclose, Catherine Blandon: Bluebird Bio: Stock - publicly traded company, Intellia Therapeutics: Stock - publicly traded company, Editas Medicine: Stock - publicly traded company, David Kaplan: AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Sirtex: Advisor, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research Support

◆ 3451 | LONG-TERM OUTCOMES OF LIVER TRANSPLANTATION FOR ALCOHOL-ASSOCIATED HEPATITIS

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Background: While studies of liver transplantation (LT) for alcohol-associated hepatitis (AH) have demonstrated excellent short-term survival and acceptable alcohol relapse rates, long-term outcomes are unknown. The aim of this study is to examine the long-term patient survival, allograft and alcohol outcomes after LT for AH as compared with other steatotic

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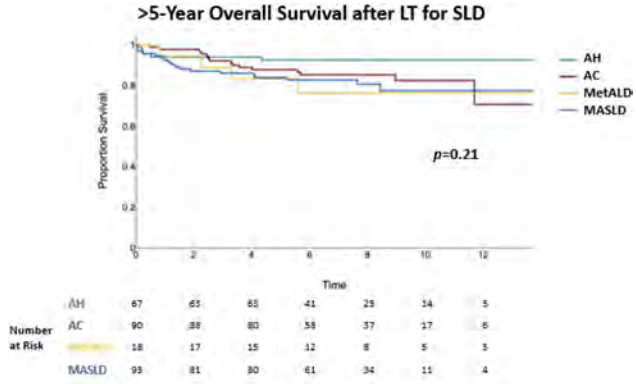
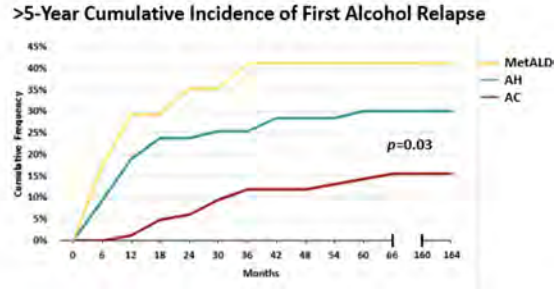
liver disease (SLD) subtypes. **Methods:** We performed a retrospective study of patients who underwent LT for AH (and SLD), at Mount Sinai Hospital from 2012-2025 with a minimum of 5-year follow-up after LT, representing long-term outcomes of the first published experience of LT for AH in North America. Clinicodemographic, pathology and laboratory data were collected and analyzed. A LT cohort comparison analysis was performed for different SLD subtypes: AH, alcohol-associated cirrhosis (AC), MetALD and MASLD. Patients with co-occurring viral hepatitis, HIV, and HCC were excluded. The primary endpoint was overall survival and secondary endpoints were biomarker-confirmed alcohol relapse as per NIAAA definitions, reabstinence, and biopsy-proven allograft rejection (BPAR). Analysis of the primary endpoint was based on Kaplan-Meier and Cox regression analysis using R version 4.5.0. **Results:** Over the 13-year study period, 268 LT for SLD with long-term follow-up were analyzed: 93 (35%) MASLD, 18 (7%) MetALD, 90 (34%) AC, and 67 (25%) AH with median 7.3 years [5.4-9.3], including 11 (16%) AH patients >10 years. For the AH subgroup, median age was 43 years [37-51], mostly male (64%) and White (72%). Lab medians at LT for AH were bilirubin 32 mg/dL, INR 2.5, creatinine 3.1 mg/dL, mDF 107, MELD 40, and ACLF grade 3, consistent with grim prognosis. Psychosocial summary variables include median last drink 25 days [12-55] prior to presentation, 10 [5.5-12] drinks/day around presentation, 81% with severe AH as their first decompensation, and 19% prior failed alcohol rehabilitation. Alcohol biomarker monitoring rates after LT were 100% AH, 70% AC, 64% MetALD, and 17% MASLD. Alcohol relapse post-LT was higher for AH (30%, initial event median 261 days [131-516]; PEth 58 ng/mL [36-155]) and MetALD (41%, median 281 days [127-558]; PEth 76 [n/a]) compared to AC (15.5%, 830 days [430-1308]; PEth 90 [63-223]), $p=0.03$. Reabstinence rates were similar: 37% AH, 54% AC, and 71% MetALD, $p=0.27$. BPAR rates were similar: 16% AH, 21% AC, 28% MetALD, 20% MASLD, $p=0.67$. Overall and 5-year survival after LT for AH were both 92.5%, similar to AC (81%, 85%), MetALD (78%, 83%), and MASLD (81%, 85%), respectively; $p=0.21$ overall, $p=0.43$ at 5-years. Cox regression adjusted for age and sex demonstrated similar survival between SLD subgroups, $p=0.3$. **Conclusion:** Long-term patient survival, allograft and alcohol outcomes after LT for AH remain excellent, and similar to other steatotic liver disease subtypes. While relapse rates were higher in LT for AH and MetALD compared to AC, reabstinence was similar.





Disclosures: Gene Im: KorroBio: Consultant, Echosens: Device support for research, Novo Nordisk: Advisor, Alimentiv: Consultant, Thomas Schiano: Nothing to Disclose, Sander Florman: Nothing to Disclose, Ashish Bibireddy: Nothing to Disclose, Giuseppe Cullaro: Ocelot Bio: Consultant, Retro Sciences: Consultant, Ipsen: Consultant, Smruti Rath: Nothing to Disclose

◆ 3452 | DEVELOPMENT AND INTERNATIONAL VALIDATION OF THE LIVING-DONOR LIVER ALLOGRAFT DYSFUNCTION SCORE FOR EARLY GRAFT LOSS PREDICTION: MULTICENTER ANALYSIS OF 1,034 CASES

Jiro Kusakabe[1] Chase Wehrle[1] Yuki Miyazaki[1] Masaru Kubota[2] Takashi Ito[3] Hikaru Aoki[3] Hajime Matsushima[4] Yuta Kawaguchi[5] Matthew Byrne[6] Mariana Chavez Villa[7] Eduardo Fernandes[8] Tetsuya Tajima[3] Andrea Schlegel[1] CH David Kwon[1] Alejandro Pita[1] Koji Tomiyama[7] Benjamin Samstein[9] Tomoaki Kato[2] Susumu Eguchi[5] Etsuro Hatano[3] Charles Miller[10] Koji

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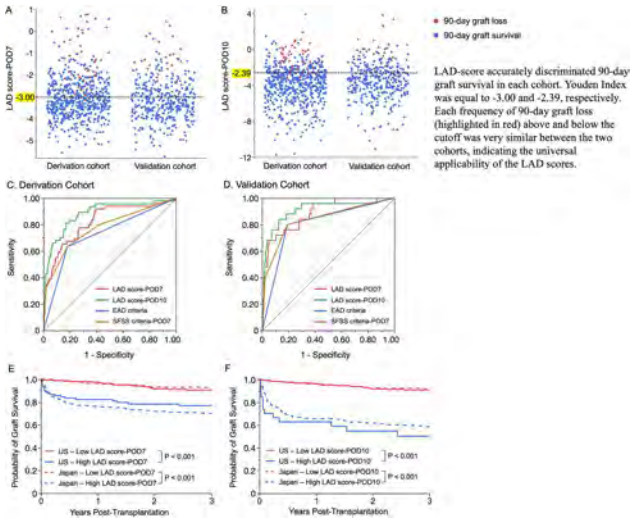
Background: Early Allograft Dysfunction (EAD) and Small-For-Size Syndrome (SFSS) are commonly used to predict the outcomes of living donor liver transplantation (LDLT). However, they were not derived from large-scale LDLT databases and their binary definitions limit predictive accuracy compared to continuous scoring methods. The aim of this study was to devise and validate the novel Living-donor Allograft Dysfunction (LAD) score using early post-operative factors to predict early graft loss after LDLT. **Methods:** This study included primary adult LDLT-recipients from six centers in the US and Japan, divided into the derivation (n = 645) and validation cohorts (n = 389). The primary outcome was 90-day graft loss. Post-operative bilirubin, INR, and PLT were selected to create LAD scorebased on clinical relevance and a comprehensive literature review. The model was developed using logistic regression and evaluated with receiver operating characteristic (ROC) curves and Kaplan-Meier analyses. The optimal cut-off values for the LAD scores were calculated using the Youden index obtained from the ROC analysis. **Results:** Significant differences were observed between the derivation and validation cohorts in several factors, including graft type (right lobe: 61.3% vs. 53.6%; $P = 0.030$) and GRWR (0.91% vs. 0.84%; $P < 0.001$), highlighting the relevance of this validation study. Bilirubin, INR, and PLT on POD7 and 10 were associated with 90-day graft loss ($P < 0.001$). Higher LAD score was associated with increased risk of 90-day graft loss in both cohorts (Figure A and B). In the derivation cohort, LAD score-POD7 and -POD10 showed superior predictive accuracy versus EAD (AUROC 0.82 and 0.88 vs 0.73; $P < 0.001$, respectively) and SFSS-POD7 (vs 0.77; $P = 0.041$ and $P < 0.001$) (Fig. C). The validation cohort confirmed robust performance (AUROC 0.89 on POD7 and 0.91 on POD10), outperforming EAD (vs 0.80, $P < 0.001$ and $P = 0.004$) and SFSS-POD7 (vs 0.84, $P = 0.055$ and $P = 0.094$) (Fig. D). LAD score cutoffs of -3.00 (POD7) and -2.39 (POD10) effectively and similarly stratified graft survival between the US and Japan, indicating the generalizability of the score application despite population differences (Fig. E and F). **Conclusion:** The novel LAD score was developed and validated as a generalizable tool to provide accurate estimation of 90-day graft loss following LDLT compared to existing criteria. This can facilitate early treatment of graft dysfunction within 10 days during a potential window of opportunity. With its global applicability, the LAD score may also serve as a surrogate endpoint for LDLT research worldwide, as traditional metrics like graft loss become increasingly rare in certain areas.



Disclosures: Jiro Kusakabe: Nothing to Disclose, Chase Wehrle: HistoSonics: Above, Yuki Miyazaki: Nothing to Disclose, Masaru Kubota: Nothing to Disclose, Takashi Ito: Nothing to Disclose, Hikaru Aoki: Nothing to Disclose, Hajime Matsushima: Nothing to Disclose, Yuta Kawaguchi: Nothing to Disclose, Matthew Byrne: Nothing to Disclose, Mariana Chavez Villa: Nothing to Disclose, Eduardo Fernandes: Nothing to Disclose, Tetsuya Tajima: Nothing to Disclose, Andrea Schlegel: Nothing to Disclose, CH David Kwon: Histosonics: Consultant, GE HealthCare: Consultant, Medtronics: Consultant, Alejandro Pita: Nothing to Disclose, Koji Tomiyama: Nothing to Disclose, Benjamin Samstein: Nothing to Disclose, Tomoaki Kato: Nothing to Disclose, Susumu Eguchi: Nothing to Disclose, Etsuro Hatano: Nothing to Disclose, Charles Miller: Nothing to Disclose, Koji Hashimoto: Nothing to Disclose, Antonio Pinna: Nothing to Disclose, Masato Fujiki: Nothing to Disclose

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◆ 3453 | TEMPORAL CHANGES IN RACIAL DISPARITIES IN LIVER TRANSPLANT OUTCOMES

ATSUSHI NISHIMAGI[1] Rikako Oki[1] Luckshi Rajendran[1] Emily Kerby[1] Adhnan Mohamed[1] Ahmed Nassar[1] Abbas Al-Kurd[1] Atsushi Yoshida[1] Marwan Abouljoud[1] Shunji Nagai[1], [1]Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital

Background: It has been reported that Black experience inferior graft survival (GS) following liver transplantation (LT), compared to White. However, it remains unclear about the impact of race on very long-term post-transplant outcomes. We evaluated and compared the racial influence on very long-term GS in LT. **Methods:** Adult LT alone performed from 2003-2013 were evaluated, using the United Network for Organ Sharing database. To mitigate the prognostic effects of early to mid-term post-transplant complications, we assessed conditional 10-year GS in 5-year graft survivors post-transplant, which was defined as the probability of GS after 5 years in those who survived for the first 5 years. The impact of race on GS was evaluated by Cox proportional hazard model. In Model 1, the risks were adjusted for HLA mismatch, recipients' age, gender, BMI, diabetes, MELD score at transplant, as well as donor age, gender, race, BMI, and donor types. In Model 2, in addition to the variables included in Model 1, socioeconomic factors including employment status, educational level, and insurance type were additionally adjusted for. **Results:** In total, 71,679 adult LT were performed from 2003-2013, of which 46,659 recipients survived at 5 years post-transplantation. Multivariable Cox regression analysis showed that Black had significantly poorer 5-year GS compared to White in both Model 1 and Model 2 ($p < 0.001$ for both, Fig.1). In contrast, when evaluating conditional 10-year GS among 5-year graft survivors, there was no significant difference in outcomes between Black and White in either Model 1($p = 0.097$) or Model 2 ($p = 0.928$). (Fig.2) The rate of cardiovascular disease and malignancy as a cause of death was higher in White compared to Black. (28.5% vs 24.8%, 34.4% vs 23.8%, $p < 0.001$) **Conclusion:** Black was associated with lower 5-year GS, whereas 10-year conditional GS between Black and White was comparable. Higher incidence of deaths due to CVD or malignancy in White might contribute to this finding. Further evaluations of factors contributing to disparities, including comorbid conditions and access to follow-up care, are necessary to address racial inequities in long-term post-transplant outcomes.

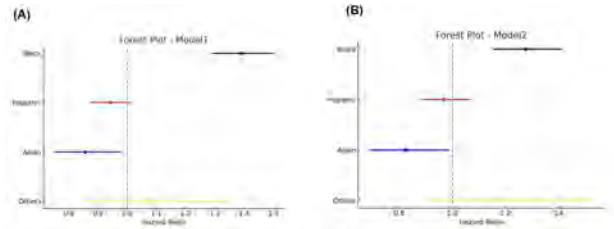

Fig. 1 Forest Plot of Multivariate Cox hazard model for 5-year graft failure.

(A) Model1: adjusted for HLA mismatch, recipients' age, gender, BMI, diabetes, MELD score at transplant, as well as donor age, gender, race, BMI, and donor type.
(B) Model2: adjusted for factors in (A) with socioeconomic factors.

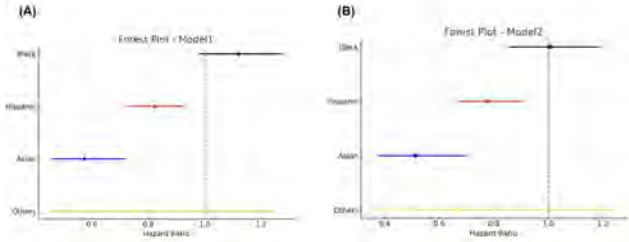

Fig. 2 Forest Plot of Multivariate Cox hazard model for 10-year conditional graft failure in 5-year graft survivors.
(A) Model1: adjusted for HLA mismatch, recipients' age, gender, BMI, diabetes, MELD score at transplant, as well as donor age, gender, race, BMI, and donor type.
(B) Model2: adjusted for factors in (A) with socioeconomic factors.

Disclosures: ATSUSHI NISHIMAGI: Nothing to Disclose, Rikako Oki: Nothing to Disclose, Luckshi Rajendran: Nothing to Disclose, Emily Kerby: Nothing to Disclose, Adhnan Mohamed: Nothing to Disclose, Ahmed Nassar: Nothing to Disclose, Abbas Al-Kurd: Nothing to Disclose, Atsushi Yoshida: Nothing to Disclose, Marwan Abouljoud: Nothing to Disclose, Shunji Nagai: Nothing to Disclose

◆ 3454 | RESULTS: AND UPDATED DATA OF THE NOTABLE-HCC PHASE 1B TRIAL: NEOADJUVANT TISLELIZUMAB PLUS STEREOTACTIC BODY RADIOTHERAPY AND ADJUVANT TISLELIZUMAB IN EARLY-STAGE RESECTABLE HEPATOCELLULAR CARCINOMA

zhongchao li[1] Lei Zhao[2] Jing Liu[2] Jinbo Yue[3] Bo Zhang[2] Xuetao Shi[2] Kai Cui[2] Zhaogang Liu[2] Zhibin Chang[2] Zhicheng Sun[2] Mingming Li[2] Yue Yang[2] Zhao Ma[2] Lei Li[2] Chengsheng Zhang[2] Pengfei Sun[2] Jingtao Zhong[2], [1]Shandong Cancer Hospital Affiliated to Shandong First Medica, [2]Shandong Cancer Hospital Affiliated to Shandong First Medical University, [3]Shandong Cancer Hospital and Institute, Shandong First Medical Universityand Shandong Academy of Med

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Background: There is no neoadjuvant therapy recommended by the primary hepatocellular carcinoma (HCC) guidelines. We conducted the Notable-HCC phase 1b trial to evaluate the safety, tolerability and preliminary effectiveness of neoadjuvant tislelizumab (TIS, a PD-1 inhibitor) plus stereotactic body radiotherapy (SBRT) followed by resection and adjuvant TIS in early stage resectable HCC. **Methods:** Patients received 3×8 Gy SBRT and two cycles of TIS as adjuvant therapy, then underwent the curative HCC resection scheduled 4 weeks later, followed by 16 cycles adjuvant PD-1 for up to 1 year. Primary endpoints were the surgery delay, radiographic and pathological tumor response, and safety. Secondary endpoint was survival. **Results:** A total of 20 patients were enrolled and 19 (95%) underwent surgical resection (one [5%] undergoing radiofrequency ablation). Curative R0 resection was achieved in all patients, and none postponed surgery for more than 6 weeks following neoadjuvant therap. The neoadjuvant therapy did not increase the difficulty of surgical resection, nor did it increase the incidence of post-operative complications. Per RECIST v1.1, ORR was 42.1% (8/19) and DCR was 100%. 2 patients achieved complete pathological response (pCR), and 6 reached major pathological response (MPR). In the adjuvant phase, 14 (73.7%) patients received regular adjuvant TIS, with a median cycle of 15 (range, 6-16). TRAEs of any grade during the adjuvant phase were reported in all these patients, with the majority being grade 1 to 2. Grade 3 TRAEs occurred in 4 patients, including decrease lymphocyte count, immune pneumonia and decreased platelet count. None of patients experienced grade 4 or 5 TRAEs. As of data cutoff (Jan 31, 2025). median follow-up duration was 18.23 months (range, 16.47-33.03) since the resection. Disease recurrence developed in 4 out of 19 patients, with DFS of 14.8, 11.0, 3.0 and 8.6 months, respectively. Median DFS and OS were not reached, with DFS and OS rates at 1 year of 86.4% and 100%, respectively. **Conclusion:** In patients with early-stage resectable HCC, neoadjuvant TIS combined with SBRT followed by adjuvant TIS yields clinical promising treatment response without delaying surgical resection, and achieved satisfactory survival benefits with preliminary follow-up data. Continued follow-up is being conducted to assess long-term efficacy and safety.

Disclosures: zhongchao li: Nothing to Disclose, Lei Zhao: Nothing to Disclose, Jing Liu: Nothing to Disclose, Jinbo Yue: Nothing to Disclose, Bo Zhang: Nothing to Disclose, Xuetao Shi: Nothing to Disclose, Kai Cui: Nothing to Disclose, Zhaogang Liu: Nothing to Disclose, Zhibin Chang: Nothing to Disclose, Zhicheng Sun: Nothing to Disclose, Mingming Li: Nothing to Disclose, Yue Yang: Nothing to Disclose, Zhao Ma: Nothing to Disclose, Lei Li: Nothing to Disclose, Chengsheng Zhang: Nothing to Disclose, Pengfei Sun: Nothing to Disclose, Jingtao Zhong: Nothing to Disclose

3455 | SIMULTANEOUS LIVER-KIDNEY AND KIDNEY-AFTER-LIVER TRANSPLANTATION BEFORE AND AFTER THE 2017 ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK POLICY: A SINGLE-CENTER EXPERIENCE

Carolina Lopez-Silva[1] Malak Elsawy[1] Manuj Shah[1] Fizza Naqvi[1] Benjamin Philosophe[1] Ahmet Gurakar[1], [1]Johns Hopkins University

Background: Simultaneous liver-kidney (SLK) and kidney-after-liver (KAL) transplantation are two modalities for managing patients with end-stage liver disease and renal dysfunction. Simultaneous liver-kidney (SLK) transplantation involves performing both transplants during the same surgery, while kidney-after-liver (KAL) refers to delayed kidney transplantation following liver transplant alone. In 2017, the Organ Procurement and Transplantation Network (OPTN) established stricter eligibility criteria for SLK transplantation. The impact of this policy on SLK and KAL utilization remains under investigation. **Methods:** We conducted a retrospective cohort study of patients undergoing SLK or KAL transplantation at Johns Hopkins Hospital from January 1st, 2009, to June 1st, 2024. Baseline demographic and clinical characteristics were compared between groups. Logistic regression was used to estimate the odds of receiving SLK versus KAL before and after the 2017 OPTN policy change. Post-transplant mortality was assessed using Cox proportional hazards models, with survival time defined from transplant date to death or end of follow-up. **Results:** A total of 152 patients were included (118 SLK, 34 KAL). KAL recipients were older (60.4 vs. 55.9 years, $p = 0.038$) and had higher mean BMI (30.7 vs. 27.7, $p = 0.028$). Sex, race, and MELD scores did not significantly differ between groups. Liver disease etiology differed significantly ($p = 0.025$), with hepatocellular carcinoma more common among KAL recipients (29.4% vs. 6.8%). The odds of receiving SLK were significantly higher during the pre-policy period (OR 4.91, 95% CI: 2.13–12.5, $p < 0.001$). In Cox models, transplant type and policy era were not associated with mortality. However, older age was associated with higher post-transplant mortality (HR 1.06 per year, 95% CI: 1.00–1.13, $p = 0.047$), and patients > 65 years old had a significant higher risk of post-transplant mortality (HR 4.02, 95% CI: 1.60-10.1, $p = 0.003$), compared to younger patients, after adjusting for sex, BMI and MELD score. **Conclusion:** SLK and KAL recipients differed by BMI and liver disease etiology. The 2017 OPTN policy was associated with reduced SLK use but not with changes in mortality. Older age, and specifically age > 65, was independently associated with higher risk post-transplant

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mortality. These findings highlight the influence of policy on clinical decision-making and the need for individualized risk assessment around transplant care.

Characteristics	Total	KAL	SLK	P Value
N	152	34	118	
Age	56.9 (11.1)	60.4 (7.9)	55.9 (11.7)	0.038
Sex				0.555
Women	58 (38.2%)	11 (32.4%)	47 (39.8%)	
Men	94 (61.8%)	23 (67.6%)	71 (60.2%)	
Race				0.253
Asian	1 (0.7%)	1 (2.9%)	0 (0%)	
Black	35 (23%)	5 (14.7%)	30 (25.4%)	
Hispanic	3 (2%)	1 (2.9%)	2 (1.7%)	
Other	7 (4.6%)	1 (2.9%)	6 (5.1%)	
White	81 (53.3%)	20 (58.8%)	61 (51.7%)	
Unknown	25 (16.4%)	6 (17.6%)	19 (16.1%)	
BMI	28.3 (6.2)	30.7 (6.9)	27.7 (5.9)	0.028
Liver Disease Etiology				0.025
Alcohol-associated	32 (21.1%)	8 (23.5%)	24 (20.3%)	
HBV	2 (1.3%)	0 (0%)	2 (1.7%)	
HCC	18 (11.8%)	10 (29.4%)	8 (6.8%)	
HCV	35 (23%)	6 (17.6%)	29 (24.6%)	
MASH	29 (19.1%)	4 (11.8%)	25 (21.2%)	
Other	36 (23.7%)	6 (17.6%)	30 (25.4%)	
MELD	27.1 (8.0)	28.1 (10.2)	26.9 (7.3)	0.58
Policy Period				<.001
Before 2017 Policy	79 (52%)	8 (23.5%)	71 (60.2%)	
After 2017 Policy	73 (48%)	26 (76.5%)	47 (39.8%)	

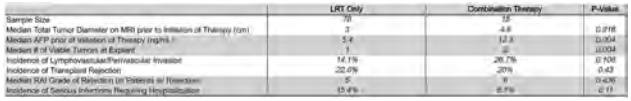
Table 1. Demographic and clinical characteristics of patients receiving Kidney After Liver (KAL) and Simultaneous Liver Kidney (SLK) transplant during the study period. Data presented as mean (standard deviation) and counts (%). Continuous variables were assessed for normality prior to analysis. Group comparisons were conducted using t-tests. Chi-square tests were used for categorical variables, except for race and liver disease etiology, which were compared using Fisher's exact test due to low cell counts.

Disclosures: Carolina Lopez-Silva: Nothing to Disclose, Malak Elsawy: Nothing to Disclose, Manuj Shah: Nothing to Disclose, Fizza Naqvi: Nothing to Disclose, Benjamin Philosophe: Nothing to Disclose, Ahmet Gurakar: DURECT: Grant/Research Support, Orphalan: Advisor

3456 | THE IMPACT OF SYSTEMIC CHEMOIMMUNOTHERAPY IN COMBINATION WITH LOCOREGIONAL THERAPIES ON REJECTION IN LIVER TRANSPLANT SECONDARY TO HEPATOCELLULAR CARCINOMA (HCC).

Khadyoth Nanneboyina[1] Ali Khurram[1] Judith Pozzerle[2] Ashwini Mehta[2] Parvez Mantry[2], [1]Methodist Dallas Medical Center, [2]The Liver Institute at Methodist Dallas Medical Center

Background: Liver transplantation (LT) is the gold standard treatment for unresectable HCC. However, many patients with HCC are outside of the Milan criteria for LT eligibility. In such cases, downstaging therapies decrease tumor burden and increase transplant eligibility. Traditional downstaging methods include locoregional therapy (LRT) but recently, systemic therapy, particularly immune checkpoint inhibitors (ICIs), have shown promise. The use of ICIs in the treatment of HCC raises the concern for increased possibility of rejection following LT. **Methods:** This study was a single-center retrospective outcome analysis of all patients diagnosed with HCC who underwent LT between June 2018 and March 2024 (n = 93) with primary endpoints being a) post-LT transplant rejection and b) Rejection Activity Index (RAI) grade. Explant pathology was examined to assess tumor viability, grade, and lymphovascular invasion. Patients were categorized into 2 groups: 1) LRT alone and 2) combination of LRT and systemic therapy. LRT included Transarterial chemoembolization, Radioembolization, Microwave Ablation, and Stereotactic Beam Radiation Therapy. Systemic therapies included Nivolumab + Ipilimumab, Atezolizumab + Bevacizumab, Sorafenib, Lenvatinib, Ramuricumab, and Cabozantinib. Data analysis was performed with T-test. **Results:** 78 patients received LRT alone and 15 patients received combination therapy. Median total tumor diameter on MRI prior to treatment initiation of the LRT group was 3 cm vs. 4.6 cm in the combination group ($p = 0.02$). Median alpha-fetoprotein (AFP) prior to treatment initiation of the LRT group was 5.4 ng/mL vs. 12.3 ng/mL in the combination group ($p = 0.004$). Within the combination group, 2 patients received Nivolumab + Ipilimumab, 7 received Atezolizumab + Bevacizumab, 6 received Sorafenib, 3 received Lenvatinib, 1 received Ramucirumab, and 2 received Cabozantinib. The incidence of transplant rejection in the LRT group was 22.6% vs. 20% in combination group ($p = 0.43$). The median RAI grade of rejection (in patients who had evidence of rejection) in the LRT group was 5 vs. 6 in the combination group ($p = 0.44$). The incidence of serious infections requiring hospitalization in the LRT group was 15.4% vs. 6.7% in the combination group ($p = 0.11$). **Conclusion:** Our results show that combination therapy for the treatment of HCC was associated with similar rates of transplant rejection, RAI grade of rejection, and serious infections requiring hospitalization compared to patients who received LRT only. This preliminary data suggests that systemic therapies, such as ICIs, are safe to use for downstaging of HCC to potentially improve outcomes and increase transplant eligibility.



	LRT Only	Combination Therapy	P-Value
Sample Size	78	15	
Median Total Tumor Diameter on MRI prior to Initiation of Therapy (cm)	3	4.6	0.018
Median AFP prior of Initiation of Therapy (ng/mL)	5.4	12.3	0.004
Median # of Viable Tumors at Explant	1	2	0.004
Incidence of Lymphovascular/Perivascular Invasion	14.1%	26.7%	0.100
Incidence of Transplant Rejection	22.6%	20%	0.43
Median RAI Grade of Rejection (in Patients w/ Rejection)	5	6	0.436
Incidence of Serious Infections Requiring Hospitalization	15.4%	6.7%	0.11

Disclosures: Khadyoth Nanneboyina: Nothing to Disclose, Ali Khurram: Nothing to Disclose, Judith Pozzerle: Nothing to Disclose, Ashwini Mehta: Nothing to Disclose, Parvez Mantry: Akero: Grant/Research Support, Abbvie: Speaker and Advisory Board, BMS: Research Grants & Speaker, Boston Scientific: Advisory Board and Speaker, Chemomab: Grant/Research Support, Cymabay: Research Grants & Advisory Board, Care Dx: Grant/Research Support, Eisai: Speaker and Advisory Board, Genfit: Grant/Research Support, Gilead: Speaker, Advisory Board, & Research Grants,

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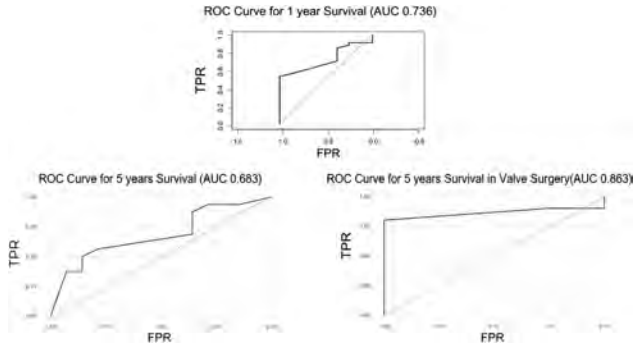
3457 | LONG-TERM FOLLOW-UP IN LIVER TRANSPLANTATION AND COMBINED CARDIAC SURGERY: VALIDATION AND REFINEMENT OF THE LT+CS RISK SCORE USING ADVANCED MACHINE LEARNING

Laura Batista de Oliveira[1] Chase Wehrle[2] Sarah Wehbe[2] Jason Singer[2] Mazhar Khalil[2] Masato Fujiki[1] Michael Tong[3] Charles Miller[2] Sobia Laique[1] Alejandro Pita[2] Koji Hashimoto[2] Cristiano Quintini[2] Teresa Diago-Uso[2] Maan Fares[4] Andrea Schlegel[2] Nicholas Ruthmann[4] Jamak Modaresi Esfeh[5], [1]Cleveland Clinic, [2]Digestive Disease Institute, Cleveland Clinic, Cleveland, OH, [3]Heart, Vascular and Thoracic Institute, Cleveland, [4]Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland OH, [5]Cleveland Clinic Foundation

Background: Combined liver transplantation (LT) and cardiac surgery (CS) is a therapeutic option for patients with end-stage liver disease (ESLD) and severe cardiac dysfunction. Despite its potential, evidence on long-term outcomes and prognostic factors remains limited. In 2023, our center published the LT-CS-1.0 risk score. Of note, the previously defined LT+CS risk score has not yet been prospectively validated. **Methods:** Forty-six patients underwent single-staged LT+CS (2005-2023) and had a minimum 1-year follow-up. Univariate and multivariate analyses Cox proportional hazards models assessed independent predictors of long-term survival (1 and 5 years) and a machine learning based Leave One Out Cross Validation (LOOCV) technique was used to validate and refine the LT-CS-2.0 risk score. Patients aged <18 years, those without combined intervention, and those lacking ≥ 1-year active follow-up were excluded. **Results:** One- and five-year survival rates were 74.2% and 50%, respectively. Negative predictors of 5-year survival included GFR (OR = 1.02, p = 0.031), CKD (OR = 0.13, p = 0.026), and valve surgery (OR = 6.67, p = 0.045). CKD had the strongest multivariate impact (HR = 12.28, 95%CI = 1.01–152.43). After implementing LT-CS-1.0 in 2022, survival improved (log-rank $p<0.001$). LOOCV highlighted MASH (2.66), renal dysfunction (2.63), and aortic stenosis (2.20) as key contributors. The LT-CS-2.0 score predicted 5-year OS with an AUC of 0.683 (p = 0.03), and 0.863 ($p<0.0001$) in valve surgery patients. Kaplan-Meier analysis showed significantly higher survival in low-risk vs. high-risk groups (log-rank p = 0.001).

Post-operative morbidity was also compared between high and low-risk groups. High-risk patients according to the LT+CS-2.0 score experienced more complications (OR = 3.12, p = 0.0781) inpatient, at 3 months (OR = 9.71, p = 0.00152), 6-months (OR = 7.97, p = 0.00335) and 12-months (OR = 6.61, p = 0.00705). During the in-hospital period, high-risk patients showed a non-significant increase in the odds of complications (OR: 3.12; p = 0.0781). CCI (Comprehensive Complication Index) was higher at 3-months (OR: 9.71; p = 0.00152), 6 months (OR: 7.97; p = 0.00335), and 12-months (OR: 6.61; p = 0.00705) in the LT+CS-2.0 High-risk cohort. **Conclusion:** This study provides the largest analysis to date of long-term outcomes following combined liver transplantation and cardiac surgery. This study provides prospective validation of the LT+CS-1.0 risk score, confirms key predictors of survival and refines risk stratification with the LT+CS-2.0 score.



Disclosures: Laura Batista de Oliveira: Nothing to Disclose, Chase Wehrle: HistoSonics: Above, Sarah Wehbe: Nothing to Disclose, Jason Singer: Nothing to Disclose, Mazhar Khalil: Nothing to Disclose, Masato Fujiki: Nothing to Disclose, Michael Tong: Nothing to Disclose, Charles Miller: Nothing to Disclose, Sobia Laique: Madrigal Pharmaceutical: Consultant, Novo Nordisk: MASH Curriculum Steering Committee, Madrigal Pharmaceutical: Consultant, Novo Nordisk: MASH Curriculum Steering Committee, Alejandro Pita: Nothing to Disclose, Koji Hashimoto: Nothing

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3458 | PRE-TRANSPLANT PROTON PUMP INHIBITOR USE IS ASSOCIATED WITH INCREASED RISK OF LIVER ALLOGRAFT REJECTION, FAILURE, AND MORTALITY: A PROPENSITY-MATCHED MULTI-CENTER COHORT STUDY

ali osman[1] Mohammad Adam[2] Abdelaziz Mohamed[3] Jeffrey Crippin[1], [1]Washington University St. Louis, [2]University of Missouri-Kansas City, [3]One brooklyn health/interfaith medical center

Background: Proton pump inhibitors (PPIs) are commonly prescribed to patients with liver cirrhosis awaiting liver transplantation. However, their impact on post-transplant outcomes—including graft rejection, failure, and mortality—remains unclear. This study evaluates the association between pre-transplant PPI use and liver transplant outcomes. **Methods:** We conducted a retrospective cohort study using data from 146 healthcare organizations in the TriNetX Global Collaborative Network. Adult liver transplant recipients were categorized based on PPI exposure within one month (n = 9,516) and within six months (n = 13,095) prior to transplant. Three comparisons were analyzed: (1) PPI use within one month vs. no PPI use (n = 24,078); (2) PPI use within six months vs. no PPI use; and (3) PPI use vs. H2 blocker use (n = 1,578) within six months. Propensity score matching was applied to adjust for demographics, clinical comorbidities (e.g., cirrhosis, portal hypertension, hepatic encephalopathy, CKD, diabetes, and primary liver cancer), and baseline laboratory values (e.g., total bilirubin, sodium, albumin, INR, prothrombin time, BMI). To confirm continuity of PPI therapy post-transplant, we conducted a separate analysis using PPI use as an outcome. Among 6,771 patients in the PPI group, 5,247 had documented PPI prescriptions after transplant, whereas the control group had 0% documented PPI use. Additionally, a Kaplan-Meier curve was generated to assess PPI continuation over time, demonstrating sustained PPI use in the PPI group post-transplant. **Results:** Pre-transplant PPI use was significantly associated with increased risk of liver allograft rejection or failure across all comparisons. In the 1-month comparison, the rate of rejection/failure was 13.4% in PPI users vs. 7.1% in non-users (RR = 1.87; $p < 0.0001$). Five-year survival probability was lower among PPI users (63.0%) compared to non-users (68.2%) (HR = 1.40; $p < 0.0001$). Compared to H2 blocker users, PPI users also demonstrated a significantly higher incidence of rejection or graft failure. **Conclusion:** Pre-transplant PPI use is associated with increased risk of liver transplant rejection, graft failure, and reduced survival. These findings warrant further investigation to confirm causality and guide peri-transplant acid suppression strategies.

Demographics After Matching

Cohort Comparison: Values for 'PPI within 1 month prior to transplant, no H2 blockers' are shown in purple, and values for 'No PPI, No H2 blockers' are shown in green.

Characteristic	Cohort Comparison	P-Value	Std diff.
Age at Index	54.2 ± 14.9 / 54.9 ± 15.6	0.005	0.049
White	61.8% / 63.5%	0.041	0.036
Unknown Race	19.6% / 17.9%	0.013	0.043
Female	37.7% / 38.0%	0.694	0.007
Unknown Ethnicity	38.7% / 38.4%	0.735	0.006
Not Hispanic or Latino	52.3% / 52.3%	0.945	0.001
Hispanic or Latino	9.0% / 9.3%	0.488	0.012
Black or African American	6.6% / 6.8%	0.755	0.005
Male	60.8% / 60.7%	0.873	0.003
Other Race	7.5% / 7.7%	0.623	0.009
Asian	3.6% / 3.3%	0.394	0.015

Disclosures: ali osman: Nothing to Disclose, Mohammad Adam: Nothing to Disclose, Abdelaziz Mohamed: Nothing to Disclose, Jeffrey Crippin: CRISPR: Chair of DSMB, eGenesis: Grant/Research Support

3459 | PSYCHOLOGICAL SYMPTOM BURDEN BEFORE AND AFTER LIVER TRANSPLANTATION: PATTERNS AND PREDICTORS IN A SINGLE-CENTER COHORT

Kishore Botla[1] Hannah Klatzkow[1] Alvaro Noriega Ramirez[1] Dyanna Gregory[1] Arjmand Mufti[1] Thomas Kerr[1] Lisa VanWagner[1] Amit Singal[1] Sarah Lieber[1], [1]University of Texas Southwestern Medical Center

Background: Liver transplantation (LT) significantly impacts physical and psychological wellbeing. Beyond anxiety and depression, patients frequently experience social isolation and stress; however, how these symptoms evolve from pre- to post-LT remains unclear. Aging is also increasingly recognized as a key factor influencing psychological health in transplant recipients, yet its role in shaping recovery trajectories is understudied. We aimed to characterize psychological symptoms pre- vs. post-LT and identify factors associated with greater psychological burden. **Methods:** Adult LT recipients (LTRs) prospectively enrolled at a large academic center completed baseline (waitlist) and either 6- or 12-month post-LT surveys, including: 1) PROMIS (Patient-Reported Outcomes Measurement Information System) anxiety, depression, and social isolation; 2) NIH Perceived Stress Scale; and 3) Brief-COPE (survey that assesses reliance on certain coping strategies). Primary analyses assessed differences between pre- vs. post-transplant scores using t-tests or ANOVA. Change scores were calculated as both absolute and percent differences between pre- and post-LT values to characterize the

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magnitude and direction of psychological symptom evolution. Multivariable analyses were used to evaluate factors associated with increased psychological symptoms post-LT. **Results:** 68 LTRs completed pre- and post-LT assessments (mean age 50.1 ± 14.1 years; 38.2% female; 83.8% white; 23.5% Hispanic). Psychological symptoms did not vary by sex, race/ethnicity, income, employment, psychiatric history, or hospitalization duration at pre- or post-LT timepoints. Compared to recipients aged 65 or younger, older recipients had lower reliance on acceptance coping strategies pre- (5.3 ± 1.6, p = 0.02) and post-LT (3.0 ± 1.7, p = 0.002), with a greater decline over time. More early post-LT hospitalizations were also linked to reduced acceptance coping (5.0 ± 4.2, p = 0.03). A history of substance use was associated with elevated anxiety (54.6 ± 10.4, p = 0.008), depression (52.1 ± 9.2, p = 0.01), and stress (15.1 ± 6.6, p = 0.03) pre-LT, but also with significant reductions in depression (45.5 ± 8.8, p = 0.01) and stress (11.1 ± 6.1, p = 0.03) post-LT. **Conclusion:** Older LTRs and those with frequent early hospitalizations demonstrated lower usage of adaptive coping strategies post-LT. While recipients with a history of substance use demonstrated higher psychological burden pre-LT, they showed notable improvements post-transplant —highlighting an opportunity for resilience-focused interventions spanning both the pre- and post-transplant periods. These findings underscore the psychological heterogeneity of LTRs and support the need for tailored psychosocial support, particularly for aging recipients and those with early post-LT complications.

Figure 1. Psychological Symptom Mean Survey Scores and Change Scores Pre- vs. Post-LT, Stratified by Subgroup

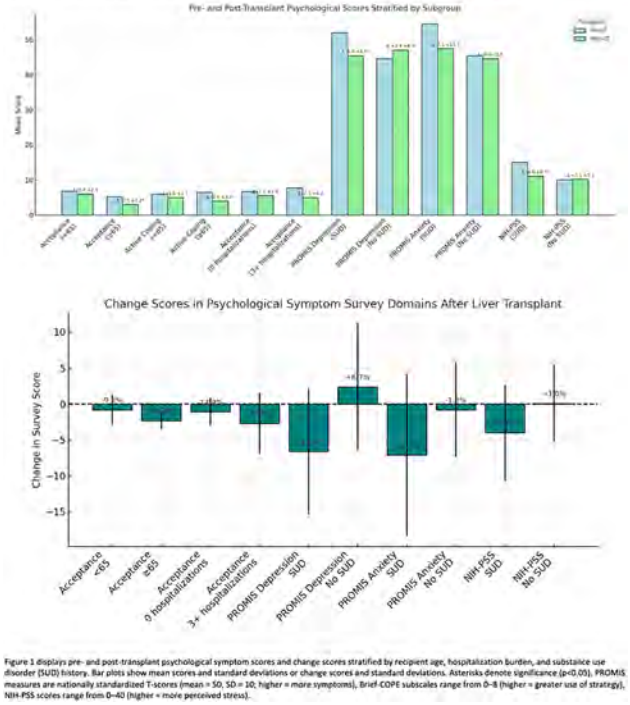

Figure 1 displays pre- and post-transplant psychological symptom scores and change scores stratified by recipient age, hospitalization burden, and substance use disorder (SUD) history. Bar plots show mean scores and standard deviations or change scores and standard deviations. Asterisks denote significance (p<0.05). PROMIS measures are nationally standardized T-scores (mean = 50, SD = 10; higher = more symptoms), Brief-COPE subscales range from 0–8 (higher = greater use of strategy), NIH-PSS scores range from 0–40 (higher = more perceived stress).

Disclosures: Kishore Botla: Nothing to Disclose, Hannah Klatzkow: Nothing to Disclose, Alvaro Noriega Ramirez: Nothing to Disclose, Dyanna Gregory: Nothing to Disclose, Arjmand Mufti: Nothing to Disclose, Thomas Kerr: Madrigal: Consultant, GSK: Grant/Research Support, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Sarah Lieber: Nothing to Disclose

3460 | MOLECULAR PATTERNS ASSOCIATED WITH RECURRENCE AND SURVIVAL IN INTRAHEPATIC CHOLANGIOCARCINOMA (ICCA) / HEPATOCHOLANGIOCARCINOMA (HCC-CCA) AFTER LIVER TRANSPLANTATION

Maarouf Hoteit[1] Peter Abt[1] Salvatore Priore[1] Rashmi Tondon[1] Samir Abu-Gazala[1] Parul Agarwal[1] Kelley Weinfurtner[1] Moira Hilscher[2] Kirk Wangensteen[2], [1]University of Pennsylvania, [2]Mayo Clinic Rochester

Background: The Organ Procurement and Transplant Network (OPTN) recently approved a pathway for exception points in patients with unresectable intrahepatic cholangiocarcinoma (iCCA) with single tumors 3 cm or less in size. Various oncogene mutations have been described that may modulate tumor behavior and clinical outcomes in intrahepatic choangiocarcinoma. This cohort study aims to explore oncogene mutations in iCCA found in explanted livers, and whether the genetic changes are associated with post transplant recurrence and survival. **Methods:** We reviewed the liver transplant registry at the University of Pennsylvania (1997-2022) to identify subjects with iCCA or hepatocholangiocarcinoma (HCC-CCA) found on explant. Tumor nodules with histologically confirmed iCCA or HCC-CCA were identified and sampled for molecular testing. Tumor tissue DNA was sequenced and analyzed for mutations in 247 genes commonly mutated in cancers (PennSeq Comprehensive Tumor Panel). We correlated the molecular patterns with post liver transplant outcomes. **Results:** Over a 25-year period, a total of 947 liver transplants were performed with either a preoperative or postoperative diagnosis of primary

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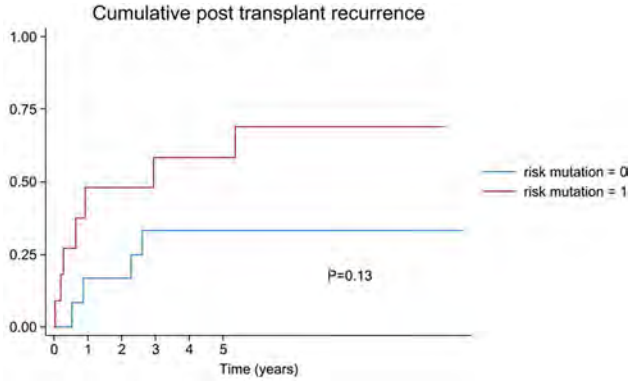
liver cancer. A total of 44 (4.6%) had evidence of iCCA or HCC-CCA on explant pathology. Of the 44 patients, 23 had tumor tissue samples were amenable to molecular testing and were included in the analysis. Patients were 96% Male, 74% White, and 48% had hepatitis C. The histology was consistent with HCC-CCA in 14/23 (61%) and iCCA in 9/23 (39%). The median size of the largest tumor was 2.3 cm, the median tumor nodule number was 3. 21/23 (91%) had either a nodule $>$ 3cm (6/23, 26%) or more than one tumor nodule (20/23, 87%). Most tumors analyzed had no necrosis (15/23, 65%). The median 3-year overall survival of the cohort was 56%, and 3-year recurrence-free survival was 43%. The overall recurrence rate was 48% (11/23). Mutations that previously have been associated with aggressive tumor behavior were found in 48% (11/23) of patients (9 *TP53*, 1 *KRAS*, 1 *CDKN2A*). In patients with any high-risk mutations detected compared to those without any mutation in these genes, there was a trend of a higher 3-year cumulative recurrence risk (58% vs 33%, $p = 0.13$), and of worse recurrence-free survival (36% vs 50%, $p = 0.22$), and worse overall survival (45% vs 67%, $p = 0.29$) at 3 years. **Conclusion:** In this single center study, we noted a trend for worse post transplant outcome in patients with iCCA and HCC-CCA and somatic mutations in *TP53*, *KRAS*, or *CDKN2A*. Multicenter studies are needed to confirm the findings, which may allow for improved ability to risk-stratify patients with iCCA undergoing evalaution for liver transplantation.



Disclosures: Maarouf Hoteit: HepQuant, LLC: Advisor, Cook Medical: Consultant, Peter Abt: Nothing to Disclose, Salvatore Priore: Nothing to Disclose, Rashmi Tondon: Nothing to Disclose, Samir Abu-Gazala: Nothing to Disclose, Parul Agarwal: Nothing to Disclose, Kelley Weinfurtner: Nothing to Disclose, Moira Hilscher: Orphalan: Consultant, Kirk Wangensteen: Nothing to Disclose

3461 | MULTIMODAL MULTIPHASIC IMAGE-BASED DEEP TRANSFER LEARNING FOR PREDICTION OF HEPATOCELLULAR CARCINOMA RECURRENCE AFTER LIVER TRANSPLANT

Rex Wan-Hin Hui[1] Keith Chiu[2] Chenlu Wang[3] Ho-Ming Cheng[1] Trevor Wu[1] Sarah Choy Sin Yu[1] Tiffany Cho-Lam Wong[4] Lung-Yi Mak[1] James Fung[1] Man-Fung Yuen[1] Philip Leung-Ho Yu[3] Albert Chi-Yan Chan[4] Wai-Kay Seto[1], [1]Department of Medicine, The University of Hong Kong, [2]Department of Radiology and Imaging, Queen Elizabeth Hospital, Hong Kong, [3]Department of Mathematics and Information Technology, The Education University of Hong Kong, [4]Department of Surgery, The University of Hong Kong

Background: Liver transplant (LT) is the best curative treatment option for early stage hepatocellular carcinoma (HCC). Despite stringent patient selection, HCC recurrence can still occur after LT. We studied the use of deep transfer learning for predicting post-LT HCC recurrence. **Methods:** Recurr-NET LT, a multimodal multiphasic residual-network random survival forest model, was developed for predicting post-LT recurrence. Recurr-NET LT was trained based on transfer learning from the original Recurr-NET model (a deep learning model trained, tested and externally validated on 1231 patients receiving curative resection for HCC), and further incorporated pre-LT computed tomography scans and clinical parameters from LT patients. All patients receiving LT for HCC between 2009 and 2020 in Queen Mary Hospital, Hong Kong were included in this study, and were divided in a 6:4 ratio into training and validation cohorts. The diagnostic performance of Recurr-NET LT was compared against other clinical prediction scores (RETREAT score and MORAL score) for post-LT recurrence. **Results:** This analysis included 163 patients (Age 58.3 +/- 7.2 years at LT, 75.5% male, 91.4% with viral hepatitis, 65.6% deceased donor LT (DDLT) and 34.4% living donor LT (LDLT), 82.8% within UCSF criteria, 56.4% received pre-LT bridging therapy). The cumulative 2-year and 5-year recurrence risks were 8.6% and 16.6% respectively. The Recurr-NET LT model predicted recurrence within 2 years and 5 years with area under curve (AUC) of 0.871 (specificity 0.823, sensitivity 0.333) and 0.805 (specificity 0.811, sensitivity 0.667) respectively. The Recurr-NET LT model significantly outperformed the original Recurr-NET (2-year AUC 0.519, 5-year 0.646) in predicting post-LT recurrence (both $p < 0.001$). The Recurr-NET LT model also outperformed the RETREAT and MORAL scores respectively (2-year AUC ranging from 0.546-0.769, 5-

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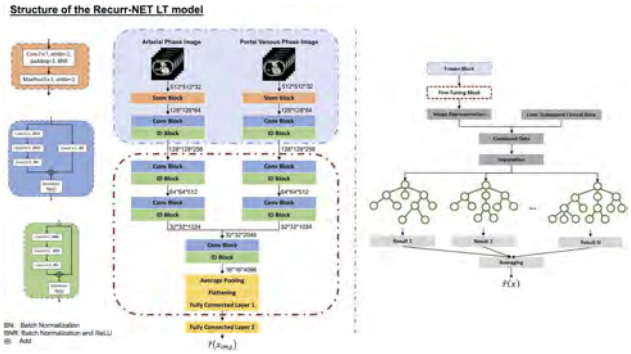
year AUC ranging from 0.544-0.684) (all $p < 0.05$). The diagnostic performance of Recurr-NET LT remained robust in various subgroup analysis (stratified by DDLT/LDLT, in/ out of UCSF criteria, use of bridging therapy respectively), with AUC remaining > 0.7 at all time-points. **Conclusion:** Recurr-NET LT had superior diagnostic performance over conventional clinical prediction scores, highlighting its potential as a prognostication model in LT for HCC.



Disclosures: Rex Wan-Hin Hui: Nothing to Disclose, Keith Chiu: Nothing to Disclose, Chenlu Wang: Nothing to Disclose, Ho-Ming Cheng: Nothing to Disclose, Trevor Wu: Nothing to Disclose, Sarah Choy Sin Yu: Nothing to Disclose, Tiffany Cho-Lam Wong: Nothing to Disclose, Lung-Yi Mak: Nothing to Disclose, James Fung: Nothing to Disclose, Man-Fung Yuen: Nothing to Disclose, Philip Leung-Ho Yu: Nothing to Disclose, Albert Chi-Yan Chan: Nothing to Disclose, Wai-Kay Seto: Nothing to Disclose

3462 | CYTOMEGALOVIRUS-RNA ACCURATELY IDENTIFIES CLINICALLY SIGNIFICANT INFECTION NEEDING PREEMPTIVE THERAPY IN LIVER TRANSPLANTED CHILDREN: A PROOF-OF-CONCEPT STUDY

Emanuele Nicastro[1] Eleonora Severi[1] Ilaria Passera[1] Michele Totaro[1] Lorenza Matarazzo[1] Laura Fornataro[1] Francesco Morotti[1] Alessandra Tebaldi[1] Ezio Bonanomi[1] Michela Bravi[1] Angelo Di Giorgio[1] Samuele Covini[1] Marta Dolci[1] Domenico Pinelli[1] Marco Enrico Giovanni Arosio[1] Lorenzo D'Antiga[1], [1]ASST Papa Giovanni XXIII, Bergamo, Italy

Background: Preemptive therapy (PET) is safe and effective in controlling Cytomegalovirus (CMV) infection after pediatric liver transplantation (LT) and allows to observe the kinetics of quantitative CMV-DNA viral load till it reaches the treatment thresholds. While an early detection of low-to-moderate CMV-DNA levels may not indicate active viral replication, awaiting the viral load to exceed the treatment threshold may lead to viremic breakthroughs and CMV disease. We assessed the capacity of quantitative CMV-RNA (UL21.5 mRNA) to identify active viral replication, and its accuracy in predicting clinically significant CMV infection (csCMVi) in LT children. **Methods:** This is a prospective observational proof-of-concept study. Children were followed for 6 months after LT, and both CMV-DNA and CMV-RNA were determined once a week in the first 12 weeks and at +4, +5, +6 months. Children were treated with iv ganciclovir for PET and in case of CMV disease. Cut-off for PET was CMV-DNA ≥ 100,000 IU/mL (142,800 cp/mL) in low-intermediate risk, and ≥ 50,000 IU/mL CMV-DNA (71,400 cp/mL) in high-risk children. csCMVi was defined in presence of CMV disease or the need for PET. **Results:** One-hundred and forty-four comparative quantitative CMV-RNA and CMV-DNA determinations were obtained from 12 children. Of 52 CMV-DNA-positive specimens, 17 (32%) were also CMV-RNA-positive, while CMV-RNA was undetectable in CMV-DNA-negative specimens. CMV-DNA was significantly higher in CMV-RNA-positive (56,499 ± 102,577 copies/mL) than in CMV-RNA-negative specimens (1,189 ± 1,382; $P < 0.0001$) (Figure). All children with csCMVi had early detectable CMV-RNA, peaking simultaneously to CMV-DNA (median CMV-DNA: 65,906 cp/mL; median CMV-RNA: 767 cp/mL); conversely, none of those with persistently low DNAemia proved CMV-RNA-positive. **Conclusion:** In this first pilot study, CMV-RNA had 100% sensitivity and specificity in predicting csCMVi after pediatric LT. The early detection of CMV-RNA marks virion assembly and a substantial risk of organ damage, and could guide the initiation of antivirals without risk of overtreatment.

Disclosures: Emanuele Nicastro: Nothing to Disclose, Eleonora Severi: Nothing to Disclose, Ilaria Passera: Nothing to Disclose, Michele Totaro: Nothing to Disclose, Lorenza Matarazzo: Nothing to Disclose, Laura Fornataro: Nothing to Disclose, Francesco Morotti: Nothing to Disclose, Alessandra Tebaldi: Nothing to Disclose, Ezio Bonanomi: Nothing to Disclose, Michela Bravi: Nothing to Disclose, Angelo Di Giorgio: Ipsen Pharma: Consultant, Mirum Pharma: Consultant, Samuele Covini: Nothing to Disclose, Marta Dolci: Nothing to Disclose, Domenico Pinelli: Nothing to Disclose, Marco Enrico Giovanni Arosio: Nothing to Disclose, Lorenzo D'Antiga: Selecta: Advisor, Vivet: Advisor, Spark: Advisor, Genespire: Advisor, Tome: Advisor, Mirum: Advisor, Ipsen/Albireo: Advisor, Intercept/Advanz Pharma: Advisor, Alexion/Astra Zeneca: Advisor, Fractyl: Advisor

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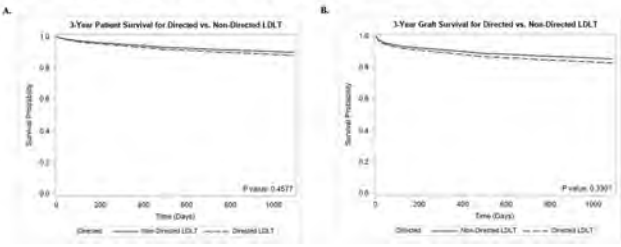
3463 | POST-TRANSPLANT OUTCOMES IN DIRECTED VERSUS NON-DIRECTED LIVING DONOR LIVER TRANSPLANTATION

Avesh Thuluvath[1] Talan Zhang[2] Russell Rosenblatt[3] Alyson Fox[1] Jason Hawksworth[4] Benjamin Samstein[5] Jean Emond[4] Elizabeth Verna[1], [1]Division of Digestive and Liver Diseases, Columbia University Irving Medical Center, New York, NY, [2]Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, [3]Division of Gastroenterology and Hepatology, Weill Cornell Medicine, New York, NY, [4]Center for Liver Disease & Transplantation, Columbia University Irving Medical Center, New York, NY, [5]Center for Liver Disease & Transplantation, Weill Cornell Medicine, New York, NY

Background: Living donor liver transplantation (LDLT), including non-directed living donation, offers a critical opportunity to overcome the current organ shortage and decrease waitlist mortality. The impact of non-directed living donation on post-liver transplant (LT) outcomes is unclear. In this retrospective United Network for Organ Sharing (UNOS) study, we compared post-LT patient and graft survival in directed versus non-directed LDLT. **Methods:** We analyzed the UNOS database to identify adult patients who underwent LDLT from 1/1/2002-12/31/2022. Patients who underwent multi-organ transplantation or were waitlisted with status 1 designation were excluded. The effects of directed versus non-directed grafts on post-LT patient and graft survival were estimated using a weighted Cox proportional hazards model after applying inverse probability of treatment weighting (IPTW) based on a propensity score model including recipient age, sex, MELD score, blood type, and graft type. **Results:** A total of 5158 directed and 212 non-directed LT recipients were identified. Non-directed LT recipients were more likely to be female (58% vs. 45%, $p < 0.01$), blood type A (50% vs 42% $p < 0.01$), have metabolic dysfunction-associated steatotic liver disease (21% vs 14%, $p < 0.01$) and receive a left lobe graft (17% vs 10% $p < 0.01$) compared to directed LT recipients. Non-directed LT recipients were less likely to have blood type O (34% vs 47%, $p < 0.01$) and have HCV (8% vs 22%, $p < 0.01$). Non-directed LT recipients had similar MELD scores at LT compared to directed LT recipients (15.7 vs 15.4, $p = 1.0$). Non-directed donors were older than directed donors (39.7 vs 36.9 years, $p < 0.01$). After IPTW, 1-year patient and graft survival were significantly higher in non-directed LT recipients compared to directed LT recipients ($p = 0.03$ for patient and graft survival). However, at 2- and 3-years post-transplant, patient and graft survival were similar between both groups (Figure). **Conclusion:** Long term outcomes after directed and non-directed LDLT are similar after accounting for critical factors such as recipient age, sex, MELD, blood type and graft type. While 1-year patient and graft survival are higher in non-directed LT recipients, longer term outcomes are comparable. This early difference could reflect differences in surgical techniques and immediate post-LT care at LT centers that perform more non-directed LDLT. Overall, our findings demonstrate that non-directed LDLT results in excellent outcomes and presents an important opportunity to increase the potential donor pool.

FIGURE: 3-Year Patient and Graft Survival after IPTW, Directed vs Non-Directed LDLT



Disclosures: Avesh Thuluvath: Nothing to Disclose, Talan Zhang: Nothing to Disclose, Russell Rosenblatt: Nothing to Disclose, Alyson Fox: Nothing to Disclose, Jason Hawksworth: Nothing to Disclose, Benjamin Samstein: Nothing to Disclose, Jean Emond: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose

3464 | FROM BURDEN TO RECOVERY: PREDICTING POST-TRANSPLANT WELLBEING FROM BASELINE FINANCIAL TOXICITY

Hannah Klatzkow[1] Kishore Botla[1] Alvaro Noriega Ramirez[1] Dyanna Gregory[1] Arjmand Mufti[2] Thomas Kerr[2] Lisa VanWagner[2] Amit Singal[1] Sarah Lieber[1], [1]University of Texas-Southwestern, [2]University of Texas Southwestern Medical Center

Background: Liver transplant recipients (LTRs) face significant financial challenges before and after surgery; it remains unclear how this burden evolves post-transplant, or how it impacts psychological wellbeing. We aimed to evaluate associations between pre- vs. post-LT financial toxicity and associated psychological distress. **Methods:** Adult LTRs were prospectively followed at a large academic transplant center from baseline (waitlist) to post-LT (12 months) and completed the following surveys: 1) Comprehensive Score for Financial Toxicity - Functional Assessment of Chronic Illness Therapy (COST-FACIT), 2) Patient-Reported Outcomes Measurement Information System (PROMIS)-Anxiety/Depression, 3) Decision Regret Scale. COST-FACIT, scored from 0-44 with lower scores indicating greater financial toxicity, was collected at baseline and 12 months; psychological measures were assessed at 6-12 months post-LT. Clinical variables were manually extracted from the electronic health record. General linear models were used to assess the association between waitlist financial toxicity

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and post-LT outcomes, adjusting for age, sex, race/ethnicity, education, transportation access, and if transplant was performed for an alcohol-related indication. COST-FACIT was modeled as a continuous predictor and change in score was also assessed as a continuous outcome. **Results:** Among 64 adult LTRs (mean age 49.8 ±14.3 years; 39.1% female; 85.9% White, 21.9% Hispanic), those with higher pre-LT financial toxicity had significantly greater improvement in COST-FACIT scores post-transplant ($p < 0.001$); however, higher pre-LT financial toxicity was associated with higher post-LT anxiety ($p = 0.003$) and depression scores ($p = 0.002$). Having access to transportation was associated with worse financial toxicity at 1 year ($p = 0.017$) and higher anxiety scores ($p = 0.045$), potentially reflecting unmeasured social or structural vulnerabilities. Other covariates, including age, sex, race/ethnicity, education, and alcohol-related transplant indication were not significantly associated with post-LT financial or psychological outcomes. Models adjusted for demographic covariates but did not assess for effect modification. **Conclusion:** Greater baseline financial toxicity was associated with higher post-transplant psychological distress, including anxiety and depression scores. However, these patients experienced greater improvement in financial toxicity post-LT. These findings highlight the importance of early risk identification and support for LTRs who may be experiencing financial toxicity.

Table 1: Multivariable Linear Regression Models Evaluating the Association Between Baseline Financial Toxicity, Sociodemographic Factors, and Post-Transplant Financial and Psychological Outcomes

	Effect of Baseline COST-FACIT		Effect of Transportation Availability		Effect of Age		Effect of Alcohol-Related Transplant	
Parameter	Estimate (Standard Error)	P-Value	Estimate (Standard Error)	P-Value	Estimate (Standard Error)	P-Value	Estimate (Standard Error)	P-Value
COST-FACIT at 1-Year Post LT	0.69 (0.14)	<0.001	-13.56 (5.44)	0.017	-0.07 (0.10)	0.473	0.81 (2.77)	0.772
PROMIS Anxiety T-Score	-0.45 (.14)	0.003	11.43 (5.51)	0.045	0.02 (0.10)	0.850	-1.68 (2.81)	0.553
PROMIS Depression T-Score	-0.42 (.126)	0.002	11.38 (4.88)	0.025	-0.03 (0.09)	0.736	-4.02 (2.49)	0.114
Decision Regret Scale	-0.01 (0.09)	0.928	-0.94 (4.47)	0.834	0.05 (0.07)	0.461	1.18 (1.90)	0.538
Change in COST-FACIT Score (Numeric)	-0.31 (0.14)	0.029	-13.56 (5.44)	0.017	-0.07 (.10)	0.473	0.81 (2.77)	0.772
Change in COST-FACIT (%)	-1.92 (0.76)	0.015	-25.59 (30.45)	0.406	-0.05 (0.54)	0.929	-1.30 (15.54)	0.934

Disclosures: Hannah Klatzkow: Nothing to Disclose, Kishore Botla: Nothing to Disclose, Alvaro Noriega Ramirez: Nothing to Disclose, Dyanna Gregory: Nothing to Disclose, Arjmand Mufti: Nothing to Disclose, Thomas Kerr: Madrigal: Consultant, GSK: Grant/Research Support, Lisa VanWagner: Gerson Lehrman Group: Consultant, AlphaSights: Consultant, Slingshot Insights: Consultant, Madrigal Pharmaceuticals: Grant/Research Support, W.L. Gore & Associates: Grant/Research Support, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Sarah Lieber: Nothing to Disclose

3465 | COVID-19 AND POST-TRANSPLANT AND BILIARY OUTCOMES AMONG LIVER-TRANSPLANT RECIPIENTS: A PROPENSITY SCORE MATCHED ANALYSIS

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Background: The impact of the COVID-19 Pandemic on higher morbidity and mortality among solid organ transplant (SOT) recipients has already been well described [1,2]; however, its association with increased mortality and post-transplant and biliary complications among liver-transplant (LT) recipients remains unclear and is not well explored. This study aims to assess the impact of COVID-19 infection on mortality and post-transplant and biliary outcomes among LT patients from a nationwide perspective. **Methods:** A retrospective cohort study was conducted using data from the TriNetX research network. Patients aged ≥18 years having a liver transplant recipient status secondary to any etiology of liver cirrhosis and before the index diagnosis of COVID-19 infection were identified using ICD-10-CM codes. Data on demographics and clinical outcomes were extracted. Cohorts were stratified based on their COVID-19 status and matched on characteristics, including demographics (age, gender, race), comorbidities (Charlson Comorbidity Index), and immunosuppressive therapies, using propensity score. Univariate regression analysis was used to assess the primary outcome, i.e., all-cause mortality. Secondary outcomes included liver transplant complications, biliary complications, ERCP interventions, thrombotic complications, sepsis, acute kidney injury (AKI), and need for ventilatory support. Odds ratios (ORs) and 95%

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confidence intervals (CIs) were calculated. **Results:** After propensity score matching, 7,437 patients in each cohort were analyzed for primary and secondary outcomes. All-cause mortality was found to be significantly higher among the COVID-19 LT group (OR (95% CI):1.13[1.024, 1.244]) compared to the control group. Among secondary outcomes, transplant-related complications, i.e., failure, rejection, and infections (OR (95% CI): 1.48 [1.37,1.61]), biliary complications including cholangitis (OR (95% CI): 1.80 [1.54,2.11]), and biliary obstruction (OR (95% CI): 1.31 [1.18,1.45]), sepsis (OR (95% CI): 1.52[1.4,1.65]), and AKI (OR (95% CI): 1.23 [1.15,1.31]) were significantly higher among the COVID-19 LT group compared to the control group. Other outcomes i.e., thrombotic complications, bile duct leak/perforation, and ERCP with interventions i.e., dilatation of ampulla/CBD and endoscopic stone removal, were higher among the COVID-19 LT cohort compared to control, but did not yield statistical significance. **Conclusion:** Study suggests that COVID-19 increases the risk of all-cause mortality and post-transplant and biliary complications among LT patients. A plausible explanation for this could be the complex interplay between proinflammatory state induced by coronavirus and the immunocpmromised status of LT patients, but the exact causal mechanism is unknown to date. Large prospective longitudinal studies are warranted to ascertain the causal relationship.

Clinical Outcomes	Incidence % (N)		Propensity matching analysis
	LT recipients With COVID-19 N=7,437	LT recipients w/o COVID-19 N= 7,437	aOR [95%CI]
All-Cause Mortality	13.1% (977)	11.8% (879)	1.13[1.024, 1.244]
Liver-Transplant related Complications (Failure, Rejection, infection and other complications)	24% (1,785)	17.4 (1,305)	1.48 [1.37,1.61]
Biliary Complications			
Cholangitis	5.8%(435)	3.33% (248)	1.80 [1.54,2.11]
Bile Duct Obstruction CBD stones with/without cholangitis	12.8% (957)	10%(754)	1.31 [1.18,1.45]
Bile Duct Leak/perforation	0.4% (31)	0.35% (26)	1.19 [0.71,2.01]
ERCP	0.57%(43)	0.62% (46)	0.93[0.62,1.42]
ERCP with Intervention			
Endoscopic Dilatation of ampulla and bile duct	1.05%(78)	0.98% (73)	1.07[0.778,1.47]
Endoscopic dilatation and drainage through NB tube or Stent Placement	3.6%(267)	4.5%(331)	0.79 [0.68,0.94]
Endoscopic stone removal	1.92%(143)	1.68(125)	1.15[0.9,1.46]
Thrombotic Complications			
Portal Vein Thrombosis/ Hepatic Artery thrombosis	2.6%(194)	2.4%(179)	1.16[0.94,1.42]
Other Clinical Outcomes			
Sepsis	22% (1,639)	15.6%(1,165)	1.52[1.4,1.65]
AKI	43.3%(3,219)	38.5%(2,853)	1.23 [1.15,1.31]
Ventilatory Support	3.8% (283)	3.8% (283)	1.0 [0.85,1.18]

Disclosures: Iqra Arshad: Nothing to Disclose, Ahmed Basil Nasir: Nothing to Disclose, Kamran Qureshi: Nothing to Disclose

3466 | EXAMINING THE IMPACT OF INFLAMMATORY BOWEL DISEASE REGARDING POST-TRANSPLANT OUTCOMES IN PRIMARY SCLEROSING CHOLANGITIS

Yashasavi Sachar[1] Gurpreet Malhi[1] Luis Antonio Diaz[2] Gopika Punchhi[1] Rokhsana Mortuza[1] Mayur Brahmania[3] Vipul Jairath[1] Juan Pablo Arab[4] Mohammad Qasim Khan[1], [1]Division Of Gastroenterology, Department Of Medicine, Western University, [2]Pontificia Universidad Católica de Chile, [3]O'Brien Institute of Public Health, Cumming School of Medicine, University of Calgary, [4]Virginia Commonwealth University

Background: Primary sclerosing cholangitis (PSC) is an immune-mediated disease characterized by biliary inflammation and fibrosis. PSC has a high comorbidity rate with Inflammatory Bowel Disease (IBD). Approximately 40% of patients with PSC progress to Liver Transplantation (LT). This study assesses the impact of IBD in individuals with PSC undergoing liver transplantation (LT), in terms of overall survival and post-transplant complications. **Methods:** This retrospective cohort study included individuals with PSC identified and underwent LT between Jan 1, 2000, to December 31, 2021, with follow-up up till December 31, 2023. Statistical analysis included a Kaplan-Meier survival curve, descriptive statistics regarding post-transplant characteristics and logistic regression analysis of binary primary and secondary outcones. Primary outcomes included 1 and 5-year mortality, with secondary outcomes including post-transplant malignancy and all-cause infection. **Results:** A total of 251 patients with PSC were identified. Of those, 114 LT recipients were included, with 92 (80%) diagnosed with PSC & IBD, and 22 (20%) diagnosed with PSC only. Baseline characteristics were similar for PSC and PSC-IBD groups in terms of age, sex, MELDNa, and immunosuppression used. The PSC-IBD population largely had Ulcerative Colitis (N = 72, 78%), with diagnosis being made before PSC (N = 54, 59%). Regarding transplant, significantly more DCD patients were identified in PSC cohort, with N = 10, 43%, vs N = 12, 13% in PSC-IBD, p = 0.02. The most common PSC phenotype was classic (N = 93, 71%). No differences in immunosuppression choice were noted between PSC and PSC-IBD groups. Overall survival post-LT was 77%, with no significant difference in 1-year (91% vs 85%, p = 0.537), or 5-year mortality (84% vs 82%, p = 0.861) between PSC and PSC-IBD groups, respectively. Overall, the most common cause of death was sepsis

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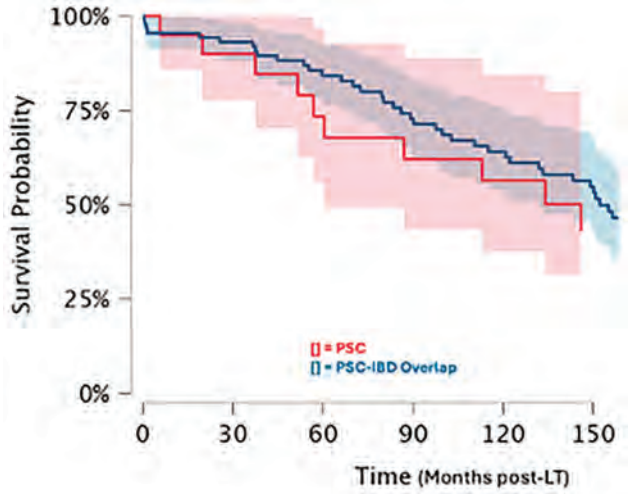
(43%), followed by malignancy (30%) and graft dysfunction (30%). No differences in the cause of survival were identified between PSC and PSC-IBD groups. Multivariate analysis did not demonstrate concurrent IBD diagnosis with PSC as a significant determinant affecting 1-year, 5-year survival, post-op infection, or post-op malignancy. However, increasing MELD-Na (OR 1.11 CI 1.03-1.20, $p < 0.05$), and need for pre-LT ERCP (OR 9.27, CI 1.52-56.5, $p < 0.05$) were both associated with increased risk of post-LT 5-year mortality. **Conclusion:** Over a 22-year evaluation period, concurrent IBD did not appear to confer increased risk of mortality, infection- or malignancy-related complications in PSC patients undergoing LT. This is likely reflective of the availability of more robust therapies to manage IBD during this period, and ongoing close follow-up by specialists in an IBD center of excellence.



Disclosures: Yashasavi Sachar: Nothing to Disclose, Gurpreet Malhi: Nothing to Disclose, Luis Antonio Diaz: Nothing to Disclose, Gopika Punchhi: Nothing to Disclose, Rokhsana Mortuza: Nothing to Disclose, Mayur Brahmania: Nothing to Disclose, Vipul Jairath: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose, Mohammad Qasim Khan: Nothing to Disclose

3467 | STEATOTIC LIVER DISEASE PHENOTYPES AND RISK OF SIMULTANEOUS LIVER-KIDNEY TRANSPLANTATION ELIGIBILITY: A COMPETING RISK ANALYSIS OF NATIONAL REGISTRY DATA

Roy Wang[1] Nadim Mahmud[1], [1]Hospital of the University of Pennsylvania

Background: Steatotic liver disease (SLD) can precipitate renal dysfunction through chronic kidney disease and acute kidney injury. However, among patients initially listed for liver transplant alone (LTA), little is known about progression of renal disease and ultimate need for simultaneous liver-kidney transplantation (SLKT) among different SLD phenotypes. We aimed to evaluate the association between SLD phenotype and rates of SLKT listing using national registry data. **Methods:** This was a retrospective cohort study using United Network for Organ Sharing data from 2002 to 2023. Adult patients initially listed for LTA were included. SLD was categorized into metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-associated liver disease (ALD), and metabolic and alcohol-associated liver disease (MetALD) using a validated algorithm. Time-updated glomerular filtration rate (GFR) was computed per the 2021 CKD-EPI formula using waitlist follow-up data. The primary outcome was waitlist development of SLKT criteria, defined as either (1) GFR ≤ 60 for 90 days with dialysis initiation or GFR ≤ 30, or (2) 6 consecutive weeks of GFR ≤ 25 or dialysis. We used both cause-specific hazard models and Fine and Gray competing risk regression, adjusted for *a priori* selected variables and with 5-year maximum follow-up, to evaluate the association between SLD phenotype and development of SLKT criteria. Competing events included death and liver transplantation. **Results:** A total of 69,627 patients were listed for LTA, of which 26,729 had MASLD, 15,554 had MetALD, and 27,344 had ALD. MASLD patients tended to be older (median age 61 vs 54 [MetALD] vs 53 [ALD]; $p < 0.001$) and more often female (47.9% vs 20.7% vs 31.9%; $p < 0.001$). Patients with ALD had lower median BMI ($p < 0.001$), but higher rates of ascites ($p < 0.001$) and higher median MELD score at listing ($p < 0.001$). MASLD patients had the lowest GFR at listing (75.0 vs 80.0 [MetALD] vs 83.3 [ALD]; $p < 0.001$) and the largest portion of patients meeting SLKT criteria (6.4% vs 3.0% vs 1.9%; $p < 0.001$) during follow-up. In cause-specific hazards regression, SLD phenotype was significantly associated with waitlist development of SLKT criteria ($p = 0.01$), with MASLD (hazard ratio [HR]: 1.30, 95% CI: 1.08-1.56) and MetALD (HR: 1.31, 95% CI: 1.06-1.61) demonstrating higher risk relative to ALD (Figure A/B). Cumulative incidence function curves, as estimated from Fine and Gray models, demonstrated numeric differences among SLD phenotypes in probability of meeting SLKT criteria, however these differences were not statistically significant ($p = 0.10$; Figure C). **Conclusion:** Patients with MASLD and MetALD had higher biological hazard of meeting SLKT criteria while listed for LTA, potentially from higher rates of competing events in ALD patients. Future investigation is needed to evaluate real-world differences in SLKT eligibility between SLD phenotypes.

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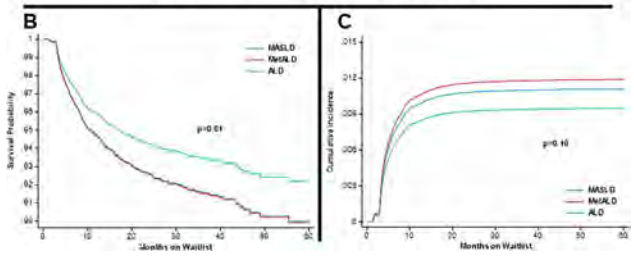
Factor	Hazard Ratio (95% CI)	p-value
SLD Type		0.01
ALD	Reference	
MASLD	1.30 (1.08-1.56)	
MetALD	1.31 (1.06-1.61)	
Age	1.01 (1.00-1.02)	0.04
Male Sex	0.68 (0.60-0.77)	<0.001
Race		
White	Reference	
Black	1.06 (0.72-1.55)	0.77
Hispanic	1.19 (1.02-1.40)	0.03
Asian	0.99 (0.59-1.65)	0.97
Other	0.95 (0.56-1.62)	0.86
BMI at Waitlisting	1.02 (1.00-1.03)	0.004
History of Ascites	1.47 (1.20-1.79)	<0.001
MELD Score at Waitlisting	0.99 (0.97-1.01)	0.06
GFR at Waitlisting	0.94 (0.94-0.94)	<0.001
Functional Status		
No Assistance	Reference	
Some Assistance	1.01 (0.89-1.16)	0.83
Total Assistance	1.00 (0.82-1.21)	0.96



Disclosures: Roy Wang: Nothing to Disclose, Nadim Mahmud: Grifols: Grant/Research Support

3468 | PERIOPERATIVE OUTCOMES WITH THE ADDITION OF NORMOTHERMIC REGIONAL PERFUSION TO NORMOTHERMIC MACHINE PERFUSION IN DCD LIVER TRANSPLANTATION

ATSUSHI NISHIMAGI[1] Rikako Oki[1] Saleh Al-Juburi[1] Luckshi Rajendran[1] Emily Kerby[1] Adhnan Mohamed[1] Ahmed Nassar[1] Abbas Al-Kurd[1] Atsushi Yoshida[1] Marwan Abouljoud[1] Shunji Nagai[1], [1]Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital

Background: The use of normothermic machine perfusion (NMP) and normothermic regional perfusion (NRP) in liver transplantation (LT) has increased in recent years, due to the expansion of the utilization of donation after circulatory death (DCD) donors. However, the clinical benefit of adding NRP to NMP remains unclear. The aim of this study was to investigate the potential clinical advantage of adding NRP to NMP in LT from DCD donors. **Methods:** We evaluated adult LT cases from DCD donors using NMP with or without NRP, performed between January 2024 and May 2025. Patients were divided into two groups based on the use of NRP. All NMPs were initiated at donor hospitals (on-site NMP). Post-operative liver function tests, lactate values, and short-term outcomes were compared between the two groups. **Results:** This study included 82 adult LT patients. Among them, 24 patients underwent LT using NMP combined with NRP, whereas 58 patients underwent LT using NMP alone. Donor age was significantly higher in the NMP+NRP group than in the NMP group (61 vs 52 years; $p = 0.001$). The incidence of early allograft dysfunction (EAD) was similar between the NMP+NRP and NMP groups (16.7%, [$n = 4$] vs 13.8%, [$n = 8$]; $p = 0.74$). There were no significant differences in peak of AST (840 vs 775 IU/L; $p = 0.53$), ALT (220 vs 218 IU/L; $p = 0.37$), INR (2.05 vs 2.06; $p = 0.68$), and total bilirubin (5.0 vs 3.6 mg/dL; $p = 0.33$) (NRP with NMP vs NMP alone). The median lactate level at 1.5 days postoperatively was significantly higher in the NMP+NRP group (1.7 vs 1.4 mmol/L; $p = 0.02$); however, both values remained within the normal reference range. Furthermore, the proportion of patients with lactate levels above the normal range (>2.1 mmol/L) at 1.5 days post-operatively was significantly higher in the NMP+NRP group compared to the NMP group (25.0%, [$n = 6$] vs 5.9%, [$n = 4$]; $p = 0.02$). There were no significant differences in postoperative ICU stay (3 vs 3 days; $p = 0.54$) or hospital stay (8 vs 10 days; $p = 0.33$) between the groups. In the NMP+NRP group, there was one case of graft loss due to postoperative hepatic ischemia which occurred immediately after transplant that required re-transplantation. There were no cases of perioperative mortality in either group. Patients who received LT from donors aged 60 years or older were divided into two groups based on use of NRP. There were 13 cases of NMP+NRP and 8 cases of NMP alone. We also compared perioperative outcomes, but no differences were found between the two groups. **Conclusion:** The results of this study showed that adding NRP to NMP did not provide significant benefits in perioperative outcomes.This study compares short-term outcomes. Comparisons of mid- to long-term outcomes remains necessary.

Disclosures: ATSUSHI NISHIMAGI: Nothing to Disclose, Rikako Oki: Nothing to Disclose, Saleh Al-Juburi: Nothing to Disclose, Luckshi Rajendran: Nothing to Disclose, Emily Kerby: Nothing to Disclose, Adhnan Mohamed: Nothing to Disclose, Ahmed Nassar: Nothing to Disclose, Abbas Al-Kurd: Nothing to Disclose, Atsushi Yoshida: Nothing to Disclose, Marwan Abouljoud: Nothing to Disclose, Shunji Nagai: Nothing to Disclose

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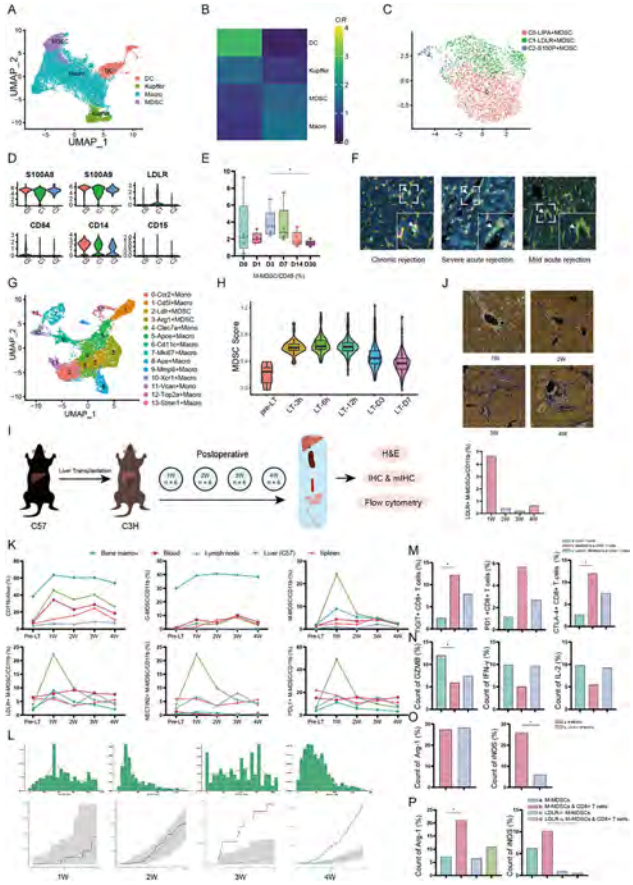
3469 | THE ROLE OF LDLR+ MYELOID-DERIVED SUPPRESSOR CELLS (MDSCS) IN LIVER TRANSPLANTATION

Jinzhen Cai[1] Xin Zhou[1] Xinqiang Li[1], [1]the Affiliated Hospital of Qingdao University

Background: Liver transplantation (LT) epitomizes a convergence of medical innovation and complex surgical prowess, providing a lifeline for patients grappling with end-stage liver diseases. However, immune rejection profoundly impacts patient prognosis. Investigating the underlying mechanisms of immune rejection is crucial for enhancing clinical outcomes and advancing scientific knowledge. Understanding these processes provides vital insights that can lead to improved therapies, better patient prognoses, and a deeper comprehension of immunological responses in the context of transplantation. **Methods:** We employed multi-omics approaches to analyze liver transplant samples from clinical patients and mice, utilizing single-cell RNA sequencing (scRNA-seq) and bulk RNA sequencing (bulk RNA-seq). Phenotypic and functional validation of MDSCs and their subtypes was conducted using flow cytometry, multiplex immunohistochemistry (mIHC) and co-culture experiments. **Results:** Analysis of scRNA-seq in human and murine revealed an association between MDSCs and liver transplant rejection. In mice, MDSC scores at various time points within the first week post-liver transplantation (LT) displayed a normal distribution trend, mirroring the flow cytometry results from peripheral blood of clinical patients one-month post-LT. Furthermore, the analysis identified a unique subset of LDLR+ M-MDSCs, with mIHC confirming the spatial expression of relevant proteins. Flow cytometry demonstrated the dynamic changes of LDLR+ M-MDSCs within multiple tissues (liver, spleen, blood, bone marrow and lymph nodes) in the mouse orthotopic liver transplantation (OLT) models, highlighting their elevated levels during the acute postoperative phase. Co-culture experiments demonstrated that LDLR-/- M-MDSCs exhibited reduced expression levels of functional molecules (Arg-1 and iNOS) and a significantly diminished capacity to induce the expression of inhibitory receptors (TIGIT, PD1 and CTLA-4) and functional molecules (GZMB, IFN-β and IL-2) in CD8+ T cells. **Conclusion:** LDLR+ M-MDSCs demonstrated superior immunosuppressive properties, indicating their potential clinical value in mitigating rejection and inducing immune tolerance.



Disclosures: Jinzhen Cai: Nothing to Disclose, Xin Zhou: Nothing to Disclose, Xinqiang Li: Nothing to Disclose

3470 | EFFECTIVENESS OF HCC DOWNSTAGING STRATEGIES FOR PATIENTS WITHIN AND BEYOND UNOS DS CRITERIA

Nishtha Singh Erin Duggan[1] Ian Dinmore[2] Sarah Stucky[2] Tea Binder[2] Dustin Carpenter[2] Benjamin Samstein[2] Juan Rocca[2] Alexander Berman[2], [1]Weill Cornell Medicine, NYP, [2]Weill Cornell Medicine

Background: Hepatocellular carcinoma (HCC) beyond Milan criteria for liver transplant is typically managed with downstaging strategies including locoregional therapies and/or systemic therapies. While the United Network for Organ Sharing has a defined criteria for downstaging towards transplant eligibility (UNOS-DS criteria), many patients initially staged beyond the

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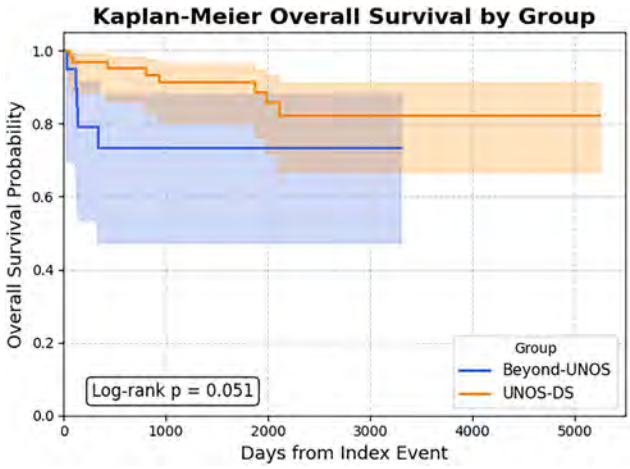
UNOS-DS criteria can also respond to treatment and eventually become eligible to transplant listing. This study aims to compare the effectiveness in downstaging strategies for patients with HCC within versus beyond UNOS DS criteria. **Methods:** We retrospectively reviewed our institutional database of HCC patients locoregional therapies (LRT) and/or systemic therapies with the goal of downstaging toward transplant listing eligibility. Patients were stratified into two cohorts based on initial tumor burden: within UNOS DS criteria versus beyond UNOS DS criteria. Clinical, radiological, and biochemical data were collected, including demographic details, tumor characteristics, treatment modalities, alpha-fetoprotein (AFP) dynamics, and survival outcomes. Primary endpoints were effective downstaging to Milan criteria. **Results:** A total of 91 patients were included in the analysis: 70 (77.7%) met UNOS downstaging (DS) criteria, while 21 (23%) were categorized as beyond UNOS DS. Baseline characteristics—including age, gender distribution, etiology of cirrhosis, ECOG status, and comorbidities—were largely comparable between groups, except for a significantly larger tumor size and a higher number of lesions in the beyond UNOS group ($p < 0.05$). The downstaging success rate was 34.3% (n = 24) in the UNOS DS group and 57.1% (n = 12) in the beyond UNOS group. Locoregional therapy (LRT) was utilized as the primary downstaging approach in 76% (n = 16) of beyond UNOS patients and 60% (n = 42) of UNOS DS patients ($p < 0.05$). The most common LRT modalities employed were Y90 radioembolization (16 in UNOS DS vs. 12 in beyond UNOS, $p < 0.05$), followed by TACE, SBRT, and MWA. Of the 91 patients, 33 underwent surgical resection and were excluded from the focused transplant analysis. The proportion of downstaged patients subsequently listed for transplants was similar between both the groups, UNOS DS group (24/42, 57.1%) and the beyond UNOS group (10/16, 62.5%). Actual transplant rates were more frequent 66.7% (n = 16/24) in the UNOS DS group and 50% (n = 5/10) in the Beyond UNOS group. **Conclusion:** Effective downstaging with locoregional therapies allows many HCC patients beyond UNOS criteria to achieve transplant eligibility. While both groups show similar listing rates after downstaging, actual transplant rates remain higher for those within UNOS criteria, highlighting the importance of patient selection and tailored management.



Disclosures: Nishtha Singh: Nothing to Disclose, Erin Duggan: Nothing to Disclose, Ian Dinmore: Nothing to Disclose, Sarah Stucky: Nothing to Disclose, Tea Binder: Nothing to Disclose, Dustin Carpenter: Nothing to Disclose, Benjamin Samstein: Nothing to Disclose, Juan Rocca: Nothing to Disclose, Alexander Berman: Nothing to Disclose

3471 | PLATELET RECOVERY AFTER LIVER TRANSPLANTATION: A NEW LOOK AT TIMING AND RISK FACTORS

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Background: Thrombocytopenia, a marker of clinically significant portal hypertension, occurs in up to 90% of patients following liver transplantation (LT). While prior studies suggest platelet counts typically recover within 2 to 4 weeks, some patients experience delayed or persistent thrombocytopenia, which has been linked to poorer graft function and reduced survival. However, the precise timeline and contributing factors remain

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poorly defined. We aimed to quantify the duration of platelet recovery after LT and assess whether socio-demographic factors influence this process. **Methods:** We conducted a retrospective study of 735 liver transplant recipients within a large health system. After excluding patients with normal pre-transplant platelet counts (n = 69), 666 patients with pre-transplant thrombocytopenia were included. Platelet resolution was defined as a count $> 150 \times 10^9$/L. Demographic data—including age, sex, race, and ethnicity—were collected. Platelet counts were tracked monthly for up to 5 years post-transplant, and at each time point, the proportion of patients with platelet resolution was calculated. Multivariate analysis was then used to evaluate associations between demographic factors and platelet recovery. **Results:** Our cohort consisted of 666 patients (60.0% male, 45.2% Hispanic, 45% non-white, mean age 57 years). Platelet resolution occurred in 50% of patients between 3 and 8 months post-transplant, and in 75% between 23 and 31 months (Figure 1). Multivariate analysis showed that female sex was significantly associated with faster platelet recovery (Recovery Ratio 1.59, 95% CI 1.32–1.92; $p < 0.0001$), as was younger age less than 45 (RR 1.39, 95% CI 1.07–1.80; $p < 0.05$). Hispanic patients tended to have slower recovery, while Black patients showed a trend toward faster recovery, though these differences were not statistically significant. **Conclusion:** In this large, diverse cohort of liver transplant recipients, platelet recovery occurred more gradually than previously reported, with most patients achieving resolution over several months to years. Female sex and younger age were independently associated with faster recovery. The longer recovery timeline may reflect our stricter definition of resolution, extended follow-up, and the real-world diversity of our population. Given the link between persistent thrombocytopenia and adverse outcomes, ongoing monitoring of platelet trends may help identify patients at risk for post-transplant complications.

Disclosures: Jamie Yang: Nothing to Disclose, Phillip Chen: Nothing to Disclose, Daniela Markovic: Nothing to Disclose, Nilofar Najafian: Nothing to Disclose, Yetunde Adebambo: Nothing to Disclose, Steven-Huy Han: Madrigal: Speaking and Teaching

3472 | SPATIAL MOLECULAR ANALYSIS REVEALS NOVEL MECHANISMS AND CELLULAR PARTICIPANTS IN THE PROGRESSION OF ANTIBODY-MEDIATED LIVER ALLOGRAFT INJURY.

Mylarappa Ningappa[1] Catherine Gestrich[2] Brandon Higgs[1] Lori Schmitt[2] Kyle Soltys[1] George Mazariegos,[1] Chethan Ashokkumar[1] Rakesh Sindhi[1], [1]Children's Hospital of Pittsburgh of UPMC, Hillman Center for Pediatric Transplantation, [2]Children's Hospital of Pittsburgh of UPMC, Department of Pathology

Background: To define spatial molecular and cellular landscape of antibody-mediated injury in liver transplant rejection. **Methods:** Residual formalin-fixed-paraffin embedded 'for cause' liver biopsy sections were obtained from recipients with no rejection, T-cell-mediated and antibody-mediated rejection (NR, TCMR, ABMR). We first compared the spatial whole transcriptome of TCMR biopsies with (n = 7) and without (n = 4) circulating donor-specific anti-HLA antibodies (DSA) with Visium, technology (10X Genomics) to identify DSA-related mechanisms. Next, spatial molecular imaging (SMI) with 6000 genes (CosMx, Nanostring) defined the cellular landscape of independent biopsies with ABMR (n = 2) compared with 4 TCMR and 3 NR biopsies. Cell-specific genes were used to enumerate liver parenchymal and immune cells. **Results:** Twenty subjects with median (range) age 3.1 years (0.97-26.3) included 11 males, 9 females, 17 white and 3 non-white recipients. While TCMR is associated with portal and pericentral proteasomal and immune synapse signaling, DSA during TCMR was associated with an intralobular germinal-center-like allograft response with upregulated (p-adj. < 0.01) CD40 (CD40, TRAF1, ICAM1), chemokine (CXCL10, CX3CL1), T-follicular (ICOS, IRF7, PDCD1) and complement (C1QC, CD55) signaling. For each signaling pathway, gene counts increased progressively along the direction of sinusoidal blood flow from portal to central regions. SMI of 398 fields of view (FOVs), 0.25mm by 0.25 mm each, across nine independent biopsies (mean 44 FOVs per biopsy) revealed progressive increases in cell proportions (Figure 1) from NR to TCMR and ABMR for B-cells (1% vs 2% vs 4%), T-helper/Tc-memory (1% vs 2% vs 4%), Th17 (1% vs 1% vs 2%), Tc (3% vs 6% vs 6%), erythroblastoid macrophages (3% vs 4% vs 8%), and fibroblasts (3% vs 5% vs 7%). Spatial localization of CD40, ICOS, C1QC, and antibody-secreting IGHG2+B-cells to the

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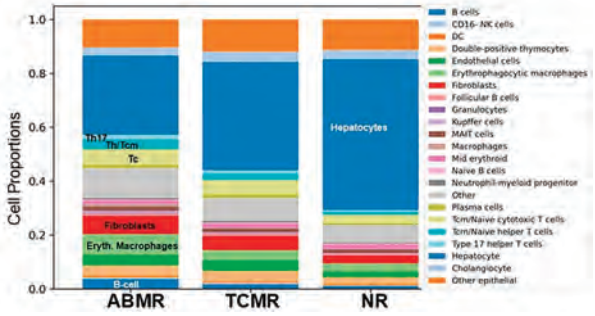
intralobular region was confirmed in a rejection biopsy with DSA. **Conclusion:** Antibody-mediated liver allograft injury likely begins with intralobular germinal-center-like reaction during T-cell-mediated rejection. Progression to frank antibody-mediated rejection is associated with increasing liver graft infiltration by B-cells, Th/TH17 cells, macrophages, and fibroblasts.

Figure 1



Disclosures: Mylarappa Ningappa: Nothing to Disclose, Catherine Gestrich: Nothing to Disclose, Brandon Higgs: Nothing to Disclose, Lori Schmitt: Nothing to Disclose, Kyle Soltys: Nothing to Disclose, George Mazariegos,: Bridge to Life: Honorarium, Optum: Honorarium, Takeda: Honorarium, Chethan Ashokkumar: Nothing to Disclose, Rakesh Sindhi: Plexision: Executive role

3473 | COMPARISON OF THE 6-MINUTE WALK TEST AND THE LIVER FRAILTY INDEX IN PREDICTING LIVER TRANSPLANT MORTALITY

Amani Elshaer[1] Bridgette McNally[1] Carolyn Mead-Harvey[1] Elizabeth Carey[1], [1]Mayo Clinic Arizona

Background: Recent years have emphasized the importance of assessing functional status in liver transplant candidates, given its prognostic value pre- and post-transplant. Although multiple assessment tools exist, comparative studies are lacking, leaving uncertainty about the optimal method to use in clinical practice. The AASLD guidance does not specify a preferred frailty tool, allowing centers to choose based on practice. At our institution, we use both the Six Minute Walk Distance (6MWD) and Liver Frailty Index (LFI) to evaluate candidates, enabling a comparison of their prognostic value. **Methods:** This retrospective study analyzed 298 patients evaluated for liver transplant; 213 had 6MWD and 82 had LFI assessments. We stratified 6MWD as frail (<250 m), prefrail (250–350 m), and robust (>350 m). LFI was categorized as frail (≥ 4.5), prefrail (3.2–4.4), and robust (<3.2). Multivariate analysis compared outcomes between the two tools. The primary endpoint explored pretransplant outcomes (waitlist/transplant or deceased/denied). Secondary endpoints were post-transplant ICU stay, hospital stay, readmission rate, graft loss, and mortality. **Results:** The patient's baseline characteristics were similar across both groups. Pre-transplant outcomes (waitlist/transplanted vs deceased/denied) showed no significant differences by frailty category for LFI ($p=0.252$) or 6MWD ($p=0.468$). Post-transplant outcomes were comparable between the 6MWD ($n=196$) and LFI ($n=59$) groups, with no significant differences in ICU days (2.0 vs. 2.6; $p=0.319$), total hospital stay (8.3 vs. 9.4 days; $p=0.890$), or 30-day readmissions (2.4 vs. 2.6 days; $p=0.379$). However, graft loss was higher in the LFI group (10.2% vs. 3.1%; $p=0.035$), while mortality rates were similar (8.7% vs. 10.2%; $p=0.796$). Within LFI strata, no outcome differed significantly by frailty, though frail patients trended toward increased graft loss (18.2%, $p=0.564$) and mortality (27.3%, $p=0.144$). Among 6MWD categories, only hospitalization duration varied significantly ($p<0.001$), with frail (11.7 ± 10.1 days) and prefrail (10.3 ± 12.0 days) patients having longer stays than robust patients (7.2 ± 5.7 days). **Conclusion:** Our research showed that 6MWD and LFI are similar, lacking significant differences in predicting outcomes before and after transplantation. Due to their similarities, 6MWD serves as a user-friendly assessment tool, requiring minimal personnel training per patient, making it practical for clinical settings. Ongoing research and data collection are essential for identifying the most reliable assessment tool for evaluating patients in transplantation.

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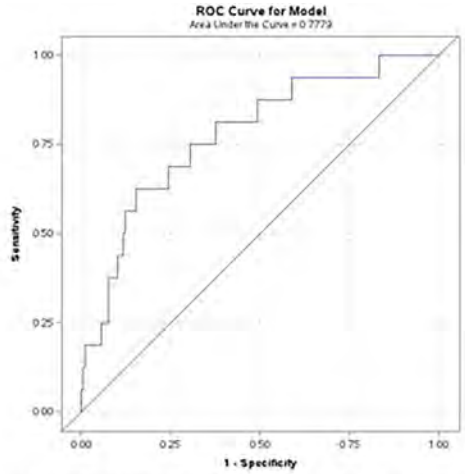
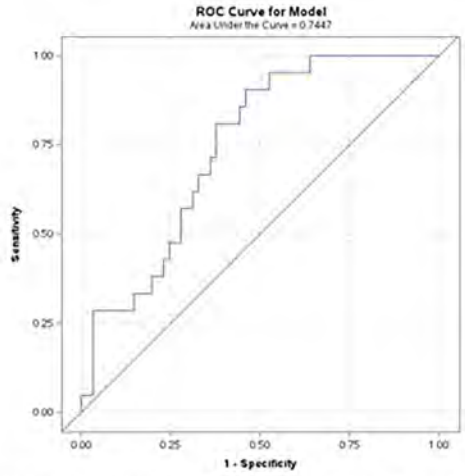


(A) 6MWD receiver operator curve (ROC) model after adjusting for potential confounders.



(B) LFI receiver operator curve (ROC) model after adjusting for potential confounders.

Disclosures: Amani Elshaer: Nothing to Disclose, Bridgette McNally: Nothing to Disclose, Carolyn Mead-Harvey: Nothing to Disclose, Elizabeth Carey: GlaxoSmithKline: Advisor

3474 | TRENDS AND REGIONAL VARIATION IN UTILIZATION OF U.S. LIVING LIVER DONORS WITH CLASS II/III OBESITY AND ASSOCIATED RECIPIENT SURVIVAL, 2002-2023

Leandro Sierra[1] Chase Wehrle[1] Jamak Modaresi Esfeh[1] Alejandro Pita[1] Koji Hashimoto[1] Sobia Laique[1], [1]Cleveland Clinic Foundation

Background: Rising obesity in living liver donors (LLDs) raises safety and outcome concerns. Organ shortages, despite these risks, have prompted centers to include LLDs with Class II and III obesity. This study characterizes U.S. trends in utilizing these donors and associated recipient survival across U.S. regions. **Methods:** Using the UNOS database, we identified adult LLDs from 2002 to 2023. We excluded pediatric donors and recipients, multi-organ transplants, and retransplants to focus on first-time adult LDLT. Donor BMI was classified according to WHO criteria, focusing on Class II (BMI 35–39.9) and Class III (BMI $\geq$40). Class I obesity was excluded from this specific analysis as most centers will use donors with Class I obesity, and this study aimed to evaluate trends associated with higher classes of obesity. We assessed temporal trends in the number of donors with obesity overall and by UNOS region. Recipient survival was analyzed using Kaplan-Meier curves and log-rank tests, initially comparing broader Western (Regions 5 and 6) and Eastern (Regions 1, 2, 3, 9, 11) groupings, with further analysis exploring individual UNOS regions. **Results:** Among a total of 142 LLDs with Class II or III obesity identified from 2002 to 2023, the utilization of such donors increased over the study period, accounting for 9.2% of all LLDs by 2023. The highest proportion of these 142 donors with obesity were observed in Regions 2 (21.8% of the total cohort of donors with obesity), 4 (14.1%), and 9 (17.6%). Western regions utilized a similar absolute number of Class II and III donors with obesity compared to Eastern regions (69 vs. 73 total donors, respectively; $P > 0.05$). Donor mean age was 35.1 $\pm$ 9.2 years (West vs. East, $P > 0.05$), with 45% male donors overall (West 40% vs. East 50%, $P = 0.17$). While initial analysis showed higher recipient 1-, 5-, and 10-year survival rates in Western regions (95.6%, 85.4%, and 79.0%) versus Eastern regions (91.2%, 70.8%, and 57.1%; $p = 0.04$), subsequent region-specific analysis indicated this Western advantage was predominantly driven by markedly higher survival in Region 6. No significant differences in recipient MELD scores or comorbidities were observed between the broad Western and Eastern regions. **Conclusion:** Recipient survival with livers from donors with obesity was higher in Western versus Eastern UNOS regions, primarily driven by exceptionally high survival rates in UNOS Region 6. This suggests that specific center practices, regional expertise, or patient selection protocols in Region 6 may significantly influence LDLT outcomes when using donors with obesity. Disseminating best practices from such high-performing regions is crucial to improve national LDLT survival rates and address these disparities.

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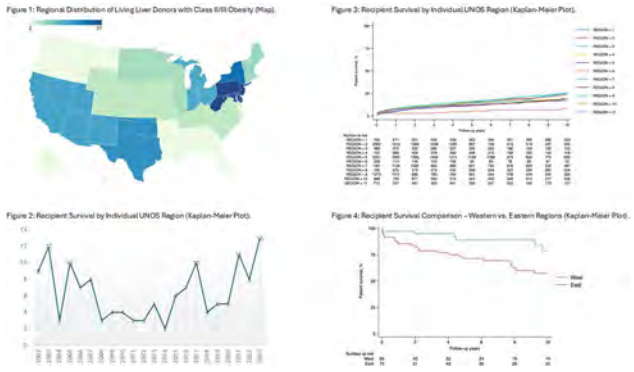


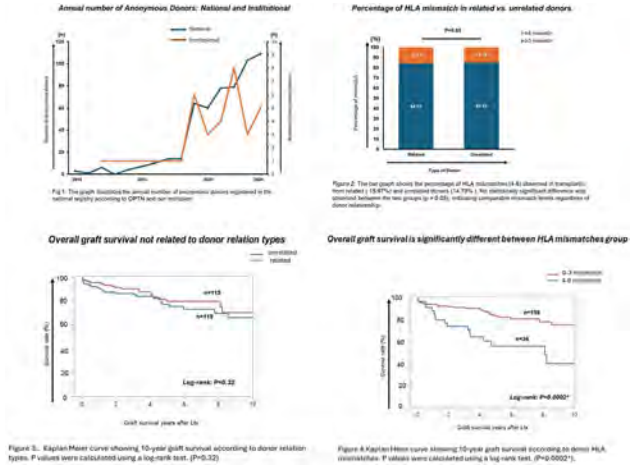
Disclosures: Leandro Sierra: Nothing to Disclose, Chase Wehrle: HistoSonics: Above, Jamak Modaresi Esfeh: Nothing to Disclose, Alejandro Pita: Nothing to Disclose, Koji Hashimoto: Nothing to Disclose, Sobia Laique: Madrigal Pharmaceutical: Consultant, Novo Nordisk: MASH Curriculum Steering Committee, Madrigal Pharmaceutical: Consultant, Novo Nordisk: MASH Curriculum Steering Committee

3475 | IMPACT OF DONOR-RECIPIENT RELATIONSHIP AND HLA MATCHING ON LONG-TERM GRAFT SURVIVAL IN LIVING DONOR LIVER TRANSPLANTATION

MUHAMMAD AHMAD NADEEM[1] Sapana Verma[1] Tetsuya Tajima[1] Chase Wehrle[1] Puneet Bansal[1] Antonio Giuseppucci[1] Koki Takase[1] Hiroshi Horie[1] Jaekeun Kim[1] David Kwon[1] Charles Miller[1] Jiro Kusakabe[1] Koji Hashimoto[1] Alejandro Pita[1] Masato Fujiki[1], [1]Cleveland Clinic

Background: The use of anonymous living donors has significantly increased, expanding unrelated living donor liver transplantation (LDLT) in the United States. This raises concerns regarding potential adverse outcomes associated with increased human leukocyte antigen (HLA) mismatches. We report our experience with anonymous donation, focusing on the impact of HLA matching on transplant outcomes. **Methods:** A retrospective cohort study was conducted, including adult and pediatric patients who underwent LDLT at a single academic center between 2012 and 2024. Recipients were categorized based on donor genetic relationship into related or unrelated donors (including emotionally related and anonymous donors). HLA mismatches at classical class I and II loci were classified into two groups: 0–3 and 4–6 mismatches. The primary outcome measured was graft survival, analyzed using Kaplan-Meier survival curves, with differences between groups assessed by the log-rank test. **Results:** A total of 234 primary LDLT recipients were included: 22 (9.6%) received left lateral segment grafts, 96 (41.0%) left lobe, 106 (45.3%) right lobe, and 10 (4.3%) other graft types. The proportion of anonymous donors increased substantially over the study period (Fig. 1), with 115 (49.1%) LDLTs involving unrelated donors. Of these, 10 were prior kidney donors.

Among related donor-recipient pairs, 100 (84.0%) had 0–3 HLA mismatches, which was similar to unrelated pairs, with 98 (85.2%) ($p = 0.85$) (Fig. 2). The incidence of rejection did not significantly differ between genetically related and unrelated donor-recipient pairs (27.0% vs. 25.2%, $p = 0.76$). Similarly, ten-year graft survival was comparable between the two groups ($p = 0.32$). However, recipients with 4–6 HLA mismatches had significantly lower ten-year graft survival compared to those with 0–3 mismatches ($p < 0.05$) (Fig. 3, 4). **Conclusion:** Anonymous and unrelated donors represent an increasingly important source of donors in LDLT. Our findings underscore the significance of optimal HLA matching. Strategies aimed at minimizing HLA mismatches are recommended to maximize the benefits of anonymous donations.



Disclosures: MUHAMMAD AHMAD NADEEM: Nothing to Disclose, Sapana Verma: Nothing to Disclose, Tetsuya Tajima: Nothing to Disclose, Chase Wehrle: HistoSonics: Above, Puneet Bansal: Nothing to Disclose, Antonio Giuseppucci: Nothing to Disclose, Koki Takase: Nothing to Disclose, Hiroshi Horie: Nothing to Disclose, Jaekeun Kim: Nothing to Disclose, David Kwon: Medtronics: Consultant, GE medical: Consultant, Histosonics: Consultant, Charles Miller: Nothing to Disclose, Jiro Kusakabe: Nothing to Disclose, Koji Hashimoto: Nothing to Disclose, Alejandro Pita: Nothing to Disclose, Masato Fujiki: Nothing to Disclose

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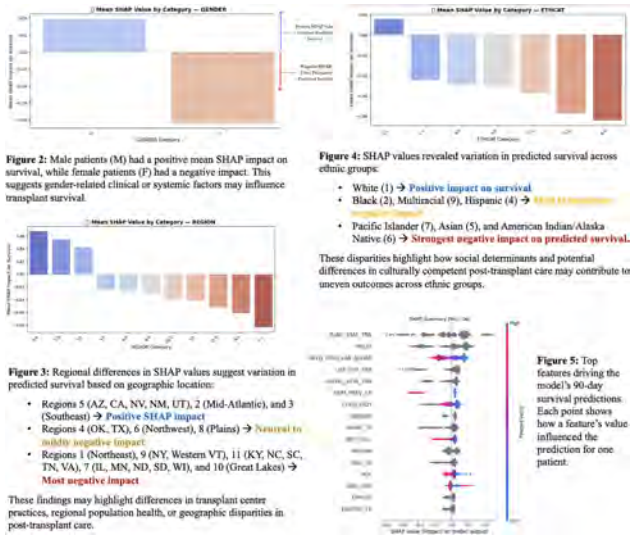
3476 | TRANSPLANTXAI: AN EXPLAINABLE AI/ML MODEL FOR PREDICTING PATIENT SURVIVAL FOLLOWING LIVER TRANSPLANTATION

Bhavik Tadigotla[1] Prasun Jalal[1] Abbas Rana[1], [1]Baylor College of Medicine

Background: Accurate post-transplant mortality prediction is critical for early intervention, patient counseling, and resource allocation. Yet risk scores often exclude sociodemographic factors and rely on static thresholds, limiting transparency and individualized risk interpretation. Our aim was to develop an explainable machine learning model (ML), trained on clinical and sociodemographic features, to predict recipient survival 90 days post-liver transplant. **Methods:** TransplantXAI is a supervised ML model built on a cohort of 42,384 recipients from the United Network for Organ Sharing (UNOS). It uses 13 recipient clinical features identified as significant predictors of survival in the Survival Outcomes Following Liver Transplant (SOFT) score, and 3 recipient sociodemographic features: sex, race/ethnicity, and region. The cohort was split 70/30 (training/testing), with 5-fold cross-validation in the training set to optimize model performance. For model explainability, we used SHapley Additive exPlanations (SHAP) to generate global and individual-level feature contributions, clarifying each variable's influence on survival. **Results:** With an AUC of 0.7045, TransplantXAI outperformed MELD and matched other ML models predicting 90 day survival post-liver transplant. SHAP analysis found functional status at transplant, prior malignancy, and MELD as the top 3 drivers influencing model predictions. TransplantXAI also revealed non-clinical disparities in survival within our cohort. Specifically, male sex correlated with positive SHAP values (indicating a contribution to improved survival), while female sex correlated with negative SHAP values (indicating a contribution to poorer outcomes). In race/ethnicity, White recipients had positive SHAP values, while all other groups (Black, Multiracial, Hispanic, Pacific Islander, Asian, and American Indian) had negative SHAP values. Geographic disparities were also evident: UNOS regions 2, 3, and 5 had positive SHAP values, while all others had negative values. **Conclusion:** Our explainable ML model enables actionable opportunities for intervention by identifying patient-specific risk drivers. In revealing non-clinical disparities, TransplantXAI enables clinicians to tailor care plans—such as prioritizing size-matched donor livers for female recipients, or addressing language and community health barriers. By merging clinical and sociodemographic insights, TransplantXAI sets a precedent for transparent and equity-aware tools in transplant hepatology.



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3477 | ASSOCIATION BETWEEN GUT MICROBIOTA AND CARDIOVASCULAR RISK IN LIVER TRANSPLANT RECIPIENTS

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Background: Liver transplant (LT) recipients are at a heightened risk for atherosclerotic cardiovascular disease (ASCVD); however, the underlying mechanisms responsible for this association remain poorly defined. In the general population, emerging research suggests that gut microbiota may function as mediators in the development of ASCVD by promoting plaque formation, instability, and endothelial dysfunction. Given the absence of corresponding data in LT recipients, we conducted the present study to examine the relationship between gut microbiota and the risk of ASCVD in LT recipients. **Methods:** The study prospectively enrolled 170 LT recipients into a natural history study evaluating cardiometabolic complications after LT surgery. All patients had blood work done after an overnight fast at time of enrollment and patients were followed every 3-6 months after enrollment. Trimethlyamine-N-oxide (TMAO) is a gut microbiota-dependent metabolite that has been associated with CVD risk and was used in the current study. All ASCVD events were adjudicated by

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study investigators. Diagnostic performance and time to event analysis was performed. **Results:** The median TMAO value of the study cohort was 4.95 (1st, 3rd quartiles: 2.70, 10.18) and patients receiving a LT for HCV or MASH cirrhosis had higher values when compared to other etiologies. No significant differences in TMAO levels were noted in patients who developed post-LT metabolic dysfunction associated steatotic liver disease (MASLD) compared to those who did not (9.87 ± 14.0 vs. 9.42 ± 13.0, $p = 0.83$). A total of 32 ASCVD events occurred after a median follow up of 26 months after enrollment. After adjusting for age, gender, and ethnicity, TMAO was significantly associated with higher risk of ASCVD (HR 1.032, 95% CI 1.015, 1.049, $p < 0.001$) and a trend towards all-cause mortality was noted (HR 1.026, 95% CI 1.000, 1.054, $p = 0.052$). At the max Youden Index to predict 2-year future risk of ASCVD, the diagnostic performance are: AUROC 0.71 (95% CI: 0.59, 0.84), Sensitivity 0.67, Specificity 0.66, NPV 0.85, and PPV 0.41. **Conclusion:** The research highlights the potential role of gut microbiota in ASCVD development, particularly focusing on the metabolite trimethylamine-N-oxide (TMAO). Although a trend between all-cause mortality and TMAO levels was noted, it wasn't statistically significant, likely due to the small sample size. Larger studies are needed to determine how TMAO can improve risk stratification in LT recipients.

Disclosures: Rehan Razzaq: Nothing to Disclose, Nicole Lulkin: Nothing to Disclose, Shilpa Jasti: Nothing to Disclose, Madison Nguyen: Nothing to Disclose, Alexis Kim: Nothing to Disclose, Vaishali Patel: Nothing to Disclose, Amon Asgharpour: Galectin: Clinical Endpoint Committee, NovoNordisk: Advisor, Madrigal: Advisor, Chronic Liver Disease Foundation: Speaking and Teaching, Intercept: Consultant, Idris Yakubu: Nothing to Disclose, Anh Bui: Nothing to Disclose, Margery Connelly: Labcorp: Employee, Mohammad Siddiqui: NovoNordisk: Grant/Research Support, NovoNordisk: Grant/Research Support, NovoNordisk: Grant/Research Support, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Sagimet: DSMB, NovoNordisk: Grant/Research Support, NovoNordisk: Grant/Research Support, NovoNordisk: Grant/Research Support, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Sagimet: DSMB, NovoNordisk: Grant/Research Support, NovoNordisk: Grant/Research Support, NovoNordisk: Grant/Research Support, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Sagimet: DSMB

3478 | LIVER-SPECIFIC DELETION OF NAT10 IMPAIRS LIVER REGENERATION IN A MOUSE PARTIAL HEPATECTOMY MODEL

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Background: Impaired liver regeneration after injury or surgery can lead to life-threatening complications such as liver failure and small-for-size syndrome, highlighting the need to identify key molecular regulators of this process. N-acetyltransferase 10 (NAT10), the only known enzyme that catalyzes N4-acetylcytidine (ac4C) modification on RNA, regulates mRNA stability and translation. While NAT10 is implicated in various cellular processes, its role in liver regeneration remains unknown. This study aims to investigate whether NAT10 promotes hepatocyte proliferation and liver regeneration and to elucidate the underlying mechanisms driving this process. **Methods:** Liver regeneration was induced by 70% partial hepatectomy (PHx) in 8-week-old C57BL/6J mice. RNA sequencing was performed to identify key regulators involved in liver regenerative by using liver tissue at 48 hours post-PHx. Liver-specific *Nat10* knockout mice ($Nat10^{LKO}$) were generated by crossbreeding $Nat10^{fl/fl}$ mice with Alb-Cre transgenic mice. Liver tissues and serum samples were collected at 0, 48, 72, and 120 hours post-PHx. The liver-to-body weight ratio was calculated to assess regenerative progression. Serum biochemical analyses were performed to evaluate liver function. Liver tissues were subjected to immunohistochemistry (IHC) and western blotting (WB). **Results:** RNA sequencing analysis showed that NAT10 expression was significantly upregulated in liver tissues following PHx compared to sham-operated controls. $Nat10^{LKO}$ mice exhibited a significantly lower liver-to-body weight ratio at both 48 and 120 hours post-PHx compared to $Nat10^{fl/fl}$ mice. Serum biochemical analysis indicated delayed liver function recovery in $Nat10^{LKO}$ mice, as evidenced by persistently elevated AST and ALT levels. IHC showed reduced Ki67 and PCNA expression, indicating impaired hepatocyte proliferation. WB analysis revealed decreased expression of cell cycle regulators, including Cyclin D1, Cyclin A2, Cyclin E1, CDK1, and CDK4. In addition, phosphorylated STAT3 levels were also reduced in $Nat10^{LKO}$ mice, suggesting impaired activation of regenerative signaling pathways. **Conclusion:** Liver-specific deletion of NAT10 impairs

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liver mass restoration, delays liver function recovery, reduces proliferative activity, and suppresses key cell cycle and regenerative signaling pathways, including STAT3 phosphorylation. These results suggest that NAT10 may serve as a potential therapeutic target for improving liver regeneration in the context of liver injury or resection.

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3479 | EFFICACY AND SAFETY OF TENOFOVIR ALAFENAMIDE FOR HBV PROPHYLAXIS IN HBV-NEGATIVE LIVER TRANSPLANT RECIPIENTS WITH HBCAB-POSITIVE DONORS:UPDATED 24-WEEK INTERIM ANALYSIS

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Background: Liver transplantation (LT) remains the definitive treatment for end-stage liver disease, yet donor organ shortages persist. Strategic utilization of HBcAb-positive grafts may expand the donor pool, though this necessitates effective HBV prophylaxis given the risk of *de novo* infection. Tenofovir alafenamide (TAF) demonstrates comparable antiviral efficacy to tenofovir disoproxil fumarate (TDF) with superior renal and bone safety profiles. This interim analysis evaluates TAF's prophylactic efficacy and safety through 24-week follow-up in HBV-negative recipients with HBcAb-positive liver allografts within a Chinese transplant cohort. **Methods:** This prospective single-arm study enrolled HBsAg-negative and HBV-DNA-negative LT recipients (aged ≥ 12 years) receiving allografts from HBsAg-negative/HBcAb-positive deceased donors. TAF prophylaxis (25 mg/day) was initiated immediately after LT and continued until treatment-limiting adverse events (AEs) or consent withdrawal. Protocol-defined monitoring included weekly laboratory tests (week 1-4), transitioning to biweekly (week 5-12) and monthly (week 12-24), and transient elastography (FibroScan) at week 12 and 24. Key efficacy endpoint of this interim analysis was the positive rate of HBV-DNA or HBsAg at week 24. Safety endpoints included changes in hepatic and renal function, and incidence of treatment-emergent AEs. This trial is registered with ClinicalTrials.gov, number NCT04703465. **Results:** Between July 30, 2022 and May 25, 2025, 17 patients (mean age 50.7 years; 64.7% male) were enrolled, with 16 patients (94.1%) completing 24 weeks of TAF treatment and follow-up. During the study, no patient was detected HBV-DNA-positive or HBsAg-positive. Liver function remained stable at week 24: mean ALT 23.3 U/L (95% CI, 17.0 to 29.7), AST 25.2 U/L (95% CI, 20.9 to 29.3), and median TBIL 13.6 μmol/L (IQR, 9.6 to 18.7). Liver stiffness (mean LSM 7.0 kPa; 95% CI, 6.5 to 7.5) at week 24 showed minimal change from week 12 (Δ +0.1 kPa; IQR, -1.1 to +0.3). Renal function exhibited a median eGFR decline of -9.5 mL/min/1.73 m² (IQR, -18.3 to -3.3) between week 24 and week 0, with serum creatinine increasing by +6.8 μmol/L (95% CI, -8.3 to +21.9). Seven patients (41.2%) experienced serious AEs, none treatment-related, and no proteinuria or grade ≥ 3 hepatic abnormalities were observed. **Conclusion:** TAF provides effective HBV prophylaxis in HBV-negative LT recipients with HBcAb-positive allografts, with no virological breakthroughs observed. Hepatic parameters remained stable throughout follow-up. Despite a modest decline exhibited in renal function, no proteinuria occurred. These findings support the feasibility of utilizing HBcAb-positive donors under TAF prophylaxis to address organ shortages, with preserved graft and renal safety over 24-week follow-up. Future studies should prioritize randomized comparisons with TDF and extended monitoring of renal function.

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3480 | MATERNAL AND FETAL OUTCOMES IN PATIENTS WITH AUTOIMMUNE HEPATITIS POST LIVER TRANSPLANTATION

Madeline Koehn[1] Caroline Conlon[1] Richard Hass[2] Sarah Boudova[1] Tammy Tran[1] Lisa Coscia[3] Michael Moritz[3] Serban Constantinescu[3] Tatyana Kushner[4] Danielle Tholey[1], [1]Thomas Jefferson University Hospital, [2]Jefferson College of Public Health, Thomas Jefferson University, [3]Transplant Pregnancy Registry International, [4]Weill Cornell Medicine

Background: Autoimmune hepatitis (AIH) is a chronic, immune-mediated liver disease with a higher prevalence in women. AIH is associated with an increased risk of rejection, recurrent AIH and graft loss post-LT compared to other etiologies. Pregnancy in LT patients can be associated with increased risk of maternal and fetal complications. Yet, data on pregnancy outcomes for AIH patients post-LT are scarce. This study analyzes

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the impact of AIH-indicated LT on maternal and fetal outcomes. **Methods:** A retrospective analysis was done evaluating post-LT pregnancies in the Transplant Pregnancy Registry International (TPRI) between 1985-2024. Descriptive analyses were performed, including Chi-squared test for categorical variables and t-tests for continuous variables ($p < 0.05$ significant), to assess maternal and fetal outcomes for pregnancies in patients transplanted for AIH compared to a control group of all other indications. **Results:** In total, 429 women with 846 pregnancies were included (AIH cohort: 62 women, 125 pregnancies; control cohort: 367 women, 721 pregnancies). The majority of patients were white with similar age, BMI and rate of planned pregnancies. Transplant to conception interval <1-year post-LT was significantly shorter in the AIH group (11% vs 4%, $p = 0.002$). Pregnancy, maternal and neonatal outcomes were similar in each cohort (table 1). Incidence of gestational diabetes (8% vs 7%, $p = 0.89$), hypertensive related complications (pre-eclampsia 17% vs 15%, $p = 0.46$; HELLP 2% vs 1%) and infections during pregnancy (15% vs 17%, $p = 0.82$) were similar. The AIH group had more prednisone (62% vs 29%, $p < 0.001$) and mycophenolate exposure (11% vs 5%, $p = 0.03$) during pregnancy. Live birth rate (68% vs 74%, $p = 0.25$), miscarriage (27% vs 20%, $p = 0.11$), stillbirth (2% vs 1%, $p = 0.54$) and birth defects (8% vs 8%, $p = 0.34$) were not different between groups. AIH patients had a higher rate of graft loss at any time after pregnancy (24% vs 13%, $p = 0.002$). There was a nonsignificant trend to higher rates of rejection during (8% vs 4%, $p = 0.11$) and after (7% vs 5%, $p = 0.33$) pregnancy. Neonatal jaundice (13% vs 9%, $p < 0.001$) and NICU admission (20% vs 15%, $p < 0.001$) were increased in the AIH group. **Conclusion:** Pregnancy outcomes are overall similar in women post-LT for AIH vs allcomers. However, AIH patients displayed higher rates of graft loss, neonatal jaundice and NICU admission. Increased graft loss may be due to shorter LT to conception intervals in the AIH group and altered immune factors post-LT and post-partum. Despite higher mycophenolate exposure in the AIH group, there were no differences in birth defects, miscarriage, live birth or still birth rates. More data is needed to assess mycophenolate's impact on our other neonatal outcomes. Improved preconception counselling, closer monitoring of liver tests in the peri- and post- partum periods, and multidisciplinary management with maternal fetal medicine and neonatology may be beneficial in this cohort.

PREGNANCY OUTCOMES	AIH (n=125)		Control (n=721)		
Median BMI per pregnancy (kg/m^2)	24.92		23.24		
Median conception age (years)	30.25		29.08		
Median transplant to conception interval (years)	4.04		7.5		p < 0.001
Transplant to conception interval <1 year	14	11%	32	4%	p = 0.002
Planned pregnancy	69	55%	404	56%	
Prenatal care	77	62%	467	65%	
Gestational DM	10	8%	52	7%	p = 0.89
Gestational HTN	4	3%	43	6%	p = 0.36
Pre-eclampsia	21	17%	105	15%	p = 0.46
Infections during pregnancy	19	15%	124	17%	p = 0.82
Rejection during pregnancy	10	8%	30	4%	p = 0.11
Graft loss during pregnancy	0	0%	2	0%	
Rejection after pregnancy	9	7%	33	5%	p = 0.33
Graft loss after pregnancy	30	24%	92	13%	p = 0.002
Graft loss within 2 years of pregnancy	4	3%	17	2%	p = 0.51
Maternal death (during pregnancy or within 42 days of delivery)	0	0%	1	0%	
Live birth	88	68%	554	74%	p = 0.25
Miscarriage	35	27%	154	20%	p = 0.11
Stillbirth	3	2%	9	1%	p = 0.54
Spontaneous labor	22	25%	153	28%	p = 0.84
Induced labor	44	50%	249	45%	p = 0.80
C-section	35	40%	153	28%	p = 0.63
NEONATAL OUTCOMES	**AIH (n=86)**		**Control (n=545)**		
Neonatal death	0	0%	6	1%	
Birth defects	7	8%	41	8%	p = 0.34
Low birth weight (<2500g)	27	31%	159	29%	p = 0.63
Early preterm < 34 weeks	15	17%	69	13%	
Preterm < 37 weeks	31	36%	199	37%	p = 0.87
Jaundice	11	13%	47	9%	p < 0.001
NICU admission	17	20%	84	15%	p < 0.001

Table 1. Pregnancy and neonatal outcomes in the AIH cohort compared with the control cohort. AIH: autoimmune hepatitis; BMI: body mass index; C-section: cesarean section; DM: diabetes; HTN: hypertension; NICU: neonatal intensive care unit.

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3481 | TEMPORAL TRENDS IN MEDIAN WAIT TIME FOR LIVER TRANSPLANTATION AND WAITLIST OUTCOMES IN THE U.S.

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Background: Major policy changes have reshaped liver transplant allocation over the past two decades, including Share 35 and acuity circles. Evaluating trends in waitlist outcomes—transplantation, death, and dropout—can help assess the real-world impact of

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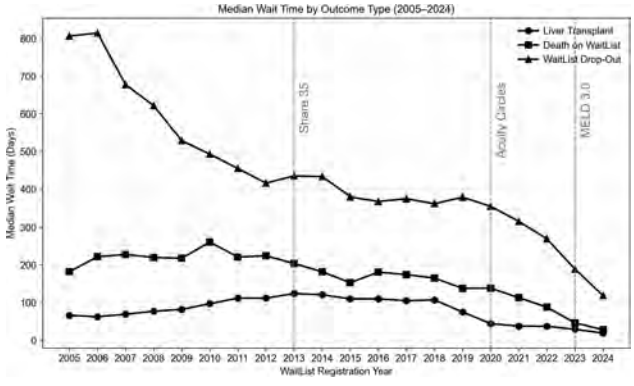
these policies. **Methods:** We conducted a retrospective cohort study using the United Network for Organ Sharing registry to examine temporal changes in waitlist outcomes. We included adult candidates waitlisted for liver transplantation between 1/1/2005 and 6/30/2024 and excluded those listed for multi-organ transplants or with missing data. Primary outcome was time from waitlist registration to one of three mutually exclusive events: transplant, death on the waitlist, or dropout (removal for reasons other than transplant or death). We estimated annual median times of each outcome overall and by MELD score, hepatocellular carcinoma (HCC) status, and liver etiology. Trends over time were assessed using Joinpoint software. **Results:** We included 205,437 patients. Overall, median wait time to transplant increased by 8 days/year from 2005–2013, plateaued between 2013–2017, and then declined by 22 days/year from 2017–2020 and 7 days/year from 2020–2024. In contrast, median time to death and dropout declined throughout the study period (p-values < 0.01). Lower MELD scores were associated with longer wait times. In patients with MELD ≤ 14, median time to transplant increased between 2005-2013, then decreased by 6 days/year from 2014–2022 and 58 days/year after 2022. Median time to death and dropout also decreased consistently in this group. Compared to those without HCC, patients with HCC experienced longer wait times. For this group, median time to transplant increased steadily, peaking at 250 days in 2016, then plateaued between 2016-2022 before declining to 128 days in 2024. Time to dropout peaked at 330 days in 2019 then falling to 163 days in 2024. By etiology, patients with alcohol-associated liver disease had the shortest wait time to transplant, followed by those with metabolic-dysfunction associated steatohepatitis and hepatitis C. Three groups had similar decreasing wait time to death and dropout. **Conclusion:** Waitlist outcomes for liver transplant candidates have improved over the past two decades, but disparities persist by MELD score, diagnosis of HCC, and etiology. Our study highlights the impact of evolving allocation policies, shifting clinical populations, and expanded eligibility on access. Continued monitoring is needed to ensure equitable and timely allocation.



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3482 | PUMP-SOFT SCORE: MACHINE PERFUSION AS A PREDICTOR OF SHORT-TERM POSTOPERATIVE MORTALITY IN LIVER TRANSPLANTATION

Gwendolyn Henry[1] Carter Burns[1] George Cholankeril[1] Abbas Rana[1], [1]Baylor College of Medicine

Background: Liver transplantation is the only curative procedure for patients with end-stage liver disease, and the growing disparity between donor organs and eligible recipients represents a considerable barrier to treatment. One avenue for addressing this discrepancy is through the use of machine perfusion to maximize graft preservation and increase the utility of marginal allografts. Early evidence suggests that machine perfusion could also have a positive impact on decreasing short-term postoperative mortality. Currently, there are no liver transplant risk scores that take into account whether machine perfusion was utilized for the donor organ when assessing a patient's post-transplant mortality risk. Our aim for this study was to create a novel risk index for assessing 90-day post-transplant mortality which incorporates machine

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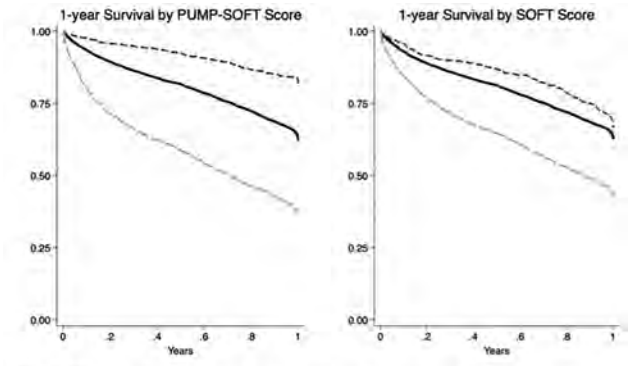
perfusion as a predictive variable, the PUMP-SOFT score. **Methods:** Through univariable and multivariable regression of de-identified patient-level data collected by the Organ Transplant and Procurement Network, we identified significant risk and protective factors from a sample of 64,791 patients. Points were allocated according to odds ratios from 25 significant recipient factors and 2 significant donor factors to generate the PUMP-SOFT score. **Results:** Machine perfusion had a significantly protective effect on survival, reducing short-term postoperative mortality risk by 40% (OR 0.601, CI 0.47-0.77). The most significant risk factors identified through our analysis were two previous transplants (OR 4.2., CI 2.50-7.19), recipient serum sodium 155-160 mEq/L (OR 3.7, CI 1.90-7.27) and 150-155 mEq/L (OR 2.2, CI 1.53-3.22), and moribund pre-transplant clinical presentation based on Karnofsky scores (OR 1.7, CI 1.42-2.11).

The PUMP-SOFT score has a *C*-statistic of 0.68 (CI 0.666-0.689) for 90-day mortality, which is significantly higher than that of both the original SOFT score (0.65, CI 0.639-0.662) and the BAR score (0.61, 0.594-0.618) when applied to this modern cohort of patients. Figure 1 includes Kaplan-Meier curves showing the 1-year survival probability for both the PUMP-SOFT score and original SOFT score where patients are divided into the 10th, 50th, and 90th percentiles. **Conclusion:** The PUMP-SOFT score is an novel approach to characterization of postoperative mortality risk because it incorporates the effect of machine perfusion as a predictive variable. This novel scoring system represents an improvement upon established risk scores like the SOFT score and BAR score. Our results from this study also support the notion that machine perfusion could have a protective effect on short-term post-transplant mortality. Thus, perfusion should be incorporated as a predictive factor in future risk assessment indices, especially as utilization of machine perfusion systems continues to grow in order to ameliorate the current organ shortage associated with liver transplantation.



PUMP-SOFT Risk group	OR	p-value	CI
10th percentile (low)	0.302	0.000	0.247,0.371
50th percentile (moderate)	0.603	0.000	0.553,0.658
90th percentile (high)	3.376	0.000	3.08,3.70

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3483 | A RANDOMIZED MULTI-CENTER TRIAL OF A TELEMETRIC INTERVENTION TO PREVENT REJECTION IN ADOLESCENTS AT RISK AFTER LIVER TRANSPLANTATION (IMALT)

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Background: Nonadherence is a major cause of late acute cellular rejection (ACR) and a risk for graft loss in liver transplant recipients. Identifying and treating clinically significant nonadherence remains an unmet medical need in liver transplantation and throughout medicine. The Improving Medication Adherence in Adolescents who had a Liver Transplant (iMALT – NCT03691220) study sought to address this need. **Methods:** iMALT was a prospective, block-randomized, controlled multisite study in 13 pediatric transplant centers in the USA and Canada. A two-year manualized telemetric intervention (TI) was compared to standard of care (SOC). Eligible adolescents at risk for rejection were identified by a medication level variability index (MLVI) of $>$ 2.0. The primary outcome was a composite end-point of ACR centrally determined by 3 masked pathologists, death, re-transplantation, or consent withdrawal. iMALT was powered for a 50% reduction in rejection based upon the MALT cohort study (Am. J. Transpl. 17:2668-2678), in which 53% of adolescents with MLVI $>$ 2.0 had ACR. Safety analyses examined medication toxicity that may be related to enhanced

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adherence. **Results:** Among 148 participants (TI n = 72, SOC n = 76), mean age was 15.5 years, averaging 10.0 years after liver transplant. There was no attrition in this complicated patient population and the study was uninterrupted by the COVID-19 pandemic. There were 6 primary events in the TI group (8.3%) and 12 in SOC (15.8%) (OR 0.50, 95% CI 0.17-1.45, p = 0.203). There were improvements in all secondary outcomes in the intervention relative to SOC, including significant changes in maximal ALT (Table). No adverse/safety events were observed. **Conclusion:** iMALT did not observe a statistically significant improvement in its primary end-point, however improvements were noted in all relevant outcomes in the intervention group compared to SOC. The study was unexpectedly underpowered, as rejection incidence was lower than observed in the precursor MALT study. In iMALT unlike in MALT, participating sites used MLVI to detect nonadherence and inform clinical care, which made standard of care more effective. This likely led to reduced incidence of rejection compared to the MALT study. We posit that objective and reliable identification of nonadherence using MLVI, coupled with telemetric intervention, is a powerful approach to addressing clinically significant nonadherence in adolescents after liver transplant.

Table (Other Endpoints)

	Rejection		ALT Parameter				GGT Parameter			
	Central Review	Local Review	Mean[1]	>150[2]	Max[3]	SD[1]	Mean[1]	>150[2]	Max[3]	SD[1]
Telemetric Intervention	8.3%	13.9%	40.5	13.9%	86.6*	19.6*	72.8	19.4%	142.7	32.4
Standard of care	13.2%	18.4%	45.7	23.7%	110.5	27.1	84.1	26.3%	165.5	41.5

ALT = Alanine Aminotransaminase; GGT = Gamma-Glutamyl Transferase; * p<.05 vs standard of care, [1] group mean of the parameter as calculated for each participant during the study, [2] % of participants with at least one value > 150 during follow up, [3] group mean of maximal value for all participants, [4]

Disclosures: Eyal Shemesh: Nothing to Disclose, Ravinder Anand: Nothing to Disclose, Rachel Annunziato: Nothing to Disclose, Emily Fredericks: Nothing to Disclose, Jennifer Garcia: Nothing to Disclose, Nitika Gupta: Nothing to Disclose, Alyssa Kriegermeier: Mirum Pharmaceuticals: Advisor, Krupa Mysore: Nothing to Disclose, Vicky Ng: Nothing to Disclose, Steven Lobritto: Orphalan: Grant/Research Support, Mirum: Advisor, Ibsen: Speaking and Teaching, IPRO: Consultant, NIH: Grant/Research Support, Shreena Patel: Nothing to Disclose, Emily Perito: Mirum: Consultant, Mirum: Consultant, Mirum: Consultant, Ultragenyx: Consultant, Ultragenyx: Consultant, Ultragenyx: Consultant, BridgeBio: Consultant, BridgeBio: Consultant, BridgeBio: Consultant, Amagma: Consultant, Amagma: Consultant, Amagma: Consultant, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Albireo: Grant/Research Support, Albireo: Grant/Research Support, Albireo: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Dicerna: Grant/Research Support, Dicerna: Grant/Research Support, Dicerna: Grant/Research Support, Takeda: Grant/Research Support, Mirum: Consultant, Mirum: Consultant, Mirum: Consultant, Ultragenyx: Consultant, Ultragenyx: Consultant, Ultragenyx: Consultant, BridgeBio: Consultant, BridgeBio: Consultant, BridgeBio: Consultant, Amagma: Consultant, Amagma: Consultant, Amagma: Consultant, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Albireo: Grant/Research Support, Albireo: Grant/Research Support, Albireo: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Dicerna: Grant/Research Support, Dicerna: Grant/Research Support, Dicerna: Grant/Research Support, Takeda: Grant/Research Support, Elizabeth Rand: Nothing to Disclose, Rene Romero: Nothing to Disclose, Robert Venick: Nothing to Disclose, Sarah Duncan-Park: Nothing to Disclose, Jeffrey Mitchell: Nothing to Disclose, Sarah Anderson: Nothing to Disclose, Margaret Stuber: Nothing to Disclose, Miguel Reyes-Múgica: Nothing to Disclose, George Mazariegos: Bridge to Life: Honorarium, Protera Therapeutics: Honorarium, Optum Health: Honorarium, Benjamin Shneider: Nothing to Disclose

3484 | RISK-ADAPTED PROTOCOL FOR CORONARY ARTERY DISEASE ASSESSMENT IN LIVER TRANSPLANT CANDIDATES: IMPACT OF PRE-TRANSPLANT CARDIAC CATHETERIZATION FINDINGS ON POST-TRANSPLANT OUTCOMES – A RETROSPECTIVE COHORT ANALYSIS

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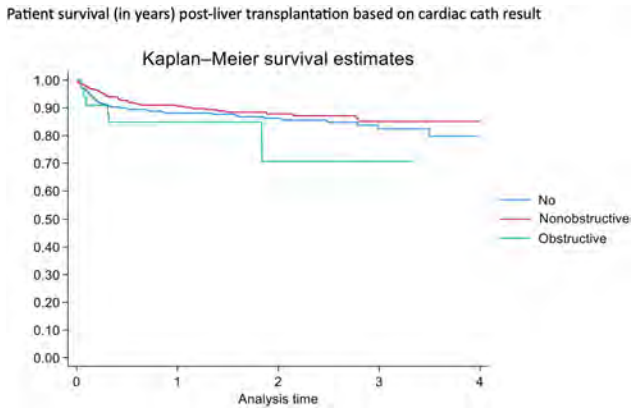
Background: Coronary artery disease (CAD) assessment in liver transplantation (LT) candidates remains challenging. This study evaluates the clinical utility of a risk-adapted protocol for pre-LT CAD evaluation, integrating cardiac catheterization (Cath) and functional testing, and its impact on post-LT outcomes. **Methods:** A retrospective cohort analysis of 745 LT recipients (2020–2024) managed under a protocol stratifying candidates by cardiovascular risk. High-risk patients underwent pre-LT Cath, with CAD severity categorized as non-obstructive ($<75\%$ stenosis, $n=328$) or obstructive ($\geq 75\%$ stenosis, $n=36$). Outcomes included cardiac death, myocardial infarction (MI), graft survival, and mortality. Adjusted Cox regression and Kaplan-Meier survival analyses were performed. **Results:** Implementation of the protocol achieved high 3-year patient (82–85%) and graft survival (80–85%) across all groups (no cardiac Cath, non-obstructive, and obstructive CAD groups), despite prevalent comorbidities (diabetes: 46.9%, HTN (33.5%), obesity (33.5%), and dyslipidemia (19.9%). Post-LT MI occurred in 19 patients (2.6%), 12 patients underwent cardiac Cath and 7 patients managed conservatively. Adjusted Cox models showed no independent association between CAD severity and mortality (obstructive CAD HR 1.96, 95% CI 0.83–4.66, *p* = 0.12) or graft failure (HR 1.49, 95% CI 0.68–3.29, *p* = 0.31). 14 patients (3.8%) developed contrast induced nephropathy and only one patient required dialysis. **Conclusion:** A risk-adapted CAD assessment protocol demonstrated significant clinical utility, facilitating tailored management and yielding low post-LT cardiac complications and excellent survival rates despite high comorbidity burdens. These results advocate for protocol-driven, multidisciplinary risk stratification to optimize LT outcomes. Prospective validation is warranted to refine criteria and expand applicability.



Disclosures: Bandar Aljudaibi: Nothing to Disclose, Manhal Izzy: Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Dieter Broering: Nothing to Disclose, Maryam Abdulla: Nothing to Disclose, Waleed Haj Ahmad: Nothing to Disclose, Dimitri Raptis: Nothing to Disclose, Syeda Shamsi: Nothing to Disclose, Ahmad Alissa: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Saad Alghamdi: Nothing to Disclose, Mohamed Tahir: Nothing to Disclose

3485 | THE PROFILE AND OUTCOMES OF LIVER TRANSPLANTATION IN THE UNITED STATES AND 30 EUROPEAN COUNTRIES

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Background: Due to varying etiologies of chronic liver disease (CLD) and differences in clinical and demographic factors, regional differences in liver transplantation (LT) may exist. We aimed to describe LT recipients in the United States and 30 European countries over the past two decades. **Methods:** We combined data from two large transplant registries: the U. S. Scientific Registry of Transplant Recipients (SRTR) and the European Liver Transplant Registry (ELTR), years 2000-2022. Common clinical parameters and post-LT mortality were collected. **Results:** We included 237,813 LT recipients (109,048 LT from Europe [30 countries], 128,765 from the U.S.). Compared to SRTR, LT recipients from ELTR were younger, more often male, and had lower BMI, lower MELD scores, and few cirrhosis complications (all $p<0.0001$). Hepatocellular carcinoma (HCC) was more frequent in ELTR: 29% vs. 20%. ELTR also had more chronic hepatitis B (CHB) (9% vs. 3%) and alcohol related liver disease (ALD) (30% vs. 23%), and less chronic hepatitis C (CHC) (18% vs. 27%) and NASH/MASH (7% vs. 19%) (all $p<0.0001$). Over time, HCC rates initially increased (peak of 30% in 2015 for SRTR, 35% in 2016 for ELTR), then declined. Major trends included rising ALD (15% to 45% in SRTR, 25% to 41% in ELTR) and decreasing CHC (40% to 7%; 25% to 7%) (all trend $p<0.0001$) (Figure). NASH/MASH also increased: 9% to 28% in SRTR, 5% to 12% in ELTR, while CHB decreased: 6% to 2%; 11% to 6%. In patients without HCC, the three most common CLD etiologies were identical: ALD, NASH/MASH, and primary sclerosing cholangitis. In patients with HCC, NASH/MASH has become the most common etiology in the U.S. by 2022, while ALD was the most common and the fastest growing in ELTR. In proportional hazards models, a

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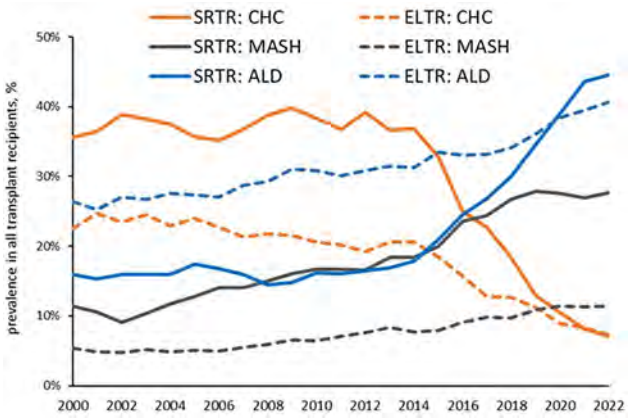
more recent calendar year was independently associated with lower mortality in both registries: ELTR aHR = 0.983 (0.979 - 0.987), SRTR aHR = 0.955 (0.953 - 0.957) per year ($p < 0.0001$). Other predictors of higher post-LT mortality included older age, male sex, higher MELD score, grade III/IV hepatic encephalopathy, HCC, and CHC (all aHR > 1.0, $p < 0.01$), consistent across registries and HCC status. **Conclusion:** Data from two large regional transplant registries confirm that ALD and NASH/MASH are continuing to emerge as major etiologies for liver transplantation, emphasizing the importance of improving global awareness of both metabolic and alcohol-related comorbidities contributing to steatotic liver disease.



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3486 | ANTI-THYMOCYTE GLOBULIN-BASED INDUCTION IMMUNOSUPPRESSION IN LIVER TRANSPLANT RECIPIENTS WITH NON-IMMUNE CHRONIC LIVER DISEASES

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Background: Use of anti-thymocyte globulin (ATG) as induction immunosuppression (IS) is not common practice in liver transplantation (LT). There is lack of studies describing the use of ATG in this population, particularly so in disease-specific patient populations. Our study reports on impact of IS in patients with non-immune primary diagnoses such as alcohol-associated liver disease, MASH, viral hepatitis, and other diagnoses. **Methods:** In April 2020 a practice change was incorporated in our program in response to the COVID-19 pandemic; wherein patients with non-immune primary diseases no longer received ATG-based IS. Patients with immune diseases (autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), or primary sclerosing cholangitis (PSC)) continued to receive ATG, whereas patients with age > 65, extreme frailty, or recent infection did not receive ATG and both subsets were excluded from analysis. Pediatric recipients, simultaneous multiorgan transplants, and retransplants were also excluded. In this cohort study, our primary endpoint was acute rejection (AR), diagnosed based on clinical suspicion and histologic confirmation. Outcomes were compared across the two eras stratified by ATG-based IS (Era 1: 1/2016-3/2020, Era 2: 4/2020-12/2023). **Results:** Of a total of 867 patients with non-immune primary liver diseases, 447 were in Era 1 and 420 in Era 2. Baseline characteristics and differences between cohorts are reported in Figure 1. ATG was given to 87% of patients in Era 1 and 3% in Era 2 ($p < 0.001$). Overall, 124 patients (14.3%) experienced AR. AR was more common in Era 2 (19.1% vs. 9.8% in Era 1, $p < 0.001$). In multivariable Cox regression, the predictors of AR were MELD at transplant (HR 1.02, $p = 0.024$), non-ATG IS (HR 1.61, $p = 0.013$), male donor (HR 1.54, $p = 0.04$) and Black race (HR 2.90, $p < 0.001$). In subgroup analysis, Black race was only significantly associated with AR in patients who did not receive ATG ($p < 0.001$ vs. $p = 0.056$ in Black patients with ATG IIS). Death after transplant ($p = 0.30$) or graft loss ($p = 0.40$) were not statistically different between the two eras. **Conclusion:** A shift in IS strategy to omit ATG from induction in patients with non-immune etiologies was associated with increased AR, at-risk population being recipients with Black race or male donors. There may be a role for ATG-based IS in a select group of patients.

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Table 1: Baseline characteristics and outcomes for two eras of induction immunosuppression (Era 1 - ATG for patients without autoimmune liver diseases, Era 2 – no ATG for these patients)

	Overall N=867	Era 1 N=447	Era 2 N=420	p-value Era 1 vs. Era 2
Age at transplant (years), mean (S.D.)	56.3 (10.7)	57.1 (10.0)	55.5 (11.4)	0.089
Male gender, N (%)	550 (63.4%)	296 (66.2%)	254 (60.5%)	0.353
Race				
White, N (%)	782 (90.2%)	412 (92.2%)	370 (88.1%)	0.646
Black, N (%)	32 (3.7%)	19 (4.3%)	13 (3.1%)	0.795
Asian, N (%)	12 (1.4%)	6 (1.3%)	6 (1.4%)	0.760
Arab or Middle Eastern, N (%)	3 (0.3%)	3 (0.7%)	0 (0.0%)	0.010
Unknown, N (%)	38 (4.4%)	7 (1.6%)	31 (7.4%)	0.389
Hispanic ethnicity, N (%)	29 (3.3%)	20 (4.5%)	9 (2.1%)	0.114
Indication for transplant				
Alcohol, N (%)	397 (45.8%)	193 (43.2%)	204 (48.6%)	0.412
Viral (Hep B + Hep C), N (%)	180 (20.8%)	111 (24.8%)	69 (16.4%)	0.424
MASH, N (%)	308 (35.5%)	171 (38.3%)	137 (32.6%)	0.441
HCC, N (%)	216 (24.9%)	118 (26.4%)	98 (23.3%)	0.682
AIH/PBC/PSC, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	N.S.
All others, N (%)	128 (14.8%)	69 (15.4%)	59 (14.0%)	0.314
BMI at transplant, mean (S.D.)	30.1 (5.6)	30.2 (5.8)	30.2 (5.4)	0.986
Carlson comorbidity index at transplant, mean (S.D.)	7.7 (4.0)	7.8 (3.9)	7.6 (4.0)	0.367
MELD at Transplant, mean (S.D.)	22.7 (7.6)	22.2 (6.9)	23.2 (8.2)	0.040
Donor Gender Male, N (%)	552 (63.7%)	275 (61.5%)	277 (66.0%)	0.369
Donor Type, N (%)				
CAD	689 (79.5%)	358 (80.1%)	331 (78.8%)	0.280
DCD	162 (18.7%)	89 (19.9%)	73 (17.4%)	0.297
Living Donor	16 (1.8%)	0 (0.0%)	16 (3.8%)	< 0.001
ATG given for induction, N (%)	401 (46.3%)	387 (86.6%)	14 (3.3%)	< 0.001
Acute rejection, N (%)	124 (14.3%)	44 (9.8%)	80 (19.1%)	< 0.001
Time to rejection, days [median, IQR]	131 [30.75-235.25]	139.5 [36.00-281.50]	125.5 [30.00-205.25]	0.326
Time to rejection, days, N (%)				
7-30 days	31 (3.6%)	10 (2.2%)	21 (5.0%)	0.870
31-90 days	16 (1.8%)	7 (1.6%)	9 (2.1%)	
91-365 days	53 (6.1%)	18 (4.0%)	35 (8.3%)	
365 days over	24 (2.8%)	9 (2.0%)	15 (3.6%)	
Death after transplant, N (%)^	102 (11.8%)	70 (15.7%)	32 (7.6%)	0.305
Graft loss after transplant, N (%)^	112 (12.9%)	75 (16.8%)	37 (8.8%)	0.395

*p-value: Chi-square test for categorical variables, and Mann-Whitney U test was used for the continuous variable.
^Survival and graft loss differences were analyzed using Kaplan-Meier curves and log-rank test.

Disclosures: Alexander Scherer: Nothing to Disclose, Andrej Sikoski: Nothing to Disclose, Albert Zhang: Nothing to Disclose, Marco Lacerda: Nothing to Disclose, Marwan Ghabril: Nothing to Disclose, Naga Chalasani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Eric Orman: Sitero: Consultant, Biovie: Advisor, Chandrashekhar Kubal: Nothing to Disclose

3487 | NON-ABO ANTIBODIES AND THEIR IMPACT ON LIVER TRANSPLANT REJECTION: A RETROSPECTIVE STUDY

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Background: Non-ABO antibodies are immune proteins that target blood group antigens outside the ABO system. They are clinically significant in both transfusion medicine and transplantation. Key systems include Rh, Kell, Kidd, Duffy, MNS and Lewis. We decided to undertake a study to determine the correlation between non-ABO antibodies and its association with antibody-mediated rejection, and T cell-mediated rejection (ATCMR). **Methods:** The study evaluated 183 liver transplant recipients over five years, excluding 14 patients (13 due to post-transplant mortality, 1 lost to follow-up) from an initial cohort of 197. Participants were stratified based on non-ABO antibody status: 7 positive and 176 negative. Data on liver allograft rejection episodes were extracted from medical records and categorized as clinically suspected rejection, definite or indeterminate T-cell mediated rejection (TCMR), and definite, indeterminate, or probable antibody-mediated rejection (AMR).

Comparisons between groups utilized Chi-square or Fisher's Exact tests, depending on expected cell counts, with 2×2 contingency tables constructed for each rejection category.

The study protocol received approval from the Institutional Review Board, adhering to ethical standards for research involving human subjects. **Results:** The study aimed to investigate whether the presence of non-ABO antibodies is associated with an increased risk of rejection in transplant patients. While the non-ABO positive group exhibited higher rates of both clinically suspected and biopsy-proven T cell-mediated rejection compared to the non-ABO negative group, these differences did not reach statistical significance. This lack of significance may be attributed to the small sample size of the non-ABO positive group, limiting the study's power to detect meaningful differences.

Gender-based analysis revealed that non-ABO positive females had higher rates of both clinically suspected and biopsy-proven T cell-mediated rejection compared to their non-ABO negative counterparts. However, these differences were not statistically significant. In males, all non-ABO positive patients experienced clinically suspected rejection, with half having biopsy-proven T cell-mediated rejection. These rates were higher than those in non-ABO negative males but did not achieve statistical significance. **Conclusion:** These findings suggest a potential trend toward increased rejection rates in patients with non-ABO antibodies, particularly among females. However, due to the limited sample size, especially in the non-ABO positive group, definitive conclusions cannot be drawn. Further studies with larger cohorts are necessary to validate these observations and to explore the underlying mechanisms contributing to these potential differences.

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Rejection Outcomes by Non-ABO Antibody Status and Gender

Rejection Type	Non-ABO Positive Female (n=5)	Non-ABO Negative Female (n=54)	P-Value (Female)	Non-ABO Positive Male (n=2)	Non-ABO Negative Male (n=122)	P-Value (Male)
Clinically suspected	4(80%)	29 (53.7%)	0.62	2 (100.0%)	55 (45.1%)	0.20
Biopsy-Proven T cell Mediated Rejection	4(80%)	21 (38.9%)	0.14	1 (50%)	34 (27.9%)	0.56
Indeterminate T cell Mediated Rejection	0 (0.0%)	3 (5.6%)	-	0 (0.0%)	2 (1.6%)	-
Definite Antibody Mediated Rejection	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	4 (3.3%)	-
Indeterminate Antibody Mediated Rejection	1 (20%)	1 (1.9%)	-	0 (0.0%)	2 (1.6%)	-
Probable Antibody Mediated Rejection	0 (0.0%)	2 (3.7%)	-	0 (0.0%)	0 (0.0%)	-

Disclosures: Nino Gudushauri: Nothing to Disclose, Irakli Lemonjava: Nothing to Disclose, Irakli Tskhakaia: Nothing to Disclose, Richard Kalman: Gilead: Speaking and Teaching, Victor Navarro: Nothing to Disclose, Salvatore Mignano: Nothing to Disclose, Manjula Balasubramanian: Nothing to Disclose

3488 | CAD-LT SCORE PREDICTS CARDIAC MORTALITY AND GRAFT SURVIVAL IN LIVER TRANSPLANT RECIPIENTS: A RETROSPECTIVE COHORT ANALYSIS

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Background: Cardiovascular disease significantly impacts outcomes in liver transplantation (LT). The CAD-LT score, a risk-stratification tool, may enhance pre-transplant cardiac evaluation yet the score has not been validation in LT cohorts in Asia. This study assesses its predictive utility for post-LT cardiac events and survival in a cohort of middle eastern LT recipients. The aim of the study is to to evaluate the association of CAD-LT scores with cardiac complications, mortality, and graft survival in LT recipients. **Methods:** Retrospective analysis of 745 LT adult recipients (2020–2024). Data included demographics, comorbidities, pre/post-transplant cardiac assessments (echocardiography, nuclear stress tests, cardiac catheterization), and CAD-LT scores (stratified as high-, intermediate-, or low-risk). Outcomes included cardiac events (myocardial infarction [MI], arrhythmias, cardiac death), patient survival, and graft survival. Statistical analyses utilized chi-square tests and Kaplan-Meier survival curves. **Results:** The cohort had median age 56.9 years, 62.9% male, with prevalent comorbidities: diabetes (46.9%), hypertension (33.5%), and obesity (33.5%). CAD-LT scores categorized 41.1% as high-risk, 37.7% intermediate-risk, and 20.1% low-risk. High-risk patients exhibited higher cardiac mortality (12/97 deaths, 12.3%) and MI rates (19/97 events, 19.6%) versus low-risk (1.6% mortality, $p < 0.001$) post-LT. Survival analysis revealed high-risk CAD-LT patients had significantly lower 1-year survival (84.1% vs. 41.2% low-risk, $p < 0.001$) post-LT and graft survival (77.1% vs. 41.2%, $p = 0.003$). Non-obstructive cardiac cath findings correlated with better survival (alive: 289/327 vs. obstructive: 30/37, $p = 0.02$). **Conclusion:** This is the first study to validate CAD-LT in Middle Eastern LT recipients. The CAD-LT score effectively stratifies cardiac risk in LT candidates, with high-risk scores strongly associated with post-transplant mortality, graft failure, and cardiac events. Integration of this tool into pre-LT evaluation may guide tailored management, improving outcomes. Further prospective validation is warranted

Disclosures: Maryam Abdulla: Nothing to Disclose, Waleed Haj Ahmad: Nothing to Disclose, Syeda Shamsi: Nothing to Disclose, Ahmad Alissa: Nothing to Disclose, Dimitri Raptis: Nothing to Disclose, Dieter Broering: Nothing to Disclose, Manhal Izzy: Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Khalid Bzeizi: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Fuat Saner: Nothing to Disclose, Bandar Aljudaibi: Nothing to Disclose

3489 | AN INCREASE IN REGULATORY B CELLS AND A REDUCTION IN T HELPER 17 CELLS PLAY A CRUCIAL ROLE IN ACHIEVING TOLERANCE IN LIVER TRANSPLANTATION

Soon Kyu Lee[1] Seon-Yeong Lee[1] Ho Joong Choi[1] Young Kyoung You[1] Jeong Won Jang[1] Pil Soo Sung[1] Ji Won Han[1] Mi-La Cho[1] Jong Young Choi[1], [1]College of Medicine, The Catholic University of Korea

Background: This study investigates the dynamics of regulatory B cells (Bregs) during immunosuppression (IS) tapering and their contribution to tolerance in liver

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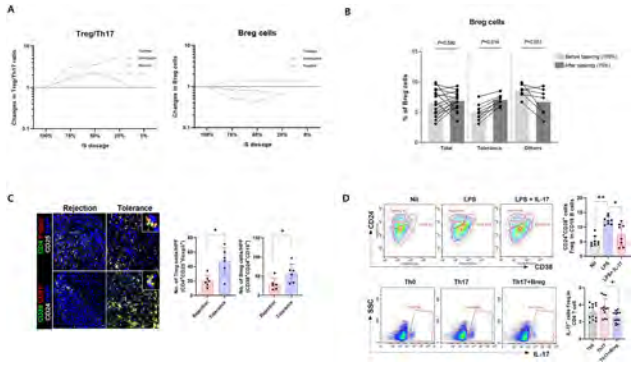
transplantation (LT) patients. **Methods:** We prospectively enrolled 15 LT patients who had normal liver function, no history of rejection, and had undergone LT more than five years ago. Patients were followed up every three months, and IS doses were tapered by 25% every 6–9 months. At each visit, blood samples were collected, and the proportions of T cells and B cells were analyzed by flow cytometry. Confocal microscopy and in vitro analysis were also performed to assess Breg function in LT patients. **Results:** Over a median follow-up of 42 months, eight patients successfully discontinued IS without rejection (tolerance group). One patient experienced rejection (rejection group), while the remaining six patients reduced their IS dose to 25% without rejection (minimization group). During IS tapering, Treg cells and the Treg/Th17 ratio increased in the tolerance group but decreased before rejection in the rejection group (Figure A). Similarly, the tolerance group exhibited an increase in Bregs and the Breg/Th17 ratio, whereas a decrease was observed in the rejection group (Figure A, B). Moreover, a negative correlation between Bregs and Th17 cells and a significant positive association between Bregs and plasmablast B cells were identified. In liver tissue, confocal analysis showed a significant increase in Tregs and Bregs in the tolerance group compared to the rejection group (Figure C). In vitro analysis demonstrated a reduction in Th17 cells following Breg treatment, and vice versa (Figure D). Furthermore, treatment with *Faecalibacterium*, enriched in the tolerance group, led to an increase in Bregs and IL-10 levels. **Conclusion:** During IS tapering, Bregs increase and contribute to the achievement of tolerance in LT patients. These findings suggest that Bregs may serve as potential biomarkers and therapeutic targets for promoting tolerance in LT.



Disclosures: Soon Kyu Lee: Nothing to Disclose, Seon-Yeong Lee: Nothing to Disclose, Ho Joong Choi: Nothing to Disclose, Young Kyoung You: Nothing to Disclose, Jeong Won Jang: Nothing to Disclose, Pil Soo Sung: Nothing to Disclose, Ji Won Han: Nothing to Disclose, Mi-La Cho: Nothing to Disclose, Jong Young Choi: Nothing to Disclose

3490 | CONSEQUENCES OF MELD CUTOFFS AND SCORE TRAJECTORIES IN LIVER TRANSPLANTATION

Tomohiro Tanaka[1] Michael Jones[2] George Wehby[2] David Axelrod[3], [1]University of Iowa School of Medicine, [2]University of Iowa, College of Public Health, [3]University Hospitals

Background: The effects of applying specific MELD score thresholds under the current Acuity Circle (AC) policy, compared to the prior Share-35 (S35) policy, and the consideration of MELD dynamics remain insufficiently examined. This study investigates how MELD-based cutoffs and intra-individual MELD changes and trajectories affect liver transplant (LT) outcomes under current allocation frameworks. **Methods:** We analyzed all adult LT candidates recorded in the OPTN waitlist dataset from January 2016 to Decemer 2023, reformatted into a person-day structure to enable daily event modeling. Candidates who were inactivated on the waitlist or listed as Status 1 were excluded. MELD reflected MELD-Na before July 2023 and MELD 3.0 thereafter, based on the date of the observation. Regression discontinuity was applied at MELD thresholds (35 for S35; 33 and 37 for AC) using pooled logistic regression (PLR) to estimate the causal effect of MELD on transplant offers and completions. Separately, using a 70:30 split into development and validation sets, we constructed PLR models to estimate next-day waitlist death / dropout, defined as death or removal the day after the respective MELD was recorded. Predictors of interest included current MELD, MELD change (absolute ΔMELD), rate of change (ΔMELD/day), and their interactions. Coefficient-based scores reflecting the dynamics of MELD (MELD-DY) were derived using MELD and absolute ΔMELD or ΔMELD/day, with interactions when applicable. **Results:** We evaluated 19,193,222 person-day observations across 63,028 unique patients. Regression discontinuity models revealed that, during the S35 era, the MELD threshold of 35 was associated with marked increases in both offer and transplant rates (RR 2.40; 95% CI: 2.25–2.56 and OR 2.15; 95% CI: 1.83–2.53). In contrast, the AC thresholds showed more modest effects at MELD 33 (RR 1.29; 1.21–1.38 and OR 1.15; 0.92–1.44) and MELD 37 (RR 1.25; 1.10–1.42 and OR 1.38; 1.14–1.67). Absolute ΔMELD was associated with reduced waitlist mortality among patients with lower MELD scores (<28), but with increased mortality in those with higher MELD scores. This crossover was driven by a significant interaction between MELD and ΔMELD ($p < 0.001$). ΔMELD/day was associated with higher waitlist mortality (OR 1.23; 1.21-1.27). In the validation cohort of 1,734 decedents, 211 (12.1%) were reclassified to higher priority with MELD-DY scores

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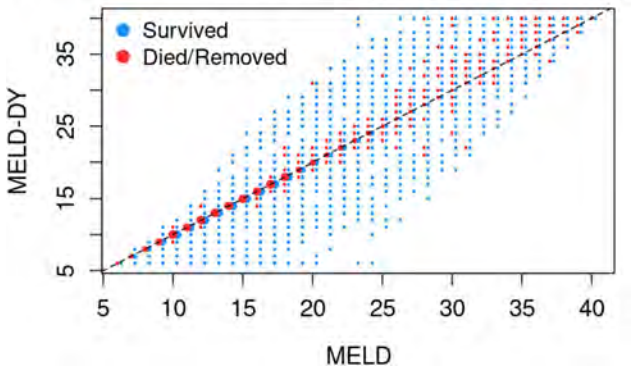
derived from ΔMELD/day compared to the original MELD (Figure), although the concordance index did not differ significantly (0.784 vs. 0.781; p = 0.38). **Conclusion:** MELD thresholds continue to pose challenges to seamless score-based allocation under the Acuity Circle policy. MELD dynamics are significantly associated with waitlist mortality and may enhance future allocation models. Together, these findings highlight the need to move beyond fixed cutoffs toward more continuous, trajectory-informed approaches to MELD-based allocation.

$$MELD_DY = round\left(MELD + 1.20 * \frac{absolute\ \Delta MELD}{Days\ since\ last\ recorded\ MELD}\right)$$



Disclosures: Tomohiro Tanaka: Nothing to Disclose, Michael Jones: Nothing to Disclose, George Wehby: Nothing to Disclose, David Axelrod: Nothing to Disclose

3491 | ILEAL BILE ACID TRANSPORTER INHIBITORS FOR REFRACTORY PRURITUS IN LIVER TRANSPLANT RECIPIENTS: A CASE SERIES

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Background: Persistent pruritus after liver transplantation (LT) can significantly impact quality of life and is often linked to biliary complications. Standard treatments may be ineffective. Ileal bile acid transporter (IBAT) inhibitors, such as odevixibat and maralixibat, have demonstrated efficacy in treating cholestatic pruritus in other contexts but remain underexplored in the post-LT setting. **Methods:** We present three liver transplant recipients with persistent, treatment-resistant pruritus who were treated with IBAT inhibitors. Clinical response, tolerability, and impact on immunosuppression levels were assessed. **Results:** Case 1: A 56-year-old male living donor LT recipient developed persistent pruritus six weeks post-transplant due to biliary strictures requiring repeated endoscopic retrograde cholangiopancreatographies (ERCPs) and stenting. Pruritus persisted despite standard treatments. Odevixibat 3600 mcg daily was initiated nine months post-LT, leading to significant symptom improvement. Early diarrhea resolved within days. Pruritus remained controlled until acute rejection and recurrent biliary complications caused transient recurrence. Symptoms remained manageable on odevixibat. Tacrolimus levels remained stable and in goal on IBAT therapy.
Case 2: A 49-year-old female living donor LT recipient developed pruritus three weeks post-LT, coinciding with a bile leak and biliary stricture requiring ERCP and stenting. Symptoms persisted despite standard treatments. Odevixibat 3600 mcg daily was initiated 10 months post-LT, resulting in near-complete pruritus resolution. Six weeks later, she was hospitalized for diarrhea of unclear etiology, but symptoms improved without stopping IBAT therapy. Immunosuppression levels remained stable, and pruritus control persisted.
Case 3: A 31-year-old female deceased donor LT recipient, transplanted at 22 months old, developed pruritus 27 years post-LT during pregnancy. Symptoms continued postpartum despite standard treatments. Maralixibat 28.5 mg daily was started 29 years post-LT, leading to significant improvement, with itching reduced to 1–2 days per week. She continued hydroxyzine and doxepin as needed but reports improved quality of life. Tacrolimus levels remained stable without dose adjustment. **Conclusion:** IBAT inhibitors may represent a safe and effective option for managing refractory pruritus in liver transplant recipients, with potential benefits extending beyond symptom control to meaningful improvements in quality of life. Importantly, these agents were well-tolerated and did not disrupt immunosuppressive regimens or graft function. Given the significant burden of post-LT pruritus and the limited efficacy of existing treatments, further prospective studies are warranted to evaluate long-term safety, efficacy, and optimal clinical use of IBAT inhibitors in this population.

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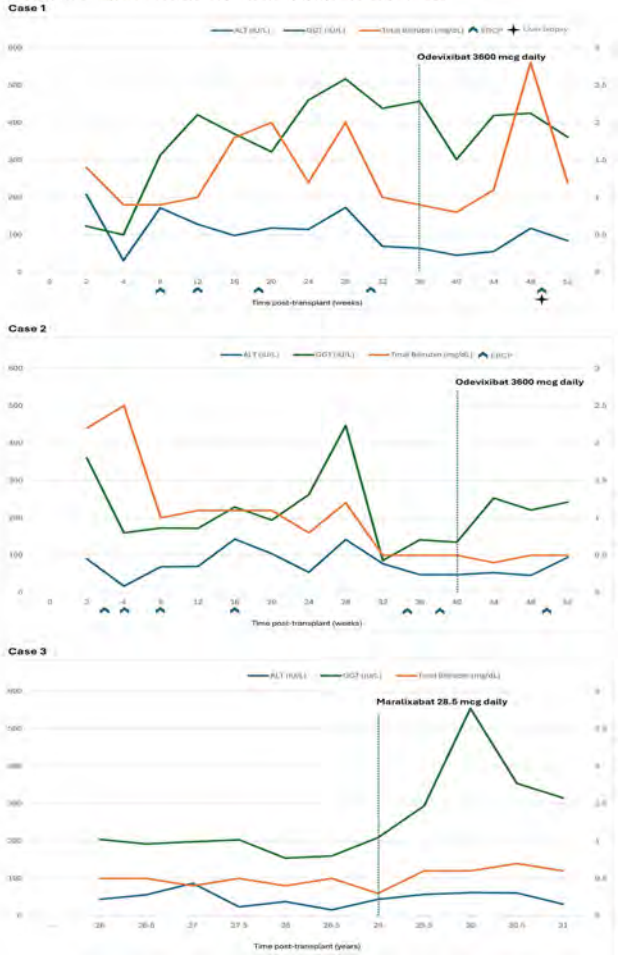
Table 1. Baseline characteristics and pruritis treatment

Case	Patient	Indication for LT	Transplant Type	Medications for pruritis	IBAT agent	IBAT initiation
1	56-year-old Black Male	Autoimmune hepatitis/ Primary sclerosing cholangitis Hepatocellular carcinoma	Living Donor	• Naltrexone 50 mg daily • Ursodiol 300 mg three times daily • Cholestyramine 4000 mg daily • Hydroxyzine 25 mg every 8 hours PRN	Odevixibat 3600 mcg (40 mg/kg) daily	9 months post-LT
2	49-year-old White Female	Metabolic dysfunction-associated steatotic liver disease (MASLD) Alpha 1 Antitrypsin Deficiency	Living Donor	• Loratadine 10 mg daily • Ursodiol 300 mg three times daily • Hydroxyzine 25 mg every 8 hours PRN	Odevixibat 3600 mcg (40 mg/kg) daily	10 months post-LT
3	31-year-old White Female	Biliary Atresia Alagille Syndrome	Deceased Donor	• Doxepin 20 mg nightly • Ursodiol 300 mg twice daily • Hydroxyzine 25 mg every 8 hours PRN	Maralixibat 28.5 mg (0.38 mg/kg) daily	29 years post-LT

Figure 1. Liver function test changes relative to IBAT inhibitor initiation



Disclosures: Mary Chandran: Nothing to Disclose, Shaurya Prakash: Nothing to Disclose, Neil Shah: GSK: Advisor, Ipsen: Advisor, GSK: Consultant, Ipsen: Consultant

3492 | SEX MISMATCH AND BODY SIZE MISMATCH IN DECEASED DONOR LIVER TRANSPLANTATION IN THE UNITED STATES: MISMATCHING IS ASSOCIATED WITH WORSE OUTCOMES

Nolberto Jaramillo[1] Bryan Cabrera Valdes[1] Maria Mosquera[1] Ryosuke Misawa[1] Seigo Nishida[1] Kenji Okumura[1], [1]Westchester Medical Center

Background: Sex-based differences exist not only in waitlist but also in post-transplant outcomes. Sex mismatch may be associated with increased mortality in heart transplantation, however, this remains unknown in liver transplantation (LT). The aim of this study is to assess sex mismatch in LT recipients in a nationwide cohort. **Methods:** Adult deceased donor LT recipients between January 2004 and December 2023 in the UNOS database were included in this study. Multi-organ transplant and re-transplant cases were excluded. Body surface area index (BSAi), defined as the ratio of donor BSA to recipient BSA, was used to categorize the size match (small-for-size: BSAi < 0.78; normal-for-size BSAi 0.78-1.24; large-for-size BSAi > 1.24). **Results:** A total of 124,192 recipients (sex match: female recipient F-F N = 20,155 and male recipient M-M N = 52,709; sex mismatch: female recipient F-M N = 21,472 and male recipient M-F N = 29,856) were identified during the study period. Small-for-size grafts were seen more in the female to male group (18%) and large-for-size grafts were seen more in the male to female group (15%) ($P < 0.001$).

Unadjusted analysis showed that male recipients of female grafts had an increased risk of 5-year graft failure (hazard ratio [HR]: 1.08; 95% confidence interval [CI]: 1.05, 1.12; $P < 0.001$) and 1-year graft failure (HR: 1.13; 95% CI: 1.08, 1.18; $P < 0.001$) compared to male recipients of male grafts. Multivariable Cox regression analysis showed that sex mismatch was associated with 5-year graft failure (HR: 1.04; 95% CI: 1.01-1.06; $P = 0.007$) and 1-year graft failure (HR: 1.05; 95% CI: 1.01-1.09; $P = 0.008$). In the F-F group, small-for-size and large-for-size were associated with graft failure and mortality. In M-M and M-F groups, small-for-size was associated with 1-year graft failure and mortality but not large-for-size. In F-M, large-for-size was associated with 1-year graft failure and mortality but not small-for-size.

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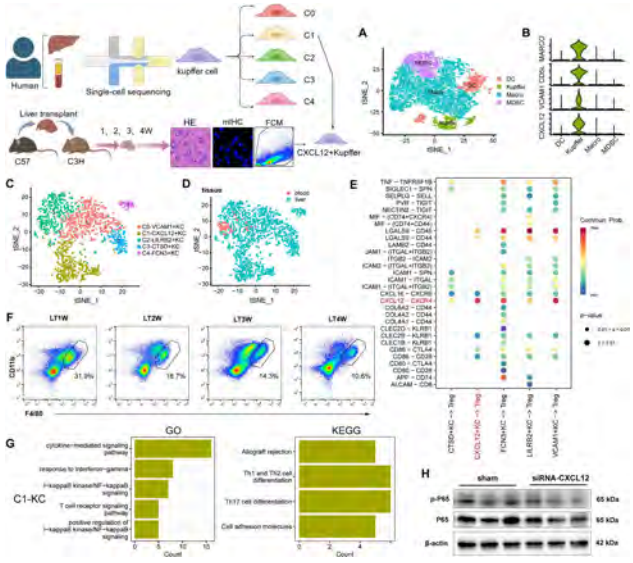
Conclusion: Sex mismatching is associated with post-transplant mortality and graft failure. In addition to sex matching, body size mismatch was also associated with post-transplant mortality and graft failure.
Disclosures: Nolberto Jaramillo: Nothing to Disclose, Bryan Cabrera Valdes: Nothing to Disclose, Maria Mosquera: Nothing to Disclose, Ryosuke Misawa: Nothing to Disclose, Seigo Nishida: Nothing to Disclose, Kenji Okumura: Nothing to Disclose

3493 | SINGLE CELL RNA-SEQUENCING REVEALS IMMUNOMODULATORY ROLE OF HEPATIC CXCL12+ KUPFFER CELLS IN TREG-MEDIATED LIVER GRAFT TOLERANCE THROUGH CXCR4 AXIS

Yurong Luo[1] Jinzhen Cai[1], [1]The Affiliated Hospital of Qingdao University

Background: Acute rejection after liver transplantation involves the participation and interaction of various immune cells. Kupffer cells (KCs) regulate the inflammatory and immune environment in the graft region by secreting multiple chemokines and cytokines. CXCL12 (SDF-1) and its receptor CXCR4 play key roles in immune cell migration, activation, and regulation, with their significance in liver transplantation gaining increasing attention. **Methods:** Single-cell sequencing and mIHC were used to analyze clinical samples from patients with mild, severe and chronic rejection, as well as liver transplant model samples from mice at different stages of rejection. C57BL/6 to C3H acute rejection model was established. At 1, 2, 3, and 4 weeks post-transplant, FMC, H&E staining, and IHC were used to assess surface markers and functional changes in KC subsets. Macrophage and Treg subsets in the liver, spleen, lymph nodes, bone marrow, and peripheral blood were also monitored. In vitro, primary human and mouse KCs and $CD4^+$ T cells were isolated, and a co-culture system was established by KC transfection. Enrichment analysis and WB were performed to investigate underlying signaling pathways. **Results:** This study analyzed macrophage heterogeneity and gene expression, identifying five distinct KC subsets, with $CXCL12^+$ KCs gene expression, identifying five distinct KC subsets, with $CXCL12^+$ KCs primarily located in Cluster C1. We revealed interactions and functional differences between human and mouse KC subsets and Tregs during liver transplant rejection, with a notable activation of the NF-κB signaling pathway. Further analysis indicated that ligand-receptor signaling between $CXCL12^+$ KCs and Tregs significantly increased during rejection. $CXCL12^+$ KCs likely play a crucial role throughout the rejection process, especially during acute and chronic phases. In early acute rejection, $CXCL12^+$ KCs were highly adjacent to $CXCR4^+$ Tregs, suggesting potential immunoregulatory interactions. Experimental validation showed dynamic immune cell changes, with $CXCL12^+$ KCs and $CXCR4^+$ Tregs significantly colocalizing in early acute rejection. Additionally, we explored the role of immune cell dynamics in liver transplant tolerance. In vitro, CXCL12 enhanced KC regulation of Treg proliferation via NF-κB pathway activation, providing a novel therapeutic target for immune tolerance and regulation in liver transplant rejection. **Conclusion:** This study found that the expression specificity of CXCL12 was increased in KCs during acute liver rejection, and the ligand receptor signaling between CXCL12+Kupffer cells and CXCR4 +Treg was significantly enhanced. CXCL12 activated the NF-κB signaling pathway in KCs, thereby promoting Treg cell activation and enhancing immune tolerance, providing a possible new target for clinical treatment.



Disclosures: Yurong Luo: Nothing to Disclose, Jinzhen Cai: Nothing to Disclose

3494 | SEVERE ACTIGRAPHY-MEASURED SLEEP DYSFUNCTION IS ASSOCIATED WITH DISEASE SEVERITY AND POOR QUALITY OF LIFE IN ADVANCED CHRONIC LIVER DISEASE: UK PROSPECTIVE CASE-CONTROL STUDY

Felicity Williams[1] Jonathan Quinlan[2] Amritpal Dhaliwal[3] Leigh Breen[1] Carolyn Greig[1] Ahmed Elsharkawy[3] Thomas Marjot[4] Alex Rowlands[5] Janet Lord[1] Matthew Armstrong[3], [1]University of Birmingham, [2]University of Birmingham, UK, [3]University Hospitals Birmingham NHS Foundation Trust, [4]University of Oxford, [5]University of Leicester

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Background: Prevalence of patient-reported sleep disturbance is high in advanced chronic liver disease (AdvCLD), but objective, home-based evidence is lacking. To effectively treat sleep disturbance in AdvCLD, a thorough understanding of variability (vs other disease populations), predictors and impact of sleep disturbance is needed. Using wrist-worn actigraphy, we aimed to investigate (a) sleep indices in AdvCLD compared to healthy controls (HC) and chronic inflammatory disease (CID; inflammatory bowel or arthritis), (b) predictors of poor sleep and (c) the impact on quality of life (QoL). **Methods:** Outpatients with AdvCLD awaiting liver transplant, in parallel to age/sex matched CID and HC were recruited from Birmingham, UK. All wore a GENEActivâ wrist accelerometer for 14-days at home. Clinical characteristics, disease severity (UKELD), and quality of life (QoL) (Chronic liver disease questionnaire [CLDQ]) were recorded. Sleep window, sleep onset, the midpoint of sleep, sleep duration (excluding any waking periods during the sleep window) and sleep efficiency were calculated for each valid day and averaged across all valid days. **Results:** 44 AdvCLD (63% male, mean age 54, UKELD 52, 50% ArLD), 13 CID (46% male, age 45) and 17 HC (59% male, age 47) participants were recruited. The AdvCLD group had a later sleep onset (mean[standard deviation (SD)] 00:01[1.76] vs 22:56[0.84hrs], $p = 0.02$, 95% CI -2.01 to -0.17hrs) and midpoint (03:55[1.73] vs 03:01 [0.81], $p = 0.02$), shorter sleep duration (5.99hrs[1.34] vs 6.95hrs[0.88], $p = 0.01$, 95% CI 0.23 to 1.68hrs) and lower sleep efficiency (77.8%[7.35] vs 85.4%[9.06], $p = < 0.001$) compared to HC (Fig. 1A&C). Additionally, sleep duration (5.99hrs[1.34] vs 6.95hrs[0.92], $p = < 0.001$ 95% CI 2.81 to 11.9hrs) and efficiency (77.8%[7.35] vs 84.8%[6.5], $p = 0.02$ 95% CI 0.17 to 1.76%) were significantly less compared to those with CID (Fig. 1B&D). Worse sleep efficiency was associated with increased fatigue and reduced emotional function ($r = 0.37$ $p = 0.02$; $r = 0.37$, $p = 0.03$, respectively). UKELD independently predicted sleep duration ($B = -1.58$, $p = 0.02$). Longitudinal assessment ($n = 13$) showed liver transplant for AdvCLD improved sleep window and sleep duration (7.2hrs[1.4] vs 8.8hrs[1.9], $p = 0.003$, 95% CI 0.66-2.53hrs; 5.5hrs[0.9] vs 6.9hrs [1.5], $p = 0.003$ 95% CI 0.58-2.17hrs, respectively). **Conclusion:** Patients with AdvCLD have significantly worse actigraphy-measured sleep disturbances (onset, duration, efficiency) compared to healthy individuals and patients with other chronic inflammatory conditions. Sleep disturbance was independently predicted by disease severity, and negatively associated with QoL measures, but improved with liver transplant. Tailored sleep interventions in AdvCLD are required to enhance patient QoL, with particular focus on those patients with severe disease.

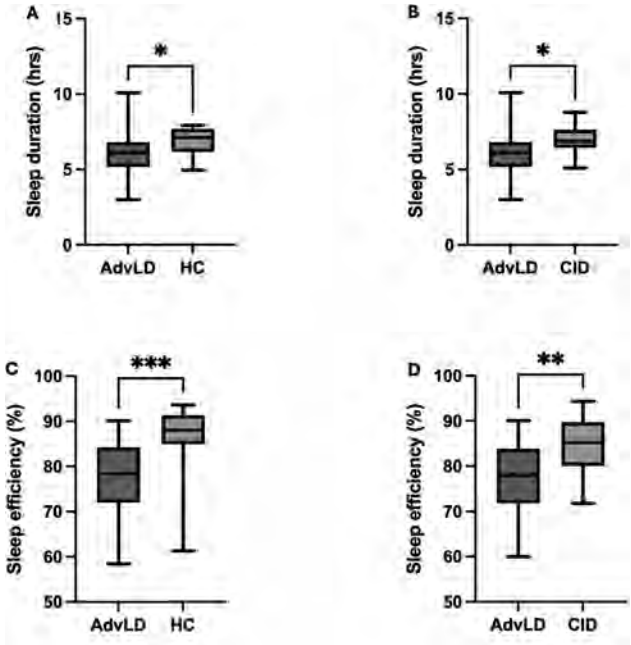

Figure 1. Comparison of sleep duration and efficiency between patients with advanced chronic liver disease (AdvLD), healthy controls (HC), and chronic inflammatory disease (CID)

A: Comparison of sleep duration between AdvLD and HC

B: Comparison of sleep duration between AdvLD and CID

C: Comparison of sleep efficiency between AdvLD and HC

D: Comparison of sleep efficiency between AdvLD and CID

Key: **<0.05, **<0.01, ***<0.001*

Disclosures: Felicity Williams: Nothing to Disclose, Jonathan Quinlan: Nothing to Disclose, Amritpal Dhaliwal: Nothing to Disclose, Leigh Breen: Nothing to Disclose, Carolyn Greig: Nothing to Disclose, Ahmed Elsharkawy: Gilead: Advisor, GSK: Advisor, Ipsen: Advisor, Alfasigma: Advisor, Thomas Marjot: Nothing to Disclose, Alex Rowlands: Nothing to Disclose, Janet Lord: Nothing to Disclose, Matthew Armstrong: Nothing to Disclose

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3495 | SUPERIOR BIOAVAILABILITY OF TACROLIMUS IN LIVER TRANSPLANT RECIPIENTS TREATED WITH EXTENDED-RELEASE LCP-TACROLIMUS (ENVARSUS) COMPARED TO PROLONGED-RELEASE TACROLIMUS (ADVAGRAF) AFTER 12 WEEKS OF CONTROLLED THERAPY WITHIN A MULTICENTRE, RANDOMISED, CONTROLLED CLINICAL TRIAL ("ENGRAFT")

Hans Schlitt[1] Ben James[2] Ines Holub-Hayles[2] Edward Geissler[2] The Germany EnGraft Study Group[3], [1]Surgery, Univ. Hosp. Regensburg, [2]Univ. Hosp. Regensburg, Germany, [3]Germany

Background: Oral tacrolimus formulations exhibit low and variable bioavailability, leading to high dose requirements and dose-dependent toxicities. Our clinical trial in liver transplant recipients tests if extended-release LCP tacrolimus (LCPT, administered as Envarsus®) improves systemic tacrolimus exposure per milligram of drug versus prolonged-release tacrolimus (PR-Tac, administered as Advagraf™); potential pharmacokinetic and clinical outcome advantages are also explored. **Methods:** Between December 2020 and October 2023, the planned 268 liver transplant recipients were enrolled at 15 German sites in a phase IV, investigator-initiated trial sponsored by the University Hospital Regensburg ("EnGraft"; EUCT: 2024-518033-28-00) and funded in part by Chiesi GmbH. Participants were randomised 1:1 within 14 days post-transplant to a standard immunosuppressive regimen containing either once-daily LCPT (test) or once-daily PR-Tac (comparator). After a 12-week *Controlled Treatment Phase*, blood tacrolimus trough levels were centrally measured to mitigate bias and the dose-normalised trough concentration (C/D ratio) was calculated as an estimate of drug bioavailability (primary endpoint; two-sided $\alpha = 0.05$; 90% power to show a difference of 0.4 ng/ml mg^{-1} in C/D ratio). Clinical parameters are being collected during a 3-year *Follow-up Phase* to explore whether a superior C/D ratio confers longer-term benefits. **Results:** The *Controlled Treatment Phase* was completed in 2024 and analysed in 2025. In 243 (90.7%) patients producing primary endpoint data, a highly statistically significant difference between the mean C/D ratio measured in the LCPT arm (1.80 ng/ml mg^{-1}) and the PR-Tac arm (1.13 ng/ml mg^{-1}; $p < 0.0001$, ANCOVA) was characterised by similar mean blood trough levels across both groups (7.6 mg/ml LCPT; 7.3 mg/ml PR-Tac), but an appreciably lower mean daily dose in the LCPT arm (5.7 mg/day LCPT; 8.1 mg/day PR-Tac). Rates of biopsy-proven rejection (2.3% LCPT; 4.5% PR-Tac) and *de novo* tremor (18.2% LCPT; 21.8% PR-Tac) were not substantially different. Kidney function at 12 weeks shows a similar decreasing trend. The 3-year *Follow-up Phase* is currently ongoing. **Conclusion:** For the first time in liver transplantation, superior bioavailability of LCPT has been unequivocally demonstrated in a large, multicentre, prospective study statistically powered to test the C/D ratio as a primary endpoint. After the last study visit in October 2026, the final analysis will reconcile drug pharmacokinetics with long-term efficacy and safety data.

Disclosures: Hans Schlitt: Chiesi: Grant to own institution, Sanofi China: Speaking and Teaching, Ben James: Chiesi Germany GmbH: Consultant, Chiesi Germany GmbH: Grant/Research Support, Ines Holub-Hayles: Nothing to Disclose, Edward Geissler: Chiesi GmbH: Fund in-part an investigator initiated clinical trial, The Germany EnGraft Study Group: Nothing to Disclose

3496 | CLOSING THE GAP: THE IMPACT OF A CULTURALLY AND LINGUISTICALLY TAILORED LIVER TRANSPLANT PROGRAM

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Background: Hispanic patients represent the largest minority group on the liver transplantation (LT) waiting list. The Hispanic Transplant Program (HTP) at Northwestern Memorial Hospital (NMH) was created in 2006 to provide culturally and linguistically competent and congruent care to remove barriers to kidney transplantation. This program led to a 91% increase in waiting list additions and a 74% and 62% increase in living donor kidney transplants (LDKT) and deceased donor kidney transplants (DDKT), respectively. The mean annual ratio of Hispanics to Non-Hispanic Whites (NHW) increased by 70% in LDKT and 43.8% in DDKT, suggesting a significant reduction in disparities between Hispanics and NHW. In 2010, the program expanded to include liver transplantation services, forming the Hispanic Liver Transplant Program (HLTP). The HTP was adapted from an English-only program that incorporates Spanish in all patient-facing materials, employs a bilingual and bicultural staff, and addresses deep seated cultural values for Hispanic transplant candidates. No resources were diverted from the English-speaking program towards the HTP. **Methods:** Program-specific data from the OPTN center data for NMH as of 11/30/2024, were used to assess changes in transplant program characteristics before (1999-2009) and after (2011-2021) HLTP implementation. Data collection included the number of waiting list additions, living donor liver transplants (LDLTs), and deceased donor liver transplants (DDLTs) for both Hispanics and NHWs. The percent change of LDLTs and DDLTs between the pre-HLTP period and post-HLTP period was calculated. The mean annual ratio of Hispanic to NHW patients was calculated for LDLTs and DDLTs using the formula ([Hispanic LDLT / All LDLT] / [NHW LDLT / All LDLT]) to evaluate disparities in transplant access. Unpaired t-tests were performed to compare differences in the mean annual ratios between the two time periods. **Results:** During the post-HLTP period, Hispanic waiting list additions rose by

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69%, LDLTs by 89%, and DDLTs by 99%. The mean annual ratio for Hispanic to NHWs increased by 13% (pre-HLTP: 0.15; post-HLTP: 0.16; $p = 0.85$). The DDLT ratio rose significantly by 85% (pre-HLTP: 0.11; post-HLTP: 0.21; $p < 0.001$). Among NHWs, waiting list additions decreased by 24%, LDLTs by 12%, while DDLTs increased by 14%. **Conclusion:** Culturally competent programs can offer a scalable strategy to increase access to LT among Hispanic patients. The number of Hispanic patients added to the waiting list, LDLTs, and DDLTs increased in the post-transplant period, suggesting that the HTP potentially contributed to increased awareness, subsequent access, and acceptance of LT services. Since the establishment of the HTP, new centers have taken the initiative to implement this model of transplant care into their own programs. The center-level and national-level impact of these programs should be assessed in future studies.

	NHW			Hispanic			Mean Ratio (SD)			
	Pre HLTP (1999-2009)	Post HLTP (2011-2021)	% Change	Pre-HLTP (1999-2009)	Post-HLTP (2011-2021)	% Change	Pre HLTP (1999-2009)	Post HLTP (2011-2021)	% Change	p-value
Waiting List Additions	1495	1129	-24	145	248	69	-	-	-	-
LDLT	114	100	-12	9	17	89	0.15 (.28)	0.16 (.16)	13	0.85
DDLT	658	752	14	79	157	99	0.11 (.04)	0.21 (.03)	85	<0.001

1. Liver Transplant metrics between the Pre-HLTP and Post-HLTP period at NMH

Disclosures: Luis Lopez: Nothing to Disclose, Gonzalo Hagerman-Sucar: Nothing to Disclose, Juan Caicedo-Ramirez: Nothing to Disclose

3497 | A STEPWISE INSTITUTIONAL PROGRESSION TO TOTAL ROBOTIC LIVER TRANSPLANTATION: FIRST U.S. EXPERIENCE USING BOTH DECEASED AND LIVING DONOR GRAFTS

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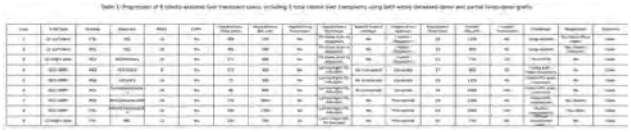
Background: Robotic liver transplantation (RLT) remains a technical frontier in minimally invasive liver surgery, with only a handful of programs worldwide having completed total robotic liver transplantation (TRLT). We report the stepwise progression of our New York-based program culminating in three consecutive TRLTs in April–May 2025, becoming the first U.S. center to perform TRLT using both deceased and living donor grafts. **Methods:** We retrospectively reviewed nine RLT cases performed between 2023 and 2025, evaluating recipient and donor selection, graft type, surgical technique for hepatectomy and implantation, incision approach, intraoperative conversions, anastomotic times, blood loss, reoperations, and transplant outcomes. **Results:** The first three cases employed a hybrid approach: robotic native hepatectomy with open implantation of partial grafts from laparoscopic living donor hepatectomy. During our transition to robotic donor hepatectomy (RDH), logistical limitations in robotic team availability redirected our TRLT efforts toward whole grafts from deceased donors. Of five such cases, three required conversion, while the last two were completed entirely robotically. After this experience, and once we were able to run two simultaneous robotic teams, we successfully performed a TRLT using a right lobe graft fully recovered robotically from a living donor. Indications and outcomes were consistent with accepted transplant standards (Table 1). Technical refinements included a left-to-right piggyback hepatectomy, partial caval clamping for side-to-side cavocavostomy, omission of venovenous bypass, and Pfannenstiel incision with hand assistance. Prior U.S. reports described TRLT using only deceased donors (Washington University) or only living donors (Virginia Commonwealth University), but not both. **Conclusion:** To our knowledge, we are the first program in the United States to complete TRLT using both deceased-donor and living-donor grafts. Our stepwise progression and cumulative experience confirm the feasibility and reproducibility of a technically simplified approach adapted from prior reports and our own institutional refinement. This evolution underscores the importance of strategic program development, dual-robotic team capability, and progressive case complexity—laying the foundation for broader, safe adoption of TRLT in centers with advanced minimally invasive liver surgery expertise.



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3498 | SUBJECTIVE SLEEP DISTURBANCE, OBJECTIVE SLEEP QUALITY, AND PATIENT REPORTED QUALITY OF LIFE: INTERIM RESULTS: FROM THE MULTI-CENTER LIVCOG COHORT STUDY

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Background: Subjective poor sleep is common among liver transplant recipients (LTRs). Further study of relationships between objective sleep measures, reported sleep-quality, and quality of life (QoL) measures is needed. **Methods:** This is an interim analysis of the prospective NIDDK-funded LivCog cohort study, which investigates LTR cognition, QoL,

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health behaviors, and outcomes. At 3-, 12- and 24-months post-LT participants wore a wrist Actigraph (ActiGraph GT3X-BT) for 8 consecutive days to measure time in bed, sleep duration, and sleep efficiency (percent time spent sleeping while in bed). Indicator variables for sleep quality were created for short sleep duration (<6h), poor sleep efficiency (<80%), and late sleep timing (sleep midpoint after 4:00am). Patient reported QoL measures include PROMIS Depression, Anxiety, Pain, Fatigue, Social Isolation, and Sleep Disturbance (T-Score >55). We modeled each QoL measure using the generalized estimating equations (GEE) version of logistic regression, adjusted for age, sex, liver disease diagnosis, pre-transplant hepatic encephalopathy (HE), and month of follow-up. **Results:** Among n = 174 LTRs, median age is 55 (IQR 50-63); 84.3% are white; 63.95% are male; 25.6% had alcohol associated liver disease (ALD); 20.1% had MASLD/MASH;16.3% had hepatocellular carcinoma (HCC); and 50.58% had pre-LT HE. At 3 months post-LT, 32.6% reported subjective sleep disturbance, and Actigraphy data showed that 39.5% had short sleep duration; 21.5% had poor sleep efficiency; and 26.7% had late sleep timing. Pre-transplant HE (OR = 3.30 95%CI: 1.45, 7.71) and short sleep duration were significantly associated with subjective sleep disturbance (OR = 2.74; 95%CI: 1.18, 6.40). Poor sleep efficiency was significantly associated with anxiety (OR = 3.10; 95%CI: 1.18, 8.84); late sleep timing was significantly associated with fatigue (OR = 2.29; 95%CI: 1.04, 5.08), social isolation (OR = 2.99; 95%CI: 1.20, 7.47), and subjective sleep disturbance (OR = 2.89; 95%CI: 1.31, 6.35). Additionally, subjective sleep disturbance was predictive of anxiety (OR = 3.81; 95%CI: 1.73, 8.39), pain (OR = 2.50; 95%cI: 1.16, 5.39), and fatigue (OR = 3.07; 95%CI: 1.39, 6.80). **Conclusion:** Both actigraphy collected sleep data and patient reported sleep disturbance are associated with poorer patient reported QoL measures. Pre-transplant HE is associated with subjective sleep disturbance.

Table 1. Covariate-adjusted odd ratios (OR). PROMIS score indicator is the outcome (separate models) and sleep quality indicator is the exposure of primary interest.

	PROMIS Score (>55) Domain					
Impaired sleep Quality Indicator	Depression	Anxiety	Pain	Fatigue	Social Isolation	Sleep Disturbance
Total sleep <6 hours	0.64	1.38	1.08	0.77	0.94	2.74*
Sleep efficiency <80%	2.07	3.10*	0.81	1.27	1.22	0.85
Sleep mid-point after 4:00 a.m.	1.00	1.36	1.32	2.29*	2.99*	2.89*
PROMIS T-score >55 Sleep disturbance	2.06	3.81*	2.50*	3.07*	2.14	n/a

*Statistically significant (p<0.05); higher PROMIS scores=worse symptoms

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3499 | GEOGRAPHIC DISTANCE AND IMMUNOSUPPRESSIVE ADHERENCE IN LIVER TRANSPLANT PATIENTS

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Background: Geographic and rural-urban disparities are known to impact health outcomes, but remain understudied in adult liver transplant populations. Our transplant center has outreach clinics extending up to 160 miles from the main hospital. We aim to evaluate the impact of distance from our transplant center on medication adherence and clinical outcomes. **Methods:** We conducted a single-center, retrospective cohort study of adult liver transplant recipients (greater than 18 years) who underwent transplant at Loyola University Medical Center from 09/2012-05/2023. Inclusion required ≥ 3 tacrolimus trough levels between 1–6 years post-transplant with exclusion of levels drawn after biopsy-confirmed rejection. We measured the Medication Level Variability Index (MLVI) which is the standard deviation of Tacrolimus troughs to determine adherence. Demographics, SIPAT, and Charlson and Elixhauser comorbidity indexes were collected. Distance and drive time were calculated via Google Maps from home Zip Code to transplant center. The primary outcome was non-adherence as defined by an MLVI >2.0. Secondary outcomes included death and re-transplantation. Multivariable logistic regression was used to assess associations between distance from transplant center and outcomes. **Results:** Of the 365 patients included, 246 (67.4%) were male. The mean age at transplant was 58.16 years with a mean MELD of 25.44 at transplant. The range of distances was from 1.4 miles up to 366 miles. Of the patients, 176 lived less than 25 miles, 88 lived 25 to 50 miles, 57 lived 50 to 100 miles, and 44 lived greater than 100 miles from the center. Patients living <25 miles from the center were older and with higher Charlson (p = 0.024) and Elixhauser (p = 0.002) comorbidity indices. Multivariable logistic regression showed those living 25-50 miles away had significantly lower odds of non-adherence (OR 0.44, 95% CI 0.20-0.94, p = 0.038) compared to those within 25 miles. Otherwise there was no significant differences in adherence at other distances. There was no difference in mortality based on distance. **Conclusion:** In this cohort of liver transplant recipients, geographic distance from the transplant center was not associated with worse immunosuppressive adherence. Although comorbidities differed

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significantly, they did not affect outcomes with our analyses. Interestingly, patients living 25 to 50 miles away had significantly better adherence, but the significance is unclear. These findings suggest that factors beyond proximity influence adherence and mortality.

Table 1: Demographics and Multivariable Analysis

Characteristic	Overall, N = 385	1: <25, N = 176	2: 25-50, N = 88	3: 50-100, N = 57	4: >=100, N = 44	p-value
Age at Tx (y)						0.044
Mean (SD)	56.16 (10.14)	59.35 (10.12)	54.41 (9.49)	57.90 (10.52)	57.26 (10.68)	
Median (Range)	60.29 (21.71, 75.20)	61.63 (29.61, 74.47)	56.05 (29.35, 71.96)	60.25 (28.97, 75.30)	58.96 (21.71, 72.35)	
Gender						0.098
F	119 (32.60%)	64 (36.36%)	32 (36.36%)	12 (21.05%)	11 (25.00%)	
M	246 (67.40%)	112 (63.64%)	56 (63.64%)	45 (78.95%)	33 (75.00%)	
MELD at tx						0.906
Mean (SD)	25.44 (9.49)	25.11 (9.21)	25.60 (9.71)	24.19 (9.15)	26.11 (10.53)	
Median (Range)	27.00 (6.00, 40.00)	27.00 (6.00, 40.00)	27.00 (6.00, 40.00)	25.00 (9.00, 40.00)	30.00 (8.00, 40.00)	
Death	16 (4.38%)	10 (5.68%)	1 (1.14%)	1 (1.75%)	4 (9.09%)	0.088
Charlson Comorbidity Index at tx						0.024
Mean (SD)	7.05 (2.95)	7.55 (3.18)	6.85 (2.79)	6.51 (2.52)	6.14 (2.48)	
Median (Range)	7.00 (0.00, 19.00)	7.00 (1.00, 19.00)	7.00 (0.00, 14.00)	7.00 (0.00, 13.00)	6.00 (3.00, 12.00)	
Elixhauser Comorbidity Index at tx						0.002
Mean (SD)	2.85 (1.51)	3.10 (1.58)	2.88 (1.52)	2.51 (1.24)	2.30 (1.30)	
Median (Range)	3.00 (0.00, 9.00)	3.00 (0.00, 9.00)	3.00 (0.00, 7.00)	2.00 (0.00, 6.00)	2.00 (1.00, 6.00)	
Taco STDev						0.247
Mean (SD)	1.92 (1.05)	2.05 (1.22)	1.71 (0.89)	1.87 (0.78)	1.79 (0.79)	
Median (Range)	1.61 (0.15, 7.53)	1.89 (0.26, 7.53)	1.44 (0.15, 5.14)	1.61 (0.58, 4.12)	1.63 (0.73, 4.56)	
Taco STDev > 2	123 (33.88%)	67 (38.29%)	21 (23.86%)	19 (33.93%)	16 (36.36%)	0.127

Group	Characteristic	Global p-value	N	OR	95% CI	p-value
Multivariable Analysis	Age at Tx (y)		239	0.99	0.96, 1.03	0.67
	Gender		239			
	Female			—	—	
	Male			0.78	0.41, 1.47	0.43
	Race	0.044	239			
	Asian			—	—	
	Black			0.26	0.04, 1.50	0.13
	Hispanic			3.49	0.35, 82.9	0.33
	Other			0.59	0.14, 2.54	0.47
	White			0.32	0.08, 1.24	0.092
	Etiology	0.52	239			
	Alcohol			—	—	
	NAFLD/NASH			1.24	0.52, 2.95	0.62
	Other			2.06	0.54, 7.51	0.27
	Hepatitis B/C			0.76	0.33, 1.83	0.57
	PSC/PBC			0.51	0.07, 2.59	0.46
	Sipal Score		239	1.02	0.99, 1.05	0.23
	Elixhauser Comorbidity Index at Tx		239	1.06	0.86, 1.34	0.51
	Creatinine STDev		239	2.71	1.48, 5.46	0.002
	Categorized Distance	0.17	239			
	1: <25			—	—	
	2: 25-50			0.44	0.20, 0.94	0.038
	3: 50-100			1.04	0.42, 2.62	0.93
	4: ≥100			0.81	0.26, 2.28	0.70

Disclosures: Daniel Gryzlo: Nothing to Disclose, Irene Helenowski: Nothing to Disclose, Jonah Rubin: Nothing to Disclose

3500 | TEMPORAL TRENDS IN LIVER TRANSPLANTATION IN THE UNITED STATES (2016-2022) : A NATIONWIDE ANALYSIS OF PROCEDURAL VOLUME, MORTALITY, AND HEALTHCARE COSTS

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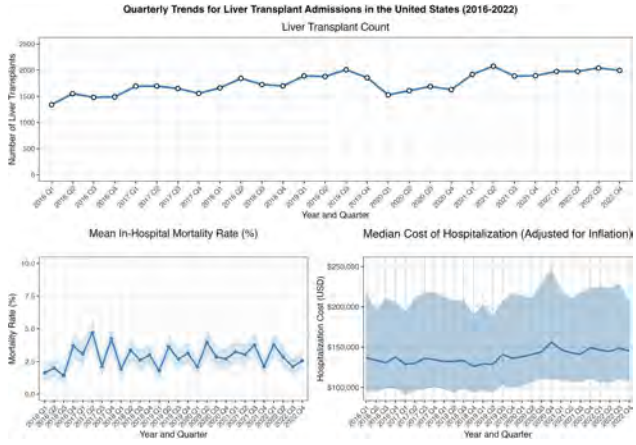
Background: Liver transplantation remains a definitive treatment for end-stage liver disease and select hepatic malignancies. Understanding national trends in liver transplant volumes, outcomes, and healthcare utilization is essential for optimizing resource allocation and guiding future health policy. We aimed to evaluate recent trends in liver transplantation in the United States, focusing on transplant volume, in-hospital mortality, and inflation-adjusted hospitalization costs. **Methods:** In this descriptive study, we analyzed data from the National Inpatient Sample (NIS) from 2016 to 2022. We included adult patients who underwent liver transplantation, identified using ICD-10 Procedure Coding System (PCS) codes. We assessed quarterly trends in three key outcomes: number of liver transplants performed, in-hospital mortality rates, and the median cost of hospitalization (adjusted to 2022 USD using the average quarterly Consumer Price Index data from the U.S. Bureau of Labor Statistics). **Results:** A total of 49,223 liver transplant-related hospitalizations were identified between 2016 and 2022. The mean age of the cohort was 52.3 years (standard deviation [SD]: 16.2), with a predominance of male patients (62.6%). The racial and ethnic distribution comprised 66.7% White, 8.1% Black, and 16.4% Hispanic individuals. The vast majority of procedures (95.4%) were performed at urban teaching hospitals. The annual volume of liver transplants demonstrated an overall upward trajectory, increasing from 5,879 in 2016 to 7,987 in 2022. A transient decline was noted in 2020, likely attributable to the disruptions associated with the COVID-19 pandemic. Despite the rising procedural volume, the overall in-hospital mortality rate remained stable throughout the study period, with a mean mortality rate of 2.9%. The median hospitalization cost, adjusted for inflation, showed a gradual increase over time. Specifically, the median annual cost rose from $136,761 in 2016 to $145,261 in 2022, reflecting a modest upward trend in resource utilization. **Conclusion:** From 2016 to 2022, the volume of liver transplants in the United States increased substantially, while in-hospital mortality rates remained stable. The consistent mortality rate despite increased transplant volume may reflect improvements in perioperative care and patient selection. However, rising hospitalization costs highlight the need for continued evaluation of cost-efficiency in liver transplant care.



Disclosures: Yordanos Tafesse: Nothing to Disclose, Bekure Siraw: Nothing to Disclose, Parth Patel: Nothing to Disclose, Ashok Kumar: Nothing to Disclose, Ebram Said: Nothing to Disclose

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3501 | METTL3-MEDIATED M6A MODIFICATION PROMOTES ACTIVATION OF CD8+T CELLS THROUGH UP-REGULATING AUTOPHAGY IN ACUTE REJECTION AFTER LIVER TRANSPLANTATION

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Background: Previous studies and ours have demonstrated the critical role of CD8+T cells in acute rejection (AR) after liver transplantation (LT). m6A RNA modification has been reported to be involved in the regulation of immune cell function and survival recently. However, its role in AR remains to be elucidated. **Methods:** m6A RNA modification levels in activated T cells were assessed in liver grafts from AR patients after LT. Rat acute hepatic rejection model and one-way mixed lymphocyte reaction model were then established to confirm the methylation levels of CD8+T cells. Moreover, changes of RNA in activated CD8+T cells were examined and MeRIP-seq was conducted to identify the specific targets of methyltransferases. Furthermore, underlying mechanisms of methylation in the regulation of function and survival CD8+T cells were explored. **Results:** m^6A RNA levels in CD8+T cells were elevated in both AR patients and rats after liver transplantation. METTL3 was confirmed to mediate m^6A RNA modification of activated CD8+T cells in vitro, which promoted their activation. RNA sequencing results indicated that the autophagy related signaling plays an important role in allo-antigen triggered activation of CD8+T cells. ATG12 was determined as the direct target of METTL3 through MeRIP-qPCR. Mechanistically, METTL3 enhances autophagy of T cells by up-regulating Atg12 expression through IGF2BP2 recognized stabilizing of Atg12 mRNA, resulting in promotion of T cell survival, proliferation and function. **Conclusion:** METTL3-mediated m^6A modification promotes activation of CD8+T cells through up-regulating autophagy in acute rejection after liver transplantation, thereby offering a theoretical foundation for identifying novel therapeutic targets for the prevention and treatment of AR following liver transplantation.

Disclosures: Xiaolong Chen: Nothing to Disclose, Wenfeng Zhu: Nothing to Disclose, Xuejiao Li: Nothing to Disclose

3502 | ABSTRACT WITHDRAWN

3503 | LIVER TRANSPLANTATION IN THE SETTING OF PRE-OPERATIVE ACUTE PANCREATITIS: IS DELAY JUSTIFIED?

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Background: Acute pancreatitis (AP) triggers both local and systemic inflammatory responses, increasing the risk of surgical interventions due to potential complications such as bleeding, infection, and abdominal compartment syndrome. Consequently, there is a general consensus to postpone surgical procedures—including liver transplantation (LT)—during necrotizing AP. However, the safety of early surgical intervention in patients with mild AP remains unclear. Furthermore, in liver transplant candidates presenting with acute liver failure or acute-on-chronic liver failure, delaying in LT is associated with a higher risk of mortality. We aim to assess the safety of LT in patients identified with mild AP in peri-operative period. **Methods:** We conducted a retrospective study in patients who underwent LT between 1/2015 and 4/2024 at Stanford University Hospital. Peri-transplant pancreatitis was defined as acute pancreatitis, identified via ICD-10 code, occurring within 30 days before or 7 days after transplantation. The primary outcome was the need for re-transplantation between 30 days and 1 year from index liver transplantation. Secondary outcomes included hospital and intensive care unit (ICU) length of stay, dialysis requirement within 30 days, readmission within 30 days and 6 months. Propensity score matching was employed to minimize the impact of confounding variables. **Results:** A total of 738 patients underwent LT during the study period. Among them, 29 patients (3.9%) had peri-transplant AP. Patients with AP were younger (mean age 50.1 vs. 55.6 years), higher proportion of males (82.8% vs. 64.6%), and had higher rates of pre-transplant renal dysfunction (62.1% vs. 48.1%). They also had higher baseline bilirubin levels (8.6 ± 8.5 vs. 5.5 ± 7.0 mg/dL), MELD scores (27.4 ± 12 vs. 18.7 ± 11.5), and MELD-Na scores (28.8 ± 12.4 vs. 19.3 ± 12.8).

Overall, the rate of organ failure requiring re-transplantation was low with no significant difference between the two groups; one patient in the AP group and three patients in the non-AP group ($p = 0.148$). After propensity score matching, no statistically significant differences were found between the groups for ICU length of stay, hospital length of stay, dialysis requirement, or 30-day and 6-month readmissions. **Conclusion:** Peri-transplant AP did not deteriorate post-operative outcomes in patients undergoing LT. Randomized clinical trials are warranted to determine safety of liver transplant in patients with peri-

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operative AP.

Table 1 Demographics and Baselines		Unmatched		Propensity matched	
		w/o Pancreatitis	Pancreatitis	w/o Pancreatitis	Pancreatitis
Total		709	29	29	29
Female (%)		251 (35.4%)	5(17.2%)	3 (10.3%)	5 (17.2%)
Mean age (SD)		55.6 (12)	50.1 (11.5)	51.9 (12.6)	50.1 (11.5)
Race (%)	White	326 (46%)	11 (37.9%)	14 (48.3%)	11 (37.9%)
	Asian	112 (15.8%)	5 (17.2%)	7 (24.1%)	5 (17.2%)
	Black	14 (2%)	1 (3.4%)	0 (0%)	1 (3.4%)
	Other	257 (36.2%)	12 (41.4%)	8 (27.6%)	12 (41.4%)
Hispanic (%)		269 (37.9%)	10 (34.5%)	7 (24.1%)	10 (34.5%)
Etiology of Cirrhosis (%)	EtOH	437 (61.64%)	20 (68.97%)	18 (62.07%)	20 (68.97%)
	Metabolic	320 (45.13%)	11 (37.93%)	18 (62.07%)	11 (37.93%)
	Viral	264 (37.24%)	10 (34.48%)	8 (27.59%)	10 (34.48%)
	Autoimmune	41 (5.78%)	1 (3.45%)	2 (6.9%)	1 (3.45%)
On dialysis prior (%)		90 (12.69%)	5 (17.24%)	5 (17.24%)	5 (17.24%)
Baseline (SD)	MELD	18.7 (11.5)	27.4 (12)	24.2 (13.3)	27.4 (12)
	MELD Na	19.3 (12.8)	28.8 (12.4)	24.7 (13.7)	28.8 (12.4)
	Sodium	135 (5.6)	134.3 (4.6)	134.4 (5.5)	134.3 (4.6)
	Creatinine	1.3 (0.9)	1.7 (1.4)	1.5 (1.1)	1.7 (1.4)
	Bilirubin	5.5 (7)	8.6 (8.5)	9.3 (9.5)	8.6 (8.5)
	Platelet	104.9 (67.4)	131.1 (102.9)	93 (57.7)	131.1 (102.9)
	INR	1.7 (0.7)	1.9 (0.6)	2.1 (0.8)	1.9 (0.6)
Comorbidity score (SD)		8 (3.3)	7.4 (3.3)	7.5 (3.2)	7.4 (3.3)

Table 2 Clinical Outcomes	w/o Pancreatitis	Pancreatitis	Unmatched (OR 95%CI)	p-Value	Propensity matched (OR 95%CI)	p-Value
30-day readmission	307 (43.3%)	17 (58.62%)	1.86 (0.873, 3.94)	0.108	1.15 (0.407, 3.26)	0.79
6-month readmission	389 (54.87%)	20 (68.97%)	1.83 (0.821, 4.07)	0.14	1.36 (0.456, 4.03)	0.58
ICU length of stay	7.81 (20.07)	15.38 (37.35)	2.7 (0.632, 11.5)	0.18	0.482 (0.0413, 5.63)	0.56
Hospital length of stay	18.96 (32.91)	34.59 (70.75)	2.22 (0.296, 16.6)	0.44	<0.001 (<0.001, >9999)	1
On dialysis	122 (17.21%)	10 (34.48%)	**2.53 (1.15, 5.58)**	**0.021**	1.63 (0.527, 5.2)	0.39
Re-transplant within 30 days to a year	3 (0.42%)	1 (3.45%)	8.34 (0.155, 108)	0.148	NA	1

Disclosures: Niwen Kong: Nothing to Disclose, Nikki Duong: Nothing to Disclose, Amir Hossein Gougol: Nothing to Disclose

3504 | ARRB2 IN HEPATOCYTES PROMOTE M2 MACROPHAGE POLARIZATION AMELIORATES HEPATIC ISCHEMIA-REPERFUSION INJURY THROUGH UPREGULATING METABOLITE 6-KETOLCA

genshu wang[1] qiwei yang[1] Tao Huang[1] Xiaowen Wang[2], [1]Guangdong Provincial Hospital of Chinese Medicine, [2]The Third Affiliated Hospital of Sun Yat-sen University

Background: Hepatic ischemia-reperfusion injury (IRI) is an important factor affecting the prognosis of liver transplantation patients. The role of Arrb2 in liver injury is unclear. Our study aimed to determine the role of Arrb2 in hepatic IRI and to identify its underlying mechanisms. **Methods:** An analysis of clinical samples was conducted to assess the association between Arrb2 expression and prognosis of liver transplantation; A 70% hepatic ischemia/reperfusion model in mice was established to verify the mechanism of Arrb2 in hepatocytes promoting M2 macrophage polarization in attenuating hepatic IRI by regulating 6-ketoLCA; A model of hypoxia/reoxygenation in vitro was established to investigate the molecular mechanism of 6-ketoLCA in promoting M2 macrophage polarization and pharmacological screening. **Results:** Arrb2 in hepatocytes has been shown to provide significant liver protection against hepatic IRI, primarily through promoting the polarization of liver macrophages to M2; Arrb2 remodels bile acids and the up-regulates 6-ketoLCA through Cyp7a1 in hepatocytes, promoting M2 polarization of macrophages, thereby alleviating hepatic IRI; Mechanistically, TGR5 plays a crucial role in promoting the induction of M2 polarization in macrophages by 6-ketoLCA; Pharmacological screening indicates that dutasteride enhances the activity of the Arrb2 promoter and upregulates Arrb2 expression in hepatocytes, thereby mitigating hepatic IRI. **Conclusion:** Arrb2 in hepatocytes attenuates hepatic IRI by promoting macrophages towards the M2 phenotype through bile acid. Moreover, dutasteride, a selective agonist of Arrb2, emerges as a promising targeted therapeutic agent for the clinical management of liver injury.

Disclosures: genshu wang: Nothing to Disclose, qiwei yang: Nothing to Disclose, Tao Huang: Nothing to Disclose, Xiaowen Wang: Nothing to Disclose

3505 | IMPACT OF OBESITY ON PRE- AND POST-LIVER TRANSPLANTATION OUTCOMES: A COMPARATIVE ANALYSIS ACROSS BMI CLASSES

Nazli Begum Ozturk[1] Ahmed Aref[1] Usman Bin Hameed[1] Tatjana Blazin[1] Ewelina Niedzialkowska[1] Laith Jamil[1], [1]Beaumont Hospital, Royal Oak

Background: The number of overweight and obese patients undergoing liver transplantation (LT) in the United States is rising. Obesity is a known risk factor for perioperative complications in abdominal surgery in general, but its specific impact on LT remains debated. Previous research has suggested increased length of stay and morbidity, including vascular and biliary complications in obese patients. We aimed to investigate our tertiary center's experience in overweight and obese patients undergoing LT. **Methods:** A single-center analysis of all adult patients who underwent LT at our transplant center between 2013-2023 was conducted. Clinical, laboratory, histological, and follow-up data were retrieved from electronic medical records. Patients were stratified into six BMI classes:

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underweight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), class I obesity (BMI 30.0–34.9), class II obesity (BMI 35.0–39.9), and class III obesity (BMI ≥ 40.0). Primary outcomes were intensive care unit (ICU) and hospital length of stay. The categorical variables are reported as numbers and percentages, and the continuous variables are reported as means and standard deviation or median with interquartile range. Kaplan-Meier curves with Log-rank test were applied to compare survival outcomes. Statistical significance was defined as $p \leq 0.05$ for all the parameters. **Results:** A total of 239 LT recipients were identified, with 15% of the patient with normal weight, 30% with overweight, 26% with class I obesity, 9% with class II obesity, and 5% with class III obesity and 0.01% underweight. Pre-LT total bilirubin levels were markedly elevated in class III obesity (24 mg/dL) compared to both class I obesity (6.2 mg/dL, $p = 0.01$) and normal weight (4.8 mg/dL, $p = 0.02$). Class III obesity patients had significantly lower hemoglobin (8.4 g/dL) than normal weight (10 g/dL), $p = 0.01$, and lower platelet counts (52 x 10^3/mm^3) compared to normal weight (84 x 10^3/mm^3), $p = 0.03$. Class III obesity patients required longer ICU length of stay (LOS) (median = 12 days) compared to normal weight (median = 5 days), $p = 0.001$, and longer hospital LOS (25 days) compared to normal weight (11 days), $p = 0.01$. Moreover, post-LT infections were more frequent in class III obesity patients (50%) compared to normal weight patients (13.9%), $p = 0.05$. **Conclusion:** Patients with class III obesity exhibited significantly inferior pre- and post-LT outcomes compared to normal weight. Elevated bilirubin, lower hemoglobin, and lower platelet counts in patients with class III obesity suggest greater pre-LT frailty. Postoperatively, patients with class III obesity required prolonged hospital, and ICU stays and experienced higher infection rates. However, survival outcomes were not significantly different across BMI groups.

Disclosures: Nazli Begum Ozturk: Nothing to Disclose, Ahmed Aref: Nothing to Disclose, Usman Bin Hameed: Nothing to Disclose, Tatjana Blazin: Nothing to Disclose, Ewelina Niedzialkowska: Nothing to Disclose, Laith Jamil: Nothing to Disclose

3506 | PRE-TRANSPLANT LIPASE ELEVATION AND ITS PROGNOSTIC IMPLICATIONS: DIFFERENTIATING BIOCHEMICAL ABNORMALITIES FROM CLINICALLY SIGNIFICANT PANCREATITIS IN PATIENTS UNDERGOING LIVER TRANSPLANTATION

Peyton Crest[1] Francis Yao[1] Chris Freise[1] John Roberts[1] Nghiem Ha[1], [1]University of California, San Francisco

Background: Lipase elevation is common in critically ill patients, including those awaiting liver transplantation, but its clinical significance—whether indicative of pancreatitis or a transient biochemical abnormality—remains unclear. We aimed to assess the relationship between pre-transplant lipase elevation, radiographic (RP) or intraoperative pancreatitis (IOP), and post-transplant outcomes. **Methods:** Included were adults who underwent liver transplantation between 1/2020 and 3/2025 with elevated lipase (≥ 78 U/L) within 14 days pre-transplant. RP was defined by imaging evidence of peripancreatic inflammation, necrosis, or fluid collections. IOP was defined as gross evidence of inflammation, necrosis, firmness, and/or surrounding saponification. Kaplan-Meier and Cox regression were used to assess associations with post-transplant mortality (death or graft failure). **Results:** Among 90 patients, 60% were male with a median age of 57; transplant etiologies were alcohol-associated (39%) followed by MASLD (23%). Overall, 20 patients (22%) died or had graft failure within 36 months. RP or IOP was found in 10 patients (11%); all 5 patients with IOP died within 1 month while the majority (60%) with RP died by 13 months. Cumulative rates of post-transplant mortality at 12 months did not differ among patients with clinically significant elevated lipase

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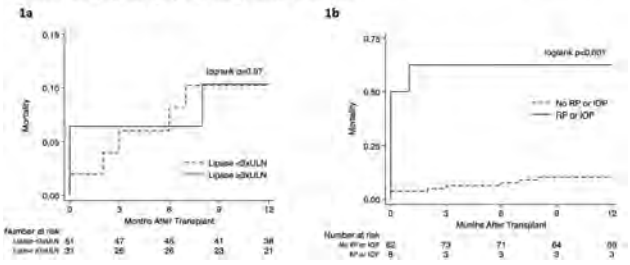
(≥3xULN) but differed in those with either RP or IOP (Figure). Clinically significant lipase elevation (≥3xULN) alone was not associated with mortality (HR 1.03, 95%CI 0.25-4.32). RP/IOP was associated with post-transplant mortality (HR 8.51, 95%CI 3.16-22.97), even after adjusting for age, alcohol-associated etiology, creatinine, MELD, and lipase (HR 17.32, 95%CI 4.42-67.80). RP/IOP was associated with postoperative complications including pancreatitis, biliary complications, or intraabdominal infection (HR 3.57, 95%CI 1.59-7.97). Lipase ≥5xULN predicted RP/IOP (OR 7.97, 95%CI 1.40-45.10), remaining significant after adjusting for age, alcohol-associated etiology, MELD, and renal dysfunction (OR 6.75, 95%CI 1.01-45.03). **Conclusion:** In patients undergoing liver transplant, radiographic or intraoperative evidence of pancreatitis—but not isolated biochemical lipase elevation ≥3xULN—is a significant predictor of post-transplant morbidity and mortality. Elevated lipase ≥5xULN warrants further evaluation with dedicated cross-sectional pancreatic imaging to identify clinically significant pancreatitis and guide perioperative management.

Figure 1. Cumulative Post-Transplant Mortality at 12 Months According to (1a) Clinically Significant Lipase ≥3xULN and (1b) Radiographic/Intraoperative Pancreatitis



Disclosures: Peyton Crest: Nothing to Disclose, Francis Yao: Nothing to Disclose, Chris Freise: Nothing to Disclose, John Roberts: Nothing to Disclose, Nghiem Ha: Nothing to Disclose

3507 | NORMOTHERMIC MACHINE PERFUSION REDUCES EARLY ALLOGRAFT DYSFUNCTION IN TECHNICALLY CHALLENGING DCD LIVER TRANSPLANTATION

ATSUSHI NISHIMAGI[1] Rikako Oki[1] Luckshi Rajendran[1] Emily Kerby[1] Adhnan Mohamed[1] Ahmed Nassar[1] Abbas Al-Kurd[1] Atsushi Yoshida[1] Marwan Abouljoud[1] Shunji Nagai[1], [1]Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital

Background: Normothermic machine perfusion (NMP) has been shown to reduce the incidence of early allograft dysfunction (EAD), minimize various postoperative complications, and improve overall survival in liver transplantation(LT). Intraoperative blood transfusion is known to be associated with the risk of EAD, it remains unclear how the advent of NMP may modify the impact of such intraoperative risk factors for EAD. The aim of this study is to evaluate the effects of NMP in technically challenging DCD LT requiring massive transfusion. **Methods:** Adult LT alone from DCD donor which were performed from 2015-2024 were evaluated. Patients were divided into two groups based on the amount of intraoperative blood transfusion. Logistic regression analysis was performed to identify risk factors associated with the development of EAD in each group. All NMPs were initiated at donor hospitals (on-site NMP). **Results:** This study included 201 adult DCD liver transplant patients, in which LT was performed using NMP in 100 patients and non-NMP- in 101 patients. The incidence of EAD was significantly lower in the NMP group compared to the non-NMP group (22.0% [n = 22] vs 57.4% [n = 58]; $p < 0.001$). We divided patients into two groups based on transfusion volume: the high blood transfusion group (RBC + Cell Saver ≥10 units, n = 78) and the low blood transfusion group (<10 units, n = 123). NMP significantly reduced the incidence of EAD compared to non-NMP in both the high transfusion group (26.2%, [11/42] vs 55.6%, [20/36]; $p = 0.008$) and the low transfusion group (19.0%, [11/58] vs 59.4%, [38/64]; $p < 0.001$). The risk of EAD was evaluated after adjustment for donor and recipient characteristics. In the high transfusion group, NMP was independently associated with a significantly lower risk of EAD (OR = 0.17, 95% CI: 0.05–0.53, p = 0.002). Donor age (OR = 1.06, 95% CI: 1.01–1.12, p = 0.02) and donor BMI (OR = 1.10, 95% CI: 1.02–1.18, p = 0.02) were also identified as independent risk factors. In the low transfusion group, NMP remained a protective factor against EAD (OR = 0.15, 95% CI: 0.06–0.37, $p < 0.001$). donor gender (male) (OR = 3.50, 95% CI: 1.29–9.50, p = 0.01), and donor BMI(OR = 1.08, 95% CI: 1.01–1.16, p = 0.023) were also identified as independent risk factors. **Conclusion:** NMP significantly reduced the risk of EAD. This benefit is also seen in challenging liver transplant cases that involve large amounts of blood transfusion.

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High blood transfusion group (RBC + Cell Saver ≥ 10 units)

	Univariate			Multivariate		
	OR	95%CI	p	OR	95%CI	p
Normothermic Machine Perfusion	0.28	(0.11-0.74)	0.009	0.17	(0.05-0.53)	0.002
Donor Age	1.04	(1.00-1.09)	0.04	1.06	(1.01-1.12)	0.02
Donor Gender (Male)	1.07	(0.40-2.82)	0.90			
Donor BMI	1.07	(1.00-1.15)	0.045	1.10	(1.02-1.18)	0.02
Recipient Age	1.04	(0.99-1.09)	0.15			
Recipient Gender	1.12	(0.46-3.11)	0.77			
Recipient BMI	1.01	(0.93-1.10)	0.77			
MELD score	0.92	(0.85-0.999)	0.05			

Low blood transfusion group (RBC + Cell Saver < 10 units)

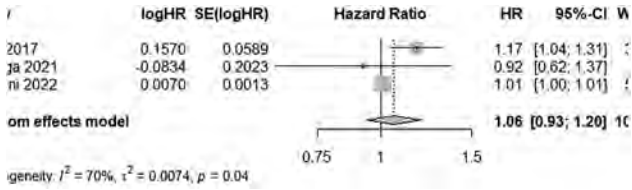
	Univariate			Multivariate		
	OR	95%CI	p	OR	95%CI	p
Normothermic Machine Perfusion	0.17	(0.07-0.38)	<0.001	0.15	(0.06-0.37)	<0.001
Donor Age	1.01	(0.98-1.04)	0.52			
Donor Gender (Male)	3.08	(1.32-7.19)	0.009	3.50	(1.29-9.50)	0.01
Donor BMI	1.05	(1.00-1.11)	0.07	1.08	(1.01-1.16)	0.023
Recipient Age	1.01	(0.97-1.050	0.57			
Recipient Gender	2.06	(0.92-4.57)	0.08	0.76	(0.30-1.93)	0.556
Recipient BMI	0.96	(0.89-1.02)	0.20			
MELD score	0.97	(0.92-0.97)	0.31			

Disclosures: ATSUSHI NISHIMAGI: Nothing to Disclose, Rikako Oki: Nothing to Disclose, Luckshi Rajendran: Nothing to Disclose, Emily Kerby: Nothing to Disclose, Adhnan Mohamed: Nothing to Disclose, Ahmed Nassar: Nothing to Disclose, Abbas Al-Kurd: Nothing to Disclose, Atsushi Yoshida: Nothing to Disclose, Marwan Abouljoud: Nothing to Disclose, Shunji Nagai: Nothing to Disclose

3508 | A META-ANALYSIS OF THE EFFECT OF CIRRHOSIS ON MORTALITY AFTER HEART TRANSPLANT ALONE IN THOSE WITH A FONTAN

Christopher Danford[1] Sophie Hansen[2] James Trotter[1] Ian Lindsay[2] Ross Butschek[1], [1]Intermountain Medical Center, [2]University of Utah

Background: Hepatic complications are increasingly recognized after the Fontan operation. The majority of patients with a Fontan will ultimately developed advanced hepatic fibrosis and cirrhosis[1], but the effect of this on outcomes after heart transplant alone and who may benefit from combined heart-liver transplant is not well established. We conducted a systematic review and meta-analysis of the effect of cirrhosis and measures of liver function on mortality after heart transplant alone in those with a Fontan. **Methods:** We searched PubMed, CINAHL, and MEDLINE databases for articles reporting the effect of liver-related variables on mortality after heart transplant alone in the Fontan population on July 18, 2024. We excluded cross-sectional studies or review articles. Studies were required to be case reports, case series, retrospective or prospective cohort studies and report the effect of liver-related variables such as cirrhosis, MELD score (and components thereof) on mortality after heart transplant alone in those who had previously undergone the Fontan operation. Two reviewers independently reviewed studies for inclusion and extracted variables of interest. A single-arm random effects meta-analysis was conducted in RStudio (version 1.3.1093). **Results:** We identified three studies including a total of 598 patients that met criteria for inclusion. All three studies reported the effect of MELD-Xi on post-transplant mortality. MELD-Xi was not associated with increased risk of mortality after heart transplant alone (HR 1.06, 95% CI 0.93-1.20) (Figure 1). Heterogeneity was high (I^2 = 70%). The effect of cirrhosis on mortality after heart transplant alone was only reported in two studies, but was also not significant (HR 5.08, 95% CI 0.98-26.3). **Conclusion:** While neither cirrhosis nor MELD-Xi was statistically significantly associated with increased mortality after heart transplant alone in those with a Fontan, there was a trend towards increased risk of mortality in those with cirrhosis and higher MELD-Xi score. One limitation is the definition of cirrhosis used as imaging characteristics alone are not reliable in diagnosing cirrhosis in those with congestive hepatopathy. Berg et al. did not provide the definition used for cirrhosis while Sganga et al. allowed for both imaging or biopsy findings to diagnose cirrhosis. While there is likely a point where patients would benefit from combined heart-liver transplant as compared to heart transplant alone, further research is needed with precise definitions of cirrhosis and liver function to determine this.



Disclosures: Christopher Danford: Ipsen Pharmaceuticals: Advisor, Sophie Hansen: Nothing to Disclose, James Trotter: Nothing to Disclose, Ian Lindsay: Nothing to Disclose, Ross Butschek: Nothing to Disclose

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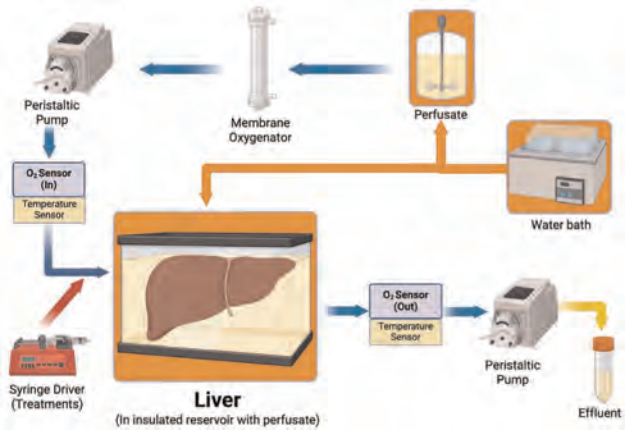
3509 | A MULTI-STAGE-RESOLVED FLUX PLATFORM QUANTIFIES SUBSTRATE-SPECIFIC MODULATION OF HEPATIC METABOLISM DURING EX VIVO LIVER PERFUSION

Amin Amin[1] Shawn Burgess[2], [1]University of Texas Southwestern Medical Center, [2]University of Texas Southwestern

Background: Normothermic machine perfusion (NMP) has transformed liver preservation, yet the optimal metabolic conditions to sustain or rehabilitate marginal grafts remain undefined. Defining how specific substrates regulate hepatic metabolism ex-vivo is critical to designing targeted perfusates for organ maintenance or metabolic rescue. We developed a stage-resolved, isotopically traced ex-vivo liver perfusion platform capable of quantifying substrate-specific metabolic fluxes. Glucose and glycerol were chosen as physiologically relevant substrates that are routinely modulated in clinical NMP protocols and represent key metabolic nodes in gluconeogenesis, glycolysis, and mitochondrial oxidation. **Methods:** Livers from fed and fasted mice were perfused with a 3% BSA based perfusate in a non-recirculating oxygenated system (figure) and subjected to serial lobectomies at 30-minute intervals. Real-time oxygen consumption was monitored using inline sensors. Two independent multi-stage experiments were performed. In the glucose experiment, livers were perfused through three stages: Stage 1 with 0 mM glucose; Stage 2 with either 5 or 20 mM unlabeled glucose alongside [U-$^{13}C_3$]lactate and [U-$^{13}C_3$]pyruvate; and Stage 3 with the same glucose concentration but with tracer switched to [U-$^{13}C_6$]glucose, allowing resolution of specific and important fluxes. In the glycerol experiment, tracer composition remained constant ([3-^{13}C]lactate and [U-$^{13}C_3$]pyruvate), while glycerol was increased stepwise across stages (0, 0.3, 1.5 mM). Lobes were snap-frozen after each stage for GC-MS analysis. Fluxes were quantified using Isotopomer Network Compartmental Analysis (INCA). **Results:** Metabolic flux analysis revealed that glucose concentration was a major determinant of hepatic carbon routing. In fasted livers, 20 mM glucose suppressed gluconeogenic flux and enhanced PDH activity relative to 5 mM Glucose, reflecting greater glycolytic engagement. In contrast, fed livers exhibited stable fluxes across glucose stages, consistent with lower catabolic demand. Insulin did not significantly impact fluxes within either nutritional state. In the glycerol experiment, increasing glycerol concentrations led to dose-dependent suppression of lactate-derived gluconeogenesis and altered pyruvate cycling and TCA fluxes—despite minimal effects on oxygen consumption. These substrate-driven changes were resolved with high temporal precision using serial lobectomy, confirming both liver viability and methodological robustness. **Conclusion:** This platform enables high-resolution, quantitative mapping of hepatic metabolism during ex vivo perfusion. By revealing distinct, substrate-specific flux patterns with intra-organ resolution, it provides a mechanistic foundation for optimizing perfusate composition and developing targeted strategies to preserve or rehabilitate donor livers under NMP.



Disclosures: Amin Amin: Nothing to Disclose, Shawn Burgess: Nothing to Disclose

3510 | NON-TRADITIONAL INDICATIONS IN PEDIATRIC LIVER TRANSPLANTATION: A 20-YEAR SINGLE-CENTER RETROSPECTIVE STUDY OF LONG-TERM OUTCOMES

Stephanie Chau Nguyen[1] William Zhu[1] Kimberly Chapman[2] Udeme Ekong[3] Khalid Khan[3] Gabriel Gondolesi[3] Nada Yazigi[3], [1]Georgetown University School of Medicine, [2]Children's Hospital Los Angeles, [3]Georgetown University Hospital

Background: Liver transplantation has become a viable and safe option for pediatric patients with indications beyond traditional diagnoses often including biliary atresia, autoimmune hepatitis, and hepatoblastoma. Given the relative novelty of these expanded indications, this abstract aims to briefly summarize our single center experience performing liver transplantation for nontraditional indications. **Methods:** We conducted a single-center retrospective review of pediatric liver transplantation from 2003 to 2024. A comprehensive chart review was performed to identify transplant

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indication, patient and graft survival, graft rejection, retransplantation rate, biliary complications, and vascular complications. Statistical analysis was performed using Pearson's Chi-squared test of independence. **Results:** Among the 315 pediatric liver transplant recipients in our cohort, 112 patients (35.6%) underwent transplantation for nontraditional indications. Patient survival at 1, 3, and 5 years post-transplant was 97.3%, 97.3%, and 96.4% in patients with nontraditional indications compared to 94.6%, 92.6%, and 91.6% in those with traditional indications. Similarly, graft survival at 1, 3, and 5 years post-transplant was 96.6%, 96.6%, and 94.8% in the nontraditional group and 93.7%, 91.8%, and 91.0% in the traditional group. In terms of retransplantation, 5.36% (n = 6) of nontraditional patients as compared to 8.87% (n = 18) of traditional patients were retransplanted. Rejection rates were 25.9% (n = 29) in the nontraditional group compared to 19.7% (40) in the traditional group. Biliary complications were documented in 18.8% (n = 21) of nontraditional recipients and 23.6% (n = 48) of traditional recipients. Vascular complications occurred in 19.2% (n = 39) of traditional patients and 4.47% (n = 5) of nontraditional patients. Of note, vascular complications occurred significantly more frequently in patients with traditional indications ($p < 0.001$). There were no other significant comparisons among the two groups. **Conclusion:** Our findings suggest that while patient and graft survival, rejection rate, and biliary complication rates were comparable between traditional and nontraditional transplant recipients, pediatric patients with nontraditional indications had significantly less vascular complications. These results highlight the need for a larger multicenter study to better define long-term outcomes for nontraditional pediatric liver transplantation.

Disclosures: Stephanie Chau Nguyen: Nothing to Disclose, William Zhu: Nothing to Disclose, Kimberly Chapman: Nothing to Disclose, Udeme Ekong: Nothing to Disclose, Khalid Khan: Nothing to Disclose, Gabriel Gondolesi: Nothing to Disclose, Nada Yazigi: Nothing to Disclose

3511 | LIVER TRANSPLANTATION IN INDIVIDUALS WITH HIV – CHANGES IN INDICATIONS AND OUTCOMES AFTER THE ADVENT OF DIRECT-ACTING ANTIVIRALS FOR HEPATITIS C VIRUS

Ewan Glassey[1] Abdul Rahman Hakeem[2] Bruno Sensi[1] Kaushik Agarwal[1] Varuna Aluvihare[3] Kate Childs[4], [1]King's College Hospital, London, [2]King's College Hospital NHS Trust, [3]King's College Hospital, [4]Kings College Hospital, London

Background: Liver transplantation (LT) in a person living with human immunodeficiency virus (PLWH) was first performed in 1995 and was seen as a challenging indication. Early case series into this population revealed hepatitis C virus (HCV) as the most common aetiology requiring transplant. The introduction of direct acting antivirals (DAAs) for HCV in 2015 significantly improved outcomes in all HCV patients. We aim to demonstrate the impact of curative HCV treatment on LT in PLWH in a single centre review. **Methods:** Cases were reviewed of all LT performed in PLWH at King's College Hospital, London since 2007. Data was extracted from NHS Blood and Transplant (NHSBT) as well as local medical records. Data on demographics, liver disease, HIV treatment and complications, post-LT complications and long-term outcomes were reviewed. Further analysis was made between pre and post 2015 - when DAAs for HCV were introduced. **Results:** 35 LTs were performed in PLWH since 2007. 5-year overall survival to date was 21/29 (72.4%) and 1-year overall survival 31/34 (91.2%). Common aetioloies for LT were HCV 8 (22.9%), non-cirrhotic portal hypertension 7 (20%) with MASLD 4 (11.4%), drug induced liver injury 3 (8.6%), hepatitis B virus 2 (5.7%), hepatitis B plus delta 2 (5.7%) less common.

In the 2007-2014 group (before DAAs) there were 18 LT compared with 17 in 2015-2024. All 8 of the HCV patients were in the pre-2015 group, accounting for 8/18 (44.4%) as a cause for liver disease requiring transplant. Only 1 of those had achieved cure with interferon/ribavirin prior to transplant. From 2015 onwards no LT were performed for HCV infection, with the most common cause leading to transplant being non-cirrhotic portal hypertension 5/16 (31.2%).

Survival between groups: 5-year overall survival pre-2015 was 61.1% vs 90.9% 2015 onwards ($p = 0.041$), 1-year overall survival pre-2015 83.3% vs 100% 2015 onwards ($p = 0.045$).

The overall rate of thrombotic complications in 90-days post-transplant was low: hepatic artery thrombosis 3 (8.5%), portal venous thrombosis 1 (2.9%), hepatic venous thrombosis 1 (2.9%). Incidence of sepsis 90 days post LT was not significant pre-2015 6/18 (33.3%) vs 3/17 (17.6%) in 2015 onwards ($p = 0.14$). **Conclusion:** This single centre review demonstrates a clear shift in most common cause for LT in PLWH. We also demonstrate that overall outcomes in this population in the post DAA era are much improved. Medical and surgical care advances have improved LT outcomes in this population.

Disclosures: Ewan Glassey: Nothing to Disclose, Abdul Rahman Hakeem: Nothing to Disclose, Bruno

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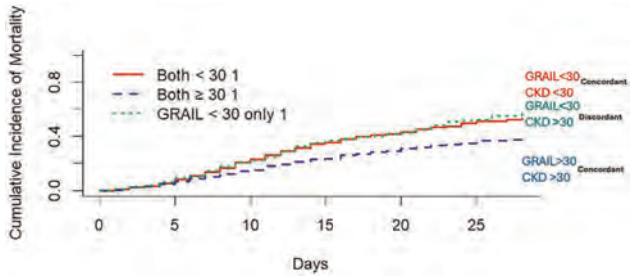
Sensi: Nothing to Disclose, Kaushik Agarwal: Nothing to Disclose, Varuna Aluvihare: Nothing to Disclose, Kate Childs: Nothing to Disclose

3512 | ASSESSING KIDNEY DYSFUNCTION IN INPATIENTS WITH DECOMPENSATED CIRRHOSIS: A GLOBAL-AKI COHORT STUDY

Kavish Patidar[1] Giovanna Saracino[2] Ann Ma[3] Adrià Juanola[4] Elsa Solà[5] Simone Incicco[6] Salvatore Piano[6], [1]Houston Methodist Hospital, [2]Baylor University Medical Center, [3]Clichy France, [4]Hospital Clinic i Provincial de Barcelona, [5]Stanford, [6]University of Padova

Background: Accurate assessment of kidney function is important in patients with cirrhosis, though inadequately captured by current glomerular filtration rate (GFR) estimating equations that were developed for patients with chronic kidney disease (eg CKDI-EPI 2021). Recently, we updated a validated a novel race neutral equation to estimate GFR in patients with cirrhosis (GFR Assessment In Liver disease, GRAIL 2.0). We showed that it estimates GFR better than current estimating equation in stable outpatients with decompensated cirrhosis as compared to measured GFR. However, the use of eGFR in unselected hospitalized patients with dynamic kidney function (acute kidney injury) is not well characterized. **Methods:** In this prospective, multicenter, cohort study, we examined adults ($\geq$18 years) with decompensated cirrhosis who were hospitalized for AKI, at 65 centers across five continents. Inclusion criteria were adult patients with cirrhosis admitted to hospital for the treatment of a complication of liver disease and diagnosed with AKI. We compared GRAIL 2.0 (age,BUN,albumin,creatinine,sex, Asrani AASLD 2024) to the reference standard (CKD-EPI 2021, Inker NEJM 2021). The primary outcome of interest was need for renal replacement therapy or death. Cumulative incidence functions of mortality were developed through competing risks analysis and compared with Gray's test. Liver transplantation was considered a competing risk for mortality **Results:** Between July 1, 2022, and May 31, 2023, we enrolled 1210 patients who were hospitalized with AKI and had the variables needed to compute GRAIL 2.0. Overall 139 patients required RRT (11.5%), 55 received a LT (n = 4.5%) and 380 patients died (31.4%).

Overall, both GRAIL and CKD-EPI during index hospitalization were associated with RRT and mortality within 28-days. Patients with an estimated GFR < 30 ml/min had higher incidence of mortality. Discordance was noted where 309 patients (25.5%) were classified as having a GFR < 30 ml/min according to GRAIL 2.0 but not with CKD-EPI (overestimation). Those patients had a cumulative incidence of mortality similar to patients with both GRAIL 2.0 and CKD-EPI < 30 ml/min, and significantly higher than those with both $\geq$ 30 ml/min (Figure; $p < 0.001$). Results were consistent in male and female and in patients with MELD **Conclusion:** Use of eGFR for prognosis is acceptable in the inpatient setting with dynamic changes in kidney function. CKD-EPI may overestimate kidney function. In patients with decompensated cirrhosis, use of race neutral eGFR developed in patients with liver disease (GRAIL 2.0) may serve as a viable alternative for prediction of kidney related outcomes as well as transplantation decisions.



Disclosures: Kavish Patidar: Madrigal Pharmaceuticals: Medical Advisory Board, Mallincrodt Pharmaceuticals: Consultant, Giovanna Saracino: Nothing to Disclose, Ann Ma: Nothing to Disclose, Adrià Juanola: Nothing to Disclose, Elsa Solà: Nothing to Disclose, Simone Incicco: Nothing to Disclose, Salvatore Piano: Nothing to Disclose

3513 | NEIGHBORHOOD SOCIOECONOMIC DEPRIVATION IS ASSOCIATED WITH DELAYS AND MORTALITY IN THE LIVER TRANSPLANT CARE CONTINUUM

Carolina Lopez-Silva Lynette Sequeira[1] Vedant Jain[2] Valerie Thompson[2] Juliette Dixon[2] Tyrus Vong[2] Alexandra Strauss[2], [1]Johns Hopkins Hospital, [2]Johns Hopkins University

Background: Social determinants of health significantly influence liver transplant (LT) access and outcomes. The area deprivation index (ADI), a composite measure of neighborhood-level socioeconomic status (nSES), has been used to evaluate the impact of nSES on health-related outcomes. We examined the association between nSES (as estimated by ADI) and timing of transplant care and outcomes. **Methods:** We conducted a retrospective cohort study of adults referred for LT evaluation at an urban transplant center between August 1, 2016, and December 31, 2019. ADI was dichotomized at the sample median. Demographic and clinical characteristics were compared by ADI group. Time from referral to evaluation, listing, and death were assessed using Kaplan-Meier curves with log-rank tests. Cox proportional hazards models adjusted for age and sex were used to evaluate associations between ADI and each outcome. **Results:** Among 1,377 referred patients, 712 lived in low nSES (high ADI) neighborhoods and 665 in high nSES (low ADI) areas. Patients from low nSES

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neighborhoods were more likely to be Non-Hispanic Black (23.3% vs. 11.1%, $p < 0.001$), insured by Medicaid (25% vs. 13.5%, $p < 0.001$), and less likely to have alcohol-related liver disease (19.4% vs. 29.6%, $p < 0.001$). Age, sex, and median MELD scores did not significantly differ between groups. Kaplan-Meier analysis showed statistically significant delays for patients from low nSES neighborhoods in evaluation (median 26 vs. 25 days, $p = 0.031$) and listing (791 vs. 626 days, $p < 0.001$), and shorter survival after referral (774 vs. 822 days, $p < 0.001$). In adjusted Cox models, low nSES was independently associated with reduced likelihood of evaluation (HR 0.870, 95% CI 0.768–0.986, $p = 0.029$), listing (HR 0.703, 95% CI 0.581–0.851, $p < 0.001$), and increased risk of death (HR 1.407, 95% CI 1.148–1.726, $p = 0.001$). **Conclusion:** We found that neighborhood disadvantage leads to significant delays along the transplant care continuum and is associated with a higher risk of mortality. This highlights the role of neighborhood-level social determinants in influencing transplant access and outcomes and underscores the need for targeted interventions to address these inequities.

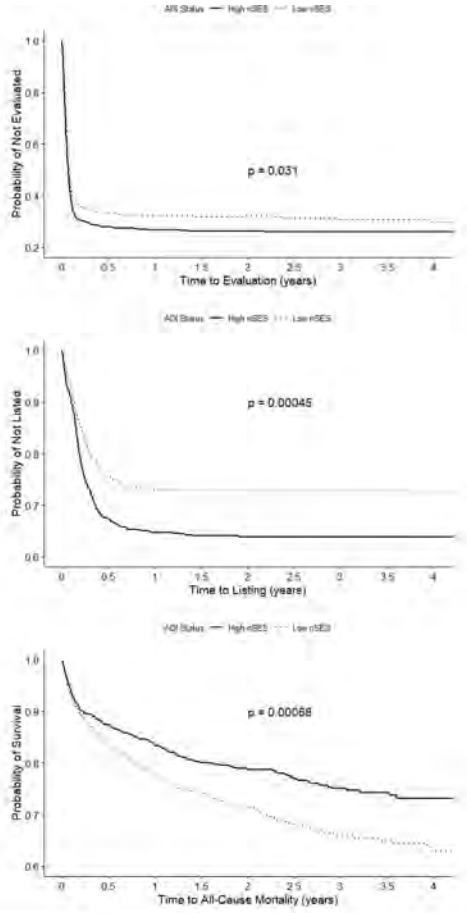

Figure 1. Kaplan-Meier curves comparing time to evaluation, time to transplant listing, and all-cause mortality following referral for liver transplant evaluation, stratified by neighborhood socioeconomic status (nSES). Time is shown in years from the date of referral. Log-rank tests were used to assess statistical differences between nSES groups.

Disclosures: Carolina Lopez-Silva: Nothing to Disclose, Lynette Sequeira: Nothing to Disclose, Vedant Jain: Nothing to Disclose, Valerie Thompson: Nothing to Disclose, Juliette Dixon: Nothing to Disclose, Tyrus Vong: Nothing to Disclose, Alexandra Strauss: Nothing to Disclose

3514 | COMPARISON OF MELD, MELD-NA, AND MELD 3.0 SCORING SYSTEMS IN TRANSPLANT PRIORITIZATION IN THE TURKISH POPULATION: A MULTICENTER STUDY

Kenan Moral[1] MUHSIN MURAT MUHIP HARPUTLUOGLU[2] Haydar Adanır[3] Nilay Danış[4] Murat Kıyıcı[5] Murat Dayangac[6] Sencan Acar[7] Derya Arı[8] Ramazan Idilman[9] Zeki Karasu[10] Sabahattin Kaymakoğlu[11] Nimet Yılmaz[12] Gupse Adali[13] Murat Akyıldız[14] Ahmet Uyanikoglu[15] Onur Keskin[16] Murat Kekilli[1] Sezai Yılmaz[2] Gülşah Fidan Özkumur[3] Doğancan Gavcar[17] Efe Erbay[17] Mesut Akarsu[4] Fatih Eren[5] Mehmet Refik Göktuğ[5] Amir Salar Nazari[18] Meral Akdoğan Kayhan[8] Dilara Turan Gökçe[8] Hale Gökcan[9] Zeynep Melekoğlu Ellik[9] Ilker Turan[10] Fulya Günşar[10] Elvan Işık[10] Mehmet Akif Yağlı[11] Alper Akın[11] Baver Ordu[13] Genco Gencdal[19] Osman Yüksekyayla[15] Burcu Gürbüz[16] Mehmet Cindoruk[1] Tarkan Karakan[1] Gökhan Kabacam[20], [1]Gazi University Department of Gastroenterology and Hepatology, [2]Inönü University Liver Transplantation Institute, [3]Akdeniz University Department of Gastroenterology and Hepatology, [4]Dokuz Eylül University Department of Gastroenterology and Hepatology, [5]Uludağ University Department of Gastroenterology and Hepatology, [6]Medipol University Mega Hospital Department of General Surgery, [7]Florence Nightingale Hospital Liver Transplant Unit, [8]Ankara Bilkent City Hospital Department of Gastroenterology and Hepatology, [9]Ankara University Department of Gastroenterology and Hepatology, [10]Ege University Department of Gastroenterology and Hepatology, [11]Istanbul University Istanbul Faculty of Medicine Department of Gastroenterology and Hepatology, [12]Sanko University Department of Gastroenterology and Hepatology, [13]University of Health Sciences Umraniye Research and Training Hospital, [14]Koç University Deparment of Gastroenterology and Hepatology, [15]Harran University Department of Gastroenterology and Hepatology, [16]Hacettepe University Department of Gastroenterology and Hepatology, [17]Dokuz Eylül University Department of Internal Medicine, [18]Medipol University Mega Hospital School of Medicine, [19]Koç University Department of Gastroenterology and Hepatology, [20]Guven Hospital Liver Transplantation Center

Background: The Model for End-stage Liver Disease Sodium (MELD-NA) score is widely used to predict mortality in patients awaiting liver transplantation. Recently, MELD-3.0 has been proposed as an alternative model for mortality prediction in patients with cirrhosis. This study aims to evaluate the effectiveness of the MELD-3.0 score in predicting mortality among patients listed for liver

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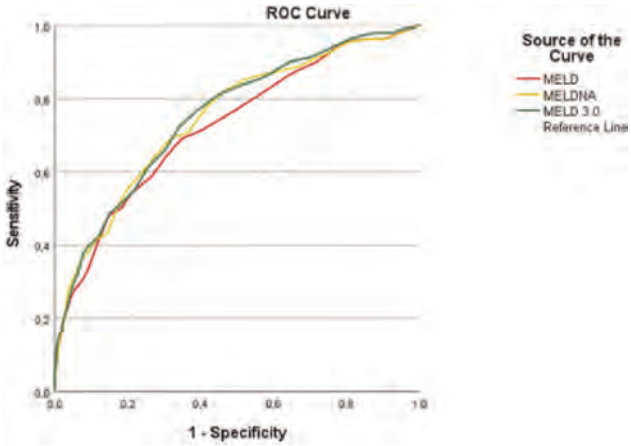
transplantation, and to compare its performance with that of the MELD and MELD-NA scores. **Methods:** The area under the receiver operating characteristic curves (AUROC) were calculated to assess the discriminative power of MELD-3.0, MELD-Na, and MELD in predicting mortality at 3 months. DeLong's test was used to compare the AUROC values. The cutoff score for MELD3.0, indicating a high risk of 3 month mortality, was identified using Youden's Index. Kaplan–Meier method was employed to estimate transplant free survival (date of listing to date of transplantation or death) curves for patients with MELD3.0 scores above and below this cutoff, and these curves were compared using log-rank analysis. **Results:** The study included a total of 1689 patients. Hepatitis B was identified as the primary cause of cirrhosis, affecting 491 individuals (29%), while MASH was the second most common cause, with 335 cases (20%). In the context of three-month mortality, the MELD 3.0 score had the highest predictive score with an AUC of 0.753 ($p < 0.05$). In comparison, the MELD-Na score demonstrated an AUC of 0.747 ($p < 0.05$), while the MELD score had an AUC of 0.725 ($p < 0.05$). The optimal cutoff value for the MELD score was determined to be 18, yielding a sensitivity of 69% and a specificity of 65%. For the MELD-Na and MELD 3.0 scores, the ideal cutoff was 21, with the MELD-Na score exhibiting a sensitivity of 69% and a specificity of 68%, and the MELD 3.0 score showing a sensitivity of 72% and a specificity of 66%. A statistically significant difference was observed between the MELD score and MELD-Na/ MELD 3.0 scores ($p < 0.001$). However, no statistically significant difference was found between the MELD-Na and MELD 3.0 scores ($p = 0.170$). For individuals with MELD > 21, transplant free survival was 1.6 years, whereas for those with MELD ≤ 21, it was 3.3 years, with a statistically significant difference ($p < 0.05$). **Conclusion:** Although both MELD 3.0 and MELD-Na are superior to the MELD score in forecasting 3-month mortality, there is no statistically significant difference between MELD 3.0 and MELD-Na in terms of mortality prediction at 3 months. Larger studies from various countries are necessary to validate the MELD 3.0 score.



Disclosures: Kenan Moral: Nothing to Disclose, MUHSIN MURAT MUHIP HARPUTLUOGLU: Nothing to Disclose, Haydar Adanır: Nothing to Disclose, Nilay Danış: Nothing to Disclose, Murat Kıyıcı: Nothing to Disclose, Murat Dayangac: Nothing to Disclose, Sencan Acar: Nothing to Disclose, Derya Arı: Nothing to Disclose, Ramazan Idilman: Nothing to Disclose, Zeki Karasu: Nothing to Disclose, Sabahattin Kaymakoğlu: Nothing to Disclose, Nimet Yılmaz: Nothing to Disclose, Gupse Adali: Nothing to Disclose, Murat Akyıldız: Nothing to Disclose, Ahmet Uyanikoglu: Nothing to Disclose, Onur Keskin: Nothing to Disclose, Murat Kekilli: Nothing to Disclose, Sezai Yılmaz: Nothing to Disclose, Gülşah Fidan Özkumur: Nothing to Disclose, Doğancan Gavcar: Nothing to Disclose, Efe Erbay: Nothing to Disclose, Mesut Akarsu: Nothing to Disclose, Fatih Eren: Nothing to Disclose, Mehmet Refik Göktuğ: Nothing to Disclose, Amir Salar Nazari: Nothing to Disclose, Meral Akdoğan Kayhan: Nothing to Disclose, Dilara Turan Gökçe: Nothing to Disclose, Hale Gökcan: Nothing to Disclose, Zeynep Melekoğlu Ellik: Nothing to Disclose, Ilker Turan: Nothing to Disclose, Fulya Günşar: Nothing to Disclose, Elvan Işık: Nothing to Disclose, Mehmet Akif Yağlı: Nothing to Disclose, Alper Akın: Nothing to Disclose, Baver Ordu: Nothing to Disclose, Genco Gencdal: Nothing to Disclose, Osman Yüksekyayla: Nothing to Disclose, Burcu Gürbüz: Nothing to Disclose, Mehmet Cindoruk: Nothing to Disclose, Tarkan Karakan: Nothing to Disclose, Gökhan Kabacam: Nothing to Disclose

3515 | RISK FACTORS FOR SEVEN-DAY GRAFT LOSS IN PEDIATRIC LIVER TRANSPLANTATION: A RETROSPECTIVE ANALYSIS OF THE SRTR DATABASE

Louis Borsellino[1] Sohail Khan[1] Melanie Vugelman[1] Katherine Connors[1] Alexandra Zois[2] Olzhas Zhorayev[3] Jorge Ortiz[2], [1]Touro College of Osteopathic Medicine, [2]Garnet Health Medical Center, [3]George Mason University

Background: Early graft loss (EGL) in pediatric liver transplantation (pLT) is a rare but catastrophic complication, resulting in significant morbidity, mortality, and strain on the donor pool. This report aimed to identify clinical and perioperative risk factors associated with graft failure within the first seven days post-pLT (7-day GL). **Methods:** We conducted a retrospective analysis of the Scientific Registry of Transplant Recipients (SRTR) database between 2015 and 2024. Cases of 7-day GL were compared to a control cohort of patients with one-year graft survival. Donor, recipient, and operative variables were evaluated using multivariable

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logistic regression. **Results:** Among 4,112 pLT procedures, 137 cases (3.3%) experienced 7-day GL, including 63 deaths within the first 7 days. Primary causes of graft failure included primary nonfunction (PNF), vascular thrombosis (arterial or venous), infection, rejection and recurrent disease. Key risk factors for 7-day GL were retransplantation (OR: 2.42, $p = 0.002$), donor-to-patient height ratio (OR: 1.73, $p < 0.001$) and prolonged cold ischemia time (OR: 1.08, $p = 0.019$). Male donor sex was associated with a lower risk of 7-day GL (OR: 0.67, $p = 0.033$). Partial liver grafts had significantly higher odds of PNF compared to whole liver grafts (OR: 6.03, $p = 0.008$), as well as cold ischemia time (OR: 1.22, $p = 0.001$). Predictors of patient mortality within seven days included PNF (OR: 129.18, $p < 0.001$), thrombosis (OR: 65.11, $p < 0.001$), higher PELD scores (OR: 1.04, $p = 0.003$) and increased donor-to-patient height ratio (1.66, $p = 0.043$). Living donor transplantation was not significantly associated with reduced 7-day GL ($p = 0.124$) or mortality within the first 7 days ($p = 0.056$) compared to deceased donor pLT, although it comprised only 14.8% of the cohort ($n = 609$). **Conclusion:** Although accounting for only 3% of pLT cases, 7-day EGL represents the most serious adverse clinical outcomes. Clinicians must remain vigilant in improving modifiable risk factors, particularly graft size matching and minimizing cold ischemia time, which may improve early outcomes in pLT.

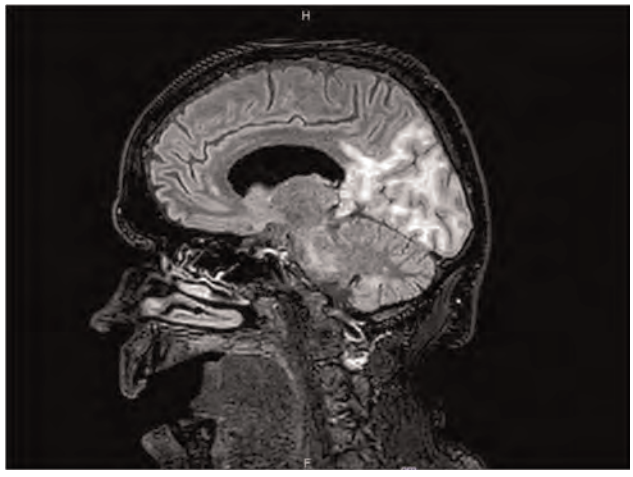
Disclosures: Louis Borsellino: Nothing to Disclose, Sohail Khan: Nothing to Disclose, Melanie Vugelman: Nothing to Disclose, Katherine Connors: Nothing to Disclose, Alexandra Zois: Nothing to Disclose, Olzhas Zhorayev: Nothing to Disclose, Jorge Ortiz: Nothing to Disclose

3516 | CONFRONTING THE COMPLEXITY OF PML: DIFFICULT MANAGEMENT DECISIONS

Ahmer Khan[1] Kinga Grzybowski[1] Aheed Javaid[2] Richard Kalman[1] Maria Lagarde[1], [1]Jefferson Einstein Philadelphia hospital, [2]Jefferson Abington Hospital

Background: Progressive multifocal leukoencephalopathy (PML) is caused by reactivation of JC virus (JCV). Initial infection with JCV occurs in childhood and antibodies can be found in most adults. JCV remains latent in kidneys and lymphoid organs, but in the context of profound cellular immunosuppression, JCV can reactivate. We present a therapeutic dilemma in a patient post liver transplantation who presented with concerns for PML. **Methods:** 56-year-old male with a past medical history of HCV cirrhosis post liver transplantation in early 2024 and multiple episodes of biopsy proven T-cell mediated rejection presented with a chief complaint of bilateral vision loss and intermittent confusion that were progressive over three weeks. **Results:** Current medications included mycophenolate and prednisone. Previously on tacrolimus, this was held due to development of PRESS. Physical examination and laboratory studies including liver function testing were unremarkable. An MRI of the brain demonstrated an increased burden of white matter signal abnormalities in multiple regions of the brain that were suspicious for PML. Other leading differentials included CNS immune reconstitution syndrome, atypical PRESS or posttransplant lymphoproliferative disorder. He underwent a lumbar puncture with CSF analysis as well as a brain biopsy. Unfortunately, his CSF PCR demonstrated JC virus, and a brain biopsy was consistent with PML. When we attempted to minimize his immunosuppression, his aminotransferases rose significantly, reflecting acute rejection which was reflected on a subsequent liver biopsy. **Conclusion:** PCR is the preferred approach to the diagnosis of PML. Brain biopsy remains the gold standard in patients who are difficult to diagnose. In patients without evidence of HIV infection who develop PML, the mainstay of therapy is discontinuation or reduction of any immunosuppressants when feasible. Unfortunately, when we attempted to reduce the doses of his immunosuppressants, he developed severe acute rejection with his ALT and AST rising to 2550 IU/L and 1600 IU/L respectively.

We were unable to reduce his immunosuppressants to suitable levels to treat his biopsy proven acute rejection and concurrently prevent progression of PML. After conversations with the patient's family, the decision was made to send him home on hospice without any of his immunosuppressive medications. This case highlights the difficult and rare balancing act that we encounter with HIV negative patients on immunosuppression who develop PML.



Disclosures: Ahmer Khan: Nothing to Disclose, Kinga Grzybowski: Nothing to Disclose, Aheed Javaid:

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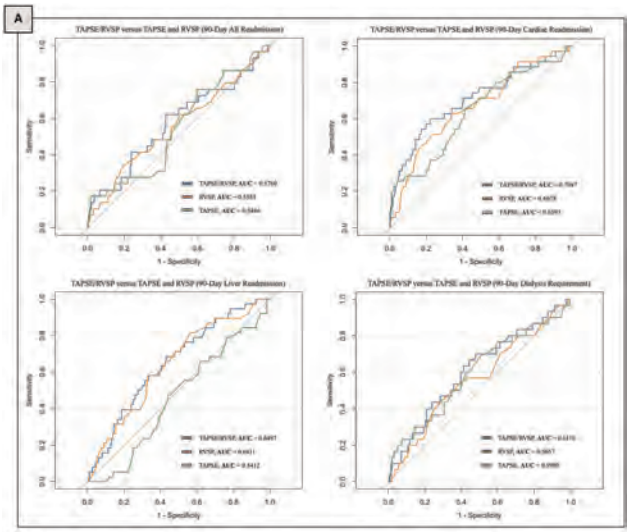
Nothing to Disclose, Richard Kalman: Gilead: Speaking and Teaching, Maria Lagarde: Nothing to Disclose

3517 | TRICUSPID ANNULAR PLANE SYSTOLIC EXCURSION (TAPSE) TO RIGHT VENTRICULAR SYSTOLIC PRESSURE (RVSP) RATIO: A NOVEL TOOL TO PREDICT CARDIAC OUTCOMES IN LIVER TRANSPLANT RECIPIENTS

Hong Lin[1] Melica Nikahd[2] Antonio Alvarez Castaneda[1] Khalid Mumtaz[1] Chathur Acharya[1], [1]The Ohio State University Wexner Medical Center, [2]The Ohio State University

Background: Patients with right ventricular (RV) dysfunction and portopulmonary hypertension (PoPH) face worse outcomes after liver transplantation (LT). Right ventricular systolic pressure (RVSP) is commonly used to assess RV hemodynamics prior to LT, but it only reflects afterload and does not account for RV adaptability, potentially overestimating risk in preserved RV function. Tricuspid annular plane systolic excursion (TAPSE) measures RV contractility and detects compensatory hypertrophy but ignores afterload. We hypothesize that the TAPSE/RVSP ratio may better assess RV-pulmonary coupling and predict post-LT cardiac outcomes. **Methods:** This retrospective study examined data from LT patients at The Ohio State University (2016-2020), analyzing pre-transplant transthoracic echocardiograms (TTE) within one year of LT. Receiver operating characteristic (ROC) curves assessed TAPSE/RVSP ratio, RVSP, and TAPSE in predicting 90-day all-cause and cause-specific (cardiac, hepatic, renal) readmissions as well as hemodialysis (HD) requirement. DeLong's test was used to compare areas under the curve (AUC); Wilcoxon rank-sum test and logistic regression were used to evaluate associations. **Results:** Out of 464 LT recipients, 226 had complete data. A majority were male (60.2%) and white (93.3%). Median values: RVSP 30.9 mmHg (12–61), TAPSE 2.60 cm (0.8–4.2), TAPSE/RVSP 0.092 cm/mmHg (0.014–0.217). ROC analysis of 90-day outcomes of all-cause, cardiac, and liver-related readmissions, as well as HD requirement (Figure 1A) revealed that TAPSE/RVSP outperformed RVSP alone ($p = 0.042$) and TAPSE alone ($p = 0.008$) in predicting cardiac readmission. Additionally, it was superior to RVSP ($p = 0.044$) for predicting HD requirement and to TAPSE ($p = 0.03$) for liver-related readmission, while performing similarly for 90-day all-cause readmissions. Wilcoxon/logistic regression supported these findings, though TAPSE/RVSP showed borderline significance for HD prediction (Figure 1B). On multivariate analysis (adjusted for age/sex/race/ESRD/PoPH), TAPSE/RVSP was associated with cardiac ($p = 0.0001$), liver ($p = 0.015$), and all-cause readmission ($p = 0.024$). **Conclusion:** The TAPSE/RVSP ratio, a novel, previously unreported metric in LT, predicts 90-day cardiac readmission better than RVSP or TAPSE alone while performing comparably for other outcomes. A lower ratio reflects impaired RV-pulmonary coupling, identifying maladaptive RV dysfunction and patients with high risk of cardiac morbidity post-LT.

A



B

Wilcoxon Rank Sum Test: TAPSE/RVSP Comparison Group	No Readmission	Readmission	P-value	Interpretation
90-day cardiac readmission	0.09 (0.07, 0.11)	0.07 (0.05, 0.09)	<0.001	**Significant**
90-day hepatic readmission	0.09 (0.07, 0.11)	0.07 (0.06, 0.09)	0.0036	**Significant**
90-day hemodialysis requirement	0.09 (0.07, 0.11)	0.08 (0.06, 0.1)	0.050	Borderline significance; needs more data
90-day all-cause readmission	0.09 (0.07, 0.11)	0.08 (0.06, 0.1)	0.014	**Significant**

Logistic Regression: TAPSE/RVSP Comparison Group	OR (95% CI)	P-value	Interpretation
90-day cardiac readmission	0.77 (0.66, 0.89)	0.0004	**Significant**
90-day hepatic readmission	0.83 (0.73, 0.95)	0.0054	**Significant**
90-day hemodialysis requirement	0.89 (0.78, 1.01)	0.0783	Not significant
90-day all-cause readmission	0.90 (0.83, 0.98)	0.0142	**Significant**

Disclosures: Hong Lin: Nothing to Disclose, Melica Nikahd: Nothing to Disclose, Antonio Alvarez Castaneda: Nothing to Disclose, Khalid Mumtaz: Nothing to Disclose, Chathur Acharya: Nothing to Disclose

3518 | COMPARABLE LONG-TERM OUTCOMES FOLLOWING LIVER TRANSPLANTATION IN PSC AND PSC-AIH OVERLAP SYNDROME: AN INTERNATIONAL COHORT STUDY

Matthew Peverelle[1] Andrew Chen[1] Ryan Hirsch[2] Deepak Joshi[3] Remco van Dijk[4] Adam Testro[1] Jeremy Nayagam[3], [1]Austin Hospital, [2]Monash Health, [3]King's College Hospital, [4]Leiden University Medical Center

Background: Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease that often requires

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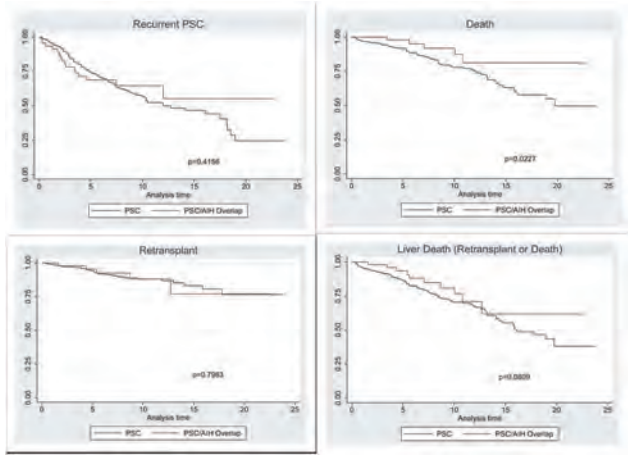
liver transplantation (LT). It is complicated by PSC recurrence (rPSC) in up to 27% of cases which increases the risk of graft failure and need for re-transplantation. A subset of patients present with PSC-autoimmune hepatitis (AIH) overlap syndrome, characterized by features of both biliary stricturing and hepatocellular inflammation. Treatment for PSC-AIH typically involves immunosuppression directed at the AIH component; however, LT is often still required. Outcomes after LT for PSC-AIH remain poorly defined. The aim of this study was to compare long-term post-LT outcomes between patients with PSC and PSC-AIH overlap syndrome. **Methods:** This retrospective cohort study included adult patients who underwent their first LT for PSC or PSC-AIH between 2000–2018 at three transplant centers: Austin Hospital (Melbourne, Australia), King's College Hospital (London, United Kingdom) and Leiden University Medical Centre (LUMC)(Leiden, Netherlands). Patients with early post-LT mortality, early retransplantation (<3 months from LT) or cholangiocarcinoma on explant were excluded. Data collected included demographics, liver disease characteristics, transplant details, immunosuppression and post-LT outcomes including rPSC, graft rejection, retransplantation, and survival. **Results:** A total of 265 patients were included in the analysis (218 PSC; 47 PSC-AIH) (84 Austin Hospital; 138 King's College; 43 LUMC) with mean follow-up of 9.9 years (no difference between groups). PSC-AIH patients were significantly younger at diagnosis (mean 25.1 vs. 38.3 years) and more frequently female (49% vs. 33%). Donor graft features were comparable as were cold and warm ischaemia times. Hepaticojejunostomies were more common in PSC patients than PSC-AIH patients (66% vs. 40%; $P=0.001$). Post-LT immunosuppression were similar in each group.

There was no significant difference in rates of rPSC (34.8% PSC-AIH vs. 41.3% PSC), $P=0.46$), rejection after 12 months (26% vs. 17%, $P=0.15$) or retransplantation (10.6% vs.12%, $P=0.79$). However, PSC-AIH patients had lower overall mortality (26.2% vs. 10.6%, $P=0.023$). After multivariate adjustment for confounders, this trended towards but did not remain significant ($P=0.078$). Hepaticojejunostomy emerged as an independent risk factor for rPSC (HR: 2.08 (1.13-3.83),$P=0.018$) and retransplantation (HR: 10.58 (2.35-47.58), $P=0.002$) in the overall cohort. In PSC patients, higher ALP levels at year 1 predicted rPSC diagnosis in year 2 (2.20 ± 1.40 x ULN vs.1.05 ± 0.71, $P=0.04$). **Conclusion:** Patients with PSC-AIH overlap have comparable rates of rPSC, graft rejection, retransplantation tand survival to those with isolated PSC following LT. These findings suggest that LT outcomes in PSC-AIH are at least equivalent to PSC, supporting similar management and surveillance strategies post-transplant.



Disclosures: Matthew Peverelle: Nothing to Disclose, Andrew Chen: Nothing to Disclose, Ryan Hirsch: Nothing to Disclose, Deepak Joshi: Mirum pharma: Speaking and Teaching, Ipsen Pharma: Speaking and Teaching, Mirum Pharma: Speaking and Teaching, Gilead Pharma: Speaking and Teaching, Q3 Medical: Speaking and Teaching, Advanz Pharma: Speaking and Teaching, Dr Falk: Speaking and Teaching, Remco van Dijk: Nothing to Disclose, Adam Testro: Nothing to Disclose, Jeremy Nayagam: Ipsen pharmaceuticals: Speaking and Teaching, Dr Falk: Speaking and Teaching, Ipsen pharmaceuticals: Consultant

3519 | MYOCARDIAL PERFUSION IMAGING: LIMITED PREDICTIVE VALUE FOR OBSTRUCTIVE CAD AND POST-TRANSPLANT OUTCOMES IN LIVER TRANSPLANT CANDIDATES

Ibrahim Alrajhi[1] Maryam Maryam[2] Waleed Haj Ahmad[3] Syeda Shamsi[3] Ahmad Alissa[2] Dieter Broering[4] Manhal Izzy[5] Mohamed Tahir[1] Saleh Alqahtani[6] Saad Alghamdi[7] waleed Alhamoudi[1] Bandar Aljudaibi[1], [1]King Faisal Specialists Hospital and Research Centre, [2]Alfaisal Univeristy, [3]Alfailsal Univeristy, [4]King Faisal Specialisits Hospital and Research Centre, [5]Vanderbilt University Medical Center, [6]Johns Hopkins University, [7]Washington University in St. Louis

Background: Cardiovascular risk assessment, including myocardial perfusion imaging (MPI), is routinely done in liver transplant (LT) candidates due to the high prevalence of coronary artery disease (CAD). However, the predictive value of MPI for obstructive CAD and post-LT outcomes remains unclear. The aim of the study is to to evaluate whether pre-transplant MPI can predict obstructive CAD and post-LT mortality and cardiac events. **Methods:** Retrospective analysis of 745 LT recipients (2015–2022) with pre-transplant MPI

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stress testing. Significant CAD was defined as ≥75% stenosis on cardiac catheterization. Outcomes included mortality, graft failure, and cardiac events (cardiac death, myocardial infarction [MI], arrhythmia, heart failure). Statistical analysis utilized chi-square tests, logistic regression, and Kaplan-Meier survival analysis. **Results:** Among 514 patients undergoing MPI, 91% (468/514) had normal results, while 8.5% (44/514) showed abnormalities. Only 34.6% (178/514) received β-blockers during testing. Abnormal MPI demonstrated poor sensitivity for obstructive CAD (4.3%). Post-LT, 13% (97/745) died, with 12.3% (12/97) attributed to cardiac causes. Cardiac catheterization revealed significant CAD in 4.8% (36/745). However, 93%% (29/31) of significant CAD patients had normal MPI results. MPI abnormalities did not independently predict mortality (OR 1.2, 95% CI 0.7–2.1) while the presence of significant of CAD on cardiac cath (OR 1.7, 95% CI 0.73-4.28) may indicate a clinically relative risk of mortality. The sensitivity and specificity of MPI for predicting significant CAD were 4.3% and 93.8%, respectively, with positive and negative predictive values of 6.5% and 90.9 %. **Conclusion:** MIBI has limited utility in predicting obstructive CAD or post-LT outcomes in LT candidates, as most obstructive CAD cases occurred in patients with normal MIBI. Over-reliance on MIBI may underdetect high-risk CAD, highlighting the need for integrated risk stratification, including invasive angiography in select patients. Further studies should optimize peri-transplant cardiac screening protocols.

	Significant CAD	Not Significant CAD	Total
MPI Abnormal	2	44	46
MPI Normal	29	439	468
Total	31	483	514

Disclosures: Ibrahim Alrajhi: Nothing to Disclose, Maryam Maryam: Nothing to Disclose, Waleed Haj Ahmad: Nothing to Disclose, Syeda Shamsi: Nothing to Disclose, Ahmad Alissa: Nothing to Disclose, Dieter Broering: Nothing to Disclose, Manhal Izzy: Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Mohamed Tahir: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Saad Alghamdi: Nothing to Disclose, waleed Alhamoudi: Nothing to Disclose, Bandar Aljudaibi: Nothing to Disclose

3520 | NEAR-INFRARED SPECTROSCOPY (NIRS) COULD PREDICT GRAFT QUALITY IN ADULT LIVER DONORS

Noelia De Armas[1] Julen Ramon[1] Diego López[1] Isabel Jaén[1] Adela Rojas[1] Gerardo Blanco-Fernández[1] Demetrio Pérez[1], [1]University Hospital Complex Badajoz

Background: In recent years, there has been an improvement in the outcomes of liver transplantation (LT), leading to an increase in its indications and demand for donor livers. To address this shortage, the use of livers from donors with expanded criteria has been introduced, where monitoring the degree of hepatic steatosis (HS) is crucial. The presence of HS >30% in donor livers has been associated with worse outcomes, with reduced survival of both the recipient and the graft and increased postoperative complications. In the process of the evaluation of the donor liver, significant discrepancies have been observed between the subjective opinion of the surgeon regarding the degree of HS and the results of the pathology study of the liver biopsy.

In recent years, the use of near-infrared spectroscopy (NIRS) systems, such as the INVOS device has become more widespread. This device measures the regional oxygen saturation (rSO2) of a tissue using infrared light.

The aim of the present study is to determine the usefulness of monitoring hepatic rSO2 using the INVOS system in the assessment of liver donors. **Methods:** An observational, longitudinal, and prospective study was conducted of adult patients undergoing liver transplantation at our center between 08/01/2020 and 06/01/2022.

We measured rSO2 by placing the sensor on the donor skin at the right hypochondrium and on the liver surface. At the end of the LT, a biopsy of the liver graft is taken, which is sent to the Pathology Service for analysis. **Results:** The rSO2 measurements on the donor skin were obtained in 27 patients (93.1%), while the measurements on the donor liver were taken in 18 patients (62.1%).

Donors with lower preoperative AST values had statistically significantly higher rSO2 values measured on the skin ($p = 0.046$). This same trend toward higher rSO2 values on donor skin in patients with lower transaminase values was also observed in the case of ALT, although the difference was not significant ($p = 0.110$). A trend was also observed toward higher rSO2 values on donor skin in patients with a lower Donor Risk Index (DRI), although the results did not reach statistical significance ($p = 0.07$)

We found a statistically significant relationship between the rSO2 values measured on the donor liver and the degree of steatosis ($p = 0.001$). Patients with lower rSO2 values had a higher degree of HE in the subsequent pathology study. rSO2 values >57% measured on the donor liver were associated with HS <30% (S:92%; E:75%). **Conclusion:** The measurement of hepatic rSO2, both through the skin and directly on the donor liver, is associated with key parameters of LT success, such as DRI, transaminases, and the degree of HS.

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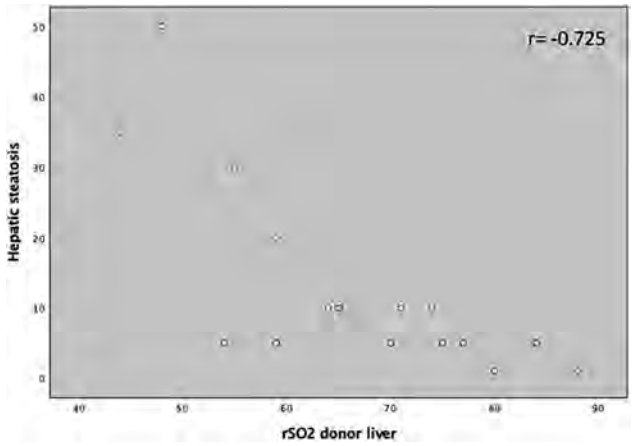


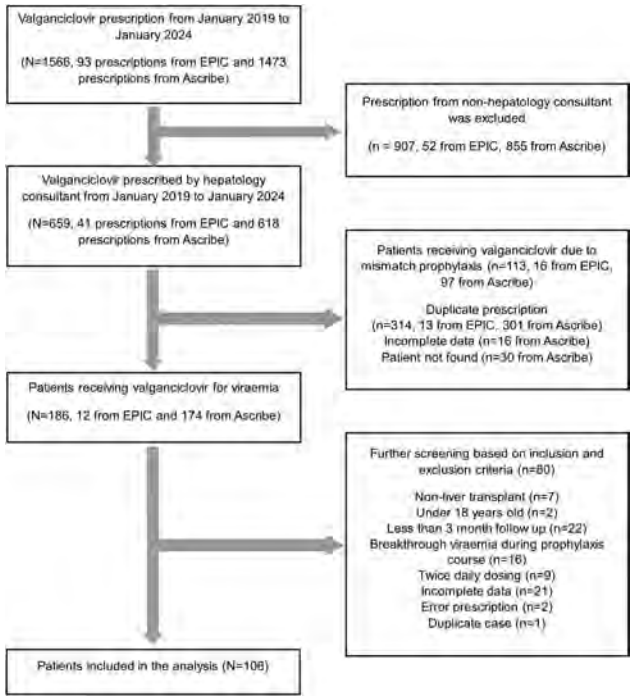
Disclosures: Noelia De Armas: Nothing to Disclose, Julen Ramon: Nothing to Disclose, Diego López: Nothing to Disclose, Isabel Jaén: Nothing to Disclose, Adela Rojas: Nothing to Disclose, Gerardo Blanco-Fernández: Nothing to Disclose, Demetrio Pérez: Nothing to Disclose

3521 | OUTCOMES OF LOW-DOSE VALGANCICLOVIR IN TREATMENT OF POST LIVER TRANSPLANT CYTOMEGALOVIRUS VIRAEMIA: A RETROSPECTIVE, SINGLE-CENTRE STUDY

Alison Rowley[1], [1]King's College Hospital

- **Background:** Cytomegalovirus (CMV) viraemia is associated with direct and indirect adverse effects in post-liver transplant patients [1].
- To date, valganciclovir (VGV) 900 mg BD is a standard dose for post-transplant CMV viraemia treatment [2]. However, haematological adverse reaction and renal function limit its use.
- In prophylaxis context, lower dose VGV has shown non-inferiority [3], but limited studies evaluating lower dose VGV in treatment context.

At King's College Hospital, VGV 900 mg OD has been prescribed in post-liver transplant CMV viraemia. Anecdotal experience has shown good outcomes and tolerability. **Methods:** A retrospective, descriptive service evaluation was conducted at a liver transplant centre at King's College Hospital NHS Foundation Trust. From January 2019 to January 2024, patients receiving valganciclovir for post-liver transplant CMV viraemia were identified and followed up for at least 3 months. Baseline characteristics and outcomes representing response to treatment (time to eradicate CMV, incidence of CMV infection, and treatment escalation), tolerability (haematological adverse reaction, renal function, and early discontinuation or dose reduction), and resistance were documented. **Results:** A total of 106 patients were included in the study. 98% of the population had asymptomatic viraemia. 72% of the population achieved viral eradication within 1 month, with only 2% had to undergo treatment escalation. Despite leukopenia (34%), neutropenia (33%), and thrombocytopenia (17%) occurred within 3-month course, only 10% of the patients need dose adjustment (7%) or early discontinuation (3%). Resistance was observed in 1 patient, leading to prolonged treatment course. **Conclusion:** In this hospital setting, most of the population receiving once-daily dosing of valganciclovir attain favourable outcomes with good tolerability. Resistance event was infrequent but should be carefully managed.



Disclosures: Alison Rowley: Nothing to Disclose

3522 | THE NATURAL HISTORY OF SPUR CELL ANEMIA AFTER LIVER TRANSPLANTATION AND ITS IMPACT ON SURVIVAL

Hasan Alroobi[1] Kevin Houston[1] Richard Stravitz[2] Amon Asgharpour[2] Scott Matherly[2] Joel Wedd[2] Hannah Lee[3] Mohammad Siddiqui[2] Vaishali Patel[2] Sayed Aseem[2] David Bruno[4] Richard Sterling[2], [1]Virginia Commonwealth University Health System, [2]Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University Health Sys, [3]Division of

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Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University Health S, [4]Hume-Lee Transplant Center, Virginia Commonwealth University Health System; Richmond VA

Background: Spur cell anemia (SCA) is common in patients (pts) undergoing liver transplant (LT). The prevalence of SCA, its natural history and how it impacts survival in pts undergoing LT is poorly defined. To address this gap in knowledge, we examined the prevalence of SCA and its associations in those undergoing LT and its impact on 1 year survival. **Methods:** In this retrospective analysis, all pts receiving LT transplanted between 10/18-4/24 with 1 year of follow up data were included. All data were extracted from the electronic medical records from the time of listing until the time of most recent follow up post-LT under the approved Liver Transplant Registry. SCA was defined by the presence of spur cells on peripheral smear or by clinical record. Those with and without spur cell anemia were compared by univariate and multivariate analysis. The primary outcomes were prevalence and predictors of SCA and its impact on 1-year pt survival. **Results:** 451 pts met eligibility: mean (SD) age was 52 (13), 56% were male, 77% White/16% Black/3% Asian, and 95% non-Hispanic. The etiologies of liver disease were MASLD (25%), alcohol (49%), HCV (11%), autoimmune hepatitis (3%), PBC (2.5%), and PSC (6%) with MELD 23.3 (11.5). At LT, 55% had SCA. Pts with SCA were younger (49 vs 56), had higher total (13.7 vs 4.8 mg/dL) and direct (8.2 vs 3.1 mg/dL) bilirubin, INR (2.29 vs 1.56), MELD (28 vs 17), lower Hgb (9.1 vs 11.3 g/dL)(all $p < .0001$), were more likely to have ascites (61% vs 33%; $p < .001$), hepatic encephalopathy (HE) (63% vs 42%), acute kidney injury (AKI) (79% vs 38%) and more likely to have alcohol-related liver disease (71% vs 41%)(all $p < .0001$) and less likely to have diabetes (46% vs 58%; $p = .03$). Independent predictors of SCA at LT were age ($p = .0002$), HE ($p = .02$), AKI ($p < .0001$), and alcohol-related liver disease with < 6mo sobriety ($p = .01$). SCA resolved by 1-year after LT in 94% and developed in 4%. Those with SCA at the time of LT had slightly lower 1-year survival (96% vs 98%; $p = .01$). After adjusting for liver disease etiology and MELD, SCA remained associated with lower 1-year survival ($p = .04$). **Conclusion:** SCA is common in those undergoing LT and related to both demographic and clinical factors and more common in those with alcohol-related liver disease. While it resolves in the majority, it is associated with lower 1-year survival. Future studies to determine why those with SCA at time of LT have lower survival are needed. **Disclosures:** Hasan Alroobi: Nothing to Disclose, Kevin Houston: Nothing to Disclose, Richard Stravitz: Nothing to Disclose, Amon Asgharpour: Nothing to Disclose, Scott Matherly: Nothing to Disclose, Joel Wedd: Nothing to Disclose, Hannah Lee: Nothing to Disclose, Mohammad Siddiqui: Nothing to Disclose, Vaishali Patel: Nothing to Disclose, Sayed Aseem: Kezar: Consultant, David Bruno: Nothing to Disclose, Richard Sterling: ABIM: GI Specialty Board, Abott: Grant/Research Support, AbbVie: Grant/Research Support, Roche: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research Support

3523 | DISPARITIES IN SCREENING FOR AND PREVALENCE OF LOW BONE MINERAL DENSITY FOLLOWING LIVER TRANSPLANT

Katherine Cooper Darya Herscovici[1] Jenna Patel[1] Deepika Devuni[1], [1]UMass Chan Medical School

Background: Liver transplant recipients (LTR) experience accelerated bone loss, especially in the first post-LT year, placing them at increased the risk of osteoporosis and its associated complications. There are limited recent data regarding screening for and the incidence of low bone mineral density (BMD) in LTR. In this study, we characterize BMD screening, treatment, and follow up in adult LTR. **Methods:** This is a retrospective analysis of LTRs at a safety net hospital and LT center between 2017-2022. We assessed the rate BMD screening, defined as receipt of a dual x-ray absorptiometry (DEXA) scan, following LT. Timing of screening was categorized as early ($\leq$ 6 months), standard (6-18 months), and delayed ($\geq$ 18 months). To identify factors associated with screening, we compared sociodemographic factors in those with and without a DEXA scan. Screening recipients were categorized as Low BMD or Normal BMD. Low BMD included those with either osteoporosis (OPo, T-score $\leq$ -2.5) or osteopenia (OPe, -2.4 $\geq$ T-scores $\leq$ -1.0) on initial DEXA scan. Treatment of Low BMD was categorized as None, Calcium/Vitamin D only, and BMD-specific treatment. Repeat DEXA scans were assessed for improvement as available. Factors associated with Low BMD, BMD Treatment and BMD improvement were explored. **Results:** Among 266 LTR, 44% ($n = 118$) underwent BMD screening (27 early, 33 standard, 58 delayed). The median time to DEXA was 512 days (IQR 201-1143). Receipt of post-LT DEXA did not differ by age ($p = 0.20$), sex ($p = 0.35$), race/ethnicity ($p = 0.34$), or liver disease etiology ($p = 0.36$). Low BMD was identified in 76.3% patients ($n = 90$) with OPe prevalence of 47.5%($n = 56$) and OPo prevalence of 28.8% ($n = 34$). The most common site of low BMD site was the femoral neck ($n = 82$) followed by lumbar spine ($n = 53$) and total hip ($n = 33$). Prevalent Low BMD decreased with increasing BMI: $<$ 22 -

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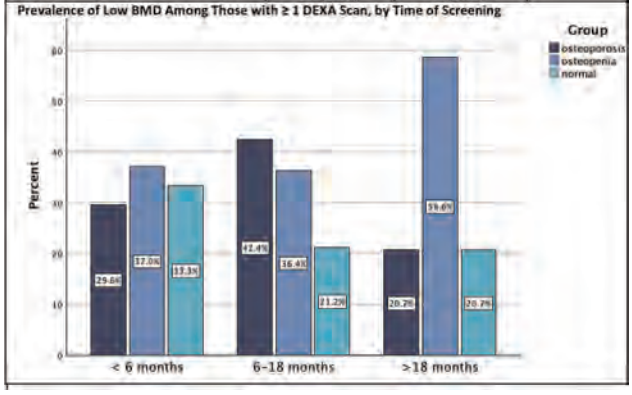
88.9%, 22-24 - 85.7%, 25-29 - 77.5%, 30-34 - 67.9%, and ≥ 35 - 66.7%. Most Low BMD patients (n = 66) received treatment but only 25 received BMD-specific therapy with Alendronate (n = 8), Denosumab (n = 3), Zoledronic Acid (n = 11) or Biologics (n = 4). Patients who received BMD-specific therapy were more likely to have OPo (84.0% vs. 20.0%, p < 0.01) and MASLD (32.0% vs. 15.1%, p-0.05). BMD status varied by timing of DEXA scan, where early scans identified lower rates of Low BMD compared to standard/delayed DEXA (66.7% vs. 79.8%). Patients with normal DEXA (7.1%, n = 2) were less likely to have a repeat scan than patients with OPe (14.3%, n = 8) or OPo (26.5%,n = 9). Improvement in BMD was noted in 82% of those with initial Low BMD, and this was mostly observed in those who received BMD-specific treatment (90.9% vs. 44.4%, p = 0.02). **Conclusion:** Less than 50% of LTR in this cohort received screening for BMD, and among those screened the prevalence of Low BMD was exceedingly high. Early screening may miss cases low BMD, suggesting that repeat testing is needed after ≥ 6-18 months, even when initial scans are normal, to allow for adequate treatment.

	No DEXA (n=148)	DEXA (n=118)	p value
Age group			0.202
<45 years	38 (25.7%)	23 (19.5%)	
45-59 years	57 (38.5%)	58 (49.2%)	
≥ 60 years	53 (35.8%)	37 (31.4%)	
Patient Sex			0.350
Female	73 (49.3%)	65 (55.1%)	
Male	75 (50.7%)	53 (44.9%)	
Race/ethnicity			0.337
White, non-Hispanic	119 (80.4%)	92 (78.0%)	
White, Hispanic	11 (7.4%)	8 (6.8%)	
Non-white, Hispanic	12 (8.1%)	7 (5.9%)	
No-white, non-Hispanic	6 (4.1%)	11 (9.3%)	
Liver Disease Etiology			0.359
Alcohol	81 (54.7%)	70 (59.3%)	
MASLD	21 (14.2%)	22 (18.6%)	
Hepatitis C	21 (14.2%)	10 (8.5%)	
AILD	10 (6.8%)	9 (7.6%)	
Other	15 (10.1%)	7 (5.9%)	
Hepatocellular carcinoma			0.683
No HCC	136 (91.9%)	110 (93.2%)	
HCC	12 (8.1%)	8 (6.8%)	



Disclosures: Katherine Cooper: Nothing to Disclose, Darya Herscovici: Nothing to Disclose, Jenna Patel: Nothing to Disclose, Deepika Devuni: Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Avania Medical: Grant/Research Support, Intercept: Grant/Research Support, Avania Medical: Grant/Research Support, Intercept: Grant/Research Support

3524 | PLASMA CELL-RICH REJECTION AFTER LIVER TRANSPLANTATION: NEW INSIGHTS INTO EVOLVING RISK FACTORS AND ETIOLOGIES

Thuy-Duyen Nguyen[1], [1]Mayo Clinic

Background: Plasma cell-rich rejection (PCRR) is an important and potentially severe cause of allograft dysfunction following liver transplantation (LT), with the potential to progress to graft failure and necessitate re-transplantation. PCRR is considered part of the spectrum of antibody-mediated rejection (AMR) and T-cell mediated rejection (TCMR). Despite its clinical significance, there is limited research on the risk factors that predispose liver transplant recipients to developing PCRR, highlighting a critical gap in the current understanding of its pathogenesis and prevention. **Methods:** Our study involved comprehensive data collection across 3 institutional sites of liver transplant recipients with liver biopsies demonstrating evidence of PCRR based on the 2016 update from the Banff Working Group on liver allograft pathology – plasma-cell rich infiltrate with etiology of liver disease other than autoimmune hepatitis (AIH). We compared this group to those who were transplanted for autoimmune hepatitis with liver biopsies demonstrating plasma cell hepatitis. **Results:** A total of 60 patients were identified in our patient cohort with 45 patients transplanted for an etiology excluding AIH and 15 patients transplanted for AIH. In the Non-AIH group, the most common etiology for liver transplant was primary sclerosing cholangitis (26.7%) and metabolic associated steatohepatitis (24.4%). The AIH group had more females (86.7% vs 49%, p = 0.03). Similar allografts were seen in both groups with no significant difference in average age of donor, donor:recipient gender mismatch and cold ischemic time. PCRR was more common within the first 2 years of transplant. The average rejection activity index score was 6.7 in the non-AIH group despite immunosuppression being therapeutic in 80% at time of PCRR. Sixteen percent of the PCRR cases had a prior infection with cytomegalovirus. **Conclusion:** This study represents the largest case series to our knowledge in evaluating PCRR. In the most recent series published in 2023, Ozturk et al. identified hepatitis C virus (HCV) as the most common underlying cause associated with

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PCRR. However, with the advent of highly effective antiviral therapies, the incidence of HCV-related liver transplantation has significantly declined. In contrast, our findings suggest that patients undergoing transplantation for primary sclerosing cholangitis (PSC) and metabolic dysfunction-associated steatohepatitis (MASH) exhibit a higher incidence of PCRR, indicating a potential shift in the at-risk population. Further when compared to those transplanted for AIH, overall treatment and risk factors appeared similar between the two groups.

Ozturk et al. Histologic and clinical outcomes of patients developing post-liver transplant plasma cell-rich rejection. Am J Clin Pathol. 2023. 160(1): 49-57

Table 1. Patient Characteristics

	Transplant Indication Not Autoimmune Hepatitis	Transplant Indication Autoimmune Hepatitis	Sig
N	45	15	
Female (%)	22 (49%)	13 (86.7%)	**p=0.03**
Mean age at transplantation, years (SD)	52 (14.6)	47 (19.2)	p=0.42
Allograft type			
Live Donor	2.2%	-	
DBD	71.1%	66.7%	p=0.99
DBD using NMP	12.5%	-	
DCD	22.2%	20.0%	p=0.99
DCD using NMP	70.0%	33.3%	p=0.51
Mean donor age, years (SD)	48.5 (20.5)	38.8 (22.5)	p=0.13
Donor:recipient gender mismatch (%)	46.3%	50.0%	p=0.76
Cold ischemia time, min (SD)	459.2 (282.2)	423.5 (278.2)	p=0.78
Primary etiology of liver disease			
Autoimmune hepatitis	-	15	
Alcohol-related	9	-	
Metabolic dysfunction-associated	11	-	
Primary biliary cholangitis	4	-	
Primary sclerosing cholangitis	12	-	
Chronic viral hepatitis	4	-	
Other*	5	-	
ACR within 2 years of transplantation	55.6%	26.7%	p=0.07
Mean RAI at ACR diagnosis (0-9 Scale)**	8.7	5.5	p=0.13
Prior episodes of acute cellular rejection	35.6%	60.0%	p=0.07
Initial ACR treatment regimen			
Methylprednisolone or prednisone	86.7%	100.0%	p=0.32
Thymoglobulin	6.7%	-	
Other	6.7%	-	
>1 ACR treatment regimen	11.1%	13.3%	p=0.99
Immunosuppression therapeutic at ACR diagnosis	79.5%	69.2%	p=0.47
Prior CMV infection within 12 months of ACR	16.3%	30.8%	p=0.42
Mean time from CMV infection to ACR, months (SD)	5.4 (4.1)	3.1 (1.4)	p=0.39
Concurrent autoimmune disease	28.9%	40.0%	p=0.52
Allograft failure due to chronic rejection	-	-	

Table 1 Legend:
Statistical significance was assessed using the Mann-Whitney Test given non-parametric data distribution
ACR = acute cellular rejection; CMV = cytomegalovirus; DBD = donation after brain death; DCD = donation after circulatory death; RAI = rejection activity index
* Other = Wilson disease (1), acute liver failure (1), congenital hepatic fibrosis (1), polycystic liver disease (1), drug induced liver injury (1)
**Rejection Activity Index score was missing in 51% patients transplanted for non-AIH causes and 67% of patients transplanted for AIH

Disclosures: Thuy-Duyen Nguyen: Nothing to Disclose

3525 | PULMONARY FUNCTION TESTS AND FRAILTY ARE NOT ASSOCIATED WITH POST-LIVER TRANSPLANT VENTILATOR TIME, LENGTH OF INDEX HOSPITALIZATION OR RESPIRATORY COMPLICATIONS

Elina Stoffel[1] Avesh Thuluvath[2] Yuan Zhang[1] Elizabeth Verna[1], [1]Columbia University Medical Center, [2]Columbia University Irving Medical Center

Background: Pulmonary function tests (PFTs) are routinely performed during liver transplant (LT) evaluation, but their impact on post-LT outcomes is unclear. The interplay between pulmonary function and frailty is also unknown. We hypothesized that frailty could impair thoracic respiratory muscles, resulting in prolonged ventilator dependence and increased risk of respiratory complications after LT. In this retrospective study, we examined associations between pre-LT frailty, PFTs, and post-LT outcomes. **Methods:** We conducted a retrospective study of adults with cirrhosis who received LT at a large volume LT center from 2/2016-12/2024 and underwent pre-LT PFTs and frailty assessment using the Liver Frailty Index (LFI: grip strength, chair stands, balance). Patients with multi-organ or prior liver or lung transplants were excluded. Patients were classified as frail or not frail using established LFI cut-offs. Pulmonary function (FVC, FEV_1, FEV_1/FVC ratio, and DLCO) was assessed using spirometry $\pm$ body plethysmography and categorized as normal (FEV_1/FVC ratio $\geq 70\%$, FVC $\geq 80\%$, FEV_1 $\geq 80\%$), obstructive (FEV_1/FVC ratio $< 70\%$), or restrictive (FEV_1/FVC ratio $\geq 70\%$, FVC $< 80\%$) patterns. Primary outcomes were post-LT ventilator time, index ICU length of stay (LOS), and total index hospital LOS. The secondary outcome was post-transplant respiratory complications (a composite endpoint including pneumonia, pulmonary edema and pleural effusions) during the index admission. Multivariable linear and logistic regression were used to assess associations. **Results:** 175 patients were included (Table 1); 65% were male and the mean age was 60.7 years (SD $\pm$ 13.4). The most common etiologies included alcohol-associated liver disease (25%) metabolic-associated liver disease (17%) and autoimmune etiologies (AIH, PSC < PBC) (18%). Mean MELD score at LT was 15.3 $\pm$ 6.9. Mean LFI was 4.13 $\pm$ 0.79; 41 (23.4%) classified as frail. On univariable analysis, obstructive lung disease was associated with longer ventilator time ($p = 0.05$) but not index ICU LOS, hospital LOS, or respiratory complications. On multivariable analysis adjusting for age, BMI, MELD score, intra-op fluids, and history of COPD, asthma or CHF, obstructive lung disease was no longer associated with ventilator time or hospital LOS. Obstructive lung disease with frailty was associated with greater ventilator time ($p < 0.01$) and ICU LOS ($p = 0.04$) compared to obstructive lung disease without frailty. However, this association did not persist in adjusted models. **Conclusion:** Pre-LT PFT patterns were not associated with post-LT ventilator time, ICU LOS, or hospital LOS. These results differ from prior data suggesting that restrictive lung disease is associated with longer post-LT ventilator time, ICU LOS and hospital LOS. Additionally, our findings suggest that frailty is not associated with ventilator time or respiratory outcomes as hypothesized.

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Table 1 Baseline Characteristics of Liver Transplant Recipients by Frailty Status

Characteristic	Frail (N=41)	Non-Frail (N=134)	p-value[1]
Age	64 (11.4)	59.7 (13.8)	0.48
Sex (% male)	21 (52.5%)	93 (69.4%)	**0.04**
BMI, mean +/- SD	26.9 (7.03)	27.5 (5.53)	0.28
Race			0.08
White	24 (58.5%)	88 (65.7%)	
Black	2 (4.9%)	12 (9.0%)	
Asian	1 (2.4%)	12 (9.0%)	
Unknown	14 (34.1%)	22 (16.4%)	
MELD at LT +/- SD	17.8 (7.72)	14.5 (6.40)	**0.01**
Etiology of ESLD (%)			0.13
ALD	14 (34.1%)	29 (21.6%)	
MAFLD	9 (22.0%)	21 (15.7%)	
Hepatitis B/C	4 (9.8%)	22 (16.4%)	
Autoimmune	3 (7.3%)	28 (20.9%)	
Etiologies	11 (26.8%)	34 (25.4%)	
PFT Pattern			0.002
Normal	10 (24.4%)	69 (51.5%)	
Restrictive	14 (34.1%)	18 (13.4%)	
Obstructive	2 (4.9%)	10 (7.5%)	

[1] *t-test, Fisher's exact test, Wilcoxon rank sum test*

Disclosures: Elina Stoffel: Nothing to Disclose, Avesh Thuluvath: Nothing to Disclose, Yuan Zhang: Nothing to Disclose, Elizabeth Verna: Nothing to Disclose

3526 | DELISTING DUE TO CLINICAL IMPROVEMENT (DCI) AS A SURROGATE FOR RECOMPENSATION IN THE ERA OF EFFECTIVE TREATMENTS FOR SEVERAL ETIOLOGIES OF DECOMPENSATED CIRRHOSIS: ANALYSIS OF UNOS DATA

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Background: Recompensation is increasingly being recognized as a tangible outcome for patients with decompensated cirrhosis for whom therapeutic strategies exist to interrupt and potentially reverse disease progression. Delisting from the liver transplant (LT) waitlist due to clinical improvement may be utilized as a surrogate for recompensation. Given that existing data in this context remain limited, we aimed to examine their rates and predictors. **Methods:** This retrospective cohort study using the Organ Procurement and Transplantation Network database identified ≥18-year-old patients listed for first LT alone between 01/01/2005 and 12/31/2024. Patients with acute liver failure or listed for primary liver malignancy were excluded. Characteristics of patients were obtained at waitlisting and waitlisting removal. Delisting due to clinical improvement (DCI) was identified using waitlist removal codes and was compared by disease etiology. A secondary outcome of relisting after prior DCI was also examined. We developed two recompensation criteria: (i) DCI plus MELD/MELD-Na by ≥3 points (DCI-MELD3) and (ii) DCI plus improvement in Child-Turcotte-Pugh (CTP) class (DCI-CTP). **Results:** Among 127,168 patients listed for LT, there were 8,747 that had DCI. Delisting rates were highest in hepatitis B (HBV) at 9.9%, alcohol-associated liver disease (ALD) at 8.3%, and autoimmune hepatitis (AIH) at 8.2%. Patients who were delisted within 3 years of initial listing had higher MELD, bilirubin, and INR and were more likely to have ascites at both initial listing and removal when compared to those delisted in ≥3 years (all $p < .001$). Among the patients with DCI, 49.1% achieved DCI-MELD3 and 48.6% DCI-CTP. Additionally, 9.6% were subsequently relisted after DCI, of which 33.0% were for hepatocellular carcinoma. On univariable analysis, meeting DCI-MELD3 or DCI-CTP were equivalent in their association with reduced relisting for LT: HR 0.77 and HR 0.79 versus meeting neither, respectively ($p = 0.005$ and $p = 0.03$; Table). In multivariable analyses, only patients who met both definitions had a significantly lower likelihood of relisting with an adjusted HR 0.52 ($p < 0.001$, Table). Other factors independently associated with increased relisting included: albumin <3.5 g/dL at initial DCI, male sex, and diagnosis of metabolic dysfunction-associated steatohepatitis, hepatitis C, primary biliary cholangitis, and primary sclerosing cholangitis (versus ALD as reference) (all $p < .001$). **Conclusion:** DCI occurred in a meaningful proportion of patients listed for LT, especially in HBV, ALD, and AIH. Nearly half of patients met criteria for improvement by MELD or CTP criteria alone at the time of delisting, with close to ten percent being subsequently relisted. Meeting both MELD and CTP-based definitions was linked to the lowest relisting risk, which may support their use in identifying true recompensation.

	HR (95% CI)	p-value
Unadjusted Recompensation criteria met at delisting		
Neither criteria	Reference	
MELD improvement ≥3 points only	0.769 (0.640-0.925)	0.005
Improvement in CTP class	0.792 (0.642-0.977)	0.03
Improvement MELD ≥3 points and CTP class	0.467 (0.383-0.569)	<.001
Adjusted* Recompensation criteria met at delisting		
Neither criteria	Reference	
MELD improvement ≥3 points only	0.865 (0.718-1.04)	0.13
Improvement in CTP class	0.861 (0.697-1.06)	0.164
Improvement MELD ≥3 points and CTP class	0.525 (0.429-0.643)	<.001

**Multivariable model adjusted for sex, age at delisting, and primary liver disease*

Disclosures: Alexandra McCullough: Nothing to Disclose, Nadim Mahmud: Grifols: Grant/Research

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Support, K Rajender Reddy: Nothing to Disclose, Therese Bittermann: Nothing to Disclose

3527 | ASSOCIATION BETWEEN PRE-LIVER TRANSPLANT CORONARY ARTERY DISEASE RISK AND ALL-CAUSE MORTALITY AFTER LIVER TRANSPLANT: A SINGLE CENTER EXPERIENCE

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Background: CVD is a leading cause of death after LT. Pre-LT CAD risk stratification guides pre-op optimization. Limited data exists on the relationship between pre-LT CAD risk stratification and all-cause mortality post-LT. The primary aim of this study was to examine the association between pre-LT CAD risk classification and all-cause mortality post-LT. **Methods:** Patients who had LT at a single center from 2012 to 2018 with follow-up through 2024 were reviewed. Pre-LT CAD risk groups were: low (no CAD risk factors, age < 40, and achieves ≥ 4 METs), intermediate (< 2 CAD risk factors, no diabetes, and no MASH), high (silent MI on ECG, new wall motion abnormality on ECHO, new EF $< 50\%$, diabetes, MASH, or ≥ 2 CAD risk factors), and very high (prior CAD, PCI, MI, CABG, or CVD). CVD included CAD, CVA, PAD, or aortic atherosclerosis. CAD risk factors included: hypertension, hyperlipidemia, CKD with eGFR < 40, left ventricular hypertrophy, tobacco use, family history of early CAD, and age > 60. Post-LT all-cause mortality for the other CAD risk groups were compared to low risk. **Results:** Among 576 LT recipients, 37.5% were female, mean age at LT 57 $\pm$ 10 years, 92.0% White. Primary indication for LT was MASH 29.9%, and alcohol 24.0%. Before LT, average BMI was 30 $\pm$ 6, tobacco use 51%, hypertension 46.5%, diabetes 36.5%, hyperlipidemia 22.1%, CAD 13.9%, CHF 7.1% and atrial fibrillation 5.0%. Pre-LT CAD risk groups included 7.3% low risk, 16.5% intermediate risk, 60.5% high risk, and 15.7% very high risk. By the end of 2024, 147 deaths (25.5%) had occurred. Infections accounted for 32% of deaths, cancer 16.3%, liver allograft failure 13.6%, CVD 11.6%, respiratory failure 3.4%, renal failure 2.7%, other 13.6%, and undetermined 6.8%. All-cause mortality in the CAD low risk group was 19.5%, intermediate risk 23.7%, high risk 25.4%, and very high risk 31.5%. Compared to low CAD risk, all-cause mortality OR in intermediate risk was 1.28 (95% CI 0.52, 3.17), high risk 1.41 (95% CI 0.63, 3.16), and very high risk 1.89 (95% CI 0.78, 4.6). **Conclusion:** Most LT recipients were considered to be high CAD risk based on the pre-LT CAD risk classification protocol at a single center. Increasing pre-LT CAD risk was associated with higher odds of all-cause mortality post-LT which were not statistically significant.

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3528 | LONG TERM OUTCOME AND TIPS PLACEMENT FOR THE TREATMENT OF VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME AFTER LIVER TRANSPLANTATION: A SINGLE CENTRE EXPERIENCE

Michela Triolo[1] Mauro Viganò[1] Filippo Leonardi[1] Luisa Pasulo[1] Massimo De Giorgio[1] Paolo Marra[1] Aurelio Sonzogni[2] Elisa Licini[1] Stefania Camagni[1] Cinzia Giaccherini[1] Riccardo Muglia[3] Domenico Pinelli[3]

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Background: Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) after liver transplantation (LT) is a rare complication, and best treatment and long-term outcome are still undefined. Aim of this study is to evaluate the management and outcome of VOD/SOS after LT. **Methods:** All patients transplanted at Liver Transplant Center of the ASST Papa Giovanni XXIII Hospital in Bergamo who consecutively developed VOD/SOS were retrospectively evaluated. **Results:** Among the 1123 adult patients who underwent LT between 1997-2022, 37 (3%) patients [70% males, median age 51 years, 49% viral-etiology, 19 % Hepatocellular carcinoma (HCC), Model for End-Stage Liver Disease (MELD)-Na 14 (11-26)] had histologically proven VOD/SOS. All patients presented with ascites, associated with hydrothorax in 4 (11%) cases. Median time of VOD/SOS onset was 45 (10-432) days and median hepatic venous pressure gradient (HVPG) was 13.5 (8-22) mmHg. In 6 (16%) patients VOD/SOS developed 24 (13-201) days after acute cellular rejection (ACR), whereas 2 (5%) patients had concomitant ACR and VOD/SOS occurrence. After two months from VOD/SOS onset, 18 (49%) of patients solved ascites: 5 (28%) spontaneously, 2 (11%) with defibrotide and 11 (61%) after transjugular intrahepatic portosystemic shunt (TIPS) placement. TIPS placement was independently associated with ascites resolution at 2 months [HR 3.26 (1.25-8.46), $p = 0.015$]. Overall, during a median follow up of 62 months, 14 (38%) patients showed spontaneous clinical improvement after a median time of 41 days (17-259) and 23 (62%) underwent TIPS placement, The latter patients had HVPG reduced from 14 (3-40) to 8 mmHg (2-20), 3 (13%) developed porto-systemic encephalopathy, which resolved with medical therapy in 2 cases and with TIPS caliber reduction in the other one. Patients treated with TIPS had higher HVPG values and were younger compared those patients who experienced spontaneous clinical improvement [HR 4.4 (1.61-12.10), $p = 0.004$ and HR 0.96 (0.93-0.99), $p = 0.016$, respectively]. Overall, 4 (11%) patients needed re-OLT, 1 (3%) for tipsitis, 1 (3%) for hepatic arterial thrombosis and 2 (5%) for delayed dysfunction of graft whereas 15 patients died, 3 (8%) for HCV recurrence, 3 (8%) for hepatocellular carcinoma (HCC) recurrence, 4 (11%) for sepsis, 1 (3%) for lung cancer, 2 (5%) for myocardial infarction, 2 (5%) for ictus. The 1-, 3-, and 5-year survival rates did not differ significantly between patients who experienced spontaneous resolution of ascites and those who required TIPS placement [100%, 97% and 71% vs 95%, 73%, and 56%, respectively (HR = 4.75; 95% CI: 0.58–38.7)]. **Conclusion:** VOD/SOS is a rare post-LT complication associated with ACR in nearly a quarter of cases. HVPG $\geq$ 13.5 mmHg at VOD/SOS diagnosis identified patients without spontaneous clinical improvement that need TIPS placement. TIPS appears to be a safe and effective treatment for SOS/VOD, with no significant impact on long-term survival.

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3529 | PRE-TRANSPLANT ECHOCARDIOGRAPHIC PREDICTORS OF POST-TRANSPLANT CARDIAC EVENTS

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Background: Echocardiography is integral to pre-LT cardiac risk assessment and Cardiac disease is a leading cause of morbidity and mortality post-LT. The pre-LT echocardiographic assessment has significantly evolved in the recent years. This study explores its predictive value for post-LT cardiac outcomes. The aim of the study is to determine the utility of contemporary echocardiographic markers in predicting post-LT cardiac events. **Methods:** Among 745 adult LT recipients, pre-transplant echocardiograms assessed left ventricular function (systolic and diastolic), and valvular disease. Outcomes included cardiac death, MI, and arrhythmias. **Results:** The mean age at LT was 56 years, with 267 female patients constituting 37.1%

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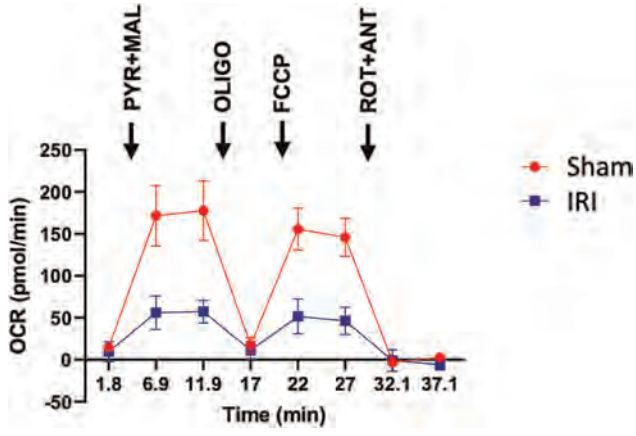
of the cohort. Among the patients, 220 (29.7%) developed liver cirrhosis secondary to Metabolic Associated Fatty Liver Disease. The prevalence of systolic dysfunction, defined by an ejection fraction (EF) of $<45\%$, was low(0.4%). Diastolic dysfunction, characterized by abnormal left ventricular (LV) relaxation, filling, diastolic distensibility, or diastolic stiffness, was present in 12.3% of patients pre-LT and was associated with higher rates of cardiac death (3.2% vs. 1.1%, $*p^* = 0.04$) and heart failure (4.8% vs. 0.9%, $*p^* < 0.01$), after controlling for confounding factors such age, gender, diabetes, hypertension, obesity and, smoking history. An EF $<45\%$ (0.4%) correlated with 100% mortality ($n = 3$). Trace tricuspid regurgitation was observed in 78.1% of patients. Patients with abnormal right ventricular pressure (RVP) (2.6%) exhibited an increased risk of MI (HR = 2.4, $*p^* = 0.02$). Notably, 95.7% of patients with a normal EF ($>55\%$) still experienced cardiac events, with a 19.6% incidence of MI. **Conclusion:** Diastolic dysfunction, valvular abnormalities, and elevated RVP on pre-LT echocardiography predict post-transplant cardiac morbidity. Comprehensive cardiac evaluation beyond EF and right ventricular systolic pressure is essential for risk stratification.

Disclosures: Ali Albenmousa: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Dieter Broering: Nothing to Disclose, Dimitrios Raptis: Nothing to Disclose, Mohamed Tahir: Nothing to Disclose, Maryam Abdulla: Nothing to Disclose, Waleed Haj Ahmad: Nothing to Disclose, Syeda Shamsi: Nothing to Disclose, Ahmad Alissa: Nothing to Disclose, Manhal Izzy: Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Bandar Aljudaibi: Nothing to Disclose

3530 | FROM BENCH TO COMPUTATIONAL MODELING: INTEGRATING MITOCHONDRIAL STRESS DATA FROM A RAT HEPATIC ISCHEMIA-REPERFUSION INJURY MODEL INTO A PRECLINICAL AND HUMAN QUANTITATIVE SYSTEMS TOXICOLOGY PLATFORM

Joohyun Kim[1], [1]Yale University School of Medicine

Background: Hepatic ischemia-reperfusion injury (IRI) is a key driver of liver dysfunction after surgery and transplantation, involving intricate mitochondrial, oxidative, and inflammatory mechanisms. Quantitative systems toxicology (QST) modeling provides a powerful framework to integrate mechanistic experimental data, simulate injury dynamics, and evaluate biomarkers and therapeutic strategies in IRI. **Methods:** Hepatic mitochondria were isolated from sham- and IRI-treated rats ($n = 5$/group, 1 h ischemia + 1 h reperfusion), after which mitochondrial respiration was assessed via extracellular flux analysis. Sequential addition of substrates (pyruvate/malate, succinate/rotenone, or NADH) and modulators (oligomycin, FCCP, rotenone, antimycin A) allowed evaluation of electron transport chain (ETC) function. Cytochrome c addition assessed outer membrane integrity, while alamethicin was used to permeabilize the inner membrane for NADH delivery to mitochondrial complex I. DPI and azide were used to inhibit complexes I and IV, respectively. A QST model of preclinical and human liver biochemistry (DILIsym®) was used to explore mechanistic hypotheses in hepatic IRI based on the obtained experimental data. **Results:** In the IRI group, pyruvate/malate-induced oxygen consumption rate (OCR) was reduced to 40%, indicating impairment in the TCA cycle or complex I. Succinate/rotenone treatment yielded similar OCR between groups, suggesting intact complex II and downstream ETC function. NADH-driven respiration was preserved in IRI, indicating functional complex I and implicating TCA cycle dysfunction upon IRI. These and additional biomarker data were used to estimate a proof-of-concept parameterization of hepatic IRI in DILIsym®, which recapitulated maximum aminotransferase levels observed in IRI rats, and generated predicted aminotransferase profiles that aligned with historical human IRI data following 60 minutes of liver ischemia. **Conclusion:** Subcellular bioenergetic data from animal models of hepatic IRI offer mechanistic insights that can be leveraged in QST modeling to inform human translation. This integrative approach serves as a bridge between preclinical findings and clinical trial design, supporting hypothesis generation while helping to reduce reliance on further animal experimentation.



Disclosures: Joohyun Kim: Nothing to Disclose

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3531 | HEPATIC RESERVE AND REGENERATION IN LIVING DONORS AFTER RIGHT HEPATIC LOBECTOMY: A PILOT STUDY OF THE ORAL CHOLATE CHALLENGE TEST

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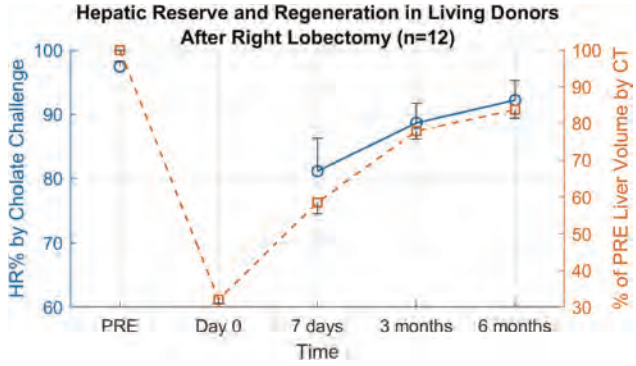
Background: Donor safety and outcomes are a primary concern for living donor programs. Although regeneration typically occurs rapidly after resection, short-term functional impairment is common. In this study, we used the oral cholate challenge test to measure the recovery of function over 6 months in living donors who underwent right lobectomy. **Methods:** 12 donors were recruited from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) (Everson et al., 2013) at two clinical centers. Donors were tested pre-donation and post-donation (7 days, 3 months, and 6 months). HepQuant DuO test parameters, including portal hepatic filtration rate (HFR) and hepatic reserve (HR%), were quantified from 20- and 60-min concentrations of orally administered d4-cholate (40 mg) (McRae et al., 2024). Hepatic volumes (mL/kg body weight) after right lobectomy were measured at the same intervals using CT. HR%, which is a score from 100% (full hepatic reserve) to 0% (no hepatic reserve) representing cholate clearance indexed to healthy controls with lean body mass, was compared to the percentage of pre-donation liver volume by CT. **Results:** The mean age of donors was 38 years (range 21–54), body mass index 25 ± 3, and M:F ratio of 4:8. The liver volume remaining immediately after right lobectomy was estimated at 32% ± 4% of pre-donation. Pre-donation laboratory values were normal; by day 7, bilirubin, INR, and ALT were higher and albumin was lower; by 3 months, values trended towards the pre-donation levels and by 6 months, all values returned to pre-donation levels. The mean portal HFR, 26 ± 9 mL/min/kg pre donation, was significantly lower post donation at day 7 (13 ± 6 mL/min/kg, $p = 0.003$). At 3 months, portal HFR recovered to 17 ± 6 mL/min/kg but was still significantly lower than pre donation ($p = 0.014$). At 6 months, portal HFR recovered to pre-donation levels, 24 ± 16 mL/min/kg ($p = 0.682$). The initial loss and recovery of hepatic function further quantified by HR% mirrored the regeneration of liver volume by CT (Pearson $r = 0.6$, $p < 0.001$) (Figure). **Conclusion:** The oral cholate challenge test measured alterations in the portal circulation and cholate uptake following right lobe donation and quantified the recovery of function associated with regeneration of liver volume. Although additional studies with longer term follow up are warranted, the oral cholate challenge test may be useful in the initial assessment and monitoring of liver function in living donors.



Disclosures: Michael McRae: HepQuant, LLC: Consultant, Joanne Imperial: Nothing to Disclose, touraj shokati: Nothing to Disclose, Gregory Everson: Nothing to Disclose

3532 | PREDICTORS AND RISK STRATIFICATION OF SIGNIFICANT CORONARY ARTERY CALCIFICATION IN LIVER TRANSPLANT CANDIDATES: A CROSS-SECTIONAL ANALYSIS

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Background: Coronary artery calcium (CAC) scoring by computed tomography is increasingly used for cardiovascular risk assessment in liver transplant candidates, but predictors of significant calcification remain poorly characterized. **Methods:** We conducted a cross-sectional study of 254 liver transplant candidates based on our institutional risk stratification protocol, 66 underwent CAC scoring. Significant coronary calcification was defined as CAC score ≥100. Clinical, demographic, and laboratory parameters were analyzed using univariate and multivariate logistic regression to identify predictors of significant calcification. A clinical risk score was developed and validated. **Results:** Of 66 patients who underwent CAC scoring out of 254 patients, 32 (48.5%) had significant coronary calcification. In multivariate analysis, male sex (OR 4.17, 95% CI 1.31-16.53, $p = 0.025$), metabolic dysfunction-associated steatohepatitis (MASH) (OR 4.44, 95% CI 1.47-13.62, $p = 0.008$), and Other/Multiracial ethnicity (OR 3.23, 95% CI 1.20-8.70, $p = 0.019$) were independently associated with increased odds of significant calcification. Conversely, higher MELD scores were protective (OR 0.94 per point, 95% CI 0.88-0.99, $p = 0.031$). A clinical risk score incorporating age, MELD score, race, MASH, sex, and cardiovascular

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risk factors (hyperlipidemia, hypertension, diabetes) was developed. The score stratified patients into low (≤ 3 points), intermediate (4-6 points), and high risk (>6 points) categories, demonstrating good discrimination for identifying patients with significant coronary calcification. **Conclusion:** Male sex, MASH, and Other/Multiracial ethnicity are independent predictors of significant coronary calcification in liver transplant candidates, while higher MELD scores appear protective. The proposed clinical risk score may help identify patients who would benefit most from CAC screening before liver transplantation.

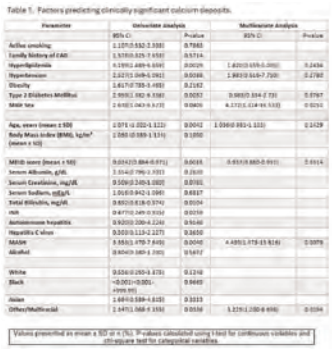
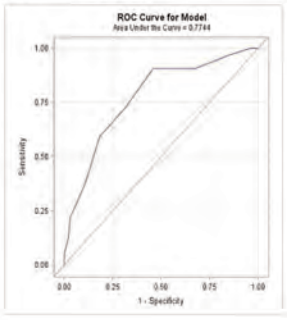


Figure 1. ROC curve for clinical risk model



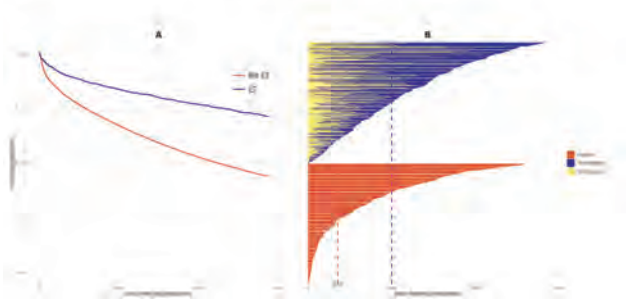
Disclosures: Sohil Khurana: Nothing to Disclose, Reanay Berezovskiy: Nothing to Disclose, Toby Bradford: Nothing to Disclose, Nabil Dagher: Nothing to Disclose, David Stern: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support

3533 | SURVIVAL BENEFIT OF LIVER TRANSPLANTATION IN ALCOHOL-ASSOCIATED LIVER DISEASE: INSIGHTS FROM A NATIONAL CLAIMS DATABASE

Wanzhu Tu[1] Lauren Nephew[1] Yining Li[1] Shihui Jiang[1] Yang Li[1] Chi Nguyen[1] Jing Su[1] Naga Chalasani[2] Suthat Liangpunsakul[1] Samer Gawrieh[1], [1]Indiana University, [2]Indiana University Medical Center

Background: Alcohol-associated liver disease (ALD) is a leading indication for liver transplantation (LT), yet access remains limited and practice varies among transplant centers. Few studies have quantified the real-world survival benefit of LT in this population, which is critical to inform clinical and policy decisions. **Methods:** We conducted an observational study using the Optum claims database, which includes individuals covered by commercial insurance and Medicare Advantage plans. Using validated ICD codes, we identified 373,025 adults with incident ALD between January 1, 2017, and August 31, 2024, excluding those with prior LT. Among them, 3,453 received LT. Logistic regression was used to examine factors associated with receiving LT. Cox proportional hazards regression was applied to compare mortality between LT recipients and non-recipients, while controlling for patient demographics and comorbidities. **Results:** Female sex (OR = 0.78; 95% CI:0.73–0.84), older age (OR = 0.949; 95% CI:0.947—0.952), African American race (OR = 0.597; 95% CI:0.509–0.700), and the presence of non-liver-related chronic diseases were associated with a lower likelihood of receiving LT. In contrast, cirrhosis (alcoholic or unspecified), ascites, hepatic encephalopathy (HE), and gastrointestinal (GI) bleeding were associated with increased likelihood of LT. The median time from initial ALD diagnosis to LT was 330 days. Among the 369,572 patients who did not undergo LT, 38.2% died, compared to 13.2% of those who received LT. Among those who died, the median survival after the initial ALD diagnosis was approximately 1,000 days for LT recipients and 355 days for non-recipients. In adjusted analyses, LT was associated with a significantly lower risk of mortality (HR = 0.37; 95% CI: 0.34–0.40). Other factors associated with reduced mortality included female sex (HR = 0.88; 95% CI: 0.87–0.89), Asian race (HR = 0.71; 95% CI: 0.68–0.74), and Hispanic ethnicity (HR = 0.95; 95% CI: 0.93–0.97). Conversely, the presence of ascites (HR = 2.07; 95% CI: 2.04–2.09), HE (HR = 1.62; 95% CI: 1.59–1.66), hepatorenal syndrome (HR = 1.55; 95% CI: 1.53–1.58), and GI bleeding (HR = 1.08; 95% CI: 1.06–2.0) was associated with increased mortality. Chronic conditions such as diabetes, heart failure, cancer, and kidney disease also elevated mortality risk. **Conclusion:** LT is associated with substantially improved survival in patients with ALD but remains underutilized in certain subgroups, including women and African Americans. Fndings from the current study highlight the life-saving potential of LT and support the need for initiatives to promote more equitable access for all eligible ALD patients.

Figure (A) Kaplan-Meier survival curves comparing overall survival between patients who received liver transplantation (LT) and those who did not. **(B)** Distribution of survival times among deceased patients, stratified by LT status. Vertical dashed lines indicate the median survival time for deceased LT recipients and non-recipients.



Disclosures: Wanzhu Tu: Nothing to Disclose, Lauren Nephew: NovoNordisk: Consultant, Yining Li: Nothing to Disclose, Shihui Jiang: Nothing to Disclose, Yang Li:

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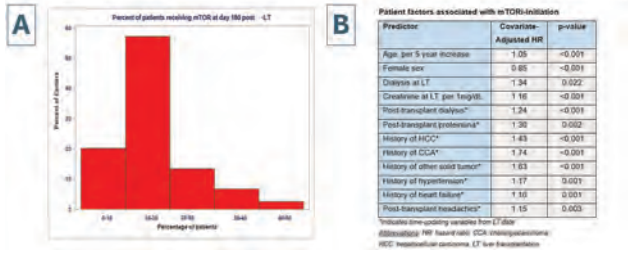
Nothing to Disclose, Chi Nguyen: Nothing to Disclose, Jing Su: Nothing to Disclose, Naga Chalasani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Suthat Liangpunsakul: DURECT: Consultant, Durect Corporation: Consultant, Surrozen: Consultant, Korro Bio: Consultant, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research Support, dsm: Grant/Research Support, Sonicincytes: Grant/Research Support, Novo Nordisk: Consultant

3534 | MECHANISTIC TARGET OF RAPAMYCIN INHIBITORS (MTORI) UTILIZATION AMONG U.S. LIVER TRANSPLANT RECIPIENTS IS LARGELY DRIVEN BY CENTER PREFERENCE

Therese Bittermann[1] David Goldberg[2] David Kaplan[3] Douglas Schaubel[4], [1]Perelman School of Medicine, [2]University of Miami, [3]University of Pennsylvania, [4]University of Pennsylvania Perelman School of Medicine

Background: Clinical trials have suggested that mechanistic target of rapamycin inhibitors (mTORi) may offer benefits for liver transplant (LT) recipients with renal dysfunction or hepatocellular carcinoma (HCC). Real world data on the utilization of mTORi in LT on a broad scale are lacking. Yet, these data are vital to understand barriers to evidence-based prescribing, quantify missed opportunities or inappropriate medication use, and inform future practice guidelines and new drug development. **Methods:** This was a retrospective cohort study using a data linkage of Medicare inpatient, outpatient and prescription claims and the Organ Procurement and Transplantation Network database. Adult (age 18+) recipients of first LT between 1/1/2007-12/31/2019 were included. mTORi utilization was identified from claims data with follow-up starting at LT date for all patients. Using Cox regression, we modeled the time until mTORi initiation, stratified by center and adjusting for predictors observed at transplant and a set of 18 time-updating Medicare-derived comorbidity indicators. In addition, we modeled duration of mTORi use (which accounted for stoppages) using linear regression and adjusting for predictors observed at LT. **Results:** Of 17,239 patients with overall median follow-up time 3.8 years (IQR: 1.2-7.1), 20.5% were prescribed mTORi. Median time from LT to mTORi initiation was 5.0 months (IQR: 2.0-14.6). Considerable heterogeneity in mTORi utilization was observed across the 120 LT centers (Figure 1A). Over 50% of centers prescribed mTORi to 10-20% of patients. Patient factors independently associated with mTORi initiation are shown in Figure 1B. mTORi initiation decreased over time (adjusted HR = 0.98 per calendar year, $p < 0.001$). Prediction of mTORi initiation improved minimally with addition of time-updating post-LT comorbidity variables (c-index 0.63 from 0.60 with baseline variables at LT only), but a significant increase in predictive power was observed when center also included in the model (c-index 0.70). Among the 3,535 patients prescribed mTORi, median (total) duration of use was 12.9 months (IQR: 4.8-37.0 months). Patient factors independently associated with increased mTORi duration included increasing age at LT (1.3 months per 5 year increase; $p < 0.001$) and primary sclerosing cholangitis diagnosis (10.2 months; $p < 0.001$). mTORi duration was not associated with history of hepatocellular carcinoma or renal dysfunction at LT (all $p > 0.05$). **Conclusion:** Patients initiating mTORi appear to have a less favorable risk factor profile, with rates being significantly increased among patients who are older or incur comorbidities. mTORi use varies considerably across centers, independent of patient case-mix. Duration of therapy is overall short. These issues must be accounted for in future studies evaluating the relationship between mTORi utilization and outcomes such as survival.

Factors affecting mTORi utilization among U.S. liver transplant recipients (n=17,239)



Disclosures: Therese Bittermann: Nothing to Disclose, David Goldberg: Nothing to Disclose, David Kaplan: AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Sirtex: Advisor, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research Support, Douglas Schaubel: Nothing to Disclose

3535 | USING THE ROCHESTER EXPERIENCE IN LIVING DONOR LIVER TRANSPLANTATION (LDLT) FOR UNRESECTABLE COLORECTAL LIVER METASTASIS (CRLM) TO EVALUATE THE UTILITY OF CIRCULATING TUMOR DNA (CTDNA) IN SURVEILLANCE FOR DISEASE RECURRENCE

Abigail Loszko[1] Matthew Byrne[1] Cristina Jimenez-Soto[2] Mariana Chávez-Villa[3] Jennifer Melaragno[4] Nicholas

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[1]Department of Surgery, University of Rochester Medical Center, [2]Transplant Institute, University of Rochester Medical Center, [3]Division of Transplant Surgery, Mayo Clinic, [4]Department of Pharmacy, University of Rochester Medical Center

Background: CRLM is a growing indication for liver transplantation in the United States, with 153 cases performed across 33 centers as of March 2025. ctDNA is also emerging as a powerful biomarker in transplant oncology, offering improved surveillance and early recurrence detection. We report our institutional experience using ctDNA in LDLT for CRLM. **Methods:** Single-center, retrospective cohort analysis of adults who underwent LDLT for CRLM from 9/2019-10/2024. ctDNA results from Signatera molecular residual disease assays were assessed when available. Descriptive statistics and Kaplan-Meier analysis were performed using Stata MP 18. **Results:** 25 patients underwent LDLT for CRLM: 15 (60%) male; median age 44 years (IQR 40-53). 24 (96%) had synchronous liver metastases. Median time to LDLT was 18.9 months (IQR 14.3-22.5) from CRLM diagnosis and 9 months (IQR 6.6-15.1) from primary resection.

Postoperatively, 11 (44%) patients had biliary leaks. 7 (28%) returned to the operating room for bleeding or vascular complications. 1 patient underwent deceased donor retransplant for acute hepatic artery thrombosis. 3 (12%) were medically treated for biopsy-proven rejection. Overall survival (OS) at 1, 2, and 3 years was 100%, 90%, and 90%; recurrence-free survival (RFS) was 71%, 51%, and 38% (Figure). 13 patients (52%) developed post-transplant recurrence, most commonly in the lung (n = 9), followed by liver (2), peritoneum (2), colorectal resection site (1), and bone (1). 2 patients had multi-organ involvement at detection. All 5 deaths followed disease recurrence; both patients with liver recurrence died.

ctDNA results were available in 19 patients (76%). All 5 with pre-transplant testing had negative results, with median RFS of 12.2 months (IQR 11.7–26.9) after LDLT. Among 18 patients with post-transplant ctDNA results, 9 (50%) remained persistently negative (median RFS 26.9 months, IQR 12.6–36.2), and the other 9 (50%) had at least one positive result (median RFS 11.8 months, IQR 9.3–12.6). Of 9 patients with both imaging-confirmed recurrence and post-transplant ctDNA data, ctDNA was positive in 7 (sensitivity 78%), preceding imaging in 2 cases by 1 and 9 months. Among the 9 with persistently negative ctDNA, 7 remained recurrence-free (negative predictive value 78%). **Conclusion:** Our transplant oncology experience with LDLT for CRLM demonstrates acceptable outcomes, likely driven by careful selection and multidisciplinary management. ctDNA in post-LT surveillance shows promise in recurrence risk stratification.

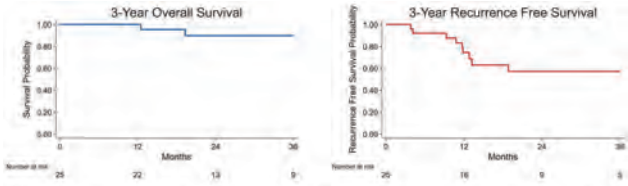

Figure. Overall and recurrence free survival proportions of living donor liver transplant recipients for colorectal liver metastases over a three-year period.

Disclosures: Abigail Loszko: Nothing to Disclose, Matthew Byrne: Nothing to Disclose, Cristina Jimenez-Soto: Nothing to Disclose, Mariana Chávez-Villa: Nothing to Disclose, Jennifer Melaragno: Nothing to Disclose, Nicholas Lim: Nothing to Disclose, Benyam Addissie: Nothing to Disclose, Yuki Bekki: Nothing to Disclose, Amit Nair: Nothing to Disclose, Koji Tomiyama: Nothing to Disclose, Roberto Hernandez-Alejandro: HistoSonics: Share holder

3536 | UTILIZATION AND OUTCOMES OF MARGINAL LIVER DONORS AT A HIGH-VOLUME TRANSPLANT CENTER

Yasmeen Saker[1], [1]University of Florida

Background: The demand for liver transplantation continues to rise and outpaces donor availability. This has led to increased utilization of marginal liver donors (MLDs) across transplant centers. Most center outcomes compare single risk factor MLDs and do not encompass the multiple risk factors that define MLDs. This study aimed to describe utilization patterns of MLDs, and graft survival outcomes associated with the use of these MLDs at a high-volume center. **Methods:** We conducted a retrospective cohort study of adult liver transplant recipients at the University of Florida who received liver transplant between January 2019 and September 2024. Donors were classified as MLDs if they met at least one predefined high-risk criterion: age > 65 years, BMI > 30, ICU stay > 4 days, serum sodium > 160 mmol/L, abnormal liver function tests (ALT > 105 U/L, AST > 90 U/L, or bilirubin > 3 mg/dL), substance use history, extrahepatic malignancy, donation after circulatory death (DCD), cold ischemic time > 12 hours, and/or viral hepatitis (HBsAg, HBcAb, or HCV Ab positivity). Patients were followed until graft failure or their last clinic visit. Graft failure was defined as the need for

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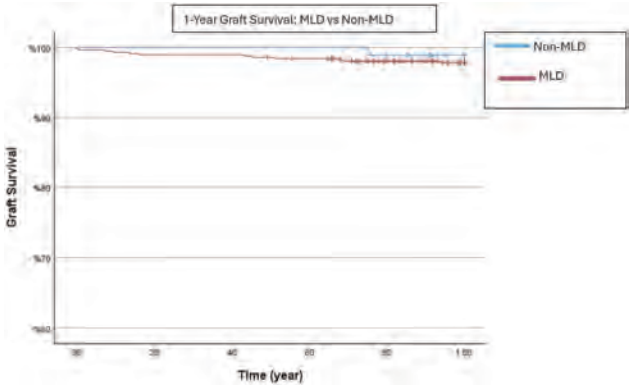
retransplantation or death. Graft survival at 1 and 3 years was estimated using Kaplan-Meier analysis and compared to recipients of non-MLD grafts using log-rank testing ($p < 0.05$ considered significant). **Results:** During the study period, a total of 649 liver transplants were performed at our center, of which 559 (86.1%) were classified as MLDs. Among these, 58.7% had substance use history, 45.4% had demographic risk (age, BMI, or cancer), and 31.7% had abnormal labs. Viral hepatitis was present in 24.7%, DCD in 11.3%, and ICU stay >4 days in 4.1%. Over half (55.6%) had multiple marginality criteria. Donors had a median age of 42 years; recipients had a mean age of 53.5, mean MELD-Na of 26.5, and 60.8% were male.

One- and three-year graft failure rates were 5.6 vs 1.1% and 8.1% vs 2.3% in the MLD vs non MLD groups respectively ($P = 0.4$). One- and three-year graft survival for the MLD recipients was 97.8% and 88.3%, respectively, which was not significantly different from non-MLDs (98.9% and 91.2%, $p = 0.514$ and $p = 0.58$, respectively). **Conclusion:** At a high-volume center, MLDs comprised the majority of transplants and yielded excellent short- and long-term graft survival, comparable to non-MLDs. These findings support broader, data-driven use of marginal donors and challenge traditional risk assumptions in liver allocation.



Disclosures: Yasmeen Saker: Nothing to Disclose

3537 | NEW SUBMISSION: INSTITUTIONAL APPROACHES TO LIVER TRANSPLANT EVALUATION FOR ALCOHOL-ASSOCIATED LIVER DISEASE (ALD): A PROTOCOL-BASED COMPARISON

Esra Alagoz[1] Megan Saucke[1] Brian Fisher[1] Marina Serper[2] Sheila Eswaran[3] Keren Ladin[4] John Rice[5] Brian Lee[6] George Therapondos[7] Mohamed Shoreibah[8] Marc Ghobrial[9] Neha Jakhete[10] Christine Hsu[11] Michael Lucey[5], [1]University of Wisconsin School of Medicine and Public Health, [2]University of Pennsylvania Health System, [3]Rush University Medical Center, [4]Tufts University, [5]University of Wisconsin, [6]Keck School of Medicine, [7]Ochsner Medical Center, [8]University of Alabama at Birmingham, [9]Houston Methodist, [10]University of Maryland, [11]National Institute of Diabetes, Digestive

Background: Background:: Despite increasing acceptance of early liver transplantation (LT) for selected patients with alcohol-associated liver disease (ALD) (i.e. patients with <6 months abstinence), national guidelines leave room for center-level discretion, resulting in differing interpretations and applications of key criteria and the potential for institutional variation in evaluation and listing practices. **Methods:** Methods:: We conducted a comparative analysis of internal LT evaluation protocols dated from 2019 to 2025 from a purposive sample of seven sites in the geographically diverse ACCELERATE LT consortium. We reviewed all documents that included alcohol-specific criteria. Protocols were analyzed based on the principles of qualitative document analysis using inductive thematic analysis. **Results:** Results:: Across institutions, we found heterogeneity and ambiguity in how evaluation criteria for ALD were articulated. Only 4 centers had explicit criteria for early LT. Themes that emerged during analysis include approaches to evaluation, criteria for abstinence, psychiatric conditions, social support, and patient collaborativeness. All centers had flexible language in their policies, allowing for evaluation criteria to be applied on a case-by-case basis, subject to committee approval. The urgency of LT was addressed across all centers, with explicit benchmarks for MELD and/or MDF scores guiding prioritization decisions. The presence of unmanageable psychiatric conditions was an exclusion criterion at all centers. The most elaborate aspects of the protocols pertained to assessments of social support systems and patient collaborativeness, which referred to the patient's demonstrated prior engagement with care, including insight into their diagnosis of alcohol use disorder and a willingness to adhere to post-LT care plans. All centers evaluated social support systems that might mitigate the risk of post-LT return to drinking. Factors that were considered inconsistently across centers included patient finances, housing, history of incarceration, and negative legal consequences of alcohol use. **Conclusion:** Conclusion:: Our analysis demonstrated differences in how transplant centers define eligibility for ALD patients, challenging the consistency in access to LT and highlighting a need for greater transparency to promote fair and evidence-informed selection processes. A prospective study is needed to demonstrate whether center-specific policies align with clinical decision making and post-LT outcomes.

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	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7
ELT specific protocols/criteria			√	√	√	√	
Flexible language	√	√	√	√	√	√	√
Committee approval	√		√	√		√	√
Urgency criteria	√	√	√	√	√	√	√
Unmanagable psychiatric conditions	√	√	√	√	√	√	√
Social support systems	√	√	√	√	√	√	√
Patient collaborativeness	√	√	√	√	√	√	√
Finances	√		√	√	√	√	√
Housing	√					√	
Imprisonment/parole	√						
Legal consequences of alcohol use			√	√	√		√

Table 1: Comparison of themes across seven institutions

Disclosures: Esra Alagoz: Nothing to Disclose, Megan Saucke: Nothing to Disclose, Brian Fisher: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Eurofins: Grant/Research Support, Sheila Eswaran: Nothing to Disclose, Keren Ladin: Nothing to Disclose, John Rice: Nothing to Disclose, Brian Lee: NIAAA: Grant/Research Support, Novo Nordisk: Advisor, GSK: Advisor, DURECT: Advisor, HepaTx: Advisor, CymaBay: Consultant, Ipsen: Consultant, Siemens Healthineers: Grant/Research Support, AltImmune: Advisor, Assertio: Consultant, George Therapondos: Novo Nordisk: Consultant, Intercept: Speaking and Teaching, Madrigal: Speaking and Teaching, Ipsen: Speaking and Teaching, Gilead: Speaking and Teaching, Mohamed Shoreibah: Nothing to Disclose, Marc Ghobrial: Nothing to Disclose, Neha Jakhete: Nothing to Disclose, Christine Hsu: Nothing to Disclose, Michael Lucey: Nothing to Disclose

3538 | PSYCHOLOGICAL, SOCIODEMOGRAPHIC AND SEX-RELATED PREDICTORS FOR WAITLIST ENROLLMENT, LIVER TRANSPLANTATION AND SURVIVAL

Maria Rosina Troppmair[1] Johanna Lentsch[1] Claudia Kohl[2] Nadin Haslwanter-Egger[2] Messina Bath[1] Marlene Panzer[1] Lorenz Michael Pammer[1] Rupert Oberhuber[3] Katharina Huefner[2] Herbert Tilg[1] Heinz Zoller[1] Benedikt Schaefer[1], [1]Department of Medicine I, Medical University of Innsbruck, Innsbruck, Austria, [2]Department of Psychiatry, Medical University of Innsbruck, Innsbruck, Austria, [3]Department of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck, Innsbruck

Background: End-stage liver disease and liver transplantation (LT) are strongly associated with psychological distress, depression and addiction. A comprehensive psychiatric evaluation is integrated in the pre-transplant assessment at our center. This study aims to evaluate the impact of psychiatric risk factors, social environment and sex on pre- and post-transplant outcomes. **Methods:** In this single-center retrospective study, candidates for LT that underwent standardized psychiatric evaluation at our center were included. We analyzed the impact of psychological and sociodemographic covariates on waitlist enrollment, LT and overall survival. **Results:** Between 2007 and 2021, 991 patients were evaluated (25.3% females), 695 (70.1%) of them were listed for transplantation (23.2% females) and 572 (82.3%) of the listed patients underwent LT (23.4% females). Transplanted patients showed a significantly longer median survival (12.9 years) than patients who did not undergo LT (2.2 years, $p < 0.001$). The majority of LT candidates had a history of harmful drinking (51% of females, 65.4% of males), which was associated with significantly worse survival in the overall cohort, but not in the subgroup of patients that underwent LT. Similarly, patients with high psychiatric risk estimate had significantly shorter survival in the overall cohort (Figure A), but not if they underwent LT (Figure B). Patients who were not listed or transplanted (n = 419) were more often living alone (26.3% vs. 17.9%, $p = 0.004$), had a weaker social network (86.7% vs. 95.1%, $p < 0.001$) and lower educational attainment (apprenticeship/blue collar: 63.5% vs. 53.5%, $p = 0.006$; higher education: 6.1% vs. 10.9%, $p = 0.017$), higher rates of addiction treatment (24.2% vs. 13.4%, $p < 0.001$), psychiatric disorders (41.4% versus 32%, $p = 0.004$), and an higher AUDIT risk score (> 15 points 34.8% vs. 19.4%, $p < 0.001$). Female sex was identified as a negative predictor for being listed for LT (*OR* 0.58, $p = 0.032$), whereas strong social support increased listing probability (*OR* 2.4, $p = 0.018$) in a multivariate regression analysis. **Conclusion:** Psychological disorders, limited social support and substance abuse were associated with a lower likelihood of being listed for liver transplantation and receiving a transplant. However, these factors did not affect post-transplant survival, highlighting the importance of an impartial approach when assessing transplant eligibility.

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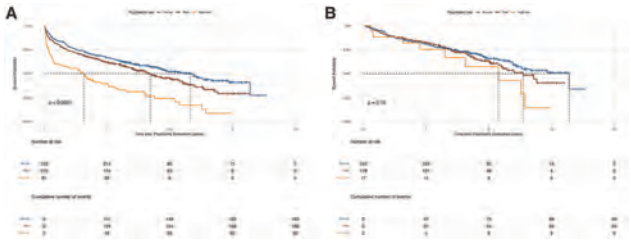

Disclosures: Maria Rosina Troppmair: Nothing to Disclose, Johanna Lentsch: Nothing to Disclose, Claudia Kohl: Nothing to Disclose, Nadin Haslwanter-Egger: Nothing to Disclose, Messina Bath: Nothing to Disclose, Marlene Panzer: Nothing to Disclose, Lorenz Michael Pammer: Nothing to Disclose, Rupert Oberhuber: Nothing to Disclose, Katharina Huefner: Nothing to Disclose, Herbert Tilg: Nothing to Disclose, Heinz Zoller: Nothing to Disclose, Benedikt Schaefer: Nothing to Disclose

3539 | TRENDS AND DEMOGRAPHIC DIFFERENCES IN REASONS FOR REMOVAL FROM THE LIVER TRANSPLANT WAITLIST: A NATIONWIDE OPTN ANALYSIS FROM 1988 TO 2025

Razan Aburumman[1] Saqr Alsakarneh[2] Saif Aburumman[3] Saine Tahmazian[1] Mohammad Abuassi[4] Syed-Mohammed Jafri[5], [1]Henry Ford Hospital, [2]University of Missouri, [3]The University of Medicine, [4]UCF/HCA Florida North Florida Hospital, [5]Henry Ford Health System

Background: Equity in liver transplantation access and outcomes remains a national priority. This study examines patterns and disparities in removal from the liver transplant waitlist across gender, race, ethnicity, citizenship, and insurance type. **Methods:** We conducted a retrospective analysis of patients removed from the liver transplant waitlist using data from the Organ Procurement and Transplantation Network (OPTN) spanning January 1988 to April 2025. Removal reasons and demographic characteristics were analyzed. SPSS IBM version 26.0 was used for the analysis. Chi-square tests were used to compare the distribution of reasons for removal across groups. **Results:** A total of 345,472 individuals were removed from the liver transplant waitlist between January 1988 and April 2025. The top three reasons for removal were deceased donor transplant (196,201 patients; 56.8%), death while on the waitlist (44,332; 12.8%), and being deemed too sick to transplant (28,033; 8.1%). Males were more likely than females to be removed due to deceased donor transplant (58.5% vs. 54.0%, $p < 0.001$). In contrast, females were more likely to be removed for living donor transplant (3.6% vs. 2.5%, $p < 0.001$), death (13.9% vs. 12.2%, $p < 0.001$), and condition improvement (7.4% vs. 5.3%, $p < 0.001$). Non–U.S. citizens were more likely to be removed for being too sick (9.1% vs. 8.1%, $p < 0.001$) and for receiving a transplant in another country (0.2% vs. 0.0%, $p < 0.001$). Patients with public insurance were more likely to be removed for being too sick (9.7%) compared to those with private insurance (7.2%), self-pay (6.0%), or other insurance types (5.4%, $p < 0.001$). Black patients had the highest proportion of removal for deceased donor transplant (60.2% vs. 56.7% for White and 55.7% for other races, $p < 0.001$), while White patients had the highest rate of removal for living donor transplant (3.2% vs. 1.8% Black and 2.6% other races, $p < 0.001$). non-Hispanic patients were more likely to undergo deceased donor transplant (57.1% vs. 55.2% Hispanic, $p < 0.001$), while Hispanic individuals were more likely to be removed due to being too sick (9.5% vs. 7.9%, $p < 0.001$) or dying on the waitlist (13.9% vs. 12.6%, $p < 0.001$). **Conclusion:** Significant disparities exist in removal from the liver transplant waitlist by gender, race, ethnicity, citizenship, and insurance type. These findings highlight the need for targeted interventions to address structural inequities in transplant access and outcomes

	Gender		Citizenship		Race			Ethnicity	
Reason for Removal	Male	Female	U.S. Citizen	non us citizen	White, Non-Hispanic	Black, Non-Hispanic	other race	Hispanic/Latino	non hispanic
Deceased Donor Transplant	124802 (58.5%)	71399 (54.0%)	186963 (56.8%)	9238 (56.5%)	137369 (56.7%)	17821 (60.2%)	41011 (55.7%)	29557 (55.2%)	166644 (57.1%)
Living Donor Transplant	5293 (2.5%)	4785 (3.6%)	9601 (2.9%)	477 (2.9%)	7647 (3.2%)	527 (1.8%)	1904 (2.6%)	1451 (2.7%)	8647 (3.0%)
Deceased Donor Emergency Tx	60 (0.0%)	23 (0.0%)	73 (0.0%)	0 (0.0%)	57 (0.0%)	6 (0.0%)	10 (0.0%)	8 (0.0%)	65 (0.0%)
Deceased Donor Multi-Organ Tx	0 (0.0%)	3 (0.0%)	3 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.0%)	1 (0.0%)	1 (0.0%)	2 (0.0%)
Patient died during TX procedure	362 (0.2%)	286 (0.2%)	608 (0.2%)	40 (0.2%)	422 (0.2%)	77 (0.3%)	149 (0.2%)	105 (0.2%)	543 (0.2%)
Transplanted in another country	55 (0.0%)	46 (0.0%)	93 (0.0%)	38 (0.2%)	26 (0.0%)	1 (0.0%)	44 (0.1%)	14 (0.0%)	57 (0.0%)
Unable to contact candidate	2429 (1.1%)	1687 (1.3%)	3728 (1.1%)	388 (2.4%)	2751 (1.1%)	344 (1.1%)	1054 (1.4%)	772 (1.4%)	3344 (1.1%)
Medically Unsuitable	67 (0.0%)	47 (0.0%)	111 (0.0%)	3 (0.0%)	82 (0.0%)	9 (0.0%)	23 (0.0%)	16 (0.0%)	98 (0.0%)
Refused transplant	1684 (0.8%)	1026 (0.8%)	2540 (0.8%)	170 (1.0%)	1775 (0.7%)	196 (0.7%)	739 (1.0%)	408 (0.8%)	2362 (0.8%)
Transferred to another center	3514 (1.6%)	2302 (1.7%)	5637 (1.7%)	179 (1.1%)	4264 (1.8%)	390 (1.3%)	1162 (1.6%)	842 (1.6%)	4974 (1.7%)
Died	26022 (12.2%)	18310 (13.9%)	42362 (12.9%)	1970 (12.0%)	30961 (12.8%)	3748 (12.7%)	9623 (13.1%)	7457 (13.9%)	36875 (12.6%)
Other	15077 (7.1%)	8772 (6.6%)	22632 (6.9%)	1217 (7.6%)	16678 (6.9%)	1802 (6.1%)	5569 (7.3%)	3981 (7.4%)	19868 (6.8%)
Condition Improved	11238 (5.3%)	9833 (7.4%)	20160 (6.1%)	911 (5.6%)	14904 (6.2%)	1828 (6.2%)	4359 (5.9%)	2967 (5.5%)	18104 (6.2%)
Too Sick to Transplant	17189 (8.1%)	10844 (8.2%)	26544 (8.1%)	1489 (9.1%)	18820 (7.8%)	2388 (8.1%)	6825 (9.3%)	5090 (9.5%)	22943 (7.9%)
Transplanted At Another Center	5528 (2.6%)	2829 (2.1%)	8137 (2.5%)	220 (1.3%)	6543 (2.7%)	483 (1.6%)	1331 (1.8%)	922 (1.7%)	7435 (2.5%)

Table 1: Reasons for Liver Transplant Waitlist Removal Stratified by Gender, Citizenship, and Race/Ethnicity

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3540 | REAL-WORLD CLINICAL OUTCOMES OF ADJUVANT RADIOTHERAPY AFTER CURATIVE LIVER RESECTION FOR STAGE IIIB INTRAHEPATIC CHOLANGIOCARCINOMA

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Background: The benefit of adjuvant radiotherapy (ART) for intrahepatic cholangiocarcinoma (ICC) with lymph node metastasis after curative liver resection remains unclear, primarily due to a lack of clear comparisons between ART and non-ART groups in existing studies. **Methods:** Using a large single-center database and validating with the SEER database, we analyzed ICC patients who underwent liver resection with confirmed hilar lymph node metastasis. Inverse probability of treatment weighting (IPTW) and multivariate Cox regression analyses were employed to evaluate the effect of adjuvant radiotherapy on long-term overall survival (OS) and time to recurrence (TTR). **Results:** Among 366 ICC patients with pathologically confirmed hilar lymph node metastasis after surgery, 85 received adjuvant radiotherapy, while 279 did not. IPTW created weighted cohorts of 278.8 non-ART patients and 87.4 ART patients. After IPTW adjustment, ART was associated with significantly lower 1-, 3-, and 5-year recurrence rates and improved 1-, 3-, and 5-year OS (TTR: 40.80% vs. 55.90%, 62.41% vs. 80.49%, 70.87% vs. 83.49%, P = 0.011; OS: 74.11% vs. 54.51%, 39.46% vs. 25.13%, 33.51% vs. 17.12%, P = 0.005).In the subgroup of patients with fewer than 6 lymph nodes dissected, ART significantly reduced recurrence rates and prolonged survival at all timepoints (TTR: 52.2% vs. 70.03%, 68.40% vs. 86.61%, 78.06% vs. 91.37%, P = 0.014; OS: 72.01% vs. 36.70%, 30.37% vs. 15.23%, 26.34% vs. 10.64%, P = 0.006). However, in patients with >6 lymph nodes dissected, ART did not significantly affect recurrence or survival (TTR: 51.8% vs. 37.57%, 68.31% vs. 79.07%, 60.79% vs. 79.07%, P = 0.085; OS: 74.76% vs. 59.93%, 42.80% vs. 28.93%, 35.47% vs. 21.10%, P = 0.058).In the SEER validation cohort, among patients with <6 lymph nodes dissected (55 ART vs. 212 non-ART), 1-, 3-, and 5-year OS was significantly better in the ART group (90.27% vs. 67.72%, 36.68% vs. 24.63%, 18.06% vs. 13.05%, P = 0.043). In patients with >6 lymph nodes dissected (23 ART vs. 102 non-ART), there was no significant difference in OS (90.91% vs. 68.39%, 30.08% vs. 25.00%, 12.51% vs. 17.40%, P = 0.710). **Conclusion:** For ICC patients with hilar lymph node metastasis, adjuvant radiotherapy is recommended to improve long-term prognosis if fewer than 6 lymph nodes are dissected during surgery.

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3541 | SEX-SPECIFIC PERFORMANCE OF NON-INVASIVE BIOMARKERS FOR PREDICTING GRAFT LOSS AND MORTALITY AMONG LIVER TRANSPLANT RECIPIENTS

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Background: Biological sex influences liver disease progression, yet its impact on post-transplant outcomes and the performance of non-invasive biomarkers remains underexplored. In liver transplant recipients, graft steatosis and fibrosis are common complications contributing to graft loss and mortality. Understanding whether biomarker performance differs by sex is critical for optimizing long-term care. We aimed to evaluate sex-specific differences in

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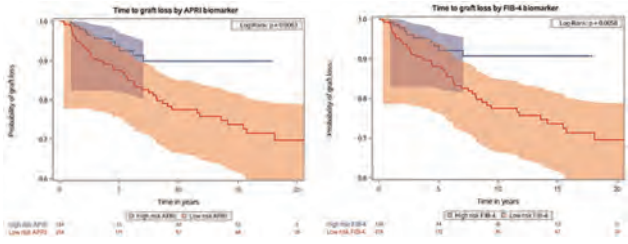
post-transplant outcomes and in the prognostic performance of non-invasive fibrosis and steatosis biomarkers for predicting graft loss and mortality. **Methods:** This retrospective longitudinal study included all adult liver transplant recipients at a single center in Montreal, Canada, between 2000 and 2021. Primary outcomes were graft loss (defined as death or re-transplantation) and all-cause mortality. We assessed the performance of the biomarkers AST-to-Platelet Ratio Index (APRI), fibrosis-4 index (FIB-4), and hepatic steatosis index (HSI), using sex-stratified survival analyses. Fibrosis was defined as APRI >1 or FIB-4 >3.64, and hepatic steatosis was defined as HSI >36. **Results:** Among 608 liver transplant recipients included (30% women), incidence of graft loss was higher in men (20.6, 95% CI 16.5-25.9 per 100 person-years) than women (11.8, 95% CI 7.5-8.4). All-cause mortality rates were similar between men (40.7, 95% CI 34.7-47.6 per 100 person-years) and women (39.3, 95% CI 30.9-50.1). In men, high BMI was associated with graft loss ($p=0.028$) while high AST was associated with mortality ($p=0.034$). In women, donor age and high FIB-4 were associated with mortality ($p=0.054$ and $p=0.0202$, respectively). Kaplan-Meier analysis showed APRI >1 and FIB-4 >3.64 predicted graft loss in men ($p=0.006$ and $p=0.005$, respectively, see Figures). No biomarkers predicted mortality in men or any outcome in women. **Conclusion:** APRI and FIB-4 were predictive of graft loss in men but not in women, highlighting significant sex-based differences in biomarker performance and post-transplant risk factors. These findings underscore the need for sex-specific approaches in the prognostication and management of liver transplant recipients.



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3542 | CYSTATIN C-TO-SERUM CREATININE RATIO IS INDEPENDENTLY ASSOCIATED WITH KEY CLINICAL OUTCOMES FOLLOWING LIVER TRANSPLANTATION

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Background: Sarcopenia, marked by the loss of skeletal muscle mass, strength, and function, portends worse outcomes following liver transplantation. Despite the high prevalence of sarcopenia in the advanced cirrhosis community, a readily accessible serum biomarker to characterize its presence remains elusive. The ratio of cystatin C-to-serum creatinine (cystatin C/sCr, or the "CC ratio") has been proposed in other disciplines as a potential marker of sarcopenia given the robust influence of muscle mass on creatinine (but not on cystatin C). We sought to investigate the association between the pre-transplant CC ratio and key clinical outcomes post-transplantation to elucidate the value of this metric. **Methods:** We conducted a single center, retrospective cohort study of patients who underwent liver transplantation at an urban academic medical center from 2019-2024 with a pre-operative CC ratio measured as part of standard medical care. Outcomes of interest included post-transplant hospital length of stay (LOS), ICU LOS, and 30-day and one-year hospital re-admission. We assessed for the association of the CC ratio with these outcomes using multivariable linear (for numerical outcomes) or logistic (for categorical outcomes) regression. Covariates included age, BMI, sex, Liver Frailty Index score, simultaneous liver-kidney transplantation, and MELD-Na score. **Results:** We identified 51 patients for inclusion (Table 1). Adjusting for our covariates, we found that the CC ratio was independently associated with post-transplant hospital LOS (OR 1.81, 95% CI 1.57-2.10, $p<0.01$), ICU LOS (OR 1.63, 95% CI 1.25-2.13, $p<0.01$), and one-year hospital re-admission (OR 1.54, 95% CI 1.08-2.21, $p=0.02$). Among all covariates assessed, the CC ratio had the greatest strength of association with post-transplant hospital LOS. Other than MELD-Na, the CC ratio was the only variable that independently associated with the outcomes of ICU LOS and one-year hospital re-admission. **Conclusion:** Our study demonstrates the potential for the CC ratio to serve as a tool for risk stratification among those with advanced cirrhosis being considered for liver transplantation. Our results also underscore the benefit of quantifying pre-transplant metabolic status by using an easily repeatable metric that could be monitored over time. Larger, prospective multi-center trials are needed to further assess the practical utility of this novel measurement.

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Table 1: Demographics of Selected Participants

Demographics (N=51)	N (%), or Median (IQR)
Age (years)	62 (9.5)
Sex	
Male	31 (61)
Female	20 (39)
BMI (kg/m²)	27 (6.8)
Race	
White	38 (75)
Hispanic	5 (10)
Black	4 (8)
Asian	3 (6)
Native Hawaiian or Other Pacific Islander	1 (2)
Etiology of Liver Disease	
Alcohol-Related	24 (47)
MASH	9 (18)
Viral	3 (6)
Other	15 (29)
Type of Transplant	
Liver Alone	35 (69)
Simultaneous Liver-Kidney	16 (31)
Post-Transplant Discharge Destination	
Home with Services	40 (78)
Long Term Acute Care Hospital	7 (14)
Acute Rehab Facility	1 (2)
Subacute Rehab/Skilled Nursing Facility	1 (2)
Death Prior to Discharge	2 (4)

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3544 | HAPLOIDENTICAL LIVING DONOR LIVER TRANSPLANTATION FOR STEROID-REFRACTORY HEPATIC GVHD IN A PEDIATRIC PATIENT POST-HSCT

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Background: Hepatic graft-versus-host disease (GVHD) is a rare but life-threatening complication following allogeneic hematopoietic stem cell transplantation (HSCT). Patients with steroid-refractory GVHD have high mortality, with limited salvage options. Liver transplantation post-HSCT poses unique challenges due to dual alloimmunity and is rarely pursued, particularly in pediatric patients. We report the first known case of a pediatric patient with steroid-refractory hepatic GVHD successfully treated with haploidentical living donor liver transplantation (LDLT). **Methods:** This is a single-patient case report conducted via retrospective chart review. Clinical, laboratory, and transplant data were collected and analyzed to evaluate disease course, treatment response, and post-transplant outcomes. **Results:** An 11-year-old male, who received a matched unrelated allogeneic HSCT for severe aplastic anemia, developed progressive hepatic GVHD characterized by profound ductopenia and severe cholestasis. His disease was refractory to corticosteroids and multiple additional lines of therapies, including ruxolitinib, mesenchymal stromal cells, infliximab, sirolimus, anti-thymocyte globulin, alpha-1 antitrypsin, cyclophosphamide, and emapalumab. His course was further complicated by Epstein-Barr virus (EBV)–associated post-transplant lymphoproliferative disorder (PTLD), which was successfully treated with rituximab. Fifteen months after HSCT, and seven months following resolution of EBV viremia, he underwent successful LDLT from a haploidentical parental donor. The haploidentical donor was selected to preserve the potential for future treatment with EBV-specific cytotoxic T lymphocytes (CTLs) in the event of EBV recurrence. Post-transplant immunosuppression included tacrolimus and mycophenolate mofetil (MMF). At six months following LDLT, the patient remains clinically well, with normal liver function, sustained full donor chimerism, and no evidence of GVHD or PTLD. **Conclusion:** This case demonstrates that haploidentical LDLT can be a viable and life-saving salvage therapy in select pediatric patients with progressive, treatment-refractory hepatic GVHD. Despite the risks of dual alloimmunity, a successful outcome was achieved through careful patient selection, timing, and multidisciplinary coordination. This approach may warrant consideration in cases of irreversible hepatic injury. Additionally, the case underscores the absence of liver-specific GVHD

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therapies and the urgent need for research into targeted treatments to promote hepatic recovery in GVHD.

Keywords: Hepatic GVHD, liver transplantation, haploidentical donor, pediatric HSCT, steroid-refractory GVHD

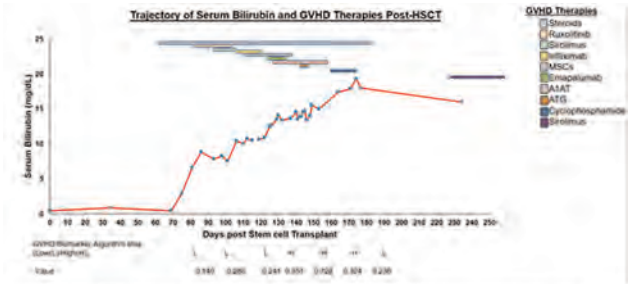

Figure – Trajectory of serum bilirubin levels and graft-versus-host disease (GVHD) therapies following hematopoietic stem cell transplantation (HSCT). The red line represents serum bilirubin levels over time. Color-coded horizontal bars indicate the duration of individual therapies administered for hepatic GVHD. Therapy names and corresponding colors are detailed in the legend.

Abbreviations: GVHD – Graft-versus-host disease; HSCT – Hematopoietic stem cell transplantation; MSCs – Mesenchymal stromal cells; A1AT – Alpha-1 antitrypsin; ATG – Anti-thymocyte globulin

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3545 | EXPANDED UTILIZATION OF LIVER TRANSPLANTATION IN CRITICALLY ILL CANDIDATES WITH CHRONIC LIVER DISEASE DOES NOT THREATEN CENTER-BASED OUTCOME METRICS

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Background: Liver transplantation (LT) in patients with chronic liver disease (CLD) may be high-risk when patients are critically ill in the intensive care unit (ICU). Recent studies show that outcomes in LTs from the ICU have improved significantly. The impact of center experience with ICU LTs on outcomes is unknown outside of acute liver failure (ALF). This study aimed to assess center heterogeneity in practices and the impact of center ICU LT experience on post-transplant outcomes. **Methods:** Using United Network for Organ Sharing data, we performed a retrospective analysis of all adult LTs performed between 1/1/2014-12/31/2023 in which patients were in an ICU prior to transplant (tx). The last follow-up date was 12/31/2024. We excluded re-tx, multi-organ tx (except liver-kidney), and ALF. Resource utilization, in-hospital mortality and 1- and 3-year mortality were compared by center ICU LT volume quartiles. The association between center ICU LT volume in the prior year and 1-year post-LT mortality was evaluated using multivariable logistic regression. **Results:** In total, 9,542 LTs were performed in ICU patients across 130 centers (12.8% of total LTs). By comparison, ICU LTs represented 8.8% of total LTs from 2004-2013 ($p = < 0.001$). There were no ICU LTs at 16/146 (11.0%) centers. ICU LT patients were 58% male, median age 54 (IQR 45, 62) and 52% with disease etiology of alcohol-associated liver disease. At LT, 61% were on dialysis, 21% on a ventilator and 47% on life support. Median center ICU LT volume from 2014-2023 was 48 (IQR 20,90). Proportion of overall LT volume in ICU recipients was nearly 4x greater at centers in the highest vs lowest quartile of ICU LT volume (19.4% vs 5.9%; $p < 0.001$). Utilization of dialysis, life support and of concurrent critical care therapies in ICU LT recipients was higher at high volume centers ($p < 0.001$ for all; Table). In-hospital, 1-year and 3-year mortality for ICU LTs overall were 6.2%, 10.4% and 23.1%, respectively, with no differences across center volume quartiles (all $p > 0.05$). Though statistically significant, minimal differences in overall 1-year and 3-year mortality were observed (Table). Adjusting for severity of illness, center volume of ICU LTs in the prior year was associated with a small but significant reduction in 1-year post-LT mortality: aOR 0.96 per 5 ICU LTs ($p < 0.001$). **Conclusion:** Experience with and selection of LT candidates with CLD patients in the ICU varies widely across centers. Expansion of LT for ICU candidates does not appear to threaten center-based metrics and may ultimately lead to a small, yet measurable improvement in short-term survival post-LT.

Resource Utilization and Outcome Metrics by Center Volume Quartile of ICU LT 2014-2023 (N=130 centers)

	Center ICU LT volume 1-20	Center ICU LT volume 20-50	Center ICU LT volume 51-89	Center ICU LT volume 90+	P-value
ICU recipients (N=9,542)	**(n=263)**	**(n=1,150)**	**(n=2,085)**	**(n=6,044)**	
Ventilator at LT, n(%)	58 (22.1)	200 (17.4)	369 (17.7)	1,378 (22.8)	<0.001
Dialysis at LT, n(%)	122 (46.4)	584 (50.8)	1,165 (55.9)	3,952 (65.4)	<0.001
Life support at LT, n(%)	68 (25.9)	360 (31.3)	728 (34.9)	3,304 (54.7)	<0.001
Ventilator & Dialysis at LT, n(%)	37 (14.1)	122 (10.6)	238 (11.9)	1,049 (17.4)	<0.001
Ventilator, Dialysis, & Life Support, n(%)	37 (14.1)	122 (10.6)	238 (11.9)	1,049 (17.4)	<0.001
In-hospital mortality, n(%)	22 (8.4)	80 (7.0)	123 (5.9)	369 (6.1)	0.30
1-year mortality, n(%)	32 (14.6)	126 (12.2)	204 (11.0)	627 (11.5)	0.417
3-year mortality, n(%)	44 (27.3)	176 (22.4)	300 (22.7)	955 (23.2)	0.579
Retransplantation, n(%)	10 (3.8)	30 (2.6)	43 (2.1)	139 (2.3)	0.239
All recipients (N=74,208)	**(n=4,478)**	**(n=18,559)**	**(n=19,949)**	**(n=31,222)**	
ICU LT, n(%)	263 (5.9)	1,150 (6.2)	2,085 (10.5)	6,044 (19.4)	<0.001
In-hospital mortality, n(%)	172 (3.8)	503 (2.7)	501 (2.5)	965 (3.1)	<0.001
1-year mortality, n(%)	335 (8.4)	1,180 (7.1)	1,176 (6.5)	2,062 (7.3)	<0.001
3-year mortality, n(%)	569 (18.7)	2,034 (16.1)	2,038 (15.4)	3,640 (17.4)	<0.001
Retransplantation, n(%)	111 (2.5)	493 (2.7)	506 (2.5)	766 (2.5)	0.573

Disclosures: Laura Barr: Nothing to Disclose, Therese Bittermann: Nothing to Disclose

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3546 | ONE YEAR POST TRANSPLANT OUTCOMES IN HCV POSITIVE DONOR TO HCV NEGATIVE RECIPIENT LIVER TRANSPLANTATION: A DESCRIPTIVE ANALYSIS OF AN ARIZONA TRANSPLANT CENTER'S EXPERIENCE

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Background: The persistent gap between the demand for liver transplantation (LT) and the availability of suitable donor organs continues to drive morbidity and mortality among patients on the LT waiting list. The advent of direct-acting antiviral agents (DAAs) has transformed the management of hepatitis C virus (HCV), offering an opportunity to safely expand the donor pool using HCV positive (+) grafts. We present one year post transplant outcomes following the use of HCV+ grafts in HCV negative (-) LT recipients at Banner University Medical Center in Phoenix (BUMCP), Arizona. **Methods:** This is a retrospective cohort study of patients who underwent LT at BUMCP from 2015 - 2021. Data and outcomes were manually collected from 520 patient charts and compared between (1) LT recipients who received an HCV – graft (n = 478) and (2) HCV – LT recipients who received an HCV + graft (n = 42). Descriptive analyses were performed to compare hospital admissions, infections, acute kidney injury (AKI), biliary complications, hepatic artery stenosis/thrombus, graft failure (GF), acute cellular rejection (ACR), stage of chronic kidney disease (CKD), end stage renal disease (ESRD), post transplant diabetes, and hepatocellular carcinoma (HCC) recurrence in the one year following liver transplant. **Results:** There were no statistically significant differences between the two groups in rates of hospitalization, AKI, infection, GF, ACR, hepatic artery stenosis/thrombosis, CKD stage, ESRD, PTDM, or mortality within one year post-transplant. However, HCV – LT recipients had a higher percentage of biliary stricture (p = 0.01) in the first year post LT. HCV + LT recipients had a higher percentage of HCC recurrence within the first year following LT (p = 0.02). **Conclusion:** Our findings support the safety and efficacy of utilizing HCV+ donor livers without fibrosis in HCV– recipients. The observed increase in HCC recurrence in the HCV+ may be more reflective of an overall small sample size compared to the total number of HCV – patients in the study and not actually a biological difference in the incidence of recurrent HCC post transplantation. Therefore, HCV+ grafts should not be categorically excluded for recipients with prior HCC, though careful selection and surveillance remain warranted. This strategy offers a viable pathway to expand the donor pool without compromising short-term outcomes.

Table 1: Demographics and One Year Post Transplant Outcomes

	HCV – donor to recipient (n = 478)	HCV + donor to negative recipient (n = 42)	p value
Demographics			
MELD at transplant	23.90	23.26	
Age at transplant	54.73 years	57.2 years	
Percentage female	38.28%	30.95%	
1 year post transplant outcomes			
Mean admissions in year post transplant	2.21	2.25	
Days hospitalized	19.70	16.98	
Reasons for Admission			
Infection	52.7%	47.06%	0.59
ACR or liver chemistry abnormalities	32.15%	17.65%	0.12
AKI	14.56%	14.71%	1
Biliary obstruction	11.82%	5.88%	0.4
Complications			
GF	1.26%	0%	0.80
ACR	24.27%	19.05%	0.79
AKI	37.92%	38.46%	1
Infection	42.86%	42.50%	1
Biliary stricture	25.57%	7.89%	0.02
Hepatic artery stenosis/thrombosus	22.57%	15.38%	0.42
CKD - stage 3 - stage 4 - stage 5	 19.5% 2.1% 2.52%	 14.29% 2.38% 2.38%	0.29
Post transplant diabetes	8.76%	7.69%	0.74
ESRD	2.34%	2.63%	1
HCC recurrence	1.97%	13.64%	0.02
Death in 1 year	8.12%	6.52%	1

Disclosures: Raha Sadjadi: Nothing to Disclose, Vanessa Eller: Nothing to Disclose, Leith Ghani: Nothing to Disclose, Anandalakshmi Ponnaluri: Nothing to Disclose, Pooja Rangan: Nothing to Disclose, Giorgio Roccaro: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose

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3547 | THE ASSOCIATION OF CHRONIC KIDNEY DISEASE WITH METABOLIC SYNDROME AND PERIRENAL ADIPOSE TISSUE IN LIVER TRANSPLANT RECIPIENTS

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Background: Chronic kidney disease (CKD) is a major complication affecting long-term survival after liver transplantation (LT). Its development is influenced by factors such as preoperative renal function, intraoperative hemodynamic changes, nephrotoxic drugs, metabolic syndrome (MS), and visceral adipose tissue (VAT). Perirenal fat tissue may contribute to the development of CKD through metabolic and mechanical effects. This study aims to assess the relationship between CKD, MS, andperirenal fat tissue in LT recipients. **Methods:** A total of 109 adult liver transplant recipients, with a minimum follow-up of 1 year at Ankara University Gastroenterology and Hepatology Polyclinics between 2005-2024 were enrolled in the analysis. Demographics, laboratory and radiological data were collected. Based on abdomen CT analysis, measurements of VAT, subcutaneous adipose tissue (SAT), total fat area (TFA), VAT/TFA ratio, VAT/SAT ratio, and right-left perirenal fat thickness (PFT) were performed, and their associations with MS and CKD development were analyzed. **Results:** Among 109 patients, 70 (64.2%) were male with a median age of 61 years (range 53.5–67 years). Median follow-up was 8 years (range 5.5–12.5 years). Living donor LT was performed in 87 (79.8%) of the patients. Hepatitis B virüs ($n = 39$, 35.8%).) was the main indication to LT. CKD developed in 35 (32.1%) patients, of whom 65.7% had MS. Also MS developed in 52 patients (47.7%) post-LT, 44.2% of them developed CKD.

Pre-transplant DM, anti-diabetic and antihypertensive medication use before and after, post-transplant hypertension, metabolic syndrome before and after LT, MASLD before LT, and increased post-transplant waist circumference were significantly more common in patients with CKD ($p < 0.05$). Additionally, pre-transplant fasting glucose, post-transplant triglycerides, postprandial glucose, HbA1c, and C-peptide levels were higher in these patients ($p < 0.05$).

Compared to those without MS, patients developed MS had significantly higher post-transplant VAT [165.1 (113.1-246.9) vs 116.8 (62.8-205.8) $p = 0.014$], TFA [393.2 ± 138.5 vs 319.5 ± 166.7,$p = 0.026$], right PFT [3.14 ± 1.06 vs 2.6 ± 1.07, $p = 0.010$] and mean PFT [3.62 ± 1.04 vs 3.12 ± 1.18, $p = 0.020$].VAT [161.1 (101.6-216.2) vs 146.1 (73.5-225.9)], SAT [188.8 (151.4-272.2) vs 166.3 (116.9-257.6), TFA [395.4 ± 158.4 vs 337.9 ± 154.3], and right PFT [3.13 ± 10.92 vs 2.74 ± 1.15], values were higher in the CKD group compared to the non-CKD group, however not statistically significant. **Conclusion:** The development of MS and CKD is common after LT. Visceral and perirenal fat tissue are important indicators in the diagnosis of MS. CKD is a multifactorial condition and the presence of MS increases the risk of developing CKD. The relationship between visceral and perirenal fat tissue and CKD requires large-scale studies.

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3549 | BIOLOGIC USE AND RISK OF ACUTE CELLULAR AND ANTIBODY-MEDIATED REJECTION IN LIVER TRANSPLANT RECIPIENTS WITH INFLAMMATORY BOWEL DISEASE

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Background: Inflammatory bowel disease (IBD) is a common comorbidity in liver transplant (LT) recipients, particularly those with primary sclerosing cholangitis (PSC). The management of IBD in the post-LT setting is complex, with increasing use of biologic therapies such as anti-TNF agents, anti-integrins, and interleukin inhibitors. However, the safety of these agents following LT remains unclear, notably with regard to the risk of acute cellular rejection (ACR) and antibody-mediated rejection (AMR). **Methods:** We conducted a retrospective cohort study of 85 adult LT recipients with a diagnosis of IBD at Lahey Hospital from 2000-2024. The study was approved by the institutional review board. Demographics, immunosuppressive regimen, and post-LT biologic therapy were reviewed. Patients

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were stratified by post-LT biologic use. Rejection events were identified from the electronic health record and defined based on clinician documentation and pathology reports. **Results:** Among 85 LT recipients with IBD, 68 (80%) were male and 77 (91%) were White. The predominant IBD subtype was ulcerative colitis (UC) (58%), followed by Crohn's disease (42%). PSC was the most common indication for LT, accounting for 78% of cases. The cohort was predominantly maintained on tacrolimus-based immunosuppression (87%), mycophenolate (64%), and corticosteroids (24%). Post-LT biologic therapy was used in 24 patients (28.2%), including anti-TNF agents (13/85, 15%), vedolizumab (10/85, 12%), ustekinumab or risankizumab (12/85, 14%), and upadacitinib (1/85, 1%). Rejection occurred in 4 patients overall (4.7%): 2 ACR and 2 AMR (2.35%). One episode of ACR occurred in each group (4.8% in biologic vs 1.6% in non-biologic), and both AMR episodes occurred in the non-biologic group. **Conclusion:** In this single-center cohort of LT recipients with IBD, biologic therapy was not associated with an increased risk of acute rejection. ACR occurred in only two patients, one in each treatment group, while AMR was observed exclusively in the non-biologic group. These findings suggest that the use of biologics post-LT does not confer additional risk of allograft rejection in this population. The absence of AMR among biologic users is noteworthy, given that biologics could theoretically modulate immune activation pathways involved in alloimmune response. Our cohort was largely composed of patients with PSC and UC, consistent with the established PSC-IBD overlap population. Prospective studies with larger sample sizes and longer follow-up are needed to confirm these findings and assess the long-term impact of biologic exposure on graft and patient outcomes.

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3550 | IMPACT OF RECIPIENT MELD SCORE ON OUTCOMES FOLLOWING TRANSPLANTATION WITH MARGINAL LIVER DONOR GRAFTS

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Background: The optimal allocation of marginal liver donor (MLD) grafts remains a topic of debate, particularly regarding whether high MELD recipients derive comparable benefit despite increased baseline risk. This study aimed to assess whether recipient MELD score modifies the association between marginal graft use and graft survival. **Methods:** We conducted a retrospective cohort study of adult liver transplant recipients at the University of Florida who received transplants between January 2019 and September 2024. Donors were classified as MLDs if they met at least one predefined high-risk criterion: age >65 years, BMI >30, ICU stay >4 days, serum sodium >160 mmol/L, abnormal liver tests (ALT >105 U/L, AST >90 U/L, or bilirubin >3 mg/dL), substance use, extrahepatic malignancy, donation after circulatory death (DCD), cold ischemic time >12 hours, and/or viral hepatitis (HBsAg, HBcAb, or HCV Ab positivity). Donors not meeting any of these were considered non-MLDs. Characteristics like macrosteatosis $>30\%$, prolonged hypotension, and high-dose inotropes were excluded due to inconsistent availability.

To assess whether MELD score modified the association between MLD and graft survival, recipients were stratified by MELD-Na at transplant: <15, 15–28, 29–32, 33–36, and >37—aligned with acuity circle-based allocation thresholds. Graft survival at 1 and 3 years was estimated using Kaplan-Meier analysis; differences between MELD strata were compared using the log-rank test ($p<0.05$ significant). **Results:** Among 559 adult liver transplant recipients who received MLDs during the study period, the mean MELD-Na at transplant was 26.5 (range 6–53). One-year graft survival exceeded 97% across all MELD strata, ranging from 97.4% in MELD 15–28 to 98.4% in MELD 29–32, and 98.2% in recipients with MELD >37. Three-year survival ranged from 82.1% in MELD <15 to 93.2% in MELD 29–32, with survival in the MELD >37 group reaching 84.2%. No statistically significant differences were observed across MELD categories for either one-year ($p=1.0$) or three-year ($p=0.7$) survival.

In reviewing specific MLD criteria, no donors aged >65 and only one DCD donor were used in the MELD >37 group ($p<0.001$). Donors with prolonged ICU LOS were used across all MELD strata but were most frequently utilized in the MELD 29–32 and 33–36 groups ($p<0.001$). When stratified by acuity threshold, recipients with MELD >37 demonstrated comparable outcomes to those with MELD ≤ 37, with 1 year survival rates of 98.2% vs. 97.8% ($p=0.80$) and 3 year survival rates of 84.2% vs. 89.8% ($p=0.23$). **Conclusion:** In this institutional cohort, MLD graft survival at 1 and 3 years remained high across MELD strata, with no significant differences between high- and low-MELD recipients. These findings support individualized MLD allocation to high-acuity patients, as MELD score should guide and not restrict clinical decisions.

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Disclosures: Yasmeen Saker: Nothing to Disclose

3551 | PROTON PUMP INHIBITOR USE IS ASSOCIATED WITH A TWO-FOLD INCREASED RISK OF LIVER TRANSPLANT COMPLICATIONS: A PROPENSITY-MATCHED ANALYSIS OF 48,192 RECIPIENTS

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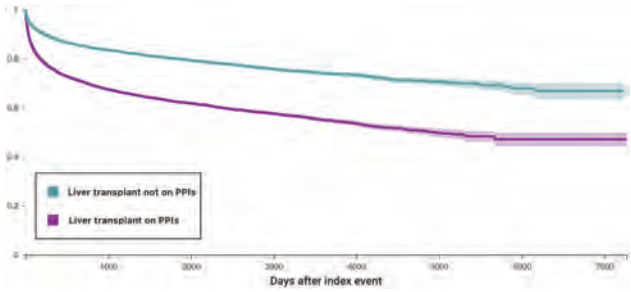
Background: While prior studies have suggested PPI-related adverse events in cirrhotic patients, the impact of PPI use on post-transplant outcomes remains poorly characterized. We aimed to evaluate the association between PPI use and liver transplant (LT) complications using a large real-world database. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network, analyzing data from 104 healthcare organizations. LT recipients were identified and stratified into two cohorts: those receiving PPIs (omeprazole, pantoprazole, esomeprazole, rabeprazole, or lansoprazole) post-transplant and those without PPI exposure. Outcomes included any transplant complication (T86.4), rejection (T86.41), transplant failure (T86.42), transplant-related infection (T86.43), need for re-transplantation, and mortality, assessed from one day post-index event. Propensity score matching was performed for demographics, underlying liver disease etiology, and immunosuppressive medications. Risk ratios and Kaplan-Meier analysis were used to compare relative risk and complication free survival, respectively. **Results:** Among 86,505 patients undergoing LT (mean age 60 ± 18 years, 66.2% White, 59.7% male, mean follow up ~1450 days), 52,312 (60.5%) had evidence of PPI use. After propensity matching, 24,096 patients were included in each cohort. The PPI cohort demonstrated significantly higher rates of any transplant complication (31.1% vs 15.4%, Risk Ratio [RR] 2.03, 95% CI 1.96-2.10, $p < 0.001$). Specifically, PPI use was associated with increased risk of rejection (17.8% vs 9.2%, RR 1.93, 95% CI 1.84-2.03), liver transplant failure (11.9% vs 6.6%, RR 1.79, 95% CI 1.69-1.90), and liver transplant infection (3.3% vs 0.8%, RR 4.06, 95% CI 3.48-4.74), all $p < 0.001$. Moreover, the need for re-transplant was significantly increased in the PPI group (9.0% vs 1.4%, RR 6.29, 95% CI 5.62-7.03) along with all-cause mortality (22.9% vs 13.0%, RR 1.76, 95% CI 1.69-1.83), both $p < 0.001$. Kaplan-Meier analysis revealed reduced transplant complication-free survival in PPI users (48.3% vs 62.1% at end of follow-up, log-rank $p < 0.001$), with a hazard ratio of 2.12 (95% CI 2.04-2.21) (Figure 1). **Conclusion:** PPI use was common in the post-transplant setting and was associated with a two-fold increased risk of overall complications, a four-fold increased risk of transplant-related infections, and a six-fold risk of re-transplantation. Several mechanisms may explain these findings, including PPI-induced reduction in mycophenolate absorption leading to subtherapeutic immunosuppression, alterations in gut microbiota promoting bacterial translocation, impaired neutrophil function, and potential drug interactions with calcineurin inhibitors. These findings suggest the need for judicious PPI prescribing in LT recipients and warrant prospective studies to establish causality and optimal acid suppression strategies.



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3552 | IMPACT OF EARLY-ONSET ARRHYTHMIAS ON OUTCOMES AFTER LIVER TRANSPLANTATION

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Background: Cardiac disease is a common cause of morbidity and mortality after liver transplantation (LT). However, data on the incidence and impact of new-onset arrhythmia in the postoperative period are sparse. We aim to assess the incidence and adverse events of arrhythmia in patients readmitted 30 days after LT. **Methods:** National Readmission Database (NRD) 2016-2021 was queried to identify patients with no pre-existing arrhythmia who underwent LT. Patients readmitted after 30 days were divided into two cohorts of with and without new onset arrhythmia. The primary outcome was all-cause mortality. Secondary outcomes included cardiac adverse events, ICU stay and respiratory failure. Statistical analysis was performed using StataCorp. 2021. **Results:** A total of 35,419 patients

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were discharged post-LT LT of which 10,485 were readmitted after 30 days. Among these, 922 were diagnosed with new-onset arrhythmia (8.79%). The most common arrhythmia was atrial fibrillation (31.47%), followed by supraventricular (5.83%) and ventricular tachycardia (4.83%). Patients with arrhythmia had higher odds of mortality (aOR 1.84, 95% CI: 1.03–3.30, p = 0.03), cardiac arrest (aOR 1.47, 95% CI: 1.09–1.97, p < 0.001, cardiogenic shock (aOR 4.39, 95% CI: 1.66–11.61, p < 0.001), and ACS (aOR 3.95, 95% CI: 2.14–7.30, p < 0.001), ICU stay (aOR 1.87, 95% CI: 1.33–2.61, p < 0.001) and respiratory failure (aOR 1.95, 95% CI: 1.43–4.22, p < 0.001). **Conclusion:** New-onset arrhythmia 30-days after LT is significantly associated with poor prognosis. These findings underscore the need for comprehensive cardiac risk assessment and ongoing surveillance in this high-risk population.

	Odds ratio	95% conf.- interval	P
Mortality	1.84	1.03- 3.30	0.039
ACS	3.95	2.14- 7.30	0.000
Cardiac arrest	5.69	2.30- 14.07	0.000
ICU	1.87	1.33- 2.61	0.000
arf	1.95	1.43- 2.65	0.000

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3553 | DIFFERENTIAL OVERALL MORTALITY AND HEALTHCARE UTILIZATION FOR LIVER TRANSPLANT RECIPIENTS BY REGIONAL, HOSPITAL AND INSURANCE CHARACTERISTICS

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Background: Liver transplantation (LT) is a lifesaving procedure for patients with end-stage liver disease. However, disparities in LT outcomes persist, resulting in barriers to health equity. The aim of this study was to evaluate associations of demographic, socioeconomic and hospital characteristics on post-LT outcomes including overall mortality and measures of healthcare utilization. **Methods:** We conducted a retrospective analysis of the National Inpatient Sample (NIS) database to identify adult LT recipients using ICD-10 coding. Demographic data, medical comorbidities, hospital characteristics, and socioeconomic indicators were examined. Outcomes included overall mortality, length of hospital stay (LOS), and total hospital charges (TOTCHG). Univariate and multivariate linear and logistic regression with propensity score matching assessed associations of covariates with outcomes of interest. **Results:** A total of 47,175 LT recipients were identified. The mean age (±SE) was 59.1 (±0.48) years, with 63.1% male sex, 67.4% White and 15.9% Hispanic ethnicity. Multivariate analysis showed that overall mortality was significantly associated with age (OR 1.04, 95% CI 1.03-1.05), teaching hospitals (OR 0.68, 95% CI 0.51-0.91), comorbidity index (OR 1.39, 95% CI 1.33-1.45), insurance type (OR 0.77, 95% CI 0.66-0.90), and hospital location (OR 0.59, 95% CI 0.38-0.91) (Table). Both length of stay (LOS) and total hospital charges (TOTCHG) were significantly associated with comorbidity burden (LOS β = +0.75 days, TOTCHG β = +$9,784; both p < 0.001). Insurance status significantly influenced outcomes, with Medicaid patients showing a markedly higher risk of overall mortality (OR: 9.78, p = 0.003) and prolonged hospital stays. Regional variations in outcomes were also noted, with some regions demonstrating better survival rates and lower healthcare costs. **Conclusion:** Long term overall mortality and healthcare utilization post-LT are independently impacted by hospital characteristics, region and insurance type, posing potential barriers to health equity for this population. Characterizing underlying drivers of these disparate outcomes are urgently needed to ensure optimal healthcare outcomes and minimize healthcare costs.

Table: Multivariate analysis showing predictors of overall mortality for liver transplant recipients.

Predictor	Odds Ratio	95% CI	P-value
Race	0.99	0.90 – 1.09	0.82
Age	1.04	1.03 – 1.05	**<0.001**
Sex (Female vs. Male)	0.86	0.67 – 1.09	0.21
Teaching Hospital	0.68	0.51 – 0.91	**0.009**
Income Quartile by ZIP Code	0.96	0.86 – 1.07	0.42
Comorbidity Index	1.39	1.33 – 1.45	**<0.001**
Insurance Type	0.77	0.66 – 0.90	**0.001**
Hospital Location	0.59	0.38 – 0.91	**0.01**

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3554 | EARLY EXTUBATION FOLLOWING LIVER TRANSPLANTATION: AN UPDATED ANALYSIS OF A PROSPECTIVE COHORT

Justin Lin[1] Jade Pace[1] Ahmed Aboseria[1] Michael Attanasi[1] Sanjaya Satapathy[1] Nabil Dagher[2], [1]Northwell Health, [2]Northshore- LIJ Health System

Background: Early extubation after orthotopic liver transplantation (OLT) may enhance recovery, though

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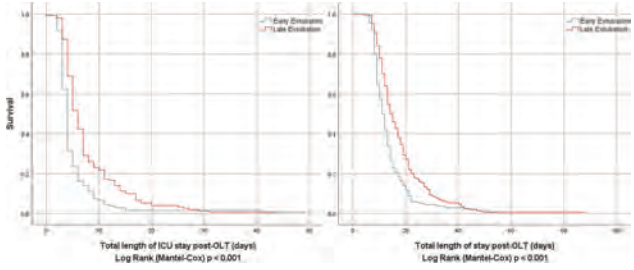
optimal timing and associated risks and benefits remain under investigation. This prospective cohort study evaluates the impact of early extubation on post-operative recovery, complications, and healthcare resource utilization. **Methods:** Adult OLT recipients at a single center between December 2019 and November 2024 were prospectively enrolled. Patients were stratified into early extubation (within 12 hours, $n = 137$) and late extubation (after 12 hours, $n = 151$) cohorts. Baseline demographics and clinical data were collected from institutional databases and reported to UNOS/OPTN. The Liver Frailty Index (LFI) was used to assess preoperative frailty. Acute kidney injury (AKI) was defined per KDIGO criteria as an increase in serum creatinine > 0.3 mg/dL within 48 hours or $\geq 50\%$ within 7 days, or initiation of renal replacement therapy within 14 days post-OLT. Patients undergoing simultaneous kidney transplantation or on pre-OLT dialysis were excluded from AKI analysis. **Results:** Early extubation was associated with significantly better preoperative functional status (Karnofsky score: 78% vs. 75%, $p = 0.039$; LFI: 4.36 vs. 4.74, $p = 0.005$), shorter ICU stays (5.2 vs. 7.8 days, $p < 0.001$), and reduced hospital length of stay (13.5 vs. 17.6 days, $p < 0.001$). These associations remained significant after adjustment for age, sex, BMI, MELD 3.0, and diabetes. The incidence of AKI was lower in the early extubation group (41.4% vs. 58.6%, $p = 0.003$), with no difference in reintubation rates between groups. **Conclusion:** Early extubation following liver transplantation is associated with improved recovery metrics, including reduced ICU and hospital stays, and a lower incidence of AKI. These findings support early extubation as a safe and cost-effective strategy that may enhance post-transplant outcomes. Broader implementation of protocolized early extubation should be considered in the absence of contraindications. Further multicenter studies are warranted to develop standardized guidelines.



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3555 | INCIDENCE AND PREDICTORS OF POST-TRANSPLANT MALIGNANCY IN LIVER TRANSPLANT RECIPIENTS: A SINGLE-CENTRE COHORT STUDY

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Background: Cancer is a significant long-term complication following liver transplantation (LT). We aimed to characterize the incidence and risk factors associated with post-transplant cancer in a cohort of LT recipients in a Canadian tertiary care center. **Methods:** Retrospective cohort study including patients who underwent LT between 2007–2018 (minimum follow-up 60 months after LT). Demographic data, immunosuppression regimens and cancer diagnoses were analyzed. The analyses included univariate and multivariate Cox regression models. **Results:** We included 575 LT recipients from a single center in Ontario, Canada. The median age was 53.6 years [IQR: 48–61], and 173 (30.0%) were women. The main causes of cirrhosis were alcohol-associated liver disease (ALD) in 22.9%, hepatitis C virus (HCV) infection in 20.8%, metabolic dysfunction-associated steatotic liver disease (MASLD) in 13.3%, and primary sclerosing cholangitis (PSC) in 11.1%. Additionally, 148 patients (25.7%) had hepatocellular carcinoma (HCC) at the time of LT. A total of 55 (9.7%) developed malignancies during follow-up; the most frequent were non-melanoma skin cancer (20 cases, 36.3% of all cancers, and 3.48% of all LT recipients), head and neck neoplasms (6 cases, 10.9% of all cancers and 1.04% of all LT recipients), post-transplant lymphoproliferative disorder (PTLD) (5 cases, 9.0% of all cancers and 0.87% of all LT recipients), gastrointestinal cancers (5 cases, 9.0% of all cancers and 0.87% of all LT recipients) and neuroendocrine

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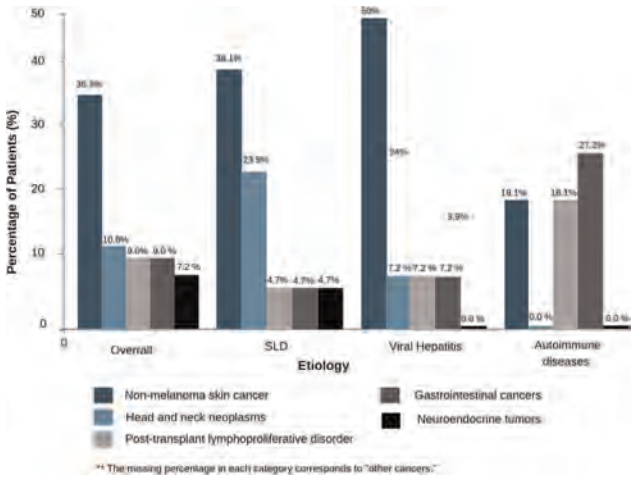
tumors (4 cases, 7.2% of all cancers and 0.70% of all LT recipients). The average time between transplant and cancer diagnosis was 27.3 ± 19.1 months. Additionally, 20 patients (3.4%) developed HCC post-transplant, of which 18 (90%) were recurrences. The types of cancer varied significantly by etiology ($p = 0.004$). Among patients with SLD and viral hepatitis, the most common cancer types were non-melanoma skin cancer (38.1% and 50%, respectively), while among those with autoimmune liver diseases, gastrointestinal cancers were the most frequent (27.2%). Among patients with a history of HCC prior to transplantation, 16.8% developed a non-HCC cancer, with non-melanoma skin cancer being the most frequent (40%). In multivariate Cox regression models, age at transplantation, gender, post-transplant alcohol use, tobacco use, and cirrhosis etiology were not associated with cancer development. However, a history of pre-transplant HCC was significantly associated with cancer risk (HR 2.66, 95% CI 1.39–5.07, $p = 0.003$). **Conclusion:** Cancer occurred in 9.7% of liver transplant recipients, typically within the first three years. Patients with a history of prior HCC at the time of transplantation were three times more likely to develop non-HCC cancer. These findings underscore the necessity of cancer surveillance in post-transplant recipients, particularly among those with a history of HCC.



Disclosures: Francisco Idalsoaga: Nothing to Disclose, Abed Saqah: Nothing to Disclose, Pedro Acuña: Nothing to Disclose, Hashaal Alkhurassi: Nothing to Disclose, Saad Moteb Aldosari: Nothing to Disclose, Abdelrahman Sallam: Nothing to Disclose, Reyad Elzaanoun: Nothing to Disclose, Siddhant Maini: Nothing to Disclose, Gopika Punchhi: Nothing to Disclose, Rokhsana Mortuza: Nothing to Disclose, Luis Antonio Diaz: Nothing to Disclose, Mohammed Qasim Khan: Nothing to Disclose, Juan Pablo Arab: Nothing to Disclose

3556 | FIBROSIS AND STEATOSIS PROGRESSION AFTER LIVER TRANSPLANTATION DIFFERS BASED ON THE PRETRANSPLANT ETIOLOGY OF LIVER DISEASE

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Background: Although liver transplantation is performed for a variety of different diseases, the natural history of fibrosis progression after liver transplantation is largely unknown. Here, we hypothesized that different causes of liver disease may be associated different progression of fibrosis progression rates after transplantation, perhaps related to the etiology of initial liver disease. **Methods:** All adults who underwent liver transplantation and had a liver biopsy at our institution from 1/1/2013 through 7/1/2021 were examined. Histology, fibrosis stage (F0-F4), rejection activity index (RAI), and complete clinical data were abstracted via the medical record through 9/21/2021. Patients who did not have a fibrosis stage recorded or who had surgical complications of transplant were excluded. The etiology of liver disease was determined pre-transplant based on typical clinical criteria and confirmed histologically on explant histology. Patients were grouped based on the pre-transplant etiology of their liver disease, and time to progression of each stage of fibrosis and grade of steatosis was recorded. The median time to developing each fibrosis stage was calculated with trendlines plotted. **Results:** Of 515 transplant patients having a liver biopsy, we identified 347 patients who met inclusion criteria, representing 1,133 biopsies. Females had a higher prevalence of AIH and PBC (respectively: 29/145 (20%) vs 10/224 (4%); 18/145 (12%) vs 1/224 (1%); $p < 0.0001$), and males had a higher prevalence of ALD and HCV (respectively: 48/224 (21%) vs 14/145 (10%); 104/224 (46%) vs 33/145 (23%); $p < 0.01$ and 0.0001). AIH, PBC, and PSC was more prevalent in Black patients then White patients (respectively: 20/80 (25%) vs 19/276 (7%); 8/80 (10%) vs 11/276 (4%); 12/80 (15%) vs 9/276 (3%); $p < 0.0001$, $p < 0.05$, and $p < 0.05$), and ALD and MASLD was more prevalent in White patients (respectively: 58/276 (21%) vs 2/80 (3%); 54/276 (20%) vs 2/80 (3%); $p < 0.0001$). Viral liver diseases had the highest rate of fibrosis progression (Figure 1a). Rejection severity was not correlated with fibrosis for any etiology. Steatosis grade progressed most rapidly with MASLD and HCV (Figure 1b) and progressed slowest in ALD. **Conclusion:** In conclusion, viral liver diseases had the most rapid fibrosis progression. The majority of HCV patients

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included in this analysis were transplanted prior to the introduction of direct acting antiviral medications, and as such serve as a baseline for expected rapid fibrosis progression. Steatosis progression is most rapid in MASLD and HCV and least rapid in patients ALD.

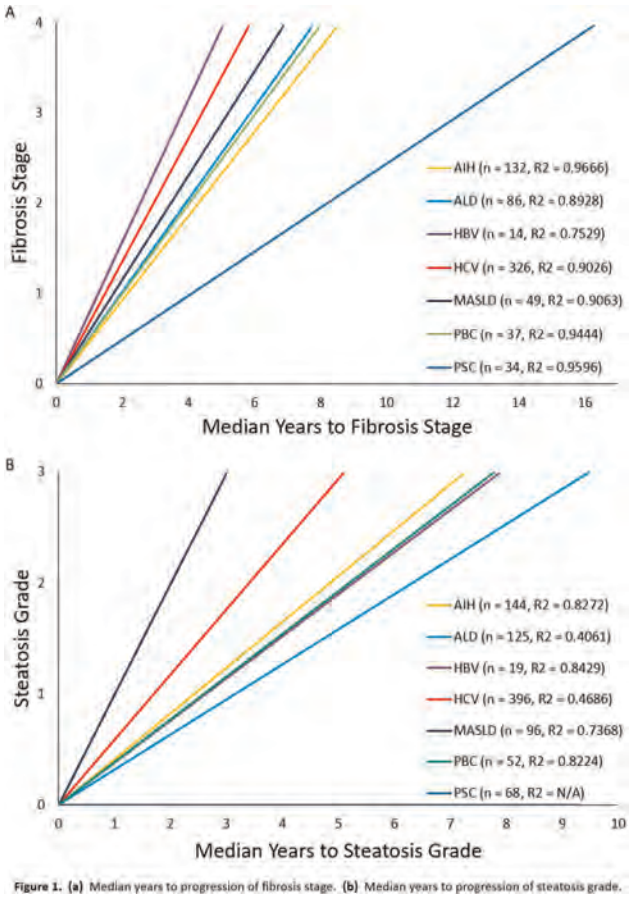

Figure 1. **(a)** Median years to progression of fibrosis stage. **(b)** Median years to progression of steatosis grade.

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3557 | GRADING CHATGPT'S RESPONSES TO QUESTIONS ABOUT LIVING DONOR LIVER TRANSPLANT

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Background: Living donor liver transplant (LDLT) provides better outcomes and improved access for patients with liver disease. However, both patients and non-transplant providers are poorly educated about LDLT. Increasingly, artificial intelligence (AI) is utilized by patients to learn about complex medical conditions and treatments. As our patients rely on this tool, physicians must evaluate their efficacy and accuracy to minimize misinformation. We assessed the performance of Chat Generative Pretrained Transformer (ChatGPT) in answering common questions about LDLT. **Methods:** Chat Generative Pretrained Transformer (ChatGPT) is a commonly used technology created by OpenAI Foundation. We asked 9 separate questions with the following themes: education (1-2), risks for donors (3-5, 7), outcomes for donors (5-7), and how to find a donor (8-9). We had 2 medical directors of LT and 4 LDLT programs grade each response based on a Likert scale – for accuracy (rated 1 to 6) and completeness (rated 1 to 3), with higher scores being better. Additionally, we had a donor champion coordinator evaluate the questions focused on how to find a donor (questions 8 and 9). Mean scores were calculated and ranges were reported. **Results:** The mean accuracy of responses was 5, with individual respondents ranging from 4.3-5.4 and individual questions from 4.3-5.3. For categories, the accuracy was highest (5.1) in the risks for donors and lowest for education (4.8). The highest mean score for a question was 5.3 for "Will I die at younger age if I donate my liver?" The lowest mean score for a question was 4.3 for both "What is a living donor liver transplant?" and "What is the risk of dying if I donate my liver?" No respondents graded any response lower than a 4/6.
Completeness of responess was graded at a mean 2.7, with individual respondents ranging from 2.5-3 and individual questions from 2.2-3. Question 5 and 6 – both discussing risk of future liver disease and mortality – were voted 3/3 by 5 of the 6 respondents. The lowest mean score was 2.3 for question 7 – "Can I drink alcohol after donating my liver?" No respondent graded any response lower than a 2/3. **Conclusion:** As AI becomes increasingly utilized to learn about medical issues and procedures, it is equally vital for providers to keep pace and remain aware of its strengths and pitfalls. The accuracy of ChatGPT was assessed quite positively by medical directors of LT programs and LDLT programs and most of the answers were graded as complete. While there were errors and omissions, ChatGPT represented LDLT as reasonably as can be expected. Further and recurrent analysis will be needed to keep up with new technologies and their changes over time.

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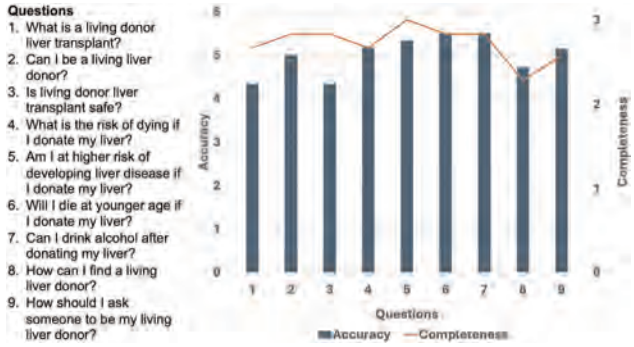

Disclosures: Russell Rosenblatt: Nothing to Disclose, Pamela Cobbs: Nothing to Disclose, Brett Fortune: Gilead Sciences: Consultant, Madrigal Pharma: Consultant, WL Gore and Associates: Consultant, BD medical: Consultant, Kristina Chacko: Nothing to Disclose, Whitney Jackson: Nothing to Disclose, Hyosun Han: Nothing to Disclose, Danielle Brandman: Gilead: Grant/Research Support, Genentech: Grant/Research Support, Novo Nordisk: Consultant

3558 | SHOULD ACUTE PANCREATITIS DELAY LIVER TRANSPLANTATION? INSIGHTS FROM A PROPENSITY-MATCHED COHORT STUDY

Sameer Rao[1] *Niwen Kong*[2] *Ritik Mahaveer Goyal*[1] *Manas Gunani*[3] *Paul Gaglio*[1] *Amir Gougol*[2] *Nikki Duong*[2], [1]*Rutgers New Jersey Medical School,* [2]*Stanford University,* [3]*Allegheny General Hospital*

Background: Liver transplantation (LT) is the definitive treatment for end-stage liver disease (ESLD). While LT is typically delayed in cases of necrotizing pancreatitis due to higher post-operative risks, the impact of mild acute pancreatitis on transplant timing remains unclear. This study evaluates the effect of pre-operative acute pancreatitis on post-transplant outcomes. **Methods:** We conducted a retrospective cohort study using the TriNetX database and International Classification of Diseases-10 codes to compare one-year post-operative outcomes in LT recipients with vs. without acute pancreatitis within 30 days prior to transplant. Patients with pancreatic neoplasms, pseudocysts, abscesses, or multi-organ transplants were excluded from the study. The two groups were 1:1 propensity score matched based on demographics and clinical covariates. The primary outcome was graft failure. Secondary outcomes included infectious (sepsis, peritonitis, cytomegalovirus infection), graft-related (rejection, infection), surgical (hemorrhage, ileus, abscess), systemic (acute kidney injury, encephalopathy, cardiovascular/cerebrovascular events) complications, and all-cause mortality. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated; $P < .05$ was considered significant. **Results:** Our study included 138 patients with acute pancreatitis ≤30 days before LT (mean age 48 ± 14.2 years; 67.4% male) and 10,611 patients without acute pancreatitis in the same period (mean age 54.5 ± 12.4 years; 76.1% male). After 1:1 propensity score matching, 136 patients per group were followed for one year. Patients with acute pancreatitis within 30 days prior to LT had similar risk of graft failure (RR 1.00; 95% CI 0.54–1.84; P = 1.00). The acute pancreatitis group also had similar risk for other clinical outcomes such as sepsis (RR 1.32; 95% CI 0.83–2.09; P = 0.24), peritoneal abscess (RR 1.10; 95% CI 0.48–2.50; P = 0.82), post-operative hemorrhage (RR 1.00; 95% CI 0.62–1.61; P = 1.00), ileus (RR 1.08; 95% CI 0.53–2.20; P = 0.84), transplant rejection (RR 0.78; 95% CI 0.50–1.20; P = 0.25), liver transplant infection (RR 1.30; 95% CI 0.59–2.86; P = 0.51), CMV infection (RR 1.25; 95% CI 0.77–2.02; P = 0.36), acute kidney injury (RR 0.99; 95% CI 0.84–1.61; P = 0.90), pneumonia (RR 1.21; 95% CI 0.62–2.36; P = 0.57), and mortality (RR 1.40; 95% CI 0.64–3.04; P = 0.39). There was a tendency towards higher risk of encephalopathy (RR 1.71; 95% CI 0.93–3.17; P = 0.08), but it did not reach statistical significance. **Conclusion:** This is the first national real-world data study to demonstrate that LT within 30 days of acute pancreatitis does not significantly increase post-transplant complications. While recent pancreatitis warrants careful evaluation, it should not be considered a strict contraindication. Further prospective studies are needed to validate these findings and guide transplant candidacy decisions in this complex patient population.

Table – Comparison of one-year post-transplant outcomes in patients with vs. without acute pancreatitis ≤30 days prior to liver transplant

Clinical outcomes after propensity matching	N (136)	%	*Relative Risk	Confidence interval	P-value
Sepsis	33	24.26	1.32	(0.83,2.09)	.24
	25	18.38			
Peritonitis	20	14.71	1.67	(0.85,3.27)	.13
	12	8.82			
Peritoneal abscess	11	8.09	1.10	(0.48,2.50)	.82
	≤ 10#	7.35			
Postprocedural hemorrhage/hematoma	27	19.85	1	(0.62,1.61)	1
	27	19.85			
Ileus	14	10.29	1.08	(0.53,2.20)	.84
	13	9.56			
Liver transplant rejection	28	20.59	0.78	(0.50,1.20)	.25
	36	26.47			
Liver transplant failure	18	13.23	1	(0.54,1.84)	1
	18	13.23			
Liver transplant infection	13	9.56	1.30	(0.59,2.86)	.51
	≤ 10#	7.35			
Cytomegalovirus infection	30	22.06	1.25	(0.77,2.02)	.36
	24	17.65			
Epstein Barr virus infection	≤ 10#	7.35	1.00	(0.43,2.32)	1
	≤ 10#	7.35			
Acute kidney injury	93	68.38	0.99	(0.84,1.61)	.90
	94	69.12			
Encephalopathy	24	17.65	1.71	(0.93,3.17)	.08
	14	10.29			
Acute respiratory distress syndrome	≤ 10#	7.35	1.00	(0.43,2.32)	1
	≤ 10#	7.35			
Pneumonia	17	12.50	1.21	(0.62,2.36)	.57
	14	10.29			
Cerebral infarction	≤ 10#	7.35	1.00	(0.43,2.32)	1
	≤ 10#	7.35			
Acute myocardial infarction	≤ 10#	7.35	1.00	(0.43,2.32)	1
	≤ 10#	7.35			
Any-cause emergency department visit	46	33.82	0.80	(0.69,1.33)	.80
	48	35.29			
Deceased	14	10.29	1.4	(0.64,3.04)	0.39
	≤ 10#	7.35			

*The relative risk is calculated as exposed (patients with acute pancreatitis ≤30 Days before liver transplant) versus unexposed (patients without acute pancreatitis <30 Days before liver transplant)
#To protect patient privacy, numbers ≤10 in TriNetX are rounded up to 10

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Disclosures: Sameer Rao: Nothing to Disclose, Niwen Kong: Nothing to Disclose, Ritik Mahaveer Goyal: Nothing to Disclose, Manas Gunani: Nothing to Disclose, Paul Gaglio: Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Mallinkrodt: Speaking and Teaching, Amir Gougol: Nothing to Disclose, Nikki Duong: Nothing to Disclose

3559 | PRE-TRANSPLANT GLP-1 RECEPTOR AGONIST USE AND POST-LIVER TRANSPLANTATION OUTCOMES: A RETROSPECTIVE COHORT STUDY

Joanna Jiang[1] Sandra Boutros[2] Stacey Culp[2] Chathur Acharya[2] Vivek Mendiratta[2] Melissa McGowan[2] Nicole Gray[3] Lindsay Sobotka[2], [1]The Ohio State Wexner Medical Center, [2]The Ohio State University Medical Center, [3]Ohio State University

Background: Glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) are increasingly used in patients with metabolic dysfunction-associated fatty liver disease (MAFLD), one of the most common etiologies for end-stage liver disease requiring liver transplantation (LT). The use of GLP-1RAs has been associated with adverse outcomes in certain surgical settings. However, their impact on post-LT outcomes has yet to be studied. **Methods:** A retrospective cohort study was conducted of adult LT recipients who underwent LT between 7/20/2016 and 12/6/2024 at The Ohio State University Medical Center. Patients were stratified by documented duration of GLP-1 use, either within 12 months or more prior to LT. Primary outcomes included: reintubation, post-LT length of stay (LOS), post-LT infection, return to OR for bleeding, hepatic artery thrombosis, acute cellular rejection, renal dysfunction requiring dialysis, biliary strictures/ischemia, graft loss, and all-cause mortality. Chi-squared and Fisher's exact tests were used. Logistic regression controlled for pre-transplant BMI. **Results:** Thirty-eight LT recipients were using GLP-1 prior to LT and were compared to 120 LT recipients not utilizing GLP-1 RA. Twenty of the GLP-1 patients had taken it within two weeks of LT. Gender, race, and age at LT did not differ significantly between the groups. Pre-LT MELD at time of waitlist was lower in the GLP-1 group (17.6 vs 21.3; $p = 0.008$). Pre-LT BMI was significantly higher in the GLP-1 group compared to controls (32.8 vs 29.4; $p = 0.002$), as was pre-transplant diabetes (92.1% vs 27.5%; $p < 0.001$), hyperlipidemia (84.2% vs 30.8%; $p < 0.001$), and coronary artery disease (63.2% vs 32.5%; $p < 0.001$). Patients taking GLP-1 medications had higher rates of return to OR for bleeding, prolonged intubation, renal dysfunction, graft loss, and LOS (Table 1). One-year mortality did not differ significantly. A sensitivity analysis that included only those who had used GLP-1 medications within two weeks of their LT ($n = 20$) showed similar significant differences in outcomes when compared to the non-GLP-1 group. **Conclusion:** Patients on GLP-1 had increased complications in the immediate post-LT course; however, further research is needed to clarify the long term benefits of GLP-1 medications on improving control of metabolic conditions which typically worsen post-LT outcomes.

Table 1: Comparison of Outcomes Between Liver Transplant Recipients on GLP-1s and Controls

Variable	Control (N=120) N (%)	GLP-1s (N=38) N (%)	p-value
Infection post LT	36 (30.3)	16 (42.1)	0.261
Return to OR for bleeding	8 (6.7)	9 (23.7)	**0.009**
Reintubated	3 (2.5)	6 (15.8)	**0.013**
Hepatic artery thrombosis	2 (1.7)	1 (2.6)	0.811
Acute cellular rejection	24 (20.2)	3 (8.1)	0.085
Renal dysfunction requiring renal replacement	13 (10.9)	11 (28.9)	**0.030**
Biliary pathology	51 (42.9)	13 (34.2)	0.297
Graft loss in 1 year	7 (5.8)	7 (18.4)	**0.020**
Mortality within 1 year	6 (5.0)	5 (13.2)	0.064
LOT in ICU (time from admit to transfer order) – hours	40 (26 – 58)	73 (42.5 – 102.5)	**< 0.001**
LOT in the hospital after OLT – days	8.5 (7 – 12)	11 (8 – 15.5)	**0.017**

Disclosures: Joanna Jiang: Nothing to Disclose, Sandra Boutros: Nothing to Disclose, Stacey Culp: Nothing to Disclose, Chathur Acharya: Nothing to Disclose, Vivek Mendiratta: Nothing to Disclose, Melissa McGowan: Nothing to Disclose, Nicole Gray: Nothing to Disclose, Lindsay Sobotka: Nothing to Disclose

3560 | EARLY POST-TRANSPLANT ENTERAL NUTRITION SHORTENS HOSPITALIZATION AND PREVENTS ICU READMISSION AFTER LIVER TRANSPLANTATION

Ali Shaat[1] Muhammad Ali Butt[1] Catherine Briere[1] Audrey Paradis[1] Han LI[1] Ming Lin[1] James Hendele[1] Amir Qamar[1] Mohamed Akoad[1] Bartholomew Kane[1] Sarah Meade[1] Raza Malik[1], [1]Lahey Hospital & Medical Center

Background: Malnutrition is a modifiable risk factor that impairs recovery after liver transplantation (LT), yet the optimal timing of postoperative enteral tube feeding (TF) remains uncertain. We aimed to evaluate how TF timing affects 28-day postoperative outcomes in LT recipients with preoperative diagnoses of moderate-to-severe malnutrition. **Methods:** In this single-center, retrospective cohort study at Lahey Hospital & Medical Center (01/01/2024–12/31/2024), 32 adult LT recipients with moderate-to-severe malnutrition were stratified by TF

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initiation: ≤48 hours (Early TF), 48 hours–7 days (Intermediate TF), and >7 days (Delayed TF). Over a 28-day period, we compared initial ICU and hospital length of stay (LOS), infection rates, readmission, ascites requiring paracentesis, graft rejection, discharge disposition, and all-cause mortality. Continuous variables were compared using Student's t-test or Mann-Whitney U test and categorical variables were assessed using Fisher's exact or Chi-square testing. **Results:** Among 32 liver transplant recipients, 20 received early TF, 6 received intermediate TF, and 6 received delayed TF. Baseline demographics are summarized in Figure 1. Hospital LOS increased progressively with delayed initiation of enteral nutrition. The early feeding group (Group 1) had a median stay of 11 days (IQR 8.8–23.5), compared to 22 days (IQR 17–27) in the intermediate group (Group 2; $p = 0.044$), and 38.5 days (IQR 25.8–54.3) in the delayed group (Group 3; $p = 0.006$ vs. Group 1).

Median initial ICU stay rose from 2 days (IQR 1–3.3) in Group 1 to 3.5 days (IQR 1.3–5.8) in Group 2 and 4 days (IQR 2.3–5.0) in Group 3, though these increases were not statistically significant ($p = 0.26$ and 0.15, respectively). ICU readmission within 28 days occurred in 0% of patients in Group 1, 33% in Group 2, and 83% in Group 3, with a statistically significant difference between Groups 1 and 3 ($p < 0.001$).

Rates of postoperative infection (55% vs. 33% vs. 67%), ascites requiring paracentesis (25% vs. 17% vs. 17%), acute rejection (0% vs. 17% vs. 0%), 30-day readmission (25% vs. 17% vs. 33%), and discharge disposition did not differ significantly across groups. There were no deaths in any cohort. **Conclusion:** In post-LT patients with moderate-to-severe malnutrition, early initiation of TF within 48 hours was associated with significantly shorter hospital LOS and markedly lower ICU readmission rates compared with delayed TF. Although trends toward shorter ICU LOS and lower complication rates were observed in the early cohort, these did not reach statistical significance. No differences were seen in infection, ascites, rejection, readmission, disposition, or mortality across groups. These findings support early TF initiation soon after transplant to enhance recovery and reduce resource utilization. Limitations of the study include the small cohort size; further prospective studies are warranted to confirm these results.

Abbreviations: A1AT = Alpha-1-Antitrypsin Deficiency; MASH = Metabolic Dysfunction-Associated Steatohepatitis; PSC = Primary Sclerosing Cholangitis; PBC = Primary Biliary Cirrhosis; DDLT = Deceased Donor Liver Transplant; LDLT = Living Donor Liver Transplant; HBV = Hepatitis B Virus.

Characteristic	Early TF ≤ 48h (n = 20)	Intermediate TF >48h to 7d (n = 6)	Delayed TF > 7d (n = 6)
Median Age at LT	61.5	62.0	58.5
Sex, M/F (%)	11 / 9 (55% / 45 %)	3 / 3 (50% / 50 %)	3 / 3 (50% / 50 %)
Race (%)	White: 17 (85 %) Hispanic/Latino: 2 (10 %) Asian: 1 (5 %)	White: 6 (100 %)	White: 5 (83 %) Asian: 1 (17 %)
Median MELD-3.0 at LT	23.5	27.5	16.5
Cirrhosis Etiology and LT Indication (%)	Alcohol-associated cirrhosis: 14 (70 %) MASH cirrhosis: 5 (25 %) A1AT deficiency: 1 (5 %)	Alcohol-associated cirrhosis: 4 (67 %) MASH cirrhosis: 1 (17%) PSC cirrhosis: 1 (17%)	Alcohol-associated cirrhosis: 3 (50 %) HBV cirrhosis: 1 (17%) Polycystic liver disease: 1 (17%) PBC: 1 (17%)
Liver Transplant Type (%)	DDLT: 20 (100 %)	DDLT: 5 (83 %) LDLT: 1 (17 %)	DDLT: 5 (83 %) LDLT: 1 (17 %)
Diabetes Mellitus (%)	6 (30 %)	2 (33 %)	2 (33 %)
Preoperative Malnutrition Status (%)	Moderate: 7 (35 %) Severe: 13 (65 %)	Moderate: 4 (67 %) Severe: 2 (33 %)	Moderate: 6 (100 %)
Median Preoperative BMI, kg/m²	27.8	28.9	27.2

Disclosures: Ali Shaat: Nothing to Disclose, Muhammad Ali Butt: Nothing to Disclose, Catherine Briere: Nothing to Disclose, Audrey Paradis: Nothing to Disclose, Han LI: Nothing to Disclose, Ming Lin: Nothing to Disclose, James Hendele: Nothing to Disclose, Amir Qamar: Nothing to Disclose, Mohamed Akoad: Nothing to Disclose, Bartholomew Kane: Nothing to Disclose, Sarah Meade: Nothing to Disclose, Raza Malik: Nothing to Disclose

3561 | PRELIMINARY STUDY ON PREDICTING HEPATOCELLULAR CARCINOMA RECURRENCE POST-LIVER TRANSPLANT USING LI-RADS AND LESION VOLUME METRICS

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Background: Liver transplantation (LT) is associated with lower hepatocellular carcinoma(HCC) recurrence rates than resection but despite this, post-LT HCC recurrence still occurs in 5-15% of cohorts. Most of recurrence prediction models utilize tumor characteristics discovered on liver explant tissue, but there can be approximately 22%-30% discordance between pathological and radiological tumor characteristics. Therefore, we explore radiomics in predicting HCC recurrence. **Methods:** This is retrospective study with patients who were liver transplanted for HCC at a tertiary center. Primary outcomes evaluated included HCC recurrence and mortality. Each patient had multiphasic contrast-enhanced T1 MRI scans pre-LT. Total tumor volume (TTV) was analyzed with three groups by summing volumes of 1) LIRADS-3 or higher lesions, 2) LIRADS-4 or higher lesions, 3) only LIRADS-5 lesions. Treated lesions were included in the TTV summation. All except 6 patients had untreated HCC on MRI images. Wilcoxon tests compared median TTV, age, and gender between recurrence and mortality groups at varying time points. The Cox proportional hazards model was used to evaluate the association between TTV, age, and gender with time to post-transplant recurrence and mortality to identify independent predictors of these outcomes. **Results:** Out of 168 patients, 21 had HCC recurrence, thus resulting in a cumulative incidence rate of 0.31% and median time to recurrence of about 34 months (IQR: 11.4, 65.5). Median age of age of cohort is 70 (IQR: 66,74) and majority is male (n = 130, 77%). 66 were Caucasian, 50 Black, 22 Asian, 11 Hispanic, and 25 were multi-racial/other/unknown. All HCC recurrence occurred within 2 years post-LT. Etiology of liver disease was predominantly Hepatitis C

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(54%), followed by chronic hepatitis B (13%), steatotic liver disease (alcohol and non-alcohol) (20%), others (13%). LI-RADS 5+ TTV had a statistically significant association with overall recurrence (p = 0.02), and recurrence at 6- and 12-months post-LT (p = 0.04 and p = 0.002 respectively). The optimal TTV cutoff to differentiate overall recurrence from non-recurrence was 42.2 cm3 (p = 0.001) with any volumes greater being associated with recurrence. However, in an age and gender adjusted multi-variate analysis, TTV LIRADS-5+ group (HR = 1.2 [0.8-1.8], p = 0.5) did not independently predict recurrence. In the multivariate analysis, with TTV of LI-RADS 3 or greater group, increased age independently predicted 12-month morality (HR = 1.96 [1.06-3.62], p = 0.031). **Conclusion:** HCC recurrence occurred early in this cohort and TTV of LIRADS-4 or greater lesions is associated with HCC recurrence but did not independently predict in age and sex adjusted multivariate analysis. Age was the strongest predictor of post-LT mortality. This highlights that TTV alone is not able to predict mortality but when combined with patient factors, such as age, it can result in significant associations.

	LI-RADS 3+ Lesion Patients			LI-RADS 4+ Lesion Patients			LIRADS 5+ Lesion Patients		
	TTV p-value	Age p-value	Gender p-value	TTV p-value	Age p-value	Gender p-value	TTV p-value	Age p-value	Gender p-value
Overall Recurrence	0.24	0.85	0.83	0.07	0.31	0.7	0.02	0.14	0.6
6 Month Recurrence	0.45	0.2	0.76	0.46	0.8	0.66	0.04	0.98	0.42
12 Month Recurrence	0.28	0.51	0.36	0.04	0.8	0.61	0.002	0.3	0.34
Overall Death	0.78	0.08	0.96	0.63	0.31	0.68	0.53	0.34	0.01
6 Month Death	0.97	0.27	0.67	0.83	0.06	0.31	0.31	0.07	0.83
12 Month Death	0.61	0.01	0.99	0.73	0.02	0.26	0.82	0.02	0.96

Table 1: Wilcoxon test results evaluating the association between TTV, age, and gender from three patient subgroups (patients who have at least one LIRADS 3+ lesion, LI-RADS 4+ lesion, or LIRADS 5+ lesion) against recurrence and mortality groups. The median was calculated for each predictor (TTV, age, and gender) when compared to recurrence and mortality groups

(LI-RADS: Liver Imaging Reporting and Data System, TTV: Total Tumor Volume)

Disclosures: Emma Stevenson: Nothing to Disclose, Stephanie Harmon: Nothing to Disclose, Ross Filice: Bunkerhill Health: Advisor, Sirona Medical: Advisor, Peter Choyke: Nothing to Disclose, Theo Heller: Nothing to Disclose, Ismail Turkbey: Nothing to Disclose, Christine Hsu: Nothing to Disclose

3562 | OUTCOMES OF RETRANSPLANTATION FOR AUTOIMMUNE LIVER DISEASES: A NATIONAL RETROSPECTIVE COHORT STUDY

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Background: Liver retransplantation (reLT) is indicated after primary allograft failure and accounts for up to 10% of liver transplants (LT) in the United States. Late graft loss (LGL), ≥ 1 year (y) from primary transplant, in autoimmune liver disease (AILD) is often due to rejection or recurrence of primary disease. Outcomes after reLT for LGL in AILD compared to other indications are not well understood. **Methods:** This retrospective cohort study included adult recipients with reLT between March 2002 and December 2021 in the United Network for Organ Sharing database. Those with < 1y between primary and reLT or diagnosis of hepatitis C virus were excluded. ReLT indication was classified as AILD (autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC)) or non-AILD. Outcomes included LGL (death with recurrent disease or 2nd reLT, censoring at death without recurrence, death or reLT within 1 y of LT, or at last follow-up and patient survival. Kaplan-Meier estimates of outcomes were compared via the log-rank test. Cox regression estimated hazard ratios (HR) for risk of LGL. **Results:** A total of 1,969 patients (38.4% AILD, 61.6% non-AILD; median age 45 and 47 y, 43.3% and 42.5% female, respectively) were included. Over a median follow-up time of 4.8 y (IQR 2.0-9.0), LGL was identified in N = 80 for AILD and N = 62 for non-AILD. Fifteen-year cumulative incidence of LGL was higher for AILD (0.22, 95% CI 0.18-0.28) vs. non-AILD (0.13, 0.09-0.18; p = 0.002) and for AIH (0.24, 0.15-0.36) and PSC (0.25, 0.19-0.33) vs. PBC (0.03, 0.008-0.12; p = 0.002 and 0.006, respectively). In univariable analysis among AILD, risk of LGL was higher for AIH (HR 7.54, 1.77-32.08, p = 0.006) and PSC (HR 5.64, 1.38-23.13, p = 0.02) vs. PBC, and MELD (HR 1.02 per unit increase, 1.00-1.05, p = 0.06), while age (HR 0.94 per y increase, 0.93-0.96, p < 0.001) was associated with decreased LGL. After adjusting for age and MELD, risk of LGL remained elevated for AIH (HR 3.23, 0.74-14.14, p = 0.12) and PSC (HR 3.93, 0.95-16.27, p = 0.06) though the associations were attenuated. Patient survival at 15 y was higher for AILD (0.48, 0.43-0.54) than non-AILD (0.45, 0.40-0.50, p = 0.01) and higher for PSC (0.54, 0.47-0.60) compared to AIH (0.39, 0.26-0.52, p = 0.04) and PBC (0.37, 0.24-0.50, p = 0.03). **Conclusion:** AILD was associated with a two-fold increase in LGL after reLT compared to other indications, but superior patient survival. Among AILD, LGL was more common in AIH and PSC compared to PBC. Though LGL is more common in AILD, excellent survival supports the continued practice of reLT in this group.

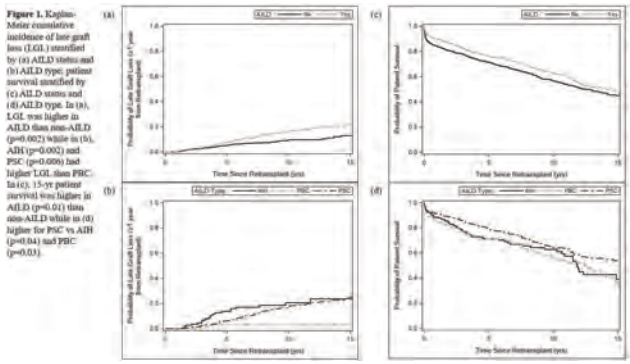

Figure 1. Kaplan-Meier cumulative incidence of late graft loss (LGL) stratified by (a) AILD status and (b) AILD type; patient survival stratified by (c) AILD status and (d) AILD type. In (a), LGL was higher in AILD than non-AILD (p=0.002) while in (b), AIH (p=0.002) and PSC (p=0.006) had higher LGL than PBC. In (c), 15-yr patient survival was higher in AILD (p=0.01) than non-AILD while in (d) higher for PSC vs AIH (p=0.04) and PBC (p=0.03).

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Disclosures: Justin Ong: Nothing to Disclose, Brian Horwich: Nothing to Disclose, Jeffrey Kahn: Nothing to Disclose, Jennifer Dodge: Nothing to Disclose, Oluwakemi Ayeni: Nothing to Disclose, Susie Lee: Nothing to Disclose, Steve Kim: Nothing to Disclose

3563 | IMPACT OF PRE-EXISTING DIABETES ON POST-TRANSPLANT INFECTIONS AND MORTALITY IN LIVER RECIPIENTS: A TIME-INTERVAL PROPENSITY-MATCHED ANALYSIS

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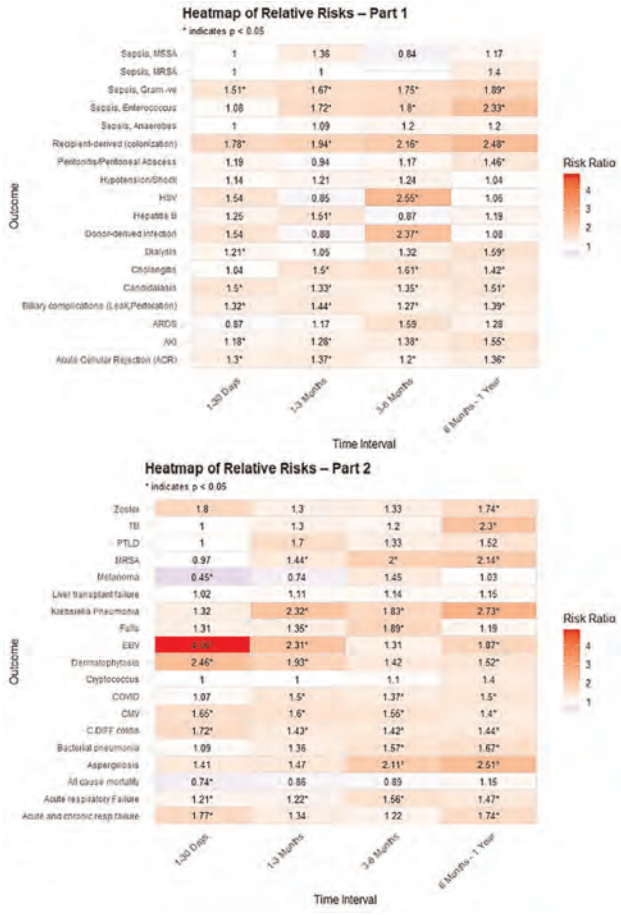
Background: Diabetes mellitus (DM) is prevalent among liver transplant (LT) recipients, but its impact over distinct postoperative intervals remains insufficiently explored. We assessed the incidence of infections, including cholangitis, sepsis, and all-cause mortality over four distinct postoperative intervals. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network, a global federated health platform aggregating de-identified electronic health records from over 120 healthcare organizations. Adult LT recipients (2014–2024) were stratified by DM status and matched 1:1 (n = 17,065/group) using propensity scores for demographics and MELD-Na components. We evaluated infections (including cholangitis), sepsis, and all-cause mortality across four postoperative intervals: 0–30 days, 1–3 months, 3–6 months, and 6–12 months. Risk ratios (RR) with 95% confidence intervals (CI) were calculated. **Results:** DM was associated with persistently higher infection risks. In the early postoperative period (0–30 days), diabetic recipients had increased rates of surgical site infections (1.10% vs 0.65%, RR 1.68, 95% CI 1.32–2.14), candidiasis (1.00% vs 0.67%, RR 1.50, 95% CI 1.17–1.92), and Gram-negative sepsis (0.46% vs 0.30%, RR 1.51, 95% CI 1.05–2.16). The heightened risk of surgical site infections, candidiasis, and Gram-negative sepsis persisted into the 6–12 month postoperative period. Cholangitis incidence was higher in diabetic recipients across multiple intervals, including 1–3 months (0.9% vs 0.6%, RR 1.50, 95% CI 1.15–1.94) and 3–6 months (1.3% vs 0.8%, RR 1.61, 95% CI 1.23–2.12). Despite increased infection risks, 1-year survival remained slightly higher in diabetic recipients (92.53% vs 91.68%, HR 0.88, 95% CI 0.81–0.95, p = 0.0003). **Conclusion:** Pre-existing diabetes compounds infection risk conferred by immunosuppression in liver transplant recipients. This dual vulnerability is associated with significantly higher rates of infections and related complications but does not result in diminished 1-yr survival potentially reflecting improved perioperative management strategies. These findings highlights the need for individualized prophylactic protocols, enhanced microbiologic surveillance, and proactive management strategies to improve outcomes and resource utilisation in diabetic recipients. The impact of optimizing diabetes control pre and perioperatively on these complications is unknown and should be studied using more granular data.



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3564 | GRAFT SURVIVAL FOLLOWING LIVER TRANSPLANTATION FROM MARGINAL DONORS: DO SPECIFIC RISK CRITERIA IMPACT OUTCOMES DIFFERENTLY?

Yasmeen Saker[1], [1]University of Florida

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Background: The 2023 OPTN/SRTR Annual Data Report highlights an 8.5% rise in liver transplant waitlist registrations, emphasizing the need to expand donor utilization, including marginal liver donors (MLDs). Although MLD features often inform clinical decisions, their specific impact on graft survival remains unclear. This study examined whether commonly used MLD criteria are associated with differences in 1- and 3-year graft survival. **Methods:** We retrospectively analyzed adult liver transplant recipients at the University of Florida between 01/2019 and 09/2024. Donors were classified as MLDs if they met at least 1 predefined high-risk criterion: age >65 years, BMI >30, ICU stay >4 days, serum sodium >160 mmol/L, abnormal LFTs (ALT >105 U/L, AST >90 U/L, or bilirubin >3 mg/dL), substance use, extrahepatic malignancy, donation after circulatory death (DCD), cold ischemic time >12 hours, and/or viral hepatitis (HBsAg, HBcAb, or HCV Ab positivity). Data on steatosis, hypotension, and inotropic support were unavailable and excluded. Donor risk factors were grouped into six clinically relevant categories to reflect common allocation considerations: demographic risk (age, BMI, and history of cancer), viral hepatitis, abnormal labs (liver tests and sodium), history of any substance use, DCD status, and ICU LOS. A seventh category captured donors with >1 risk factor. Graft survival at 1 and 3 years was estimated using Kaplan-Meier analysis and compared across groups via log-rank testing. Statistical significance was defined as a p-value <0.05. **Results:** We analyzed 559 liver transplant recipients of grafts from MLDs. Overall graft survival was 97.8% at 1 year and 88.3% at 3 years. Initial survival comparisons across the defined donor risk categories did not demonstrate significant differences in survival. Similarly, the presence of multiple marginal risk factors was not associated with worsened graft outcomes ($p=0.5$).

Subsequently, each donor risk category was independently compared against its respective control group—recipients whose donors did not meet that specific criterion. Across these pairwise analyses, most donor risk factors—including DCD status, viral hepatitis, substance use history, abnormal liver chemistries, and high-risk demographics—were not associated with statistically significant differences in graft survival. The presence of multiple marginal risk factors did not correlate with worsened survival ($p=0.5$). Only the criteria of donor ICU stay >4 days was significantly associated with reduced 1 and 3-year graft survival (91.3% vs 98.1%, $p=0.02$ and 56.2% vs. 89.0%, $p=0.009$ respectively). **Conclusion:** Most individual and combined MLD risk factors were not associated with inferior graft survival. However, prolonged donor ICU stay (>4 days) was linked to significantly worse outcomes and should be a key consideration in donor selection and allocation strategies.

Table: Graft Survival by Donor Marginal Risk Factor

Donor Risk Criteria	1-Year Survival (%)	P-value	3-Year Survival (%)	P-value
Substance Use	98.8	0.07	88.0	0.73
Viral Hepatitis	99.3	0.19	87.4	0.86
DCD	100	0.22	96.8	0.06
Abnormal Labs	98.3	0.19	89.0	0.79
ICU LOS	91.3	**0.02**	56.2	**0.009**
Demographic Risk	97.2	0.37	89.4	0.65

Disclosures: Yasmeen Saker: Nothing to Disclose

3565 | FEW PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE INITIALLY DECLINED FOR LIVER TRANSPLANTATION RECEIVE TRANSPLANT AND HAVE HIGH 3-YEAR MORTALITY

Jennifer Flemming[1] Nazia Selzner[2] Kyla Naylor[3] Graham Smith[3], [1]Queen's University Cancer Research Institute, [2]University of Toronto, [3]ICES-Western

Background: Outcomes are excellent for patients receiving liver transplant (LT) with <6 months of alcohol abstinence for alcohol-associated liver disease (ALD). However, limited data have described outcomes of those with <6 months of abstinence who were referred and ultimately declined for LT wait-listing. We describe the long-term outcomes of patients with <6 months of abstinence who were initially declined LT wait-listing for ALD. **Methods:** Individuals declined for LT waitlisting from the University of Toronto ALD pilot program from May 2018 – October 2020 were linked to administrative healthcare data and followed to October 2023. The primary objective was to describe 6-month, 1-year and 3-year overall survival which was calculated using the Kaplan-Meier method and factors associated with LT-free survival were evaluated with adjusted Cox regression. We also assessed healthcare utilization, medical alcohol use disorder (MAUD) treatment and LT re-referral. **Results:** We included 391 individuals declined for LT waitlisting for ALD (median age 54, 29% female, 59% co-morbid viral hepatitis, 11% hepatocellular carcinoma) with a median MELD-Na of 18 (IQR 14-24) and followed for a median of 20 months (IQR 3-43). Overall, 282 (72%) had further decompensation events and 205 (52%) received MAUD treatment. The median number of gastroenterology/hepatology outpatient visits was 9 (IQR 3-19), emergency room visits was 3 (IQR 1-6) and hospital admissions was 2 (IQR 0-3). In total, 40 (10%) were re-referred for LT and 17 (5%) ultimately received LT. Overall, 252 (64%) died with a median survival of

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22 months (IQR 3-55). 6-month, 1-year and 3-year survival was 68%, 59% and 38% respectively (Figure). After adjusted Cox regression, older age was the only factor associated with mortality (per 5-year increase HR 1.07, 95% CI 1.01-1.14). **Conclusion:** After being declined for LT for ALD, patients have high ongoing healthcare utilization and 3-year mortality. Few are re-referred for evaluation and only 5% receive LT. These results can be used in discussion with ALD patients declined LT for goals of care discussions.

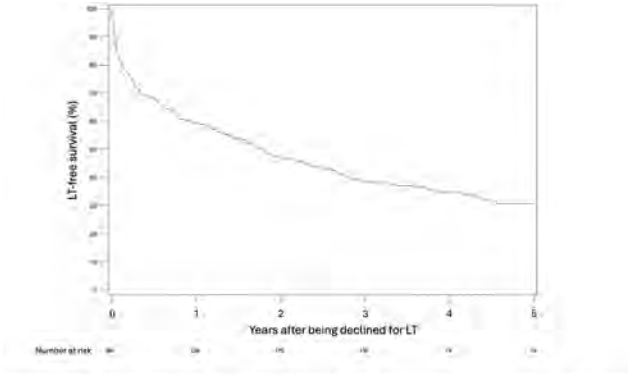


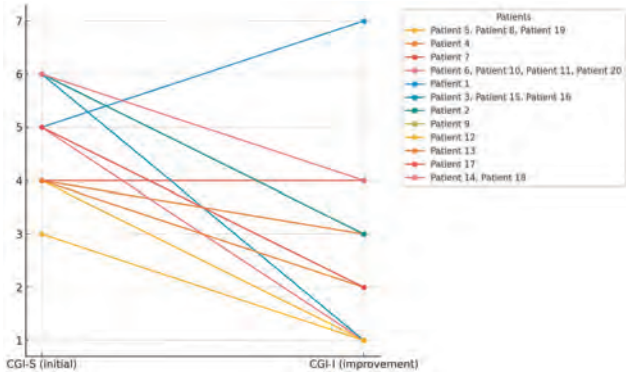
Figure: Liver transplant (LT) free survival for individuals declined for LT wait-listing for alcohol-associated liver disease.

Disclosures: Jennifer Flemming: Nothing to Disclose, Nazia Selzner: Nothing to Disclose, Kyla Naylor: Nothing to Disclose, Graham Smith: Nothing to Disclose

3566 | IMPACT OF SWITCH FROM STANDARD-RELEASE TACROLIMUS (PROGRAF®, ADVAGRAF®) TO MELTDOSE® TACROLIMUS (LCPT) (ENVARSUS®) ON HEADACHES/ MIGRAINES: THE E-MIG STUDY

LUCY MEUNIER[1] Karim Gebara[1] José Ursic-Bedoya[1] Magdalena Meszaros[1] Stephanie Faure[1] Georges-Philippe Pageaux[1], [1]CHU Montpellier

Background: Tacrolimus (Tac) has long been the cornerstone of immunosuppressive therapy in liver transplantation (LT). However, its use is sometimes limited by toxicity, particularly neurotoxicity, which primarily manifests as tremors, headaches, and migraines. A prolonged-release formulation known as life cycle pharma (Tac-LCP) offers a more stable pharmacokinetic profile, potentially reducing neurological adverse effects such as tremors. Nonetheless, studies specifically evaluating the impact of this new formulation on headaches and migraines remain scarce. The aim of this study was to assess the evolution of neurological symptoms, particularly headaches and migraines, following therapeutic conversion to Tac-LCP. **Methods:** We conducted a retrospective, single-center study including adult patients who underwent conversion to Tac-LCP after LT, either due to toxicity associated with standard Tac formulations or for bioavailability-related reasons. The primary endpoint was the impact of Tac-LCP conversion on the improvement of headaches and migraines. Diagnosis and classification of headaches and migraines were based on the International Classification of Headache Disorders, 3rd edition (ICHD-3). Symptom severity and improvement were assessed using the Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) scales, respectively. **Results:** A total of 82 patients were included, 59.8% of whom were male, with a mean age of 58 years. The primary indication for LT was alcohol-related liver disease (35.4%). Neurological toxicity accounted for 61% of conversions, with 30.5% (n = 25) directly related to headaches or migraines. Among patients suffering from headaches or migraines, 28% (n = 7) rated themselves as severely or extremely ill according to the CGI-S. The median time from LT to conversion to Tac-LCP was 369 days (range: 15–12,967 days). Compared with patients converted for other reasons, those with Tac-associated headaches or migraines were predominantly female (68% vs. 28.1%; p = 0.002) and had significantly more family history of headaches or migraines (40% vs. 8.9%; p = 0.005). Tacrolimus trough levels prior to conversion were higher in patients with headaches or migraines (6.9 vs. 5.5 ng/mL; p = 0.007), although no significant difference was observed in post-conversion levels between patients whose symptoms resolved and those who did not. Following conversion to Tac-LCP, 72% (n = 18) experienced clinical improvement in headache or migraine symptoms, with 48% (n = 12) achieving complete symptom resolution (Figure 1). **Conclusion:** Conversion to Tac-LCP appears to be effective in alleviating Tac-associated neurotoxicity, particularly in patients with headaches and migraines. These findings warrant confirmation in other centers, and a multicenter study is currently underway.



Disclosures: LUCY MEUNIER: Nothing to Disclose, Karim Gebara: Nothing to Disclose, José Ursic-Bedoya: Nothing to Disclose, Magdalena Meszaros: Nothing to

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3567 | VALIDATION OF GEMA-NA AND GEMA-AI IN AN AMERICAN COHORT OF PATIENTS ON THE LIVER TRANSPLANT WAITING LIST

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Background: The most used liver transplantation (LT) allocation system is the Model for End-Stage Liver Disease (MELD). Women are disadvantaged with higher dropout rates and lower transplant rates. The Gender-Equity Model for Liver Allocation (GEMA) model and its variant GEMA-Na improved 90-day mortality prediction in wait-listed patients, with a greater effect in women. A new artificial intelligence variant, GEMA-AI, showed an even better discrimination in predicting mortality or delisting. No head-to-head comparison of MELD-based and GEMA-based models has been performed in the United States. **Methods:** We retrospectively analyzed data from all adults listed for LT (2016-2023) at the University of Iowa. Severity of liver disease was assessed with both the MELD-based scores (MELD, MELD-Na, MELD 3.0) and GEMA-based scores (GEMA, GEMA-Na, GEMA-AI). Data was collected until the time of transplant, exclusion from the WL (due to worsening or death, or to improvement), or until February 28, 2025. The ROC curve (receiver operating characteristic curves; AUC) of the different allocation systems was compared at 90 and 180 days of listing. Reclassification of patients using MELD 3.0, GEMA-Na, and GEMA-AI against MELD-Na as the reference category was estimated. **Results:** The study included 297 patients, 69% male, mean age 56 ± 11.2 years. The most common etiology of cirrhosis was alcohol (41%), followed by metabolic associated steatotic liver disease (27%), viral (14%), and other (18%). 42% had refractory ascites. 77 (26%) received a transplant, 59 (20%) were excluded due to worsening or death and 108 (36%) were excluded due to improvement. Mean MELD, MELD-Na, MELD3.0, GEMA, GEMA-Na and GEMA-AI scores were 18 ± 9, 20 ± 9, 18 ± 12, 19 ± 10, 21 ± 10 and 22 ± 8, respectively. No significant differences were found in AUC using any measure (MELD-Na, MELD3.0, GEMA, GEMA-Na, GEMA-AI) when compared to MELD-Na, although GEMA-AI had the highest AUC for women numerically (Figure 1). This difference was not statistically significant, likely due to our limited sample size and limited number of events. When compared to MELD-Na, 36 (12%) patients reclassified with MELD 3.0. Of them, 8 (3%) gained points, of which 3 were women. When compared to MELD-Na, 54 (21%) patients reclassified with GEMA-Na. Of them, 26 (10%) gained points, of which 12 were women. When compared to MELD-Na, 61 (23%) patients reclassified with GEMA-AI. Of them, 46 (18%) gained points, of which 30 were women. **Conclusion:** In our study, neither MELD3.0 nor any of the GEMA derived systems were able to demonstrate a statistically significant improvement in prediction of mortality when compared to MELD-Na. The limited number of events and the small sample size are the most likely explanation. However, GEMA-AI showed the greatest numerical AUC for women. Larger multicenter studies with a more diverse patient population are needed to better understand potential differences between these allocation models.

		Death at 90 days			Death at 180 days		
Measure	Subset	AUC	95% Upper	95% Lower	AUC	95% Upper	95% Lower
MELD	Global	0.922	0.872	0.972	0.848	0.769	0.927
	Men	0.918	0.861	0.976	0.864	0.775	0.953
	Women	0.945	0.847	1.000	0.817	0.644	0.990
MELD-Na	Global	0.914	0.861	0.968	0.861	0.790	0.933
	Men	0.901	0.833	0.968	0.847	0.756	0.937
	Women	0.963	0.906	1.000	0.906	0.812	0.999
MELD 3.0	Global	0.912	0.858	0.966	0.856	0.783	0.928
	Men	0.906	0.848	0.966	0.849	0.759	0.938
	Women	0.965	0.909	1.000	0.891	0.784	0.997
GEMA	Global	0.872	0.798	0.947	0.804	0.717	0.891
	Men	0.866	0.783	0.949	0.827	0.731	0.922
	Women	0.948	0.844	1.000	0.764	0.558	0.970
GEMA-Na	Global	0.873	0.798	0.949	0.817	0.731	0.902
	Men	0.858	0.769	0.947	0.815	0.713	0.917
	Women	0.950	0.876	1.000	0.830	0.664	0.996
GEMA-AI	Global	0.897	0.830	0.964	0.841	0.759	0.923
	Men	0.883	0.804	0.961	0.833	0.735	0.931
	Women	0.974	0.923	1.000	0.866	0.707	1.000

Disclosures: Austin Halupnik: Nothing to Disclose, Patrick Ten Eyck: Nothing to Disclose, MANUEL LUIS RODRIGUEZ PERALVAREZ: Nothing to Disclose, Antonio Sanchez: Abbvie: Grant/Research Support, Boehringer-Ingelheim: Grant/Research Support, Gilead: Grant/Research Support, Merck: Grant/Research Support, Mirum Pharmaceuticals: Grant/Research Support, Takeda: Grant/Research Support, Inventiva: Grant/Research Support, Salix Pharmaceuticals: Grant/Research Support, Marta Tejedor: Nothing to Disclose

3568 | DYNAMIC CHANGES OF SPLEEN STIFFNESS IN LIVER TRANSPLANTED PATIENTS: PRELIMINARY FINDINGS FROM A SINGLE-CENTRE STUDY

Sofia Ridolfo[1] Clara Dibenedetto[1] Valentina Cardone[2] Michele Sagasta[1] Enrico Sguazzini[1] Barbara Antonelli[1]

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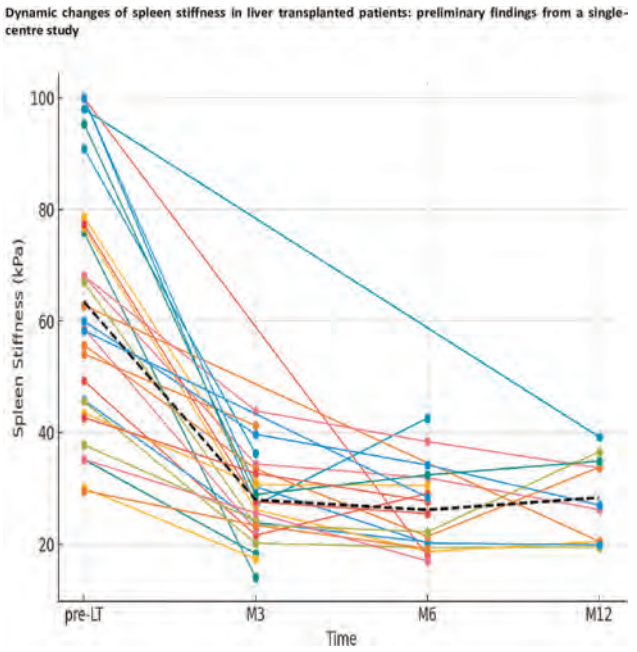
Lucio Caccamo[1] Mirella Fraquelli[1] Maria Francesca Donato[1] Pietro Lampertico[1], [1]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [2]University of Milan, Milan, Italy

Background: Vibration controlled transient elastography (VCTE; Fibroscan®) is a non-invasive method to assess liver stiffness measurement (LSM) and evaluate liver fibrosis. VCTE has also been widely used in post-liver transplantation (LT) setting to identify graft damage. Spleen stiffness measurement (SSM) is known to improve non-invasive diagnosis of clinically significant portal hypertension (CSPH) but data in the post-LT setting are limited. The aim of this study was to evaluate changes in SSM, spleen size and liver stiffness following LT. **Methods:** From January 2022 to July 2024, all consecutive LT recipients transplanted at our centre with available SSM pre-LT were enrolled. Patients with re-LT, splenectomy or without SSM pre-LT were excluded. SSM was measured by VCTE Fibroscan® (Echosens, Paris) before LT and at 3-6-12 months after surgery, while LSM was assessed only after LT at the same time points. Ultrasonographic and biochemical data were also collected. Single linear regression models were performed at different time points to evaluate the relationship between SSM, platelet count and spleen diameter. **Results:** Twenty-nine recipients (median age 63 years, 59% males, 38% viral-etiology, 28% with HCC; 7 DCD grafts; donor age 58 years, 100% on CNI-based immunosuppression) were studied. Median SSM significantly decreased from 60 kPa pre-LT to 27, 25.5, 27 kPa at 3, 6, 12 months post-LT, respectively ($p < 0.05$). Spleen diameter reduced from 15 cm pre-LT to 14, 12, 12.4 cm at 3, 6, 12 months post-LT ($p < 0.05$), whereas platelet count significantly improved over time (67,000, 155,000, 147,000, 145,000/mm^3, $p < 0.05$). A significantly negative relationship between platelet count and SSM was found at 12 months and persisted significant after accounting for potential confounders (recipient and donor age, gender). Notably 4 patients experienced an increase in SSM and a positive relationship between SSM and vascular complications was found. **Conclusion:** Our study showed that SSM significantly decrease early after LT and this reduction remains stable over time, reflecting the resolution of portal hypertension. This improvement was further supported by the concurrent increase in platelet count and decrease in spleen size. Our results indicate that platelet increase after LT and SSM reduction are both good non-invasive markers of portal hypertension improvement. Further studies are needed to explore the role of SSM after LT in predicting vascular complications.



Disclosures: Sofia Ridolfo: Nothing to Disclose, Clara Dibenedetto: Nothing to Disclose, Valentina Cardone: Nothing to Disclose, Michele Sagasta: Nothing to Disclose, Enrico Sguazzini: Nothing to Disclose, Barbara Antonelli: Nothing to Disclose, Lucio Caccamo: Nothing to Disclose, Mirella Fraquelli: Nothing to Disclose, Maria Francesca Donato: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose

3569 | LONG-TERM LIVER TRANSPLANT OUTCOMES IN AMERICAN INDIANS ARE COMPARABLE TO OTHER ETHNICITIES DESPITE UNIQUE CHALLENGES

Alejandro Gonzalez[1] Sandra Elmasry[1] Blanca Lizaola-Mayo[1] Nathan Delafield[1] Adam Milam[1] Rolland Dickson[1] David Chascsa[1], [1]Mayo Clinic Arizona

Background: American Indian (AI) patients experience disproportionately lower access to liver transplantation (LT) compared to non-Hispanic White (NHW) patients. At Mayo Clinic Arizona (MCA), deferral and denial of AI patients have been attributed to psychosocial and multifactorial challenges. To reduce these disparities, a Navajo Patient Navigator program was implemented to provide longitudinal support and improve transplant candidacy. The aim of this study was to assess long-term post-transplant outcomes among AI patients pre- and post-navigator implementation, compared to other ethnicities, to determine whether healthcare disparities persist beyond access and into post-transplant outcomes. **Methods:** We performed a retrospective cohort

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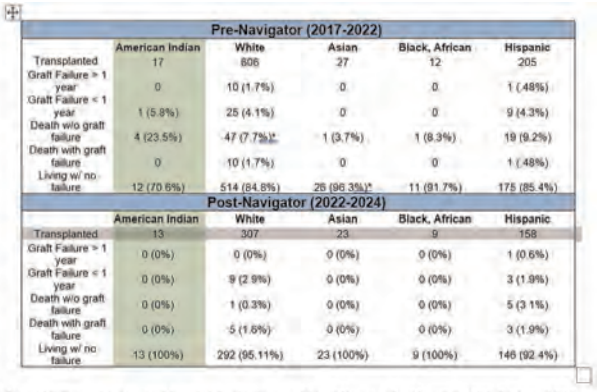
analysis of all transplanted patients at MCA with pre Navigator data from January 2017-April 2022 and post Navigator data from May 2022-October 2024. Pre-transplant data included demographics, transplant indication, and psychosocial parameters. Post-transplant data included graft failure and mortality from a liver or non-liver cause. The data was analyzed using Fisher's exact test for comparison of AI against other demographic groups and a p-value for significance was set at 0.05. **Results:** Pre-navigator data included 2405 LT referrals to MCA with 83 (3.5%) being AI. AI had a lower rate of evaluation, presenting and listing for transplant. The most common cause for deferral or denial of AI patients was either psychosocial alone or multifactorial parameters. Post transplant, four AI patients died and one patient had a graft failure while 47 NHW patients and 19 Hispanics died (Table 1).
Post-navigator data included 1649 LT referrals to MCA with 133 (8.1%) being AI. AI patients had a lower rate of evaluation, presentation, and listing. The most common cause for deferral or denial of AI patients was medical reasons with a significant decrease in denial due to psychosocial reasons. There have been no graft failures or mortality events in the transplanted AI population. **Conclusion:** AI populations face well-documented healthcare disparities throughout the LT process. Our results indicate that after hiring a Navigator there was an increase in referrals for LT and a decrease in deferral or denial due to psychosocial or multifactorial factors. Post transplant survival with a functioning graft increased in the AI and non AI patients in the post Navigator period, most pronounced in AI patients. These data suggest the Navigator has improved both pre- and post- transplant metrics. Post-transplant care such as follow up or medication adherence is likely improved; however, further studies would be required to characterize this more clearly. While our data are limited by the single-center design and follow up time as other studies show the full impact of navigators may take up to 566 days to emerge, our findings highlight the critical importance of early interventions in addressing LT disparities.



Pre-Navigator (2017-2022)					
	American Indian	White	Asian	Black, African	Hispanic
Transplanted	17	806	27	12	205
Graft Failure > 1 year	0	10 (1.7%)	0	0	1 (.48%)
Graft Failure < 1 year	1 (5.8%)	25 (4.1%)	0	0	9 (4.3%)
Death w/o graft failure	4 (23.5%)	47 (7.7%)*	1 (3.7%)	1 (8.3%)	19 (9.2%)
Death with graft failure	0	10 (1.7%)	0	0	1 (.48%)
Living w/ no failure	12 (70.6%)	514 (84.8%)	26 (96.3%)*	11 (91.7%)	175 (85.4%)
Post-Navigator (2022-2024)					
	American Indian	White	Asian	Black, African	Hispanic
Transplanted	13	307	23	9	158
Graft Failure > 1 year	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Graft Failure < 1 year	0 (0%)	9 (2.9%)	0 (0%)	0 (0%)	3 (1.9%)
Death w/o graft failure	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	5 (3.1%)
Death with graft failure	0 (0%)	5 (1.6%)	0 (0%)	0 (0%)	3 (1.9%)
Living w/ no failure	13 (100%)	292 (95.11%)	23 (100%)	9 (100%)	146 (92.4%)

Table 1: Trend between races for post-transplant outcome pre and post Navajo Patient Navigator. (*) Indicates $p < 0.05$ on Fisher exact test when compared against American Indians.

Disclosures: Alejandro Gonzalez: Nothing to Disclose, Sandra Elmasry: Nothing to Disclose, Blanca Lizaola-Mayo: Nothing to Disclose, Nathan Delafield: Nothing to Disclose, Adam Milam: Nothing to Disclose, Rolland Dickson: Nothing to Disclose, David Chascsa: Nothing to Disclose

3570 | ECHOING RISK: THE ROLE OF RIGHT VENTRICULAR SYSTOLIC PRESSURE (RVSP) IN LIVER TRANSPLANT OUTCOMES

Hong Lin[1] Antonio Alvarez Castaneda[1] Khalid Mumtaz[1] Chathur Acharya[1], [1]The Ohio State University Wexner Medical Center

Background: Right ventricular systolic pressure (RVSP), a key measure of right heart function on transthoracic echocardiogram (TTE), plays a critical role in assessing cardiopulmonary hemodynamics in liver transplantation (LT) candidates. Elevated RVSP is strongly associated with portopulmonary hypertension (PoPH) and right ventricular dysfunction, both of which increase post-LT morbidity and mortality. However, the predictive value of RVSP for short-term independent post-LT outcomes remains incompletely characterized. Our study investigates the relationship between pre-LT RVSP and post-LT morbidity, leveraging a large cohort to determine its utility as a prognostic marker. **Methods:** This single-center retrospective study analyzed LT recipients at The Ohio State University (2016–2020) who underwent TTE within one year prior to LT. Using the Youden J statistic, we derived optimal RVSP thresholds for predicting 90-day readmission (all-cause, cardiac, hepatic, and renal) and hemodialysis requirement. We then compared these data-driven cutoffs against conventional fixed thresholds (30, 35, 40, and 45 mmHg). **Results:** Of 243 patients, the mean age was 55.5 years (SD 10.1), with a majority being male (60%) and white (91.3%). The optimal RVSP thresholds for predicting 90-day hemodialysis need, cardiac readmission, and hepatic readmission were 32.8, 32.8, and 28 mmHg, respectively. For all-cause readmissions, the optimal thresholds were 36 mmHg (30-day) and 32.65 mmHg (90-day) (Figure 1A). ROC analysis (Figure 1B) revealed that RVSP best predicted cardiac readmission (AUC 0.673), followed by hepatic readmission (AUC 0.641), 90-day all-cause readmission (AUC 0.597), hemodialysis requirement (AUC 0.566), and 30-day all-cause readmission (AUC 0.557). All thresholds outperformed fixed cutoffs (30-45 mmHg; McNemar's test p-value < 0.05). On multivariate analysis (adjusted for age, sex, race, ESRD/PoPH), RVSP has a strong association with cardiac ($p = 0.002$), hepatic ($p = 0.033$), and all-cause readmission ($p = 0.029$). **Conclusion:** Our data reveal

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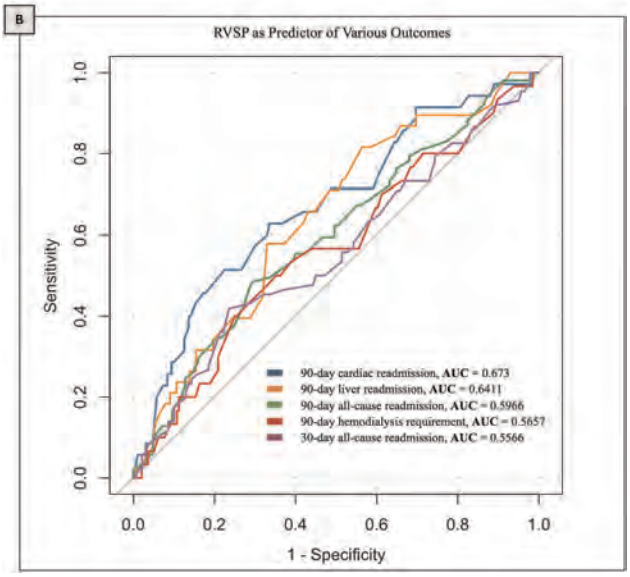
RVSP as a valid predictive marker for post-LT readmissions, with optimized thresholds (28-36 mmHg) offering superior risk stratification. RVSP demonstrated the strongest association with cardiac and liver readmission, while maintaining modest predictive value for other outcomes. Optimal thresholds for cardiac mortality from larger cohorts are warranted.

A

Outcome Measure	Optimal RVSP threshold (mmHg)	Sensitivity	Specificity	AUC	Youden J
90-day cardiac readmission	32.8	0.629	0.665	0.673	0.293
90-day liver readmission	28	0.816	0.436	0.641	0.252
90-day all-cause readmission	32.65	0.486	0.703	0.597	0.189
90-day hemodialysis requirement	32.8	0.453	0.664	0.542	0.118
30-day all-cause readmission	36	0.400	0.750	0.566	0.150

B



Disclosures: Hong Lin: Nothing to Disclose, Antonio Alvarez Castaneda: Nothing to Disclose, Khalid Mumtaz: Nothing to Disclose, Chathur Acharya: Nothing to Disclose

3571 | IMPACT OF TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT ON WAITLIST AND POST-TRANSPLANT OUTCOMES IN LIVER TRANSPLANT CANDIDATES

Li Peng Margaret Teng[1] Shyna Gunalan[2] Ethan Tham[2] Ryan Lim[2] Do Han Kim[3] Daniel Huang[4] Mazen Noureddin[5] Mark Muthiah[6] Eunice Tan[7] Mohammad Siddiqui[8], [1]National University Health System, [2]Yong Loo Lin School of Medicine, National University of Singapore, [3]Department of Medicine, Mount Sinai Morningside and West, Icahn School of Medicine at Mount Sinai, [4]National University Hospital, Singapore, [5]Houston Methodist Hospital, [6]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, [7]Division of Gastroenterology and Hepatology, National University Hospital, Singapore, [8]Division of Gastroenterology, VCU & Richmond VA Med Center, VA, USA

Background: Transjugular intrahepatic portosystemic shunt (TIPS) is utilized to manage refractory ascites or variceal hemorrhage in patients with decompensated cirrhosis. However, its effects on transplant candidacy, perioperative outcomes, and long-term prognosis remain unclear. This study aims to evaluate the clinical indications, outcomes, and peri-transplant implications of TIPS in liver transplant candidates. **Methods:** We conducted a retrospective cohort study of adult liver transplant candidates listed in the United Network for Organ Sharing (UNOS) database from January 1, 2000, to January 3, 2025. Waitlist outcomes include the presence of portal hypertension-related complications, time-to-transplant and waitlist survival. Post-transplant outcomes include graft survival and overall post-transplant survival. These outcomes were compared between patients with and without TIPS, and across liver etiologies among TIPS recipients. **Results:** Among 169,681 waitlist registrants (19,940 with TIPS, 149,741 without TIPS), TIPS was associated with higher odds of portal vein thrombosis during waitlist (OR: 1.414, 95% CI: 1.317 to 1.518, $p < 0.001$) and lower odds of ascites during waitlist (OR: 0.924, 95% CI: 0.866 to 0.987, $p = 0.02$). TIPS recipients had significantly higher 90-day and 1-year time-to-transplant and waitlist survival. There were minimal differences in graft survival and overall post-transplant survival between patients with TIPS and without TIPS. Among TIPS recipients, patients with alcohol-associated liver disease and metabolic dysfunction-associated steatotic liver disease (MASLD) had significantly lower 90-day and 1-year time-to-transplant and higher 1-year waitlist survival compared to patients with hepatitis C (HCV). **Conclusion:** TIPS is associated with improved waitlist survival and timely transplantation without negatively impacting post-transplant outcomes. These findings support the use of TIPS as a bridging and management strategy in liver transplant candidates with portal hypertension.

Disclosures: Li Peng Margaret Teng: Nothing to Disclose, Shyna Gunalan: Nothing to Disclose, Ethan Tham: Nothing to Disclose, Ryan Lim: Nothing to Disclose, Do Han Kim: Nothing to Disclose, Daniel Huang: Gilead: Consultant, Roche: Speaking and Teaching, Mazen Noureddin: Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor: Terns, Takeda, Zydus., Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK: Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, Rivus Pharma, Cytodyn,

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3572 | RISK OF LIVER TRANSPLANT REJECTION AFTER COVID-19 VACCINATION

Jordan Voss[1] Mridula Bethi[1] Wei-Wen Hsu[1] Matthew Still[1] Ralph Quillin[1] Shimul Shah[2] Khurram Bari[3], [1]University of Cincinnati, [2]Massachusetts General Hospital, [3]University of Cincinnati, University Hospital Inc Program

Background: T cell-mediated rejection (TCMR), also known as acute cellular rejection, affects over 30 percent of liver transplant recipients resulting in increased morbidity and mortality. One hypothesized risk factor for TCMR is COVID-19 vaccination which may provide the inflammatory stimuli necessary for T cell activation and proliferation. In contrast to existing protein subunit and viral vector vaccines, two of the FDA-approved COVID-19 vaccines employ novel mRNA vaccine systems and thus may cause unique side effects. To date, 12 cases of TCMR following immunization for COIVD-19 have been reported. These are limited to case reports which are subject to reporting bias and do not establish causality. Here we present the first study to systematically evaluate the risk of TCMR following COVID-19 vaccination. **Methods:** We retrospectively identified all patients at our institution undergoing liver transplantation between 2014 and 2023 who also received one or more doses of any COVID-19 vaccine AND had a history of biopsy-proven TCMR occurring after 9/15/2020 (90-days prior to first vaccine availability in the United States). Using a self-controlled case series (case-crossover) study design and mixed-effects logistic regression models, we calculated the odds ratio of rejection in the 30 days following COVID-19 vaccination (case window) compared to the odds of rejection prior to or greater than 30 days after vaccine administration (control window). **Results:** In our cohort, 106 biopsy-proven rejection events occurred in 83 patients. Fifty-five percent were male, and 83% were Caucasian. The most common etiology of liver disease was alcohol (40%) followed by MASH (31%). Eleven cases of TCMR occurred within 30 days of administration of a COVID-19 vaccine. The odds ratio for rejection within 30 days of receiving a COVID-19 vaccination is 0.675 (95% CI 0.216 – 2.114, $P = 0.494$). Rates of immunosuppression non-adherence were similar in the case (12%) and control windows (11%). **Conclusion:** COVID-19 vaccination does not increase the risk of T cell-mediated rejection in liver transplant patients.

Disclosures: Jordan Voss: Nothing to Disclose, Mridula Bethi: Nothing to Disclose, Wei-Wen Hsu: Nothing to Disclose, Matthew Still: Nothing to Disclose, Ralph Quillin: Nothing to Disclose, Shimul Shah: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Khurram Bari: Mallinckrodt Pharma: Speaking and Teaching, Madrigal Pharma: Advisor

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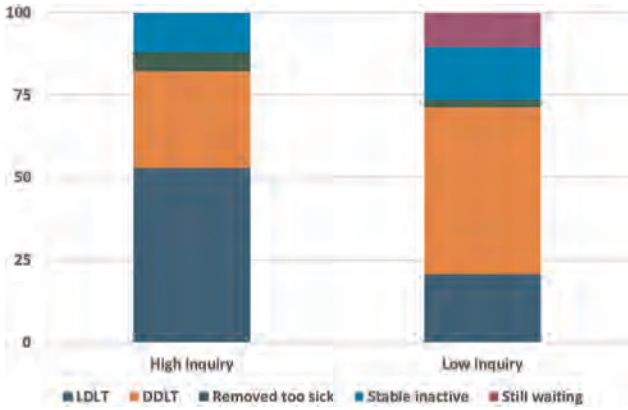
3573 | IS IT BETTER TO HAVE ONE COMMITTED DONOR OR MANY POTENTIAL LIVING LIVER DONORS?

Lauren Callans[1] Nicole Ng[2] Nathaly Llore[3] Alyson Fox[4] Juan Rocca[5] Jason Hawksworth[4] Benjamin Samstein[2] Danielle Brandman[6] Russell Rosenblatt[6], [1]New York Presbyterian - Weill Cornell, [2]NYP Weill Cornell, [3]NewYork- Presbyterian/Columbia University Medical Center, [4]Columbia University Medical Center, [5]NewYork-Presbyterian/Weill Cornell Medical Center, [6]Weill Cornell Medicine

Background: With persistent organ shortages, living donor liver transplant (LDLT) is an attractive alternative to deceased donor LT (DDLT), as it both mitigates the time on the waitlist and confers better outcomes. Identifying factors that lead to successful LDLT is critical to increasing LDLT. It remains unclear whether having one committed donor is better than many potential donors, due to concerns like the bystander effect. This study evaluated the differences in outcomes of high or low numbers of donor inquiries on LT-related outcomes. **Methods:** Adult patients undergoing LT evaluation at two large academic medical centers in New York City with transplant listing dates between 2023-2024 were retrospectively reviewed. Patients were stratified into either a high (more than 5 donor inquiries per patient) or a low inquiry group (1-2 donor inquiries). The primary outcome of this study was LDLT, with secondary outcomes including receiving any LT and waitlist time. Multivariate analysis was performed, controlling for age at listing, sex, and MELD at listing. This study was IRB approved. **Results:** 17 patients and 87 patients were included in the high and low inquiry groups, respectively. The high inquiry group had a higher prevalence of white race (94% vs 59%, $p = 0.006$), and both groups were mostly male. The mean MELD (13) and age at listing (41 vs. 55) were not significantly different. 53% of the high inquiry group received LDLT while 29% received DDLT (Figure). Among the low inquiry group, 51% received DDLT while 21% underwent LDLT. Although there was no significant difference in receiving any type of transplant (LD or DD) between the two groups (82% vs. 77%, $p = 0.48$), in multivariable analysis, patients in the high inquiry group were more than four times more likely to receive LDLT (OR 4.59, CI 1.35-15.6, $p = 0.02$). The high inquiry group had a shorter waitlist time on average (59 vs. 116 days), but this difference was not statistically significant ($p = 0.33$). In the high inquiry group, 82% of the prospective donors underwent further evaluation, and 59% were approved, as compared to the lower inquiry group with 56% inquiries evaluated and 28% approved ($p = 0.045$ and $p = 0.01$, respectively). **Conclusion:** Donor inquiry amount did not change the odds of receiving any transplant. However, patients with a higher number of inquiries were more than four times more likely to receive a LDLT than their lower inquiry counterparts. Those with a high number of inquiries tended to spend less time on the waitlist and had a higher proportion of donor evaluations and approvals, suggesting that more inquiries increases the probability of a possible donor match without an observed bystander effect. Future directions include evaluating the recipient and donor characteristics, including factors such as socioeconomic, psychological, and/or medical that may be related to higher approval rates, and strategies used by recipients to obtain increased donor inquiry frequency.



Disclosures: Lauren Callans: Nothing to Disclose, Nicole Ng: Nothing to Disclose, Nathaly Llore: Nothing to Disclose, Alyson Fox: Nothing to Disclose, Juan Rocca: Nothing to Disclose, Jason Hawksworth: Nothing to Disclose, Benjamin Samstein: Nothing to Disclose, Danielle Brandman: Gilead: Grant/Research Support, Genentech: Grant/Research Support, Novo Nordisk: Consultant, Russell Rosenblatt: Nothing to Disclose

3574 | OUTCOMES OF LIVER TRANSPLANTATION FROM HCV-NAT-POSITIVE DONORS IN HCV-NAT-NEGATIVE RECIPIENTS: A SYSTEMATIC REVIEW AND SINGLE-ARM META-ANALYSIS

Mariana Del Col[1] Dante Souza[2] Maria Cirleide Farias[3] Maria Carolina Martins[4], [1]Universidad Nacional de Mar del Plata, [2]TriHealth Good Samaritan Hospital, [3]Faculdade de Ciências Médicas Afya - Itabuna, [4]Universidade Salvador

Background: With the advent of direct-acting antiviral agents (DAA), liver transplantation from Hepatitis C Virus (HCV) Nucleic Acid Test (NAT)-positive donors in HCV-negative recipients has been proposed to increase the organ pool. **Methods:** PubMed, Embase,

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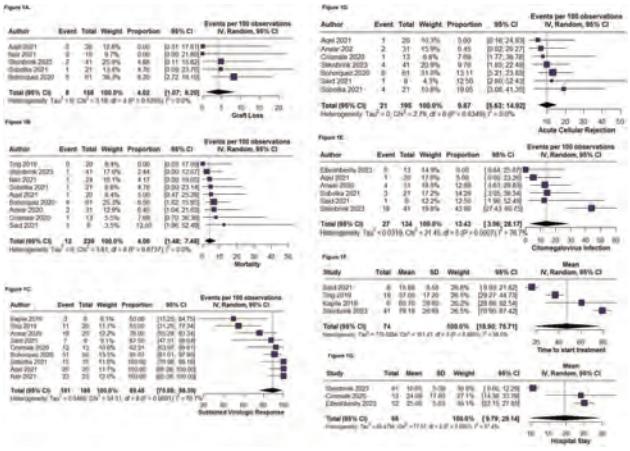
and Cochrane databases were searched for randomized controlled trials and observational studies evaluating outcomes from HCV-NAT-negative patients receiving grafts from HCV-NAT-positive donors. A single-arm meta-analysis of proportions estimated the graft loss, mortality, sustained virologic response (SVR) to DAA by 12 weeks after the end of therapy, acute cellular rejection (ACR), cytomegalovirus (CMV) infection, while a meta-analysis of means estimated time to start treatment and hospital stay. Quality assessment was performed per Cochrane recommendations. Heterogeneity was examined with I2 statistics, and a random-effects model was used. **Results:** A total of 11 observational studies met inclusion criteria, comprising 258 transplants, with 19 (7.4%) being simultaneous liver-kidney transplantations. The mean age of recipients and donors ranged from 56 to 60 and 32 to 42, respectively. Recipients had a mean Model for End-Stage Liver Disease (MELD) at transplantation ranging from 19 to 25.7, and 164 (63.6%) were male. The most common end-stage liver disease (ESLD) etiology was Nonalcoholic steatohepatitis (30.4%), followed by Alcohol-associated liver disease (27.6%) and HCV (10.8%). The median follow-up ranged from 6 to 16.4 months. Graft loss occurred in 4.02% (95% CI: 1.07% to 8.20%; fig. 1A), mortality was 4.05% (95% CI: 1.48% to 7.48%; fig. 1B), SVR by 12 weeks was achieved in 89.45% (95% CI: 75.98% to 98.39%; fig. 1C), ACR occured in 9.87% (95% CI: 5.63% to 14.92%; fig 1D), and CMV infection transpired in 13.43% (95% CI: 3.06% to 28.17%; fig. 1E). The pooled mean time from transplant to DAA initiation was 46.3 days (95% CI: 18.9 to 75.71; fig 1F) and hospital stay 19.9 days (95% CI: 9.79 to 29.14; fig 1G). **Conclusion:** These findings suggest that, in carefully selected patients, the use of HCV-NAT-positive grafts in HCV-NAT-negative patients in the DAA era appears to be efficacious and well tolerated. However, due to the limitations of observational studies and inherent heterogeneity, further comprehensive and controlled trials are needed to validate these findings and understand the long-term outcomes.



Disclosures: Mariana Del Col: Nothing to Disclose, Dante Souza: Nothing to Disclose, Maria Cirleide Farias: Nothing to Disclose, Maria Carolina Martins: Nothing to Disclose

3575 | MORE THAN THE SUM? EVALUATING LIVER TRANSPLANT OUTCOMES IN METALD VERSUS SINGLE-ETIOLOGY DISEASE

Avi Toiv[1] Neal Doshi[1] Syed-Mohammed Jafri[2], [1]Henry Ford Hospital, [2]Henry Ford Health System

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD) are the leading indications for liver transplantation (LT) in the United States. Recently, we have recognized a growing subset of patients with metabolic dysfunction and alcohol-related liver disease (MetALD) attributed to a dual pathology, raising new questions about post-transplant risk profiles. While ALD and MASLD have been individually studied in relation to transplant outcomes, the postoperative course and complication burden in patients with combined disease remains poorly characterized. This study aimed to compare post-transplant survival and complications among patients with ALD, MASLD, and MetALD. **Methods:** A retrospective cohort study of all LT recipients who underwent LT for ALD, MASLD, or MetALD at a high-volume academic transplant center between January 2014 and September 2023. Kaplan-Meier analysis was used to evaluate survival. Descriptive statistics and regression analysis were used to assess complication rates. **Results:** 578 LT recipients were included: 40 (7%) with ALD, 199 (34%)with MASLD, and 339 (59%) with MetALD. Mean age at transplant ALD 50.4 ± 10.0 years; MASLD 60.7 ± 6.9; MetALD 54.1 ± 9.5; $p < 0.01$) and sex varied significantly across groups ($p = 0.003$), with a higher proportion of men in the MetALD group (69.5%) versus ALD (55%) and MASLD (55.8%). Mean hospital length of stay was similar across etiologies (composite mean 13.5 days, $p = 0.92$). Rate of biliary stricture in the MetALD group (30.3%) was significantly higher than in ALD (22.5%) and MASLD (19.1%) ($p = 0.015$). Post-transplant complications, including bile leak, early rejection, and graft loss, did not differ significantly between groups. No significant differences in survival were seen between groups (Figure). **Conclusion:** Post-transplant survival and overall complication burden were equivalent among patients with ALD, MASLD, and MetALD; however, biliary stricture occurred at a significantly higher rate in patients with MetALD. These findings suggest that although LT recipients may have similar risk profiles for survival and most post-transplant

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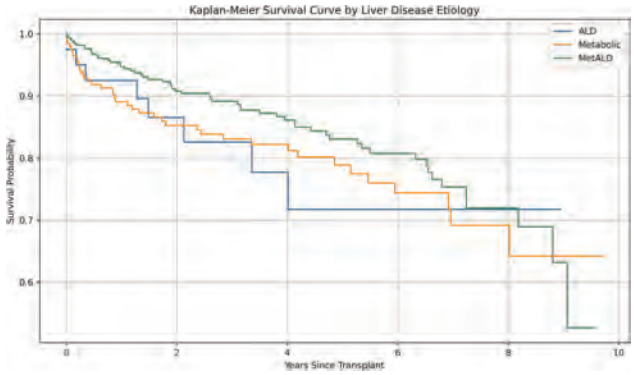
complications, patients with MetALD may be at elevated risk for unique biliary complications that warrant further investigation.



Disclosures: Avi Toiv: Nothing to Disclose, Neal Doshi: Nothing to Disclose, Syed-Mohammed Jafri: Takeda: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ironwood: Advisor, Intercept: Speaking and Teaching

3576 | ASSOCIATION OF PRE-TRANSPLANT CORONARY CT ANGIOGRAPHY VERSUS DOBUTAMINE STRESS ECHOCARDIOGRAM WITH MAJOR ADVERSE CARDIAC EVENTS WITHIN ONE YEAR OF LIVER TRANSPLANTATION

Hoang Anh Richardson[1] Ashley Spann[1] Samuel Nwosu[1] Donald Sengstack[1] Benjamin French[1] Jayant Bagai[1] Alexandra Shingina[2] Jeffrey Carr[1] Manhal Izzy[1], [1]Vanderbilt University Medical Center, [2]University of Michigan Health

Background: Cardiovascular complications are a major cause of non-graft related morbidity and mortality after liver transplantation (LT). Non-invasive cardiac testing is common in transplant evaluation, however, whether coronary computed tomography angiography (CCTA) or dobutamine stress echocardiogram (DSE) are predictive of major adverse cardiac events (MACE) after LT warrants investigation. **Methods:** This retrospective cohort study of adult patients with cirrhosis evaluated for LT between Janurary 2019 and December 2023 included all candidates with CCTA obtained during LT evaluation. The primary outcome was MACE [atrial/ventricular arrhythmia, acute coronary syndrome, revascularization, angina, heart failure, cardiac arrest, all-cause mortality] within one-year after LT. CCTA findings were categorized into none-to-mild coronary artery disease (CAD) as defined by CAD-RADS 0-1 and moderate-severe CAD by CAD-RADS 2-5. Successfully completed DSEs, defined as achieving target heart rate and satisfactory quality, were categorized as positive or negative for ischemia. Multivariable logistic regression models evaluated CCTA and DSE findings for associations with MACE, adjusting for age, sex, diabetes, and pre-event statin use. Predictive accuracy for each model was assessed using C-statistic. **Results:** Among 153 eligible patients, 108 underwent DSE. The incidence of MACE at one year was 32.0% (Table 1). The leading etiology of cirrhosis was metabolic dysfunction-associated steatohepatitis, followed by alcohol-associated liver disease. Moderate-severe CAD vs none-to-mild CAD by CCTA was not associated with an elevated risk of MACE after adjusting for covariates (OR 0.92, 95% CI [0.409, 2.073], p = 0.842); C-Stat for CAD-RADS was 0.62. Of the successfully completed DSEs (103/108), 6.8% were positive for ischemia. Positive DSE was not significantly associated with MACE (OR 2.78, 95% CI [0.66, 11.75], p = 0.163) after adjusting for covariates; C-Stat for DSE was 0.65. Pre-event statin use was associated with an approximately 2-fold increase in odds of a MACE event (OR = 2.10, p = 0.055) on multivariate analysis. **Conclusion:** CCTA and DSE results were not significantly associated with increased odds of MACE at one year post transplant, whereas pre-event statin use was associated with increased odds of MACE, reflecting the high-risk profile for this subgroup. The modest predictive performance of both modalities highlights the need for improved cardiac risk stratification tools in this high-risk population.

Table 1. Study group characteristics and outcomes

Variable	No MACE Event	MACE Event	Overall
Total	104	49	153
Sex			
Male	66 (63.5%)	29 (59.2%)	95 (62.1%)
Female	38 (36.5%)	20 (40.8%)	58 (37.9%)
Race			
White	99 (95.2%)	46 (93.9%)	145 (94.8%)
Non-White	5 (4.8%)	2 (4.1%)	7 (4.6%)
Unknown	0 (0%)	1 (2.0%)	1 (0.7%)
Diabetes Mellitus			
Diabetic	68 (65.4%)	32 (65.3%)	100 (65.4%)
Non-Diabetic	36 (34.6%)	17 (34.7%)	53 (34.6%)
Pre-Event Statin			
Statin use	42 (40.4%)	29 (59.2%)	71 (46.4%)
Non-Statin use	62 (59.6%)	20 (40.8%)	82 (53.6%)
CCTA Grade			
None-to-mild CAD	46 (44.2%)	21 (42.9%)	67 (43.8%)
Moderate-Severe CAD	46 (44.2%)	20 (40.8%)	66 (43.1%)
Inconclusive	12 (11.5%)	8 (16.3%)	20 (13.1%)
DSE			
Positive for Ischemia	3 (2.9%)	4 (8.2%)	7 (4.8%)
Negative for Ischemia	70 (67.3%)	26 (53.1%)	96 (62.7%)
Inadequate or Unavailable DSE Results	31 (29.8%)	19 (38.8%)	50 (32.7%)

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Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Bristol Myers Squibb Foundation: Grant/Research Support, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Samuel Nwosu: Nothing to Disclose, Donald Sengstack: Nothing to Disclose, Benjamin French: Nothing to Disclose, Jayant Bagai: Nothing to Disclose, Alexandra Shingina: Nothing to Disclose, Jeffrey Carr: Nothing to Disclose, Manhal Izzy: Mallinckrodt: Speaking and Teaching, Madrigal: Advisor

3577 | CHARACTERIZING OUTCOMES AND DONOR CHARACTERISTICS OF LIVER TRANSPLANT RECIPIENTS WITH HIGH NUMBER OF DONOR INQUIRIES

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Background: Living donor liver transplantation (LDLT) provides excellent outcomes and improves survival compared to deceased donation at all MELD scores. Nevertheless, LDLT is still underutilized, in part due to both medical and non-medical barriers affecting both recipients and donors. It is unclear whether a high number of donor inquiries translates to better outcomes, including shorter waitlist time and decreased mortality, or if there is a bystander effect. This study assessed the outcomes of LT recipients who generated high volumes of inquiries and their donor characteristics. **Methods:** Adult patients undergoing LT evaluation between 2018-2024 with over five donor inquiries at two large academic medical centers were retrospectively reviewed. The primary outcome of the study is whether patients received LDLT. The secondary outcomes are waitlist mortality, post-LT 1-year survival, number of donors evaluated and approved, and donor's relation to the patient. Descriptive statistics were performed. This study was IRB approved. **Results:** 55 patients who underwent LT evaluation had over five donor inquiries per recipient, with a mean of 21 inquiries per person. 53 patients were listed. The majority of recipients were White (91%) and male (62%). 47 patients (85%) underwent LT, with 24 (44%) LDLT and 23 (42%) DDLT. The mean age at listing and LT were 45 and 46 years, respectively, with low MELD scores at listing (14) and LT (16). The mean MELD score at LT for LDLT was 16 compared to 18 for DDLT. There were no significant differences in age, gender, or MELD for those receiving LDLT vs DDLT. The most common primary liver diagnoses were Metabolic Dysfunction-Associated Steatotic Liver Disease (22%), primary sclerosing cholangitis (18%), and hepatocellular carcinoma (11%). Only 5% of patients died while awaiting any LT. The mean time to transplant was 331 days, but 328 days for LDLT and 349 days for DDLT ($p > 0.05$). Of the 38 patients transplanted $>$ 1 year ago, there was 100% 1-year survival.

There were a total of 1076 donor inquires with 82% who underwent further evaluation and 59% approved. Most living donors were friends (46%) and family members, excluding parents and children (21%). The majority of donors were White (92%), and half were female. There was no correlation between the number of donor inquiries and time to transplant, age at listing, MELD at listing, or MELD at transplant. **Conclusion:** In this observational study, most individuals with over 5 donor inquiries underwent LT and half received LDLT. Those who received a LDLT spent less time on the waitlist and had lower MELD scores at time of transplant than that of DDLT. Further studies are needed to investigate whether the number of donor inquiries directly correlates to better outcomes.

Disclosures: Nicole Ng: Nothing to Disclose, Lauren Callans: Nothing to Disclose, Nathaly Llore: Nothing to Disclose, Alyson Fox: Nothing to Disclose, Juan Rocca: Nothing to Disclose, Jason Hawksworth: Nothing to Disclose, Benjamin Samstein: Nothing to Disclose, Danielle Brandman: Gilead: Grant/Research Support, Genentech: Grant/Research Support, Novo Nordisk: Consultant, Russell Rosenblatt: Nothing to Disclose

3578 | THE EFFECT OF REDUCED DOSE RABBIT ANTI-THYMOCYTE GLOBULIN INDUCTION IN LIVER TRANSPLANTATION: A RETROSPECTIVE, SINGLE-CENTER COHORT STUDY

Jinzhen Cai[1], [1]The Affiliated Hospital of Qingdao University

Background: Liver transplantation (LT) is effective for end-stage liver disease. However, the induction dose of rabbit anti-thymocyte globulin (rATG) is still controversial. This study aimed to evaluate the effect of a novel reduced dose of rATG in Chinese LT patients. **Methods:** This retrospective study at Qingdao University Affiliated Hospital enrolled LT patients receiving intraoperative 50 mg rATG followed by 25 mg/d for 3 consecutive days post-LT. Baseline data, liver and renal function, blood routine, acute rejection and infections

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within 30 days were analyzed. **Results:** A total of 29 LT patients were enrolled, with an average age of 51.7 years, including 18 liver cancer patients. For all patients, ALT and AST levels quickly returned to normal within one-month post-LT. Total bilirubin decreased to normal, and lymphocyte counts increased to normal within the same period. In the 18 liver cancer patients, there were no significant differences in liver function between those meeting Hangzhou criteria and those beyond, except for total bilirubin, during the one-month follow-up. Additionally, 8 of the 29 patients had viral infections (CMV and EBV), and only one patient showed signs of acute rejection. **Conclusion:** This study is the first to report reduced-dose rATG induction therapy for LT recipients in China. Liver cancer or cirrhosis patients who received this therapy during LT showed rapid recovery of liver function and lymphocyte levels to normal ranges without significant renal function impact, along with a low acute rejection rate and no increase in CMV infections. however, this promising strategy needs validation through multicenter studies with larger, more diverse cohorts to confirm its clinical applicability.

Disclosures: Jinzhen Cai: Nothing to Disclose

3579 | LIVER FRAILTY INDEX IS ASSOCIATED WITH INCREASED INTRA-OPERATIVE BLOOD PRODUCT REQUIREMENTS DURING LIVER TRANSPLANTATION

Jade Pace[1] Ahmed Aboseria[1] Justin Lin[2] Michael Attanasi[1] Anwesha Satapathy[2] William Han[2] Bheesham Dayal[2] Sanjaya Satapathy[1], [1]Zucker School of Medicine at Hofstra/Northwell, [2]Northwell Health

Background: Frailty is an emerging predictor for pre- and post-transplant adverse outcomes in liver transplant patients. However, research on its intra-operative impact is lacking. This study utilizes the Liver Frailty Index (LFI) to examine how pre-operative frailty translates into blood transfusion requirements at the time of transplantation. **Methods:** All patients from December 2019 to November 2024 from our institution who received liver transplants were collected. Blood products administered intra-operatively were recorded, including packed red blood cells (pRBCs), platelets, fresh frozen plasma (FFP), and cryoprecipitate. Physical function was evaluated using the LFI, which includes gender, dominant hand grip strength, time to do five chair stands, and balance testing in three different positions, with patients classified as non-frail (<4.5), or frail (≥ 4.5). All assessments were conducted by a licensed physical therapist using standardized protocols. Kruskal-Wallis analysis was used to determine the relationship between frailty categories of non-frail and frail with the amount of blood products used intra-operatively. Logistic regression comparing age, BMI, sex, race, MELD, and LFI to total blood products and with pRBCs was performed. Statistical significance was determined at $p<0.05$. **Results:** We identified 288 patients that met inclusion criteria. Of these, 227 patients had Liver Frailty Indices. The mean LFI was 4.5. The mean number of units of total blood products, pRBCs, platelets, FFP, and cryoprecipitate given intra-operatively was 26, 11, 3, 9, and 3 units, respectively. There were significant increases in median total blood product (24 ± 24 vs 18 ± 20, $p=0.005$), pRBC (10 ± 10 vs 8 ± 8, $p=0.004$), platelets (4 ± 3 vs 3 ± 2, $p=0.014$), FFP (10 ± 8 vs 6 ± 8, $p=0.013$), and cryoprecipitate (3 ± 3 vs 2 ± 2, $p=0.012$) requirements for frail patients compared to non-frail patients (Figure 1). Logistic regression adjusting for age, BMI, sex, race, and MELD demonstrated that $LFI>4.5$ was significantly associated with total blood products (Odds Ratio [OR] 1.018; 95% Confidence Interval [CI] 1.005-1.032; $p=0.009$) and with pRBCs (OR 1.047; CI 1.013-1.081; $p=0.006$). **Conclusion:** Frail patients required more units of blood products intra-operatively during liver transplant after adjusting for age, BMI, sex, race, and MELD score.

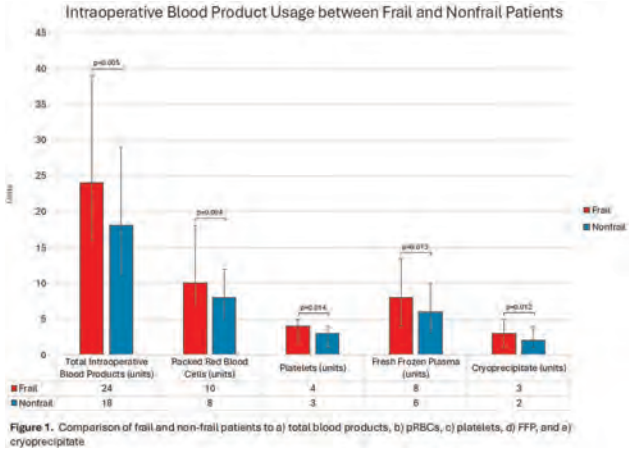

Figure 1. Comparison of frail and non-frail patients to a) total blood products, b) pRBCs, c) platelets, d) FFP, and e) cryoprecipitate

Disclosures: Jade Pace: Nothing to Disclose, Ahmed Aboseria: Nothing to Disclose, Justin Lin: Nothing to Disclose, Michael Attanasi: Nothing to Disclose, Anwesha Satapathy: Nothing to Disclose, William Han: Nothing to Disclose, Bheesham Dayal: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support

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3580 | EXPEDITED LT EVALUATION IN THE AGE OF THE COVID-19 PANDEMIC AND BEYOND: A COMPARATIVE STUDY INVESTIGATING WAITLIST DECISIONS IN PATIENTS WITH AND WITHOUT ALCOHOLIC LIVER DISEASE

Claire Maher[1] *Kwang Il Seo*[2] *Brian Wentworth*[1], [1]*University of Virginia School of Medicine,* [2]*Kosin University College of Medicine*

Background: Alcoholic liver disease (ALD) is the leading indication for liver transplantation (LT) in the US. The social isolation of the COVID-19 pandemic further exacerbated this trend, resulting in an increase in ALD-related hospital admissions and LT during this period. Many of these patients undergo expedited LT evaluation, although listing practices compared to similar expedited LT evaluation in non-ALD patients are unknown. **Methods:** We conducted a retrospective cohort study of all adult patients who underwent expedited LT evaluation during an inpatient admission at a single tertiary care, LT center from February 2021 to December 2024. Patients were divided into alcoholic-liver disease (ALD) and non-alcoholic liver disease (non-ALD) groups. Clinical characteristics and components of the LT evaluation, including waitlist decision, were collected. Normality was assessed with the Shapiro-Wilk test. Categorical variables were compared using the Chi-square test and continuous variables utilized the Mann-Whitney U test given all were non-parametric. A multivariate logistic regression model utilizing significant variables on univariate analysis was created to evaluate predictors of placement on the LT waitlist; collinear variables with the SIPAT score were excluded. **Results:** One hundred and eighty-one patients met inclusion criteria, of which 102 (56%) patients had ALD and 79 (44%) had non-ALD. Patients with ALD tended to be younger (50 vs. 57 years, $p = 0.002$), male (68% vs 34%, $p < 0.001$), and more likely to be uninsured or insured by Medicaid (49% vs. 27%, $p = 0.002$). They also had higher SIPAT (26 vs. 16, $p < 0.001$) and MELD 3.0 (35 vs. 32, $p = 0.001$) scores. There was no difference between groups with respect to race, hospital length of stay, or LT evaluation outcome. ALD was positively predictive (OR 3.540, 95%CI 1.518-8.257, $p = 0.003$) of waitlist placement, while higher SIPAT scores were negatively predictive (OR 0.938, 95%CI 0.909-0.968, $p < 0.001$). **Conclusion:** Patients with ALD requiring expedited LT evaluation had a different demographic profile than non-ALD candidates, including presentation at a younger age, more severe liver disease, and higher SIPAT scores. However, the presence of ALD did not deter waitlist approval. These findings support recent literature noting excellent short-term survival in patients with ALD while also highlighting some of the challenges in ensuring equitable access to LT for non-ALD patients.

Table 1: Multivariate logistic regression for predictors of placement on transplant waitlist

Variable	Odds Ratio	95% CI	*p*
ALD	3.540	1.518–8.257	**0.003**
Age*	0.971	0.940–1.003	0.075
Female sex	1.583	0.762–3.289	0.219
MELD 3.0 score*	1.014	0.966–1.064	0.579
SIPAT score*	0.938	0.909–0.968	**<0.001**
Severe malnutrition	0.956	0.473–1.931	0.900
Medicaid/uninsured	1.046	0.498–2.196	0.906

*Represents odds ratio for each incremental 1 year or point.

Disclosures: Claire Maher: Nothing to Disclose, Kwang Il Seo: Nothing to Disclose, Brian Wentworth: Nothing to Disclose

3581 | MORTALITY, INTENSIVE CARE UNIT AND HOSPITAL LENGTH OF STAY IN PATIENTS UNDERGOING SIMULTANEOUS LIVER-KIDNEY TRANSPLANTATION COMPARED TO LIVER TRANSPLANTATION ALONE

Nazli Begum Ozturk[1] *Ahmed Aref*[1] *Usman Bin Hameed*[1] *Ewelina Niedzialkowska*[1] *Tatjana Blazin*[1] *Laith Jamil*[1], [1]*Beaumont Hospital, Royal Oak*

Background: Simultaneous liver-kidney transplantation (SLK) is the treatment of choice in patients with concomitant end-stage liver and kidney diseases. The number of patients undergoing SLK is rising in the United States. In this study, we aimed to compare the characteristics and outcomes of patients undergoing SLK compared to liver transplantation alone (LTA) at our transplant center. **Methods:** A retrospective analysis was performed of all adult patients who underwent LT or SLK at our transplant center between 2013-2023. Clinical, laboratory, histological, and follow-up data were obtained. Patients were be included to the study only once, thus excluded when a repeat transplant was done. The primary outcome was post-transplant mortality. Categorical variables are reported as numbers and percentages, and continuous variables are reported as means and standard deviation or median with interquartile range. Statistical significance was defined as $p < 0.05$. **Results:** Of all patients with ESRD, 37 patients (66.1%) underwent SLK, and 19 patients (33.9%) underwent LTA. Most common etiologies for patients underwent SLK were alcohol-associated liver disease (ALD) (29.5%), metabolic-dysfunction associated steatotic liver disease (MASLD) (23.0%), and hepatitis C virus (HCV) (9.8%); whereas for LTA those were ALD (23.6%), MASLD (16.3%), and hepatocellular carcinoma (12.3%). Patients who underwent SLK had a significantly higher MELD at listing (26.4 $\pm$8.62 vs 21.0 $\pm$9.62, $p = 0.0002$) and at LT (30.7 $\pm$8.46 vs 25.0 $\pm$9.49, $p = 0.0001$), more commonly had hepatic encephalopathy (78.7% vs 65.2%, $p = 0.0498$), and more commonly had DM (41% vs 25%,$p = 0.020$) compared to patients who underwent LTA. Post-transplant,

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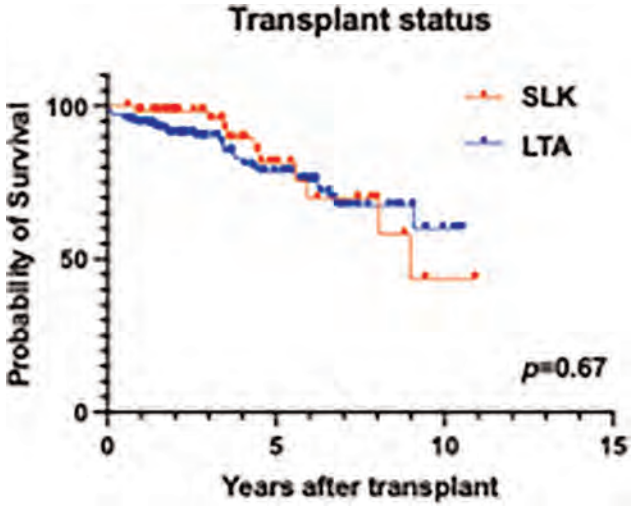
patients who underwent SLK had longer ICU (9.0 (5.0-17.5) vs 5.0 (3.0-8.5), $p = 0.0001$) and hospital stay (16.0 (11.0-27.5) vs 12.0 (8.0-19.5), $p = 0.0003$) compared to patients who underwent LTA. There was no difference in overall survival in patients who underwent SLK vs LTA ($p = 0.6783$), and no survival difference in patients with ESRD that underwent SLK or LTA ($p = 0.6476$). Overall, 1-year survival was 98.3% in patients who had SLK compared to 94.3% in LTA, 3-year survival was 95.6% in SLK vs 90.0% in LTA, and 5-year survival was 81.4% in SLK vs 78.3% in LTA. **Conclusion:** Despite MELD at listing was significantly higher in SLK group, waitlist time was not significantly different in between both groups. Both ICU and hospital length of stays were significantly longer after SLK compared to LTA. Patient mortality was similar in patients underwent SLK and LTA. As the incidence of MASLD is increasing, the proportion of patients in need for SLK are expected to rise and the investigating the risk factors for survival would enhance the post-transplantation length of stay and overall survival.



Disclosures: Nazli Begum Ozturk: Nothing to Disclose, Ahmed Aref: Nothing to Disclose, Usman Bin Hameed: Nothing to Disclose, Ewelina Niedzialkowska: Nothing to Disclose, Tatjana Blazin: Nothing to Disclose, Laith Jamil: Nothing to Disclose

3582 | A 10-YEAR RETROSPECTIVE SINGLE-CENTER STUDY ON VACCINATION STATUS OF PEDIATRIC LIVER TRANSPLANT RECIPIENTS

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[1]Georgetown University School of Medicine,
[2]Georgetown University Hospital

Background: Despite published guidelines requiring the administration of all age-appropriate immunizations, vaccine-preventable infections following transplantation remain common and are associated with increased morbidity, mortality, and graft injury. Amid rising vaccine hesitancy in the United States driven by a myriad of sociopolitical factors, it is increasingly important to assess the vaccination status and immunity of pediatric transplant recipients to guide evidence-based immunization strategies in this vulnerable population. **Methods:** A retrospective chart review was conducted on pediatric patients who underwent liver transplantation between 2014 and 2023. Variables assessed included pre-transplant vaccination status, serologic immunity at the time of transplant, and serologic titers one year post-transplant. The vaccines evaluated in this study included measles, mumps, and rubella; varicella; hepatitis A and B; diphtheria, tetanus, and pertussis; meningococcal; and pneumococcal vaccines. **Results:** Between 2014 and 2023, a total of 194 pediatric patients underwent liver transplantation at our center. Of these, 66 patients (34%) had no documented immunizations in their medical records. Among the 135 patients who were at least one year old at the time of transplant and thus eligible for serologic testing, 61 patients (45.2%) had no immunization titers documented at the time of transplantation, and 29 patients (21.5%) had no titers documented at either the time of transplant or at one year post-transplant. **Conclusion:** This retrospective review evaluated the impact of our current protocol on our ability to determine patients' immunity to common childhood vaccine-preventable diseases. Despite the protocol, our findings reveal that a substantial portion of patients did not have available vaccination records either at the time of transplant or one year post-transplant. This gap highlights the need for a more streamlined and integrated care pathway, as many patients currently must visit external sites, such as their pediatrician, to receive necessary immunizations. A more coordinated approach, such as administering vaccines in-office during transplant evaluations, may better protect immunosuppressed pediatric patients from vaccine-preventable infections.

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3583 | IMPACT OF LIVER DISEASES ON DE-NOVO ALLOGENEIC LIVER TRANSPLANT OUTCOMES

Renuka Verma[1] Kamleshun Ramphul[2] Kaitlyn Gernhard[3] Himsikhar Khataniar[3] Leandro Sierra[4] Nikki Duong[5], [1]Kirk Kerkorian School of Medicine at UNLV, [2]Independent researcher, [3]Allegheny General Hospital, [4]Cleveland Clinic Foundation, [5]Stanford Health Care

Background: While liver transplant(LT) is a long-term treatment option for patients with end-stage liver disease(ESLD), the short-term complications based on its etiologies have not been well understood. We sought to explore further using the most extensive hospitalization data from the United States. **Methods:** Allogenic LT procedures, coded as a primary procedure, were studied from the National Inpatient Sample (2016-2022). We excluded patients with prior LTs, COVID-19, those under 18 years of age, and those with missing data. Our sample was stratified as: chronic hepatitis B (CHB), chronic hepatitis C(CHC), metabolic dysfunction-associated steatohepatitis(MASH), alcohol abuse(AA), primary biliary cholangitis(PBC), primary sclerosing cholangitis(PSC), and hepatocellular carcinoma(HCC). We removed patients who had more than one of these risk factors. Complications experienced among each group were compared via multivariable regression models. **Results:** In this study, we evaluated 27185 LT procedures. Around 48.17% were due to AA, 26.47% had MASH, 9.66% were HCC patients, 4.95% had PSC, 4.75% had CHC, 4.25% had PBC, and 1.77% had CHB. Patients with HCC were the oldest, while our youngest cohort consisted of those with PSC (Table 1a). Compared to those with AA, patients with CHB and HCC had higher odds of acute rejection during their current stay, while those with PSC and CHC had higher odds of LT failure. Events of acute kidney injury (AKI) were less common among patients with CHC, MASH, PBC, PSC, and HCC than those with AA. Meanwhile, MASH patients also reported fewer cases of sepsis than AA patients. The need for transfusion was less among PSC and HCC patients(vs AA). Odds of Clostridium difficile infection, postprocedural hematoma, and pulmonary embolism/deep venous thromboembolism during their current admission were comparable in all groups. In addition, in-hospital mortality and major adverse cardiac and cerebrovascular events (MACCE) did not differ among them(Table 1b). Patients with CHB reported the longest hospital stays, while PSC cases were discharged the earliest(Table 1a). **Conclusion:** Short-term in-hospital outcomes among LT patients differ based on etiology. Although the all-cause in-hospital mortality rates were comparable in our sample, we strongly advocate for further studies to understand their long-term survival outcomes.

Table 1a. Comparing the mean age, length of stay(LOS), and hospital charges

	Mean age (years)	Mean LOS (days)	Mean Hospital charge (USD)
Alcohol Abuse	51.6	21.6	679047.8
Chronic Hepatitis B	54.2	24.2	856702.9
Chronic Hepatitis C	58.5	16.5	562316.8
Metabolic dysfunction-associated steatohepatitis	59.4	18.5	568086.9
Primary Biliary Cholangitis	54.9	16.8	540974.5
Primary Sclerosing Cholangitis	45.2	14.7	524975.1
Hepatocellular Carcinoma	60.2	17.3	577715.1
p-value	<0.01	<0.01	<0.01

Table 1b. Adjusted odds ratio(aOR) of complications seen

All-cause death	aOR	p-value	Lower 95% CI	Upper 95% CI
Alcohol Abuse as reference				
Chronic Hepatitis B	0.912	0.903	0.208	4.006
Chronic Hepatitis C	1.259	0.557	0.583	2.722
Metabolic dysfunction-associated steatohepatitis	1.246	0.388	0.756	2.056
Primary Biliary Cholangitis	0.686	0.530	0.211	2.230
Primary Sclerosing Cholangitis	0.409	0.222	0.097	1.723
Hepatocellular Carcinoma	1.129	0.705	0.602	2.117
Liver rejection	**aOR**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
Alcohol Abuse as reference				
Chronic Hepatitis B	2.719	0.021	1.163	6.358
Chronic Hepatitis C	1.252	0.550	0.598	2.625
Metabolic dysfunction-associated steatohepatitis	0.806	0.326	0.524	1.240
Primary Biliary Cholangitis	1.530	0.154	0.852	2.750
Primary Sclerosing Cholangitis	1.413	0.253	0.780	2.558
Hepatocellular Carcinoma	1.653	0.040	1.022	2.673
Liver transplant failure	**aOR**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
Alcohol Abuse as reference				
Chronic Hepatitis B	2.511	0.210	0.594	10.605
Chronic Hepatitis C	3.062	0.018	1.208	7.760
Metabolic dysfunction-associated steatohepatitis	1.845	0.068	0.955	3.566
Primary Biliary Cholangitis	1.245	0.775	0.276	5.623
Primary Sclerosing Cholangitis	4.708	<0.01	2.239	9.900
Hepatocellular Carcinoma	2.306	0.048	1.006	5.285
C difficile infection	**aOR**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
Alcohol Abuse as reference				
Chronic Hepatitis B	1.001	0.999	0.212	4.726
Chronic Hepatitis C	0.535	0.237	0.190	1.509
Metabolic dysfunction-associated steatohepatitis	0.659	0.077	0.415	1.046
Primary Biliary Cholangitis	0.801	0.606	0.345	1.861
Primary Sclerosing Cholangitis	0.834	0.689	0.342	2.033
Hepatocellular Carcinoma	0.527	0.105	0.243	1.144
Acute Kidney Injury	**aOR**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
Alcohol Abuse as reference				
Chronic Hepatitis B	0.648	0.085	0.396	1.062
Chronic Hepatitis C	0.489	<0.01	0.373	0.640
Metabolic dysfunction-associated steatohepatitis	0.843	0.036	0.719	0.989
Primary Biliary Cholangitis	0.503	<0.01	0.379	0.668
Primary Sclerosing Cholangitis	0.293	<0.01	0.227	0.378
Hepatocellular Carcinoma	0.280	<0.01	0.226	0.347
Sepsis	**aOR**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
Alcohol Abuse as reference				
Chronic Hepatitis B	1.290	0.397	0.715	2.328
Chronic Hepatitis C	0.673	0.073	0.436	1.038
Metabolic dysfunction-associated steatohepatitis	0.668	<0.01	0.525	0.850
Primary Biliary Cholangitis	0.661	0.096	0.405	1.077
Primary Sclerosing Cholangitis	0.797	0.313	0.513	1.239
Hepatocellular Carcinoma	0.722	0.055	0.518	1.006
PE/DVT/Thromboembolism	**aOR**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
Alcohol Abuse as reference				
Chronic Hepatitis B	1.636	0.142	0.848	3.158
Chronic Hepatitis C	1.277	0.272	0.825	1.977
Metabolic dysfunction-associated steatohepatitis	0.784	0.078	0.598	1.028
Primary Biliary Cholangitis	0.642	0.180	0.336	1.228
Primary Sclerosing Cholangitis	1.071	0.787	0.651	1.761
Hepatocellular Carcinoma	0.997	0.988	0.681	1.459
Postprocedural hematoma	**aOR**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
Alcohol Abuse as reference				
Chronic Hepatitis B	0.539	0.324	0.157	1.846
Chronic Hepatitis C	0.863	0.644	0.462	1.612
Metabolic dysfunction-associated steatohepatitis	0.815	0.226	0.584	1.136
Primary Biliary Cholangitis	1.006	0.985	0.517	1.959
Primary Sclerosing Cholangitis	0.889	0.726	0.461	1.715
Hepatocellular Carcinoma	0.578	0.083	0.311	1.074
Blood transfusion	**aOR**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
Alcohol Abuse as reference				
Chronic Hepatitis B	0.764	0.287	0.466	1.254
Chronic Hepatitis C	0.959	0.782	0.715	1.288
Metabolic dysfunction-associated steatohepatitis	0.896	0.172	0.765	1.049
Primary Biliary Cholangitis	0.743	0.053	0.550	1.004
Primary Sclerosing Cholangitis	0.527	<0.01	0.376	0.738
Hepatocellular Carcinoma	0.653	<0.01	0.519	0.822
Major adverse cardiac and cerebrovascular events	**aOR**	**p-value**	**Lower 95% CI**	**Upper 95% CI**
Alcohol Abuse as reference				
Chronic Hepatitis B	1.38	0.47	0.57	3.34
Chronic Hepatitis C	0.70	0.30	0.36	1.38
Metabolic dysfunction-associated steatohepatitis	0.79	0.22	0.54	1.16
Primary Biliary Cholangitis	0.50	0.15	0.20	1.29
Primary Sclerosing Cholangitis	0.44	0.12	0.15	1.24
Hepatocellular Carcinoma	0.60	0.06	0.35	1.02

Disclosures: Renuka Verma: Nothing to Disclose, Kamleshun Ramphul: Nothing to Disclose, Kaitlyn

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Gernhard: Nothing to Disclose, Himsikhar Khataniar: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Nikki Duong: Nothing to Disclose

3584 | IMPACT OF ACUTE HEART FAILURE ON OUTCOMES AFTER LIVER TRANSPLANTATION

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Background: Acute severe heart failure (AHF) developing after liver transplantation (LT) is a distinct entity with a poor prognosis. There is limited data regarding AHF in the postoperative period in liver transplant patients. This study aims to determine the incidence and adverse events of AHF in patients readmitted 30 days after LT. **Methods:** National Readmission Database (NRD) 2016-2021 was queried to identify LT patients. Patients readmitted after 30 days were divided into two cohorts: with and without new onset AHF. The primary outcome was all-cause mortality. Secondary outcomes included adverse events, ICU stay and respiratory failure. Statistical analysis was performed using Stata-Corp. 2021. **Results:** Of 43239 patients discharged post-LT, 12978 were readmitted after 30 days, of which 306 had VTE (2.3%). Patients with AHF had higher odds of mortality (aOR 4.37, 95% CI: 2.21–8.61, p <0.001), AKI (aOR 2.27, 95% CI: 1.54–3.34, p $<$ 0.001) ICU stay (aOR 3.93, 95% CI: 2.45–6.29, p $<$ 0.001) and respiratory failure (aOR 5.17, 95% CI: 3.35–7.97, p $<$ 0.001). **Conclusion:** Despite low incidence and poorly understood pathophysiology AHF in LT, it is associated with significant morbidity and mortality, emphasising the need for vigilant perioperative cardiac assessment and prompt management to improve post-transplant outcomes.

	Odds ratio	95% conf.-interval	P
Mortality	4.37	2.21 - 8.61	0.000
AKI	2.27	1.54 - 3.34	0.000
ICU	3.93	2.45 - 6.29	0.000
Acute respiratory failure	5.17	3.35 - 7.97	0.000

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3585 | EPIDEMIOLOGIC DIFFERENCES IN HIGH-RISK CYTOMEGALOVIRUS MISMATCH BETWEEN ADULT AND PEDIATRIC LIVER TRANSPLANT (LT) RECIPIENTS

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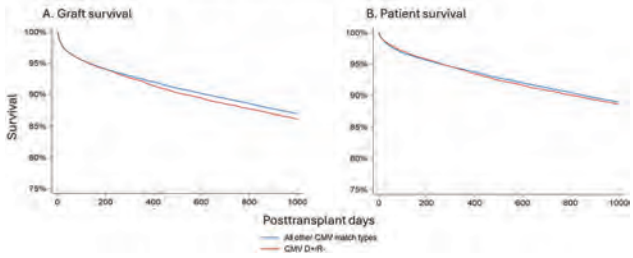
Background: Cytomegalovirus (CMV) Donor-positive/Recipient-negative (D+/R-) serostatus has been implicated in delayed graft loss after solid organ transplantation, but little is known about its epidemiology in pediatric LT. We aimed to determine differences in D+/R- serostatus between pediatric and adult LT. **Methods:** In this cross-sectional study, isolated first-time pediatric (age <21 yrs) LT recipients were identified from the Scientific Registry of Transplant Recipients between 2014 and 2022. CMV serologic status was categorized by both donor and recipient positivity into four categories: D+/R-, D-/R+. D+/R+, and D-/R-. Least absolute shrinkage and selection operator (LASSO) identified predictors of CMV mismatch (Poisson regression) and graft and patient survival (Cox regression). **Results:** We identified 62,945 primary LT recipients (n = 4386, 7% pediatric). The overall high-risk CMV mismatch (D+/R-) rate increased from 21.1% in 2014 to 25.5% in 2022. Pediatric patients were more likely to be R- (63% vs 38%, $p<0.001$) but less likely to receive D+ grafts (50% vs 63%, $p<0.001$). Pediatric patients were 48% (95% CI: 38-60%, $p<0.001$) more likely to receive a CMV D+/R- transplant. Controlling for age, recipients with CMV D+/R- status had an increased risk of graft loss (HR 1.09, 95% CI 1.03–1.16, p = 0.004) and death (HR 1.06, 95% CI 1.00–1.13, p = 0.046) compared to other combinations (Figure). **Conclusion:** Pediatric recipients are at higher risk of CMV D+/R- transplant, which are associated with higher rates of graft loss and death. These results may have significant implications for the monitoring and treatment needs of these patients.

Figure. Graft and patient survival stratified by CMV status



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3586 | EXPANDING THE DONOR POOL: SAFE RECOVERY IN LIVING LIVER DONORS OVER AGE 50

Hojung Park[1] Lauren Leung[1] Andrew Park[1] Rohan Rathi[1] Kyeong Ri Yu[1] Seung Duk Lee[1] Yuzuru Sambommatsu[1] Daisuke Imai[1] Aamir Khan[1] Muhammad Saeed[1] Amit Sharma[1] Adrian Cotterell[1] Marlon Levy[1] David Bruno[1] Vinay Kumaran[1], [1]Virginia Commonwealth University Medical Center

Background: Older age is often considered a contraindication for living liver donation. However, as global demand for liver transplantation rises, increasing the donor pool to include well-selected older individuals could improve transplant availability. This study compares the recovery of living liver donors aged > 50 to younger donors to evaluate the feasibility and safety of donations in this patient population. **Methods:** This retrospective cohort study analyzed 52 donors who underwent open or robot-assisted donor hepatectomy from February 2020 and December 2024 at a single tertiary care center. Patients were stratified into older donors (> 50 years, n = 10) and younger controls (n = 42). Data included demographics, surgical history, intraoperative characteristics, and postoperative outcomes. Primary endpoints included length of stay, postoperative complications (such as ileus, bile leak, and bleeding), liver function outcomes (measured by total bilirubin, ALT, AST, and INR), and incidence of liver dysfunction prior to discharge. **Results:** Older donors were more likely to have a history of prior abdominal surgery (90% vs 38.1%, p < 0.001). BMI was similar between groups (26.9 vs 27.6, p = 0.826), with no statistically significant difference. Intraoperative characteristics, including estimated blood loss, parenchymal transection time, warm ischemic time, and operative time showed no statistically significant differences. Postoperatively, ileus was the most common complication, occurring at a significantly higher rate in older donors compared to younger donors (50% vs. 35.7%, p = 0.045). Aside from a significantly lower peak INR in the older donors (1.5 vs 1.7, p = 0.046), there were no statistically significant differences in postoperative lab values at POD3, POD5, or peak between the groups. No older donors experienced liver dysfunction prior to discharge, whereas three younger donors did (0% vs 7.1%, p = 0.007). **Conclusion:** Older living liver donors (> 50 years) had similar intraoperative outcomes and liver function recovery to younger donors, despite higher rates of prior abdominal surgery and postoperative ileus. No older donors experienced liver dysfunction. These findings suggest that carefully selected older donors can safely undergo living liver donation.

Table 1. Patient demographics

	Older Donors (n=10)	Control (n=42)	p-value
Age, mean (sd)	54.4 (3.9)	37.9 (7.8)	<0.001
Sex			<0.001
Male, n (%)	1 (10)	17 (40.5)	
Female, n (%)	9 (90)	25 (59.5)	
ABO Blood Type			<0.001
A+, n (%)	1 (10)	9 (21.4)	
A-, n (%)	3 (30)	4 (9.5)	
B+, n (%)	1 (10)	0 (0)	
AB+, n (%)	0 (0)	1 (2.4)	
O+, n (%)	3 (30)	17 (40.5)	
O-, n (%)	2 (20)	11 (26.2)	
BMI, n (sd)	26.9 (3.5)	27.6 (10.1)	0.826
Operation Type			0.117
Open, n (%)	5 (50)	16 (38.1)	
Robot-Assisted, n (%)	5 (50)	26 (61.9)	
Previous abdominal surgery, n (%)	**9 (90)**	**16 (38.1)**	**<0.001**
Liver volume remaining (%), mean (sd)	18.9 (18.2)	14.6 (14.0)	0.480

Table 2. Intraoperative characteristics

	Older Donors (n=10)	Control (n=42)	p-value
Open Conversion, n (%)	1 (20)	3 (11.5)	0.117
EBL (mL), mean (sd)	515.0 (391.6)	478.0 (459.6)	0.816
Parenchymal Time (min), mean (sd)	121.0 (75.0)	140.2 (61.1)	0.417
Warm Ischemic Time (min), mean (sd)	5.3 (2.8)	7.1 (4.4)	0.261
Operation Time (min), mean (sd)	396.6 (88.4)	428.5 (74.5)	0.290

Table 3. Postoperative characteristics and complications

	Older Donors (n=10)	Control (n=42)	p-value
Length of Stay (days), mean (sd)	7.3 (2.0)	7.0 (1.9)	0.616
Complications, n (%)	**5 (50)**	**15 (35.7)**	**0.045**
Ileus	5 (50)	10 (23.8)	
Bile leak	1 (10)	1 (2.4)	
Postoperative bleeding	0 (0)	1 (2.4)	
Other	0 (0)	3 (7.1)	
ICU stay (days), mean (sd)	1.5 (0.5)	1.5 (0.8)	0.897
Follow-up (days), mean (sd)	176.4 (186.1)	160.9 (176.8)	0.814
POD3 values, mean (sd)			
Total bilirubin	2.0 (0.5)	2.3 (1.0)	0.312
ALT	184.6 (84.0)	163.9 (76.6)	0.474
AST	102.8 (44.0)	104.0 (45.8)	0.943
INR	1.3 (0.1)	1.4 (0.2)	0.120
POD5 values, mean (sd)			
Total bilirubin	1.4 (0.4)	1.6 (0.9)	0.504
ALT	133.2 (63.8)	137.5 (52.8)	0.841
AST	83.0 (36.2)	89.8 (39.5)	0.653
INR	1.1 (0.0)	1.2 (0.3)	0.409
Peak values, mean (sd)			
Total bilirubin	2.7 (0.9)	3.5 (1.2)	0.065
ALT	350.8 (162.7)	317.6 (194.9)	0.636
AST	344.9 (165.6)	300.8 (192.5)	0.527
INR	**1.5 (0.2)**	**1.7 (0.2)**	**0.046**

Disclosures: Hojung Park: Nothing to Disclose, Lauren Leung: Nothing to Disclose, Andrew Park: Nothing to Disclose, Rohan Rathi: Nothing to Disclose, Kyeong Ri Yu: Nothing to Disclose, Seung Duk Lee: Intuitive: Consultant, Yuzuru Sambommatsu: Nothing to Disclose, Daisuke Imai: Nothing to Disclose, Aamir Khan: Nothing to Disclose, Muhammad Saeed: Nothing to Disclose, Amit Sharma: Nothing to Disclose, Adrian Cotterell: Nothing to Disclose, Marlon Levy: Nothing to Disclose, David Bruno: Nothing to Disclose, Vinay Kumaran: Nothing to Disclose

3587 | DIRECT BILIRUBIN-BASED MELD SCORE: IMPACT OF HEPATIC VS. EXTRA-HEPATIC HYPERBILIRUBINEMIA ON STAGING OF CIRRHOSIS

mete ucdal Yigit Berk Sahin[1] Ibrahim Sendur[1] Osman Dag[2] Yasemin Balaban[3], [1]Hacettepe University Faculty of Medicine, [2]Hacettepe University, Faculty of Medicine, [3]Hacettepe University

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

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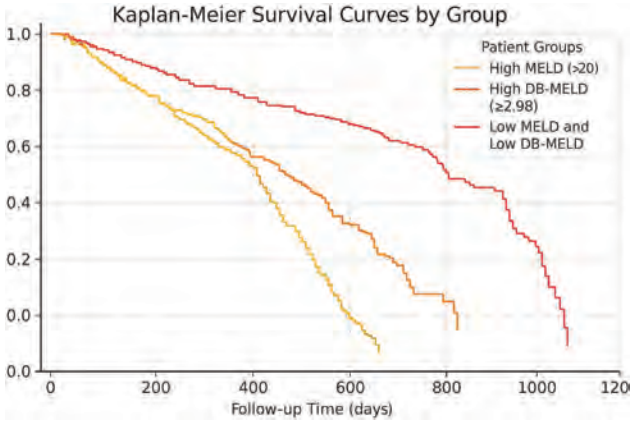
Background: The Model for End-Stage Liver Disease (MELD) score is based on total bilirubin, which may be affected by non-hepatic conditions such as hemolysis or Gilbert's syndrome. This may be confounding in assessment of liver dysfunction and cause over-staging of cirrhotic patients. The aim of this study was to evaluate the impact of using direct (conjugated) bilirubin (DB-MELD score) instead of total bilirubin on survival. **Methods:** This single-center retrospective cohort study included 826 cirrhotic patients diagnosed between January 2015–December 2020. Patients with missing survival data were excluded from the analysis. Three distinct groups emerged: double high (high MELD and high DB-MELD), intermediate (high MELD and low DB-MELD), and double low (low MELD and low DB-MELD). The median DB-MELD score was similar among patients in the low MELD group. Welch's ANOVA test for unequal variances(a) was used to analyze differences between follow-up durations with Bonferroni-corrected post-hoc analyses for multiple comparisons(b); chi-square test(c) was used for categorical data. Survival was estimated by the Kaplan–Meier method, and differences between curves were assessed by the log-rank test(d). Statistical significance threshold was $p < 0.05$. **Results:** The median MELD and DB-MELD scores were 20.0 and 19.8, respectively. There were 190 double high patients, 199 intermediate patients, and 437 double low patients. The respective survivals in these groups were 13.16 ± 0.52 months, 16.05 ± 0.66 months, and 18.57 ± 0.52 months ($F(2, 458.279) = 26.958$; $p < 0.001$[a]). The follow-up period of intermediate patients was 2.89 months longer than the double high group ($p = 0.011$; 95% CI 0.51–5.28[b]) and 2.52 months shorter than the double low group ($p = 0.008$; 95% CI –4.53 to –0.51[b]). Mortality rates during the study period were 68% for the double high group, 55% for the intermediate group, and 30% for the double low group ($\chi^2 = 87.24$; $p < 0.001$[c]). Survival analysis confirmed significantly better survival of patients with high MELD and low DB-MELD (log-rank $p < 0.001$[d]), validating DB-MELD's ability to identify a subgroup of patients with better survival among patients with high MELD scores. **Conclusion:** Improved survival was observed in patients with high MELD scores together with low DB-MELD scores compared to patients with both high MELD and DB-MELD scores. This suggests that DB-MELD may enhance prognostic stratification in cirrhotic patients beyond MELD. This significant mortality difference between patients with identical MELD scores but varying DB-MELD scores has clinical implications, not only for transplant listing decisions but also for the involvement of cirrhotic patients in clinical trials.



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3588 | RELATIONSHIP BETWEEN POST-LIVER TRANSPLANT RELAPSE IDENTIFIED WITH PHOSPHATIDYLETHANOL (PETH) TESTING AND MORTALITY AMONG PATIENTS WITH ALCOHOL USE DISORDER

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Background: Background: Phosphatidylethanol (PEth) testing—a sensitive, quantitative, and persistent biomarker for ethanol consumption—has replaced traditional blood tests for monitoring patients with alcohol use disorder (AUD) after liver transplant. We hypothesize that better detection of relapse may allow clinicians to intervene, resulting in improved outcomes for transplant patients. This preliminary study was performed to evaluate the relationship between mortality and positive PEth results after transplant. **Methods:** Methods: We used the Fisher exact test to compare time-to-event (mortality/last follow-up) by post-transplant PEth status (positive/ negative) as well as 12-month mortality among adult patients who received liver transplants secondary to AUD at a single integrated US health system between 2019–2022. Kaplan Meier curves were used to illustrate results. **Results:** Results: In a sample of 225 patients, 13 (6%) died during follow-up, including 2 who died at the time of surgery. After transplant, a total of 110 patients had negative tests, 86 were untested, and 29 patients (13%) had ≥1 positive test after transplant, indicating relapse. Those with positive post-transplant PEth results had significantly

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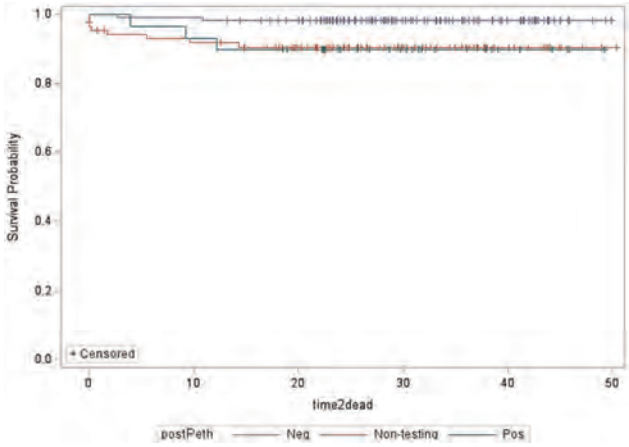
higher mortality ($p = 0.04$ [0.03 after excluding patients without testing]) and 12-month mortality ($p = 0.3$). However, the effect became non-significant after adjusting for MELD score at transplant ($p = 0.09$). **Conclusion:** Conclusion: Our analysis suggests that alcohol use detected by PEth after liver transplant may be associated with increased mortality, supporting the need for early intervention. However, the low incidence of death in our sample limited our statistical power. Larger samples with longer follow-up are needed.



Disclosures: Humberto Gonzalez: Nothing to Disclose, Yara Dababneh: Nothing to Disclose, Sheri Trudeau: Nothing to Disclose, Christina Melkonian: Nothing to Disclose, Stuart Gordon: Nothing to Disclose, Mei Lu: Nothing to Disclose

3589 | CLUSTERING RIGHT LOBE GRAFTS BASED ON ANATOMICAL COMPLEXITY USING UNSUPERVISED MACHINE LEARNING FOR DONOR HEPATECTOMY

Nishtha Singh[1] Erin Duggan[2] Angela Chen[3] Ellie Brandon[4] Carolyn Waite[4] Dustin Carpenter[4] Benjamin Samstein[4] Juan Rocca[4], [1]NewYork-Presbyterian/Weill Cornell Medical College, [2]NewYork-Presbyterian, CUIMC, NY, NY, [3]Weill Cornell Medicine, NewYork-Presbyterian, NY, NY, [4]Weill Cornell Medicine, NewYork-Presbyterian, NY, NY,

Background: The Minimally Invasive Living Donor Hepatectomy (MIS-DH) lacks a standardized framework to differentiate simple from complex grafts. Traditional classifications rely on arbitrary anatomical thresholds hindering reliable stratification, impacting surgical approach. Thus, we aim to develop a novel data-driven machine learning classification model for right lobe graft complexity using 2-step clustering, enabling objective preoperative stratification and surgical planning. **Methods:** A retrospective analysis of 49 right lobe MIS-DH (2018?2025) was performed at a single center. Due to limited sample size, bootstrapped datasets were generated to resample the data for improved stability and accuracy. Two-step clustering using SPSS was applied on continuous and categorical variables graft volume, future liver remnant (FLR), hepatic artery (HA), portal vein (PV), hepatic vein (HV), bile ducts (BD), and estimated blood loss (EBL) to differentiate simple and complex graft. Cluster performance was evaluated via BIC, silhouette score. Mann Whitney U- Test and chi-square were performed to validate the quality of final clusters. **Results:** The 500-bootstrap clustering model outperformed others (BIC = 3038.82, silhouette score = 0.3146), identifying 2 distinct clusters. Cluster 1 (57.8%), denoting complex grafts, had significantly lower FLR(34.6%) and higher EBL (490.5 mL) compared to Cluster 2(42.2%), which had FLR of 37.8% and EBL of 234 mL($p < 0.001$). Cluster1 includes all cases with 3BD, 3PV, 2HV/3HV, and 2HA significantly greater anatomical complexity ($p < 0.001$). Cluster 2 is dominated by type 2 PVs and single-structure variants, representing simpler graft. Further, Cluster1 was associated with younger age, higher weight, BMI, and graft volume ($p < 0.05$). Surgical approach varied significantly between clusters($p = 0.001$), with Cluster 1(Complex grafts) surgeries performed mostly via hybrid (n = 136) and robotic (n = 93)approach, whereas Cluster2 was evenly distributed across all surgical approaches. Despite anatomical and operative complexity, Cluster1 had fewer CD ≥ 3 complications($p = 0.04$), possibly due to enhanced surgical preparedness and technique selection. **Conclusion:** Unsupervised clustering of right lobe grafts based on combined anatomical and operative variables offers a novel reproducible, objective method to stratify graft complexity. The model reveals significant associations with surgical approach and outcomes, reinforcing its potential to enhance preoperative planning for surgical approaches and decision-making. Future directions include regression modeling for outcome prediction and integration into prospective donor evaluation algorithms.

Variable	Type	No of group
BD (Bile Duct)	Categorical	1BD, 2BD (trifurc/aberrRAHD/PD) 3BD(multiple sect duct/ lowBifurcs/ opNote)
HA (Hepatic Artery)	Categorical	1HA, 2HA(accessory/replaceRHA)
HV (Hepatic Vein)	Categorical	1 HV (RHV+V5+V8 drainingin MHV) 2HV(accessory V6/V7 or drain into IVC) 3 HV (3 in numbers/multibranches/opnote)
PV (Portal Vein)	Categorical	1 PV 2PV (2 veins or short RPV) 3PV (trifurcation+short RPV+multi sectors/opnote)
EBL (Estimated Blood Loss)	Continuous	Higher values suggest surgical complexity
FLR (Future Liver Remnant)	Continuous	Lower values indicate more complex grafts

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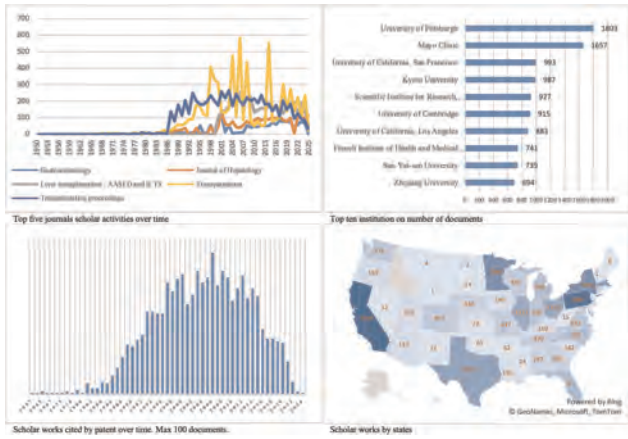
Disclosures: Nishtha Singh: Nothing to Disclose, Erin Duggan: Nothing to Disclose, Angela Chen: Nothing to Disclose, Ellie Brandon: Nothing to Disclose, Carolyn Waite: Nothing to Disclose, Dustin Carpenter: Nothing to Disclose, Benjamin Samstein: Nothing to Disclose, Juan Rocca: Nothing to Disclose

3590 | LIVER TRANSPLANTATION SCHOLARLY WORKS: A FOCUSED BIBLIOMETRIC ANALYSIS USING THE LENS DATABASE

Hussam Almasri[1] Rahul Karna[2] John Bassett[3], [1]University of North Dakota, [2]University of Minnesota Medical Center, [3]Sanford Health

Background: Since the first human liver transplantation (LT) in 1963, there have been significant enhancements of various aspects of LT, including patient risk stratification, liver preservation, immunosuppression, and surgical techniques. LT is now performed routinely in many countries, with markedly improved outcomes compared to previous decades. These advancements are largely attributed to impactful, practice-changing research in the field. Here, we present a comprehensive bibliometric analysis of scholarly works in LT, focusing on those cited by patents. **Methods:** The Lens database was utilized to identify English-language scholarly articles related to LT. A focused search strategy using keywords was implemented to increase specificity. Document types, including preprints, datasets, and reference entries, were excluded. Scholarly works were categorized based on citation by patents or other scholarly works. Additional metadata, such as institution, country, and state of origin, were extracted. Due to the redundancy of non-specific documents when including abstracts, we updated the search strategy to be title-limited to ensure that we were primarily focusing on LT research, acknowledging that this might have resulted in the exclusion of a few relevant papers. **Results:** From 1890 to 2024, a total of 88,584 scholarly works related to LT were identified. Of these, 2,006 had been cited by patents, while 54,192 were cited by other scholarly works. The number of scholarly works in top-contributing journals has plateaued since 2019–2020. Scholarly works cited by patents peaked between 2003 and 2010, followed by a gradual decline. The top authors of patent-cited works primarily specialized in surgery, pathology, biology, and hepatology. The top institutions contributing to patent-cited works included the University of Pittsburgh, Harvard University, and the Mayo Clinic. The United States produced the highest number of total (19,293) and patent-cited (772) scholarly documents, followed by China with 5,667 and 112, respectively. Within the U.S., California, Pennsylvania, and Minnesota were the leading states for scholarly output. **Conclusion:** This bibliometric analysis highlights the progression and global distribution of impactful research in liver transplantation over more than five decades. Liver transplantation (LT) recipients have a 75% five-year survival rate, which necessitates innovation in this field to improve patient outcomes. The observed decline in patent citations since 2010 could be due to changes in research focus, patenting strategies, or the maturation of surgical techniques. The concentration of patent-cited works among U.S.-based institutions highlights the country's leadership in LT research. Identifying highly cited works and their sources offers valuable insights into research trends, helping to inform funding and collaboration priorities.



Disclosures: Hussam Almasri: Nothing to Disclose, Rahul Karna: Nothing to Disclose, John Bassett: Nothing to Disclose

3591 | ROBOTIC CAUDATE LOBE RESECTION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PERIOPERATIVE AND POSTOPERATIVE OUTCOMES

Mohammad Abuassi[1] Ayham Hussein[2] Mahmoud Y Madi[3] Badi Rawashdeh[4] Kia Saeian[4] K Raj Prasad[4], [1]University of Central Florida, [2]Al-Balqa Applied University, Faculty of Medicine, [3]University of Texas Austin Dell Medical School, [4]Medical College of Wisconsin

Background: Caudate lobe resection is technically challenging due to its deep anatomical location and proximity to major vascular structures. Despite the growing adoption of minimally invasive techniques, data on robotic caudate lobectomy remain sparse, primarily limited to small case series. This study systematically evaluates the safety, feasibility, and outcomes of robotic caudate lobe resection to inform

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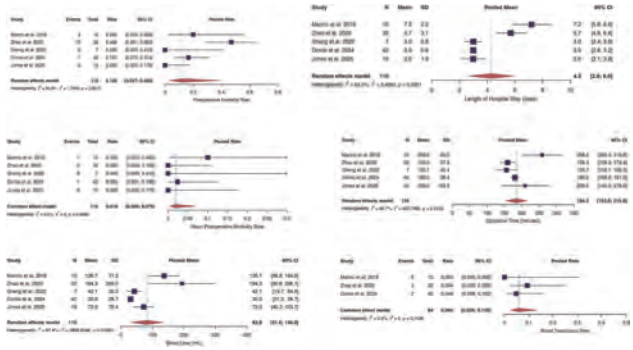
practice and future guideline development. **Methods:** We conducted a systematic review and meta-analysis in accordance with PRISMA guidelines. A comprehensive search of PubMed, Scopus, Web of Science, and the Cochrane Library was performed through February 2025. We included studies reporting outcomes of isolated robotic caudate lobe resections. Data were extracted on intraoperative metrics (operative time, blood loss, transfusion) and postoperative outcomes (morbidity, major complications, length of stay). Pooled estimates were calculated using random-effects models for continuous outcomes and common-effect models for binary outcomes. Between-study heterogeneity was assessed using the I^2 statistic. Leave-one-out sensitivity analyses tested the robustness of results. Study quality and bias were assessed using the ROBINS-I tool. **Results:** Five studies comprising 110 patients were included. The pooled mean operative time was 184.3 minutes (95% CI: 153.0–215.6), and the estimated blood loss was 82.8 mL (95% CI: 31.5–134.0). The blood transfusion rate was 6.0% (95% CI: 2.5–13.5). Postoperative morbidity was 12.0% (95% CI: 2.7–40.0), and major complications were rare at 1.8% (95% CI: 0.5–7.0). The mean hospital stay was 4.3 days (95% CI: 2.6–6.0). Leave-one-out sensitivity analyses reinforced the stability of results, showing no significant change in pooled estimates upon exclusion of individual studies. Heterogeneity was substantial for operative time and hospital stay but minimal for complication rates. **Conclusion:** Robotic caudate lobe resection is a feasible and safe alternative to traditional approaches, demonstrating low blood loss, short hospital stays, and a favorable morbidity profile, including a remarkably low rate of major complications. These findings support the growing role of robotic platforms in minimally invasive liver surgery, potentially enhancing precision and reducing morbidity for complex resections. Further multicenter prospective studies are needed to validate these results and refine patient selection.



Disclosures: Mohammad Abuassi: Nothing to Disclose, Ayham Hussein: Nothing to Disclose, Mahmoud Y Madi: Nothing to Disclose, Badi Rawashdeh: Nothing to Disclose, Kia Saeian: Abbvie: Grant/Research Support, K Raj Prasad: Nothing to Disclose

3592 | DE NOVO MALIGNANCY AFTER LIVER TRANSPLANTATION IN PATIENTS WITH AND WITHOUT HEPATOCELLULAR CARCINOMA: A PROPENSITY-MATCHED ANALYSIS

Mohammad Abuassi[1] Mahmoud Y Madi[2] Razan Aburumman[3] Badi Rawashdeh[4] Kia Saeian[4] K Raj Prasad[4], [1]UCF/HCA Florida North Florida Hospital, [2]University of Texas Austin Dell Medical School, [3]Henry Ford Hospital, [4]Medical College of Wisconsin

Background: Liver transplantation (LT) offers curative treatment for hepatocellular carcinoma (HCC) in carefully selected patients. However, long-term immunosuppression increases the risk of de novo malignancies, a growing cause of late post-transplant morbidity and mortality. While cancer risk in transplant recipients is well documented, limited data exist comparing post-transplant malignancy patterns between patients with and without pre-existing HCC. Given potential differences in immunologic profiles, oncogenic drivers, and surveillance intensity, understanding how HCC history influences de novo cancer risk is critical to guiding personalized post-LT care. **Methods:** We conducted a retrospective cohort analysis using the TriNetX US Collaborative Network, encompassing 68 healthcare organizations. Two propensity-matched cohorts of adult LT recipients were identified: those with HCC ($n = 7{,}595$) and those without ($n = 7{,}595$). Matching was based on demographics, viral hepatitis status, history of tobacco and alcohol use, and relevant comorbidities. Primary outcomes included the incidence of de novo malignancies and overall survival. Odds ratios (ORs) with 95% confidence intervals (CIs) and Kaplan-Meier survival analyses were used to compare groups. **Results:** LT recipients with HCC had significantly higher odds of developing bronchus and lung malignancies (OR 2.07, 95% CI 1.62–2.64, $p < 0.001$) and prostate cancer (OR 1.54, 95% CI 1.19–1.99, $p = 0.001$) compared to non-HCC recipients. Other cancer types including colon, pancreas, esophagus, stomach, larynx, and melanoma/skin cancers, showed no statistically significant differences. The incidence of post-transplant lymphoproliferative disorder (PTLD) was also comparable (OR 0.94, 95% CI 0.71–1.24, $p = 0.653$). **Conclusion:** Liver transplant recipients with pre-existing HCC were found to have a higher risk of developing bronchopulmonary and prostate cancers post-transplant. This may partly reflect differences in post-transplant surveillance intensity. These findings highlight the need for personalized oncologic surveillance, particularly for bronchopulmonary and prostate

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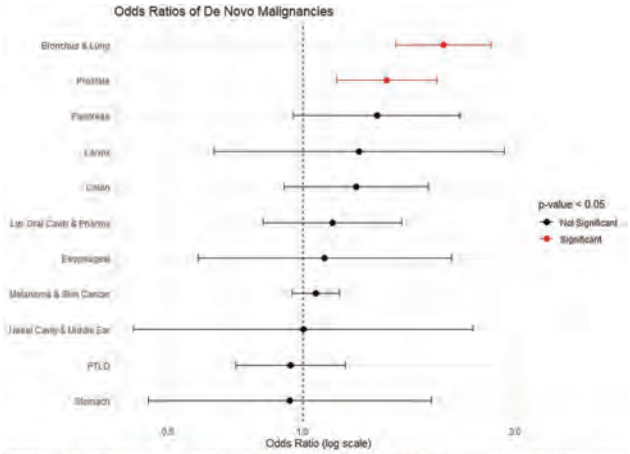
malignancies, among liver transplant recipients with HCC.



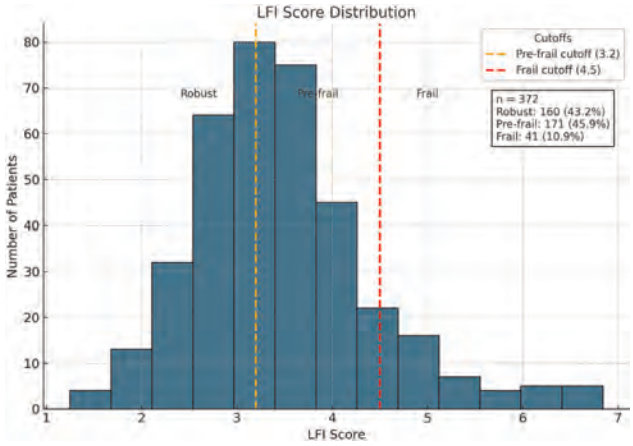
Malignancy Type	Odds Ratio (OR)	95% CI	p-value
Colon	1.315	(0.905, 1.911)	0.149
Pancreas	1.464	(0.951, 2.253)	0.082
Esophageal	1.118	(0.581, 2.152)	0.739
Stomach	0.934	(0.450, 1.936)	0.854
Melanoma & Skin CA	1.069	(0.946, 1.207)	0.283
Bronchus & Lung	2.068	(1.618, 2.643)	0.0001
Larynx	1.335	(0.631, 2.824)	0.448
Nasal Cavity & Middle Ear	1.001	(0.416, 2.405)	0.999
Prostate	1.54	(1.190, 1.994)	0.001
Lip, Oral Cavity & Pharynx	1.162	(0.812, 1.664)	0.411
PTLD	0.937	(0.706, 1.244)	0.653

Disclosures: Mohammad Abuassi: Nothing to Disclose, Mahmoud Y Madi: Nothing to Disclose, Razan Aburumman: Nothing to Disclose, Badi Rawashdeh: Nothing to Disclose, Kia Saeian: Abbvie: Grant/Research Support, K Raj Prasad: Nothing to Disclose

3593 | LIVER FRAILTY INDEX: A VITAL SIGN IN A TRANSPLANT HEPATOLOGY CLINIC

Sahak Hovsepian[1] Amandeep Sahota[1] An Ly[1], [1]Kaiser Permanente Los Angeles Medical Center

Background: Frailty, characterized by reduced physiologic reserve due to impaired muscle function, is a key predictor of many adverse outcomes in patients with cirrhosis, namely increased waitlist mortality, post-transplant mortality, and functional decline. Furthermore, frail patients are at increased risk for hospital readmission, post-transplant hospitalization and post-transplant ICU stay. Traditional metrics fail to fully capture this risk. The Liver Frailty Index (LFI) is a validated, objective tool used to assess frailty in liver transplant candidates. Despite its clinical utility and ease of use, LFI implementation across hepatology clinics remains inconsistent, leaving many frail patients underdiagnosed and undermanaged. We aimed to describe how LFI is implemented, tracked, and used to guide care in a liver transplant clinic in an integrated health system to inform broader adoption of frailty screening in routine practice. **Methods:** We conducted an Institutional Review Board (IRB #12191) approved retrospective descriptive study of adult patients with cirrhosis seen in the liver transplant clinic at Kaiser Permanente Los Angeles Medical Center between January 1, 2023, and May 20, 2025. LFI was assessed at each clinic visit using standardized tests of grip strength, chair stands, and balance. Scores were calculated using the validated formula developed by University of California San Francisco and categorized as robust (LFI $<$ 3.2), pre-frail (LFI 3.2–4.4), or frail (LFI $\geq$ 4.5). LFI scores were documented and discussed with patients during clinic visits. All patients received frailty education, handouts on physical activity and diet, and those with elevated LFI scores were referred to physical therapy and nutrition services. **Results:** A total of 372 patients were included in the study. The average age of our population was 59.8 years and 60.5% of patients were male. LFI scores are reported as a histogram attached as an image (skewness = 0.68; kurtosis = 0.93) with a mean LFI of 3.43 $\pm$ 0.89, median of 3.35 (IQR 1.04) and a mode of 3.74. Based on their LFI scores, 10.9% of patients were frail, 45.9% pre-frail, and 43.2% of patients were robust. **Conclusion:** Our findings demonstrate that routine use of LFI in a community-based liver transplant clinic is feasible, effective, and supports targeted interventions such as physical therapy and dietician referrals. As a simple, validated, and prognostically meaningful tool, LFI should be standardized across all liver transplant clinics—including those in a unique position as non-transplant center—to stratify risk and guide pre-transplant optimization. Broader implementation of utilizing and tracking LFI scores over time can improve recognition of frailty, facilitate multidisciplinary care, and potentially enhance transplant readiness and outcomes for a particularly vulnerable patient population.



Disclosures: Sahak Hovsepian: Nothing to Disclose, Amandeep Sahota: Nothing to Disclose, An Ly: Nothing to Disclose

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3594 | EXTERNAL VALIDATION OF MELD 3.0 PERFORMANCE IN A LATIN AMERICAN LIVER TRANSPLANT COHORT

Josefina Pages[1] Manuel Mendizabal[2] Federico Pinero[2] Graciela Castro-Narro[3] Alejandra Villamil[4] Fernando Cairo[5] Ignacio Roca[6] Nicolas Dominguez[6] Florencia Antinucci[7] Rodrigo Zapata[8] Julio Benitez Perez[9] Estefanía Liza Baca[10] Bertha Cardenas[11] Gustavo Pereira[12] Angelo Mattos[13] Iván López-Méndez[14] Aldo Torre[15] Marcelo Silva[16] Natalia Baumgartner Ayres[17] Carmen Alexandra Ginesta Frings[18], [1]Hospital Universitario Austral., [2]Hospital Universitario Austral, [3]Instituto Nacional de Ciencias Médicas y Nutrición " Salvador Zubiran", Mexico., [4]Hospital Italiano de Buenos Aires, Argentina, [5]HOSPITAL EL CRUCE, [6]Hospital El Cruce, Argentina, [7]Hospital Alemán, Argentina, [8]Clinica Alemana de Santiago/Facultad Medicina, Universidad del Desarrollo, [9]Complejo Asistencial Dr Sotero del Rio, Brasil, [10]Hospital Nacional Edgardo Rebagliati Martins, Peru., [11]Hospital Nacional Guillermo Almenara, Peru, [12]Hospital Federal de de Bonsucesso, Brasil, [13]Universidade Federal de Ciências da Saúde de Porto Alegre, Brasil, [14]Hospital Medica Sur Unidad de Hepatología y Trasplantes. Ciudad de México, México, [15]Centro Médico ABC, Mexico, [16]Hospital Universitario Austral, Argentina, [17]Irmandade Santa Casa de Misericórdia de Porto Alegre, Brasil., [18]Clinica Alemana

Background: The MELD 3.0 score has demonstrated superior discriminatory performance for predicting 90-day waitlist mortality among liver transplant (LT) candidates in the US. However, its performance remains unvalidated in regions with limited access to transplantation and high waitlist mortality. This study aimed to validate the MELD 3.0 in a Latin American cohort, coordinated by ALEH special interest group. **Methods:** We conducted a retrospective cohort study including adults LT candidates listed between January 2016 and December 2023 across five Latin American countries. Patients receiving MELD exception points were excluded. Baseline data were registered at listing. Continuous variables were transformed as per each original score´s specifications. A time-to-event analysis using Cox regression models was performed, with 90-day mortality as the primary outcome and LT as censored observation. Discriminative performance was assessed using Harrell´s c-index for MELD, MELD-Na and MELD 3.0. Net Reclassification Index (NRI) was also calculated. **Results:** We included 1,013 patients: mean age 51 years (±11.8); 41.4% females, and 25.8% obese. Ascites and encephalopathy were present in 58.1% and 38.3% of cases, respectively. Median laboratories values at listing were: Sodium 137 mEq/L (IQR 133–139), creatinine 0.8 mg/dL (IQR 0.65–1.05), total bilirubin 3.51 mg/dL (IQR 1.9–7.16), albumin 3.0 g/dL (IQR 2.55–3.4), and INR 1.5 (IQR 1.3–1.8). The most common causes of liver disease were autoimmune (23.7%), metabolic-associated steatotic liver disease (18.5%), and alcohol-related liver disease (17.2%). Median MELD score was 16.9 (IQR 13.3–21.1), MELD-Na 18.3 (IQR 14.6–24), and MELD 3.0 19.5 (IQR 15.1–24.8). At 90 days, 26.3% underwent LT and 66.8% remained on the waitlist. The mortality incidence was 29.4 deaths per 1,000 patient-months of follow up, with a cumulative mortality of 8.3% (95% CI 6.6–10.4%) at 3 months. Hazard ratios for 90-day mortality were: MELD 1.15 (95% CI 1.12-1.19), MELD-Na 1.16 (95% CI 1.13-1.20), and MELD 3.0 1.15 (95% CI 1.12-1.19). Harrell's c-index showed no significant differences (Table 1).NRI showed no significant improvement in risk reclassification using MELD 3.0. **Conclusion:** In a region showing high waitlist mortality, MELD 3.0 did not demonstrate superior predictive performance over MELD or MELD-Na. These findings underscore the need for regional validation of predictive models before implementation in transplant priorization policies.

Table 1: Discriminative Performance of MELD-Based Scores for Predicting 90-Day Waitlist Mortality

Model	Harrell's C-index	95% Confidence Interval	p vs MELD	p vs MELD-Na
MELD	0.809	0.76 – 0.86	—	—
MELD-Na	0.821	0.77–0.86	0.41	—
MELD 3.0	0.822	0.78 – 0.87	0.27	0.88
MELD 3.0 (no Alb)	0.822	0.78– 0.87	0.25	0.81

Note: All models evaluated at the time of listing. No statistically significant difference in discrimination was observed between scores.

Disclosures: Josefina Pages: Nothing to Disclose, Manuel Mendizabal: Gilead: Speaking and Teaching, Biosidus: Speaking and Teaching, Gador: Speaking and Teaching, Knight: Speaking and Teaching, Federico Pinero: Nothing to Disclose, Graciela Castro-Narro: Nothing to Disclose, Alejandra Villamil: Novartis: Advisor, Intercept: Speaking and Teaching, Gilead: Advisor, Zydus: Advisor, Fernando Cairo: Nothing to Disclose, Ignacio Roca: Nothing to Disclose, Nicolas Dominguez: Nothing to Disclose, Florencia Antinucci: Nothing to Disclose, Rodrigo Zapata: Nothing to Disclose, Julio Benitez Perez: Nothing to Disclose, Estefanía Liza Baca: Nothing to Disclose, Bertha Cardenas: Nothing to Disclose, Gustavo Pereira: Nothing to Disclose, Angelo Mattos: Nothing to Disclose, Iván López-Méndez: Nothing to Disclose, Aldo Torre: Nothing to Disclose, Marcelo Silva: Nothing to Disclose, Natalia Baumgartner Ayres: Nothing to Disclose, Carmen Alexandra Ginesta Frings: Nothing to Disclose

3595 | IT IS SAFE TO ACCEPT LIVING LIVER DONORS WITH POSITIVE AUTOIMMUNE MARKERS

Saad Alghamdi[1] Dimitri Raptis[1] Naryman Albadawi[1] Faisal Al Yahya[1] Shaden Alamro[2] Khalid Bzeizi[1] Ali

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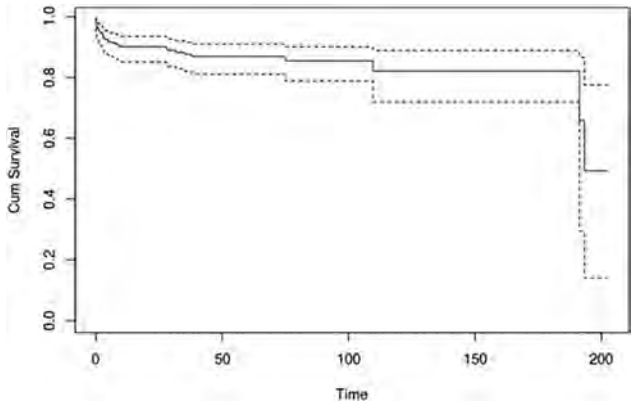
Albenmousa[1] Bandar Aljudaibi[1] Saleh Alqahtani[1] Dieter Broering[1] Waleed Al Hamoudi[3], [1]KFSHRC, [2]Princess Noura University, [3]King Saud University/KKUH

Background: the presence of autoimmune markers is common in general population the absence of autoimmune diseases. The safety of accepting such individuals as living liver donors is unknown and the literature is lacking. We aim in the study to evaluate the safety of accepting such donors on donors themselves and recipients. **Methods:** Using our electronic medical record system, we retrospectively collected data of patients who underwent liver transplantation from January 2001 until December 2021 at King Faisal Specialist Hospital & Research Center (KFSH&RC) in Riyadh. We usually exclude candidates with evidence of an underlying autoimmune disease or high antibodies titers. We collected demographicdata for donors and recipients. For the donors, we collected the data of antinuclear (ANA), smooth muscles (ASMA) and mitochondrial antibodies (AMA). We also looked at the impact of positive autoimune antibodies on the recipient in term of development of rejection and graft and patient survival. **Results:** 206 donors had at least one positive autoantibodies. The median age of the donors was 28 and 67% were male. Forty-eight donors (23%) had positive ANA, 159 (77%) had positive ASMA and 7 (3.39%) had positive AMA. The patient survival was 90.1% at one year and 87.6% at 3 years. The survival was similar when compared to the cohort of 1600 recipients in our registry (90.1 % vs 92.3, p value 0.93) and (87.6% vs 88.4%, p value 0.9) at one and three years, respectively. Thirty-nine patients (19%) developed at least one episode of rejection. None of the donors developed long term complications. **Conclusion:** if carefully selected, it is safe to accept potential living donors with positive autoantibodies.



Disclosures: Saad Alghamdi: Nothing to Disclose, Dimitri Raptis: Nothing to Disclose, Naryman Albadawi: Nothing to Disclose, Faisal Al Yahya: Nothing to Disclose, Shaden Alamro: Nothing to Disclose, Khalid Bzeizi: Nothing to Disclose, Ali Albenmousa: Nothing to Disclose, Bandar Aljudaibi: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Dieter Broering: Nothing to Disclose, Waleed Al Hamoudi: Nothing to Disclose

3597 | DEFINING WEIGHT TRAJECTORY AFTER LIVER TRANSPLANTATION USING GENERATIVE ARTIFICIAL INTELLIGENCE

Alexis Kim[1] Linxi Li[2] Reem Hamraz[3] Madison Nguyen[1] Rehan Razzaq[1] Vaishali Patel[1] Amon Ashgharpour[1] Idris Yakubu[1] Leslee Garland[1] Kavin Parmar[1] Mark Muthiah[4] Wen Hui Lim[4] Cheng Han Ng[4] Samarth Patel[5] Anh Bui[2] Mohammad Siddiqui[1], [1]Virginia Commonwealth University Health System, [2]Virginia Commonwealth University, [3]Integral University, [4]National University of Singapore, [5]Penn Medicine

Background: Better understanding of weight trajectories in liver transplant (LT) recipients is essential to improving clinical outcomes, however, current statistical approaches utilize aggregate data that does not account for unique patient trajectories. We utilized Generative Artificial Intelligence (GenAI) to identify factors that exist but are not observable (latent factors or LF) that result from limitation in current knowledge or statistical approach to model weight in LT recipients. **Methods:** Weight trajectories were modeled in 562 adult LT recipients with available weight data up to 36 months post-LT. Patients who died within 36 months post-LT, had multi-visceral transplants, or had incomplete follow-up data were excluded. Each weight trajectory was treated as an 8-dimensional vector, allowing us to convert longitudinal weight data into cross-sectional data. Multivariate analyses were also performed to determine the relationship between weight trajectories and clinical parameters. **Results:** The plotted weight trajectories represent complex data (Figure 1A) and conventional statistical approaches (Figure 1B) are not able to fully account for the individual patient-level data. Using GenAI, two discernable patterns, or latent factors were identified (LF_1 and LF_2), incorporating individual patient trajectories that explained 99% of the weight after LT (Figure 1C). Each patient's weight trajectory, thus, represented the combination of the LF_1 and LF_2. LF_1, the dominant latent factor, demonstrated rapid weight flux (increase or decrease) early after transplant (< 12 months), followed by gradual persistent weight gain for 36 months. LF_2 was less prevalent and demonstrated two distinct patterns: (A) initial weight gain in the first 12 months followed by weight loss and weight stabilization by 24-30 months, and (B) initial weight loss followed by rapid and continued weight gain after first 12 months post-LT. In multivariate analysis, MASH cirrhosis and male gender were the strongest clinical predictors of future

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weight gain. **Conclusion:** Applying GenAI identified key weight gain trajectories in LT recipients that accounted for nearly all weight change observed following LT. Better understanding weight change in LT recipients can facilitate development of better risk mitigation strategies that can improve clinical outcomes.

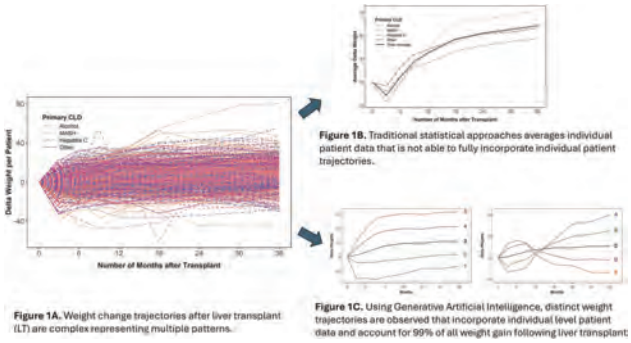

Figure 1A. Weight change trajectories after liver transplant (LT) are complex representing multiple patterns.

Figure 1B. Traditional statistical approaches averages individual patient data that is not able to fully incorporate individual patient trajectories.

Figure 1C. Using Generative Artificial Intelligence, distinct weight trajectories are observed that incorporate individual level patient data and account for 99% of all weight gain following liver transplant

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3598 | PRE-LIVER TRANSPLANT CORONARY ARTERY DISEASE RISK IS ASSOCIATED WITH INCIDENCE OF ADVERSE CARDIOVASCULAR EVENTS AFTER LIVER TRANSPLANT: A SINGLE CENTER EXPERIENCE

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Background: CVD is a leading cause of death after LT. Pre-LT CAD risk stratification guides pre-op optimization. Limited data exists on the relationship between pre-LT CAD risk stratification and adverse CV events (CVE) post-LT. The primary aim of this study was to examine the association between pre-LT CAD risk classification and post-LT CVE. **Methods:** Patients who had LT at a single center from 2012 to 2018 with follow-up through 2024 were reviewed. Pre-LT CAD risk groups were: low-risk (no CAD risk factors, age < 40, and ≥ 4 METs), intermediate risk (< 2 CAD risk factors, no diabetes, and no MASH), high risk (silent MI on ECG, new WMA on ECHO, new EF $< 50\%$, diabetes, MASH, or ≥ 2 CAD risk factors), and very high risk (prior CAD, PCI, MI, CABG, or CVD). CVD included CAD, CVA, PAD, or aortic atherosclerosis. CAD risk factors included: hypertension, hyperlipidemia, CKD, LVH, tobacco use, family history of early CAD, and age > 60. CVE was defined as hospitalization or death from MI or coronary revascularization, CHF, atrial fibrillation, ventricular arrhythmia, cardiac arrest, and stroke. **Results:** Among 576 LT recipients, 37.5% were female, mean age at LT 57 $\pm$ 10 years, 92.0% White. Primary indication for LT was MASH 29.9%, and alcohol 24.0%. Before LT, average BMI was 30 $\pm$ 6, tobacco use 51%, hypertension 46.5%, diabetes 36.5%, hyperlipidemia 22.1%, CAD 13.9%, CHF 7.1% and atrial fibrillation 5.0%. Pre-LT CAD risk groups included 7.3% low risk, 16.5% intermediate risk, 60.5% high risk, and 15.7% very high risk. By the end of 2024, 156 (27.1%) LT recipients had at least one CVE with 17 CV deaths. Most frequent CVEs were atrial fibrillation 10.2%, CHF 8.2%, cardiac arrest 5.6% and MI 5.4%. Incidence of CVE was 7.3% in low CAD risk, 19.4% intermediate risk, 29.2% high risk, and 39.3% very high risk. Compared to low CAD risk, CVE odds ratio in intermediate risk was 3.0 (95% CI 0.84, 10.97), high risk 5.23 (95% CI 1.58, 17.35), very high risk 8.21 (95% CI 2.35, 28.66). There was no significant difference in post-LT CV deaths between pre-LT CAD risk groups. **Conclusion:** Although most LT recipients were classified as high CAD risk pre-LT, the incidence of CVE was relatively low post-LT. Increasing pre-LT CAD risk was associated with significantly higher odds of post-LT CVE. Future studies should examine the impact of pre-LT CV interventions for high CAD risk on post-LT outcomes.

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3599 | PATIENTS TRANSPLANTED FOR METALD CIRRHOSIS HAVE RATES OF METABOLIC DISORDERS POST-TRANSPLANT THAT ARE INTERMEDIATE BETWEEN MASLD AND ALCOHOL CIRRHOSIS

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Background: Metabolic complications are common after liver transplantation (LT) and negatively affect outcomes. While post-transplant metabolic disorders are well-described in patients with MASLD, data are more limited for MetALD. We characterized and compared metabolic disorders pre-LT and post-LT among patients with MASLD, ALD, and MetALD. **Methods:** This retrospective study evaluated patients at a single center who underwent LT from 1/12-1/22 with cirrhosis related to MASLD, ALD, or MetALD according to recent criteria (Rinella ME et al., Hepatology 2023). HTN was defined by use of antihypertensive medication or elevated measurements, hyperlipidemia by statin use or abnormal lipid profile, obesity as BMI >30, and DM as HbA1c $>6.5\%$ or treatment with insulin or oral medications.

Results: 295 patients were included: ALD (n = 61), MASLD (n = 121), and MetALD (n = 113). Prior to LT, the MASLD group was older and had a higher percentage of female sex than the other two groups (all $p < 0.05$). In pairwise comparisons of pre-LT variables, the MASLD group had a higher rate of DM ($p < 0.05$) but similar rates of obesity, HTN, and hyperlipidemia compared to the MetALD group . The MetALD group had higher rates of obesity, DM, and HTN compared to ALD group (all $p < 0.05$), and a similar rate of hyperlipidemia. The rate of ascites, which affects BMI pre-LT was similar among groups. At 1-year post-LT, there were differences among groups in BMI, obesity, DM, HTN, and hyperlipidemia (Table). There was no difference in major cardiac events. Pairwise comparisons showed that at 1-yr post-LT, BMI, obesity, DM, HTN, and hyperlipidemia were more frequent in the MASLD group than in the MetALD group and more frequent in the MetAld group than in the ALD group (all $p < 0.05$). **Conclusion:** Metabolic disorders were more frequent in MetALD patients compared to those with ALD, but less common in MetALD compared to MASLD at 1-year post-LT. These findings emphasize the importance of early identification and management of metabolic risk factors in MetALD patients post-LT.

Characteristic	ALD (N = 61)	MASLD (N = 121)	MetALD (N = 113)	P-value
Age at Transplant (Mean ± SD)	52.55 (10.36)(n=59)	61.33 (8.20)(n=121)	56.60 (10.05)(n=113)	<0.001
Sex				<0.001
Female	21.43% (12/56)	46.61% (55/118)	22.32% (25/112)	
Male	78.57% (44/56)	53.39% (63/118)	77.68% (87/112)	
BMI at Transplant (Median, range)	26.33 (15.79, 41.50) (n=58)	32.16 (10.13, 52.00) (n=118)	30.48 (20.28, 52.97) (n=110)	<0.001
Metabolic Complications at 1 Year Post-Transplant				
BMI (Median, range)	26.68 (15.55, 35.95)(n=52)	31.11 (19.91, 49.30)(n=109)	29.40 (16.68, 51.41)(n=103)	<0.001
Obesity (BMI >30)	23.08% (12/52)	59.63% (65/109)	45.63% (47/103)	<0.001
Diabetes Mellitus	8.93% (5/56)	44.07% (52/118)	23.21% (26/112)	<0.001
Hypertension	12.50% (7/56)	75.42% (89/118)	39.29% (44/112)	<0.001
Hyperlipidemia	22.45% (11/49)	59.63% (65/109)	42.42% (42/99)	<0.001

Disclosures: Mohammed Abourahma: Nothing to Disclose, Dinkar Ahuja: Nothing to Disclose, Ryan Meader: Nothing to Disclose, Irena Helenowski: Nothing to Disclose, Puja Brahmbhatt: Nothing to Disclose, Kartik Devgan: Nothing to Disclose, Michelle Lee: Nothing to Disclose, Emma Schnittka: Nothing to Disclose, Jonah Rubin: Nothing to Disclose, Steven Scaglione: Nothing to Disclose, Natasha Von Roenn: Nothing to Disclose, Eric Kallwitz: Nothing to Disclose, Scott Cotler: Nothing to Disclose

3600 | IMPACT OF PRE-TRANSPLANT TREATMENTS MODALITIES ON TRANSPLANTABLE HCC AGGRESSIVENESS

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Background: Milan criteria are robust and widely used to select patients for liver transplantation (LT) as they are strongly associated to pejorative histopathological (HP) features in hepatocellular carcinoma (HCC). Pre-transplant treatment may be needed to control cancer in the setting of organ shortage and it has shown to impact survival. The goal of this study was to evaluate whether treatments modalities impact the correlation between static morphological parameters and signs of aggressiveness of HCC. **Methods:** A retrospective monocentric series of 400 consecutive patients undergoing liver transplantation between Jan 2007 and Mar 2025 were included. The presence of vascular invasion (VI), poor differentiation (PD) and microsatellites (MS) was retrieved from the histopathological report. Only the viable tumors were considered to assess Milan status. Chi-2 test was used to correlate the presence of VI, PD and MS to Milan status on the explant in the whole population and in groups of patients according to number of preLT treatment line (< 3 or > 3), type of treatment (surgery, local ablation, radiotherapy, locoregional treatment) and timing of treatment (pre- or post-listing). Recurrence-free survival was calculated from the time of transplant to the first radiological examination showing sign of recurrence. **Results:** In the whole cohort, 93 patients (23%) were out of Milan on the explant. Pejorative HP parameters were identified in 116 patients (29%) (VI in 50 (13%), PD in 59 (15%) and MS in 31 (8%)). There was a significant correlation between all 3 pejorative HP parameters and Milan status in the whole population ($p < 0.0001$). However, in the 53 patients needing more than 3 treatments (13%), Milan status was no more correlated to VI ($p = 0.189$), PS ($p = 0.567$) and MS ($p = 0.099$). In the 140 patients undergoing local ablation (35%), there was no correlation between Milan status and presence of VI or MS ($p = 0.443$ and 0.056). The correlation between Milan status and pejorative HP parameters was significant in patients treated before listing ($p < 0.0001$) but not if treated after listing ($p = 0.128$). Patients having more than 3 treatments had a significantly shorter time to recurrence ($p = 0.001$). Interestingly, the 32 patients within Milan needing more than 3 treatments had a comparable survival to the patients out of Milan ($p = 0.655$). **Conclusion:** Multiple treatments may be necessary to control HCC before transplant but they may induce an increased risk of pejorative histopathological features independently from the morphological criteria usually considered for selection. **Disclosures:** Francois Faitot: Nothing to Disclose, Pietro Addeo: Nothing to Disclose, Camille Besch: Nothing to Disclose, Chloe Paul: Nothing to Disclose, Thierry Artzner: Nothing to Disclose, Baptiste Michard: Nothing to Disclose, Philippe Bachellier: Nothing to Disclose

3602 | LIVER GRAFT CHARACTERISTICS OF LOW-MELD (6-9) VERSUS HIGH-MELD (35+) RECIPIENTS: INSIGHTS FROM THE UNOS DATABASE

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Background: Waitlist mortality for MELD6-9 ("low-MELD") candidates is lower than for high MELD recipients (35+). Despite this, a significant proportion of LT occurs in patients with MELD6-9. Whether MELD 6-9 candidates may be receiving marginal quality livers compared to MELD35+ candidates ("high-MELD"), and whether this translates into poorer post-transplant outcomes is unknown. **Methods:** We analyzed 34,327 adults who underwent LT from a deceased donor between 2014-2024 from the UNOS database, along with potential organ offers from the Potential Transplant Recipient (PTR) database. The primary exposure was MELD < 9 compared to MELD35+ at the time of LT. MELD 20-24 recipients were also included for reference. Primary outcome was a composite of graft failure and death. We examined LT organ offers and acceptance decisions by differential MELD categories, specifically the donor risk index (DRI) and primary refusal codes. We generated Kaplan Meier curves for post-transplant survival and Cox models using discrete time-interval MELD categories. **Results:** Deceased donor characteristics varied by MELD category by age, (45 [MELD 6-9] vs 44 [MELD 20-24] vs 36 [MELD 35+]), DCD (21% vs 19% vs 2%), diabetes (17% vs 15% vs 8%), hypertension (40% vs 40% vs 26%), cold ischemic time (6.7 vs 5.7 vs 6.1 hours), and donor risk index (DRI, 2.3 vs 2.2 vs 1.8). Organs transplanted in MELD35+ were allocated on 3rd offer (median), versus 26th offer in MELD < 9 and 13th offer in MELD20-24. For organs transplanted into low-MELD, common refusal codes were donor age/quality, donor age, and unacceptable organ-specific test results. Late curve separation was seen in 5-year graft survival for MELD < 9 and MELD35+ (Figure), suggesting later worse survival in MELD < 9 recipients. In adjusted Cox regressions, higher DRI was associated with an increased hazard of graft failure (aHR1.24, 95%CI 1.14-1.34). Averaged over 5 years, compared with MELD35+, MELD < 9 did not show a differential hazard for graft failure (aHR0.95, 95CI 0.82-1.11. Compared with MELD35+, MELD < 9 had a lower hazard of graft failure in the first year (aHR0.71, 95%CI 0.60-0.85), and a higher hazard of graft failure between years 1-5 (aHR1.42, 95%CI 1.14-1.76). **Conclusion:** Low-MELD recipients are ultimately transplanted with deceased donors

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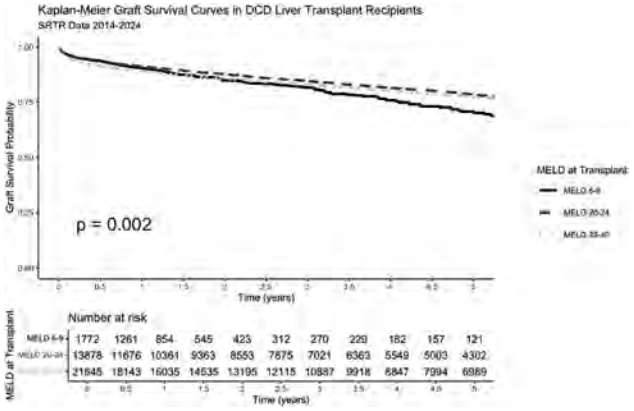
with greater median numbers of prior offer declines, higher DRI, and higher donor comorbidity burden. This evidence suggests that poorer outcomes in low-MELD patients may be driven by donor quality.



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3603 | COMORBIDITIES AND SURVIVAL IN LIVER TRANSPLANT RECIPIENTS

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Background: Pre-liver transplant (LT) comorbidities significantly influence post-transplant outcomes, yet their cumulative impact on survival and graft function remains understudied. This study evaluates how the burden of pre-LT comorbidities correlates with mortality and graft failure in LT recipients. **Methods:** Data from LT adult recipients at a large tertiary center in the Middle East, were analyzed, focusing on diabetes mellitus, hypertension, obesity, renal impairment, and coronary artery disease (CAD). The aim of the study is to assess how comorbidities pre-LT affect post-LT survival. Statistical analysis was done using Cox proportional hazards regression for survival outcomes, chi-square tests for categorical comparisons, and multivariable models adjusted for age, sex, MELD-Na score, and HCC status. **Results:** A total of 745 adult LT were analyzed. Mean age at LT was 56 and 267 female patients constituted 37.1% of the cohort. Pre-LT comorbidities were prevalent: DM (46.9%), HTN (33.5%), obesity (33.5%), renal impairment (5.0%), and CAD (17.9%). While increasing comorbidity burden (1–4 conditions) showed no linear mortality risk (listed in table.1). However, specific comorbidities independently predicted outcomes. Heart failure conferred the highest mortality risk (HR 7.78, 95% CI 4.81–12.5, $p < 0.001$), followed by MELD-Na ≥ 30 (HR 2.01, CI 1.21–3.34, $p = 0.007$). DM, HTN, obesity, and personal history of CAD showed no significant associations (listed in table. 2). Sepsis caused 61.9% of deaths, disproportionately affecting recipients with metabolic comorbidities. **Conclusion:** Multimorbidity alone does not linearly predict post-LT mortality, but specific conditions—particularly heart failure and high MELD-Na—significantly elevate risk. These findings underscore the necessity of pre-transplant optimization of cardiovascular health and rigorous sepsis prevention in metabolically compromised recipients. Future studies should explore targeted interventions to mitigate risks associated with high-acuity comorbidities.

Table 1: Comorbidity Burden and Mortality

Number of comorbidities	Odd ratio (95% CI)	p-value
1	0.71(0.40-1.25)	0.238
2	0.81 (0.44– 1.47)	0.500
3	0.89 (0.48– 1.65)	0.717
4	0.22 (0.02– 1.67)	0.144

Table 2: Estimated Mortality Risk of Pre-LT Comorbidities

Comorbidity	Adjusted Hazard Ratio (HR)	95% CI	p-value
Personal CAD	1.04	0.58–1.88	0.88
Heart Failure	7.78	4.81-12.5	0.000
Diabetes Mellitus (DM)	0.75	0.46–1.21	0.24
Chronic Renal Impairment	1.72	0.79–3.79	0.17
Hypertension (HTN)	1.09	.66–1.79	0.72
Obesity	0.90	0.57–1.42	0.66
MELD-Na ≥30	2.01	1.21–3.34	0.007

Disclosures: Lama Amer: Nothing to Disclose, Bandar Aljudaibi: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Dimitri Raptis: Nothing to Disclose, Ehab Abu-Farhaneh: Nothing to Disclose, Manhal Izzy: Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Dieter Broering: Nothing to Disclose, Tahir Mohamed: Nothing to Disclose, Maryam Abdulla:

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3604 | INFECTIONS IN THE IMMEDIATE POST-LIVER TRANSPLANT PERIOD: INCIDENCE, MICROBIAL PROFILE, AND IMPACT ON EARLY MORTALITY

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Background: Liver transplantation is the definitive treatment for end-stage liver disease, hepatocellular carcinoma, and acute liver failure. Despite advancements in surgical techniques, immunosuppressive regimens, and perioperative care, the immediate post-transplant period remains a high-risk window for infectious complications. These infections significantly impact graft function, morbidity, and early mortality. This study aimed to evaluate the incidence, microbiological spectrum, infection sites, and the effect of early infections on 30-day mortality in liver transplant recipients **Methods:** We retrospectively analyzed 312 liver transplant recipients at our center. Patients who developed infections within 30 days post-transplant were included. These patients were stratified based on survival status at 30 days. Demographic data, microbial etiology, site of infection, presence of multidrug-resistant (MDR) organisms, preoperative infections, episodes of rejection, and reexploration rates were compared between survivors and non-survivors.
Results: Among 312 patients, 87.1% underwent living donor liver transplantation and 12.9% received grafts from deceased donors. Three patients underwent retransplantation. The overall 30-day mortality was 8.7%, with intracerebral hemorrhage, graft dysfunction, and infections being the primary causes. Infections were identified in 92 patients (29.5%) within 30 days post-transplant, including 12 with pre-existing infections. Bacterial infections predominated (93.5%), with *Klebsiella* spp. (43.5%) being the most frequent, followed by *E. coli* (16.3%). Fungal and viral infections accounted for 12% and 3.3% of cases, respectively. Bloodstream infections were most common (52.2%), followed by pulmonary and urinary tract infections (29.3% each). Notably, 31.5% of patients had infections involving multiple sites. MDR organisms were isolated in 50% of cases. Bloodstream infections, pulmonary involvement, multi-site infections, and fungal etiologies were significantly associated with non-survivors. The infection-related mortality rate within 30 days was 18.5%. **Conclusion:** Infections during the immediate post-liver transplant period are predominantly bacterial, with bloodstream infections being the most frequent and severe. The presence of MDR organisms and fungal infections significantly increases the risk of mortality. Despite advances in transplantation care, early infections remain a critical determinant of post-transplant outcomes and warrant robust preventive and management strategies.

Table 3 Comparison of survivors vs Non survivors having infections

	Survivors (%)	Non survivors (%)	p value
Number	75	17	
LDLT	70 (93.3)	15 (88.2)	.609
Blood stream infection	35 (46.7)	13 (76.5)	.033
Ascitic/Peritoneal infection	17 (22.7)	5 (29.4)	.543
Chest infection	15 (20)	12 (70.6)	<.005
Urine infection	26 (34.7)	1 (5.9)	.019
MDR	36 (48)	10 (58.8)	.592
Polymicrobial	17 (22.7)	6 (35.3)	.353
More than 1 site of infection	18 (24)	11 (64.7)	.003
Bacterial	71 (94.7)	15 (88.2)	.306
viral	1 (1.3)	2 (11.8)	.087
Fungal	5 (6.7)	6 (35.3)	.004
Rejection	12 (16)	2 (11.8)	1.00
Bile leak	57 (76)	16 (94.1)	.181
Peritonitis	12 (16)	0 (0)	.114
Pre op infection	10 (13.3)	2 (11.8)	1.0
Length of stay (days)	74	17	.010
Re-exploration	22 (29.3)	2 (11.8)	.221

Disclosures: Radhika Nittala: Nothing to Disclose, Fathimathu Zahra: Nothing to Disclose, Mohamed Fawas: Nothing to Disclose, Sudheer Mohammed: Nothing to Disclose, Biju Chandran: Nothing to Disclose, Mathew Jacob: Nothing to Disclose, Charles Panackel: Nothing to Disclose

3605 | THE AI AGENT IN THE ROOM: INFORMING OBJECTIVE DECISION MAKING AT THE TRANSPLANT SELECTION COMMITTEE

Bima Hasjim[1] Ghazal Azafar[2] Frank Lee[3] Tayyab Diwan[3] Shilpa Raju[2] Jed Gross[2] Aman Sidhu[2] Hirohito Ichii[1] Rahul Krishnan[2] Muhammad Mamdani[2] Divya Sharma[4] Mamatha Bhat[5], [1]University of California, Irvine, [2]University of Toronto, [3]Mayo Clinic, [4]York University, [5]Toronto General Hospital

Background: Transplantation is one of the few areas in medicine where the definitive treatment is rationed. Subjective decision-making pose challenges towards the transplant selection process. Large language

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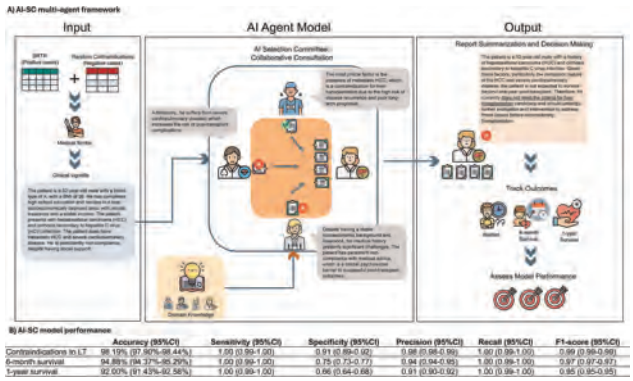
models (LLMs) through autonomous artificial intelligent (AI) agents have exciting implications in objective decision-making to solve complex problems, but there are gaps in the literature regarding its clinical applications. Thus, we examined the performance of a multidisciplinary selection committee of AI agents (AI-SC) in the liver transplant (LT) candidate selection process as a proof-of-concept towards objective decision-making. **Methods:** This was a hybrid cohort study of adult ($\geq$18-years-old) LT candidates between 2004-2023 from the Scientific Registry of Transplant Recipients (SRTR) database. The AI-SC consisted of four LLMs: transplant hepatologist, transplant surgeon, cardiologist, social worker, and medical scribe (Figure A). Patients receiving LT were retrospectively analyzed and, because the SRTR only contains patients who were already placed on the LT waitlist, a hypothetical cohort of patients with standard absolute contraindications to LT were generated to simulate cases of patients who would have been rejected from the waitlist. The AI-SC was tasked with classifying each patient as a valid transplant candidate if they 1) had no contraindication to LT, 2) were predicted to benefit from LT with $\geq$6-month survival or 3) $\geq$1-year survival. The temperature was set to a standard of 0.7 and variables $>$20% missingness were excluded to mitigate hallucinations. Cosine similarity index analysis identified the most prevalent variables used by each AI agent of the AI-SC in their decision making. **Results:** Of 8,412 patients, 83.6% were waitlisted and 16.4% had contraindications to LT. In this cohort, the 6-month and 1-year mortality rate was 4.0% and 7.5%, respectively. The AI-SC was able to accurately identify contraindications to LT (accuracy: 98.2%, 95%CI 97.9%-98.4%), and predict 6-month (94.9%, 95%CI 94.4%-95.3%) and 1-year (92.0%, 95%CI 91.4%-92.6%) survival (Figure B). Malignancy was the most common cause of death prior to 6-month (21.7%) or 1-year (28.5%) end points (false positive cases). The most common reason for rejection in false negative cases were tumors outside of the Milan Criteria (53.8% contraindications to LT; 53.8% 6-month survival; 60.9% 1-year survival). Each AI agent used different variables in their decision making and report generation, but indication for LT and recipient age were among the top 5 most important variables used by all members of the AI-SC. **Conclusion:** AI agents can be leveraged to simulate the LT-SC meetings and provide accurate, objective insights on patients who may or may not benefit from LT. Lessons learned from this study are a provocative step towards making the LT selection process more equitable and objective.



	Accuracy (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	Precision (95%CI)	Recall (95%CI)	F1-score (95%CI)
Contraindications to LT	98.17% (97.90%-98.44%)	1.00 (0.99-1.00)	0.91 (0.89-0.92)	0.88 (0.86-0.89)	1.00 (0.99-1.00)	0.99 (0.99-0.99)
6-month survival	94.88% (94.37%-95.29%)	1.00 (0.99-1.00)	0.75 (0.73-0.77)	0.94 (0.94-0.95)	1.00 (0.99-1.00)	0.97 (0.97-0.97)
1-year survival	92.00% (91.43%-92.56%)	1.00 (0.99-1.00)	0.86 (0.84-0.88)	0.91 (0.90-0.92)	1.00 (0.99-1.00)	0.95 (0.95-0.95)

Disclosures: Bima Hasjim: Nothing to Disclose, Ghazal Azafar: Nothing to Disclose, Frank Lee: Nothing to Disclose, Tayyab Diwan: Nothing to Disclose, Shilpa Raju: Nothing to Disclose, Jed Gross: Nothing to Disclose, Aman Sidhu: Nothing to Disclose, Hirohito Ichii: Nothing to Disclose, Rahul Krishnan: Nothing to Disclose, Muhammad Mamdani: Nothing to Disclose, Divya Sharma: Nothing to Disclose, Mamatha Bhat: Transplant Genomics: Grant/Research Support, Novo Nordisk: Grant/Research Support, Roche: Grant/Research Support, Natera: Grant/Research Support, Oncoustics: Grant/Research Support, Paladin: Grant/Research Support, Astra Zeneca: Consultant, Merck: Grant/Research Support

3606 | ASSOCIATION BETWEEN RECIPIENT/DONOR CHARACTERISTICS AND LIVER STIFFNESS MEASUREMENT IN THE FIRST YEAR POST-LIVER TRANSPLANTATION

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Background: Liver stiffness measurement (LSM) is widely used in the management of long-term liver transplantation (LT) recipients to non-invasively evaluate graft function. However, its clinical application in the early period post-LT needs further investigations. Our primary aim was to evaluate the relationship between LSM trend during the first 12 months post-LT and recipient/donor features at LT. **Methods:** This is a single centre retrospective study enrolling consecutive patients undergoing LT between 2015 and 2023. Deceased LT recipients within 6 months as well as those undergoing re-LT or without LSM were

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excluded. LSM was performed at 6 and 12 months by vibration-controlled transient elastography (Fibroscan, Echosens, Paris). We investigated the association between LSM > 8 kPa, defining presumptive graft damage, and donor/recipients features at LT. Chi-square and Student T-test were used to analyse categorical and continuous variables, respectively.
Results: 326 LT recipients were enrolled, median age 58 (18-72) years, 73% males.The major etiologies of liver diseases were viral hepatitis (54%) followed by Met-ALD (29%), immune-mediated (10%) and others (7%); 55% were transplanted for HCC, 8% of grafts were DCD and 100% of recipients undergone a CNI-based immunosuppressive regimen. Median LSM was 6.6 (2.5-30.5) kPa with 87 patients (27%) showing LSM > 8 kPa at 6 months and 6.1 (range 2.5-24.1, p = 0.02) kPa with 65 patients (20%) with LSM > 8 kPa at 12 months. By univariate analysis, among all the LT baseline features, including type of grafts (deceased cardiac donor, deceased brain donor, whole or split livers), donor (age, sex, body mass index, BMI) and recipients characteristics (aetiology, MELD, BMI, diabetes), only donor age was associated with LSM > 8 kPa both at 6 and 12 months (6-month OR = 1.04, 95%CI 1.02-1.05, p < 0.01; 12-month OR = 1.03, 95%CI 1.01- 1.06, p < 0.01). **Conclusion:** Our findings indicate that baseline recipient and graft characteristics do not significantly influence early trends in liver stiffness measurement (LSM) during the first year after liver transplantation, apart from donor age. These results suggest that the early increase in LSM observed in grafts from older donors is consistent with the well-established negative impact of advanced donor age on graft outcomes.
Disclosures: Clara Dibenedetto: Nothing to Disclose, Enrico Sguazzini: Nothing to Disclose, Michele Sagasta: Nothing to Disclose, Lucio Caccamo: Nothing to Disclose, Barbara Antonelli: Nothing to Disclose, Maria Francesca Donato: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose

3607 | LONG-TERM OUTCOMES AFTER LIVER TRANSPLANTATION OF PATIENTS WITH HEPATITIS D VIRUS INFECTION IN A VERY HIGH-VOLUME TRANSPLANT CENTER

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Background: Although there are few studies reporting outcomes of patients with hepatitis D virus (HDV) infection after liver transplantation (1, 2), data on the long-term outcomes of patients with HDV recurrence are quite limited.
Methods: A total of 182 patients who underwent liver transplantation due to HDV in our center were retrospectively analyzed in terms of age, gender, transplantation type, pre-transplantation HBeAg, HBV-DNA, HDV-RNA, MELD-Na score, presence of hepatocellular carcinoma (HCC), antiviral treatment, post-transplantation HBsAg, Anti-HBs, HDV-RNA, HBV-DNA levels, survival, HCC, HBV and HDV recurrence, antiviral treatment, HBIG dose and duration, and follow-up duration. HDV-RNA positivity after transplantation was considered as HDV recurrence (HDVr). Factors that influence HDV recurrence were analyzed. Kolmogorov-Smirnov test, Fisher's Exact test, Mann-Whitney U tests were used where appropiate. Cumulative survival of patients with and without HDV recurrence was estimated by the The Kaplan-Meier method and compared with the log-rank test. P < 0.05 was accepted as significant . **Results:** A total of 12 patients had HDV recurrence, while 170 patients did not have HDV recurrence. Median follow-up was 85.00 (4-151) months in the HDVr group and 74.00 (6-196) months in the non-HDVr group. Median time to HDV recurrence was 12.00 (2-53) months. The 1, 3, 5, and 10-year survival rates were 91.6%, 83.3%, 83.3%, and 75%, and 98.2%, 93.5%, 91.1%, and 87.6% in patients with and without HDV recurrence, respectively (p < 0.001 by the Kaplan Meier method). In the HDVr group, one patient (8.3%) developed acute rejection. Post-transplant liver biopsy disclosed hepatitis in 3 patients and rejection in 1 patient in the HDVr group. The causes of mortality in the 4 patients with HDVr were sepsis in 2 patients, unknown cause at an external center in 1 patient, and one patient died during the big Türkiye earthquake in 2023. Pre-transplant HBV-DNA, post-transplant nucleos(t)ide analog (NA) use, hepatitis B immunoglobulin (HBIG) administration duration and dose significantly affected HDV recurrence (Table 1). **Conclusion:** Survival rates of patients with HDVr after transplantation were lower than those without recurrence but mortality etiologies make it unlikely to blame HDVr-induced liver disease for the shorter survival. HDVr was not associated with more severe liver disease. Inappropriate use of NAs and HBIG may affect HDV recurrence.
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Table 1. Analysis of factors affecting HDV recurrence.

Variable	B	SE	p	Hazard ratio	95% CI Lower	95% CI Upper
Gender	-0.069	0.212	0.747	0.934	0.616	1.415
Age	0.006	0.01	0.535	1.006	0.987	1.025
Transplantation type	-0.042	0.376	0.912	0.959	0.459	2.004
Pre-transplant HCC	0.405	0.229	0.077	1.5	0.957	2.35
Pre-transplant HDV-RNA	0.0	0.0	0.101	1.0	1.0	1.0
Pre-transplant HBV-DNA	0.0	0.0	<.001	1.0	1.0	1.0
Pre-transplant HBeAg	0.129	0.313	0.68	1.138	0.616	2.102
Pre-transplant Anti-HBs	0.031	0.034	0.352	1.032	0.966	1.102
Post-transplant Antiviral TAF	6.064	1.8	<.001	430.276	12.623	14666.771
Post-transplant Antiviral TDF	5.116	1.837	0.005	166.688	4.552	6103.861
Post-transplant Antiviral ETV	5.903	1.823	0.001	366.018	10.284	13026.722
Post-transplant Antiviral LAM	2.969	2.358	0.125	19.299	0.441	843.854
HBIG duration (months)	0.031	0.015	0.039	1.031	1.002	1.061
Total HBIG dose	0.0	0.0	<.001	1.0	1.0	1.0
12th month HBsAg	0.001	0.0	<.001	1.001	1.0	1.001
12th month Anti-HBs	0.001	0.001	0.866	1.0	0.998	1.002

B: regression coefficient (B), SE:standard error, CI : Confidence Interval HCC: Hepatocellular carcinoma, TAF: Tenofovir Alafenamide, TDF: tenofovir disoproxil fumarate, ETV: entecavir, LAM: Lamivudine, HBIG: Hepatitis B immunoglobuline.

Disclosures: Muhammed Furkan Keser: Nothing to Disclose, Muhsin Murat Muhip Harputluoglu: Nothing to Disclose, Cihan Yurdaydin: Nothing to Disclose, Sezai Yilmaz: Nothing to Disclose

3608 | SEPSIS AS A LEADING CAUSE OF MORTALITY IN LIVER TRANSPLANT RECIPIENTS: A SINGLE-CENTER EXPERIENCE

abdullah alfhaid[1] Saleh Alqahtani[2] Maryam Abdulla[3] Waleed Haj Ahmad[4] Syeda Shamsi[4] Ahmad Alissa[5] Reem Alameer[3] Bandar Aljudaibi[3], [1]King Faisal Specialists Hospital and Reseach Centre, [2]Johns Hopkins University, [3]KIng Faisal Specialists Hospital and Research Centre, [4]Alfaisal Univeristy, [5]Alfaisal University

Background: Sepsis remains one of the most critical complications following liver transplantation (LT), frequently leading to mortality despite advances in surgical techniques and perioperative care. Its true burden and contributory factors remain undercharacterized in contemporary liver transplant cohorts. This study aims to evaluate the prevalence of sepsis-related mortality in liver transplant recipients and explore potential associations with metabolic and clinical risk factors. **Methods:** We conducted a retrospective analysis of 745 adult liver transplant recipients at a high-volume tertiary transplant center between January 2020 and December 2024. Sepsis was diagnosed based on physician documentation corroborated by clinical and microbiological evidence. Patients had a median age of 56.9 years, and 62.9% were male. Common comorbidities included diabetes (46.9%), hypertension (33.5%), obesity (33.5%), dyslipidemia (19.9%), and fatty liver disease (35.7%). MELD-Na scores were distributed as follows: ≤ 20 (49.8%), 21–29 (38.7%), and ≥ 30 (11.5%). Hepatocellular carcinoma (HCC) was present in 24.8% of recipients. Regarding transplant type, 114 patients (15.3%) received deceased donor liver transplants, while 631 (84.7%) received living donor liver transplants. Statistical analyses were conducted using Cox regression and Kaplan-Meier survival models to identify mortality predictors and sepsis-related trends. **Results:** Of 97 total deaths during the study period, 60 (61.9%) were attributed to sepsis, often accompanied by multisystem organ failure (41.2%). Despite their high prevalence, metabolic comorbidities—including diabetes, hypertension, obesity, and dyslipidemia—were not significantly associated with mortality. Additionally, a higher burden of comorbidities (ranging from 1 to 4) did not show a linear correlation with sepsis-related deaths. Post-LT dialysis was required in 8.6% of cases but was not an independent predictor of poor outcomes. The overall cohort survival rate was 86.9%. Importantly, a MELD-Na score ≥ 30 was significantly associated with increased mortality (HR 2.01, 95% CI 1.21–3.34, $p = 0.007$). **Conclusion:** Sepsis is the predominant cause of mortality among liver transplant recipients in our cohort, often presenting alongside multisystem organ failure. While metabolic comorbidities and dialysis were frequently observed, they did not independently predict mortality, indicating that further research is needed into immune response or microbiome-related risk profiles. Our findings underscore the importance of early recognition, standardized infection prevention measures, and risk stratification tools in improving post-LT outcomes. Future multicenter prospective studies should refine sepsis definitions and evaluate

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short-term mortality indicators to guide better clinical decision-making

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3609 | SHOULD HBA1C LEVELS IMPACT CANDIDACY FOR LIVER TRANSPLANTATION? EVALUATING HBA1C CUTOFFS ON POST-LT OUTCOMES

Taylor Seacor[1] Garrick Gu[1] Charanpreet Sasan[1] Anita Krishnarao[2], [1]University of Massachusetts Chan Medical School, [2]Umass Memorial Medical Center

Background: Hemoglobin A1C (HbA1C) is a frequently used seromarker of glycemic control with implications for post-surgical outcomes. The validity of HbA1C remains unclear in patients with chronic liver disease, however, due to high erythrocyte turnover and splenic sequestration which may impact the accuracy and predictive value of HbA1C on outcomes after liver transplantation (LT). HbA1C levels are only variably incorporated into an assessment of LT candidacy at many centers since particular HbA1C cutoffs have not been established in regards to their potential impact on post-LT outcomes. We therefore sought to assess if there are specific HbA1C values above which post-LT outcomes are impacted including mortality, graft rejection, and hospital readmission. **Methods:** We collected data from a global de-identified database (TriNetX) and identified 9018 patients with an HbA1C recorded within 3 months prior to LT. Patients were stratified into cohorts based on a pre-LT HbA1C of $\leq 6.5\%$ or pre-LT HbA1C of $> 6.5\%$. Propensity score matching was used to control for etiology of cirrhosis, BMI, and prior exposure to GLP-1 agonists. Rates of mortality, graft rejection, and hospital readmission rates at 1 year following LT were assessed. Similar analyses were performed using an HbA1C cutoff of 8% as well as 10% with assessment of outcomes at 1 year. **Results:** When comparing the HbA1C of $> 6.5\%$ cohort to the HbA1C of $\leq 6.5\%$ cohort, no difference in mortality was noted at 1 year post-LT ([OR]: 1.08, $P = 0.23$). Similarly, there was no mortality difference noted using HbA1C cutoff values of $> 8\%$ or $> 10\%$. Comparing the HbA1C of $> 6.5\%$ cohort to the HbA1C of $\leq 6.5\%$ cohort, rates of graft rejection were lower in the HbA1C of $> 6.5\%$ cohort at 1 year post-LT ([OR]: 0.75, $P = 0.01$). No significant difference in graft rejection rates was observed using HbA1C cutoff values of $> 8\%$ or $> 10\%$. Comparing the HbA1C of $> 6.5\%$ cohort to the HbA1C of $\leq 6.5\%$ cohort, rates of hospital readmissions were reduced in the HbA1C of $> 6.5\%$ cohort 1 year post-LT ([OR]: 0.94, $P = 0.03$). This difference in hospital readmissions did not persist when stratifying cohorts by HbA1C cutoff values of $> 8\%$ or $> 10\%$. **Conclusion:** When comparing cohorts with pre-LT HbA1C cutoffs of above or below 6.5%, 8% and 10%; there were no demonstrated differences in mortality rates at 1 year after LT. Graft rejection and hospital readmission rates were marginally reduced in the HbA1C of $> 6.5\%$ cohort vs HbA1C of $\leq 6.5\%$ cohort at 1 year, an effect that may represent some degree of advantage from glycemic reserve in the immediate post-LT period. Patients with HbA1C values of $> 8\%$ or $> 10\%$ in the pre-LT period, however, did not have increased rates of rejection or readmission. HbA1C levels in pre-LT period therefore appear to have minimal impact on post-LT outcomes even at values suggestive of poor glycemic control. This data may be useful when attempting to utilize pre-LT HbA1C values to assess post-LT risk as part of LT candidate selection.

Disclosures: Taylor Seacor: Nothing to Disclose, Garrick Gu: Nothing to Disclose, Charanpreet Sasan: Nothing to Disclose, Anita Krishnarao: Nothing to Disclose

3610 | SAFETY AND FEASIBILITY OF IMMUNOTHERAPY POST LIVER TRANSPLANTATION– PROSPECTIVE MULTICENTERED STUDY OF A STANDARDIZED CLINICAL PRACTICE PROTOCOL

Kymberly Watt[1] Saurav Panda[1] Valeria Pierluissi Ruiz[1] Amanda Tapia[1] David Chaska[1] Hassan Azhari[2], [1]Mayo Clinic, [2]Memorial Sloan-Kettering Cancer Center

Background: Immune checkpoint-inhibitors (ICI) have improved cancer prognosis significantly, but their use has been avoided in liver transplant (LTr) recipients due to poorly characterized rejection risk based on sub-optimal data including case reports/series with highly variable immunosuppression approaches and followup that do not account for the learning curve. **Methods:** A standardized institutional clinical practice protocol was developed in 2021 and followed for LTr

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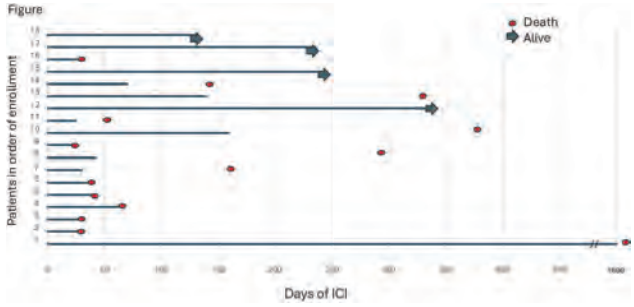
immunosuppression management to fascilitate ICI therapy. Careful discussion of rejection risk was performed with every patient. Patients were followed with routine interval protocol lab testing including immunosuppression levels. Retrospective analysis of data was performed. **Results:** Of 18 LTr, 10 (56%) were male, 89% were white with a mean age 52.8(SD11.1) years. 11/18 had 3 or more failed cancer therapies before ICI. HCC (n = 5), lung (N = 3) and melanoma (N = 3) were the most common cancers treated.Time from first infusion to death was < 30days (N = 4), 30-60 days (N = 3), 61-90 days(N = 1), > 91 days(N = 6).All deaths were cancer related, reflecting the late stage of disease before ICI usage. ICI related toxicity occurred in 3 LTr; pneumonitis (N = 1,5.6%), myocariditis (N = 1,5.6%) and acute cellular rejection (N = 1,5.6%). This rejection related to inadequate everolimus level 3 weeks after first infusion. This patient experienced cholestatic allograft dysfunction and melanoma progression off ICI resulting in death 5 months after ICI due to sepsis in the setting of metastatic melanoma. Four patients continue on ICI thus far 131-236 days with stable allograft function and slow reduction in immunosuppression. 3/4 have partial cancer response and 1 with slowed progression of disease. **Conclusion:** ICI treatment in the immunosuppressed LTr is feasible with careful immunosuppression management and structured followup.Rejection occurred in 5.6%, a much lower rate than early uncontrolled experiences suggest. Patients were initially referred far too late in their disease to have benefitted from the ICI. With positive experience, patients are receiving ICI earlier in their treatment course and are experiencing treatment response. Demonstrating safety/feasibility should allow for earlier utilization of these agents, with a better impact on cancer prognosis. Optimizing rejection risk with cancer response requires ongoing study.



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3611 | APPLICATION OF NEW STEATOTIC LIVER DISEASE NOMENCLATURE TO LIVER TRANSPLANT RECIPIENTS

Nicole Lulkin[1] Madison Nguyen[2] Alexis Kim[3] Rehan Razzaq[4] Vaishali Patel[2] Amon Asgharpour[5] Idris Yakubu[2] Anh Bui[2] Mohammad Siddiqui[2], [1]Virginia Commonwealth University School of Medicine, [2]VCUHS, [3]Virginia Commonwealth University Health System, [4]VCU Health System, [5]Virginia Commonwealth University

Background: Steatotic liver disease (SLD) has been widely adopted, and multiple studies have demonstrated its performance in the general population. The recognition of metabolic and alcohol-related liver disease (MetALD) has resulted in enhanced characterization of a phenotype that was previously overlooked. There is currently no data on application of SLD nomenclature to liver transplant (LT) recipients. Compared to the general population, the burden from metabolic diseases is considerably higher in LT recipients. Moreover, with an increasing number of transplants being performed for alcoholic liver disease (ALD) with higher risk of alcohol recidivism, it is important to understand how well the new nomenclature performs in LT recipients. **Methods:** We conducted a retrospective cohort study involving adult LT recipients who had quantification of liver fat via controlled attenuation parameter (CAP). Patients were classified into five groups: No SLD, metabolic-associated steatotic liver disease (MASLD), MetALD, ALD, and SLD not otherwise specified. Demographic, clinical, laboratory,

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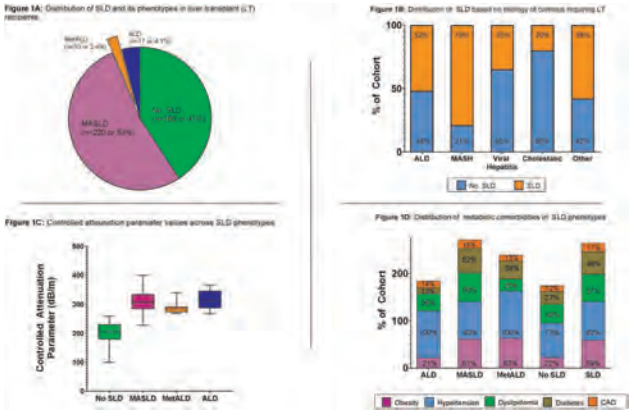
and vibration controlled transient elastography (VCTE) variables were extracted from medical records. Alcohol use was quantified via patient history and phosphatidylethanol. **Results:** SLD was present in 247 (59%) patients (Fig. 1A). Patients transplanted for MASH cirrhosis were most likely to develop SLD post LT (Fig. 1B). Most patients with SLD had MASLD (n = 220), however, ALD and MetALD was present in 4.1% (n = 17) and 2.4% (n = 10) of LT recipients. Males and Caucasians were more likely to develop SLD. The severity of hepatic steatosis as measured by CAP was higher among patients with MASLD and ALD (Fig. 1C). Among patients transplanted for alcohol cirrhosis, 42% consumed some alcohol (15% severe, 10% moderate), however, only 28% of patients consuming any alcohol had SLD. Expectedly, the burden from metabolic comorbidities was considerably higher among patients who developed MASLD compared to MetALD and ALD (Fig. 1D). Biochemically, the serum aminotransferases (ALT, AST) were higher among patients with ALD and MetALD when compared to MASLD ($p < 0.01$ and $p = 0.035$, respectively), however, no differences in alkaline phosphatase, and bilirubin were noted. Patients with MASLD (GFR 77.5) and MetALD (73.0) had lower renal function ALD (88.0) and no SLD (82.0). **Conclusion:** The present study provides initial data with application of the novel SLD nomenclature to LT recipients with distinct clinical phenotypes. Additional studies are needed to link these phenotypes to clinical outcomes.



Disclosures: Nicole Lulkin: Nothing to Disclose, Madison Nguyen: Nothing to Disclose, Alexis Kim: Nothing to Disclose, Rehan Razzaq: Nothing to Disclose, Vaishali Patel: Nothing to Disclose, Amon Asgharpour: Galectin: Clinical Endpoint Committee, NovoNordisk: Advisor, Madrigal: Advisor, Chronic Liver Disease Foundation: Speaking and Teaching, Intercept: Consultant, Idris Yakubu: Nothing to Disclose, Anh Bui: Nothing to Disclose, Mohammad Siddiqui: NovoNordisk: Grant/Research Support, NovoNordisk: Grant/Research Support, NovoNordisk: Grant/Research Support, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Sagimet: DSMB, NovoNordisk: Grant/Research Support, NovoNordisk: Grant/Research Support, NovoNordisk: Grant/Research Support, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Sagimet: DSMB, NovoNordisk: Grant/Research Support, NovoNordisk: Grant/Research Support, NovoNordisk: Grant/Research Support, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Sagimet: DSMB

3612 | SLEEVE GASTRECTOMY IN LIVER TRANSPLANT RECIPIENTS IS SAFE AND EFFECTIVE: A PAIRED ANALYSIS

Jacob Bornstein[1] Tyler Lunow-Luke[2] Amy Shui[1] Garrett Roll[1] Andrew Posselt[1], [1]University of California, San Francisco, [2]University of California, Irvine

Background: Liver transplant recipients are at an increased risk of obesity due to post-transplant metabolic changes, and this in turn can increase the risk of allograft dysfunction and long-term graft deterioration. Laparoscopic sleeve gastrectomy (LSG) is an effective treatment for patients with obesity refractory to lifestyle and pharmacologic interventions, but many centers remain hesitant to perform LSG in liver transplant recipients due to perceived additional risk. This retrospective one-group pretest-posttest design study evaluates the safety and efficacy of LSG in severely obese patients who had previously undergone a liver transplant (LT). **Methods:** Medical records of 21 LT recipients who underwent LSG at our institution were evaluated for BMI, DM, and HTN at baseline (pre-LSG), 1-year [n = 20], and 5-year [n = 9] post-LSG. Paired t-tests were used to compare BMI, and Exact McNemar tests and Cohen's kappa coefficient were used to assess changes in DM and HTN prevalence. **Results:** Mean BMI reduction at 1-year post-LSG was 10.4 kg/m² (SD 4.2; $p < 0.001$) and was maintained (10.0 kg/m² (SD 5.0; $p < 0.001$) at the latest available time point. DM prevalence showed modest decreases at 1 year (57% [12/21] vs. 48% [10/21], $p = 0.50$) and at last follow-up (57% vs. 43% [9/21], $p = 0.25$). HTN status remained unchanged at both time points ($p > 0.99$). Kappa

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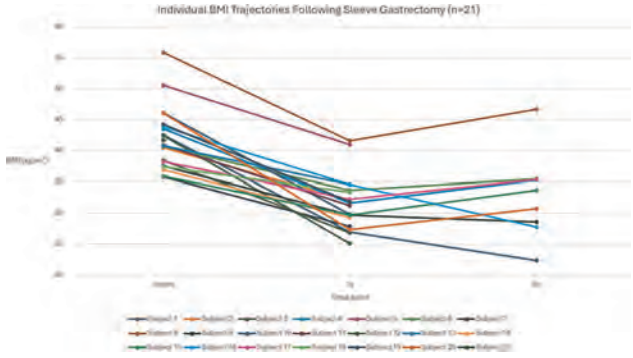
coefficients indicated moderate to substantial agreement in DM and HTN classifications pre- and post-LSG. Within 5 years post-LSG, the only complication attributable to LSG was a subclinical anastomotic leak in one patient, which was successfully treated with endoscopy and dietary modification. There were no other complications directly attributable to LSG. **Conclusion:** LSG in LT recipients resulted in substantial BMI reduction and was not associated with significantly increased complications. While DM or HTN status did not show significant improvements during the study period, their prevalence and severity did not increase over time, as is often seen in post-LT patients. These findings support LSG as a safe and effective weight-loss option in LT recipients, though continued monitoring of metabolic outcomes is warranted.



Disclosures: Jacob Bornstein: Nothing to Disclose, Tyler Lunow-Luke: Nothing to Disclose, Amy Shui: Nothing to Disclose, Garrett Roll: Nothing to Disclose, Andrew Posselt: Nothing to Disclose

3613 | IMPACT OF NON-VARICEAL UPPER GASTROINTESTINAL BLEEDING ON OUTCOMES AFTER LIVER TRANSPLANTATION

umesh bhagat[1] ankit agrawal[1] mohamed abdelbaky[2] Faris Hamad[1] archana kharel[1] prabhat kumar[3] shalini tripathi[1] luisa recinos[4], [1]Cleveland clinic, [2]Presbyterian Hospital, [3]Virginia Commonwealth university, [4]Saint peters university hospital

Background: Liver transplant (LT) is the only curative treatment for end-stage liver disease. Bleeding is a postoperative complication and a leading cause of morbidity and mortality post-LT. Although postoperative bleeding has been described in several clinical situations, data regarding non-variceal upper gastrointestinal bleeding (NVUGIB) after 30 days are lacking. We aim to assess the incidence and adverse events of NVUGIB diagnosed 30 days post-LT. **Methods:** National Readmission Database (NRD) 2016-2021 was queried to identify LT patients. Patients readmitted after 30 days were divided into two cohorts with and without new onset NVUGIB. The primary outcome was all-cause mortality. Secondary outcomes included adverse events, ICU stay and respiratory failure. Statistical analysis was performed using StataCorp. 2021. **Results:** Of 40,871 patients discharged post-LT, 12,227 were readmitted after 30 days, of which 392 had NVUGIB (3.2%). Patients with NVUGIB had higher odds of mortality (aOR 7.10, 95% CI: 3.35–15.06, p $<$0.001), vasopressor use (aOR 3.97, 95% CI: 1.96–8.04, p $<$ 0.001) ICU stay (aOR 3.80, 95% CI: 2.49–5.79, p $<$ 0.01) and respiratory failure (aOR 2.61, 95% CI: 1.67–4.10, p $<$ 0.001). **Conclusion:** Non-variceal upper gastrointestinal bleeding in liver transplant recipients is associated with significant morbidity and mortality, highlighting the importance of early identification, targeted prophylaxis, and multidisciplinary management to improve post-transplant outcomes

	Odds ratio	95% conf.- interval	P
Mortality	7.10	3.35- 15.06	0.000
Vasopressor use	3.97	1.96- 8.04	0.000
ICU stay	3.80	2.49- 5.79	0.000
arf	2.61	1.67- 4.10	0.000

Disclosures: umesh bhagat: Nothing to Disclose, ankit agrawal: Nothing to Disclose, mohamed abdelbaky: Nothing to Disclose, Faris Hamad: Nothing to Disclose, archana kharel: Nothing to Disclose, prabhat kumar: Nothing to Disclose, shalini tripathi: Nothing to Disclose, luisa recinos: Nothing to Disclose

3614 | EVALUATING THE PREDICTIVE ABILITY OF FIB-4 FOR IDENTIFYING FIBROSIS IN POST-LIVER TRANSPLANT ALCOHOL ASSOCIATED LIVER DISEASE

Adam Khalaf[1] Alessandra Martorella[1] Manotri Chaubal[2] Sungyoung Auh[3] Amol Rangnekar[1] Christine Hsu[3], [1]MedStar Georgetown University Hospital, [2]Georgetown University, [3]National Institutes of Health

Background: Return to alcohol use (AR) after liver transplantation (LT) contributes to progressive liver injury, and up to 54% develop cirrhosis within 10 years. Despite relapse rates nearing 25%

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within 3-5 years post-LT, no standardized fibrosis surveillance strategies for post-LT patients currently exist. Liver biopsy remains the gold standard but is invasive. Noninvasive scores such as the Fibrosis-4 (FIB-4) index is commonly used in pre-LT populations, but its validity in post-LT patients needs further elucidation. We aim to evaluate the accuracy of FIB-4 in patients undergoing liver biopsy after LT. **Methods:** We conducted a single-center retrospective cohort study of 76 adult LT recipients transplanted for alcohol associated liver disease (ALD) from 2015 to 2022. All patients underwent for-cause liver biopsy and had laboratory data available at the time of biopsy, 30 ± 15 days and 90 ± 15 days before biopsy. Demographic, metabolic, and histologic data were collected. The primary outcome was biopsy-confirmed fibrosis. Outcomes included significant fibrosis (F2-F4) and advanced fibrosis/cirrhosis (F3-F4). Optimized cutoffs of FIB-4 were obtained by using Youden's J statistic. Also, we evaluated published cutoff values of 1.5 or 2.67. Diagnostic performance was assessed using area under the curve (AUC) with 95% confidence intervals, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). **Results:** A total of 76 adult post–LT patients transplanted for alcoholic liver disease underwent for-cause liver biopsies. In this cohort, 12 (16%) had F2–F4 fibrosis, 58% of which occurred within two years post-LT. AR was documented in 34.7% of the cohort (Table 1). Most patients were male (75%) and Caucasian (75%). When assessing FIB-4 at time of biopsy, 30, and 90 days prior, FIB-4 at 30 days prior best predicted F3–F4 fibrosis with the highest AUC of 0.649 (95% CI, 0.282–0.996) using an optimized cutoff of 4.14. This threshold yielded a sensitivity of 75%, specificity of 59.7%, NPV of 97.7%, and PPV of 9.4%. In contrast, published cutoffs (2.67 for F3–F4, 1.5 for F2–F4) had poor AUCs (0.52–0.54). However, FIB-4 ≥ 1.5 at time of biopsy was highly specific (89.3%) for predicting F2–F4 fibrosis, while FIB-4 ≥ 2.67 at time of biopsy and 30 days prior was highly specific for predicting F3–F4 fibrosis (96.1% and 97.1%, respectively). **Conclusion:** Currently, fibrosis surveillance post-LT is not standardized and varies across centers. FIB-4 in this study showed high specificity for F2–F4 and F3–F4 fibrosis at cutoffs of 1.5 and 2.67, respectively, but limited predictive accuracy. An optimized threshold of 4.14 improved performance for identifying F3–F4 fibrosis (AUC 0.65). This suggests that if FIB-4 > 1.5, then it should warrant further evaluation with transient elastography or biopsy. Our study suggests that fibrosis may occur rapidly post-LT, as the majority of patients developed F2-F4 fibrosis within 2 years of LT.

Category	Characteristic	Number (% of Total)
Demographics	Age (Mean ± SD in years)	50.6 ± 11.2
Sex	Male	57 (75.0%)
	Female	19 (25.0%)
Race	White	56 (73.7%)
	Black	8 (10.5%)
	Hispanic	9 (11.8%)
	Asian	1 (1.3%)
	Other	2 (2.6%)
Metabolic Comorbidities	Obesity (BMI ≥ 30)	26 (34.2%)
	Hypertension	45 (59.2%)
	Diabetes	17 (22.4%)
	Hyperlipidemia	16 (21.1%)
Liver Biopsy Findings	Steatohepatitis on Biopsy	11 (14.5%)
	Steatosis on Biopsy	22 (28.9%)
	Rejection on Biopsy	23 (30.3%)
Fibrosis Stage (METAVIR)	F0	43 (56.6%)
	F1	21 (27.6%)
	F2	8 (10.5%)
	F3	3 (3.9%)
	F4	1 (1.3%)
Return to Drinking	Alcohol Relapse	26 (34.2%)
Timing	Years from Transplant to Biopsy (Mean ± SD)	1.06 ± 1.08

Table 1: Characteristics of adult post-LT patients with ALD

Disclosures: Adam Khalaf: Nothing to Disclose, Alessandra Martorella: Nothing to Disclose, Manotri Chaubal: Nothing to Disclose, Sungyoung Auh: Nothing to Disclose, Amol Rangnekar: Nothing to Disclose, Christine Hsu: Nothing to Disclose

3615 | INTENT-TO-TREAT ANALYSIS OF LIVER TRANSPLANT (LIVING DONOR VS DECEASED DONOR) FOR HEPATOCELLULAR CARCINOMA IN THE UNITED STATES

Madeleine Wong[1] Hiroshi Sogawa[2] David Samson[3], [1]Stony Brook University Hospital, [2]Yale School of Medicine/Yale New Haven Hospital, [3]Westchester Medical Center

Background: Liver transplant is a key treatment for locoregional hepatocellular carcinoma (HCC) with

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cirrhosis. However, organ shortage and prolonged waitlist times serve as fatal barriers to deceased donor liver transplant (DDLT). Living donor liver transplant (LDLT) offers reduced waiting times, fewer waitlist dropouts, and liberalized transplant eligibility. While studies attempting to compare survival outcomes and HCC recurrence between LDLT and DDLT show mixed results, a few have used intention-to-treat (ITT) analysis for a more accurate comparison. We aim to conduct a nationwide ITT analysis of survival outcome between LDLT and DDLT for HCC in the United States. **Methods:** Clinicopathological and demographic data for HCC patients who underwent LT between 1985-2017 were retrospectively collected from the SRTR database. Two cohorts were formed: an ITT cohort (patients who were waitlisted/recipient for a DDLT vs. LDLT recipients) and a post-transplant cohort (recipients of DDLT vs. LDLT). Propensity score models using multivariable logistic regression were applied with LDLT as the dependent variable. The absolute standardized mean difference (ASMD) score quantified differences in each variable. Overlap weighting derived from the propensity scores was used to control confounding factors and achieve balance between both groups. Via Kaplan-Meier curves and median survival estimates, we analyzed survival outcomes between the waitlist/DDLT and LDLT groups in both cohorts. Hazard ratios from cox regression were also calculated. Between-group differences in median waitlist time was assessed using the Mann-Whitney U Test. **Results:** A total of 26,930 patients were identified from the SRTR database during the study period (262 LDLT and 26,668 DDLT). Prior to overlap weighting, LDLT patients were more likely to be female, aged $\geq$ 50 years, Asian, Black, on government insurance, have a BMI $\geq$ 30kg/sqm, had moderate encephalopathy, a history of portal vein thrombosis, MELD scores $\geq$ 20, and have abnormal bilirubin/creatinine levels. After the application of overlap weighting, the two donor type groups were remarkably well-balanced except for the presence of moderate encephalopathy or alpha fetoprotein values $\geq$ 20 ng/mL. In the ITT-cohort, LDLT had significantly higher survival of 11.35 years compared to the Waitlist/DDLT group of 8.28 years ($P < 0.000$). The median waitlist time of 6.1 months in the waitlist/DDLT group was significantly higher than the LDLT group with 5.2 months ($P < 0.005$). In the non-ITT analysis of overall survival, the DDLT group had medial survival of 10.94 years, but was still lower than the LDLT group of 11.04 years, although these findings were not significant ($P = 0.82$). **Conclusion:** LDLT patient survival was significantly better than DDLT patient survival for HCC in an ITT basis in the United States. This may be associated with significantly improved waitlist times in the LDLT group compared to the DDLT group.

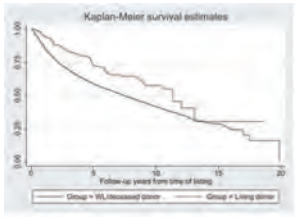

Figure 1A. Kaplan-Meier intention-to-treat survival functions for waiting list/deceased donor liver transplant vs living donor liver transplant, without overlap weighting

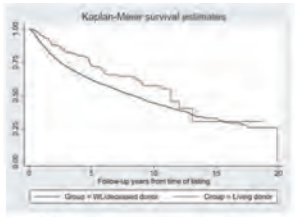

Figure 1B. Kaplan-Meier intention-to-treat survival functions for waiting list/deceased donor liver transplant vs living donor liver transplant, with overlap weighting

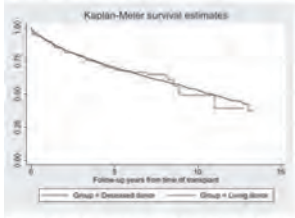

Figure 2A. Kaplan-Meier post-transplant survival functions for waiting list/deceased donor liver transplant vs living donor liver transplant, without overlap weighting

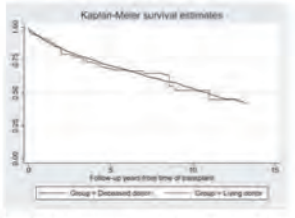

Figure 2B. Kaplan-Meier post-transplant survival functions for waiting list/deceased donor liver transplant vs living donor liver transplant, with overlap weighting

Disclosures: Madeleine Wong: Nothing to Disclose, Hiroshi Sogawa: Nothing to Disclose, David Samson: Nothing to Disclose

3616 | PROGNOSTIC IMPACT OF COMBINED DIASTOLIC AND SYSTOLIC DYSFUNCTION WITH GLOBAL LONGITUDINAL STRAIN ON OUTCOMES IN LIVER TRANSPLANT RECIPIENTS

Ebehiwele Ebhohon[1] David Lee[2] Muhammad Hammami[1] Haytham Allaham[1] Zulqarnain Khan[1] Youngjae Cha[1] Adaobi Ahanotu[1] sabtain saroya[3] Michael Chang[1] Trent Johnson[1] Nathalie Urrunaga[4], [1]University of Maryland Medical Center, [2]University of Maryland School of Medicine, [3]Howard University School of Medicine, [4]University of Maryland, Baltimore

Background: Diastolic dysfunction, systolic dysfunction, and global longitudinal strain (GLS) abnormalities—have been identified as significant factors influencing patient outcomes. This study evaluates the composite impact of these three markers of cardiac dysfunction on liver transplant outcomes, focusing on mortality, inpatient rehabilitation needs, and overall hospital course in a cohort of patients from the University of Maryland Medical Center (2016–2018). **Methods:** The study cohort consisted of 274 liver transplant recipients with a mean age of 53.9 years, predominantly male (63.1%) and white (70.8%). Cardiac assessment revealed that systolic dysfunction was present in 24.8% of patients, diastolic dysfunction in varying grades in 27.4%, and the mean GLS value was -19.2 $\pm$ 3.71. Significant cardiac history, including coronary artery disease and atrial fibrillation, was noted

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in 13.5% of patients. Outcomes were analyzed using a composite endpoint derived from these three measures, adjusted for age, sex, race, and BMI. **Results:** Post-transplant outcomes demonstrated that the composite cardiac endpoint significantly increased the likelihood of inpatient rehabilitation admission (HR: 2.13, 95% CI: 1.23–3.69, p = 0.007) (Table 2). Although trends towards extended ICU and total hospital stays were observed, these did not reach statistical significance. Mortality rates were unaffected by the composite cardiac endpoint (HR: 0.48, 95% CI: 0.16–1.47, p = 0.197)(Table2). **Conclusion:** These findings emphasize the nuanced role of cardiac dysfunction in influencing functional recovery and resource utilization post-liver transplant, highlighting the need for comprehensive pre-transplant cardiac evaluation and optimization in liver transplant candidates.

Table 2 Association between presence of Left and Right Diastolic Dysfunction[&] and Post-transplant Outcomes

	HR	95% CI	p-value
PTBS with Stent placed	1.30	0.63, 2.66	0.478
MACE	1.34	0.58, 3.10	0.495
ICU LOS	1.67	0.83, 3.40	0.153
Total Inpatient LOS	1.48	0.94, 2.34	0.092
Rehab Admission	**2.13**	**1.23, 3.69**	**0.007**
Mortality	0.48	0.16, 1.47	0.197

*Adjusted for Age at liver transplant, Sex, Race, and BMI
[&] combines the exposures for the diastolic dysfunction (any criteria), systolic dysfunction, and GLS cutoff criteria to create a composite endpoint
HR: Hazard Ratio, CI: Confidence Interval, LOS: length of Stay. Significant at *p < 0.05

Disclosures: Ebehiwele Ebhohon: Nothing to Disclose, David Lee: Nothing to Disclose, Muhammad Hammami: Nothing to Disclose, Haytham Allaham: Nothing to Disclose, Zulqarnain Khan: Nothing to Disclose, Youngjae Cha: Nothing to Disclose, Adaobi Ahanotu: Nothing to Disclose, sabtain saroya: Nothing to Disclose, Michael Chang: Nothing to Disclose, Trent Johnson: Nothing to Disclose, Nathalie Urrunaga: Nothing to Disclose

3617 | MELD-NA SCORE STRATIFICATION AND POST-LIVER TRANSPLANT OUTCOMES

Ahmad Alissa[1] Waleed Haj Ahmad[2] Maryam Abdulla[2] Saleh Alqahtani[3] Manhal Izzy[4] Syeda Shamsi[1] Bandar Aljudaibi[5], [1]Alfaisal Univeristy, [2]Alfailsal Univeristy, [3]Johns Hopkins University, [4]Vanderbilt University Medical Center, [5]King Faisal Specialists Hospital and Reseach Centre

Background: The Model for End-Stage Liver Disease-Sodium (MELD-Na) score is pivotal for liver transplant (LT) prioritization, yet its prognostic utility for post-LT complications remains incompletely defined. This study evaluates associations between MELD-Na stratification and post-LT survival, graft failure, and morbidity. **Methods:** Among 745 LT recipients, MELD-Na scores were categorized as ≤20 (49.8%), 21–29 (38.7%), and ≥30 (11.5%). Patients with acute liver failure and were non-cirrhotic were excluded from the analysis Outcomes included all-cause mortality, graft failure, sepsis, and cardiac events. **Results:** Higher MELD-Na scores correlated with increased mortality (MELD-Na ≥30: 13.0% vs. ≤20: 11.5%, *p* < 0.01) and graft failure (13.7% vs. 12.4%, *p* = 0.02). Sepsis was the leading cause of death (44/97 deaths, 45.4%), with a trend toward higher sepsis-related mortality in MELD-Na ≥30 (68.2% vs. ≤20: 58.1%, *p* = 0.04). Cardiac events (myocardial infarction: 2.6%, cardiac death: 1.6%) did not differ across MELD-Na groups. Lower MELD-Na (≤20) was associated with superior 1-year survival (89.2% vs. 76.7% in ≥30, *p* < 0.001). Renal impairment (GFR ≤60: 22.4%) was more prevalent in MELD-Na ≥30 (34.9% vs. ≤20: 18.1%, *p* = 0.01). **Conclusion:** MELD-Na ≥30 predicts higher mortality and sepsis risk, underscoring the need for tailored post-LT management in high-score recipients

Disclosures: Ahmad Alissa: Nothing to Disclose, Waleed Haj Ahmad: Nothing to Disclose, Maryam Abdulla: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Manhal Izzy: Mallinckrodt: Speaking and Teaching, Madrigal: Advisor, Syeda Shamsi: Nothing to Disclose, Bandar Aljudaibi: Nothing to Disclose

3618 | IMPACT OF GRAFT REJECTION AND BILIARY COMPLICATIONS ON LIVER STIFFNESS MEASUREMENTS DURING THE FIRST YEAR AFTER LIVER TRANSPLANTATION

Michele Sagasta[1] Clara Dibenedetto[1] Enrico Sguazzini[1] Lucio Caccamo[1] Barbara Antonelli[1] Maria Francesca Donato[1] Pietro Lampertico[1], [1]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Background: Liver stiffness measurement (LSM) is a simple, non-invasive tool for long-term graft monitoring after liver transplantation (LT). The early post-LT period is often complicated by events that may impact LSM values, but this relationship has not been clearly studied. We aimed to evaluate the association between early (<12 months) post-LT complications and LSM changes. **Methods:** This single-center retrospective study included all consecutive LT recipients from 2015 to 2023. Patients who died within 6 months, underwent re-LT, or lacked LSM at 6 (T1) or 12 (T2) months were excluded. LSM was assessed by vibration-controlled transient elastography (Fibroscan®, Echosens, Paris). LSM >8 kPa was considered indicative of presumed graft damage. All rejection episodes were biopsy-proven. Categorical and continuous variables were analyzed using chi-square and t-test, respectively. **Results:** A total of 326 recipients were included (median age 58 years, range 18–72), 73% male. Pre-LT liver diseases included viral hepatitis (54%), Met-ALD (29%), immune-mediated (10%), and other etiologies (7%). LT was performed for HCC in 55% and for decompensated cirrhosis in 38% of patients.

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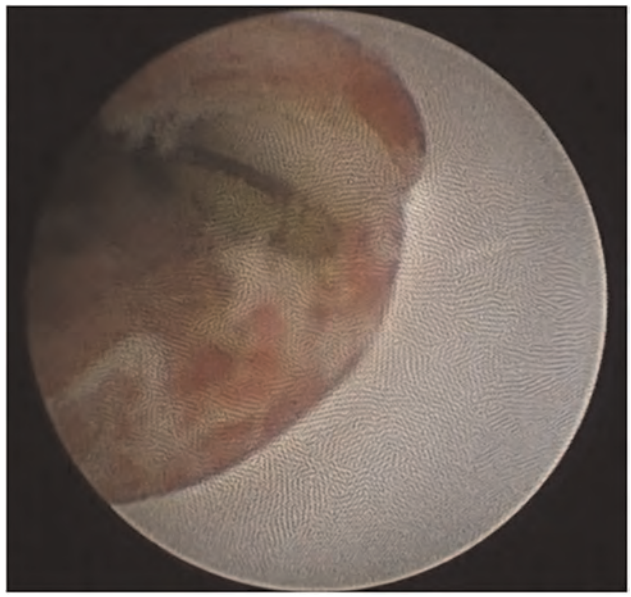
All received calcineurin inhibitor-based immunosuppression. Median LSM was 6.6 kPa at T1 and 6.1 kPa at T2 ($p = 0.02$). LSM > 8 kPa occurred in 27% at T1 and 20% at T2. Rejection was reported in 22% at T1 and 3% at T2 while biliary complications in 17% and 9% and vascular complications in 12% and 1% at T1 and T2, respectively. CMV reactivation occurred in 27% exclusively within 6 months. The most common comorbidities were arterial hypertension (67%), steroid-induced diabetes (32%), and CKD grade > 3 (15%). At T1, LSM > 8 kPa was significantly associated only with graft rejection (37% vs 17%, $p < 0.01$). At T2, elevated LSM was significantly linked to biliary complications (15% vs 7%, $p = 0.03$) and CKD (25% vs 13%, $p = 0.02$). **Conclusion:** Elevated LSM during the first 6 months post-LT is mainly associated with graft rejection, while LSM increases observed in the second semester are more often linked to biliary complications and CKD. These findings support incorporating LSM into early post-LT monitoring to aid in the detection of graft-related complications.

Disclosures: Michele Sagasta: Nothing to Disclose, Clara Dibenedetto: Nothing to Disclose, Enrico Sguazzini: Nothing to Disclose, Lucio Caccamo: Nothing to Disclose, Barbara Antonelli: Nothing to Disclose, Maria Francesca Donato: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose

3619 | DIRECT PERCUTANEOUS TRANSHEPATIC CHOLANGIOSCOPY VISUALIZATION FOR SAFE AND RADIATION-FREE REMOVAL OF BILIARY FOREIGN BODY: A MIGRATED NON-ABSORBABLE HEMOSTATIC CLIP

Tianhao Chen[1] Rongxing Zhou[1] Jingyi Zhang[1] Jie Zhang[1] Rui Chen[1], [1]West China Hospital of Sichuan University

Background: Clip migration is a rare but increasingly recognized complication following laparoscopic cholecystectomy (LC), which can lead to biliary obstruction and secondary stone formation. While endoscopic retrograde cholangiopancreatography (ERCP) is commonly used for foreign body extraction, its efficacy may be limited in cases where the object is firmly embedded. Percutaneous transhepatic cholangioscopy (PTCS) offers direct visualization and radiation-free access for biliary interventions. **Methods:** An 83-year-old man with a history of LC 6 years prior presented with right upper quadrant pain and recurrent fever. Imaging revealed a dilated common bile duct (CBD) with multiple stones. PTCS was performed via a percutaneous tract to facilitate stone removal. During the procedure, a foreign body resembling a "stubborn stone" was noted adherent to the upper CBD wall. After superficial stone removal, the object was identified as a non-absorbable hemostatic clip. A migrated clip may serve as a nidus for secondary common bile duct stone formationTo prevent ductal injury, two biopsy forceps were employed—one for stabilization and one for blunt dissection of surrounding tissue. **Results:** The embedded clip was successfully divided into three fragments and retrieved without damaging the bile duct. All residual stones were removed under direct cholangioscopic visualization. Final inspection confirmed an intact bile duct and no remaining foreign material. The reassembled fragments confirmed the complete retrieval of the hemostatic clip. The patient's postoperative recovery was uneventful, with no complications or discomfort reported. Removal of the underlying lesion may also help prevent recurrence of common bile duct stones. **Conclusion:** This case highlights the effectiveness and safety of PTCS in managing complex biliary foreign bodies, particularly those that are tightly adherent to the bile duct wall. Unlike ERCP, which may be limited by indirect visualization and anatomical constraints, PTCS offers direct endoscopic control, enabling precise dissection and foreign body retrieval without the use of fluoroscopy, thus avoiding radiation exposure for both patients and physicians. The identification of a migrated non-absorbable hemostatic clip as the nidus for stone formation underscores the importance of careful consideration regarding the use and placement of such clips during laparoscopic cholecystectomy. In conclusion, PTCS may be considered a valuable adjunct in the armamentarium for biliary interventions, particularly in managing complications related to surgical materials. Simultaneously, this case advocates for the judicious use of hemostatic clips and suggests further evaluation of absorbable alternatives or secure placement strategies to minimize the risk of migration and late biliary complications.



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Disclosures: Tianhao Chen: Nothing to Disclose, Rongxing Zhou: Nothing to Disclose, Jingyi Zhang: Nothing to Disclose, Jie Zhang: Nothing to Disclose, Rui Chen: Nothing to Disclose

◆ 3620 | NEXT GENERATION GENE THERAPY FOR WILSON'S DISEASE: CLINICAL SAFETY AND EFFICACY OF LY-M003, A COPPER-RESPONSIVE AAV GENE THERAPY VECTOR

Andrew Lin[1] chaohui yu[2] Yi Chen[2] Chao Lu[2] Zhe Shen[2] Jianyong Wang[2] Yixiong Chen[3] Tianqi Jiang[1] Yuzhe Peng[3] Rihong He[3] Chenming Lu[3] Guofang Yan[3] Jian Wang[3] Juan Chen[3], [1]Lingyi Biotech Co., Ltd, [2]The First Affiliated Hospital of Zhejiang University, School of Medicine, [3]Lingyi Biotech co., ltd.

Background: Wilson disease (WD) is a rare autosomal recessive metabolic disorder caused by mutations in the ATP7B gene, leading to deficient ATP7B activity and progressive copper accumulation in the liver, brain, and kidney. LY-M003, an investigational AAV8-based gene therapy product, is designed to restore copper metabolism by delivering a modified miniATP7BLY protein. LY-M003 utilizes the Copper Responsive Engineering of ATP7B Expression (CREATE™) platform, which dynamically regulates protein expression in response to hepatic copper levels. This novel approach aims to enhance both efficacy and safety in the treatment of Wilson disease. **Methods:** A clinical study (NCT06650319) is currently underway at the First Affiliated Hospital of Zhejiang University, China, to evaluate the safety and efficacy of a single intravenous infusion of LY-M003 in patients with WD. Stable treated WD patients are eligible for enrollment, with the option to continue SoC therapy post-administration until clinical improvements are observed. A prophylactic immune supression regimen is administered to all participants. The study's primary objectives are to assess the safety and efficacy of escalating doses of LY-M003. Participants will undergo a 52-week post-treatment evaluation, followed by a four-year long-term follow-up phase. **Results:** Since September 2024, seven participants have received LY-M003, demonstrating a favorable tolerability profile across all dosage cohorts. No anti-drug antibodies (ADA) against ATP7B were detected, and no serious adverse events (SAEs) were reported. Mild elevations in liver enzymes were observed in some participants but were effectively managed with immune modulation therapy. Key therapeutic outcomes include: • Hepatic Copper Transport Restoration: Most participants exhibited significantly increased ceruloplasmin levels, with peak values exceeding 50% of the normal range in one patient, indicating reestablished hepatic ATP7B function. • Reduction in Chelation Therapy Dependence: Five out of seven participants successfully discontinued chelation therapy(cut off Apr 2025) following normalized urinary copper levels. Neurological and Psychiatric Symptom Improvement: Participants experiencing neurological and psychiatric manifestations showed functional improvements within three months, as evidenced by reductions in UWDRS scores related to writing ability, language skills, and motor function. **Conclusion:** LY-M003 is an innovative AAV8-based gene therapy for Wilson disease, currently under clinical investigation. Early clinical data across different dosage groups indicate a strong safety profile and promising therapeutic efficacy, with benefits observed in both peripheral and neurological symptoms. These findings highlight LY-M003's potential to revolutionize Wilson disease treatment, paving the way for a transformative therapeutic paradigm.

Disclosures: Andrew Lin: Nothing to Disclose, chaohui yu: Nothing to Disclose, Yi Chen: Nothing to Disclose, Chao Lu: Nothing to Disclose, Zhe Shen: Nothing to Disclose, Jianyong Wang: Nothing to Disclose, Yixiong Chen: Nothing to Disclose, Tianqi Jiang: LINGYI BIOTECH: Employee, Yuzhe Peng: Nothing to Disclose, Rihong He: Nothing to Disclose, Chenming Lu: Nothing to Disclose, Guofang Yan: Nothing to Disclose, Jian Wang: Nothing to Disclose, Juan Chen: Nothing to Disclose

◆ 3621 | UX701 GENE THERAPY FOR WILSON DISEASE: RESULTS: FROM THE PHASE 1/2 PORTION OF CYPRUS^{2+}

Danny Bega[1] Jeff Bronstein[2] Hélder Cardoso[3] Russell Goodman[4] Sihoun Hahn[5] Paul Kwo[6] Craig Lammert[7] Valentina Medici[8] Andrew Muir[9] Nicole Davis[10] Serap Sankoh[10] Grace Wang[10] Andrew Grimm[10], [1]Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA, [3]Centro Hospitalar Universitário de São João, Alameda Prof. Hernâni Monteiro, 4200-319, Porto, Pt, [4]Massachusetts General Hospital, Boston, MA, USA, [5]Seattle Children's Hospital/Univ of Washington, [6]Stanford University Medical Center, [7]Indiana University Health, Indianapolis, IN, USA, [8]University of California Medical Center, [9]Duke University, [10]Ultragenyx Pharmaceutical, Inc.

Background: Wilson disease is a rare, progressive, genetic disorder of biliary copper (Cu) excretion due to pathogenic *ATP7B* variants. Hepatic manifestations can

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include hepatitis, acute liver failure, chronic liver disease, and cirrhosis. Current standard of care (SOC) of Cu chelators and zinc can be burdensome, and compliance is challenging. UX701 is an investigational AAV9 gene therapy (GT) designed to restore ATP7B function in patients with Wilson disease. **Methods:** Cyprus^{2+} (NCT04884815) is a global, seamless Phase 1/2/3 first-in-human study of UX701 in adults with Wilson disease. In Phase 1/2 Cyprus^{2+}, subjects enrolled in 3 groups: 5.0X10^{12}, 1.0X10^{13}, and 2.0X10^{13} genome copies/kg. After UX701 administration, subjects were followed for at least 52 weeks during Stage 1 of Cyprus^{2+}. Key outcomes were changes from baseline in biomarkers of Cu metabolism, tolerance to discontinuing SOC medications, Patient Global Impression of Change (PGIC), and safety outcomes. **Results:** Five subjects were enrolled in each dose group (15 total). ATP7B transgene presence and mRNA expression in hepatocytes were observed by in-situ hybridization and confirmed with immunohistochemistry at 52 weeks, showing new ATP7B expression on the apical surface of hepatocytes (Figure 1). Five of 15 (33%) subjects showed biomarker improvement (total serum Cu, Ceruloplasmin [Cp]-bound Cu, and Cp concentration and activity). Eight of 15 (53%) subjects tapered and ultimately discontinued SOC through present analysis (median [range]: 44.5 [7-120] weeks). Subjects reported reduced disease severity with 10/15 (67%) reporting PGIC of $\geq$+1 at Week 52, and 8/15 (53%) reporting $\geq$+2. Of those who discontinued SOC, 6/8 (75%) reported PGIC improvement, with 5/8 reporting scores $\geq$+2. No patient who discontinued SOC reported worsening PGIC.

Safety data were consistent with the expected profile of AAV gene therapy, including transient asymptomatic liver enzyme elevations during the first 4 months following UX701 administration, which were responsive to corticosteroids. **Conclusion:** Cyprus^{2+} is the first systematic evaluation of long-term hepatic transgene expression in subjects receiving gene therapy. Durable changes in Cu homeostasis were observed along with new ATP7B apical expression. Most were able to discontinue SOC medications.

Additional long-term data are expected, including biliary Cu excretion. A fourth cohort with a higher dose and optimized immunomodulation regimen will be presented.

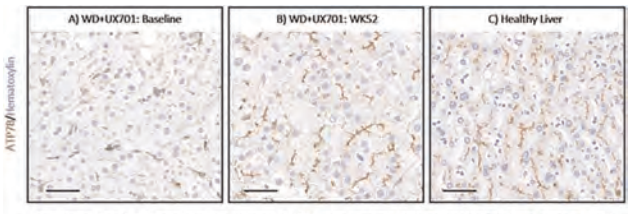

Figure legend: New ATP7B expression was observed at WK52 using immunohistochemistry staining of Liver biopsy with anti-ATP7B antibody. Representative images of ATP7B staining of A) baseline sample showed ATP7B+ Kupffer cells without apical surface staining of hepatocytes. B) the same subject showed new apical surface (canalicular membrane) staining of hepatocytes at WK52. C) a healthy control liver showed canalicular membrane staining of hepatocytes. Scale bars: 50μm

Disclosures: Danny Bega: Nothing to Disclose, Jeff Bronstein: Prime Medicine: Consultant, ARBORMED: Consultant, ETON: Consultant, Hélder Cardoso: Nothing to Disclose, Russell Goodman: Nothing to Disclose, Sihoun Hahn: Key Proteo: Stock – privately held company, Paul Kwo: Nothing to Disclose, Craig Lammert: Eli Lilly: Consultant, Kezar Life Sciences: Consultant, Amgen: Consultant, Autoimmune Hepatitis Association: Consultant, RegCell: Consultant, Valentina Medici: Orphalan: Advisor, Arbormed: Research Grant, Ultragenix: Research Grant, Alexion: Advisor, Vivet: Grant/Research Support, Eton Pharmaceuticals: Consultant, Mars Inc.: Advisor, Andrew Muir: Gilead: Grant/Research Support, Cymabay: Grant/Research Support, Ultragenyx: Grant/Research Support, Regcell: Consultant, Nicole Davis: Nothing to Disclose, Serap Sankoh: Nothing to Disclose, Grace Wang: Nothing to Disclose, Andrew Grimm: Nothing to Disclose

◆ 3622 | IN VIVO GENE EDITING THERAPY AS A TREATMENT FOR ALPHA-1 ANTITRYPSIN DEFICIENCY

Jeff An[1] Erin Spofford[2] Zsanett Jancso[2] April Hayes[2] Carol Cai[2] Guangde Li[2] Sudeepa Syamala[2] Tong Wu[2] Mugdha Bedekar[2] Sumanprava Giri[2] Sarah Ducat[2] Kenneth Ganley[2] Gulen Tonga[2] Tom Colace[2] Sherry He[2] Gang Sun[2] James Rottman[2] Anne Bothmer[2] Jane Wang[2] Cecilia Cotta-Ramusino[2] Michael Holmes[2] William Querbes[2], [1]Tessera Therapeutics, [2]Tessera Tx

Background: Alpha-1 antitrypsin deficiency (AATD) is an inherited autosomal recessive disorder that affects 1 in 2,000 to 3,500 newborns. It arises from mutations in the *SERPINA1* gene that encodes a serum protease inhibitor. Individuals homozygous for the E342K mutation (PI*ZZ genotype) account for 95% of AATD-related disease, leading to low serum AAT levels, accumulation of misfolded mutant Z-AAT protein, and clinical sequelae consistent with chronic obstructive pulmonary disease and liver disease. **Methods:** To develop a new class of therapy for AATD, we generated an RNA Gene Writer that is designed to correct the E342K mutation (PiZ allele) to wild- type in the *SERPINA1* gene. **Results:** LNP-RNA delivery of our RNA Gene Writers corrected this mutation in the NSG-PiZ mouse, a transgenic mouse model with ~20 copies of the mutation, where we precisely edited more than 90% of the hepatocytes, based on the assumption that 60% of liver cells are comprised of hepatocytes, after a single intravenous administration at 0.5 mg/kg. We also observed significant increases in serum AAT levels with no detectable circulating Z-AAT protein, restored neutrophil elastase inhibition, and reductions in protein aggregates in the liver with durable mutation correction and phenotypic rescue demonstrated for up to 10

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weeks post-treatment. Separately, we generated a humanized mouse model with only two PiZ alleles to better approximate the efficacy of our product in patients with the homozygous PiZZ genotype. LNP-RNA delivery of our RNA Gene Writers achieved an estimated 82% correction of hepatocytes after a single low dose (0.1 mg/kg treatment in this mouse model). Finally, we evaluated RNA Gene Writer in cynomolgus macaques and showed that a single dose of 1.5 mg/kg LNP-RNA achieved an average of 76% editing of hepatocytes. Genomic assessments from treated NHPs showed LNP delivery of the RNA Gene Writers displayed high specificity of editing to the liver with only spleen showing quantifiable levels of editing above background (0.14%) among 30 additional tissues and biofluids tested. Importantly, editing was not detected in germline tissues, including testes and ovaries. Editing was also highly specific to the intended SERPINA1 locus, with no off-target activity detected by rhAmpSeq at other genetic loci. **Conclusion:** In summary, we demonstrated that our LNP formulated RNA Gene Writers efficiently edited the *SERPINA1* gene responsible for AATD in the liver of mice and NHP with a single administration at therapeutically relevant doses.

Disclosures: Jeff An: Nothing to Disclose, Erin Spofford: Nothing to Disclose, Zsanett Jancso: Nothing to Disclose, April Hayes: Nothing to Disclose, Carol Cai: Nothing to Disclose, Guangde Li: Nothing to Disclose, Sudeepa Syamala: Nothing to Disclose, Tong Wu: Nothing to Disclose, Mugdha Bedekar: Nothing to Disclose, Sumanprava Giri: Nothing to Disclose, Sarah Ducat: Nothing to Disclose, Kenneth Ganley: Nothing to Disclose, Gulen Tonga: Nothing to Disclose, Tom Colace: Nothing to Disclose, Sherry He: Nothing to Disclose, Gang Sun: Nothing to Disclose, James Rottman: Nothing to Disclose, Anne Bothmer: Nothing to Disclose, Jane Wang: Nothing to Disclose, Cecilia Cotta-Ramusino: Nothing to Disclose, Michael Holmes: Nothing to Disclose, William Querbes: Nothing to Disclose

3623 | COPPER OVERLOAD RESHAPES THE HEPATIC IMMUNE LANDSCAPE IN WILSON&RSQUO;S DISEASE

Mugagga Kalyesubula[1] Som Dev[1] Andreas Patsalos[1] James Hamilton[1], [1]Johns Hopkins University School of Medicine

Background: Wilson's disease (WD) arises from ATP7B mutations that disrupt copper (Cu) homeostasis, resulting in hepatic Cu accumulation and progressive liver dysfunction. This pathological copper overload drives liver inflammation and fibrosis, with potential progression to liver failure, alongside a suppressed LXR signaling axis. The immunologic basis for liver inflammation and injury remains largely unknown. **Methods:** Single-nucleus RNA sequencing (snRNA-seq) was utilized in a WD mouse model to delineate the immunological landscape reshaped by Cu toxicity, followed by validation using immunofluorescence (IF) and RNAscope. *Atp7b*$^{-/-}$ mice and Heterozygote controls of the C57BL/6x129S6/SvEv background of 20 wk of age were employed in the study. The LXR agonist (T0901317 (Cayman Chemical, Ann Arbor, MI)) was administered to test its potential treatment effect in WD management. **Results:** Our analyses reveal that Cu overload reduces hepatocyte clusters and disrupts immune subset heterogeneity, leading to an expansion of distinct macrophage subsets, dendritic cells (DCs), and T cells, with an increase in pro-inflammatory and pro-fibrotic pathways. Furthermore, IF and RNA scope validation demonstrate a decrease in central hepatocytes and an increase in macrophages under copper overload. Strikingly, pharmacological activation of Liver X Receptor (LXR) using a synthetic agonist reverses these Cu-induced immune shifts. LXR treatment restores immune homeostasis by modulating key targets (*Mylip, Pltp, Il6, Il1b, Scd1*, and *Tnf*), attenuating inflammation, and reprogramming macrophages toward a reparative phenotype. **Conclusion:** These findings establish a novel link between Cu overload, immune dysregulation, and liver pathology in WD, highlighting LXR agonists as a potential therapeutic strategy to mitigate immune-driven hepatic damage in WD patients.

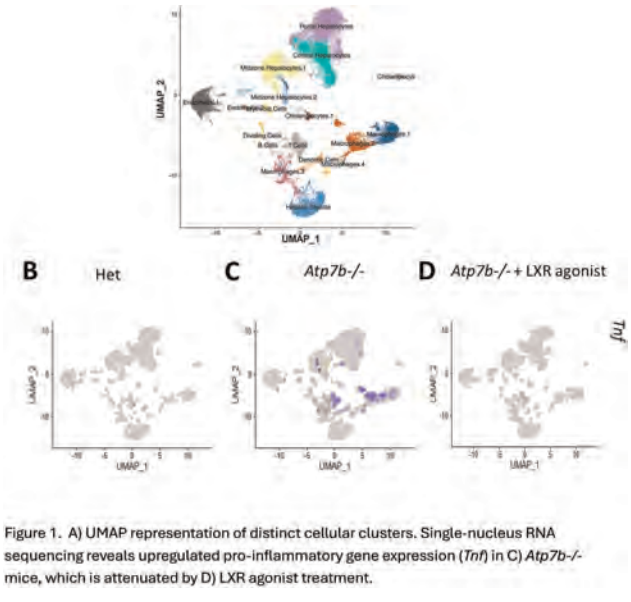

Figure 1. A) UMAP representation of distinct cellular clusters. Single-nucleus RNA sequencing reveals upregulated pro-inflammatory gene expression (*Tnf*) in C) *Atp7b-/-* mice, which is attenuated by D) LXR agonist treatment.

Disclosures: Mugagga Kalyesubula: Nothing to Disclose, Som Dev: Nothing to Disclose, Andreas Patsalos: Nothing to Disclose, James Hamilton: orphalan pharmaceuticals: Advisor

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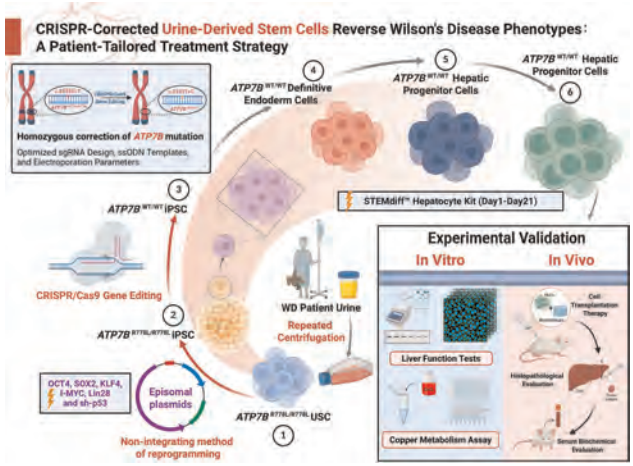
3625 | CRISPR-CORRECTED URINE-DERIVED STEM CELLS REVERSE WILSON'S DISEASE PHENOTYPES:A PATIENT-TAILORED TREATMENT STRATEGY

Jiaqi Li[1] Pengfei Yu[1] Jiateng Zhang[1] Huaibin Zou[1] Yu Chen[1] Zhongping Duan[1], [1]Beijing YouAn Hospital, Capital Medical University

Background: Wilson disease (WD), also known as hepatolenticular degeneration (HLD), is an autosomal recessive disorder caused by mutations in the ATP7B gene. Although liver transplantation can be curative, its clinical application is limited by donor shortages, immune-mediated graft rejection, and complications associated with long-term immunosuppression. To address critical unmet clinical needs in WD, we established an innovative autologous cell therapy platform by reprogramming WD patient-derived urine stem cells (USCs) into iPSCs, precisely correcting ATP7B mutations via CRISPR, and differentiating them into functional hepatocyte-like cells. **Methods:** USCs were reprogrammed into iPSCs via electroporation of non-integrating episomal plasmids carrying six factors: OCT4, SOX2, KLF4, l-MYC, Lin28, and sh-p53. We engineered an optimized CRISPR/Cas9 platform enabling precise homozygous correction of the pathogenic ATP7BR778L/R778L, generating genetically matched ATP7BWT/WT iPSC lines for functional rescue studies and therapeutic development. To facilitate comprehensive in vivo therapeutic assessment, we engineered a novel immunodeficient WD mouse model (ATP7B−/−; M-NSG) using CRISPR/Cas9 technology. The regulatory capacity of hepatic-like cells (HLCs) in improving liver function and copper metabolism in WD was systematically evaluated through in vitro functional validation and in vivo cell transplantation therapy. **Results:** We successfully isolated USCs from a 13-year-old patient with WD harboring a homozygous ATP7B p.R778L (c.2333G > T) mutation. USCs exhibited robust proliferation and maintained functionality over multiple passages in our optimized culture medium. iPSCs derived from the reprogramming of USC exhibit characteristics of stem cells and express multiple pluripotency markers, including OCT4, SOX2, NANOG, KLF4, FBX15, REX1, and others. Through optimization of sgRNA design, ssODN templates, and electroporation parameters, we achieved homozygous correction of the ATP7B c.2333G > T variant in iPSCs via CRISPR/Cas9 editing. Both uncorrected and genetically corrected iPSCs were robustly differentiated into HLCs. The WD model (ATP7B−/−; M-NSG) recapitulates key disease phenotypes, with biochemical profiling and histopathological analysis confirming characteristic pathological manifestations. Both in vitro and in vivo studies demonstrated that genetically repaired HLCs ameliorated liver function and reversed key pathological features including steatosis, hepatic fibrosis, and copper accumulation. **Conclusion:** The autologous cell therapy platform based on the non-invasive accessibility and broad therapeutic potential of USCs has demonstrated the feasibility of patient-specific USC generation, CRISPR/Cas9-mediated gene repair, and differentiation into functional hepatocytes, providing novel insights and ideas for the gene and cell therapy of Wilson's disease.



Disclosures: Jiaqi Li: Nothing to Disclose, Pengfei Yu: Nothing to Disclose, Jiateng Zhang: Nothing to Disclose, Huaibin Zou: Nothing to Disclose, Yu Chen: Nothing to Disclose, Zhongping Duan: Nothing to Disclose

3626 | METABOLIC RISK FACTORS PROMOTE ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE

Malin Fromme[1] Christina Schrader[1] Paul Ellis[2] Audrey Payance[3] Mattias Mandorfer[4] Jan Stolk[5] Bart Van Hoek[6] Katrine Thorhauge[7] Monica Pons[8] Marc Miravitlles[9] Guido Stirnimann[10] Sona Frankova[11] Jan Šperl[11] Andreas Kremer[12] Katharina Remih[1] Emily Weber[1] Lorenz Balcar[13] Annelot Sark[5] Benedikt Schäfer[14] Joanna Chorostowska-Wynimko[15] Elmar Aigner[16] Sophie Gensluckner[16] Heike Bantel[17] Jef Verbeek[18] ZOE MARIÑO MENDEZ[19] Heinz Zoller[14] Michael Trauner[13] Joan Genesca[8] Virginia Clark[20] Aleksander Krag[21] Noel McElvaney[22] William Griffiths[23] Alice Turner[2] Pavel Strnad[1], [1]University Hospital RWTH Aachen, Aachen, Germany, [2]University of Birmingham, Birmingham, United Kingdom, [3]Université Paris Cité, Paris, France, [4]Medical University of Vienna, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Leiden University Medical Center, [7]Odense University Hospital, Odense, Denmark, [8]Universitat Autonoma de Barcelona, Barcelona, Spain, [9]Instituto de Salud Carlos

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Background: Alpha-1 antitrypsin deficiency (AATD) is a prevalent rare genetic condition that increases the risk of lung and liver disease. We assessed the impact of metabolic factors, i.e. body mass index (BMI) and diabetes, on baseline liver parameters and the development of liver/lung endpoints. **Methods:** We collected an international, multi-centric Pi*ZZ cohort of 1,862 individuals from 17 different countries with severe AATD (Pi*ZZ), of whom 929 had a follow-up after a minimum of 6 months. At baseline, participants received a clinical evaluation, laboratory tests, and liver stiffness measurement (LSM) via transient elastography (Fibroscan®). Liver endpoints were defined as liver transplantation, liver-related mortality, and first hepatic decompensation, lung endpoints as lung transplantation and lung-related mortality. We compared the results with data from 16,715 Pi*MZ and 415,208 non-AATD (Pi*MM) individuals from the population-based UK Biobank. **Results:** At baseline, 64 Pi*ZZ participants had diabetes, 614 were overweight (BMI 25.0 - 29.9 kg/m²), and 295 obese (BMI $\geq$ 30 kg/m²). Participants with diabetes had significantly higher liver enzymes compared to those without. Surrogates of advanced fibrosis (APRI ³1.0 units / LSM ³15.0 kPa) were four to five times more frequent in subjects with diabetes (aOR = 3.7/5.0, p $<$ 0.01). Among normal-weight Pi*ZZ individuals, elevated transaminases were rare (9/12%), but more common in overweight (14/23%; aOR 1.7/2.1) and obese individuals (17/29%; aOR 2.2/3.1). During a median follow-up of 4.5 years, 56 Pi*ZZ participants experienced a liver and 55 a lung endpoint. Diabetic and obese Pi*ZZ subjects had an increased risk of hepatic endpoints (aHR = 4.1/5.7, p $<$ 0.001), whereas overweight status was associated with a decreased risk for lung endpoints (aHR = 0.3, p = 0.004). In the diabetic Pi*MZ and Pi*MM subcohorts from the UK Biobank, the ORs for elevated liver markers, advanced fibrosis, and hepatic endpoints were smaller than in the diabetic Pi*ZZ subcohort. Overweight was associated with a decreased (aHR = 0.6/0.8, p = 0.001) and diabetes with an increased risk (aHR = 2.1/2.3, p $<$ 0.001) for lung endpoints in Pi*MZ and Pi*MM subjects. **Conclusion:** Diabetes and obesity are associated with elevated liver markers and an increased risk of decompensation, independent of genotype, but their impact is most pronounced in Pi*ZZ individuals. These findings will inform patient counseling and risk stratification.

Disclosures: Malin Fromme: Takeda Pharmaceuticals: Consultant, CSL Behring: Speaking and Teaching, Grifols Inc: Speaking and Teaching, Takeda Pharmaceuticals: Speaking and Teaching, Christina Schrader: Nothing to Disclose, Paul Ellis: Takeda: Consultant, Audrey Payance: Nothing to Disclose, Mattias Mandorfer: Echosens: Speaking and Teaching, Echosens: Grant/Research Support, Ipsen: Consultant, Takeda: Consultant, Takeda: Speaking and Teaching, W.L. Gore & Associates: Speaking and Teaching, Eli Lilly: Consultant, Eli Lilly: Speaking and Teaching, Jan Stolk: Nothing to Disclose, Nothing to Disclose, Bart Van Hoek: Nothing to Disclose, Katrine Thorhauge: Nothing to Disclose, Monica Pons: Nothing to Disclose, Marc Miravitlles: Grifols: Grant/Research Support, Takeda: Speaker, CSL Behring: Speaker, Sanofi: Advisor, Boehringer Ingelheim: Speaking and Teaching, Menarini: Speaking and Teaching, Chiesi: Advisor, Mereo: Advisor, GSK: Advisor, Kamada: Speaking and Teaching, Zambon: Speaking and Teaching, BEAM therapeutics: Advisor, Inhbrix: Advisor, Guido Stirnimann: Nothing to Disclose, Sona Frankova: Gilead Sciences: Speaking and Teaching, Merck: Speaking and Teaching, Abbvie: Speaking and Teaching, AOP Orphan: Speaking and Teaching, Ipsen: Speaking and Teaching, Jan Šperl: Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Ipsen: Speaking and Teaching, Andreas Kremer: Abbvie: Advisor, Abbvie: Consultant, Advanz: Advisor, Advanz: Consultant, Alentis: Advisor, AlphaSigma: Consultant, AlphaSigma: Speaking and Teaching, AstraZeneca: Advisor, Avior: Advisor, Bayer: Advisor, CymaBay: Advisor, Escient: Advisor, Falk: Consultant, Falk: Speaker, Gilead: Consultant, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GSK: Consultant, GSK: Speaking and Teaching, GSK: Advisor, Intercept: Consultant, Intercept: Grant/Research Support, Intercept: Speaking and Teaching, Ipsen: Consultant, Ipsen: Speaking and Teaching, Mirum: Consultant, Mirum: Advisor, Mirum: Speaking and Teaching, MSD: Consultant, MSD: Speaking and Teaching, MSD: Advisor, Roche: Consultant, Roche: Grant/Research Support, Roche: Speaking and Teaching, Takeda: Consultant, Takeda: Advisor, Takeda: Advisor, Viofor: Advisor, Viofor: Speaking and Teaching, Viofor: Advisor, Astellas: Consultant, BMS: Consultant, Böhringer-Ingelheim: Consultant, Curatis: Consultant, Novo Nordisk: Consultant, Rectify Pharma: Consultant, Advanz: Speaking

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3627 | UNCOVERING THE CRITICAL ROLE OF CUPROPTOSIS IN WILSON DISEASE: IDENTIFICATION OF DIAGNOSTIC BIOMARKERS AND THERAPEUTIC TARGETS

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Background: Wilson disease (WD) is an inherited disorder caused by ATP7B mutations, resulting in toxic copper accumulation primarily in the liver and brain. While copper-induced hepatotoxicity is a hallmark of WD, the mechanisms linking copper overload to liver injury remain unclear. This study aimed to investigate the role of cuproptosis—a copper-dependent form of regulated cell death—in WD pathogenesis and identify key cuproptosis-related genes (CRGs). **Methods:** We utilized ATP7B$^{-/-}$ mice and HepG2 cells to model WD. Liver injury was assessed histologically and biochemically. Transcriptomic analysis identified differentially expressed CRGs, followed by machine learning (LASSO, SVM-RFE) to identify key genes. Functional enrichment and protein validation were performed. Candidate biomarkers were evaluated in WD patient serum and confirmed in the mouse model. **Results:** ATP7B$^{-/-}$ mice showed marked hepatocellular injury with elevated AST, ALT, and LDH. Cuproptosis markers (FDX1, DLST, DLAT, LIAS) were upregulated in both liver tissue and HepG2 cells. Copper exposure decreased cell viability and increased LDH release—exacerbated by Elesclomol and alleviated by Tetrathiomolybdate. Transcriptomics revealed 14 CRGs; Lox, App, and Alb were identified as central hub genes. Machine learning highlighted Afp, Alb, Gpc1, Gls, and App as key diagnostic candidates, associated with copper homeostasis

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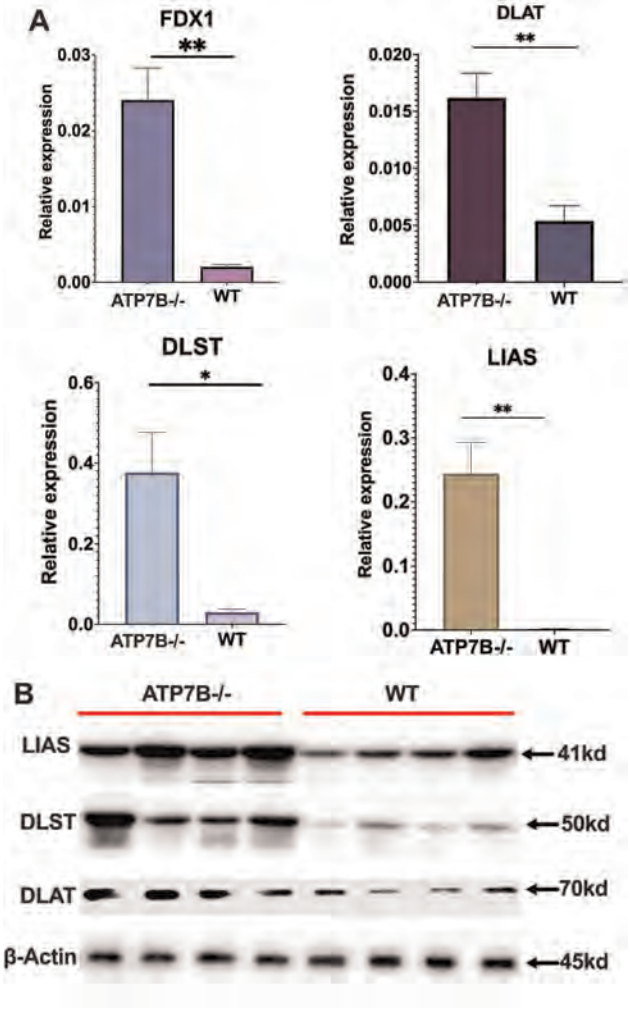
and metabolic regulation. Serum Afp and Alb effectively distinguished WD from chronic hepatitis B. **Conclusion:** Cuproptosis contributes significantly to copper-induced liver injury in WD. Key mediators include Lox, Afp, Alb, Gpc1, Gls, and App, with Afp and Alb showing potential as diagnostic biomarkers. These findings offer new insights into WD pathogenesis and potential therapeutic targets.



Disclosures: Shan Tang: Nothing to Disclose, Sujun Zheng: Nothing to Disclose, Feng Ren: Nothing to Disclose, Wei Hou: Nothing to Disclose

3628 | COGNITIVE FUNCTION IN PATIENTS WITH WILSON DISEASE: PROSPECTIVE ANALYSIS FROM THE WILSON DISEASE REGISTRY STUDY

Michael Schilsky[1] Asim Ulcay[1] Hatice Maras[1] Sefa Keserci[1] Amar Patel[1] Susan Rubman[1] Regino Gonzalez-Peralta[2] Isabelle Mohr[3] Ayse Coskun[4] Uyen To[1] Kaitlin Maciejewski[5] Yanhong Deng[5] ZOE MARIÑO MENDEZ[6] Paula Zimbrean[1], [1]Yale University Medical Center, [2]AdventHealth for Children, [3]University Hospital Heidelberg, Heidelberg, Germany, [4]Creighton University, Omaha, Nebraska, [5]Yale University, [6]Hospital Clinic of Barcelona, Spain

Background: Few prospective data are available to assess cognition in patients with Wilson disease (WD). The Montreal Cognitive Assessment (MOCA) instrument is used to assess cognitive function and has several domains and standardized scoring methodology. From a possible total score of 30, <26 is considered abnormal, whereas ≥ 26 reflects normal cognition. Aims: to evaluate cognitive function in WD patients enrolled in the WD Registry (WDR) study using data at entry into the study, and longitudinally during follow-up. **Methods:** Cross-sectional (baseline at study entry) and longitudinal assessment of adult WD patients from the WDR with MOCA and neurologic (UWDRS) evaluations were performed. Patients were characterized as asymptomatic, hepatic, neurologic based on historical data at WD diagnosis. Repeated MOCA measurements were assessed by linear mixed models (ANCOVA) controlling for the time as the main confounder. Variables were expressed as mean (standard deviation).
Results: The cohort included 138 patients: 51% female, age 39y (14); time since WD diagnosis 15.8y (15); phenotype: hepatic 47%, neurologic 39%, asymptomatic 14%. For all patients, MOCA at baseline was 26.3 (3.1), with 44 (32%) patients scoring <26 [mean 22.9 (3)] (asymptomatic 21%, hepatic 30% and neurologic 37%). At baseline, MOCA negatively correlated with UWDRS ($r=-0.47$, $p=<0.001$, Pearson). Patients with lower cognitive function (MOCA <26) had significantly higher UWDRS scores ($p=0.0003$). Globally, MOCA increased by 1 point on average from enrollment to years 2 and 3 (both $p=0.001$), suggesting cognitive improvement could occur with treatment. In longitudinal analysis, adjusted for MOCA at enrollment, only those with baseline MOCA <26 scores presented significant improvements over time (years, 2, 3, 4 and 5, all $p<0.01$) with at least 1-point improvement year-over-year. When adjusting for phenotype, only the Hepatic group had significant changes in MOCA, ranging from 0.6 to 1.8 increase from baseline. **Conclusion:** MOCA was capable of detecting and quantifying the degree of cognitive impairment in our cohort of WD patients. Though most patients were unaffected (MOCA ≥ 26), in those with impairment (MOCA <26), the degree of altered cognition negatively correlated with higher UWDRS scores, suggesting CNS injury was worse in

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more severely affected patients with neurologic disease. That cognition could improve significantly over time highlights the importance of early detection and treatment on WD patient outcomes.

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3629 | PERFORMANCE OF VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY RELATIVE TO BIOPSY FOR LIVER FIBROSIS STAGING IN PATIENTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE AND A PI*ZZ GENOTYPE

Virginia Clark[1] Doneal Thomas[2] Gerald Lebovic[2] Flávia Soares Peres[3] Cláudia Ribeiro[3] Chitra Karki[4] Tami Nussbaum[4] Suna Park[4] Kaili Ren[4] May Hagiwara[4], [1]University of Florida, Gainesville, FL, USA, [2]IQVIA Real World Solutions, Mississauga, ON, Canada, [3]IQVIA Real World Solutions, Lisbon, Portugal, [4]Takeda Development Center Americas, Inc., Cambridge, MA, USA

Background: Alpha-1 antitrypsin deficiency-associated liver disease (AATD-LD) is caused by the protease inhibitor (Pi)*ZZ genotype. No study has validated vibration-controlled transient elastography (VCTE) relative to liver biopsy for the longitudinal assessment of liver fibrosis in patients (pts) with AATD-LD. The performance of VCTE versus liver biopsy for fibrosis staging in AATD-LD was assessed using data from the Alpha-1 Liver Fibrosis/Natural History Study, University of Florida (UoF). **Methods:** This longitudinal cohort study included pts with AATD-LD and a Pi*ZZ genotype (Nov 2013–Sept 2019). Liver fibrosis was assessed at baseline and Year 3 by liver biopsy (METAVIR fibrosis stage; interpreted by a single pathologist) and VCTE. Previously defined VCTE fibrosis stage thresholds were used: F1, $>$ 2.0–$\leq$ 7.1 kPa; F2, $>$ 7.1–$\leq$ 10.0 kPa; F3, $>$ 10.0–$\leq$ 15.0 kPa; F4, $>$ 15.0 kPa (Strnad P *et al. Hepatol* 2023;78:S1485). The performance of VCTE versus liver biopsy was determined according to the area under the receiver operating curve (AUC) and previously defined VCTE thresholds; for the UoF data, optimal cut-off values for VCTE were derived by maximizing Youden's J statistic (sensitivity + specificity – 1). Liver disease progression ($\geq$ 1 stage advancement in fibrosis), regression ($\geq$ 1 stage reduction in fibrosis) or stable disease (no change in fibrosis stage) were assessed. VCTE was considered reliable if there were $\geq$ 10 measurements with $\geq$ 60% success rate and an IQR/median value $\leq$ 30%; any VCTE was defined as all measurements. **Results:** The optimal F2 cut-off values were 6.3 at baseline and 6.1 at Year 3 for both reliable VCTE (AUC baseline 0.82; Year 3, 0.88) and any VCTE (AUC baseline 0.79; Year 3, 0.86). The optimal F3 cut-off value was 8.8 at baseline for both reliable VCTE (AUC 0.95) and any VCTE (AUC 0.94); at Year 3, the optimal cut-off value was 6.1 for reliable

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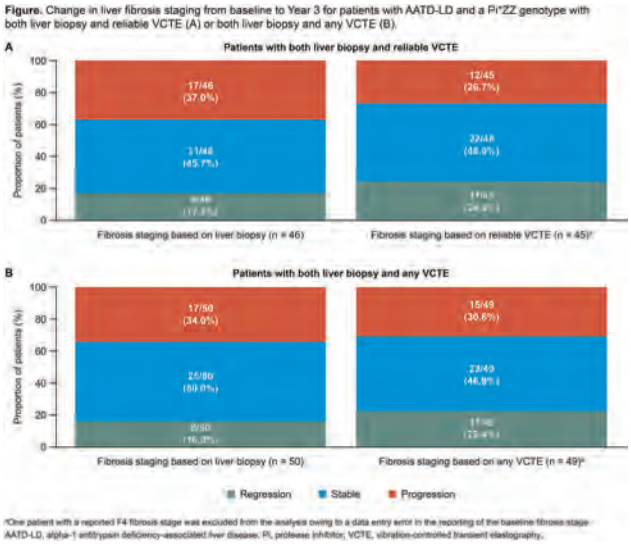
VCTE (likely owing to the small sample size for F3; AUC 0.87) and 9.2 for any VCTE (AUC 0.86). Among pts with both liver biopsy and reliable VCTE results, 46 and 45 were staged by liver biopsy or reliable VCTE, respectively; at Year 3, 17 (37.0%) and 12 (26.7%) progressed, 21 (45.7%) and 22 (48.9%) were stable and 8 (17.4%) and 11 (24.4%) regressed, respectively (Figure A). Among pts with both liver biopsy and any VCTE, 50 and 49 were staged by liver biopsy or any VCTE, respectively; at Year 3, 17 (34.0%) and 15 (30.6%) progressed, 25 (50.0%) and 23 (46.9%) were stable and 8 (16.0%) and 11 (22.4%) regressed, respectively (Figure B). **Conclusion:** In this study on the performance of VCTE versus liver biopsy for fibrosis staging in adults with AATD-LD and a Pi*ZZ genotype, VCTE performed similarly to biopsy in staging F2/F3 fibrosis. The optimal cut-off values of VCTE-based staging for UoF data were slightly lower than predefined thresholds based on clinical practice. Findings should be interpreted with caution and validated in larger studies.

Writing support provided by R Tooze, Oxford PharmaGenesis.



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3630 | LIVER DISEASE PROGRESSION IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS WITH AND WITHOUT ALPHA-1 ANTITRYPSIN DEFICIENCY: RESULTS: FROM A RETROSPECTIVE COHORT STUDY IN THE USA

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a chronic liver disease (LD) characterized by steatosis, hepatocyte injury, and inflammation. Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder that can lead to liver fibrosis and cirrhosis and subsequent progression to end-stage LD/liver failure. Patients (pts) may have ≥ 1 LD etiology. Real-world evidence on LD progression in pts with MASH and AATD is limited. We aimed to evaluate LD progression in adults with MASH with and without AATD. **Methods:** This retrospective observational study included adults with MASH in the USA captured in Health Verity (Mar 2018–Sep 2024). Index date was defined as the earliest of either ≥ 2 diagnosis (dx) codes for MASH (ICD-10 K75.81) ≥ 90 days apart or ≥ 1 dx code for hepatic fibrosis (ICD-10 K74.0) preceded by ≥ 1 dx code for fatty liver (ICD-10 K76.0). Baseline period was defined as ≤ 180 days before index date. Eligible pts with MASH were considered to have cirrhosis if they had ≥ 1 dx code for hepatic cirrhosis (ICD-10 K74.6/60/69) ≤ 180 days before index date. Additionally, pts with AATD (≥ 2 dx codes for AATD [ICD-10 E88.01] ≥ 90 days apart or a laboratory serum AAT value < 120 mg/dL) and without AATD were identified and propensity score matched in a 1:2 ratio based on age, sex, race, and relevant key comorbidities. Standardized mean difference (SMD) was used to compare clinical features in pts with and without AATD (SMD > 0.1 is considered a notable difference). LD progression was defined as the earliest of either an advancement to cirrhosis or occurrence of LD-related clinical event. Kaplan–Meier analyses were used to assess time to LD progression and a log-rank test was performed. **Results:** Overall, 170,260 pts with MASH (3,766 with and 166,494 without AATD) were included.

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For pts with and without AATD, respectively, median (range) age at index date was 53 (18, 97) and 55 (18, 97) years, 52% and 60% were female, and 9% and 8% had cirrhosis at index date. A lower proportion of pts with than without AATD had diabetes and obesity (35% vs 41% for both comorbidites; $p < 0.0001$). After matching, 3,766 pts with and 7,532 pts without AATD were evaluated; of those, median (range) age was 53 (18, 97), 52% were female, and 8% had cirrhosis at index date. For all covariates, SMD was < 0.1 after matching. The probability of LD progression in pts with MASH was higher with than without AATD (Figure A). Among pts with MASH and cirrhosis at index date, median (95% confidence interval) time to LD progression was significantly shorter for pts with than without AATD (31 [23, 49] vs 48 [34, not estimable] months; $p < 0.05$; Figure B). **Conclusion:** In this matched cohort study, pts with MASH and AATD were more likely to have LD progression than pts with MASH alone, underscoring the incremental clinical burden associated with AATD. Testing for AATD in pts with MASH may guide treatment decisions and inform monitoring of LD progression.

Writing support provided by R Tooze, Oxford PharmaGenesis.

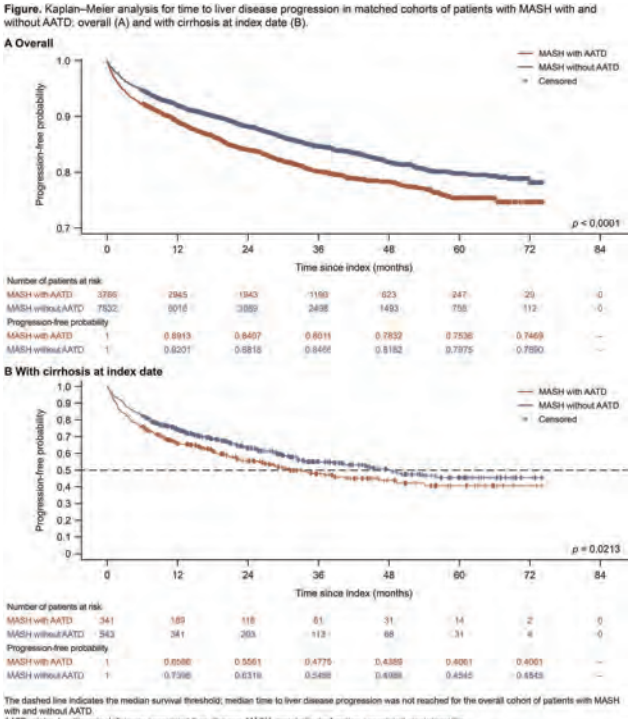

Figure. Kaplan–Meier analysis for time to liver disease progression in matched cohorts of patients with MASH with and without AATD: overall (A) and with cirrhosis at index date (B).

The dashed line indicates the median survival threshold; median time to liver disease progression was not reached for the overall cohort of patients with MASH with and without AATD.
AATD, alpha-1 antitrypsin deficiency-associated liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

Disclosures: Suna Park: Nothing to Disclose, Sudhakar Manne: Nothing to Disclose, Kunali Ghelani: Nothing to Disclose, Chitra Karki: Takeda Development Center Americas, Inc.: Employee, Takeda Development Center Americas, Inc.: Stock - publicly traded company, May Hagiwara: Nothing to Disclose, Tami Nussbaum: Nothing to Disclose, George Marek: Nothing to Disclose, Harmeet Malhi: MERCK: Consultant, Takeda: Consultant

3631 | SERUM MICRORNA SEQUENCING IDENTIFIED FAZIRSIRAN TREATMENT-RESPONSIVE MICRORNAS IN PATIENTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE AND A PI*ZZ GENOTYPE

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Background: Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disorder that can lead to AATD-associated liver disease (AATD-LD); the protease inhibitor (Pi)*ZZ genotype is associated with the most severe forms of disease. MicroRNAs (miRNAs) are post-translational regulators of gene expression that are emerging as potential biomarkers for the diagnosis and monitoring of liver disease. However, miRNA data in patients (pts) with AATD-LD are lacking. We aimed to detect treatment-responsive miRNAs and elucidate their function(s) in pts with AATD-LD treated with fazirsiran in the phase 2 AROAAT-2002 trial. **Methods:** In AROAAT-2002 (NCT03946449), pts with AATD-LD and a Pi*ZZ genotype received fazirsiran 100 mg or 200 mg on Day 1 and Week 4 and then every 12 weeks for 24 weeks or 48 weeks (Strnad P *et al. N Engl J Med* 2022;387:514–24). miRNAs in serum samples at baseline (BL) and after treatment were isolated and captured with RNA-seq or next-generation sequencing; miRNA expression was quantified with miRDeep2. Differential abundance and likelihood ratio test analyses were performed to identify altered miRNAs after fazirsiran treatment versus BL and temporal patterns of miRNA regulation. miRNAs were mapped to protein targets using *in silico* predicted and experimentally supported miRNA-target interactions (DIANA-microT/-TarBase). Serum Olink proteomics data from AROAAT-2002 (Chuang J-C *et al. J Hepatol* 2024;80:S698) were integrated with serum miRNA data to further define the potential functional link between fazirsiran-induced changes in miRNAs and proteins. **Results:** miRNA species were detected in serum samples from 13 pts at BL and post-treatment; the number of expressed miRNAs per sample ranged from 321 to 555. Differentially expressed miRNAs after fazirsiran treatment (Figure A) mapped to targets related to functional

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pathways, including extracellular matrix (ECM) interactions, TGF-β pathway, ephrin signaling, phagocytosis and metabolism; 16 and 36 miRNAs showed a time-dependent decrease and increase, respectively (Figure B). The downregulated miRNA cluster included miRNA-15 family members involved in regulation of TGF-β signaling (mir-16, mir-122 and mir-195); the upregulated miRNA cluster included miRNA-29 family members involved in the induction of apoptosis of hepatic stellate cells (HSCs; mir-1, mir-29 and mir-200). Cross-referencing with serum Olink data revealed interactions between the upregulated miRNAs and corresponding downregulated ECM proteins such as COL3A1, CLEC11A, FN1 and ITGAV. **Conclusion:** Changes in miRNA expression suggest that there is reduced HSC activity in pts with AATD-LD treated with fazirsiran and support the potential clinical benefit of fazirsiran among pts with AATD-LD and a Pi*ZZ genotype. The utility of these miRNAs as potential non-invasive biomarkers for AATD-LD require validation in larger studies.

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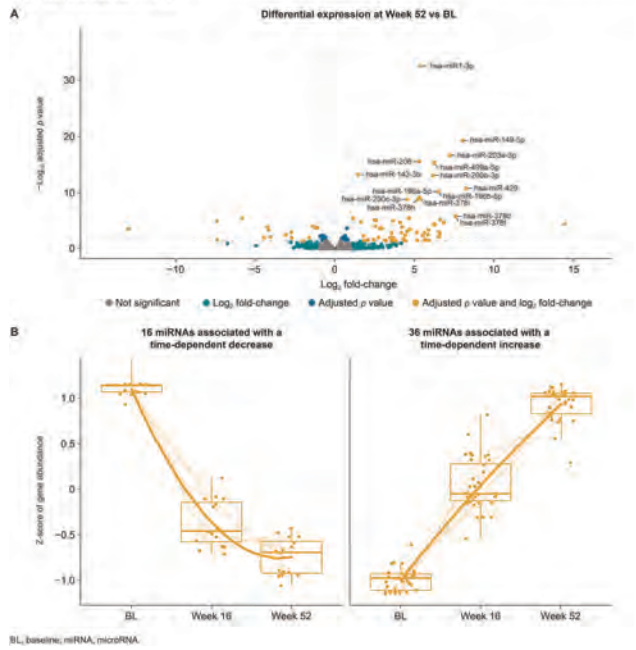
Figure. Differentially expressed miRNAs at Week 52 versus BL (A) and longitudinal analysis of miRNA expression changes at BL, Week 16 and Week 52 (B).



BL, baseline; miRNA, microRNA.

Disclosures: Maria Paraskevopoulou: Nothing to Disclose, Ruixue Hou: Takeda Pharmaceuticals: Employee, Jen-Chieh Chuang: Takeda: Employee, Loredana Cuccia: Nothing to Disclose, Susana Gonzalez: Nothing to Disclose, Tami Nussbaum: Nothing to Disclose, James Hamilton: Nothing to Disclose, Thomas Schluep: Nothing to Disclose, Pavel Strnad: Arrowhead Pharmaceuticals: Grant/Research Support, CSL Behring: Grant/Research Support, CSL Behring: Speaking and Teaching, BioMarin Pharmaceutical: Consultant, GSK: Consultant, Intellia: Consultant, Takeda Pharmaceuticals: Speaking and Teaching, Novo Nordisk: Consultant, Swedish Orphan Biovitrum: Consultant, Swedish Orphan Biovitrum: Speaking and Teaching, IPSEN: Consultant, Albireo: Consultant, AiRNA: Consultant, BioMarin: Consultant, Korro Bio: Consultant, Wave: Consultant, AiRNA: Consultant, Tessera: Consultant, Vertex: Material transfer, IQVIA: Material transfer, Arrowhead: Grant/Research Support, Takeda: Consultant, GSK: Consultant, BioMarin: Consultant, IPSEN: Consultant, Korro Bio: Consultant, CSL Behring: Grant/Research Support, CSL Behring: Speaking and Teaching, CSL Behring: Consultant, Sobi: Speaking and Teaching, Sobi: Advisor, Sanofi: Grant/Research Support

3632 | COMPARISON OF FERRISMART™ AND FERRISCAN™ FOR LIVER IRON QUANTIFICATION IN C282Y HOMOZYGOUS HAEMOCHROMATOSIS PATIENTS

Andrea Jasareno[1] Vanoo Jayasekeran[2] Timothy St Pierre[3] James Chen[2] John Olynyk[2], [1]Fiona Stanley Hospital, [2]Department of Gastroenterology, Fiona Stanley Hospital, [3]School of Physics, Mathematics, and Computing from The University of Western Australia

Background: Non-invasive MRI techniques are recommended as the method of choice for measurement of liver iron concentration (LIC). Regulatory authorities in Australia, the USA and Europe have approved use of FerriScan™ (an R2 relaxometry technique). Whilst accurate, this method requires trained personnel to conduct the analyses. A new automated method, called FerriSmart™, using a deep-learned algorithm based on the original FerriScan™ method has been developed. Validation of the accuracy of the new method against the original method in subjects with *HFE* C282Y homozygous haemochromatosis is limited. We compared LIC measurements in clinically well characterised C282Y homozygous subjects using both methods to determine the performance of FerriSmart™ compared with FerriScan™. **Methods:** LIC measurements were calculated from the same MRI scans using both the FerriScan™ and FerriSmart™ methods in 28 C282Y homozygous subjects. Measurements were compared using Bland-Altman analysis. **Results:** LICs, ranging between 0.8 to 38.6 Fe mg/g dry weight, were evaluated in 22 male and 6 female C282Y homozygous subjects, of mean age 49 ± 3 years. Bland-Altman analysis indicated a statistically significant difference between FerriSmart and FerriScan, with a geometric mean ratio of 0.91 (95% CI 0.85 to 0.98). Plot analysis showed heteroscedasticity as LIC increased (Figure 1). **Conclusion:** FerriSmart reports approximately a 9% lower LIC in C282Y homozygous subjects compared with FerriScan in this study. For comparison purposes, this bias is small relative to the known 19-40% coefficient of variation of LIC by chemical assay of liver biopsy in haemochromatosis.

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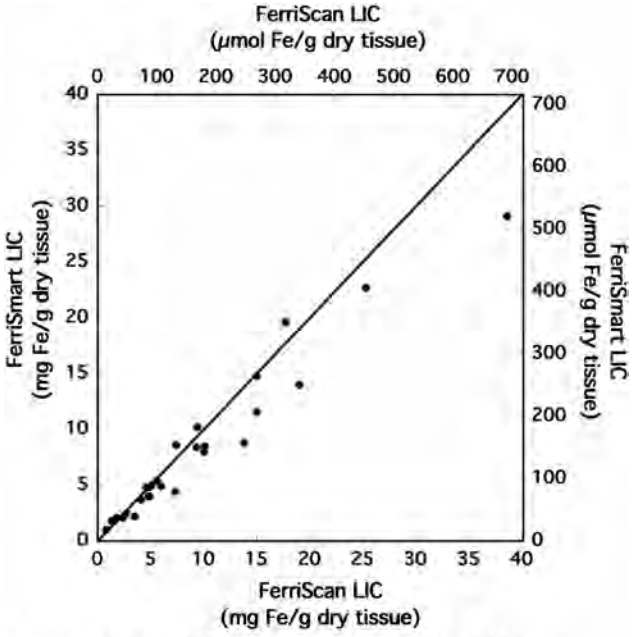

Figure 1: Plot of LIC by FerriSmart™ against LIC by FerriScan™ for 28 homozygous C282Y hereditary haemochromatosis patients. Solid line is the line of equivalence.

Disclosures: Andrea Jasareno: Nothing to Disclose, Vanoo Jayasekeran: Nothing to Disclose, Timothy St Pierre: Nothing to Disclose, James Chen: Nothing to Disclose, John Olynyk: Resonance Health Pty Ltd: Consultant

3633 | UNDERSTANDING THE REAL-WORLD BURDEN OF WILSON&RSQUO;S DISEASE: A DECADE OF DATA FROM A MULTINATIONAL ANALYSIS

Do Han Kim[1] Donghyun Ko[2] Carlos Diola[3] Christina Lee[4] Frank Lukens[5] Pojsakorn Danpanichkul[6] Paul Kroner[7] Raffi Karagozian[4], [1]Department of Medicine, Mount Sinai Morningside and West, Icahn School of Medicine at Mount Sinai, [2]Department of Medicine, Bridgeport Hospital, Yale New Haven Health, Bridgeport, CT, USA, [3]Department of Medicine, Mount Sinai Morningside and West, New York, NY, USA, [4]Division of Gastroenterology and Hepatology, Tufts University School of Medicine, Boston, MA, [5]Division of Gastroenterology and Hepatology, Mayo Clinic Florida, Jacksonville, FL, [6]Texas Tech University Health Sciences Center, [7]Department of Gastroenterology, Riverside Health System, Newport News, VA

Background: Wilson's disease (WD) remains a diagnostic and therapeutic challenge in hepatology, given its variable trajectory and manifestations. While treatment can be life-altering, real-world data on the burden of hepatic and systemic complications are limited. Using a large, multi-national dataset, we aimed to characterize the clinical outcomes of WD to raise awareness for earlier recognition, risk stratification, and long-term management. **Methods:** We conducted a retrospective cohort study using population-based data from the TriNetX Global Collaborative Network. Patients with WD were identified by ICD-10 codes. The risk and incidence proportion of clinical outcomes were assessed from 2014 to 2024 using TriNetX analytics. **Results:** A total of 8,820 patients with WD were identified with a median follow-up time of 1,103 days (IQR: 2,322). The mean age was 43.1 years (SD:20.7) and 50.5% were female. The all-cause mortality rate was 10.8% (891/8,253). Acute kidney injury occurred in 9.5% (701/7,393), while hemolytic anemia in 0.8% (64/8,157). ICU admission was required in 9.7% (745/7,700) of cases. Rates of acute liver failure and orthotopic liver transplantation were 2.6% (201/7,858) and 2.7% (217/7,937), respectively. Hepatocellular carcinoma was identified in 0.9% (81/8,738). Liver biopsy was performed in 6.4% (563/8,808), and hepatic decompensation occurred in 15.0% (1,317/8,808). Emergency department visits and hospital admissions were frequent, occurring in 31.9% (2,812/8,808) and 44.7% (3,935/8,808) of patients, respectively. **Conclusion:** WD is a complex disease that frequently involves multiple organ systems beyond hepatic impairment. The variability in disease progression underscores the importance of an early detection strategy, especially in at-risk populations. Our findings support that despite the new advances in technology and treatment of WD, a significant number of patients experience substantial morbidity. Hence, these insights raise awareness for earlier recognition and long-term management in this subset of patients.

Disclosures: Do Han Kim: Nothing to Disclose, Donghyun Ko: Nothing to Disclose, Carlos Diola: Nothing to Disclose, Christina Lee: Nothing to Disclose, Frank Lukens: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose, Paul Kroner: Nothing to Disclose, Raffi Karagozian: Nothing to Disclose

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3634 | TRACKING IRON IN THE BRAIN: THE IMPACT OF CERULOPLASMIN VARIANTS ON NEURODEGENERATION

Marlene Panzer[1] Christoph Birkl[2] Elisabetta Indelicato[3] Bernhard Glodny[4] Maria Rosina Troppmair[5] Benedikt Schäfer[5] Christoph Scherfler[3] Elke Gizewski[6] Herbert Tilg[5] Heinz Zoller[5], [1]Department of Medicine I, Medical University of Innsbruck, [2]Department of Neuroradiology, Medical University of Innsbruck, Innsbruck, Austria, [3]Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria, [4]Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria, [5]Department of Medicine I, Medical University of Innsbruck, Innsbruck, Austria, [6]Department of Neuroradiology/Neuroimaging Research Core Facility, Medical University of Innsbruck

Background: Aceruloplasminemia is a rare autosomal recessive disorder caused by mutations in the ceruloplasmin gene, leading to progressive iron accumulation in the brain, liver, and pancreas. Early biochemical hallmarks include low ceruloplasmin levels, hyperferritinemia, and reduced transferrin saturation, with neurological symptoms typically appearing between the ages of 40 and 60. This study aims to characterize the radiological and phenotypic patterns of aceruloplasminemia, with a particular focus on brain iron deposition and its impact on neurological function. Additionally, we aim to establish a patient registry to improve understanding of the phenotypic variability in aceruloplasminemia. **Methods:** We examined the clinical and radiological features of neurodegeneration in five patients with homozygous or compound heterozygous ceruloplasmin mutations and four heterozygous carriers. Demographic, biochemical, and clinical data were collected from patient records, and neurological impairment was assessed using the Unified Wilson Disease Rating Scale (UWDRS) and the Montreal Cognitive Assessment (MoCA). All participants underwent 3 Tesla MRI of the brain, including R2* relaxometry for iron quantification. Deep gray matter structures were segmented using FSL FIRST, and R2* values were analyzed. Brain volumetric measurements and R2* values were compared against sex- and age-matched healthy controls. **Results:** All patients presented with plasma ceruloplasmin concentrations below the lower limit of normal. Homozygous patients exhibited elevated ferritin levels, with four showing reduced transferrin saturation. Neurological presentation among homozygous patients ranged from asymptomatic to severe impairment, while all heterozygous individuals remained asymptomatic. MRI analyses revealed significantly increased R2* values, indicating iron overload in the basal ganglia, hippocampus, and nucleus accumbens in homozygous patients compared to heterozygous carriers and controls. Volumetric analysis showed pronounced atrophy in the cerebellum and deep gray matter, particularly in the putamen, globus pallidus, and thalamus. **Conclusion:** Our findings indicate that aceruloplasminemia is associated with a distinct pattern of brain iron accumulation, extending beyond the basal ganglia. The broad spectrum of neurological impairment suggests that factors beyond iron overload may contribute to disease severity. Furthermore, quantitative MRI proves to be a valuable tool for assessing neurodegeneration in aceruloplasminemia, offering potential for monitoring disease progression and exploring genotype-phenotype correlations.

Disclosures: Marlene Panzer: Nothing to Disclose, Christoph Birkl: Nothing to Disclose, Elisabetta Indelicato: Nothing to Disclose, Bernhard Glodny: Nothing to Disclose, Maria Rosina Troppmair: Nothing to Disclose, Benedikt Schäfer: Nothing to Disclose, Christoph Scherfler: Nothing to Disclose, Elke Gizewski: Nothing to Disclose, Herbert Tilg: Nothing to Disclose, Heinz Zoller: Nothing to Disclose

3635 | TMED10 IS A NOVEL ATZ CARGO RECEPTOR AND THERAPEUTIC TARGET FOR LOWERING ATZ ACCUMULATION IN ALPHA-1 ANTITRYPSIN DEFICIENCY

Fabian Suri-Payer[1] Joseph Kaserman[2] Wei Chou Tseng[1] Juan Pablo[1] Andrew Wilson[2] Anna Greka[1], [1]Broad Institute of MIT and Harvard, [2]Boston University

Background: Alpha-1 Antitrypsin Deficiency (AATD) is a rare genetic disease caused by SERPINA1 variants which manifests as chronic liver and lung disease. There is currently no cure, and only supportive treatment available for AATD. The most common AATD allele, the Z allele (E342K, known as ATZ) – destabilizes AAT, making it prone to misfold and polymerize. ATZ accumulation within the endoplasmic reticulum (ER) of liver cells causes chronic liver disease, while the corresponding absence of protective AAT in the lung leads to lung disease. It remains unclear what decides the cellular fate of ATZ within the ER, and how this contributes to ATZ being insufficiently degraded in disease. Further understanding of the molecular mechanisms underlying ATZ trafficking is required for the identification and development of novel therapeutic targets and strategies. **Methods:** We conducted immunoprecipitation coupled with unbiased mass spectrometry to identify new potential regulators of ATZ in Huh7.5 cells. We then validated proteins of interest with pharmacological and genetic perturbation assessed by high-content imaging and native blotting in Huh7.5 cells and hepatocytes from patient-derived induced pluripotent stem cells (iHeps). Finally, we assess the therapeutic potential to ameliorate AATD disease progression in the Pi*Z mouse model. **Results:**

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We identified 731 potential regulators of ATZ in Huh7.5 cells, including known regulators of ATZ trafficking. Our hit validation identified ATZ as a novel cargo of the transmembrane emp24 domain-containing proteins (TMEDs), a family of ER-Golgi resident proteins that act as cargo receptors for misfolded protein cargo in protein accumulation disorders. Crucially, we show that targeting TMED receptors lessens ATZ accumulation by up to 70% without affecting AAT secretion, in a mechanism dependent on TMED2 and TMED10. We are further exploring TMED-ATZ biology in iHeps and the Pi*Z mouse model. **Conclusion:** Here we identify TMED10 as a novel cargo receptor and regulator of the misfolding and disease-causing Z-variant of Alpha-1 Antitrypsin in endogenous models of AATD. Knockdown of TMED10 results in a significant reduction of intracellular ATZ accumulation without affecting secretion, suggesting a mechanism contributing uniquely to ATZ accumulation but not canonical trafficking. As chronic liver disease in AATD remains without treatments, targeting TMED10 may present a novel therapeutic target for preventing ATZ accumulation leading to liver disease.

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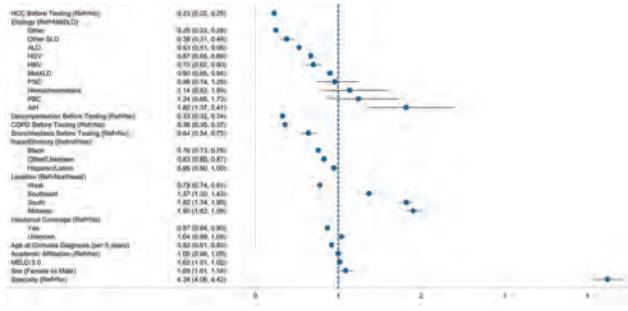
3636 | PREDICTORS OF TESTING AND TEST POSITIVITY FOR ALPHA-1 ANTITRYPSIN DEFICIENCY IN PATIENTS WITH CIRRHOSIS IN A U.S. NATIONAL COHORT

Binu John[1] Dustin Bastaich[2] Andres Samos[3] Austen Hentschel[3] Sunny Sandhu[4] Raphaella Ferreira[5] Tamar Taddei[6] Brian Garnet[7] David Kaplan[8] Michael Campos[1] Bassam Dahman[2], [1]University of Miami and Miami VA, [2]Virginia Commonwealth University, [3]Herbert Wertheim College of Medicine, Florida International University, Miami, FL, [4]University of Miami - Jackson Memorial Hospital, [5]HCA HealthONE Sky Ridge Medical Center, Lone Tree, CO, [6]Yale University, [7]University of Miami, [8]University of Pennsylvania

Background: Alpha-1 antitrypsin deficiency associated liver disease (AATDLD) is a well-recognized genetic condition but may be undertested and underdiagnosed. Diagnosis of AATD is crucial for both genetic counselling, and for ensuring appropriate treatment options as new therapies continue to emerge. There is limited national data on rates of testing of AATD in patients with cirrhosis. Furthermore, the factors associated with higher rates of testing, as well as the test-positivity rates among those tested are mostly unknown.

The primary aim of this study was to examine the rates of testing of AATD in patients with cirrhosis, and patient and provider-level factors influencing AATD testing rates. The secondary aim was to identify factors associated with intermediate and severe AATD, in those who underwent testing. **Methods:** We included participants aged >18 years who had one inpatient or two outpatient ICD 9/10 code for cirrhosis with a first diagnosis of cirrhosis between January 2008 to December 2020 with follow up until 2/23/2023. An AAT value <100 mg/dl was used to define intermediate AATD, and a cut-off <57 mg/dL for severe AATD. AAT genotype or phenotypes were identified either from the extraction of a laboratory result comment, or a laboratory or clinical report mentioning alpha-1 antitrypsin genotype or phenotype using natural language processing. Patients with PiMS, PiMZ, and PiSS, PiSZ were considered to have intermediate disease, while those with PiSZ or PiZZ genotype/phenotypes were considered to have severe AATD.

We used logistic regression models to identify the patient, center and provider-level factors associated with AATD testing and those associated with test-positivity among those who were tested. **Results:** Of 126,210 patients with cirrhosis, 42,403 (33.6%) were tested for AATD, including 38,189 (30.3%) by AAT levels only, 1103 (0.8%) by genotype/phenotype only, and 3011 (2.4%) with both. Factors associated with higher AATD testing include specialist evaluation (adjusted Odds Ratio [aOR] 4.24, 4.06-4.42) and among individuals of White race. Older age at cirrhosis diagnosis (aOR per 5 years 0.92, 0.91-0.93), patients with COPD (aOR 0.36, 0.35-0.37), bronchiectasis (aOR 0.64, 0.54-0.75), and hepatic decompensation (aOR 0.33, 0.32-0.34), were less likely to be tested. When tested, veterans without an alternative cirrhosis etiology (aOR 4.49, 2.49-8.07), and with COPD (aOR 1.37, 1.03-1.82) were more likely, while older individuals (aOR per 5 years 0.85, 0.80-0.91), and those of black (aOR 0.23, 0.12-0.43), or hispanic race (aOR 0.40, 0.21-0.76), were less likely to have severe AATD. **Conclusion:** AATD testing rates in Veterans with cirrhosis is low, and patients at high risk are less likely to be tested. This calls for guidelines to emphasize universal AATD testing in patients with cirrhosis.



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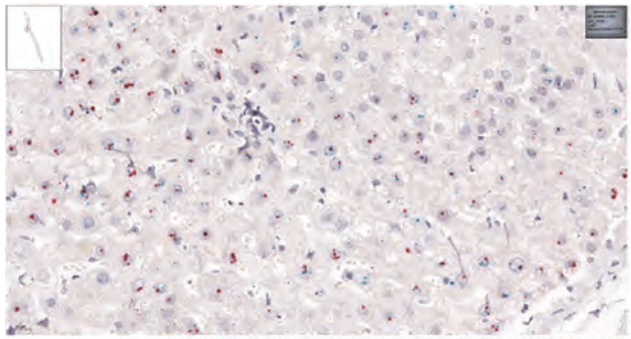
3637 | INTERIM RESULTS: OF THE INTERNATIONAL PHASE I/II GATEWAY GENE THERAPY TRIAL WITH VTX-801 CONDUCTED IN ADULT PATIENTS WITH WILSON DISEASE

Michael Schilsky[1] Frederick Askari[2] Thomas Sandahl[3] William Lee[4] Aftab Ala[5] Regino Gonzalez-Peralta[6] Valentina Medici[7] Sean Rudnick[8] Ulrich Lauer[9] Christoph Berg[10] Hartmut Schmidt[11] Sonia Valero[12] Jean Philippe Combal[13] Gloria Gonzalez-Aseguinolaza[14] Lorenzo D'Antiga[15] Bernard Benichou[13], [1]Yale University Medical Center, [2]University of Michigan Medical Center, [3]Aarhus University Hospital, [4]University of Texas Southwestern Medical Center, [5]Kings College Hospital, [6]AdventHealth for Children, [7]University of California Medical Center, [8]Atrium Health Wake Forest Baptist, [9]Medical University Hospital Tuebingen, Germany, [10]Medical University Hospital, Tuebingen, Germany, [11]University of Essen, Germany, [12]Vivet Therapeutics, Paris, France, [13]Vivet Therapeutics, Paris, France, [14]Vivet Therapeutics SL, Pamplona, Spain, [15]University of Bergamo, Italy

Background: Wilson Disease (WD) is a disorder of copper (Cu) homeostasis due to pathogenic variants in the ATP7B copper-transportergene that impair biliary Cu excretion and cause tissue Cu accumulation and reduced circulating ceruloplasmin (Cp). Limitations of management include treatment side effects, and poor adherence affecting long-term outcomes and survival. VTX-801 is a recombinant adeno-associated viral vector (rAAV) carrying a shortened *ATP7B* gene with a liver-specific promoter. Previous studies with VTX-801 in 6 to 12-week-old WD mice demonstrated restoration of biliary Cu excretion, increased levels of plasma Cp, reduced liver Cu, improved hepatic histology and 100% long-term survival. **Methods:** GATEWAY is an international phase I/II, open-label, 5-y follow-up, single dose-escalation study of VTX-801 in adults with WD (NCT04537377). This first-in-human study assessed safety, pharmacodynamics and efficacy of VTX-801. VTX-801 response at 3- or 9-month post-infusion was based upon ^{64}Cu pharmacokinetic assessments. **Results:** Results:: VTX-801 Cohort 1 (low dose) was completed (N = 2 patients), and Cohort 2 (intermediate dose) were treated (N = 2). One SAE was reported (DILI). Two patients had infusion-associated reactions managed with symptomatic treatment. All 4 had mild, resolving ALT increases following VTX-801 infusion without affecting liver function. One in Cohort 1 had a delayed, mild ALT elevation to 104 IU/l, and one in Cohort 2 had ALT elevation to 245 IU/l meeting criteria for DILI and had a liver biopsy; both resolved rapidly with a course of oral steroid treatment. Overall, insufficient VTX-801 response was observed, and standard of care treatment was not withdrawn. Follow-up liver biopsy at 1 y in a patient from Cohort 1 showed miniATP7B mRNA expression in up to 50% of hepatocytes, and an unscheduled biopsy after DILI in the Cohort 2 patient showed miniATP7B mRNA expression in up to 75% of hepatocytes. Available pharmacodynamic data for Cohorts 1 and 2 will be presented. **Conclusion:** Delivery of ATP7B is possible in human liver using AAV. VTX 801 transduction was successful, however changes in Cu parameters were subtherapeutic. Further study is needed to understand factors affecting the degree of functional transgene expression and its ability to increase biliary copper excretion and Cp levels in humans.



Disclosures: Michael Schilsky: Vivet Therapeutics: Grant/Research Support, Vivet Therapeutics: Grant/Research Support, Vivet Therapeutics: Grant/Research Support, Orphalan: Grant and Advisory, Orphalan: Grant and Advisory, Orphalan: Grant and Advisory, DepYmed: Advisor, DepYmed: Advisor, DepYmed: Advisor, Arbomed: Advisor and Consultant, Arbomed: Advisor and Consultant, Arbomed: Advisor and Consultant, Wilson Disease Association: Grant/Research Support, Wilson Disease Association: Grant/Research

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3638 | INTESTINAL-FAILURE ASSOCIATED LIVER DISEASE AND HEPATIC MANIFESTATIONS OF SHORT BOWEL SYNDROME: EXPLORING PREDICTORS OF DISEASE AND NATIONWIDE OUTCOMES

Michael Gianarakis[1] Adam Mikolajczyk[1] Robert Carroll[1], [1]University of Illinois Chicago

Background: Intestinal Failure-Associated Liver Disease (IFALD) is a progressive disease with high mortality in patients with short bowel syndrome (SBS) dependent on parenteral nutrition (PN). It encompasses a spectrum of hepatic manifestations including cholestasis, steatosis, cirrhosis, and portal hypertension (PHT). Risk factors include chronic PN use, remaining bowel length, choline and carnitine deficiency, recurrent sepsis, and cholelithiasis. We present the first nationwide study evaluating characteristics, outcomes, and predictors of hepatic disease in adults with SBS. **Methods:** We analyzed the Nationwide Inpatient Sample (2016–2020), identifying adult SBS hospitalizations stratified by the presence of liver disease (steatosis, cirrhosis, hepatic failure). Patients with primary hepatic disorders (viral, autoimmune, metabolic), alcoholic liver disease, and hepatic vessel thrombosis were excluded. Primary outcomes were mortality and complications including malnutrition, nutritional deficiencies, portal hypertension, cholelithiasis, sepsis and respiratory failure; secondary outcomes included predictors of liver disease. Multivariate regression was performed, adjusting for patient and hospital factors. **Results:** Among 119,750 weighted SBS hospitalizations, 7,630 (6.4%) had liver disease (steatosis $n = 4,610$; cirrhosis $n = 2,120$; hepatic failure $n = 1,865$) (Table 1). In patients with liver disease, in-hospital mortality rates were higher (8.6% vs. 2.1%, p-value < 0.001), mean length of stay was longer (11.2 vs. 8.5 days, $p < 0.001$) and admission costs were greater ($141,401 vs. $90,897 USD, $p < 0.001$) (Table 1). The mortality rate among patients with steatosis was similar to those without liver disease (2.93% vs 2.1%, $p = 0.1$). Independent predictors of steatosis/cirrhosis included female gender (aOR: 1.28, $p = 0.001$), malnutrition (aOR: 1.18, $p = 0.013$), fat-soluble vitamin deficiency (aOR: 1.68, $p < 0.001$), B12 deficiency (aOR: 1.89, $p = 0.014$), inflammatory bowel disease (IBD) (aOR: 1.34, $p = 0.001$), cholelithiasis (aOR: 1.75, $p < 0.001$), alcohol use (aOR: 1.99, $p < 0.001$), and obesity (aOR: 2.01, $p = 0.001$) (Table 1). Liver failure was associated with malnutrition (aOR 1.5, $p = 0.001$), PHT (aOR 3.3, $p < 0.001$), cholelithiasis (aOR 1.79, $p = 0.042$), sepsis (aOR 1.98, $p < 0.001$), and prior liver transplant (aOR 3.09, $p = 0.006$) (Table 1). **Conclusion:** This analysis highlights the significant

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burden of hepatic complications in SBS, with IFALD markedly increasing mortality and healthcare utilization. Risk factors such as malnutrition, vitamin deficiencies, IBD, and cholelithiasis highlight the multifactorial pathogenesis of IFALD. Notably, sepsis and evidence of PHT strongly predicted progression to liver failure. These findings underscore the need for early monitoring for nutritional deficiencies and hepatic steatosis to mitigate progression and improve outcomes in this high-risk population.

Table 1 Demographics and clinical outcomes in patients hospitalized with SBS with and without diagnosis of hepatic disease. Multivariate logistic regression of predictors of steatosis/cirrhosis and liver failure.

Demographics	SBS without hepatic disease	SBS with hepatic disease	P-value
Baseline demographics	112,120 (93.63%)	7630 (6.37%)	
Type of Liver Disease			
- Steatosis	-	4610 (60.42%)	
- Cirrhosis	-	2120 (21.20%)	
- Failure (inc. cirrhosis and steatosis)	-	1895 (24.84%)	
Sex			
- Female	77,519 (69.14%)	5400 (70.77%)	0.2030
- Male	34,601 (30.86%)	2230 (29.23%)	0.2030
Mean Age (years)	57.47	55.86	<0.001***
Inpatient mortality rate	2,400 (2.14%)	655 (8.60%)	<0.001***
- Steatosis		135 (2.93%)	0.1007
- Cirrhosis		120 (5.67%)	<0.001***
- Failure		500 (26.39%)	<0.001***
Mean length of stay (days)	8.53	11.16	<0.001***
Mean total healthcare cost (USD)	$90,897	$141,404	<0.001***
Predictors of steatosis/cirrhosis	**Adjusted odds ratio**	**95% CI**	**P-value**
Female	1.28	1.102-1.475	0.001**
Malnutrition	1.18	1.035-1.349	0.013*
Fat soluble vitamin deficiency	1.68	1.383- 2.048	<0.001***
B12 deficiency	1.89	1.140- 3.146	0.014*
Folate deficiency	2.58	0.951-7.024	0.063
Cholelithiasis	1.75	1.292-2.368	<0.001***
Alcohol use	1.99	1.420- 2.773	<0.001***
Inflammatory bowel disease	1.34	1.121- 1.603	0.001**
Obesity	2.01	1.677- 2.412	0.001**
Diabetes mellitus	0.69	0.565-0.834	<0.001***
Chronic kidney disease	0.37	0.312-0.428	<0.001***
Tobacco smoking	0.76	0.640-0.907	0.002**
Predictors of hepatic failure	**Adjusted odds ratio**	**95% CI**	**P-value**
Malnutrition	1.50	1.190-1.890	0.001**
Fat soluble vitamin deficiency	0.67	0.372-1.200	0.177
Portal hypertension	3.30	2.409-4.515	<0.001***
Cholelithiasis	1.79	1.022-3.133	0.042*
Sepsis	1.98	1.454-2.703	<0.001***
Acute kidney injury	2.43	1.875-3.160	<0.001***
Shock	2.99	2.140-4.181	<0.001***
Acute respiratory failure	2.06	1.551-2.725	<0.001***
Alcohol use disorder	1.59	0.867-2.902	0.134
Inflammatory bowel disease	0.74	0.495-1.094	0.129
Diabetes	0.55	0.350-0.8554	0.008**
Diabetes with complications	0.52	0.357-0.764	0.001**
Chronic kidney disease	0.41	0.304-0.549	<0.001***
Tobacco use	0.69	0.487-0.980	0.038*
Prior liver transplant	3.09	1.387-6.875	0.006**
Anxiety	0.72	0.531-0.975	<0.001***

Disclosures: Michael Gianarakis: Nothing to Disclose, Adam Mikolajczyk: Nothing to Disclose, Robert Carroll: Nothing to Disclose

3639 | IMMUNE CELL EFFECTOR FUNCTION AND METABOLIC DYSREGULATION IN WILSON DISEASE: IMPLICATIONS FOR IMMUNE-METABOLIC CROSSTALK IN COPPER TOXICITY

Robert Hughes[1] Svetlana Lutsenko[1] James Hamilton[1], *[1]Johns Hopkins University*

Background: Wilson Disease is an autosomal recessive disorder caused by mutations in the gene encoding the copper transporter, ATP7B. Inactivation of ATP7B results in copper accumulation in various tissues including the liver, but clinical presentation and disease severity do not necessarily correlate with hepatic copper content. While the genetic cause of Wilson Disease is clear, the mechanism of disease remains only coarsely defined.

Prior work has demonstrated that a global *Atp7b* knockout mouse model recapitulates the hepatic phenotype of Wilson Disease (copper accumulation, ballooning hepatocytes, inflammation, fibrosis). Interestingly, however, when the *Atp7b* gene is specifically knocked out in hepatocytes, the inflammatory pattern is muted. In this study, we sought to better understand the effects of global loss of Atp7b on immune cell populations, and how this contributes to the persistent pro-inflammatory state in the liver. **Methods:** Immune cell populations were isolated from the bone marrow and spleen of 20 week old *Atp7b* global knockout (KO) and age-matched wild-type (WT) mice. These immune cell populations were then characterized by expression markers using flow cytometry, induced toward different activation states ex vivo, and their metabolic profiles assessed via Seahorse assay. **Results:** Macrophages derived from the *Atp7b* knockout (KO) mice demonstrated enhanced M1 polarization, as suggested by increased NOS2 expression (Figure 1A) and a trend towards enhanced basal ECAR via Seahorse assay (1B), when compared to macrophages derived from the WT mice. There was no significant difference in M2 polarization between the WT and KO-derived macrophages (1C), but the KO-derived M2 macrophages demonstrated a significantly increased maximum respiratory capacity (1D). In addition, there is enhanced activation of CD8+ and CD4+ T-cells derived from the KO mice, as evidenced by these populations being skewed toward a CD44 +CD62L- phenotype with significantly increased CD69 expression (1E, 1G). KO-derived effector T cells demonstrated a higher basal rate of oxygen consumption, higher basal rate of glycolysis, and non-mitochondrial respiration as determined by Seahorse assay (1F). Despite a more activated phenotype, however, there was reduced TNF production by KO-derived CD8+ T-cells (1E). **Conclusion:** Immune cells derived from the *Atp7b* knockout mice exhibit a pro-inflammatory predominant phenotype but demonstrate some signs of defective effector function, as evidenced by the reduced TNF production seen in CD8+ T cells. This could be due to an exhaustive effect of extracellular factors secreted by the diseased liver onto immune cells or an inherent defect within the immune cells due to a lack of functional Atp7b. Future

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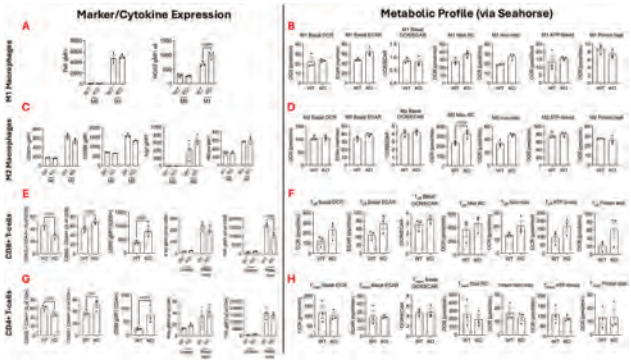
studies will focus on further characterizing the liver-resident and infiltrating immune cells as well as quantification of the copper content with these immune cell populations.



Disclosures: Robert Hughes: Nothing to Disclose, Svetlana Lutsenko: Nothing to Disclose, James Hamilton: orphalan pharmaceuticals: Advisor

3640 | GENETIC DRIVERS OF LIVER CIRRHOSIS: THE ROLE OF SERPINA1 AND PNPLA3 VARIANTS IN DISEASE ONSET AND PROGRESSION

Sona Frankova[1] Mikolas Holinka[1] Svetlana Adamcova Selcanova[2] Lubomir Skladaný[2] Ondrej Fabian[1] Martin Kveton[1] Dusan Merta[1] Vera Adamkova[1] Jaroslav Hubacek[1] Veronika Pitova[1] Sarka Vesela[1] Tomas Hucl[1] Milan Jirsa[1] Jan Šperl[1], [1]Institute for Clinical and Experimental Medicine, Prague, Czech Republic, [2]F.D. Roosevelt Hospital Banska Bystrica, Slovakia

Background: Variant alleles *SERPINA1 Z* (alpha-1-antitrypsin (AAT) rs28929474) and *PNPLA3* G (patatin-like phospholipase domain-containing protein rs738409) are the most potent genetic risk modifiers of liver cirrhosis in chronic liver disease (CLD). We aimed to test the impact of concomitant carriage of these variant alleles on the progression of CLD of various aetiologies. **Methods:** The genotyping for *SERPINA1* rs28929474 and *PNPLA3* rs738409 was performed in the study group consisting of 1583 liver transplant candidates with cirrhosis of various aetiology: alcoholic 577 (ALD), metabolic dysfunction-associated 208 (MASLD), viral 264 (VIR), autoimmune and cholestatic 443 (AIH-CHOL), and metabolic 91 (MET) and in the group of 3,483 healthy population controls. Samples of explanted livers were immunostained for AAT aggregates. **Results:** The frequency of *SERPINA1* MZ heterozygotes (M means wildtype allele) was significantly higher ($p < 0.0001$) in the entire cirrhosis group (84 of 1583; 5.3%) than in controls (89 of 3483; 2.6%); OR 2.57; 95% CI 1.92–3.44 for liver cirrhosis. The frequency of *SERPINA1* MZ heterozygotes was significantly higher in the subgroups with ALD and MASLD cirrhosis (37 of 557; 6.4% and 23 of 208; 11.1%, respectively, $p < 0.0001$) than in controls; the frequency in the subgroups VIR, AIH-CHOL and MET did not differ vs. controls. The frequency of the *PNPLA3* G allele was significantly higher ($p < 0.0001$) in the entire cirrhosis group (880 of 1583; 55.6%) than in controls (1418 of 3402; 41.6%); OR 1.48; 95% CI 1.36–1.99 for liver cirrhosis. The G allele frequency was significantly higher only in the subgroups with ALD, MASLD and VIR cirrhosis (392 of 577, 67.9%; 133 of 208, 63.9% and 139 of 264, 52.7%; $p < 0.0001$ and $p = 0.0005$, respectively) than in controls. The frequency of the *PNPLA3* G allele was the same in cirrhotic patients carrying *SERPINA1* MM and MZ genotypes (824 of 1483, 55.6% vs. 50 of 84, 59.2%, N.S.). The *PNPLA3* genotype had no impact on the density and extent of AAT aggregates in the liver tissue of *SERPINA 1* MZ heterozygotes. *SERPINA1* MZ heterozygotes with ALD and MASLD were significantly younger (56.9 vs. 60 years, $p = 0.046$) and had a higher MELD score (17 vs. 15 points, $p = 0.0003$) at waitlisting, whereas the *PNPLA3* genotype had no impact on the age and MELD score at waitlisting. **Conclusion:** We conclude that both variant alleles increase the risk of liver cirrhosis in ALD and MASLD; however, *SERPINA1* MZ heterozygotes have more progressive chronic liver disease and need liver transplantation at a younger age.

Disclosures: Sona Frankova: Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ipsen: Speaking and Teaching, Mikolas Holinka: Nothing to Disclose, Svetlana Adamcova Selcanova: Nothing to Disclose, Lubomir Skladaný: Worwag: Speaking and Teaching, ProMed: Speaking and Teaching, Abbvie: Speaking and Teaching, Gilead: Speaking and Teaching, RegPharm: Speaking and Teaching, Astellas: Speaking and Teaching, Ondrej Fabian: Nothing to Disclose, Martin Kveton: Nothing to Disclose, Dusan Merta: Nothing to Disclose, Vera Adamkova: Nothing to Disclose, Jaroslav Hubacek: Nothing to Disclose, Veronika Pitova: Nothing to Disclose, Sarka Vesela: Nothing to Disclose, Tomas Hucl: Nothing to Disclose, Milan Jirsa: Nothing to Disclose, Jan Šperl: Gilead Sciences: Speaking and Teaching, Abbvie: Speaking and Teaching, Ipsen: Speaking and Teaching

3641 | LONGITUDINAL STUDY OF ACUTE HEPATIC PORPHYRIAS IN THE US: BASELINE FEATURES OF 400 SUBJECTS FROM THE PORPHYRIAS CONSORTIUM

Bruce Wang[1], [1]University of California San Francisco

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Background: The longitudinal study (LS) of the porphyrias is a NIH funded natural history study of the porphyrias in the United States. The goal is to assess the natural history, biochemical changes, therapeutic effects, and potential association with other medical conditions. To date more than 400 patients with acute hepatic porphyrias (AHP) have been enrolled, with some patients followed for more than 10 years. We previously described the baseline characteristics of the first 108 AHP patients. Here we provide an update to describe the baseline characteristics of more than 400 AHP patients. **Methods:** From 2009 to 2023, 404 patients of AHP were enrolled in the LS, including AIP (330 cases), VP (49 cases), HCP (24 cases), and ADP (1 case). Data including demographic characteristics (gender, race, ethnicity, family history), signs and symptoms, genetic testing, biochemical parameters (ALA, PBG, urine/serum creatinine, AST, ALT), as well as treatment history involving Hematin and Givosiran was entered into a centralized database. Selected features were compared to normal population values using various statistical analysis tools, including the Chi-Square test, T-test, and Pearson correlation. These analyses were performed within the SPSS Statistics 27.0.1 environment. **Results:** Among 404 patients in the study, 85% (345) were white, 80% (322) were females, and, mostly were diagnosed within ages of 33.1 ± 14.58. Patients were categorized based on their clinical presentation and frequency of attacks into 3 groups: recurrent (4 or more attacks annually), sporadic, and asymptomatic. Asymptomatic patients were further separated into those with abnormal ALA/PBG and those with normal ALA/PBG. We looked for clinical correlation between these groups with biochemical factors, DNA mutation, and diversity and severity of symptoms. The most common symptoms associated with acute attacks were abdominal pain, nausea, weakness, heartburn, and high blood pressure, and their incidences were significantly increased in porphyria compared to normal population as control. AHP diagnosis remains delayed, with a mean of 9 years after the onset of symptoms, though this is improved from our earlier report. Forty one percent (167) of patients have received intravenous Hematin, the majority of whom had recurrent acute attacks. Such a delayed diagnosis would significantly increase the occurrence of chronic medical conditions including chronic kidney disease with different stages (mean estimated GFR = 72.00) over the period before the diagnosis of porphyria. **Conclusion:** AHP remain undiagnosed for many years following the onset of symptoms. This delayed diagnosis can impact the quality of life and lead to the development of chronic medical conditions over time. A comprehensive understanding of the porphyria population in the United States can assist healthcare providers in achieving earlier diagnoses and implementing appropriate management strategies.

Disclosures: Bruce Wang: Alnylam Pharmaceuticals: Consultant, Recordati Rare Diseases: Consultant, Disc Medicine: Consultant, Mitsubishi Tanabe Pharma: Consultant, Mitsubishi Tanabe Pharma: Grant/Research Support, CRISPR Therapeutics: Consultant

3642 | A NOVEL NOMOGRAM BASED ON COMMON CLINICAL INDICATORS FOR DIFFERENTIAL DIAGNOSIS OF INHERITED UNCONJUGATED HYPERBILIRUBINEMIA WITH HEMOLYTIC DISEASES

Haitian Yu[1] Meihan Li[1] Dacheng Sheng[1] Shan Tang[1] Jianxia Dong[1] Wei Hou[1] Sujun Zheng[1], [1]Department of Hepatology, Beijing YouAn Hospital, Capital Medical University, Beijing, China

Background: This study was designed to create and validate a nomogram model incorporating common clinical indicators to distinguish between unconjugated hyperbilirubinemia associated with UGT1A1 gene mutations and hemolytic diseases. **Methods:** We conducted a retrospective analysis of a cohort of patients diagnosed with unconjugated hyperbilirubinemia at Beijing YouAn Hospita, Capital Medical University from January 2022 to January 2025. Clinical and laboratory data from 379 subjects were extracted and participants were randomly assigned to training and validation groups in a 7:3 ratio. Significant variables associated with differential diagnosis were identified using least absolute shrinkage and selection operator regression(Lasso) and multivariate logistic regression models. Cutoff values derived from univariate receiver operating characteristic (ROC) curves were utilized to convert nonlinear continuous variables into binary categorical variables, establishing the diagnostic nomogram. The nomogram's predictive accuracy and clinical utility were evaluated in both the training and validation sets using ROC curves, calibration curves, and decision curve analysis(DCA). **Results:** A total of 317 patients with UGT1A1 gene mutation-associated unconjugated hyperbilirubinemia were enrolled, including 106 cases of Gilbert's syndrome and 11 cases of Crigler-Najjar type II. Additionally, 62 patients with hemolytic disease-associated unconjugated hyperbilirubinemia were included, comprising 36 cases of hereditary spherocytosis, 8 cases of autoimmune hemolytic anemia, 4 cases of hereditary stomatocytosis, 1 case of thalassemia, 1 case of BPGM gene mutation-related erythrocytosis, and 12 cases of unexplained hemolysis. Through variable selection using Lasso regression and logistic regression, four key variables were identified: abnormality of peripheral blood smear, hematocrit, red cell distribution width standard

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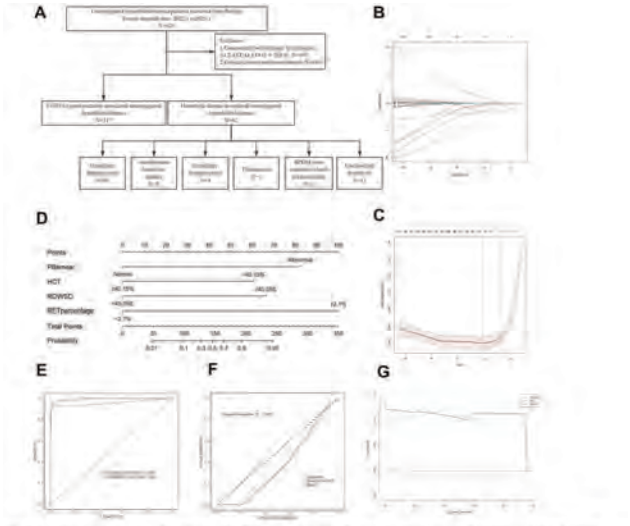
deviation, and reticulocyte percentage. These variables were used to construct a differential diagnostic nomogram model with an optimal cutoff value of 126 points. The nomogram demonstrated excellent performance, with areas under the ROC curve of 0.99 (0.98–1.00) in the training set and 0.96 (0.88–1.00) in the validation set. Calibration curves showed good agreement between predicted and actual outcomes, with Hosmer-Lemeshow test p-values >0.05. DCA further confirmed the clinical utility of this nomogram. **Conclusion:** We successfully developed an effective nomogram model that can differentiate between UGT1A1 gene mutation-associated and hemolytic disease-associated unconjugated hyperbilirubinemia. This model significantly enhances the preliminary screening efficiency for patients with unconjugated hyperbilirubinemia.



(A) Subject Selection Process.(B & C) Variable Selection via Lasso Regression Analysis.(D) Development of Differential Diagnostic Nomogram for Unconjugated Hyperbilirubinemia. (PB: Peripheral Blood, HCT: Hematocrit, RDWSD: Red Cell Distribution Width Standard Deviation, RET: Reticulocyte)(E) Receiver Operating Characteristic Curves of the Nomogram in the Training and Validation Groups.(F) Calibration Curve of the Nomogram in the Validation Group.(G) Decision Curve Analysis of the Nomogram in the Validation Group.

Disclosures: Haitian Yu: Nothing to Disclose, Meihan Li: Nothing to Disclose, Dacheng Sheng: Nothing to Disclose, Shan Tang: Nothing to Disclose, Jianxia Dong: Nothing to Disclose, Wei Hou: Nothing to Disclose, Sujun Zheng: Nothing to Disclose

3643 | ALPHA-1 FOUNDATION RESEARCH REGISTRY: COMPARISON OF LIVER-AFFECTED ALPHA-1 ANTITRYPSIN DEFICIENCY PATIENTS WITH PIZZ AND PIMZ GENOTYPES IN A UNITED STATES COHORT

Nadine Nuchovich[1] Alison Keaveny[1] Monica Goldklang[2] Jennifer Illarramendi[1] Randel Plant[1] Jeanine D'Armiento[2], [1]Alpha-1 Foundation, [2]Columbia University Irving Medical Center

Background: Alpha-1 Antitrypsin Deficiency (AATD) is a genetic condition characterized by accumulation of misfolded AAT protein in hepatocytes, leading to lung and liver disease. While the PiZZ genotype constitutes the largest burden of AATD liver disease, evidence suggests PiMZ genotype may also be at increased risk for liver complications highlighting the need to better understand the differences between these genotypes. **Methods:** The Alpha-1 Foundation (A1F) Research Registry is an online database of AATD patients in the United States and has enrolled over 4,100 participants from June 2019 to May 2025. We reviewed liver-affected participants with PiZZ and PiMZ genotypes who reported cirrhosis, MASH /MASLD, ascites, cholestasis, hepatopulmonary syndrome, portopulmonary hypertension, or bacterial peritonitis. **Results:** A total of 598 PiZZ participants reported to be liver-affected (mean age 52.6, +/- 17.99), along with 420 PiMZ (50.5, +/- 13.62). PiZZ participants were more likely to be tested for AATD due to lung symptoms (39.7% vs. 28.5% PiMZ), while both groups had similar rates for testing for liver symptoms (19.0% PiZZ vs 18.0% PiMZ). Although those with the PiZZ genotype had higher rates of reported cirrhosis (22.8%, vs. 9.2% PiMZ), rates of MASH/MASLD were similar in both groups (49.7% PiZZ, 50.4% PiMZ) as well as cholestasis (6.2% PiZZ, 5.9% PiMZ). Among liver-affected PiZZ participants, 53.6% reported additional diagnoses of COPD or emphysema. Augmentation therapy (42.1%) and use of oral or inhaled corticosteroids (42.4%) was notably higher compared to those with the PiMZ genotype (24.1%, 11.2%, and 30.5%, respectively). Fibroscan testing was performed on 24.8% of liver-affected PiZZ participants compared to liver-affected PiMZ's who reported 10.8%. Rates of alcohol consumption were noted in 22.1% of PiZZ individuals at least 2-3 times per week, compared to 17% of MZ's. **Conclusion:** Liver-affected PiZZ participants exhibited higher rates of lung disease and cirrhosis and had higher rates of Fibroscan elastography as compared to PiMZ participants. However, both genotypes exhibited comparable rates of MASH/MASLD and cholestasis. Alcohol and corticosteroid use were found to be higher in PiZZ participants and could contribute to higher rates of more severe liver disease. The A1F Research Registry is a useful tool for comparing AATD genotypes and has the capability to provide for a deeper dive into factors affecting disease burden and progression.

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3644 | PXR DELETION PROMOTES HEPATOCELLULAR METABOLIC REPROGRAMING IN ATP7B$^{-/-}$ MICE

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Background: Wilson's disease (WD) is an autosomal recessive disorder caused by inactivating mutations in the copper (Cu^{++}) transporting P-type ATPase. Loss of Atp7b function prevents translocation of Cu^{++} into the trans-Golgi network and excretion into bile, resulting in oxidative stress, inflammation, mitochondrial dysfunction, fibrosis, cirrhosis, and liver failure. WD patients and *Atp7b*$^{-/-}$ mice have a progressive course of hepatocellular pathology, including regenerative hepatic nodule growth. Previously, we demonstrated that deletion of PXR in *Atp7b*$^{-/-}$ mice (DKO$^{Atp7b/PXR}$) worsened hepatocellular pathology and increased regenerative nodular growth relative to *Atp7b*$^{-/-}$ mice. To determine the factors that promote the accelerated pathology in DKO$^{Atp7b/PXR}$ mice, we tested the hypothesis that loss of PXR results in cellular signaling and metabolic reprograming in WD. Methods:: RNA-Sequencing and targeted metabolic analysis (fatty acids, bile acids, amino acids, glycolytic, TCA cycle, pentose phosphate metabolites) was performed with 12-month-old wild-type mice and nodule and normal adjacent liver tissues of *Atp7b*$^{-/-}$ and DKO$^{Atp7b/PXR}$ mice. Hepatic metabolites were measured with LC/MS quadrupole mass spectrometry. **Results:** Normal liver tissue of *Atp7b*$^{-/-}$ and DKO$^{Atp7b/PXR}$ mice shared transcriptomic pathways representing metabolism (PPAR signaling and fatty acid metabolism) and metabolic stress (cardiomyopathy pathways). Although normal liver tissue of *Atp7b*$^{-/-}$ and DKO$^{Atp7b/PXR}$ mice had similar transcriptomic and metabolic profiles, DKO$^{Atp7b/PXR}$mice had unique transcriptomic profiles associated with advanced metabolic reprogramming and immune activation, which agreed with greater hepatic accumulation of TCA cycle and glycolytic intermediates in normal liver tissues of DKO$^{Atp7b/PXR}$ vs. *Atp7b*$^{-/-}$ mice. Nodular liver tissue of *Atp7b*$^{-/-}$ mice had profound enrichment of immune disease pathways and associated metabolites (palmitoleic acid, docosahexaenoic acid, malate, betaine, and bile acids). Conversely, nodular liver tissue of DKO$^{Atp7b/PXR}$ mice had transcriptomic and metabolic (glutamine, and eicosatetraenoic acid) signatures associated with structural and tissue remodeling. **Conclusion:** In agreement with our previous findings of exacerbated hepatocellular pathology and nodular regeneration in DKO$^{Atp7b/PXR}$ vs. *Atp7b*$^{-/-}$ mice, DKO$^{Atp7b/PXR}$ mice display transcriptomic and metabolic signatures reflective of advanced metabolic stress and tissue remodeling in comparison with *Atp7b*$^{-/-}$ mice. These findings support previous work demonstrating that PXR has an essential role in mediating hepatocellular stress in WD and is a viable therapeutic target for the treatment of WD.

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3645 | STRUCTURAL ANALYSIS AND PATHOGENICITY PREDICTION OF ATP7B GENE VARIANTS IN WILSON DISEASE

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Background: ATP7B gene testing enables precise diagnosis of Wilson's disease. However, emerging mutations of uncertain pathogenicity complicate clinical interpretation. This study aims to characterize the structural and functional impacts of these novel variants. **Methods:** Following informed consent, clinical data from 62 patients were collected and ATP7B genotyped. Novel variants of uncertain significance were functionally characterized via bioinformatics and in vitro minigene splicing assays. Statistical analysis of genotype-phenotype correlations was performed using SPSS 27.0. **Results:** A total of 48 mutations were identified across 17 exons, 5 introns, and the 5'UTR, with exon 8 harboring the highest mutation density. Eight novel mutations were discovered, four of which were classified as variants of uncertain significance. Following in silico prediction by REVEL and SpliceAI, two were deemed "deleterious," one "benign," and one predicted to disrupt splicing. Bioinformatics analysis of the top three exonic VUS characterized their sequence conservation, protein domains, transmembrane structure, and tertiary conformation. Minigene assays confirmed that intron 2 mutation c.1286-481A > G causes retention of a 136-bp intronic fragment containing a premature stop codon, resulting in truncated protein synthesis. Patients with p.R778L exhibited lower serum copper levels, while those without this mutation showed higher prevalence of loss-of-function (LOF) mutations. LOF mutation carriers were 68.4% male and had elevated ALP/GGT levels. Non-transmembrane domain mutations were associated with increased LOF frequency. p.E1173K was enriched in liver failure patients with age of onset $\leq$15 years. **Conclusion:** Of 48 identified mutations, 8 were novel. Bioinformatics and in vitro

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minigene assays characterized structural changes in 4 novel variants of uncertain significance (VUS) and re-evaluated their pathogenicity. Additionally, correlations were found between p.R778L/LOF mutations and serum copper/liver function markers, with p.E1173K associated with severe clinical phenotypes.

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3646 | LONGITUDINAL STUDY OF PSYCHIATRIC FEATURES AND DISEASE OUTCOMES IN WILSON DISEASE AT THE LARGEST UK PSYCHIATRIC CENTER

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Background: Wilson disease (WD) is a multi-systemic condition that can present with many different symptoms. Those that present with purely psychiatric presentation can have a longer time to diagnosis with irreversible symptoms.

South London and Maudsley NHS Foundation Trust (SLaM) is the largest provider of secondary mental health services in the UK and is the largest neuropsychiatric research centre in Europe.

We investigated the outcomes and progression of WD patients' psychiatric symptoms referred to a tertiary psychiatric hospital. **Methods:** We used national hospital episode statistics for the diagnosis of Wilson disease within the psychiatric cohort at SlaM and investigated outcomes and cause of death.

Using the validated natural language processing algorithm at SLaM within electronic patient records, able to detect 58 different psychiatric symptoms, we documented symptoms at presentation and then cumulatively across their follow up period. **Results:** In total 81 patients were identified as diagnosed with WD across the time-period with available electronic records.

At presentation patients reported anxiety (49%), cognitive impairment (49%), disturbed sleep (42%), tearful, hallucination, poor insight, mood instability, suicidal ideation, guilt and agitation. Cumulatively symptoms reported were of anxiety, cognitive impairment, disturbed sleep, hallucination, poor insight, tearful, suicidal ideation, paranoia, mood instability and agitation.

We found that the mortality rate of WD patients was 27%. The age range at death was 18 to 89 years with a mean time to death after referral of 83 months, with a range of 7 to 204 months. Gender and ethnicity variation within the cohort was similar to the overall WD distribution. **Conclusion:** Symptoms in our cohort at presentation and cumulatively were similar across patients. This provides evidence as to the common presenting psychiatric symptoms in WD, and over time these symptoms do not significantly change.

A higher than expected mortality rate was found within our patient cohort across a range of ages and time, this requires further investigation to better understand.

This work supports the evidence that psychiatric symptoms in WD are under recognised, often irreversible and may be linked to delay in diagnosis and premature death. It highlights the needs to crucially improve detection and diagnosis within this population. The data on mortality warrants further investigation to identify modifiable risks factors.

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3647 | PERTINENCE OF NON-INVASIVE METHODS: FOR LIVER FIBROSIS ESTIMATION AND TO IDENTIFY PATIENTS AT RISK OF COMPLICATIONS IN WILSON&RSQUO;S DISEASE

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Background: Wilson's disease (WD) can lead to liver fibrosis and cirrhosis. Liver biopsy remains the gold standard to assess fibrosis but is invasive with possible sampling errors. In this context, non-invasive tests (NITs) appear to be useful and easily reproducible, however they have not been yet validated in WD. The aim of this study was to evaluate the diagnostic performance of transient elastography (TE) and other NITs in predicting liver fibrosis (LF) in patients with WD, using histological staging as the reference standard. **Methods:** We retrospectively analyzed 2 cohorts of adult patients with a confirmed diagnosis of WD. Patients were evaluated clinically, biologically and morphologically. We included patients who had a liver biopsy and non-invasive liver fibrosis assessment by NITs (TE, APRI, FIB4, GUCI, CDS, Lok Index) with a time interval between biopsy and NITs of less than 3 months. Spearman's coefficient was calculated for the correlation between METAVIR staging and NITs. The

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AUROC was used to determine the predictive values of the quantitative variables. The performance of TE in predicting various clinical conditions was evaluated. **Results:** We retrospectively included 58 patients, with a mean age at WD diagnosis of 25.7 years (SD ± 11.4). All patients included in the study had liver involvement and 27 (46.55%) also presented neuro-psychiatric manifestations. There was a significant correlation between TE and METAVIR score ($p = 0.001$). The optimal thresholds identified for the diagnosis of cirrhosis was > 11.1 kPa (AUC 0.97, Se 100%, Sp 90%). For advanced fibrosis (F3) the cut-off was > 8.6 kPa, for mild/moderate fibrosis (F1) $\leq$ 7.9 kPa and $\leq$ 6.1 kPa for the absence of fibrosis (F0). We found a significant correlation between all the other NITs and F4 METAVIR staging: APRI: $\rho = 0.52$, $p < 0.0001$; FIB4: $\rho = 0.50$, $p < 0.0001$; GUCI: $\rho = 0.49$, $p < 0.0001$; CDS: $\rho = 0.57$, $p < 0.0001$; Lok Index: $\rho = 0.60$, $p < 0.0001$. The TE measurements could predict the risk of cirrhosis decompensation with ascites, using a threshold of 14 kPa (AUC = 0.83, Se 89%, Sp 78%). **Conclusion:** TE measurements correlate with METAVIR staging in WD patients and can identify different stages of LF and those at risk of cirrhosis decompensation. The other NITs appear to be useful tools in identifying or excluding cirrhosis supporting measurements at TE.

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3648 | LIVER DISEASE PROGRESSION IN INDIVIDUALS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED GENOTYPES: INSIGHTS FROM A LARGE GENETIC DATABASE LINKED TO ELECTRONIC MEDICAL RECORDS IN THE USA

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Background: Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disorder that can lead to liver and/or lung disease and is often underdiagnosed. This study used genetic information from a large electronic medical record (EMR)-linked biobank in the USA (BioVU) to evaluate progression of liver disease and associated clinical events and their potential predictors in individuals with AATD genotypes. **Methods:** A retrospective cohort of adults with AATD genotypes (protease inhibitor [Pi] MS/MZ/SS/SZ/ZZ) was identified using genetic data from BioVU among consented care recipients at Vanderbilt University Medical Center from 2018 to 2022. Based on their linked EMRs, individuals with one or more ICD-9/-10-CM code(s) for hepatic cirrhosis/fibrosis or one or more aspartate aminotransferase to platelet ratio index (APRI) score (calculated from laboratory measures within 3 months) were included and categorized at index as cirrhosis (APRI $>$ 1.5), fibrosis (APRI $>$ 0.43), or no fibrosis (APRI $\leq$ 0.43) (Wu T *et al. Aliment Pharmacol Ther* 2023;58:1075–85). A Kaplan–Meier analysis was conducted for liver disease progression to cirrhosis or a decompensating liver event. A Cox regression model was fit to assess time to liver disease progression using population characteristics as potential predictors. **Results:** In total, 6,804 individuals with an AATD genotype were included (mean age 52.3 years; 56.1% female; 93.1% White; 4.5% with lung disease), of whom 5.4%, 17.9%, and 76.7% had cirrhosis, fibrosis, and no fibrosis at index, respectively. The analytic cohort comprised 6,258 individuals, excluding those with evidence of liver decompensation on or before index date (median [interquartile range] follow-up: 5.2 [1.2–11.5] years). Time to liver disease progression is presented by index liver state (Figure A) or by AATD genotype (Figure B). Based on the Cox analysis, male sex, older age, Pi*ZZ genotype, use of augmentation therapy, and history of neonatal jaundice were all significantly ($p \leq 0.01$) associated with an increased rate of liver disease progression. Additionally, each of the incremental APRI score categories (referenced to APRI $\leq$ 0.43) was significantly ($p < 0.005$) associated with increased risk of liver disease progression: adjusted hazard ratio 1.33 (95% confidence interval 1.09–1.61), 2.56 (2.02–3.24), and 3.95 (2.84–5.50) for APRI 0.43 to $<$ 0.63, 0.63 to $<$ 1.50, and $\geq$ 1.5, respectively. **Conclusion:** This study leveraged genetic data with linked EMRs and provides evidence that patients carrying the Pi*ZZ genotype have the highest risk of liver disease progression, followed by Pi*SZ and other genotypes. Additionally, a higher APRI score at index was a strong predictor of liver disease progression, underscoring its value in identifying patients at higher risk for liver-related outcomes.

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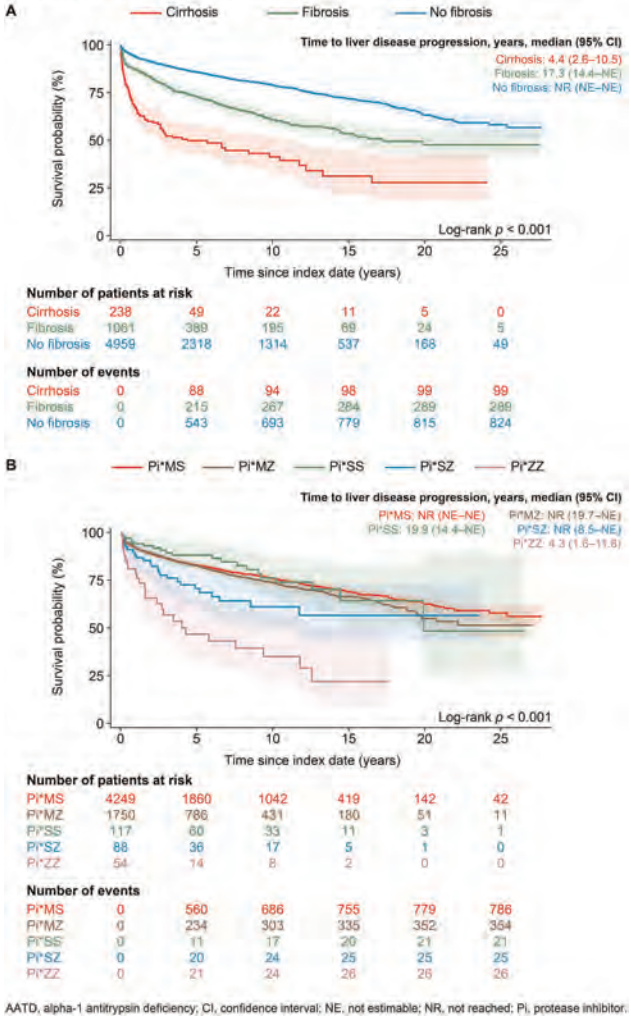
Figure. Kaplan–Meier plots for liver disease progression to cirrhosis or decompensating liver event: by liver disease state at index (A) and by AATD genotype (B).



AATD, alpha-1 antitrypsin deficiency; CI, confidence interval; NE, not estimable; NR, not reached; Pi, protease inhibitor.

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3649 | DIURNAL VARIATION IN BLOOD AMMONIA LEVELS IN PATIENTS WITH ADULT-ONSET TYPE II CITRULLINEMIA

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Background: Adult-onset type II citrullinemia (CTLN2) is a disorder characterized by neuropsychiatric symptoms such as impaired consciousness, abnormal behavior, and seizures, resulting from hyperammonemia and hypercitrullinemia caused by mutations in *SLC25A13*, which encodes citrin, a mitochondrial inner membrane transporter protein. Although the pathophysiology of CTLN2 has been described, there are few reports on the diurnal variation of blood ammonia levels in these patients. Based on our clinical experience with CTLN2 patients who exhibited normal fasting ammonia levels, we hypothesized that blood ammonia levels may show significant diurnal variation. This study aimed to investigate the diurnal fluctuations in blood ammonia levels in patients with CTLN2. **Methods:** We studied three hospitalized patients with CTLN2: a 50-year-old man, a 62-year-old man, and a 62-year-old woman. During hospitalization, patients were instructed to avoid snacks between breakfast, lunch, and dinner. Blood ammonia levels were measured at the following time points: 7:30, 9:00, 11:30, 13:00, 17:30, 19:00, and 22:00, both before and after meals and before bedtime. **Results:** In the 50-year-old male patient (Case 1), the citrulline concentration was 102.1 nmol/mL (normal: 17.1–42.6), with albumin 4.4 g/dL, total bilirubin 1.3 mg/dL, AST 33 U/L, ALT 47 U/L, ALP 235 U/L, γ-GTP 84 U/L, platelet count 19.6×10^4/μL, prothrombin time (PT) 92%, and ICG retention at 15 minutes of 9%. Blood ammonia levels at the designated time points were 100, 215, 411, 470, 121, 142, and 358 μg/dL, showing a maximum diurnal fluctuation of 370 μg/dL. The 62-year-old male patient (Case 2) had a citrulline concentration of 131.4 nmol/mL, albumin 3.4 g/dL, total bilirubin 1.2 mg/dL, AST 50 U/L, ALT 55 U/L, ALP 367 U/L, γ-GTP 96 U/L, platelet count 12×10^4/μL, PT 82%, and ICG (15 min) 8%. His ammonia levels were 44, 100, 121, 163, 79, 269, and 182 μg/dL, with a maximum variation of 225 μg/dL. The 62-year-old female patient (Case 3) showed a citrulline level of 486.4 nmol/mL, albumin 3.4 g/dL, total bilirubin 0.8 mg/dL, AST 36 U/L, ALT 37 U/L, ALP 352 U/L, γ-GTP 64 U/L, platelet count 19.6×10^4/μL, PT 120%, and ICG (15 min) 8%. Her blood ammonia values were 57, 94, 134, 136, 193, 125, and 203 μg/dL, with a maximum fluctuation of 146 μg/dL. In all three cases, fasting morning ammonia levels were within the normal range, and there was a clear tendency for levels to increase toward the evening. The magnitude of diurnal variation was considerable, with maximum differences of 370 μg/dL in Case 1, 225 μg/dL in Case 2, and 146 μg/dL in Case 3. **Conclusion:** Blood ammonia levels in CTLN2 exhibit marked diurnal variation, and some patients may show

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normal values during early morning fasting, which could lead to missed diagnoses. Although ammonia levels tend to peak at night, measuring post-lunch ammonia levels in outpatient settings may be more useful for accurate diagnosis.

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3650 | LIVER-HUMANIZED MICE REPOPULATED WITH HEPATOCYTES FROM A HEMOPHILIA B DONOR EXHIBIT DELAYED BLOOD CLOTTING AND HAVE A PHYSIOLOGIC RESPONSE TO GENE THERAPY CORRECTION OF HUMAN FIX

Devorah Goldman[1] Zoe Dimond[1] Riffat Ahmed[2] Robert Copenhaver[3], [1]Yecuris, [2]Yecuris Corp., [3]Yecuris Corporation

Background: Hemophilia B (HEMB), a single gene disorder affecting Factor IX (FIX), is an ideal target for gene therapies. In order to establish a relevant model for evaluating such therapeutics, primary hepatocytes from a patient with HEMB were evaluated for clotting defects and gene therapy correction in vivo in liver-humanized mice. **Methods:** Primary hepatocytes from a male HEMB donor carrying a pathogenic, missense mutation c.316 G > A (rs137852233) in FIX were transplanted into male FRG® mice on the NOD background (FRGN). This mutation converts a highly conserved Gly to Ser in the EGF1 domain of FIX and is associated with mild to moderate hemophilia B. Primary hepatocytes from a non-hemophilic human male donor were transplanted into male FRGN mice as a control. Donor performance and blood clotting in mice with human albumin levels of >4000 μg/mL, indicative of livers repopulated with $>70\%$ human hepatocytes, were compared. **Results:** Humanized mice repopulated with control donor cells ($n=3$) had average circulating human FIX (hFIX) levels of 1436ng/mL, whereas mice repopulated with the HEMB donor ($n=6$) had circulating hFIX levels of 647ng/mL. Measurement of partial thromboplastin time (PTT) in plasma samples from liver-humanized mice created with the control donor cells ($n=9$) revealed a mean PTT of 28.49 seconds. In HEMB liver-humanized mice ($n=9$), the average PTT was increased by 24% to 35.34 seconds. Thus, physiologically relevant defects in clotting could be modelled in liver-humanized mice reconstituted with a HEMB donor. To demonstrate that this model could be used to assess efficacy of gene therapies, HEMB mice were injected i.v with $2.5x10^{11}$ copies per mouse of a liver-tropic AAV expressing hFIX (AAVDJ-CAG-hFIX). One week after injection, increased expression of hFIX (14,266ng/mL) and a significant decrease in PTT (30.25s, $p<0.005$) was observed compared to untreated HEMB liver-humanized mice. Even without optimization of AAV-mediated correction, there was no significant difference in clotting time between HEMB liver-humanized mice that received hFIX gene therapy and mice that were liver-humanized with hepatocytes from a control donor. **Conclusion:** Our findings demonstrate that primary human hepatocytes from donors with genetic disease such as hemophilia B can successfully repopulate FRG mice, recapitulate physiologic disease pathologies, and be used to evaluate relevant in vivo therapeutic approaches.

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3651 | HEPATIC OUTCOMES IN PORPHYRIA: AN UNDERSTUDIED AND UNDER EVALUATED COMPLICATION

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Background: Porphyrias are rare metabolic disorders traditionally associated with cutaneous or neurovisceral manifestations. Porphyria Cutanea Tarda (PCT) and Erythropoietic Protoporphyria (EPP) are frequently linked to hepatic complications, including steatosis, cirrhosis, and liver failure. Although potentially severe, these complications remain under-evaluated and under-recognized. This study aims to evaluate factors associated with hepatology referral and to compare hepatic outcomes in porphyria patients based on whether they received hepatology care. **Methods:** We conducted a retrospective study of all patients diagnosed with EPP or PCT at our center. Following IRB approval, individual chart reviews were performed. Patients were divided into two groups: those seen by hepatology, forming the hepatology group (HG) and those not seen by hepatology, forming the control group (CG). Demographics, liver function tests, imaging findings, liver biopsy data, and transplant status were compared between the groups. **Results:** Of the 93 patients identified, 25 (27%) patients were evaluated by hepatology, formed the HG and 68 (73%) patients were not, forming the CG. There were no significant differences in gender, porphyria type, or alcohol use between the groups. A total of 20 (80%) patients in the HG and 56 (82.4%) in the CG were on porphyria

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treatment (p = 0.767), with no significant differences in treatment modality. Patients in the HG had significantly higher mean ALT levels (70.3 vs. 37.3 IU/L, p = 0.03). While AST (80.2 ± 101.9 vs. 39.1 ± 31.3, p = 0.1005), ALP (96.4 ± 57.2 vs. 83.7 ± 36.0, p = 0.3811), and bilirubin (2.2 ± 3.0 vs. 1.2 ± 3.1, p = 0.212) levels were also elevated in this group, the differences were not statistically significant. Liver ultrasound (US) was more frequently performed in the HG (72% vs. 39.7%), with a higher frequency of cirrhosis (16% vs. 4.4%), steatosis (24% vs. 8.8%), and hepatic malignancy (8% vs. 0%) (p = 0.0074). Liver biopsies were more commonly performed in the HG (24% vs. 1.5%, p = 0.001), and 5 patients (20%) in this group underwent liver transplantation compared to none in the CG (p = 0.0003). For the patients in the HG, 10 (40%) were on active treatment for Hepatitis C, 2 (8%) were on bile acid sequestrants, and 1 (4%) was on steroids and ursodiol per hepatology recommendations. **Conclusion:** Porphyria patients who were evaluated by hepatology exhibited a significantly higher burden of hepatic complications, including cirrhosis, malignancy, and need for liver transplantation. These findings emphasize the importance of early hepatology referrals, particularly for patients with abnormal liver enzymes or imaging results. Greater awareness and multidisciplinary follow-up may improve detection, intervention, and outcomes of hepatic complications in porphyria.

	Seen by Hepatology N=25	Not Seen by Hepatology N=68	p-value
Sex, M. n (%)	16 (64.0%)	40 (58.8%)	0.8311
Race			0.3713
• White n (%)	23(92.0%)	64 (94.1%)	
• Black n (%)	0 (0.0%)	1 (1.5%)	
• Arab n (%)	2 (8.0%)	(0.0%)	
• Others n (%)	0 (0.0%)	2 (2.9%)	
Alcohol Use, n (%)	8 (32.0%)	13 (19.1%)	0.3788
Type of Porphyria			0.9499
• PCT n (%)	13 (52%)	33 (48.5%)	
• EPP n (%)	12 (48%)	35 (51.5%)	
Presenting Symptoms			0.0597
• Cutaneous n (%)	16 (64.0%)	58 (85.3%)	
• Hepatic n (%)	4 (16.0%)	3 (4.4%)	
• Others n (%)	5 (20.0%)	7 (10.3%)	
Treatment for Porphyria			0.767
• Afamelanotide n (%)	6 (24.0%)	24 (35.3%)	
• Phlebotomy n (%)	6 (24.0%)	15 (22.1%)	
• Others n (%)	8 (32.0%)	17 (25.0%)	
• No treatment n (%)	5 (20.0%)	12 (17.6%)	
ALT (IU/L) Mean ± SD	70.3 ± 58.2	37.3 ± 34.9	0.0307
AST (IU/L) Mean ± SD	80.2 ± 101.9	39.1 ± 31.3	0.1005
ALP (IU/L) Mean ± SD	96.4 ± 57.2	83.7 ± 36.0	0.3811
Total Bilirubin (mg/dL) Mean ± SD	2.2 ± 3.0	1.2 ± 3.1	0.212
Ultrasound Performed	18 (72%)	27 (39.7%)	0.0074
• Malignancy n, %	2 (8.0%)	0 (0.0%)	
• Steatosis n, %	6 (24.0%)	6 (8.8%)	
• Cirrhosis n, %	4 (16.0%)	3 (4.4%)	
• Others n, %	1 (4.0%)	2 (2.9%)	
• Normal n, %	5 (20.0%)	16 (23.5%)	
Splenomegaly n (%)	7 (28.0%)	9 (13.2%)	0.1942
Liver Biopsy	6 (24.0%)	1 (1.5%)	0.001
• F0-F1 n (%)	2 (8%)	0 (0%)	
• F2 n (%)	2 (8%)	0 (0%)	
• F3 n (%)	0 (0%)	1 (1.5%)	
• F4 n (%)	2 (8%)	0 (0%)	
Liver transplant status			0.0003
• Transplanted n (%)	5 (20.0%)	0 (0.0%)	
• Listed n (%)	1 (4.0%)	0 (0.0%)	
• Not listed n (%)	17 (68.0%)	66 (97.1%)	
• Deceased n (%)	2 (8.0%)	2 (2.9%)	

Table 1. Comparing demographics, disease characteristics, imaging, liver biopsy, and liver transplant between the two groups

Disclosures: Muhammad Saad Faisal: Nothing to Disclose, Razan Aburumman: Nothing to Disclose, Anju Pradeep: Nothing to Disclose, Minahil Fatima: Nothing to Disclose, Ammad Chaudhary: Nothing to Disclose, Abdulmalik Saleem: Nothing to Disclose, Muhammad Salman Faisal: Nothing to Disclose, Syed-Mohammed Jafri: Takeda: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ironwood: Advisor, Intercept: Speaking and Teaching

3652 | UNDERSTANDING THE EXPERIENCE OF ADULTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY LIVER DISEASE: A CONCEPT ELICITATION INTERVIEW STUDY

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Background: Alpha-1 Antitrypsin Deficiency (AATD) is a genetic disease characterized by low serum level of alpha-1-antitrypsin (A1AT) and accumulation of A1AT polymers in the liver. There is very limited qualitative evidence describing the experience of individuals living with AATD liver disease (LD). This study aimed to describe the symptoms of AATD LD in adults and its associated impacts on functioning. **Methods:** Adults (≥ 18 years) with AATD LD and clinicians managing individuals with AATD LD located in the US participated in one-on-one, semi-structured, concept elicitation interviews. Participants were identified through a recruitment vendor. Interviews were conducted virtually and recorded. Deidentified transcripts of interview recordings were analyzed using qualitative analytic software (ATLAS.ti v22 [Scientific Software Development GmbH, Berlin]). **Results:** Twenty adults diagnosed with AATD LD and four clinicians were interviewed. Adults with AATD LD had a mean age of 61.4 years, were 70% female, and had a mean duration since diagnosis of 9.9 years; genotypes were protease inhibitor [Pi]-ZZ (n = 15), PiSZ (n = 3), and PiMZ (n = 2); fibrosis stages were F2 (n = 7), F3 (n = 2), F3/F4 (n = 2), F4 (n = 8), and unknown (n = 1). Clinicians had mean 23.5 years of AATD experience. Symptoms endorsed by at least 3 adults with AATD LD were shortness of breath (n = 6), cough (n = 5), pain in the upper right abdomen (n = 5), fatigue/weakness (n = 4), and fluid buildup in the abdomen (n = 3). Symptoms endorsed as worst symptoms were fatigue/weakness (n = 3), shortness of breath and pain in the upper right abdomen (n = 2 each). Adults with AATD LD endorsed impacts on emotional (n = 18),

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physical (n = 15), and social function (n = 14), relationships (n = 12) and work (n = 9). Clinicians endorsed fatigue/weakness (n = 4) and itchy skin (n = 3) as the most frequently reported symptoms of AATD LD. Both symptoms were endorsed by clinicians (n = 2 each) as the worst symptom reported by individuals with AATD LD. Clinicians endorsed similar impacts as those reported by adults with AATD LD. **Conclusion:** This study offers critical insights into the experience of adults with AATD LD across three genotypes and fibrosis stages. Adults with AATD LD and clinicians endorsed similar symptoms and impacts. These findings demonstrate that AATD LD is a heterogenous disease with substantial symptom and impact burden on adults living with AATD LD.

Table 1. Summary of frequently endorsed symptoms and impacts of AATD LD

Concepts		Adults with AATD LD (N=20)		Clinicians (N=4)	
		Endorsed the concept N (%)	Endorsed as the worst/most bothersome concept* N (%)	Endorsed the concept N (%)	Endorsed as the worst/most bothersome concept* reported by patients N (%)
Symptoms	Shortness of breath	6 (30%)	2 (10%)	1 (25%)	0 (0%)
	Cough	5 (25%)	0 (0%)	0 (0%)	0 (0%)
	Pain in upper right abdomen	5 (25%)	2 (10%)	1 (25%)	1 (25%)
	Fatigue/weakness	4 (20%)	3 (15%)	4 (100%)	2 (50%)
	Fluid buildup in the abdomen (ascites)	3 (15%)	0 (0%)	3 (75%)	0 (0%)
	Swelling in lower extremities	2 (10%)	0 (0%)	0 (0%)	0 (0%)
	Itchy skin	2 (10%)	1 (5%)	3 (75%)	2 (50%)
	Migraine	2 (10%)	0 (0%)	0 (0%)	0 (0%)
	Infections	2 (10%)	2 (10%)	0 (0%)	0 (0%)
Impacts	Emotional function	18 (90%)	6 (30%)	3 (75%)	1 (25%)
	Physical function	15 (75%)	5 (25%)	3 (75%)	1 (25%)
	Social function	14 (70%)	6 (30%)	3 (75%)	0 (0%)
	Relationship	12 (60%)	1 (5%)	0 (0%)	0 (0%)
	Work	9 (45%)	2 (10%)	4 (100%)	1 (25%)

*Worst/most bothersome concept was explored separately for symptoms and impacts

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3653 | METFORMIN TREATMENT TO IMPROVE MITOCHONDRIAL MORPHOLOGY AND FUNCTION IN A MOUSE MODEL OF WILSON DISEASE

Valentina Medici[1] Noreene Shibata[2] Isabel Snodgrass[2] Dohee Kim[3] John Newman[2] Aldo Vorkapich[2] Zoe Lee Greenblatt[2] Atena Tork[2] Jennifer Dang[2] Ieleen Li[2] Cecilia Giulivi[2], [1]University of California Medical Center, [2]University of California, Davis, [3]United States Department of Agriculture, Agricultural Research Service

Background: Wilson Disease (WD) is a genetic disorder caused by mutations affecting the *ATP7B* gene with consequent accumulation of copper in the liver and brain. Women with WD tend to experience more liver-related symptoms. WD is associated with liver mitochondrial dysfunction, suggesting that targeting the mitochondrial function could provide an effective treatment approach. The oral hypoglycemic agent metformin forms high-affinity pseudo-aromatic complexes with metals, including copper. We hypothesized that metformin could improve liver mitochondrial morphology in WD. **Methods:** We treated male (n = 5) and female (n = 5) *Atp7b* global knockout mice on a C57Bl/6 background (KO), a WD model, with 500 mg/kg/d metformin in their drinking water for 2 weeks. In samples collected before and after treatment, we analyzed mitochondrial structure and activity and mitochondria lipid mediator concentrations in the liver. **Results:** We implemented a scoring methodology to conduct a quantitative analysis of liver mitochondrial ultrastructure. The scores were analyzed by fitting them into a linear regression model to elucidate the contribution of sex, treatment, and their interaction. The analysis of mitochondrial scores indicated that sex ($P = 0.025$), treatment ($P = 0.0021$), and the sex × treatment interaction were significant. At baseline, females presented with worse liver mitochondrial scores than males ($P < .0001$). Metformin treatment resulted in improved scores for mitochondria from females compared to untreated females ($P < .0001$) and treated males ($P = 0.0473$). Quantification of the lipid vacuole areas revealed a significant sex effect ($P = 0.0299$) and a sex × treatment interaction ($P = 0.0412$). Compared to treated females, treated males showed increased size of lipid vacuoles in terms of area ($P < .0001$) and perimeter ($P = 0.019$). In females, metformin treatment improved mitochondrial overall morphology, the ratio of supercomplexes, and decreased lipid vacuole size compared to males treated with the same medication. Mitochondrial omega-6 oxylipins had a sex ($P = 0.010$), and a sex* treatment interaction ($P = 0.0003$). After metformin treatment, females' omega-6 oxylipins decreased to values similar to those of males (prostanoids and F2 isoprostane) or lower (hydroxy fatty acids). **Conclusion:** Metformin improves mitochondrial morphology and function in WD. This study highlights the importance of considering sex-based differences in the diagnosis and treatment of WD to improve patient outcomes.

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Noreene Shibata: Nothing to Disclose, Isabel Snodgrass: Nothing to Disclose, Dohee Kim: Nothing to Disclose, John Newman: Nothing to Disclose, Aldo Vorkapich: Nothing to Disclose, Zoe Lee Greenblatt: Nothing to Disclose, Atena Tork: Nothing to Disclose, Jennifer Dang: Nothing to Disclose, Ieleen Li: Nothing to Disclose, Cecilia Giulivi: Nothing to Disclose

3654 | EVALUATION OF NONINVASIVE TESTING FOR HEPATIC STEATOSIS: RESULTS: FROM THE MULTICENTER WILSON DISEASE REGISTRY INCLUDING YALE, AARHUS AND BARCELONA COHORTS

ZOE MARIÑO MENDEZ[1] Frederik Kirk[2] Uyen To[3] Asim Ulcay[3] Hatice Maras[3] Sefa Keserci[3] Regino Gonzalez-Peralta[4] Sanjiv Harpavat[5] Rima Fawaz[6] Alba Diaz[1] Kaitlin Maciejewski[3] Yanhong Deng[3] Thomas Sandahl[7] Michael Schilsky[3], [1]Hospital Clinic of Barcelona, Spain, [2]Aarhus University, Denmark, [3]Yale University, New Haven, CT USA, [4]AdventHealth for Children, [5]Texas Children's Liver Center - Baylor College of Medicine, [6]Yale University Medical Center, [7]Aarhus University, Aarhus, Denmark

Background: Hepatic steatosis due to copper induced mitochondrial toxicity is an early histological finding in Wilson Disease (WD). There is no reported data on the use of non-invasive tools for evaluating steatosis in WD. The Hepatic Steatosis Index (HSI) [calculated from AST/ALT ratio, BMI, presence of diabetes, and sex] identifies significant steatosis in liver biopsies (LB) from MASLD (cutoff >36). The elastographic Controlled Attenuation Parameter (CAP) detects moderate-severe steatosis in MASLD using a cutoff of ≥ 268 dB/m. Aims: to explore the accuracy of HSI and CAP in WD, using LB as the gold standard. **Methods:** Cross-sectional study of WD from registries at Yale, Aarhus and Barcelona with available LB. Clinical data were obtained from chart review. Steatosis in LB (according to NASH-CRN system) was graded as: 0, no steatosis; 1, mild 5-33%; 2, moderate 34-66%; or 3, severe $>66\%$. Moderate-severe steatosis (MSSt, $>33\%$) were considered together. HSI was calculated at the date of registry entry. Variables are expressed as median (IQR). The ROC curves for previously validated thresholds (HSI >36, CAP ≥ 268 dB/m) were calculated and optimal cutoffs determined by use of the Youden index. **Results:** We included 102 WD: 48% female, median age at LB 22.6y (12, 35[ZMM1]); median time from WD diagnosis 3m; 6 were diabetic; median BMI 22.8 kg/m^2. MSSt was present in 36 (35%) and was associated with higher BMI [26.1 (20.3, 30.5) vs 22.2 (19.9, 24.3), $p=0.021$]. HSI was available in 93 (91%) patients at a median time from LB of 11m; CAP was available in 29 patients (28%) close to time of LB. Although median HSI was significantly higher in MSSt vs non-MSSt (44.5 vs 36.9, $p=0.007$), the >36 threshold did not accurately predict MSSt (AUC 0.51). A higher HSI cutoff of 42.2 increased AUC to 0.67. CAP was also significantly higher in MSSt vs non-MSSt (324.5 vs 224 dB/m); the AUC was 0.80 for the ≥ 268 cutoff with a positive predictive value of 0.70 (0.35, 0.93). A cutoff of 292.5 dB/m increased AUC to 0.87. **Conclusion:** CAP with ≥ 292.5 cutoff improved the accuracy for detecting moderate or severe steatosis in patients with WD. HSI >36 was not accurate in predicting MSSt, though a higher cutoff did improve discrimination to a limited degree, possibly due to the different pathophysiology of steatosis in WD and greater delay in time from LB to HSI in this study. Further study is needed to determine whether MSSt impacts WD outcomes, and the best means for its non-invasive measurement.

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3655 | A CLINICAL DECISION SUPPORT TOOL FOR THE IDENTIFICATION OF PATIENTS AT RISK OF DEVELOPING ALPHA-1 ANTITRYPSIN DEFICIENCY-ASSOCIATED LIVER DISEASE: INTERIM RESULTS:

Jeffrey Teckman[1] Virginia Clark[2] Leslie Hinyard[3] Nadejda Leavitt[4] Suyin Lee[4] Amanda Sees[4] Chitra Karki[5] Suna Park[5] Kaili Ren[5] May Hagiwara[5] Rohit Loomba[6], [1]Saint Louis University School of Medicine, St. Louis, MO, USA, [2]University of Florida, Gainesville, FL, USA, [3]Saint Louis University School of Medicine, St. Louis, MO, USA; AHEAD Institute, St. Louis, MO, USA, [4]IQVIA, Plymouth Meeting, PA, USA, [5]Takeda Development Center Americas, Inc., Cambridge, MA, USA, [6]University of California at San Diego, San Diego, CA, USA

Background: Alpha-1 antitrypsin deficiency (AATD)-associated liver disease (AATD-LD) is a rare genetic disorder that is underdiagnosed owing to its asymptomatic nature. To help clinicians identify patients (pts) at risk of developing AATD-LD, an artificial intelligence/machine learning-clinical decision support tool (AI/ML-CDST) was developed using data from the IQVIA US National Ambulatory Electronic Medical Records (AEMR) database. Here, we refine and validate the AEMR model (foundational), using electronic medical records from the Sisters of St Mary Health/Saint Louis University (SSM/SLU) database. **Methods:** The study comprised adults with ≥ 1 encounter for any medical activity in the SSM/SLU database (Oct 2015–Oct 2022). The positive cohort comprised pts with a recorded AATD diagnosis (dx) code (ICD-9/10 or SNOMED) and either a liver transplant or AATD-related liver condition. The negative cohort comprised all other pts. For each pt, cross-sectional (CS) data with 12-month lookback and outcome periods with 4-month shift were generated. Data were split into training and validation sets for model development and a hold-out set for independent evaluation. The foundational model was localized and refined using the SSM/SLU database (localized model). A combined 'ensemble' model was also generated. Model performance was assessed according to precision, area under the curve (AUC) and fold-improvement in pt detection over database records. **Results:** Overall, 1,883/77,000,000 (0.002%) and 274/6,200,000 (0.004%) pts in the AEMR and SSM/SLU databases, respectively, had AATD-LD. In CS data, baseline incidences of AATD-LD among the general population were 909/214,800,000 (0.0004%) in AEMR and 80/5,200,000 (0.0015%) in SSM/SLU. Among pts with AATD, more pts in the SSM/SLU than the AEMR database had AATD-LD (Figure; 5.9% vs 1.2%). At 15.0% recall, the ensemble model achieved the greatest precision (11.6%; AUC 0.84) versus the localized (4.9%; AUC 0.84) and foundational models (2.5%; AUC 0.83). Compared with incidence rates in the SSM/SLU database (Figure), the ensemble model achieved a 2.4×-, 233×- and > 9,300×-fold improvement in the rate of identification of pts with AATD-LD among pts with AATD, liver disease (LD), and the general population, respectively. Of the top 100 pts based on ensemble model score, 14 had AATD-LD: 6 had a prior AATD dx, 5 had a prior LD dx and 3 had no prior AATD/LD dx. The top five predictors in the ensemble model were AATD dx, LD dx, recency of gastroenterologist visit or AATD-LD dx, and White ethnicity. **Conclusion:** The ensemble model provided the best performance of the models evaluated, achieving a 233×- and > 9,300×-fold improvement in AATD-LD diagnosis versus incidence in pts with LD or the general population, respectively, in the SSM/SLU database. Prospective validation is in progress to support use of this AI/ML-CDST for the diagnosis of AATD-LD.

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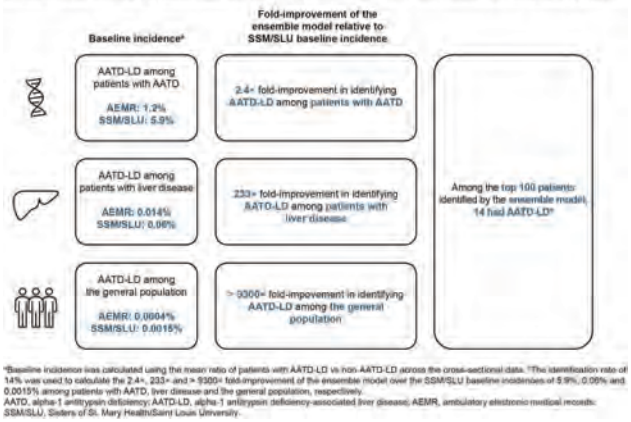
Figure. Incidence baselines for AATD-LD in the SSM/SLU and IQVIA US AEMR databases, and the performance of the ensemble model in identifying patients with AATD-LD among patients with AATD, liver disease and the general population



[a]Baseline incidence was calculated using the mean ratio of patients with AATD-LD vs non-AATD-LD across the cross-sectional data. *The identification rate of 14% was used to calculate the 2.4×, 233× and > 9300× fold-improvement of the ensemble model over the SSM/SLU baseline incidences of 5.9%, 0.06% and 0.0015% among patients with AATD, liver disease and the general population, respectively.
AATD, alpha-1 antitrypsin deficiency; AATD-LD, alpha-1 antitrypsin deficiency-associated liver disease; AEMR, ambulatory electronic medical records; SSM/SLU, Sisters of St. Mary Health/Saint Louis University.

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3656 | PATIENT CHARACTERISTICS OF ADULT CYSTIC FIBROSIS LIVER DISEASE AND THE EFFECTIVENESS OF NONINVASIVE FIBROSIS TESTS IN DETERMINING DISEASE STATUS

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Background: Adult cystic fibrosis-associated liver disease (CFLD) is a significant cause of morbidity and mortality in patients with cystic fibrosis (CF). However, a standard approach to CFLD screening and diagnostic criteria has not yet been defined. The aim of this study was to determine the prevalence of CFLD in a cohort of adult CF patients and to evaluate the effectiveness of noninvasive fibrosis tests in the diagnosis of CFLD. **Methods:** The study included 42 patients (23F/19M; mean age: 24.7 ± 5.7) diagnosed with CF and followed at the Pulmonology Department of Hacettepe University. All patients were examined in the Gastroenterology Clinic and underwent liver stiffness measurement (LSM) using transient elastography. Patients with LSM > 8 kPa were considered to have $\geq$F2 fibrosis, while patients with LSM > 10kPa in combination with ultrasonographic evidence of chronic liver disease were considered to have advanced chronic liver disease. Patients were stratified based on fibrosis severity, and clinical and biochemical parameters were compared between groups. **Results:** LSMs were detected as > 8 kpa in 11 (26%) patients (9F/2M; p:0.07), there were 7 (%16) diabetic patients and all had LSM > 8 kpa. Compared to those without fibrosis, patients with $\geq$F2 fibrosis had significantly elevated levels of ALT (63 ± 85 vs. 23 ± 10; p:0.01), AST (48 ± 31 vs. 24 ± 7;$p < 0.01$), and GGT (46 ± 56 vs. 19 ± 12;p:0.01), as well as reduced serum albumin levels (4.1 ± 0.4 vs. 4.4 ± 0.3;p:0.02). FIB4 (0.97 ± 0.6 vs. 0.5 ± 0.23; $p < 0.01$) and APRI values (0.71 ± 0.45 vs. 0.28 ± 0.15; $p < 0.01$) were found to be higher in the fibrosis group. Of the patients, 6 (14%) (5F/1M; p:0.19) had LSM > 10kPa and chronic liver disease findings in ultrasonographic examination, 5 of whom were diabetic ($p < 0.01$). GGT (58 ± 76 vs. 21 ± 13; $p < 0.01$) and INR (1.26 ± 0.1 vs. 1.09 ± 0.17; p: 0.03) levels were higher, serum albumin levels (3.97 ± 0.56 vs. 4.41 ± 0.3; $p < 0.01$) was lower and FIB-4 score was found to be higher (1.09 ± 0.27 vs 0.54 ± 0.27;p:0.002) in the advanced chronic liver disease group. Using a FIB-4 cut-off of 0.74, advanced fibrosis was identified with a sensitivity of 67% and specificity of 77% (Area under curve: 0.72). Although the APRI score was higher in the advanced fibrosis group, it did not reach statistical significance (0.61 ± 0.32 vs. 0.35 ± 0.30; p:0.06). **Conclusion:** In this cohort, 16% of CF patients had advanced fibrosis and 26% had $\geq$F2 fibrosis. 5 of 6 diabetic patients had advanced fibrosis. Due to the relatively young age of the population and preserved platelet counts even in advanced disease, the use of FIB-4 and APRI with the cut-off values in the literature may not be appropriate for fibrosis prediction.

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◆ 4001 | ★ MAJOR CARDIOVASCULAR EVENT REDUCTION IN MASLD: TIRZEPATIDE VS. SEMAGLUTIDE; A PROPENSITY-MATCHED REAL-WORLD STUDY

Himsikhar Khataniar[1] Hany Habib[1] Kaitlyn Gernhard[1] Muhammad Ali Butt[2] Nabeeha Mohy-ud-din[1] Nikki

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Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) affects nearly one-third of adults and is the second leading cause for liver transplantation in the United States. Cardiovascular disease (CVD) is the primary driver of mortality in patients with MASLD, yet pharmacotherapy addressing cardiometabolic risk factors are scarce. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) address weight and hyperglycemia, but dual incretin agonists that also stimulate glucose-dependent insulinotropic polypeptide (GIP) receptors may confer additional benefits. Tirzepatide, the first GLP-1/GIP co-agonist has outperformed semaglutide for weight and glycemic control in clinical trials, however direct CVD data in MASLD are limited. **Methods:** Using the U.S. TriNetX network, we included adults ≥ 18 years with an ICD-10 code for fatty liver disease plus ≥1 metabolic risk factor (diabetes, obesity, hypertension, dyslipidemia) who first filled a prescription of tirzepatide or semaglutide from 1 Jan 2015 to 31 Dec 2021. We excluded other liver diseases, prior GLP-1 RA use, bariatric surgery, critical-care stay, liver transplant, previous major adverse cardiovascular events (MACE), or major liver outcomes. One-to-one propensity matching balanced age, sex, race, body-mass index (BMI), diabetes, hypertension, and dyslipidemia. The primary endpoint was 3-year composite MACE. Secondary endpoints were individual CV events, acute heart failure, all-cause mortality, all-cause hospitalization, and BMI change. **Results:** Of 15,538 eligible MASLD patients, 1,500 began tirzepatide and 14,038 semaglutide; matching produced 1,497 per cohort with similar baseline characteristics. Over three years, tirzepatide users had fewer MACE than semaglutide users (1.27% vs 4.08%; adjusted odds ratio [aOR] 0.30, 95% CI 0.18–0.51; p <0.0001). Myocardial infarction rates decreased by two-thirds (0.74% vs 2.00%; aOR 0.36, 0.18–0.72; p = 0.0028). Stroke and acute heart-failure rates were numerically lower but not significant. All-cause hospitalization decreased (21.31% vs 30.66%; aOR 0.61, 0.52–0.72; p <0.0001). Mortality was ≤0.67 % in both groups. BMI decreased more with tirzepatide (-4.1 kg m^{-2}) than with semaglutide (-2.2 kg m^{-2}; p < 0.001). **Conclusion:** Over a three-year period involving nearly 1,500 patients per cohort, tirzepatide was associated with a 70% reduction in MACE, fewer hospitalizations, and greater weight loss than semaglutide. These findings suggest that dual GLP-1/GIP receptor agonism provides superior cardiometabolic protection compared to GLP-1 monotherapy. Prospective head-to-head clinical trials are warranted to validate these cardiovascular and liver-related benefits and to guide optimal therapeutic strategies for this high-risk population.

Table 1: Three-Year Cardiovascular, Hospitalisation, Mortality, and Weight Outcomes After Propensity Matching

Outcome	Tirzepatide (n = 1,497)	Semaglutide (n = 1,497)	Adjusted OR	95 % CI	p-Value
Composite MACE	19 (1.27 %)	61 (4.08 %)	**0.30**	0.18–0.51	**< 0.0001**
Myocardial infarction	11 (0.74 %)	30 (2.00 %)	**0.36**	0.18–0.72	**0.0028**
Ischaemic stroke	≤ 10 (0.67 %)	14 (0.94 %)	0.71	0.32–1.61	0.41
Acute heart failure	≤ 10 (0.67 %)	16 (1.07 %)	0.62	0.28–1.38	0.24
All-cause hospitalisation	319 (21.31 %)	459 (30.66 %)	**0.61**	0.52–0.72	**< 0.0001**
All-cause mortality	≤ 10 (0.67 %)	≤ 10 (0.67 %)	1.00	0.42–2.41	1.00
BMI (kg m^{-2})	38.8 ± 7.65 → 34.7 ± 7.84	38.4 ± 7.59 → 36.2 ± 7.83	—	—	**< 0.001**

*MACE = major adverse cardiovascular events. ≤ 10 indicates suppressed cell counts for privacy compliance.

Disclosures: Himsikhar Khataniar: Nothing to Disclose, Hany Habib: Nothing to Disclose, Kaitlyn Gernhard: Nothing to Disclose, Muhammad Ali Butt: Nothing to Disclose, Nabeeha Mohy-ud-din: Nothing to Disclose, Nikki Duong: Nothing to Disclose

◆ 4002 | EFFICACY AND SAFETY OF TIME-RESTRICTED EATING IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background: Time-restricted eating (TRE) may improve weight loss, insulin resistance, and body composition, key factors in the pathophysiology of metabolic dysfunction-associated steatotic liver disease (MASLD). However, evidence in patients with MASLD is limited. This study aimed to evaluate the potential benefits of TRE in patients with overweight or obese MASLD. **Methods:** This 16-week randomized controlled trial included patients who were overweight or obese and had MASLD randomized into three groups in a 1:1:1 ratio: standard of care (SOC), calorie restriction (CR), and TRE. The primary endpoint was an improvement in hepatic steatosis, measured using magnetic resonance imaging proton density fat fraction. Changes in liver fibrosis, body composition, lipid profiles, glucose homeostasis, and sleep quality were also

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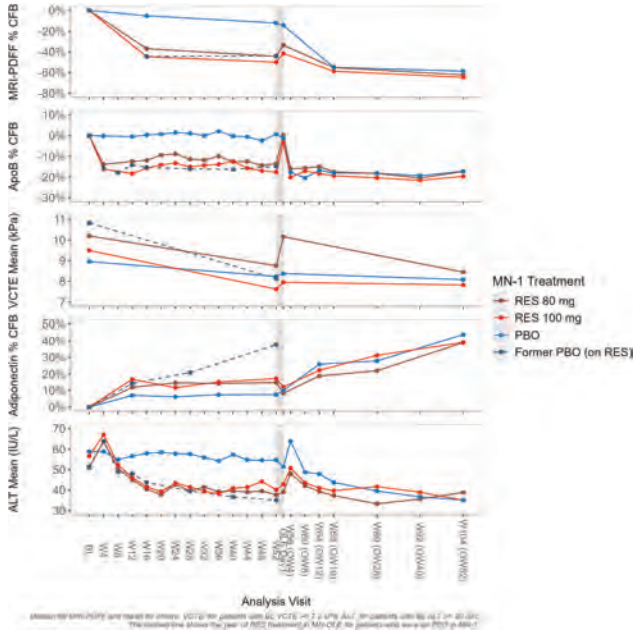
analysed. This study is registered at ClinicalTrals.gov, NCT05579158. **Results:** Among the 337 participants randomized, 333 were included in the full analysis set (113 in SOC, 110 in CR, and 110 in TRE). After the 16-week intervention, hepatic steatosis significantly decreased in the TRE group (- 25.8%) than in the SOC group (0.7%, $p < 0.001$), with no significant difference between TRE and CR (- 24.7%, $p = 1.00$). The TRE group also showed greater reductions in body weight, waist circumference, and body fat mass compared to those of SOC, with similar changes between TRE and CR. No significant differences were observed between TRE and CR in liver stiffness, glucose homeostasis, or sleep quality. No serious adverse events were reported. **Conclusion:** TRE effectively reduces hepatic steatosis in MASLD, with comparable benefits on weight loss, body composition, and metabolic parameters as CR. This approach may serve as a practical dietary strategy for MASLD management.

Disclosures: Dae Won Jun: Nothing to Disclose, Ju Hyun Oh: Nothing to Disclose, Hyun Woo Oh: Nothing to Disclose, Hyo Young Lee: Nothing to Disclose, Eileen Yoon: Nothing to Disclose, Sang Bong Ahn: Nothing to Disclose, HA IL KIM: Nothing to Disclose

◆ 4003 | DURABILITY OF RESMETIROM RESPONSE IN MASLD PATIENTS AFTER TWO YEARS OF TREATMENT IN MAESTRO-NAFLD-OLE

Naim Alkhouri[1] Rebecca Taub[2] Xiaomin Lu[2] Matthew Dauphin[3] Kathryn Lucas[4] Sam Moussa[5], [1]Summit Clinical Research, [2]Madrigal Pharmaceuticals, [3]Madrigal Pharmacueticals, [4]Lucas Research, [5]University of Arizona for Medical Sciences

Background: Resmetirom (RES) is approved for the treatment of patients with MASH and liver fibrosis. MAESTRO-NAFLD-1 (MN-1) (NCT04197479) was a randomized double-blind (DB) Phase 3 clinical trial of placebo (PBO) versus RES, a once-a-day oral selective thyroid hormone receptor ?? agonist, in which 972 MASLD patients identified non-invasively were randomized 1:1:1 to receive RES 80mg, 100mg or placebo for 52 weeks. MAESTRO-NAFLD-OLE NCT04951219 (MN-OLE) was a one year extension study in which 515 DB patients from MN-1 entered a second 52 weeks of treatment and received treatment for 52 weeks with RES. Efficacy was evaluated after two years of RES treatment (patients randomized to RES in MN-1) and one year of RES treatment in patients treated with PBO in MN-1. **Methods:** MN-1 is described [Nat. Med https://doi.org/10.1038/s41591-023-02603-1]. Inclusion requirements were 3 metabolic risk factors, FibroScan VCTE $\geq$5.5 kPa/CAP $\geq$280 dBm, MRI-PDFF $\geq$8%. After a treatment interruption of mean(SD) 120(84) days, 515 double-blind patients from MN-1 enrolled in MN-OLE, previous treatment in MN-1: n = 168, RES 80mg; 175, RES 100mg; 172, PBO. Enrolled MN-OLE patients received either 80mg or 100mg RES for the first 12 weeks and 100mg from weeks 12-52. PBO in MN-1 (blue line) was compared to same patients treated with RES in MN-OLE (figure, dashed blue line, baseline Day 1 MN-OLE). **Results:** At baseline in MN-1 the MN-OLE population (n = 515) was age 57 (11); female, 52%; hispanic 29%; BMI 35(6); type 2 diabetes 56%; hypertension 79%; dyslipidemia 77%; VCTE 7.4(4.7) kPa. RES treatment for a second year resulted in persistent effects on biomarkers, including lipids (mean [SE]) % change in LDL -15% [2%], ApoB -19% [1%], TRIGS -23% [2%]; liver enzymes (mean [SE] % change), ALT -25% [3%], AST -9% [4%], GGT -27% [3 %] i(baseline ALT $\geq$ 30IU/L); MRI-PDFF (median % reduction) -63%; and VCTE (median % reduction) -18% (baseline VCTE $\geq$ 7.2 kPa) (figure). Responses were similar in PBO from MN-1 treated for one year with RES in MN-OLE (solid blue line, year 1, PBO; dashed blue line, MN-OLE, year 2, RES). Adiponectin, a biomarker associated with fibrosis reduction, showed a mean % increase at one (16% [2%]) and 2 years (39% [4%]). The treatment gap between year 1 and 2 resulted in loss of effect on several biomarkers that was recovered with reinitiation of RES. RES was well-tolerated, reinitiation of RES therapy or uptitration to 100 mg at week 12 MN-OLE did not generally result in new or recurrent GI AEs. **Conclusion:** In a 52-week (extension of MN-1) Phase 3 clinical trial (MN-OLE) in patients with MASLD and high metabolic risk, RES treatment for a second year resulted in durable effects on biomarkers including reductions atherogenic lipids, VCTE, MRI-PDFF and improvements in markers of liver injury and fibrosis. PBO patients from MN-1 who received treatment with RES in MN-OLE showed an improvement in biomarkers with RES in MN-OLE compared to treatment with PBO in MN-1.



Disclosures: Naim Alkhouri: Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk:

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◆ 4004 | EMPAGLIFLOZIN REDUCES INCIDENT CIRRHOSIS, HEPATIC DECOMPENSATION, AND MORTALITY IN MASLD/MASH PATIENTS WITH DIABETES: A PROPENSITY-MATCHED ANALYSIS OF A MULTI-INSTITUTIONAL EHR DATABASE

Ludovic Saba[1] Thomas Cotter[1], [1]UT Southwestern Medical Center

Background: Randomized trials and meta-analyses have shown that the SGLT2 inhibitor, empagliflozin, reduces hepatic fat, improves liver enzymes, and ameliorates insulin resistance in metabolic dysfunction–associated steatotic liver disease (MASLD) and its inflammatory form, MASH, regardless of diabetes status. However, its effect on liver-related major clinical outcomes (e.g. incident cirrhosis, decompensation and mortality) is poorly understood. Thus, we examined these endpoints in a large, real-world MASLD/MASH population with type 2 diabetes (T2DM). **Methods:** Adults ≥18 years with MASLD/MASH (ICD-10 K76.0 or K75.81) and T2DM (E11.x) recorded in the TriNetX Research Network (2015-2024) were identified. Patients with competing liver diseases (e.g., alcoholic liver disease, viral or autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis) or baseline cirrhosis were excluded. Exposure required an empagliflozin prescription ≥ 90 days after MASLD/MASH diagnosis; unexposed controls had no SGLT2 inhibitor use. Propensity-score matching (1:1, 17 covariates) generated two balanced cohorts (n = 69,385 each). Follow-up outcomes from day +1 through three years included incident cirrhosis (ICD-10 K74.60 or K74.69), first hepatic decompensation (ascites, variceal bleeding, jaundice or hepatic encephalopathy) and all-cause mortality. Risks were compared with risk ratios (RR, 95 % CI) and survival with Kaplan–Meier log-rank and hazard ratios (HR). **Results:** Baseline characteristics before and after matching are reported in Table 1. Median follow-up was 665 days in empagliflozin users and 544 days in controls. Empagliflozin was associated with a lower three-year risk of cirrhosis (0.5 % vs 0.9 %; RR 0.57, 95 % CI 0.50–0.65; $p < 0.0001$) and of composite decompensation (1.4 % vs 2.4 %; RR 0.61, 95 % CI 0.56–0.66; $p < 0.0001$) and of all-cause mortality (HR 0.39, 95 % CI 0.37–0.41; $p < 0.0001$). **Conclusion:** In this large, propensity-matched cohort of MASLD/MASH with T2DM, empagliflozin use halved the risk of incident cirrhosis, reduced early decompensation, and was associated with markedly better survival over three years. These real-world findings extend prior imaging-based studies and support prospective trials to confirm empagliflozin's potential to modify the clinical course of MASLD.

Table 1: Baseline Characteristics – Full vs Propensity-Matched Cohorts

Variable	All patients (N=578 480)				Propensity score-matched patients (N=138 770)			
	Non-Empagliflozin (n=508 637)	Empagliflozin (n=69 843)	p-value	Std Diff	Non-Empagliflozin (n=69 385)	Empagliflozin (n=69 385)	p-value	Std Diff
Age at index, mean ± SD (yrs)	57.5 ± 14.3	59.9 ± 12.4	<0.001	0.181	60.0 ± 13.5	59.8 ± 12.4	0.039	0.011
Female, n (%)	281 216 (55.3)	33 899 (48.5)	<0.001	0.138	33 923 (48.9)	33 621 (48.7)	0.584	0.003
Male, n (%)	207 086 (40.7)	33 581 (48.1)	<0.001	0.149	33 279 (48.0)	33 211 (47.9)	0.715	0.002
Black, n (%)	60 737 (11.9)	8 722 (12.5)	<0.001	0.017	8 597 (12.1)	8 678 (12.5)	0.022	0.012
White, n (%)	339 349 (66.7)	46 765 (67.0)	0.207	0.005	47 636 (68.7)	46 445 (66.9)	<0.001	0.037
Asian, n (%)	26 251 (5.2)	4 231 (6.1)	<0.001	0.039	3 955 (5.7)	4 194 (6.0)	0.006	0.015
Hispanic/Latino, n (%)	73 640 (14.5)	8 195 (11.7)	<0.001	0.081	7 421 (10.7)	8 163 (11.8)	<0.001	0.034
Heart failure, n (%)	33 731 (6.6)	12 196 (17.5)	<0.001	0.337	10 364 (15.0)	11 783 (17.0)	<0.001	0.055
CKD, n (%)	46 314 (9.1)	12 908 (18.5)	<0.001	0.274	11 524 (16.6)	12 715 (18.3)	<0.001	0.045
Diabetes mellitus, n (%)	254 311 (50.0)	64 384 (92.2)	<0.001	1.051	64 215 (92.5)	63 926 (92.1)	0.004	0.016
Hyperlipidemia, n (%)	150 225 (29.5)	35 048 (50.2)	<0.001	0.431	34 310 (49.4)	34 662 (50.0)	0.059	0.010
BMI, mean ± SD (kg/m²)	35.3 ± 8.3	34.9 ± 7.7	<0.001	0.053	34.7 ± 8.2	34.9 ± 7.7	<0.001	0.025
HbA1c, mean ± SD (%)	7.2 ± 1.8	8.0 ± 1.7	<0.001	0.464	7.4 ± 1.8	8.0 ± 1.7	<0.001	0.367
Antihypertensive agents, n (%)	157 746 (31.0)	44 896 (64.3)	<0.001	0.706	44 065 (63.5)	44 438 (64.0)	0.037	0.011
Insulin, n (%)	87 005 (17.1)	27 104 (38.8)	<0.001	0.498	26 036 (37.5)	26 705 (38.5)	<0.001	0.020
Diuretics, n (%)	108 142 (21.3)	26 223 (37.5)	<0.001	0.363	24 685 (35.6)	25 812 (37.2)	<0.001	0.034

Disclosures: Ludovic Saba: Nothing to Disclose, Thomas Cotter: Nothing to Disclose, Nothing to Disclose

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◆ 4005 | COMBINATION THERAPY IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: GLP-1R AGONIST WITH OTHERS

Hui Li[1] Jiliang Zhang[1] Yan Zhou[1] Miao Yuan[1] Chen Liu[1] Luxia Wei[1] Xiuxiu Shen[1] Lijuan Jiang[1] Jing Li[1] Zhixiang Zhang[1] Qingyang Gu[1], [1]Wuxi AppTec

Background: Metabolic Dysfunction-Associated Steatohepatitis (MASH) is a progressive liver disease characterized by steatosis, inflammation, and fibrosis. Current therapeutic options are limited, necessitating the exploration of novel pharmacological interventions. This study evaluates the efficacy of GLP-1 receptor agonists, specifically Semaglutide, in combination with other agents such as MGL3196, GFT505, Efruxifermin, and Retatrutide in a murine MASH model. **Methods:** The study employed an HFD+CCl4 induced MASH mice model. A healthy control group receiving vehicle treatments, while MASH groups receiving vehicle, Semaglutide and combinations of Semaglutide with MGL3196, GFT505, Efruxifermin, or Retatrutide with specific dosages and administration frequencies tailored to each combination. After 6 weeks of treatment, endpoints included the assessment of hepatic steatosis, inflammation, and fibrosis on histological and molecular levels were taken and compared. **Results:** The combination therapies involving semaglutide demonstrated improvements in NAS score and liver fibrosis compared to the model group at different levels. Notably, the combination of Semaglutide with MGL3196 and Retatrutide showed relatively better therapeutic effects, suggesting a potential synergistic interaction between these agents. **Conclusion:** The findings indicate that combination therapies involving GLP-1 receptor agonists, particularly Semaglutide, with other pharmacological agents hold promise in the treatment of MASH, offering a potential strategy to address the complex pathophysiology of MASH.

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◆ 4006 | JAMUN-DERIVED EXTRACELLULAR VESICLES RESTORE INTESTINAL HISTIDINE–ADIPONECTIN SIGNALING AND HEPATIC LIPID METABOLISM TO ATTENUATE HIGH CARB-HIGH FAT-INDUCED MASLD

Sukriti Baweja[1] P. Debishree Subudhi[2] Vibhuti R Jakhmola[2] Sakshi Bhatt[2] Ashmit Mittal[2] Anupama Kumari[2] Shiv Kumar Sarin[2], [1]Institute of Liver and Biliary Sciences, New Delhi, [2]Institute of Liver and Biliary Sciences

Background: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a metabolic disorder closely related to diet and the gut microbiota. Plant-derived edible extracellular vesicles (EEVs) are emerging as novel nutraceutical therapies. We evaluated the therapeutic efficacies of functional food derived EVs from, ginger (GinEx), turmeric (TurEx), carrot (CarEx), garlic (GarEx), and jamun (JamEx) in a diet-induced murine model of MASLD. **Methods:** EVs were isolated by differential ultracentrifugation and characterized using nanoparticle tracking analysis. Male C57BL/6J mice fed on high carb (32%) high fat (58%) diet for 20-weeks, followed by oral EV treatment (50nm-300nm; zeta potential: -17 ± -2.4mV; 4×10^4 particles/kg) for 3 or 6 weeks along with HFD diet. Metabolic assessment included body weight monitoring, insulin tolerance test (ITT), and oral glucose tolerance test (OGTT). Liver pathology was evaluated by H&E and Oil Red O staining. Biochemical markers and genes associated with inflammation, lipid metabolism, apoptosis, gut permeability were studied. Fecal metabolome was analyzed using mass spectrometry. **Results:** HFD-fed mice exhibited significant metabolic dysfunction, including weight gain ($p < 0.001$), insulin resistance ($p < 0.01$), and glucose intolerance ($p < 0.01$). EEV treatment significantly reduced body weight ($p < 0.05$) and improved insulin/glucose tolerance (ITT/OGTT AUC; $p < 0.05$ at week 23). By week 26 CarEx, GarEx, and JamEx significantly reduced macro- and micro-vesicular hepatic steatosis, serum ALT ($p < 0.002$), and AST ($p < 0.001$). These effects were associated with downregulation of intestinal TNF-α and IL-17α ($p < 0.02$) and upregulation of adiponectin ($p < 0.003$). While GarEx markedly reduced hepatic inflammation (TNF-α, IL-17α; $p < 0.001$), JamEx

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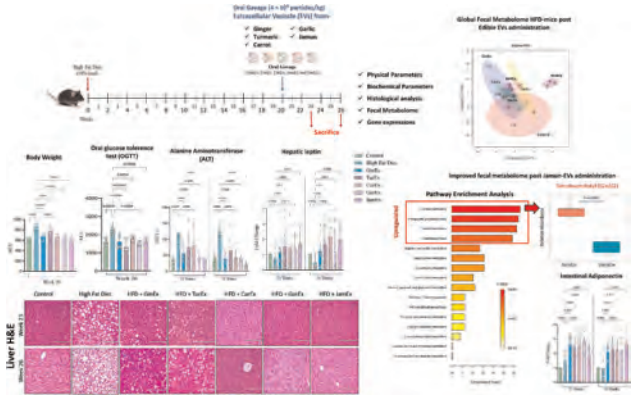
showed the strongest effect on lipid metabolism, increasing hepatic leptin ($p < 0.05$) and decreasing resistin ($p < 0.04$). Fecal metabolomics (378 annotated compounds) in EV-treated mice resembled the control profile, with JamEx forming a distinct cluster. JamEx most strongly upregulated fecal histidine metabolism ($p = 0.03$), correlating with increased intestinal adiponectin, improved barrier integrity, reduced inflammation indicated favorable microbial colonization, collectively ameliorating MASLD. Conversely, GarEx upregulated fecal pantothenate–CoA biosynthesis and sphingolipid metabolism, enhancing CoA-mediated lipid metabolism and contributing to MASLD improvement. **Conclusion:** Edible EVs effectively mitigate HFD-induced MASLD by modulating lipid metabolism, inflammation, and gut barrier function. JamEx acts through histidine-mediated adiponectin induction to restore gut–liver axis homeostasis and MASLD amelioration. Other EEVs also help restore gut-liver altered metabolic milieu. Wider evaluation of EEVs is strongly recommended.



Disclosures: Sukriti Baweja: Nothing to Disclose, P. Debishree Subudhi: Nothing to Disclose, Vibhuti R Jakhmola: Nothing to Disclose, Sakshi Bhatt: Nothing to Disclose, Ashmit Mittal: Nothing to Disclose, Anupama Kumari: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

◆ 4007 | RANDOMIZED, PLACEBO CONTROLLED PHASE 1B TRIAL OF APL-18881, A NOVEL FGF21 AND GLP-1 BISPECIFIC DUAL RECEPTOR AGONIST, EVALUATING MEASURES OF METABOLIC AND LIVER HEALTH IN PATIENTS WITH TYPE 2 DIABETES AFTER 5 WEEKS OF TREATMENT

Matthew Cardinal[1] Rohit Loomba[2] Rachel Gurrell[1] Sanjay Aggwaral[1] Xiaoping Lee[3] Linfeng Guo[3] Can Xie[3] Jiangyu Yan[3], [1]Apollo Therapeutics Ltd, [2]University of California, San Diego, [3]Dongguan HEC Biopharmaceutical R&D Co., Ltd

Background: Fibroblast growth factor 21 (FGF21) and glucagon-like peptide 1 (GLP-1) receptor agonists are in development as single agents for the treatment of steatotic liver disease (SLD). APL-18881 (also HEC88473) is a bispecific FG21 and GLP-1 dual receptor agonist. APL-18881 is currently in development in a Phase 2 trial for the treatment of Type 2 Diabetes (T2D). **Methods:** HEC88473-DM-101 was a single-centre, randomized, double-blind, placebo-controlled Phase 1b trial to evaluate the safety, tolerability, PK, and PD of APL-18881. This multiple ascending dose trial was conducted in participants ($n = 60$) with T2D at dose levels of 5.1 mg, 15.3 mg, 30.6 mg, 45.9 mg, and 68.0 mg. Participants received APL-18881 on a QW schedule for 5 weeks. Those treated at doses $\geq$ 30.6 mg underwent a dose titration regimen, with the dose titrated up at 1 or 2-week intervals. Assessments included fasting blood glucose (FBG) and lipids, insulin, HbA1c, adiponectin, glucagon, ALT, AST, MRI-PDFF and FibroScan. Results of the trial have been published. Here we present data for the subset of participants with baseline MRI-PDFF $\geq$ 8% ($n = 32$). **Results:** In the overall population, APL-18881 dose-dependent changes in FBG, HbA1c and adiponectin were observed, along with trends in lipid and AST/ALT changes towards higher APL-18881 dose levels. Dose-dependent changes in MRI-PDFF ($p < 0.01$ at 30.6 mg and higher) and trends in liver stiffness were also observed.

Characteristics and results in the subset of T2D participants with baseline MRI-PDFF $\geq$ 8% are summarized in Table 1. There was at least a 15% placebo adjusted difference in the change from baseline (CFB) between the 30.6 mg (-42.3%), 45.9 mg (-45.2%) and 68.0 mg (-51.6%) APL-18881 dose groups, compared to placebo (-27.2%). The proportion of participants achieving $\geq$ 30% CFB in MRI-PDFF was significantly higher in these APL-18881 groups, compared to placebo ($p < 0.05$, $p < 0.10$, and $p < 0.01$ for 30.6 mg, 45.9 mg, and 68.0 mg, respectively). Reductions in liver stiffness (CAP) were also observed across the higher APL-18881 dose groups (CFB range -10.5% to -15.9%, vs. +2.5% for placebo). **Conclusion:** APL-18881 demonstrated robust dose-dependent improvement in measures of metabolic and liver health in a Phase 1b MAD trial in participants with T2D after 5 weeks of treatment. The effects observed on MRI-PDFF and liver stiffness support the potential of APL-18881 to be an effective therapeutic in SLD.

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Table 1. Baseline Characteristics and Results in T2D Participants with Baseline MRI-PDFF ≥8%

		APL-18881 Dose Groups				
	Placebo	5.1 mg	15.3 mg	30.6 mg	45.9 mg	68.0 mg
N	4	4	6	6	7	5
Baseline mean						
MRI-PDFF (%)	10.1	15.1	13.0	14.7	11.0	14.0
Adiponectin (µg/ml)	4.9	5.2	5.9	4.1	5.1	4.9
CAP (dB/m)	270.5	308.8	324.2	282.5	306.0	301.0
% Change from Baseline to Day 38						
MRI-PDFF	-27.2%	-32.8%	-31.6%	-42.3%	-45.2%	-51.6%
≥30% MRI-PDFF Responder Rate	25%	50%	50%	83.3%**	71.4%*	100%***
Adiponectin	-7.9%	17.1%	13.3%	29.9%	82.1%	76.8%
CAP	2.5%	-0.9%	-10.5%	-12.8%	-15.9%	-10.8%

* P <0.10
** P <0.05
*** P <0.01

Disclosures: Matthew Cardinal: Apollo Therapeutics Ltd: Employee, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Rachel Gurrell: Nothing to Disclose, Sanjay Aggwaral: Nothing to Disclose, Xiaoping Lee: Nothing to Disclose, Linfeng Guo: Nothing to Disclose, Can Xie: Nothing to Disclose, Jiangyu Yan: Nothing to Disclose

◆ 4008 | EFFICACY OF SAROGLITAZAR IN REAL WORLD PATIENTS WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE WITH COMPENSATED ADVANCED CHRONIC LIVER DISEASE

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Background: Saroglitazar, a dual PPARα/γ agonist, is useful in management of metabolic dysfunction associated steatotic liver disease (MASLD) and diabetic dyslipidemia. The data on efficacy of saroglitazar on patients with compensated advanced chronic liver disease (cACLD) is sparse. Here we report the efficacy of saroglitazar in MASLD patients with cACLD. **Methods:** Patients diagnosed as MASLD with F4 fibrosis were started on saroglitazar (4 mg) and were prospectively evaluated for 24 weeks in a tertiary care hospital. Primary outcome was reduction in Liver stiffness measurement (LSM) at 24 weeks. Secondary outcomes were assessment of improvement in Alanine transferase and triglyceride. **Results:** A total of 236 patients with cACLD were enrolled in the study out of which 74 patients were finally included in the study. Mean age was 52.4 ± 10.7 with 73% male. Thirty-two (43%) patients were diabetic and 72 % patients had body mass index of more than 25. There was significant improvement of LSM from baseline (19.2 ± 3.3) to 24 weeks (15.6 ± 2.76) ($p < 0.001$). Significant reduction in ALT and triglyceride levels ($p < 0.001$) was also seen. There was no significant change in weight. All patients very well tolerated saroglitazar. **Conclusion:** Saroglitazar is effective in improving biochemical parameters of metabolic syndrome and LSM value in patients with cACLD. Patients with cACLD tolerate saroglitazar well without progression to decompensation.

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TABLE 1. General Characteristics and comparison of patients treated with saroglitazar (n=74)

VARIABLE	PREVALENCE/MEDIAN VALUES
AGE(YRS)	29-75(66.5)
GENDER(MALE)%	54(73)
(FEMALE)%	20(27)
BMI	28.74(19.72-46.48)
METABOLIC SYNDROME	
DIABETES	32(42.7)
HYPERTENSION	28(37.84)

BIOCHEMICAL TEST AND LIVER STIFFNESS MEASUREMENT

	LSM at baseline	LSM AFTER 6 months of therapy	ALT at baseline	ALT after 6 months of therapy	TRIGLYCERIDE levels at baseline	TRIGLYCERIDE levels after 6 months of therapy
MEAN	19.17	15.57	41.59	37.03	176.39	148.2
MEDIAN	19.2	15.5	40	34.5	177.5	146
RANGE(MIN)	13.5	8.2	12	9	151	130
MAX	24.6	21.9	91	85	200	172
p-value		<0.001		<0.001		<0.001

ALT- Alanine transferase; LSM- Liver stiffness measurement

Disclosures: Virendra Singh: Nothing to Disclose, Jahnvi Dhar: Nothing to Disclose, Upasna Rajput: Nothing to Disclose, Nitesh Bassi: Nothing to Disclose, sandeep kaur toor: Nothing to Disclose, Himanshu Gupta: Nothing to Disclose, Rashmeet Brar: Nothing to Disclose, Amandeep Singh: Nothing to Disclose

◆ 4009 | OBESE PATIENTS ON GLUCAGON-LIKE PEPTIDE-1 INHIBITORS (GLP-1) HAVE LOWER RATES OF LIVER RELATED MORBIDITY COMPARED TO BARIATRIC SURGERY PATIENTS- A NATIONWIDE RETROSPECTIVE ANALYSIS

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Background: Metabolic dysfunction–associated steatotic liver disease (MALD) and obesity are closely associated disorders. Obesity is an independent predictor of hepatic steatosis. Furthermore, MASLD is a progressive disease that can result in liver fibrosis and cirrhosis. Weight loss is associated with improvement in MASLD and thus, liver outcomes. GLP-1 inhibitors are emerging as a safe and reasonable alternative to bariatric surgery in assisting weight loss. We hereby aim to examine liver outcomes among obese patients undergoing bariatric surgery vs GLP-1 inhibitors. **Methods:** This study is a retrospective cohort analysis utilizing TrinetX database, which aggregates real-time patient data from participating healthcare organizations. Adult obese patients were defined by body mass index (BMI) > 30. Bariatric surgery was defined by ICD-10 code for bariatric status or procedure codes for sleeve gastrectomy or gastric bypass in the past 10 years.

Cohort was divided into obese patients with bariatric status never on GLP-1 inhibitors vs obese patients on GLP-1 inhibitors, who never had bariatric surgery. The two cohorts were propensity score matched (PSM) for baseline demographics, age, sex, race, BMI and comorbidities. **Results:** Around 217,000 adult patients were identified on GLP-1 inhibitors with no prior bariatric surgery vs 77,000 who underwent bariatric surgery in the past 10 years. GLP-1 inhibitors group were older in age (52 vs 46 years old), less predominantly female (62% vs 80%) and more likely to have co-morbidities including hypertension (HTN) (72.5% vs 54.6%), hyperlipidemia (HLD) (59% vs 33%), diabetes (DM) (67.4% vs 26.5%), ischemic heart disease (22% vs 11%), liver fibrosis and cirrhosis (2.4% vs 1.4%), alcoholic liver disease (0.79% vs 0.62%), nicotine dependance (22% vs 11%) and cerebrovascular accidents (CVA) (12.7% vs 7.1%) compared to bariatric group respectively with otherwise comparable opioid use disorders and alcohol dependance.

After PSM, GLP-1 group had significantly lower odds ratio (OR) of liver cirrhosis (OR 0.42) and decompensations including ascites (OR 0.20), hepatic encephalopathy (OR 0.25) and esophageal varices (OR 0.39). Odds were also lower for alcoholic liver disease (OR 0.12), liver failure (OR 0.22), need for liver transplant (OR 0.34) and overall mortality (OR 0.32) compared to bariatric surgery group. **Conclusion:** Obese patients on GLP-1 inhibitors had more comorbidities compared to obese patients who underwent bariatric surgery but lower odds of liver related outcomes after PSM.

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	Before propensity score match			After propensity score match	
	Obese GLP-1 no bariatric	Obese bariatric no GLP-1		Obese GLP-1 no bariatric	Obese bariatric no GLP-1
Number of patients	217,236	77,127		68,694	68,694
Age at index	52.1 +/- 13.2	46.7 +/-12.6		47.2 +/- 13.1	47.3 +/- 12.6
Female	62.9%	80.0%		79.3%	78.3%
Race					
Hispanic	8.9%	9.7%		9.3%	9.5%
White	46.8%	48.9%		49.4%	48.5%
Black	19.9%	18.0%		17.3%	18.2%
Other	8.2%	8.1%		7.7%	7.9%
BMI	36.9 +/- 5.9	38.4 +/-6.7		37.2 +/- 5.9	38.4 +/- 6.7
Comorbidities					
HTN	72.5%	54.6%		55.6%	56.2%
HLD	59.4%	33.3%		35.1%	36.1%
DM	67.4%	26.5%		30.4%	29.8%
Nicotine dependance	22.2%	11.6%		16.6%	17.4%
Ischemic heart disease	22.3%	11.6%		11.6%	12.5%
Alcoholic liver disease	0.79%	0.62%		0.46%	0.62%
Fibrosis and cirrhosis of the liver	2.4%	1.45%		1.2%	1.5%
CVA	12.7%	7.1%		7.0%	7.6%
CKD	13.4%	5.7%		5.6%	6.2%
Opiod related disorders	3.8%	3.8%		3.3%	3.7%
Alcohol dependance	2.9%	3.0%		2.5%	2.8%
ESRD	1.6%	1.1%		1.0%	1.1%
Results					
	Obese GLP-1 no bariatric	Obese bariatric no GLP-1	OR (CI)	P	
	68,694	68,694			
Cirrhosis of the liver	438 (0.64%)	1,029 (1.5%)	0.42 (0.37-0.47)	<0.0001	
Ascites	530 (0.78%)	2,450 (3.6%)	0.20 (0.19-0.22)	<0.0001	
Hepatic Encephalopathy	71 (0.1%)	281 (0.4%)	0.25 (0.19-0.32)	<0.0001	
Esophageal varices	116 (0.16%)	291 (0.42%)	0.38 (0.30-0.47)	<0.0001	
Alcoholic liver disease	98 (0.14%)	757 (1.1%)	0.12 (0.10-0.15)	<0.0001	
Liver Failure	196 (0.28%)	848 (1.24%)	0.22 (0.19-0.26)	<0.0001	
Mortality	1,171 (1.7%)	3,452 (5.0%)	0.32 (0.30-0.35)	<0.0001	
Liver Transplant	49 (0.07%)	141 (0.2%)	0.34 (0.25-0.48)	<0.0001	

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◆ 4010 | SAMARA: SEMAGLUTIDE TREATMENT IN THE REAL-WORLD FOR FIBROTIC MASH IN OBESITY AND T2DM

SEMAGLUTIDE VERSUS PLACEBO IN NIT-ASSESSED MASH: A REAL WORLD PRAGMATIC MULTICENTER RANDOMIZED PLACEBO-CONTROLLED TRIAL (SAMARA), *Rohit Loomba[1] Raj Vuppalanchi[2] Mandana Khalili[3] Muhammad Sheikh[4] Joseph Risser[5] Samuel Klein[6] Egbert Madamba[5] Seema Singh[5] Harris Siddiqi[5] Diana Cortez-Moreno[5] Darryl Contrano[5] Jenna Roulan[5] Heather Hofflich[5] Ruth Abeles[5] Eduardo Grunvald[5] Ricki Bettencourt[5] Feng He[5] Sonia Jain[5] Monica Tincopa[1] Lisa Richards[1] Veeral Ajmera[5]*

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Background: Semaglutide has been shown to be effective in a Phase 3 study among patients with biopsy-proven MASH and stage 2 or 3 fibrosis. However, liver biopsy assessment is not routinely used to determine candidacy for starting treatment in MASH in clinical practice. Therefore, we designed a pragmatic, real-world, multicenter trial to examine the clinical utility of non-invasive tests (NIT) in determining eligibility and treatment response in patients with suspected at-risk MASH who were randomized to semaglutide versus placebo. **Methods:** In this multicenter, randomized, double-blind placebo controlled trial, we screened 202 patients across 7 sites and randomized 55 patients to either Semaglutide 2.4 mg subcutaneously once a week or placebo in individuals who either had BMI $\geq$ 27 kg/m^2 or BMI $\geq$ 25 kg/m^2 and met ADA criteria for prediabetes or type 2 diabetes mellitus and a FAST score $\geq$ 0.5 (suggestive of at-risk MASH non-invasively) and LSM by VCTE $\geq$ 8 kPa who met AASLD criteria for MASLD. The primary outcome was a change in the FAST score. Secondary outcomes included changes in body weight, MRI-PDFF, ALT, and HbA1c. **Results:** The mean (SD) age, BMI and FAST at baseline was 48.8 (14) years, 40.2 (15) kg/m^2, 0.62 (0.12), respectively. 55% were women and 20% had T2DM. The mean (SD) VCTE, CAP and AST at baseline were 11.47 (3.23) kPa, 327 (38.8) dB/m and 51.7 (20.0) U/L respectively and did not differ between treatment groups. The mean (SD) duration of treatment was 6.5 (3.7) months and was similar between treatment groups [semaglutide 6.4 (3.7) months and placebo 6.5 (3.7) months]. The mean (SD) change in FAST from baseline to the end of treatment was significantly greater in the semaglutide group, at -0.28 (0.19), compared with placebo, at −0.12 (0.17), P = 0.002. More participants in the semaglutide group than in the placebo group achieved weight reductions of 5% or more (64% vs. 8.3%), at the end of treatment (P < 0.001). Semaglutide was better than placebo in achieving a clinically meaningful MRI-PDFF response ($\geq$30% reduction), 60% vs 17%, P = 0.047. Semaglutide led to a significantly greater reduction in ALT, AST, GGT, HbA1c, and LDL cholesterol (P < 0.05, Table). The most common side effects were gastrointestinal (GI), with 50 occurring in 50% of participants in the semaglutide group, compared to 35 in 41% of participants in the placebo group (P = 0.59). Four patients discontinued treatment early in the semaglutide group versus two in the treatment group P = 0.67 and one early termination was related to GI side effects in the semaglutide group. **Conclusion:** A real-world NIT-based screening approach for semaglutide treatment is feasible and effective. FAST, ALT, AST, and MRI-PDFF can monitor treatment responses. This study provides randomized controlled data to guide clinical practice for AASLD.

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Table 1.

Differences in Primary and Secondary Outcomes at the End of Treatment for Semaglutide vs Placebo.

	Semaglutide (N=28)	Placebo (N=27)	P
Primary Outcome			
FAST			
Mean Change (SD)	-0.28 (0.19)	-0.12 (0.17)	0.002
Percent Change (SD)	-44% (34)	-20% (28)	0.003
Secondary Outcomes			
MRI-PDFF			
30% Change, N, (%)	9 (60%)	2 (17%)	0.047
ALT (U/L)			
Absolute Change (SD)	-31.8 (27.6)	-8.6 (29.5)	0.021
Percent Change (SD)	-39% (23)	-9% (35)	<0.001
AST (U/L)			
Absolute Change (SD)	-18.2 (18.0)	-7.5 (21.2)	0.017
Percent Change (SD)	-31% (25)	-10% (27)	0.01
GGT (U/L)			
Absolute Change (SD)	-15.6 (24.3)	-0.6 (28.8)	0.009
Percent Change (SD)	-7% (106)	-4% (28)	0.004
VCTE (kPa)			
Absolute Change (SD)	-2.0 (5.4)	-1.81 (3.1)	0.292
Percent Change (SD)	-16% (44)	-13% (25)	0.216
CAP (dB/m)			
Absolute Change (SD)	-30.3 (37.6)	-29.0 (58.8)	0.489
Percent Change (SD)	-8% (12)	-8% (18)	0.512
Body weight			
≥5% weight loss, N (%)	14 (63.6%)	2 (8.3%)	<0.001
Percent Change (SD)	-8% (6)	-1% (4)	<0.001
LDL cholesterol mg/dL			
Absolute Change (SD)	-7.3 (25.1)	6.1 (31.9)	0.019
Percent Change (SD)	-4% (24)	13% (30)	0.024
Triglycerides mg/dL			
Absolute Change (SD)	-26.8 (40.4)	-23.6 (67.8)	0.759
Percent Change (SD)	-13% (27)	-9% (32)	0.644
HbA1c			
Absolute Change (SD)	-0.56 (0.49)	0.02 (0.53)	<0.001
Percent Change (SD)	-9% (7)	0% (7)	<0.001

- For continuous variables, P values are from Wilcoxon Rank Sum test; For categorical variable, P values are from Fisher's Exact Test.

Disclosures: Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Raj Vuppalanchi: Nothing to Disclose, Mandana Khalili: gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant, Muhammad Sheikh: Nothing to Disclose, Joseph Risser: Nothing to Disclose, Samuel Klein: Merck: Consultant, Alnylum: Consultant, Boehringer Ingelheim: Consultant, Abbvie: Consultant, Altimmune: Consultant, 89Bio: Advisor, Verdiva Bio: Advisor, Egbert Madamba: Nothing to Disclose, Seema Singh: Nothing to Disclose, Harris Siddiqi: Nothing to Disclose, Diana Cortez-Moreno: Nothing to Disclose, Darryl Contrano: Nothing to Disclose, Jenna Roulan: Nothing to Disclose, Heather Hofflich: Nothing to Disclose, Ruth Abeles: Nothing to Disclose, Eduardo Grunvald: Novo Nordisk: Consultant, Novo Nordisk: Grant/Research Support, Eli Lilly: Consultant, B2M Medical: Advisor, Ricki Bettencourt: Nothing to Disclose, Feng He: Nothing to Disclose, Sonia Jain: Nothing to Disclose, Monica Tincopa: Nothing to Disclose, Lisa Richards: Novo Nordisk: Advisor, Madrigal: Advisor, Veeral Ajmera: Nothing to Disclose

◆ 4011 | DENIFANSTAT ELICITED A SIGNIFICANT &GE;2-STAGE IMPROVEMENT IN FIBROSIS IN F3 MASH PATIENTS, AND IMPROVED LIVER FIBROSIS AND BIOMARKERS IN QFIBROSIS STAGE 4 MASH PATIENTS: SECONDARY ANALYSIS OF PHASE 2B FASCINATE-2 STUDY

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Background: New therapies are needed for MASH cirrhosis, particularly those that treat liver fibrosis, the primary predictor of poor clinical outcomes. Denifanstat (TVB-2640), an oral fatty acid synthase (FASN) inhibitor, demonstrated significant improvements in fibrosis and MASH resolution, and prevented progression to cirrhosis in the Ph2b FASCINATE-2 study. AI-based digital pathology, an advanced tool that complements conventional histopathology, was used to identify a subpopulation of MASH patients with advanced fibrosis, defined as qFibrosis stage 4 (qF4), and to explore liver histology improvement with denifanstat in this subset. **Methods:** 168 patients with biopsy-

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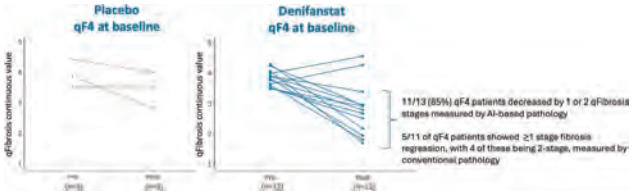
confirmed MASH and F2/F3 fibrosis were randomized 2:1 to once daily oral denifanstat (DENI) 50 mg or placebo (PBO) for 52 weeks. Pre- and post-treatment liver biopsy slides were read by a central pathologist using MASH CRN criteria. A separate unstained slide was evaluated by second harmonic generation (SHG) AI digital pathology (HistoIndex) to identify patients with baseline qF4 (DENI n = 13, PBO n = 3). All analyses of qF4 were post-hoc. **Results:** In F3 patients, by CRN scoring the response rate for fibrosis improvement by ≥ 2 stages without worsening of MASH was 34% (16/47) for DENI vs 4% (1/23) for PBO ($p = 0.0065$). In qF4 patients, by CRN the response rate for fibrosis improvement by ≥ 1 stage without worsening of MASH was 39% (5/13) for DENI, which 4 out of 5 had ≥ 2 stages improvement, vs 0% (0/4) for PBO ≥ 1 stage. By SHG digital pathology, the response rate for ≥ 1 qFibrosis stage regression was 85% (11/13) for DENI vs. 33% (1/3) for PBO. Several biomarkers were decreased by DENI in qF4 patients (mean change at week 52 from baseline):

- DENI -29% vs. +26% PBO, FibroScan (kPa)
- DENI -21% vs. +4% PBO, CAP (Db/m)
- DENI -45% vs. +9% PBO, FAST score
- DENI -34% vs. +14% PBO, MRI-PDFF (% liver fat)
- DENI -43% vs. +5% PBO, ALT
- DENI -37% vs. -1% PBO, AST
- DENI -0.3 vs. +0.0 PBO, ELF
- DENI -26% vs. +84% PBO, CK18 (M30)
- DENI -35% vs. +40% PBO, CK18 (M65). **Conclusion:** Denifanstat demonstrated a robust anti-fibrotic effect as measured by both conventional and AI-based digital pathology. Digital pathology identified a subpopulation of MASH patients with advanced baseline fibrosis (qF4), and denifanstat reduced fibrosis and multiple NIT biomarkers that indicate improvements in steatosis, inflammation and fibrosis in this subgroup. These findings support further clinical evaluation of denifanstat in MASH patients with advanced fibrosis, including compensated liver cirrhosis.



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◆ 4012 | DA-1241, A GPR119 AGONIST, DEMONSTRATES HEPATOPROTECTIVE EFFECTS THROUGH IMPROVING INFLAMMATION AND METABOLISM IN THE LIVER: A 16-WEEK RANDOMIZED PLACEBO-CONTROLLED TRIAL IN PRESUMED METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) PATIENTS

Rohit Loomba[1] Mi-Kyung Kim[2] Hyung Heon Kim[3] Yuna Chae[2] Robert Homolka[3] Ji Eun Lee[3] Kyunghyun Lee[2] Chris Fang[3] Sung-Jin Kim[2], *[1]University of California, San Diego, [2]Dong-A ST Co., Ltd., [3]MetaVia Inc.*

Background: DA-1241 is a potent and selective agonist for G protein-coupled receptor 119 (GPR119). Non-clinical studies have shown that GPR119 agonism may have direct therapeutic potential on not only hepatic steatosis but also inflammation and fibrosis, in the pathogenesis of MASH. This phase 2a trial (NCT06054815) evaluated the efficacy and safety of DA-1241 as a potential treatment for MASH, alone and in combination with a dipeptidyl peptidase 4 inhibitor (DPP4i) to augment endogenous glucagon-like peptide-1 action. **Methods:** Total 109 subjects with presumed MASH and qualifying baseline alanine transaminase (ALT) and imaging analysis were randomized to receive DA-1241 50 mg, DA-1241 100 mg alone, DA-1241 100 mg with a DPP4i, or placebo (PBO) in a 1:2:2:2 ratio, once daily for 16 weeks. The primary efficacy endpoint was the change from baseline in ALT after 16 weeks of treatment. **Results:** In the subgroup with $40 \leq$ ALT $<$ 200 U/L at baseline, DA-1241 treatment resulted in dose-dependent reductions in ALT, with the 100 mg dose demonstrating a significant decrease of 22.8 U/L at week 16 ($p < 0.05$ vs. PBO). Accordingly, plasma inflammatory (hs-CRP, CCL2) and fibrosis (TIMP1)-related parameters significantly decreased compared to PBO ($p < 0.05$). Cytokeratin 18, a marker of hepatocyte apoptosis, was significantly decreased by 30.5% ($p < 0.05$ vs. PBO). Additionally, the mean FibroScan-aspartate aminotransferase score improved from 0.559 to 0.371, indicating reductions in liver fibrosis and steatosis. Liver fat content decreased by 23.0 dB/m in Controlled Attenuation Parameter, along with a mean relative reduction of 19.9% in Magnetic Resonance Imaging-Proton Density Fat Fraction.

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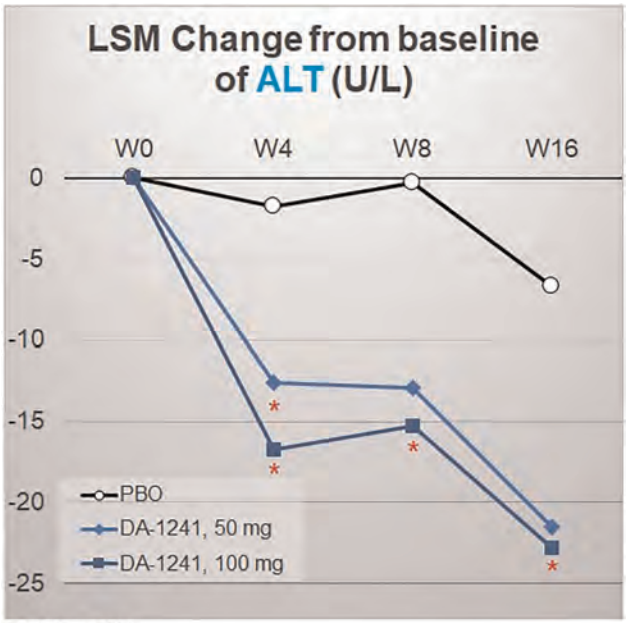
In plasma lipidomic profiles, administration of DA-1241 100 mg reduced both plasma glycerolipids (DG36:4, TG52:4) and glycerophospholipids (PE38:4, PE38:5), which are known to be pathogenic lipids ($p < 0.05$ vs baseline). Notably, on top of the hepatic effects, DA-1241 100 mg rapidly and markedly lowered mean hemoglobin A1c by 0.37, 0.41, and 0.54%p at week 4, 8, and 16 from the baseline of 6.99%, despite nearly half of them being non-diabetic ($p < 0.05$ vs. PBO). Additionally, co-administration with DPP4i augmented metabolic effects without body weight loss. **Conclusion:** DA-1241 is the first oral GPR119 agonist to demonstrate both hepatoprotective and glucose-regulating effects in presumed MASH patients. These findings support its further development as a potential monotherapy or combination therapy for MASH and metabolic disorders.



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◆ 4013 | MACHINE-LEARNING ENABLED GENETIC DISCOVERY, IN VIVO VALIDATION, AND LIVER-SPECIFIC THERAPEUTIC TARGETING OF IRS1 IN MASLD

David Lloyd[1] Santhosh Satapati[1] Hari Somineni[1] Colm O'Dushlaine[1] Tanaya Walimbe[1] Arijit Bhowmick[1] Sumit Mukherjee[1] Vaishaali Natarajan[1] Chinmayi Kashyap[1] Anup Sarakki[1], [1]insitro

Background: Genetic discovery in metabolic dysfunction-associated steatotic liver disease (MASLD) has been limited by the lack of scalable, clinically relevant phenotypes. To address these limitations, we: (i) used machine learning (ML) to impute liver fat (LF) from widely available data modalities, increasing sample size; and (ii) improved the precision of the phenotype by adjusting for adipose tissue volume (ATV), increasing statistical power and identifying genes with direct effects in the liver. **Methods:** We applied ML to predict LF and ATV using four data modalities from the UK Biobank: magnetic resonance imaging (MRI; n = 25,474 participants), dual-energy X-ray absorptiometry (DXA, n = 48,494), plasma metabolites (n = 82,138), and blood-based and anthropometric markers (biomarkers; n = 262,927). We conducted a genome-wide association study (GWAS) of LF for each modality, adjusting for ATV. For top targets, we identified therapeutically optimised liver-targeted small-interfering RNAs (siRNAs) and assessed their efficacy in vitro and in vivo in mice and monkeys. **Results:** GWAS identified a total of 480 genetic loci, significantly expanding the genetic architecture of LF accumulation, including the first human association of FGF21. We observed strong genetic correlation between predicted LF content across

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modalities (0.79 – 0.97) and with clinical MASLD (0.73 – 0.87), with multimodal hits having the highest concordance. We identified several novel genes involved in de novo lipogenesis (DNL), including IRS1, which was the strongest novel association ($p = 2 \times 10\text{-}82$ biomarker-imputed LF adjusted for ATV) and supported across all four modalities ($p < 5 \times 10\text{-}8$). We identified a potent, selective liver-targeted GalNAc-siRNA against IRS1 (IC50~0.04 nM) that completely suppressed lipid droplet accumulation in primary human hepatocytes. Treatment of diet-induced obese mice with a single dose (0.3 – 10 mg/kg) resulted in dose-dependent reduction in hepatic IRS1 expression (85% vs. vehicle) and hepatic triglycerides (45%), improved histologic NAS score (2.2 ± 0.2 vs. vehicle 4.3 ± 0.2, $p = 0.0002$), and suppressed DNL (59%) after one month. Treatment of cynomolgus monkeys (30 – 300 mg/kg) reduced hepatic IRS1 expression by up to 70% after 15 days, without impacting glucose homeostasis. **Conclusion:** IRS1 can be effectively targeted using a liver-targeted GalNAc-siRNA demonstrating efficacy and tolerability in preclinical models of MASLD.

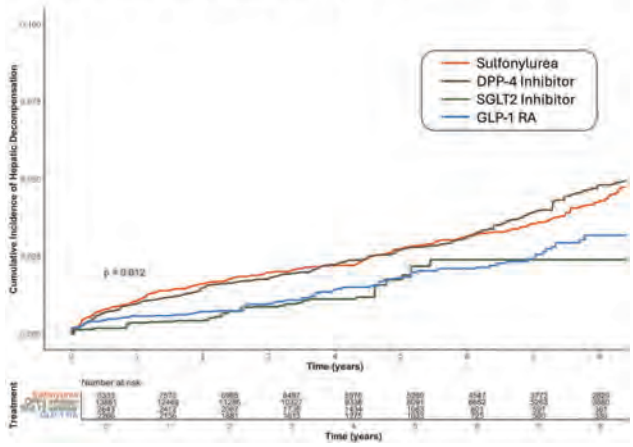
Disclosures: David Lloyd: Nothing to Disclose, Santhosh Satapati: Nothing to Disclose, Hari Somineni: Nothing to Disclose, Colm O'Dushlaine: Nothing to Disclose, Tanaya Walimbe: Nothing to Disclose, Arijit Bhowmick: Nothing to Disclose, Sumit Mukherjee: Nothing to Disclose, Vaishaali Natarajan: Nothing to Disclose, Chinmayi Kashyap: Nothing to Disclose, Anup Sarakki: Nothing to Disclose

◆ 4014 | COMPARATIVE RISK OF HEPATIC DECOMPENSATION AND HEPATOCELLULAR CARCINOMA AMONG ANTIDIABETIC THERAPIES IN PATIENTS WITH TYPE 2 DIABETES AND CHRONIC LIVER DISEASE

Ana Verma[1] Jonggi Choi[2] Eric Przybyszewski[3] Jiunn Song[3] Allison Carroll[3] Megan Michta[3] Erik Almazan[4] Tracy Simon[3] Raymond Chung[3], [1]Harvard Medical School, [2]Asan Medical Center, University of Ulsan. Massachusetts General Hospital, [3]Massachusetts General Hospital, [4]Brigham and Women's Hospital

Background: The comparative hepatic safety, or advantage, of second-line glucose-lowering therapies in patients with type 2 diabetes (T2DM) and chronic liver disease (CLD) remains uncertain. We evaluated the association of SGLT2 inhibitors (SGLT2i), GLP-1 receptor agonists (GLP-1RA), DPP-4 inhibitors (DPP4i), and sulfonylureas with the risk of hepatic decompensation and hepatocellular carcinoma (HCC) in this population. **Methods:** We conducted a multinational retrospective cohort study using electronic health records from Mass General Brigham (United States) and Asan Medical Center (Korea). Adults (≥ 18 years) with T2DM and CLD who newly initiated SGLT2i, GLP-1RA, DPP4i, or sulfonylurea therapy between 2013 and 2023 were included. Patients with prior HCC, decompensation, or liver transplantation were excluded. The primary outcome was incident hepatic decompensation; the secondary outcome was incident HCC. Inverse probability of treatment and censoring weighting (IPTW/IPCW) was applied to balance baseline covariates. Weighted Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). **Results:** Among 21,951 eligible patients, MASLD was the predominant CLD etiology (70–93%), and baseline cirrhosis was present in 3.6–7.4% across groups. After weighting, covariate balance was achieved (standard mean difference, SMD < 0.1). A total of 692 hepatic decompensation events and 291 HCC cases occurred during follow-up. SGLT2i and GLP-1RA use were each associated with a significantly lower risk of hepatic decompensation when compared with sulfonylureas (HR for SGLT2i vs SU, 0.57; 95% CI, 0.35–0.92; HR for GLP-1RA vs SU, 0.68; 95% CI, 0.48–0.97). Similar protective associations were observed when DPP4i was used as the reference for SGLT2i (HR, 0.50; 95% CI, 0.31–0.81) and GLP-1RA (HR, 0.60; 95% CI, 0.42–0.85). No significant difference was observed between SGLT2i and GLP-1RA (HR, 1.20; 95% CI, 0.69–2.10), suggesting comparable effectiveness. For HCC, SGLT2i and GLP-1RA use were each associated with significantly lower risk compared with sulfonylureas (HR for SGLT2i vs SU, 0.47; 95% CI, 0.23–0.97; HR for GLP-1RA vs SU, 0.07; 95% CI, 0.03–0.19). **Conclusion:** In patients with T2DM and CLD, use of SGLT2i or GLP-1RA was associated with a significantly lower risk of hepatic decompensation and HCC compared to sulfonylureas and DPP4i. These findings support the preferred use of SGLT2i or GLP-1RA in this high-risk population.

Figure. Cumulative Incidence of Hepatic Decompensation by Antidiabetic Drug Class in Patients with T2DM and Chronic Liver Disease



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◆ 4015 | VITAMIN E DOSING STUDY (VEDS) IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A RANDOMIZED-PLACEBO CONTROLLED TRIAL

Srinivasan Dasarathy[1] Emily Mitchell[2] Laura Wilson[2] Bilal Hameed[3] Brent Neuschwander-Tetri[4] Rohit Loomba[5] Ayako Suzuki[6] Liyun Yuan[7] Naga Chalasani[8] Jeanne Clark[9] Kris Kowdley[10] Arun Sanyal[11], [1]Cleveland Clinic, [2]Johns Hopkins University, [3]UCSF, [4]SLU, [5]University of California, San Diego, [6]Duke University, [7]University of Southern California, [8]Indiana University Medical Center, [9]Rutgers RWJ Medical School, [10]Liver Institute Northwest, [11]Virginia Commonwealth University

Background: The NASH CRN PIVENS study showed that 800 IU natural vitamin E (d-alpha-tocopherol) daily was more effective than placebo in resolving MASH. However, safety concerns with higher doses of vitamin E and lack of data on lower doses have limited its wide-scale use for treating MASH. The Vitamin E Dosing Study (VEDS) was a multicenter, randomized, placebo-controlled, dose-ranging trial to determine the efficacy and safety of lower doses of natural vitamin E on serum ALT levels over 24 weeks. **Methods:** Subjects $\geq$18 years with MASLD and controlled attenuation parameter (CAP) $>$280 dB/m and ALT $\geq$60 U/L were randomized to 24 weeks of once daily vitamin E (200, 400, or 800 IU [Pharmavite]) or placebo. Major exclusions were vitamin E or anticoagulant use and HbA1c $>$9.5%. Primary outcome was relative change from baseline in mean ALT at 24 weeks with the 3 doses of vitamin E vs placebo using analysis of covariance (ANCOVA). Secondary outcomes included changes in other liver tests, CAP and liver stiffness, and adverse events. **Results:** 200 participants were randomized. The 4 groups were well matched for sex (62% male), mean age (47.0 years), ALT (89 U/L), BMI (34.5 kg/m^2), and frequency of diabetes (31%) and dyslipidemia (48%). 192 patients (96%) completed the 24-week visit. All 3 doses of vitamin E significantly reduced mean ALT vs. placebo (-12%): 200 IU (-37%), 400 IU (-36%), and 800 IU (-36%) (all P $<$ .01) with no evidence of a dose response (Table 1). Reductions in ALT by $>$20% occurred in 43% on placebo vs 83% on 200 IU, 73% on 400 IU, and 75% on 800 IU of vitamin E. AST levels were also reduced in all vitamin E groups vs. placebo ($p < 0.01$), but changes in alkaline phosphatase, GGT, and BMI did not differ between vitamin E and placebo. While CAP scores and liver stiffness declined more in patients on vitamin E than placebo, the differences were not significant. Overall, adverse event rates were similar between the vitamin E and placebo groups. **Conclusion:** In MASLD patients, natural vitamin E at 200 IU once daily resulted in significant reductions in serum ALT levels similar to those treated with higher doses. After 24 weeks of treatment, there was a trend in improvements in liver fat and stiffness. Longer-term trials of natural vitamin E using doses of 200 IU and lower in patients with steatotic liver disease to evaluate its safety and efficacy further are warranted.

Table 1. Primary and secondary outcomes after 24 weeks of treatment (N=192)

	Placebo	Vitamin E 200 IU	Vitamin E 400 IU	Vitamin E 800 IU	P 200 IU vs. Plbo.	P 400 IU vs. Plbo.	P 800 IU vs. Plbo
N with Primary Outcome	46	49	49	48			
Primary Outcome: Relative change in ALT(U/L) (24 wks-BL) - %*	-12.2 (33.4)	-38.4 (31.9)	-36.3 (31.1)	-36.4 (43.1)	<0.0001	<0.0001	0.001
Secondary Outcomes– 24 wks-BL							
ALT % decrease ≥20%	20 (43%)	40 (82%)	36 (73%)	36 (75%)	0.0003	0.004	0.002
Mean change in ALT (U/L)	-12.4 (33.5)	-42.3 (42.4)	-43.5 (48.8)	-42.9 (58.5)	<0.0001	<0.0001	<0.0001
Mean change in AST (U/L)	-3.3 (20.3)	-22.1 (32.9)	-24.4 (46.4)	-23.7 (31.7)	<0.001	0.009	<0.0001
Mean change in GGT (U/L)	-19.8 (63.8)	-9.4 (47.1)	-25.1 (53.0)	-17.0 (27.4)	0.25	0.24	0.35
Mean change in Controlled Attenuation Parameter (CAP) (dB/m)	-11.2 (45.8)	-26.0 (46.3)	-9.0 (41.2)	-20.1 (47.3)	0.04	0.94	0.50
Mean change in Liver Stiffness Measure (LSM) (kPa)	0.4 (4.5)	-0.7 (4.7)	-1.2 (4.3)	-2.7 (7.5)	0.92	0.39	0.10
Mean change in BMI (kg/m2)	-0.2 (2.4)	-0.9 (2.7)	-0.6 (2.0)	-0.3 (1.7)	0.16	0.39	0.76

Data are mean (SD) or N(%).
*P values for mean change from baseline were calculated using ANCOVA, regressing change from baseline to 24 weeks on treatment group and clinical center. P values for categorical variables were calculated using the Cochran-Mantel-Haenszel chi-square test, stratified by clinic. Per protocol, complete case analysis used since <10% missing primary outcome.

Disclosures: Srinivasan Dasarathy: Nothing to Disclose, Emily Mitchell: Nothing to Disclose, Laura Wilson: Nothing to Disclose, Bilal Hameed: Gilead: Grant/Research Support, Intercept: Grant/Research Support, Pliant: Grant/Research Support, Novo Nordisk: Grant/Research Support, Madrigal: Grant/Research Support, Salix: Grant/Research Support, Mallinckrodt: Advisor, Pleiogenix: Advisor, CLDF: Advisor, Gilead: Consultant, Pioneering Medicine VII Inc: Consultant, Surrozen: Consultant, Pleiogenix: Stock – privately held company, Scholars In Medicine: Speaking and Teaching, Madrigal: Advisor, Akero: Grant/Research Support, Brent Neuschwander-Tetri: Akero: Consultant, Aligos: Consultant, Arrowhead: Consultant, Corcept: Consultant, GSK: Consultant, Hepion: Consultant, HIstoIndex: Consultant, Madrigal: Consultant, Madrigal: Grant/Research Support, Merck: Consultant, Mirum: Consultant, Sagimet: Consultant, Senseion: Consultant, HepGene: Stock – privately held company, HeptaBio: Stock – privately held company, Abbvie: Consultant, Pliant: Consultant, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma:

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◆ 4016 | SGLT2 INHIBITORS SUPPRESSED THE ONSET OF EXTRAHEPATIC CANCER COMPARED TO DPP4 INHIBITORS IN TYPE 2 DIABETIC PATIENTS WITH MASLD: A NATIONWIDE MEDICAL CLAIMS DATABASE STUDY IN JAPAN

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Background: Extrahepatic cancer is one of the main causes of death in patients with MASLD. Sodium-glucose transporter 2 inhibitors (SGLT2i), anti-diabetic medication, have been reported to improve MASLD in patients with type 2 diabetes mellitus (T2DM). We aimed to investigate the impact of SGLT2i on the incidence of extrahepatic cancer compared with dipeptidyl-peptidase 4 inhibitors (DPP4i) in T2DM patients with MASLD using a nationwide medical claims database in Japan. **Methods:** We conducted a retrospective cohort study using the Medical Data Vision database. From T2DM patients prescribed SGLT2i or DPP4i (n = 1,628,656), eligible patients were classified into SGLT2i (n = 4,204) and DPP4i (n = 4,204) groups after adjustment by propensity score matching using 67 covariates. Effects of SGLT2i on the incidence of cardiovascular events and extrahepatic cancer were compared to DPP4i during 12 months. **Results:** At baseline, both the SGLT2i and DPP4i groups had a mean age of 62 years and a same sex distribution. There was no significant difference in the use of other anti-diabetic medications between the SGLT2i and DPP4i groups. No significant differences were observed in HbA1c levels, ALT levels, or FIB-4 index between the two groups.

Outcomes: There was no significant difference in the incidence of cardiovascular events between the SGLT2i and DPP4i groups. However, SGLT2i significantly reduced the incidence of extrahepatic cancer compared to DPP4i (HR 0.5, 95%CI 0.30-0.84). Kaplan–Meier curve also demonstrated a significant reduction in the probability of extrahepatic cancer in the SGLT2i group compared to the DPP4i group. We further performed a stratified analysis to identify patients' characteristics associated with SGLT2i-caused suppression of the incidence of extrahepatic cancer. SGLT2i significantly suppressed the incidence of extrahepatic cancer in patients aged ≥65 years, ALT >30 U/L, FIB-4 index ≥1.3, eGFR <60 mL/min/1.73m^2, HbA1c <7.0%, and triglyceride ≥150 mg/dL. **Conclusion:** SGLT2i was more beneficial than DPP4i in suppressing the

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incidence of extrahepatic cancer compared to DPP4i in T2DM patients with MASLD. This cancer-suppressing effect was more evident in patients with advanced age, hepatitis, liver fibrosis, chronic kidney disease, mild diabetes, and hypertriglyceridemia. Thus, SGLT2i may be beneficial to improve the prognosis of patients with T2DM and MASLD through inhibition of the onset of extrahepatic cancer.

Disclosures: Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching, Yoshiyuki Fujishima: Nothing to Disclose, Fusayo Io: Nothing to Disclose, Yuri Sato: Nothing to Disclose, Saeko Uchida: Taisho pharmaceutical CO., Ltd: Employee, Yukiko Kitajima: Nothing to Disclose

◆ 4017 | EFFECT OF BARIATRIC SURGERY, GLP-1 RA, AND SGLT2I ON COMPOSITE LIVER EVENTS IN NON-CIRRHOTIC MASLD PATIENTS: A RETROSPECTIVE COHORT STUDY

Diwanshu Soni[1] Leith Ghani[1] Majd Aboona[1] Pooja Rangan[1] Derek Scholes[1] Chih-Hua Chung[1] Mark Wong[1] Karn Wijarnpreecha[2] Rohit Nathan[1] Moises Nevah Rubin[1] Michael Fallon[1] Farah Husain[1] Ma Ai Thanda Han[3], [1]University of Arizona College of Medicine - Phoenix, [2]University of Arizona College of Medicine-Phoenix, [3]University of Arizona College of Medicine Phoenix

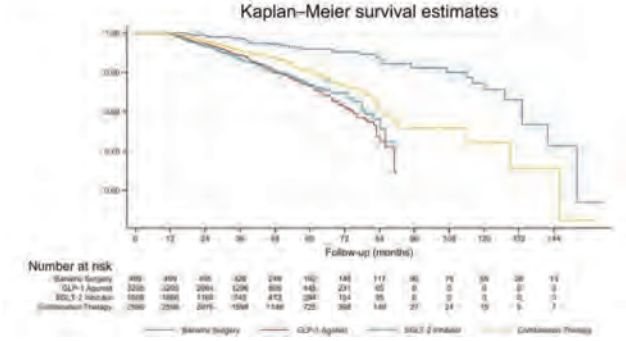
Background: Globally, metabolic dysfunction-associated steatotic liver disease (MASLD) emerged as a leading cause of chronic liver disease, contributing to cirrhosis and its complications, hepatocellular carcinoma (HCC), and liver transplant. Bariatric surgery, GLP-1 receptor agonists (GLP-1 RA), and SGLT2 inhibitors (SGLT2i) have each demonstrated efficacy in reducing disease progression, however comparative analysis of their effects in composite liver events is lacking in the literature. This study compares these interventions' effect on the incidence of composite liver events in MASLD patients without cirrhosis at intervention. **Methods:** This multicenter retrospective cohort study conducted at Banner Health evaluated the effect of specific interventions on MASLD patients without cirrhosis at intervention, who were identified with ICD codes. The patients received the following interventions and were followed for at least 12 months post intervention: bariatric surgery, GLP-1 RA, SGLT2i, or combination therapies. Composite liver events were defined as follows: 1. New Onset of Cirrhosis, 2. LREs- ascites, hepatic encephalopathy, or esophageal varices, 3. Hepatocellular carcinoma (HCC), and 4. Liver transplant 12 months post intervention. Medication reconciliation was done to verify medication use, while bariatric procedures were confirmed via ICD codes. Competing risk analysis evaluated the incidence of liver events across treatment groups using bariatric surgery as reference, while adjusting for confounders. A Kaplan-Meier survival curve was generated to depict composite liver event free survival. **Results:** The study cohort comprised of 13,694 patients of which 4.8% underwent bariatric surgery, 45.6% received GLP-1 RA, 26.5% SGLT2i therapy, and 23.1% combination therapy. Among this cohort, multivariate and univariate analysis show bariatric surgery treatment group had statistically significant lower rates of composite liver events — new onset cirrhosis, LREs, HCC and liver transplant — 12 months post treatment compared to the GLP1-RA, SGLT2i and combination therapy groups (Table 1). Kaplan-Meier survival analysis demonstrated superior composite liver event free survival in the bariatric surgery group (Figure 1). **Conclusion:** The findings suggest that in MASLD patients without cirrhosis, bariatric surgery performs better than GLP1-RA, SGLT2i or combination therapy in lowering composite liver events 12 months post intervention even when adjusting for confounding factors. Future studies should use prospective cohort study design to investigate the mechanisms driving the impact of these therapies, strengthen temporal associations, and address retrospective cohort study limitations.

Table 1

Intervention	Composite Liver Events in Non-Cirrhotic MASLD Patients			
	HR (95% CI)	p-value	aHR (95% CI)	p-value
Bariatric Surgery	Reference			
Glucagon-Like Peptide-1 Agonist (GLP-1 RA)	3.28 (2.22-4.85)	0.000	2.25 (1.47-3.45)	0.000
Sodium-Glucose Cotransporter 2 Inhibitor (SGLT2i)	3.23 (2.15-4.88)	0.000	2.25 (1.43-3.54)	0.000
Combination Therapy	2.34 (1.58-3.45)	0.000	1.74 (1.13-2.66)	0.011

HR: Hazard Ratio
aHR: Adjusted Hazard Ratio for tobacco use, age, BMI, sex, race, HTN, HLD, DM
CI: Confidence Interval

Figure 1



Disclosures: Diwanshu Soni: Nothing to Disclose, Leith Ghani: Nothing to Disclose, Majd Aboona: Nothing

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to Disclose, Pooja Rangan: Nothing to Disclose, Derek Scholes: Nothing to Disclose, Chih-Hua Chung: Nothing to Disclose, Mark Wong: Nothing to Disclose, Karn Wijarnpreecha: Nothing to Disclose, Rohit Nathan: Nothing to Disclose, Moises Nevah Rubin: Madrigal Pharmaceutical: Speaking and Teaching, Mallinckrodt Pharmaceutical: Speaking and Teaching, Michael Fallon: Nothing to Disclose, Farah Husain: Nothing to Disclose, Ma Ai Thanda Han: Nothing to Disclose

◆ 4018 | PRECLINICAL CHARACTERIZATION OF CVI-2742: A HIGHLY SELECTIVE, LIVER-TARGETED THR-β FULL AGONIST WITH ROBUST EFFICACY AND SAFETY IN MASH MODELS

Jingwen Liu[1] Dafang Zhong[2], [1]CVI Pharmaceuticals Shanghai Limited, [2]LVI Pharmaceuticals Shanghai Limited

Background: Thyroid hormone receptor beta (THR-β) selective agonists represent a breakthrough in metabolic dysfunction-associated steatohepatitis (MASH) treatment, with Resmetirom (MGL-3196) being the first FDA-approved THR-β agonist that avoids cardiac THR-α activation. Building on this, CVI-2742 is a next-generation, highly potent, liver-targeted THR-β full agonist designed to exhibit superior hepatic specificity and efficacy. This study comprehensively evaluates the preclinical profile of CVI-2742, including its in vitro potency, pharmacodynamic (PD) and pharmacokinetic (PK) properties, and toxicological safety, to establish its potential as a best-in-class therapeutic candidate for MASH. **Methods:** CVI-2742 was characterized through a series of in vitro and in vivo assays. In vitro efficacy was assessed using: (1) a cell-free coactivator binding assay, (2) a thyroid response element (TRE)-luciferase reporter assay in HEK293 cells, (3) an OATP1B1 co-expression reporter assay to evaluate liver transporter-mediated uptake, and (4) qPCR-based gene expression analysis in Huh-7 cells. In vivo efficacy was evaluated in a high-fat diet (HFD)-CCl4-induced DIO mouse model of MASH and a hyperlipidemic mouse model to assess lipid-lowering effects. PK studies included single- and multiple-dose assessments in mice, rats, and beagle dogs, with tissue distribution analyzed via LC-MS/MS. Liver targeting was further examined in mice, rats, and cynomolgus monkeys. Four-week repeat-dose toxicity studies were conducted in rats and dogs to evaluate safety margins. **Results:** CVI-2742 demonstrated potent THR-β agonism with an EC_{50} of 8.6 nM and 100% maximal T3 activity, while showing minimal THR-α activation (EC_{50} = 507 nM), yielding a 65-fold β-selectivity. OATP1B1 co-expression enhanced THR-β activation by 26-fold (EC50 = 13 nM vs. 333 nM without OATP1B1), confirming liver-specific uptake. In the HFD-CCl4 mouse model, C2742 resolved steatohepatitis and reduced fibrosis at a minimal effective dose (MED) of 0.5 mg/kg. In hyperlipidemic mice, it significantly lowered LDL-c (44.2%) and liver index (13.2%) at 0.17 mg/kg. Tissue distribution studies revealed exceptional liver targeting, with liver-to-plasma ratios of 37.9 (mouse), 58.2 (rat), and 54.9 (monkey). Toxicology studies in beagle dogs showed no adverse effects at 15 mg/kg (4-week dosing), indicating a safety window exceeding 60-fold. No histopathological abnormalities or organ weight changes were observed. **Conclusion:** CVI-2742 exhibits best-in-class potential as a liver-targeted THR-β full agonist, combining high potency, robust hepatic selectivity, and an outstanding safety profile. Its ability to ameliorate MASH pathology and dyslipidemia at low doses, coupled with favorable PK and toxicology data, strongly supports its advancement into clinical trials for MASH therapy.

Disclosures: Jingwen Liu: Nothing to Disclose, Dafang Zhong: Nothing to Disclose

◆ 4019 | A 5-WEEK TREATMENT WITH RETATRUTIDE STRONGLY REDUCES LIVER FAT CONTENT AND SHOWS MULTIPLE METABOLIC BENEFITS IN DIET-INDUCED OBESE MASH MOUSE AND HAMSTER MODELS

Francois Briand[1] Estelle Grasset[1] Natalia Breyner[1] Claire Bigot[1] Thierry Sulpice[1], [1]Physiogenex

Background: Retatrutide (RETA) is a novel GIP/GLP-1/glucagon receptors triple agonist that demonstrated significant body weight loss and liver fat reduction in patients with obesity. Our aim was to evaluate the effectiveness of RETA in diet induced obese MASH mouse and hamster models, two preclinical models that we routinely use for assessing new therapies targeting obesity and MASH. **Methods:** To induce obesity and MASH in both models, C57BL/6JRj male mice were fed a modified AMLN-diet for 35 weeks. Male golden Syrian hamsters were fed a 20-week free choice diet, which presents hamsters with a choice between control chow diet or high fat/cholesterol diet, and normal water or 10% fructose water. Both models were then treated with vehicle or RETA 15nmol/kg Q3D for 5 weeks. **Results:** In mice, RETA strongly reduced body weight by 31% ($p < 0.0001$ vs. vehicle) which was associated with significant reduction in fat and lean mass, a strong inhibition of food and water intake during the first days of treatment, and a significantly greater energy expenditure at the end of treatment. RETA significantly reduced fasting glycemia and plasma insulin, leading to a 69% lower HOMA-IR index of insulin resistance

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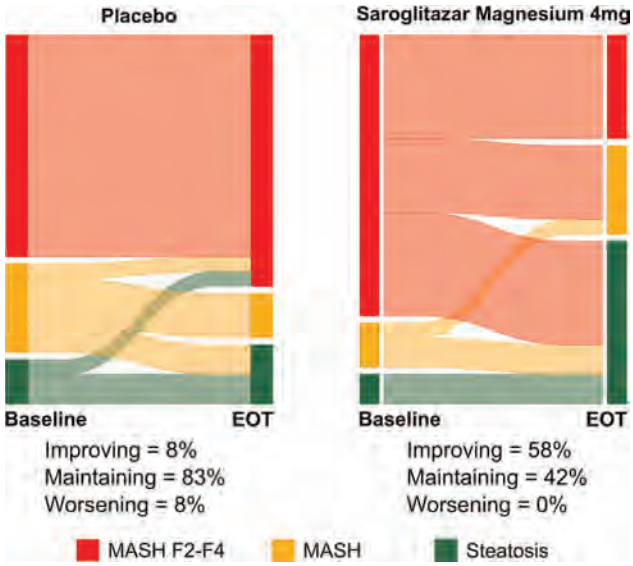
($p < 0.0001$) and strongly reduced hepatic fatty acids, triglycerides and total cholesterol content (-66%, -75% and 45%, all $p < 0.001$). Although it did not reduce hepatic inflammation and portal fibrosis, histology analysis also showed a 2-fold lower steatosis score with RETA ($p < 0.0001$).
In hamsters, RETA altered food preference with greater chow diet intake and lower high fat/cholesterol diet and 10% fructose water intake. Compared with vehicle, the significant weight loss was associated with significant reduction in fat and lean mass, but the lean mass was not different after 5 weeks of treatment. RETA had no effect on bone density/microarchitecture as evaluated by μ-CT. RETA reduced HOMA-IR by 81% ($p < 0.0001$ vs. vehicle) and markedly improved dyslipidemia with significantly reduced plasma free fatty acids and triglycerides, lower VLDL- and LDL-cholesterol levels but unchanged HDL-cholesterol levels. As in mice, a 5-week treatment with RETA was not sufficient to reduce histopathological scoring, but there was a 50% reduction in hepatic triglycerides content ($p < 0.01$). **Conclusion:** RETA reduces liver fat content and shows multiple metabolic benefits in both mice and hamster models. Our preclinical setting will help to assess the efficacy of new therapies versus RETA as a reference. **Disclosures:** Francois Briand: Physiogenex: Employee, Physiogenex: Stock – privately held company, Estelle Grasset: Nothing to Disclose, Natalia Breyner: Nothing to Disclose, Claire Bigot: Nothing to Disclose, Thierry Sulpice: Nothing to Disclose

◆ 4020 | SAROGLITAZAR TREATMENT REDUCED SEVERITY OF MASLD PHENOTYPES BY LIPIDOMIC-BASED TEST OWLIVER IN SUBJECTS WITH MASLD IN A 16-WEEK PHASE 2 TRIAL

Cristina Alonso[1] Ibon Martinez-Arranz[1] Deven Parmar[2] Naga Chalasani[3] Samer Gawrieh[3], [1]Rubio Metabolomics, [2]Zydus Therapeutics INC, [3]Indiana University Medical Center

Background: Saroglitazar magnesium, a dual peroxisome proliferator activated receptor-α/γ agonist, improves ALT, liver fat content, insulin resistance, atherogenic dyslipidemia and reduces cardiovascular risk in patients with MASLD/MASH. OWLiver is a lipidomics-based test that allows non-invasive discrimination of different MASLD phenotypes [steatosis, MASH or MASH with significant fibrosis (at-risk MASH)]. This study aimed to evaluate the evolution of MASLD phenotypes in patients with MASLD treated with Saroglitazar based on the diagnostic panel OWLiver. **Methods:** OWLiver test was analyzed in 96 participants of the Evidences IV Phase 2 clinical trial that received different daily doses of Saroglitazar (1 mg, 2 mg or 4 mg) or placebo for 16 weeks (NCT03061721). The OWLiver test was used to further evaluate the efficacy of Saroglitazar on MASLD evolution from baseline to end of treatment (EoT) visits. The Z-test was used to assess differences in the proportion of patients with an improved or worsened diagnosis between arms. **Results:** At baseline, 73% of the analyzed patients had at-risk MASH, while the rest of patients were diagnosed with steatosis or MASH (13.5% of patients in each case) by OWLiver. On assessing the effect of interventions by comparing baseline and EoT diagnoses, most placebo-treated patients maintained their initial diagnosis (84%). Saroglitazar treatment led to favorable disease evolution in a 41% of patients, especially regarding 1mg [35% of subjects with improved diagnosis ($p = 0.016$ *vs.* Placebo), with no patients showing worsening (n.s.)] and 4mg doses [58% of improved diagnoses ($p < 0.001$ *vs.* Placebo) and no worsenings (n.s.)] (Figure: Sankey Plots). Saroglitazar 2mg patients showed both improved (29%) and worsened (14%) diagnoses (n.s. in comparison to Placebo). **Conclusion:** Most patients treated with Saroglitazar 4 mg regressed to less severe MASLD phenotypes after 16-weeks treatment. Evaluation of the effects of Saroglitazar on MASLD/MASH using OWLiver test provides further evidence supporting the beneficial effects of the intervention, especially the 4mg dose.



Disclosures: Cristina Alonso: Rubió Metabolomics, S. L.U.: Employee, Ibon Martinez-Arranz: Nothing to Disclose, Deven Parmar: Nothing to Disclose, Naga Chalasani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Samer Gawrieh: Transmedics: Consultant, pfizer: Consultant, kowa: Consultant, spruce: Consultant, viking: Grant/Research Support, zydus: Grant/Research

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4021 | CARDIOMETABOLIC RISK FACTORS ARE HIGHLY PREVALENT AND UNDERTREATED IN MASLD WITH ADVANCED LIVER FIBROSIS-ANALYSIS OF A LARGE REGIONAL VETERANS' AFFAIRS COHORT

Suria Devarapalli[1] Srikanth Vallurupalli[1] Timothy Morgan[2] Ragesh Thandassery[1], [1]Central Arkansas Veterans Healthcare System & University of Arkansas Medical Science, [2]VA Long Beach Healthcare System

Background: Metabolic dysfunction associated steatotic liver disease (MASLD) is the most common chronic liver disease in the US. In this study, we analyzed the cardiometabolic risk characteristics of veterans with MASLD in South Central Veterans Affairs (VA) Health Care Network (VISN-16), a region with the highest obesity prevalence in the US. **Methods:** A retrospective cohort study was conducted using data from the Veterans Health Administration. We identified 315,578 veterans with MASLD for the fiscal year 2024 (alcohol liver disease excluded). Veterans with BMI above 30 (37.1%) and advanced liver fibrosis (3.3%) were included and those with decompensated cirrhosis excluded. Fibrosis-4 (FIB-4) score >2.67 was used to identify advanced liver fibrosis (age capped at 65 for FIB-4 calculation). To determine age related differences, patients were grouped based on age $\leq$ 65 and $>$ 65 years. Atherosclerotic cardiovascular disease (ASCVD) risk scores were calculated for those between 40 and 75 years of age. **Results:** 4107 veterans met inclusion criteria. Median age was 67 (61-72) years, 94.6% males, 72.4% Caucasian (17.9% African American). Median BMI was 33.5 (IQR 31.6-36.6). 51.2% had diabetes mellitus (DM) and 20.8% prediabetes. 35.8% had a diagnosis of cardiovascular disease (CVD), and 37.9% had metabolic syndrome as defined by the National Cholesterol Education Program ATP III ($\geq$ 3 criteria). As expected, veterans >65 years had higher prevalence of DM, CVD and higher 10-year ASCVD risk (Table 1). 61.4% were on HMG-CoA reductase inhibitors (statins). 56.1% had high ASCVD risk and 24.1% had intermediate ASCVD risk. Only 34.1% with high ASCVD risk received high intensity statin and 28.3% with intermediate risk received high intensity statin. 33.3% with high ASCVD risk and 45.8% with indeterminate ASCVD risk received no statins. A significant number of veterans with intermediate/high ASCVD risk, specifically those <65 years were not receiving statins. Similarly, when used, the intensity of statin therapy was often lower than that recommended for the degree of ASCVD risk. **Conclusion:** Statin treatment is significantly underutilized and underdosed in this high-risk advanced liver fibrosis cohort, likely reflecting the commonly held misconceptions regarding safety of statins in liver disease. System wide educational efforts are needed to improve ASCVD risk factor modification and adequate use of statins since CVD is the most important cause of death in MASLD.

Table 1

Comparison of veterans with MASLD and advanced liver fibrosis

	Age ≤65 years (n=1052)	Age > 65 yrs (n=3055)	
Age (years)*	59(54-63)	72(69-74)	
BMI (kg/m2)	35.1 (32.3-38.3)	33.5(31.5-36.3)	p<0.001
Albumin (g/dl)	3.9 (3.6-4.2)	3.8(3.5-4.0)	p<0.001
NAFLD fibrosis score	2.2(2.1-3.2)	2.7(2.2-3.3	p<0.001
Metabolic syndrome (%)	36.8%	38.2%	p=0.424
Type 2 diabetes mellitus (%)	39.0	55.1	p=0.002
HbA1c	6.2(1.4)	6.3(1.2)	p=0.002
Prediabetes (%)	23.5	19.3	p=0.627
ASCVD risk score (%)			p<0.001
Low	8.1	0	
Borderline	9.6	0.3	
Intermediate	57.4	11.6	
High	21.3	69.3	
CVD (%)	15.4	43.5	p<0.001
Statin use (overall) (%)	41.9	68.7	p<0.001
Statin use (%)			p=0.040
Intermediate risk	47.4	66.7	
High risk	41.4	69.6	
Statin intensity in high ASCVD risk			p=0.236
High intensity statin	13.8	36.4	
Intermediate intensity statin	27.6	30.8	

*Parenthesis indicate median (interquartile range) or mean (±standard deviation)

ASCVD: atherosclerotic cardiovascular disease, MASLD: Metabolic dysfunction associated steatotic liver disease

High-dose statin: atorvastatin 40 to 80 mg once daily; rosuvastatin 20 to 40 mg once daily

Moderate-dose statin: atorvastatin 10 to 20 mg once daily; fluvastatin 40 mg twice daily; lovastatin 40 to 50 mg once daily; pravastatin 40 to 80 mg once daily; rosuvastatin 5 to 10 mg daily; simvastatin 20 to 40 mg once daily.

Disclosures: Suria Devarapalli: Nothing to Disclose, Srikanth Vallurupalli: Nothing to Disclose, Timothy Morgan: Nothing to Disclose, Ragesh Thandassery: Nothing to Disclose

4022 | TRANSCRIPTOMIC PROFILING IDENTIFIES STATIN-ASSOCIATED MODULATION OF AGING AND FERROPTOSIS PATHWAYS IN MASLD

David Umbaugh[1] Kuo Du[1] Rajesh Dutta[1] Liuyang Wang[1] Georgia Sofia Karachaliou[1] Manal Abdelmalek[2] Ayako Suzuki[1] Anna Mae Diehl[1], [1]Duke University, [2]Mayo Clinic Rochester

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease, with aging as a key risk factor. Cellular senescence, a hallmark of aging, contributes to hepatic inflammation and fibrosis via the senescence-

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associated secretory phenotype (SASP). Ferroptosis, an iron-dependent form of regulated cell death, has also been implicated in liver injury and may intersect with aging-related processes in MASLD. While both senescence and ferroptosis have been linked to MASLD progression, the effects of statins on these pathways remain unclear. Age and sex influence MASLD risk and treatment response, yet their interactions with senescence and ferroptosis are poorly understood. In this study, we analyzed bulk RNA sequencing data from 368 obese patients with and without MASLD to investigate transcriptomic signatures of aging, senescence, and ferroptosis. We further assessed how statin use modulates these pathways across age (≤ 50 vs > 50 years) and sex (male vs female) strata to better understand context-specific effects of statin therapy. **Methods:** Gene signature scores were calculated using gene set variation analysis (GSVA) on bulk RNA-seq data. Pathway enrichment and differential expression analyses were performed by stratifying patients by age, sex, and through propensity score matching to adjust for demographic variables. **Results:** Across the full cohort, statin use was associated with increased cholesterol homeostasis and reduced gene signatures of cellular senescence, DNA damage, and oxidative stress–induced senescence. The most enriched pathways across all subgroups (old, young, male, female) included cholesterol biosynthesis, lipid homeostasis, the farnesyl diphosphate metabolic process, and SREBF/miR-33 regulatory networks. Hierarchical clustering revealed that transcriptomic profiles of males and older individuals were more similar, while those of younger patients more closely resembled females. Notably, in both male and female statin users, the ferroptosis signature positively correlated with age. **Conclusion:** Statin use is linked to reduced senescence and enhanced lipid homeostasis in MASLD, with effects consistent across subgroups. However, age- and sex-related differences in transcriptomic profiles, particularly in ferroptosis, suggest context-specific modulation of liver aging by statins.

Disclosures: David Umbaugh: Nothing to Disclose, Kuo Du: Nothing to Disclose, Rajesh Dutta: Nothing to Disclose, Liuyang Wang: Nothing to Disclose, Georgia Sofia Karachaliou: Nothing to Disclose, Manal Abdelmalek: 89Bio, Akero, Madrigal, Inventiva, Novo Nordisk, Intercept, Merck,: Advisor, Hanmi, Novo Nordisk: Consultant, Madrigal, Gilead, Inventiva, 89Bio, Akero, Hanmi: Research paid to my institution, Pfizer, Merck: Stock – privately held company, Medscape; Clinical Care Options; Fishawack Inc, LLC; CLDF: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Ayako Suzuki: Nothing to Disclose, Anna Mae Diehl: Nothing to Disclose

4023 | INCRETIN MIMETIC THERAPY IN PATIENTS WITH MASLD IS ASSOCIATED WITH EARLY BODY COMPOSITION CHANGES WITH BLUNTING OF DIFFERENCES WITH LONGER-TERM TREATMENT

Oscar Shaver[1] Renwei Wang[1] Jessica Izenas[1] Olivia Popovich[1] Trevor Dean[1] Olivia Hansol Lee[1] Jian-Min Yuan[1] Jaideep Behari[1], [1]University of Pittsburgh

Background: Incretin mimetics benefit patients with metabolic dysfunction-associated steatotic liver disease (MASLD), promote weight loss and lower blood glucose. This study aimed to assess the impact of incretin mimetic therapy on body composition and muscle function in a cohort of patients with MASLD. **Methods:** The study prospectively enrolled 729 patients with MASLD from a subspecialty MASLD clinic in the mid-Atlantic U.S. between 2021 and 2025. Demographic and clinical data were collected at baseline and at Year 1 (Y1) follow-up. At each visit, subjects completed dietary and physical activity questionnaires. Hepatic steatosis and liver fibrosis stage were determined by Transient Elastography, body composition by bioelectrical impedance analysis, and muscle strength by a hand-held dynamometer. 61 of the 729 subjects were on incretin mimetic therapy (treated) for Type 2 diabetes beginning before baseline through Y1 visit. We compared this cohort to 61 subjects with MASLD not on incretin mimetic therapy who were matched by age (± 5 years), sex, and body mass index (BMI, ± 5 kg/m^2). **Results:** The treated and control cohorts were well matched at baseline (all p values = ns) for age (mean 57 years), sex (67% female) and race (97% vs 93% White), and similar in BMI (35.2 vs 35.7 kg/m^2), liver stiffness measurement (mean 11.1 vs 11.8 kPa), Fibrosis-4 index (1.4 vs 1.5), ALT (40 vs 36 U/L), platelet count (242 vs 250 x10^3/L), waist circumference (113 vs 116 cm), skeletal muscle mass (31 vs 33 kg), body fat mass (42 vs 43.6 kg), percent body fat (43 vs 42%), and hand grip strength (25.2 vs 25.7 kg). The change from the baseline to Y1 visit between the two cohorts was significant in muscle mass (-3.14 vs -1.06%, $p = .049$) and borderline significant in body weight (-3.41 vs -.89%, $p = .06$). In subgroup analysis, the change between treated and their matched controls was significant in BMI (-1.77 vs +.74 kg/m^2, $p < .01$), weight (-5.49 vs +1.33 kg, $p < .01$), muscle mass (-4.53 vs -.48%, $p < .01$), and body fat mass (-3.31 vs +1.59 kg, $p = .01$) among subjects with < 1 y of incretin mimetic therapy initiation prior to baseline (median total duration from initiation to Y1 visit was 1.4 years). Conversely, no significant change was observed among those treated for ≥ 1 years prior to baseline (median total duration 3.4 years). **Conclusion:** In patients with MASLD, significant body composition changes occurred in the first 1-2 years on incretin mimetic therapy but not afterward.

Disclosures: Oscar Shaver: Nothing to Disclose, Renwei Wang: Nothing to Disclose, Jessica Izenas:

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Nothing to Disclose, Olivia Popovich: Nothing to Disclose, Trevor Dean: Nothing to Disclose, Olivia Hansol Lee: Nothing to Disclose, Jian-Min Yuan: Nothing to Disclose, Jaideep Behari: Pfizer: Grant/Research Support, Endra Life Sciences: Grant/Research Support, AstraZeneca: Grant/Research Support, Gilead: Grant/Research Support, Pfizer: Institutional research contract, Intercept: Institutional research contract, Madrigal: Institutional research contract, Inventiva: Institutional research contract, Rhythm: Institutional research contract, Galectin: Institutional research contract, Akero: Institutional research contract

4024 | ANTISENSE-MEDIATED UPREGULATION OF HNF4α AS A POTENTIAL THERAPEUTIC STRATEGY FOR LIVER FIBROSIS

Lingdi Zhang[1] Terry Lin[1] Surendra Jian[1] Jian Li[1] Rich Thai[1] Lansha Peng[1] Xing xian Yu[1] Yanfeng Wang[1] Xuehai Liang[1], *[1]ARNATAR THERAPEUTICS INC*

Background: Hepatocyte nuclear factor 4 alpha (HNF4α) is a master regulator of hepatic gene expression and plays a critical role in maintaining metabolic homeostasis. Downregulation of HNF4A is observed in various metabolic disorders and contributes to disease pathogenesis. Although increasing HNF4α expression via mRNA or AAV delivery has demonstrated therapeutic benefit in NASH and fibrosis mouse models, there remains an unmet need for alternative strategies that can safely and effectively elevate HNF4α protein levels. **Methods:** We applied our Antisense-Coupled Translation Upregulation (ACT-UP1) platform to design antisense oligonucleotides (ASOs) targeting the 3′ UTR of *HNF4A* to enhance translational efficiency. Upregulation of HNF4α protein was assessed following ASO treatment in Hep3B cells or primary hepatocytes, with protein levels measured via Western blot or ELISA. In vivo, BALB/c mice received two subcutaneous ASO doses, and liver HNF4α protein level was analyzed by Western blot. In disease models, ASOs were administered weekly, followed by evaluation of HNF4α protein and disease-related markers through Western blot. The expression of downstream target genes was quantified using qRT-PCR. Tolerability studies were performed in BALB/c mice. **Results:** These ASOs enhanced HNF4α protein expression by approximately 50–150% in both human and murine cells. Importantly, HNF4α protein was increased after ASO treatment up to 2 fold in mouse liver. The upregulation of HNF4A in the liver in BALB/c mice can last at least 3 weeks. In different liver fibrosis mouse models, subcutaneous ASO administration increased hepatic HNF4α protein levels up to two-fold, accompanied by upregulation of HNF4α-regulated genes and improved disease phenotypes. **Conclusion:** These results indicate that ACT-UP ASO can increase HNF4A both in vitro and in vivo. The increased protein appeared functional. Given the advantages of ASO as a drug, these findings support ACT-UP1 ASO-mediated HNF4α upregulation as a novel therapeutic strategy for liver fibrosis and associated metabolic diseases.

Disclosures: Lingdi Zhang: Nothing to Disclose, Terry Lin: Nothing to Disclose, Surendra Jian: Nothing to Disclose, Jian Li: Nothing to Disclose, Rich Thai: Nothing to Disclose, Lansha Peng: Nothing to Disclose, Xing xian Yu: Nothing to Disclose, Yanfeng Wang: Nothing to Disclose, Xuehai Liang: Nothing to Disclose

4025 | RNA EDITING OF PNPLA3 I148M DECREASES HEPATOCYTE FAT CONTENT

Ginnie Yang[1] Chikdu Shivalila[1] Pachamuthu Kandasamy[1] Stearne Briem[1] Michael Byrne[1] Alyse Faraone[1] Naoki Iwamoto[1] Tomomi Kawamoto[1] Richard Looby[1] Frank Favaloro[1] Stephany Standley[1] Suma Veeramachineni[1] Hailin Yang[1] Yuan Yin[1] Hui Yu[1] Genliang Lu[1] Chandra Vargeese[1] Erik Ingelsson[1], *[1]Wave Life Sciences*

Background: The *PNPLA3 I148M* variant disrupts PNPLA3 function and hepatic lipid metabolism and is associated with substantially increased risk of liver disease, including MASH and hepatic steatosis. We have developed RNA editing oligonucleotides, or AIMers, that are designed to edit *PNPLA3 I148M* transcripts and restore functional protein. Emerging evidence showing that PNPLA3 plays an important role in hepatic lipid metabolism suggests that an RNA editing approach that restores PNPLA3 protein function may be preferable to silencing *PNPLA3* expression to treatment. **Methods:** We synthesized GalNAc-conjugated chemically modified AIMers to edit the I148M variant using endogenous adenosine deaminase acting on RNA (ADAR) enzymes. GalNAc-AIMer editing efficiency was quantified in concentration-response experiments in human primary hepatocytes. The impact of editing or silencing (with GalNAc-siRNA) on intracellular lipid droplet density was evaluated using the human HEPATOPAC system. Transgenic mice expressing human wild-type *PNPLA3* (148I) were dosed subcutaneously with GalNAc-AIMers, and tissue concentrations in liver were quantified by ELISA after one week. **Results:** We evaluated chemically modified PNPLA3 GalNAc-AIMers in human homozygous *PNPLA3 I148M* primary hepatocytes. The most effective AIMers directed potent (EC_{50} ~15 nM) and efficient (>60%) editing of *PNPLA3* transcripts. In a human HEPATOPAC system with homozygous I148M hepatocytes, PNPLA3 GalNAc-AIMers significantly decreased lipid droplet density (>50%) compared to mock treatment or a GalNAc-siRNA designed to silence expression of *PNPLA3* ($p < 0.0001$). In a human HEPATOPAC system with homozygous wild-type *PNPLA3* hepatocytes, GalNAc-siRNA-mediated silencing significantly increased lipid

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droplet density (3 to 5-fold, $p < 0.001$) compared to controls, consistent with PNPLA3 playing an important role in lipid homeostasis. In mice expressing wild-type *PNPLA3*, GalNAc-AIMers dosed subcutaneously reached 500-1,000 mg/g in liver, concentrations expected to yield substantial RNA editing based on experiments in hepatocytes. **Conclusion:** These data demonstrate that AIMers supporting potent and efficient *PNPLA3 I148M* editing decrease fat content in hepatocytes, and editing to restore PNPLA3 function outperforms *PNPLA3* silencing. Overall, these data support continued advancement of AIMers for the treatment of *PNPLA3 I148M* liver disease.
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4026 | COVID-19 VACCINE LOWERS THE RISK OF ADVERSE HEPATIC OUTCOMES IN PATIENTS WITH NAFLD: A POPULATION-BASED COHORT STUDY

Hang Dong[1] Xiude Fan[1], [1]Shandong Provincial Hospital

Background: Non-alcoholic liver disease (NAFLD) affects approximately 30% of the global population. However, approved pharmacological interventions are still lacking. COVID-19 can cause liver injury, aggravate metabolic disorders, and increase the mortality rate of NAFLD. Previous studies have demonstrated that the COVID-19 vaccine has cardiovascular benefits beyond the prevention of COVID-19. However, there remains a lack of clinical evidence regarding whether the COVID-19 vaccine can improve the prognosis of NAFLD. **Methods:** This retrospective cohort study was conducted based on the Optimum Patient Care Research Database (OPCRD), an electronic medical record database covering 22% of the population of the UK, and includes information on demographics, diagnoses, and prescriptions. According to the prescriptions, patients with NAFLD were divided into the COVID-19 vaccinated group and the non-vaccinated group. The primary outcome was severe NAFLD, which was defined as a composite outcome, including chronic hepatitis, cirrhosis, hepatocellular carcinoma, and liver failure. The Cox proportional hazards model was used to adjust for the confounding factors, including age, gender, BMI, smoking status, drinking status and metabolic disorders. **Results:** A total of 82,360 patients with NAFLD were included in the study (mean [SD] age, 55.3[26.8] years; 40,324[49.0%] females). Among them, 31,154(37.8%) were COVID-19 vaccine recipients and 51,206(62.2%) were non-recipients. During the median follow-up of 3.9 years, the incidence of severe NAFLD in the vaccinated group (1.5%) was significantly lower than that in the non-vaccinated group (4.5%), with a hazard ratio (HR) of 0.48 (95% CI: 0.44 - 0.54) after adjustment for confounding factors. Compared with the non-vaccinated group, the vaccinated group had a lower incidence of hepatitis (0.3% vs 1.4%; HR: 0.25 [0.19 - 0.31]), cirrhosis (1.2% vs 3.0%, HR: 0.57 [0.50 - 0.64]), hepatocellular carcinoma (0.1% vs 0.3%, HR: 0.76 [0.49 – 1.18]), and liver failure (0.1% vs 0.5%; HR: 0.26 [0.17 - 0.39]). The subgroup analysis showed that the vaccinated group was associated with a lower risk of severe NAFLD in male (HR: 0.47 [0.41 - 0.55]), female (HR: 0.41 [0.35 - 0.48]), the elder subgroup(HR: 0.53 [0.46 - 0.61]), and the younger subgroup (HR: 0.36 [0.30 - 0.43]). **Conclusion:** The COVID-19 vaccine may have potential benefits in improving the prognosis of NAFLD.
Disclosures: Hang Dong: Nothing to Disclose, Xiude Fan: Nothing to Disclose

4027 | LOWER LIVER STIFFNESS AMONG ADULTS WITH TYPE II DIABETES AT RISK OF MASLD IS INDEPENDENTLY ASSOCIATED WITH STATIN USE: ANALYSIS OF A PROSPECTIVE COHORT OF 548 INDIVIDUALS

Monica Tincopa[1] Suruchi Ramanujan[2] Lisa Richards[1] Egbert Madamba[2] Seema Singh[2] Harris Siddiqi[2] Veeral Ajmera[1] Rohit Loomba[1], [1]University of California, San Diego, [2]UCSD

Background: Individuals with type 2 diabetes (T2DM) are at high risk of developing metabolic dysfunction-associated steatotic liver disease (MASLD). T2DM is also a risk factor for higher disease severity in MASLD. Prior data have shown potential benefit of statin therapy on MASLD prevalence and severity, though results are conflicting. The aim of this study was to determine the association of statin use on MASLD prevalence and severity using advanced MRI biomarkers in a prospective, well-phenotyped cohort of adults with T2DM. **Methods:** This prospective study enrolled adults age $\geq$ 50 years with T2DM recruited from primary care and endocrinology clinics. Participants underwent a standardized clinical research visit with vibration controlled transient elastography (VCTE) with controlled

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attenuation parameter (CAP) and magnetic resonance imaging with proton density fat fraction (MRI-PDFF) and MR elastography (MRE). A subset completed genetic testing. Participants with alcohol intake exceeding AASLD guidance for MASLD were excluded. MASLD was defined as MRI-PDFF of $\geq 5\%$. Univariate and multivariate regression analyses were performed to assess the impact of statin use on MASLD prevalence and severity. **Results:** 548 patients (34.4% male, 43% Hispanic) with T2DM were included. The median age was 65 years (95% CI 57-70) and body mass index (BMI) was 30.7 (95% CI 27.4-34.3) kg/m2. In the overall cohort, 363 (66%) were on statins and 361 (N = 65.8%) had MASLD. Individuals on statins were older (66 vs 62 years), had higher prevalence of hypertension (64 vs 55%), and lower prevalence of TM6SF2 high risk variants. Among those with MASLD, individuals on statins were also more likely to be on glucagon-like peptide 1 (GLP1s) receptor agonist. On multivariate analysis accounting for difference in baseline characteristics by statin use, individuals on statins had lower liver stiffness measurement (LSM) on MRE compared to those not on statins (coefficient -0.34, 95% CI -0.66, -0.03, $p = 0.03$) (Table). In the MASLD subset, after accounting for baseline covariates, statin use was not independently associated with markers of MASLD severity. **Conclusion:** In a well-phenotyped, prospective cohort of adults with T2DM, statin use was independently associated with lower LSM on MRE, indicating a potential liver-specific benefit of statins in T2DM. Future randomized controlled trials assessing the independent impact of statin therapy on reducing MASLD prevalence and severity in T2DM are needed.

Table. Association of Statin Use with MASLD Prevalence and Severity Among Adults with T2DM

Overall Cohort N= 548	Unadjusted OR or coefficient	P value	Multivariate Model* OR or coefficient	P value
VCTE CAP	-1.55 (-11.6-8.5)	0.76	-0.20 (-15.30-14.89)	0.97
MRI PDFF	-1.67 (-3.0, -0.27)	**0.02**	0.22 (-1.79-2.24)	0.82
MASLD	0.79 (0.54-1.16)	0.24	1.36 (0.73-2.51)	0.32
FAST score	-0.02 (-0.07-0.01)	0.15	-0.03 (-0.09-0.03)	0.33
ELF	0.00 (-0.17-0.18)	0.99	-0.09 (-0.32-0.14)	0.44
VCTE kPa	-0.92 (-1.77, -0.06)	**0.03**	-0.99 (-2.14-0.15)	0.08
MRE kPa	-0.18 (-0.03-0.01)	0.07	-0.34 (-0.66, -0.03)	**0.03**
MRE kPa ≥3.3	0.99 (0.64-1.52)	0.97	0.62 (0.31-1.21)	0.16

*Model: includes age, gender, HTN, hyperlipidemia, LDL, TM6SF2 genotype

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4028 | EFFICACY OF GLP-1 RECEPTOR AGONISTS IN IMPROVING LIVER ENZYMES, METABOLIC INDICES, AND FIBROSIS SURROGATES IN NON-ALCOHOLIC FATTY LIVER DISEASE: A META-ANALYSIS

Madia Ahad[1] Anwar Uddin[1] Aisha Elamin[1] Rafat Uddin[1], [1]Suny Downstate Medical Center

Background: Fatty liver disease tied to metabolic dysfunction, historically called non-alcoholic fatty liver disease (NAFLD), affects a growing number of adults. Although recently renamed metabolic dysfunction–associated steatotic liver disease (MASLD), most studies, including those in this analysis, still use NAFLD. For consistency, we use NAFLD throughout. GLP-1 receptor agonists (GLP-1 RAs), initially developed for type 2 diabetes, also promote weight loss and reduce liver enzymes. Given NAFLD's strong ties to insulin resistance and obesity, GLP-1 RAs are being evaluated as a potential treatment. This meta-analysis compiles existing data to assess their impact on liver enzymes, insulin resistance, metabolic outcomes, and fibrosis surrogates in adults with NAFLD. **Methods:** We included randomized controlled trials and large-scale cohort studies evaluating GLP-1 receptor agonists in adults with NAFLD. Eligible studies reported at least one of the following: ALT, AST, body weight, HOMA-IR, HbA1c, non-invasive fibrosis scores (FIB-4, NAFLD Fibrosis Score), or liver outcomes (cirrhosis, liver failure, or liver-related mortality). Four studies were included: a phase II RCT (Newsome et al., NEJM), two meta-analyses (Ghosal et al., Zhu et al.), and a retrospective cohort (Yen et al.). Pooled estimates were

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calculated using weighted mean differences (WMD) or adjusted hazard ratios (aHR) with 95% confidence intervals via a random-effects model (DerSimonian–Laird). Heterogeneity was assessed with I^2 and τ^2; publication bias was evaluated with a funnel plot for ALT. **Results:** GLP-1 receptor agonists were associated with consistent improvements in liver enzymes and metabolic indices. ALT decreased by −7.93 U/L (95% CI: −13.44 to −2.42) and AST by −5.29 U/L (95% CI: −9.04 to −1.55), with moderate-to-high heterogeneity (I^2 = 69.9% and 72.5%). Weight dropped by −3.56 kg, HOMA-IR by −1.62, and HbA1c by −0.43%, all with low heterogeneity (I^2 < 15%). Benefits were consistent across trials and real-world data. Only one study (Newsome et al.) reported biopsy-confirmed fibrosis improvement, which was not pooled. Non-invasive scores (FIB-4, NAFLD Fibrosis Score) from Zhu et al. showed no significant change. In the Yen cohort, GLP-1 RAs were not linked to reduced cirrhosis or liver failure but were associated with lower liver-related mortality (aHR 0.32, 95% CI: 0.13 to 0.75). Heterogeneity in ALT and AST likely reflects differences in study design, duration, population, and GLP-1 agent. Trial overlap was minimized across meta-analyses (Ghosal and Zhu), and pooled estimates remained consistent. The ALT funnel plot appeared symmetric, suggesting no major publication bias. **Conclusion:** GLP-1 receptor agonists improve liver enzymes, glycemic control, and metabolic parameters in adults with NAFLD, but their effect on fibrosis remains unclear. Further long-term trials with biopsy-confirmed outcomes and advanced liver endpoints are needed.

Table 1. Summary of Pooled Clinical and Metabolic Outcomes from Studies of GLP-1 Receptor Agonists in NAFLD

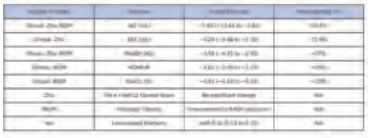
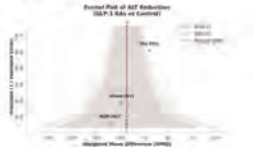


Figure 1. Pooled Effect of Studies

Figure 2. Funnel Plot



Disclosures: Madia Ahad: Nothing to Disclose, Anwar Uddin: Nothing to Disclose, Aisha Elamin: Nothing to Disclose, Rafat Uddin: Nothing to Disclose

4029 | PRESCRIBING PATTERNS OF STATINS IN DECOMPENSATED CIRRHOSIS: A MULTI-CENTER COHORT STUDY

Rishaan Sharma[1] John McMichael[1] Xaralambos Zervos[2] Kalyan Bhamidimarri[2] Nicholas Ruthmann[1] Omar Sims[1] William Carey[1] Shilpa Junna[1], [1]Cleveland Clinic Foundation, [2]Cleveland Clinic Florida

Background: Statins are increasingly prescribed for their liver-specific benefits, with a notable preference for lipophilic agents. However, detailed insights into prescribing patterns—including statin type and dose—remain limited. This study aimed to characterize statin use in patients with advanced liver disease listed for liver transplantation. **Methods:** This was a multi-center retrospective cohort study (Cleveland Clinic OH and FL) evaluating statin use for ≥60 days prior to liver transplant listing in patients with decompensated cirrhosis between January 2000 and October 2023. Exclusion criteria included age <18, acute liver failure, and multi-organ transplantation. Data collected included statin type, dose, and start/stop dates. Chi-square testing was used to assess distributions across statin type and dose. **Results:** Among 4,906 liver transplant candidates, 277 (5.6%) were prescribed statins through LT listing. Atorvastatin was the most commonly used (50.9%), followed by simvastatin (24.2%), pravastatin (12.3%), rosuvastatin (10.1%), lovastatin (2.2%), and pitavastatin (0.4%) ($p < 0.001$). Lipophilic statins were used in 77.6% of cases, while hydrophilic statins accounted for 22.4% ($p < 0.001$).

Statin dosage also varied significantly ($p < 0.001$): 3.2% were prescribed <10 mg, 63.9% received 10–20 mg, 27.8% were on 20–40 mg, and 5.1% were prescribed 40–80 mg daily. **Conclusion:** Statins are actively prescribed in patients with decompensated cirrhosis awaiting transplantation, despite prior concerns about hepatotoxicity. The clear predominance of lipophilic statins reflects existing evidence supporting their potential benefits in cirrhosis. These findings emphasize the need for prospective studies to better define the optimal statin type and dosage in this high-risk population.

n=4,906	Statin users (n=277, 5.60%)	P value:
Statin name		
Atorvastatin	141 (50.9%)	**<0.001**
Simvastatin	67 (24.2%)	
Pravastatin	34 (12.3%)	
Rosuvastatin	28 (10.1%)	
Lovastatin	6 (2.20%)	
Pitavastatin	1 (0.40%)	
Statin Type		
Lipohillic	215 (77.6%)	**<0.001**
Hydrophilic	62 (22.4%)	
Statin Dosage		
<10mg	9 (3.25%)	**<0.001**
10mg-20mg	177 (63.9%)	
20mg-40mg	77 (27.8%)	
40mg-80mg	14 (5.10%)	

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Zervos: Nothing to Disclose, Kalyan Bhamidimarri: Nothing to Disclose, Nicholas Ruthmann: Nothing to Disclose, Omar Sims: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, William Carey: Nothing to Disclose, Shilpa Junna: Nothing to Disclose

4030 | ALTERNATIVE LIPID MANAGEMENT IN MASLD: CARDIOVASCULAR ADVANTAGES AND LIVER RISKS OF BEMPEDOIC ACID COMPARED TO STATINS

Mohamad-Noor Abu-Hammour[1] Barish Eren[1] Mohammad Alabbas[1] Mohamad Mahdi Osman[1] Leandro Sierra[1] Hussam Kawas[1] Walid Hazem[2] Omar Sims[1] Dian Chiang[3], [1]Cleveland Clinic Foundation, [2]University Hospitals, [3]Cleveland Clinic

Background: Metabolic-associated steatotic liver disease (MASLD) patients are at elevated risk for cardiovascular and hepatic complications. Statins are commonly utilized for their cardioprotective benefits; however, tolerability issues drive the need for alternative lipid-lowering therapies like bempedoic acid. This study compares outcomes in MASLD patients treated with bempedoic acid versus high-intensity (HI) statins. **Methods:** Utilizing the TriNetX global research network, a retrospective cohort analysis identified adult patients ($\geq$18 years) diagnosed with MASLD receiving either bempedoic acid (n = 479) or HI statins (atorvastatin 40-80 mg or rosuvastatin 20-40 mg, n = 479). Cohorts were balanced through propensity score matching on demographics, comorbidities, medications, and laboratory values. Outcomes assessed included major adverse cardiovascular events (MACE), all-cause mortality (ACM), hospitalizations (ACH), progression to cirrhosis, hepatocellular carcinoma (HCC) development, drug-induced liver injury (DILI), and liver enzyme (ALT and AST) levels over a 3-year follow-up. **Results:** After propensity matching, the bempedoic acid cohort was associated with significantly lower risk of MACE (13.2% vs. 18.8%; HR 0.645, 95% CI 0.467-0.890, p = 0.015) and ACH (16.1% vs. 23.8%; HR 0.618, 95% CI 0.463-0.826, p = 0.001) compared to the HI statin cohort. No significant differences were observed for ACM, cirrhosis progression, HCC incidence, stroke, or heart failure. However, DILI occurred exclusively in the bempedoic acid group (2.1%, p = 0.001). Liver enzymes (ALT, AST) were similar between groups at 3 years. **Conclusion:** In MASLD patients, bempedoic acid use was associated with fewer cardiovascular events and hospitalizations compared to HI statins, but with a notable risk for drug-induced liver injury. These findings highlight the potential benefits and risks of bempedoic acid as an alternative lipid-lowering therapy in MASLD, necessitating careful patient selection and monitoring.

Disclosures: Mohamad-Noor Abu-Hammour: Nothing to Disclose, Barish Eren: Nothing to Disclose, Mohammad Alabbas: Nothing to Disclose, Mohamad Mahdi Osman: Nothing to Disclose, Leandro Sierra: Nothing to Disclose, Hussam Kawas: Nothing to Disclose, Walid Hazem: Nothing to Disclose, Omar Sims: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Dian Chiang: Ipsen: Advisor

4031 | VARIATION IN PLACEBO RESPONSE OF RANDOMISED CONTROLLED TRIALS EVALUATING GLP-1 RECEPTOR AGONIST ACTIVITY ON METABOLIC-DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

Katie Denver[1] Timothy Jobson[2] Kushala Abeysekera[3], [1]Predictive Health Intelligence, [2]Somerset NHS Foundation Trust, [3]Bristol University

Background: Drugs with GLP-1 receptor agonists activity (GLP-1 RAs) are unlicensed but have shown promising benefits for metabolic dysfunction–associated steatotic liver disease (MASLD). Trials have shown a major benefit with disease resolution rates ranging from 36%-63%, with a significant benefit over placebo. MASLD also responds to diet and exercise and results in treatment arms are likely to be additive to those seen with lifestyle changes in trials. To replicate the impressive drug benefits seen in clinical trials it will be important to achieve the lifestyle related responses as represented by the placebo groups. In MASLD trials the placebo responses were as high as 34%. We looked at a range of GLP-1 study placebo arms to understand variation and identify barriers to real world responses. **Methods:** Studies were identified from clinical trial and publication databases, and conference proceedings. There were 2 distinct types – a) biopsy-based studies looking for resolution of MASH without worse fibrosis or improved fibrosis without worse inflammation) and b) liver fat storage / inflammation assessed non-invasively. Placebo responses were compared across all trials, and by category. Where available, trial protocols were reviewed to identify potential non-pharmacological interventions that contributed to MASLD resolution. **Results:** 10 randomised controlled phase 2b and 3 studies were found with a median of 30 (IQR 44) patients in placebo arms. Placebo responses showed statistically significant variability (0% to 34.1%; n = 10 p < 0.001). Pooled data from biopsy and non-biopsy studies (n = 6, n = 4) showed that placebo response in biopsy studies (25%) was 5 times higher than those relying on non-invasive testing (5%) (P < 0.001). While the end points being compared here are different, further evidence for

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reduced placebo responses came from CT1 measurements in a non-invasive trial – showing no reduction - compared to steatohepatitis resolution in biopsy trials. Inclusion of biopsies appeared to be a significant factor driving placebo responses. **Conclusion:** Patients in placebo arms in MASLD GLP-1 studies achieved much higher response rates when biopsy was part of the protocol. Patients may be more motivated to engage with lifestyle measures when having serial liver biopsies. Placebo responses in non-invasive studies were near zero. In real world use, outcomes from GLP-1 RAs may fall short of responses seen in trials, as the baseline lifestyle changes will be unlikely to match those seen in biopsy studies.

Disclosures: Katie Denver: Nothing to Disclose, Timothy Jobson: Nothing to Disclose, Kushala Abeysekera: Nothing to Disclose

4032 | DECREASED SERUM CONCENTRATIONS OF PRO-INFLAMMATORY OXYLIPINS IN MASH PATIENTS TREATED WITH ICOSABUTATE (ICONA STUDY)

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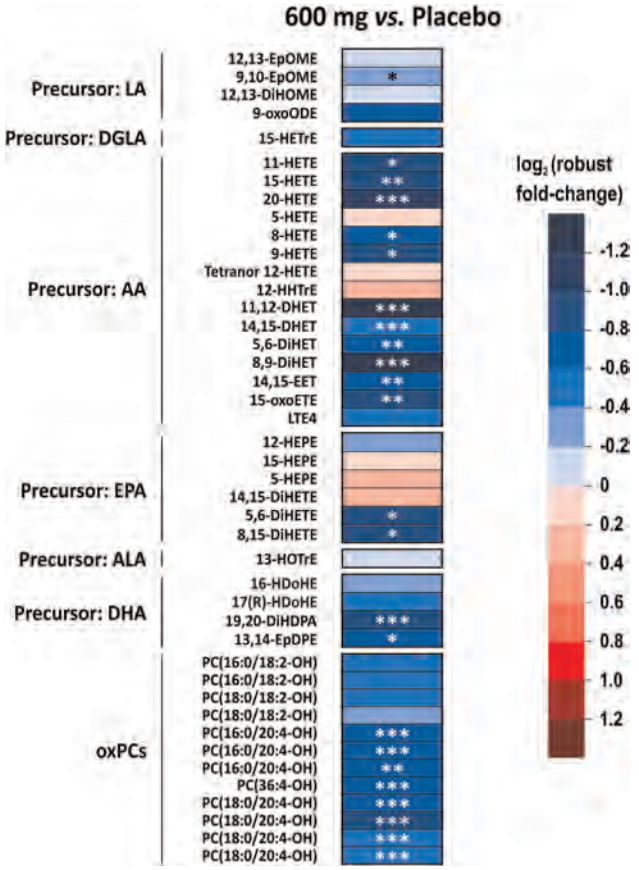
Background: Treatment for 52 weeks with icosabutate, an oral free fatty receptor 1 and 4 agonist, has recently demonstrated significant anti-inflammatory and anti-fibrotic effects in F1-F3 MASH patients (ICONA study, NCT04052516). Icosabutate has also been shown to markedly reduce hepatic oxidative stress and MASH-associated oxylipins [oxidised PUFAs, including oxidised phospholipids (oxPLs)] in multiple fibrosing murine MASH models. To assess whether these findings may translate to humans, we compared serum levels of oxylipins in MASH patients treated with either icosabutate or placebo as part of the ICONA study. **Methods:** Serum samples were collected at 52 weeks (study end) in MASH patients participating in the ICONA trial. Sample collection and storage were performed in accordance with a pre-defined protocol for lipidomic analysis. A total of 31 oxylipins, in addition to oxPLs, were quantified by UHPLC-MS/MS. Univariate statistical analyses included the assessment of data normality by the Shapiro-Wilk test, and the calculation of group fold changes and unpaired p-values for placebo vs. 600 mg icosabutate was performed. **Results:** Serum samples were collected from 44 and 45 patients treated with 600 mg icosabutate or placebo respectively. Significantly lower levels of multiple oxylipins and oxPLs were observed in the icosabutate treated patients versus placebo, primarily in arachidonic acid (AA) derived oxylipins (Figure). Five of 6 AA-derived hydroxyeicosatetraenoic acid (HETE) species were significantly reduced (8-, 9-, 11-, 15- and 20-HETE) in icosabutate treated patients, with the most pronounced decrease seen for 20-HETE [-0.68 $\log_2$ (fold-change), $p < 0.001$ vs. placebo]. Marked and significant decreases in oxidized eicosatrienoic acids (DiHET, DHET) were also observed, in addition to linoleic acid-derived species (5,6-DiHETE and 8,15-DiHETE, and 9,10-EpOME). Interestingly, despite lack of incorporation into phospholipid membranes, treatment with icosabutate was also associated with significantly lower oxPLs [-0.54 $\log_2$ (fold-change), $p < 0.001$ vs. placebo]. **Conclusion:** Treatment with icosabutate for 52 weeks was associated with markedly lower serum concentrations of multiple MASH associated oxylipins, in particular HETEs and oxPLs. These findings in patients confirm hepatic changes observed in pre-clinical MASH models, indicating that icosabutate is potently reducing both enzymatic (LOX/COX/CYP450) and non-enzymatic (oxidative stress) oxidation of PUFAs in MASH patients. Reductions in oxylipins, in particular oxPLs for which a causal role has been established in pre-clinical MASH models, may underlie the improvements in fibrosis observed in patients treated with icosabutate.



Disclosures: David Fraser: Nothing to Disclose, Cristina Alonso: Rubió Metabolomics, S.L.U.: Employee, Sophie Jeannin: Northsea Therapeutics:

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4033 | MRI-PDFF ≥ 70% REDUCTION WAS ASSOCIATED WITH FIBROSIS IMPROVEMENT WITH TIRZEPATIDE: POST-HOC ANALYSIS OF THE SYNERGY-NASH PHASE 2B TRIAL

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Background: Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) is a quantitative biomarker of liver fat content and a reduction in MRI-PDFF by at least ≥ 30% is associated with resolution of MASH in MASH trials. However, there are limited data whether a greater MRI-PDFF reduction may be associated with fibrosis improvement in MASH. Tirzepatide, a GIP/GLP-1 agonist, improved both MASH resolution and fibrosis in the SYNERGY-NASH phase 2B trial in patients with MASH and fibrosis stages 2 and 3 (NCT04166773; Loomba et al NEJM 2024). The aim of this post hoc analysis was to examine the association between 30%, 50% and 70% relative reduction in MRI-PDFF and fibrosis improvement in this trial. **Methods:** Among randomized 190 participants, 116 had both evaluable liver-biopsy and MRI-PDFF results at week 52. The outcome of interest was ≥ 1 stage improvement in fibrosis without worsening of MASH. The proportion of participants achieving this endpoint (fibrosis responders) was evaluated by whether the MRI-PDFF reduction thresholds of 30%, 50% and 70% were met and compared using the Chi-square test. All treatment groups were pooled for this analysis. **Results:** The mean percent reduction from baseline at week 52 in MRI-PDFF ranged from 49.7% to 63.8% across the three tirzepatide dose arms (5 mg, 10 mg and 15 mg) compared with 2.6% in the placebo group ($p < 0.001$ for all tirzepatide doses versus placebo). Among 80 participants achieving a ≥30% reduction in MRI-PDFF, the proportion of fibrosis responders did not differ significantly from that observed in the 36 participants not meeting the 30% threshold for MRI-PDFF reduction (53.8 vs 41.7%, $p = 0.23$). Similarly, the proportion of fibrosis responders did not differ significantly among those meeting ($n = 66$) versus those not meeting ($n = 50$) the ≥50% MRI-PDFF reduction threshold (57.6 vs 40.0%, $p = 0.06$). However, among participants achieving a ≥70% reduction in MRI-PDFF ($n = 40$), 65.0% met the endpoint of fibrosis improvement without worsening of MASH; a significantly lower ($p = 0.02$) proportion of fibrosis responders was observed (42.1%) if the ≥70% reduction in MRI-PDFF was not achieved ($n = 76$). None of the participants in the placebo group achieved 70% reduction in MRI-PDFF. **Conclusion:** In this post hoc analysis of the SYNERGY-NASH trial, a super response rate of 70% relative reduction in liver fat assessed by MRI-PDFF was associated with a higher rate of fibrosis improvement with tirzepatide treatment.

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4034 | SGLT2 INHIBITORS AND RISK OF LIVER FIBROSIS PROGRESSION IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND TYPE 2 DIABETES

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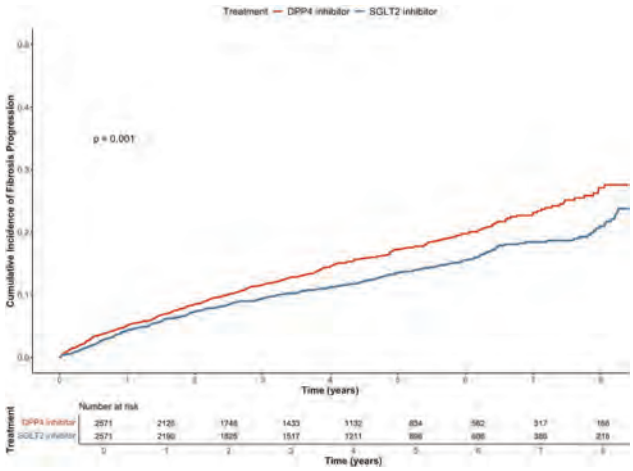
Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing cause of cirrhosis and its complications. Given the strong link between MASLD and type 2 diabetes (T2DM), evaluating whether antidiabetic agents such as sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduce liver fibrosis progression is of clinical interest. This study examined the association between SGLT2i use and both liver fibrosis progression and its complications in patients with MASLD and T2DM. **Methods:** We conducted a target trial emulation study using a retrospective, active comparator, new-user design among adults $\geq$18 years old with MASLD, T2DM, and low/intermediate Fibrosis-4 index (FIB-4 $\leq$2.67) who initiated either a SGLT2i or dipeptidyl peptidase-4 inhibitor (DPP-4i) at Mass General Brigham or Asan Medical centers between January 1, 2013 and December 31, 2023. Patients with prior cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), or liver transplantation were excluded. Propensity score matching accounted for differences in demographic, clinical, laboratory, and treatment characteristics. The primary outcome was progression to a high risk for advanced fibrosis category (FIB-4 $>$ 2.67) confirmed on $\geq$2 occasions within 1 year to ensure robustness. The secondary outcome was development of major adverse liver outcomes (MALO), a composite endpoint comprising incident cirrhosis, decompensation events, HCC, and liver transplant. Time-to-event analyses were conducted using Cox proportional hazards models and cumulative incidence curves were constructed. **Results:** From the eligible cohort of 16,901 adults, SGLT2i users were matched 1:1 to DPP-4i users yielding 2,571 matched pairs (n = 5,142) with well-balanced baseline characteristics (all standardized mean differences $<$ 0.1). During a median follow-up of 3.7 years, FIB-4 progression occurred at a rate of 4.44 per 100 person-years in DPP-4i users and 3.46 per 100 person-years in SGLT2i users. SGLT2i use was significantly associated with a lower risk of FIB-4 progression compared to DPP-4i use (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.67–0.89; p $<$ 0.001). No significant difference was observed in the incidence of MALOs. In subgroup analyses stratified by concurrent medication use, the inverse association between SGLT2i use and FIB-4 progression remained consistent among users of putative chemopreventive agents including metformin (n = 1,641; HR, 0.81; 95% CI, 0.68–0.97; p = 0.021), statins (n = 1,780; HR, 0.79; 95% CI, 0.67–0.93; p = 0.005), and aspirin (n = 1,186; HR, 0.84; 95% CI, 0.70–1.01; p = 0.059), although the latter did not reach statistical significance. **Conclusion:** SGLT2i use was associated with a lower risk of fibrotic progression compared to DPP-4i use in adults with MASLD and T2DM. Prospective studies are needed to confirm this association in MASLD.



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4035 | ASSOCIATION OF GLP-1 RECEPTOR AGONIST USE WITH LIVER FIBROSIS PROGRESSION IN PATIENTS WITH MASLD AND TYPE 2 DIABETES

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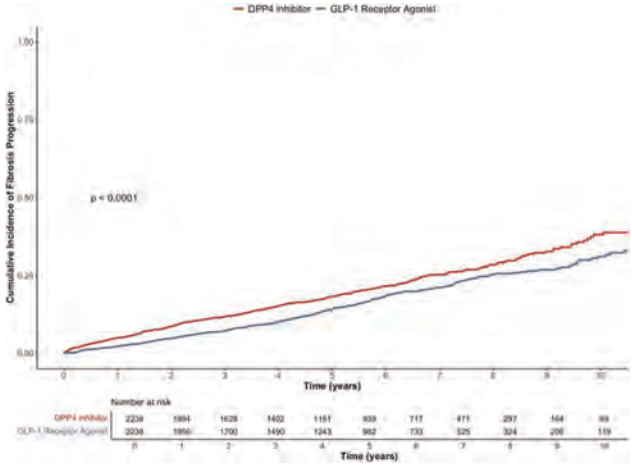
Background: Fibrosis progression is a key determinant of liver-related outcomes in metabolic dysfunction-associated steatotic liver disease (MASLD). However, large-scale data on GLP1-RA use and risk of fibrosis progression is limited in real-world healthcare settings. **Methods:** We conducted a target trial emulation using electronic health record data from the Mass General Brigham network via the Research Patient Data Registry, identifying patients from 2010 to 2023. We included adults aged 18–80 years with type 2 diabetes (T2DM) and MASLD and low-to-intermediate fibrosis risk (FIB-4 score less than 2.67). We additionally excluded patients with a prior diagnosis of cirrhosis, liver-related decompensation, hepatocellular carcinoma (HCC), liver transplant, or prior use of GLP-1RA/DPP4 inhibitor (DPP4i) before the index date. DPP4i served as the active comparator and reference group to evaluate the effect of GLP-1RA.

Among 18,439 initially eligible patients, exclusion criteria and subsequent 1:1 propensity score matching yielded 4,476 patients, equally split across arms of newly initiated GLP-1RA or DPP4i. Covariates for matching included demographics, diabetes-related comorbidities, laboratory values, fibrosis-related indices, healthcare utilization, and concurrent medications.

The primary outcome was FIB-4 progression, defined as transition from low/intermediate to high-risk (FIB-4 >2.67) confirmed on at least two occasions within one year. The secondary outcome was development of a MASLD-associated liver outcome (MALO), defined as new cirrhosis, decompensation, HCC or liver transplant.

Results: During a median follow-up of 4.3 years, FIB-4 progression occurred at a rate of 4.29/100 person-years (PY) in the DPP4i group and 3.25/100 PYs in the GLP-1RA group. GLP-1RA use was associated with a significantly lower risk of FIB-4 progression (hazard ratio [HR]: 0.75, 95% confidence interval [CI]: 0.65–0.87, $p < 0.001$). No significant difference was observed in secondary liver-related outcomes. In stratified subgroup analyses among aspirin ($n=1,269$), statin ($n=1,840$), and metformin users ($n=1,751$), GLP-1RA use consistently showed a lower risk of FIB-4 progression with a HR of 0.74 (95% CI 0.62–0.88), 0.74 (95% CI 0.63–0.86), and 0.67 (95% CI 0.57–0.80), respectively. **Conclusion:** GLP-1RA use was associated with a lower incidence of liver fibrosis progression compared to use of DPP4i among patients with MASLD and T2DM, supporting the role of this medication in modifying outcomes in MASLD.



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4036 | SEMAGLUTIDE IMPROVES MARKERS OF CARDIOVASCULAR RISK IN PEOPLE WITH HIV AND MASLD: THE SLIM LIVER STUDY

Jordan Lake[1] Doug Kitch[2] Amy Kantor[2] Cristina Alonso[3] Pablo Belaunzaran-Zamudio[4] Carl Fichtenbaum[5] Todd Brown[6] Fred Sattler[7] Kristine Erlandson[8], [1]UTHealth Houston, [2]Harvard T.H.Chan School of Public Health, [3]OWL Metabolomics, [4]NIH/NIAID, [5]University of Cincinnati, [6]Johns Hopkins University, [7]University of Southern California, [8]University of Colorado Denver-Anschutz Medical Campus

Background: We previously reported that, among with people with HIV (PWH) and metabolic dysfunction-associated steatotic liver disease (MASLD), the glucagon-like peptide-1 receptor agonist semaglutide (SEMA) improved weight, intra-hepatic triglyceride (IHTG) content, insulin resistance (IR), glucose and triglycerides (TG); here we report novel lipidomic, lipoprotein and glycoprotein profiling pre-/post-SEMA. **Methods:** PWH at least 18 years old on suppressive antiretroviral therapy (ART) with $>5\%$ IHTG on MRI-PDFF received SEMA 1mg subcutaneously per week for 24 weeks. Those with >2.27 kg weight loss had serum lipidomic, lipoprotein and glycoprotein profiling at OWL Metabolomics. Wilcoxon signed-rank tests and Spearman's rank correlations were performed. **Results:**

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Of 36 participants: median age was 52 years, BMI 34 kg/m^2, 39% Hispanic, 28% Black, 45% female and 77% integrase strand transfer inhibitor-based ART. Lipidomics: SEMA reduced TG and diglycerides, especially polyunsaturated species, reduced sphingomyelins and increased some bile acids (deoxycholic acid and chenodeoxycholic acid) and phosphatidylcholines, Table 1. Non-esterified fatty acids generally did not change. Lipoproteins: Cardiovascular disease (CVD)-linked species (total TG, VLDL-TG, HDL-TG, HDL-TG/HDL-C, Remnant-C and VLDL particle number) decreased; LDL particle size and large HDL-P increased. Glycoproteins: 69% and 53% of participants had elevated baseline GlycA and GlycB, CVD-associated markers of systemic inflammation. While no overall glycoprotein changes were observed, 56% with elevated baseline Glyc A had a reduction and 32% of those normalized; 41% with elevated Glyc B had a reduction and 42% normalized. Changes in total glycoprotein and GlycA correlated with changes in IL-6 ($r = -0.43$, $p = 0.01$) and leptin ($r = 0.50$, $p = 0.002$). Lipoprotein and glycoprotein concentrations generally did not correlate with baseline or change in weight, IHTG or IR. **Conclusion:** Among PWH and MASLD, lipidomic changes with SEMA suggest reduced lipotoxicity and hepatic insulin resistance, consistent with MASLD improvement. Significant reductions in CVD risk-associated lipoprotein and glycoprotein species were observed that did not correlate with changes in weight, IHTG or IR, suggesting an independent mechanism. Larger studies with clinical endpoints are needed to optimize CVD risk reduction in PWH and MASLD.

Table 1. Changes in and Success of Achieving Lipid Goals Before and After Semaglutide. (Based on European Society of Cardiology/European Atherosclerosis Society Guidelines for the Management of Dyslipidaemias, 2019)

Lipoprotein	Goal Concentration	Median (Q1, Q3) 24-W change	Not at Goal Week 0	Newly at Goal Week 24
Total Cholesterol (C) (mg/dL)	<200	-4.72 (-13.7, 4.58) p=0.11	53%	17%
Non-HDL-C (mg/dL)	<130	-4.08 (-13.7, 5.63) p=0.09	92%	3%
LDL-C (mg/dL)	<100	-2.24 (-8.68, 11.2) p=0.75	83%	8%
HDL-C (mg/dL)	>40 (M) >50 (F)	0.208 (-3.67, 3.45) p=0.94	14%	0%
Total TG (mg/dL)	<150	-10.5 (-44.4, -1.42) p<0.001	25%	17%
Remnant-C (mg/dL)	<30	-2.29 (-9.97, 0.081) p=0.001	42%	17%
HDL-TG (mg/dL)	<12	-0.773 (-3.08, 0.841) p=0.028	58%	14%
HDL-TG/HDL-C	<0.25	-0.021 (-0.050, 0.011) p=0.007	53%	11%
IDL-TG (mg/dL)	<12	-0.032 (-1.64, 0.606) p=0.54	33%	19%
LDL-TG (mg/dL)	<19	-0.215 (-1.45, 1.26) p=0.84	6%	0%
VLDL-TG (mg/dL)	<98	-10.2 (-39.9, -0.160) p<0.001	28%	19%
VLDL-C (mg/dL)	<22	-1.32 (-8.91, 0.254) p=0.001	36%	22%
IDL-C (mg/dL)	<9	-0.494 (-1.86, 0.962) p=0.21	47%	0%
VLDL-Particle Number (P) (nmol/L)	<70	-7.74 (-27.2, -0.471) p<0.001	31%	19%
Large VLDL-P (nmol/L)	<1.62	-0.221 (-0.659, -0.013) p<0.001	39%	25%
Medium VLDL-P (nmol/L)	<7.51	-0.101 (-2.21, 0.733) p=0.13	19%	14%
Small VLDL-P (nmol/L)	<61	-5.84 (-23.8, 0.075) p<0.001	31%	19%
LDL-P (nmol/L)	<1150	-28.1 (-100.5, 95.5) p=0.60	61%	14%
Large LDL-P (nmol/L)	<180	2.12 (-10.0, 22.1) p=0.23	42%	14%
Medium LDL-P (nmol/L)	<340	1.90 (-37.6, 39.0) p=0.76	47%	11%
Small LDL-P (nmol/L)	<630	-29.6 (-55.0, 40.5) p=0.16	81%	11%
HDL-P (µmol/L)	>24	0.645 (-2.76, 2.60) p=0.60	28%	11%
Large HDL-P (µmol/L)	>0.24	-0.020 (-0.030, -0.000) p<0.001	6%	6%
Medium HDL-P (µmol/L)	>8.2	-0.239 (-1.09, 0.390) p=0.13	3%	0%
Small HDL-P (µmol/L)	>15	0.005 (-2.26, 2.54) p=0.69	42%	6%
LDL-Particle Diameter (Z) (nm)	>20.91	0.085 (-0.044, 0.210) p=0.031	61%	19%
VLDL-Z (nm)	42.03-42.36	0.069 (-0.139, 0.205) p=0.30	48%	22%
HDL-Z (nm)	>8.2	0.002 (-0.079, 0.042) p=0.58	14%	8%

Disclosures: Jordan Lake: Gilead Sciences: Consultant, CytoDyn: Consultant, ViiV: Consultant, Doug Kitch: Nothing to Disclose, Amy Kantor: Nothing to Disclose, Cristina Alonso: Rubió Metabolomics, S.L.U.: Employee, Pablo Belaunzaran-Zamudio: Nothing to Disclose, Carl Fichtenbaum: Nothing to Disclose, Todd Brown: Nothing to Disclose, Fred Sattler: Nothing to Disclose, Kristine Erlandson: Nothing to Disclose

4038 | THERAPEUTIC FAILURES WITH SEMAGLUTIDE - LESSONS DRAWN FROM OBESITY AND TYPE 2 DIABETES MELLITUS TRIALS

Donghyun Ko[1] Do Han Kim[2] Faith Xin Ning Tan[3] Glenn Ho[3] Pojsakorn Danpanichkul[4] Mazen Noureddin[5] Mark Muthiah[3] Mohammad Siddiqui[6] Cheng Han Ng[7], [1]Bridgeport Hospital, Yale New Haven Health, [2]Department of Medicine, Mount Sinai Morningside and West, Icahn School of Medicine at Mount Sinai, [3]Yong Loo Lin School of Medicine, [4]Department of Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA, [5]Houston Methodist Hospital, [6]Division of Gastroenterology, Hepatology and Nutrition, Section of Hepatology, Virginia Commonwealth, [7]Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital,

Background: Semaglutide, a glucagon-like-peptide-1 receptor agonist (GLP1-RA), has gained increasing popularity for its efficacy in glycemic control, weight reduction, cardiovascular outcomes, and metabolic dysfunction-associated steatotic liver disease outcomes. Although numerous randomized clinical trials (RCTs) have analyzed its benefit, studies assessing the overall outcomes are still lacking. This study aims to evaluate the rate of failure to achieve therapeutic endpoints across a broad patient population. **Methods:** Medline (Ovid) and Embase databases were searched to include RCTs reporting weight reduction and hemoglobin A1c (HbA1c) reduction associated with weekly administration of semaglutide in obesity and type 2 diabetes mellitus (T2DM), respectively. Proportions from the semaglutide arm of each RCT were extracted, and the Copper Pearson method was conducted to obtain the pooled proportion with its respective confidence interval. Studies that reported outcomes in metabolic dysfunction-associated steatohepatitis (MASH) spectrum were analyzed separately. **Results:** A total of 32 RCTs were included. Overall, 33%, 65%, 64%, and 75% of patients treated with semaglutide did not achieve $\geq$ 5%, $\geq$10%, $\geq$15%, and $\geq$20% weight reduction, respectively. In the group without T2DM, 14%, 30%, 50%, and 70% did not achieve $\geq$ 5%, $\geq$10%, $\geq$15%, and $\geq$20% weight reduction,

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respectively. In the group with T2DM, 46%, 80%, 90%, and 95% did not achieve ≥ 5%, ≥10%, ≥15%, and ≥20% weight reduction, respectively. In terms of HbA1c, 22% and 38% of patients treated with semaglutide did not achieve HbA1c ≤7% and ≤6.5%, respectively. Lastly, 61% and 87% of patients with MASH and MASH cirrhosis, respectively, did not achieve ≥ 1 stage improvement in fibrosis NASH CRN. **Conclusion:** Semaglutide has shown tremendous progress in the treatment of metabolic disease, and its effect has been well proven in promoting weight reduction, HbA1c reduction, and improving cardiovascular as well as hepatic outcomes. While the use of semaglutide is encouraged to provide these benefits to the patient, it is important to note that some degree of therapeutic failure is expected.

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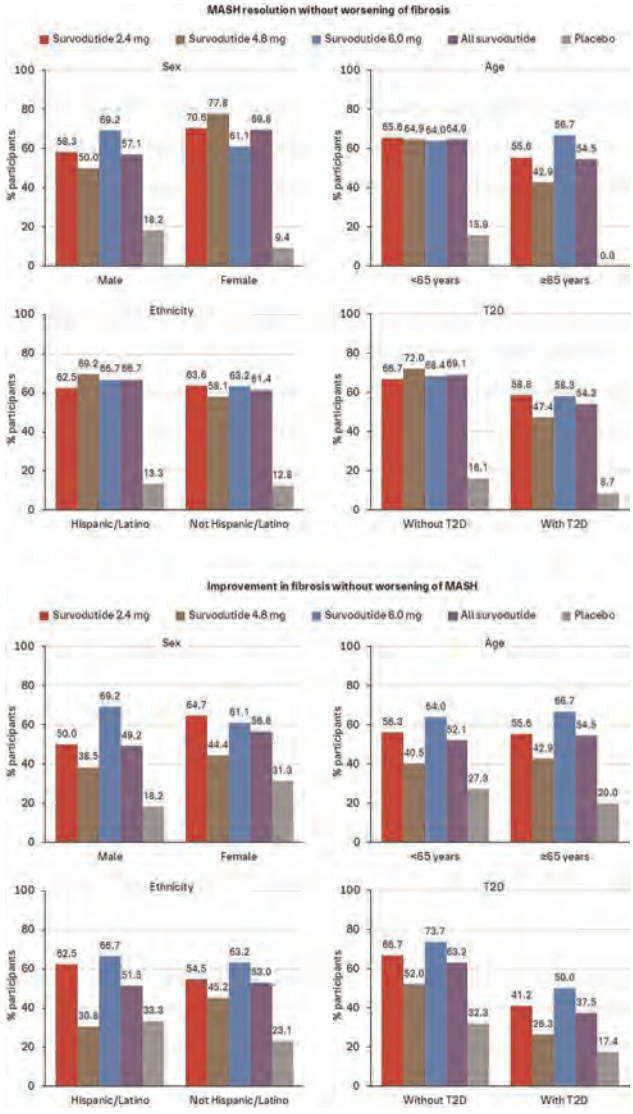
4039 | SURVODUTIDE IMPROVED LIVER HISTOLOGY IN PEOPLE WITH MASH AND MODERATE-TO-SEVERE FIBROSIS REGARDLESS OF AGE, SEX, ETHNICITY, OR TYPE 2 DIABETES: SUBGROUP ANALYSIS OF A RANDOMIZED PHASE 2 TRIAL

Naim Alkhouri[1] Jörn Schattenberg[2] Elisabetta Bugianesi[3] Vincent Wai-Sun Wong[4] Mandy Fraessdorf[5] Samina Ajaz Hussain[6] Renee Marshall[7] Ramy Younes[6] Arun Sanyal[8], [1]Summit Clinical Research, [2]Department of Internal Medicine II, University Medical Center Homburg, Homburg & Saarland University, [3]University of Turin, [4]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, [5]Boehringer Ingelheim Pharma GmbH & Co. KG, [6]Boehringer Ingelheim International GmbH, [7]Boehringer Ingelheim Pharmaceuticals, Inc., [8]Virginia Commonwealth University

Background: Survodutide is a glucagon receptor/glucagon-like peptide-1 receptor (GCGR/GLP-1R) dual agonist in phase 3 trials for treatment of metabolic dysfunction-associated steatohepatitis (MASH) and obesity. In a phase 2 trial in people with biopsy-confirmed MASH and F1–F3 liver fibrosis, survodutide improved both steatohepatitis and liver fibrosis. We evaluated its efficacy in clinically important subgroups. **Methods:** This 48-week, multinational, double-blind trial (NCT04771273) randomized 295 people aged 18–80 years with biopsy-proven MASH (Non-alcoholic fatty liver disease Activity Score [NAS] ≥ 4) and liver fibrosis stage F1–F3 to once-weekly subcutaneous placebo or survodutide, escalated over ≤ 24 weeks to maintenance doses of 2.4, 4.8, or 6.0 mg. Endpoints included: resolution of MASH (absence of ballooning [score of 0], no or mild inflammation [score of 0 or 1], and possible steatosis [score of 0 to 3]) without worsening of fibrosis; improvement in fibrosis (≥ 1 stage decrease) without worsening of MASH; % change in liver fat content (LFC) by magnetic resonance imaging–proton density fat fraction; absolute change in Enhanced Liver Fibrosis (ELF™) score; and % change in N-terminal propeptide of type III collagen (PRO-C3). We analyzed these endpoints post hoc by age (<65/≥ 65 years), sex (male/female), ethnicity (Hispanic/Latino or not), and presence or absence of type 2 diabetes (T2D) in participants with F2–F3 fibrosis who received ≥ 1 dose of trial drug and had baseline and end of treatment biopsies (n = 170). **Results:** At baseline, 138 (81.2%) participants were aged <65 years, while 85 (50.0%) were female, 48 (28.2%) Hispanic/Latino, and 71 (41.8%) had T2D. Resolution of MASH without worsening of fibrosis, and improvement in fibrosis without worsening of MASH, occurred in more of the survodutide groups than the placebo group across subgroups based on age, sex, ethnicity, and T2D (Figure). Similarly, survodutide was associated with larger reductions in LFC, ELF™ score, and PRO-C3 level across these subgroups. **Conclusion:** Survodutide reduced MASH, fibrosis, and LFC across participant subgroups in this phase 2 trial, suggesting consistent benefits of this GCGR/GLP-1R dual agonist in different patient populations. There was no difference in MASH resolution based on age, sex, ethnicity, or T2D —and no difference in fibrosis improvement based on age, sex, or ethnicity, although response rate was possibly lower in those with T2D.



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4040 | TARGETING NUCLEAR PROTEIN IMPROVES NAFLD ACTIVITY SCORE AND SHOWS ANTIFIBROTIC AND HEPATOPROTECTIVE EFFECTS SUPERIOR TO LANIFIBRANOR IN THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF MASH

Jacob Nøhr-Meldgaard[1] Michael Feigh[2] Stefan Hoenow[3] Kristoffer Voldum-Clausen[1] Susanne Pors[1] Christopher Shepard[4], [1]Gubra A/S, [2]Gubra, [3]NuLa Therapeutics, [4]Apollo Health Ventures

Background: NLT-101 is a first-in-class compound that functions by proximity engagement with a target in the nuclear envelope that mediates its activity. NLT-101 is in preclinical development for metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis driven indications. The present study aimed to investigate the therapeutic benefits of NLT-101 on metabolic, biochemical, histopathological and transcriptome profile in the translational GAN diet-induced obese (DIO) and biopsy-confirmed mouse model of MASH with liver fibrosis. Lanifibranor, a late-stage clinical candidate (Ph3) for the treatment of patients with MASH and liver fibrosis, was included for comparison. **Methods:** Male C57BL/6 mice were fed the GAN diet high in fat, fructose and cholesterol for 36 weeks prior to study start. A liver pre-biopsy was collected 4 weeks before treatment start. Only GAN DIO-MASH mice with biopsy-confirmed NAFLD Activity Score (NAS ≥ 5) and fibrosis (stage F2-F3) were included and stratified into treatment groups ($n = 16$ per group). Mice were administered once daily oral vehicle, NLT-101 (30 (low) and 60 (high) mg/kg), lanifibranor (30 mg/kg) for 12 weeks. Histopathological pre-to-post individual assessment of NAS and fibrosis stage was performed. Other terminal endpoints included quantitative liver histology, blood and liver biochemistry in addition to RNAsequencing-Bioinformatic analysis. **Results:** NLT-101 demonstrated vehicle-corrected weight loss of 25% (low) and 30% (high) after 12 weeks of treatment, which was comparable with lanifibranor (34%). High dose NLT-101 resulted in a 4-point improvement in NAS in 30% of the animals, driven by reduction in steatosis and lobular inflammation score. A 2-point improvement was observed in 95% of the animals ($p < .001$). High dose NLT-101 showed distinguishably better effects compared to lanifibranor. NLT-101 showed superiority towards lanifibranor for plasma transaminases lowering and comparable effects on plasma total cholesterol. Benefits on NAS were supported by quantitative liver histology on steatosis (hepatocytes with lipids, liver lipids) and marker of inflammation (galectin-3). No treatments improved fibrosis stage, however improvement in histological markers for fibrosis (PSR, Col1a1) and hepatic stellate activation (α-SMA), indicating effect on fibrogenesis was numerically superior for NLT-101 compared to lanifibranor. Finally, all treatments induced significant gene regulation and suppressed genes involved in extracellular matrix and inflammation pathways. **Conclusion:** NLT-101 treatment improved metabolic, biochemical and histopathological parameters of MASH, including hepatic transcriptomic profile, in the GAN DIO-MASH mouse model. Notably, NLT-101 treatment dose-dependently improved NAFLD Activity Score superior to late-stage clinical candidate lanifibranor, introducing NLT-101 as a promising first-in-class treatment for MASH.

Disclosures: Jacob Nøhr-Meldgaard: Nothing to Disclose, Michael Feigh: Nothing to Disclose, Stefan Hoenow: NuLa Therapeutics: Employee, Kristoffer Voldum-Clausen: Nothing to Disclose, Susanne Pors: Nothing to Disclose, Christopher Shepard: Nothing to Disclose

4041 | TIRZEPATIDE REDUCES TUMOR BURDEN IN THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF MASH-HCC WITH ADVANCED FIBROSIS

Jacob Nøhr-Meldgaard[1] Michael Feigh[2] Nicolas Eskesen[1] Susanne Pors[1] Henrik Hansen[1], [1]Gubra A/S, [2]Gubra

Background: The GLP-1: GIP receptor dual agonist Tirzepatide, approved for the treatment of obesity and type 2 diabetes, has demonstrated therapeutic efficacy on clinical endpoints in a recent phase 2 clinical trial (SYNERGY-NASH) in patients with metabolic-dysfunction associated steatohepatitis (MASH) and liver fibrosis (Loomba et al.; NEJM; 2024). The present study aimed to evaluate therapeutic efficacy of tirzepatide on clinical endpoints and outcome in the GAN (Gubra-Amylin NASH) diet-induced obese (DIO) mouse model of MASH with advanced fibrosis and hepatocellular carcinoma (HCC). **Methods:** Male C57BL/6J mice were fed the GAN diet high in fat, fructose, and cholesterol for extended 52 weeks prior to study start. Only animals

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with liver biopsy-confirmed NAFLD Activity Score (NAS ≥ 5) and advanced fibrosis (stage F3) were included and stratified into treatment groups. DIO-NASH-HCC mice received (SC, QD) vehicle (n = 15) or tirzepatide (10 nmol/kg, n = 17) for 14 weeks. Vehicle-dosed chow-fed C57BL/6J mice (n = 9) served as lean healthy controls. Untreated DIO-MASH-HCC mice (n = 12) were terminated at baseline. Tumor histopathological evaluation was performed by an expert pathologist. Pre-to-post liver biopsy histopathology was performed for within-subject evaluation of NAFLD Activity Score (NAS) and fibrosis stage. Additional endpoints included blood and liver biochemistry and quantitative liver histology. **Results:** Compared to baseline, DIO-MASH-HCC mice demonstrated progressive tumor burden over the 14-week study period. Tumors showed consistent architectural and cytologic features of HCC with a marked lack of reticulin trabecular framework in addition to diffuse/reduced glutamine synthetase staining, representing standard diagnostic criteria for HCC, and with tumors clearly demarked by extensive Ki67 expression (proliferative phenotype). Notably, tirzepatide completely prevented progression in tumor burden and reduced histological marker for hepatocellular proliferation (Ki67). Concurrently, tirzepatide improved hallmarks of MASH, including hepatomegaly, transaminases (ALT/AST), plasma and liver lipids (TG/TC), in addition to histopathological NAS (≥ 2 point improvement). In agreement, tirzepatide reduced quantitative histological markers of steatosis (lipids, hepatocytes with lipid droplets) and inflammation (CD45, galectin-3). Tirzepatide did not improve fibrosis stage, albeit reduces clinical-derived plasma fibrosis markers (TIMP-1, PIIINP) and histological marker for hepatic stellate cell activation (α-SMA), indicating anti-fibrogenic action. **Conclusion:** This is the first study to demonstrate that tirzepatide reduces tumor burden and improves clinical biomarkers and histopathological endpoints for NAFLD Activity Score in a preclinical translational diet-induced obese mouse model of MASH-driven HCC with advanced fibrosis.

Disclosures: Jacob Nøhr-Meldgaard: Nothing to Disclose, Michael Feigh: Nothing to Disclose, Nicolas Eskesen: Gubra A/S: Employee, Susanne Pors: Nothing to Disclose, Henrik Hansen: Nothing to Disclose

4042 | EFFICACY RESPONSE IN SUBGROUPS OF PARTICIPANTS IN ESSENCE DEMONSTRATE THAT SEMAGLUTIDE IS EFFECTIVE IN IMPROVING LIVER FIBROSIS ACROSS A DIVERSE POPULATION

Mary Rinella[1] Manal Abdelmalek[2] Elisabetta Bugianesi[3] Anna Cali[4] Laurent Castera[5] Mette Kjær[4] Jacob George[6] Wah Kheong Chan[7] Niels Krarup[4] Michelle Long[4] Philip Newsome[8] Claudia Oliveira[9] George Papatheodoridis[10] Ahsan Shoeb[4] Salvatore Petta[11] Michael Roden[12] Arun Sanyal[13] Yusuf Yilmaz[14] Vlad Ratziu[15], [1]Division of Gastroenterology, Hepatology and Nutrition, University of Chicago, Chicago, IL, USA, [2]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA, [3]Department of Medical Sciences, University of Turin, Turin, Italy, [4]Novo Nordisk A/S, Copenhagen, Denmark, [5]Université Paris Cité, INSERM UMR1149, Centre de Recherche sur l'Inflammation, Paris, France, [6]Westmead Institute for Medical Research, Westmead Hospital, University of Sydney, NSW, Australia, [7]Department of Medicine, Faculty of Medicine, University of Malaya, Malaysia, [8]School of Immunology & Microbial Sciences, Foundation for Liver Research and King's College Hospital, [9]Hospital das Clínicas (LIM07) da Faculdade de Medicina da Universidade de São Paulo, São Paulo, [10]Medical School of National and Kapodistrian University of Athens, General Hospital of Athens, [11]Sezione di Gastroenterologia, PROMISE, University of Palermo, Italy, [12]Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Düsseldorf, [13]Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, VCU School of Medicine, Richmond, [14]School of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey, [15]Sorbonne Université,Hospital Pitié-Salpêtrière, INSERM UMRS 1138 CRC, Paris, France

Background: In part 1 of the phase 3 ESSENCE trial (NCT04822181), once-weekly subcutaneous semaglutide 2.4 mg demonstrated significant improvement in liver fibrosis and resolution of steatohepatitis over 72 weeks versus placebo in participants with MASH and liver fibrosis (stage 2 or 3). Histological benefits were reflected in improvements of pre-specified non-invasive tests (NITs). The aim of this secondary analysis was to evaluate if the efficacy of semaglutide in the combined histologic endpoint of resolution of steatohepatitis and improvement in liver fibrosis and fibrosis-related NITs differed across age, sex, race and ethnicity subgroups. **Methods:** The first 800 randomized participants were stratified by race (Asian vs. non-Asian), ethnicity (Hispanic or Latino vs Non-Hispanic or Latino), sex (male and female) and age (<45, ≥ 45–64 and ≥ 65 years). Participants were evaluated for the combined histologic endpoint of resolution of steatohepatitis and improvement in liver fibrosis, and fibrosis-related NITs (a decrease of $\geq 25\%$ from baseline in liver stiffness measurement by vibration-controlled transient elastography [VCTE LSM], or a decrease of ≥ 0.5 units from baseline in enhanced liver fibrosis [ELF] score). A Cochran–Mantel–Haenszel test stratified by baseline diabetes status and baseline fibrosis stage was conducted. Missing data were handled by multiple

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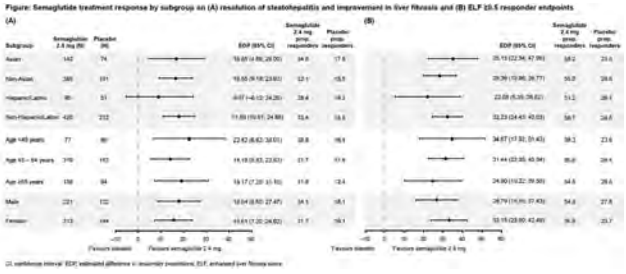
imputation informed by data from placebo participants. **Results:** Asian participants (n = 216) showed treatment benefits with semaglutide vs placebo across all outcomes (estimated difference in responder proportions for combined histology: 16.9% [95% CI: 4.7; 29.0], ELF 35.2% [95% CI: 22.3; 48.0], VCTE LSM ≥25% 24.3% [95% CI: 9.2; 39.6]), as did non-Asians (n = 576) (combined histology 16.6% [95% CI: 9.18; 23.93], ELF 28.4% [95% CI: 20.0; 36.8], VCTE LSM ≥25% 23.5% [95% CI: 13.3; 33.6]). Semaglutide demonstrated consistent treatment benefits vs placebo for non-Hispanic/Latino participants (n = 632) (combined histology 17.9% [95% CI: 10.91; 24.9], ELF 32.2% [95% CI: 24.4; 40.0], VCTE LSM ≥25% 27.0% [95% CI: 17.7; 36.3]); more modest effects were observed in Hispanic or Latino participants. Males (n = 343) and Females (n = 457) both showed treatment benefits for combined histology and ELF (Figure), along with VCTE LSM ≥25% (24.3% [95% CI: 12.0; 36.5] and 23.7% [95% CI: 12.2; 35.2], respectively). Across <45 (n = 126), ≥45–64 (n = 472) and ≥65 years (n = 202) subgroups, consistent treatment benefits for semaglutide were observed for combined histology and ELF (Figure); VCTE LSM ≥25% improvement was better demonstrated among patients aged ≥45 years. **Conclusion:** Semaglutide demonstrated consistent efficacy across multiple subgroups for histologic and liver fibrosis-related NIT responder endpoints. These data support the benefits of semaglutide across a diverse population for the treatment of MASH with stage 2 or 3 fibrosis.



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4043 | COMPARATIVE SYSTEMATIC REVIEW AND META-ANALYSIS: EFFICACY OF EMPAGLIFLOZIN VERSUS DAPAGLIFLOZIN IN MANAGING METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Vikash Karmani[1] Ruchir Paladiya[2] Krishan Joshi[3] Vikash Kumar[4] Aalam Sohal[4] Neil Parikh[5], [1]Jinnah Singh Medical University, [2]University of Connecticut Health Center, [3]California University Health Sciences University, [4]Creighton University, [5]Hartford Hospital

Background: The use of sodium-glucose cotransporter-2 inhibitors in patients with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) has received increasing attention. This systematic review and meta-analysis were conducted to assess and compare the effectiveness of empagliflozin and dapagliflozin as potential treatments for patients with MASLD. **Methods:** We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched the PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) databases from their inception through December 2023. The outcomes evaluated

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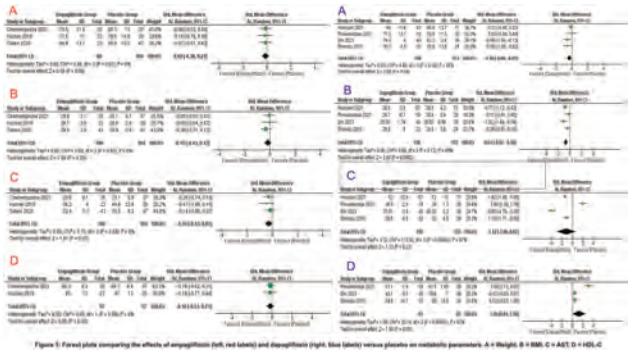
included hepatic enzymes—alanine aminotransferase (ALT) and aspartate aminotransferase (AST)—as well as body mass index (BMI), body weight, and serum lipid profile parameters: high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triacylglycerol (TAG). We calculated the standard mean difference (SMD) with a 95% confidence interval (CI) for continuous outcomes across all studies and applied a random-effects model for data synthesis, regardless of heterogeneity. Heterogeneity was assessed using the I^2 statistic. **Results:** We screened 1028 articles and included 7 randomized controlled trial studies (515 patients). Dapagliflozin exhibited a statistically significant decrease in both weights (SMD: −0.30, 95% CI:−0.60 to −0.01, $I^2 = 36$, $p = 0.04$) as well as BMI ((SMD: −0.64, 95% CI: −0.97 to -0.30, $I^2 = 49\%$, $p = 0.0002$), an increase in HDL-C levels (SMD: 1.26, 95% CI: 0.01 to 2.50, $I^2 = 92\%$, $p = 0.05$), and an insignificant change in LDL-C ($p = 0.38$) and TAG ($p = 0.45$). Conversely, Empagliflozin exhibited statistically non-significant reductions in body weight ($p = 0.56$), BMI ($p = 0.28$), HDL-C levels ($p = 0.40$), LDL-C ($p = 0.15$), and TAG ($p = 0.35$). Regarding hepatic enzymes, the changes observed in ALT levels for dapagliflozin and empagliflozin were non- significant, with p-values of (0.22) and (0.50), respectively. Similarly, there were non-significant changes in AST levels, with p-values of (0.08) for dapagliflozin and (0.07) for empagliflozin. **Conclusion:** Our results suggest that dapagliflozin treatment is more effective than empagliflozin in patients with MASLD, as evidenced by a significant reduction in weight and BMI, along with a noteworthy increase in HDL-C levels. Further prospective clinical data is needed to corroborate these findings.



Disclosures: Vikash Karmani: Nothing to Disclose, Ruchir Paladiya: Nothing to Disclose, Krishan Joshi: Nothing to Disclose, Vikash Kumar: Nothing to Disclose, Aalam Sohal: Nothing to Disclose, Neil Parikh: Nothing to Disclose

4044 | PHARMACOLOGICAL TARGETING OF IKKA FOR RESOLUTION OF STEATOSIS, INFLAMMATION, AND FIBROSIS: A MECHANISTIC DISTINCT DEVELOPMENT OF HPN-01 FOR MASH

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Background: The pathogenesis of metabolic dysfunction-associated steatohepatitis (MASH) involves a multifactorial interplay among hepatic steatosis, inflammation, and fibrogenesis, yet few therapeutic agents effectively target all three processes. **Methods:** HPN-01 is a novel, orally bioavailable small-molecule inhibitor of IKKα (IκB kinase alpha), developed to modulate key pathogenic pathways driving MASH and its progression to hepatocellular carcinoma (HCC). Here, we describe the mechanistic basis and preclinical efficacy of HPN-01, with supporting early-phase clinical safety data. **Results:** KKα is activated in hepatocytes by metabolic, inflammatory and infectious stimuli, including obesity, insulin resistance, and HCV infection. Phosphorylated IKKα translocates to the nucleus, promoting transcriptional activation of sterol regulatory element-binding proteins (SREBP-1/2), thereby enhancing de novo lipogenesis through NF-κB-independent mechanisms. Knockdown of IKKα or pharmacologic inhibition via HPN-01 suppresses lipogenic gene expression and lipid droplet accumulation. In an STZ + high-fat diet-induced MASH model, HPN-01 treatment significantly reduced hepatic steatosis.

HPN-01 also attenuates hepatic inflammation by inhibiting IKKα-mediated NF-κB signaling, resulting in reduced serum ALT/AST and histologic inflammation scores in the mouse model. Composite MASH activity scores, incorporating steatosis, lobular inflammation, and ballooning, were significantly improved. Beyond inflammation, HPN-01 suppresses fibrogenic pathways regulated by IKKα, leading to reduced hepatic collagen content and fibrosis scores following a five-week treatment.

Furthermore, in a murine model that recapitulates the progression of MASH to HCC, HPN-01 markedly decreased serum alpha-fetoprotein (AFP), HCC formation and overall tumor burden. **Conclusion:** HPN-01 is currently under evaluation in a U.S. Phase I clinical trial in healthy volunteers. Preclinical toxicology and initial clinical data indicate a favorable safety profile. Collectively, these findings position HPN-01 as a mechanistically distinct, first-in-class therapeutic candidate capable of addressing the multifaceted pathobiology of MASH and preventing HCC development.

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4045 | GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONIST, SEMAGLUTIDE, REDUCES METABOLIC AND ALCOHOL-ASSOCIATED LIVER DISEASE (METALD)

Ramesh Bellamkonda[1] Sundararajan Mahalingam[1] Ojeshvi Ethiraj[1] Sathish kumar Perumal[2] Ramachandran Rajamanickam[2] Carol Casey[3] Kusum Kharbanda[2] Karuna Rasineni[1], [1]University of Nebraska Medical Center, Omaha, NE, [2]Veterans Affairs Nebraska-Western Iowa Health Care System, Omaha, NE, [3]University of Nebraska Medical Center

Background: Steatotic liver disease (SLD), which affects over 35% of the global population, is driven by high-caloric diet intake/obesity, excessive alcohol consumption, or a combination of both. The co-occurrence of obesity and chronic alcohol use significantly increases the risk of progressive liver injury and liver failure. Our lab's previous research has demonstrated that disruptions in metabolic hormone levels from chronic alcohol exposure or a high-caloric diet intake play a causative role in the development of metabolic-associated fatty liver disease (MASLD) and alcohol-associated liver disease (ALD), respectively. We and others have further reported that glucagon-like peptide 1 (GLP-1), an incretin, improves metabolic homeostasis and reduces hepatic fat accumulation in both MASLD and ALD. Building on this knowledge, our study aimed to investigate the effects of semaglutide, a GLP-1 receptor agonist, in an experimental mouse model of metabolic and alcohol-associated liver disease (MetALD), an emerging form of SLD resulting from diet-induced obesity and alcohol consumption. **Methods:** To replicate the features of MetALD, two-month-old mice were given 15% alcohol (gradual ramp-up over a 10-day period) in their drinking water along with an ad libitum access to Western diet [ResearchDiets D12079B]. The control group was fed a chow diet. After 12 weeks of this feeding regimen, a subset of MetALD mice received semaglutide (60 μg/kg BW/every other day for 4 weeks) while continuing their respective diet. At the end of the treatment period, the animals were fasted for 6 hours and underwent a glucose tolerance test. The following day, the animals were euthanized, and blood and tissue samples were collected for analysis. **Results:** Semaglutide (SG) treatment moderately reduced body weight in the MetALD groups. SG-treated MetALD mice showed a reduced adipose/body weight ratio, insulin resistance, serum AST, ALT, endotoxin, NEFA, and cholesterol compared to the untreated MetALD group. Additionally, SG treatment reduced hepatic steatosis, inflammation, and hydroxyproline content in the MetALD group. The hepatic S-adenosylmethionine (SAM):S-adenosylhomocysteine (SAH) ratio reflective of the methylation potential, was significantly reduced in the MetALD group compared to the control group; SG treatment significantly improved this ratio by increasing SAM levels. **Conclusion:** These results strongly suggest that semaglutide reduces MetALD pathology by improving insulin sensitivity, hepatic SAM levels, and gut permeability.

Disclosures: Ramesh Bellamkonda: Nothing to Disclose, Sundararajan Mahalingam: Nothing to Disclose, Ojeshvi Ethiraj: Nothing to Disclose, Sathish kumar Perumal: Nothing to Disclose, Ramachandran Rajamanickam: Nothing to Disclose, Carol Casey: Nothing to Disclose, Kusum Kharbanda: Nothing to Disclose, Karuna Rasineni: Nothing to Disclose

4046 | DISCOVERY OF SIRNA THERAPEUTICS TARGETING PNPLA3 I148M FOR THE TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Chuan He[1] Chunxue Zhou[2] Huaye Pan[1] Xiaowei Sun[2] Rongyao Zhu[1] Haixia Yu[2] Xu Yang[1] Xiaochen Xu[2] Xiaobei Wang[1] Xiaochuan Cai[2] Shiyu Wang[2] Dongzhou Liu[1], [1]Hangzhou Zhongmei HuaDong Pharmaceutical CO. LTD, [2]sanegenebio

Background: The PNPLA3 I148M variant (rs738409) represents a critical genetic determinant of MAFLD/MASH pathogenesis, driving disease progression through gain-of-function effects on hepatic lipid metabolism. This mutation impairs triglyceride hydrolysis while promoting lipotoxic injury and fibrogenesis, creating an urgent need for therapies in this high-risk population. We developed a GalNAc-conjugated siRNA to address this unmet clinical need. **Methods:** GalNAc-siRNA sequences targeting PNPLA3 were rationally designed, and the IC50 efficacy was determined by high-

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throughput screening in Huh-7 cells. The lead compounds were optimized using primary hepatocyte assays and whole-transcriptome off-target profiling. In vivo validation included humanized PNPLA3 I148M knock-in mice and cynomolgus monkeys. Comprehensive repeat-dose toxicology evaluations were conducted in both rodent and non-rodent species to establish the therapeutic safety window. **Results:** In in vivo studies where human PNPLA3 was expressed exogenously in the mouse liver, the top-performing compound achieved more than 85% target mRNA knockdown following single-dose administration, and exhibited favorable dose-dependent responses in multiple-dose regimens. In humanized PNPLA3 I148M knock-in mice, RNAi treatment resulted in sustained silencing activity and maintained target suppression 4 weeks after dosing. In cynomolgus monkey pharmacodynamic studies, more than 80% target mRNA silencing was achieved after 4 weeks and persisted through 12 weeks after a single subcutaneous dose. In in vivo safety studies, the test article showed good tolerability in both rodent and non-rodent species. **Conclusion:** Based on established delivery and screening platforms, we have identified a series of potent and durable PNPLA3-targeting molecules. GalNAc-PNPLA3 siRNA demonstrates exceptional liver targeting, deep and durable silencing, and favorable safety profiles. Taken together, these data support its advancement as preclinical candidate compounds (PCCs) for MAFLD/MASH precision therapy, especially for PNPLA3 I148M homozygous patients. The IND-enabling studies are planned.

Disclosures: Chuan He: Nothing to Disclose, Chunxue Zhou: Nothing to Disclose, Huaye Pan: Nothing to Disclose, Xiaowei Sun: Nothing to Disclose, Rongyao Zhu: Nothing to Disclose, Haixia Yu: Nothing to Disclose, Xu Yang: Nothing to Disclose, Xiaochen Xu: Nothing to Disclose, Xiaobei Wang: Nothing to Disclose, Xiaochuan Cai: Nothing to Disclose, Shiyu Wang: Nothing to Disclose, Dongzhou Liu: Nothing to Disclose

4047 | EFFICACY AND SAFETY OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS IN METABOLIC DYSFUNCTION–ASSOCIATED STEATOHEPATITIS AND HEPATIC FIBROSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS WITH TRIAL SEQUENTIAL ANALYSIS

Eliabe Abreu[1] Rafael Borges[2] Luiza Paula[2] Ana Conegundes[2] Jefferson Martins[3] Marcelo Martins[4] Giovanni Gosch Berton[5] Alladin Dahbour[6] Erica Holanda[7] Manal Abdelmalek[1], [1]Mayo Clinic Rochester, [2]Federal University of Minas Gerais, [3]Federal University of Pará, [4]Federal University of Ouro Preto, [5]University of Passo Fundo, [6]Indiana University, [7]University Center Christus

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease. Metabolic dysfunction-associated steatohepatitis (MASH), the progressive form of MASLD, is a risk factor for progressive hepatic fibrosis and cirrhosis. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have revolutionized the treatment of obesity and diabetes; however, the role of GLP-1 RAs in the treatment of MASH with moderate-to-advanced (F2-F3) hepatic fibrosis, those 'at-risk' for adverse clinical outcomes, remains under investigation. This systematic review and meta-analysis evaluate the efficacy and safety of GLP-1 RAs in patients with MASH with fibrosis. **Methods:** We systematically reviewed and analyzed all randomized controlled trials (RCTs) from PubMed, Embase, and Cochrane databases about GLP-1 RAs and MASH. Primary outcomes included MASH resolution without worsening fibrosis or fibrosis improvement without worsening of MASH as defined by NASH CRN grading /staging criteria. Secondary outcomes included adverse events (AE), laboratory, and anthropometric data. Trial Sequential Analysis (TSA) was performed for the primary outcomes and used to assess evidence sufficiency and control random errors in the meta-analysis. **Results:** Six RCTs (1,480 patients, mean follow-up: 150.8 weeks) were included. GLP-1 RAs were superior to placebo on histologic improvement of fibrosis without worsening MASH (RR 1.66; 95%CI 1.37-2.02, $p < 0.001$; $I^2 = 0\%$) and histological resolution of MASH without worsening of fibrosis (RR 2.69; 95%CI 1.65-4.39, $p < 0.001$; $I^2 = 66.3\%$). Patients treated with GLP-1 RAs reported higher rates of treatment-emergent gastrointestinal adverse events, but no significant differences in serious AE in GLP-1 RA versus placebo groups were observed. GLP-1 RAs improved hepatic aminotransferases, MRI-PDFF, HbA1c, serum lipids, blood pressure, and anthropometric parameters in RCTs of MASH with F2-F3 fibrosis. The TSA showed an adequate sample size and evidence unlikely to change with additional studies. **Conclusion:** GLP-1 RAs improve cardiometabolic risk factors in patients with MASH while also lending improvement and/or resolution of MASH and MASH-associated hepatic fibrosis. Ongoing studies will define whether these surrogate endpoints will translate into a decrease in liver- and all-cause morbidity and mortality in patients with 'at-risk' MASH.

Disclosures: Eliabe Abreu: Nothing to Disclose, Rafael Borges: Nothing to Disclose, Luiza Paula: Nothing to Disclose, Ana Conegundes: Nothing to Disclose, Jefferson Martins: Nothing to Disclose, Marcelo Martins:

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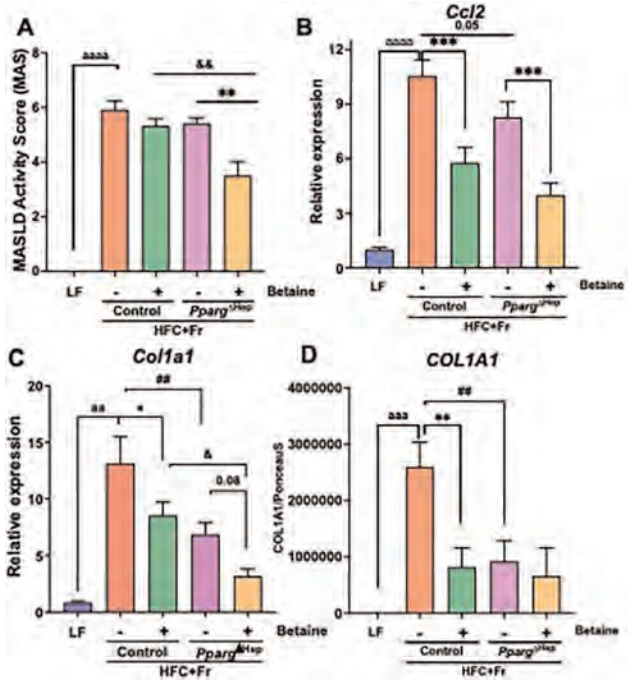
4048 | BETAINE REDUCES HEPATIC INFLAMMATION AND FIBROSIS IN A PRE-CLINICAL MOUSE MODEL OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Izabela Hawro[1] *Sara Osorio-Valencia*[1] *Grace Guzman*[1] *Kusum Kharbanda*[2] *Mercedes Del Rio-Moreno*[1] *Rhonda Kineman*[1], [1]*University of Illinois at Chicago,* [2]*University of Nebraska*

Background: Dysregulated hepatic methionine metabolism and increased homocysteine (Hcy) levels may promote hepatic inflammation and fibrosis. In hepatocytes, betaine-homocysteine S-methyltransferase (BHMT) reduces Hcy levels by utilizing betaine as a methyl donor to convert Hcy into methionine. We have shown that diet-induced metabolic dysfunction-associated steatohepatitis (MASH) reduces hepatic *Bhmt* expression and increases Hcy levels in male mice. Furthermore, we have reported that the knock-out of peroxisome proliferator-activated receptor gamma (*Pparg*) in hepatocytes ($Pparg^{\Delta Hep}$) increased hepatic *Bhmt* expression, reduced Hcy levels, and improved liver histology in mice with diet-induced MASH. Here, we sought to determine whether betaine supplementation reduces pre-established MASLD induced with fructose in the drinking water and high-fat and cholesterol diet (HFC+Fr) in both control and $Pparg^{\Delta Hep}$ mice. **Methods:** We fed male *Pparg*-floxed mice with a HFC+Fr diet for sixteen weeks to induce obesity, insulin resistance, and MASLD. Then, we generated control and $Pparg^{\Delta Hep}$ mice with AAV8-TBG-Null or AAV8-TBG-Cre injections, respectively. Half of the HFC+Fr-fed mice were supplemented with 1% betaine in the drinking water for eight additional weeks. **Results:** The HFC+Fr diet promoted dyslipidemia and insulin resistance, and increased body weight, plasma ALT levels, liver weight, steatosis, MASLD activity score (MAS), and fibrosis. $Pparg^{\Delta Hep}$ did not reduce body weight or adipose tissue mass, but increased plasma insulin levels in obese mice, which might be indicative of worsened insulin resistance. However, $Pparg^{\Delta Hep}$ improved liver health by reducing liver weight, steatosis, and plasma ALT levels. Furthermore, $Pparg^{\Delta Hep}$ reduced hepatic Hcy level, and increased S-adenosylhomocysteine, as well as the expression of key hepatic methyltransferases: *Mat1a*, *Pemt*, *Gnmt*, *Cbs*, and *Bhmt*. Of note, although betaine reduced liver weight in HFC+Fr-fed control mice, it did not alter the Hcy level or the MAS score. However, betaine was able to reduce the hepatic inflammation score and MAS in $Pparg^{\Delta Hep}$ mice (See Figure). This positive effect of betaine on the liver was associated with a dramatic reduction in fibrosis, as indicated by reduced gene expression of *Col1a1*, *Mmp13*, and *Timp1*, as well as decreased COL1A1 protein levels in both control and $Pparg^{\Delta Hep}$ mice (See Figure). In addition, betaine consistently reduced the expression of *Tnfa*, *Ccl2*, *Cd8a*, and *IL-17a* in the liver of both control and $Pparg^{\Delta Hep}$ mice (See Figure). **Conclusion:** Taken together, betaine had a robust and positive effect on the liver because it reduced hepatic inflammation and fibrosis in a mouse model with pre-established MASLD. This effect was enhanced by increased *Bhmt* expression in hepatocytes of $Pparg^{\Delta Hep}$ mice.



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4049 | FIBROSIS REGRESSION WITH RESMETIROM: EARLY OBSERVATIONS IN REDUCING FIBROSIS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Rachel Patel[1] Corey Savard[2] Cristina Angelo[2] She-Yan Wong[3] Adam Peyton[4], [1]Lehigh Valley Health Network, [2]Lehigh Valley Health Network / Division of Gastroenterology, [3]Thomas Jefferson University Hospital, [4]Eastern Pennsylvania Gastroenterology & Liver Specialists

Background: Metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis is a leading cause of progressive liver disease, with limited effective pharmacotherapies. Resmetirom, a novel medication, has shown potential in clinical trials to reduce hepatic fibrosis. We aim to evaluate real-world outcomes of Resmetirom using FibroScan-derived liver stiffness measurements (LSMs) in patients with biopsy-confirmed or clinically suspected MASH with fibrosis. **Methods:** We conducted a prospective observational study of patients with MASH and fibrosis who began Resmetirom at Lehigh Valley Health Network between April–October 2024. Inclusion criteria: (1) age ≥18 years; (2) MASH with fibrosis confirmed by FibroScan or biopsy; (3) Resmetirom initiation during enrollment. Common metabolic comorbidities (e.g., diabetes, hypertension, hypertriglyceridemia, obesity) were not exclusionary. One patient was excluded post-enrollment due to financial inability to start therapy. Of 26 enrolled, 25 completed baseline assessment. Collected data included fibrosis stage, comorbidities, and GLP-1 receptor agonist use. Follow-up LSMs were planned ~12 months post-initiation. At submission, post-treatment LSMs were available for seven patients. Adverse events were monitored during treatment. Full cohort data are expected by the AASLD Liver Meeting 2025. **Results:** Among 25 patients initiating therapy, baseline fibrosis ranged F2–F4; 72% began at F3. The cohort was 64% female with a median age of 62. Comorbidities included diabetes (60%), hypertension (60%), obesity (76%), and hypertriglyceridemia (68%). Six patients (24%) were on GLP-1 receptor agonists at baseline. Among seven patients with follow-up LSMs: five demonstrated at least one-stage fibrosis regression (from F2–F4 to F0–F1), two remained stable and none showed fibrosis progression. Adverse events were minimal—two reported self-limited diarrhea, with no therapy discontinuations. Final statistical analysis, including paired pre- and post-treatment LSM comparisons, will be completed once follow-up for the full cohort is available. **Conclusion:** Preliminary findings suggest that Resmetirom may be associated with fibrosis regression in patients with MASH. Real-world safety and tolerability appear favorable to date. As additional post-treatment data are collected, we anticipate further insight into the potential for Resmetirom to promote fibrosis regression and improve liver stiffness measurements in this population. Full cohort analysis will be presented upon completion of ongoing data collection.

Disclosures: Rachel Patel: Nothing to Disclose, Corey Savard: Nothing to Disclose, Cristina Angelo: Nothing to Disclose, She-Yan Wong: Nothing to Disclose, Adam Peyton: MADRIGAL: Speaking and Teaching, GILEAD: Speaking and Teaching, ABBVIE: Speaking and Teaching, IPSEN: Speaking and Teaching, NOVO-NORDISC: Advisor, SALIX/BAUSCH: Speaking and Teaching, MALLINCKRODT: Speaking and Teaching

4050 | BEYOND BODY WEIGHT CONTROL: TRANSCRIPTOMIC ANALYSIS REVEALS ADDITIONAL BENEFICIAL EFFECT OF GIPR/GLP-1R AGONISTS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS THERAPY

Hui Li[1] Jiliang Zhang[1] Jingxuan Yan[1] Yan Zhou[1] Miao Yuan[1] Chen Liu[1] Luxia Wei[1] Xiuxiu Shen[1] Lijuan Jiang[1] Zhixiang Zhang[1] Qingyang Gu[1], [1]Wuxi AppTec

Background: Metabolic Dysfunction-Associated Steatohepatitis (MASH) poses a significant global health challenge. The lack of regulatory-approved MASH medications underscores the critical need for innovative treatments. Various gastric inhibitory polypeptide receptor (GIPR) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are undergoing clinical trials at different stages for MASH, potentially providing new avenues for MASH therapy. Semaglutide (SEM) and Tirzepatide (TZP) are both under clinical investigation for MASH therapy, with promising therapeutic potential.

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This study aimed to investigate the differential responses to SEM and TZP at the transcriptional level in MASH mice. Additionally, this study also examined the mechanism of action of SEM and TZP beyond satiety and food consumption regulation by introducing corresponding dietary restriction groups. **Methods:** MASH mice were either treated with SEM or TZP for 6 weeks. Meanwhile, a dietary restriction control groups for each drug were set respectively. Transcriptional profiling then was done with liver samples collecting from each group. **Results:** In this study, SEM and TZP both exhibited a significant reduction in the NAS score in MASH murine models, though with no substantial changes in liver fibrosis scores. The transcriptomic analysis of the HDF+CCl4 MASH model, effectively replicating human MASH histopathology, revealed significant perturbations in lipid metabolism, xenobiotic metabolism, inflammation, extracellular matrix regulation, retinol metabolism, and PPAR signaling pathways. On a molecular level, SEM and TZP demonstrated overlapping effects on pathways such as steroid biosynthesis, PPAR signaling regulation, and arachidonic acid and retinol metabolism. Notably, both SEM and TZP showed distinctive modulation effects on retinol metabolism, PPAR signaling, and other inflammatory pathways compared to their respective dietary restriction controls. **Conclusion:** These findings suggest additional beneficial effects beyond food intake regulation for SEM and TZP, emphasizing their therapeutic potential for MASH and underscore the importance of delineating the molecular mechanisms driving these beneficial effects in MASH treatment to fully harness the therapeutic potential of SEM and TZP.

Disclosures: Hui Li: Nothing to Disclose, Jiliang Zhang: Nothing to Disclose, Jingxuan Yan: Nothing to Disclose, Yan Zhou: Nothing to Disclose, Miao Yuan: Nothing to Disclose, Chen Liu: Nothing to Disclose, Luxia Wei: Nothing to Disclose, Xiuxiu Shen: Nothing to Disclose, Lijuan Jiang: Nothing to Disclose, Zhixiang Zhang: Nothing to Disclose, Qingyang Gu: Nothing to Disclose

4051 | REAL WORLD RESMETIROM 6-MONTH FOLLOW UP DATA

Nadia Blessing Benjamin Robinson[1] Phoebe Shackelford[2] Nicole Cowgill[1] Jake McCarty[2] Neel Ravela[2] Andrew deLemos[1] Niharika Samala[2], [1]Wake Forest University Atrium Health, [2]Indiana University

Background: Metabolic dysfunction associated steatohepatitis (MASH) is the second leading cause of liver transplantation in the United States. In March 2024, the FDA conditionally approved resmetirom, a thyroid hormone receptor-b agonist for MASH with stage 2/3 fibrosis. Follow up data on patients on resmetirom for at least 6 months are needed. **Methods:** We report retrospective study of the patients approved to start resmetirom between March 14, 2024 and November 19, 2024, ensuring at least 6-months on medication, at two academic health centers- Indiana University Health (IUH) (N = 111) and Atrium Health and Wake Forest University (AHWF) (N = 33). Once approved patients were provided laboratory orders and clinic visit at 6 month follow up. Early experience with resmetirom in a portion of the study cohort was described in an earlier publication. **Results:** A total of 148 patients received resmetirom for at least 6 months, 69% females, 94% White, and 4% Hispanic with mean age of 52.8 $\pm$ 13.6 years and mean BMI of 37 $\pm$ 8Kg/m^2. Type 2 diabetes was seen in 50% and hypothyroidism in 27% of the cohort. All patients had health insurance - Medicare in 28% (42), Medicaid in 11% (17) and private in 60% (89). Median time from treatment approval to actual start was available in 69% of the cohort and was 26 $\pm$ 30 days. Additionally, 48% (63) were on GLP-1 R agonists, 39% (51) on statins and 32% (45) were on vitamin E. Of 132 (88%) who started the treatment, 17% (22) discontinued treatment within 6 months of initiation, of which 82% (18) were related to side effects, 3 could not afford the medication and 1 opted to participate in a clinical trial. There were no further discontinuations at 6 months follow up visits. Side effects were seen in 36 (27%) early in course of medication exposure – diarrhea in 16 (44%), abdominal pain/discomfort in 9 (25%), nausea or vomiting in 6 (17%), itching or rash in 6 (17%), and dizziness or headache in 4 (11%). Of those who continued the medication (n = 110), mean ALT at 6-months (n = 98) was lower than at baseline (44 $\pm$ 36 U/L vs. 56 $\pm$ 53 U/L, $p < 0.009$). Follow up liver stiffness measurement was only seen in 39 patients, with no significant difference from baseline (13.9 $\pm$ 7kPa vs. 12 $\pm$ 8kPa, $p = 0.3$). **Conclusion:** Most patients tolerated resmetirom well, with only 17% discontinuations, mostly related to side effects, which presented early in medication exposure, within 6 months. Compared to baseline, ALT was significantly lower after 6 months of treatment with resmetirom.

Disclosures: Nadia Blessing: Nothing to Disclose, Benjamin Robinson: Nothing to Disclose, Phoebe Shackelford: Nothing to Disclose, Nicole Cowgill: Nothing to Disclose, Jake McCarty: Nothing to Disclose, Neel Ravela: Nothing to Disclose, Andrew deLemos: Madrigal Pharmaceuticals: Consultant, Ipsen: Consultant, Niharika Samala: Novo Nordisk: Consultant

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4052 | RESMETIROM IMPROVES MORTALITY, LIVER AND CARDIO-RENAL-METABOLIC (CRM) OUTCOMES IN INDIVIDUALS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE IN ROUTINE CLINICAL PRACTICE

Vinay Jahagirdar[1] Kavin Parmar[1] Neha Shah[1] Amon Asgharpour[1] Velimir Luketic[1] Ekaterina Smirnova[1] Juan Pablo Arab[1] Arun Sanyal[1], [1]Virginia Commonwealth University

Background: Resmetirom is conditionally approved for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis based on histological improvement in clinical trials. Its benefits on liver and cardio-renal-metabolic (CRM) outcomes, that are competing threats to life, are unknown. The aim of this study was to evaluate the impact of resmetirom on liver- and CRM-outcomes. **Methods:** Patients with MASLD who received resmetirom were included along with controls matched for age, race, sex, BMI, type 2 diabetes mellitus (T2DM), smoking status, prior known coronary artery disease (CAD), chronic kidney disease (CKD), LDL-cholesterol (LDL-C), alcohol use and GLP-1 use. The key outcome measures included 5-point major cardiovascular adverse events (MACE), major adverse liver outcomes (MALO) (ascites, overt hepatic encephalopathy, variceal hemorrhage), new onset hypertension, CKD, T2DM and death. The period of observation was up to 1 year since the drug was only recently approved. Those with events prior to start date were excluded for specific outcome analyses. Proportions of patients with outcomes and Kaplan Meier estimates of time to outcomes were analyzed. **Results:** A total of 1304 individuals each with MASLD who received resmetirom and matched controls were identified; 27% were on a GLP-1 agonist. Baseline demographics included (mean or %): age-56 yrs., white-74%, T2DM-46% while laboratory data were (resmetirom vs control): AST-44 vs 33 IU/l, Bilirubin-0.6 vs 0.7 mg/dl, platelets- 237 vs 247K/mm3, A1C- 6.2 vs 6.4%, LDL-C-92 vs 96 mg/dl. Resmetirom (vs control) improved mortality (absolute risk (AR): 0.7 vs 2%, $p < 0.0009$, Odds ratio (OR) 0.31 95% CI (0.2-0.6), time to death ($p < 0.003$ logrank). It improved MACE (AR): 0.74 vs 3.1% $p < 0.0001$, OR: 0.23 (0.11-0.47) and time to MACE (logrank $p = 0.008$), MALO: (AR: 1 vs 2.2%, $p < 0.01$, OR: 0.45 (0.24-0.85) without affecting time to outcome. It improved other CRM outcomes also: new onset CKD: AR: 0.9 vs 2.9%, $p = 0.0001$, OR:0.3 (0.15-0.55), new onset hypertension: (AR: 4.7 vs 13.3%, $p < 0.00001$, OR:0.32 (0.2-0.5) and new onset T2DM (AR: 4.5 vs 7.4%, $p = 0.01$, OR: 0.6, 0.4-0.9). It did not affect overall cancer incidence (AR: 0.8 vs 0.9%, p = NS). These benefits were independent of statin use or weight change. **Conclusion:** In a real-world clinical practice, resmetirom improved mortality, liver and CRM outcomes in patients with MASLD.

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Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor

4053 | HARNESSING THE PERIPHERAL SEROTONIN SIGNALING: NON-PSYCHEDELIC PSILOCIN ANALOGUES DESIGNED FOR THE TREATMENT OF MASLD

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Background: In a diet-induced model of MASLD, chronic low dose psilocybin reduced liver steatosis, limited body weight (BW) gain, and improved glucose and lipid homeostasis. Psilocybin is the prodrug of psilocin, a serotonin analogue that binds 5-HT receptors (5-HTRs) in both the CNS and peripheral tissues. We hypothesized that a gastrointestinal (GI)-targeted, CNS-sparing, psilocin derivative might retain metabolic benefits without psychedelic effects. **Methods:** A library of psilocin conjugates with polyethylene-glycols (PEGs) of different length (4, 6, 8, 10 monomers) was designed, synthetized and pharmacologically profiled using FLIPR assay in CHO-cells overexpressing 5-HT2A, 2B or 2C receptors. A standard toxicology evaluation was performed in rats. PK analyses were performed in C57BL6J mice by measuring drug concentration in plasma, liver and brain by LC-MS. Head-twitch response (HTR) in mice was tested at increasing doses. The metabolic effects of 12 weeks of daily oral gavage with 0.05 mg/kg psilocybin, PEG-8-psilocin (equiv. dose) or placebo were tested in mice ($n = 10$ per group) fed on high fat (60% kcal from fat) and high fructose (30% in drinking water) diet (HFHFD) for 5+12 weeks. Mice fed with standard diet were included as healthy controls. Liver steatosis was evaluated by H&E and ORO staining. Hepatic lipids were evaluated by LC-MS/MS untargeted lipidomic analysis. An oral glucose tolerance test was performed before sacrifice. Pancreas ultrastructure was evaluated by transmission electron microscopy. **Results:** PEG-8 psilocin was identified as the lead candidate due to its low oral bioavailability and negligible brain exposure. It maintained psilocin-like activity at 5-HT2 receptors, was well-tolerated in rats, did not elicit HTR.Chronic treatment with PEG-8-psilocin, similarly to psilocybin, resulted in marked reduction of liver steatosis and significantly reduced BW gain vs healthy mice ($p < 0.01$ for PEG-8 psilocin and $p < 0.05$ for psilocybin). At lipidomic analysis, PEG-8-psilocin restored hepatic di- and triglycerides, increased by HFHFD, back to healthy control levels, with a stronger effect than psilocybin. Furthermore, PEG-8-psilocin normalized glucose tolerance curves and improved pancreatic β-cell ultrastructure, as evidenced by insulin granule number and morphology. **Conclusion:** In this MASLD mouse model, the GI-targeted, brain-impermeable, psilocin derivative PEG-8-psilocin significantly reduced liver steatosis and improved key metabolic parameters, supporting the role of gastrointestinal 5-HTRs as likely mediators of the metabolic benefits observed with both psilocybin and PEG-8-psilocin.

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4054 | A MICROFLUIDIC HUMAN LIVER SLICE MODEL FOR ANTIFIBROTIC DRUG SCREENING: GLP1-R AGONIST LIRAGLUTIDE DEMONSTRATES ANTIFIBROTIC ACTIVITY

María Andrés-Rozas[1] Peio Aristu[2] Gabriela Chullo[3] Yilliam Fundora[4] Anabel Fernandez-Iglesias[1] Sergi Guixé-Muntet[2] Jordi Gracia-Sancho[1], [1]Liver Vascular Biology Lab, IDIBAPS - Hospital Clínic de Barcelona -

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CIBEREHD, [2]Liver Vascular Biology, IDIBAPS - Hospital Clínic de Barcelona - CIBEREHD, [3]Hospital Clínic de Barcelona, [4]Hospital Clínic de Barcelona - CIBEREHD

Background: Liver fibrosis is a major contributor to chronic liver disease, currently lacking effective pharmacological therapy. Understanding extracellular matrix (ECM) remodeling is essential for characterizing fibrosis progression and resolution. Precision-cut liver slices (PCLS) represent a valuable ex vivo tool, maintaining native liver architecture and enabling multicellular ECM assessment. However, traditional static cultures limit slice viability and induce phenotypic drift, constraining long-term studies. This work aimed to establish a novel human 3D liver model using PCLS cultured in a microfluidic device that preserves tissue viability, architecture, and cirrhotic phenotype for up to 7 days, and to assess liraglutide's antifibrotic effects within this system. **Methods:** Human PCLS from cirrhotic explant livers (ALD and MetALD etiologies) were cultured under conventional or microfluidic conditions ($n = 5$ per group). Viability, necrosis, sinusoidal fibrosis, and liver function were evaluated at 24h, 72h, and day 7. Expression of LSECs, HSCs and macrophages specific phenotypic markers was assessed by qPCR, and cellular interactions were visualized by immunofluorescence co-localization of vimentin (HSC marker) and endomucyn (LSEC marker). Cirrhotic PCLS were treated with liraglutide (200 μM) or vehicle (PBS) for 7 days ($n = 6$–7 slices/condition), and fibrogenic profile was analyzed at the transcript, protein and histological levels. **Results:** Microfluidic-cultured PCLS showed markedly reduced necrosis (−59%), sinusoidal fibrosis (−33%), and release of LDH, ALT, and AST at day 7 compared to static culture. Albumin secretion increased under flow at 24 h (+52%). Cirrhotic phenotypes of LSECs, HSCs, and macrophages were better retained within the device, with maintenance of HSC–LSEC interaction. Liraglutide treatment significantly reduced mRNA expression of ACTA2 (−65%), COL1A1 (−69%), and PDGFRB (−61%), alongside protein reductions in α-SMA (−41%), VIM (−51%), and COL1A1 (−56%), which were associated with an improvement in Sirius-Red stained area (-24%), altogether consistent with HSC deactivation and ECM remodeling. All $p < 0.05$. **Conclusion:** This study introduces a robust human 3D liver model based on microfluidic-cultured PCLS, preserving tissue integrity and cellular phenotypes up to 7 days. Furthermore, it demonstrates liraglutide's ability to deactivate HSCs and remodel ECM in human cirrhotic liver tissue. This platform offers a physiologically relevant and translationally meaningful system for antifibrotic drug evaluation, bridging experimental research with clinical application.

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4055 | EFFECTS OF PEMAFIBRATE ON IMPROVEMENT AND RECURRENCE IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

Takamasa Ohki[1], [1]Shioda Memorial Hospital

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a liver condition closely associated with metabolic syndrome and frequently accompanied by dyslipidemia. Pemafibrate (PEM), a selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα), exerts a strong triglyceride-lowering effect and has also been reported to improve alanine aminotransferase (ALT) levels and hepatic steatosis. However, as MASLD is primarily driven by lifestyle factors, recurrence after improvement is a concern. This study aimed to evaluate the therapeutic effect of PEM and the recurrence of abnormal ALT levels in MASLD patients with dyslipidemia. **Methods:** A total of 127 MASLD patients with dyslipidemia who were prescribed PEM between July 2019 and October 2024 were retrospectively analyzed. The primary outcome was normalization of ALT levels, defined as ≤ 30 IU/L. The secondary outcome was recurrence, defined as ALT returning to ≥ 31 IU/L on two consecutive measurements after normalization. Factors associated with ALT normalization and recurrence were also analyzed. **Results:** Among the 127 patients, 96 (76%) were male, the median age was 55 years, and the median BMI was 27.8 kg/m². Diabetes mellitus was present in 62 patients (49%). The median baseline ALT was 64 IU/L, triglycerides were 289 mg/dL, and the median PEM treatment duration was 21 months. At 12 months, ALT decreased to a median of 37 IU/L and triglycerides to 190 mg/dL, both showing significant improvement ($P < 0.01$). ALT normalization

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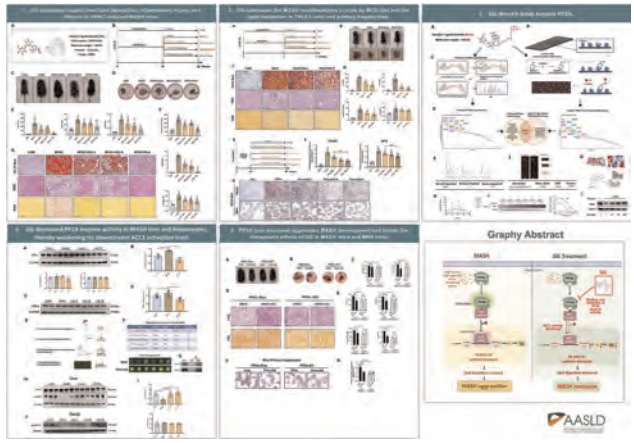
was achieved in 73 patients (57%). The cumulative normalization rates were 37% at 6 months, 50% at 12 months, and 65% at 24 months. In univariate analysis, only age was significantly associated with ALT normalization (HR 1.02, P = 0.048). Among the 73 patients with normalized ALT, 13 (18%) experienced recurrence. The cumulative recurrence rates were 7% at 6 months, 20% at 12 months, and 20% at 24 months. **Conclusion:** PEM therapy led to normalization of ALT levels in approximately half of MASLD patients with dyslipidemia. However, about 20% experienced recurrence, highlighting the importance of sustained lifestyle modification alongside pharmacotherapy.
Disclosures: Takamasa Ohki: Nothing to Disclose

4056 | GENIPIN 1-β-D-GENTIOBIOSIDE ALLEVIATES MASH BY INHIBITING HEPATIC PP2A ENZYMATIC ACTIVITY

Xin Xin[1] Cheng Chen[1] Xu Xiao[1] Chen Zou[1] Qinmei Sun[1] Cen Xie[2] Yiyang Hu[1] Feng Qin[1], [1]Shuguang Hospital affiliated to Shanghai University of Tradional Chinese Medicine, [2]Shanghai Institute of Materia Medica, Chinese Academy of Sciences

1. **Background:** Genipin 1-β-D-gentiobioside (GG) is a key bioactive component derived from the herb Gardenia jasminoides. This study aims to investigate the therapeutic potential of GG in treating metabolic-associated steatohepatitis (MASH) and to elucidate its underlying pharmacological mechanisms. **Methods:** The anti-MASH effects of GG were evaluated using two murine models induced by a high-fat, high-carbohydrate (HFHC) diet and a methionine/choline-deficient (MCD) diet, as well as a rat model induced by a high-fat diet (HFD).
2. *In vitro* studies utilized free fatty acid (FFA)-induced THLE2 cells and primary hepatocytes to assess lipid accumulation and inflammation.
3. Potential GG-binding proteins were identified through HuProt protein microarray screening and pull-down mass spectrometry. Binding interactions were validated using surface plasmon resonance (SPR), drug affinity responsive target stability (DARTS), and cellular thermal shift assay (CETSA). Phosphoproteomic profiling was employed to identify downstream effectors of the GG target protein.
4. *In vivo* and *in vitro* liver-specific gene editing models were used to confirm the mechanistic role of GG in MASH. **Results:** GG significantly reduced hepatic lipid accumulation, inflammation, and early-stage fibrosis in MASH animal models. *In vitro*, GG effectively mitigated FFA-induced lipid deposition in hepatocytes.

1. Combined analyses identified protein phosphatase 2A (PP2A) as a direct binding target of GG, with strong binding affinity confirmed by SPR (KD = 7.99 × 10^{-6} M). Notably, while GG did not alter PP2A expression levels, it significantly inhibited its enzymatic activity, which was upregulated under metabolic stress conditions.
2. Phosphoproteomic analysis identified acetyl-CoA carboxylase 1 (ACC1), a key enzyme in de novo lipogenesis, as a downstream substrate of PP2A. Co-immunoprecipitation confirmed the interaction between PP2A and ACC1. GG-mediated inhibition of PP2A activity led to increased phosphorylation of ACC1, suppressing its lipogenic activity.
3. Hepatocyte-specific deletion of PP2A *in vivo* and *in vitro* abolished the therapeutic effects of GG, confirming PP2A as a critical mediator of GG's action against MASH. **Conclusion:** GG alleviates MASH by inhibiting hepatic PP2A enzymatic activity, thereby enhancing ACC1 phosphorylation and suppressing *de novo* lipogenesis. These findings highlight GG as a promising therapeutic candidate for MASH treatment.



Disclosures: Xin Xin: Nothing to Disclose, Cheng Chen: Nothing to Disclose, Xu Xiao: Nothing to Disclose, Chen

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Zou: Nothing to Disclose, Qinmei Sun: Nothing to Disclose, Cen Xie: Nothing to Disclose, Yiyang Hu: Nothing to Disclose, Feng Qin: Nothing to Disclose

4057 | IMPACT OF LEVOTHYROXINE ON PROGRESSION TO AND COMPLICATIONS OF CIRRHOSIS IN MASH

Abhinav Rao[1] Don Rockey[1], [1]Medical University of South Carolina

Background: Resmetirom, a liver-targeted thyroid hormone receptor-β (THR-β) agonist, used to treat MASH, shares a similar mechanism of action with levothyroxine, a nonselective (THR-α/β) receptor agonist used to treat hypothyroidism. Given the potential effect of levothyroxine on THR-β, we hypothesized that it may have beneficial effects in MASH patients. **Methods:** We used TriNetX to examine patients aged ≥18 years with MASH treated with levothyroxine from 1/1/16-1/1/25. Patients prescribed levothyroxine (levothyroxine group) were compared to those not receiving them (control group). Patients with previous cirrhosis or liver transplant were excluded. To control for disease severity and underlying comorbidities, propensity score matching (PSM) was performed. **Results:** Of 109,268 patients with MASH, 17,629 (16%) received levothyroxine. Following PSM, we examined 15,076 patients in each group. MASH patients with or without levothyroxine treatment were predominantly White females, with a mean [SD] bilirubin, INR, and creatinine of 0.6 [0.7], 1.1 [0.4], and 0.9 [1.2], respectively. Comorbidities, BMIs and MASH therapies including GLP-1s, SGLT-2s, and statins were similar in both groups. Over a mean [SD] follow-up of 2.8 [1.8] years, patients receiving levothyroxine had a similar rate of progression to cirrhosis (HR:1.08;95% CI:0.97–1.21;p = 0.16) as patients not on levothyroxine. In patients who developed cirrhosis, those receiving levothyroxine had a small, but statistically significantly higher risk of developing any portal hypertensive complication (HR:1.33;95% CI:1.18–1.49; p < 0.001) than those not receiving levothyroxine. **Conclusion:** MASH patients prescribed levothyroxine had a similar rate of progression to cirrhosis and a slightly higher rate of portal hypertension complications than those not prescribed levothyroxine.

Table 2. Clinical Outcomes

Outcomes (%)*	Levothyroxine (N = 15,076)	No Levothyroxine (N = 15,076)	HR (95% CI)	P value (Log-Rank)
MASH Cirrhosis	698 (4.6)%	579 (3.8%)	1.08 (0.97-1.21)	NS
Any portal hypertensive complication	698 (4.6)%	484 (3.2%)	1.33 (1.18-1.49)	<0.001
Ascites	251 (1.7%)	201 (1.3%)	1.14 (0.95-1.38)	NS
Hepatic encephalopathy	525 (3.5%)	337 (2.2%)	1.44 (1.25-1.65)	<0.001
Variceal bleeding	14 (0.1%)	12 (0.1%)	1.06 (0.49-2.28)	NS
Spontaneous bacterial peritonitis	11 (0.1%)	11 (0.1%)	0.92 (0.40-2.12)	NS
Hepatorenal syndrome	14 (0.1%)	10 (0.1%)	1.40 (0.61-3.24)	NS
HCC	34 (0.2%)	23 (0.2%)	1.36 (0.80-2.30)	NS
Liver transplant	10 (0.1%)	10 (0.1%)	1.38 (0.23-8.25)	NS
All-cause mortality	768 (5.1%)	641 (4.2%)	1.10 (0.99-1.20)	NS

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4058 | REALWORLD USE PATTERNS OF RESMETIRON IN PATIENTS WITH MASH: ANALYSIS OF A NATIONAL COHORT

Tatyana Kushner Kate Solpari[1] Scarlet Yang[1] Stephanie Rutledge[1] Allysa Saggese[1] Adam Buckholz[1] Sonal Kumar[1], [1]Weill Cornell Medicine

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Background: Resmetiron was FDA approved for use in MASH with advanced fibrosis in March 2024. We evaluated current prevalence and predictors of resmetiron use in a national realworld cohort. **Methods:** We performed a population-based retrospective study of individuals with a prescription for resmetiron compared to individuals with a diagnosis code for metabolic dysfunction associated steatohepatitis (MASH) not on resmetiron based on ICD10 code K75.81 from 2000-2025 using the TriNetX research network, which contains deidentified electronic health record data from 100 U.S. health care organizations. Prevalence and predictors of resmetiron prescriptions were assessed. **Results:** We identified a total of 1638 individuals with a prescription for resmetiron, compared to a total of 247155 individuals with a diagnosis code for MASH who were not on resmetiron. Interestingly, only 66% of individuals on resmetiron had a diagnosis code for MASH in their medical record. A total of 24 health system providers had records of prescriptions of resmetiron. Individuals on resmetiron were lower age and more likely to be White and Asian compared to individuals with MASH not on resmetiron ($P < 0.05$), see Table 1. They were also more likely to have a diagnosis of obesity, type 2 DM, and hyperlipidemia ($p < 0.05$). Interestingly, 59% had a diagnosis code for hepatic fibrosis (compared to 20% in non-resmetiron group, $p < 0.0001$). Of note, 22% had a diagnosis of cirrhosis (compared to 41% in MASH comparison group). Among patients on resmetiron, 27% also had a prescription for semaglutide, 16% for tirzepatide; 32% were on atorvastatin. Patients on resmetiron had mean follow up of 128 days (SD 108). A total of 5% of individuals in both groups had a diagnosis of alcohol related disorders. **Conclusion:** Resmetiron is still uncommonly prescribed nationally, with a small number of health systems currently prescribing it. Patient characteristics of resmetiron group reflect high burden of metabolic comorbidities, with over 25% also being on glp-1 therapies. Relatively high rates of prescriptions among people with diagnosis of cirrhosis suggests off label prescribing practices. Given current short duration of real-world follow up of patients on resmetiron, longer follow up is needed in order to assess influence on disease outcomes in the real world.

Table 1. Characteristics of patients on resmetiron compared to control MASH population not on resmetiron.

	Individuals on Resmetiron (n=1638)	Individuals with MASH not on Resmetiron (n=253797)	P value
Demographics			
Age (mean, SD)	56.8 (13.7)	61 (15)	<0.0001
Female (n, %)	954 (60%)	137470 (54%)	<0.001
Hispanic	640 (40%)	106479 (42%)	0.114
Race			
White	1193 (75%)	183509 (72%)	0.0443
Asian	144 (9%)	10699 (4%)	<0.0001
Unknown Race	92 (6%)	30636 (12%)	<0.001
Black	74 (5%)	14352 (4%)	0.0753
Comorbidities			
Overweight/ obesity	1039 (65%)	151975 (50%)	<0.0001
Hyperlipidemia	1115 (70%)	166624 (66%)	0.0007
Type 2 diabetes	802 (50%)	134564 (53%)	0.0863
Ischemic Heart Disease	306 (19%)	74010 (29%)	<0.001
Liver Disease			
Hepatic fibrosis	943 (59%)	50023 (20%)	<0.0001
Cirrhosis	347 (22%)	104100 (41%)	<0.0001

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4059 | SEMAGLUTIDE-INDUCED WEIGHT LOSS IS THE MAIN DETERMINANT FOR THE IMPROVEMENT OF HEPATIC BIOCHEMISTRY AND ELASTOGRAPHIC REPEATED MEASUREMENTS WITH FIBROSCAN® IN PATIENTS WITH T2DM AND MASLD

Savvoula Savvidou[1] Electra Avgousti-Varela[1] Aikaterini Damianakou[1] Miltos Chalkias[1] Ioannis Stergiou[1] Georgios Petridis[1], [1]"G.GENNIMATAS" General Hospital of Thessaloniki

Background: Semaglutide is currently being investigated for its effectiveness in MASLD (anticipated ESSENCE trial results), even though recent studies have concluded on its usefulness in MASH-related cirrhosis. Aim of this study was to examine the effect of semaglutide on hepatic parameters of patients with T2DM and MASLD in real-world clinical practice, and to further assess the significance of weight loss during treatment. **Methods:** In consecutive patients with T2DM and MASLD, hepatic biochemistry, non-invasive score of FIB-4 (= age x AST / platelets x $\sqrt{}$ALT), and elastographic measurements with FibroScan® mini+430 (Echosens, Paris) of liver stiffness (LSM) and Controlled Attenuation Parameter (CAP) were recorded before and after treatment with semaglutide. All participants had ultrasonographic evidence of fatty liver, while respective

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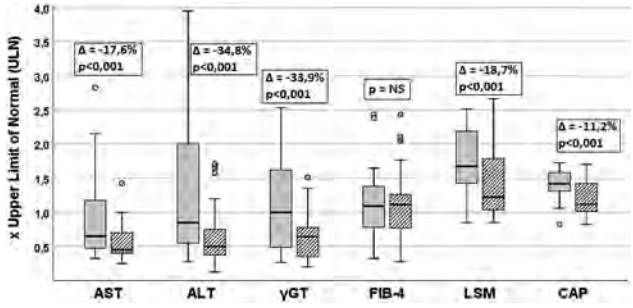
CAP measurements exceeded 220 dB/m. Differences (Δ) were calculated as % percentages of (final – baseline) / baseline values. For within group comparisons, Wilcoxon Signed Ranked test for related samples was performed, while the effect of weight loss was investigated statistically with MANCOVA. **Results:** A total of 111 patients were investigated: 31 males (27.9%), mean age 56.4 ± 9.7 years-old, BMI 32.7 ± 6.3 kg/m^2, median HbA1c 5.8% (IQR 5.6-6.2). Prevalence of metabolic factors: dyslipidemia 66.7%, obesity 64.9%, arterial hypertension 74.8%. Semaglutide (0.5-2.4mg/week sc.) was administered for a median of 12 months (IQR 6.6-17). Baseline lab: AST 26U/L (IQR 19-47), ALT 31U/L (IQR 22-81), γGT 45U/L (IQR 22-73), FIB-4 1.09 (IQR 0.78-1.38). Thirty-three patients (29.7%) had AST and/or ALT above upper limit of normal (ULN), and 35 (31.5%) FIB-4 > 1.30 (cut-off for intermediate/high-risk of advanced hepatic fibrosis). Apart from an overall drop in HbA1c of 5.6% (IQR 1.6-8.6) and weight loss of 10% (IQR 3.2-19.6), statistical significant reductions were recorded in liver enzymes, and elastographic parameters [GRAPH].
Improvements in AST, ALT, γGT, LSM and CAP correlated independently to weight loss and semaglutide treatment duration (Pearson correlation, $p < 0.001$). In multivariate analysis of covariance, weight loss was found to be associated with Δ_ALT ($p = 0.016$), Δ_AST ($p = 0.001$), Δ_LSM ($p = 0.030$) and Δ_CAP ($p = 0.001$), irrespective of treatment duration and baseline FIB-4 score. **Conclusion:** In this cohort of T2DM/MASLD patients with baseline satisfactory glycemic control, semaglutide-induced weight loss led to significant improvements of all hepatic parameters (biochemistry, liver stiffness and steatosis assessed with CAP), even in MASLD patients with baseline liver enzymes within normal. This study supports the advantages of semaglutide administration in T2DM patients with concomitant MASLD of any stage.



Disclosures: Savvoula Savvidou: Nothing to Disclose, Electra Avgousti-Varela: Nothing to Disclose, Aikaterini Damianakou: Nothing to Disclose, Miltos Chalkias: Nothing to Disclose, Ioannis Stergiou: Nothing to Disclose, Georgios Petridis: Nothing to Disclose

4060 | KEY INTERACTION BETWEEN ASPIRIN, MEDITERRANEAN DIET AND MORTALITY IN HIGH-RISK MASLD: ANALYSIS OF NHANES 2011-2018

Tsubasa Tsutsumi[1] Mary Rinella[2] Takumi Kawaguchi[1] Sarah Kolb[3] Hee Yeon Kim[3] Dejan Micic[4] Matthew Odenwald[3] Edwin Mcdonald[3] Michael Charlton[5], [1]Kurume University School of Medicine, [2]The University of Chicago, [3]University of Chicago, [4]University of Chicago Medical Center, [5]Madrigal Pharmaceuticals

Background: The benefit–risk profile of low-dose aspirin (ASA) in individuals with metabolic dysfunction–associated steatotic liver disease (MASLD) remains uncertain. The extent to which dietary patterns modulate this relationship is largely unexplored. We examined whether degree of adherence to the Mediterranean-style diet, assessed by Mediterranean diet score (MDS) modifies the impact of ASA use on all-cause mortality in patients with MASLD in a nationally representative cohort. **Methods:** We analyzed 4,541 adults (median follow-up 4.8 years) from NHANES 2011–2018 with linked mortality data. MASLD was defined by US-FLI > 60 and at least one cardiometabolic risk factor; habitual ASA use was self-reported. A 24-h dietary recall–derived MDS was categorized into tertiles (Low, Mid, High). Cox models accounting for complex survey design included ASA, MASLD, MDS, all lower-order terms, and the ASA × MASLD × MDS interaction. Covariate adjustment was stepwise: Model 0, unadjusted; Model 1, demographics (age, sex, race/ethnicity, marital status, education, poverty index); Model 2, Model 1 plus smoking, cancer history, and cardiovascular disease. The outcome was all-cause mortality. **Results:** In the fully adjusted survey-weighted model, the three-way interaction (ASA × MASLD × MDS) reached statistical significance ($p = 0.02$). In crude analysis, participants prescribed prophylactic ASA, who inherently carried higher baseline cardiovascular risk, showed elevated mortality (HR 6.51, 95 %CI 3.32–12.75). This excess risk was attenuated after demographic adjustment (HR 2.35) and became non-significant in the fully adjusted model (HR 2.07, 0.95–4.52), indicating substantial confounding rather than a harmful pharmacologic effect. MASLD itself doubled mortality risk (HR 2.32, 1.18–4.58). Diet quality showed no association with mortality in participants without MASLD (Mid vs Low 95% CI 0.81–2.74; High vs Low 95%CI 0.51–1.66). In contrast, among MASLD participants a High MDS reduced mortality by 68 %—interaction-derived HR 0.32 (95% CI 0.12–0.87)—whereas a Mid-level score was essentially neutral

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(combined HR ≈ 0.82). Among patients with MASLD using ASA, diet quality displayed a non-linear pattern. Using the low-MDS subgroup as reference (combined HR = 1.49), mid-level adherence of MDS was neutral (HR 1.37, 95 % CI 0.68–2.76), whereas high adherence tended to reduce mortality (HR 0.68, 0.32–1.42) although not statistically significant. **Conclusion:** In patients with MASLD, diet quality modulates aspirin's impact in a threshold-like fashion: high MDS tends to attenuate mortality, whereas both low (non-adherence) and mid-range scores show no clear benefit. These findings highlight the need for diet-informed, personalized aspirin prophylaxis and for prospective studies that minimize indication bias.

Disclosures: Tsubasa Tsutsumi: Nothing to Disclose, Mary Rinella: akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching, Sarah Kolb: Nothing to Disclose, Hee Yeon Kim: Nothing to Disclose, Dejan Micic: Nothing to Disclose, Matthew Odenwald: Nothing to Disclose, Edwin Mcdonald: Nothing to Disclose, Michael Charlton: Nothing to Disclose

4061 | LUSEOGLIFLOZIN REDUCED CVD RISK BY IMPROVING BLOOD PRESSURE AND HDL CHOLESTEROL LEVELS IN DIABETIC PATIENTS WITH MASLD: A POOLED META-ANALYSIS OF PHASE III CLINICAL TRIALS USING A CAUSAL INFERENCE ANALYSIS

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Background: Luseogliflozin, a sodium-glucose cotransporter 2 inhibitor, potentially exerts pleiotropic effects on the heart and liver. We aimed to investigate the effects of luseogliflozin on cardiovascular disease (CVD) risk in diabetic patients with MASLD by a pooled meta-analysis of phase III clinical trials. Furthermore, we investigated the direct causal interactions between changes in CVD risk and cardiometabolic risk factors (CMRFs) by luseogliflozin. **Methods:** In this pooled meta-analysis, we enrolled diabetic patients with MASLD who participated in phase III clinical trials of luseogliflozin (luseogliflozin group n = 259; placebo group n = 153). The primary outcomes were changes in the Framingham Risk Score (FRS) and the classification of FRS (high, intermediate, low risks) after 24

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weeks. We also investigated the direct causal interactions between changes in FRS and CMRFs affected by luseogliflozin using a directed acyclic graph. **Results:** At the baseline, there were no significant differences in FRS and the classification of FRS between the luseogliflozin and placebo groups. No significant differences were also observed in any CMRFs between the two groups. Primary outcomes: Luseogliflozin significantly decreased FRS compared to placebo after 24 weeks (FRS 0.00 vs. -0.53 points, $P = 0.0039$). Luseogliflozin also significantly improved the classification of FRS compared to placebo (improvement in the classification 5.0% vs. 12.0%, $P = 0.0187$). There was no significant difference in changes in triglycerides and total cholesterol levels between the two groups. In contrast, luseogliflozin significantly improved body mass index (-0.1 vs. -0.7, $P < 0.0001$) and levels of HbA1c (0.17% vs. -0.44%, $P < 0.0001$), blood pressure (0.0 vs. -3.7 mmHg, $P = 0.0178$), and HDL-cholesterol (1.5 vs. 3.4 mg/dL, $P = 0.0106$) compared to placebo. The directed acyclic graph revealed that the improvement of FRS was directly caused by the changes in blood pressure and HDL-cholesterol levels, but not by other CMRFs induced by luseogliflozin. **Conclusion:** This pooled meta-analysis demonstrated that 24-week treatment with luseogliflozin improved FRS in diabetic patients with MASLD. Furthermore, the improvement in CVD risk was directly caused by the improvement of blood pressure as well as HDL-cholesterol levels. Thus, luseogliflozin may be useful for reducing CVD risk through the improvement of circulatory dynamics and lipid metabolism in diabetic patients with MASLD.

Disclosures: Takumi Kawaguchi: ASKA Pharmaceutical Co., Ltd.: Speaking and Teaching, Taisho Pharmaceutical Co., Ltd.: Speaking and Teaching, Kowa Company, Ltd.: Speaking and Teaching, AbbVie GK.: Speaking and Teaching, Eisai Co., Ltd.: Speaking and Teaching, Novo Nordisk Pharma Ltd.: Speaking and Teaching, Janssen Pharmaceutical K.K.: Speaking and Teaching, Otsuka Pharmaceutical Co., Ltd.: Speaking and Teaching, EA Pharma Co.,Ltd.: Speaking and Teaching, Hiromitsu Kajiyama: Nothing to Disclose, Hironori Yamaguchi: Nothing to Disclose, Yutaka Seino: Nothing to Disclose

4062 | UNCOUPLER SKQ1 INDUCES WEIGHT LOSS AND NORMALIZES LIVER FUNCTION IN DIO RABBITS

Anton Petrov[1] Maksim Skulachev[2] Ivan Senin[2],
[1]Mitotech, [2]Mitolab

Background: SkQ1 is a small molecule that accumulates in mitochondria with high specificity and can stimulate mitochondrial uncoupling at much lower doses than conventional uncouplers. Antioxidant properties of SkQ1 provide additional protection against ferroptosis in liver tissue, which was demonstrated in animal models of both obesity and MASH. With combined potential effect of weight loss via uncoupling mechanism and positive impact on the liver SkQ1 may be ideal candidate for the next-generation treatment of MASH. **Methods:** In our first study study, to examine the effects of SkQ1 in DIO rabbit model of obesity, female NZW rabbits were exposed to the high fat diet for circa 14 weeks. SkQ1 was administered orally at low, medium and high doses QD. GLP-1 agonist treatment was administered at 0.03 mg/kg subcutaneously once every three days. The treatment window was approximately 8 weeks. Animals were monitored daily for body wight and weekly for food intake. Rabbit plasma was analyzed for ALT/AST and lipid levels at the end of the study to assess liver function.

To evaluate the effect of SkQ1 in STAM model of MASH, male C57BL/6J mice were subcutaneously injected with a low dose of streptozotocin solution 2 days after birth and were fed with high fat diet after 4 weeks of age. SkQ1 was administered at the dose of 2 mg/kg BID for four weeks. **Results:** In DIO rabbit study, all SkQ1 treatments demonstrated significant dose-dependent weight loss in the first part of the experiment. At the highest dose SkQ1 monotherapy induced 27% weight loss in DIO rabbits over approximately nine weeks of treatment ($p < 0.001$). Plasma lipids were also significantly reduced pointing to normalization of liver function. In the second part of the experiment, we used GLP-1 agonist injections to induce rapid weight loss in DIO rabbits over the course of two weeks. After two weeks of GLP-1 treatment, GLP-1 treatment was withdrawn, and oral SkQ1 treatment was introduced instead. SkQ1 treatment was able to prevent weight re-gain normally occurring when GLP-1 treatment is stopped in animal models and in human patients.

In the STAM model study no weight loss was observed, as in that model MASH was induced in lean animals. The study demonstrated SkQ1-induced reduction of both steatosis and ballooning in the liver ($p < 0.05$ vs. vehicle for both), as well as reduction of the combined NAFLD activity score ($p < 0.01$ vs. vehicle). Interestingly, these effects were accompanied by a significant reduction in fibrosis grade in the liver ($p < 0.05$ vs. vehicle). **Conclusion:** The two studies highlighted SkQ1 potential as a candidate for next-generation treatment of obesity and comorbidities both as a monotherapy and in a combination with GLP-1 agonists.

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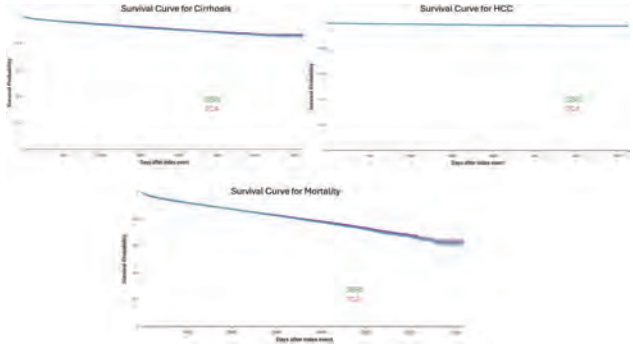
Disclosures: Anton Petrov: Mitotech Ltd: Employee, Maksim Skulachev: Nothing to Disclose, Ivan Senin: Nothing to Disclose

4063 | EVALUATING ANTIDEPRESSANT CHOICE: TCAS VS SSRIS IN MASLD PATIENTS WITH COMORBID MAJOR DEPRESSIVE DISORDER

Saad Ahmed[1], [1]Northwell Health NS-LIJ

Background: MASLD has been on the rise in recent years and it's link to diabetes, hypertension, and obesity is well known. However, depression is also noted to be prevalent among patients with MASLD. Specifically, it is estimated that 20% of patients with MASLD also suffer from MDD. SSRIs have long been established as the first line treatment for patients with MDD. Morever, there is evidence TCAs play a role in mitigating liver fibrosis. However, the literature is sparse in comparing the effect of TCAs and SSRIs for patients with MASLD and MDD. Thus, our project examined the effects of each class of these medications in patients with both MASLD and MDD in progression to cirrhosis, HCC, and mortality. **Methods:** This was a retrospective cohort study conducted using the TriNetX database and the US Collaborative Network, which includes healthcare information records from 60 healthcare organizations. Two cohorts were generated for patients with both MASLD and MDD and they were assigned to a group with treatment with either SSRIs or TCAs. These cohorts were propensity matched to age of diagnosis, sex, race, and metabolic comorbidities of hyperlipidemia, hypertension, and obesity. This generated two cohorts each with 291,573 patients and were examined for risk and Kaplan-Meier analysis. **Results:** At the end of the 20 year period, 10,030 patients in the TCA group (3.7%) and 11,076 in the SSRI group (4%) experienced cirrhosis. This corresponded to a risk difference of 0.3% ($p = 0$) with a risk ratio of 0.906 (95% CI 0.882, 0.930). Next, 1,361 patients in the TCA group (0.5%) and 1,484 patients in the SSRI group (0.05%) advanced to HCC. The risk ratio was 0.917 (95% CI 0.852, 0.987). Lastly, 26,270 patients in the TCA group (9%) and 27,044 in the SSRI group (9.2%) experienced mortality. This yielded a risk difference of 0.2% ($p = 0$) and a risk ratio of 0.972 (95 CI 0.956, 0.987). **Conclusion:** We found the use of TCAs was associated with a lower risk of progression to cirrhosis, HCC, and overall morality when compared to SSRI use. Although these differences were not robust, they were significant. It is thought the increased serotonergic effects of SSRIs can contribute to lipogenesis and hepatic steatosis. SSRIs have also thought to be associated with increased mitochondrial dysfunction and generation of reactive oxygen species. Similarly, TCAs may reduce liver fibrosis due to optimizing endoplasmic reticulum functioning and autophagy. This is consistent with other studies, including one that found TCAs can reduce liver fibrosis in patients with Hepatitis C when compared to SSRI use. Ultimately, our study is unique as we compared the effects of TCAs and SSRIs for patients with MASLD and MDD. Further investigation should be done to explore the mechanism of these findings. More weight should be given to using TCAs for such patients, especially when SSRIs are intolerable, while balancing side effect profiles.



Disclosures: Saad Ahmed: Nothing to Disclose

4064 | SUPERIOR HEPATOPROTECTIVE EFFECTS OF OPK-88006, A NOVEL GLP-1/GLUCAGON RECEPTOR DUAL AGONIST, TO SEMAGLUTIDE AND SURVODUTIDE IN THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF MASH

Jacob Nøhr-Meldgaard[1] Michael Feigh[2] Jane Hsiao[3] Kristian Pedersen[1] Susanne Pors[1] Martin Rønn Madsen[1] Grzegorz Maciag[1] Miri Gerzon-Zakar[3] Tony Cruz[3] Amit Rivkin[3] Laura Moschcovich[3], [1]Gubra A/S, [2]Gubra, [3]Opko Health Inc.

Background: OPK-88006, a novel GLP-1/Glucagon receptor dual agonist, is in preclinical development for metabolic disease including obesity and metabolic dysfunction-associated steatohepatitis (MASH). The present study aimed to investigate the therapeutic benefits of OPK-88006 on metabolic, bichemical, histopathological and transcriptome profile in the translational Gubra Amylin NASH (GAN) diet-induced obese and biopsy-confirmed mouse model of MASH with liver fibrosis. The late-stage clinical candidates semaglutide (GLP-1) and survodutide (GLP-1/Glucagon) for the treatment of patients with MASH and liver fibrosis, were included for comparison. **Methods:** Male C57BL/6 mice were fed the GAN diet high in fat, fructose and cholesterol for 38 weeks prior to study start. A liver pre-biopsy was collected 4 weeks before treatment start. Only GAN DIO-MASH mice

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with biopsy-confirmed NAFLD Activity Score (NAS ≥ 5) and moderate/advanced fibrosis (stage F2-F3) were included and stratified into treatment groups (n = 16-18 per group). Mice were administered once daily subcutaneous vehicle, semaglutide (30 nmol/kg), survodutide (10 (low) and 15 (high) nmol/kg) and OPK-88006 (10 (low) and 20 (high) nmol/kg) for 12 weeks. Histopathological pre-to-post individual assessment of NAS and fibrosis stage was performed. Other terminal endpoints included quantitative liver histology, blood and liver biochemistry in addition to RNAsequencing-Bioinformatic analysis. **Results:** GAN DIO-MASH mice demonstrated robust vehicle-corrected weight loss of approx. 12%, 24% and 26% after 12 weeks of OPK-88006 (high), semaglutide and survodutide (high) treatment, respectively. All treatments similarly improved hepatomegaly, plasma transaminases and plasma lipids levels. All treatments promoted a 1-point significant improvement in NAS, predominantly driven by reduction in steatosis score, albeit only OPK-88006 induced 2-point significant improvement in NAS. Benefits on NAS were supported by quantitative liver histology on steatosis (hepatocytes with lipids, liver lipids) and marker of inflammation (galectin-3). No treatments improved fibrosis stage, however reduced markers for fibrosis (TIMP-1 PIIINP) and hepatic stellate activation (α-SMA), indicating effect on fibrogenesis. Finally, all treatments induced significant gene regulation and suppressed genes involved in extracellular matrix and inflammation pathways. **Conclusion:** OPK-88006 treatment improved metabolic, biochemical and histopathological parameters of MASH, including hepatic transcriptomic profile, in the GAN DIO-MASH mouse model. Notably, OPK-88006 treatment improved NAFLD Activity Score superior to late-stage clinical candidates semaglutide and survodutide, introducing OPK-88006 as a promising treatment for MASH.

Disclosures: Jacob Nøhr-Meldgaard: Nothing to Disclose, Michael Feigh: Nothing to Disclose, Jane Hsiao: Nothing to Disclose, Kristian Pedersen: Gubra A/S: Employee, Susanne Pors: Nothing to Disclose, Martin Rønn Madsen: Nothing to Disclose, Grzegorz Maciag: Nothing to Disclose, Miri Gerzon-Zakar: Nothing to Disclose, Tony Cruz: Nothing to Disclose, Amit Rivkin: Nothing to Disclose, Laura Moschcovich: Nothing to Disclose

4065 | TREATMENT WITH SGLT2 INHIBITORS IS ASSOCIATED WITH A REDUCTION IN ESOPHAGEAL AND GASTRIC VARICES IN PATIENTS WITH CIRRHOSIS

Siham Abdelgani[1] Sasha Tverski[1] Oren Shibolet[1] Helena Katchman[1], [1]Tel-Aviv Sourasky Medical Center, Faculty of Medicine, Tel-Aviv University

Background: Clinically significant portal hypertension (CSPH) is associated with substantial morbidity and mortality. Currently, only nonselective beta-blockers have been shown to reduce portal pressure. Recent reports suggest that sodium-glucose cotransporter 2 (SGLT2) inhibitors may have a beneficial effect on portal hypertension. **Methods:** We aimed to evaluate the effect of SGLT2 inhibitors on esophageal and gastric varices as a surrogate marker for portal hypertension.

We retrospectively reviewed the medical records of cirrhotic patients followed in our Liver Unit between 2016 and 2025. Forty-three patients who met the Baveno VII criteria for CSPH (liver stiffness > 15 kPa and platelet count $< 150 \times 10^9$/L) were included. Of these, 28 patients were treated with SGLT2 inhibitors for various indications, while 15 served as matched controls without treatment. Thirty-six participants underwent at least two surveillance endoscopies. Data were analyzed using SPSS version 27. **Results:** The majority of patients had cirrhosis due to metabolic-associated steatohepatitis (MASH). The mean follow-up period was four years. The treatment and control groups were comparable in terms of cirrhosis severity and beta-blocker use (60%), with a mean age of 66 years and BMI of 27. The SGLT2 group had higher rates of diabetes (96% vs. 73%), chronic kidney disease (42% vs. 13%), and GLP-1 receptor agonist use (67% vs. 33%). Variceal ligation was performed in 9 patients (32%) in the treatment group and 4 patients (26%) in the control group.

Esophageal or gastric varices were present in 15 of 28 patients (53%) in the treatment group, compared to 11 of 15 (73%) in the control group (p = NS). Treatment with SGLT2 inhibitors was associated with either stability or a reduction of at least one grade in varices in 21 patients (95.5%) versus 7 patients (50%) in the control group (p = 0.03). Variceal progression occurred in only 1 patient (4.5%) in the SGLT2 group compared to 7 patients (50%) in the control group (p = 0.03). The risk of variceal progression was significantly higher in the control group (OR = 20.8; 95% CI, 2.1–200). **Conclusion:** We demonstrated that SGLT2 inhibitors treatment in cirrhotic patients was associated with improvement or stabilization of esophageal and gastric varices, suggesting a potential reduction in portal hypertension. A prospective interventional trial is warranted to validate these findings and further explore the underlying mechanisms

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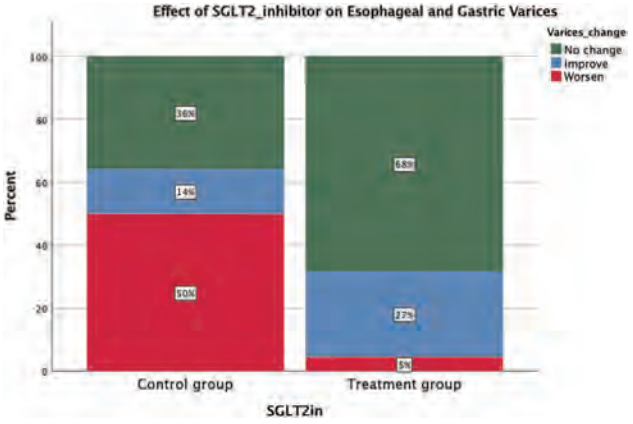

Disclosures: Siham Abdelgani: Nothing to Disclose, Sasha Tverski: Nothing to Disclose, Oren Shibolet: nonvonordisk: Advisor, roche: Speaking and Teaching, Helena Katchman: Nothing to Disclose

4066 | SHARED AND DISTINCT PATHWAYS IN STEATOTIC LIVER DISEASE SUBCATEGORIES: UNVEILING THE ROLE OF GUT HORMONES

Sundararajan Mahalingam[1] Ramesh Bellamkonda[1] Ojeshvi Ethiraj[1] Srilaasya Nedunoori[1] Carol Casey[1] Kusum Kharbanda[2] Karuna Rasineni[1], [1]University of Nebraska Medical Center, Omaha, NE, [2]Veterans Affairs Nebraska-Western Iowa Health Care System, Omaha, NE

Background: Steatotic liver disease (SLD) affects more than 35% of the global population and is primarily driven by obesity, chronic alcohol use, or a combination of both. While the pathophysiological mechanisms of metabolic dysfunction-associated liver disease (MASLD) and alcohol-associated liver disease (ALD) are relatively well-characterized, a critical gap exists in our understanding of metabolic and alcohol-associated liver disease (MetALD). This emerging condition results from the co-occurrence of diet-induced obesity and alcohol consumption. Understanding its distinct pathological mechanisms and potential therapeutic targets is crucial. Leveraging our expertise in differentiating MASLD and ALD and our knowledge of the role of gut hormones in ALD, this study aimed to distinguish the shared and unique pathological mechanisms among these three SLD subcategories, with a particular focus on gut hormones and organ crosstalk. **Methods:** We established experimental mouse models for MetALD (Western diet (ResearchDiets D12079B) + 15% alcohol in drinking water), ALD (chow diet + 15% alcohol in drinking water), and MASLD (Western diet + regular water). This feeding regimen was maintained for 16 weeks. At the end of the treatment, the animals underwent a 6-hour fast followed by a glucose tolerance test. The next day, the animals were euthanized, and blood and tissue samples were collected for further analysis. **Results:** Despite histological similarities, we identified key differences in metabolism-related events between these SLD subcategories, particularly in hormone levels. Mice in the MASLD group exhibited high serum insulin and low levels of two gut hormones, GLP-1 and ghrelin, whereas the ALD group showed the opposite pattern. Differences were also observed in hepatic methionine metabolism between these two models. Additionally, increased adipose lipolysis was observed only in the ALD group. Interestingly, mice with MetALD displayed higher insulin resistance and more pronounced liver inflammatory changes compared to those with MASLD or ALD. Moreover, MetALD mice showed increased serum levels of ghrelin and GLP-1, characteristics typically associated with chronic alcohol consumption. Unique features such as apoptosis and cell death were observed only in MetALD mice. **Conclusion:** These findings strongly suggest that MetALD pathogenesis is influenced by a complex interplay of shared and unique pathways from both ALD and MASLD. This underscores the need for targeted research to develop effective treatments for MetALD.

Disclosures: Sundararajan Mahalingam: Nothing to Disclose, Ramesh Bellamkonda: Nothing to Disclose, Ojeshvi Ethiraj: Nothing to Disclose, Srilaasya Nedunoori: Nothing to Disclose, Carol Casey: Nothing to Disclose, Kusum Kharbanda: Nothing to Disclose, Karuna Rasineni: Nothing to Disclose

4067 | PATIENT CHARACTERISTICS AND TREATMENT PATTERNS AMONG PATIENTS USING RESMETIROM IN THE REAL-WORLD SETTING

Meena Bansal[1] Andrew Rava[2] Cynthia Gutierrez[2] Haiyan Sun[2] Damon Van Voorhis[2] Joanna MacEwan[2] Liana Bruce[2] Nipun Atreja[3] Francis Lobo[3] John O'Donnell[3], [1]MASH/NASH Center of Excellence, Icahn School of Medicine, [2]Genesis Research Group, [3]Madrigal Pharmaceuticals, Inc.

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) involves hepatic steatosis with inflammation and hepatocellular injury, often progressing to fibrosis. In March 2024, the United States (US) Food & Drug Administration approved resmetirom as the first therapy for MASH patients with moderate to advanced liver fibrosis. Given its recent approval, real-world evidence on resmetirom use remains limited. This analysis describes US patients prescribed resmetirom and their treatment patterns following initiation. **Methods:** This was a descriptive, retrospective analysis of adults with ≥ 1 paid claim for resmetirom (first paid claim = index date) on or after 3/14/2024 in the Optum® de-identified Market Clarity data (study period: 3/14/2023–12/31/2024). Patients in the 12-month pre-index period coded with cirrhosis-related complications, ≥ 1 diagnosis for non-MASH liver conditions, or heavy metal exposure were excluded. Baseline demographic and clinical characteristics were summarized. Treatment patterns, including duration; persistence; discontinuation (>45-day gap); restart; and adherence (proportion of days covered [PDC]) were described. **Results:** In total, 341 patients met study inclusion criteria. Results are presented in Table 1. Mean (SD) patient age was 60.6 yrs (12.5); 210 (61.6%) were female and 237 (69.5%) were White. Most patients had commercial insurance (39.6%) or Medicare (54.8%); only 5.6% were Medicaid beneficiaries. Based on BMI, 5.5% were normal/underweight, 15.3% were overweight, and 79.2% were obese. Mean (SD) BMI among the 78 patients with continuous BMI reported was 32.9 (6.5) kg/m^2. Almost half (46.9%) of patients had type 2 diabetes mellitus. Many (42.2%) patients used at least one GLP-1 during the baseline period and 61.9% used statins. Overall, 98.2% of patients were persistent. Over half (57.8%) had ≥ 3-month follow-up; of these, 97.0% remained persistent, and all who discontinued later restarted resmetirom. Mean (SD) PDC was 0.84 (0.24) at 3 months and 0.75 (0.30) at 6 months. **Conclusion:** This study provides an early look at real-world resmetirom use in the US. Half of the patients treated with resmetirom were obese, and nearly half had diabetes. Adherence was high, with most patients remaining persistent for at least three months. Future studies with longer follow-up are needed to evaluate clinical outcomes in real-world resmetirom users.

Table 1. Baseline demographics and clinical characteristics

	Resmetirom Cohort (N = 341)
Baseline Demographic Characteristics	
Age, years	
Mean (SD)	60.6 (12.5)
Sex, n (%)	
Female	210 (61.6)
BMI, continuous, kg/m^2	
Mean (SD)	32.9 (6.5)
Comorbidities	
Obesity, n (%)	176 (51.6)
Type 2 diabetes mellitus, n (%)	160 (46.9)
Baseline MASH Treatments	
GLP-1s	
Any GLP-1, n (%)	144 (42.2)
Semaglutide 2.4 mg (Wegovy®), n (%)	12 (3.5)
Semaglutide (Ozempic®)[1], n (%)	79 (23.2)
Statins	211 (61.9)
Treatment Patterns During Follow-up	
Duration of resmetirom treatment (days, PPPM)	
Mean (SD)	25.1 (8.1)
Duration of follow-up	
≥1 month, n (%)	295 (86.5)
≥3 months, n (%)	197 (57.8)
≥6 months, n (%)	54 (15.8)
Persistence	
1 month, n (%)	290 (98.3)
3 months, n (%)	191 (97.0)
6 months, n (%)	53 (98.2)
Resmetirom discontinuation	
1 month, n (%)	5 (1.7)
3 months, n (%)	6 (3.1)
6 months, n (%)	1 (1.9)
Resmetirom restart[2]	
1 month, n (%)	5 (100.0)
3 months, n (%)	6 (100.0)
6 months, n (%)	1 (100.0)
PDC	
1 month, (Mean [SD])	1.00 (0.00)
3 months, (Mean [SD])	0.84 (0.24)

Disclosures: Meena Bansal: Nothing to Disclose, Andrew Rava: Nothing to Disclose, Cynthia Gutierrez: Nothing to Disclose, Haiyan Sun: Nothing to Disclose, Damon Van Voorhis: Nothing to Disclose, Joanna MacEwan: Nothing to Disclose, Liana Bruce: Nothing to Disclose, Nipun Atreja: Madrigal Pharmaceuticals: Employee, Immunovant: Employee, Bristol Myers Squibb: Employee, Francis Lobo: Madrigal Pharmaceuticals: Employee, John O'Donnell: Nothing to Disclose

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4068 | ENHANCED SCREENING EFFICIENCY: OVER 90% PREVALENCE OF F2–F4 FIBROSIS IN PNPLA3 HOMOZYGOUS PARTICIPANTS WITH MASH IN THE AZD2693 FORTUNA PHASE 2B STUDY

Rohit Loomba[1] Atsushi Nakajima[2] Marco Arrese[3] Elisabetta Bugianesi[4] Linda Wernevik[5] Mathias Liljeblad[5] Weier Qi[6] Ola Fjellström[5] Anna Ramne[5] Anna Rudvik[6] Janeli Sarv[6] James Sherwood[7] Javier Armisen[7] Lars Hansen[6] Vincent Wong[8], [1]University of California, San Diego, [2]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [3]Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile, [4]University of Turin, Turin, Italy, [5]AstraZeneca, Gothenburg, Sweden, [6]AstraZeneca, Gaithersburg, USA, [7]AstraZeneca, Cambridge, UK, [8]The Chinese University of Hong Kong, Hong Kong

Background: High biopsy screen-failure rate to identify participants with significant fibrosis is common in metabolic dysfunction-associated steatohepatitis (MASH) clinical trials. AZD2693 is an anti-sense oligonucleotide designed to silence hepatic PNPLA3 mRNA expression under development for treating MASH with fibrosis. **Methods:** The FORTUNA Phase 2b study (NCT05809934) is designed to evaluate the safety, tolerability, and efficacy of AZD2693 in participants who have non-cirrhotic MASH with fibrosis and are homozygous for the *PNPLA3* 148M risk allele over a 52-week treatment period. Primary and secondary endpoints are the histological resolution of MASH without worsening of fibrosis and the improvement of histological fibrosis without worsening of MASH. **Results:** Out of 2479 participants screened, a total of 217 (9%) were randomized. Homozygous carriers eligible for biopsy (N = 363) had a mean (SD) age of 53 (13) years; 53% were female, mean (SD) BMI of 32 (6) kg/m^2 with 31% exhibiting type 2 diabetes and 54% with at least one associated cardiometabolic disease (e.g. hypertension, dyslipidemia). The main reason for screen failure (SF) was participants who were not homozygous carriers for the *PNPLA3* rs738409 148M risk allele, with a SF rate of 74%. Among the 363 biopsies from homozygous carriers, 5 (1%) had F0 and 30 (8%) had F1 fibrosis, while the remaining of the homozygous carriers (91%) had significant fibrosis (184 (51%) had F2; 111 (31%) had F3 and 34 (9%) had cF4). Overall SF due to biopsy criteria was 36%. **Conclusion:** In this study, homozygosity for the *PNPLA3* rs738409 148M risk allele enhanced clinical biopsy-screening efficiency for participants with significant F2–F4 fibrosis.

Disclosures: Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder, Atsushi Nakajima: Nothing to Disclose, Marco Arrese: Nothing to Disclose, Elisabetta Bugianesi: Nothing to Disclose, Linda Wernevik: Nothing to Disclose, Mathias Liljeblad: AstraZeneca: Employee, AstraZeneca: Stock - publicly traded company, Weier Qi: Nothing to Disclose, Ola Fjellström: AstraZeneca: ownership of AstraZeneca stocks, Anna Ramne: Nothing to Disclose, Anna Rudvik: AstraZeneca: Employee, Janeli Sarv: Nothing to Disclose, James Sherwood: Nothing to Disclose, Javier Armisen: Nothing to Disclose, Lars Hansen: Nothing to Disclose, Vincent Wong: Abbott: Speaking and Teaching, AbbVie: Consultant, Boehringer Ingelheim: Consultant, Echosens: Speaking and Teaching, Eli Lilly: Consultant, Gilead: Consultant, Gilead: Grant/Research Support, Intercept: Consultant, Inventiva: Consultant, Illuminatio Medical Technology: Stock – privately held company, Merck: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet: Consultant, TARGET PharmaSolutions: Consultant, Unilab: Speaking and Teaching, Visirna: Consultant, AstraZeneca: Consultant

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4069 | PRESCRIBING PATTERNS AND CLINICAL CHARACTERISTICS OF RESMETIROM RECIPIENTS: REAL-WORLD INSIGHTS

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[1]Virginia Commonwealth University

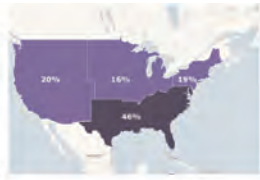
Background: Resmetirom was conditionally approved in March 2024 for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) with F2-F3. The aim of this study was to evaluate real-world prescribing patterns, patient characteristics, and early biochemical trends among adults initiated on resmetirom. **Methods:** Data were obtained from the TriNetX U.S. Collaborative Network, to identify adults prescribed resmetirom between 3/2024 and 4/2025. Data were extracted on demographics, diagnoses, procedures, medications, most recent laboratory values and vital signs recorded within the preceding 24 months. Changes in weight, BMI, and liver enzymes (ALT, AST) were assessed at baseline, 1–90 days, and beyond 90 days. Continuous variables were summarized using means with standard deviations (SD) or medians with interquartile ranges (IQR). Differences in repeated measures across timepoints were assessed using repeated measures ANOVA, with a p-value <0.05 considered statistically significant. **Results:** A total of 1,438 patients were prescribed resmetirom (mean age 57 $\pm$ 13 years); females were more prevalent in the 80 mg group (70%), while males predominated in the 100 mg group (57%) (Fig A). Most patients were White (74%) and geographically clustered in the southern U.S. (46%) (Fig B). The most common comorbidities included dyslipidemia (69%), hypertension (65%), obesity (64%), type 2 diabetes (49%). Co-prescription of GLP-1 receptor agonists was common, including semaglutide (27%) and tirzepatide (15%), with higher use in the 100 mg group.

ALT and AST levels increased modestly from baseline to 1–90 days (ALT: 49.7 $\rightarrow$ 58.4 U/L; AST: 40.5 $\rightarrow$ 44.8 U/L), followed by improvement beyond 90 days (ALT: 45.6 U/L; AST: 37.0 U/L). These changes were statistically significant (ALT: $p=0.03$; AST: $p=0.01$). In contrast, weight and BMI remained stable over time (baseline BMI: 33.9 $\pm$ 7.6; >90 days: 33.7 $\pm$ 7.5; $p=0.72$ for BMI, $p=0.89$ for weight) (Fig C). **Conclusion:** In this national real-world cohort, resmetirom was more frequently prescribed to females and individuals with cardiometabolic comorbidities. Frequent co-prescription with GLP-1 receptor agonists reflects integrated management of metabolic disease. A transient but statistically significant rise in liver enzymes was observed in the first 90 days, followed by improvement beyond 3 months, while anthropometric measures remained unchanged. Longer-term follow-up will be important to evaluate sustained biochemical response, weight trends, and treatment durability over time.

A

	All	80 mg	100 mg
Total patients	1438	819	555
Mean Age ± SD (years)	57 ± 13	59 ± 13	53 ± 13
Female	58.76%	69.8%	42.88%
Hispanic or Latino	21.35%	23.4%	18.28%
White	73.71%	69%	80.82%
Hypertensive diseases	65%	67%	62%
Disorders of lipoprotein metabolism	69%	70%	65%
Overweight and obesity	64%	57%	76%
Type 2 Diabetes mellitus	49%	50%	47%
CKD	10%	10%	10%
Ischemic heart diseases	18%	18%	17%
Semaglutide	27%	25%	30%
Tirzepatide	15%	12%	21%
Empagliflozin	12%	13%	11%
Dapagliflozin	5%	6%	5%
Insulin	23%	24%	23%
Levothyroxine	16%	15%	16%
Atorvastatin	32%	32%	30%
Rosuvastatin	20%	21%	18%
Ezetimibe	8%	9%	8%
Pravastatin	9%	10%	7%

B



C

	Baseline	1-90 days	> 90 days	P-value
Mean Follow up (Days)		69 ± 31	136 ± 102	
Weight (Mean, SD)	210 ± 55	211 ± 54	210 ± 56	0.89
BMI	34 ± 7.6	34 ± 7.4	33.7 ± 7.6	0.72
ALT	49.7 ± 34.8	58.4 ± 74.2	45.7 ± 33.3	0.03
AST	40.5 ± 24.2	44.8 ± 37.5	37 ± 23.3	0.01

Disclosures: Vinay Jahagirdar: Nothing to Disclose, Nothing to Disclose, Kaanthi Rama: Nothing to Disclose, Amon Asgharpour: Galectin: Clinical Endpoint Committee, NovoNordisk: Advisor, Madrigal: Advisor, Chronic Liver Disease Foundation: Speaking and Teaching, Intercept: Consultant, Richard Sterling: ABIM: GI Specialty Board, Abott: Grant/Research Support, AbbVie: Grant/Research Support, Roche: Grant/Research Support, GSK: Grant/Research Support, HCV Vax: Grant/Research Support, Gilead: Grant/Research Support, Zydus: Grant/Research Support, Vertex: Consultant, Madrigal: Advisor, Gigagen: Grant/Research Support, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Juan Pablo Arab: Nothing to Disclose

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4070 | SAFETY PROFILE AND ADVERSE EVENTS OF RESMETIROM: PHARMACOVIGILANCE ANALYSIS OF THE FDA ADVERSE EVENTS REPORTING SYSTEM (FAERS) DATABASE

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Background: Metabolic dysfunction associated steatohepatitis (MASH) is a leading cause of chronic liver disease contributing to the rise in cirrhosis, liver cancer and need for liver transplantation. While lifestyle modification to improve cardiometabolic risk factors remains foundational, it may be insufficient in those with advanced fibrosis. Resmetirom (Rezdiffra™), a selective thyroid hormone b-receptor agonist, is the first FDA-approved drug for patients with moderate-to-severe MASH without cirrhosis. In the phase 3 MAESTRO NASH, resmetirom was superior to placebo in MASH resolution and fibrosis improvement. Diarrhea and nausea were most frequent adverse events (AEs) compared to placebo. The incidence of serious AEs (SAEs) was similar across trial groups in the 80 mg, 100 mg and placebo group (10.9%, 12.7% and 11.5%, respectively). The aim of this study is to analyze the real-world reported AEs of resmetirom as compared to those in MAESTRO NASH. **Methods:** A retrospective analysis of the public FDA Adverse Events Reporting System (FAERS) Database of resmetirom use (March 14, 2024-March 31, 2025) and reported AEs attributable to its use was performed. **Results:** 390 AEs were reported with resmetirom, 294 (75%) non-serious, and 96 (25%) SAEs. The majority of reported AEs (93%) were solicited through a Sponsor-supported pharmacovigilance program. Consistent with the MAESTRO study results, the most common real-world treatment emergent AEs were nausea (23.1%) and diarrhea (18.2%). Elevations of aminotransferases and elevated bilirubin were observed in 19.5% and 6.7%, respectively. Of the SAEs, 29 (7.4%) were hospitalizations, 1 (0.3%) life-threatening, 1 (0.3%) requiring surgical intervention and 8 deaths [cause unknown (n = 4), liver failure (n = 1), sepsis with multi-organ failure (n = 2) and ventricular fibrillation (n = 1)] were reported. Three SAEs occurred in the setting of malignancies (pancreas, renal and liver). The liver-related death was attributed to off-label use of drug not in accordance with FDA label. **Conclusion:** To date, post-marking safety reporting of resmetirom (Rezdiffra™) suggests a safety profile comparable to that observed in the phase 3 MAESTRO study when prescribed in accordance with the FDA-approved label. To minimize the risk of SAEs, due diligence should be made in patient selection and risk stratification to exclude those with cirrhosis and/or other serious co-morbid conditions prior to prescribing resmetirom for patients with MASH.

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4071 | BEYOND THE LIVER,IMPACT OF MASLD TREATMENT ON SUBCLINICAL ATHEROSCLEROSIS AND CARDIOMETABOLIC RISK: A SYSTEMIATIC REVIEW AND META-ANALYSIS

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with elevated cardiovascular risk, but the impact of MASLD-targeted interventions on subclinical atherosclerosis and cardiometabolic risk markers remains unclear. Our systematic review and meta-analysis aimed to evaluate the impact of MASLD treatment on markers of subclinical atherosclerosis and cardiometabolic risk, synthesizing current evidence to inform clinical management. **Methods:** We conducted a systematic review and meta-analysis of randomized controlled trials and cohort studies assessing lifestyle or pharmacologic interventions for MASLD and reporting outcomes on subclinical atherosclerosis including carotid intima-media thickness(CIMT), pilse wave velocity(PWV), coronary artery calcium and/or cardiometabolic risk (e.g., HOMA-IR, blood pressure, lipid profile). Searches were run across five major databases and clinical trial registries through March 15, 2025. Data extraction, bias assessment (Cochrane RoB 2.0, Newcastle-Ottawa Scale), and synthesis followed PRISMA guidelines. Meta-analyses used random-effects models. **Results:** Out of 4,276 records, 38 studies (n = 5,422 participants) met inclusion criteria. Interventions included GLP-1 receptor agonists (8 studies), SGLT2 inhibitors (6), pioglitazone (9), omega-3 fatty acids (3), and lifestyle modifications (12). GLP-1 RAs significantly reduced CIMT (MD – 0.09 mm; 95% CI –0.13 to –0.05) and HOMA-IR (MD –2.3; 95% CI –3.0 to –1.6). Lifestyle changes and SGLT2 inhibitors showed similar benefits on HOMA-IR and lipid profiles, though SGLT2 data on atherosclerosis markers were less consistent. Table illustrates pooled effect sizes, MASLD therapies significantly improved markers of cardiovascular risk (see Table). Results were consistent across pharmacologic and lifestyle interventions, with GLP-1 RAs and SGLT2 inhibitors showing the most robust dual benefit. **Conclusion:** Our findings support the beneficial impact of MASLD-targeted interventions—especially GLP-1 RAs and lifestyle changes—on surrogate markers of cardiovascular risk. Improvements in CIMT, HOMA-IR, LDL-C, and systolic blood pressure suggest that integrated management of MASLD may concurrently mitigate early cardiovascular disease risk. Meta-regression highlighted baseline BMI and age as moderators of treatment effect. Publication bias was minimal, and GRADE certainty was rated moderate to high for primary outcomes. Further longitudinal and comparative trials are warranted to confirm these effects and guide clinical strategies targeting the hepatic-cardiovascular interface in MASLD.

Table 2. Pooled Effects of Interventions on Key Cardiometabolic Outcomes

Outcome	Intervention Type	No. of Studies	Mean Difference (95% CI)	I^2 (%)
Carotid Intima-Media Thickness (CIMT)	GLP-1 RAs	6	–0.09 mm (–0.13 to –0.05)	58
	SGLT2 inhibitors	4	–0.07 mm (–0.12 to –0.02)	61
	Lifestyle interventions	5	–0.05 mm (–0.09 to –0.01)	66
HOMA-IR	GLP-1 RAs	7	–2.3 (–3.0 to –1.6)	54
	SGLT2 inhibitors	5	–1.8 (–2.5 to –1.1)	63
	Lifestyle interventions	6	–1.5 (–2.1 to –0.9)	72
LDL Cholesterol (mg/dL)	GLP-1 RAs	5	–14.2 (–19.1 to –9.3)	49
	SGLT2 inhibitors	4	–11.6 (–17.0 to –6.1)	57
	Lifestyle interventions	6	–12.4 (–18.2 to –6.7)	60
Triglycerides (mg/dL)	Pharmacologic (mixed)	7	–15.9 (–22.4 to –9.4)	64
Systolic Blood Pressure (mmHg)	All interventions	9	–4.6 (–6.8 to –2.4)	52

CI: Confidence Interval; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; LDL: Low-Density Lipoprotein; RAs: Receptor Agonists; I^2: Heterogeneity index—source: Authors' Creations.

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4073 | EVALUATING THE EARLY REAL-WORLD IMPACT OF RESMETIROM IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH): A UNITED STATES COHORT STUDY USING ELECTRONIC MEDICAL RECORDS

Yestle Kim[1] John O'Donnell[1] Romina Fakhraei[2] Karissa Johnston[2] Rosie Sun[2] Melissa Bather[2] Yael Silberberg[3] Amit Sabban[3] Reem Mustafa[2] Michael Charlton[1] Robert Eisdorfer[3] Shira Reznik Balter[3] Rajagopal Chadalavada[4] Naim Alkhouri[5] Pradeep Bekal[4], [1]Madrigal Pharmaceuticals, [2]Broadstreet HEOR, [3]Latica, [4]Gastro Health, [5]Arizona Liver Health

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Background: Resmetirom (Rezdiffra™) is a thyroid hormone receptor β-selective agonist conditionally approved in the United States in March 2024 for the treatment of noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced fibrosis. This study describes baseline characteristics, medication use, and 6-month real-world effectiveness based on changes in non-invasive fibrosis markers among patients initiated on resmetirom in routine gastroenterology care. **Methods:** This retrospective cohort study used electronic medical records from the Latica real-world gastroenterology data repository. Adults with ≥1 prescription for resmetirom between January 2023 and April 2025 and ≥6 months of follow-up were included. The index date was the first recorded resmetirom prescription. Baseline characteristics were assessed during the 12 months prior to the index date. Demographics, comorbidities, medication use, and laboratory values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], platelet count, and Fibrosis-4 [FIB-4] index) were evaluated at baseline and at 6-month follow-up, where available. **Results:** Of 848 patients who initiated resmetirom, 347 (40.8%) had documented ≥6 months of follow-up and were included in the analysis. The median duration of pre-treatment data was 3.4 years (IQR: 0.7–7.3). The mean age was 59.1 years (SD: 12.5); nearly half were aged 45–64 and 15% were ≤44. The cohort was predominantly female (56%), from Florida (63%), and 41% identified as White. All patients had commercial insurance, and 43% were also Medicare enrollees. At baseline, mean BMI was 33.8 (SD: 6.5), with 69.5% classified as obese, 23.1% overweight, and 6.3% with BMI <25. The most common comorbidities were hypertension (71.2%), hyperlipidemia (65.1%), and type 2 diabetes (53.9%). At baseline, GLP-1RA use was observed in 23.3% of patients, with semaglutide being the most prescribed (11%). Thirteen percent of patients had concomitant GLP-1RA use that began prior to resmetirom initiation and continued through follow-up, most commonly with semaglutide (7%). Among those with values at baseline and follow-up, median AST declined from 32.0 to 28.5 U/L in statin users (n = 41) and from 44.0 to 32.0 U/L in non-users (n = 44). Similarly, ALT declined from 39.0 to 39.0 U/L in statin users and from 53.0 to 37.5 U/L in non-users. FIB-4 scores decreased from 1.8 to 1.6 (n = 32), while platelet counts remained stable (median 198.5 to 198.0, n = 38). **Conclusion:** In this real-world cohort, patients initiating resmetirom commonly had obesity, cardiometabolic comorbidities, and prior GLP-1RA use. Modest improvements in non-invasive fibrosis markers were observed over 6 months, supporting early real-world effectiveness of resmetirom in routine clinical practice. Ongoing follow-up and cohort expansion are needed to confirm long-term effectiveness.

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4074 | ANALYSIS OF BIOMARKERS PRO-C3 AND ELF COMPONENTS IN BASELINE MASH/MASLD AND MASH CIRRHOSIS PATIENTS; CORRELATIONS BETWEEN CHANGE IN PRO-C3 AND ELF IN RESMETIROM-TREATED PATIENTS FROM THE MAESTRO-NASH TRIAL

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Background: Resmetirom (RES) is approved for the treatment of adults with MASH and liver fibrosis by the accelerated approval pathway based on improvements in MASH and fibrosis. Non-invasive tests including ELF and PRO-C3 have been used to characterize fibrosis stage in MASH and predict liver outcomes. RES reduces ELF and its components P3NP and TIMP-1 but not hyaluronic acid (HA) ((N Engl J Med 2024;390:497-509). This study

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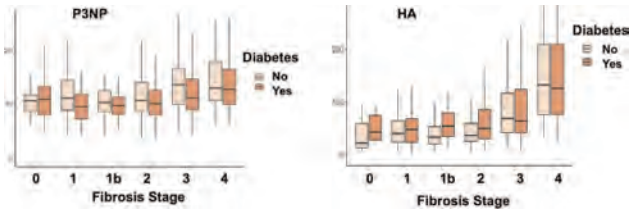
evaluated baseline ELF and its individual components, TIMP-1, P3NP and hyaluronic acid (HA) according to biopsy fibrosis stage; in MAESTRO-NASH (NCT03900429) correlations between baseline and Week-52 ELF/P3NP and PRO-C3 and the effect of RES compared with placebo (PBO) on PRO-C3 and P3NP/ELF were determined. **Methods:** ELF and ELF components were determined by a central laboratory in biopsy proven cohorts from MAESTRO-NASH and MAESTRO-NAFLD-1 (NCT04197479): F0 (N = 51), F1a/1c (N = 126), F1b (N = 126), F2 (N = 356), F3 (N = 540), and F4 (N = 107)). PRO-C3 analyses were assessed in MAESTRO-NASH F1b/F2/ F3 using the ELISA GEN2 assay. ANCOVA was used for comparisons between RES 80 or 100 mg vs. PBO in PRO-C3 and ELF change from baseline at week 52 (wk52CHG). Mean difference with 95% CI and nominal p-values were obtained from the ANCOVA. Scatterplots and Spearman's correlations with 95% CIs assessed P3NP/ELF and PRO-C3 both at baseline and wk52CHG. **Results:** In biopsy confirmed MASH, ELF increased from mean 9.4-9.6 (F0-F2), 10.0 (F3),10.6 (F4). Components TIMP1 and P3NP did not increase between F0 and F2, increased by 20% between F2 and F3/F4. HA was variable and higher in diabetics (F0 to F2) and increased 1.9 fold between F3 and F4, explaining the increase in ELF in F4 patients (Figure). Baseline P3NP and ELF were correlated with baseline PRO-C3 (0.563 and 0.458, respectively). At week 52, PRO-C3 wk52CHG for RES 100mg -23.05 (4.76), 80mg, -17.93 (4.61), PBO, -0.19, (4.07) with mean difference (95% CI) in PRO-C3 wk52CHG, 80mg and PBO, -16.9 (-27.0, -6.76), p = 0.0011; 100mg and PBO, -22.1 (-32.3, -11.84, p < 0.0001). Larger reductions in PRO-C3 mean (SD) in the RES arms were observed in F3 patients: 80 mg,-22.42 (6.38); 100mg, -27.42 (6.72); PBO, -0.50 (5.46). Wk52CHG in P3NP was positively associated with wk52CHG in PRO-C3, 0.557, 0.548 and 0.524 for 100mg, 80mg and PBO; respectively. A correlation was observed between wk52CHG for ELF and PRO-C3, 0.483, 0.484 and 0.487 for 100mg, 80mg and PBO, respectively.

Conclusion: The increase in ELF in F3/F4 patients is explained by the increase in HA, an extracellular matrix protein made outside the liver and cleared from blood by liver sinusoidal endothelial cells that are dysfunctional in F4. PRO-C3 and P3NP, markers of liver fibrosis, were correlated and significantly reduced by RES vs PBO; the reduction was more pronounced in F3 patients. Evaluation of changes in ELF with treatment should include assessment of individual ELF components.



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4075 | COMPARATIVE EFFECTIVENESS OF LIRAGLUTIDE VERSUS SEMAGLUTIDE ON CLINICAL OUTCOMES IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH): A REAL-WORLD TWO-YEAR RETROSPECTIVE COHORT STUDY

Aditya Sood[1] Nathaniel Herman[2] Stephanie Chain[1] Saad Ahmed[1] Alex Chang[3] Sanjaya Satapathy[1], [1]Northwell, New Hyde Park, NY, [2]Stony Brook School of Medicine, [3]Brown University

Background: Real-world data directly comparing clinical outcomes of Liraglutide and Semaglutide in patients with MASH over extended follow-up periods remain limited. **Aim:** To compare 1- and 2-year risks of major adverse liver outcomes (cirrhosis, hepatocellular carcinoma [HCC], mortality) and safety events (pancreatitis, gallbladder/biliary disease) among MASH patients initiating Liraglutide vs. Semaglutide. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network, a large U.S. electronic medical record database. Adults with MASH (ICD-10: K75.81), confirmed by imaging (e.g., elastography) or liver biopsy, initiating Liraglutide (N = 697) or Semaglutide (N = 4,385) were identified. Propensity score matching (1:1, 696 pairs, 19 covariates) was performed. Outcomes were assessed at 1 and 2 years using logistic regression for risk ratios and Cox proportional hazards models for hazard ratios. This study used de-identified data, was exempt from IRB approval, and adhered to the Declaration of Helsinki. **Results:** After matching, no significant differences were observed between the Liraglutide and Semaglutide cohorts for any outcome. Two-year hazard ratios (HR [95% CI]) were: • Cirrhosis: HR 1.19 (0.73–1.93), $p = 0.45$. • HCC: HR 1.31 (0.47–3.69), $p = 0.997$. • Mortality: HR 1.23 (0.55–2.75), $p = 0.465$. • Pancreatitis: HR 1.01 (0.41–2.48), $p = 0.555$. • Gallbladder/biliary disease: HR 0.86 (0.52–1.44), $p = 0.806$. One-year risk ratios and event counts were similarly non-significant across all outcomes. Time course was restricted to two years based on limitations on length of real-world semaglutide data availability. **Conclusion:** In this large, real-world cohort of MASH patients, initiation of Liraglutide or Semaglutide was associated with comparable 1- and 2-year risks of cirrhosis, HCC, mortality, and key safety events. These findings suggest that short-term choice between these GLP-1 receptor agonists may be guided more by individualized clinical factors rather than differential risk of hepatic or safety outcomes.

Table: Comparative Risk of Clinical Outcomes in MASH Patients Treated with Liraglutide vs. Semaglutide

Outcome	1-Year Risk Ratio (95% CI)	p-value	2-Year Hazard Ratio (95% CI)	p-value	Event Count (Lira vs. Sema)
Cirrhosis	1.20 (0.67–2.15)	0.758	1.19 (0.73–1.93)	0.450	38 vs. 29
Hepatocellular Carcinoma (HCC)	1.01 (0.42–2.40)	0.989	1.31 (0.47–3.69)	0.997	<10 vs. <10
All-Cause Mortality	1.00 (0.42–2.38)	0.997	1.23 (0.55–2.75)	0.465	15 vs. <10
Acute Pancreatitis	1.03 (0.43–2.45)	0.951	1.01 (0.41–2.48)	0.555	<10 vs. <10
Gallbladder/Biliary Disease	0.80 (0.42–1.53)	0.497	0.86 (0.52–1.44)	0.806	29 vs. 29

Disclosures: Aditya Sood: Nothing to Disclose, Nathaniel Herman: Nothing to Disclose, Stephanie Chain: Nothing to Disclose, Saad Ahmed: Nothing to Disclose, Alex Chang: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support

4076 | PRESCRIBING PATTERNS OF GLP-1 RA ACROSS STEATOTIC LIVER DISEASE PHENOTYPES

Natalia Salinas Parra[1] Dilara Hatipoglu[1] David Kaplan[2] Nadim Mahmud[1], [1]Hospital of the University of Pennsylvania, [2]University of Pennsylvania

Background: Glucagon-like peptide-1 receptor agonists (GLP-1RA) have emerged as valuable therapeutic options for weight loss and metabolic comorbidities. Real-world utilization has not been studied in patients with cirrhosis under the new steatotic liver disease (SLD) nomenclature, which includes MASLD, MetALD, and ALD. Understanding prescribing patterns is valuable as patients with MetALD may benefit from GLP-1RA but may not be managed accordingly. We investigated the independent effect of SLD phenotype on GLP-1RA prescription in a national cohort of patients

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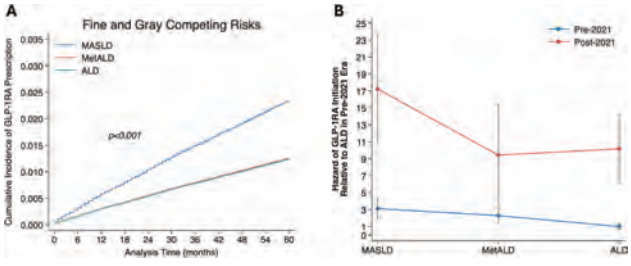
with cirrhosis in the Veteran's Health Administration (VHA). **Methods:** This was a retrospective cohort study in adult patients with incident cirrhosis related to MASLD, ALD, or MetALD, identified using established algorithms; the date of cirrhosis diagnosis was the index date. Those with prior GLP-1RA prescriptions were excluded. Demographic, body mass index, comorbidity data, and all GLP-1RA prescriptions in the VHA were obtained. Adjusted Fine and Gray competing risk regression and cause-specific hazards models were fit to evaluate cumulative incidence and the independent association between SLD phenotype and GLP-1RA prescription, treating death as a competing event (Figure panel A). An interaction between SLD phenotype and era (pre/post 2021) was also evaluated. **Results:** A total 97,357 patients were included. Of these, 58.4% had MASLD, 28.4% had ALD, and 13.2% had MetALD. Patients were predominantly male and white. Diabetes was more prevalent in MASLD (69.8%) and MetALD (70.8%) versus ALD (40.9%). Over a median follow-up time of 33.5 months (IQR 9.7, 71.1), 3,710 patients were newly initiated on GLP-1RA agents. In Fine and Gray models adjusted for *a priori* confounders, patients with MASLD had a significantly higher cumulative incidence of GLP-1 RA initiation through 5 years ($p < 0.001$), around 2.3%, versus MetALD and ALD at approximately 1.2%. In cause-specific hazards models, MASLD patients were significantly more likely to receive GLP-1 RA medications (HR 1.79, 95% CI 1.60-2.01) relative to ALD patients; there was no difference in MetALD versus ALD patients (HR 0.94, 95% CI 0.82-1.09). There was a significant interaction between SLD phenotype and era ($p < 0.001$), with MASLD patients more likely to receive GLP-1RA prescription post-2021 relative to other SLD phenotypes (Figure panel B). **Conclusion:** In this large VA cohort, overall GLP-1RA utilization was low among patients with cirrhosis and SLD. Patients with MASLD had higher GLP-1RA use than those with MetALD or ALD. Despite the substantial metabolic burden of patients with MetALD, they are no more likely than patients with ALD to be initiated on GLP-1RA. Notably, the era effect post-2021 following expanded FDA indications for GLP-1RA for weight loss was associated with increased relative GLP-1RA use in MASLD versus ALD.



Disclosures: Natalia Salinas Parra: Nothing to Disclose, Dilara Hatipoglu: Nothing to Disclose, David Kaplan: AstraZeneca Inc: Grant/Research Support, Roche Genentech: Independent Contractor, Exact Sciences: Grant/Research Support, Glycotest: Grant/Research Support, Sirtex: Advisor, Exelixis: Advisor, AstraZeneca: Advisor, Gilead: Grant/Research Support, Nadim Mahmud: Grifols: Grant/Research Support

4077 | GLP-1 RECEPTOR AGONIST THERAPY REDUCES FIB-4 INDEX IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Anderson Huang[1] Jonathan Weng[1] Tamiru Berake[1] Sarah Chen[1] Brian Yan[1] Raffi Karagozian[1], [1]Tufts Medical Center

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects one-third of the global population and is a prominent driver of liver-related morbidity. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated potential in improving MASLD-related outcomes, including lowering liver enzyme levels, reducing intrahepatic fat content, and improving histologic features of steatohepatitis. However, their effect on hepatic fibrosis remains unclear. This study aims to evaluate the impact of GLP-1 RA therapy on liver fibrosis, utilizing the validated fibrosis-4 (FIB-4) index as a non-invasive marker of fibrosis severity. **Methods:** In this retrospective cohort study, we identified patients diagnosed with MASLD who were treated with GLP-1 RAs at a large academic medical center between 2020 and 2024. Inclusion criteria consisted of a baseline FIB-4 index of 1.3 or greater—indicating at least intermediate risk for hepatic fibrosis—and at least two GLP-1 RA prescriptions within a 90-day window. Patients with cirrhosis or alcohol use disorder were excluded. FIB-4 index was calculated as: (Age [yr] × AST [U/L]) / (platelets [K/mcL] × (ALT [U/L]) ^ 0.5). Values were collected at treatment initiation and 12 months later. One-tailed paired *t*-tests were performed to test for a post-treatment reduction in FIB-4 index. We similarly assessed differences in the secondary outcomes, which included the components of the FIB-4 index, body mass index (BMI), and hemoglobin A1c (A1c). **Results:** Of 229 MASLD patients exposed to GLP-1 RAs, 29 had a baseline FIB-4 index of 1.3 or greater. At GLP-1 RA initiation, the mean age was 62.0 years and mean BMI was 37.5 kg/m^2. GLP-1 RAs were prescribed for type 2 diabetes in 18 patients (62%) and for obesity in 11 patients (38%). At 12 months, mean FIB-4 index decreased by 0.21 (95% CI, -0.38 to -0.05; $p = 0.019$). Significant reductions were also observed in AST (-15.8 U/L), ALT (-21.9 U/L), BMI (-2.6 kg/m^2), and A1c (-1.1%; all $p < 0.001$) (Table 1). **Conclusion:** In MASLD patients with at least intermediate risk for hepatic

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fibrosis, GLP-1 RA therapy was associated with a significant reduction in FIB-4 index over one year, alongside improvements in liver enzymes, weight, and glycemic control. These findings support a potential antifibrotic role for GLP-1 RAs.

Table 1. Mean values of primary and secondary outcomes at baseline and after 12 months of GLP-1 RA therapy. Abbreviations: SD, standard deviation; CI, confidence interval.

	Pre-exposure (SD)	Post-exposure (SD)	Difference (95% CI)	P-value
FIB-4	1.94 (0.61)	1.73 (0.62)	-0.21 (-0.38, -0.05)	0.019
AST (U/L)	48.9 (22.4)	33.1 (17.4)	-15.8 (-22.3, -9.3)	< 0.001
ALT (U/L)	60.3 (34.3)	38.4 (27.0)	-21.9 (-30.8, -13.0)	< 0.001
Platelets (K/mcL)	212.2 (51.1)	215.3 (57.6)	3.1 (-4.9, 11.1)	0.742
BMI (kg/m^2)	37.5 (7.0)	34.9 (6.8)	-2.6 (-3.7, -1.5)	< 0.001
A1c (%)	7.4 (1.8)	6.3 (1.0)	-1.1 (-1.5, -0.6)	< 0.001

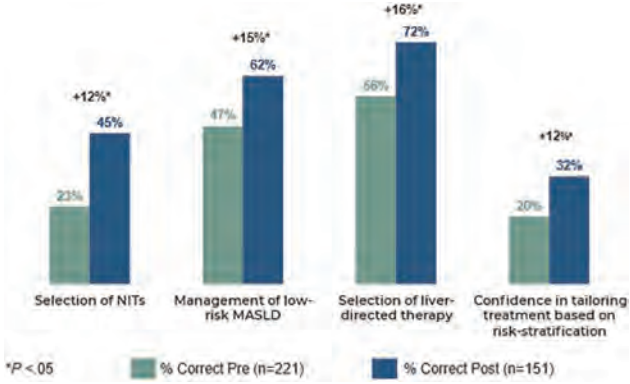
Disclosures: Anderson Huang: Nothing to Disclose, Jonathan Weng: Nothing to Disclose, Tamiru Berake: Nothing to Disclose, Sarah Chen: Nothing to Disclose, Brian Yan: Nothing to Disclose, Raffi Karagozian: Nothing to Disclose

4078 | ONLINE CERTIFIED MEDICAL EDUCATION IMPROVED COMPETENCE AND CONFIDENCE IN MANAGING METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Shari Dermer[1] Briana Betz[1] Julie Schrand[1], [1]Medscape Education

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a common cause of liver disease whose prevalence is increasing along with the rise in metabolic syndrome. The aim of this study was to examine the role of case-based online continuing medical education (CME) on competence and confidence in risk stratification and treatment selection for patients with MASH. **Methods:** Learners participated in an online activity on MASH that featured video and synchronized slides. A repeated pairs pre-/post-assessment study included 3 multiple choice competence questions and a confidence assessment question. Chi-squared test ($P < .05$) assessed educational effect. The educational activity launched on May 31, 2024, and data were collected on May 15, 2025. **Results:** We report on data from gastroenterologists/hepatologists (n = 221 pre; n = 151 post) who participated in the online CME activity. Among these learners 40% self-reported as practicing in hepatology. Data are presented as % pre vs %post education.

- Selection of noninvasive tests (NITs) to identify patients with liver fibrosis increased by 12% following education (23% pre/45% post; $p < .05$)
- Evidence-based management of patients at low risk of MASH as determined by FIB-4 and VCTE increased by 15% after education (47% pre/62% post; $p < .05$)
- Selection of evidence-based liver-directed treatment for patients with MASH increased by 16% (56% pre/72%; $p < .05$)
- 12% had a measurable increase in confidence in tailoring MASLD/MASH management strategies based on patients' risk factors (20% pre/32%; $p < .05$). **Conclusion:** Online case-based CME resulted in increased competence and confidence regarding the risk stratification and management of MASH. The results from this study also indicate that gastroenterologists and hepatologists would benefit from additional education to help improve the care of individuals with MASH.



Disclosures: Shari Dermer: Nothing to Disclose, Briana Betz: Nothing to Disclose, Julie Schrand: Nothing to Disclose

4079 | THE LIPID SYNTHESIS INHIBITORS ACC (FIRSOCOSAT) AND DGAT2 (ERVOGASTAT) REDUCE TRIGLYCERIDE CONTENT INDEPENDENTLY, BUT ONLY ERVOGASTAT ALSO REDUCES FIBROSIS BIOMARKERS IN HUMAN LIVER SPHEROIDS

Francisco Verdeguer[1] Philipp Vonschallen[1] Jesus Glaus[1] Radina Kostadinova[1] Joel Zvick[1], [1]InSphero

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive severe disease characterized by hepatic lipid accumulation, inflammation, and fibrosis which lacks any approved drug therapy. Novel approaches to identify therapeutic candidates that predict clinical responses are needed. Human pre-clinical models, including organoids/spheroids, are powerful models for drug testing and discovery. Pre-clinical models combining fast, robust, high-throughput compatible and predictive outputs are still a limiting factor to identify novel clinical therapies. We aimed at performing a comparison of the efficacy of existing clinical

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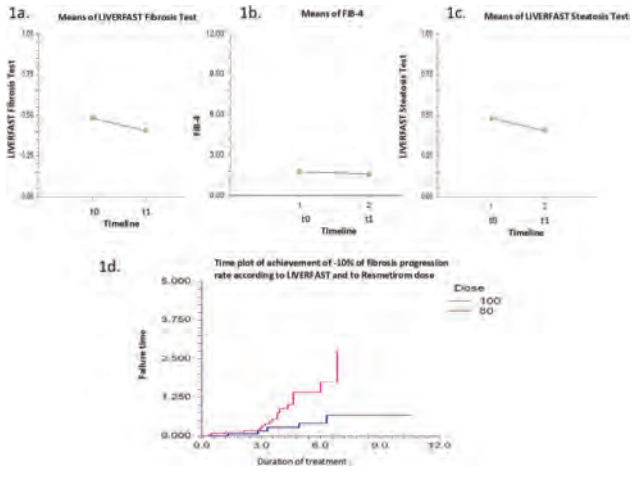
candidates for MASH using a human-derived 3D spheroid model. **Methods:** We used human-derived 3D spheroid model, containing primary human hepatocytes, Kupffer cells, liver endothelial cells, and stellate cells from healthy donors to induce a MASH phenotype. We screened simultaneously for the toxicity and MASH efficacy of 20 current clinical candidates in a dose-dependent manner. We selected secreted lactate dehydrogenase (LDH), intracellular triglycerides (TGs) and secreted pro-collagen 1 (PC-1) as surrogate markers of cytoxicity, steatosis and fibrosis. LDH was measured at day 3, 5, 7 and 10, TGs at day 10 and PC-1 at day 7 and 10. **Results:** Incubation with a MASH-inducing cocktail for 10 days lead to the recapitulation the main hallmarks of MASH including steatosis, and fibrosis by 10 fold increase of triglyceride levels and PC-1 secretion compared to healthy control. The DGAT2 inhibitor Ervogastat and ACC inhibitor Firsocostat did not show any significant elevation of LDH secretion. Both compounds showed a 25.3% (p-value < 0.01) and 35% decrease (p-value < 0.0001) of triglyceride content versus healthy control respectively. However, only Ervogastat showed a 24.8% reduction PC-1 at 6.3 micromolar (p-value < 0.05). **Conclusion:** We show a robust platform for MASH drug candidates and identify the DGAT2 inhibitor as a clinical candidate improving steatosis and fibrosis in human liver spheroid model. This data show that supressing steatosis would result in fibrosis prevention.

Disclosures: Francisco Verdeguer: InSphero: Employee, Philipp Vonschallen: Nothing to Disclose, Jesus Glaus: Nothing to Disclose, Radina Kostadinova: Nothing to Disclose, Joel Zvick: Nothing to Disclose

4080 | NONINVASIVE INITIATION AND MONITORING OF THE THERAPY WITH TNR-BETA AGONIST RESMETIROM (RT) USING LIVERFAST (LFAST), FIB-4 AND VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY (VCTE, FIBROSCAN) IN PATIENTS WITH MASH

Jeevin Sandhu[1] Shaheen Mehrara[2] Mona Munteanu[3] Mangesh Pagadala[4] Ashwini Mehta[5] Juan Manuel Munoz Perez[3] Obinna Okolo[6] Parker Woods[7] Parvez Mantry[2], [1]Methodist Dallas Medical Center, [2]Methodist Dallas Medical Center, Division of Hepatology, Dallas, United States, [3]Fibronostics, [4]Methodist Dallas Medical Center, Division of Hepatology, Dallas, TX, United States, [5]Methodist Dallas Medical Center, Division of Hepatology, Internal Medicine, Dallas, TX, United Stat, [6]Methodist Dallas Medical Center, Liver Institute, Dallas, TX, United States, [7]Methodist Dallas Medical Center, Liver Institute, Dallas, TX, United States

Background: The RT impact using non-invasive tests (NITs) in real-life patients has not been assessed. LFAST is a blood-based AI-test that generates scores (0.00-1.00) proportional to the severity of fibrosis (F), activity (A), and steatosis (S), useful for initiating and for monitoring RT. The aims were to assess the dynamic of LFAST, FIB-4 and VCTE in monitoring patients on RT [mean change and fibrosis progression rate (PR) from baseline to repeated NIT]. **Methods:** Patients on RT with baseline (t0) and repeated (t1) LFAST, VCTE and FIB4 have been included retrospectively. NITs dynamics have been assessed using Kaplan Meier non-parametric statistics censored at -10% PR occurrence from t0, Tukey-Kramer Multiple-Comparison Test (repeated measurements ANOVA), descriptive and subgroup analysis (dose and GLP-1 receptor agonists (GLP-1RA) analysis. **Results:** 86 patients have been eligible without RT discontinuation (61.4% 80mg-dose), 39% male, 47% T2D, 40% on GLP-1RA, mean(se) age 61.5(1.3), BMI 32.6(0.7), ALT 45(3), FIB4 1.78(0.14). Using LFAST and VCTE, the baseline prevalence of F2F3 were 63% and 44%. Median (max) delays (months) t0-to-t1 were 3.4 for LFAST and 2.23 for FIB4. 60% patients had t0-FIB4 ≥ 1.3 and 50 patients already had t1-FIB4, without significant change from t0 (1.75vs1.60, Fig.1b), ALT (45vs41)or AST (40vs36), platelets count (232vs241*109), all p = ns. In 9 patients with repeated VCTE there were no significant changes (9.2 vs 10.7KPa). 40 patients achieved t1-LFAST: median fibrosis (0.49 vs 0.39,$p < 0.001$, Fig 1a), steatosis (0.48 vs 0.40,$p < 0.05$, Fig. 1c), activity (0.42 vs 0.44,p = ns). The median (range) PR t0-to-t1 per month were: FIB4 -0.0007 (-9.8;1.5), LFAST fibrosis -0.02 (-0.79;0.23) and steatosis -0.005 (-1.33;0.17). LFAST fibrosis At 3.6months of RT, LFAST PR of -10% or lower from t0 has been achieved more. with the 80mg group than 100mg (54.6% vs 27.3%, Cox Mantel $P < 0.05$). (Fig 1d) Similar PR were observed with FIB-4 and LSTAT according to the GLP-1RA therapy. The significant decreases t0-to-t1 in total cholesterol have not impacted the Apolipoprotein A1 [132 vs 147mg/dl] or LFAST score. **Conclusion:** Initiation of RT based on assessment of patients using LFAST, FIB4 (fibrosis only) and VCTE is efficient and allows further non-invasive monitoring. A rapid trend in fibrosis and steatosis improvement was observed, mainly in the 80mg RT group. LFAST is an efficient monitoring tool not impacted by RT-induced drop in cholesterol.



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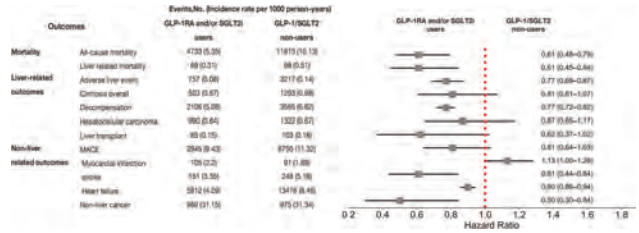
4081 | LOWER RISK OF NON-LIVER MORTALITY AND COMPLICATIONS IN GLP-1RA AND/OR SGLT2I USERS WITH MASLD: A SYSTEMIC REVIEW AND META-ANALYSIS

Jie Wang[1] Taotao Yan[1] Xiangrong Gao[1] Haruki Uojima[1] Michael Le[1] Ramsey Cheung[1] Mindie Nguyen[2],
[1]Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, Californ, [2]Stanford University Medical Center

Background: Metabolic dysfunction associated steatotic liver disease (MASLD) has become the leading cause of chronic liver disease worldwide. Glucagon-like peptide-1 receptor agonist (GLP-1RA) and sodium–glucose cotransporter-2 inhibitors (SGLT2i) have shown hepatoprotective signals such as improvement of liver enzymes, hepatic inflammation and fibrosis. However, data on their impact on long-term clinical events such as mortality (liver and non-liver related) as well as specific liver (e.g. cirrhosis, decompensation, hepatocellular carcinoma [HCC], liver transplant) and non-liver (e.g. cardiovascular, non-liver cancer) complications remain sparse. Using a systematic review and meta-analytic approach, we aimed to compare the risk of liver and non-liver related complications and mortality between GLP-1RA and/or SGLT2i users and their nonusers counterparts. **Methods:** We searched PubMed, Embase, Web of Science, Scopus, and Cochrane Library for studies reporting long-term adverse clinical outcomes of patients with MASLD who received GLP-1RA and/or SGLT2i and those who did not receive either medications from inception to Jan 23, 2025. Long-term adverse clinical outcomes include mortality (overall, liver-related and non-related), liver-related events (cirrhosis, decompensation, HCC, liver transplant or combination of) and non-liver related events (major adverse cardiovaslular events [MACE], myocardial infarction, stroke, heart failure and non-liver cancer). We used a randoms effect model to estimate the hazard ratio relating GLP-1RA and/or SGLT2i use with adverse clinical events. **Results:** We initially identified 7,228 studies and 66 were retrieved for full-text review after title and abstract review. Finally, 18 eligible studies involving 1,152,344 patients with MASLD (568,568 GLP-1RA and/or SGLT2i users, 583,776 nonusers) were included in study analysis. Therapy with GLP-1RA and/or SGLT21 use was associated with lower risks of all-cause mortality (hazard ratio [HR] 0.61, 95%CI 0.48–0.79), liver-related mortality (0.61, 0.45-0.84), adverse liver events (0.77, 0.69-0.87), as well as non-liver events such as stroke (0.61, 0.44–0.84) and heart failure (0.90, 0.86–0.94). **Conclusion:** Treatment with GLP-1RAs and/or SGLT2is is associated with significant long-term reductions in both hepatic and extra-hepatic complications and mortality in patients with MASLD. These data support the incorporation of these agents into comprehensive MASLD management.



Disclosures: Jie Wang: Nothing to Disclose, Taotao Yan: Nothing to Disclose, Xiangrong Gao: Nothing to Disclose, Haruki Uojima: Nothing to Disclose, Michael Le: Nothing to Disclose, Ramsey Cheung: Nothing to Disclose, Mindie Nguyen: Nothing to Disclose

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4082 | DIGOXIN USE AND CLINICAL OUTCOMES IN MASLD AND MASH: A REAL-WORLD RETROSPECTIVE COHORT STUDY

Yazan Al Jabiri[1] Mohammad Aldiabat[1] Sura Issa[2] Thabet Qapaja[1] Kamran Qureshi[3] Wing-Kin Syn[3], [1]Washington University in saint louis, [2]Jordan University, [3]Saint Louis University School of Medicine

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), are increasingly prevalent causes of chronic liver disease. Preclinical studies have identified digoxin as a potential hepatoprotective agent through inhibition of the PKM2–HIF-1α signaling pathway, leading to reductions in hepatic steatosis, inflammation, and mitochondrial dysfunction in murine models. To date, no clinical studies have assessed the real-world effects of digoxin on MASLD or MASH outcomes in human populations. We conducted a retrospective cohort analysis to assess the association of digoxin use with clinical outcomes in patients with MASLD or MASH and concurrent heart failure or arrhythmia. **Methods:** This retrospective cohort study utilized the TriNetX US Collaborative Network, comprising data from 67 healthcare organizations. Adults (≥18 years) with MASLD or MASH and comorbid heart failure or arrhythmia—with left ventricular ejection fraction (LVEF) between 30–70%—were identified and stratified by digoxin use. Propensity score matching (1:1) was performed to balance cohorts based on LVEF, metabolic and cardiovascular comorbidities, MELD score components, metabolic-related labs, and anticoagulant use. Outcomes over a 10-year period included cirrhosis, all-cause mortality, hepatic encephalopathy (HE), hepatocellular carcinoma (HCC), liver transplantation (LT), spontaneous bacterial peritonitis (SBP), hospitalization, emergency department (ED) visits, and MASH occurrence. Hazard ratios (HRs), 95% confidence intervals (CIs), and P-values were reported. **Results:** In the matched MASLD cohort (n = 3,159 per group), digoxin use was associated with increased risks of cirrhosis (HR 1.351, $p < 0.001$), mortality (HR 1.637, $p < 0.001$), hospitalization (HR 1.524, $p < 0.001$), and ED visits (HR 1.229, $p < 0.001$). No significant differences were observed in HE, variceal bleeding, HCC (HR 0.802, $p = 0.469$), LT (HR 2.625, $p = 0.090$), or SBP (HR 1.414, $p = 0.323$). In the matched MASH cohort (n = 669 per group), digoxin use was associated with increased mortality (HR 1.291, $p = 0.008$), hospitalization (HR 1.391, $p < 0.001$), ED visits (HR 1.177, $p = 0.022$), and SBP (HR 2.363, $p = 0.010$), with no significant differences in cirrhosis, HE, variceal bleeding, HCC, or LT. **Conclusion:** In this real-world retrospective study of patients with MASLD or MASH and concurrent heart failure or arrhythmia, digoxin use was associated with significantly higher risks of mortality, hospitalization, and ED visits. In the MASH cohort, it was also linked to increased risk of SBP. No significant associations were observed with HE, variceal bleeding, HCC, or LT. These findings highlight the need for prospective studies to clarify the clinical utility, safety profile, and appropriate patient selection for digoxin in individuals with MASLD or MASH. This presentation discusses investigational, unlabeled use of digoxin for MASLD and MASH

Disclosures: Yazan Al Jabiri: Nothing to Disclose, Mohammad Aldiabat: Nothing to Disclose, Sura Issa: Nothing to Disclose, Thabet Qapaja: Nothing to Disclose, Kamran Qureshi: Nothing to Disclose, Wing-Kin Syn: Nothing to Disclose

4083 | INHIBITION OF THE PROSTAGLANDIN-DEGRADING ENZYME 15-PGDH AMELIORATES MASH-ASSOCIATED APOPTOSIS AND FIBROSIS IN MICE

Utibe-Abasi Udoh[1] Mathew Schade[1] Jacqueline Sanabria[1] PRADEEP KUMAR RAJAN[1] Rodrigo Aguilar[1] Micheal Andryka[1] Alexei Gorka[1] Sandrine Pierre[1] Juan Sanabria[1], [1]Marshall University

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects more than 30% of the world population. Progression to its inflammatory state- metabolic dysfunction-associated steatohepatitis (MASH) is associated with increasing liver fibrosis, leading to end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC). SW033291, an inhibitor of 15-PGDH (PGE2 degradation enzyme) has been shown to increase in vivo regeneration of liver parenchyma and ameliorates oxidative stress and inflammation. We hypothesized that SW033291 abrogates MASH progression through a paucity of the initial apoptotic switch restoring physiological collagen microenvironment. **Methods:** Plasma non-targeted metabolomics was measured by LC-MS/MS in a diet-induced MASH-mouse model at 24 weeks (24W). Liver morphology and apoptotic activity were quantitated by the NAS score and TUNEL assay, respectively. Statistical analyses (Control = NMC, HFD and HFD+SW03321) were determined by ANOVA/Principal Component Analysis (PCA) using GraphPad, or SPSS / R-Lab. Statistical significance was set at $p < 0.05$, n = 7/group. All mice used in this study were 7 weeks old (at start of experiment) female C57BL/6J strain. **Results:** The SW033291 group showed a significant decrease in total body fat, cellular oxidative stress and inflammation, and an increase in total lean mass with improved insulin resistance compared with the HFD group ($p < 0.05$). In addition, SW033291 significantly decreased GS:SG, citric acid and corticosterone, NAS score (9.4 ± 0.2 vs. 6.2 ± 0.1), liver

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fibrosis score (1.3 ± 0.5 vs. 0.25 ± 0.1), and apoptotic activity (43.9 ± 4.6 vs. 0.38 ± 0.1%, $p < 0.05$) when compared to HFD at 24W. **Conclusion:** Inhibition of 15-PGDH normalizes the metabolic and morphological disturbances during experimental MASH progression with a paucity of the initial apoptotic switch, restoring normal collagen architecture. SW033291 warrants further investigation for clinical translation.

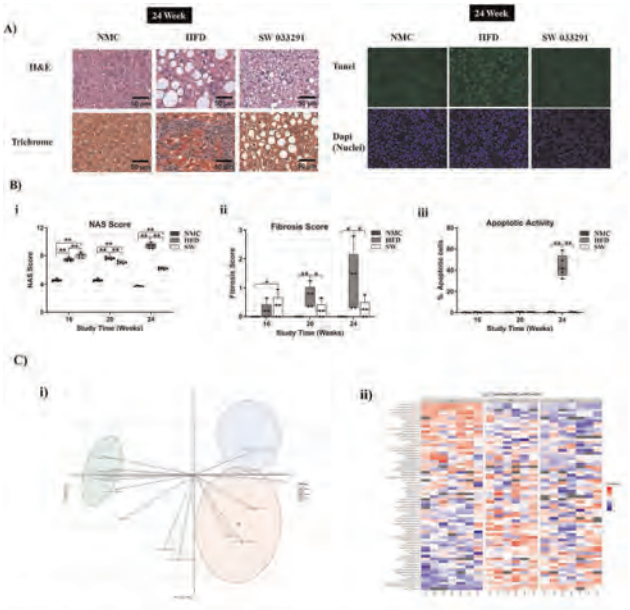

Fig 1. **(A)** *Liver Morphology of MASH at 24W, using H&E, Trichrome, and TUNEL staining techniques.* Observe the pronounced steatosis, fibrosis, and apoptosis in the HFD mice compared to both the NMC and SW033291-treated mice. **Bi-iii)** *NAS score, fibrosis and apoptotic activity in NMC vs. HFD vs. SW033291-treated mice.* Notice the significant reduction in the NAS and fibrosis scores and apoptotic activity in the SW03329-treated group vs. HFD and NMC groups (** $p < 0.01$, * $p < 0.05$). **C)**. *PCA plots of plasma Non- targeted Metabolomics in the MASH mice.* **i)** Biplot of principal component scores (points) and variable loadings (arrows); **ii)** Heat map displaying discrimination in metabolites in mice serum (NMC vs. HFD vs. SW033291). **NMC** = Normal mouse chow group, **HFD**= High fat diet group, **SW033291**= SW033291-treated group.

Disclosures: Utibe-Abasi Udoh: Nothing to Disclose, Mathew Schade: Nothing to Disclose, Jacqueline Sanabria: Nothing to Disclose, PRADEEP KUMAR RAJAN: Nothing to Disclose, Rodrigo Aguilar: Nothing to Disclose, Micheal Andryka: Nothing to Disclose, Alexei Gorka: Nothing to Disclose, Sandrine Pierre: Nothing to Disclose, Juan Sanabria: Nothing to Disclose

4084 | COMBINATION THERAPY WITH RESMETIROM AND GLP-1 RECEPTOR AGONISTS DEMONSTRATES SUPERIOR EFFICACY IN REDUCING LIVER FIBROSIS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: A REAL-WORLD MULTI-COHORT ANALYSIS

Kate Solpari Allysa Saggese[1] Scarlet Yang[2] Jessica Siguencia[2] Tatyana Kushner[2] Reem Sharaiha[2], [1]Weill Cornell Medicine, [2]Weill Cornell Medical College

Background: Resmetirom, a selective thyroid hormone receptor-beta agonist, was approved by the FDA in March 2024 as the first treatment for noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced fibrosis. While glucagon-like peptide-1 receptor agonists (GLP-1RA) have shown promise in MASH, combining these agents with resmetirom may offer complementary mechanisms—with GLP-1RAs targeting extrahepatic metabolic pathways and resmetirom addressing intrahepatic mechanisms. This real-world study compared outcomes in MASH patients treated with resmetirom plus GLP-1RAs versus resmetirom monotherapy. **Methods:** Using the TriNetX research network, we conducted a retrospective cohort analysis of adults (≥ 18 years) with MASH initiated on resmetirom between March 2024 and May 2025. Patients were stratified into two cohorts: resmetirom plus GLP-1RA combination therapy versus resmetirom monotherapy. Propensity score matching (1:1) was performed based on demographics, comorbidities (including type 2 diabetes and obesity), and baseline medications. Primary outcomes included progression to fibrosis, and composite fibrosis and cirrhosis risk. Secondary outcomes included ALT/AST normalization and lipid profiles. Kaplan-Meier survival analysis and risk ratios were calculated. **Results:** The initial cohort included 224 patients receiving combination therapy and 419 receiving resmetirom monotherapy. After propensity score matching, 132 patients remained in each group with well-balanced baseline characteristics (mean age 56.5 vs 58.0 years, 62.1% vs 65.2% female, 68.2% hypertension, 55.3% vs 56.8% diabetes). At a median follow-up of 130 days, combination therapy demonstrated significantly lower risk of fibrosis progression compared to monotherapy (25.0% vs 38.6%, RR 0.65, 95% CI 0.45-0.93, p = 0.017). Patients in the combination therapy arm experienced significantly less progression to fibrosis over time, as demonstrated by the Kaplan-Meier analysis (hazard ratio 0.521) (Figure 1). The composite endpoint of fibrosis/cirrhosis was also reduced (27.3% vs 40.2%, RR 0.68, 95% CI 0.48-0.96, p = 0.027). No significant differences were observed in ALT normalization (50.0% vs 47.6%, p = 0.879) or AST normalization (35.7% vs 35.7%, p = 1.0). Lipid profiles showed no significant differences between groups. **Conclusion:** In this real-world analysis, combination therapy with resmetirom and GLP-1RAs demonstrated superior efficacy in reducing fibrosis progression compared to resmetirom monotherapy in patients with MASH. These findings support the complementary mechanisms of action hypothesis, with GLP-1RAs addressing upstream metabolic dysfunction and resmetirom targeting intrahepatic pathways. Prospective randomized trials are needed to confirm these promising real-world findings and establish optimal combination strategies for MASH management.

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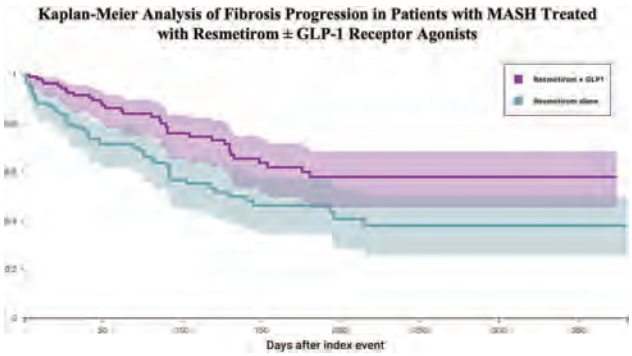

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4085 | AI-POWERED HISTOLOGY ANALYSIS OF HARMONY REVEALS EFRUXIFERMIN-DRIVEN CHANGES IN THE LIVER MICROARCHITECTURE IN F2/F3 MASH

Jörn Schattenberg[1] Vlad Ratziu[2] Ylaine Gerardin[3] Lara Murray[3] Christina Jayson[3] Robert Egger[3] Geetika Singh[3] Jacqueline Brosnan-Cashman[3] Doreen Chan[4] Jimmie Zhang[4] Erica Fong[4] Brittany De Temple[4] Matthew Minerva[4] Mark Burch[4] Kimberly Barrett[4] Reshma Shringarpure[5] Erik Tillman[4] Timothy Rolph[4] Andrew Cheng[4] Kitty Yale[4] Mazen Noureddin[6],
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Background: In Phase 2b trials for metabolic dysfunction-associated steatohepatitis (MASH), Efruxifermin (EFX) reversed cirrhosis in participants (pts) with F4 MASH (SYMMETRY) and improved fibrosis without worsening MASH in pts with F2-F3 disease (HARMONY). An opportunity remains to understand EFX-induced changes at the structural, cell, and tissue level. Here, we conducted a retrospective analysis of HARMONY (NCT04767529) using Liver Explore[1], an AI-powered tool for the comprehensive characterization of liver microarchitecture, to assess liver histology changes that occur with EFX. **Methods:** In HARMONY, pts (N = 128) were randomized to placebo (Pbo), 28 mg EFX (EFX-28), or 50 mg EFX (EFX-50), and biopsies were taken at baseline (BL), week 24 (w24), and week 96 (w96). Hematoxylin and eosin-stained whole slide images of biopsies from all study arms and timepoints were analyzed using Liver Explore to detect, classify, and quantify liver tissue regions, cells, and fibrosis subtypes. For each study arm, fold changes in each feature from BL to w24 and w96 were calculated and compared to Pbo using ANCOVA. **Results:** Eight Liver Explore features relevant to MASH were selected to measure changes from BL at w24 and w96 (Figure 1). At wk24, we observed treatment-specific reductions from BL in early-stage fibrosis (-40% EFX-28; -44% EFX-50), hepatocellular ballooning (-85%; -95%) and steatotic hepatocytes (-49%; -70%). Macrophages (-17%) and total immune cells (-15%) were reduced in EFX-50, and normal hepatocytes increased at both doses (40% EFX-28; 71% EFX-50) at wk24. These improvements were largely sustained at wk96, with macrophages and total immune cells showing improvement in EFX-28, as well. While not significant at wk24, total and advanced fibrosis improved at wk96, with a 59% reduction in advanced fibrosis in EFX-50. These results reveal dose- and time-dependent effects of EFX: histologic features related to MASH disease activity, inflammation, and early-stage fibrosis resolve most quickly, while resolution of advanced fibrosis requires a longer EFX duration and higher dose. **Conclusion:** Liver Explore analysis of HARMONY revealed improvements in histologic features related to MASH disease activity and fibrosis severity beyond categorical scoring. These results highlight the multimodal and antifibrotic nature of EFX as a MASH therapeutic and corroborate the improvements observed by conventional histology in HARMONY.
[1]Liver Explore is for research use only. Not for use in diagnostic procedures.

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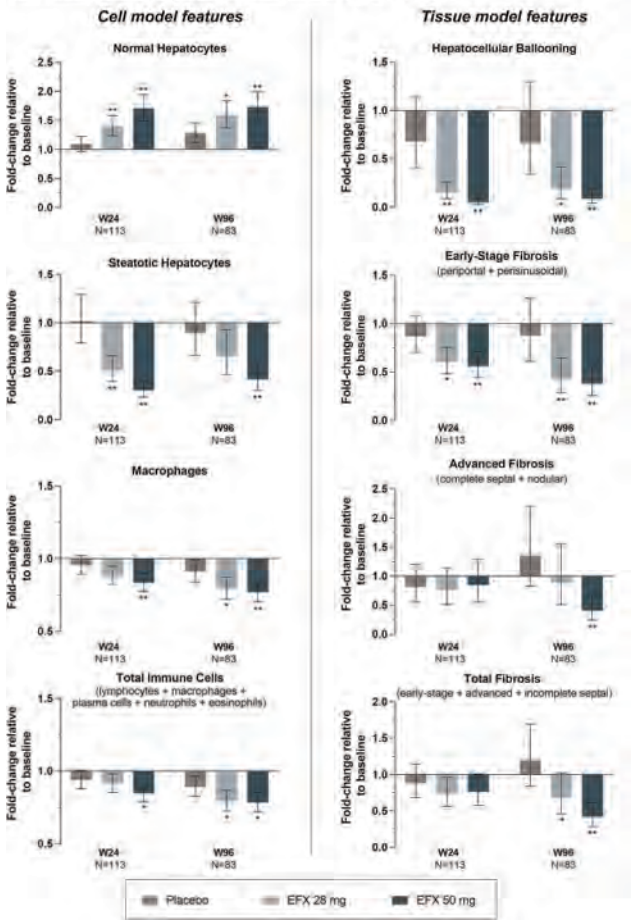

Figure 1. Change from baseline in select histological parameters. Cell type features (left column) are derived as count proportions relative to all cells. Normal (healthy) heptaocytes excludes steatotic, degenerating, and ballooned hepatocytes. Tissue features (right column) are derived as area proportions relative to total tissue. Error bars represent 95% confidence intervals. Stars indicate nominally significant treatment effects (*p<0.05, **p<0.01).

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4086 | A BISPECIFIC ANGPTL3-DGAT2 SIRNA FOR CONCURRENT TREATMENT OF BOTH HEPATIC STEATOSIS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Michael Khan[1] Gerda Gasiunaite[1] Mitchell Geer[1] Dan Mitchell[1] Owen Cox[1] Antonio Vidal-Puig[2] Stella Pelengaris[1], [1]Argonaute RNA Ltd, [2]University of Cambridge

Background: Hepatic steatosis is a well-established risk factor for severe diseases of the liver. Moreover, not only is hepatic steatosis a risk factor for atherosclerotic cardiovascular disease (ASCVD) *per se*, but recent studies demonstrate that otherwise promising treatments for liver complications, such as targeting *PNPLA3*, can increase ASCVD risk factors, particularly atherogenic LDL-C. Conversely, treatments for Residual Risk (RR) of ASCVD, targeting triglyceride-rich lipoproteins or ApoB, are associated with the development of hepatic steatosis. There is, therefore, an urgent need for new synergistic therapies to prevent or improve both hepatic steatosis and risk of ASCVD.

We present our approach, which utilises a proprietary Argonaute platform technology for the simultaneous silencing of two or more hepatocyte target genes using a single, multi-valent molecular entity. Data will be presented to confirm that the Argonaute therapy remains intact until linker cleavage in the hepatocyte endosomal compartment. Next, the effect of simultaneous bispecific silencing of *Angptl3* and *Dgat2* in a diet-induced obese (DIO) mouse model *in vivo* will be discussed. **Methods:** Bispecific *ANGPTL3-DGAT2* siRNAs were designed, developed and administered to DIO mice at 4, 10 and 20 mg/kg doses *in vivo* by a single subcutaneous injection. Changes in plasma lipids, hepatic mRNA and hepatic lipid profile were assessed at 7-, 21- and 42-day time points. Controls included equivalent doses of monospecific siRNAs, vehicle and a control siRNA. **Results:** Administration of a single dose of a bispecific siRNA targeting *ANGPTL3* and *DGAT2* produced a robust ($>90\%$) and sustained reduction in mRNA for both target genes. The therapy was safe and well-tolerated, with no markers of liver toxicity. Comprehensive lipidomic analyses confirm substantial reductions in hepatic steatosis (-50%), extending to liver diacylglycerols as well as triacylglycerols, and without accumulation of hepatotoxic precursors or contributors to insulin resistance. Moreover, there was a marked reduction in genetically validated genes implicated in MASLD/MASH, including a 70% reduction in the apical risk factor *Pnpla3*. Notably, there was a profound concurrent reduction in atherogenic plasma lipids, including LDL-C (-70%) and triglycerides (-38%). **Conclusion:** These results justify further development of bispecific *ANGPTL3-DGAT2* siRNAs for the prevention and treatment of MASLD/MASH, as well as for RR of ASCVD and cardiometabolic disease more broadly.

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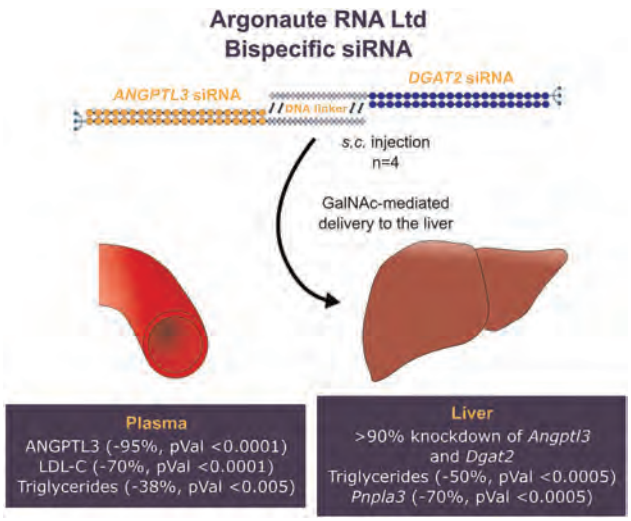


Disclosures: Michael Khan: Nothing to Disclose, Gerda Gasiunaite: Nothing to Disclose, Mitchell Geer: Nothing to Disclose, Dan Mitchell: Nothing to Disclose, Owen Cox: Nothing to Disclose, Antonio Vidal-Puig: Nothing to Disclose, Stella Pelengaris: Nothing to Disclose

4087 | US HEALTHCARE PROFESSIONALS&RSQUO; MANAGEMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS AND KNOWLEDGE OF GLUCAGON, GLP-1, AND GIP RECEPTOR AGONISTS AND DUAL AGONISTS

Alfred Barritt IV[1] Diana Canseco[2] Jonathan Pak[2] Teresa Oliveria[2] Harold Bays[3], [1]The University of North Carolina at Chapel Hill, [2]Boehringer Ingelheim Pharmaceuticals, Inc., [3]Louisville Metabolic and Atherosclerosis Research Center

Background: Various combinations of agonists of the glucagon receptor (GCGR), glucose-dependent insulinotropic polypeptide receptor (GIPR), and glucagon-like peptide-1 receptor (GLP-1R) are in clinical trials for the treatment of metabolic dysfunction-associated liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). We explored how US healthcare professionals (HCPs) treating people with MASLD/MASH perceive these investigational agents. **Methods:** Between November 2024 and January 2025, an online survey was completed by US hepatologists/gastroenterologists (HEP/GASTRO, n = 179), endocrinologists (ENDO, n = 172), primary care physicians (PCP, n = 177) and advanced practice providers (APP, n = 232) currently treating people with MASLD/MASH to assess their knowledge of GCGR, GIPR, and GLP-1R agonists. **Results:** Respondent HCPs reported managing a mean of 13–25 patients per week having MASLD/MASH. Ultrasound was the most common imaging technique to initially diagnose MASH across specialty (ENDO, 64.0%; PCP, 75.7%; APP, 74.0%), with the exception of HEP/GASTRO where vibration-controlled transient elastography (FibroScan®) was most common (77.7%). Liver enzymes (79.7%) and FIB-4 (55.8%) were the most frequently ordered biomarker tests for diagnosing MASH. Significant barriers to treatment reported were cost, paucity of FDA-approved treatments, and delayed diagnosis due to the asymptomatic nature of the disease. Only 30.2% and 53.9% of HCPs were "very" or "extremely familiar" with GCGR and GIPR, respectively, but most (76.8%) HCPs were "very" or "extremely familiar" with GLP-1R (Figure 1A). HCPs were also less familiar with the therapeutic effects associated with activation of GCGR and GIPR compared with GLP-1R. A total of 87.0%, 75.9% and 90.3% of respondents expected GCGR, GIPR, and GLP-1R agonists, respectively, to benefit people with MASH. Most HCPs expected dual GCGR/GLP-1R agonists to be better than GLP-1R mono-agonists for control of many cardiometabolic conditions including MASLD (88.3%), MASH (89.3%), obesity (90.1%), and type 2 diabetes (88.8%) (Figure 1B). **Conclusion:** HCPs report substantial barriers to treating people with MASH, including costs and lack of approved medications. HCPs were generally more familiar with GLP-1R, and the therapeutic effects of its activation, than with GCGR and GIPR. HCPs anticipate that dual GCGR/GLP-1R agonists will have meaningful clinical benefits for MASLD/MASH and many other cardiometabolic conditions.

Figure 1A: Familiarity with GCGR, GIPR, and GLP-1R among total respondents

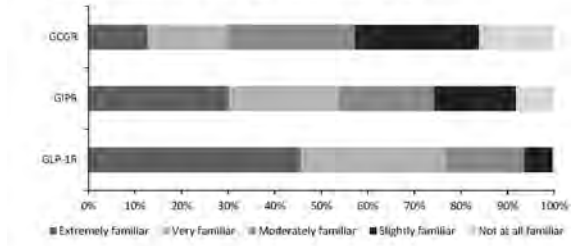
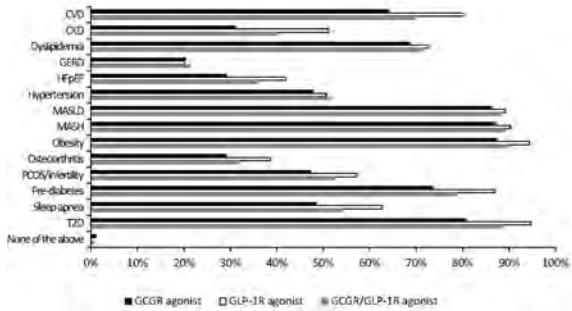


Figure 1B: Perceived benefits of GCGR agonists, GLP-1R agonists, and GCGR/GLP-1R dual agonists



CKD, chronic kidney disease; CVD, cardiovascular disease; GCGR, glucagon receptor; GERD, gastroesophageal reflux disease; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1R, glucagon-like peptide-1 receptor; HFpEF, heart failure with preserved ejection fraction; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated liver disease; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes.

Disclosures: Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant, Target-RWE: Consultant, Madrigal Pharmaceuticals: Consultant,

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Merck (Any division): Consultant, Boehringer Ingleheim: Consultant, Diana Canseco: Nothing to Disclose, Jonathan Pak: Nothing to Disclose, Teresa Oliveria: Nothing to Disclose, Harold Bays: Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Grant/Research Support, HighTide,: Grant/Research Support, Madrigal: Grant/Research Support

4088 | EFFECTS OF ORAL SEMAGLUTIDE ON FIB-4 SCORE IN ADULTS WITH TYPE 2 DIABETES IN REAL-WORLD CLINICAL PRACTICE: AN INDIAN OBSERVATION STUDY

Ramakrishnan Santosh[1], [1]Magna Centres for Obesity, Diabetes and Endocrinology

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is an important common comorbidity in subjects with type 2 diabetes, and liver fibrosis is a factor directly related to its prognosis. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are useful treatment options for MASLD; however, the efficacy of oral semaglutide in treating liver steatosis/fibrosis has not been fully evaluated. **Methods:** This was a single-arm, multicentre, retrospective study of 6 months oral semaglutide treatment for T2DM in patients with MASLD. Among 309 consecutive patients with MASLD and T2DM who newly received oral semaglutide, 121 patients had data necessary for FIB-4 calculation at baseline and 6 months and were included in the analysis. Dose adjustments of oral semaglutide were determined by the treating endocrinologist while monitoring efficacy and adverse events. **Results:** The mean age of the participants was 44.04 ± 11.37 years. 72 (59.5%) were males. Significant improvements in fibrosis score, body weight, BMI, liver enzymes, creatinine, and glycaemic control (HbA1c) were found at 6 months compared with baseline values (Table 1). Changes in alanine aminotransferase ($r = 0.32$, $p < 0.01$), aspartate aminotransferase ($r = 0.36$, $p < 0.01$) and fibrosis score ($r = 0.43$, $p < 0.01$) were significantly correlated with changes in body weight. No serious adverse events were reported. **Conclusion:** Oral semaglutide might be a useful treatment option for adults with type 2 diabetes at high risk for liver fibrosis, even when switching from conventional medications for diabetes.

Table 1:

Parameter	Baseline	Follow-up	p-value
Fib-4 Score, Median (IQR)	1.81 (1.32-2.39)	1.16 (0.81-1.51)	<0.001
ALT (U/L), Mean ± SD	58.45 ± 25.33	47.02 ± 20.75	<0.001
AST (U/L), Mean ± SD	64.95 ± 30.87	46.41 ± 21.91	<0.001
HbA1c (%), Mean ± SD	7.73 ± 1.05	6.95 ± 0.63	<0.001
Systolic BP, Mean ± SD	126.7 ± 17.93	123.42 ± 18.17	0.181 (NS)
Diastolic BP, Mean ± SD	84.30 ± 11.31	83.73 ± 10.41	0.715 (NS)
Weight (kg), Mean ± SD	90.46 ± 12.03	87.39 ± 11.13	<0.001
BMI (kg/m²), Mean ± SD	32.25 ± 4.36	31.41 ± 4.19	0.001
Creatinine (mg/dL), Mean ± SD	0.79 ± 0.16	0.72 ± 0.16	0.019

p<0.05 considered as statistically significant

Disclosures: Ramakrishnan Santosh: Nothing to Disclose

4089 | REAL-WORLD EXPERIENCE WITH RESMETIROM TO TREAT MASH IN A UNIVERSITY HOSPITAL SYSTEM

Arthi Thirumalai[1] Erin Cleveland[1] Meredith Pearson[1] Philip Vutien[1] Meagan Alvarado[1] Muyi Li[1] Lei Yu[1] Rotonya Carr[2] Paula Cox-North[2] John Scott[3] Nicole Kim[1], [1]University of Washington, [2]University of Washington Medical Center, [3]Harborview Medical Center

Background: Resmetirom, a THR-b agonist, is the first drug approved for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis. We developed and implemented a protocol to standardize resmetirom use within our health system. **Methods:** Patients were prescribed resmetirom for suspected MASH with F2-F3 fibrosis based on liver biopsy, FibroScan (FS), MR-elastography, and/or Enhanced Liver Fibrosis score. We recommended use of a GLP-1 receptor agonist prior to resmetirom initiation in patients with diabetes. We monitored labs at baseline and at months 1, 3, 6, and 12. Wilcoxon signed rank test was used to assess for changes in median liver test values over time. **Results:** Since July 2024, 21 patients (median age 57 yrs [IQR 49-63], 52.4% male, 47.6% female, 52.4% White, 33.3% Asian/Pacific Islander, 14.3% Hispanic, 52.4% commercial insurance, 38.1% Medicaid, 19.1% Medicare) initiated resmetirom in our health system. Fibrosis stage was F2 in 33.3% and F3 in 66.7% of patients. Metabolic comorbidities were common (33.3% diabetes, 66.7% hypertension, 52.4% hyperlipidemia, 76.2% obesity, median BMI 35.3 kg/m^2) and 9.5% had thyroid disease. By May 2025, 20, 13, and 10 patients had completed 1, 3, and 6 months of therapy, respectively. Baseline tests included median (IQR): AST 40 (24-50), ALT 52 (32-93), bilirubin 0.7 (0.5-0.8), alkaline phosphatase (ALP) 79 (68-102), FIB-4 1.37 (1.08-1.60), SAFE 72 (46-158), LSM 10.9 kPa (10-12.8), and CAP score 314 dB/m (288-333). Median AST increased to 41 (IQR 27-87) then declined to 35.5 (25-53) and 25 (24-28) at months 1, 3, and 6 respectively ($p = 0.03$ month 3 vs. 6). Median ALT increased to 67 (31-140) then declined to 61 (31.5-88.5) and 38 (26-48) at months 1, 3, and 6 respectively ($p = 0.047$ month 1 vs. 6; $p = 0.02$ month 3 vs. 6). There were no significant changes in bilirubin or ALP levels over time. Common side effects included 33.3% elevated liver tests, 19.0% diarrhea, 14.2% upset stomach, 9.5% nausea, and 9.5% pruritus, with 1 patient discontinuing resmetirom due to diarrhea. **Conclusion:** In this real-world cohort of

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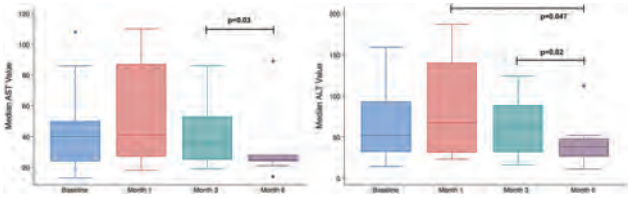
patients with MASH and F2-F3 fibrosis treated with resmetirom, AST and ALT levels increased at month 1, then declined thereafter, suggestive of subsequent improvement in liver inflammation. The medication was well-tolerated by most patients. Long-term monitoring of liver tests and correlation with changes in fibrosis stage will be needed to assess treatment response.



Disclosures: Arthi Thirumalai: Fractyl Health: Grant/Research Support, Novo Nordisk Inc: Grant/Research Support, Novo Nordisk: Consultant, Erin Cleveland: Nothing to Disclose, Meredith Pearson: Nothing to Disclose, Philip Vutien: Nothing to Disclose, Meagan Alvarado: Nothing to Disclose, Muyi Li: Nothing to Disclose, Lei Yu: Nothing to Disclose, Rotonya Carr: Nothing to Disclose, Paula Cox-North: Nothing to Disclose, John Scott: Nothing to Disclose, Nicole Kim: Madrigal: Grant/Research Support, Madrigal Pharmaceuticals: Clinical trial (to institution), Madrigal: Grant/Research Support

4090 | NEW SUBMISSION

DEMOGRAPHIC VARIABLES AND CO-MORBID CONDITIONS PREDICT PRESCRIBING OF GLP-1 RECEPTOR AGONISTS FOR INDIVIDUALS WITH METABOLIC DYSFUNCTION

Emily Currier[1] Xinyuan Zhang[2] Michelle Lai[1]

[1]Beth Israel Deaconess Medical Center, [2]Harvard Medical School

Background: While metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent liver disease nationwide, it remains notoriously underdiagnosed despite aDecting over 67% of people with Type II Diabetes (T2DM) or obesity. While GLP-1 receptor agonists (GLP-1RAs) are not FDA approved for treatment of MASLD, there is data showing that GLP1RAs resolve steatohepatitis and delay the progression of liver fibrosis. They are currently used oD-label in the treatment of MASH. Access to these medications is often limited by multiple social determinants of health. Little data exists on predictors of GLP-1RA access. The aim of this research is to evaluate if patient demographics aDect GLP-1 RA prescribing and access in those with diagnosed MASLD and those at high risk for underlying MASLD/MASH (T2DM or obesity or metabolic syndrome), while controlling for disease severity and comorbid conditions. **Methods:** An IRB approved retrospective chart review was conducted at a diverse, academic hospital system and medical records were screened to identify patients with T2DM, obesity, metabolic syndrome, or documented MASLD/MASH as defined by ICD-10 codes from January 2020 to December 2024. Over 16,000 subjects were included in the study. Variables collected included demographic data (age, sex, race, zip code, language spoken), history of HTN/HLD, BMI, A1c, LFTs, and history of GLP-1 prescriptions. FIB-4 scores were able to be calculated on 8,084 patients. Logistic regression was performed to assessforpredictorsof GLP-1RAuseanddi-DerencesinFIB-4datawasanalyzedusing multivariable adjusted linear regression. **Results:** Individuals of young age, female sex, history of hyperlipidemia, and elevated BMI were more likely to receive GLP-1 RAs (all $p < 0.001$). Factors associated with decreased rate of GLP-1 use included Black or Asian self-identified race, primary language as non- English, history of hypertension (all $p < 0.01$). Factors with no significant impact included A1c prior to GLP-1RA, prior documented liver disease, and patient income. Analysis of FIB- 4 data indicated that individuals of GLP-1 had significantly lower FIB-4 scores than those not (beta = -0.12, $p < 0.001$). 2,000 subjects in the study had ICD-10 corresponding to diagnosed MASLD/MASH. **Conclusion:** Patient demographic and co-morbid conditions are predictive of GLP-1RA prescribing in patients at risk of having underlying MASLD/MASH. Interestingly, patient typically at higher risk for MASLD based upon race, age, etc, are less likely to receive a GLP- 1, which is important given those on GLP-1 had lower fibrosis scores than their counterparts. Secondarily, this highlights ongoing underdiagnosis of MASLD given that only 2,000 of the patients included in the study have formal diagnosis of liver dysfunction in contrast to the approximately 10,000 individuals who likely have MASLD/MASH.

Disclosures: Emily Currier: Nothing to Disclose, Xinyuan Zhang: Nothing to Disclose, Michelle Lai: Nothing to Disclose

4091 | COMPARATIVE ANALYSIS OF RESMETIROM AND TIRZEPATIDE IN THE TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: INSIGHTS FROM A LARGE DATABASE

Liza Bagashvili Nino Gudushauri[1] Irakli Tskhakaia[1] Zurab Azmaiparashvili[2], [1]Jefferson Einstein Hospital Philadelphia, [2]Jefferson Einstein Philadelphia Hospital

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Background: The emergence of glucagon-like peptide-1 (GLP-1) receptor agonists has significantly advanced the management of metabolic syndrome. Among the related conditions, metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) remain frequently underdiagnosed and undertreated. This analysis aimed to compare clinical outcomes associated with resmetirom and tirzepatide in the management of MASLD/MASH. **Methods:** A retrospective observational analysis was conducted using the TriNetX research network to evaluate treatment outcomes. The study population included 75,899 patients diagnosed with MASLD/MASH who received tirzepatide and 914 patients who received resmetirom. Following propensity score matching, 896 patients in each group were identified. Clinical and demographic variables were analyzed both before and after matching. The primary outcomes assessed were the incidence of cirrhosis and all-cause mortality. **Results:** Before propensity score matching, patients receiving tirzepatide exhibited an absolute risk reduction (ARR) of 7.86% in the development of cirrhosis compared to those receiving resmetirom ($p < 0.0001$). To control for potential confounding factors, patients were matched based on key clinical and demographic characteristics, including age, race, and body mass index (BMI), as well as laboratory parameters such as platelet count, aspartate aminotransferase (AST), and bilirubin levels. After matching, the lower risk of cirrhosis in the tirzepatide group persisted, with an ARR of 7.93% ($p < 0.0001$). However, data on all-cause mortality were insufficient for meaningful comparison at this time. **Conclusion:** Treatment with GLP-1 receptor agonists such as tirzepatide may be associated with a reduced risk of cirrhosis in patients with MASLD/MASH. Broader implementation of these therapies could potentially lower the incidence of cirrhosis linked to these conditions.

Disclosures: Liza Bagashvili: Nothing to Disclose, Nino Gudushauri: Nothing to Disclose, Irakli Tskhakaia: Nothing to Disclose, Zurab Azmaiparashvili: Nothing to Disclose

4092 | LONG-TERM REAL-LIFE EXPERIENCE OF SEMAGLUTIDE IN A MONOCENTRIC METABOLIC DYSFUCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) DIABETIC COHORT

Giovanni Petralli[1] Antonio Salvati[2] Simone Cappelli[1] Lidia Surace[2] Laura De Rosa[3] Maurizia Brunetto[4], [1]Università di Pisa, [2]Hepatology Unit, University Hospital Pisa, Italy, [3]Institute of Clinical Physiology, National Research Council, Pisa, Italy, [4]University of Pisa

Background: MASLD is the liver specific manifestation of a multifaceted affection with high global prevalence and a strong association with type 2 diabetes (T2D). Subcutaneous semaglutide, largely effective in T2D treatment, was recently shown to induce steatohepatitis resolution although at dosage of 2.4 mg weekly. **Methods:** We longitudinally evaluated 90 diabetic patients (pts.) [60.7 ± 9.9 yrs old, 38% female, 5 (1-8) yrs diabetes duration] after 1 mg weekly semaglutide introduction for diabetes management optimization to evaluate its long-term effect on liver disease activity and its correlation with metabolic variables improvement. Patients were non-invasively evaluated with anthropometry, biochemistry, and transient elastography by Fibroscanâ at t1 [6 (5-8) months, in all cohort] and t2 [24 (21-31) months, in a 67pts sub cohort]. ALT, controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) variations (D) were used as proxies of liver disease burden. PNPLA3 I148M polymorphism was determined too. **Results:** BMI (baseline 32.6 ± 5.7, D t1 -2.0, D t2 -2.2 kg/m^2, $p < 0.001$), glycated haemoglobin (HbA1c, baseline 53 ± 13 D t1 -10, D t2 -8 mmol/mol, $p < 0.001$), ALT [baseline 35 (22-54), D t1 -18, D t2 -20 U/L, $p < 0.001$], CAP [baseline 339 (288-372), D t1 -22, D t2 -31 dB/m, $p < 0.01$], and LSM [baseline 8.2 (5.5-11.0), Dt1 -1.6, Dt2 -1.7 kPa, $p < 0.001$] reductions were observed. At t1 60% and 22% of the cohort showed a BMI reduction of 5% and 10%, respectively, while a 30% reduction of CAP and LSM was observed in 14% and 39%, respectively; a -17 U/L reduction of ALT was shown in 36%. At t2 65% and 22% of cohort showed a BMI reduction of 5% and 10%; a 30% reduction of CAP and LSM was observed in 13% and 35%, respectively; a -17 U/L reduction of ALT was shown in 33%. ALT, CAP, and LSM variations were not influenced by PNPLA3 polymorphisms, nor with baseline BMI or HbA1c. ALT and CAP's reduction correlated with D BMI at t1 ($r = 0.351$ $p = 0.004$, $r = 0.441$ $p < 0.001$, respectively). Only D ALT was associated with D HbA1c both at t1 ($r = 0.296$, $p = 0.016$) and at t2 ($r = 0.397$, $p = 0.008$). **Conclusion:** Semaglutide is effective in reducing both steatotic and fibro-inflammatory liver involvement with persistency of the early response at 6 months. Whilst baseline anthropometry/glycemic compensation, as PNPLA3 polymorphism, do not influence semaglutide effect on liver disease, their variations in time are relevant for MASLD improvement.

Disclosures: Giovanni Petralli: Nothing to Disclose, Antonio Salvati: Nothing to Disclose, Simone Cappelli: Nothing to Disclose, Nothing to Disclose, Lidia Surace: Nothing to Disclose, Laura De Rosa: Nothing to Disclose, Maurizia Brunetto: Nothing to Disclose

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4093 | ANALYSIS OF MAESTRO-NASH, RESMETIROM RELATIVE TO PLACEBO PATIENTS, ON PRIMARY AND SECONDARY LIVER BIOPSY ENDPOINTS BASED ON ALIGNED BIOPSY ENDPOINTS AND STATISTICAL METHODS: FROM MASH CLINICAL TRIALS

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

Background: MAESTRO-NASH (MN) (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo (PBO)-controlled Phase 3 trial evaluating the efficacy of RES in patients with MASH. 917 patients with biopsy (bx)-confirmed F2F3 MASH were randomized 1:1:1 to RES 80mg, RES 100mg, or PBO once daily. Dual primary endpoints at Week 52 were achieved at both doses: NASH resolution (ballooning 0, inflammation 0,1) with no worsening of fibrosis (NR) with at least 2-point reduction in NAFLD Activity Score (NAS) or ≥1-stage improvement in fibrosis with no worsening of NAS (FI) (N Engl J Med 2024;390:497-509). Several NASH clinical trials utilized slightly different biopsy endpoints and PBO response imputation as the primary statistical methodology, including ESSENCE (ESS). Given the similarity in design and size to MN, ESS a Phase 3 trial evaluating SEMA (SEMA) (2.4 mg weekly) was used as the primary comparator (DOI: 10.1056/NEJMoa2413258). A comparison was made using aligned biopsy endpoints and statistical methods. **Methods:** Bx eligibility in MN and other NASH trials required F2/F3 stage fibrosis and NAS ≥4 with all 3 NAS components. Statistical analyses were conducted according to the statistical plan and subsequent analyses were conducted (MN) to use the assumption (PBO response multiple imputation for missing data in the PBO and RES groups) for the primary endpoints. NR without the requirement for a 2-pt reduction in NAS was analyzed. **Results:** Baseline characteristics of the F2/F3 populations were similar across MASH trials. Using a PBO-based imputation for missing data, RES 100 mg showed a ~2.4-fold odds ratio (OR) and 14.6% increment relative to PBO of FI comparable to a ~2-fold OR and a 14.4% FI with SEMA. Comparison of NR versus NR with ≥ 2 pt reduction in NAS showed that 83% of patients in MN had ≥ 2 pt improvement in NASH components to achieve NR, 17% had <2-pt reduction. In ESS 31% of the SEMA with NR and 45% of the PBO with NR had <2 pt reduction in MASH components, decreasing the rate of NR from 62.9% to 43.5% and 34.3% to 18.8% in the SEMA and PBO arms, respectively. Approximately equal numbers of drug treated and PBO patients in each study had ≥ 2-pt reduction in NAS. Ballooning reduction by RES was achieved in (66%) of RES treated patients with a difference from PBO (35%) compared with SEMA (61%, difference from PBO, 21%). **Conclusion:** Both RES and SEMA achieved both liver biopsy endpoints, improving NASH and liver fibrosis in the MN and ESS Phase 3 studies. Using an aligned statistical method, RES and SEMA showed 14-15% improvement of drug treatment relative to PBO in ≥1 stage fibrosis improvement at 1 and 1.5 years, respectively. RES and SEMA difference from PBO were 21% (3-fold relative to PBO) and 25% (2-fold relative to placebo), respectively, for NR requiring ≥2-pt NAS reduction. When evaluated for a 2-pt reduction in NAS, PBOs in MN and ESS had a similar response suggesting that PBOs responded comparably in the two studies.

	MAESTRO-NASH[1]				ESSENCE[1]		
Biopsy Endpoints	RES 80 mg po qd	RES 100 mg po qd	PBO po qd	Difference 100 mg from PBO	SEMA 2.4mg sc qw	PBO	Difference SEMA from PBO
≥1 Stage Fibrosis Improvement without worsening of NAS (FI)	27.3%	29.5%	15.0%	14.6%	36.8%	22.4%	14.4%
NASH resolution (NR)	29.8%	35.8%	13.3%	23.0%	62.9%	34.3%	28.7%
NR with ≥2-pt NAS reduction	26.1%	29.9%	9.1%	21.4%	43.5%	18.8%	24.8%
2 pt-NAS reduction	46.0%	50.5%	25.1%	25.1%	50.1%	25.0%	25.3%
NAS Components[2] (% of biopsies with improvement)							
Ballooning	60%	66%	31%	35%	61%	40%	21%
Inflammation	46%	48%	32%	16%	39%	21%	18%
Steatosis	61%	68%	31%	37%	74%	43%	31%
NAS	79%	81%	51%	30%	86%	57%	29%

[1]Missing data set as PBO response for biopsy endpoints; [2] observed data, bx completer analysis; other analyses include PBO imputed response for missing data in treatment arms

Disclosures: Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck:

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4094 | IMPACT OF ENDOSCOPIC GASTRIC REMODELLING IN METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Metabolic dysfunction-associated fatty liver disease (MAFLD), a leading cause of chronic liver disease in the United States, is linked to obesity and insulin resistance. Endoscopic gastric remodelling (EGR) has proven to be safe, effective, and less invasive than bariatric surgery in the management of obesity. It includes two primary approaches, mainly endoscopic sleeve gastroplasty, endoscopic gastric plication, and primary obesity surgery endoluminal. Our meta-analysis aims to evaluate MAFLD and other metabolic parameters post-EGR. **Methods:** We performed a comprehensive, systematic search of multiple

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electronic databases, including conference proceedings, from inception through November 2024 to identify studies that evaluated MAFLD and other metabolic parameters post EGR. Weighted mean differences and pooled proportions were calculated using both Mantel-Haenszel method (fixed effects model) and Der Simonian Laird method (random effects model). The heterogeneity among studies was tested using Cochran's Q test based upon inverse variance weights. The primary outcomes were improvement in non-alcoholic fatty liver disease (NAFLD) fibrosis score, hepatic steatosis index (HSI) score, and alanine aminotransferase (ALT). The secondary outcomes were improvement in fibrosis-4 score (FIB4), % excess weight loss (%EWL), % total weight loss (%TWL), body mass index (BMI), and glycated hemoglobin (HbA1c). **Results:** A total of 6 studies met our inclusion criteria and comprised 220 patients that underwent EGR. The pooled analysis showed a reduction of 0.65 in NAFLD fibrosis score (95% CI = -0.89 to -0.42), 0.07 in FIB4 score (95% CI = -0.22 to 0.07), 14.39 U/L in ALT (95% CI = -18.93 to -9.84), 6.30 kg/m2 in BMI (95% CI = -7.30 to -5.30), and 0.32% in HbA1c (95% CI = -0.43 to -0.21). The weighted mean HSI reduced from 50.36 +/- 3.00 to 42.66 +/- 2.38 post EGR. The pooled %EWL was 47.80% (95% CI = 41.03 to 54.57), and %TWL was 16.24% (95% CI = 14.98 to 17.50). The Begg-Mazumdar indicator gave Kendall's tau b value of -0.33 (p = 0.33), suggesting no publication bias. **Conclusion:** EGR provides weight loss and improvement in liver parameters. It is a safe and effective treatment strategy for MAFLD in obese patients.

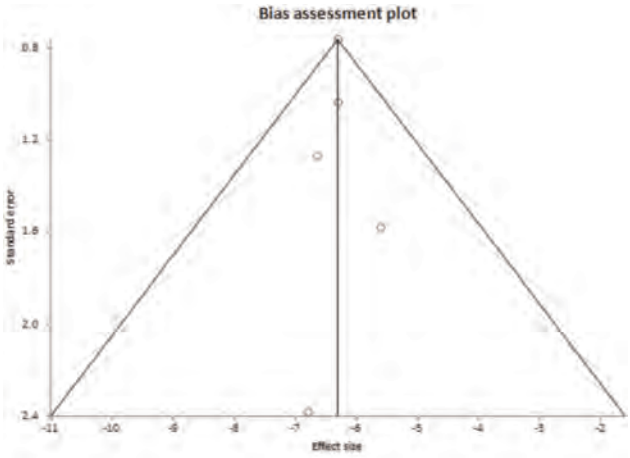

Figure 1:Funnel plot showing publication bias.

Disclosures: Yusuf Kagzi: Nothing to Disclose, Abuzar Asif: Nothing to Disclose, Srinivas Puli: Nothing to Disclose

4095 | EXERCISE PARTLY PROTECTS AGAINST SEMAGLUTIDE-INDUCED MUSCLE LOSS IN OBESE LDLR$^{-/-}$.LEIDEN MICE

Eveline Gart[1] Jose Inia[1] Jessica Snabel[1] Simone Droog[1] Anita van Nieuwkoop[1] Simon Folkertsma[1] Aswin Menke[1] J Wouter Jukema[2] Hans Princen[1] Anita van den Hoek[1], [1]TNO Metabolic Health Research, [2]LUMC

Background: Semaglutide, a glucagon-like peptide-1 receptor agonist, is an antidiabetic medication that has recently been approved for treatment of obesity as well. While the benefits of semaglutide for weight management are encouraging, concomitant muscle loss can be a potential drawback. Here, we evaluated the metabolic effects of semaglutide, exercise and the combination thereof in a translational model of obesity and associated complications. **Methods:** Ldlr$^{-/-}$.Leiden mice received a high fat diet (HFD) for 20 weeks to induce obesity, insulin resistance and hyperlipidemia. Mice were subsequently left untreated (control) or were treated for 14 weeks with semaglutide, exercise (running-wheel) or the combination thereof. Body weight, lean body mass (EchoMRI) and plasma parameters were evaluated during the study and liver, muscles, adipose tissue depots, hearts and brain were collected at end-point for histological analysis and future transcriptomics. **Results:** Already after 2 weeks of treatment, semaglutide either alone (-21%), or in combination with exercise (-23%) significantly decreased body weight, while exercise monotreatment tended to slightly reduce body weight (with -3%, p = 0.056). Semaglutide monotreatment significantly reduced both fat mass (-43%) and lean body mass (-11%), while in combination with exercise fat mass was significantly decreased (-50%), but loss of lean body mass could be prevented.

At the end of the study, lean body mass and muscle mass were decreased with semaglutide monotreatment but also when combined with exercise, although to a lesser extent. Absolute grip strength was significantly increased as compared to the HFD control group in combination treatment only. Semaglutide treatment either alone, or in combination with exercise significantly improved blood glucose, plasma insulin, cholesterol and triglyceride levels. Liver steatosis and inflammation in liver and adipose tissue improved with all interventions, while hepatic fibrosis was not significantly affected. Significant additional effects for the combined semaglutide/exercise intervention vs. semaglutide monotreatment were observed for plasma insulin, grip strength and macrovesicular steatosis.

Transcriptomics analyses are currently still ongoing and will be used to further evaluate the underlying pathways

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and organ cross-talk. **Conclusion:** Using a translational model of obesity and the Metabolic Syndrome, we demonstrated that semaglutide has broad beneficial effects on plasma, adipose and liver parameters, but decreased lean body mass and muscle mass. Adding exercise to semaglutide intervention further improved plasma insulin, muscle strength and liver steatosis.
Disclosures: Eveline Gart: Sagimet: Independent Contractor, Verge Genomics: Independent Contractor, PRD therapeutics: Independent Contractor, Logick Energetics: Independent Contractor, Jose Inia: Nothing to Disclose, Jessica Snabel: Nothing to Disclose, Simone Droog: Nothing to Disclose, Anita van Nieuwkoop: Nothing to Disclose, Simon Folkertsma: Nothing to Disclose, Aswin Menke: Nothing to Disclose, J Wouter Jukema: Nothing to Disclose, Hans Princen: Nothing to Disclose, Anita van den Hoek: ProQR: Independent Contractor, Yoxlo: Independent Contractor, E-Therapeutics: Independent Contractor, Abbott: Independent Contractor, Amarin Corporations: Independent Contractor, Enveda Biosciences: Independent Contractor, NorthSea Therapeutics: Independent Contractor, Calico: Grant/Research Support, Reckitt: Grant/Research Support, New Amsterdam Pharma: Independent Contractor, Clasado Biosciences: Grant/Research Support, PRD Therapeutics: Independent Contractor

4096 | LEVERAGING GLUCAGON ACTIVITY TO TARGET HEPATIC STEATOSIS, FIBROSIS, AND INFLAMMATION

Sarah Anissa Hannou[1] David Bouslov[1] Sean Ferrano[1] Danielle Leander[1] Donald Wothe[1] Marshall Paisley[1] Alex Chen[1] David D'Alessio,[1] Phillip White[1] Jonathan Campbell[1], [1]Duke Molecular Physiology Institute, Duke University, Durham, North Carolina, USA

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) and steatohepatitis (MASH) have limited effective therapeutic treatments. Incretin-based therapies have revolutionized the treatment of diabetes and obesity, with emerging evidence supporting their use in liver disease. Semaglutide, a glucagon-like peptide-1 receptor (GLP-1R) agonist, reduces liver fat with limited improvements of fibrosis or inflammation. Moreover, the GLP-1R is not expressed in hepatocytes and it remains unclear whether the effects of semaglutide are independent of weight loss. The glucagon receptor (GCGR) is expressed in hepatocytes and agonism increases catabolic metabolism including lipid oxidation. GCGR:GLP-1R co-agonism is being pursued for the treatment of both obesity and MASH, however, there are gaps in our understanding of how GCGR agonism can impact features of MASH including fibrosis and inflammation. Moreover, patients with MASH may display hepatic GCGR resistance, which could limit the use of GCGR agonism. **Methods:** We hypothesized that chronic GCGR agonism would improve hepatic steatosis, fibrosis and inflammation in a mouse model of MASH. To test this, we fed mice housed at thermoneutrality a MASH inducing diet (GAN; Gubra-Amylin NASH) for 23 weeks to produce hepatic steatosis, inflammation, and fibrosis. **Results:** Hepatic GCGR signaling, assessed through the quantification of canonical signaling pathways following an acute bolus of a GCGR agonist (IUB288, 10 nmol/kg), was significantly reduced in mice fed a GAN diet compared to controls, indicating GCGR resistance. Next, we chronically treated groups of mice with PBS (control), semaglutide (3 nmol/kg), IUB288 (10 nmol/kg) or the combination of both daily for three weeks. Compared to control, all groups lost weight (semaglutide - 12%; IUB288 -18%, combination -21%). Histological and biochemical analysis of liver samples after three weeks showed reductions in steatosis and fibrosis in the IUB288 and combinations groups only. Interestingly, markers of immune cells (MAC-2) did not change in any of the treatment groups relative to control. **Conclusion:** Collectively, our data indicate that GCGR agonism can effectively reduce steatosis and fibrosis, despite the observed GCGR resistance. Moreover, semaglutide alone did not reduce either steatosis or fibrosis, however, did add to the effects of GCGR agonism. These findings provide support for GCGR agonism as a therapeutic means for improving features of MASH.
Disclosures: Sarah Anissa Hannou: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co: Grant/Research Support, David Bouslov: Nothing to Disclose, Sean Ferrano: Nothing to Disclose, Danielle Leander: Nothing to Disclose, Donald Wothe: Nothing to Disclose, Marshall Paisley: Nothing to Disclose, Alex Chen: Nothing to Disclose, David D'Alessio,: Eli Lilly: Consultant, Sun Pharmaceuticals: Consultant, MBX: Consultant, Phillip White: Nothing to Disclose, Jonathan Campbell: Nothing to Disclose

4097 | APPLYING CLINICAL TRIAL RESULTS: TO INDIVIDUAL PATIENT CARE: A GUIDE FOR CLINICIANS

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Background: Clinicians are often challenged in translating the results of clinical trials into treatment decisions for individual patients. We demonstrate how clinical trial information can be used to estimate an individual patient's likelihood of responding to treatment. **Methods:** Resmetirom, recently approved by the FDA for the treatment of metabolic dysfunction-associated steatohepatitis (MASH), was used as an example based on

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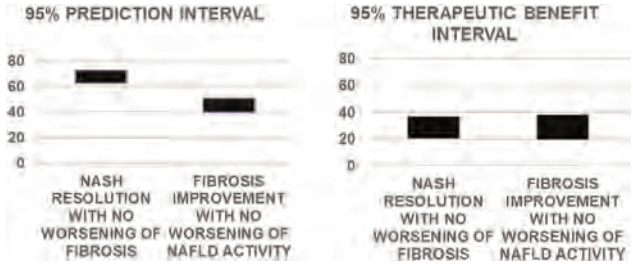
data from a placebo-controlled clinical trial (N Engl J Med 2024;390:492–509). Two concepts were applied:
Prediction Interval estimates the range within which the response rate for an individual patient is likely to fall. It is derived by expanding the trial's confidence interval slightly to account for individual variability and uncertainty due to sample size.
Probability of Therapeutic Benefit estimates the likelihood that a positive treatment response in an individual is actually due to the treatment, rather than to chance or placebo effect. It is calculated by comparing the treatment and placebo response rates—specifically, by expressing the difference between them as a percentage of the total treatment response rate. **Results:** The figure accompanying this summary illustrates the calculated prediction intervals and probabilities of therapeutic benefit for subjects receiving 100 mg of Resmetirom: Prediction Interval indicates that an individual patient's likelihood of responding to Resmetirom is at least 62% for NASH resolution and 40% for improvement in fibrosis. Therapeutic Benefit Estimate indicates that among patients who respond to Resmetirom, the probability that their improvement is directly attributable to the drug—rather than to a placebo effect—is at least 20% for NASH resolution and 16% for fibrosis improvement.
Importantly, the prediction intervals are broader and higher than the therapeutic benefit estimates because they reflect the overall likelihood of a response, regardless of its cause, while the therapeutic benefit estimates isolate the effect of the treatment itself. **Conclusion:** Data from clinical trials can be used to personalize treatment decisions. The prediction interval provides an estimate of the chance that an individual will show a clinical response to therapy, while the probability of therapeutic benefit evaluates whether a positive outcome is likely due to the treatment. Both measures help clinicians make more informed decisions when applying group-level trial data to individual patients.



Disclosures: Shobha Joshi: Gilead Sciences: other, Jerry Gardner: Nothing to Disclose

4098 | SAFETY AND EFFICACY OF DUAL INCRETIN RECEPTOR AGONISTS FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: The role of dual incretin receptor agonists in metabolic dysfunction-associated steatotic liver disease (MASLD) remains debated but may offer added benefits due to the liver's lack of GLP-1 receptor expression. Given the emerging interest in incretin co-agonists, we performed a meta-analysis to evaluate their efficacy and safety in MASLD. **Methods:** We systematically searched PubMed, Embase, and Cochrane for studies comparing incretin co-agonists to placebo in patients with MASLD, with or without fibrosis. Primary outcomes included the absolute reduction in hepatic fat fraction (HFF), resolution of metabolic dysfunction-associated steatohepatitis (MASH) without worsening of fibrosis, and regression of fibrosis without worsening of MASH. Secondary outcomes included liver transaminases, weight changes, and gastrointestinal (GI) side effects. Statistical analysis was performed using Review Manager 5.4, with doses stratified into three categories: low, medium, and high. **Results:** A total of 651 patients across four randomized controlled trials were included in the analysis. Incretin co-agonists were administered to 73.9% (n = 481) of participants: 34.9% (n = 168) received low-dose, 29.5% (n = 142) received medium-dose, and 35.6% (n = 171) received high-dose. Significant reductions in absolute HFF were observed at all dosage levels, with the most pronounced reduction seen at the medium dose: (Mean Difference [MD] –10.50%; 95% CI –15.78 to –5.21; $p < 0.0001$). Fibrosis regression without worsening of MASH was significantly better in the incretin co-agonists group at all doses, and, in patients with F2/F3 fibrosis, significant improvements in fibrosis by at least one stage were observed across all doses, with the highest significance at the high dose group (RR

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1.80; 95% CI 1.22 to 2.66; p = 0.003). Reductions in ALT (MD -23.53 U/L; 95% CI -37.94 to -9.12; p = 0.001) and AST (MD -23.70 U/L; 95% CI -31.27 to -16.12; p < 0.00001) were greater at high doses. Additionally, weight loss was dose-dependent (MD -6.63%; 95% CI -12.44% to -0.82%; p = 0.03), as well as GI side effects. **Conclusion:** Incretin co-agonists were associated with improvements in liver fibrosis, fat content, and inflammation in patients with MASLD/MASH compared to placebo. Notably, their effect appears to be dose-dependent.

Table 1. Summary of Key Outcomes

Outcomes	Low Dose	Medium Dose	High Dose
Absolute Reduction in HFF (MD, %)	-6.43 (95% CI -10.17 to -2.69; p=0.0007)	-10.50 (95% CI -13.79 to -5.21; p<0.0001)	-8.51 (95% CI -11.26 to -5.76; p<0.00001)
MASH resolution without worsening of fibrosis (RR)	3.02 (95% CI 2.31 to 6.66; p<0.00001)	5.13 (95% CI 3.07 to 8.58; p<0.00001)	4.29 (95% CI 2.53 to 7.28; p<0.00001)
Fibrosis regression without worsening of MASH (RR)	1.72 (95% CI 1.18 to 2.51; p=0.005)	1.70 (95% CI 1.16 to 2.49; p=0.007)	1.69 (95% CI 1.15 to 2.47; p=0.007)
F2/F3 liver fibrosis improvement by ≥ 1 stage (RR)	1.71 (95% CI 1.15 to 2.53; p=0.008)	1.59 (95% CI 1.06 to 2.37; p=0.02)	1.69 (95% CI 1.22 to 2.66; p=0.003)
ALT Reduction (MD, U/L)	-21.29 (95% CI -36.13 to -6.44; p=0.005)	-23.53 (95% CI -40.69 to -6.37; p=0.007)	-23.53 (95% CI -37.94 to -9.12; p=0.001)
AST Reduction (MD, U/L)	-20.37 (95% CI -28.70 to -12.03; p<0.00001)	-23.21 (95% CI -29.24 to -17.18; p<0.00001)	-23.70 (95% CI -31.27 to -16.12; p<0.00001)
Weight Loss (MD, %)	-4.18 (95% CI -8.37 to 0.01; p=0.05)	-5.52 (95% CI -7.11 to -3.93; p<0.00001)	-6.63 (95% CI -12.44 to -0.82; p=0.03)
Diarrhea (RR)	1.57 (95% CI 1.08 to 2.29; p=0.02)	2.00 (95% CI 1.40 to 2.86; p=0.0002)	1.54 (95% CI 0.75 to 3.13; p=0.24)
Appetite suppression (RR)	3.07 (95% CI 1.50 to 6.28; p=0.002)	2.44 (95% CI 1.10 to 5.38; p=0.03)	3.80 (95% CI 1.12 to 10.35; p=0.03)
Vomiting (RR)	7.18 (95% CI 2.88 to 17.91; p<0.0001)	8.19 (95% CI 3.14 to 21.37; p<0.0001)	9.25 (95% CI 3.77 to 22.68; p<0.00001)

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CI: Confidence Interval; HFF: Hepatic Fat Fraction; MASH: Metabolic dysfunction-associated steatohepatitis; MD: Mean Difference; RR: Risk Ratio

Disclosures: Najwaa Kirmani: Nothing to Disclose, Bezalel Hakkeem: Nothing to Disclose, Abdullah Alharran: Nothing to Disclose, Imran Reshi: Nothing to Disclose, Ali Artam Alajmi: Nothing to Disclose, Amal Alsubaiei: Nothing to Disclose, Dhruvi Joshi: Nothing to Disclose, Eliabe Abreu: Nothing to Disclose

4099 | GSK4532990 PHARMACOKINETIC–PHARMACODYNAMIC (PK–PD) MODELING SUPPORTS QUARTERLY AND MONTHLY SIRNA DOSING FOR MASH IN THE HORIZON PHASE 2B STUDY

Itziar Irurzun-Arana[1] Hardik Chandasana[2] Nieves Lopez-Barrera[3] Nikhil Vergis[4] Diogo Ferrinho[2] Sumanta Mukherjee[2] Mindy Magee[2] Stuart Kendrick[5] Brandon Swift[6], [1]GSK, Madrid, Spain, [2]GSK, Collegeville, PA, USA, [3]GSK, San Francisco, CA, USA, [4]GSK, London, UK, [5]GSK, Stevenage, UK, [6]GSK, Durham, NC, USA

Background: Loss-of-function (LOF) mutations in the *hydroxysteroid 17-β-dehydrogenase-13 (HSD17B13)* gene are associated with a reduced risk of alcohol- and non-alcohol-related liver disease, including metabolic dysfunction-associated steatohepatitis (MASH). GSK4532990 is a GalNAc-siRNA-based therapeutic, that selectively targets *HSD17B13* in hepatocytes, and is being evaluated for the treatment of MASH in the Phase 2b HORIZON study (NCT05583344). Our objective was to select GSK4532990 doses with maximum reduction in hepatic HSD17B13 protein and a prolonged PD effect to allow for infrequent dosing (e.g. quarterly) to test the hypothesis that this will translate to a similar protective effect on the liver as *HSD17B13* LOF mutations. This analysis used PK–PD modeling to support Phase 2b dose selection. **Methods:** A population PK–PD model was built using GSK4532990 plasma concentrations and serum alanine aminotransferase (ALT) levels from the Phase 1/2a study in healthy volunteers (N = 16) and participants (N = 18) with clinically suspected MASH (NCT04202354). An additional PK–PD model of target engagement was developed using the hepatic HSD17B13 protein levels from the suspected MASH participants (N = 15). Standard evaluation techniques were used to assess model adequacy and robustness. **Results:** The PK–PD models accurately described the observed time course and magnitude of ALT reduction and HSD17B13 protein knockdown. The models were able to describe the interindividual variability on the PK and PD response across a wide range of doses. Consistent with other GalNAc-siRNAs, average plasma half-life of GSK4532990 was very short (8 hours or less) due to rapid hepatocyte uptake. However, the PD effect was predicted to be far longer and potentially maintained for up to 3 months, enabling infrequent dosing. Reductions in hepatic HSD17B13 protein were less variable with increasing doses and were high (> 80% on average) at 100 and 200mg, demonstrating a robust on-target pharmacologic response in the liver. **Conclusion:** PK–PD modeling of hepatic HSD17B13 protein and ALT predicted that doses of 100mg every 4 weeks and 200mg every 3 months have the potential to maintain robust HSD17B13 and ALT reduction over the respective dosing intervals despite the rapid elimination of GSK4532990 from the systemic circulation. These data support the once-quarterly or once-monthly dosing strategy in the ongoing HORIZON Phase 2b study.

Disclosures: Itziar Irurzun-Arana: GSK: Employed by GSK and hold financial equities in GSK, Hardik Chandasana: Nothing to Disclose, Nieves Lopez-Barrera: Nothing to Disclose, Nikhil Vergis: GSK: Holds financial equities, Diogo Ferrinho: Nothing to Disclose, Sumanta Mukherjee: Nothing to Disclose, Mindy Magee: Nothing to Disclose, Stuart Kendrick: Nothing to Disclose, Brandon Swift: GSK: Employee, GSK: Stock - publicly traded company

4100 | TURNING THE TIDE ON FATTY LIVER: EFFICACY AND SAFETY OF GLP-1 RECEPTOR AGONISTS IN THE TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND STEATOHEPATITIS – A SYSTEMATIC REVIEW

Harika Dadigiri[1] Hriday Shah[1] Komal Arora[1] Pramil Cheriyath[1], [1]NYMC Saint Clare's and Saint Mary's General hospital

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Background: MASH and MASLD are linked to obesity and metabolic syndrome, but there are currently no effective pharmacological treatments for these conditions. Targeting liver pathology and related metabolic risk factors has shown promise for GLP-1 RAs, which were initially created to treat type 2 diabetes and obesity. In patients with MASLD/MASH, this systematic review investigates the safety and effectiveness of GLP-1 RAs. **Methods:** A comprehensive literature search was conducted according to PRISMA guidelines across major databases from inception to January 2025. Randomized controlled trials and Observational studies investigating GLP-1 RA in adults with MASLD or MASH were included. The primary outcomes assessed were hepatic fat reduction, resolution of MASH, and improvement in fibrosis stage. Secondary outcomes included changes in body weight, glycemic control, liver enzymes, cardiovascular risk, and quality of life. Data extraction and quality assessment were independently performed by two reviewers. **Results:** Eight studies with MASLD/MASH patients and treatment durations ranging from 24 to 72 weeks were included. Semaglutide was primarily studied. Semaglutide 0.4 mg achieved MASH resolution in 59% of patients, compared to 17% with a placebo ($p < 0.001$) in patients with F1–F3 fibrosis. GLP-1 RAs consistently decreased the amount of fat in the liver. However, patients with compensated cirrhosis did not show a significant improvement in their fibrosis. Body weight, liver enzyme levels, and glycemic control (HbA1c reduction of 1.0–1.5%) were all significantly improved by all GLP-1 RAs. Additionally, semaglutide improved physical health and pain scores and significantly decreased cardiovascular events. Cotadutide produced greater weight loss than liraglutide. Although they were usually mild and temporary, gastrointestinal side effects (diarrhea, nausea) were the most frequent, occurring in 42–46% of patients. Discontinuation rates were low similar to those of a placebo. **Conclusion:** GLP-1 receptor agonists, particularly semaglutide, offer significant benefits in reducing hepatic fat, resolving MASH, and improving cardiometabolic parameters in MASLD/MASH patients, especially those with early-stage fibrosis. Their safety profile is favorable, with manageable gastrointestinal side effects. While benefits in advanced fibrosis are limited, GLP-1 RAs are poised to become a cornerstone in the management of MASLD/MASH, especially for patients with metabolic comorbidities. Further research is warranted to define their role in advanced liver disease and in combination regimens.

Table 1: Efficacy of GLP-1 receptor agonists in MASLD/MASH

Study (Year)	Intervention	Patient Population	Duration	Primary Outcome	Results
Armstrong et al. (2025)	Semaglutide	MASLD/MASH (with and without T2DM)	48-72 wks	Hepatic fat and weight loss	Significant hepatic fat and weight reduction
Liu et al. (2025)	Dulaglutide	T2DM, NAFLD	26 wks	Hepatic fat reduction	Significant hepatic fat reduction and glycemic control
Newsome et al. (2021)	Semaglutide 0.4 mg	NASH, F1–3 fibrosis	72 wks	NASH resolution, fibrosis	NASH resolution significant (59% vs. 17%), no fibrosis difference
Loomba et al. (2023)	Semaglutide 2.4 mg weekly	NASH, compensated cirrhosis	48 wks	Fibrosis, NASH resolution	No significant fibrosis or NASH resolution; improved liver enzymes, liver fat, cardiometabolic parameters
Romero-Gómez et al. (2023)	Semaglutide (various doses)	NASH, F1–3 fibrosis	72 wks	Health-related quality of life	Improved physical HRQoL; no mental HRQoL improvement
Harreiter et al. (2021)	Exenatide + Dapagliflozin vs. Placebo + Dapagliflozin	T2DM, MASLD	24 wks	Reduction of hepatocellular lipids (HCL)	Significant HCL reduction in both groups, no additional benefit from Exenatide
Zhang et al. (2020)	Liraglutide vs. Pioglitazone	T2DM, NAFLD	24 wks	Hepatic fat, fetuin-A	Liraglutide significantly restored hepatic fat, fetuin-A more than Pioglitazone
Nahra et al. (2021)	Cotadutide vs. Liraglutide	T2DM, overweight/obesity	54 wks	Metabolic, hepatic parameters	Cotadutide superior in metabolic parameters, liver biomarkers, and weight loss

Disclosures: Harika Dadigiri: Nothing to Disclose, Hriday Shah: Nothing to Disclose, Komal Arora: Nothing to Disclose, Pramil Cheriyath: Nothing to Disclose

★ 4101 | EFFECTIVENESS OF SEMAGLUTIDE IN NON-ALCOHOLIC STEATOHEPATITIS RESOLUTION A META-ANALYSIS AND SYSTEMATIC REVIEW

Claudine Feliciano[1], [1]Skyline Hospital and Medical Center, Philippines

Background: Non-alcohol related fatty liver disease (NAFLD) is characterized by steatosis resulting from factors unrelated to excessive alcohol consumption. It frequently coexists with other metabolic disorders such as high cholesterol, obesity, and diabetes. NAFLD can lead to complications such as fibrosis, cirrhosis, and an elevated risk of hepatocellular carcinoma, cardiovascular disease, chronic kidney disease, and mortality.
The use of glucagon-like peptide-1 (GLP-1) analogues is currently being studied as a possible treatment option in NAFLD. GLP-1 receptor agonists have pleiotropic effects on several aspects of metabolic syndrome relevant to treatment of NASH, including body weight, inflammation, and glucose and lipid metabolism. **Methods:** A comprehensive literature search showed 4 randomized controlled trials (N = 604) comparing Semaglutide (0.4mg/day or 2.4mg/week) with placebo. Two reviewers independently selected studies, assessed quality, and extracted and pooled outcomes

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including liver histology, aspartate transaminase (AST), alanine transaminase (ALT), Triglyceride, Hba1c levels and body weight . All selected studies were found to be of low risk of bias based on Cochrane risk of bias assessment tool for randomized trials. **Results:** 4 RCTs (604 patients) were analyzed, improvement of NASH as compared to those receiving placebo was noted (WMD = 0.23 95%CI: 0.12; 0.46) with a p-value of 0.0001; I2 = 66%, fibrosis stage (WMD = 2.21 95%CI: 1.04; 4.52) with a p-value of 0.03; I2 = 0%, serum ALT activity (WMD = -0.19; 95% CI: -1.73; 1.34) with a p-value of 0.36 ; I2 = 0% (low heterogeneity) and AST activity (WMD = -0.23 95% CI: -1.90; 1.43) with a p-value of 0.33; I2 = 0%, body weight (WMD = -1.05 95%CI: -1.81; -0.29) with a p-value of 0.02; I2 = 83%, Hba1c (WMD = 0.39 95% CI: -0.84; 0.06) with a p-value of 0.07; I2 = 59%, Triglycerides (WMD = -0.28 95%CI: -0.17; 0.17) with a p-value of 0.12; I2 = 30%. **Conclusion:** Our meta-analysis of randomized controlled trials reveals that semaglutide did not significantly improve liver fibrosis, stiffness and steatosis but offers notable liver enzyme, and cardiometabolic benefits for patients with non-alcoholic fatty liver disease, while demonstrating a favorable safety profile. Currently, Semaglutide is available in the Philippines as a once-weekly subcutaneous injection, with price ranging from 7,000 to 8,000 pesos per pen which may be a deciding factor in patients considering this type of medication.

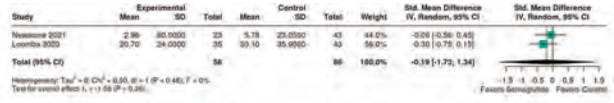

Figure 7. Forrest plot on the effect of Semaglutide vs placebo in the change of liver enzyme: ALT

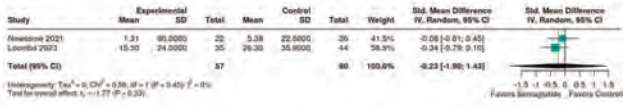

Figure 8. Forrest plot on the effect of Semaglutide vs placebo in the change of liver enzyme: AST

Disclosures: Claudine Feliciano: Nothing to Disclose

4102 | MITOCHONIC ACID-5, A NOVEL MITOCHONDRIAL CRISTAE-STABILIZING AGENT, RESTORES MITOCHONDRIAL FUNCTION AND AMELIORATES MASH PROGRESSION IN DIETARY MURINE MODELS

Masaaki Mino[1] Eiji Kakazu[1] Taiji Yamazoe[1] Michitaka Matsuda[1] Tatsuya Kanto[1], [1]Japan Institute for Health Security, National Institute of Global Health and Medicine

Background: Mitochondrial dysfunction drives hepatic lipotoxicity, oxidative stress and fibrosis in metabolic dysfunction–associated steatohepatitis (MASH), yet no approved agent directly targets these defects. Mitochonic Acid-5 (MA-5), an indole-derived compound, binds to the mitochondrial inner membrane protein mitofilin, stabilizes cristae and enhances ATP synthesis. A phase II trial in patients with primary mitochondrial disease is currently recruiting in Japan. We examined whether MA-5 can rescue hepatocyte mitochondrial dysfunction and attenuate MASH progression in diet-induced murine models. **Methods:** Fifty-week-old male C57BL/6 mice were fed for 25 weeks with a normal chow (NC), a high-fat, high-fructose, high-cholesterol diet (FFC), or an FFC + MA-5 (0.012 % w/w) (n = 7 per group). Serum biochemistry and body weight (BW) were assessed at 15 and 25 weeks. Steatohepatitis was graded by NAFLD Activity Score (NAS) and progression of fibrosis (Masson-Trichrome staining). Mitochondrial ultrastructure (TEM) and hepatic metabolomics (CE-TOFMS) were assessed at 25 weeks. External validation used a high-fat, methionine-restricted, and tyrosine-deficient diet (HF-MRTD) (Hepatology, 2021), treated with MA-5 for 22 weeks. In vitro, PXB® human hepatocytes were exposed to palmitic acid with or without MA-5. Mitochondrial morphology and reactive oxygen species (ROS) were evaluated by fluorescence imaging. Data are presented as mean ± SD. **Results:** The FFC-fed mice developed significant liver injury compared to the NC group by 15 weeks, which persisted at week 25 (ALT 455 ± 40 U/L). MA-5 treatment reduced ALT by 48% (ALT 218 ± 27 U/L, $p < 0.01$) and significantly improved NAS (5.8 ± 0.8 vs 3.2 ± 0.4, $p < 0.01$) and fibrosis scores (2.2 ± 0.4 vs 1.0 ± 0.0, $p < 0.01$). BW did not differ significantly between FFC and FFC + MA-5 (53.5 ± 7.6 vs 51.7 ± 5.2 g, $p = 0.68$), indicating that liver benefits were independent of weight loss. Electron microscopy revealed that the swollen, cristae-depleted mitochondria observed in the FFC group were restored to elongated mitochondria with dense cristae and a normalized endoplasmic reticulum in the MA-5 group. Metabolomic analysis revealed recovery of hepatic amino acids, including TCA-cycle substrates, and a 20% increase in hepatic ATP ($p < 0.01$). In the HF-MRTD mice, MA-5 similarly reduced ALT (227 ± 106 vs 94 ± 36, $p < 0.05$), NAS (4.6 ± 1.1 vs 2.0 ± 1.4, $p < 0.05$), and abolished fibrosis (1.6 ± 0.5 vs 0 ± 0, $p < 0.05$). In hepatocyte cultures, MA-5 ameliorated palmitic-acid–induced mitochondrial fragmentation and ROS generation. **Conclusion:** MA-5 rescues mitochondrial function in hepatocytes and mitigates biochemical, histologic, and metabolic progression of MASH in two independent murine models. These findings support the therapeutic potential of MA-5 as a mitochondria-targeted treatment for patients with MASH.

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4103 | FAT, FIBROSIS, AND FIX: TRANSFORMING CIRRHOTIC OUTCOMES VIA MULTI-MODALITY WEIGHT LOSS APPROACHES

Yashowardhan Taparia[1] Gowri Priya Nair[1] Arathi Venu[1] Sudheer OV[1] Rajesh G[1] Arun Valsan[2], [1]Amrita Institute of Medical Sciences, [2]Amrita Institute of Medical Sciences, Kochi

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of end-stage liver disease and exhibits increased rates of both overall and specific mortality. Most often decompensated cirrhosis is considered irreversible without timely liver transplant. We highlight three cases of obese MASLD cirrhosis who have recompensated with multimodality management aimed at weight reduction. **Methods:** Case 1: 42M MASLD decompensated cirrhosis, BMI 41kg/m^2, on continuous BiPAP, presented with grade II ascites, moderate hepatic hydrothorax and hepatorenal syndrome, was listed for transplant. He was initially managed with initial optimization followed by oral semaglutide, followed by injectable tirzepatide (once commercially available in India), and has now resumed normal activities of daily living. He currently has been recompensated and has only mild lymphedema of right lower limb and is off BiPAP.

Case 2: 53M with MASLD decompensated cirrhosis (Child B9, MELD Na-18) and morbid obesity (BMI 48kg/m^2) with decompensations of encephalopathy and grade III ascites, was initially controlled on diuretics and salt restriction, followed by oral semaglutide for 3 months followed by Endoscopic (Spatz) balloon insertion, achieved around 94 kg weight loss over 1.5 years and has recompensated.

Case 3: 44M, MASLD compensated cirrhosis (CAP-341, LSM-18.1kpa), BMI 44kg/m^2, severe sleep apneoa on domiciliary nocturnal oxygen therapy. Following initial optimization, he was managed by elective laparoscopic sleeve gastrectomy, achieving weight loss of 31 kgs. He no longer requires oxygen, and has significantly reduced non-invasive fibrosis scores (4.6kpa). **Results:** All three patients are traditionally thought to be unfit for any significant clinical interventions other than LT. We demonstrate that with significant control of ascites and other decompensations, a wide array of therapeutic interventions are still possible that may help in downstaging or even recompensating, obviating the need for early LT. All cases have been on a median follow-up of one year and continue to remain recompensated, with adequate diabetic control, improvement in quality of life and improved physical performance. **Conclusion:** Targeted weight loss—pharmacologic, endoscopic or minimally invasive surgical—can reverse liver dysfunction and decompensation in carefully selected patients. These cases show the importance of integrating metabolic therapy into advanced liver care as an option that has to be continually evaluated and offered at specialized centres.

Disclosures: Yashowardhan Taparia: Nothing to Disclose, Gowri Priya Nair: Nothing to Disclose, Arathi Venu: Nothing to Disclose, Sudheer OV: Nothing to Disclose, Rajesh G: Nothing to Disclose, Arun Valsan: Nothing to Disclose

◆ 4104 | LIVER-TARGETED DELIVERY OF HUMAN PLATELET LYSATE-DERIVED HYDROGELS PROMOTE HEPATOCYTE PROLIFERATION, ANGIOGENESIS AND SURVIVAL IN POST-HEPATECTOMY LIVER FAILURE

Ashwini Vasudevan[1] DEEPIKA JAKHAR[1] Doyel Ghoshal[2] Anupama Parasar[1] Simran Sharma[1] Aarti Sharma[1] Dinesh Mani Tripathi[1] Shiv Kumar Sarin[1] Dr. Ashish Maheshwari[3] Sachin Kumar B[2] Savneet Kaur[1], [1]Department of Molecular and Cellular Medicine, Institute of Liver and Biliary Sciences, India, [2]Centre for Biomedical Engineering, Indian Institute of Technology, New Delhi, India, [3]Department of Transfusion Medicine, Institute of Liver and Biliary Sciences, India

Background: Post-hepatectomy liver failure (PHLF) and small for size syndrome (SFSS) are critical complications presenting after liver resection or transplantation. These complications arise due to significant hepatocyte loss and sinusoidal damage. Thus, therapies for PHLF need to address both these challenges simultaneously. Platelet Lysate (PL) has pro-regenerative and angiogenic properties, however its clinical utility

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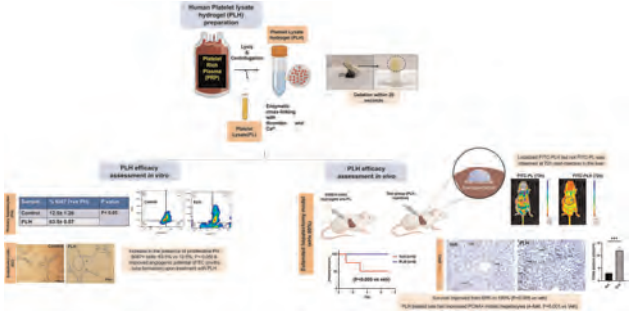
is limited due to rapid diffusion and poor retention. Here, we developed injectable human PL hydrogel (PLH) and studied its efficacy in rat models of PHLF. **Methods:** PL prepared from human platelet-rich plasma, was enzymatically cross-linked with thrombin and calcium to form PLH. Proteomics and biophysical properties of PLH were studied. In vitro, effect of PLH on primary hepatocytes (PH) and endothelial cells (EC) was assessed by flow cytometry and tube formation assay. PLH was injected in 80% extended hepatectomy (eHx) rats in liver sub-capsular region. eHX rats given hydrogel without PL served as vehicle (veh). FITC-PL and FITC-PLH were used in control rats for biodistribution studies by in vivo imaging. Thrombogenicity, survival, hepatic regeneration and angiogenesis were analysed at 72h post injection. **Results:** PLH showed gelation within 20 sec with shape retention properties. LC/MS analysis revealed 1809 and 1812 proteins in PL and PLH respectively with 99.6% common proteins. An abundant expression of albumin, PDGF, IGF-2, and stem cell/ hepatocyte nuclear growth factors was recorded in both PL and PLH. In vitro, compared to control, PLH enhanced proliferation of PH (Ki67+ cells: 12.5 vs 63.5%, $P < 0.05$) and tube length in EC culture ($P < 0.05$). In vivo, FITC-PLH but not FITC-PL was observed at 72h post-injection. No thrombosis was seen in PLH treated rats. Survival improved from 60 to 100% ($P < 0.005$ vs veh) and liver to body weight ratio increased by 60% ($P < 0.005$ vs veh) in PLH treated eHx rats. As compared to that seen in veh, PLH treated rats had increased PCNA+ mitotic hepatocytes (4-fold, $P < 0.001$) and CD31+ sinusoids (2-fold, $P < 0.05$) along with higher serum albumin levels (2-fold, $P < 0.05$). **Conclusion:** Following eHx, liver-targeted delivery of human PLH enables its site-specific retention. PLH enhances both vascular reconstitution and hepatocyte proliferation improving survival after major liver resection. Human PLH has potential as a therapeutic strategy for PHLF and SFSS.



Disclosures: Ashwini Vasudevan: Nothing to Disclose, DEEPIKA JAKHAR: Nothing to Disclose, Doyel Ghoshal: Nothing to Disclose, Anupama Parasar: Nothing to Disclose, Simran Sharma: Nothing to Disclose, Aarti Sharma: Nothing to Disclose, Dinesh Mani Tripathi: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Dr. Ashish Maheshwari: Nothing to Disclose, Sachin Kumar B: Nothing to Disclose, Savneet Kaur: Nothing to Disclose

◆ 4105 | EXPANDABLE, FUNCTIONAL HEPATOCYTES DERIVED FROM PRIMARY CELLS ENABLE LIVER THERAPEUTICS

Sophie Cazanave[1] Sunil Mallana[1] Soujanya Karanth[1] Joseph Marturano[1] Abhijith Kudva[1] Marcus Lehmann[1] Julie Morse[1] Morgan Jamiel[1] Timothy Norman[1] Christopher Wilson[1] Fabiola Munarin[1] David Broderick[1] Maxwell Van Buskirk[1] Esha Uddin[1] Michael Ret[1] Christopher Steele[1] Mehar Cheema[1] Justin Black[1] Eric Vanderploeg[1] Christopher Chen[2] Sangeeta Bhatia[3] Alireza Rezania[1] Thomas Lowery[1] Arnav Chhabra[1], [1]Satellite Bio, [2]Department of Biomedical Engineering, Boston University, Boston, MA 02215, USA, [3]David H. Koch Institute for Integrative Cancer Research, MIT, Cambridge, MA 02139, USA

Background: Cell therapy is a promising approach for end-stage liver disease, yet limited by the lack of a scalable source of functional hepatocytes and poor engraftment. To address these gaps, we hypothesized that combining expanded human hepatocytes (EHHs) with stromal support cells into 3D multicellular aggregates or "seeds," would enhance functional stability across metabolic and detoxification pathways, and improve engraftment at ectopic sites in rodents. **Methods:** EHHs were generated from multiple Primary Human Hepatocyte (PHH) donors using Satellite Bio's proprietary expansion process. To form seeds, EHHs were combined with stromal cells in suspension bioreactors. Seeds were cryopreserved, then evaluated post-thaw for viability, structural integrity, and function across protein synthesis, drug metabolism, and ammonia detoxification axes. Seeds were transplanted into NSG mice and assessed for engraftment via plasma biomarkers, immunohistochemistry of explanted tissue and Alu-based real-time PCR method. Variables such as stromal cell type, cell ratio, and immune modulation with dexamethasone (DEX) were tested across multiple extrahepatic sites (kidney capsule, spleen, fat pad) to optimize engraftment. **Results:** The expansion protocol enabled robust hepatocyte expansion across 13 donors, with 46% achieving >20-fold expansion at passage 0 and a mean fold expansion >4,000 by passage 1 for the three highest expanding donors. Aggregation of EHHs with normal human dermal fibroblasts (NHDFs) into seeds improved function, with *in vitro* albumin and A1AT secretion levels comparable to or exceeding those from PHH seeds. CYP3A4 activity in EHH seeds showed a 5.5-fold induction following rifampin treatment. Cryopreserved seeds demonstrated high stability, with 90% post-thaw recovery, preserved size distribution, and comparable viability (85.0% vs. 86.3% for PHH seeds, p

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= 0.43). *In vivo*, NHDF-seeded constructs exhibited significantly higher engraftment than MSC-seeded or fibroblast-free counterparts (human albumin AUC: 258 μg·day/mL vs. 48 μg·day/mL for MSC, p < 1E-4). DEX treatment further enhanced engraftment in the spleen (AUC: 175 μg·day/mL vs. 132 μg·day/mL, p < 0.01). Stable engraftment across extrahepatic sites was confirmed by sustained human albumin levels and positive staining for OTC and CPS1. **Conclusion:** This work demonstrates that scalable expansion and stromal-supported aggregation can overcome key limitations of hepatocyte-based therapies, offering a clinically viable platform for advancing regenerative treatments in liver disease.

Disclosures: Sophie Cazanave: Nothing to Disclose, Sunil Mallana: Nothing to Disclose, Soujanya Karanth: Nothing to Disclose, Joseph Marturano: Nothing to Disclose, Abhijith Kudva: Nothing to Disclose, Marcus Lehmann: Nothing to Disclose, Julie Morse: Nothing to Disclose, Morgan Jamiel: Nothing to Disclose, Timothy Norman: Nothing to Disclose, Christopher Wilson: Satellite Bio: Employee, Fabiola Munarin: Nothing to Disclose, David Broderick: Nothing to Disclose, Maxwell Van Buskirk: Nothing to Disclose, Esha Uddin: Nothing to Disclose, Michael Ret: Nothing to Disclose, Christopher Steele: Nothing to Disclose, Mehar Cheema: Nothing to Disclose, Justin Black: Nothing to Disclose, Eric Vanderploeg: Satellite Biosciences: Employee, Christopher Chen: Nothing to Disclose, Sangeeta Bhatia: Nothing to Disclose, Alireza Rezania: Nothing to Disclose, Thomas Lowery: Nothing to Disclose, Arnav Chhabra: Nothing to Disclose

◆ 4106 | LIPOPOLYSACCHARIDE BINDING PROTEIN AS A POTENTIAL PREDICTIVE BIOMARKER FOR ACUTE KIDNEY INJURY ONSET IN CIRRHOSIS

Tadashi Namisaki[1] NORIHISA NISHIMURA[2] Shinya Sato[2] Kosuke Kaji[2] Hitoshi Yoshiji[1], [1]Nara Medical University, [2]奈良医大　消化器代謝・内科

Background: Hepato-renal syndrome (HRS) is a type of acute kidney injury (AKI) in patients with liver cirrhosis (LC). The International Club of Ascites (ICA-AKI) has proposed new diagnostic criteria based on changes in serum creatinine (sCr) levels, as even minor increases are associated with high short-term mortality. Most patients with AKI have no AKI-related clinical symptoms. Nonetheless, assessing renal function through sCr in cirrhotic patients is limited due to factors such as sarcopenia and gender-based differences in muscle mass. Endotoxin is a component of gram negative bacterial cell walls, and is a potent trigger of AKI in sepsis. Therefore, there is an urgent need for reliable biomarkers that can predict AKI onset and improve patient outcomes. We aimed to identify a potential biomarker for the outcomes of AKI in LC. **Methods:** This retrospective cross-sectional study included patients with LC who developed AKI (AKI group: n = 91) and patients with LC who did not develop AKI [non-AKI (NAKI) group, n = 91] as a control group. Plasma levels of lipopolysaccharide binding protein (LBP), soluble CD163 (sCD163) and soluble mannose receptor (sMR) were measured in patients with AKI or NAKI. Moreover, risk factors for onset of AKI, AKI-associated 90-day mortality, and poor AKI treatment response were investigated.All parameters were measured from 6 months to onset of AKI onset. **Results:** The AKI group had a significantly higher angiotensin 2, renin, LBP, sCD163, sMR than the NAKI group. In multivariate analysis, values of LBP ≥2550ng/ml were identified as a risk factor for AKI onset in patients with LC (odds ratio [OR], 4.3; 95% CI, 1.82–10.2; p < 0.001). Among patients with AKI, sMR was significantly higher in patients who died within 90days from AKI onset than those who survived over 90days from AKI onset. Values of sMR ≥ 1595 (ng/ml) were identified as risk factors for 90-day mortality (OR 5.98; 95% CI, 1.70– 21.1; p = 0.0054). Cumulative survival was significantly lower in those with high group (sMR ≥1595 ng/ml) than in those with low group (sMR < 1595 ng/ml). Furthermore, among patients with AKI, sMR was significantly higher in patients whose AKI improved than those whose AKI did not improve. Values of sMR ≥1460 (ng/ml) were identified as risk factor for poor treatment response (OR 3.52; 95% CI, 1.09–11.3; p = 0.035). The treatment response rates were significantly higher in those with low (sMR <1460 ng/ml) group than in those with high (sMR ≥1460 ng/ml) group. **Conclusion:** LBP potentially predicts the AKI onset, and sMR predicts survival, and treatment response of AKI in patients with LC.

Disclosures: Tadashi Namisaki: Nothing to Disclose, NORIHISA NISHIMURA: Nothing to Disclose, Shinya Sato: Nothing to Disclose, Kosuke Kaji: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose

◆ 4107 | TREM2 DEFICIENCY EXACERBATES ACUTE LIVER FAILURE BY IMPAIRING MACROPHAGE EFFEROCYTOSIS VIA DISRUPTION OF S100A4-MEDIATED GLYCOLYSIS

SIDUO XU[1] lingzhu zhao[1] SHOUHAN YAO[1] Jingkang Zhang[1] Guohua Lou[1] YANNING LIU[1] Min Zheng[1], [1]The first affiliated hospital of zhejiang university

Background: Acute liver failure (ALF) is a clinical syndrome characterized by rapid deterioration of liver function and high mortality. The clearance of dead cells

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by macrophages (Efferocytosis) is crucial for maintaining liver homeostasis, promoting liver injury repair, and improving the prognosis of ALF. Triggering receptor expressed on myeloid cells 2 (TREM2) is known to regulate macrophage efferocytosis, but its specific mechanism and potential role in ALF remain to be fully elucidated. **Methods:** To investigate the impact of TREM2 deficiency on ALF, wild-type and TREM2 knockout mice were treated with Lipopolysaccharide and D-galactosamine (LPS/D-GalN) to induced ALF model. Bone marrow-derived macrophages (BMDM) were isolated from both genotypes of mice for efferocytosis assay and transcriptome sequencing. Western blotting, real-time quantitative polymerase chain reaction, flow cytometry, and immunofluorescence assays were utilized to explore the potential molecular mechanisms by which TREM2 regulated macrophage efferocytosis. **Results:** TREM2 knockout exacerbated liver injury in mice with ALF and attenuated macrophage efferocytosis both in vivo and in vitro. Transcriptome sequencing and assays found that TREM2 knockout impaired macrophage efferocytosis by attenuating S100A4-mediated glycolysis. Mechanistically, TREM2 knockout inhibited the nuclear translocation of β-Catenin, thus reducing the expression of S100A4. The rescue assay showed that β-Catenin agonist could restore macrophage efferocytosis impaired by TREM2 deficiency and alleviated liver injury in TREM2 knockout mice with ALF. **Conclusion:** The TREM2-β-Catenin-S100A4 axis regulated macrophage efferocytosis, suggesting that TREM2 could be a potential therapeutic target for ALF.

Disclosures: SIDUO XU: Nothing to Disclose, lingzhu zhao: Nothing to Disclose, SHOUHAN YAO: Nothing to Disclose, Jingkang Zhang: Nothing to Disclose, Guohua Lou: Nothing to Disclose, YANNING LIU: Nothing to Disclose, Min Zheng: Nothing to Disclose

4108 | CLINICAL PROFILE, PROGNOSTIC FACTORS AND OUTCOMES IN ACUTE LIVER INJURY DUE TO YELLOW PHOSPHORUS/ METAL PHOSPHIDE POISONING: A LARGE REAL-WORLD COHORT ANALYSIS

Arun Valsan[1] Zubair Mohamed[1] Arathi Venu[1] Nipun Verma[2] Sudhindran Surendran[1] Dinesh Balakrishnan[1] Nimitha Mohan[3] G Unnikrishnan[1] ST Binoj[1] Shwetha Mallick[1] Krishnanunni Nair[1] Gowri Priya Nair[1] Menon Ramachandran[1] Nair Priya[1] Kartha Anandajith[1] Raja Rajat[1] Christi Titus Varghese[1] Zachariah Paul Polachirakal[1] Anoop K Koshy[1] Dr George Eapen Puthusseril[1] Guhan Venkatakrishnan[1] Saraswathy Sivaprasadan[1] KN Anila[1] Haritha Rajakrishnan[1] Smitha Krishnamoorthy[1] Kumar Dhruv[1] Ajay Duseja[2] Rohit Loomba[4], [1]Amrita Institute of Medical Sciences, Kochi, [2]Postgraduate Institute of Medical Education and Research, Chandigarh, [3]Aster Medcity, [4]University of California, San Diego

Background: Yellow phosphorus/Metal phosphide (YPMP) poisoning is a leading cause of toxin-induced acute liver injury (ALI) and acute liver failure (ALF) in India and other developing nations. YPMP, commonly found in rodenticides, induces hepatocellular necrosis and has been responsible for a growing number of ALF cases in tertiary care centers across India. Despite its growing prevalence, the clinical trajectory and outcome predictors in YPMP-induced ALI/ALF are not fully understood. **Methods:** We conducted a retrospective cohort study at a tertiary liver care center between 2005 and 2023. ALF was defined based on the evidence of coagulopathy (INR $>$ 1.5), any degree of hepatic encephalopathy, and an illness of less than 26 weeks' duration. ALI defined as liver injury with INR $>$ 1.5 without encephalopathy. All adults $>$ 18 years with clinically and/ or toxicologically confirmed ALI/ALF were included. Patients were followed up for a minimum of 28 days or until death or liver transplantation (LT). Laboratory and clinical variables were compared across outcome groups and prognostic models evaluated using AUROC analysis to identify predictors of transplant-free survival. **Results:** The median age of the cohort was 24years(IQR:19–30), with M~F. At baseline, 46% had ALF, which was significantly higher among non-survivors (59.5% vs 32.4%, $p = 0.002$). Overall LT-free survival at 90 days was 37.2%, with 51% experiencing death and 16.6% undergoing LT. Cumulative survival was further low in those who had ALF or progressed to ALF on follow up vs those that did not (29.8% vs. 51%, $p = 0.019$). On multivariate analysis, ALF and vasopressor use ($p < 0.05$, M1), HE-grade-III/IV and INR ($p < 0.05$, M2), HE-any grade, INR $>$ 6.0 ($p < 0.039$ and 0.150, M3) were significantly associated with mortality and need for LT. ALFED and MELD models had good prognostic discrimination (AUROC for ALFED = 0.819; MELD = 0.689) for predicting 90-day LT-free survival. Use of mechanical ventilation, vasopressors, RRT, combined CRRT and PLEX was significantly associated with poor prognosis ($p <$ 0.001). 30 did not undergo LT due to financial constraints and 4 due to acuity of organ. **Conclusion:** In this largest real-world cohort of YPMP-induced liver injury, ALF was present in half, and was strongly associated with poor transplant-free survival. These findings underscore the need for early identification of high-risk patients and timely referral for liver transplant evaluation, especially in resource-limited settings. Significant proportion of patients who met LT criteria but could be transplanted due to lack of insurance coverage/ financial constraints. Public health strategies focusing on poison control and improved access to specialized care are warranted.

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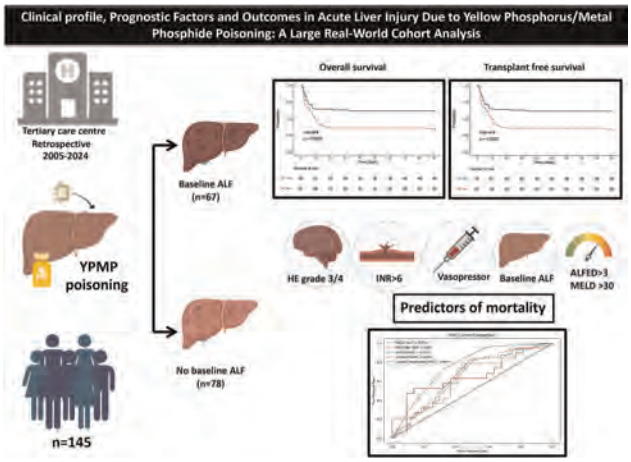

Disclosures: Arun Valsan: Nothing to Disclose, Zubair Mohamed: Nothing to Disclose, Arathi Venu: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Sudhindran Surendran: Nothing to Disclose, Dinesh Balakrishnan: Nothing to Disclose, Nimitha Mohan: Nothing to Disclose, G Unnikrishnan: Nothing to Disclose, ST Binoj: Nothing to Disclose, Shwetha Mallick: Nothing to Disclose, Krishnanunni Nair: Nothing to Disclose, Gowri Priya Nair: Nothing to Disclose, Menon Ramachandran: Nothing to Disclose, Nair Priya: Nothing to Disclose, Kartha Anandajith: Nothing to Disclose, Raja Rajat: Nothing to Disclose, Christi Titus Varghese: Nothing to Disclose, Zachariah Paul Polachirakal: Nothing to Disclose, Anoop K Koshy: Nothing to Disclose, Dr George Eapen Puthusseril: Nothing to Disclose, Guhan Venkatakrishnan: Nothing to Disclose, Saraswathy Sivaprasadan: Nothing to Disclose, KN Anila: Nothing to Disclose, Haritha Rajakrishnan: Nothing to Disclose, Smitha Krishnamoorthy: Nothing to Disclose, Kumar Dhruv: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant, Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder

4109 | NOVEL PREDICTORS OF 30-DAY MORTALITY IN ACUTE LIVER FAILURE: A MULTI-CENTER ACUTE LIVER FAILURE STUDY GROUP (ALFSG) COHORT ANALYSIS

Taranika Sarkar Das[1] Kimberly Ho[2] Xucong Meng[1] Madhavi Reddy[3] Nikki Duong[4], [1]NYU Langone Health, [2]Brown University, [3]The Brooklyn Hospital Center, [4]Stanford Health Care

Background: Traditional prognostic models for acute liver failure (ALF), such as MELD and King's College Criteria, often fall short in accurately capturing the dynamic physiologic decline in these patients who have high short-term mortality. Using the Acute Liver Failure Study Group (ALFSG) registry, this study evaluates novel predictors of 30-day mortality using both established and emerging physiologic markers to enhance risk stratification. **Methods:** We retrospectively analyzed 1,601 adult patients with ALF enrolled in the ALFSG database. Predictor variables included demographics (age, sex), laboratory data (WBC count, bilirubin, creatinine), SOFA sub-scores (renal, hepatic, coagulation, neurologic, respiratory using PaO_2/FiO_2), CLIF-C organ failure (OF) score, liver transplant status, and ALF etiology. Logistic regression models were used to identify predictors of 30-day mortality. **Results:** In univariate analysis, factors associated with increased 30-day mortality included older age (OR 1.02 per year, $p < 0.001$), elevated white blood cell count (OR 1.04 per 1,000/mm³, $p = 0.002$), higher renal SOFA score (OR 1.42, $p < 0.001$), hepatic SOFA score (OR 1.34, $p = 0.001$), and neurologic SOFA (Glasgow Coma Scale) score (OR 1.34, $p < 0.001$). A higher CLIF-C OF score was also associated with increased mortality (OR 1.06 per point, $p < 0.001$), as were "other" etiologies of acute liver failure (ALF) (OR 4.02, $p < 0.001$). Liver transplantation was strongly protective (OR 0.13, $p < 0.001$). On multivariate analysis, etiologies associated with significantly higher 30-day mortality compared to acetaminophen-induced ALF included autoimmune hepatitis, Budd-Chiari syndrome, drug-induced liver injury (DILI), viral hepatitis, idiopathic ALF, mushroom poisoning, and other causes (OR 3.25, $p < 0.001$). A higher CLIF-C OF score remained an independent predictor of 30-day mortality (OR 1.15 per point, $p < 0.001$). **Conclusion:** To our knowledge, this is the first multi-center cohort analysis identifying several novel predictors of short-term mortality in ALF. This underscores the prognostic importance of CLIF-C OF scores,

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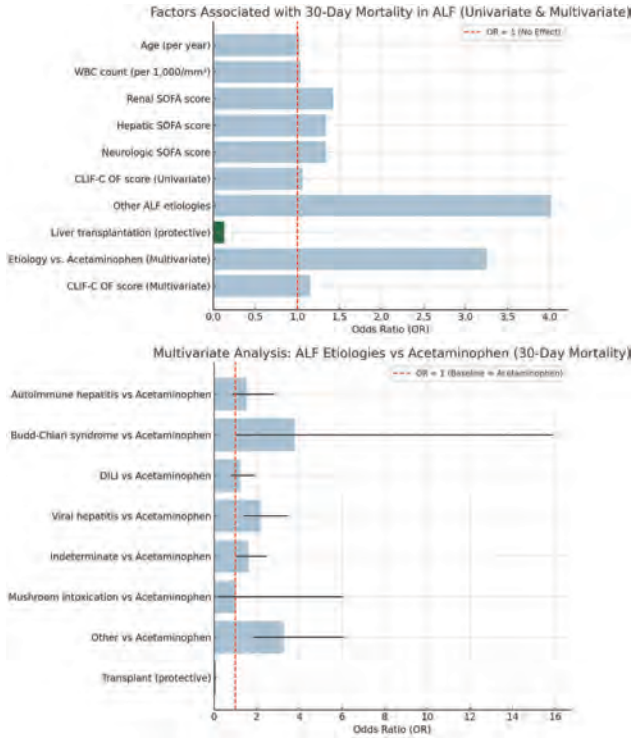
disaggregated SOFA subcomponents, WBC count, and detailed subtypes of ALF. These findings highlight the limitations of traditional scoring systems and support the need for refined prognostic models that integrate systemic inflammation and organ failure metrics to guide timely therapeutic interventions.



Disclosures: Taranika Sarkar Das: Nothing to Disclose, Kimberly Ho: Nothing to Disclose, Xucong Meng: Nothing to Disclose, Madhavi Reddy: Nothing to Disclose, Nikki Duong: Nothing to Disclose

4110 | TREATMENT OF ALCOHOLIC LIVER DISEASE AND LIVER FAILURE USING A NOVEL 3D-PRINTED PLG-BASED IMPLANTABLE THERAPY

Regeant Panday[1] Caitie Chismarich[1] Andrew Golin[1] Xin Li[1] Kirstin Kebo[1] Matthew Remy[1] Jon Burke[1] Ramille Shah[1] Rafal Witek[1], [1]Dimension Bio

Background: Alcoholic liver disease (ALD) is a leading cause of liver failure-related mortality worldwide. Severe forms, such as alcohol-associated hepatitis (AH) and severe alcohol-associated hepatitis (SAH), carry a high mortality rate of up to 50% at 28 days for AH and up to 70% at six months for SAH. Current treatments offer limited benefit, with liver transplantation remaining the only curative option. Alternatively, ectopic implants delivering functional hepatocytes could provide immediate and sustained liver support, serving as a bridge to transplantation or recovery. In this study, we investigated the use of 3D-printed, poly(lactide-co-glycolide) (PLG) scaffolds for subcutaneous delivery of high-density, functional hepatocytes as a novel, minimally invasive treatment for liver failure. **Methods:** 3D-printed PLG scaffolds were seeded with primary hepatocytes. In vitro, cell-loaded scaffolds were cultured for 2+ weeks and evaluated for cell viability, albumin and urea synthesis, and CYP3A4 activity. In vivo, scaffolds were implanted subcutaneously in healthy NOD SCID mice and C57BL/6 mice with CCl_4-induced liver failure. Circulating human albumin (hALB) levels and survival rates were monitored. Explanted scaffolds were analyzed histologically and immunohistochemically for tissue integration and vascularization. **Results:** In vitro, hepatocyte-laden scaffolds maintained stable albumin and urea production with preserved metabolic activity for 2+ weeks. In vivo, sustained hALB levels were detected up to 8 weeks post-implantation. Histological analysis revealed dense vascular networks and healthy connective tissue formation within the explanted scaffolds. In contrast, hepatocyte-loaded hydrogel controls exhibited minimal tissue integration and vascularization in the same period. Kaplan–Meier analysis in liver failure rescue models implanted with syngeneic mouse hepatocytes and xenogeneic human hepatocytes under immunosuppression, exhibited survival improvements of $>70\%$ (Fig. 1) and $>50\%$, respectively, relative to the controls. **Conclusion:** Dimension Bio's 3D-printed scaffolds represent a promising platform for ectopic liver implantation as demonstrated by efficient hepatocyte delivery and sustained functional phenotype (synthetic and metabolic), supported by robust vascularization and integration. Future studies will evaluate the efficacy of using PLG scaffolds to deliver hepatocytes to treat rapid loss of hepatic function, such as in liver failure.

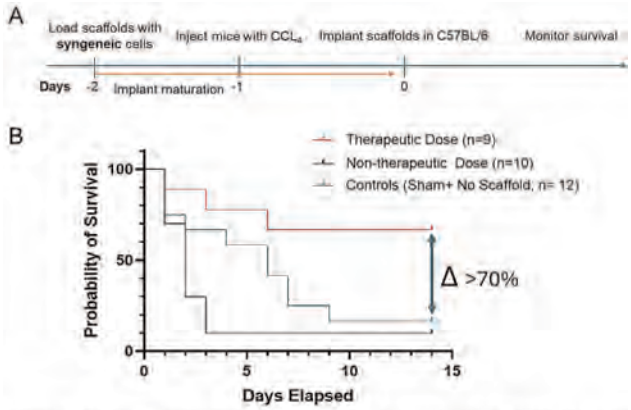


Figure 1. Syngeneic transplantation of primary mouse hepatocytes in Dimension Bio's 3D-printed scaffolds allows for significant rescue of liver failure in CCl_4-treated C57BL/6 mice. (**A**) Study timeline (**B**) CCl_4-treated mice implanted with a therapeutic dose of syngeneic hepatocytes in the scaffolds exhibited >70% improvement in survival compared to the controls.

Disclosures: Regeant Panday: Nothing to Disclose, Caitie Chismarich: Nothing to Disclose, Andrew Golin: Nothing to Disclose, Xin Li: Nothing to Disclose, Kirstin

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Kebo: Nothing to Disclose, Matthew Remy: Nothing to Disclose, Jon Burke: Nothing to Disclose, Ramille Shah: Nothing to Disclose, Rafal Witek: Nothing to Disclose

4111 | ENHANCEMENT OF LIVER REGENERATION IN MICE THROUGH DDX3X-CD36 PATHWAY-MEDIATED PROMOTION OF HEPATIC LIPID ACCUMULATION

Ling Xu[1] Zhenzhen Pan[1] Zihao Fan[1] Feng Ren[1], [1]Beijing Institute of Hepatology/Beijing Youan Hospital, Capital Medical University, China

Background: The liver possesses a unique regenerative capacity, which is indispensable for the recovery process following liver resection and the management of various liver diseases. Accumulation of lipids in hepatocytes has been recognized as a pivotal factor during liver regeneration, yet the intricate mechanisms underlying this process remain elusive. This study endeavors to elucidate the mechanism through which DDX3X mediates lipid accumulation during liver regeneration. **Methods:** We collected serum samples from patients at various time points post-hepatectomy. A liver regeneration model in C57BL/6 mice was established by performing a two-thirds partial hepatectomy (PH). Hepatocyte-specific DDX3X knockout (DDX3XΔhep) mice were generated using CRISPR/Cas9/Cre-LoxP technology to investigate the pivotal role of DDX3X in liver regeneration. High-throughput RNA sequencing was conducted to dissect the downstream signaling pathways in DDX3XΔhep mice during liver regeneration. Oil Red O staining was utilized to visualize liver lipid accumulation. qPCR and Western blotting were employed to assess the expression levels of target genes and proteins, respectively. **Results:** Patients undergoing PH exhibited a progressive decrease in serum DDX3X levels. In the mouse liver regeneration model, hepatic DDX3X expression initially surged (0-12 hours) and subsequently declined (24-96 hours). Following two-thirds PH, DDX3XΔhep mice demonstrated a significantly augmented regenerative capacity compared to controls, accompanied by a marked increase in liver lipid levels. RNA sequencing revealed enhanced fatty acid uptake in DDX3XΔhep mice during liver regeneration. Notably, knockdown of the key fatty acid receptor CD36 significantly reduced hepatocyte lipid accumulation and impeded liver regeneration in DDX3XΔhep mice. **Conclusion:** During liver regeneration, hepatocyte DDX3X deficiency promotes hepatocyte proliferation by augmenting liver lipid accumulation through CD36 regulation. Our findings offer novel insights into the mechanisms underlying liver regeneration and identify potential targets for accelerating post-surgical recovery in patients.

Disclosures: Ling Xu: Nothing to Disclose, Zhenzhen Pan: Nothing to Disclose, Zihao Fan: Nothing to Disclose, Feng Ren: Nothing to Disclose

4112 | TARGETING RAC1 AS A NOVEL STRATEGY TO REDUCE INFLAMMATION AND LIVER DAMAGE IN ACUTE LIVER FAILURE

Barbara Bueloni[1] Esteban Fiore[2] María Jose Cantero[2] Lucia Lameroli Mauriz[2] Catalina Atorrasagasti[2] Matias Ciarlantini[3] Andrea Barquero[4] Lucia Gandolfi Donadio[3] Francisco Orozco[5] Martin Fauda[6] MARIA JULIETA Comin[3] Ali Canbay[7] Juan Bayo[2] Guillermo Mazzolini[2], [1]IIMT-Universidad Austral, CONICET, [2]IIMT-Universidad Austral, CONICET, [3]Departamento de Ingredientes Activos y Biorrefinerías, Instituto Nacional de Tecnología Industrial, [4]IQUIBICEN- Universidad de Buenos Aires, CONICET, [5]Hepatobiliary Surgery and Liver Transplant Unit, Hospital Universitario Austral, [6]Hepatobiliary Surgery and Liver Transplant Unit, Hospital Universitario Austral., [7]Universitätsklinikum Knappschaftskrankenhaus Bochum

Background: Acute liver failure (ALF) is a life-threatening condition with high mortality and limited therapeutic options. There is a critical need to identify novel molecular targets to improve clinical outcomes. RAC1, a Rho GTPase, regulates inflammation and oxidative stress, two critical drivers of ALF pathogenesis. Our goal was to explore the therapeutic potential of RAC1 inhibition as a strategy to mitigate ALF progression. **Methods:** RAC1 activation in human ALF (HBV- and APAP-related) was assessed through Ingenuity Pathway Analysis and immune cell deconvolution. Three murine ALF models (ConA, APAP, D-Gal/LPS) were used to evaluate the therapeutic potential of the RAC1 inhibitor 1D-142. RNA-seq of murine livers was integrated with human datasets to identify RAC1-modulated transcriptional programs. Immune cell infiltration and reactive oxygen species were measured by flow cytometry. Cytokine profiling, NF-κB activation and apoptosis were assessed by qPCR, immunofluorescence and caspase activity assay. Liver explants from patients with liver injury were treated ex vivo with 1D-142 to assess transaminase release and cytokine expression. **Results:** Bioinformatic analyses identified RAC1 as a pivotal upstream regulator in human ALF, associated with genes involved in inflammation, oxidative stress, and cell death. In murine models, 1D-142 treatment reduced liver damage (ALT and AST), even when administered in advanced ALF. Mechanistically, 1D-142 reduced ROS production in hepatocytes, decreased cytokine release, and limited immune cell infiltration into the liver. It also reprogrammed macrophages to an anti-inflammatory phenotype and limited their migration and viability, while directly protecting hepatocytes from apoptosis. RNA-seq confirmed that 1D-142 modulates RAC1-driven transcriptional programs dysregulated in human ALF, while restoring hepatocyte metabolic pathways. In human explants,

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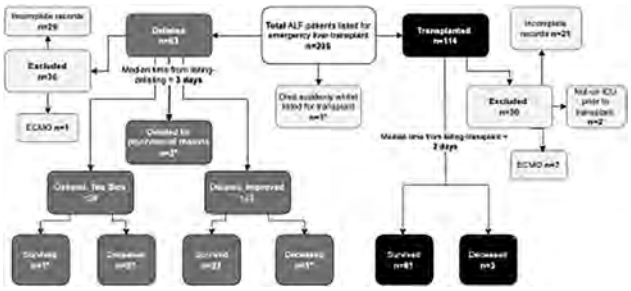
1D-142 reduced transaminase release and modulated cytokine expression, underscoring its translational potential. **Conclusion:** This study identifies RAC1 as a central regulator of sterile inflammation and oxidative stress in ALF. Pharmacological inhibition of RAC1 with 1D-142 confers robust hepatoprotection across multiple preclinical models and in human liver explants, highlighting RAC1 as a promising and translationally relevant therapeutic target for ALF treatment.

Disclosures: Barbara Bueloni: Nothing to Disclose, Esteban Fiore: Nothing to Disclose, María Jose Cantero: Nothing to Disclose, Lucia Lameroli Mauriz: Nothing to Disclose, Catalina Atorrasagasti: Nothing to Disclose, Matias Ciarlantini: Nothing to Disclose, Andrea Barquero: Nothing to Disclose, Lucia Gandolfi Donadio: Nothing to Disclose, Francisco Orozco: Nothing to Disclose, Martin Fauda: Nothing to Disclose, MARIA JULIETA Comin: Nothing to Disclose, Ali Canbay: Nothing to Disclose, Juan Bayo: Nothing to Disclose, Guillermo Mazzolini: Nothing to Disclose

4113 | INDICATIONS AND OUTCOMES FOR PATIENTS DELISTED FOR EMERGENCY LIVER TRANSPLANT IN ACUTE LIVER FAILURE – A SINGLE CENTRE REVIEW OVER 30 YEARS

Lily Scourfield[1] Tasneem Pirani[2] Robert Loveridge[2] Marc Zentar[2] Julia Wendon[3] William Bernal[4] Sameer Patel[2], [1]King's College Hospital, [2]Liver Intensive Care Unit, Institute of Liver Studies, King's College Hospital NHS Foundation Trust, [3]King's College London, [4]Liver Intensive Care Unit, Institute of Liver Studies, King's College Hospital NHS Foundation Trust,

Background: Acute Liver Failure (ALF) is a rare but severe condition which can rapidly progress to multi-organ failure, with high mortality without emergency liver transplantation (ELT). Tools such as the King's College Criteria are widely used to identify patients who are unlikely to survive without ELT. However, there is a lack of evidence to support the clinical decision to remove a patient from the emergency waiting list (WL) due to either clinical deterioration, as ELT will not result in patient survival, or more rarely, improvement on the WL such that ELT is not thought to improve patients outcome. We sought to address this evidence gap. **Methods:** Retrospective, single centre cohort study of 205 ALF patients listed for ELT from January 1990-December 2019. Patients were excluded if they were not transplanted from ICU, received extracorporeal membrane oxygenation (ECMO) peri-ELT, or whose notes had been destroyed. Demographics, admission characteristics, and delta organ failure scores reflecting change in physiology from listing to delisting or listing to transplant were captured. Subgroup univariate logistical regression analysis of those delisted for improvement vs deterioration compared to a transplanted ALF cohort was performed. **Results:** Fifty three patients were included: 28 were delisted for being 'too sick' (deterioration), 23 for improvement, and 2 for psychosocial reasons. Median age was 37 years, 67% female, paracetamol overdose the most common cause of ALF (44%) and time from listing to delisting 3 days. Fewer complications (refractory raised ICP, vasoplegic shock) and increasing ICU survival (18% in 1990s vs 74% in 2010s, $p < 0.01$) were observed over time. Compared to those proceeding to ELT, the delisted 'too sick' group had a deterioration in median cardiovascular (delta VIS 50, $p < 0.01$), respiratory (delta Murray 1 $p < 0.01$, delta P/F -87 mmHg $p < 0.01$), neurological (refractory raised ICP in 10 vs 6, $p < 0.01$) and ICU organ failure scores (delta SOFA 4, $p < 0.01$) on the WL. Those delisted for improvement experienced improvement in liver (delta MELD -Na -2, IQR -6-0, $p < 0.01$), and cardiovascular (delta VIS -19 IQR -41-0, $p < 0.01$) scores compared to transplanted patients, but did not show a difference in change in SOFA scores (delta SOFA 0 IQR -2-2 $p = 0.09$). ICU mortality was 96% ($n = 27$) in the delisted 'too sick' group vs 4% in transplanted ($n = 3$) and 4% ($n = 1$) delisted for improvement groups. **Conclusion:** Changes in physiological scores of organ dysfunction from listing to delisting for ELT mirror the reasons for delisting, are closely related to transplant-free survival (TFS) and may support clinical decision making.



Disclosures: Lily Scourfield: Nothing to Disclose, Tasneem Pirani: Nothing to Disclose, Robert Loveridge: Nothing to Disclose, Marc Zentar: Nothing to Disclose, Julia Wendon: Nothing to Disclose, William Bernal: Genfit: Advisor, Flagship Pioneering: Advisor, Sameer Patel: Nothing to Disclose

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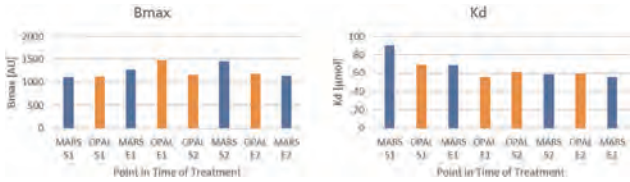
4114 | TARGETING ALBUMIN BINDING FUNCTION TO DESCRIBE REMOVAL OF PROTEIN-BOUND TOXINS IN PERSONALIZED EXTRACORPOREAL THERAPIES

Stine Koball[1] Adrian Dominik[2] Sebastian Koball[2] Jan Stange[3], [1]ProMedTec Germany GmbH, [2]Universität Rostock, [3]University of Rostock

Background: Liver failure is a critical clinical condition marked by impaired liver function and accumulation of metabolic byproducts, often transported by albumin. Extracorporeal therapies aiming at detoxifying patient's toxin-overloaded albumin are available, but demand improved diagnostic tools. This work introduces a novel dansylsarcosine-based kinetic modeling method for serum albumin binding to enhance therapeutic decision-making in hepatic failure, aiming to provide insights into albumin's dynamic interactions and offering a more comprehensive assessment of albumin overload or damages that both affect binding function. **Methods:** We employed a titration approach to measure albumin binding function under varying concentrations of dansylsarcosine, thereby analyzing the binding kinetics of albumin's Sudlow II binding site.

The data is analyzed using a modified Michaelis-Menten model, which accounts for quenching, and intrinsic absorbance and allows to calculate Bmax (maximum number of binding sites) and Kd (ligand concentration at half-saturation). This new indicator was evaluated in a database of patients treated with OPAL or MARS extracorporeal liver support systems to test for correlations with clinical scores and evaluate therapeutic effects between startpoints (S) and endpoints (E) of treatments. **Results:** The method demonstrated significant correlations with established biomarkers, clinical scores, and therapeutic effects. Analysis of patient samples from the database revealed that Bmax and Kd were strongly associated with existing albumin biomarkers. Further subgroup analysis indicated that these kinetic parameters had meaningful correlations with clinical scores such as GCS, SOFA, MELD, ACLF, CLIF-OF, and ABiC, underscoring their clinical significance. Evaluation of therapeutic effects using the OPALESCE database showed that Bmax and Kd were effective in describing therapy outcomes. Notable differences in Bmax and Kd were observed between the beginning and end of the first treatment session for MARS and OPAL respectively. These values aligned with established parameters like ABiC and the CLIF-OF Score, highlighting their potential as reliable markers for assessing the impact of liver support interventions. **Conclusion:** This study enhances understanding of albumin binding dynamics in hepatic failure, offering a valuable tool for guiding treatment decisions. The parameters Bmax and Kd reflect treatment impact and correlate with established clinical scores, adding to a more accurate assessment of patient condition. Importantly, Bmax can detect irreversible albumin damage, helping to identify cases where alternative therapies, like plasma exchange, may be more effective if standard extracorporeal methods fall short. This biomarker thus supports a more personalized approach to managing hepatic failure, with the goal of achieving better patient outcomes.



Disclosures: Stine Koball: ProMedTec Germany GmbH: Employee, Albutec GmbH: Employee, Adrian Dominik: Nothing to Disclose, Sebastian Koball: Nothing to Disclose, Jan Stange: Nothing to Disclose

4115 | DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PEDIATRIC DRUG-INDUCED ACUTE LIVER FAILURE: A NATIONAL INPATIENT ANALYSIS

Janvi Bhavsar[1] Vivian Tang[2] Raj Shah[3], [1]Maimonides Medical Center, [2]The Children's Hospital of Philadelphia, [3]KU School of Medicine-Wichita

Background: Acute liver failure in pediatric populations is a rare but life-threatening condition with diverse etiologies, ranging from infectious and metabolic disorders to drug-induced injury. Among the pharmacological causes, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), including salicylates and aspirin, are recognized as significant contributors to acute hepatic dysfunction in children and adolescents. Understanding the demographic and clinical characteristics associated with drug-induced liver failure is essential for improving early recognition, intervention, and outcomes in affected patients. **Methods:** We conducted a retrospective analysis using the 2022 National Inpatient Sample (NIS) database, identifying pediatric patients (ages 1–18) with acute liver failure via ICD-10 codes. Two primary cohorts were established: one comprising cases of acetaminophen-induced liver failure, and another including cases attributed to salicylates, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs). Demographic and clinical variables—including race, gender, age, median household income, mean length of hospitalization, cost of hospitalization, and mortality rate—were extracted and analyzed using logistic regression with STATA BE 18.0. These drug-induced liver failure cohorts were then compared to a cohort representing all other causes of pediatric acute liver failure. **Results:** Among 4,470 pediatric patients with acute liver failure, 505 cases

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were attributed to acetaminophen and 45 to salicylates/NSAIDs/aspirin. Notably, 77% of acetaminophen-induced and 100% of salicylate/NSAID/aspirin-induced cases occurred in females, compared to 46% in the non-drug-induced cohort. The mean age for the drug-induced cohort was 14 years, significantly higher than the mean age of 5 years in the other causes cohort. Mortality was substantially lower in the drug-induced group (3%) compared to the non-drug-induced group (26%). More details in the tables attached. **Conclusion:** Common drug-induced liver failure in pediatric patients disproportionately affects females, particularly adolescent girls (mean age 14). These findings highlight the need for targeted interventions and heightened clinical vigilance in this demographic to facilitate early diagnosis and treatment.

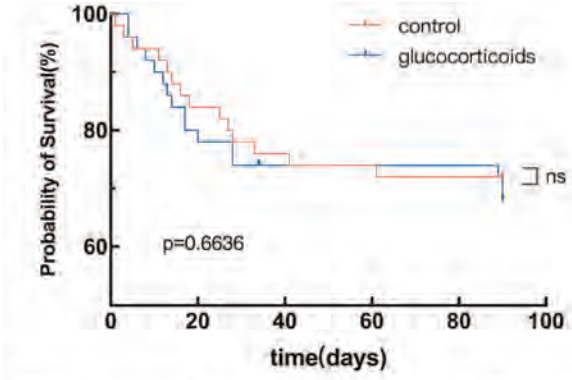
Variables	Acetaminophen toxicity causing liver failure	Salicylates+NSAID's+aspirin causing liver failure
Age	14.13 (sd+/- 0.31)	14.3 (sd+/- 0.34)
Race- White	55%	62%
Hispanic	18%	25%
Black	13%	0%
Other	14%	13%
Gender-male	27%	0%
Female	77%	100%
Zip quartile of median household income	Lowest-28th percentile, highest -21st percentile	Lowest 33rd percentile, highest -11th percentile
mortality	15 patients	0 patients
Mean length of stay	7 days	4.5 days
Total hospitalization charge	$110383	$37000
Variables	Drugs (acetaminophen and NSAIDs/Salicylates/Aspirin) causing liver failure	All other causes of liver failure
Age	14 years	5.8 years
Gender: Female	77%	46%
Male	27%	54%
Race: White	55%	45%
Hispanic	19%	25%
Black	13%	19%
Other	13%	21%
Mortality rate	3%	27%

Disclosures: Janvi Bhavsar: Nothing to Disclose, Vivian Tang: Nothing to Disclose, Raj Shah: Nothing to Disclose

4116 | COMBINATION WITH GLUCOCORTICOIDS DURING ARTIFICIAL LIVER SUPPORT SYSTEM TREATMENT DOES NOT IMPROVE THE SURVIVAL RATE OF ACUTE-ON-CHRONIC LIVER FAILURE PATIENTS: A RETROSPECTIVE COHORT STUDY

Fu-Xia Ta[1], [1]HuaShan Hospital, FUDAN University

Background: To investigate retrospectively the efficacy of glucocorticoids in acute-on-chronic liver failure (ACLF) patients receiving artificial liver support system (ALSS) therapy. **Methods:** ACLF patients treated with ALSS were categorized into glucocorticoids-treated group and control group based on whether they receive glucocorticoids treatment. Propensity score matching (PSM) was utilized in a 1:1 ratio to balance baseline characteristics. Subgroups were stratified by the Model for End-Stage Liver Disease (MELD) scores and Chinese Group on the Study of Severe Hepatitis B ACLF 2.0 (COSSH-ACLF 2.0) scores. Survival outcomes were analyzed by using Kaplan-Meier curves and log-rank tests. Univariate and multivariate analyses identified predictors of 90-day transplant-free survival (TFS). **Results:** From 2014 to 2025, a total of 124 ACLF patients treated with ALSS were include and 100 patients (control: n = 50; glucocorticoids: n = 50) were matched by PSM. The glucocorticoids group received dexamethasone at an average dose of 5 mg/d before each ALSS procedure. At 90 days, overall survival was comparable between control and glucocorticoids groups (72.0% vs. 67.8%, p = 0.6636), with TFS rates of 58.1% versus 67.8% (p = 0.3553). Patients with MELD scores > 24 or COSSH-ACLF 2.0 scores > 7.3 exhibited significantly lower 90-day TFS (both p < 0.0001). Glucocorticoids treatment failed to show a survival benefit in any subgroup. Overall infections show no statistically significant between control group and glucocorticoids group (36% vs 30%, p = 0.3912). In the univariate analysis, neutrophil count, serum creatinine, blood urea nitrogen (BUN), INR, PT, APTT, ALSS procedures, baseline MELD scores > 24 and COSSH-ACLF 2.0 scores > 7.3 were 90-day mortality predictors. Multivariate analysis confirmed that BUN (HR = 1.19, 95% CI = 1.04–1.37, p = 0.013), ammonia (HR = 1.02, 95% CI = 1.01–1.03, p = 0.005), ALSS procedures (HR = 0.51, 95% CI = 0.32–0.80, p = 0.003), and new infections (HR = 3.99, 95% CI = 1.16–13.74, p = 0.028) as independent 90-day mortality determinants. **Conclusion:** Glucocorticoids therapy did not improve transplant-free survival in ACLF patients undergoing ALSS. Key prognostic factors included BUN, ammonia levels, and new infections.



Characteristic	28-day	60-day	90-day	p-value[1]
Overall	76.0% (68.1%, 84.8%)	74.0% (65.9%, 83.1%)	69.9% (61.5%, 79.5%)	
Group				0.7
Control	78.0% (67.3%, 90.4%)	74.0% (62.8%, 87.2%)	72.0% (60.6%, 85.6%)	
Glucocorticoids	74.0% (62.8%, 87.2%)	74.0% (62.8%, 87.2%)	67.8% (56.0%, 82.2%)	

[1]Log-rank test

Disclosures: Fu-Xia Ta: Nothing to Disclose

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4117 | THE COMBINED ENGINEERING OF HLA GENE DISRUPTION AND BCL2 AUGMENTATION FOR HUMAN LIVER ORGANOID-BASED EXTRACORPOREAL SUPPORT SYSTEM IN TREATING LIVER FAILURE

Kentaro Ichimura[1] Yosuke Yoneyama[2] Hitomi Yamaguchi[1] Kanae Otsu[1] Akinobu Taketomi[3] Takanori Takebe[4], [1]Institute of Science Tokyo, [2]The University of Osaka, [3]Hokkaido University Graduate School of Medicine, [4]Children's Hospital Medical Center

Background: There is an urgent need for bridging therapies to support patients waiting for liver transplantation. Bioartificial liver (BAL) supporting systems are promising alternatives that incorporates extracorporeal bioreactors containing hepatocytes facilitate liver regeneration. Recent advances in human stem cell-derived organoid technology has evolved to dictate arrays of hepatic functions such as biosynthesis and detoxification, positioning these organoids as a potential cellular source for BAL systems. However, clinical translation remains challenged by alloimmunogenicity and poor tolerance to inflammatory and toxic insults present in patient blood. **Methods:** We established an extracorporeal circuit with HLA-A, HLA-B, and CIITA triple knockout human induced pluripotent stem cell (hiPSC)-derived liver organoids (HLO). We further edited the organoids by lentiviral transduction of a *B-cell lymphoma 2 (BCL2)* gene expressed under a doxycycline-inducible promoter. The efficacy was tested after direct blood exposure of the alginate-encapsulated organoids through venous flow in an hepatectomized rat model. In rats subjected to 80% hepatectomy followed by whole-blood BAL perfusion, acute liver failure ensued, as evidenced by elevated serum liver injury markers, coagulopathy, and hyperammonemia. We histologically assessed post-operative injury and regeneration of the remnant rat liver. **Results:** After whole blood perfusion by the BAL in the hepatectomized rats, HLOs retrieved from these circuits exhibited widespread apoptosis, with the majority staining positive for cleaved caspase-3. RNA-seq analysis confirmed concomitant downregulation of mitochondrial genes, a potent inducer of apoptosis. Regulation against apoptosis is mainly exerted by the BCL-2 protein family's anti-apoptotic members, which serve to preserve cell survival by inhibiting pro-apoptotic mechanisms. Therefore, we induced BCL2 expression in HLO, resulting in a significant protection of apoptosis without compromising the gene expression of hepatic metabolism including ammonia detoxification or bilirubin conjugation. The BAL treatment with BCL2-engineered HLO demonstrated the mortality benefit in rats post hepatectomy, accompanied by improved steatosis, nuclear condensation, and sinusoidal damage. In the remnant liver, the treatment with the engineered HLO reduced the number of pericentral hepatocytes positive for p21, a key protein arresting cell cycle. **Conclusion:** The BCL2 engineering of liver organoids provides a significant improvement for the duration of hepatic support in the BAL, and offered the protection from the recipient liver damage in a post-hepatectomy liver failure rat model. Understanding the hepato-protective mechanism against acute liver failure is crucial to accelerate the development of whole blood extracorporeal system with genetically-augmented organoids.

Disclosures: Kentaro Ichimura: Nothing to Disclose, Yosuke Yoneyama: Nothing to Disclose, Hitomi Yamaguchi: Nothing to Disclose, Kanae Otsu: Nothing to Disclose, Akinobu Taketomi: Nothing to Disclose, Takanori Takebe: Nothing to Disclose

4118 | FACTORS CONTRIBUTING TO TECHNICAL SUCCESS AND ITS PREDICTORS IN TRANSJUGULAR LIVER BIOPSY

NAOHIRO WADA[1] Takashi Kobayashi[1] Asako Nogami[1] Michihiro Iwaki[1] Satoru Saito[2] Atsushi Nakajima[3] Masato Yoneda[1], [1]Yokohama City University, [2]Sanno Hospital, [3]International University of Health and Welfare, Atami Hospital

Background: Transjugular liver biopsy (TJLB) is a valuable diagnostic alternative to percutaneous liver biopsy, particularly in patients with ascites or coagulopathy. However, procedural failure occasionally occurs, and the factors and predictors of technical failure in TJLB have not been fully elucidated. This study aimed to identify the factors and predictors of technical failure in TJLB. **Methods:** We conducted a retrospective analysis of 100 TJLB procedures between November 2014 and May 2024 at a single tertiary center. We collected and analyzed patient characteristics and imaging data. The anatomical relationship between the hepatic vein and inferior vena cava (IVC) was measured on CT or MRI. The predictors of technical failure in TJLB were assessed using univariate and multivariate analyses. **Results:** TJLB was successful in 87 of 100 cases. Complications occurred in 6% of cases. No procedure-related mortality was observed. The primary reason for failure was the inability to advance the catheter into the hepatic vein (77% of failed cases). The patients of successful TJLB group were significantly younger (54.0 $\pm$ 15.0 vs. 64.5 $\pm$ 11.0 years; $p = 0.007$) and taller (162.1 $\pm$ 8.1 cm vs. 157.4 $\pm$ 9.3 cm; $p = 0.048$) than those who did not. There were significant differences with respect to gender; males were unsuccessful in 2 of 43 cases,

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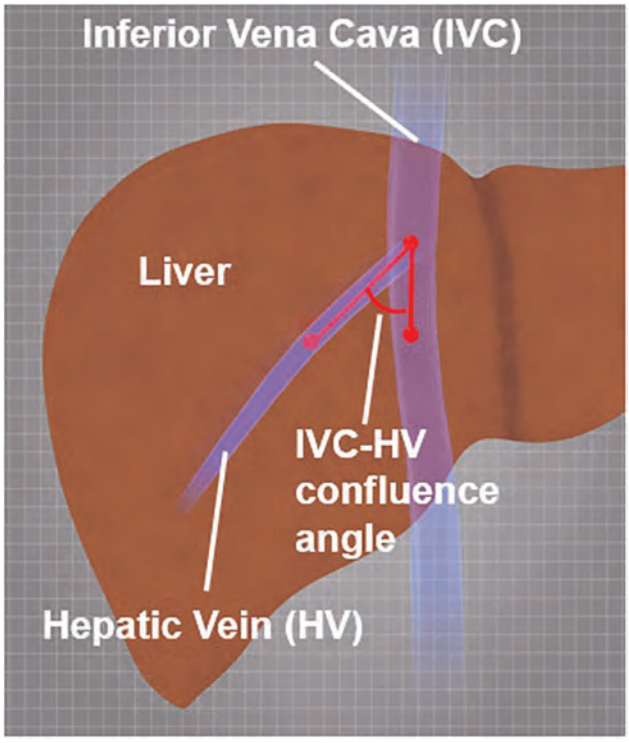
while females were unsuccessful in 11 of 57 cases ($p = 0.037$). The confluence angle between the hepatic vein and IVC was significantly smaller in the successful group than in the unsuccessful group (43.8 ± 11.1° vs. 60.0 ± 11.8°; $p = 0.001$). Regarding the confluence angle, a ROC curve analysis was performed, and the optimal cutoff value of 57° for predicting TJLB failure was determined using the Youden Index. We conducted multivariate analysis, adjusted for age, height, sex and the angle. When the angle between the hepatic vein and IVC was ≥ 57°, the odds ratio for failure was 84.3, and the result was statistically significant ($p = 0.001$). In contrast, no significant differences were observed for age, height, or sex after adjustment. **Conclusion:** The most significant predictor of technical failure in TJLB was identified as a larger confluence angle between the hepatic vein and IVC, particularly when the angle exceeded 57°. The confluence angle may need to be assessed before performing TJLB, and the indications for TJLB may be reconsidered when it exceeds 57°.



Disclosures: NAOHIRO WADA: Nothing to Disclose, Takashi Kobayashi: Nothing to Disclose, Asako Nogami: Nothing to Disclose, Michihiro Iwaki: Nothing to Disclose, Satoru Saito: Nothing to Disclose, Atsushi Nakajima: Nothing to Disclose, Masato Yoneda: Nothing to Disclose

4119 | ACTIVATION OF A TUMOR SUPPRESSOR P53 DRIVES ACUTE LIVER FAILURE VIA UPREGULATION OF LEUKEMIA INHIBITORY FACTOR (LIF)

Jihyun Sung[1] Yuki Makino[1] Seiya Kato[1] Yasuharu Kawamoto[1] Yoichi Sasaki[1] Kenji Fukumoto[1] Yuta Myojin[1] Kazuhiro Murai[1] Yoshinobu Saito[2] Takahiro Kodama[3] Hayato Hikita[2], [1]Department of Gastroenterology and Hepatology, University of Osaka Graduate School of Medicine, [2]Osaka University Graduate School of Medicine, [3]Osaka University

Background: Acute liver failure (ALF) is characterized by massive hepatocyte death, with no effective treatment except liver transplantation. We previously reported that constitutive activation of p53 in hepatocytes promotes chronic liver diseases. However, its impact on ALF remains unknown. This work aims to study the roles of p53 in ALF. **Methods:** We used genetically modified mice including hepatocyte-specific Mdm2-deficient mice (Alb-CreER $Mdm2^{fl/fl}$ + Tamoxifen: Mdm2ΔHep mice), Mdm2 and p53 double-deficient mice (Alb-CreER $Mdm2^{fl/fl}$ $p53^{fl/fl}$ + Tamoxifen), and LIF-deficient mice (LIF+/-). Serum and liver samples were obtained from ALF patients and healthy controls. Hepatocyte cell lines (HepG2, CL2), a hepatic stellate cell line (LX-2), and a liver sinusoidal endothelial cell line (TMNK-1) were used for in vitro experiments. **Results:** In the publicly available human ALF datasets (GDS4387), hepatic p21, a representative target of p53, was upregulated in ALF patients compared with the normal liver. acetaminophen (APAP) or concanavalin A (ConA)-induced ALF in wild type mice showed upregulation of p21 mRNA and p53 protein in the liver, indicating the activation of the p53 pathway. Loss of hepatocyte Mdm2, a negative regulator of p53, induced p53 activation, resulting in extensive hepatocyte death resembling ALF, and ultimately caused 100% mortality. Further deletion of hepatocyte p53 completely negated these ALF phenotypes. scRNA-seq and multiplex cytokine assay showed elevation of multiple inflammatory cytokines in hepatocytes, hepatic non-parenchymal cells and serum in Mdm2ΔHep mice. Among them, LIF was the most elevated inflammatory cytokine predominantly upregulated in hepatocytes. LIF upregulation was also observed in APAP and ConA models. Compared with the healthy control, hepatic LIF expression and serum LIF levels were elevated in ALF patients. In HepG2 and CL2 cells, treatment with a Mdm2 inhibitor Nutlin-3 increased LIF expression, while p53 knockdown suppressed it, indicating that LIF is

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regulated downstream of p53 in hepatocytes. In LIF+/− mice subjected to APAP-induced ALF, serum ALT levels were decreased and survival was improved. Histologically, hepatic necrosis and the infiltration of CD11b-positive cells were drastically reduced in LIF-deficient mice. scRNA-seq revealed that the infiltrating CD11b-positive cells, consisting of macrophages and neutrophils, abundantly express proinflammatory cytokines and chemokines that can exacerbate liver injury and inflammation. Mechanistically, LIF accelerated the production of inflammatory cytokines and chemokines by hepatic stellate cells and liver sinusoidal endothelial cells, which in turn can promote the infiltration of CD11b-positive cells. **Conclusion:** p53 activation in hepatocytes drives ALF via LIF-mediated liver injury. Targeting p53-LIF axis may offer a novel therapeutic approach for ALF.

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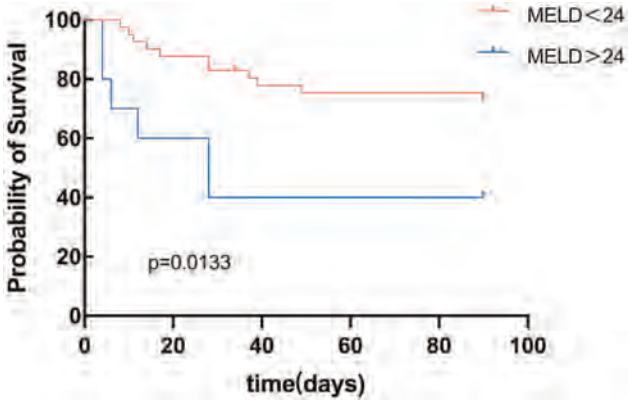
4120 | EFFICACY, SAFETY AND PROGNOSTIC FACTORS OF DUAL PLASMA MOLECULAR ADSORPTION SYSTEM COMBINED WITH PLASMA EXCHANGE ON ACUTE-ON-CHRONIC LIVER FAILURE:A SINGLE-CENTER RETROSPECTIVE COHORT STUDY

Wen-Juan Shi[1], [1]The Second People's Hospital of LanZhou

Background: To investigate retrospectively the efficacy and safety of dual plasma molecular absorption system (DPMAS) combined with plasma exchange (PE) in patients with acute-on-chronic liver failure (ACLF). **Methods:** A single-center retrospective study included 51 ACLF patients receiving DPMAS+PE from 2014 to 2025. Clinical characteristics, 28/90-day overall survival (OS), infection rates and complications were analyzed. Subgroups were classified by the model for end-stage liver disease (MELD) score. Survival analyses was performed by Kaplan–Meier method and compared by the log-rank test. Cox regression identified survival predictors for 90-day OS. **Results:** This study included 51 patients (mean age 49 ± 12 years; 74.5% male), predominantly with liver cirrhosis (76.5%) and ascites (68.6%). Laboratory profiles demonstrated elevated liver enzymes (ALT 573 ± 505 U/L, AST 569 ± 450 U/L), hyperbilirubinemia (total bilirubin 416 ± 122 μmol/L), and prolonged coagulation (PT 23.5 ± 4.8 s; INR 1.99 ± 0.43). The mean MELD score was 22.5 ± 3.3. Survival rates were 74.5% at 28 days and 66.4% at 90 days. Patients with MELD scores > 24 exhibited significantly lower 90-day OS (p = 0.0133). New infections occurred in 39.2% (pulmonary 23.5%, intra-abdominal 9.8%) with 3.9% thromboembolic complications. In multivariate analysis, prolonged APTT (HR 1.09; 95% CI, 1.02–1.17; p = 0.009), ammonia (HR 1.02; 95% CI, 1.00–1.03; p = 0.021), fewer artificial liver support system procedures (HR 0.50; 95% CI, 0.26–0.95; p = 0.034) and MELD scores > 24 (HR 8.49; 95% CI, 1.49–48.31; p = 0.016) were independent predictors of 90-day mortality. **Conclusion:** DPMAS combined with PE demonstrates clinically efficacy in ACLF. MELD scores >24, prolonged APTT, hyperammonemia independently predict mortality.



Disclosures: Wen-Juan Shi: Nothing to Disclose

4121 | BEYOND ACETAMINOPHEN: AN UMBRELLA REVIEW OF N-ACETYLCYSTEINE IN NON- ACETAMINOPHEN-INDUCED LIVER FAILURE

Raja Chandra Chakinala[1] Abdullah Sultany[1] Adishwar Rao[1] Vikash Kumar Karmani[2] Rahul Chikatimalla[3] Chaitanya K Chandrala[1], [1]Guthrie Robert Packer Hospital, [2]Jinnah Sindh Medical University, [3]Kamineni Institute of Medical Sciences

Background: N-acetylcysteine (NAC), widely recognized for its role in treating acetaminophen toxicity, has gained attention for its potential benefits in non-acetaminophen-induced acute liver failure (NAI-ALF). This umbrella review synthesizes evidence from meta-analyses to evaluate the efficacy and safety of NAC in improving outcomes among patients with NAI-ALF. **Methods:** In adherence to the PRIOR guidelines, PubMed, Google Scholar, Web of Science, and Scopus were searched from database inception to April 2025 to identify articles related to NAI-ALF. The outcomes of interest included mortality rate,

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length of hospital stay, and transplant-free survival. Various effect measures, such as risk ratios, odds ratios, and mean differences, were compared across the studies. A corrected covered area (CCA) assessment was performed to evaluate the degree of overlap among the included reviews. The quality and methodological rigor of each review were assessed using the AMSTAR-2 tool. **Results:** From the 6,743 articles identified, five meta-analyses were included, showing a significant overlap with a corrected covered area of 45.8%. Two reviews reported mortality: Shrestha et al. (2021) found a significant reduction with NAC (OR 0.47, 0.29 to 0.75), while Amjad et al. (2022) showed a non-significant trend toward reduction (RR 0.73, 0.48 to 1.09). Four reviews assessed transplant-free survival with mixed results: Amjad et al. (2022) reported improved survival (RR 0.56, 0.33 to 0.94), whereas Jawaid et al. (2021) (RR 1.54, 1.19 to 1.98), Hu et al. (2015) (OR 1.61, 1.11 to 2.34) and Walayat et al (2021) (OR 2.85, 2.11 to 3.85) indicated worse outcomes. Length of hospital stay was reduced in all three reviews reporting this outcome: Shrestha et al. (2021) (MD –6.52 days, –12.91 to –0.13), Amjad et al. (2022) (SMD –1.62, –1.84 to –1.40), and Jawaid et al. (2021) (SMD –0.405, –1.44 to –0.63).

Refer to Table 1 for a summary of key findings from each meta-analysis. **Conclusion:** N-acetylcysteine appears to reduce mortality and shorten hospital stays in patients with non-acetaminophen-induced acute liver failure. However, evidence regarding its effect on transplant-free survival is inconsistent, with some studies suggesting benefits and others indicating potential harm. Further high-quality research is needed to clarify the role of NAC in improving transplant-free survival outcomes in this population.

Table 1. Summary of Meta-Analyses Evaluating N-Acetylcysteine in Non-Acetaminophen- Induced Acute Liver Failure

Study and Year	Metric of Measure	Effect Size [95% CI]
Mortality rate		
Shrestha et al 2021	OR	0.47(0.29 to 0.75)
Amjad et al. 2022	RR	0.73 (0.48 to 1.09)
Transplant-Free Survival		
Amjad et al. 2022	RR	0.56 (0.33 to 0.94)
Jawaid et al. 2021	RR	1.54 (1.19 to 1.98)
Hu et al. 2015	OR	1.61 (1.11 to 2.34)
Walayat et al. 2021	OR	2.85 (2.11 to 3.85)
Length of Stay in Hospital		
Shrestha et al. 2021	MD	-6.52 (- 12.91 to -0.13)
Amjad et al. 2022	SMD	-1.62 (-1.84 to -1.40)
Jawaid et al. 2021	SMD	–0.405 (–1.44 to -0.63)

Disclosures: Raja Chandra Chakinala: Nothing to Disclose, Abdullah Sultany: Nothing to Disclose, Adishwar Rao: Nothing to Disclose, Vikash Kumar Karmani: Nothing to Disclose, Rahul Chikatimalla: Nothing to Disclose, Chaitanya K Chandrala: Nothing to Disclose

4122 | SPATIOTEMPORAL-OMICS REVEALS THE ROLE OF MLXIPL$^+$ HEPATOCYTES IN LIVER REPAIR IN ACUTE LIVER INJURY MICE

Jun Li[1] Binggi Li[1] Heng Yao[1] Jing Jiang[1] Jiaojiao Xin[1] Xi Liang[1] Dongyan Shi[1], [1]The First Affiliated Hospital, Zhejiang University School of Medicine

Background: The liver possesses a remarkable regenerative capacity, restoring the structure and function following acute liver injury (ALI). Although hepatic mesenchymal stromal cells (MSCs) are known to be rapidly activated during ALI, the regulatory mechanisms of the liver injury microenvironment in repair remain unclear. This study aims to uncover the precise mechanism through which endogenous MSCs orchestrate Mlxipl$^+$ hepatocytes to promote liver tissue regeneration. **Methods:** The ALI mouse model was established by intraperitoneal injection of the anti-CD95 antibody JO2 into a SCID mouse. Liver tissues and blood samples were collected at Day 0, 1, 3 and 7 post-injury. Single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics (ST) of liver tissues were conducted to explore the mechanism driving self-repair. scRNA-seq data were clustered using dimensionality reduction, followed by cell annotation and spatial mapping via deconvolution. Cell–cell interactions, particularly between hepatocytes and MSCs, were analyzed to identify and validate key signaling pathways involved in liver repair. **Results:** The ALI mouse model was successfully established, with regional necrosis of liver tissue and elevated liver function. By integrating scRNA-seq and ST data, a spatiotemporal atlas of liver injury and repair was constructed. Eleven major liver cell types were annotated, and the ratio of hepatocytes, endothelial cells, MSCs, and cholangiocytes significantly decreased during the acute injury phase and gradually recovered during repair. Notable ligand–receptor interactions were observed between these four cell types, especially between hepatocytes, endothelial cells and MSCs. Interestingly, the similarity in cell communication patterns at Day 3 and Day 7 indicated that the process of liver repair stabilized on Day 3. Sub-clustering further revealed strong interactions between hepatic stellate cells and both classical hepatocytes and Mlxipl$^+$ hepatocytes through the regulation of extracellular matrix. **Conclusion:** The spatiotemporal dynamics of liver injury and repair in ALI mice was delineated. The decline and rebound of hepatic MSCs and hepatocytes during injury and recovery. The prominent interaction between hepatic stellate cells and MLXIPL$^+$ hepatocytes suggests that Mlxipl$^+$ hepatocytes are crucial in liver regeneration and represent a potential therapeutic target for liver injury.

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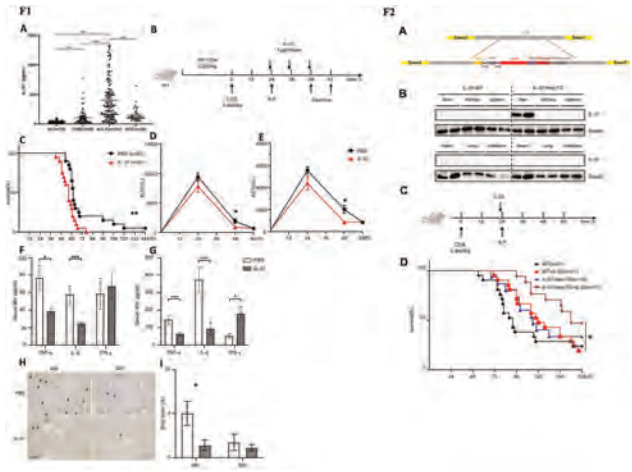
Disclosures: Jun Li: Nothing to Disclose, Bingqi Li: Nothing to Disclose, Heng Yao: Nothing to Disclose, Jing Jiang: Nothing to Disclose, Jiaojiao Xin: Nothing to Disclose, Xi Liang: Nothing to Disclose, Dongyan Shi: Nothing to Disclose

◆ 4123 | IL-37 COMBINED WITH IL-22 COULD SERVE AS A THERAPEUTIC STRATEGY FOR ACLF WITH THE EFFECT OF BOTH INHIBITING SYSTEMIC INFLAMMATION AND PROMOTING LIVER REGENERATION

Dabao Shang[1] Xiaogang Xiang[2] Jinming Zhang[2] Yifan Xu[2] Zihan Zhou[2] Jingting Liu[2], [1]Ruijin Hospital, Shanghai Jiao Tong University School of Med, [2]Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

Background: Acute-on-chronic liver failure (ACLF) is a critical clinical syndrome in patients characterized by an acute intrahepatic or extrahepatic insult and subsequent rapid deterioration of liver function on the basis of chronic liver diseases resulting in high short-term mortality. Systemic inflammation is a driving force in developing ACLF, however, treatments targeted systemic inflammation are lacking till now. Interleukin 37 (IL-37), a newly identified member of the IL-1 family, functions as an inherent immunosuppressant capable of concurrently modulating both adaptive and innate immune responses. The specific role of IL-37 in the pathogenesis of ACLF is not fully elucidated. **Methods:** ACLF patients were enrolled and serums were collected. Transgenic mice with liver-specific expression of human IL-37 (IL-37-Hep-TG) were constructed. ACLF mouse model was developed {three steps: chronic liver injury (injection of carbon tetrachloride [CCl4] for 8 weeks), acute hepatic insult (injection of a double dose CCl4), and bacterial infection (intraperitoneal injection of Klebsiella pneumoniae)}. Recombinant human IL-37 (rhIL-37) was used. IL-22, a cytokine that could promote liver regeneration, was also used. **Results:** Serum levels of IL-37 were markedly elevated in ACLF patients comparing to healthy controls (HC), chronic hepatitis B patients (CHB) and hepatocellular carcinoma patients (HCC). Intravenous injection of IL-37 in ACLF mice showed ameliorative ALT and AST levels, as well as the levels of TNF-α, IL-6 and IFN-γ. However, the mortality in IL-37 group was higher than control group. Notably, BrdU staining indicated that liver regeneration was inhibited in IL-37 group. In IL-37-Hep-TG and wild type (WT) mice, IL-22 injection showed the highest survival rate among all the groups. **Conclusion:** Serum IL-37 expression is elevated in ACLF patients. Intravenous injection of IL-37 in ACLF mice could down-regulate systemic inflammation but liver regeneration is inhibited at the same time. IL-37 combined with IL-22 might serve as a potential therapeutic strategy for ACLF with systemic inflammation inhibited and liver regeneration promoted synergistically.



Disclosures: Dabao Shang: Nothing to Disclose, Xiaogang Xiang: Nothing to Disclose, Jinming Zhang: Nothing to Disclose, Yifan Xu: Nothing to Disclose, Zihan Zhou: Nothing to Disclose, Jingting Liu: Nothing to Disclose

◆ 4124 | GUT MICROBIAL SUCCESSION AND ESCALATING ANTIBIOTIC RESISTANCE FROM CHRONIC HEPATITIS B TO ACUTE-ON-CHRONIC LIVER FAILURE: A METAGENOMIC STUDY

Jiyang Chen[1] Xianbin Xu[1] Sisi Yang[1] Zelu Meng[1] Xia Yu[1] Ying Nie[1] Yani Zhou[1] Yining Zhang[1] Siqi Sun[1] Huilan Tu[1] Yingfeng Lu[1] Jiangshan Lian[1] Hongyu Jia[1] Yu Shi[1] Yida Yang[1], [1]The First Affiliated Hospital, Zhejiang University School of Medicine

Background: Disruption of the gut microbiota is increasingly recognized as a pivotal driver of chronic liver disease progression, promoting systemic inflammation, immune dysregulation, and bacterial translocation. We performed a comprehensive metagenomic analysis to characterize the ecological and functional shifts in the gut microbiota across patients with chronic hepatitis B (CHB), acute decompensation (AD), and acute-on-chronic liver failure (ACLF). **Methods:** Fecal samples (n = 90) collected from patients with CHB, AD, and ACLF were subjected to whole-genome shotgun metagenomic sequencing. Microbial diversity was assessed using alpha and beta diversity metrics, principal coordinate analysis (PCoA), and non-metric multidimensional scaling (NMDS). Differential taxa were identified using linear discriminant analysis effect size (LEfSe). Functional annotation of antibiotic resistance

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genes (ARGs) and virulence factors (VFs) was performed using the Comprehensive Antibiotic Resistance Database (CARD) and the Virulence Factors Database (VFDB). **Results:** Alpha diversity decreased progressively from CHB to ACLF, while beta diversity demonstrated significant group-wise separation (Kruskal-Wallis test, $p < 1 \times 10^{-100}$). Symbiotic genera, including Blautia, Ruminococcus, and Coprococcus, were enriched in AD, whereas pathobionts such as Escherichia coli and Enterococcus faecium dominated in ACLF. ARG profiling revealed a substantial increase in resistance burden in ACLF, characterized by the enrichment of β-lactamases, efflux pumps, and multidrug resistance elements (e.g., ARO:3005041, ARO:3000833). VFDB analysis showed upregulation of virulence determinants including type III secretion systems, lipopolysaccharides (LPS), and β-hemolysins. Functional analysis indicated a shift from a commensal-driven resistance profile in CHB and AD to a pathogen-dominated profile in ACLF, largely mediated by Enterococcus, Klebsiella, and Streptococcus species. **Conclusion:** Progression from CHB to ACLF is associated with a stepwise ecological succession of the gut microbiota, culminating in pathogen-driven dysbiosis and heightened antimicrobial resistance. These findings highlight the gut microbiota as a potential biomarker for disease staging and a target for microbiota-directed therapeutic interventions in advanced liver disease.

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◆ 4125 | SECONDARY SBP PROPHYLAXIS WORSENS SURVIVAL WITHOUT AFFECTING LIVER TRANSPLANT RATES IN VETERANS WITH CIRRHOSIS FOLLOWED AFTER THEIR FIRST DECOMPENSATION

Shari Rogal[1] Jasmohan Bajaj[2] Scott Silvey[3] Nilang Patel[4] Jacqueline O'Leary[5] Timothy Morgan[6] John Markley[7] Sofia Jakab[8] Heather Patton[9], [1]University of Pittsburgh, [2]Virginia Commonwealth University, [3]VCU, [4]Richmond VA, [5]Dallas VA, [6]VA Long Beach Healthcare System, [7]Richmond VAMC, [8]West Haven VA, [9]VA San Diego Healthcare

Background: After index decompensation, the impact of SBP occurrence, recurrence & secondary SBP prophylaxis (SecSBPPr) on mortality & liver transplant (LT) remains unclear. Aim: Define the interaction between SecSBPPr on SBP recurrence, mortality and LT . **Methods:** Using the Veterans Affairs Corporate Data Warehouse (VA-CDW), cirrhosis pts with index decompensation (HE, ascites, VB) between 2009-2023 and were followed untill Jan 2024. Demographics, labs, cirrhosis details & medications were collected. Outcomes: SBP episodes (0, 1, or ≥2), SecSBPPr initiation (continuous ciprofloxacin/Bactrim usage with ≥2 refills in 120-days post-SBP), death & LT were evaluated. Primary analysis was time-to-death & time-to-LT using Cox proportional hazards models of each cause-specific hazard separately to account for competing risks. In survival analysis, SBP groups (0, 1 or ≥2 episodes), SecSBPPr, and other predictors (i.e., MELD 3.0, medications, etc.) were analyzed as time-varying covariates to account for immortal time bias. Adjusted models were fit, controlling different covariates between SBP groups. Finally, we fit an interactive effect between SecSBPPr & SBP groups for death & LT. **Results:** 52,526 Veterans with index cirrhosis decompensation were included, of which 20.0% developed one SBP episode & 2.4% ≥2 SBP episodes (Fig A). Overall mortality was 78.1% & 2.4% received LT. After the first SBP episode, 4439 (42.2%) were put on SecSBPPr. Pts with SBP recurrence were younger, more likely to have alcohol etiology & have more advanced disease (Fig B).
Outcomes: 1st SBP was linked to 1.74×risk of death ([1.69-1.79], $p < 0.001$), while ≥2 episodes was linked with 2.31×risk of death ([2.16-2.46], $p < 0.001$). Having

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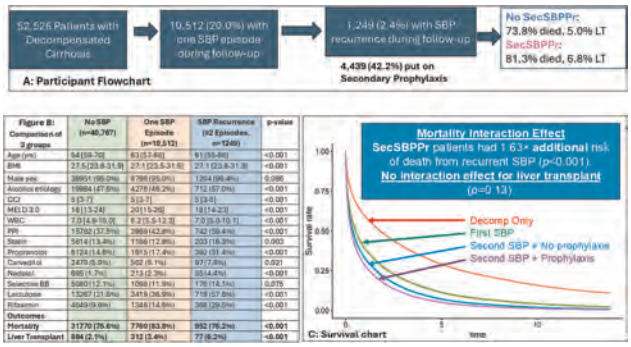
one episode of SBP was also linked to 2.79×risk of LT ([2.40-3.24], $p < 0.001$), while ≥2 episodes was linked with 4.95× risk of LT ([3.79-6.45], $p < 0.001$). After covariate adjustment, these results remained consistent. When incorporating SecSBPPr into the model, we found a positive interaction (adj. HR for interaction: 1.63 [1.39-1.92], $p < 0.001$) – implying that patients taking SecSBPPr prior to their recurrent SBP episode were more likely to die (Fig. C). There was no interactive effect observed for LT, indicating that patients with SBP recurrence had similar rates of LT regardless of SecSBPPr ($p = 0.13$). **Conclusion:** In a national cohort of Veterans after index decompensation, SBP occurrence & recurrence was associate with a greater risk of mortality & receiving a LT in multivariable analysis controlling for MELD3.0 and other factors. Secondary SBP prophylaxis was started in <50% of patients after index SBP, increased mortality but did not impact LT risk. In Veterans with decompensated cirrhosis & prior SBP, withholding SecSBPPr improved survival & did not affect their chance of LT.



Disclosures: Shari Rogal: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Genfit: Grant/Research Support, Enterobiotix: Advisor, Boehringer Ingelheim: Advisor, Scott Silvey: Nothing to Disclose, Nilang Patel: Nothing to Disclose, Jacqueline O'Leary: Genfit: Consultant, Grifols: Advisor, CVS: Stock - publicly traded company, Mallinckrodt: Advisor, Novo Nordisk: Advisor, PharmaIn: Advisor, Grifols: Consultant, Cellion: Advisor, Mallinckrodt: Advisor, PharmaIn: Consultant, Genfit: Consultant, PharmaIn: Consultant, Genfit: Consultant, Timothy Morgan: Nothing to Disclose, John Markley: Nothing to Disclose, Sofia Jakab: Nothing to Disclose, Heather Patton: Bristol-Myers Squibb: Spouse is employee of BMS

◆ 4126 | NUTRITIONAL SUPPORT INTERVENTION IN PATIENTS WITH HEPATITIS B VIRUS-RELATED ACUTE-ON-CHRONIC LIVER FAILURE AT NUTRITIONAL RISK: A RANDOMIZED CONTROLLED CLINICAL TRIAL

Zhipeng Li[1] Jia Chen[1] Yeqiong Zhang[1] Xiyao Chen[1] Wenxiong Xu[1] Liang Peng[1], [1]Third Affiliated Hospital of Sun Yat-sen University

Background: Malnutrition, a prevalent but often underrecognized complication in acute-on-chronic liver failure (ACLF), is linked to reduced quality of life, hepatic decompensation, and increased mortality. This study evaluates the safety and efficacy of individualized nutritional support in hepatitis B virus-related ACLF (HBV-ACLF) patients at nutritional risk. **Methods:** In this open-label, randomized controlled trial, 60 HBV-ACLF patients with a nutritional risk score (NRS 2002 ≥ 3) were randomized 1:1 to receive either individualized nutritional support (targeting 1.2 times resting energy expenditure [REE] per day and 1.2 g/kg/day protein, n = 30) or a standard diet (1600 kcal/day, 70 g protein, n = 30) for 10 days. The primary outcome was non-liver transplant mortality at 30 and 90 days. Secondary outcomes included the incidence of adverse clinical events (ascites, gastrointestinal bleeding, infection, hepatic encephalopathy, hepatorenal syndrome, rehospitalization, ICU admission) and changes in nutritional status (mid-arm circumference [MAC], mid-arm muscle circumference [MAMC]), muscle strength (grip strength), physical function (Short Physical Performance Battery [SPPB]), and quality of life (EQ-5D scale) at 30 and 90 days. **Results:** Of 60 enrolled patients, 58 were analyzed (intervention: 29, control: 29; mean age: 42.3 ± 7.9 years; 93.1% male; BMI: 23.9 ± 2.63; MELD score: 20.9 ± 3.82; COSSH score: 6.77 ± 0.58). Non-liver transplant mortality was lower in the intervention group at 30 days (3.4% vs. 17.2%, p = 0.196) and 90 days (20.7% vs. 31%, p = 0.782), but differences were not statistically significant. The intervention group had significantly fewer adverse clinical events at 30 days (29.4% vs. 65.4%, p = 0.036) and 90 days (37.9% vs. 79.3%, p = 0.001). At 30 days, the intervention group showed significant improvements in MAC (Δ0.02 ± 1.32 vs. Δ-1.77 ± 1.21, p = 0.001), MAMC (Δ0.44 ± 1.41 vs. Δ-1.14 ± 1.39, p = 0.001), grip strength (Δ4.54 ± 4.93 vs. Δ-1.82 ± 6.32, p = 0.007), and EQ-5D scores (Δ20.4 ± 17.2 vs. Δ1.83 ± 29.2, p = 0.021). These improvements persisted at 90 days for MAC (Δ0.68 ± 1.56 vs. Δ-1.85 ± 0.82, p = 0.002), grip strength (Δ7.93 ± 4.5 vs. Δ0.2 ± 8.82, p = 0.007), and SPPB scores (Δ2.77 ± 0.83 vs. Δ1.5 ± 0.83, p = 0.021). The intervention was well-tolerated with no serious adverse events. **Conclusion:** Individualized nutritional

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support is safe and effective in reducing adverse clinical events and improving nutritional status and quality of life in HBV-ACLF patients at nutritional risk. However, larger trials are needed to confirm potential survival benefits.

Figure1. The flowchart of the study.

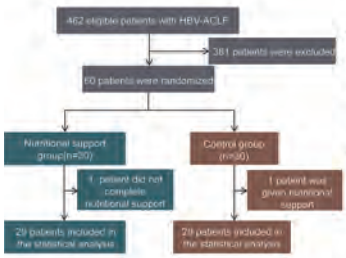


Table1.The outcomes of the study.

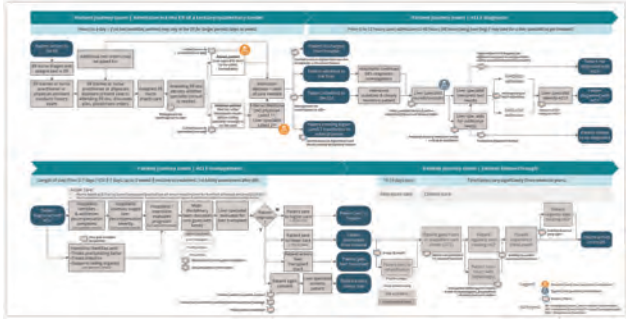
	Intervention group(n=29)	Control group(n=29)	P value
The primary outcome			
Non-liver transplant mortality at 30 days	3.4%(1/29)	17.2%(5/29)	0.196
Non-liver transplant mortality at 90 days	20.7%(6/29)	31.0%(10/29)	0.782
The secondary outcome			
Incidence of adverse clinical events within 30 days	29.4%	65.4%	0.036
Incidence of adverse clinical events within 90 days	37.9%	79.3%	0.001

Disclosures: Zhipeng Li: Nothing to Disclose, Jia Chen: Nothing to Disclose, Yeqiong Zhang: Nothing to Disclose, Xiyao Chen: Nothing to Disclose, Wenxiong Xu: Nothing to Disclose, Liang Peng: Nothing to Disclose

◆ 4127 | SYSTEMIC CHALLENGES IN MANAGING ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) IN THE U.S.: DIAGNOSTIC DELAYS, REFERRAL BARRIERS, AND FRAGMENTED POST-DISCHARGE CARE

Constantine Karvellas[1] Jasmohan Bajaj[2] Armaghan Dabbagh[3] Dean Hum[3] Pierbruno Ricci[3] Katharina Staufer[3] Richard Moreau[4] Arun Sanyal[2], [1]University of Alberta, [2]Virginia Commonwealth University, [3]GENFIT S.A., [4]European Foundation for the Study of Chronic Liver Failure (EF CLIF)

Background: Acute-on-chronic liver failure (ACLF) is a high-mortality syndrome requiring prompt, specialized care. However, systemic inefficiencies across the healthcare continuum hinder optimal care, and management of patients with ACLF remains fragmented. The lack of a unified definition, an ICD code, as well as suboptimal referral and outpatient care may contribute to adverse patient outcomes. This study aimed to explore multidisciplinary challenges in ACLF care and to identify priority areas for improvement across the care continuum. **Methods:** 15 physicians were recruited for this qualitative study using purposive sampling. Data was collected via 60-minute phone interviews. Participants included 5 transplant hepatologists, 4 hepatologists, 5 hospital internists, and 2 emergency physicians from 11 U.S. states. Participants worked at 5 secondary, 7 tertiary, and 3 quaternary centers. The interview guide included over 100 open-ended and semi-structured questions across four themes: hospital admission, ACLF diagnosis, treatment, and follow-up. An inductive thematic analysis was used to identify and interpret key patterns and themes across the dataset. **Results:** In total, 4 physicians were fully familiar with the condition of ACLF, while 11 had partial familiarity. The participants estimated that ~20% of patients with ACLF are referred too late to a liver specialist, while ~10% were not referred at all. Among liver specialists, ~25% of ACLF cases are reportedly misdiagnosed, while those correctly identified are classified using varying definitions (60% EASL-CLIF, 40% NACSELD) and rely on clinical judgment rather than fixed criteria. All participants emphasized the urgent need for a unified definition and noted that the absence of a dedicated ICD code hampers systematic patient tracking and complicates reimbursement. Participants reported that about one in three patients with ACLF are readmitted within 30 days of discharge. Commonly reported barriers to effective post-discharge management included limited access to hepatologists, geographical distance from care centers, and patient non-adherence to follow-up consultations. **Conclusion:** Management of ACLF is challenging due to delayed referrals, diagnostic inconsistency, and poor post-discharge support. Findings highlight the need for a globally unified definition of ACLF, ICD coding, and improved patient follow-up post discharge. Integrated, multidisciplinary care across specialties and institutions is essential to improve outcomes and ensure timely, specialized care.



Disclosures: Constantine Karvellas: Grifols: Advisor, Miromatrix: Data safety monitoring board for clinical trial, Baxter: Advisor, Mallinckrodt: Consultant, Genfit: Consultant, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo: Grant/Research Support, Grifols: Grant/Research Support, Bausch: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Genfit: Grant/Research Support, Enterobiotix: Advisor, Boehringer Ingelheim: Advisor, Armaghan Dabbagh: Nothing to Disclose, Dean Hum: Nothing to Disclose, Pierbruno Ricci: GENFIT: Employee, Katharina Staufer: Nothing to Disclose, Richard Moreau: Nothing to Disclose, Arun Sanyal: Genfit, Akarna,

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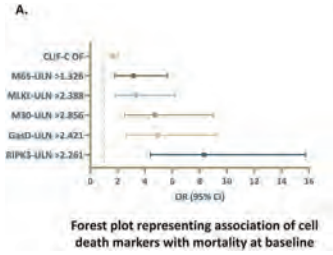
◆ 4128 | IDENTIFICATION AND VALIDATION OF RECEPTOR-INTERACTING PROTEIN KINASE 3 AS A PROGNOSTIC BIOMARKER TO GUIDE PERSONALIZED THERAPY IN ACUTELY DECOMPENSATED CIRRHOSIS: A MULTICOHORT VALIDATION STUDY

Pratibha Garg[1] Nipun Verma[2] Parminder Kaur[2] Saloni Munjal[2] Dr. Ashwin Vinod[2] Arun Valsan[3] Fausto Andreola[4] Arka De[2] Madhumita Premkumar[1] Sunil Taneja[2] Rajeshwar Mookerjee[4] Ajay Duseja[1] Rajiv Jalan[4], [1]Postgraduate Institute of Medical Education & Research, [2]Post Graduate Institute of Medical Education and Research, Chandigarh, India, [3]Amrita Institute of Medical Sciences, Kochi, [4]University College London Medical School

Background: Identifying predominant mode of cell death and their temporal patterns in acutely decompensated cirrhosis (AD) and acute-on-chronic liver failure (ACLF) may inform personalised therapeutic strategies. We investigated the prognostic value of circulating cell death markers in relation to organ dysfunction, disease trajectory, and outcomes in AD/ACLF. **Methods:** A total of 556 patients with acutely decompensated cirrhosis were enrolled across four cohorts. A derivation cohort of 200 AD patients (47 without and 153 with ACLF) was assessed for baseline and day-7 plasma levels of Cytokeratin-18 (M30, M65), Gasdermin-D (pyroptosis), Mixed-Lineage Kinase-Like Protein (MLKL: necroptosis), and Receptor-Interacting Protein Kinase 3 (RIPK3). For standardization, expression levels were interpreted relative to the upper limit of normal defined using expression in healthy control population. A RIPK3-integrated mortality prediction model was developed and validated in two external cohorts (n = 106, 150), with temporal validation in a third cohort (n = 100). **Results:** All cell death markers correlated with disease severity, while RIPK3 showed the strongest association with ACLF grade and extra-hepatic organ failures, especially renal and hepatic ($p < 0.05$). Elevated baseline RIPK3 independently predicted worsening clinical course [adjusted OR: 4.85 (95% CI: 2.36–9.94), $p < 0.001$] and 30-day mortality [adjusted OR: 4.74 (95% CI: 2.38–9.44), $p < 0.001$]. Higher baseline RIPK3 was independently associated with worsening disease course [adjusted OR: 4.85 (95%CI: 2.36-9.94), $p < 0.001$] and mortality [adjusted OR: 4.74; (95%CI: 2.38-9.44), $p < 0.001$]. RIPK3 levels increased over time with worsening course and in non-survivors but declined in those who improved and survived ($p < 0.001$). A model including RIPK3-ULN > 2.261, CLIF-C OF, and leucocytosis/leucopoenia showed strong predictive accuracy (AUC: 0.839), validated across cohorts (AUC: 0.752, 0.794), and confirmed using longitudinal data (AUC: 0.796). **Conclusion:** RIPK3-linked necroptosis is a key contributor to organ failure and mortality in AD/ACLF. Incorporating RIPK3 into prognostic models improves risk stratification and may guide selection of patients for future personalised therapies targeting necroptotic pathways.



Forest plot representing association of cell death markers with mortality at baseline

Temporal expression of cell death markers stratified by outcome

Disclosures: Pratibha Garg: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Parminder Kaur: Nothing to Disclose, Saloni Munjal: Nothing to Disclose, Dr. Ashwin Vinod: Nothing to Disclose, Arun Valsan: Nothing to Disclose, Fausto Andreola: Nothing to Disclose, Arka De: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, Sunil Taneja: Nothing to Disclose, Rajeshwar Mookerjee: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, Rajiv Jalan: Yaqrit Limited: Founder, Cyberliver: Founder

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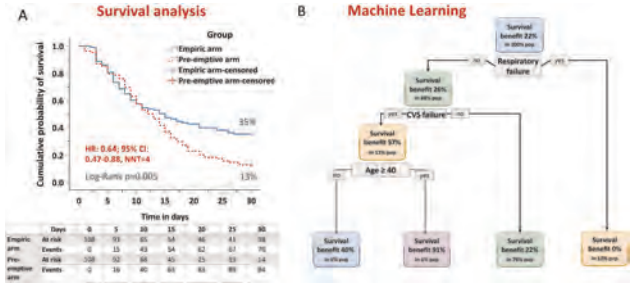
◆ 4129 | EMPIRIC VERSUS PRE-EMPTIVE ANTIFUNGAL IN ACUTE-ON-CHRONIC LIVER FAILURE WITH SUSPECTED INVASIVE FUNGAL INFECTIONS: A PRAGMATIC RANDOMIZED CONTROLLED TRIAL WITH MACHINE LEARNING

Nipun Verma[1] Arun Valsan[2] Pratibha Garg[3] Shreeja Sarabu[4] Parminder Kaur[4] Nimitha Mohan[5] Arka De[4] Madhumita Premkumar[3] Sunil Taneja[4] Shankar Prinja[4] Arunaloke Chakrabarti[4] Nusrat Shafiq[4] Ajay Duseja[3], [1]Postgraduate Institute of Medical Education and Research, [2]Amrita Institute of Medical Sciences, Kochi, [3]Postgraduate Institute of Medical Education & Research, [4]PGIMER Chandigarh, [5]Aster Medicity Kochi

Background: The optimal timing of antifungal therapy in acute-on-chronic liver failure (ACLF) patients with suspected invasive fungal infections (IFIs) remains uncertain. We conducted a pragmatic, randomized controlled trial to compare the efficacy, safety, and cost-effectiveness of empirical versus pre-emptive antifungal therapy in this high-risk population. **Methods:** This investigator-initiated, unblinded, parallel-group randomized trial with blinded endpoint adjudication (NCT04157465) enrolled 216 hospitalized ACLF patients with predefined host and clinical risk factors for IFI at a large tertiary-care center between 2019 and 2024. Participants were randomized 1:1 to receive either empirical antifungal therapy at enrollment or pre-emptive therapy upon laboratory, radiological, or mycological confirmation of IFI, with stewardship-based early stopping rules guided by fungal cultures and biomarkers. The primary endpoint was 28-day overall survival. Secondary outcomes included incidence of IFI, in-hospital mortality, changes in MELD-Na and CLIF-C OF scores, ventilation-free survival, adverse events, and cost-effectiveness. Treatment effect heterogeneity was explored using decision tree-based causal inference. **Results:** Baseline characteristics were balanced between groups. Empirical antifungal therapy significantly improved 28-day survival (hazard ratio: 0.64, 95% CI: 0.47–0.88; $p = 0.005$), with a relative risk reduction of 25.5% and number needed to treat of 4.5 (Fig.1A). Ventilation-free survival (35.2% vs. 13.0%; $p < 0.001$) and treatment success (37.4% vs. 16.9%; $p = 0.002$) were higher in the empirical group. In-hospital mortality was lower, with fewer adverse events. No differences were noted in new-onset IFI, fungal spontaneous bacterial peritonitis, urinary tract infections, or hospital length of stay. The empirical approach was cost-effective, yielding higher quality-adjusted life years (QALYs) (29.9 vs. 10.1) and an incremental cost-effectiveness ratio (ICER) of INR 1,42,737 per QALY gained. Decision tree analysis identified patients aged ≥ 40 years with cardiovascular failure and no respiratory failure as deriving the greatest benefit (Fig.1B). **Conclusion:** Empirical antifungal therapy, guided by clinical suspicion and risk stratification, improves short-term survival and key outcomes in ACLF patients with suspected IFI. This approach is safe, clinically effective, and cost-effective. Machine learning-based subgroup identification offers promising avenues for individualized antifungal strategies in ACLF.



Disclosures: Nipun Verma: Nothing to Disclose, Arun Valsan: Nothing to Disclose, Pratibha Garg: Nothing to Disclose, Shreeja Sarabu: Nothing to Disclose, Parminder Kaur: Nothing to Disclose, Nimitha Mohan: Nothing to Disclose, Arka De: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, Sunil Taneja: Nothing to Disclose, Shankar Prinja: Nothing to Disclose, Arunaloke Chakrabarti: Nothing to Disclose, Nusrat Shafiq: Nothing to Disclose, Ajay Duseja: Nothing to Disclose

4130 | DRUG-INDUCED ACLF (DI-ACLF) ASSOCIATED WITH A HIGH MORTALITY IN PATIENTS WITH MAFLD: A MULTICENTER COHORT STUDY FROM THE AARC REGISTRY

Gupse Adali[1] Ashok Kumar Choudhury[2] VINOD ARORA[2] Rakhi Maiwall[3] Mohamed Rela[4] Dinesh Jothimani[4] Mamun Mahtab[5] Harshad Devarbhavi[6] C Eapen[7] Ashish Goel[7] Cesar Yaghi[8] Qing Ning[9] Tao Chen[9] Jidong Jia[9] Duan Zhonping[10] Saeed Hamid[11] Amna Subhan[11] Wasim Jafri[11] Akash Shukla[12] Soek Siam Tan[13] Dong Joon Kim[14] Anoop Saraya[15] jinhua hu[16] AJIT SOOD[17] Omesh Goyal[18] Vandana Midha[17] Girish Kumar Pati[19] Guan-Huei Lee[20] Sombat Treeprasertsuk[21] Kessarin Thanapirom[21] Ameet Mandot[22] SAMIR SHAH[22] Ravikiran Maghade[22] P. Nagaraja Rao[23] Anand Kulkarni[24] Mithun Sharma[25] Hasmik Ghazinyan[26] V.G.Mohan Prasad[27] Abdulkadir Dokmeci[28] Jose Sollano[29] Zaigham Abbas[30] Ananta Shrestha[31] George Lau[32] Diana Payawal[33] Gamal Shiha[34] Ajay Duseja[35] Sunil Taneja[36] Nipun Verma[36] Cosmas Rinaldi Lesmana[37] Fazal Karim[38] Radha Dhiman[39] Ajay Mishra[39] Shah Alam[40] Osamu Yokosuka[41] Debashis Chowdhury[42] Chandan Kumar[43] Sanjiv Saigal[44] Anil Arora[45] Ashish Kumar[45] Ghulam

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Yattoo[46] Abraham Koshy[47] Ajay Patwa[48] Mohamed Elbastawisy[49] PRAVIN RATHI[50] Sudhir Maharshi[51] Vm Dayal[52] Ashish Jha[52] Kemal Kalista[53] Man-Fung Yuen[54] Virendra Singh[55] Ayaskanta Singh[56] Violeta Sargsyan[57] Chien-Hao Huang[58] Saurabh Mukewar[59] Xianyu Shao[60] Ruveena Rajaram[61] Charles Panackel[62] Sunil Dadhich[63] Sanjeev Sachdeva[64] AJAY KUMAR[65] sanatan behera[66] Prabir Maji[67] Lubna Kamani[68] Hemamala Ilango[69] Joy Varghese[70] Pathik Parikh[71] Javed P[72] Neeraj Saraf[73] Narendra Choudhary[74] Akash Roy[75] Mahesh Goenka[75] Suprabhat Giri[76] Manoj Sahu[76] Dibyalochan Praharaj[76] Krishnadas Devadas[77] Arun Valsan[78] H Janaka Da Silva[79] Tarana Gupta[80] Shalimar S[81] Chetan Kalal[3] AARC Group[2] Shiv Kumar Sarin[2], [1]University of Health Sciences Istanbul Umraniye Training and Research Hospital, [2]Institute of Liver and Biliary Sciences, New Delhi, India, [3]Institute of Liver and Biliary Sciences, [4]Dr. Rela Institute, Chennai (India), [5]Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, [6]Department of Hepatology, St John Medical College, Bangalore, India., [7]Department of Hepatology, CMC, Vellore, India, [8]Saint Joseph University, Lebanon, Beirut, [9]Tongji Hospital, Wuhan, China, [10]Hepatology Institute Capital Medical University, China, [11]Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan, [12]Department of Gastroenterology, Lokmanya Tilak Municipal General Hospital and Lokmanya Tilak Mun, [13]Department of Medicine, Hospital Selayang, Bata Caves, Selangor, Malaysia, [14]Hallym University Medical Center, [15]All India Institute of Medical Sciences, New Delhi (India), [16]302, Military Hospital, China, [17]Dayanand Medical College, Ludhiana, India, [18]D.M.C. and Hospital, [19]Department of Gastroenterology and Hepatology Sciences, IMS & SUM Hospital, Bhubaneswar, Odisha, [20]National University Hospital, [21]Department of Medicine, Chulalongkorn University, Bangkok, Thailand., [22]Department of Hepatology, Global Hospitals, Mumbai, India, [23]Asian Institute of Gastroenterology, Hyderabad, India., [24]Asian Institute of Gastroenterology, [25]AIG Hospitals, [26]Department of Hepatology, Nork Clinical Hospital of Infectious Disease, Yerevan, Armenia., [27]Department of Gastroenterology, VGM Hospital, Coimbatore, India, [28]Ankara University, [29]Department of Medicine, University of Santo Tomas, Manila, Philippines, [30]Ziauddin University Hospital, [31]Department of Hepatology, Alka Hospital, Nepal, [32]Department of Medicine, Humanity and Health Medical Group, New Kowloon, Hong Kong, [33]Fatima University Medical Cent, [34]Egyptian Liver Research Institute And Hospital, Egypt, [35]Postgraduate Institute of Medical Education & Research, [36]Postgraduate Institute of Medical Education and Research, Chandigarh, India, [37]Digestive Disease and GI Oncology Centre, Medistra Hospital, Jakarta, Indonesia, [38]Sir Salimullah Medical College Hospital, Bangladesh, [39]SGPGI, Lucknow, India, [40]Crescent Gastroliver and General Hospital, Bangladesh, [41]Chiba University, Japan., [42]CMOSH Medical College, Bangladesh, [43]Global Hospitals, Hyderabad, [44]Max Super Specialty Hospital, Saket New Delhi, India, [45]Sir Ganga Ram Hospital, [46]SKIMS, Srinagar, India, [47]Lakeshore Hospital, [48]KGMC, Lucknow (India), [49]Mansoura University, Egypt, [50]TN Medical College and BYL Nair Hospital, Mumbai, [51]SMS Jaipur, India, [52]IGIMS, Patna, India, [53]Cipto Mangunkusumo Hospital, Indonesia, [54]The University of Hong Kong, [55]Punjab Institute of Liver and Biliary Sciences, Mohali, India, [56]SUM Ultimate Medicare, Bhubaneswar, India, [57]Violeta Medical Centre, Armenia, [58]Chang Gung Memorial Hospital, [59]Mayo Clinic Rochester, [60]Medical school of Chinese PLA, China, [61]University of Malaya Medical Centre, Malaysia, [62]Aster Medicity, Kochi, India, [63]SMNC, Jodhpur, India, [64]G.B. Pant Hospital, New Delhi, India, [65]AIRFORCE HOSPITAL, [66]SCB Medical College & Hospital, Cuttack (Odisha), India, [67]IMS & SUM Hospital- II, [68]Liaquat National Hospital, Pakistan, [69]MIOT International Hospital, Chennai, India, [70]Gleneagles Global Health City, Chennai, India, [71]Zydus Hospital, Ahmedabad, India, [72]Aster MIMS Hospital, Kannur, India, [73]Institute of Digestive & Hepatobiliary Sciences, [74]Medanta, The Medicity Multispeciality Hospital, Gurgaon, India, [75]Apollo Multispeciality Hospital, Kolkata, India, [76]Kalinga Institute of Medical Sciences (KIMS), Bhubaneshwar, India, [77]Government Medical College, Thiruvananthapuram, [78]Amrita Institute of Medical Sciences, Kochi, [79]University of Kelaniya, Ragama, Srilanka, [80]Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, India, [81]All India Institute of Medical Sciences, New Delhi, India

Background: Drug-induced liver injury (DILI) leading to ACLF or drug-induced ACLF (DI-ACLF) inherits the dual challenges of DILI and ACLF. Impact of drugs on individual etiology of chronic liver disease (CLD) is unknown. This study aimed to evaluate the association of MAFLD as an underlying CLD, and impact of drug induced liver injury leading to ACLF. **Methods:** Data from prospectively collected 10,994 patients from the AARC registry were analyzed. The diagnosis of DI-ACLF was defined as acute hepatic insult from DILI as a precipitating event. The patients were then divided into the MAFLD-ACLF and non-MAFLD-ACLF groups. MAFLD-ACLF was diagnosed when the etiology of the underlying CLD was MAFLD. The primary outcome was the 30-day mortality. **Results:** A total of 10,994 patients, enrolled in the AARC between April 2009 and April 2024, and 661 (6%) were diagnosed with DI ACLF. In the DI-ACLF group, 5% were MAFLD-related DI-ACLF. Complementary alternative medicine (CAM) and Herbal

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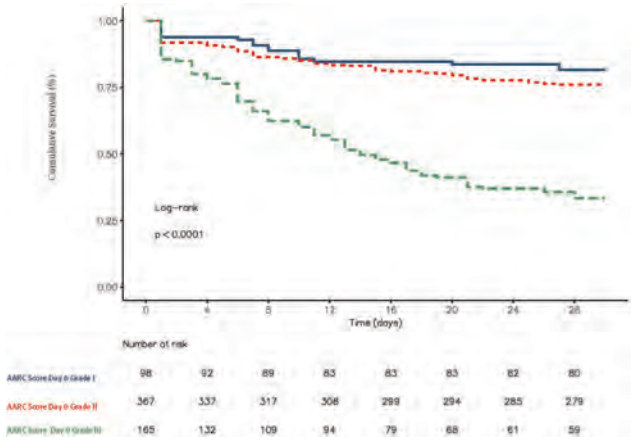
Dietary Supplements (HDS) constituted 16 % of the DI-ACLF cases, with anti-tuberculosis therapy (ATT), antiretroviral, antimicrobials, and antiepileptics accounting 6% of the cases. The most common underlying liver disease etiology was alcohol (63.4%), followed by viral (21.3%), autoimmune hepatitis and cholestatic etiology (6.8%). The overall 30-day mortality rate was greater in MAFLD-related DI-ACLF patients than in non-MAFLD-related DI-ACLF patients (48.5% vs. 31.8%, $p = 0.047$). Patients with MAFLD-related DI-ACLF had higher baseline respiratory failure, baseline hepatic encephalopathy, and > 2 organ failures on day 7 (6.1% vs.0.6%, $p = 0.032$; 21.2% vs. 8.1%, $p = 0.019$; and 69.7% vs. 44.9%, $p = 0.005$, respectively). AARC Score Grade 3 at day 0 (HR: 5.52 95% CI 3.14-9.71, $p < 0.001$), and age (HR: 1.01 95% CI 1.00-1.03, $p = 0.013$) were independent predictors of 30-day mortality in DI-ACLF patients. **Conclusion:** Drugs are an important identifiable cause of ACLF, and MAFLD is increasingly becoming the underlying cause of liver disease globally. The 30-day mortality was higher in MAFLD-related DI-ACLF patients and AARC Score of day 0 was the strongest predictor of mortality in DI-ACLF patients.



Disclosures: Gupse Adali: Nothing to Disclose, Ashok Kumar Choudhury: Nothing to Disclose, VINOD ARORA: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, Mohamed Rela: Nothing to Disclose, Dinesh Jothimani: Nothing to Disclose, Mamun Mahtab: Nothing to Disclose, Harshad Devarbhavi: Nothing to Disclose, C Eapen: Nothing to Disclose, Ashish Goel: Nothing to Disclose, Cesar Yaghi: Nothing to Disclose, Qing Ning: Nothing to Disclose, Tao Chen: Nothing to Disclose, Jidong Jia: Nothing to Disclose, Duan Zhonping: Nothing to Disclose, Saeed Hamid: Nothing to Disclose, Amna Subhan: Nothing to Disclose, Wasim Jafri: Nothing to Disclose, Akash Shukla: Nothing to Disclose, Soek Siam Tan: Nothing to Disclose, Dong Joon Kim: Nothing to Disclose, Anoop Saraya: Nothing to Disclose, jinhua hu: Nothing to Disclose, AJIT SOOD: Nothing to Disclose, Omesh Goyal: Nothing to Disclose, Vandana Midha: Nothing to Disclose, Girish Kumar Pati: Nothing to Disclose, Guan-Huei Lee: Nothing to Disclose, Sombat Treeprasertsuk: Nothing to Disclose, Kessarin Thanapirom: Nothing to Disclose, Ameet Mandot: Nothing to Disclose, SAMIR SHAH: Nothing to Disclose, Ravikiran Maghade: Nothing to Disclose, P. Nagaraja Rao: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose, Mithun Sharma: Nothing to Disclose, Hasmik Ghazinyan: Nothing to Disclose, V.G.Mohan Prasad: Nothing to Disclose, Abdulkadir Dokmeci: Nothing to Disclose, Jose Sollano: Nothing to Disclose, Zaigham Abbas: Nothing to Disclose, Ananta Shrestha: Nothing to Disclose, George Lau: Nothing to Disclose, Diana Payawal: Nothing to Disclose, Gamal Shiha: Nothing to Disclose, Ajay Duseja: Nothing to Disclose, Sunil Taneja: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Cosmas Rinaldi Lesmana: Nothing to Disclose, Fazal Karim: Nothing to Disclose, Radha Dhiman: Nothing to Disclose, Ajay Mishra: Nothing to Disclose, Shah Alam: Nothing to Disclose, Osamu Yokosuka: Nothing to Disclose, Debashis Chowdhury: Nothing to Disclose, Chandan Kumar: Nothing to Disclose, Sanjiv Saigal: Nothing to Disclose, Anil Arora: Nothing to Disclose, Ashish Kumar: Roche: Consultant, Viatris: Consultant, Ghulam Yattoo: Nothing to Disclose, Abraham Koshy: Nothing to Disclose, Ajay Patwa: Nothing to Disclose, Mohamed Elbastawisy: Nothing to Disclose, PRAVIN RATHI: Nothing to Disclose, Sudhir Maharshi: Nothing to Disclose, Vm Dayal: Nothing to Disclose, Ashish Jha: Nothing to Disclose, Kemal Kalista: Nothing to Disclose, Man-Fung Yuen: Nothing to Disclose, Virendra Singh: Nothing to Disclose, Ayaskanta Singh: Nothing to Disclose, Violeta Sargsyan: Nothing to Disclose, Chien-Hao Huang: Nothing to Disclose, Saurabh Mukewar: Nothing to Disclose, Xianyu Shao: Nothing to Disclose, Ruveena Rajaram: Nothing to Disclose, Charles Panackel: Nothing to Disclose, Sunil Dadhich: Nothing to Disclose, Sanjeev Sachdeva: Nothing to Disclose, AJAY KUMAR: Nothing to Disclose, sanatan behera: Nothing to Disclose, Prabir Maji: Nothing to Disclose, Lubna Kamani: Nothing to Disclose, Hemamala Ilango: Nothing to Disclose, Joy Varghese: Nothing to Disclose, Pathik Parikh: Nothing to Disclose, Javed P: Nothing to Disclose, Neeraj Saraf: Nothing to Disclose, Narendra Choudhary: Nothing to Disclose, Akash Roy: Nothing to Disclose, Mahesh Goenka: Nothing to Disclose, Suprabhat Giri: Nothing to Disclose, Manoj Sahu: Nothing to Disclose, Dibyalochan Praharaj: Nothing to Disclose, Krishnadas Devadas: Nothing to Disclose, Arun Valsan: Nothing to Disclose, H Janaka Da Silva: Nothing to Disclose, Tarana Gupta: Nothing to Disclose, Shalimar S: Nothing to Disclose, Chetan Kalal: Nothing to Disclose, AARC Group: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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4131 | A SIMPLE MACHINE LEARNING MODEL CONSIDERING SERUM BILIRUBIN, PT-INR AND AGE CAN ACCURATELY PREDICTS THE RISK OF EARLY RENAL FAILURE IN PATIENT OF ACUTE ON CHRONIC LIVER FAILURE(ACLF)

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Background: In Acute-on-chronic liver failure (ACLF), renal failure is most common non-hepatic organ failure

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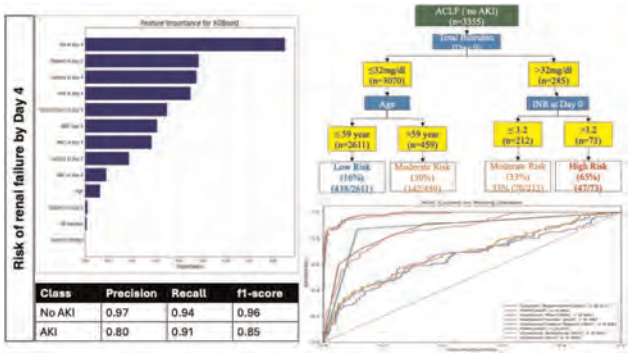
and had a significant impact on disease course. We aimed to build a machine learning (ML) model for precise prediction of renal failure among hospitalised ACLF patients. **Methods:** We analysed data from the AARC registry, including clinical information-laboratory parameters and organ failure. After data pre-processing and random splitting (80:20) into derivation-and validation-sets, machine learning models (XGBoost, Random Forest, K-Nearest Neighbours, Decision Trees, Gradient boosting, Logistic Regression, Support Vector Machine (SVM), Gaussian Naive Bayes) were developed on the derivation-set. Model performance was evaluated using area under the curve (AUC), accuracy, precision, and recall/sensitivity to predict renal failure development by day 4 in initially non-affected patients. **Results:** Among 9929 patients (51.6 ± 11.8 years, 87% male), 31.5% (3132) had renal failure at presentation and another 20.8% develop new onset by 4days of hospitalization. Presence of renal failure increases mortality by 31% at 90 days. After data preparation, 46 features used to train eight ML models, and the top 13 features made the best-performing model. The XGBoost model performed best (AUC: 0.98; sensitivity: 0.92; specificity: 0.94). The top predictive variables were baseline total bilirubin, leukocyte and platelet count and 4th day PT-INR, and serum sodium. A decision tree was made with baseline bilirubin of > 32 mg/dL and INR > 3.3 and age > 58 years to predict the risk of renal failure as low risk (15%), moderate risk (30-33%) and high risk (65%) for developing renal failure with the precision, recall, and F1 score of 0.80, 0.91, and 0.85, respectively. **Conclusion:** Renal failure is the common extra-hepatic renal failure with one third at presentation and additional one fourth develop by 4 days, leading to increased mortality. The ML-based model significantly improves prediction of renal failure and simple parameters like age, serum bilirubin and PT-INR can stratify the at-risk group. This tool may enable predictions, timely interventions to improve survival outcome.



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4132 | LIVER FRAILTY INDEX IS ASSOCIATED WITH DECREASED RECOVERY IN EGFR AFTER LIVER TRANSPLANTATION

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Background: Frailty has emerged as a significant predictor of adverse outcomes in patients with cirrhosis. While its role in pre-transplant evaluation is well recognized, the association between the Liver Frailty Index (LFI) and post-transplant renal recovery remains unclear. This study investigates the relationship between pre-transplant frailty and changes in renal function, as measured by estimated glomerular filtration rate (eGFR), following liver transplantation. **Methods:** We conducted a retrospective analysis of adult liver transplant recipients from December 2019 to November 2024 at a single center. eGFR was calculated using the CKD-EPI 2021 equation on post-transplant days 0, 1, 7, 14, 28, and 90. LFI was determined prior to transplantation using grip strength, chair stands, and balance testing, and categorized as robust (<3.2), pre-frail (3.2–4.4), or frail (≥ 4.5). Multivariable logistic regression was used to assess the association between LFI and renal recovery, defined as any increase in eGFR compared to baseline (Day 0), after adjusting for age, sex, BMI, MELD, diabetes, pre-transplant hospitalization, and intraoperative blood product usage. **Results:** Among 288 transplant recipients, 227 had available LFI data (mean LFI 4.55, range 2.43–7.04). Higher LFI was significantly associated with reduced odds of eGFR recovery at post-transplant days 7 (OR 0.605, 95% CI 0.416–0.881, $p = 0.009$), 14 (OR 0.617, 95% CI 0.429–0.888, $p < 0.01$), 28 (OR 0.425, 95% CI 0.285–0.633, $p < 0.001$), and 90 (OR 0.611, 95% CI 0.423–0.882, $p < 0.01$). No significant association was observed on postoperative day 1. **Conclusion:** Pre-transplant frailty, as assessed by the Liver Frailty Index, is independently associated with diminished renal recovery following liver transplantation. These findings suggest that frailty may play a critical role in post-transplant kidney function and highlight the need for frailty-targeted interventions and prospective multicenter studies to optimize outcomes in this high-risk population.

Table 1. Association Between Liver Frailty Index (LFI) and Post-Transplant eGFR Recovery

Time Point	LFI OR (95% CI)	p-value
POD 1	0.747 (0.520–1.073)	0.114
POD 7	★ 0.605 (0.416–0.881)	0.009
POD 14	★ 0.617 (0.429–0.888)	0.008
POD 28	★ 0.425 (0.285–0.633)	<0.001
POD 90	★ 0.611 (0.423–0.882)	0.009

Footnotes:

- eGFR recovery was defined as any increase in eGFR compared to post-transplant Day 0.
- Odds ratios (ORs) reflect the effect of pre-transplant Liver Frailty Index (LFI) on the odds of eGFR improvement at each postoperative time point.
- ★ Statistically significant ($p < 0.05$).
- Models adjusted for age, sex, BMI, MELD score, diabetes, pre-OLT hospital length of stay, and intraoperative blood product usage.

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4133 | DYNAMIC CHANGES IN THE A-TANGO ORGAN FAILURE SCORE OVER 7-DAYS ACCURATELY DEFINES MORTALITY AND COULD BE USED AS A SURROGATE END POINT IN CLINICAL TRIALS

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Background: Acute-on-chronic liver failure (ACLF) is characterised by multiorgan failure and high short-term mortality. The A-TANGO consortium is conducting a clinical trial of a novel drug to reverse ACLF (www.a-tango.eu). Given the variability in the diagnosis of ACLF using the CLIF OF score, the consortium developed the A-TANGO organ failure (OF) score to improve accuracy. This study evaluated whether the dynamic change in the A-TANGO score at day-7 can define 28-day mortality and allow it to be used as an early surrogate biomarker of response to therapy and therefore as an endpoint for clinical trials. **Methods:** *Derivation cohort:* 3896 patients with acute decompensated liver cirrhosis from the CANONIC, PREDICT and ACLARA. A-TANGO OF score was calculated at baseline, day-7 at day-28. For the analysis of disease dynamics, the final A-TANGO ACLF grade was determined within a time frame of 4-weeks, aligned with the occurrence of a clinical endpoint (death or liver transplant, at 28-days). *Validation cohort*: The Ambi-spective cohort, India (2055 patients). **Results:** The A-TANGO OF score at day-7 demonstrated improved prognostic accuracy compared to baseline, increasing from 0.793 to 0.822 (c-index) in predicting 28-day mortality. A one unit increase in the A-TANGO OF score at day-7 was associated with a hazard ratio (HR) of 1.479 and 1.369 for 28-day and 90-day mortality, which was confirmed in the validation cohort. Of 407 patients with A-TANGO ACLF at baseline, 44.9% achieved complete resolution, 33.4% remained stable, while 12.5% worsened within day-28.

Among patients without A-TANGO ACLF at baseline, 92 out of 1230 (7.5%) progressed to A-TANGO ACLF. The resolution of A-TANGO ACLF was associated with 28-day and 90-day mortality that is observed in patients with no ACLF; 3.5% and 16.7%. Reduction of A-TANGO ACLF grade corresponded to mortality rates of 7.7% and 20.4%, respectively. Worsening A-TANGO ACLF or development of new ACLF (in those without) had mortality rates of 59% and 21.8% at 28-days. These findings were consistent in the validation cohort. **Conclusion:** The results of this study show that A-TANGO ACLF is a dynamic condition, the course of which can be captured by the A-TANGO score, which responds to clinical intervention and makes it a suitable model to be used as an early surrogate marker of mortality. Improved precision helps reduce sample size and statistical errors and, strengthens the endpoint of ACLF resolution, ultimately optimizing the design and outcomes of clinical trials.

Clinical course patterns according to ATANGO organ failure score

Initial grade	Final grade				
	No ACLF (n=1321)	ACLF-1 (n=201)	ACLF-2 (n=61)	ACLF-3 (n=21)	ACLF-4 (n=33)
No ACLF (%)					
Prevalence (n=1230)	1138 (92.52)	71 (5.77)	17 (1.38)	1 (0.08)	3 (0.24)
28-day tx-free mortality	31/1088 (2.77)	12/67 (17.91)	5/16 (31.25)	1/1 (100)	1/3 (33.00)
90-day tx-free mortality	135/1082 (12.48)	20/58 (34.48)	11/15 (73.33)	1/1 (100)	3/3 (100)
ACLF-1 (%)					
Prevalence (n=283)	151 (53.36)	102 (36.04)	21 (7.42)	4 (1.41)	5 (1.77)
28-day tx-free mortality	4/144 (2.78)	12/95 (12.63)	9/17 (52.94)	0/4 (0)	5/5 (100)
90-day tx-free mortality	23/134 (17.16)	24/84 (29.27)	12/16 (75.00)	3/4 (75.00)	5/5 (100)
ACLF-2 (%)					
Prevalence (n=81)	28 (34.57)	24 (29.63)	16 (19.75)	6 (7.41)	7 (8.64)
28-day tx-free mortality	2/25 (8.00)	3/23 (13.04)	4/13 (30.77)	1/6 (16.67)	6/6 (100)
90-day tx-free mortality	3/24 (12.50)	6/21 (28.57)	6/11 (54.55)	5/6 (83.33)	6/6 (100)
ACLF-3 (%)					
Prevalence (n=29)	3 (10.34)	4 (13.79)	6 (20.69)	8 (27.59)	8 (27.59)
28-day tx-free mortality	1/3 (33.33)	1/4 (25.00)	4/6 (66.67)	6/7 (85.71)	5/6 (83.33)
90-day tx-free mortality	1/3 (33.33)	1/4 (25.00)	4/6 (66.67)	7/7 (100)	6/6 (100)
ACLF-4 (%)					
Prevalence (n=14)	1 (7.14)	0 (0)	1 (7.14)	2 (14.29)	10 (71.43)
28-day tx-free mortality	0/1 (0)	0/0 (0)	0/1 (0)	1/1 (100)	8/9 (88.89)
90-day tx-free mortality	0/1 (0)	0/0 (0)	0/1 (0)	1/1 (100)	8/9 (90.00)

* Final ACLF grade has been assessed with a time limit of 4 weeks to replicate the table in the paper. Initial grade has been considered as the first non-missing ACLF grade given to a patient (between inclusion and week 1).

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4134 | IMPACT OF HEPATIC ENCEPHALOPATHY ON PROGNOSIS IN CIRRHOTIC PATIENTS WITH ACUTE DECOMPENSATION: THE CRUCIAL ROLE OF UNDERLYING LIVER FUNCTION AND COAGULATION FAILURE

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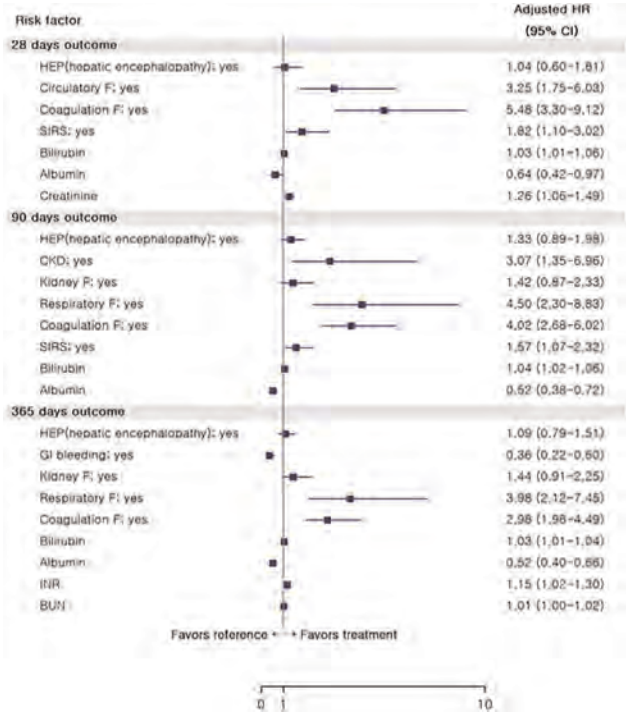
Background: Hepatic encephalopathy (HEP) is a major complication of cirrhosis, resulting in significant impairment of the quality of life and frequent hospitalizations. HEP is considered one of the major components in the diagnosis of acute-on-chronic liver failure (ACLF), HEP is well known that it is associated with high mortality. However, there is controversial to whether HEP itself has a direct effect on the patient's prognosis and whether underlying liver function is important. This study aimed to investigate the impact of HEP on acute decompensation (AD) and adverse outcome (death or liver transplantation), utilizing real-world data. **Methods:** We analyzed prospective multicenter data collected from 31 hospitals in South Korea from 2015 to 2019. We included 1,315 patients diagnosed with liver cirrhosis who were admitted due to acute decompensation. A comparative analysis was conducted to assess the risk factors and the incidence of death or liver transplantation between patients with and without HEP. Propensity score (PS) matching was employed at a 1:3 ratio for accurate comparisons. PS were computed using the following 4 variables: age; sex; etiology of cirrhosis; and MELD score. **Results:** The mean age of the entire cohort was 54.7 years, with 74.9% being male. HE was noted in 14.7% of the cohort. Patients with HEP had positive correlations with ascites, jaundice and upper gastrointestinal bleeding. The median follow-up period was 8.0 months (range, 1.0–15.0 months), during which 332 patients (23.7%) either died or underwent liver transplantation. After adjusting for various factors, coexisting HEP did not increase the risk of death or liver transplantation for short-term and long-term. However, coagulation failure, underlying liver function such as prolonged prothrombin time, low serum albumin and elevated total bilirubin were revealed as major risk factors for short-term and long-term adverse outcomes. **Conclusion:** In patients with acute decompensation of liver cirrhosis, hepatic encephalopathy (HEP) was not an independent predictor of mortality or liver transplantation after adjusting for confounding factors. While HEP frequently coexisted with other severe complications, prognosis was more strongly influenced by underlying hepatic dysfunction, including coagulation failure, prolonged prothrombin time, hypoalbuminemia, and hyperbilirubinemia. These results highlight the prognostic importance of liver functional reserve rather than the presence of HEP alone.



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4135 | NUTRITIONAL INTERVENTION FOR PATIENTS WITH LIVER FAILURE REDUCES THE RISK OF CLINICAL COMPLICATIONS

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Background: Liver failure patients are at a high risk of developing various clinical complications. However, it remains unclear whether nutritional intervention can reduce the occurrence of adverse complications. **Methods:** This study included hospitalized patients diagnosed with liver failure at West China Hospital, Sichuan University. The Nutrition Risk Screening (NRS 2002) was used to assess the nutritional risk of the patients. For patients with nutritional risk, personalized additional enteral or parenteral nutrition was provided. To compare the differences between groups, the Kruskal-Wallis test was used for continuous variables, and the chi-square test was used for categorical variables. Multivariate logistic regression analyses were performed to calculate the odds ratios (OR) and 95% confidence intervals (CI) for the relationship between nutritional intervention and adverse clinical outcomes. **Results:** A total of 6097 liver failure patients were included in this study, with a median age of 53 years [interquartile range (IQR) 43, 64], and 69.2% of them were male. Hepatitis B accounted for 62.2% of the etiologies in the patients, and 1197 (19.6%) had liver cirrhosis. 555 (9.1%) were diagnosed with ascites, 191 (3.1%) with hepatorenal syndrome, 346 (5.7%) with hepatic encephalopathy, 792 (13.0%) with infection, 577 (9.46%) with coagulation disorder, 733 (12.0%) with spontaneous bacterial peritonitis. Among them, 3201 (52.5%) patients were at nutritional risk. Patients with nutritional risk were older and weighed less. Additionally, the incidence of hepatorenal syndrome, hepatic encephalopathy, infection, coagulation disorder, and all-cause mortality was significantly higher ($P < 0.01$). However, there was no change in the risk of ascites, spontaneous bacterial peritonitis. After adjusting for age, gender, height, weight, smoking, drinking, hypertension, diabetes mellitus, and education, for patients receiving nutritional intervention with nutritional risk, the OR and 95% CI of the risk of developing ascites were 0.50 (0.31-0.81), for infection were 0.70 (0.52-0.94), and for spontaneous bacterial peritonitis were 0.34 (0.24-0.49). However, there was no difference in the risk of hepatic encephalopathy, hepatorenal syndrome, and in the risk of coagulation disorder. Moreover, for patients without nutritional risk, nutritional intervention can also reduce the incidence of ascites [0.26 (0.12-0.55)], abnormal coagulation function [0.35 (0.17-0.72)], and spontaneous bacterial peritonitis [0.30 (0.17-0.54)]. **Conclusion:** Among patients with liver failure, 52.5% were found to be at nutritional risk. Personalized nutritional intervention can significantly reduce the risks of clinical complications regardless of nutritional risk.

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4136 | ESTABLISHING A RANK-ORDERED HEIRARCHY OF ACLF RELATED MORTALITY RISK ASSOCIATED WITH ORGAN SUPPORT IN REAL WORLD CLINICAL PRACTICE

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Background: The number of organ failures (OF) and need for organ support are linked to mortality in ACLF. The impact of varying combinations of OFs and need for organ support on mortality in real-world clinical practice is unknown. Hypothesis: The number and type of OFs and need for organ support are differentially related to 30-day mortality in ACLF. Aims: To define (1) the impact of OFs, alone and in combination, on mortality in ACLF in real-world clinical practice and (2) within 2-4 OF combinations, the relationship of need for organ support to mortality. **Methods:** A retrospective analysis of hospitalized patients was performed using the TriNetX global collaborative network. ACLF was defined by diagnosis codes for cirrhosis with decompensation (ascites, encephalopathy or variceal hemorrhage) with one or more OFs, i.e. circulatory (hypotension, DIC etc.), brain (overt hepatic encephalopathy), renal (acute kidney injury [AKI]) and lung (respiratory failure). The use of pressors, renal replacement therapy (RRT), and ventilator support represented need for organ support. Odds ratio (OR) for 30-day mortality for those with one or combinations of OF versus controls admitted with cirrhosis decompensation without ACLF matched for age, race/ethnicity, sex, BMI, smoking status, type 2 Diabetes Mellitus, heart failure, chronic kidney disease, hypertension and chronic obstructive pulmonary disease were computed. Within combinations of OFs, the relationship between mortality and need for types of organ support was measured. **Results:** Up to 54,592 cases of ACLF with various combinations of OF were identified with matched controls. The rank-order of outcomes in single OF was: OR (95% CI): brain- 1.42 (1.3-1.6), circulatory- 1.87 (1.7-2), kidney- 3.2 (3-3.3), lung- 4 (3.7-4.3). The rank-order of outcomes for 2 OF were: circulatory-brain- 2.9 (2.5-3.4), kidney-brain- 5.2

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(4.6-5.8), kidney-circulatory- 5.5 (5.1-5.8), lung-circulatory- 6.2 (5.5-6.9), lung-brain- 8.9 (7.1-11.3), lung-kidney- 11.9 (11.2-12.7). Those with 3-OF lung-kidney-brain- 18.1 (15.4-21.1) and 4-OF lung-kidney-brain-circulatory- 19.7 (18-21.5) had the highest mortality. The impact of type of organ support for each 2-4 OF combinations on mortality is shown in the Table. **Conclusion:** ACLF is heterogeneous in its outcome-profile with a hierarchy of mortality risk based on types of OF and organ support. These can inform trial design and development of hierarchical endpoints.

2-organ failures	Circulation + Brain	Kidney + Brain	Kidney + Circulation	Lung + Circulation	Lung + Brain	Lung + Kidney
Number of patients	8145	11992	38136	12497	2772	34999
	Odds ratio (95% confidence interval) vs. those who did not get organ support					
Pressors only	1.4 (1.1-1.7)	2 (1.7-2.3)	1.9 (1.8-2.1)	1.7 (1.5-1.9)	1.8 (1.3-2.5)	2.7 (2.5-3)
RRT only	-	2.5 (1.3-4.9)	1.8 (1.3-2.5)	-	-	1.7 (1.4-2.2)
Ventilator only	-	-	2.8 (1.7-4.8)	2.1 (1.5-2.8)	0.8 (0.4-1.4)	1.5 (1.3-1.8)
Pressor + RRT	-	3.3 (1.6-5.7)	4.1 (3.5-4.9)	-	-	4.5 (3.7-5.5)
Pressor + Ventilator	4 (1.9-8.3)	2.5 (1.5-4.1)	5.5 (4.6-6.6)	2.9 (2.5-3.3)	2.2 (1.5-3.4)	4 (3.7-4.3)
Ventilator + RRT	-	-	-	-	-	1.8 (1.2-2.7)
Pressor +Ventilator +RRT	-	-	9.8 (7.4-13.1)	-	-	5.7 (4.9-6.6)

3-4 organ failures	Circulatory + Kidney + Brain	Circulatory + Lung + Brain	Lung + Kidney + Circulatory	Lung + Kidney + Brain	Lung +Kidney + Brain + Circulatory
Number of patients	17209	3141	48401	5855	19791
Pressors only	1.4 (1.3-1.6)	1.7 (1.3-2.2)	1.9 (1.8-2)	2.1 (1.8-2.5)	1.5 (1.3-1.6)
RRT only	1.6 (0.9-2.8)	-	1.8 (1.5-2.1)	2.8 (1.5-5.4)	1.8 (1.3-2.6)
Ventilator only	-	0.9 (0.5-1.7)	1.5 (1.3-1.8)	1 (0.6-1.7)	0.8 (0.6-1.2)
Pressors + RRT	3.2 (2.5-4.2)	-	3.2 (2.9-3.6)	3.9 (2.6-5.9)	2.8 (2.3-3.3)
Pressors + Ventilator	2.5 (1.8-3.4)	1.9 (1.3-2.7)	3 (2.8-3.1)	3.2 (2.5-4)	2.2 (2-2.5)
Ventilator + RRT	-	-	1.5 (1.1-2.1)	-	-
Pressor +Ventilator +RRT	2.6 (1.7-4)	-	3.5 (3.2-3.7)	4.2 (2.8-6.1)	2.4 (2.1-2.8)

Table 1: Impact of need for organ support in ACLF with 2-4 organ failures (columns are in order of increasing mortality risk from left to right). Impact of organ support on mortality within each combination are shown with increasing intensity of organ support (read from top to bottom in each column)

'-'= not available due to insufficient data, e.g., too few individuals who received organ support to compute.

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4137 | DEVELOPMENT AND VALIDATION OF THE ATANGO ORGAN FAILURE SCORE FOR DIAGNOSIS AND PROGNOSIS OF ACUTE-ON-CHRONIC LIVER FAILURE IN GLOBAL COHORTS

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Background: Acute-on-chronic liver failure (ACLF) is characterised by multiorgan failure and high short-term mortality in hospitalised cirrhosis patients with acute decompensation (AD). While the EASL-CLIF criteria are widely used for its diagnosis and prognosis, evolving definitions of organ dysfunction and emerging therapies call for updated, tailored criteria to ensure accurate diagnosis, enable effective treatment assessment, and enhance applicability in clinical trials. The aims of the study were to develop and validate the new ATANGO organ failure (OF) score to enhance the diagnosis of ACLF and improve its utility for assessing treatment response and risk stratification for clinical trials. **Methods:** A retrospective analysis of prospective, observational cohort studies. Derivation cohort: 3 studies performed by the EF-CLIF consortium in Europe and Latin America (CANONIC, PREDICT, and ACLARA; n = 3896). Validation cohorts: 1 from India (Ambi-spective, n = 2055) and 1 from China (Catch-life, n = 2568). Patients were enrolled in these studies between 2011 and 2023 and last follow-up was completed in 2023. The main outcome was to redefine thresholds of organ dysfunction and failure based on 3 subscores per organ, with subscore 3 indicating $\geq$ 15% 28-day mortality and defining OF. **Results:** Compared to the CLIF-C OF score, the ATANGO OF score

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introduced significant changes to thresholds for diagnosing OF and included an additional ACLF grade 4, addressing the wide range of mortality in the CLIF-C OF grade 3 subgroup. The ATANGO OF score identified a significantly higher number of OFs, increasing the diagnosis of ACLF from 24% to 36% and improving the net reclassification index by 16%. The ATANGO OF score exhibited non-inferior predictive accuracy for 28- and 90-day mortality. In addition, two new prognostic ACLF scores were developed (ATANGO ACLF-WBC and ACLF-CRP score), showing strong correlations with 28-day and 90-day mortality. The diagnostic and prognostic ability of the ATANGO scores were confirmed in the validation cohorts. **Conclusion:** The ATANGO OF score is a more accurate, reproducible, and comprehensive tool for diagnosing ACLF with well maintained prognostic ability, validated in large global cohorts. The ATANGO OF score offers a robust tool for clinical trials enabling more reliable diagnosis, reducing the required sample size and providing readily assessable clinical endpoints, such as ACLF resolution, to define treatment responses effectively.

Table 1. Cut-off values and outcome data of the ATANGO OF scoring system.

Organ system	Subscore 1	Subscore 2	Subscore 3[a]
Liver (n=2911)			
Cut-off value	Bilirubin <6 mg/dL	Bilirubin ≥6 and <20 mg/dL	Bilirubin ≥20 mg/dL
Amount of patients (%)	77.5 (n=2256)	18.8 (n=547)	3.7 (n=108)
28-day mortality (%)	5.1 (n=115)	11 (n=60)	22 (n=24)
28-day mortality, HR (95% CI)	1	2.24 (1.64-3.06)	4.84 (3.12-7.5)
Kidney (n=2933)			
Cut-off value	Creatinine <1.4 mg/dL	Creatinine ≥1.4 and <2 mg/dL or terlipressin	Creatinine ≥2 mg/dL or RRT or AKI 1b, 2 or 3
Amount of patients (%)	70.5 (n=2068)	18 (n=528)	11.5 (n=337)
28-day mortality (%)	5 (n=103)	11(n=58)	22 (n=74)
28-day mortality, HR (95% CI)	1	1.57 (1.09-2.25)	4.33 (3.18-5.88)
Brain (n=2740)			
Cut-off value	Grade 0-1[b]	Grade 2[b]	Grade 3-4[b] or mechanical ventilation[c]
Amount of patients (%)	82 (n=2246)	14.6 (n=400)	3.4 (n=93)
28-day mortality (%)	5.3 (n=119)	8.8 (n=35)	10.6 (10)
28-day mortality, HR (95% CI)	1	1.68 (1.15-2.44)	2.11 (1.10-4.04)
Coagulation (n=2747)			
Cut-off value	INR <1.8	INR ≥1.8 and <2.2 mg/dL	INR ≥2.2
Amount of patients (%)	65.6 (n=1802)	26.1 (n=717)	8.3 (n=228)
28-day mortality (%)	4.6 (n=83)	7.8 (n=56)	16.2 (n=37)
28-day mortality, HR (95% CI)	1	1.77 (1.26-2.48)	3.83 (2.59-5.64)
Circulation (n=2664)			
Cut-off value	MAP ≥70	MAP <70	Vasopressor use[c]
Amount of patients (%)	89 (n=2371)	9.1 (n=242)	1.9 (n=51)
28-day mortality (%)	5.7 (n=135)	5.4 (n=13)	23.5 (n=12)
28-day mortality, HR (95% CI)	1	0.96 (0.54-1.7)	4.51 (2.52-8.06)
Respiration (n=2425)			
Cut-off value	PaO_2/FiO_2 >350 or SpO_2/FiO_2 >440	PaO_2/FiO_2 >225 and ≤350 or SpO_2/FiO_2 >325 and ≤ 440	PaO_2/FiO_2 ≤225 or SpO_2/FiO_2 ≤325 or mechanical ventilation[c]
Amount of patients (%)	87.8 (n=2129)	9.8 (n=238)	2.4 (n=58)
28-day mortality (%)	5.4 (n=115)	9.3 (n=22)	16.9 (n=10)
28-day mortality, HR (95% CI)	1	1.79 (1.13-2.83)	3.46 (1.78-6.71)

[a]Individual organ failures are defined by an ATANGO subscore of 3. The definitions of ATANGO ACLF grades are as follows. **No ATANGO ACLF:** patients without liver, kidney, coagulation and respiration failure or patients with single brain or single circulatory failure without reaching for subscore 2 for the other 4 organs (n=2340, 64.2%). These patients had a 28-day mortality of 4.9% and a 90-day mortality of 14.4%. **ATANGO ACLF grade 1:** single liver, kidney, coagulation or respiration failure. Respiratory failure did not reach the 3% minimum sample size for subscore 3 but was significantly different from subscore 1, hence improving the sample size included in subscore 3. Brain failure did not meet the minimum criteria for subscore 3, so an additional organ dysfunction is required to diagnose ATANGO ACLF. For circulatory failure no improvement was achieved, meaning that the old threshold included in CLIF-OF still applies, and an additional organ dysfunction is required to diagnose ATANGO ACLF. These patients had a 28-day mortality of 19.9% and a 90-day mortality of 31.8%. **ATANGO ACLF grade 2:** patients with two organ failures (subscore 3). These patients had a 28-day mortality of 36.2% and a 90-day mortality of 47.7%. **ATANGO ACLF grade 3:** patients with three organ failures (subscore 3). These patients had a 28-day mortality of 55.5% and a 90-day mortality of 59.4%. **ATANGO ACLF grade 4:** patients with four or more organ failures to allow better prognostic discrimination. This adjustment was made because the mortality rate differed significantly between patients with three organ failures and those with four to six organ failures (28-day mortality p=0.0029, 90-day mortality p=0.0016) (eFigure. 1). Patients with ATANGO ACLF grade 4 had a 28-day mortality of 76.1% and a 90-day mortality of 80.7%.
[b]Grades are defined by the West Haven criteria; [c]Mechanical ventilation for the indication of cerebral failure; [d]Vasopressor use for the indication of circulatory failure; [e]Mechanical ventilation for the indication of respiratory failure.

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4138 | MACROPHAGE POLARIZATION MEDIATED BY THE INTERACTIONS OF HYPOXIA-INDUCIBLE FACTOR 1A AND CBP/P300 INTERACTING TRANS-ACTIVATOR PLAYS AN IMPORTANT ROLE IN DISEASE PROGRESSION OF HEPATITIS B VIRUS-RELATED ACUTE-ON-CHRONIC LIVER FAILURE

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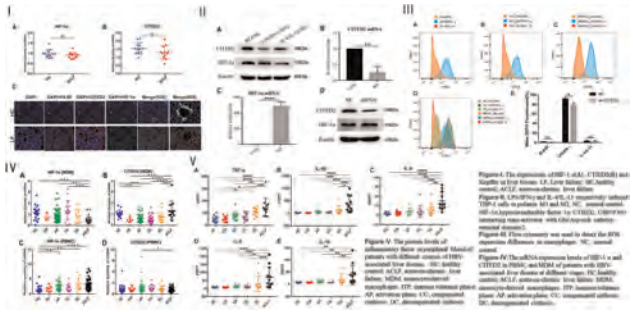
Background: Acute-on-chronic liver failure (ACLF) is a deadly disease state of HBV infection that is often accompanied by immune paralysis. Our previous work has demonstrated the significant role of macrophage polarization in immune paralysis, but the specific mechanism of macrophage polarization in HBV-ACLF remains unclear. We aim to investigate the role of Hypoxia-Inducible Factor 1α (HIF-1α) and CBP/P300 interacting trans-activator with Glu/Asp-rich carboxy-terminal domain 2(CITED2) in mediating macrophage polarization during the onset and development of HBV-ACLF. **Methods:** We constructed a THP-1 macrophage model to verify the interaction of HIF-1α and CITED2 in macrophage polarization. Simultaneously, we investigated the expression levels of HIF-1α and CITED2 in peripheral blood mononuclear cells (PBMC) and monocyte-derived macrophages (MDM) from hepatitis B virus-infected patients with immune tolerance phase (n = 13), immune activation phase (n = 107), compensated cirrhosis(CC)(n = 55), decompensated cirrhosis (n = 36), HBV-ACLF (n = 54), and healthy controls (n = 30). Additionally, we conducted further tests on the expression and distribution of HIF-1α and CITED2 in normal liver tissues as well as liver tissues from patients with HBV-related liver failure. **Results:** HIF-1α and CITED2 were competitively expressed in the THP-1 macrophage polarization model(Figure-II. A-D). Pro-inflammatory macrophage M1 produced more ROS than anti-inflammatory macrophage M2, and this effect was more significant after CITED2 knockdown(Figure-III. A-E). With the progression of HBV-related liver disease, the expression of HIF-1α in peripheral blood MDM of patients showed a tendency to rise and then fall, and reached the peak at CC stage. Meanwhile, CITED2 expression showed a completely opposite trend and reached the lowest point in CC stage. Interestingly, HIF-1α expression tended to be opposite in PBMC and MDM (Figure-IV. A-D). Pro-inflammatory and anti-inflammatory factors in plasma of the ACLF group were significantly higher than those in the chronic hepatitis B group and CC group, indicating that inflammatory response increased with the progression of disease severity(Figure-V.A-E). Expression level of HIF-1α and CTIED2 were significantly increased in liver failure liver tissue compared with normal liver tissue, same as the number of Kupffer cell(Figure-I. A-C). **Conclusion:** This study showed that macrophage polarization mediated by HIF-1α and CITED2 interactions plays an important role in HBV-ACLF. And the knockdown of CITED2 can induce macrophage polarization to M1 to rescue immune paralysis of ACLF.



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4139 | EFFICACY AND SAFETY OF TENOFOVIR AMIBUFENAMIDE FUMARATE IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE: A MULTI-CENTER, PROSPECTIVE COHORT STUDY

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Background: Tenofovir amibufenamide fumarate (TMF) is a novel nucleotide reverse transcriptase inhibitor and the first-line oral drug developed originally in China for the treatment of adults with chronic hepatitis B virus (HBV) infection. However, the efficacy and safety of TMF in patients with acute-on-chronic liver failure (ACLF) has not been explored. **Methods:** A total of 196 patients with ACLF from 13 tertiary hospitals in China were divided into TMF, tenofovir alafenamide fumarate (TAF), tenofovir disoproxil fumarate (TDF), and entecavir (ETV) groups based on the antiviral drugs used. The complete blood count, liver and kidney function, coagulation function, and virological data were assessed for patients in each group at baseline and after 4 weeks of treatment. Additionally, the 28-day mortality rate was evaluated. **Results:** There were no significant statistical differences in the baseline data among the four groups of patients with ACLF, ensuring comparability and allowing for a robust analysis of the treatment effects. The 28-day survival rates for patients in the TMF, TAF, TDF, and ETV groups were 89.62%, 85.19%, 79.31%, and 82.76%, respectively, with no significantly differences ($P = 0.410$). After four weeks of antiviral therapy, patients in the TMF (Median, 5.35×105 vs. 6.37×102 IU/ml, $P < 0.001$), TAF (Median, 7.84×105 vs. 2.54×102 IU/ml, $P < 0.001$), TDF (Median, 8.84×104 vs. 8.13×102 IU/ml, $P = 0.004$), and ETV (Median, 5.89×105 vs. 1.00×102 IU/ml, $P < 0.001$) groups all experienced an obvious reduction in HBV DNA levels. Patients in the TMF group experienced significant declines in aspartate aminotransferase (AST) levels (Median, 240 vs. 59 U/L, $P < 0.001$), alanine aminotransferase (ALT) levels (Median, 304 vs. 42 U/L, $P < 0.001$), bilirubin levels (Median, 214.0 vs. 144.8 μmol/L, $P = 0.002$), and international normalized ratio (INR) levels (Median, 1.80 vs. 1.66, $P = 0.014$), and patients in the TAF group also showed similar improvements. However, in the TDF and ETV groups, only AST and ALT levels significantly reduced after 4 weeks of treatment, while bilirubin ($P = 0.840$ for TDF group, $P = 0.053$ for ETV group) and INR ($P = 0.815$ for TDF group, $P = 0.544$ for ETV group) levels remained largely unchanged. Additionally, there were no significant changes in blood cell counts, creatinine levels, and estimated glomerular filtration rate (eGFR) levels among all four groups of patients. **Conclusion:** TMF exhibits an antiviral activity in patients with HBV-related ACLF, enhances liver and coagulation functions, and without adverse effects on renal function.

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4140 | DIRECT CHEMICAL REPROGRAMMING OF URINE-DERIVED STEM CELLS FROM ACLF PATIENTS INTO FUNCTIONAL HEPATOCYTE-LIKE CELLS FOR LIVER INJURY THERAPY

Jiateng Zhang[1] Pengfei Yu[1] Jiaqi Zhang[1] Huaibin Zou[1] Yu Chen[1] Zhongping Duan[1], [1]Beijing YouAn Hospital, Capital Medical University

Background: The high mortality rate of acute-on-chronic liver failure (ACLF) and the shortage of liver donors for transplantation must be urgently addressed. Urine-derived stem cells (USCs) are a highly promising source of autologous chemotaxis cells due to their simple and non-invasive acquisition, strong proliferative and immunomodulatory properties. In this study, we innovatively adopted a direct chemical reprogramming strategy to avoid the risk of genetic modification and directly transformed ACLF patient-derived USCs (LF-USCs) into chemically induced hepatocytes (CiHeps) through a combination of small molecule compounds, aiming to establish a safe, efficient, and patient-specific hepatocyte preparation system for new pathway for individualized treatment of ACLF. **Methods:** LF-USCs were isolated from urine samples of ACLF patients via centrifugation, expanded in culture, and characterized by surface marker analysis. Using a defined combination of small molecule compounds and cytokines, we directly reprogrammed LF-USCs into CiHeps without genetic modification. To evaluate hepatic functionality, CiHeps were transplanted into a Fah−/−Rag2−/−Il2rg−/− (FRG) mouse model of liver failure. **Results:** We successfully extracted LF-USCs from the urine of ACLF patients and cultured them for multiple generations. Importantly, we established a stage-specific induction protocol that enables rapid differentiation of LF-USCs into CiHeps within 15 days in vitro by using a specific chemical mixture, which consists of three stages: stereotyped endoderm (DE), hepatic progenitor cells (HPC), and hepatic differentiation and growth. The results showed that the cell morphology gradually changed from an initial “rice grain” shape to a tightly packed cube, similar to hepatocytes. After induction, most CiHeps expressed genes specific to mature hepatocytes and possessed the basic functions of hepatocytes. RNA sequencing, metabolic assays, and in vivo functional studies demonstrated that CiHeps exhibit hepatic activity and functionality comparable to

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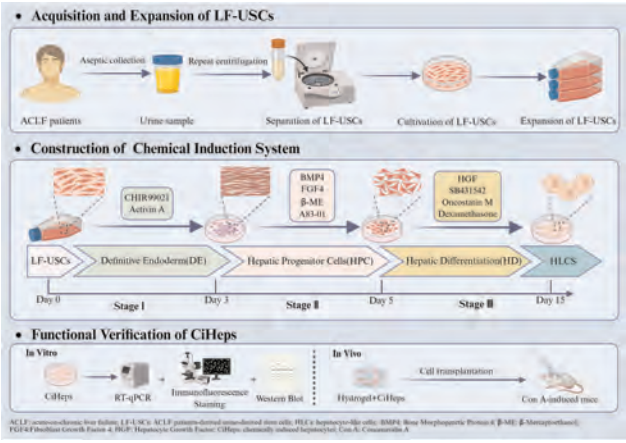
primary hepatocytes. Notably, in the Fah−/−Rag2 −/−Il2rg−/− (FRG) mouse model, CiHeps effectively contributed to liver repopulation and ameliorated liver failure in vivo. **Conclusion:** We established a safe and efficient chemical reprogramming strategy to convert patient-derived urine stem cells into functional hepatocyte-like cells. These CiHeps demonstrated comparable function to primary hepatocytes and effectively rescued liver failure in FRG mice, highlighting their potential for personalized cell therapy in ACLF.



Disclosures: Jiateng Zhang: Nothing to Disclose, Pengfei Yu: Nothing to Disclose, Jiaqi Zhang: Nothing to Disclose, Huaibin Zou: Nothing to Disclose, Yu Chen: Nothing to Disclose, Zhongping Duan: Nothing to Disclose

4141 | HDL-C, CHOLESTEROL AND THE ALT/HDL-C RATIO ARE PREDICTORS OF SURVIVAL IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

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Background: Progression to cirrhosis is commonly linked to reduced high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol, reflecting hepatic dysfunction. As HDL-C modulates systemic inflammation, hypolipoproteinemia may impact on acute-on-chronic liver failure (ACLF). This study aimed to characterize lipid profile trajectories (HDL-C, LDL-C, total cholesterol, and triglycerides) and assess their prognostic utility in ACLF. **Methods:** We retrospectively identified patients with ACLF (EASL-CLIF criteria) at the Vienna General Hospital between 11/2003 and 11/2022. Data were collected at pre-ACLF (30-365 days before diagnosis), at diagnosis (D0), and days 7 (D7), 28 (D28), and 90 (D90) thereafter. Primary endpoints were mortality at D28 and D90. Discrimination was evaluated using area under the receiver operating characteristic curve (AUROC) compared via DeLong's test. Cox regression models – adjusted for MELD, age, sex and C-reactive protein (CRP) – were used to identify independent predictors of mortality. **Results:** The study included 164 patients with ACLF (G1: 80 (48.8%), G2: 53 (32.3%), G3: 31 (18.9%)). By D28 and D90 respectively, 60 (36.6%) and 85 (51.8%) patients died. HDL-C and total cholesterol concentrations were significantly higher pre-ACLF compared to D0 ($p < 0.001$) and recovered by D90 ($p < 0.001$ vs. D0). LDL-C showed similar dynamics (pre-ACLF vs. D0: $p = 0.022$; D0 vs. D90: $p = 0.009$), while triglyceride levels remained largely stable.
At D0, HDL-C exhibited comparable AUROCs to the CLIF-C ACLF score for D28 (0.724 vs. 0.787) and D90 (0.736 vs. 0.752) mortality. With higher alanine aminotransferase (ALT) levels in advanced ACLF (G1 vs. G3: $p < 0.001$; G2 vs. G3: $p = 0.020$), prognostic impact of the ALT/HDL-C ratio was analyzed, yielding numerically higher AUROCs for D28 (0.817) and D90 (0.816) mortality discrimination than the CLIF-C ACLF score. ALT/HDL-C independently predicted both D28 (aHR: 1.028, $p < 0.001$) and D90 (aHR: 1.030, $p < 0.001$) mortality in multivariable models. Stratification using the ALT/HDL-C ratio (< 2 vs. ≥ 2), HDL-C (< 20 vs. ≥ 20 mg/dL) and total cholesterol (< 80 vs. ≥ 80 mg/dL), proved effective (all log-rank $p < 0.01$). **Conclusion:** Reductions in HDL-C and total cholesterol are common in ACLF and reflect ACLF trajectory. The ALT/HDL-C ratio represents a robust and easily accessible prognostic ACLF biomarker score enabling bed-side risk stratification using routine laboratory parameters.
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4142 | NEW SUBMISSION THE ALBUMIN-BILIRUBIN (ALBI) SCORE PREDICTS KIDNEY FAILURE AND MORTALITY IN PATIENTS WITH ALCOHOL RELATED ACUTE ON CHRONIC LIVER FAILURE- AN ANALYSIS FROM THE AARC

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Background: Acute-on-chronic liver failure (ACLF) patients frequently have hyperbilirubinemia and hypoalbuminemia. The albumin-bilirubin (ALBI) score has been developed as an index of liver dysfunction for prognostication in hepatocellular carcinoma patients. Ithas not been evaluated in the context of ACLF patients. We studied ALBI score in determining organ failures and mortality in a large multicentric-multinational cohort of ACLF patients of alcohol etiology. **Methods:** In a prospective cohort of alcohol-related ACLF patients from AARC (n = 2427) we evaluated whether ALBI score could determine the development of extrahepatic organ failures mortality and ICU admission. **Results:** ACLF patients, aged 46.8 ± 21.3 years, 87% males, mean MELD score 30.1 < i style = 'mso-bidi-font-style:normal' > ± 7.6 < v: shapetype id = "_x0000_t75" coordsize = "21600,21600" o:spt = "75" o:preferrelative = "t" path = "m@4@5l@4@11@9@11@9@5xe" filled = "f" stroked = "f" > o:title = "" chromakey = "white"/ > , AARC 9.6 ± 2.1 and ALBI score of 1.7 ± 0.15 were assessed. At enrolment 30% had acute kidney injury, 10% had sepsis. At day 4, 19% developed kidney failure (KF), 54% circulatory failure (CF), 1.9% respiratory failure (RF) while 2.9% developed cerebral failure (CBF). A significant correlation of ALBI score was observed with the number of organ failures ($p = 0.001$, $r = 0.29$), with KF ($p < 0.001$, $r = 0.20$) and CF ($p < 0.001$, $r = 0.58$) but not with CBF ($p = 0.95$) and RF ($p = 0.90$). On multivariable binary logistic regression analysis, ALBI score (OR 2.85, 1.08-7.55), higher leucocyte counts (OR 1.03, 1.02-1.05) and lower serum bicarbonate (OR 0.87, 0.85-0.90) predicted kidney failure. The ALBI score (OR 6.9, 2.9-16.7) was an independent predictor of KF after adjusting for MELD and AARC scores but not for CF (OR 0.67, 0.38-1.19). Stratification by ALBI score Grade 1 < -1.59 (as ref), grade 2 (1.59-1.76) (HR 1.19, 1.02-1.37) and grade 3 > 1.76 (HR 1.52, 1.30-1.780) predicted mortality. The ALBI score was independently associated with ICU admission (OR 5.03, 1.42-17.77) along with higher arterial lactate (OR 1.42, 1.21-1.67), serum creatinine (OR 1.42, 1.22-1.65) and presence of systemic inflammatory response syndrome (OR 2.29, 1.62-3.24). **Conclusion:** The ALBI could be a very simple and easy screening tool which could identify alcohol-related ACLF patients at risk of kidney failure, transfer to ICU and mortality. It however, was not sensitive for cerebral failure. Stratification using a combination of ALBI and AARC could be useful for prediction of mortality. Targetting the components of ALBI using extracorporeal therapies or intravenous albumin and dynamic assessment should be evaluated for improving outcomes of ACLF patients.

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4143 | DYNAMIC CHANGES IN SPLEEN STIFFNESS PREDICTS OUTCOME OF ACLF PATIENTS BY DAY-7 - A PROSPECTIVE STUDY [NCT06069284]

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Background: Early identification of acute on chronic liver failure (ACLF) patients with high risk of mortality is important to prioritize the need for ICU monitoring and liver transplantation (LT). In ACLF, inflammation and acute rise in portal pressure drives the outcome and can raise liver (LSM) and spleen stiffness (SSM). Compared to liver cirrhosis, studies evaluating dynamic changes in LSM and SSM assessing outcomes in ACLF are lacking. We prospectively evaluated whether acute changes in LSM and SSM on day 7 and 14 from baseline predicts day-90 outcome in ACLF patients. **Methods:** Patients of ACLF (APASL criteria) between 18 to 70 years of age were included. The primary objective was to assess predictive accuracy of dynamic LSM and SSM changes on day 7 from day 0 for transplant-free survival at day-90. The secondary objective was to compare LSM and SSM on day-14 from day-0 between those with or without transplant free survival at day-90. **Results:** Study included 117 patients{mean age 40.9 $\pm$8.6 yrs, males 88.9.%, alcohol associated 83.76 %} with ACLF. At day-90, 80 (68.4%) patients had LT free survival, with 32 (27.35%) deaths and 5 (4.27%) LT. Mean baseline AARC score among survivors and non-survivors was 7.68 $\pm$ 1.37 and 10.14 $\pm$ 1.25 respectively ($p < 0.001$). Baseline SSM among survivors and non-survivors was 77.4 $\pm$ 20.8 and 86.3 $\pm$ 16.3 kPa respectively ($p = 0.034$). Mean change in SSM(Δ SSM) at day-7 among survivors and non-survivors was-2.14 $\pm$ 1.22(-2.76%) and +4.83 $\pm$ 2.16(+5.5%) respectively ($p = 0.004$). Δ SSM at day-14 from day-0 among survivors and non-survivors was-10.12 $\pm$ 1.67(-13.07%) and + 6.40 $\pm$ 2.71(+7.41%) respectively ($p < 0.001$). Baseline LSM among survivors and non-survivors were 70.95 $\pm$ 9.13 and 73.56 $\pm$ 4.63 kPa respectively($p = 0.11$). Mean change in LSM among survivors and non-survivors at day 7 { -0.69 $\pm$ 0.63(0.95%) and -0.11 $\pm$ 0.85(0,15%) ($p = 0.6$)} and day14 {-1.83 $\pm$ 0.95 and -0.08 $\pm$ 0.75 kPa respectively ($p = 0.15$)} were not different. Other predictors of LT free survival on day-7 were delta AARC score (OR 1.79, 95% CI: 1.17-2.77, $p = 0.008$), delta TNF a (OR 1.09, 95% CI:1.03-1.15, $p = 0.003$), delta CRP (OR 1.03, 95% CI: 0.99-1.06, $p = 0.07$) and baseline SSM (OR1.03, 95% CI:1.01-1.05, $p = 0.03$). **Conclusion:** Baseline SSM and serial changes in SSM on day 7 and 14 are reliable and a promising tool for predicting 90-days outcome in ACLF patients. A lower SSM, with further reduction favors survival, while an increase of 5.5% in SSM at day 7 indicate non-survival.

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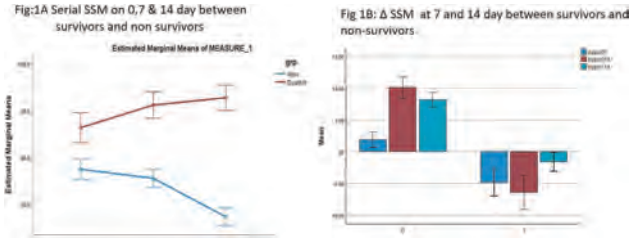


Disclosures: Sudhir Verma: Nothing to Disclose, Chitranshu Vashishtha: Nothing to Disclose, Manoj Kumar Sharma: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, Saggere Muralikrishna Shasthry: Nothing to Disclose, Rajan Vijaraghvan: Nothing to Disclose, VINOD ARORA: Nothing to Disclose, Harsh Vardhan Tevethia: Nothing to Disclose, Satender Pal Singh: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

4144 | HIGH RISK READMISSION FOLLOWING DISCHARGE HOME FROM EXPEDITED LIVER TRANSPLANT EVALUATION

Katherine Cooper Kathy Nguyen[1] Mary Flynn[1] Navine Nasser-Ghodsi[1], [1]UMass Chan Medical School

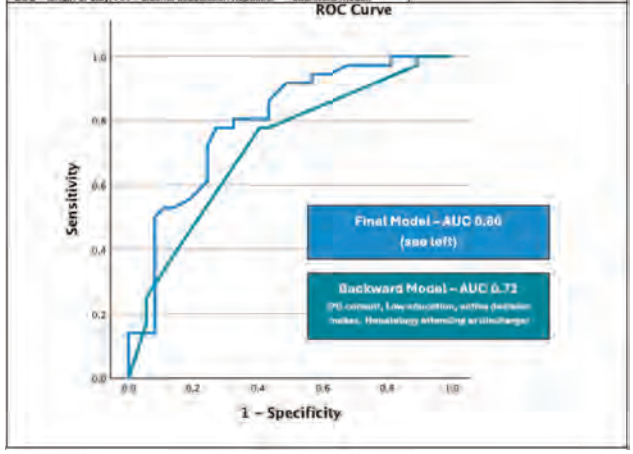
Background: An expedited, inpatient liver transplant evaluation (eLTe) is necessary for some critically ill patients with chronic liver disease (CLD) and acute on chronic liver failure (ACLF) but is associated with poor outpatient, transplant-free survival. We assessed risk factors for readmission following discharge to home from eLTe, with a focus on advanced care planning (ACP) initiatives. **Methods:** This is a single center, retrospective study of patients with CLD/ACLF who underwent eLTe from 2019-2021. The primary outcome was readmission within 30 days of home-discharge, referred to as high-risk home discharge (HR-HDC).We fit multivariable logistic regression models to identify the strongest predictors of HR-DC using backward elimination. The final model was developed using stepwise addition of clinically relevant covariates to maximize model discrimination via area under the receiver operating curve (AUROC). Significance was evaluated at $p < 0.05$ and $p < 0.15$ was considered a trend. A risk calculator was created, which is housed in NetLify, and accessible publically via QR code (Figure 1). **Results:** Among 165 patients with eLTe, 24.8% underwent LT (n = 42), 16.4% died or transitioned to hospice (n = 27), 13.2% discharged to a facility (n = 22), and 46.1% discharged home (n = 74), following eLTe. Among those discharged (n = 96), 45.8% were remitted, without differences by discharged location (p = 0.31). Among those discharged home, 36 patients (48.6%) were HR-DC. HR-DC patients had higher rates of ACP documentation (14% vs. 3%, p = 0.09), goals of care conversations (17% vs. 3%, p = 0.05) and palliative care (PC) consult during eLTe (17% vs. 5%, p = 0.14); they were also less likely to be evaluated for alcohol associated hepatitis (8.3% vs. 23.7%, p = 0.05). There were no differences by gender (p = 0.61), age (p = 0.68), MELD-Na (p = 0.37), or hospital length of stay (p = 0.84, LOS). A similar proportion of listed and non-listed patients were readmitted as well (p = 0.80). On backward regression, education less than high school (OR 3.3, 95% CI 0.9-12.5) and PC consult (OR 5.3, 0.8-34.4, p = 0.08) were risk factors and activated medical decision maker (OR 0.10, 95% CI 0.01-1.10, p = 0.06) and discharge from the hepatology versus hospital medicine service (OR 0.35, 95% CI 0.12-1.01, p = 0.05) were protective factors against HR-HDC. A final model with inclusion age, LOS > 14 days, CLD etiology, relationship status, and albumin level at admission had significantly higher discrimination than significant predictors alone (AUROC 0.80 vs. 0.72, p = 0.05) (Figure 1). **Conclusion:** Many patients with eLTe experience short-term readmission, independent of listing decision. Contrary to our hypotheses, ACP endpoints conferred higher risk of early readmission. This may reflect providers' ability to risk stratify patients, rather than the potential effect of a PC consult or ACP. Further research is needed to explore the role of ACP in this high-risk group.

High Risk Readmission Following Discharge Home from Expedited Liver Transplant Evaluation

Variable in Final Model	OR	95% CI	p
Palliative care consult*	10.73	1.1-102	0.039
Did not graduate HS*	2.58	0.6-11.1	0.203
MDM activated*	0.17	0.0-2.1	0.170
Hepatology attending at d/c*	0.33	0.1-1.0	0.054
Age>50 years	0.40	0.1-2.0	0.267
LOS< 14 days	1.67	0.3-8.1	0.525
Albumin <2.5 mg/dl	2.07	0.5-8.6	0.317
Listed or pending decision at d/c	0.70	0.2-2.3	0.554
Early sobriety/AH	0.09	0.0-0.8	0.032
Stable partner/relationship	0.79	0.2-2.5	0.691

*Abbreviations: HS = high school; MDM = medical decision maker; d/c = discharge; LOS = length of stay; AH = alcohol association hepatitis. * = backward model.*

QR for Risk Calculator



Disclosures: Katherine Cooper: Nothing to Disclose, Kathy Nguyen: Nothing to Disclose, Mary Flynn: Nothing to Disclose, Navine Nasser-Ghodsi: Boston Scientific: Consultant

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4145 | WINDOW FOR PLASMA EXCHANGE (PLEX) IN ALCOHOL-RELATED ACLF (KYOTO CONSENSUS): PSM ANALYSIS OF 1-YEAR SURVIVAL WITH PLEX (WITH LOW DOSE STEROID) VS STANDARD MEDICAL TREATMENT

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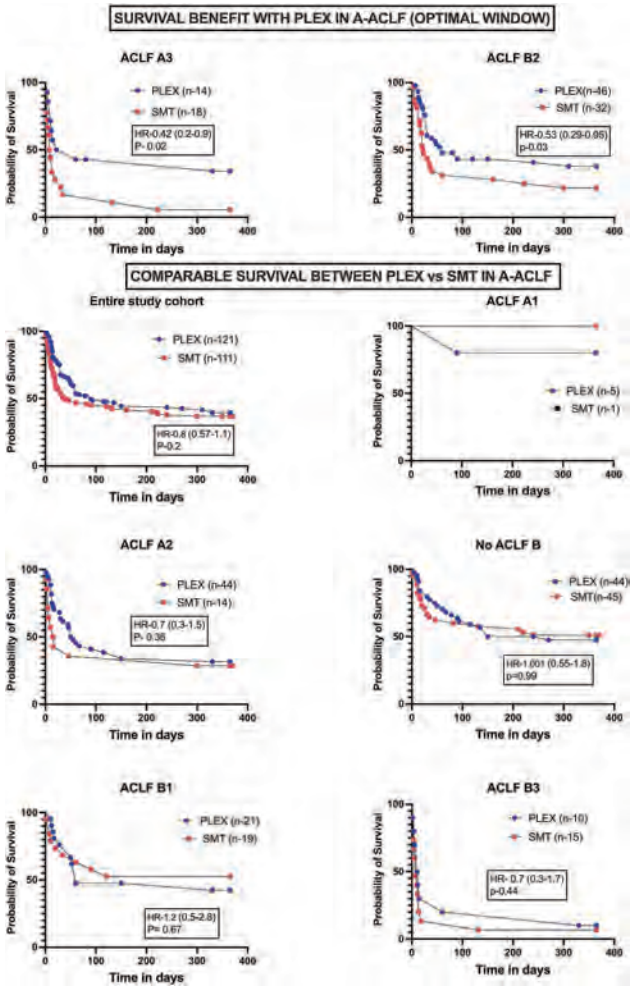
Background: Plasma exchange for Alcohol-related Acute on Chronic Liver Failure (A-ACLF) has shown survival benefit. The optimal patient for PLEX in this group is not known. We compared survival in A-ACLF patients treated with centrifugal PLEX (cPLEX) (with low-dose steroid) versus standard medical treatment (SMT). **Methods:** We included consecutive A-ACLF patients treated from a single centre between 2018 to 2024. We excluded patients with active infection and hypotension. Patients with A-ACLF were classified as ACLF A (implies APASL ACLF) or ACLF B (implies EASL ACLF) as per the Kyoto consensus definition. PLEX-treated patients received centrifugal low-volume (0.5 x plasma volume per session) and low-dose steroids (during the peri-PLEX period). SMT patients received supportive care without steroids. The primary outcome was 1-year transplant-free survival. Propensity score matching was done using the nearest neighbour technique with a match tolerance (calliper) of 0.03 adjusting for differences in MELD and CLIF-SOFA. Survival analysis was done using the log-rank test. **Results:** Of 300 patients with A-ACLF in the study period, 124 patients received PLEX and 176 received SMT. Following PSM there were 124 patients in each group. Baseline liver severity parameters were similar between PLEX vs SMT for MELD 30.2 (±6.6) vs 30.8 (±7.3), CLIF SOFA 9.5 (±1.3) vs 9.5(±1.5)] and significantly different for bilirubin 22.3 (±7.5) mg/dl vs 19.2 (±9.1) mg/dl, creatinine 1.1 (0.7-1.6) mg/dl vs 1.2 (0.8-2.2) mg/dl and DF 104 (77-138) vs 88 (68-111) respectively. No patient was intubated or on vaso-pressors before initiation of PLEX. Three and 13 patients each were lost to follow-up in PLEX and SMT groups respectively. ACLF A classification into sub-groups (A1, A2, A3) was possible for only 96 patients (due to missing serum lactate). On follow-up [73 (16-365) days,median (IQR)] of PSM matched groups (121 PLEX vs. 111 SMT), there was no difference in patient survival, HR 0.8 (0.57-1.1), p-0.2. Survival among ACLF A1, A2, A3, no EASL ACLF, B1, B2 and B3 are shown in the Figure below. Survival was significantly better with PLEX compared to SMT in ACLF A3 and ACLF B2 subgroups. Limitations of the study include retrospective cohorts and small sample in certain subgroups. **Conclusion:** ACLF A3 and ACLF B2 sub-groups of A-ACLF patients (with no infection/shock) have better one-year transplant-free survival when treated with PLEX and low-dose steroids compared to SMT. Our study findings may help in selecting A-ACLF patients for PLEX therapy.



Disclosures: Santhosh Kumar: Nothing to Disclose, Lakshmi Nivedana: Nothing to Disclose, Gayathiri Chellaiya: Nothing to Disclose, Dolly Daniel: Nothing to Disclose, Uday Zachariah: Nothing to Disclose, Ashish Goel: Nothing to Disclose, Ashwani Singal: Madrigal: Speaking and Teaching, Pleiogenix: Stock – privately held company, Pleiogenix: Consultant, GSK: Grant/Research Support, CLD Foundation: Advisor, Medical Speaker's Network: Speaking and Teaching, Up-to-Date: Royalties or patent beneficiary, Medscape: Speaking and Teaching, University of Louisville School of Medicine: Employee, Avera Medical Group: Employee, NIAAA: Grant/Research Support, Gastro Endo News: Executive role, Durect: Advisor, University of Louisville Health: Other, C Eapen: Nothing to Disclose

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4146 | INFECTION RATHER THAN BILE ACID LEVELS PREDICT MORTALITY IN ALCOHOL ASSOCIATED ACUTE ON CHRONIC LIVER FAILURE

Jaifrin Daniel[1] Shiv Kumar Sarin[2] Ankur Jindal[2] Ashok Kumar Choudhury[2] VINOD ARORA[2] Omkar Rudra[2] Guresh Kumar[2], [1]Institute of Liver And Biliary Sciences, New Delhi, [2]Institute of Liver & Biliary Sciences, New Delhi

Background: Acute on chronic liver failure due to severe alcoholic hepatitis is associated with high 28-day mortality. Ethanol is the primary hepatotoxic insult. Bile acids which are traditionally considered injurious in cholestatic liver diseases may have a role in ACLF pathophysiology. Bile acids are increasingly recognized not only for their cytotoxic potential but also for their regulatory functions in inflammation and metabolism. In this study, we aimed to explore the prognostic significance of serum bile acid levels and other inflammatory markers in patients with ACLF due to SAH. **Methods:** It is a retrospective study of patients admitted with ACLF due to severe alcoholic hepatitis and had serum bile acids at baseline. The study period was from January 2015 to April 2025. Electronic medical records were assessed to get the relevant information and were analysed. **Results:** There was total 225 patients in our study. There was male predominance noted, among non survivors all individuals were male. Mortality was seen in 74 (32.8%) individuals. We did univariate analysis to assess the predictors of mortality, WBC count: 19.6 +/- 10.3 vs 15.2 +/- 7.7, p:0.002, S. Creatinine: 2.3 +/- 1.5 vs 1.5 +/- 1.2, p:0.019, Procalcitonin: 1.02 (0.6-2.2) vs 0.63 (.42-1.1), p:0.02 were elevated among the non survivors. Serum Bile acid was 128.6 +/- 62.1 vs 150.7 +/-53.1, p:0.01 among non-survivors and survivors respectively. Baseline MELD, CTP and AARC score was higher among the non survivors as compared to survivors. Inflammatory markers (C- Reactive protein and TNF alpha) were statistically non-significant between the two groups. Multivariate analysis was done to predict the factors associated with mortality, it showed that serum Procalcitonin with HR of 1.066 (CI: 1.039 - 1.094, p:0.000) was associated with increased mortality while serum bile acid with HR of 0.992 (CI: 0.987 - 0.997, p:0.002 was associated with reduced mortality. **Conclusion:** In our study baseline procalcitonin and bile acids were the predictors of mortality in acute on chronic liver failure due to severe alcoholic hepatitis. Elevated procalcitonin reflects systemic inflammatory burden and is associated with poor prognosis, while higher serum bile acids may provide a survival advantage. This highlights the need for further research in the role of bile acids in ACLF.

Disclosures: Jaifrin Daniel: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose, Ankur Jindal: Nothing to Disclose, Ashok Kumar Choudhury: Nothing to Disclose, VINOD ARORA: Nothing to Disclose, Omkar Rudra: Nothing to Disclose, Guresh Kumar: Nothing to Disclose

4147 | DEVELOPMENT AND VALIDATION OF AN EXPLAINABLE MACHINE LEARNING MODEL FOR PREDICTING INVASIVE FUNGAL INFECTION IN ACUTE-ON-CHRONIC LIVER FAILURE WITHIN 28 DAYS

Ronghua Jin[1] Feixiang Xiong[1] Xuejie Zhang[1] Yang Zhou[1] Xiaomin Ji[1] Yixin Hou[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: Acute-on-chronic liver failure (ACLF) is associated with significantly higher short-term mortality, and the presence of invasive fungal infection (IFI) further increases this risk. This study aims to develop an ML model that predicts the risk of IFI in ACLF patients. **Methods:** This study included 1,112 patients divided into a training set and a validation set, with another 188 patients serving as an external validation cohort. The Recursive Feature Elimination (RFE) method was used to select the most significant variables for model development. Four machine learning algorithms were compared to identify the optimal model. The models were evaluated and compared using C-index, time-dependent ROC curves, decision curve analysis (DCA), and calibration curves. The LIME (Local Interpretable Model-Agnostic Explanations) method was used to identify the high-risk populations utilized by the model. **Results:** 778 patients were included in the training set, 334 in the internal validation set, and 188 in the external validation set. The study found that Random Forest (RF) was the best-performing ML algorithm. In the training set, the RF model achieved an AUROC of 0.922 (0.911-0.933), significantly higher than MELD (0.854, 0.835-0.873, $P < 0.001$), CLIF-C OF (0.753, 0.724-0.783, $P < 0.001$), and CLIF-C ACLF (0.879, 0.863-0.896, $P = 0.020$). The same trend was observed in both the internal and external validation sets. The time-dependent ROC curve showed that the RF model outperformed the other scores for predicting the risk of IFI in 28 days. DCA and calibration curves also demonstrated superior clinical benefits for the RF model across all datasets. LIME revealed bacteria infection (BI), Na < 136 mmol/L, CRP (C-reactive protein) > 20.1 g/L, and TBIL(Total Bilirubin) > 196.7 μmol/L as the high-risk groups. **Conclusion:** The RF model effectively predicts the risk of IFI in ACLF patients. The application of LIME enables the identification of high-risk populations, providing clinical value for patient management.

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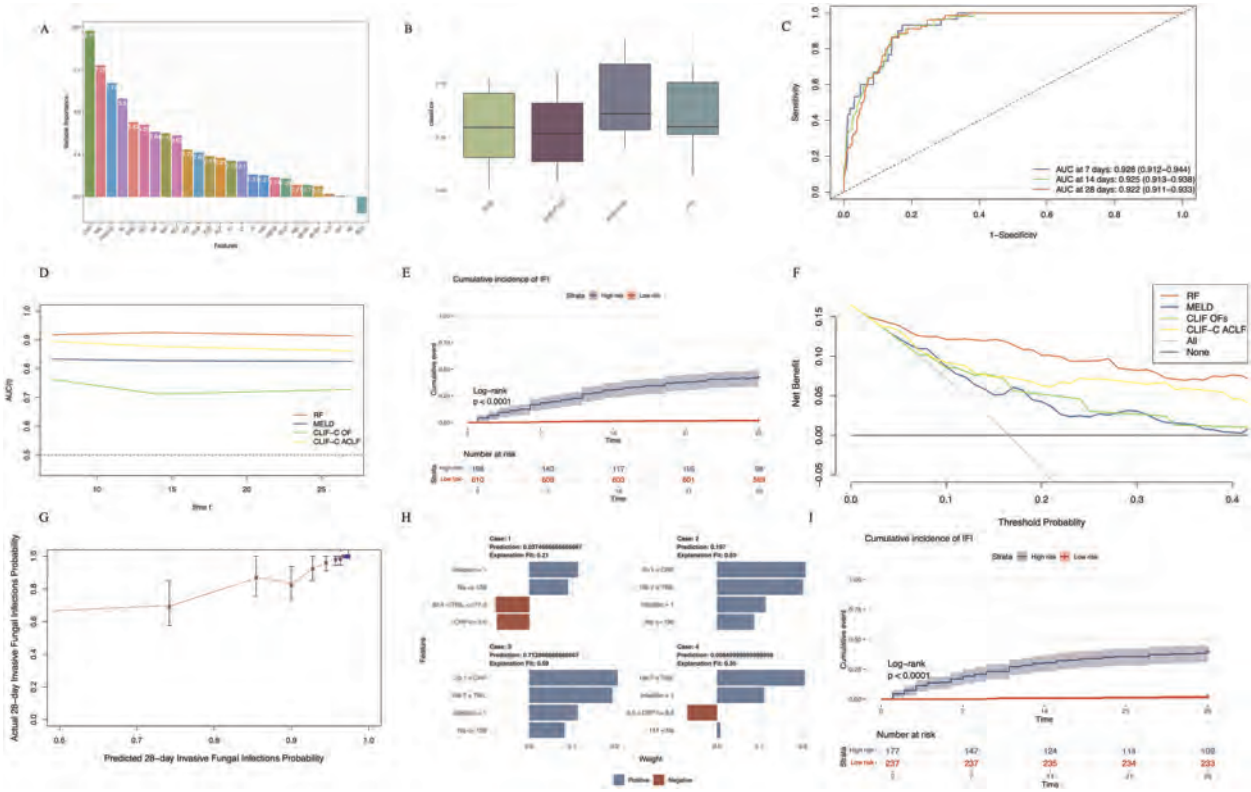

Disclosures: Ronghua Jin: Nothing to Disclose, Feixiang Xiong: Nothing to Disclose, Xuejie Zhang: Nothing to Disclose, Yang Zhou: Nothing to Disclose, Xiaomin Ji: Nothing to Disclose, Yixin Hou: Nothing to Disclose

4148 | PERFORMANCE OF THE CHINA-CLIF FRAMEWORK IN ACUTE-ON-CHRONIC LIVER FAILURE: A MULTI-COHORT STUDY ACROSS ALL AETIOLOGIES

Jun Li[1] Jinjin Luo[1] Meiqian Hu[1] Tingting Feng[2] Liyuan Zhang[3] Yan Huang[4] Yuxian Huang[5] Feng Ye[6] Jiang Li[7] Ferran Aguilar[8] Cristina Sánchez-Garrido[8] Eva Maria Uson Raposo[8] Paolo Angeli[9] Rajiv Jalan[10] Bingliang Lin[11] Yu Chen[12] Shaoli You[13] Xin Chen[14] Alberto Queiroz Farias[15] Jonel Trebicka[16] Jing Jiang[1] Richard Moreau[8], [1]The First Affiliated Hospital, Zhejiang University School of Medicine, [2]The First Affiliated Hospital of Suzhou University, [3]The Second Affiliated Hospital of Hainan Medical University, [4]Xiangya Hospital, Central South University, [5]Huashan Hospital, Fudan University, [6]The First Affiliated Hospital of Xi'an Jiaotong University, [7]The First Affiliated Hospital of Anhui Medical University, [8]European Foundation for the Study of Chronic Liver Failure (EF CLIF), [9]University of Padova, [10]University College London Medical School, [11]The Third Affiliated Hospital of Sun Yat-sen University, [12]Beijing Youan Hospital, Capital Medical University, [13]The Fifth Medical Center of Chinese PLA General Hospital, [14]Zhejiang University School of Medicine, [15]Hospital das Clínicas, University of São Paulo School of Medicine, [16]Department of Internal Medicine B University Clinic Münster

Background: Acute-on-chronic liver failure (ACLF) of various aetiologies is a complex syndrome with high short-term mortality and significant global burden. This study aimed to explore easily applicable diagnostic criteria and an accurate prognostic score for ACLF. **Methods:** Clinical data from 5288 patients (after exclusions from 7388 screened) with acute deterioration of chronic liver disease across various aetiologies were used to evaluate the performance of European Chronic Liver Failure (CLIF) and Chinese Group on the Study of Severe Hepatitis B (COSSH) criteria. Three non-Asian cohorts were performed to validate the results. **Results:** CLIF criteria categorised 844 patients as ACLF (28-/90-day liver transplantation (LT)-free mortality: 40.7%/57.0%; 321 with non-hepatitis B virus (HBV) aetiology, 523 with HBV aetiology), while COSSH criteria categorised 2038 patients as ACLF (28-/90-day LT-free mortality: 27.3%/41.0%; 602 with non-HBV aetiology, 1436 with HBV aetiology). COSSH criteria identified 22.6% (1194/5288) more patients (28-/90-day LT-free mortality: 19.1%/31.4%) compared to CLIF criteria, including 14.2% non-HBV patients (28-/90-day LT-free mortality: 15.9%/33.3%). COSSH criteria produced a

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more reasonable epidemiological pyramid-like distribution across severity grades (Grade 1–3: 63.4%/27.5%/9.1% vs. CLIF's Grade 1–3: 25.8%/56.3%/17.9%). COSSH-ACLF II score showed the highest predictive values for 28-/90-day LT-free mortality in both cirrhotic and all ACLF patients with various aetiologies, outperforming the CLIF-C ACLF and other scores. A mimic validation, using a matching analysis of the frequency of six organ failures observed in the CANONIC cohort, further confirmed the high discriminatory ability of COSSH-ACLF II score in non-HBV patients. The comparable performance of China-CLIF score (renamed from COSSH-ACLF score) was validated in three non-Asian cohorts. **Conclusion:** This study evaluated the broader applicability of the China-CLIF framework across diverse aetiologies and varying severity levels of ACLF. These findings may provide a valuable foundation for harmonizing ACLF diagnostic and prognostic system.

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4149 | A HDL-BASED CIRRHOSIS RISK SCORE IMPROVES THE PREDICTION OF SHORT-TERM MORTALITY IN ACUTELY DECOMPENSATED CIRRHOSIS

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Background: Cirrhosis is associated with multiple lipidomic alterations including markedly reduced high-density lipoprotein cholesterol (HDL-C) levels. We previously demonstrated that HDL-C levels have excellent prognostic value comparable to that of MELD. In the present study we aimed to develop a new prognostic model containing HDL-C and other readily available biomarkers for prediction of 90-day mortality in patients with acutely decompensated (AD) cirrhosis without acute-on-chronic liver failure (ACLF). **Methods:** We studied a subset of the European multicentre CANONIC and PREDICT cohorts in whom HDL-C was retrospectively measured in stored plasma samples. Multivariable competing risk analysis was performed with death as the event of interest and liver transplantation as a competing risk. Cox proportional hazards regression was used to construct a new prognostic model and its performance was evaluated using Harrell's concordance index (c-index) and compared that of MELDNa, MELD 3.0 and CLIF-C AD score by the Integrated Discriminating Improvement (IDI) statistics test. The new model was validated externally in a combined AD/ACLF cohort recruited from the Vienna General Hospital. **Results:** We analyzed 823 patients with AD (median age 59 years; 69% male; etiology alcohol 58%; 90-day mortality 15%). Multivariable analysis identified 6 independent prognostic variables associated with 90-day mortality, i.e. age, HDL-C, creatinine, sodium, WBC and INR, that were incorporated in the new prognostic model termed integrated MELD (iMELD)-HDL. The new model yielded superior discrimination ability for prediction of mortality as compared to other prognostic scores (Table). In the external validation cohort including 185 patients with AD/ACLF (median age 57 years; 62% male; ACLF at inclusion 48%; etiology alcohol 55%; 90-day mortality 32%), the new model showed numerically better performance for prediction of 90-day mortality by c-index (95% CI): iMELD-HDL 0.78 (0.70-0.85), MELDNa 0.75 (0.68-0.83; p = 0.170 vs. iMELD-HDL), MELD 3.0 0.75 (0.68-0.83; p = 0.175 vs. iMELD-HDL). **Conclusion:** A new prognostic iMELD-HDL model yielded superior accuracy for prediction of short-term mortality as compared to other prognostic scores. Further external validation in larger cohorts of patients with AD cirrhosis is warranted.

	iMELD-HDL	MELD-Na	MELD3.0	CLIF-C AD score
	C-index (95% CI)			
28-day mortality	0.78 (0.71-0.84)	0.69 (0.62-0.77)	0.68 (0.61-0.76)	0.71 (0.64-0.78)
p value vs. iMELD-HDL*		0.001	<0.001	<0.001
90-day mortality	0.75 (0.71-0.79)	0.70 (0.65-0.74)	0.70 (0.66-0.74)	0.71 (0.67-0.76)
p value vs. iMELD-HDL*		<0.001	<0.001	<0.001
180-day mortality	0.73 (0.69-0.77)	0.68 (0.64-0.72)	0.68 (0.64-0.72)	0.70 (0.66-0.74)
p value vs. iMELD-HDL*		<0.001	<0.001	<0.001
365-day mortality	0.71 (0.68-0.74)	0.65 (0.61-0.68)	0.65 (0.62-0.69)	0.68 (0.65-0.72)
p value vs. iMELD-HDL*		<0.001	<0.001	<0.001

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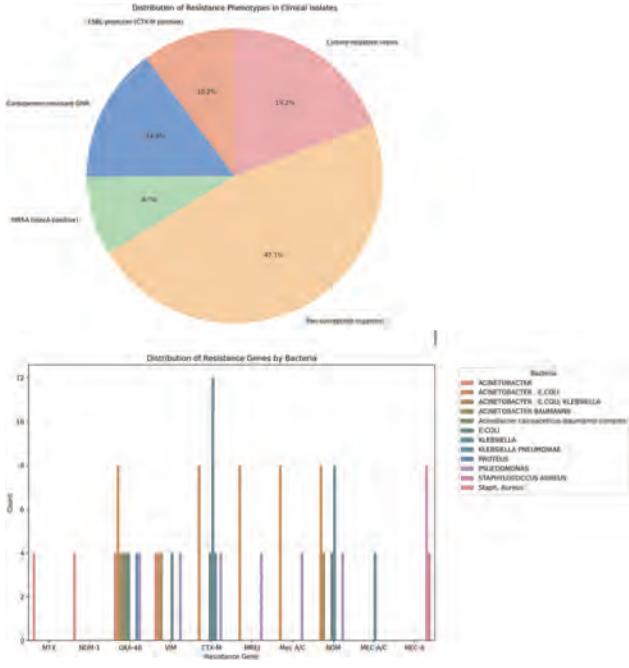
4150 | ANTI-MICROBIAL RESISTANCE PATTERNS IN ACUTE-ON-CHRONIC LIVER FAILURE AND ITS IMPACT ON CLINICAL OUTCOME

Yaduvir Singh[1], [1]SNMC, Jodhpur, India

Background: Acute-on-chronic liver failure is a distinct clinical entity characterized by acute hepatic decompensation in patients with pre-existing chronic liver disease (diagnosed or undiagnosed), leading to multiorgan failure and high short-term mortality. Infections not only act as a common trigger for ACLF but also complicate its clinical course, further worsening prognosis. **Methods:** A total of 274 patients diagnosed with Acute-on-Chronic Liver Failure, as defined by CLIF-C criteria, and with proven infections were included in the study. Of these, 78 patients underwent testing with the BioFire® Respiratory + Pneumonia Panel to detect pathogenic organisms and resistance genes. Antibiotic escalation or de-escalation was guided accordingly based on the results. **Results:** A total of 39 patients were diagnosed with multidrug-resistant (MDR) infections, 12 patients with extensively drug-resistant (XDR) infections, and 4 patients with pandrug-resistant (PDR) infections, underscoring a substantial burden of antimicrobial resistance within the cohort. Genotypic analysis identified key molecular mechanisms underlying resistance. Among *Klebsiella* isolates, 50% harbored the NDM gene (indicative of metallo-β-lactamase production), 33.3% carried VIM, and 16.7% were positive for OXA-48. All *Acinetobacter* isolates carried OXA-48, with 66.7% also harboring NDM and 50% carrying VIM. *E. coli* isolates displayed a comparable resistance pattern: 80% co-expressed NDM and OXA-48, and 40% harbored mecA, mecA/C, and MREJ. *Proteus* isolates were uniformly positive (100%) for OXA-48. *Pseudomonas* isolates exhibited universal expression of all tested resistance genes (mecA, mecA/C, MREJ, NDM, OXA-48, and VIM), consistent with an extensively drug-resistant phenotype.
Infections caused by drug-resistant organisms—including carbapenem-resistant Gram-negative bacilli (GNRs) and MRSA—were associated with significantly higher 30-day mortality in ACLF patients compared to infections caused by susceptible organisms (48.3% vs. 19.2%, $p < 0.001$). **Conclusion:** The high prevalence of MDR pathogens in ACLF patients demands stringent infection control measures, early pathogen identification, and personalized antimicrobial therapy. Rapid diagnostic tools like the BioFire panel, demonstrated in this study, significantly enhance timely detection of pathogens and resistance genes, enabling targeted treatment. Early initiation of appropriate antibiotics guided by local antibiograms, along with regular reassessment, is crucial to curbing the progression of infection-driven organ failure.



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4151 | IMPACT OF LIVER TRANSPLANT AND THERAPEUTIC PLASMA EXCHANGE ON CLINICAL OUTCOMES IN ACLF PATIENTS WITH AND WITHOUT INFECTION: A PROPENSITY SCORE-MATCHED STUDY FROM THE AARC DATABASE

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Mohan Prasad[26] Abdulkadir Dokmeci[27] Jose Sollano[28] Zaigham Abbas[29] Ananta Shrestha[30] George Lau[31] Diana Payawal[32] Gamal Shiha[33] Ajay Duseja[34] Sunil Taneja[35] Nipun Verma[35] Cosmas Rinaldi Lesmana[36] Cesar Yaghi[13] Kessarin Thanapirom[37] Hasmik Ghazinyan[38] Fazal Karim[39] Radha Dhiman[40] Ajay Mishra[40] Shahinul Alam[41] Osamu Yokosuka[41] Debashis Chowdhury[42] Chandan kumar Kedarisetty[43] Sanjiv Saigal[44] Anil Arora[45] Ashish Kumar[45] Ghulam Yattoo[46] Abraham Koshy[47] Mohamed ELbasiony[48] Pravin Rathi[49] Sudhir Maharshi[50] Vm Dayal[51] Ashish Jha[52] Kemal Kalista[53] Rino Gani[54] Man-Fung Yuen[55] Virendra Singh[56] Ayaskanta Singh[57] Violeta Sargsyan[58] Chien-Hao Huang[59] Saurabh Mukewar[60] Shaojie Xin[61] Ruveena Bhavani[62] Charles Panackel[63] Sunil Dadhich[64] Sanjeev Sachdeva[65] Ajay Kumar[65] sanatan behera[66] Prabir Maji[66] Lubna Kamani[67] Hemamala Ilango[68] Joy Varghese[69] Pathik Parikh[70] Neeraj Saraf[71] Javed P[72] Neeraj Saraf[73] Narendra Choudhary[73] Akash Roy[74] Mahesh Goenka[74] Suprabhat Giri[75] MANOJ KUMAR SAHU[75] Dibyalochan Praharaj[75] Krishnadas Devadas[76] Arun Valsan[77] Janaka De Silva[78] Tarana Gupta[79] Dr. Shalimar[80] AARC Group[81], [1]King George Medical University, Lucknow., [2]Institute of Liver and Biliary Sciences, New Delhi, India, [3]Institute of Liver and Biliary Sciences, [4]Dr. Rela Institute, Chennai (India), [5]Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, [6]Department of Hepatology, St John Medical College, Bangalore, India., [7]Department of Hepatology, CMC, Vellore, India, [8]Huazhong University of Science and Technology, [9]Tongji Hospital, Wuhan, China, [10]Hepatology Institute Capital Medical University, China, [11]Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan, [12]Seth GS Medical College & KEM Hospital, [13]Saint Joseph University, Lebanon, Beirut, [14]Department of Medicine, Hospital Selayang, Bata Caves, Selangor, Malaysia, [15]Hallym University Medical Center, [16]All India Institute of Medical Sciences, New Delhi (India), [17]302, Military Hospital, China, [18]Dayanand Medical College, Ludhiana, India, [19]D.M.C. and Hospital, [20]Division of Gastroenterology and Hepatology, Department of Medicine, National University Health, [21]Chulalongkorn University, [22]Department of Hepatology, Global Hospitals, Mumbai, India, [23]Asian Institute of Gastroenterology, Hyderabad, India, [24]Asian Institute of Gastroenterology, [25]AIG Hospitals, [26]Department of Gastroenterology, VGM Hospital, Coimbatore, India, [27]Ankara University, [28]Department of Medicine, University of Santo Tomas, Manila, Philippines, [29]Ziauddin University Hospital, [30]Department of Hepatology, Alka Hospital, Nepal, [31]Department of Medicine, Humanity and Health Medical Group, New Kowloon, Hong Kong, [32]Fatima University Medical Center Manila, Manila, Philippines, [33]Egyptian Liver Research Institute And Hospital, Egypt., [34]Postgraduate Institute of Medical Education & Research, [35]Postgraduate Institute of Medical Education and Research, Chandigarh, India, [36]Digestive Disease and GI Oncology Centre, Medistra Hospital, Jakarta, Indonesia., [37]Department of Medicine, Chulalongkorn University, Bangkok, Thailand., [38]Department of Hepatology, Nork Clinical Hospital of Infectious Disease, Yerevan, Armenia., [39]Sir Salimullah Medical College Hospital, Bangladesh, [40]SGPGI, Lucknow, India, [41]Crescent Gastroliver and General Hospital, Bangladesh, [42]CMOSH Medical College, Bangladesh, [43]Global Hospitals, Hyderabad, [44]Max Super Specialty Hospital, Saket New Delhi, India, [45]Sir Ganga Ram Hospital, [46]SKIMS, Srinagar, India, [47]Lakeshore Hospital, [48]Mansoura University, Egypt, [49]TN Medical College and BYL Nair Hospital, Mumbai, [50]SMS Jaipur, India, [51]vmdayal@rediffmail.com, [52]IGIMS, Patna, India, [53]Cipto Mangunkusumo Hospital, Indonesia, [54]Indonesian Association for Study of the Liver, [55]The University of Hong Kong, [56]Punjab Institute of Liver and Biliary Sciences, Mohali, India, [57]SUM Ultimate Medicare, Bhubaneswar, India, [58]Violeta Medical Centre, Armenia, [59]Chang Gung Memorial Hospital, [60]Mayo Clinic Rochester, [61]Medical school of Chinese PLA, China, [62]University of Malaya Medical Centre, Malaysia, [63]Aster Medicity, Kochi, India, [64]SMNC, Jodhpur, India, [65]G.B. 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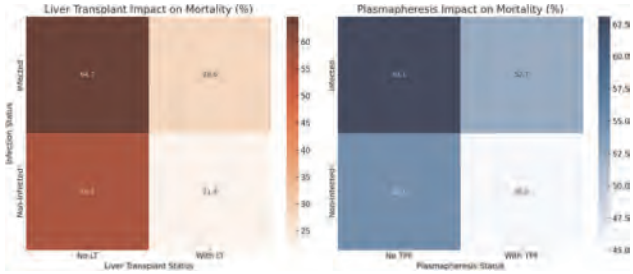
Background: Acute-on-Chronic Liver Failure (ACLF) is a rapidly progressive condition characterized by acute hepatic decompensation with or without extra-hepatic organ failure leading to a high short-term mortality. Often the infection and sepsis are the major cause of deterioration. Liver transplantation (LT) and therapeutic plasma exchange (TPE) have emerged as potential rescue strategies in this context. However, their comparative efficacy in infected versus non-infected ACLF patients is underexplored, particularly in large, real-world cohorts. This study aims to study the LT and TPE feasibility and 90-day survival outcome among patients of ACLF with or without infection. **Methods:** The prospectively collected AARC registry data of 3478 patients, having information on infection at baseline in the first weeks, were analyzed. The data was grouped for those with or without infection, and a matching cohort was done with adjustments for age, gender, etiology of CLD, and disease severity scores (MELD, SOFA, AARC). A comparison of both groups in relation to 90-day survival, organ failure, ICU need, TPE, and LT was made. Infection was defined as those with any positive culture, consolidation in chest imaging, or SBP in ascitic fluid analysis. **Results:** 1824 patients with complete data were included in the study. The mean age of patients was 48.6 $\pm$ 10.4 years, and the gender ratio (male:female) was 3.5:1 (approximately 78% male, 22% female). Mortality was highest in bloodstream infections (64.35%, 148/230), followed by urine (63.11%, 65/103) and ascitic fluid infections (60.53%, 161/266). At 90 days, infected patients had higher rates of renal (50.8% vs. 41.2%), respiratory (52.4% vs. 42.1%), cerebral (37.6% vs. 33.0%), circulatory (51.3% vs. 38.8%), coagulopathy (40.0% vs. 32.0%), and liver failure (54.3% vs. 44.6%) (all $P < 0.05$). LT reduced mortality from 64.7% to 28.6% in infected (n = 78) and from 56.5% to 21.4% in non-infected (n = 76) patients ($P < 0.001$). Mean ICU stay post-LT was 5.4 days in both groups. TPE (n = 312) improved bilirubin (infected: 18.5→13.3 mg/dL; non-infected: 17.2→12.5 mg/dL), INR (2.4→1.8 vs. 2.3→1.7), and creatinine (2.3→1.9 vs. 2.1→1.8 mg/dL) ($P < 0.05$). Infected TPE recipients had lower renal failure progression (26.7% vs. 38.3%) and improved cerebral recovery (34.4% vs. 26.1%) vs. controls ($P < 0.05$). MELD, SOFA, and AARC scores improved significantly in both groups, with greater gains in non-infected patients ($P < 0.05$). **Conclusion:** Infection significantly worsens ACLF outcomes, but both LT and TPE provide substantial mortality and clinical benefit across infected and non-infected patients. These findings support early consideration of LT and TPE irrespective of infection status.



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4152 | SYSTEMIC AND MULTI-ORGAN INFLAMMATION PATTERNS ACROSS THE SPECTRUM OF EXPERIMENTAL AND HUMAN CIRRHOSIS AND ACUTE-ON-CHRONIC LIVER FAILURE

Vlad Taru[1] Georg Kramer[1] Thomas Sorz-Nechay[1] Katharina Bonitz[1] Henriette Horstmeier[1] Katja Sommer[1] Lorenz Balcar[1] Benedikt Silvester Hofer[1] Nina Dominik[1] Nicholaus Michalitsch[1] Kerstin Zinober[1] Bogdan Procopet[2] Michael Trauner[1] Philipp Schwabl[1] Thomas Reiberger[1] Benedikt Simbrunner[1], [1]Medical University of Vienna, [2]"Iuliu Hatieganu" University of Medicine and Pharmacy, Romania

Background: Decompensated cirrhosis is a fragile state, with some patients rapidly progressing to multi-organ failures (i.e. acute-on-chronic liver failure, ACLF), while others remain stable. This study analyzed systemic inflammation (SI) in different stages of decompensation in humans and dissemination of inflammation on a multi-organ level in experimental ACLF. **Methods:** Patients with decompensated cirrhosis were prospectively enrolled in the Vienna Cirrhosis Study (VICIS) between 2017 and 2021 and classified according to their 3-months follow-up as: stable decompensation (SDC; without subsequent admission); unstable decompensation (UDC; non-elective admission but without ACLF); pre-ACLF (admission with ACLF); and ACLF at baseline. Plasma biomarkers (IL-6, TIMP1) were measured by ELISA.

In two murine cirrhosis models (carbon tetrachloride, CCl4; DDC diet), ACLF was induced by a single LPS injection (i.p.,1x 200 μL/kg), followed by follow-up examination including portal pressure readings after 24h. Gene expression was quantified by qPCR and plasma biomarkers by Luminex multiplex immunoassay. **Results:** In the clinical study, 372 patients (median age: 57 years; 64.2% male; 57.8% alcohol-related liver disease) were included: 299 (80.4%) SDC, 27 (7.3%) UDC, 25 (6.7%) pre-ACLF and 21 (5.6%) ACLF. Median MELD was significantly higher in ACLF but similar between the other groups (SDC vs. UDC vs. preACLF vs. ACLF: 13 [7] vs. 17 [11] vs. 14 [8] vs. 29 [9], $p < 0.001$). IL-6 showed a significant stepwise increase across groups (SDC vs. UDC vs. pre-ACLF vs. ACLF: 12.3 [19.8] vs. 20.6 [29.2] vs. 25.5 [31.9] vs. 41.8 [59.9] pg/mL; $p < 0.001$). Enhanced Liver Fibrosis test (ELF) and TIMP1 showed a strong correlation to IL-6 (Spreaman's rho ELF: 0.51 and TIMP1: 0.63, both $p < 0.001$).

In the murine ACLF models, hepatic *Timp1* and hepatic, renal and pulmonary *Ccl2, Cxcl1, Il6, Il1b, Tnf* gene expression as well as plasma chemokines (G-CSF, CCL4, CCL5) were increased as compared to experimental cirrhosis (without ACLF) groups in both models.

Conclusion: Systemic inflammation significantly increases across the spectrum of decompensated cirrhosis and ACLF in humans and is linked to biomarkers reflecting hepatic fibrogenesis. Experimental ACLF models corroborate this mechanistic link and indicate that systemic inflammation quickly disseminates on a multi-organ level, affecting both the liver and extrahepatic organs.

Disclosures: Vlad Taru: Nothing to Disclose, Georg Kramer: Nothing to Disclose, Thomas Sorz-Nechay: Nothing to Disclose, Katharina Bonitz: Nothing to Disclose, Henriette Horstmeier: Nothing to Disclose, Katja Sommer: Nothing to Disclose, Lorenz Balcar: Nothing to Disclose, Benedikt Silvester Hofer: Nothing to Disclose, Nina Dominik: Nothing to Disclose, Nicholaus Michalitsch: Nothing to Disclose, Kerstin Zinober: Nothing to Disclose, Bogdan Procopet: Nothing to Disclose, Michael Trauner: Albireo: Grant/Research Support, Alnylam: Grant/Research Support, Cymabay: Grant/Research Support, Falk: Grant/Research Support, Gilead: Grant/Research Support, Intercept: Grant/Research Support, MSD: Grant/

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4154 | ROLE OF AGE AND FRAILTY IN MORTALITY AMONG PATIENTS WITH CIRRHOSIS: A 5-YEAR POPULATION-BASED ANALYSIS

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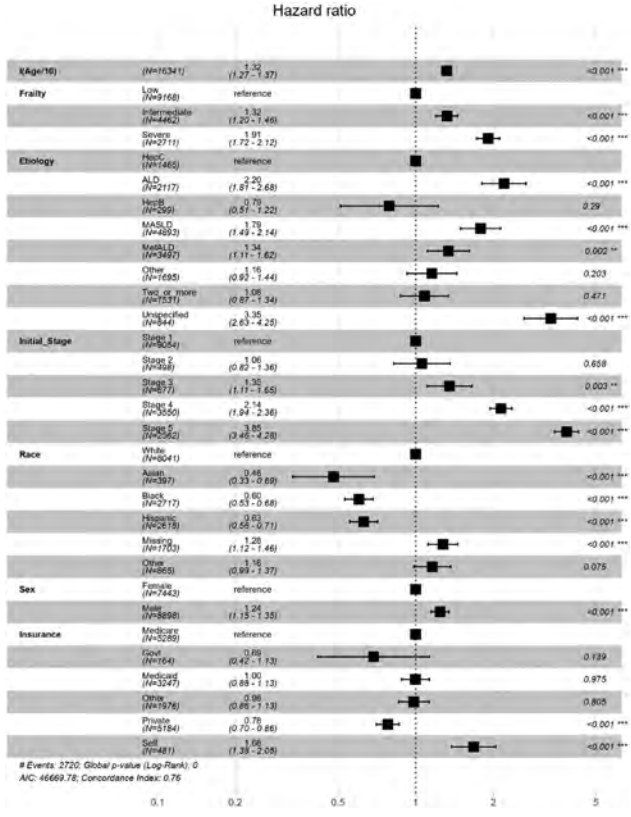
Background: Up to a third of patients with cirrhosis live with frailty. Comorbid cirrhosis and frailty mark the intersection of two broad population health problems that are further influenced by aging. **Methods:** We conducted a retrospective, longitudinal cohort study from 1/1/2016-12/31/2021 using the Chicago Area Patient-Centered Outcomes Research Network (CAPriCORN), a clinical research repository across seven healthcare systems in the metropolitan area of Chicago, IL. Our outcome of interest was mortality, ascertained from the Veritas Data Research fact-of-death records. Covariates included sex, race/ethnicity, decompensation status, and cirrhosis etiology. We estimated frailty using the validated High Frailty Risk Score (HFRS), categorizing patients into low/mild (HFRS < 5), intermediate (HFRS 5-15), and high/severe (HFRS > 15) frailty levels. We conducted a multivariable Cox regression to investigate risk factors for mortality. **Results:** The cohort included 16,341 patients with cirrhosis. Median age of the cohort was 61 years with a mean follow-up time of 1.2 years. There were 7,443 (45.6%) female patients in the cohort, and 2,774 patients (17.0%) died during the study period. Overall, 9,310 (57.0%) were decompensated. Regarding frailty, 9,168 (56.1%) patients were classified as having low frailty; 4,462 (27.3%) had intermediate frailty; and 2,711 (16.6%) had severe frailty. Mortality risk increased approximately 30% with every 10 years of chronological age gained. In adjusted analyses, 10 years of age was equal to the risk of mortality associated with intermediate frailty. Severe frailty was associated with nearly 100% increased risk of mortality, irrespective of age. **Conclusion:** Mortality risk in this cirrhosis cohort increased by approximately 30% with every 10 years of chronological age gained, the same as intermediate versus low frailty.



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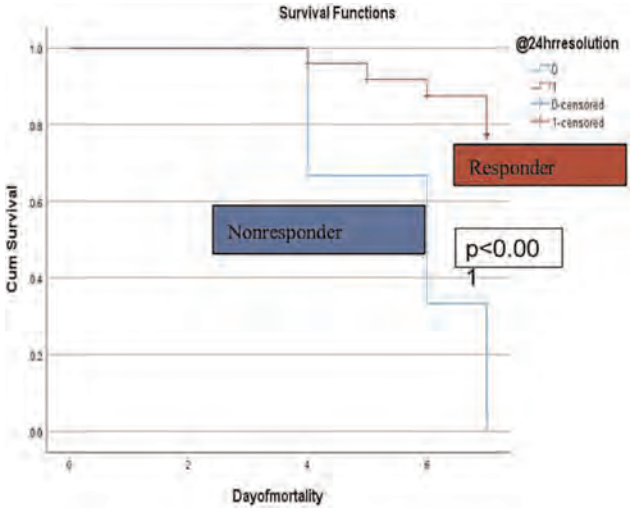
4156 | TITLE- TO STUDY THE EFFICACY OF INTRAVENOUS NEOSTIGMINE IN RESOLUTION OF ACUTE GI PARALYSIS IN CRITICALLY ILL CIRRHOSIS- PROSPECTIVE OBSERVATIONAL STUDY (NCT- 06462872)

NEW SUBMISSION, *Ibrar Ahmed Khan[1] Rajan Vijayaraghavan[2] Rakhi Maiwall[3] Babu Lal Meena[4] Harsh Vardhan[3] Prashant Aggarwal[3] shalini thapar[3] Manoj Sharma[4] Shiv Kumar Sarin[3]*

[1]ILBS NEW DELHI,Deemed university, [2]Institute of liver and biliary science,new delhi, [3]ILBS,NEW DELHI, [4]Institute of Liver and Biliary Sciences

Background: Gastrointestinal failure (GIF) is a common morbidity in liver ICU leading to interruption of feeding, raised intra-abdominal pressures, infections and increased mortality. Treatment options are limited, and symptoms may persist even after correction of precipitating factors. IV neostigmine has shown efficacy in cirrhosis patients with hepatic encephalopathy but its role in Critically Ill Cirrhosis (CIC) is not known. We aimed to determine the efficacy of IV neostigmine in the resolution of acute GI paralysis in patients with CIC. **Methods:** All consecutive patients of CIC admitted in liver ICU were prospectively screened and assessed for development of new onset GI failure, defined as the presence of 3 of 5 variables- absence of bowel sounds, gastric residual volume $\geq$ 500 ml, vomiting, diarrhoea and bowel distension on either abdominal x-ray or CT scan. Primary objective was proportion of patients reinitiated on enteral nutrition within 24 hours of after radiological improvement and secondary objectives were time to passage of stool, changes in intra-abdominal pressure (IAP), serial change in GRV, recurrence of GIF and 7-day survival. **Results:** Total of 32 patients of CIC were enrolled with ACLF (n = 19, 59.4%) and decompensated cirrhosis (n = 13, 40.6%). Mean age was 43.2 ± 10.9 yrs. Median ICU stay prior to GIF was 7 (4-10) days and ventilatory days was 4.4 days. The spectrum of GIF includes, all patients with new onset abdominal distension (n = 32), dilated bowel loops in x-ray (n = 24, 75%) and GRV > 500ml seen in 68.7% patients (n = 22). These patients were sicker {MELD = 30.6 ± 10.6, SOFA = 11.2 ± 3, and AARC score = 11 (9.75-13)}and had organ failures at the time of development of GIF (shock-78.1%, RRT-56.3% and mechanical ventilation- 71.8%). Within 24-hours of IV neostigmine, 78% (n = 25) patients had reinitiation of enteral nutrition with mean time of reinitiation = 11.04 ± 4.90 hrs. and time to passage of first stool = 7.5 ± 3.7 hrs. Recurrence after 24-hours was seen in 18.8 % (n = 6) patients and failure of treatment in 15.6% (n = 5) patients. Significant reduction was seen in GRV with maximum reduction within 72-hours ($p < 0.001$). IAP reduction was significant (15.4 ± 1.77 to 13.9 ± 1.87 mmHg, $p = 0.001$) in responders. Non-responder patients had need for 2nd vasopressor (71.4% vs. 28%, $p = 0.038$) and prolonged ventilatory days (7.29 ± 4.3 vs 3.3 ± 1.8 days). KM analysis shows better 7-day survival in responders ($p = 0.001$) (Fig. 1). **Conclusion:** GI failure is common in liver ICU and have worse clinical outcomes. Early detection and treatment initiation may improve survival and prevent clinical deterioration.



Disclosures: Ibrar Ahmed Khan: Nothing to Disclose, Rajan Vijayaraghavan: Nothing to Disclose, Rakhi Maiwall: Nothing to Disclose, Babu Lal Meena: Nothing to Disclose, Harsh Vardhan: Nothing to Disclose, Prashant Aggarwal: Nothing to Disclose, shalini thapar: Nothing to Disclose, Manoj Sharma: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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4157 | DISPARITIES IN LIVER TRANSPLANT EVALUATION FOR ACUTE-ON-CHRONIC LIVER FAILURE: THE IMPACT OF RACE AND SEX

Kelly Bowen[1] Alaina Miller[2] Wesam Aleyadeh[3] William Carey[2] Aanchal Kapoor[2] Omar Sims[2] Christina Lindenmeyer[2], [1]Cleveland Clinic Lerner College of Medicine, [2]Cleveland Clinic, [3]Cleveland Clinic Akron General

Background: Liver transplantation (LT) is the only definitive treatment for acute-on-chronic live failure (ACLF), yet disparities in access to LT persist based on sociodemographic factors. ACLF is associated with rapid clinical deterioration and high mortality; timely LT evaluation is critical. Studies have highlighted racial and sex-based inequities in LT access, but few have examined how these disparities manifest among critically ill patients with ACLF. We aimed to investigate whether race and sex were associated with LT evaluation status among patients admitted to a quaternary care center medical intensive liver unit (MILU) with ACLF. **Methods:** Data were collected from a prospective registry of patients admitted to the MILU between 2018 and 2023 and analyzed retrospectively. Patients were included in the analysis if they met EASL-CLIF criteria for ACLF on day one of their first MILU admission. LT evaluation status was categorized as: (1) not evaluated, (2) evaluation started in the MILU, or (3) already in evaluation on admission. A multinomial logistic regression model was constructed using "not evaluated" as the reference outcome. Covariates in the multivariate model included age, sex, race (collapsed to white and non-white), MELD-Na, ACLF grade, liver disease etiology, and Area Deprivation Index as a proxy for neighborhood-level socioeconomic disadvantage. A secondary model evaluated predictors of LT listing using the same covariates. **Results:** 428 patients were included in the analysis. After adjusting for clinical and sociodemographic covariates, non-white race was associated with lower odds of being in LT evaluation upon MILU admission compared to white race (OR 0.34, 95% CI 0.16-0.72) (Table 1). However, there were no major racial or sex-based differences in the odds of *starting* LT evaluation during the MILU stay. In the adjusted listing model, non-white race was associated with lower odds of LT listing (OR 0.42, 95% 0.20-0.84). No significant differences in LT evaluation or listing were observed by sex. **Conclusion:** Racial disparities in access to LT evaluation and listing exist among critically ill patients with ACLF, particularly in the likelihood of already being in evaluation upon ICU admission. These findings underscore the need for early outreach and structural interventions to promote equitable access to LT evaluation, especially prior to ICU-level deterioration. Sex-based differences were minimal in this cohort. Importantly, a subspecialty ICU like the MILU, staffed with teams educated and focused on bridging critically ill patients to transplant, may help mitigate disparities by standardizing evaluation pathways. Future work should explore upstream referral patterns and system-level contributors to delayed evaluation.

LT Evaluation: Odds Ratio Estimates

Reference level: not evaluated

Outcome Level	Predictor	Odds Ratio	Std. Error	z-statistic	p-value	95% CI Lower	95% CI Higher
Started in MILU	(Intercept)	0.164	0.978	−1.851	0.064	0.024	1.113
Started in MILU	Age	0.976	0.011	−2.190	0.029	0.955	0.997
Started in MILU	Male (ref:Female)	0.789	0.250	−0.950	0.342	0.483	1.287
Started in MILU	Non-white (ref:White)	0.692	0.331	−1.112	0.266	0.362	1.324
Started in MILU	ADI	0.997	0.006	−0.531	0.595	0.986	1.008
Started in MILU	ACLF-2 (ref:ACLF-1)	2.102	0.451	1.648	0.099	0.869	5.083
Started in MILU	ACLF-3 (ref:ACLF-1)	2.442	0.442	2.020	0.043	1.027	5.807
Started in MILU	Non-EtOH (ref:EtOH)	1.343	0.272	1.084	0.278	0.788	2.290
Started in MILU	MELD-Na D1	1.061	0.018	3.197	0.001	1.023	1.100
Already in Eval	(Intercept)	0.297	0.941	−1.290	0.197	0.047	1.879
Already in Eval	Age	0.991	0.011	−0.857	0.391	0.969	1.012
Already in Eval	Male (ref:Female)	1.137	0.252	0.509	0.610	0.694	1.864
Already in Eval	Non-white (ref:White)	0.336	0.387	−2.822	0.005	0.157	0.716
Already in Eval	ADI	1.000	0.005	−0.025	0.980	0.989	1.011
Already in Eval	ACLF-2 (ref:ACLF-1)	0.700	0.332	−1.075	0.283	0.365	1.342
Already in Eval	ACLF-3 (ref:ACLF-1)	0.530	0.338	−1.876	0.061	0.273	1.029
Already in Eval	Non-EtOH (ref:EtOH)	1.342	0.263	1.121	0.262	0.802	2.246
Already in Eval	MELD-Na D1	1.044	0.018	2.349	0.019	1.007	1.082

Disclosures: Kelly Bowen: Nothing to Disclose, Alaina Miller: Nothing to Disclose, Wesam Aleyadeh: Nothing to Disclose, William Carey: Nothing to Disclose, Aanchal Kapoor: Nothing to Disclose, Omar Sims:

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Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Christina Lindenmeyer: Nothing to Disclose

4158 | FROM COLONIZATION TO INFECTION: CLINICAL CONSEQUENCES OF MULTIDRUG-RESISTANT ORGANISMS IN CIRRHOSIS IN THE ICU

Iva Kosuta[1] Jaksa Babel[1] Frano Susak[1] Laura Peretin[2] Viktor Domislovic[2] Radovan Radonic[2] Anna Mrzljak[2], [1]University Hospital Centre Zagreb, Zagreb, Croatia, [2]University Hospital Center Zagreb, Zagreb, Croatia

Background: Bacterial infections are a major complication in cirrhosis, often triggering organ failure. The rise in multidrug-resistant organisms (MDROs) complicates treatment and worsens prognosis. Critically ill cirrhotic patients frequently harbor MDROs at ICU admission, and colonization may precede infection. Understanding colonization patterns could help optimize empirical therapy and improve outcomes. The primary aim of this study was to assess concordance between colonizing and infecting strains. Secondary aims included colonization and infection epidemiology, outcomes, and differences between patients with acute decompensation (AD) and acute-on-chronic liver failure (ACLF). **Methods:** This retrospective cohort study included cirrhotic patients admitted to the ICU at University Hospital Centre Zagreb, Croatia (2018–2024). Colonization was assessed by nasal, pharyngeal, and rectal swabs at admission and within five days. Clinical, laboratory, and severity scores (MELD, SOFA, CLIF-ACLF) were collected and analyzed. **Results:** Among 107 ICU admissions, 29.9% were colonized with MDROs. Colonization was more common in ACLF than AD patients (34.5% vs. 10.0%, $p = 0.033$). Colonization was not independently associated with MDRO infection (OR: 2.18; $p = 0.383$) or 28-day transplant-free mortality (OR: 1.14; $p = 0.813$), but strain concordance between colonizing and infecting organisms was high (82%). MDRO infection was significantly associated with worse outcomes, including increased need for mechanical ventilation (59.3% vs. 18.8%, $p = 0.005$), vasopressors (53.8% vs. 18.8%, $p = 0.013$), longer ICU stay (median 9.0 vs. 5.0 days, $p = 0.003$), and lower hospital survival (37.4% vs. 68.8%, $p = 0.038$). ACLF patients had significantly worse clinical outcomes than AD patients, including lower 28-day survival (39.1% vs. 75.0%, $p = 0.008$), ICU survival (43.7% vs. 85.0%, $p = 0.001$), and hospital survival (34.5% vs. 75.0%, $p = 0.002$). **Conclusion:** MDRO colonization at ICU admission was common, particularly in ACLF, but did not independently predict infection or mortality. However, the high concordance between colonizing and infecting strains supports the use of colonization data to guide early empirical therapy. Infection—not colonization—was strongly linked to worse outcomes, emphasizing the need for early recognition and intervention in this high-risk group. **Disclosures:** Iva Kosuta: Nothing to Disclose, Jaksa Babel: Fresenius Kabi: Speaking and Teaching, Frano Susak: Nothing to Disclose, Laura Peretin: Nothing to Disclose, Viktor Domislovic: Nothing to Disclose, Radovan Radonic: Nothing to Disclose, Anna Mrzljak: Nothing to Disclose

4159 | COMBINATION OF NOVEL PLASMA METABOLITES AND WEARABLE-DERIVED PHYSIOLOGIC PARAMETERS PROVIDE HIGH PROGNOSTIC VALUE FOR RISK OF HOSPITALIZATION FOR PATIENTS WITH CIRRHOSIS

Gautham Pranesh[1] Nikhil Zachariah[2] Sachin Subramanian[3] Alisha Chaubal[4] HARDIK SHAH[4] Ameet Mandot[5] AMRIK SHAH[6] Shyam Kottilil[7] Mani Subramanian[8] SAMIR SHAH[4], [1]SensEarly, [2]Mitopower Inc, [3]UC Davis, [4]Nanavati Max Super Speciality Hospital, [5]Gleneagles Hospital, [6]Sensearly Inc, [7]University of Maryland, [8]TLC

Background: The clinical course of patients with decompensated cirrhosis varies considerably and early identification of patients who progress to decompensation or Acute on Chronic Liver Failure (ACLF) is a major unmet need. Our aim is to identify biomarkers that will improve risk stratification of patients with cirrhosis and further enhance early detection of acute hepatic decompensation. **Methods:** The "Prospective Observational Study to Evaluate Biomarkers of Metabolic Dysfunction Among Patients with Liver Failure" (CTRI/2022/09/045668) was a 24-week prospective observational study conducted at a tertiary liver center in western India. Quantitative profiling of plasma acylcarnitines and plasma aminoacids, was performed using standard LC-MS techniques. Patients were monitored using the Garmin Vivosmart 5 wearable, capturing continuous data on heart rate, heart rate variability, actigraphy, respiration, SpO_2, and sleep over 6 months. Clinical outcomes were hospitalization for

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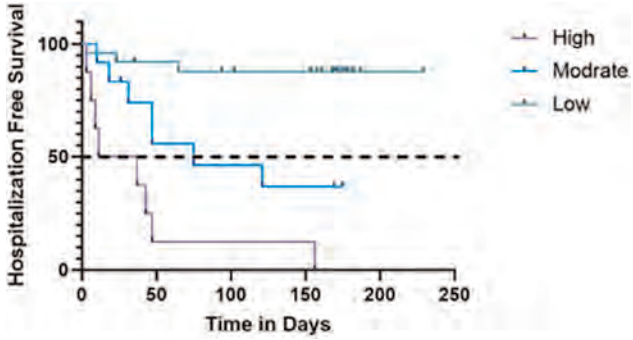
liver decompensation events, mortality, and liver transplantation during the period of observation. Associations between plasma biomarker levels and MELD scores were assessed using Spearman rank correlation. Unsupervised clustering methods (hierarchical and k-means) were applied to identify phenotypic subgroups based on biomarker profiles. Clinical events leading to hospitalization or mortality were examined across these phenotypes. **Results:** Fifty-six patients with cirrhosis were enrolled (mean age: 52 years; 84% male; 52% alcohol-related). 62.5% had Child-Pugh B/C cirrhosis and 48.2% had MELD >15. A panel of plasma metabolites and aminoacids associated with mitochondrial dysfunction showed strong correlations with MELD. These included 4-hydroxyproline ($r=0.781$, $p<0.001$), threonine ($r=0.613$, $p<0.001$), methionine ($r=0.578$, $p<0.001$), alpha-amino-n-butyric acid ($r=0.502$, $p<0.001$), hexadecenoylcarnitine ($r=0.612$, $p<0.001$), malonylcarnitine/3OH butyryl carnitine ($r=0.594$, $p<0.001$), acetylcarnitine ($r=0.585$, $p<0.001$), and octadecenoylcarnitine ($r=0.541$, $p<0.001$). Unsupervised clustering using a novel metabolite panel at baseline, identified three distinct phenotype with low to high risk of future hospitalization, with a median time to hospitalization of 24 days and a 100% hospitalization rate in the high-risk group (Figure 1). Wearable-derived physiological parameters monitored over a 6-month period including 24-hour average heart rate (AUC 0.90; 95% CI, 0.88–0.92), beat-to-beat interval (AUC 0.88; 95% CI, 0.86–0.90), and daily step count (AUC 0.70; 95% CI, 0.67–0.72) were significantly associated with subsequent clinical events. **Conclusion:** For patients with decompensated cirrhosis, the novel metabolite panel representative of mitochondrial dysfunction enables improved risk stratification, and the wearable derived signature enables early detection of patients at high risk of hospitalization.



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4160 | THE LINOLEIC ACID-DERIVED LEUKOTOXIN 9,10-DIHOME DRIVES IMMUNOSUPPRESSION IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

Bryan Contreras[1] Berta Romero-Grimaldo[1] Mireia Casulleras[1] Marta Duran Güell[1] María Belén Sánchez-Rodríguez[1] Maria Papp[2] Jonel Trebicka[3] Richard Moreau[4] MICROB-PREDICT Consortium[5] Cristina López-Vicario[1] Joan Claria[1], [1]Biochemistry and Molecular Genetics Service, Hospital Clínic–IDIBAPS, CIBERehd, Barcelona, Spain, [2]University of Debrecen, Faculty of Medicine, Department of Gastroenterology, Debrecen, Hungary, [3]Department of Internal Medicine B, University of Münster, Münster, Germany, [4]European Foundation for the Study of Chronic Liver Failure (EF CLIF), [5]MICROB-PREDICT Consortium

Background: Patients with acutely decompensated (AD) cirrhosis present persistent immunosuppression rendering them at increased risk of recurrent bacterial infections and developing acute-on-chronic liver failure (ACLF). Here, we investigated the profile of immunomodulatory lipid mediators in patients with AD cirrhosis and their effects on leukocyte host defense mechanisms. **Methods:** Targeted lipidomics of 101 well-annotated lipid mediators was performed by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) in 308 samples of plasma from 93 AD patients with and without ACLF at hospital admission and during 90-day follow up. For comparison, 31 healthy donors were also included. Immune responses were assessed in vitro in polymorphonuclear (PMN) and mononuclear leukocytes. In vivo studies were performed in peritoneal and liver macrophages from mice with CCl_4-induced cirrhosis. **Results:** LC-MS/MS

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analysis identified the linoleic acid-derived 9,10-dihydroxy-12-octadecenoic acid (9,10-DiHOME), also known as leukotoxin, as the only lipid mediator specifically elevated in ACLF patients in comparison to those without. Moreover, follow-up analysis revealed that 9,10-DiHOME levels followed the severity course of the disease and were significantly higher at the time patients developed an active infection and at ACLF presentation. Consistent with these findings, leukocytes from AD patients showed increased expression of soluble epoxyde hydrolase (sEH), the enzyme responsible for 9,10-DiHOME biosynthesis. In *in vitro* assays, 9,10-DiHOME impaired PMN degranulation, phagocytosis, and respiratory burst capacities. In addition, in mononuclear leukocytes, 9,10-DiHOME induced the expression of the immunosuppressive marker MerTK, distorted required mechanisms for the adequate host defense response against pathogens including the ability to produce cytokines in response to LPS and impaired mitochondrial dynamics and autophagic responses. In *in vivo* studies, inhibition of sEH in mice with CCl_4-induced cirrhosis impeded immunosuppressive responses in peritoneal macrophages and significantly attenuated MerTK expression in liver macrophages. **Conclusion:** Taken together, these findings indicate that increased circulating levels of the leukotoxin 9,10-DiHOME weakens immune-cell defensive responses, thus enhancing the susceptibility of AD patients to bacterial infection and precipitating ACLF. These data also position sEH as an actionable drug target in this condition.

Disclosures: Bryan Contreras: Nothing to Disclose, Berta Romero-Grimaldo: Nothing to Disclose, Mireia Casulleras: Nothing to Disclose, Marta Duran Güell: Nothing to Disclose, María Belén Sánchez-Rodríguez: Nothing to Disclose, Maria Papp: Nothing to Disclose, Jonel Trebicka: Nothing to Disclose, Richard Moreau: Nothing to Disclose, MICROB-PREDICT Consortium: Nothing to Disclose, Cristina López-Vicario: Nothing to Disclose, Joan Claria: Nothing to Disclose

4161 | DOSE-DEPENDENT RISK OF HEPATIC ENCEPHALOPATHY WITH CHRONIC PPI USE IN CIRRHOSIS: A MULTICENTER COHORT ANALYSIS

Ahmed Salem[1] Mohammed Abusuliman[2] Hazem Abosheaishaa[3] Mohamed Eldesouki[4] Sherif Elhanafi[5] Aaron Tokayer[1], [1]Maimonides Medical Center, [2]Henry Ford Hospital, [3]Mount Sinai Queens, [4]New York Medical College at Saint Michael Medical Center, [5]Texas Tech University Elpaso

Background: Despite widespread use, proton pump inhibitors (PPIs) have been implicated as a potential modifiable risk factor for hepatic encephalopathy (HE) in patients with cirrhosis. However, real-world data delineating this relationship remain limited, especially regarding dose and duration effects.

Aim: To investigate the association between PPI use and risk of incident hepatic encephalopathy among cirrhotic patients, accounting for exposure duration and dose intensity. **Methods:** We conducted a retrospective multicenter cohort study using TriNetX, aggregating EHRs from 90+ U.S. health systems. Adults ($\geq$18 years) with cirrhosis (ICD-10: K70.3, K74.6, K76.9) from Jan 1, 2015–Dec 31, 2023 were included. Exclusions: prior HE, HCC, TIPS, or recent sepsis.

Patients were stratified into:

- Non-users (no PPI exposure)
- Low-dose users ($\leq$20 mg omeprazole-equivalent/day)
- High-dose users ($\geq$40 mg/day)

Index date was first PPI prescription or matched pseudo-date. All had $\geq$12 months follow-up. Propensity score matching (1:1:1) used age, sex, MELD-lab equivalents (bilirubin, INR, albumin, creatinine), comorbidities (diabetes, CKD, alcohol use, varices, ascites), and medications (lactulose, rifaximin, diuretics, NSAIDs, beta-blockers).

The primary outcome was incident HE within 12 months, defined via ICD-10 codes and initiation of lactulose or rifaximin. Cox models provided adjusted hazard ratios (aHRs), with Kaplan-Meier curves illustrating incidence.

Results: 18,991 patients met criteria (6,423 per group). Baseline variables were balanced (SMD $<$ 0.1). Median follow-up: 11.2 months.

HE incidence:

- High-dose: 18.1%
- Low-dose: 13.6%
- Non-users: 9.8% (log-rank $p <$ 0.001)

Risk comparisons:

- High-dose vs non-users: aHR 1.62 (95% CI: 1.39–1.87), $p <$ 0.001
- High-dose vs low-dose: aHR 1.27 (95% CI: 1.10–1.47), $p = 0.002$
- Low-dose vs non-users: aHR 1.31 (95% CI: 1.14–1.50), $p <$ 0.001

Findings were consistent across subgroups (alcoholic vs non-alcoholic cirrhosis, sex, MELD strata). Sensitivity analyses controlling for lactulose, rifaximin, and diuretic

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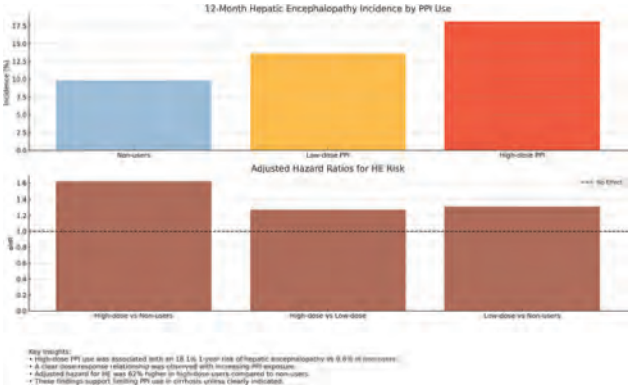
use confirmed robustness. KM curves showed early divergence by month 3. **Conclusion:** In cirrhotic patients, chronic PPI use—especially high-dose—was independently linked to increased HE risk. These real-world data support cautious PPI use, favoring dose reduction or discontinuation when appropriate. Prospective studies are needed to validate causality and mechanisms.



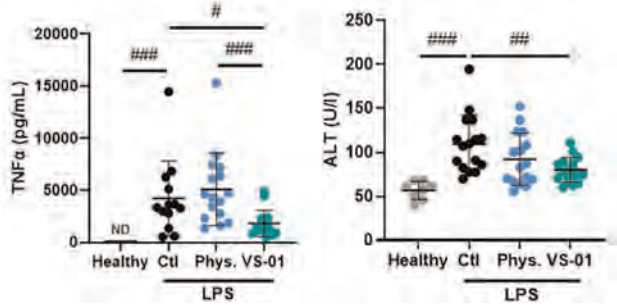
Disclosures: Ahmed Salem: Nothing to Disclose, Mohammed Abusuliman: Nothing to Disclose, Hazem Abosheaishaa: Nothing to Disclose, Mohamed Eldesouki: Nothing to Disclose, Sherif Elhanafi: Nothing to Disclose, Aaron Tokayer: Nothing to Disclose

4162 | EFFECT OF VS-01 ON SYSTEMIC INFLAMMATION AND LIVER INJURY IN A RAT MODEL OF ENDOTOXEMIA

Marie Bobowski-Gerard[1] Philippe Delataille[1] Valérie Daix[1] Zouher Majd[1] Bart Staels[2] Dean Hum[1] Katharina Staufer[3] Jonel Trebicka[4] Sakina Sayah Jeanne[1], [1]Genfit SA, Loos, France, [2]Univ. Lille, Institut Pasteur de Lille, CHU Lille, Inserm U1011, Lille, France, [3]Versantis AG (GENFIT group), Zurich, Switzerland, [4]Hospital of the Goethe University Frankfurt, University Hospital Münster, Germany

Background: Systemic inflammation, triggered by bacteria or Pathogen-Associated Molecular Patterns (PAMPs), is a primary driver of acute-on-chronic liver failure (ACLF), a severe syndrome affecting patients with acutely decompensated cirrhosis. VS-01 is an intraperitoneal pH-gradient investigational liposomal drug under development for the treatment of ACLF by enhancing the clearance of ammonia and other toxins. We previously demonstrated that VS-01 counteracts lipopolysaccharide (LPS)-induced inflammatory response in a cellular model, on top of its ability to bind hydrophobic bile acids *in vitro* (Bobowski-Gerard *et al.*, Hep, 2024). The aim of this study was to assess the effect of VS-01 on ACLF-related toxins using a rat model of endotoxemia. **Methods:** Endotoxemia was induced in healthy Sprague Dawley rats by intravenous injection of 1 mg/kg LPS (E.Coli). VS-01 or a control dialysis solution (Physioneal 35, glucose 1.36%) was administered at 60 mL/kg, one hour before LPS administration. Serum was collected at 3h and at 5h post-LPS for measurement of cytokines and hepatic function and injury markers. The efficacy of VS-01 on ammonia capture was verified through ammonia measurement in the peritoneal fluid. **Results:** Intravenous administration of LPS in rats induced an increase in serum circulating cytokines levels. As an example, TNF-alpha concentrations (not detectable in healthy rats) were 4235 pg/mL and 746 pg/mL at 3h and 5h post-LPS, respectively. VS-01 reduced LPS-induced TNF-alpha levels by 65% at 3h ($p < 0.001$, Figure) and 35% at 5h ($p = 0.02$); when compared to the control dialysis group. IL-10 and IFN-gamma also decreased upon VS-01 treatment (-43%, $p = 0.02$ at 3h and -35%, $p < 0.001$ at 5h, respectively). This anti-inflammatory effect was associated with a reduction of LPS-induced ALT (-56%, $p = 0.001$, Figure) and urea (-23%, $p = 0.003$) at 5h, when compared to the control group. **Conclusion:** A single administration of VS-01 in rats with endotoxemia decreases systemic inflammation and improves liver function, supporting the ability of VS-01 to counteract the activity of ACLF-related toxins in an animal model. These studies further support the development of VS-01 in ACLF (Phase 2a study UNVEIL-IT™ NCT05900050, status: recruiting).

Figure: Serum levels of TNFα (T+3h post-LPS) and ALT (T+5h post-LPS)
#: p<0.05, ##: p<0.01, ###: p<0.001. Ctl: control, Phys.: physioneal (control dialysis)



Disclosures: Marie Bobowski-Gerard: Nothing to Disclose, Philippe Delataille: Nothing to Disclose, Valérie Daix: Nothing to Disclose, Zouher Majd: Nothing to Disclose, Bart Staels: Genfit SA: Consultant, Dean Hum: Nothing to Disclose, Katharina Staufer: Nothing to Disclose, Jonel Trebicka: Nothing to Disclose, Sakina Sayah Jeanne: Nothing to Disclose

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4163 | LONGITUDINAL SINGLE-CELL MULTIMODAL ANALYSIS REVEALS THE DYNAMIC IMMUNE MECHANISMS UNDERLYING HBV-ACLF PROGRESSION

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Background: Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome involving dysfunction of multiple immune cell types. This study aimed to comprehensively depict the dynamic trajectory of immune responses throughout the disease course of hepatitis B virus-related ACLF (HBV-ACLF). **Methods:** Single-cell RNA sequencing (scRNA-seq) and single-cell proteomics were performed on the peripheral blood mononuclear cells (PBMCs) of 45 samples from 17 hospitalized patients (progressive/stable/recovering course of HBV-ACLF, 6/5/6) and 15 control subjects (liver cirrhosis, chronic hepatitis B and healthy controls, 5/5/5). Functional and mechanistic experiments were validated in vivo and in vitro. **Results:** Single-cell multiomics analysis revealed specific changes in the peripheral immune response in ACLF. VCAN+CD14 +-monocytes with activated interferon-stimulated genes and enhanced inflammatory functions, stimulated by HBV relapse and expanded in ACLF-1, contributing to early inflammatory storm. The subsequent apoptotic hepatocytes predominantly induce hyperinflammatory CXCR2+-neutrophils and M2 macrophage-like CD163 +-monocytes, which were prevalent in progressive ACLF patients, serving as significant markers of disease deterioration. Cytotoxic T-cells were functionally impaired and significantly decreased in progressive patients. CXCR2+-neutrophils were found to exhibit immunosuppressive activity and induce the exhaustion of cytotoxic T-cells. Inhibition of CXCR2 significantly reduced neutrophils infiltration, restored cytotoxic T-cells and showed therapeutic effect in ACLF mice. Six immune patterns were established to stratify patients, with CM2 and CM6 showing good predictive ability for disease outcomes and highlighting CM3 as an early therapeutic window. **Conclusion:** Our longitudinal multiomics study revealed the dynamic evolution of the immune response in HBV-ACLF and characterized diverse immune patterns for the precise management and therapeutic intervention.

Disclosures: Jun Li: Nothing to Disclose, Xi Liang: Nothing to Disclose, Jinjin Luo: Nothing to Disclose, Qian Zhou: Nothing to Disclose, Jiaojiao Xin: Nothing to Disclose, Jiaqi Li: Nothing to Disclose, Xin Chen: Nothing to Disclose, Dongyan Shi: Nothing to Disclose

4164 | IDENTIFICATION OF PLASMA EXTRACELLULAR VESICLE MICRORNA PROFILES AS DIAGNOSTIC AND PROGNOSTIC BIOMARKERS FOR HBV-ASSOCIATED ACUTE-ON-CHRONIC LIVER FAILURE

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Background: Chronic hepatitis B virus (CHB) infection can lead to hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF), a condition characterized by high mortality. Currently, there is a lack of biomarkers with high sensitivity and specificity for diagnosing HBV-ACLF. Extracellular vesicles (EVs) are bilayer lipid vesicles containing RNA.This study aims to elucidate alterations in plasma EVs miRNAs associated with HBV-ACLF, thereby developing diagnostic and prognostic scoring systems for HBV-ACLF. **Methods:** To explore the feasibility of early HBV-ACLF diagnosis, EVs were isolated from plasma of HBV-ACLF patients and CHB patients, followed by characterization of particle size and protein markers. EV-derived miRNAs specific to HBV-ACLF were identified via miRNA microarray analysis. Candidate miRNAs were further validated in a large cohort (67 HBV-ACLF patients, 57 CHB patients) to screen potential biomarkers. For early diagnosis, machine learning models (EMR6-RF, EMR6-SVM, EMR6-LR) were developed using combinations of 6 EV miRNAs. For mortality risk assessment, a multivariate Cox proportional hazards model (EMR3I) was established by integrating EV miRNAs with clinical parameters. **Results:** Microarray analysis identified 33 differentially expressed miRNAs between HBV-ACLF and CHB patients. Six EV miRNAs (hsa-miR-548aq-3p, hsa-miR-545j-5p, hsa-miR-185-3p, hsa-miR-1455-5p, hsa-miR-6731-3p, hsa-miR-320e) showed strong diagnostic power. The EMR6 machine learning models achieved high accuracy in distinguishing CHB and HBV-ACLF: EMR6-RF: AUC 0.85 (95% CI: 0.71–0.95), EMR6-SVM: AUC 0.75 (95% CI: 0.59–0.90) and EMR6-

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LR: AUC 0.83 (95% CI: 0.68–0.95), outperforming the MELD score (AUC:0.76;95%CI:0.60-0.92). The prognostic model EMR3I (integrating hsa-miR-548aq-3p, hsa-miR-545j-5p, hsa-miR-320e, and INR) robustly predicted survival: 30 days AUC: 0.82 (95% CI: 0.74–0.90) and 90 days AUC: 0.83 (95% CI: 0.76–0.90). And the EMR3I scoring system stratifies HBV-ACLF patients into risk subgroups, with significant differences in 30 days and 90 days mortality between high- and low-risk groups. **Conclusion:** Plasma EV-derived miRNAs serve as diagnostic and prognostic biomarkers for HBV-ACLF. The EMR6 scoring model enhances early diagnosis, while the EMR3I scoring model improves risk stratification capabilities.

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4165 | EFFICACY OF NITAZOXANIDE (NTZ) ON SYSTEMIC INFLAMMATION AND ORGAN FUNCTION IN DISEASE MODELS OF ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) WHEN ADMINISTERED POST-ACLF TRIGGER

Marie Bobowski-Gerard[1] Philippe Delataille[1] Simon Debaecker[1] Camille Vanbésien[1] Dean Hum[1] Vanessa Legry[1] Bart Staels[2] Jonel Trebicka[3] Sakina Sayah Jeanne[1], [1]Genfit SA, Loos, France, [2]Univ. Lille, Institut Pasteur de Lille, CHU Lille, Inserm U1011, Lille, France, [3]Hospital of the Goethe University Frankfurt, University Hospital Münster, Germany

Background: Systemic inflammation is a primary driver of acute-on-chronic liver failure (ACLF), a severe syndrome affecting patients with acutely decompensated cirrhosis. In rodent disease models, we previously demonstrated the beneficial effect of the anti-parasitic drug nitazoxanide (NTZ) on systemic inflammation and organ damage when added concomitantly or before the precipitating trigger of ACLF. The aim of this study was to better assess the activity of NTZ on preexisting inflammation, by investigating NTZ efficacy when administered after the pathological stimulus in preclinical models of inflammation and ACLF. **Methods:** TZ (the active metabolite of NTZ) was added to human PBMCs concomitantly or 30 min after the trigger (LPS) to assess its effect on cytokine secretion. *In vivo*, endotoxemia was induced in healthy rats by intraperitoneal (i.p.) injection of 1 mg/kg lipopolysaccharide (LPS). A single oral dose of NTZ pro-drug (300 mg/kg) was administered concomitantly or 15 min after LPS. Serum was collected 3 and 5h after LPS. ACLF was triggered by injecting LPS (1μg/kg, i.p.) in rats with bile duct ligation (BDL)-induced cirrhosis. A single oral dose of NTZ (300 mg/kg) or vehicle was orally administered 15 min after LPS injection. Serum was collected 3h post LPS. **Results:** In human PBMCs, TZ blunted LPS-induced IL-6 secretion with similar efficacy when added after or concomitant to LPS challenge: IC50 = 5μM and Emax = 93% vs IC50 = 7.6μM and Emax = 92%, respectively.

In rats with endotoxemia, NTZ lowered LPS-induced serum IL-6 levels at 3h: -34% ($p = 0.01$) in the post-trigger condition and -38% ($p = 0.01$) in the co-trigger condition. Hepatic marker levels were also reduced in both post-trigger and co-trigger groups: -78% ($p = 0.03$) and -86% ($p = 0.01$) of ALT, -98% ($p < 0.001$) and -100% ($p = 0.001$) of total bile acids at 5h, respectively.

In ACLF rats, NTZ administered after LPS decreased the LPS-induced increase of pro-inflammatory cytokines IL-6 by -65% ($p = 0.07$) and TNF-alpha by -58% ($p = 0.08$). NTZ also resolved liver injury as shown by a decrease of ALT by -97% ($p = 0.02$). Moreover, the levels of renal function markers were reduced upon NTZ treatment: -39% ($p = 0.04$) for cystatin C and -78% ($p = 0.08$) for creatinine. **Conclusion:** TZ lowered cytokine secretion post-LPS challenge *in vitro*. This rapid anti-inflammatory effect was also observed *in vivo*, as a single dose of NTZ reduced systemic inflammation and restored organ functions in an ACLF model. These findings further support the development of NTZ (G1090N) as a new therapeutic approach for ACLF.

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4166 | AARC SCORE PREDICTS SURVIVAL OUTCOMES BETTER THAN OTHER SCORES IN PATIENTS WITH ACUTE ON CHRONIC LIVER FAILURE PATIENTS HAVING HISTOPATHOLOGICALLY-PROVEN MILD LIVER FIBROSIS

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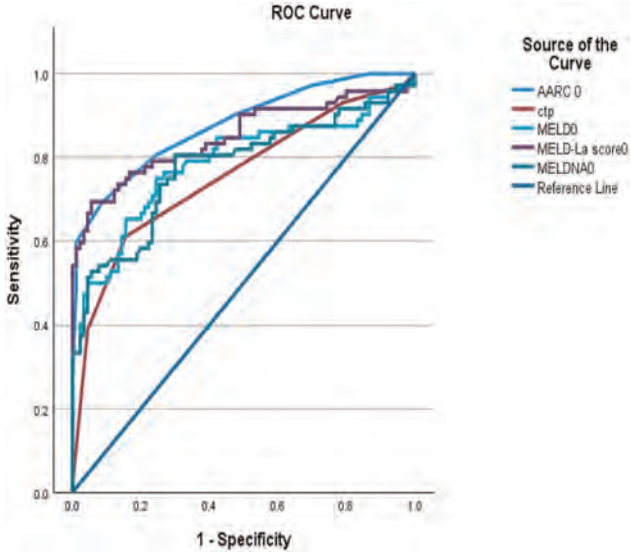
Background: and aims: ACLF in chronic liver disease (CLD) patients is not well understood. The severity of the illness and the mortality do not often correlate well with the histological picture. Unlike cirrhosis, ACLF is associated with property of reversibility if appropriate interventions are taken in the golden window period. We aimed to see the survival outcomes in ACLF patients having mild fibrosis in liver biopsy using different liver disease severity indices such as AARC score with MELD-lactate. **Methods:** This was a retrospective cohort study from the data records of the hospitalised ACLF patients in Institute of liver and biliary Sciences, New Delhi who underwent liver biopsy between period from 2013 to 2025. The patients who were proven as having mild fibrosis ($<$F2) on liver biopsy were assessed for their outcomes. Patient's demographic details, clinical history, blood investigations were recorded along with outcomes. **Results:** A total of 1277 ACLF patients (males-928) who underwent liver biopsy were assessed. Altogether, 237 (males-139), mean age 43 ± 12.5 years were found to have mild fibrosis on the liver biopsy. Their baseline investigations were recorded along with the natural outcomes of the disease progression (survival, deaths, repeat hospitalisations, liver transplantations, bridge therapies) either from the hospital records or telephonic conversations or by a follow up OPD visit. Overall, only 12 patients underwent live donor liver transplantation.Irrespective of the treatment, the 3-month mortality was 26.26% while 6-month and 12-month mortality rates were similar (32.32%). On univariate analysis, clinical parameters like higher grade of ascites, presence of spontaneous bacterial peritonitis, hepatic encephalopathy, acute kidney injury and variceal bleeding were associated with poorer survival outcomes. On multivariate analysis, the higher baseline serum total bilirubin (OR 1.063, CI:1.008-1.121, $p=0.024$), serum creatinine (OR 1.862, CI:1.049-3.305, $p=0.034$), INR (OR 2.211, CI: 1.191-4.107, $p=0.012$) as well as arterial lactate (OR 3.377, CI:1.460-7.810, $p=0.004$), which already are components of AARC and MELD-lactate scores predicted poorer outcomes in these group of patients. The ROC analysis showed that the AARC score (which additionally has the component of grade of hepatic encephalopathy), had larger AUC (0.876, CI:0.823-0.930) than the MELD-lactate score (AUC = 0.850, CI:0.784-0.916), MELD score (AUC = 0.786, CI:0.710-0.863), MELD-Na score (AUC = 0.778, CI:0.702-0.855) and CTP (AUC = 0.755, CI:0.679-0.831) score. **Conclusion:** Baseline AARC scores and MELD-lactate scores predict poor survival outcomes better than other scores in patients with ACLF patients with mild fibrosis.



Disclosures: Rohit Wagh: Nothing to Disclose, Archana Rastogi: Nothing to Disclose, VINOD ARORA: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

4167 | TREATMENT OF HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY (HRS-AKI) WITH TITRATABLE NOREPINEPHRINE OUTSIDE OF INTENSIVE CARE UNIT (ICU): A SINGLE CENTER EXPERIENCE

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Background: HRS-AKI is a significant, late-stage complication of liver cirrhosis that presents as renal impairment. It is difficult to treat and often requires ICU admission. A mainstay of treatment is splanchnic vasoconstriction to maintain a mean arterial pressure (MAP) to sustain and improve kidney perfusion[BA1] . However, vasoconstrictors, such a norepinephrine, are often only available in the ICU, thereby limiting access and increasing healthcare associated costs. Here, we present a cohort of patient who underwent treatment with norepinephrine in a step-down unit with telemetry using a well-vetted administration protocol. **Methods:** We retrospectively analyzed 23 patients with HRS-AKI who were treated in a step-down unit between November 2023 and February 2025 in a single center using our norepinephrine protocol (Table 1). The guidelines from 2021 International Club of Ascites were used to define response to treatment. A partial response to therapy was defined as a decrease in serum creatinine (SCr) by more than 0.3mg/dL from initiation of norepinephrine, complete response was a return to within 0.3 mg/dL of baseline, and all other responses as failure of therapy. **Results:** 23 patients total (16 male, 69.6%, 7 female, 30.4%) with a median age at start of treatment of 55 years (IQR 46-64). Etiologies for liver disease were alcoholic cirrhosis (18, 78.3%), MASLD (3, 13.1%), PBC (1, 4.3%), and HCV (1, 4.3%). Median serum creatinine at time of admission was 1.0 (0.7, 1.8). Characteristics are outline in Table 2. 9 patients (39.1%) required transfer to ICU. 8 patients (34.8%) received liver transplant during hospitalization, with one of them (1, 4.3%) also receiving a kidney transplant. 7 patients (30.4%) were complete responders, 10 patients (43.5%) were partial responders, and 6 patients (26.1%) were non-responders. There were no reported cardiovascular events reported while on norepinephrine. At 1 month, 14 (82.3%) of the responders and partial responders and 5 (83.3%) of the non-responders survived. Characteristics summarized in Table 2. **Conclusion:** Use of titratable norepinephrine outside of the ICU is a viable, safe and effective method to treat HRS-AKI. It can be used to help decrease overall cost of treatment as well as provide a viable platform for sustaining adequate MAP's to ensure renal perfusion in a majority of patients. Larger and perhaps multicenter studies are needed to validate this benefit and applicability.

- Initiate infusion at 2.5 mcg/min. Increase or decrease by 1 mcg/min every 1 hour to maintain MAP between *** and *** mmHg. Do not exceed 10 mcg/min.
- MAP goals are customizable, and determined by provider, to ideally target 10-15 mmHg above baseline MAP.

Table 1 Description of Norepinephrine Protocol

Characteristic	Value			
Response (%)				
Full	7 (30.4)	7 (30.4)	0 (0)	0 (0)
Partial	10 (43.5)	0 (0)	10 (43.5)	0 (0)
None	6 (26.1)	0 (0)	0 (0)	6 (26.1)
Gender (Male), n (%)	16, (69.6)	3, (42.8)	7, (70)	3, (50)
Ethnicity, n (%)				
White	15, (65.2)	4, (57.1)	5 (50)	4 (66.7)
Hispanic	7, (30.4)	2 (28.6)	4 (40)	1 (16.7)
African American	1, (4.3)	0 (0)	0 (0)	1 (16.7)
Etiology of Liver Disease				
Alcoholic Cirrhosis	18, 78.3%	5 (71.4)	7 (70)	6 (100)
MASLD	3, 13.1%	1 (14.3)	2 (20)	0 (0)
PBC	1, 4.3%	1 (14.3)	0 (0)	0 (0)
HCV	1, 4.3%	0 (0)	1 (10)	0 (0)
Age, median (Q1-Q3)	55, (46, 64)	68 (47, 70.5)	57 (46, 62.75)	49.5 (46.75, 59.75)
DM, n (%)	6, (26.1)	1 (14.3)	5 (50)	0 (0)
HTN, n (%)	8,(34.9)	3 (42.9)	3 (30)	2 (33.3)
Proteinuria, n (%)	3, (13.0)	1 (14.3)	0 (0)	2 (33.3)
Sepsis, n (%)	4, (17.4)	0 (0)	2 (20)	2 (33.3)
LOS (days), median (Q1-Q3)	26.0, (8.0, 32.0)	26 (9.5, 31.5)	26.5 (12.75, 29.5)	9.5 (8, 14)
ICU Transfer, n (%)	9, (39.1)	2 (28.6)	4 (40)	3 (50)
Adverse Events, n (%)	0, (0.0)	0, (0.0)	0, (0.0)	0, (0.0)
Baseline SCr, median (Q1-Q3)	1.0, (0.7, 1.8)	1.0 (0.8, 1.05)	0.9 (0.73, 1.85)	0.85 (0.7, 2.73)
Total Time on Drip (hrs), median (Q1-Q3)	70.68, (29.04, 86.16)	70.68 (69.12, 137.77)	73.3 (51.31, 87.23)	27.87 (22.01, 68.96)
MELD 3.0	35 (27.5, 39)	35 (29.5,40)	37 (27, 38.5)	32 (25.5, 34.75)
Median Peak Norepinephrine Dose (mcg/min)	6, (2.75, 9.12)	7.5 (5.75, 9)	5 (3.5, 7.5)	2.5 (2.5, 8.13)
Median Cystatin C	3.19 (2.44, 3.41)	2.4 (2.0, 2.79)	3.2 (2.44, 3.41)	3.56 (3.33, 3.83)

Table 2 Baseline Characteristics. MASLD = Metabolic Dysfunction-associated Liver Disease, PBC = Primary Biliary Cholangitis, HCV = Hepatitis C Virus, DM = Diabetes Mellitus, Type 2, HTN = Hypertension, LOS = Length of Stay, SCr = Serum Creatinine

Disclosures: Kyle Schneider: Nothing to Disclose, Alicia Reeve: Nothing to Disclose, Mahintha Karthik: Nothing to Disclose, Kinnari Modi: Nothing to Disclose, Jeevin Sandhu: Nothing to Disclose, Jeffrey Weinstein: Nothing to Disclose, Parvez Mantry: Akero: Grant/Research Support, Abbvie: Speaker and Advisory Board, BMS: Research Grants & Speaker, Boston Scientific: Advisory Board and Speaker, Chemomab: Grant/Research Support, Cymabay: Research Grants & Advisory Board, Care Dx: Grant/Research Support, Eisai: Speaker and Advisory Board, Genfit: Grant/Research Support, Gilead: Speaker, Advisory Board, & Research Grants, GSK: Grant/Research Support, Gore: Speaking and Teaching, Genentech: Grant/Research Support, Intercept: Speaker, Advisory Board, & Research Grants, Ipsen: Speaker and Advisory Board, Inventiva: Grant/Research Support, Fibronostics: Grant/Research Support, Hanmi: Grant/Research Support, Hepquant: Research Grants & Advisory Board, Lip-

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4168 | PRESENCE OF SEPSIS IS ASSOCIATED WITH INCREASED RISK OF ACUTE VARICEAL BLEEDING AND INCREASED MORATLITY IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE: A PROPENSITY-MATCHED MULTINATIONAL COHORT OF THE APASL ACLF RESEARCH CONSORTIUM (AARC)

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Background: Acute variceal bleeding (AVB) is associated with poor survival in patients with acute-on-chronic liver failure (ACLF), especially in regard to coagulation dysfunction and sepsis. We evaluated the predictors and outcomes of AVB in patients with ACLF in a propensity-matched multinational cohort of the APASL ACLF Research Consortium (AARC). **Methods:** We assessed the predictors of AVB within 90 days of presentation with AARC-ACLF. Then, the sites, risk factors and outcomes of AVB (ACLF-AVB) within 90 days of presentation were assessed as compared with a propensity score matched (PSM) cohort of ACLF matched for severity of liver disease (Age, gender, and baseline MELD) without AVB (ACLF without AVB). **Results:** Of the 3380 patients with ACLF (mean age 44.5 ± 11.9years, 83.8% men, 70.6% alcohol-associated ACLF, mean MELD-Na 34.7 ± 7.4), the mortality in ACLF-AVB ($n = 140$) [mean age—44.6 ± 11 years, 83.8% men, 63.1 % with alcohol-associated disease, AARC score: 10.5 ± 2.1, MELD -Na score: 35.5 ± 5.6] were worse as compared to those without AVB despite similar age, MELD-Na, and AARC score (66.7% vs 60.7%, P = 0.043). On multivariable binary logistic regression, predictors of AVB included Platelet count (aOR 0.994, 95%CI 0.992-0.997,P < 0.001) and sepsis in the first 7 days (aOR 1.2, 95%CI 1.1-2.1, P = 0.003). The long-term transplant-free mortality was compared in patients with and without AVB in a PSM cohort selected in a ratio of 1:2 ($n = 120$: 240) Despite propensity matching for age,gender, etiology and MELD-Na, ACLF patients with AVB had a higher 90-day mortality than those without AVB. (63.3% vs% and 43.8%, respectively ($P = 0.001$). On multivariable binary logistic regression, predictors of mortality were the AARC score at admission (aOR 1.13, 95%CI 1.06-1.22, P = 0.001), and presence of sepsis (aOR 1.1, 95% CI 1.1-1.3, P = 0.010).
Table1: Disease severity, site of bleeding, and outcomes in patients with ACLF and the subset with acute variceal bleeding in the total cohort and after propensity matching. **Conclusion:** Development of AVB confers poor outcomes in patients with ACLF with a high 90-day mortality. Presence of sepsis at baseline represents a potential risk factor for future AVB and mortality in ACLF.

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Table1 : Disease severity, site of bleeding, and outcomes in patients with ACLF and the subset with acute variceal bleeding in the total cohort and after propensity matching.

	Total AARC Cohort				Propensity-matched cohort			
Indicator	Total (n=3380)	No Acute variceal bleed (n=3239)	Acute variceal bleed (n=141)	P value	Total (n=360)	No Acute variceal bleed (n=240)	Acute variceal bleed (n=120)	P value
Sex (Male)	2832(83.8)	2714(83.8)	118(83.7)	0.974	354(98.3)	237(98.9)	117(97.5)	0.405
Etiology				0.009				0.267
Acute Alcohol	2387(70.6)	2298(70.9)	89(63.1))		234(65)	157(65.4)	77(64.2)	
HAV	57(1.7)	57(1.8)	0		4(1.1)	4(1.7)	-	
HBV	326(9.6)	307(9.5)	19(13.5)		45(12.5)	30(12.5)	15(12.5)	
HEV	174(5.1)	159(4.9)	15(10.6)		26(7.2)	14(5.8)	12(10)	
Another virus	67(2)	67(2.1)	0		6(1.7)	6(2.5)	-	
Autoimmune	81(2.4)	77(2.4)	4(2.8)		7(1.9)	3(1.3)	4(3.3)	
Drug Induced	131(3.9)	122(3.8)	9(6.4)		26(7.2)	18(7.5)	8(6.7)	
Wilson	7(0.2)	7(0.2)	0		-	-	-	
Other	150(4.4)	145(4.5)	5(3.5)		12(3.3)	8(3.3)	4(3.3)	
Unknown								
Chronic				0.451				0.186
Chronic Alcohol	2957(88)	2848(87.9)	127(90.1)		318(88.3)	206(85.8)	112(93.3	
HBV	267(7.9)	260(8)	7(5)		38(10.6)	31(12.9)	7(5.8)	
HCV	16(0.5)	16(0.5)	0		-	-	-	
Autoimmune	31(0.9)	29(0.9)	2(1.4)		-	-	-	
PBC	-	-	-		-	-	-	
PSC	-	-	-		-	-	-	
Wilson	12(0.4)	12(0.4)	0		-	-	-	
NASH	33(1)	31(1)	1		3(0.8)	2(0.8)	1(0.8)	
Cryptogenic	46(1.4)	42(1.3)	4(2.8)		-	-	-	
Variceal status				<0.001				<0.001
No varices, only PHG	54(1.6)	54	-		5(1.4)	5(2.1)	-	
Grade 1 varices	300(8.9)	296(9.1)	4(2.8)		29(8.1)	25(10.4)	4(3.3)	
Small varices, low risk Rcs-	268(7.9)	268(8.3)	0		11(3.1)	11(4.6)	-	
Small varices, high risk Rcs+	63(1.9)	60(1.9)	3(2.1)		7(1.9)	4(1.7)	3(2.5)	
Large high-risk varices (EVL done)	112(3.3)	2(0.1)	110(78)		93(25.8)	-	93(77.5)	
Gastric varix (glue done)	16(0.5)	-	16(11.3)		16(4.4)	0	16(13.3)	
PHG/coagulopathy-related bleed	69(2)	69(2.1)	-		9(2.5)	9(3.8)	0	
Endoscopy not done	2498(73.9)	2490(76.9)	8(5.7)		190(52.8	186(77.5)	4(3.3)	
No of organ failures				0.458				<0.001
1	122(5.3)	117(5.4)	5(4)		22(8)	18(10.8)	4(3.7)	
2	600(26.1)	562(25.8)	38(30.4)		73(26.6)	45(26.9)	28(26.6)	
3	914(39.7)	870(39.9	44(35.2)		122(44.5)	83(49.7)	39(36.4)	
4	519(22.5	492(22.6)	27(21.6)		45(16.4)	20(12)	25(23.4)	
5	136(5.9)	125(5.7)	11(8.8)		12(4.4)	1(0.6)	11(10.3)	
6	12(0.5)	12(0.6)	0		-	-	-	
Respiratory failure	73(2.1)	69(2.1)	4(1)	0.572	83(23.4)	39(16.5)	44(37)	<0.001
SIRS at baseline	458(50.8)	420(51.2)	38(46.3)	0.419	65(45.8)	32(47.8)	33(44)	0.736
Circulatory failure D0					250(95.8)	160(98.8)	90(90.9)	0.003
Renal failure D0					83(23.4)	39(16.5)	44(37)	0.001
Renal failure at D7	1333(40.6)	1284(40.8)	49(36)	0.269				
Coagulation failure at D7	1026(63.7)	972(63.7)	54(63.5)	0.975				
Cerebral fail at D7	79(2.3)	72(2.2)	7(1.6)	0.034	42(11.6)	21(8.7)	21(17.5)	0.004
Liver failure	1414(82)	1341(82)	73(81.1)	0.780	246(68.3)	147(61.3)	99(82.5)	0.001
Sepsis baseline	271(8)	244(7.5)	27(6.5)	0.001	250(95.8)	160(98.8)	90(90.9)	0.003
Sepsis at D7	341(10)	312(9.6)	29(7)	0.083				
New Sepsis	247(7.3)	225(7)	22(5.3)	0.001				
Liver transplant	239(7.1)	236(7.3)	3(2.1)	0.017	14(3.9)	12(5)	2(1.7)	0.155
Death	2061(61)	1967(60.7)	94(66.7)	0.186	181(50.3)	105(43.8)	76(63.3)	0.001

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4169 | TIMING MATTERS: DELAYED ANTIBIOTIC THERAPY INCREASES MORTALITY IN PATIENTS WITH ACLF. A SINGLE-CENTER RETROSPECTIVE STUDY

German Barrientos - Cabrera[1] Jacqueline Cordova Gallardo[2] Mercedes Elena Rodriguez - Garcia[1] Daniela Diaz De la Vega Broissin[3] Froylan David Martinez-Sanchez[1] Samantha Melanie Armendariz Pineda[1] Andres Manuel Vargas Beltran[1], [1]Hospital General Dr. Manuel Gea Gonzalez, [2]Hospital General Dr Manuel Gea González, [3]Hospital General Dr. Manuel Gea González

Background: Acute-on-chronic liver failure (ACLF) is a life-threatening clinical condition that occurs in patients with cirrhosis who develop acute decompensation, severe systemic inflammation and multiple organ failures. Bacterial infections are the most frequent precipitating factor for ACLF.

Current guidelines from the American Association for the Study of Liver Diseases (AASLD) recommend initiating antibiotic therapy in the emergency room; given the relationship between delayed treatment and increased mortality. However, these recommendations are based on expert opinion, as no prior studies have examined the relationship between antibiotic timing and mortality in ACLF. **Methods:** A retrospective study was conducted at a single hospital in Mexico City including adults diagnosed with ACLF between 2018 and 2024 to determine the association between delayed antibiotic therapy initiation and mortality in patients with ACLF. Data were collected from medical records. The primary outcome was in-hospital mortality. **Results:** A total of 178 patients were included, mean age was 55.2 $\pm$13.1 years, 63% were women. The overall mortality rate was 52%. The mean Meld 3.0 score among deceased patients was 19 $\pm$19.9. Alcoholic liver disease (ALD) was the most common etiology (47%), followed by metabolic dysfunction–associated steatotic liver disease (13%) and hepatitis C virus infection (6.5%). The most frequent types of infection were urinary tract infection (48%), pneumonia (25%) and spontaneous bacterial peritonitis (14%).

The identification of a multidrug-resistant pathogen as the etiology of the infection was associated with an OR of mortality of 11.12 (5.24–24.94; $p < 0.001$). Delayed antibiotic initiation was significantly associated with higher mortality. For every hour of delay, the OR of death increased (OR 1.014; 95% CI: 1.004–1.024; $p = 0.005$). Antibiotic initiation $\geq$12 hours and $\geq$ 24 hours

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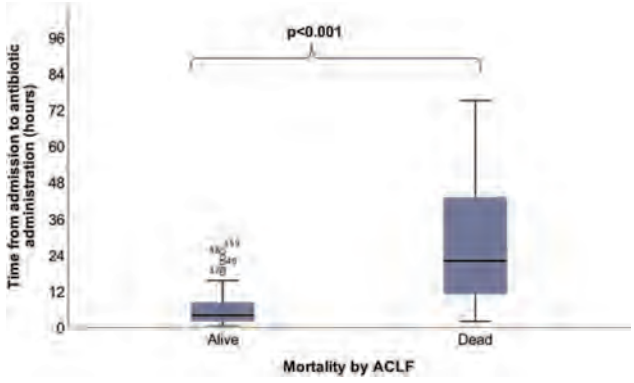
after admission were associated with ORs for mortality of 13.12 (6.38–26.94; $p < 0.001$) and 9.79 (4.08–23.15; $p < 0.001$), respectively.
When multivariate analysis was adjusted for age, sex, MELD 3.0 score, and ACLF grade, each hour of delay had an OR for mortality of 1.012 (1.001–1.024; $p = 0.03$). For delays of ≥ 12 hours and ≥ 24 hours, the ORs were 14.4 (5.52–37.5; $p < 0.001$) and 13.1 (3.63–47.5), respectively. **Conclusion:** Delayed initiation of antibiotic therapy is significantly associated with increased mortality in patients with ACLF.
This research represents the first study to directly evaluate one of the primary recommendations from current ACLF management guidelines regarding the importance of early antibiotic initiation. The present study provides evidence supporting the critical role of early antibiotic administration in patients with ACLF.



Disclosures: German Barrientos - Cabrera: Nothing to Disclose, Jacqueline Cordova Gallardo: Nothing to Disclose, Mercedes Elena Rodriguez - Garcia: Nothing to Disclose, Daniela Diaz De la Vega Broissin: Nothing to Disclose, Froylan David Martinez-Sanchez: Nothing to Disclose, Samantha Melanie Armendariz Pineda: Nothing to Disclose, Andres Manuel Vargas Beltran: Nothing to Disclose

4170 | ELEVATED FIBRIN DEGRADATION PRODUCT LEVEL PREDICT POOR OUTCOMES IN HEPATITIS B VIRUS-RELATED ACUTE-ON-CHRONIC LIVER FAILURE PATIENTS TREATED WITH ARTIFICIAL LIVER SUPPORT SYSTEM THERAPY

Xiaoqi Zhou[1] Xu Yang[1] Shiying Li[1], [1]The Second Affiliated Hospital of Chongqing Medical University

Background: Acute-on-chronic liver failure (ACLF) is a very severe clinical syndrome, often accompanied by systemic inflammation, coagulation dysfunction and fibrinolysis abnormalities. Fibrin degradation product (FDP) is a product of fibrinolysis, reflecting the state of fibrinolysis. Our aim is to explore the relationship between FDP levels and the 28-day mortality rate of patients with ACLF. **Methods:** We retrospectively enrolled 520 HBV-ACLF patients treated with artificial liver support system therapy and collected data prior to their first therapy. Restricted cubic splines (RCS) and COX regression were used to analyze the relationship between FDP and the 28-day mortality rate of HBV-ACLF patients, while receiver operating characteristic (ROC) curves were utilized to assess the predictive value of FDP. **Results:** Among the 520 eligible patients, the 28-day mortality rate was 20.2%. The FDP levels in surviving patients were significantly lower than those in deceased patients [6.15 (3.23-10.97) vs 16.98 (9.58-28.93), $P < 0.001$]. Multivariate Cox proportional hazards analysis, after adjusting for confounding factors, showed that FDP levels were significantly associated with an increased risk of 28-day mortality [HR = 1.014 (95% CI: 1.006–1.022), $P = 0.001$]. Patients with high FDP levels (≥ 11.1 μg/ml) had a significantly higher risk of death compared to those with low levels [HR = 3.114 (95% CI: 1.921-5.049), $P < 0.001$]. The restricted cubic spline (RCS) model further revealed a non-linear relationship between FDP and 28-day mortality. Among the prognostic scores, the COSSH ACLF score had the largest AUROC, comparable to FDP ($P = 0.891$), and the predictive performance of FDP was superior to that of FIB and D-dimer. Additionally, in patients who received three or more artificial liver support system therapy, the 28-day mortality risk was significantly reduced in those with high FDP levels. **Conclusion:** Elevated FDP levels are associated with the 28-day prognosis of HBV-ACLF patients, and multiple sessions of artificial liver treatment can significantly improve the prognosis of patients with high FDP levels (≥ 11.1 μg/ml).
Disclosures: Xiaoqi Zhou: Nothing to Disclose, Xu Yang: Nothing to Disclose, Shiying Li: Nothing to Disclose

4171 | ASK1 INHIBITOR SRT-015 REDUCES SYSTEMIC INFLAMMATION WHILE PROMOTING IMMUNE DEFENSE MECHANISMS IN PRECLINICAL IN VITRO AND IN VIVO MODELS RELATED TO ACLF

Vanessa Legry[1] Berta Romero-Grimaldo[2] Cristina López-Vicario[2] Bryan Contreras[2] María Belén Sánchez-Rodríguez[2] Alba Diaz[3] Carla Montironi[3] Richard Moreau[4] Dean Hum[5] Bart Staels[6] Sakina Sayah Jeanne[7] Joan Claria[8], [1]GENFIT SA, [2]Hospital Clinic-IDIBAPS, CIBEREHD, EF CLIF, Barcelona, Spain, [3]Hospital Clinic-IDIBAPS, CIBEREHD, Barcelona,

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Spain, [4]European Foundation for the Study of Chronic Liver Failure (EF CLIF), [5]GENFIT CORP, [6]University Lille 2, [7]Genfit, [8]Fundacio de Recerca Clinic Barcelona-IDIBAPS

Background: Acute-on-chronic liver failure (ACLF) is characterized by multiple organ failures and high short-term mortality. ACLF is closely associated with the presence of intense systemic inflammation, impaired immune defense responses against pathogens (i.e. decreased neutrophil degranulation and phagocytosis) and oxidative stress. Apoptosis-signal-regulating kinase 1 (ASK1) is a key mediator of the inflammatory response, activated by ROS produced after recognition of PAMPs. Its phosphorylation results in activation of JNK and p38 that regulate cell death and cytokine production. The aim of this study was to investigate the effects of SRT-015, a new investigational drug inhibiting ASK1, on systemic inflammation in a new model of ACLF (Flores-Costa, Hepatol Commun 2025) that recapitulates the human condition, as well as on human leukocyte functions *in vitro*. **Methods:** ACLF was induced by acute induction of polymicrobial peritonitis secondary to the ligation and puncture of the cecum (CLP) in mice with CCl_4-induced cirrhosis. CCl_4+CLP mice received oral SRT-015 (20 mg/kg) administrations 19h and 0.5h before CLP, and 20h after CLP, and samples were collected 24h post-CLP for analyses. Polymorphonuclear leukocytes (PMNs) isolated from healthy subjects were incubated with SRT-015 (2 and 10 μM) for 1.5-2h and degranulation and phagocytic capacities assessed by myeloperoxidase (MPO) release/activity and internalization of fluorescent-labeled *Escherichia coli,* respectively. The effects of SRT-015 on cytokine release were tested on mononuclear leukocytes. **Results:** CCl_4+CLP mice had elevated circulating cytokines and liver, kidney, brain, coagulation, circulation and respiratory impairments, as expected. SRT-015 administration to CCl_4+CLP mice significantly reduced circulating TNFα (25.7 vs. 70.4 pg/ml, $p = 0.02$), MCP-1 (224 vs. 921 pg/ml, $p = 0.04$), MIP-1β (147 vs. 183 pg/ml, $p = 0.02$), CXCL10 (233 vs 504 pg/ml, $p = 0.0005$) and IL-17 (3.18 vs. 5.94 pg/ml, $p = 0.03$) levels, compared to placebo. *In vitro* experiments confirmed the inhibitory effects of SRT-015 on cytokine release. While SRT-015 had no effect on MPO levels, it significantly increased PMN phagocytosis in a concentration-dependent manner. **Conclusion:** These data confirm the beneficial effect of SRT-015 on systemic inflammation in a preclinical model of ACLF and uncover its ability to improve anti-bacterial function. These results support the development of the investigational drug SRT-015 for the treatment of patients with ACLF.

Disclosures: Vanessa Legry: GENFIT SA: stock - privately held company, Berta Romero-Grimaldo: Nothing to Disclose, Cristina López-Vicario: Nothing to Disclose, Bryan Contreras: Nothing to Disclose, María Belén Sánchez-Rodríguez: Nothing to Disclose, Alba Diaz: Nothing to Disclose, Carla Montironi: Nothing to Disclose, Richard Moreau: Nothing to Disclose, Dean Hum: Nothing to Disclose, Bart Staels: Genfit SA: Consultant, Sakina Sayah Jeanne: Nothing to Disclose, Joan Claria: Nothing to Disclose

4172 | NONCANONICAL INFLAMMASOME-TRIGGERED PYROPTOSIS EXACERBATES COAGULOPATHY IN ACUTE-ON-CHRONIC LIVER FAILURE VIA RELEASING HISTONE H3 AND ENHANCING TISSUE FACTOR ACTIVITY

Xueyun Zhang[1] Qiankun Hu[2] yuxian huang[3], [1]Huashan Hospital Fudan University Department of Infectious D, [2]Shanghai public health clinical center, [3]Huashan Hospital, Fudan University

Background: Coagulation failure is one of the most key independent prognostic risk factors in acute-on-chronic liver failure (ACLF) patients. We aim to study the potential role of pyroptosis in coagulopathy and pathogenesis of ACLF. **Methods:** We examined the activation of inflammasome-pyroptosis pathway as well as coagulation-related indexes in ACLF patients and mice. Also, we investigated the effect of inflammatory caspase-GSDMD activation on coagulation and prognosis in ACLF mice using *Casp11* and *Gsdmd* knockout mice. We induced pyroptosis in the THP-1 cell line, and performed thrombin production assay with cell supernatant to explore the specific mechanism by which pyroptosis affects thrombin production. **Results:** Inflammatory caspase-4 were activated in the liver macrophage of HBV-ACLF patients, and the plasma LPS, IL-1β and IL-18 were also elevated, indicating that noncanonical inflammasome-pyroptosis axis was activated in HBV-ACLF patients. Noncanonical inflammasome activity positively correlated with coagulation disorder. To figure out the underlying mechnism we established a non-canonical pyroptosis model by electroporating LPS (2 μg/ml) into THP-1 cells, and found that the pyroptosis cell supernatant promoted thrombin production. The coagulation process is mediated by the tissue factor (TF)-activated coagulation cascade, and pyroptosis mediate coagulation disorders in mice by enhancing

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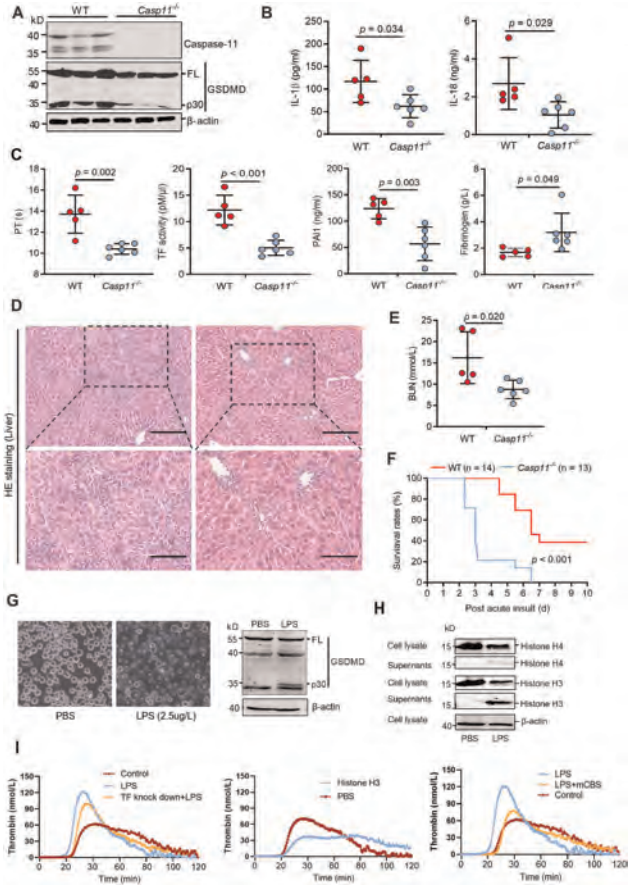
TF activity. However, blocking TF fails to fully restore the increased thrombin production induced by pyroptosis in our experiments, suggesting that pyroptosis may affect the coagulation system through other pathways. Histone is an important DAMP molecule released during cell death, and it is also an important way to activate the coagulation system in addition to the TF-coagulation cascade, and we speculate that pyroptosis may affect coagulation activation by releasing histones. Further experiments showed histone H3 was significantly elevated the supernatant of pyroptosis cells. Recombinant histone H3 directly promotes thrombin production, and neutralizing histone by mCBS leads to a significant decrease in pyroptosis-induced thrombin production. Knockout of *Casp11 and Gsdmd* in ACLF mice also reduced the serum histone H3 levels, mameliorated coagulation and renal injury, alleviated liver inflammation, and improved survival. **Conclusion:** Caspase 4/11-GSDMD participates in aggravating coagulation disorders in ACLF patients and mice by releasing histone H3 and increasing TF activity and thereby activating the coagulation system.



Disclosures: Xueyun Zhang: Nothing to Disclose, Qiankun Hu: Nothing to Disclose, yuxian huang: Nothing to Disclose

4173 | SINGLE-NUCLEUS TRANSCRIPTOMICS IDENTIFIES A CD44⁺ REGENERATIVE HEPATOCYTE SUBPOPULATION IN HEPATITIS B VIRUS-RELATED ACUTE-ON-CHRONIC LIVER FAILURE

Xiaohan Qian[1] Xiayao Li[1] Yangfan Shen[1] Diwenxin Zhou[1] Lingxiao Zhu[1] Keting He[1] Shangci Chen[1] Ke Zhou[1] Zhangya Pu[1] Zhongyang Xie[1], [1]The First Affiliated Hospital, Zhejiang University School of Medicine

Background: Acute-on-chronic liver failure (ACLF) arises from acute exacerbation of chronic liver diseases, and is characterized by multi-organ failure and high short-term mortality. Liver regeneration is a key determinant of clinical outcomes in patients with severe liver injury, yet remains poorly understood in ACLF. Besides, there is no definite therapy specifically targeting on it. Here, we use a single-nucleus RNA sequencing (snRNA-seq) approach to explore the heterogeneity of hepatocytes and cholangiocytes and to identify potential regenerative subsets in patients with hepatitis B virus (HBV)-related ACLF. **Methods:** We performed snRNA-seq on explanted liver tissues from five patients with HBV-ACLF who underwent liver transplantation at the First Affiliated Hospital of Zhejiang University between January 1 2023 and December 31 2024. Public snRNA-seq dataset of healthy human livers were integrated as controls using Harmony. Following quality control and normalization, hepatocytes and cholangiocytes were extracted and re-clustered. Pathway enrichment was assessed using AddModuleScore, developmental trajectories were inferred by Monocle, and intercellular communication was analyzed by CellChat. **Results:** After analyzing 47,822 hepatocytes and cholangiocytes, we identified 7 hepatocyte and 3 cholangiocyte subpopulations. Compared to healthy controls, HBV-ACLF livers exhibited a marked depletion of hepatocytes but a significant expansion of cholangiocytes. Notably, we identified an ACLF-specific hepatocyte subpopulation (Hep_CD44), present in all ACLF samples, characterized by high expression of CD44, KRT23, and other progenitor-associated genes, suggesting a regenerative phenotype. This subset was enriched for pathways related to cell migration and PI3K-Akt signaling. In a trajectory analysis, Hep_CD44 cells located at the branch between mature hepatocytes and cholangiocytes, indicating bipotent lineage potential. Cell-cell interaction analysis revealed enhanced interactions between CD44 + hepatocytes and liver endothelial cells via the LIF-LIFR axis. **Conclusion:** We identified a CD44⁺ hepatocyte subset with progenitor-like features that expands in HBV-ACLF livers. The regenerative hepatocyte

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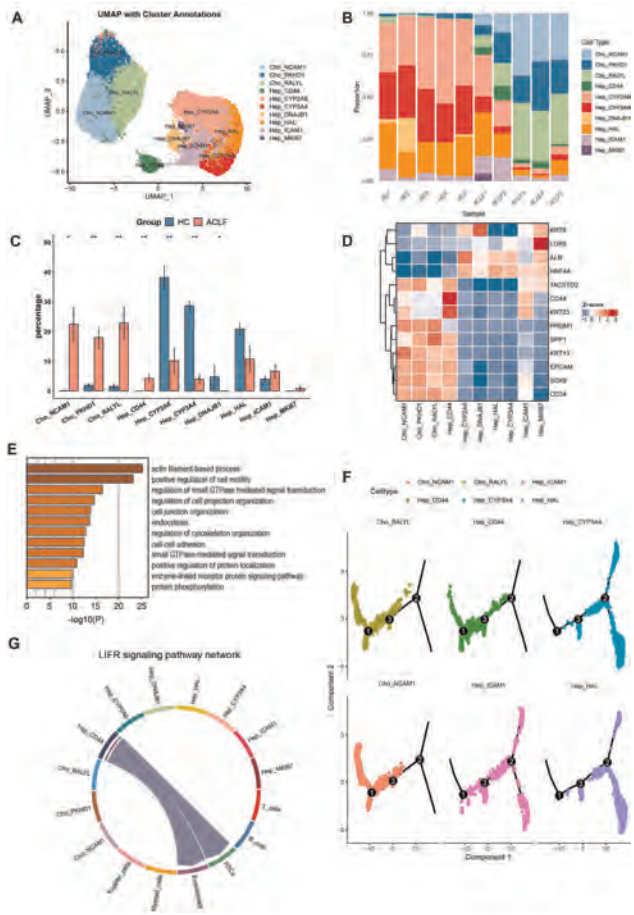
subset represents a promising target for hepatocyte-based cell therapies in ACLF.



Disclosures: Xiaohan Qian: Nothing to Disclose, Xiayao Li: Nothing to Disclose, Yangfan Shen: Nothing to Disclose, Diwenxin Zhou: Nothing to Disclose, Lingxiao Zhu: Nothing to Disclose, Keting He: Nothing to Disclose, Shangci Chen: Nothing to Disclose, Ke Zhou: Nothing to Disclose, Zhangya Pu: Nothing to Disclose, Zhongyang Xie: Nothing to Disclose

4174 | EVALUATION OF THE VALIDITY AND RELIABILITY OF THE GLIM CRITERIA IN DIAGNOSING MALNUTRITION AMONG OUTPATIENTS WITH LIVER CIRRHOSIS

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Background: Liver cirrhosis is a global health issue and a leading cause of mortality. Its clinical progression often leads to malnutrition; a factor associated with morbidity and mortality. However, diagnosing malnutrition is challenging due to the disease's complications. The Global Leadership Initiative on Malnutrition (GLIM) criteria have been proposed for nutritional assessment, yet evidence their validity is limited. This study aimed to evaluate the validity and reliability of the GLIM criteria for diagnosing malnutrition in adult outpatients with liver cirrhosis. **Methods:** This cross-sectional study included 71 outpatients with liver cirrhosis recruited in Mexico City. Clinical, biochemical, and anthropometric parameters were recorded alongside the Child-Pugh and MELD scores. Malnutrition according to GLIM criteria was defined by the presence of at least one phenotypic criterion (weight loss $>5\%$ within 6 months or $>10\%$ beyond 6 months; BMI <20 kg/m² for patients <70 years or <22 kg/m² for ≥ 70 years; or reduced muscle mass assessed via skeletal muscle index [SMI] using CT) and one etiologic criterion (reduced energy intake $<50\%$ of requirements for ≥ 1 week, or inflammation indicated by a neutrophil-lymphocyte ratio >5). The Subjective Global Assessment (SGA) was used as the reference standard to evaluate validity, calculating sensitivity, specificity, PPV, NPV and AUC. Reliability was assessed using Kappa for inter-observer agreement and Cronbach's α for internal consistency. **Results:** Among the 71 patients, 26 had compensated cirrhosis, and 45 had decompensated cirrhosis. The prevalence of malnutrition was 45.1% according to SGA and 38.0% by GLIM criteria. Patients with malnutrition showed lower mid-arm circumference ($p<0.001$), calf circumference ($p<0.001$), BMI ($p<0.001$), and SMI ($p=0.002$), as well as greater weight loss over the past 6 months ($p=0.016$) and beyond 6 months ($p=0.006$). The GLIM criteria limited diagnostic validity (0.53 sensitivity, 0.74 specificity, 0.63 PPV, 0.65 NPV, 0.66 AUC) and good inter-observer agreement (0.669 Kappa). However, internal consistency was low (0.189 Cronbach's α). **Conclusion:** The GLIM criteria showed limited validity and internal consistency for diagnosing malnutrition in outpatients with liver cirrhosis, despite acceptable inter-observer agreement. Further studies with larger populations are warranted to refine items, cutoff points, and validate these criteria in this clinical setting.

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Table 1. Demographic and clinical characteristics

		N= 71	GGS			GLIM criteria		
			Well-nourished 39 (54.9%)	Malnourished 32 (45.1%)	p (<0.05)	Well-nourished 44 (62.0%)	Malnourished 27 (38%)	p (<0.05)
Sex	Male	34 (47.9%)	17 (43.6%)	17 (53.1%)	0.424[1]	21 (47.7%)	13 (48.1%)	0.973[1]
	Female	37 (52.1%)	22 (56.4%)	15 (46.9%)		23 (52.3%)	14 (51.9%)	
Age (years)		60 (50.5, 67.5)	56 (49.5, 65.5)	63 (54.2, 69.2)	0.094[2]	60.5 (50.5, 67.2)	58.0 (51.0, 67.0)	0.929[2]
Etiology	MASLD	18 (25.4%)	12 (30.8%)	6 (18.8%)	0.070[3]	9 (20.5%)	9 (33.3%)	0.713[3]
	Alcohol	14 (19.7%)	7 (17.9%)	7 (21.9%)		10 (22.7%)	4 (14.8%)	
	Autoimmune	13 (18.3%)	10 (25.6%)	3 (9.4%)		9 (20.5%)	4 (14.8%)	
	HCV	7 (9.9%)	1 (2.6%)	6 (18.8%)		5 (11.4%)	2 (7.4%)	
	Others	19 (26.8%)	9 (23.1%)	10 (31.3%)		11 (25.0%)	8 (29.6%)	
State	Compensated	26 (36.6%)	15 (38.5%)	11 (34.4%)	0.722[3]	20 (45.5%)	6 (22.2%)	0.049[3]
	Decompensated	45 (63.4%)	24 (61.5%)	21 (65.6%)		24 (54.5%)	21 (77.8%)	
MELD-Na		12 (9.0, 15.0)	12 (9.0, 14.0)	12 (9, 16)	0.684[2]	12.5 (9.0, 15.0)	12.0 (9.5, 15.5)	0.540[2]
MELD 3.0		13 (10.0, 17.0)	13 (10.0, 15.0)	14 (12, 17)	0.157[2]	13.0 (9.7, 15.0)	15 (12.5, 17.0)	0.069[2]
Mid-arm (cm)		27.6 (25.2, 30.4)	30.3 (27.6, 31.1)	25.1 (23.3, 26.8)	<0.001[2]	27.9 (25.6, 30.4)	26.2 (24.2, 30.4)	0.477[2]
Calf (cm)		36.2 (31.7, 37.8)	37.4 (35.1, 38.8)	32.2 (30.7, 34.8)	<0.001[2]	35.9 (31.9, 37.6)	34.6 (31.5 (37.6)	0.546[2]
IMC (Kg/m^2)		25.8 (22.3, 29.3)	28.9 (26.3, 30.6)	21.8 (19.4, 23.3)	<0.001[2]	26.3 (23.4, 29.7)	23.4 (21.6, 27.7)	0.150[2]
SMI (cm^2/m^2)		39.05 ± 8.2)	38.6 ± 8.7	32.7 ± 6.5	0.002[2]	37.0 ± 8.97	34.4 ± 8.09	0.210[2]
6-month weight loss (%)		2.9 (0.0, 8.4)	0.9 (0.0, 6.1)	6.7 (3.6, 10.3)	0.016[2]	0.67 (0.0, 7.3)	6.4 (3.6, 9.2)	0.054[2]
More than 6-month weight loss (%)		11.09 (3.8, 22.7)	8.5 (1.3, 14.3)	20.0 (7.3, 28.2)	0.006[2]	10.7 (5.0, 22.3)	12.9 (0.3, 23.2)	0.927[2]
Reduced food intake (%)		12 (16.9%)	4 (10.3%)	8 (25.0%)	0.121[3]	0.0	12 (44.4%)	<0.001[3]
Inflammation (%)		12 (16.9%)	5 (12.8%)	7 (21.9%)	0.311[3]	1 (2.3%)	11 (40.7%)	<0.001[3]

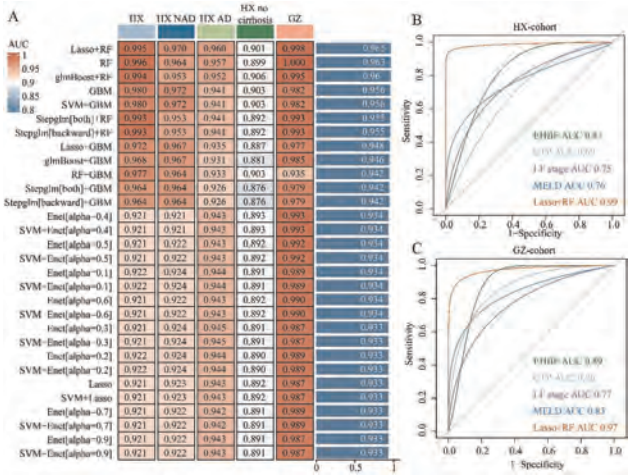
Statistical analysis with: [1] de Student; [2] de Mann-Whitney; [3] χ^2 y [4] prueba exacta de Fisher.

Disclosures: Araceli López Nepomuceno: Nothing to Disclose, Alondra Rosales Padrón: Nothing to Disclose, MARTÍN PACHECO SERRANO: Nothing to Disclose, Fatima Manzo Santana: Nothing to Disclose, Tania del Socorro Grimaldo Galeana: Nothing to Disclose, Ignacio Garcia-uarez: Nothing to Disclose, Jorge Hernández Calleros: Nothing to Disclose, María Luisa Peralta-Pedrero: Nothing to Disclose, Lucía Méndez Sánchez: Nothing to Disclose

4175 | USING MACHINE LEARNING TO ACCURATELY PREDICT THE 90 DAY PROGNOSIS OF ACUTE-ON-CHRONIC LIVER FAILURE BASED ON LIVER RESERVE FUNCTION AND CLINICAL FEATURES

Xia Zhu[1] Hong Tang[1] Yuanji Ma[1] Libo Yan[1] Jianhao Li[1] Ming Wang[1], [1]West China Hospital of Sichuan University

Background: Acute-on-chronic liver failure (ACLF) presents a substantial risk of short-term mortality, emphasizing the critical need for early and accurate prognosis to enhance patient care. Research has shown that liver reserve function is a key determinant of patient outcomes. This research utilizes advanced machine learning techniques to combine liver reserve parameters with clinical data, with the goal of creating a more precise prognostic model for ACLF. **Methods:** We retrospectively collected baseline demographics, clinical features, laboratory results, and 90-day survival follow-up data from 497 HBV-ACLF patients (HX cohort) and 52 patients (GZ cohort). Differential analysis and univariate logistic regression were used to pinpoint potential factors influencing prognosis in HBV-ACLF. A total of 12 machine learning algorithms were systematically tested to establish the most effective prognostic model, and ROC curve analyses were performed to evaluate predictive accuracy. The XGBoost algorithm was applied to identify critical clinical factors impacting HBV-ACLF prognosis, and an interactive web tool was developed using the Shiny R package to enhance usability in clinical practice. **Results:** We initially screened 21 potential clinical risk factors for predicting ACLF prognosis. Subsequently, using the LASSO-RF model, 15 key variables were selected for model construction: effective hepatic blood flow (EHBF), liver failure (LF) stage, Model for End-Stage Liver Disease (MELD) score, indocyanine green retention rate at 15 minutes (ICG-R15), age, hepatic encephalopathy (HE) stage, ascites score, hepatorenal syndrome (HRS), absolute neutrophil count, total bilirubin (TBIL), international normalized ratio (INR), prothrombin activity (PTA), sodium (Na), ammonia (NH3), and Child-Turcotte-Pugh (CTP) score. The final LASSO-RF model achieved an AUC of 0.99 in the training cohort and 0.98 in the validation cohort for predicting 90-day survival, outperforming conventional scoring systems such as MELD and CTP. To facilitate clinical application, an online tool (https://syx123.shinyapps.io/deploy_shiny/) was developed to provide real-time risk scores and 90-day survival predictions for individual patients. **Conclusion:** Liver reserve function indicators, especially EHBF and ICG-R15, are crucial for predicting 90-day survival in HBV-ACLF. Combining liver reserve assessment with clinical parameters via machine learning enables more accurate and individualized prognostic evaluation, supporting optimized clinical management.



Disclosures: Xia Zhu: Nothing to Disclose, Hong Tang: Nothing to Disclose, Yuanji Ma: Nothing to Disclose, Libo Yan: Nothing to Disclose, Jianhao Li: Nothing to Disclose, Ming Wang: Nothing to Disclose

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4176 | COMBINATION OF MELD SCORE WITH NEUTROPHIL-TO-LYMPHOCYTE RATIO PREDICTS IN-HOSPITAL MORTALITY IN ACUTE-ON-CHRONIC LIVER FAILURE

Vasilis Papastergiou[1] Panagiotis Kanellopoulos[1] Dimitra Kozompoli[1] Konstantinos Mousourakis[1] Georgios Kalogiros[1] Dimitra Provi[1] Vasilis Karampatsos[1] Konstantinos Fiagkousakis[1] Alexandra Agorogianni[1] Maria Mela[1] Nikos Viazis[2], [1]Evangelismos General Hospital, [2]Gastroenterology Department, Evangelismos Hospital

Background: Introduction: Prediction of early mortality is crucial in patients with Acute on Chronic Liver Failure (ACLF), a highly fatal syndrome characterized by intense systemic inflammation and organ failure. Performance of the Model of End-stage Liver Disease (MELD) appears to be suboptimal in ACLF, although the prognostic potential of combining MELD with inflammatory indexes remains uncertain.
Aims: To evaluate a combination of MELD with neutrophil-to-lymphocyte ratio (NLR) for in-hospital mortality prediction in patients with ACLF. **Methods:** Retrospective cohort study evaluating consecutive ACLF patients followed till hospital discharge. The predictive ability and optimal cut-points of MELD and NLR calculated on admission were determined by ROC analyses. Four prognostic groups, determined by score combinations below or above the optimal cut-points, were analyzed with respect to in-hospital mortality. **Results:** A total of 122 patients (50.8% males, mean age 61.8 ± 12.1) were hospitalized with ACLF between April 2021 and February 2023. The etiology of pre-existing liver disease was alcoholic in 44.3% and in-hospital mortality was 31.1%. The areas under ROC were 0.79 for MELD and 0.68 for NLR, with optimal cut-off points 20 (sensitivity/specificity: 0.89/0.57) and 5.1 (sensitivity/specificity: 0.84/0.60), respectively. Compared to patients with low MELD and NLR scores, patients with high scores displayed significantly higher in-hospital mortality (73.7% vs 6.7%; adjusted OR = 13.96, $p = 0.007$), whereas those with a single elevated score did not (high-MELD/low-NLR: 15.4%; adjusted OR = 1.98, $p = 0.49$; low-MELD/high NLR: 14.2%; adjusted OR = 1.30, $p = 0.79$). **Conclusion:** In patients hospitalized with ACLF, a combination of high baseline MELD and NLR appears to delineate poor prognosis, correlating with a high risk of in-hospital death.

Disclosures: Vasilis Papastergiou: Nothing to Disclose, Panagiotis Kanellopoulos: Nothing to Disclose, Dimitra Kozompoli: ABBVIE: Independent Contractor, Konstantinos Mousourakis: Nothing to Disclose, Georgios Kalogiros: Nothing to Disclose, Dimitra Provi: Nothing to Disclose, Vasilis Karampatsos: Nothing to Disclose, Konstantinos Fiagkousakis: Nothing to Disclose, Alexandra Agorogianni: Nothing to Disclose, Maria Mela: Nothing to Disclose, Nikos Viazis: Nothing to Disclose

4177 | IMPACT OF FRAILTY AND OBESITY ON HOSPITAL LENGTH OF STAY AFTER LIVER TRANSPLANTATION

Ahmed Aboseria[1] Jade Pace[1] Michael Attanasi[1] Justin Lin[1] Anwesha Satapathy[1] William Han[1] Bheesham Dayal[1] Sanjaya Satapathy[1], [1]Northwell Health

Background: Frailty and obesity are independent predictors of adverse outcomes after liver transplantation (LT), but their combined impact on hospital length of stay (LOS) remains understudied. **Methods:** We analyzed data from 227 adult LT recipients categorized into four frailty-obesity phenotypes: Frail-Obese, Frail-NonObese, NonFrail-Obese, and NonFrail-NonObese. Total LOS was compared across groups using generalized linear modeling (GLM) and survival analysis with the Kaplan-Meier method and log-rank tests. Covariates included age at transplant, sex, and BMI. Interactions between frailty-obesity group and sex were also examined. **Results:** The study cohort ($n = 227$) was predominantly male (66%), with 32% of patients classified as obese and 43% as frail. Mean hospital length of stay (LOS) varied significantly among the frailty-obesity groups ($p = 0.0041$); the Frail-Obese group experienced the longest mean LOS (31.7 ± 14.2 days), while the NonFrail-Obese group had the shortest (21.3 ± 11.7 days). In adjusted generalized linear modeling, both Frail-Obese ($\beta = 10.76$, $p = 0.0024$) and Frail-NonObese ($\beta = 8.61$, $p = 0.0020$) patients had significantly longer LOS compared to the NonFrail-Obese group. The Liver Frailty Index showed a positive association with LOS ($\beta = 4.25$, $p < 0.0001$), whereas age at transplant was inversely associated with LOS ($\beta = -0.19$, $p = 0.0285$). No significant interaction was found between the frailty-obesity group and sex. Kaplan-Meier curves further demonstrated a clear separation in LOS by group (log-rank $p = 0.0087$). **Conclusion:** Frailty is a key determinant of prolonged hospital LOS post-LT, regardless of obesity status. Non-frail obese patients had the shortest stays, suggesting potential protective effects of obesity in non-frail individuals. Pre-transplant frailty screening may improve post-transplant planning and recovery.

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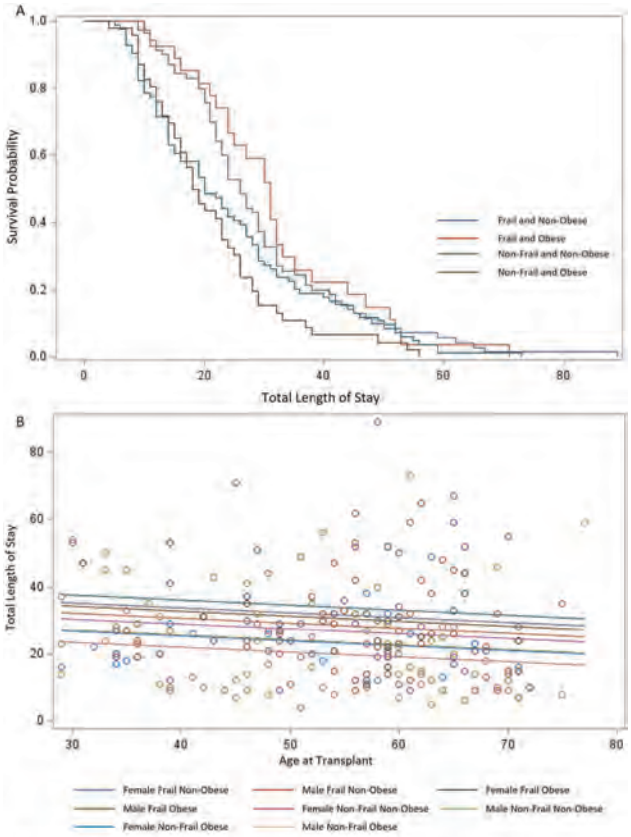

Figure 1. ***A)*** *Kaplan-Meier survival curves for total hospital length of stay by frailty-obesity group.* Frail-Obese and Frail-NonObese groups had significantly longer stays than NonFrail groups (log-rank p = 0.0087).

B) *Analysis of covariance plot showing TotalLOS vs. Age at Transplant, stratified by frailty-obesity group and sex.* LOS generally decreased with increasing age, and frailty-obesity subgroups showed distinct trajectories. No consistent sex-based difference was observed.

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4178 | TRANSCRIPTION AND TRANSLATION OF HUMAN ENDOGENOUS RETROVIRUS (HERV)-DERIVED ELEMENTS DEFINES POST-TRANSPLANT ALLOIMMUNE HEPATITIS

Kumar Subramanian[1] Nada Yazigi[1] Khalid Khan[1] Carolina Rumbo[1] Gabriel Gondolesi[1] Alexander Kroemer[1] Thomas Fishbein[1] Udeme Ekong[1], [1]Medstar Georgetown Transplant Institute, Medstar Georgetown University Hospital, 3800 Reservoir Rd,

Background: HERVs are inherited genetic germline elements derived from exogenous retroviral infections throughout the evolution of the human genome. Epigenetic mechanisms serve to transcriptionally silence HERV-derived elements through DNA methylation and/or repressive histone modifications. We and others have reported HERV reactivation and elevated HERV expression in a variety of autoimmune disorders, including post-transplant alloimmune hepatitis and autoimmune hepatitis (AIH). We sought to determine, using an independent patient cohort, if upregulation of HERV transcripts and protein in liver tissue, and HERV antigenemia in plasma, represent linked molecular signatures of post-transplant alloimmune hepatitis, and potential biomarkers for early detection of disease risk. **Methods:** Using an independent cohort for validation, we assessed HERV-T levels by qRT-PCR and Western Blot in livers with post-transplant alloimmune hepatitis and AIH ($n = 3$) and normal livers procured and subsequently transplanted in recipients ($n = 15$). Circulating HERV1-env transcript and protein was measured in plasma by qRT-PCR and ELISA in liver transplanted children with: post-transplant alloimmune hepatitis ($n = 8$), acute rejection (AR) ($n = 13$), normal graft function (LTC) ($n = 41$); and in non-transplanted children with: AIH ($n = 14$), and healthy children (HC, $n = 30$). Statistical analyses were performed using GraphPad Prism. Mann Whitney test was used for non-parametric measurements. **Results:** ***HERV-T*** was upregulated in livers with alloimmune and AIH ($p = 0.02$). Of the 15 normal livers that were procured and subsequently transplanted, ***HERV-T*** upregulation was present in three. Elevated ***HERV1*** transcript and antigenemia were seen in the plasma of children with alloimmune and AIH ($p = 0.01$; $p = 0.001$, respectively). Two children with normal graft function also had HERV1 antigenemia. None of the transplanted children are on DNA-demethylating therapy, neither were the deceased donors of

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the procured livers. These **Results:** from a validation cohort confirm our previous published observation of HERV reactivation in post-transplant alloimmune hepatitis. **Conclusion:** Our results confirm enhanced transcription and translation of HERVs in children with alloimmune hepatitis. Understanding T cell recognition of HERVs in patients with alloimmune hepatitis and autoimmune hepatitis could lead to improved future immunotherapeutic strategies.

Disclosures: Kumar Subramanian: Nothing to Disclose, Nada Yazigi: Nothing to Disclose, Khalid Khan: Nothing to Disclose, Carolina Rumbo: Nothing to Disclose, Gabriel Gondolesi: Nothing to Disclose, Alexander Kroemer: Nothing to Disclose, Thomas Fishbein: Nothing to Disclose, Udeme Ekong: Nothing to Disclose

4179 | LIVER CIRRHOSIS IS ASSOCIATED WITH INCREASED PREVALENCE OF INTESTINAL POLYPS IN RHEUMATOID ARTHRITIS: A RETROSPECTIVE ANALYSIS

Anwar Uddin[1] Madia Ahad[1] Narinderjeet Kaur[1] Selome Yewedalsew[1] Savanna Thor[1], [1]Suny Downstate Medical center

Background: Rheumatoid arthritis (RA) and liver cirrhosis (LC) are chronic systemic diseases that independently increase the risk of gastrointestinal (GI) complications, including bleeding, ulcers, bacterial overgrowth, portal hypertensive enteropathy, and increased malignancy risk. In RA, GI injury may result from chronic inflammation, NSAID use, and immunosuppressive therapy. LC contributes through portal hypertension and immune dysfunction, leading to varices, intestinal edema, and mucosal changes. Intestinal polyps, frequently found on colonoscopy and known precursors to colorectal cancer, may be more common in this high-risk population. However, their prevalence and clinical predictors have not been studied in patients with both RA and LC. This study aims to evaluate the national prevalence and predictors of intestinal polyp diagnosis among hospitalized RA patients, comparing those with and without LC. **Methods:** We performed a retrospective cross-sectional analysis using the 2016–2020 HCUP Nationwide Inpatient Sample (NIS). Adult hospitalizations with RA were identified via ICD-10-CM codes and stratified by the presence of LC. Intestinal polyps were identified using ICD-10-CM codes. Survey-weighted multivariable logistic regression assessed the independent association between LC and polyp detection, adjusting for age, sex, race, insurance, CCI, hospital bed size, region, and teaching status. **Results:** Total of 2,734,274 RA-related hospitalizations, 63,325 (2.3%) had LC. Intestinal polyps were more prevalent in RA patients with LC than without (1.3% vs. 0.6%). LC was independently associated with higher odds of polyp diagnosis (adjusted OR 2.35, 95% CI 1.99–2.78, $p < 0.001$). Among RA patients with LC, increased odds were linked to older age (OR 1.02/year, 95% CI 1.01–1.02, $p < 0.001$), male gender (female OR 0.84, 95% CI 0.78–0.91, $p < 0.001$), Black race (OR 1.27, 95% CI 1.14–1.40, $p < 0.001$), and Hispanic ethnicity (OR 1.15, 95% CI 1.01–1.31, $p = 0.036$). Private insurance was associated with higher odds (OR 1.13, 95% CI 1.02–1.25, $p = 0.020$), while Medicaid and other non-Medicare payers had lower odds. Medium (OR 1.12, 95% CI 1.01–1.24, $p = 0.034$) and large hospitals (OR 1.10, 95% CI 1.00–1.21, $p = 0.050$) had higher detection rates than small hospitals; urban non-teaching hospitals showed lower odds (OR 0.69, 95% CI 0.60–0.80, $p < 0.001$). **Conclusion:** RA patients with liver cirrhosis are more than twice as likely to be diagnosed with intestinal polyps compared to those without cirrhosis. Male patients and those of Black or Hispanic race were at particularly elevated risk. Although RA patients with liver cirrhosis had more than twice the odds of being diagnosed with intestinal polyps, the absolute prevalence remained low at 1.3%, compared to 0.6% in those without cirrhosis. This suggests that while the relative risk is increased, the overall likelihood of polyp detection is still low.

Disclosures: Anwar Uddin: Nothing to Disclose, Madia Ahad: Nothing to Disclose, Narinderjeet Kaur: Nothing to Disclose, Selome Yewedalsew: Nothing to Disclose, Savanna Thor: Nothing to Disclose

4180 | TARGETING STRESS INDUCIBLE HSP90 REDUCES EXTRACELLULAR MATRIX AND AMELIORATES LIVER FIBROSIS

Vidyasagar Naik Bukke[1] Jeevitha Thanikasalam[2] Alan Mullen[2] Pranoti Mandrekar[2], [1]Umass Chan Medical School, [2]University of Massachusetts Medical School

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Background: Hepatic fibrosis is characterized by excessive accumulation of the extracellular matrix that occurs during most types of chronic liver diseases. Oxidative stress induced heat shock proteins (HSPs) maintain cellular proteostasis by acting as chaperones and promoting cell survival. Our previous studies show that HSP90AA1, a stress inducible chaperone, is increased in alcohol associated cirrhosis and in murine liver fibrosis. We hypothesize that HSP90AA1 plays an important role in hepatic stellate cell activation and contributes to fibrosis. **Methods:** C57BL/6 mice were injected i.p. with 0.5 μl/g BW CCl4 for 6 weeks. 17-DMAG, specific HSP90AA1 inhibitor, was administered i.p. at 5.0 mg/kg twice a week for the last 4 weeks (preventive regimen) or 50 mg/kg BW twice during the last week (treatment regimen). Serum ALT, pro-inflammatory, pro-fibrotic cytokines were measured. Effect of 17-DMAG on hepatic stellate cell activation was assessed using human primary hepatic stellate cells and stellate cell line LX-2 cells. **Results:** Stress-inducible HSP90AA1 but not HSP90AB1 is elevated in human cirrhotic livers and murine fibrotic livers induced by CCl4.17-DMAG administration in preventive and treatment regimens reduced serum ALT ($p < 0.01$), αSMA at mRNA and protein levels as well as Col1A1 mRNA levels, confirmed by Sirius red staining. Bioavailability of HSP90AA1 inhibition in vivo was confirmed by HSP70 expression. HSP90 inhibition reduced pro-fibrotic genes HSP47 and TIMP1, pro-inflammatory cytokine IL-1β and monocyte markers CD11b and Ly6C after 17-DMAG administration. Moreover, HSP90 inhibition induced GATA4, a marker of inactive quiescent like HSCs. 17-DMAG administration significantly reduced glycolytic genes such as HK2, PKM2 in liver fibrosis. The effect of HSP90AA1 inhibition on HSC activation was investigated in vitro using human primary hepatic stellate cells and LX-2 cell line. 17-DMAG treatment reduced its TGFβ mediated Col1A1 expression in both primary and LX-2 stellate cells. To understand whether HSP70 induction contributes to decreased Col1A1 expression, we transfectedHSP70 siRNA in LX-2 cells. and found that the inhibition of HSP70 did not affect 17-DMAG mediated reduction in Col1A1 expression, emphasizing a direct role for HSP90AA1 in stellate cell activation. **Conclusion:** HSP90AA1 plays an important role in hepatic stellate cell activation and pro-fibrogenic responses suggesting its potential as a therapeutic target in liver fibrosis.

Disclosures: Vidyasagar Naik Bukke: Nothing to Disclose, Jeevitha Thanikasalam: Nothing to Disclose, Alan Mullen: Nothing to Disclose, Pranoti Mandrekar: Nothing to Disclose

4181 | REAL-WORLD DATA ON ACUTE-ON-CHRONIC LIVER FAILURE: IMPLICATIONS FOR CLINICAL MANAGEMENT AND POLICY

Hidehiro Kamezaki[1] Arisa Kato[2] Takaaki Ikegami[2] Nana Yamada[2] Terunao Iwanaga[2] Takafumi Sakuma[2] Koji Takahashi[2] Junichi Senoo[2], [1]Department of Gastroenterology, Eastern Chiba Medical Center, [2]Eastern Chiba Medical Center

Background: Acute-on-chronic liver failure (ACLF) is a rapid decline in liver function in patients with chronic liver disease, causing high morbidity and mortality. We aimed to evaluate real-world data on the incidence, characteristics, outcomes, and prognostic factors of ACLF. **Methods:** We retrospectively analyzed 363 patients with cirrhosis hospitalized between April 2014 and December 2022. Data on demographics, clinical characteristics, treatments, and outcomes were collected. ACLF was diagnosed based on the following criteria in Japan: patients with cirrhosis (Child-Pugh score of 5–9) who develop severe liver dysfunction within 28 days due to triggers such as alcohol consumption, infections, gastrointestinal bleeding, or exacerbation of the primary disease. The two ACLF categories were confirmed ACLF (prothrombin time-international normalized ratio (PT-INR) ≧1.5 or PT≦40%, and total bilirubin (T-Bil) ≧5.0 mg/dL) and extended ACLF (PT-INR≧1.5, PT≦40%, or T-Bil≧5.0 mg/dL). Statistical analyses included descriptive statistics, logistic regression, and sensitivity analysis. **Results:** Among the 363 patients (mean age, 64.4 years), 10 (2.8%) had confirmed ACLF, and 30 (8.3%) had extended ACLF. Exacerbating factors included gastrointestinal bleeding in 17 (42.5%), alcohol consumption in 15 (37.5%), and infections in 13 (32.5%) with some overlap. The mean Model for End-Stage Liver Disease Sodium (MELD-Na) score was 20.7. The 90-day and 5-year cumulative survival rates were 69.5% and 40.9%, respectively. Older age ($\geq$66 years) and a higher MELD-Na score ($\geq$21) predicted poor outcomes(P values for multivariate analysis were <0.01 and 0.01, respectively). **Conclusion:** ACLF in hospitalized patients with cirrhosis has high incidence and mortality rates. Age, MELD-Na score, gastrointestinal bleeding, alcohol use, and infection were key factors. These findings highlight the need for early risk identification and effective management.

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4182 | PROGNOSTIC MODELS AND INFECTION-RELATED MORTALITY IN ACLF: A PROSPECTIVE MEXICAN COHORT STUDY

Emilio Sandoval-Gonzalez[1] Francisco Bosques-Padilla[2] Miguel Escobedo-Belloc[3] Jorge Zuñiga-Hernandez[3] Hannia Zumaya-Flores[4] Wendy Ruiz-Gallegos[4] Lilia Chavez-García[4] Leonel Castillo-Peña[4] Andres Zapata-Navarro[4], [1]Hospital Universitario Dr. Jose Eleuterio Gonzalez Universidad Autónoma de Nuevo León,Mx, [2]Hospital Universitario Dr. José Eleuterio González, Universidad Autónoma de Nuevo León, Mx, [3]Hospital Universitario Dr. José Eleuterio González, Universidad Autónoma de Nuevo León, Monterrey,Mx, [4]Facultad de Medicina, Universidad Autónoma de Nuevo León, Monterrey, Mexico

Background: Acute-on-chronic liver failure (ACLF) is characterized by acute decompensation (AD), systemic inflammation, and multi-organ failure, associated with high short-term mortality. Although several prognostic models exist, their comparative performance and stage-based utility remain underexplored in Latin American populations. **Methods:** A prospective cohort of 140 adults with AD cirrhosis admitted to an academic referral hospital in Mexico was evaluated. Baseline clinical and laboratory data, including liver severity scores, were collected at admission. ACLF was defined and graded according to AASLD–EASL criteria using the CLIF-C OF score. All patients were assessed using Child-Pugh, MELD, MELD-Na, and MELD-Lactate. In patients meeting ACLF criteria (n = 55), CLIF-C ACLF and AARC scores were additionally applied. The primary outcome was in-hospital mortality. Predictive performance was assessed via ROC analysis; logistic regression identified clinical precipitants. **Results:** The cohort had a mean age of 54.8 ± 10.4 years, with 77.1% male. Alcohol-associated liver disease was the most frequent etiology (81.3%). In-hospital mortality was 18.6% (n = 26). Infections (OR: 6.55; 95% CI: 1.61–28.4; p = 0.008) and spontaneous bacterial peritonitis (OR: 4.16; 95% CI: 1.44–11.78; p = 0.007) were independently associated with death. Patients who did not survive had significantly elevated WBC (14.1 ± 6.9 vs. 10.0 ± 5.8; p < 0.01) and CRP (8.9 ± 6.5 vs 3.9 ± 4.9 mg/L; p = 0.0028).
In the full cohort, CLIF-C OF showed the highest prognostic accuracy (AUC 0.855, specificity 92%, accuracy 86%), followed by MELD-Na (AUC 0.765). MELD, MELD-Lactate, and Child-Pugh had moderate performance.
Within the ACLF subgroup, CLIF-C ACLF demonstrated the strongest discriminative ability (AUC 0.929, sensitivity 100%, specificity 80%, accuracy 94%), while AARC provided high sensitivity (AUC 0.803, sensitivity 88%, NPV 96%). **Conclusion:** In this prospective Latin American cohort, CLIF-C OF and CLIF-C ACLF demonstrated the strongest prognostic performance for mortality prediction in ACLF, supporting their use in clinical triage and decision-making. AARC and MELD-Na provided complementary value in earlier stages of decompensation. These findings underscore the need for stage-adapted, context-sensitive prognostic tools in cirrhotic populations, particularly in underrepresented regions such as Latin America.

VARIABLE	OVERALL (N=140)	SURVIVORS (N=114)	NON-SURVIVORS (N=26)	P-VALUE
AGE (YEARS)	54.8 ± 10.4	54.8 ± 10.5	54.8 ± 10.3	0.983
MALE SEX, N (%)	108 (77.1%)	89 (78.1)	19 (73.1)	0.733
ALCOHOL-RELATED CIRRHOSIS, N (%)	113 (81.3%)	94 (83.2)	19 (73.1)	0.105
ADMISSION DIAGNOSIS				
HEMATEMESIS	38 (27.3%)	34 (30.1)	4 (15.4)	0.14
MELENA	24 (17.3%)	21 (18.6)	3 (11.5)	
HEPATIC ENCEPHALOPATHY	38 (27.3%)	29 (25.7)	9 (34.6)	
ASCITES	33 (23.7%)	26 (23)	7 (26.9)	
JAUNDICE	6 (4.3%)	3 (2.7)	3 (11.5)	
PRECIPITATING EVENTS				
INFECTION	9 (6.4%)	4 (3.5)	5 (19.2)	0.0114
SPONTANEOUS BACTERIAL PERITONITIS	19 (13.6%)	11 (9.6%)	8 (30.8%)	0.009
ACUTE ALCOHOLIC HEPATITIS	11 (7.85%)	11 (9.6)	0 (0)	0.217
ACLF GRADE (CLIF-C CRITERIA:				
GRADE 0	85 (60.7%)	81 (71.1%)	4 (15.4%)	< 0.001
GRADE 1	23 (16.4%)	18 (15.8%)	5 (19.2%)	
GRADE 2	19 (13.6%)	13 (11.4%)	6 (23.1%)	
GRADE 3	13 (9.3%)	2 (1.8%)	11 (84.6%)	
LABORATORY VALUES				
LEUKOCYTES (×10³/μL)	10.7 ± 5.9	10.0 ± 5.8	14.1 ± 6.9	< 0.01
C-REACTIVE PROTEIN (CRP MG/L)	4.9 ± 5.4	3.9 ± 4.9	8.9 ± 6.5	0.0028
PROGNOSTIC SCORES				
CHILD-PUGH SCORE	10.1 ± 2.6	9.7 ± 2.6	11.9 ± 1.9	0.0000
MELD SCORE	19.4 ± 8.1	17.8 ± 6.7	28.3 ± 9.8	0.0002
MELD-NA SCORE	22.5 ± 8.2	21.1 ± 7.5	29.1 ± 8.5	0.0001
MELD-LACTATE SCORE	16.1 ± 4.8	15.2 ± 4.1	20.1 ± 5.7	0.0004
CLIF-C OF SCORE	8.4 ± 2.3	7.8 ± 1.7	11.1 ± 2.6	0.0000
CLIF-C ACLF SCORE	58.3 ± 11.4	45.8 ± 7.9	63.1 ± 8.5	0.0000
AARC SCORE (N = 54)	8.4 ± 2.1	9.75 (1.3)	10.71 (1.52)	0.02

Figure 1. Baseline characteristics, precipitating events, labs, and prognostic scores in cirrhotic patients with AD, stratified by in-hospital mortality. Non-survivors showed higher infection rates, leukocyte counts, CRP, and severity scores. **Abbreviations:** AD, acute decompensation; CRP, C-reactive protein; MELD, Model for End-Stage Liver Disease; MELD-Na, MELD with sodium; CLIF-C OF, Chronic Liver Failure Consortium Organ Failure score; CLIF-C ACLF, CLIF-C Acute-on-Chronic Liver Failure score; AARC, APASL ACLF Research Consortium.

Disclosures: Emilio Sandoval-Gonzalez: Nothing to Disclose, Francisco Bosques-Padilla: Nothing to

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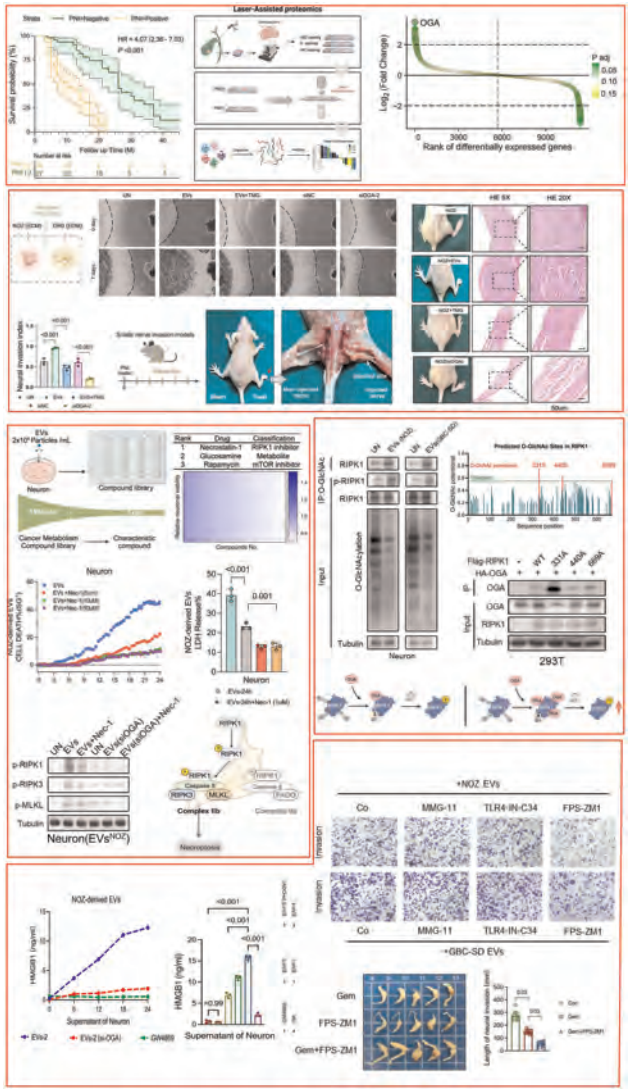
Disclose, Miguel Escobedo-Belloc: Nothing to Disclose, Jorge Zuñiga-Hernandez: Nothing to Disclose, Hannia Zumaya-Flores: Nothing to Disclose, Wendy Ruiz-Gallegos: Nothing to Disclose, Lilia Chavez-García: Nothing to Disclose, Leonel Castillo-Peña: Nothing to Disclose, Andres Zapata-Navarro: Nothing to Disclose

◆ 4183 | OGA INDUCES NEURONAL NECROPTOSIS VIA EXTRACELLULAR VESICLES DRIVING PERINEURAL INVASION IN GALLBLADDER CANCER

Jingwei Zhao[1] Danyang Shen[2] Wei Gong[1], [1]Xinhua Hospital, Affiliated to Shanghai Jiao Tong University, [2]The First Affiliated Hospital of Soochow University

Background: Peripheral nerve invasion (PNI) is a critical early event in the progression of gallbladder cancer (GBC) and significantly influences the prognosis of patients undergoing surgery at advanced stages. Despite its importance, the precise mechanisms underlying GBC's invasion of perineural spaces remain poorly understood. **Methods:** Laser microdissection and proteomic profiling was used to construct molecular maps of the neural microenvironment for patients with PNI-positive and PNI-negative GBC. Clinical cohort analyses were conducted to assess the correlation between neuronal O-linked N-acetylglucosamine (OGA) expression, PNI severity, and overall survival. A non-contact co-culture system (including three-dimensional dorsal root ganglion explant cultures) and untargeted metabolomics were employed to investigate how GBC cells influence neuronal OGA expression. A mouse sciatic nerve invasion model was used to test the role of EV-associated OGA in promoting perineural invasion in vivo. Metabolic drug library screening and Real-time Cell Death Kinetics Assays were used to explore the functional role of OGA in neurons. Further mechanical studies focused on identifying specific sites involved in OGA-mediated regulation, and functional assays evaluated the therapeutic potential of RAGE inhibition. **Results:** We found that OGA expression was abnormally elevated in neurons following GBC invasion. Increased neuronal OGA expression correlated with greater PNI severity and poorer OS in GBC patients. GBC cells were shown to upregulate neuronal OGA expression through extracellular vesicle-mediated communication. Elevated OGA promoted neuronal necroptosis by inhibiting RIPK1 glycosylation and enhancing RIPK1 phosphorylation and activation via the RIPK1/RIPK3/MLKL pathway. RIPK1 S440 was identified as a critical site for OGA-mediated regulation. Neuronal necroptosis resulted in the release of HMGB1, which activated RAGE receptors on GBC cells, enhancing their neurotropic invasiveness. Treatment with the RAGE inhibitor FPS-ZM1, especially in combination with gemcitabine, significantly improved anticancer efficacy in experimental models. **Conclusion:** Our study reveals a novel mechanism by which GBC-derived extracellular vesicles induce neuronal necroptosis to promote PNI. OGA-mediated modulation of RIPK1 glycosylation and the subsequent release of HMGB1 play central roles in this process. Targeting the HMGB1-RAGE signaling axis offers a promising therapeutic strategy for combating PNI in GBC.



Disclosures: Jingwei Zhao: Nothing to Disclose, Danyang Shen: Nothing to Disclose, Wei Gong: Nothing to Disclose

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◆ 4184 | LIVER-SPECIFIC S1PR2 DELETION REDUCES HEPATIC INJURY AND FIBROSIS IN A MOUSE MODEL OF PRIMARY SCLEROSING CHOLANGITIS

Meiyi Song[1] Derrick Zhao[1] Hui Li[1] Sayed Obaidullah Aseem[2] Grayson Way[2] NAN WU[1] Yunling Tai[1] Sareh Bayatpour[1] Lianyong Su[1] Xuan Wang[1] Emily Gurley[1] Phillip Hylemon[1] Arun Sanyal[2] Huiping Zhou[2], [1]School of Medicine, Virginia Commonwealth University and Richmond Veterans Affairs Medical Center, [2]Virginia Commonwealth University

Background: Sphingosine-1-phosphate receptor 2 (S1PR2) is a GPCR. Our previous studies showed that conjugated primary bile acids (CBAs) activate S1PR2 in hepatocytes and cholangiocytes, triggering ERK1/2 and AKT signaling pathways and contributing to hepatic injury and fibrosis in bile duct ligation (BDL) and Mdr2$^{-/-}$ mice. In addition, S1PR2 is highly expressed in macrophages, where its activation by CBAs promotes inflammation, contributing to biliary injury. Global knockout of S1PR2 significantly reduced biliary fibrosis in the BDL mouse model. These findings underscore S1PR2 as a critical mediator of cholestatic liver pathology. The current study aims to define the liver-specific role of S1PR2 in cholestatic liver disease. **Methods:** Publicly available GEO datasets (GSE179993 & 268905) were analyzed. Liver-specific *S1pr2* knockout mice (S1PR2^{LKO}) were generated by crossbreeding S1pr2$^{fl/fl}$ with Alb-Cre) and further crossed with Mdr2$^{-/-}$ mice to generate Mdr2$^{-/-}$S1pr2^{LKO} double knockout mice (DKO) on a C57BL/6J background. DKO and Mdr2$^{-/-}$ (male and female, 26-week old) were used. Liver samples were processed for H&E and Picrosirius red staining. Serum lipids and liver functional enzymes were measured using the Alfa Wassermann Vet ACE Axcel System. The expression levels of the key genes involved in cholestatic liver fibrosis were measured by qPCR and Western blot analysis. **Results:** Hepatic *S1pr2* expression is upregulated in cholestatic mouse models, including Mdr2$^{-/-}$ mice. Liver-specific deletion of *S1pr2* in Mdr2$^{-/-}$ mice led to a marked reduction of inflammation and fibrosis. Biochemically, ALP levels were significantly decreased, and ALT and AST levels were modestly reduced, supporting reduced liver injury. *Ck19, Col1a1, and Col3a1* expression was downregulated, indicating a reduction of ductular reaction and fibrogenesis. Liver-specific deletion of *S1pr2* had a more prominent protective effect on liver fibrosis in male mice than in female mice, suggesting a sex-specific difference in cholestatic disease mechanisms of S1PR2 signaling. **Conclusion:** Liver-specific deletion of *S1pr2* significantly reduced biliary fibrosis, ductular reaction, and cholestatic liver injury in Mdr2$^{-/-}$ mice. Together with our previous findings that S1PR2 promotes cholangiocyte proliferation and inflammatory signaling, these results support S1PR2 as a pathogenic mediator and potential therapeutic target in cholestatic liver diseases such as PSC.

Disclosures: Meiyi Song: Nothing to Disclose, Derrick Zhao: Nothing to Disclose, Hui Li: Nothing to Disclose, Sayed Obaidullah Aseem: Galmed Pharmaceuticals: Grant/Research Support, Kezar pharma: Consultant, Grayson Way: Nothing to Disclose, NAN WU: Nothing to Disclose, Yunling Tai: Nothing to Disclose, Sareh Bayatpour: Nothing to Disclose, Lianyong Su: Nothing to Disclose, Xuan Wang: Nothing to Disclose, Emily Gurley: Nothing to Disclose, Phillip Hylemon: Nothing to Disclose, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Huiping Zhou: Nothing to Disclose

◆ 4185 | SPLEEN TYROSINE KINASE IS A POTENTIAL THERAPEUTIC TARGET FOR DUCTULAR REACTION AND SUBSEQUENT TUMOR FORMATION

Hengdong Qu[1] Di Zhang[1] Ping Tao[1] Pengqing Sun[1] Kexin Zeng[2] Zhiwei Chen[3] Zijian Xu[2] Zhibo Zhuang[2] Tingzhen Wu[1] Jian Hong[1] Nan Yao[1], [1]State Key Laboratory of Bioactive Molecules and Druggability Assessment, Jinan University, [2]Jinan University, [3]The First Affiliated Hospital of Jinan University

Background: Ductular reaction has been recognized as a critical pathogenic factor for primary sclerosing cholangitis (PSC) and cholangiocarcinoma (CCA) carcinogenesis. We previously reported that

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pharmacological inhibition of spleen tyrosine kinase (SYK) effectively ameliorated liver fibrosis [Hepatology 2018;68(3):1125], concomitant with reduced ductular reaction. This study aims to explore the role and therapeutic potential of SYK in ductular reaction and subsequent tumor formation. **Methods:** Expression patterns and clinical relevance of SYK were assessed in murine PSC tissues and further confirmed in human livers using multiplex immunofluorescence. Pharmacological efficacy of SYK inhibitor on ductular reaction and tumor formation were determined in three distinct murine models, ranging from bile duct ligation (BDL) and 3,5-Diethoxycarbonyl-1,4-Dihydrocollidine (DDC) diet-induced cholangitis models to *Mdr2* knockout-induced carcinogenesis model, respectively. Additionally, the therapeutic potential of a liver-specific cholesterol-conjugated heteroduplex oligonucleotides (Cho-HDO) targeting SYK on ductular reaction was evaluated. **Results:** By analysis of murine PSC livers, we found that SYK expression was dynamically upregulated in non-parenchymal cells, especially in cholangiocytes of reactive bile ducts as PSC progress. In patients with PSC ($n = 18$), we confirmed that SYK expression was markedly enhanced in ductular reactive cholangiocytes, which positively correlated with ductular reaction severity. Importantly, R788 (Fostamatinib), an FDA-approved SYK inhibitor, effectively attenuated BDL- and DDC diet-induced ductular reaction, accompanied by reduced hepatic inflammation and liver fibrosis. Moreover, R788 greatly inhibited ductular reaction and tumor formation in *Mdr2* knockout mice (both $P < 0.001$). Functional studies demonstrated that SYK promotes cholangiocyte proliferation and ductular reaction via the Hippo signaling pathway. Furthermore, pharmacological or genetic inhibition of SYK suppressed chemokine (e.g., CXCL2) released by cholangiocytes, and thereby ameliorating ductular reaction-associated neutrophils infiltration and disease progression. Clinically, tyrosine kinase inhibitors often lead to severe kidney injuries in the context of anti-tumor therapy. To improve the delivery efficacy and minimize the potential side effects, we administered liver-specific Cho-HDO. Interestingly, single administration of SYK-targeting Cho-HDO efficiently ameliorates ductular reactions, biliary fibrosis and even tumor formation in *Mdr2* knockout mice without observable hepatic and renal toxicity. **Conclusion:** Targeting SYK represents a promising therapeutic strategy for ductular reaction and carcinogenesis in PSC. Liver-specific Cho-HDO delivery may further enhance the translational potential of SYK-targeted therapy for patients with PSC.

Disclosures: Hengdong Qu: Nothing to Disclose, Di Zhang: Nothing to Disclose, Ping Tao: Nothing to Disclose, Pengqing Sun: Nothing to Disclose, Kexin Zeng: Nothing to Disclose, Zhiwei Chen: Nothing to Disclose, Zijian Xu: Nothing to Disclose, Zhibo Zhuang: Nothing to Disclose, Tingzhen Wu: Nothing to Disclose, Jian Hong: Nothing to Disclose, Nan Yao: Nothing to Disclose

◆ 4186 | THE CLINICAL EFFICACY OF A PPARA AGONIST ON MURINE PRIMARY BILIARY CHOLANGITIS

Masahiro Umemura[1] アキラ ホンダ [2] Yuya Ida[1] Maho Yamashita[1] Takeshi Chida[3] Hidenao Noritake[1] Teruo Miyazaki[2] Mayuko Ichimura[4] Koichi Tsuneyama[4] Patrick Leung[5] M Gershwin[5] Kazuhito Kawata[6], [1]Hamamatsu University School of Medicine, [2]Tokyo Medical University Ibaraki Medical Center, [3]Hamamatsu University School of Medicine, Japan, [4]Tokushima University Graduate School, [5]University of California, Davis, [6]Hamamatsu University

Background: Peroxisome Proliferator-Activated Receptor (PPAR) agonists, such as bezafibrate, elafibranor, and seladelpar, are recognized as one of the second-line treatments for primary biliary cholangitis (PBC). However, the underlying mechanisms of PPAR agonists remain unclear. This study aimed to investigate the impact of PPARα agonists on a well-defined murine model of PBC. **Methods:** We took advantage of our previously published murine PBC model that includes hepatic fibrosis: the Cyp2c70/Cyp2a12 double knockout mouse, which have a human-like bile acid (BA) composition and develop progressive cholangitis following immunization with a PDC-E2 mimic, 2-octynoic acid. Mice were fed either a normal/control diet ($n = 8$) or a diet containing low (0.01 mg/100 g, $n = 6$) or high (0.03 mg/100 g, $n = 6$) doses of pemafibrate (PEM), a selective PPARα modulator, for 8 weeks. We evaluated liver histology and expression of inflammatory cytokines and chemokines, hepatic fibrosis markers, nuclear receptor-related genes, and BA compositions in serum, liver, and bile. **Results:** PEM treatment significantly ameliorated portal inflammation, bile duct damage, and hepatic fibrosis in a dose-dependent manner. Similarly, the hepatic mRNA expressions of *Il-1b*, *Il-6*, *Cx3cl1*, *Col1a1*, and *Mmp2* were significantly suppressed. Additionally, *Ostb* mRNA expression was downregulated, whereas mRNA expressions of *Ntcp* and *Cyp7a1* were upregulated. PEM-treated mice exhibited decreased total BA concentrations in serum and liver, with a trend toward increased biliary BA concentrations, suggesting attenuation of cholestasis. Moreover, the ratio of chenodeoxycholic acid-derived BAs to cholic acid-derived BAs was decreased. High-dose PEM also significantly suppressed hepatic *Nfkb, Ikba* and *Nlrp3* mRNA expression. **Conclusion:** Our findings suggest that PPARα agonist exerts anti-inflammatory and anti-fibrotic effects in PBC through FXR suppression and improved BA composition. These effects collectively contribute to the

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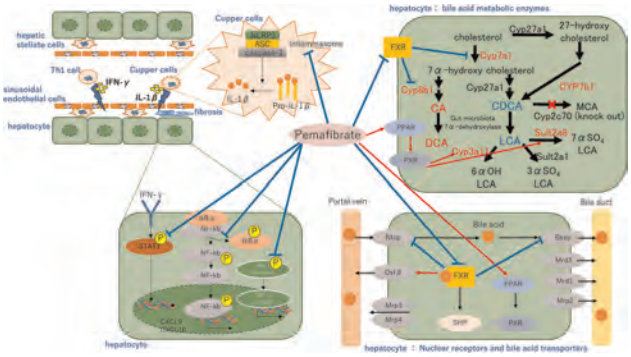
amelioration of cholangitis and hepatic fibrosis in this PBC murine model. These findings support PPARα agonists as a rational adjunct therapy for PBC.



Disclosures: Masahiro Umemura: Nothing to Disclose, アキラ ホンダ : Nothing to Disclose, Yuya Ida: Nothing to Disclose, Maho Yamashita: Nothing to Disclose, Takeshi Chida: Nothing to Disclose, Hidenao Noritake: Nothing to Disclose, Teruo Miyazaki: Nothing to Disclose, Mayuko Ichimura: Nothing to Disclose, Koichi Tsuneyama: Nothing to Disclose, Patrick Leung: Nothing to Disclose, M Gershwin: Cour Pharma: Consultant, Kazuhito Kawata: Nothing to Disclose

◆ 4187 | PREDICTING TRANSPLANT-FREE SURVIVAL IN PRIMARY BILIARY CIRRHOSIS USING RANDOM SURVIVAL FORESTS AND SERIAL CLINICAL MEASUREMENTS

Sri Harsha Boppana[1] Manaswitha Thota[2] Gautam Maddineni MD[3] Sachin Sravan Kumar Komati MS[4] Sai Lakshmi Prasanna Komati[5] C. David Mintz MD PhD[6], [1]Nassau University Medical Center / Johns Hopkins University, [2]Virginia Commonwealth University, [3]Creighton university school of medicine, [4]Florida International University, [5]Government Medical College, Ongole, [6]Johns Hopkins University

Background: The course of primary biliary cirrhosis often defies prediction, complicating decisions about the timing of advanced therapies. To address this, we built and tested a random survival forest model that forecasts transplant-free survival and uncovers the most influential prognostic variables in a cohort of 418 patients. **Methods:** We identified 418 individuals diagnosed with primary biliary cirrhosis and compiled repeated measures of serum bilirubin, albumin, copper, prothrombin time and 13 additional clinical parameters. Continuous gaps were imputed with the cohort mean and categorical gaps with the most common category. All continuous variables were scaled to a mean of zero and a standard deviation of one, and categorical factors were converted into binary indicators. The composite endpoint included death, liver transplantation or censoring at last follow-up. The data were randomly split into 80 percent for model training and 20 percent for validation. We fitted a random survival forest of 1 000 decision trees and evaluated its discrimination using the concordance index. To rank the predictors, we applied a permutation importance analysis. **Results:** The model achieved a concordance index of 0.94 in the training sample and 0.88 in the test sample. Permutation importance identified baseline bilirubin and albumin as the top two predictors, with prothrombin time and serum copper also contributing substantially. We calculated individual risk scores and divided patients into low-risk (n = 82), intermediate-risk (n = 134) and high-risk (n = 202) groups. The average scores were 20.1, 31.8 and 93.9 in the low-, intermediate- and high-risk strata, respectively. Kaplan-Meier survival curves displayed clear separation among all three risk categories. **Conclusion:** This machine-learning approach delivered strong prognostic discrimination and sorted patients into distinct risk tiers, with bilirubin and albumin emerging as the principal markers. These findings support further validation of such models to guide personalized management in primary biliary cirrhosis.

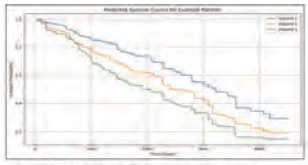


Figure 1: Survival Curves for Representative Patients

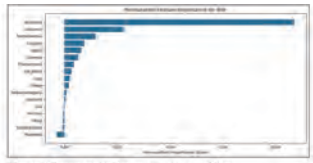


Figure 2: Permutation Feature Importance Plot

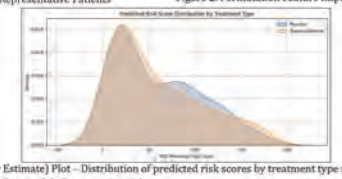


Figure 3: KDE (Kernel Density Estimate) Plot – Distribution of predicted risk scores by treatment type shows a heavier right-skew in placebo patients, indicating higher modeled progression risk.

Disclosures: Sri Harsha Boppana: Nothing to Disclose, Manaswitha Thota: Nothing to Disclose, Gautam Maddineni MD: Nothing to Disclose, Sachin Sravan Kumar Komati MS: Nothing to Disclose, Sai Lakshmi Prasanna Komati: Nothing to Disclose, C. David Mintz MD PhD: Nothing to Disclose

◆ 4188 | CHOLANGIOCYTE HUMAN ENDOGENOUS RETROVIRUSES DRIVE A TYPE-I INTERFERON RESPONSE VIA RIG-I/MAVS PATHWAY IN PSC

Patrick Splinter[1] Antonia Felzen[2] Olivia Morgenthaler[1] Carys Turner[1] Gregory Gores[1] Nicholas LaRusso[1] Steven O'Hara[1], [1]Mayo Clinic Rochester, [2]University of Groningen

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Background: Primary Sclerosing Cholangitis (PSC) is a life-threatening disease without approved pharmacotherapy in need of innovative pathogenic insights and new druggable targets. We reported that DNA hypomethylation, cholangiocyte senescence and associated inflammatory secretome characterize PSC. Here, we provide evidence supporting the novel concept that PSC is a disease in which cholangiocytes, in response to aberrantly expressed human endogenous retroviruses (HERVs), display features of viral infection in the absence of virus (viral mimicry), driving sterile fibroinflammation. **Methods:** We used normal human cholangiocytes (NHC), induced senescent (sen)NHC, PSC patient-derived cholangiocyte organoids, PSC patient liver tissue, and PSC mouse models (DDC-fed and Mdr2$^{-/-}$). For gene expression analyses, we used methylome and RNAseq data, and quantitative PCR (qPCR). We assessed chromatin modification by chromatin immunoprecipitation (ChIP)-qPCR and analyzed RNA: protein interactions by RNA IP (RIP)-qPCR, and protein: protein interactions by co-IP and proximity ligation assay (PLA). **Results:** Pathway analyses of senNHC RNAseq showed a Type I interferon (IFN) response. Methylome data revealed hypomethylation at HERV loci in PSC patient cholangiocytes, including the HERV, MLT1F. qPCR showed upregulation of MLT1F (~9-fold), senescence markers p16 and p21 (~5-fold), the dsRNA receptor Retinoic acid inducible gene I (RIG-I, ~10-fold), and interferon response genes (IRGs; 3-6 – fold) in senNHC and PSC patient-derived cholangiocyte organoids. ChIP-qPCR revealed increased histone acetyltransferase p300 (15-fold), the chromatin mark, H3K27ac (28-fold), the epigenetic reader BRD2 (7-fold) and the transcription factor ETS1 (10-fold) at the MLT1F locus in senNHC. RIP-PCR showed MLT1F: RIG-I interaction in senNHC (10-fold increase). IP and PLA demonstrated that RIG-I interacted with mitochondrial antiviral signaling protein (MAVS, a mediator of RIG-I signaling), in senNHC, PSC mouse models, and PSC patient tissue. Deletion of MAVS in senNHC by Crispr decreased mRNA of IRGs (~40%) and fibroinflammatory cytokines (~50%). **Conclusion:** These results implicate aberrant cholangiocyte HERV expression, resultant viral mimicry, and a RIG-I/MAVS mediated IFN-response as drivers of fibroinflammation in PSC. Our data uniquely inform on PSC pathogenesis and identify novel therapeutic targets including DNA hypomethylation, HERV transcription, and the RIG/MAVS anti-viral signaling cascade.

Disclosures: Patrick Splinter: Nothing to Disclose, Antonia Felzen: Nothing to Disclose, Olivia Morgenthaler: Nothing to Disclose, Carys Turner: Nothing to Disclose, Gregory Gores: Nothing to Disclose, Nicholas LaRusso: NIH: R01 DK 24031, NIH: R01 DK 57993, NIH: P30 DK 84567, NIH: P30 DK90728, NIH: R01 DK117133, NIH: T32 DK 07198, Steven O'Hara: Nothing to Disclose

4189 | 3A,12B-DIHYDROXYCHOLANOIC ACID-INDUCED GPAT4 PHOSPHORYLATION ELEVATES LPA LEVELS AND EXACERBATES LIVER FIBROSIS AND INFLAMMATION

yuhao zhu[1] Xingyang Luo[2] Wenhu Li[2] Linxinag Zhou[2] Jintao Xiao[2] Xiaomei Zhang[2] Xiaowei Liu[2] Haiyue He[2], [1]Xiangya Hospital, Central South University, [2]Department of Gastroenterology, Xiangya Hospital, Central South University, Changsha 410008, Hunan,

Background: Disrupted bile acid metabolism represents a central characteristic of cholestatic liver disease (CLD), resulting from obstruction of bile flow through intra or extrahepatic bile ducts. Lysophosphatidic acid (LPA) signaling has been linked to bile acid metabolism, and elevated LPA levels have been detected in cholestatic patients. The glycerophosphate acyltransferase (GPAT1-4) family catalyzes the first step in triglyceride synthesis by converting G-3-P to LPA. Among these four isoforms, GPAT4 is highly expressed in the liver and serves as the principal source of LPA production in the liver. However, the role of the GPAT4-LPA axis in CLD remains unknown. **Methods:** Gpat4-deficient (Gpat4$^{-/-}$) and wild-type control mice were subjected to bile duct ligation (BDL) or fed a 3,5-Diethoxycarbonyl-1,4-Dihydrocollidine (DDC) Diet to construct CLD mouse models. Conditioned medium (CM) was collected from primary hepatocytes transfected with either Gpat4-overexpressed (CM-Gpat4-OE) or control (CM-Control) plasmid. Bone marrow-derived macrophages (BMDMs) were treated with LPS for 12 h prior to 1-hour exposure to a conditioned medium. Primary hepatocytes isolated from wild-type mice were treated with 36 distinct bile acid species or vehicle control. Co-immunoprecipitation (Co-IP) products from 3α,12β-DHCA-treated hepatocytes were analyzed by proteomics. Computational virtual screening was employed to discover small-molecule compounds with selective inhibitory activity against GPAT4. **Results:** We observed increased GPAT4 protein levels in both CLD patients and mouse models. Deletion of Gpat4 in liver alleviated BDL/DDC-induced hepatic inflammation and fibrosis, evidenced by decreases in plasma ALT and AST levels, collagen deposition and α-SMA protein levels. In vitro, after LPS stimulation, mRNA levels of inflammatory factors were increased in BMDMs treated with CM-Gpat4-OE, compared to CM-control. Among 36 distinct bile acids, only 3α,12β-DHCA treatment increased the p-Tyr-Gpat4 /Gpat4 ratios and total Gpat4 protein in primary hepatocytes. We also observed enhanced collagen deposition and inflammation in C57BL/6J mice intraperitoneal injected with 3α,12β-DHCA. Proteomics identified APPL2 as the top differentially expressed protein after 3α,12β-DHCA treatment. APPL2 konckdown

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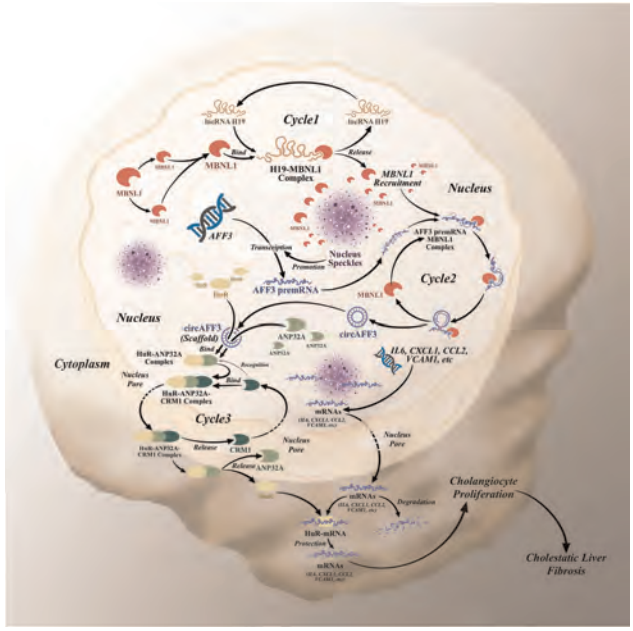
increased p-Tyr-GPAT4 and total GPAT4 protein levels. We also found several Gpat4 inhibitors by Computational virtual screening and verified by detecting the GPAT activity using a commercial kit. **Conclusion:** GPAT4 protein levels are significantly upregulated in CLD patients and mouse models. Deletion of GPAT4 alleviates hepatic injury and fibrosis by reducing LPA accumulation in CLD mouse models. Bile acid, particularly 3α,12β-DHCA, aggravates liver injury and fibrosis by suppressing the APPL2 expression, which upregulates GPAT4 protein levels through tyrosine phosphorylation-mediated mechanisms.

Disclosures: yuhao zhu: Nothing to Disclose, Xingyang Luo: Nothing to Disclose, Wenhu Li: Nothing to Disclose, Linxinag Zhou: Nothing to Disclose, Jintao Xiao: Nothing to Disclose, Xiaomei Zhang: Nothing to Disclose, Xiaowei Liu: Nothing to Disclose, Haiyue He: Nothing to Disclose

4190 | THE H19–CIRCAFF3–HUR AXIS: A NOVEL REGULATORY CIRCUIT IN CHOLESTATIC LIVER FIBROSIS

Hui Li[1] Grayson Way[1] Yun-Ling Tai[1] Nan Wu[1] Meiyi Song[1] Sareh Bayatpour[1] Derrick Zhao[1] Sayed Obaidullah Aseem[1] Lianyong Su[1] Xuan Wang[1] Emily Gurley[1] Phillip Hylemon[1] Saul Karpen[1] Arun Sanyal[1] Huiping Zhou[1], [1]Virginia Commonwealth University

Background: Cholestatic liver fibrosis is a progressive disease with limited treatment options. Prior work identified the long noncoding RNA (lncRNA) H19 as a key pro-fibrotic driver in Mdr2$^{-/-}$ mice, a model of cholestatic liver disease, yet the downstream mechanisms remain poorly defined. Circular RNAs (circRNAs), a class of covalently closed noncoding RNAs, have recently emerged as important regulators in liver pathology. This study investigates the role of H19-regulated circRNAs in cholestatic fibrosis and explores their molecular mechanisms. **Methods:** Livers from wild-type, Mdr2$^{-/-}$, and Mdr2$^{-/-}$/H19$^{-/-}$ (DKO) mice (C57BL/6, males, 10–12 weeks, n = 3) were analyzed by circRNA microarray. Candidate circRNAs were validated by qRT-PCR in primary hepatic cells and human PSC liver tissues. Functional assays in mouse large cholangiocytes (MLE) and cholangiocyte-derived organoids assessed effects on proliferation. RNA pull-down, RNA Immunoprecipitation (RIP), and public bioinformatics tools identified RNA-binding proteins (RBPs). Subcellular fractionation, confocal microscopy and FISH determined intracellular localization. **Results:** Among six circRNAs upregulated in Mdr2$^{-/-}$ and suppressed in DKO mice, circAFF3 showed the highest enrichment in primary cholangiocytes. Both H19 and circAFF3 were predominantly nuclear in MLE cells. Bioinformatic and RIP analyses indicated that H19 binds the splicing factor muscleblind-like splicing regulator 1 (MBNL1) to promote circAFF3 biogenesis. Overexpression of circAFF3 increased proliferation in MLE cells and organoids. Mechanistically, circAFF3 served as a scaffold to enhance interaction between RBP HuR and ANP32A, a nuclear export co-factor involved in Exportin 1 (CRM1)-dependent pathways. This interaction promoted HuR export to the cytoplasm, leading to stabilization of pro-inflammatory mRNAs, including IL6, CXCL1, CCL2, and VCAM1, which were upregulated 1.5- to 3.4-fold as measured by qRT-PCR ($n = 3$, $P < 0.001$). **Conclusion:** This study identifies a novel H19–circAFF3–HuR signaling axis in cholestatic liver fibrosis. H19 promotes circAFF3 expression through MBNL1, while circAFF3 facilitates HuR nuclear export by modulating ANP32A, stabilizing pro-inflammatory mRNAs. These events contribute to cholangiocyte proliferation and fibrosis. Our findings highlight circAFF3 and its associated proteins as potential therapeutic targets in cholangiopathies such as primary sclerosing cholangitis (PSC).



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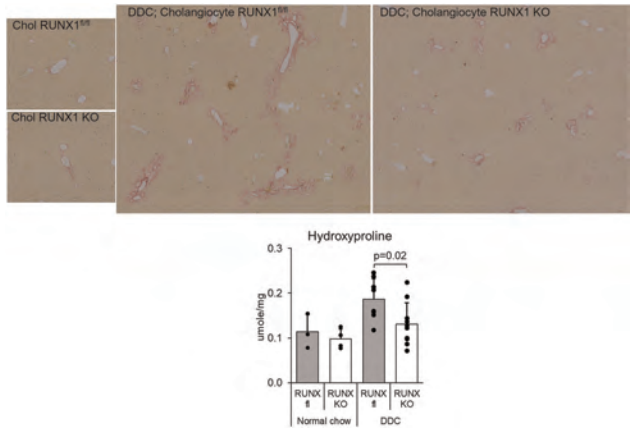
4191 | CHOLANGIOCYTE RUNX1 ORCHESTRATES FIBROGENIC AND INFLAMMATORY SIGNALING TO DRIVE BILIARY FIBROSIS

Sayed Obaidullah Aseem[1] Jing Wang[1] Grayson Way[1] Yunling Tai[1] Derrick Zhao[1] Xuan Wang[1] Emily Gurley[1] Nidhi Jalan-Sakrikar[2] Robert Huebert[2] Phillip Hylemon[1] Saul Karpen[3] Arun Sanyal[1] Huiping Zhou[1], [1]Virginia Commonwealth University, [2]Mayo Clinic Rochester, [3]VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health

Background: Biliary fibrosis and inflammation are key drivers of cholangiopathies such as primary sclerosing cholangitis (PSC). We previously identified RUNX1 as overexpressed in PSC and a mediator of inflammatory signaling in transforming growth factor-β (TGFβ)-stimulated cholangiocytes and multidrug resistance 2 knockout (Mdr2$^{-/-}$) mice. However, the mechanistic role of RUNX1 in targeted modulation of cholangiocyte function to drive biliary inflammation and fibrosis remains ill-defined. **Methods:** PSC-derived cholangiocytes (PSC-C) and mouse large biliary epithelial cell line (MLEs) were treated with RUNX inhibitors (Ro5-3335, AI-10-104) or siRNA. Cytokines in PSC-C conditioned media were analyzed using Luminex xMAP multiplexing. Chromatin immunoprecipitation (ChIP), ChIP-seq and mass spectrometry (MS) of nuclear RUNX1 immunoprecipitant were performed on MLEs. Cholangiocyte-selective *Runx1* knockout mice (CK19-Cre) were fed 3,5-diethoxycarboncyl-1,4-dihydrocollidine (DDC) diet, and hepatic fibrosis was assessed by qPCR, Picrosirius red staining and hydroxyproline measurement by MS. **Results:** RUNX1 knockdown in PSC-C reduced secretion of cytokines, including interleukin (IL)-6, -4 and -11, tumor necrosis factor (TNF)-α/β, and granulocyte-macrophage colony-stimulating factor. TGFβ increased RUNX1 binding of *Il6* promoter in MLEs (>2-fold, $p<0.05$). ChIP-seq identified 729 differential RUNX1 binding sites (FDR < 0.05); Ingenuity Pathway Analysis (IPA) of associated genes revealing enrichment in hepatic fibrosis and inflammation pathways. Predicted upstream regulators included TGFB1, TNF, and lipopolysaccharide (LPS). RUNX1 inhibitors suppressed *Il6* expression in TGFβ- or LPS-stimulated MLEs. MS of nuclear immunoprecipitant showed RUNX1 interactions with transcriptional and epigenetic regulators; TGFβ promoted RUNX1 interaction with SMAD2 and transcription factor 7-like 2 (TCF7L2), also predicted by IPA. *In vivo*, cholangiocyte-selective *Runx1* deletion reduced hepatic *Acta2* (α-smooth muscle actin) expression, Picrosirius red staining, and hydroxyproline content in DDC-fed mice ($N=9$/group, $p<0.05$). Similarly, Ro5-3335 reduced these fibrosis markers in Mdr2$^{-/-}$ mice (~45%, $N=8$/group, $p<0.05$), consistent with attenuated biliary fibrosis. **Conclusion:** RUNX1 functions as a key transcriptional co-regulator in cholangiocytes, integrating fibrogenic and inflammatory signals. Its inhibition attenuates biliary fibrosis in cholestatic mouse models, positioning RUNX1 as a potential therapeutic target in fibroinflammatory cholangiopathies.



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4192 | LOSS OF B-CATENIN IN CHOLANGIOCYTES PROMOTES ANGIOGENESIS AND HEPATOCYTE REPROGRAMMING DURING MURINE CHOLESTASIS

Matthew Carson[1] Jamie Fornsaglio[2] Laura Molina[1] Pamela Cornuet[1] Jia-jun Liu[1] Silvia Liu[1] Kari Nejak-Bowen[1], [1]University of Pittsburgh, [2]Seton Hull University

Background: Primary sclerosing cholangitis (PSC) is a chronic liver condition with unknown etiology characterized by inflammation, fibrosis, and biliary strictures. We have previously shown that hepatocyte b-catenin plays a pleiotropic role in cholestatic injury. However, the role of cholangiocyte b-catenin during cholestasis remains unclear. The purpose of this study was to define the role of cholangiocyte b-catenin on hepatobiliary injury responses in mice with cholestasis. **Methods:** Inducible-Osteopontin (OPN)-Cre-β-catenin-floxed C57BL/6 mice were used in two cholestasis models. Mdr2 KO-β-catenin-floxed:OPN-Cre (DKO) mice were administered tamoxifen to delete β-catenin from cholangiocytes. Wild-type and cholangiocyte β-catenin KO mice were also administered a 5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet for four weeks. Serum was collected to evaluate liver enzymes. qRT-PCR and immunohistochemistry were performed on whole livers to assess injury, angiogenesis, and hepatocyte reprogramming. RNA-seq analysis was performed on isolated cholangiocytes. Cholangiocytes were treated with β-catenin siRNA *in vitro* to determine changes in angiogenic factors. Conditioned media from cholangiocytes were used to evaluate endothelial cell expansion *in vitro*. **Results:** Animals lacking cholangiocyte β-catenin have similar levels of hepatobiliary injury compared to controls. Notably, cholangiocyte β-catenin KOs had fibrotic hepatic arteries and increased periportal angiogenesis compared to controls. Isolated β-catenin KO cholangiocytes showed increased expression of angiogenesis pathways and genes that were associated with NF-kB activation. Paralleling RNA-seq findings, *in vitro* silencing of cholangiocyte β-catenin increased the expression of *Vegfa* and *Pdgfb*. Stimulated cholangiocyte media from these cells promoted endothelial cell proliferation, recapitulating the angiogenic phenotype found *in vivo*. Immunofluorescent staining showed β-catenin KO mice had an increased number of hepatocytes expressing cholangiocyte markers and ductular cells expressing β-catenin, indicating hepatocyte reprogramming. **Conclusion:** This work reveals a novel role of cholangiocyte β-catenin in regulating vasculature and hepatocyte reprogramming during cholestasis, which highlights cholangiocyte β-catenin as a potential target for therapeutic interventions.

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4193 | LOSS OF DNMT1 DISRUPTS LIVER REGENERATIVE PATHWAYS AND PROGENITOR CELL ACTIVATION IN CHOLESTATIC LIVER DISEASE

Juliana Marques Affonso[1] Jovana Castven[1] Lina Jegodzinsk[1] Carolin Zimpel[1] Martha Kirstein[1] Diana Becker[2] Benjamin Heckelmann[1] Rüdiger Braun[1] Darko Castven[1] Jens Marquardt[1], [1]University of Lübeck, [2]University Medical Center of the Johannes Gutenberg University

Background: DNA methylation, a key epigenetic mechanism, plays a crucial role in regulating gene expression during development and maintainance of tissue and stem cell homeostasis in response to both acute and chronic injury. DNA methyltransferase 1 (DNMT1) is central to this process, as it preserves postmitotic DNA methylation patterns. Although DNMT1's function during development is well established, its role in the activation of stem and progenitor cells during tissue regeneration is less well explored. This project aims to explore the impact of hepatocyte-

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specific DNMT1 loss on liver progenitor cell-induced regeneration. **Methods:** Cholestatic liver injury was induced using the 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) model, wherein 8-week-old liver-specific Dnmt1 knockout (Dnmt1-KO) and wild-type (WT) control mice were administered a diet containing 0.1% DDC for up to 4 weeks. Animals from each group (n = 5) were sacrificed at 1, 2, and 4 weeks post-treatment, and liver tissues were collected for further analysis. Liver injury was assessed by histopathology and the spatial distribution of CK19, a marker of biliary/progenitor cell, was evaluated. Global transcriptomic alterations were investigated using RNA sequencing. **Results:** Macroscopically, livers from both groups exhibited a pronounced dark discoloration due to cholestatic liver damage. No significant differences in macroscopic nodule count were observed. Histological examination revealed significantly more pronounced liver injury, progressive structural abnormalities, and a higher degree of infiltrating immune cells in Dnmt1-KO animals in comparison to WT. Additionally, Dnmt1-KO animals had a reduced liver/body weight ratio, reflecting impaired regenerative capacity. Supporting this, expansion of CK19-positive cells was significantly reduced in Dnmt1-KO animals, indicating impaired activation of progenitor cells . Distinct gene clustering and enrichment analysis highlight that DNMT1 deletion significantly impacts expression of pathways associated with liver homeostasis and regeneration. Specifically, DNA replication and repair, cell cycle progression, and maintenance of immune regulatory and memory-like phenotypes were notably suppressed in Dnmt1-KO animals. Notably, FOXP3-regulated immune targets were downregulated, suggesting impaired Treg function and a disrupted pro-regenerative immune microenvironment. **Conclusion:** Our findings highlight a critical role for DNMT1 in preserving liver homeostasis by sustaining key cellular programs during injury. Loss of postmitotic DNA methylation due to DNMT1 deficiency disrupts pathways essential for cell cycle progression, DNA repair and immune regulation, thereby impairing stem cell activation and effective liver regeneration in the context of cholestatic damage.

Disclosures: Juliana Marques Affonso: Nothing to Disclose, Jovana Castven: Nothing to Disclose, Lina Jegodzinsk: Nothing to Disclose, Carolin Zimpel: Nothing to Disclose, Martha Kirstein: Nothing to Disclose, Diana Becker: Nothing to Disclose, Benjamin Heckelmann: Nothing to Disclose, Rüdiger Braun: Nothing to Disclose, Darko Castven: Bayer: Stock owner, Jens Marquardt: AstraZeneca: and Grant Support, Eisai: Advisor, MSD: Speaking and Teaching, NovoNordisk: Advisor, Roche: Advisor, Merz: Speaking and Teaching, Falk: Speaking and Teaching

4194 | THERAPEUTIC TARGETING OF THBS1-AS1, A FIBROSIS-ASSOCIATED LNCRNA IN BILIARY DISEASE

Purnima Tyagi[1] Abid Anwar[2] Usman Yaqoob[3] Papawee Sutthirat[4] Sofia Jerez[3] Maleeha Farheen Kalaiger[2] Moira Hilscher[2] Nidhi Jalan-Sakrikar[4] Vijay Shah[4] Robert Huebert[4], [1]Mayoclinic Rochester, [2]Mayo Clinic, [3]Mayoclinic, [4]Mayo Clinic Rochester

Background: Biliary diseases like primary sclerosing cholangitis (PSC) involve progressive fibrosis and inflammation, with no curative treatments available. Emerging evidence implicates long non-coding RNAs (lncRNAs) as epigenetic regulators of cholangiocyte function, though their role in pro-fibrotic signaling remains unclear. This study explores the function of a novel lncRNA, THBS1-AS1, in driving cholangiocyte fibrogenic responses. **Methods:** Transcriptomic analysis was conducted using RNA sequencing of TGF-β treated human cholangiocytes and cholangiocytes isolated from 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) and Mdr2$^{-/-}$ mice, murine models of PSC. Differential lncRNA expression was profiled using the UClncR pipeline. Candidate lncRNAs were validated via RNA in situ hybridization (RNA-ISH), RT-PCR, and digital droplet PCR (ddPCR). Nuclear localization was assessed by cell fractionation. RNA immunoprecipitation (RIP) was performed to determine lncRNA-protein interactions. Functional studies utilized antisense oligonucleotide (ASO) mediated knockdown of lncRNA *in vitro* and *in vivo*. Epigenetic silencing was performed using guide RNAs in organoids isolated from genetically modified mice. Protein expression was assessed by western blot and immunofluorescence. **Results:** UClncR analysis identified 267 upregulated lncRNAs in TGF-β-treated cholangiocytes and 553 in DDC and Mdr2$^{-/-}$ cholangiocytes, with THBS1-AS1 emerging as the most upregulated lncRNA in both human and mouse datasets. ddPCR showed a ~10-fold increase in THBS1-AS1 expression in diseased cholangiocytes, while RT-PCR further validated its elevated levels in Mdr2$^{-/-}$ (2.2-fold, $p < 0.05$) and PSC patient livers (3-fold, $p < 0.05$). Nuclear fractionation and RNA-ISH confirmed predominant nuclear localization of THBS1-AS1, with strong expression in bile ducts of PSC patient livers and Mdr2$^{-/-}$ mice. RIP revealed that THBS1-AS1 interacts with the epigenetic silencer, EZH2, following TGF-β stimulation (2-fold, $p < 0.01$). ASO-mediated silencing of THBS1-AS1 significantly reduced TGFβ-mediated expression of key fibrogenic genes: FN1 (4-fold, $p < 0.01$), Serpine1 (4.2-fold, $p < 0.01$), CTGF (2.5-fold, $p < 0.05$) and THBS1 (2.2-fold, $p < 0.05$) confirmed at the RT-PCR level, protein level by western blotting and immunofluorescence. Administration of ASO via the tail vein resulted in decreased

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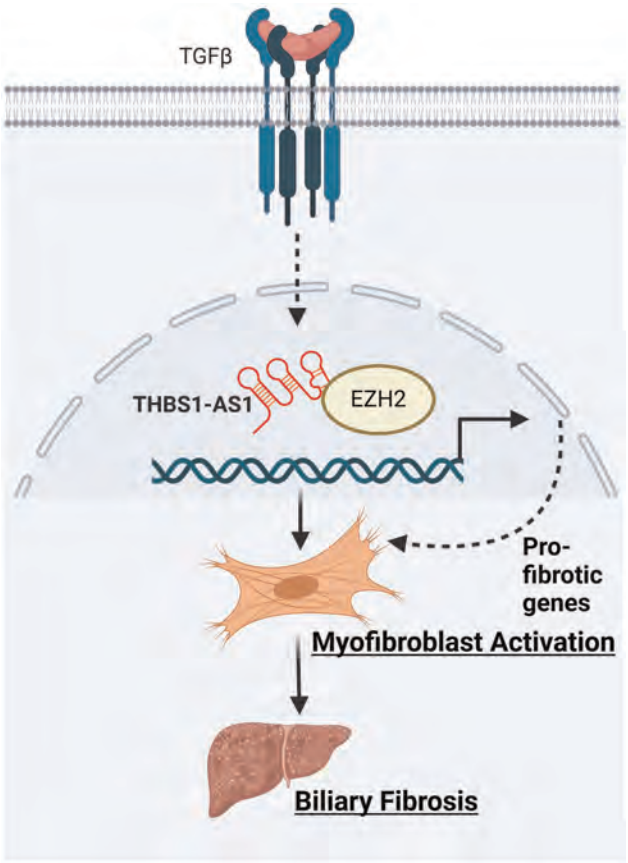
liver injury markers in Mdr2$^{-/-}$ mice. Concurrently, epigenetic silencing of THBS1-AS1 using guide RNAs in biliary organoids from DDC-treated mice led to a 3-fold reduction in Serpine1 and a 1.7-fold reduction in FN1 ($p < 0.05$). **Conclusion:** THBS1-AS1 is a TGF-β-responsive lncRNA that is selectively upregulated in cholangiocytes and interact with epigenetic regulator EZH2. Its silencing reduces TGF-β-induced fibrogenic gene expression, likely by excluding EZH2 from chromatin, highlighting its potential as a therapeutic target in biliary fibrosis.



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4195 | GENE EDITED IPSC-DERIVED BILIARY ORGANOIDS REVEAL CFTR MUTATION-SPECIFIC IMPACTS ON CHOLANGIOCYTE FUNCTION AND PROVIDES PATHOPHYSIOLOGICAL INSIGHTS RELEVANT FOR TREATMENT OF CF-RELATED LIVER DISEASE

Shakila Afroz Taleb[1] Camilla Venturin[1] Santo Diprima[1] Mario Strazzabosco[2] Romina Fiorotto[2], [1]Yale School of Medicine, [2]Yale University

Background: Cystic Fibrosis-associated liver disease (CFLD) causes significant morbidity and mortality in patients with CF. Using CF animal models and human induced pluripotent stem cells (iPSC)-derived cholangiocytes bearing the DF508 mutation, we showed that CFTR-defective biliary cells have altered secretion, polarity and innate immune responses. However, how different CFTR mutations affect CFLD phenotype and response to therapies remains unclear. In this study, we generated human cholangiocyte carrying different CFTR mutations using gene editing of iPSC and studied the effects on biliary cell physiology. **Methods:** Isogenic iPSC lines carrying W1282X (class I), ΔF508 (class II), and G551D (class III) mutations were generated via CRISPR/Cas9 from a control line. iPSC lines were differentiated to cholangiocytes and used to generate biliary organoids. Cholangiocyte specification was verified by RT-PCR and immunohistochemistry. Bulk RNA-sequencing was performed in monolayers. Forskolin-induced swelling (FIS) was used to test response to CFTR modulators. Immunofluorescence was performed for ZO1, b-catenin and F-actin. **Results:** iPSC-derived biliary organoids maintained morphological and functional properties of mature biliary epithelium. iPSC organoids with different CFTR mutations had no or minimal response to FIS. CFTR modulators (elexacaftor/tezacaftor/ivacaftor) improved FIS in ΔF508 and G551D but not W1282X organoids. β-catenin and ZO-1 staining showed disarrangement of cellular polarity in all CF lines while F-actin distribution was altered in W1282X and ΔF508 but not G551D organoids. Transcriptome analysis identified 11 differentially expressed genes (DEGs) shared across mutations. Enrichment of genes related to cytoskeletal components was observed in all mutated lines. Treatment with an Src-inhibitor (PP2) improved the effect of CFTR modulators in ΔF508 organoids. Gene and protein expression of NLRP2, a relatively uncharacterized component of the inflammasome and a negative regulator of TNF-mediated NF-kB signaling, were consistently low in all the CF lines, and possibly mechanistically linked to the pro-inflammatory phenotype described in CF cholangiocytes. **Conclusion:** Gene edited iPSC-derived cholangiocytes and organoids reveal mutation-specific

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effects on morphology, transcriptome, secretory function and response to modulators. This iPSC-based platform enables mechanistic insights and will be useful to identify new therapeutics for CFLD.
Disclosures: Shakila Afroz Taleb: Nothing to Disclose, Camilla Venturin: Nothing to Disclose, Santo Diprima: Nothing to Disclose, Mario Strazzabosco: Nothing to Disclose, Romina Fiorotto: Nothing to Disclose

4196 | TGFβ2 UPREGULATION ON REACTIVE CHOLANGIOCYTES LIMITS THE THERAPEUTIC EFFICACY OF TGFβ TRAP RAP-1332 IN MOUSE MODELS OF CHRONIC BILIARY INJURY AND FIBROSIS

Pinzhu Huang[1] Monica Shipman[1] Zaur Abilov[1] Maram Alenzi[1] Zhensheng Zhang[1] Richard (Xiwu) Chen[2] Rajasekhar Suragani[3] Patrick Andre[3] Chandra sekar Shankar[1] Yury Popov[1], [1]BIDMC Harvard Medical School, [2]Merck & Co., Inc; Acceleron Pharma Inc, [3]Acceleron Pharma Inc

Background: We report therapeutic effect of RAP-1332 (a ligand trap for TGFβ1 and TGFβ3) in comparison with pan-TGFβ signaling inhibitor (ALK5i), in mouse models of primary sclerosing cholangitis (PSC)-like biliary injury. **Methods:** RAP-1332 (1, 3 and 10 mg/kg twice a week) or TGFb/ALK5 inhibitor (SB-525334, 30 mg/kg/day) was tested in a BALBc.Mdr2$^{-/-}$ mice starting at 4 weeks (early therapy) or 6 weeks (delayed therapy) of age for the following 4-6 weeks, respectively. Portal venous pressure (PVP), serum liver function tests and histologic analyses were assessed. A second sclerosing cholangitis model due to 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) feeding model of PSC was for validation. Inn vitro experiments were conducted in immature murine ductular cell line 603B. **Results:** Alk5 inhibitor led to readily detectable improvement of liver injury and fibrosis parameters in both Mdr2$^{-/-}$ and DDC models. In contrast, both early and delayed administration of RAP-1332 into Mdr2$^{-/-}$ mice did not ameliorate liver injury and liver fibrosis, and led to paradoxical worsening of disease at the high dose. In delayed therapy arm, ALT and AST were increased by 53.50% and 44.14%, respectively at 10 mg/kg dose RAP-1332. Exacerbated ductular reaction and worsened periductular fibrosis was observed in mice receiving high dose of RAP-1332, with 2-fold increase of collagen compared to placebo. Likewise, high dose of RAP-1332 in DDC model led to similar exacerbation of biliary injury and fibrosis. Realtime PCR and *in situ* hybridization showed remarkable upregulation of TGFβ2 expression on actively proliferating reactive cholangiocytes. This was accompanied by adjacent expansion of α-SMA+ hepatic stellate cell and exacerbated inflammation (CD45+ and CD68+ cells). In vitro, TGFβ1/3 trapping by RAP-13323 directly promoted proliferation of immature ductular cells 603B. **Conclusion:** Our results suggest that selective blocking TGFβ1 and TGFβ3 in chronic biliary fibrosing disease is inefficient due to compensatory upregulation of TGFβ2 isoform on reactive cholangiocytes. This should be taken into account in rational design of TGFb inhibitors for cholangiopathies and liver diseases associated with ductular reaction.
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4197 | IMPAIRING BILE DUCT FORMATION DISRUPTS HEPATIC ARTERY FORMATION IN A MOUSE MODEL OF GENETIC CHOLESTASIS

Laura Molina[1] Tyler Yasaka[1] Mara Sullivan[1] Akshita Piedy[1] Shuchang Liu[1] Lori Schmitt[2] Catherine Gestrich[2] Kari Nejak-Bowen[1], [1]University of Pittsburgh, [2]Children's Hospital of Pittsburgh

Background: We previously showed that loss of Yes-associated protein 1 (YAP) in early liver development (Foxa3-Cre YAP KO) leads to an Alagille syndrome-like phenotype, with failure of intrahepatic bile duct development and severe cholestasis. Given the close relationship between the bile ducts and hepatic arteries, we questioned whether these mice showed defects in hepatic artery formation as well. **Methods:** We deleted *Yap1* during early liver development using the *Foxa3* promoter to drive Cre expression. We evaluated the vasculature of these mice using light microscopy, transmission electron microscopy (TEM), and RNA-sequencing. **Results:** We examined WT and YAP KO liver tissue with immunohistochemistry for CD31 (general vasculature), alpha-smooth muscle actin (a-SMA; marks pericytes particularly thick around hepatic arteries), and Lyve1 (lymphatic vessels and some sinusoids). We found that most portal tracts in YAP KO mice lacked hepatic arteries and instead had visible lymphatic vessels which seemed to be dilated in contrast to those in WT mice. We also found that the expression of CD31 and Lyve1 was decreased in the midzonal and pericentral liver sinusoids in YAP KO mice relative to WT, suggesting potential capillarization. The liver vasculature plays a significant role in regulating zonation, and indeed we found that YAP KO mice showed an expansion of periportal (Cyp2f2) and midzonal (Ccnd1) areas, while no change was found

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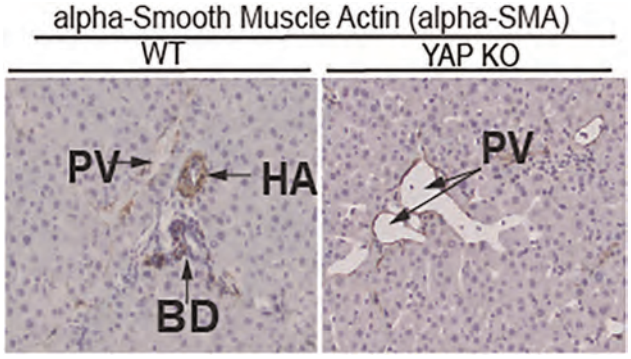
in the pericentral area (GS, Cyp2e1). We next asked if there was a change to the ultrastructure of the liver vasculature, but TEM analysis showed there was no significant change in the fenestrations of the sinusoids and their relationship with the hepatocyte brush border. We examined RNA-sequencing data and did not find a significant enrichment in hypoxia-related genes in YAP KO liver relative to WT liver. Next, we are examining the hepatic vasculature in early biopsies from patients with pediatric cholestasis from the Children's Hospital of Pittsburgh to determine whether our murine findings show relevance in conditions like Alagille syndrome (bile duct paucity) and congenital hepatic fibrosis with Caroli syndrome (bile duct overgrowth), in contrast to hepatocyte-driven cholestasis like PFIC1 and alpha-1-antitrypsin deficiency (no direct genetic damage to bile duct formation). **Conclusion:** We show that in our YAP KO mice, hepatic artery formation is developmentally dependent on bile duct formation. These mice show altered hepatic zonation and vascular marker expression but retain sinusoidal fenestration. Further is ongoing to address the functional implications of this change as well as to query whether abnormalities in hepatic artery formation can be found in patient specimens of pediatric cholestasis.



Disclosures: Laura Molina: Nothing to Disclose, Tyler Yasaka: Nothing to Disclose, Mara Sullivan: Nothing to Disclose, Akshita Piedy: Nothing to Disclose, Shuchang Liu: Nothing to Disclose, Lori Schmitt: Nothing to Disclose, Catherine Gestrich: Nothing to Disclose, Kari Nejak-Bowen: Surrozen, Inc.: Consultant

4198 | DOES CHOLANGIOCYTE FERROPTOSIS PROMOTE A PRO-FIBROGENIC MACROPHAGE PHENOTYPE IN CHOLESTASIS?

Maria Eugenia Guicciardi[1] Anuradha Krishnan[1] Kirsta Olson[1] Alexander Wixom[1] Nidhi Jalan-Sakrikar[1] Gregory Gores[1], [1]Mayo Clinic Rochester

Background: Cholangiopathies, i.e., primary sclerosing cholangitis (PSC), are characterized by oxidative stress, increased serum levels of IL-17A, periductal infiltration of Th17 cells and macrophages, and fibrosis. To date, a parsimonious mechanism to explain these disparate observations has not been proposed. Herein, we explore the concept that cholangiocyte ferroptosis, a lytic form of cell death characterized by phospholipid peroxidation, may unify these observations. Our approach was as follows: 1) Can cholangiocyte oxidative damage be identified in liver specimens? 2) Does IL-17A sensitize cholangiocytes to ferroptosis *in vitro*? and, 3) Do oxidized phospholipids skew macrophage polarization into a profibrogenic phenotype?. **Methods:** The presence of oxidized phospholipids in liver tissue was examined by immunofluorescence for 4-hydroxynonenal (4-HNE) and hyperoxidized peroxiredoxin-3 (PRDX3). Lipidomics analysis for oxidized phospholipids was performed on murine bile using mass spectrometry. Ferroptosis was induced *in vitro* in normal human cholangiocyte cell lines (NHC, H69) by RSL3 (potent inducer of ferroptosis) and measured by propidium iodide uptake and flow cytometry using the fluorescent sensor for lipid peroxidation BODIPY C11. Bone marrow-derived macrophages (BMDM) were isolated from wild type mice and treated with a mixture of oxidized phospholipids (OxPAPC; 25μg/ml). **Results:** Cholangiocyte oxidative damage was identified in bile ducts from liver tissue of PSC patients and mouse models of cholestatic injury (*Mdr2*$^{-/-}$ and DDC-fed mice). Fourteen oxidized phospholipids were detected in the bile of DDC-fed mice, but not in chow-fed mice, and decreased in mice simultaneously receiving the ferroptosis inhibitor liproxstatin 1 (Lip-1). *In vitro*, NHC and H69 cells demonstrated sensitivity to RSL3-induced ferroptosis, which was further enhanced in the presence of IL-17A. BMDM significantly upregulated *Tgfβ* and *Pdgfb* following exposure to OxPAPC, supporting a profibrotic macrophage response. Consistent with a role for ferroptosis in the cholestasis-associated fibrosis, *Mdr2*$^{-/-}$ mice injected with Lip-1 displayed reduced peribiliary macrophage accumulation and fibroblast activation. **Conclusion:** Our data identify cholangiocyte ferroptosis as a potential contributor to the fibroinflammatory biliary injury in human and murine cholestasis by releasing oxidized lipid mediators of macrophage profibrotic polarization.

Disclosures: Maria Eugenia Guicciardi: Nothing to Disclose, Anuradha Krishnan: Nothing to Disclose, Kirsta Olson: Nothing to Disclose, Alexander Wixom: Nothing to Disclose, Nidhi Jalan-Sakrikar: Nothing to Disclose, Gregory Gores: Nothing to Disclose

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4199 | SPATIOTEMPORAL RELATIONSHIP BETWEEN WNT/β-CATENIN AND YAP SIGNALING PATHWAYS IN A CHOLESTATIC MOUSE MODEL

Veronica Lee[1] Kari Nejak-Bowen[1], [1]University of Pittsburgh

Background: Treatments for cholestatic liver disease remain limited. Often, patients develop cirrhosis and liver failure requiring a liver transplant. Therefore, it is important to study regenerative pathways to halt disease progression. Both the Wnt/β-catenin and Yap signaling pathways are involved in liver injury responses such as hepatocyte-to-cholangiocyte trans-differentiation; however, the interaction between these two pathways is unknown. The purpose of this study was to define the spatiotemporal relationship between the Wnt/β-catenin and Yap pathways in cholestatic injury. **Methods:** Wildtype (WT) mice and S45D transgenic (TG) mice, expressing a non-degradable form of β-catenin, were bred to have dual reporters for Wnt and Yap activity. These mice were placed on 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet to induce cholestasis and were sacrificed after 30 and 60 days of treatment. Livers were harvested and ductular reaction, inflammation and fibrosis were analyzed using immunohistochemistry (IHC). Wnt and Yap activity were evaluated by dual immuno-fluorescence (IF) staining. **Results:** TG mice with non-degradable β-catenin had increased ductular reaction and inflammation after 30 days of DDC diet. This corresponded to decreased fibrosis in these mice following prolonged (60 day) DDC. On the other hand, ductular reaction and inflammation did not increase in WT mice until 60 days after DDC. Notably, fibrosis was also significantly higher in WT mice than in TG at this time point. TG mice showed enhanced Wnt activation after 30 days, while in WT, levels of Wnt activation did not increase until after 60 days of DDC. Wnt activation was predominantly present in the nuclei of pericentral hepatocytes while Yap activation was seen in the cytoplasm of periportal cholangiocytes. Yap activity was equivalent in both WT and TG at both time points, indicating no contribution of Wnt signaling to Yap activation. Further, we did not observe co-localization of Wnt or Yap activity. **Conclusion:** Findings from this study suggest early compensatory responses to injury in TG mice may attenuate disease progression, which is likely due to early Wnt activation and subsequent Yap activity. Separation of Wnt and Yap expression in different cell types suggest that these two pathways may function independently or through paracrine mechanisms. Further research is necessary to elucidate the indirect and direct cross-talk between Wnt and Yap signaling in cholestatic injury.

Disclosures: Veronica Lee: Nothing to Disclose, Kari Nejak-Bowen: Surrozen, Inc.: Consultant

4200 | PHARMACOLOGICAL MANIPULATION OF MYC PHOSPHORYLATION IN PSC ANIMALS MODELS DRIVES CHOLANGIOCYTE CELL FATE

Patrick Splinter[1] Steven O'Hara[1] Antonia Felzen[2] Carys Turner[1] Olivia Morgenthaler[1] Gregory Gores[1] Nicholas LaRusso[1], [1]Mayo Clinic, [2]University of Groningen

Background: Using in vitro systems, we showed that stress-induced MYC phosphorylation promotes either cholangiocyte proliferation (pS62 via p38) or senescence (pT58 via GSK3B) and proposed both phenotypes influence PSC pathogenesis. Our in vitro studies also revealed that pharmacologic inhibition of MYC [with MYCi975 (MYCi)] promoted cholangiocyte senescence while inhibition of GSK3 [with CHIR99021 (CHIR)] drove cholangiocyte proliferation, results identifying dual kinase mediators of cholangiocyte cell fate. Here, we further tested this hypothesis in PSC animal models using drugs to selectively modify MYC phosphorylation. **Methods:** We used two accepted animal models of PSC, *Mdr2*$^{-/-}$ and DDC-fed mice. DDC-fed and *Mdr2*$^{-/-}$ mice were treated by intraperitoneal injection of MYCi (50 mg/kg) or CHIR (10 mg/kg) 3 times per week for 3 weeks. Mice were sacrificed and measurements made on serum (liver function tests) and liver including H&E, Sirius red staining, IF for MYC, Keratin 7 (KRT7) and proliferating cell nuclear antigen (PCNA) and qRT-PCR for *Krt7*, *Pcna*, and the senescence marker, *p16*. **Results:** MYCi inhibition of MYC reduced fibrosis in DDC-fed mice (>70%) and in *Mdr2*$^{-/-}$ mice (~30%) versus respective vehicle controls. MYCi treatment improved serum biochemistries (20-50%) in DDC-fed mice, and improved TBILI (~60%) in *Mdr2*$^{-/-}$ mice. Immunofluorescence revealed that total KRT7 and percent PCNA-positive cholangiocytes were decreased in both DDC (25% and 40%, respectively) and *Mdr2*$^{-/-}$ mice (25% and 50%, respectively) following MYCi treatment. MYCi also reduced total liver *Krt7* (>30%) and *Pcna* (>40%) mRNA and increased *p16* mRNA (~50%) in both mouse models. GSK3 inhibition with CHIR increased fibrosis (~1.5-fold) in DDC-fed mice and *Mdr2*$^{-/-}$ mice (1.2-fold) versus respective vehicle controls. Immunofluorescence revealed that CHIR increased total KRT7 and percent PCNA-positive cholangiocytes in both DDC-fed (1.5- and 1.2-fold, respectively) and *Mdr2*$^{-/-}$ mice (1.2- and 1.5-fold, respectively) particularly in parenchymal areas (ductular reaction) and increased total liver *Krt7* (1.7-fold) and *Pcna* (1.25-fold) mRNA and decreased *p16* (>50%) mRNA in both mouse models. **Conclusion:** The data

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demonstrate that MYC is a driver of cholangiocyte proliferation in PSC animal models and identify the kinase mediators that determines cholangiocyte cell fate. Together, the results support the notion that MYC is a "molecular switch" in that determines cholangiocyte responses to stress.

Disclosures: Patrick Splinter: Nothing to Disclose, Steven O'Hara: Nothing to Disclose, Antonia Felzen: Nothing to Disclose, Carys Turner: Nothing to Disclose, Olivia Morgenthaler: Nothing to Disclose, Gregory Gores: Nothing to Disclose, Nicholas LaRusso: NIH: R01 DK 24031, NIH: R01 DK 57993, NIH: P30 DK 84567, NIH: P30 DK90728, NIH: R01 DK117133, NIH: T32 DK 07198

4201 | THE INFLUENCE OF HYDROPHOBIC BILE ACIDS ON THE ONSET OF PRIMARY SCLEROSING CHOLANGITIS VIA CHOLEHEPATIC AND ENTEROHEPATIC CIRCULATIONS

Teruo Miyazaki[1] Hajime Ueda[1] Tadashi Ikegami[1] アキラ ホンダ[1], [1]Tokyo Medical University Ibaraki Medical Center

Background: Primary sclerosing cholangitis (PSC), caused by unknown triggers, is characterized by fibrosis around the large bile duct (onion-skin fibrosis) and frequently complicates inflammatory bowel diseases. Hydrophobic (Hbic) bile acids (BAs) circulating in the cholangio- and entero-hepatic axes are considered as the potential PSC trigger, because PSC lesion was observed in double KO mice (HuBA) of *Cyp2c70* and *Cyp2a12*, which convert a Hbic BA, chenodeoxycholic acid (CDCA), into a hydrophilic mouse-specific BA, muricholic acid, and the secondary BA, lithocholic acid (LCA), back to CDCA, respectively. This study investigated the roles of Hbic BAs on the onset of PSC in the HuBA mice, and cultured human cholangiocytes. **Methods:** Male HuBA mice (5 weeks of age) were treated with CDCA or LCA or no BAs (NT) for 15 weeks via drinking water at low dose (75 mg/L). BA profiles in the liver, serum, and feces were analyzed, along with histological examination and gene expression analysis in the liver and intestines. Serum lipopolysaccharide (LPS) level was also measured. Intestinal permeability was assessed by the FITC-dextran loading test. Highly differentiated immortalized human cholangiocyte cell line (MMNK1) was exposed to 100 μM of CDCA or LCA for 48 hours, and then, gene expression was evaluated by RNA-sequencing and RT-qPCR. **Results:** The BA composition of all examined samples in HuBA mice, which is converted to human-type BA profile, was not significantly affected by the BA administrations. The incidence rate of onion-skin fibrosis was 50-60% by CDCA and no BA treatments, but was 100% by LCA treatment with the significantly larger fibrotic area. In the LCA-treated HuBA mice, intestinal permeability and serum LPS level were significantly higher than in the others, accompanied with a low density of the large intestinal crypts. In the liver and small intestine, the gene expression of *Tnfα, Tgfβ, Tlr4,* and *Integrins-αv/β6* were significantly increased by LCA treatment. In the MMNK1 cells, *CDH1* (*E-cadherin*) gene expression was down-regulated, while *SNAI1* (*Snail*), *CDH3/10/24,* and *TLR4* genes were up-regulated, following CDCA treatment. **Conclusion:** The results support that CDCA and LCA may induce disruption of tight junctions in the cholangiocytes and enterocytes, respectively, contributing to the onset of PSC. Additionally, CDCA-induced TLR-4 expression in the cholangiocytes may promote onion-skin fibrosis and inflammation through endotoxin influx induced by LCA. Hbic BAs (CDCA and LCA) might be the principal triggers of bile duct and intestinal damages via the cholehepatic and enterohepatic circulations.

Disclosures: Teruo Miyazaki: Nothing to Disclose, Hajime Ueda: Nothing to Disclose, Tadashi Ikegami: Nothing to Disclose, アキラ ホンダ : Nothing to Disclose

4202 | VITAMIN D SUPPLEMENTATION AMELIORATES DUCTULAR REACTION, LIVER INFLAMMATION AND FIBROSIS BY UPREGULATING TXNIP IN DUCTULAR CELLS

Jun-Yeop Song[1] Hyuk Soo Eun[1] Seok-Hwan Kim[1] Youngsuk Won[2] Hyojung Kwon[1], [1]Chungnam National University, [2]Korea Research Institute of Bioscience and Biotechnology

Background: Ductular reaction is associated with liver disease progression, but there are currently no pharmacologic drugs targeting ductular reaction. Vitamin D deficiency is common in chronic
liver diseases (CLDs) and related to disease progression, but the underlying mechanisms by which vitamin D supplementation regulates CLD progression remain unclear. **Methods:** Here, we used clinical liver samples and an experimental animal model to examine whether vitamin D supplementation ameliorates ductular reaction and subsequently reduces liver inflammation and fibrosis, and the underlying mechanisms were explored. **Results:** We found that vitamin D plasma levels were negatively correlated with the degree of ductular reaction in patients with chronic liver diseases. $1,25(OH)_2D_3$, the active form of vitamin D, reduced 3,5-diethoxycarbonyl-1,4-dihydrocollidin (DDC)-induced

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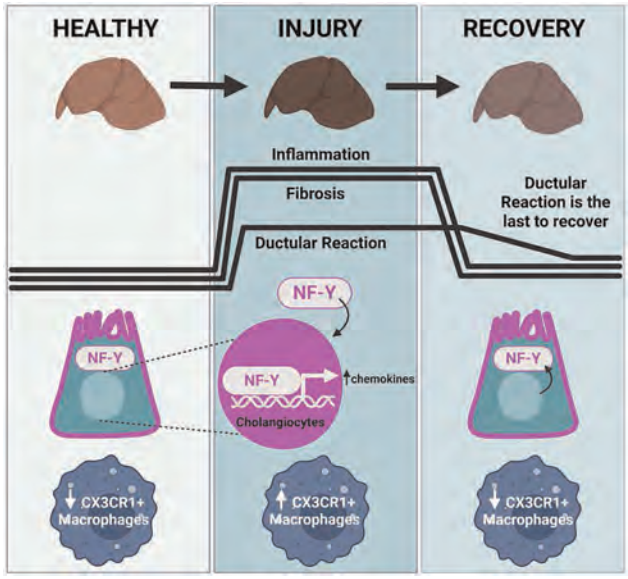
ductular reaction, liver inflammation, and fibrosis in mice and upregulated the vitamin D target gene, TXNIP (encoding thioredoxin-interacting protein), in ductular cells. Cholangiocyte-specific *Txnip*-knockout mice were more susceptible to DDC-induced ductular reaction, inflammation, and fibrosis. Deletion of *Txnip* in cholangiocytes promoted proliferation and suppressed death. Furthermore, *Txnip* deficiency increased TNF-α and TGF-β secretion by cholangiocytes to stimulate Kupffer cells and hepatic stellate cells, consequently leading to inflammation and collagen deposition. Biliary *Txnip* deficiency abolished the protective effects of vitamin D, and TXNIP overexpression attenuated DDC-induced ductular reaction and hepatic inflammation and fibrosis. **Conclusion:** Collectively, our findings identify new mechanism how vitamin D ameliorates liver diseases and suggest that the vitamin D/TXNIP axis is a therapeutic target for addressing ductular reaction and liver diseases.

Disclosures: Jun-Yeop Song: Nothing to Disclose, Hyuk Soo Eun: Nothing to Disclose, Seok-Hwan Kim: Nothing to Disclose, Youngsuk Won: Nothing to Disclose, Hyojung Kwon: Nothing to Disclose

4203 | THE NF-Y HETEROTRIMERIC TRANSCRIPTION FACTOR COMPLEX AS A REGULATOR OF THE CHOLANGIOCYTE PROLIFERATION-ASSOCIATED PHENOTYPE IN A MODEL OF MURINE CHOLESTASIS

Kirsta Olson[1] Anuradha Krishnan[1] Patrick Splinter[1] Alexander Wixom[1] Maria Eugenia Guicciardi[1] Kevin Pavelko[1] Nidhi Jalan-Sakrikar[1] Adiba Azad[1] Nicholas LaRusso[1] Gregory Gores[1], [1]Mayo Clinic

Background: In cholestatic liver diseases, proliferating ductular reactive (DR) cells secrete chemokines promoting liver inflammation. However, the cellular processes regulating this cholangiocyte proliferation associated secretory phenotype (PASP) are incompletely understood. To provide insight into the cholangiocyte PASP, our approach was as follows: 1) first categorize a consequence of the cholangiocyte PASP, namely recruitment of a periportal macrophage subset; 2) ascertain the cholangiocyte chemokine responsible for the macrophage recruitment; and 3) identify the transcription factor(s) increasing expression of his chemokine and other components of the cholangiocyte PASP. **Methods:** Mice were fed a DDC diet for 10 days and then switched to a chow diet to permit recovery (designated as R days). **Results:** Total intrahepatic leukocytes were isolated and profiled by mass spectrometry (CyTOF), where an abundant periportal CX3CR1^{+} macrophage population was demonstrated in the DDC mice. To verify the CyTOF observations, we employed CX3CR1^{GFP} mice and noted that the CX3CR1^{GFP+} periportal macrophages increased 4-fold on the DDC diet and returned to basal values by day R10. Spatial transcriptomics identified cholangiocyte expression CX3CL1, the ligand of CX3CR1, in DR cells. To further interrogate the regulation of the cholangiocyte PASP, cholangiocytes were isolated from control, DDC, and R15 mice and RNA-seq performed. IPA Canonical pathway analysis revealed activation of the "pathogen induced cytokine storm" pathway in cholangiocytes activated from DDC fed mice, and resolution of this pathway in R15 isolated cholangiocytes. SCENIC regulon analysis identified that the NF-Y transcription factor heterotrimeric complex (A, B, and C subunits) was activated on the DDC diet and repressed at control and R15 timepoints. To examine this transactivation in human cholangiocytes, normal human cholangiocytes (NHC) were treated with an siRNA targeting the NF-YA subunit (knockdown validated by immunoblot analysis). Indeed, chemokine expression was decreased in the cells transfected with the targeting siRNA, but not the scrambled siRNA. **Conclusion:** These observations implicate the NF-Y transcription factor complex as a regulator of the cholangiocyte PASP in a model of murine cholestasis. The results also support a cholangiocyte CX3CL1/CX3CR1^{+} macrophage axis in cholestatic liver injury.



Disclosures: Kirsta Olson: Nothing to Disclose, Anuradha Krishnan: Nothing to Disclose, Patrick Splinter: Nothing to Disclose, Alexander Wixom: Nothing to Disclose, Maria Eugenia Guicciardi: Nothing to Disclose, Kevin Pavelko: Nothing to Disclose, Nidhi Jalan-Sakrikar: Nothing to Disclose, Adiba Azad: Nothing to Disclose, Nicholas LaRusso: NIH: R01 DK 24031, NIH: R01 DK 57993, NIH: P30 DK 84567, NIH: P30

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4204 | SCHISANTHERIN A, A NEW TYPE OF PPARα LIGAND ATTENUATES CHOLESTATIC LIVER INJURY IN MICE

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Background: Schisantherin A (Sin A), the natural compound from *Schizandra chinensis (Turcz.) Baill.*, exhibits anti-hepatic fibrosis effects, but the efficacy and underlying mechanism in treating cholestatic liver injury is poorly understood. **Methods:** In this study, two mouse models, including 3,5-Diethoxycarbonyl-1,4-Dihydro-2,4,6-Collidine (DDC)-induced and *Mdr2*$^{-/-}$ spontaneous cholestatic liver injury, and the peroxisome proliferator-activated receptor alpha (Pparα) gene knockout (*Pparα*$^{-/-}$) mice were used to investigate the therapeutic effect and mechanisms of Sin A. Furthermore, proteomics and RNA-sequencing analyses, luciferase reporter assay, as well as drug affinity responsive target stability (DARTS), cellular thermal shift assay (CESTA) and surface plasmon resonance (SPR) experiments were performed. Degradation of the PPARα protein was measured after the treatment of cycloheximide (CHX) with or without Sin A at the indicated time points *in vitro*. **Results:** Treatment with Sin A significantly ameliorated the cholestasis-related disorder of bile acid metabolism, liver injury, ductular reaction (DR), inflammation and fibrosis in both DDC-induced and *Mdr2*$^{-/-}$ mice. Proteomics and RNA-sequencing analyses of both DDC-induced liver and *Mdr2*$^{-/-}$ liver samples before and after treatment with Sin A suggested that Sin A activated PPAR signaling. Further validation revealed that Sin A significantly up-regulated hepatic PPARa protein expression in these two mice models. Subsequently, luciferase reporter assay revealed that Sin A significantly activated PPARa. DARTS and CETSA experiments indicated that Sin A inhibited the PPARα degradation caused by pronase and the temperature-induced denaturation in AML12 cell lysates, thereby implying a direct interaction between herpetrione and PPARα. SPR analysis validated the interaction of Sin A with PPARα, demonstrating an equilibrium dissociation constant (KD) of 63.26 μM. The results of degradation of the PPARα protein with CHX showed that Sin A weakened PPARα degradation compared to the control group. These results revealed that Sin A bound directly to the PPARα protein to improve the stability of the PPARα protein and activate PPARa. Furthermore, PPARa deletion abolished the anti-biliary fibrotic effect of Sin A in DDC-induced mice, suggesting that Sin A alleviated cholestasis, bile acid metabolism, DR and inflammation in mice by targeting up-regulation of PPARα, thereby alleviating cholestatic liver injury. **Conclusion:** Our findings provided compelling evidence for Sin A treatment in cholestatic liver injury, as well as the broader prospects for cholestatic liver injury treatment by targeting PPARα.

Disclosures: Jiamei Chen: Nothing to Disclose, Zheng Zhang: Nothing to Disclose, En-qi Tang: Nothing to Disclose, Yue Liang: Nothing to Disclose, Wei Liu: Nothing to Disclose, Ping Liu: Nothing to Disclose

4205 | UDP-GLUCURONOSYLTRANSFERASE (UGT) ENZYME POLYMORPHISMS MAY IMPACT CLINICAL VARIABLES, TREATMENT RESPONSE, AND CALCULATED RISK SCORES IN PBC AND PSC

Colleen Hayes[1] Mahesh Krishna[2] Christopher Hemme[1] Bonnie Chen[3] Scott Roberts[3] James Boyer[2] David Assis[2] Nisanne Ghonem[1], [1]University of Rhode Island, [2]Yale University, [3]Yale

Background: PBC and PSC are characterized by the accumulation of toxic bile acids. Glucuronidation is a major pathway of bile acid detoxification, conjugating glucuronic acid to the parent bile acid by UGT enzymes. Human bile acid glucuronidation is catalyzed by UGT1A1, -1A3, -1A4, -2B4, and -2B7, which are encoded by the polymorphic *UGT1A* and *-2B* genes. Single nucleotide polymorphisms (SNP) in these genes can influence glucuronidation and bile acid levels in PBC and PSC. We investigated the frequency of UGT polymorphisms in genomic data provided by the PBC and PSC cohorts in the NIH *All of Us (AoU)* database and compared those frequencies to PBC and PSC patients requiring second-line treatment with fenofibrate. We also analyzed the impact of UGT genotypes on clinical markers and risk scores in PBC and PSC. **Methods:** UGT SNP frequencies in PBC (n = 421) and PSC (n = 178) were determined from the AoU genomic database (Controlled Tier Dataset, v8). Genomic DNA was isolated from plasma samples of PBC patients on second-line therapy with UDCA + fenofibrate (n = 59), and from PSC patients with persistent cholestasis despite UDCA who received fenofibrate (n = 28), obtained from the Yale Liver Center Biorepository (New Haven, CT). Genotyping was performed for *UGT1A3* -66T > C, *UGT1A3* 31T > C, *UGT2B4* 1374A > T, and *UGT2B7* 802T > C. UGT genotypes

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were correlated with clinical variables (ALP, bilirubin) and risk scores for PBC and PSC (UK, PREsTO, Mayo Risk Score (MRS)). **Results:** The *All of Us* database revealed genotype frequencies for specific UGT SNPs in PBC and PSC. Specifically, alternate genotype (heterozygote + homozygote mutant) frequencies were found for *UGT1A3* -66 T > C: 61% (PBC and PSC), *UGT1A3* 31T > C (PBC: 59%, PSC: 58%), *UGT2B4* 1374 A > T (PBC: 26%, PSC:30%), and *UGT2B7* 802 T > C (PBC: 65%, PSC: 67%). By contrast, alternate genotype frequencies in our patient cohorts requiring second-line therapy were notably different for PBC (67%, 66%, 0% ($p < 0.05$), and 34% ($p < 0.001$)) and for PSC (81% ($p = 0.08$), 82% ($p < 0.05$), 0% ($p < 0.05$), and 35% ($p < 0.01$)), respectively. Furthermore, analyses of clinical data and risk scores revealed that *UGT1A3* -66T > C, *UGT1A3* 31T > C, and *UGT2B7* 802T > C influenced ALP and bilirubin levels for PBC ($p < 0.05$), and ALP and MRS for PSC ($p = 0.09$). **Conclusion:** Our study identified UGT polymorphisms in PBC and PSC in both the AoU cohorts and our study cohorts. Our findings also revealed significant differences between the frequency of UGT SNPs in the *AoU* database and in our study cohorts. These findings raise the possibility that UGT SNPs may impact the need for second-line therapy in PBC and added anti-cholestatic therapy in PSC. Preliminary data also suggest that the *UGT1A3* -66T > C, *UGT1A3* 31T > C, and *UGT2B7* 802T > C SNPs may impact clinical variables and calculated risk scores in PBC and PSC. These findings support further investigation into UGT polymorphisms as potential factors underlying the response to anti-cholestatic therapy, and on clinical outcomes.

Disclosures: Colleen Hayes: Nothing to Disclose, Mahesh Krishna: Ipsen: Patient Experience Consultant, Christopher Hemme: Nothing to Disclose, Bonnie Chen: Nothing to Disclose, Scott Roberts: Nothing to Disclose, James Boyer: Mirum Pharmaceuticals: grant recipient, IPSEN: Clinical Evenets Committee for clinical trial, AstroZenica: Member of Clinical Events Committe, David Assis: Nothing to Disclose, Nisanne Ghonem: Nothing to Disclose

4206 | DISTINCT BILE MYCOBIOME SIGNATURE IDENTIFIES FUNGAL PEPTIDE PANEL PREDICTIVE FOR GALLBLADDER CARCINOMA

Sanju Yadav[1] NUPUR SHARMA[1] manisha yadav[1] neha sharma[1] gaurav tripathi[1] sushmita pandey[1] jaswinder singh Maras[2], [1]Institute of liver and biliary sciences, [2]NSTITUTE OF LIVER AND BILIARY SCIENCES

Background: Background: and **Aim:** Carcinoma of Gallbladder cancer (CAGB) has poor prognosis. While the bile microbiome and lipidome are associated with CAGB development, the contribution of fungal microbiota is unexplored. Our study aims to investigate the contribution of fungal microbiome and identify top fungal peptides to potentially stratify CAGB patients. **Methods:** Bile samples were collected from patients undergoing cholecystectomy for Gall Stone (GS) disease ($n = 10$), patients undergoing surgery for CAGB ($n = 16$) and healthy liver donors ($n = 16$) were subjected to fungal peptide-based diversity analysis and metabolomics. Results were cross-validated on the plasma samples, correlated with clinical parameters, and subjected to machine learning analysis. **Results:** Fungal peptide-based diversity analysis identified 6 Phylum and 24 Fungal Species differentially regulated in the bile samples of the study cohort. Fungal diversity (alpha and beta diversity) was significantly higher in CAGB as compared to GS or HC ($p < 0.05$). 93 fungal peptides were upregulated and 63 were downregulated in CAGB ($p < 0.05$, FC > 1.5). Linear discriminant analysis significantly segregated CAGB patients with marked increase in Aspergillus wentii (log2FC-12.21), Nosema bombycis (log2FC-11.25), Saccharomyces (log2FC-10.89), Saccharomyces cerevisiae (log2FC-10.68) and Schizosaccharomyces pombe (log2FC-10.38; $p < 0.05$)in the bile samples. Fungal-metabolite correlation analysis ($r2 > 5$, $p < 0.05$) identified Aspergillus wentii, Nosema bombycis, and others directly associated with lysine biosynthesis, taurine, and hypotaurine metabolism, fatty acid, and other in bile, and cysteine and methionine metabolism, ascorbate metabolism, purine metabolism and other in plasma. Probability of detection (POD) calculated using fungal peptides showed a diagnostic efficiency of 96% for segregation of CAGB patients. The identified top 5 fungal peptides were validated using Single reaction monitoring analysis with which it predicted early mortality > 90% accuracy/sensitivity and specificity in Machine Learning model. **Conclusion:** Bile fungal diversity correlates with CAGB development and identified fungal panel capable of segregation and early diagnosis of CAGB patients.

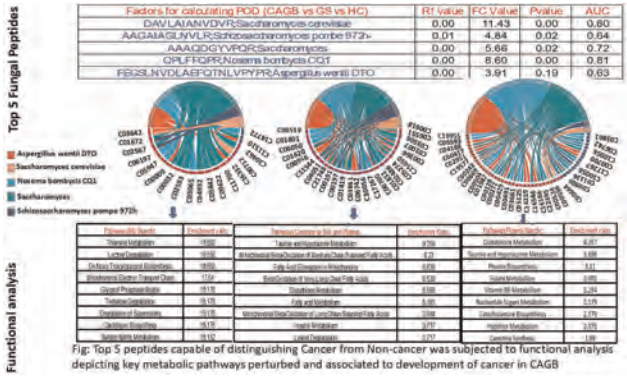

Fig: Top 5 peptides capable of distinguishing Cancer from Non-cancer was subjected to functional analysis depicting key metabolic pathways perturbed and associated to development of cancer in CAGB

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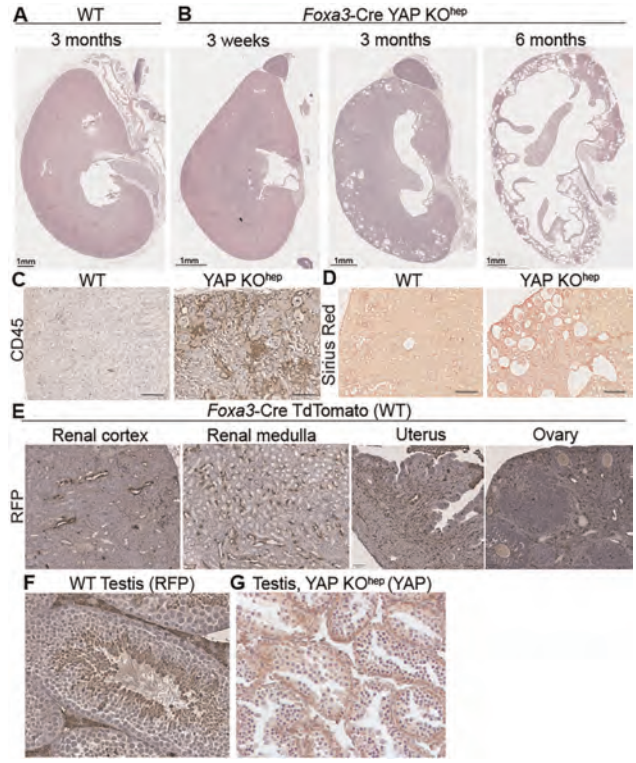
4207 | MORE THAN JUST LIVER: ELUCIDATING GENETIC AND CHOLESTATIC CAUSES OF CHRONIC KIDNEY DISEASE IN A MOUSE MODEL OF BILE DUCT PAUCITY

Laura Molina[1] Jia-jun Liu[1] Akshita Piedy[1] Shuchang Liu[1] Jianhua Luo[1] Minakshi Poddar[1] Sucha Singh[1] Pamela Cornuet[1] Kari Nejak-Bowen[1], [1]University of Pittsburgh

Background: We previously showed that loss of Yes-associated protein 1 (YAP) in early liver development (*Foxa3*-Cre YAP KO) leads to an Alagille syndrome-like phenotype, with failure of intrahepatic bile duct development and severe cholestasis. However, these mice also develop severe chronic kidney injury. Here we investigate the renal pathology and differentiate the genetic defects caused by YAP deletion from long-term exposure to severe cholestasis. **Methods:** We used microscopy, serum biochemistry, and RNA-sequencing to study *Foxa3*-Cre *Yap1*$^{fl/fl}$ mice and littermate controls, as well as *Foxa3*-Cre TdTomato healthy reporter mice. **Results:** YAP KO mice have grossly normal renal development, with no visible abnormalities at 1 month. They develop glomerular dilation and polycystic kidney disease over the first three to six months of life, accompanied by chronic inflammation and fibrosis (panels A-D). A similar phenotype was observed in a previously published mouse model of bile duct ligation (PMID37939855), although these mice were not observed past 12 weeks post-injury. However, chronic renal disease has rarely been investigated in other mouse models of cholestasis.

We next examined whether *Foxa3*-Cre may affect genitourinary tissues. Using *Foxa3*-Cre TdTomato reporter mice, we found reporter expression not just in organs derived from foregut endoderm, but also throughout the genitourinary tract, including some of the renal tubules, most urothelium, and hormone-producing cells in the testes and ovaries (panels E-F). The testosterone-producing Leydig cells and maturing spermatids in the testes were strongly positive; notably, we found that YAP KO testes lack Leydig cells and fail to produce mature sperm (panel G), demonstrating a critical role for YAP in male fertility and raising the possibility that altered testosterone levels may be affecting other organs in this model.

We next performed bulk RNA-sequencing on 3-week-old kidneys. YAP KO kidneys show changes in primary cilia-related genes, bile salt metabolism, and decreased RXR signaling. Further study is ongoing to identify mechanisms connecting YAP deficiency with polycystic kidney disease and male infertility in this model. We are also testing the effect of Vitamin A supplementation in improving renal function by activating RXR. **Conclusion:** Many genetic syndromes impact both liver and kidney function, while adults with liver injury often progress to multi-organ dysfunction. We demonstrate for the first time that the *Foxa3* promoter is active in genitourinary tissues, and consequently the YAP KO model exhibits complex multi-organ pathology. This model presents an opportunity to (1) study the combined effects of genetics and cholestasis on renal function; (2) study the impact of low testosterone on cholestatic liver injury; and (3) presents YAP as a possible disease modifier in a variety of cholestatic and renal diseases.



Disclosures: Laura Molina: Nothing to Disclose, Jia-jun Liu: Nothing to Disclose, Akshita Piedy: Nothing to Disclose, Shuchang Liu: Nothing to Disclose, Jianhua Luo: Nothing to Disclose, Minakshi Poddar: Nothing to Disclose, Sucha Singh: Nothing to Disclose, Pamela Cornuet: Nothing to Disclose, Kari Nejak-Bowen: Surrozen, Inc.: Consultant

4208 | EFFECT OF SEX, RACE AND DONOR TYPE ON LIVER TRANSPLANT OUTCOMES IN BILIARY ATRESIA

Alejandro chiodo ortiz[1] David Ford[2] Syeda Rabab Fatima[3] Meng-Hao Li[4] Yang Yu[4] Naoru Koizumi[4] Jorge

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Ortiz[5], [1]Columbia University, [2]Albany Medical College, [3]king edward medical university, [4]George Mason University, [5]Garnet Health Medical Center

Background: Biliary atresia (BA) is a progressive fibro-obliterative cholangiopathy historically managed with portoenterostomy. However, suboptimal outcomes and long-term sequalae necessitate liver transplant (LTX) as salvage or primary therapy for most children with BA. As a result, BA is the most common indication for pediatric LTX. The impact of donor and recipient characteristics has not been well studied. We investigated the effect of sex, race and donor type on recipient outcomes. **Methods:** A retrospective analysis using the UNOS database between January 1, 2000 and September 30, 2024 was performed. 1,427 pediatric liver transplants for BA were identified. Donor, recipient and transplant characteristics were compared by sex, race and donor type using t-/Wilcoxon-Mann-Whitney, ANOVA or Chi-sq/Fishers exact tests. Graft failure and patient mortality were analyzed using Kaplan-Meier and COX regression. **Results:** BA LTX recipients had no difference in acute rejection in hospitalization ($p = 0.283$), 1 year rejection ($p = 0.457$) or graft failure at 1, 3 or 5 years ($p = 0.121$) when compared by sex. There were no differences in acute rejection in hospitalization ($p = 0.74$), rejection within 1 year ($p = 0.108$) or graft failure due to ischemic cholangiopathy ($p = 0.872$) by recipient race. However, Asian recipients experienced significantly higher rates of graft failure due to hepatic artery thrombosis ($p = 0.038$). Deceased donor LTXs with IL2 induction were at lower risk of graft failure (HR = 0.376, $p = 0.007$). Living donor LTXs with recipient age > 10 (HR = 13.02, $p = 0.037$) and prolonged total preservation time (HR = 1.338, $p = 0.032$) were at increased risk of graft failure. IL2 induction was associated with a lower risk of patient mortality (HR = 0.516, $p = 0.039$) in living donors. **Conclusion:** LTX recipients with BA experience similar rates of rejection and graft failure regardless of sex, race or donor type. Induction, age and preservation time are important considerations as feasibility and utilization of LTX continue to improve.

Disclosures: Alejandro chiodo ortiz: Nothing to Disclose, David Ford: Nothing to Disclose, Syeda Rabab Fatima: Nothing to Disclose, Meng-Hao Li: Nothing to Disclose, Yang Yu: Nothing to Disclose, Naoru Koizumi: Nothing to Disclose, Jorge Ortiz: Nothing to Disclose

4209 | A NEW CLASS OF ORALLY AVAILABLE NTCP INHIBITORS DEMONSTRATES POTENT EFFICACY AGAINST HBV AND CHOLESTASIS IN HUMANIZED MICE MODELS

Stan van de Graaf[1] Hendrik Jan Thibaut[2] Philip Meuleman[3] Kaliopi Pervolaraki[4] Jean-Christoph Vanherck[4] Charlène Marcadet[4] Lieven Verhoye[3] Amse De Meyer[3] Madina Rasulova[2] Heyrhyoung Lyoo[2] Jasmine Paulissen[2] Kristof De Vos[2] Isabelle Bolt[5] Esther Vogels[5] Dagmar Tolenaars[6] Patrick Chaltin[7] Arnaud Marchand[4] Matthias Versele[4] Johan Neyts[2] Pieter Annaert[2], [1]Amsterdam UMC, [2]KU Leuven, [3]Ghent University, [4]CISTIM Leuven, [5]Amsterdam UMC, Tytgat Institute for Liver and Intestinal Research, [6]Amsterdam MC, Tytgat Institute for Liver and Intestinal Research, [7]Centre for Drug Design and Discovery, Leuven, Belgium

Background: The sodium taurocholate co-transporting polypeptide (NTCP, *SLC10A1*) is solely expressed at the basolateral membrane of hepatocytes. Here, it constitutes the main transporter of conjugated bile acids and serves as the entry receptor for the hepatitis B virus (HBV) and hepatitis delta virus (HDV). Daily injection with a Pre-S1 mimicking synthetic peptide called bulevirtide (also called Myrcludex-B) is approved in the EU for treatment of patients co-infected with HBV and HDV. We and others have previously demonstrated that pharmacological inhibition of hepatic bile salt uptake using bulevirtide ameliorates cholestatic liver injury in mice. As both treatment of viral hepatitis and cholestatic liver diseases require chronic treatment, we aimed to develop orally available small molecule NTCP inhibitors. **Methods:** Radiolabeled or fluorophore-coupled conjugated bile salts were used to identify and optimize potent and selective small-molecule inhibitors of NTCP-mediated bile acid uptake and HBV/HDV entry inhibitors with adequate *DMPK* characteristics, suitable for oral dosing. Effects of the lead candidate were assessed in a DDC-induced cholestasis mouse model transgenic for human NTCP. Urokinase-type plasminogen activator-severe combined immunodeficiency (uPA-SCID) mice engrafted with human hepatocytes were used to determine *in vivo* impact on bile acid kinetics and HBV infection. **Results:** In a comprehensive drug discovery effort we identified a novel chemical series of NTCP inhibitors with multiple compounds with single-digit nM potency for NTCP and high selectivity (> 100x) against ASBT and BSEP mediated bile salt transport. Consistently, these compounds dose-dependently reduced intracellular bile acid levels in sandwich-cultured human hepatocytes. *In vitro* infection studies demonstrated low nM HBV and HDV entry inhibition, similar to bulevirtide. A lead molecule, CIM212930, with good oral bioavailability and excellent liver distribution was prioritized. PK/PD experiments with CIM212930 in uPA/SCID mice with humanized livers illustrated dose-dependent and prolonged elevation of serum bile acid levels demonstrating both target engagement and indicative of a once-daily oral dosing regimen. Finally, CIM212930 largely reduced liver damage in DDC-induced cholestasis models and completely blocked HBV infection in a humanized liver mouse model. **Conclusion:** We describe novel and specific small-molecule orally

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bioavailable NTCP inhibitors that have the potential to treat HBV/HDV and cholestatic liver disease.

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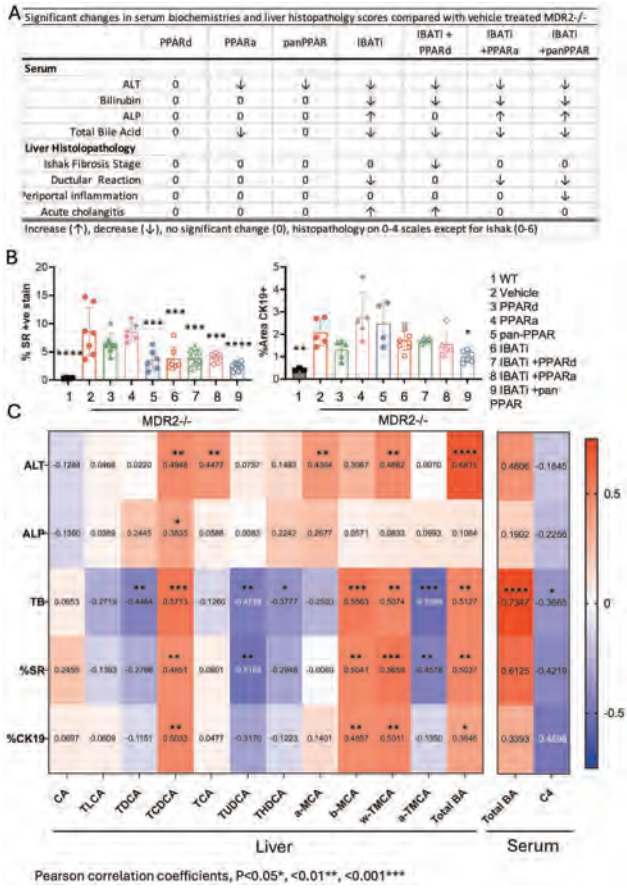
4210 | COMBINATION OF PHARMACOLOGICAL IBAT INHIBITION AND PPAR ACTIVATION IMPROVES LIVER HISTOPATHOLOGY OF SCLEROSING CHOLANGITIS IN MDR2$^{-/-}$ MICE

Manavi Singh[1] Pamela Sylvestre[2] Liva Pfuhler[2] Rebekah Karns[2] Annika Yang Vom Hofe[1] RAMESH KUDIRA[1] Mary Mullen[1] Priya Bariya[2] wujuan zhang[2] Kenneth Setchell[2] Jennifer Kasten[2] Cory Kostrub[3] Pamela Vig[4] Alexander Miethke[1], [1]Cincinnati Children's Hospital Medical Center, [2]CCHMC, [3]Mirum Pharmaceuticals, [4]Mirum Phamaceuticals

Background: We showed before that combination of pharmacological inhibition of intestinal bile acid uptake with IBAT inhibitors (IBATi) in combination with agonists of isoforms of peroxisome proliferator–activated receptors (PPAR) reduced serum markers of hepatocellular injury and cholestasis in the MDR2$^{-/-}$ mouse model of sclerosing cholangitis (SC). Here we examine the effects of these treatments on liver histopathology. **Methods:** 30-day-old female MDR2$^{-/-}$ FVB mice were treated for 14 days with daily orogastric gavage of either vehicle, 100 mg/kg/day Bezafibrate (pan-PPAR agonist), 100 mg/kg/day Fenofibrate (PPAR -alpha agonist), 10 mg/kg Seladelpar (PPAR-delta agonist), 0.008% SC-435 (IBATi) admixed to chow, or a combination of IBATi and PPAR agonists. End of treatment liver histopathology was assessed by a pathologist blinded to treatment groups (n = 6 per group) and by image analysis of liver sections subjected to Sirius Red (SR) staining or CK19-IHC. Hepatic bile acid (BA) composition and transcriptome were quantitated by mass-spectrometry and bulk RNA-seq, respectively. **Results:** Compared with vehicle treated MDR2$^{-/-}$ mice, reduction in Ishak stage of fibrosis was only observed in mice treated with IBATi and PPAR-delta agonist (mean ± SEM of 2.8 ± 0.4 vs 4 ± 0.3 stage, $p < 0.01$). Significant reductions in ductular reaction and periportal inflammation were observed in mice receiving IBATi alone or in combination with PPAR agonists (Fig 1A). Image analysis revealed diminished percent area fibrosis in all treatment groups containing IBATi and following monotherapy with pan-PPAR agonist; whereas, decrease in intrahepatic biliary mass was significant only in mice receiving IBATi and pan-PPAR agonist (Fig 1B). Across all treatment groups, liver concentrations of total BA, TCDCA, omega(w)-TMCA, and beta(b)-MCA, were positively correlated with serum levels of liver injury, percent area fibrosis, and intrahepatic biliary mass (Fig 1C). Principal component analysis of differentially expressed genes in bulk liver RNA-seq data revealed that mice receiving IBATi and PPAR-delta agonist more closely segregated with wild type mice compared with MDR2$^{-/-}$ vehicle and the other treatment groups. **Conclusion:** While monotherapies of PPAR agonists or IBATi improve serum biomarkers of liver injury, prevention of progression of liver fibrosis or ductular reaction requires combination therapy of IBATi and PPAR agonist. The synergistic effects may originate from specific changes in hepatic BA composition under these treatments.



Disclosures: Manavi Singh: Nothing to Disclose, Pamela Sylvestre: Nothing to Disclose, Liva Pfuhler: Nothing to Disclose, Rebekah Karns: Nothing to Disclose, Annika Yang Vom Hofe: Nothing to Disclose, RAMESH KUDIRA: Nothing to Disclose, Mary Mullen: Nothing to Disclose, Priya Bariya: Nothing to Disclose, wujuan zhang: Nothing to Disclose, Kenneth Setchell:

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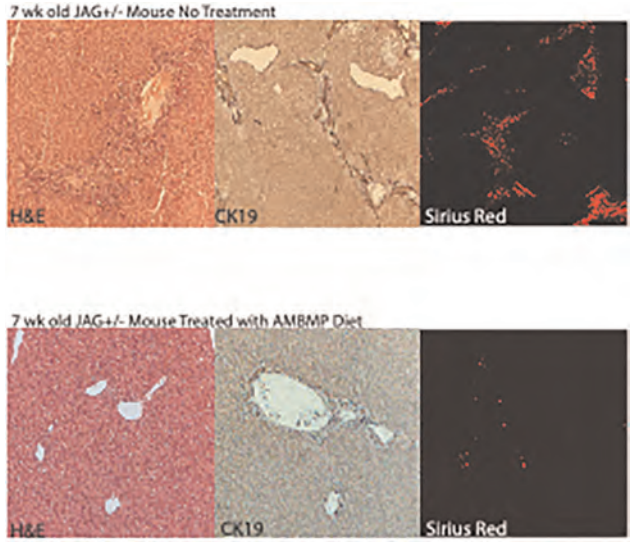
4211 | EXPLORING THE ROLE OF THE WNT SIGNALING PATHWAY IN AN ALAGILLE MOUSE MODEL OF CHOLESTATIC LIVER DISEASE

Sarah Bedoyan[1] Kari Nejak-Bowen[2] Pamela Cornuet[2], [1]University of Pittsburgh Medical Center, [2]University of Pittsburgh

Background: Alagille syndrome (ALGS) is a rare, autosomal dominant systemic disease with wide variability in disease penetrance. It is caused by pathogenic variants in JAG1 which encode crucial components of the Notch signaling pathway that develop intrahepatic bile ducts. Alteration of this pathway leads to intrahepatic bile duct paucity and cholestasis. The Wnt- β -catenin signaling pathway is crucial in hepatobiliary repair, cell proliferation, apoptosis, zonation and regeneration after cholestasis-induced injury. Activators of this pathway present potentially druggable targets in cholangiopathies. Here we demonstrate the effects of augmenting this pathway in a $Jag^{+/-}$ mouse model of ALGS. **Methods:** We characterized the time course and extent of liver injury in $Jag^{+/-}$ mice, then used 2-amino-4-[3,4-(methylenedioxy) benzylamino]-6-(3-methoxyphenyl) pyrimidine (AMBMP), a small molecule Wnt agonist mixed into mouse chow at a concentration of 3.33 mg/kg. $Jag^{+/-}$ as well as WT litter mates were fed AMBMP diet starting 5 weeks after birth for a duration of 2 weeks. Liver was stained for histology and markers of cell proliferation and apoptosis. RNA was measured for expression of b-catenin, albumin, Glutamine Synthetase (GS), cyclin-D1, and biliary markers CK19, Sox9, and EpCAM. Serum biochemical markers of hepatic and biliary injury were also measured. **Results:** $Jag^{+/-}$ mice showed liver injury as early as 3 weeks post-natal age, which significant ductular reaction and fibrosis peaking at 7 weeks, before showing a visually improved phenotype at 9.5 weeks on H&E staining. $Jag^{+/-}$ mice at 9.5 weeks showed significantly more CD45 staining (a pan-leukocyte marker), indicating more inflammatory cell infiltration. Preliminary results show that when treated with AMBMP, the $Jag^{+/-}$ mouse group has higher beta-catenin and GS RNA expression by qPCR. Comparison of serum biomarkers between $Jag^{+/-}$-treated with AMBMP diet vs. regular mouse chow shows a decrease in serum alkaline phosphatase level. **Conclusion:** The Wnt-β-catenin is crucial in liver development and metabolism and augmenting its activity in models of cholestasis may reduce hepatocyte injury and help promote liver repair. $Jag^{+/-}$ mice have extensive liver injury shortly after weaning, and while studies are ongoing, treatment with AMBMP diet shows early promise in activating β -catenin and its downstream targets (GS) and reducing serum biomarkers of liver injury.



Disclosures: Sarah Bedoyan: Nothing to Disclose, Kari Nejak-Bowen: Surrozen, Inc.: Consultant, Pamela Cornuet: Nothing to Disclose

4212 | BETA-CATENIN OVEREXPRESSION DAMPENS HEPATITIS, FIBROSIS, AND DUCTULAR PROLIFERATION IN A MOUSE CHOLESTATIC LIVER DISEASE MODEL AND COINCIDES WITH INCREASED HEPATOCYTE-TO-CHOLANGIOCYTE TRANSDIFFERENTIATION

Tony (Chun-Cheng) Chiang[1] Pamela Cornuet[1] Kari Nejak-Bowen[1], [1]University of Pittsburgh

Background: Cholestatic liver diseases are characterized by impaired bile flow and bile acid accumulation. Transdifferentiation provides a safe way to mitigate damage to the biliary epithelial cells (cholangiocytes). Our preliminary data showed that Wnt/beta-catenin signaling is increased during hepatocyte-to-cholangiocyte transdifferentiation in vitro. Knockout or inhibition of Wnt/beta-catenin reduced transdifferentiation markers and worsened biliary injury. Therefore, we hypothesize that overexpression of beta-catenin augments hepatocyte-to-cholangiocyte transdifferentiation, thus alleviating biliary injury and restoring liver functions. To test

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this, we overexpressed non-degradable serine-45-aspartate mutated (S45D) beta-catenin in the mdr2 $^{-/-}$ mouse model of cholestasis and studied the impact and underlying mechanism. **Methods:** Transgenic beta-catenin S45D+ mice crossed with mdr2 knockout mice (TG/KO), mdr2 knockout alone (KO) mice, and their wildtype littermates, all carrying Rosa26-stopf/f-EYFP alleles, were injected with AAV8-TBG-Cre at 5 weeks old to label hepatocytes and then sacrificed at 12 weeks old. Biochemical markers of hepatobiliary injury were assessed. Livers were studied for histopathology and fibrosis, and ductular proliferation was quantified by CK-19 immunohistochemistry. Immunofluorescence for Sox9 and EYFP was used to trace hepatocyte-to-cholangiocyte transdifferentiation, and the number of EYFP+ cholangiocytes and Sox9+ hepatocytes was quantified for each group. **Results:** Serum biochemical studies suggested that worsening hepatitis in the injury-alone genotype (KO) can be rescued by S45D beta-catenin overexpression (TG/KO). Histopathology revealed more inflammation, fibrosis, and ductular proliferation in the KO group, which were reversed partially in the TG/KO group. Histopathology also disclosed that sex differences exist in the mice. Immunofluorescence staining showed more EYFP+ cholangiocytes and Sox9+ hepatocytes in the portal zone of the TG/KO group, indicating that more hepatocyte-to-cholangiocyte transdifferentiation occurs when beta-catenin is overexpressed in hepatocytes. **Conclusion:** S45D beta-catenin overexpression slows the progression of injury in mdr2 KO mice. Further studies are needed to separate genders to compare the effects between groups. Based on the finding of increased cellular plasticity in the S45D mice, we plan to elucidate more detailed mechanisms using both biased and unbiased approaches in the future.

Disclosures: Tony (Chun-Cheng) Chiang: Nothing to Disclose, Pamela Cornuet: Nothing to Disclose, Kari Nejak-Bowen: Surrozen, Inc.: Consultant

4213 | IMPACT OF IGG4-RELATED DISEASE ON BILIARY OBSTRUCTION IN PRIMARY SCLEROSING CHOLANGITIS: A MULTI-CENTER RETROSPECTIVE COHORT STUDY USING TRINETX

Hazem Abosheaishaa[1] Ahmed Salem[2] Amr Dokmak[3] Mohamed Eldesouki[4] Khaled Elfert[5] Omar Abdelhalim[6] Mohamed El-Kassas[7] Mohammed Abusuliman[8] Nermin Elhossiny[9] Madhavi Reddy[3], [1]Icahn school of medicine at mount sinai, [2]Maimonides Medical Center, [3]The Brooklyn Hospital Center, [4]New York Medical College at Saint Michael Medical Center, [5]West Virginia University, [6]Queens Hospital Center, [7]Helwan University, [8]Henry Ford Hospital, [9]St Mary General hospital prime healthcare

Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive inflammation and fibrosis of the bile ducts. The coexistence of IgG4-related disease (IgG4-RD) in PSC patients has been reported, yet its impact on clinical outcomes remains poorly understood. This study aimed to evaluate the differences in biliary obstruction between PSC patients with and without IgG4-RD using a large multi-center electronic health record (EHR) database. **Methods:** We conducted a retrospective cohort study utilizing the TriNetX research network, including 102 healthcare organizations. Adult patients ($\geq$ 18 years) with a diagnosis of PSC (ICD-10: K83.01) were identified and stratified into two groups: those with concurrent IgG4-RD (ICD-10: D89.84) and those without. Propensity score matching was performed 1:1 based on demographics and comorbidities, yielding 111 patients in each cohort. The primary outcome was the occurrence of biliary obstruction (ICD-10: K83.1). Secondary outcomes included survival probability and number of biliary obstruction events. Kaplan-Meier survival analysis, risk ratios, and hazard ratios were calculated. Statistical significance was set at $p < 0.05$. **Results:** After matching, the cohort included 111 PSC patients with IgG4-RD and 111 PSC patients without IgG4-RD. The risk of biliary obstruction was higher in the PSC with IgG4-RD group compared to the PSC without IgG4-RD group (45.0% vs. 29.7%; risk difference 0.153; 95% CI 0.027–0.279; $p = 0.018$). The risk ratio was 1.515 (95% CI 1.065–2.155), and the odds ratio was 1.937 (95% CI 1.115–3.367). Kaplan-Meier analysis demonstrated reduced survival in the PSC with IgG4-RD group, with a median survival of 697 days compared to non-reached median survival in the control group (Log-Rank $p = 0.043$). The hazard ratio for biliary obstruction in the IgG4-RD group was 1.570 (95% CI 1.009–2.442). The mean number of biliary obstruction episodes was higher in the IgG4-RD group (9.52 ± 15.66 vs. 6.15 ± 11.69; $p = 0.294$), though this difference was not statistically significant. **Conclusion:** PSC patients with IgG4-RD exhibit a higher risk of biliary obstruction and reduced survival compared to those without IgG4-RD. These findings underscore the importance of recognizing IgG4-RD as a potential risk factor in PSC and highlight the need for further research to guide optimal management strategies in this high-risk population.

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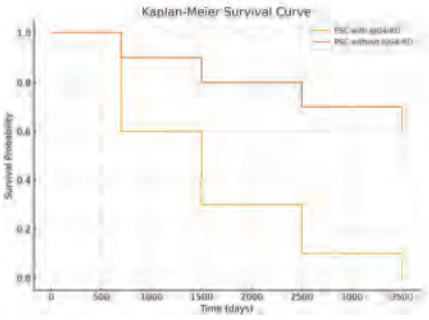
Characteristic	PSC + IgG4-RD (n=111)	PSC without IgG4-RD (n=111)	p-value
Age (years)	56.8 ± 17.3	57.0 ± 16.4	0.937
Age at Index	52.9 ± 17.0	52.9 ± 16.5	1.000
Female (%)	31.5%	32.4%	0.886
Male (%)	65.8%	66.7%	0.887
White (%)	61.3%	60.4%	0.891
Black or African American (%)	17.1%	19.8%	0.604
Asian (%)	9.0%	9.0%	1.000
Other Race (%)	9.0%	9.0%	1.000
Unknown Race (%)	9.9%	9.0%	0.819
Hispanic or Latino (%)	9.0%	10.8%	0.653
Not Hispanic or Latino (%)	73.0%	71.2%	0.765



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4214 | SC435, AN INTESTINAL BILE ACID TRANSPORTER INHIBITOR (IBAT), IMPROVES LIVER FUNCTION IN CHOLESTATIC MDR2$^{-/-}$ MICE BUT NOT IN ARE-DEL$^{-/-}$ MICE

James Boyer[1] Shi-Ying Cai[1] Scott Roberts[2] David Assis[3] Ziqian Xu[4] Cory Kostrub[5] Pamala Vig[5], [1]Yale University, [2]Yale Universiiety School of Medicine, [3]Yale University School of Medicine, [4]Yale School of Medicine, [5]Mirum Pharmaceuticals

Background: Hepatic bile acid BA) accumulations in cholestatic disorders elicits a cytokine mediated inflammatory response leading to in liver injury. We postulated that decreasing BA pool size by blocking its intestinal reabsorption using an IBAT inhibitor (SC435) should reduce liver injury in cholestatic Mdr2$^{-/-}$ and ARE-Del$^{-/-}$ mice. **Methods:** 6-week-old Mdr2$^{-/-}$ male FVB mice (n = 7-8) were used as a positive control and fed a standard chow diet with or without the IBAT inhibitor for 4 weeks. ARE-del$^{-/-}$ black 6 female mice (n = 11-12) were fed the same diet for 4 weeks starting at 16 weeks of age. Blood was obtained for liver function and serum BA at start of treatment and 4 weeks later when the animals were terminated. Liver tissue and feces were obtained for fecal BA and histology. **Results:** As expected,SC435 fed Mdr2$^{-/-}$ male mice showed significant reductions in ALT (31% of the control goup, p = 0.0003), serum BA levels (41% of the control group, p = 0.017) and increased fecal BA (2.45+/-0.17 vs 1.90 +/-0.41 umole/g, p. = 0.006) with no change in ALP, compared to control mice . Significant reductions in periportal inflammatory infiltrates, bile duct proliferation but not fibrosis were also seen. Interestingly, in the ARE-Del$^{-/-}$mice that developed moderate cholestatic liver injury, the SC435 IBAT inhibitor did not substantially reduce serum levels of ALT, ALP and BA compared to the controls. Assessment of liver histology did not show significant improvements in inflammation either. Most surprisingly, fecal BA were substantially reduced rather than increased as expected (2.09+/-0.24 vs 1.73+/-0.14 umole/g, p. = 0.0003). Subsequent analysis of the bile salt export pump (Bsep) gene expression revealed a marked and significant reduction in this important bile acid transporter (mRNA WT 1.01 +/-0.19 vs KO 0.49 +/-0.29, p = 0.007), indicating that a functional Bsep is needed for IBATs to have an effect. **Conclusion:** SC435, an IBAT inhibitor, significantly improved liver function, serum BA, liver histology and fecal BA excretion in Mdr2$^{-/-}$ male mice as previously demonstrated. In contrast, it did not improve liver function in the ARE-del $^{-/-}$ mice compared to the control mice. where BA pool size was not reduced in these S435 fed animals. Because Mdr2$^{-/-}$ and ARE-Del$^{-/-}$ models pose different pathogenic mechanisms of cholestasis, this study indicates that novel approaches may be needed to restore BA homeostasis in cholestasis iver injury mediated by inflammatioin.

Disclosures: James Boyer: Mirum Pharmaceuticals: grant recipient, IPSEN: Clinical Evenets Committee for clinical trial, AstroZenica: Member of Clinical Events Committe, Shi-Ying Cai: Nothing to Disclose, Scott Roberts: Nothing to Disclose, David Assis: Nothing to Disclose, Ziqian Xu: Nothing to Disclose, Cory Kostrub: Mirum Pharmaceuticals: Employee, Pamala Vig: Mirum Pharmaceuticals: employee

4215 | THE HISTONE DEACETYLASE INHIBITOR MS-275 MITIGATES HEPATOBILIARY INJURY BY MAINTAINING QUIESCENCE AND METABOLIC REPROGRAMMING IN A MURINE MODEL OF CHOLESTATIC LIVER DISEASE

Tony (Chun-Cheng) Chiang[1] Donghun Shin[1] Shuchang Liu[1] Satdarshan (Paul) Monga[1] Kari Nejak-Bowen[1], [1]University of Pittsburgh

Background: Liver transplantation remains the sole life-extending option for patients suffering from end-

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stage cholestatic liver disease; thus, a therapeutic alternative is urgently needed. Histone deacetylase (HDAC) inhibitors such as MS-275 were developed as treatments for oncologic diseases given the ability to inhibit cell growth and induce apoptosis, while their value in hepatobiliary disease is unknown. We aimed to evaluate the drug responses in mice subject to 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC)-induced biliary injury and understand the drug's underlying mechanism. **Methods:** Mice were given 0.1% DDC diet for 4 weeks. Starting 3 weeks after DDC, mice were given either DMSO or MS-275 along with DDC for 7 days and sacrificed 4 weeks after starting DDC. Serum and liver were collected at experiment endpoints. Real-time quantitative PCR (qPCR) was used to determine transcript levels. RNA-seq was performed to identify differential gene expression and pathways. Immunostainings were applied to validate RNA-seq results. Bile acid composition was analyzed using ultra-performance liquid chromatography-mass spectrometry. Total bile acids were measured with a colorimetric assay. AML12 mouse hepatocytes were used to confirm in vivo results. **Results:** MS-275 significantly reduced DDC-induced hepatobiliary injury, and alleviated liver pathological changes including fibrosis. Cluster analysis and differential gene expression indicated that MS-275 normalized DDC-injured livers toward baseline controls. Enrichment analysis disclosed gene expression changes in cell cycle, senescence, bile acid secretion, oxidative phosphorylation, and immune cell activation pathways between DDC alone and MS-275 groups. MS-275 decreased not only G1/S cyclins but also proliferative marker Ki-67 and senescence marker p21. This finding was reproduced in a mouse hepatocyte cell line. MS-275 preserved liver functions by increasing expression of metabolic enzymes, transporters, and autophagy proteins compared to injury alone. Though bile acid composition did not differ between DDC alone and MS-275 groups, total bile acid levels were significantly reduced after MS-275 treatment. **Conclusion:** MS-275 exerts hepatoprotective effects against DDC-induced injury in mice by restoring quiescence. Additionally, MS-275 rescues metabolic enzymes and proteins suppressed by DDC injury. Further epigenetic studies are needed to dissect a more detailed mechanism and correlate with RNA-seq findings.

Disclosures: Tony (Chun-Cheng) Chiang: Nothing to Disclose, Donghun Shin: Nothing to Disclose, Shuchang Liu: Nothing to Disclose, Satdarshan (Paul) Monga: Mermaid Bio: Advisor, Vicero: Advisor, AntlerA: Advisor, Genentech: Speaking and Teaching, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Mermaid Bio: Consultant, Fog Pharmaceuticals: Grant/Research Support, Surrozen: Consultant, Genentech: Independent Contractor, Kari Nejak-Bowen: Surrozen, Inc.: Consultant

◆ ★ 4216 | LIPID–IMMUNE CROSSTALK IN HCC: FXR DISRUPTS SPHINGOSINE-1-PHOSPHATE SIGNALING TO LIMIT TREG TRAFFICKING

Yasmeen Attia[1] Rasha Tawfiq[1] Aya Ali[2] Olfat Hammam[3] Mohamed Elmazar[1], [1]Department of Pharmacology, Faculty of Pharmacy, the British University in Egypt, [2]Health Research Center of Excellence, The British University in Egypt, [3]Department of Pathology, Theodor Bilharz Research Institute

Background: The paradigm of the liver as an immune graveyard—where T cells met deletion, not direction—has given way to a more dynamic view of its immunological function. Nowhere is this shift more apparent than in hepatocellular carcinoma (HCC), where the liver actively sculpts an immunosuppressive niche, with regulatory T cells (Tregs) densely infiltrating the tumor and reinforcing its "cold" immune phenotype. Beyond classical cytokine circuits, recent data suggest that Treg recruitment is shaped by lipid cues—particularly sphingosine-1-phosphate (S1P), which guides immune cell migration *via* its receptor, S1PR1. The upstream control of this axis remains incompletely defined. Farnesoid X receptor (FXR), a metabolic sentinel in the liver, has emerged as a regulator of sphingolipid pathways. This study investigates whether pharmacologic activation of FXR *via* obeticholic acid (OCA) can disrupt S1P–S1PR1–mediated Treg trafficking and help reprogram the immune architecture of HCC. **Methods:** HCC was induced in 3-week-old Swiss albino male mice using diethylnitrosamine (DEN; 1 mg/kg, i.p.) followed by carbon tetrachloride (CCl_4; 0.2 mL/kg, i.p., twice weekly). At week 20, mice received obeticholic acid (OCA; 10 mg/kg/day, p.o.) for 12 weeks. Liver tissue was assessed histologically and by immunohistochemistry for alpha-fetoprotein (AFP). FXR activation was evaluated by ELISA quantification of hepatic FXR and its downstream target, CYP7A1. Treg polarization was assessed by qRT-PCR of *Foxp3* and *Il2ra*, while sphingolipid signaling was probed by measuring *S1pr1* gene expression and S1P levels by ELISA. Hepatic concentrations of TGF-β1, IL-10, and p-SMAD2/3 were also determined by ELISA. **Results:** Histological analysis confirmed HCC in DEN +CCl_4-treated mice with OCA attenuating tumor burden. AFP immunostaining was markedly reduced in the OCA group, along with hepatic CYP7A1 levels, supporting effective FXR activation. DEN+CCl_4 exposure increased the hepatic expression of Treg markers *Foxp3* and *Il2ra*, consistent with an immunosuppressive tumor milieu. OCA treatment led to their downregulation, suggesting a suppression of Treg polarization. These changes paralelled reductions in TGF-β1, p-SMAD2/3, and IL-10 levels. Also, both hepatic S1P and *S1pr1* expression were elevated in HCC-bearing mice and diminished following FXR activation, pointing to a potential link between

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sphingolipid signaling and Treg trafficking. **Conclusion:** These findings reveal a previously unrecognized role for FXR in modulating the sphingolipid axis that governs Treg recruitment in HCC. By disrupting S1P–S1PR1 signaling, FXR activation might attenuate the cues that sustain immune tolerance in the tumor microenvironment. This lipid–immune intersection offers a mechanistically distinct pathway for reprogramming hepatic immunosuppression and may inform future strategies for converting "cold" tumors into immunologically responsive ones.

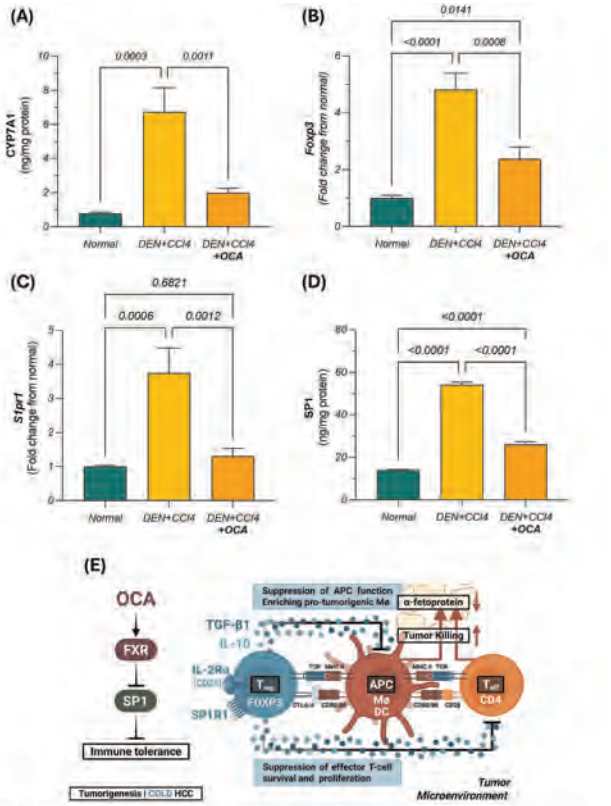

Figure 1. FXR activation modulates Treg markers and sphingolipid signaling in HCC.
(A) Hepatic CYP7A1 protein levels. **(B)** *Foxp3* and **(C)** *S1pr1* gene expression, and **(D)** S1P concentrations in DEN+CCl_4–and OCA-treated mice. Data are presented as mean ± SD. Statistical significance was assessed using one-way ANOVA followed by Tukey's post hoc test. **(E)** Schematic illustration of FXR-mediated regulation of the sphingolipid-S1P-S1PR1 axis and its influence on Treg polarization.

Disclosures: Yasmeen Attia: Nothing to Disclose, Rasha Tawfiq: Nothing to Disclose, Aya Ali: Nothing to Disclose, Olfat Hammam: Nothing to Disclose, Mohamed Elmazar: Nothing to Disclose

◆ 4217 | A CHAMELEON LIKE ROLE OF DIABETES GENE HNF4A IN REGULATING HEPATIC GENE REGULATION UPON NUCLEAR RECEPTOR ACTIVATION

Fathima Nafrisha Cassim Bawa[1] Mohit Midha[1] Abigail Holland[1] Mitchell Lazar[1], [1]Perelman School of Medicine, University of Pennsylvania

Background: The nuclear receptor Hepatocyte Nuclear Factor alpha (HNF4α) is a well-established as lineage determining factor in the liver during development that regulates lipid, glucose, and xenobiotic metabolism in the adult. Here we report that in addition to this general lineage-specific function, HNF4α genomic binding and gene regulation are also coupled to specific signals that canonically activate other nuclear receptors (NR) in the liver. Thereby HNF4α plays a role in regulating hepatic transcriptome in response to specific NR activation. **Methods:** We utilized wildtype mice with C57BL/6J background to study the changes in the HNF4α and respective NR cistromes and associated transcriptomes in response to NR activation by treating mice with specific NR agonists. We studied the effects of NR agonists on HNF4α genomic binding and related gene expression to elucidate the functional importance of non-canonical HNF4α binding regulating NR dependent drug response and associated metabolic pathways in the liver. **Results:** Our data show that lipid lowering drug fenofibrate regulates HNF4α binding and HNF4α-dependent gene regulation at specific genomic loci in a manner that is dependent upon fibrate receptor PPARα even in the absence of nearby binding by PPARα. In a similar manner, HNF4α is required for regulation of genes controlled by the glucocorticoid receptor and its cognate ligands, thyroid hormone receptor and thyroid hormones, and the oxysterol-regulated nuclear receptor LXR and its pharmacological ligands. Motif analysis at these signal-regulated sites of HNF4α binding and gene expression identified the canonical HNF4α binding motif and mostly in the intronic and intergenic regions. Remarkably, despite the known role of HNF4α to open chromatin and allow signal-dependent factors to bind, the sites where HNF4α is recruited to the genome in a signal-dependent manner are already open in the absence of signaling ligand. Our data shows that the non-canonical binding of HNF4α upon activation of NR is specific for NR being activated and the genes are specific for the function of the specific NRs. **Conclusion:** The dependence of HNF4α binding on promiscuous signals of NR activation is also reflected in the signal-dependent transcription of these gene targets. The data thus suggest a dual function of HNF4α, whereby in addition to its lineage-specific role in transcriptional regulation it has additional gene-specific regulatory functions in response to specific signals with pleotropic phenotypic repercussions that determines the downstream effects on liver metabolism by NR activation.

Disclosures: Fathima Nafrisha Cassim Bawa: Nothing to Disclose, Mohit Midha: Nothing to Disclose, Abigail Holland: Nothing to Disclose, Mitchell Lazar: Pfizer: Advisor, Flare Therapeutics: Advisor, Eccogene: Advisor

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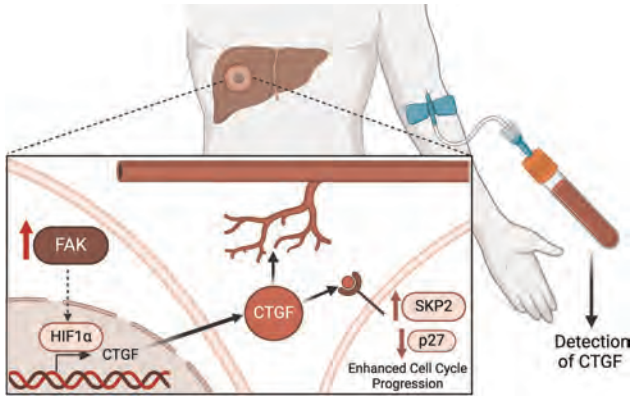
◆ 4218 | CHARACTERIZATION OF THE FAK-CTGF AXIS FOR THERAPEUTIC EXPLOITATION IN HCC

Claudia Rose Keating[1] Kyle Boedeker[1] Ruisong Ye[1] Zoe Pointer[1] Yucel Yankol[2] Oswaldo Aguirre[2] Xianzhong Ding[2] Scott Cotler[2] Wei Qiu[2], [1]Loyola University Chicago, [2]Loyola University Health System

Background: There is a pressing need to better understand the pathogenesis of HCC to identify novel therapeutic targets. Focal adhesion kinase (FAK) is as a driver of HCC, where patients with high FAK have decreased overall survival. FAK targeting therapies have been studied in clinical trials for decades, however these agents have been ineffective when applied broadly. We hypothesize that patients specifically with high tumoral FAK will have better responses to these treatments, but at this time, noninvasive markers for FAK remain unknown. **Methods:** We used a proteolysis-targeting chimera (FP) to degrade FAK. RNA-seq and mass spec were used for unbiased screening. We used qPCR, western blot, CUT&RUN, ELISA, and CCK-8 for analyses. For *in vivo* experiments, we used subcutaneous and orthotopic xenografts, DEN/CCl_4 model, and oncogene-driven models. We collected a new cohort of matched HCC tumor and serum samples from patients undergoing liver transplantation for HCC to assess protein levels. **Results:** HCC cell lines with high FAK showed significant growth inhibition following FP treatment. RNA-seq of FP-treated cells showed connective tissue growth factor (CTGF) was significantly downregulated. CTGF is secreted and can be detected in serum, making it a suitable serum marker candidate. RNA-seq results were confirmed *in vitro*, with FP treatment significantly decreasing CTGF mRNA, intracellular protein, and secreted protein in both a dose- and time-dependent manner. Conversely, overexpression of FAK led to an increase in intracellular and secreted CTGF protein. Next, we found FAK regulates CTGF expression through HIF1a and showed direct HIF1a binding to the *CTGF* promoter driven by FAK. We found that the addition of recombinant CTGF rescued growth after FP treatment *in vitro*; CTGF expression can compensate for FAK loss in the MET/CAT model; and CTGF can replace FAK in the FAK/CAT model to induce tumors. We found that shCTGF significantly inhibited cell growth *in vitro* and *in vivo*. Similarly, treatment with a CTGF neutralizing antibody inhibited cell growth. RNA-seq of shCTGF cells showed an increase in SKP2 and a decrease in p27. Using the DEN/CCl_4 model, serum CTGF increased during tumor formation and progression in WT mice, whereas serum CTGF was dramatically reduced in FAK KO mice. Finally, FP treatment inhibited FAK/CAT-driven tumorigenesis *in vivo*. In primary HCC patient samples, we observed a strong correlation in tumoral protein expression as well as colocalization between FAK and CTGF in tissue samples, and we observed a strong correlation in FAK intratumoral protein levels and serum CTGF levels. **Conclusion:** Overall, FAK promotes the expression and secretion of CTGF, which promotes HCC, and there is a significant positive correlation between tumor FAK expression and serum CTGF. FAK is a promising therapeutic target in HCC, and identification of CTGF as a downstream target of FAK suggests CTGF as a treatment-indicating marker for FAK in HCC.



Disclosures: Claudia Rose Keating: Nothing to Disclose, Kyle Boedeker: Nothing to Disclose, Ruisong Ye: Nothing to Disclose, Zoe Pointer: Nothing to Disclose, Yucel Yankol: Nothing to Disclose, Oswaldo Aguirre: Nothing to Disclose, Xianzhong Ding: Nothing to Disclose, Scott Cotler: Nothing to Disclose, Wei Qiu: Nothing to Disclose

◆ 4219 | HYPOXIA-INDUCIBLE FACTOR SIGNALING IN ENDOTHELIAL CELLS IS REQUIRED TO MAINTAIN NORMAL LIVER HOMEOSTASIS AND FOR REGENERATION AFTER PARTIAL HEPATECTOMY

Chang Kyung (Joanna) Kim[1] Prerna Chakkingal[2] Minakshi Poddar[2] Sucha Singh[2] Satdarshan (Paul) Monga[2], [1]UPMC, [2]University of Pittsburgh

Background: To maximize functional efficiency, the liver ascribes it's metabolic functions to three zones, based on location along the porto-central blood flow and oxygen gradient, a phenomenon termed as zonation. Zone 1 (periportal) receives the highest oxygen supply from oxygen-rich blood entering through the portal vein and hepatic artery, while Zone 3 (pericentral) receives the lowest oxygen levels due to progressive oxygen consumption along the sinusoid. Hypoxia-inducible factor (HIF) signaling is critical for cellular adaptation

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to hypoxic conditions and is predominantly active in Zone 3, where it regulates a range of metabolic processes. What remains unclear is the role of HIF signaling in endothelial cells, which are in contact with blood and a source of angiocrine factors with wide-ranging effects on hepatic cells. **Methods:** To investigate the function of HIF signaling in endothelial cells, we generated *Lyve1-Cre; Arnt$^{f/f}$* (*Lyve1$^{\Delta Arnt}$*) mice to delete *Arnt* (Hif-1β) from central vein and sinusoidal endothelial cells (SECs). Partial hepatectomy (PHx) was performed on 10–12-week-old mice for assessing proliferation at 40 hour post-PHx. **Results:** *Arnt* deletion in *Lyve1^{+}* endothelial cells in mice resulted in 80% embryonic lethality and surviving 20% mice were female in gender. At baseline, *Arnt* deletion resulted in significant histological changes with abnormal vasculature, areas of necrosis, immune cell infiltration, ductular reaction, and increased periportal collagen accumulation. Liver zonation was significantly altered in *Lyve1$^{\Delta Arnt}$* mice. There was a significantly contracted Zone 3 based on decreased radius of CYP1A2 staining. Additionally, unlike controls which showed uniform 1-2 layers of glutamine synthetase (GS)$^{+}$ hepatocytes around central vein, *Lyve1$^{\Delta Arnt}$* mice showed random dropout of GS^{+} hepatocytes around the central vein. On the contrary, the expression pattern of IGFBP2 (Zone 2 marker) shifted towards the central vein, and the expression of CYP2F2 (Zone 1 marker) also remarkably expanded towards the central vein. Furthermore, several factors associated with hypoxia were upregulated in *Lyve1$^{\Delta Arnt}$* mice at baseline, including *Epo, Pdgfb, Tgfb1,* and *Tnfa,* indicating endothelial HIF signaling is required for maintaining homeostasis under physiological hypoxia. Additionally, in *Lyve1$^{\Delta Arnt}$* mice, there was significantly decreased Ki-67^{+} hepatocytes at 40 hours post-PHx, as compared to control mice, which showed peak proliferation at this time, indicating HIF signaling in endothelial cells is critical to normal tissue regeneration. **Conclusion:** Taken together, our results suggest that endothelial HIF signaling is required for maintenance of liver zonation, homeostasis under physiological hypoxia, and regeneration post-Phx.

Disclosures: Chang Kyung (Joanna) Kim: Nothing to Disclose, Prerna Chakkingal: Nothing to Disclose, Minakshi Poddar: Nothing to Disclose, Sucha Singh: Nothing to Disclose, Satdarshan (Paul) Monga: Mermaid Bio: Advisor, Vicero: Advisor, AntlerA: Advisor, Genentech: Speaking and Teaching, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Mermaid Bio: Consultant, Fog Pharmaceuticals: Grant/Research Support, Surrozen: Consultant, Genentech: Independent Contractor

◆ 4220 | SORGANELLOMICS REVEALS NUTRIENT-DEPENDENT HEPATOCYTE HETEROGENEITY THROUGH ORGANELLE ARCHITECTURE AT SINGLE-CELL RESOLUTION

Raghabendra Adhikari[1] Alexander Hillsley[1] Alana Johnson[2] Isabel Espinosa-Medina[1] Jan Funke[1] Daniel Feliciano[1], [1]Howard Hughes Medical Institute Janelia Research Campus, [2]Janelia-Meyerhoff Undergraduate Scholars Program 2024

Background: Hepatic functions—and many liver diseases—are spatially zonated, with hepatocyte heterogeneity driven by gradients of nutrients, oxygen, and signaling molecules across the liver lobule. These gradients induce hepatocytes to adapt via changes in gene expression, protein abundance, and subcellular organization. While organelle remodeling has been extensively characterized in cultured cells, how organelle architecture is spatially distributed in intact tissue—and whether it can define hepatocyte heterogeneity in situ—remains unclear. Furthermore, although hepatocyte physiology shifts with nutritional perturbations, whether organelle architecture reflects these changes remains unknown. **Methods:** To address these questions, we developed sOrganellomics, a spatial analysis pipeline that quantifies organelle features at single-cell resolution. Using confocal fluorescence microscopy, we imaged mitochondria, peroxisomes, and lipid droplets in mouse liver tissue. We then applied custom Cellpose-based models to segment cells and organelles, extracting over 100 quantitative organelle features while preserving spatial coordinates along the portal–central axis. Liver samples from control, fasted, and Western diet-fed mice were analyzed. Organelle features were used to classify hepatocyte subtypes and train machine learning to predict physiological states. **Results:** sOrganellomics revealed spatially zonated organelle architectures across liver acini, enabling classification of hepatocytes into five distinct classes. Although central vein-adjacent regions were enriched in a specific class, all zones contained a mixture of classes with zone-specific proportions. Nutritional perturbations reduced this heterogeneity: fasted livers showed four hepatocyte classes, while Western diet livers showed only two. Machine learning models (MLPs) trained on organelle features predicted hepatocyte class and nutritional status with $>80\%$ accuracy. Interestingly, our approach also detected progressive subcellular remodeling during hepatic steatosis in a diet-induced mouse model of early MASLD, enabling quantitative assessment of disease progression following up to two months of

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Western diet feeding. **Conclusion:** sOrganellomics enables spatially resolved, quantitative analysis of organelle architecture in liver tissue. Our findings suggest that organelle features can serve as functional signatures of hepatocyte identity and reveal altered hepatic organization under nutritional stress, offering a feasible alternative to transcriptomic profiling.

Disclosures: Raghabendra Adhikari: Nothing to Disclose, Alexander Hillsley: Nothing to Disclose, Alana Johnson: Nothing to Disclose, Isabel Espinosa-Medina: Nothing to Disclose, Jan Funke: BLASTID: Consultant, Daniel Feliciano: Nothing to Disclose

◆ 4221 | DISTINCT MORPHOLOGICAL AND FUNCTIONAL CHARACTERISTICS OF PERIDROPLET AND CYTOPLASMIC MITOCHONDRIA IN HUMAN LIVER BIOPSIES

Norihiro Imai[1] Hanna Kawecka[2] Yuki Ohsaki[3] Jinglei Cheng[4] Shinya Yokoyama[4] Kenta Yamamoto[4] Takanori Ito[4] Yoji Isihzu[4] Takashi Honda[4] Tetsuya Ishikawa[4] Michał Woźniak[2] Hiroaki Wake[4] Hiroki Kawashima[4],
[1]Nagoya University Graduate School of Medicine,
[2]Medical University of Gdańsk, Gdańsk, Poland,
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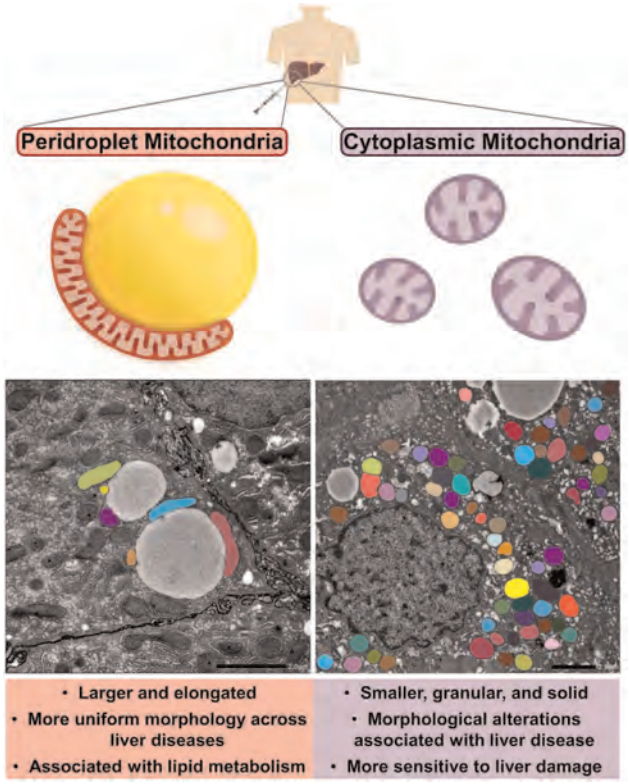
[4]Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan

Background: Mitochondrial dysfunction and lipid droplet accumulation contribute to the pathogenesis of several liver diseases. Mitochondria located adjacent to lipid droplets, known as peridroplet mitochondria (PDM), form a distinct subpopulation with unique metabolic functions, proteomes, bioenergetics, and dynamics compared to cytoplasmic mitochondria (CM). Although the close interplay between mitochondria and lipid droplets suggests the potential for analyzing the mitochondrial cytoarchitecture in the context of liver pathology, the morphology of PDM has not been characterized in *in vivo* human liver studies. This study aimed to investigate the morphological differences between PDM and CM in human liver biopsy specimens and evaluate their association with clinical parameters. **Methods:** In total, 3,079 transmission electron microscopy (TEM) images of liver samples from 145 patients were analyzed to identify PDM. The mitochondria were automatically segmented using a deep learning model trained on a diverse dataset for rapid detection and visualization. Based on the extracted outlines, the morphological parameters related to the size and shape were quantified for each PDM and CM. Clinical data including lipid profiles, liver enzyme levels, and degree of steatosis were collected from the enrolled patients. **Results:** In total, 263 PDM and 3,016 CM were identified from the human liver biopsy TEM dataset. Morphologically, the hepatic CM were significantly smaller and more spherical and solid, whereas the PDM were larger and more elongated. PDM exhibited a more uniform morphology, whereas CM displayed morphological variations specific to liver disease. Analysis of the patients' blood test results revealed an association between CM and liver enzyme levels, suggesting sensitivity to liver damage. In contrast, PDM were associated with serum triglyceride levels, indicating their role in lipid metabolism. Additionally, a positive correlation was observed between the numbers of PDM and lipid droplets, reinforcing the close functional interactions between these organelles. **Conclusion:** PDM and CM represent distinct mitochondrial subpopulations with unique morphologies, and are associated with different pathophysiological pathways. This study highlights the significance of mitochondrial interactions with lipid droplets, which contribute to the heterogeneity of human liver mitochondria. These findings provide insight for future research and diagnostic applications.



Disclosures: Norihiro Imai: Nothing to Disclose, Hanna Kawecka: Nothing to Disclose, Yuki Ohsaki: Nothing to Disclose, Jinglei Cheng: Nothing to Disclose, Shinya Yokoyama: Nothing to Disclose, Kenta Yamamoto: Nothing to Disclose, Takanori Ito: Nothing to Disclose, Yoji Isihzu: Nothing to Disclose, Takashi Honda: Nothing to Disclose, Tetsuya Ishikawa: Nothing to Disclose, Michał Woźniak: Nothing to Disclose, Hiroaki

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Wake: Nothing to Disclose, Hiroki Kawashima: Nothing to Disclose

◆ 4222 | MECHANISMS OF GENE TRANSCRIPTION REGULATION BY NUCLEAR LIPID DROPLETS IN LIVER DISEASES

Norihiro Imai[1] Yuki Ohsaki[2] Jinglei Cheng[3] Hanna Kawecka[4] Shinya Yokoyama[3] Kenta Yamamoto[3] Takanori Ito[3] Yoji Ishizu[3] Takashi Honda[3] Tetsuya Ishikawa[3] Michał Woźniak[4] Hiroaki Wake[3] Hiroki Kawashima[3], [1]Nagoya University Graduate School of Medicine, [2]Sapporo Medical University, [3]Nagoya University, [4]Medical University of Gdańsk

Background: Lipid droplets are organelles found in adipocytes and other cell types throughout the body. Recently, lipid droplets have been identified within the nuclei of hepatocytes, and their formation and function have attracted increasing attention. This study aimed to explore the pathophysiological role of nuclear lipid droplets in liver diseases. **Methods:** In total, 152 patients (79 men and 73 women; mean age, 58 years) who underwent liver biopsy between 2020 and 2024 were included in this study. Portions of the biopsy specimens were double-fixed for electron microscopy and examined by transmission electron microscopy after embedding and sectioning. The presence of intranuclear lipid droplets in hepatocytes was assessed independently of the clinical data. Additionally, RNA sequencing was performed on liver biopsy samples with electron microscopic observations, along with adjacent tissues, to conduct comprehensive genetic analysis. **Results:** Intranuclear lipid droplets were detected in the hepatocyte nuclei of 63% of the biopsy samples, with an average occurrence rate of 3.7%. These droplets were most frequently observed in cases of metabolic dysfunction-associated steatotic liver disease, drug-induced liver injury, and autoimmune hepatitis. No significant correlation was observed between the frequency of nuclear lipid droplets and the degree of hepatic steatosis, suggesting that their formation is not a direct reflection of cytoplasmic lipid accumulation. However, the frequency of intranuclear lipid droplets was significantly positively correlated with serum AST and ALT levels, indicating that their formation may be a stress response to liver injury. RNA sequencing identified 1,526 and 537 genes that were positively and negatively correlated, respectively, with the frequency of nuclear lipid droplets. Pathway analysis revealed that nuclear lipid droplets were associated with the upregulation of nucleoside-triphosphatase activity and downregulation of glutathione transferase and antioxidant activity. Analysis of DNA-binding motifs in the promoter regions showed a positive correlation with p53, a key tumor suppressor involved in DNA repair, and a negative correlation with FOXI1, a factor involved in chromatin remodeling. **Conclusion:** Intranuclear lipid droplets, which are characteristic of hepatocytes, appear to form in response to liver injury and may help maintain cellular homeostasis by regulating gene transcription.

Disclosures: Norihiro Imai: Nothing to Disclose, Yuki Ohsaki: Nothing to Disclose, Jinglei Cheng: Nothing to Disclose, Hanna Kawecka: Nothing to Disclose, Shinya Yokoyama: Nothing to Disclose, Kenta Yamamoto: Nothing to Disclose, Takanori Ito: Nothing to Disclose, Yoji Ishizu: Nothing to Disclose, Takashi Honda: Nothing to Disclose, Tetsuya Ishikawa: Nothing to Disclose, Michał Woźniak: Nothing to Disclose, Hiroaki Wake: Nothing to Disclose, Hiroki Kawashima: Nothing to Disclose

◆ 4223 | NUCLEAR RECEPTOR CAR AS A REGULATOR OF LIPID METABOLISM IN HEPATOCELLULAR CARCINOMA

Bingning Dong[1], [1]Baylor College of Medicine

Background: Lipid metabolic reprogramming is a hallmark of hepatocellular carcinoma (HCC), supporting tumor growth, immune evasion, and therapy resistance. However, efforts to inhibit lipid biosynthesis clinically have been limited by systemic toxicity. The constitutive androstane receptor (CAR, NR1I3) is a nuclear receptor enriched in hepatocytes, known for xenobiotic metabolism but not previously studied for its role in HCC lipid remodeling or immune modulation. Here, we identify CAR as a tumor-intrinsic driver of lipogenesis and immune suppression, and demonstrate that targeting CAR with a selective inverse agonist (CAR-IA) suppresses HCC progression in preclinical models without systemic toxicity. **Methods:** We used two HCC mouse models (DEN and HDTVi-AKT/N-Ras) to evaluate CAR-IA treatment. Tumor burden, toxicity, and gene expression were assessed. RNA-seq and lipidomics analyzed lipid pathway activity; ChIP-seq and ChIP-qPCR determined CAR binding to lipid gene promoters. Rescue experiments included high-fat diet feeding and Srebf1 overexpression. Single-nucleus RNA-seq profiled CAR-high tumors, and immune–tumor cell interactions were inferred using CellChat analysis. **Results:** CAR-IA significantly reduced tumor burden in both models without toxicity. It suppressed key lipid biosynthetic genes (e.g., Srebf1 and Fasn) and decreased tumor lipid content. Lipid restoration via diet or Srebf1 overexpression reversed CAR-IA's antitumor effect, confirming CAR's role in driving lipogenesis. CAR-high tumors were identified as a poor-prognosis subtype with elevated lipid metabolism but low proliferation. These

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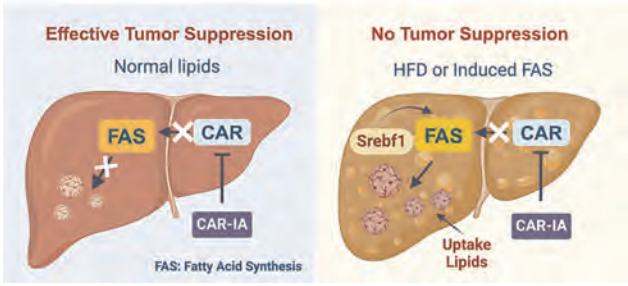
tumors showed increased interactions with T cells, and CAR-IA induced T cell exhaustion markers and inflammatory gene signatures, suggesting CAR-mediated immune suppression. **Conclusion:** CAR is a liver-specific regulator of lipid metabolism and immune remodeling in HCC. Its inhibition reduces tumor growth by blocking lipogenesis and altering the immune microenvironment without affecting normal physiology. CAR-high tumors represent a lipid-metabolic, immune-suppressive HCC subtype with poor prognosis. These findings support a tissue-selective therapeutic strategy targeting CAR and offer a framework for repurposing CAR inhibitors, such as meclizine, for HCC treatment



Disclosures: Bingning Dong: Nothing to Disclose

◆ 4224 | IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT IN HEPATOCELLULAR CARCINOMA ORCHESTRATED BY CD90-POSITIVE CANCER STEM CELLS

Kouki Nio[1] Hikari Okada[1] Taro Yamashita[1], [1]Kanazawa University

Background: Since the clinical application of cancer immunotherapy for hepatocellular carcinoma (HCC), there has been increasing research aimed at identifying factors that determine its therapeutic efficacy. Previously, we reported that laminin γ2 monomer (LG2m) is highly expressed in CD90-positive HCC, which harbors mesenchymal stem cell-like properties, and that serum LG2m levels are associated with poor prognosis, distant metastatic recurrence, and future liver carcinogenesis in HCC patients. In this study, we aimed to investigate the impact of CD90-positive HCC cells on the immunosuppressive tumor microenvironment (TME). **Methods:** To analyze the expression of CD90-positive HCC cells and their cell–cell interactions with stromal cells within the TME, single-cell spatial analysis of resected HCC specimens was performed. We also examined whether serum LG2m levels could serve to stratify therapeutic responses to cancer immunotherapy in HCC patients. **Results:** Single-cell spatial analysis using PhenoCycler™ was conducted on HCC specimens with varying LG2m expression levels. In LG2m-high HCCs, the tumor–non-tumor boundary regions were infiltrated by a large number of CD90-positive cells and CD206-positive macrophages, while infiltration of Ki67-positive activated $CD4^+$ and $CD8^+$ T cells was limited. Cellular neighborhood analysis revealed that CD90-positive cells were densely located at the tumor boundary in LG2m-high HCC, with relatively little proximity to Ki67-positive activated T cells. To further investigate the impact of LG2m on the efficacy of cancer immunotherapy, we measured serum LG2m levels in HCC patients undergoing immunotherapy and compared them with the therapeutic response to sorafenib treatment. Among patients with low LG2m levels, treatment with atezolizumab plus bevacizumab resulted in a significantly prolonged progression-free survival (PFS) compared to sorafenib (HR 0.33, $P < 0.001$). In contrast, no significant PFS benefit was observed in patients with high LG2m levels (HR 0.65, $P = 0.15$). **Conclusion:** These findings suggest that CD90-positive liver cancer stem cells with high LG2m expression contribute to the development of an immunosuppressive TME. Moreover, LG2m may serve as a potential biomarker for predicting the efficacy of cancer immunotherapy in HCC.

Disclosures: Kouki Nio: Nothing to Disclose, Hikari Okada: Nothing to Disclose, Taro Yamashita: Nothing to Disclose

◆ 4225 | IDENTIFICATION OF A SIGNALING MICRODOMAIN IN THE HEPATOCYTE NUCLEUS THAT REGULATES CELL PROLIFERATION AND BECOMES DISRUPTED IN CHRONIC LIVER DISEASE

Jittima Weerachayaphorn[1] Mateus Guerra[1] Emma Kruglov[1] Kathy Harry[1] Vitoon Saengsirisuwan[2] Michele Rodrigues[1] Michael Nathanson[1], [1]Yale University, [2]Mahidol University

Background: A billion people worldwide have chronic liver disease. Despite diverse etiologies, a unifying feature is the liver's impaired ability to regenerate, which may relate to progression to cirrhosis. We investigated whether and how calcium (Ca^{2+}) signals in the hepatocyte nucleus become impaired in chronic liver disease, because growth factors selectively increase Ca^{2+} in the nucleus, and cell proliferation depends on these Ca^{2+} signals. **Methods:** Mouse hepatocytes (provided in part by R24AA012885) and HepG2 cells were used as model systems. Intra-nuclear binding partners of the type 2 inositol trisphosphate receptor (ITPR2), the principal calcium channel in hepatocytes, were identified by mass spectrometry (MS), and interactions were confirmed by co-IP, proximity ligation assay (PLA), and super-resolution imaging. Ca^{2+}

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signaling was detected by time-lapse confocal microscopy, and protein expression was examined in mouse models and liver biopsies from patients with various chronic liver diseases. **Results:** Subcellular fractionation and immunoblot showed that ITPR2 is expressed in the hepatocyte nucleus, and super-resolution microscopy localized ITPR2 to the inner nuclear membrane. Nuclear Ca^{2+} signals in the hepatocytes were entirely generated by this ITPR2 pool, and MS identified, and co-IP and PLA confirmed that nucleoporin 62 (Nup62) localizes ITPR2 to the nucleus. ITPR2 and Nup62 both were lost from the hepatocytes of patients with MASLD, alcohol-associated liver disease (ALD), chronic hepatitis B and hepatitis C infections, and cirrhosis, and the loss of ITPR2 and Nup62 were highly correlated ($R^2 = 0.95$, $p < 0.001$). Similar results were observed in mouse models of MASH and ALD. Translocation of ß-catenin to the nucleus was reduced by buffering Ca^{2+} in the nucleus but not the cytosol, and Ca^{2+} signaling in the nucleus and nuclear pore permeability both were diminished in Nup62-KO cells. **Conclusion:**: Nup62 anchors ITPR2 in the nucleus of hepatocytes, which is necessary for nuclear Ca^{2+} signals and entry of ß-catenin into the nucleus. Nup62 is lost from the hepatocyte nucleus in patients with chronic liver disease and related mouse models, suggesting this contributes to impaired liver regeneration. This previously unrecognized signaling microdomain in the hepatocyte nucleus may provide a potential therapeutic avenue to preserve liver regeneration in chronic liver disease.

Disclosures: Jittima Weerachayaphorn: Nothing to Disclose, Mateus Guerra: Nothing to Disclose, Emma Kruglov: Nothing to Disclose, Kathy Harry: Nothing to Disclose, Vitoon Saengsirisuwan: Nothing to Disclose, Michele Rodrigues: Nothing to Disclose, Michael Nathanson: Nothing to Disclose

◆ 4226 | DFNA5-DEPENDENT HEPATOCYTE DEATH PROMOTES TNF PRODUCTION IN KUPFFER CELLS AND CONTRIBUTES TO HEPATOCARCINOGENESIS

Yoshinobu Saito[1] Tomoya Hamabe[1] Yoichi Sasaki[1] Hayato Hikita[1] Yuta Myojin[1] Kazuhiro Murai[1] Yuki Makino[1] Yuki Tahata[1] Takahiro Kodama[1] Hayato Hikita[1], [1]The University of Osaka Graduate School of Medicine

Background: Hepatocyte death is a key driver of chronic liver disease (CLD) progression. We previously demonstrated that persistent hepatocyte apoptosis promotes hepatocarcinogenesis, while non-apoptotic cell death contributes to metabolic dysfunction-associated steatotic liver disease (MASLD). Dfna5 (Gasdermin E), a pore-forming protein activated by caspase cleavage, induces membrane rupture and the release of pro-inflammatory contents. Although Dfna5 is implicated in inflammation and pyroptosis-like processes, its role in hepatocyte death and hepatocellular carcinoma (HCC) remains unclear. This study aimed to investigate the role of Dfna5-mediated hepatocyte death in liver injury and inflammation-associated hepatocarcinogenesis. **Methods:** DFNA5 was silenced using siRNA in Huh7 and AML12 cells, and intrinsic apoptosis was induced with ABT-737, a Bcl-xL inhibitor. Caspase activity and LDH release were assessed. Hepatocyte-specific Dfna5 knockout (Dfna5 L-KO) mice were generated by AAV8-TBG-Cre injection into Dfna5 fl/fl mice and treated with Fas ligand (FasL) to induce extrinsic apoptosis. Alb-Cre Mcl-1 fl/fl (Mcl-1 L-KO) mice, which develop spontaneous hepatocyte apoptosis and HCC, were crossed with Dfna5 fl/fl mice to generate Mcl-1/Dfna5 L-KO mice. To examine the role of TNFα, Alb-Cre Mcl-1 fl/fl mice were also crossed with Tnf −/− mice to create Mcl-1/Tnf double knockout (DKO) mice. Kupffer cells were depleted using clodronate liposomes to assess their contribution to cytokine production. The clinical relevance of DFNA5 was evaluated using TCGA-LIHC survival data. **Results:** ABT-737 increased caspase-3/7 activity and Dfna5 cleavage in vitro. DFNA5 knockdown reduced LDH release without affecting caspase activity, indicating suppression of secondary necrosis. Dfna5 L-KO mice showed no baseline abnormalities but had significantly lower serum ALT levels after FasL challenge. In Mcl-1 L-KO mice, Dfna5 deletion markedly reduced hepatic Tnfa mRNA without altering ALT or caspase activity. Kupffer cell depletion abolished Tnfa expression, confirming them as the main TNFα source. HCC developed in 100% (17/17) of Mcl-1 L-KO mice by 18 months, but only in 47.8% (11/23) of Mcl-1/Tnf DKO mice ($p = 0.0008$), despite comparable liver injury and apoptosis at 6 weeks. High DFNA5 expression in TCGA-LIHC was associated with worse survival (HR = 1.72, $p = 0.002$). **Conclusion:** Dfna5 promotes secondary necrosis and Kupffer cell-mediated TNFα production, fueling inflammation and hepatocarcinogenesis. Targeting the Dfna5–TNFα axis may represent a novel therapeutic strategy for CLD-associated liver cancer.

Disclosures: Yoshinobu Saito: Nothing to Disclose, Tomoya Hamabe: Nothing to Disclose, Yoichi Sasaki: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Nothing to Disclose, Yuta Myojin: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Yuki Makino: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Takahiro Kodama: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Nothing to Disclose

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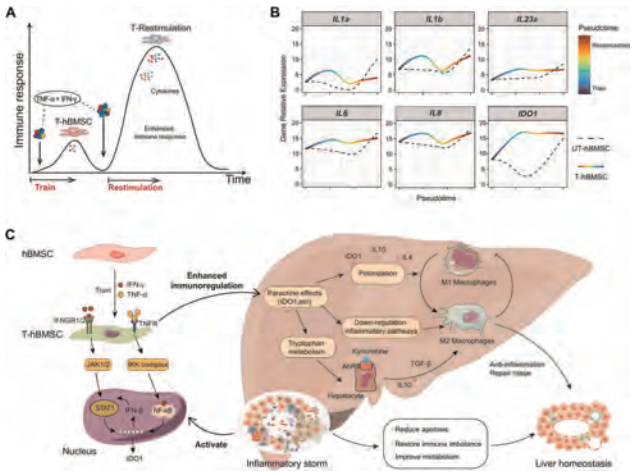
◆ 4227 | TRAINED HUMAN BONE MARROW MESENCHYMAL STEM CELLS RESTORE TISSUE IMMUNO-MICROENVIRONMENT IN FULMINANT HEPATIC FAILURE MICE

Jun Li[1] Bingqi Li[1] Xiaofei Zeng[2] Jing Jiang[1] Jiaojiao Xin[1] Xi Liang[1] Dongyan Shi[1], [1]The First Affiliated Hospital, Zhejiang University School of Medicine, [2]Zunyi Medical University of Medicine

Background: Trained immunity with human bone marrow mesenchymal stem cells (hBMSC) is a promising approach to liver regeneration. This study aimed to clarify the trained-hBMSC (T-hBMSC) in restoring tissue immuno-microenvironment in fulminant hepatic failure (FHF) mice. **Methods:** hBMSC trained with tumor necrosis factor-α and interferon-γ were phenotypically characterized in vitro. FHF mouse models were established in male Balb/c mice via tail vein injection of concanavalin A. The therapeutic potential of T-hBMSC was evaluated through transplantation into FHF mice. Transcriptomic analysis was performed to elucidate the mechanism of liver regeneration post-transplantation of T-hBMSC. **Results:** T-hBMSC with the characteristics of trilineage differentiation potential showed that pro-inflammatory (IL1β, IL8, both $p < 0.0001$) and immunoregulatory genes (PDL1, IDO1, both $p < 0.0001$) were significantly upregulated compared to untrained-hBMSC (UT-hBMSC). Time-trajectory analysis revealed downregulation of pro-inflammatory genes (IL6, IL8, and CXCL9) and upregulation of immunomodulatory genes (IDO1) in T-hBMSC upon mimic-stimulation, characterized with distinct transcriptional programs. The liver function (ALT, AST) and inflammatory cytokines (IL6, MCP1, both $p < 0.01$) levels were significantly improved in T-hBMSC treatment mice. The survival status of the T-hBMSC group was superior to UT-hBMSC group, although there was no statistical significance. Histological analysis confirmed reduced necrosis and fewer infiltrating $CD45^+$ immune cells in T-hBMSC treatment mice. Significant downregulation of immune response (TNF&IL-17 signaling pathways, and neutrophil chemotaxis) and upregulation of metabolic pathways were observed in T-hBMSC group, associated with enhanced liver regeneration. The proportion of anti-inflammatory $F4/80^+CD163^+$ macrophages was increased in the liver of T-hBMSC group. **Conclusion:** T-hBMSC exhibited enhanced immunomodulation, effectively rescuing liver failure and reducing inflammation via restoring the immune-microenvironment. These findings highlighted the potential of trained immunity as a novel strategy to treatment for liver failure.



Disclosures: Jun Li: Nothing to Disclose, Bingqi Li: Nothing to Disclose, Xiaofei Zeng: Nothing to Disclose, Jing Jiang: Nothing to Disclose, Jiaojiao Xin: Nothing to Disclose, Xi Liang: Nothing to Disclose, Dongyan Shi: Nothing to Disclose

4228 | MUTATIONS IN THE ER-PHAGY RECEPTOR FAM134B REDUCE ER-CENTRIC LIPOPHAGY OF NASCENT LDS LEADING TO HEPATIC STEATOSIS

Mark McNiven[1] Hong Cao[2] Shaun Weller[3] Jing Chen[2] Eugene Krueger[2] Micah Schott[4], [1]Mayo Foundation for Medical, [2]Mayo Clinic Rochester, [3]Mayo Clinic, [4]University of Nebraska Medical Center

Background: Hepatic steatosis is a central feature of MASLD that is driven by an aberrant accumulation of cytoplasmic lipid droplets (LDs) within hepatocytes. We have observed that lipophagic catabolism of LDs in hepatocytes can occur at the surface of the endoplasmic reticulum (ER) where lysosomes act to degrade nascent LDs as they form. From this finding, the CENTRAL GOAL of this study was to define the hepatocellular machinery that supports this novel lipophagic process and test if this is altered in patients with MASLD. **Methods:** To this end, we conducted an siRNA screen in AML12 cells and primary mouse hepatocytes (PMHs) to test the role of 6 known Selective Autophagic Receptors (SARs) that might regulate lipophagy of nascent ER-associated LDs. Cellular lipid levels were measured using biochemical assays, while LD numbers and area were quantitated using confocal microscopy and ImageJ software. **Results:** We find that reducing the levels of the ER-phagy receptor/adapter protein FAM134B leads to a 6-8

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fold increase in LD content while overexpression of wt-FAM134B in these cells reduces LD number by over 80%. This adapter is well known to mediate selective degradation of the ER by autophagy during cellular stress, while a putative role in catabolizing nascent LDs forming at the ER surface is unreported. In support of this finding, IHC of human liver tissue revealed a marked reduction of FAM134B levels in patients with MASLD. Based on this, we sought to define the role of FAM134B in an inducible, liver-specific KO mouse model. Using FAM134B$^{flox/flox}$ mice injected with AAV8-Cre, we were encouraged to find FAM134 KO in liver exhibited a 5-7-fold increase in LD number compared to control mice in a fasting/refeeding model. Importantly, these mice had reduced glucose tolerance as assessed by GTT blood glucose assays. Finally, we examined the genomes of 9,000 Mayo patients with MASLD to identify variants in FAM134B and observed 300 patients possessing 2 predominant variations that resided within the transmembrane domains. Significantly, expression of these variants into cultured cells leads to increased LD content. **Conclusion:** These findings provide mechanistic insights into a newly identified ER-phagy centric lipophagic process that plays a key role in the regulation of hepatic lipid stores with direct relevance to MASLD patients. Supported by DK44650 to MAM.
Disclosures: Mark McNiven: Nothing to Disclose, Hong Cao: Nothing to Disclose, Shaun Weller: Nothing to Disclose, Jing Chen: Nothing to Disclose, Eugene Krueger: Nothing to Disclose, Micah Schott: Nothing to Disclose

4229 | DISCOVERY OF PORCINE GREATER OMENTUM-DERIVED STEM CELL AND ITS THERAPEUTIC POTENTIAL FOR LIVER REGENERATION

Min-Gyeong Seo[1] *Jinsun Jeong*[1] *Il-Hwa Hong*[1],
[1]*Gyeongsang National University*

Background: Mesenchymal cells derived from adipose tissue are the most widely utilized stem cells (SCs) due to their accessibility and multipotent differentiation capacity. However, conventional sources of adipose tissue for SC isolation typically require invasive procedures, such as liposuction or laparotomy, and are unsuitable for large-scale SC production. For a more sustainable and abundant SC production, we investigated the porcine greater omentum (pGO), an adipose-rich tissue discarded during slaughter. This study is the first to isolate SCs from pGO, along with evaluation of their biological characteristics and therapeutic potential for liver regeneration. **Methods:** Porcine greater omentum-derived stem cells (pGOSCs) were isolated following standard SC protocols. Expression of surface markers for mesenchymal cells was analyzed by flow cytometry. Differentiation of pGOSCs to hepatocytes, osteocytes, chondrocytes and adipocytes was analyzed by histological examination and qRT-PCR. For conditioned medium (CM), pGOSCs were cultured in serum-free conditions, and growth factors were analyzed by western blot and ELISA. The viability of AML12 cells treated with CM was evaluated using CCK assay. Exosomes isolated from CM were analyzed by LC-MS/MS. **Results:** pGOSCs were confirmed to express mesenchymal stromal markers and successfully differentiate into hepatocytes, osteocytes, chondrocytes, and adipocytes, *in vitro*. Various growth factors, including hepatocyte growth factor (HGF), epidermal growth factor, vascular endothelial growth factor, and platelet-derived growth factor were identified in the CM, with HGF especially abundant. The viability of AML12 cells treated with CM was significantly increased up to 1.5-fold, compared to non-CM control. Proteomic analysis of exosomes identified 3,288 proteins enriched in biological processes related to cell adhesion, migration, and proliferation, with the highest fold enrichment in oxidant detoxification. **Conclusion:** The present study demonstrates that pGO contains multipotent mesenchymal stem cells, capable of producing CM enriched with growth factors, especially HGF, and exosomes possessing regenerative and antioxidative properties, which consequently promote hepatocyte proliferation. Given the genetic and immunological similarities between pigs and humans, pGOSCs and their secretomes may serve as promising candidates for the development of cell-based or cell-free therapeutic agents for liver regeneration in humans.
Disclosures: Min-Gyeong Seo: Nothing to Disclose, Jinsun Jeong: Nothing to Disclose, Il-Hwa Hong: Nothing to Disclose

4230 | PORCINE GREATER OMENTUM-EXTRACTS PROMOTE LIVER REGENERATION BY STIMULATING CELL CYCLE PROGRESSION IN MICE AFTER PARTIAL HEPATECTOMY

Min-Gyeong Seo[1] *Jinsun Jeong*[1] *Il-Hwa Hong*[1],
[1]*Gyeongsang National University*

Background: The greater omentum (GO) has been occasionally utilized for tissue regeneration, such as bone fracture and cardiac injury. Based on a few reports of clinical trials, we hypothesize that GO may contain regenerative components which also contribute to liver regeneration. To prove this hypothesis, we employed the greater omentum from domestic pigs (pGO), which is easily available as it is routinely discarded during slaughter. This study aims to extract aqueous

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components from pGO and evaluate their biological characteristics as well as liver regenerative effects. **Methods:** Aqueous porcine greater omentum-extract (pGOEs) were extracted via DPBS, followed by filtration, pasteurization, and lyophilization. Growth factors and antioxidant activity were analyzed by western blot, ELISA, and DPPH assay. Proteins and exosomes were identified by 2D-electrophoresis and LC-MS/MS. *In vitro*, the viability of AML12 cells treated with pGOEs was evaluated by CCK assay. *In vivo*, pGOEs were administered intraperitoneally to mice after 70% partial hepatectomy (PHx). Livers were collected at 0-96h for histology and western blot. **Results:** *In vitro*, various growth factors, including HGF, EGF, VEGF, PDGF, and IGF-1, were confirmed in pGOEs, with HGF, EGF, and IGF-1 being particularly abundant. Proteomic analysis of pGOEs revealed a large number of protein spots, among which antioxidant-related proteins, such as superoxide dismutase, peroxiredoxin, and hemopexin, were predominantly detected. Proteomic analysis of exosomes identified 729 proteins enriched in biological processes related to cell migration and oxidant detoxification. The viability of AML12 cells treated with pGOEs was significantly increased compared to non-treated controls. In PHx mice treated with pGOEs, liver regeneration rates were enhanced, with notably higher mitotic activity than vehicle-treated mice. Interestingly, expression of cell cycle proteins and phosphorylation of growth factor-related receptors was upregulated in pGOE-treated mice. **Conclusion:** The present study demonstrates that pGOEs, enriched with various growth factors and antioxidant proteins, promote hepatocyte proliferation *in vitro* and enhance liver regeneration *in vivo*. Our findings suggest that pGOEs possess therapeutic potential for liver regeneration and may be applicable for various liver injuries.

Disclosures: Min-Gyeong Seo: Nothing to Disclose, Jinsun Jeong: Nothing to Disclose, Il-Hwa Hong: Nothing to Disclose

4231 | SPATIALLY RESOLVED IMMUNO-ENDOTHELIAL INTERACTOME ACROSS LIVER NICHES IN END-STAGE ALCOHOL-RELATED LIVER DISEASE

Oleksandr Petrenko[1] Thomas Sorz-Nechay[1] Martin Bilban[1] Sophia Derdak[1] Lukas Van Melkebeke[2] Wenxin Huang[2] Jef Verbeek[2] Schalk van der Merwe[2] Benedikt Hofer[1] Benedikt Simbrunner[1] Thomas Reiberger[1] Tim Hendrikx[1], [1]Medical University of Vienna, [2]KU Leuven

Background: Alcohol-related liver disease (ALD) remains a major healthcare burden yet lacks high-resolution spatial characterization. We applied ultra-high resolution spatial transcriptomics (2 μm spots) to delineate cellular interactions across tissue niches in end-stage ALD. **Methods:** We obtained a cirrhotic caudate-lobe sample during liver transplantation in the Vienna General Hospital (ethical approval 2318/2019). Picrosirius red and α-SMA areas were quantified in HALO. 5 μm H&E sections were subjected to the 10x Visium HD workflow and sequenced (NextSeq 2000, paired-end). Cells were segmented from H&E nuclei with bin2cell algorithm (on sequenced 2 μm spots), with QC and downstream analysis in Scanpy. Cells were annotated with canonical markers and refined by the pre-trained CellTypist model. QuPath was used to annotate 50x50 px niches: vascular (n = 6), fibrotic (n = 11), and parenchymal (n = 5). We computed median pairwise Euclidean distance matrices to profile cell–type-specific niche relationships. We generated directed interaction graphs per niche using LIANA +-inferred ligand-receptor interactions; hub nodes were identified as those in the top decile by combined standardized degree and betweenness (NetworkX). **Results:** Histomorphometry revealed 33.4% collagen and 28.2% α-SMA-positive areas. Post-QC, 265 573 cells were annotated (e.g., vascular endothelial cells, EC: *VWF*, *CD34*; liver sinusoidal endothelial cells, LSEC: *STAB2*, *CLEC4G*). We found that proximity patterns varied in tissue niches: in perivascular zones, EC co-localized with T cells; in perifibrotic niches, LSEC–fibroblast proximity predominated. EC in fibrotic zones were more active in overall ligand-receptor expression than LSEC; in vascular zones, LSEC had prevailing ligand expression. Reciprocal interaction analysis uncovered LSEC–stellate and LSEC–fibroblast signaling in perivascular and fibrotic contexts, and EC–immune cell crosstalk in the vascular niches. Hub network analysis highlighted SPARC-ENG signaling among EC, CD4+ T cells, and fibroblasts in fibrotic niches and CXCL12–CXCR4 interactions between EC, T cells, macrophages, and monocytes in vascular niches. The ligand-receptor pairs prioritized through the network analysis also demonstrated significant co-localization patterns. **Conclusion:** Ultra-high resolution (on 2 μm spots) spatial transcriptomics in end-stage ALD revealed niche-specific EC-immune interactomes, uncovering spatially resolved signaling networks for candidate biomarkers and therapeutic targets investigation.

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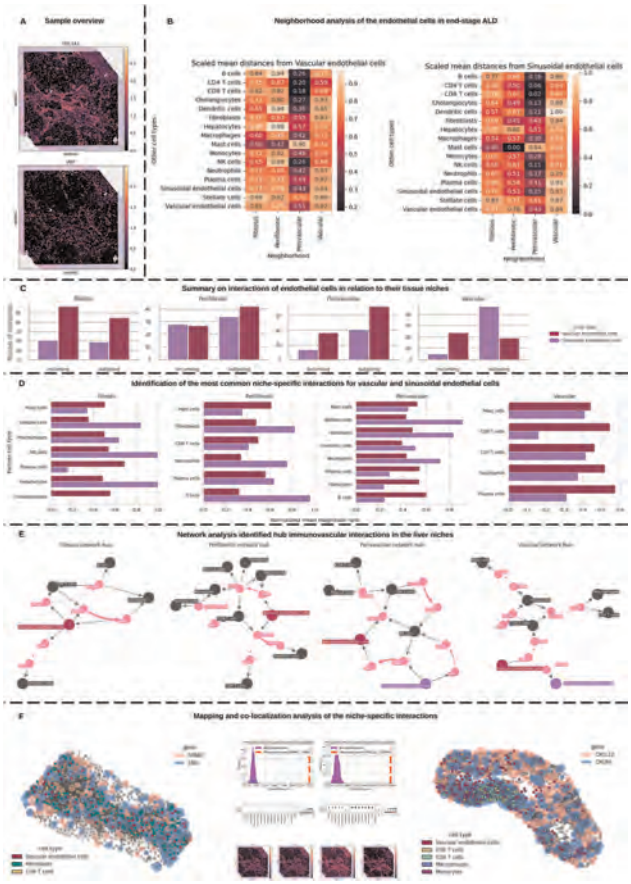

Disclosures: Oleksandr Petrenko: Nothing to Disclose, Thomas Sorz-Nechay: Nothing to Disclose, Martin Bilban: Nothing to Disclose, Sophia Derdak: Nothing to Disclose, Lukas Van Melkebeke: Nothing to Disclose, Wenxin Huang: Nothing to Disclose, Jef Verbeek: Nothing to Disclose, Schalk van der Merwe: Nothing to Disclose, Benedikt Hofer: Nothing to Disclose, Benedikt Simbrunner: Nothing to Disclose, Thomas Reiberger: Nothing to Disclose, Tim Hendrikx: Nothing to Disclose

4232 | ZONE-SPECIFIC Β-CATENIN EXPRESSION IS REQUIRED FOR MAINTENANCE OF LIVER ZONATION AND REGENERATION AFTER PARTIAL HEPATECTOMY

Chang Kyung (Joanna) Kim[1] Prerna Chakkingal[1] Vik Meadows[2] Tyler Yasaka[1] Minakshi Poddar[1] Sucha Singh[1] Satdarshan (Paul) Monga[2], [1]UPMC, [2]University of Pittsburgh

Background: The adult liver carries out diverse set of vital functions including metabolism (fat, protein, carbohydrate, xenobiotic), synthesis (bile, protein, vitamins) and detoxification. Liver zonation defines the spatial division of functions based on location of cells along the porto-central blood flow and largely divides into three zones: zone 1 (periportal), zone 2 (midlobular), and zone 3 (pericentral). Under various disease conditions, specific zones exhibit differential vulnerabilities, ultimately leading to a disruption of normal liver zonation. Despite recent progress elucidating Wnt/β-catenin signaling as the master regulator of liver zonation, particularly in maintaining zone 3 hepatocyte identity and function, significant gaps remain with respect to the zone-specific functions of β-catenin at baseline and after partial hepatectomy (PHx), since its upstream effectors Wnt2 and Wnt9b in endothelial cells are expressed in a decreasing gradient from zone 3 to zone 1. **Methods:** To investigate the zone-specific function of β-catenin, we generated *Igfbp2-Cre^{ERT2};Ctnnb1$^{fl/fl}$* (*Igfbp2$^{\Delta Ctnnb1}$*) and *Cyp1a2-Cre^{ERT2};Ctnnb1$^{fl/fl}$* (*Cyp1a2$^{\Delta Ctnnb1}$*) mice to delete β-catenin in zone 2 and 3, respectively. Deletion was induced by tamoxifen injection and livers were harvested after 12 days of washout period. Partial hepatectomy (Phx) was performed on 10–12-week-old mice for assessing proliferation at 40 hour post-Phx. **Results:** β-catenin deletion in zone 2 hepatocytes in *Igfbp2$^{\Delta Ctnnb1}$*mice at baseline showed a spatial shift in expression of midzonal markers IGFBP2 and Cyclin-D1 toward zone 3, with reciprocal contraction of CYP2E1 (zone 3 marker) expression. Interestingly, the expression pattern of CYP2F2 (zone 1 marker) did not expand but rather showed a trend toward contraction. β-Catenin deletion in zone 3 hepatocytes in *Cyp1a2$^{\Delta Ctnnb1}$* mice resulted in loss of glutamine synthetase (GS) and CYP2E1 expression in the 1-3 cell layers around the central vein and gain of ectopic expressions of zone 1 markers E-cadherin and CYP2F2 in these cells. No significant changes were seen in the expression of midzone markers IGFBP2 and HAMP1/2. Previous studies have suggested that midzone hepatocytes initiate proliferation during liver regeneration after PHx. At 40 hour post-PHx, at the peak of mitotic activity, loss of β-catenin in zone 3 in *Cyp1a2$^{\Delta Ctnnb1}$* mice resulted in increased proliferation of zone 1 and 2 hepatocytes compared to control mice as indicated by higher % of Ki-67^{+} expression in cell layers 2-5. On the contrary, β-catenin deletion in zone 2 hepatocytes in *Igfbp2$^{\Delta Ctnnb1}$*mice resulted in decreased proliferation across the lobule. **Conclusion:** Taken together these data suggest that β-catenin is required for zone 2 and 3 hepatocytes to maintain part of their zonal identity. These results also confirm that midzone hepatocytes are the main drivers of liver regeneration after PHx, and that β-catenin is critical to this process.

Disclosures: Chang Kyung (Joanna) Kim: Nothing to Disclose, Prerna Chakkingal: Nothing to Disclose, Vik Meadows: Nothing to Disclose, Tyler Yasaka: Nothing to Disclose, Minakshi Poddar: Nothing to Disclose,

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Sucha Singh: Nothing to Disclose, Satdarshan (Paul) Monga: Mermaid Bio: Advisor, Vicero: Advisor, AntlerA: Advisor, Genentech: Speaking and Teaching, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Mermaid Bio: Consultant, Fog Pharmaceuticals: Grant/Research Support, Surrozen: Consultant, Genentech: Independent Contractor

4233 | ENGINEERING BIOACTIVE MICROCAPSULES FOR HEPATIC DIFFERENTIATION OF PLURIPOTENT STEM CELLS

Kianna Nguyen[1] Quang Tuan Che[1] Youngmin Hwang[1] Kihak Gwon[2] Gulnaz Stybayeva[1] Quinn Peterson[1] Alexander Revzin[1], [1]Mayo Clinic, [2]Kyungpook National University

Background: Stem cell-derived liver organoids have many promising applications from drug discovery to cellular therapies. There remains a need for scalable hepatic differentiation protocols. Core-shell microcapsules promote cell spheroid formation and may be used to establish high-density suspension cultures. Incorporation of heparin into the shell promotes capsule retention of growth factors to enable local and continuous delivery of inductive cues to cells. As the next step in evolution of this capsule technology, Matrigel, an extracellular matrix that is commonly used for differentiation studies, has been incorporated into the core of microcapsules. We demonstrate that Matrigel retains integrity in microcapsules over the course of differentiation and that its presence is associated with improved in-capsule hepatic differentiation outcomes. **Methods:** Pluripotent stem cells and Matrigel are encapsulated using a co-axial flow focusing microfluidic device to generate aqueous core-shell droplets in oil. Eight-arm-polyethylene-glycol-maleimide and methacrylated heparin in the shell are then crosslinked to form microcapsules with an aqueous core, allowing for spheroid formation, and a hydrogel shell. Liver organoid differentiation, as adapted from Takebe et al, is then carried out in capsules. Differentiation efficiency was evaluated via gene expression, functional assays, and protein expression. **Results:** Microcapsules retained mechanical integrity for at least 28 days of culture in a stirred bioreactor. Matrigel incorporation into the core of the microcapsules was characterized with fluorescence labeling and immunohistochemical staining, demonstrating retention of Matrigel for at least 28 days. With confirmed mechanical stability and composition of microcapsules, pluripotent stem cells were encapsulated and differentiated with a multi-stage liver organoid differentiation protocol. Encapsulated spheroids produced high levels of albumin and were composed of cells from both epithelial and mesenchymal origins. Hepatic function and cellular composition of encapsulated differentiated liver organoids was comparable to standard Matrigel dome control cultures. **Conclusion:** We have engineered microcapsules with synthetic hydrogel shells and Matrigel cores, offering a scalable and tunable stem cell differentiation platform. Encapsulated pluripotent stem cells were differentiated into well characterized liver organoids within these capsules. We envision that after completing hepatic differentiation, microcapsules may be transplanted and will offer immunoisolation in vivo.

Disclosures: Kianna Nguyen: Nothing to Disclose, Quang Tuan Che: Nothing to Disclose, Youngmin Hwang: Nothing to Disclose, Kihak Gwon: Nothing to Disclose, Gulnaz Stybayeva: Nothing to Disclose, Quinn Peterson: Nothing to Disclose, Alexander Revzin: Nothing to Disclose

4234 | MYOSTATIN ACTIVATES AMPK DURING HYPERAMMONEMIC STRESS RESPONSE TO CAUSE SARCOPENIA OF CIRRHOSIS VIA TRANSFORMING GROWTH FACTOR BETA RECEPTOR-1, ACTIVIN LIKE KINASE 5 (ALK5)

Muaz Alsabbagh Alchirazi[1] Saurabh Mishra[1] Seshu Pothabathula[1] Pugazhendhi Kannan[1] Annette Bellar[1] Amy Attaway[1] Nicole Welch[1] Srinivasan Dasarathy[1], [1]Cleveland Clinic

Background: Sarcopenia in cirrhosis is caused by increased myostatin (MSTN) expression during hyperammonemic stress response (HASR). Canonical myostatin signaling is mediated via TGF beta receptor-1 kinases (ALK4/5) that phosphorylate the smad2/3 transcription factor(s) with nuclear translocation and expression of genes that regulate muscle mass. However, during HASR, dysregulated protein homeostasis and sarcopenic phenotype are medaited via myostatin-dependent phosphorylatoin and activation of AMPKa2 in skeletal muscle. The kinase for AMPK phosphorylation activated by myostatin during HASR were investigated. **Methods:** Skeletal muscle from mice with muscle-specific knockout of AMPK and MSTN knockout, portacaval anastamosis and sham-operated rats, human induced pluripotent stem cell (hiPSC)-derived myotubes, and diferentiated murine C2C12 myotubes with knockdown (KD) of MSTN, AMPK, ALK4, ALK5, and double KD of ALK4/5 using shRNA wwere studied. HASR was induced with 10mM ammonium acetate (AmAc) for 24h in myotubes and 2.5mmol $AmAc.kg^{-1}.d^{-1}$ or saline for 28 days infused subcutaneously via a miniosmotic pump in mice. Protein synthesis was assessed by puromycin incorporation. Phosphorylation/activation of AMPK,

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mTORC1, and functional responses were quantified by immunoblots. Protein-protein interactions were studied by co-immunoprecipitation/live cell imaging. **Results:** During HASR, in skeletal muscle from a comprehensive array of models (patients with cirrhosis, mice, rats, and murine/hiPSC myotubes), expression of myostatin, ALK4,and ALK5 were increased with greater phosphorylation of AMPKa2 compared to controls. Consequences of phosphorylation/activation of AMPKa2 during HASR include impaired mTORC1 signaling, lower protein synthesis, increased autophagy markers, and a sarcopenic phenotype in myotubes and muscle tissue. Molecular and phenotype responses to HASR were reversed by myostatin and AMPKa2 depletion in mouse muscle tissue and myotubes. Co-immunoprecipitation and live cell imaing showed direct interaction between ALK5 and AMPK. ALK5 KD but not ALK4 KD reduced phosphorylation AMPK and restored mTORC1 signaling, protein synthesis with reversal of sarcopenic phenotype during HASR. In contrast, double KD of ALK4+5 also reversed AMPK phosphorylation confirming ALK5 as the primary functional TGFB receptor mediating MSTN-induced AMPK activation. **Conclusion:** Sarcopenia in cirrhosis is due to HASR-dependent upregulation of MSTN and activation of AMPKa2 via ALK5. Downstream signaling responses to AMPKa2 activation include impaired mTORC1 signaling with dysregulated protein homeostasis and a sarcopenic phenotype that were reversed by sequential depletion of MSTN, AMPKa2, and ALK5 (but not ALK4) in skeletal muscle in preclinical models. These data provide the rationale for targeting ALK5 using currently available pharmacologic agents to target sarcopenia of cirrhosis.

Disclosures: Muaz Alsabbagh Alchirazi: Nothing to Disclose, Saurabh Mishra: Nothing to Disclose, Seshu Pothabathula: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

4235 | DEVELOPMENT OF AN INTRAHEPATIC CHOLANGIOCYTE-DERIVED CHOLANGIOCARCINOMA MOUSE MODEL

Bin Wang[1] Jiale Wang[1] Liu Yang[1] Gordon He[1] Yasmin Jahan-mihan[1] Muhammad Faheem[1] Jie Hu[1] Yuxi Wang[1] Zhu Zhu[1] Bi Yan[1] Baoan Ji[1], [1]Mayo Clinic

Background: Intrahepatic cholangiocarcinoma (iCCA) is a highly aggressive liver cancer with a poor prognosis and limited response to chemotherapy. Intrahepatic cholangiocytes are believed to be the cell of origin of iCCA. Genetically engineered iCCA mouse models derived from intrahepatic cholangiocytes are essential for studying pathogenesis and testing preclinical therapies. Currently, most existing iCCA models rely on a single recombination strategy (e.g., Cre/loxP) driven by Cytokeratin 19 (CK19) or Albumin (Alb) promoters to activate oncogenes or inactivate tumor suppressors. However, Alb promoter targets all liver parenchymal cells including hepatocytes as well as cholangiocytes. CK19 promotor targets intrahepatic cholangiocytes in the liver. Yet, CK19 is also positive in many ductal cells of other organs throughout the body. Therefore, these models may not recapitulate the features of human iCCA. An iCCA animal model derived from intrahepatic cholangiocytes is lacking because there is no known gene promoter specifically targets intrahepatic cholangiocytes. To overcome this limitation, we aimed to develop an iCCA model uniquely derived from intrahepatic cholangiocytes. **Methods:** We developed a dual-recombinase system (DRS)-based mouse model using a combination of CK19 and Alb promoters. The Alb promoter, which is active in cholangiocytes, hepatocytes, and hepatic progenitor cells (HPCs) during embryogenesis, was used to express Flp recombinase (Alb-Flpo). The CK19 promoter, which is specific in duct cells of many organs including the liver, was used to drive CreERT expression but only after Flp-mediated recombination (CK19-FSF-CreERT). By crossing these two mouse lines, we expected that CreERT would be expressed only in intrahepatic cholangiocytes. **Results:** To examine Cre recombination specificity, Alb-Flpo/CK19-FSF-CreERT double transgenic mice were crossed with LacZ reporter mice. After tamoxifen (TM) induction, positive X-gal staining was only observed in intrahepatic cholangiocytes, but not in the epithelial cells of other organs. To generate the iCCA model, we further crossed Alb-Flpo/CK19-FSF-CreERT mice with $PTEN^{L/L}$, $P53^{L/L}$, and LSL-$Kras^{G12D}$ mice for conditional oncogenic Kras expression and tumor suppressor gene PTEN and P53 deletion. Upon TM induction, iCCA were developed in these compound mice. Lineage tracing showed that the iCCA cells originated from cholangiocytes. In contrast, liver tumors developed from Alb promoter-driven recombination developed a mixture of iCCA and hepatocyte carcinoma (HCC). **Conclusion:** We developed a novel genetic iCCA mouse model that uniquely originates from intrahepatic cholangiocytes.

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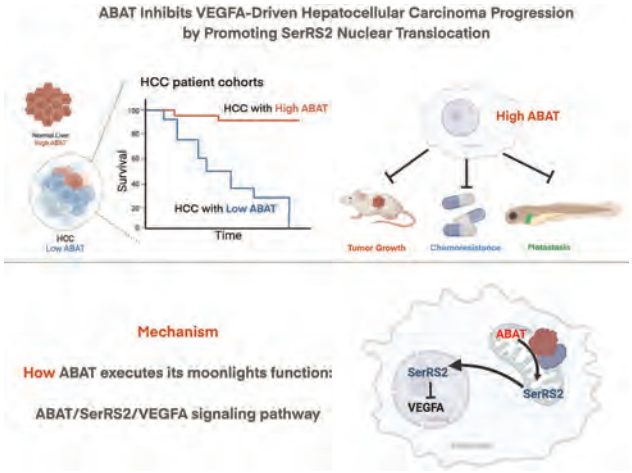
4236 | ABAT INHIBITS VEGFA-DRIVEN HEPATOCELLULAR CARCINOMA PROGRESSION BY PROMOTING SERRS2 NUCLEAR TRANSLOCATION

Baojia Zou[1] Peiping Li[1] Yihua Dai[1] Shanglin Cai[1] Decheng Li[1] Jianzhong He[1] Jiali Zhao[1] En Lin[1] Bailiang He[1] Genglong Zhu[1] Jian Li[1], [1]the Fifth Affiliated Hospital of Sun Yat-sen University

Background: 4-Aminobutyrate aminotransferase (ABAT), a mitochondrial enzyme in the GABA metabolic pathway, has been implicated in various cancers beyond its canonical metabolic functions. However, its role in hepatocellular carcinoma (HCC) remains unclear. This study explores the function of ABAT in modulating HCC progression and its regulatory link to VEGFA expression. **Methods:** ABAT expression was analyzed in HCC patient samples and public datasets (TCGA, Human Protein Atlas). Functional assays, including gain- and loss-of-function studies in multiple HCC cell lines, evaluated its role in proliferation, migration, invasion, and cisplatin sensitivity. In vivo validation was performed using subcutaneous xenografts in nude mice and metastasis models in zebrafish. Mechanistic investigations involved co-immunoprecipitation, Alphafold3 prediction and simulation for protein-protein interaction, nuclear-cytoplasmic fractionation, RNA sequencing, and ELISA. Clinical associations were assessed by immunodetection of ABAT, SerRS2, and VEGFA in HCC specimens. **Results:** Low ABAT Expression Predicts Poor Prognosis in HCC: Transcriptomic and clinical sample analysis revealed significantly decreased ABAT in HCC, correlating with poor overall and disease-free survival, especially post-TACE.

1. ABAT Suppresses EMT and Metastatic Traits: ABAT overexpression inhibited EMT markers and reduced invasion and migration; zebrafish models confirmed anti-metastatic effects.
2. ABAT Enhances Chemosensitivity: Functional studies showed reduced colony formation and increased cisplatin sensitivity with ABAT overexpression. Knockdown promoted proliferation and resistance in vitro and in vivo.
3. ABAT Facilitates Nuclear Translocation of SerRS2: Proteomic and biochemical assays identified ABAT–SerRS2 interaction, as validated in Alphafold 2/3 prediction and simulation; ABAT promoted nuclear localization of SerRS2.
4. ABAT Loss Activates VEGFA: ABAT depletion caused cytoplasmic retention of SerRS2 and upregulated VEGFA expression and secretion. Blocking VEGFA or SerRS2 knockdown reversed this phenotype. **Conclusion:** ABAT functions as a suppressor of HCC progression by facilitating the nuclear translocation of SerRS2 and limiting VEGFA expression. These findings suggest that ABAT-SerRS2-VEGFA axis may serve as both a prognostic biomarker and a novel target in managing advanced or chemoresistant HCC.



Disclosures: Baojia Zou: Nothing to Disclose, Peiping Li: Nothing to Disclose, Yihua Dai: Nothing to Disclose, Shanglin Cai: Nothing to Disclose, Decheng Li: Nothing to Disclose, Jianzhong He: Nothing to Disclose, Jiali Zhao: Nothing to Disclose, En Lin: Nothing to Disclose, Bailiang He: Nothing to Disclose, Genglong Zhu: Nothing to Disclose, Jian Li: Nothing to Disclose

4237 | DEVELOPMENT AND CHARACTERIZATION OF A NOVEL LONG-TERM CULTURE SYSTEM FOR HUMAN IPSC-DERIVED HEPATIC ORGANOIDS

Taro Shimizu[1] Masato Miyoshi[1] Sei Kakinuma[1] Jun Tsuchiya[1] Daisuke Yamane[2] Tomohiro Mochida[1] Kento Inada[1] Kaho Yamada[1] Kotomi Shinozaki[2] Shun Kaneko[1] Fukiko Kawai-Kitahata[1] Miyako Murakawa[1] Sayuri Nitta[1] Mina Nakagawa[1] Yasuhiro Asahina[1] Ryuichi Okamoto[1], [1]Institute of Science Tokyo, [2]Tokyo Metropolitan Institute of Medical Science

Background: Recent advances in human induced pluripotent stem cell (iPSC) culture have enabled the generation of 3D liver organoids. However, the long-term expansion of iPSC-derived hepatocytes with preserved hepatocyte function remains a major challenge, limiting the utility of these organoids as chronic liver disease models. We have established a novel iPSC-derived hepatic organoid (iHO) culture system capable of long-term maintenance and passaging. Here, we further characterized iHOs and evaluated

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their potential as models of chronic liver diseases, including viral hepatitis. **Methods:** Human iPSCs were differentiated into hepatocyte-like cells under 2D conditions (2D-iPS-Hep), followed by embedding in hydrogel for 3D culture using our iHO medium containing bile acids. We compared gene expression and albumin production among iHOs, 2D-iPS-Heps, and cryopreserved primary human hepatocytes (Cryo-Hep). Bulk and single-cell RNA sequence analyses were performed to determine the transcriptomic profiles of iHOs in comparison with 2D-iPS-Heps, Cryo-Heps, and publicly available datasets of human liver tissues and other iPSC-derived hepatic organoids. To assess the potential for a disease model, iHOs were infected with genotype 1a hepatitis C virus (HCV), and viral replication in iHOs was compared to that in other iPSC-derived organoids. **Results:** iHOs continuously expressed hepatocyte-related genes, including albumin, and could be passaged for over three months across different iPSC lines. Albumin production by iHOs was more than 15-fold higher than that of 2D-iPS-Heps ($p = 0.0145$; mean $\pm$ SEM: iHOs = 4.921 $\pm$ 1.318 μg/10,000 cells/48 h, 2D-iPS-Heps = 0.311 $\pm$ 0.101 μg/10,000 cells/48 h), and was almost equal to that of Cryo-Heps. Morphologically, iHOs formed "grape-like" clusters and exhibited bile canaliculi-like structures, confirmed by microscopy and dye secretion assays. Bulk RNA-seq analysis showed that iHOs resembled fetal hepatocytes, whereas 2D-iPS-Heps and other iPSC-derived organoids were closer to cholangiocytes or intestinal cells. Single-cell RNA-seq showed that over 90% of cells in passaged iHOs displayed hepatocyte-like gene expression profiles, including a proliferative subpopulation without cholangiocyte-like signature. Furthermore, iHOs supported robust HCV infection, with viral replication exceeding that of DAA-treated controls by more than 40-fold, demonstrating their strong potential for modeling viral hepatitis. **Conclusion:** Building on our previously established culture system, this study provides detailed molecular and functional characterization of iHOs and confirms their utility as a robust in vitro platform for chronic liver disease research.

Disclosures: Taro Shimizu: Nothing to Disclose, Masato Miyoshi: Nothing to Disclose, Sei Kakinuma: Nothing to Disclose, Jun Tsuchiya: Nothing to Disclose, Daisuke Yamane: Nothing to Disclose, Tomohiro Mochida: Nothing to Disclose, Kento Inada: Nothing to Disclose, Kaho Yamada: Nothing to Disclose, Kotomi Shinozaki: Nothing to Disclose, Shun Kaneko: Nothing to Disclose, Fukiko Kawai-Kitahata: Nothing to Disclose, Miyako Murakawa: Nothing to Disclose, Sayuri Nitta: Nothing to Disclose, Mina Nakagawa: Nothing to Disclose, Yasuhiro Asahina: Nothing to Disclose, Ryuichi Okamoto: Nothing to Disclose

4238 | AUTOPHAGY ZONATION AND ITS ROLE IN LIVER METABOLISM

Kamal Baral[1] Arya Chandrasheker[1] Leah Spade[1] Ramsey Rohner[1] Xiao-Ming Yin[1] Bilon Khambu[2], [1]School of Medicine, Tulane University, [2]Tulane University School of Medicine

Background: Autophagy is a conserved lysosomal pathway essential for metabolic homeostasis. Its deficiency contributes to chronic liver diseases (CLD) such as hepatitis, cirrhosis, and cancer. Hepatic metabolic homeostasis relies on liver zonation, where hepatocytes in pericentral (PC) and periportal (PP) zones perform specific metabolic functions. The role of autophagy in liver zonation and its impact on metabolic homeostasis remain unclear, but both processes are disrupted in liver disease development and progression. **Methods:** Wild-type mouse livers were analyzed for autophagy-related protein and gene expression to determine zonation. The Human Protein Atlas (HPA) database was screened for upstream autophagy transcriptional regulators. Various mouse models of autophagy deficiency and activation were used to investigate autophagy's role in hepatic zonation. Liver sections were immunostained for zonal markers, and qPCR and immunoblot analyses assessed zonal expression of autophagy and drug metabolism-related genes. Autophagy rescue experiments were performed using the AAV8-TBG-Atg7 system in autophagy-deficient mice. Drug metabolites were analyzed using LC/MS to evaluate autophagy's impact on hepatic drug metabolism. Normal and CLD preclinical liver samples, along with human liver sections, were examined for autophagy zonation and drug metabolism enzyme expression. **Results:** Autophagy gene expression in normal livers was zonated, with higher expression in the pericentral (PC) zone compared to the periportal (PP) zone. This zonal expression of autophagy genes was consistent with the zonal expression of autophagy proteins. Human Protein Atlas (HPA) screening revealed that transcriptional regulators of autophagy, including FOXO1, GATA4, NF-kB1, SMAD2, and SREBP2, were pericentrally zonated. Genetic deletion of core autophagy genes, such as Atg7 and Atg5, led to downregulation of Wnt/β-catenin signaling, a key regulator of liver zonation, causing disturbed liver zonation. Additionally, autophagy deficiency reduced the expression of phase I Cyps, major drug-metabolizing enzymes (DMEs), resulting in altered drug metabolite profiles. Similar disruptions in autophagy, liver zonation, and phase I Cyp expression were observed in human non-alcoholic fatty liver disease (NAFLD) autopsy samples and in mice fed a high-fat diet, underscoring the clinical significance of these findings. **Conclusion:** Hepatic autophagy function is

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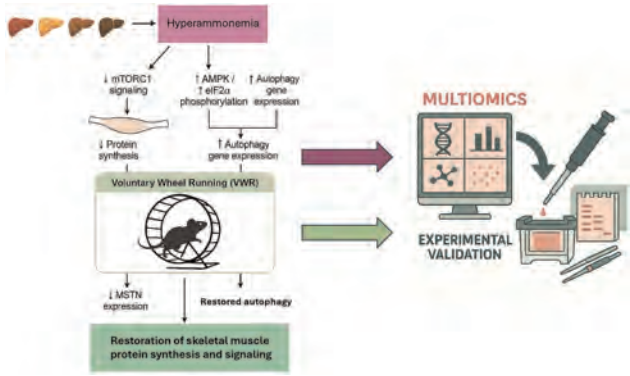
predominantly zonated in the pericentral (PC) zone and plays a crucial role in drug metabolism.
Disclosures: Kamal Baral: Nothing to Disclose, Arya Chandrasheker: Nothing to Disclose, Leah Spade: Nothing to Disclose, Ramsey Rohner: Nothing to Disclose, Xiao-Ming Yin: Nothing to Disclose, Bilon Khambu: Nothing to Disclose

4239 | REVERSAL OF HYPERAMMONEMIC STRESS RESPONSE PERTURBATIONS-INDUCED SARCOPENIA OF CIRRHOSIS BY VOLUNTARY WHEEL RUNNING: AN INTEGRATED MULTIOMICS-EXPERIMENTAL VALIDATION APPROACH

Srinivasan Dasarathy Takhar Kasumov[1] Lopa Mishra[2] Annette Bellar[3] Nicole Welch[3] saurabh mishra[3] Muaz Alsabbagh Alchirazi[3] Amy Attaway[3] Ryan Musich[3] Pugazhendhi Kannan[3] Seshu Vardhan Pothabathula[3], [1]NEOMED, [2]Feinstein Institutes for Medical Research & Cold Spring Harbor Laboratory, [3]Cleveland Clinic

Background: Hyperammonemia, a common complication of liver dysfunction, impairs skeletal muscle protein homeostasis by suppressing mTORC1 signaling, reducing protein synthesis, and enhancing catabolic AMPK and eIF2α phosphorylation. While exercise induces muscle ammoniagenesis, its impact on ammonia-induced signaling disruptions remains unclear. This study aimed to determine whether voluntary wheel running (VWR) reverses hyperammonemia-mediated impairments in muscle protein synthesis and signaling. via AMPK and eIF2α phosphorylation. We determined if voluntary wheel running (VWR) reverses hyperammonemia-mediated impairments in muscle protein synthesis and signaling pathways. **Methods:** Hyperammonemic mice, an established model of cirrhotic sarcopenia were compared with control mice. Miniosmotic pumps were implanted in wild type, male C57BL6 mice aged 8-9 weeks to deliver 2.5mM ammonium acetate (AmAc) or phosphate buffered saline (PBS) as vehicle for 6 weeks. After 2 weeks recovery from implantation surgery, mice were randomized to either voluntary wheel running (VWR) or usual activity (UA) for 4 weeks. Protein synthesis in gastrocnemius muscle was measured via puromycin incorporation. Phosphorylation of mTORC1 signaling pathway proteins (p-mTOR^{Ser248}, p-S6$^{Ser240/244}$, p-4EBP1$^{Thr37/45}$), AMPK (p-AMPK^{Thr172}), eIF2α (p-eIF2α^{Ser51}), and myostatin (MSTN) expression were quantified by immunoblots. Multi-omics analysis (RNAseq and proteomics) was performed to integrate autophagy, mTOR, and eIF2α pathway gene and protein expression. Integrated multiomics analyses of untargeted data (tissue RNAseq, proteomics, metabolomics) and plasma (proteomics, metabolomics) were performed. **Results:** AmAc-UA mice had less muscle protein synthesis vs. PBS-UA ($p < 0.05$). VWR increased synthesis in both PBS ($p < 0.01$) and AmAc groups ($p < 0.001$), as compared to their respective UA groups (Fig. 1). VWR elevated p-mTOR^{Ser248} ($p < 0.01$) and reversed AmAc-associated reductions in p-S6$^{Ser240/244}$ ($p < 0.05$). MSTN expression was increased in AmAc-UA and decreased with VWR ($p < 0.001$). p-AMPK^{Thr172} was increased by both AmAc and VWR ($p < 0.05$). Integrarted multiomics analysis revealed hyperammonemia-induced upregulation of autophagy-related genes (e.g., *Sqstm1, Rubcn, Ddit3*), decreased mTOR effectors (e.g., *Pdk1, Gsk3b, Immt*), and increased *Eif2ak1/4* expression which were reversed with VWR. **Conclusion:** VWR restores skeletal muscle protein synthesis during HASR of cirrhosis by increased mTORC1 signaling, less MSTN expression, and reversing transcriptomic/proteomic changes in autophagy and mTOR related pathways. These findings support exercise as a non-pharmacologic strategy to counteract sarcopenia in chronic liver disease.



Disclosures: Srinivasan Dasarathy: Nothing to Disclose, Takhar Kasumov: Nothing to Disclose, Lopa Mishra: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Nicole Welch: Nothing to Disclose, saurabh mishra: Nothing to Disclose, Muaz Alsabbagh Alchirazi: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Ryan Musich: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Seshu Vardhan Pothabathula: Nothing to Disclose

4240 | THE XBP1 ACTIVATOR IXA4 REGULATES HUMAN BILE ACID AND FATTY ACID SYNTHESIS GENES IN IPSC-HEPATOCYTES

Moloud Aflaki Sooreshjani[1] Xiaoying Liu[2] Ekta Minocha[3] John G Purdy[3] Jason A Wertheim[3] Richard Green[1], [1]Northwestern University, [2]Northwestern University Feinberg School of Medicine, [3]Arizona University

Background: Metabolic dysfunction-associated fatty liver diseases are the most common cause of abnormal liver function tests in the United States and are a major

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cause of cirrhosis and hepatocellular carcinoma. Human induced pluripotent stem cells (iPSCs) and iPSC-hepatocytes provide valuable models for studying the mechanisms of liver disease. Using murine models, we have previously shown that the X-box binding protein 1 (XBP1) pathway of unfolded protein response (UPR) regulates fatty acid and bile acid metabolism. We used the human iPSC-hepatocytes to investigate the role of pharmacologic XBP1 activation on the gene expression of bile acid and fatty acid metabolism. **Methods:** Normal human pluripotent stem cells were differentiated into iPSC-hepatocytes over 21 days. During differentiation, cells were treated with either 10 μM of IXA4, a selective IRE1/XBP1 activator, or vehicle control for the last 1, 3, 5, or 10 days of differentiation. iPSC-hepatocytes were harvested on day 21 and gene expression was analyzed for XBP1 activation, bile acid synthesis genes, and fatty acid synthesis genes using qPCR. iPSC-hepatocytes were similarly treated with 50 μM of tauroursodeoxycholic acid (TUDCA) for 5 days and gene expression was analyzed. **Results:** Following IXA4 treatment, gene expression of the XBP1 downstream target *ERdj4* increased by 1.4- to 1.7-fold at all time points compared to vehicle controls ($p < 0.05$), confirming drug effectiveness. Gene expression of the major bile acid synthesis gene *CYP7A1* was decreased 40-90% at 3, 5, and 10 da*ys* ($p < 0.001$). In addition, the bile acid synthesis gene *CYP8B1* was also decreased 32-74% at these time points ($p < 0.05$) with the greatest reduction of both genes occurring at 3 days. In contrast, *CYP27A1* was unchanged. The fatty acid synthesis gene *SCD-1* was increased by 2- to 4.2-fold at 3 and 5 days ($p < 0.01$), with similar increase in *LCAD* expression ($p < 0.002$). There was a strong trend of 2- to 2.4-fold increase in *FASN* gene expression ($p < 0.08$). In contrast, the lipid regulatory gene *SREBP-1a* was unchanged. We subsequently treated iPSC-hepatocytes with 50 μM of TUDCA for 5 days, and KEGG pathway analysis demonstrated an increase in the bile acid secretion pathway (padj = 0.006). **Conclusion:** Treating human iPSC-hepatocytes with the pharmacologic XBP1 activator IXA4 profoundly suppressed the bile acid synthesis genes *CYP7A1* and *CYP8B1*. *SHP* expression did not increase and therefore cannot account for these changes in gene expression. In contrast, XBP1 activation increased the expression of several lipid synthesis genes. TUDCA treatment also increased the bile acid synthesis pathway. We speculate that the XBP1 pathway regulates bile acid and fatty acid metabolism in both mice and humans.

Disclosures: Moloud Aflaki Sooreshjani: Nothing to Disclose, Xiaoying Liu: Nothing to Disclose, Ekta Minocha: Nothing to Disclose, John G Purdy: Nothing to Disclose, Jason A Wertheim: Nothing to Disclose, Richard Green: Mirum Pharmaceuticals: Advisor

4241 | ETIOLOGY-SPECIFIC CHROMOSOME 8Q24 AMPLIFICATION ASSOCIATED WITH HUMAN INTRAHEPATIC CHOLANGIO- AND HEPATOCELLULAR CARCINOMAS PREDICTS MYC/ZEB1/MIZ1 TRANSCRIPTIONAL REGULATION AND POOR PROGNOSIS

Saniya Davis[1] Joeffrey Chahine[2] Pamela Tuma[1], [1]The Catholic University of America, [2]Medstar Georgetown University Hospital

Background: Genomic instability, in particular chromosome 8q24 amplification, is highly associated with late stage hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (iCCA) and epithelial mesenchymal transition (EMT). Limited HCC patient studies suggest that 8q24 amplification may also be etiology-dependent. On this amplified region, is the known oncogene, *c-myc*. Not only does MYC overexpression activate targets that promote cell proliferation, it also activates ZEB1 which drives EMT. Further reinforcing EMT, overexpressed MYC also represses tumor suppressors that antagonize EMT, including MIZ1. The connection between *c-myc* amplification and the corresponding changes in ZEB1 and MIZ1 have been reported, but not all three together. Nor have these relationships been characterized in the context of HCC or iCCA across grades or with respect to etiologies. **Methods:** We confirmed 8q24 amplification using FISH and established the temporal expression patterns of MYC, ZEB1 and MIZ1 in human HCC (n = 147) and iCCA (n = 114) patient resections using immunohistochemistry and retrospectively compared them to patient histories. To directly test MYC/ZEB1/MIZ1 transcriptional regulation, we examined EMT in human HCC-derived Hep3B or iCCA-derived HUCCT1 cells with amplified *c-myc*. **Results:** We found that chromosome 8 duplication and focal *c-myc* 8q24 amplification occurs only in grade III/IV HCC and grade III iCCA which correlates with increased MYC and ZEB1 nuclear expression. In contrast, MIZ1 cytosolic expression was lost and only nuclear expression retained. We found that of the high grade cancer patients that exhibited amplified *c-myc*, high MYC and ZEB1 expression and only nuclear MIZ1 expression were all associated with metastasis and poorer prognosis. Additionally, although majority of the cohort had a history of viral hepatitis, only those that also had a history of alcohol consumption exhibited this transcriptional regulation. Analysis performed in Hep3B or HUCCT1 cells revealed that alterations in MYC expression led to the predicted changes in ZEB1 and MIZ1 expression/distribution and in EMT further confirming MYC/ZEB1/MIZ1 transcriptional regulation drives EMT. **Conclusion:** Based on expression profiles of these markers, the clinician will be better able to grade a patient's HCC or iCCA, better predict its drug resistance and better decide what treatment

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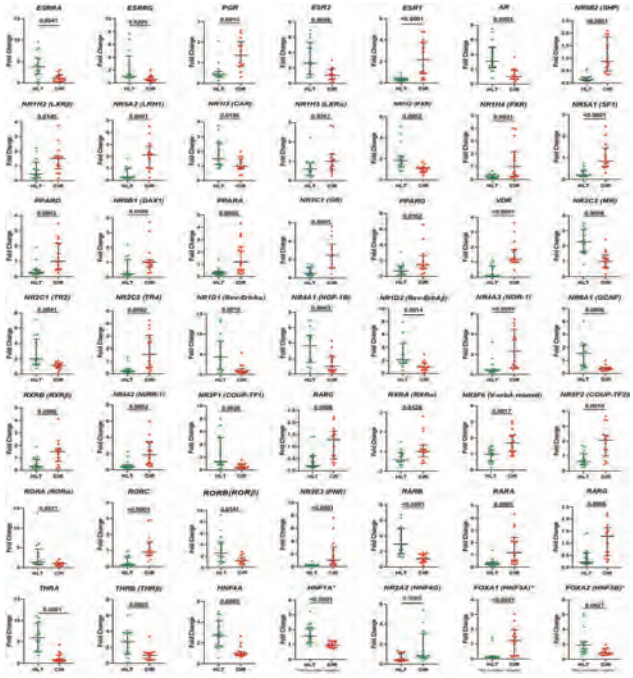
options are available. As we continue to perform the basic science to define EMT more precisely, we will uncover novel therapeutic strategies for the treatment of alcohol-induced HCC and iCCA.

Disclosures: Saniya Davis: Nothing to Disclose, Joeffrey Chahine: Nothing to Disclose, Pamela Tuma: Nothing to Disclose

4242 | NUCLEAR RECEPTOR EXPRESSION IS DYSREGULATED IN ADIPOSE TISSUE IN CIRRHOSIS

Sanal Madhusudana Girija[1] Sarita Gupta[1] Kumaraswamy P[2] RAHUL SAHA[1] Archana Rastogi[1] Viniyendra Pamecha[1] Shiv Kumar Sarin[1], [1]Institute of Liver and Biliary Sciences, [2]AIG Hospital, Hyderabad

Background: Cirrhosis is a multisystem disease that predominantly affects the kidneys, lungs, heart, muscles, and brain. However, its impact on adipose tissue—the body's largest endocrine organ—remains poorly understood. Our previous research demonstrated that adipose tissue in cirrhosis exhibits a proangiogenic state, characterized by elevated expression of various angiogenic factors due to oxidative inactivation of protein phosphatases (PTPs). Nuclear receptors are critical in the development and homeostasis of adipose tissue. In this study, we investigated the differential expression of 46 nuclear receptors (NRs) and 3 developmentally important transcription factors in adipose tissue from cirrhosis patients. **Methods:** Adipose tissue samples were collected from 25 liver cirrhosis patients undergoing Living Donor Liver Transplantation (LDLT) and 15 healthy donors. Patients with acute or acute-on-chronic liver failure, non-cirrhotic portal hypertension, or those who did not provide consent were excluded. Real-time PCR was employed to identify differentially expressed transcripts, while Western blot analysis was conducted to evaluate protein levels. **Results:** Mean age: Healthy vs. cirrhosis –33 ± 10 vs. 46 ± 8 years; mean BMI: Healthy vs. cirrhosis –25 ± 3 kg/m² vs. 25 ± 5 kg/m²; sex distribution: 92% of cirrhosis patients and 87% of healthy controls were men; mean MELD score: 23 ± 6 (for cirrhosis patients); mean fasting blood sugar: Controls vs. patients vs. 79 ± 12 mg/dL vs. 115 ± 34 mg/dL; diabetes prevalence: 28% of cirrhosis patients were diabetic. Controls: All biochemical and imaging parameters in healthy donors were within normal limits. Gene Expression Analysis: Real-time PCR analysis revealed upregulation of VDR, NOR, SHP, SF1, PNR, ER1, RORC, RARB, LRH1, GR, TR4, NURR1, PPARG, PPARA, PPARD, RARA, PR, DEX1, RXRA, LXRA, LXRB, V-ERB-A, RXRB, FXR, HNF4G, and FOX1 in cirrhosis patients compared to healthy controls. Conversely, the transcripts of HNF1A, TR2, PXR, HNF4A, AR, GCNF, RXRG, MR, COUPTF1, REVERBA and B, ESR2, RORB, CAR, RORA, RARB, HNF3B, ESSRA, and ESSRG were less abundant in cirrhosis patients. **Conclusion:** This is the first comprehensive study screening all nuclear receptor transcripts in adipose tissue from cirrhosis patients. Being critical regulators of metabolism, targeting nuclear receptor modulation could offer potential therapeutic strategies for lifestyle-associated diseases such as diabetes, obesity, dyslipidaemia, and fatty liver disease.



Disclosures: Sanal Madhusudana Girija: Nothing to Disclose, Sarita Gupta: Nothing to Disclose, Kumaraswamy P: Nothing to Disclose, RAHUL SAHA: Nothing to Disclose, Archana Rastogi: Nothing to Disclose, Viniyendra Pamecha: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

4243 | MZB1 ORCHESTRATES HEPATIC REGENERATION: ESSENTIAL ROLE IN CELL CYCLE PROGRESSION FOLLOWING LIVER INJURY

Jiang Li[1] Noriko Kitano[1] Sudrishti Chaudhary[1] Samuel Taborski[1] Juliane Beier[1] Oliver Eickelberg[1] Marta Bueno[1] Gavin Arteel[1], [1]University of Pittsburgh

Background: Marginal Zone B and B1 Cell-Specific Protein (MZB1) is a B-cell-specific protein in the endoplasmic reticulum involved in B cell function, cellular proliferation, and inflammation. Deep proteome profiling shows MZB1-positive plasma B cells in human lung and skin fibrosis, with MZB1 knockout (KO) mice

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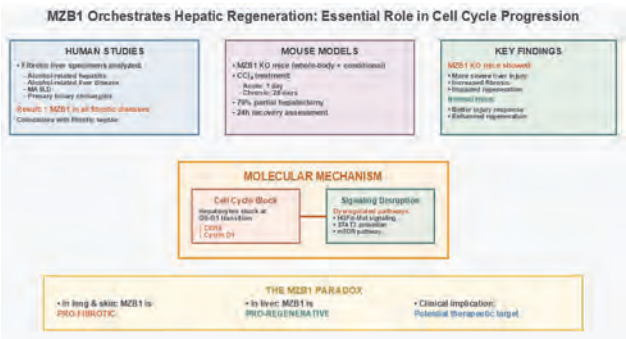
protected from bleomycin-induced fibrosis in these organs. This study investigated MZB1's role in liver fibrosis and regeneration, a function previously unexplored. **Methods:** Human fibrotic liver specimens from alcohol-related hepatitis, alcohol-related liver disease, MASLD, and primary biliary cholangitis were immunostained for MZB1. For mechanistic studies, two MZB1 knockout mouse models (whole-body and inducible conditional) were utilized. Mice were administered CCl_4 for acute (1 day) or chronic (28 days) exposure to induce liver injury and fibrosis. To assess regenerative capacity, mice underwent 70% partial hepatectomy with 24-hour recovery. Liver tissues were analyzed through histology, biochemical analyses, and gene expression profiling. **Results:** Immunofluorescence analysis revealed elevated MZB1 expression in all examined fibrotic liver diseases, with MZB1 signal colocalizing with fibrotic septae. MZB1 KO mice developed more severe liver injury and fibrosis following CCl_4 treatment compared to controls. Importantly, these mice exhibited impaired regenerative capacity in the CCl_4 model, prompting further investigation using partial hepatectomy. Following hepatectomy, MZB1 deficiency dramatically impaired liver regeneration, with hepatocytes blocked at the G0-G1 cell cycle transition due to downregulation of CDK6 and cyclin D1. Transcriptomic analysis revealed fundamental alterations in gene expression profiles governing cell cycle progression and growth factor signaling, with dysregulation of HGF/c-Met signaling, STAT3 activation, and mTOR pathway components. **Conclusion:** MZB1 plays a critical role in hepatocyte proliferation and liver regeneration, despite its presence in fibrotic areas of human liver disease. The exacerbated liver injury in MZB1 KO mice reflects its role in supporting hepatocyte proliferation rather than a direct antifibrotic effect, contrasting with its apparent profibrotic function in lung and skin. Mechanistically, MZB1 loss disrupts the crosstalk between cell cycle proteins and growth factor signaling. These findings identify MZB1 as a potential target for enhancing liver regeneration in clinical settings.



Disclosures: Jiang Li: Nothing to Disclose, Noriko Kitano: Nothing to Disclose, Sudrishti Chaudhary: Nothing to Disclose, Samuel Taborski: Nothing to Disclose, Juliane Beier: Nothing to Disclose, Oliver Eickelberg: Nothing to Disclose, Marta Bueno: Nothing to Disclose, Gavin Arteel: Nothing to Disclose

4244 | SINGLE CELL TRANSCRIPTOMIC PROFILE REVEALS PRIMARY TUMOR ORIGIN DEFINES THE IMMUNE MICROENVIRONMENT IN LIVER METASTASIS FROM COLORECTAL AND PANCREATIC CANCER

So Yeon Kim[1] Jieun Kim[1] Ekihiro Seki[1], [1]Cedars-Sinai Medical Center

Background: Liver metastasis is a common and lethal outcome of advanced malignancies, with colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC). While the liver provides a shared metastatic site, the immune microenvironment within liver metastases may differ substantially depending on the primary tumor origin, but underlying mechanisms are still unclear. Understanding these differences is essential for immunotherapeutic strategies and improving treatment outcomes. **Methods:** We performed single-cell RNA sequencing on tumor-infiltrating immune cells isolated from mouse liver metastases originating from CRC and PDAC. Immune cells were enriched via CD45+ sorting from freshly extracted metastatic liver tumor tissues. Transcriptomic profiles were analyzed using Seurat, with clustering, dimensionality reduction (UMAP), and cell type annotation guided by canonical markers and reference datasets. Differential gene expression and gene enrichment analysis were performed. Cell-cell interactions were inferred using CellChat. **Results:** We identified distinct immune cell composition patterns between CRC- and PDAC-derived liver metastases by scRNAseq. CRC metastases were enriched in monocytes and macrophages, suggesting a more phagocytic and antigen-processing microenvironment. Notably, Ms4a7+ macrophages, a population marked by their distinct metabolic reprogramming and immune response, were enriched. This may lead to M1/M2 polarization and contribute to tumor progression. In contrast, liver metastases from PDAC showed a higher proportion of Mmp9+ neutrophils and Xcr1+ dendritic cells, along with a slightly increased abundance of CD8 T cells and B cells. These Mmp9+ neutrophils play a critical role in promoting tumor progression along with infiltration and invasion. Additionally, cell-cell interaction analysis suggested enhanced chemokine signaling in PDAC-derived liver metastases, potentially driving neutrophil recruitment. **Conclusion:** Our findings demonstrate that the primary tumor origin significantly influences the immune architecture of liver metastasis. The predominance of monocyte/macrophage populations in CRC and neutrophil/DC populations in PDAC metastases may reflect

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underlying differences in immune evasion strategies and therapeutic vulnerabilities. These insights support that PDAC-derived hepatic metastasis leads to more severe outcomes, and this emphasizes the necessity of developing immunotherapies that account for the primary cancer type.

Disclosures: So Yeon Kim: Nothing to Disclose, Jieun Kim: Nothing to Disclose, Ekihiro Seki: Nippon Zoki: Research Grant Support, Novonordisc: Consultant

4245 | RAPID AND VERSATILE MULTIPLEX LIVER GENE EDITING IN MICE USING ADENO-ASSOCIATED VIRAL 8 OR LIPID NANOPARTICLES

Dandan Wu[1] Isabelle Bolt[1] Dagmar Tolenaars[1] Wietse In het Panhuis[1] Coen Paulusma[1] Roy van der Meel[2] Stan van de Graaf[1], [1]Tytgat Institute for Liver and Intestinal Research, [2]Institute for Complex Molecular Systems

Background: Somatic liver knockout (SLiK) is an advanced technique for rapidly knocking out multiple genes in the adult mouse liver. However, the original SLiK protocol relies on hydrodynamic tail vein injection (HTVI), which carries a risk of cardiac failure in mice. This limitation hinders its application in regions with strict animal welfare regulations, such as the European Union. To address this challenge, we replaced HTVI with adeno-associated virus serotype 8 (AAV8) and lipid nanoparticles (LNPs) to test whether these alternative delivery systems could effectively support SLiK gene editing. **Methods:** Our system leverages selective pressure from tyrosine metabolism to achieve rapid gene editing. Fumarylacetoacetate hydrolase (Fah) deficiency has a lethal phenotype, which can be rescued by disrupting upstream enzyme 4-hydroxyphenylpyruvate dioxygenase (Hpd). Mice lacking both *Fah* and *Hpd* are without phenotype. In this study, we generated $Fah^{-/-}$/spCas9Tg mice that constitutively express the spCas9 recombinase. These mice were injected with two AAV8 vectors, each containing two gRNAs targeting an intron of Hpd and an exon of a gene of interest (GOI). The Hpd-edited hepatocytes gain a survival advantage, enabling highly efficient deletion of two GOIs. Each AAV8 vector also contains a CMV promotor flanked by a multiple cloning site, allowing overexpression of any desired genes as long as it can be packed in AAV8 vector. This system theoretically allows for 2 knockouts and 2 overexpression within same hepatocytes. Additionally, LNPs were tested to deliver individual gRNAs. **Results:** Complete Hpd knockout was achieved in murine liver within two months in both systems, without significant changes in body weight or liver enzymes. With the AAV8 approach, we successfully generated humanized NTCP and AGXT mice by simultaneously deleting endogenous murine gene and overexpressing the human gene within 1-3 months. Additionally, attempts to knock out two genes (*Cyp2c70* and *mAgxt*) and overexpress another gene (*hAGXT)* led to severe biliary injury in mice, requiring euthanasia 6 weeks post-injection. At this time point, knockdown of *Cyp2c70* was confirmed at the mRNA level only. **Conclusion:** Both AAV8 and LNP are practical alternatives for HTVI to achieve rapid and multiplex gene editing in SLiK system. The successful generation of humanized NTCP and AGXT mice demonstrates the potential of this platform for creating advanced humanized mouse models. However, further studies are needed to further explore the system's capacity.

Disclosures: Dandan Wu: Nothing to Disclose, Isabelle Bolt: Nothing to Disclose, Dagmar Tolenaars: Nothing to Disclose, Wietse In het Panhuis: Nothing to Disclose, Coen Paulusma: Nothing to Disclose, Roy van der Meel: SERVIER: Consultant, Pfizer: Speaking and Teaching, Stan van de Graaf: ProQR: Consultant

4246 | SENSING OF PHOSPHATIDIC ACID BY MTORC1 IN LIVER AND DEVELOPMENT OF MASLD

Chandrima Gain[1] Henrietta Bains[2] Debajyoti Das[3] Rajat Singh[3], [1]University of California, Los Angeles, [2]Albert Einstein College of Medicine, Bronx, NY, USA, [3]Comprehensive Liver Research Center at the David Geffen School of Medicine, University of California

Background: mTOR is a serine/threonine kinase that senses nutrients to stimulate growth and proliferation. There is a strong association of mTOR hyperactivation with metabolic dysfunction-associated steatotic liver disease (MASLD) and its progression to poorly differentiated hepatocellular carcinoma. While amino acid-mediated mTOR activation is well-studied, lipid-driven mTOR activation and its relevance to MASLD remain understudied. Here, we examined the mechanism of mTOR activation by a physiologically relevant lipid, phosphatidic acid (PA), and we determined if increased PA production drives hepatic mTOR hyperactivation during obesity. **Methods:** We used mice (injected with liver-specific AAV8 vectors) or Cas9-cultured AML12 hepatocytes (exposed to specific sgRNAs) to knock-out *Raptor*, or *Lipin1*, which encodes for a phosphatidic acid phosphohydrolase that dephosphorylates PA to yield diacylglycerol, to determine if and how PA activates mTORC1 signaling. Liver homogenates and cell lysates were immunoblotted for markers of mTORC1 signaling. HEPG2-cells transfected with Flag-mTOR or Flag-empty were treated with PA, and immunoprecipitated mTOR (via Flag beads) was digested in S-trap columns,

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and peptides (of binding partners) analyzed by nLC-MS/MS. Statistical analyses were performed using unpaired Student's t-test or one or two-way ANOVAs followed by appropriate post-hoc testing. **Results:** We have found that exposure of cultured AML12 hepatocytes to PA leads to activation of mTORC1 signaling. PA-driven mTORC1 activation is marked induced in AML12 hepatocytes KO for *Lipin1*, indicating that PA accumulation upon loss of *Lipin1* leads to greater mTORC1 activity. This mTORC1 hyperactivation upon loss of *Lipin1* is Raptor-dependent since deletion of Raptor dampens mTORC1 signaling. Proteomic analyses of mTOR pulldowns has revealed a number of potential mTOR binding partners, which we are screening to determine their role in PA-driven mTORC1 activation. mTORC1 suppresses autophagy, which plays an important hepatoprotective role. Consistently, loss of *Lipin1* in livers leads to mTORC1 activation, autophagy blockage, and a MASLD phenotype. **Conclusion:** This study enhances our understanding of whether PA is sensed by mTORC1 in livers, and whether this PA-mediated mTORC1 activation has relevance to the pathophysiology of MASLD. These studies will reveal new approaches to dampen lipid-driven mTORC1 hyperactivation and delay the onset of metabolic diseases of the liver.

Disclosures: Chandrima Gain: Nothing to Disclose, Henrietta Bains: Nothing to Disclose, Debajyoti Das: Nothing to Disclose, Rajat Singh: Nothing to Disclose

4247 | DISCOVERY OF A NOVEL DNA APTAMER TO FACILITATE IN VIVO TARGETED GENE THERAPY IN CHOLANGIOCARCINOMA

Enis Hikmet Ozmert[1] Ayano Kabashima[1] Brandon Wilbanks[1] Julia Driscoll[2] Irene Yan[2] Jack Sample[1] Danielle Carlson[3] Hidemi Nishi[1] Brooke Kimball[4] Jayla Millender[5] Caroline Doherty[6] Jim Maher[6] Gregory Gores[3] Tushar Patel[7] Rory Smoot[8], [1]Department of Surgery, Mayo Clinic, Rochester, MN, [2]Department of Transplantation, Mayo Clinic, Jacksonville, Florida, [3]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, [4]Division of Hematology, Mayo Clinic, Rochester, MN, [5]Division of Oncology, Mayo Clinic, Rochester, MN, [6]Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN, [7]Mayo Clinic Florida, [8]Mayo Clinic Rochester

Background: Cholangiocarcinoma (CCA) is an aggressive hepatobiliary malignancy with limited treatment options. Current standard-of-care therapies cause significant adverse effects, while personalized medicine approaches offer only modest survival benefits. We previously demonstrated that milk-derived nanovesicles (MNVs) show therapeutic potential against CCA. Aptamers —oligonucleotides with unique 3D structures— can be used to direct MNVs to a certain target. This study aims to discover a CCA-specific aptamer and to demonstrate that aptamer-MNV constructs effectively deliver RNA therapeutics in murine CCA models. **Methods:** We employed a Systematic Evolution of Ligands by Exponential Enrichment (SELEX) strategy to identify a CCA specific aptamer by toggling a library of 2 trillion random oligonucleotides between target (CCA) and non-target (hepatocyte/cholangiocyte) cells. Cell binding efficacies of enriched aptamers were quantified using Incucyte SX5 and validated by qPCR. The biodistribution of the lead candidate, 'Aptamer 1', was assessed in an orthotopic SB1 model of CCA. For therapeutic evaluation, mice bearing SB1 tumors received intravenous injections of Aptamer 1-MNV loaded with siRNAs targeting *Yap/Wwtr1/Lck* (siTriple) alongside appropriate controls. **Results:** After 10 selection rounds, deep sequencing revealed 'Aptamer 1' was exponentially enriched in the library. This aptamer demonstrated specificity toward various human and murine CCA cell lines with minimal binding to normal hepatocytes, confirmed by *ex vivo* staining and confocal imaging. Biodistribution analysis revealed preferential accumulation of Aptamer 1 in tumor tissue without significant off-target binding. We successfully incorporated Aptamer 1 into MNVs via 3' cholesterol modification and confirmed incorporation efficiency using ImageStream X Mk II Flow Cytometer. In vitro evaluation demonstrated that Aptamer 1-MNV loaded with siTriple effectively knocked down target genes. In the murine orthotopic CCA model, intravenous delivery of Aptamer 1-siTriple (7 doses over 14 days) achieved significant target gene and protein knockdown in CCA cells without affecting adjacent liver tissue. In conjunction with the roles *Yap/Wwtr1/Lck* play in CCA pathobiology, immunohistochemical analysis showed significantly decreased Ki-67 and increased cleaved caspase-3 staining in the Aptamer 1-siTriple group, indicating reduced proliferation and enhanced apoptosis. **Conclusion:** We identified 'Aptamer 1' as a highly specific CCA-targeting aptamer and successfully integrated it with MNVs to create a platform for precise delivery of therapeutic RNA payloads to tumors in live animals. This study establishes proof-of-concept for aptamer-guided nanovesicle delivery in CCA as a viable and generalizable approach for targeted RNA therapeutics, potentially extending beyond siRNAs to other therapeutic modalities.

Disclosures: Enis Hikmet Ozmert: Nothing to Disclose, Ayano Kabashima: Nothing to Disclose, Brandon Wilbanks: Nothing to Disclose, Julia Driscoll: Nothing to Disclose, Irene Yan: Nothing to Disclose, Jack Sample: Nothing to Disclose, Danielle Carlson: Nothing to Disclose, Hidemi Nishi: Nothing to Disclose, Brooke Kimball: Nothing to Disclose, Jayla Millender: Nothing to Disclose, Caroline Doherty: Nothing to Disclose, Jim

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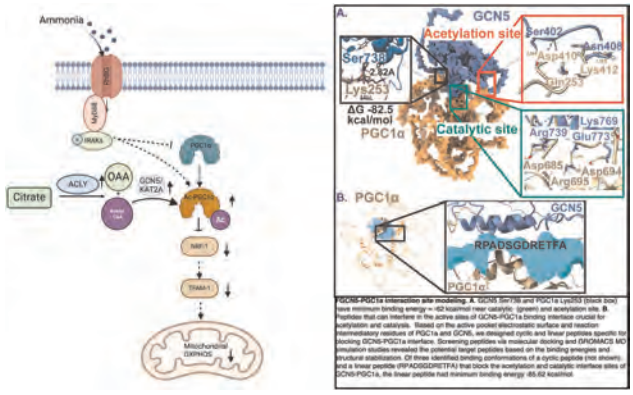
Maher: Nothing to Disclose, Gregory Gores: Nothing to Disclose, Tushar Patel: Nothing to Disclose, Rory Smoot: Nothing to Disclose

4248 | PGC1 ALPHA HYPERACETYLATION DURING HYPERAMMONEMIC STRESS OF CIRRHOSIS WITH SARCOPENIA/ FRAILTY IS MEDIATED VIA PROTEIN STABILIATION OF LYSINE ACETYLTRANSFERASE 2A (GCN5)

Saurabh Mishra[1] Pugazhendhi Kannan[1] Volha Mezhnina[1] Seshu Pothabathula[1] Dhanachandra Khuraijam[1] Annette Bellar[1] Muaz Alsabbagh Alchirazi[1] Vandana Aggarwal[1] Jasmin Cunningham[1] Amy Attaway[1] Sadashiva Karnik[1] Yuxin Wang[1] Sathyamangla Prasad[1] Nicole Welch[1] Srinivasan Dasarathy[1], [1]Cleveland Clinic

Background: Hyperammonemic stress response (HASR) causes sarcopenia/frailty in cirrhosis via mitochondrial oxidative dysfunction. PGC1a is a critical positive regulator of mitochondrial function. We therefore investigated the molecular mechanisms, functional consequences, and designer peptide-based approaches targeting PGC1a-dependent mitochondrial regulation including post-translational modifications of PGC1a during HASR via lysine acetyltransferase 2A (KAT2A/GCN5). **Methods:** Mouse muscle and differentiated murine C2C12 myotubes were studied. GCN5 knockout (KO) was acchieved by CRISPR/Cas9. GCN5 mRNA levels were quantified by qPCR. Protein interactions were assessed by immunoprecipitation of GCN5 and immunoblots for STAGA complex subunits (TAF10, DR1, SUPT7L, ADA2B, SGF29)/PGC-1α. Protein stability of GCN5 was determined through cycloheximide (CHX) pulse-chase analysis. Ubiquitination of GCN5 was assessed using the TUBE (Tandem Ubiquitin Binding Entities) assay. Molecular docking-dynamics (MDD) of 3D structures of GCN5/KAT2A (Q9JHD2) and PGC-1α (O70343) were used to assess binding energies and interaction conformations followed by degron motif(s) identification (DEGRONOPEDIA). Linear (RPADSGDRETFA) and cyclic (CGKIRPDTRC) peptides (10–12 residues) were designed using PyMOL and optimized through energy minimization. Peptide incubation with lysates from myotubes without/with HASR followed by pulldown assays were done to evaluate PGC-1α-GCN5 interaction. **Results:** GCN5 protein expression was higher (due to protein sabilization) with unaltered mRNA during HASR. GCN5 interacted with and acetylates PGC-1α during HASR as part of the STAGA complex (ADA2B, SUPT7L, SGF29, TAF10), while interaction with DR1 (inhibitory transcription factor) was reduced. Ubiquitinylation-dependent activation of GCN5 was identified at 6 and 24 hours of HASR. GCN5 knockout reversed acetylation of PGC-1α during HASR. PGC-1α acetulation. Consistently, decreased expression of downstream targets, NRF1 and TFAM as well as critical components of the electron transport chain (OXPHOS) during HASR were reversed by GCN5 KO. MDD analyses showed GCN5–PGC-1α binding with a minimum energy of −82 kcal/mol. Key interactions were identified at Ser738–Lys253 (buried) and Asn408–Lys412 (exposed), contributing to acetylation and complex stabilization. Electrostatic interactions (Glu773–Arg695, Lys769–Asp694) supported catalytic intermediate stability. The linear peptide showed optimal blocking while the icircular peptide was only partially effective in disrupting GCN5-PGC1a complex. **Conclusion:** GCN5 impairs PGC-1α via acetylation with mitochondrial dysfunction during HASR by interacting with and activating components of the STAGA complex t. Our novel designer peptide-based competitive inhibitor(s) targeting GCN5-PGC1a interaction is a promising novel approach to treat sarcopenia of cirrhosis.



Disclosures: Saurabh Mishra: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Volha Mezhnina: Nothing to Disclose, Seshu Pothabathula: Nothing to Disclose, Dhanachandra Khuraijam: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Muaz Alsabbagh Alchirazi: Nothing to Disclose, Vandana Aggarwal: Nothing to Disclose, Jasmin Cunningham: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Sadashiva Karnik: Nothing to Disclose, Yuxin Wang: Nothing to Disclose, Sathyamangla Prasad: Nothing to Disclose, Nicole Welch: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

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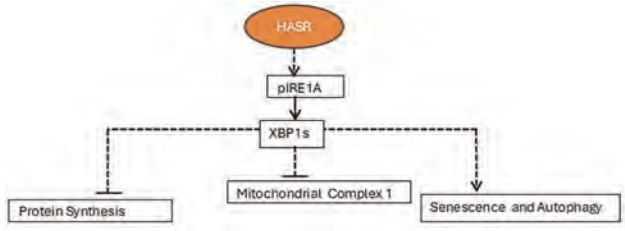
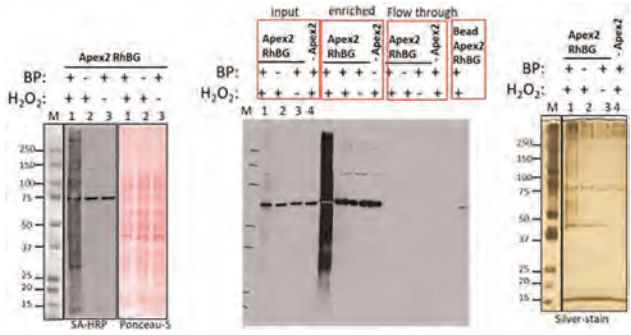
4249 | TRANSCEPTOR RHBG-DEPENDENT ACTIVATION OF INOSITOL REQUIRING ENZYME-1 ALPHA (IRE1A) AND X-BOX BINDING PROTEIN-1 (XBP1) SPLICING IN SKELETAL MUSCLE DURING HYPERAMMONEMIC STRESS RESPONSE CAUSES SARCOPENIA OF LIVER DISEASE

Pugazhendhi Kannan[1] Nicole Welch[1] saurabh mishra[1] Annette Bellar[1] Shashi Shekhar Singh[2] Amy Attaway[1] Muaz Alsabbagh Alchirazi[1] Seshu Vardhan Pothabathula[1] Vandana Agrawal[1] Jasmin Cunningham[1] Maria Hatzoglou[2] Srinivasan Dasarathy[1], [1]Cleveland Clinic, [2]Case Western Reserve University

Background: Sarcopenia in cirrhosis is caused by an hyperammonemic stress response (HASR) in skeletal muscle. HASR shares properties of general amino acid deficiency response (GCN2 activation) and unfolded protein response (UPR) with other characteristics distinct from the integrated stress response (PMID 27318325). The membrane transceptor (transporter/receptor), Rhesus blood group-associated B glycoprotein (RhBG) initiates molecular, metabolic, and functional consequences of HASR with sarcopenia. Given activation of some components of ISR during HASR, we evaluated if canonical IRE1a-dependent spliced XBP1 (XBP1s) mediates RhBG-dependent HASR with sarcopenia of cirrhosis. **Methods:** Studies were done in differentiated C2C12 myotubes, and muscle from inducible XBP1 and RhBG muscle specific knockout/parental control mice. HASR was induced by 10 mM ammonium acetate (myotubes) and 2.5 mmol. $kg^{-1}.d^{-1}$/saline infusion by a miniosmptic pump for 28 days in mice. Integrated multiomics analyses were done in myotubes/muscle tissue. Expression of signaling/regulatory proteins (mTORC1 signaling, autophagy markers) and measures of post-mitotic senescence were quantified by immunoblots . Binding partners for RhBG were determined by ascorbic acid peroxidase (APEXII) assay followed by liquid chromatography-mass spectrometry. Mitochondrial oxidative function was determined by high-sensitivity respirofluorometry and immunoblots for expression of proteins in the electron transport chain. **Results:** During HASR, XBP1 splicing efficiency and XBP1s protein expression were increased. Multiomics analyses showed mTORC1, oxidative phosphorylation, and senescence pathways were enriched during HASR with reversal of these changes with RhBG KO and XBP1 KO in myotubes and muscle tissue. Experimentally, XBP1 KO in myotubes and muscle tissue reversed HASR induced impaired mTORC1 signaling, protein synthesis, electron transport chain Complex I expression, mitochondrial oxidative dysfunction, and diminished global protein synthesis. Increased autophagy flux and post-mitotic senescence in muscle HASR were also reversed by XBP1 KO in myotubes and mouse muscle. Consistent with canonical IRE1a mediated XBP1 splicing, phosphorylatoin of IRE1a was higher during HASR, and IRE1a inhibitor (4u8C) reversed IREa phosphorylation, increased XBP1s, and impaired mTORC1 signaling. Activation of IRE1a was mediated by RhBG dependent Bip binding that released IRE1a for autophosphorylation and downstream XBP1s and functional consequences with molecular phenotype of sarcopenia of HASR. **Conclusion:** Transceptor RhBG initiates IRE1a-dependent XBP1s by binding to BIP1 and initiates a multicomponent response (mitochondrial oxidative dysfunction, accelerated post-mitotic senescence, and sarcopenic phenotype). Targeting RhBG-dependant XBP1s during HASR is a potential approach to treat sarcopenia in cirrhosis.





Disclosures: Pugazhendhi Kannan: Nothing to Disclose, Nicole Welch: Nothing to Disclose, saurabh mishra: Nothing to Disclose, Annette Bellar: Nothing to Disclose, Shashi Shekhar Singh: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Muaz Alsabbagh Alchirazi: Nothing to Disclose, Seshu Vardhan Pothabathula: Nothing to Disclose, Vandana Agrawal: Nothing to Disclose, Jasmin Cunningham: Nothing to Disclose, Maria Hatzoglou: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

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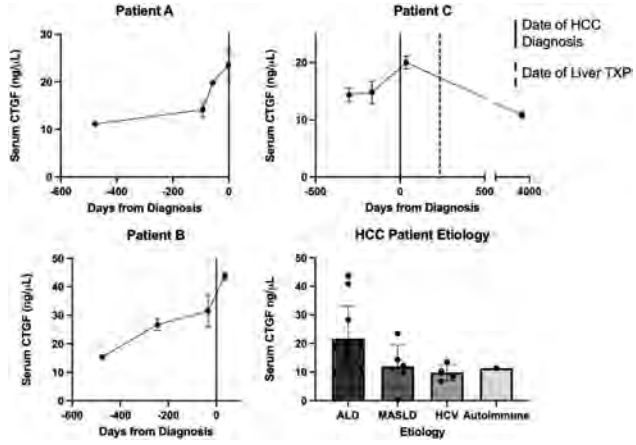
4250 | ASSESSING THE UTILITY OF SERUM CTGF AS A CLINICAL MARKER FOR HCC TUMOR FORMATION

Claudia Rose Keating[1] Irene Helenowski[1] Kyle Boedeker[1] Wei Qiu[2] Scott Cotler[2], [1]Loyola University Chicago, [2]Loyola University Health System

Background: There is a critical need for serum biomarkers to identify patients with cirrhosis who are at increased risk of developing hepatocellular carcinoma (HCC). Focal adhesion kinase (FAK) is overexpressed in more than 40% of HCC specimens and preliminary data indicate that FAK promotes the expression of connective tissue growth factor (CTGF), which is a secreted protein. Serum CTGF levels were correlated with a high degree of tumor angiogenesis, advanced staging, metastasis, and ultimately poor prognosis in HCC patients. The aim of this study was to assess serum CTGF as a clinical marker for HCC formation in patients with cirrhosis. **Methods:** In this cohort study, we used prospectively banked serum samples from 29 patients with cirrhosis who had routine surveillance and eventually progressed to HCC development. Each of these patients had between 2 and 9 serum samples collected prior to their HCC diagnosis, with a median first sample collection 1.2 years prior to diagnosis and at least one sample collected within one year of their diagnosis. Serum CTGF levels were quantified by ELISA, and a spline regression was used to determine the change in CTGF over time for each individual patient. **Results:** Using the serum CTGF measurement for each patient closest to the time of their HCC diagnosis, there was no significant difference in serum CTGF levels by sex or age at diagnosis. When patients were grouped by cirrhosis etiology, there was a trend toward higher serum CTGF levels in patients with alcohol-associated liver disease compared to metabolic dysfunction-associated steatotic liver disease, hepatitis C virus, and autoimmune etiologies (Figure). The spline regression showed that serum CTGF levels increased significantly in a subset of patients prior to their diagnosis of HCC (Figure). Additionally, the model showed a significant decline in serum CTGF levels following loco-regional therapy for HCC. **Conclusion:** Serum CTGF levels increased in a subset of patients prior to the diagnosis of HCC. We hypothesize that these individuals had high tumoral levels of FAK, driving this increase in serum CTGF. The findings suggest that CTGF merits further study as a potential circulating biomarker for HCC.



Disclosures: Claudia Rose Keating: Nothing to Disclose, Irene Helenowski: Nothing to Disclose, Kyle Boedeker: Nothing to Disclose, Wei Qiu: Nothing to Disclose, Scott Cotler: Nothing to Disclose

4251 | IDENTIFICATION AND VALIDATION OF BIOMARKERS FOR QUALITY CONTROL OF IN VITRO CULTURED HUMAN HEPATOCYTES

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Background: Hepatocyte heterogeneity and plasticity are essential for fulfilling the diverse liver functions and its robust regenerative and trans-differentiation capacities, respectively. These properties are disregarded when cultured in vitro, wherein cells are presumed to represent a homogeneous population, discounting their substantial propensity to deteriorate their functional and phenotypic characteristics. In vitro cultured human hepatocytes (HHs) display density-dependent variations in morphology and function; lower densities lead to loss of authentic hepatocyte characteristics, while higher densities support their identity preservation. Nevertheless, the optimal seeding density to maintain genuine characteristics of hepatocytes has yet to be elucidated. **Methods:** HHs, either primary or derived from humanized liver chimeric mice, seeded at varying densities as 2D monolayer were maintained for 7 days. Microscopic analysis was performed to evaluate cellular morphology and dimensions. Bulk and single-cell

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mRNA sequencing analyses were performed to decipher seeding density-dependent changes at the level of the whole population and individual cells. Transcriptomic profiles were also compared against a reference panel of representative hepatocyte marker genes to determine the optimal seeding density. scRNA-seq data were further utilized to identify threshold seeding densities permitting the emergence of cell populations lacking hepatocyte marker genes, and characterize their transcriptomic divergence, and identify biomarkers. The utility of these biomarkers was assessed via functional analyses of hepatocytes. **Results:** Density-dependent heterogeneity in cell size was observed, with a higher proportion of cells exceeding physiological size ranges at lower seeding densities. This correlated with a loss of hepatocyte identity as determined by bulk RNA-seq analysis. scRNA-seq identified up to 16 distinct biomarkers representing hepatocyte populations that had lost their identity. Notably, the proportion of cells expressing these biomarkers increased as seeding density decreased. Validation studies demonstrated that HH populations with more than 5% of cells expressing at least one of these biomarkers, as determined by IHC staining, exhibit compromised overall hepatic functions, including detoxification capacity, nutrient metabolism, and bile secretion machinery. **Conclusion:** This work established an IHC-based quality assessment of in vitro cultured HHs through the detection of biomarkers representing suboptimal hepatocyte populations. This approach could be exploitable as a standardized quality control protocol to enhance the scientific integrity and translational relevance of studies utilizing primary human hepatocyte culture systems.

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4252 | AGING TRIGGERS ALCOHOL-INDUCED ENDOTOXIN TOLERANCE BY REPROGRAMMING MONOCYTE RESPONSES IN A NICHE-SPECIFIC MANNER

Marti Ortega Ribera[1] Radhika Joshi[1] Sergi Guixe-Muntet[2] Veronika Brezani[1] Prashanth Thevkar Nagesh[3] Viliam Brezani[1] Arman Patel[1] Mrigya Babuta[1] Yuan Zhuang[4] Jordi Gracia-Sancho[5] Gyongyi Szabo[4], *[1]BIDMC - Harvard Medical School, [2]IDIBAPS, [3]Beth Israel Medical Center, [4]Beth Israel Deaconess Medical Center, [5]IDIBAPS - Hospital Clínic Barcelona*

Background: Bacterial infections are the leading cause of mortality in patients with alcohol-associated hepatitis (AH), and this risk is further elevated with aging. We previously showed that acute alcohol exposure suppresses immune functions. Specifically, monocyte (MO) responses to lipopolysaccharide (LPS) are blunted following acute alcohol exposure, contributing to a state of endotoxin tolerance (ET) and increased susceptibility to infections. Given the baseline inflammation state associated with aging ("inflammaging"), we hypothesized that aging would modulate alcohol-induced ET and alter MO responses during an inflammatory insult in a niche-specific fashion. **Methods:** Young (3 months) and aged (20–24 months) female C57BL/6N mice received 10 alcohol binges (3.5 g/kg) or water every other day. Twelve hours after the final binge, mice were randomized to receive LPS (1 mg/kg i.p.) or saline to mimic sepsis. Tissues were harvested 18 hours post-alcohol exposure. Three MO populations were isolated and RNA-sequenced using SMART-Seq (n = 4–6/group): 1-Liver MO, 2-microglia & 3-bone marrow MO (BM-MO). **Results:** LPS induced a robust pro-inflammatory transcriptomic response in both young and aged groups. Notably, aged liver MO and microglia exhibited exaggerated LPS responses, while aged BM-MO showed reduced responsiveness (lower number of differentially expressed genes [DEG]), indicating niche-specific reprogramming. Compared to LPS alone, alcohol pretreatment significantly reduced LPS-induced DEGs in all MO populations consistent with alcohol-induced ET. Importantly, this was exclusively observed in the aged population. This was corroborated by reduced circulating cytokines (IL-13, IL-6, MIP-2) in the aged ethanol-LPS group.

Mechanistically, aged liver MOs showed downregulation of Pattern Recognition Receptors (PRRs) including *Tlr1/2/4/6/7/8/13*, *Nlrp3* and its key signaling mediators (*Ticam2*, *CD300a*, *CD86*, *Trem1/2*), suggesting impaired pathogen sensing and response. Microglia isolated from aged mice receiving alcohol exhibited upregulation of epigenetic regulators (*Uhrf1, Wdhd1, Xist*), anti-inflammatory genes (*Igf1, Apoe, Ptpn2*), and tolerance markers (*Pdcd1, Lilrb4a/b*), confirming the establishment of an ET phenotype. Finally, BM-MO transcriptomes revealed coordinated engagement of epigenetic mechanisms and downregulation of PRR-related pathways, further supporting systemic tolerance programming. **Conclusion:** This study uncovers previously unrecognized mechanisms by which alcohol and aging synergistically impair MO phenotype, offering critical insights into the heightened susceptibility to infection in elders with alcohol misuse.

Disclosures: Marti Ortega Ribera: Nothing to Disclose, Radhika Joshi: Nothing to Disclose, Sergi Guixe-

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Muntet: Nothing to Disclose, Veronika Brezani: Nothing to Disclose, Prashanth Thevkar Nagesh: Nothing to Disclose, Viliam Brezani: Nothing to Disclose, Arman Patel: Nothing to Disclose, Mrigya Babuta: Nothing to Disclose, Yuan Zhuang: Nothing to Disclose, Jordi Gracia-Sancho: Gilead Sciences: Independent Contractor, Novo Nordisk: Independent Contractor, Inventiva: Independent Contractor, Barcelona Liver Bioservices: Stock – privately held company, Oncomatryx: Independent Contractor, Quinton: Independent Contractor, Gyongyi Szabo: CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property

4253 | COMPREHENSIVE ANALYSIS OF THE ROLE OF TUMOR-ASSOCIATED ANTIGEN TBC1D13 IN HEPATOCELLULAR CARCINOMA

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Background: The TBC1D13 gene is a member of the TBC (Tre-2/Bub2/Cdc16) domain family, encoding proteins with GTPase-activating protein (GAP) activity specific to certain RAB GTPases. This gene has garnered attention for its critical role in cellular processes, particularly regarding insulin signaling and glucose transport. Recent studies have highlighted the multifaceted functions of TBC1D13, indicating its implications in conditions such as obesity and diabetes through the regulation of GLUT4 trafficking in adipocytes. Moreover, TBC1D13 has been identified as an important tumor-associated antigen (TAA) and plays a significant role in the development of hepatocellular carcinoma (HCC). However, detailed information regarding the regulatory mechanisms of HCC progression and the clinically aggressive phenotypes associated with tumor-associated antibodies (TAAbs) remains limited. This study aims to conduct a comprehensive analysis of the role of tumor-associated anti- TBC1D13 autoantibodies in HCC. **Methods:** Study cases were acquired from multiple databases, including GEO (GSE144269, GSE14520, GSE22058, GSE25097, GSE36376), ICGC, and TCGA_GTEx. Proteomic data were obtained from PDC000198 in the CPTAC data portal and PXD008373 from the ProteomeXchange Datasets. We utilized the R package and the online tool hccTAAb to perform gene and protein expression analysis, survival analysis, immune infiltration analysis, and similarity analysis. **Results:** The expression of TBC1D13 in cancer tissues compared to normal tissues showed a significant increase across seven transcriptomic datasets. Additionally, proteomic data from PDC000198 and PXD008373 corroborated the elevated expression of TBC1D13 in HCC cases compared to healthy controls. Survival analysis indicated that higher TBC1D13 expression is associated with poor prognosis. Log-rank tests revealed significant differences in survival outcomes between high- and low-expression groups. Cox regression analysis yielded a hazard ratio (HR) of 1.44 (95% CI: 1.11−1.87, $P < 0.0001$) for the TCGA-LIHC dataset and HR = 1.68 (95% CI: 0.98−2.86, $P < 0.0001$) for the ICGC-LIRI dataset. Immune infiltration analysis using ssGSEA and CIBERSORT demonstrated significant differences in natural killer (NK) cells between the high- and low-

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expression groups (adjusted P = 0.018). Furthermore, TBC1D13 exhibited significant correlations with six immune cell types, including NK cells. Similarity analysis identified the top 10 genes (MED22, NELFB, REXO4, TMEM250, WDR5, CIZ1, ZER1, URM1, GTF3C5, PYGO2) that exhibited positive correlations, while genes such as TAT, SLC10A1, PCK1, SERPING1, CYP2A6, SDS, HP, RIDA, AKR7A3, and SLC27A5 demonstrated negative correlations. **Conclusion:** Our findings underscore the role of tumor-associated antigen TBC1D13 and its prognostic significance in HCC. These studies warrant further molecular assays to elucidate the potential role of TBC1D13 in tumorigenesis and provide important insights into the underlying mechanisms and potential therapeutic targets related to TBC1D13 in HCC.
Disclosures: Wei Hou: Nothing to Disclose

4254 | CHARACTERIZING SECRETED MIRNAS FROM HEPATIC SPHEROID MODELS FOR MASLD BIOMARKER DISCOVERY

Amila Iriskic Atic[1] Alexander Munk[2] Louise Torp Dalgaard[1] Helene Lykkegaard[2] Mugdha Joglekar[3] Anandwardhan Hardikar[3] Andrea De Pieri[2], [1]Roskilde University, [2]Novo Nordisk, [3]Western Sydney University

Background: Metabolism-associated liver steatotic disease (MASLD) is a spectrum of disease ranging from simple hepatic steatosis (to metabolism-associated steatohepatitis (MASH) which may progress to cirrhosis and liver cancer. MASLD is rapidly becoming a global health challenge, and there is a need for improved diagnostic- and prognostic tools and for effective pharmacotherapies to treat MASH.
In MASLD circulating extracellular vesicles (EVs) can affect hepatic cells and are involved in intercellular signaling, tissue injury and repair, and matrix remodeling. Specific cargo molecules carried by EVs are utilized for intercellular signal transduction. Among these molecules, small non-coding microRNA (miRs)s have important epigenetic functions, post-transcriptionally regulating gene expression, indicating their importance as biomarker candidates for diagnosing, monitoring and prognosis in MASH. **Methods:** Primary human hepatocytes, stellate and Kupffer cells were obtained from Fibscore 0/1 donors and cultivated as both mono- and coculture spheroids in low-attachment plates using established protocols. A -MASH model was induced after two days in the coculture system by switching to a high free fatty acid (FFA) culture media (180μM oleic acid, 125 μM palmitic acid). To increase secretion of EVs, cells were treated with 250μM palmitic acid (PA) for 6 hours. EVs were prepared from the culture supernatant using ultracentrifugation, and Cellular RNA and EV RNA was purified using Trizol and submitted for miR analysis using ThermoFisher OpenArrays. Group t-test or nonparametric test were used for comparison between groups. Statistical significance was set at $p < 0.05$. **Results:** Nine microRNAs (miRs)—*hsa-miR-572, hsa-miR-21, hsa-miR-223, hsa-miR-221, hsa-miR-665, hsa-miR-206, hsa-miR-147b*, and *hsa-miR-449b*—were significantly downregulated in RNA from hepatocyte monocultures by PA treatment. In hepatic stellate cells, three miRNAs, *hsa-miR-125a-3p, hsa-miR-432,* and *hsa-miR-192*, were also significantly downregulated by PA treatment. A comparison of cellular and EV-miRNA profiles revealed that seven miRs were selectively secreted via EVs from hepatocytes, while four miRs were secreted from hepatic stellate cells. In the co-culture model, EVs carried both hepatocyte- and stellate cell–specific miRs; however, these were not regulated by short PA treatment. **Conclusion:** These findings suggest that distinct subsets of miRs are differentially expressed by hepatocytes and hepatic stellate cells, with limited impact from short term PA exposure. Moreover, certain miRs appear to be selectively packaged into EVs, indicating potential cell-type-specific patterns of miR secretion. While most miRNAs remain intracellular, the observed EV-associated signatures may reflect underlying cell communication or regulatory mechanisms. Further studies are warranted to explore these dynamics in more detail.
Disclosures: Amila Iriskic Atic: Novo Nordisk: Employee, Alexander Munk: Nothing to Disclose, Louise Torp Dalgaard: Nothing to Disclose, Helene Lykkegaard: Nothing to Disclose, Mugdha Joglekar: Nothing to Disclose, Anandwardhan Hardikar: Nothing to Disclose, Andrea De Pieri: Nothing to Disclose

4255 | ALBUMIN RESCUES ENDOTHELIAL CELL MITOCHONDRIAL MORPHOLOGY IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

Susan Fischer[1] Rudmer Postma[1] Roel Bijkerk[1] Annarein Kerbert[1] Anton Jan Van Zonneveld[1] Minneke Coenraad[1], [1]Leiden University Medical Center

Background: Endothelial cell (EC) activation is a critical driver of disease progression in patients with liver cirrhosis, contributing to acute decompensation (AD) and acute-on-chronic liver failure (ACLF). The administration of human albumin in cirrhotic patients with hypoalbuminemia has been shown to improve EC function. However, the direct effects of albumin on ECs in cirrhosis are unknown. Furthermore, it is unknown which specific patient category might benefit from albumin treatment. This study investigates *ex vivo* the

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impact of human albumin administration on EC morphology, exposed to plasma derived from patients with different stages of cirrhosis aiming to explore the mechanisms underlying its protective effects and therapeutic response. **Methods:** A high-throughput *in vitro* EC model was used to observe EC responses to patient-derived plasma with or without albumin administration. Cultured human umbilical vein ECs were exposed to plasma from patients with decompensated cirrhosis and hypoalbuminemia (serum albumin < 30g/L, $n = 20$), patients with compensated cirrhosis (serum albumin > 30 g/L, $n = 20$), or healthy controls ($n = 20$). Albumin was administered to the plasma samples of patients with decompensated cirrhosis and healthy controls, aiming at physiological levels (~40 g/L) in patients with decompensated cirrhosis and similar doses to samples of healthy controls resulting in supraphysiological levels. The modulatory effects of albumin on EC activation were tested for well-described circulating factors involved in EC dysfunction (lipopolysaccharide (LPS), TNFα and bilirubin). Multiple cellular components were investigated using high-content imaging and multivariate analysis. **Results:** Factor analysis identified mitochondrial morphology as a key feature responsible for the discrimination between patients with decompensated cirrhosis from those with compensated cirrhosis and healthy controls. Multivariate analysis revealed that albumin administration shifted EC morphology in plasma of decompensated cirrhosis toward a healthier phenotype, resembling the plasma of patients with compensated cirrhosis and healthy controls. No significant shifts in morphology were observed upon titration of albumin to ECs stimulated by LPS, TNFα or bilirubin. **Conclusion:** Plasma from patients with decompensated cirrhosis and hypoalbuminemia induces important morphological changes to ECs, of which changes in mitochondrial morphology are most discriminative. Albumin administration reduces EC activation and dysfunction induced by plasma from patients with decompensated cirrhosis and hypoalbuminemia. These data underline the crucial role of albumin in EC function and point towards a potential therapeutic role of albumin in reducing vascular dysregulation and liver disease progression. Further research is required to explore the potential of this assay in predicting therapeutic responses to albumin.

Disclosures: Susan Fischer: Nothing to Disclose, Rudmer Postma: Nothing to Disclose, Roel Bijkerk: Nothing to Disclose, Annarein Kerbert: Nothing to Disclose, Anton Jan Van Zonneveld: Nothing to Disclose, Minneke Coenraad: Nothing to Disclose

4256 | CHARACTERIZATION OF HUMAN LIVER SPHEROIDS USING STABLE ISOTOPE TRACING

Kanani Hokutan[1] Hyun Young Kim[2] Samuel Kerk[3] Wonseok Lee[2] Sadatsugu Sakane[2] Karin Diggle[1] Tatiana Kisseleva[2] Christian Metallo[3] David Brenner[4], [1]University of California San Diego, [2]University of California, San Diego, [3]Salk, [4]Sanford Burnham Prebys

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) progresses from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis. Dysregulation of lipid and glucose metabolism is a major factor in MASH development. However, progress in target discovery and drug development for MASH is limited by available methodologies to mimic metabolically injured human livers. Here we generate human 3D liver spheroids to study 'liver in a dish' and induce metabolic liver injury using a MASH-cocktail containing glucose, palmitate, and oleate. We identified significant lipid accumulation in MASH spheroids, leading to investigate the source of lipids. **Methods:** Spheroids were generated using cryopreserved primary human liver cells containing 60% hepatocytes and 40% non-parenchymal cells (NPCs) including Hepatic Stellate Cells (HSCs). Upon formation, spheroids were incubated with media supplemented isotope-labeled MASH cocktail components that can be a source for intracellular lipid synthesis; U-^{13}C-glucose, $^{13}C_2$-acetate, or $^{13}C_{18}$-BSA-oleate. Spheroids and supernatant were collected after two days and analyzed for isotope enrichment using gas chromatography-mass spectrometry and liquid chromatography with tandem mass spectrometry. Next, spheroids were generated using freshly isolated steatotic hepatocytes and NPCs, and cryopreserved HSCs, and cultured in MASH cocktail. Upon spheroid formation, culture medium was changed to MASH cocktail containing U-^{13}C-glucose. Two days later spheroids and supernatant were collected and analyzed. **Results:** Isotope-labeled glucose, acetate, and oleate are catabolized in the TCA cycle of human liver spheroids. We found that $^{13}C_{18}$-BSA-oleate is incorporated into DGs, TGs, PEs, and PCs. Spheroids produced M+3 glycerol-3P that was incorporated into lipid head groups. Minor $^{13}C_2$-acetate was incorporated into DGs, TGs, PEs, and PCs, indicating our conditions facilitate uptake of exogenous oleate, but do not undergo *de novo* lipogenesis (DNL). In MASH spheroids generated using freshly isolated steatotic hepatocytes, we found decreased glucose carbon utilization and an increased lactate/pyruvate ratio. We also observed reduced DNL from glucose in MASH; however intracellular levels are

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unchanged. **Conclusion:** 3D human liver spheroids can uptake exogenous fatty acids and use them to synthesize complex lipids. Human liver spheroids recapitulate metabolism in the human liver and can be a useful tool for translational research.
Disclosures: Kanani Hokutan: Nothing to Disclose, Hyun Young Kim: Nothing to Disclose, Samuel Kerk: Nothing to Disclose, Wonseok Lee: Nothing to Disclose, Sadatsugu Sakane: Nothing to Disclose, Karin Diggle: Nothing to Disclose, Tatiana Kisseleva: Nothing to Disclose, Christian Metallo: Nothing to Disclose, David Brenner: Nothing to Disclose

4257 | SUGGESTED IMPORTANCE OF THE MICROENVIRONMENT SURROUNDING CANCER CELLS IN THE PROGRESSION OF HEPATOCELLULAR CARCINOMA

Hirayuki Enomoto[1] Yukihisa Yuri[1] Nobuhiro Aizawa[1] Tomoyuki Takashima[1] Naoto Ikeda[1] Ryota Nakano[1] Hideyuki Shiomi[1] Shinya Fukunishi[1] Takashi Nishimura[1] Hiroko Iijima[1] Shinichiro Shinzaki[1], [1]Hyogo Medical University

Background: The xenograft model is frequently used to examine antitumor effects in vivo by transplanting human-derived cancer cells into immunosuppressed mice. This experimental system is an extremely useful model to verify the effects of drugs in vivo, but tumors are formed from human-derived cancer cells and mouse-derived tumor stromal cells. Although tumors are formed from human-derived cancer cells and mouse-derived tumor stromal cells, few studies have discussed on this point. In this study, we focused on the fact that interferon (IFN) is a highly species-specific bioactive substance. We compared the antitumor effects of human interferon (h-IFN) and murine interferon (m-IFN) in the xenograft model. **Methods:** We compared the expression of human and mouse type I IFN receptors in the human hepatocellular carcinoma cell line Hep3B. Hep3B cells were cultured and the inhibitory effects of m-IFN and h-IFN on cell proliferation were compared in vitro. In the xenograft model in which Hep3B cells are transplanted subcutaneously into SCID mice (tumor cells are of human origin and stromal cells are of mouse origin), 5 weeks after transplantation, h-IFN or m-IFN were administered (peri-tumor injection) for 2 weeks, and in vivo anti-tumor effects were compared. **Results:** (1) Hep3B cells strongly expressed h-IFN-bound IFN receptors, but the expression level of m-IFN-bound receptors was quite low (approximately one-tenth). (2) In vitro proliferation of Hep3B cells was inhibited by the h-IFN treatment, but not by the m-IFN treatment. (3) In the in vivo model, h-IFN treatment inhibited the proliferation of Hep3B-derived cancer cells, while m-IFN did not influence the proliferation of cancer cells. However, m-IFN treatment suppressed the angiogenesis in the tumor stromal tissue, which were shown by the decreased number of the CD34-positive cells, and caused the antitumor effect comparable to that of h-IFN in vivo. **Conclusion:** In the xenograft model, h-IFN mainly act on the cancer cells of human origin, whereas m-IFN mainly affects stromal cells of mouse origin. Since cancer cells and stromal cells in the xenograft model are derived from different species, it is possible to examine the roles of cancer cells and stromal cells separately. The significant antitumor effects of m-IFN suggest the important role of the microenvironment surrounding cancer cells in the progression of the hepatocellular carcinoma.
Disclosures: Hirayuki Enomoto: Nothing to Disclose, Yukihisa Yuri: Nothing to Disclose, Nobuhiro Aizawa: Nothing to Disclose, Tomoyuki Takashima: Nothing to Disclose, Naoto Ikeda: Nothing to Disclose, Ryota Nakano: Nothing to Disclose, Hideyuki Shiomi: Nothing to Disclose, Shinya Fukunishi: Nothing to Disclose, Takashi Nishimura: Canon Medical Systems: Grant/Research Support, GE HealthCare: Grant/Research Support, Philips Japan: Grant/Research Support, Hiroko Iijima: Nothing to Disclose, Shinichiro Shinzaki: Nothing to Disclose

4258 | POLYENYLPHOSPHATIDYLCHOLINE (PPC) ATTENUATES OXIDATIVE STRESS-INDUCED LIVER INJURY BY STABILIZING LYSOSOMAL MEMBRANE INTEGRITY

yongzhi li[1] Jie Lin[1] Dan Zhang[1] jiyao sheng[1], [1]The Second Hospital of Jilin University

Background: Oxidative stress, a core mechanism of liver injury, disrupts redox homeostasis, impairing organelle function. Lysosomes are key targets of ROS, and their membrane instability worsens ROS accumulation, creating a vicious cycle that accelerates hepatocyte damage. Thus, stabilizing lysosomal membranes and blocking oxidative stress are vital for liver function. Polyenylphosphatidylcholine (PPC), a clinical hepatoprotectant, is known to repair hepatocyte membranes, but its role in lysosomal protection remains unclear. This study explores PPC's novel mechanism in preserving lysosomal integrity, offering new therapeutic strategies for liver diseases. **Methods:** In vitro, H_2O_2-induced oxidative stress models in L02 and THLE-2 hepatocytes were used to assess PPC's cytoprotective effects. Cell viability (CCK-8), ROS levels (DCFH-DA flow cytometry), and apoptosis (Annexin V-FITC/PI) were measured. Lysosomal function was evaluated via Cathepsin B/D expression (Western blot), cholesterol

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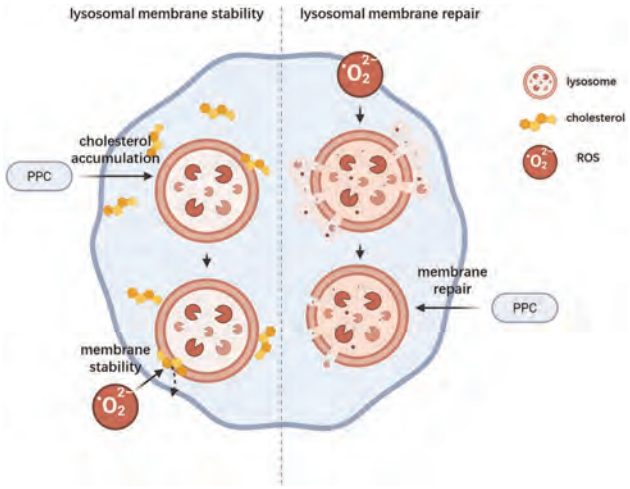
content (Filipin staining/confocal microscopy), and membrane integrity (galectin-3 puncta assay). Lysosomal dynamics (Lysotracker Red/confocal), ultrastructure (TEM), and repair protein localization were analyzed. In vivo, a CCl4-induced liver injury model assessed serum ALT/AST, histopathology (HE/Masson staining), and lysosomal markers (immunofluorescence). RNA-seq and bioinformatics identified key pathways, while molecular docking predicted PPC-lysosomal protein interactions, elucidating PPC's hepatoprotective role via lysosomal cholesterol homeostasis and PITT-mediated repair. **Results:** PPC treatment protected against oxidative liver injury both in vitro and in vivo. In H_2O_2-treated hepatocytes, PPC enhanced cell viability, reduced ROS levels, and inhibited apoptosis. Filipin staining and galectin-3 puncta assays showed PPC increased lysosomal cholesterol content, improving membrane stability and reducing permeabilization. Confocal microscopy revealed PPC activated the PITT repair pathway to restore damaged lysosomes, while TEM confirmed preserved lysosomal ultrastructure. In CCl4-treated mice, PPC decreased serum ALT/AST, attenuated histopathological damage, and upregulated lysosomal markers. Transcriptomics indicated PPC maintains lysosomal integrity through cholesterol homeostasis and membrane repair mechanisms. **Conclusion:** This study demonstrates that PPC protects against oxidative liver injury by maintaining lysosomal membrane integrity through cholesterol enrichment and PITT-mediated repair, offering new therapeutic strategies for oxidative stress-related liver diseases.



Disclosures: yongzhi li: Nothing to Disclose, Jie Lin: Nothing to Disclose, Dan Zhang: Nothing to Disclose, jiyao sheng: Nothing to Disclose

4259 | AGING DISRUPTS HEPATOCYTE ZONATION HOMEOSTASIS IN MICE AND HUMANS

Erika Hissong[1] Robert Schwartz[1] Jason Sethiadi[1] Silvia Hanna[1] Duc Nguyen[1] Tuo Zhang[1] Qazi Ali[1] Saloni Sinha[1], [1]Weill Cornell Medicine

Background: Background and Aims: The mammalian liver performs vital physiological functions and maintains whole-body homeostasis. Thanks to its remarkable regenerative ability, age-related declines in liver function occur more slowly than in most organs. Liver aging is driven by genomic and epigenomic changes and is characterized by reduced volume and blood flow, impaired metabolism, delayed regeneration, hepatocyte polyploidy, increased numbers of hepatic stellate cells (HSCs), liver sinusoidal endothelial cells, and Kupffer cells, along with heightened inflammation and senescence. Aging-induced degenerative changes in the liver are not inherently pathologic but pose an increased risk for liver diseases. However, the molecular mechanisms underlying aging-induced hepatic dyshomeostasis remain incompletely characterized. **Methods:** Approach and **Results:** Histological analyses of aged (>24-month-old) wild-type mouse livers showed no fibrosis, but a uniform cellular enlargement compared to young (2-month-old) mouse livers was noted. For an unbiased characterization of aging-driven changes, we used single-nucleus RNA sequencing and found that aged livers had altered cell-cell interactions and hepatocyte zonation with zone-specific transcriptomic changes. Immunostaining confirmed aging-induced expansion of ASS1+, CYP2E1+ and GS+ hepatocytes, and an aberrant expression of ASS1+-GS+ "bi-zonal" hepatocytes, causing collapse of zonation. To investigate translational value, we assessed young (<25YO) and aged (>60YO) human liver biopsies and identified similar phenotypes. **Results:** See Above. **Conclusion:** In this study, we present a detailed analysis of the liver's cell type-specific transcriptome across aging, uncovering significant changes in cellular composition, gene expression, and zonation contributing to the age-related decline in structure and function. Our analyses identify profound transcriptional changes within major liver cell types, including hepatocytes, HSCs, and LSECs, and offer insights into the disruption of hepatic functions and intercellular communication. Aging causes a loss of distinct hepatic zonation, marked by an expansion and blurring of zonal boundaries. The emergence of "bi-zonal" hepatocytes near the central vein, co-expressing markers from both periportal (ASS1) and pericentral (GS) zones—mutually exclusive in young livers—

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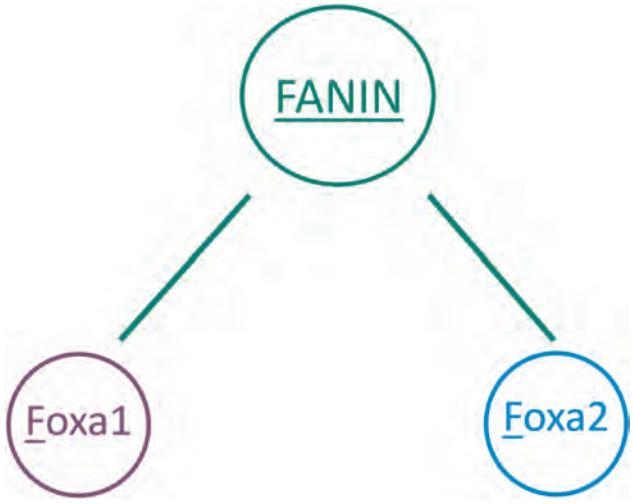
indicates aging significantly modifies the liver microenvironment. Parallels between aged mouse and human livers strongly evidence that mechanisms driving zonation dysregulation and bi-zonal hepatocyte emergence are conserved across species. Future research aimed at restoring hepatocyte zonal integrity, balancing intercellular communication, and targeting key transcriptional regulators could mitigate age-associated liver dysfunction and disease.

Disclosures: Erika Hissong: Nothing to Disclose, Robert Schwartz: Miromatrix Inc: Advisor, Lime Therapeutics: Advisor, Otsuka Inc.: Grant/Research Support, Alnylam Pharmaceuticals: Speaking and Teaching, Alnylam Pharmaceuticals: Consultant, Jason Sethiadi: Nothing to Disclose, Silvia Hanna: Nothing to Disclose, Duc Nguyen: Nothing to Disclose, Tuo Zhang: Nothing to Disclose, Qazi Ali: Nothing to Disclose, Saloni Sinha: Nothing to Disclose

4260 | ZINC FINGER TRANSCRIPTION FACTOR FANIN IS THE UPSTREAM REGULATOR OF PIONEER FACTORS FOXA1 AND FOXA2 IN THE LIVER

Joseph Schinderle[1] Anqi Wu[1] Riya Shah[1] Irina Bochkis[1], [1]University of Pittsburgh

Background: Transcription factors regulate gene expression that orchestrates many processes, including development and physiology. Winged-helix (*forkhead*) factor paralogs Foxa1 and Foxa2, originally named HNF3α and HNF3β, are called pioneer factors for their ability to independently bind closed chromatin and change chromatin accessibility allowing other factors to bind. Foxa1 and Foxa2 are essential to liver function, both in development and differentiated tissue. Based on computational analysis, we have identified the upstream regulator of Foxa1 and Foxa2 we named FANIN. **Methods:** We performed ChIP-Seq to identify FANIN binding, and ATAC-Seq & RNA-Seq in FANIN liver-specific mutants to assess chromatin accessibility and differential gene expression. Functional analysis of genomic data was completed to identify the role of FANIN in the liver. **Results:** Deletion of FANIN leads to loss of Foxa1 and Foxa2 expression in the liver. Since Foxa1 and Foxa2 are pioneer factors, we assessed whether deletion of FANIN affects chromatin accessibility. Indeed, ATAC-Seq signal is reduced in both male and female FANIN mutants, in contrast to Foxa2 mutants in control condition. Pathway analysis of FANIN ChIP targets in males identified targets regulating collagen synthesis and ECM proteins, and we confirmed presence of collagen in male FANIN mutants. Pathway analysis of FANIN ChIP targets in females identified targets associated with liver inflammation, injury and proliferation and was confirmed by H&E and Ki67 staining. **Conclusion:** FANIN is likely a pioneer factor regulating 2 established pioneer factors, which is unprecedented. Mechanisms of regulation of ECM targets by FANIN are crucial to understanding, treating, and reversing liver fibrosis. Understanding how FANIN modulates liver injury and inflammation is critical to treatment of chronic and end-stage liver disease.



Disclosures: Joseph Schinderle: Nothing to Disclose, Anqi Wu: Nothing to Disclose, Riya Shah: Nothing to Disclose, Irina Bochkis: Nothing to Disclose

4261 | EXOSOME-DEPENDENT MECHANISM OF LIVER REGENERATION AFTER PARTIAL HEPATECTOMY

Mina McGinn[1] Christopher Rabender[1] Ross Mikkelsen[1] Vasily Yakovlev[1], [1]Virginia Commonwealth University/ Massey Cancer Center

Background: The liver is known for its remarkable ability to regenerate precisely after massive tissue loss or injury. Liver regeneration is studied by performing the partial hepatectomy (PHx) to remove 2/3 of the liver mass in rodents. Following regeneration, the liver grows back precisely to its original mass without exceeding it. Different studies have shown that loss of liver mass affects putative tissue-specific mitogenic inhibitors in the blood, which, in turn, regulate the proliferation of remaining hepatocytes and liver regeneration. Although well-documented in numerous publications, the inhibitory substances or 'sensor molecules' that control the regeneration mechanisms remain unknown. Approximately 80 years ago, a series of now classic studies suggested that within any cell line, functionally active differentiated cells may signal their existence to the mitotically active precursor cells through a tissue-

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specific or cell-line-specific inhibitory substance. Exosomes are small (30–150 nm) vesicles containing unique RNA and protein cargo, secreted by all cell types in culture and in vivo. Their proposed role is stable intercellular carriers of proteins and RNAs, mostly microRNA, from secreted to recipient cells. Exosomes taken up by the recipient cells can significantly modulate their biological functions. **Methods:** Hepatocyte-derived exosomes (HD-Exos) were selectively labeled, analyzed, and isolated from mouse plasma. HD-Exos and non-HD-Exos RNA content from mouse plasma was also analyzed by Nanostring and RT-PCR methods. Using in vivo and in vitro models, we assessed the role of HD-Exos and the RNA they contain in regulating hepatocyte proliferation and liver regeneration. **Results:** We demonstrated that after PHx, the concentration of HD-Exos in the blood of animals changes in proportion to the total mass of the liver. At the same time, exosomes secreted by liver hepatocytes into the blood actively block hepatocyte proliferation in vitro and liver regeneration after PHx in vivo. We also demonstrated that miRNA-26a, miRNA-30a, and miRNA-33 carried by HD-Exos play an active part in the downregulation of hepatocyte proliferation. Thus, HD-Exos released into the bloodstream are a key element of the negative feedback mechanism regulating liver proliferation. **Conclusion:** This work opens up a completely new and unexplored area of liver biology regarding the role of liver-derived exosomes and their cargo in the regulation of liver regeneration and homeostasis.

Disclosures: Mina McGinn: Nothing to Disclose, Christopher Rabender: Nothing to Disclose, Ross Mikkelsen: Nothing to Disclose, Vasily Yakovlev: Nothing to Disclose

4262 | THE CALORIC RESTRICTION MIMETIC, HYDROXYCITRATE, IS A PROMISING SUPPLEMENTAL DIETARY THERAPY TO PREVENT ALCOHOL-INDUCED LIVER INJURY

Oluwaseyi Okesooto[1] Erik Tweten[1] Pamela Tuma[1], [1]The Catholic University of America

Background: Caloric restriction has emerged as a promising therapeutic strategy for mitigating metabolic diseases, including alcohol-associated liver disease. This study investigates the potential of hydroxycitrate, a caloric restriction mimetic, as a novel therapeutic intervention. This mimetic is a competitive inhibitor of ATP citrate lyase, an enzyme that converts citrate to oxaloacetate and acetyl-CoA. Because acetyltransferases transfer the acetyl group from acetyl-CoA to the ε -amino group of lysines, ATP citrate lyase inhibition is predicted to decrease cellular acetyl-CoA levels, promoting global protein deacetylation by reducing the substrate availability for acetyltransferases. Decreased acetyl-coA levels have also been linked to decreased lipid biosynthesis such that hydroxycitrate also has the potential to prevent alcohol-induced steatosis. **Methods:** For these studies we used polarized, hepatic WIF-B cells. Importantly, these cells exhibit endogenous alcohol metabolism as observed in liver *in situ.* Cells were treated with hydroxycitrate in the absence or presence of alcohol to determine its capacity to prevent selected alcohol-induced hepatic cellular alterations. **Results:** We determined that hydroxycitrate treatment prevented alcohol-induced tubulin acetylation in a dose-dependent manner, consistent with its proposed function in global protein deacetylation. It also prevented alcohol-induced peroxisome proliferation and alcohol-induced oxidative stress (as observed by decreased ROS accumulation), suggesting it might additionally function as an anti-antioxidant. Furthermore, when alcohol-treated WIF-B cells were additionally treated with oleic acid (to mimic the Western diet), the addition of hydroxycitrate ameliorated lipid accumulation as observed by decreased numbers of lipid droplets of reduced size, consistent with its proposed function in reducing body fat. We further determined that hydroxycitrate addition prevented known alcohol-induced defects in microtubule plus-end and minus-end directed protein trafficking due to tubulin acetylation. Finally, live cell imaging revealed that hydroxycitrate prevented alcohol-induced defects in microtubule-based organelle motility. **Conclusion:** Together, these results suggest that hydroxycitrate, used alone or with aldehyde scavengers, could be a potential dietary supplement with therapeutic effects in preventing and/or attenuating alcohol-induced liver injury progression.

Disclosures: Oluwaseyi Okesooto: Nothing to Disclose, Erik Tweten: Nothing to Disclose, Pamela Tuma: Nothing to Disclose

4263 | INCREASING MATRIX HETEROGENEITY PROMOTES CELL-MATRIX INTERACTIONS AND THE AGGRESSIVENESS OF LIVER CANCER CELLS

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Background: Remodeling of the extracellular matrix (ECM) is a key feature of tumor development in the liver, particularly in cases of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCC). A stiffened and heterogeneous ECM promotes the proliferation, migration and invasion of tumor cells.

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Fibronectin (FN) is an important ECM glycoprotein that facilitates cell adhesion, migration, and proliferation within the ECM. The way in which HCC/iCC cells interact with heterogeneous ECMs is not well understood.
The aim is to analyze cell-matrix interactions with collagen and collagen-FN-based networks, and to identify the resulting cell-specific factors in the context of increasing ECM heterogeneity. **Methods:** ECM stiffness and structural parameters were combined to define ECM heterogeneity. HCC and iCC cell lines, represented by Huh7 and KKU-213 cells respectively, were analyzed in contact with the ECM model system. Stiffness was measured using atomic force microscopy, invasiveness using 3D invasion assays, and the mechanotransductive interaction of the cells with the network structures as a function of increasing ECM heterogeneity using 3D fiber displacement analyses. **Results:** An increase in ECM heterogeneity from low to high resulted in a 2.3-fold decrease in HCC cell stiffness and a 3.0-fold decrease in iCC cell stiffness. Analysis of invasiveness with increasing ECM heterogeneity revealed cell-specific effects. The invasiveness of the HCC cell line under FN-influence increased from 26% ± 4% in low-heterogeneous ECM to 38% ± 6% in increased-heterogeneous ECM and 51% ± 3% in highly-heterogeneous ECM, compared to 32% ± 9% in increased-heterogeneous ECM and 46% ± 9% in highly-heterogeneous ECM without FN. In addition, the highly invasive behavior of all examined cells was evident in highly heterogeneous ECM. The invasiveness of iCC cells increased independently of FN, rising from 24% ± 2% in low- to 62% ± 8% in highly heterogeneous ECM. 3D fiber displacement analyses investigated the interaction of invasive cells with ECM structural changes. **Conclusion:** The HCC and iCC cell lines examined exhibited decreased stiffness and increased invasiveness in the presence of increased ECM heterogeneity. The role of ECM heterogeneity as a risk factor for the spread of intrahepatic tumors and cell dedifferentiation needs to be investigated in vivo.
Disclosures: Alexander Hayn: Nothing to Disclose, Madlen Matz-Soja: Nothing to Disclose, Thomas Berg: Nothing to Disclose, Florian van Bömmel: Nothing to Disclose

4264 | LOSS OF APOE IN CCL19^{+} STROMAL CELLS EXACERBATES LIVER DAMAGE IN EXPERIMENTAL LUPUS HEPATITIS

Yekaterina Krutsenko[1] Jiang Li[1] Sudrishti Chaudhary[1] Juliane Beier[1] Gavin Arteel[1] Catherine Poholek[1],
[1]University of Pittsburgh

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting multiple organs. Hepatic manifestations affect up to 30% of SLE patients and include elevated liver enzymes, MASLD, autoimmune/lupus hepatitis, and cirrhosis, but underlying mechanisms remain poorly understood. Emerging evidence suggests that immune-stromal interactions in secondary lymphoid organs contribute to systemic inflammation in SLE. CCL19-producing lymph node stromal cells (LNSCs) regulate T cell activation and are increased in secondary lymphoid organs and inflamed tissues in lupus models. Here we show that production of apolipoprotein E (apoE), a lipid transport protein with immunomodulatory roles, regulates CCL19^{+} LNSC function, and examine how apoE loss in CCL19^{+} LNSCs affects hepatic pathology in murine lupus. **Methods:** We induced lupus in 20-week-old female mice with targeted deletion of *Apoe* in CCL19^{+} LNSCs (CCL19^{Cre}Apoe$^{fl/fl}$ (CCL19$^{\Delta apoE}$)) and control mice (CCL19^{WT}Apoe$^{fl/fl}$ (CCL19^{Ctrl})) using chronic topical application of the TLR7 agonist imiquimod (3 times weekly to ear skin for 5 weeks), then assessed liver pathology by histology and qRT-PCR. **Results:** Imiquimod induced periportal lymphocytic and plasma cell infiltration with interface inflammation and occasional necrotic foci, characteristic of lupus hepatitis, with more severe changes in CCL19$^{\Delta apoE}$ mice compared to CCL19^{Ctrl} mice. RT-qPCR revealed no differences in macrophage populations (F4/80, CD68), but immunohistochemical analysis showed mildly increased MPO-positive neutrophil infiltration and NET formation in CCL19$^{\Delta apoE}$ animals, as demonstrated by citrullinated histone H3 staining. Polarized light imaging revealed "chicken-wire" fibrotic changes that were exacerbated in CCL19$^{\Delta apoE}$ mice despite similar TGFβ1, Col1a1, and α-SMA fibrosis marker expression. CCL19$^{\Delta apoE}$ mice, but not controls, showed increased hepatic plasminogen activator inhibitor-1 (PAI-1) expression but paradoxically decreased fibrinogen deposition. **Conclusion:** ApoE deficiency in CCL19-expressing cells exacerbated imiquimod-induced hepatic manifestations that mimic features of lupus hepatitis. The paradoxical finding of elevated PAI-1 with reduced fibrinogen deposition suggests complex compensatory ECM remodeling pathways mediated by LNSC apoE. These results highlight apoE's role in LNSCs for modulating hepatic immune and fibrotic responses during systemic autoimmunity and provide insights into LNSC contributions to organ-specific lupus pathology.
Disclosures: Yekaterina Krutsenko: Nothing to Disclose, Jiang Li: Nothing to Disclose, Sudrishti Chaudhary: Nothing to Disclose, Juliane Beier: Nothing to Disclose, Gavin Arteel: Nothing to Disclose, Catherine Poholek: Nothing to Disclose

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4265 | ASSOCIATION OF LIVER-SPECIFIC MIR-122 EXPRESSION WITH COVID-19 SEVERITY

Nicoleta Mihai[1] Catalin Tiliscan[1] Iulia Iancu[2] Oana-Alexandra Ganea[1] Aida-Isabela Adamescu[1] Violeta Molagic[1] Anca Saran[1] Isabela Staicu[1] Adrian Marinescu[1] Sorin Arama[1] Andreea Arsene[1] Simona Ruta[1] Victoria Arama[1], [1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [2]"Stefan S. Nicolau" Institute of Virology, Bucharest, Romania

Background: miR-122 is a liver-specific microRNA that has been extensively studied in hepatitis C virus infection, hepatocellular carcinoma, and drug-induced liver injury. Compared to aminotransferases, miR-122 is a more sensitive and specific biomarker of liver involvement. In this study, we aimed to determine the expression of miR-122 in COVID-19 patients. **Methods:** We conducted a prospective cohort study in which we included adult patients confirmed with COVID-19 who presented in a tertiary hospital in Bucharest, Romania, between March 2022 and May 2023. Patients who had previously received antiviral treatment for SARS-CoV-2, who had liver disease and/or chronic kidney disease were excluded. Total RNA was extracted from plasma samples using a commercial kit and following the manufacturer's protocol. Circulating miR-122 levels were measured using quantitative polymerase chain reaction. Expression levels of miR-122 were normalized to U6 small nuclear RNA, which served as an endogenous control. Results were expressed as $\log_{10}2^{-\Delta CT}$ (the logarithmic transformation of relative gene expression changes). Statistical analysis of patient data was performed using SPSS version 23. $P < 0.05$ was set for statistical significance. **Results:** We enrolled 35 patients with a median (range) age of 48 (26-72) years and a female-to-male ratio of 1.9. Median BMI was 24 (17-39) kg/m2. Most patients (27, 77.1%) had a mild form of COVID-19, while 8 (22.9%) had a moderate form. Only 5 (14.3%) patients had elevated aminotransferase levels. Approximately 63% of patients had associated comorbidities. The most common were cardiovascular diseases (11, 31.4%) and dyslipidemia (8, 22.9%). Seventeen (48.6%) patients had chronic treatment, of which 6 (17.1%) had statin. In bivariate analysis, the relative expression of miR-122 was directly correlated with COVID-19 severity (Spearman coefficient [SC] = 0.397, p = 0.018) and inversely correlated with BMI (SC = −0.402, p = 0.017). In addition, we found an association of miR-122 expression with statin treatment (p = 0.021). After multivariate analysis, the correlation of miR-122 with COVID-19 severity was maintained (p = 0.04). Aminotransferase levels were not correlated with either miR-122 expression or COVID-19 severity. **Conclusion:** In our study, the relative expression of miR-122 was significantly and positively correlated with COVID-19 severity.

Disclosures: Nicoleta Mihai: Nothing to Disclose, Catalin Tiliscan: Nothing to Disclose, Iulia Iancu: Nothing to Disclose, Oana-Alexandra Ganea: Nothing to Disclose, Aida-Isabela Adamescu: Nothing to Disclose, Violeta Molagic: Nothing to Disclose, Anca Saran: Nothing to Disclose, Isabela Staicu: Nothing to Disclose, Adrian Marinescu: Nothing to Disclose, Sorin Arama: Nothing to Disclose, Andreea Arsene: Nothing to Disclose, Simona Ruta: Nothing to Disclose, Victoria Arama: Nothing to Disclose

4266 | NUCLEAR LOCALIZATION OF ACOT12 SUGGESTS TRANSCRIPTIONAL ROLES IN SUPPRESSING HEPATOCARCINOGENESIS

Logan Carr[1] Xu Xu[2] Susan Hagen[2] Eric Ortlund[3] David Cohen[1] Mariana Acuna[1], [1]Brigham and Women's Hospital, Harvard Medical School, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, [3]Emory University

Background: Acot12 is the primary enzyme that hydrolyzes acetyl-CoA into acetate in liver cytosol. Acot12 is strongly upregulated by PPARalpha under fasting conditions. We and others have demonstrated that Acot12 modulates histone H3 acetylation, leading to suppression of hepatocarcinogenesis and metastasis. Suggestive of Acot12 activity within the nucleus, amino acid sequence analysis has identified a putative nuclear localization signal (NLS) in Acot12. A conformational change in response to metabolic stimuli or protein interactions that exposes the NLS would raise the potential for stimulus-coupled nuclear translocation. The aim of this study was to garner direct evidence for nuclear localization of Acot12.

Methods: Alpha mouse liver (AML) 12 cells were transfected for 24 h with an Acot12-GFP expression vector, using GFP as control. Acot12 localization was assessed by live cell microscopy. Cells were pretreated with leptomycin B for 2 h to inhibit nuclear efflux and then exposed to a broad spectrum of metabolic stimuli including serum depletion, forskolin, phorbol 12-myristate 12-acetate, acetate, glucagon, and fatty acids. Acot12-interacting proteins were identified using a GFP-trap approach to immunoprecipitate interacting proteins together with Acot12-GFP, using GFP as a control. Proteins were identified by mass spectrometry, and AlphaFold 3 (DeepMind) was used to predict direct Acot12-protein interactions.

Results: Of the metabolic stimuli tested, only oleic acid promoted the nuclear translocation of Acot12. We identified 43 proteins that were immunoprecipitated by Acot12-GFP but not GFP. Of these proteins, 47% were nuclear, 26% were cytosolic, 16% were mitochondrial

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and 12% were from other organelles or membranes. AlphaFold 3 predicted that 46% interacted directly with Acot12, 50% of which were nuclear proteins. **Conclusion:** Our findings reveal evidence for fatty acid-induced nuclear translocation of Acot12, where it interacts with a number of nuclear proteins. Because fatty acid uptake into liver is maximal under fasting conditions, we speculate that Acot12 participates in the transcriptional response to nutrient deprivation including suppression of cellular proliferation, thereby rationalizing its function in inhibiting hepatocarcinogenic and metastatic activities.

Disclosures: Logan Carr: Nothing to Disclose, Xu Xu: Nothing to Disclose, Susan Hagen: Nothing to Disclose, Eric Ortlund: Nothing to Disclose, David Cohen: Pfizer: Data monitoring committee, Astra Zenica: Data monitoring committee, Ipsen: Data monitoring committee, Amryt: Data monitoring committee, Spruce Biosciences: Data monitoring committee, Esperion: And grant support; Investigator initiated basic research, Novo Nordkisk: Advisor, Mariana Acuna: Nothing to Disclose

4267 | HEPATIC STELLATE CELL-DERIVED HB-EGF SUPPRESSED HEPATOCYTE APOPTOSIS IN ACUTE LIVER INJURY

Yoichi Sasaki[1] Yoshinobu Saito[1] Jihyun Sung[1] Seiya Kato[1] Kenji Fukumoto[1] Yuta Myojin[1] Kazuhiro Murai[1] Yuki Makino[1] Hayato Hikita[1], [1]The University of Osaka Graduate School of Medicine

Background: Hepatocyte apoptosis is a key pathological feature in liver injury. In chronic liver injury, it drives liver fibrosis, primarily through hepatic stellate cells (HSCs), which exhibit both progressive and protective roles. However, the function of HSCs in acute liver injury, especially regarding hepatocyte apoptosis, remains unclear. This study aimed to investigate the impact of HSCs on hepatocyte apoptosis during acute liver injury. **Methods:** We utilized Lrat-Cre iDTR mice expressing diphtheria toxin receptor (DTR) specifically in HSCs, followed by diphtheria toxin (DT) administration to deplete HSCs. Liver injury was induced using lipopolysaccharide (LPS) and ABT-737, a Bcl-xL inhibitor. Single-cell RNA sequencing (scRNA-seq) of wild-type mice treated with ABT-737 was conducted to analyze HSC-hepatocyte interactions to identify soluble factors regulating hepatocyte apoptosis. HepG2 cells were cultured with LX-2-conditioned media or with HepG2-conditioned media containing ABT-737 to examine the effect of HSC-derived factors. Cell viability, supernatant Caspase-3/7 activity, and Annexin V-positive area were evaluated. **Results:** DT-treated Lrat-Cre iDTR mice exhibited reduced expression of Lrat and Gfap gene expression from day 4 to one week post-DT administration, along with a decrease in Desmin-positive cells in liver tissues. The number of F4/80-positive cells in liver tissues did not significantly differ between Lrat-Cre iDTR and control mice following combined DT and LPS either ABT-737 treatment. However, the number of TUNEL-positive hepatocytes, serum ALT levels, and Caspase-3/7 activity were significantly elevated in the Lrat-Cre iDTR group, indicating increased hepatocyte apoptosis. scRNA-seq–based interaction analysis between HSCs and hepatocytes identified five candidate secreted proteins upregulated in HSCs of ABT-737–treated mice, including HB-EGF.

Under ABT737 treatment, both LX-2–conditioned media and recombinant HB-EGF reduced HepG2 cell death markers—including Annexin V-positive area and caspase-3/7 activity—and improved cell viability compared to HepG2–conditioned media; these effects were abrogated by co-treatment with a HB-EGF neutralizing agent (CRM197). **Conclusion:** Depletion of HSCs exacerbates hepatocyte apoptosis during acute liver injury. Our findings suggest that HSC-derived HB-EGF plays a protective role by mitigating hepatocyte apoptosis and liver damage.

Disclosures: Yoichi Sasaki: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Jihyun Sung: Nothing to Disclose, Seiya Kato: Nothing to Disclose, Kenji Fukumoto: Nothing to Disclose, Yuta Myojin: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Yuki Makino: Nothing to Disclose, Hayato Hikita: Nothing to Disclose

4268 | A NOVEL MICROFLUIDIC CELL SORTING APPROACH FOR ISOLATING VIABLE PRIMARY HEPATOCYTES

Crystal Montoya[1] Hannah Johannsen[1] Nadine Chelius[1] Carsten Poggel[1] Timo Adams[1], [1]Miltenyi Biotec

Background: Hepatocytes are crucial for understanding liver function and regeneration. However, their large size, complex morphology, and high metabolic activity make them particularly vulnerable to sorter-induced cellular stress (SICS). Conventional cell sorters often cause cellular damage and reduced-cell viability; yet that is not an issue with the MACSQuant® Tyto® Cell Sorter (Miltenyi Biotec). Utilizing microchip-based, low-pressure, and fully closed sterile technology; it minimizes cellular stress and prevents contamination. The poster describes a workflow for sorting primary mouse hepatocytes using gentleMACS™ Perfusion Technology and the MACSQuant Tyto Cartridge LC, optimized for sorting larger cells. **Methods:** Mouse hepatocytes were dissociated from the liver utilizing the Liver Perfusion Kit and GentleMACS Octo Dissociator with Heaters (Miltenyi Biotec). The primary hepatocytes were stained with APC-conjugated REAfinity® CD95

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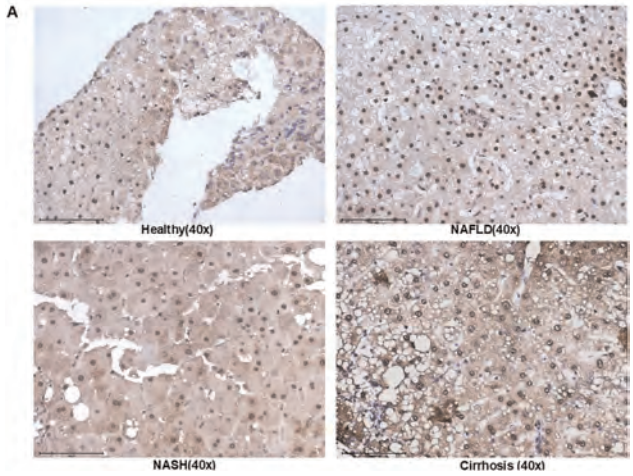
(FAS) Antibody and isolated utilizing the MACSQuant Tyto cell Sorter and MACSQuant Tyto Cartridge LC. Hepatocytes were then cultured to confirm cell survivability. **Results:** The MACSQuant Tyto sorter enriched the target antigen-specific CD95+ hepatocyte cells from 63.9% to 96.2% with cell viability was statistically comparable to non-sorted cells (above 77% viability). The survivability of hepatocytes was confirmed after 24 hours of cell culture, with cell attachment, hexagonal cell shape, and nuclei duplication visible with brightfield imaging. **Conclusion:** The isolated hepatocytes showed robust post-sorting plating capacity and exhibited typical morphological features, including hexagonal shape and nuclei duplication. These findings demonstrate that the sorting process effectively preserved both the viability and phenotypic properties of the primary hepatocytes in culture.

Disclosures: Crystal Montoya: Nothing to Disclose, Hannah Johannsen: Nothing to Disclose, Nadine Chelius: Nothing to Disclose, Carsten Poggel: Nothing to Disclose, Timo Adams: Nothing to Disclose

4269 | TARGETING FTO DEMETHYLASE ACTIVITY IMPROVES METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE IN PRECLINICAL MODELS

Sunita Giri[1] Vijay Kumar[1], [1]Institute of liver and biliary sciences

Background: NAFLD is a chronic liver disease characterized by the buildup of excess fat in the liver. Elevated expression of FTO has been implicated in steatosis and NAFLD development. There is no standard treatment for NAFLD. To address this, we investigated the therapeutic potential of entacapone - a pharmacological inhibitor of FTO - in preclinical models. **Methods:** A NAFLD mouse model was developed by feeding animals a high-fat and high-carbohydrate diet. Mice were given a daily intraperitoneal dose of 10 or 30 mg of entacapone up to 12 weeks. Changes in obesity, lipid accumulation, and liver fibrosis were monitored. Biomarkers of hepatic and metabolic functions were measured by a bioanalyzer. The mRNA levels of FTO and metabolic genes were quantified by RT-qPCR whereas N6-methyladenosine levels were measured by ELISA. The hepatic expression of FTO protein in preclinical and clinical (NAFLD, NASH, and cirrhosis) samples was visualized by immunohistochemical staining. FTO gene regulation was investigated in cell culture. **Results:** Treatment with entacapone led to a significant reduction in obesity, hepatic fat build-up, normalization of NAS score, and metabolic functions in mice. m6A levels in gene transcripts were high, coinciding with reduced expression of FTO, lipogenic, and inflammatory genes. FTO-1, FTO-5 and FTO-12 were expressed at high levels in NAFLD patients, whereas FTO-5 and FTO-12 were at basal levels in NASH and cirrhosis. Entacapone could downregulate FTO in immortalized hepatocytes. **Conclusion:** Pharmacological inhibition of FTO by entacapone normalized hepatic functions and ameliorated NAFLD in the mouse model, highlighting its therapeutic potential.



Disclosures: Sunita Giri: Nothing to Disclose, Vijay Kumar: Nothing to Disclose

4270 | HEPATIC MITOCHONDRIAL METABOLISM ASSESSED IN VIVO BY HYPERPOLARIZED [1-^{13}C]- AND [2-^{13}C]PYRUVATE WITH EX VIVO ISOTOPOMER ANALYSIS

Baljeet Seniwal[1] Andrew Cho[1] Zohreh Erfani[1] Blanka Kucejova[1] Sasanka Wathukara Dewage[1] Sung-Han Lin[1] Shawn Burgess[1] Jae Mo Park[1], [1]UT Southwestern Medical Center

Background: ^{13}C NMR with hyperpolarized (HP) [^{13}C] pyruvate enabled *in vivo* assessment of enzyme activities, including pyruvate dehydrogenase (PDH), pyruvate carboxylase (PC), and phosphoenolpyruvate carboxykinase (PEPCK), which regulate pyruvate metabolism towards oxidative phosphorylation and gluconeogenesis. Due to the complexity of these metabolic processes and limited ^{13}C-labeling in HP products, interpretation of *in vivo* HP results has been challenging. This study compares the capabilities of HP [1-^{13}C]pyruvate and [2-^{13}C]pyruvate in describing hepatic mitochondrial metabolism and provides an

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analytical framework for interpreting the HP data. **Methods:** Five fed and five fasted male rats were studied *in vivo* using a Bruker 3T MRI and a $^{13}C/^{1}H$ surface RF coil. Each rat received two injections of HP pyruvate ([1-^{13}C]pyruvate and [2-^{13}C]pyruvate), and time-resolved ^{13}C spectra were acquired from the liver following each injection. In parallel, five fed and five fasted rats were injected a bolus of thermal [U-$^{13}C_3$] pyruvate, and their livers were harvested 90 sec later for isotopomer analysis using NMR and GC-MS. **Results:** [^{13}C]Bicarbonate, an indicator of decarboxylation of HP [1-^{13}C]pyruvate via either PDH or PC-PEPCK, was detected under both fed and fasted conditions, although it was higher in fed condition. PC-specific [^{13}C]aspartate and [^{13}C]malate were often difficult to resolve from the crowded ^{13}C resonances at 175 – 178 ppm. In contrast, HP [2-^{13}C]pyruvate distinguished gluconeogenic (PC-PEPCK) and oxidative (PDH-TCA) pathways via [2-^{13}C] PEP and [5-^{13}C]glutamate, respectively. [1-^{13}C]Acetyl-L-carnitine (ALCAR) appeared only in fed livers, serving as a PDH-specific biomarker. GC-MS and ^{13}C NMR analyses of liver extracts confirmed that fasting reduced fractional PDH flux in the liver. MS analysis also calculated labeling fractions of ~50% for pyruvate, lactate, and alanine, 25-40% for TCA intermediates, and 20-30% of glutamate and PEP. Following fasting, ^{13}C-labeling increased across all measured metabolites. **Conclusion:** HP [2-^{13}C]pyruvate could monitor mitochondrial metabolic shifts in the liver by resolving HP products specific to gluconeogenic and oxidative pathways, whereas HP [1-^{13}C]pyruvate could not distinguish these individual routes. The *ex vivo* isotopomer analysis confirmed the sensitivity of these approaches to nutritional state, demonstrating reduced PDH flux and enhanced redistribution of ^{13}C through the TCA cycle and gluconeogenesis during fasting.

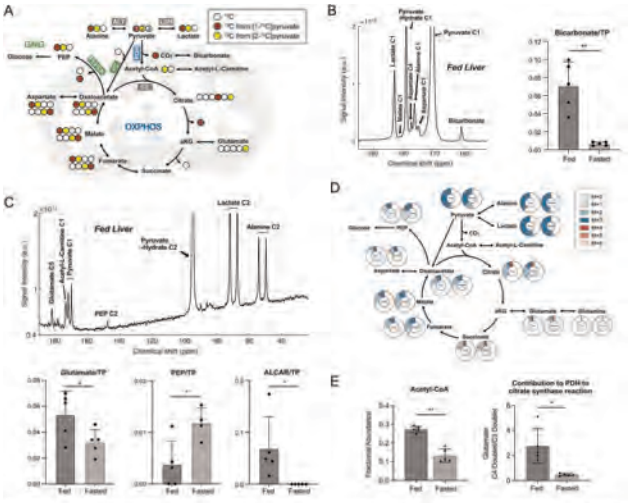

Figure 1. (A) Metabolic pathways of labeled carbon (^{13}C) in [1-^{13}C]pyruvate (red circle) and [2-^{13}C]pyruvate (yellow circle). Representative ^{13}C spectra acquired using **(B)** HP [1-^{13}C]pyruvate and **(C)** HP [2-^{13}C]pyruvate. Mitochondrial HP products were normalized to total HP product [TP]. **(D)** Fractional ^{13}C-labeling in metabolites measured by GC-MS and **(E)** fractional PDH flux measured by ^{13}C NMR *ex vivo* using non-HP [U-$^{13}C_3$]pyruvate. *: P < 0.05, **: P < 0.01

Disclosures: Baljeet Seniwal: Nothing to Disclose, Andrew Cho: Nothing to Disclose, Zohreh Erfani: Nothing to Disclose, Blanka Kucejova: Nothing to Disclose, Sasanka Wathukara Dewage: Nothing to Disclose, Sung-Han Lin: Nothing to Disclose, Shawn Burgess: Nothing to Disclose, Jae Mo Park: Nothing to Disclose

4271 | MRP1-MEDIATED AUTOPHAGY STAGNATION DRIVES HCC DEVELOPMENT AFTER SVR FOR HEPATITIS C

Katsuya Nagaoka[1] Masaya Onishi[2] Atsushi Tanaka[3] Satoshi Narahara[1] Sotaro Kurano[1] Kentaro Tanaka[1] Hiroki Inada[1] Etsuko Iio[1] Yoko Yoshimaru[1] Takehisa Watanabe[1] Hiroko Setoyama[1] Yutaka Suzuki[2] Yasuhito Tanaka[1], [1]Graduate School of Life Sciences, Kumamoto University, [2]Graduate School of Frontier Sciences, The University of Tokyo, [3]Department of Medicine, Yamagata University

Background: Despite the increase in sustained virological response (SVR) after direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection, the risk of hepatocellular carcinoma (HCC) remains high. This study aimed to elucidate the mechanisms of HCC development after SVR by analyzing gene expression changes in non-cancerous liver tissue from patients who developed HCC post-SVR. **Methods:** RNA sequencing (RNA-seq) was performed on non-cancerous liver tissues from 13 patients who developed HCC after SVR (SVR-HCC group) and 9 patients who did not (SVR-non HCC group). The obtained data were integrated with existing RNA-seq datasets from 65 patients with chronic HCV-HCC, 65 patients with non-B/non-C HCC, and 12 normal liver tissues. Additionally, in vitro experiments using HCV infection models and a Tet-On expression system were conducted to investigate functional mechanisms. **Results:** Gene expression analysis of adjacent non-cancerous tissues revealed prominent mitochondrial dysfunction and significantly increased expression of MRP1, a protein involved in mitochondrial fission, in the SVR-HCC group. In vitro validation showed that MRP1 gene expression tended to gradually increase after HCV clearance in HCV-infected cells. Overexpression of MRP1 in cells induced mitochondrial fragmentation, increased reactive oxygen species (ROS), and caused autophagy pathway arrest, which collectively promoted carcinogenesis. Furthermore, RNA-seq analysis comparing cancerous and adjacent non-cancerous tissues revealed the activation of mTORC1 signaling, an autophagy inhibitory factor, in the SVR-HCC group. These findings suggest that MRP1-mediated mitochondrial dysfunction and mTORC1-mediated autophagy inhibition contribute to

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HCC development through enhanced oxidative stress and impaired cellular quality control. **Conclusion:** Elevated MRP1 expression was specifically observed in SVR-HCC patients, suggesting its potential as a biomarker for increased HCC risk. MRP1-mediated mitochondrial dysfunction is implicated in HCC development after SVR, positioning MRP1 as a potential novel therapeutic target and surveillance marker.

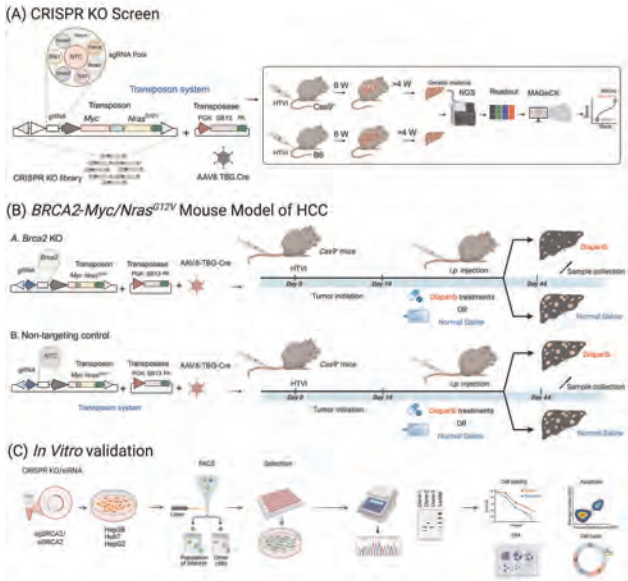
Disclosures: Katsuya Nagaoka: Nothing to Disclose, Masaya Onishi: Nothing to Disclose, Atsushi Tanaka: Nothing to Disclose, Satoshi Narahara: Nothing to Disclose, Sotaro Kurano: Nothing to Disclose, Kentaro Tanaka: Nothing to Disclose, Hiroki Inada: Nothing to Disclose, Etsuko Iio: Nothing to Disclose, Yoko Yoshimaru: Nothing to Disclose, Takehisa Watanabe: Nothing to Disclose, Hiroko Setoyama: Nothing to Disclose, Yutaka Suzuki: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

4272 | LOSS OF BRCA2 SENSITIZES HEPATOCELLULAR CARCINOMA TO PARP INHIBITION

Salah Adlat[1] Chunmiao Cai[2] Dingzi Yin[2] Markcus Lee[2] Kirk Wangensteen[2], [1]Mayo Clinic, Rochester, [2]Mayo Clinic

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality and still lacks effective targeted therapies. In many cancers, loss of DNA damage repair (DDR) pathways, particularly homologous recombination (HR), renders tumors sensitive to poly(ADP-ribose) polymerase inhibitors (PARPi). Although loss of HR genes is a recognized risk factor for the development of breast and ovarian cancers, loss of one copy of *BRCA2*, *FANCA*, *FANCM*, *FANCD2*, *CHEK2*, or *BRIP1* is reported only rarely in HCC, and its therapeutic relevance remains unknown. We therefore tested the hypothesis that HR genes loss promotes HCC progression and creates a therapeutic vulnerability to PARPi. **Methods:** To identify HR-DDR genes that drive HCC, we performed an *in vivo* CRISPR knockout (KO) screen targeting six HR-DDR genes (*Fanca, Fancm, Fancd2, Chek2, Brip1, Brca2*) including *Trp53* as a positive control. A pool of plasmids containing a gRNA targeting each gene or non-targeting control gRNAs, plus *Myc/Nras^{G12V}* oncogenes, was delivered to the liver hepatocytes of Cas9-expressing mice via hydrodynamic tail-vein injection (HTVI). Tumor burden was assessed 40–41 days post-injection, and the gRNA sequences present in tumors were quantified by sequencing. In validation experiments, *Brca2* was targeted in mice *in vivo* using HTVI, and mice received PARPi olaparib or vehicle control.

For *in vitro* studies, BRCA2 was disrupted in Hep3B, HepG2, and HuH7 cells using CRISPR or siRNA. Cell viability, colony formation, migration, apoptosis (Annexin V), DNA damage (γ-H2AX), and cell cycle were assessed ± olaparib. **Results:** In a pooled CRISPR screen of HR genes driving HCC *in vivo*, there was significant enrichment of gRNAs targeting *Brca2* relative to the other HR genes and non-targeting controls. Additional assays *in vivo* indicated that targeting *Brca2* in HCCs led to sensitivity to PARPi therapy, which otherwise has no effect on HCC progression. Targeting *BRCA2 in vitro* in human HCC cell lines impaired viability, and this effect was further enhanced by adding olaparib. Mechanistically, *BRCA2* depletion induced apoptosis, elevated γ-H2AX foci, and caused G2/M arrest. Critically, the addition of olaparib to *BRCA2*-depleted cells significantly potentiated these effects, leading to a further increase in apoptosis compared to *BRCA2* depletion alone. This highlights the synthetic-lethal interaction between *BRCA2* deficiency and PARP inhibition in HCC. **Conclusion:** *BRCA2* loss is a key HCC vulnerability. *In vivo*, *Brca2* loss does not impair tumor growth, whereas cells grown *in vitro* are sensitive to BRCA2 loss. Functional studies showed a critical vulnerability to PARPi therapy in the absence of *BRCA2*. These findings provide support for PARPi therapy in the rare HCCs with *BRCA2* loss.



Disclosures: Salah Adlat: Nothing to Disclose, Chunmiao Cai: Nothing to Disclose, Dingzi Yin: Nothing to Disclose, Markcus Lee: Nothing to Disclose, Kirk Wangensteen: Nothing to Disclose

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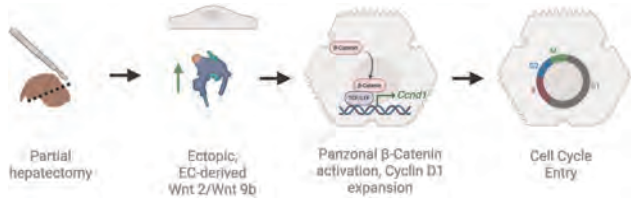
◆ 4273 | ECTOPIC ACTIVATION OF THE WNT/β-CATENIN/CYCLIN-D1 AXIS DURING EARLY LIVER REGENERATION

Tyler Yasaka[1] Brandon Lehrich[1] Shuchang Liu[1] Satdarshan (Paul) Monga[1], [1]University of Pittsburgh

Background: The hepatic lobule displays functional polarity along the portal-central axis, a phenomenon known as metabolic zonation (MZ), in which hepatocytes engage in distinct metabolic roles from the portal vein (zone 1; Z1) to the central vein (zone 3; Z3), with zone 2 (Z2) residing in the middle. During homeostasis, Wnt/β-catenin signaling maintains Z3 identity by promoting Z3 gene expression. Further, we have shown that ablation of hepatocyte β-catenin abrogates Z2 Cyclin-D1 expression both at baseline and following partial hepatectomy (PH), where loss of β-catenin results in delayed liver regeneration (LR). In wild-type livers, Cyclin-D1 expands across the entire lobule from 24 hours (24h)-96h post-PH, enabling the rapid proliferative response. Despite its established role in homeostasis and proliferation, the function of Wnt/β-catenin signaling during the acute regenerative response, particularly in relation to the proliferative "wave" across the lobule, remains poorly understood. **Methods:** Immunohistochemistry (IHC) was used to observe protein expression of key zonation markers at 1-, 3-, 6-, and 10-hours post-PH in both wild type and AAV8-Cre/CTNNB1-Floxed (CTNNB1-KO) murine models. Immunofluorescence (IF) staining for β-galactosidase in Axin2-LacZ reporter mice was used to assess β-catenin activity during early LR. Single cell spatial transcriptomics (SCST) was leveraged to investigate the spatiotemporal changes in expression of 100 zonated genes at these time points. **Results:** IHC revealed Z2 Cyclin-D1 expansion as early as 10h post-PH, which was abrogated in CTNNB1-KO mice. Further, IF of β-galactosidase in Axin2-LacZ reporter mice demonstrated ectopic expression extending towards the portal vein at 10h, indicating panzonal β-catenin activation at this time point. Unbiased clustering of SCST data captured spatiotemporal trends, delineating distinct sets of zonated cell populations at baseline, from 1-6h, and at 10h post-PH. We observed panzonal expansion of β-catenin targets such as *Axin2* and *Glul* along with ectopic expression of the Z3 genes *Wnt2* and *Wnt9b* in Z2 and Z1 endothelial cells. **Conclusion:** Our study identifies dramatic transcriptional changes during early LR from 1-10h post-PH. These include panzonal upregulation of endothelial cell Wnt2 and Wnt9b and hepatocyte β-catenin targets. We further demonstrate ectopic β-catenin activation during early LR occurring in tandem with β-catenin-dependent expansion of Cyclin-D1 in Z2, elucidating a Wnt/β-catenin/Cyclin-D1 axis which is transiently upregulated across the lobule to enable cell cycle entry for rapid proliferation from 40-96h post-PH, thereby serving a central role in LR.



Disclosures: Tyler Yasaka: Nothing to Disclose, Brandon Lehrich: Nothing to Disclose, Shuchang Liu: Nothing to Disclose, Satdarshan (Paul) Monga: Mermaid Bio: Advisor, Vicero: Advisor, AntlerA: Advisor, Genentech: Speaking and Teaching, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Mermaid Bio: Consultant, Fog Pharmaceuticals: Grant/Research Support, Surrozen: Consultant, Genentech: Independent Contractor

◆ 4274 | CANCER-ASSOCIATED FIBROBLAST (CAF) ATLAS IN HCC AND ASSOCIATION WITH IMMUNOTHERAPY RESPONSE

Guillem Cano Segarra[1] Ana Hernández de Sande[1] Anna Vila[1] Albert Gris-Oliver[1] Marta Piqué-Gili[1] David Camell-Raventos[2] Ezequiel Mauro[1] Agavni Mesropian[1] Ugne Balaseviciute[1] Marcus Zeitlhoefler[3] Sarah Cappuyns[4] Yulei Wang[5] Jeroen Dekervel[6] Daniela Sia[3] Roser Pinyol[1] Josep M Llovet[1], [1]Liver Cancer Translational Research Laboratory, IDIBAPS, Hospital Clínic, Universitat de Barcelona, [2]Liver Cancer Translational Research Laboratory, Hospital Clínic, Universitat de Barcelona, [3]Mount Sinai Liver Cancer Program, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, [4]Digestive Oncology, Department of Gastroenterology, University Hospitals Leuven, [5]Translational Medicine Oncology Genentech, Inc, [6]Laboratory of Clinical Digestive Oncology, Department of Oncology, KU Leuven

Background: The combination of atezolizumab+bevacizumab (atezo+bev) is a first-line therapy for advanced-stage hepatocellular carcinoma (HCC). Cancer-associated fibroblasts (CAF) support survival of cancer cells by promoting immunosuppression. This study aims to characterize CAF subtypes in HCC and evaluate their impact on immunotherapy responses. **Methods:** CAF subtypes were identified by integrating a single-cell atlas from 7 HCC cohorts (192 patients; 446,075 cells). Stromal fractions were defined using Louvain clustering and established signatures. CAF

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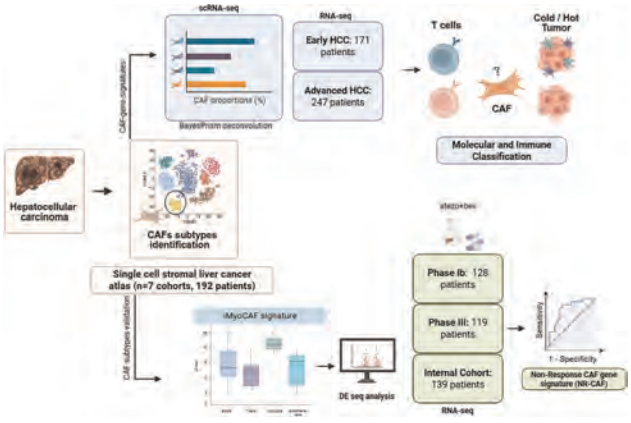
proportions in early and late HCC (n = 171 & 247 patients) were inferred using RNAseq datasets by applying 4 single cell-derived CAF signatures with BayesPrism. Differential Expression and LASSO analyses applied to atezo+bev scRNAseq HCC data (20 patients; 40,598 cells) allowed defining a non-response CAF gene signature (NR-CAF) which was tested and validated in bulk RNAseq (386 atezo+bev cases; 33% responders, 67% non-responders). **Results:** CAFs represented ~10% of the cells identified by the single-cell HCC atlas (5% and 15% in early and advanced HCCs, respectively). We identified 6 CAF clusters, each with a unique transcriptional profile. Four CAF subtypes presented with high specificity to be used in deconvoluting RNAseq data. The most abundant CAF cluster (myofibroblastic CAFs; iMyoCAFs) was present in early (38%) and advanced (81%) HCC, displayed both inflammatory and extracellular matrix remodeling features and was enriched in the molecular proliferative class (S1, 42%-51% vs others subtypes; $p < 0.001$). Further, inflamed HCCs were significantly enriched with endothelial-like CAFs (eCAFs; 80%-83%) and iMyoCAFs (75%-94%), being the latter specifically enriched in immune exhausted tumors (41%-76% vs others; $p < 0.001$). None of the CAF clusters was associated with atezo+bev response. Conversely, the NR-CAF signature accurately segregated non-responders (242/258, 94%) in the IMbrave150 cohort (AUCs 0.77; CI 0.71-0.83) and in-house cohort (AUC 0.73; CI 0.63-0.83); and was enriched in non-inflammed tumors. **Conclusion:** CAFs represent 10% of the HCC tumor microenvironment cells. iMyoCAF - the most abundant subtype, particularly in advanced HCC- is characterized by proliferative features and an immune-exhausted phenotype. The NR-CAF signature demonstrated high accuracy in identifying non-responders to immunotherapy, thus providing insights on its potential clinical utility.



Disclosures: Guillem Cano Segarra: Nothing to Disclose, Ana Hernández de Sande: Nothing to Disclose, Anna Vila: Nothing to Disclose, Albert Gris-Oliver: Nothing to Disclose, Marta Piqué-Gili: Nothing to Disclose, David Camell-Raventos: Nothing to Disclose, Ezequiel Mauro: Nothing to Disclose, Agavni Mesropian: Nothing to Disclose, Ugne Balaseviciute: Nothing to Disclose, Marcus Zeitlhoefler: Nothing to Disclose, Sarah Cappuyns: Nothing to Disclose, Yulei Wang: Genentech/Roche: Employee, Jeroen Dekervel: Nothing to Disclose, Daniela Sia: Nothing to Disclose, Roser Pinyol: Nothing to Disclose, Josep M Llovet: Nothing to Disclose

◆ 4275 | TRANSCRIPTOMIC AND CELLULAR TRAITS OF LIVER FIBROSIS REGRESSION IN ON-TREATMENT CHRONIC HEPATITIS B PATIENTS

Wei Chen[1] Shuyan Chen[2] Yameng Sun[2] Wen Zhang[2] Hong Li[2] Wenyue Wu[2] Ruoyu Gao[2] xiaoning wu[2] Xuzhen Yan[2] Aiting Yang[2] Natalia Nieto[3] Hong You[4], [1]Capital Medical University, China, [2]Beijing Friendship Hospital, Capital Medical University, [3]University of Illinois at Chicago, [4]Capital Medical University

Background: Antiviral therapy (AVT) fails to consistently induce liver fibrosis remission in chronic hepatitis B (CHB) patients. This study aimed to elucidate transcriptomic and cellular signatures underlying fibrosis regression in CHB patients receiving AVT. **Methods:** We longitudinally analyzed 68 liver biopsy (LBx) specimens from 42 CHB patients with liver fibrosis undergoing AVT. Bulk or single-cell RNA sequencing analysis, deconvolution analysis, and multiplex immunofluorescence were performed. **Results:** Transcriptomic profiling of serial LBx samples collected at baseline, 78 weeks, and 260 weeks post-AVT revealed that fibrosis regressors exhibited rapid transcriptomic and functional reprogramming throughout treatment. Baseline characterization identified a triad of features in regressors: (1) an activated immune microenvironment, (2) suppressed metabolic signaling pathways, and (3) upregulated cell cycle (CC)-related gene expression. Stratification of CHB patients into CClow and CChigh subgroups based on baseline CC gene expression demonstrated that CChigh status predicted fibrosis regression during AVT across two independent cohorts. Integrated single-cell RNA sequencing, deconvolution analysis, and multiplex immunofluorescence identified a novel CD8+ T-cell subset—proliferative T (Tpro) cells—as the primary cellular driver of CC-associated transcriptional changes. Tpro cells were functionally characterized by (1) heightened proliferative potential, (2) tissue-resident memory features, and (3) enhanced cytotoxic activity. Patients with baseline Tpro cell enrichment exhibited superior control of low-level viremia and increased odds of fibrosis regression during long-term AVT. **Conclusion:** This study defines three

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critical attributes of CHB fibrosis regressors: (1) rapid initiation of transcriptomic and functional reprogramming post-AVT, (2) baseline CChigh transcriptional signatures, and (3) pre-treatment enrichment of cytotoxic Tpro cells. These findings provide novel insights for risk stratification, therapeutic monitoring, and personalized management of on-treatment CHB patients with liver fibrosis.

Disclosures: Wei Chen: Nothing to Disclose, Shuyan Chen: Nothing to Disclose, Yameng Sun: Nothing to Disclose, Wen Zhang: Nothing to Disclose, Hong Li: Nothing to Disclose, Wenyue Wu: Nothing to Disclose, Ruoyu Gao: Nothing to Disclose, xiaoning wu: Nothing to Disclose, Xuzhen Yan: Nothing to Disclose, Aiting Yang: Nothing to Disclose, Natalia Nieto: Nothing to Disclose, Hong You: Nothing to Disclose

◆ 4276 | THE TEXAS HISPANIC HCC COLLABORATIVE: FIRST RESULTS: OF AN EXOME-WIDE RARE, DELETERIOUS VARIANT ANALYSIS OF HEPATOCELLULAR CARCINOMA IN HISPANIC AMERICAN INDIVIDUALS

Aaron Thrift[1] Xiangnan Li[1] Spiridon Tsavachidis[1] Sumeet Asrani[2] Amit Singal[3] Hashem El-Serag[1] Yanhong Liu[1], [1]Baylor College of Medicine, [2]Baylor University Medical Center, [3]University of Texas Southwestern Medical Center

Background: Hispanic Americans in Texas have the highest incidence rate of hepatocellular carcinoma (HCC) in the United States. Differential genetic predisposition could influence racial/ethnic differences in HCC risk. In particular, rare and low frequency variants may play an essential role in the etiology of HCC. Thus, we conducted the first exome-wide rare, deleterious (or pathogenic, damaging, or functional important) variant analysis of HCC in Hispanic American individuals to identify potential novel predisposition genes and pathways for HCC in this population. **Methods:** We performed whole-exome sequencing on constitutional DNA extracted from blood of 455 Hispanic HCC cases and 264 Hispanic controls. Variants were prioritized and filtered based on minor allele frequencies $<5\%$ in gnomAD global population, enrichment of rare and potential deleterious variants in cases (risk alleles) or controls (protective alleles), and a high pathogenicity prediction (CADD score ≥ 15). Allelic association analyses of single-variant and gene-based burden tests of multiple variants were performed. **Results:** We identified 38 rare variants with deleterious effects. Among the top 10 candidates were three in *PABPC3* (Polyadenylate-binding protein 3): p.G574R (OR = 6.9), p.M579I (OR = 6.9), and p.L588V (OR = 4.3); and two in *PDCD7* (Programmed cell death protein 7): p.R222W (OR = 20) and p.P685L (OR = 9.8). The most significant variant was p.V678M (OR = 20) in *CILP* (Cartilage Intermediate Layer Protein 1). Other notable findings included a pathogenic *ClinVar*-reported p.R119W (OR = 13) in *RTN4R* (Reticulon-4 receptor), p.R429C (OR = 8.5) in *CGN* (Cingulin), and a stop-gain truncating variant p.E6X (OR = 5.3) in *HMGA2* (High Mobility Group A2). There 18 potentially novel variants that require follow up. **Conclusion:** Our results extend the catalogue of regions associated with HCC and highlight the importance of germline rare coding variants in HCC susceptibility. These analyses are ongoing and will contribute to knowledge about the genetic architecture of HCC.

Disclosures: Aaron Thrift: Nothing to Disclose, Xiangnan Li: Nothing to Disclose, Spiridon Tsavachidis: Nothing to Disclose, Sumeet Asrani: Nothing to Disclose, Amit Singal: Genentech: Consultant, AstraZeneca: Consultant, Bayer: Consultant, Eisai: Consultant, Exelixis: Consultant, Merck: Consultant, Elevar: Consultant, FujiFilm Medical Sciences: Consultant, Exact Sciences: Consultant, Glycotest: Consultant, Boston Scientific: Consultant, Sirtex: Consultant, HistoSonics: Consultant, HelioGenomics: Consultant, ImCare: Consultant, DELFI: Consultant, Curve Biosciences: Consultant, Catalym: Consultant, Verve: Consultant, Hashem El-Serag: Nothing to Disclose, Yanhong Liu: Nothing to Disclose

◆ 4277 | A LIVER-TARGETING LNCRNA MOTIF FOR DURABLE GLUCOSE AND LIPID LOWERING: GULF AS A FIRST-IN-CLASS THERAPEUTIC AGENT

Haiming Cao[1], [1]National Institutes of Health

Background: RNA-based therapeutics have gained significant momentum with the success of mRNA vaccines and siRNA/antisense oligonucleotide (ASO) drugs. However, no FDA-approved therapies currently target long non-coding RNAs (lncRNAs)—the most abundant and largely untapped class of human transcripts. We identified a liver-enriched human lncRNA, GULL (GlUcose and Lipid Lowering), with potent metabolic regulatory activity and therapeutic promise. **Methods:** Expression quantitative trait locus (eQTL) analyses were performed to link hepatic GULL expression to improved metabolic traits in humans. Functional characterization involved adenoviral and AAV-mediated overexpression of GULL in mouse liver. RNA pulldown assays identified CRTC2 as a key GULL-binding partner. To identify a druggable element, we mapped the minimal CRTC2-binding region on GULL—termed GULF—and synthesized GalNAc-conjugated GULF

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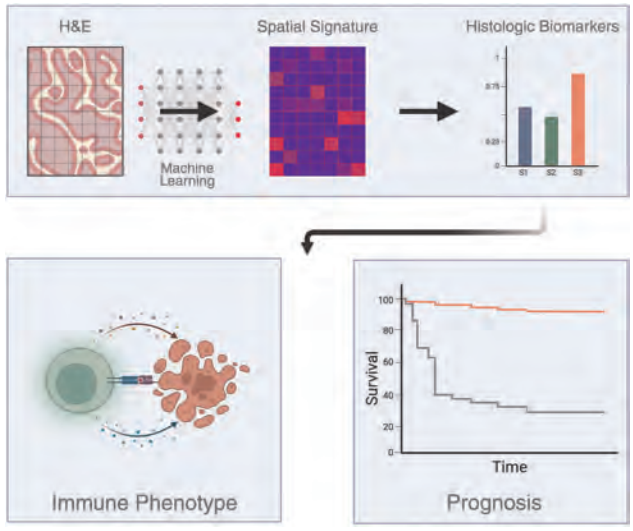
oligonucleotides for targeted liver delivery. **Results:** GULL overexpression in mice rapidly reduced circulating and hepatic triglyceride levels and significantly enhanced glucose tolerance within one week. Prolonged expression further improved insulin sensitivity (HOMA-IR), reduced HbA1c, and decreased body weight. Mechanistically, GULL interacts with CRTC2, thereby modulating gluconeogenesis through CREB and lipogenesis via SREBP1. A single dose of GalNAc-GULF led to marked improvements in glucose and lipid metabolism in obese mice, with effects sustained for over one month—surpassing the duration of standard treatments like metformin. The GULF motif (~30 nucleotides) is comparable in size to clinically approved siRNA and ASO drugs, enabling compatibility with established RNA delivery platforms. **Conclusion:** GULF represents the first-in-class lncRNA-derived RNA therapeutic motif for metabolic disease, demonstrating robust, long-lasting metabolic benefits through liver-targeted delivery. These findings establish a new therapeutic paradigm leveraging lncRNA biology to expand the scope of RNA-based drug development.
Disclosures: Haiming Cao: Nothing to Disclose

4278 | INFERRING SPATIAL SUBTYPE SIGNATURES OF HEPATOCELLULAR CARCINOMA FROM HISTOLOGIC IMAGES: A COMPUTATIONAL PATHOLOGY APPROACH

Tyler Yasaka[1] Po-Yuan Chen[1] Rebekah Dadey[1] Riyue Bao[1] Satdarshan (Paul) Monga[1] Yu-Chiao Chiu[1],
[1]University of Pittsburgh

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality. The Hoshida system stratifies HCC into 3 subtypes (S1, S2, and S3) with distinct pathomolecular features. With the advancement of clinical trials for targeted therapies, tissue biopsies are being increasingly utilized. Thus, there is an emerging opportunity to pioneer the use of computational pathology approaches to advance precision medicine for HCC. **Methods:** We accessed publicly available spatial transcriptomics data, paired with corresponding hematoxylin and eosin (H&E) images, from 12 HCC slides. Moran's I was used to characterize the spatial correlations between S1, S2, and S3 subtypes, and spatial deconvolution was performed to estimate the cell type composition of sequenced spots and assess their relationship with subtype signatures. The H&E images were partitioned into tiles corresponding to the spatial transcriptomic spots. Building on a deep learning foundation model, neural networks were trained to predict each signature (S1, S2, and S3) from the H&E tiles and were evaluated using leave-one-out cross-validation. External validation was performed on a second spatial transcriptomic dataset of 2 HCC samples. Trained models were then applied to H&E whole-slide images from HCC patients in The Cancer Genome Atlas (TCGA; $n = 350$) and from an in-house cohort ($n = 11$). Tile-level predictions were averaged to obtain a patient-level histologic score for each signature (HIST_S1, HIST_S2, and HIST_S3). We assessed the correlation between the histologic scores available for each patient H&E and (1) their *TP53* and *CTNNB1* mutation status, (2) immune phenotype, and (3) overall survival (OS). **Results:** Spatial analysis revealed strong spatial autocorrelation (0.79-0.92; $p < 0.001$) of S1, S2, and S3 signatures. The S1 signature was associated with non-parenchymal cells, while S2 and S3 signatures were associated with hepatocytes. Our models achieved AUROCs of 0.65, 0.68, and 0.678 for S1, S2, and S3, respectively. Histologic sores positively correlated with their respective bulk RNA signatures ($p = 0.03$; $p < 0.001$; $p < 0.001$). While HIST_S1 and HIST_S2 were associated with *TP53* mutation ($p = 0.019$; $p < 0.001$), HIST_S3 was associated with *CTNNB1* mutation ($p < 0.001$). HIST_S1 and HIST_S2 were elevated in T cell-inflamed tumors ($p = 0.102$; $p = 0.024$), while HIST_S3 was increased in immune non-T cell-inflamed tumors ($p = 0.074$). Finally, all models were prognostic, with HIST_S1 and HIST_S2 portending lower OS ($p = 0.005$; $p < 0.001$) and HIST_S3 predicting improved OS ($p < 0.001$). **Conclusion:** Our results demonstrate the use of deep learning models to extract histologic biomarkers from H&E images. These signatures recapitulate established paradigms in HCC, inform immune phenotype, and provide improved prognostic value compared to bulk RNA-based signatures alone. This highlights a promising role for computational pathology in HCC precision medicine.



Disclosures: Tyler Yasaka: Nothing to Disclose, Po-Yuan Chen: Nothing to Disclose, Rebekah Dadey:

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Nothing to Disclose, Riyue Bao: Nothing to Disclose, Satdarshan (Paul) Monga: Mermaid Bio: Advisor, Vicero: Advisor, AntlerA: Advisor, Genentech: Speaking and Teaching, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Mermaid Bio: Consultant, Fog Pharmaceuticals: Grant/Research Support, Surrozen: Consultant, Genentech: Independent Contractor, Yu-Chiao Chiu: Nothing to Disclose

4279 | AI ASSISTED IMAGING ANALYSIS IMPROVING RISK PROGNOSTICATION OF HEPATOCELLULAR CARCINOMA IN VETERANS WITH CHRONIC LIVER DISEASE

Peng Zhang[1] Patrick Belancourt[2] Sven Holcombe[1] Sameer Saini[1] Grace Su[3], [1]University of Michigan, [2]VA Ann Arbor Healthcare System, [3]University of Michigan Medical Center

Background: Hepatocellular carcinoma (HCC) is a leading cause of death in patients with chronic liver disease (CLD) due to late diagnosis. Surveillance guidelines from the AASLD recommend identification of high-risk patients, particularly those with cirrhosis. But cirrhosis is underdiagnosed, and surveillance rates remain unacceptably low. Of the alternative strategies to identify high risk individuals, FIB 4 is one of the most predictive but may fail to capture nuanced disease characteristics. This study evaluates an automated computed tomography (CT) imaging analysis pipeline to predict 5-year HCC risk in Veterans with CLD, integrating high-dimensional radiomic and clinical features to improve accuracy over FIB-4. **Methods:** We developed and utilized a fully automated deep learning pipeline to extract high-dimensional radiomic features from liver and spleen regions on CT images, transforming unstructured imaging data into quantitative metrics, including textural, morphological, and intensity-based characteristics. These features were combined with clinical variables to create a comprehensive dataset. Competing risk analysis was conducted using gradient boosting models to predict 5-year HCC risk, accounting for competing events including non-HCC mortality and hepatic decompensation. The predictive performance of the combined model was compared to the standard FIB-4 model using the area under the receiver operating characteristic curve (AUROC). Statistical comparison was conducted through DeLong's test with 5-fold cross-validation to ensure robust model evaluation and prevent overfitting. **Results:** We analyzed a regional cohort of 4,615 [GS1] Veterans with CLD who had an incidental clinical CT scan at the time of CLD diagnosis between 01/2008 to 12/2014. The combined model, integrating clinical and radiomic features, achieved an AUROC of 0.84 (95% CI: 0.80–0.88) for 5-year HCC risk prediction, significantly outperforming the FIB-4 model, which yielded an AUROC of 0.80 (95% CI: 0.75–0.84). The performance difference was statistically significant ($p = 0.038$), highlighting the added predictive value of radiomic features extracted from liver and spleen CT images. **Conclusion:** An automated CT imaging analysis pipeline, combining high-dimensional radiomic features with clinical data, modestly improves 5-year HCC risk prediction in patients with CLD. Future work should focus on validation in diverse cohorts, integration with other imaging modalities, and clinical utility.

Disclosures: Peng Zhang: Nothing to Disclose, Patrick Belancourt: Nothing to Disclose, Sven Holcombe: Nothing to Disclose, Sameer Saini: Nothing to Disclose, Grace Su: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose

4280 | TARGETED RESEQUENCING IDENTIFIES PREDISPOSING GENETIC CORRELATES IN LEAN AND OBESE MASH SUBTYPES: FINDING THE MISSING HERITABILITY IN INDIAN POPULATION

Pramod Gautam[1] Nisha Choudhary[2] Vipin Singh[2] Mamta Maurya[2] Nikita Yadav[2] Ankit Bhardwaj[2] Rajan Vijayaraghavan[2] Chhagan Bihari[2] Shiv Kumar Sarin[2], [1]Institute of Liver and Biliary Sciences, [2]ILBS

Background: Lean metabolic dysfunction-associated steatohepatitis (MASH) is part of the MASLD spectrum. The metabolic dysfunction in lean-MASH among other things can be genetically precipitated. We undertook to investigate the genetic markers of this subtype of MASLD. **Methods:** We sequenced 68 genes related to MASH/MASLD pathology in 1827 patients (from Feb 23-April 25), who were stratified into Lean and Obese-MASH (BMI < 23 or > 25). We further categorized the cohort into two subgroups following their fibroscan CAP parameter (CAP $<$ 250 or $\geq$ 250) and looked for variants predisposing towards clinical phenotypes of fibrosis, Lean vs Obese-MASH, serum ALT, serum triglycerides and FIB-4 score. Following standard QC measures, the clinical impact of selected mutations was assessed by multiple professional and public databases for pathogenicity/functional effects. **Results:** From a total of 13275 genotyped non-synonymous SNPs, we filtered only those having literature supported pathogenicity assigned to them. Further we only focussed on top 10 most frequent missense variants. We found multiple genotypes to be associated with clinical phenotype and showed sex-wise variability adjusted by age (Figure 1). The significant findings includes:

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PNPLA3 and GCKR mutations irrespective of CAP parameter and sex associates with high serum ALT levels while SOD2.Ala16Val is significantly associated with high ALT levels only in patients with normal CAP values (Fig1a). Mutation in UCP2 increases the odds of Obese-MASH phenotype in Normal-CAP cohort (Fig1b). Although GCKR and PCSK9 mutations together known for hypertriglyceridemia, but we report effect size to be prominent in Normal-CAP group.

PNPLA3.Ile148Met consistently increases the LSM-based fibrosis and provides a valid lead to be a genetic marker for advanced fibrosis staging(Fig1d). Interestingly, PNPLA3.Ile148Met increases the FIB-4 score in both CAP categories with prominent variability by patient's sex(Fig1e). It is to be noted that the mutation in MBOAT7 well-studied in Caucasian populations is not found to be informative in Indian population. **Conclusion:** The present study for the first time not only aims to fill the gap in genetic propensities for lean vs obese-MASH in a large Indian cohort. The study also holds a promise in further probing into genetic correlates in sex-differences for Lean-MASH. Further it paves the way to develop a multi-SNP scoring to prognosticate liver diseases to better equip researchers and clinicians alike.

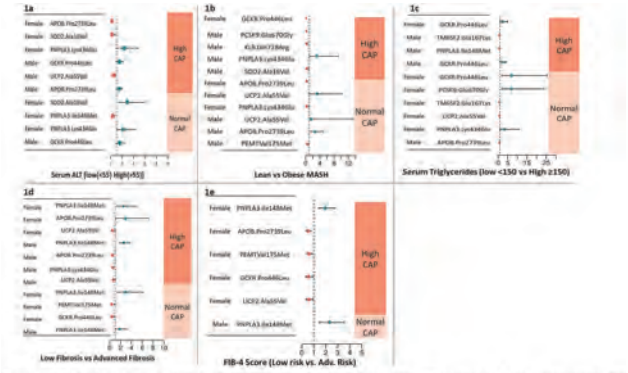

Figure1- SNP association and odds ratio for serum triglycerides, Lean- and Obese-MASH, serum ALT and fibrosis grades and FIB-4 Score. Models with lowest AIC (Akaike information) only are shown. All Odds ratio depicted are statistically significant.

Disclosures: Pramod Gautam: Nothing to Disclose, Nisha Choudhary: Nothing to Disclose, Vipin Singh: Nothing to Disclose, Mamta Maurya: Nothing to Disclose, Nikita Yadav: Nothing to Disclose, Ankit Bhardwaj: Nothing to Disclose, Rajan Vijayaraghavan: Nothing to Disclose, Chhagan Bihari: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

4281 | CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL IS ASSOCIATED WITH AN INCREASED RISK OF HCC IN PATIENTS WITH MASLD

Gopanandan Parthasarathy[1] Renumathy Dhanasekaran[1] Christopher Maximilian Arends[1] Brian Sharber[2] Yash Pershad[3] Siddhartha Jaiswal[1] Alexander Bick[2], [1]Stanford University, [2]Vanderbilt University Medical Center, [3]Vanderbilt University

Background: Clonal Hematopoiesis of Indeterminate Potential (CHIP) refers to an age-associated accumulation of somatic mutations in myeloid neoplasm driver genes in hematopoietic stem cells without an overt hematological disorder. These mutations lead to dysregulated inflammatory responses in bone marrow derived macrophages and are associated with an increased risk of chronic inflammatory conditions including progression of chronic liver disease (CLD). Given that an inflammatory immune milieu in CLD is associated with hepatocellular carcinoma (HCC), we hypothesized that the presence of CHIP is associated with an increased risk of HCC among patients with metabolic dysfunction–associated steatotic liver disease (MASLD). **Methods:** We leveraged the National Institute of Health's All of Us Research program which is an ongoing US-based observational cohort study, with linked genetic and electronic health record data. CHIP has previously been ascertained using read-level whole genome sequencing data in a cohort of 98,560 participants that was released in June 2022, with an overall prevalence of CHIP of 4.8%. Individuals were enrolled between 2018 and 2021, with a median age at enrolment of 53 years (interquartile range, 37-65). Standard SNOMED codes for MASLD, MASH (metabolic dysfunction–associated steatohepatitis), MASH cirrhosis and HCC were used to identify patients with these diagnoses and those with alcohol related liver disease were excluded. According to All of Us Statistics Dissemination Policy, patient counts have been coarsened when between 1 and 20. **Results:** Among patients with any stage of MASLD (N = 6098), any HCC (N = 162), and MASLD-HCC (N = 92), CHIP was present in 361 (5.9%), < 20 (< 10%), and < 20 (< 15%) individuals respectively. The prevalence of CHIP in MASLD-HCC was greater among those without cirrhosis (15.4%), compared to with cirrhosis (7.5%). Among patients with MASLD, presence of CHIP was associated with an increased risk of developing HCC (OR = 1.96, 95% CI [1.01-3.82], $P < .05$). In a multiple logistic regression model, presence of CHIP in MASLD patients was independently associated with an increased risk of HCC, after adjusting for age, sex, and presence of cirrhosis (OR = 1.62, $P < .01$). There were no specific associations between risk of HCC and type or number of gene mutations, or the variant allele frequency. **Conclusion:** Presence of CHIP as an independent risk factor for HCC among patients with MASLD represents a potentially fibrosis-independent risk factor for HCC. This offers a clinically relevant, precision medicine-based approach to risk stratify patients with MASH and cirrhosis. Further analyses to understand the relationship between CHIP and HCC prognosis as well as treatment responses, including in the UK biobank are ongoing.

Disclosures: Gopanandan Parthasarathy: Nothing to Disclose, Renumathy Dhanasekaran: Nothing to

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Disclose, Christopher Maximilian Arends: Nothing to Disclose, Brian Sharber: Nothing to Disclose, Yash Pershad: Nothing to Disclose, Siddhartha Jaiswal: Nothing to Disclose, Alexander Bick: Nothing to Disclose

4282 | TWO DISTINCT GENETIC SUBTYPES DEFINE NON-CIRRHOTIC HCC CHARACTERIZED BY INACTIVATION OF TUMOR SUPPRESSORS (TP53, RB1, ARID1A) AND ACTIVATION OF TERT-DRIVEN ONCOGENIC PATHWAY

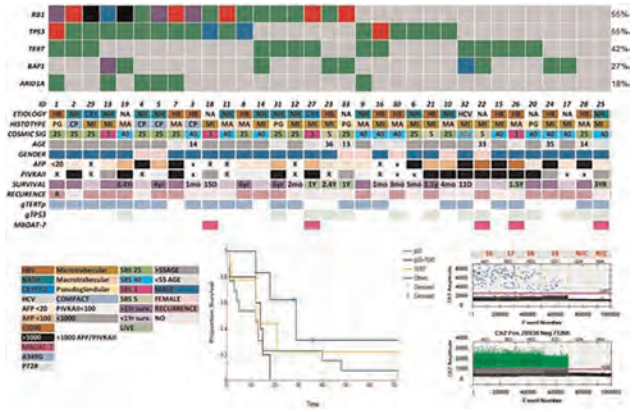
Khushboo Agrawal[1] Archana Rastogi[1] pramod Gautam[1] Vaishali Yadav[2] Rishab Shrama[1] Vanya Garg[1] Deepti Sharma[1] Nirupma Trehanipati[1] Shiv Kumar Sarin[1], [1]institute of liver and biliary sciences, [2]institute of liver nad biliary sciences

Background: There is an increase recognition of non-cirrhotic hepatocellular carcinoma (NC-HCC) in patients with MASLD and Hepatitis B. We employed targeted molecular profiling to examine the genetic landscape of NC-HCC aiming to uncover major oncodrivers and their impact on survival. **Methods:** 33 Formalin fixed NC-HCC cases were analysed using a 40 gene somatic mutation panel. DNA libraries were sequenced by NGS, aligned to hg38 (BWA), and variants called using FreeBayes. Filtering used depth and Phred score. COSMIC database was used to identify identified SBS signatures and pathogenic variants were classified via ClinVar. Digital PCR was used to validate TERT C228T hotspot. **Results:** NASH was the predominant (18/33; 57.5%) followed by HBV (12/33; 36.3%), HCV (1/33), and cryptogenic (2/33). Most patients were male (28M:5F). COSMIC mutational signature analysis revealed SBS25 (chemotherapy related, 39.4%), SBS40 (35%, C > T due to deamidation) SBS3 (DNA repair; 12.1%), SBS5 (clock-like; 9%), and SBS4 (tobacco-related; 21.2%).

Frequent gene mutations included RB1 (18/33; 54.5%), TP53 (18/33, 54.5%), TERT (14/33; 42.4%), BAP1 (9/33;27.3%), ARID1A (6/33;18.2%), and CTNNB1 (4/33;12.1%). TERT mutations were mutually exclusive with BAP1 ($P < 0.05$) and TP53 ($P < 0.1$). Co-occurring mutations of TP53 and RB1 were seen in 36.3% of cases. All TERT-mutated cases carried the hotspot C228T variant. TP53 variants included R249S linked to aflatoxin exposure. Common RB1 variants were Q846* and R7Q. p53 mutation was major driver of HBV, while TERT was prominent in NASH although not statically significant (χ^2, $P = 0.437$)

Germline variants included MBOAT7 rs641738 (78%), TERT rs2853669 (63%), and TP53 rs1042522 (42%). Rare actionable mutations included RET C611Y, KIT W557, TP53 Y220*, and a non-V600E BRAF mutation. Co-occurrence of TP53 and TERT mutations was associated with poor survival, indicating a worse prognosis (Log Rank, $P = 0.328$). BAP1 mutations showed better outcomes, though not statistically significant due to small sample size.

TERT C228T was validated by ddPCR in all 14 NGS (+ve) cases, with copy numbers ranging from 26 to 23,800/20 μL. 3 additional NGS(-ve) cases were detected at low abundance, highlighting higher sensitivity with ddPCR. **Conclusion:** NC-HCC exhibits distinct molecular subclasses: one with tumor suppressor disruption (TP53/RB1, BAP1, ARID1A), and another with oncogenic activation via TERT. BAP1 appeared as a novel signature of non-cirrhotic HCC. TERT C228T is a promising biomarker for molecular screening of HCC using sensitive ddPCR platform.



Disclosures: Khushboo Agrawal: Nothing to Disclose, Archana Rastogi: Nothing to Disclose, pramod Gautam: Nothing to Disclose, Vaishali Yadav: Nothing to Disclose, Rishab Shrama: Nothing to Disclose, Vanya Garg: Nothing to Disclose, Deepti Sharma: Nothing to Disclose, Nirupma Trehanipati: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

4283 | KIF12 DEFICIENCY UNRAVELED IN CHOLESTATIC LIVER DISEASE: LINKING ORGANELLE MISPOSITIONING TO HEPATIC PATHOLOGY

Anubha Seth[1] Joseph Brancale[1] Nina Dashti-Gibson[2] Chigoziri Konkwo[3] Silvia Vilarinho[1], [1]Yale University, [2]Virginia Commonwealth University, [3]Icahn School of Medicine at Mount Sinai

Background: Cholestasis is a major cause of pediatric liver transplantation, yet effective treatments for its underlying causes remain scarce, pointing to a critical

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unmet medical need. Recent studies, including ours, uncovered that biallelic rare loss-of-function mutations in KIF12 cause pediatric high-GGT cholestasis, fibrosis, ductular reaction, and bile duct loss. Despite the discovery of kinesins over 40 years ago, their roles in the liver are poorly understood. While KIF12 has been putatively identified as a microtubule-associated motor protein, our understanding of its precise functionality and role in cholestasis pathogenesis remains elusive. **Methods:** Human liver single-cell atlas showed that KIF12 is predominantly expressed in cholangiocytes. To model the patient variant, we introduced homozygous Arg219* in iPSCs using CRISPR-Cas9. WT and Arg219 * iPSCs were then differentiated into cholangiocyte-like cells (iCCs) and 3D biliary organoids. Confocal microscopy is used to examine protein and organelle localization. Bulk RNAseq identified transcriptomic changes. A lentiviral overexpression approach was used to evaluate potential rescue effects. **Results:** WT and Arg219* iPSCs were differentiated into iCCs and validated. Arg219* iCCs showed elevated GGT activity, consistent with patient phenotype. Single-molecule TIRF microscopy showed that WT KIF12 moves along microtubules at 1.17 $\mu m^2/s$, confirming its motor protein function. RNAseq analysis identified downregulation of ARMCX1—a gene associated with mitochondria trafficking in neurons, in both Arg219* hepatic endoderm (iHE) and iCCs, relative to WT. In Arg219* iCCs, there was a striking disruption in organelle distribution, with both mitochondria and lysosomes showing a perinuclear localization. These findings were corroborated through immunostaining with organelle-specific markers. Seahorse assay also revealed a significant decrease in maximal respiration, indicating impaired mitochondrial function. Cilia were also mislocalized, as reported by immunostaining and cilia-specific assay, revealing a fourfold increase in bent cilia and intracellular cilia compared to WT. The organoid model further validated cilia's altered position in Arg219*, independent of membrane polarization. Importantly, over-expressing WT KIF12 in Arg219* rescues organelle mislocalization, including cilia defects seen in Arg219* iCCs. **Conclusion:** The KIF12-Arg219* variant leads to elevated GGT levels and transcriptional alterations with pronounced organelle mislocalization, suggesting impaired organelle trafficking. This evidence provides novel insights into the cellular and molecular mechanisms driving the pathogenesis of human cholestatic liver disease. The successful rescue of ciliary defects through KIF12 overexpression not only highlights the essential role of KIF12 but and identifies it as a promising target for therapeutic intervention.

Disclosures: Anubha Seth: Nothing to Disclose, Joseph Brancale: Nothing to Disclose, Nina Dashti-Gibson: Nothing to Disclose, Chigoziri Konkwo: Nothing to Disclose, Silvia Vilarinho: Moderna Therapeutics Inc: Grant/Research Support, Albireo: Speaking and teaching, Mirum Pharma: Consultant, Ipsen: Consultant

4284 | PLASMA CELL-FREE DNA FRAGMENTOMICS AND METHYLOMICS ANALYSIS OF INDIVIDUALS WITH GALLSTONES AND GALLBLADDER CANCER FROM THE SHANGHAI BILIARY TRACT CANCER CASE-CONTROL STUDY

Michael Daniels[1] R. Taylor Sundby[2] Ling Su[3] Xiaolin Wu[3] Bin Zhu[4] Jonathan Hernandez[5] Ann Hsing[6] Yu-Tang Gao[7] Jill Koshiol[1], [1]National Cancer Institute, [2]National Cancer Institute, Center for Cancer Research, Pediatric Oncology Branch, [3]National Cancer Institute, Center for Cancer Research, Genomics Technology Laboratory, [4]National Cancer Institute, Division of Cancer Epidemiology and Genetics, Biostatistics Branch, [5]National Cancer Institute, Center for Cancer Research, Surgical Oncology Program, [6]Stanford Cancer Center, Stanford University, [7]Shanghai Cancer Institute, Department of Epidemiology

Background: Gallstones (GS) are a key risk factor for gallbladder cancer (GBC), which is often diagnosed in advanced stages due to non-specific symptomology, inadequate screening options, and lack of sensitive and specific noninvasive biomarkers. Enzymatic methylation sequencing of circulating cell-free DNA (cfDNA) aims to noninvasively detect cancer signals through assessing fragmentomics and methylomics features, which have been minimally studied in gallbladder disease. The purpose of this project was to evaluate whether individuals with GBC display aberrant cancer-related cfDNA alterations compared to a GS control group. **Methods:** Low-coverage enzymatic methylation sequencing of cfDNA from plasma samples derived from individuals with GS ($N = 100$), and individuals with GBC ($N = 100$) from the Shanghai Biliary Tract Cancer Case-Control Study was conducted. Data were processed using a Bismark pipeline. Copy number alterations (CNAs) were determined using ichorCNA (size selected and low tumor fraction settings) with paired cfDNA samples and whole exome sequencing data from gallbladder tumor samples. Transcription factor binding site (TFBS) accessibility was determined using Griffin and end motif analyses/motif diversity score by FinaleToolkit. Differentially methylated regions (DMRs) and related features were generated using DMRichR. **Results:** Compared to GS controls, GBC cases displayed enriched shorter (90-150bp) cfDNA fragment percentages (Fig. A). CNAs were detected in 55% of GBC cases with higher detection in late-stage cancers. In GBC cases with estimated tumor fractions $> 3\%$, detected CNAs mirrored what was observed in paired

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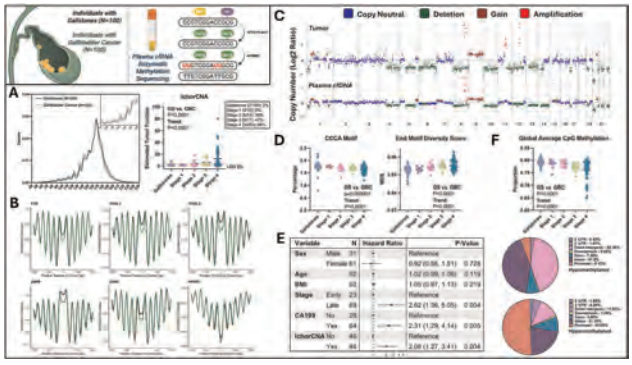
tumor tissue (Fig. C) and positively associated with worse survival (adjusted HR of 2.08; 95% CI:1.27, 3.41) (Fig. E). Increased TFBS accessibility in GBC cases was observed for AP-1 related genes (FOS, FOSL1, FOSL2, JUNB, JUND), and NFKB1 (Fig. B). Likewise, 4-mer end motifs were profoundly altered in GBC cases, as was the motif diversity score (Fig. D). Lastly, GBC cases displayed significant reductions in global average CpG methylation; hypomethylated DMRs predominantly occurred within intron and intergenic regions, whereas hypermethylated DMRs were found in promoter regions (Fig. F). **Conclusion:** Comprehensive fragmentomics and methylomics profiling of plasma cfDNA uncovered distinct cancer-associated signatures in GBC cases relative to GS controls. These noninvasive biomarkers warrant further evaluation to help identify early detection and risk stratification strategies.



Disclosures: Michael Daniels: Nothing to Disclose, R. Taylor Sundby: Nothing to Disclose, Ling Su: Nothing to Disclose, Xiaolin Wu: Nothing to Disclose, Bin Zhu: Nothing to Disclose, Jonathan Hernandez: Nothing to Disclose, Ann Hsing: Nothing to Disclose, Yu-Tang Gao: Nothing to Disclose, Jill Koshiol: Nothing to Disclose

4285 | HIGH-RESOLUTION SPATIAL TRANSCRIPTOMICS OF HCC IDENTIFIES DISTINCT IMMUNE CELL ARCHITECTURES LINKED TO RESPONSE AND RESISTANCE TO ATEZOLIZUMAB–BEVACIZUMAB THERAPY

Anna Vila[1] Marta Piqué-Gili[1] Marta Casado-Pelaez[2] Roser Pinyol[1] Ana Hernández de Sande[1] Veronica Davalos[2] Albert Gris-Oliver[1] Carla Montironi[3] Judit Peix[1] Eduard Porta[4] Daniela Grases[4] Sarah Cappuyns[5] Ezequiel Mauro[1] Guillem Cano-Segarra[1] Igor Figueiredo[6] Giorgio Ioannou[6] Edgar Gonzalez-Kozlova[6] Tim Meyer[7] Anja Lachenmayer[8] Jens Marquardt[9] Helen Reeves[10] Julien Edeline[11] Fabian Finkelmeier[12] Jörg Trojan[12] Jean-Frederic Blanc[13] Richard Hubner[14] Matthias Pinter[15] Tom Luedde[16] Arndt Vogel[17] Sacha Gnjatic[6] Daniela Sia[18] Vincenzo Mazzaferro[19] Jeroen Dekervel[20] Manel Esteller[4] Josep Llovet[21], [1]Liver Cancer Translational Research Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer, [2]Cancer Epigenetics Group, Josep Carreras Leukaemia Research Institute (IJC), [3]Pathology Department and Molecular Biology Core, Hospital Clínic of Barcelona, Barcelona, Spain, [4]Josep Carreras Leukemia Research Institute (IJC), [5]Digestive Oncology, Department of Gastroenterology, University Hospitals Leuven, [6]Department of Immunology and Immunotherapy, Icahn School of Medicine at Mount Sinai, [7]Research Department of Oncology, UCL Cancer Institute, University College London, [8]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, [9]University of Lübeck, [10]The Newcastle University Centre for Cancer, Newcastle University, [11]. Department of Medical Oncology, Centre Eugène Marquis, Rennes, France, [12]Department of Gastroenterology, University Liver and Cancer Centre, Frankfurt, Germany, [13]Department of Hepatogastroenterology and Medical Oncology, CHU de Bordeaux Hôpital Haut-Lévêque, [14]Department of Medical Oncology, The Christie NHS Foundation Trust, Wilmslow Road, Manchester, [15]Division of Gastroenterology and Hepatology, Department of Medicine III,Medical University of Vienna, [16]Department of Gastroenterology, Hepatology and Infectious Diseases, University Hospital Dusseldorf, [17]University of Toronto, [18]Mount Sinai Liver Cancer Program, Division of Liver Diseases, Tisch Cancer Institute, ISMMS, [19]Department of Oncology and Hemato-Oncology, University of Milan, Milan, [20]Laboratory of Clinical Digestive Oncology, Department of Oncology, KU Leuven, [21]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: HCC patients at advanced stage receive atezolizumab + bevacizumab (atezo+bev) as first-line treatment, eliciting objective responses in ~30% of patients. $CD8^+$ T exhausted cells (CD8_Tex) and $CXCL10^+$ macrophages (Macro_CXCL10) are associated with treatment efficacy, whereas the presence of $CD14^+$ monocytes (Mono_CD14) and immunosuppressive $TREM2^+$ macrophages (Macro_TREM2) alongside these populations was a trait of resistant tumors. Our hypothesis is that the spatial location and the distance among these immune populations fundamentally influence treatment response. **Methods:** Spatial transcriptomics analysis with the Xenium Prime 5000-gene panel customized with 100 additional target genes (10x Genomics) was used to profile 14 HCC samples: 11 inflamed tumors (5 responders and 6 non-responders to atezo+bev) and 3 non-inflamed resistant tumors, all obtained prior to atezo+bev therapy. The distance between cell types was calculated using the frNN function ("dbscan" R package). Specifically, we

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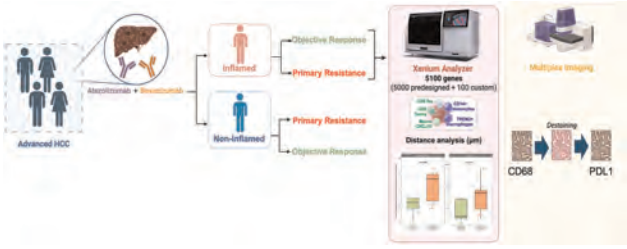
defined a 300-μm search radius around each target cell and computed the distance to the nearest-neighboring cell type of interest. The spatial location of Macro_CXCL10 was validated by multiplexed immunohistochemistry (IHC) of $CD68^{pos}$ $PDL1^{pos}$ $TREM2^{neg}$. **Results:** A total of 2.4 million cells were profiled from the 14 samples by spatial transcriptomics. Within inflamed tumors, the CD8_Tex and Macro_CXCL10 distribution differed between atezo+bev responders and non-responders. Particularly, Macro_CXCL10 and CD8_Tex laid significantly closer to malignant cells (median distances of 80.2μm and 82.0μm, respectively) in responders compared to resistant tumors (median distance of 117.4μm and 135.8μm, respectively; $p = 0.04$ and $p = 0.1$). In addition, resistant tumors exhibited both an accumulation of Macro_CXCL10 at the tumor margins -validated by multiplexed IHC- and an increased proportion of Mono_CD14 (5.2% *vs* 1.3% of all immune cells; $p = 0.02$), with a shorter median distance to Macro_TREM2 (82 μm *vs.* 118 μm in responders; $p = 0.02$) and CD8_Tex (80.5μm *vs* 131μm in responders; $p = 0.02$). **Conclusion:** Single-cell spatial transcriptomics of HCC tumors from atezo +bev-treated patients revealed that response was associated with Macro_CXCL10 and CD8_Tex being located closer to malignant cells, while Macro_CXCL10 was confined to the tumor periphery in resistant tumors. The presence of immunosuppressive niches composed of Mono_CD14 and Macro_TREM2 cells was a characteristic trait of resistance.



Disclosures: Anna Vila: Nothing to Disclose, Marta Piqué-Gili: Nothing to Disclose, Marta Casado-Pelaez: Nothing to Disclose, Roser Pinyol: Nothing to Disclose, Ana Hernández de Sande: Nothing to Disclose, Veronica Davalos: Nothing to Disclose, Albert Gris-Oliver: Nothing to Disclose, Carla Montironi: Nothing to Disclose, Judit Peix: Nothing to Disclose, Eduard Porta: Nothing to Disclose, Daniela Grases: Nothing to Disclose, Sarah Cappuyns: Nothing to Disclose, Ezequiel Mauro: Nothing to Disclose, Guillem Cano-Segarra: Nothing to Disclose, Igor Figueiredo: Nothing to Disclose, Giorgio Ioannou: Nothing to Disclose, Edgar Gonzalez-Kozlova: Nothing to Disclose, Tim Meyer: MSD: Grant/Research Support, Signant Health: Consultant, Roche: Consultant, Astra Zeneca: Consultant, Geubet: Consultant, grey wolf: Consultant, Anja Lachenmayer: roche: Advisor, Astra Zeneca: Advisor, CAScination: Advisor, Jens Marquardt: AstraZeneca: and Grant Support, Eisai: Advisor, MSD: Speaking and Teaching, NovoNordisk: Advisor, Roche: Advisor, Merz: Speaking and Teaching, Falk: Speaking and Teaching, Helen Reeves: Nothing to Disclose, Julien Edeline: Roche: Consultant, AstraZeneca: and speaker and institutional funding of research, AstraZeneca: and speaker and institutional funding of research, Fabian Finkelmeier: Nothing to Disclose, Jörg Trojan: Nothing to Disclose, Jean-Frederic Blanc: Roche: Speaking and Teaching, astra-zeneca: Speaking and Teaching, BMS: Consultant, MSD: Advisor, Richard Hubner: Servier: Consultant, Sirtex: Speaking and Teaching, Novartis: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Pfizer: Advisor, Roche: Speaking and Teaching, Matthias Pinter: BMS: Consultant, AstraZeneca: Consultant, Eisai: Consultant, Ipsen: Speaking and Teaching, Roche: Consultant, MSD: Speaking and Teaching, Tom Luedde: Nothing to Disclose, Arndt Vogel: Roche: Advisor, Sacha Gnjatic: Patent on multiplex immunohistochemistry, unlicensed: Royalties or patent beneficiary, Daniela Sia: Nothing to Disclose, Vincenzo Mazzaferro: Nothing to Disclose, Jeroen Dekervel: Nothing to Disclose, Manel Esteller: Nothing to Disclose, Josep Llovet: Nothing to Disclose

4286 | CARDIOMETABOLIC COMORBIDITIES ARE CAUSAL FOR HEPATIC STEATOSIS: MENDELIAN RANDOMIZATION ANALYSIS

Blake Czapla[1] Stephan Buch[2] Eric Trepo[3] Vincent Chen[4], [1]University of Michigan, [2]Uniklinikum Dresden, [3]Université libre de Bruxelles, [4]University of Michigan Medical Center

Background: Metabolic-associated steatosis liver disease (MASLD) and metabolic alcohol-related liver disease (MetALD) are characterized by hepatic steatosis and cardiometabolic risk factors (CMRF), with or without alcohol intake. However, whether all CMRF are causal for hepatic steatosis is unclear. We used genetic cause inference analysis using Mendelian randomization to investigate causality of CMRF on steatosis. **Methods:** We conducted two-sample Mendelian randomization to assess CMRF effects (exposures) on liver outcomes, using data from genetic variants associated at $p < 5x10^{-8}$ in GWAS in European populations. The primary analysis utilized inverse variance weighting (IVW) and a sensitivity analysis used Egger which can identify horizontal pleiotropy. Effects were reported as number of standard deviation (SD) unit change in the outcome per SD change in the predictor. Exposures were alcohol intake (27 instruments, 274,424 participants); BMI (1,082 instruments, 456,426 participants); Systolic blood pressure (SBP)

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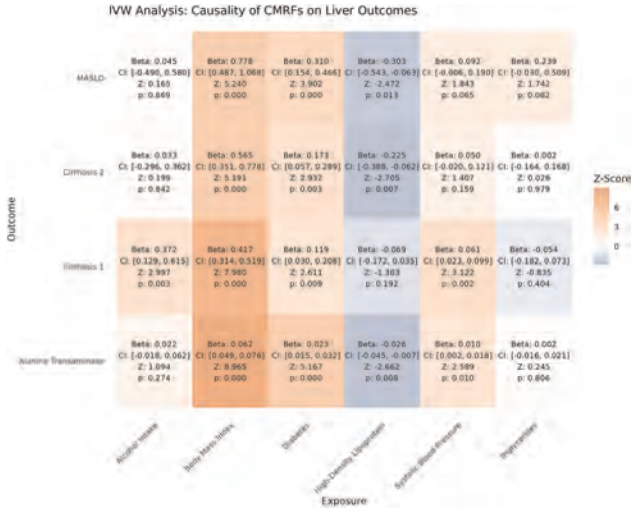
(18 instruments, 220,501 participants); type 2 diabetes (425 instruments, 1,042,540 participants); HDL (379 instruments, 1,244,544 participants); and triglycerides (TGs) (388 instruments, 1,253,236 participants). The effect of these instruments on exposures were from published studies on ALT (222,603 participants), cirrhosis (1,580,010 and 69,589 participants), and MASLD (228,992). **Results:** Mendelian randomization revealed BMI was positively associated with ALT (β = 0.062 [0.049, 0.076], p = 3.1e-19), cirrhosis (β = 0.416 [0.314, 0.519], p < 1.5e-15), and MASLD (β = 0.778 [0.487, 1.068], p = 1.6e-07). Diabetes was positively associated with ALT (β = 0.023 [0.015, 0.032], p = 2.4e-07) and MASLD (β = 0.310 [0.154, 0.466], p = 9.6e-05). Conversely, higher HDL was associated with reduced ALT (β = -0.026 [-0.045, -0.007], p = 0.0078) and cirrhosis (β = -0.225 [-0.388, -0.062], p = 0.0068). SBP was linked to cirrhosis (β = 0.061 [0.023, 0.099], p = 0.0018) and ALT (β = 0.010 [0.002, 0.018], p = 0.0096). Alcohol intake was associated with higher cirrhosis risk (β = 0.372 [0.129, 0.615], p = 0.0027). TGs showed no causal effects. **Conclusion:** Genetically-predicted CMRFs are causal for ALT, cirrhosis, and MASLD. These effects are strongest for BMI, diabetes, and HDL, with SBP having weaker effects and TGs having none. Future MASLD nomenclature updates should reflect the disparate effects of different CMRF on risk of hepatic steatosis.



Disclosures: Blake Czapla: Nothing to Disclose, Stephan Buch: Nothing to Disclose, Eric Trepo: Nothing to Disclose, Vincent Chen: AstraZeneca: site PI on industry-sponsored trial, Ipsen: site co-I on industry-sponsored trial, Kowa: site co-I on industry-sponsored trial

4287 | EXTERNAL VALIDATION ON AN HCC RISK STRATIFICATION SCORE, PAAM, IN PATIENTS WITH CHRONIC LIVER DISEASE OF VARYING SEVERITY

Christine Hsu[1] Ece Janet Dinc[2] Hiroaki Kanzaki[2] Naoto Fujiwara[3] Christopher Sollenberger[1] Hiroyuki Suzuki[2] Courtney Katz[2] Pratibha Selvakumar[2] Indu Raman[2] Prithvi Raj[2] Jonathan Lim[1] Jake Liang[1] Yujin Hoshida[2], [1]National Institute of Diabetes and Digestive and Kidney Diseases, [2]University of Texas Southwestern Medical Center, [3]Graduate School of Medicine, Mie University

Background: HCC risk stratification is an unmet medical need for patients with chronic liver disease. We previously reported an HCC risk score, PAaM, integrating clinical variables and a serum proteome biomarker, which was validated in patients with cirrhosis (Gastro 168;556,2025). The clinical utility of this score in a broader patient population, including non-cirrhotic subjects, has yet to be explored. In this study, we conducted an external validation of PAaM in patients with chronic liver diseases, including non-cirrhotics. **Methods:** We analyzed archived serum samples from a retrospective cohort of patients with chronic liver disease who were followed up at the U.S. National Institute of Health (NIH) Clinical Center between 1980 and 2023. Patients with follow-up time shorter than 6 months or an HCC diagnosis within 6 months of the initial visit were excluded. The serum proteome biomarker assay (PLSec) and PAaM score calculation were performed, and the patients were classified as having high-, intermediate-, or low-risk of incident HCC development as previously reported. The association of the risk prediction and time to incident HCC was assessed by uni- and multivariable Cox and Fine-Gray regression. **Results:** We included 295 patients in the analysis, among which 33 patients developed incident HCC during a median follow-up of 7.8 years (IQR 3.2 – 12.3 years). There were 147 (49.8%) non-Hispanic white, 59 (20%) black, 57 (19.3%) Asian, and 26 (8.8%) Hispanic patients. Median age was 50 years (IQR 41 - 57 years). 180 (61%) patients were male. Major etiology was HCV (55.3%; active/cured infection 15%/85%) followed by HBV (16.6%), MASLD (10.5%), ALD (2.7%). Annual HCC incidence rate was 3.04%. The PAaM score categorized 63 (21.4%), 74 (25.1%), and 158 (53.6%) patients as having high-, intermediate-, and low-risk, with annual HCC incidence rates of 3.0%, 1.9%, and 0.4%, respectively. Hazard ratios for the high- and intermediate-risk groups were 3.67 (95% CI 1.58 – 8.5) and 2.23 (95% CI 0.95 – 5.25), respectively,

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compared to the low-risk group. Exploratory subgroup analysis is planned using clinical variables relevant to the risk of HCC development. **Conclusion:** The PAaM score was successfully validated in a multi-ethnic cohort of patients with chronic liver diseases of mixed etiologies at a tertiary center in the U.S.
Disclosures: Christine Hsu: Nothing to Disclose, Ece Janet Dinc: Nothing to Disclose, Hiroaki Kanzaki: Nothing to Disclose, Naoto Fujiwara: Nothing to Disclose, Christopher Sollenberger: Nothing to Disclose, Hiroyuki Suzuki: Nothing to Disclose, Courtney Katz: Nothing to Disclose, Pratibha Selvakumar: Nothing to Disclose, Indu Raman: Nothing to Disclose, Prithvi Raj: Nothing to Disclose, Jonathan Lim: Nothing to Disclose, Jake Liang: Nothing to Disclose, Yujin Hoshida: Helio Genomics: Advisor, Alentis Therapeutics: Stock – privately held company, Espervita Therapeutics: Stock – privately held company, Elevar Therapeutics: Advisor, Espervita Therapeutics: Advisor, Roche Diagnostics: Advisor

4288 | CHARTING SINGLE-CELL METABOLISM CO-EVOLUTION DURING METASTASIS

Yingcheng Wu[1] Qiang Gao[2], [1]Fudan University, [2]Fudan University Zhongshan Hospital

Background: Metastasis, the leading cause of cancer death, exhibits a highly heterogeneous and suppressive cancer microenvironment. **Methods:** Here, we sequenced 97 matched samples by using single-cell RNA sequencing and spatial transcriptomics of colorectal cancer liver metastasis. **Results:** Strikingly, the metastatic microenvironment underwent remarkable spatial reprogramming of immunosuppressive cells such as MRC1+ CCL18+ M2-like macrophages. We further developed *scMetabolism*, a computational pipeline for quantifying single-cell metabolism, and observed that those macrophages harbored enhanced amino acid metabolic activity. Interestingly, neoadjuvant chemotherapy could block this status and restore the antitumor immune balance in responsive patients, whereas the nonresponsive patients deteriorated into a more suppressive one. In parallel, metastatic cancer cells displayed the metabolic switch from OXPHOS to glycolysis, which is dependent on the metabolic master regulator LY6E. **Conclusion:** Our work described the metabolism co-evolution of both immune and cancer cells during metastasis and uncovered the black box of how tumors respond to neoadjuvant chemotherapy.
Disclosures: Yingcheng Wu: Nothing to Disclose, Qiang Gao: Nothing to Disclose

4289 | IN SITU ANALYSIS OF THE HBV-ASSOCIATED HEPATOCELLULAR CARCINOMA MICROENVIRONMENT USING IMAGING-BASED SINGLE-CELL RESOLUTION XENIUM SPATIAL TRANSCRIPTOMICS

Wei Hou[1], [1]Translational Medicine Research Center, School of Clinical Medicine, Qilu Medical University, CHINA

Background: Hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) presents a complex tumor microenvironment (TME) that contributes to oncogenesis and treatment resistance. **Methods:** Utilizing the Xenium platform's imaging-based spatial transcriptomics at single-cell resolution, we systematically characterized the spatial architecture and molecular interactions within HBV-HCC tissues. Our multi-omics approach integrated spatial transcriptomic profiling with single-cell RNA sequencing to delineate the spatial distributions of tumor cells, immune subsets, and stromal components across tumor core, paracancerous, and normal liver regions. **Results:** Employing the Xenium platform's high-resolution spatial transcriptomics workflow, we analyzed 5,000 cancer-relevant genes across 605,057 cells (with a median of 194 transcripts per cell). Cell segmentation through Xenium Explorer revealed distinct spatial compartmentalization of hepatocyte subpopulations, immune cell infiltrates (including PD-1+CD8+ T cells and SPP1+ macrophages), endothelial networks, and activated fibroblasts. Subsequent dimensionality reduction using Seurat identified five principal cellular communities with unique spatial patterns: malignant hepatocytes clustered within tumor nests, immunosuppressive myeloid cells forming peri-tumoral barriers, endothelial networks delineating angiogenic hotspots, and activated fibroblasts establishing stromal partitions. Differential gene expression analysis highlighted tumor-specific upregulation of oncogenic driver PEG10 (log2FC = 4.567, P. **Conclusion:** This study establishes a spatial atlas of HBV-associated HCC at single-cell resolution, identifying key therapeutic opportunities targeting PEG10/ IGF2 signaling and ferroptosis pathways. Our findings provide a spatial framework for the development of microenvironment-targeted strategies aimed at overcoming immunotherapy resistance in virally-driven HCC.
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4290 | THE GENOMIC MUTATION OF HEPATOCELLULAR CARCINOMA IN FONTAN-ASSOCIATED LIVER DISEASES CHARACTERIZED BY CHROMOSOMAL REARRANGEMENTS

Taiji Yamazoe[1] Eiji Kakazu[1] Masaaki Mino[1] Michitaka Matsuda[1] Tatsuya Kanto[1], [1]Japan Institute for Health Security

Background: The Fontan-associated liver disease (FALD) is a congestive hepatopathy growing the number of patient and develops liver cirrhosis and hepatocellular carcinoma (HCC) after 15-20 years of the Fontan procedure. The prognosis of FALD-HCC patients is significantly worse compered to non-HCC FALD patients, thus indicating the importance of the understanding of genomic signature of FALD hepatocarcinogenesis. To this aim, we utilized the whole genome sequences (WGS). **Methods:** We performed WGS analyses of the surgically resected tissues from five FALD HCC patients, two post non-Fontan congenital heart surgery (CHS) HCC patients, and one FALD focal nodular hyperplasia (FNH) patient, respectively. To infer mutation mechanisms of FALD HCC, we utilized COSMIC signature analysis with comparison of the publicly available viral and non-viral HCC cohorts. To check the progression of liver injury, we used pIVC mouse model and examined reactive oxygen species (ROS) and the time course of phosphorylation of histone H2Ax (γH2Ax). **Results:** Eight tumors, including FALD HCCs, FALD FNH and non-Fontan CHS HCCs had relatively higher tumor mutational burden than HCCs in the databases. Based on the COSMIC v3.3, we identified the signatures related to the homologous recombination deficiency, the ROS DNA injury and the repair of DNA double-strand breaks (DSB) by non-homologous DNA end-joining mechanisms across eight tumors. The study on short variants shown that FALD HCC did not have the commonly observed mutations of HCCs in the public databases, such as *CTNNB1*, *TP53*, or *TERT*. The study on structural variants (SVs) shown that FALD HCC had significantly higher amount of <1Mb deletion and translocation than that of HCCs in the database. The unbiased clustering based on the copy number alterations (CNAs) and SVs classified FALD and non-Fontan CHS HCC as an HCC subclass characterized by the gain of chromosome 1q and a loss of 16q. On the other hand, FALD FNH had few CNAs and SVs and had been classified no chromosomal rearrangement subclass. The subclass of HCC with 1q gain and 16q loss in the database shows poor progression-free interval.

In the mouse model, we confirmed ROS production and the γH2Ax positivity were gradually increased after pIVC ligations. The γH2Ax positive hepatocytes preferentially localized in the peripheral area of the liver. **Conclusion:** Our WGS study identified distinctive genomic mutational characteristics of FALD HCCs from HCCs in the public databases. These findings would have implications for the establishment of FALD specific patient management and HCC therapy.

Disclosures: Taiji Yamazoe: Nothing to Disclose, Eiji Kakazu: Nothing to Disclose, Masaaki Mino: Nothing to Disclose, Michitaka Matsuda: Nothing to Disclose, Tatsuya Kanto: Nothing to Disclose

4291 | CLINICO-RADIOMIC FEATURES CAN STRATIFY CLINICALLY SIGNIFICANT PORTAL HYPERTENSION (CSPH) IN PATIENTS OF CIRRHOSIS NON-INVASIVELY

Ashok Kumar Choudhury[1] Tranjit Kaur[2] Garima Singhal[3] shalini thapar[4] Tapan Gandhi[5] Shiv Kumar Sarin[6], [1]Institute of Liver and Biliary Sciences, [2]Indian Institute Technology, Jodhpur. India, [3]Institute of Liver and Billiary Sciences, New Delhi India, [4]Institute of Liver and Biliary Sciences, New Delhi. India., [5]Indian Institute of Technology, Delhi, [6]Institute of Liver and Billiary Sciences

Background: Clinically significant portal hypertension, defined by a hepatic venous pressure gradient (HVPG) of >10mmHg, is associated with increased risk of decompensation and poor survival. Non-invasive measurement of portal pressure by radiomics and clinical parameters is an unmet need. We aimed to assess CSPH from CT images (radiomics) and clinical parameters as non-invasive surrogates of HVPG. **Methods:** We retrospectively analyzed EMRs of compensated cirrhosis patients, incorporating clinical, contrast CT scan images and HVPG measured within past 3 months. Patients were grouped as CSPH (HVPG >10mmHg) or no CSPH. Liver segmentation was performed on the venous phase images using a U-Net deep learning model; and 1,606 radiomic features were extracted using 3D Slicer software. These imaging-derived features, clinical parameters, were compiled for each patient to train four supervised machine learning models —Logistic Regression, Random Forest, K-Nearest Neighbors (KNN), and XGBoost—to classify as CSPH or no-CSPH. Stratified 5-fold cross-validation done for preserve class distribution and model performance was assessed using ROC curves to compare classifier performance. **Results:** Total of 50 patients (median age: 58.9+11.2 years; 76% male), mean HVPG 17.5 ± 3.8 mm Hg, were grouped as no CSPH ($n=20$) and CSPH ($n=30$). They were comparable in all parameters except HVPG (18.5 ± 4.7 versus 5.3 ± 1.7 mm Hg). Liver segmentation using the U-Net model achieved a Dice Similarity Coefficient of 96.5. Using only radiomic features, logistic regression emerged as

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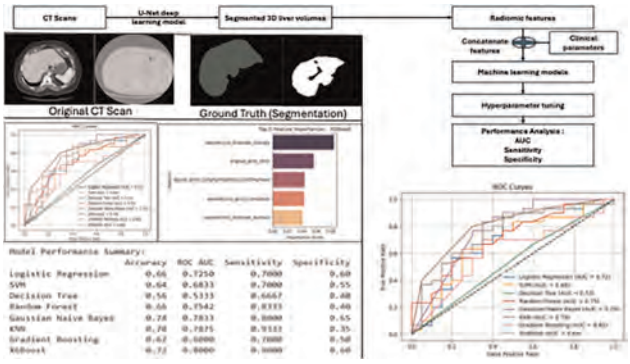
the best-performing model with an AUC of 0.733, sensitivity of 0.70, and specificity of 0.60 in distinguishing the two groups. Upon inclusion of clinical parameters (age, serum bilirubin, albumin, urea, AST, ALT and INR) the model performance improved, with the XGBoost classifier achieving the highest AUC of 0.80, sensitivity of 0.80, specificity of 0.60, PPV -74%, NPV-77% and F1-75% for identifying those with CSPH. **Conclusion:** Radiomic features extracted from CT images and simple laboratory parameters (clinico-radiomics) together can effectively stratify patients of cirrhosis with CSPH. Virtual measurement of HVPG (vHVPG) may be accepted for clinical practice in future, pending analysis of larger data.



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4292 | SINGLE-CELL AND SINGLE-NUCLEI TRANSCRIPTOMICS REVEAL HEPATOBLASTOMA TUMOR SIGNATURES FOR PRECISION ONCOLOGY

Abhishek Murti[1] Elise Lelou[1] Simon Bucher[1] Saphia Nguyen[1] Matthew Choi[1] Soo-Jin Cho[1] Amar Nijagal[1] Bruce Wang[1], [1]University of California, San Francisco

Background: Pediatric hepatoblastoma (HB) is the most common primary liver cancer in infants and children. While early diagnosis and treatment can lead to a 70% five-year survival rate, prognosis remains poor for patients with unresectable or metastatic tumors. HB tumors exhibit marked heterogeneity, and current clinical risk stratification relies on imaging and histology, with serum alpha-fetoprotein as the only molecular biomarker. Therefore, there is an urgent need for improved molecular characterization to enable more accurate patient risk stratification. Single-cell RNA sequencing (scRNA-seq) enables the dissection of tumor complexity and identification of cell-type–specific expression programs. In our prior work, we used scRNA-seq to profile resected HB tumors and discovered five distinct tumor signatures predictive of treatment response in patient-derived spheroids. We now expand this analysis to include freshly resected and frozen biobanked HB specimens using single-cell and single-nuclei RNA sequencing (snRNA-seq), respectively. **Methods:** Fresh tumors were processed using Seq-Well for scRNA-seq, and frozen samples were profiled via snRNA-seq using the 10x Genomics Chromium platform. Libraries were sequenced on an Illumina NovaSeqX. Data preprocessing and downstream analysis were conducted using Scanpy. Quality control included filtering based on gene counts, mitochondrial content, doublet removal, and ambient RNA correction. Datasets were integrated using scvi-tools; clustering and differential gene expression was performed to define tumor signatures. Correlation analyses assessed cross-platform concordance. **Results:** Our expanded single cell dataset confirms the presence and reproducibility of previously identified tumor signatures, including a signature enriched in aggressive, high-risk tumors. Strong concordance between matched scRNA-seq and snRNA-seq profiles confirms the reproducibility of tumor signatures across platforms. These findings highlight the utility of snRNA-seq for profiling archived HB samples and expand our understanding of tumor heterogeneity diversity. **Conclusion:** This study demonstrates that both scRNA-seq and snRNA-seq can effectively resolve hepatoblastoma heterogeneity and identify biologically and clinically meaningful tumor signatures. The ability to analyze fresh and frozen tumors expands the utility of transcriptomic profiling, especially for rare or high-risk cases. These insights lay the foundation for a precision oncology framework in HB, enabling molecular stratification and personalized treatment strategies tailored to each patient's tumor biology.

Disclosures: Abhishek Murti: Nothing to Disclose, Elise Lelou: Nothing to Disclose, Simon Bucher: Nothing to Disclose, Saphia Nguyen: Nothing to Disclose, Matthew Choi: Nothing to Disclose, Soo-Jin Cho: Nothing to Disclose, Amar Nijagal: Nothing to Disclose, Bruce Wang: Alnylam Pharmaceuticals: Consultant, Recordati Rare Diseases: Consultant, Disc Medicine: Consultant, Mitsubishi Tanabe Pharma: Consultant, Mitsubishi Tanabe Pharma: Grant/Research Support, CRISPR Therapeutics: Consultant

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4293 | PHENOTYPE-GUIDED EXOME-BASED GENE PANEL TESTING IMPROVES DIAGNOSTIC YIELD FOR RARE GENETIC CHOLESTATIC LIVER DISEASE

Akihiro Asai[1] Wenying Zhang[1] Chunyue Yin[1] Emily Vincent[1] William Balistreri[1], [1]Cincinnati Children's Hospital Medical Center

Background: Cholestatic jaundice affects one in 2,500 full-term infants; inherited conditions account for 25–50% of the cases. Identifying a genetic etiology enables early diagnosis and targeted management, improving patient outcomes. However, ~30% of patients with isolated/primary cholestasis lack mutations in known cholestasis-associated genes, limiting personalized care. Whole-exome (WES) and whole-genome sequencing (WGS) often detect numerous variants in genes with uncertain relevance. This ambiguity hinders interpretation and reduces diagnostic yield. **Methods:** We developed the Cincinnati Undiagnosed and Rare Liver (CURL) Disease Panel, a phenotype-guided test leveraging exome sequencing and targeting 1,445 genes curated for relevance to liver biology. The gene list is continuously refined by clinicians, liver researchers, and geneticists. From over 50 patients screened, we prioritized those with unknown chronic cholestasis where a genetic diagnosis could inform care. Test results were interpreted through multidisciplinary review. **Results:** The CURL panel was piloted in eight patients (seven pediatric, one adult), six with trio-based testing. All had undergone prior clinical genetic testing, including the 72-liver gene panel at CCHMC and, in two cases, commercial WGS. The CURL panel confirmed previously reported variants in three patients: Patient 1 (neonatal cholestasis) had compound heterozygous missense variants in *ABCB11* (p.Ile611Thr; p.Met185Ile); Patient 2 (bile duct paucity) had a heterozygous missense variant in *NOTCH2* (p.Gly700Val); and Patient 3 (intrahepatic cholestasis of pregnancy) had a heterozygous in-frame deletion in *ABCB4* (p.Lys620del). In three additional patients, the CURL panel identified novel variants consistent with clinical phenotypes: Patient 4 (high-GGT neonatal cholestasis) had compound heterozygous missense variants in *LARS1* (p.Asn1148Ser; p.Glu124Lys); Patient 5 (cholestasis and pancreatic insufficiency) had a hemizygous missense variant in *ATP6AP1* (p.Leu148Pro); and Patient 6 (severe lobular cholestasis) had a heterozygous missense variant in *PLEC* (p.Leu2380Pro). **Conclusion:** The CURL panel enables collaborative review and focused interpretation of the most up-to-date liver-relevant genes using a phenotype-guided exome approach. Early data indicate improved diagnostic yield over standard gene panels, WES, and WGS in patients with undefined cholestatic liver diseases.

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4294 | PNPLA3-I148M HOMOZYGOSITY PROMOTES VISCERAL FAT ACCUMULATION AND REDUCES SUBCUTANEOUS FAT INDEPENDENT OF BMI

Eleonora Scorletti[1] David Zhang[1] Marijana Vujkovic[1] Kyong-Mi Chang[1] Garret FitzGerald[1] Daniel Rader[1], [1]University of Pennsylvania

Background: The *PNPLA3*-I148M genetic variant is strongly associated with hepatic fat accumulation and liver disease risk, yet its effects on adipose tissue distribution and function remain incompletely characterized. Given the critical role of adipose tissue in systemic metabolism and inflammation, understanding *PNPLA3*-I148M's influence on adiposity may illuminate novel pathways linking adipose biology to hepatic and metabolic disorders. Our preliminary data indicate that adipose tissue of *PNPLA3*-I148M carriers accumulates polyunsaturated fatty acids (PUFAs) with aging, suggesting an age-dependent metabolic impact. Here, we aimed to evaluate how *PNPLA3*-I148M homozygosity affects abdominal adipose distribution. **Methods:** We analyzed abdominal computed tomography (CT)-derived adiposity metrics from 2,109 homozygous PNPLA3-I148M (MM) carriers and 25,782 wild-type (WT) individuals enrolled in the Penn Medicine Biobank (PMBB). Primary outcomes included adipose tissue thickness (distance from skin to fascia), subcutaneous fat pixel volume, and visceral fat pixel volume. Associations between genotype (MM vs. WT) and adiposity measures were assessed using linear regression models, adjusted for age, sex, and BMI. **Results:** We found that MM carriers had lower BMI (mean 29.0, SD $\pm$6.0 kg/m²) compared to WT controls (mean 29.7, SD $\pm$6.5 kg/m², $p < 0.001$). Adjusting for age, sex, and BMI, adipose thickness did not significantly differ between groups ($\beta = +0.0036$ mm; 95% CI –0.046 to +0.054; $p = 0.89$). However, subcutaneous fat volume was significantly lower in MM carriers ($\beta = –73{,}610$ pixels; 95% CI –118,800 to –28,420; $p = 1.4\times10^{-3}$), whereas visceral fat volume was significantly higher ($\beta = +74{,}350$ pixels; 95% CI +40,811 to +107,890; $p = 1.4\times10^{-5}$). We are currently replicating these

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findings in the Million Veteran Program (MVP) cohort and will present additional adipose tissue data on PUFA-derived eicosanoids at The Liver Meeting. **Conclusion:** Our study is the first to explore the effect of PNPLA3-I148M on adipose tissue distribution. Homozygosity for *PNPLA3*-I148M distinctly alters adipose tissue distribution, characterized by reduced subcutaneous fat and increased visceral fat independent of BMI, age, and sex. These findings highlight the potential role of altered adipose tissue partitioning in driving the metabolic and hepatic complications associated with the *PNPLA3*-I148M variant.

Disclosures: Eleonora Scorletti: Nothing to Disclose, David Zhang: Nothing to Disclose, Marijana Vujkovic: Nothing to Disclose, Kyong-Mi Chang: Virion Therapeutics: Data Monitoring Committee member, GSK: Advisor, Garret FitzGerald: Nothing to Disclose, Daniel Rader: Nothing to Disclose

4295 | MOLECULAR RELATIONSHIP BETWEEN STEATOHEPATITIS AND ADVANCED FIBROSIS IN HUMAN MASLD: AN INVESTIGATION BASED ON MULTIPLE HUMAN RNASEQ DATASETS

Tae-Hwi Schwantes-An[1] Marco Abreu[1] Callie Zaborenko[1] Jingyi Tan[2] Xiuqing Guo[2] Jerome Rotter[2] Brent Neuschwander-Tetri[3] Arun Sanyal[4] Naga Chalasani[5], [1]Indiana University School of Medicine, [2]Lundquist Institute, [3]Saint Louis University, [4]Virginia Commonwealth University, [5]Indiana University Medical Center

Background: The molecular basis for steatohepatitis and advanced fibrosis and their sequential relationships in human MASLD are not fully understood. We sought to identify differentially expressed genes in the liver tissue in patients with MASLD which stratify risk for higher disease activity or fibrosis stages and understand their relationships. **Methods:** Differential gene expression (DGE) analyses were conducted for advanced fibrosis ($F \geq 3$) and NAFLD Activity Score (NAS) ≥ 4 from the bulk RNAseq from NASH-CRN liver samples performed by the Regeneron Genetics Center. We adjusted for age, sex, race, ethnicity, fibrosis (for NAS outcome), and NAS (for fibrosis outcome). The significant DGEs (padj < 0.05 and up/down expressed ≥ 2-folds) were used with gene set variation analysis to compute gene enrichment scores in two independent bulk RNA-seq data of patients with MASLD. In total 4 scores; 1) fibrosis, 2) NAS, 3) fibrosis adjusting for NAS, and 4) NAS adjusting for fibrosis were generated. We then assessed the performance of the scores in stratifying risks for NAS $\geq$ 4 and advanced fibrosis. **Results:** In total, 499 NASH-CRN adult participants were included in DGE analysis. There were 309 DGE associated with advanced fibrosis, after adjusting for age, sex, race/ethnicity (RNA-Fib score) and 229 DGE after also adjusting for NAS. For NAS ≥ 4, there were 268 DGE with significant association after adjusting for age, sex, race/ethnicity (RNA-NAS score), and 79 after also adjusting for fibrosis stage. Using these genes, four enrichment scores were computed in GSE135251 (Anstee et al., N = 216) and GSE225740 (Chalasani et al., N = 93).

In GSE135251, we observed that RNA-NAS score not only predicted risk for NAS ≥ 4 (OR = 18.7, $p = 2.8 \times 10^{-14}$, Rsq = 23.4%), but also fibrosis (OR = 11.9, $p = 3.9 \times 10^{-28}$, Rsq = 43.0%). After adjusting for fibrosis, the RNA-NAS score still predicted both NAS and fibrosis (Table). RNA-Fib score was associated with both fibrosis (OR = 8.7, $p = 5.9 \times 10^{-21}$, Rsq = 34%) and NAS (OR = 4.9, $p = 6.6 \times 10^{-05}$, Rsq = 6.8%). However, after adjusting for NAS, RNA-Fib score was no longer associated with NAS (p = 0.2) and showed reduced performance for fibrosis (OR = 6.3, $p = 4.7 \times 10^{-11}$, Rsq = 18%). We observed similar patterns of association in GSE225740 (data not shown). **Conclusion:** Our finding shows the genes that drive steatohepatitis also drive fibrosis while the genes that drive fibrosis do not drive NAS. These molecular data highlight the importance of steatohepatitis in driving advanced fibrosis.

Enrichment Scores	Outcomes	OR (95%C.I.)	Pvalue	Rsq	Comments/Interpretation
RNA-Fib score	Fibrosis	8.73 (5.82-13.10)	5.93E-21	33.5%	The fibrosis score is highly associated with risk for advanced fibrosis
RNA-Fib score adjusted for NAS	Fibrosis	6.30 (3.74-10.59)	4.71E-11	18.0%	The fibrosis score is still associated with the risk, however there is a decrease in performance
RNA-Fib score	NAS	4.93 (2.29-10.64)	6.61E-05	6.8%	The fibrosis score explains some variance in NAS but not as much as it does for fibrosis
RNA-Fib score adjusted for NAS	NAS	1.83 (0.73-4.57)	1.98E-01	0.3%	The fibrosis score after adjusting for NAS does not predict NAS
RNA-NAS score	NAS	18.68 (9.25-37.73)	2.78E-14	23.4%	The RNA-NAS score is highly associated with risk for higher NAS
RNA-NAS score adjusted for fibrosis	NAS	22.88 (11.62-45.03)	8.36E-17	27.4%	The RNA-NAS score shows improved performance for NAS after adjusting for fibrosis
RNA-NAS score	Fibrosis	11.85 (8.11-17.32)	3.86E-28	43.0%	The RNA-NAS score is also highly associated with risk for advanced fibrosis
RNA-NAS score adjusted for fibrosis	Fibrosis	7.15 (4.68-10.91)	5.96E-17	27.6%	The RNA-NAS score still is highly associated with advanced fibrosis after adjusting for fibrosis

Disclosures: Tae-Hwi Schwantes-An: Nothing to Disclose, Marco Abreu: Nothing to Disclose, Callie Zaborenko: Nothing to Disclose, Jingyi Tan: Nothing to Disclose, Xiuqing Guo: Nothing to Disclose, Jerome Rotter: Nothing to Disclose, Brent Neuschwander-Tetri: Akero: Consultant, Aligos: Consultant, Arrowhead: Consultant, Corcept: Consultant, GSK: Consultant, Hepion: Consultant, HIstoIndex: Consultant, Madrigal: Consultant, Madrigal: Grant/Research Support, Merck: Consultant, Mirum: Consultant, Sagimet: Consultant, Senseion: Consultant, HepGene: Stock – privately held company, HeptaBio: Stock – privately held company, Abbvie: Consultant, Pliant: Consultant, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (< 5K), Terns (< 5K), Merck (< 5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (< 5K),: Consultant, Novo Nordisk: Consultant, Regeneron (< 5K), Alnylam (< 5K), Akero (< 5K),: Consultant,

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4296 | TOWARDS A HUMAN-LIKE BILE ACID POOL IN MICE: DISSECTING THE ROLE OF CYP2C70 AND AGXT IN BILE ACID COMPOSITION AND CONJUGATION

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Background: Bile acids (BAs) are key regulators of lipid and glucose metabolism, as well as immune homeostasis. Alterations in BA metabolism are critically involved in cardiometabolic, inflammatory, and neoplastic diseases. While mouse models remain indispensable in studying these processes, significant species differences in BA composition and downstream signaling hinder translational relevance. Cytochrome P450 2C70 (*Cyp2c70*) converts chenodeoxycholic acid (CDCA) into muricholic acids (MCAs), hydrophilic bile acids unique to rodents. In contrast, humans lack MCAs and exhibit a CDCA-enriched BA pool. Alanine-glyoxylate aminotransferase (*Agxt*) catalyzes glycine production. Species differences in glycine synthesis, potentially linked to distinct subcellular localization of *Agxt*, have been proposed to explain the predominance of glycine-conjugated bile acids in humans versus taurine conjugation in mice. However, this hypothesis remains untested. In this study, we aimed to humanize the murine bile acid profile by targeting both *Cyp2c70* and *Agxt* in mouse hepatocytes. **Methods:** Using AAV8-mediated somatic liver knockout, we generated the following mouse models: a. *Cyp2c70* knockout (*Cyp2c70* ^{KO}); b. Murine *AGXT (mAgxt)* knockout combined with human AGXT (*hAGXT*) overexpression (*mAgxt* ^{KO}/*hAGXT* ^{OE}); c. Triple-modified mice with *Cyp2c70* and *Agxt* knockout plus hAGXT overexpression (*Cyp2c70* ^{KO}/*mAGXT* ^{KO}/*hAGXT* ^{OE}). AAV8 vectors were administered at a dose of $1*10^{13}$ vg/kg via tail vein injection to adult mice. Knockout and overexpression were confirmed via qPCR and western blot. Bile acid composition and liver function were assessed 6, 9, and 12 weeks after AAV injection. **Results:** *Cyp2c70* ^{KO} mice exhibited a marked reduction in MCAs and a significant increase in CDCA within 9 weeks. In *mAgxt* ^{KO}/*hAGXT* ^{OE} mice, total BA levels increased, while the proportion of glycine-conjugated BAs remained comparable to controls, suggesting maintained conjugation function. No significant liver injury was observed in *Cyp2c70* ^{KO} or *mAgxt* ^{KO}/*hAGXT* ^{OE} mice after 12 weeks. However, *Cyp2c70* ^{KO}/*mAGXT* ^{KO}/*hAGXT* ^{OE} mice developed severe biliary injury, necessitating euthanasia 6 weeks post-injection. **Conclusion:** Hepatocyte-specific Cyp2c70 deletion leads to a more human-like BA profile, whereas Agxt manipulation alone failed to humanize bile acid conjugation in mice, indicating that additional factors govern species-specific conjugation.

Disclosures: Dandan Wu: Nothing to Disclose, Isabelle Bolt: Nothing to Disclose, Dagmar Tolenaars: Nothing to Disclose, Wietse In het Panhuis: Nothing to Disclose, Coen Paulusma: Nothing to Disclose, Stan van de Graaf: ProQR: Consultant

4297 | HEPATOCELLULAR CARCINOMA MICROENVIRONMENT ANALYSIS USING SINGLE-CELL RNA-SEQ TO EXPLORE NOVEL THERAPEUTIC TARGETS

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Background: Angiogenesis inhibitors and immune checkpoint inhibitors targeting the tumor microenvironment (TME) have recently become the mainstay of treatment for hepatocellular carcinoma (HCC), but response rates remain unsatisfactory. Therefore, we performed TME analysis by single-cell RNA-seq to explore novel therapeutic targets in HCC. **Methods:** Flex scRNA-seq analysis was performed using 81 frozen tissue samples (63 HCC samples undergoing hepatectomy, 10 noncancerous liver tissue samples, and 8 donor liver tissue samples) to examine the association between cell type frequency, gene expression, cell-cell interactions, and clinical characteristics. We also performed TME classification by hierarchical clustering based on the cell type frequency of noncancerous cells and cancer cell classification based on the Chiang molecular classification, and examined the

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association with clinical characteristics. **Results:** The 63 cases consisted of 69.8% males, 49.2% MASLD, Stage (I/II/III/IV: 46%/31.7%/19%/3.2%), and 31.7% positive for portal vein invasion (VP). The approximately 60,000 noncancerous cells were classified into four major clusters (lymphocytes, myelocytes, vascular endothelial cells, and hepatic stellate cell) and further subdivided into 29 cell types. VP-positive cases showed a significantly higher frequency of TREM2+ macrophages and increased expression of PD-1, TIM-3, LAG-3 and TIGIT in CD8-positive T cells, and anti-tumor immunity was suppressed in TME. The 63 cases were stratified into 4 groups according to TME classification, with about 30% of the group rich in Lymphoid, which is considered Immune Hot, and the group characterized by tumor-associated endothelial cells (VECs) and tumor-associated fibroblasts (CAFs), which had a shorter PFS. In the classification of approximately 250,000 cancer cells, the CTNNB1 group was mostly consistent with the TME classification characterized by VECs, while the PROLIFERAION group was largely divided into two groups: the Lymphoid-rich TME group and the CAF-rich TME group. **Conclusion:** Our results suggest that scRNA-seq analysis may enable a detailed TME classification of HCC and identify subtypes that may be associated with the efficacy of immunotherapy. **Disclosures:** Ryo Takahashi: Nothing to Disclose, Takahiro Kodama: Nothing to Disclose, Takeru Hirao: Nothing to Disclose, Yu Sato: Nothing to Disclose, Yuta Myojin: Nothing to Disclose, Satoshi Shigeno: Nothing to Disclose, Kazuhiro Murai: Nothing to Disclose, Yuki Tahata: Nothing to Disclose, Yoshinobu Saito: Nothing to Disclose, Hayato Hikita: Nothing to Disclose, Tetsuo Takehara: Nothing to Disclose

4298 | IDENTIFICATION OF LIVER CANCER NEOANTIGENS FROM RARE TUMOR CELLS IN MALIGNANT ASCITES

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Background: In liver cancer immunotherapy, neoantigen-based immunotherapies have demonstrated remarkable clinical efficacy in patients due to their strong immunogenicity. Studies have confirmed that pre-existing neoantigen-specific T cells in tumor patients are the targets of immune checkpoint blockade (ICB) therapy and serve as the core driver of clinical benefits in immunotherapy. Therefore, neoantigen-based therapeutic vaccines represent a promising breakthrough in tumor immunotherapy.

Liver cancer is often insidious in onset, with more than half of patients diagnosed at intermediate or advanced stages, missing the optimal window for surgical intervention. This makes it difficult to obtain neoantigen profiles from surgical samples. In contrast, malignant ascites, as a key component of liquid biopsy, contains metastatic tumor cells and provides a convenient source for detecting neoantigen profiles in cancer patients. The primary objective of this study is to establish a comprehensive strategy for identifying neoantigens from malignant ascites samples of advanced liver cancer patients. **Methods:** First, ascites samples were collected from patients with liver cirrhosis and advanced liver cancer. Using flow cytometry (FCM), we isolated the 7-AAD$^-$ CD45$^-$ CD326$^+$ tumor cell subpopulation (P7 population) from malignant ascites of advanced liver cancer. For P7 populations containing fewer than 2,000 cells, RNA and DNA were separately extracted and amplified using Smart-seq2 and Discover-sc Single Cell WGA Kit technologies, respectively. The samples were then subjected to transcriptome sequencing and whole-exome sequencing, followed by comprehensive bioinformatics analysis to characterize genetic variations and expression profiles. Simultaneously, the Variant Effect Predictor (VEP) algorithm was employed to predict mutant proteins from somatic mutations and subsequently process these proteins to derive potential mutant peptides. Binding affinity between mutant peptides and patient HLA molecules was calculated using the NetMHCpan-4.1 algorithm. Potential neoantigens were predicted by applying the following criteria: mutated peptide affinity (MutAff $\leq$ 200 nM) or a ratio of referenced (wild-type) peptide affinity to mutated peptide affinity (RefAff/MutAff $\geq$ 10), while excluding duplicates and cases of HLA loss-of-heterozygosity. Finally, tetramer staining was performed to detect neoantigen-specific T cells in malignant ascites. **Results:** In this study, we developed an integrated approach combining flow cytometry (FCM) with next-generation sequencing to isolate and characterize rare tumor cells (CSCs) from malignant ascites. Our results demonstrated that liver cancer patients exhibited significantly higher numbers of P7 tumor cell subpopulations in their ascites compared to both matched peripheral blood samples and ascites from cirrhosis patients. Single-cell sequencing analysis revealed partial overlap in mutational profiles between individual tumor cells in ascites and those from primary and metastatic lesions. Whole-exome and transcriptome sequencing of P7 cells from 8 HCC cases identified C > T/G > A transitions as the predominant substitution pattern, with mutational signatures 1, 3, 12, 15 and 30 being most prominent. Using NetMHCpan-4.1 algorithm, we successfully predicted potential neoantigens derived from these ascites P7 cells, including mutant peptides from TOP3A, TUBB6, NUTM2G, FGD2, NFKBIZ and CLDND1. Importantly, we detected neoantigen-specific T cells in HCC malignant ascites, which showed characteristic high expression of CD39.

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Conclusion: This finding demonstrates that neoantigens can be effectively identified from malignant ascites in advanced liver cancer, which would provide patient-specific targets for precision immunotherapy.
Disclosures: Dongbo Chen: Nothing to Disclose, Hongsong Chen: Nothing to Disclose

4299 | ELECTROPORATION IN HEPATOCYTES TO EVALUATE A CELL-BASED GENE EDITING STRATEGY FOR TREATING HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Callie Clark[1] Menam Pokhrel[1] Benjamin Arthur[1] Pramita Suresh[1] Ilayda Ates[1] Justin Gibson[1] Abishek Dhungana[1] Ryan Mehlem[1] Andrew Boysia[1] Mugdha Padalkar[2] Jing Echesabal-Chen[1] Anne Vonada[3] Alexis Stamatikos[1] Olga Savinova[2] Markus Grompe[3] Renee Cottle[1], [1]Clemson University, [2]New York Institute of Technology College of Osteopathic Medicine, [3]Oregon Health & Science University

Background: We previously showed that LNP-mediated delivery of cytochrome P450 oxidoreductase (*Cypor*)-Cas9 ribonucleoproteins (RNP) combined with transient APAP treatment enables selective liver repopulation and phenotypic rescue in a phenylketonuria mouse model. Separately, we demonstrated that electroporation of CRISPR-Cas9 mRNA and RNPs corrects hereditary tyrosinemia type I. Here, we apply electroporation of Cypor-targeting Cas9 RNPs into wild-type hepatocytes, followed by APAP-driven selection, as a potential cell therapy for homozygous familial hypercholesterolemia (*Ldlr*$^{-/-}$). **Methods:** Hepatocytes from C57BL/6J mice were electroporated with *Cypor*-Cas9 RNPs and transplanted into 6-week-old male *Ldlr*$^{-/-}$ mice. At 12 days post-transplantation, recipients were randomized to receive biweekly APAP injections (n = 8) or no treatment (n = 8). After 10 days of APAP selection, half of each group (n = 4) was switched to a Western diet. Blood was collected after a 5-hour fast at baseline, post-APAP selection, and after 5 weeks on the Western diet for lipid profiling (total cholesterol, LDL-C, TG). At study endpoints (post-APAP or 12-week Western diet), livers and hearts were collected for indel analysis, atherosclerosis quantification (Oil Red O staining), and assessment of liver and kidney function markers in serum. **Results:** We observed up to 13% engraftment of electroporated Cypor-deficient hepatocytes with indels in the livers of *Ldlr*$^{-/-}$ mice following APAP administration, while negligible engraftment was observed in no-APAP controls (mean 9% and 2%, respectively, p = 0.0121). Engraftment of Cypor-deficient Ldlr-expressing hepatocytes reduced total cholesterol (5%), LDL-C (18%), and TG (52%) levels relative to untransplanted *Ldlr*$^{-/-}$ mice on the 5-week Western diet, but did not mitigate aortic atherosclerosis or steatosis. While biochemical markers for liver damage normalized post-APAP, we observed lipid accumulation in Cypor-deficient hepatocytes of *Ldlr*$^{-/-}$ grafted mice maintained on a regular chow diet, likely due to impaired cholesterol metabolism and clearance resulting from *Cypor* disruption. **Conclusion:** In contrast to findings from phenylketonuria mouse model studies, the disruption of Cypor function in recipient *Ldlr*$^{-/-}$ mice could not be compensated by unedited native hepatocytes, suggesting that a one-size-fits-all gene editing cell-based therapy approach may not be viable for inherited metabolic liver diseases. In ongoing studies, we will evaluate the use of CRISPR-Cas9-mediated gene editing to disrupt Cyp enzymes required for APAP metabolism, specifically Cyp2E1, with and without simultaneous disruption of Cyp1A2. In contrast to Cypor knockdown, the simultaneous knockdown of Cyp2E1 and Cyp1A2 is predicted to clear lipids more efficiently from the liver.
Disclosures: Callie Clark: Nothing to Disclose, Menam Pokhrel: Nothing to Disclose, Benjamin Arthur: Nothing to Disclose, Pramita Suresh: Nothing to Disclose, Ilayda Ates: Nothing to Disclose, Justin Gibson: Nothing to Disclose, Abishek Dhungana: Nothing to Disclose, Ryan Mehlem: Nothing to Disclose, Andrew Boysia: Nothing to Disclose, Mugdha Padalkar: Nothing to Disclose, Jing Echesabal-Chen: Nothing to Disclose, Anne Vonada: Nothing to Disclose, Alexis Stamatikos: Nothing to Disclose, Olga Savinova: Nothing to Disclose, Markus Grompe: Nothing to Disclose, Renee Cottle: Nothing to Disclose

4300 | NEXT GENERATION WHOLE EXOME SEQUENCING OF LIVER TISSUES IN INDIAN HEPATOCELLULAR CARCINOMA PATIENTS TO IDENTIFY THE ACTIONABLE MUTATIONS

Baibaswata Nayak[1] SONU KUMAR[1] Neeti Nadda[1] Dibyabhabha Pradhan[1] Shivanand Gamanagatti[1] Nihar Dash[1] . Shalimar[1], [1]All India Institute of Medical Sciences, New Delhi, India

Background: Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and third leading causes of cancer-mortality worldwide. HCC occurs mostly in the background chronic liver disease (CLD) either due to viral (HBV and HCV) and non-viral (alcohol, Fatty liver) etiology. Hepatocarcinogenesis usually initiated from chronic necro-inflammation of liver resulting inflammation mediated DNA damage, somatic mutations, virus induced molecular alterations in cancer hallmark genes. HCC often diagnosed at an advanced stage and not

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found suitable for curative surgical options and mostly managed by locoregional therapy (LRT) and systemic chemotherapy using multikinase inhibitor (MTKI), combination therapy of immune check-point inhibitor and VEGF inhibitor. Next Generation Sequencing (NGS) of liver tissue can reveal HCC tumor heterogeneity and molecular profile. It can identify actionable somatic mutations those can influence treatment decisions and selection of targeted therapies or immunotherapies. **Methods:** Trans-jugular liver biopsies (TJLB) samples were obtained from 20 HCC cases by interventional radiologist and surgically resected normal liver tissues from 10 disease control were taken by GI surgeon. The genomic DNA from liver tissues were isolated using the QIAamp mini genomic DNA isolation kit (Qiagen). Twist Human comprehensive exome kit was used for library preparation. Sequencing was performed on a NovaSeq 6000 platform 550 (Illumina, San Diego, USA) following the manufacture's instructions. Quality checks and analysis was performed using the GATK pipeline. Pathogenic/likely pathogenic exonic variants were annotated. Kyoto Encyclopaedia of Genes and Genomes (KEGG) and Gene ontology analysis was done for pathogenic / likely pathogenic variants and functional annotation was done using DAVID tool. **Results:** The HCC patients recruited (n = 20) are of both viral (75%) and nonviral (25%) etiology. The disease control (n = 10) included patients of periampullary carcinoma, carcinoma of gallbladder, oesophagus and pancreas. In whole exome sequencing, we observed pathogenic/ likely pathogenic mutations in 35 genes of HCC patients and 14 genes for disease control, of which 8 genes were common in both HCC and disease control. The somatic mutationswere observed in 27 genes were unique to HCC patients. Actionable mutations are functionally annotated to PD-L1/ PD-1 checkpoint pathway, VEGF, B and T cell receptor signalling pathway, chemical carcinogenesis, stem cells pluripotency signalling pathways and hepatocarcinogensis. The prevalent somatic mutations which could be considered as actionable mutation are KRAS (p.Q61H), PI3KCA (p.H1047R), PRKCQ (p.P330L, 30%), HSP27 (p.Q190H), NQO1 (p.P115S), CTNNB1 (p.D32G) and BCL10 (p.I46X). **Conclusion:** We have identified actionable mutations in HCC tissue which may contribute to clinical selection and modulate treatment response.

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4301 | B-ARRESTIN2 FACILITATES LIVER REGENERATION IN CIRRHOSIS BY INHIBITING BECLIN1-MEDIATED FERRITINOPHAGY-DEPENDENT FERROPTOSIS

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Background: The presence of cirrhosis is a critical factor contributing to inadequate regeneration following partial hepatectomy (PHx), significantly impacting postoperative recovery and patient prognosis. Currently, the underlying mechanisms responsible for inadequate liver regeneration in the context of cirrhosis remain poorly understood, and effective clinical interventions to address regenerative deficits post-hepatectomy in cirrhotic patients are lacking. **Methods:** Initially, we conducted RNA sequencing on liver specimens obtained from both cirrhotic patients and healthy controls undergoing Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) to elucidate the relationship between ferritinophagy-dependent ferroptosis and liver regeneration in the context of cirrhosis. Subsequently, employing mass spectrometry analysis on liver specimens from both cirrhotic and normal mice pre- and post-70% hepatectomy, alongside database predictions and investigations in β-arrestin2 (ARRB2) knockout mice and their wild-type counterparts, we elucidated the regulatory function of the ARRB2 protein in ferritinophagy within a cirrhotic environment. Furthermore, utilizing mass spectrometry analysis, molecular docking, and co-immunoprecipitation (Co-IP), we identified the potential mechanism through which ARRB2 modulates ferritinophagy. Ultimately, we explored the impact of the ARRB2 agonist carvedilol on enhancing liver regeneration in cirrhotic conditions. **Results:** Ferritinophagy was found excessively activated in cirrhotic liver, and inhibiting ferritinophagy could mitigate ferroptosis in the liver and enhance PHx regeneration in murine models of liver fibrosis. Subsequent investigations demonstrated a significant upregulation of ARRB2 expression during liver regeneration in mice with liver fibrosis, and ARRB2 facilitates liver regeneration by modulating ferritinophagy-dependent ferroptosis. Further mechanistic exploration revealed that ARRB2 can competitively bind with Beclin1 against Atg14. Preclinical validation indicated that carvedilol, an ARRB2 agonist, effectively inhibited ferritinophagy and promoted liver regeneration following PHx in fibrotic liver models.

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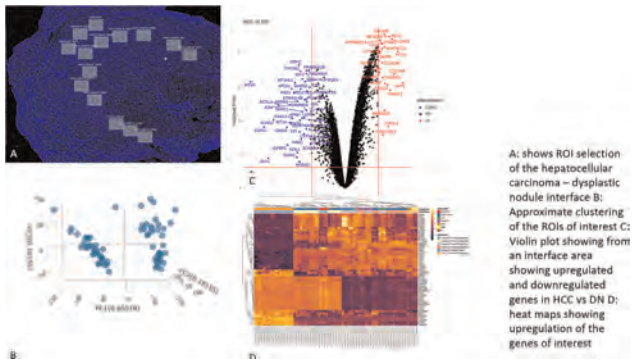
Conclusion: Our results demonstrated that ARRB2 enhances PHx regeneration in cirrhotic conditions by competitively binding to Beclin1, thereby downregulating ferritinophagy-dependent ferroptosis.
Disclosures: WenFeng Zhu: Nothing to Disclose, xijing yan: Nothing to Disclose, Genshu Wang: Nothing to Disclose, 小峰 蒋: Nothing to Disclose

4302 | MAPPING THE UNKNOWNS IN TUMOR EVOLUTION: SPATIAL TRANSCRIPTOMIC INSIGHTS INTO GENE EXPRESSION HETEROGENEITY AT THE HCC–DYSPLASTIC NODULE INTERFACE

Nigar Khurram[1], [1]University of Pittsburgh

Background: A comprehensive understanding of molecular, cellular, and tissue-level changes—and the dynamic interactions among diverse cell types—is essential for elucidating cancer development and progression. This is particularly crucial for characterizing the poorly understood transition from premalignant lesions to invasive carcinomas. At the hepatocellular dysplasia–carcinoma interface (HCC-DN), spatial transcriptomics (ST) enables high-resolution mapping of cellular composition and heterogeneity, offering insights into tumor initiation and progression, and identifying novel gene signatures that may guide personalized therapy and targeted treatments in HCC.We used GeoMx platform by Nansotring to further elucidiate HCC-DN interface areas. **Methods:** Slides were prepared according to the manufacturer's protocol without modification (Manual 10150-04, nanoString, Seattle, WA). FFPE samples were sectioned at 5 μm onto positively charged slides, dried overnight at 37° C, and stored at 4°C in sealed containers with desiccant (Drierite, Fisher Scientific) until use.
Antigen retrieval was performed using IHC Antigen Retrieval Solution (Invitrogen), followed by proteinase K digestion (Invitrogen) to expose mRNA. Whole transcriptome profiling was performed via in situ hybridization using HuWTA DNA oligonucleotide probes (nanoString), which contain UV-photocleavable linkers and unique molecular identifiers (UMIs) for downstream sequencing. SYTO13 nuclear stain was used for morphological reference.
Slides were imaged using the GeoMx Digital Spatial Profiler (nanoString) to generate whole-slide images at single-cell resolution. Circular regions of interest (ROIs; 600 × 785 μm) were selected based on SYTO13 staining and anatomical landmarks. UV light was used to photocleave bound oligonucleotides, which were aspirated from each ROI into individual wells of a 96-well plate.
Collected probes were processed and sequenced on an Illumina NextSeq 1000/2000. Sequencing depth was calculated from the total ROI area per sample. FASTQ files were decoded and processed into count matrices using the GeoMx NGS Pipeline (v2.0.21) in Illumina BaseSpace. Final count files were reuploaded and indexed to matched slide scans for spatially resolved transcriptomic analysis in the GeoMx DSP platform. **Results:** Spatial transcriptomioc analysis with GeoMx profiling showed HCC-DN interface with high SPP1 and ASPH (tumor markers) with extensive tumoral heterogeneity (see attached graphs for detailed analysis (word limit- full data presentedat conference). **Conclusion:** By leveraging spatial transcriptomics, we identified distinct gene expression profiles differentiating dysplastic tissue from invasive carcinoma, revealing a gradient of transcriptional and microenvironmental changes across this critical transition zone which serve as early biomarkers of malignant transformation for preventive intervention.



Disclosures: Nigar Khurram: Nothing to Disclose

4303 | IDENTIFICATION OF KEY PROTEINS IN CIRRHOSIS PROGRESSION VIA A BIOLOGICAL NETWORK (RICH-CLUB) ANALYSIS APPROACH

Paola Barrios[1] Indira Pla[2] Praneet Polineni[1] Aniel Sanchez[2] Michael Caldwell[2] Therese Banea[1] Neil Kelleher[2] Carl Atkinson[1] Daniela Ladner[3], [1]Northwestern University Comprehensive Transplant Center, [2]Northwestern University, Proteomics Center of Excellence, [3]Northwestern Memorial Hospital

Background: Cirrhosis affects millions, with 5-7% annually progressing to decompensation, yet current diagnostics cannot reliably predict this transition and no therapies to halt progression are currently available, creating an urgent need for novel approaches to identify key drivers. **Methods:** Plasma samples from 30 cirrhosis patients at 3 stages (compensated, portal hypertension (pHTN), decompensated) were analyzed. Protein interaction networks were constructed using correlation analysis ($r > 0.7$) on top-down proteomics data previously published by our group. Rich-club (RC) analysis measured non-random interconnectivity among hub proteins. Raw (φ; fraction of possible

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connections) and normalized RC coefficients (ρ; connectivity compared to 1,000 random networks) were calculated to identify and compare regulatory proteins (hubs) across stages. **Results:** Characterizing protein network: We analyzed 44 proteins across compensated, pHTN, decompensated cirrhosis. Connections per protein decreased from compensated (12.9) to pHTN (11.4) to decompensated (6.5), as did network density (0.6, 0.52, 0.48), revealing decreasing network complexity with disease progression (Fig 1A). Normalized network coefficients at $\rho > 1$ confirmed meaningful, non-random, biologically relevant networks (Fig 1B). Identifying significant proteins: Compensated cirrhosis exhibited RC structure at degree threshold $k = 6$ ($\varphi = 0.6$; $\rho = 1.44$) with 28 proteins having > 6 connections. Portal hypertension showed tighter RC at $k = 9$ ($\varphi = 0.8$; $\rho = 1.49$) with 23 proteins having > 9 connections. Decompensated cirrhosis showed RC at $k = 5$ ($\varphi = 0.7$; $\rho = 1.54$) with 18 proteins having > 5 connections, demonstrating network reorganization with fewer central hubs in decompensated cirrhosis. Identifying unique proteins: Apolipoprotein A-II (apoA-II) emerged as the sole unique hub protein in decompensated cirrhosis, and there were no unique hub proteins in pHTN. **Conclusion:** Protein networks show distinct Rich-Club organization across cirrhosis stages. pHTN exhibits highest raw RC coefficient and no unique hub proteins, suggesting tightly regulated adaptation of a compensated state. Decompensated cirrhosis shows breakdown of the protein network. ApoA-II emerged as a unique hub in decompensation, representing a potential biomarker to detect imminent decompensation before clinical signs appear.

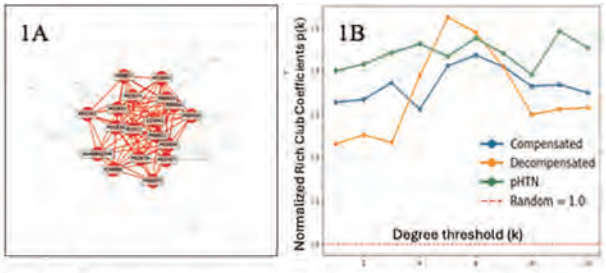

Fig 1A. Protein interaction network in decompensated cirrhosis.
Fig 1B. Normalized rich club coefficients (ρ) across different degree thresholds (k) for cirrhosis stages. Above the red dashed line (ρ>1.0) statistically significant rich club organization.

Disclosures: Paola Barrios: Nothing to Disclose, Indira Pla: Nothing to Disclose, Praneet Polineni: Nothing to Disclose, Aniel Sanchez: Nothing to Disclose, Michael Caldwell: Tempus AI: Stock - publicly traded company, Amgen: Stock - publicly traded company, Therese Banea: Nothing to Disclose, Neil Kelleher: Nothing to Disclose, Carl Atkinson: Nothing to Disclose, Daniela Ladner: Nothing to Disclose

4304 | ESTABLISHMENT OF ASSAY LIMITS FOR DIFFERENTIAL GENE EXPRESSION AND DNA METHYLATION TO CHARACTERIZE SPECIFICITY OF EPIGENETIC EDITING

Erica Hildebrand[1] Amber DiPiazza[1] Ava Zhai[1] Alaina Villarreal[1] Parthu Koppana[1] Sameer Abraham[1] Xiaoyun Guo[1] Yasamun Rezvani[1] Jhon Medina[1] Yesseinia Anglero-Rodriguez[1] Melissa Bonner[1] Ricardo Ramirez[1], [1]nChroma Bio

Background: Epigenetic editing is a novel therapeutic modality that leverages DNA methylation with the intention to durably silence target genes at the level of transcription without cutting or nicking the DNA. Quantification of intended and unintended modifications of DNA methylation and gene expression are important for understanding the potential for therapeutic benefit and safety implications, respectively. A novel and comprehensive analytical approach was used to establish robust metrics for epigenetic specificity assessment. **Methods:** Control RNA and DNA experiments were utilized to determine the assay limits and data quality requirements for RNA-seq and both targeted and genome-wide (WGMS) DNA methylation assays. Appropriate thresholds and parameters for nominating differentially expressed genes (DEG) and differentially methylated regions (DMR) were established using a tool PCSK9 epigenetic editor (PCSK9-EE) in vitro in the Hep3B cell line, paired with an in silico mixing strategy. Finally, these data quality requirements and analysis parameters were applied to epigenetically edited primary cells. **Results:** To ensure robust detection of unique genes and coverage of CpGs, minimum sequencing depth requirements were determined for total RNA-seq libraries (> 50M read-pairs), targeted methylation sequencing (> 120M read-pairs), and WGMS (> 1B read-pairs). With these requirements, the LLOQ of the total RNA-seq assay was determined to be 585.94 attomoles/1 μg total RNA, which corresponds to 3.5 TPM. Analysis thresholds and parameters to nominate a DEG or DMR for confirmatory assays were determined by balancing detection of false positives with the detection of true positives using an in silico mixing strategy and parameter sweep for RNA-seq, targeted hybrid capture, and WGMS. Application of these data quality requirements and DEG/DMR specificity parameters demonstrate no substantial unintended increases in methylation with associated decreases in gene expression in an epigenetically edited primary cell experiment. **Conclusion:** We have established a robust standard for quantification of intended and unintended methylation and gene expression changes induced by epigenetic editors, a key component in the assessment of potential therapeutic

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benefit and safety implications of this novel therapeutic modality.

Disclosures: Erica Hildebrand: nChroma Bio: Employee, nChroma Bio: Stock – privately held company, Chroma Medicine: Employee, Chroma Medicine: Stock – privately held company, Amber DiPiazza: Nothing to Disclose, Ava Zhai: Nothing to Disclose, Alaina Villarreal: Nothing to Disclose, Parthu Koppana: Nothing to Disclose, Sameer Abraham: Nothing to Disclose, Xiaoyun Guo: Nothing to Disclose, Yasamun Rezvani: Nothing to Disclose, Jhon Medina: nChroma Bio: Employee, Yesseinia Anglero-Rodriguez: Nothing to Disclose, Melissa Bonner: Nothing to Disclose, Ricardo Ramirez: Nothing to Disclose

4305 | MACHINE LEARNING–BASED FRAMEWORK FOR EARLY DETECTION, SEVERITY STRATIFICATION, AND PROGNOSTIC MODELING OF LIVER DISEASE IN AN INDIAN PATIENT COHORT

Sri Harsha Boppana[1] Manaswitha Thota[2] Gautam Maddineni[3] Sachin Sravan Kumar Komati[4] Sai Lakshmi Prasanna Komati[5] C. David Mintz MD PhD[6], [1]Nassau University Medical Center / Johns Hopkins University, [2]Virginia Commonwealth University, [3]Creighton university school of medicine, [4]Florida International University, [5]Government Medical College, Ongole, [6]Johns Hopkins University

Background: Chronic liver conditions frequently remain asymptomatic until reaching advanced stages, posing a significant burden worldwide. We employed a combination of supervised and unsupervised machine learning methods—including random forest classification, k-means clustering, and long short-term memory (LSTM) networks. Our objectives were to improve early identification of liver disease, derive severity stages without predefined labels, and predict future bilirubin values and disease progression. **Methods:** Data were drawn from the Indian Liver Patient Dataset (583 records) containing demographic information (age, gender) and biochemical markers (total and direct bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, albumin–globulin ratio). We imputed missing albumin–globulin ratios using the mean, encoded gender as a binary variable, and engineered interaction features (age × total bilirubin; gender × alkaline phosphatase). Continuous variables were standardized, and the cohort was split into 80% training and 20% testing sets. A random forest classifier distinguished diseased from non-diseased cases. To infer disease severity in an unsupervised manner, we applied k-means clustering (k = 3) on the normalized features and labeled clusters as mild, moderate, or severe based on their biochemical profiles. A second random forest was then trained on these inferred labels to predict severity in new patients. Finally, we generated synthetic longitudinal data by simulating five visits at 30-day intervals with added Gaussian noise. We trained LSTM networks to forecast next-visit bilirubin levels and severity stages using the previous three visits' data. **Results:** On the held-out test set, the disease classifier achieved 81.2% accuracy, with precision and recall both exceeding 0.80 for the positive class. Clustering produced three subgroups of roughly equal size, each characterized by distinct biochemical signatures. The severity classifier attained 99.1% accuracy in assigning mild, moderate, or severe labels. The bilirubin-forecasting LSTM yielded a mean absolute error of 1.07 mg/dL, while the severity-forecasting LSTM reached 96% overall accuracy and achieved an F1-score of 0.92 for the severe category. These outcomes demonstrate that a multi-modal machine learning pipeline can accurately detect liver disease, stratify its severity, and anticipate biomarker and stage trajectories. (Figure1). **Conclusion:** Our integrative approach—combining classification, clustering, and sequence modeling—delivered robust performance across key tasks: disease detection, severity stratification, bilirubin prediction (MAE = 1.07 mg/dL), and stage forecasting (96% accuracy). This framework shows promise for enabling earlier diagnosis, personalized risk assessment, and proactive management in liver disease care.

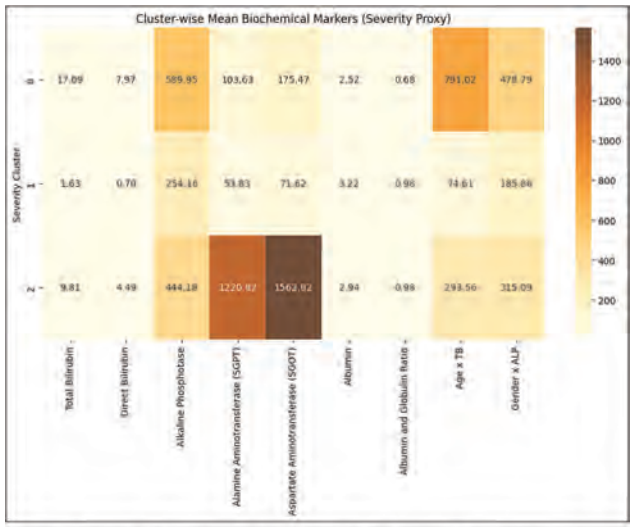

Figure 1 : Cluster wise mean Biochemical markers.

Disclosures: Sri Harsha Boppana: Nothing to Disclose, Manaswitha Thota: Nothing to Disclose, Gautam Maddineni: Nothing to Disclose, Sachin Sravan Kumar Komati: Nothing to Disclose, Sai Lakshmi Prasanna Komati: Nothing to Disclose, C. David Mintz MD PhD: Nothing to Disclose

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4306 | SHARED GENETIC VARIANTS BETWEEN LONG COVID AND VIRAL HEPATITIS B AND C INDIVIDUALS: ASSOCIATION WITH POLYMORPH IN THE PLXNA4 AND DPP9 GENES

Lucas da Silva[1] Douglas Maya-Miles[2] Juliana Maul[3] Iolanda Paulo[3] Lia Lewis[3] Vanessa de Paula[4] LIVIA VILLAR[5] Manuel Romero-Gomez[6], [1]Oswaldo Cruz Foundation, FIOCRUZ, Viral Hepatitis Laboratory, [2]SeLiver Group, Institute of Biomedicine of Seville, University of Seville, Seville, Spain., [3]National Reference Laboratory for Viral Hepatitis, Institute Oswaldo Cruz, Fiocruz, Rio de Janeiro, [4]Molecular Virology and Parasitology Laboratory, Institute Oswaldo Cruz, Oswaldo Cruz Foundation, [5]FIOCRUZ, [6]SeLiver Group, Institute of Biomedicine of Seville, University of Seville, Seville, Spain

Background: Long COVID is defined by symptoms lasting over 90 days after SARS-CoV-2 infection. It may share molecular and immune features with chronic infections like hepatitis B and C. Genetic factors, particularly single nucleotide polymorphisms (SNPs), influence susceptibility and disease progression. Studying SNPs in these conditions may uncover shared mechanisms. This study aims to investigate associations between specific SNPs and the presence of viral hepatitis B or C and Long COVID, exploring potential shared genetic signatures. **Methods:** 96 individuals were recruited from the Viral Hepatitis Outpatient Clinic, Fiocruz, Rio de Janeiro, Brazil. For analysis, participants were grouped as Hepatitis B and C carriers ($n = 49$) vs. non-carriers ($n = 47$), and Long COVID carriers ($n = 49$) vs. non-carriers ($n = 47$). Peripheral blood was collected for genomic DNA extraction (Qiagen). Eighteen SNPs were selected from literature related to COVID-19 and viral hepatitis. SNP genotyping was performed by real-time PCR (ThermoFisher) at the Institute of Biomedicine of Seville at the University of Seville, Spain, in collaboration with the SeLiver Group. Statistical analysis utilized the SNPStats tool. **Results:** Hepatitis carriers were significantly more probable to have the A allele of SNP rs1424597 G > A (*PLXNA4* gene, linked to a higher risk of long COVID-19), with 47.8% carrying this variant. This corresponded to a risk of more than double among this group (OR = 2.36; 95% CI: 1.01-5.49; $p < 0.05$). For Long COVID individuals, SNP rs12610495 A > G (*DPP9* gene, associated with clinical worsening and increased risk of developing Long COVID) was identified in codominant model as a risk factor in Long COVID individuals (OR = 2.41; 95% CI: 1.01–5.73). The A/G genotype was present in most Long COVID individuals (49%). Confirmed in the overdominant model, comparing A/G to homozygotes (OR: 2.44; CI 95%: 1.04–5.71). **Conclusion:** Genetic variants previously associated with long COVID have been identified as risk factors in individuals with hepatitis or long COVID, suggesting possible shared genetic pathways that contribute to chronicity in both conditions.

Disclosures: Lucas da Silva: Nothing to Disclose, Douglas Maya-Miles: Nothing to Disclose, Juliana Maul: Nothing to Disclose, Iolanda Paulo: Nothing to Disclose, Lia Lewis: Nothing to Disclose, Vanessa de Paula: Nothing to Disclose, LIVIA VILLAR: Nothing to Disclose, Manuel Romero-Gomez: Nothing to Disclose

4307 | N-LOREM FOUNDATION: A NON-PROFIT BIOTECH IS TRANSFORMING THE LANDSCAPE OF PERSONALIZED MEDICINES IN GENETIC LIVER DISEASES

Konstantina Skourti Stathaki[1] Craig McIntosh[2] Lesley Saldana[2] Wei Zhang[2] Anthony Vu[2] Emily Miyoshi[2], [1]n-Lorem Foundation, [2]N-Lorem Foundation -

Background: The n-Lorem Foundation is pioneering a new paradigm in the development of individualized medicines for patients with ultra-rare genetic diseases. As a unique non-profit biotech, n-Lorem provides *free, lifetime treatment* to patients with liver genetic diseases who would otherwise be invisible to traditional drug development pathways- those with mutations found in one or a few individuals worldwide. **Methods:** In this presentation, we will share how we are building a scalable and sustainable model to treat liver diseases today that challenges the conventions of therapeutic development. Since our inception, we have received over 330 applications, launched more than 160 patient-directed drug discovery programs, submitted 25+ INDs, and treating 27 patients today. Our approach is deeply rooted in our over 35-year of experience in RNA-targeted therapies, especially antisense oligonucleotides (ASOs), offering precision tools that match the urgency and specificity of each patient's liver mutation and condition. **Results:** We will provide an overview of our mission and model, outline our end-to-end discovery and development process for two liver targets that we are developing ASOs for—one for a 9-month-old infant and another for a 13-year-old child—and discuss the scientific considerations that shape our work. We will also highlight how our close working relationship with the FDA, our unwavering focus on individual patients, and our deep scientific and clinical expertise are allowing us to deliver highly personalized RNA-targeted treatments for liver diseases where no other options exist. **Conclusion:** The n-Lorem Foundation is redefining what is possible in the treatment of ultra-rare liver genetic diseases by advancing a patient-first, mutation-specific approach to RNA-targeted drug development. Our model demonstrates that individualized, lifelong treatment can be both scientifically rigorous and operationally scalable. As we continue to expand our programs, we aim to set a precedent for how the rarest patients - those traditionally left behind - can be meaningfully and sustainably served. Our work offers

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unprecedented hope and a new vision for precision medicine, driven by compassion, innovation, and impact.
Disclosures: Konstantina Skourti Stathaki: Nothing to Disclose, Craig McIntosh: Nothing to Disclose, Lesley Saldana: Nothing to Disclose, Wei Zhang: Nothing to Disclose, Anthony Vu: Nothing to Disclose, Emily Miyoshi: Nothing to Disclose

◆ 4308 | PARALLELIZED IN VIVO SCREENING IN A NON-HUMAN PRIMATE MODEL PREDICTS PHENOTYPIC EFFECTS OF GWAS VARIANTS AND CLINICAL OUTCOMES

Joanne Hsieh Jingshu Chen[1] Linda Chio[1] Christopher Carrico[1] Daniel Fuentes[1] Arnav Gupta[1] Shengping Wang[1] Vinay Kartha[1] Hikaru Miyazaki[1] Dimitry Popov[1] Chris Towne[1] Martin Borch Jensen[1] Francisco LePort[1], [1]Gordian Biotechnology

Background: Murine hepatic metabolism differs from humans in multiple pathways, including lipoprotein handling, bile acid production, and xenobiotic metabolism. Knocking out genes that were identified in human GWAS to be associated with MASLD, such as *Pnpla3* and *Hsd17b13*, showed very mild phenotypes in mouse models. One locus, *ADH1B*, is primate-specific. Modeling the functional effects of these human genetic associations may require a more translatable species. **Methods:** A male African Green Monkey (*Chlorocebus aethiops sabaeus*) was fed a high fat, cholesterol, and fructose diet for 82 weeks to induce MASH. A cocktail of barcoded AAV8 interventions was administered intravenously at a dose that transduced about 2% of hepatocytes to minimize crosstalk between perturbed cells. The left lobe was resected 6 weeks later. Individual hepatocyte transcriptomic responses to these interventions was profiled by single nucleus RNA-Sequencing. **Results:** The AAV8 cocktail induced transient hepatic inflammation that largely resolved within 6 weeks. The NHP recovered well post-partial hepatectomy, with continued weight gain for at least 6 months. Overexpression of *PNPLA3* I148M increased expression of inflammasome and senescence genes and reduced hepatocyte support for micronutrient delivery. Overexpression of the *HSD17B13* transcript isoform D reduced genes in the complement and coagulation pathways. *ADH1B* overexpression, mimicking the protective *ADH1B*2* allele, enhanced NAD generation, mitochondrial oxidation, and anaplerotic pathways. Ectopic hepatocyte expression of a GLP-1 analogue reduced expression of genes involved in cholesterol, glycosphingolipid, and sphingomyelin synthesis. These changes were unexpected, as hepatocytes lack GLP-1R, implying a paracrine mechanism driven by GLP-1R agonism in neighboring cells. C57Bl/6N mice fed an obesogenic MASH diet and treated daily with semaglutide lost weight rapidly during the first 2 weeks. Thereafter, semaglutide-treated animals resumed weight gain at rates similar to vehicle-treated animals, yet ALT remained suppressed. **Conclusion:** Our target discovery platform enables multiple hepatocyte-directed interventions to be queried in a single NHP without euthanizing the animal. We were able to detect changes induced by a GLP-1 analogue at the hepatocyte level through second-order transcriptomic effects. Some beneficial effects of GLP-1 on hepatocytes therefore appear to occur through paracrine interactions and independent of weight loss.
Disclosures: Joanne Hsieh: Nothing to Disclose, Jingshu Chen: Nothing to Disclose, Linda Chio: Gordian Biotechnology: Employee, Gordian Biotechnology: Stock – privately held company, Christopher Carrico: Nothing to Disclose, Daniel Fuentes: Nothing to Disclose, Arnav Gupta: Nothing to Disclose, Shengping Wang: Nothing to Disclose, Vinay Kartha: Nothing to Disclose, Hikaru Miyazaki: Nothing to Disclose, Dimitry Popov: Nothing to Disclose, Chris Towne: Nothing to Disclose, Martin Borch Jensen: Nothing to Disclose, Francisco LePort: Nothing to Disclose

◆ 4309 | FECAL MICROBIOTA TRANSPLANTATION IMPROVES GUT MICROBIAL DIVERSITY AND REDUCES ANTIMICROBIAL RESISTANCE IN CIRRHOSIS: RESULTS: FROM A RANDOMIZED CONTROLLED TRIAL

Ankit Agarwal[1] Samagra Agarwal[1] Daizee Talukdar[2] Sagnik Biswas[1] Bhabatosh Das[2] . Shalimar[1], [1]All India Institute of Medical Sciences, New Delhi, [2]Microbial Research Centre, BRIC-THSTI, Faridabad, Haryana

Background: Fecal microbiota transplantation (FMT) has demonstrated clinical benefits in conditions such as *Clostridioides difficile* infection and inflammatory bowel disease. Emerging evidence also suggests that FMT may reduce hepatic encephalopathy recurrence rates. In this randomized trial, we evaluated whether two infusions of FMT could enhance the resolution of minimal hepatic encephalopathy (MHE) and modulate gut microbiota composition and antimicrobial resistance (AMR), compared to standard daily lactulose therapy. **Methods:** In this randomized trial, 130 patients with cirrhosis and MHE (1:1) received either two sessions of FMT (one-month apart) or daily oral lactulose for 3 months. The primary outcome was MHE resolution at 3 months (PHES $>$ -5). Gut microbiome composition was analyzed using targeted metagenomic sequencing via next-generation sequencing (NGS). To

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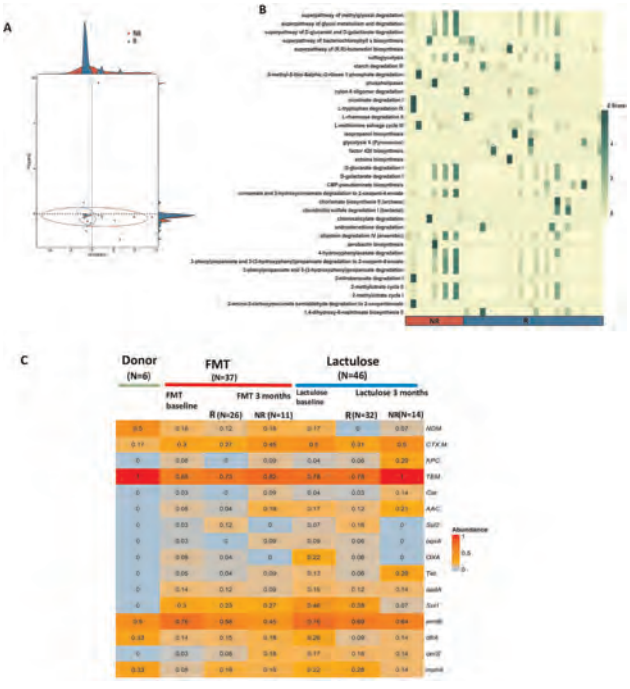
assess the antimicrobial resistance (AMR) gene profile, fecal samples were screened with gene-specific oligonucleotide probes targeting 16 distinct resistance genes. **Results:** Of 122 patients analyzed (FMT: 60; lactulose: 62; age: 44.3 ± 8.9 years; 96.7% male; Child A/B/C: 32.1% / 53.3% / 14.6%; median MELD: 13), 3-months MHE resolution was similar between FMT and lactulose group (68.3% vs 66.1%; p = 0.80). A total of 172 fecal samples were analyzed, including paired samples from FMT arm: 37/60 (61.7%) and lactulose arm: 46/62 (74.2%). FMT resulted in a modest, non-significant increase in microbial richness, as assessed by the Observed and Chao1 indices. At the taxonomic level, *Bifidobacterium* was significantly enriched in the MHE responders (3 months post-treatment) compared to the non-responders within the FMT cohort (p = 0.02), a difference not observed in the Lactulose group (p = 0.69). Conversely, *Escherichia* (p = 0.20) and *Enterococcus* (p = 0.37) showed lower mean relative abundances in the MHE responders after FMT at 3 months. Functional pathway analysis identified upregulation of creatinine degradation in the MHE responders (Figure). Notably, AMR gene prevalence was higher in the MHE non-responders across both treatment arms. **Conclusion:** While both FMT and lactulose demonstrated comparable efficacy in improving MHE, FMT offered additional benefits, including enhanced gut microbial diversity and a reduction in AMR. Larger, multicenter studies with longer follow-up are required to validate our findings and optimise FMT protocols for clinical use.



Disclosures: Ankit Agarwal: Nothing to Disclose, Samagra Agarwal: Nothing to Disclose, Daizee Talukdar: Nothing to Disclose, Sagnik Biswas: Nothing to Disclose, Bhabatosh Das: Nothing to Disclose, . Shalimar: Nothing to Disclose

◆ 4310 | AN INNOVATIVE DREAM (DISTAL RECIRCULATION OF ENTERAL CONTENTS AUGMENTED MECHANICALLY) PROTECTS AGAINST LIVER INJURY AND PROMOTES INTESTINAL ADAPTATION

Shaurya Mehta Kento Kurashima[1] chandrashekhara manithody[1] Ashlesha Bagwe[1] Marzena Swiderska-Syn[1] Austin Sims[1] Sree Kolli[1] Aditya Jain[2] Miguel Guzman[1] Sherri Besmer[1] Sonali Jain[1] Paula Buchanan[1] Keith Pereira[1] Chien-Jung Lin[1] John Long[1] Matthew McHale[1] Chelsea Hutchinson[1] Ajay Jain[1], [1]Saint Louis University, [2]Johns Hopkins University

Background: Short bowel syndrome (SBS) prevents sustenance of nutritional needs via regular enteral nutrition (EN) and requires parenteral nutrition, resulting in detrimental side effects. Intestinal adaptation (IA), which is driven by EN remains a major goal. We have developed a revolutionary DREAM system (Distal Recirculation of Enteral contents Augmented Mechanically, US patent 63/413,988), Fig 1-1, which allows full EN despite SBS and tested its impact on SBS related complications. **Methods:** 20 neonatal pigs were randomly allocated to EN, SBS (75% bowel resection) or DREAM. Weight gain, serum chemistries, cytokines, intestinal morphology, tight junction integrity, hepatic histology, and gene expression were analyzed. **Results:** DREAM animals demonstrated significant attenuation of liver and intestinal injury compared to SBS. DREAM reduced serum bilirubin (0.11 mg/dL vs. SBS 5.14 mg/dL, $p = 0.0008$), GGT (23.2 IU/L vs. SBS 114.6 IU/L, $p < 0.0001$), and total bile acids (9.7 μmol/L vs. SBS 39 μmol/L, $p = 0.0026$), Fig 1-2. DREAM also normalized inflammatory cytokines (e.g., IFN-γ, $p = 0.0296$; IL-1β, $p = 0.0349$; IL-6, $p = 0.0189$) and decreased LPS levels ($p = 0.0130$) versus SBS, Fig 1-3. DREAM preserved hepatic expression of BSEP and Cyp7A1 ($p = 0.0034$ vs. SBS), restored intestinal EGF and TGR5 signaling ($p < 0.01$), and reduced hepatic cholestasis scores ($p = 0.0012$ vs. SBS), Fig 1-4. IA markers, including linear gut density (proximal: 0.237 g/cm vs. SBS 0.121, $p = 0.0042$), villus-to-crypt ratio ($p = 0.0026$), Fig 1-5, and tight junction protein

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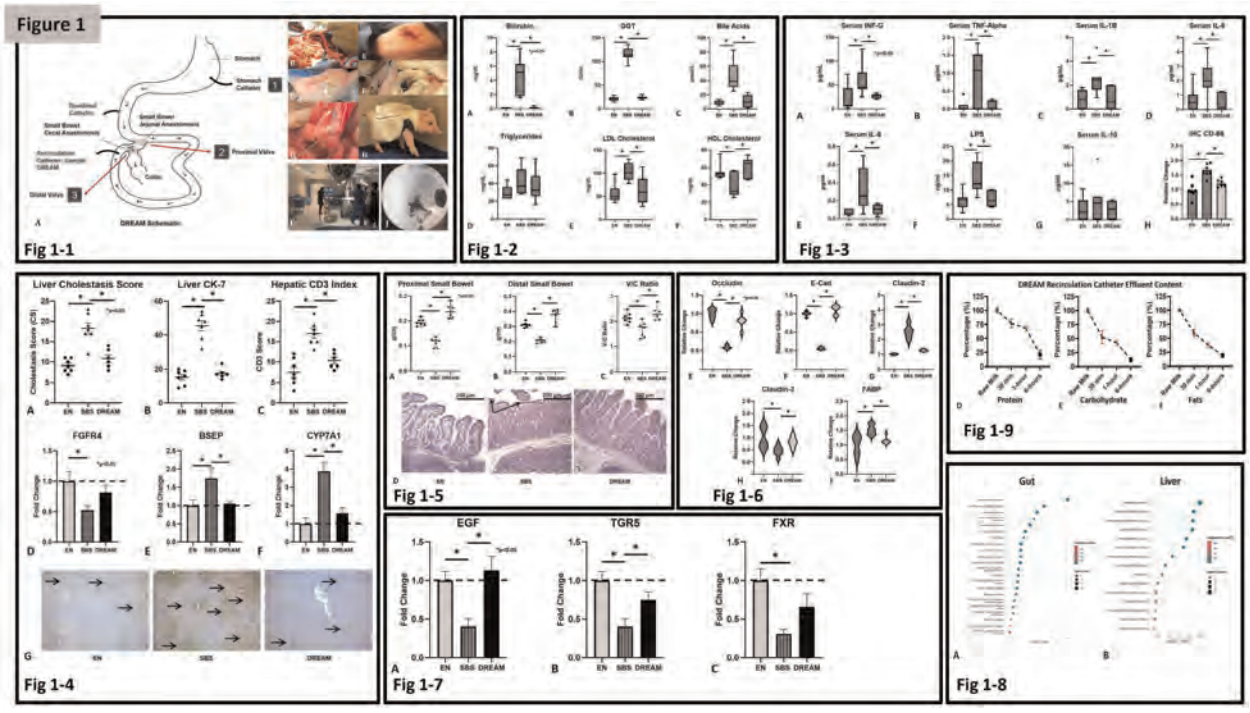
expression (e.g., Occludin, $p < 0.0001$; E-cadherin, $p = 0.0002$) mirrored EN animals and significantly improved with DREAM, Fig 1-6. DREAM reduced transcriptional dysregulation, Fig 1-7 and reactivated key functional pathways, resulting in a gene expression profile more similar to EN, Fig 1-8. Macronutrient absorption from recirculated enteral feeds was rapid and sustained, with >80% absorption of protein and fat by 6 hours ($p < 0.0001$), Fig 1-9. **Conclusion:** DREAM enables full EN despite SBS to restore nutrient absorption and gut derived signaling, mitigating intestinal and hepatic injury. This innovative, translation system highlights a major advancement in SBS management bringing a paradigm shift to life saving strategies for SBS patients.



Disclosures: Shaurya Mehta: Nothing to Disclose, Kento Kurashima: Nothing to Disclose, chandrashekhara manithody: Nothing to Disclose, Ashlesha Bagwe: Nothing to Disclose, Marzena Swiderska-Syn: Nothing to Disclose, Austin Sims: Nothing to Disclose, Sree Kolli: Nothing to Disclose, Aditya Jain: Nothing to Disclose, Miguel Guzman: Nothing to Disclose, Sherri Besmer: Nothing to Disclose, Sonali Jain: Nothing to Disclose, Paula Buchanan: Nothing to Disclose, Keith Pereira: Nothing to Disclose, Chien-Jung Lin: Nothing to Disclose, John Long: Nothing to Disclose, Matthew McHale: Nothing to Disclose, Chelsea Hutchinson: Nothing to Disclose, Ajay Jain: Nothing to Disclose

◆ 4311 | TARGETING THE GUT–LIVER AXIS: GRAPHENE OXIDE NANOPARTICLES RESTORE BARRIER FUNCTION, REBALANCE MICROBIOTA, AND SUPPRESS MIR-203A–TLR4 PATHWAY IN ALCOHOL ASSOCIATED LIVER DISEASE

Hiral Aghara[1] Manali Patel[2] Prashsti Chadha[2] Palash Mandal[2], [1]Department of Biological sciences, [2]P D Patel Institute of Applied Sciences

Background: Alcohol-induced liver disease (ALD) remains a major global health concern, driven in part by chronic gut barrier dysfunction, microbial imbalance (dysbiosis), and inflammation. Excessive alcohol consumption disrupts intestinal tight junctions, increasing gut permeability and allowing toxic microbial metabolites to translocate to the liver via the portal vein. This promotes liver inflammation through the activation of the TLR4 signalling pathway, a process exacerbated by the upregulation of miR-203a. Graphene oxide nanoparticles (GONPs) have shown potential as anti-inflammatory and antioxidant agents. In this study, we explored whether GONPs could protect against ALD by restoring gut barrier integrity, rebalancing gut microbiota, and modulating inflammatory responses. **Methods:** Male Wistar rats (n = 6 per group) were allocated into five groups: Control, Diseased (ethanol-fed), Pair-fed,

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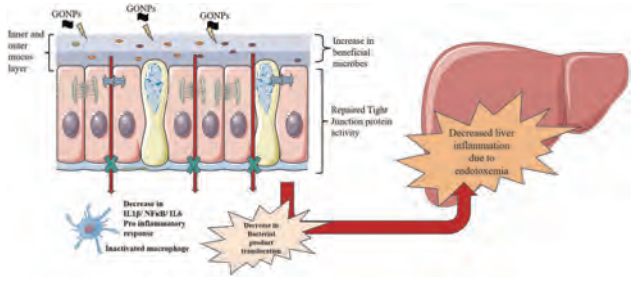
GONPs alone, and Treatment (ethanol + GONPs). Control and GONPs groups received standard chow diet, while the Diseased, Pair-fed, and Treatment groups were fed Lieber-DeCarli liquid diets. The Pair-fed group received an isocaloric maltodextrin substitute, while Diseased and Treatment groups received 5% ethanol continuously for 28 days, with binge doses of 30.5% ethanol administered for 2 consecutive days every 10 days. GONPs were administered orally five times during the study at 5-6 day intervals. Fecal samples underwent 16S rRNA gene sequencing for microbial analysis. Colon and liver tissues were evaluated histologically by hematoxylin and eosin staining. RT-qPCR assessed expression of tight junction genes and miR-203a. **Results:** GONPs treatment led to notable changes in the gut microbial community, including an increase in short-chain fatty acid producing bacteria associated with intestinal health. Histological analysis revealed improved colonic architecture and tight junction preservation in GONP and ethanol treated rats compared to the ethanol-only group. Gene expression analysis showed enhanced expression of tight junction markers (Zona occludin-1, Occludin and Claudin) of colon and reduced levels of miR-203a of liver tissue. These molecular changes were accompanied by decreased activation of the TLR4 pathway and reduced liver inflammation like TNF-α. **Conclusion:** Our findings suggest that GONPs offer protective effects against alcohol-induced liver injury by strengthening the gut barrier, restoring microbial balance, and down-regulating the miR-203a–TLR4 inflammatory axis. This study highlights the promise of GONPs as a novel nanotherapeutic strategy for managing ALD by targeting the gut–liver axis.



Disclosures: Hiral Aghara: Nothing to Disclose, Manali Patel: Nothing to Disclose, Prashsti Chadha: Nothing to Disclose, Palash Mandal: Nothing to Disclose

◆ 4312 | EXTENT OF BILIARY β- AND γ-CATENIN LOSS REGULATES INTESTINAL INFLAMMATION AND MICROBIOME DYSBIOSIS IN CHOLESTATIC MICE

Vik Meadows[1] Chang Kyung (Joanna) Kim[1] Elena Provencal[1] Minakshi Poddar[1] Satdarshan (Paul) Monga[1], [1]University of Pittsburgh

Background: Loss of β- and γ-catenin in cholangiocytes disrupts bile duct structure, leading to impaired bile flow and subsequent bile leakage. The expression of cholangiocyte markers in hepatocytes suggests that hepatocyte transdifferentiation may aid in repairing β- and γ-catenin-deficient bile duct loss over time. The response of the intestinal and gut microbiome to bile duct loss or hepatocyte transdifferentiation has not been studied. In this study, we characterize gut pathology and microbiome composition in models of acute and reparative cholestasis through the deletion of β- and γ-catenins from the biliary epithelium. **Methods:** We utilized Ctnnb fl/fl; Jup fl/fl mice with Opn-iCreERT2+/- to delete both β-catenin (Ctnnb1) and γ-catenin (Jup) from cholangiocytes. Littermate control with no Opn-iCreERT2+/+ were used as controls. All mice received tamoxifen (100 mg/kg) dissolved in corn oil injected intraperitoneally. Mice were randomly assigned to two groups: DKO2 received 2 doses of tamoxifen and DKO4 received 4 doses of tamoxifen. Male and female mice were used in this study. Plasma, liver, ileum, colon, feces, and cecum content were collected from all mice. **Results:** DKO4 mice exhibited increased morbidity with over 20% body weight loss, along with elevated serum levels of ALT, AST, and total bilirubin compared to DKO2 and control mice. DKO4 mice show reduced fecal TBA levels and circulating secondary bile acids compared to DKO2 and control mice. DKO2 mice display decreased fecal TBA two weeks after tamoxifen injection, which is restored by six weeks post-injection. DKO4 mice demonstrate significant inflammation, an increased number of goblet cells per crypt/villi unit, a rise in lysozyme-positive cells in the ileal villi, and heightened fecal lipocalin 2 levels compared to DKO2 and control mice. Additionally, microbial sequencing indicates that DKO4 mice have an increase in pathogenic bacterial genera, such as Prevotella, compared to WT mice, suggesting a favorable environment for pathobiont expansion due to decreased bile acid

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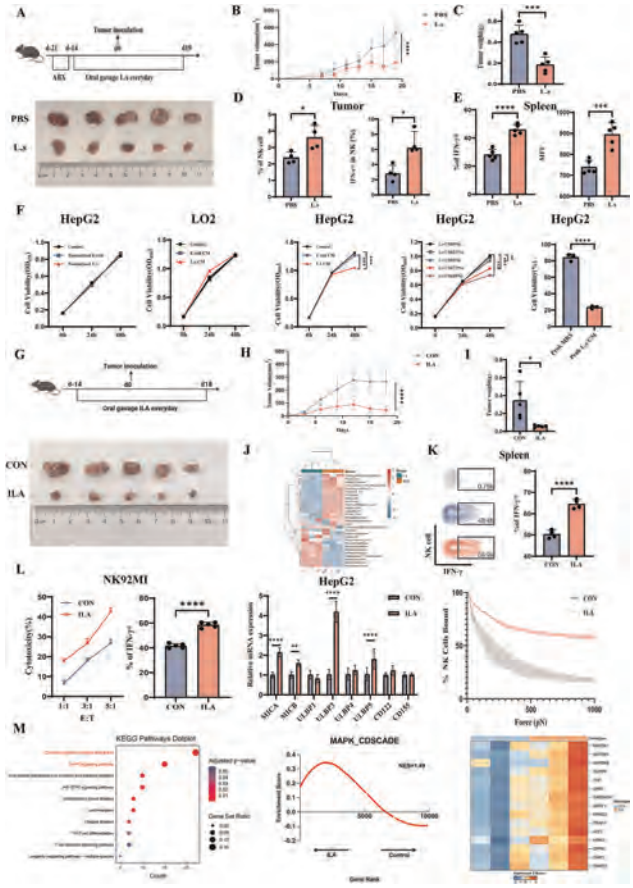
circulation. **Conclusion:** Dual loss of β- and γ-catenin from cholangiocytes causes severe intrahepatic cholestatic injury in mice which disrupts ileal epithelial cell populations. Severe bile duct loss in DKO4 mice results in decreased colonic mucin production and increased colonic inflammation, suggesting that bile duct health may influence gut function and bacterial clearance. Understanding the role of cholangiocytes in the gut-liver axis may assist in patient stratification based on fecal biomarkers and microbial signatures.

Disclosures: Vik Meadows: Nothing to Disclose, Chang Kyung (Joanna) Kim: Nothing to Disclose, Elena Provencal: Nothing to Disclose, Minakshi Poddar: Nothing to Disclose, Satdarshan (Paul) Monga: Mermaid Bio: Advisor, Vicero: Advisor, AntlerA: Advisor, Genentech: Speaking and Teaching, Alnylam: Grant/Research Support, Alnylam: Consultant, UbiquiTx: Consultant, Mermaid Bio: Consultant, Fog Pharmaceuticals: Grant/Research Support, Surrozen: Consultant, Genentech: Independent Contractor

◆ 4313 | INDOLE-3-LACTIC ACID DERIVED FROM LACTOBACILLUS SALIVARIUS ENHANCES NK CELL FUNCTION VIA THE MAPK PATHWAY TO SUPPRESS HEPATOCELLULAR CARCINOMA PROGRESSION

Zhewen Zhou[1] Xuefeng Huang[1] Yipeng Wang[1] Huichun Xing[1], [1]Beijing Ditan Hospital, Capital Medical University

Background: Lactobacillus species, as dominant beneficial members of the gut microbiota, have been increasingly supported by evidence indicating their antitumor activity through immune modulation. Our previous studies demonstrated that Lactobacillus salivarius alleviated alcoholic hepatitis in murine models; however, its mechanistic involvement in hepatocellular carcinoma (HCC) has yet to be elucidated. Natural killer (NK) cells are critical effectors in tumor immune surveillance. This study aimed to evaluate the therapeutic potential of L. salivarius and its metabolite indole-3-lactic acid (ILA) in HCC and to explore the potential mechanisms underlying the antitumor effects of ILA. **Methods:** A subcutaneous Hepa1-6 tumor model was established in C57BL/6 mice. Metabolomic profiling of L. salivarius culture supernatant was performed using liquid chromatography–mass spectrometry (LC-MS). The effects of L. salivarius and ILA on Hepa1-6 tumors and HepG2 cells were assessed. NK cell infiltration and function in tumors and spleens, as well as in vitro NK activity, were analyzed by flow cytometry. Integrated multi-omics analyses, including RNA-seq, ChIP-seq, and ATAC-seq, were conducted to elucidate the molecular mechanisms regulated by ILA. **Results:** Oral administration of L. salivarius significantly inhibited Hepa1-6 tumor growth in vivo, enhanced NK cell infiltration and functional activation in the tumor microenvironment, and increased splenic NK cytotoxicity. In parallel, its culture supernatant inhibited HepG2 cell proliferation and migration and induced apoptosis, with metabolomic analysis identifying ILA as the principal active compound. In vivo experiments confirmed that ILA alone also suppressed tumor growth and enhanced NK cell function. In vitro, ILA markedly promoted the tumor-killing capacity of NK cell lines. Mechanistically, ILA induced chromatin remodeling and upregulated MAP3K8, thereby activating the MAPK signaling pathway and enhancing NK cell activation and cytotoxic function. **Conclusion:** L. salivarius and its metabolite ILA exhibit inhibitory effects against HCC. Epigenetic upregulation of MAP3K8 and activation of the MAPK pathway, resulting in enhanced NK cell–mediated antitumor immunity, may represent one of the key mechanisms underlying the antitumor action of ILA. This study provides a basis for developing microbiota-derived immunotherapeutic strategies targeting HCC.



Disclosures: Zhewen Zhou: Nothing to Disclose, Xuefeng Huang: Nothing to Disclose, Yipeng Wang: Nothing to Disclose, Huichun Xing: Nothing to Disclose

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◆ 4314 | ENTEROCYTES REGULATE HEPATIC BILE ACID SYNTHESIS IN CO-CULTURED GUT AND LIVER ORGANOIDS WITH INTERRUPTION UPON SIRNA TRANSFECTION

Shaurya Mehta[1] Ashlesha Bagwe[1] chandrashekhara manithody[1] Kento Kurashima[1] Sree Kolli[1] Miguel Guzman[1] Uthayashanker Ezekiel[1] Ajay Jain[1], [1]Saint Louis University

Background: Intestinal failure-associated liver disease (IFALD) is driven by bile acid dysmetabolism, yet the mechanisms underlying gut-liver signaling remain incompletely understood. The enterohepatic circulation plays a crucial role in bile acid homeostasis, with enterocyte-derived fibroblast growth factor 19 (FGF19) regulating hepatic bile acid synthesis via CYP7A1 suppression. To evaluate this complex interaction, we developed a physiologically relevant human enteroid–liver organoid co-culture transwell system to assess hepatic responses to enterocytes exposed to FXR ligands. **Methods:** We developed a human protocol for matrigel-based 3D culture systems to generated enteroids from the small bowel biopsies from humans. Human enteroids and liver organoids were co-cultured in a transwell system to assess bile acid–induced gut-liver crosstalk. RNA strands for Dicer-substrate siRNAs (DsiRNAs) were synthesized as single-strand RNAs (ssRNAs) by Integrated DNA Technologies and resuspended in an RNase-free buffer. DsiRNA targeted Sus scrofa, FXR gene (KF597010.1). Porcine enteroids were cultured and transfected with FXR-specific siRNA and control siRNA using Lipofectamine RNAiMAX reagent. Enteroids were treated with escalating CDCA concentrations (25μM to 50μM) for 24 and 48 hrs. Real-time PCR and functional assays were performed to assess changes in bile acid uptake and efflux following transfection. **Results:** 50 μM CDCA treatment of human enteroids led to increased 2-fold increase in FXR expression, with inhibition of hepatic CYP7A1 in co-cultured liver organoids, confirming a regulatory gut-liver signaling axis. To test mechanisms, we used our established porcine enteroids. Data from 3 separate experiments of intestinal crypts showed similar results in enhanced FXR expression with CDCA against control ($p < 0.01$). CDCA resulted in a dose-dependent increase in FXR mRNA expression, reaching peak levels after 48 hours of exposure (2.8X increase) with enhanced nuclear localization. Functionally, CDCA-treated enteroids displayed increased bile acid uptake and reduced efflux, validating FXR's role in mediating bile acid driven enterohepatic circulation. There was a 68% reduction in FXR expression against scramble. FXR silencing led to decreased bile acid uptake and increased efflux. No significant effects were observed in enteroids transfected with control siRNA. **Conclusion:** The human enteroid–liver organoid co-culture system provides an ex vivo model for studying enterohepatic circulation and shows hepatic bile acid metabolism is regulated by enterocytes in IFALD. By mimicking the cellular architecture and function of the gut-liver axis, this human system enables studies of interorgan signaling pathways and holds significant promise for identifying therapeutic targets for IFALD and other bile acid–related disorders.

Disclosures: Shaurya Mehta: Nothing to Disclose, Ashlesha Bagwe: Nothing to Disclose, chandrashekhara manithody: Nothing to Disclose, Kento Kurashima: Nothing to Disclose, Sree Kolli: Nothing to Disclose, Miguel Guzman: Nothing to Disclose, Uthayashanker Ezekiel: Nothing to Disclose, Ajay Jain: Nothing to Disclose

4315 | EARLY SHIFT IN GUT MYCOBIOME EXACERBATES ALCOHOLIC LIVER DISEASE PROGRESSION

Satya Priya Sharma[1] Ki Tae Suk[1], [1]Institute for Liver and Digestive Diseases, Hallym University, Chuncheon, Republic of Korea

Background: Despite its minor but crucial representation in gut, the role of gut fungal community remains underexplored particularly in alcohol-associated liver disease (ALD). Here, we meticulously assessed the pathophysiological role of gut mycobiome, in ALD severity progression. **Methods:** Feces collected from 68 ALD and 21 healthy individuals for Internal Transcribed Spacer 2 (ITS2) based comparative mycobiome assessment, followed a by gut fungal and bacterial suppressed NIAAA alcoholic mice model to explain the role of gut fungus in ALD. **Results:** MELD score-based classification showed a decisive MELD score severity-associated shift in fecal fungal ecology in ALD, while target read counts followed the MELD score severity pattern, but no changes were observed in operational taxonomic units (OTUs) or in alpha diversity indexes. Significant alterations occurred in phylum's (Basidiomycota, Plantae_p, and Mucoromycota) and in genus (*Saccharomyces*, *Kazachstania*, *Geotrichum*, and *Trichosporon*). Among 105 common fungal species, 3 (*S. cerevisiae*, *S. kudriavzevii*, and *A. penicillioides*) exhibited ALD-associated rises. Fungus species including *A. penicillioides* (AUC: 0.82) and *P. polonicum* (AUC: 0.80) served as biomarkers, and their combined ability improved the AUC upto 0.87. Interestingly, alcohol-producing fungal species showed significant increments in ALD patients, with their highest abundance observed at the early stage of ALD, and inversely correlated with MELD scores. Furthermore, antibiotic treatment (ABX),

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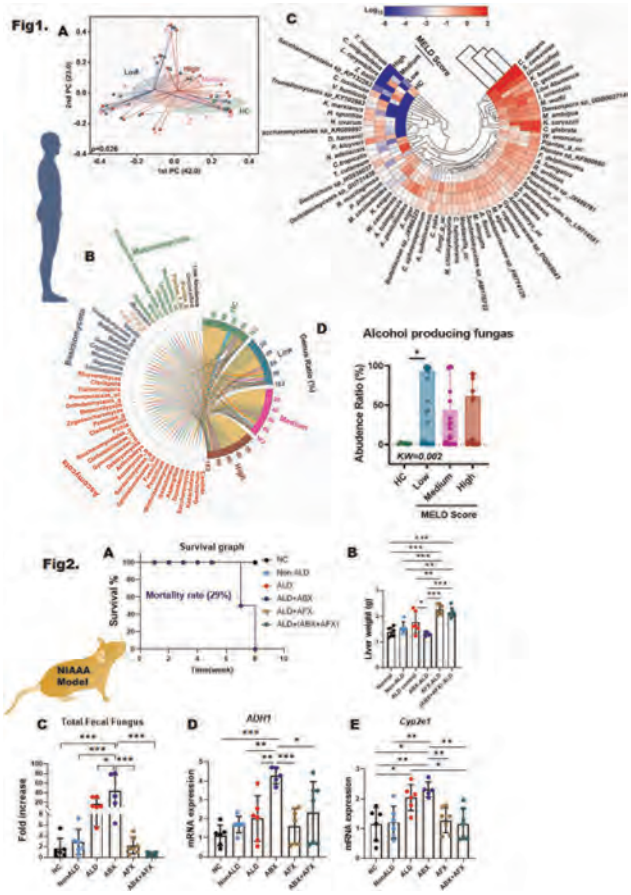
in NIAAA murine model showed significantly higher mortality, decreased body weight and liver weight compared to the alcoholic control and antifungal treatment groups, ABX also presented elevated serum AST, cholesterol, and total bilirubin levels, and upregulated the expression of alcohol dehydrogenase (***ADH1***) and Cytochrome P450 IIE1 (***CYP2E1***) genes involved in oxidative alcohol metabolism in the liver. Total fecal fungal load increased significantly in ABX treatment group compared to other groups. Relative expression of liver fibrotic markers genes such ***TGF-β***, ***TNF-α***, ***Col1a1*** and ***ACTA2*** showed significant increment in ABX group. **Conclusion:** Chronic alcohol abuse significantly altered the gut fungal composition at early stage of the ALD and potentially exacerbating ALD severity.



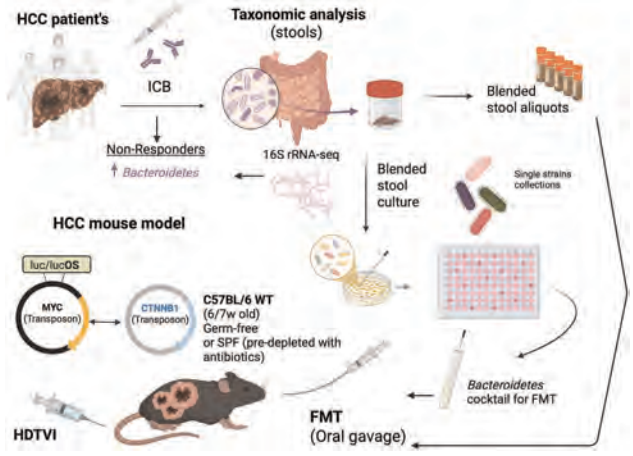
Disclosures: Satya Priya Sharma: Nothing to Disclose, Ki Tae Suk: Nothing to Disclose

4316 | "BACTEROIDETES ENRICHMENT INFLUENCES HEPATOCELLULAR CARCINOMA PROGRESSION AND RESPONSE TO IMMUNOTHERAPY"

Marina Barcena Varela[1] Joan Shang[2] Ilaria Mogno[2] Anthony Lozano[3] Jeremiah Faith[2] Amaia Lujambio[3],

[1]Instituto de investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain, [2]The Precision Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, USA., [3]Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, USA.

Background: The gut microbiome plays a critical role in cancer progression and response to immunotherapy, but its impact on hepatocellular carcinoma (HCC) remains poorly understood. **Methods:** We analyzed 81 stool samples from 10 responders and 40 non-responders with HCC treated with immune-checkpoint blockade (ICB). To investigate the role of gut microbiome in HCC, we used mouse models of HCC driven by MYC and CTNNB1 mutations, incorporating a luciferase reporter fused to model tumor-associated antigens (TAAs). We manipulated the gut microbiome composition *in vivo* by antibiotic-induced dysbiosis and fecal microbiome transplants (FMT) from patient´s stools. We also colonized mice with specific bacteria (*Bacteroidetes* species) isolated from patient's samples. **Results:** We identified an enrichment of the *Bacteroidetes* phylum in non-responders HCC patients to ICB. We found that antibiotic-induced dysbiosis accelerated tumor growth in TAA-expressing tumors, accompanied by enrichment of *Parabacteroides distasonis*. Colonization with this strain alone promoted tumorigenesis *in vivo*. Transferring human microbiota from a high-*Bacteroidetes* non-responder donor also enhanced tumor growth compared to microbiota from a responder with low-*Bacteroidetes*. A cocktail of six *Bacteroidetes* strains, isolated from the same non-responder donor, replicated the protumoral effect in colonized mice. Importantly, these microbiome-driven effects depended on TAA expression; tumors lacking immunogenic TAAs were unaffected in any of the tested conditions. **Conclusion:** Our findings highlight *Bacteroidetes* enrichment as a potential biomarker of ICB resistance in HCC and show that microbiome composition can modulate HCC progression in an antigen-dependent manner.



Disclosures: Marina Barcena Varela: Nothing to Disclose, Joan Shang: Nothing to Disclose, Ilaria

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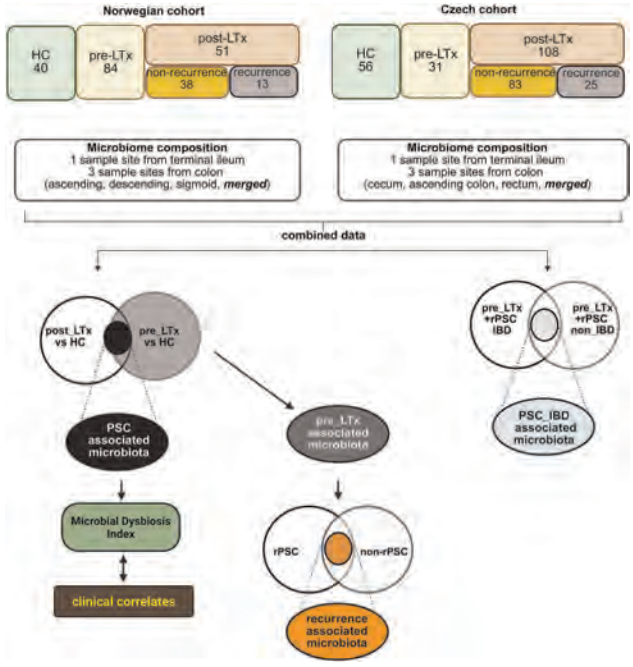
Mogno: Nothing to Disclose, Anthony Lozano: Nothing to Disclose, Jeremiah Faith: Vedanta Biosciences: Consultant, Janssen Research & Development: Grant/Research Support, Genfit: Consultant, Amaia Lujambio: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose

4317 | MUCOSAL MICROBIOTA ALTERATION IN PRIMARY SCLEROSIS CHOLANGITIS PERSISTS AFTER LIVER TRANSPLANTATION AND IS ASSOCIATED WITH CLINICAL FEATURES INDEPENDENTLY OF GEOGRAPHY

Lukas Bajer[1] Petra Polakovicova[1] Marie Heczkova[1] Kristian Holm[2] Mikal Jacob Hole[2] Mojmir Hlavaty[1] Alena Bohdanecka[1] Pavel Drastich[1] Filip Tichanek[1] Malin Meyer-Myklestad[3] Asle Medhus[4] Dag Reikvam[4] Kristin Kaasen Jørgensen[2] Jan Brezina[1] Peter Macinga[1] Pavel Wohl[1] Johannes Hov[5] Monika Cahova[1], [1]Institute for Clinical and Experimental Medicine, Prague, [2]Norwegian PSC Research Center, Oslo, [3]Oslo University Hospital, Oslo, [4]Institute of Clinical Medicine, University of Oslo, Oslo, [5]University of Oslo

Background: Primary sclerosing cholangitis (PSC) is a chronical progressive liver disease with multi-factorial pathogenesis involving gut microbiota. Majority of PSC patients develop inflammatory bowel disease (IBD). In previous studies, PSC and PSC-IBD were associated with specific gut microbiota alterations. However, there is a lack of data on microbiota alteration in context of liver transplantation (LTx) for PSC. In this multicentric cross-sectional study, we aimed to explore the disease-specific mucosal microbial pattern independent of regional conditions with respect to LTx, gut inflammation, and PSC recurrence (rPSC). **Methods:** Sequencing of the 16S ribosomal RNA gene (V3–V4) isolated from ileocolonic biopsies was performed on 115 PSC patients (pre_LTx), 159 patients after liver transplant for PSC (post_LTx) and 96 healthy controls (HC) from the Czech Republic and Norway. For the purpose of statistical correlation, clinical data and laboratory results were obtained at the time of sampling. Sequencing data were processed with QIIME 2 and all statistical analyses were conducted using R v4.3.1. **Results:** Alpha diversity was lower in all PSC groups compared with HC. Elastic Net model discriminated well both pre_LTx (avg_AUC ileum 0.97; colon 0.93) and post_LTx PSC patients (avg_AUC ileum 0.97; colon 0.97) from HC, while the separation between pre_LTx and post_LTx (avg_AUC ileum 0.83; colon 0.83) was less precise. The model's performance on merged and cohort-specific datasets was comparable. The shared cohort-independent PSC microbiota was dominated by *Enterococcus*, *Pseudomonas*, *Veillonella*, *Klebsiella*, and *Streptococcus*, while some common commensals were underrepresented. Microbial Dysbiosis Index negatively correlated with alpha diversity and serum albumin, while a positive correlation was observed with markers of cholestatic disease (ALP, GGT) and liver fibrosis (APRI). Although no rPSC microbiota signature reached statistical significance, several genera deregulated in pre_LTx PSC (*Klebsiella*, *Bilophila*, *Coprococcus*, *Odoribacter*) showed similar trend in rPSC. Microbial composition analysis revealed no significant differences in alpha diversity, beta diversity, or the relative abundance of any bacterial taxa between PSC patients with and without IBD. **Conclusion:** This international cross-sectional study represents the largest sample-size up-to-date in patients after liver transplant for PSC and it provides a novel insight to mucosa-associated dysbiosis in patients with PSC. The results demonstrated a distinct mucosal microbiota composition associated with PSC persisting after LTx which correlates with serological and clinical features of advanced liver disease. The results suggest a microbial shift driven by rPSC which will be studied in a subsequent prospective cohort.



Disclosures: Lukas Bajer: Nothing to Disclose, Petra Polakovicova: Nothing to Disclose, Marie Heczkova: Nothing to Disclose, Kristian Holm: Nothing to Disclose, Mikal Jacob Hole: Nothing to Disclose, Mojmir Hlavaty: Nothing to Disclose, Alena Bohdanecka: Nothing to Disclose, Pavel Drastich: Nothing to Disclose, Filip Tichanek: Nothing to Disclose, Malin Meyer-Myklestad: GSK ViiV: Speaking and Teaching, Asle Medhus: Nothing to Disclose, Dag Reikvam: Gilead: Independent

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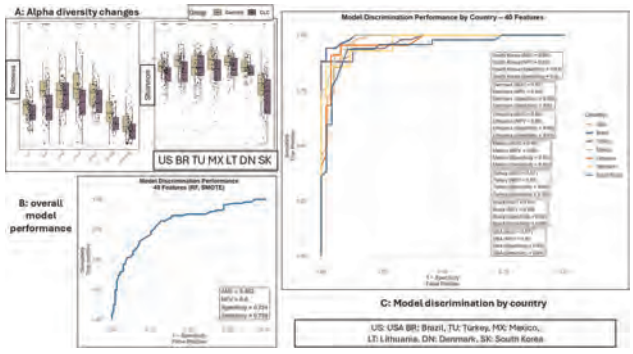
Contractor, Kristin Kaasen Jørgensen: BMS: Travel grant, IPSEN: Speaking and Teaching, CSL Vifor: Travel grant, Orphalan: Advisor, dr.Falk: Advisor, Advanz Pharma: Travel grant, celltrion: Travel grant, Jan Brezina: Nothing to Disclose, Peter Macinga: Nothing to Disclose, Pavel Wohl: Nothing to Disclose, Johannes Hov: Nothing to Disclose, Monika Cahova: Nothing to Disclose

4318 | A GUT METAGENOMIC PROFILE DISTINGUISHES COMPENSATED CIRRHOSIS FROM HEALTHY CONTROLS ACROSS MULTIPLE COUNTRY COHORTS

Darja Nikitina[1] Aldo Torre[2] Ki Tae Suk[3] Ramazan Idilman[4] Mario Alvares-da-Silva[5] Mette Lauridsen[6] Satya Priya Sharma[7] Edita Kiudeliene[1] Elise Jonasson[8] Andrew Fagan[9] Alexander Khoruts[10] Jurgita Skieceviciene[11] Masoumeh Sikaroodi[12] Juozas Kupcinskas[13] Patrick Gillevet[12] Jasmohan Bajaj[14], [1]LSMU, Lithuania, [2]Nutricion Mexico City, [3]Hallym University, Korea, [4]Ankara University, Turkiye, [5]Hospital de Clínicas de Porto Alegre, [6]University of Ejsberg, Denmark, [7]Hallym University, [8]University of Ejsberg, [9]Richmond VAMC, [10]University of Minnesota, [11]LSMU, [12]GMU, [13]LSMU Lithuania, [14]Virginia Commonwealth University

Background: Cirrhosis is increasing in prevalence but is hard to diagnose in the compensated stage. Gut microbiota are altered in cirrhosis, but studies find greatest differences centered on the easily diagnosable decompensated cirrhosis. Also there are major country-level variations. **Aim:** determine a gut metagenomic signature separating compensated cirrhosis from healthy controls across a global cohort. **Methods:** Compensated cirrhosis (comp) patients & healthy controls were recruited from seven countries. Clinical data, including demographics, cirrhosis severity (MELD, complications, medications), & dietary were collected. Stool samples underwent deep metagenomic sequencing & analysis using MetaPhlAn & MaAsLin2.
Model evaluation was performed using repeated stratified 3-fold cross-validation with SMOTE applied within each training fold to address class imbalance. Models were trained on 70% of the full dataset & internally validated on the remaining 30%. Random forest (RF) model performance was assessed on the held-out test folds only. The final model was also tested separately in each country cohort. **Results:** We enrolled 618 participants (Comp = 299; controls = 319) from 7 countries (USA n = 109, Türkiye n = 95, South Korea n = 99, Denmark n = 66, Lithuania n = 72, Brazil n = 101, & Mexico n = 85) . Comp pts were older (59 ± 9 vs 50 ± 16, $p < 0.001$) & more likely to be men (57 vs 42%, $p < 0.001$) consistently across countries. Major etiologies were alcohol 25%, HCV 24%, MASH 21% & HBV 16%.
Microbiome analysis: Shannon diversity & richness (FigA) were lower in comp in all countries except Türkiye & Denmark (where only richness showed a significant decrease). β-diversity adjusting for demographics showed significant differences in microbial community structure between comp & controls.
Microbial differences: In the entire cohort, 381 species were significantly different between controls and comp. 6 species were significantly different in five of seven countries. A set of 182 bacteria, significantly different in ≥ 2 countries, was selected as input features for RF model development. The final RF model, consisting of 40 species (*Erysipelatoclostridium ramosum, Streptococcus anginosus, Veillonella parvula, Rothia mucilaginosa, Eubacterium rectale, Coprococcus catus, Bifidobacterium dentium,* & *Parabacteroides goldsteinii* among others), achieved an AUC of 80.6% with an NPV of 83.2% (Fig B). Country-specific testing of the globally trained model demonstrated consistently strong within-cohort performance across all seven countries (Fig C). **Conclusion:** Gut metagenomic profiles effectively distinguish compensated cirrhosis from healthy controls across diverse geographic populations with granular metadata. Despite inter-country variability, a shared subset of bacterial features enabled robust and consistent model performance. These findings support the potential of microbiome-based tools for early detection of cirrhosis.



Disclosures: Darja Nikitina: Nothing to Disclose, Aldo Torre: Nothing to Disclose, Ki Tae Suk: Nothing to Disclose, Ramazan Idilman: Nothing to Disclose, Mario Alvares-da-Silva: Nothing to Disclose, Mette Lauridsen: Nothing to Disclose, Satya Priya Sharma: Nothing to Disclose, Edita Kiudeliene: Nothing to Disclose, Elise Jonasson: Nothing to Disclose, Andrew Fagan: Nothing to Disclose, Alexander Khoruts: Nothing to Disclose, Jurgita Skieceviciene: Nothing to Disclose, Masoumeh Sikaroodi: Nothing to Disclose, Juozas Kupcinskas: Nothing to Disclose, Patrick Gillevet: Nothing to Disclose, Jasmohan Bajaj: Bausch: Grant/Research Support, Sequana: Grant/Research Support, Cosmo:

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4319 | MODIFIED FORMS OF SECONDARY BILE ACID LEVELS COULD BE BIOMARKERS OF HEPATOCELLULAR CARCINOMA PATHOGENESIS IN STEATOTIC LIVER DISEASE PATIENTS

Yoshimi Yukawa-Muto[1] Hideki Fujii[1] Tomonori Kamiya[1] Norifumi Kawada[1] Naoko Ohtani[1], [1]Osaka Metropolitan University

Background: Gram-positive gut microbial metabolite deoxycholic acid (DCA) has been reported to promote MASLD-associated hepatocellular carcinoma (HCC) development in mice (*Nature*, 2013). Recent studies also suggest that specific bile acids accumulate in HCC and suppress anti-tumor immunity (*Science*, 2025). Given the recent redefinition of fatty liver disease under the term steatotic liver disease (SLD), we analyzed serum bile acid profiles in HCC patients with MASLD, MetALD, and ALD to identify novel pathophysiological mechanisms involved in hepatocarcinogenesis. **Methods:** The study includes 30 healthy controls (HC), 50 MASLD patients (35 non-HCC and 15 HCC), and Alcohol-Associated group (MetALD and ALD) patients (10 non-HCC and 12 HCC). The comparative analyses were conducted measuring a series of serum bile acid levels as follows: a) a comparative analysis between two subgroups among 15 HCC patients: 6 patients with ursodeoxycholic acid (UDCA) treatment and 9 patients without UDCA treatment. b) a comparative analysis across three groups of HC, MASLD-non-HCC and MASLD-HCC. c) a comparative analysis across three groups of HC, Alcohol-Associated-non-HCC and Alcohol-Associated-HCC. These comparisons were performed excluding patients taking UDCA. **Results:** a) In the UDCA-treated group, levels of UDCA and its glycine and taurine conjugates were significantly higher than in the untreated group. However, no significant differences were detected in other bile acid levels. b) In the HCC group, glycine and taurine conjugated DCA levels were higher than in the HC groups. Moreover, levels of lithocholic acid (LCA) and 3-oxo-LCA were significantly higher than in the non-HCC group. c) Taurine-conjugated DCA levels were markedly elevated in the HCC group compared to both the HC and non-HCC groups. Similar to MASLD-HCC, LCA was significantly higher in the HCC group. **Conclusion:** LCA and 3-oxo-LCA levels as well as glycine and taurine conjugated DCA levels were elevated in the HCC group. 3-oxo-LCA has been reported to suppress Th17 cell differentiation (Nature, 2022), while Th17 cells are known to promote cytotoxic T cell activation in tumor immunity (Immunity, 2009). Therefore, increased 3-oxo-LCA may reduce antitumor immune responses and contribute to HCC development. These findings suggest that altered bile acid metabolism may play a role in MASLD-HCC carcinogenesis, and further studies are needed to clarify the underlying mechanisms.

Disclosures: Yoshimi Yukawa-Muto: Nothing to Disclose, Hideki Fujii: Nothing to Disclose, Tomonori Kamiya: Nothing to Disclose, Norifumi Kawada: Nothing to Disclose, Naoko Ohtani: Nothing to Disclose

4320 | E-CADHERIN/β-CATENIN COMPLEX SUPPRESSION DRIVES BARRIER DYSFUNCTION AND IMMUNE ACTIVATION IN SHORT BOWEL SYNDROME

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Background: Short bowel syndrome (SBS) is a devastating cause of intestinal failure in children. While total parenteral nutrition (TPN) supports growth, it paradoxically induces mucosal atrophy, barrier breakdown, and gut-derived sepsis. β-Catenin, a multifunctional protein, mediates both adherens junction stability (via E-cadherin binding) and transcriptional activity through canonical Wnt signaling. We hypothesized that loss of E-cadherin disrupts the β-catenin pool, leading to impaired junctional integrity and transcriptional downregulation, thereby contributing to epithelial failure in SBS and TPN. **Methods:** Neonatal piglets were randomly assigned to three groups: enteral nutrition (EN, $n=4$), TPN-only ($n=4$), or SBS with TPN ($n=4$) for 14 days. Distal small intestine tissues were assessed by qPCR, immunohistochemistry, FITC-dextran permeability assays, cytokine profiling, and histology. Quantitative analysis was performed using GraphPad Prism (v10.1.2); statistical significance was set at $p<0.05$. **Results:** Both TPN and SBS significantly reduced E-cadherin and β-catenin expression ($p<0.001$ vs. EN), accompanied by cytoplasmic mislocalization of β-catenin. Wnt pathway effectors (LEF1, TCF, Cyclin D1) were markedly suppressed ($p<0.01$), while GSK3β, a Wnt antagonist, was upregulated. SPDEF and MUC2 expression were significantly diminished ($p<0.01$), consistent with impaired goblet cell differentiation and reduced mucus barrier integrity. Tight junction disruption was evident: Occludin and Claudins 1, 3, 4, 5, and 8 were downregulated, while Claudin-2 and Claudin-6 were upregulated ($p<0.05$),

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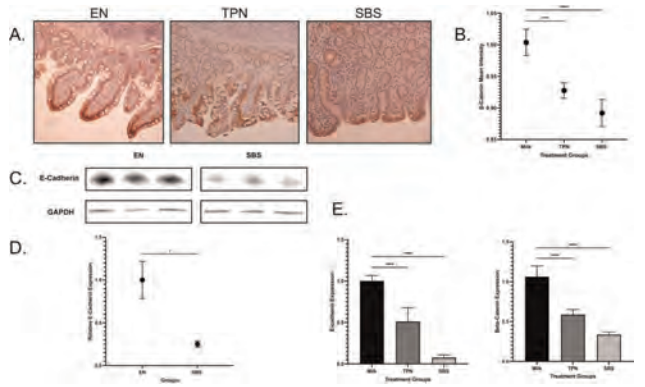
indicating a shift to a leaky barrier phenotype. Functionally, this was corroborated by increased FITC-dextran permeability and elevated serum lipopolysaccharide (LPS). Histologic analysis showed severe villus blunting (V/C ratio: TPN = 1.67; SBS = 1.51; EN = 2.13, $p < 0.01$) and gut atrophy (distal gut density: SBS = 0.13 g/cm vs. EN = 0.34 g/cm). Proinflammatory cytokines (TNF-α, IL-6, IL-8, IL-1β, IFN-γ) were increased, while IL-10 was suppressed ($p < 0.01$), indicating a dysregulated immune response. $CD3^+$ T cell infiltration was also elevated ($p < 0.001$). **Conclusion:** TPN and SBS elicit a coordinated disruption of epithelial structure and intercellular signaling. Central to this disruption is the breakdown of the E-cadherin/β-catenin complex and suppression of Wnt signaling, which impairs junctional integrity, goblet cell maturation, and epithelial regeneration. These effects are exacerbated by cytokine-driven immune activation and permeability defects. Together, these findings provide a mechanistic framework for therapeutic strategies aimed at restoring barrier function in SBS.



Disclosures: Shaurya Mehta: Nothing to Disclose, chandrashekhara manithody: Nothing to Disclose, Kento Kurashima: Nothing to Disclose, Sree Kolli: Nothing to Disclose, Marzena Swiderska-Syn: Nothing to Disclose, Ashlesha Bagwe: Nothing to Disclose, Chien-Jung Lin: Nothing to Disclose, John Long: Nothing to Disclose, Ajay Jain: Nothing to Disclose

4321 | ACYL-COA THIOESTERASE 12 PROTECTS AGAINST MASH BY COORDINATING INTESTINAL FATTY ACID UPTAKE AND ABSORPTION

Akiko Sugiyama[1] Susan Hagen[2] David Cohen[3], [1]Brigham and Women's Hospital, Harvard Medical School, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, [3]Brigham and Women's Hospital, Harvard Medical School

Background: Acyl-CoA thioesterase 12 (Acot12), a cytosolic enzyme that converts acetyl-CoA into acetate, is markedly induced in small intestinal epithelial cells (IECs) in response to excessive nutrition. We previously reported that intestinal Acot12 deletion promotes metabolic dysfunction-associated steatohepatitis (MASH) by increasing intestinal permeability, which is due to IEC necroptosis and anti-inflammatory gene expression. This study aimed to determine whether Acot12 may protect against lipotoxicity, which can lead to necroptotic IEC cell death, by regulating lipid absorption and trafficking. **Methods:** Male intestine-specific Acot12 knockout (*I-Acot12*$^{-/-}$) mice and littermates (controls) were fed a high-fat diet (HFD) for 12 w and then challenged with an olive oil gavage. Plasma was collected over 2 h and tissues were harvested. Plasma triglyceride (TG) concentrations were measured enzymatically, and apoB48 levels were assessed by immunoblotting. Cytosolic lipid droplets (CLDs) in IECs were visualized by oil red O staining and chylomicron secretion was quantified using negative staining/transmission electron microscopy (NS/TEM). Jejunal organoids (enteroids) were prepared from *Acot12*$^{-/-}$ mice and controls after 4 w of HFD feeding. To assess rates of fatty acid (FA) uptake, enteroids were treated with 5μM of C1-BODIPY C12 for 30 min, and intracellular accumulation was quantified by confocal microscopy. To examine FA incorporation into CLDs and chylomicron (CM) secretion, enteroids were exposed to 400 μM oleic acid for 2 h. CLDs were assessed by confocal microscopy following BODIPY staining. Secreted CMs were analyzed by NS/TEM. Gene expression was quantified by qPCR. **Results:** Indicative of impaired lipid absorption, *I-Acot12*$^{-/-}$ mice exhibited 45% and 35% reductions in plasma TG and ApoB48 concentration, respectively. This was accompanied by increased lipid accumulation and enlarged CLDs in IECs. Rates of FA uptake were increased in *Acot12*$^{-/-}$ enteroids, which also exhibited increased CLD size and abundance. Suggestive of impaired secretion of CM TGs, secreted CMs were 46% smaller than controls. Additionally, expression levels of *Pnpla2* and *Abhd5*, which mediate CLD TG hydrolysis and CM assembly, were reduced by 42% and 33%, respectively. **Conclusion:** Intestinal Acot12 coordinates luminal FA uptake with the assembly and secretion of CMs. We speculate that Acot12 activity limits lipid accumulation in IECs and thereby prevents lipotoxicity, preserving barrier integrity and protecting against MASH.

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4322 | GUT MICROBIOME DERIVED SHORT CHAIN FATTY ACIDS INCREASE RISK OF HEPATOCELLULAR CARCINOMA

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Background: Hepatocellular carcinoma (HCC) makes up 80-90% of primary liver cancers and is typically detected at an advanced stage because of its silent nature of progression and a lack of effective non-invasive early detection biomarkers. Gut-derived metabolites such as short-chain fatty acids (SCFAs) may impact the progression of early non-malignant stages of liver disease to malignant transformation to HCC. Although most studies have shown that SCFAs including acetate, butyrate, and propionate have been associated with lower risk of intestinal disease, some experimental studies have shown dysregulated metabolism of SCFAs may induce proinflammatory milieu for liver disease progress. The goal of this study is to investigate whether metabolomic profiling of SCFAs in baseline serum is associated with risk of HCC development. **Methods:** We performed a nested case-control study with 100 incident HCC cases and 100 individually matched healthy controls within the Singapore Chinese Health Study, a cohort of 63,257 men and women aged 45-74 years at enrollment in 1993-1998. The incidence of HCC was annually surveilled with the nationwide Singapore Cancer Registry. Serum acetic, butyric, propionic, and valeric acids were quantified using ultra-performance liquid chromatography triple-quadrupole mass spectrometry assays. The conditional logistic regression was used to evaluate the association between SCFAs and HCC risk using odds ratios (ORs) and their 95% confidence intervals (CI). **Results:** Cases and controls were comparable by age, body mass index (BMI), alcohol consumption and smoking status distributions. Individuals with HCC were more likely to be HBsAg positive and have a history of diabetes than controls. Among controls, the summed SCFAs and total butyric acid and its metabolites were positively associated with BMI (P trend < 0.05). The summed and most individual SCFAs measured were significantly elevated in HCC compared with controls. Compared to the lowest tertile, the OR (95% CI) of HCC for the highest tertile of summed all SCFAs and total butyric acids was 3.24 (1.45-7.24) and 2.78 (1.27-6.12) after adjusting for age, sex, BMI, alcohol consumption, smoking status, type 2 diabetes, and HBsAg status (both P's for trend < 0.01). **Conclusion:** The present analysis demonstrated a statistically significant association between elevated SCFA levels and increased risk of HCC in a prospective cohort of Singaporean Chinese. These results align with increased risk of HCC within this cohort with elevations in other metabolites such as bile acids. Mapping metabolic profile changes in liver disease progression to cancer will provide clinicians with a novel biomarker for risk stratification and early detection.

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4323 | HIGHER PLASMA KYNURENINE-TRYPTOPHAN RATIO PREDICTS INCIDENT HEPATIC FIBROSIS IN WOMEN WITH HIV

Maria Duarte[1] Phyllis Tien[1] Audrey French[2] Seble Kassaye[3] Deborah Gustafson[4] Robert Burk[5] Steven Wolinksy[6] Mallory Witt[7] Yue Chen[8] Chloe Thio[9] Svenja Albrecht[10] Margaret Fischl[11] Cecile Lahiri[12] Michelle Floris-Moore[13] Eric Seaberg[14] Jennifer Price[1] Yifei Ma[1] Ani Kardashian[15], [1]University of California, San Francisco, [2]Stroger Hospital of Cook County, [3]Georgetown University, [4]State University of New York Downstate Health Sciences University, [5]Albert Einstein College of Medicine, [6]Northwestern Feinberg School of Medicine, [7]Geffen School of Medicine at UCLA, [8]University of Pittsburgh, [9]Johns Hopkins University School of Medicine, [10]University of Mississippi Medical Center, [11]University of Miami Miller School of Medicine, [12]Emory University School of Medicine, [13]University of North Carolina Chapel Hill School of Medicine, [14]Johns Hopkins University Bloomberg School of Public Helath, [15]Keck School of Medicine at the University of Southern California

Background: The tryptophan kynurenine pathway is activated in chronic inflammation, gut dysbiosis and gut microbial translocation, and may contribute to liver disease pathogenesis. Linkage of the kynurenine to tryptophan ratio (KT ratio), a measure of the tryptophan catabolism pathway, to hepatic fibrosis in people with HIV are sparse. We evaluated whether elevated KT ratio is associated with incident liver fibrosis in women with HIV (WWH). **Methods:** We included 709 WWH from the MACS-WIHS Combined Cohort Study

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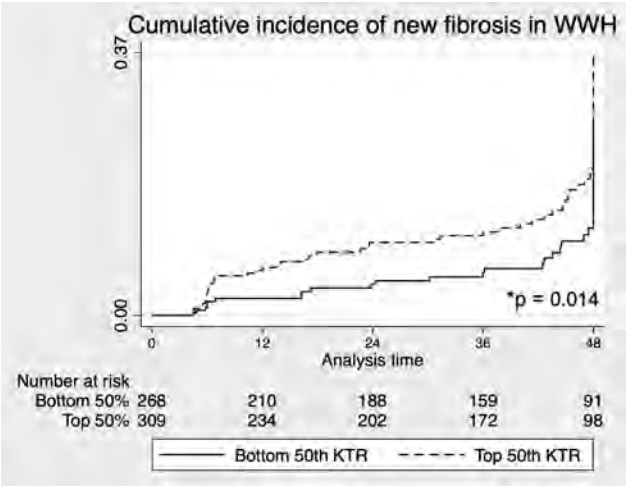
(MWCCS) with available plasma KT ratio measurements at baseline; baseline liver stiffness (LS) measurement <7.1 kPa; ≥ 1 follow-up vibration-controlled transient elastography (VCTE) assessment; and no evidence of chronic viral hepatitis. KT ratio values were log-transformed and standardized. Hepatic steatosis was defined as VCTE controlled attenuation parameter (CAP) score of $\geq$ 248 dB/m. Poisson regression with robust standard errors clustered by participant was used to estimate the association of KT ratio with incidence rate of new fibrosis (LS ≥ 7.1 kPa) and new advanced fibrosis (LS >9.5 kPa). Models were adjusted for age, BMI, waist circumference, alcohol use, smoking, CAP score, HIV viral load, and CD4 count, and included the log of follow-up interval as an offset to account for varying person-time between visits. Kaplan-Meier estimator examined KT ratio above vs. below median with cumulative incidence of fibrosis over a 4 year follow-up. Cox proportional hazards and log rank test were used to test for differences in the cumulative incidence. **Results:** Over follow-up (mean 24.5 months, maximum 72 months), 18.7% and 8.3% of participants developed new or advanced fibrosis, respectively. Most fibrosis (74%) was associated with hepatic steatosis. In multivariable analysis, each log unit increase in KT ratio was associated with higher incidence rate of both new fibrosis (IRR 1.34, 95% CI: 1.15–1.56) and new advanced fibrosis (IRR 1.56, 1.32–1.86). In Kaplan-Meier analysis limited to 48 months, KT ratio values above the median were associated with greater cumulative incidence of fibrosis over 4 years compared to those below the median (hazard ratio 2.1, 95% CI: 1.16—3.83 p = 0.014.) (Figure). **Conclusion:** Higher KT ratio is a strong independent predictor of new and advanced fibrosis in WWH, supporting a mechanistic link between gut microbial dysbiosis, chronic immune activation, and liver disease progression. KT ratio may serve as a non-invasive biomarker to identify WWH at-risk individuals for liver disease progression.



Disclosures: Maria Duarte: Nothing to Disclose, Phyllis Tien: Nothing to Disclose, Audrey French: Nothing to Disclose, Seble Kassaye: Nothing to Disclose, Deborah Gustafson: Nothing to Disclose, Robert Burk: Nothing to Disclose, Steven Wolinksy: Nothing to Disclose, Mallory Witt: Nothing to Disclose, Yue Chen: Nothing to Disclose, Chloe Thio: Nothing to Disclose, Svenja Albrecht: Nothing to Disclose, Margaret Fischl: Nothing to Disclose, Cecile Lahiri: Merck Pharmaceuticals: Grant/Research Support, Theratechnologies, Inc: Consultant, Michelle Floris-Moore: Nothing to Disclose, Eric Seaberg: Nothing to Disclose, Jennifer Price: AbbVie: Grant/Research Support, Gilead: Grant/Research Support, Genentech: Grant/Research Support, VIR: Grant/Research Support, Cepheid: Grant/Research Support, Aligos: Grant/Research Support, Yifei Ma: Nothing to Disclose, Ani Kardashian: Nothing to Disclose

4324 | ASSOCIATION BETWEEN GUT MICROBIOTA AND TACROLIMUS DOSE-RESPONSE AFTER LIVER TRANSPLANT

Yael Nobel[1] Heekuk Park[2] Christopher McLaughlin[2] Dwayne Seeram[2] Alice Tillman[2] Tal Korem[2] Elizabeth Verna[2] Anne-Catrin Uhlemann[2], [1]Columbia University Irving Medical Center, [2]Columbia University Medical Center

Background: The ability to predictably achieve therapeutic tacrolimus levels after liver transplant (LT) is critical for preventing acute cellular rejection while minimizing drug toxicity. However, the tacrolimus levels resulting from a given dose vary widely across patients. Gut microbiota have been shown to alter the pharmacokinetics of multiple drugs. We investigated the association between the gut microbiota and tacrolimus levels after LT. **Methods:** This was a nested prospective cohort study of LT recipients taking tacrolimus who underwent post-transplant stool specimen collection within 2 weeks post-LT. Fecal bacterial V3-V4 16S rRNA sequencing from one stool specimen per patient was performed to identify associations between early post-transplant microbial features and dose-normalized tacrolimus level at 30 days post-LT, calculated as the ratio of tacrolimus trough level (ng/mL) to tacrolimus dose (mg) (L/D ratio). L/D ratio was evaluated as a continuous outcome and a binary outcome with levels above or below the mean. Clinical and tacrolimus data were extracted from the electronic medical record. **Results:** Among 107 LT recipients, median age was 59 (IQR 52-64) years, and 24%, 30%, and 46% were Childs Pugh Class A, B, and C at transplant, respectively. The most common LT indications were hepatitis C (31%), alcohol-associated liver disease (24%), and metabolic-associated steatotic liver disease (24%). The

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average tacrolimus L/D ratio in the study was 1.9 (SD 2.1) ng/mL/mg. While alpha and beta diversity were not significantly associated with tacrolimus L/D ratio, the subjects with the highest alpha diversity (Chao1 index > 200; $n = 6$) all had a low tacrolimus L/D ratio (< 1.9 ng/mL/mg) (Fig. 1A and 1B). Using Analysis of Compositions of Microbiomes with Bias Correction (ANCOM-BC), there was significantly increased abundance of *Roseburia inulivorans* and *Clostridium perfringens* in subjects with a low tacrolimus L/D ratio (Fig. 1C). **Conclusion:** Subjects with low tacrolimus L/D ratio had enrichment of *R. inulivorans*, a short-chain fatty acid (SCFA) producer, and a trend toward increased alpha diversity. SCFAs have previously been shown to impact expression of intestinal drug efflux pumps and activity of hepatic drug metabolism enzymes. Future studies can quantify SCFA levels to determine associations with dose-normalized tacrolimus level. Gut microbiota composition, or concentration of metabolites such as SCFAs, offer future directions that may ultimately help inform personalized tacrolimus dosing after LT.

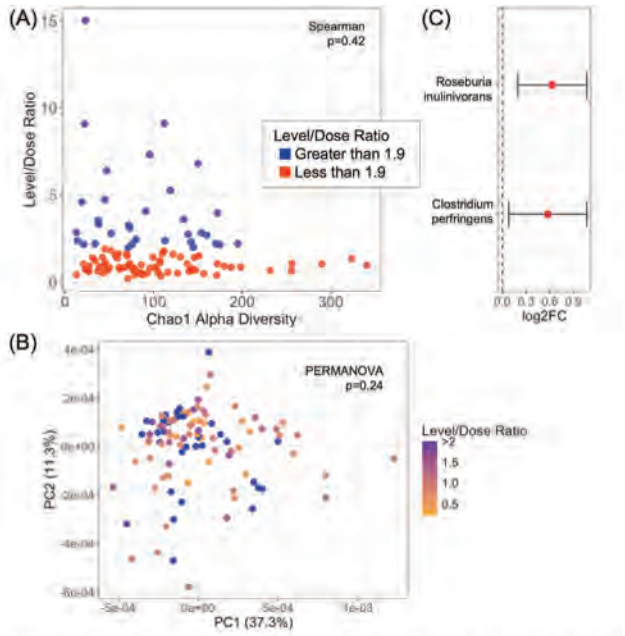

Figure 1. (A) Tacrolimus level/dose ratio according to Chao1 alpha diversity. (B) Weighted Unifrac PCoA of all samples. (C) Differentially abundant species between subjects with tacrolimus level/dose ratio above or below 1.9 ng/mL/mg ($p<0.05$ adjusting for multiple comparisons). log2FC: log2 fold change.

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4325 | C-C MOTIF CHEMOKINE RECEPTOR 9 ABLATION WORSENS WHEREAS THERAPEUTIC BLOCKING PROTECTS MICE FROM WESTERN DIET-INDUCED STEATOHEPATITIS

Reben Raeman[1] Daniel Rossmiller[1] Ravi Rai[1] Vineet Mahajan[1] Michael Oertel[1], [1]University of Pittsburgh

Background: Intestinal epithelial permeability, fueled by gut microbial dysbiosis-associated mucosal inflammation, is central to metabolic dysfunction-associated steatohepatitis (MASH) pathogenesis; however, the mechanisms underlying mucosal inflammation in MASH remain incompletely understood. The gut-trophic chemokine receptor, CC chemokine receptor 9 (CCR9), regulates intestinal immune homeostasis. However, its pathogenic roles in chronic gastrointestinal diseases reveal the complex role of CCR9 on gut health. Here, we investigated the role of CCR9 in modulating intestinal mucosal inflammation in MASH. **Methods:** Male littermate $Ccr9^{+/+}$ (control) and $Ccr9^{-/-}$ mice were fed a normal diet or a Western diet (WD) consisting of 0.2% cholesterol, 20% protein, 43% carbohydrate, 23% fat (6.6% trans fat), and 2.31% fructose (TD.130885; Harlan Laboratories) for 24 weeks. C57BL/6J mice fed a WD for 24 weeks were randomized to receive subcutaneous injections of 50 mg/kg vercirnon (GSK-1605786; MedChemExpress, NJ, USA), resuspended in 5% Cremophor EL (EMD Millipore Corporation, Germany), or vehicle on alternate days for four weeks starting at week 20 of WD feeding. Liver and intestinal tissues were analyzed by histology, immunofluorescence microscopy, and quantitative reverse transcription PCR (qRT-PCR). **Results:** Our studies revealed inherent defects in the intestinal epithelial barrier (IEB) and higher intestinal mucosal inflammation in *Ccr9*$^{-/-}$ mice relative to *Ccr9*$^{+/+}$ mice. Consequently, compared to WT mice, when fed a WD, *Ccr9*$^{-/-}$ mice developed severe intestinal mucosal inflammation and IEB dysfunction. Heightened mucosal injury in WD-fed *Ccr9*$^{-/-}$ mice correlated with more severe hepatic inflammation and fibrosis relative to WT mice. In contrast, the CCR9 antagonist, vercirnon-mediated CCR9 blockade improved mucosal inflammation and restored IEB function in MASH mice. This correlated with improved biochemical, histologic, and metabolic parameters associated with MASH. **Conclusion:** Collectively, these findings emphasize the significance of CCR9 in maintaining gut health and highlight the potential of selective, intermittent CCR9 targeting as a therapeutic strategy for MASH.

Disclosures: Reben Raeman: Nothing to Disclose, Daniel Rossmiller: Nothing to Disclose, Ravi Rai: Nothing to Disclose, Vineet Mahajan: Nothing to Disclose, Michael Oertel: Nothing to Disclose

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4326 | BREAKING BARRIERS AND TRIGGERING DEATH: DUAL BACTERIAL MECHANISMS OF JUNCTION DAMAGE AND PARAPTOSIS IN SPONTANEOUS BACTERIAL PERITONITIS

Noah Sendtner[1] Noah Brandl[1] Martha Ernst[1] Celina Macek[1] Carina Steindl[1] Annika Scholtis[1] Philip Neubert[1] Natalie Fischer[1] Marika Haderer[1] Christoph Brochhausen[2] Arne Kandulski[1] Claudia Kunst[1] Karsten Gülow[1] Martina Müller-Schilling[1], [1]University of Regensburg, University Hospital Regensburg, Regensburg, Germany, [2]Institute of Pathology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Background: Spontaneous bacterial peritonitis (SBP) reflects a breakdown of the gut-liver axis, triggered by microbial translocation across a disrupted mucosal barrier in cirrhosis. Loss of epithelial integrity permits microbe-host interaction, inducing stress responses, junctional breakdown, and regulated cell death. Here, we investigate how bacteria isolated from the ascitic fluid of patients with SBP affect epithelial junction integrity and cell death morphology. **Methods:** Colonic biopsies from patients with liver cirrhosis and healthy controls were analyzed for mucus thickness, epithelial junction proteins, and stress signaling markers. *In vitro*, human intestinal epithelial HCT116 cells with or without specific deletion of p53 were co-cultured with *Escherichia coli (E. coli)* strains, including clinical isolates from SBP ascites. Z-VAD-fmk and Actinomycin D were used to define the cell death modality. Flow cytometry (Annexin V/DAPI) quantified cell death, while Western blotting and electron microscopy assessed protein expression and ultrastructure. **Results:** Patients with liver cirrhosis exhibited reduced mucus thickness and diminished epithelial junction protein levels. *In vitro* exposure of epithelial cells to *E. coli* resulted in rapid degradation of occludin and E-cadherin, accompanied by a form of regulated cell death consistent with paraptosis, as evidenced by vacuolization, organelle dilation, and chromatin condensation observed via electron microscopy. CRISPR/Cas9-mediated knockdown of p53 delayed the induction of bacteria-induced paraptosis, suggesting that p53 plays a regulatory role in bacteria-mediated paraptosis. Of note, Actinomycin D suppressed paraptotic features across all genetic backgrounds, indicating a transcription-dependent mechanism. **Conclusion:** Our findings identify paraptosis as a relevant form of epithelial cell death in the context of bacterial exposure during SBP. The observed disruption of epithelial junctions and associated cell death processes point to a key role of host–bacteria interaction in compromising gut barrier function within the gut-liver axis. Targeting the underlying mechanisms of epithelial destabilization may offer new therapeutic avenues to mitigate disease progression in SBP.

Disclosures: Noah Sendtner: Nothing to Disclose, Noah Brandl: Nothing to Disclose, Martha Ernst: Nothing to Disclose, Celina Macek: Nothing to Disclose, Carina Steindl: Nothing to Disclose, Annika Scholtis: Nothing to Disclose, Philip Neubert: Nothing to Disclose, Natalie Fischer: Nothing to Disclose, Marika Haderer: Nothing to Disclose, Christoph Brochhausen: Nothing to Disclose, Arne Kandulski: Nothing to Disclose, Claudia Kunst: Nothing to Disclose, Karsten Gülow: Nothing to Disclose, Martina Müller-Schilling: Nothing to Disclose

4327 | AN ALTERED HUMAN GUT MICROBIOME FROM HIGH FRUCTOSE INTAKE INDUCES METABOLIC RISK PHENOTYPES WHEN TRANSPLANTED INTO GERM-FREE MICE

Wontack Han[1] Jeanine Albu[1] John Hong[1] Rollie Hampton[1] Taylor Stein[1] Andrew Dorsey[1] Yanbo Zhang[2] Qibin Qi[2] Jaime Chu[3] Sarah Stanley[1] Jeremiah Faith[1] Ryan Walker[1], [1]Icahn School of Medicine at Mount Sinai, [2]Albert Einstein College of Medicine, [3]Icahn School of Medicine at Mount Sinai (ISMMS)

Background: Excess fructose (Fru) intake has adverse impacts on metabolic health, including T2D and MASLD. Malabsorbed Fru reaches the colon where it may alter the gut microbiome and its metabolites, yet causal links between the microbiome changes and metabolic risk phenotypes have not been studied. **Methods:** We enrolled 5 healthy participants in a pilot clinical dietary intervention (added Fru at 25% of total daily calories). Fecal samples were collected daily for 16s rRNA sequencing and closed reference clustering taxonomy (QIIME2). Alpha, beta diversity, and taxonomic abundance were calculated. An ex-vivo carbon tracer assay was used to analyze microbiome Fru metabolism. We used human donor samples for a fecal transplant (FMT) study in 6 C57Bl6 germ free mice in 3 groups: Control (C): chow no FMT, Fru-Baseline (F-B): 25% Fru diet + baseline FMT and Fru-Fru (F-F): 25% Fru diet + Fru FMT. Fecal samples were collected for 16s rRNA sequencing. Whole-body MRIs, plasma and tissue samples were obtained. **Results:** Human study: We observed an increase in mean alpha diversity (# unique features) from baseline to intervention (107.3 vs 109.8 ± 8.7). Beta diversity (unweighted UniFrac) showed clustering separation by intervention phase. At day 1 of Fru intervention mean abundance (CLR fold change) for *Bacteroides* decreased to -0.037 while increasing to 0.022 for *Firmicutes.* Mean abundance increased for *Blautia* (0.02) and decreased for

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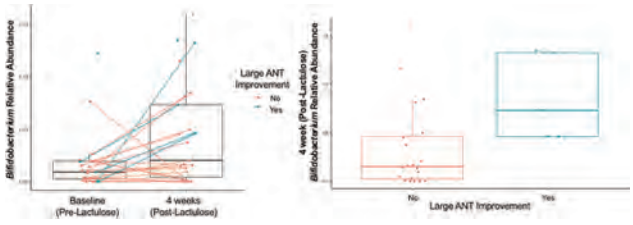
Ruminoccocus (-0.011) and *Prevotella* (-0.041). Mean *Firmicutes* to *Bacteroidetes* ratio (F:B) increased after Fru intervention (F:B = 3.31 vs 3.73). The microbiome showed enhanced ability to metabolize Fru compared to baseline (^{13}C $C0_2$ = 2560 vs 2100ppm).
FMT: Final alpha diversity (# unique features) was lower in the C (60.5) vs the F-F (136) group. Beta diversity (Bray Curtis) showed distinct group clustering. Comparing the F-F and F-B groups, mean *Firmicutes* abundance was higher (81.6% [8.2] vs. 60.8% [4.4]) while mean *Bacteroidetes* was lower (7.3% [3.5] vs. 28.2% [7.1]), mirroring our clinical results. The F-F group had lowest body weight, yet body fat % was double that of the C group. Plasma NEFAs and TGs differed between the F-F and C groups and IL-6 and ALT were highest in the F-F group. **Conclusion:** These results are consistent with observations that excess dietary Fru elicit acute effects on the structure and function of the gut microbiome. These alterations appear to be causally linked to metabolic risk in mice suggesting a unique contribution of Fru to metabolic disease risk.
Disclosures: Wontack Han: Nothing to Disclose, Jeanine Albu: Nothing to Disclose, John Hong: Nothing to Disclose, Rollie Hampton: Nothing to Disclose, Taylor Stein: Nothing to Disclose, Andrew Dorsey: Nothing to Disclose, Yanbo Zhang: Nothing to Disclose, Qibin Qi: Nothing to Disclose, Jaime Chu: Nothing to Disclose, Sarah Stanley: Nothing to Disclose, Jeremiah Faith: Vedanta Biosciences: Consultant, Janssen Research & Development: Grant/Research Support, Genfit: Consultant, Ryan Walker: Nothing to Disclose

4328 | LACTULOSE EFFICACY IS LINKED TO BIFIDOBACTERIUM AND SHORT-CHAIN FATTY ACID PRODUCTION

Patricia Bloom[1] Christine Bassis[1] Elliot Tapper[2] Krishna Rao[1] Anna Lok[2] Vincent Young[1], [1]University of Michigan, [2]University of Michigan Medical Center

Background: Lactulose is the primary treatment for hepatic encephalopathy (HE), yet it prevents only 50% of HE episodes. Data regarding the effect of lactulose on microbiome composition and function is limited – and may clarify individual differences in lactulose efficacy. **Methods:** Patients with cirrhosis and clinically significant portal hypertension were prospectively enrolled prior to initiating lactulose in clinic or as part of an open-label randomized clinical trial of lactulose. Patients had no antibiotic or alcohol use in at least the prior month. At baseline and at 4 weeks, all patients underwent the animal naming test (ANT) and fecal samples were obtained for sequencing the V4 region of the 16S rRNA gene and short-chain fatty acid (SCFA) quantification. Cognitive improvement was defined as an increase in ANT of 4 or more animals. AMOVA was used to evaluate beta diversity differences between groups and Wilcoxon or t-tests were used to compare continuous variables between groups. **Results:** Thirty patients with cirrhosis who started lactulose were enrolled: 73% female, median age 65 years, MELD 10, 60% MASLD and 20% alcohol-related. Patients reported a median daily lactulose dose of 20 g (range 2 to 56 g). Median change in ANT from baseline to week 4 was 0 (range -8 to +9) with 6 (20%) patients having increase in ANT by 4 or more animals. While the overall community structure of the microbiome did not change with lactulose administration, specific taxa did appear to respond following treatment. *Bifidobacterium* increased in abundance with lactulose ($P < 0.05$, Figure). Patients with cognitive improvement had a higher relative abundance of *Bifidobacterium* at week 4 than those without (median 7.3% vs 1.5%, $P = 0.02$, Figure).
Patients with cognitive improvement maintained the concentration of the top 3 fecal SCFA (total of butyrate, propionate, and acetate) on lactulose, while those without cognitive improvement experienced a decline in SCFA (0 [SD 10] nmol/mg vs. -31 [SD 66] nmol/mg, $P = 0.04$). Specifically, fecal butyrate concentrations were maintained in patients with cognitive improvement and dropped in those without improvement (0 [SD 2] nmol/mg vs. -4 [SD 6] nmol/mg, $P = 0.004$). **Conclusion:** An increase in *Bifidobacterium* abundance specifically was associated with cognitive improvement in patients with cirrhosis and portal hypertension on lactulose. Fecal SCFA concentrations were maintained in patients with cognitive improvement and declined in patients without cognitive improvement, possibly reflecting a dilution effect due to increased stool volume by lactulose. Therapies to augment *Bifidobacterium* might benefit patients with no cognitive improvement on lactulose.



Disclosures: Patricia Bloom: Vedanta Biosciences: Research grant, Nexilico: Consultant, Christine Bassis: Nothing to Disclose, Elliot Tapper: Madrigal: Grant/Research Support, Krishna Rao: Nothing to Disclose, Anna Lok: Abbott Diagnostics: Consultant, Chroma: Consultant, Grifols: Consultant, GlaxoSmithKline: Consultant, Novo Nordisk: Advisor, Pfizer: Consultant, Precision Biosciences: Consultant, Roche Diagnostics: Consultant, Virion: Consultant, Zenasbio: Consultant, Brii Biosciences: Advisor, Moderna: Advisor, Pioneering: Advisor, Vincent Young: Nothing to Disclose

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4329 | CHARACTERIZING THE GUT MICROBIOME IN NON-CIRRHOTIC PORTAL HYPERTENSION

Jenna Oringher[1] Meital Gewirtz[1] Yue Zhang[2] Neelam Redekar[2] James Haddad[1] Rownock Afruza[1] Moumita Chakraborty[1] Julian Hercun[3] Maria Mironova[3] Anjali Rai[4] Justin Lack[2] David Kleiner[5] Michail Lionakis[2] Christopher Koh[1] Theo Heller[4], [1]NIDDK, [2]NIAID, [3]National Institutes of Health, [4]NIH/NIDDK, [5]National Cancer Institute, Bethesda

Background: Non-cirrhotic portal hypertension (NCPH) is a heterogenous group of conditions which increase the likelihood for an individual to develop portal hypertension. By studying NCPH we may better elucidate mechanisms leading to complications of PH without the confounding factor of synthetic dysfunction that occurs in cirrhosis. While it is well known that cirrhosis is associated with gut dysbiosis, the microbiome in NCPH has not been previously characterized. **Methods:** Cross-sectional analysis of 26 NCPH and 32 healthy controls (HCs) was performed via shot-gun sequencing of DNA and RNA isolated from the stool. Microbial and functional profiles were compared in NCPH vs HCs to uncover disease-specific alterations. **Results:** NCPH patients had significantly lower richness ($p = 4.3e-5$) and Shannon index ($p = 2.5e-5$) than HCs. There were also significant between-group differences in beta diversity, with NCPH having greater within-group variation. There were 89 species significantly associated with NCPH, 45 belonging to the class Clostridia. The species *F. prausnitzii*, *D. Longicatena*, and *R. gnavus*, are known to affect bile acid metabolism and have been associated with progression of gastrointestinal and liver disease. Evaluation of the functional profile revealed 111 pathways that were differentially abundant in NCPH vs HCs, all upregulated in NCPH. The pathways peptidoglycan biosynthesis and superpathway of N-acetylglucosamine (a major component of mucin) degradation were significantly upregulated in NCPH (FC: 1.99, 3.34). **Conclusion:** In NCPH there are significant microbial and functional alterations of the gut microbiome, demonstrating dysbiosis independent of cirrhosis. Alterations in several species under the class Clostridia responsible for bile acid metabolism suggests a mechanism for altered immune signaling in disease, which may influence progression of portal hypertension. Additionally, upregulation of peptidoglycan production and mucin degrading pathways in NCPH increases pathogen associated molecular patterns and may contribute to loss of barrier integrity, further activating inflammatory pathways. Overlapping microbial changes in NCPH to liver diseases of varying etiologies suggests common mechanisms of disease progression independent of the presence of cirrhosis.

	Control	NCPH	t-test
n	32	26	
Sex (M)	15 (47%)	10 (39%)	p= 0.396
Age (Mean ± SD)	38.7 (±12.9)	49.1 (±15.4)	p= 0.0078
BMI (Mean ± SD)	24.1 (±4.4)	25.9 (±5.2)	p= 0.17
Portal Pressure (Mean ± SD)*	–	7.56 (±4.7)	
Platelets (Mean ± SD)*	–	125.7±88.69	
CAP (Mean ± SD)	–	191.7 (±49)	
TE (Mean ± SD)	–	11.1 (±7.8)	
Portal Hypertension (Yes)	–	15 (58%)	
NRH (Yes)	–	13 (50%)	
OPV (Yes)	–	4 (15%)	
Collaterals (Yes)	–	14 (54%)	
Varices (Yes)	–	15 (58%)	
LT (Yes)	–	2 (7.7%)	
Death (Yes)	–	4 (15%)	
Variceal Bleed (Yes)	–	4 (15%)	

*NCPH n=25
*NCPH n=22

Disclosures: Jenna Oringher: Nothing to Disclose, Meital Gewirtz: Nothing to Disclose, Yue Zhang: Nothing to Disclose, Neelam Redekar: Nothing to Disclose, James Haddad: Nothing to Disclose, Rownock Afruza: Nothing to Disclose, Moumita Chakraborty: Nothing to Disclose, Julian Hercun: Gilead: Consultant, Ipsen: Consultant, GSK: Consultant, Advanz: Consultant, Maria Mironova: Nothing to Disclose, Anjali Rai: Nothing to Disclose, Justin Lack: Nothing to Disclose, David Kleiner: Nothing to Disclose, Michail Lionakis: Nothing to Disclose, Christopher Koh: Nothing to Disclose, Theo Heller: Nothing to Disclose

4330 | CLOSTRIDIUM DIFFICILE COLONIZATION AS A PREDICTOR OF POOR OUTCOMES IN ACUTE ALCOHOLIC HEPATITIS

Isaac Swartzman[1] James Vu[1] Robert Pecha[1] Scott Crabtree[1] Vikrant Rachakonda[1], [1]University of California Davis Medical Center

Background: The gut-liver axis plays a critical role in liver disease, with gut dysbiosis and increased intestinal permeability contributing to disease progression. Clostridioides difficile (C. difficile) is a nosocomial pathogen associated with reduced microbial diversity, and C. Difficle colonization may serve as a surrogate marker of gut dysbiosis. Although the microbiome's role in alcohol-associated hepatitis (AH) is still emerging, early evidence links dysbiosis to increased disease severity. We evaluated C. difficile colonization as a predictor of adverse clinical outcomes in AH. **Methods:** We conducted a retrospective cohort study of patients admitted with acute AH who underwent *C. difficile* surveillance at our center from July 2017 to September 2024. *C. difficile* colonization (CDC) was defined as positive *C. difficile* rectal swab PCR without symptoms. Patients were followed from hospitalization up to 90 days after admission. Primary outcomes included infection, acute kidney injury (AKI), transplant-free survival, ICU admission, and hospital length of stay.

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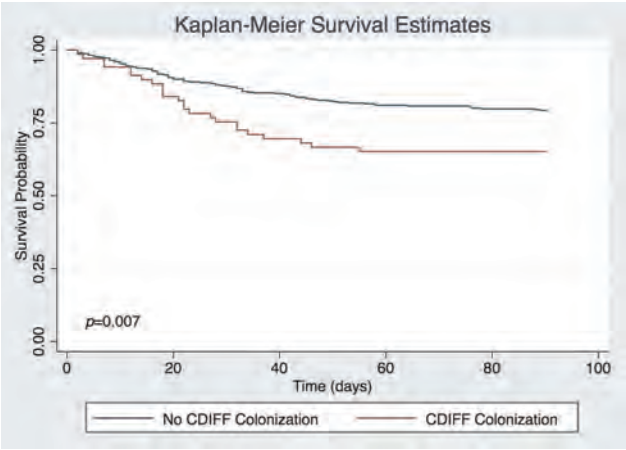
Results: Of 582 patients hospitalized with acute AH, 471 underwent C. difficile surveillance and 69 (14.7%) had CDC. CDC was associated with higher rates of infection [37 (53.6%) vs 126 (31.3%), $p = 0.001$], including *C. Difficile* infection (CDI) [4 (5.7%) vs 1 (0.2%), $p = 0.002$]. Patients with CDC had higher rates of ascites [54 (78.3%) vs. 225 (60.0%), $p < 0.001$], gastrointestinal bleeding [27 (39.1%) vs. 112 (27.9%), $p = 0.042$], and ICU admission [32 (46.4%) vs. 139 (34.6%), $p = 0.042$]. Serum albumin was lower [2.4 (IQR 2.0 – 3.0) vs. 2.8 (IQR 2.3 – 3.3) g/dl, $p = 0.001$] and WBC count was higher [11.0 (IQR 6.8 – 14.8) vs. 8.4 (IQR 5.9 – 13.1), $p = 0.044$] in CDC patients, but MELD 3.0 was similar between groups [28 (IQR 23 – 35) vs. 26 (IQR 21 – 31), $p = 0.065$]. No differences were observed in rates of AKI or hepatic encephalopathy between groups, and hospital length of stay was similar between patients with and without CDC. Kaplan Meier analysis demonstrated lower survival time in patients with CDC [66.7 (95% CI 58.9 – 74.4) days vs. 77.2 (95% CI 74.6 – 79.9) days, $p = 0.007$ by log rank test]. On multivariate Cox proportional hazards models, age [HR 1.039 (95% CI 1.021 – 1.057), $p < 0.001$] MELD 3.0 [HR 1.103 (95% CI 1.083 – 1.124), $p < 0.001$] and CDC [HR 1.604 (95% CI 1.014 – 2.537), $p = 0.043$] were associated with 90-day mortality. **Conclusion:** In patients with acute AH, CDC is associated with higher rates of infection, ascites, gastrointestinal bleeding, and ICU admission, and independently predicts reduced 90-day survival. Our study suggests that C. difficile colonization may serve as a surrogate marker of intestinal dysbiosis, disease severity, and infection risk in patients with AH.



Disclosures: Isaac Swartzman: Nothing to Disclose, James Vu: Nothing to Disclose, Robert Pecha: Nothing to Disclose, Scott Crabtree: Nothing to Disclose, Vikrant Rachakonda: Nothing to Disclose

4331 | LPS INDUCES TLR4 AND CYTOKINES IN A 3D PORCINE ENTEROID SYSTEM TO DRIVE MULTISYSTEM INJURY INCLUDING IFALD

Shaurya Mehta[1] Ashlesha Bagwe[1] chandrashekhara manithody[1] Sree Kolli[1] Marzena Swiderska-Syn[1] Uthayashanker Ezekiel[1] Ajay Jain[1], [1]Saint Louis University

Background: The intestinal epithelium plays a pivotal role in gut-liver axis signaling, acting as a barrier and immunological interface. Disruption of this interface as see in Total Parenteral Nutrition (TPN) dependent individuals, where enteral nutrient flow is bypasses; can potentiate hepatic injury. Lipopolysaccharide (LPS), a bacterial endotoxin, is a key driver of intestinal permeability and hepatic inflammation via Toll-like receptor 4 (TLR4) activation. We utilized a porcine 3D enteroid model to explore how LPS modulates epithelial immune signaling and barrier function, with implications for Intestinal Failure Related Liver Disease (IFALD). **Methods:** Enteroids were generated from the small intestine of neonatal Yorkshire pigs using Matrigel-based 3D culture. After 7 days, cultures were exposed to LPS (1, 2, or 5 μg/mL). Key markers of epithelial barrier integrity (ZO1) and immune signaling (TLR4, IL-8, IL-10) were assessed. Serum cytokine profiles from TPN- and enterally-fed (EN) animals were compared to explore systemic inflammatory responses relevant to hepatic outcomes. **Results:** High-dose LPS (5 μg/mL) significantly reduced ZO1 expression, indicating impaired epithelial barrier integrity. TLR4 expression was elevated in both 2 and 5 μg/mL LPS groups, peaking at 2 μg/mL. IL-8 and IL-10 levels increased in parallel, reflecting pro- and anti-inflammatory signaling. In vivo, TPN animals demonstrated higher serum IFN-γ ($p = 0.009$), IL-8 ($p = 0.011$), and circulating LPS ($p < 0.0001$) versus EN-fed controls—cytokine changes known to drive hepatic inflammation and cholestasis. **Conclusion:** Our enteroid model recapitulates intestinal epithelial responses to microbial stimuli, including barrier compromise and inflammatory activation, both of which may contribute to hepatic inflammation via gut-derived signals. These findings underscore the critical role of epithelial integrity in gut-liver communication and support the use of intestinal enteroids to dissect mechanisms underpinning TPN-associated liver disease.

Disclosures: Shaurya Mehta: Nothing to Disclose, Ashlesha Bagwe: Nothing to Disclose, chandrashekhara manithody: Nothing to Disclose, Sree Kolli:

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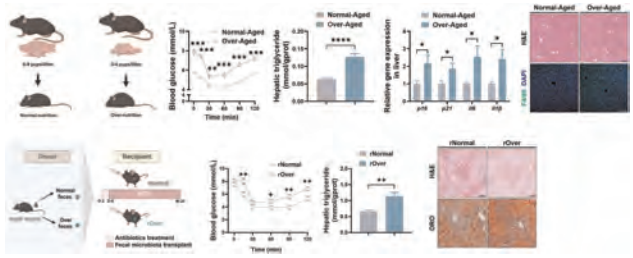
Nothing to Disclose, Marzena Swiderska-Syn: Nothing to Disclose, Uthayashanker Ezekiel: Nothing to Disclose, Ajay Jain: Nothing to Disclose

4332 | NEONATAL OVERFEEDING ACCELERATES AGE-RELATED LIVER PATHOLOGIES AND METABOLIC DYSFUNCTION THROUGH GUT MICROBIOTA

Jiangao Fan[1] Cen Xie[2] Yameng Liu[2] Jingyi Xu[3], [1]Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, [2]Shanghai Institute of Materia Medica, Chinese Academy of Sciences, [3]Nanjing University of Chinese Medicine

Background: Childhood obesity increases lifelong risk of metabolic diseases, yet its direct effects on liver aging remain unknown. Although gut microbiota regulates metabolic aging, how obesity-altered microbes accelerate age-related liver pathologies requires mechanistic investigation. **Methods:** We utilized an established neonatal overfeeding model via litter size reduction to induce childhood obesity. On postnatal day 3, mouse litters were standardized to either 3-4 pups (over-nutrition group) or 8-9 pups (normal-nutrition controls) per dam. Aged male mice (24-28 months) underwent comprehensive phenotyping including: survival analysis, glucose and insulin tolerance tests, serum biochemistry, hepatic lipid quantification, muscle function assessments, and whole-body metabolic profiling. Tissue analyses included histopathology and qPCR quantification. To interrogate gut microbiota's role, we performed fecal microbiota transplantation (FMT) from aged donors (normal-nutrition [rNormal] vs. over-nutrition [rOver]) to young recipients fed a high-fat diet (HFD) for 20 weeks to induce MASLD. Microbial community analysis via 16S rRNA sequencing characterized taxonomic shifts. **Results:** Survival analysis demonstrated that neonatal caloric excess significantly decreased median lifespan in aged mice. Compared to normal-nutrition controls, aged over-nutrition mice exhibited accelerated metabolic dysfunction, including obesity, severe insulin resistance, dyslipidemia, increased hepatic injury markers, and exacerbated ectopic lipid deposition in the liver. Neonatal overfeeding further aggravated sarcopenia, resulting in greater reductions in muscle mass and function. Indirect calorimetry revealed significantly lower VO_2, VCO_2, energy expenditure, and physical activity in aged over-nutrition mice. Histologically, over-nutrition intensified age-associated hepatic inflammation, evidenced by heightened F4/80$^+$ macrophage infiltration. Molecular analyses demonstrated upregulation of senescence markers (*p16*, *p21*) and SASP factors (*IL-6*, *IL-1β*) in both hepatic and skeletal muscle tissues. FMT studies showed that rOver mice developed severe metabolic perturbations, including hepatomegaly, increased hepatic triglyceride content, impaired insulin sensitivity, and progressive MASLD. Notably, rOver mice displayed marked sarcopenic phenotypes. Taxonomic analysis revealed a significant depletion of *Akkermansia* in over-nutrition cohorts based on 16S rRNA sequencing. Strikingly, these microbial disparities were conserved in FMT recipients, with rNormal mice sustaining higher *Akkermansia* abundance than rOver mice. **Conclusion:** This study demonstrates that early-life over-nutrition reprograms systemic aging trajectories, establishing a causal role for gut microbial communities in driving concurrent hepatic metabolic dysfunction and sarcopenic progression.



Disclosures: Jiangao Fan: Nothing to Disclose, Cen Xie: Nothing to Disclose, Yameng Liu: Nothing to Disclose, Jingyi Xu: Nothing to Disclose

4333 | ALTERATIONS IN SERUM METABOLOMIC PROFILES IN LIVER FIBROSIS MOUSE MODEL

Lei Ma[1] HUICHUN XING[1], [1]Center of Liver Diseases Division 3, Beijing Ditan Hospital, Capital Medical University

Background: Liver fibrosis is a consequence of chronic or recurrent liver injury and is a key pathological feature of progressive chronic liver disease. While many studies have shown alterations in the gut microbiota associated with liver fibrosis, research on serum metabolomic changes driven by gut microbiota dysbiosis remains limited. Yet, it may be a major contributor to the host metabolic dysfunction observed in liver fibrosis. **Methods:** Liver fibrosis was induced in C57 mice by intraperitoneal injection of carbon tetrachloride (CCl_4) for 8 weeks. Serum samples were collected at the end of the 8-week period, and non-targeted metabolomic profiling was performed using liquid chromatography–mass spectrometry (LC-MS). **Results:** Orthogonal projections to latent structures discriminant analysis (OPLS-DA) revealed distinct serum metabolic profiles between the CCl_4-treated group and the control group (Figure 1A). Based on the criteria of VIP $>$ 1, $|\log_2(FC)| > 1$, and $p < 0.05$, a total of 121 significantly altered serum metabolites were identified (Figure 1B). Among them, 81 metabolites were significantly upregulated, while 40 were downregulated in the CCl_4 group. KEGG annotation and enrichment analysis indicated that these differential metabolites were mainly enriched in

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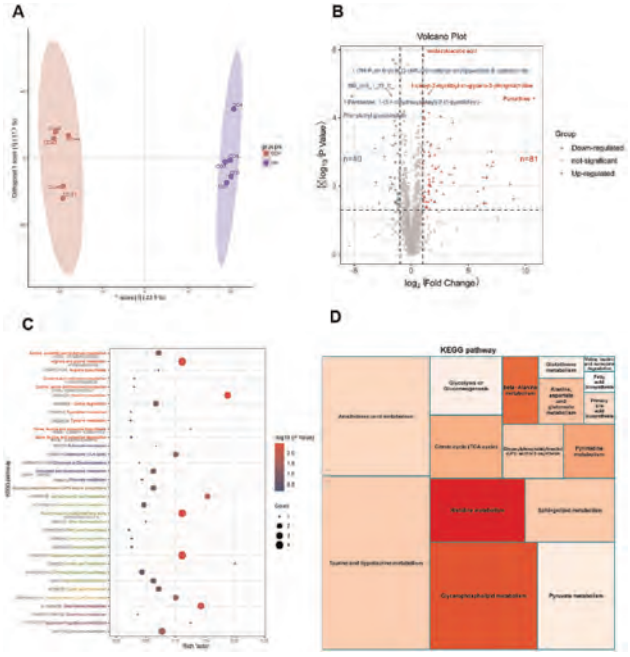
pathways related to amino acid metabolism and lipid metabolism (Figure 1C). Further topological analysis identified four key metabolic pathways with significant biological relevance: histidine metabolism, glycerophospholipid metabolism, pyrimidine metabolism, and β-alanine metabolism (Figure 1D). **Conclusion:** Liver fibrosis in mice leads to significant alterations in serum metabolic profiles, with major changes enriched in histidine metabolism, glycerophospholipid metabolism, pyrimidine metabolism, and β-alanine metabolism pathways.



Disclosures: Lei Ma: Nothing to Disclose, HUICHUN XING: Nothing to Disclose

4334NEW SUBMISSION | CHARACTERISTICS OF GUT MICROBIOME IN DECOMPENSATED ALCOHOLIC LIVER DISEASE, ALCOHOL USE DISORDER, NAFLD, AND A HEALTHY POPULATION

Ajay Jain[1] Mustafa Malvi[1] Shohini Sikdar[1], [1]Shalby Hospital

Background: In recent years, gut dysbiosis has been implicated in many diseases, including Alcohol related liver disease. The present study was conducted to characterize gut microbiota of decompensated alcoholic liver disease (DALD), Metabolic syndrome associated fatty liver disease (NAFLD), Alcohol use disorder (AUD) & healthy population. **Methods:** This observational study was conducted from December 2022 to June 2024. The total sample size was 100 (25 in each group). DNA extraction from the fecal samples was performed using the Qiagen DNeasy PowerSoil Pro kit. Based on the quantitation using a 1x dsDNA HS assay on a QUBIT fluorometer, Nanodrop and gel electrophoresis-passed samples were selected for amplification of the 16S rRNA region. The amplification was performed using V1 to V9 full-length 16S barcoded universal primers from Pacific Biosciences. **Results:** The alpha diversity analyses indicated that the gut microbiota in DALD was less diverse than healthy and NAFLD across all tested indices, showing a negative effect of alcohol intake on gut microbiome diversity. The beta diversity analyses also revealed a significant difference between the gut of alcohol consumers and those who do not consume alcohol. The pairwise comparisons showed significant difference between AUD vs. healthy ($P = 0.043$), DALD vs. healthy ($P = 0.002$), NAFLD vs. AUD ($P = 0.002$), and NAFLD vs. DALD ($P = 0.002$). The difference was insignificant between NAFLD vs. healthy ($P = 0.431$) and AUD vs. DALD ($P = 0.156$). At the Genus level, Bifidobacterium was observed to have the highest abundance overall. At the family rank, Bifidobacteriaceae, Prevotellaceae, Bacteroidaceae, Lachnospiraceae, Streptococcaceae, and Lactobacillaceae were some of the most abundant identified families. While at the phylum level, some of the most abundant were Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia. **Conclusion:** 1. A significant reduction in microbial diversity is seen in the DALD group. 2. Alcohol even in the absence of liver disease, has a significant detrimental effect on the composition of human gut microbiota.

Disclosures: Ajay Jain: Nothing to Disclose, Mustafa Malvi: Nothing to Disclose, Shohini Sikdar: Nothing to Disclose

4335 | GUT MICROENVIRONMENT RESTORATION AFTER HCV ERADICATION: INSIGHTS FROM MICROBIOTA AND BILE ACID DYNAMICS

Takako Inoue[1] Hisayoshi Watanabe[2] Kei Moriya[3] Hideto Kawaratani[3] Goki Suda[4] Tatsuya Ide[5] Satoru Kakizaki[6] Etsuko Iio[7] Takehisa Watanabe[7] Katsuya Nagaoka[7] Hitoshi Yoshiji[3] Yasuhito Tanaka[8], [1]Nagoya City University Hospital, [2]Tohoku Central Hospital of the Mutual Aid Association of Public School Teachers, [3]Nara Medical University, [4]Hokkaido University, [5]Kurume University Medical Center, [6]NHO Takasaki General Medical Center, [7]Kumamoto University, [8]Nagoya City University Graduate School of Medical Sciences

Background: In chronic hepatitis C (CHC), the gut microenvironment experiences progressive alterations. This study aims to compare the gut microenvironment before and after sustained virological response (SVR)

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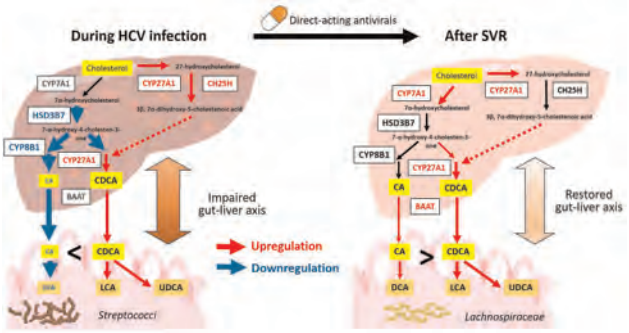
and elucidate the mechanisms responsible for gut microenvironment restoration following SVR. **Methods:** In the cross-sectional study, HCV-infected patients were categorized into chronic hepatitis (CH) group (n = 95) and cirrhosis/hepatocellular carcinoma (LC/HCC) group (n = 79). Similarly, post-SVR patients (CH, n = 29; LC/HCC, n = 46) had their gut microbiota and BA profiles compared with healthy individuals (n = 23). In the longitudinal study, stool samples from CHC patients were collected before HCV eradication and at 24 and 48 weeks after SVR. Gut microbiota and BA profiles were compared among the CH group (n = 29), LC/HCC group (n = 20), and healthy individuals (n = 23). Additionally, the expression levels of BA metabolic enzymes in HCV-infected patients (n = 65) and post-SVR CHC (n = 28) were compared with those of healthy individuals (n = 12). Ethical approval for this study was obtained from the appropriate institutional review boards. **Results:** In HCV-infected patients, expression levels of HSD3B7 and CYP8B1 were significantly lower than in healthy controls ($p < 0.0001$, $p = 0.071$) but normalized in post-SVR CH patients ($p = 1.0$, $p = 0.64$). Deoxycholic acid levels were significantly reduced during HCV infection ($p < 0.01$) but recovered following SVR ($p = 0.8$). HCV-associated increases in *Streptococcus* abundance were significantly reduced in the CH group 48 weeks after SVR ($p = 0.01$) but remained unchanged in the LC/HCC group. Improvements in FIB-4 index and ALT post-SVR correlated with increases in *Lachnospiraceae* abundance ($p < 0.0001$, $p = 0.0344$). **Conclusion:** In CHC, dysbiosis-driven alterations in BA metabolic enzyme expression and BA composition correlate with disease severity and are partially reversible with SVR, particularly in non-cirrhotic patients. Restoration of the gut microenvironment—including normalization of BA profiles and microbiota—was associated with improved liver fibrosis and function. Notably, *Lachnospiraceae* may play a key role in liver recovery after HCV eradication (Figure).



Disclosures: Takako Inoue: Nothing to Disclose, Nothing to Disclose, Hisayoshi Watanabe: Nothing to Disclose, Kei Moriya: Nothing to Disclose, Hideto Kawaratani: Nothing to Disclose, Goki Suda: Nothing to Disclose, Tatsuya Ide: Nothing to Disclose, Satoru Kakizaki: Nothing to Disclose, Etsuko Iio: Nothing to Disclose, Takehisa Watanabe: Nothing to Disclose, Katsuya Nagaoka: Nothing to Disclose, Hitoshi Yoshiji: Nothing to Disclose, Yasuhito Tanaka: Nothing to Disclose

4336 | DEFICIENCY OF SENESCENCE MARKER PROTEIN 30 (SMP30) AGGRAVATES INTESTINAL PERMEABILITY DUE TO E-CADHERIN DYSFUNCTION IN VIVO AND IN VITRO

Jin-Kyu Park[1] Woo Jun Kim[1] Su-Min Baek[1] Tae-Un Kim[1] Jae-Hyuk Yim[1], [1]Kyungpook National University

Background: SMP30 is a key molecule that mediates vitamin c synthesis, antioxidant effect, and anti-apoptotic effect. However, it has not been reported that SMP30 regulates intestinal permeability. Therefore, we investigated the role of intestinal SMP30 in alcohol-induced permeability models. Meanwhile, nanoplastics (NPs) are ubiquitous pollutants that can affect both humans and the environment. Given the exposure route of NPs, the disruption of intestinal epithelium aggravates the accumulation of NPs. Therefore, we used fluorescence-dyed NPs as an indicator to analyze distribution and toxicity of NPs. **Methods:** Alcohol-induced permeability mouse model was induced by Lieber-deCarli diet, and polystyrene nanoplastics (PS-NP) was administered 5 times a week for 3 weeks. Histopathological analysis, immunofluorescence (IF), immunohistochemistry (IHC), serum biochemistry, and western blot (WB) were performed to analyze phenotypes and related pathogenesis. To elucidate the underlying mechanisms, SMP30 knockdown was performed using the human colon carcinoma cell line Caco-2 with ethanol treatment. **Results:** The SMP30 KO EtOH (KE) group exhibited more severe vacuolization in the intestinal villi compared with the WT EtOH (WE) group. The expression of junctional proteins, such as E-cadherin and F-actin, was significantly decreased in IF and WB in the KE group. Due to the disruption of junctional proteins, more NPs were observed in the lamina propria of injured villi. Moreover, NP accumulation was increased in the liver, spleen, and brain in the SMP30 KO mice. In the liver tissue, the KE group showed more severe hepatic steatosis and higher ALT level compared with WE group. These patterns were confirmed in serum TG assay and Oil Red O stain. In the cell experiments, SMP30 knockdown did not alter the protein levels of E-cadherin and β-catenin. However, si-SMP30 treated cells exhibited cytoplasmic E-cadherin redistribution in regardless of ethanol treatment. **Conclusion:** This study demonstrates that SMP30 deficiency aggravates intestinal permeability due to

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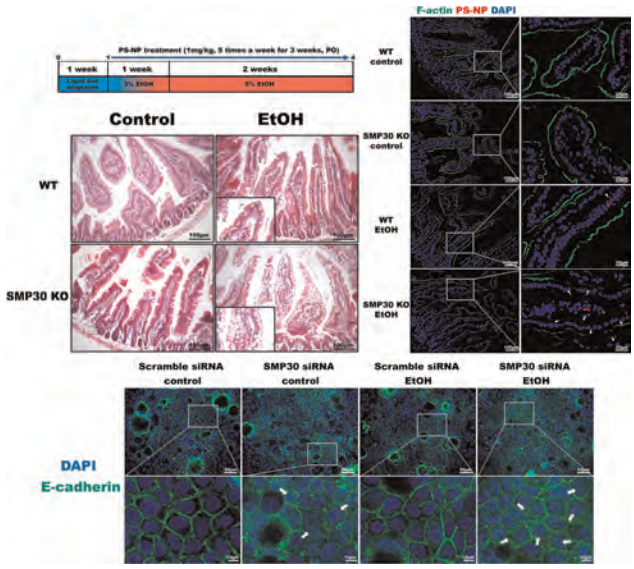
E-cadherin dysfunction. The KE group showed severe intestinal damage accompanied with NP accumulation in parenchymal organs. These patterns resulted from the disruption of E-cadherin and F-actin. In Caco-2 cells, SMP30 knockdown induced cytoplasmic E-cadherin redistribution, suggesting impaired cell-cell adhesion. This study elucidates the novel function of SMP30 in intestinal epithelium, emphasizing E-cadherin mediated gut permeability.



Disclosures: Jin-Kyu Park: Nothing to Disclose, Woo Jun Kim: Nothing to Disclose, Su-Min Baek: Nothing to Disclose, Tae-Un Kim: Nothing to Disclose, Jae-Hyuk Yim: Nothing to Disclose

4337 | HYPERAMMONEMIA AND VOLUNTARY WHEEL RUNNING MODULATE THE GUT MICROBIOME TO PROTECT AGAINST SARCOPENIA IN LIVER DISEASE

Annette Bellar[1] Nicole Welch[1] saurabh mishra[1] Muaz Alsabbagh Alchirazi[1] Amy Attaway[1] Pugazhendhi Kannan[1] Seshu Pothabathula[1] Takhar Kasumov[2] Lopa Mishra[3] Aaron Miller[1] Naseer Sangwan[1] Srinivasan Dasarathy, [1]Cleveland Clinic, [2]NEOMED, [3]Feinstein Institutes for Medical Research & Cold Spring Harbor Laboratory,

Background: Liver disease results in and may be caused in part by alterations to the gut microbiome which can further lead to frailty and sarcopenia. Hyperammonemic stress response (HASR) is A consequence of liver disease which causes sarcopenia. Hyperammonemia and HASR may be worsened by ammoniagenesis that in turn contributes to alterations in the gut microbiome as an adaptive (ammonia removal) or maladaptive (increase ammoniagenesis) responses. Endurance exercise potentially reverses sarcopenia/frailty in cirrhosis and modulate the gut microbiome to support ammonia disposal. The effects of hyperammonemia and voluntary wheel running (VWR) on the gut microbiome were evaluated in mice. **Methods:** Male C57/BL6 mice aged 8-9 week (wk) with a subcutaneous implanted osmotic pump delivering 2.5mmol/kg/d of ammonium acetate (AmAc) or vehicle (PBS) for 6 week were randomized to either voluntary wheel running (VWR) or usual activity (UA) for 4wk. Stool samples were collected when the osmotic pump was placed (pump) 2 weeks after the osmotic pump surgery and prior to 4 weeks of UA or VWR (pre-intervention) and at the end of the 4-week intervention period (post-intervention). 16S sequencing was done and analyzed in R, generating mean ASV abundance, correlation matrices, heatmaps, and Shannon diversity metrics. Pairwise Wilcoxon tests were used to asses temporal changes. **Results:** Alpha diversity (AD) was decreased with both AmAc treatment and VWR intervention between the pre and post-intervention timepoint ($p < 0.05$). In PBS-UA mice there was a strong correlation between the timepoints (pump to pre and pre to post) suggesting a stable microbiome (r 0.68 $p < 1.4e-8$) while PBS VWR mice exhibited compositional shifts ($r = 0.385$ $p = 0.01$) in the microbiome pre to post-intervetnion. AmAc-UA mice had a significant shift in bacterial taxa between the pump and pre and pre and post ($r = 0.28$, p 0.12) timepoints suggesting large changes in the gut microbial enviroment. At the genus level we found a decrease in *Akkermansia* between the pump placement and post-intervention timepoints. ($p < 0.05$). Similar to PBS treated groups AmAc-VWR correlation at timepoints was moderate (r0.567 p4.2e-5) with an initial increases in *Bacteroides* with AmAc-treatment which returned to baseline with VWR intervention (Fig1).In both PBS groups of mice and the AmAc VWR mice the 3 most abudnant species included Bacteriodales wile in the AmAc-UA groups 3 species of Akkermansi suggesting AmAc-UA mice mean abundance is different from that of other groups. **Conclusion:** HASR and VWR alter microbial diversity. While VWR resulted in moderate changes to the microbiome of PBS-treated mice, AmAc-treatment caused overall disruption in the microbiome. Interestingly VWR resulted in greater correlation and remodeling of the microbiome in AmAc-treated mice. These findings support physical activity as a modulator of microbiome dynamics with potential metabolic and skeletal muscle benefits in cirrhosis.

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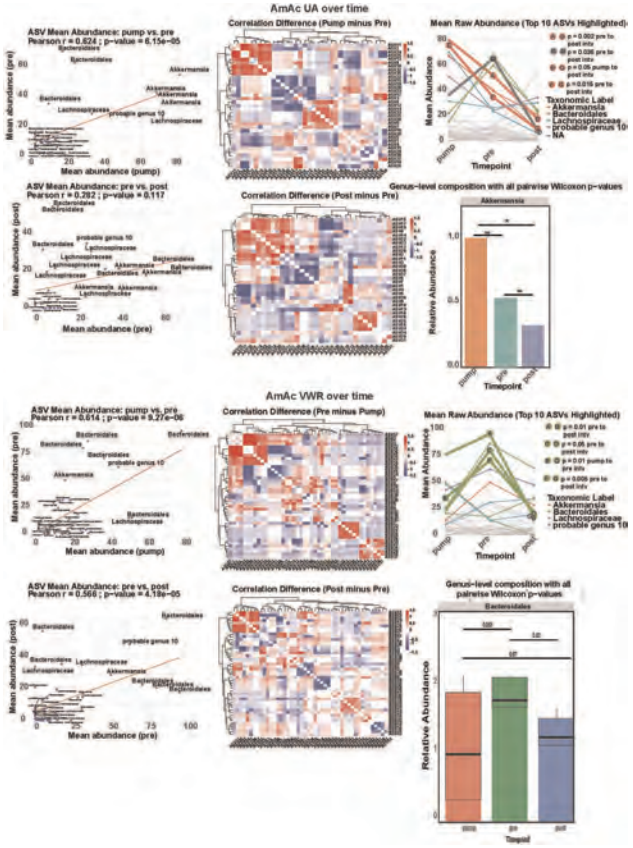
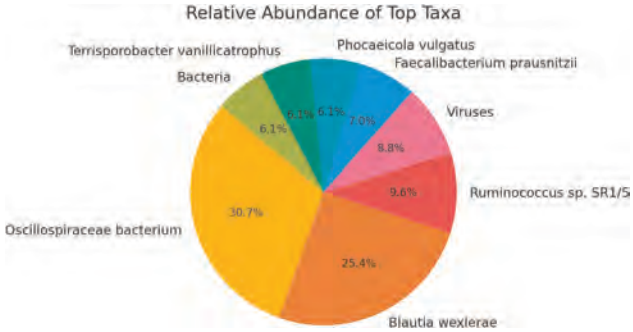


Disclosures: Annette Bellar: Nothing to Disclose, Nicole Welch: Nothing to Disclose, saurabh mishra: Nothing to Disclose, Muaz Alsabbagh Alchirazi: Nothing to Disclose, Amy Attaway: Nothing to Disclose, Pugazhendhi Kannan: Nothing to Disclose, Seshu Pothabathula: Nothing to Disclose, Takhar Kasumov: Nothing to Disclose, Lopa Mishra: Nothing to Disclose, Aaron Miller: Nothing to Disclose, Naseer Sangwan: Nothing to Disclose, Srinivasan Dasarathy: Nothing to Disclose

4338 | GUT MICROBIOTA COMPOSITION IN LIVER TRANSPLANT CANDIDATES: A METAGENOMIC ANALYSIS FROM PUBLIC DATA USING OPEN-SOURCE TOOLS

Rosa Ragozzino[1], [1]*Catholic University of the Sacred Heart, Italy*

Background: The presence of dysbiosis—an imbalance in gut microbiota composition—has been associated with several pathological conditions, including non-alcoholic fatty liver disease, cirrhosis, and hepatocellular carcinoma. Recent advances in molecular biology, particularly 16S rRNA sequencing, have enhanced the identification of microbial taxa and their role in liver disease. In cirrhosis, a reduction in microbial diversity, depletion of Bacteroidetes, and expansion of Proteobacteria and Fusobacteria have been linked to disease progression and complications. This study aims to explore the gut microbial landscape in patients awaiting liver transplantation by analyzing publicly available metagenomic data. **Methods:** Ten paired-end fecal metagenomic samples from the PRJNA1039781 project, involving liver transplant candidates, were processed using the Galaxy platform (usegalaxy.org). Reads were quality-filtered with Trimmomatic and taxonomically classified using Kraken2 against a comprehensive database. Results were visualized via Krona and exported for statistical inspection. The analysis focused on the 59 most frequent microbial taxa identified across samples. **Results:** The most frequently detected genera included *Bacteroides*, *Faecalibacterium*, *Escherichia*, and *Prevotella*. While some profiles showed preservation of beneficial commensals such as *Faecalibacterium*, others revealed elevated levels of potentially pathogenic genera like *Enterococcus* and *Clostridium sensu stricto*. This variation may reflect different stages of dysbiosis and disease severity among patients awaiting transplantation. Notably, *Bacteroidetes* remained dominant, but the emergence of opportunistic taxa supports prior evidence of microbial imbalance in cirrhotic patients. **Conclusion:** This pilot study demonstrates the feasibility of using open-access fecal metagenomic data and open-source bioinformatics tools to investigate gut microbiota in liver transplant candidates. The findings align with known patterns of dysbiosis in cirrhosis and may serve as a basis for future research on microbiome-based prognostic indicators in hepatic disease.



Disclosures: Rosa Ragozzino: Nothing to Disclose

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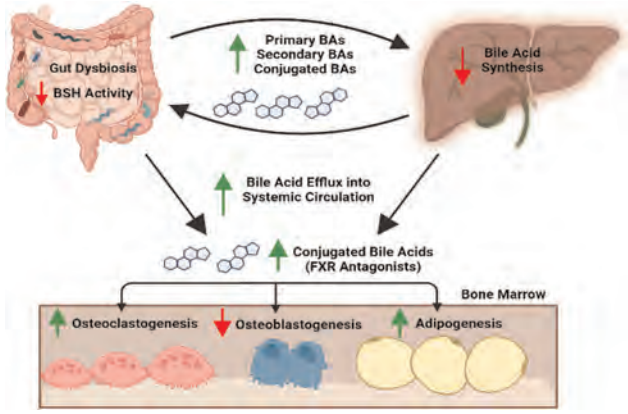
4339 | DYSBIOSIS IN THE GUT-LIVER AXIS DRIVES BONE LOSS DURING CHOLESTATIC LIVER DISEASE

Matthew Carson[1] Brooke Hutchison[1] Jamie Fornsaglio[1] Kari Nejak-Bowen[1], [1]University of Pittsburgh

Background: Cholestatic liver diseases (CLDs) are characterized by disrupted bile acid homeostasis. Patients with CLD often develop metabolic bone diseases. These patients lose bone faster and have a higher incidence of fractures than healthy individuals. Despite the prevalence of metabolic bone diseases in CLD patients, the mechanisms underlying bone loss are unclear. The gut-liver axis refers to the bidirectional relationship between the gut microbiota and the liver. Gut-liver metabolites, such as bile acids, are critical regulators of gut microbiota signaling actions on bone. However, bile acids' role on skeletal function during chronic liver cholestasis is unclear. Purpose was to investigate the role of the gut-liver axis and bile acid signaling on bone loss during CLD. **Methods:** Mice were administered 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) from age 11-15 weeks. 16s rDNA sequencing was performed on colons. Liver bile acid synthesis and transporter expression were determined by qRT-PCR. Ex vivo micro-CT was performed in femur. Osteoblast and osteoclast outcomes were evaluated by histomorphometry. Bone marrow bile acids were evaluated by mass spectrometry. Osteoblasts and osteoclasts were treated with the bone marrow bile acid profile found in experimental mice to assess their effects on bone cell functions. **Results:** DDC-treated mice exhibit reduced bone mass, attributed to decreases in bone-forming osteoblasts and increases in bone-resorbing osteoclasts. DDC-treated mice show genus-level shifts in their gut microbiota that are linked to disrupted bile acid metabolism. Furthermore, hepatic bile acid efflux transporter genes are dysregulated in mice with cholestasis, indicating a disturbance in gut-liver bile acid homeostasis. Mice with chronic cholestasis have increases in conjugated bile acids in their bone marrow. In vitro stimulation with the bone marrow bile acid profile of DDC-treated mice suppressed osteoblast mineralization potential and enhanced osteoclastogenesis compared to controls. **Conclusion:** No known studies have measured the concentration of bile acids in the bone marrow and evaluated their direct effects on bone cell outcomes. This work is the first to demonstrate that bile acids are direct regulators of skeletal outcomes in the setting of cholestatic liver disease. Future research is necessary to determine whether targeting the gut-liver axis and bile acids are viable therapeutic approaches for treating CLD-induced bone loss.



Disclosures: Matthew Carson: Nothing to Disclose, Brooke Hutchison: Nothing to Disclose, Jamie Fornsaglio: Nothing to Disclose, Kari Nejak-Bowen: Surrozen, Inc.: Consultant

4340 | THE MICROBIOME IN PATIENTS WITH CIRRHOSIS AND CLINICAL SIGNIFICANT PORTAL HYPERTENSION: A PILOT CASE-CONTROL STUDY

Giuseppe Colucci[1] Sonia Stella[2] Alberto Castagnetti[3] Luisa Di Rito[3] Marina Lucà[2] Giulia Tosetti[4] Pietro Lampertico[5], [1]IRCCS Fondazione Cà Granda-Policlinico, University of Milan, [2]IRCSS Fondazione Ca' Granda, [3]Wellmicro Srl, [4]IRCCS Ca' Granda, [5]University of Milan

Background: Alterations in the composition of the intestinal microbiome may affect the gut-liver axis and influence the status of liver cirrhosis with Clinical Significant Portal Hypertension (CSPH) a condition at risk of hepatic encephalopathy and decompensation. In the present study we investigated a representative group of patients for their microbiota and micobiota composition to identify pathological profiles amenable to treatment with antibiotics, dietary and specific probiotic supplementation. **Methods:** We performed a single center, prospective, case-control study in 25 patients wih cirrhosis and CSPH compared to healthy controls. Fecal samples were collected using SMART eNAT® with nucleic acid preservation buffer and shipped at room temperature to the Wellmicro laboratory. The hypervariable regions V3 and V4 of the 16S rRNA gene (bacterial component) and the ITS2 region (fungal component) from extracted DNA are sequenced on the MiSeq - Illumina® platform for massively parallel sequencing. Dysbiosis index returns a measurement of the overall deviation of the ARs of the sample with

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respect to the reference intervals of healthy subjects at the taxonomic level of genus. Diversity index is based on number of species, phylogenetic distance (P.D. Whole Tree) and distribution of species (Pielou Index). **Results:** Twentyfive patients with cirrhosis and CSPH were enrolled in the study and compared to healthy donors. All patients (mean age 60 years, 88% male) had compensated cirrhosis and CSPH (esophagel varices or splenomegaly), 34% were treated with NSBB and 32% with diuretics. The macrobiota composition of our patients included 5 Phyla: Firmicutes (57%), Bacteroidites (35%), Elusimicrobia (3%), Protebacteria (2.5%), and Actinobacteria (2.4%) with significant differences compared to normal controls in the proportion of Elusimicrobia (3% vs. 1%, $p < 0.001$), Protebacteria (2.5% vs 1.4, $p < 0.003$) and Verrucomicrobia (0% vs 0.34%, $p < 0.004$). As to the micobiota Malassezia R. and Candida A. were found in 70% and 30% of cases. Overall, the Dysbiosis and Diversity Indexes were significantly higher in patients than in controls (median 2.2 vs 1.3, $p < 0.01$; 2.9 vs 1.2, $p < 0.01$). **Conclusion:** The observed difference in the microbiota composition, in the Dysbiosis and Diversity indexes between patients and controls as well as the presence of bacterial and fungal pathobionts may suggest the need for antibiomicrobiol therapy and changes in the dietary habits with the supplementation of specific probiotics.

Disclosures: Giuseppe Colucci: Nothing to Disclose, Sonia Stella: Nothing to Disclose, Alberto Castagnetti: Nothing to Disclose, Luisa Di Rito: Nothing to Disclose, Marina Lucà: Nothing to Disclose, Giulia Tosetti: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose

4341 | CROSS-KINGDOM SHIFTS IN THE BLOOD MICROBIOME DURING HCV-ASSOCIATED LIVER FIBROSIS AND POST-VIRAL CLEARANCE

Rownock Afruza[1] Theo Heller[2] Christopher Koh[2] Moumita Chakraborty[2] Jenna Oringher[2] Nicole Minerva[2] Rabab Ali[2] Grace Zhang[2] Elizabeth Townsend[2] Elliott Levy[2] Ohad Etzion[2] David Kleiner[2] Justin Lack[2] Neelam Redekar[2] Yue Zhang[2] Kareen Akiva[2] Lisa Scheuing[2], [1]National Institutes of Health, [2]NIH

Background: Liver disease is a major cause of global death and has been linked to gut microbiota imbalances. While bacterial changes are associated with liver disease severity and progression, the roles of fungi, viruses, and archaea in this context are still not well defined. This study investigates the portal and peripheral blood microbiome during active HCV infection and after viral clearance, focusing on fibrosis and cross-kingdom interactions, particularly involving fungi. **Methods:** Cell-free DNA was extracted from peripheral and portal blood plasma in patients before (HCVi, $n = 29$) and after (SVR, $n = 23$) DAA treatment. DNA was sequenced, filtered for human reads, and aligned to a curated microbial reference. Fibrosis was staged using the Ishak score, grouping subjects into cirrhotic and non-cirrhotic. Microbial associations were explored using SparCC. **Results:** Bacteria were the most abundant taxa, followed by fungi, viruses, and archaea. In cirrhotic patients, fungal DNA significantly increased after SVR ($p = 0.02$), while bacterial DNA decreased in portal plasma ($p = 0.02$). Microbial profiles in portal blood differed between HCVi and SVR in cirrhotics (Bray-Curtis, $p = 0.008$), with similar trends in fungal diversity. Fungal alpha diversity was lower post-SVR. Dominant bacterial phyla included *Pseudomonadota*, *Bacillota*, *Actinomycetota*, and *Bacteroidota*; fungal phyla were *Ascomycota* and *Basidiomycota*, with the latter increasing post-SVR. *Euryarchaeota* was the main archaeal phylum, and viral profiles were led by *Uroviricota* and *Cressdnaviricota*. SparCC revealed significant interkingdom correlations ($p < 0.05$), mostly between bacteria and fungi. **Conclusion:** This is the first detailed analysis of the blood microbiome in HCV-related fibrosis. Although fungal levels elevated after SVR, diversity declined, suggesting loss of richness and dominance by fewer species. Significant microbiome shifts between HCVi and SVR in cirrhotics and previously underappreciated strong cross-kingdom interactions underscore fungi's key role in blood microbiome dynamics during liver disease.

Disclosures: Rownock Afruza: Nothing to Disclose, Theo Heller: Nothing to Disclose, Christopher Koh: Nothing to Disclose, Moumita Chakraborty: Nothing to Disclose, Jenna Oringher: Nothing to Disclose, Nicole Minerva: Nothing to Disclose, Rabab Ali: Nothing to Disclose, Grace Zhang: Nothing to Disclose, Elizabeth Townsend: Nothing to Disclose, Elliott Levy: Nothing to Disclose, Ohad Etzion: Nothing to Disclose, David Kleiner: Nothing to Disclose, Justin Lack: Nothing to Disclose, Neelam Redekar: Nothing to Disclose, Yue Zhang: Nothing to Disclose, Kareen Akiva: Nothing to Disclose, Lisa Scheuing: Nothing to Disclose

4342 | MASLD-RELATED ORAL MICROBES WERE ASSOCIATED WITH OBESOGENIC METABOLITES AND CLINICAL PARAMETERS

Dae Won Jun[1] Hyo Young Lee[1] Sang Bong Ahn[2] Hyunwoo Oh[3] Eileen Yoon[4] Ju Hyun Oh[5] HA IL KIM[4], [1]Hanyang University, [2]Department of Internal Medicine, Nowon Eulji Medical Center, Eulji University, College of Medicine, [3]Department of Internal Medicine, Kangbuk

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Samsung Hospital, Sungkyunkwan University School of Medicin, [4]Department of Internal Medicine, Hanyang University College of Medicine, [5]Department of Internal Medicine, Bundang Medical Center, CHA University College of Medicine, Seoul,

Background: Previous studies have primarily focused on the role of the intestinal microbiome in metabolic dysfunction-associated steatotic liver disease (MASLD). While the impact of the gut microbiome is well-documented, the role of the oral microbiome in influencing the gut microbial environment and metabolic pathways has been unveiled. We aimed to investigate the association between the oral microbiome and its potential impacts on gut microbiomes, metabolites, and metabolic risk factors. **Methods:** This study was conducted as a multicenter cross-sectional study involving 206 healthy individuals and 206 diagnosed with MASLD. The oral and stool microbiomes were analyzed using the V3–V4 hypervariable region of the 16S rRNA gene, following the Illumina 16S Metagenomic Sequencing Library Preparation protocol. Serum and stool metabolites were also analyzed using LC-MS. **Results:** There was a lower diversity of oral microbiota and distinct microbial distributions in MASLD compared to controls. Notably, prevalence of oral Neisseria sp. 0031, Veillonella sp. 0011, and Streptococcus sp. 0009 were higher in MASLD compared to non-SLD. These oral microbiomes showed positive associations with body mass index, waist circumference, and adverse lipid profiles, alongside a correlation with elevated liver enzymes. Additionally, specific gut microbes like Weissella sp.001 and Tyzzerella sp. 001 were more abundant in MASLD. Interestingly oral Neisseria sp. 0031, Veillonella sp. 0011, and Streptococcus sp. 0009 showed positive correlation with intestinal Weissella sp.001 and Tyzzerella sp. 001. Presence of Streptococcus sp. 0009 in MASLD was associated with higher levels of lysophosphatidylcholines (15:0), (17:0) and negative correlation with correlation with N-(1-Deoxy-1-fructosyl) aline, succinylcarnitine in serum. **Conclusion:** The oral microbiome, specifically Streptococcus sp. 0009, showed a positive correlation with intestinal microbiome, obethogenic metabolites as well as cardiometabolic parameters in patients with MASLD.

Disclosures: Dae Won Jun: Nothing to Disclose, Hyo Young Lee: Nothing to Disclose, Sang Bong Ahn: Nothing to Disclose, Hyunwoo Oh: Nothing to Disclose, Eileen Yoon: Nothing to Disclose, Ju Hyun Oh: Nothing to Disclose, HA IL KIM: Nothing to Disclose

◆ 4343 | CARBOXYMETHYLCELLULOSE AND POLYSORBATE 80: BRIDGING ULTRAPROCESSED FOOD AND MASLD-ASSOCIATED HEPATOCARCINOGENESIS

Gabriel Bacil[1] Leticia Valente[1] Heloiza Ferreira[2] Julia Noveti[3] Keila Cavalcante[4] Diego Alonso[3] Paulo Ribolla[3] Daniel Cardoso[4] Guilherme Romualdo[3] Luis Fernando Barbisan[3], [1]Sao Paulo State University, [2]Sao Paulo State Unviersity (UNESP), [3]Sao Paulo State University (UNESP), [4]University of Sao Paulo (USP)

Background: Hepatocellular carcinoma (HCC) is the main primary liver neoplasia and the 3rd deadliest type of cancer worldwide, whereas metabolic-dysfunction associated liver disease (MASLD) has become the fastest-growing cause of liver disease. Carboxymethylcellulose (CMC) and polyssorbate 80 (P80) emulsifiers are extensively consumed as food additives by the global population and regarded as potential drivers of metabolic diseases by disrupting the gut-liver axis balance. Nevertheless, it is still uncertain whether these compounds modulate MASLD-associated liver carcinogenesis. **Methods:** Male 14-day-old C57BL/6 mice received an intraperitoneal protocol of diethylnitrosamine (DEN, 25 mg/kg of b.w., 1x/week) or saline vehicle, for 4 weeks, and were allocated into 8 experimental groups (G1-G8). From the 6th week on, mice (G2-G8) were kept for 24 weeks on a western diet (WD) protocol or regular diet (G1). Mice also received daily intragastric doses (5x/week), for 20 weeks, of CMC (370 and 740 mg/kg of b.w., G3 and G4, respectively), P80 (100 and 200 mg/Kg of b.w., G5 and G6, respectively), or their combination (370 +100 and 740 +200 mg/Kk of b.w., G7 and G8, respectively) or ultrapure water vehicle. A glucose tolerance test (GTT) was performed and obesity-related outcomes assessed. Hepatic tumoral/non-tumoral samples were collected for further histopathological and molecular analysis. Fecal samples were collected for gut microbiome profiling. Data were analyzed by one/two-way ANOVA or Kruskal-Wallis and Tukey's/Dunn's *post hoc* tests ($p \leq 0.05$). The Shannon's test was used for checking fecal samples' diversity. For the transcriptomic data, a Log2 Fold Change > 1 and padj < 0.05 were defined for the identification of differentially expressed genes. **Results:** G5/G7 had increased final body weight and adiposity index ($p < 0.0001$), while G6/G8 groups showed a higher proportion of larger tumors (> 50 mm^3, $p < 0.0001$). All WD-fed groups showed a glucose

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intolerance state, as depicted by the GTT area under the curve ($p < 0.0001$), and no effects were observed on serum parameters (alanine aminotransferase, total cholesterol, and triglycerides). Surprisingly, G5-G7 had a pronounced MASLD activity score, featuring a mixed macro/microvesicular steatosis background ($p < 0.0001$) with clear signs of hepatocellular hypertrophy ($p < 0.0001$). G3/G7 featured profound gut microbiome changes, following Shannon's diversity test ($p = 0.0282$ and $p = 0.0472$) at phylum, classes, order, and genera levels. Our bulk RNA-seq analysis revealed a dissimilar impact of food additives on both tumor and adjacent liver, with prominent effects of P80 over inflammation-, lipid-, and microbiome-related genes. **Conclusion:** Our findings revealed that the exposure to populational-relevant doses of CMC and P80 or their combination promote MASLD-associated liver carcinogenesis through the modulation of the gut-liver axis.
Disclosures: Gabriel Bacil: Nothing to Disclose, Leticia Valente: Nothing to Disclose, Heloiza Ferreira: Nothing to Disclose, Julia Noveti: Nothing to Disclose, Keila Cavalcante: Nothing to Disclose, Diego Alonso: Nothing to Disclose, Paulo Ribolla: Nothing to Disclose, Daniel Cardoso: Nothing to Disclose, Guilherme Romualdo: Nothing to Disclose, Luis Fernando Barbisan: Nothing to Disclose

◆ 4344 | LOSS OF HEPATIC VACUOLE MEMBRANE PROTEIN 1 PROTECTS AGAINST ACETAMINOPHEN-INDUCED LIVER INJURY

Hong-Min Ni[1] Khue Nguyen[1] Mengwei Niu[1] Wen-Xing Ding[2], [1]The University of Kansas Medical Center, [2]University of Kansas Medical Center

Background: Acetaminophen (APAP) is an analgesic and antipyretic drug that is commonly used worldwide. Although APAP is considered safe at therapeutic doses, APAP overdose may cause severe liver injury and acute liver failure (ALF). Metabolism of APAP results in formation of APAP protein adducts (APAP-AD) in hepatocytes and triggers mitochondrial dysfunction and necrosis. One proposed mechanism to counteract APAP-induced hepatotoxicity is autophagy, a highly conserved intracellular degradation pathway protecting the cell via the removal of APAP adducts and damaged mitochondria. Vacuole membrane protein 1 (VMP1) is an ER transmembrane protein essential for the elongation and closure of autophagosomes. Deletion of VMP1 in the liver leads to impaired autophagy. However, the role of VMP1 in APAP-induced liver injury is unknown. **Methods:** RNAseq database from human APAP ALF and mouse APAP overdose livers were analyzed. Liver-specific VMP1 knockout ($Vmp1^{LKO}$) and matched wild-type ($Vmp1^{LWT}$), and the liver tissues were collected at different time points. Liver injury and necrosis were assessed by serum ALT, hematoxylin and eosin (H&E), and TUNEL staining. APAP metabolism, autophagy, APAP adduct formation, and liver regeneration were also examined. **Results:** Increased mRNA levels of *VMP1* and autophagy genes, *LC3B* and *SQSTM1/p62* in human APAP ALF livers. Serum ALT and necrosis were increased in WT mice following APAP treatment and peaked at 6 hours with increased phosphorylated JNK in mouse livers. LC3B-II and p62 were increased and peaked at 24 hours, but VMP1 protein was decreased in WT mouse livers following APAP treatment. Liver injury was markedly decreased in $Vmp1^{LKO}$ mice compared with their WT littermates with reduced serum ALT and necrotic areas. No difference in basal levels of Cyp2E1 and GSH was found between WT and KO mouse livers. The protein level of phosphorylated JNK was reduced in $Vmp1^{LKO}$ mouse livers. Interestingly, APAP adduct formation and mitochondrial damage were similar in WT and $Vmp1^{LKO}$ mouse livers after APAP, but peroxynitrite formation was decreased in $Vmp1^{LKO}$ mouse livers. Furthermore, GSH replenishment was faster in $Vmp1^{LKO}$ mice than in WT. The number of PCNA-positive cells and hepatic protein levels of PCNA were higher in $Vmp1^{LKO}$ mouse livers. **Conclusion:** Loss of hepatic VMP1 does not affect APAP metabolism and APAP adduct formation but protects APAP-induced liver injury by reducing peroxynitrite formation and enhancing liver regeneration.
Disclosures: Hong-Min Ni: Nothing to Disclose, Khue Nguyen: Nothing to Disclose, Mengwei Niu: Nothing to Disclose, Wen-Xing Ding: Nothing to Disclose

◆ 4345 | KINASE INHIBITOR INDUCED LIVER INJURY

Lily Dara[1] Aria Baktash[1] Yi-Ju Li[2] Elizabeth Phillips[3] Raj Vuppalanchi[4] Robert Fontana[5] LUCY MEUNIER[6] Jiezhun Gu[2] Andrew Delinger[2] Huiman Barnhart[2] Jay Hoofnagle[7], [1]University of Southern California, [2]Duke University, [3]Vanderbilt University, [4]Indiana University, [5]University of Michigan Hospitals and Health Centers, [6]Montpellier Hospital Medical Center, [7]NIH, NIDDK

Background: Protein Kinase Inhibitors (KIs) are important therapies for both neoplastic and serious non-neoplastic diseases. Since 2003, more than 100 KIs have been approved for use in the US. Many KIs are associated with aminotransferase elevations during therapy, but little has been reported on serious and clinically apparent KI-induced liver injury (KILI). We aimed to assess the frequency, clinical features, and genetic associations of KILI enrolled in the Drug-Induced Liver Injury Network (DILIN) retrospective and prospective studies. **Methods:** Cases of KILI enrolled in

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DILIN between 2004 and 2024 were identified and reassessed for causality and clinical features and compared to 1520 non-KI DILI patients. HLA sequencing was performed on both cases and controls. **Results:** 33 cases of KILI scored as probable, highly likely, or definite were identified; the frequency increased from 0.6% of cases enrolled in 2004-09, 1.6% in 2010-14, 2.4% in 2015-19, and to 4.2% in 2020-24. Of the 33 cases, 10 were attributed to imatinib, 5 to pazopanib, 2 each to dabrafenib, lapatinib, and ribociclib, and 1 each to 12 other KI's. Clinical features varied. Overall, 58% were hepatocellular (HC), 18% mixed, and 24% cholestatic; half were anicteric, 33% hospitalized, 48% had liver biopsy, and only 1 fatal (palbociclib). Imatinib caused HC injury, with long latencies, median 7 mo (3 to 47 mo), with autoantibodies in 4, and corticosteroid therapy in 4 patients. In contrast, pazopanib usually caused cholestatic injury, with latencies of 1 to 2 mo, infrequent immune features, and prolonged course. Lapatinib cases were HC with somewhat long latencies (median 4 mo). Six patients were rechallenged and all had DILI again, one adapted eventually. Five patients were exposed to immune checkpoint inhibitors (ICI) within 6 mos of starting a KI. Genetic analysis of 25 KILI cases revealed a significant association with the extended haplotype HLA DQA1*02:01, DRB1*07:01, C*06:02 compared to 1520 DILIN controls ($P = 9.3x10^{-7}$). The HLA DQA1*02:01 allele frequency was 0.30 overall, 0.44 with imatinib and 0.50 with lapatinib compared to 0.12 in DILIN controls (Table 1). **Conclusion:** KILI is an increasingly recognized cause of serious liver injury, rising in incidence with the growing use of targeted and combination ICI–KI therapies. Imatinib was the KI most frequently linked to liver injury, had a distinct phenotype, and a close association with HLA DQA1*02:01, DRB1*07:01, C*06:02, alleles with links to multiple autoimmune diseases. Interestingly, five cases of KILI occurred within 150 days of ICI exposure, suggesting a heightened risk of KILI following immunotherapy.

Allele1	Allele2	Allele3	P-value	KILI Freq	DILIN Control Freq	Known Associations
DRB1*13:04	DRB3*02:02		3.8 E-06	0.04	0.003	DRB3*02:02 Type 1 diabetes Graves' disease
DRB1*07:01	DRB4*01:01		0.0001	0.30	0.12	DRB1*07:01 Lapatinib DILI DRB4*01:01 AIH, PBC
DRB1*07:01	DQA1*02:01		<0.001	0.30	0.12	Type 2 AIH DQA1*02:01 Celiac disease
DRB1*07:01	DQA1*02:01	C*06:02	9.3 E-07	0.20	0.04	C*06:02 Psoriasis

Table 1: Haplotype Frequencies in KILI vs DILIN Controls and Autoimmune Associations.

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◆ 4346 | ESTROGEN SIGNALING IN THE DEVELOPMENT OF TOXICANT-ASSOCIATED STEATOTIC LIVER DISEASE IN FEMALES

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Background: Persistent organic pollutants (POPs) such as PCB126 (formerly used as industrial chemical) and Chlordane (organochlorine pesticide) are linked to steatotic liver disease (SLD) development. Our prior work demonstrated that females were more susceptible to POP-induced steatosis and metabolic dysfunction compared to males. However, the underlying sex-specific mechanisms driving this disparity remain poorly understood with mechanistic studies in SLD development in women currently lacking. This study investigates how POPs contribute to SLD, with emphasis on female-specific hepatic responses and estrogen signaling. **Methods:** Female C57BL/6 mice underwent ovariectomy or sham surgery. Post recovery, mice were administered either the vehicle control or a mixture of environmentally relevant POPs, namely, Chlordane(20 mg/kg)+PCB126(20μg/kg) via oral gavage. After 2 weeks, mice were euthanized and samples collected for downstream analyses. **Results:** Ovariectomized (OVX) mice generally had higher body fat composition

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and liver weights than sham (control) mice. However, exposure to POPs resulted in higher liver to body weight ratios in sham but not OVX mice. Histological analysis of liver sections (H&E) revealed that despite OVX mice showing higher frequency of lipid droplets (steatosis), POP exposure did not exacerbate this effect. However, POP-exposed sham mice exhibited greater steatosis and inflammatory foci infiltration than their unexposed controls. In contrast, serum triglycerides and lipoprotein levels, but not liver triglyceride levels, were down-regulated in POP-exposed sham mice, implicating dyslipidemia. A glucose tolerance test performed 10 days post exposure demonstrated that POP-exposed sham but not OVX mice showed signs of glucose intolerance vs. their unexposed counterparts. Hepatic expression of key target genes was also assessed. POPs increased liver mRNA levels of *Tnfa* only in sham mice while *Hnf4a* was decreased in this group. Further, POP exposure activated hepatic xenobiotic receptors known to negatively interact with estrogen signaling, namely the AHR (*Cyp1a1*, *Cyp1a2* induction) and CAR (*Cyp2b10*, *Cyp2c29* induction) in both groups. This was accompanied by lower liver *Esr1* expression in exposed sham mice, implicating xenobiotic receptor-sex hormone receptor interactions as drivers of POP-induced metabolic and liver dysfunction. **Conclusion:** Taken together, the findings revealed that POP exposure led to steatosis only in sham mice, thereby validating AHR/CAR activation and altered estrogen signaling as a mechanism in SLD development. POPs did not exacerbate steatosis or metabolic dysfunction in OVX mice as this mechanism was absent. Studies using estradiol supplementation in liver *Esr1* null mice will provide insights on potential sex-specific interventions in toxicant-associated SLD.
Disclosures: Banrida Wahlang: Nothing to Disclose, Yuan Hua: Nothing to Disclose, Oluwanifemi Esther Bolatimi: Nothing to Disclose, Gavin Phillips: Nothing to Disclose, Zayna Qaissi: Nothing to Disclose, Jeffrey Kim: Nothing to Disclose

◆ 4347 | IDENTIFICATION OF NOVEL BIOMARKERS FOR CHOLESTATIC DRUG-INDUCED LIVER INJURY

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Background: Drug-induced liver injury (DILI) remains a significant clinical challenge, contributing to over 10% of acute liver failure cases. Conventional liver biomarkers—ALT, AST, ALP, and total bilirubin—are often non-specific and may be influenced by extra-hepatic factors, limiting their utility in accurately diagnosing DILI. Thus, there is a critical need to identify novel, reliable biomarkers that can enhance diagnostic precision for DILI. **Methods:** We conducted a multi-center study involving 66 patients with DILI, 60 healthy controls, and 486 patients with other liver diseases, including viral hepatitis, autoimmune hepatitis (AIH), alcoholic liver injury, metabolic-associated fatty liver disease (MAFLD)/steatohepatitis (MASH), primary biliary cholangitis (PBC), obstructive jaundice (OJ), liver cirrhosis, and hepatocellular carcinoma (HCC). Serum samples from DILI patients (in both acute and recovery phases) and healthy individuals were analyzed using liquid chromatography-mass spectrometry (LC-MS)-based metabolomics. Candidate metabolites were identified based on significant differences (adjusted FDR < 0.01, effect size > 1.5) between acute and recovery phases, as well as between acute DILI and healthy controls. The serum levels of the candidate biomarkers were then quantified and evaluated for their diagnostic performance in distinguishing DILI from other liver diseases. **Results:** Of the 66 DILI patients (37 females, 29 males; age 20–87 years, mean 60.8), 40 had hepatocellular, 13 mixed, and 13 cholestatic injury. Three metabolites—pyroglutamylglycine (pyroGluGly), phenylalanyltryptophan (PheTrp), and phenylalanine (Phe)—emerged as strong candidate biomarkers. These metabolites demonstrated excellent discrimination between acute and recovery phases in mixed and cholestatic DILI (AUCs: 0.967 for pyroGluGly, 0.950 for PheTrp, and 0.984 for Phe in mixed DILI; 0.960 for pyroGluGly, 0.980 for PheTrp, and 1.00 for Phe in cholestatic DILI). In contrast, performance in hepatocellular DILI was modest (AUCs: 0.799 for pyroGluGly, 0.888 for PheTrp, and 0.718 for Phe). Notably, serum pyroGluGly concentrations were significantly elevated in patients with mixed/cholestatic DILI compared to those with other liver diseases. The ability of pyroGluGly to distinguish mixed/cholestatic DILI from other liver diseases was excellent, with AUCs of 0.98 for viral hepatitis, 0.97 for AIH, 0.90 for alcoholic liver injury, 0.97 for MAFLD/MASH, 0.92 for PBC, 0.98 for cirrhosis, and 0.98 for HCC. **Conclusion:** Our study identified pyroGluGly, PheTrp, and Phe as potential serum biomarkers for DILI, particularly cholestatic subtype. These metabolites

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may provide a valuable tool for improving the diagnostic accuracy of DILI, facilitating earlier and more specific clinical decision-making.

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◆ 4348 | DEVELOPMENT AND EVALUATION OF RETRIEVAL-AUGMENTED GENERATION-BASED LARGE LANGUAGE MODEL FOR ANSWERING CLINICAL QUESTIONS IN DRUG-INDUCED LIVER INJURY USING LIVERTOX DATA

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Background: Idiosyncratic drug-induced liver injury (DILI) remains a major clinical challenge requiring accurate, real-time clinical decision support. LiverTox provides the most comprehensive DILI evidence base with over 1,300 drug monographs, yet its encyclopedic format challenges point-of-care navigation. Healthcare providers increasingly query general AI chatbots for rapid clinical answers, risking harm from hallucinations or non-medical sources (Figure 1, left). We hypothesize that retrieval-augmented generation (RAG), which constrains AI responses to LiverTox's expert-curated content, could deliver accurate, real-time DILI guidance without hallucinations (Figure 1, right). **Methods:** We systematically processed 1,343 LiverTox drug files into 8,759 semantically indexed segments using BioBERT embeddings. Our retrieval system employs drug-specific prioritization and section-aware weighting to identify the most relevant content per query. 25 standardized DILI clinical questions were used to evaluate four RAG-integrated language models: the smaller, open-source Mistral-7B and larger, proprietary Claude-3-Haiku, Claude-3-Opus, and GPT-4o. Each model's responses were restricted to retrieved LiverTox content. Three trained hepatologists, blinded to model type, evaluated responses for accuracy, completeness, and conciseness using standardized 5-point Likert scales. Statistical analyses included intraclass correlation coefficients and Friedman tests with Bonferroni-corrected post-hoc comparisons. **Results:** Inter-rater agreement was moderate (accuracy = 0.51, completeness = 0.52, conciseness = 0.55). RAG-integrated Claude-3-Haiku, Claude-3-Opus, and GPT-4o models significantly outperformed Mistral-7B in accuracy and completeness ($p < 0.005$). Claude-3-Haiku offered the fastest responses (57s) at minimal cost ($0.01) but was less concise than GPT-4o ($p = 0.004$). GPT-4o achieved the highest scores overall with reasonable efficiency (66s, $0.15). Notably, RAG eliminated hallucinations across all responses, with every answer traceable to LiverTox content. **Conclusion:** We developed and evaluated the first RAG system integrating language models with LiverTox for evidence-based DILI management. The three larger proprietary models demonstrated performance advantages, likely due to scale and training resources, with GPT-4o providing the optimal balance of performance, speed, and cost. Importantly, all LLMs produced hallucination-free responses when constrained to LiverTox content through RAG. Our LiverTox integrated RAG-LLM system provides a safe, practical alternative to commercial AI tools and enables reliable answers to drug hepatotoxicity questions at the point of care. Future work will explore supervised fine-tuning on expert-generated question-answer pairs to align responses with clinical reasoning and decision making.

Figure 1. Left: Hallucinated response from GPT-4o when queried directly without context retrieval, incorrectly identifying LiverTox Likelihood Score for phenytoin. **Right:** RAG-LLM pipeline. The system extracts and filters clinically relevant sections from LiverTox documents, segments them into chunks, and embeds them using a BioBERT model. Embeddings are indexed in a vector database for efficient retrieval. When a clinician submits a query, relevant context is retrieved and passed to a large language model (LLM), which synthesizes a response grounded in the retrieved content.

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Nothing to Disclose, Fasiha Kanwal: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Hashem El-Serag: Nothing to Disclose

◆ 4349 | PPARA-MEDIATED HEPATIC RESPONSES TO PFOS EXPOSURE IN A HUMANIZED AND KNOCKOUT MOUSE MODEL OF ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: Perfluorooctane sulfonate (PFOS) exposure is increasingly linked to metabolic dysfunction-associated steatotic liver disease (MASLD; PMID: 35475652), yet its role in ALD remains understudied. Our recent wild-type studies showed that PFOS worsened ALD severity via PPARα (PMID: 40347464), yet the exact role of PPARα in mediating these effects remains elusive. Given that PFOS is a strong mouse but weak human PPARα agonist, the relevance of murine models to human health risk is uncertain. Here, we sought to investigate species-specific hepatic responses to PFOS-ethanol co-exposure in humanized PPARα (hPPARα) and PPARα-knockout (KO) mice. **Methods:** Male hPPARα and PPARα-KO mice (C57BL/6J) received modified Lieber-DeCarli diet (5% EtOH vs. control) for 15 days with concurrent PFOS gavage (1 mg/kg) from day 6-15, followed by EtOH binge (5 g/kg) and sacrifice 5-6h later. Assessments included body composition, biochemistry, liver histology (H&E), and high-content imaging of primary hepatocytes. **Results:** EtOH decreased body weight with trends toward differential liver-to-body weight ratios (decrease in hPPARα, increase in PPARα-KO). Both genotypes showed ethanol-induced triglyceride and VLDL elevations, with PFOS augmenting VLDL levels. Notably, PFOS attenuated EtOH-induced ALT and AST increases in both genotypes, contrasting with wild-type studies where PFOS exacerbated hepatotoxicity (PMID: 40347464). Histological examination revealed marked genotype-dependent differences in hepatic architecture. While hPPARα mice maintained normal liver morphology in controls and developed progressive steatosis from mild (PFOS alone) to moderate (ethanol alone) to severe (PFOS+ethanol combination), PPARα-KO mice demonstrated significant baseline steatosis even in vehicle-treated controls, with persistent severe steatosis across all treatment groups. High-content imaging confirmed striking cellular differences: hPPARα hepatocytes showed 4-fold increased mitochondrial function with PFOS-ethanol, while PPARα-KO hepatocytes exhibited heightened oxidative stress and 5-fold increased lipid peroxidation, indicating compromised homeostasis. **Conclusion:** These findings reveal species-specific PPARα-mediated responses to PFOS-EtOH co-exposure. Baseline steatosis in PPARα-KO controls demonstrates PPARα's fundamental role in hepatic lipid homeostasis. Attenuation of EtOH-induced liver injury suggests varying PPARα activity levels modulate injury mechanisms differently than wild-type mice. More data are needed on species-specific nuclear receptor signaling that may vary with environmental pollutant exposure, particularly in alcohol consumers.
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◆ 4350 | IMPACT OF ACUTE KIDNEY INJURY AT THE TIME OF DIAGNOSIS OF IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY: COMPREHENSIVE ANALYSIS OF TWO LARGE PROSPECTIVE COHORTS

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Background: Acute kidney injury (AKI) is a significant prognostic factor in cases of decompensated liver cirrhosis and liver transplantation. However, the literature has not specifically evaluated acute renal failure in the context of idiosyncratic drug-induced liver injury (DILI). This study aimed to assess the severity and mortality/liver transplantation rates in cases of DILI with acute kidney injury (DILI-AKI). **Methods:** A comprehensive analysis was conducted on cases of drug-induced liver injury (DILI) prospectively included in the Spanish DILI Registry and the LATINDILI Network for hepatotoxicity, from the inception of both registries until November 2024. Cases with acute kidney injury at the time of DILI diagnosis were compared with those without. The KDIGO 2012 criteria were used to define AKI at the time of hepatic event diagnosis: (1) an increase in serum creatinine of ≥ 0.3 mg/dL within 48 hours; (2) an increase in serum creatinine to ≥ 1.5 times the baseline value within the first seven days; or (3) urine output of < 0.5 ml/kg/hour for more than six hours. Patients with missing creatinine values in previous tests and at the onset of DILI were excluded. DILI severity criteria were those described by Aithal et al. in 2011: elevated total bilirubin and/or INR and/or hepatic encephalopathy/ascites. **Results:** After excluding cases for which creatinine value information was unavailable, 993 cases of drug-induced liver injury (DILI) were analysed, with 5.4% (54 cases) meeting the criteria for acute kidney injury (AKI). The pharmacological agent most frequently associated with AKI was amoxicillin-clavulanate, accounting for six cases (11%). DILI-AKI cases were characterised by a significantly older mean age (60 vs. 52 years, $p < 0.001$). These cases occurred more frequently in male patients (63% vs. 47%, $p < 0.001$) and had a higher prevalence of diabetes mellitus (20% vs. 11%, $p < 0.001$) and arterial hypertension (46% vs. 24%, $p < 0.001$). There was also a higher proportion of cholestatic injury in DILI-AKI cases (38% vs. 21%; $p = 0.014$). Biochemically, the median total bilirubin level was higher in DILI-AKI cases than in DILI without AKI (7.5 vs. 4.8, $p = 0.011$). The DILI-AKI group had a higher rate of hospitalisation, increased severity of cases and higher rates of death from hepatic and non-hepatic causes, reaching statistical significance. See Table 1. **Conclusion:** Acute kidney injury is not uncommon in patients with idiosyncratic drug-induced liver injury (DILI) and is associated with older age, male sex, and the presence of diabetes and hypertension. It is also associated with an increased risk of hospitalisation, disease severity, and ultimately, liver-related and non-liver mortality. Consequently, patients with DILI and acute renal dysfunction require more rigorous monitoring.

	DILI with acute renal failure (n=54)	DILI without acute renal failure (n=939)	p value
Age (y), mean±SD	60±18	52±18	0.001
Female sex, n (%)	20 (37)	498 (53)	0.022
Body mass index (kg/m²), mean±SD	27±5.8	26±4.2	0.090
Diabetes, n (%)	11 (20)	104 (11)	0.040
Dyslipidemia, n (%)	9 (17)	108 (12)	0.252
Hypertension, n (%)	21 (46)	182 (24)	0.001
Underlying hepatic disease, n (%)	7 (13)	64 (6.8)	0.099
History of drug allergy, n (%)	5 (13)	73 (10)	0.596
Charlson comorbidity index, n (%)			0.059
<2 points	41 (87)	540 (94)	
>2 points	6 (13)	32 (5.6)	
Type of liver injury, n (%)			0.008
Hepatocellular	29 (55)	562 (61)	
Cholestatic	20 (38)	192 (21)	
Mixed	4 (7.5)	166 (18)	
DILI episode characteristics			
Jaundice, n (%)	45 (83)	624 (67)	0.014
Hospitalisation, n (%)	36 (72)	481 (54)	0.015
Hypersensitivity features*, n (%)	31 (63)	402 (54)	0.219
Fever, n (%)	11 (21)	106 (12)	0.045
Rash, n (%)	7 (15)	83 (9.4)	0.207
Eosinophilia, n (%)	16 (33)	214 (24)	0.158
Lymphopenia, n (%)	22 (42)	141 (17)	<0.001
Arthralgia, n (%)	2 (5.4)	32 (4.8)	0.697
Positive autoantibody titres, n (%)	6 (11)	125 (13)	0.836
Total oral daily dose (mg), median (IQR)	300 (50-563)	400 (50-1,875)	0.109
Duration of therapy (d), median (IQR)	22 (8-46)	26 (8-66)	0.603
Time to onset (d), median (IQR)	17 (7-40)	23 (9-62)	0.104
Concomitant drugs, n (%)			0.002
None	10 (19)	263 (28)	
1-2	18 (33)	393 (42)	
3-4	12 (22)	189 (20)	
>5	14 (26)	94 (10)	
Laboratory parameters at onset (x ULN), median (IQR)			
Total bilirubin	7.5 (3.2-14)	4.8 (1.2-10)	0.005
Aspartate aminotransferase (AST)	7.2 (2.5-23)	6.4 (3.0-20)	0.930
Alanine aminotransferase (ALT)	10 (3.7-21)	9.8 (4.9-23)	0.673
Alkaline phosphatase (ALP)	2.0 (0.8-3.2)	1.7 (1.0-2.6)	0.435
International Normalized Ratio (INR), median (IQR)	1.1 (1.0-1.9)	1.1 (1.0-1.3)	0.144
Creatinine (mg/dL), median (IQR)	1.6 (1.3-2.4)	0.8 (0.7-1.0)	<0.001
Maximum creatinine level (mg/dL), median (IQR)	1.6 (1.4-2.8)	0.9 (0.8-1.1)	<0.001
Platelets (x10³/µL), mean±SD	220±85	235±85	0.257
Severity, n (%)			0.002
Mild	7 (13)	297 (32)	
Moderate	37 (69)	545 (58)	
Severe	4 (7.4)	58 (6.2)	
Fatal/transplantation	6 (11)	34 (3.6)	
Liver-related death, n (%)	4 (7.4)	18 (1.9)	0.028
Liver transplantation, n (%)	2 (3.7)	16 (1.7)	0.256
Death due to other causes†, n (%)	3 (5.6)	7 (0.7)	0.014
Time to resolution (d), median (IQR)	71 (43-135)	94 (48-183)	0.355

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DILI: drug-induced liver injury; INR: international normalized ratio; IQR: interquartile range; SD: standard deviation; ULN: upper limit of normal.
*If the subject presents at least one of the following: fever, rash, eosinophilia, lymphopenia, or arthralgia.
† During time of follow-up

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4351 | DEFINING THE ROLE OF BASOLATERAL AMYGDALA 5-HT$_7$ RECEPTORS IN ANXIETY: INSIGHTS FROM CCL$_4$-INDUCED HEPATIC INJURY

Yuming Zhang[1] *Haiyan Huo*[1] *Jinyao Su*[1] *SongYan Guo*[1], [1]*Shaanxi Provincial People's Hospital*

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

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Background: Hyperammonemia, a common consequence of both acute and chronic liver injury, is increasingly implicated in the pathogenesis of emotional disturbances, particularly anxiety. Carbon tetrachloride (CCl_4), a well-established hepatotoxin, is widely used to model liver injury–associated anxiety in rodents. However, the underlying neurobiological mechanisms remain poorly characterized, and therapeutic strategies are limited. Recent evidence highlights the basolateral amygdala (BLA) as a key hub for anxiety regulation, enriched with serotonergic projections. Among serotonin receptors, 5-HT_7 has emerged as a critical modulator of affective behavior. Building on our prior findings in Parkinsonian models, we investigated the involvement of BLA 5-HT_7 receptors in CCl_4-induced anxiety. **Methods:** Anxiety-like behavior was induced in rats via intraperitoneal injection of CCl_4 (dissolved in olive oil); vehicle-only controls received olive oil alone. Behavioral assays included the elevated plus maze and open field tests. 5-HT_7 receptors function was modulated by intra-BLA microinjection of AS19 (agonist) or SB269970 (antagonist). Electrophysiological recordings, neurochemical profiling of monoamines in limbic and cortical regions, and immunofluorescent colocalization studies were conducted to explore underlying mechanisms. **Results:** In control rats, intra-BLA administration of AS19 induced anxiogenic effects, whereas SB269970 was anxiolytic. Remarkably, in CCl_4-treated rats, this pattern was reversed: AS19 produced anxiolytic-like effects, while SB269970 increased anxiety-like behavior. Neurochemical analyses revealed that AS19 and SB269970 respectively decreased and increased dopamine, serotonin, and noradrenaline levels across the medial prefrontal cortex, amygdala, habenula, and ventral hippocampus in both groups. Electrophysiological recordings showed that AS19 enhanced the firing rate of BLA GABAergic interneurons, whereas SB269970 suppressed it, with responses prolonged in CCl_4-treated rats. Notably, CCl_4 exposure did not alter the colocalization of 5-HT_7 receptors with GABAergic neurons. **Conclusion:** These findings reveal a state-dependent, bidirectional role for BLA 5-HT_7 receptors in the regulation of anxiety under hepatotoxic conditions. This is the first study to characterize a paradoxical shift in receptor sensitivity following liver injury. Our results offer novel insights into liver–brain communication and identify BLA 5-HT_7 signaling as a promising therapeutic target for anxiety disorders associated with hepatic dysfunction.

Disclosures: Yuming Zhang: Nothing to Disclose, Haiyan Huo: Nothing to Disclose, Jinyao Su: Nothing to Disclose, SongYan Guo: Nothing to Disclose

4352 | IMPACT OF STEROID DURATION ON OUTCOMES IN IMMUNE CHECKPOINT INHIBITOR HEPATITIS

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Background: Immune checkpoint inhibitors (ICIs) can cause hepatitis, for which corticosteroids remain the mainstay of therapy, however, the optimal duration of steroid therapy remains contested. This study evaluates whether short (0–8 weeks), intermediate (8–16 weeks), or prolonged (16–24 weeks) steroid therapy affects clinical outcomes. **Methods:** Using a multicenter electronic health record network, TrinetX, we retrospectively identified adult patients with ICI hepatitis treated with corticosteroids. Patients were stratified into three groups based on total steroid exposure. Key outcomes included all-cause mortality, all-cause hospitalization, acute liver failure (ALF) and normalization of liver enzymes defined as ALT < 50 U/L, AST < 30 U/L, ALP < 150 U/L, total bilirubin < 1.2 mg/dL up to 1-year after initial exposure to steroids. Patients with viral hepatitis, autoimmune, and other forms of hepatitis were excluded. Propensity-matched analyses were conducted for each duration comparison using odds ratios (ORs), 95% confidence intervals (CIs), and p-values. **Results:** After matching, patients in the short duration cohort had significantly higher all-cause mortality compared to the intermediate duration cohort (47.5% vs 29.2%, OR 2.20 [95% CI: 1.29–3.74], $p = 0.003$). Rates of hospitalization (51.7% vs 41.7%, OR 1.50 [0.90–2.49], $p = 0.121$) and ALF (10.0% vs 8.3%, OR 1.22 [0.51–2.95], $p = 0.655$) were similar between the two groups. Normalization of ALP (< 150 U/L) at 1 year was significantly less frequent in the short-course group (57.5% vs 70.8%, OR 0.56 [0.33–0.95], $p = 0.031$), while normalization for AST, ALT, and bilirubin did not differ significantly between both groups.

Among intermediate and prolonged steroid duration groups there was no significant difference in mortality (25.0% vs 23.3%, OR 1.10 [0.48–2.53], $p = 0.831$). The intermediate group had higher rates of ALF (16.7% vs 0%, $p = 0.001$) and all-cause hospitalizations (46.7% vs 25.0%, OR 2.63 [1.21–5.69], $p = 0.013$) compared to the prolonged group.

When comparing outcomes between the short and long duration groups, all-cause mortality and all-cause hospitalization events were noted to be significantly higher in the short duration group (54.1% vs 23.0%, OR 3.95 [1.94–8.01], $p < 0.001$, 47.3% vs. 64.9%, OR 3.01 [1.48-6.11], respectively. **Conclusion:** Across all

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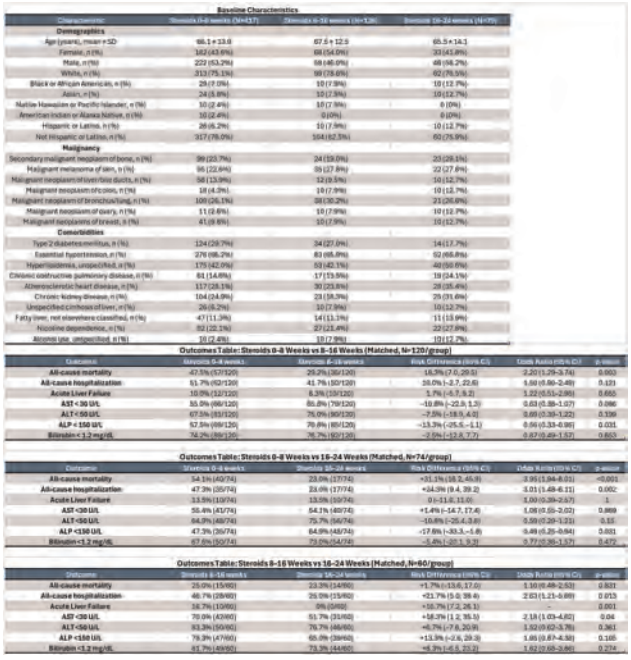
comparisons, short steroid duration (< 8 weeks) was associated with the highest mortality and hospitalization rates, supporting the use of at least 8 weeks of steroid treatment in ICI hepatitis. Intermediate steroid duration (8–16 weeks) appeared to lower mortality relative to short courses, but was associated with a higher risk of hospitalization and ALF compared to prolonged treatment. Further study is needed to determine if a longer course of steroid treatment albeit at a lower dosage may be necessary to prevent these outcomes.



Baseline Characteristics

Characteristic	Steroids 0-8 weeks (N=120)	Steroids 8-16 weeks (N=120)	Steroids 16-24 weeks (N=59)
Demographics			
Age (years), mean ± SD	66.1 ± 13.6	67.5 ± 12.5	65.5 ± 14.1
Female, n (%)	162 (43.6%)	68 (56.0%)	33 (41.8%)
Male, n (%)	222 (53.2%)	68 (46.0%)	68 (58.2%)
White, n (%)	313 (75.1%)	99 (78.6%)	62 (76.5%)
Black or African American, n (%)	29 (7.0%)	10 (7.9%)	10 (12.7%)
Asian, n (%)	24 (5.8%)	10 (7.9%)	10 (12.7%)
Native Hawaiian or Pacific Islander, n (%)	10 (2.4%)	10 (7.9%)	0 (0%)
American Indian or Alaska Native, n (%)	10 (2.4%)	0 (0%)	0 (0%)
Hispanic or Latino, n (%)	26 (6.2%)	10 (7.9%)	10 (12.7%)
Not Hispanic or Latino, n (%)	317 (76.0%)	104 (82.5%)	60 (75.9%)
Malignancy			
Secondary malignant neoplasm of bone, n (%)	99 (23.7%)	24 (19.0%)	23 (28.1%)
Malignant melanoma of skin, n (%)	95 (22.6%)	35 (27.8%)	22 (27.8%)
Malignant neoplasm of liver/bile ducts, n (%)	58 (13.9%)	12 (9.5%)	10 (12.7%)
Malignant neoplasm of colon, n (%)	18 (4.3%)	10 (7.9%)	10 (12.7%)
Malignant neoplasm of bronchus/lung, n (%)	108 (26.1%)	30 (23.8%)	21 (26.6%)
Malignant neoplasm of ovary, n (%)	11 (2.6%)	10 (7.9%)	10 (12.7%)
Malignant neoplasms of breast, n (%)	41 (9.8%)	10 (7.9%)	10 (12.7%)
Comorbidities			
Type 2 diabetes mellitus, n (%)	124 (29.7%)	34 (27.0%)	14 (17.7%)
Essential hypertension, n (%)	276 (66.2%)	83 (65.9%)	52 (65.8%)
Hyperlipidemia, unspecified, n (%)	175 (42.0%)	53 (42.1%)	40 (50.6%)
Chronic obstructive pulmonary disease, n (%)	61 (14.6%)	17 (13.5%)	19 (24.1%)
Atherosclerotic heart disease, n (%)	117 (28.1%)	30 (23.8%)	28 (35.4%)
Chronic kidney disease, n (%)	104 (24.9%)	23 (18.3%)	25 (31.6%)
Unspecified cirrhosis of liver, n (%)	26 (6.2%)	10 (7.9%)	10 (12.7%)
Fatty liver, not elsewhere classified, n (%)	47 (11.3%)	14 (11.1%)	11 (13.9%)
Nicotine dependence, n (%)	92 (22.1%)	27 (21.4%)	22 (27.8%)
Alcohol use, unspecified, n (%)	10 (2.4%)	10 (7.9%)	10 (12.7%)

Outcomes Table: Steroids 0–8 Weeks vs 8–16 Weeks (Matched, N=120/group)

Outcome	Steroids 0–8 weeks	Steroids 8–16 weeks	Risk Difference (95% CI)	Odds Ratio (95% CI)	p-value
All-cause mortality	47.5% (57/120)	25.2% (30/120)	18.3% (7.0, 29.5)	2.20 (1.29–3.74)	0.003
All-cause hospitalization	51.7% (62/120)	41.7% (50/120)	10.0% (−2.7, 22.8)	1.50 (0.86–2.60)	0.123
Acute Liver Failure	10.0% (12/120)	8.3% (10/120)	1.7% (−5.7, 9.2)	1.22 (0.51–2.90)	0.665
AST <30 U/L	55.0% (66/120)	65.8% (79/120)	−10.8% (−22.9, 1.3)	0.63 (0.38–1.07)	0.086
ALT <50 U/L	67.5% (81/120)	76.0% (90/120)	−7.5% (−18.9, 4.0)	0.69 (0.38–1.22)	0.199
ALP <150 U/L	57.5% (69/120)	70.8% (85/120)	−13.3% (−25.6, −1.1)	0.56 (0.33–0.98)	0.035
Bilirubin <1.2 mg/dL	74.2% (89/120)	76.7% (92/120)	−2.5% (−12.8, 7.7)	0.87 (0.49–1.57)	0.653

Outcomes Table: Steroids 0–8 Weeks vs 16–24 Weeks (Matched, N=74/group)

Outcome	Steroids 0–8 weeks	Steroids 16–24 weeks	Risk Difference (95% CI)	Odds Ratio (95% CI)	p-value
All-cause mortality	54.1% (40/74)	23.0% (17/74)	+31.1% (18.2, 45.8)	3.95 (1.94–8.01)	<0.001
All-cause hospitalization	47.3% (35/74)	23.0% (17/74)	+24.3% (9.4, 39.2)	3.01 (1.48–6.11)	0.002
Acute Liver Failure	13.5% (10/74)	13.5% (10/74)	0 (−11.0, 11.0)	1.00 (0.39–2.57)	1
AST <30 U/L	58.4% (43/74)	54.1% (40/74)	+4.4% (−14.7, 17.4)	1.08 (0.55–2.02)	0.869
ALT <50 U/L	64.9% (48/74)	75.7% (56/74)	−10.8% (−25.4, 3.8)	0.59 (0.29–1.21)	0.15
ALP <150 U/L	47.3% (35/74)	64.9% (48/74)	−17.6% (−33.3, −1.8)	0.49 (0.25–0.94)	0.031
Bilirubin <1.2 mg/dL	67.6% (50/74)	73.0% (54/74)	−5.4% (−20.1, 9.3)	0.77 (0.36–1.57)	0.472

Outcomes Table: Steroids 8–16 Weeks vs 16–24 Weeks (Matched, N=60/group)

Outcome	Steroids 8–16 weeks	Steroids 16–24 weeks	Risk Difference (95% CI)	Odds Ratio (95% CI)	p-value
All-cause mortality	25.0% (15/60)	23.3% (14/60)	+1.7% (−13.6, 17.0)	1.10 (0.48–2.53)	0.831
All-cause hospitalization	46.7% (28/60)	25.0% (15/60)	+21.7% (5.0, 38.4)	2.63 (1.21–5.69)	0.013
Acute Liver Failure	16.7% (10/60)	8% (5/60)	+10.7% (−2.2, 25.1)	–	0.061
AST <30 U/L	70.0% (42/60)	51.7% (31/60)	+18.3% (1.2, 35.1)	2.19 (1.03–4.62)	0.04
ALT <50 U/L	83.3% (50/60)	76.7% (46/60)	+6.7% (−7.8, 20.9)	1.52 (0.62–3.76)	0.361
ALP <150 U/L	78.3% (47/60)	65.0% (39/60)	+13.3% (−2.6, 29.3)	1.85 (0.87–4.58)	0.105
Bilirubin <1.2 mg/dL	81.7% (49/60)	73.3% (44/60)	+8.3% (−6.5, 23.2)	1.82 (0.65–5.84)	0.274

Disclosures: Mohamed Nadeem: Nothing to Disclose, Shilpa Junna: Nothing to Disclose, prabhat kumar: Nothing to Disclose

4353 | LOW DOSE ENVIRONMENTAL DIOXIN MIXTURE DISRUPTS HEPATIC HOMEOSTASIS VIA SEX- AND DIET-SPECIFIC MECHANISMS

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Background: Persistent organic pollutants (POPs) such as “dioxins” are widely released through anthropogenic and/or natural combustion processes and exposure to these toxicants have shown causal and correlation effects in metabolic dysfunction-associated steatotic liver disease (MASLD) development. Population studies have highlighted sex-specific vulnerability to POP-induced liver damage, yet toxicological models rely on male models and the combined effects of dioxin mixtures remain poorly defined. This study addresses a critical knowledge gap by investigating sex-dependent effects from exposure to a mixture of dioxins: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), 2,3,4,7,8-Pentachlorodibenzofuran (PeCDF) and Polychlorinated biphenyl 126 (PCB126), in the context of hypercaloric and western diets. **Methods:** Male and female C57BL/6 mice were fed either a high-fat (HFD) or low-fat (LFD) and administered a weekly dose of TCDD(10ng/kg) +PeCDF(80ng/kg)+PCB 126(140ng/kg) or vehicle control, for 12 weeks. At euthanasia, plasma and tissue were collected for downstream analyses. **Results:** HFD-fed male mice exhibited marked micro- and macro-vesicular steatosis compared to their sex- and diet-matched controls. This was reflected in H&E staining and quantifications of hepatic triglycerides/cholesterol. Notably, LFD-fed female mice exposed to the dioxin mixture displayed reduced liver weight but elevated hepatic triglycerides alongside upregulation of the hepatic fatty acid transport gene *Cd36*. This observation was absent in the diet-matched males. Instead, dioxin exposed LFD-fed males showed suppressed expression of de novo lipogenesis regulators *Fasn* and *Scd1*. Elevated ALT and AST levels were observed in both sexes with HFD, and particularly, ALT increased significantly in dioxin-exposed LFD-fed females. Mechanistically, dioxin exposure activated the hepatic xenobiotic receptors AHR and CAR with sex- and diet-specific modulation. AHR activation was observed (*Cyp1a1* and *Cyp1a2* induction) regardless of sex or diet, although HFD decreased inducibility in males specifically. CAR activation (*Cyp2b10* and *Cyp2c29* induction) showed sex differences and were basally upregulated in females. However, dioxin exposure increased induction in LFD-fed males only, suggesting sex-specific receptor activation. **Conclusion:** Exposure to dioxin mixture resulted in sex- and diet-dependent hepatic metabolic dysregulation. Curiously, LFD-fed mice showed greater susceptibility and effects were less pronounced with HFD-feeding. Future studies will address the temporal sequence of exposure by administering the dioxin mixture prior to initiation of high-fat diet feeding, to elucidate how toxicant exposure primes and modulates sex-specific hepatic responses during the transition into a hypercaloric metabolic state.

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

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4354 | RULE-OF-TWO AND DILISCORE FOR DRUG-INDUCED LIVER INJURY RISK ASSESSMENT ARE ASSOCIATED WITH RISK MITIGATION ACTIONS IN DRUG APPLICATIONS EVALUATED AT THE FDA

Minjun Chen[1] Edwige Chiogo Vouffo[1] Paul Hayashi[1], *[1]FDA*

Background: Predicting drug-induced liver injury (DILI) during drug development remains challenging. Developed at the National Center for Toxicological Research (NCTR), Rule-of-Two (RO2) and DILIscore are *in silico* models using drug physicochemical and pharmacological properties to predict post-market DILI risk. RO2 outputs a (+) or (-) for DILI risk while DILIscore gives a numeric value that assigns risk as mild, moderate, or high. These models are based on post-market drug labels through 2010, but their association with regulatory actions for drug candidate development since they were developed has not been assessed. **Aim:** To assess associations among RO2, DILIscore, and the presence of Hy's law cases (HL (+/-)) with DILI related risk mitigation actions (RMAs). **Methods:** We analyzed drug applications between 2021 and 2024 with NCTR RO2 and DILIscore assessments, and DILI Team assessments for HL (+/-). We assessed RO2, DILIScore, and HL (+ or -) for associations with RMAs, defined as a pause or cessation in drug development, clinical hold, or labeled box warning. Positive and negative predictive values (PPV, NPV), and sensitivities were used to further describe the associations. **Results:** Thirty-six applications (25 initial drug applications [IND]; 11 new drug applications [NDA]) had RO2, DILIscore and HL assessments from 2021 to 2024. DILIscores were indeterminable in 15; RO2 and HL (+ or -) were determined in all 36. RO2, DILIscore and HL were all statistically associated with RMA (Table). PPVs for RO2, DILIscore, and HL (+) were 68% (13 /19), 83% (10 /12), and 87% (13 of 15) respectively; while NPVs were 71% (12 of 17), 89% (8 of 9) and 76% (16 of 21), respectively. RO2 (+), a high-risk DILIscore, and HL (+) sensitivities were 72%, 91% and 72%, respectively. For HL (-) applications, having either a RO2 (+) or high-risk DILI score had a sensitivity for RMA of 80% (4 of 5) with PPV and NPV of 36% and 90%, respectively. **Conclusion:** Summary: RO2, DILIscore, and presence of HL cases were all significantly associated with RMAs ($p < 0.05$) in applications assessed by the NCTR and DILI Team. Having a high risk DILIscore had the highest sensitivity for such actions when a DILIscore could be determined. Conclusions: RO2 and DILIscore have strong associations with RMAs for DILI and may play a meaningful role in supporting regulatory decision-making during review. In silico models may be useful adjuncts for early identification of potential hepatotoxicity.

Table: RO2 results, DILIscore, presence of Hy's Law cases and risk mitigations actions in 36 drug applications evaluated by FDA NCTR and DILI Team.

Characteristic	Overall N = 36[1]	Risk mitigation actions: None N = 18[1]	Risk mitigation actions: WD/Hold/BW[3] N = 18[1]	p-value[2]
RO2[4]				0.019
Positive	19	6 (32%)	13 (68%)	
Negative	17	12 (71%)	5 (29%)	
DILIscore[5]				0.002
High risk	12	2 (17%)	10 (83%)	
Moderate/Low	9	8 (89%)	1 (11%)	
(Missing data for DILIscore)	15	8	7	
Hy's law[6]				<0.001
Positive	15	2 (13%)	13 (87%)	
Negative	21	16 (76%)	5 (24%)	

[1]n (%)
[2]Pearson's Chi-squared test; Fisher's exact test
[3]WD: INDs were terminated or withdrawn by sponsor with DILI concern; Hold: INDs were fully or partially hold due to DILI concern; BW: NDAs were approved with boxed warnings for DILI in labels.
[4]If a drug is given at daily dose ≥ 100 mg/day and with AlogP ≥ 3, RO2 test is positive, otherwise negative. Please refer to Chen et al. Hepatology, 2013
[5]DILIscore is calculated from daily dose, AlogP and reactive metabolites formation. If DILIscore >6, the DILI risk is high, otherwise is moderate or low. Please refer to Chen et al. Hepatology, 2016
[6]Hy's Law positive means at least one DILI case meets the definition of Hy's law according to the FDA DILI guidance, 2009.

The content in this abstract is the responsibility of the authors and does not necessarily represent the official views of the Food and Drug Administration.

Disclosures: Minjun Chen: Nothing to Disclose, Edwige Chiogo Vouffo: Nothing to Disclose, Paul Hayashi: Nothing to Disclose

4355 | THE HIGH PREDICTIVE POWER OF THE MODEL OF END-STAGE LIVER DISEASE SCORE IN DRUG-INDUCED LIVER INJURY

Sabine Weber[1] Izabel Mircheva[2] Rochell Balakumar[2] Julian Allgeier[2] Didem Saka[2] Nirali Donga[2] Franziska Erhardt[2] Christian Lange[2] Alexander Gerbes[2], *[1]Department of Medicine II, LMU Klinikum, Munich, [2]Department of Medicine II, LMU Klinikum Munich*

Background: Drug-induced liver injury (DILI) can have disastrous consequences possibly leading to acute liver failure, liver transplantation or death[1]. Traditionally, Hy's law has being used to predict severe DILI, specificity however is low[2]. Thus, identifying patients at risk of an adverse outcome early in the course of disease is of outmost importance. **Methods:** We aimed to identify prognostic factors that can identify patients with high risk of a fatal outcome. To this end, the data of 273 DILI patients from our prospective study on acute liver injury with potential drug-related cause were analyzed. 479 patients with initial suspicion of DILI were enrolled, out of which 273 were diagnosed with DILI. DILI diagnosis was based on clinical, laboratory and histological features and an expert adjudication process[3]. Alternative causes of liver injury were ruled out by a thorough

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hepatological work-up. The primary endpoint was an adverse outcome defined as liver transplantation (LT) or death. **Results:** 27 (10%) of patients reached the primary endpoint of having an adverse outcome. Univariate logistic regression analysis revealed that alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, INR, the Model of End-stage Liver Disease (MELD) score and the R ratio at the time of DILI recognition as well as Hy's law positivity were significantly associated with an adverse outcome. Interestingly, the burden of comorbidity, represented by the Charlson Comorbidity Index, did not have a significant association with an adverse outcome in our DILI cohort. On multivariate logistic regression analysis only ALT (odds ratio [OR] 0.97, 95% confidence interval [CI] 0.923-0.989, $p = 0.056$), AST (OR 1.06, 95 % CI 1.02-1.10, $p = 0.005$) and MELD score (OR 1.23, 95% CI 1.13-1.34, $p < 0.001$) were independently associated with an adverser outcome. The MELD score in particular showed an extraordinarily high concordance statistic (c-statistic) of 0.93 (95% CI 0.89-0.97). At a cut-off of ≥ 20, the MELD score could predict a fatal outcome in DILI patients with a sensitivity of 89% and specificity of 82% and with this performed better than Hy's law, new Hy's law and the prognostic score published by Robles et al. in terms of prognosis[2]. **Conclusion:** The MELD score at the time of DILI recognition has a high predictive power in DILI patients. Our data shows that DILI patients with a baseline MELD score of 20 or higher are at high risk of needing high urgency liver transplantation or having a lethal outcome.

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Table 1 Logistic regression analysis for adverse outcome in DILI patients

	Univariate logistic regression [1]			Multivariate logistic regression [2]		
	OR	95 % CI	p	OR	95 % CI	p
Age	1.001	0.978-1.025	0.927			
BMI	1.002	0.920-1.090	0.969			
Gender	1.087	0.488-2.421	0.837			
R-Ratio [3]	1.020	1.004-1.036	**0.014***			
AP onset	0.918	0.721-1.169	0.486			
ALT onset	1.020	1.009-1.031	**<0.001***	0.969	0.938-1.001	0.056
AST onset	1.045	1.028-1.063	**<0.001***	1.059	1.018-1.102	**0.005***
TBIL onset	1.138	1.078-1.202	**<0.001***			
INR onset	1.543	1.172-2.029	**0.002***			
MELD onset	1.278	1.175-1.390	**<0.001***	1.229	1.128-1.339	**<0.001***
IgG	1.038	0.965-1.116	0.318			
Hy's law positivity	8.562	1.983-36.961	**<0.001***			
CCI	1.081	0.944-1.238	0.260			

[1] Shown are the odds ratios (OR) and the 95% confidence intervals (CI) for baseline laboratory parameters with regards to adverse outcome in univariate analysis. Adverse outcome was defined as death or liver transplantation. [2] Variables considered in the multivariate logistic regression analysis were parameters with p<0.200 in univariate analysis. [3] The R-ratio is defined as (ALT/ULN)/(ALP/ULN), with R≥5 defining a hepatocellular, R≤2 a cholestatic and 2<R<5 a mixed type of injury. * indicates a statistical significance (p≤0.05).

Abbreviations: ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CCI: Charlson Comorbidity Index; IgG: Immunoglobulin G; INR: International normalized ratio; MELD: Model for end-stage liver disease; TBIL: Total bilirubin; ULN: Upper limit of normal.

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4356 | SINGLE-CELL RNA SEQUENCING ELUCIDATES THE PATHOGENIC ROLE OF CD74 IN ACETAMINOPHEN-INDUCED ACUTE LIVER INJURY

Pengzhan Deng[1] Qiuli Xie[1] Mingjiang Liu[1] Tingfeng Xu[1] Lijuan Liao[1] Jie Zhang[1] Songqing He[1] Wenli Xu[1], [1]First Affiliated Hospital of Guangxi Medical University

Background: Although acetaminophen (APAP) is the leading cause of drug-induced liver injury (DILI), current therapeutic strategies for this condition remain substantially limited. The inflammatory microenvironment plays a pivotal role in the progression of APAP-induced liver injury (AILI). CD74 regulates pro-inflammatory cytokine production in various hepatic pathologies and is involved in macrophage-mediated inflammatory responses and leukocyte recruitment. This study aims to elucidate the role and molecular mechanisms of CD74 in AILI, providing novel therapeutic targets for clinical management. **Methods:** In this study, wild-type (WT) and CD74-knockout ($CD74^{-/-}$) mice were intraperitoneally injected with 300 mg/kg APAP or saline. Peripheral blood and liver tissues were collected at multiple time points for single-cell RNA sequencing (scRNA-seq), biochemical, histopathological, and molecular analyses to characterize the dynamic immune landscape during the AILI progression and explore the relationship between CD74 and the immune microenvironment. **Results:** CD74 expression was upregulated in mice with AILI. Notably, a sustained accumulation of pro-inflammatory macrophages was detected in the liver post-APAP injury. In contrast, $CD74^{-/-}$ mice exhibited a phenotypically distinct subset of anti-inflammatory macrophages within hepatic tissues. Co-localization of CD74 with F4/80-positive macrophages and CXCR4 was observed in WT mice after APAP treatment. $CD74^{-/-}$ mice showed a reduction in hepatic necrotic areas and an increase in Ki-67-positive zones. These findings suggest that CD74 participates in macrophage recruitment and inflammatory cell chemotaxis during AILI. Furthermore, $CD74^{-/-}$ mice demonstrated attenuated hepatic injury accompanied by enhanced hepatocyte proliferative capacity. **Conclusion:** CD74 deficiency mitigates APAP-induced hepatotoxicity and enhances hepatocyte regeneration in mice. These findings indicate that CD74 may serve as a potential therapeutic target for AILI.

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Disclose, Jie Zhang: Nothing to Disclose, Songqing He: Nothing to Disclose, Wenli Xu: Nothing to Disclose

4357 | CLINICAL, LABORATORY AND GENETIC VARIANTS ASSOCIATED WITH IMMUNE MEDIATED LIVER INJURY FROM CHECKPOINT INHIBITORS VERSUS OTHER CAUSES OF LIVER INJURY

Linnea Swanson[1] Andrew Tucker[1] LaVana Greene-Higgs[1] Venkata Sai Jasty[1] Jessica Sheehan[1] Yi-Ju Li[2] Vincent Chen[3] Robert Fontana[4], [1]University of Michigan, [2]Duke, [3]University of Michigan Medical Center, [4]University of Michigan Hospitals and Health Centers

Background: Immune-mediated liver injury from checkpoint inhibitors (ILICI) arises in 5 -10% of oncology patients, often prompting early drug discontinuation and corticosteroid use. Previous studies have found genetic variants in the immune response and drug metabolism associated with ILICI. The aim of our study was to characterize the clinical features, outcomes and genetic variants in a large cohort of ILICI cases compared to those with other causes of liver injury. **Methods:** Solid tumor patients who received immune checkpoint inhibitors (ICI) from 2010-2024 and enrolled in the Michigan Genomics Initiative were analyzed. Liver injury was defined as AST or ALT $\geq$ 5x ULN, ALP $\geq$ 2x ULN, bilirubin $\geq$ 2.5, or INR $\geq$ 1.5. Causality assessment was based on the DILIN expert opinion scale [1-3 = probable ILICI, 4-5 = alternative cause (non-ILICI liver injury)] by consensus of 3 reviewers. Candidate gene associated tests for previously described single nucleotide polymorphisms (SNPs) and genome-wide association study (GWAS) was conducted using Regenie version 3.4, adjusted for age, sex, and principal components 1-2. We ran one GWAS where cases were ILICI patients and another where cases were non-ILICI patients; both use ICI-treated patients without liver injury as controls. **Results:** 979 patients received ICI therapy with 187 (19.1%) developing biochemical evidence of liver injury. Of the 187 liver injury patients, 67 (35.8%) were due to ILICI with DILIN score 1-3 and 120 were non-ILICI causes of liver injury. Mean age was 64, 62% male and 97% Caucasian (Table 1). Common malignancies were melanoma (37%), genitourinary cancers (19.5%) and non-small cell lung cancer (9.5%). Pembrolizumab (48%), ipilimumab (21%) and nivolumab (18%) were the most frequently used ICIs. Patients with ILICI were more likely to have received dual ICI therapy ($p < 0.001$), normalize their LFTs ($p < 0.001$) and receive corticosteroids ($p < 0.001$) during follow-up. Those with non-ILICI liver injury had more hepatic metastasis (33% vs 15%; $p = 0.011$) and worse cancer outcomes ($p < 0.001$) and survival in comparison to those with ILICI ($p < 0.001$). The liver injury from ILICI was more hepatocellular (*R* ratio 4.6 vs 2.5; $p < 0.001$) and less likely to result in jaundice ($p = 0.04$). A series of 17 SNPs from prior studies of DILIN were tested but not associated with a phenotype of ILICI alone or any cause of liver injury. Two and three independent variants associated with ILICI and non-ILICI liver injury, respectively, at $p < 10^{-5}$. **Conclusion:** ILICI occurred in 7% of ICI-treated patients and was associated with acute hepatocellular injury, LFT normalization, corticosteroid use, and improved survival compared to non-ILICI liver injury. Previously reported SNPs were not replicated, but novel loci were identified, meriting further investigation.

Table 1. Comparison of clinical features of ILICI versus non-ILICI liver injury

	Non ILICI N = 120[1]	ILICI N = 67[1]	p-value[2]
Age (yrs)	63 (13)	62 (14)	0.6
Male	81 (68%)	36 (54%)	0.062
Caucasian	111 (96%)	65 (97%)	>0.9
Follow-Up Duration (mon)	68 (76)	101 (72)	**<0.001**
Type of Immunotherapy			**0.005**
Pembrolizumab	52 (43%)	26 (39%)	
Ipilimumab	26 (22%)	28 (42%)	
Nivolumab	19 (16%)	10 (15%)	
Other	23 (19%)	3 (4.5%)	
Duration of ICI Treatment (mon)	20 (26)	13 (22)	0.054
Type of Cancer			**0.002**
Melanoma	39 (33%)	40 (60%)	
RCC	11 (9.2%)	8 (12%)	
Urothelial	19 (16%)	4 (6.0%)	
NSCLC	8 (6.7%)	3 (4.5%)	
Other	43 (36%)	12 (18%)	
Presence of Liver Metastases	38 (33%)	10 (15%)	**0.011**
Combination ICI	24 (20%)	34 (51%)	**<0.001**
Other non-hepatic irAE	32 (27%)	33 (49%)	**0.002**
Cancer Outcome			**<0.001**
Progression	90 (75%)	27 (41%)	
Stable/Remission	27 (23%)	35 (53%)	
Unknown	3 (2.5%)	4 (6.1%)	
Death	98 (82%)	25 (37%)	**<0.001**
Time to Onset of Liver Injury (days)	317 (374)	109 (122)	**<0.001**
Normalized LFTs to baseline during follow up	38 (39%)	41 (77%)	**<0.001**
Steroid Treatment	11 (15%)	39 (81%)	**<0.001**
LFTs at liver injury onset			
AST (U/l)	164 (211)	171 (117)	**0.006**
ALT (U/l)	145 (153)	242 (163)	**<0.001**
ALP (U/l)	342 (213)	291 (249)	**0.031**
Total Bilirubin (mg/dl)	1.25 (1.59)	1.05 (1.72)	0.2
R Ratio	2.5 (4.8)	4.6 (4.4)	**<0.001**
Developed Jaundice (Tbili ≥2.5)	27 (23%)	7 (10%)	**0.040**

[1] Mean (SD) for continuous variables; n (%) for categorical variables
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Disclosures: Linnea Swanson: Nothing to Disclose, Andrew Tucker: Nothing to Disclose, LaVana Greene-Higgs: Nothing to Disclose, Venkata Sai Jasty: Nothing to Disclose, Jessica Sheehan: Nothing to Disclose, Yi-Ju Li: Nothing to Disclose, Vincent Chen: AstraZeneca: site PI on industry-sponsored trial, Ipsen: site co-I on industry-sponsored trial, Kowa: site co-I on industry-sponsored trial, Robert Fontana: kezar pharmaceuticals: Grant/Research Support, Takeda Pharmaceuticals: Grant/Research Support, moderna: Consultant,

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MasterSwitch Bio: Stock ownership, Fractyl: Grant/Research Support, MiroMatrix: Grant/Research Support

4358 | A LIMITED REVISED ELECTRONIC CAUSALITY ASSESSMENT METHOD (RECAM) ALGORITHM FOR DILI CASE PRIORITIZATION IN CLINICAL TRIALSSUBMISSION

Mark Gordon[1] Mark Avigan[2] Paul Hayashi[1], [1]FDA, [2]Food and Drug Adminstration

Background: Most liver injury in clinical trials is not due to drug-induced liver injury (DILI). Yet many meet criteria for detailed assessment for DILI due to the investigational products (IP). No diagnostic model can negate the need for meticulous clinical review, but we aimed to create an algorithm that identifies cases as high or low probability DILI to better prioritize case reviews. **Methods: Methods:** We retrospectively analyzed the FDA DILI Team's database from Jul 2000 to Apr 2024 for variables that predict DILI Network (DILIN) likelihood scores assigned by clinical reviewers. We excluded large protein (>40 amino acids) IPs and post-market cases. Variables, including RECAM domains, demographics, and R-values, were tested by ordinal logistic regression (OLR) to predict three outcomes: (i) at least probable; (ii) possible; or (iii) unlikely DILI assigned by the DILI Team. Data were split into training and validation sets. We used decision tree analyses to optimize predictive values for independent variables in the OLR model. **Results: Results:** There were 1330 subjects across 74 applications; 678 met inclusion criteria and had adequate data for OLR modeling. Only shorter interval (latency) between IP start and injury onset; shorter latency between IP stop and onset; and higher R value were statistically associated with at least probable DILI. Of 174 cases in the validation dataset, 69 were at least probable, 61 possible, and 44 unlikely DILI. Accuracy of modeling was 61%; kappa score 41%. For 794 cases with complete latency data, decision tree analysis found combinations of latencies after IP start and stop that identified 243 cases of which 231 (95%) were unlikely DILI and 485 cases of which 247 (51%) were at least probable DILI (Figure). **Conclusion:** Summary: Of RECAM and other variables, only shorter latencies from IP start and stop, and higher R values were predictive of probable DILI. Overall, model accuracy for predicting clinical reviewer attribution to DILI was modest, but certain long latency cut-offs had high negative predictive value for probable DILI. Conclusions: The threshold for cases with potential DILI in clinical trials requiring detailed assessment is low (e.g., peak ALT >3-5x ULN) leading to substantial work for clinical reviewers when most cases will not be DILI. No diagnostic algorithms are accurate enough to replace careful case-by-case assessment for DILI; however, combinations of long latency parameters could identify cases with low likelihood of being considered DILI.

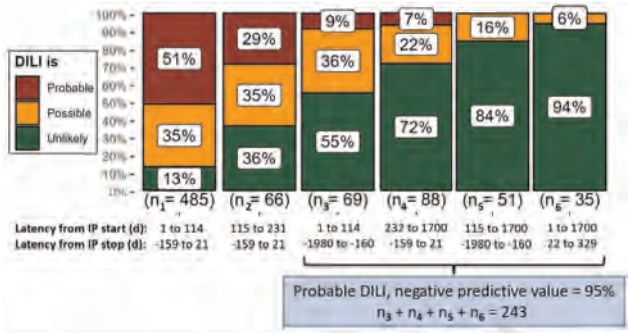

FIGURE: Bar graph proportions of liver injury cases by clinical reviewers' attribution category (at least probable, possible, unlikely DILI) and various cut-offs for latency from drug start and stop. Cut-offs determined by decision tree analyses to optimize predictive values for probable DILI. A negative Latency form IP stop value means the drug was continued for that many days after liver injury onset. A positive value means the injury onset occurred that many days after last dose. The four groups on the right yielded a negative predictive value of 95%. The content in this abstract & figure are the responsibility of the authors and do not necessarily represent the official views of the FDA.

Disclosures: Mark Gordon: Nothing to Disclose, Mark Avigan: Nothing to Disclose, Paul Hayashi: Nothing to Disclose

4359 | THE EFFECT OF A FIXED AMINOTRANSFERASE UPPER LIMIT OF NORMAL ON EDISH ASSESSMENT OF LIVER INJURY RISK IN CLINICAL TRIALS

Mark Gordon[1] Ling Lan[1] Mark Avigan[1] Paul Hayashi[1] Yang Veronica Pei[1], [1]FDA

Background: Aminotransferase (AT) upper limits of normal (ULN) vary and many ULNs are higher than recommended. Evaluation for Drug Induced Severe Hepatotoxicity (eDISH) uses multiples of ULN (xULN), and it is unclear how fixed AT ULNs may affect eDISH outputs. **Aim:** To assess the use of American College of Gastroenterology (ACG) ALT ULNs of 33 U/L for males & 25 U/L for females (M33/F25) on eDISH. **Methods: Methods:** We assessed phase 2 and 3 trials having a comparator arm, enrolling ≥ 18 y-olds, and having ≥ 85% normal baseline AT & bilirubin values by trial provided ULNs (tr-ULN) submitted to the FDA in 2022. We applied M33/F25 to both ALT & AST. We compared eDISH quadrant counts using tr-ULN vs M33/F25. We also tallied subjects in Temple's Corollary quadrant (TCQ) with ALT > 5xULN. We assessed differences in proportions with 3x to 8x ULN using tr-ULN and M33/F25 stratified by sex. We determined how many active-to-comparator arm pairs did not meet Temple's Corollary (TC) using tr-ULN but met TC using M33/F25. **Results: Results:** Fifty-seven qualifying studies had

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23141 subjects (12123 F;11018 M; 70% white, 15% Asian, 11% black, 4% other/unknown). Mean age = 54.5 y (±15.6). Female mean age was lower (52.8 vs 56.7 y). Median number of subjects for active arms was 81 (range: 11 to 1487). M33/F25 increased the number of subjects in both Hy's law and TC quadrants from 35 (0.15% of total) to 44 (0.19%), and 437 (1.9%) to 977 (4.2%), respectively. For TCQ cut-off of >5x ULN, the number increased from 154 (0.67%) to 301 (1.3%). The proportions >3x thru 8x ULN increased more for females (Figure). Of 93 active-comparator pairings, 7 (7.5%) did not meet Temple's Corollary (TC) using tr-ULNs (<1% difference between arms) but met TC using M33/F25 ULNs. Of these 7 pairings, 3 met TC by >2% difference between arms and 2 met TC by >3% difference. **Conclusion:** Summary: ACG based AT ULNs (33 U/L males; 25 U/L females) doubled the trial subjects plotting to TCQ at 3xULN and 5xULN cut-offs. Increases were higher for women. The proportion of subjects plotting to Hy's law quadrant increased by 25% but absolute numbers were small (35 to 44) considering the large number of subjects (>23000). An additional 7.5% of active-to-comparator arm pairs met TC using M33/F25. Conclusions: ACG based ULNs substantially increase the number of subjects identified as potential DILI on eDISH but may have a smaller effect on the number of subjects and trials meeting Hy's law and Temple's Corollary, respectively.

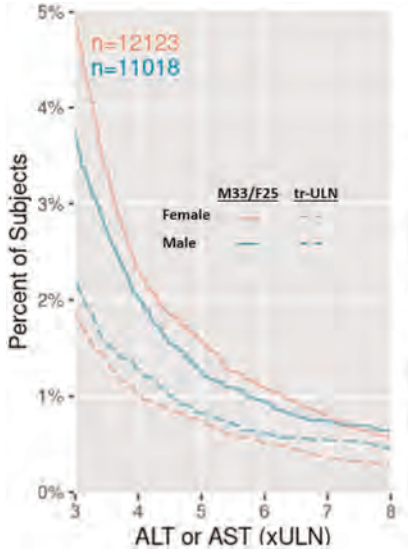

FIGURE: Percent of subjects meeting ALT or AST cut-offs of 3x ULN to 8x ULN by sex and use of trial reported ULNs (tr-ULN) versus ACG ULNs of 33 U/L and 25 U/L for males and females, respectively. The content in this figure and abstract are the responsibility of the authors and does not necessarily represent the official views of the Food and Drug Administration.

Disclosures: Mark Gordon: Nothing to Disclose, Ling Lan: Nothing to Disclose, Mark Avigan: Nothing to Disclose, Paul Hayashi: Nothing to Disclose, Yang Veronica Pei: Nothing to Disclose

4360 | AN PHD2-TARGETED INTRABODY PROTECTS ACETAMINOPHEN-INDUCED LIVER INJURY BY IMPROVING REDOX HOMEOSTASIS AND ATTENUATING FERROPTOSIS

Ze Ren[1] Xinze Yu[1] Ying Wang[1] yanfei Liu[1] Yuchong Wei[1] cheng cheng[1] zhaoyang liu[1] jiayin Yu[1] Zijian Shi[1] Guiying Li[1], [1]School of Life Sciences, Jilin University

Background: Acetaminophen (APAP) overdose is a major cause of drug-induced acute liver failure. Although inhibiting prolyl hydroxylase 2 (PHD2)-mediated degradation of hypoxia-inducible factor-1α (HIF-1α) can alleviate APAP toxicity, the role of HIF-1α in mitigating ferroptosis during APAP toxicity remains unclear. This study developed a novel anti-PHD2 cytosolic intrabody (INP2) disrupting PHD2 and HIF-1α interaction to enhance HIF-1α protein stability and explored its protective mechanisms against APAP-induced liver injury (AILI). **Methods:** a human anti-PHD2 single-chain fragment variable (scFv) was screened from phage antibody display library and was used as template to synthesize INP2. Western blot and immunofluorescence were used to validate INP2 expression and localization in cells. The regulation of INP2 on PHD2 activity and HIF-1α level was assessed by Western blot and co-IP detection of Pro564/Pro402 hydroxylation. For APAP toxicity studies, mice received pretreatment with pINP2 or control vector and then challenged with APAP (250 mg/kg). Liver injury was evaluated through serum ALT/AST and histopathology. Antioxidant systems and lipid peroxidation markers were analyzed in liver tissue. RNA-seq of liver tissues from different groups and significantly changed pathways were validated. Finally, A liver-targeted nanoformulation (IRB@MSN@RM) was developed for INP2 delivery in vivo. **Results:** INP2 expressed in the cytoplasm specifically bound to PHD2 and disrupted PHD2 and HIF-1α interaction, effectively inhibiting HIF-1α hydroxylation and degradation. In murine models of APAP hepatotoxicity, INP2 pretreatment significantly attenuated liver injury. INP2 protects against AILI by reducing oxidative stress and lipid oxidation. Importantly, RNA-seq of liver tissues revealed that INP2 treatment led to significant changes in glutathione metabolism pathway. INP2 restored glutathione biosynthesis and anti-oxidative stress by upregulating SLC7A11 and GPX1, improving glutathione metabolism and inhibiting ferroptosis through H2O2 and 12-HPETE clearance. Finally, using the delivery system, INP2 can effectively enter cells and block intracellular PHD2 activity. By employing erythrocyte membrane camouflage, the half-life and hepatic retention time of INP2 were significantly prolonged. **Conclusion:** The PHD2-targeted intrabodies protect the liver from APAP-induced injury by upregulating the HIF-1α/GPX1 axis to improve redox

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homeostasis and attenuate ferroptosis, offering a potential strategy for the prevention and treatment of AILI.
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4361 | HEPATOCYTE-SPECIFIC DELETION OF BETAINE HOMOCYSTEINE METHYLTRANSFERASE PROMOTES AGE-DEPENDENT PROGRESSION OF LIVER DISEASE THROUGH ALTERING ONE-CARBON METABOLISM

Sathish kumar Perumal[1] Ramachandran Rajamanickam[1] Ramesh Bellamkonda[2] Sundararajan Mahalingam[2] Kurt Fisher[2] Natalia Osna[2] Hua Jiang[3] Kenneth Maclean[3] Benita McVicker[2] Karuna Rasineni[2] Kusum Kharbanda[1], [1]Research Service, Veterans Affairs Nebraska-Western Iowa Health Care System, Omaha, Nebraska, USA, [2]University of Nebraska Medical Center, Omaha, Nebraska, USA, [3]University of Colorado School of Medicine, Aurora, CO, USA

Background: Betaine homocysteine methyltransferase (BHMT) is an essential enzyme involved in one-carbon metabolism and liver health. Our previous research highlighted the importance of BHMT in preventing liver disease by removing harmful metabolites homocysteine and S-adenosylhomocysteine (SAH). To further understand BHMT's function in the liver, we created BHMT floxed mice and liver-specific BHMT knockout (LKO) mice. This study aimed to explore how the liver-specific deletion of BHMT impacts the development of liver disease focusing on other one-carbon metabolism enzymes and metabolites. **Methods:** One-year-old male and female C57BL/6 BHMT floxed and liver-specific BHMT knockout (BHMT LKO) mice were fed a standard chow diet and housed under ambient conditions. Liver tissues were collected for histopathological and biochemical analyses. **Results:** Compared to floxed mice, BHMT KO mice had significantly higher serum homocysteine, hepatocellular homocysteine, and SAH levels, despite a 2.5-fold compensatory increase in 5-methyltetrahydrofolate-homocysteine methyltransferase ($p < 0.01$), an alternate enzyme for homocysteine remethylation and SAH removal. Hepatic S-adenosylmethionine (SAM) levels were unchanged in LKO mice, but a seven-fold increase in SAH resulted in a significantly reduced SAM:SAH ratio ($p < 0.001$), suggesting widespread cellular methylome disturbances. Liver glutathione levels dropped significantly due to lower protein levels of cystathionine β-synthase, a key enzyme in glutathione synthesis. While compensatory increases in cystathionine γ-lyase protein levels were observed, other important enzymes remained unchanged between BHMT LKO and floxed mice. Histological and biochemical analyses showed increased steatosis, higher inflammation indices, fibrotic changes, and epigenetic alterations in the livers of BHMT LKO mice compared to age-matched floxed controls, correlating with a loss of liver methylation potential and antioxidants. **Conclusion:** The liver-specific deletion of BHMT results in increased liver injury markers in aging male and female BHMT LKO mice, reflecting significant alterations in one-carbon metabolism pathway enzymes and metabolites. This indicates that individuals with a loss-of-function BHMT polymorphism could be predisposed to developing liver disease as they age and may experience more severe liver damage with additional factors such as alcohol consumption, high-caloric intake, or viral infections.
Disclosures: Sathish kumar Perumal: Nothing to Disclose, Ramachandran Rajamanickam: Nothing to Disclose, Ramesh Bellamkonda: Nothing to Disclose, Sundararajan Mahalingam: Nothing to Disclose, Kurt Fisher: Nothing to Disclose, Natalia Osna: Nothing to Disclose, Hua Jiang: Nothing to Disclose, Kenneth Maclean: Nothing to Disclose, Benita McVicker: Nothing to Disclose, Karuna Rasineni: Nothing to Disclose, Kusum Kharbanda: Nothing to Disclose

4362 | DRUG INDUCED LIVER INJURY IN PATIENTS WITH DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS) SYNDROME

Kimberly Felipe[1] Neel Ravela[1] Elizabeth Phillips[2] Naga Chalasani[3] Sahand Rahnama[4], [1]Indiana University School of Medicine, [2]Vanderbilt University Medical Center, [3]Indiana University Medical Center, [4]Indiana University

Background: Drug induced liver injury (DILI) can occur in patients with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) but its frequency and significance are not fully understood. We report on a cohort of patients with DRESS to better characterize hepatic involvement. **Methods:** Cases of DRESS syndrome were identified from the Indiana University Dermatology Inpatient Consult log from the years 2014 to 2017 via ICD9/ICD10 diagnoses and manual search. Eligible cases were subsequently adjudicated via RegiSCAR as a tool. Cases designated as "possible", "probable", and "definite" were used in the analysis. Demographic, laboratory, and clinical data were collected through manual chart review. DILI was defined using the

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DILIN criteria with minor modifications. **Results:** 52 patients were identified during the study period. The average age at DRESS onset was 43.5 years and 48 self-reported as White and 50 as Non-Hispanic White. 25 out of 52 patients were female. The average BMI was 28.2 kg/m2 and 18 were obese. 18/52 (35%) of our patients had pre-existing MASLD and 2 had pre-existing cirrhosis. In 23 cases, multiple agents were considered possible. In 15/52 (29%) cases of DRESS, vancomycin was either a sole culprit or considered among different agents. Beta-lactam agents were considered in 23/52 (44%) cases. Allopurinol and lamotrigine were considered in 3 cases each. No other anti-epileptic drug was a culprit in this cohort. The latency period was on average 17 days before the rash onset. The rash was "morbilliform" or "maculopapular' in 42 cases and "pustular" in 5 cases. Concomitant DILI was present in 40% of patients. The average peak ALT was 178 U/L, AST 196 U/L, peak alkaline phosphatase (ALP) was 242.9 U/L. 2 patients needed liver transplantation, and 11/52 (21%) patients died within 6 months of diagnosis. **Conclusion:** Antibiotics were most frequently implicated agents, with few anti-epileptics for causing DRESS in this experience. Concomitant liver injury was present in 40% of cases. Twenty five percent either died or needed a liver transplantation within six months after suffering from DRESS.

Table: Selected Characteristics of patients with DRESS seen at our institution over a 3-year period

Total Patients, n=52	Mean (SD) or N (%)
Age of Onset	43.5 (23.9)
BMI (kg/m2)	28.2 (9.6)
Rash latency (days)	16.7 (11.8)
Female	25 (48%)
White	48 (92%)
Not Hispanic/Latino	50 (96%)
Pre-existing Cirrhosis	2 (4%)
Pre-existing MASLD	18 (35%)
Multiple drugs possible	23 (44%)
Vancomycin possible	15 (29%)
Beta-Lactam possible	23 (44%
Allopurinol possible	3 (6%)
Lamotrigine possible	3 (6%)
Other AED possible	0 (0%)
Morbilliform rash	42 (81%)
Pustular rash	5 (10%)
Peak WBC (k/cumm)	19.4 (11.7)
Peak Eosinophil (k/cumm)	1.2 (2.5)
Peak AST (U/L)	196 (406.7)
Peak ALT (U/L)	177.9 (378.7)
Peak ALP ((U/L)	242.9 (240.8)
Peak Bilirubin (mg/dL)	2.1 (3.4)
Jaundice (Bilirubin > 2.5 mg/dL)	10 (19%)
DILI	21 (40%)
Pattern of Liver injury in DILI cases	
- Hepatocellular	4 (19%)
- Cholestatic	12 (57%)
- Mixed	5 (34%)

Abbreviations: BMI: Body mass index; MASLD: Metabolic dysfunction associated steatotic liver disease; AED: Antiepileptic drugs; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline Phosphatase; DILI: Drug induced liver injury

Disclosures: Kimberly Felipe: Nothing to Disclose, Neel Ravela: Nothing to Disclose, Elizabeth Phillips: Johnson and Johnson: Consultant, UpToDate: Royalties or patent beneficiary, Verve: Consultant, Elion: Consultant, Astra Zeneca: Consultant, Servier: Consultant, Rapt: Consultant, Esperion: Consultant, Glenmark: Consultant, Naga Chalasani: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Sahand Rahnama: Nothing to Disclose

4363 | LIVER TEST PATTERN AND HISTOLOGIC BILE DUCT INJURY DO NOT PREDICT RESPONSE TO TREATMENT OF IMMUNOTHERAPY HEPATOTOXICITY

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Background: Immune checkpoint-inhibitor (ICI) cholangitis is an uncommon immune-related adverse event affecting the biliary ducts that is considered distinct from ICI hepatitis. The aim of this study is to examine whether the liver injury pattern or presence of histologic bile duct damage determines response to immunosuppression. **Methods:** This multi-center retrospective cohort study includes 298 consecutive patients with cancer who received immunotherapy between 2010 and 2021 and were originally classified as grade 3 or higher ICI-related hepatitis (alanine aminotransferase (ALT) $\geq$ 200 U/L). Response to immunosuppression was stratified by pattern of liver injury (hepatocellular, cholestatic, or mixed) as defined by R-value, the presence of histologic bile duct damage, and the Drug-Induced Liver Injury Network (DILIN) severity score. The primary outcome was time to normalization of ALT ($\leq$ 40 U/L). Secondary outcomes included time to grade 1 liver injury (ALT $\leq$100 U/L), and need for additional immunosuppression. **Results:** The pattern of liver injury was hepatocellular in 60%, cholestatic in 13%, and mixed in 27%. All patients received corticosteroids as first-line therapy. There was no difference in corticosteroid dose, need for an additional immunosuppressive agent, time to normalization of ALT, or time to grade 1 liver injury between groups. Outcomes were similar among patients with or without histologic bile duct damage and between those with a DILIN severity score of 3+ versus lower score. **Conclusion:** The response of high-grade ICI hepatotoxicity to standard immunosuppression is similar regardless of the pattern of liver injury or the presence of bile duct damage.

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Table 1 – Outcomes stratified by liver injury pattern

		Cholestatic (n=39)	Hepatocellular (n=179)	Mixed (n=80)	P value
Liver Biopsy, (yes/no), n (%)		13 (33%)	60 (34%)	29 (36%)	0.905
	Cholangitis seen on pathology	4 (31%)	4 (6.7%)	4 (14%)	0.046
	Bile duct injury/loss	9 (69%)	8 (13%)	11 (38%)	<0.0001
	Cholangitis and/or bile duct injury/loss (n, % patients with biopsy)	10 (77%)	8 (13%)	11 (38%)	<0.0001
Hospitalized, n (%)		19 (49%)	102 (57%)	49 (61%)	0.432
ALT improved to <100 U/L (Grade 1 injury), n (%)		38 (97%)	178 (99%)	79 (99%)	0.221
Time (days) to grade 1 liver injury, median (range)		17 (3 – 142)	21 (4 – 176)	21 (3 – 132)	
ALT improved to <40 U/L, n (%)		36 (92%)	170 (95%)	76 (95%)	0.704
Time (days) to ALT normalization, median (range)		28 (9 – 196)	46 (7 – 308)	36 (7 – 180)	
Initial steroid dose in mg/kg prednisone equivalent, median (range)		1.0 (0.5 – 4.0)	1.0 (0.5 – 20.0)	1.2 (0.2 – 15.0)	0.532
Initial therapy with intravenous methylprednisolone, n (%)		19 (49%)	92 (51%)	42 (53%)	0.927
Maximum steroid dose in mg/kg methylprednisolone equivalent, median (range)		1.0 (0.5 – 5.0)	1.3 (0.5 – 20.0)	1.6 (0.3 – 15.0)	0.170
Steroid refractory, n (%)		10 (26%)	56 (31%)	18 (23%)	0.324
	Mycophenolate mofetil (MMF), n (%)	10 (26%)	52 (29%)	14 (18%)	
	Tacrolimus	0	6 (3.4%)	3 (3.8%)	
	Azathioprine, n (%)	0	1 (0.6%)	1 (1.3%)	
	Abatacept	0	1 (0.6%)	1 (1.3%)	
	IVIG, n (%)	0	2 (1.1%)	0	
Time (days) from steroid initiation to addition of MMF, median, range		7 (2 – 66)	9 (0 – 164)	12 (3 – 64)	0.446
Mycophenolate mofetil maximum dose (mg), median (range)		2000 (1000 – 2000)	2000 (1000 – 3000)	2000 (500 – 3000)	0.389
Death during follow-up (all-cause), n (%)		15 (38%)	69 (39%)	43 (54%)	0.063
Death prior to ALT normalization, n (%)		2 (5.1%)	6 (3.4%)	3 (3.8%)	0.747
Death prior to ALT improvement to <100 U/L (Grade 1 injury), n (%)		0 (0%)	1 (0.6%)	0 (0%)	1.000

Disclosures: Benjamin Rabin: Nothing to Disclose, Michael Li: Nothing to Disclose, Jordan Sack: Nothing to Disclose, Stephen Zucker: Nothing to Disclose

4364 | EFFICACY OF PLASMA EXCHANGE IN SEVERE IMMUNE CHECKPOINT INHIBITOR-INDUCED HEPATITIS (CHILI): PLASMACHILI STUDY

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Background: Current management guidelines for immune checkpoint inhibitor-induced hepatitis (CHILI) recommend corticosteroids as first-line therapy, followed by immunosuppressive agents in case of non-response. In severe or refractory cases, plasma exchange (PE) may be considered as a salvage treatment, as already implemented in other ICI-related toxicities. **Methods:** All French referral centers for hepatic and ICI-related hepatotoxicity were contacted for participation. Demographic, clinical, and biological data were retrospectively collected. Ethics committee approval was obtained. **Results:** We report all French cases of PE performed for this indication between March 2021 and September 2024. Ten patients (6 females, mean age: 61.3 years) underwent PE. The ICIs involved were: nivolumab (n = 5), atezolizumab (n = 1), and pembrolizumab (n = 4), with 5 patients receiving combination therapy with anti-CTLA-4 or anti-TIGIT agents. The median interval between ICI initiation and CHILI onset was 100 days. The median MELD score at diagnosis was 14. All cases were grade 4 according to CTCAE and classified as severe per DILIN or DILI-IEGW criteria. The median peak total bilirubin was 305.5 μmol/L (range: 93–561), and the lowest median prothrombin time was 44.5% (range: 7–84). All patients received corticosteroids as first-line treatment (1 mg/kg), with dose escalation in 7 patients. Nine patients received mycophenolate mofetil (MMF) as second-line therapy, and 7 required third-line immunosuppressants (tacrolimus or MMF). Adverse events related to corticosteroids occurred in 6 patients: infections (n = 5), hyperglycemia (n = 1). PE was initiated after a median of 28.5 days (range: 13–64) from diagnosis and 9 days (range: 0–43) from the last treatment line. The number of sessions was 3 (n = 5), 5 (n = 4), and 6 (n = 1), performed via centrifugation (n = 2) or filtration (n = 8). Two PE-related adverse events were reported (hypercalcemia, hemorrhage). Median MELD score was 21 (range: 10–40) at PE initiation and 18 (range: 8–34) at the end of treatment. Median follow-up was 141 days (range: 51–842). Three patients died: one from septic shock 62 days after CHILI onset, one from tumor progression, and one from acute liver failure. In 5 patients, anticancer treatment (excluding immunotherapy) was resumed after normalization of liver tests. **Conclusion:** This first national case series, despite a limited sample size, suggests that plasma exchange may represent a therapeutic option in severe acute ICI-induced hepatitis. The optimal timing for its initiation, particularly following corticosteroid failure, remains to be clarified.

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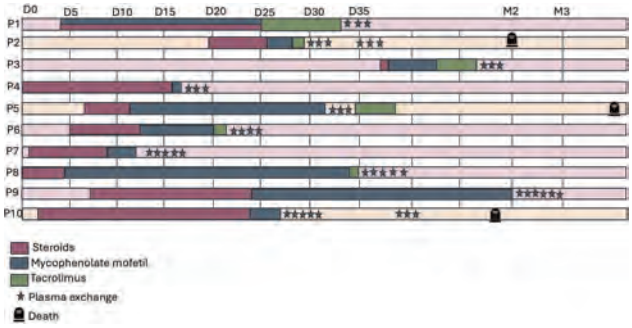

Disclosures: LUCY MEUNIER: Nothing to Disclose, Clément Monet: Nothing to Disclose, Antonio Saviano: Nothing to Disclose, Marwin Farrugia: Nothing to Disclose, François Villeret: Nothing to Disclose, Marion Khaldi: Nothing to Disclose, Olivier Moranne: Nothing to Disclose, rodolphe anty: Nothing to Disclose, Simona TRIPON: Nothing to Disclose, Mialy Randrianarisoa: Nothing to Disclose, Lina Hountondji: Nothing to Disclose, Eleonora De Martin: Nothing to Disclose

4365 | STUDY ON THE MEDIATING EFFECT OF SLEEP DISORDERS BETWEEN ANXIETY AND QUALITY OF LIFE IN PATIENTS WITH LIVER CIRRHOSIS

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Background: To investigate the mediating role of sleep disorders between anxiety and quality of life in patients with liver cirrhosis, providing potential intervention targets to improve patients' quality of life. **Methods:** A total of 377 patients with liver cirrhosis were enrolled. Demographic data (age, sex), clinical indicators (Child-Turcotte-Pugh [CTP] score, Model for End-Stage Liver Disease [MELD] score), Pittsburgh Sleep Quality Index (PSQI), anxiety scores, and the 36-Item Short Form Health Survey (SF-36) were collected. Correlation analysis and multiple linear regression analysis were performed using SPSS 27.0. The mediating effect was tested using Model 4 in the SPSS macro PROCESS, and the significance of the mediating pathway was verified using the Bootstrap method proposed by Hayes. **Results:** Among the 377 enrolled patients with liver cirrhosis, 195 (51.7%) were male, with a mean age of 60 $\pm$ 11.6 years. The median CTP score was 7 (5, 9), and the median MELD score was 10 (7, 13). The prevalence rates of sleep disorders and anxiety were 61.8% and 47.7%, respectively. A significant positive correlation was observed between anxiety scores and PSQI ($r = 0.534$, $P < 0.001$), while a significant negative correlation was found between anxiety scores and SF-36 total scores ($r = -0.72$, $P < 0.001$). Structural equation modeling revealed that sleep disorders partially mediated the relationship between anxiety and quality of life, accounting for 34.2% of the total effect ($\beta = -0.6$, 95% CI: -0.73 to -0.47). The total effect was -1.62 ($P < 0.001$), and the direct effect was -1.02 ($P < 0.001$). This mediating effect remained significant after adjusting for age, sex, CTP score, and MELD score. **Conclusion:** Sleep disorders serve as a significant mediator in the impact of anxiety on quality of life in patients with liver cirrhosis. Clinical interventions should prioritize sleep management to enhance overall health outcomes in this population.

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4366 | CHRONIC OVERNUTRITION DEPOLARIZES MITOCHONDRIA AND DISASSEMBLES MITONEET IN MOUSE LIVERS

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Background: The shortage of donor livers is a major obstacle in organ transplantation. However, steatotic donor livers are often discarded due to its hypersensitivity to ischemia/reperfusion (I/R) injury. mitoNEET (mNT) is a homo-dimeric mitochondrial outer membrane protein. We have shown that the dissociation of mNT dimers (mNTd) into mNT monomers (mNTm) contributes to autophagic and mitochondrial dysfunction after I/R in steatotic livers. How steatosis accumulates mNTm remains unknown. **Methods:** Age-matched male mice were fed either a chow diet (CD) or a high fat diet (HFD: 60 Kcal % fat) for 8 weeks. Hepatocytes were isolated either from CD- or from HFD-fed mice. To separate mNTm and oligomers (mNTo) from mNTd, we crosslinked mNTd with dithiobis (succinimidyl propionate). Changes in mNT expression, mitochondrial membrane potential (DYm) and steatosis were assessed by immunoblot and imaging analysis. Some experiments were conducted with mouse and human livers. To investigate roles of DYm in steatosis-mediated disassembly of mNTd, hepatocytes from CD mice were incubated with 500 nM of carbonyl cyanide m-chlorophenylhydrazone (CCCP), a mitochondrial

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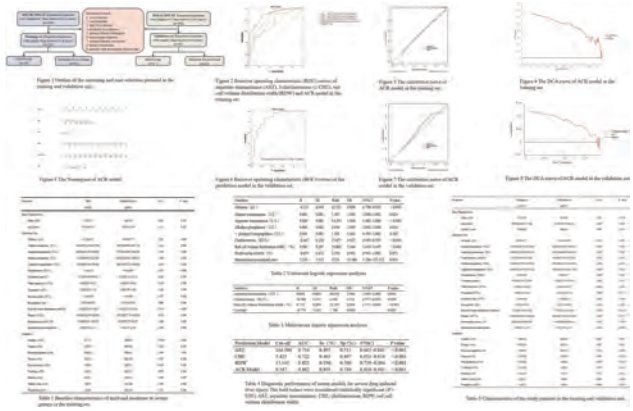
uncoupler, for up to 90 min. **Results:** The expression of mNTm and mNTo in HFD hepatocytes and livers, dysfunctional forms of mNT, was significantly greater than that of CD counterparts. Accumulation of mNTm was evident in human steatotic livers. Confocal imaging analysis of Bodipy 493/503 revealed that most hepatocytes isolated from HFD mice were microsteatotic, while some cells were non-steatotic. Fluorometry of tetramethylrhodamine methylester demonstrated that DYm of HFD hepatocytes was 28.1% of CD hepatocytes. Noticeably in HFD livers, DYm of hepatocytes with steatosis was significantly lower than that of cells without steatosis, implying the effects of steatosis on DYm. To induce mitochondrial depolarization, we conducted immunoblot and confocal analysis in lean CD hepatocytes with and without CCCP. Treatment with CCCP progressively accumulated mNTm followed by mNTo. Confocal microscopy confirmed rapid loss of DYm followed by mNTo accumulation by CCCP, suggesting the disassembly of mNTd by mitochondrial depolarization. **Conclusion:** Chronic overnutrition depolarizes mitochondria, leading to the accumulation of dysfunctional mNTm and mNTo. These pathological events contribute to enhanced oxidative stress, defective autophagy, mitochondrial dysfunction, and severe I/R injury in steatotic livers.

Disclosures: Yiing Lin: Nothing to Disclose, Jae-Sung Kim: Nothing to Disclose, William Chapman: Nothing to Disclose, junkyu shin: Nothing to Disclose

4367 | ACR SCORE: A NOVEL PREDICTIVE MODEL FOR DRUG-INDUCED LIVER INJURY SEVERITY ASSESSMENT

Chengjie Cui[1] Shuxian Zang[1] Jing Cui[1] Na Fu[1] Yuemin Nan[1], [1]Hebei Medical University Third Hospital

Background: Drug-induced liver injury (DILI) is caused by drugs or their metabolites, which is one of the common causes in liver injury. In severe cases, it leads to acute liver failure or even death. Due to low acceptance of liver biopsy, DILI faces challenges such as difficulties in identification and diagnosis, predicting severity and prognosis, and clinical management. **Methods:** A retrospective analysis was used to enroll 125 patients diagnosed with DILI in Hebei Medical University Third Hospital from June 2021 to October 2024 as the training set. According to the 2023 DILI guideline, 39 cases were classified as mild (grade 1) and 86 as moderate to severe ($\geq$ grade 2). Additionally, clinical data from 45 patients diagnosed with DILI in the same hospital from November 2024 to May 2025 were collected as the validation set (Fig. 1). SPSS 27.0.1 was used to analyze data and generate the ROC curve. The calibration curve, DCA curve and nomogram were created using the CNSknowall platform (https://cnsknowall.com). **Results:** In the training set, the general information of two groups was shown in Tbl. 1. Laboratory indicators with P. **Conclusion:** The predictive performance of ACR model is significantly better than that of AST, CHE and RDW. It is expected to serve as a new prediction model for evaluating the severity of DILI. However, these results need to be validated in larger, multi-center studies.



Disclosures: Chengjie Cui: Nothing to Disclose, Shuxian Zang: Nothing to Disclose, Jing Cui: Nothing to Disclose, Na Fu: Nothing to Disclose, Yuemin Nan: Nothing to Disclose

4368 | SIMULATED MILITARY BURN PIT INHALATION EXPOSURES CAUSE RAPID-ONSET HEPATIC PATHOLOGY IN A RAT MODEL

Shannon Heinig[1] Pooja Muddasani[1] Charis-Marie Vanderpuye[1] Anna Rutkowski[1] Joshlyn Mensah[1] Fodilat Ibraheem[1] hamda siddiqui[1] Donna Stolz[1] William Goldsmith[2] Anand Ranpara[2] Thomas Batchelor[2] Timothy Nurkiewicz[2] Juliane Beier[1], [1]University of Pittsburgh, [2]West Virginia University

Background: Open-air waste incineration, referred to as military "burn pits", represents a standard operational component of military installations. Since 2001, nearly 3 million U.S. service personnel have been deployed to Middle Eastern regions. Throughout these assignments, personnel encountered burn pit emissions from incineration of up to 85,000 pounds of waste, accelerated with jet fuel, daily. Veterans report chronic health complications including fatigue, gastrointestinal, cardiopulmonary, and hepatic dysfunction following these exposures. The pathophysiological mechanisms underlying liver disease remain incompletely understood. Here, the hepatic consequences of burn pit emission inhalation exposure were investigated, using a

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validated model. **Methods:** A modified pellet stove combusted materials commonly disposed of in burn pits (80% wood, 10% rubber, 10% plastic, and jet fuel). The combustion emissions were delivered to an exposure chamber. Male Sprague Dawley rats underwent inhalation exposures to generated emissions (~10 mg/m^3; 5 hr/day, 2 days, 89 μg cumulative lung deposition). Hepatic tissue and plasma were analyzed for pathological changes and injury markers. Transmission electron microscopy evaluated ultrastructural alterations. **Results:** After 2 days of burn pit emission exposure, animals produced pronounced hepatic pathological changes across multiple assessment parameters. Exposed animals exhibited disrupted hepatic zonation architecture, enhanced collagen accumulation throughout the parenchyma, and robust inflammatory cell infiltration with macrophage activation. Ultrastructural examination revealed extensive smooth endoplasmic reticulum fragmentation, sinusoidal endothelial capillarization and dysfunction, and numerous autophagosomes. Notably, electron-dense particulate matter, consistent with inhaled emission components, was detected within hepatocyte and Kupffer cell autophagosomes and lipid droplets. **Conclusion:** These data provide the first evidence of acute hepatic pathology following 2 days of controlled burn pit inhalation exposure, establishing hepatotoxicity as an immediate consequence of inhalation exposures. The observed morphological and cellular alterations suggest direct mechanistic pathways linking burn pit emissions to hepatic dysfunction and metabolic perturbation. The findings support incorporating hepatic biomarkers into Veteran health screening protocols to identify novel therapeutic approaches for liver injury.

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4369 | HORMONAL CONTRACEPTIVE-ASSOCIATED DRUG-INDUCED LIVER INJURY IN THE MODERN ERA: INSIGHTS FROM THE DRUG-INDUCED LIVER INJURY NETWORK

Raj Vuppalanchi[1] Alfred Barritt IV[2] Anjali Rai[3] Sherry Gu[4] Yi-Ju Li[5] Huiman Barnhardt[4] Naga Chalasani[1], [1]Indiana University School of Medicine, [2]University of North Carolina, [3]NIH/NIDDK, [4]Duke Clinical Research Institute, [5]Department of Biostatistics and Bioinformatics, Duke University School of Medicine

Background: Hormonal agents, particularly combined oral contraceptives, are widely used for both contraceptive and therapeutic purposes; however, their potential to cause DILI remains a clinical concern. This study aimed to characterize clinical and biochemical features of hormonal contraceptive-associated DILI (HC-DILI) and to explore its association with candidate genes implicated in cholestasis. **Methods:** In the DILIN study between 2004 and 2024, among 1553 high-confidence cases, 20 HC-DILI cases (1.3%) were identified after excluding 14 cases due to low causality scores or used for non-contraception purposes. Clinical presentation, laboratory parameters, and outcomes were compared with those of age- and sex-matched cases of DILI (n = 60). We examined the association between HC-DILI and candidate genetic variations associated with cholestasis, comparing it with the matched control group and a second control group comprising of other high-confidence DILI cases in women (n = 899). **Results:** The median age (15 White, 3 Black, 2 Other) was 22.1 years, with a latency of 2–12 weeks, and most presented with jaundice and pruritus. Eighteen received hormonal agents orally (combination = 14, estrogen-only = 3, and progesterone-only = 1), with one receiving it intramuscularly and one receiving it as a topical patch. The injury was mainly cholestatic or mixed, with 50% requiring liver biopsy or hospitalization. One patient who received (intravenous conjugated estrogen followed by oral estradiol) experienced prolonged jaundice with vanishing bile duct syndrome, but there were no fatalities or liver transplantation. Compared to the control group, patients with HC-DILI exhibited a cholestatic pattern, characterized by markedly lower aminotransferase levels but similar alkaline phosphatase levels (Table). There was a higher prevalence of jaundice (80% vs. 48%, P = 0.013) and pruritus (80% vs. 38%, P = 0.001), but hypersensitivity features, such as fever (0% vs. 35%, P = 0.002), were less common. Autoantibodies (ANA and SMA) were less frequent in the HC-DILI group (Table). Tight Junction Protein 2 (*TJP2*) genetic variation (rs3812536 on chr9:71869473, G > A) was significantly associated with HC-DILI compared to the matched other DILI cases (OR: 3.08,95% CI: 1.29-7.35; P = 0.01) and all other female DILI cases (n = 899) (OR: 2.75, 95% CI: 1.4-5.36; P = 0.003) with apparent minor allele frequency difference (0.68 in cases vs. 0.42 in both control groups). **Conclusion:** Hormonal agent-induced liver injury presents with a unique cholestatic phenotype, mostly lacking hypersensitivity. *TJP2* is a crucial gene in tight junction function and hepatocyte integrity, and its genetic variation has been associated with progressive familial intrahepatic cholestasis type 4. Further studies

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are warranted to assess the potential role of *TJP2* in HC-DILI and risk factors contributing to this distinct presentation.

Feature	Hormonal agent (N=20)	Control (N=60)	P-value
Initial ALT (U/L)	353 (337)	952 (969)	0.001
Initial AST (U/L)	187 (183)	772 (846)	<0.001
Initial ALP (U/L)	213 (157)	196 (160)	0.32
Initial Total Bilirubin (mg/dL)	7.5 (5.5)	3.9 (4.4)	0.003
Initial *R* value	5.0 (5.8)	16.0 (20.4)	<0.001
Liver injury pattern			0.003
Hepatocellular (*R* ≥ 5)	5/18 (27.8%)	40/57 (70.2%)	
Mixed (*R* >2 to <5)	6/18 (33.3%)	11/57 (19.3%)	
Cholestatic (*R* ≤ 2)	7/18 (38.9%)	6/57 (10.5%)	
Peak ALT (U/L)	504 (397)	1311 (1379)	<0.001
Peak AST (U/L)	326 (458)	1308 (1894)	<0.001
Peak ALP (U/L)	280 (176)	269 (229)	0.39
Peak Total Bilirubin (mg/dL)	13.0 (9.18)	8.4 (9.78)	0.003
Peak INR	1.2 (0.51)	1.6 (1.58)	0.044
Peak Eosinophils (cells/μL)	203.1 (216.40)	401.7 (794.44)	0.19
Peak Eosinophils >500 cells/μL	1/20 (5.0%)	10/57 (17.5%)	0.27
ANA	2/20 (10.0%)	28/58 (48.3%)	0.002
SMA	4/17 (23.5%)	12/56 (21.4%)	0.013
Severity Assessment			0.09
Mild (Anicteric)	4/20 (20.0%)	23/60 (38.3%)	
Moderate (Jaundiced)	5/20 (25.0%)	8/60 (13.3%)	
Moderate & Hospitalized	10/20 (50.0%)	15/60 (25.0%)	
Severe (Decompensation)	1/20 (5.0%)	11/60 (18.3%)	
Fatal (Death or Transplant)	0/20 (0.0%)	3/60 (5.0%)	
Liver Biopsy	10/20 (50%)	26/60(43.3%)	0.60
Treated with prednisone or corticosteroids	3/20 (15.0%)	21/60 (35.0%)	0.09
Chronic DILI*	2/19 (10.5%)	8/52 (15.4%)	0.72
Death or Liver Transplant	0	0	

*Persistent liver injury 6 months after DILI onset

Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, INR: international normalized ratio, ANA: antinuclear antibody, SMA: smooth muscle antibody.

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4370 | DRUG-INDUCED DUCTOPENIA IN THE SPANISH AND LATINDILI REGISTRIES

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Background: Ductopenia is a rare phenotype of drug-induced liver injury (DILI), typically manifesting after prolonged cholestasis induced by DILI. This study aimed to evaluate the clinical features, histopathological characteristics, and outcomes of drug-induced ductopenia (DID) enrolled in the Spanish and LATINDILI registries. **Methods:** From a total of 1,564 DILI cases, we identified 10 cases (0.6%) of ductopenia attributable to drugs registered within the Spanish (n = 1,037) and LATINDILI (n = 527) networks. DID was defined as vanishing interlobar ducts in more than 50% of portal tracts. Clinical data, biochemical parameters, histological findings, and clinical outcomes were analyzed and compared between groups. **Results:** The mean age of DID patients was 50 ± 19 years ; female 45%. The predominant clinical presentation was hepatocellular (40%), with cholestatic and mixed patterns accounting for 20% and 40%, respectively. The implicated medications included ciprofloxacin, amoxicillin-clavulanate, metformin, ticlopidine, stanozolol, carbamazepine, sertraline, captopril, and droxicam. The majority (90%) presented with jaundice, and 80% required hospitalization. Rash and eosinophilia were observed in 40% of cases, and autoantibodies were detected in two patients. The median time to onset was 34 days (range 21–65), with an average therapy duration of 32 days (range 8–66). Biochemical parameters revealed

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elevated levels of AST (mean 4.3×ULN), ALT (8.9×ULN), ALP (2.8×ULN), GGT (10×ULN), and total bilirubin (mean 11 mg/dL). Histological examination showed varying degrees of cholestasis with inflammatory portal changes, fibrosis, ductular proliferation, and interphase hepatitis. Compared with non-ductopenic DILI patients in both registries, no significant differences were observed in the latency period or clinical pattern at presentation; however, hypersensitivity phenomena were more frequent in DID cases. While the outcomes were favourable, with no fatalities case; the bilirubin level was notably higher in DID patients. During follow-up, liver enzyme normalization occurred within a range of 2 months to 2 years (median 3,5 months). **Conclusion:** Drug-induced ductopenia is characterized by higher bilirubin levels and a greater association with hypersensitivity reactions, such as rash and eosinophilia. Unlike other series, DID exhibits an overall benign prognosis, with no reported fatalities.

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4371 | SENTINEL SURVEILLANCE FOR HERBAL AND DIETARY SUPPLEMENT INDUCED LIVER INJURY IN THE UNITED STATES: A PILOT INITIATIVE IN DILIN

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Background: The Drug-Induced Liver Injury Network (DILIN) has seen a rise in herbal and dietary supplement (HDS) cases. Our aim is to report the early results of sentinel surveillance for HDS-induced liver injury (HILI) that includes chemical analysis of suspect HDS and coordination with the Human Foods Program (HFP) of the FDA for early signal detection and outbreak management. **Methods:** De-identified information (medical history, HDS use, exam, lab data) is assembled from HILI cases enrolled as previously described (Drug safety 2009;32:55-68) at 6 DILIN sites, with available products sent for chemical analysis at the National Center for Natural Products Research using Liquid Chromatography Quadrupole Time-of-Flight Mass Spec, to verify label ingredients and detect adulterants. All information is recorded onto a case report form, and investigators (DH, AS, VN) provide a DILIN expert opinion for overall case causality score (1 = definite to 5 = unlikely). The case information with chemical analysis is sent to FDA via MedWatch to determine the presence of an injury signal and, based on other reports to the agency, if an outbreak may be occurring. It was agreed with the HFP that a 30-day turnaround time (TAT), between the date of case enrollment to MedWatch submission, would be consistent with an effective surveillance program. **Results:** Between 1/1/25 and 5/1/25, 8 suspected HILI cases were enrolled and adjudicated; 4 cases were judged to be overall highly likely, 3 possible, and one unlikely (Table) HILI. Median age was 43 years, 50% were female, 75% White, 25% Black. Six had jaundice, and all but one were hospitalized. Median ALT at onset was 706 U/L (range 65-4820), AST 718 U/L (41-4373), Alk Phos 205 U/L (120-792), and bilirubin 5.9 mg/dL (0.4-22). 15 HDS products were submitted for chemical analysis from the 8 cases. The mean TAT was 26 days (range 17-38). Chemical analyses confirmed the presence of the ingredients listed on the labels, with no adulterants. Turmeric was the most common suspected cause of HILI. **Conclusion:** Sentinel surveillance for HILI via a prospective, multicenter research network like DILIN is feasible, achieving an acceptable TAT from a regulatory standpoint. Surveillance tended to detect serious liver injury, insofar as most patients had jaundice and were hospitalized. Surveillance will support early identification of HILI safety signals that can trigger outbreak investigations, identify potentially injurious ingredients, and facilitate expedient regulatory action to enhance early warning and consumer safety.

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Case	Overall Case Causality Score	Implicated HDS Product	Turn-around Time (Days)	Chemical Verification of Label
1	Unlikely	Super Youth Multi-Collagen Peptides	38	**Labeled/Present:** Citric Acid, malic acid, stevia leaf, beet root juice, monk fruit extract, peptides
2	Highly Likely	Organic Turmeric Curcumin with Black Pepper	36	**Labeled/Present:** Black pepper, fruit extract, turmeric powder
3		Curcumin Phytosome	37	**Labeled/Present:** Phospholipids, turmeric extract
	Possible	Collagen peptides	37	**Labeled/Present:** Peptides
4	Possible	Premium CLA 3-6-9	17	**Labeled/Present:** Conjugated linoleic acid, omega-3 and omega-6
5	Possible	GOLD STANDARD WHEY EXTREME MILK CHOCOLATE	22	**Labeled/Present:** Whey protein
6		GI Microbi-X	21	**Labeled/Present:** Tribulus extract, magnesium caprylate, berberine, bearberry extract, black walnut powder, barberry extract, artemisinin
	Highly Likely	GI Revive	21	**Labeled/Present:** Quercetin, MSM, prune powder, aloe vera leaf, glutamine, acetyl glucosamine, *Glycyrrhiza glabra*, slippery elm, chamomile, *Althaea officinalis* root, *Abelmoschus esculentus* fruit, cat's claw
7		DOSE	23	**Labeled/Present:** Dandelion, turmeric root extract, ginger powder, milk thistle extract
		iSatori L-Carnitine LS3 3000	23	No product received
		Turmeric Curcumin	23	**Labeled/Present:** Turmeric root extract
		Fenugreek	23	**Labeled/Present:** Fenugreek seed powder
		DHEA	23	**Labeled/Present:** DHEA
	Highly Likely	Nitric Oxide	23	**Labeled/Present:** Citrulline, arginine, taurine, norvaline, *Tribulus terrestris*, Muira puama, Asian ginseng
8		Turmeric + Ginger + ACV	17	**Labeled/Present:** Ginger root, black pepper fruit extract, turmeric root powder, hawthorn berry powder
	Highly Likely	Oil of Oregano with Black Seed Oil	17	**Labeled/Present:** Oil of oregano leaf, black seed oil

Abbreviations used: DHEA, dehydroepiandrosterone; MSM, methylsulfonylmethane. Highlighted product considered at least possible cause.

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4372 | ASSOCIATION OF GLP-1RA USE WITH LOWER SEPSIS AND URINARY TRACT INFECTION IN ALCOHOL-ASSOCIATED LIVER DISEASE

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Background: Individuals with alcohol-associated liver disease (ALD) are particularly vulnerable to infections due to compromised immune function. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) offer metabolic and anti-inflammatory advantages, but their impact on infection risk among ALD patients is not well established. This study evaluated whether GLP-1RA use influences infection-related outcomes in this population. **Methods:** Using the TriNetX database, we performed a retrospective cohort study comparing adults with ALD who initiated either GLP-1RA or metformin. Propensity score matching (1:1) was applied to balance key variables including demographics, comorbidities, and concomitant medications. The primary outcome was sepsis; secondary outcomes included urinary tract infection (UTI), pneumonia, spontaneous bacterial peritonitis (SBP), and Clostridioides difficile infection (CDI). Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazards models over a five-year follow-up. **Results:** After matching, the final cohort included 1,432 patients (716 in each group). GLP-1RA use was associated with a significantly lower risk of sepsis (HR 0.62, 95% CI 0.44–0.87) and UTI (HR 0.63, 95% CI 0.46–0.87) compared to metformin. A trend toward reduced pneumonia risk was noted (HR 0.72, 95% CI 0.51–1.02), though not statistically significant. No significant differences were observed for SBP, skin infections, or CDI. **Conclusion:** Among matched ALD patients, GLP-1RA therapy was linked to a lower risk of sepsis and UTI relative to metformin. These results suggest an added potential benefit of GLP-1RAs in this high-risk population and support further prospective investigation.

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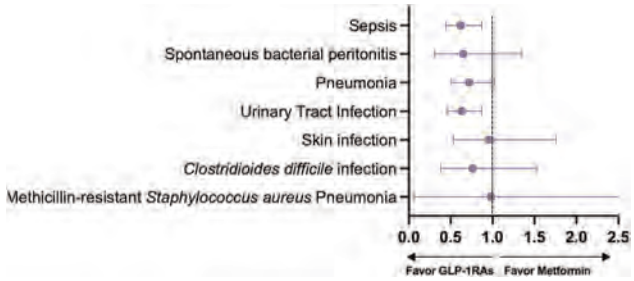

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4373 | UNCOVERING TWO CLINICAL PATTERNS OF IMMUNE-RELATED LIVER INJURY: METABOLIC DYSFUNCTION AS A KEY RISK FACTOR FOR THE PERSISTENT TYPE

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Background: Immune checkpoint inhibitors (ICIs) are widely used in cancer therapy, but immune-related liver injury (irLI) remains a major concern, especially in patients with preexisting liver disease. However, its

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pathological features and risk factors are not fully understood. To better understand its clinical course and underlying mechanisms, we aimed to analyze the clinical and histological features of irLI. **Methods:** A total of 1,512 patients who received immune checkpoint inhibitors between 2014 and 2023 were retrospectively reviewed. The diagnosis of irLI was made by hepatologists through systematic exclusion of other potential causes of liver injury, including tumor progression, biliary obstruction, viral hepatitis, autoimmune liver diseases, and other drug-induced hepatotoxicity. Liver biopsy was performed prior to prednisolone administration whenever deemed feasible by the attending hepatologist based on clinical evaluation. Both clinical and histopathological findings were thoroughly examined to categorize irLI and explore potential risk factors. **Results:** A total of 71 patients (4.7%) were clinically diagnosed with irLI. Based on the R ratio, injury was classified as cholestatic (n = 35, 47.3%), mixed (n = 26, 35.1%), and hepatocellular (n = 13, 17.6%). Clinically, irLI was categorized into transient-type ($\leq$40 days, n = 39) and persistent-type ($>$40 days, n = 32), based on the time for ALT to decline by 50%. Transient-type was more common in patients $<$75 years, while persistent-type was more frequent in those $\geq$75. Multivariable Cox analysis showed that baseline ALT elevation and metabolic comorbidity independently predicted persistent, but not transient irLI. Kaplan–Meier analysis confirmed a higher incidence of persistent irLI in patients with this risk profile. Liver biopsies were performed in 21 cases, and in 9, pre-treatment specimens were available, enabling comparison before and after irLI onset. In the transient group, liver tissue often showed hepatocellular injury with centrilobular necrosis and granulomas. In contrast, the persistent group more frequently showed fibrosis, portal inflammation, and coexisting steatohepatitis. Paired biopsies (n = 9) further revealed that persistent irLI was often preceded by histological steatohepatitis, which worsened after ICI therapy, suggesting a predisposing hepatic substrate for persistence. **Conclusion:** Our findings revealed two distinct clinical patterns of irLI: transient-type and persistent-type, each characterized by different risk profiles and histopathological features. Persistent-type irLI appears to result from pre-existing steatotic hepatitis, which may predispose patients to sustained hepatitis following ICI therapy. In patients with clinical features suggestive of steatotic liver disease, pre-treatment liver biopsy may help identify those at increased risk for persistent irLI and guide risk-adapted management strategies.

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4374 | RUST BELT ENVIRONMENTAL TOXICANTS TRANSFORM WESTERN DIET FROM METABOLIC CHALLENGE TO HEPATOTOXIC CRISIS IN MICE

hamda siddiqui[1] Shannon Heinig[1] Pooja Muddasani[1] Charis-Marie Vanderpuye[1] Jiang Li[1] Natalie Price[1] Zachary Zimmerman[1] Shuai Yuan[1] Sudrishti Chaudhary[1] Noriko Kitano[1] Gavin Arteel[1] Alison Sanders[1] Juliane Beier[1], [1]University of Pittsburgh

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects over 30% of Western populations with disproportionate impact on lower socioeconomic communities. While early-stage MASLD prevalence approaches 100% in at-risk individuals, progression to severe forms is not inevitable, suggesting additional risk factors drive disease severity. Environmental chemical mixtures may be such a risk factor and transform manageable dietary stress into severe liver injury. "Rust to Resilience" (R2R) chemical mixtures contain legacy toxicants (lead, cadmium, arsenic) and emerging PFAS relevant to industrialized countries and of high priority concern in southwestern Pennsylvania. This study investigated whether R2R-mixture exposure transforms Western diet-induced metabolic stress into severe hepatotoxicity. **Methods:** C57Bl/6J mice were fed Western or control diets for 12 weeks, with subgroups receiving R2R mixtures at 1× and 100× concentrations. Analysis included plasma biochemistry, histopathological assessment, and RNA-sequencing with integrated pathway analysis to determine molecular mechanisms of toxicant-diet interactions. **Results:** R2R-mixture exposure synergistically enhanced Western diet-induced liver injury, causing severe inflammation, coagulative necrosis, and portal expansion. Toxicant exposure promoted pathological lipid accumulation and hepatocyte ballooning - indicative of mitochondrial dysfunction. RNA-sequencing revealed that Western diet background amplified toxicant transcriptional responses 4.6-fold (137 vs 30 significant GO pathways) and uniquely enabled

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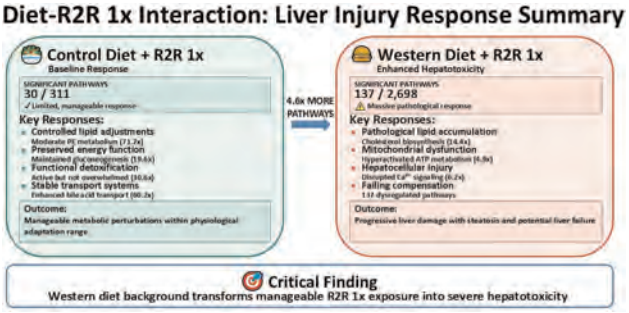
carcinogenic pathway activation absent under control diet conditions (15 vs 0 significant KEGG pathways). Western diet transformed manageable environmental exposure into severe hepatotoxicity characterized by metabolic dysregulation and activated carcinogenesis pathways. **Conclusion:** This study reveals a critical paradigm shift: environmental toxicant exposure doesn't merely add to Western diet-induced liver injury - it fundamentally transforms the hepatic response from metabolic adaptation to pathological crisis. Western diet creates a permissive environment where otherwise manageable environmental exposures trigger severe hepatotoxicity and activate carcinogenic pathways. These findings highlight complex environmental chemical exposure as a crucial risk-modifying factor explaining interindividual variability in MASLD progression.



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4375 | SEX-DEPENDENT HEPATOTOXICITY OF TRICHLOROETHYLENE IN HUMANIZED PPARA MICE FED A WESTERN DIET

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Background: Trichloroethylene (TCE), a commonly used industrial solvent, is linked to hepatic steatosis and metabolic dysfunction. Military personnel, their families and some civilians were exposed to TCE-contaminated drinking water at Camp Lejeune USMC Base between 1953 and 1987. TCE is known to activate peroxisome proliferator-activated receptor alpha (PPARα) in mice, but it is unclear whether human PPARα responds to TCE in the same manner. It is established that lipids activate mouse and human PPARα differently. Thus, we sought to test the hypothesis that TCE exposure exacerbates high fat diet-induced metabolic dysfunction and liver injury in a sex-dependent manner using a humanized PPARα mouse model. **Methods:** Male and female humanized PPARα C57BL/6J mice aged 9-12 weeks were placed on either a control diet (CD; 10% fat) or a Western diet (WD; 42% fat) with concurrent exposure to 0.5 mg/mL of TCE or 1% ethoxylated castor oil (used to emulsify TCE) in drinking water for 12 weeks. Body weight and water consumption were measured each week. A glucose tolerance test was performed at week 10 of exposure, and EchoMRI was performed at week 11. At week 12, blood and tissues were collected for measurement of plasma AST and ALT, tissue weights, and analysis of liver histopathology with H&E and Oil Red O. Statistical analyses were performed using two- and three-way ANOVA followed by Tukey's post hoc test, with significance set at $p \leq 0.05$. **Results:** TCE exposure combined with WD resulted in sex-specific effects. Male mice compared to females exhibited increased body weight, fat mass, white adipose tissue, and liver weight across all treatment groups. Analysis of the exact amount of TCE consumed by mice showed that females ingested significantly higher volumes across both dietary groups compared to their male counterparts. Amongst all groups, glucose tolerance was lower in response to WD in male mice only, and TCE did not affect this. Further, relative liver weight was increased by WD in males only, whilst TCE did not affect this. The only group amongst both sexes with elevated plasma AST and ALT was the male mice fed a WD and co-exposed to TCE. Histological analysis revealed enhanced steatosis in WD-fed males, regardless of TCE exposure, confirmed by H&E and Oil Red O staining. **Conclusion:** Generally, the study confirmed sex-specific differences hinging on diet and TCE exposure in humanized male and female mice. Male mice tend to be more susceptible to liver injury and toxicity but not their female counterparts.

Disclosures: Abigail Ekuban: Nothing to Disclose, Paxton Ames: Nothing to Disclose, Frederick Ekuban: Nothing to Disclose, Jianzhu Luo: Nothing to Disclose, Oluwanifemi Bolatami: Nothing to Disclose, Yuan Hua: Nothing to Disclose, Megana Iyer: Nothing to Disclose, Collette Gorga: Nothing to Disclose, Josiah Hardesty: Nothing to Disclose, Banrida Wahlang: Nothing to Disclose, Jennifer Schlezinger: Nothing to Disclose, Matthew Cave: Nothing to Disclose, Walter Watson: Nothing to Disclose

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4376 | LIVER INJURY INDUCED BY APAP IS ATTENUATED BY MESENCHYMAL STEM CELL-DERIVED SMALL EXTRACELLULAR VESICLES IN VITRO AND IN VIVO

Ana Serras[1] Sérgio Camões[1] Joana S Rodrigues[1] Joel Vej-Nielsen[2] Rui Vitorino[3] Busra Korkmaz[4] Gulcin Cakan-Akdogan[4] Joana Miranda[1], [1]Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, [2]Department of Biochemistry and Molecular Biology, University of Southern Denmark, [3]LAQV/REQUIMTE, Mass Spectrometry Center; iBiMED, Universidade de Aveiro, [4]Izmir Biomedicine and Genome Center

Background: Drug-induced liver injury, including by paracetamol (APAP) overdose, is the most common cause of acute hepatic failure but current treatments present important limitations. Human neonatal mesenchymal stem cells (MSC) can constitute an alternative treatment as it has been shown that the MSC-derived secretome and small extracellular vesicles (sEV) present important immunomodulatory and regenerative effects. Physiologically, MSC adapt and respond to the microenvironment and we have previously shown that MSC primed with SOS signals from APAP-injured hepatic cells have an upregulated pro-regenerative genetic profile. As such, the aim of this study was to unravel the role of sEV derived from primed MSC on liver regeneration. **Methods:** MSC were primed with the SOS signals of APAP-injured HepG2 (pMSC) for collection of the secretome and subsequent isolation of sEV by size-exclusion chromatography. sEV were characterized by nanoparticle tracking analysis, western blot and GE-LC-MS/MS proteomics. APAP-injured hepatocyte-like cells (HLCs) were treated with sEV 1 μg/mL to assess cell viability (MTS) and gene expression (RT-qPCR). Liver reported transgenic zebrafish (2 to 5 dpf) were treated concomitantly with 5 mM of APAP and sEV 20 μg/mL and liver area was measured. **Results:** sEVs kept their physicochemical characteristics after priming with the SOS signals. The proteomic analysis showed that MSC priming promoted a higher secretion of proteins related to stress, extracellular matrix organization and metabolic process regulation. Specifically, proteins which have been functionally linked to cell proliferation, inflammation and oxidative stress regulation, *e.g.,* apolipoprotein E or apolipoprotein A, have been found to be upregulated or unique to the primed condition. Importantly, treatment of APAP-injured HLCs with sEV-pMSC led to an increase of 30% in cell viability as well as a reversion of proliferation- (*e.g., ccnd1, c-met*), oxidative stress- (*e.g., gss, cyp2e1*) and metabolism-associated genes (*e.g., fas*) to levels similar to the basal state. Most interestingly, treatment of injured zebrafish with sEV-pMSC diminished the extent of liver injury promoted by APAP. **Conclusion:** Our results indicate that priming of MSC with hepatic SOS signals resulted in a pro-regenerative enriched sEV cargo, which further promoted hepatocyte regeneration *in vitro* and decreased liver injury *in vivo*.

Disclosures: Ana Serras: Nothing to Disclose, Sérgio Camões: Nothing to Disclose, Joana S Rodrigues: Nothing to Disclose, Joel Vej-Nielsen: Nothing to Disclose, Rui Vitorino: Nothing to Disclose, Busra Korkmaz: Nothing to Disclose, Gulcin Cakan-Akdogan: Nothing to Disclose, Joana Miranda: Nothing to Disclose

4377 | REAL-WORLD INCIDENCE OF LIVER ENZYME ELEVATION DUE TO MEDICATIONS IN HOSPITALIZED INDIVIDUALS: CHALLENGES AND OPPORTUNITIES OF USING BIG DATA TO STUDY HEPATOTOXICITY

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Background: Liver injury from medications poses a significant risk, especially in inpatients, where polypharmacy is common. Traditional hepatotoxicity risk assessments rely heavily on case reports or small cohorts, limiting generalizability. We aimed to leverage a large database for an unbiased assessment of medication-associated liver enzyme (LE) increases. **Methods:** We used the MIMIC-IV database, containing all admissions to BIDMC (Boston, MA) between 2008-2019. We included hospital admissions with length of stay (LOS) $\geq$ 3 days, that had $\geq$2 documented LE tests, baseline ALT $\leq$ 70 U/L, AST $\leq$ 70 U/L, ALP $\leq$ 150 U/L and total bilirubin $\leq$ 1.5 mg/dL, and no major confounding diagnoses such as chronic liver disease or shock. Primary endpoint was LE increase defined as ALT, AST or ALP increase $>$2X the patient's baseline at any time during admission. List of medications administered prior to LE increase was evaluated. Cases of LE increase were matched to controls with a 1:4 optimal pair matching on LOS and admission unit. Medication-specific incidence rates were calculated, and logistic regression identified medication associations with elevated LE. **Results:** Of 546,028 admissions, 19,729 met inclusion criteria. Most admissions were excluded due to LOS $<$3 days, or LE checked $<$2 times. 585 patients (3.0%) met the primary endpoint of LE increase. Among medications with the highest crude incidence were high-dose methotrexate (MTX), fosphenytoin, and neostigmine. After adjusting for age, sex, baseline AST & ALT, only four medications—high-dose MTX, neostigmine, phenylephrine, and fospropofol—

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were significantly associated with LE increase (FDR $q < 0.05$).(Table) In MTX, 64% of discharge notes attributed liver injury to treatment, while association with neostigmine was likely confounded by cardiac unit admissions, suggesting surgical, hemodynamic factors or a myocardial source for LE elevation rather than hepatotoxicity. **Conclusion:** Large-scale clinical data enables identification of both known and less studied potential drug-induced liver injury causes. Our unbiased approach validated known hepatotoxicity of high-dose MTX as a positive control and highlighted the importance of considering confounding factors. Despite limitations in confounding and diagnostic specificity, this method may represent an important advance in pharmacoepidemiologic research on hepatic safety. These inpatient findings may differ from outpatient patterns due to different medication exposures and populations, warranting comparative studies.

Table. Example of unadjusted and adjusted odds ratio of acute elevation of LE with 95% CI for top-3 medications with the highest incidence of LE elevation in the cohort. Results are derived from separate logistic regression models for each medication.

Medication (likelihood score of causing liver injury (LiverTox))	Crude incidence of elevated LE (%)	Univariable analysis			Multivariable analysis			
		OR	CI	p-value		OR	CI	p-value
Methotrexate, high-dose (A, high-dose)	46.8	3.69	2.34-5.80	<0.0001	Methotrexate, high-dose	3.72	2.35-5.94	<0.0001
					Age (per year)	0.992	0.987-0.998	0.006
					Female	0.89	0.74-1.07	0.21
					AST baseline (per one U/L)	1.02	1.01-1.03	<0.0001
					ALT baseline (per one U/L)	1.02	1.01-1.02	<0.0001
Fosphenytoin (A)	29.8	1.72	0.94-3.01	0.06	Fosphenytoin	1.66	0.90-2.92	0.09
					Age (per year)	0.991	0.986-0.997	0.002
					Female	0.88	0.73-1.06	0.17
					AST baseline (per one U/L)	1.02	1.01-1.02	<0.0001
					ALT baseline (per one U/L)	1.02	1.01-1.02	<0.0001
Neostigmine (X, unknown)	33.0	2.04	1.34-3.05	0.0007	Neostigmine	2.08	1.36-3.15	0.0006
					Age (per year)	0.991	0.986-0.996	<0.0001
					Female	0.86	0.71-1.03	0.1
					AST baseline (per one U/L)	1.02	1.01-1.02	<0.0001
					ALT baseline (per one U/L)	1.02	1.01-1.02	<0.0001

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4378 | ANALYSIS OF THE PROSPECTIVE TURKISH DRUG-INDUCED LIVER INJURY REGISTRY

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Background: Numerous drugs can fundamentally cause hepatotoxicity through a variety of mechanisms. The clinical spectrum of drug-induced liver injury (DILI) is different among countries. Prospective DILI registries are important sources of detailed information on DILI. In the present study, we aimed to determine patients with DILI enrolled in the Turkish DILI Registry. **Methods:** This prospective multicenter study focuses on identifying patients with DILI. Data collection and patient enrolment in this registry were conducted according to international guidelines. The data included clinical features, drug information, and disease outcomes. **Results:** A total of 131 patients who fulfilled the criteria of DILI were enrolled in this registry between January 2022 and January 2025. Sixty percent of the patients were female. The median age was 45.2 years (range:18-84 years). The predominant liver injury pattern was hepatocellular (76.3%), followed by a mixed pattern (13.0%) and a cholestatic pattern (10.7%). According to the RUCAM scale, the classification was probable in 55% of patients, highly probable in 26.7%, possible in 15.3%, and unlikely in 3.1%. Liver biopsy was performed in 24% of the patients. Acute hepatocellular liver injury was the most common histopathological feature (76.3 %).

The causative agents were mainly drugs in 111 patients (84.7%), followed by herbal and dietary supplements (13.7%). The main groups of drugs included antimicrobials (41.5%), followed by nonsteroidal anti-inflammatory drugs (19.8%), and anti-neoplastic drugs (6.1%). Amoxicillin/clavulanate was the most frequently implicated antibiotic (13.7%), followed by ornidazole (10.7%).

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Hospitalization was necessary for 101 patients (77,1%). Treatment was initiated in 79 patients, with N-Acetylcysteine being the most commonly used. Recovery was observed in 105 patients. The mean time for serum ALT values to return to normal was 61.7 days among recovered patients. Chronicity occurred in 3 three patients. Three patients underwent liver transplantation due to DILI-induced acute liver failure. Three patients died as a result of the progression of their primary diseases. Additionally, sixteen patients were lost to follow-up. **Conclusion:** DILI registry is a valuable tool for determining the causative agents, clinical features, and prognostic factors associated with disease outcomes in patients with DILI.

Disclosures: Ali Rıza Caliskan: Nothing to Disclose, sezgin vatansever: Nothing to Disclose, Serkan Yaras: Nothing to Disclose, İlker Sen: Nothing to Disclose, Mujdat Zeybel: Nothing to Disclose, Dilara Turan Gokce: Nothing to Disclose, Meral Akdoğan Kayhan: Nothing to Disclose, Dinc Dincer: Nothing to Disclose, Gulsah Fidan Ozkumur: Nothing to Disclose, Elvan Isık: Nothing to Disclose, Fulya Günşar: Nothing to Disclose, Zeki Karasu: Nothing to Disclose, Coskun Ozer Demirtas: Nothing to Disclose, Tugba Tolu: Nothing to Disclose, Volkan YILMAZ: Nothing to Disclose, Emin Bodakci: Nothing to Disclose, Galip Büyükturan: Nothing to Disclose, Cemal Nuri Ercin: Nothing to Disclose, Ramazan Idılman: Nothing to Disclose

4379 | THE IMPACT IMMUNE-MEDIATED HEPATOTOXICITY ONSET ON LONG-TERM PROGNOSIS IN PATIENTS WITH ADVANCED CANCER WHO RECEIVED IMMUNE CHECKPOINT INHIBITORS

Yu Akazawa[1] Takuto Nosaka[1] Yosuke Murata[1] Tomoko Tanaka[1] Tatsushi Naito[1] Kazuto Takahashi[1] Masahiro Ohtani[1] Yasunari Nakamoto[1], [1]Department of Gastroenterology, Faculty of Medical Sciences, University of Fukui

Background: With the widespread use of immune checkpoint inhibitors (ICIs), the diagnosis and treatment of immune-related adverse events (irAEs) has become increasingly important. Immune-mediated hepatotoxicity (IMH) is one of the most common irAEs, and in recent years, novel diagnostic guidelines for IMH have been published in Western and Japan. However, the impact of IMH on long-term prognosis in patients with advanced cancer has varied among previous reports, and remain unclear. The aim of this study was to clarify the association between development of IMH and long-term prognosis in patients with advanced cancer who received ICIs. **Methods:** The patients with advanced cancer who received ICIs from September 2014 to December 2024 in our department were enrolled for this retrospective study. In enrolled patients, the incidence of IMH was evaluated, and long-term prognosis including overall survival compared between the two groups with IMH and non-IMH using the Kaplan-Meier method. In addition, we performed landmark analysis on three time points (3, 6, and 12 months) to control immortal-time bias. The diagnosis and grading of irAEs including IMH were defined according to CTCAE version 5.0, and adverse events of $\geq$ Grade 2 were extracted. **Results:** A total of 966 patients (691 males, 275 females; median age, 71.1 years) were enrolled in this study. Of all, 87 patients (9.0%) developed IMH: Grade 2 (G2), Grade 3, and Grade 4 in 52 (5.4%), 31 (3.2%), and 4 (0.4%) patients, respectively. The median time from the first administration of ICI to the onset of IMH was 51.0 days. The types of liver damage in IMH patients were hepatocellular, cholestatic, and mixed damage in 66.7% (58/87), 8.0% (7/87), and 25.3% (22/87), respectively. Also, the multivariate analysis revealed the onset of irAE ($\geq$G2) in other organs ($p < 0.001$) and ICI combination therapy ($p = 0.004$) were significantly independent factors associated for the onset of IMH. The median OS in the IMH onset group was significantly longer than that in non-IMH onset group (not reached vs 440 days, $p < 0.001$). Also, in the 3- ($p = 0.013$) and 6-month ($p = 0.025$) landmark analysis, patients who developed IMH had significantly better OS than those who did not, consistent with the findings of the conventional analysis. In addition, the group of patients with irAE onset in multiple organs had significantly better OS than the other groups, including the groups of patients with irAE onset in a single organ and no irAE onset ($p < 0.001$), and the results of landmark analysis (3-, 6-, and 12-month) were consistent with those of conventional analysis. **Conclusion:** The onset of IMH was closely associated with the better long-term prognosis in patients with advanced cancer who received ICIs. This finding suggests that early detection and thorough management for IMH may result in sufficient anti-tumor effects, which contribute to improve survival in patients with ICIs.

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4380 | PREDICTIVE MODEL FOR CHOLESTATIC DRUG-INDUCED LIVER INJURY

Jie Liu[1] Lili Zhao[1] Ping Han[2] Yuying Jin[3] Jia Li[1], [1]Department of Hepatology, Tianjin Second People's

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Background: Drug-induced liver injury (DILI) is one of the important causes of acute liver injury. Biochemical and histological injury types were classified as hepatocellular, cholestatic or mixed injury. The cholestatic DILI has longer and poor prognosis. Therefore, it is very important to identify the type of DILI as early as possible. There is still a lack of sensitive biochemical indicators in clinic. Although liver pathology is the gold standard for diagnosis, it is an invasive examination and may cause certain risks to patients, so its clinical application is limited. The Roussel Uclaf causality assessment method used the R value to distinguish cholestatic DILI. But R value was considered to have underestimated the proportion of cholestatic DILI. Therefore, this study collected biochemical indicators of patients who diagnosed as DILI by liver pathology, analyzed the characteristics of each indicators and established prediction models, trying to provid a new idea for diagnosis of cholestatic DILI. **Methods:** Patients with hepatic pathological diagnosis of DILI in Tianjin Second People's Hospital and Tianjin First Central Hospital from July 2012 to December 2024 were retrospectively analyzed. The clinical data of patients during hospitalization were collected and analyzed. The patients were divided into cholestatic group and non-cholestatic group based on the liver pathology of cholestatic drug-induced liver injury. Then we summarized the clinical characteristics of patients with cholestatic DILI, and established the cholestatic drug-induced liver injury prediction model. **Results:** A total of 480 patients with DILI were collected in this study, including 220 (41.8%) patients with cholestatic DILI and 260 (54.2%) patients with non-cholestatic DILI. According to univariate analysis, there were significant differences in peak severity, peak ALP, peak GGT, peak TBIL, peak DBIL, peak TBA, peak INR, peak PT, peak PTA, peak TG, peak ALB, peak PA and peak CHE between the two groups ($P < 0.05$). Based on the multivariate analysis and clinical recommendations, peak TBA, peak PTA, peak TG, peak ALP, peak GGT and peak CHE were incorporated into the nomogram model with high prediction accuracy and the area under ROC curve was 0.75. Using peak TBA predict cholestatic DILI, the area under ROC curve is also 0.75. The sensitivity and specificity of the nomogram model were 0.645 and 0.745. Using peak TBA predict, the sensitivity and specificity were 0.775 and 0.589. **Conclusion:** Peak TBA can predict cholestatic DILI perfectly, the sensitivity is higher and recommend it for preliminary clinical screening for cholestatic drug-induced liver injury. The nomogram model established with six variables including peak TBA, peak PTA, peak TG, peak ALP, peak GGT and peak CHE has high specificity. We recommend it for further diagnosis.

Table 1. Baseline table of patients.

Variable	All (N=480)	Non-Cholestasis (N=260)	Cholestasis (N=220)	*P* value
Gender:				0.371
Male	324(67.5%)	181(69.7%)	142(64.5%)	
Female	156(32.5%)	79(30.4%)	78 (35.5%)	
Age(year)	50.5 (40.0-58.0)	49.5 (40.0-57.0)	52.0 (40.0-59.0)	0.307
R value	8.75 (2.73-19.3)	8.15 (2.58-18.2)	9.70 (3.45-22.8)	0.200
Severe:				
1	179 (37.2%)	122 (46.9%)	53 (23.1%)	
2	278(57.9%)	129 (49.6%)	151 (69.1%)	
3	23 (4.9%)	9 (3.46%)	16 (7.3%)	
ALT(U/L)	559 (182-1090)	303 (164-1050)	611 (237-1160)	0.278
AST(U/L)	454 (136-803)	372 (124-740)	521 (172-842)	0.039
ALP(U/L)	161 (114-231)	144 (102-209)	176 (133-250)	<0.001
GGT(U/L)	223 (122-375)	194 (96.8-349)	264 (164-434)	<0.001
TBIL(μmol/L)	63.2 (20.4-163)	41.4 (16.2-143)	99.0 (35.9-197)	<0.001
DBIL(μmol/L)	38.9 (7.23-121)	19.7 (5.77-104)	72.8 (17.8-160)	<0.001
TBA(μmol/L)	35.0 (9.60-133)	15.8 (5.00-82.8)	88.5 (26.2-168)	<0.001
INR	1.00 (0.93-1.10)	1.00 (0.90-1.03)	1.00 (0.99-1.15)	<0.001
PT(s)	12.6 (11.3-13.8)	12.5 (11.2-13.4)	12.8 (11.5-14.3)	0.026
PTA(%)	109 (97.0-120)	110 (101-122)	105 (93.0-118)	0.013
TC(mmol/L)	5.27 (4.47-6.07)	5.14 (4.50-5.99)	5.50 (4.47-6.18)	0.081
TG(mmol/L)	2.14 (1.48-3.08)	1.91 (1.35-2.75)	2.38 (1.72-3.40)	<0.001
ALB(g/L)	37.2±5.04	38.4±4.71	35.5±4.99	<0.001
PA(mg/L)	116 (60.8-186)	135 (74.6-207)	94.5 (54.0-157)	0.001
CHE(U/L)	6423±1930	6829±1816	5859±1950	<0.001
AFP(ng/ml)	5.70 (3.30-13.4)	4.48 (2.83-9.57)	6.53 (3.80-19.2)	<0.001

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase GGT: gamma-glutamyl transpeptidase; TBIL:total bilirubin; DBIL:direct bilirubin; TBA: total biliary acid; INR: international normalized ratio; PT: prothrombin time; PTA: prothrombin activity; TC: total cholesterol; TG: triglyceride; ALB: albumin; PA: prealbumin; CHE: cholinesterase; AFP: alpha fetoprotein

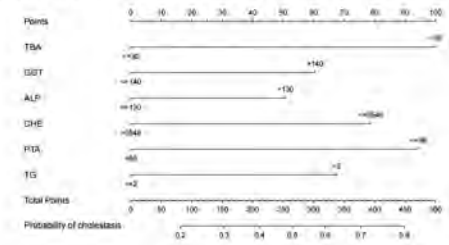

Figure. The nomogram model for cholestatic type DILI

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4381 | IMMUNE CHECKPOINT INHIBITOR HEPATITIS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: DIAGNOSTIC COMPLEXITY, SHORTER ONSET, AND DELAYED BIOCHEMICAL RECOVERY

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Background: Diagnosis and management of immune checkpoint inhibitor (ICI) hepatitis are complex in patients with hepatocellular carcinoma (HCC) due to underlying liver disease and liver tumor burden. We

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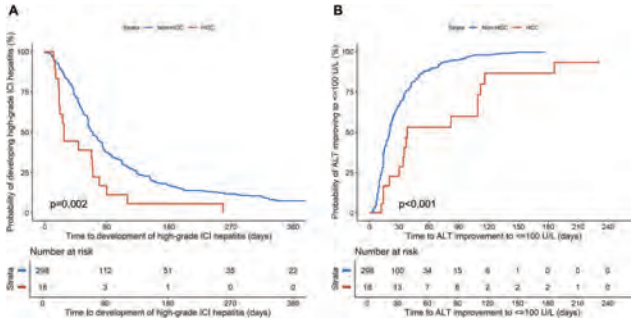
investigated diagnostic challenges and compared outcomes of ICI hepatitis in patients with HCC versus non-HCC cancers. **Methods:** In this multicenter, retrospective cohort study, all HCC patients who received corticosteroid treatment for suspected high-grade ICI hepatitis from one center were reviewed by two specialists who independently performed RUCAM causality assessments to adjudicate ICI hepatitis cases. True cases were compared to a non-HCC multicenter cohort of high-grade ICI hepatitis. The primary outcome was biochemical recovery, defined as time to ALT improvement to $\leq$100 U/L (grade 1 per CTCAE criteria) after corticosteroid initiation. **Results:** Out of 350 ICI-treated HCC patients, 25 received $\geq$0.5 mg/kg/day of prednisone for suspected ICI hepatitis. After adjudication, 18 (72%) were assessed as true cases; 6/7 false cases were attributed to cancer progression. When compared to ICI monotherapy, dual checkpoint inhibition was associated with increased hepatitis risk (RR 2.7, 95% CI 1.7-4.3, $p < 0.001$).

When compared to 298 non-HCC patients with ICI hepatitis, HCC cases had higher pre-ICI liver tests (median AST: 66 vs 21; ALT: 65 vs 19; bilirubin: 0.9 vs 0.5; alkaline phosphatase: 181 vs 76; $p < 0.001$ for all tests), though peak liver tests after developing ICI hepatitis were similar between the two groups. HCC patients had shorter time to development of high-grade ICI hepatitis (median 28 vs 70 days, log-rank $p = 0.002$; Fig A) when compared to non-HCC patients, including after multivariable adjustment (HR 1.9, 95% CI 1,1-3.1, $p = 0.017$). Fifteen (83%) HCC cases and 295 (99%) non-HCC cases reached the outcome of biochemical recovery. HCC cases had longer time to biochemical recovery (median 38 vs 20 days, log-rank $p < 0.001$; Fig B) compared to non-HCC cases, including after adjusting for ALT level at time of corticosteroid initiation, presence of liver tumors, and dual checkpoint inhibition (HR 0.3 for HCC, 95% CI 0.2-0.6, $p < 0.001$). **Conclusion:** Diagnosing ICI hepatitis in HCC patients can be challenging due to potential competing etiologies for elevated liver tests, and imaging to rule out liver tumor progression is prudent. HCC patients develop ICI hepatitis faster than non-HCC patients and experience slower biochemical recovery after steroid treatment.



Disclosures: Isaac Benque: Nothing to Disclose, Jordan Sack: Nothing to Disclose, Shilpa Grover: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Stephen Zucker: Nothing to Disclose, Michael Li: Nothing to Disclose

4382 | ANTITUBERCULAR THERAPY INDUCED HEPATITIS IN CHILDREN: INCIDENCE, RISK FACTORS, ROLE OF CYTOKERATIN 18 AND OUTCOME

Shivani Randev[1] Aakanksha Mangotra[1] Seema Gupta[2] Pankaj Kumar[2] Vishal Guglani[2], [1]Government Medical College and Hospital, Chandigarh, [2]Government Medical College and Hospital

Background: Drug-induced liver injury (DILI) is a significant complication of antitubercular therapy (ATT) in children. Early identification of at-risk patients is crucial to prevent severe hepatotoxicity and treatment interruptions. Current monitoring relies heavily on clinical symptoms and liver function tests(LFT), which may rise only after significant liver injury has occurred, thus, highlighting need for a reliable biomarker for early detection. This study aimed to evaluate clinical and biochemical predictors of DILI in children receiving ATT, with a focus on cytokeratin18(CK18) as a potential early biomarker. **Methods:** This prospective observational cohort study included 136 children diagnosed with tuberculosis. Patients were followed clinically for up to 24 weeks after initiation of ATT. Liver function tests (LFTs) were conducted at baseline and at 2, 4, 8, and 12 weeks post-ATT initiation, and additionally if symptoms suggestive of DILI appeared. CK18 levels were measured at baseline, 2 weeks, and at the time of DILI diagnosis. **Results:** DILI developed in 26 (19.1%; 95% CI: 13.1–26.9) patients at a median of 6.5 (IQR:11.5—31) days after ATT initiation. Patients who developed DILI were less likely to have Mantoux positivity, had lower body mass index (BMI) and serum albumin and higher mean rifampicin dose ($p < 0.05$). Nine patients (34%) developed a recurrence of DILI after re-initiation of ATT. Factors significantly associated with occurrence of DILI were BMI of less than 13 Kg/m^2 BSA [OR 4.38 (1.74-11.01)], Rifampicin dose $\geq$ 13mg/kg/day [OR 4.58 (1.48-14.18)], Pyrazinamide dose $\geq$ 35mg/kg/day [OR 3.37 (1.08-10.52)]; baseline ALT $>$ 27 IU/L [OR2.70 (1.08-6.73)]; 2-week ALT $>$ 76 IU/L [OR 103.31 (23.7-450.27)]. Baseline serum CK18 level above 17892 units/L and 2-week level above 9693 units/L were seen to have a significant association with occurrence of DILI, with the area under ROC curve of 0.523 (95% CI:0.293 - 0.754) and 0.61 (95%CI:0.423 - 0.797),

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respectively ($p > 0.05$). The time taken for resolution of DILI and re-initiation of the first ATT drug was 13.71 ± 10.18 days. The total duration from DILI onset to full reintroduction of ATT ranged from 12 to 87 days, with a median duration of 27.50(IQR 16-47) days. **Conclusion:** Approximately one in five pediatric patients on ATT develop DILI. Monitoring ALT levels, especially in those with identifiable risk factors, may aid early diagnosis. Although CK18 shows promise as an early biomarker for DILI, further validation is needed.
Disclosures: Shivani Randev: Nothing to Disclose, Aakanksha Mangotra: Nothing to Disclose, Seema Gupta: Nothing to Disclose, Pankaj Kumar: Nothing to Disclose, Vishal Guglani: Nothing to Disclose

4383 | REAL-TIME HEPATIC SURVEILLANCE IN RESIDENTS FOLLOWING THE EAST PALESTINE, OH CHEMICAL DISASTER

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Background: The February 2023 train derailment in East Palestine, Ohio, released vinyl chloride and other hepatotoxic chemicals, creating urgent need for health surveillance. This study represents the first systematic liver function assessment in residents potentially exposed to these environmental toxicants, establishing critical baseline data for long-term health monitoring. **Methods:** Adults ≥18 years within 8 miles of the derailment site have been recruited since June 2024. Participants provided informed consent for blood sampling and complete questionnaires on demographics, alcohol consumption, medical history, and health status. Liver function was assessed via serum ALT and AST levels. Body mass index (BMI) was calculated from measured anthropometric data. **Results:** To date, 47 participants enrolled (mean age 65.9 years, range 32-81), representing robust community response. All participants self-identified as White. Mean BMI was 29.0 kg/m² with 25% overweight (BMI 25-29.9 kg/m²) and 56% obese (BMI ≥30 kg/m²). Alcohol consumption: 75% drank <4 times weekly, 19% abstained, and 6% consumed alcohol ≥4 times weekly. Mean liver enzyme levels remained within normal ranges: ALT 18.25 U/L (7-56 U/L) and AST 20.13 U/L (10-40 U/L). Only one participant demonstrated elevated ALT (48 U/L); this individual had BMI of 30 and abstained from alcohol, while all others exhibited normal values. No correlation was observed between enzyme levels and alcohol consumption or BMI. As recruitment remains active, these preliminary findings may evolve. **Conclusion:** This pioneering surveillance study reveals preliminary findings: despite potential vinyl chloride exposure, the vast majority demonstrate normal liver enzyme levels, though traditional biomarkers ALT and AST may not detect early hepatotoxicity. Continued vigilance remains essential, as one participant showed ALT elevation warranting monitoring. Future analyses of the bio banked samples will include CK-18, which has demonstrated superior predictive value for vinyl chloride-related liver damage. These baseline data enable longitudinal tracking of hepatic health in this uniquely exposed population. This study represents a critical model for environmental health response with implications extending beyond East Palestine to communities worldwide facing similar toxicant exposure threats.
Disclosures: Olisa Okonkwo: Nothing to Disclose, Alexander Monroe: Nothing to Disclose, Kimberly Stello: Nothing to Disclose, James Fabisiak: Nothing to Disclose, Carla Ng: Nothing to Disclose, Fredrick Schumacher: Nothing to Disclose, Maureen Lichtveld: Nothing to Disclose, Juliane Beier: Nothing to Disclose

4384 | EXPRESSION OF IL-8, IL-10, AND CXCL-14 IN LIVER TISSUES OF PATIENTS WITH DRUG-INDUCED LIVER INJURY AND THEIR ASSOCIATION WITH PATHOLOGICAL FEATURES

diandian Hao[1] Xiaoyu Wen[2] JiaLin Du[3], [1]The First Hospital of Jilin University, [2]15804301609@163.com, [3]dujl9907@163.com

Background: Drug-induced liver injury (DILI) is a clinically significant hepatic disorder with complex pathogenesis involving interactions among drug-metabolizing enzyme abnormalities, host genetic susceptibility, and immune responses. Cytokines play pivotal roles in DILI progression, yet the expression profiles of IL-8, IL-10, and CXCL-14 in liver tissues and their associations with pathological features remain unclear. This study aimed to investigate the clinical and pathological characteristics of DILI patients, quantify hepatic IL-8, IL-10, and CXCL-14 expression, and evaluate their roles in DILI pathogenesis, particularly CXCL-14's regulatory mechanisms and potential as a prognostic biomarker. **Methods:** Forty DILI patients (diagnosed via liver biopsy with confirmed drug/environmental toxin exposure) from Jilin University First Hospital (January 2023–August 2024) and 10 healthy controls were enrolled. Immunohistochemistry (IHC) was performed to quantify IL-8, IL-10, and CXCL-14 expression in liver tissues. Pathological features (inflammatory activity, fibrosis stage, clinical subtypes) were analyzed. Statistical analyses, including Spearman's correlation and logistic regression, were conducted using SPSS 27.0. **Results:**

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Among 40 DILI patients (90% female, mean age 50 years, BMI 22.7 kg/m²), herbal decoctions/proprietary Chinese medicines accounted for 47.5% of causative agents. Pathological subtypes exhibited distinct features: Cholestatic type: bile stasis in hepatocytes/canaliculi, intrahepatic pigment deposition, microvesicular steatosis. Hepatocellular injury type: interface hepatitis, spotty necrosis, hydropic degeneration, mixed inflammatory infiltration. Mixed type: combined features. Compared to controls, DILI patients showed significantly elevated IL-8, IL-10, and CXCL-14 expression (all $P < 0.05$) (Fig.1). IL-8 and CXCL-14 levels varied significantly across inflammatory activity grades and fibrosis stages (all $P < 0.05$). Spearman analysis revealed positive correlations between cytokine levels (IL-8, IL-10, CXCL-14) and inflammatory activity ($r = 0.53$, 0.43, 0.37; $P < 0.05$), as well as associations of IL-8 and CXCL-14 with fibrosis ($r = 0.36$, 0.38; $P < 0.05$). CXCL-14 correlated positively with AST and GGT ($r = 0.381$, 0.404; $P < 0.05$) and independently predicted poor prognosis (OR = 0.786, 95% CI: 0.633–0.975, $P = 0.028$), outperforming traditional biomarkers. **Conclusion:** DILI predominantly affects elderly females, with herbal agents as leading triggers. Early drug withdrawal and standardized treatment yield favorable outcomes in most patients.IL-8 and CXCL-14 demonstrate significant associations with inflammation and fibrosis progression, highlighting their utility in evaluating disease severity. CXCL-14 emerges as an independent prognostic risk factor, offering superior sensitivity/specificity over conventional biochemical markers.

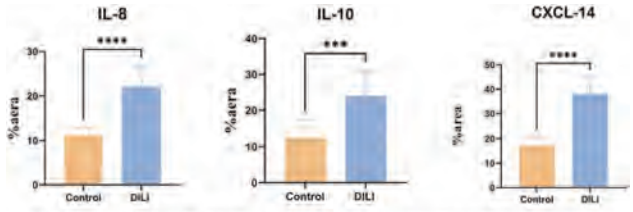


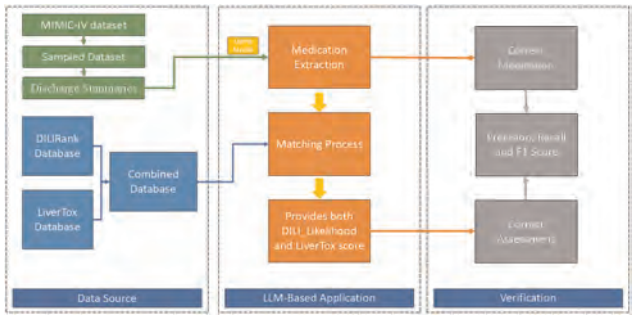
Fig.1 Comparison of IL-8, IL-10, and CXCL-14 levels between the DILI group and the healthy control group

Disclosures: diandian Hao: Nothing to Disclose, Xiaoyu Wen: Nothing to Disclose, JiaLin Du: Nothing to Disclose

4385 | ENABLING DILI SURVEILLANCE THROUGH AUTOMATED MEDICATION EXTRACTION FROM CLINICAL NOTES: A REAL-WORLD LLM VALIDATION STUDY

Thanathip Suenghataiphorn[1] Kanachai Boonpiraks[2] Vitchapong Prasitsumrit[3] Narathorn Kulthamrongsri[4] Pojsakorn Danpanichkul[5], [1]Yale/Griffin Hospital, [2]University of Kansas Medical Center, [3]Texas Tech Lubbock Health Science Center, [4]University of Hawaii, [5]Texas Tech University Health Sciences Center

Background: Drug-induced liver injury (DILI) presents a significant diagnostic challenge often leading to delayed detection. Unstructured clinical notes contain comprehensive medication data vital for DILI surveillance but are difficult to analyze systematically. Large language models (LLMs) show promise for automated extraction but require real-world clinical data validation to assess feasibility for clinical applications like DILI surveillance. **Methods:** We retrospectively validated an LLM system on 100 randomly sampled MIMIC-IV discharge summaries. Gold standard unique medication lists were derived via manual annotation and manual deduplication based on normalized drug names. LLM outputs underwent identical deduplication. Performance was assessed using precision, recall, and F1-score comparing deduplicated lists. MIMIC-IV DUA compliance was ensured. **Results:** Comparison yielded a precision of 0.85, recall of 1.00, and an F1-score of 0.92 for unique medication identification. The 174 false positives resulted from parsing or normalization errors; no medication hallucinations occurred. A subsequent DILI database lookup failed for approximately 6.2% of correctly identified unique medications, evaluated as a separate feasibility measure. **Conclusion:** The LLM demonstrates high accuracy and perfect recall for unique medication extraction and identification from complex clinical notes, establishing technical feasibility. This represents a feasible and possible integration of large language model towards developing automated tools for enhanced DILI surveillance and improved patient safety.



Disclosures: Thanathip Suenghataiphorn: Nothing to Disclose, Kanachai Boonpiraks: Nothing to Disclose, Vitchapong Prasitsumrit: Nothing to Disclose, Narathorn Kulthamrongsri: Nothing to Disclose, Pojsakorn Danpanichkul: Nothing to Disclose

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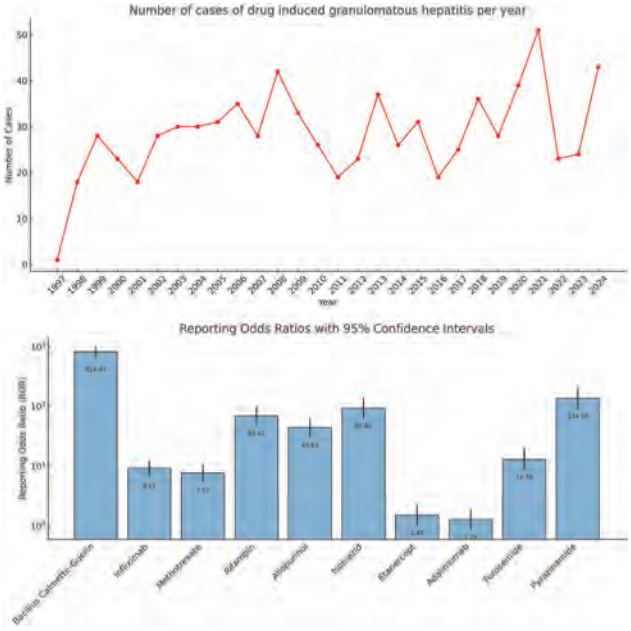
4386 | DRUG INDUCED GRANULOMATOUS HEPATITIS – A DISPROPORTIONALITY ANALYSIS USING THE FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) DATABASE

Rohan Karkra[1] Mahinaz Mohsen[1] Sameer Rao[1] Ritik Mahaveer Goyal[1] Drew Fletcher[1] Ahmed Al-Khazraji[1] Paul Gaglio[1], [1]Rutgers New Jersey Medical School

Background: Granulomatous hepatitis is a form of chronic liver inflammation characterized by the presence of organized macrophages in the form of granulomas. These granulomas can result from various etiologies, including infections (e.g., tuberculosis, fungal infections), systemic diseases (e.g., sarcoidosis), drug reactions, and idiopathic causes. Clinically, it often presents with fevers, chills, night sweats, weight loss, and elevated liver enzymes, particularly alkaline phosphatase and γ-glutamyl-transferase. This is a real world pharmacovigilance study evaluating medications suspected to be associated with drug induced granulomatous hepatitis. **Methods:** The Food and Drug Administration (FDA) maintains the Adverse Event Reporting System (FAERS) database. As of December 31, 2024, the database contained 30,179,725 reported events. This database was queried to identify all reported cases of 'Granulomatous Liver Disease'. All medications implicated were identified by their generic names. The database does not report how the diagnosis was confirmed, or whether other causes were ruled out. A disproportionality analysis was conducted, wherein Reporting Odds Ratios (ROR) were calculated. An ROR >1 is considered a significant signal. **Results:** A total of 795 cases were reported to the FAERS from 1997-2024. 785 were characterized as severe, including 77 deaths (9.68%). The most common reported drugs were – Bacillus Calmette-Guerin (11.82%; ROR: 814.4 [655.43, 1011.92]; $p<0.05$), Infliximab (6.04%; ROR: 9.11 [6.8, 12.2]; $p<0.05$), Methotrexate (4.78%; ROR: 7.57 [5.46, 10.49]; $p<0.05$), Rifampin (4.03%; ROR: 69.42 [48.72, 98.9]; $p<0.05$), Allopurinol (3.52%; ROR: 43.81 [30.04, 63.9]; $p<0.05$), Isoniazid (3.14%; ROR: 92.4 [62.01, 137.67]; $p<0.05$), Etanercept (3.02%; ROR: 1.49 [0.99, 2.24]; $p<0.05$), Adalimumab (3.02%; ROR: 1.26 [0.84, 1.89]; $p<0.05$), Furosemide (2.89%; ROR: 12.79 [8.45, 19.37]; $p<0.05$), and Pyrazinamide (2.89%; ROR: 134.10 [88.51, 203.17]; $p<0.05$). **Conclusion:** Bacillus Calmette-Guerin (BCG), used in tuberculosis vaccinations and for making tuberculin extracts, was the most reported cause of drug-induced granulomatous hepatitis (11.82% of all reports), as well as the agent with the highest ROR (814) amongst the most frequently reported agents. After BCG, Isoniazid had the highest ROR (92.4). A high degree of suspicion should be employed when patients present with symptoms of chronic inflammation and elevated liver enzymes. Such patients should discontinue these medications when possible.



Disclosures: Rohan Karkra: Nothing to Disclose, Mahinaz Mohsen: Nothing to Disclose, Sameer Rao: Nothing to Disclose, Ritik Mahaveer Goyal: Nothing to Disclose, Drew Fletcher: Nothing to Disclose, Ahmed Al-Khazraji: Nothing to Disclose, Paul Gaglio: Nothing to Disclose, Nothing to Disclose

4387 | LIVER INJURY DUE TO MEDICATIONS FOR MENTAL HEALTH: AN ANALYSIS OF THE DRUG-INDUCED LIVER INJURY NETWORK PROSPECTIVE STUDY

Cassey Cha[1] Hersh Shroff[1] Huiman Barnhart[2] Raj Vuppalanchi[3] Alfred Barritt IV[1], [1]UNC Chapel Hill, [2]Duke University, [3]Indiana University

Background: Medications for mental health are amongst the most prescribed agents in the United States. This study characterizes drug-induced liver injury (DILI) attributed to antidepressants and antipsychotic (AP) medications. **Methods:** We queried the Drug-Induced Liver Injury Network (DILIN) prospective study (2004 to 2025) database for high-confidence causality cases of acute DILI (cases rated as definite, highly likely, or probable) due to antidepressants and APs. Agents with the same mechanisms of action (MOA) were combined for analysis. Descriptive statistics were used to describe data on demographics, clinical and laboratory characteristics, and patient

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outcomes. **Results:** As of January 2025, among 2,678 cases in the DILIN Prospective Study database, we identified 37 cases (1.5%) of DILI ascribed to antidepressants or APs (Table 1). These included 8 selective serotonin reuptake inhibitors (SSRIs), 14 serotonin-norepinephrine reuptake inhibitors (SNRIs), and 8 atypical APs. Bupropion (6 cases) and imipramine (1 cases) were the only agents of their respective classes (aminoketone and tricyclic antidepressant). In total, 70% of subjects were women, and mean ages ranged from 30.2 (SSRIs) to 48.2 (SNRIs) years. Patterns of injury (and median R-values) were 56% hepatocellular (median R-value 11.8), 35% cholestatic (R-value 1.4), and 3% mixed (R-value 2.8). Peak mean serum aminotransferase levels across all cases ranged from 320 to 1505 U/L for AST and 425 to 2109 U/L for ALT, the highest values being among SNRI cases. Mean peak serum total bilirubin (TB) levels ranged from 4.1 to 15.0 mg/dL. Corticosteroid treatment was given to 27% of patients. Across all cases, improvement was rapid, with a mean time from peak values to $\geq$50% reduction ranging from 3 to 11 days for AST/ALT and 2 to 10.5 days for TB. Persistent elevations in liver enzymes after 6 months ("chronic DILI") were seen in 16% of cases. 11 cases met criteria for modified Hy's law (defined as initial R value $\geq$ 5 and TB $\geq$ 2.5mg/dL), with one liver-related death in a case of DILI due to bupropion. No other death nor liver transplant occurred in this cohort. **Conclusion:** Despite frequent use, the frequency of DILI cases due to antidepressants and APs in the US is low, and most cases showed rapid improvement. However, severe cases leading to chronic DILI or death rarely occur. It is important for practitioners to keep in mind the rare possibility of DILI as an adverse effect of these agents.

Table 1: Characteristics of DILI

Characteristic	SSRI* (n=8)	SNRI † (n=14)	Atypical AP^ (n=8)	Bupropion (n=6)	Imipramine (n=1)
Causality score					
Definite	2 (25)	5 (36)	0 (0)	0 (0)	-
Highly likely	4 (50)	8 (57)	5 (63)	4 (66)	1 (100)
Probable	2 (25)	1 (7)	3 (37)	2 (33)	-
Age, years – mean (SD)	30.2 (11.5)	48.2 (10.3)	37.7 (22.5)	39.4 (16.5)	35.4
Gender – n (%)					
Male	3 (37)	3 (21)	4 (50)	1 (17)	-
Female	5 (63)	11 (79)	4 (50)	5 (83)	1
Race – n (%)					
White/Caucasian	8 (100)	12 (86)	5 (63)	6 (100)	-
Black/AA	0	1 (7)	0	0	-
Asian	0	1 (7)	2 (25)	0	-
Other	0	0	1 (12)	0	1
Days to DILI onset – median (IQR)	53 (31 – 63)	58 (42 – 62)	22 (17- 76)	287 (121 – 476)	32
Pattern of injury (at onset) – n (%)					
Hepatocellular	5 (63)	7 (58)	3 (43)	3 (50)	1
Cholestatic	1 (13)	5 (42)	4 (57)	2 (33)	-
Mixed	2 (25)	0 (0)	0 (0)	1 (17)	-
Peak liver enzyme values – mean (SD)					
AST (U/L)	445 (362)	1505 (2062)	324 (295)	1105 (1031)	320
ALT (U/L)	529 (493)	2109 (2766)	425 (297)	1476 (1451)	637
ALP (U/L)	311 (152)	507 (508)	524 (484)	383 (337)	295
Total bilirubin (mg/dL)	15 (12.8)	12.5 (10.4)	14.5 (20.7)	11.9 (14.1)	4.1
INR	1.4 (0.3)	1.5 (0.5)	1.2 (0.3)	2.3 (2.9)	1.0
Days from peak value to ≥50% improvement – median					
AST (U/L)	9	3	4	5	4
ALT (U/L)	10	6	9	11	6
ALP (U/L)	23	17	43	55	14
Total bilirubin (mg/dL)	9	8	11	7	2
Treatment and outcomes – n (%)					
Corticosteroid use	2 (25)	4 (29)	2 (25)	2 (33)	0
Developed chronic DILI	2 (25)	3 (21)	1 (12)	0	0
Death	0	0	0	1 (17)	0

* SSRIs included escitalopram (n=4), fluoxetine (n=1), paroxetine (n=1), sertraline (n=1), and vortioxetine (n=1)
† SNRIs included duloxetine (n=11), nefazodone (n=1), trazodone (n=1), and venlafaxine (n=1)
^ APs included chlorpromazine (n=1), olanzapine (n=3), quetiapine (n=3), and risperidone (n=1)

Disclosures: Cassey Cha: Nothing to Disclose, Hersh Shroff: Nothing to Disclose, Huiman Barnhart: Nothing to Disclose, Raj Vuppalanchi: Eli LIlly: Grant/Research Support, GSK: Consultant, Madrigal: Consultant, Zydus Therapeutics: Grant/Research Support, Galectin Therapeutics: Grant/Research Support, Kowa: Grant/Research Support, Takeda: Grant/Research Support, GSK: Consultant, UBC: Consultant, Gilead: Grant/Research Support, GSK: Grant/Research Support, 89 Bio: Consultant, Alfred Barritt IV: Merck (Any division): Advisor, Madrigal: Consultant, Life Edit: Consultant, Boehringer Ingelheim: Consultant, Target-RWE: Consultant, Target-RWE: Consultant, Madrigal Pharmaceuticals: Consultant, Merck (Any division): Consultant, Boehringer Ingleheim: Consultant

4388 | EXPERIMENTAL STUDY ON THE REGULATION OF LY6CHI/LY6CLO MACROPHAGE BALANCE BY YIGAN XIAOJI FORMULA IN LIVER CIRRHOSIS MICE

Shihao Zheng[1] qiuyue wang[2] Xiaoke Li[2] Peng Zhang[2] Yongan Ye[2], [1]Dongzhimen Hospital, Beijing University of Chinese Medicine, [2]Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing 100700, China

Background: Liver cirrhosis (LC) is the end stage of chronic liver disease, which is a serious threat to the health of people around the globe, and nowadays there is no completely effective therapeutic drug, while in the clinical practice, traditional Chinese medicine (TCM) has shown good therapeutic effect on LC. Yigan xiaoji formula (YGXJ) is a commonly used TCM, but the specific mechanism of action in the treatment of LC is not fully understood. **Methods:** C57BL/6 mice were divided into blank, model, and herbal intervention groups (YGXJ low, medium, and high dose groups), and a mixture of 20% carbon tetrachloride and olive oil was injected intraperitoneally at 0.2 ml/100 g body weight 3 times/week for 9 weeks to induce early cirrhosis models in the mice of the model group and the herbal intervention group, and the blank group was given an equal volume (0.2 ml/100 g body weight) of olive oil The blank group was given equal volume of olive oil solution. After 5 weeks of modeling, the treatment group was given the TCM YGXJ in low, medium and high concentrations by gavage of the TCM, while the blank group and the model group were given distilled water by gavage of 0.1 ml/10 g gavage 1 time/day for a period of 4 weeks, and then at the end of the 9-week modeling period, the mice of each group were sampled. We observed the vital activities of mice and the condition of liver tissues taken from mice; we detected the levels of ALT and AST, which are the indicators of liver function, and used Masson staining to observe the pathology of liver tissues, immunohistochemistry to detect the expression of F4/80, LY6C, and α-SMA, as well as qRT-PCR to detect the TNF-α, IL1-β, MMP9 and MMP12 mRNA levels. **Results:** After 4 weeks of YGXJ intervention, compared

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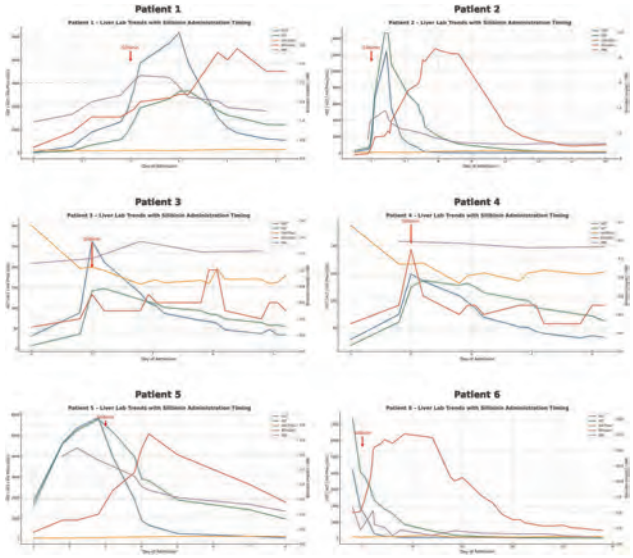
with the model group, the expression of ALT and AST in each dose group had a decreasing trend, of which the medium dose group of YGXJ had the lowest content; Comparing the TCM group with the model group, after YGXJ intervention, collagen fiber deposition was significantly reduced in early cirrhotic mice, which could improve the degree of lesions, with the YGXJ medium-dose group being the most obvious; Finally, YGXJ was also able to further regulate the balance of Ly6Chi/Ly6Clo macrophages, and the number of F4/80 macrophages showed a significant downward trend after treatment, and the expression of LY6C and α-SMA was also significantly reduced; meanwhile, YGXJ was also able to down-regulate the mRNA expression of TNF-α and IL1-β, and at the same time, it up-regulated the expression of MMP9 and MMP12. **Conclusion:** YGXJ medium-dose group can improve the liver function of early cirrhotic mice; it has a role in inhibiting the structural state, hepatocyte degeneration, collagen fibers, and hepatic stellate cell activation in the liver of early cirrhotic mice; YGXJ also prevents the disease progression in the early cirrhotic mice by modulating the Ly6Chi/Ly6Clo macrophage balance.

Disclosures: Shihao Zheng: Nothing to Disclose, qiuyue wang: Nothing to Disclose, Xiaoke Li: Nothing to Disclose, Peng Zhang: Nothing to Disclose, Yongan Ye: Nothing to Disclose

4389 | LIVER INJURY FROM THE DEATH CAP MUSHROOM: THE PHILADELPHIA EXPERIENCE AND ROLE FOR SILIBININ

Stefanie Gallagher[1] Jonathan Fenkel[1] Rebecca Loh[1] Dina Halegoua-DeMarzio[1], [1]Thomas Jefferson University Hospital

Background: Amanita phalloides, commonly known as the death cap mushroom, is highly hepatotoxic via heat-resistant amatoxin. Native to Europe, it now grows in places like Pennsylvania, often under oaks, where its white cap is mistaken for edible mushrooms. Clinical manifestations of poisoning typically progress through stages – often initially asymptomatic followed by gastrointestinal symptoms, transient improvement and progression to liver injury. Severe cases can lead to fulminant liver failure and need for liver transplant. There are no standardized treatment protocols in the United States. Treatment focuses on limiting toxin absorption and promoting elimination, such a silibinin, a derivative of milk thistle, which inhibits amatoxin uptake. When unavailable, Penicillin G can be used. We present a case series from our health system detailing the severity to liver injury, silibinin administration, and liver transplant needs in confirmed cases. **Methods:** We retrospectively reviewed electronic medical records from our health system which includes two high-volume liver transplant centers. We investigated clinical presentation and course, laboratory values and trends, treatment initiation, need for liver transplant evaluation (LTE) and liver transplant. **Results:** We identified 10 cases of Amanita phalloides ingestion from 2016-2023. 7 cases involved a family who all ingested misidentified mushrooms after foraging, of which 5 were children. Regarding treatment, 6 patients received silibinin, through compassionate use, and 3 required LTE. 9 patients received activated charcoal, 8 patients received n-acetylcysteine, 1 patient received Penicillin G and 2 patients received penicillin-derivatives. The degree of liver injury and silibinin initiation is depicted in Figure 1. Of the patients not given silibinin, 3 had mild liver injury and 1 required a transplant. Early identification of intoxication occurred on presentation in all cases except the patient requiring a transplant. There were no fatalities. **Conclusion:** Despite exceptionally high peak liver chemistries and synthetic dysfunction, all patients who received silibinin exhibited biochemical improvement and none ultimately required liver transplantation. This case series highlights that patients with Amanita phalloides ingestion have significant risk of liver injury and should be ideally treated at a transplant center. Additionally, silibinin may be an effective treatment for toxicity compared to supportive therapy alone, though further studies are needed.



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Novo Nordisk: Grant/Research Support, Bausch: Advisor, Akero: Grant/Research Support

4390 | CHARACTERISATION OF LIVER INJURY INDUCED BY TRASTUZUMAB WITHIN THE FRENCH-SPEAKING NETWORK FOR THE STUDY OF HEPATOTOXICITY IN HEALTH PRODUCTS (REFHEPS)

Bénédicte Delire[1] LUCY MEUNIER[2] Magdalena Meszaros[2] Amel Zaahaf[2] Eleonora De Martin[3] François Duhoux[4] Cedric Van Marcke[4] Yves Horsmans[1] Dominique Larrey[2], [1]Department of Hepatology, Cliniques Universitaires Saint-Luc, Brussels, Belgium, [2]Liver unit, Hopital St Eloi, CHU Montpellier, France, [3]APHP, Hôpital Paul Brousse, Centre Hépato-Biliaire, Unité INSERM 1193, Villejuif, France, [4]Department Of Medical Oncology, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Background: Trastuzumab (TRA) is a targeted therapy that exists as either a monoclonal antibody or an antibody-drug conjugate: TRA-deruxtecan (T-DXd) and TRA-emtansine (T-DM1). All are used to treat breast cancer (BC) and other solid tumors and are associated with drug-induced liver injury (DILI). **Methods:** Patients assessed by the Réseau Francophone pour l'étude de l'Hépatotoxicité des Produits de Santé (REFHEPS) between January 2022 and May 2025 were evaluated. Those with TRA/T-DXd/T-DM1-induced liver toxicity were included. Hepatotoxicity was defined as ALT or AST $\geq$ 5x ULN, ALP $\geq$ 2x ULN, or total bilirubin $\geq$ 2x ULN associated with ALT $\geq$ 3x ULN or the appearance of signs of portal hypertension (PH). Causality was assessed using the CIOMS and the DILIN method and severity using the DILIN score. Approval by an ethics committee (IRB number: 198711). **Results:** Thirteen of the 322 cases collected in the REFHEPS involved TRA/T-DXd/T-DM1: 5 T-DM1, 2 T-DXd, 1 T-DM1 and nivolumab, 1 TRA, and 1 TRA+pertuzumab+tucatinib. All but one of the patients were female, median age 62 years (39–82). Eleven patients were treated for BC, 1 for ovarian tumor and 1 for bladder carcinoma. DILI phenotype was cholestatic in 5 cases, cytolytic in 3 and mixed in 1. Four patients did not meet the biological criteria for DILI but had signs of PH. When applicable, DILIN grade was probable in 8 cases and possible in 1. Same results were observed using the CIOMS method (median RUCAM score = 7 (4-8)). Hepatic damage was symptomatic in 3 cases, one had variceal haemorrhage. Six patients in the cholestatic and PH groups had liver biopsy. Histological analysis was consistent with porto-sinusoidal vascular liver disease (PSVD) in all patients whose evolution was chronic. PSVD was related to T-DM1 in 5 cases, to T-DXd in 2, to T-DM1 and nivolumab in 1 and to TRA in 1. In the cytolytic and mixted group, 2 patients had a biopsy showing an acute lobular hepatitis in one case and a cholestatic hepatitis in the other. Three patients experienced resolution of liver enzymes; one of these patients received corticosteroids, while another patient only showed improvement in hepatic tests after three months. Acute hepatitis was associated with T-DM1 in 2 cases, to T-DXd in 1 and to a combination of TRA-Pertuzumab-Tucatinib in 1. **Conclusion:** TRA, T-DXd and T-DM1 are associated with DILI, including acute hepatitis and chronic PSVD. Further data are needed to predict the development of clinical PH in patients treated with these molecules.
Disclosures: Bénédicte Delire: Nothing to Disclose, LUCY MEUNIER: Nothing to Disclose, Magdalena Meszaros: Nothing to Disclose, Amel Zaahaf: Nothing to Disclose, Eleonora De Martin: Nothing to Disclose, François Duhoux: Nothing to Disclose, Cedric Van Marcke: Nothing to Disclose, Yves Horsmans: Nothing to Disclose, Dominique Larrey: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose

◆ 4391 | THE IMPACT OF CYP2E1 DELETION IN MOUSE LIVER

Kristina Stayer[1] Zaria Killingsworth[1] Madison Thornton[1] Kylie Driggers[1] Taia Mendenhall[1] Mi-Hye Lee[1] Lauren Ball[1] Kristi Helke[1] Don Rockey[1] Mindy Engevik[1] Jessica Hartman[1], [1]Medical University of South Carolina

Background: Cytochrome P450 2E1 (CYP2E1) is a mammalian enzyme present at high levels in liver that is highly conserved in mammals. Prior studies have documented the hepatotoxic effects of CYP2E1 via the production of toxic metabolites from its substrates, such as acetaldehyde from ethanol and NAPQI from acetaminophen. A global CYP2E1-knockout (KO) mouse was developed by Dr. Frank Gonzalez in the late 1990s and has no documented phenotypic abnormalities except for dramatic protection against hepatic insult from acetaminophen, ethanol, high-fat diet, Western diet, carbon tetrachloride, N,N-dimethylformamide, and many other CYP2E1-relevant challenges. CYP2E1 inhibition has been proposed as both a treatment for liver disease and a prophylactic against liver damage. **Methods:** In this study, we used 12-14 week adult mice from the 129S1/SvImJ background (WT) or 129/Sv-Cyp2e1^{tm1Gonz}/J (KO). For organoids, we embedded freshly isolated primary hepatocytes in Matrigel and used Hepatic Organoid Media from StemCell Technologies and observed organoid

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formation over 6 days. For histology, we fixed liver in 10% neutral buffered formalin and embedded in paraffin before slicing and staining with H&E or antibodies against macrophages (F480 and CD68), T-cells (CD3e and CD49d), B cells (CD20), or mitochondrial HSP60 with fluorescent secondary antibodies and imaged by fluorescent microscopy. RNA and proteins were isolated from bulk liver tissue for transcriptomics (Novogene) and protein mass spectrometry (MUSC Proteomics). Mitochondria were isolated from bulk liver tissue for determination of respiratory complex activities. **Results:** We have observed that CYP2E1-KO livers from both male and female mice are impaired in forming organoids, with male livers forming significantly smaller and fewer organoids than the WT livers and female livers failing to form organoids. We also observed pathology in formalin-fixed liver tissue, including biliary hyperplasia, pericentral necrosis, and inflammatory cell infiltration in female livers. Follow-up immunofluorescent staining revealed that the infiltrating immune cell populations included macrophages and T-cells. RNA-seq and proteomic investigation of female liver tissue revealed common upregulated pathways of SREBP signaling, ER stress, and steroid metabolism and downregulated pathways of DNA damage repair, mitochondria, and anti-inflammatory response. We observed changes in mitochondrial morphology and mitochondrial respiratory complex activities in both male and female KO liver compared to WT liver. **Conclusion:** These results suggest that CYP2E1-KO has deleterious consequences that are most prevalent in female liver. In ongoing experiments, we are interrogating the endogenous activities of CYP2E1 (fatty acid hydroxylation, ketone metabolism, and ROS production) to determine the mechanism underlying these intriguing findings.
Disclosures: Kristina Stayer: Nothing to Disclose, Zaria Killingsworth: Nothing to Disclose, Madison Thornton: Nothing to Disclose, Kylie Driggers: Nothing to Disclose, Taia Mendenhall: Nothing to Disclose, Mi-Hye Lee: Nothing to Disclose, Lauren Ball: Nothing to Disclose, Kristi Helke: Nothing to Disclose, Don Rockey: WL Gore and Associates: Consultant, Cook Medical: Consultant, BD Medical: Consultant, AstraZeneca: Grant/Research Support, Bio89: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Durect: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Intercept: Grant/Research Support, Inventiva: Grant/Research Support, Madrigal: Grant/Research Support, Ocelot: Grant/Research Support, Salix: Grant/Research Support, Novonordisk: Grant/Research Support, Galectin: Grant/Research Support, Versantis: Grant/Research Support, Viking: Grant/Research Support, Mindy Engevik: Nothing to Disclose, Jessica Hartman: Surrozen, Inc: Consultant

◆ 4392 | UNRAVELING THE PARADOX: CLINICAL OUTCOMES IN PRIMARY BILIARY CHOLANGITIS WITH HYPERLIPIDEMIA – A MULTINETWORK COHORT STUDY

Tinsae Tsegaye Anebo[1] Karecia Byfield[1] Laith Alomari[1] Delano Carty[1] Ghideon Ezaz[1], [1]Thomas Jefferson University

Background: Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease often associated with significant hyperlipidemia. Historically, despite elevated lipid levels, PBC patients were thought to have low atherosclerotic cardiovascular disease (ASCVD) rates, suggesting a benign lipid profile. However, recent studies have questioned this assumption, citing a rising burden of cardiovascular and metabolic comorbidities, particularly as the disease advances. This disconnect has complicated clinical management, especially decisions regarding lipid-lowering therapies. To address this gap, we conducted a multi-center, retrospective cohort study to assess the true impact of hyperlipidemia on cardiovascular and liver-related outcomes in PBC, and to evaluate the relevance of traditional lipid risk models in this population. **Methods:** Using the TriNetX US Collaborative Network, we identified adult PBC patients diagnosed between 2012 and 2024. Patients were divided into two cohorts: those with hyperlipidemia, determined via lipid panels or ICD codes, and those without. We excluded individuals with coexisting chronic liver diseases, pre-existing cardiovascular conditions, or prior statin use to minimize confounding. Propensity score matching was performed based on demographics and clinical variables. The primary outcome was the incidence of major adverse cardiovascular events (MACE). Secondary outcomes included liver-related complications. Kaplan-Meier curves assessed event-free survival, while Cox proportional hazards models evaluated associations between hyperlipidemia and clinical outcomes, adjusting for age, sex, BMI, smoking, diabetes, and hypertension. **Results:** After matching, each cohort included 7,299 patients. PBC patients with hyperlipidemia showed significantly higher rates of cardiovascular and metabolic outcomes, including ischemic heart disease, stroke/TIA, peripheral arterial disease, heart failure, hypertension, and type 2 diabetes. Interestingly, all-cause mortality was lower, while hospitalization risk was modestly higher. Liver-related complications such as ascites, hepatic encephalopathy, variceal bleeding, and spontaneous bacterial peritonitis were significantly reduced. No differences were seen in hepatocellular carcinoma or liver transplantation rates. **Conclusion:** Our findings challenge the long-standing

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notion that hyperlipidemia in PBC is benign. While associated with lower mortality and fewer liver complications, hyperlipidemia in PBC confers a significantly higher burden of cardiovascular and metabolic disease. These results underscore the need for revised cardiovascular risk stratification and a personalized, proactive management approach in PBC, especially as traditional lipid metrics may underestimate true risk in this unique population.

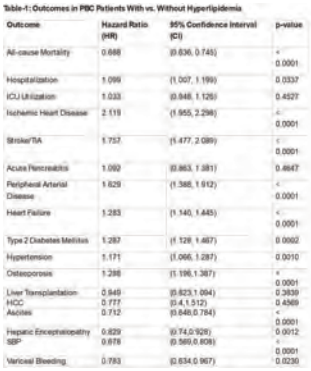

Table-1: Outcomes in PBC Patients With vs. Without Hyperlipidemia

Outcome	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
All-cause Mortality	0.668	(0.636, 0.745)	< 0.0001
Hospitalization	1.099	(1.007, 1.199)	0.0337
ICU Utilization	1.033	(0.948, 1.126)	0.4527
Ischemic Heart Disease	2.119	(1.955, 2.298)	< 0.0001
Stroke/TIA	1.757	(1.477, 2.089)	< 0.0001
Acute Pancreatitis	1.092	(0.863, 1.381)	0.4647
Peripheral Arterial Disease	1.629	(1.388, 1.912)	< 0.0001
Heart Failure	1.283	(1.140, 1.445)	< 0.0001
Type 2 Diabetes Mellitus	1.287	(1.128, 1.467)	0.0002
Hypertension	1.171	(1.066, 1.287)	0.0010
Osteoporosis	1.298	(1.196, 1.387)	< 0.0001
Liver Transplantation	0.949	(0.823,1.094)	0.3839
HCC	0.777	(0.4,1.512)	0.4569
Ascites	0.712	(0.648,0.784)	< 0.0001
Hepatic Encephalopathy	0.829	(0.74,0.928)	0.0012
SBP	0.878	(0.569,0.808)	< 0.0001
Variceal Bleeding	0.793	(0.634,0.967)	0.0230

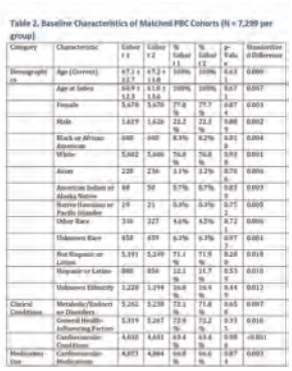

Table 2. Baseline Characteristics of Matched PBC Cohorts (N = 7,239 per group)

Category	Characteristic	Cohort 1	Cohort 2	% Cohort 1	% Cohort 2	p-Value	Standardized Difference
Demographics	Age (Correct),	67.2 ± 12.7	67.2 ± 13.0	100%	100%	0.63	0.000
	Age at Index	64.9 ± 12.5	65.0 ± 13.0	100%	100%	0.67	0.007
	Female	5,678	5,676	77.6 %	77.7 %	0.87	0.003
	Male	1,619	1,620	22.2 %	22.2 %	0.88	0.002
	Black or African American	648	640	8.9%	8.2%	0.01	0.004
	White	5,602	5,600	76.8 %	76.8 %	0.93	0.001
	Asian	228	236	3.1%	3.2%	0.76	0.006
	American Indian or Alaska Native	68	50	0.7%	0.7%	0.03	0.003
	Native Hawaiian or Pacific Islander	25	21	0.3%	0.3%	0.75	0.005
	Other Race	316	327	4.6%	4.5%	0.72	0.006
	Unknown Race	650	659	8.9%	9.0%	0.97	0.001
	Not Hispanic or Latino	5,391	5,249	73.1 %	71.9 %	0.28	0.018
	Hispanic or Latino	840	856	12.1 %	11.7 %	0.53	0.010
	Unknown Ethnicity	1,220	1,194	16.8 %	16.4 %	0.44	0.012
Clinical Conditions	Metabolic/Endocrine Disorders	5,262	5,230	72.1 %	71.8 %	0.65	0.007
	General Health-Influencing Factors	5,319	5,267	72.9 %	73.2 %	0.93	0.010
	Cardiovascular Conditions	4,610	4,633	63.4 %	63.6 %	0.98	<0.001
Medications Use	Cardiovascular Medications	4,873	4,884	66.8 %	66.6 %	0.87	0.003

Disclosures: Tinsae Tsegaye Anebo: Nothing to Disclose, Karecia Byfield: Nothing to Disclose, Laith Alomari: Nothing to Disclose, Delano Carty: Nothing to Disclose, Ghideon Ezaz: Nothing to Disclose

◆ 4393 | REDUCTION IN INTERLEUKIN (IL)-31 WITH LINERIXIBAT IS ASSOCIATED WITH PRURITUS RESPONSE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC) AND CHOLESTATIC PRURITUS IN THE PHASE 3 GLISTEN STUDY

Christopher Bowlus[1] Andreas Kremer[2] Janelle Lennie[3] Bishoy Hanna[3] Kerri Fuller[4] Sugato Das[5] Linda Casillas[3] Alexander Cobitz[3] Ciara Gorey[6] Jennifer Shannon[7] Philip Troke[6] Megan McLaughlin[3] Sumanta Mukherjee[3] Brandon Swift[7], [1]University of California Davis, Sacramento, CA, USA, [2]University Hospital Zurich, University of Zurich, Zurich, Switzerland, [3]GSK, Collegeville, PA, USA, [4]GSK, Stevenage, UK, [5]GSK, Hyderabad, India, [6]GSK, London, UK, [7]GSK, Durham, NC, USA

Background: Cholestatic pruritus is common in PBC and negatively impacts quality of life. Several potential mediators of cholestatic pruritus have been identified, including bile acids, endogenous opioids and lysophosphatidic acid (LPA); however, the precise mechanisms leading to itch are not well understood. IL-31 has been associated with atopic dermatitis and more recently with PBC and primary sclerosing cholangitis; reductions correlate with improved itch in patients treated with a peroxisome proliferator-activated receptor agonist in PBC. Ileal bile acid transporter (IBAT) inhibition is known to impact bile acids and LPA (as measured by autotaxin), but its impact on IL-31 is unknown. Linerixibat, a minimally absorbed IBAT inhibitor, is a twice-daily oral tablet for the treatment of pruritus in PBC. Here, we report the effects of linerixibat compared with placebo on IL-31 in participants in GLISTEN (NCT04950127), the largest investigational study of pruritus in PBC. **Methods:** GLISTEN was a Phase 3, randomized, double-blind, placebo-controlled study of 238 adults with PBC and moderate-to-severe pruritus. In the primary intervention period, patients received oral linerixibat 40 mg or placebo twice daily for 24 weeks. Serum IL-31 levels were measured at baseline and Weeks 4, 8, 12, 16, 20 and 24. This analysis includes 135 patients (linerixibat $n = 65$; placebo $n = 70$) who had IL-31 measured. Correlation analyses were post hoc. Pruritus severity was assessed using a 0–10 worst itch numerical rating scale. Itch responders were defined as those achieving a ≥ 3-point improvement from baseline in weekly itch score (average of worst daily itch scores in one week) at Week 24. **Results:** Over 24 weeks, IL-31 reduction was greater in the linerixibat group compared with placebo (ratio of linerixibat to placebo change from baseline [CFB]: 0.53, 95% confidence interval [CI] 0.44, 0.65; $p < 0.001$). Change in IL-31 with linerixibat correlated with change in pruritus over time ($r = 0.21$, $p < 0.0001$). At Week 4, there was a 49.2% reduction from baseline in median IL-31 levels in the linerixibat group versus placebo, and a weak but significant correlation between CFB in IL-31 and pruritus (linerixibat $r = 0.24$, $p = 0.05$; placebo $r = 0.17$, $p = 0.17$). In itch responders, reductions from baseline in IL-31 at Week 24 were greater with linerixibat versus placebo (least squares mean ratio to baseline: linerixibat, 0.41 [95% CI 0.31, 0.54]; placebo, 0.84 [95% CI 0.65, 1.07]; Figure 1A). In linerixibat-treated patients, IL-31 levels at Week 24 were lower in itch responders than non-responders, and in comparison with placebo (Figure 1B). **Conclusion:** IL-31 reduction with linerixibat correlated with an improvement in itch at Week 24 and as early as Week 4. This reduction correlated with change in itch and was associated with treatment response. These data provide key insights into the mechanisms by which linerixibat may mediate itch reduction via IL-31 in PBC.

Funding: GSK (212620)

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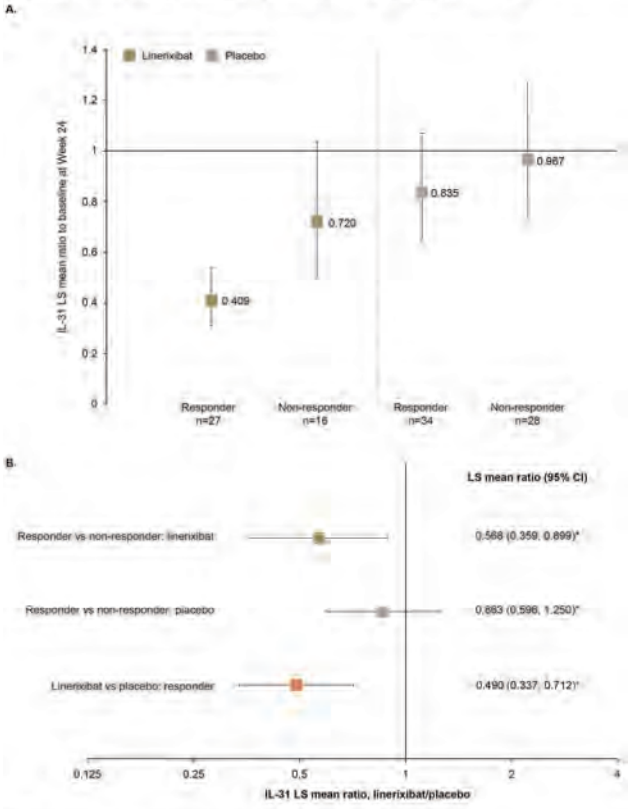

Figure 1. (A) IL-31 LS mean ratio to baseline in itch responders and non-responders treated with linerixibat or placebo at Week 24 (post hoc analyses); (B) IL-31 LS mean ratio of responders to non-responders in linerixibat-treated patients and placebo recipients, and ratio of linerixibat to placebo responders at Week 24 (post hoc analyses)

Error bars in panel A represent confidence intervals.
*LS mean ratio <1 favors responder, mean ratio >1 favors non-responder; †LS mean ratio <1 favors active treatment.
CI, confidence interval; LS, least squares.

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◆ 4394 | TOFACITINIB AS A STEROID-FREE INDUCTION THERAPY IN AUTOIMMUNE HEPATITIS: AN INITIAL EXPERIENCE

Arnav Aggarwal[1] Sarthak Saxena[1] Sagnik Biswas[1] Shekhar Swaroop[1] Ayush Agarwal[1] . Shalimar[1], [1]All India Institute of Medical Sciences, Delhi

Background: Steroids remain the cornerstone of induction therapy in autoimmune hepatitis (AIH), but long-term use is associated with significant adverse effects. Although steroid-sparing agents such as azathioprine or mycophenolate mofetil are frequently added, sustained remission often necessitates prolonged steroid use. Janus kinase inhibitors, such as tofacitinib, have emerged as potential alternatives. We report our initial real-world experience with a completely steroid-free induction regimen using tofacitinib in AIH. **Methods:** We retrospectively analysed AIH patients (simplified AIH score $>=6$) who were initiated on tofacitinib. Biochemical parameters were monitored at 1, 3 and 6 months. Liver stiffness measurement (LSM) was performed at 6 months using Fibroscan 630 Expert®. Outcomes included normalisation of serum transaminases and immunoglobulin (IgG), and adverse events. **Results:** Sixteen patients (median age: 36 years (23-44); 9 (56.2%) female) received tofacitinib 10 mg/day for 6 months. Cirrhosis was present in 13 (81.3%), and 9 (56.2%) had prior decompensation. Baseline median bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and IgG were 1.4 (0.6-2.3) mg/dL, 84 (56-115) IU/L, 56 (34-85) IU/L and 2.4 (2.1-2.7) gm/dL. Elevated AST, ALT, and IgG were noted in 14, 11 and 15 patients, respectively, at baseline. Fourteen patients completed 6 months of treatment; 2 discontinued (one patient refused and one due to malignancy: ovarian carcinoma. At 6 months, normalisation of AST/ALT (among those with elevated AST/ALT) was seen in 7/14 (50.0%), IgG (among those with elevated IgG) in 4/15 (26.7%) and complete biochemical response (CBR) achieved in 3/16 (18.8%) (Table 1). The median change in LSM at 6 months was 0.8 (-4.6 to +5.5) kPa. Among cirrhosis patients, normalisation of AST/ALT was seen in 6/11 (54.5%), IgG in 4/13 (30.8%) and CBR in 3/13 (23.1%) patients. No major adverse events were noted. **Conclusion:** Tofacitinib appears safe and potentially effective as a steroid-free induction agent in AIH, though with a lower response rate. Low response rates observed may be explained by the high proportion of patients with cirrhosis. Prospective randomised controlled trials are needed to further explore its use in AIH as a steroid-free regimen

Table1. Response assessment withing 6 months of treatment initiation

Table 1. Response assessment within 6 months of treatment initiation

	Whole cohort (n=16)	Response in patients with abnormal baseline parameters	Response in cirrhosis patients with abnormal baseline parameters
AST Normalisation within 6 months[1]	8/16 (50%)	8/14 (57.1%)	6/11 (54.5%)
ALT Normalisation within 6 months[2]	12/16 (75%)	7/11 (63.6%)	6/8 (75.0%)
AST/ALT normalisation within 6 months	7/16 (43.8%)	7/14 (50.0%)	6/11 (54.5%)
IgG normalisation within 6 months[3]	5/16 (31.3%)	4/15 (26.7%)	4/13 (30.8%)
CBR within 6 months	3/16 (18.8%)	3/16 (18.8%)	3/13 (23.1%)

[1]Elevated AST was present in 14 patients at baseline
[2]Elevated ALT was present in 11 patients at baseline
[3]Elevated IgG was present in 15 patients at baseline

Disclosures: Arnav Aggarwal: Nothing to Disclose, Sarthak Saxena: Nothing to Disclose, Sagnik Biswas: Nothing to Disclose, Shekhar Swaroop: Nothing to Disclose, Ayush Agarwal: Nothing to Disclose, . Shalimar: Nothing to Disclose

◆ 4395 | LONG-TERM BONE HEALTH IN OBETICHOLIC ACID–TREATED PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: A POISE POST HOC ANALYSIS

Kimberly Brown[1] Tatyana Kushner[2] Nikeshia Dunkelly-Allen[3] Jing Li[3] Radhika Nair[3] Joseph Konen[3] Marlyn Mayo[4], [1]Henry Ford Hospital Transplant Institute, Detroit, Michigan, USA, [2]Icahn School of Medicine at Mount Sinai, New York, New York, USA, [3]Intercept Pharmaceuticals, Inc., Morristown, New Jersey, USA, [4]University of Texas Southwestern, Dallas, Texas, USA

Background: Patients with primary biliary cholangitis (PBC) are at increased risk for metabolic bone disease, including osteopenia and osteoporosis. Obeticholic acid (OCA) is an approved second-line therapy for PBC, but its long-term effect on bone health is unclear. In this post hoc analysis, we evaluated bone health in OCA-treated patients from the phase 3 POISE study (NCT01473524). **Methods:** Patients with PBC who had inadequate response or intolerance to ursodeoxycholic acid were randomized to receive oral placebo ($n=73$), OCA 5–10 mg ($n=70$), or OCA 10 mg ($n=73$) daily in the 12-month double-blind phase. At the end of the double-blind phase, patients on OCA continued therapy, and patients on placebo were initiated on OCA during the 5-year open-label extension (OLE). Bone mineral density (BMD; g/cm^2) and T-scores of the femoral neck and lumbar spine were assessed at baseline and each year for up to 72 months by dual X-ray absorptiometry. Baseline measures for OCA-treated patients were recorded at the start of the double-blind phase, while baseline measures for

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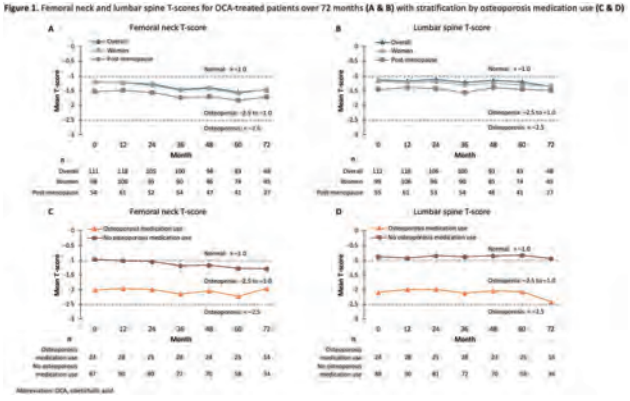
placebo-treated patients were recorded at the start of the OLE. Bone health data were pooled starting from the time of OCA initiation, and descriptive analyses showing trends in mean BMD and T-scores were performed. Subgroup analyses were performed in women and postmenopausal women, as well as in patients on osteoporosis medications (eg, bisphosphonates, abaloparatide, denosumab, and raloxifene) and those not on osteoporosis medications. **Results:** T-scores demonstrated a modest decline from baseline during the OLE with OCA (Figure 1A/B). Femoral neck and lumbar spine BMD (g/cm^2) remained relatively stable with OCA over 72 months (change from baseline, −0.07 and −0.06, respectively). Similar results were observed in the subgroup analyses of women and postmenopausal women, with postmenopausal women exhibiting lower T-scores at baseline and throughout the 72-month study compared with the overall patient population and women overall. OCA-treated patients on osteoporosis medication had mean femoral neck and lumbar spine T-scores in the osteopenia range (T-score between −2.5 and −1.0) at baseline. BMD and T-scores in this subgroup remained relatively stable over 72 months (Figure 1C/D). **Conclusion:** While there was a slight decline in T-scores over 72 months with OCA treatment, BMD remained relatively stable, including in high-risk subgroups and patients being treated for osteoporosis.



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◆ 4396 | SAFETY AND ACTIVITY OF NEBOKITUG OVER 48 WEEKS IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: OPEN-LABEL EXTENSION RESULTS: FROM THE SPRING STUDY

Christopher Bowlus[1] Stephen Barclay[2] Deepak Joshi[3] Maria Carlota Londono[4] Parvez Mantry[5] Rifaat Safadi[6] Revital Aricha[7] Chris Cirillo[7] Matthew Frankel[7] John Lawler[7] Ilan Vaknin[8] Adi Mor[8] Douglas Thorburn[9], [1]University of California, Davis, [2]Glasgow Royal Infirmary, [3]Institute of Liver Studies, King's College Hospital, NHS Foundation Trust, [4]Hospital Clinic, [5]Methodist Dallas Medical Center, [6]Hadassah Hebrew University Hospital, [7]Chemomab Therapeutics, [8]ChemomAb Ltd., [9]Royal Free Hospital & University College of London

Background: Nebokitug is an anti-CCL24 monoclonal antibody being evaluated for the treatment of primary sclerosing cholangitis (PSC). Here we describe the safety, tolerability, and activity of nebotikug in the open-label extension (OLE) of the phase 2 SPRING study. **Methods:** Patients with large duct PSC and ALP >1.5 x ULN who had completed the 15-week double blind (DB) period of the SPRING study (NCT04595825) were eligible to enroll in the OLE to receive either nebokitug 10mg/kg or 20mg/kg every 3 weeks for 11 doses (33 weeks), for a total nebokitug treatment of up to 48 weeks. Key biomarkers including enhanced liver fibrosis (ELF) score, liver stiffness measurements (LSM) by transient elastography, and liver tests were evaluated in all patients and in a prespecified subgroup with moderate/advanced disease, defined as an ELF score $\geq$ 9.8 at baseline. **Results:** 50 of 54 patients eligible to participate enrolled in OLE. 12 patients from the placebo group received either nebokitug 10mg/kg (n = 1) or 20mg/kg (n = 11) for a total of 33 weeks of nebokitug exposure. 38 patients continued to receive nebokitug 10mg/kg (n = 11) or 20mg/kg (n = 27) for a total of 48 weeks of nebokitug exposure. Nebokitug continued to be well tolerated, and no new safety signal was observed. The most common adverse events (AEs) reported were fatigue, headache, and pruritus, which were consistent with those reported in the DB period. There were 3 serious AEs with 2 reported to be possibly related by the investigators to study drug [hospitalization due to obstructive pancreatitis (n = 1) and cholangitis (n = 1)].

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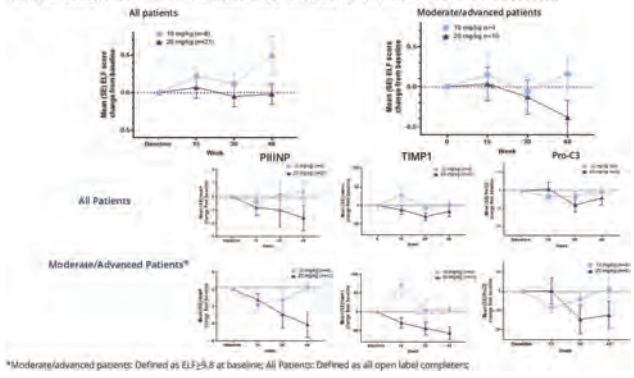
Patients who received placebo in the DB and rolled over to receive nebokitug in OLE had stabilization and/or improvements in ELF score, LSM, and liver tests, consistent with observations in patients treated with nebokitug during the DB period.

For patients who received nebokitug 10 mg/kg in the DB period and continued to OLE, ELF score and its fibrotic components, proc-3, LSM, and liver tests remained stable. Patients treated with nebokitug 20mg/kg in DB period and continued to OLE, showed either a stabilization or an improvement in these biomarkers over 48 weeks, especially in patients with moderate/advanced disease. **Conclusion:** Nebokitug appears safe and well tolerated for up to 48 weeks of treatment. Sustained or continual improvements in inflammatory and fibrosis makers were observed, especially in patients with moderated/advanced disease receiving nebokitug 20mg/kg. These results support the evaluation of nebokitug 20mg/kg in a phase 3 study in patients with PSC.

Figure 1. Changes in ELF score, its components, and PROC-3 up to 48 weeks of nebokitug treatment



*Moderate/advanced patients: Defined as ELF≥9.8 at baseline; All Patients: Defined as all open label completers;

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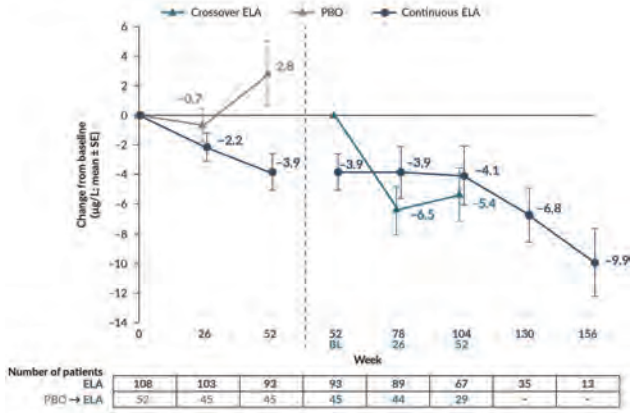
◆ 4397 | TREATMENT WITH ELAFIBRANOR LEADS TO STABILIZATION OF PRO-C3, A MARKER OF FIBROSIS, IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

Christopher Bowlus[1] Christophe Corpechot[2] Michael Heneghan[3] Cynthia Levy[4] Marlyn Mayo[5] Jörn Schattenberg[6] Mark Swain[7] John M. Vierling[8] Nuno Antunes[9] George Harb[9] Marwan Sleiman[10] Nathan Touati[10] Kris Kowdley[11], [1]Division of Gastroenterology and Hepatology, UC Davis School of Medicine, Sacramento, CA, USA, [2]Saint-Antoine Hospital & Research Center, Sorbonne University, Paris, France, [3]Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, UK, [4]Schiff Center for Liver Diseases, University of Miami, Miami, FL, USA, [5]University of Texas Southwestern Medical Center, Dallas, TX, USA, [6]Saarland University Medical Center, Homburg, Germany, [7]Liver Unit, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [8]Baylor College of Medicine, Houston, TX, USA, [9]Ipsen, Cambridge, MA, USA, [10]Ipsen, Paris, France, [11]Liver Institute Northwest, Seattle, WA, USA

Background: Elafibranor (ELA) led to significant biochemical improvements in patients with primary biliary cholangitis (PBC) in the phase III ELATIVE® trial (NCT04526665), but its long-term effects on liver fibrosis are still being evaluated.[1] N-terminal type III collagen propeptide (PRO-C3) is a marker of fibrogenic activity, supplementing other non-invasive tests (NITs) for fibrosis, including enhanced liver fibrosis (ELF) and liver stiffness measurement (LSM).[2] We report data exploring changes in PRO-C3 levels with elafibranor treatment in patients with PBC. **Methods:** Patients completing the ELATIVE® double-blind period (DBP) were eligible to enter the open label extension (OLE) and receive daily ELA 80 mg. Baseline (BL) values for this analysis were set as the last value before the first ELA dose, whether that was at the start of randomization or start of OLE. Changes over time in PRO-C3, ELF, and ELF components (HA, PIINP, and TIMP-1) were assessed. Correlations between the NITs (PRO-C3, ELF, and LSM), and between the NITs and alkaline phosphatase (ALP) and total bilirubin (TB) at baseline were performed. **Results:** At data cutoff (June 2024), 153 patients had received ELA; 108 started ELA in the DBP and were followed for 156 weeks (continuous ELA), and 52 patients received placebo (PBO) for 52 weeks, 45 of whom switched to ELA in the OLE for 78 weeks (crossover ELA). Mean PRO-C3 values at DBP BL for the ELA and PBO groups, and OLE BL for the crossover ELA group were 51.4 μg/L, 46.7 μg/L, and 48.5 μg/L, respectively. There was a trend for decline in PRO-C3 among patients who received ELA in the DBP, while values increased overall in those on PBO (Figure). Patients on continuous ELA had stable values, maintained or decreased to W156. In those who switched to ELA in the OLE, there was a decrease from baseline of similar magnitude to that in patients on ELA during the DBP (mean [standard error]: continuous ELA −3.9 [1.3] μg/L vs crossover ELA −5.4 [1.8] μg/L). Similar changes were observed in ELF scores.[2] In analyses of the ELF score components, no clear trends or separation from PBO were observed. There was a moderate correlation between PRO-C3 and ELF (0.69) and LSM (0.59). There were weak-to-moderate correlations between TB and ELF (0.28), PRO-C3 (0.31), and LSM (0.38), and between ALP and ELF (0.37), PRO-C3 (0.35), and LSM (0.30). **Conclusion:** Long-term PRO-C3 data from ELATIVE® support previous findings that ELA stabilizes NITs for fibrosis in patients with PBC; the relationship between NITs and clinical outcomes will be assessed with continued data from the ongoing OLE. PRO-C3 correlates well with established NITs in PBC, therefore serving as a potentially useful marker of disease progression.

References: 1. Kowdley K. V., et al. *N Eng J Med* 2024;390:795–805; 2. Kowdley K. V., et al. *Hepatology* 2025;81:60[Abstract #5041].

Figure. Mean change from baseline in PRO-C3 to Week 156



For crossover elafibranor data, baseline in this graph refers to the open-label extension baseline. BL: baseline; ELA: elafibranor; PBO: placebo; PRO-C3: N-terminal type III collagen propeptide; SE: standard error.

Disclosures: Christopher Bowlus: Calliditas: Grant/Research Support, ChemoMab: Grant/Research Support, ChemoMab: Consultant, COUR Phamaceuticals: Grant/Research Support, Cymabay: Grant/Research Support, Cymabay: Consultant, Gilead: Grant/Research Support, GSK Pharmaceuticals: Grant/Research Support, GSK Pharmaceuticals: Consultant, Hanmi: Grant/

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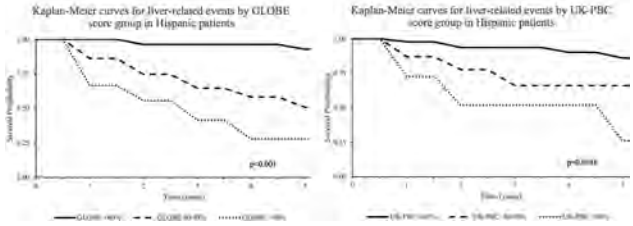
◆ 4398 | VALIDATION OF PROGNOSTIC MODELS IN HISPANIC PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: RESULTS: FROM THE ELLA-PBC COHORT

Paul Yoon[1] Adriana Shen[1] Matthew Chen[1] Tara Foroohar[1] Isai Martinez Rios[1] Sade Brown[1] Kali Zhou[1] Jeffrey Kahn[1] Saro Khemichian[2] Brian Lee[3] Jennifer Dodge[1] Lily Dara[2], [1]University of Southern California Keck School of Medicine, [2]University of Southern California, [3]Hoag Hospital

Background: Ursodeoxycholic acid (UDCA) response criteria and prognostic scoring systems are widely used to predict outcomes in primary biliary cholangitis (PBC), yet their performance in Hispanic patients remains largely unknown. In prior work, we found that Hispanic patients had 80% lower complete biochemical remission rates at 1-year compared to White patients. We aimed to evaluate the predictive accuracy of UDCA response criteria and prognostic scores for liver-related events (LE) in Hispanic patients with PBC. **Methods:** The East Los Angeles Latinx PBC (ELLA-PBC) cohort includes predominantly Hispanic patients at the University of Southern California Medical Centers (2006-2022). Patients with liver decompensation or liver transplant (LT) prior to UDCA initiation were excluded. UDCA response criteria (Barcelona, Paris I/II, Rotterdam, Toronto) and prognostic scores (GLOBE, UK-PBC) were evaluated. LE included decompensation, LT, or liver-related death. Cox proportional hazards models estimated hazard ratios (HRs), and Harrell's C-statistic assessed model discrimination. Kaplan-Meier curves were generated for risk-stratified groups. **Results:** The study included 312 patients (80 with LE) with a median follow-up of 48 months (IQR 25-74). At baseline, patients with LE were more likely to have cirrhosis ($p < 0.001$), elevated ALP ($p = 0.0016$), ALT ($p = 0.026$), AST ($p < 0.001$), bilirubin ($p < 0.001$), and lower albumin and platelets (both $p < 0.001$). The GLOBE and UK-PBC scores outperformed UDCA response criteria. Each 1 standard deviation increase in GLOBE score was associated with a near 3-fold higher risk of LE (HR 2.94, 95% CI 2.10-4.13, $p < 0.001$), with strong discrimination ($C = 0.80$). UK-PBC score also predicted LE (HR 2.21, 95% CI 1.67-2.92, $p < 0.001$, $C = 0.74$). As Hispanic patients made up 64.7% of the cohort, subgroup analysis was conducted. GLOBE (HR 2.67, 95% CI 1.86-3.83, $p < 0.001$, $C = 0.79$) and UK-PBC (HR 2.09, 95% CI 1.58-2.78, $p < 0.001$, $C = 0.77$) maintained predictive accuracy in Hispanic patients. Kaplan-Meier curves showed clear survival separation across GLOBE and UK-PBC score tertiles ($p < 0.001$ and $p = 0.0016$, respectively) in Hispanic patients. **Conclusion:** This study provides important validation of the GLOBE and UK-PBC scores in predicting LE among Hispanic patients with PBC, a population underrepresented in prognostic research. While UDCA response criteria showed variable utility, prognostic scores consistently predicted outcomes, supporting the use of GLOBE and UK-PBC scores to guide risk stratification and clinical decisions in Hispanic patients. Further studies with larger, racially diverse cohorts are needed to evaluate potential differences across racial and ethnic groups.

Predictive performance of biochemical response criteria and prognostic scores

	Overall				Hispanic			
Model	n	HR (95% CI)	p-value	C-statistic	n	HR (95% CI)	p-value	C-statistic
Barcelona	130	1.16 (0.53–2.55)	0.72	0.47	97	0.98 (0.40–2.39)	0.96	0.57
Paris I	130	2.84 (1.33–6.09)	0.0073	0.62	97	2.83 (1.21–6.64)	0.017	0.63
Rotterdam	150	5.11 (2.52–10.33)	<0.001	0.69	107	5.32 (2.42–11.69)	<0.001	0.71
Toronto	130	1.31 (0.63–2.75)	0.47	0.49	97	1.32 (0.57–3.07)	0.51	0.49
Paris II	130	4.10 (1.24–13.56)	0.021	0.59	97	5.39 (1.26–23.04)	0.023	0.63
GLOBE*	127	5.82 (2.47–13.70)	<0.001	0.71	97	8.44 (2.84–25.06)	<0.001	0.75
GLOBE**	127	2.94 (2.10–4.13)	<0.001	0.80	97	2.67 (1.86–3.83)	<0.001	0.79
UK-PBC**	112	2.21 (1.67–2.92)	<0.001	0.74	85	2.09 (1.58–2.78)	<0.001	0.77



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◆ 4399 | CNP-104 DEMONSTRATES CLINICAL BENEFITS IN PRIMARY BILIARY CHOLANGITIS (PBC) THROUGH IMPROVED COMPOSITE BIOCHEMICAL MARKERS AND PROGNOSTIC SCORES

Molly Frey[1] Christopher Bowlus[2] Adam Elhofy[1] Derrick McCarthy[1] Erik Wambre[3] Stephen Caldwell[4] Roberto

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Background: Primary biliary cholangitis (PBC) is a progressive autoimmune liver disease with significant unmet needs, particularly for the 40% of patients who fail first-line UDCA therapy. Current treatments targeting bile acid metabolism do not address the underlying autoimmune pathogenesis, representing an opportunity for novel immunotherapies. To this end, CNP-104 nanoparticles encapsulating PDC-E2 antigen were designed to restore PDC-E2 tolerance, offering a mechanistically distinct approach to PBC disease-modification. Here we present the effects of CNP-104 on validated prognostic tools including the UK-PBC score (liver-related outcomes), GLOBE score (transplant-free survival), and ALBI (liver function) to risk-stratify and evaluate treatment response in PBC. **Methods:** In this randomized, placebo-controlled trial, 41 PBC patients with an incomplete biochemical response (ALP $>1.5\times$ULN) received two doses of CNP-104 or placebo one week apart. Shown here are the 4 mg/kg CNP-104 (n = 11) and placebo (n = 16) groups. The study assessed safety (reported previously) and exploratory clinical endpoints including UK-PBC 5-year risk score, GLOBE score, and ALBI score ($<$ 0.065-point increase). **Results:** CNP-104 demonstrated consistent benefit across prognostic measures. Patients treated with CNP-104 showed a between-group difference in UK-PBC 5-year risk score (Δ −3.51%) compared to placebo (p = 0.010). An exploratory analysis of the less established ALBI score, where response is defined as a change $\leq$ 0.065 /6 months favored CNP-104, with 80% (8/10) of treated patients achieving response versus 26.7% (4/15) in placebo (p = 0.0154). The more established GLOBE score also showed a between-arm difference that was worse in placebo (Δ 0.227, p = 0.0125), suggesting attenuated long-term risk. **Conclusion:** CNP-104 improved UK-PBC and GLOBE scores, indicators of long-term risk reduction, in a treatment-refractory PBC population, highlighting its potential to modify disease course in those with limited therapeutic options. Notably, these benefits were observed after two loading doses, supporting further evaluation of a chronic dosing regimen in Phase 2b trials. CNP-104 represents a multidimensional therapeutic strategy for PBC patients, warranting advancement to confirmatory studies.

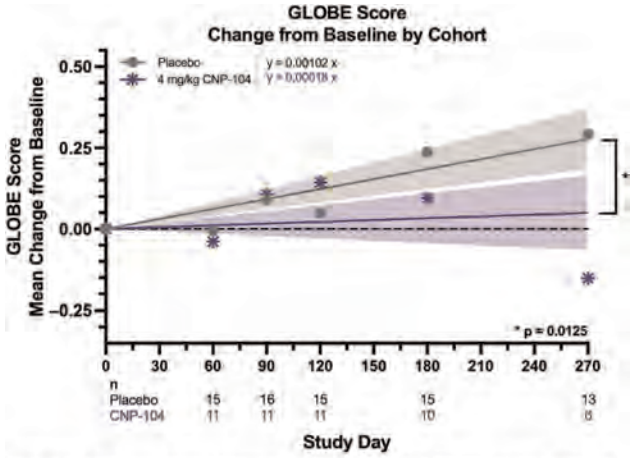

Figure 1. CNP-104 treatment suggests a separation in transplant-free survival by GLOBE Score. Plotted datapoints are representative of the mean change from baseline in GLOBE Score for each treatment group at each study timepoint. The line of best-fit displayed for each cohort is fitted by least squares regression with shading to indicate 95% confidence intervals. Statistical testing: comparison of slope via extra sum of squares F-test; * p ≤ 0.05.

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◆ 4400 | NEBOKITUG TARGETS MACROPHAGE-MEDIATED MECHANISMS IN PRIMARY SCLEROSING CHOLANGITIS WITH POTENTIAL IMPACT ON DISEASE PROGRESSION

Revital Aricha[1] Tom Snir[1] John Lawler[1] Ilan Vaknin[1] Raanan Greenman[1] Adi Mor[1], [1]Chemomab Therapeutics

Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive inflammatory and fibrotic injury to the biliary tree. A key element of PSC pathogenesis is sustained innate immune activation, prominently involving hepatic macrophages. Elevated levels of macrophage-associated proteins-including soluble CD14, Mannose receptor C-type 1 (MRC1), and osteopontin (SPP1) observed

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in patients with PSC and correlate with poor clinical outcomes. Macrophage stimulating 1 (MST1), a driver of anti-inflammatory macrophage polarization, is functionally impaired by a genetic variant that is linked to PSC. Nebokitug, a monoclonal antibody against CCL24, has shown promising modulation of inflammation and fibrosis markers in the Phase 2 SPRING trial (NCT04595825) as well as modulation of macrophages activity in pre-clinical studies. Here, we evaluated its effect on macrophage-driven activity in patients with PSC by assessing changes in key macrophage related biomarkers that are known to be clinically meaningful through their association with clinical outcomes. **Methods:** SPRING study is a randomized, double-blind, placebo-controlled trial in patients with PSC receiving nebokitug 10 or 20 mg/kg IV every 3 weeks for 15 weeks or placebo. Levels of sCD14, MRC1, LBP, SPP1, and MST1 were assessed by Olink® proximity extension assay (PEA) on serum samples available from 66 patients (placebo n = 18; nebokitug 10 mg/kg n = 21 and 20 mg/kg n = 27) at baseline and week 15. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of these biomarkers to predict treatment response as measured by changes in ELF score and liver stiffness measurement (LSM). **Results:** Nebokitug treatment led to dose-dependent reductions in serum macrophage-related proteins as compared to placebo treated patients, predominantly in patients with moderate/advanced disease (LSM > 8.7 Kpa at baseline), including soluble CD14 (20 mg/kg p = 0.03; 10 mg/kg p = 0.17) MRC1 (20 mg/kg p = 0.005; 10 mg/kg p = 0.2) and SPP1 (p = 0.003; 10 mg/kg p = 0.06). In addition, MST1 expression increased dose-dependently (20 mg/kg p < 0.0001; 10 mg/kg p = 0.0018). Macrophage activity is known to play a role in PSC pathophysiology and its modulation may impact disease progression. It was further shown that the changes seen in these biomarkers following treatment with nebokitug were associated with improvements seen in ELF score and LSM (AUC = 0.87). **Conclusion:** Nebokitug modulates key macrophage-related biomarkers in patients with PSC that have been shown to correlate with disease progression. These data suggest a potential role for nebokitug in modifying disease biology and support continued clinical evaluation.

Disclosures: Revital Aricha: Nothing to Disclose, Tom Snir: Nothing to Disclose, John Lawler: Nothing to Disclose, Ilan Vaknin: Nothing to Disclose, Raanan Greenman: Chemomab: Employee, Adi Mor: Nothing to Disclose

◆ 4401 | TARGETING CCL24 RESTORES MST1 EXPRESSION: A MECHANISTIC INSIGHT FROM THE SPRING TRIAL

Revital Aricha[1] Tom Snir[1] John Lawler[1] Ilan Vaknin[1] Raanan Greenman[1] Adi Mor[1], [1]Chemomab Therapeutics

Background: Macrophage Stimulating 1 (MST1), acts as a negative regulator of macrophage-associated inflammation. In patients with primary sclerosing cholangitis (PSC), a disease characterized by inflammation and fibrosis of the bile ducts, MST1 function is impaired due to a disease-associated Single nucleotide polymorphism, and its expression in the liver is significantly lower in PSC compared to healthy individuals. Nebokitug, a monoclonal antibody against CCL24, has shown promising modulation of inflammation and fibrosis related markers in the Phase 2 SPRING trial (NCT04595825). Here, we evaluated the association between CCL24 blockade and MST1 as a disease relevant pharmacodynamic (PD) marker. **Methods:** SPRING phase 2 study is a randomized, double-blind, placebo-controlled study in PSC patients treated with nebokitug (10 or 20 mg/kg IV) or placebo every 3 weeks for 15 weeks. Serum MST1 levels were assessed by Olink® proteomics at baseline and week 15. Associations between MST1, CCL24 and changes in liver stiffness measurement (LSM) were evaluated. MST1 levels were also evaluated in nebokitug –treated metabolic dysfunction-associated steatohepatitis (MASH) patients (5 mg/kg SC Q2W for 16 weeks) and in two relevant preclinical models: $Mdr2^{-/-}$ and TAA-induced liver fibrosis. **Results:** Serum levels of MST1 in PSC patients were found to be reduced compared to healthy individuals. In the SPRING study, nebokitug induced a dose-dependent increase in MST1 (10 mg/kg $p = 0.0018$; 20 mg/kg $p < 0.0001$), with no change in the placebo group. A significant correlation was observed between change in MST1 and CCL24 (Pearson $R = 0.62$, $p = 3.9e{-}08$), supporting MST1 as a downstream marker of CCL24 blockade that is also relevant to liver diseases. Notably, MST1 increase was associated with a greater reduction in LSM. MASH patients treated with nebokitug showed a 1.6–1.85-fold increase in MST1 by week 16, detectable as early as week 2. In addition, in preclinical models, liver MST1 mRNA expression was increased by approximately two-fold in nebokitug treated mice compared to vehicle controls, consistent with the clinical observations. **Conclusion:** Nebokitug treatment in PSC patients leads to a significant dose-dependent increase in MST1,

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correlating with CCL24 target engagement and reduction in LSM. These results from the SPRING trial suggest that MST1 may serve as a PD biomarker of nebokitug activity and further support its anti-inflammatory mechanism of action.

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◆ 4402 | ESTABLISHING THE SAFETY PROFILE OF LINERIXIBAT FOR THE TREATMENT OF CHOLESTATIC PRURITUS IN PRIMARY BILIARY CHOLANGITIS: POOLED SAFETY ANALYSIS OF GLIMMER AND GLISTEN STUDIES

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Background: Linerixibat is a minimally absorbed ileal bile acid transporter inhibitor in development for the treatment of cholestatic pruritus in primary biliary cholangitis (PBC). Gastrointestinal effects are anticipated adverse events (AEs) consistent with the mechanism of action of ileal bile acid transporter inhibitors. A pooled safety analysis from the Phase 2 GLIMMER study (NCT02966834) and the Phase 3 GLISTEN study (NCT04950127) was conducted to further assess the safety profile of linerixibat. **Methods:** The analysis included safety data from Part A of GLISTEN (participants received linerixibat 40 mg twice daily [BID] or matching placebo for 24 weeks) and participants concurrently randomized to the linerixibat 40 mg BID and placebo groups from the 12-week GLIMMER study. A subgroup analysis by age, race, ethnicity, sex, and cirrhosis at baseline was performed. **Results:** The analysis included 270 participants (placebo, n = 128; linerixibat, n = 142). Overall, 127 (89%) participants in the linerixibat group and 94 (73%) in the placebo group experienced ≥1 adverse event (AE) (Table); the maximum intensity experienced by most participants was mild/moderate (n = 200/221; 90%). The most common AEs in the linerixibat group were gastrointestinal (GI) events: diarrhea (n = 84; 59%) and abdominal pain (n = 24; 17%). Most participants experienced diarrhea events that were mild (n = 49/84; 58%) in intensity and occurred within 1 week of initiating treatment. Overall, 18 (13%) participants reported AEs that led to treatment discontinuation in the linerixibat group; discontinuation due to diarrhea was infrequent (n = 6; 4%). Liver-related AEs were reported more frequently in the linerixibat group (n = 22; 15%) compared with placebo (n = 10; 8%), and were mostly due to alanine aminotransferase and/or aspartate aminotransferases increases; however, these were transient and asymptomatic. There were no serious AEs (SAEs) reported in the placebo or linerixibat 40 mg BID groups in GLIMMER. In the GLISTEN study, SAEs were reported in 14 (12%) participants in the linerixibat group and 4 (3%) in the placebo group; none were fatal and were of singular frequency, with no discernible patterns. No differences were observed across all intrinsic factors in the subgroup analysis. **Conclusion:** Linerixibat was generally well-tolerated. GI events, including diarrhea and abdominal pain, were the most frequently reported AEs. There was no laboratory evidence that linerixibat causes drug-induced liver injury. These results further support the acceptable safety profile of linerixibat.

Funding: GSK (212620; 201000)

Table. Overall summary of AEs

	Pooled placebo (n=128)		Pooled linerixibat 40 mg BID (n=142)	
	n (%)	Rate/100 PY*	n (%)	Rate/100 PY*
Any AE	94 (73)	390.20	127 (89)	1049.71
AE related to study treatment	30 (23)	68.45	91 (64)	374.17
Any AEs leading to permanent discontinuation of study treatment	8 (5)	11.29	18 (13)	34.23
AEs leading to withdrawal from study	2 (2)	3.75	5 (4)	9.35

*The number of participants with occurrence of a specific event divided by the total exposure duration in years, multiplied by 100.
AE, adverse event; BID, twice daily; PY, person-years.

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◆ 4403 | POSSIBLE/UNLIKELY DRUG INDUCED LIVER INJURY CASES WITH AUTOIMMUNE FEATURES ARE SIGNIFICANTLY ENRICHED WITH TRADITIONAL AIH HLA RISK ALLELES

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Background: Drug induced liver injury (DILI) can mimic many liver conditions and can be misdiagnosed. Discerning sporadic, autoimmune hepatitis (AIH) from idiosyncratic DILI with autoimmune features is challenging as both can have similar laboratory and histological features. Our aim was to compare clinical, histological and genetic features of suspected DILI cases enrolled into DILIN studies which were ultimately adjudicated as probable AIH to a cohort of well characterized sporadic AIH cases. **Methods:** Cohort 1: 103 patients enrolled in the Drug-Induced Liver Injury Network (DILIN) studies which were adjudicated as "possible or unlikely" by the causality committee and given an alternate diagnosis of probable AIH. Cohort 2: Sporadic AIH, 254 patients from the Genetic Repository of Autoimmune Liver Disease and Contributing Exposures (GRACE) cohort at Indiana University from 2014 to 2019. Clinical, laboratory, and histological features were compared between Cohorts 1 and 2. AIH risk alleles in both cohorts were compared to healthy controls (HC) without known liver disease from the Indiana Biobank (n = 3,016). Genetic analysis was limited to patients of European descent. **Results:** Demographic features between cohorts were similar (Table 1). Liver biochemistries were significantly higher in DILIN cases compared to sporadic AIH at diagnosis ($p = 0.001$, for all). DILIN cases were less likely than sporadic AIH cases to have positive SMA (55.7% vs 75.2%, $p = 0.004$) and increased IgG (1689 mg/dL vs 1961 mg/dL, $p = 0.007$). DILIN cases were less likely than sporadic DILIN cases to be categorized as "Definite" AIH vs DILIN cases (26.5% vs 60.8%, $p = 0.004$). Among cases with available liver biopsy (~: 85%), DILIN and sporadic AIH cases were scored relatively similarly (57.4% vs 72.3% as "likely"). Allele frequencies of *HLA-DRB1*03:01* in both DILIN cases (22.9%) and sporadic AIH (29.2%) were higher relative to HC (14.2%, $p = 2.6\times10^{-8}$ and 1.7×10^{-2}, respectively). Allele frequencies of having either *HLA DRB1*0301* or *DRB1*0401* were increased in both DILIN (34.7%) and AIH (40.6%) groups compared to HC (25%, $p = 1.6\times10^{-8}$ and 3.4×10^{-2}, respectively). **Conclusion:** AIH cases enrolled into the DILIN masquerading as suspected DILI have distinct clinical features but share HLA risk alleles. Testing for traditional AIH HLA risk alleles may facilitate the causality adjudication in selected cases of suspected DILI when it is difficult to distinguish DILI from sporadic AIH.

Table 1: Comparison of DILIN Cases ultimately adjudicated as unlikely/possible with an alternate diagnosis of probable autoimmune hepatitis and Sporadic AIH cases

	Unlikely/Possible DILIN cases (n=103)	Sporadic AIH cases from GRACE (n=254)	p-value
Age at enrollment (yrs)	51.2 (14.6)	51.9 (16.4)	0.71
Age at diagnosis (yrs)	51.2 (14.6)	46.9 (17.4)	0.03
% Females	84.5%	79.3%	0.78
% White	74.5%	85.3%	0.26
BMI (kg/m2)	28.6 (7.2)	29.7 (7.9)	0.22
AST (U/L)	945 (765)	290 (421)	<0.0001
ALT (U/L)	1,022 (867)	328 (454)	<0.0001
Alk Phos (U/L)	227 (163)	160 (133)	0.0001
Total Bilirubin (mg/dL)	8.1 (7.1)	3.2 (5.1)	<0.0001
INR	1.6 (1.68)	1.2 (0.3)	0.0003
IgG (mg/dL)	1689 (830)	1961 (888)	0.007
% ANA +	55%	54.2%	0.91
% AMSA+	55.7%	75.20%	0.0004
Simplified AIH Score	17.6% - Probable AIH 26.5% – Definite AIH	12.1% -Probable AIH 60.8% – Definite AIH	0.0007
DILIN illness severity score			<0.0001
1	17.5%	75.7%	
2	11.7%	20.7%	
3	38.8%	3.6%	
4	27.2%	0	
5	4.9%	0	
Pattern of injury (R value)	5.3% Cholestatic 15.1% Mixed 79.5% Hepatocellular	39% Cholestatic 21% Mixed 39% Hepatocellular	<0.0001
Liver biopsy completed, %	84.5%	84.9%	
% Liver biopsy, possible	34.5%	23.5%	0.07
% Liver biopsy, likely	57.4%	72.3%	
% Liver biopsy, atypical	9.3%	4.2%	
Liver transplant, %	1.9%	9.6%	0.01
Death, %	4.9%	3.2%	0.53
DRB1*03:01, % allele frequency *vs controls (14.2%)*	22.9% $p = 1.6\times10^{-8}$	29.2% $p = 2.6\times10^{-4}$	
DRB1*04:01, % allele frequency *vs controls (10.8%)*	11.9% $p = 0.75$	11.4% $p = 0.60$	
DRB1*03:01 or DRB1*04:01, % allele frequency *vs controls (25%)*	34.7% vs 25% controls $p=3.4\times10^{-2}$	40.6% vs 25% controls $p=1.6\times10^{-8}$	

* Data reported as Mean (SD)

Abbreviations: BMI: Body mass index; MASLD: Metabolic dysfunction associated steatotic liver disease; AED: Antiepileptic drugs; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline Phosphatase; DILIN: Drug induced liver injury network; ANA: Anti-nuclear antibody; SMA: Smooth muscle antibody; INR: International normalized ratio; IgG: Immunoglobulin G. AIH: Autoimmune hepatitis; GRACE: Genetic Repository of Autoimmune Liver Disease and Contributing Exposures.

Disclosures: Craig Lammert: Eli Lilly: Consultant, Kezar Life Sciences: Consultant, Amgen: Consultant, Autoimmune Hepatitis Association: Consultant,

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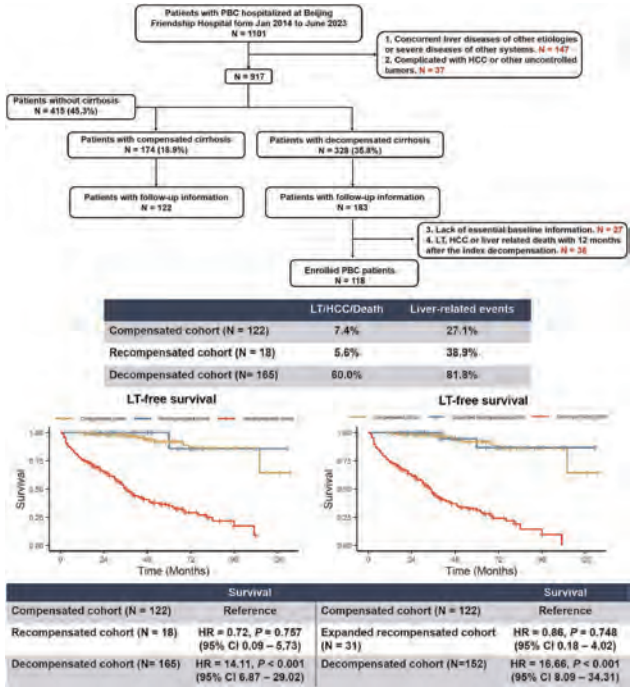
◆ 4404 | FACTORS ASSOCIATED WITH RECOMPENSATION AND CRITERIA FOR AETIOLOGICAL CONTROL IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

Li Shen[1] Tingting Lv[1] Shuxiang Li[1] Sha Chen[1] Buer Li[1] Xin Zeng[1] Qin Xiao[1] Yuanyuan Kong[2] Yu Wang[1] Hong Ma[1] Xinyan Zhao[1] Hong You[1] Weijia Duan[1] Jidong Jia[1], [1]Liver Research Center, Beijing Friendship Hospital, Capital Medical University, [2]Beijing Friendship Hospital, Capital Medical University, National Clinical Research Center for Diges

Background: A successful aetiological therapy may lead to hepatic recompensation in patients with decompensation cirrhosis. However, the criteria for recompensation of cirrhosis in primary biliary cholangitis (PBC) patients is not well defined. Therefore, our study aimed to explore the criteria for aetiological control and provide preliminary insights into PBC recompensation. **Methods:** In this retrospective-prospective study, we enrolled hospitalized patients with PBC from January 2014 to June 2023. Recompensation was defined according to the Baveno VII criteria. Additionally, expanded recompensation criteria were evaluated for patients on low dose diuretics and/or lactulose/rifaximin. The long-term prognosis between recompensated/expanded recompensated and compensated patients was compared. We explored whether the biochemical response to UDCA could serve as a surrogate marker for aetiological control. **Results:** A total of 305 PBC patients with follow-up data were included in the study, comprising 122 compensated cases and 183 decompensated cases. Among the 183 decompensated patients, 118 with complete data were further analyzed, with a median follow-up of 50.0 (31.0, 72.0) months. 18 (15.3%) out of 118 patients achieved hepatic recompensation. 31(26.3%) patients met the expanded recompensation criteria. The recompensated rate was highest in the variceal hemorrhage group at 52.9%, followed by the Ascites/HE group at 9.8%, and the Mixed group at 7.5%. Patients who experienced decompensation before starting UDCA therapy could achieve better biochemical response and showed a higher rate of recompensation compared with those who experienced decompensation after starting UDCA therapy for at least 12 months (23.2% *vs.* 8.1%, SHR = 2.93, $P = 0.04$). Both recompensated and expanded recompensated patients showed a similar long-term outcome with compensated patients. Achieving the response to Paris I criteria (SHR = 21.65, $P < 0.001$), Paris II criteria (SHR = 35.46, $P < 0.001$) and Momah/Lindor criteria (SHR = 33.44, $P < 0.001$) is associated with a higher incidence of recompensation. **Conclusion:** Patients with decompensated cirrhosis due to PBC may regress to recompensation stage and show a similar prognosis with compensated patients after achieving biochemical response to UDCA therapy. Paris I criteria, Paris II criteria and Momah/Lindor criteria could be used as surrogate markers for successful aetiological control of PBC.



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◆ 4405 | IMMUNOMODULATION OF CYTO/CHEMOKINES AND T CELL ACTIVATION BY PPAR AGONISTS IN PBC: A COMPARATIVE ANALYSIS

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Background: Second-line treatment of PBC has been revolutionized by fibrates and more recently PPAR agonists. Their immunomodulatory effects, however, have not been characterized in PBC and it is not known if these PPAR agonists have different effects on blunting hepatocyte secretion of cyto/chemokines induced by toxic bile acids. Therefore, we studied the effect of fibrates and PPAR agonists on hepatocyte production of bile acid-induced cyto/chemokines, and on peripheral T cell activation. **Methods:** Primary human hepatocytes isolated from residual surgical specimens were plated then treated with GCDCA (100 uM) ± individual fibrates/PPAR agonists: bezafibrate, fenofibrate, seladelpar, elafibranor, or saroglitazar for 24 hrs. Hepatocytes were harvested for mRNA analysis and supernatants collected for sandwich ELISA (n = 4-6). Peripheral CD4 T cells from healthy individuals were activated with CD3/CD28 beads then treated with each of the above drugs for 48 hrs (n = 5-7) followed by flow cytometry. Peripheral CD4 T cells from PBC patients with an incomplete response to UDCA, or responding to UDCA + fenofibrate, were isolated, activated, and analyzed *ex vivo* (n = 4-5). **Results:** Stimulation with GCDCA significantly increased hepatocyte expression and secretion of inflammatory cyto/chemokines, whereas co-treatment with GCDCA and each fibrate/PPAR agonist significantly reduced gene expression of cytokines *CCL2* and *CCL15*. Secretion of CCL20 and IL-8, however, were significantly reduced only by seladelpar (mean 835 ± 404 vs. 144 ± 44 pg/mL, p = 0.02; 299 ± 135 vs. 76 ± 35 pg/mL, p = 0.07, respectively). Interestingly, treatment of activated healthy control peripheral CD4 T cells showed that seladelpar, elafibranor, and bezafibrate significantly reduced T cell activation marker CD69, while other drugs had no effect. Finally, *ex vivo* activated CD4 T cells from PBC patients, responding to UDCA + fenofibrate, expressed lower intracellular IL-17 vs. T cells from patients with incomplete response to UDCA (1.2 ± 0.5 vs. 3.7 ± 0.8%, p = 0.001). **Conclusion:** Our findings reveal heterogeneity among PPAR agonists' ability to modulate bile acid-induced cyto/chemokine secretion by hepatocytes, and to reduce peripheral T cell activation. Among the PPAR agonists tested, seladelpar was the most effective *in vitro,* while fenofibrate reduced reactivity of T cells from PBC patients *ex vivo*. Further studies comparing immunomodulatory properties of PPAR agonists in PBC patients receiving treatment are warranted.

Disclosures: Scott Roberts: Nothing to Disclose, Shi-Ying Cai: Nothing to Disclose, Ziqian Xu: Nothing to Disclose, Marina Silveira: Nothing to Disclose, Nisanne Ghonem: Nothing to Disclose, James Boyer: Mirum Pharmaceuticals: grant recipient, IPSEN: Clinical Event-ets Committee for clinical trial, AstroZenica: Member of Clinical Events Committe, David Assis: Nothing to Disclose

◆ 4406 | ODEVIXIBAT TREATMENT IN PATIENTS WITH ALAGILLE SYNDROME: CHARACTERIZATION OF OUTCOMES BY SERUM BILE ACID LEVELS AFTER 24 WEEKS OF TREATMENT IN AN INTEGRATED ANALYSIS FROM ASSERT AND ASSERT-EXT

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Background: Robust long-term data demonstrate improvements in pruritus, reductions in serum bile acids (sBA), and manageable safety with odevixibat (ODX) in patients with Alagille syndrome (ALGS) across the phase III ASSERT and ASSERT-EXT studies with up to 96 weeks of treatment (NCT04674761 and NCT05035030). Here we characterize the impact of ODX on liver parameters and clinical outcomes according to sBA level at 24 weeks. **Methods:** Outcomes for patients with ALGS treated with ODX (120 μg/kg/day) in ASSERT and ASSERT-EXT were stratified by Week 24 sBA levels $\leq$102 μmol/L (versus $>$102 μmol/L); this threshold was associated with better clinical outcomes in patients with cholestatic ALGS in the GALA study (Murillo Perez, EASL 2023). Patients with sBA levels $\leq$102 μmol/L at baseline (BL) were excluded. Endpoints included: clinically meaningful pruritus response (defined as $\geq$1 point reduction in observer-reported scratching score [0−4 scale]), liver parameters, and clinical outcomes. **Results:** 52 patients with ALGS received ODX during ASSERT and ASSERT-EXT. Of these, 7 patients with BL sBA $\leq$102 μmol/L were excluded; 40 patients with available 24-week data were included in this *post-hoc* analysis. 40% (16/40) of patients achieved sBA $\leq$102 μmol/L with ODX at Week 24. Patients who achieved this threshold had lower bilirubin levels (Table) and lower mean (SD) sBA levels at BL (226.2 [91.64] vs 290.2 [125.54] μmoL/L) than patients who did not achieve sBA $>$102 μmol/L at Week 24. Pruritus responses were achieved at Weeks 21−24 in 81.3% (13/16) of patients with sBA $\leq$102 μmol/L and 69.6% (16/23) with sBA $>$102 μmol/L. At Weeks 69−72, pruritus responses were achieved in 93.3% (14/15) and 85% (17/20) patients with sBA $\leq/>$102 μmol/L, respectively. Liver parameters and platelet counts $\leq$150 x 10^9/L are reported by sBA $\leq$102/$>$102 μmol/L groups (Table). Data assessing outcomes by sBA percentage change will be presented. **Conclusion:** Patients with ALGS treated with ODX achieved clinically meaningful improvements in pruritus by Week 24 that were sustained long-term, independent of sBA level at Week 24. Higher bilirubin and sBA levels at BL, indicating more advanced disease, were seen in patients who did not achieve sBA $\leq$102 μmol/L after 24 weeks of treatment with ODX. Further study is warranted to explore sBA thresholds predictive of clinical outcomes in patients with ALGS receiving ODX.

Table. Liver parameters and clinical outcomes stratified by sBA levels (≤102 μmol/L and >102 μmol/L) after 24 weeks of treatment with ODX

	Baseline, mean (SD)*		Week 72, mean (SD)		Change from baseline to Week 72, mean (SD)*		
	sBA ≤102 μmol/L at Week 24 (n=15)	sBA >102 μmol/L at Week 24 (n=21)	sBA ≤102 μmol/L at Week 24 (n=15)	sBA >102 μmol/L at Week 24 (n=21)	sBA ≤102 μmol/L at Week 24 (n=15)	sBA >102 μmol/L at Week 24 (n=21)	p-value†
Direct bilirubin, μmol/L	38.13 (31.03)	70.82 (48.82)	36.53 (27.13)	68.52 (51.10)	0.41 (25.82)	−2.30 (23.42)	0.745
Total bilirubin, μmol/L	38.04 (30.99)	79.82 (53.92)	41.27 (30.22)	75.51 (53.27)	3.23 (26.09)	−4.31 (26.35)	0.401
Direct bilirubin, mg/dL	2.11 (1.81)	4.14 (2.88)	2.14 (1.59)	4.01 (2.99)	0.02 (1.51)	−0.13 (1.37)	0.745
Total bilirubin, mg/dL	2.22 (1.81)	4.67 (3.15)	2.41 (1.77)	4.42 (3.12)	0.19 (1.53)	−0.25 (1.54)	0.401
ALT, U/L	183.5 (108.20)	175.8 (64.97)	237.9 (105.17)	256.0 (119.14)	54.4 (102.69)	80.2 (96.61)	0.447
AST, U/L	168.9 (108.30)	161.6 (62.28)	194.5 (87.83)	235.7 (126.02)	25.6 (61.81)	74.1 (98.11)	0.101
	Baseline, n (%)		Week 72, n (%)				
	sBA ≤102 μmol/L at Week 24 (n=15)	sBA >102 μmol/L at Week 24 (n=21)	sBA ≤102 μmol/L at Week 24 (n=15)	sBA >102 μmol/L at Week 24 (n=21)			
Platelet count ≤150 x 10^9/L	1 (6.3)	3 (12.5)	2 (13.3)	3 (14.2)			

* Only includes data for the subset of patients remaining on treatment at Week 72. Patients with sBA levels ≤102 μmol/L at baseline were excluded. † p-value for sBA ≤102 μmol/L vs sBA >102 μmol/L groups based on 2-sample 2-sided t-test
ALT, alanine transaminase; AST, aspartate transaminase; sBA, serum bile acid

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◆ 4407 | HIGH RATE OF EARLY ALP NORMALIZATION WITH UDCA–BEZAFIBRATE COMBINATION THERAPY IN TREATMENT-NA&IUML; VE PRIMARY BILIARY CHOLANGITIS: PRELIMINARY RESULT

Juan Sorda[1] Fernando Barreyro[2] Guillermo Fernandez[3] Matias Bori[1] Esteban Gonzalez Ballerga[1], [1]Hospital de Clinicas, Universidad de Buenos Aires, [2]National University of Misiones, [3]Hospital Teodoro J. Schestakow

Background: Ursodeoxycholic acid (UDCA) is the standard first-line therapy for primary biliary cholangitis (PBC). Normalization of alkaline phosphatase (ALP) after one year of therapy is associated with improved transplant-free survival, and the one-year response can be predicted by the ALP level at six months. Bezafibrate (BZF) improves liver biochemistry in incomplete UDCA responders, but early ALP normalization with up-front UDCA + BZF has not been evaluated. We therefore assessed ALP normalization at six months with UDCA alone versus UDCA + BZF at two different doses. **Methods:** In this open-label, prospective study, anti-mitochondrial-antibody–positive, non-cirrhotic PBC patients (enrolled from January 2022) were randomized 2:2:1 to receive UDCA (13–15 mg/kg/day) alone, UDCA + BZF 400 mg, or UDCA + BZF 800 mg daily. Liver function tests, blood urea nitrogen, serum creatinine, and creatine kinase were measured monthly for six months. The primary end point was ALP $\leq 1 \times$ upper limit of normal (ULN) at month 6; secondary end points were changes in other liver enzymes, pruritus, and safety parameters. Data were analyzed with χ^2 tests, ANOVA, linear mixed-effects models, and Dunnett- or Tukey-adjusted post-hoc tests (two-sided $\alpha = 0.05$). **Results:** This interim analysis includes 52 patients who completed six months of therapy. Baseline histological stages 1/2/3 were present in 23/16/13 patients; mean age was 57 $\pm$ 11 years; 94 % were female; 38 % were symptomatic (pruritus); BMI was 25 $\pm$ 6 kg/m². Twenty-one patients received UDCA, 23 received UDCA + BZF 400 mg, and eight received UDCA + BZF 800 mg; baseline characteristics were comparable. At six months, ALP normalized in 100 % of UDCA + BZF 800 mg, 78 % of UDCA + BZF 400 mg, and 36 % of UDCA patients (χ^2 $p < 0.01$). Mean ALP ($\times$ ULN) at six months was 1.5 $\pm$ 0.7 (UDCA), 0.98 $\pm$ 0.2 (UDCA + BZF 400 mg), and 0.8 $\pm$ 0.2 (UDCA + BZF 800 mg) (ANOVA $p < 0.001$; post-hoc vs UDCA $p = 0.001$). Linear mixed-effects analysis showed significant time-dependent ALP declines in all groups; BZF intensified these monthly slopes ($\beta = -0.34$ for 400 mg and -0.44 for 800 mg vs UDCA, both Tukey-adjusted $p < 0.01$). Pruritus at six months occurred in 14 % of UDCA patients but in none of the BZF groups. Blood urea nitrogen and serum creatinine did not differ between groups at any time point. **Conclusion:** Up-front combination therapy with UDCA + BZF yields significantly higher six-month ALP normalization rates than UDCA alone and accelerates biochemical improvement in a dose-responsive manner. Notably, the 800-mg BZF combination achieved a 100 % response at six months. The clinical impact of early ALP normalization should be investigated in future studies. These preliminary results support initiating combination therapy, particularly in symptomatic patients.

Disclosures: Juan Sorda: Nothing to Disclose, Fernando Barreyro: Nothing to Disclose, Guillermo Fernandez: Nothing to Disclose, Matias Bori: Nothing to Disclose, Esteban Gonzalez Ballerga: Nothing to Disclose

4408 | THERAPEUTIC EFFECT OF PPAR AGONISTS ON PRURITUS AND QUALITY OF LIFE IN PBC: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PLACEBO-CONTROLLED TRIALS

ADRIELLY MARTINS[1] Nidah Khakoo[2] Christophe Corpechot[3] John Reynolds[4] Alexandra Rousseau[5] M Hassan Murad[6] Shahnaz Sultan[7] Andreas Kremer[8] Cynthia Levy[9], [1]Schiff Center for Liver Diseases - University of Miami, [2]Emory University, [3]Reference Center for Inflammatory Biliary Diseases and Autoimmune Hepatitis, ERN Rare-Liver, [4]Louis Calder Memorial Library, University of Miami Miller School of Medicine, Miami, FL, USA, [5]Clinical Research Platform of East of Paris, Saint-Antoine Hospital, APHP, [6]Mayo Clinic, Rochester, [7]University of Minnesota and and Minneapolis Veterans Affairs Medical Center, [8]University of Zürich, [9]University of Miami

Background: Pruritus is a frequent and debilitating symptom in primary biliary cholangitis (PBC), with substantial impact on health-related quality of life. Peroxisome proliferator-activated receptor (PPAR) agonists have emerged as promising second-line therapies for patients inadequately controlled with ursodeoxycholic acid (UDCA). We conducted a systematic review and meta-analysis to assess the comparative effectiveness of PPAR agonists on pruritus and quality of life in PBC. **Methods:** We systematically searched for randomized controlled trials (RCTs) of PPAR agonists in PBC through April 2024. Eligible studies included patients with moderate-to-severe pruritus, defined as a

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worst-itch numerical rating scale (WI-NRS) score ≥4 at baseline, and reported outcomes related to itch severity and quality of life, including WI-NRS, PBC-40 total score, PBC-40 itch domain, and 5-D itch score. The co-primary outcomes were mean change in WI-NRS and PBC-40 total score. Secondary outcomes included changes in the PBC-40 itch domain and 5-D itch score. Data were pooled using a random-effects model and expressed as mean differences (MD) with 95% confidence intervals (CI). **Results:** Five RCTs (n = 274 experimental, n = 162 control) met the inclusion criteria. WI-NRS improvements with PPAR agonists were observed at all assessed timepoints, including 3 months (MD −1.01; 95% CI −2.73 to 0.70), 6 months (MD −1.13; 95% CI −2.01 to −0.24), and 12 months (MD −1.73; 95% CI −2.97 to −0.48), demonstrating sustained pruritus reduction over time (Figure). PBC-40 total score and all secondary outcomes were assessed at 12 months. At that timepoint, PPAR agonists significantly improved PBC-40 total scores (MD −1.97; 95% CI −3.18 to −0.75). Significant improvements were also observed in the PBC-40 itch domain (MD −2.68; 95% CI −4.15 to −1.21) and 5-D itch score (MD −3.27; 95% CI −5.23 to −1.31). **Conclusion:** Treatment with PPAR agonists is associated with a sustained reduction in pruritus severity and improvement in health-related quality of life in patients with PBC and moderate-to-severe pruritus. These findings support their role as an effective therapeutic option in this patient population.

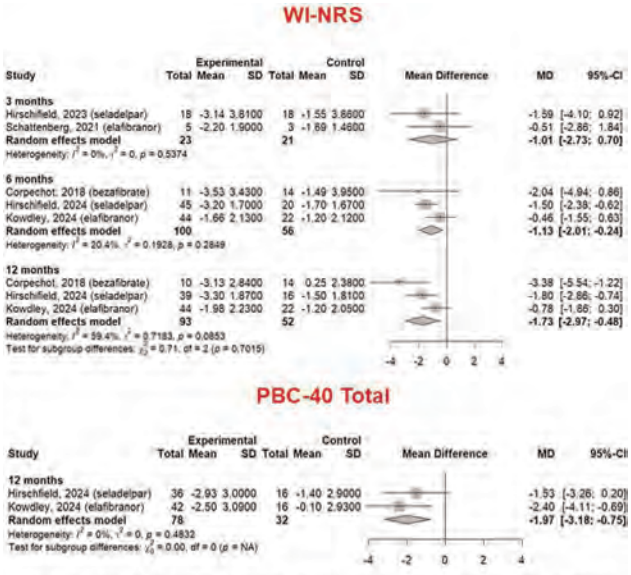

Figure. Effect of PPAR agonists on pruritus severity and quality of life in patients with PBC

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4409 | CLINICAL COURSE OF AUTOIMMUNE HEPATITIS AND RECOMPENSATION RATES IN DECOMPENSATED CIRRHOSIS

Anand Kulkarni[1] Ashirwad Pasumarthy[2] Akash Roy[3] Karan Kumar[4] Madhumita Premkumar[5] Mithun Sharma[2] Manasa Alla[2] Shantan Venishetty[2] Sowmya T R[2] Padaki Nagaraja Rao[2] Nageshwar Reddy[2] K Rajender Reddy[6], [1]Asian Institute of Gastroenterology,

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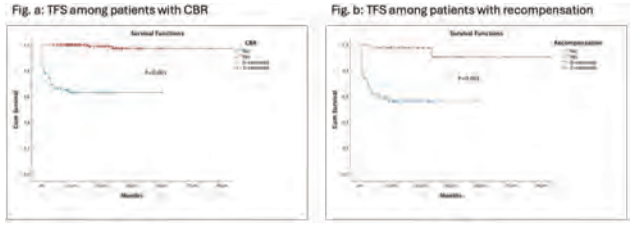
Background: Autoimmune hepatitis (AIH) is an uncommon cause of liver disease and can have varied presentations. The rate of recompensation in those with decompensation in AIH, and survival, is not well known, and thus we aimed to address this. **Methods:** A multicenter retrospective study included patients with AIH with varying presentations between 2018 and 2025. Demographics, clinical features at presentation and during follow-up, and survival data were collected. Recompensation (defined as Baveno VII) and complete biochemical response (CBR) rates, survival, and proportion of patients achieving MELD <10 were evaluated. **Results:** 255 patients (age-46 $\pm$ 13.8 years; women-73.3%; MELD-15.7; median bilirubin 3.1 mg/dl) with AIH with a median simplified score of 6 (6-8) and a median follow-up of 18.5 (0.2-94) months were included. Twenty per cent (52/255) had concurrent PBC, and 4% (10/255) had PSC. 84.3% received corticosteroids, 69% azathioprine as an additional first-line agent and 7% received mycophenolate mofetil and 2% received tacrolimus as second-line agents. Four patients underwent living donor liver transplantation. TFS was 87.5% (223/255; 95% CI, 82.7-91.2). Of the 223 alive patients, 60% (134/223) had achieved MELD scores less than 10 by the end of follow up. Of the 255 patients, 66% (168/255) achieved CBR. Of these 168, 25.6% experienced flares after drug discontinuation/non-compliance. On Kaplan Meier analysis, TFS among those who achieved CBR was 98.8% (166/168) compared to 65.5% (57/87) among those who did not achieve CBR ($P<0.001$). The incidence of hepatocellular carcinoma was 1.5% (4/255).

Of the 149 patients with cirrhosis at diagnosis, 75.8% (113/149) had evidence of decompensations (ascites, hepatic encephalopathy, variceal bleed) at diagnosis, with 15.4% (23/149), 48.3% (72/149), and 36.2% (54/149) patients in CTP A, B and C, respectively. Among the decompensated patients, 38.1% (43/113; 95%CI, 29.1-47.7) had recompensated by 8 (0.2-58) months. The TFS rate among recompensated patients was 95.3% (41/43) compared to 60% (42/70) among those who did not ($P<0.001$). Of the 119 cirrhosis patients who were alive at the end of follow-up, 57.1% (68/119) were in CTPA, 33.6% (40/119) in CTP B and the rest in CTP C (9.2%;11/119). On multivariable stepwise cox regression analysis use of beta blocker (HR, 0.5 [95% CI, 0.3-0.8];$P=0.01$), use of azathioprine (HR, 0.37 [95%CI, 0.22-0.61];$P<0.001$) and MELD score (HR, 1.04 [95%CI, 1.007-1.07];$P=0.01$) predicted lack of recompensation. **Conclusion:** Recompensation occurs in nearly 40% of patients and more than 60% achieve CBR. Recompensation and CBR were associated with improved survival.



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4410 | BRUTON'S TYROSINE KINASE REGULATES INFLAMMATION AND FIBROSIS IN PRIMARY BILIARY CHOLANGITIS

Prashanth Thevkar Nagesh[1] Marti Ortega Ribera[2] Yuan Zhuang[3] Arman Patel[2] Viliam Brezani[2] Aditi Ashish Datta[2] Scott Minchenberg[3] Bruna Santos[2] Veronika Brezani[2] Gyongyi Szabo[3], [1]Beth Israel Medical Center, [2]BIDMC - Harvard Medical School, [3]Beth Israel Deaconess Medical Center

Background: Liver fibrosis is a progressive scarring process due to chronic liver injury and remains without FDA-approved therapies. While causes like alcohol use, high-fat diet, and viral infection contribute to fibrosis, the pathogenesis of primary biliary cholangitis (PBC), an autoimmune liver disease involving inflammation and fibrosis of bile ducts, remains poorly understood. PBC progression is driven by dysregulated inflammation, hepatocyte injury, and cholangitis, which appear as promising therapeutic targets. Recently, we showed that Bruton's tyrosine kinase (BTK) is a key regulator of innate immune responses in neutrophil-driven liver injury in alcohol-associated hepatitis. BTK inhibitors are in clinical trials for autoimmune diseases, but their role in liver fibrosis, especially in PBC, is unknown. **Methods:** BTK activation (phospho-BTK Y223) was measured by ELISA in liver tissues from PBC patients and healthy controls. In mice, liver fibrosis was induced by (1) carbon tetrachloride (CCl_4; 0.6 µL/g in corn oil) injected weekly for 6 weeks or (2) bile duct ligation (BDL) in wild-type (WT) and BTK knockout ($BTK^{-/-}$) mice. Mice were euthanized 72 hours post-final CCl_4 injection or 14 days post-BDL. Liver fibrosis

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was assessed via Sirius Red staining and Western blot for α-SMA and gene expression of vimentin, Timp1 and Col1a2. Serum ALT and pro-inflammatory cytokines (TNFα, IL1β, MCP1) were quantified by ELISA. Flow cytometry was used to analyze liver non-parenchymal cells. Human primary hepatocytes, stellate cells, monocytes, and neutrophils were treated with LPS, TGFβ with or without BTK inhibitor evobrutinib, and inflammatory gene expression assessed by qPCR. **Results:** Our data reveal elevated BTK expression and activation (p-Y223) in livers from human PBC patients and in mouse models of cholangitis and CCL_4-induced fibrosis. In both models, $BTK^{-/-}$ mice showed attenuated fibrosis and serum cytokines (TNFα, IL1β, MCP1) compared to WT. Further, in $BTK^{-/-}$ mice with cholangitis, liver injury markers were reduced (ALT, bilirubin) compared to WT mice. In BDL model, WT mice showed increase in $EpCam^+$ cells (Cholangiocyte proliferation), and pBTK levels in $EpCam^+$ cells which was attenuated in the $BTK^{-/-}$ mice. Notably, myeloid-specific $BTK^{-/-}$ mice also showed reduced fibrosis (α-SMA and mRNA markers). Mechanistically, LPS induced BTK phosphorylation and inflammation (TNFα, IL1β, MCP1) in hepatocytes, macrophages, neutrophils, and activated stellate cells (α-SMA), which was attenuated by BTK inhibition (evobrutinib). **Conclusion:** These findings uncover a novel role for BTK in liver fibrosis and support its potential as a therapeutic target in PBC and chronic liver diseases.

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4411 | MARALIXIBAT, AN ILEAL BILE ACID TRANSPORTER INHIBITOR, REDUCES CHOLESTATIC PRURITUS IN PSC: REAL-WORLD EXPERIENCE

Jessica Hochberg[1] Robert Brown[2] David Goldberg[3] Joseph Cioffi[4] Adrielly Martins[5] Aparna Goel[6] Mercedes Martinez[7] Maria Carlota Londono[8] Taisa Kohut[9] Karan Emerick[10] Samantha Lee[11] Gloria Rothenberg[2] Cynthia Levy[3], [1]Jackson Memorial Hospital, [2]Weill Cornell Medicine, [3]University of Miami, [4]University of Miami School of Medicine, Miami, Florida, [5]Schiff Center for Liver Diseases, University of Miami Miller School of Medicine, Miami, Florida, [6]Stanford University Medical Center, [7]NewYork-Presbyterian, [8]Hospital Clinic, [9]Miller School of Medicine, University of Miami and Holtz Children's Hospital, Miami, Florida, [10]Connecticut Children's Medical Center, Hartford, Connecticut, [11]Connecticut Children's Medical Center, Hartford Connecticut

Background: Primary sclerosing cholangitis (PSC) is a progressive, autoimmune, cholestatic liver disease that may be associated with profound and debilitating pruritus. Maralixibat (MRX) is a minimally absorbed ileal bile acid transporter (IBAT) inhibitor that prevents enterohepatic bile acid recirculation. The drug is approved for the treatment of cholestatic pruritus in patients with Alagille syndrome and progressive familial intrahepatic cholestasis and led to reductions in pruritus and serum bile acids (sBA). This case series aimed to evaluate the efficacy, safety and tolerability of MRX in individuals with PSC treated through compassionate

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use (CU). **Methods:** The medical records of patients with PSC and treated with MRX through a CU program were retrospectively reviewed at 7 North American tertiary referral hospitals. Pruritus was assessed with the Clinician Scratch Scale (CSS), a 0-4 scale where $\geq$1-point reduction is considered clinically meaningful. **Results:** Eight patients (50% females) were included with the median (range) age of MRX initiation being 35.5 (7.0, 44.0) years, and the initial dose ranged from 190 to 380 μg/kg QD or BID. The median duration of treatment was 7.5 (4.0, 11.0) months. All patients had large-duct PSC. At baseline (BL), CSS was 4 in three patients, 3 in two patients and 2 in three patients. Following MRX, 7/8 patients had a $>$2-point improvement, with 4 having complete resolution (CSS = 0) and 3 having minimal itch (CSS = 1). 6/7 showed reduction of median sBA from 142 (62-506) to 37 (14-106) μmol/L, while 1 patient, known to have history of chronically elevated transaminases with significant fluctuations, had an increase in sBA from 317 to 433 μmol/L; sBA levels at BL and final follow-up (FF) were missing for 1 patient. Moderate fluctuations of ALT were noted, with reductions in median BL total bilirubin (TB) levels in 5 patients and mild increases in 2 (TB at FF was missing for 1 patient). GGT levels were reduced from BL to FF (CFB: -89 U/L [-281, -56]) in the 4 patients with complete measurements. Diarrhea was reported in 2 patients, with moderate-severe diarrhea over BL levels, with dose adjustment and interruptions required in 1 patient, while the diarrhea was mild and transient in the other patient. **Conclusion:** A clinically meaningful reduction in pruritus was observed in all MRX-treated patients with PSC, and a substantial reduction in sBA levels was observed in the majority. These findings indicate a potential role for IBAT inhibitors in treating pruritus in PSC.

Table. Clinical laboratory data at baseline and last clinical follow-up, following treatment with MRX in individuals with Primary sclerosing cholangitis (PSC)

Subjects	CSS Score		sBA, μmol/L		TB, mg/dL		ALP, U/L		GGT, U/L	
	BL	FF	BL	FF	BL	FF	BL	FF	BL	FF
001	4	1	196	38	3.3	2.4	640	635	NR	NR
002	4	2	62	31	5.3	2.6	348	348	NR	NR
003	3	0	506	79	2.3	1.7	757	552	129	NR
004	3	0	70	14	0.5	1.1	230	584	377	321
005	2	0	148	106	3.2	1.6	718	673	290	218
006	4	1	317	433	11.9	13.2	407	367	821	540
007	2	0	136	35	3.6	1.9	847	1275	379	273
008	2	1	NR	NR	0.6	NR	227	249	131	NR

BL, baseline; CSS, clinician scratch scale; FF, final clinical follow up, NR, not reported; sBA, serum bile acids; TB, total bilirubin.

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4412 | CLINICAL UTILITY OF COMPREHENSIVE GENETIC TESTING IN ADULT CHOLESTASIS: INSIGHTS FROM 856 PANEL TESTS

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Background: Cholestasis encompasses a broad spectrum of underlying causes, with genetic disorders being an underrepresented subset. Diagnostic evaluation is often complicated by variable clinical presentations and phenotypic overlap. The use of next-generation sequencing (NGS) panels enables more timely and comprehensive identification of genetic etiologies. This

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abstract presents data from over 800 panel tests in adult patients with cholestasis, offering key insights into diagnostic yield and the utility of genetic testing in clinical practice. **Methods:** Data from a 77-gene cholestasis panel were reviewed for patients who underwent genetic testing between March 2016 and January 2022 due to a current or prior history of cholestasis without an identifiable cause or unexplained chronic liver disease. DNA sequencing was performed using custom-designed and optimized capture libraries [SureSelect by Eurofins/Emory Genetics Laboratory (2016–2021) and PGxome® by PreventionGenetics (2021–2022)]. Variants were classified according to diagnostic laboratory protocols and ACMG criteria as benign, likely benign, variant of unknown significance (VUS), likely pathogenic (LP), or pathogenic (P). A definitive diagnosis was defined as either two P or LP variants in the same gene (homozygous or compound heterozygous), or a single P or LP variant in *JAG1* or *NOTCH2*. A potential diagnosis included one P or LP variant plus one VUS in the same gene for autosomal recessive conditions. **Results:** A total of 856 samples were analyzed between March 2016 and January 2022. Ages ranged from 18 to 88 years. Among the tests, there were 261 P, 40 LP, and 1,255 VUS identified. The overall diagnostic yield was 4% and 3.5% among subjects with a definitive diagnosis (34/856) and a potential diagnosis (30/856), respectively. Definitive diagnoses were most common in genes *ABCC2* (n = 7), *ABCB11* (n = 4), *CFTR* (n = 4), *POLG* (n = 4), and *SERPINA* (n = 4). Genes with the most potential diagnoses included *ABCB4* (n = 14), *CFTR* (n = 5), and *ABCB11* (n = 4), *ABCC2* (n = 2), and *PKHD1* (n = 2). Monoallelic variants occurred most often in genes *SERPINA1* (n = 34), *CFTR* (n = 32), *ABCB4* (n = 31), *ABCB11* (n = 10), *PKHD1* (n = 8). **Conclusion:** Genetic testing using a comprehensive cholestasis panel identified a definitive or potential diagnosis in 7.5% of cases, supporting its role in the evaluation of unexplained cholestasis and chronic liver disease in adults. Definitive diagnoses were most commonly associated with *ABCC2* (Dubin-Johnson syndrome), *ABCB11* (progressive familial intrahepatic cholestasis type 2), *CFTR* (cystic fibrosis), *POLG* (mitochondrial disorders), and *SERPINA1* (alpha-1-antitrypsin deficiency). These results demonstrate the clinical utility of panel-based sequencing while also emphasizing the challenges of interpreting uncertain variants in a genetically heterogeneous population.

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4413 | ASSOCIATION BETWEEN PRETREATMENT GLOBE SCORE AND HISTOLOGICAL CIRRHOSIS IN PRIMARY BILIARY CHOLANGITIS

Manabu Hayashi[1] Naoto Abe[1] Tatsuro Sugaya[1] Yosuke Takahata[1] Masashi Fujita[1] Kazumichi Abe[1] Hiromasa Ohira[1], [1]Fukushima Medical University

Background: Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease that can progress to cirrhosis and liver failure. Although liver cirrhosis diagnosed by biopsy is a robust predictor of poor prognosis, biopsy carries a risk of hemorrhage. A noninvasive test to predict liver cirrhosis and prognosis may be useful for patients with PBC. In this study, we analyzed the association between the pretreatment GLOBE score and histological cirrhosis in patients with PBC. **Methods:** In this retrospective study, we included PBC patients who underwent liver biopsy. The pretreatment GLOBE score was calculated using baseline values of age, bilirubin, alkaline phosphatase (ALP), albumin, and platelet count. Diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis. We also assessed the association between the pretreatment GLOBE score and transplant-free survival. **Results:** A total of 183 PBC patients were analyzed. The median age was 58 years, and 19% were male. The numbers of patients with Scheuer stage 1, 2, 3, and 4 were 76, 47, 21, and 39, respectively. The median pretreatment GLOBE score was 0.61. The pretreatment GLOBE score significantly increased with histological stage: stage 1, 0.25; stage 2, 0.53; stage 3, 0.68; and stage 4, 2.11 ($P < 0.001$). The pretreatment GLOBE score showed a higher area under the ROC curve (AUROC) compared with other noninvasive tests, including the ALBI score, FIB-4 index, FIB-3 index, AST to platelet ratio index, and the AST/ALT ratio. The optimal cutoff value of the pretreatment GLOBE score for predicting histological cirrhosis was 1.27 (AUROC: 0.868; sensitivity: 0.84; specificity: 0.84). Patients with a pretreatment GLOBE score < 1.27 had significantly longer transplant-free survival than those with a score ≥ 1.27 ($P < 0.001$). The 10-year cumulative transplant-free survival was 94.6% (95% CI: 85.1–98.1) in patients with a pretreatment GLOBE score < 1.27, compared to 45.6% (95% CI: 27.1–62.3) in untreated patients with a score ≥ 1.27. **Conclusion:** The pretreatment GLOBE score was significantly associated with baseline histological cirrhosis, and the identified cutoff value was predictive of prognosis in PBC patients. These findings suggest that the pretreatment GLOBE score may serve as a useful noninvasive test for assessing liver cirrhosis and prognosis in patients with PBC.

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Nothing to Disclose, Yosuke Takahata: Nothing to Disclose, Masashi Fujita: Nothing to Disclose, Kazumichi Abe: Nothing to Disclose, Hiromasa Ohira: Nothing to Disclose

4414 | CORRELATION BETWEEN OPIOID LIGANDS AND RESPONSE TO OPIOID ANTAGONIST IN CHOLESTATIC PATIENTS WITH PRURITUS

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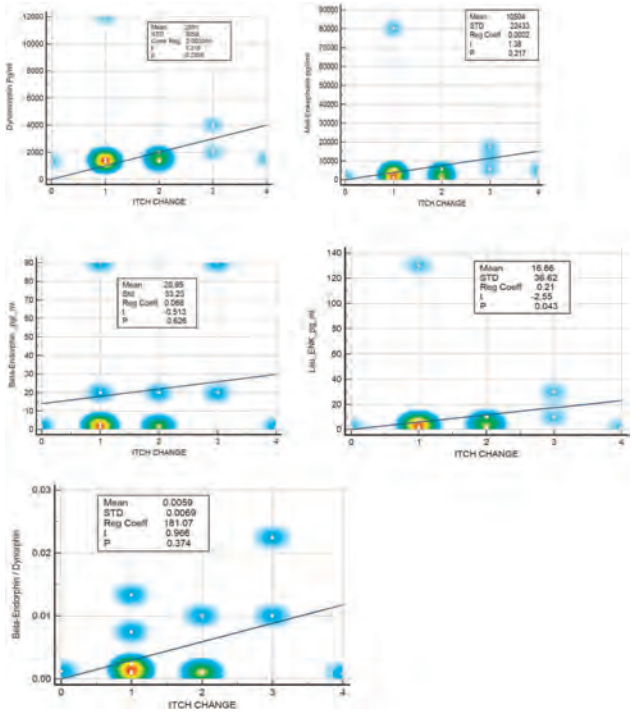
Background: Endogenous opioid ligands are thought to contribute to the development of pruritus in cholestatic liver disease, based on the observation that opioid antagonists can alleviate itching. However, studies have not found a consistent correlation between endogenous opioid levels and itch severity in these patients. In our recent work, we showed that nalmefene —a Mu and delta opioid receptor antagonist and kappa receptor agonist—reduced pruritus intensity in individuals with cholestatic liver disease. We have now expanded our analysis to investigate whether levels of endogenous opioids are associated with the extent of itch relief. **Methods:** This study was approved by the local IRB and competent authorities. In this study, we used TH104, a proprietary formulation of Nalmefene, 2 mg in strength formulated to a buccal film. Patients with cholestatic liver disease and a known history of persistent generalized pruritus for at least 4 weeks prior to screening were included. After an overnight fasting, subjects received one dose of 2 mg of TH104. Patients were monitored for itch severity using an 11-point NRS scale (0 – no itch, 10 – worst itch). ELISA kits (Qayeebio, China) were used to test the following ligands: Dynorphin (Kappa agonist), Beta-Endorphin (Mu agonist), Met-Enkephalin and Leu-Enkephalin (Mu and Kappa agonists). ANCOVA (D'Agostino-Pearson) test was used to assess correlation. **Results:** Nineteen patients were screened, and twelve patients were enrolled in this study. Ten subjects were male, and two were female; six were Child-Pugh class A, and six were Child-Pugh class B. A total of 2 AEs (headache) were reported in 2 subjects over the course of the study. These AEs were mild and possibly related to study drug. Mean decline in itch scores at 24-hours was 33.3% and was correlated with the pharmacokinetics of Nalmefene (Barak N et al, 2024).

Levels of all ligands were correlated with disease severity. There was no correlation between opioid ligand levels and baseline pruritus intensity, but the levels of Leu-Enkephalin correlated ($p = 0.043$) with the reduction in pruritus severity (See attached figure). **Conclusion:** Leu-Enkephalin is an endogenous opioid peptide that primarily acts on delta-opioid receptors but also interacts with mu-opioid receptors. Previous studies, such as Dull (2021), found no correlation between endogenous opioid ligand levels and pruritus severity in cholestatic liver disease. Our findings represent the first reported association between Leu-enkephalin levels and itch reduction following treatment with an opioid antagonist, and suggest a potential role for delta opioid receptors in cholestatic pruritus (Smith KM, 2023).



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4415 | EXPLORING THE ROLE OF ILEAL BILE ACID TRANSPORTER INHIBITORS, LIKE VOLIXIBAT, IN THE REGULATION OF IL-31 AND SERUM BILE ACIDS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: PRELIMINARY RESULTS: FROM THE VANTAGE TRIAL

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Background: Pruritus can be a debilitating symptom in patients with primary biliary cholangitis (PBC). While the etiology of pruritus in PBC is unknown, past research has shown an association between elevated serum bile acid (sBA), IL-31 levels, and pruritus. Volixibat (VLX) is a minimally absorbed ileal bile acid transporter inhibitor which blocks the enterohepatic recirculation of bile acids. Here, we explore the relationship between the antipruritic effect of VLX and serum levels of IL-31 and sBA in patients with PBC from the completed Part 1 (dose selection) period of the VANTAGE trial. **Methods:** VANTAGE is a 28-week randomized, multicenter, double-blind, placebo (PBO)-controlled Phase 2b study in adults with PBC and cholestatic pruritus. The study has an adaptive design: a completed Part 1 period (1:1:1 randomization, VLX 20mg, 80mg or PBO BID) and an ongoing Part 2 confirmatory period (1:1 randomization, VLX 20mg BID or PBO BID). The primary efficacy endpoint of change in pruritus (Adult ItchRO) score from Baseline (BL) to Week 28 has been previously reported. Here we report data on IL-31 and sBA levels from Part 1 to Weeks 16 (interim analysis) and 28 (final analysis). VLX 20mg and 80mg arms (VLX) were pooled for this analysis. Correlation coefficients and descriptive statistics were calculated. **Results:** Thirty-one participants with moderate-to-severe pruritus were randomized (VLX = 20; PBO = 11). At BL, sBA levels were elevated across groups, while IL-31 levels were elevated in the VLX group, but minimally in the PBO group. At BL, there was a positive correlation between IL-31 and sBA ($R = 0.63$; $p < 0.0001$). Both sBA and IL-31 levels were reduced from BL to Week 28 after VLX treatment (sBA [LS mean [SE]]: -14.2 [6.6]; IL-31: -8.2 [1.0]), whereas the PBO group observed smaller changes. There were positive correlations following VLX treatment at Week 16 between reductions from BL in both sBA and pruritus ($R = 0.27$; $p = 0.12$), as well as in IL-31 and pruritus ($R = 0.49$; $p = 0.0047$). Similar correlations between sBA and IL-31 were observed ($R = 0.65$; $p < 0.0001$). At Week 28, results were maintained albeit less pronounced, potentially reflecting increasing variability due to the small sample size. **Conclusion:** Reductions in pruritus after VLX treatment were associated with decreases in both IL-31 and sBA. These findings support the connection between sBA and IL-31 as potential mediators of pruritus in PBC.

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4416 | NON-INVASIVE ASSESSMENT OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION RISK IN PATIENTS WITH COMPENSATED ADVANCED PRIMARY BILIARY CHOLANGITIS

Giulia Francesca Manfredi[1] Ilkay Ergenç[2] Maria Cristina Neglia[3] Christian Sebesta[4] Elisabetta Degasperi[5] Georg Semmler[4] Thomas Reiberger[4] Benedikt Hofer[4] Carla De Benedittis[1] Mario Pirisi[1] Vincenza Calvaruso[3] Pietro Lampertico[5] Yusuf Yilmaz[6] Michael Trauner[4] CRISTINA RIGAMONTI[1], [1]Università del Piemonte Orientale, Novara, Italy, [2]Marmara University, Istanbul, Turkey. King's College Hospital, London, UK, [3]University of Palermo, Palermo, Italy, [4]Medical University of Vienna, Vienna, Austria, [5]University of Milan, Milan, Italy, [6]Recep Tayyip Erdoğan University

Background: Primary biliary cholangitis (PBC) is a progressive cholestatic disease that may lead to clinically significant portal hypertension (CSPH). PBC patients with compensated advanced chronic liver disease (cACLD), defined according to the Baveno VI criteria based on a liver stiffness measurement (LSM) $\geq$ 10 kPa, are at risk of developing CSPH and liver decompensation (LD). Spleen stiffness measurement (SSM) is a novel tool to assist in the non-invasive estimation of CSPH, but data in PBC-related cACLD are scarce and further links with hepatic decompensation needed. **Methods:** Multicentric study including 100 cACLD patients with PBC from 5 hepatology tertiary centres (Novara, Milan, Palermo, Istanbul, Vienna) who underwent vibration-controlled transient elastography (VCTE)-based LSM and SSM. The Baveno VII-SSM single SSM cut-off ($\leq$40 kPa vs. $>$40 kPa) criterion for ruling out or ruling in CSPH was applied. Moreover, the newly proposed Non-Invasive CSPH Estimated Risk (NICER) model was applied to calculate CSPH probability. **Results:** Among the 100 PBC cACLD patients,

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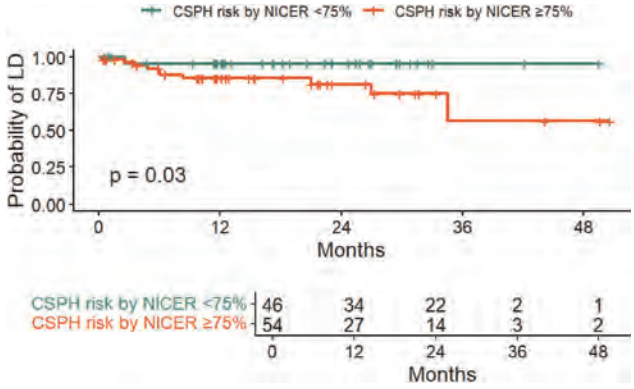
82% were women, median age was 62.5 (IQR 55.1-73.7) years, median BMI 25.1 (IQR 22.7-27.0) kg/m^2, median time from PBC diagnosis 2.9 (IQR 0.2-7.9) years, median ALP 1.3 (IQR 1.0-2.3) xULN, median total bilirubin 0.7 (IQR 0.5-1.1) mg/dL, median LSM 16.3 kPa (IQR 11.9-32.8), median SSM 47.4 kPa (IQR 27.8-63.2). Thirty-four (43.9%) out of the 78 patients with available esophagogastroduodenoscopy had (any size) oesophageal varices, 15 (19.2%) had high-risk oesophageal varices. Using the rule of five for LSM-based stratification, SSM differed significantly across LSM classes ($p < 0.001$). SSM >40 kPa was found in 30.4% of patients with LSM 10–14.9 kPa and 83% of those with LSM ≥ 15 kPa (85.7% in LSM 15–19.9 kPa and LSM 20-24.9 kPa; 81.8% in LSM ≥ 25 kPa). According to Baveno VII-SSM criteria, CSPH was ruled out in 47%, ruled in in 46%, and 7% remained in the grey zone. Based on the NICER model, CSPH risk distribution was: $\leq 25\%$ in 41 patients, 26-74% in 5 patients and $\geq 75\%$ in 54 patients. During a median follow-up of 17.4 months after VCTE examination, 12 patients developed LD. Two-year probability of LD was significantly higher in patients with CSPH risk by NICER $\geq 75\%$ vs those with risk $<75\%$ (19% vs 5% respectively; p 0.03). **Conclusion:** These findings support the applicability of SSM-based non-invasive risk estimation models in patients with PBC, particularly in predicting the risk of decompensation.



Disclosures: Giulia Francesca Manfredi: Nothing to Disclose, Ilkay Ergenç: Nothing to Disclose, Nothing to Disclose, Maria Cristina Neglia: Nothing to Disclose, Christian Sebesta: Nothing to Disclose, Elisabetta Degasperi: Gilead: Speaking and Teaching, Roche: Advisor, Abbvie: Speaking and Teaching, IPSEN: Speaking and Teaching, Georg Semmler: Amgen: Travel Support, Thomas Reiberger: Nothing to Disclose, Benedikt Hofer: IPSEN: Travel support, FALK: Travel support, Carla De Benedittis: Nothing to Disclose, Mario Pirisi: Nothing to Disclose, Vincenza Calvaruso: Nothing to Disclose, Pietro Lampertico: Nothing to Disclose, Yusuf Yilmaz: Nothing to Disclose, Michael Trauner: Albireo: Grant/Research Support, Alnylam: Grant/Research Support, Cymabay: Grant/Research Support, Falk: Grant/Research Support, Gilead: Grant/Research Support, Intercept: Grant/Research Support, MSD: Grant/Research Support, Takeda: Grant/Research Support, Ultragenyx: Grant/Research Support, Abbvie: Travel Grants, Falk: Travel Grants, Gilead: Travel Grants, Intercept: Travel Grants, Janssen: Travel Grants, Abbvie: Advisor, Albireo: Advisor, BiomX: Advisor, Boehringer Ingelheim: Advisor, Falk Pharma GmbH: Advisor, Genfit: Advisor, Gilead: Advisor, Hightide: Advisor, Intercept: Advisor, Ipsen: Advisor, Janssen: Advisor, MSD: Advisor, Novartis: Advisor, Phenex: Advisor, Pliant: Advisor, Regulus: Advisor, Siemens: Advisor, Shire: Advisor, BMS: Speaking and Teaching, Falk: Speaking and Teaching, Gilead: Speaking and Teaching, Intercept: Speaking and Teaching, Ipsen: Speaking and Teaching, Madrigal: Speaking and Teaching, MSD: Speaking and Teaching, Medical Universities of Graz and Vienna: Co.Inventor of patents for medical use of norUDCA filed by, Genentech: Grant/Research Support, Mirum: Advisor, Agomab: Advisor, Chemomab: Advisor, ProQR Therapeutics: Advisor, Rectify: Advisor, CRISTINA RIGAMONTI: Nothing to Disclose

4417 | AUTOIMMUNE DISEASE CLUSTERING IN AUTOIMMUNE HEPATITIS: PATTERNS IN A LARGE MULTI-CENTER COHORT

Kate Solpari[1] Emma Leipsner[1] Scarlet Yang[1] Jessica Siguencia[1] Tatyana Kushner[1], [1]Weill Cornell Medical College

Background: Autoimmune hepatitis (AIH) frequently coexists with other autoimmune diseases, but the patterns of clustering remain incompletely characterized. This study investigated the co-occurrence between AIH and comorbid autoimmune conditions across race, gender, and age strata. **Methods:** We analyzed electronic health record data from patients with AIH across 99 healthcare organizations in the TriNetX research network. Prevalence of systemic lupus erythematosus (SLE), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), Crohn's disease, ulcerative colitis, autoimmune (Hashimoto's) thyroiditis, Graves' disease, celiac disease, rheumatoid arthritis (RA), and type 1 diabetes (T1DM). were calculated for the entire cohort and stratified by gender, age groups, and race. **Results:** Among 52,992 patients with AIH, 72.7% were female with a mean age of 59 $\pm$ 19 years; they were White (62.4%), Black (13.4%), and Asian (5.94%). The most common documented autoimmune comorbidities were PBC (10.7%), Crohn's disease (10.0%), ulcerative colitis (9.1%), RA (7.7%), and SLE (7.0%) (Figure 1). Sex-stratified analysis showed that

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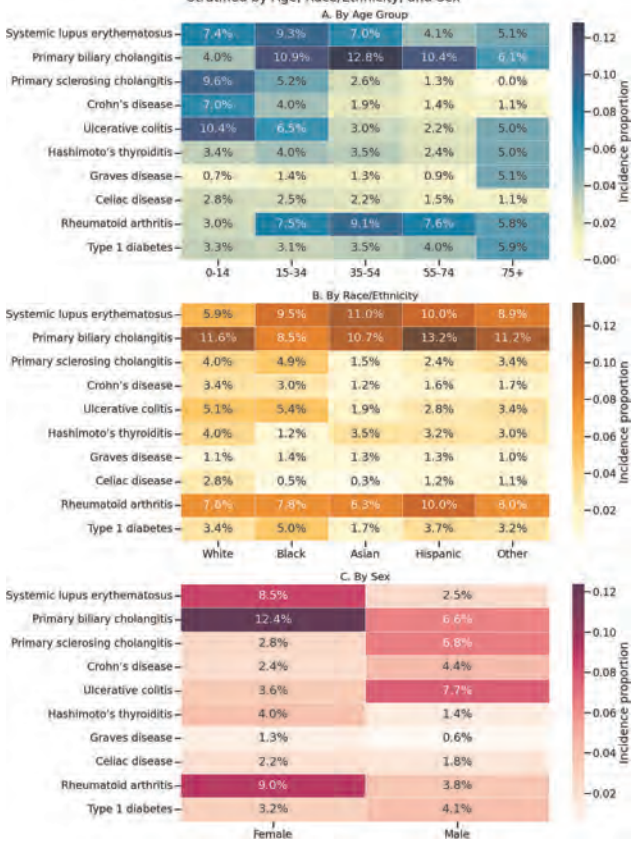
SLE, PBC, and Hashimoto's thyroiditis were more common in females, while Crohn's disease, ulcerative colitis, PSC, and T1DM were more frequent in males. Age stratification revealed that SLE co-occurrence peaked in young adults (15–34 years), PBC and RA were most prevalent in middle age (35–54 years), PSC was concentrated in pediatric and adolescent patients (0–14 years), and ulcerative colitis was distributed more evenly across the lifespan. Race and ethnicity stratification showed higher SLE prevalence in Asian and Black patients, while PBC was more frequent among White individuals. Hispanic/Latino patients exhibited disproportionately high rates of PBC, PSC, and T1DM, while Native Hawaiian/Pacific Islander patients had the highest prevalence of ulcerative colitis. **Conclusion:** Autoimmune hepatitis exhibits clear, demographically patterned clustering—SLE in young adults, PBC/RA in middle-aged women, PSC/IBD in boys/men, and PBC/PSC/T1DM in Hispanic and Native Hawaiian/Pacific Islander patients—supporting age-, sex-, and race-stratified surveillance and routine multidisciplinary referral.

Figure 1. Co-occurrence of Autoimmune Conditions with AIH Stratified by Age, Race/Ethnicity, and Sex



Disclosures: Kate Solpari: Nothing to Disclose, Emma Leipsner: Nothing to Disclose, Scarlet Yang: Nothing to Disclose, Jessica Siguencia: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support

4418 | RED CELL DISTRIBUTION WIDTH IS INDEPENDENTLY ASSOCIATED WITH FATIGUE AND COGNITION IN PRIMARY BILIARY CHOLANGITIS

Matthew Smith[1] Narmeen Umar[1] Allison Mella[1] Rahima Bhanji[1] Charmaine van Eeden[1] Mohammed Osman[1] YU JUN WONG[2] Aldo Montano-Loza[1] Andrew Mason[1], [1]University of Alberta, [2]Changi General Hospital

Background: Fatigue is the most common symptom associated with primary biliary cholangitis (PBC). The pathophysiology of fatigue and cognitive impairment is poorly understood and these symptoms are often discordant with prognostic scoring or disease severity. Red cell distribution width (RDW) is a measure of erythrocyte size variability and identified as a potential biomarker of oxidative stress and hypoxia. RDW was associated with symptom severity in other autoimmune conditions such as systemic sclerosis and lupus, but its utility in PBC has not been fully evaluated. We assessed whether RDW is independently associated with fatigue and cognitive symptoms in PBC, after adjusting for hematologic parameters, liver disease severity, and clinical decompensation. **Methods:** A multi-center retrospective analysis of 160 non-transplant patients with PBC was performed between January 2018 and January 2025 in Alberta, Canada. Fatigue and cognitive scores were collected and combined into one composite score derived from validated patient-reported PBC-40 surveys. Multiple linear regression was used to assess associations between RDW and composite PBC-40 scores with hepatic and hematologic covariates including presence of cirrhosis, cirrhosis status and GLOBE scores. **Results:** The average age of our cohort was 64 years old, the majority were female (85%) and 53 patients had cirrhosis with 20 having decompensated cirrhosis. The mean RDW was 14.5, the median GLOBE score was 0.2082, the median PBC-40 scores were 29 for fatigue, 13 for cognition, and the composite median score was 42.5. The regression model was significant ($F = 2.16$, $p = 0.041$) and explained 9.3% of the variance in the composite score (adjusted $R^2 = 0.050$). RDW was associated with higher composite scores ($B = 1.77$, 95% CI: 0.08 to 3.45, $p = 0.041$). Age, presence of cirrhosis, liver decompensation and GLOBE scores were not significantly associated with fatigue and cognitive scoring. Residuals were normally distributed, with no violations of model assumptions or evidence of multicollinearity (all VIFs < 1.7). **Conclusion:** RDW was found to be independently associated with worse

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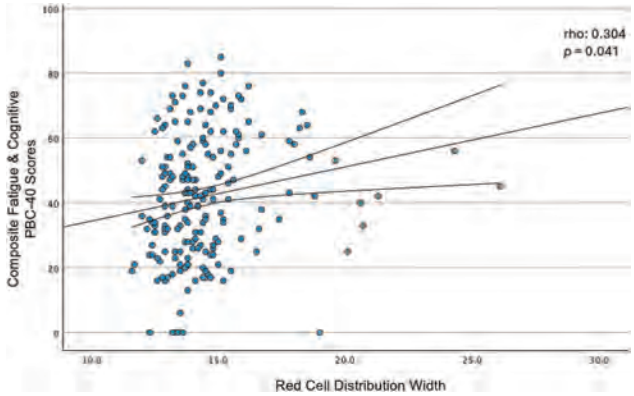
PBC-40 fatigue and cognitive composite scores, even after adjusting for hematologic confounders and liver disease severity. These findings suggest that RDW may reflect fatigue-related symptom burden and pathophysiology and support its potential as a low-cost, accessible biomarker for symptom stratification in PBC. Further research into potential predictive biomarkers and pathophysiology behind symptoms such as fatigue in PBC is required.



Disclosures: Matthew Smith: Nothing to Disclose, Narmeen Umar: Nothing to Disclose, Allison Mella: Nothing to Disclose, Rahima Bhanji: Nothing to Disclose, Charmaine van Eeden: Nothing to Disclose, Mohammed Osman: Nothing to Disclose, YU JUN WONG: Nothing to Disclose, Aldo Montano-Loza: Nothing to Disclose, Andrew Mason: Nothing to Disclose

4419 | FIBROSIS AT FIRST GLANCE: CLINICAL CHARACTERISTICS AND OUTCOMES OF ADULTS WITH AUTOIMMUNE HEPATITIS WITH AND WITHOUT CIRRHOSIS AT DIAGNOSIS IN A DIVERSE U.S. COHORT

Ryan Murphy Sheng-Fang Jiang[1] Sreepriya Balasubramanian[1] Nirmala Ramalingam[1] Kavita Radhakrishnan[2], [1]Kaiser Permanente Medical Center, [2]The Permanente Medical Group

Background: Autoimmune hepatitis (AIH) is a chronic, immune-mediated liver disease that can lead to progressive hepatic injury, decompensation, and death if not diagnosed and treated in a timely manner. The clinical presentation can range from asymptomatic transaminase elevations to acute liver failure. Prior global studies indicate that up to 25% of patients have cirrhosis at AIH diagnosis, which is associated with increased liver-related complications and death. However, there are limited data on baseline characteristics and outcomes of AIH patients with cirrhosis at diagnosis in ethnically diverse U.S. populations. **Methods:** We conducted a retrospective study of adults newly diagnosed with AIH between 2010–2021 within Kaiser Permanente Northern California, a large integrated healthcare system. AIH diagnoses were identified by ICD codes (ICD-9: 571.42; ICD-10: K75.4) and confirmed with serologies and/or liver biopsy. Patients were stratified by the presence or absence of cirrhosis at the time of diagnosis. Demographic data, comorbidities, and clinical outcomes including hospitalizations, transplantation, and death were compared using chi-square and t-tests. **Results:** Among 997 patients with AIH (80% female, 17% Asian, 9% Black, 27% Hispanic, 43% White), 211 (21.2%) had cirrhosis at diagnosis. Compared to those without cirrhosis, patients with cirrhosis were older, more likely to be Hispanic, non-English-speaking, and have diabetes (all $p < 0.05$, Table 1). Those with cirrhosis also had higher prevalence of hypertension ($p = 0.02$), alcohol use disorder ($p < 0.01$), and greater comorbidity burden as reflected by the Charlson Comorbidity Index (52.1% vs. 29.0% with score ≥ 2, $p < 0.001$). Cirrhosis at diagnosis was associated with worse outcomes, including higher rates of hospitalization (28.9% vs. 13.0%, $p < 0.001$), liver transplantation (8.1% vs. 1.4%, $p < 0.001$), and death (23.7% vs. 11.8%, $p < 0.001$). There were no significant differences between groups by sex, body mass index (BMI), hyperlipidemia, or neighborhood deprivation index. **Conclusion:** In this large and diverse U.S. cohort, over 1 in 5 adults with AIH presented with cirrhosis at diagnosis. Cirrhosis at presentation was associated with worse clinical outcomes, including hospitalization, liver-related complications, and mortality. These findings underscore the importance of earlier detection and treatment of AIH, particularly among higher-risk and understudied demographic groups, to prevent disease progression and reduce adverse outcomes.

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Table 1. Patient Characteristics by Cirrhosis Status at AIH Diagnosis

Variables	Total (n=997)	No Cirrhosis at Diagnosis (n=786)	Cirrhosis at Diagnosis (n=211)	P Value
Age at Diagnosis				0.029
Mean ± SD	57.0±15.7	56.3±16.2	59.5±13.4	
Age Group (y)				0.006
18-34	112 (11.2%)	102 (13.0%)	10 (4.7%)	
35-54	264 (26.5%)	208 (26.5%)	56 (26.5%)	
55-74	508 (51.0%)	386 (49.1%)	122 (57.8%)	
75+	113 (11.3%)	90 (11.5%)	23 (10.9%)	
Sex				0.065
Female	792 (79.4%)	634 (80.7%)	158 (74.9%)	
Male	205 (20.6%)	152 (19.3%)	53 (25.1%)	
Race/Ethnicity				0.001
Asian	166 (16.6%)	136 (17.3%)	30 (14.2%)	
Black	92 (9.2%)	79 (10.1%)	13 (6.2%)	
Hispanic	265 (26.6%)	186 (23.7%)	79 (37.4%)	
Other	53 (5.3%)	46 (5.9%)	7 (3.3%)	
White	421 (42.2%)	339 (43.1%)	82 (38.9%)	
BMI (kg/m2)				0.43
<25	344 (34.5%)	279 (35.5%)	65 (30.8%)	
25 to <30	320 (32.1%)	252 (32.1%)	68 (32.2%)	
>=30	309 (31.0%)	235 (29.9%)	74 (35.1%)	
Unknown	24 (2.4%)	20 (2.5%)	4 (1.9%)	
Language				<0.001
non-English	113 (11.3%)	74 (9.4%)	39 (18.5%)	
Neighborhood Deprivation Index Quartile				0.50
1 (least)	158 (15.8%)	129 (16.4%)	29 (13.7%)	
2	303 (30.4%)	243 (30.9%)	60 (28.4%)	
3	282 (28.3%)	221 (28.1%)	61 (28.9%)	
4 (most)	254 (25.5%)	193 (24.6%)	61 (28.9%)	
Charlson Comorbidity Index				<.001
0	424 (42.5%)	382 (48.6%)	42 (19.9%)	
1	235 (23.6%)	176 (22.4%)	59 (28.0%)	
2+	338 (33.9%)	228 (29.0%)	110 (52.1%)	
Diabetes				<0.001
No	772 (77.4%)	629 (80.0%)	143 (67.8%)	
Yes	225 (22.6%)	157 (20.0%)	68 (32.2%)	
Hyperlipidemia				0.80
No	531 (53.3%)	417 (53.1%)	114 (54.0%)	
Yes	466 (46.7%)	369 (46.9%)	97 (46.0%)	
Hypertension				0.02
No	736 (73.8%)	593 (75.4%)	143 (67.8%)	
Yes	261 (26.2%)	193 (24.6%)	68 (32.2%)	
Alcohol Use Disorder				<.001
No	929 (93.2%)	749 (95.3%)	180 (85.3%)	
Yes	68 (6.8%)	37 (4.7%)	31 (14.7%)	

Disclosures: Ryan Murphy: Nothing to Disclose, Sheng-Fang Jiang: Nothing to Disclose, Sreepriya Balasubramanian: Nothing to Disclose, Nirmala Ramalingam: Nothing to Disclose, Kavita Radhakrishnan: Nothing to Disclose

4420 | PREVALENCE OF CONCOMITANT ORAL CONTRACEPTIVE AND HORMONE REPLACEMENT THERAPY USE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: RESULTS: FROM A LARGE US CLAIMS DATABASE

Tatyana Kushner[1] Sarjita Naik[2] Nirali Kotowsky[2] Eva Flahavan[2] Catherine Frenette[2], [1]Weill Cornell Medicine, [2]Gilead Sciences, Inc.

Background: Primary biliary cholangitis (PBC) affects women predominantly and is usually diagnosed in middle age although is diagnosed in up to 25% of women during childbearing years. PBC in women has been associated with irregular menses, reduced fertility, and higher rates of osteoporosis. Treatment with estrogen-based therapies for these conditions is commonly recommended, although there is often provider hesitancy to initiate these therapies in the context of chronic liver disease. We aim to understand the background medication use of oral contraceptives (OCPs) and hormone replacement therapy (HRT) in women being treated for PBC. **Methods: Methods:**: This is a retrospective, descriptive study evaluating the prevalence of OCP and HRT among females living with PBC with a prescription claim for ursodeoxycholic acid (UDCA) alone or with second line (2L) agents, obeticholic acid (OCA) or fibrates in the Health Verity database. Health Verity covers 84 million lives and contains both medical and pharmacy insurance claims from over 150 payers, representing commercial, Medicare and Medicaid. Patients with a PBC diagnosis were identified using the ICD-10 K74.3 code between October 1, 2015 to June 30, 2024. Treatment for PBC with UDCA, OCA or fibrates was captured using National Drug Codes from prescription claims. **Results:** We identified 46,028 individuals with PBC; 40,921(89%) were on UDCA only and 5,107(11%) were on 2L treatment: 3,796(8.2%) on OCA and 1,311(2.8%) on fibrates. Baseline patient demographics for overall cohort (n = 46,028) are shown in the Table. The majority were female (89%), median age over 50, and identified as White, consistent with the known demographics of PBC. After restricting the cohort to females (n = 40,963), 18% were considered of childbearing age and the remaining were either at menopause or post-menopausal. Among patients on UDCA only, 3253(8.9%) were either on OCP or HRT compared to 651(13.9%) also on 2L therapies. **Conclusion:** The use of OCP and HRT use was numerically higher in PBC patients receiving 2L treatment versus UDCA alone. The higher

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prevalence in women on 2L treatment may reflect those with advanced or longer duration of disease. Given the high prevalence of cardiovascular disease and osteoporosis in PBC patients, treatment with HRT is beneficial and special attention is warranted to address their need in women. With the availability of new 2L agents for PBC, patient features, which may include concomitant medications, can have implications on treatment selection.

Table. Patient demographics for overall cohort (n=46,028) during the baseline period

	Patients with UDCA only	Patients with UDCA plus OCA	Patients with UDCA plus fibrates
Number of patients	40921	3796	1311
Median age [IQR]	63.00 [55.00, 71.00]	57.00 [50.00, 64.00]	57.00 (50.00, 65.00)
Gender, n (%)			
Male	4,607 (11.3%)	317 (8.4%)	130 (9.9%)
Female	36,304 (88.7%)	3,478 (91.6%)	1,181 (90.1%)
On OCP, n (%)	581 (1.6%)	119 (3.4%)	47 (3.9%)
On HRT, n (%)	2,672 (7.4%)	375 (10.8%)	110 (9.3%)
Race, n (%)			
White	7,100 (17.4%)	698 (18.4%)	263 (20.1%)
Black	886 (2.2%)	89 (2.3%)	27 (2.1%)
Hispanic	2,009 (4.9%)	239 (6.3%)	87 (6.6%)
Asian	486 (1.2%)	42 (1.1%)	15 (1.1%)
Other	1,228 (3.0%)	181 (4.8%)	48 (3.7%)
Missing	29,212 (71.4%)	2,547 (67.1%)	871 (66.4%)
Insurance Status, n (%)			
Commercial	16,034 (39.2%)	1,716 (45.2%)	621 (47.4%)
Medicaid	4,137 (10.1%)	466 (12.3%)	168 (12.8%)
Medicare	3,586 (8.8%)	239 (6.3%)	85 (6.5%)
Closed Claims, n (%)			
Pharmacy	24,232 (59.2%)	2,395 (63.1%)	871 (66.4%)
Medical	13,951 (34.1%)	1,560 (41.1%)	532 (40.6%)
Comorbidities, n (%)			
Cardiovascular Diseases	9,125 (22.3%)	579 (15.3%)	217 (16.6%)
Hyperlipidemia	17,969 (43.9%)	1,547 (40.8%)	608 (46.4%)
Osteoporosis or Osteopenia	5,494 (13.4%)	395 (10.4%)	138 (10.5%)

Disclosures: Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support, Sarjita Naik: Gilead Sciences: Employee, Gilead Sciences: Stock – privately held company, Nirali Kotowsky: Nothing to Disclose, Eva Flahavan: Gilead Sciences: Employee, Roche: Employee, Catherine Frenette: Gilead Sciences: Employee

4421 | PROTEOMIC CHARACTERIZATION OF CIRCULATING EXTRACELLULAR VESICLES REVEALS NOVEL DIAGNOSTIC AND PROGNOSTIC BIOMARKERS IN AUTOIMMUNE HEPATITIS

Swati Thangariyal[1] Chhagan Bihari[1] Ashmit Mittal[1] Sukriti Baweja[2] Shiv Kumar Sarin[1], [1]Institute Of Liver And Biliary Sciences, New-Delhi, India, [2]Institute of Liver and Biliary Sciences, New Delhi

Background: Autoimmune Hepatitis (AIH) is a chronic liver disease of unknown etiology with systemic inflammation. There is an unmet need to identify the biomarkers of diagnosis and prognosis of AIH. Emerging evidence has suggested that proteomic characterization of Extracellular vesicles (EVs) might reveal potential biomarkers for the diagnosis and prognosis of AIH. **Methods:** Pre-therapy plasma samples were collected from biopsy-proven AIH patients ($n = 20$, international simplified scoring ≥ 7, HAI score > 5, ALT 129 $\pm$ 16 U/L, AST 148 $\pm$ 16 U/L), PBC patients ($n = 4$), and age- and sex-matched healthy controls (HC) ($n = 20$). These samples were fractionated, and EVs were isolated utilizing iodixanol-sucrose density gradient ultracentrifugation. The isolated EVs were characterized by transmission electron microscopy (TEM) and nanoparticle tracking analysis (NTA). Proteomic analysis was conducted using LC-MS, and the results were interpreted with Proteome Discoverer 3.0. **Results:** Plasma EV mean levels were higher in AIH (1.2×10^8 particles/mL) and PBC (3.1×10^8 particles/mL) compared to healthy controls (7.5×10^7 particles/mL). The average diameter of EVs in AIH and PBC (157 nm) was greater than that in healthy controls (68.8 nm). EV proteomics analysis identified five proteins related to the immune response that were dysregulated among the groups. Differential expression of proteins (DEP) revealed the upregulation of immune response proteins [fold change (FC) > 2, $p = 0.005$], such as immunoglobulin gamma-1 heavy chain (IgG) and alpha-2-macroglobulin (A2M), in AIH and PBC EVs. IgG overexpression indicates liver injury, and A2M, an acute phase protein, inhibits the catabolism of matrix proteins during liver inflammation, thus causing liver fibrosis. In healthy EVs, DNA synthesis and repair-associated proteins (DNA helicase, DNA polymerase alpha) were upregulated (FC > 2, $p > 0.005$). Additionally, haptoglobin-related proteins, involved in the clearance of cell-free hemoglobin for hepatic recycling of heme iron, were upregulated in healthy EVs (FC > 2, $p > 0.005$). **Conclusion:** Our results provide the first evidence that EVs from AIH patients are enriched in immune effector proteins such as IgG and A2M, which may participate in immune complex formation and systemic inflammation. These findings propose that circulating EVs serve not only as disease reporters but also as mediators of liver injury. EV proteomics offers a promising, non-invasive tool for diagnosing and monitoring AIH and potentially for stratifying disease severity and therapeutic response.

Disclosures: Swati Thangariyal: Nothing to Disclose, Chhagan Bihari: Nothing to Disclose, Ashmit Mittal: Nothing to Disclose, Sukriti Baweja: Nothing to Disclose, Shiv Kumar Sarin: Nothing to Disclose

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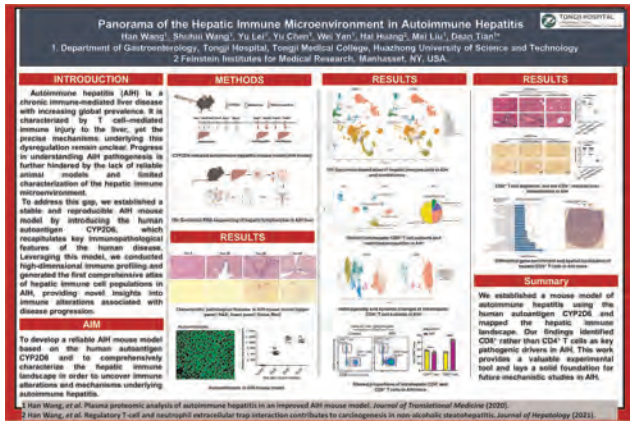
4422 | PANORAMA OF THE HEPATIC IMMUNE MICROENVIRONMENT IN AUTOIMMUNE HEPATITIS

Han Wang[1], [1]Tongji Hospital

Background: Autoimmune hepatitis (AIH) is a chronic immune-mediated liver disease with rising global prevalence. Progress in basic research is hindered by the lack of reliable animal models and comprehensive characterization of the hepatic immune microenvironment. To address this, we developed a stable AIH mouse model and provided the first panoramic view of the hepatic immune landscape in AIH. **Methods:** The novel AIH mouse model was established by transfecting the human CYP2D6 gene into the liver. Liver pathology and fibrosis were assessed using H&E and Sirius Red staining. Serum autoantibody titers were measured via ELISA. The hepatic immune microenvironment was characterized through 10× Genomics RNA sequencing, spatial transcriptomics, and flow cytometry. $CD4^+$ T cell and $CD8^+$ T depletion experiments were performed in vivo. **Results:** Liver inflammation was evident by day 14 post-injection, with chronic lymphocyte aggregation around the portal vein and detectable autoantibodies by day 28. Peak inflammation at day 35 featured hallmark AIH pathology, including interface hepatitis, rosette formation, and fibrosis, closely mirroring human AIH. 10× Genomics RNA sequencing and flow cytometry revealed significant shifts in hepatic immune cell populations, particularly $CD8^+$ T cells, NK cells, and activated Tregs. Subtype analysis highlighted changes in effector $CD8^+$ T cells and tissue-resident memory T cells (TRM). Spatial transcriptomics showed increased $CD8^+$ T cell clustering in portal areas and liver parenchyma, uncovering spatial interactions with hepatocytes that underpin AIH pathogenesis. Notably, $CD8^+$ T cell depletion significantly alleviated hepatic inflammation, whereas $CD4^+$ T cell depletion had minimal effect, underscoring the pivotal pathogenic role of CD8+ T cells in AIH. **Conclusion:** We established a mouse model of autoimmune hepatitis using the human autoantigen CYP2D6 and mapped the hepatic immune landscape. Our findings identified $CD8^+$ rather than $CD4^+$ T cells as key pathogenic drivers in AIH. This work provides a valuable experimental tool and lays a solid foundation for future mechanistic studies in AIH.



Disclosures: Han Wang: Nothing to Disclose

4423 | RESEARCH WITHOUT BORDERS? A CRITICAL LOOK AT GEOGRAPHIC AND TEMPORAL DISPARITIES IN PSC PUBLICATIONS

Renan Prado[1] Luma Tavares[2] Julia TIrelli Rocha[3] Melissa Lou Silva[4], [1]Cleveland Clinic Foundation, [2]Universidade Federal do Ceara, Brazil, [3]Jundiai Medical School, Brazil, [4]University of California San Diego

Background: Primary sclerosing cholangitis (PSC) is a chronic, progressive cholestatic liver disease characterized by inflammation and fibrotic stricturing of the intra- and extrahepatic bile ducts, often culminating in cirrhosis and end-stage liver disease. Although PSC is considered rare in the general population, current epidemiological data are predominantly derived from high-income regions, leading to potential biases in global understanding. The reliance on advanced imaging techniques such as magnetic resonance cholangiopancreatography (MRCP) for diagnosis may further contribute to disparities in detection and reporting. Despite increasing scientific interest, the global distribution of PSC-related research remains uneven. **Methods:** To assess global publication trends, citation patterns, and geographic disparities in PSC-related literature indexed in the Web of Science Core Collection (WoSCC), including all PSC-related articles and reviews published between 1965 and 2025. Meeting abstracts were excluded. Bibliometric indicators were

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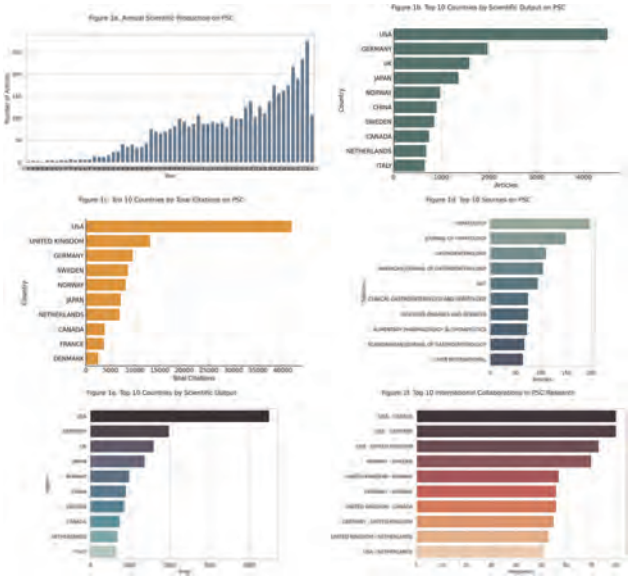
analyzed using the *Bibliometrix* R package. Variables included publication volume, citation metrics, author affiliations, and country-level contributions. **Results:** A total of 4,565 PSC-related documents were published in 1,158 journals, with an annual growth rate of 6.87%, indicating increasing research attention. Based on first author affiliation, the top contributing countries were the United States (1,085 publications), Germany (415), the United Kingdom (352), Japan (334), and China (227). Low- and middle-income countries accounted for 853 publications (18.7%). The most productive journals were Hepatology, Journal of Hepatology, and Gastroenterology. The most cited article accrued 850 citations. Citation impact was highest in the United States, United Kingdom, and Norway. Oslo University Hospital emerged as the most frequent author affiliation—an unusual finding given the dominance typically seen by U.S.-based institutions. Among the ten most cited articles, five originated from the United States and five from Europe (Sweden, United Kingdom, Norway, and the Netherlands). International collaboration was moderate, with high-income countries disproportionately represented in multi-country publications. Developing nations remained significantly underrepresented. **Conclusion:** The global PSC research landscape is largely shaped by high-income countries, underscoring persistent disparities in scientific output and visibility. Efforts to promote international collaboration, support research infrastructure, and foster inclusion of underrepresented regions are essential for a more comprehensive and equitable understanding of PSC worldwide.



Disclosures: Renan Prado: Nothing to Disclose, Luma Tavares: Nothing to Disclose, Julia TIrelli Rocha: Nothing to Disclose, Melissa Lou Silva: Nothing to Disclose

4424 | THE ROLE OF KILLER IMMUNOGLOBULIN-LIKE RECEPTOR (KIR) GENE VARIANTS IN AUTOIMMUNE HEPATITIS AND PRIMARY BILIARY CHOLANGITIS: ASSOCIATION WITH DISEASE SEVERITY AND DEEP REMISSION

mete ucdal[1] Ayse Burus[1] Ahmet Yalcinkaya[1] Basak Celtikci[1] Osman Dag[1] Yasemin Balaban[1], [1]hacettepe university

Background: Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) are immune-mediated liver diseases with distinct clinical phenotypes but overlapping immunopathogenic mechanisms. Killer immunoglobulin-like receptors (KIRs) regulate natural killer (NK) cell activity and contribute to autoimmunity. This study investigated the distribution of KIR variants and their association with disease severity and treatment response in AIH and PBC. **Methods:** AIH (n = 25) and PBC (n = 30) patients diagnosed per international criteria were enrolled. Peripheral blood DNA was used for KIR genotyping (activating: KIR2DS1, KIR2DS2, KIR3DS1; inhibitory: KIR2DL1, KIR3DL1; dual-function: KIR2DL4) via quantitative PCR. Disease severity was defined biochemically (AST/ALT $\geq$10×ULN in AIH; ALP/GGT $\geq$3×ULN in PBC). Treatment response was assessed after standard therapy (prednisolone/azathioprine for AIH; UDCA for PBC). Statistical analyses included Fisher's exact (a), chi-square (b), Mann–Whitney U (c), Kruskal–Wallis (d), and Bonferroni correction (e). Medians (Q1–Q3) were reported for nonparametric comparisons. **Results:** Activating KIR variants were predominant in AIH (68.0%) versus PBC (23.3%, p = 0.002[a]), notably KIR2DS2 (AIH: 32.0% vs. PBC: 3.3%, p = 0.013[a]). In contrast, inhibitory KIRs, particularly KIR3DL1, were more frequent in PBC (13.3%, p = 0.001[a]). KIR2DS2 correlated with severe AIH (p = 0.031[a]), while KIR3DS1 predicted non-response to immunosuppression (p = 0.015[b]).When examining transaminases and IgG, treatment response differed significantly across KIR genotypes ($p < 0.001$[d]). Carriers of the activating variants KIR3DS1 and KIR2DS2 exhibited markedly higher biochemical non-response than KIR2DL1 carriers (KIR3DS1, $p < 0.001$[e]; KIR2DS2, $p = 0.006$[e]). Bonferroni-corrected pairwise comparisons confirmed significant differences for KIR3DS1 vs. KIR2DL1 ($p = 0.002$[e]) and KIR2DS2 vs. KIR2DL1 ($p = 0.017$[e]). KIR genotyping effectively predicts deep remission in PBC patients in that KIR2DL1 status was a significant biomarker for 12th month treatment response according to Paris II criteria. Out of 30 PBC patients, 73% (n = 22) of them were responder. All KIR2DL1-positives (3 patients) were treatment resistant while 85.2% (23/27) of responder had other KIR genotypes (p = 0.014[a]). These patients

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also had higher Globe scores compared to those with other genotypes (KIR2DL1 median 0.55 vs. 0.15–0.45 across other alleles, p = 0.0105[c]). **Conclusion:** AIH and PBC displayed distinct KIR profiles; activating KIRs were dominant in AIH, inhibitory KIRs in PBC. Certain variants correlated with disease severity and deep remission. KIR2DS2 predicted severe AIH, while KIR2DL1 negativity predicted deep remission in PBC. These KIR profiles may serve as valuable biomarkers for disease stratification and personalized treatment approaches.

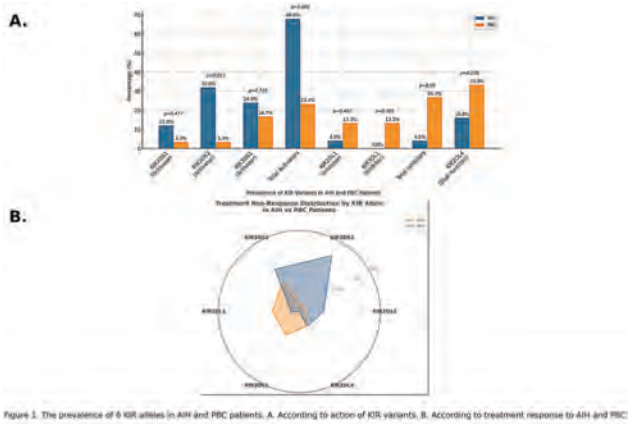


Figure 1. The prevalence of 6 KIR alleles in AIH and PBC patients. A. According to action of KIR variants. B. According to treatment response to AIH and PBC

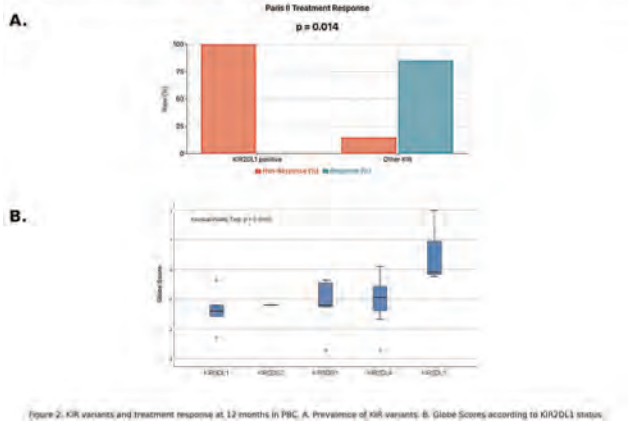


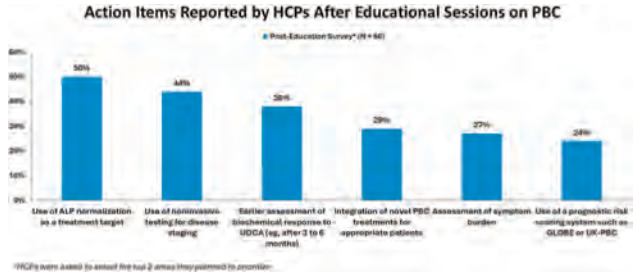
Figure 2. KIR variants and treatment response at 12 months in PBC. A. Prevalence of KIR variants. B. Globe Scores according to KIR2DL1 status

Disclosures: mete ucdal: Nothing to Disclose, Ayse Burus: Nothing to Disclose, Ahmet Yalcinkaya: Nothing to Disclose, Basak Celtikci: Nothing to Disclose, Osman Dag: Nothing to Disclose, Yasemin Balaban: Nothing to Disclose

4425 | CLINICAL PRACTICE PATTERNS IN THE MANAGEMENT OF PRIMARY BILIARY CHOLANGITIS IN COMMUNITY SETTINGS

Robert Gish[1] Sara Atcheson[2] Jenniffer Meza Jimenez[2] Jeffrey Carter[2] Leah Molloy[2] Laura Simone[2], [1]Robert G Gish Consultants LLC, [2]PRIME Education

Background: For patients with primary biliary cholangitis (PBC), liver disease assessment, risk stratification, and monitoring are critical for optimizing treatment plans. We sought to assess current practices in community-based clinics and identify opportunities for improving PBC care. **Methods:** From December 2024 to April 2025, surveys were conducted among clinical teams at 8 community-based gastroenterology and hepatology clinics as part of an educational initiative. Survey items focused on current practices and challenges in PBC management. **Results:** A total of 81 healthcare professionals (HCPs) completed the survey (13% gastroenterologists, 4% hepatologists, 54% NPs/PAs, 29% nurses and other clinical professions). The top challenges in assessing liver disease in PBC were difficulty interpreting tests due to comorbidities (eg, MASLD; 52%) and limited training (28%). Most HCPs (71%) reported very low to moderate confidence in using noninvasive techniques for liver disease staging in PBC and 51% reported routine use of liver biopsy in PBC. The most common strategies for risk-stratification were biochemical response to ursodeoxycholic acid (62%), FIB-4 index (49%), and elastography (49%); only 17% reported using a validated score (eg, GLOBE, UK-PBC) for risk stratification. Less than half (46%) of HCPs reported re-assessing risk of disease progression annually in all patients. Tests used to monitor treatment response included alkaline phosphatase (ALP; 88%), alanine transferase/aspartate transferase (69%), bilirubin (59%), albumin (43%), and platelets (31%). 33% of HCPs reported that more than half of their patients with PBC were currently prescribed second-line therapy. The top barriers to the use of new second-line PBC therapies were limited knowledge of clinical data (47%), uncertainty in identifying treatment candidates (44%), and lack of guideline recommendations (37%). After participation in team-based educational sessions on PBC, the top action items HCPs intended to take were use of ALP normalization as a treatment target (50%), use of non-invasive tests (44%), and earlier assessment of response to UDCA (38%; Figure). **Conclusion:** This study uncovered variation in clinical practices for the assessment and management of patients with PBC in community settings. Targeted educational and implementation initiatives are needed to more closely align PBC care with evidence-based practices.



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Disclosures: Robert Gish: please see full disclosures document: Consultant, Sara Atcheson: Ardelyx: Stock - publicly traded company, Jenniffer Meza Jimenez: Nothing to Disclose, Jeffrey Carter: Nothing to Disclose, Leah Molloy: Nothing to Disclose, Laura Simone: Nothing to Disclose

4426 | ANALYSIS OF CIRCULATING BIOMARKERS IN THE RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PORTOLA PHASE 2A STUDY EVALUATING ZETOMIPZOMIB, A SELECTIVE IMMUNOPROTEASOME INHIBITOR, IN PATIENTS WITH AUTOIMMUNE HEPATITIS

Janet Anderl[1] Neel Anand[1] David Bade[1] Eric Lowe[1] Kathryn Ray[1] Brian Tuch[1] Jennifer Whang[1], [1]Kezar Life Sciences

Background: Pathogenesis of autoimmune hepatitis (AIH) is still poorly understood, but involves a complex interplay of immune effector cells, including liver-invasive antigen-presenting cells, dysfunctional T cells, and autoantibody-producing plasma cells. Clinical studies in systemic lupus erythematosus (SLE) have demonstrated the ability of zetomipzomib (zeto), a selective inhibitor of the immunoproteasome, to reduce inflammatory cytokine production and modulate T and B cell gene expression and circulating populations (Fan, EULAR 2022; Furie, ACR 2024). Here we describe peripheral blood-derived biomarker changes observed following zeto administration in AIH patients from the randomized, double-blind, placebo-controlled Phase 2a PORTOLA study (NCT05569759). **Methods:** In the PORTOLA study (n = 24 patients with active AIH), zeto 60 mg was administered subcutaneously weekly for 24 weeks. Complete response (CR) was defined as normalization of ALT, AST, and IgG (if elevated at baseline) with steroid dose not higher than baseline dose. Whole blood was collected at Weeks 0, 8, 16, and 24 for transcriptomic analysis, plasma proteomics by tandem mass spectrometry, plasma cytokine immunoassay, and cryopreserved immune cell profiling by flow cytometry. **Results:** Proteomic assessment of plasma demonstrated a reduction in immunoglobulins following zeto administration, consistent with transcriptomic changes observed in SLE and despite comparable infectious adverse events between zeto and placebo in PORTOLA. In patients achieving CR, decreases in several neutrophil proteins implicated in liver inflammation, including LCN2, were observed. Plasma cytokine analysis showed an increase in BAFF associated with zeto administration, consistent with observations from studies in SLE. Elevated TGF-β1 and the macrophage chemokines, MDC and MIP-3β, correlated with CR following 6 months of treatment. Immune phenotyping following zeto administration revealed reductions in B cells and monocytes and increased Treg cells in patients achieving CR. **Conclusion:** In the PORTOLA Phase 2a study, zeto administration resulted in notable alterations in biomarker activity across both the innate and adaptive immune systems that correlated with clinically relevant biochemical responses in AIH. Circulating biomarker changes following zeto treatment were consistent with previous reports from clinical studies in patients with SLE. These findings provide intriguing starting points for further mechanistic studies and validation in the AIH population.

Disclosures: Janet Anderl: Kezar Life Sciences: Employee, Kezar Life Sciences: Stock - publicly traded company, Neel Anand: Kezar Life Sciences: Employee, Pfizer: Stock - publicly traded company, Exelixis: Stock - publicly traded company, Johnson & Johnson: Stock - publicly traded company, Celldex: Stock - publicly traded company, David Bade: Kezar Life Sciences: Employee, Eric Lowe: Nothing to Disclose, Kathryn Ray: Kezar Life Sciences: Employee, Brian Tuch: Nothing to Disclose, Jennifer Whang: Kezar Life Sciences: Employee

4427 | A DIAGNOSIS WITH LASTING IMPACT: CURRENT SEX- AND AGE-SPECIFIC EPIDEMIOLOGICAL TRENDS IN PRIMARY BILIARY CHOLANGITIS

Kristel Leung[1] Wenbin Li[2] Aliya Gulamhusein[3] Bettina Hansen[4] Abdel Aziz Shaheen[5] Jennifer Flemming[6] Gideon Hirschfield[3], [1]Queen's University; Autoimmune and Rare Liver Disease Programme; University of Toronto - IHPME, [2]ICES Queen's, [3]Autoimmune and Rare Liver Disease Programme; University Health Network, [4]Erasmus MC Rotterdam, [5]University of Calgary, [6]Queen's University, ICES Queen's

Background: Understanding sex- and age-specific epidemiology of primary biliary cholangitis (PBC) is valuable amid emerging second-line therapies, increasing multimorbidity in older adults, and a need for personalized patient counselling. **Methods:** Population-based incident and prevalent PBC cohorts in Ontario, Canada (2002–2021) were identified using health administrative data from ICES based on ICD-9/10 codes and/or anti-mitochondrial antibody positive (AMA+) status ≥1:40, with validation using a reference cohort from Toronto (total n = 18,687, with n = 913 AMA + PBC). Exclusions included viral hepatitis, genetic liver disease, acute liver failure, alcohol/toxins, drug-induced liver injury, prior liver transplant, and inflammatory

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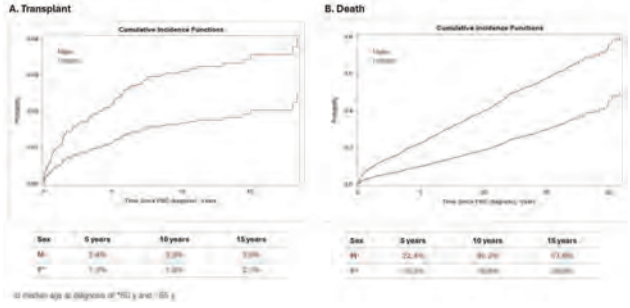
bowel disease. Sex- and age-specific incidence and prevalence (standardized to the 2011 Canadian population) were assessed, with trends analyzed via joinpoint regression. Outcomes until 2021 were assessed, including transplant-free survival, competing risk of transplant vs. death, and cause of death (available before 2019). **Results:** A validated prevalent PBC cohort (n = 6,152; sens. 72%, spec. 99%, PPV 85%) showed rising prevalence over time (annual percent change [APC] 4.73% from 2018–2021), particularly among adults > 50 y, while incidence plateaued (APC 0.82% from 2015–2021). In 2021, point prevalence was 31.7/100,000 person-years (PY) (95% CI: 30.7–32.7), with a female-to-male (F:M) ratio of ~6:1 (58.4 and 9.16/100,000 PY for females and males respectively). Between 2002–2021, 4,844 incident cases were identified (24% diagnosed before age 50, 76% diagnosed after age 50; 85% female). Males were older at diagnosis (median 65 y vs. 60 y for females, $p < 0.001$) and more often resided in areas with higher income quintile ($p = 0.018$) and % owned dwellings ($p = 0.0042$). Incidence was 2.28/100,000 PY overall (females: 3.77; males: 0.69), with F:M ratios ranging from 9:1 (ages 41–50 y) to 3:1 (> 70 y). Median unadjusted transplant-free survival was 19.2 y (females: 19.9 y; males: 10.6 y; $p < 0.001$), primarily driven by all-cause death. Liver-related causes accounted for ~40% of deaths in both sexes. Males had higher risks of transplant (adjusted hazard ratio [aHR] 2.62, 95% CI: 1.71–4.02) and death (aHR 1.62, 95% CI: 1.41–1.85). Older age was associated with lower transplant rates (aHR 0.96, 95% CI: 0.94–0.97) and higher mortality (aHR 1.09, 95% CI: 1.08–1.10). **Conclusion:** PBC epidemiology in Ontario reveals sex- and age-specific patterns, with males diagnosed later in life and more often residing in higher socioeconomic areas. The aging population reflects the disease's chronic course over decades. Despite higher rates of death and transplant in males, liver-related mortality remained substantial across sexes.

Figure. Cumulative Risk of (A) Transplant, and (B) Death by Cause-Specific Competing Risk Regression Analysis in Individuals Diagnosed with PBC.



Disclosures: Kristel Leung: Nothing to Disclose, Wenbin Li: Nothing to Disclose, Aliya Gulamhusein: Nothing to Disclose, Bettina Hansen: Nothing to Disclose, Abdel Aziz Shaheen: Nothing to Disclose, Jennifer Flemming: Nothing to Disclose, Gideon Hirschfield: Intercept: Consultant, Intercept: Consultant, GSK: Consultant, GSK: Consultant, CymaBay: Consultant, CymaBay: Consultant, Ipsen: Consultant, Ipsen: Consultant, Falk: Consultant, Falk: Consultant, Pliant: Consultant, Pliant: Consultant, Mirum: Consultant, Mirum: Consultant, Advanz: Consultant, Advanz: Consultant, Chemomab: Consultant, Chemomab: Consultant, Gilead: Consultant, Gilead: Consultant, Kowa: Consultant, Kowa: Consultant, Kezar: Consultant, Intercept: Consultant, Intercept: Consultant, GSK: Consultant, GSK: Consultant, CymaBay: Consultant, CymaBay: Consultant, Ipsen: Consultant, Ipsen: Consultant, Falk: Consultant, Falk: Consultant, Pliant: Consultant, Pliant: Consultant, Mirum: Consultant, Mirum: Consultant, Advanz: Consultant, Advanz: Consultant, Chemomab: Consultant, Chemomab: Consultant, Gilead: Consultant, Gilead: Consultant, Kowa: Consultant, Kowa: Consultant, Kezar: Consultant

4428 | VALIDATION OF ALP AND BILIRUBIN BIOCHEMICAL RESPONSE CRITERIA IN PATIENTS RECEIVING SECOND-LINE TREATMENT FOR PRIMARY BILIARY CHOLANGITIS: INSIGHTS FROM THE FIOCA STUDY

Vincenzo Ronca[1] Antonio De Vincentis[2] Francesca Terracciani[2] Christophe Corpechot[3] Guilherme Cançado[4] Nadir Abbas[5] Kathryn Olsen[5] Sergio Rodriguez-Tajes[6] Maria Carlota Londono[7] Vasiliki Lygoura[8] Nikolaos Gatselis[8] George Dalekos[9] Miki Scaravaglio[10] Daphne D'Amato[10] Alessio Gerussi[10] Laura Cristoferi[10] Nora Cazzagon[11] Francesca Colapietro[12] Vincenza Calvaruso[13] Ellina Lytvyak[14] Aldo Montano-Loza[15] Rodrigo Motta[16] Emma Culver[16] Esmée Eikelenboom[17] Adriaan van der Meer[18] Ehud Zigmond[19] Alejandra Villamil[20] Frederik Nevens[21] Leandro Sierra[22] Romelia Barba[23] Alan Bonder[24] Xavier Verhelst[25] Mauro Vigano[26] Raffaella Vigano[27] YU JUN WONG[28] Adrielly Martins[29] Henriette Ytting[30] Cynthia Levy[29] Atsushi Tanaka[31] Ana Lleo[1] Palak Trivedi[32] Umberto Vespasiani-Gentilucci[33] Pietro Invernizzi[34] Gideon Hirschfield[35] Bettina Hansen[36] Marco Carbone[37], [1]Humanitas University, [2]Unit of Internal Medicine, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy, [3]Saint-Antoine Hospital, Assistance Publique - Hôpitaux de Paris, Paris, France, [4]Instituto Alfa de Gastroenterologia, Hospital das Clínicas da Universidade Federal de Minas Gerais, [5]Liver Unit, University Hospitals Birmingham, Birmingham, United Kingdom, [6]Liver Unit, Hospital Clínic Barcelona, Barcelona, [7]Hospital Clinic, [8]Department of Medicine and Research Laboratory of

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Background: Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease that can lead to fibrosis and cirrhosis. While ursodeoxycholic acid (UDCA) is the first-line therapy, up to 40% of patients show an incomplete biochemical response, requiring second-line (SL) treatments. Although response criteria are well-established for UDCA, their utility in SL-treated populations is less clear. The FiOCA study aims to validate biochemical response criteria as predictors of transplant-free survival across diverse SL therapies. **Methods:** This retrospective study included 1843 patients with inadequate UDCA response from 24 international liver centers part of the Global PBC study group. After applying strict inclusion criteria—12-month follow-up, complete biochemical data, and single SL therapy—866 patients were analyzed. Data included demographics, liver histology, and biochemical markers. Transplant-free survival outcomes were assessed using Kaplan-Meier and Cox proportional hazards models. **Results:** Patients were predominantly female (87.9%) with a median age of 56 year, and a median follow-up time of 37 months. At initiation of second-line therapy, the median alkaline phosphatase (ALP) was 1.93 (IQR 1.44-2.90) xULN, 126 (23.3%) patients were cirrhotic, with 15 (2.8%) of them Child-Pugh B. In univariate Cox analyses, achieving ALP $< 1.67\times$ULN at 12 months was associated with a 43.5 % reduction in transplant-free survival (HR 0.56, 95 % CI 0.33–0.97; $p = 0.039$). After adjustment for treatment (fibrates vs OCA), this effect persisted (adjusted HR 0.52, 95 % CI 0.30–0.91; $p = 0.021$), and the ALP×treatment interaction was non-significant indicating similar prognostic value regardless of the second-line agent. An ALP decline $\geq$ 15 % at month 12 also predicted better outcome when adjusted for treatment (HR 0.49, 95 % CI 0.27–0.87; $p = 0.015$); the interaction term remained non-significant. Normalization of bilirubin yielded the strongest association, with an adjusted HR of 0.14 (95 % CI 0.08–0.25; $p < 0.001$). The composite responder definition—normal bilirubin and ALP $< 1.67\times$ULN and $\geq$ 15 % ALP decline- was associated with a 66 % risk reduction (adjusted HR 0.34, 95 % CI 0.18–0.66; $p = 0.0015$), again without a significant treatment interaction. In Kaplan–Meier analyses pooled across both treatment arms, biochemical responders had significantly higher event-free survival than non-responders for every surrogate definition at 12 months (log-rank $p = 0.037$ for ALP $< 1.67\times$ULN, $p = 0.013$ for $\geq$ 15% ALP decline, $p < 0.001$ for bilirubin normalization, and $p < 0.001$ for the composite response). **Conclusion:** We confirm that biochemical response criteria measured at 12 months reliably predict transplant-free survival in PBC patients treated with either obeticholic acid or fibrates. The composite responder definition (normal bilirubin and ALP $< 1.67\times$ULN or $\geq$ 15% ALP decline), was found to be independent of the specific second-line agent used.

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4429 | IMPACT OF PRURITUS ON CLINICAL OUTCOMES IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: A PROPENSITY SCORE-MATCHED ANALYSIS

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Background: Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic liver disease frequently accompanied by debilitating symptoms such as fatigue and pruritus, both of which can significantly impair patients' quality of life. Although prior studies have suggested a potential association between pruritus, fatigue and adverse mental health outcomes, large-scale comparative analyses in PSC populations are lacking. This study aims to evaluate clinical outcomes, particularly fatigue and antidepressant use, among patients with PSC, in the presence and absence of pruritus, using real world data. **Methods:** We conducted a retrospective cohort study using data from the TriNetX US Collaborative Network, which includes electronic health records from 68 healthcare organizations. Adult patients with PSC were identified using ICD-10 codes and were stratified into two cohorts: those with pruritus (n = 3,164) and those without (n = 11,160). Propensity score matching (1:1) was performed to balance 16 baseline covariates including cirrhosis, inflammatory bowel disease, mood disorders, and other comorbidites that could cause fatigue, resulting in a matched cohort of 2,988 patients in each cohort. Primary outcomes included fatigue and antidepressant use. Statistical analyses were performed using risk estim. **Results:** The prevalence of fatigue was more than double in the pruritus group (27.1% vs. 12.5%, RR 2.17, 95% CI 1.95-2.43), with earlier onset (median time to diagnosis 1,292 days vs. 3,522 days, HR 1.87, 95% CI 1.65-2.11). Antidepressant use was also higher in the pruritus

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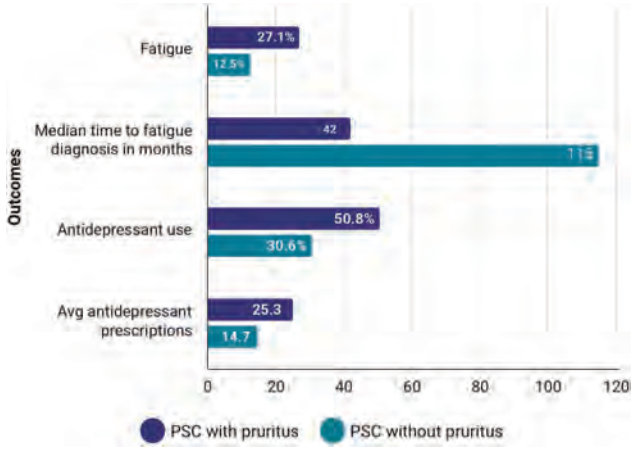
cohort (50.8% vs. 30.6%, RR 1.66, 95%CT 1,56-1.77), along with a greater number of antidepressant prescriptions on average (25.3 vs. 14.7 per patient, $p < 0.001$). All the comparisons between groups were statistically significant ($p < 0.001$) with well balanced baseline characteristics after matching balance (standardized differences < 0.1 for all variables). **Conclusion:** Patients with PSC experiencing pruritus exhibit significantly higher risks of fatigue and antidepressant use, with earlier onset and greater severity of symptoms. These findings suggest that pruritus in PSC may reflect a broader systemic disease burden rather than being a purely symptomatic manifestation. A more holistic approach to history-taking, including systematic assessment of pruritus and associated psychosocial impacts is essential for effective management.



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4430 | SINGLE-CELL SPATIAL TRANSCRIPTOMICS REVEALS TNFSF SIGNALING DYNAMICS AND POTENTIAL TREATMENT TARGETS IN PEDIATRIC ONSET AUTOIMMUNE LIVER DISEASES

Yunguan Wang[1] David Adeleke[1] Michelle Damen[1] Zi Yang[1] Cyd Castro Rojas[1] Mosab Alquraish[1] Emily Miraldi[1] Pamela Sylvestre[1] Alex Miethke[1] Liva Pfuhler[1] Ramesh Kudira[1], [1]Cincinnati Children Hospital

Background: Autoimmune liver diseases (AILD) features auto inflammation and focal fibrosis surrounding interlobular bile ducts or portal tracts. Biologics blocking TNFa signaling emerge as therapy for a wide range of autoimmune conditions including IBD, commonly associated with primary sclerosing cholangitis (PSC), and autoimmune hepatitis AIH. To gain insights into the functional states of TNFSF genes in AILDs, this study presents a fine-resolution mapping of the expression levels of TNFSF ligands and receptors across diverse cell types in AIH, PSC, autoimmune sclerosing cholangitis (ASC), and healthy controls (HC). **Methods:** We performed MERSCOPE-based, single cell spatially resolved transcriptomic (scSRT) profiling using a customized 500-gene panel including 47 TNFSF ligands and receptors on archived tissue samples from diagnostic liver biopsies ($n = 8$) and explants ($n = 6$). In-house single-cell RNA-seq (scRNA-seq) data derived from patients with AILD and from livers of DDC-treated mice and liver bulk RNAseq data from patients with AILD stratified by stage of fibrosis were used for validation. **Results:** We identified major cell types involved in AILD, including macrophages (MPs), T and B cells, hepatic stellate cells (HSCs). M2-polarized MP, activated HSCs, T- and B cells were enriched in fibrotic periductal regions. Within these areas, expression levels for *LTBR, TNFRSF12A/14/19/21* were upregulated in cholangiocytes, and to a lesser extent in hepatocytes, in patients with end-stage disease from AIH, ASC, or PSC. TNFSF ligand genes, including LTB and TNFSF8/12, were primarily expressed in immune cells, sinusoidal cells, and HSCs. Consistent with scSRT, TNFSF14 and TNFRSF12A/19/21 were upregulated in bulk RNAseq data from AILD patients with established liver fibrosis compared with early disease. In mice exposed to DDC precipitating toxic bile induced liver injury, Tnfrsf12a/19/21 were upregulated in cholangiocytes during DDC challenge and recovery compared to baseline. **Conclusion:** These findings underscore the distinct, cell type–specific expression patterns of TNFSF receptors and ligands across autoimmune liver diseases. They support the involvement of TNFSF signaling in coordinating immune and epithelial responses in pediatric onset AILD. The disease-associated overexpression of TNFRSF12A/19/21 in both human AILD and the murine DDC model warrants further investigation to abrogate bile duct epithelial injury.

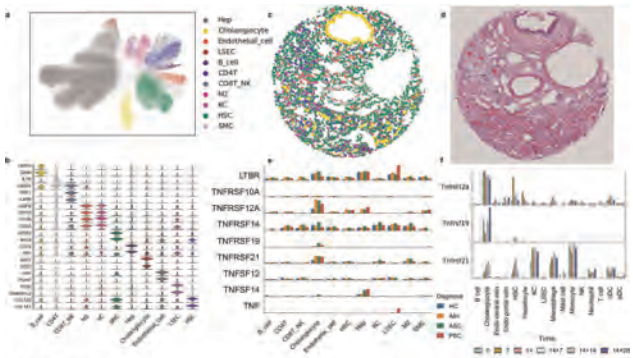

Figure legend
a, UMAP representation of cell types identified in scSRT data from HC, AIH, ASC and PSC samples. b, Expression of marker genes for each cell type. c and d, Cell segmentation mask (c) and matching H&E staining image (d) from a representative ASC sample. Cell masks were colored based on the cell types. e, Expression of selected TNFSF ligand and receptor genes in human scSRT data. f, Expression of selected TNF receptor genes in scRNA-seq data from mouse treated with DDC.

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4431 | CNP-104 INDUCES ANTIGEN-SPECIFIC IMMUNE TOLERANCE IN PBC VIA PATHOGENIC CYTOKINE REDUCTION AND TOLEROGENIC T CELL EXPANSION

Molly Frey Adam Elhofy[1] Christopher Bowlus[2] Derrick McCarthy[1] Erik Wambre[3] Stephen Caldwell[4] Roberto Firpi-Morell[5] Brett Fortune[6] Michael Galambos[7] Stuart Gordon[8] Denise Harnois[9] Tarek Hassanein[10] Matthew Kappus[11] Eric Lawitz[12] Scott McHenry[13] Bhaktasharan Patel[14] Raymond Phillips[15] Daniel Pratt[16] Jatinder Pruthi[17] Govarthanan Rajendiran[18] K. Gautham Reddy[19] Manuel Rodriguez[20] Marina Silveira[21] Xaralambos Zervos[22] Paul Peloso[23] M Gershwin[2], [1]COUR Pharmaceuticals, [2]University of California, Davis, [3]Precision Immunology Institute, Icahn School of Medicine at Mount Sinai, [4]University of Virginia, [5]University of Florida, [6]Montefiore Medical Center, [7]Digestive Healthcare of Georgia, [8]Henry Ford Health System, [9]Mayo Clinic Florida, [10]Southern California Research Center, [11]Duke University, [12]Texas Liver Institute, [13]Washington University in St. Louis, [14]Peak Gastroenterology Associates, [15]GI Pros Research, [16]Massachusetts General Hospital, [17]Om Research, [18]Sanford Medical Center, [19]University of Chicago, [20]Florida Research Institute/ Florida Digestive Health Specialists, [21]Yale University, [22]Cleveland Clinic Florida, [23]COUR

Background: Primary biliary cholangitis (PBC) is an archetypical autoimmune disease driven by loss of tolerance to the mitochondrial autoantigen PDC-E2, leading to immune-mediated progressive bile duct injury and fibrosis. Emerging evidence highlights Th17 cells and type 3 cytokines as drivers of biliary inflammation. Currently approved PBC therapeutics target downstream processes such as bile acid metabolism without addressing the underlying autoimmune process. CNP-104, a first-in-class tolerogenic nanoparticle encapsulating PDC-E2, aims to restore immune tolerance. We leverage antigen-specific immune biomarkers to assess the therapeutic mechanisms of CNP-104 in a Phase 2a trial in PBC. **Methods:** In this randomized, placebo-controlled trial, 41 PBC patients with an incomplete biochemical response (ALP $>1.5\times$ULN) received two doses of CNP-104 or placebo one week apart. Shown here are the 4 mg/kg CNP-104 (n = 11) and placebo (n = 16) groups. Immune profiling included antigen-specific Th17 and CD8+ TIGIT + T cells by flow cytometry and serum IL-17 by Olink. Liver stiffness via FibroScan was assessed as translational clinical endpoint. **Results:** CNP-104-treated subjects exhibited a reduction in the percentage of PDC-E2-specific Th17 T cells (-27.3%) compared to placebo (+2.5%, p = 0.034), consistent with diminished autoreactive T cell activity. Concurrently, the responder rate of PDC-E2-specific CD8+ TIGIT+ cell counts (change from baseline $\leq$ 0) was larger in CNP-104 (66.7%) compared to placebo (22.2%, p = 0.136), suggesting expansion of regulatory T cell populations. Cytokine analyses demonstrated a decrease in IL-17 levels in participants treated with CNP-104 compared to placebo, further supporting attenuation of pro-inflammatory pathways. Clinically, participants classified as Th17 responders (change from baseline $\leq$ 0) correlated to lower liver stiffness measurements compared to non-responders, suggesting a direct link between immunomodulation and reduced fibrosis progression (Figure 1). **Conclusion:** CNP-104 modulates PBC-relevant immune pathways by reducing pathogenic PDC-E2-specific Th17 cells and IL-17 while expanding tolerogenic TIGIT+ CD8 + T cells, demonstrating dual immune modulation toward tolerance. Furthermore, Th17 responders had a corresponding slowed progression of liver stiffness, suggesting a mechanism to explain CNP-104's anti-fibrotic effects. These findings support CNP-104 as a disease-modifying therapy that targets core immune dysfunction in PBC, with potential to improve outcomes beyond current standard of care.

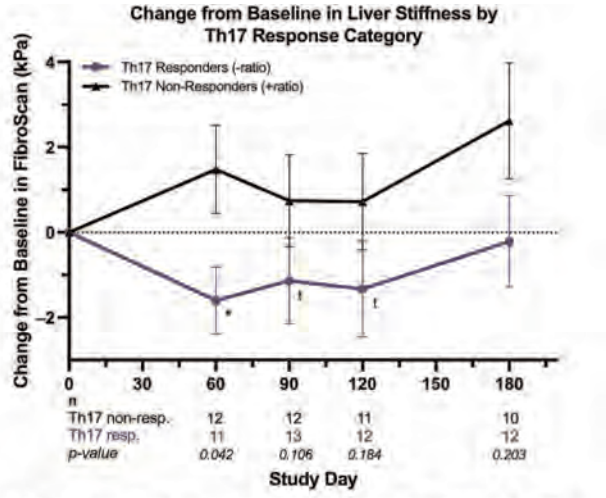

Figure 1. Antigen-specific Th17 T cell activity correlates with changes in liver stiffness. PBMCs were isolated, stimulated with DMSO (control) or PDC-E2 peptide, and enriched for antigen-specific CD4 T cells. Cells were analyzed by flow cytometry, and event counts were normalized to pre-enrich samples. Th17 CD4 T cells were gated as effector memory > CD154+CCR6+. The percentage was calculated by subtracting the normalized percent of parent in the DMSO negative control condition from the PDC-E2 stimulation condition. A Th17 responder was defined as having a Th17 ratio equal to or less than the baseline value. Liver stiffness was measured by FibroScan and had to meet validity criteria of having an IQR/median less than 30%. Mean ± SEM is shown for each timepoint. Statistical testing: Wilcoxon Rank Sum test for the median change from baseline between treatment groups; * $p \leq 0.05$; † $p \leq 0.20$.

Disclosures: Molly Frey: COUR Pharmaceuticals: Employee, Adam Elhofy: Nothing to Disclose,

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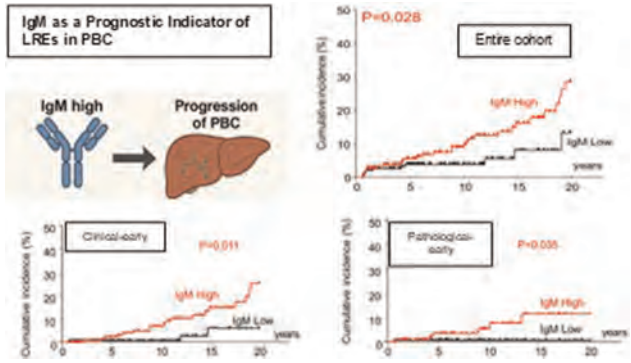
4432 | SERUM IGM LEVELS AS A PROGNOSTIC INDICATOR OF LIVER-RELATED EVENTS IN PRIMARY BILIARY CHOLANGITIS

Taiki Okumura[1] Takanobu Iwadare[1] Shun-Ichi Wakabayashi[1] Hiroyuki Kobayashi[1] Yuki Yamashita[1] Takefumi Kimura[1], [1]Shinshu university school of medicine

Background: Elevated serum IgM levels are frequently observed in patients with primary biliary cholangitis (PBC), but few studies have examined the association between IgM and prognosis. This study aimed to investigate whether serum IgM levels could serve as a predictor of liver-related events (LREs) in PBC. **Methods:** A total of 427 patients diagnosed with PBC between at four institutions in Japan were retrospectively analyzed (273 with liver biopsy, 154 without). We assessed the association between serum IgM levels and the occurrence of LREs alongside other clinicopathological parameters. Due to sex differences in normal IgM levels, the IgM/upper limit of normal (ULN; male: 183 mg/dL, female: 269 mg/dL) ratio was used as a variable. LREs were defined as the occurrence of ascites, gastroesophageal varices, hepatic encephalopathy, or hepatocellular carcinoma. **Results:** The median age at diagnosis was 58 years, and the cohort included 70 males and 357 females. Clinical stage by Nakanuma classification was 1/2/3/4/NA in 105/126/36/6/154 patients, and ALBI grades were 1/2/3 in 325/90/12 patients. The median observation period was 9.0 years. The cumulative incidence of LREs at 20 years was 22.7%, with 39 LREs observed during the entire study period. In multivariate Cox proportional hazards analysis excluding histological factors, low serum albumin (hazard ratio [HR] 0.18, $p < 0.001$) and high IgM levels (HR 1.53, $p < 0.001$) were independently associated with LREs. Patients with IgM/ULN ≥ 1 ($n = 224$) had a significantly higher incidence of LREs than those with IgM/ULN < 1 ($n = 203$) (18.4% vs. 13.2% at 20 years, $p = 0.03$).
Further analyses in clinically earlu cases (ALBI grade 1, $n = 325$) showed that patients with IgM/ULN ≥ 1 ($n = 162$) had a significantly higher LRE incidence than those with IgM/ULN < 1 ($n = 163$) (25.3% vs. 6.1% at 20 years, $p = 0.01$). Similarly, among pathologically early cases (Nakanuma stages 1 and 2, $n = 231$), the IgM/ULN ≥ 1 group ($n = 106$) had a significantly higher incidence than the IgM/ULN < 1 group ($n = 125$) (11.4% vs. 0.8% at 20 years, $p = 0.03$). **Conclusion:** Our findings suggest that serum IgM levels are an independent predictor of LREs in PBC, even in patients with clinical and pathological early stage.



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4433 | PROTOCOLLED THIOPURINE METABOLITE MONITORING LEADS TO BETTER QUALITY CARE OUTCOMES IN PATIENTS WITH AUTOIMMUNE HEPATITIS

Cindy Ho[1] Ed Reece Ansaar[2] Joshua Abasszade[3] Ruyi Tan[1] Atul Shrestha[1] Tobie Abrahams[4] Teagan Wanigaratne[2] Suzannah Henshaw[2] Dilip Ratnam[5] Marcus Robertson[3], [1]Monash Health, Clayton, Victoria, Australia, [2]Peninsula Health, Frankston, Victoria, Australia, [3]Monash Health, Clayton, Victoria, Australia and Peninsula Health, Frankston, Victoria, Australia, [4]Alfred Health, Melbourne, Victoria, Australia, [5]Monash Health, Clayton, Victoria, Australia and Monash University, Clayton, Victoria, Australia

Background: Autoimmune hepatitis (AIH) is an immune-mediated inflammatory hepatopathy characterised by hypergammaglobulinemia, specific autoantibodies and interface hepatitis which carries a

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significant risk of cirrhosis in the absence of timely and effective therapy. Initial treatment traditionally comprises glucocorticoids and a thiopurine (TP) with a view to maintaining steroid-free remission on TP monotherapy. Although well established in the inflammatory bowel disease population, the role of routine TP metabolite (TM) testing in AIH remains uncertain. We aimed to evaluate the utility of routine TM testing in TP dose-optimisation and disease remission. **Methods:** We conducted a prospective observational study of adult patients with newly diagnosed AIH who were commenced on a TP as the first steroid-sparing agent at a metropolitan tertiary health network between 2014 and 2023. International AIH Group simplified diagnostic criteria were used to standardise diagnosis of AIH. Baseline demographic, biochemical, serologic and histologic data were recorded along with TP dosing regimens and TM levels. The primary outcomes were: i) biochemical remission (alanine transaminase (ALT) <40 U/L within 12-months of diagnosis) and, ii) the frequency of TP dose adjustment following TM testing. The secondary outcome was identification of TP non-compliance and shunting. **Results:** In total, 41 patients with a male predominance (63.4%) and median age of 59 years (IQR 42-67) were included, with a median follow up time of 2.9 (IQR 1-5.4) years. At the time of diagnosis, 6 (14.6%) patients were cirrhotic, and median ALT was 1112 U/L (IQR 565-1262). Biochemical remission was achieved in 24 (58.5%) patients at 6-months and 36 (87.8%) at 12-months. Azathioprine (AZA) was commenced in 92.7% patients (median dose 100 mg daily (IQR 50-100)); the remaining 7.3% patients were commenced on 6-mercaptopurine. Median 6-thioguanine nucleotide and 6-methyl mercaptopurine levels were 220 pmol/8x10^8 RBC (IQR 129-372) and 527 pmol/8x10^8 RBC (IQR 229-1249) respectively. There was no significant difference in metabolite levels between patients who achieved biochemical remission at 12 months and those that did not. During the study period, 195 TM tests were performed, with a median of 4 (IQR 3-6) per patient. TP dose adjustment occurred following 68.6% of TM measurements. Non-compliance was identified in 29.3% patients and shunting in six patients necessitating allopurinol treatment. Six patients (14.6%) ceased TP due to side effects. One patient with identified TP shunting had a self-limiting AZA-induced liver injury. **Conclusion:** In patients with AIH treated with a TP, protocolled TM measurements optimised TPMT metabolites with high biochemical remission rates of 87.8% at 12-months. TM measurement led to TP dose alteration in 68.6% of cases and identified both medication non-compliance and metabolite shunting.

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4434 | SUSTAINED EFFICACY AND SAFETY OF SELADELPAR FOR UP TO 36 MONTHS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS FROM THE PLACEBO-CONTROLLED RESPONSE STUDY TO THE OPEN-LABEL ASSURE STUDY

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Background: Seladelpar (SEL) is a first-in-class delpar (selective PPAR-delta agonist) indicated for the treatment of primary biliary cholangitis (PBC) combined with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients (pts) intolerant to UDCA. In the Phase 3, randomized, placebo (PBO)-controlled RESPONSE study (NCT04620733), SEL significantly reduced biochemical markers of cholestasis and pruritus. After completing RESPONSE, pts were eligible to enroll in ASSURE (NCT03301506), an ongoing, open-label, Phase 3 trial. Here, we report interim, long-term efficacy and safety data for pts enrolled in RESPONSE and upon rollover to ASSURE with up to 3 yrs of data. **Methods:** Data were analyzed from RESPONSE and ASSURE up to 1/31/2025. Pts with PBC with an inadequate response or intolerance to UDCA and ALP $\geq 1.67 \times$ the upper limit of normal (ULN) received blinded, daily oral SEL 10 mg or PBO in RESPONSE; pts who enrolled in ASSURE received open-label, daily oral SEL 10 mg. Pts were analyzed based on receipt of SEL (continuous SEL) or PBO (crossover SEL) in RESPONSE. Efficacy endpoints included a composite

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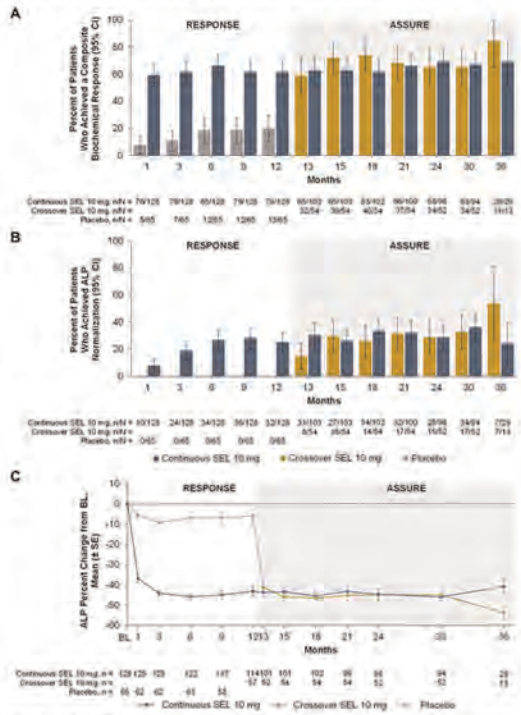
biochemical response (CBR; ALP $<1.67 \times$ ULN, ALP decrease $\geq 15\%$, and total bilirubin $\leq$ ULN), ALP normalization, ALT normalization (among pts with ALT $>$ ULN at baseline [BL]), and ALP percent change from BL. Exposure-adjusted adverse events (AEs) were analyzed. **Results:** Of 193 pts enrolled in RESPONSE (SEL, n = 128; PBO, n = 65), 158 pts (SEL, n = 104; PBO, n = 54) enrolled in ASSURE. As of the cutoff date, 94% of continuous SEL pts (98/104) received SEL for ≥ 2 yrs and 27% (28/104) received SEL for ≥ 3 yrs; 24% of crossover SEL pts (13/54) received SEL for ≥ 2 yrs. Among continuous SEL pts, the CBR, ALP normalization, and ALT normalization rates were 69% (20/29), 24% (7/29), and 56% (10/18) through 36 months (M). Among crossover SEL pts, the CBR rate at 6M was 74% (40/54) and remained similar through 24M (85% [11/13]). Among crossover SEL pts, ALP normalized in 26% of pts (14/54) at 6M and 54% of pts (7/13) at 24M; ALP percent change from BL was also assessed (Figure). 71% (20/28) achieved ALT normalization at 6M and 75% (3/4) at 24M. Exposure-adjusted pt incidence of AEs was 90.9 per 100 pt-yrs for SEL vs 91.4 for PBO in RESPONSE; rates were generally similar or lower in yrs 2 and 3 of SEL exposure in ASSURE. **Conclusion:** Biochemical efficacy and safety with SEL in the pivotal RESPONSE study was sustained up to 36M in the open-label ASSURE study.

Figure. Composite Biochemical Response (A), ALP Normalization (B), and ALP Percent Change From BL (C) Through 36 Months of Seladelpar Treatment



n/N = number of responders at each time point/total number of evaluable patients at each time point.

n = number of evaluable patients at each time point.

ALP, alkaline phosphatase; BL, baseline; SEL, seladelpar.

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4435 | SEX DISPARITIES IN CLINICAL OUTCOMES AND HEALTH RESOURCE UTILIZATION IN PRIMARY BILIARY CHOLANGITIS IN THE UNITED STATES: A RETROSPECTIVE COHORT STUDY

Nisreen Shamseddine[1] Hongbo Yang[2] Su Zhang[2] Dongni Ye[2] Sherry Shi[2] Anyu Zhu[2] Julius Wilder[3], [1]Ipsen, Cambridge, MA, USA, [2]Analysis Group Inc., Boston, MA, USA, [3]Duke University School of Medicine, Durham, NC, USA

Background: Primary biliary cholangitis (PBC) is a chronic liver disease with adverse outcomes including cirrhosis and end-stage liver disease. Early diagnosis and treatments can help prevent or delay progression. While sex differences in PBC prevalence have been documented, data on PBC care by sex in the United States (US) are limited. This retrospective cohort study assessed differences in PBC treatment rates, clinical outcomes, and healthcare resource use (HRU) between males and females with PBC in the US. **Methods:** Adult patients with PBC were identified in the Komodo Research Database (01/2016–09/2023). Baseline data were assessed for 12 months before PBC diagnosis date (pre-diagnosis). Treatment rates were assessed at baseline as proportions and at follow-up (post-diagnosis; PBC diagnosis to the earliest of death, end of continuous enrollment, or end of data-cut) as time to event using Cox models comparing males and females. HRU (reported as per patient per year [PPPY]) was assessed at baseline and compared between males and females at follow-up using generalized linear models. Time to selected adverse health outcomes at follow-up were compared between males and females using Cox models (Table). All analyses at follow-up were adjusted for key baseline characteristics. **Results:** The study included 9,308 females and 2,283 males; median follow-up was 24.1 and 19.2 months, respectively. Mean age at diagnosis was comparable between males and females (57.9 versus [vs] 58.6 years; $p = 0.054$). Males, compared to females, had a significantly higher comorbidity burden (mean Charlson Comorbidity Index: 4.0 vs 2.6; $p < 0.001$) and significantly higher rates of PBC-related complications pre-diagnosis. Treatment rate was significantly lower in males pre-diagnosis (36.3% vs 42.2%; $p < 0.001$) and post-diagnosis (HR: 0.73; $p < 0.001$). Males had significantly higher risks of developing all selected adverse clinical outcomes post-diagnosis (Table). Inpatient admission number (incidence rate ratio [IRR]: 1.45; $p < 0.001$) and length of stay (IRR: 1.56; $p < 0.001$) PPPY were significantly higher in males than females post-diagnosis. **Conclusion:** This study highlights sex differences in PBC care in the US. Males had more advanced disease and a higher comorbidity burden but

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were less likely to receive treatment. Males were also more likely to have adverse outcomes related to PBC and higher HRU. These findings suggest that sex may influence both the care and clinical outcomes of PBC and should be considered in disease management.

Table. Summary of hazard ratios (95% CIs) based on adjusted Cox models comparing males vs. females, probabilities of event-free over time, and median time to event (95% CI) for adverse clinical outcomes during the post-diagnosis period

	HR (95% CI) of males vs. females	Cohort	Probability of event-free					Median time to event (95% CI) (months)
			Year 1	Year 2	Year 3	Year 4	Year 5	
Cirrhosis	1.25 (1.09, 1.38)	Male:	81.1%	75.1%	69.8%	63.4%	59.5%	Not reached
		Female:	87.1%	81.0%	76.1%	72.6%	69.0%	Not reached
Clinically significant portal hypertension	1.77 (1.56, 2.02)	Male:	80.9%	75.0%	69.9%	65.9%	60.5%	Not reached
		Female:	91.1%	87.1%	84.3%	81.1%	79.2%	Not reached
Hepatic decompensation	1.49 (1.30, 1.72)	Male:	83.1%	77.9%	74.5%	71.3%	66.7%	Not reached
		Female:	93.0%	90.7%	88.3%	86.1%	83.8%	Not reached
Hospitalization due to hepatic decompensation	1.68 (1.41, 2.00)	Male:	89.5%	85.2%	81.4%	79.1%	75.2%	Not reached
		Female:	96.5%	94.9%	93.5%	92.0%	90.9%	Not reached
End-stage liver disease	1.82 (1.23, 1.64)	Male:	87.5%	81.5%	78.3%	76.4%	74.0%	Not reached
		Female:	95.2%	93.4%	91.9%	90.7%	89.3%	Not reached
Hepatocellular carcinoma	1.54 (1.12, 2.11)	Male:	97.7%	96.6%	95.7%	95.3%	93.9%	Not reached
		Female:	99.4%	98.9%	98.4%	98.0%	97.0%	Not reached
Liver transplant	2.16 (1.68, 2.78)	Male:	94.8%	92.2%	90.3%	89.2%	88.0%	Not reached
		Female:	99.0%	98.6%	98.3%	98.1%	98.1%	Not reached
All-cause death	1.51 (1.33, 1.72)	Male:	89.0%	84.0%	79.7%	74.5%	68.3%	Not reached
		Female:	96.8%	94.3%	91.1%	87.8%	84.1%	Not reached
Earliest of any clinical outcomes	1.30 (1.14, 1.68)	Male:	73.7%	65.7%	58.5%	51.7%	43.5%	50.0 (41.5, 58.0)
		Female:	83.8%	73.8%	69.4%	64.4%	59.2%	79.4 (72.6, not reached)

Notes: The multivariable Cox model for adverse clinical outcomes adjusted for the following key baseline characteristics: race/ethnicity, age at diagnosis, CCI score, presence of liver diseases resembling PBC and PBC-related complications, ever used PBC treatment during baseline, number of outpatient admissions, and number of emergency room visits.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; PBC, primary biliary cholangitis.

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4436 | A QUANTITATIVE SYSTEMS PHARMACOLOGY (QSP) MODEL TO INTERROGATE THE UNDERLYING MECHANISMS OF CHOLESTATIC PRURITUS (ITCH) IN PRIMARY BILIARY CHOLANGITIS (PBC) AND THE IMPACT OF LINERIXIBAT TREATMENT

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Background: PBC is marked by impaired bile secretion in the liver, resulting in hepatic inflammation and pruritogen release into the blood. Cholestatic pruritus (itch) strongly affects patients' (pts) quality of life, yet the underlying pathophysiological mechanisms remain poorly understood. A QSP model was developed to explore these mechanisms in PBC and how they are impacted during treatment with linerixibat (IBAT inhibitor) alone or with seladelpar (peroxisome proliferator-activated receptor agonist). **Methods:** The QSP model comprises 3 modules: PBC disease, itch and treatment. The disease module describes the concentrations of known itch mediators in PBC (i.e. bile acids, bilirubin, lysophosphatidic acid [LPA; as assessed by the surrogate autotaxin] and IL-31) based on publications, the linerixibat GLISTEN study (NCT04950127) and the seladelpar ENHANCE study (NCT03602560). These biomarkers trigger an itch signal via an individual pt data-calibrated activation function of the LPAR5, MRGPRX4 and IL-31 nerve receptors in the skin to predict a WI-NRS score. The treatment module affects the PBC disease model variables, shifting the system's equilibrium after administration of linerixibat and/or

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seladelpar. The model was calibrated using a subset of pts in GLISTEN who took both placebo and linerixibat for whom IL-31 was measured; seladelpar biomarkers and WI-NRS data were calibrated using ENHANCE data. Calibration steps allowed reproduction of pruritogen concentrations and itch scores before and after treatment, yielding digital twins for each real pt. An *in silico* clinical trial was performed; each digital twin received placebo or linerixibat (thereby acting as its own control) to investigate the characteristics of the best responders. **Results:** The model accurately captured baseline, change in biomarkers and WI-NRS scores after linerixibat, placebo or seladelpar administration. The effect of treatment on itch was quantified as mechanistic (due to changes in pruritogens; ~50%) or contextual (caused by other non-mechanistic factors e.g. placebo effect; ~50%) (Fig A). Model analysis found high heterogeneity of itch signal strengths, with 24% and 16% of pts having itch driven by bile acids and LPA, respectively, and the remaining 60% driven by an IL-31 sensitization mechanism modulated by farnesoid X receptor signaling (Fig B). In the digital twin analysis, virtual pts with high baseline IL-31 (Fig C) or a 50% IL-31 decrease after treatment were most likely to have the best itch response to linerixibat. Simulation of virtual pts receiving linerixibat or linerixibat with seladelpar revealed an additive effect in reducing itch. **Conclusion:** The QSP model highlights the heterogeneous nature of itch in pts with PBC, with IL-31 signaling an important contributor to itch and putative marker of linerixibat efficacy. Simulations also predict further itch reduction when combining linerixibat with seladelpar.

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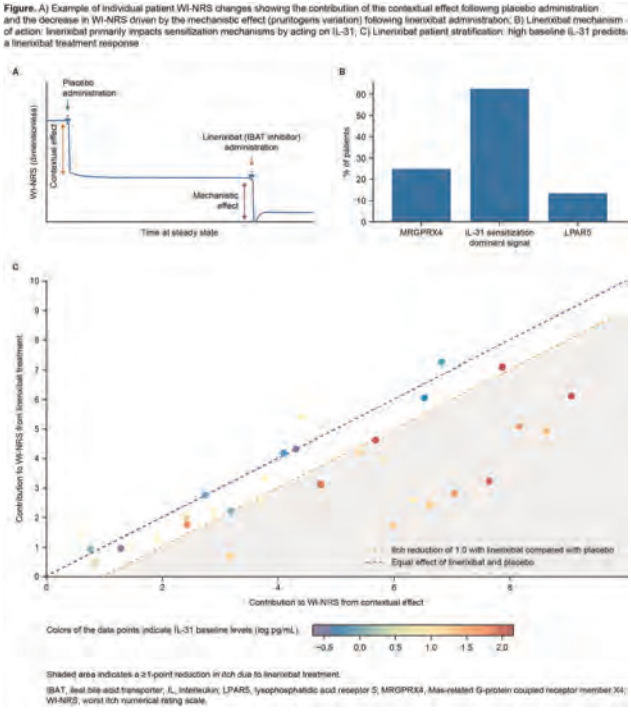

Figure. A) Example of individual patient WI-NRS changes showing the contribution of the contextual effect following placebo administration and the decrease in WI-NRS driven by the mechanistic effect (pruritogens variation) following linerixibat administration; B) Linerixibat mechanism of action: linerixibat primarily impacts sensitization mechanisms by acting on IL-31; C) Linerixibat patient stratification: high baseline IL-31 predicts a linerixibat treatment response

Disclosures: Mario Giorgi: Nothing to Disclose, Matthias Hanke: Nova In Silico: Employee, Perrine Masson: Nothing to Disclose, Eulalie Courcelles: Nothing to Disclose, Janelle Lennie: Nothing to Disclose, Bishoy Hanna: Nothing to Disclose, Linda Casillas: GSK: Employee, GSK: Stock - publicly traded company, Abdul-Azim Hassan: GSK: Employee, GSK: Stock – privately held company, Sumanta Mukherjee: Nothing to Disclose, Mindy Magee: Nothing to Disclose, Megan McLaughlin: Nothing to Disclose, Jim Bosley: Nothing to Disclose, Simon Arsene: Nova In Silico: Employee, Hippolyte Darre: Nothing to Disclose, Anna Sher: Nothing to Disclose, Andreas Kremer: Abbvie: Advisor, Abbvie: Consultant, Advanz: Advisor, Advanz: Consultant, Alentis: Advisor, AlphaSigma: Consultant, AlphaSigma: Speaking and Teaching, AstraZeneca: Advisor, Avior: Advisor, Bayer: Advisor, CymaBay: Advisor, Escient: Advisor, Falk: Consultant, Falk: Speaker, Gilead: Consultant, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GSK: Consultant, GSK: Speaking and Teaching, GSK: Advisor, Intercept: Consultant, Intercept: Grant/Research Support, Intercept: Speaking and Teaching, Ipsen: Consultant, Ipsen: Speaking and Teaching, Mirum: Consultant, Mirum: Advisor, Mirum: Speaking and Teaching, MSD: Consultant, MSD: Speaking and Teaching, MSD: Advisor, Roche: Consultant, Roche: Grant/Research Support, Roche: Speaking and Teaching, Takeda: Consultant, Takeda: Advisor, Takeda: Advisor, Viofor: Advisor, Viofor: Speaking and Teaching, Viofor: Advisor, Astellas: Consultant, BMS: Consultant, Böhringer-Ingelheim: Consultant, Curatis: Consultant, Novo Nordisk: Consultant, Rectify Pharma: Consultant, Advanz: Speaking and Teaching, AOP Orphan,: Speaking and Teaching, Johnson & Johnson,: Speaking and Teaching, Abbvie: Advisor, Advanz Pharma: Advisor, Alentis Therapeutics: Advisor, Alfasigma: Advisor, Astellas: Advisor, AstraZeneca: Advisor, Attovia Therapeutics: Advisor, Avior Bio: Advisor, Bayer: Advisor, Bristol Mysers Squibb: Advisor, Böhringer-Ingelheim: Advisor, Curatis: Advisor, CymaBay: Advisor, Dr. Falk Pharma: Advisor, Gilead Sciences: Advisor, GSK: Advisor, Ipsen: Advisor, Mirum Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Merck Sharp & Dohme: Advisor, Novo Nordisk: Advisor, Roche: Advisor, Takeda: Advisor, Abbvie: Speaking and Teaching, Advanz Pharma: Speaking and Teaching, Bayer: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, CymaBay Therapeutics: Speaking and Teaching, Falk Foundation: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, GSK: Speaking and Teaching, Ipsen: Speaking and Teaching, Johnson & Johnson: Speaking and Teaching, Medscape: Speaking and Teaching, Mirum Pharmaceuticals: Speaking and Teaching, Merck Sharp & Dohme: Speaking and Teaching, Novartis: Speaking and Teaching, Roche: Speaking and Teaching, Viofor:

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4437 | MULTIMODAL ANALYSIS REVEALS NEUTROPHIL-CHOLANGIOCYTE CROSSTALK VIA MIF-CD74 PATHWAY TO DRIVE INFLAMMATORY RESPONSES IN PRIMARY SCLEROSING CHOLANGITIS

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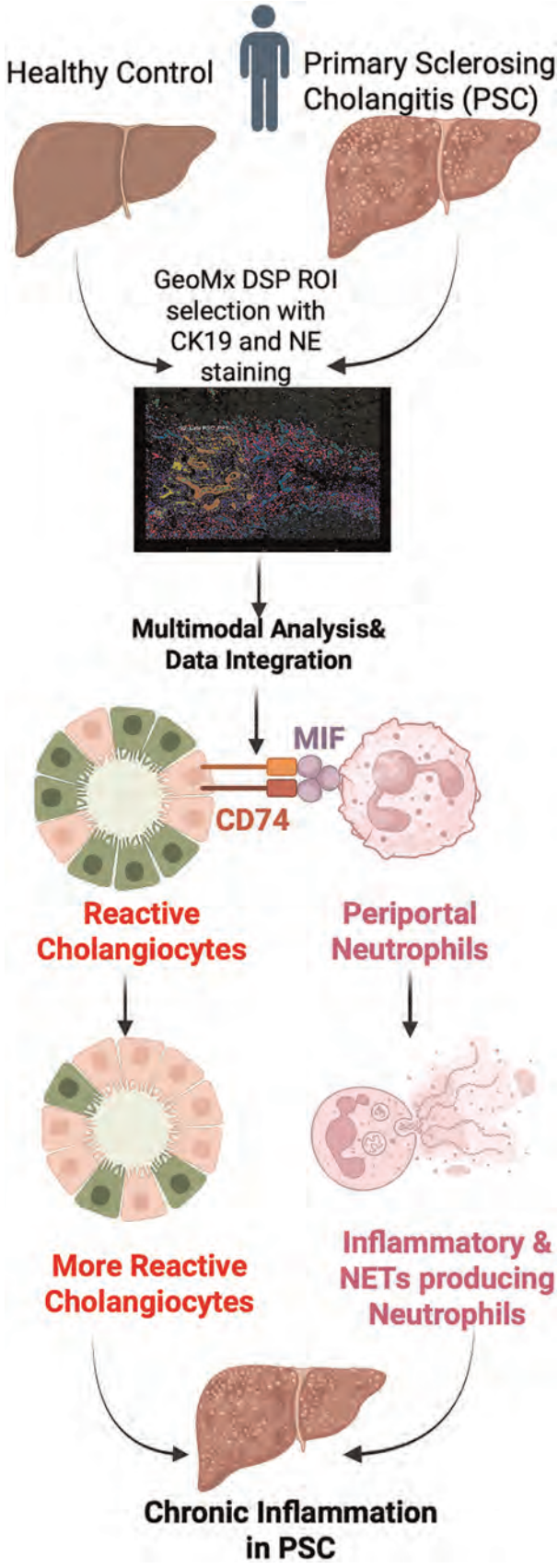
Background: Primary Sclerosing Cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive bile duct inflammation and fibrosis. Neutrophil infiltration and cholangiocyte activation are central features of PSC, but the spatial and molecular mechanisms underlying their interaction remain poorly defined. We aimed to elucidate the cholangiocyte–neutrophil communication axis to better understand neutrophil-mediated pathogenesis in PSC. **Methods:** GeoMx Digital Spatial Profiling on PSC and normal human liver tissues (stained for cholangiocytes [CK19] and neutrophils [neutrophil elastase, NE]) was interrogated with pathway, cell-scoring, CellChat, and Euclidean distance analysis. Single-cell, single-nucleus RNA sequencing (scRNA-seq, snRNA-seq), and bulk RNA-seq datasets from human PSC livers were integrated with our spatial data. Mechanistic studies in primary murine and human cholangiocytes were performed using RNA-seq, RT-PCR, western blot, immunohistochemistry (IHC), and immunofluorescence (IF). **Results:** Spatial transcriptomic profiling revealed a marked increase in neutrophil degranulation and neutrophil extracellular traps (NETs) formation pathway activity in the periportal regions of PSC livers compared to healthy controls. Quantitative inflammatory cell scores, reflecting the relative abundance and activation of cholangiocytes and neutrophils, were significantly elevated in PSC tissues (cholangiocyte score: mean 1.4 vs. 0.4, $p < 0.05$; neutrophil score: mean 2.0 vs. 1.4, $p < 0.05$).Cell-cell communication analysis using CellChat identified the Macrophage Migration Inhibitory Factor (MIF)–CD74 axis as the predominant signaling axis for neutrophils and cholangiocytes. Spatial proximity analysis confirmed that cholangiocytes and neutrophils expressing MIF and CD74, respectively, exhibited higher density at a shorter Euclidean distance among the analyzed ligand-receptor pairs, suggesting spatially confined signaling. Integrated transcriptomic analysis further revealed significantly increased MIF expression (3-fold, $p < 0.05$) in PSC-associated neutrophils. RNA-seq of primary mouse cholangiocytes from a cholestatic model showed 7-fold upregulation of Cd74 ($p < 0.0001$), while human cholangiocytes stimulated with TNFα exhibited an 8-fold increase in CD74 expression ($p < 0.01$). Concordantly, IHC and IF confirmed elevated MIF and CD74 protein expression in periportal neutrophils and cholangiocytes in PSC liver tissue. **Conclusion:** Our multimodal analysis uncovers a novel, spatially localized neutrophil–cholangiocyte communication axis in PSC livers mediated by the MIF–CD74 signaling pathway. This pathway likely drives NET formation, cholangiocyte activation, and sustained inflammation in the periportal niche, offering new insights into disease pathogenesis and potential therapeutic targets.



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4438 | EFFICACY AND SAFETY OF SELADELPAR VS. ELAFIBRANOR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: A MATCHING-ADJUSTED INDIRECT COMPARISON

David Jones[1] Robert Gish[2] Cynthia Levy[3] Howard Thom[4] Gianluca Baio[5] Marvin Rock[6] Chong Hoon Kim[6] Mirko von Hein[7] Oskar Eklund[8] Ryan Thaliffdeen[6] Barinder Singh[9] Akanksha Sharma[9] DILIP MAKHIJA[6] Gideon Hirschfield[10], [1]Institute of Cellular Medicine & NIHR Newcastle Biomedical Research Centre, Newcastle University, UK, [2]Robert G. Gish Consultants, LLC, San Diego, CA, USA and Hepatitis B Foundation, Doylestown, PA, USA, [3]University Of Miami Miller School Of Medicine, Miami, Florida, USA, [4]Bristol Medical School, University of Bristol, UK, [5]University College London, London, UK, [6]Gilead Sciences, Inc., Foster City, CA, USA, [7]Gilead Sciences, UK, [8]Gilead Sciences Sweden AB, Solna, Sweden, [9]Pharmacoevidence, SAS Nagar Mohali, India, [10]The Autoimmune and Rare Liver Disease Programme, Toronto General Hospital, Toronto, Canada

Background: Seladelpar and elafibranor are recently approved second-line treatments for primary biliary cholangitis (PBC), both improving alkaline phosphatase (ALP) levels. However, only seladelpar significantly improves pruritus. We conducted an indirect treatment comparison (ITC) of their biochemical efficacy and safety in adult PBC patients using data from the RESPONSE and ELATIVE trials. **Methods:** Due to significant heterogeneity in effect modifiers, biochemical response thresholds, and placebo responses among trials, an anchored matching-adjusted indirect comparison (MAIC) was performed in accordance with UK NICE TSD 18 guidance. Individual-level data from RESPONSE were adjusted for age, ALP, bilirubin, and cirrhosis rates to match ELATIVE baseline characteristics. Binary biochemical efficacy endpoints of ALP normalization ($\leq$1 upper limit of normal [ULN]) and the composite biochemical response (ALP $<$ 1.67$\times$ULN, $\geq$15% ALP decrease from baseline, and total bilirubin $\leq$1.0$\times$ULN) were recalculated to account for differences in ULN thresholds for ALP and total bilirubin for a robust ITC. Additional efficacy comparison involved ALP change from baseline (CFB), which is not sensitive to normal range differences. Safety was compared based on the incidence of overall treatment emergent adverse events (TEAEs), pruritus as TEAE, and all-cause discontinuations. Several sensitivity analyses were conducted, including an unanchored MAIC for the composite response outcome, which adjusts for population imbalances between treatments without relying on a common comparator. **Results:** Seladelpar showed numerically better results for ALP normalization and ALP CFB, while a numerically lower effect was observed for the composite biochemical endpoint; none of the results were statistically significant (Table 1). In the unanchored MAIC, seladelpar was associated with a numerically better composite response. Seladelpar was also associated with lower odds of overall TEAEs, pruritus as TEAE, and all-cause discontinuations. Sensitivity analyses results were aligned with the base case. **Conclusion:** Using a robust MAIC approach to address heterogeneity, seladelpar demonstrated overall numerically better biochemical efficacy and improved safety compared to elafibranor; however, statistical significance was not achieved.

Table 1: MAIC results for comparison between seladelpar 10 mg vs. elafibranor 80 mg at 12 months

ALP normalization	Composite response	ALP change from baseline	Pruritus as TEAE*	Any TEAE*	All-cause discontinuations
RR (95% CI)		MD (95% CI)	OR (95%CI)		
1.66 (0.03, 85.54)	0.70 (0.13, 3.78) 1.02 (0.76,1.36)†	-30.43 (-97.84, 36.99)	0.35 (0.06, 2.10)	0.37 (0.06, 2.24)	0.46 (0.11, 4.06)

ALP: Alkaline Phosphatase; CI: Confidence Interval; MD: Mean Difference; OR: Odds Ratio; RR: Risk Ratio; TEAEs: Treatment-emergent adverse events; *At least one event recorded for any TEAE and pruritus as TEAE, which were reported over a longer follow-up in the ELATIVE trial (data in the 48 EPOCH); †Unanchored MAIC results using four effect modifiers

Disclosures: David Jones: Umecrine: Consultant, Advanz: Consultant, Intercept: Consultant, GSK: Consultant, Robert Gish: please see full disclosures document: Consultant, Cynthia Levy: Cymabay: Grant/Research Support, Cymabay: Consultant, Intercept: Grant/Research Support, Intercept: Consultant, Calliditas: Grant/Research Support, Calliditas: Consultant, GSK: Consultant, GSK: Grant/Research Support, Ipsen: Grant/Research Support, Ipsen: Consultant, Mirum: Grant/Research Support, Mirum: Consultant, Zydus: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Consultant, Escient: Grant/Research Support, Kowa: Grant/Research Support, Kowa: Consultant, Genfit: Grant/Research Support, COur: Advisor, Chemomab: Consultant, Howard Thom: Nothing to Disclose, Gianluca Baio: Nothing to Disclose, Marvin Rock: Nothing to Disclose, Chong Hoon Kim: Gilead Sciences, Inc.: Employee, Mirko von Hein: Gilead Sciences: Employee, Oskar Eklund: Nothing to Disclose, Ryan Thaliffdeen: Gilead Sciences, Inc.: Employee, Barinder Singh: Gilead Sciences, Inc.: Independent Contractor, Akanksha Sharma: Nothing to Disclose, DILIP MAKHIJA: Gilead Lifesciences: Employee, Gideon Hirschfield: Intercept: Consultant, Intercept: Consultant, GSK: Consultant, GSK: Consultant, CymaBay: Consultant, CymaBay: Consultant, Ipsen: Consultant, Ipsen: Consultant, Falk: Consultant, Falk: Consultant, Pliant: Consultant, Pliant: Consultant, Mirum: Consultant, Mirum: Consultant, Advanz: Consultant, Advanz: Consultant, Chemomab: Consultant,

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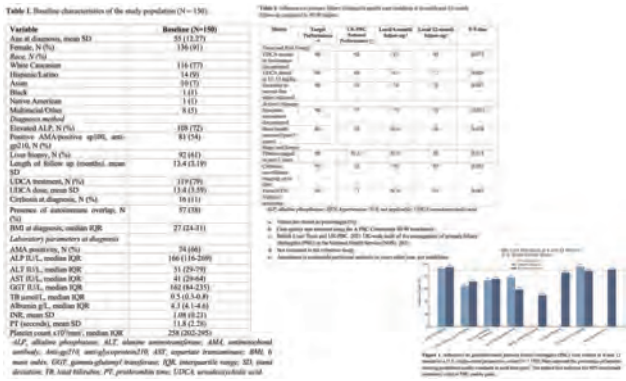
4439 | REAL-WORLD ADHERENCE TO PRIMARY BILIARY CHOLANGITIS CARE GUIDELINES: A U.S. SINGLE-CENTER COHORT STUDY

Ana Marenco-Flores[1] Natalia Rojas-Amaris[1] Romelia Barba[2] Daniela Goyes[3] Tamara Kahan[1] Denisse Rubio Cruz[1] Esli Medina Morales[4] Behnam Saberi[5] Vilas Patwardhan[1] Alan Bonder[5], [1]Beth Israel Deaconess Medical Center, [2]Texas Tech University, [3]Yale School of Medicine, [4]Rutgers New Jersey Medical School, [5]Beth Israel Deaconess Medical Center, Harvard Medical School

Background: Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease that, without early diagnosis and appropriate treatment, can progress to cirrhosis and liver failure. Although international guidelines provide clear recommendations for biochemical monitoring, ursodeoxycholic acid (UDCA) dosing, symptom assessment, and escalation to second-line therapy, gaps in care delivery remain common in clinical practice. The 90:90 PBC care initiative sets an aspirational standard, aiming for 90 percent of patients to receive 90 percent of the recommended care, with a focus on timely intervention, individualized treatment, and comprehensive disease management. This study aims to evaluate the alignment of real-world PBC care at a single U.S. tertiary center with the targets set by the 90:90 initiative. **Methods:** We conducted a prospective cohort study of 150 patients with PBC at a U.S. tertiary care center to assess adherence to guideline-based care at 6- and 12-month follow-up. Evaluated components included UDCA dosing, biochemical response, symptom assessment, risk stratification, and treatment escalation, using the 90:90 PBC Care Initiative benchmarks. Statistical analyses included t-tests, Mann–Whitney U, Kruskal–Wallis, and chi-square tests, with significance set at $P < 0.05$. **Results:** We evaluated 150 patients with PBC, predominantly female (91%) and White (77%), with a mean age at diagnosis of 55 years. The majority received ursodeoxycholic acid (UDCA) (79%; mean dose 13.4 mg/kg), and median follow-up was 13.4 months. Autoimmune overlap (AIH or PSC) was present in 38%, and 11% had cirrhosis at diagnosis. Compared to the UK-PBC audit and 90:90 targets, our center met or exceeded benchmarks for UDCA initiation (93% at 6 months, 95% at 12 months), second-line therapy escalation (74%, 76%), and cirrhosis surveillance (96%, 89%). However, optimal UDCA dosing (65% and 72%) and symptom assessment (79% and 59%) fell short. Bone health evaluation reached only 50% by 12 months. Fibrosis staging (86%) and variceal screening (91%) also exceeded UK-PBC rates and targets. **Conclusion:** Structured PBC care pathways met 90:90 benchmarks for UDCA initiation, therapy escalation, and cirrhosis surveillance but fell short on dosing and symptom monitoring. Embedding UDCA dose protocols and standardized patient assessments into care bundles is necessary for closing these gaps and improving outcomes.



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4440 | TREATMENT OUTCOMES AND UNDERUTILIZATION OF SECOND-LINE THERAPIES FOR PRIMARY BILIARY CHOLANGITIS IN LATIN AMERICA: A CALL TO BRIDGE THE GAP

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Background: Approximately 40% of patients with primary biliary cholangitis (PBC) exhibit an incomplete biochemical response to ursodeoxycholic acid (UDCA) and require add-on therapy. Data on treatment outcomes and clinical practice in Latin America remain scarce. This study aims to evaluate the treatment outcomes of PBC patients from Latin America. **Methods:** This is an ongoing, retrospective, international multicenter cohort study (ALLATIN) sponsored by ALEH, enrolling PBC patients from several Latin American countries. **Results:** Data from 1,204 PBC patients (92.3% female; mean age at diagnosis 53 $\pm$ 13 years) from the ALLATIN database were reviewed to assess treatment outcomes. Median follow-up was 80 months (IQR 30–133). Cirrhosis was present at diagnosis in 22.2%, and 30.2% developed advanced liver disease during follow-up. Patients with overlap syndrome with autoimmune hepatitis (AIH) (N = 164) were excluded from the treatment analysis. UDCA was prescribed to 975 patients (95.2%). At 12 months, 27.7% normalized alkaline phosphatase (ALP), 60.8% and 46.6% met Toronto and POISE criteria, respectively. Deep response (normalized ALP with bilirubin $<$ 0.6 $\times$ ULN) was obtained in 15.3%. Fibrates (bezafibrate, fenofibrate or ciprofibrate) were used in 28.8%, mostly for incomplete response (67.4%) and pruritus (15.4%). Only 31-41% of those with incomplete UDCA response received second-line therapies. Liver transplantation was performed in 5.5%, while 8.6% died. The combined endpoint (liver transplantation or death) occurred at a median follow-up of 67 months (IQR 28–116) and were independently associated with cirrhosis at diagnosis (OR = 7.12, 95%CI: 4.4-11.6; p $<$ 0.001) and UDCA response by POISE criteria (OR = 0.39; 95%CI: 0.2-0.7); 1- and 5-year transplant-free survival were 84.5 $\pm$ 0.4% and 52.4 $\pm$ 0.5%, respectively. **Conclusion:** Response to UDCA as first line PBC therapy was lower than expected. Second-line therapies remain underused in Latin America, highlighting a critical gap evidence-based recommendations and real-world clinical practice in the region. Addressing this gap requires urgent action from healthcare systems, prioritizing physician awareness, the implementation of targeted educational initiatives, and expanded access to second-line therapies to improve patient outcomes.

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4441 | PRIMARY BILIARY CHOLANGITIS: ANALYSIS OF GENDER DIFFERENCES IN DISEASE PROGRESSION AND TIME TO HEPATIC DECOMPENSATION

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Background: Primary biliary cholangitis (PBC) is an autoimmune disease leading to the destruction of small bile ducts. Although initial studies favored PBC as a female-dominant condition, more recent research suggests a female-male ratio closer to 4-6:1. Additionally, males may present with more severe disease, but such data is sparse and limited by underdiagnosis. We conducted a retrospective cohort study to investigate if the male gender is associated with more severe disease and poorer outcomes. **Methods:** All patients above 18 years of age with an ICD-10 code diagnosis of PBC and positive anti-mitochondrial antibody titer $\geq$1:40 were identified over the past 10 years at 23 Northwell Care sites. The primary outcome of interest was the development of cirrhosis. A multiple logistic regression model was utilized to assess odds of cirrhosis. A subgroup analysis was performed of cirrhotic patients within this population that were followed for at least 90 days. Categorical variables were compared using Chi-squared tests. The log-rank test was used to compare Kaplan-Meier survival curves between male and female groups for time to decompensation, defined as a composite of first occurrence of ascites, bilirubin >3.0, encephalopathy, or esophageal GI bleed. **Results:** Of 378 patients with PBC, 47 (12%) were male, the median age was 71 years, and 67% were non-Hispanic White. Of 93 cirrhotic patients followed for at least 90 days, 17 (18%) were male, the median age was 72 years, and 61% were non-Hispanic White. Demographics and clinical characteristics were generally similar between male and female patients, with the exception of alcohol use disorder, which was more prevalent in males (14% vs 0%, $p=0.047$). Overall, there was an adjusted odds ratio of 1.98 (95% Confidence Interval [CI] [1.01-3.89], $p=0.048$) of males versus females in the development of cirrhosis. Among cirrhotic patients, no significant difference in time to decompensation was observed between males and females (Hazard Ratio [HR] 1.11, 95% CI [0.52-2.38], $p=0.788$). Mortality rates showed a trend toward being higher in males (41% vs 18%, $p=0.056$), though this did not reach statistical significance. **Conclusion:** Overall, male gender was found to be an independent predictor of cirrhosis in patients with PBC. Despite some baseline differences in alcohol use disorder history, time to decompensation was similar between male and female cirrhotic patients. Further research with larger sample sizes is needed to better understand gender-specific factors affecting disease progression in cirrhosis.

Table 1. Key Characteristics and Outcomes by Gender in Cirrhotic Patients with Primary Biliary Cirrhosis with ≥ 90 Day Follow-Up

	Female (n=76)	Male (n=17)	P-value
Characteristic			
Age, median (IQR)	71 (61, 78)	73 (57, 79)	0.800
Non-Hispanic White, n (%)	46 (61%)	11 (65%)	0.749
MELD 3.0, median (IQR)	15.0 (10.0, 20.0)	15.0 (13.5, 18.0)	0.657
Clinical Event			
Decompensation Events*	HR 1.11 (95% CI [0.52-2.38])	Reference	0.788
Mortality, n (%)	14 (18%)	7 (41%)	0.056
Treatment			
Ursodiol Use, n (%)	46 (61%)	11 (65%)	0.749
Steroid Use, n (%)	18 (24%)	8 (47%)	0.073

*Decompensation defined as first occurrence of esophageal GI bleed, ascites, encephalopathy, or bilirubin >3.0.

IQR = Interquartile Range; HR = Hazard Ratio; CI = Confidence Interval

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4442 | SYMPTOM BURDEN AND TREATMENT PATTERNS IN PRIMARY BILIARY CHOLANGITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Patients with primary biliary cholangitis (PBC) often suffer debilitating symptoms, yet the overall symptom burden has not been systematically quantified. This study aims to systematically review the prevalence and severity of the symptom burden in PBC patients. **Methods:** We conducted a systematic search of three electronic databases from inception to 24th May 2025, including studies that reported the prevalence and severity of PBC symptoms. Subgroup analyses were performed based on study type, publication year, risk of bias, geographical region, gender, and latitude.

Results: A total of 25 studies involving 13,178 patients were included. The most commonly used symptom evaluation tool was the PBC-40 questionnaire, employed in 64% of the studies (16 out of 25). Fatigue was the commonest symptom, affecting 51% of patients PBC(51%, 95%CI: 42%-60%, $I^2 = 96\%$, 13 studies), followed by pruritus at 34% (95%CI: 29%-40%, $I^2 = 92\%$, 13 studies). Severe fatigue and severe pruritus were reported in 23% (95%CI: 16%-30%, $I^2 = 95\%$, 9 studies) and 10% of patients (95%CI: 4%-18%, $I^2 = 94\%$, 5 studies), respectively. The prevalence of fatigue was significantly higher in more recent studies ($p < 0.01$), those with smaller sample sizes($p = 0.0009$), and studies published as abstracts($p = 0.03$). Fatigue was significantly greater in female patients compared to males (standard mean difference = 3.3, 95% CI: 1.5-5.1; $p < 0.01$, 4 studies). Severe fatigue was more prevalent among Caucasian patients than in non-Caucasians (26% vs 8%, $p = 0.0005$), and in studies with a higher proportion of cirrhotic patients (28% vs 8%, $p = 0.0005$). Despite the high burden, only 38% of PBC patients with pruritus received antipruritic treatment (95% CI: 20%-59%, $I^2 = 92\%$, 7studies), with antihistamines being the most frequently prescribed medication, being used in 22% of patients (95%CI: 10%–50%, $I^2 = 95\%$, 4 studies). **Conclusion:** Nearly half of PBC patients experience significant symptom burden, with significant ethnic disparities. There remains an unmet need for standardized assessment, consistent reporting, and improved management strategies for PBC-related symptoms in future research.

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4443 | PREDICTING URSODEOXYCHOLIC ACID TREATMENT RESPONSE IN PRIMARY BILIARY CHOLANGITIS USING MULTIMODAL DEEP LEARNING FRAMEWORK

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Background: Ursodeoxycholic acid (UDCA) remains the sole first-line therapy for primary biliary cholangitis (PBC), yet 40% of patients exhibit a suboptimal response. Current predictive models based on single-modal parameters (clinical, histopathology or microbiome) show limited discriminative power due to incomplete characterization of pathobiological heterogeneity. We developed Prognostic Cross-Attention Multi-Modal (ProCAMM), a transformer-based multimodal framework integrating pretreatment histopathology, serum proteomics, and clinical parameters to address this critical unmet need. **Methods:** From a retrospective PBC cohort (ChiCTR2400086289), 168 treatment-naïve patients with complete histopathology (H&E whole-slide images), serum proteomics, and clinical data were analyzed. UDCA response was assessed by Paris II criteria after $\geq$6-month therapy. ProCAMM architecture comprises: 1) UNI-derived N x 1024-dimensional histopathological embeddings from 20x whole-slide images; 2) Self-normalizing networks processing 2707-protein panel and 40 clinical parameters; 3)Cross-modal attention mechanism enabling dynamic interaction among three models' feature

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spaces; 4) Kronecker product-based tensor fusion with gated attention. Model performance was evaluated against unimodal and early-fusion baselines using five-fold cross-validation bu calculating mean area under the receiver operating characteristic curve (AUROC). **Results:** ProCAMM achieved superior discriminative performance (mean AUROC 0.721 ± 0.10) versus histopathology (0.557 ± 0.06), proteomics (0.621 ± 0.15), clinical (0.650 ± 0.09) and early-fusion models (0.579 ± 0.06). SHAP analysis identified ALP and total bilirubin as top clinical predictors. Key proteomic drivers included EH domain-binding protein 1, cathepsin B, G protein α-14, Chromosome 2 Open Reading Frame 88, and Cell Death-Inducing DFFA-Like Effector B. Histopathological attention mapping localized predictive features to interlobular bile ducts. **Conclusion:** As the first multimodal artificial intelligence framework for PBC prognosis, ProCAMM integrates histomorphometric and molecular signatures to enable clinically actionable UDCA response prediction. Biologically interpretable features highlight bile-duct-centric pathomechanisms and metabolic regulators, supporting risk stratification and combination therapy design. Future studies will validate the correlation between therapeutic targets and diseases progression, potentially guiding FXR agonist-based therapies.
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4444 | EPIDEMIOLOGY OF PRIMARY BILIARY CHOLANGITIS IN LATIN AMERICA: INSIGHTS FROM THE ALLATIN COHORT

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Background: Primary biliary cholangitis (PBC) may manifest differently based on factors such as ethnicity and genetic background. Latin America is characterized by a highly admixed population with unique genetic diversity compared to other regions, yet data on PBC in this region remain scarce. This study aims to characterize the epidemiological profile of PBC in Latin America using data from the ALLATIN cohort. **Methods:** This is an ongoing, retrospective, international multicenter cohort study sponsored by ALEH, enrolling PBC patients from several Latin American countries. **Results:** Data were collected from 1,204 patients across Latin America: Brazil (48.3%), Argentina (23.4%), Chile (10.8%), Mexico (7.4%), Cuba (3.7%), Uruguay (3.3%), Costa Rica (1.1%), and others. Most patients were female (92.3%), with a mean age at diagnosis of 53 ± 13 years. Cirrhosis was present at baseline in 22.2%. The median follow-up was 80 months (IQR 30–133). An overlap with autoimmune hepatitis was identified in 13.6% of cases, while MASLD was present in 4.2%. At diagnosis, 78.8% of patients were symptomatic, most commonly with pruritus (41.5%) and fatigue (28.9%). Anti-mitochondrial antibodies (AMA) were positive in 76.8%, antinuclear antibodies (ANA) in 71.6%, and the anticentromere pattern was found in 6.0%. Among patients tested, anti-gp210 was positive in 9.1% (n = 318) and anti-sp100 in 8.8% (n = 317). The most frequent associated extrahepatic autoimmune diseases were Hashimoto's thyroiditis (13.6%) and Sjögren's syndrome (8.5%). Other comorbidities at diagnosis were type II diabetes (11%), systemic arterial hypertension (24%), dyslipidemia (22%), obesity (8%)

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and 13% osteopenia/osteoporosis. Liver biopsy at diagnosis was performed in 601 patients (58.7%), with fibrosis stages distributed as follows: F1 (18.6%), F2 (18.6%), F3 (14.8%), and F4 (13.3%). **Conclusion:** This is the largest cohort to date describing the epidemiology of PBC in LA. The findings reveal notably lower rates of AMA positivity compared to other regions, which may have contributed to higher rates of liver biopsy at baseline, as well as a predominance of symptomatic presentation at diagnosis. These insights underscore the need for increased disease awareness, earlier detection strategies, and improved diagnostic techniques across the region. The data provide a critical foundation for future region-specific approaches to the diagnosis, management, and research of PBC.

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4445 | CHARACTERIZATION OF PRODROMAL EVENTS PRECEDING THE DIAGNOSIS OF PEDIATRIC AUTOIMMUNE HEPATITIS- A RETROSPECTIVE STUDY

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Background: Pediatric autoimmune hepatitis (AIH) is a chronic, immune-mediated liver disease that can progress to liver failure if untreated. Early diagnosis is challenging due to nonspecific presenting symptoms. Identifying prodromal symptoms may enable earlier recognition and improve outcomes. **Methods:** A retrospective chart review of patients < 18 years diagnosed with AIH between 2009–2024 was conducted at a tertiary pediatric center. Patients with other chronic liver diseases (Wilson disease, hepatitis B/C, alpha-1 antitrypsin deficiency, hereditary hemochromatosis) or post-transplant AIH were excluded. Data collected included demographics, presenting symptoms, lab values, liver histology, and immunosuppressive therapies. Prodromal symptoms within four weeks of AIH evaluation were categorized as gastrointestinal (GI), systemic, or upper respiratory (URI). Data were analyzed using descriptive and comparative statistics ($p < 0.05$). **Results:** A total of 95 patients were identified: mean age at presentation 12.5 $\pm$ 4 years, median time from presentation to diagnosis 35 days, 64% female, 75% White, 77% non-Hispanic, 82% AIH type 1. At least one prodromal symptom was identified in 61% ($n = 58$) of patients. No significant differences in age, sex, race/ethnicity, or insurance status were observed between cohorts with or without prodromal symptoms. Among symptomatic patients, GI symptoms (abdominal pain, vomiting, diarrhea) were most common (48%), followed by systemic symptoms (fatigue, fever) (23%) and URI symptoms (congestion, cough, rhinorrhea) (16%). All patients received steroids; 73% received azathioprine. At 6 months, 36% achieved biochemical remission, which was more likely in those with prodromal symptoms (50% vs. 21%, $p = 0.005$). Jaundice was present in 25%, and 95% of these jaundiced patients had prodromal symptoms ($p < 0.0001$). Patients with jaundice had shorter time to steroid initiation ($p = 0.001$). **Conclusion:** Prodromal symptoms occurred in the majority of pediatric AIH patients and were associated with higher remission rates and shorter time to treatment. GI symptoms were most common and, when present with jaundice, appeared to expedite diagnosis. Early recognition of

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prodromal signs may facilitate prompt intervention and improve clinical outcomes.

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4446 | BISPHOSPHONATE TREATMENT IS NOT ASSOCIATED WITH DECREASED FRACTURE RISK IN PRIMARY BILIARY CHOLANGITIS PATIENTS WITH OSTEOPOROSIS

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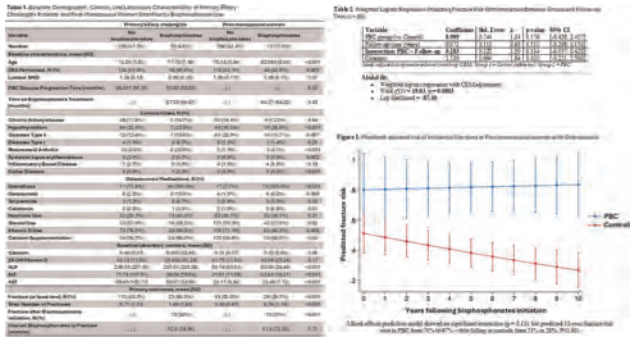
Background: Bisphosphonates (BP) improves bone mineral density (BMD) and are recommended for patients with osteoporosis. However, its benefit on fracture prevention remains unclear in Primary Biliary Cholangitis (PBC) patients with osteoporosis. We aimed to assess the relationship between BP use and fracture risk in PBC patients with osteoporosis. **Methods:** We retrospectively (2005-2025) studied women with diagnosis of PBC based on AASLD guideline and age-matched post-menopausal controls at two U.S. tertiary centers. Groups were stratified by BP exposure. BP exposure was defined as $\geq$6 months of continuous BP therapy. Baseline covariates and the main outcome of incidental fracture were calculated. Before modeling, coarsened-exact matching (CEM) on lowest T-score and lumbar BMD was conducted. CEM-weighted mixed-effects logistic regression modeled fracture odds by PBC status, BP use, follow-up time, and PBC $\times$ BP-time interaction. Mixed-effects model predicted yearly fracture BP-exposure risk. **Results:** Among 598 women $\geq$ 65 years old (289 PBC, 339 controls), fractures were more frequent in PBC (83 %) vs controls (40 %) among BP users and 43 % vs 35 % among non-users ($p < 0.001$). Mean fracture burden mirrored this excess (0.72 vs 0.50 fractures per patient in BP users and 1.69 vs 0.74 in non-users; $p < 0.001$). Notably, 50 % of PBC fractures occurred despite BP initiation, compared with 21% in BP-treated controls ($p < 0.001$). CEM-weighted regression found no independent PBC effect ($\beta = 0.99 \pm 0.74$, $p = 0.18$) and no PBC $\times$ time interaction ($\beta = 0.18 \pm 0.12$, $p = 0.13$). Nonetheless, mixed-effects estimates showed 10-year fracture probability rising from 76 % to 87 % in PBC but falling from 53 % to 28 % in controls. **Conclusion:** BP therapy is protective against fracture in post menopause women with osteoporosis but not protective against age-matched women with PBC, with rising 10-year fracture risk despite BP exposure. These findings suggest continued progression of metabolic bone disease and fracture risk unique to PBC population and underscores the need for additional therapeutic approach in this population.



Disclosures: Leandro Sierra: Nothing to Disclose, Hussam Kawas: Nothing to Disclose, Rachel McNulty: Nothing to Disclose, Juan Armijos: Nothing to Disclose, Xaralambos Zervos: Nothing to Disclose, Omar Sims: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Dian Chiang: Ipsen: Advisor

4447 | IMMUNE PROFILING IN AUTOIMMUNE HEPATITIS IDENTIFIES DISTINCT HHV-6 ANTIGENS AND AUTOREACTIVITY TO THE RELAXIN FAMILY PEPTIDE RECEPTOR 1

Arielle Klepper[1] James Asaki[1] Andrew Kung[1] Sara Vazquez[1] Aaron Bodansky[1] Anthea Mitchell[1] Sabrina Mann[1] Kelsey Zorn[1] Isaac Avila-Vargas[1] Swathi Kari[1] Melawit Tekeste[1] Javier Castro[1] Briton Lee[1] Maria Duarte[2] Mandana Khalili[1] Monica Yang[2] Paul Wolters[1] Jennifer Price[1] Emily Perito[1] Sandy Feng[1] Jacquelyn Maher[1] Jennifer Lai[1] Christina Weiler-Normann[1] Ansgar Lohse[3] Joseph DeRisi[1] Michele Tana[1], [1]University of California, San Francisco, [2]britonlee88@gmail.com, [3]University Medical Centre Hamburg-Eppendorf

Background: Autoimmune hepatitis (AIH) is a severe disease characterized by elevated immunoglobulin levels. However, the role of autoantibodies in the pathophysiology of AIH remains uncertain. **Methods:** Phage Immunoprecipitation-Sequencing (PhIP-seq) was employed to identify autoantibodies in the serum of patients with AIH (n = 115), compared to patients with other liver diseases (metabolic associated steatotic liver disease (MASH) n = 178, primary biliary cholangitis (PBC), n = 26, or healthy controls, n = 94). **Results:** Logistic regression using PhIP-seq enriched peptides as inputs yielded a classification AUC of 0.81, indicating the presence of a predictive humoral immune signature for AIH. Embedded within this signature were disease relevant targets, including SLA/LP, the target of

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a well-recognized autoantibody in AIH, disco interacting protein 2 homolog A (DIP2A), and the relaxin family peptide receptor 1 (RXFP1). The autoreactive fragment of DIP2A was a 9-amino acid stretch nearly identical to the U27 protein of human herpes virus 6 (HHV-6). Fine mapping of this epitope suggests the HHV-6 U27 sequence is preferentially enriched relative to the corresponding DIP2A sequence. Antibodies against RXFP1, a receptor involved in anti-fibrotic signaling, were also highly specific to AIH. The enriched peptides are within a motif adjacent to the receptor binding domain, required for signaling and serum from AIH patients positive for anti-RFXP1 antibody was able to significantly inhibit relaxin-2 singling. Depletion of IgG from anti-RXFP1 positive serum abrogated this effect. **Conclusion:** Conclusions: These data provide evidence for a novel serological profile in AIH, including a possible functional role for anti-RXFP1, and antibodies that cross react with HHV6 U27 protein.

Impact and implications: Our work has uncovered new aspects of antibody-mediated pathogenesis in AIH and opened new avenues for mechanistic studies on the role of herpesviruses, in particular HHV6, in the development of AIH.

Disclosures: Arielle Klepper: Nothing to Disclose, James Asaki: Nothing to Disclose, Andrew Kung: Nothing to Disclose, Sara Vazquez: Nothing to Disclose, Aaron Bodansky: Nothing to Disclose, Anthea Mitchell: Nothing to Disclose, Sabrina Mann: Nothing to Disclose, Kelsey Zorn: Nothing to Disclose, Isaac Avila-Vargas: Nothing to Disclose, Swathi Kari: Nothing to Disclose, Melawit Tekeste: Nothing to Disclose, Javier Castro: Nothing to Disclose, Briton Lee: Nothing to Disclose, Maria Duarte: Nothing to Disclose, Mandana Khalili: gilead sciences: Grant/Research Support, GSK pharmaceuticals: Consultant, Intercept pharmaceuticals: Grant/Research Support, Gilead Sciences Inc: Consultant, Monica Yang: Nothing to Disclose, Paul Wolters: Nothing to Disclose, Jennifer Price: AbbVie: Grant/Research Support, Gilead: Grant/Research Support, Genentech: Grant/Research Support, VIR: Grant/Research Support, Cepheid: Grant/Research Support, Aligos: Grant/Research Support, Emily Perito: Mirum: Consultant, Mirum: Consultant, Mirum: Consultant, Ultragenyx: Consultant, Ultragenyx: Consultant, Ultragenyx: Consultant, BridgeBio: Consultant, BridgeBio: Consultant, BridgeBio: Consultant, Amagma: Consultant, Amagma: Consultant, Amagma: Consultant, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Albireo: Grant/Research Support, Albireo: Grant/Research Support, Albireo: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Dicerna: Grant/Research Support, Dicerna: Grant/Research Support, Dicerna: Grant/Research Support, Takeda: Grant/Research Support, Mirum: Consultant, Mirum: Consultant, Mirum: Consultant, Ultragenyx: Consultant, Ultragenyx: Consultant, Ultragenyx: Consultant, BridgeBio: Consultant, BridgeBio: Consultant, BridgeBio: Consultant, Amagma: Consultant, Amagma: Consultant, Amagma: Consultant, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Albireo: Grant/Research Support, Albireo: Grant/Research Support, Albireo: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Dicerna: Grant/Research Support, Dicerna: Grant/Research Support, Dicerna: Grant/Research Support, Takeda: Grant/Research Support, Sandy Feng: Nothing to Disclose, Jacquelyn Maher: Nothing to Disclose, Jennifer Lai: Nestle Nutrition Institute: Grant/Research Support, Novo Nordisk: Consultant, Genfit: Consultant, Boehringer Ingelheim: Advisor, Lipocine: Site PI, Gilead: Site PI, Christina Weiler-Normann: Nothing to Disclose, Ansgar Lohse: Nothing to Disclose, Joseph DeRisi: Nothing to Disclose, Michele Tana: Kezar Bio: Advisor

4448 | INCREASED FRACTURE BURDEN IN PRIMARY BILIARY CHOLANGITIS COMPARED TO POST-MENOPAUSAL CONTROLS: A RETROSPECTIVE MULTICENTER STUDY

Leandro Sierra[1] Hussam Kawas[1] Rachel McNulty[2] Juan Armijos[3] Sara Valencia[1] Xaralambos Zervos[3] Omar Sims[1] Dian Chiang[1], [1]Cleveland Clinic Foundation, [2]Cleveland Clinic Akron, [3]Cleveland Clinic Florida

Background: Primary biliary cholangitis (PBC) is associated with increased risk of metabolic bone disease. The risk of osteoporosis and fracture increases with progression to cirrhosis. However, the risk and burden of bone fracture in PBC cohort compared to age-matched post-menopause population remains unclear. **Methods:** We performed a retrospective cohort study (2005–2025) across two tertiary centers, including women ≥65 years with diagnosis of PBC based on AASLD guideline and age-matched post-menopausal controls without liver disease. Exclusion criteria included liver transplant, cirrhosis, or other liver disease. Age was balanced using coarsened exact matching. Primary outcome was incident fracture; secondary outcomes

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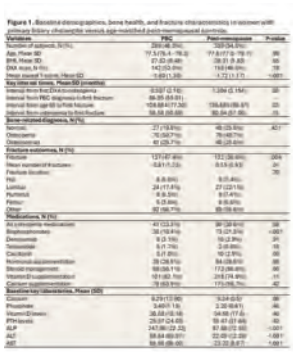
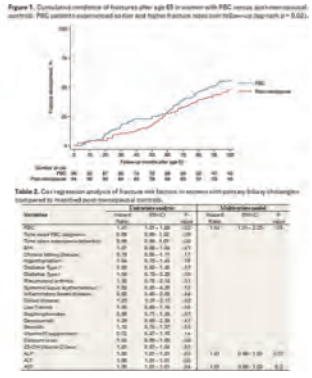
included time-to-fracture and fracture count. Cox models adjusted for T-score, BMI, comorbidities, and osteoporosis therapy. Kaplan-Meier analysis evaluated time-to-fracture. **Results:** The study included 289 women with PBC and 339 controls (mean age 77.6 ± 4.8 years). Rates of osteopenia (50.7% vs 48.7%) and osteoporosis (29.7% vs 25.6%) were similar ($p = 0.43$). At the time of fracture, 83% of PBC patients were on ursodiol (mean disease duration: 86.9 ± 55.0 months). Fracture incidence was higher in the PBC group (47.4% vs 36.0%, $p = 0.004$), with more fractures per patient (0.82 vs 0.55, $p = 0.003$) and earlier fracture onset post-age 65 (109 vs 137 months, $p = 0.03$; log-rank $p = 0.02$). Use of osteoporosis-related medications (33.3% vs 30.6%), bisphosphonates, denosumab, and hormonal therapies was similar. Vitamin D supplementation (82.1% vs 74.9%, $p = 0.11$) and baseline vitamin D levels (30.7 vs 34.6 ng/mL, $p = 0.41$) were also comparable. PBC patients had significantly higher ALP levels (248 vs 88 U/L, $p < 0.001$). In multivariable analysis, PBC remained independently associated with increased fracture risk (HR 1.64, 95% CI 1.01–2.25, $p = 0.05$). **Conclusion:** PBC is associated with a significantly higher and earlier fracture burden than age-matched post-menopausal controls, independent of bone density, T-scores and current medical therapy. These findings suggest increased risk and burden of bone fracture in PBC compared to age matched post-menopause controls. Further study to identify risk factors of metabolic bone disease progression is needed to reduce fracture burden in PBC population.





Disclosures: Leandro Sierra: Nothing to Disclose, Hussam Kawas: Nothing to Disclose, Rachel McNulty: Nothing to Disclose, Juan Armijos: Nothing to Disclose, Sara Valencia: Nothing to Disclose, Xaralambos Zervos: Nothing to Disclose, Omar Sims: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Dian Chiang: Ipsen: Advisor

4449 | ANTI-IL-23P19 AUTOANTIBODY: A HIGH-SENSITIVITY DIAGNOSTIC BIOMARKER FOR ANTIMITOCHONDRIAL ANTIBODY-NEGATIVE PRIMARY BILIARY CHOLANGITIS

Jia Zhou[1] jingyuan zhou[1] Hongqin Xu[1] Yanhang Gao[1], *[1]The First Hospital of Jilin University*

Background: Antimitochondrial antibody (AMA) serves as a pivotal diagnostic marker for primary biliary cholangitis (PBC). However, a subset of PBC patients test negative for AMA, classified as AMA-negative PBC. For these patients, non-invasive diagnosis remains challenging. Given that PBC arises from abnormal activation of the hepatic immune system, leading to attacks on bile duct epithelial cells, we focused on investigating levels of autoantibodies closely associated with immunity in PBC patients, including immune checkpoint antibodies and anti-cytokine autoantibodies (ACAAs). The objective of this study was to explore novel diagnostic biomarkers for AMA-negative PBC, with the goal of identifying more sensitive biomarkers to enable early diagnosis. **Methods:** In the initial phase of autoantibody discovery, serum samples from 9 AMA-negative PBC patients and 31 healthy controls (HC) were analyzed for 30 immune-related autoantibodies. Subsequently, an expanded cohort comprising 36 AMA-negative PBC patients, 29 disease control group members (autoimmune hepatitis), and 117 HC was was used to validate the diagnostic performance of the screened candidate antibodies, specifically IL-23P19 antibodies. The eukaryotic cell-expressed target protein antigens, including IL-23P19, IL-17A, IFN-γ, IL-6, TGF-β, CD4, IL-6Rα, IL-6Rβ, IFN-α, IL-1α, IL-3Rα, IL-4, IL-10, LAG-3, IL-22, IL-37, IL-8, CTLA-4, BAFF, CD3, TIM-3, TSLP, PD-1, FcRn, OX40L, ICOS, CD8, PD-L1, TNF-α, and CD20, were utilized to bind with specific antibodies in the samples. The antigen-antibody complexes were detected via protein tag-based chromogenic reactions. The optical signal intensity was measured using a microplate reader and expressed as relative light units (RLU). All samples were analyzed in duplicate. **Results:** The serum levels of anti-IL-23p19 antibodies in AMA-negative PBC patients are significantly higher than those in HC and disease controls ($p < .001$). Compared to other antibodies, the anti-IL-23p19 antibody assay demonstrated higher sensitivity (ranging from 83.3% to 94.4%) and specificity (ranging from

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62.1% to 84.6%) in diagnosing AMA-negative PBC, with areas under the curve (AUC) of 0.937 and 0.794 for distinguishing AMA-negative PBC from healthy individuals and disease controls, respectively. At a cutoff value of 76,530 RLU, sensitivity declined to 83.3% compared to healthy populations, while specificity improved to 91.5%. When compared to AIH, sensitivity also decreased to 83.3%, but specificity markedly increased to 62.1%, reducing the misdiagnosis risk by approximately 30%. Although the diagnostic sensitivity decreased by an absolute 11.1% at the 76,530 RLU cutoff, specificity for healthy populations and AIH improved by 6.9% and 30.8%, respectively, significantly optimizing clinical differential diagnostic performance. Therefore, to balance the risks of missed diagnosis and misdiagnosis, a cutoff value of 76,530 RLU is recommended for diagnostics.Furthermore, the positivity rate of anti-IL-23p19 antibodies (83.3%) was markedly higher than that of anti-sp100 (27.8%) and anti-gp210 (30.6%) antibodies in AMA-negative PBC patients. When this novel biomarker was combined, the diagnostic sensitivity of gp210/sp100 antibodies increased from 47.2% to 88.9%. **Conclusion:** The incorporation of IL-23p19 antibody testing into AMA and ANA serological assays significantly enhances the clinical diagnostic efficacy for PBC, particularly in AMA-negative subjects. Building upon established evidence of constitutive IL-23/Th17 axis overactivation in PBC, future multicenter studies should expand cohorts to systematically collect paired serum and liver biopsy specimens from AMA-negative PBC patients. Integrated analysis of serological autoantibody profiles, tissue-specific antibody localization, and ductal injury phenotypes will elucidate the mechanistic contributions of IL-23p19 antibodies to disease pathogenesis.

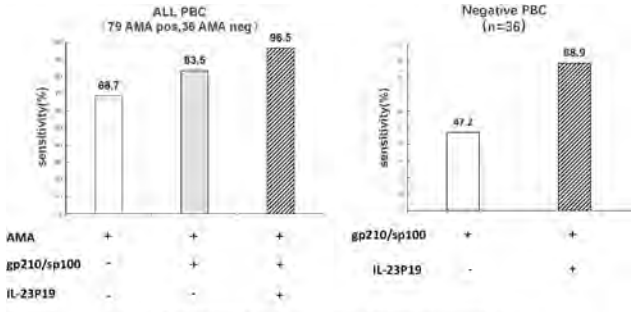

Figure1. IL-23p19 Antibody Enhances Sensitivity of Collective Serological Markers

Disclosures: Jia Zhou: Nothing to Disclose, jingyuan zhou: Nothing to Disclose, Hongqin Xu: Nothing to Disclose, Yanhang Gao: Nothing to Disclose

4450 | THE PSC-DM: DEVELOPMENT AND VALIDATION OF A CLINICAL DIAGNOSTIC MODEL TO AID THE DIAGNOSIS OF PRIMARY VS. SECONDARY SCLEROSING CHOLANGITIS IN CLINICAL PRACTICE

Miki Scaravaglio[1] Rodrigo Motta[2] Laura Cristoferi[3] Cesare Maino[3] Alberto Marini[4] Eugenia Nofit[3] Eugenia Pesatori[5] Camilla Gallo[6] Francesca Bolis[4] Daphne D'Amato[7] Armando Curto[8] Alessio Gerussi[9] Raffaella Viganò[6] Mauro Viganò[5] Stephen Rossi[10] Kris Kowdley[11] Pietro Invernizzi[9] Alessandra Nardi[12] Marco Carbone[13] Emma Culver[14], [1]University of Milano-Bicocca, University of Cambridge, [2]John Radcliffe Hospital, and Nuffield Department of Medicine, University of Oxford, [3]Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy, [4]University of Milano-Bicocca, [5]Hepatology Unit, ASST Papa Giovanni XXIII, Bergamo, Italy, [6]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy, [7]University of Turin, [8]University of Florence, [9]Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy, University of Milano-Bicocca, [10]PSC Partners Seeking a Cure, Greenwood Village, Colorado, USA, [11]Liver Institute Northwest and Elson S. Floyd College of Medicine, Washington State University, [12]Department of Mathematics, University of Rome Tor Vergata, Rome, Italy, [13]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy, University of Milano-Bicocca, [14]John Radcliffe Hospital, and Nuffield Department of Medicine, University of Oxford, NIHR Oxford BRC

Background: Sclerosing cholangitis are a spectrum of chronic cholestatic diseases, marked by progressive fibro-inflammatory destruction of the biliary tree leading to biliary cirrhosis. It can be primary (immune-mediated) or secondary to various identifiable insults. Diagnostic uncertainty between the aetiologies is common and may affect patient management and patient selection in clinical trials. This study aimed to develop and validate a clinical diagnostic tool to differentiate primary sclerosing cholangitis (PSC) from secondary sclerosing cholangitis (SSC). **Methods:** We conducted a multicentre analysis of adult cases of sclerosing cholangitis from three tertiary liver centres in Italy. Patients were classified as PSC or SSC according to international guidelines. We performed a multivariate logistic regression analysis in the derivation cohort to identify predictors of PSC diagnosis and validated it in the external cohort. **Results:** Among 234 patients in the derivation cohort (155 PSC and

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79 SSC), six baseline variables were independently associated with PSC: younger age at diagnosis ($p < 0.0001$), presence of IBD ($p < 0.0001$), absence of prior abdominal surgery ($p < 0.0001$), presence of autoimmune comorbidities ($p = 0.0038$), family history of autoimmune diseases ($p = 0.0086$), and absence of pancreatic abnormalities ($p = 0.0338$). These variables were used to develop a predictive model for PSC diagnosis (PSC-DM) with an area under the receiver operating characteristic curve (AUROC) of 0.989 (95% confidence interval (CI) 0.980-0.998). External validation in 144 patients (99 PSC and 45 SSC), confirmed high discrimination ability (AUROC 0.945, 95% CI 0.907-0.983) (Figure 1). **Conclusion:** We derived and externally validated a model based on routinely available clinical parameters that accurately differentiates PSC from SSC, with the potential to streamline patient referral, guide personalised treatment strategies, and enhance clinical trial selection.

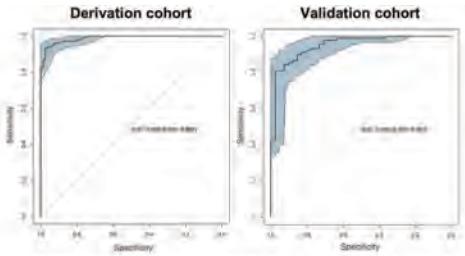

Figure 1: AUROC for the prediction of PSC diagnosis calculated by the PSC-DM in the derivation and validation cohort.

Disclosures: Miki Scaravaglio: Nothing to Disclose, Rodrigo Motta: Nothing to Disclose, Laura Cristoferi: Nothing to Disclose, Cesare Maino: Nothing to Disclose, Alberto Marini: Nothing to Disclose, Eugenia Nofit: Nothing to Disclose, Eugenia Pesatori: Nothing to Disclose, Camilla Gallo: Nothing to Disclose, Francesca Bolis: Nothing to Disclose, Daphne D'Amato: Nothing to Disclose, Armando Curto: Nothing to Disclose, Alessio Gerussi: IPSEN: Consultant, GILEAD: Consultant, SIGNANTHEALTH: Consultant, Raffaella Viganò: Nothing to Disclose, Mauro Viganò: Nothing to Disclose, Stephen Rossi: Nothing to Disclose, Kris Kowdley: Nothing to Disclose, Pietro Invernizzi: Nothing to Disclose, Alessandra Nardi: Nothing to Disclose, Marco Carbone: Nothing to Disclose, Emma Culver: Nothing to Disclose

4451 | MACHINE LEARNING PREDICTS RESPONSE TO OBETICHOLIC ACID THERAPY AND IDENTIFIES PROGNOSTIC PATHWAYS LINKED WITH PRIMARY BILIARY CHOLANGITIS

Hussain Syed[1] Ning Sun[2] Doaa Waly[2] Varinder Verma[2] Matthew Smith[1] Mohamad Osman[1] Mary Erickson[3] Katherine Siminovitch[4] Andrew Mason[1] David Shapiro[5], [1]University of Alberta, [2]Mason Lab - University of Alberta, [3]Intercept Pharma, [4]Sinai Health, [5]Integrated Quality Resources

Background: Biomarkers associated with disease progression in PBC are not well characterized. To address this, we applied machine learning to whole-blood transcriptomic data from PBC patients in the POISE clinical trial, where treatment response was classified by POISE criteria, and from a prospective clinical cohort, where disease progression was defined by clinical outcomes or estimated using the GLOBE score. **Methods:** Transcriptomic data from POISE study patients and the prospectively collected cohort was analyzed to identify genes and pathways with prognostic significance. Support vector machine was used to identify 1200 candidate prognostic genes in both cohorts which were analyzed using Ingenuity Pathway Analysis (IPA). A genetic algorithm then selected an optimal 105 gene-panel which was trained on POISE end-of-treatment ($n = 53$), tested on POISE baseline ($n = 88$) and validated on the prospective cohort ($n = 63$). Transcriptomic profiles of biliary epithelial cells (BECs) from PBC patients ($n = 4$) and non-cholestatic controls ($n = 5$) were compared to assess overlap using gene set enrichment analysis (GSEA) to identify prognostic pathways. **Results:** Our model achieved an AUROC of 0.83 in the test baseline POISE and 0.88 in the validation prospective cohort, outperforming alkaline phosphatase (test: 0.80 and validation: 0.73) and bilirubin (test: 0.64 and validation: 0.81). IPA of ML derived prognostic genes highlighted pathways associated with poor outcomes. These included autoimmune inflammation (similar to complement activation in rheumatoid arthritis and multiple sclerosis), immune regulation (loss in CD155 expression linked with CD8 and NK cell activation), epithelial-to-mesenchymal transition (MMP and KRT associated tissue remodelling), integrated stress response (upregulated PTGER1 and RLN3 involved in oxidative stress) and altered metabolism (diminished ADORA1 indicating impaired mitochondrial function). To assess whether these prognostic pathways provide a distinct transcriptomic signature in PBC peripheral blood, we performed GSEA on BEC RNA-seq comparing PBC vs. non-cholestatic liver disease cholangiocytes. We observed a comparable dysregulation in the biliary epithelium potentially linking the systemic transcriptomic signature with tissue specific pathogenesis. **Conclusion:** The machine learning approach identified transcriptional changes associated with PBC progression previously observed in PBC, such as complement activation in autoimmune disorders, epithelial-to-mesenchymal transition and abnormal mitochondrial signalling. The dysregulated gene expression supports the hypothesis that PBC is a systemic disease sharing a similar pathology in whole blood and biliary epithelium that warrants further investigation.

Disclosures: Hussain Syed: Nothing to Disclose, Ning Sun: Nothing to Disclose, Doaa Waly: Nothing to Disclose, Varinder Verma: Nothing to Disclose, Matthew Smith: Nothing to Disclose, Mohamad Osman: Nothing to Disclose, Mary Erickson: Nothing to

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Disclose, Katherine Siminovitch: Nothing to Disclose, Andrew Mason: Nothing to Disclose, David Shapiro: Nothing to Disclose

4452 | TREATING ITCH IN PRIMARY BILIARY CHOLANGITIS – WHAT IS A CLINICALLY MEANINGFUL CHANGE IN THE WORST ITCH NUMERICAL RATING SCALE?

Brooke Currie[1] Katelyn Cutts[2] Yipin Han[3] Ren Yu[2] Marlyn Mayo[4] David Jones[5] Megan McLaughlin[1] Heather Gelhorn[3], [1]GSK, Collegeville, PA, USA, [2]Evidera, Bethesda, MD, USA, [3]Evidera|PPD, Wilmington, NC, USA, [4]University of Texas Southwestern Medical Center, Dallas, TX, USA, [5]Newcastle University, Newcastle, UK

Background: Cholestatic pruritus is common in primary biliary cholangitis (PBC), affecting up to 89% of patients. A statistically significant reduction in pruritus was seen with linerixibat in the pivotal Phase 3 study (GLISTEN; NCT04950127). The Worst Itch Numerical Rating Scale (WI-NRS; range: 0–10) was the patient-reported outcome (PRO) item underlying the primary and several key secondary endpoints in GLISTEN, which included responder analyses. Understanding what amount of change in the WI-NRS represents meaningful improvement for patients is critical when assessing clinical relevance of antipruritic treatment. Analyses were conducted to determine the meaningful change threshold (MCT) for the WI-NRS. Exploratory MCT analyses were also conducted for the Sleep Interference NRS (SI-NRS), a single PRO item designed to assess itch-related sleep interference. **Methods:** Analyses were performed on interim blinded GLISTEN data (July 2024). Anchor-based methods were used with the Patient Global Impression of Severity (PGI-S) and Change (PGI-C) as primary and supportive anchor items, respectively. Correlations between WI-NRS/SI-NRS change scores and PGI scores were assessed to determine appropriateness of the anchors. Data from patients with a 1-point PGI-S improvement from baseline and those who responded "moderately improved" on PGI-C at Week 24 were prioritized when determining the MCTs, given that a majority of these patients also reported having "meaningful" improvement in itch based on their response to a meaningful change question (yes/no). Distribution-based methods examining standard deviation (SD) and standard error of measurement (SEM) values were used as supporting evidence. **Results:** WI-NRS and PGI-S data at both baseline and Week 24 were recorded in 137 participants; 140 participants had baseline and Week 24 WI-NRS and Week 24 PGI-C data. Change in WI-NRS correlated strongly with change in PGI-S ($r = 0.68$) and PGI-C ($r = 0.64$); both $p < 0.001$. Among patients reporting meaningful improvement in itch at Week 24, mean change (SD) in WI-NRS was –3.1 (1.7) for the 1-point PGI-S group and –3.2 (2.1) for the "moderately improved" PGI-C group. Distribution -based estimates for change in WI-NRS were 0.42 (0.25 SD), 0.84 (0.5 SD), and 0.71 (SEM). Cumulative distribution function plots (Figure 1) illustrate change in WI-NRS scores by anchor response. Slightly lower estimates of meaningful change were observed for SI-NRS (mean change [SD] of –2.8 [2.1] and –2.7 [2.2] for key PGI groups). **Conclusion:** A 3-point reduction in WI-NRS was identified as an appropriate MCT for patients with PBC and moderate to severe itch, as this improvement was meaningful to most GLISTEN participants. Although a preliminary MCT of 2.8 for SI-NRS was identified, further validation is warranted using concept-specific anchors. MCTs are critical for interpretation of PRO measures and help facilitate responder endpoint analyses.

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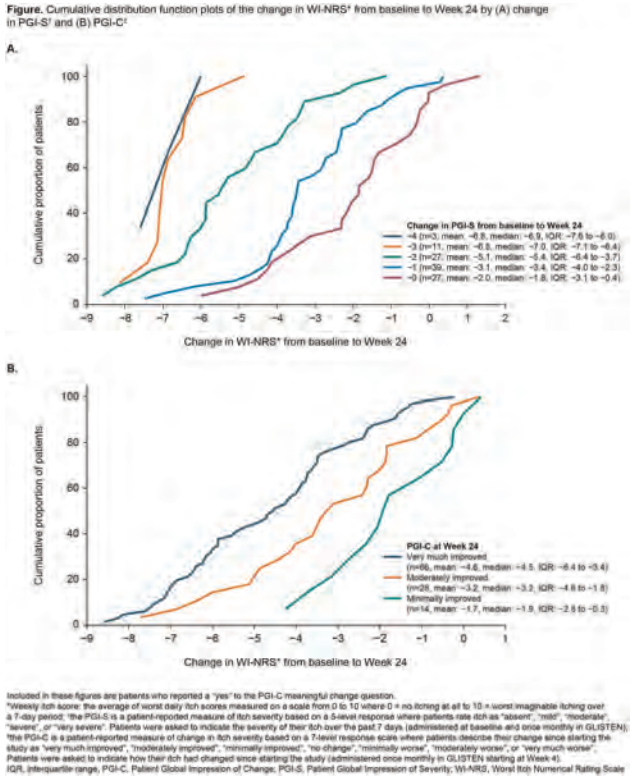

Figure. Cumulative distribution function plots of the change in WI-NRS* from baseline to Week 24 by (A) change in PGI-S† and (B) PGI-C‡

Included in these figures are patients who reported a "yes" to the PGI-C meaningful change question.
*Weekly itch score: the average of worst daily itch scores measured on a scale from 0 to 10 where 0 = no itching at all to 10 = worst imaginable itching over a 7-day period; †the PGI-S is a patient-reported measure of itch severity based on a 5-level response where patients rate itch as "absent", "mild", "moderate", "severe", or "very severe". Patients were asked to indicate the severity of their itch over the past 7 days (administered at baseline and once monthly in GLISTEN); ‡the PGI-C is a patient-reported measure of change in itch severity based on a 7-level response scale where patients describe their change since starting the study as "very much improved", "moderately improved", "minimally improved", "no change", "minimally worse", "moderately worse", or "very much worse". Patients were asked to indicate how their itch had changed since starting the study (administered once monthly in GLISTEN starting at Week 4).
IQR, interquartile range; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; WI-NRS, Worst Itch Numerical Rating Scale

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Intercept: Consultant, GSK: Consultant, Megan McLaughlin: Nothing to Disclose, Heather Gelhorn: Nothing to Disclose

4453 | CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF ACUTE-ONSET AND CHRONIC AUTOIMMUNE HEPATITIS AND THE SIGNIFICANCE OF ANTI-PD-1 AUTOANTIBODIES

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Background: Acute-onset autoimmune hepatitis (A-AIH) often presents diagnostic challenges due to the frequent absence of autoantibodies or low IgG levels. Since autoimmune hepatitis is characterized by various autoantibodies, an immunosuppressive molecule PD-1 may also be a potential target of autoantibody. To evaluate the clinical and pathological significance of circulating anti-PD-1 autoantibodies, we investigated their association with both clinical and histological characteristics of A-AIH and chronic AIH (C-AIH). **Methods:** Serum samples from 73 cases of A-AIH and 45 cases of C-AIH were analyzed. Anti-PD-1 antibody levels were measured using an ELISA assay and evaluated based on absolute values. Furthermore, in 51 cases that underwent liver biopsy (A-AIH: 15, C-AIH: 36), the relationship between histological findings and anti-PD-1 antibody levels was evaluated. **Results:** The median age was 59 years (A-AIH [A]: 56, C-AIH [C]: 63). Median peak AST, ALT, and total bilirubin levels were 404 U/L (A: 674, C: 155), 467 U/L (A: 766, C: 180), and 2.3 mg/dL (A: 7.9, C: 1.25), respectively. The median of the lowest PT-INR was 1.09 (A: 1.16, C: 1.035), and high-titer ($\geq$80x) ANA positivity was observed in 55% of cases (A: 53%, C: 57%). Compared to C-AIH, A-AIH patients were significantly younger and had higher AST, ALT, ALP, and γ-GTP levels, along with lower PT-INR. Anti-PD-1 antibody levels were significantly higher in A-AIH than in C-AIH, with median levels of 0.0705 μg/mL (A: 0.0915, C: 0.0564). Logistic regression analysis of significant parameters identified AST, PT-INR, and anti-PD-1 antibody levels as significant factors to discriminate A and C.

Pathologically, high antibody levels were observed in cases with marked lobular necrosis/inflammation and dense plasma cell infiltration in the hepatic parenchyma, although no differences were found in relation to the presence or absence of centrilobular necrosis (CN). In the portal area, high antibody levels were associated with marked inflammatory and plasma cell infiltration, interface hepatitis, and emperipolesis. In A-AIH cases, no correlation was observed between histological findings and antibody levels. However, in C-AIH, higher levels were seen in cases with intense lobular inflammation and interface hepatitis. **Conclusion:** Serum anti-PD-1 antibody levels were significantly higher in A-AIH compared to C-AIH. As these levels were not associated with CN, which is influenced by hemodynamic factors, the antibody appears to reflect immune activity. Therefore, anti-PD-1 autoantibody may serve as a useful marker of immune-mediated inflammation.

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4454 | THE LIMITS OF ANTI-MITOCHONDRIAL ANTIBODIES AS A DIAGNOSTIC TOOL FOR PRIMARY BILIARY CHOLANGITIS: A THIRTEEN-YEAR EXPERIENCE IN A LARGE HEALTHCARE SYSTEM

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Background: Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease historically diagnosed with lab testing and liver biopsy. As anti-mitochondrial antibody (AMA) testing has demonstrated high specificity (95%) and sensitivity (92%) for PBC, guidelines do not require histologic confirmation of concurrent elevated alkaline phosphatase (ALP). However, studies with small cohorts suggest that AMA may be falsely positive in steatotic liver disease (SLD), autoimmune hepatitis (AIH), and cirrhosis, leading to the potential misdiagnosis of PBC. To address the limitations of this knowledge gap, our study assessed the diagnostic accuracy of AMA among patients with liver biopsy in a large multi-ethnic cohort. **Methods:** 1736 AMA-positive tests were identified among Kaiser Permanente Northern California patients $\geq$18 years-old from 2005-2018. 616 (36%) had a liver biopsy within 12 months of the AMA result. Liver biopsy reports were reviewed by a hepatopathologist and clinical hepatologist and deemed consistent with PBC (including overlap with AIH or SLD) or demonstrating non-PBC alternate diagnoses such as SLD, AIH, or viral hepatitis. Baseline demographics, comorbidities and lab tests were compared between AMA-positive patients with liver biopsy demonstrating PBC versus alternative diagnosis. Lastly, patients were grouped by ALP levels – elevated versus normal – to see how this correlated with biopsy findings. **Results:** Among the 616 AMA-positive patients with liver biopsy, 38% had alternative histologic diagnoses: SLD (13%), AIH (4%), Hepatitis C (2%), and nondiagnostic (17%). Patients with PBC on liver biopsy were older ($p = 0.003$), female ($p < 0.001$), and had higher ALP ($p < 0.001$), ALT ($p = 0.05$) and AMA level/titer ($p < 0.001$) (Table1). Those with PBC had a higher prevalence of hyperlipidemia ($p < 0.01$) and lower rates of type 2 diabetes and hypertension (Table 1). When grouping by ALP levels, 71% had elevated ALP level, of whom 26% had biopsy with non-PBC diagnosis. In those with normal ALP levels, 34% had histological findings that correlated with PBC. **Conclusion:** Elevated AMA levels, while classically thought to be pathognomonic for PBC, were not always diagnostic for PBC, even in patients with elevated ALP. Despite meeting laboratory criteria for PBC, 26% of patients had histological findings of an alternate diagnosis, largely SLD. In the subset of AMA-positive patients with elevated ALP levels, those with PBC on biopsy had ALP (median 235) over two times and AMA levels (median 103) over five times the upper limit of normal and higher AMA titers (median 320). Our findings suggest that a subset of AMA-positive patients may benefit from a liver biopsy for an accurate diagnosis.

Table 1. Demographic and Clinical Characteristics of Biopsied Patients: PBC-Confirmed Liver Biopsy vs. Alternate Diagnosis on Liver Biopsy

Variables	PBC Liver Biopsy (N=382)	Alternate Liver Biopsy (N=234)	P Value
Age, y			0.003
Median (IQR)	57 (49-67)	54 (45-65)	
Sex, n (%)			<.001
Female	331 (86.6)	171 (73.1)	
Race/Ethnicity, n (%)			0.118
White	173 (45.3)	96 (41.0)	
Black	18 (4.7)	13 (5.6)	
Hispanic	131 (34.3)	70 (29.9)	
Asian	50 (13.1)	45 (19.2)	
Other	8 (2.1)	10 (4.3)	
Unknown	2 (0.5)		
BMI (kg/m2)			0.164
Median (IQR)	27.0 (23.3-31.8)	27.5 (23.6-32.7)	
Hypertension, n (%)			0.056
Yes	60 (15.7)	51 (21.8)	
Hyperlipidemia n (%)			<.001
Yes	107 (28.0)	34 (14.5)	
Type 2 Diabetes, n (%)			0.099
Yes	60 (15.7)	49 (20.9)	
AMA Titer (U/ml)			<.001
Median (IQR)	320.0 (160.0-640.0)	160.0 (80.0-320.0)	
AMA Level (IU/mL)			<.001
Median (IQR)	103 (53-123)	40 (30-63)	
Alk Phos Value (U/L)			<.001

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4455 | DECREASED LEVELS OF ALKALINE PHOSPHATASE DURING BEZAFIBRATE THERAPY IN PRIMARY BILIARY CHOLANGITIS ARE ASSOCIATED WITH BETTER CLINICAL OUTCOME

Maria van Hooff[1] Rozanne de Veer[1] Ellen Werner[1] Ulrich Beuers[2] Joost Drenth[2] Frans Cuperus[3] Bart van Hoek[4] Bart Veldt[5] Michael Klemt-Kropp[6] Suzanne van

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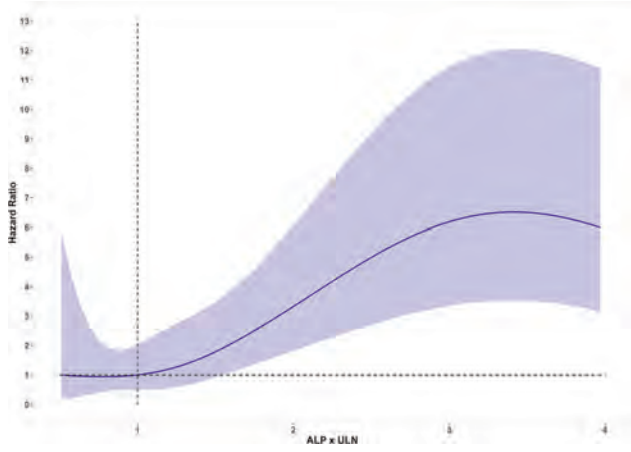
Background: To increase our confidence in alkaline phosphatase (ALP) as a potential surrogate marker in patients with primary biliary cholangitis (PBC), it is important to substantiate the prognostic relevance of ALP within the context of second line therapy. We evaluated ALP changes following off-label bezafibrate (BZF) therapy, and examined the on-treatment ALP levels in relation to clinical outcome in a real world setting. **Methods:** All consecutive patients initiating fibrates in the Dutch PBC Cohort Study – a retrospective nationwide cohort study – were included. Biochemical changes (expressed in upper limits of normal) during the first year of treatment were assessed. Survival analyses were used to assess cumulative discontinuation rates and rates of clinical disease progression, defined as occurrence of either liver decompensation, liver transplantation or death. Considering the early and profound biochemical response to BZF, time 0 was defined as the date of the first on-treatment ALP measurement after 90 days. A (mean)age-adjusted cubic spline function was applied to visualize the relation between ALP and the estimated hazard of clinical disease progression. **Results:** In total, 317 individuals (290 [92%] females) initiated fibrate therapy (98% BZF). At baseline, median age was 55.3 (IQR 48.4-64.4) year, median ALP was 2.30 (IQR 1.52–3.36) and TB was 0.58 (IQR 0.41–0.92). Total median follow-up was 30.4 (IQR 18.0-50.4) months, 241(76%) individuals were treated for at least 9 months at time of last data collection. At 12 months, the cumulative BZF cessation rate was 24.6% (95%CI 19.7–29.5). The overall on-treatment median ΔALP and ΔTB at 12 months were -1.00xULN (IQR -1.50 to -0.49) and -0.06xULN (IQR -0.20 to 0.05), respectively. Higher logALP levels during fibrate therapy were associated with a higher risk of clinical disease progression (age-adjusted HR 3.29 [per ULN], 95%CI 1.76-6.16, $p < 0.001$) (Fig.), as were higher logTB levels (age-adjusted HR 7.82, 95%CI 3.99-15.32, $p < 0.001$). Sensitivity analysis showed stable results: the aHR of logALP was 3.11 (95%CI 1.67–5.79) if further adjusted for cirrhosis, and 6.17 (95%CI 2.23-16.2, $p < 0.001$) if time 0 was set as the on-treatment ALP levels around one year of BZF therapy. **Conclusion:** In this nationwide cohort study, ALP levels declined following the initiation of BZF therapy, but a quarter of patients stopped within the first year in this real-world setting. Lower ALP levels during BZF therapy were associated with a lower risk of solid clinical endpoints. Confirming this in the setting of second-line therapy further strengthens the case for ALP as a relevant endpoint in PBC drug development.



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4456 | WOMEN WITH AUTOIMMUNE HEPATITIS ON AZATHIOPRINE HAVE SIMILAR OBSTETRIC OUTCOMES COMPARED TO THOSE NOT ON AZATHIOPRINE: A GLOBAL RETROSPECTIVE COHORT STUDY

Mikaela Nikkola Jara-Tantoco[1] Justin Riley Lam[1] Urvya Iyer[1] FNU Deepali[1] Maria Lagarde Mussa[2], [1]Jefferson Einstein Philadelphia Hospital, [2]Jefferson Einstein Hospital

Background: Women with autoimmune hepatitis (AIH) have often been treated with azathioprine through their pregnancy. There remains a theoretical risk of increased teratogenicity with these agents although previous studies have not seen this.[1,2] A meta-analysis looked at the effects of 6-mercaptopurine and azathioprine on pregnancy outcomes in individuals with inflammatory bowel disease.[2] However, there have only been smaller studies looking at this therapeutic agent in women with AIH.[3]

Our study aims to look at the pregnancy outcomes of women diagnosed with AIH on azathioprine (+AZ), comparing them to women diagnosed with AIH who are not on the medication (-AZ). **Methods:** TriNetX, a global health research network, with deidentified data was queried on May 21-27, 2025. Women aged 18 to 50 years old who had AIH (International Classification of Diseases [ICD-10] K75.4) were included. Comparison groups were AZ+ compared to AZ-. The index event considered was the diagnosis of AIH. Outcomes studied included pregnancy, premature birth, abortion, preeclampsia, eclampsia, gestational diabetes, and suspected teratogenicity with exclusion of those who had these outcomes prior to the index event. Statistical analyses performed were hazard ratio (HR), 95% confidence interval (CI), mean, standard deviation (SD), and p values <0.05 were considered as significant. Propensity score matching was performed for traditional risk factors that lead to high-risk pregnancy, medications, and laboratory values (Table 1). **Results:** Prior to propensity score matching, there were 3,296 AZ+ patients and 11,860 AZ- patients. After propensity score matching, there were 2,900 AZ+ and AZ- patients. There was a mean follow-up of 1510 ± 1291 days and 1040 ± 1141 days for AZ+ and AZ- patients, respectively. There were no differences in pregnancy (HR 0.977 [95% CI 0.722, 1.323]), preterm pregnancy (HR 1.199 [95% CI 0.934, 1.539]), abortion (HR 1.071 [95% CI 0.646, 1.776]), preeclampsia (HR 1.801 [95% CI 0.330, 9.836]), eclampsia (HR 2.616 [95% CI 0.271, 25.201]), gestational diabetes (RR 0.535 [95% CI 0.280, 1.019]), and visits for suspected teratogenicity (RR 1.105 [95% CI 0.723, 1.689]) between groups (all $p > 0.05$).

Dissimilar to previous findings, the use of azathioprine in our study does not increase the risk of preterm pregnancy.[1,2] With addressing traditional risk factors that lead to worse obstetric outcomes, there was no difference between groups. Ensuring that the disease process in AIH with or without the use of azathioprine leads to similar outcomes in pregnant patients.

This study is limited due to it being a database review and is dependent on accuracy of ICD coding. Determining outcomes of birth could not be ascertained as this was de-identified data with restriction of congenital outcomes. Only visits for suspected teratogenicity could be included. **Conclusion:** Women with AIH on azathioprine have similar obstetric outcomes as women with AIH not on azathioprine.

TABLE 1: Comparing characteristics before and after propensity matching.

	Before matching			After matching		
Characteristic	Azathioprine (n=3,269)	No azathioprine (n=12,567)	p value	Azathioprine (n=2,922)	No azathioprine (n=2,922)	p value†
Age, mean(SD), y	30.0 (10.0)	32.2 (9.5)	<0.001	30.4 (9.9)	30.8 (9.6)	0.131
Race						
White	57.9%	61.9%	<0.001	58.4%	57.9%	0.670
Black	19.3%	14.9%	<0.001	18.6%	19.8%	0.230
Hispanic/ Latino	13.8%	9.7%	<0.001	13.7%	13.1%	0.537
Comorbidities						
Cirrhosis	23.3%	6.7%	<0.001	18.1%	17.6%	0.631
Obesity	15.0%	22.8%	<0.001	15.3%	14.7%	0.485
Type 2 Diabetes	5.9%	6.5%	0.224	5.9%	5.8%	0.823
Type 1 Diabetes	1.7%	1.8%	0.666	1.7%	1.5%	0.464
Hypertension	13.1%	14.7%	0.021	12.9%	12.8%	0.937
Thyroid disorders	11.4%	12.6%	0.062	11.4%	11.9%	0.539
Medications						
Glucocorticoids	65.7%	46.6%	<0.001	61.8%	60.5%	0.306
Mycophenolate	8.6%	3.2%	<0.001	7.3%	7.7%	0.583
Contraceptives	14.7%	20.4%	<0.001	14.9%	14.3%	0.480
Progestins	11.7%	17.3%	<0.001	12.2%	12.1%	0.968
Labs, mean(SD)						
Sodium	138.1 (2.8)	138.0 (3.2)	0.492	138.1 (2.8)	137.9 (3.5)	0.080
Creatinine	0.8 (2.3)	0.9 (2.5)	0.563	0.8 (0.9)	1.0 (3.7)	0.052
Total bilirubin	1.7 (3.6)	1.3 (3.5)	<0.001	1.5 (3.1)	1.9 (4.4)	0.001
Albumin	3.8 (0.7)	4.0 (0.7)	<0.001	3.8 (0.7)	3.8 (0.7)	0.491
INR	1.2 (0.3)	1.2 (0.4)	0.741	1.1 (0.3)	1.2 (0.4)	0.149
Platelets	238.7 (110)	263.3 (101)	<0.001	240.3 (106)	244.8 (112)	0.211
Hemoglobin	12.3 (1.8)	12.4 (2.0)	0.329	12.3 (1.8)	12.1 (2.0)	<0.001
A1c	5.5 (1.5)	5.7 (1.5)	0.008	5.5 (1.5)	5.7 (1.6)	0.109
TSH	2.4 (5.5)	3.4 (27.8)	0.198	2.4 (5.8)	6.4 (54.4)	0.022

Data shown n (%), except where stated otherwise. † p-value from chi-squared test for categorical variables, from t-test for continuous. INR: international normalized ratio, TSH: thyroid-stimulating hormone

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Disclosures: Mikaela Nikkola Jara-Tantoco: Nothing to Disclose, Justin Riley Lam: Nothing to Disclose, Urvya Iyer: Nothing to Disclose, FNU Deepali: Nothing to Disclose, Maria Lagarde Mussa: Nothing to Disclose

4457 | PERFORMANCE OF THE GLOBE SCORE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH SECOND-LINE THERAPY

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Background: The GLOBE score is a continuous prognostic model for liver transplant–free survival in primary biliary cholangitis (PBC), based on UDCA-treated patients from 1990 to 2012. The performance of the GLOBE score in patients diagnosed more recently and treated with UDCA or in combination with second-line therapies is unknown. This study aims to assess the prognostic performance of the GLOBE score in more recently diagnosed patients treated with UDCA or UDCA in combination with second-line therapy. **Methods:** An international multicenter cohort study was conducted using data from four different centers within the Global PBC study group. Patients with an available GLOBE score one year after the start of first- and/or second-line therapy were included. An event was defined as liver transplantation (LT) or death. The discriminative ability of the GLOBE score at one year after start of UDCA and one year after start of add-on second-line therapy for liver transplantation or death was evaluated using Harrell's C-index. Predictive accuracy was assessed with calibration plots. **Results:** A total of 1,070 patients (1,014, 94.8% females) were included, of which 286 (26.7%) were diagnosed after 2014. The median age was 52.7 years (IQR 43.1–62.0). After one year of UDCA, the median total bilirubin was 0.6 x ULN (IQR 0.4–0.8) and the median ALP level was 1.0 x ULN (IQR 0.7–1.6). During a median follow-up of 6.5 years (IQR 2.9–11.8), 152 patients underwent LT or died. A total of 166 patients (15.5%) were treated with second line therapy (fibrates n = 88, OCA n = 78), with a median follow-up of 3.2 years (IQR 1.7–3.7) thereafter (12 events). The C-index of the GLOBE score was 0.86 (95% CI 0.85–0.88) for the overall cohort, 0.94 (95% CI 0.89–0.98) for the subgroup diagnosed after 2014, and 0.91 (95% CI 0.87–0.96) among second line therapy users. Calibration appeared reasonable in those using second-line therapy (figure 1), though the model tended to overestimate liver transplant-free survival in high-risk groups. This pattern was observed in those diagnosed after 2014 and in the overall cohort as well. **Conclusion:** The GLOBE score maintains a high discriminative ability in a recent PBC population, including those treated with second-line therapy. Further studies with longer follow-up are needed to assess if calibration is sufficient for clinical decision making or whether recalibration of the model is required.

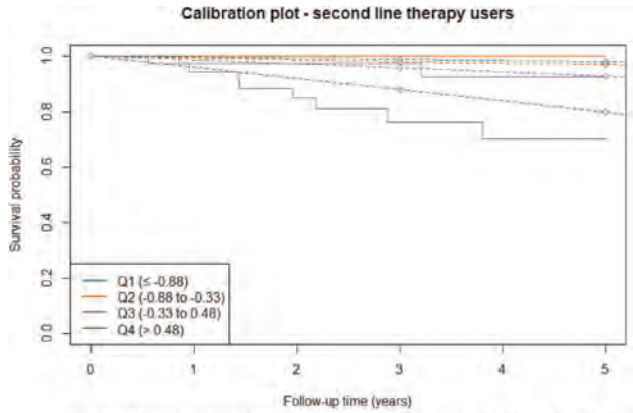

Figure 1: Dashed and straight lines represent the predicted and observed survival, respectively

Disclosures: Esmée Eikelenboom: Nothing to Disclose, Ellen Werner: Nothing to Disclose, Vincenzo Ronca: Orphan: Grant/Research Support, IPSEN: Travel Grant, Gideon Hirschfield: Intercept: Consultant, Intercept: Consultant, GSK: Consultant, GSK: Consultant, CymaBay: Consultant, CymaBay: Consultant, Ipsen: Consultant, Ipsen: Consultant, Falk: Consultant, Falk: Consultant, Pliant: Consultant, Pliant: Consultant, Mirum: Consultant, Mirum: Consultant, Advanz: Consultant, Advanz: Consultant, Chemomab: Consultant,

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4458 | MECHANISTIC INSIGHTS INTO THE PROTECTIVE EFFECTS OF FAECALIBACTERIUM PRAUSNITZII AND ITS METABOLITE SHORT CHAIN FATTY ACIDS ON BILIARY INJURY IN PRIMARY BILIARY CHOLANGITIS

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Background: Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease that primarily affects middle-aged women. Studies suggest that alterations in the gut microbiome are closely associated with the pathogenesis and treatment of PBC, but the underlying mechanisms remain unclear. **Methods:** This study first conducted gut microbiota analysis of fecal samples from PBC patients and healthy controls using metagenomic sequencing, with LEfSe and other methods employed to identify differential microbial taxa. Subsequently, a bile duct ligation (BDL) mouse model was established and treated with *F. prausnitzii* (1×10^9 CFU/day), while ductular reaction and liver fibrosis were evaluated through histopathological staining. For in vitro experiments, a GCDC-induced injury model using human primary biliary epithelial cells (HiBECs) was developed, followed by treatment with varying concentrations of short-chain fatty acids (SCFAs). Furthermore, ChIP assays were performed to detect H3K27ac modification levels, elucidating the specific mechanism by which SCFAs exert their effects through epigenetic regulation of the ELF3/PI3K-Akt pathway. All data were statistically analyzed using two-tailed t-tests/ANOVA with FDR correction ($P < 0.05$ considered statistically

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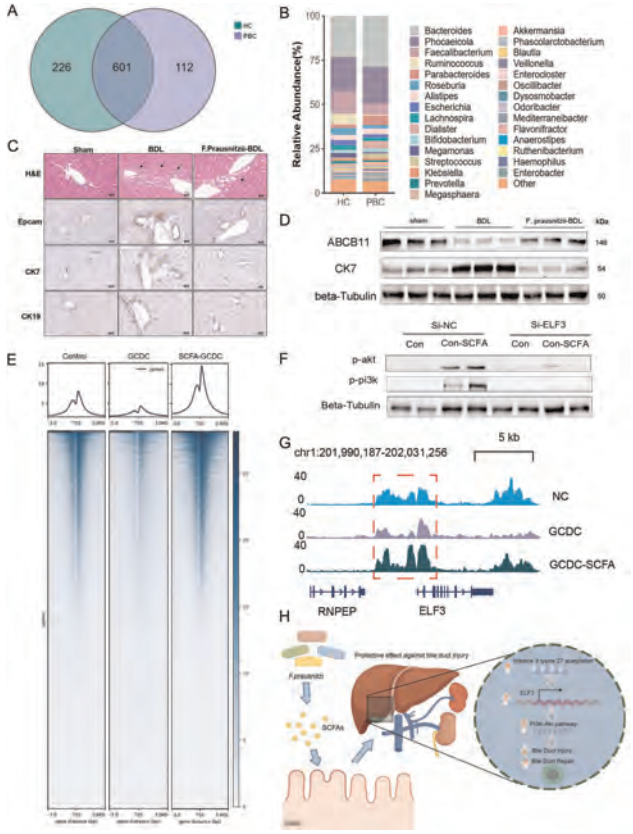
significant). **Results:** We found that *F. prausnitzii* was significantly reduced in the gut microbiota of PBC patients. Supplementation with *F.prausnitzii* markedly ameliorating BDL-induced biliary injury, including cholangitis, bile duct hyperplasia, and liver fibrosis, while also restoring gut microbial balance and intestinal barrier function. These beneficial effects were linked to SCFAs produced by *F. prausnitzii*. Further studies revealed that *F. prausnitzii*-derived SCFAs enhanced histone H3K27 acetylation, upregulating the transcription factor ELF3 and subsequently activating the PI3K-Akt signaling pathway to promote bile duct cell repair. **Conclusion:** This study demonstrates that *F. prausnitzii* exerts protective effects in PBC. Its depletion in PBC patients and its therapeutic potential in alleviating cholangitis and liver fibrosis, along with restoring gut function, highlight its promising clinical application for PBC treatment.



Disclosures: Ronghua Jin: Nothing to Disclose, Qi Wang: Nothing to Disclose, Xiaoxue Yuan: Nothing to Disclose, Song Yang: Nothing to Disclose, Xi Wang: Nothing to Disclose

4459 | EFFICACY AND SAFETY OF SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS AND ELEVATED BILIRUBIN AT BASELINE IN THE PHASE 3 PLACEBO-CONTROLLED RESPONSE TRIAL

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Background: Seladelpar (SEL) is a first-in-class delpar (selective PPAR-delta agonist) indicated for the treatment of primary biliary cholangitis (PBC) combined with ursodeoxycholic acid (UDCA) in adults with inadequate response to UDCA or as monotherapy in patients (pts) intolerant to UDCA. In the Phase 3, placebo (PBO)-controlled RESPONSE trial (NCT04620733), SEL significantly improved biomarkers of cholestasis and pruritus vs PBO in pts with PBC over 12 months (M). Here, we report efficacy and safety in prespecified subgroups of pts with total bilirubin (TB) >1 or $\leq 1\times$ the upper limit of normal (ULN) at baseline (BL) in RESPONSE. **Methods:** Pts with PBC with an inadequate response or intolerance to UDCA, ALP $\geq 1.67\times$ ULN, and TB $\leq 2\times$ ULN (ULN = 1.10 mg/dL) received daily, oral SEL 10 mg or PBO (2:1 randomization) for 12M. Prespecified subgroups of pts with TB >1 or $\leq 1\times$ ULN at BL were analyzed post hoc for the composite endpoint (ALP $<1.67\times$ ULN, ALP decrease $\geq 15\%$, and TB $\leq$ ULN), along with additional

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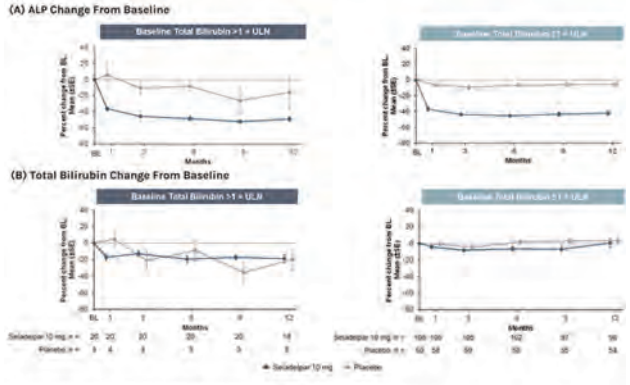
biochemical endpoints and safety. **Results:** Of 193 enrolled pts, 25 pts (13%; 20 SEL, 5 PBO) had TB $>1\times$ ULN at BL (mean TB: SEL, 1.4 mg/dL; PBO, 1.5 mg/dL). Pts with TB $>1\times$ ULN at BL had higher mean ALP (SEL, 384 U/L; PBO, 399 U/L) and higher rates of cirrhosis (SEL, 35% [7/20]; PBO, 40% [2/5]) at BL compared with pts with TB $\leq 1\times$ ULN at BL (ALP: SEL, 302 U/L; PBO, 307 U/L; cirrhosis: SEL, 10%; PBO, 12%). At 12M, 50% (10/20) of SEL pts with TB $>1\times$ ULN at BL achieved the composite endpoint compared with 20% (1/5) of PBO pts; 64% of SEL pts with TB $\leq 1\times$ ULN at BL achieved the composite endpoint compared with 20% of PBO pts. In total, 70% (14/20) of SEL pts with TB $>1\times$ ULN at BL achieved TB normalization at 12M compared with 40% (2/5) of PBO pts. ALP change from BL was similarly reduced with SEL vs PBO in pts with TB >1 or $\leq 1\times$ ULN at BL (Fig A). TB changes from BL were similar between SEL and PBO in both BL TB groups (Fig B). Greater decreases in GGT and ALT were observed with SEL vs PBO regardless of BL TB level. Adverse events (AEs) were reported in 95% and 85% of pts with TB >1 vs $\leq 1\times$ ULN at BL, respectively, with similar proportions across SEL and PBO. No treatment-related serious AEs or deaths were reported. **Conclusion:** In this small-sized, subgroup analysis of the RESPONSE trial, SEL reduced biomarkers of cholestasis and liver injury in pts with PBC who had elevated TB at BL and normalized TB in 70% (14/20) of pts by 12M. SEL was overall safe and well tolerated regardless of BL TB level.

Figure: ALP Change From Baseline Over Time (A) and Total Bilirubin Change From Baseline Over Time (B)



n = number of evaluable patients at each time point.
ALP, alkaline phosphatase; BL, baseline; ULN, upper limit of normal.

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4460 | LONG-TERM SAFETY OF COMBINATION OBETICHOLIC ACID AND BEZAFIBRATE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: INTERIM DATA FROM TWO PHASE 2 TRIALS

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Background: Obeticholic acid (OCA), a farnesoid X receptor agonist, and bezafibrate (BZF), a pan-peroxisome proliferator–activated receptor agonist, have both demonstrated improvements in hepatic serum biomarkers in primary biliary cholangitis (PBC). Here, we present long-term safety data from 2 phase 2 trials evaluating OCA and BZF combination therapy in patients (pts) with PBC who had inadequate response or intolerance to ursodeoxycholic acid. **Methods:** In Study 213 (NCT04594694), pts were randomized in a 1:1:1:1 ratio to receive once-daily oral BZF 200 mg immediate release (IR), OCA 5 mg titrated to 10 mg at week 4 + BZF 200 mg IR, BZF 400 mg sustained release (SR), or OCA 5 mg titrated to 10 mg at week 4 + BZF 400 mg SR during a 12-week, double-blind (DB) treatment period. Pts then entered a DB follow-up period before transitioning to OCA 5 mg + BZF 400 mg SR during a 96-week, open-label, long-term safety extension (LTSE). In Study 214 (NCT05239468), pts were randomized 1:1:1:1 to receive once-daily oral BZF 100 mg IR, OCA 5 mg (without titration) + BZF 100 mg IR, BZF 400 mg IR, or OCA 5 mg (without titration) + BZF 400 mg IR during a 12-week DB period. Pts then transitioned directly to OCA 5 mg + BZF 400 mg IR during a 144-week, open-label LTSE. Here, we present interim LTSE safety data from both studies as of a March 2025 data cut ($\geq$72 weeks of follow-up for each study). Safety was assessed descriptively using adverse events (AEs), with treatment assignment based on the treatment actually received. Potential events of liver injury, an AE of special interest, were reviewed by an external, blinded Hepatic Safety Adjudication Committee (HSAC). **Results:** In Studies 213 and 214, 75 and 72 pts were randomized, with 66 and 67 pts continuing to the LTSE, respectively. Among all cohorts, 11 and 7 serious AEs were reported in Studies 213 and 214, respectively (Table 1). No deaths or liver transplants were reported in either study. Eight cases of elevated liver enzymes were adjudicated by the HSAC. Of these, 5 were adjudicated as mild severity. All cases were reversible with drug interruption. No cases progressed to advanced chronic liver disease in either study, and no cases of rhabdomyolysis or renal failure were reported. **Conclusion:** OCA + BZF combination therapy was generally well tolerated across both studies, with no deaths or liver transplants and few serious AEs. The safety profile supports continued phase 3 development of fixed-dose combination therapy for pts with PBC.

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Table 1. Summary of safety data from Studies 213 and 214

Number of	Study 213 (n=75)	Study 214 (n=72)
Serious AEs	11	7
Deaths	0	0
Liver transplants	0	0
Cases sent for HSAC adjudication	5	3
Cases with no evidence of liver injury	1	2
Cases with evidence of liver injury	4*	1*

Abbreviations: AE, adverse event; HSAC, Hepatic Safety Adjudication Committee.
*All cases were deemed to be mild in severity and resolved.

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4461 | CHANGES IN FATIGUE AND PRURITUS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH ELAFIBRANOR ARE LARGELY INDEPENDENT FROM IMPROVEMENTS IN SERUM BIOMARKERS

David Jones[1] Andreas Kremer[2] Cynthia Levy[3] Nuno Antunes[4] Hugo Gomes da Silva[5] Mickael Lothgren[6] Marwan Sleiman[5] Nathan Touati[5] Mark Swain[7],
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Background: Fatigue and pruritus are common debilitating symptoms in primary biliary cholangitis (PBC). Elafibranor (ELA), approved for PBC, significantly improved biomarkers of cholestasis in the phase III ELATIVE® trial (NCT04526665). Here, the association between improvements in symptoms and cholestatic biomarkers is assessed, as well time to and durability of changes in fatigue and pruritus. **Methods:** Patients (pts) with PBC were randomized 2:1 to ELA 80 mg or placebo (PBO). Fatigue was assessed via the Patient-Reported Outcome (PRO) Measurement Information System (PROMIS) Fatigue Short Form 7a (PFSF 7a) and PBC-40 Fatigue domain; pruritus was assessed via the PBC-40 Itch domain, 5-D Itch, and Worst-Itch Numeric Rating Scale (WI NRS). Data are reported for pts with moderate-to-severe (mod−sev) fatigue (PFSF 7a $\geq$60; PBC-40 Fatigue $\geq$29) and mod−sev pruritus (WI NRS $\geq$4) at baseline (BL). Mean change from BL (CfB) in PRO scores and achievement of minimal clinically important differences for fatigue (PFSF 7a: $\geq$3.0; PBC-40 Fatigue: $\geq$5.0) and clinically meaningful thresholds for pruritus (PBC-40 Itch: $\geq$2.0; 5-D Itch: $\geq$4.5; WI NRS: $\geq$1.8) are reported to Week (Wk) 52. Spearman's rank correlation coefficients were calculated between fatigue/pruritus scores and alkaline phosphatase (ALP)/total bilirubin (TB) levels at BL and in CfB to Wk 52. **Results:** At BL, fatigue and pruritus PRO scores and ALP/TB levels had weak correlations in all pts (r = 0.03–0.14). Similarly, CfB to Wk 52 in PRO scores and ALP/TB levels had weak correlations in pts receiving ELA (r = −0.06–0.22). Similar results were seen for PBO (Table). At BL, 46/108 and 58/108 pts receiving ELA and 20/53 and 30/53 receiving PBO had mod−sev fatigue according to PFSF 7a and PBC-40 Fatigue scores, respectively. Improvements in PFSF 7a scores were seen within 4 wks with ELA compared with PBO (mean [SE] CfB: −3.7 [0.9] vs −0.7 [0.9]), with further improvements to Wk 52 (mean [standard error; SE] CfB: −6.5 [1.2] vs −2.6 [1.6]). Changes in PBC-40 Fatigue scores with ELA were similar to PBO at Wk 4 (mean [SE] CfB: −2.7 [0.7] vs −2.6 [1.1]) but improved to Wk 52 (mean [SE] CfB: −3.6 [1.0] vs −2.1 [1.0]). At BL, 44/108 pts receiving ELA and 22/108 receiving PBO had mod−sev pruritus. PBC-40 Itch and 5-D Itch improved within 4 wks with ELA versus PBO (mean [SE] CfB: −1.4 [0.5], −2.9 [0.7] vs −0.6 [0.4], −1.7 [0.8]) and continued to Wk 52 (mean [SE] CfB: −2.5 [0.5], −4.3 [0.7] vs −0.2 [0.7], −1.7 [1.0]). Reductions in WI NRS at Wks 4 and 52 were similar with ELA and PBO. The proportions of pts achieving clinically meaningful improvements in fatigue and pruritus PROs were mostly greater with ELA vs PBO at all evaluated timepoints. **Conclusion:** Weak correlations between improvements in cholestatic biomarkers and fatigue/pruritus PROs suggest that ELA may improve biochemistry and symptoms independently. Some improvements in these symptoms may be seen within four weeks of ELA treatment, continued over one year.

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Table. Correlation coefficients between cholestatic biomarkers and PROs in change from baseline to Week 52

	Elafibranor		Placebo	
	ALP	TB	ALP	TB
PFSF 7a	n=94 r=0.03, p=0.77	n=93 r=−0.06, p=0.56	n=46 r=0.01, p=0.93	n=46 r=−0.09, p=0.54
PBC-40 Fatigue domain	n=94 r=0.07, p=0.48	n=93 r=−0.01, p=0.93	n=46 r=0.11, p=0.49	n=46 r=−0.05, p=0.72
PBC-40 Itch domain	n=94 r=−0.01, p=0.96	n=93 r=0.05, p=0.66	n=46 r=−0.04, p=0.79	n=46 r=−0.12, p=0.44
5-D Itch	n=94 r=−0.02, p=0.88	n=93 r=0.22, p=0.03	n=46 r=−0.19, p=0.22	n=46 r=0.17, p=0.25
WI NRS	n=79 r=0.05, p=0.69	n=78 r=0.15, p=0.20	n=39 r=−0.31, p=0.05	n=39 r=0.14, p=0.40

Data presented for patients with moderate-to-severe fatigue (PFSF 7a ≥60; PBC-40 Fatigue domain ≥29) and moderate-to-severe pruritus (WI NRS ≥4) at baseline. ALP: alkaline phosphatase; PFSF 7a: Patient-Reported Outcome Measurement Information System Fatigue Short Form 7a; PRO: patient-reported outcome; TB: total bilirubin; WI NRS: Worst-Itch Numeric Rating Scale.

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4462 | THERAPEUTIC SILENCING OF AN UNDISCLOSED TARGET WITH A GALNAC SIRNA REVERSES LIVER INJURY AND FIBROSIS IN A HUMANIZED MOUSE MODEL OF CHOLESTATIC LIVER DISEASE

Jian Liang Xu[1] Zhi Wei Tan[2] Christine Meng Fan Goh[1] Walter Hunziker[3], [1]Institute of Molecular and Cell Biology, Agency for Sience, Technology and Research, Singapore, [2]Institute of Molecular and Cell Biology, Agency for Sience Technology and Research, SingaporeTan Zhi, [3]Agency for Science, Technology and Research Singapore

Background: Progressive familial intrahepatic cholestasis type 3 (PFIC3) is a severe autosomal recessive liver disorder caused by mutations in the *ABCB4* gene, leading to impaired biliary phosphatidylcholine secretion, bile acid toxicity, and progressive liver fibrosis. Despite recent advances, no currently approved therapy effectively reduces the bile acid toxicity or halts fibrotic progression—highlighting a significant unmet medical need for improved disease-modifying treatments. **Methods:** We evaluated the therapeutic efficacy of a GalNAc-conjugated, chemically modified small interfering RNA (GalNAc siRNA#5) targeting an undisclosed gene in *Abcb4*-deficient (KO) mice—a validated model of PFIC3. To better mimic the human pathophysiology, particularly the hydrophobicity of human bile, mice were fed a cholic acid (CA)–enriched diet, which exacerbates bile acid–mediated liver injury and fibrosis. A single subcutaneous dose (5 mg/kg) of the investigational siRNA was administered. A week later, mice were transferred to the CA supplemented diet. for two weeks, sacrificed and blood biochemistry and liver necrosis and fibrosis were analyzed. **Results:** Treated mice exhibited significant reductions in serum liver injury markers (ALT, AST, ALP, bilirubin and plasma bile acids) alongside histological evidence of fibrosis prevention. These findings demonstrate that transient silencing of the target gene is beneficial in this humanized cholestasis model. **Conclusion:** Our results support the therapeutic potential of siRNA-based approaches for cholestatic liver diseases like PFIC3

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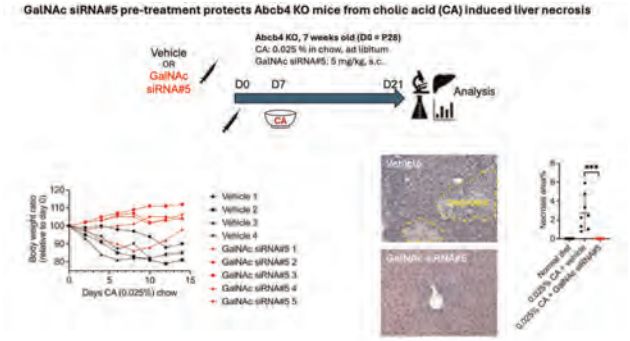
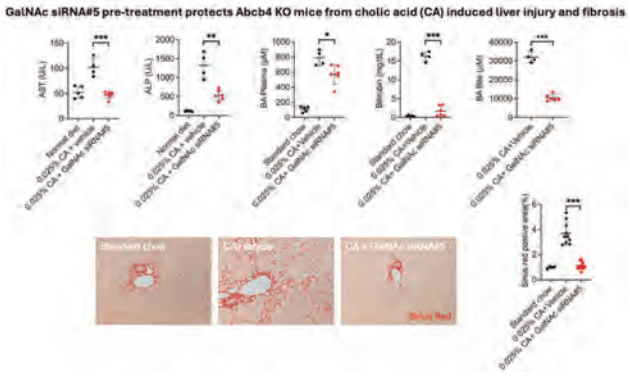
and provide preclinical evidence for considering targeted RNAi therapies in this space.





Disclosures: Jian Liang Xu: Nothing to Disclose, Zhi Wei Tan: Nothing to Disclose, Christine Meng Fan Goh: Nothing to Disclose, Walter Hunziker: Nothing to Disclose

4463 | ANTICHOLESTATIC EFFECTS OF OBETICHOLIC ACID AND BEZAFIBRATE IN COMBINATION COMPARED WITH ELAFIBRANOR AND SELADELPAR IN A HUMAN HEPATOCYTE MODEL OF CHOLESTASIS

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Background: The combination of obeticholic acid (OCA) + bezafibrate (BZF) has been shown to induce biochemical remission in primary biliary cholangitis. We used a bile acid–overloaded hepatocyte model of cholestasis to explore the mechanism of OCA + BZF and compare its effects with the peroxisome proliferator–activated receptor (PPAR) agonists elafibranor (ELA) and seladelpar (SEL). **Methods:** To mimic bile acid–induced liver injury and assess therapeutic efficacy, primary human hepatocytes were initially cultured in Williams' Medium E with a hepatocyte plating supplement pack. Cells were then incubated for 24 hours in Willams' Medium E containing a hepatocyte maintenance supplement pack, glycochenodeoxycholic acid (250 μM), and glycocholic acid (250 μM), with or without test compounds. The expression of genes regulating hepatic bile acid synthesis, transport, and metabolism (*CYP7A1*, *FGF19*, *MDR3*, *OSTß*, and *BSEP*), as well as bilirubin metabolism and secretion (*UGT1A1*), were measured by quantitative polymerase chain reaction. Bilirubin conjugation was assessed using high-performance liquid chromatography/mass spectrometry. Statistical significance was assessed by one-way analysis of variance with Dunnett's test. **Results:** While OCA (10 μM) and BZF (30 μM) independently suppressed *CYP7A1* expression, OCA + BZF had an additive effect. At 10 μM, OCA and SEL suppressed *CYP7A1* expression more than ELA or BZF but less than OCA + BZF. Hepatic *FGF19* expression was significantly induced by OCA, but not by BZF, ELA, or SEL. Notably, BZF potentiated OCA-induced *FGF19* expression. OCA and OCA + BZF also significantly induced the expression of *MDR3*, *OSTß*, and *BSEP*, whereas ELA and SEL only induced *MDR3* and *OSTß* expression, and BZF only induced *MDR3* expression. While OCA, ELA, and SEL independently induced *UGT1A1* expression, OCA + BZF more than doubled *UGT1A1* expression compared with the individual treatments. When hepatocytes were exposed to high concentrations of bilirubin (25 μg/ml [42μM]), both OCA and BZF independently increased the amount of conjugated bilirubin in the cell culture supernatant. OCA + BZF demonstrated a further increase in secreted conjugated bilirubin. **Conclusion:** The combination of OCA + BZF was more efficacious than either drug alone or the recently approved PPAR agonists, ELA and SEL, in regulating genes involved in cholestasis, resulting in enhanced suppression of bile acid synthesis, increased bile acid secretion, and increased bilirubin metabolism. **Disclosures:** Daniela Passeri: Nothing to Disclose, Francesca De Franco: Nothing to Disclose, Sanjay Kansra: Intercept Pharmaceuticals: Employee, Luciano Adorini: Nothing to Disclose, Mary Erickson: Nothing to Disclose, Roberto Pellicciari: Nothing to Disclose

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4464 | SERUM ANTI-INTEGRIN AVB6 AUTOANTIBODIES AS NON-INVASIVE BIOMARKERS FOR THE DIAGNOSIS OF PRIMARY SCLEROSING CHOLANGITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease with no approved non-invasive diagnostic biomarker. Serum anti-integrin αvβ6 autoantibodies have emerged as potential diagnostic tools, but their accuracy remains incompletely defined, particularly in the context of inflammatory bowel disease (IBD). **Methods:** We performed a systematic review and meta-analysis of studies evaluating serum anti-αvβ6 autoantibodies for PSC diagnosis. Databases searched included PubMed, Embase, Web of Science, and Cochrane through April 2025. Pooled sensitivity, specificity, diagnostic odds ratio (DOR), and area under the summary receiver operating characteristic curve (AUC) were calculated using a bivariate random-effects model. Subgroup analyses were performed by IBD status and by comparison with other cholestatic diseases. **Results:** Four studies comprising 1294 subjects (398 PSC patients, 896 controls) met inclusion criteria. Pooled sensitivity and specificity for PSC diagnosis were 62.3% and 87.3%, respectively (AUC: 0.76). In patients without IBD, specificity rose to 96% and AUC to 0.86; in those with IBD, specificity fell to 71% and AUC to 0.67. For differentiation from other cholestatic diseases, pooled sensitivity was 81%, specificity 95%, and AUC 0.90. Sensitivity analysis showed moderate variability, with specificity consistently high across subgroups. **Conclusion:** Serum anti-αvβ6 autoantibodies demonstrate high specificity and moderate sensitivity for PSC, particularly useful in patients without IBD and in distinguishing PSC from other cholestatic conditions. These findings support their clinical utility as promising non-invasive biomarkers warranting further validation.

Disclosures: Stavros Papadakos: Nothing to Disclose, Stamatina Vogli: Nothing to Disclose, Alexandra Argyrou: Nothing to Disclose, Antonios Chatzigeorgiou: Nothing to Disclose, Andreas Koutsoumpas: Nothing to Disclose, Jiannis Vlachogiannakos: Nothing to Disclose, George Papatheodoridis: Abbvie: Advisor, Abbvie: Grant/Research Support, Abbvie: Speaking and Teaching, Astra Zeneca: Advisor, Astra Zeneca: Speaking and Teaching, Genesis: Advisor, Genesis: Speaking and Teaching, Gilead: Advisor, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GlaxoSmithKline: Advisor, Ipsen: Advisor, Ipsen: Speaking and Teaching, Novo Nordisk: Advisor, Novo Nordisk: Speaking and Teaching, Roche: Advisor, Roche: Speaking and Teaching, Takeda: Advisor, Albireo: Advisor, Amgen: Advisor, BioArs: Advisor, Elpen: Advisor, Janssen: Advisor, Merck Sharp & Dohme: Advisor, Vir Biotechnology: Advisor, Gilead: Grant/Research Support, Takeda: Grant/Research Support, Vianex: Grant/Research Support

4465 | SINGLE-CELL RESOLUTION SPATIAL TRANSCRIPTOMIC ATLAS REVEALS DISTINCT PATHOGENIC LANDSCAPES IN AUTOIMMUNE HEPATITIS AND AIH-PBC OVERLAP SYNDROME

Shu Li[1] Chen-Yi Liu[1] Shi-Wen Wu[1] Jia-Wen Chen[1] Chao Cai[1] Bang-Guo Zhou[2] Ming-Qin Lu[1], [1]The First Affiliated Hospital of Wenzhou Medical University, [2]The First Affiliated Hospital of Zhejiang University

Background: Autoimmune hepatitis (AIH) and AIH-primary biliary cholangitis (PBC) overlap syndrome (OS) are complex autoimmune liver diseases with poorly understood pathogenesis. While AIH targets hepatocytes and PBC affects bile ducts, AIH-PBC OS combines features of both, leading to accelerated fibrosis and poor prognosis. Current therapies remain controversial due to limited mechanistic insights. This study leverages 10X Visium HD spatial transcriptomics and single-cell RNA sequencing to resolve spatial and cellular heterogeneity in these diseases. **Methods:** Liver biopsies from 5 patients (3 AIH, 2 AIH-PBC OS) were analyzed.Spatial transcriptomics (Visium HD) and single-cell sequencing were performed. Histopathological regions (hepatocytes, inflammatory zones) were mapped by pathologists.Data integration, clustering, and pseudotime trajectory analysis identified cell-type dynamics. CellChat and SCENIC explored intercellular interactions and regulatory networks. **Results:** Distinct Cellular Landscapes: AIH-PBC OS showed severe hepatocyte impairment (*Hepatocyte_impaired* clusters) and plasma cell infiltration (37% vs. 12% in AIH), while AIH exhibited higher hepatocyte (48% vs. 22%) and Kupffer cell proportions.

Active Inflammatory Signaling: AIH inflammatory zones displayed elevated *COLLAGEN* signaling and stronger cell-cell interactions. In contrast, AIH-PBC OS showed

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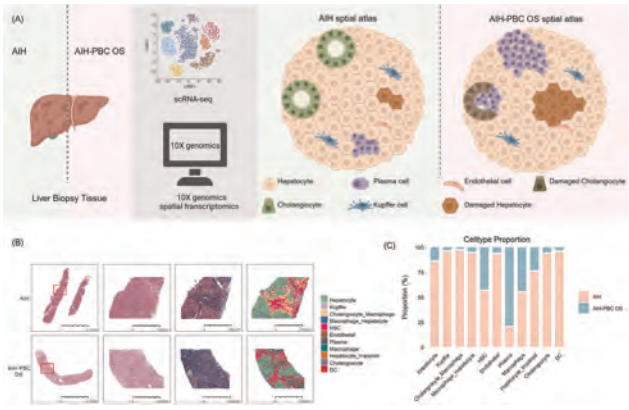
diffuse HSC distribution and fibrotic gene upregulation (*TNF*, *NF-κB* pathways).
XBP1 as a Key Regulator: Pseudotime analysis revealed progressive hepatocyte dysfunction in AIH-PBC OS, with *XBP1* regulons driving inflammatory/fibrotic modules. SCENIC identified XBP1 as a top transcription factor in hepatocyte subsets.
HSC and Plasma Cell Dynamics: HSCs in AIH localized to portal tracts with pro-inflammatory activity, while AIH-PBC OS HSCs exhibited panlobular fibrosis. Plasma cell subtypes(Plasma-c01) dominated OS but showed muted interactions. **Conclusion:** This study provides the first single-cell resolution spatial atlas of AIH and AIH-PBC OS, highlighting distinct inflammatory microenvironments and XBP1's role in disease progression. AIH-PBC OS exhibits severe hepatocyte injury and fibrosis, while AIH demonstrates active collagen signaling. Findings implicate XBP1 as a therapeutic target and underscore the utility of spatial transcriptomics in unraveling autoimmune liver disease mechanisms.



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4466 | EVALUATION OF RESPONSE TO SECOND LINE THERAPY IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC) AND INADEQUATE RESPONSE TO UDCA: A PILOT STUDY OF LIVER BIOPSIES FOLLOW UP

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Background: Response to second-line therapy in PBC is commonly defined by improvement in cholestatic markers (ALP $<1.67\times$ULN, bilirubin <1 mg/dL) and prevention of fibrosis and liver-related events. This study aimed to assess 12-month response to OCA and/or PPAR agonists and identify clinical and histological factors associated with treatment outcomes. **Methods:** Among 614 patients with PBC (Jan 2016-Dec 2023), 279 showed incomplete biochemical response to UDCA. Of these, 107 (38.3%) met eligibility criteria for second-line trials (ALP $>1.67\times$ULN, bilirubin <2 mg/dL, absence of significant portal hypertension). Fifty patients completed 12 months of therapy with obeticholic acid (n = 12), PPAR agonists (n = 29), or both (n = 9), and underwent liver biopsy at baseline and at Month 12 ± 3 months as per local practice. Histological analysis included H&E, PAS, Masson's trichrome, reticulin, and rhodanine stains. Bile duct loss was assessed with cytokeratin 7 and 19. Fibrosis was staged using the modified Scheuer system. Elastography was performed at baseline and 12 months. Statistical analysis included t-tests and one-way ANOVA. **Results:** Mean age 53.6 ± 10.6 years; 84% were female. Baseline ALP was 388.8 ± 166.6, GGT 458.8 ± 400.2, ALT 71.3 ± 40.6, and bilirubin 0.9 ± 0.4. Ten patients (20%) had cirrhosis at baseline. POISE response was achieved in 30% (n = 15); ALP normalization occurred in 14% (n = 7). Male sex ($p = 0.04$), mod/severe ductopenia ($p = 0.01$), elevated ALT (82 vs 46, $p = 0.003$), bilirubin (1.07 vs 0.7, $p = 0.02$), and baseline cirrhosis ($p = 0.02$) were associated with nonresponse. Moderate to severe portal inflammation with interface activity was observed in 56% and correlated with fibrosis progression. None of the patients with severe inflammation responded (n = 5); and only 21% with moderate inflammation showed improvement (n = 5). Response was associated with histological improvement in 11 patients. Mild ductopenia did not affect response. No biochemical marker predicted fibrosis or inflammation. Cirrhosis persisted and was associated with liver-related events (5 patients: 1 death, 3 transplants). Elastography values correlated with cirrhosis and liver events (10.4 vs 22.9 kPa, $p < 0.001$), but not with inflammation or ductopenia: no significant differences were observed among responders between baseline and Month 12. **Conclusion:** Only 30% responded by POISE criteria and 14% normalized ALP. Nonresponse was associated with male sex, cirrhosis, elevated transaminases, GGT, and bilirubin, but not ALP levels. Mod/severe inflammation and ductopenia were negative predictors. Cirrhosis and elastography values were linked to liver events. Histological findings may support early second-line intervention.
Disclosures: Alejandra Villamil: Novartis: Advisor, Intercept: Speaking and Teaching, Gilead: Advisor, Zydus: Advisor, Daniela De la Viña: Nothing to

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Disclose, Eduardo Mullen: Nothing to Disclose, Ignacio Lucero: Nothing to Disclose, Juan Bandi: Nothing to Disclose

4467 | THE PREDICTIVE ROLE OF SMOKING IN ACHIEVING BIOCHEMICAL REMISSION IN AUTOIMMUNE HEPATITIS: A U.S. SINGLE CENTER STUDY

Natalia Rojas-Amaris[1] Ana Marenco-Flores[1] Romelia Barba[2] Daniela Goyes[3] John Esli Medina Morales[4] Leandro Sierra[5] Vilas Patwardhan[1] Alan Bonder[1], [1]Beth Israel Deaconess Medical Center, [2]Texas Tech University, [3]Yale School of Medicine, [4]Rutgers New Jersey Medical School, [5]Cleveland Clinic Foundation

Background: Autoimmune hepatitis (AIH) is a chronic condition with a fluctuating course that can either progress to a severe disease state or enter remission, sometimes allowing patients to discontinue medication. We aimed to explore potential predictors of complete biochemical response (CBR) among patients with AIH. **Methods:** A cross-sectional analysis within a prospective cohort study was conducted using data from a single visit of AIH patients enrolled between January 2018 and December 2024 in the Autoimmune Liver Diseases Registry at Beth Israel Deaconess Medical Center (Boston, MA, USA). Patients with overlap syndromes involving primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC), or those who had undergone liver transplantation, were excluded. CBR was defined as normalization of aminotransferases and immunoglobulin G (IgG) levels. A logistic regression model was created to evaluate predictors of CBR. **Results:** 100 patients with AIH were included in this analysis, 75% of whom were women. CBR was achieved in 55% of patients, and 13% of them were no longer receiving immunosuppressive therapy. No significant differences in demographic characteristics were observed between patients who exhibited CBR and those who did not. Smoking was significantly associated with lower odds of achieving CBR (OR: 0.24; 95% CI: 0.07–0.80; p = 0.021), according to the multivariate logistic regression analysis adjusted for confounders such as ALT levels, albumin, platelet count, and prednisone dose. **Conclusion:** Patients with a current or former smoking history had 76% lower odds of achieving biochemical remission compared to non-smokers. Assessing smoking habits in AIH patients and implementing cessation strategies for smokers with AIH could positively influence the course of the disease.

Table 1. Baseline clinical characteristics (n=100)

Variable	CBR (n=55)	No CBR (n=45)	P Value
Age, (IQR)	65 (50 - 72)	62 (51-68)	0.486
Sex, n (%)			0.105
Female	45 (82)	30 (67)	
Male	10 (18)	15 (33)	
Race/ethnicity, n (%)			0.874
Caucasian	35 (64)	29 (65)	
African American	4 (7)	5 (11)	
Hispanic	5 (9)	3 (7)	
Asian	0	1 (2)	
Other/Multiracial	11 (18)	7 (16)	
BMI, (IQR)	28 (24 - 30)	26 (21 - 32)	0.383
Time since diagnosis, years (IQR)	6 (3 - 14)	4 (2 - 8)	0.148
Cirrhosis present at diagnosis, n (%)	12 (22)	16 (36)	0 160
Cirrhosis at latest follow-up, n (%)	30 (51)	10 (30)	0.179
MASH, n (%)	6 (11)	9 (20)	0.162
DM, n (%)	6 (11)	8 (18)	0.391
Hypertension, n (%)	21 (38)	16 (36)	0.837
Hypothyroidism, n (%)	11 (20)	13 (29)	0.212
EHAIDs, n (%)	18 (33)	13 (29)	0.424
Lifestyle habits			
Alcohol consumption, n (%)			0.391
Never	41 (75)	38 (84)	
Former	7 (13)	2 (4)	
Current	7 (13)	5 (11)	
Smoking, n (%)			0.320
Non-smoker	45 (82)	32 (71)	
Former	9 (16)	10 (22)	
Current	1 (2)	3 (7)	
Current daily medications			
Prednisone, n (%)	11 (20)	21 (47)	0.005
AZA, n (%)	31 (56)	28 (62)	0.349
MMF, n (%)	4 (7)	9 (20)	0.057
Off-immunosuppressants, n (%)	7 (13)	0	0.013
Vitamin D, n (%)	10 (19)	3 (7)	0.074
Laboratory values			
ALP, (IQR)	70 (58 - 86)	81 (65 - 110)	0.054
ALT, (IQR)	15 (13 - 19)	25 (19 - 38)	<0.001
AST, (IQR)	19 (17 - 23)	33 (24 - 44)	<0.001
Total Bilirubin, (IQR)	0.4 (0.3 - 0.6)	0.5 (0.4 - 0.8)	0.072
Albumin, (IQR)	4.5 (4.3 - 4.6)	4.4 (4 - 4.6)	0.054
INR, (IQR)	1.1 (1.1 - 1.25)	1.1 (1 - 1.2)	0.145
IgG, (IQR)	1121 (842 - 1340)	1331 (1132 - 1912)	0.002
WBC - Leukocytes (IQR)	6.4 (5 - 7.2)	5.7 (4.5 - 6.7)	0.167
Platelets, (IQR)	249 (208 - 313)	227 (137 - 270)	0.006
Creatinine, (IQR)	0.8 (0.7 - 0.94)	0.8 (0.7 - 0.9)	0.160

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, AZA: Azathioprine, BMI: body mass index, CBR: complete biochemical response, DM: diabetes mellitus, EHAIDs: extrahepatic autoimmune diseases, MASH: Metabolic dysfunction-associated steatohepatitis, MMF: Mycophenolate mofetil. EHAIDs include Rheumatoid Arthritis, Sjögren's syndrome, Systemic Lupus Erythematosus, Celiac disease, Sarcoidosis, Inflammatory bowel disease, Scleroderma, among others.

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4468 | AUTOIMMUNE HEPATIC INVOLVEMENT IN SYSTEMIC SCLEROSIS- SYSTEMATIC REVIEW AND META ANALYSIS

Bipneet Singh[1] Jahnavi Ethakota[1] Palak Grover[1] Gurleen Kaur[2] Karanbir Singh[2], [1]Henry Ford Allegiance, [2]GMC Amritsar

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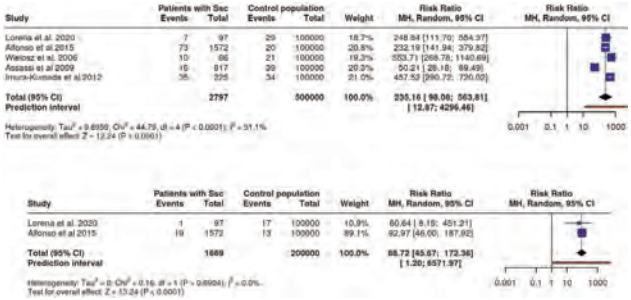
Background: Systemic sclerosis (SSc) is a heterogeneous, multisystem autoimmune disease characterized by fibrosis in genetically predisposed individuals. It can involve multiple organ systems, but hepatic involvement is rare. In this study, we aim to find the correlation of liver disease, especially primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH), in the population with SSc. Further, the correlation of anti-mitochondrial antibody (AMA) and other autoantibodies was done. **Methods:** PubMed, Cochrane, Google Scholar, and Embase were searched for liver disease in SSc, and 11 studies were selected for analysis. Cochrane risk of bias tools and meta-analysis online were used. Controls were taken from the prevalence in the respective countries around the same time. **Results:** Among 11 studies including 2,797 patients with systemic sclerosis (SSc), 190 (6.7%) had liver disease, with 157 (5.6%) attributed to autoimmune causes. Primary biliary cholangitis (PBC) was the most common (5%), followed by autoimmune hepatitis (AIH) at 1.2%. PSC was only seen in 1 patient across the studies. There was a significant association in prevalence compared to the general population (Figure 1). Anti-mitochondrial antibodies (AMA) were positive in 10.87%, and anti-sp100 in 3.1%. **Conclusion:** The increased prevalence of autoimmune hepatobiliary conditions, such as primary biliary cholangitis (PBC), in systemic sclerosis (SSc) patients is likely due to overlapping immunopathogenic features, including shared regulatory T cell abnormalities and common genetic variants (e.g., STAT4, IRF5, NF-κB, IRF8). PBC was observed in approximately 5.6% of SSc patients—significantly higher than the general population prevalence of 0.02% to 0.04%—highlighting a strong association. This link is further supported by the presence of antimitochondrial antibodies (AMA) in 10.87% of patients, suggesting a high rate of subclinical or evolving PBC in this population.



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4469 | DISTINCT PROGNOSTIC PATTERNS OF THE HEPATIC TRANSAMINASES IN PRIMARY BILIARY CHOLANGITIS: AST IS THE STRONGER PREDICTOR OF OUTCOME

Gemma Weijsters[1] Ellen Werner[1] Maria van Hooff[1] Rozanne de Veer[1] Ulrich Beuers[2] Joost Drenth[2] Frans Cuperus[3] Remco van Dijk[4] Bart Veldt[5] Michael Klemt-Kropp[6] Suzanne van Meer[7] Robert Verdonk[8] Hajo Flink[9] Jan Vrolijk[10] Tom Gevers[11] Cyriel Ponsioen[2] Robert Roomer[12] Ulrike de Wit[13] Johan Kuyvenhoven[14] Jerome Sint Nicolaas[15] Philip Friederich[16] Merel Tielemans[17] Marleen de Vree[18] Huseyin Aktas[19] Sunje Abraham[20] Mariëlle Meijnen[21] Janne van Rooij[22] Edith Kuiper[23] Stephan Schmittgens[24] Yasser Alderlieste[25] Pieter ter Borg[26] Harry Janssen[1] Nicole Erler[7] Pedro Miranda-Afonso[1] Bettina Hansen[1] Adriaan van der Meer[1], [1]Erasmus University Medical Center, [2]Amsterdam University Medical Center, [3]University Medical Center Groningen, [4]Leiden University Medical Center, [5]Reinier de Graaf Gasthuis, [6]Noordwest Ziekenhuisgroep, [7]University Medical Center Utrecht, [8]St. Antonius Hospital, [9]Catharina Hospital, [10]Rijnstate, [11]Maastricht University Medical Center, [12]Franciscus Gasthuis & Vlietland, [13]Elisabeth – Tweesteden Hospital (ETZ), [14]Spaarne Gasthuis Hospital, [15]Amphia Hospital, [16]Meander Medical Center, [17]Bravis Hospital, [18]Treant Hospital, [19]Hospital Group Twente (ZGT), [20]Alrijne Hospital, [21]St Jansdal Hospital, [22]Tjongerschans Hospital, [23]Maasstad Hospital, [24]Nij Smellinghe Hospital, [25]Beatrix Hospital, [26]Ikazia

Background: The prognostic value of alanine aminotransferase (ALT) versus aspartate aminotransferase (AST) in patients with primary biliary cholangitis (PBC) is unclear. This study aimed to evaluate how ALT and AST levels during ursodeoxycholic acid (UDCA) therapy are associated with clinical outcomes in PBC. **Methods:** The retrospective Dutch PBC Cohort Study includes every identifiable patient with PBC in the Netherlands from 1990 up to last data collection (2019–2023) in all 71 hospitals. Patients with autoimmune hepatitis, additional therapy (second-line/immunosuppressants) within the first year, or with less than 1 year of follow-up after start UDCA were excluded. Where feasible, laboratory values (presented in upper limit of normal (ULN)) were imputed using joint model multiple imputation. The Pearson correlation coefficient was calculated. Cox models were used to study the association between AST and ALT and two endpoints: liver transplant (LT)-free survival and liver-related events (decompensation, LT, or liver-related death). To study the association between ALT and AST and outcome, natural cubic splines were used. **Results:** A total of 3,139 UDCA-treated PBC patients were

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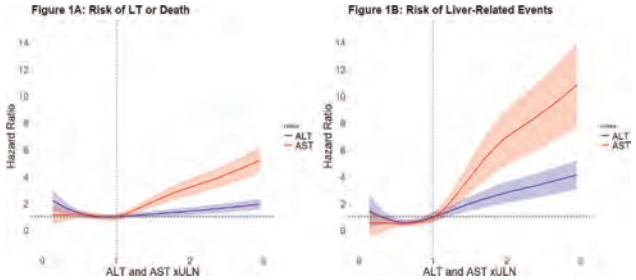
included. At baseline, median age was 58.0 years (IQR 49.7–67.2), 2745 (87.4%) were female and 203 (6.5%) had cirrhosis. During a median follow-up of 8.0 years (IQR 3.8–13.3), 295 patients developed decompensated cirrhosis, 78 patients underwent LT, and 584 patients died (152 [26%] liver-related; 115 [20%] of unknown cause). At 1 year of UDCA, AST (median 0.9, IQR 0.6–1.2) and ALT (median 0.8, IQR 0.5–1.2) were strongly correlated ($r = 0.78$, 95%CI 0.77–0.80, $p < 0.001$). In univariable analysis for LT or death, AST levels $\geq$ 1xULN showed a positive association (Fig. 1A). In contrast, ALT showed a U-shaped risk curve, with a higher risk in those with lowest ALT levels as well. This may be explained by a skewed age distribution; the median age was 64.2 years (IQR 55.3–71.8) in the lowest ALT quartile versus 51.7 years (IQR 44.1–59.1) in the highest quartile ($p < 0.001$). A rather stable increase in the risk of liver-related events for ALT and AST $\geq$ 1xULN was observed (Fig. 1B). For both endpoints, the risk curve of AST was steeper than that of ALT. The associations of the transaminases with each endpoint remained in multivariable analyses. **Conclusion:** Both AST and ALT levels after one year of UDCA were associated with LT-free survival and liver-related events in patients with PBC. Despite their strong correlation, AST and ALT demonstrated distinct prognostic patterns. For both endpoints, AST showed a stronger association. When assessing prognosis in PBC, these results indicate that the transaminases should be interpreted separately, and per endpoint of interest.



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4470 | SINGLE CELL TRANSCRIPTOMIC ATLAS OF STIMULATED PERIPHERAL T-CELL RESPONSE IN PATIENTS WITH PSC

Daniel Pratt[1] Henry Pratt[2] Taylan Erdogan[3],
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Background: Primary sclerosing cholangitis (PSC) is heritable, but the mechanisms by which genetic associations confer risk are unknown. PSC risk variants are enriched in non-coding regulatory elements which regulate gene expression in peripheral CD4+ helper T cells, particularly in response to stimulation with antigens and IL-2. We hypothesize that PSC patient T cells are predisposed to polarize toward pro-inflammatory phenotypes and away from anti-inflammatory T-reg states after stimulation. **Methods:** We performed single cell transcriptomic profiling of perturbed peripheral T cells in PSC patients and controls. We isolated peripheral blood mononuclear cells from two patients with PSC and two healthy age and sex-matched controls and used FACS to purify CD3+ CD4+ helper T cells. For each individual, half of the cells underwent stimulation using antigenic beads against the T cell receptor and IL-2 whereas the other half were left unstimulated. The cells were then inputted to CITE-seq for profiling of surface markers and gene expression. We then trained a neural network using the scGNN framework to identify T cell phenotypes and differentially-expressed genes specific to PSC patient samples as compared with controls. **Results:** Using scGNN we were able to match most cells from all samples to

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known phenotypes, including naive, memory, and regulatory T cells, based on expression of key marker transcription factors and surface markers. Even prior to stimulation, we observe that naive PSC patient T cells express a constellation of genes involved in IL-2 response, suggesting they are more primed for antigenic response than control T cells at baseline. After stimulation, we observe differential prevalence of several T cell phenotypes between patients and controls; most notably, patients have fewer T-regs after stimulation, suggesting PSC patients are deficient in mounting negative feedback during the antigenic response. We identify hundreds of genes which are differentially expressed in various cell lineages which may drive this differential immune response. **Conclusion:** To our knowledge, this is the first single cell-resolution profile of the peripheral immune response in PSC patients compared with healthy controls. Our results suggest that genetic risk for PSC influences T cells both before and after antigenic stimulation, priming naive cells for a rapid immune response and predisposing them toward pro-inflammatory phenotypes after stimulation. Using an AI-based approach we identified marker genes to aid in prioritizing translational research. We further anticipate the trained scGNN model will be extensible in the future both to predict clinical variables, such as response to particular therapies, and to identify biomarkers for PSC risk and progression from peripheral cells.

Disclosures: Daniel Pratt: RegCell: Consultant, Gilead: Advisor, Intercept: Advisor, Henry Pratt: Nothing to Disclose, Taylan Erdogan: Nothing to Disclose

4471 | IMPROVEMENTS IN PATIENT-REPORTED GENERAL HEALTH AND WELL-BEING IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH SELADELPAR IN THE RESPONSE TRIAL

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Background: Primary biliary cholangitis (PBC) is a chronic, progressive, autoimmune, cholestatic liver disease that can be debilitating and substantially impair health-related quality of life (HRQoL). In the Phase 3 RESPONSE trial (NCT04620733), seladelpar (SEL), a first-in-class delpar (selective PPAR-delta agonist), led to significant improvements in biochemical markers of cholestasis and pruritus vs placebo (PBO). Here, we report the general health status of patients (pts) in RESPONSE based on the PBC-40, a PBC-specific, pt-reported outcome measure of symptoms and HRQoL. **Methods:** In RESPONSE, pts with PBC who had an inadequate response or intolerance to ursodeoxycholic acid, alkaline phosphatase $\geq 1.67 \times$ upper limit of normal (ULN), and total bilirubin $\leq 2 \times$ ULN received daily, oral SEL 10 mg or PBO (2:1 randomization) for 12 months. A post hoc analysis of responses to 3 PBC-40 questions on general health status (A, current general health; B, general health pre-diagnosis of PBC; C, general health now vs 12 months ago) was conducted in the overall population and in pts with moderate to severe pruritus (MSP) at baseline (pruritus numerical rating scale [NRS] score of ≥ 4). A 5-point response scale for A and B ranged from “poor” to “excellent”; C ranged from “much worse” to “much better”. Responses were scored separately. **Results:** Of the 193 pts enrolled in RESPONSE (SEL, n = 128; PBO, n = 65), 72 pts were in the MSP group (SEL, n = 49; PBO, n = 23). At baseline, mean (SD) durations of PBC in the overall population and in the MSP group were 8.3 (6.6) and 7.5 (5.9) years, respectively. In the overall population, 14% and 37% of pts reported their general health pre-diagnosis (B) as “excellent” and “very good” vs 2% and 12% at baseline in RESPONSE (A). In the MSP group, 7% and 42% of pts reported their general health pre-diagnosis (B) as “excellent” or “very good” vs 1% and 5% at baseline in RESPONSE (A). In the overall population, 29% of SEL pts vs 9% of PBO pts reported that their general health was “much better” at month 12 when compared with baseline in the RESPONSE trial (C). Likewise, in the MSP group, 39% of SEL pts vs 13% of PBO pts reported that their general health was “much better” at month 12 compared with baseline in RESPONSE (C). **Conclusion:** More pts reported poorer general health and well-being than prior to PBC diagnosis. Pts who received SEL reported greater improvements in their general health and well-being after 12 months compared with those who received PBO.

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4472 | REAL WORLD ASSESSMENT OF CURRENT PBC TREATMENT, KEY GOALS, AND LEVEL OF TREATMENT SATISFACTION ACCORDING TO HEALTHCARE PROFESSIONALS ACROSS FRANCE, ITALY, GERMANY, SPAIN, UNITED KINGDOM, AND THE UNITED STATES

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Background: To describe healthcare professionals (HCPs) treatment patterns, key treatment goals and level of satisfaction with current treatment for their patients with primary biliary cholangitis (PBC). **Methods:** Data were drawn from the Adelphi Real World PBC Disease Specific Programme™, a cross-sectional survey across EUR (France, Italy, Spain, Germany, the United Kingdom (UK)) and the United States (US), from November 2024 to May 2025. Analyses focused on HCPs reported treatment for PBC, including treatment goals and level of satisfaction. Importance of PBC treatment goals were rated from 1 to 5 (where 1 = Not at all important, 5 = Extremely important). **Results:** Data from 181 physicians (EUR; 141 and US; 40) were included. Physicians reported at the time of data collection that almost all patients were prescribed treatment for PBC (EUR; 97%, US: 98%) with ursodeoxycholic acid (UDCA) the most frequently prescribed (EUR; 83%, US; 62%). Other treatments included antihistamines, fibrates, bile acid sequestrants, obeticholic acid (OCA), corticosteroids, antibiotics, SSRIs, opioids and dual PPARs. Most important goals of treatment for US and EUR HCPs included inhibiting disease progression, reducing the risk of advanced fibrosis/liver cirrhosis, slowing down damage to the liver and delaying need for a liver transplant. In terms of ability to slow down damage to the liver, very few physicians reported being 'completely satisfied' with current treatment, with 46%, EUR and 60%, US reporting they were 'not satisfied'. The main reasons for dissatisfaction in US were due to lack of efficacy and associated treatment side effects while in EUR HCPs reasons were mainly around the inability of current treatments to manage itch and fatigue. The majority of

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US and EUR HCPs reported that they "somewhat" and "strongly" agreed that there is an urgent need for more PBC-approved drug therapy options (EUR; 88%, US; 90%). In addition, US and EUR HCPs reported that their ideal treatment for PBC would address both the underlying cause of the disease in addition to effective itch reduction, improved sleep, convenient dosing and good tolerability (EUR; 95%, US; 95%). **Conclusion:** The majority of physicians reported dissatisfaction with currently available treatment options for PBC. These findings highlight the need for novel treatments that not only address the underlying cause of PBC but also improve PBC related symptoms such as pruritus and fatigue.

	EUR	US
All physicians	**181**	**40**
Percentage of patients receiving prescribed treatment for PBC		
% on treatment for PBC	97%	98%
Percentage of patients receiving each of the following treatment classes for their PBC		
Ursodeoxycholic acid (UDCA)	83%	62%
Antihistamines	18%	20%
Fibrates	18%	18%
Bile acid sequestrants	18%	19%
Obeticholic acid (OCA)	11%	18%
Corticosteroids	7%	12%
Antibiotics	7%	9%
SSRIs	4%	8%
Dual PPARs	3%	10%
Opioid antagonists	4%	7%
Goals for treatment (1=Not at all important, 5= Extremely important, mean [s.d]		
Inhibits disease progression	4.7 [0.62]	4.4 [0.83]
Reduces risk of developing advanced fibrosis/liver cirrhosis in the future	4.7 [0.60]	4.4 [0.81]
Slows down damage to the liver	4.6 [0.55]	4.4 [0.86]
Delays need for liver transplant	4.6 [0.72]	4.3 [0.94]
Satisfaction with current available treatment to slow down liver damage, n (%)		
Completely satisfied	5 (4%)	0 (0%)
Satisfied	73 (52%)	16 (40%)
Neither satisfied nor dissatisfied	40 (28%)	17 (42%)
Dissatisfied	22 (16%)	7 (18%)
Completely dissatisfied	1 (1%)	0 (0%)
Reasons for not being completely satisfied, n (%)		
Lack of efficacy	61 (45%)	20 (50%)
Not effective enough at treating patient's itch	62 (46%)	11 (28%)
Not effective enough at treating patient's fatigue	53 (39%)	11 (28%)
Side effects	21 (15%)	15 (38%)
There is an urgent need for more PBC-approved drug therapy options, n (%)		
Somewhat agree	62 (44%)	26 (65%)
Strongly agree	62 (44%)	10 (25%)
My ideal treatment for PBC would address the underlying cause in addition to offering effective itch reduction, improved sleep, convenient dosing, and good tolerability, n (%)		
Somewhat agree	57 (40%)	19 (48%)
Strongly agree	77 (55%)	19 (48%)

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4473 | CLINICAL CHARACTERISTICS, DISEASE STATUS AND SYMPTOMATOLOGY OF PATIENTS WITH PRIMARY BILIARY CHOLANGITIS IN EUROPE AND THE UNITED STATES OF AMERICA: ANALYSIS OF A REAL-WORLD DATASET

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Background: To describe demographics, clinical characteristics, diagnostic tests, disease status and symptomatology of patients with primary biliary cholangitis (PBC) in EUR (France, Germany, Italy, Spain, the United Kingdom (UK)) and the United States (US). **Methods:** Data were drawn from the Adelphi Real World PBC Disease Specific Programme™, a cross-sectional survey, with retrospective data collection in EUR and US between November 2024 to May 2025. Physicians completed patient record forms for their patients with PBC including demographics, disease status, symptoms and diagnosis tests. Analyses performed were descriptive. **Results:** Overall, 181 physicians (EUR; 141, US; 40) reported data for 582 patients with PBC (EUR; 483, US; 99), majority of patients were female (EUR; 87%, US: 73%) and white (EUR 95%, US: 81%). Mean age was 55.0, EUR [SD: 11.75] and 47.5 [SD: 11.94], US. Most common tests/assessments to diagnose PBC were clinical examination, medical history, presence of pruritus, presence of fatigue, family history, total bilirubin, alkaline phosphatase (ALP), antimitochondrial antibodies (AMA), and alanine transaminase (ALT). Liver biopsy was used in around a quarter of patients. Most patients had a physician reported disease state of PBC stage 1 or 2 (EUR; 74%, US; 71%) at diagnosis and at time of data collection (EUR; 68%, US; 65%). Physicians reported that most common symptoms experienced by patients at time of data collection were fatigue (EUR; 51%, US;

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35%) and pruritus (EUR; 43%, US; 68%). Severity of pruritus at time of data collection was reported as moderate to severe by around half of physicians in EUR and US (EUR; 46%, US; 58%). Similarly, fatigue severity was reported as moderate to severe by just over half of physicians in EUR and US (both 54%). Majority of patients were receiving prescribed core treatment for their PBC at data collection (EUR; 92%, US; 68%), of which most received Ursodeoxycholic acid (UDCA) (EUR; 95%, US; 79%). Other treatments included Obeticholic acid (OCA), fibrates and Budesonide with a small proportion receiving the newer PPAR agonists Elafibranor and Seladelpar. **Conclusion:** Across EUR and US, many patients are experiencing fatigue and pruritus despite ongoing treatment. This highlights the need for more effective therapies that can address both the underlying disease and associated symptoms. Possible differences in treatment patterns between Europe and US warrant further investigation.

All patients: n	EUR (n=423)	US (n=99)
Age, years, mean [SD]	55.0 [11.75]	47.5 [11.94]
Sex, female, n (%)	421 (87%)	72 (73%)
Time since diagnosis, mean [SD]	(n=468)	(n=72)
Years	4.3 [5.11]	3.1 [1.88]
Currently receiving prescribed core treatment for PBC?	(n=483)	(n=99)
Yes, n (%)	444 (92%)	67 (68%)
No, but the patient has received prescribed core treatment for their PBC in the past, n (%)	13 (3%)	17 (17%)
No, and the patient has never received any prescribed core treatment for their PBC	26 (5%)	15 (15%)
Current treatment, n (%)	(n=444)	(n=67)
UDCA	421 (95%)	53 (79%)
Bezafibrate	42 (9%)	0 (0%)
Fenofibrate	23 (7%)	16 (24%)
Obeticholic acid (OCA)	32 (7%)	3 (4%)
Budesonide	16 (4%)	13 (19%)
Elafibranor	8 (2%)	0 (0%)
Seladelpar	2 (<1%)	2 (3%)
Ethnicity*, n (%)	(n=397)	(n=99)
White	377 (95%)	80 (81%)
Diagnostic tests/assessments, n (%)		
Clinical examination	461 (95%)	91 (92%)
ALP	448 (93%)	57 (58%)
AMA	451 (93%)	51 (52%)
Medical history	444 (92%)	65 (66%)
Total bilirubin	439 (91%)	46 (46%)
ALT	435 (90%)	50 (51%)
Presence of pruritus	426 (88%)	62 (63%)
Family history assessment	413 (86%	57 (58%
Ultrasound	418 (87%)	31 (31%)
GGT: Gamma-glutamyl transferase	406 (84%)	36 (36%)
Presence of fatigue	399 (83%)	56 (57%)
AST	400 (83%)	48 (48%)
ANA	360 (75%)	31 (31%)
Albumin	338 (70%)	40 (40%)
Platelets	340 (70%)	32 (32%)
Liver biopsy	125 (26%)	27 (27%)
Physician reported PBC stage at diagnosis, n (%)		
Stage 1- Portal Stage associated with bile duct changes, and/or portal inflammation	240 (50%)	38 (38%)
Stage 2- Periportal fibrosis and/or inflammation with dilated but intact portal tracts	118 (24%)	33 (33%)
Stage 3- Septal stage: Septal fibrosis with active inflammation and/or paucicellular septa	33 (7%)	15 (15%)
Stage 4- Cirrhotic: Variously sized nodules and varying degrees of inflammation	25 (5%)	3 (3%)
Physician reported PBC stage currently, n (%)	(n=479)	(n=99)
Stage 1- Portal Stage associated with bile duct changes, and/or portal inflammation	213 (44%)	26 (26%)
Stage 2- Periportal fibrosis and/or inflammation with dilated but intact portal tracts	113 (24%)	38 (38%)
Stage 3- Septal stage: Septal fibrosis with active inflammation and/or paucicellular septa	36 (8%)	20 (20%)
Stage 4- Cirrhotic: Variously sized nodules and varying degrees of inflammation	39 (8%)	5 (5%)
Physician reported symptoms at diagnosis, n (%)	(n=477)	(n=99)
Fatigue	315 (66%)	46 (46%)
Pruritis	285 (60%)	79 (80%)
Physician reported current symptoms, n (%)		
Fatigue	247 (51%)	35 (35%)
Pruritis	207 (43%)	67 (68%)

*Ethnicity was not asked for patients in France

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4474 | PREDICTORS OF RESPONSE TO RITUXIMAB IN REFRACTORY AUTOIMMUNE HEPATITIS AND VARIANT SYNDROMES

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Background: Autoimmune hepatitis (AIH) is a chronic autoimmune condition responding to immunosuppressive therapy. Rituximab (RTX) has been used off-label in AIH patients who are otherwise unresponsive or intolerant to other therapies. While recent data yield encouraging results in different stages of AIH, including cirrhosis, very few data are available regarding AIH variant syndromes. **Methods:** We conducted a single-center retrospective analysis of patients with AIH or its variant forms (overlap AIH-primary biliary cholangitis or AIH-primary sclerosing cholangitis) treated with RTX from February 2016 to September 2024 and included in our institutional biobank. Complete biochemical response (CBR) was defined as normal ALT, AST and IgG levels at 12 months. Our study aimed to evaluate predictive factors of treatment response and to assess safety of RTX. **Results:** In this 7-patient cohort (mean age 48, 71% female), four (57%) had variant forms of AIH. Two (29%) had compensated cirrhosis (F4) at diagnosis; the remainder had F0–F1 fibrosis stage. Median ALT at diagnosis was 475 IU/mL (IQR 296–1106), AST 259 IU/mL (IQR 189–526), and IgG 14.3 g/L (IQR 10.5–36.2). On average, patients had trials of 3 (and up to 5) immunosuppressants prior to

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RTX; and 57% received UDCA. None achieved CBR prior to RTX. Median time from diagnosis to RTX initiation was 120 months (IQR 24–180). Overall, 5 out of 7 patients (71%) achieved CBR with RTX: 100% in pure AIH vs 50% in variant forms ($p = 0.43$). No difference in CBR was found according to the presence of cirrhosis. Higher pre-RTX ALT (489 vs 361 IU/mL, $p = 0.38$) trended towards CBR, and this finding was found more commonly in patients with classical AIH (median 1106 vs 361 IU/mL for variant forms; $p = 0.057$). Higher ALP, seen predominantly in variant forms (median 305 vs 65 IU/mL, $p = 0.057$), was more frequent in non-CBR cases (393 vs 92 IU/mL, $p = 0.19$). Three patients (42%) experienced side-effects: serum sickness-like reaction, viral infection, and alopecia. Over a mean follow-up of 59 months (SD 29; range 25–101), no patient required liver transplant or developed hepatic decompensation while on RTX. **Conclusion:** RTX allowed patients with refractory AIH disease to achieve CBR in a majority of cases, while still maintaining an encouraging safety profile. In this small cohort, AIH patients, without features of variant forms, tend to have higher levels of transaminases, and seem to respond better to RTX.

Disclosures: Juliette Labelle: Nothing to Disclose, Julian Hercun: Gilead: Consultant, Ipsen: Consultant, GSK: Consultant, Advanz: Consultant, Pascal Lapierre: Nothing to Disclose, Marc Bilodeau: Nothing to Disclose, Catherine Vincent: Nothing to Disclose, YouRan Zhao: Nothing to Disclose

4475 | TEMPORAL TRENDS IN THE EPIDEMIOLOGY OF PRIMARY BILIARY CHOLANGITIS IN THE PUBLIC HEALTHCARE SYSTEM OF BRAZIL: PRELIMINARY DATA FROM A LARGE POPULATION-BASED STUDY

Guilherme Cancado[1] Claudia Couto[2] Luciana Faria[1] Paulo Bittencourt[3] Cristiane Villela-Nogueira[4] Vivian Rotman[4] Débora Terrabuio[5] Eduardo Cançado[5] Maria Lucia Ferraz[6], [1]Universidade Federal de Minas Gerais, [2]Federal University of Minas Gerais, [3]Hospital Português, [4]Universidade Federal do Rio de Janeiro, [5]Universidade de São Paulo, [6]Universidade Federal de São Paulo

Background: Population-based data on the epidemiology of primary biliary cholangitis (PBC) in Latin America are lacking. This study aimed to describe national trends in the incidence and prevalence of PBC in Brazil using comprehensive administrative healthcare data. **Methods:** We performed a population-based study using data from the Brazilian Ministry of Health (DATASUS), accessed via the TT Disease Explorer artificial intelligence platform. The dataset includes records for approximately 230 million individuals covered by Brazil's public universal healthcare system (SUS). All adult patients receiving ursodeoxycholic acid with the ICD-10 code for PBC between January 2021 and December 2024 were included. National population estimates were obtained from the Brazilian Institute of Geography and Statistics (IBGE), and age-standardized rates were calculated using the World Health Organization standard population. Incidence, prevalence, and average annual percentage change (AAPC) were assessed. Exploratory analyses examined regional clustering and correlation with mean Human Development Index (HDI) by region (2021). **Results:** A total of 10,124 PBC patients were identified. Age-standardized incidence declined from 1.11 per 100,000 in 2021 to 0.86 per 100,000 in 2024 [AAPC: –7.76% (95% CI: –10.95% to –4.46%); $p = 0.046$], while prevalence increased from 2.95 to 5.16 per 100,000 during the same period [AAPC: +20.3% (95% CI: 14.4% to 26.5%); $p = 0.019$]. Women had significantly higher incidence rate than men [IRR: 3.56 (95% CI: 3.36–3.77); $p < 0.001$]. Age-stratified analyses showed increasing incidence and prevalence with age, peaking at ages 56–60 [IRR: 3.82 (95% CI: 3.11–4.70); PRR: 3.90 (95% CI: 3.24–4.38, both relative to the 16-20 year-old group], followed by a gradual decline in older age groups. A south-to-north gradient in PBC prevalence was evident in 2021 and was strongly correlated with regional HDI ($r = 0.95$; $p = 0.015$). **Conclusion:** This is the first population-based study of PBC in Latin America. We identified a declining incidence but rising prevalence in Brazil, with marked sex and age disparities and regional variation linked to socioeconomic development. These findings underscore the need for improved disease awareness, timely diagnosis, and equitable access to care across regions.

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4476 | IDENTIFYING GAPS IN PSC PATIENT EDUCATION AND UNDERSTANDING OF CHOLANGIOCARCINOMA SCREENING AND SURVEILLANCE PRACTICES: RESULTS: OF A MULTINATIONAL PATIENT SURVEY

Brian Thorsen[1] Martine Walmsley[2] Susan O'Dell[1] Rachel Gomel[1] Mark Chatterley[2] Mary Vyas[3] Stephen Rossi[1], [1]PSC Partners Seeking a Cure, [2]PSC Support, [3]PSC Partners Seeking a Cure Canada

Background: People with primary sclerosing cholangitis (PSC) have up to a 20% lifetime risk of cholangiocarcinoma (CCA). CCA surveillance is challenged by the poor performance of current screening methods. We report results of a multinational patient survey to assess knowledge of CCA surveillance and patient-provider communication on CCA risk and surveillance results. The primary goal was to identify gaps in knowledge and communication in anticipation of new CCA screening tests. **Methods:** A survey for adults with PSC was developed by PSC Partners and PSC Support patient organizations. Patients reported relevant medical history, CCA surveillance tests performed (MRCP, CA 19-9, ERCP), risk and results discussion, and CCA education. The data was analyzed to compare rates of proactive CCA discussion from providers by patient characteristics, region, and provider type. **Results:** A total of 623 responses met screening criteria, primarily from the US (45%) and UK (31%). 31 patients reported a biliary tract cancer diagnosis (25 CCA, 6 GBC). Only 51% of patients reported proactive discussions by their provider of CCA risks and surveillance. Among patients who had a proactive CCA discussion, 56% reported having sufficient information regarding CCA, versus only 15% among those without proactive discussion ($p < 0.001$). Patients in North America reported a higher rate of proactive discussion than Europe (58.2% / 36.9%, $p < 0.001$), and rates were higher for hepatologists than gastroenterologists (55.0% / 38.3%, $p < 0.001$). Discussion rates were not significantly different across patient gender, age, and time since PSC diagnosis.

Annual MRCP surveillance was reported by 68% of patients, with significant differences by region and provider type. Proactive CCA discussion was strongly associated with more frequent use of annual MRCP. Regular CA 19-9 testing was reported by 36% of respondents. MRCP and CA 19-9 testing results for CCA surveillance were discussed with 27% and 72% of patients who had those tests, respectively.

Only 36% of patients felt they had adequate CCA information; the majority seeking information from online search, followed by patient organizations and their care team. Patients consistently reported significant anxiety and fear regarding CCA risk and the need for a reliable, non-invasive screening test. **Conclusion:** The results show high variability in discussion of CCA risk and test results and CCA surveillance practice in a population burdened with anxiety and fear around CCA. These results are influenced by differences in regional guidelines, healthcare systems, and the lack of highly predictive non-invasive diagnostic and prognostic tools. Promising novel biomarkers to detect early CCA and risk will impact the current routine surveillance practices and patient education needs. Appropriate global patient/provider education and communication programs should be implemented to support the use and delivery of such tests.

Disclosures: Brian Thorsen: Nothing to Disclose, Martine Walmsley: Nothing to Disclose, Nothing to Disclose, Nothing to Disclose, Susan O'Dell: Nothing to Disclose, Rachel Gomel: Nothing to Disclose, Mark Chatterley: Mirum: Speaking and Teaching, Mirum: Travel & accom provided for Patient Experience talk, Mary Vyas: Nothing to Disclose, Stephen Rossi: Nothing to Disclose, Nothing to Disclose

4477 | PROTEOME-WIDE AUTOANTIBODY DISCOVERY USING PHAGE IMMUNOPRECIPITATION SEQUENCING IDENTIFIES A DISTINCT AUTOANTIBODY SIGNATURE OF PRIMARY SCLEROSING CHOLANGITIS

Arielle Klepper[1] Isaac Benque[1] Fawzy Barry[1] Julian Hou[1] Michele Tana[1] MIchael Kattah[1] Jennifer Lai[1] Joseph DeRisi[1] Michael Li[1], [1]University of California, San Francisco

Background: Primary sclerosing cholangitis (PSC) is unique among immune-mediated liver diseases in that there are currently no autoantibodies recommended for use in establishing a diagnosis. We conducted proteome-wide autoantibody discovery using phage immunoprecipitation sequencing (PhIP-seq) to identify novel targets of autoreactivity in PSC. **Methods:** PhIP-seq was performed using serum samples from 65 PSC patients, 146 healthy controls, and 60 patients with inflammatory bowel disease (IBD) who did not have PSC. Serum samples were incubated with a phage library displaying >700,000 overlapping short (49-mer) peptides encompassing the human proteome. Autoantibodies bound to phage were captured via immunoprecipitation, and the peptide-encoding phage DNA sequences were extracted and subjected to next-generation sequencing, revealing the identities of the corresponding autoantigens. Logistic regression and recursive feature elimination analysis were performed using the scikit-learn package in Python on quality

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filtered data (at least 1 read per thousand and differentially enriched relative to healthy controls). Per peptide enrichment and Z-scores were calculated comparing PSC to control patients (IBD and healthy controls). **Results:** Of the PSC cohort, 43 (66%) were male, 46 (71%) had concurrent IBD and 40 (62%) had cirrhosis. We applied recursive feature elimination to quality filtered data; using this approach we were able to identify 8 features that could be used to effectively differentiate patients with PSC from patients with IBD in a logistic regression model (mean c-statistic on five-fold cross-validation 0.89 +/- 0.02). Additional highly specific (> 96%) hits with plausible biological relevance include melanocyte inducing transcription factor, expressed in Kupffer cells, and carbonic anhydrase 9 precursor, expressed in biliary epithelial cells; the former is dysregulated in cholangiocarcinoma and the latter is a known cholangiocarcinoma prognostic marker. **Conclusion:** Using proteome-wide immune profiling, we were able to identify 8 autoreactive targets that can be used to effectively discriminate patients with PSC from those with IBD. External validation of the antibody-based predictive model is in progress. Furthermore, certain top autoantigen hits may provide insight into PSC pathogenesis, though further studies are needed to orthogonally validate these hits and to investigate potential biological disease relevance.

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4478 | COMPARATIVE EFFECTIVENESS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS AS SECOND-LINE THERAPIES FOR PRIMARY BILIARY CHOLANGITIS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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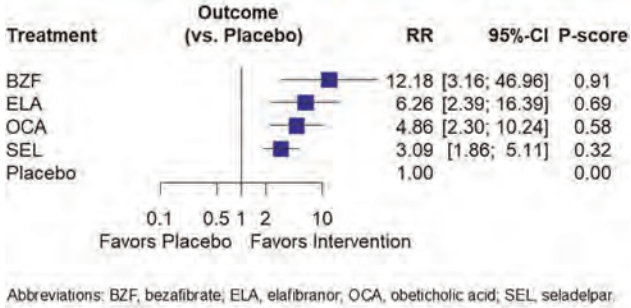
Background: Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease that may progress to cirrhosis and liver failure. For patients with inadequate response or intolerance to ursodeoxycholic acid (UDCA), peroxisome proliferator-activated receptor (PPAR) agonists have emerged as promising second-line therapies. **Methods:** We conducted a systematic review and frequentist network meta-analysis (NMA) of randomized controlled trials (RCTs) evaluating combination of UDCA + PPAR agonists versus placebo, UDCA, or both. The primary outcome was the achievement of a predefined biochemical response after 1 year of treatment (POISE); secondary outcomes included normalization of alkaline phosphatase (ALP), percentage changes in ALP and total bilirubin, and adverse events leading to treatment discontinuation. Subgroup analyses explored ALP responses across baseline ALP levels. A sensitivity analysis for the primary outcome including obeticholic acid (OCA) was also performed. **Results:** Eight RCTs comprising 727 participants and four PPAR agonists (bezafibrate, seladelpar, elafibranor and saroglitazar) were included. All agents outperformed placebo in achieving biochemical response and ALP normalization. Bezafibrate ranked highest for biochemical response; both bezafibrate and seladelpar ranked highest for ALP normalization. No significant differences were found in ALP reduction across baseline strata. Total bilirubin changes were not statistically significant. Discontinuations due to adverse events were infrequent. The sensitivity analysis including OCA confirmed the robustness of primary outcome (Figure). **Conclusion:** Add-on PPAR agonists are effective second-line therapies in PBC, bridging an important treatment gap. Treatment ranking variability may reflect heterogeneity in patient populations and drug mechanisms. In the absence of head-to-head trials, NMA provides valuable comparative insights; however, long-term safety data and patient-centered outcomes remain priorities for future studies.

Figure. Forest rank plot for biochemical response according to POISE criteria including the pivotal trials for second-line therapies in PBC



Abbreviations: BZF, bezafibrate; ELA, elafibranor; OCA, obeticholic acid; SEL, seladelpar

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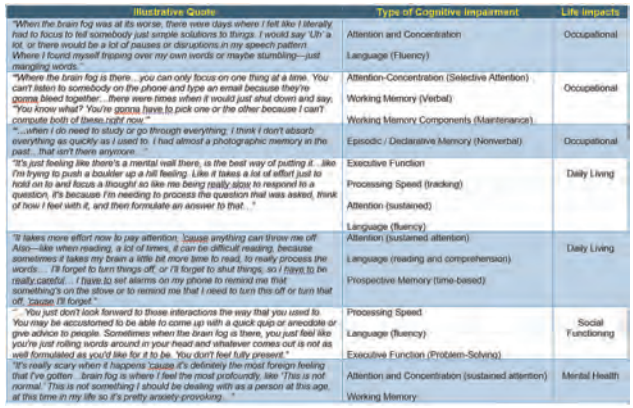
4479 | "THIS IS NOT NORMAL&RDQUO;: UNDERSTANDING COGNITIVE IMPAIRMENT THROUGH QUALITATIVE INTERVIEWS WITH ADULTS WITH PSC TO INFORM MEASURE DEVELOPMENT

Donna Evon[1] Kaya Merkler[1] Laura Mkumba[2] Lauren Wright[2] Nicole Lucas[2] Ricky Safer[3] Joanne Hatchett[3] Rachel Gomel[3] Stephen Rossi[3] Patrick Smith[1] Mark Swain[4] Sasha Deutsch-Link[1] Bryce Reeve[2], [1]UNC Chapel Hill, [2]Duke, [3]PSC Partners Seeking a Cure, [4]University of Calgary

Background: Understanding cognitive impairment experiences for adults living with PSC is essential for the development of PSC-specific, patient-reported outcome (PRO) measures that accurately reflect their real-world impact. Cognitive impairment ("brain fog") in PSC is under-recognized yet can be frequent and debilitating, and is differentiated from hepatic encephalopathy. **Methods:** Adults were recruited through the PSC Partners Patient Registry and PSC hepatologists in the U.S and screened for a range of PSC-related symptoms. Purposeful sampling was used to select 17 participants for in-depth, individual interviews focused on key symptoms, including cognitive impairment. Interviews were conducted virtually, audio-recorded, transcribed, and analyzed using NVivo software. **Results:** Eleven out of 17 participants were interviewed regarding their experience with cognitive impairment. Participants were on average 43 years old (range: 27-65), 55% male, 27% Black, 64% White, and 55% had inflammatory bowel disease. The Table below provides participants' illustrative quotes aligned with cognitive domains and life impacts. Severity ranged from mild to debilitating, with a few participants reporting inability to drive, cook independently, work full-time, or engage socially. Participants primarily characterized their cognitive impairments as occurring in the areas of working memory, verbal fluency, sustained attention, and processing speed. Others described a mental "wall" preventing them from absorbing and processing information. Half of participants endorsed experiencing some type of cognitive impairment on a daily basis, while others experienced it "a few days" a week or month. A "domino effect" can occur that begins with cognitive impairment reducing work productivity, which cuts into social time, and in turn, worsens mental health. Cognitive impairment. often accompanied fatigue, but reportedly can also occur alone. Most participants were able to differentiate PSC-related cognitive impairment from other causes based on association with severe fatigue, improvements with ERCPs and lactulose, and worsening during cholangitis attacks. **Conclusion:** PSC cognitive impairment is multi-faceted and impacts daily, work-related, and social activities among symptomatic adults with PSC. These findings will inform the customization of a PSC-specific PROMIS® Cognitive Function measure with strong content validity, enhancing its relevance for future clinical research and treatment evaluation.



Illustrative Quote	Type of Cognitive Impairment	Life Impacts
"When the brain fog was at its worse, there were days where I felt like I literally had to focus to tell somebody just simple solutions to things. I would say 'Uh' a lot, or there would be a lot of pauses or disruptions in my speech pattern. Where I found myself tripping over my own words or maybe stumbling—just mangling words."	Attention and Concentration Language (Fluency)	Occupational
"Where the brain fog is there…you can only focus on one thing at a time. You can't listen to somebody on the phone and type an email because they're gonna bleed together…there were times when it would just shut down and say, 'You know what? You're gonna have to pick one or the other because I can't compute both of these right now.'"	Attention-Concentration (Selective Attention) Working Memory (Verbal) Working Memory Components (Maintenance)	Occupational
"…when I do need to study or go through everything, I think I don't absorb everything as quickly as I used to. I had almost a photographic memory in the past…that isn't there anymore."	Episodic / Declarative Memory (Nonverbal)	Occupational
"It's just feeling like there's a mental wall there, is the best way of putting it…like I'm trying to push a boulder up a hill feeling. Like it takes a lot of effort just to hold on to and focus a thought so like me being really slow to respond to a question, it's because I'm needing to process the question that was asked, think of how I feel with it, and then formulate an answer to that…"	Executive Function Processing Speed (tracking) Attention (sustained) Language (fluency)	Daily Living
"It takes more effort now to pay attention 'cause anything can throw me off. Also—like when reading, a lot of times, it can be difficult reading, because sometimes it takes my brain a little bit more time to read, to really process the words… I'll forget to turn things off, or I'll forget to shut things, so I have to be really careful… I have to set alarms on my phone to remind me that something's on the stove or to remind me that I need to turn this off or turn that off, 'cause I'll forget."	Attention (sustained attention) Language (reading and comprehension) Prospective Memory (time-based)	Daily Living
"…You just don't look forward to those interactions the way that you used to. You may be accustomed to be able to come up with a quick quip or anecdote or give advice to people. Sometimes when the brain fog is there, you just feel like you're just rolling words around in your head and whatever comes out is not as well formulated as you'd like for it to be. You don't feel fully present."	Processing Speed Language (fluency) Executive Function (Problem-Solving)	Social Functioning
"It's really scary when it happens 'cause it's definitely the most foreign feeling that I've gotten…brain fog is where I feel the most profoundly, like 'This is not normal.' This is not something I should be dealing with as a person at this age, at this time in my life so it's pretty anxiety-provoking…"	Attention and Concentration (sustained attention) Working Memory	Mental Health

Disclosures: Donna Evon: Nothing to Disclose, Kaya Merkler: Nothing to Disclose, Laura Mkumba: Nothing to Disclose, Lauren Wright: Nothing to Disclose, Nicole Lucas: Nothing to Disclose, Ricky Safer: Nothing to Disclose, Joanne Hatchett: Nothing to Disclose, Rachel Gomel: Nothing to Disclose, Stephen Rossi: Nothing to Disclose, Patrick Smith: Nothing to Disclose, Mark Swain: Nothing to Disclose, Sasha Deutsch-Link: Nothing to Disclose, Bryce Reeve: Nothing to Disclose

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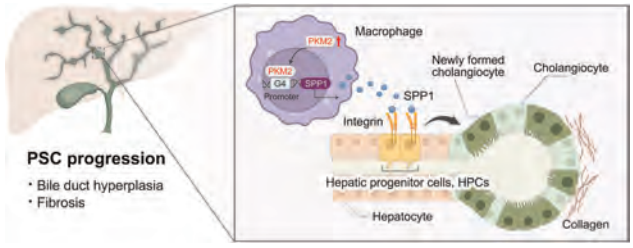
4480 | MACROPHAGE PKM2 ORCHESTRATES SPP1-MEDIATED HEPATIC PROGENITOR DIFFERENTIATION TO EXACERBATE DUCTULAR REACTION IN PRIMARY SCLEROSING CHOLANGITIS

Ping Tao[1] Di Zhang[1] Bo Hu[1] Haoxian Chen[1] Jiamin Wang[1] Zhongyan Du[1] Shan Zhang[1] Yiming Cui[1] Yuchen Lin[1] Hengdong Qu[1] Nan Yao[1] jian Hong[1], [1]Jinan University

Background: Periductal macrophages are implicated in ductular reactions during primary sclerosing cholangitis (PSC), yet the underlying mechanism of macrophage-ductular crosstalk remain undefined. This study aimed to explore the role of pyruvate kinase M2 (PKM2)-dependent macrophage reprogramming in PSC progression. **Methods:** Spatial transcriptomics and single-cell RNA sequencing (scRNA-seq) datasets from human (n = 18) and murine (n = 7) PSC livers were integrated to map macrophage niche landscape, validated by multiplex immunofluorescence. Three PSC models (DDC diet, bile duct ligation, and *Mdr2*$^{-/-}$) were employed in macrophage-specific *Pkm2* knockout mice (*Pkm2*$^{\triangle Mac}$). Mechanistic insights into PKM2-driven macrophage-ductular crosstalk were then elucidated through spatial transcriptomic profiling from *Pkm2*$^{\triangle Mac}$ models, chromatin immunoprecipitation sequencing, and human cholangiocyte organoids. Therapeutic interventions included pharmacological PKM2 inhibition (TEPP-46) and genetic knockdown (AAV8-F4/80-shPKM2) were administrated. **Results:** Integrated analyses of spatial transcriptomics and scRNA-seq revealed PKM2^{+} monocyte-derived macrophages were spatially enriched around reactive bile ducts, correlating with ductular reaction severity in human (R = 0.599, p = 0.040) and murine (R = 0.736, $p < 0.001$) PSC. *Pkm2*$^{\triangle Mac}$ mice showed reduced ductular reaction across three mouse models (DDC: -40.23 ± 0.04%; BDL: -60.12 ± 0.15%; *Mdr2*$^{-/-}$: -52.78 ± 0.20%; all $p < 0.001$ *vs.* controls), accompanied by decreased hepatic fibrosis. Our spatial transcriptomic analysis further demonstrated that periductal PKM2^{+} macrophages underwent functional reprogramming to promote differentiation of adjacent hepatic progenitor cells (HPCs) into cholangiocytes through integrin signaling. PKM2 bound the G-quadruplex in SPP1 promoter to enhance its translation and secretion in macrophages, thereby activating HPCs differentiation to exacerbate ductular reaction. Both pharmacological and genetic PKM2 inhibition effectively suppressed macrophage-driven ductular reaction and PSC progression, with corresponding reductions in hepatic SPP1/integrin signaling. **Conclusion:** PKM2 orchestrated macrophage reprogramming to aggravate ductular reaction in PSC progression via SPP1-mediated HPCs differentiation. Targeting macrophage PKM2 provides a promising therapeutic strategy for PSC.



Disclosures: Ping Tao: Nothing to Disclose, Di Zhang: Nothing to Disclose, Bo Hu: Nothing to Disclose, Haoxian Chen: Nothing to Disclose, Jiamin Wang: Nothing to Disclose, Zhongyan Du: Nothing to Disclose, Shan Zhang: Nothing to Disclose, Yiming Cui: Nothing to Disclose, Yuchen Lin: Nothing to Disclose, Hengdong Qu: Nothing to Disclose, Nan Yao: Nothing to Disclose, jian Hong: Nothing to Disclose

4481 | THE IMPACT OF THE MELD EXCEPTION POINT POLICY CHANGE ON APPLICATION APPROVAL AND WAITLIST OUTCOMES FOR PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

Isaac Benque[1] Melinda Wang[1] Jennifer Lai[1] Michael Li[1], [1]University of California, San Francisco

Background: Patients with primary sclerosing cholangitis (PSC) may be at higher risk of adverse outcomes than is reflected by the MELD score due to bacterial cholangitis. Current Organ Procurement and Transplantation Network guidelines allow centers to apply for exception points if certain sepsis-based criteria are met. In July 2021, these guidelines were modified to be less stringent. We sought to characterize the effect of the policy change on application acceptance and waitlist outcomes. **Methods:** Using the October 2024 Standard Transplant Analysis and Research (STAR) files, adult PSC patients were split into equal 38-month periods pre and post the July 2021 policy change. MELD exception applications for sepsis/cholangitis were defined as those classified as “Other” per the STAR data dictionary. Patients with exception applications for other reasons such as cholangiocarcinoma or hepatocellular

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carcinoma were excluded. If appeals were present, applications were collapsed to reflect the final decision. Logistic regression was used to assess application acceptance in the pre- vs post-policy periods. Competing risks analysis was used to investigate a composite outcome of waitlist dropout (delisting for being too sick) or mortality, with transplant as a competing risk. **Results:** Among 1778 PSC patients listed pre-policy change, 234 (13%) applied for MELD exception points while 173 (10%) patients applied out of the 1685 listed post-policy change. Out of all applications, 135 (58%) were accepted pre and 88 (51%) were accepted post (Fig A). There was no association between the post-policy period and application acceptance (OR 0.78, 95%CI 0.50-1.23, p = 0.3; Fig B). Competing risks regression demonstrated a decreased risk of waitlist dropout or mortality for patients with exception applications submitted post-policy change (HR 0.3, 95% CI 0.11-0.78, p = 0.01) compared to patients with applications submitted pre-policy change. However, the reduced risk of waitlist dropout or mortality post-policy change was re-demonstrated amongst the broader PSC population (HR 0.56, 95%CI 0.45-0.71, p < 0.001). **Conclusion:** The MELD exception policy change for PSC has not increased application submissions or lowered the threshold for application acceptance. Although there were improved pre-transplant outcomes for applicants in the post-policy period, this effect was present amongst all PSC patients. This suggests that time-based effects, such as improved organ availability due to allocation optimization and organ preservation advances, are responsible for the improved outcomes rather than the policy change.

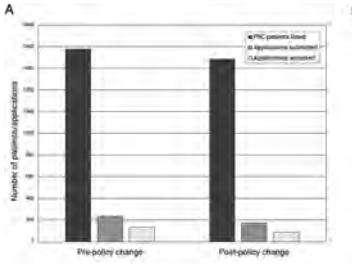

Figure 1. (A) Bar graph with number primary sclerosing cholangitis (PSC) patients listed pre vs post with the corresponding number of MELD exception points applications and number of accepted applications. (B) Multivariable logistic regression analysis of the association between time period and MELD exception point application acceptance.

B

Characteristic	OR[1]	95% CI[1]	p-value
Policy change			
Before	—	—	
After	0.78	0.50, 1.23	0.3
Age	1.02	1.00, 1.03	0.056
Gender			
Female	—	—	
Male	0.99	0.63, 1.57	>0.9
Race/Ethnicity			
Non-white	—	—	
White	1.11	0.62, 1.87	0.7
Insurance			
Other	—	—	
Medicaid	0.81	0.34, 1.78	0.6
Karnofsky performance status			
<40%	—	—	
>40%	0.39	0.19, 0.79	0.011
MELD	0.97	0.94, 1.00	0.081
ABO			
A	—	—	
AB	1.53	0.47, 5.37	0.5
B	0.87	0.40, 1.86	0.7
O	1.53	0.94, 2.49	0.085
IBD			
no IBD	—	—	
IBD	1.10	0.69, 1.77	0.7

[1] OR = Odds Ratio, CI = Confidence Interval

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4482 | EPIDEMIOLOGY, TREATMENT RESPONSE, AND GENETIC CHARACTERISTICS OF AUTOIMMUNE LIVER DISEASES: A RETROSPECTIVE AND PROSPECTIVE COHORT STUDY

Young Chang[1], [1]Soonchunhyang University

Background: Autoimmune liver diseases, including autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC), exhibit diverse clinical presentations and treatment responses. This study aimed to establish retrospective and prospective cohorts to analyze epidemiology, treatment response, and genetic differences associated with disease severity. **Methods:** A retrospective cohort included patients diagnosed with AIH or PBC between January 2005 and December 2023, while a prospective cohort was established from January 2021. Clinical characteristics, serological markers, liver biopsy findings, and treatment responses were analyzed. RNA sequencing was performed on blood samples to evaluate gene expression differences based on fibrosis stage and disease activity. **Results:** The retrospective cohort comprised 266 AIH and 40 PBC patients. AIH patients had a mean diagnosis age of 57 years, while PBC patients were diagnosed at 58.5 years, with over 80% female prevalence in both groups. AIH showed significantly higher IgG levels (1758 mg/dL) compared to PBC (1506.5 mg/dL). Antinuclear antibody positivity exceeded 90% in both groups, while anti-mitochondrial antibody was positive in 81.6% of PBC cases. After 12 months, biochemical indicators improved significantly in both groups. Steroid treatment in AIH significantly reduced immunoglobulin G, prothrombin time, and alkaline phosphatase levels. RNA sequencing revealed significant gene expression differences in AIH patients based on fibrosis severity, particularly in pathways related to cellular detoxification, response to toxic substances, steroid hormone signaling, and inflammatory regulation. In PBC, disease activity stage was associated with alterations in immune effector regulation, particularly in pathways related to natural killer cell-mediated immunity. **Conclusion:** This study highlights distinct clinical and genetic characteristics in AIH and PBC. Host factors, particularly immune-related pathways, play a crucial role in disease progression, emphasizing the need for individualized treatment approaches.

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4483 | CLINICAL CHARACTERISTICS, TREATMENT PATTERNS, AND OUTCOMES AMONG AUTOIMMUNE HEPATITIS PATIENTS WITH LATER HOSPITALIZATIONS

Chandni Kapoor[1] Sheng-Fang Jiang[2] Nirmala Ramalingam[1] Sreepriya Balasubramanian[3] Kavita Radhakrishnan[4], [1]Kaiser Permanente Oakland Medical Center, [2]Kaiser Permanente Northern California Division of Research, [3]Kaiser Permanente Roseville Medical Center, [4]The Permanente Medical Group

Background: There are limited data on risk factors and outcomes for autoimmune hepatitis (AIH) hospitalizations. We recently observed that nearly 20% of adults with AIH had a liver-related hospitalization initially or later during follow-up. Among those with liver-related hospitalization, 43% were initially diagnosed outpatient and later had hospitalization >3 months after diagnosis. Those with later hospitalization were a higher-risk subgroup more likely to present with cirrhosis at AIH diagnosis and experience higher mortality. To identify potential areas for improving clinical outcomes, this study aims to characterize the indications for later hospitalization as well as both pre-hospitalization treatment patterns and post-hospitalization treatment modifications in this high-risk population. **Methods:** Adults aged ≥18 years in an integrated healthcare system with newly diagnosed AIH between 2010-2021 were identified via ICD codes (ICD-9: 571.42; ICD-10: K75.4) and confirmed with lab data and/or liver biopsy. Hospitalizations for AIH or liver decompensation (primary discharge diagnosis) were included if the hospitalization occurred >3 months after diagnosis. Admission indication and AIH treatment prior to hospitalization and at discharge were collected using electronic health record data. **Results:** Of 997 AIH patients, 169 (20%) underwent liver-related hospitalizations of whom 72 (43%) had late hospitalizations (median 866 days from AIH diagnosis). Among the 72 patients (median age 55 years), 81% were female, 14% Asian, 8% Black, 36% Hispanic, 35% White, and 21% were non-English speaking. 21% had overlap with PBC or PSC and 53% had cirrhosis at AIH diagnosis. The most common admission indications were abnormal liver labs, altered mental status, and other decompensated liver disease (ascites, bleeding). Prior to hospitalization, 46% were not on AIH treatment. Of the 39 on treatment, 21% were on steroid monotherapy and 79% were on maintenance +/- steroid therapy. Most patients (71%) had no changes to their AIH treatment regimen. Of those with treatment modification (n=21), 67% had additive modifications primarily addition or increased dosing of steroids while 33% had medications decreased. Long-term, 38% were readmitted, 20% transplanted, and 42% died. **Conclusion:** AIH patients with late hospitalizations are a high-risk subgroup with high rates of cirrhosis at diagnosis and death. These hospitalizations are largely due to liver decompensation. Nearly half of patients were not on AIH therapy prior to hospitalization and three-quarters had no changes made, suggesting their liver disease was deemed too advanced to benefit from therapy. These findings indicate a need for earlier diagnosis in this high-risk subgroup, with the goal of treatment initiation prior to development of cirrhosis to improve outcomes.

Table: AIH Patient Characteristics with Later Hospitalizations

	Later Hospitalizations N=72
Age Group, n (%)	
18-34 y	8 (11.1)
35-54 y	26 (36.1)
55-74 y	32 (44.4)
75+ y	6 (8.3)
Sex, n (%)	
Female	58 (80.6)
Race/ethnicity, n (%)	
Asian	10 (13.9)
Black	6 (8.3)
Hispanic	26 (36.1)
Other	5 (6.9)
White	25 (34.7)
Language Spoken, n (%)	
English	57 (79.2)
Non-English	15 (20.8)
PBC overlap, n (%)	
Yes	10 (13.9)
PSC overlap, n (%)	
Yes	5 (6.9)
Cirrhosis, n (%)	
Yes	38 (52.8)
Hepatic Encephalopathy, n (%)	
Yes	13 (18.1)
Ascites, n (%)	
Yes	16 (22.2)
Pre-hospitalization Treatment, n (%)	
None	33 (45.8)
Prednisone/Budesonide	8 (11.1)
Azathioprine	14 (19.4)
6-MP	4 (5.6)
Prednisone + Azathioprine	8 (11.1)
Prednisone + 6-MP	1 (1.4)
Prednisone + Cellcept	3 (4.2)
Azathioprine + Cellcept	1 (1.4)

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4484 | HETEROGENEITY IN LIVER FIBRO-INFLAMMATION ASSESSED BY MRI IS ASSOCIATED WITH ACTIVE DISEASE IN PATIENTS WITH AUTOIMMUNE HEPATITIS

Maciej Janik[1] Magdalena Jaroszek[1] Kamil Janowski[2] CARLOS FERREIRA[3] Sylwia Chełstowska[2] Paulina Chodnicka[4] Elzbieta Jurkiewicz[4] Joanna Raszeja-

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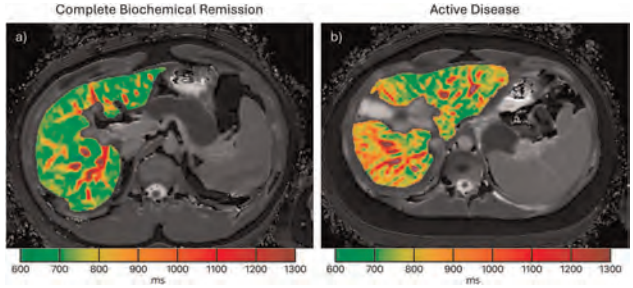
Wyszomirska[1] Piotr Milkiewicz[1] Anneli Andersson[3] Piotr Socha[4], [1]Medical University of Warsaw, [2]The Children's Memorial Health Institute, [3]Perspectum Ltd, [4]The Children's Memorial Health Institute

Background: Signs of portal inflammation and fibrosis are hallmarks of autoimmune hepatitis (AIH), and a heterogeneity in disease activity across the parenchyma has been observed by imaging. The main objective of this study was to assess the heterogeneity of fibro-inflammation in AIH by non-invasive multiparametric magnetic resonance imaging (mpMRI) and its link with treatment response. **Methods:** Adults with AIH diagnosed in paediatric service were prospectively enrolled and underwent routine blood test, abdominal MRI and liver stiffness measurement (LSM, by Fibroscan, Echosens) at baseline during the transition of care. MRI was processed by LiverMultiScan (Perspectum Ltd, Oxford) to generate corrected T1 (cT1) maps of the liver using a semiautomatic method. Heterogeneity was measured as the interquartile range (IQR) of the pixels in the cT1 map. Patients were followed up over 18 months as part of the standard of care. Complete biochemical response (CBR) was defined as AST, ALT and immunoglobulin G (IgG) within normal limits, and active disease was defined as absence of CBR. **Results:** Seventy-one young adults with AIH (55% female; median age 21 ± 4 years), 44% with CBR at baseline, were included. The median age of diagnosis was 14.1 ± 4 years, and 28% presented as AIH with primary sclerosing cholangitis (AIH-PSC) and were excluded from this analysis. cT1 IQR correlated with LSM ($Rs = 0.47$, $p < 0.05$) and platelets ($Rs = -0.31$, $p < 0.05$), but not with other biochemical markers. Patients with CBR at baseline had lower cT1 IQR (103ms ± 25ms) than those in active disease (cT1 IQR: 121ms ± 32ms; $p < 0.05$). For cT1 IQR to distinguish active disease from CBR, the AUC was 0.72 (0.55-0.88, 95% CI) with sensitivity 0.80 at 104ms. cT1 IQR was lower (100ms ± 24ms) in those with CBR throughout the study, compared to active disease throughout (125ms ± 35ms; $p < 0.05$, Figure 1) and to those transitioning into active disease during follow-up, although not significantly (126ms; $p = 0.079$). cT1 IQR was lower in those who transitioned into CBR at 6 or 18 months follow-up (not significant at 12 months), than in those who remained active ($p < 0.05$). **Conclusion:** The heterogeneity in fibro-inflammation across the liver parenchyma (cT1 IQR) is associated with biochemical disease activity in young adults with AIH, and could be an early signal of transitions of disease activity. The mpMRI-derived metric show promise for utility in AIH monitoring and patient management.



Disclosures: Maciej Janik: Nothing to Disclose, Magdalena Jaroszek: Nothing to Disclose, Kamil Janowski: Nothing to Disclose, CARLOS FERREIRA: Perspectum: Employee, Sylwia Chełstowska: Nothing to Disclose, Paulina Chodnicka: Nothing to Disclose, Elzbieta Jurkiewicz: Nothing to Disclose, Joanna Raszeja-Wyszomirska: Nothing to Disclose, Piotr Milkiewicz: Nothing to Disclose, Anneli Andersson: Nothing to Disclose, Piotr Socha: Nothing to Disclose

4485 | SYSTEMIC METABOLIC REMODELING AND ABNORMAL MITOCHONDRIAL SIGNALING IN PRIMARY BILIARY CHOLANGITIS

Ning Sun[1] Hussain Syed[1] Filip wysokinski[2] Gopinath Sutendra[1] Evangelos Michelakis[1] Andrew Mason[1], [1]University of Alberta, [2]University of Calgary

Background: Patients with primary biliary cholangitis (PBC) produce anti-mitochondrial antibodies (AMA) targeting pyruvate dehydrogenase complex-E2 subunit (PDC-E2) that is overexpressed on the cell surface of cholangiocytes and in perihepatic lymph nodes. A hypothesis of mitochondrial dysfunction in PBC is supported by an increased number of dysmorphic mitochondria in cholangiocytes, elevated serum levels of mitochondrial Mn-superoxide dismutase, and reduced recovery from exercise with elevated lactate in muscles. We aimed to investigate the presence of metabolic remodelling and mitochondrial signalling in cholangiocytes and peripheral blood from patients with PBC. **Methods:** Oxidative phosphorylation (OXPHOS) was assessed in PBC and relevant control primary cholangiocytes in culture and peripheral blood mononuclear cells using isotopic glucose tracing and the seahorse assay. Proteomics and RNA-seq were used to profile changes in metabolic pathways, the TMRM mitochondrial dye was used to study mitochondrial membrane potential ($D\psi_m$), and qPCR was used to quantify mitochondrial DNA. **Results:** PBC cholangiocytes expressing increased PDC-E2 were found to preferentially use aerobic glycolysis as confirmed by proteomic/transcriptomic profiling, immunochemistry,

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and functional studies demonstrating increased lactate production. PBC cholangiocytes expressed hyperpolarized mitochondria with increased $D\psi_m$, as well as an elevated mitochondrial DNA copy number consistent with compensatory mitochondrial biogenesis. Confocal microscopy of paraffin embedded liver samples revealed PBC cholangiocytes with activation of nuclear HIF1alpha signaling as a potential proximal factor in metabolic remodelling. Analysis of PBC whole blood revealed downregulated nuclear-encoded OXPHOS gene expression versus healthy subjects, whereas mitochondrial-encoded transcripts were increased. An increased frequency of PBC peripheral blood mononuclear cells expressed overexpression of the mitochondrial autoantigen PDC-E2, hyperpolarized mitochondria with increased $D\psi_m$, and elevated mitochondrial DNA suggesting mitochondrial biogenesis. **Conclusion:** Cholangiocytes and PBMC from PBC patients exhibited abnormal mitochondrial signalling linked with aberrant PDC-E2 expression. These findings support the hypothesis that AMA production may result from metabolic remodelling that is systemic in nature as previously reported with the overexpression of mitochondrial autoantigens in PBC lymph nodes. Further studies are merited to better understand how the metabolic remodelling impacts the development of delayed recovery from exercise, fatigue and cognitive changes in PBC.

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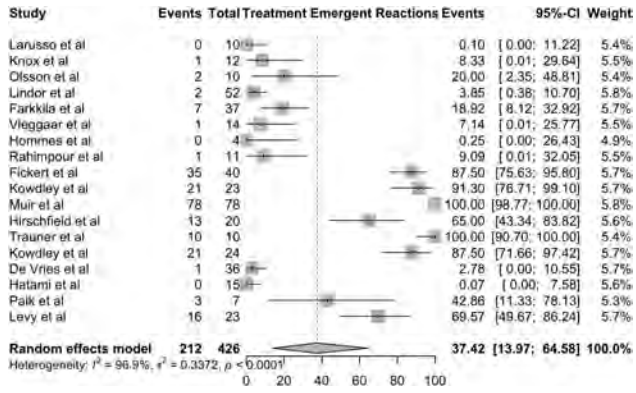
4486 | EFFICACY AND SAFETY OUTCOMES IN PLACEBO-TREATED PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Harsimran Kalsi[1] Nikita Shah[1] Nihal Khan[2] Aalam Sohal[3] Kris Kowdley[3], [1]University of Central Florida, [2]Advent Health Orlando, [3]Liver Institute Northwest

Background: Primary sclerosing cholangitis (PSC) is a rare, progressive cholestatic liver disease with no approved medical therapies, leaving liver transplantation as the only definitive treatment. Clinical trials for PSC face challenges due to the disease's heterogeneity, small patient populations, and variable outcome measures, often complicated by placebo effects influencing subjective and biochemical endpoints. Additionally, understanding safety profiles in placebo arms is critical to distinguish disease-related complications from treatment effects. This meta-analysis aims to evaluate the magnitude of the placebo effect and safety outcomes in patients with PSC randomized clinical trials (RCTs). **Methods:** A systematic search of PubMed, Ovid, Cochrane, and clinicaltrials.gov was conducted to identify RCTs that included placebo arms in adult patients with PSC. Data were extracted for demographics, Alkaline Phosphatase (ALP) reduction, and adverse events. Pooled outcomes were calculated using a random-effects model. Heterogeneity was assessed using the I^2 statistic. **Results:** A total of 22 RCTs (N = 707) were included in the analysis. The mean age across studies was 44.6 years. Gender was reported in 21 studies, with 317 of 539 participants (58.8%) being male. Inflammatory bowel disease (IBD) was present in 345 of 497 patients (69.4%). Follow-up durations ranged from 4 to 260 weeks. UDCA was administered to 201 patients in the placebo group, representing 36.8% of participants. The pooled rate of ALP reduction $\geq$20% among placebo-treated patients was 8.1% [95% CI: 2.1 - 17.5]. In terms of safety, treatment-emergent adverse events occurred in 37.4% [95% CI: 13.9 - 64.6], and serious adverse events in 4.4% [95% CI: 1.7 - 8.2]. (Figure 1) Treatment discontinuation due to adverse events was reported in 3.1% [95% CI: 1.2-5.7] of patients. **Conclusion:** In placebo-treated patients with PSC, spontaneous ALP reduction $\geq$20% was uncommon, while a large majority experienced treatment-emergent adverse events. These findings establish important baseline benchmarks for interpreting efficacy and safety outcomes in future therapeutic trials for PSC.



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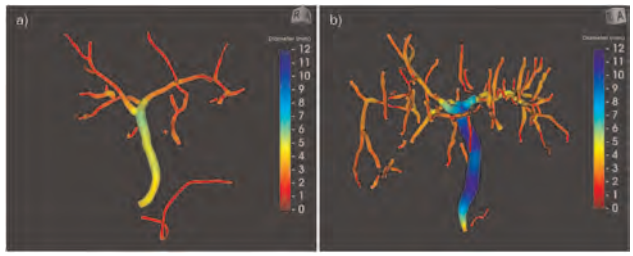
4487 | CHARACTERIZATION OF YOUNG ADULTS WITH AUTOIMMUNE HEPATITIS AND FEATURES OF PRIMARY SCLEROSING CHOLANGITIS USING MULTIPARAMETRIC MRI

Maciej Janik[1] Magdalena Jaroszek[1] Kamil Janowski[2] CARLOS FERREIRA[3] Sylwia Chełstowska[2] Paulina Chodnicka[2] Elzbieta Jurkiewicz[2] Joanna Raszeja-Wyszomirska[1] Piotr Milkiewicz[1] Anneli Andersson[4] Piotr Socha[5], [1]Medical University of Warsaw, [2]The Children's Memorial Health Institute, [3]Perspectum Ltd, [4]Perspectum Ltd, [5]The Children's Memorial Health Institute

Background: Young adults with autoimmune hepatits (AIH), despite typical features in serology and histology, sometimes present with signs of primary sclerosing cholangitis (PSC) in cholangiography-MRI (MRCP). The main objective of this study was to assess the heterogeneity of fibro-inflammation by multiparametric magnetic resonance imaging (mpMRI) and quantitative MRCP to assess biliary abnormalities in patients with AIH at the transition to adult service. **Methods:** Adults with AIH diagnosed in paediatric service were prospectively enrolled and underwent routine blood test, abdominal MRI and liver stiffness measurement (LSM, by Fibroscan, Echosens) at baseline during the transition of care. MRI was processed by LiverMultiScan (Perspectum Ltd, Oxford) to generate corrected T1 (cT1) maps of the liver using a semiautomatic method. Heterogeneity was measured as the interquartile range (IQR) of the pixels in the cT1 map. Quantitative MRCP was generated by MRCP+ (Perspectum Ltd, Oxford). Patients were followed up over 18 months as part of the standard of care. Complete biochemical remission (CBR) was defined as AST, ALT and immunoglobulin G (IgG) within normal limits. **Results:** Seventy-one young adults with AIH (55% female; median age 21 ± 4 years), 44% of them in CBR at baseline, were included. The median age of diagnosis was 14.1 ± 4 years, and 28% of patients presented AIH-PSC variant. Patients with AIH-PSC had higher cT1 IQR, ALT, AST, GGTP and ALP, and lower platelets ($132ms \pm 44$, $95IU/L \pm 93$, $67IU/L \pm 50$, $249IU/L \pm 292$ and $245IU/L \pm 229$, respectively) than AIH patients ($112ms \pm 30$,$54IU/L \pm 85$, $41IU/L \pm 40$, $56IU/L \pm 74$ and $101IU/L \pm 73$) (all $p < 0.05$). Quantitative biliary metrics showed a larger tree in AIH-PSC patients compared to pure AIH (biliary tree volume $9ml \pm 5$ vs. $6ml \pm 5$ and number of ducts 62 ± 34 vs. 45 ± 38, Figure 1). In the pure AIH, cT1 IQR correlated with LSM ($Rs = 0.47$, $p < 0.05$) and platelets ($Rs = -0.31$, $p < 0.05$), but not with other biochemical markers. LSM correlated with inflammatory markers ALT ($Rs = 0.65$), AST ($Rs = 0.62$) and IgG ($Rs = 0.47$). In the AIH-PSC, cT1 IQR correlated with platelets ($Rs = -0.23$), FIB4 ($Rs = -0.31$) and number of dilatations ($Rs = 0.27$, all $p < 0.05$). **Conclusion:** Heterogeneity in fibro-inflammation across the liver parenchyma (cT1 IQR), elevated biliary tree volume and number of ducts are associated with AIH-PSC phenotype. The mpMRI-derived metrics of the parenchyma and biliary tree show promise for utility in AIH disease differentiation and patient management.



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4488 | CORTICOSTEROID USE AND METABOLIC COMPLICATIONS IN AUTOIMMUNE HEPATITIS: INSIGHTS FROM A MULTINATIONAL PATIENT SURVEY

Libby Bell[1] Kelsey Green[1] Nadia Blessing[1] Craig Lammert[1], [1]Indiana University School of Medicine

Background: Although corticosteroid (CS)-sparing agents are the standard treatment for autoimmune hepatitis (AIH), CS use is commonly observed in clinical practice. Chronic CS therapy, even at low doses, is associated with significant adverse effects. This study assessed CS use patterns and related complications in a diverse multinational AIH cohort. **Methods:** Over a two-week period, members of the Autoimmune Hepatitis Association completed a 17-item online questionnaire regarding CS use throughout their disease course. Eligibility criteria included age ≥ 18 years and physician-confirmed AIH diagnosis. Significant CS use was defined as daily doses of ≥ 5 mg prednis(ol)one or ≥ 3 mg budesonide. Long-term CS use was defined as significant CS use exceeding 90 days per year, based on prior literature. **Results:** A total of 592 AIH patients participated (mean age 55.5 $\pm$ 15.8 years; mean disease duration 6.5 $\pm$ 4 years). The cohort was predominantly female (89.2%) and White (90.4%). At time of survey completion, 36.9% were receiving CS

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treatment (mean daily doses: prednis(ol)one 8.8 ± 7.6 mg; budesonide 4.6 ± 2.9 mg). Among 557 patients treated with CS at diagnosis, 81.4% received prednis(ol)one (mean starting dose 38.3 ± 19 mg) and 10.8% budesonide (mean 4.8 ± 2.8 mg). Within six months of diagnosis, 47.9% reported at least one new metabolic complication: weight gain >5% (40.6%), hypertension (8.6%), dyslipidemia (7%), and diabetes mellitus (4.8%). No significant differences in complications were observed between CS medication type.

Long-term CS use was reported by 68.5% of patients with at least one year of disease. Those with long-term CS use were diagnosed at a younger age (47.6 ± 17.2 vs. 52.9 ± 15.6 years, $p < 0.001$) and had increased frequency of osteoporosis, type 2 diabetes, hypertension, and significant weight gain (all $p \leq 0.05$) compared to patients without long-term CS exposure. Multivariable logistic regression adjusting for sex, race, and age at diagnosis showed long-term CS use was associated with increased odds of osteoporosis (OR 2.1; 95% CI 1.3–3.3; $p = 0.007$) and hypertension (OR 2.8; 95% CI 1.3–6.4; $p = 0.01$). **Conclusion:** Metabolic complications related to CS use are common among AIH patients both near diagnosis and during long-term follow-up. Despite the availability of steroid-sparing therapies, chronic CS use remains widespread across disease durations, highlighting an urgent need for improved steroid-sparing treatments.

Table 1: Demographic and Medical Comorbidities according to Long-Term CS Use in AIH Patients

	Long-Term CS Use (n=151)	Never Long-Term CS Use (n=389)	p-value
Age at diagnosis, mean (SD) (yrs)	47.6 (17.2)	52.9 (15.6)	**<0.001**
Duration of follow-up, mean (SD) (yrs)	7.6 (7.5)	5.8 (8.6)	**0.02**
White, %	93.7%	92.2%	0.31
Non-Hispanic, %	81.4%	77.1%	0.71
Female, %	88.7%	92.4%	0.19
Osteoporosis, %	29.2%	21.2%	**0.05**
DM2, %	10%	4.1%	**0.02**
HTN, %	19.2%	10.6%	**0.01**
Dyslipidemia, %	16.8%	17.7%	0.8
Cataracts, %	17.3%	16.5%	0.82
Weight gain >5%, %	45.7%	28.2%	**<0.001**

SD: standard deviation, yrs: years, DM2: diabetes mellitus type 2, HTN: hypertension

Disclosures: Libby Bell: Nothing to Disclose, Kelsey Green: Nothing to Disclose, Nadia Blessing: Nothing to Disclose, Craig Lammert: Eli Lilly: Consultant, Kezar Life Sciences: Consultant, Amgen: Consultant, Autoimmune Hepatitis Association: Consultant, RegCell: Consultant

4489 | PREDICTORS OF DEATH IN PATIENTS WITH SARCOIDOSIS AND ELEVATED LIVER ENZYMES

Neil Garg[1] Muhammad Saad Faisal[2] Syed-Mohammed Jafri[2], [1]Wayne State University School of Medicine, [2]Henry Ford Health System

Background: Sarcoidosis is a multisystem granulomatous disease that can involve the liver. While hepatic sarcoidosis is often subclinical, cholestatic liver pattern may be the first indication of hepatic involvement. However, the prognostic significance of elevated liver enzymes in patients with sarcoidosis remains poorly defined. This study aimed to evaluate the incidence and predictors of mortality in patients with sarcoidosis and elevated liver enzymes. **Methods:** We conducted a retrospective cohort study of patients with sarcoidosis daignosed between 1990 and 2025. Inclusion criteria were age 18 years or older and elevated liver enzymes (AST or ALT > 60 IU/L). Patients with a history of solid organ transplantation were excluded. They were followed up to death or May 10, 2025. Kaplan Meier survival analysis was performed to assess the cumulative probability of survival. We used logistic regression backward selection to assess the odds of being alive or dead at the end of follow up. The model was adjusted for cirrhosis, peak alkaline phosphate (ALP), peak total bilirubin, lowest albumin, and treatment for sarcoidosis. **Results:** Inclusion criteria were met by 101 patients. The median age was 61 years (Q1:51, Q3: 69), 61% were males, 67% were Black, 33% were White, 67.3% had multiorgan sarcoidosis involvement and 10% had biopsy proven hepatic sarcoidosis. While 27% were never treated, 31% were and 42% were on treatment at last follow-up. Nineteen percent of patients had cirrhosis, 18% had alcohol use disorder, and only 26% were seen by hepatology. Higher proportion of patients with cirrhosis were seen by hepatology compared to those who did not have cirrhosis (63.2% vs. 21.3%, $p < 0.001$). The median peak ALP and total bilirubin was 123.5 IU/L (Q1:86, Q3: 277) and 1.4 mg/dL (Q1: 0.9, Q3:2.2) respectively, and the median lowest albumin was 3.3 g/dL (Q1:2.7, Q3: 2.6). There were 18 deaths during the study period. The unadjusted 1, 3, 5-year survival rate was 92.8%, 90.4% and 88.8% (Figure 1). Total bilirubin and serum albumin were associated with increased odds of death after adjusting for cirrhosis, peak ALP, and treatment for sarcoidosis. Every unit increase in total bilirubin was associated with 45% lower odds of survival (OR = 0.55[0.35-0.85], $p = 0.0070$). Every unit increase of albumin was associated with 2.9 folds higher odds of survival (OR = 2.9 [1.10-7.68], $p = 0.03$). The model correctly identified no death in 74 out of 76 (97.4%) with an overall prediction accuracy of 86.2%. **Conclusion:** The survival in patients with sarcoidosis and elevated liver enzymes is favorable. Only 19% of the patients with sarcoidosis and elevated liver enzymes had cirrhosis. High total bilirubin and low albumin predicted mortality independent of the presence of cirrhosis. Early hepatology consultation and use of these factors to prognosticate survival may improve outcomes in patients with sarcoidosis.

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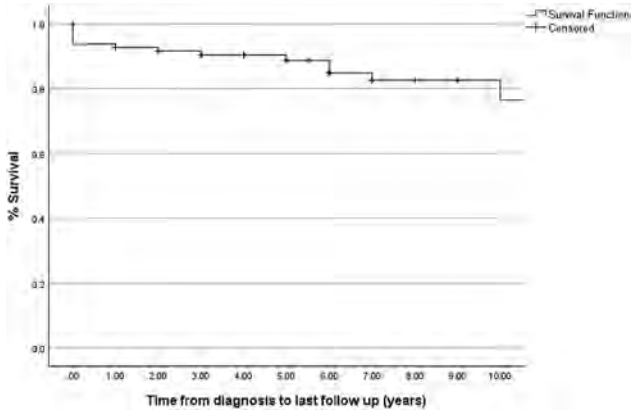

Disclosures: Neil Garg: Nothing to Disclose, Muhammad Saad Faisal: Nothing to Disclose, Syed-Mohammed Jafri: Takeda: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ironwood: Advisor, Intercept: Speaking and Teaching

4490 | COMPARATIVE ANALYSIS OF BIOCHEMICAL RESPONSE CRITERIA IN PREDICTING CLINICAL OUTCOMES IN PRIMARY BILIARY CHOLANGITIS PATIENTS WITH CIRRHOSIS

Christopher Dorizas[1] Maham Ghani[1] Michael Attanasi[1] Jade Pace[1] Bryana Belin[1] Islam Shahidul[1] Sanjaya Satapathy[1], [1]Zucker School of Medicine at Hofstra/ Northwell

Background: Primary biliary cholangitis (PBC) patients are typically treated with ursodeoxycholic acid (UDCA), with treatment response evaluated using various biochemical response (BR) criteria. This study aimed to compare the predictive performance of four BR criteria (Barcelona, Paris I, Paris II, and Rotterdam) for hepatic decompensation events in PBC patients with cirrhosis. **Methods:** In this retrospective study of 84 cirrhotic PBC patients on UDCA therapy, biochemical parameters were tracked over 12 months to determine BR using all four criteria. Hepatic decompensation events were monitored for the subsequent 12 months. The predictive performance of each criterion was analyzed using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). **Results:** Paris I criteria showed the highest overall accuracy (72.4%) with good sensitivity (74.6%) and PPV (90.4%) (OR 4.70, 95% CI: 1.41–15.60; p = 0.037). Paris II demonstrated excellent specificity (84.6%) and PPV (94.6%) (OR: 6.88, 95% CI: 1.31-36.17, p = 0.013). Rotterdam criteria, though limited to 33 evaluable cases, showed perfect specificity and PPV (100%) (OR: 25.07, 95% CI: 1.37-458.23, p = 0.002). Barcelona criteria performed poorly with non-significant results. All criteria demonstrated poor NPVs (17.8-44.4%). **Conclusion:** Paris I and Paris II criteria showed complementary strengths in predicting clinical outcomes, while Rotterdam criteria, despite promising statistics, had limited practical applicability. These findings suggest that a combined application of Paris I and Paris II criteria may be optimal for clinical practice, with Rotterdam criteria considered when applicable.

Table 1: Comparative Analysis of Biochemical Response Criteria for Predicting Decompensation in Primary Biliary Cholangitis with Cirrhosis

Criteria (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Odds Ratio	95% CI	p-value
Barcelona (67)	33.9	72.7	86.4	17.8	40.3	1.37	0.32–5.92	0.722
Paris I (76)	74.6	61.5	90.4	33.3	72.4	4.70	1.41–15.60	0.037
Paris II (76)	55.6	84.6	94.6	28.2	60.5	6.88	1.31–36.17	0.013
Rotterdam (33)	60.0	100.0	100.0	44.4	69.7	25.07	1.37–458.23	0.002

Abbreviations: PPV = Positive Predictive Value; NPV = Negative Predictive Value; CI = Confidence Interval

Disclosures: Christopher Dorizas: Nothing to Disclose, Maham Ghani: Nothing to Disclose, Michael Attanasi: Nothing to Disclose, Jade Pace: Nothing to Disclose, Bryana Belin: Nothing to Disclose, Nothing to Disclose, Islam Shahidul: Nothing to Disclose, Sanjaya Satapathy: Gilead Sciences: Grant/Research Support, Durect Pharma: Grant/Research Support, Fibronostics: Grant/Research Support, Novartis: Grant/Research Support, Zydus Pharma: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Intercept Pharma: Grant/Research Support, AKERO: Grant/Research Support

4491 | ORAL VANCOMYCIN IN ADOLESCENTS AND ADULTS WITH PSC-IBD: A SINGLE-CENTER STUDY DEMONSTRATING SAFETY AND CLINICAL BENEFIT

Judah Kupferman[1] Kathryn Czepiel[2] Abhishek Dimopoulos-Verma[1] Chiraag Kulkarni[1] Sidhartha Sinha[1] Leina Alrabadi[2] Aparna Goel[1], [1]Stanford University Medical Center, [2]Stanford/Lucile Packard Childrens Hospital

Background: Nearly 70-80% of people with primary sclerosing cholangitis (PSC) have inflammatory bowel disease (IBD). The pathophysiology of PSC involves immune dysregulation and gut dysbiosis. Oral vancomycin therapy (OVT) has demonstrated efficacy in inducing IBD remission and improving liver biochemistries in PSC-IBD. We aimed to evaluate the safety and effectiveness of OVT in the management of PSC-IBD. **Methods:** This is a single-center, retrospective study of patients 12 years and older with PSC-IBD who were treated with OVT for at least

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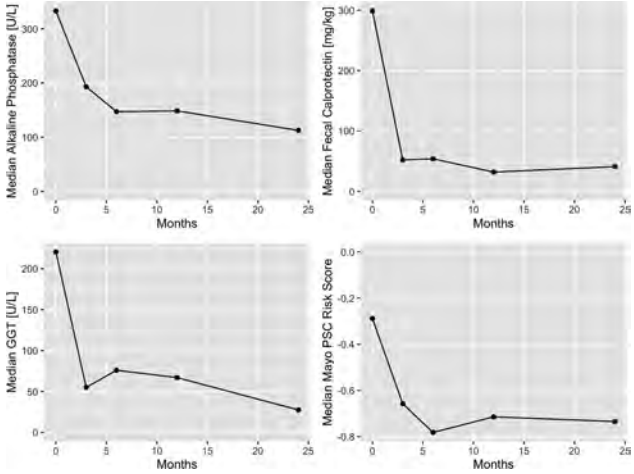
3 months from 2010-2024. Inclusion criteria were age 12 or older at time of PSC diagnosis. Patients were followed for up to 24 months from start of OVT or until discontinuation of therapy, whichever came first. Patients who received liver transplantation were excluded. Changes in alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), Mayo PSC Risk Score, fecal calprotectin, and Mayo Endoscopic Score (MES) were evaluated during the study period. **Results:** Of 24 patients included, 54.2% were men and 9 (37.5%) were on ursodeoxycholic acid. Most patients (54.7%) were aged 12-17 years, 9 (37.5%) were 18-39 years, and 2 (8.3%) were 40+ years. Fourteen (58.3%) received OVT for >2 years, 9 have ongoing treatment for <2 years, and 1 discontinued OVT after 6 months due to lack of improvement in liver biochemistries. Sixteen (66.7%) had ulcerative colitis, 5 (20.8%) had Crohn's disease, and 3 (12.5%) had indeterminate IBD. While on OVT, 33.3% received treatment with mesalamine, 16.7% with biologics, 20.8% with steroids, and 4.2% with small molecules. Median OVT dosage was 1500 mg/day. After 12 months of OVT in 23 patients, median change in ALP was -86 U/L (IQR 272 U/L), GGT -128 U/L (IQR 207 U/L), and Mayo PSC Risk Score -0.35 (IQR 0.69). Total bilirubin and albumin remained stable during the study period. Median fecal calprotectin reduced by 343 mg/kg (IQR 350 mg/kg) after 24 months. Of 11 patients with follow-up colonoscopy at 1-2 years, 9 showed stable or improved MES on OVT and no additional IBD treatment was initiated. None developed infections with vancomycin-resistant organisms. **Conclusion:** In a single-center experience spanning adolescents and adults with PSC-IBD, 23 patients (95.8%) demonstrated improved liver biochemistries, Mayo PSC Risk score, and fecal calprotectin while receiving OVT. There were no vancomycin-resistant infections during the study period. This study emphasizes the potential of OVT as a treatment for PSC-IBD and highlights the importance of investigating its underlying mechanisms and long-term efficacy. Future research will involve comparing colonic and hepatic outcomes between a larger cohort of PSC-IBD patients and a control group.



Disclosures: Judah Kupferman: Nothing to Disclose, Kathryn Czepiel: Nothing to Disclose, Abhishek Dimopoulos-Verma: Nothing to Disclose, Chiraag Kulkarni: Nothing to Disclose, Sidhartha Sinha: Intact Therapeutics: Stock – privately held company, Leina Alrabadi: Nothing to Disclose, Aparna Goel: Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant, Gilead Sciences: Consultant, Kezar Life Sciences: Consultant, Ipsen Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Amgen: Consultant

4492 | EPIDEMIOLOGY AND OUTCOMES OF PRIMARY SCLEROSING CHOLANGITIS IN AN INTEGRATED HEALTHCARE SYSTEM

Ryan Murphy[1] Mehrnaz Siavoshi[2] Nirmala Ramalingam[2] Benjamin Hassid[2], [1]Kaiser Permanente Oakland Medical Center, [2]Kaiser Permanente Medical Center

Background: Primary Sclerosing Cholangitis (PSC) is a chronic, progressive liver disease characterized by inflammation and fibrosis of the bile ducts, leading to cirrhosis, liver failure, and increased cancer risk. Despite its rarity, PSC presents clinical challenges due to its association with inflammatory bowel disease (IBD), limited treatment options, and variable progression. In the US, data on PSC prevalence are limited, and demographic variations are poorly understood. This study examines the prevalence, demographic, and clinical characteristics of adults with PSC in Kaiser Permanente Northern California (KPNC). **Methods:** We conducted a retrospective study of KPNC members aged ≥ 18 years with PSC diagnosis during 2010-2024 in electronic health records using internal diagnosis codes and ICD-10 K83.01 (available since 2018); PSC cases were confirmed by chart review. Demographic data, body mass index, and smoking were extracted at diagnosis. Outcomes included IBD, cirrhosis, liver transplant, mortality, and PSC-related cancers. PSC diagnoses were ascertained from 2010-2024 and represented as an annual diagnosis capture rate using population denominators (Figure 1). Prevalence was estimated based on adults with PSC who were members in 2019 (and 2019 population denominators), with age-sex-adjusted prevalence by race and ethnicity derived from logistic regression. Statistical comparisons were made using Kruskal-Wallis and Wald Chi-Square tests. **Results:** We identified 469 adults with PSC (average age 49.6 years, 57.6% male and 58.8% non-Hispanic White, 9.4% Black, 12.8% Hispanic, 14.3% Asian and 4.6% other/unknown race). One-fifth had obesity (21.6%) and 4.1% and 20.7% were current or

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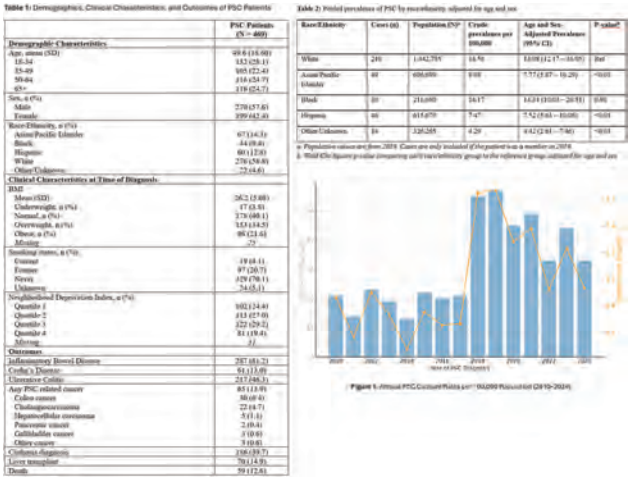
former smokers, respectively. Annual diagnoses of PSC increased from 0.65–0.75 per 100,000 before 2018 to 1.65–1.67 from 2018–2019, coinciding with the new ICD-10 code for PSC. The prevalence of PSC was 10.5 per 100,000. Adjusted for age and sex, PSC prevalence was higher among White (14.0 per 100,000) and Black (14.3) adults and lower among Asian/Pacific Islander (7.8) and Hispanic (7.5) adults ($p < 0.01$ vs White). IBD was present in 61.2% of PSC patients, with 46.3% having ulcerative colitis and 13.0% having Crohn's disease. Cirrhosis occurred in 39.7% of patients and 14.9% underwent liver transplant. Overall, 13.9% of patients experienced at least one PSC-related cancer, and 12.6% experienced mortality from any cause. **Conclusion:** In this large and diverse healthcare system, we found a substantial burden of IBD, cirrhosis, malignancy, and mortality associated with PSC. The increase in PSC diagnoses beginning in 2018 likely reflects enhanced detection through ICD-10 coding. PSC prevalence was highest among White and Black adults and lower among Asian and Hispanic adults. Understanding these disparities is crucial for early diagnosis, healthcare planning, and development of targeted management strategies for PSC.



Disclosures: Ryan Murphy: Nothing to Disclose, Mehrnaz Siavoshi: Nothing to Disclose, Nirmala Ramalingam: Nothing to Disclose, Benjamin Hassid: Nothing to Disclose

4493 | 6-MERCAPTOPURINE AND MYCOPHENOLATE MOFETIL IN PATIENTS WITH AUTOIMMUNE HEPATITIS AND AZATHIOPRINE INTOLERANCE: A COMPARATIVE MULTICENTER RETROSPECTIVE STUDY

Ludwig Jesse Horst[1] Bernardo Canhão[2] Alexander Fierenz[1] Cumali Efe[3] Álvaro Díaz-González[4] Johannes Hartl[1] Sina Hübener[1] Patricia Julianna Kovats[5] Rodrigo Liberal[6] Ansgar Lohse[1] María-Carlota Londoño[7] Ellina Lytvyak[8] Guilherme Macedo[6] João Madaleno[2] Beatriz Mateos Muñoz[9] Aldo Montano-Loza[8] Sean Morris[10] Dante Pio Pallotta[11] Maria Papp[5] Marcial Sebode[1] Palak Trivedi[10] Ye Htun Oo[12] Christoph Schramm[1], [1]University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2]Hospitais da Universidade de Coimbra, Unidade Local de Saúde de Coimbra, Coimbra, Portugal, [3]Harran University Hospital, Şanliurfa, Turkey, [4]Marqués de Valdecilla University Hospital, Santander, Spain, [5]Faculty of Medicine, University of Debrecen, Debrecen, Hungary, [6]Centro Hospitalar Sao Joao, Alameda Prof. Hernani Monteiro, Porto, Portugal, [7]Hospital Clínic Barcelona, Barcelona, Spain, [8]University of Alberta, Edmonton, Alberta, Canada, [9]Hospital Universitario Ramón y Cajal, Madrid, Spain, [10]University Hospitals Birmingham, Birmingham, UK, [11]University of Bologna, Bologna, Italy, [12]University Hospitals Birmingham, Birmingham UK

Background: Azathioprine (AZA) and corticosteroids are the recommended standard therapy for autoimmune hepatitis (AIH); however, around one-fourth of patients discontinue AZA due to intolerance. Although guidelines propose 6-mercaptopurine (6-MP) and mycophenolate mofetil (MMF) as alternatives, there is a lack of data on 6-MP and no comparative studies in AIH. This study aims to perform a comparative assessment of the efficacy and safety of 6-MP and MMF as second-line therapies for AIH patients who were intolerant to AZA. **Methods:** This multicenter retrospective cohort study involved AIH patients from eleven tertiary care centers across Europe and Canada who were intolerant to AZA and subsequently switched to either 6-MP or MMF as second-line interventions. Data on biochemical response, adverse effects, and treatment duration of second-line therapies were collected and analyzed, incorporating propensity score matching to validate the biochemical response. **Results:** We included 211 AIH patients, predominantly female (81%), with a median age of 54 years (IQR: 39–63 years). The median follow-up time was 60 months (IQR: 31–105 months). In AIH patients with prior intolerance to AZA, MMF was better tolerated than 6-MP (89% vs 67%; $p < 0.001$). Among patients who continued second-line treatment, both 6-MP and MMF exhibited comparable efficacy, achieving complete biochemical response in 61% and 66% of individuals, respectively, at the last follow-up (Figure 1). **Conclusion:** Both 6-MP and MMF are equally effective for maintaining biochemical response in AIH patients intolerant to AZA. While MMF is generally better tolerated, 6-MP may present a safer and effective treatment option in women of reproductive age. In addition, therapy with 6-MP enables clinicians to monitor drug metabolite levels, titrate dosages, and monitor adherence.

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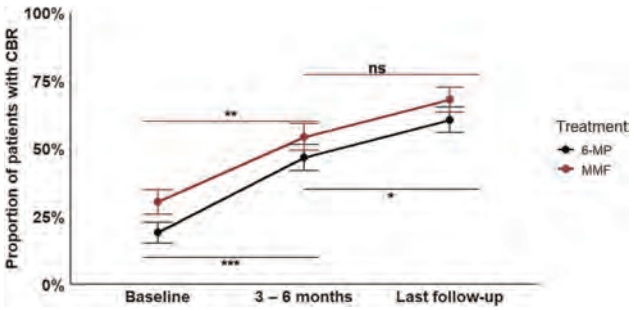
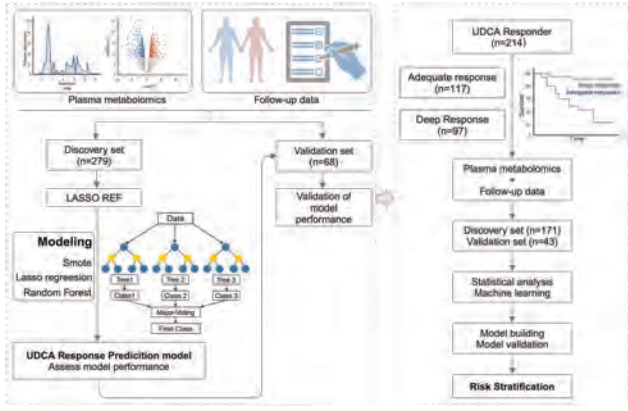


Disclosures: Ludwig Jesse Horst: Falk Foundation e. V.: Travel support, Bernardo Canhão: Nothing to Disclose, Alexander Fierenz: Nothing to Disclose, Cumali Efe: Nothing to Disclose, Álvaro Díaz-González: GSK: Advisor, IPSEN: Speaking and Teaching, AdvanzPharma: Speaking and Teaching, GILEAD: Advisor, EISAI: Speaking and Teaching, Johannes Hartl: Nothing to Disclose, Sina Hübener: Nothing to Disclose, Patricia Julianna Kovats: Nothing to Disclose, Rodrigo Liberal: Nothing to Disclose, Ansgar Lohse: Kezar Bioscience: Advisor, Servier: Advisor, Falk foundation: Speaking and Teaching, María-Carlota Londoño: Nothing to Disclose, Ellina Lytvyak: Nothing to Disclose, Guilherme Macedo: Nothing to Disclose, João Madaleno: Nothing to Disclose, Beatriz Mateos Muñoz: Nothing to Disclose, Aldo Montano-Loza: Nothing to Disclose, Sean Morris: Nothing to Disclose, Dante Pio Pallotta: Nothing to Disclose, Maria Papp: Nothing to Disclose, Marcial Sebode: Nothing to Disclose, Palak Trivedi: Nothing to Disclose, Ye Htun Oo: Nothing to Disclose, Christoph Schramm: Moonlake: Advisor, Agomab: Advisor, Falk Foundation: Speaking and Teaching, Chemomab: Consultant, Pliant: Consultant

4494 | METABOLOMIC MACHINE LEARNING PREDICTOR FOR ADEQUATE AND DEEP RESPONSE TO UDCA IN NON-CIRRHOTIC PBC

Fan Yang[1] Jin Lin[1] Xiaoli Fan[1] Li Yang[1], [1]West China Hospital of Sichuan University

Background: Primary biliary cholangitis (PBC) patients exhibit heterogeneous responses to ursodeoxycholic acid (UDCA), with partial responders remaining at significant risk of disease progression. Current prognostic tools lack metabolic insights necessary for personalized management. This study aimed to elucidate the metabolic landscape of UDCA response and develop precision prediction models integrating clinical and metabolomic features. **Methods:** A total of 347 non-cirrhotic PBC patients were classified as complete responders (n = 214, Paris-II criteria) or non-responders (n = 133). Complete responders were further subdivided into deep responders (DR; ALP normalization) and adequate responders (AR; ALP 1.0–1.5× ULN). Plasma metabolomics was performed using LC/MS, identifying differential metabolites with VIP > 1, |log2FC| > 1, and $p < 0.05$. Machine learning models (LASSO/Random Forest) integrated clinical and metabolomic features. Prognostic risk was assessed using the UK-PBC and GLOBE scores. **Results:** Metabolomic profiling revealed suppressed bile acid biosynthesis (taurochenodeoxycholate, log2FC = -1.29) and enhanced glutathione metabolism in responders. AR patients exhibited a higher risk of disease decompensation ($p < 0.001$), associated with upregulated sphingolipid signaling and phospholipase D activity. Key metabolic predictors included the environmental plasticizer BBP and the anti-inflammatory agent Meloxicam. Prognostic scoring demonstrated significant differences in 15-year outcomes (UK-PBC: DR 0.041 vs. AR 0.055, p = 0.01). The integrated prediction model achieved superior performance in UDCA response classification (AUC = 0.91) and DR stratification (AUC = 0.87), outperforming clinical-only models. **Conclusion:** This study establishes a metabolically informed framework for PBC management, identifying modifiable pathways (PPARγ activation, sphingolipid inhibition) and validating clinical-metabolic prediction models. By redefining therapeutic success as metabolic restoration, these findings facilitate patient stratification and support precision diagnosis and treatment in PBC.



Disclosures: Fan Yang: Nothing to Disclose, Jin Lin: Nothing to Disclose, Xiaoli Fan: Nothing to Disclose, Li Yang: Nothing to Disclose

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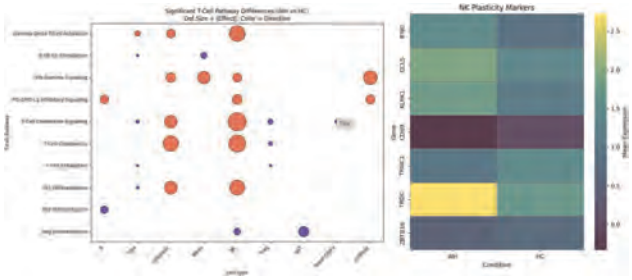
4495 | NK CELL PLASTICITY IN AUTOIMMUNE HEPATITIS: ACQUISITION OF GAMMA-DELTA–LIKE TRAITS

Kiandokht Bashiri[1] Atoosa Rabiee[2] Jessica Davis[2] Mark Mattar[3], [1]MedStar Washington Hospital Center, [2]Washington DC VA Medical Center, [3]Georgetown University Hospital

Background: Autoimmune hepatitis (AIH) is a chronic immune-mediated liver disease driven primarily by T cells. The role of innate-like lymphocytes, such as natural killer (NK) cells and gamma-delta (γδ) T cells, remains underexplored. We investigated NK cell functional adaptations in AIH to elucidate their contribution to disease pathogenesis. **Methods:** We analyzed single-cell RNA-sequencing data (GSE216064) from peripheral blood mononuclear cells of 4 AIH patients and 4 healthy controls (Abe et al, 2024). After quality control, clustering, and annotation, we identified 14 immune cell types, including NK cells (AIH: 331; HC: 159) and γδ T cells (AIH: 14; HC: 57). Curated pathway scoring and Mann-Whitney U testing with Benjamini-Hochberg correction were applied to assess differential expression. **Results:** NK cells in AIH patients showed significantly elevated scores for γδ T cell activation pathways (Δ = +0.27, padj = 1.2×10^{-10}), T cell cytotoxicity (Δ = +0.32), chemokine signaling (Δ = +0.36), and Th1 differentiation (Δ = +0.25), indicating functional reprogramming. Conversely, γδ T cells exhibited mild upregulation of exhaustion markers (e.g., PDCD1, EOMES). Overall, 28 cell type–pathway interactions were significantly altered in AIH as shown in the dotplot, underscoring widespread immune dysregulation. **Conclusion:** While NK cell plasticity has been observed in autoimmune and neoplastic conditions, the adoption of γδ T cell–like features by NK cells in AIH represents a novel finding. This hybrid phenotype likely reflects immune adaptation to chronic liver inflammation, potentially compensating for impaired γδ T cell function. However, it may also exacerbate liver injury through heightened cytotoxic and pro-inflammatory activity. Future functional studies are needed to assess the stability, reversibility, and therapeutic modulation of this NK–γδ–like state within the hepatic microenvironment.



Disclosures: Kiandokht Bashiri: Nothing to Disclose, Atoosa Rabiee: Nothing to Disclose, Jessica Davis: Nothing to Disclose, Mark Mattar: Johnson and Johnson: Speaking and Teaching, AbbVie: Speaking and Teaching, Celltrion: Speaking and Teaching, Pfizer: Speaking and Teaching, BMS: Speaking and Teaching

4496 | AUTOIMMUNE HEPATITIS PATIENTS WITH VARIABLE LEVELS OF BIOCHEMICAL RESPONSE HAVE DISTINCT DIFFERENCES IN PROTEOMIC PROFILES

Craig Lammert[1] Matthew Hamang[2] Thomas Daly[2] Christoph Preuss[2], [1]Indiana University School of Medicine, [2]Lilly Research Laboratories, Eli Lilly and Company

Background: Autoimmune hepatitis (AIH) is a prototypical auto-inflammatory liver disease that can result in liver failure and hepatic fibrosis. Normalization of liver tests (LTs) with immunosuppressive therapies have been associated with improved transplant-free survival. Treatment impact on proteins associated with immunoinflammatory response remains unknown, but clarity may provide insight into key mechanistic disease drivers. We aimed to describe proteomic differences between AIH patients at diagnosis and with varying levels of biochemical response according to LTs. **Methods:** Using a well-described AIH cohort, we utilized stored serum from distinct AIH groups and healthy controls (HC) for comparison. Group 1 (n = 9) included newly diagnosed AIH patients not currently on treatment; Group 2 (n = 24): AIH patients with normal LTs on stable treatment for at least 6 months; Group 3 (n = 26): AIH patients with abnormal liver tests despite treatment and diagnosis more than 1 year; Group 4 (n = 15): HC without known liver disease. Groups were compared using the OLINK explore platform, of which1,431 serum protein markers were assessed after QC. Proteins with log2FC changes +/- 2 were considered significant. Pathway analysis was performed using the curated KEGG pathway dataset. **Results:** 59 AIH patients satisfying the simplified criteria (69.5% female, mean age = 54 years (standard deviation (SD) = 15.2) were included in the study. Principal components analysis showed distinct clustering between Group 1 and HC which included many markers associated with inflammation and viral response (Table 1). Compared to HC, a majority of these markers remained similarly elevated in Group 3 as in Group 1, but were corrected with optimal control of inflammation (Group 2). A few markers remained elevated in Group 2 compared to Group 1 despite normalization of liver tests with ongoing treatment. While the majority of the residual markers were consistent with steroid use, KEGG pathway analysis also identified consistent PI3K-AKT-mTOR signaling in AIH patients after treatment. **Conclusion:**

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These data suggest that while treatment corrects the majority of proteomic and biochemical abnormalities in AIH patients, abnormal immune activity can persist even in patients meeting treatment goal with ALT normalization. Persistent inflammatory perturbations could contribute to risk of ongoing disease progression.

	log2FC	P.Value	adj. P.Val
Proteins increased in newly diagnosed AIH patients over controls			
BST2_Neurology	3.4	1.5e-07	5.4e-05
VAMP5_Cardiometabolic	3.3	9.6e-06	5.8e-04
HAO1_Oncology	2.8	5.5e-05	1.4e-03
CA5A_Cardiometabolic	2.7	4.7e-04	5.8e-03
ALDH1A1_Neurology	2.6	1.6e-05	7.6e-04
IL10_Inflammation	2.5	2.3e-04	3.7e-03
ACE2_Cardiometabolic	2.5	3.7e-05	1.1e-03
FBP1_Cardiometabolic	2.5	3.4e-04	4.7e-03
CCL20_Inflammation	2.4	3.5e-05	1.1e-03
PTS_Neurology	2.3	8.1e-04	9e-03
KRT18_Oncology	2.3	2.2e-04	3.6e-03
SLAMF8_Oncology	2.2	9.4e-06	5.8e-04
HAVCR1_Oncology	2.1	2.1e-05	8.9e-04
AGXT_Cardiometabolic	2.1	8.4e-06	5.7e-04
CDHR2_Oncology	2.1	1.2e-04	2.7e-03
THBS2_Neurology	2.1	9.3e-07	1.3e-04
MUC13_Neurology	2.1	5.9e-04	7.1e-03
CXCL10_Inflammation	2.1	4.1e-05	1.1e-03
DPP10_Inflammation	2.1	2e-04	3.3e-03
GRPEL1_Oncology	2	2.5e-05	9.6e-04
FCRL5_Neurology	2	1.4e-06	1.9e-04
IL1RL1_Cardiometabolic	2	1.4e-05	7.2e-04
NDUFS6_Oncology	2	8.1e-04	9e-03
Proteins decreased in newly diagnosed AIH patients over controls			
SSC4D_Cardiometabolic	-2.3	2.7e-04	4e-03
GYS1_Cardiometabolic	-2.6	1.9e-04	3.3e-03

Disclosures: Craig Lammert: Eli Lilly: Consultant, Kezar Life Sciences: Consultant, Amgen: Consultant, Autoimmune Hepatitis Association: Consultant, RegCell: Consultant, Matthew Hamang: Nothing to Disclose, Thomas Daly: Nothing to Disclose, Christoph Preuss: Nothing to Disclose

4497 | THE PERCENTAGE CHANGE OF ALKALINE PHOSPHATASE CAN BE USED TO EVALUATE RESPONSE TO URSODEOXYCHOLIC ACID BUT NOT PROGNOSIS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

Ellen Werner[1] Gemma Weijsters[1] Maria van Hooff[1] Rozanne de Veer[1] Ulrich Beuers[2] Joost P.H. Drenth[2] Frans J.C. Cuperus[3] Remco van Dijk[4] Bart Veldt[5] Michael Klemt-Kropp[6] Suzanne van Meer[7] Robert Verdonk[8] Hajo J. Flink[9] Jan Vrolijk[10] Cyiel Y. Ponsioen[2] Matthijs Kramer[11] Paul G. van Putten[12] Djuna L. Cahen[13] Laurens van der Waaij[14] Hans H.K. Thio[15] Roberta M. Manzat-Saplacan[16] Lisette J.H. van Dam[17] Ludger S.M. Epping[18] Matthias C. Jurgens[19] Marcel Cazemier[20] J. van Kemenade[21] Edith M.M. Kuiper[22] Yasser A. Alderlieste[23] Kirsten Boonstra[24] Martijn ter Borg[25] Khalida Soufidi[26] Pedro Miranda-Afonso[1] Nicole S. Erler[7] Bettina E. Hansen[1] Harry L.A. Janssen[1] Adriaan van der Meer[1], [1]Erasmus University Medical Center, [2]Amsterdam University Medical Center, [3]University Medical Center Groningen, [4]Leiden University Medical Center, [5]Reinier de Graaf Gasthuis, [6]Noordwest Ziekenhuisgroep, [7]University Medical Center Utrecht, [8]St.Antonius Hospital, [9]Catharina Hospital, [10]Rijnstate, [11]Maastricht University Medical Center, [12]Antonius Zorggroep, [13]Hospital Amstelland, [14]Martini Hospital, [15]Saxenburgh Medical Center, [16]Wilhelmina Hospital Assen, [17]Ommelander Hospital, [18]Maasziekenhuis Pantein, [19]St. Jans Gasthuis Weert, [20]Bovenlj Hospital, [21]Van Weel-Bethesda Hospital, [22]Spijkenisse Medical Center, [23]Streekziekenhuis Koningin Beatrix, [24]Radboud University Medical Center, [25]Maxima Medical Center, [26]Zuyderland Medical Center

Background: While absolute alkaline phosphatase (ALP) levels during ursodeoxycholic acid (UDCA) therapy have been associated with prognosis in patients with primary biliary cholangitis (PBC), treatment efficacy may be better evaluated by the change in ALP. The aim of this study was to assess how the reduction of ALP after start of ursodeoxycholic acid (UDCA) relates to clinical outcome in a nationwide cohort of patients with PBC. **Methods:** The retrospective Dutch PBC Cohort Study (DPCS) includes every identifiable patient with PBC in the Netherlands from 1990 up to last data collection (2019-2023) in all 71 Dutch hospitals. Clinical data were obtained through medical chart review. Where feasible, imputation was performed using joint model multiple imputation. Patients were included in case of at least one year of follow-up after start of UDCA. Laboratory values are presented in upper limits of normal (ULN). Patients were categorized according to their percentual reduction in ALP at one year after start of UDCA. The association with liver transplant (LT) and death was evaluated using Cox models. **Results:** In total, 3566 patients were included with a median age of 57.6 years (IQR 49.5–66.9) of whom 3131 (87.8%) were female. The median follow-up was 8.0 years (IQR 3.9–13.3) during which 622 patients died and 95 patients underwent LT. At one year after start of UDCA, 3054/3479 (87.8%) patients showed any ALP reduction, of whom 599 (19.6%) had a reduction of $\geq$60%. Table 1 shows that patients with greater one-year ALP reduction had higher baseline ALP levels; those without ALP reduction had a median baseline ALP of 1.09 x ULN (IQR 0.78-1.40) which was 3.84 x ULN (IQR 2.77-5.37) in the group with $\geq$60% reduction ($p < 0.001$). Adjusted for the absolute level of baseline ALP (and other prognostic parameters), the aHR was 0.93 (95% 0.90-0.96, $p < 0.001$) per 10% ALP decline. Across the subgroups based on percentage ALP reduction, the absolute ALP levels at one year were rather similar; median

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ALP at one year ranged between 1.13 x ULN (IQR 0.85-1.51) and 1.28 x ULN (IQR 0.94-1.72) ($p < 0.001$). Adjusted for the absolute level of ALP at one year of UDCA (and other prognostic parameters), the percentage reduction in ALP was no longer associated with LT or death (aHR 0.99 per 10% ALP decline, 95%CI 0.97-1.02, $p = 0.59$). **Conclusion:** The larger the percentage decline in ALP after start of UDCA therapy, the greater the reduction of the relative risk for LT or death. This substantiates that ALP can serve as surrogate endpoint to evaluate the efficacy of therapy for PBC. However, for the purpose of prognosis assessment, the percentage decline in ALP from baseline is not of additional value over the absolute ALP level at one year after start of UDCA.

ALP x ULN at start of UDCA	% reduction of ALP 1 year after start of UDCA	N	ALP x ULN 1 year after start of UDCA
1.09 (IQR 0.78 – 1.40)	No reduction	425	1.28 (IQR 0.94 – 1.72)
1.32 (IQR 1.03 – 1.72)	0%-10%	238	1.27 (IQR 0.97 – 1.66)
1.35 (IQR 1.09 – 1.82)	10%-20%	310	1.14 (IQR 0.94 – 1.52)
1.53 (IQR 1.18 – 2.01)	20%-30%	386	1.16 (IQR 0.89 – 1.51)
1.73 (IQR 1.33 – 2.49)	30%-40%	451	1.13 (IQR 0.87 – 1.60)
2.16 (IQR 1.62 – 3.23)	40%-50%	529	1.19 (IQR 0.89 – 1.77)
2.62 (IQR 1.99 – 4.13)	50%-60%	541	1.17 (IQR 0.89 – 1.81)
3.84 (IQR 2.77 – 5.37)	>=60%	599	1.13 (IQR 0.85 – 1.51)

Table 1. shows the median ALP levels of patients with PBC categorized based on their percentual reduction in ALP at one year after start of UDCA.
Abbreviations: Upper Limit of Normal (ULN), Ursodeoxycholic acid (UDCA)

Disclosures: Ellen Werner: Nothing to Disclose, Gemma Weijsters: Nothing to Disclose, Maria van Hooff: Nothing to Disclose, Rozanne de Veer: Nothing to Disclose, Ulrich Beuers: Nothing to Disclose, Joost P.H. Drenth: Nothing to Disclose, Frans J.C. Cuperus: Nothing to Disclose, Remco van Dijk: Nothing to Disclose, Bart Veldt: Nothing to Disclose, Michael Klemt-Kropp: Nothing to Disclose, Suzanne van Meer: Nothing to Disclose, Robert Verdonk: Nothing to Disclose, Hajo J. Flink: Nothing to Disclose, Jan Vrolijk: Nothing to Disclose, Cyiel Y. Ponsioen: Nothing to Disclose, Matthijs Kramer: Nothing to Disclose, Paul G. van Putten: Nothing to Disclose, Djuna L. Cahen: Nothing to Disclose, Laurens van der Waaij: Nothing to Disclose, Hans H.K. Thio: Nothing to Disclose, Roberta M. Manzat-Saplacan: Nothing to Disclose, Lisette J.H. van Dam: Nothing to Disclose, Ludger S.M. Epping: Nothing to Disclose, Matthias C. Jurgens: Nothing to Disclose, Marcel Cazemier: Nothing to Disclose, J. van Kemenade: Nothing to Disclose, Edith M.M. Kuiper: Nothing to Disclose, Yasser A. Alderlieste: Nothing to Disclose, Kirsten Boonstra: Nothing to Disclose, Martijn ter Borg: Nothing to Disclose, Khalida Soufidi: Nothing to Disclose, Pedro Miranda-Afonso: Nothing to Disclose, Nicole S. Erler: Nothing to Disclose, Bettina E. Hansen: Nothing to Disclose, Harry L.A. Janssen: Nothing to Disclose, Adriaan van der Meer: Gilead: 400.000 EUR, Gilead: Grant/Research Support, Gilead: Speaking and Teaching, Intercept: Grant/Research Support, Mirum: Grant/Research Support, Mirum: Speaking and Teaching, Mirum: Consultant, Mirum: Independent Contractor, Ipsen: Grant/Research Support, Ipsen: Speaking and Teaching

4498 | THE SHORT- AND LONG-TERM COURSE OF THE CHOLESTATIC BIOCHEMICAL PARAMETERS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH URSODEOXYCHOLIC ACID

Ellen Werner[1] Gemma Weijsters[1] Maria van Hooff[1] Rozanne de Veer[1] Ulrich Beuers[2] Joost P.H. Drenth[2] Frans J.C. Cuperus[3] Remco van Dijk[4] Bart J. Veldt[5] Michael Klemt-Kropp[6] Suzanne van Meer[7] Robert Verdonk[8] Hajo J. Flink[9] Jan Maarten Vrolijk[10] Cyriel Y. Ponsioen[2] Matthijs Kramer[11] Femke Boersma[12] Hendrik J.M. de Jonge[13] Franciscus H.J. Wolfhagen[14] L.C. Baak[15] Suzanne L. Onderwater[16] Paul G. van Putten[17] Jeroen D. van Bergeijk[18] Gijs J. de Bruin[19] Rob P.R. Adang[20] Maria N. Aparicio-Pages[21] Wink de Boer[22] Hanneke van Soest[23] Frank ter Borg[24] Elsemieke S. de Vries[25] Sander de Kort[26] Pedro Miranda-Afonso[1] Harry L.A. Janssen[1] Bettina E. Hansen[1] Nicole S. Erler[7] Adriaan van der Meer[1], [1]Erasmus University Medical Center, [2]Amsterdam University Medical Center, [3]University Medical Center Groningen, [4]Leiden University Medical Center, [5]Reinier de Graaf Gasthuis, [6]Noordwest Ziekenhuisgroep, [7]University Medical Center Utrecht, [8]St.Antonius Hospital, [9]Catharina Hospital, [10]Rijnstate, [11]Maastricht University Medical Center, [12]Gelre Hospitals, [13]Jeroen Bosch Hospital, [14]Albert Schweitzer Hospital, [15]Onze Lieve Vrouwe Gasthuis, [16]Diakonessenhuis, [17]Medical Center Leeuwarden, [18]Hospital De Gelderse Vallei, [19]Tergooi Hospital, [20]VieCuri, [21]Canisius/Wilhemina Hospital, [22]Bernhoven, [23]Medical Center Haaglanden, [24]Deventer Hospital, [25]Isala Hospital, [26]St. Anna Hospital

Background: Alkaline phosphatase (ALP), total bilirubin (TB) and gamma-glutamyl transferase (GGT) are associated with clinical outcome in patients with primary biliary cholangitis (PBC) treated with ursodeoxycholic acid (UDCA). A clear understanding of the evolution of these parameters is relevant for the discussion on the timing of response evaluation. We aimed to map the course of the cholestatic parameters following UDCA initiation in a nationwide cohort of patients with PBC. **Methods:** The Dutch PBC Cohort Study (DPCS) includes every identifiable patient with PBC in the Netherlands from 1990 up to last data collection (2019-2023) in all 71 Dutch hospitals. Clinical data were obtained through medical chart review. Laboratory values are expressed as upper limits of normal (ULN). The biochemical course after start of UDCA was explored and visualized using linear mixed-effects models with natural cubic splines, applied to the full dataset regardless of length of follow-up. Follow-up was censored at the initiation of second-line therapy and/or immunosuppressants. Effect plots were generated to show the expected biochemical values (back-transformed to their original scale) with corresponding 95% confidence intervals over 10 years. **Results:** A total of 4095 patients (3608 [88.1%] female) from the DPCS could be included. The median year UDCA was started was 2011 (IQR 2010 - 2014). At baseline, median age was 57.5 (IQR

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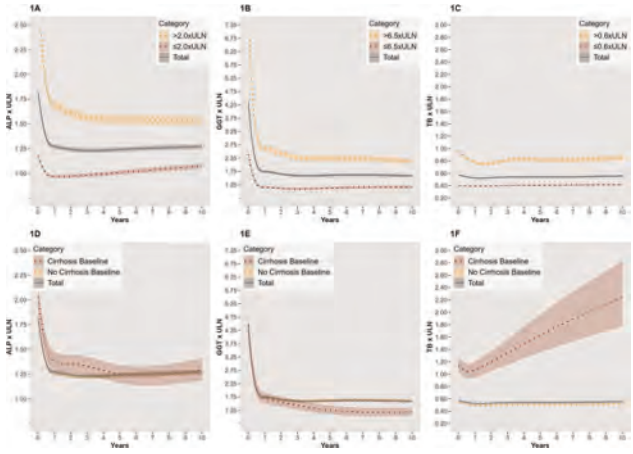
49.3-67.0) years, 292 (7.1%) patients had cirrhosis, median ALP, GGT and TB were 1.9 x ULN (IQR 1.3 - 3.2), 6.5 x ULN (IQR 3.6-11.4) and 0.5 x ULN (IQR 0.4-0.9). During a median follow-up of 8.3 (IQR 3.4 – 14.0) years, the median number of ALP measurements per patient was 11 (IQR 7-17) with a median interval of 8.3 (IQR 5.6-10.7) months. This was 11 (IQR 6-17) with a median interval of 8.4 (5.8 – 10.9) months for GGT and 10 (IQR 5 - 15) for TB with a median interval of 9.1 (IQR 6.0-12.5) months. Overall, a steep decline in ALP, GGT and TB was primarily evident during the first year after start of UDCA. A more gradual second phase decline up to three years for ALP and GGT was observed in those with higher baseline levels (Fig. 1A-C). The course of the cholestatic parameters did not differ in subgroups based on age or sex. During long-term follow-up, the levels of the cholestatic parameters were generally stable except for TB in patients with cirrhosis at baseline (Fig.1D-F). **Conclusion:** In patients with PBC, ALP, GGT and TB primarily decline during the first year after start of UDCA. In some patients, the second phase decline in ALP may be considered when deciding on the timing of UDCA response evaluation. During long-term UDCA, the cholestatic parameters were stable. The increase in TB levels in patients with cirrhosis suggests disease progression over time.



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4499 | ACHIEVING BIOCHEMICAL RESPONSE IN AUTOIMMUNE HEPATITIS: A COMPARATIVE STUDY BETWEEN KOREAN AND AMERICAN COHORTS

Kwang Il Seo[1] Laura Lavette[2] Mary McGrath[2] Sahil Khanna[2] Brian Wentworth[3], [1]Kosin University College of Medicine, [2]University of Virginia School of Medicine, [3]University of Virginia

Background: Autoimmune hepatitis (AIH) can affect patients of all ages, sex, and ethnicity. However, current standards of care are derived from research involving predominantly Western populations and less is known about AIH in East Asian populations. To address this deficiency, we conducted an international, multicenter study to assess patient profiles and time to biochemical response (BR) in Korean and American cohorts. **Methods:** We retrospectively reviewed the electronic medical records of patients with newly diagnosed AIH by compatible clinical features and liver biopsy at tertiary care centers [University of Virginia (UVA) and Kosin University Gospel Hospital (KUGH)] in the United States and Korea from January 2011 through December 2023. Normalization of transaminases within institutional laboratory reference range defined BR. Chi-square, Fisher exact, Mann-Whitney U, and two-sided t-tests were performed as appropriate for comparative univariate analysis. Time to BR between groups at 6- and 12-month intervals was assessed with the Kaplan-Meier method and log-rank test. Independent predictors of BR were analyzed via multivariate Cox proportional hazard (CPH) model. **Results:** A total of 175 patients (UVA: 140; KUGH: 35) were included. UVA patients were younger (mean 51.5 vs. 56.7, $p = 0.019$), more likely to be male (22.9% vs. 5.7%, $p = 0.022$), had higher baseline ALT (median 452 vs. 111 U/L, $p < 0.001$) and INR (median 1.2 vs. 1.1, $p = 0.021$), lower ANA positivity (60.4% vs. 77.1%, $p = 0.067$), and higher SMA positivity (47.7% vs. 15.6%, $p = 0.001$). There was no difference in mean IgG level, presence of acute severe-AIH, or degree of fibrosis between groups. Biochemical response rates were similar

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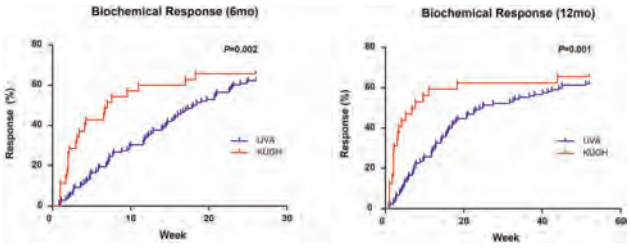
in UVA and KUGH at 6 months (65.9% vs. 65.7%, $p = 0.980$) and 12 months (65.9% vs. 65.6%, $p = 0.976$). However, KUGH patients achieved BR faster at 6 months (log-rank, $p = 0.020$) and 12 months (log-rank, $p = 0.010$). METAVIR stage 4 (cirrhosis) predicted failure to achieve BR at 6 months (OR 0.211, 95% CI 0.064–0.701, $p = 0.011$); older age predicted BR at 12 months (OR 1.034, 95% CI 1.010–1.059, $p = 0.006$). **Conclusion:** Autoimmune hepatitis patient profiles were different between representative Western and East Asian populations. While Korean patients achieved BR faster, American patients achieved comparable rates of BR by 6 months, the current treatment standard. Further research is needed to understand if guideline-suggested immunosuppression regimens should account for ethnic differences.



Disclosures: Kwang Il Seo: Nothing to Disclose, Laura Lavette: Nothing to Disclose, Mary McGrath: Nothing to Disclose, Sahil Khanna: Nothing to Disclose, Brian Wentworth: Nothing to Disclose

4500 | MONITORING AZATHIOPRINE METABOLITES IN AUTOIMMUNE HEPATITIS AND IMPACT ON DISEASE OUTCOME

Anna HADJISOTERIOU[1] Laurenda Obeng[1] Fiona Rees[1] Yazan Haddadin[1] Ala Abu Layla[1] Emily Kerr[1] adele mourad[1] Lucy Ryan[1] Anthony To[1] Sumita Verma[2], [1]University Hospitals Sussex NHS Foundation Trust, [2]Brighton and Sussex Medical School

Background: Autoimmune hepatitis (AIH) is a chronic inflammatory condition of unknown aetiology. Azathioprine is usually the first line treatment for long term management of AIH. Our aim was to assess impact of monitoring of azathioprine metabolites (6TGN) on disease outcome. **Methods:** This was a single centre retrospective cohort study (2005 and 2021), last follow up being May 31st, 2024. Patients with AIH were identified from the histopathology database. From 2020, a dedicated gastroenterology pharmacist was involved in monitoring of azathioprine metabolites. Poor outcome was defined as one or more of the following: development of cirrhosis and or cirrhosis complications, failure to achieve remission, need for liver transplant and all-cause mortality. Data are presented as mean +/- SD or median (IQR). Multiple logistic regression analysis was performed. **Results:** A total of n = 112 patients were identified, females n = 88 (79%), mean age being 55.7 + 17 years. Pre-treatment n = 59 (53%) had definite and 43 (38%) probable AIH (IAIHG criteria). At presentation, n = 83 (74%) were symptomatic, n = 15 (13%) having acute severe AIH. Mean serum bilirubin (µmol/L) and ALT (iu/L) at presentation were 46 (13-148) and 525 (180-1325) respectively. Overall, 40 (36%) had cirrhosis at presentation and 14 (13%) developed it during follow up. Forty-nine (44%) had been assessed by a dedicated pharmacist. Sixty-one (54%) had results of azathioprine metabolite available and mean 6TGN levels (closest to remission) and at last follow up were 260 +/- 17 and 254 +/- 15 respectively (therapeutic range being 235-450 pm/8x10e8c).Azathioprine metabolite levels stayed relatively stable throughout follow-up. Overall n = 46 (41%) had poor outcome. On univariate analysis, predictors of poor outcome were pharmacist involvement (OR 0.29, 95% CI 0.12-0.67, p = 0.004), any 6TGN monitoring (OR 0.15, 95% CI 0.06-0.39, p < 0.001) and 6TGN levels in therapeutic range at last follow up (OR 0.11, 95% CI 0.01-0.91, p = 0.04). On multivariate analysis, the only predictor of poor outcome was any 6TGN monitoring (OR 0.17, 95% CI 0.05-0.62, p = 0.008). Of those with TGN monitoring 25% (n = 15) had a poor outcome vs 66% (= 29) without TGN monitoring (p < 0.001). Liver histology at presentation including fibrosis stage did not predict outcome. Mean total follow up duration was 119 +/- 70 months. **Conclusion:** This retrospective cohort study shows that monitoring of azathioprine metabolites and addition of a dedicated pharmacist could improve outcomes in patients with AIH. Our results however need to be corroborated by future prospective studies. Nonetheless, based on our findings, and to optimise outcomes in our patients with AIH, all newly diagnosed patients with AIH are now also monitored by a gastroenterology pharmacist including a helpline. We have also set up a combined hepatology-pharmacy clinic.

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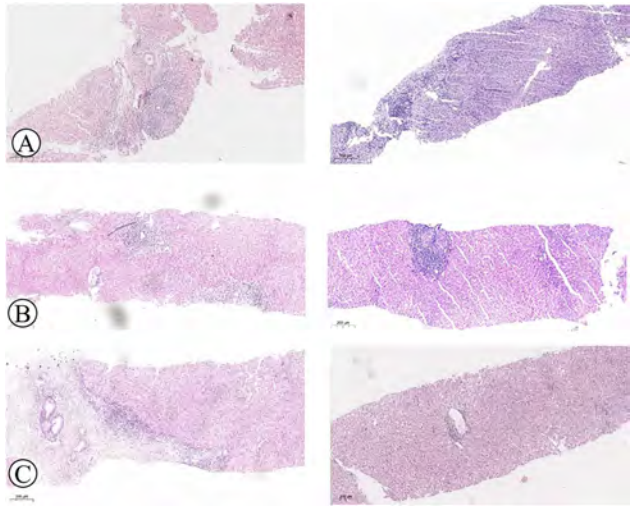
4501 | HEPATITIS B–DERIVED P-I-R CLASSIFICATION IS APPLICABLE TO ANTIBODY-POSITIVE PBC: EVIDENCE FROM REPEAT LIVER BIOPSIES

Hongli Liu[1] Xing Liu[2] Yi-Fan Hu[2] Sha-Sha Li[3] Miao-Yang Chen[4] Xi-Xuan Wang[1] Shu-Ling Chen[4] Yi-Jun Bao[4] Yu Zhang[4] Si-Wei Zheng[5] Li Wang[4] Zhi-Xiang Du[4] Qing-Fang Xiong[4] Yan-Dan Zhong[4] Du-Xian Liu[4] Cai-Yun Zhang[4] Kai Zhang[4] Yong-Feng Yang[1], [1]The Second Hospital of Nanjing, Teaching Hospital of Southeast University, [2]The Second Hospital of Nanjing, Affiliated to Nanjing University of Chinese Medicine, [3]The Second Hospital of Nanjing, Clinical Teaching Hospital of Medical School, Nanjing University, [4]The Second Hospital of Nanjing, Nanjing University of Chinese Medicine, [5]The Second Hospital of Nanjing, Clinical Teaching Hospital of Medical School, Nanjing University

Background: The P-I-R classification system (Progressive–Indeterminate–Regressive) was originally developed for assessing repeat liver biopsies in hepatitis B. Primary biliary cholangitis (PBC) is a chronic, progressive cholestatic liver disease. Traditional histological staging systems such as Ludwig and Nakanuma are limited in evaluating dynamic histological changes after treatment. Given that both hepatitis B and PBC primarily involve portal inflammation, this study aimed to explore the value of applying the P-I-R classification system in repeat liver biopsies of PBC patients. **Methods:** A retrospective analysis was conducted on the clinical and pathological data of 30 antibody-positive PBC patients who underwent two liver biopsies between December 2017 and December 2021 at Nanjing Second Hospital. The P-I-R classification was determined based on fibrous septa morphology and inflammatory activity. These results were compared with traditional histological staging systems (Ludwig, G, S, Nakanuma) and analyzed for correlations with biochemical indicators, symptom changes, and histological improvement. **Results:** The distribution of P-I-R types was equal (10 cases each for P, I, and R types). After treatment, patients classified as R-type showed significantly higher rates of histological improvement in Ludwig, S, and Nakanuma staging (all $p < 0.05$) compared to P-type, along with the greatest improvement in fatigue and pruritus symptoms (70% and 60%, respectively). Although ALP, AST, and GGT levels declined significantly ($p < 0.05$), their changes were not statistically associated with P-I-R classification ($p > 0.3$), suggesting that P-I-R provides independent histological assessment value. **Conclusion:** The P-I-R classification system effectively identifies directional histological changes in PBC patients. Compared to traditional static staging systems, it demonstrates higher sensitivity in detecting histological regression and aligns well with clinical symptom improvement. Therefore, it can serve as a valuable supplementary tool in evaluating treatment efficacy.



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4502 | A NOVEL BLYS/APRIL DUAL INHIBITOR IN TREATING REFRACTORY AUTOIMMUNE HEPATITIS: A CASE SERIES

Tianyu Mao[1] Xiao Xiao[1] Xiong MA[1], [1]Renji Hospital, School of Medicine, Shanghai Jiao Tong University

Background: Autoimmune hepatitis (AIH), a rare chronic immune-mediated liver disease, can be refractory or prone to frequent flares with conventional therapies in some patients. B-cell targeting therapies have shown potential for refractory AIH. We aimed to

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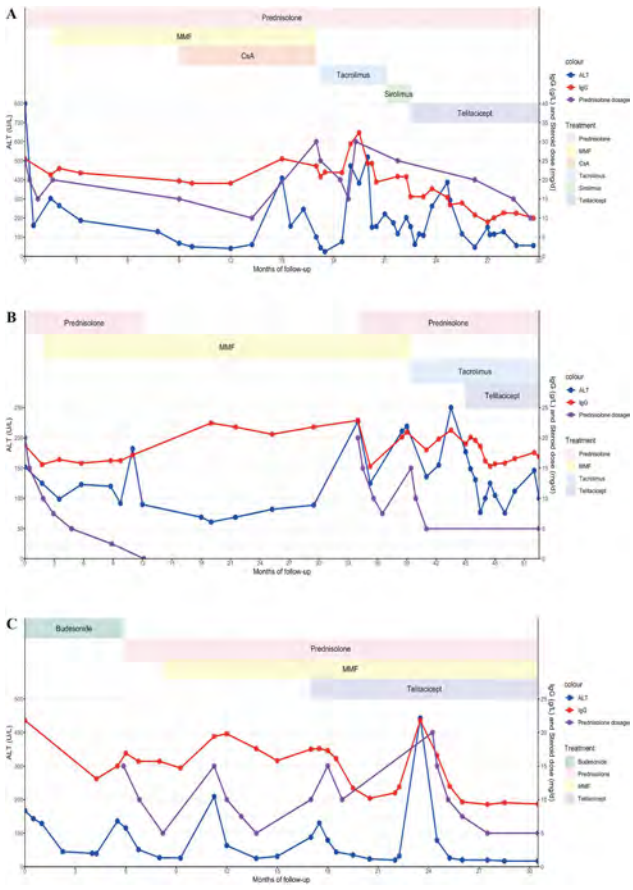
assess efficacy and safety of telitacicept, a novel BLyS/APRIL dual inhibitor, as a third-line therapy in AIH patients. **Methods:** This retrospective single-center study included 3 AIH patients diagnosed by the 2008 simplified criteria, with steroid dependence or refractory AIH. Telitacicept was initially given at 160mg weekly subcutaneously, then reduced to 160mg every two weeks in two patients. **Results:** Case 1
A 13-year-old female presented with jaundice and elevated transaminases (ALT 798U/L). Immunological tests showed positive ANA (1:100), SMA (1:100), and IgG (25.5g/L). Liver biopsy showed severe interface hepatitis (G3S3-4). Prednisolone 25mg/d improved liver function, but reducing to 15mg/d caused a flare. Subsequent combination therapies with MMF, or MMF and CsA, or tacrolimus, or sirolimus failed to achieve complete biochemical response (CBR). Steroid dose reduction always led to flares. Two months after adding telitacicept, ALT and IgG began to decline. At the end of follow-up, ALT was 56U/L and IgG 9.97g/L, with steroid doses tapered to 10mg/d. Side effects were injection site reactions and upper respiratory infection (Fig.1A).
Case 2
A 53-year-old woman with a 6-year history of recurrent liver dysfunction was diagnosed with AIH based on the liver biopsy, positive ANA (1:320), elevated ALT (152U/L) and IgG levels (19.3 g/L). She failed to achieve CBR with prednisolone and MMF. Steroids were stopped due to side effects, with MMF 0.75g/d as a maintenance therapy. After a flare, prednisolone was restarted but failed again. Switching MMF to tacrolimus provided only transient improvement. Telitacicept 160mg/week normalized IgG and reduced transaminases within 2 months. The dose was then reduced to 160mg every two weeks, keeping IgG below ULN, though transaminases were elevated. No side effects occurred (Fig.1B).
Case 3
A 48-year-old male with SLE presented with elevated transaminases (ALT 599U/L), IgG levels (20g/L) and positive ANA (1:1000). The liver biopsy showed moderate interface hepatitis (G3S3). Budesonide monotherapy or prednisolone combined with MMF could induce CBR but not prevent flares during steroid tapering. Adding telitacicept 160mg/week induced CBR and allowed steroid dose reduction. A flare occurred when tapering doses of MMF and telitacicept. Reinstituting prednisolone 20mg/d induced CBR again. Prednisolone and telitacicept doses were successfully tapered to 5mg/d and 160mg every two weeks respectively, with no side effects (Fig.1C). **Conclusion:** Our study demonstrates the potential of telitacicept in refractory AIH, marked by its ability to reduce transaminases and IgG, and decrease steroid doses. It was well-tolerated and safe.



Disclosures: Tianyu Mao: Nothing to Disclose, Xiao Xiao: Nothing to Disclose, Xiong MA: Nothing to Disclose.

4503 | CLINICAL EPIDEMIOLOGY OF AUTOIMMUNE HEPATITIS IN LATIN AMERICA: DATA FROM THE ALLATIN COHORT

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Background: Autoimmune hepatitis (AIH) is a rare, chronic, immune-mediated liver disease, with rising incidence and prevalence worldwide. Non-White ethnicity has been associated with worse clinical outcomes in AIH. However, data from Latin America remain scarce, limiting the understanding of ethnic and regional variations in disease presentation, management, and prognosis. **Methods:** Retrospective, ongoing, observational, multicenter cohort study (ALLATIN) including 515 patients with autoimmune hepatitis from eight Latin American countries: Brazil, Argentina, Chile, Ecuador, Cuba, Mexico, Costa Rica, and Peru. **Results:** Most patients were female (82.5%), mean age at diagnosis 42.8 ± 19.2 years, and diagnosed with type 1 AIH (90.9%). Type 2 AIH accounted for 2.8% of cases, while 6.4% had no detectable autoantibodies. Disease presentation was asymptomatic in 42%, with isolated liver enzyme elevation. Among those presenting acutely, 2.2% had fulminant hepatitis [defined by jaundice, coagulopathy (INR $\geq$ 1.5), and encephalopathy], 8.7% had severe acute hepatitis [jaundice and coagulopathy (INR $\geq$ 1.5) without encephalopathy], and 28.4% had acute icteric hepatitis [jaundice without coagulopathy (INR $<$ 1.5) or encephalopathy]. At diagnosis, 42.9% of patients had advanced fibrosis (F3–F4) on liver biopsy, 35.0% were cirrhotic on ultrasound, and 26.6% had clinically significant portal hypertension. Overlap with autoimmune cholangiopathies was identified in 11.0% of patients (8.6% with primary biliary cholangitis and 2.4% with primary sclerosing cholangitis). Concomitant metabolic dysfunction-associated steatotic liver disease (MASLD) was present in 4.8%. First-line therapy included prednisone in 96.5% and azathioprine in 91.9% of patients. Second-line treatment was required in 9.2%, with mycophenolate mofetil being the most frequently used (63.6%), followed by tacrolimus (13.6%), cyclosporine (13.6%), chloroquine (6.8%), and rituximab (2.3%). Data on biochemical outcomes in 6 months were available for 71.1 % of the patients and in 63.9% in 12 months. Complete biochemical response was achieved in 68.4% at 6 months and 55.7% at 12 months. Incidence of hepatocellular carcinoma was low (1.1%). Liver transplantation was required in 3.9% of patients, and all-cause mortality was 3.1% in a mean follow up of 6.72 ± 6.0 years. **Conclusion:** This is the largest cohort of AIH reported from Latin America to date. Despite the predominance of type 1 AIH and the widespread use of standard first-line therapies, a substantial proportion of patients presented with advanced liver disease at diagnosis. Biochemical response was similar to European cohorts. These findings highlight the need for increased awareness, earlier detection, and region-specific strategies to improve outcomes in underrepresented populations.

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4504 | BOLD AND BOLD-EXT, THE FIRST GLOBAL PHASE III CLINICAL PROGRAM TO EVALUATE THE LONG-TERM EFFICACY AND SAFETY OF ODEVIXIBAT IN INFANTS WITH BILIARY ATRESIA AFTER KASAI HEPATOPORTOENTEROSTOMY – STUDY DESIGN AND CURRENT STATUS

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Background: Biliary atresia is a rare, life-threatening, highly complex, progressive obstructive cholangiopathy. There are no approved pharmacologic treatments, and a Kasai hepatoportoenterostomy (HPE) is essential to restore bile flow and help prevent progression to liver failure. Patients can have elevated serum bile acids (sBA) and experience ongoing liver disease despite restoration of bile flow; 50–75% of patients will eventually require a liver transplant within 20 years of a Kasai HPE.[1] By reducing intrahepatic retention of bile acids and diverting them to the intestine, the ileal bile acid transporter (IBAT) inhibitor odevixibat could augment and sustain the native liver protective effects of Kasai HPE. BOLD is the first and only phase III clinical program investigating the disease-modifying potential of odevixibat in biliary atresia post-Kasai HPE. **Methods:** BOLD (NCT04336722) is a placebo-controlled phase III study evaluating odevixibat over 104 weeks in infants who have undergone Kasai HPE at $\leq$90 days old. Primary endpoint: time from date of first dose of study treatment to the first occurrence of liver transplant or death; secondary endpoints include time to onset of first sentinel event, total bilirubin levels, sBA levels, and time to pediatric end-stage liver disease score $>$15. BOLD-EXT (NCT05426733) is an open-label extension study to evaluate the long-term efficacy and safety of

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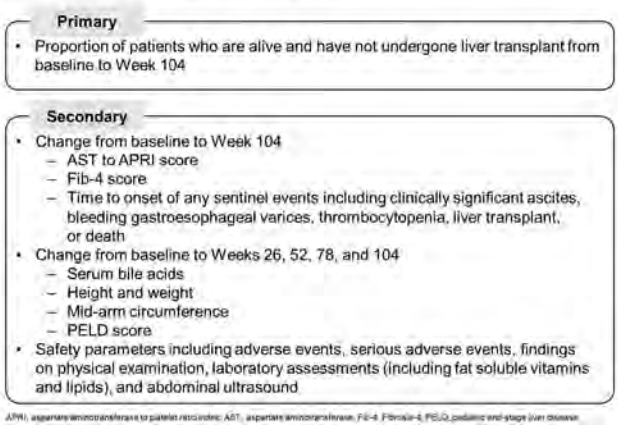
odevixibat in eligible patients with biliary atresia who completed the BOLD study. Patients receive oral odevixibat 120 μg/kg/day once daily for 104 weeks (with an optional extension period), followed by a 4-week safety follow-up. Study endpoints are shown in the Figure. **Results:** BOLD initiated in July 2020 across 66 sites in North America, Europe, the Middle East, and Asia-Pacific (N = 254) with an estimated completion in mid-2026. BOLD-EXT initiated in 2022 (target enrollment, N = 180) and is currently running in 17 countries and is estimated to be completed in 2028. **Conclusion:** BOLD and BOLD-EXT will provide the first data on the use of odevixibat to target disease pathogenesis of biliary atresia in infants and children post-Kasai HPE. Results from BOLD-EXT will help to determine whether odevixibat is efficacious and protects the native liver in the long term.

Reference:
1. Hukkinen M, *et al. Best Pract Res Clin Gastroenterol* 2022;56–57:101764.

Figure. BOLD-EXT study clinical endpoints



Disclosures: Saul Karpen: Albireo/Ipsen: Consultant, Mirum: Consultant, HemoShear: Consultant, Intercept: Consultant, Jiakang Yu: Nothing to Disclose, Henkjan Verkade: Mirum: Grant/Research Support, Mirum: Consultant, Mirum: Speaking and Teaching, Ipsen / Albireo: Consultant, Ipsen / Albireo: Grant/Research Support, Ipsen / Albireo: Speaking and Teaching, Intercept: Consultant, Orphalan: Consultant, Vertex: Consultant, ProQR: Consultant, Rectify: Grant/Research Support, Vicky Ng: Nothing to Disclose, Shan Zheng: Nothing to Disclose, Jesus Quintero: Nothing to Disclose, Andrew Wehrman: Albireo: Grant/Research Support, Mirum: Advisor, Amrita Narang: Ipsen: Consultant, Mirum: Consultant, MedaCorp: Consultant, Ipsen: Grant/Research Support, Ekkehard Sturm: Mirum: Consultant, IPSEN: Consultant, Helen Evans: Nothing to Disclose, Fernando Alvarez: Nothing to Disclose, Kathleen Loomes: Mirum: Consultant, Albireo/Ipsen: Consultant, Mirum: Clinical trials, Albireo/Ipsen: Clinical trials, Nadia Ovchinsky: Nothing to Disclose, Winita Hardikar: Ipsen: Advisor, Advanz pharma: Advisor, Reuven Cohen: Nothing to Disclose, Shikha Sundaram: mirum: Advisor, ipsen: Advisor, Mathias Ruiz: Mirum Pharmaceuticals: Consultant, ipsen: Consultant, Susan Siew: Nothing to Disclose, Antal Dezsofi-Gottl: Nothing to Disclose, Ruzaimie Noor: Nothing to Disclose, Orith Waisbourd-Zinman: Nothing to Disclose, Debra Pan: Mirum Pharmaceuticals, Inc: Consultant, Jean Molleston: Gillead: Grant/Research Support, Albireo: Grant/Research Support, Abbvie: Grant/Research Support, Mirum/Shire: Grant/Research Support, Janis Stoll: Nothing to Disclose, Emmanuel Gonzales: Nothing to Disclose, Reha Artan: Nothing to Disclose, Way Lee: Nothing to Disclose, Jaime Chu: Nothing to Disclose, Laura Bauman: Nothing to Disclose, Philip Bufler: Nothing to Disclose, Lorenzo D'Antiga: Selecta: Advisor, Vivet: Advisor, Spark: Advisor, Genespire: Advisor, Tome: Advisor, Mirum: Advisor, Ipsen/Albireo: Advisor, Intercept/Advanz Pharma: Advisor, Alexion/Astra Zeneca: Advisor, Fractyl: Advisor, Mara Cananzi: Nothing to Disclose, Florence Lacaille: Nothing to Disclose, Madeleine Aumar: Nothing to Disclose, Hayriye Gulsen: Nothing to Disclose, Ryan Fischer: Mirum Pharmaceuticals: Speaking and Teaching, Albireo/Ipsen Pharma Inc.: Speaking and Teaching, Eurofins Viracor: Grant/Research Support, Philip Rosenthal: Nothing to Disclose, M Jensen: Ipsen/Albireo: Consultant, Adebowale Adeyemi: Nothing to Disclose, Ulrich Baumann: Nothing to Disclose, Pier Luigi Calvo: Nothing to Disclose, Chayarani Kelgeri: Nothing to Disclose, James Squires: Sanofi: Data Safety Committee, Mirum: Advisor, Ipsen: Advisor, Henry Lin: Nothing to Disclose, Alyssa Kriegermeier: Mirum Pharmaceuticals: Advisor, Michael Rogers: Nothing to Disclose, Alizai Naved: Nothing to Disclose, Huey-Ling Chen: Nothing to Disclose, Kohli Rohit: MIrum: Consultant, Ipsen: Consultant, Sanofi Rare Disease: Consultant, Madrigal: Consultant, Wednesday Marie Sevilla: Ipsen: Employee, Roshawn Watson: Nothing to Disclose, Fatine Elaraki: Nothing to Disclose, Christelle Baffie: Ipsen Innovation: employee, Anna Wallebeck: Nothing to Disclose, Jennifer Grace: Nothing to Disclose, Sofia Ganzha: Nothing to Disclose, Anja Vlahovic: Nothing to Disclose, Piotr Czubkowski: Nothing to Disclose

4505 | REDUCTION IN ITCH-ASSOCIATED DISABILITY AND PRURITUS DISTRIBUTION IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH SELADELPAR IN THE RESPONSE TRIAL

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Background: Pruritus is a common symptom of primary biliary cholangitis (PBC), affecting up to 80% of patients (pts). PBC-associated pruritus may cause substantial disability, including disruptions in sleep and impacts on everyday life. Pruritus can affect any body part of a pt with PBC but is often reported on the head, lower legs, back, palms, and soles. In the Phase 3 RESPONSE trial (NCT04620733), seladelpar, a first-in-class delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist), significantly decreased pruritus in pts with PBC with moderate to severe pruritus (numerical rating scale [NRS] ≥ 4) at baseline vs placebo. A greater reduction in itch was also observed with seladelpar vs placebo as measured by the 5-D Itch and PBC-40 scales in RESPONSE. Here, we further evaluate patient-reported disability and distribution of itch from the 5-D Itch scale in RESPONSE. **Methods:** Pts with PBC who had an inadequate response or intolerance to ursodeoxycholic acid, with alkaline phosphatase $\geq 1.67 \times$ the upper limit of normal (ULN) and total bilirubin $\leq 2 \times$ ULN, were randomized 2:1 to receive daily oral seladelpar 10 mg or placebo for 12 months. Within the 5-D Itch Disability domain, trends in the leisure/social, housework/errands, and work/school items were assessed in the overall population and in pts with NRS ≥ 4 at baseline. Changes in the 5-D Itch Distribution domain across different body regions were also analyzed in pts with NRS ≥ 4 at baseline. **Results:** Of the 193 pts in RESPONSE, 128 received seladelpar and 65 received placebo; 49 pts receiving seladelpar and 23 pts receiving placebo had NRS ≥ 4 at baseline. Scores for individual questions within the 5-D Itch Disability and Distribution domains were similar between seladelpar and placebo groups at baseline. At month 12, pts with NRS ≥ 4 at baseline who received seladelpar showed greater improvements vs placebo in the impact of itching on leisure/social (mean change from baseline −1.2 vs −0.2, $P < .005$), housework/errands (−1.1 vs −0.2, $P < .005$), and work/school (−1.2 vs −0.5, $P < .05$). Greater improvements in these questions were also seen with seladelpar vs placebo in the overall population regardless of baseline itch level. Among pts with NRS ≥ 4 at baseline, fewer seladelpar-treated pts reported itching across different body regions, including on the head, back, and other regions, vs placebo at month 12. **Conclusion:** Treatment with seladelpar improved itch-related disability and decreased bodily distribution of itch vs placebo.

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4506 | CHARACTERIZATION OF A COHORT OF PATIENTS WITH ALAGILLE SYNDROME (ALGS) FROM TWO US HEALTH SYSTEMS IDENTIFIED LEVERAGING NATURAL LANGUAGE PROCESSING

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Background: Alagille syndrome (ALGS) is a rare, genetically inherited disease that primarily presents in early childhood. Though this syndrome follows an autosomal dominant inheritance pattern, its variable penetrance can lead to challenges with diagnosis. For that reason, having more published data on characteristics and profiles of diagnosed patients can aid in future identification of yet undiagnosed patients. This study aimed to identify and characterize individuals diagnosed with ALGS from electronic health record (EHR) data from two major medical health systems in the United States (US) to add to the knowledge base regarding presentation of this disease. **Methods:** This is a non-interventional study leveraging de-identified data ranging from January 1, 2005 to November 15, 2024 from Mayo Clinic and Duke Health Systems. Patients were identified using both structured and unstructured data, where natural language processing (NLP) was utilized to review unstructured data. Patients were included if they had at least one relevant ICD code (ICD 9: 759.89, ICD 10: Q44.71), unstructured instance of diagnosis, or presence of any genetic mutations reported in structured or unstructured data at any time. All records of identified patients underwent manual review to confirm diagnosis. **Results:** In total, 141 patients (Mayo Clinic = 74; Duke Health = 67) were confirmed to have evidence of ALGS. Within the combined cohort, the majority were male (53.2%), White (67.4%), and not Hispanic/Latino (82.3%). The

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median age at first available record with mention of ALGS was 3 years in the Mayo cohort and 2 years in the Duke cohort. Hepatic abnormalities were common and included jaundice (27.7%), pruritus (22%), cholestasis (22%), cirrhosis (12.1%), and end-stage liver disease (8.5%) (Table 1). Cardiac abnormalities were the second most common reported clinical feature, with hypertension (22%) and congenital heart disease (9.9%) being prevalent. Reports of skeletal, ophthalmologic, facial, and renal abnormalities were less frequent than other known common characteristics seen in ALGS patients for the identified cohort. **Conclusion:** To our knowledge, this is the first study to leverage EHR from two large medical institutions to identify and characterize a cohort of patients diagnosed with ALGS. These data will be valuable in furthering the understanding of the disease and potentially aid in faster diagnosis of yet undiagnosed patients.

Table 1: Baseline and Clinical Characteristics of Patients Diagnosed with ALGS

Variable	Mayo Clinic (n=74)	Duke Health (n=67)	Combined (N=141)
Age (years) at first available record, median (IQR)	3 (0.0 - 19.0)	2.0 (1.0 - 7.0)	N/A
Sex, n (%)			
Male	37 (50)	38 (56.7)	75 (53.2)
Female	36 (48.6)	29 (43.3)	65 (46.1)
Unknown	1 (1.4)	0 (0)	1 (0.7)
Race, n (%)			
White	60 (81.1)	35 (52.2)	95 (67.4)
Black	3 (4.1)	12 (17.9)	15 (10.6)
Asian	2 (2.7)	5 (7.5)	7 (5)
Other	3 (4.1)	0 (0)	3 (2.1)
Unknown	6 (8.1)	15 (22.4)	21 (14.9)
Ethnicity, n (%)			
Hispanic or Latino	2 (2.7)	12 (17.9)	14 (9.9)
Not Hispanic or Latino	65 (87.8)	51 (76.1)	116 (82.3)
Others	6 (8.1)	4 (6)	10 (7.1)
Unknown	1 (1.4)	0 (0)	1 (0.7)
Clinical Abnormalities, n (%)			
Hepatic abnormalities			
Jaundice	18 (24.3)	21 (31.3)	39 (27.7)
Pruritus	14 (18.9)	17 (25.4)	31 (22)
Cholestasis	16 (21.6)	15 (22.4)	31 (22)
Cirrhosis	8 (10.8)	9 (13.4)	17 (12.1)
End-stage liver disease	2 (2.7)	10 (14.9)	12 (8.5)
Cardiac abnormalities			
Hypertension	16 (21.6)	15 (22.4)	31 (22)
Congenital heart disease	6 (8.1)	8 (11.9)	14 (9.9)
Skeletal abnormalities			
Butterfly vertebrae	6 (8.1)	4 (6)	10 (7.1)
Rickets	4 (5.4)	3 (4.5)	7 (5)
Ophthalmologic abnormalities			
Posterior embryotoxon	4 (5.4)	6 (9)	10 (7.1)
Retinal pigmentary changes	2 (2.7)	0 (0)	2 (1.4)
Axenfeld anomaly	1 (1.4)	0 (0)	1 (0.7)
Facial feature abnormalities			
Broad forehead	5 (6.8)	4 (6)	9 (6.4)
Deep-set eyes	5 (6.8)	4 (6)	9 (6.4)
Pointed chin	3 (4.1)	3 (4.5)	6 (4.3)
Renal abnormalities			
Renal cysts	2 (2.7)	3 (4.5)	5 (3.5)
Renal artery stenosis	3 (4.1)	1 (1.5)	4 (2.8)
Renal tubular acidosis	1 (1.4)	1 (1.5)	2 (1.4)
Renal dysplasia	0 (0)	2 (3)	2 (1.4)

Disclosures: Seema Meloni: Ipsen Biopharmaceuticals: Employee, Ravikumar Patel: Nothing to Disclose, Praveen Kumar-M: Nothing to Disclose, Sivaprakasm G: Nothing to Disclose, Gopinath Ashokkumar: Nothing to Disclose, Fatine Elaraki: Nothing to Disclose, Marie-Cecile Fournier: Nothing to Disclose, Danielle Dray: Nothing to Disclose, Sara Hassan: Nothing to Disclose

4507 | EVALUATION OF CLINICAL EVENTS AND HEPATIC BIOMARKERS IN OBETICHOLIC ACID-TREATED PATIENTS ALIGNED TO 2021 US PRESCRIBING INFORMATION CRITERIA FROM THE HEROES STUDY

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Background: Obeticholic acid (OCA) is indicated as second-line treatment for primary biliary cholangitis (PBC) in patients (pts) with intolerance or inadequate response to ursodeoxycholic acid (UDCA). In 2021, the OCA US Prescribing Information (USPI) was updated, contraindicating use in pts with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension (PHTN). We evaluated clinical events and trends in hepatic biomarkers in OCA-treated vs non–OCA-treated pts who were aligned to OCA 2021 USPI criteria from HEROES, a fully real-world trial emulation (NCT05292872). **Methods:** HEROES analyzed pts with PBC from Komodo's Healthcare Map who experienced failure of UDCA and were either treated with OCA or eligible for but not treated with OCA from 2016 to 2021. Non–OCA-treated pts were followed from the visit date (control index) until the first occurrence of a clinical event, end of follow-up, or initiation of OCA; OCA-treated pts were followed from the date of first OCA dose (OCA index) until the first occurrence of a clinical event, end of follow-up, or OCA termination. Patients were allowed to contribute multiple control indexes. Standardized morbidity ratio weights were calculated to standardize the treatment arms. The USPI-aligned population excluded all pts with hepatic decompensation and/or presence of cirrhosis with clinical evidence of PHTN. Events of liver transplantation or death, as well as trends in total bilirubin (TB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelets, and albumin, were assessed over 60 months. **Results:** In the weighted USPI-aligned population, 308 OCA-treated pts contributed OCA indexes, and 3252 non–OCA-treated pts contributed 310.4 control indexes. Liver transplants and deaths were less frequent among OCA-treated indexes (0 and 1 [0.32%], respectively) compared with non–

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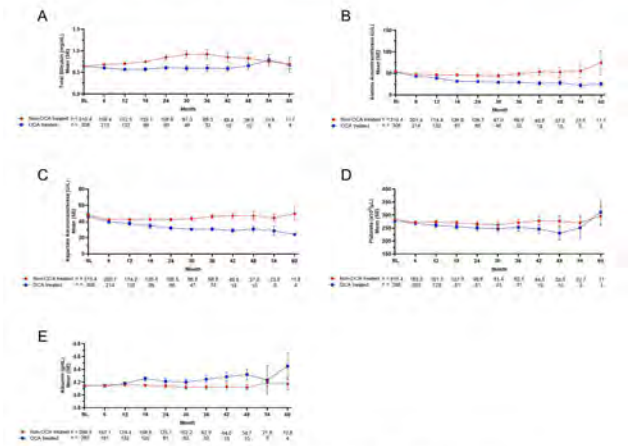
OCA-treated indexes (0.56 [0.18%] and 5.33 [1.72%], respectively). Compared with the non–OCA-treated arm, mean TB, ALT, and AST levels were consistently lower over time in the OCA-treated arm (Figure). Platelet and albumin levels generally remained the same through month 60 in the OCA-treated arm. **Conclusion:** In the real-world setting, no liver transplants were observed in the OCA-treated arm aligned to the USPI criteria, and fewer deaths occurred in the OCA-treated arm compared with the non–OCA-treated arm. Serum albumin, TB, and platelets remained stable, while ALT/AST improved over 60 months with OCA treatment.

Figure. Trends in total bilirubin (**A**), ALT (**B**), AST (**C**), platelet count (**D**), and albumin (**E**) from baseline to month 60 in the OCA-treated and non–OCA-treated arms



Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; OCA, obeticholic acid.

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4508 | RATE OF LIVER EVENTS AND RELATED COMPLICATIONS IN A PREVALENT PRIMARY BILIARY CHOLANGITIS POPULATION: A US CLAIMS DATABASE ANALYSIS

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Background: Primary biliary cholangitis (PBC) is a chronic, progressive, immune-mediated, cholestatic liver disease. Liver-related complications include portal hypertension, varices, hepatic decompensation, and hepatocellular carcinoma. Patients with PBC may also experience other complications related to liver disease, including osteoporosis leading to fractures, and fat-soluble vitamin malabsorption due to reduced bile salts in the intestinal lumen. Limited population-based data exist on incidence rates (IRs) of these events among patients with PBC. These data are needed to contextualize clinical program findings and distinguish potential drug effects from those of the underlying disease. In this study, two cohorts—an overall PBC cohort and a trial-like cohort—were defined to generate relevant data for such contextualization. **Methods:** This was a retrospective cohort study of patients with prevalent PBC using 2016–2023 administrative claims data from Merative MarketScan Commercial and Medicare Supplemental Database. Patients with PBC were identified based on $\geq$2 ICD-10 diagnosis codes for PBC on separate inpatient or outpatient visits within a 1-year period. IRs of liver events and related complications (defined using ICD-10 codes) were estimated for the overall PBC population and a trial-like cohort meeting key inclusion/exclusion criteria of the Phase 3 Global Linerixibat Itch STudy of Efficacy and Safety iN PBC (GLISTEN) trial (NCT04950127). **Results:** Overall, 7160 patients with PBC were identified (mean age: 58.2 years, 86.7% female) of whom 2796 were included in the trial-like cohort (mean age: 56.1 years, 90.5% female). The median follow-up time was 1.4 years (interquartile range [IQR]: 0.6–2.7) for each cohort. In the overall PBC cohort, the IRs of liver-related events ranged from 0 events per 1000 person-years (PYs) for vitamin K deficiency to 200.5 per 1000 PYs for cirrhosis (95% confidence interval [CI]: 191.7, 209.6) (Table). Other liver-related events and related complications with the greatest IRs were ascites (IR: 41.2 per 1000 PYs, 95% CI: 37.8, 44.9), esophageal varices (IR: 48.9 per 1000 PYs, 95% CI: 45.1, 53.0), portal hypertension (IR: 43.9 per 1000 PYs, 95% CI: 40.3, 47.8), and fracture (IR: 48.1 per 1000 PYs, 95% CI: 44.3, 52.1). IRs were consistently higher in the overall PBC cohort

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compared with the trial-like cohort. **Conclusion:** In the overall PBC cohort, cirrhosis, ascites, esophageal varices, portal hypertension, and fracture had the highest IR and cumulative occurrence. The same trend was seen in the trial-like cohort, with the exception of ascites. Overall, many of these events are common in the natural course of PBC. The higher IRs in the overall PBC cohort compared with the trial-like cohort likely reflect the trial exclusion criteria. These results provide important information to aid in contextualizing safety findings from PBC clinical trials.

Funding: GSK (222317)

Table. Incidence rates of liver events and related complications in the overall PBC cohort and trial-like cohort in Merative MarketScan Commercial and Medicare Supplemental Database 2016–2023

	Overall PBC cohort			Trial-like cohort*		
	Events, n	PY	IR per 1000 PY (95% CI)	Events, n	PY	IR per 1000 PY (95% CI)
Spontaneous bacterial peritonitis	89	13,564.2	5.1 (4.0, 6.4)	5	5186.4	1.0 (0.3, 2.3)
Ascites	530	12,858.3	41.2 (37.8, 44.9)	53	5118.0	10.4 (7.8, 13.6)
Cirrhosis	1942	9686.6	200.5 (191.7, 209.6)	478	4111.3	116.3 (106.1, 127.2)
Esophageal varices	608	12,424.0	48.9 (45.1, 53.0)	99	4986.0	19.9 (16.1, 24.2)
Varices other than esophagus	231	13,130.8	17.6 (15.4, 20.0)	67	5060.7	13.2 (10.3, 16.6)
Variceal bleeding	139	13,377.9	10.4 (8.7, 12.3)	19	5167.8	3.7 (2.2, 5.7)
Portal hypertension	551	12,543.1	43.9 (40.3, 47.6)	92	5002.5	18.4 (14.8, 22.6)
Hepatic encephalopathy	46	13,561.0	3.4 (2.5, 4.5)	0	5191.7	0
Hepatocellular carcinoma	95	13,494.6	7.0 (5.7, 8.6)	8	5168.9	1.6 (0.7, 3.1)
Liver transplant	184	13,305.3	13.8 (11.9, 16.0)	20	5168.4	3.9 (2.4, 6.0)
Fracture	609	12,668.6	48.1 (44.3, 52.1)	168	4921.6	34.1 (29.2, 39.7)
Vitamin A deficiency	31	13,561.4	2.3 (1.6, 3.2)	6	5179.2	1.2 (0.4, 2.5)
Vitamin K deficiency	0	13,628.7	0	0	5191.7	0

*Trial-like cohort met similar inclusion/exclusion criteria to the Phase 3 Global, Investigator-Blind Study of Efficacy and Safety in PBC (GLOBAL) trial (NCT04950127). CI, confidence interval; IR, incidence rate; PBC, primary biliary cholangitis; PY, person-year.

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4509 | BIOPSYCHOSOCIAL APPROACH TO FATIGUE IN PRIMARY SCLEROSING CHOLANGITIS: IDENTIFYING TREATMENT TARGETS IN THE PROSPECTIVE SOMA.LIV STUDY

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Background: Fatigue is a debilitating symptom in autoimmune liver diseases, yet research in Primary Sclerosing Cholangitis (PSC) is scarce. This study aimed to estimate the prevalence of fatigue in PSC, investigate its biopsychosocial correlates, and identify predictors of fatigue severity to inform future treatment strategies. **Methods:** In this prospective study, 226 patients with PSC were enrolled. Fatigue severity was assessed using the fatigue domain of the PBC-40 questionnaire at baseline and again after six months. Potential predictors—including biomedical, psychological, and social variables—were assessed via clinical records, laboratory tests, and self-reported measures. **Results:** At baseline, 19% of patients exhibited clinically significant fatigue, defined as a PBC-40 fatigue score >33. Compared to those without significant fatigue, these patients reported greater psychosocial burden and showed worse disease-related biomarkers, including higher bilirubin and increased liver stiffness. However, multivariate regression analysis revealed that only elevated C-reactive protein (CRP) levels ($p = 0.02$)—not markers of cholestasis or liver disease stage—were significantly associated with fatigue severity at baseline. Psychological and social factors significantly associated with greater fatigue included maternal migration status ($p < 0.001$), fear-avoidance beliefs ($p < 0.001$), depression ($p < 0.001$), and antidepressant use ($p < 0.001$). Interestingly, higher anxiety severity was negatively associated with fatigue ($p < 0.001$). Over the six-month follow-up, fatigue levels remained relatively stable: 92% of patients without significant fatigue at baseline remained below the threshold, while fatigue persisted in 79% of those initially affected. Notably, higher baseline fatigue predicted greater fatigue reduction over time ($p < 0.001$), whereas elevated IL-6 levels ($p = 0.04$) and fear-avoidance beliefs ($p < 0.001$) were associated with worsening fatigue. **Conclusion:** Fatigue is a common and persistent symptom in PSC, shaped by both biological and psychological factors. Findings highlight the need for further research into the roles of systemic inflammation, as well psychosocial factors such as depression, and maladaptive coping behaviors. Interventions targeting these domains—particularly through promoting adaptive coping strategies—may offer promising avenues for treatment.

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4510 | MODELING THE CLINICAL CONSEQUENCES OF GAPS AND DELAYS IN INITIATING SECOND-LINE THERAPIES IN PRIMARY BILIARY CHOLANGITIS PATIENTS WHO HAVE INADEQUATE RESPONSE TO URSODEOXYCHOLIC ACID

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Background: In primary biliary cholangitis (PBC), inadequate biochemical control is associated with greater risk of progression to advanced liver disease and, in turn, transplant, and death. Approximately 40% of patients respond inadequately to first-line (1L) ursodeoxycholic acid (UDCA), while up to 5% are intolerant to UDCA. For these patients, timely initiation of effective second-line (2L) therapies is critical to avoid disease progression. This study aimed to evaluate the impact of gaps and delays in initiation of 2L therapies in PBC patients who have not achieved adequate response to 1L UCDA. **Methods:** A Markov model was developed to simulate clinical outcomes for patients with PBC over a 20-year time horizon. The model included health states for PBC, defined by alkaline phosphatase (ALP) and bilirubin elevation and compensated cirrhosis status, and advanced liver disease, including decompensated cirrhosis, hepatocellular carcinoma and transplant. For a cohort of 1,000 patients, timely 2L (i.e., immediate treatment) was compared with a gaps and delays scenario considering a range of 2L delay times (1-5 years) and never 2L (10-50%) estimates; in the base case, the mean delay was 1.25 years and 25% of patients never received 2L. Transition probabilities were derived from published literature and clinical trials. UDCA-intolerant patients were not considered as this subgroup (~5-10% of PBC patients) are not well characterized and likely have a different disease trajectory. Outcomes were assessed in terms of biochemical status and advanced liver disease outcomes, namely liver transplant-free survival (LTFS). **Results:** In the base case, timely 2L resulted in more patients achieving normalization of ALP after 1 (284/1,000 vs. 0/1,000) and 3 years (271 vs. 188). Alongside, more patients had ALP $\leq$ 1.67x the upper limit of normal: 659 vs. 0; 657 vs. 464. These differences translated to higher 10- and 20-year LTFS for timely 2L: 839 patients were alive and transplant-free at 10-years vs. 767 in the gaps and delays scenario; at 20-years, 630 vs. 516 patients, respectively. Outcomes were worse for longer delays and higher percentage never 2L estimates (Table 1). **Conclusion:** Gaps and delays in initiation of 2L therapies among PBC patients with inadequate response to 1L UCDA resulted in notably lower LTFS. Therefore, timely identification of inadequate responders to 1L UDCA and prompt linkage to 2L treatment is crucial for avoiding adverse clinical consequences of PBC.

		Percentage Never 2L estimate										
		0%	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%
Delay duration (years)	1.00	-25	-34	-42	-51	-59	-68	-76	-85	-93	-102	-110
	1.25	-32	-40	-48	-56	-64	-73*	-81	-89	-97	-105	-114
	1.50	-38	-46	-54	-62	-70	-78	-86	-93	-101	-109	-117
	2.00	-52	-59	-66	-73	-81	-88	-95	-102	-109	-116	-124
	2.50	-66	-72	-79	-85	-92	-98	-105	-111	-118	-124	-130
	3.00	-79	-85	-91	-97	-102	-108	-114	-120	-126	-132	-137
	3.50	-93	-98	-103	-108	-113	-118	-124	-129	-134	-139	-144
	4.00	-106	-110	-115	-119	-124	-128	-133	-137	-142	-146	-151
	4.50	-119	-122	-126	-130	-134	-138	-142	-146	-149	-153	-157
	5.00	-131	-134	-137	-141	-144	-147	-150	-153	-157	-160	-163

*Base case estimate.

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4511 | PHYSICIAN REPORTED ASSESSMENT OF PRURITUS AMONGST PATIENTS WITH PSC: RESULTS: FROM A REAL-WORLD SURVEY IN FRANCE, GERMANY, ITALY AND THE UNITED STATES

Marlyn Mayo[1] Marco Carbone[2] William Johnson[3] Lena Amari[3] Guy Lacey[4] Lucia Quadrado[4] Jolan Terner-Rosenthal[4] Robin Howard[4] Verena Keitel-Anselmino[5], [1]University of Texas Southwestern Medical Center, [2]University of Milano-Bicocca, Milan, Italy, [3]Adelphi Real World, Bollington, United Kingdom, [4]Mirum Pharmaceuticals, Inc., Foster City, California, [5]University Hospital Magdeburg, Magdeburg, Germany

Background: Primary sclerosing cholangitis (PSC) is a chronic, progressive liver disease characterized by damage to intra- and extrahepatic bile ducts. Approximately 70% of patients with PSC indicate that they experience pruritus, but it is unclear if that frequency is also observed by the treating physicians and how often pruritus is discussed during office visits. The purpose of the current study is to describe physician reported frequency and assessment of pruritus amongst patients with PSC. **Methods:** Data were extracted from the

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Adelphi Real World PSC Disease Specific Programme™, a cross-sectional survey with retrospective data collection of physicians and their patients with PSC in France, Germany, Italy, and the United States from November 2024 to April 2025. Elements of the retrospective data collection utilized physicians' EMRs which will be presented at a later date. The current presentation is focused on physicians' perceptions and attitudes around their management of PSC. Analyses used descriptive statistics. **Results:** Overall, results from 132 physicians were included in this analysis. The mean (SD) number of patients with PSC managed by each physician was 33 (42). Physicians stated that 41% (24) of their patients with PSC had pruritus and almost all (93%) believe that pruritus has a profound impact on a patient's quality of life (QoL). The majority (81%) of physicians indicated that clinically significant pruritus may be unidentified in many patients so pruritus is proactively assessed during routine visits. The most common ways physicians assess their patients' pruritus is through visual assessment of the patient's skin (77%), and questions focused on sleep (69%) and QoL (67%). Assessment of pruritus severity (62%) and frequency of episodes (64%) is also common. Importantly, 71% of physicians agree that a standard, easy to use pruritus assessment tool is needed to determine the severity of pruritus and impact on patients' QoL. While most physicians proactively discuss pruritus with their patients with PSC, common reasons for not assessing at every visit include: discussed in previous consultations (45%), patient has not complained of pruritus (41%), lack of effective antipruritic medications (30%), and limited visit time (29%). **Conclusion:** While most physicians report that they assess the presence of pruritus in their patients with PSC, there is a lack of uniformity in how it is ascertained. Perceived barriers include lack of time and effective treatment.

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4512 | THE ROLE OF CHOLESTATIC GENETIC TESTING IN THE EVALAUTION OF PATIENTS WITH UNEXPLAINED CHOLESTASIS

Mitchell Shiffman[1] Jennifer Miller[1] Kimberly Taylor[1] Marilou Cicero[1] Sarah Hubbard[1] April Ashworth[2] Rebecca Rathburn[1] Staci Harpster[1] Karla Pray[1] Philip Alexander[1], [1]Bon Secours Mercy Health, [2]Bon Secours Liver Institute

Background: Genetic cholestatic disorders (GCD) are considered a rare form of cholestatic liver disease. These disorders are due to defective bile salt and/or phospholipid secretion into bile, the intrahepatic accumulation of toxic bile acids, liver injury, progressive fibrosis, cirrhosis, and liver failure. The most well recognized forms of GCD include Progressive Familial Intrahepatic Cholestasis (PFIC) and Alagille syndrome. These disorders typically present in infancy and early childhood and lead to the need for liver transplant at an early age. More recently, milder forms of GCD have been recognized in adults. This has been facilitated by the development of genetic panels for GCD which are now available for clinical use. Many adults have cholestasis of undefined etiology despite a thorough evaluation which would typically include serology, MRI/MRCP and liver biopsy. We hypothesized that the majority of these patients (pts) have a GCD. **Methods:** A total of 42 pts with cholestasis of undefined etiology underwent genetic testing. The criteria for genetic testing included an elevation in ALP that could not be explained by serologic testing, MRI/MRCP and/or liver histology; and either an elevation in serum bile acids, or unexplained itching. Pts were excluded if they had a defined etiology for cholestasis including PBC, PSC, sarcoidosis, amyloidosis, choledocholithiasis. **Results:** The mean age of the cohort was 56 years (16-81), 26% male, 50% Caucasian, 36% African American, 12% Hispanic. The mean ALP was 281 (61-1839), GGT 278 (17-1248), AST 54 (14-275), ALT 66 (10-488), TBILI 1.2 (0.2-24.0). Mean LS by Fibroscan was 7.2 kPa (3.2-17.3). 28/42 pts underwent liver biopsy. The most common histologic finding was mild non-specific portal inflammation with no fibrosis. 17% of pts had cirrhosis. Itching was present in 26%. Mutations in various genes associated with cholestasis were identified in 73% of pts. A total of 24 genes were affected in the 42 pts. 6 pts had 1 affected gene, 7 pts had 2 affected genes, 13 pts had 3 or more affected genes. The most commonly affected genes were: UGT1A1, CFTR, AKRIC4, ADAR. Mutations in ABCB4, a gene associated with PFIC-3 and MYO5B, a gene associated with PFIC-6, were identified in 3 and 1 pts respectively. Of the 7 pts with cirrhosis 75% had a mutation in at least one cholestatic gene. There was no relationship between which genes were affected and either the serum level of ALP, GGT, the presence of itching or cirrhosis. **Conclusion:** We conclude that mutations in genes associated with cholestasis are

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common in adults with cholestasis of undefined etiology. The majority of pts with a GCD have affected genes that are not currenly known to be associated with PFIC or Alegille syndrome. Although the natural history of GCD in adults remains undefined and the majority of these pts appear to have mild histologic findings, 17% of pts had cirrhosis. Testing for GCD appears to be useful in adults with cholestsis of undefined etiology.

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4513 | DISTINCT MOLECULAR MECHANISMS UNDERLYING PPAR-Δ–MEDIATED ALLEVIATION OF HEPATOCYTE INJURY IN PRIMARY BILIARY CHOLANGITIS

Garnik Arustamyan[1] Masashi Okawa[1] Yein Woo[1] Daniel Pinski[1] Ju Won Kim[1] Meng Li[2] Takeshi Saito[1], [1]Keck School of Medicine, University of Southern California, [2]USC Libraries Bioinformatics Service, University of Southern California

Background: Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease characterized by immune-mediated destruction of intrahepatic bile ducts, resulting in cholestasis and secondary bile acid-induced hepatocyte injury. Ursodeoxycholic acid (UDCA), the first-line therapy, achieves remission in only approximately 30% of patients, leaving the majority at risk of progressing to end-stage liver disease. Recently approved second-line treatments, PPAR-δ agonists, have demonstrated favorable clinical outcomes; however, the mechanisms through which PPAR-δ activation mitigates bile acid toxicity in hepatocytes remain poorly defined. This study, therefore, aims to delineate the molecular and biochemical effects of PPAR-δ activation in human hepatocytes (HHs) and elucidate whether these effects contribute to potential synergistic benefits with other PBC therapeutics. **Methods:** HHs were cultured in vitro and treated with PPAR-δ agonists (seladelpar or elafibranor) either as monotherapy or in combination with other PBC therapeutics, including FXR agonists (UDCA, obeticholic acid) and a PPAR-α agonist (fenofibrate). mRNA-seq-based transcriptomic profiling, followed by bioinformatics analyses, was performed to decipher hepatocellular responses unique to PPAR-δ agonism and shared pathways with other therapeutics to identify mechanisms regulating bile acid homeostasis. Additionally, the impact of PPAR-δ agonists on bile acid dynamics in HHs was evaluated using a fluorescently labeled bile acid trafficking assay and LC-MS–based bile acid profiling. Lastly, the therapeutic efficacy of PPAR-δ agonists, alone or in combination with other agents, was assessed in an in vitro cholestatic HH model through evaluation of cell death pathway activation status. **Results:** Transcriptomic analysis identified differentially expressed genes (DEGs) uniquely regulated via the PPAR-δ pathway, notably those involved in bile acid metabolism and trafficking. Comparative bioinformatics analysis indicated that gene expression changes driven by PPAR-δ were distinct, showing minimal overlap with patterns induced by FXR agonists or fenofibrate. Activation of PPAR-δ in HHs significantly decreased intracellular bile acid abundance. Quantitative LC-MS–based profiling further confirmed this reduction, particularly for highly toxic bile acid species, establishing a molecular basis for improved bile acid homeostasis via PPAR-δ activation. **Conclusion:** This study demonstrates that PPAR-δ activation restores hepatocellular bile acid homeostasis through molecular mechanisms distinct from those of other PBC therapeutics. Our findings highlight the therapeutic potential of PPAR-δ agonists for alleviating hepatocyte injury in PBC and suggest the utility of combination therapies with complemental mechanisms to enhance clinical outcomes.

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Pharma: Consultant, Quotient Therapeutics: Consultant, CytoPathfinder, Inc.: Consultant.

4514 | HIGHER CIRRHOSIS BURDEN AMONG MINORITY PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: A HEALTH DISPARITIES STUDY

Jade Pace[1] Maham Ghani[1] Michael Attanasi[1] Brittany Kwait[1] Christopher Dorizas[1] Bryana Belin[1] Shahidul Islam[1] Sanjaya Satapathy[1], [1]Zucker School of Medicine at Hofstra/Northwell

Background: Primary biliary cholangitis (PBC) outcomes may be influenced by racial disparities and social determinants of health, but this relationship remains understudied. **Methods:** We conducted a retrospective analysis of non-Hispanic White and minority patients with PBC to examine racial disparities and predictors of cirrhosis. Inclusion criteria consisted of patients at least 18 years of age with an ICD-10 code diagnosis of PBC and positive anti-mitochondrial antibody titer $\geq$1:40 that were admitted over the past 10 years at any of 23 Northwell Care sites. Demographic and clinical characteristics were compared between groups using the Chi-square or Fisher's exact test for categorical variables and Wilcoxon rank sum-test for continuous variables. Multiple logistic regression analysis was performed to identify independent predictors of cirrhosis, adjusting for relevant covariates including the Social Deprivation Index (SDI). **Results:** We identified 378 patients that met inclusion criteria (254 non-Hispanic White and 124 minority). Minority patients were younger (66 vs 73 years, $p < 0.001$), had lower BMI (24 vs 27, $p = 0.001$), and had higher SDI scores (59 vs 23, $p < 0.001$) compared to non-Hispanic Whites. They were more likely to be on Medicaid (22% vs 3.3%, $p < 0.001$) and undergo liver biopsy (9.7% vs 4.3%, $p = 0.041$). Minority patients had higher rates of cirrhosis (51% vs 37%, $p = 0.014$) and longer ICU stays (124 vs 72 hours, $p = 0.03$), but received less ursodiol treatment (44% vs 65%, $p < 0.001$). In the adjusted analysis, minority status remained an independent predictor of cirrhosis (Odds Ratio 1.95, 95% Confidence Interval [1.18-3.24], $p = 0.01$). **Conclusion:** Significant racial disparities exist in PBC care and outcomes, with minority patients having higher rates of cirrhosis despite younger age. These findings highlight the need for targeted interventions to address healthcare disparities in PBC management.

Table 1. Key Characteristics and Outcomes by Racial Groups in Patients with PBC

	Minority (n=124)	Non-Hispanic White (n=254)	P-value
Demographics			
Age, median (IQR)	66 (55, 75)	73 (63, 80)	<0.001
BMI, median (IQR)	24 (22, 28)	27 (23, 31)	0.001
SDI score, median (IQR)	59 (28, 83)	23 (8, 46)	<0.001
Medicaid Insurance, n (%)	18 (22)	7 (3.3)	<0.001
Clinical Outcomes			
Cirrhosis, n (%)	58 (51)	77 (37)	0.014
ICU Length of Stay, hours, median (IQR) *	124 (71, 277)	72 (44, 129)	0.030
Liver Biopsy, n (%)	12 (9.7)	11 (4.3)	0.041
Ursodiol Treatment, n (%)	54 (44)	165 (65)	<0.001

IQR = Interquartile Range; SDI = Social Deprivation Index *Among patients admitted to ICU

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4515 | ASSOCIATIONS BETWEEN PATIENT-REPORTED OUTCOMES AND OBJECTIVE DISEASE PARAMETERS IN PRIMARY BILIARY CHOLANGITIS: A UNITED STATES SINGLE-CENTER STUDY

Ana Marenco-Flores[1] Natalia Rojas-Amaris[1] Romelia Barba[2] Daniela Goyes[3] Esli Medina Morales[4] Leandro Sierra[5] Behnam Saberi[6] Vilas Patwardhan[1] Alan Bonder[6], [1]Beth Israel Deaconess Medical Center, [2]Texas Tech University, [3]Yale School of Medicine, [4]Rutgers New Jersey Medical School, [5]Cleveland Clinic Foundation, [6]Beth Israel Deaconess Medical Center, Harvard Medical School

Background: Primary biliary cholangitis (PBC) is a rare, chronic autoimmune liver disease marked by

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progressive bile duct damage and can progress to end-stage liver disease. While often asymptomatic at diagnosis, many patients later develop fatigue and pruritus, impacting health-related quality of life (HRQoL). The growing emphasis on HRQoL in liver disease highlights the need for patient-centered care. This study examines HRQoL in a U.S. PBC cohort by correlating clinical markers with patient-reported outcomes (PROs). **Methods:** We conducted a prospective, single-center study to assess HRQoL in U.S. PBC patients by examining associations between PROs and clinical data. Participants completed the PBC-40 and consented to medical record review. Exclusion criteria included age <18, missing data for score assessment, early ursodeoxycholic acid (UDCA) discontinuation, or missing PROs after 12 months. Clinical variables included demographics, liver biochemistry, cirrhosis status, and treatment response per Paris II criteria. GLOBE scores stratified prognostic risk, and standard cutoffs defined liver stiffness categories. Categorical variables are reported as frequencies (%), with comparisons via χ^2, Mann–Whitney U, or Kruskal–Wallis tests. Pairwise Pearson correlations assessed relationships between PBC-40 domains, GLOBE score, and liver stiffness ($p < 0.05$). **Results:** A total of 121 U.S. patients with PBC were included, with a mean age at diagnosis of 54 years; 89% were female. UDCA response was observed in 59% of patients, while only 3% were high risk by GLOBE score. Despite biochemical response, Paris II responders reported worse social, emotional, and total PBC-40 scores ($p = 0.017$, 0.015, 0.021), while the GLOBE score showed no association with HRQoL. In contrast, liver stiffness–based risk correlated with worse social, cognitive, and emotional scores ($p = 0.017$, 0.020, 0.041), with a trend toward higher total scores ($p = 0.052$). PBC-40 domains showed no significant correlations with GLOBE score or liver stiffness. GLOBE score correlated modestly with liver stiffness ($r = 0.28$, $p = 0.002$). **Conclusion:** PROs in PBC often diverged from objective disease measures, suggesting that traditional clinical parameters may not fully capture the patient experience. These discrepancies underscore the importance of a personalized approach to care, incorporating both baseline risk and PROs. Treatment should focus not only on slowing disease progression and improving liver tests but also on recognizing and addressing quality of life.

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4516 | AUTOIMMUNE-RELATED CIRRHOSIS IS ASSOCIATED WITH AN INITIAL LOWER RISK OF DECOMPENSATION AND HEALTHCARE UTILIZATION: A POPULATION-BASED ANALYSIS

Raj Vuppalanchi[1] Craig Lammert[1] LaKeisha Boyd[2] Yang Li[2] Lauren Nephew[1] Marwan Ghabril[1] Naga Chalasani[1] Eric Orman[1] Archita Desai[1], [1]Indiana University School of Medicine, [2]Indiana University School of Medicine and Richard M. Fairbanks School of Public Health

Background: Cirrhosis due to autoimmune etiologies (Autoimmune-related cirrhosis, ARC) has a distinct clinical phenotype with unique patterns in natural history. The current study aims to characterize patients with ARC and compare their outcomes with those of patients with other common etiologies of cirrhosis.

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Methods: The Indiana Digital Cirrhosis Cohort comprises 13,264 adults diagnosed with cirrhosis between 2018 and 2020. Participants were stratified into two groups based on cirrhosis etiology: (1) ARC (AIH/PBC/PSC) and (2) other etiologies (non-ARC). We compared baseline demographics, clinical characteristics, and healthcare utilization (HCU) between the two groups. Outcomes included time to first decompensation, liver transplant (LT), and death. Multivariable Cox regression models examined the time from diagnosis to these outcomes between the two groups, adjusting for age, gender, race, insurance, marital status, and MELD3.0 score. Multivariable logistic regression was used to identify predictors of initial decompensation and LT/death. **Results:** The prevalence of ARC was 11% (n = 1454), and differed from those with non-ARC in sociodemographic, clinical, and HCU features [more female (75% vs. 44%, $p < 0.0001$), White (91% vs. 87%, $p < 0.0001$), commercially insured (34% vs. 26%, $p < 0.0001$), married (57% vs. 43%, $p < 0.0001$)]. The ARC group had significantly lower prevalence of alcohol use disorder (3% vs. 20%), type 2 diabetes (22% vs. 33%), coronary artery disease (11% vs. 17%), and substance use disorder (1% vs. 8%) [all $p < 0.0001$]. They also had higher albumin (3.8 vs. 3.6 g/dL), higher platelet count (173 vs. 136 $\times 10^9$/L), and lower MELD3.0 scores (13.1 vs. 15.2, $p < 0.0001$). At baseline, 87% (n = 1267) of the ARC group and 77% of the non-ARC group were compensated. The frequency of HCU and decompensating events is reported in Table 1. A greater proportion of ARC patients remained compensated over time, with a lower risk of decompensation compared to the non-ARC group (HR: 0.58; 95% CI: 0.52-0.65). Significant predictors of decompensation for the ARC group included lower age, male gender, White race, and a MELD score of 15 or higher. After initial decompensation, the transplant-free survival rates were similar between the two groups (HR 0.997; 95% CI: 0.867-1.147). **Conclusion:** Patients with ARC have a better early prognosis with fewer comorbidities, fewer hepatic decompensations, and lower HCU. However, after the initial decompensation event, survival in the ARC group is similar to that of cirrhosis from other etiologies.

Variables	Autoimmune-related Cirrhosis (N=1454)	Cirrhosis of Other Etiology (N=11,810)	p-value
Healthcare Utilization in the prior 12 months **(N, %)**			
Patients with at least one Emergency Department visit	497 (34.2)	5435 (46.0)	<0.0001
Patients with at least one Hospitalization	349 (24.0)	4655 (39.4)	<0.0001
Cirrhosis Complications, Prevalence (N, %)			
Acute kidney injury (AKI)	73 (5.0)	1091 (9.2)	<0.0001
Ascites	132 (9.1)	1647 (13.9)	<0.0001
Hepatic Encephalopathy (HE)	94 (6.5)	1727 (14.6)	<0.0001
Spontaneous Bacterial Peritonitis (SBP)	6 (0.4)	108 (0.9)	0.0505
Sepsis	37 (2.5)	507 (4.3)	0.0015
Variceal Hemorrhage (VH)	17 (1.2)	247 (2.1)	0.0175

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4517 | ASSOCIATION BETWEEN INSOMNIA AND DISEASE SEVERITY IN PRIMARY BILIARY CHOLANGITIS: A PROPENSITY-MATCHED COHORT STUDY

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Background: Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune cholestatic liver disease characterized by immune-mediated destruction of the intrahepatic bile ducts, resulting in cholestasis, inflammation, fibrosis, and potentially cirrhosis. Recent studies have shown that patients with PBC are at increased risk for poor sleep quality, and among these patients, those with more severe sleep impairment may experience worse biochemical and clinical outcomes. Therefore, we aimed to conduct a population-level study to evaluate the impact of insomnia on outcomes in patients with PBC. **Methods:** We conducted a retrospective cohort study using the TriNetX database and International Classification of Diseases-10 codes to compare outcomes in patients with PBC with comorbid insomnia and those with PBC alone. Patients with coexisting liver diseases such fatty liver, alcoholic liver disease, viral hepatitis, primary sclerosing cholangitis, and other chronic liver conditions were excluded. Primary outcomes were major adverse liver outcomes (MALOs). Other outcomes included major cardiovascular events, biochemical parameters, and all-cause mortality. Propensity score matching (1:1) was performed to adjust for demographics, pruritus, chronic medical and psychiatric conditions, and use of hepatotoxic or psychotropic medications. Relative risks (RRs)

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and 95% confidence intervals (CIs) were calculated, with a P-value $<.05$ considered statistically significant. **Results:** We included 1,202 PBC patients with comorbid insomnia (mean age 70.3 $\pm$ 13.9 years; 85.8% female) and 15,952 without insomnia (mean age 68.0 $\pm$ 14.9 years; 82.9% female). After propensity score matching, 1,137 patients per group were followed for a mean of 3.6 $\pm$ 3.3 years. Insomnia was not associated with increased risk of MALOs, including ascites (RR 0.85; 95% CI 0.65–1.12; P = 0.25), hepatic failure (1.11; 0.82–1.51; P = 0.49), hepatic failure with coma (1.11; 0.68–1.83; P = 0.67), portal hypertension (1.00; 0.75–1.32; P = 0.98), esophageal varices (0.93; 0.67–1.31; P = 0.69), spontaneous bacterial peritonitis (0.96; 0.51–1.79; P = 0.90), hepatorenal syndrome (1.06; 0.57–1.94; P = 0.86), and liver transplantation (1.62; 0.74–3.54; P = 0.23). While rates of acute myocardial infarction (1.44; 1.00–2.08; P = 0.05) and mortality (1.16; 0.98–1.38; P = 0.09) were higher in the insomnia group, they were not statistically significant. Biochemical parameters were also comparable, including alkaline phosphatase (168.26 vs 177.47 U/L; P = 0.25), total bilirubin (1.37 vs 1.51 mg/dL; P = 0.43), albumin (3.67 vs 3.65 g/dL; P = 0.50), international normalized ratio (1.24 vs 1.33; P = 0.10), and platelet count (216.72 vs 218.28 $\times 10^9$/L; P = 0.75). **Conclusion:** PBC patients with insomnia do not appear to have worse MALOs when compared to patients without insomnia. The clinical significance of this association remains unclear and warrants further investigation.

Table – Comparison of clinical and biochemical outcomes in primary biliary cholangitis with and without insomnia

Clinical outcomes after propensity matching	N (1,137)	%	Relative Risk	Confidence interval	P-value
Acute myocardial infarction	66	6.05	1.44	(0.998,2.079)	.0500
	46	4.20			
Cerebral infarction	37	3.42	0.97	(0.62,1.52)	.9032
	38	3.52			
Ascites	85	8.48	0.85	(0.65,1.12)	.2511
	104	9.95			
Hepatic failure	79	7.71	1.13	(0.82,1.51)	.4867
	75	6.92			
Hepatic failure with coma	32	2.89	1.11	(0.68,1.83)	.6682
	29	2.59			
Portal hypertension	86	8.51	1.00	(0.75,1.32)	.9766
	92	8.54			
Esophageal varices	60	5.85	0.93	(0.67,1.31)	.6945
	68	6.26			
Spontaneous bacterial peritonitis	19	1.69	0.96	(0.51,1.79)	.8959
	20	1.76			
Hepatorenal syndrome	21	1.86	1.06	(0.57,1.94)	.8613
	20	1.76			
Liver transplantation	16	1.42	1.62	(0.74,3.54)	.2269
	< 10*	0.88			
Deceased	233	20.49	1.16	(0.98,1.38)	.0877
	201	17.68			
†Biochemical outcomes after propensity matching	**Mean (SD) in PBC with insomnia**			**Mean (SD) in PBC without insomnia**	**P-value**
AST	45.57 (154.60); N=905			65.89 (351.97); N=893	.1124
ALT	38.33 (211.95); N=908			42.62 (167.04); N=902	.0797
Alkaline phosphatase	168.26 (149.98); N=890			177.47 (188.91); N=892	.2545
Total bilirubin	1.37 (3.30); N=866			1.51 (3.96); N=892	.4254
Albumin	3.67 (0.74); N=894			3.65 (0.75); N=881	.5000
PT	13.81 (6.25); N=543			14.61 (9.94); N=573	.1095
aPTT	34.45 (16.07); N=385			35.57 (14.70); N=385	.3107
INR	1.24 (0.63); N=578			1.33 (1.16); N=636	.0980
Platelet count	216.72 (101.19); N=908			218.28 (104.77); N=902	.7470

*N represents the number of patients in each group after propensity matching. For each outcome, patients with prior occurrences before PBC diagnosis were excluded.
†The relative risk is calculated as exposed (PBC with insomnia, upper row) versus unexposed (PBC without insomnia, lower row)
‡To protect patient privacy, numbers ≤10 in TriNetX are rounded up to 10
§Calculated using latest available laboratory values in the database
Abbreviations: AST - aspartate aminotransferase, ALT - alanine aminotransferase, PT - prothrombin time, aPTT - activated partial thromboplastin time, INR - international normalized ratio, PBC - primary

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4518 | STATINS ARE SAFE AND BENEFICIAL IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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Background: Statins may potentially improve portal pressure, risk of decompensation, and survival in patients with chronic liver disease. We examine the effect of statins on alkaline phosphatase, decompensation, and liver events in patients with PBC. **Methods:** A retrospective cohort study was composed of all patients with PBC who were seen at either the private university hospital system or the public hospital system in Dallas, TX between 2002 and 2023. The primary outcome was a composite of major liver events (MLE), including decompensation (defined as variceal bleeding, hepatic encephalopathy, or ascites requiring diuretics or paracentesis), liver transplantation, hepatocellular carcinoma, and liver-related death. The secondary outcome was decompensation. Categorical variables compared with chi square, continuous variables with T test. **Results:** Patients with a MLE were less likely to be on a statin (34.2% vs 48.2%, p = 0.05), more likely to have cirrhosis at their baseline visit (70.8% vs 36.0%, p < 0.001), had a higher alkaline phosphatase (336 vs. 197 IU/L, p = 0.01), higher total bilirubin (3.9 vs. 0.8 mg/dL, p = 0.03), and a lower albumin (3.6 vs 4.1 mg/dL, p = 0.01). Over 96% of patients were taking UDCA. On multivariable cox regression analysis (table 1), statins protected against MLE (aHR 0.146, p < 0.001) and decompensation (aHR 0.128, p < 0.001) when controlling for alkaline phosphatase at 1 year, total bilirubin at 1 year, platelets at 1 year, diagnosis of cirrhosis at baseline, and concurrent MASH. Propensity matched (based on cirrhosis, alkaline phosphatase at 1 year, bilirubin at 1 year, platelets at 1 year) Kaplan Meier curves revealed improved decompensation-free survival (p < 0.001) and trend toward improved MLE-free survival (p = 0.06). Patients who received a statin and those who did not had similar alkaline phosphatase levels at baseline (258 vs 204 IU/L, p = 0.37). After one year on statin therapy, alkaline phosphatase decreased in the statin group (-17.0% [-44 IU/L] vs +17.3% [+35 IU/L] p = 0.05). Statins were used for an average of

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6.25 years. 2 patients stopped the statins due to muscle aches; there were no cases of elevated LFTs or rhabdomyolysis. **Conclusion:** In a study of two Dallas hospital systems, statins were beneficial in patients with PBC, protecting against decompensation and liver events. Statins were associated with an improvement in alkaline phosphatase and were not associated with significant adverse events. This should be further examined in a large, diverse population of patients with PBC.

Variable	MLE Endpoints	Decompensation
	aHR (95% CI) p =	aHR (95% CI) p =
Statin	0.163 (0.0530.501) p = 0.002	0.128 (0.039-0.421) p < 0.001
Alk Phos at 1 year	1.006 (1.003-1.009) p < 0.001	1.004 (1.002-1.007) p < 0.001
Total bilirubin at 1 year	1.168 (1.061-1.285) p = 0.002	1.146 (1.023-1.284) p = 0.018
Platelets at 1 year	0.996 (0.993-0.998) p = 0.002	0.997 (0.994-1.000) p = 0.029
Cirrhosis at baseline	2.414 (0.953-0.6110) p = 0.06	3.328 (1.311-8.445) p = 0.011
Concurrent MASH (biopsy proven)	4.901 (1.125-21.350) p = 0.03	4.409 (1.013-19.189) p = 0.048

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4519 | FIBROSIS IN FAST-FORWARD: MASLD DRIVES FIBROSIS IN PSC WITHOUT AFFECTING MORTALITY

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Background: The influence of Metabolic Associated Steatotic Liver Disease (MASLD) on the clinical trajectory of Primary Sclerosing Cholangitis (PSC) remains incompletely characterized. Given the rising prevalence of MASLD and its known fibrogenic potential, we aimed to evaluate the association of MASLD with fibrosis progression, hepatocellular carcinoma (HCC), liver transplantation, and all-cause mortality among patients with PSC. **Methods:** A retrospective cohort analysis was performed using the TriNetX Global Collaborative Network. Adults (≥ 18 years) diagnosed with PSC between 5–20 years ago were identified and divided into two cohorts: PSC with MASLD ($n = 506$) and PSC without MASLD ($n = 4{,}183$), excluding patients with viral hepatitis, autoimmune liver diseases, or alcohol-related liver disease. The primary outcome was fibrosis progression; secondary outcomes included HCC, liver transplantation, and all-cause mortality. Patients with outcomes prior to the index date were excluded. Kaplan-Meier survival analyses and risk comparisons were conducted. **Results:** Mean follow-up was comparable between cohorts (PSC+MASLD: 2062 days vs. PSC-only: 1882 days). The incidence of fibrosis progression was significantly higher in the PSC+MASLD group (2.0%) compared to PSC-only (0.2%), yielding a risk ratio (RR) of 8.31 (95% CI: 3.48–19.87, $p < 0.001$). There were no statistically significant differences in the risk of HCC (2.2% vs. 2.6%, $RR = 0.85$, $p = 0.603$), liver transplantation (4.3% vs. 4.9%, $RR = 0.89$, $p = 0.590$), or all-cause mortality (14.5% vs. 15.1%, $RR = 0.96$, $p = 0.717$). Kaplan-Meier analysis demonstrated a significantly reduced fibrosis-free survival in the PSC +MASLD group (log-rank $p = 0.229$), with no significant differences observed for other outcomes. **Conclusion:** MASLD is associated with an eightfold increased risk of fibrosis progression in PSC, suggesting synergistic liver injury when both conditions coexist. Incorporating routine metabolic risk assessment, lifestyle modification, and non-invasive fibrosis monitoring may help mitigate liver disease progression in this subgroup. Further prospective studies using metabolic phenotyping are warranted to clarify causality and guide management strategies.

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4520 | NON-RESPONSE TO OBETICHOIC ACID IS ASSOCIATED WITH HEIGHTENED RISKS OF DEVELOPING CLINICAL EVENTS IN PRIMARY BILIARY CHOLANGITIS

Palak Trivedi[1] Rachel Smith[2] Nadir Abbas[1] Ellina Lytvyak[3] Miki Scraravaglio[4] Neil Halliday[5] Nadia Eden[5]

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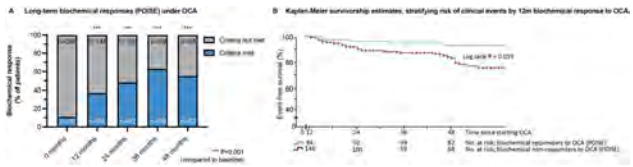
Diane Lloyd-Madden[6] Sanchit Sharma[6] James Ferguson[7] Jessica Dyson[8] Douglas Thorburn[5] David Jones[8] Aldo Montano-Loza[3] Marco Carbone[9] Pietro Invernizzi[9] George Mells[10] Emma Culver[11], [1]University of Birmingham, [2]Addenbrookes Hospital, Cambridge, [3]University of Alberta, [4]University of Cambridge, [5]Royal Free Hospital, London, [6]University Hospitals Birmingham, UK, [7]University of Birmingham, UK, [8]Newcastle University, UK, [9]University of Milano-Bicocca, [10]University of Newcastle, [11]John Radcliffe Hospital

Background: Biochemical non-response to ursodeoxycholic acid (UDCA), as a first-line therapy, is associated with a heightened risk of clinical events in primary biliary cholangitis (PBC). Herein, we determine whether biochemical non-response to obeticholic acid (OCA) is also predictive of long-term event-free survival. A further, exploratory objective was to evaluate whether responses differ between combination OCA + fibric acid derivative therapy compared to switching from OCA to bezafibrate/fenofibrate. **Methods:** Data were collected from patients (pts) initiating OCA at high-volume centres in the UK, Italy and Canada between Aug. 2017 and 2019, with follow-up continuing until Jun. 2024. Biochemical non-response was defined by POISE criteria. Clinical events were defined as decompensation, referral for transplantation, hepatocellular carcinoma or death. **Results:** Our cohort consisted of 336 pts of whom n = 150 (45%) discontinued OCA over 48 months. Over 851-pt-years of OCA use, without addition of another PBC therapy, n = 230, n = 192, n = 158 and n = 150 pts completed 12-, 24-, 36- and 48-months follow-up, respectively. Of this cohort, 37%, 48%, 63% and 55% attained biochemical response (Fig A), with 7%, 14%, 25% and 19% normalising ALP ($P < 0.01$; all comparisons vs. baseline). Over four years, 64 pts experienced a clinical event. Twelve-month biochemical non-response associated with a heightened risk of clinical events (Fig B; hazard ratio [HR]:4.50; 95% CI:1.74-20.23), as did cirrhosis (HR:20.24, 10.15-40.32), hyperbilirubinaemia (HR:2.55, 1/71-3.76), hypoalbuminaemia (HR:0.92, 0.90-0.96) and thrombocytopenia (HR:0.99, 0.98-0.99). The prognostic utility of biochemical non-response (HR:3.29, 1.72-14.96) and cirrhosis (HR:19.67, 5.09-76.08) persisted on multivariable analyses. Next, in exploratory sub-analysis on the UK group initiating fibric acid derivatives during follow-up, we compared biochemical changes in those who initiated treatment alongside OCA (combination) to those who discontinued OCA and switched to bezafibrate or fenofibrate (switch group). Of 240 UK pts treated with OCA initially, 44 initiated a fibric acid derivative in the combination group (n = 40 bezafibrate, 4 fenofibrate), of whom 31 were also taking UDCA. In turn, 74 pts switched from OCA to bezafibrate (n = 57) or fenofibrate (n = 17), with 61 also taking UDCA. Follow-up at 1, 2, 3, and 4 years was completed by 29, 25, 21 and 22 pts in the combination group and by 57, 47, 38 and 37 pts in the switch group. Biochemical response was met in 31%, 44%, 86% and 91% of pts at 1, 2, 3, and 4 yrs., respectively, in the combination therapy group. This compared to 16%, 34%, 42% and 43% in the switch group. **Conclusion:** Biochemical response stratifies risk of clinical events under OCA treatment. Whilst response rates increase over time, discontinuation rates underscore need for newer treatment paradigms, including combination therapy with fibric acid derivatives.



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4521 | INCIDENCE, CAUSES AND PATTERNS OF ELEVATED LIVER ENZYMES AFTER HEART OR LUNG TRANSPLANT FOR SARCOIDOSIS

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Background: Sarcoidosis commonly affects the lungs and heart. The true burden of clinical or subclinical

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hepatic sarcoid disease is unclear, as guidelines for monitoring or diagnosis are lacking. We examined the incidence and causes of elevated liver enzymes (LE) in recipients of non-liver solid organ transplants (Tx) with sarcoidosis. **Methods:** Data on recipients of non-liver solid organ Tx, age $>/=18$ years, due to sarcoidosis between 2018 and 2025 was collected. Patients were followed from Tx to death or the most recent follow-up. The outcomes of interest were causes of elevated liver enzymes defined as ALT or AST $>$ 60 IU/L, death and hepatology consultation. The elevated LE were defined as early (between 0-28 days after Tx) or late (>180 days after Tx). Causes of elevated liver enzymes and death were manually collected from the chart. **Results:** The study included 25 patients: 5 bilateral lung Tx, 16 heart Tx, 1 heart-lung Tx, and 3 heart-kidney Tx. The median age was 59 years (range: 29–70). Nineteen (76%) were male, and 6 (24%) were female. Nine (36%) were Caucasian, and 16 (64%) were Black. Nine patients (36%) had multisystem sarcoidosis including the heart, lungs, skin, eyes, lymphatics, and liver. Two patients had a liver biopsy showing noncaseating granulomas consistent with sarcoid prior to transplant but lacked hepatology follow-up. Median time from diagnosis to Tx was 15.1 months, and from Tx to last follow-up was 26.9 months. Twenty-one patients (81%) met the definition of elevated LE post-Tx (median peak ALT: 104 IU/L, AST: 136 IU/L, ALP: 127 IU/L, total bilirubin: 1.9 mg/dL). Eighteen (85%) had early (0-28 days), and 3 (14%) had late post-Tx elevated LE (>180 days). Causes of early post-Tx elevated LE in 18 patients were congestive hepatopathy (6; 33%), shock liver (5; 28%), post-Tx transaminitis (3; 17%), drug-induced liver injury (2; 11%), and unknown (2; 11%). Causes of late elevated LE in 3 patients were CMV viremia (1; 33%) and post-Tx transaminitis (2; 66%). These 3 had alcohol use disorder in remission. Only 7 (27%) of the 21 with elevated LE had a hepatology consult. No liver biopsies or elastography were performed to evaluate elevated LE post-Tx. However, elevated LE normalized in all 21 patients by the latest follow-up. Twenty-three (92%) were alive at the last follow-up. Two deaths occurred at 17 days (multi-organ failure) and 824 days (Nocardia infection) post-Tx. **Conclusion:** Elevated liver enzymes are commonly seen after heart, lung, and combined organ Tx for sarcoidosis in the early post-Tx period. These are transient, secondary to congestive hepatopathy and shock liver, not related to hepatic sarcoid, and generally self-limiting. However, late elevated liver enzymes is likely liver-related. Given the high prevalence of elevated LE, hepatology consultation may be considered, especially in cases of persistent elevations.

Summary of Post-Transplant Sarcoidosis Patient Data

Category	Details
Total Patients	25
Transplant Types	5 Bilateral Lung, 16 Heart, 1 Heart-Lung, 3 Heart-Kidney
Median Age (Range)	59 years (29–70)
Sex Distribution	19 Male (76%), 6 Female (24%)
Race	9 Caucasian (36%), 16 Black (64%)
Multisystem Sarcoidosis	9 patients (36%)
Pre-Tx Liver Biopsy with Sarcoid	2 patients (no hepatology follow-up)
Median Time from Diagnosis to Tx	15.1 months
Median Time from Tx to Last Follow-up	26.9 months
Elevated Liver Enzymes Post-Tx	21 patients (81%)
Median Peak Liver Enzymes (Post-Tx)	ALT: 104 IU/L, AST: 136 IU/L, ALP: 127 IU/L, Total Bilirubin: 1.9 mg/dL
Timing of Elevated LE Post-Tx	Early (0–28 days): 18 patients; Late (>180 days): 3 patients
Causes of Early Elevated LE (n=18)	Congestive Hepatopathy: 6 (33%) Shock Liver: 5 (28%) Post-Tx Transaminitis: 3 (17%) Drug-Induced Liver Injury: 2 (11%) Unknown: 2 (11%)
Causes of Late Elevated LE (n=3)	CMV Viremia: 1 (33%) Post-Tx Transaminitis: 2 (66%)
Alcohol Use Disorder (Late LE Group)	3 patients (in remission)
Hepatology Consult Post-Tx	7 patients (27%)
Liver Biopsy/Elastography Post-Tx	None performed
Liver Enzyme Normalization	All 21 patients with elevated LE normalized
Survival at Last Follow-up	23 patients (92%) alive
Deaths	2 patients (17 days – multi-organ failure; 824 days – Nocardia infection)

Disclosures: Neil Garg: Nothing to Disclose, Muhammad Saad Faisal: Nothing to Disclose, Jennifer Cowger: Nothing to Disclose, Patrick Bradley: ATYR Pharmaceutical: Clinical trial for CMK389. All funds to instituion, Novartis Pharmaceutical: Clinical trial for CMK389. All funds to instituion, ATYR Pharmaceutical: ATYR versus placebo in pulmonary sarcoidosis., Syed-Mohammed Jafri: Takeda: Speaking and Teaching, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, Ironwood: Advisor, Intercept: Speaking and Teaching

4522 | THE EFFICACY OF ELAFIBRANOR IS NOT AFFECTED BY BODY MASS INDEX IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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Background: Elafibranor is a peroxisome proliferator-activated receptor (PPAR) α and δ agonist approved for treatment of adults with primary biliary cholangitis (PBC). In the phase 3 ELATIVE® study, elafibranor significantly improved biochemical response rate and markers of disease progression compared with placebo in patients with PBC. We investigated the effect of body mass index (BMI) on elafibranor pharmacokinetics using population modelling, and on efficacy in healthy, overweight and obese subgroups of ELATIVE®. **Methods:** Population pharmacokinetic models for elafibranor and its active metabolite GFT1007 were developed using data from 17 phase 1–3 clinical studies (including ELATIVE and a phase 2 trial in patients with PBC). In ELATIVE, patients with PBC and an inadequate response to or intolerable side effects with ursodeoxycholic acid were randomized 2:1 to receive elafibranor 80 mg daily or placebo for 52 weeks. The primary endpoint was biochemical response at week 52 (alkaline phosphatase [ALP] $<1.67\times$ upper limit of normal [ULN] with $\geq 15\%$ reduction from baseline and total bilirubin $\leq$ ULN). Change in ALP levels from baseline to week 52 was a secondary efficacy endpoint. Randomized patients were classified *post hoc* into subgroups of healthy weight (BMI ≥ 18.5 to <25 kg/m^2), overweight (BMI ≥ 25 to <30 kg/m^2) or obese (BMI ≥ 30 kg/m^2); those with BMI <18.5 kg/m^2 (n = 5) were not included. Statistical tests were *post hoc* and non-inferential; *p* values were nominal. **Results:** In the pharmacokinetic models, BMI had no clinically relevant effect on exposure to elafibranor or GFT1007 in patients with PBC (Table). In ELATIVE, 161 patients were randomised to elafibranor (n = 108) or placebo (n = 53). In the elafibranor arm, biochemical response rates at week 52 were 56.3%, 46.4% and 44.8% in the healthy weight, overweight and obese subgroups, respectively (Table). Mean changes in ALP levels from baseline to week 52 in the elafibranor arm were –41.5%, –41.8% and –32.3% for elafibranor in the healthy weight, overweight and obese subgroups respectively (Table). **Conclusion:** The pharmacokinetics of elafibranor are not clinically meaningfully affected by BMI in patients with PBC. The efficacy of the clinical dose of elafibranor is stable in patients with PBC, regardless of baseline BMI or weight changes during the course of treatment.

Population PK analysis	**BMI 21.338 kg/m²**		**BMI 25.93 kg/m²**		**BMI 33.73 kg/m²**	
AUC$_T$ relative to reference (90% CI)			Reference[a]			
Elafibranor	1.00 (1.00, 1.00)		1.00 (1.00, 1.00)		1.00 (1.00, 1.00)	
GFT1007	0.956 (0.942, 0.969)		1.00 (1.00, 1.00)		1.08 (1.06, 1.11)	
C_{max} relative to reference (90% CI)			Reference[a]			
Elafibranor	1.00 (1.00, 1.00)		1.00 (1.00, 1.00)		0.998 (0.997, 0.998)	
GFT1007	0.984 (0.978, 0.989)		1.00 (1.00, 1.00)		1.03 (1.02, 1.04)	
ELATIVE subgroup analysis	**BMI ≥18.5 to <25 kg/m² (healthy weight)**		**BMI ≥25 to <30 kg/m² (overweight)**		**BMI ≥30 kg/m² (obese)**	
	Elafibranor (n = 48)	**Placebo (n = 21)**	**Elafibranor (n = 28)**	**Placebo (n = 15)**	**Elafibranor (n = 29)**	**Placebo (n = 15)**
Biochemical response, n (%)[b]	27 (56.3)	0 (0)	13 (46.4)	0 (0)	13 (44.8)	2 (13.3)
Risk difference, % (95% CI)[c]	56.3 (35.4, 69.3)[d]		46.4 (19.9, 64.2)[e]		35.5 (4.8, 56.2)[f]	
ALP level, mean (SD)						
Baseline, U/L	320.5 (113.1)	337.7 (119.7)	298.5 (84.3)	323.9 (307.8)	333.4 (138.1)	296.3 (162.5)
Week 52, U/L	193.4 (153.0)	349.6 (113.9)	184.9 (117.0)	310.4 (200.6)	227.7 (146.1)	259.0 (114.5)
Change, %	–41.5 (26.7)	+1.8 (18.5)	–41.8 (23.0)	+1.5 (15.4)	–32.3 (22.3)	+0.2 (21.5)

[a]Female patient with PBC, weight of 68 kg, BMI of 25.93 kg/m², age of 57 years, and albumin of 43.5 g/L at baseline.
[b]Defined as ALP <1.67 × ULN with reduction of ≥15% from baseline and total bilirubin ≤ULN at week 52.
[c]Stratified Cochrane–Mantel–Haenzel test and Newcombe weights for 95% CI (elafibranor vs placebo).
[d]Nominal p < 0.001.
[e]Nominal p = 0.006.
[f]Nominal p = 0.0343.
ALP, alkaline phosphatase; BMI, body mass index; CI, confidence interval; PBC, primary biliary cholangitis; SD, standard deviation; ULN, upper limit of normal.

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4523 | SYMPTOM PROFILES AMONG ADULTS WITH PRIMARY SCLEROSING CHOLANGITIS IDENTIFIES LOW, MODERATE AND HIGH BURDENED GROUPS

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Background: Patient-reported symptoms of PSC are not well documented. The study's aim was to understand the prevalence of PSC symptoms and identify distinct symptom profiles and their association with demographic and clinical characteristics among symptomatic adults. **Methods:** Adults were recruited through the PSC Partners Patient Registry and PSC hepatologists in the U.S. Individuals were eligible if they were 18 or older, symptomatic in the last year, and not waitlisted or a transplant recipient. Individuals engaged in a phone survey that screened for the presence (yes/no) of 13 PSC-associated symptoms in the last month. Sociodemographic and medical history were self-reported. Latent class analysis (LCA) was used to identify symptom-based participant profiles based on symptom presence and participants were assigned to one symptom class. Multinomial logistic regression models were used to evaluate demographic or clinical factors associated with profile membership. **Results:** Participants (n = 126) were on average 47 years old (range:20-81), 60% female, 88% white, 8% black and 3% asian, 59% had inflammatory bowel disease (IBD), 39% reported cirrhosis, 75% were taking ursodiol (UCDA), and 57% had a history of cholangitis attacks. The most prevalent symptoms in the last month included fatigue (83%), daytime drowsiness (73%), and liver pain, cognitive impairment, anxiety, sleep disturbance and itch (all 62-63%). The LCA and clinical interpretation suggested a 4-symptom profile solution: (1) "Low Symptom" class (22% of sample), (2) "Moderate Symptom" class (21%), (3) "Moderate+Distressed" class (39% of sample), and a "High Symptom" class (18%). In unadjusted models, compared to the Low Symptom class, females were more likely than males to be in the High Symptom class (OR = 4.36; 95% CI: 1.31-14.51), participants taking UCDA were less likely to be in the High Symptom class (OR = 0.25; 95% CI: 0.08-0.80) and those with a history of cholangitis attacks were less likely to be in the Moderate Symptom class (OR = 0.22; 95% CI: 0.07-0.70). In the multvariable model, only a history of cholangitis attacks ($p = 0.03$) was statistically associated with class membership. A statistically significant worsening trend

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was observed in PROMIS® Global Physical and Mental Health T-scores from the Low to the High Symptom classes. **Conclusion:** Among symptomatic adults with PSC, over 60% report fatigue, daytime drowsiness, liver pain, cognitive impairment, anxiety, sleep disturbance and itch in the past month. The four-symptom profiles ranging from low to high burden needs validation in larger cohorts as they have clinically meaningful implications for patients' health status and care of symptomatic individuals.

Figure. Four Symptom Profiles for Presence of Symptoms in Last Month

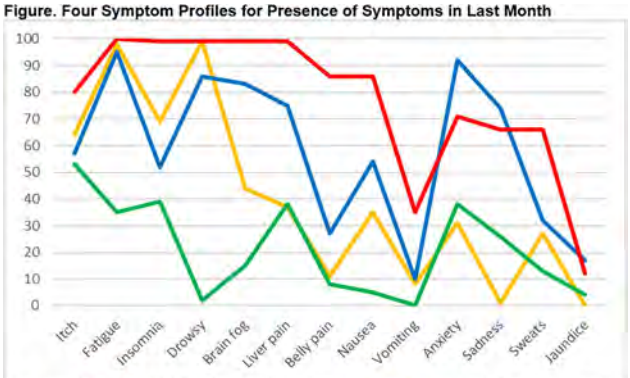

Figure Legend: Red line = High Symptom class (18% of sample); Yellow line = Moderate Symptom class (21% of sample); Blue line = Moderate+Distressed" class (39% of sample) and Green line = Low Symptom class (22% of sample)

Disclosures: Donna Evon: Nothing to Disclose, Kaya Merkler: Nothing to Disclose, Chelsea Anderson: Nothing to Disclose, Joanne Hatchett: Nothing to Disclose, Ricky Safer: Nothing to Disclose, Rachel Gomel: Nothing to Disclose, Sasha Deutsch-Link: Nothing to Disclose, Christopher Bowlus: Calliditas: Grant/Research Support, ChemoMab: Grant/Research Support, ChemoMab: Consultant, COUR Phamaceuticals: Grant/Research Support, Cymabay: Grant/Research Support, Cymabay: Consultant, Gilead: Grant/Research Support, GSK Pharmaceuticals: Grant/Research Support, GSK Pharmaceuticals: Consultant, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Invea Therapeutics: Consultant, Ipsen: Grant/Research Support, Ipsen: Consultant, Mirum: Grant/Research Support, NGM Bio: Consultant, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Pliant Therapeutics: Consultant, Viking Therapeutics: Grant/Research Support, Zydus Therapeutics: Grant/Research Support, Alnylam: Advisor, Amgen: Advisor, Amgen: Advisor, Amgen: Advisor, ArsenalBio: Advisor, Kezar: Advisor, Ono Pharmaceuticals: Advisor, Astra Zeneca: Advisor, AssemblyBio: Advisor, RegCell: Advisor, Esperion Therapeutics: Advisor, Gilead Biosciences: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, CymaBay Pharmaceuticals: Grant/Research Support, Takeda Pharmaceuticals: Grant/Research Support, GSK: Grant/Research Support, Bristol Myers Squibb: Grant/Research Support, TARGET PharmaSolutions: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Mirum: Grant/Research Support, Ipsen: Grant/Research Support, Perspectum: Grant/Research Support, Pilant: Grant/Research Support, Sydus: Grant/Research Support, Chemomab: Consultant, CymaBay: Consultant, Therapeutics: Consultant, GSK: Consultant, Gilead: Consultant, Ipsen Bioscience: Consultant, Kezar: Consultant, NGM Bio: Consultant, Pliant Therapeutics: Consultant, Alnylam: Consultant, Amgen: Consultant, ArsenalBio: Consultant, Mirum: Consultant, Ono Pharmaceuticals: Consultant, AstraZeneca: Consultant, AssemblyBio: Consultant, RecCell: Consultant, Esperion Therapeutics: Consultant, Bryce Reeve: Nothing to Disclose

4524 | EFFICACY OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS IN THE TREATMENT OF PRIMARY BILIARY CHOLANGITIS: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease marked by progressive bile duct destruction. While ursodeoxycholic acid (UDCA) is first-line therapy, approximately 40% of patients show an incomplete response. Peroxisome proliferator-activated receptor (PPAR) agonists have emerged as promising agents due to their anti-inflammatory and metabolic effects. This meta-analysis evaluates the efficacy of PPAR agonists in improving liver biochemical markers in PBC. **Methods:** A systematic search of MEDLINE, Embase, and Scopus was performed to identify randomized controlled trials (RCTs) comparing PPAR agonists to placebo in patients with PBC. Eligible studies (1) were placebo-controlled RCTs, (2) included patients with PBC regardless of disease stage or PPAR agonist dose, and (3) reported pre- and post-treatment values for alkaline phosphatase (ALP), bilirubin, and gamma-glutamyl transferase (GGT). Exclusion criteria included studies without a placebo or control group, non-human studies, trials with no relevant outcomes, and trials with incomplete or withdrawn data. Six trials met these criteria. Follow-up durations ranged from 3 to 24 months. To account for variability in treatment effect due to time,

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we used post-minus-pre-treatment mean differences and a random-effects model. Standard errors were derived using an assumed correlation coefficient (r = 0.7) between paired values. Pooled estimates were weighted by inverse variance and calculated separately for each biomarker. **Results:** PPAR agonists were associated with significant reductions in liver biomarkers compared to placebo. ALP decreased by –87.14 U/L (95% CI: –90.20, –84.08). Bilirubin declined by –1.04 mg/dL (95% CI: –1.37, –0.71). GGT was reduced by –46.90 U/L (95% CI: –51.64, –42.16). All reductions were statistically significant. **Conclusion:** In placebo-controlled trials, PPAR agonists significantly improved ALP, bilirubin, and GGT levels in patients with PBC. These findings support their potential role as effective adjunctive therapy, particularly for patients with inadequate response to UDCA.

Table 1: Pooled Treatment Effects of Biomarkers

Biomarker	Pooled Effect	Std. Error	95% Confidence Interval
Alkaline Phosphatase (ALP)	-87.14	1.56	(-90.20, -84.08)
Bilirubin	-1.04	0.17	(-1.37, -0.71)
Gamma-Glutamyl Transferase (GGT)	-46.90	2.42	(-51.64, -42.16)

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4525 | ASSESING OUTCOMES IN AUTOIMMUNE HEPATITIS PRESENTING AS ACUTE ON CHRONIC LIVER FAILURE, WITH AND WITHOUT EXTRAHEPATIC ORGAN DSFUNCTION

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Background: Autoimmune Hepatitis (AIH), presenting as Acute on Chronic liver failure (ACLF), is a challenging clinical entity, with limited clinical data regarding its management, prognosis and response to immunosuppressants. ACLF is a distinct clinical entity, with increased propensity for infection, extrahepatic organ failure and high mortality. Data is also ver limited regarding the role of steroids in AIH-ACLF populatoion. In light of these background knowledge, this study aimed to evaluate the outcomes in AIH -ACLF having both hepatic and extrahepatic organ failure, along with steroid responsiveness. **Methods:** Single centre retrospective study from a tertiary care centre where AIH subjects presenting as ACLF from January 2019 till December 2024 were included. Clinical, laboratory and histological parameteres were assessed at baseline. Various prognostic scores like model for end stage liver disease (MELD), Child Turcotte Pugh score (CTP), Asia pacific association for study of liver disease ACLF score (AARC ACLF score), Chronic Liver failure -consortium organ failure score (CLIF -OF score) were computed at baseline and also were periodically monitored during follow up. Primary outcome were 90 day and 180 day transplant free survival. Follow up clinical parameters, infections were assessed and predictors of end points were identified. **Results:** 47 subjects presenting as AIH-ACLF were included in the study. Median follow up 212 days. Two (2) subjects underwent liver transplantation (4.26%), 12 deaths (25.56%). Infections were present at baseline in 11 subjects (23.40%) and further new onset infections developed in 14 subjects (38.89%). Most common acute precipitants were flare of underling AIH (46.81%) along with sepsis (17.02%), followed by acute viral hepatitis HAV related (12.77%). All the subjects underwent liver biopsy. Underlying advanced fibrosis(F3or F4) was found in 87.23%. Of the 36 subjects started on steroids, 18 subjects required discontinuation in the follow up. Most common cause for steroid discontinuation was new onset infection. The 90 and 180 day transplant free survival rates were 73.33% (95% CI 55.2- 91.2) and 68.74 % (95% CI 48.61- 80.1). Baseline AARC- ACLF score < 11 (sensitivity 74.2%, specificity 92.78%), MELD score < 22 (sensitivity 81.3%, specificity 87%) and baseline serum creatinine < 2 mg/dl (Sensitivity 67.89%,specificity 89.12%) were the best predictors for survival. **Conclusion:** Patients of AIH presenting with ACLF have a morbid clinical course, carrying a high mortality rate. Baseline infection is often present in these group. Subjects having extrahepatic organ failure, particularly renal carry a worse prognosis. Steroids can be administered in select subgroups having a good prognostic score at baseline and no evidence of infection. Although strong vigilance is warranted for development of new onset infection and changes in prognostic scores.

Disclosures: Souveek Mitra: Nothing to Disclose, Abhijit Chowdhury: Nothing to Disclose, Ranajoy Ghosh: Nothing to Disclose, Dipankar Mondal: Nothing to Disclose, Srijan Mazumdar: Nothing to Disclose, Kishalaya: Nothing to Disclose

4526 | EFFICACY AND CLINICAL OUTCOMES WITH ODEVIXIBAT IN PATIENTS WITH MDR3 DEFICIENCY: RESULTS: FROM THE PEDFIC 2 PHASE III, OPEN-LABEL EXTENSION STUDY

Emmanuel Gonzales[1] Mohammad Shagrani[2] Etienne Sokal[3] Tassos Grammatikopolous[4] Hasan Özen[5]

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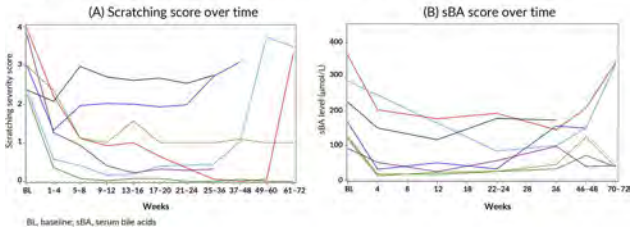
Wendy van der Woerd[6] Mary Tessier[7] Henkjan Verkade[8] Nathan Touati[9] Virginie Jacquemin[9] Fatine Elaraki[9] Praneeta Nagraj[10] Terese Wallefors[11] Richard Thompson[12], [1]Hôpital Bicêtre, AP-HP, Université Paris-Saclay, Hépatinov, Inserm U 1193, Paris, France, [2]King Faisal Specialist Hospital and Research Centre, Al Mathar Ash Shamali, Riyadh, Saudi Arabia, [3]Université Catholique de Louvain, Cliniques St Luc, Brussels, Belgium, [4]King's College Hospital NHS Trust, London, UK, [5]Hacettepe University Faculty of Medicine, Ankara, Turkey, [6]Wilhelmina Children's Hospital and University Medical Center, Utrecht, the Netherlands, [7]Baylor College of Medicine/Texas Children's Hospital, Houston, TX, USA, [8]Beatrix Children's Hospital/ University Medical Center Groningen, Groningen, the Netherlands, [9]Ipsen, Boulogne-Billancourt, France, [10]Ipsen, Cambridge, MA, USA, [11]Ipsen, Gothenburg, Sweden, [12]Institute of Liver Studies, King's College London, London, UK

Background: Long-term data demonstrate improvements in pruritus, reductions in serum bile acids (sBA), and manageable safety with odevixibat (ODX) across progressive familial intrahepatic cholestasis types in the phase III PEDFIC 1 and PEDFIC 2 open-label extension studies (NCT03659916 and NCT03566238). Multidrug resistance protein-3 (MDR3) deficiency, caused by *ABCB4* variants, leads to chronic cholangitis and secondary cholestasis. Here we analyze efficacy, liver parameters, and clinical events for patients with MDR3 deficiency treated with odevixibat in the PEDFIC 2 study. **Methods:** Patients with MDR3 deficiency treated with ODX (120 μg/kg/day) were included in the *post-hoc* analysis (data cutoff: Feb 15, 2024). Type and effect of pathologic variants were determined by ClinVar and gnomAD databases. Responses vs baseline (BL) were defined at Week 24 as ≥70% reduction in fasting sBA or sBA ≤70 μmol/L, or a pruritus response of ≥1-point reduction in observer-reported scratching score (0–4 scale). **Results:** 7 patients with MDR3 deficiency, mean (SD) age 7.61 (4.59) years, were enrolled. 6 patients had homozygous variants: missense (n = 2); nonsense (n = 1); intronic variants predicted to disrupt splicing (n = 3). 1 patient had a heterozygous missense and splice variant. At BL: 5 patients were receiving ursodeoxycholic acid (UDCA), and 1 rifampicin, 3 patients had cirrhosis; all patients had abnormal liver tests. Mean (SD) sBA level was 197.14 (99.90) μmol/L; platelet count was 188 (97) x 10^9/L (3 patients had < 150 x 10^9/L, indicating cirrhosis); bilirubin was 27.51 (11.37) μmol/L; gamma-glutamyl transferase (GGT) was 215.57 (129.58) U/L. Mean (SD) ODX duration was 110.94 (51.81) weeks. ODX initiation rapidly reduced sBA levels and improved pruritus in most patients (Figure). At Week 24, 3 patients achieved an sBA response, 4 a pruritus response, and 2 had a dual response. Treatment with ODX did not appear to impact transaminases, GGT, or bilirubin. 5 patients discontinued ODX over time, 3 due to adverse events (AEs) unrelated to ODX, and 2 due to liver transplantation (LT). 1 patient with an AE unrelated to ODX later underwent LT for an AE of disease progression; all 3 patients with LT had BL thrombocytopenia indicating portal hypertension and cirrhosis. **Conclusion:** These data suggest ODX, in addition to UDCA, may have clinical benefit, providing symptomatic relief in patients with MDR3 deficiency; further investigation is warranted.

Figure: Scratching score (A) and sBA levels (B) up to 72 weeks in patients with MDR3 deficiency treated with ODX



Disclosures: Emmanuel Gonzales: Nothing to Disclose, Mohammad Shagrani: Nothing to Disclose, Etienne Sokal: Nothing to Disclose, Tassos Grammatikopolous: Ipsen: Consultant, AstraZeneca: Consultant, Hasan Özen: Nothing to Disclose, Wendy van der Woerd: Nothing to Disclose, Mary Tessier: Albireo/ Ipsen: site PI for a pharmaceutical study, Henkjan Verkade: Mirum: Grant/Research Support, Mirum: Consultant, Mirum: Speaking and Teaching, Ipsen / Albireo: Consultant, Ipsen / Albireo: Grant/Research Support, Ipsen / Albireo: Speaking and Teaching, Intercept: Consultant, Orphalan: Consultant, Vertex: Consultant, ProQR: Consultant, Rectify: Grant/ Research Support, Nathan Touati: Nothing to Disclose, Virginie Jacquemin: Ipsen: Employee, Fatine Elaraki: Nothing to Disclose, Praneeta Nagraj: Nothing to Disclose, Terese Wallefors: Nothing to Disclose, Richard Thompson: Nothing to Disclose

4527 | LONGITUDINAL DESCRIPTION OF LIVER BIOCHEMISTRY AMONG PATIENTS WITH PRIMARY BILIARY CHOLANGITIS IN THE UNITED STATES

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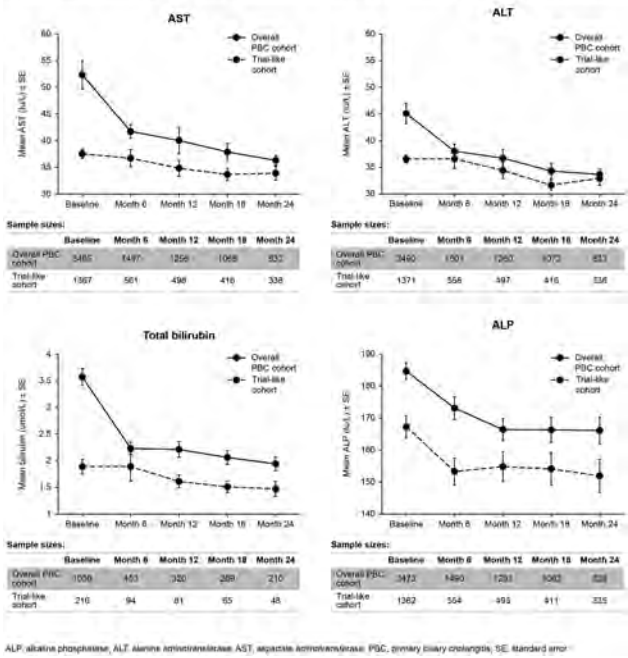
Background: Primary biliary cholangitis (PBC) is a chronic, progressive, immune-mediated cholestatic liver disease. Patients with PBC have abnormal liver tests, including elevations of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase, frequently with elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). However, there are limited data describing how liver biochemistry measures evolve over time in a population-based setting, which can inform clinical program findings and help differentiate the potential effect of the drug from that of the underlying disease. In this study, two cohorts—an overall PBC cohort and a trial-like cohort—were defined to generate relevant data for such contextualization. **Methods:** This was a retrospective cohort study of patients with prevalent PBC using 2016–2020 Optum Electronic Health Record data. Patients with PBC were identified based on ≥2 diagnosis codes on separate days within a 1-year period. Changes in liver biochemistry measures of interest (i.e., ALT, AST, ALP, total bilirubin), including stopping criteria in a Phase 3 clinical trial, were described over up to 2 years of follow-up. **Results:** Overall, 3510 patients with PBC were identified (mean age: 62.9 years, 82.7% female); 70% were receiving UDCA. Of these, 1376 met the inclusion/exclusion criteria for the trial-like cohort. Compared with the overall PBC cohort, the trial-like cohort had a similar mean age at baseline (63.0 years), a greater proportion of female patients (90.8%), and a lower comorbidity burden. In the overall cohort, at baseline, 38.6% of patients had ALT > upper limit of normal (ULN), 47.3% had AST > ULN, 69.0% had ALP > ULN, 33.1% had ALP ≥ 1.67×ULN, and 1.9% had total bilirubin > ULN (median total bilirubin [2 µmol/L] was within the normal range). In the trial-like cohort, 38.1% of patients had ALT > ULN, 40.0% had AST > ULN, 66.4% had ALP > ULN, and 29.7% had ALP ≥ 1.67×ULN. There was a general trend of decreasing mean lab values over the follow-up period for both cohorts, but it was less pronounced in the trial-like cohort compared with the overall cohort (Figure). Additionally, the changes were not as pronounced when examining change in lab values as medians compared to means. A proportion of patients had liver enzyme elevations meeting clinical trial increased monitoring and/or stopping criteria. **Conclusion:** This study leveraged data from a large dataset of electronic health records to describe how liver biochemistry parameters evolve in an overall PBC cohort and a trial-like cohort. While there was a general trend of decreasing lab values over follow-up, a proportion of patients had liver enzyme elevations over the follow-up period that would correspond to monitoring or stopping criteria in a clinical trial context. These data offer valuable insights into contextualizing liver biochemistry changes over time in PBC clinical trials. Funding: GSK (218576).

Figure. Baseline and follow-up liver laboratory measures in the real-world PBC cohort (overall PBC cohort) and the trial-like cohort



ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PBC, primary biliary cholangitis; SE, standard error

Disclosures: Kaitlin Hagan: Nothing to Disclose, Sadia Halim: Nothing to Disclose, Lina Titievsky: GSK: Employee, GSK: Stock - publicly traded company, Veronika Earley-Valovic: Nothing to Disclose, Megan McLaughlin: Nothing to Disclose, Alexander Cobitz: GlaxoSmithKline Pharmaceuticals: Employee, Kris Kowdley: Nothing to Disclose, Robert Gish: Nothing to Disclose

4528 | ESTIMATING THE PREVALENCE OF PRIMARY BILIARY CHOLANGITIS AMONG A NATIONAL COHORT OF VETERANS IN THE UNITED STATES

Zeyuan Yang[1] Ramsey Cheung[2] Robert Wong[3], [1]Palo Alto Veterans Institute for Research, [2]Stanford University Medical Center, [3]VA Palo Alto Healthcare System

Background: The prevalence of primary biliary cholangitis (PBC) in the U.S. has been estimated at approximately 40 per 100,000 persons based on administrative claims data. However, awareness of PBC is sub-optimal among patients and providers, and the aforementioned reported prevalence that is based solely on ICD-9/10 likely underestimates the true burden of PBC. We aim to provide estimates of PBC prevalence among a national cohort of Veterans using both ICD-9/10 and supporting laboratory data. **Methods:** Using the national Veterans Affairs database from 1/1/2010 to 4/30/2025, adults with PBC were identified

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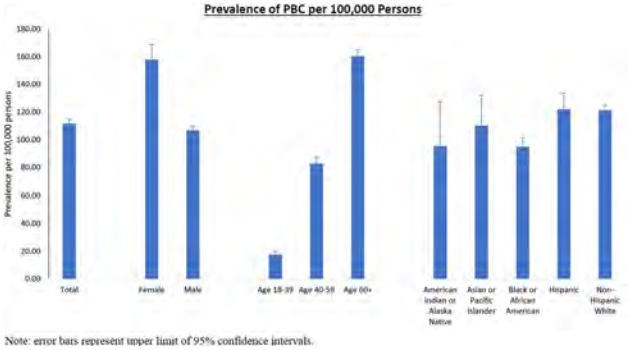
using a combination of ICD-9/10 diagnosis codes (571.6, K74.3, K74.5) and positive anti-mitochondrial antibody (AMA) laboratory testing. PBC prevalence was calculated by dividing the number of individuals meeting aforementioned criteria with a denominator of individuals who had at least 1 health encounter each year of the study period. PBC prevalence (per 100,000 persons) was stratified by sex, age groups, and race/ethnicity and compared between groups using the z-statistic. **Results:** Overall, when using ICD-9/10 diagnosis codes, 5,736 adults with PBC were identified (86.4% men, 13.6% women, 74.5% age >60y, 71.0% non-Hispanic white, 13.7% African American, 7.3% Hispanic). PBC prevalence ranged from 111.7 per 100,000 (based on ICD-9/10) to 446.1 per 100,000 based on positive AMA. PBC prevalence was significantly higher in women vs. men when using ICD-9/10 codes (157.9 vs. 106.8 per 100,000, $p < 0.01$) or positive AMA (469.1 vs. 443.6 per 100,000, $p < 0.05$). When stratified by age groups, the highest prevalence of PBC was observed among those age ≥60y when using ICD-9/10 codes (160.4 vs. 82.9 per 100,000 in age 40-59y, $p < 0.01$) and highest among age 40-59y when using positive AMA (557.0 vs. 422.8 per 100,000 in age ≥60y, $p < 0.01$). When stratified by race/ethnicity, the highest prevalence of PBC was observed among Hispanics when using either ICD-9/10 or positive AMA criteria. **Conclusion:** Among a national cohort of Veterans in the U.S., the prevalence of PBC ranged from ~112 to 446 per 100,000 persons when using ICD-9/10 diagnostic codes or positive AMA results, respectively. PBC prevalence was significantly higher in women vs. men and was observed to be highest among Hispanic Veterans. Greater awareness among patients and providers can help improve timely diagnosis of PBC, which will improve our understanding of disease prevalence and epidemiology.



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4529 | 2ND LINE THERAPY FOR PRIMARY BILIARY CHOLANGITIS (PBC) IS UNDERUTILIZED IN PATIENTS WITH SUBOPTIMAL RESPONSE TO URSODEOXYCHOLIC ACID (UDCA) AND ADVANCED FIBROSIS

Nancy Reau[1] Krishan Puri[2] Ana Maria Davila Morales[3] Zoe Post[3], [1]Rush University Medical Center, [2]University of Illinois, [3]Rush

Background: PBC is a chronic progressive liver disease characterized by the destruction of small bile ducts within the liver. PBC primarily affects older women and is diagnosed by elevated alkaline phosphatase (ALP) levels and positive antimitochondrial autoantibodies (AMA). Prognosis is worse in those that cannot achieve biochemical remission (BR) defined by ALP and bilirubin. 2nd line therapy (2LT) should be used in those that are not in BR but may be underutilized in those with advanced disease. This study aims to compare treatment outcome in those with fibrosis scores F0-F2, to those with advanced fibrosis (F3+). Utilization of 2LT will also be assessed. **Methods:** *Retrospective analysis of PBC patients followed in an off-site location from 01/01/19 to 01/01/25. Data included baseline demographics, ALP before UDCA initiation, and UDCA response. A positive UDCA response is defined as deep remission [DR] ALP < 105, normal ALP [NL] (ALP 106-120), Biochemical remission [BR] (ALP < 1.67 x ULN: 121 to 175) and not in remission [NR] (ALP > 1.67 x ULN or ALP > 175). For those without biochemical remission, initiation of second-line therapy with OCA, fibrate, or PPAR was recorded.* **Results:** *65 patients with PBC were identified after excluding those lost to follow-up (2), incomplete data (6), and death (2). Average age 65 years, 92% female, 93% white, 5% black, and 2% other. 37 (57%) were F0 to F2, and 28 (43%) had advanced fibrosis (F3-4). 17 (26%) were in DR, 7 (11%) were NL, 23 (35%) were BR, and 18 (28%) were NR. Only 6 (33%) NR patients received 2LT of these 6 patients, 4 were F0-F2 and 2 were F3-F4. F0-2 patients: nine (24%) were NR whereas 5 NL, 13 BR, and 10 DR. Compared to the 28 patients with advanced fibrosis, nine (32%) were NR whereas 2 NL, 10 BR, and 7 DR (Table1). Three F0-F2 were on no therapy and 25 received one therapy. 24% required 2LT with 6 on two therapies and 3 on three agents. Compared to patients with advanced fibrosis, four were on no therapy, 19 on one therapy. 18% received 2LT with 3 on two therapies and 2 on three therapies. There were 9 NR patients with advanced fibrosis: 2 received 2LT. However, 7 were not optimized. 2 (29%) had decompensated cirrhosis, and 5 (71%) were undertreated.* **Conclusion:** *Conclusion: Patients with PBC and advanced fibrosis (F3-4) who do not*

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achieve biochemical remission are less likely to receive 2nd line therapy compared to those with less fibrosis. Patients with more advanced fibrosis should be considered for treatment escalation.

	Total	F0-F2	F3-F4
DR	17 (26%)	10 (27%)	7 (25%)
NL	7 (11%)	5 (14%)	2 (7%)
BR	23 (35%)	13 ((35%)	10 (36%)
NR	18 (28%)	9 (24%)	9 (32%)
	65	37	28

Disclosures: Nancy Reau: Gilead: Grant/Research Support, eiger: Grant/Research Support, abbott: Consultant, Arbutus: Consultant, Gilead: Consultant, VIR: Consultant, Salix: Consultant, Salix: Grant/Research Support, AbbVie: Grant/Research Support, VIR: Grant/Research Support, Krishan Puri: Nothing to Disclose, Ana Maria Davila Morales: Nothing to Disclose, Zoe Post: Nothing to Disclose

4530 | EPIDEMIOLOGY OF PRIMARY SCLEROSING CHOLANGITIS: INSIGHTS FROM ALLATIN COHORT

Guilherme Cancado[1] Paulo Bittencourt[2] Maria Lucia Ferraz[3] Lorena Solari[4] Margarita Anders[5] Nicolas Ortiz[6] Raimundo Gama[3] Liana Codes[2] Simone Cunha[2] Janaina Narciso-Schiavon[7] Claudia Couto[8], [1]Universidade Federal de Minas Gerais, Brasil, [2]Hospital Português, Salvador, Bahia, [3]Universidade Federal de São Paulo, Brasil, [4]Clínica Universidad de los Andes, Chile, [5]Hospital Alemán, Buenos Aires, [6]Hospital Clínico Universidad de Chile, [7]Universidade Federal de Santa Catarina, Brasil, [8]Federal University of Minas Gerais

Background: Primary sclerosing cholangitis (PSC) is an immune-mediated cholestatic liver diseaswith variable presentation across populations. Latin America, characterized by high admixture and unique genetic diversity, is underrepresented in PSC research. This study describes the clinical and epidemiological profile of PSC in Latin America. **Methods:** Ongoing, retrospective, international multicenter cohort (ALLATIN) study sponsored by ALEH, enrolling PSC patients from different Latin American countries. **Results:** Data from 146 patients were analyzed: Brazil (76.7%), Chile (13.0%), Costa Rica (3.4%), Argentina (2.7%), Ecuador (2.1%), and Cuba (1.4%). Most were male (56.5%), mean age at diagnosis 35 ± 17.7 years, mean follow up time 92.1 ± 193 months. The majority had large-duct PSC (79.3%), 27.3% (36/132) cirrhotic at diagnosis. Overlap with autoimmune hepatitis was reported in 11.4%. Inflammatory bowel disease was present in 56.7% (80/141): 76% ulcerative colitis, 18.7% Crohn's disease. MRCP was the primary diagnostic tool in 93.6%. Still, liver biopsy was performed in 51.1% (70/137). UDCA was prescribed in 90.1% (118/131) and fibrates in 13.6% (18/132). During follow-up, 28.6% (36/126) developed cirrhosis, 10.4% (13/125) had recurrent cholangitis, 3.9% (5/127) hepatocellular carcinoma, 7.0% (9/129) cholangiocarcinoma, and 0.69% (1/144) colorectal cancer; no gallbladder cancers were reported. Liver transplantation was performed in 19.7% (25/127), and mortality reached 15.6% (20/128), with 65% liver-related. **Conclusion:** This is the first multinational study of PSC in Latin America. Differences in IBD prevalence, sex distribution, diagnostic and treatment approaches reflect regional heterogeneity and a broader global lack of consensus on optimal PSC management, emphasizing the need for prospective, multicenter studies.

Disclosures: Guilherme Cancado: Nothing to Disclose, Paulo Bittencourt: Nothing to Disclose, Maria Lucia Ferraz: Nothing to Disclose, Lorena Solari: Nothing to Disclose, Margarita Anders: Nothing to Disclose, Nicolas Ortiz: Nothing to Disclose, Raimundo Gama: Nothing to Disclose, Liana Codes: Nothing to Disclose, Simone Cunha: Nothing to Disclose, Janaina Narciso-Schiavon: Nothing to Disclose, Claudia Couto: Inventiva: Grant/Research Support, Novonordisc: Speaking and Teaching, Gilead: Grant/Research Support, Mirum: Grant/Research Support

4531 | PREVALENCE AND OUTCOMES OF EXTRAHEPATIC AUTOIMMUNE DISEASES IN U.S. PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: A REAL-WORLD EHR STUDY

Romelia Barba[1] Ana Marenco-Flores[2] Khawaja Hassam[3] Rubab Rizwan[4] Natalia Rojas-Amaris[2] Daniela Goyes[5] Iman Waheed Khan[6] Kanak Das[1] Hakan Akin[1] Vilas Patwardhan[2] Alan Bonder[2], [1]Texas Tech University, [2]Beth Israel Deaconess Medical Center, [3]Lahey Hospital and Medical Center, [4]Vassar Brothers Medical Center, [5]Yale University School of Medicine, [6]Reading Hospital, Tower Health

Background: Primary biliary cholangitis (PBC) often coexists with extrahepatic autoimmune diseases (EHAIDs), but U.S. real-world data on their prevalence and clinical impact are limited. Prior European and inpatient U.S. studies were constrained by small cohorts or a lack of long-term follow-up. We used a national EHR network to evaluate EHAID prevalence and outcomes in PBC. **Aim:** To assess the prevalence of EHAIDs and their association with transplant-free survival, hepatorenal syndrome (HRS), and hepatic

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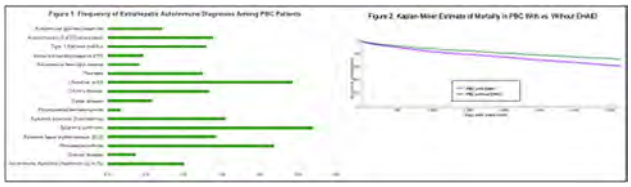
encephalopathy in a real-world cohort of PBC patients. **Methods:** We conducted a retrospective cohort study using the TriNetX U.S. Collaborative Network. Adults ($\geq$18 years) with PBC (ICD-10 K74.3) from 2010–2025 were included. Patients with autoimmune hepatitis or primary sclerosing cholangitis were excluded. Of 36,362 PBC patients, 8,304 (22.8%) had $\geq$1 EHAID diagnosis before or after PBC, while 20,536 (56.5%) had none. The remaining 7,522 had insufficient structured data to classify EHAID status and were excluded from subgroup comparisons. Outcomes included death, liver transplant, HRS, and hepatic encephalopathy over 10 years. Kaplan-Meier and risk analyses were used. Competing risks and site-level data were not available. **Results:** The most common EHAIDs were Sjögren's syndrome (5.4%), ulcerative colitis (4.9%), rheumatoid arthritis (4.4%), systemic sclerosis (3.1%), and systemic lupus erythematosus (2.8%). Compared to patients without EHAID, those with EHAID had higher risks of death (20.1% vs. 14.0%; OR 1.54, 95% CI 1.44–1.65, $p < 0.001$), HRS (2.9% vs. 2.4%; OR 1.22, $p = 0.013$), and encephalopathy (5.6% vs. 5.0%; OR 1.13, $p = 0.040$). Transplant rates were slightly higher (2.4% vs. 2.1%, $p = 0.087$). Ten-year survival was lower in the EHAID group (61.4% vs. 71.7%; HR 1.41, 95% CI 1.32–1.49, $p < 0.001$). **Conclusion:** In this large, national cohort, over one in five PBC patients had coexisting EHAIDs. Their presence was associated with higher mortality and hepatic decompensation. Unlike prior inpatient-only studies, this analysis includes outpatient and long-term data, offering a more complete view of EHAID burden in PBC.



Disclosures: Romelia Barba: Nothing to Disclose, Ana Marenco-Flores: Nothing to Disclose, Khawaja Hassam: Nothing to Disclose, Rubab Rizwan: Nothing to Disclose, Natalia Rojas-Amaris: Nothing to Disclose, Daniela Goyes: Nothing to Disclose, Iman Waheed Khan: Nothing to Disclose, Kanak Das: Nothing to Disclose, Hakan Akin: Nothing to Disclose, Vilas Patwardhan: Nothing to Disclose, Alan Bonder: GSK: Grant/Research Support, Mirium: Grant/Research Support, Gilead: Grant/Research Support, Ipsen: Grant/Research Support, Cymabay: Grant/Research Support, Intercept: Grant/Research Support, Intercept: Consultant, GSK: Consultant, Ipsen: Consultant, Chemobab: Grant/Research Support, Alnylam: Consultant, Thirammune: Consultant

4532 | IMPACT OF MARALIXIBAT ON CAREGIVER BURDEN FOR PATIENTS WITH ALAGILLE SYNDROME AND PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS: BASELINE AND 6-MONTH FOLLOW-UP

Natasha Dilwali[1] Fiona Coll[2] Yushan Kim[3] Robin Howard[4] Rachel Hallum-Montes[2] Douglas Mogul[3] Wikrom Karnsakul[5], [1]Johns Hopkins University, Baltimore, Maryland, [2]Motivo Insights, Colorado Springs, Colorado, [3]Mirum Pharmaceuticals, Inc., Foster City, California, [4]Mirum Pharmaceuticals, Inc., [5]Johns Hopkins University

Background: Alagille syndrome (ALGS) and progressive familial intrahepatic cholestasis (PFIC) are rare conditions leading to end-stage liver disease. As a result of cholestasis, patients experience pruritus, which impacts quality of life, sleep, and is a leading cause of transplant. Maralixibat (MRX) is approved to treat cholestatic pruritus in ALGS/PFIC, with trials showing improvements in pruritus are linked to better patient sleep and quality of life. This study evaluates the impact of MRX on caregiver burden before and 6 months after starting treatment. **Methods:** All MRX prescriptions in the US are dispensed through one pharmacy. Beginning in March 2024, caregivers of newly prescribed MRX for ALGS/PFIC were invited to complete a survey assessing caregiver burden. Questions addressed sleep, pruritus, financial strain, and included the Hospital Anxiety and Depression Scale (HADS) and Zarit Burden Interview (ZBI-12). Follow-up surveys were completed after six months. Data analysis included descriptive statistics, medians, standard deviations, and proportions. **Results:** A total of 21 baseline and 10 6-month follow-up surveys were completed. Most respondents were parents of children with ALGS, identified as Caucasian, and aged 30–39. Among the 10 caregivers with paired surveys, sleep metrics improved over time. On a 1–10 Likert scale (10 = extreme impact), the median sleep impact score decreased from 8 (range 1–10) at baseline to 5.5 (0–10) at 6 months (32% improvement). Similarly, at baseline, 100% reported caregiving impacted their sleep, decreasing to 60% at 6 months. Reports of fair/poor sleep dropped from 90% to 70%. Average nightly sleep increased from 5.6 to 6.3 hours (12.5% increase). ZBI-12 scores showed 6 caregivers had no/mild burden at baseline, 3 had mild/moderate, and 1 had high burden. At 6-month follow-up, 7 had no/mild burden, 1 had mild/moderate, and 2 had high burden. On the HADS, two caregivers had abnormal depression scores at baseline, decreasing to one at follow-up; three had abnormal anxiety scores

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at baseline, which remained unchanged at follow-up. **Conclusion:** These results suggest 6 months of MRX treatment may reduce caregiver sleep disruption and burden, likely due to improved pruritus in patients. ZBI-12 trends support reduced burden, though HADS results were mixed. While encouraging, these findings are preliminary. Longer-term follow-up is needed to fully understand the broader caregiver benefits of MRX therapy.

Disclosures: Natasha Dilwali: Nothing to Disclose, Fiona Coll: Mirum Pharmaceuticals: Consultant, Yushan Kim: Nothing to Disclose, Robin Howard: Mirum Pharmaceuticals: Stock - publicly traded company, Mirum Pharmaceuticals: Employee, Mirum Pharmaceuticals: Consultant, Rachel Hallum-Montes: Nothing to Disclose, Douglas Mogul: Mirum Pharmaceuticals: Employee, Wikrom Karnsakul: Nothing to Disclose

4533 | BILE ACID-MEDIATED TISSUE FACTOR ACTIVATION IN HEPATOCYTES

Alex Nartey[1] Sandra Preinstorfer[1] Katrin Panzitt[1] Marion Mussbacher[2] Martin Wagner[1] Axel Schlagenhauf[1], [1]Medical University of Graz, [2]University of Graz

Background: Cholestasis is a hepatobiliary disorder associated with decreased hepatic secretion of bile, causing long-term exposure of hepatocytes to bile acids (BAs) and subsequent liver damage. Intrahepatic coagulation activation during cholestasis can lead to microscopic thrombi that may obstruct hepatic blood flow. Anticoagulant therapy, one of the few available treatments, is often contraindicated when hepatic synthetic dysfunction has already impaired coagulation. Previously, our group showed that in hepatic cell lines, BAs induce the activity of the membrane protein tissue factor (TF, initiator of coagulation), which coincided with activation of farnesoid X receptor (FXR) signalling. Thus, we hypothesise that in cholestasis, prolonged BA exposure induces TF activation through FXR overstimulation, triggering coagulation and stress pathways ultimately leading to hepatocellular decline and thrombus formation. **Methods:** We studied the effects of 24h BA and tunicamycin (ER stress inducer) treatment on cultured hepatocytes, analysed hepatic tissue from liver surgery patients, and examined FXR-deficient mice with bile duct ligation as well as tunicamycin-treated mice. **Results:** We found an expression-independent TF activity increase coupled with FXR activation in hepatocytes treated with unconjugated BAs. Tunicamycin induced ER stress together with an increase in TF activity and early activation of FXR signalling. Both treatments resulted in a rapid viability decline accompanied by an increase in apoptosis/necroptosis that played a key role in TF activity.

Patients with high bilirubin serum levels (indicating cholestatic diseases) exhibited FXR activation with signs of enhanced coagulation.

Lastly, FXR activity and hepatic thrombin levels were elevated in mice after bile duct ligation, with a reduction in the FXR-deficient cohort. Tunicamycin-treated mice showed a similar early activation of FXR signalling. **Conclusion:** Our results suggest that prolonged exposure of hepatocytes to BAs post-translationally increases TF activity coinciding with continuous intracellular FXR activation, a similar phenotype observed after early ER stress elicited by tunicamycin. Both conditions triggered rapid hepatocellular decline, mediated at least partially by apoptosis/necroptosis-dependent pathways. We thus conclude that FXR overstimulation (via BAs) and ER stress (via tunicamycin) triggers downstream pathways like apoptosis/necroptosis and other key mechanisms regulating BA-mediated activation of the membrane protein TF. Our findings provide valuable insights into the largely elusive molecular mechanisms underlying intrahepatic coagulation activation during cholestasis.

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4534 | YOUR GUIDE TO LIVING WELL WITH PRIMARY BILIARY CHOLANGITIS: CO-CREATION OF AN EVIDENCE-BASED RESOURCE FOR SYMPTOM MANAGEMENT AND DISEASE UNDERSTANDING

Victoria Barghout[1] Laura Medina[1] Sophie Griswold[1] Gail Wright[2] Carol Roberts[3] Robert Mitchel-Thain[4] Mo Christie[4] Kerin Stevens[5] ANNIE SON[5] Jamie Zagorski[5], [1]Viver Health LLC, Morristown, NJ, USA, [2]Canada PBC Society, Toronto, Canada, [3]PBCers Organization, Rochester, NY, USA, [4]PBC Foundation, Edinburgh, UK, [5]Gilead Sciences, Inc.

Background: Primary biliary cholangitis (PBC) is a chronic, inflammatory autoimmune liver disease characterized by progressive cholestasis and high symptom burden, including pruritus, fatigue, and cognitive dysfunction. While treatments may slow disease progression, patients often experience persistent symptom burden. Patients frequently report gaps in disease education and lack tools to manage symptoms, improve quality of life (QoL), and engage in shared decision-making with healthcare providers (HCPs). **Methods:** We used a qualitative, stakeholder-informed approach with literature review and iterative resource creation. A literature review and structured interviews with a

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geographically and demographically diverse group of individuals with PBC, advocates, and HCPs identified key gaps in patient education, symptom management, and shared decision-making in PBC. Findings informed creation of Your Guide to Living Well with PBC. The same participants reviewed the Guide for clarity, usability, and relevance. Medical experts conducted a clinical review to ensure guideline alignment. Throughout development, three leading PBC advocacy groups provided input, health literacy review, and endorsement. An online survey was created to assess usage, satisfaction, behavior change, and reach. **Results:** A need was identified for a user-friendly evidence-based resource to support symptom self-management and facilitate informed discussions with HCPs. The resulting resource, Your Guide to Living Well with PBC, is an accordion, four-fold printed Guide, backed by 202 references. It covers whole-person disease management and lifestyle adaptations like stress management, nutrition, and movement, which may improve QoL. Emphasis is given to integrative approaches for managing fatigue, pruritus, and cognitive symptoms. Patients stated that "[they] would have loved this when first diagnosed." HCPs noted it "fills an unmet need" and "allows patients to take control." Early survey feedback showed greater confidence in understanding disease mechanisms, symptom management, and shared decision-making. Patients rated use likelihood as extremely likely (9.89/10). **Conclusion:** Your Guide to Living Well with PBC addresses key gaps in patient education, symptom self-management, and shared decision-making. By combining evidence-based content with patient and provider insights, the Guide offers a practical tool to support whole-person care. Ongoing metrics will guide development and dissemination.

Disclosures: Victoria Barghout: Gilead Sciences: Contracted to produce educational content, Alexion: Contracted to produce educational content, Argenx: Contracted to produce educational content, Sun Pharma: HEOR consulting work, Laura Medina: Nothing to Disclose, Sophie Griswold: Nothing to Disclose, Gail Wright: Nothing to Disclose, Carol Roberts: Nothing to Disclose, Robert Mitchel-Thain: Nothing to Disclose, Mo Christie: Nothing to Disclose, Kerin Stevens: Nothing to Disclose, ANNIE SON: Gilead Sciences: Employee, Jamie Zagorski: Nothing to Disclose

4535 | DIET QUALITY IS POSITIVELY ASSOCIATED WITH QUALITY OF LIFE IN ADULT FEMALES WITH PRIMARY BILIARY CHOLANGITIS

Audrey-Anne Lavoie[1] Mélanie Verreault[2] Jacob Lessard-Lord[1] Roxanne Rochon[3] Valérie Guay[4] Laurence Constantin[1] Mandana Salkhi[1] Catherine Vincent[3] Jean-Philippe Drouin-Chartier[1] Olivier Barbier[1], [1]Université Laval, Faculty of Pharmacy, Quebec, Canada, [2]CHU De Québec Research Center, Quebec, Canada, [3]University of Montreal Health Centre (CHUM), Quebec, Canada, [4]Institute of Nutrition and Functional Foods, Université Laval, Quebec, Canada

Background: Primary biliary cholangitis (PBC) is a rare hepatobiliary disease characterized by the destruction of the bile ducts, which leads to cholestasis, fibrosis, cirrhosis and liver failure. Although pharmacological options are effective in slowing disease progression, they offer limited relief from symptoms such as fatigue and pruritus. Diet could slow disease progression and offer an additional strategy to improve symptom burden. However, the relationship between diet and PBC remains poorly understood. *Thus, this study aimed to evaluate the association between diet, symptom management and liver-related outcomes in patients with PBC.* **Methods:** Adult female with PBC ($n = 48$) were recruited at the Department of Hepatology of the CHU de Montréal, Quebec, Canada. Liver enzymes, fibrosis, steatosis levels (CAP score) and cirrhosis were measured through blood tests or Fibroscan. Symptoms burden and diet quality were evaluated using the PBC-40 questionnaire and the Alternative Healthy Eating Index (AHEI) upon completion of 1 or more web-based 24h diet recalls. **Results:** Participants had a mean age of 63.9 ± 8.1 years and most exhibited hepatic steatosis and/or fibrosis (CAP score: 249.7 ± 52.8dB/m; fibrosis score: 5.9 ± 2.0kPa). While diet quality was suboptimal (AHEI score: 50.7 ± 11.0), better dietary habits was associated with improved liver outcomes. Each 10-points increase in the AHEI score corresponded to reductions of -1.8dB/m [95% CI: -3.2, -0.5; $P = 0.009$] in CAP score and -0.09kPa [-0.1, -0.03; $P = 0.003$] in fibrosis score. Higher polyunsaturated fatty acids (PUFA) intake was also associated with -3.9% decreased odds of developing cirrhosis [-0.09, 0.006, $P = 0.09$]. Whole vegetable intake was inversely associated with total bilirubin levels (-0.7µmol/L [-1.3, -0.1; $P = 0.02$] per 1-point increase in the $AHEI_{vegetable}$ subscore). Diet quality also aligned with improved quality of life: higher fruit intake was associated with a reduced itch score of -0.5 [-1.1, 0.04; $P = 0.07$] per 1-point increase in the $AHEI_{fruits}$ subscore, while higher PUFA intake with lower emotional and social scores of -0.5 [-0.8, -0.2; $P = 0.004$] and -1.5 [-2.8, -0.2; $P = 0.03$] per 1-point increase in the $AHEI_{PUFA}$ subscore. Higher total protein intake was associated with lower fatigue score of -0.2 [-0.5, 0.004; $P = 0.09$] per 1g increase of protein. **Conclusion:** Healthy food consumption could provide an alternative option to improve quality of life and reduce pathological parameters in patients with PBC.

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Laurence Constantin: Nothing to Disclose, Mandana Salkhi: Nothing to Disclose, Catherine Vincent: Nothing to Disclose, Jean-Philippe Drouin-Chartier: Nothing to Disclose, Olivier Barbier: Nothing to Disclose

4536 | CREATING DIAGNOSTIC ALGORITHMS TO IMPROVE IDENTIFICATION OF PRIMARY BILIARY CHOLANGITIS

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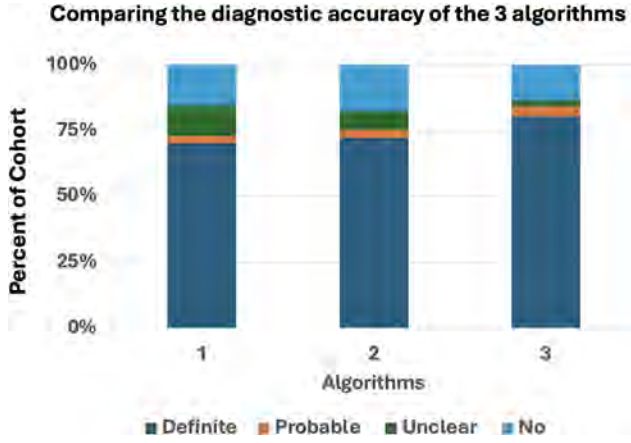
Background: Primary biliary cholangitis (PBC) remains incompletely characterized in large, population-based studies. Most available data come from academic centers, limiting generalizability and underrepresenting the broader spectrum of disease, treatment, and demographic diversity. Furthermore, the only well-validated algorithm for PBC was developed in a US Veterans Affairs cohort of predominantly men, limiting its applicability. This study aims to evaluate and compare three diagnostic algorithms to identify patients with PBC and to assess their performance across biopsied and non-biopsied populations. **Methods:** We retrospectively reviewed charts for patients using three different algorithms to identify patients with PBC. All algorithms included a diagnosis code PBC with the following:

1. Elevated alkaline phosphatase (AP);
2. Elevated AP + ursodeoxycholic acid (UDCA) prescription;
3. Elevated AP + UDCA + elevated anti-mitochondrial antibody (AMA).

We diagnosed patients with PBC according to the AASLD guidelines: 2 of the 3 – elevated AP, +AMA, or biopsy findings of PBC. Patients were identified as having PBC, not having PBC, having insufficient data to assess, or having probable PBC. Probable PBC was present when borderline findings were present. We also clarified if patients underwent biopsy confirmation or had overlap syndromes. Categorical variables were compared by chi-squared tests. **Results:** There were 860, 629, and 286 patients who were identified using algorithms 1, 2, and 3 respectively. Between 82-84% of patients were female and 53-58% were biopsied.

Using algorithm 1, 70% had definite PBC, 3% had probable PBC, and 12% had insufficient data (Figure). Using algorithm 2, 72% had definite PBC, 3% had probable PBC, and 7% had insufficient data. PBC Using algorithm 3, 80% had definite PBC, 4% had probable PBC, and 2% had insufficient data. When including only biopsied patients, all algorithms identified PBC in 90% of patients. In those without biopsy, algorithm 3 identifies PBC in 81% compared to 72% and 70% in algorithms 1 and 2, respectively.

In all algorithms, male patients were more likely to be misidentified as definite PBC. In all algorithms, patients were misidentified as PBC and instead had primary sclerosing cholangitis, other biliary diseases, or other liver diseases (usually autoimmune hepatitis). **Conclusion:** This study demonstrates that all three diagnostic algorithms effectively identified patients with PBC, with improving accuracy as additional clinical criteria are incorporated. Importantly, this study population includes mostly female patients, reflecting the known epidemiologic distribution of PBC and addressing a key limitation of the prior validated algorithm developed in a male-dominant cohort. These findings provide a framework for identifying PBC in larger datasets and support future efforts to further study disease patterns, treatment response, and clinical outcomes.



Disclosures: Alexander Zhao: Nothing to Disclose, Russell Rosenblatt: Nothing to Disclose

4537 | IMPACT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE ON HEPATOCELLULAR CARCINOMA RISK IN AUTOIMMUNE HEPATITIS

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Background: Few large-scale studies have investigated factors associated with the development of hepatocellular carcinoma (HCC) in patients with autoimmune hepatitis (AIH). This study aimed to determine the risk of HCC in AIH patients and associated risk factors, focusing on metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** We analyzed the claims data from the Korean National Health

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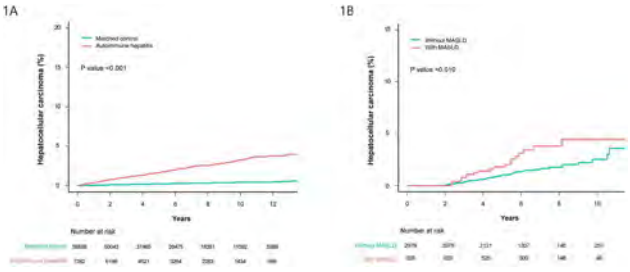
Insurance Service from 2007 to 2020. The study included 7,382 patients with AIH and a control group of 58,538 age- and sex-matched individuals, at a ratio of 1:8. We compared the incidence rates of HCC between these groups and investigated the risk factors of HCC. **Results:** During a median follow-up of 5.9 years, 160 AIH patients were diagnosed with HCC, resulting in an incidence rate of 3.60 per 1,000 person-years. The matched controls exhibited an incidence rate of 0.48 per 1,000 person-years. After adjustment, AIH patients had a 4.85-fold heightened risk of HCC compared to the control group (Figure 1A). Within the AIH cohort, the presence of coexisting MASLD further elevated the risk of HCC (Figure 1B), along with other factors such as older age, male sex, and decompensated liver cirrhosis, as observed in a two-year landmark analysis. The presence of concurrent extrahepatic autoimmune diseases did not affect the prognosis, while glucocorticoid treatment was associated with a decreased risk of HCC. **Conclusion:** Patients with AIH had an increased risk of HCC compared to matched controls, particularly those with coexisting MASLD. In addition to appropriate medical treatment, proactive interventions and lifestyle modifications for concurrent MASLD are recommended for these patients.



Disclosures: JIHYE LIM: Nothing to Disclose, Ye-Jee Kim: Nothing to Disclose, Sehee Kim: Nothing to Disclose, Ju Hyun Shim: Nothing to Disclose

4538 | ALTERED THREE DIMENSIONAL (3D) INTRAHEPATIC BILIARY STRUCTURES VISUALIZED USING TISSUE CLEARING METHODS: IN HUMAN HEPATOBILIARY DISEASE

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Background: Various biliary lesions such as ductular reactions and biliary obstruction occur in human hepatobiliary diseases. Three-dimensional (3D) intrahepatic biliary structures may alter in such diseases, however, there are few studies on 3D-imaging of biliary structures in human hepatobiliary diseases. We took advantage of tissue clearing methods and light sheet fluorescence microscopy (LSFM) to analyze pathological changes in 3D-biliary structures in human chronic liver diseases. **Methods:** Twenty-eight autopsied liver tissues were obtained from 2 patients with primary biliary cholangitis [PBC] (both advanced stage), 5 with cirrhosis (hepatitis C-related, 2; metabolic dysfunction associated steatotic liver disease [MASLD], 3), 4 with mild fibrosis (F1/2; hepatitis B-related, 1; MASLD, 3) and 17 with nonspecific reactive change (NSR). Liver tissues were formalin-fixed, then cleared using Rapid and nondestructive tissue clearing system (RAP) or the clear, unobstructed brain/body imaging cocktails (CUBIC) methods. 3D-imaging of biliary structures were obtained using immunostaining with Alexa 488- or Alexa 647-labelled anti-CK19 and LSFM. A number (No.) of CK19-positive biliary components, No. of biliary components per portal tract, degrees of biliary networks in portal tract, anastomoses, bridging formation, meandering and caliber variation were evaluated semi-quantitatively on the image. **Results:** 3D-biliary structures in human hepatobiliary diseases were clearly visualized by tissue clearing methods and imaging by LSFM. No. of biliary components and No. of biliary components per portal tract were significantly increased in cirrhosis, compared to mild fibrosis and NSR ($p < 0.05$). Degrees of biliary networks in portal tract, anastomoses, bridging formation and meandering were significantly increased in cirrhosis, compared to PBC, mild fibrosis and NSR ($p < 0.01$). There was no significant difference in caliber variation among groups. It is of interest that No. of biliary components and other factors were not increased in PBC, even in the advanced stage. **Conclusion:** 3D-imaging using the tissue clearing methods may be a promising strategy to evaluate pathological alterations of human intrahepatic biliary structures in various human hepatobiliary diseases.

Disclosures: Motoko Sasaki: Nothing to Disclose, Yasunori Sato: Nothing to Disclose, Yasuni Nakanuma: Nothing to Disclose

4539 | ANTIMICROBIAL THERAPY IN PRIMARY SCLEROSING CHOLANGITIS-INFLAMMATORY BOWEL DISEASE: REAL-WORLD EVIDENCE REVEALS CLINICAL RISKS DESPITE ALKALINE PHOSPHATASE IMPROVEMENT

Himaben Gohil[1] Lan Nguyen[1] Randy Cheung[1] Anthony Martinez[1], [1]University at Buffalo

Background: Primary sclerosing cholangitis (PSC) is closely linked to inflammatory bowel disease (IBD). The leaky gut theory proposes that disruption of the intestinal barrier in IBD allows microbial translocation to the biliary system, promoting hepatic inflammation

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and fibrosis. This gut-liver axis has driven interest in using oral antimicrobials to treat PSC. While some antibiotics have demonstrated biochemical benefits, their clinical impact remains unclear. To address this, we compared five oral antibiotics across PSC- and IBD-related outcomes using real-world multicenter data. **Methods:** We conducted a retrospective cohort analysis using TriNetX, a global database of healthcare organizations. Participants were adults over the age of 18 with both PSC and IBD. They were grouped based on exposure to vancomycin, rifaximin, metronidazole, minocycline, or azithromycin. The control group was not exposed to any of these antibiotics. Each group was propensity score-matched to the control based on demographics, comorbidities, medications, and baseline liver function labs. PSC outcomes included alkaline phosphatase (ALP) elevation, liver fibrosis, transplant, and hepatobiliary cancer. IBD outcomes included steroid use, hospitalization, IBD-related surgery, and death. Results shown in Table A are presented as risk differences, calculated as the percent risk of the outcome in the control group minus that in the treatment group. **Results:** All antimicrobials, except azithromycin, showed a statistically significant decrease in ALP elevation. Vancomycin was associated with higher risks of liver transplant, steroid use, hospitalization and death. Rifaximin not only raised the risk of liver fibrosis and transplant but also had the highest associated mortality. Metronidazole was linked to increased risks of liver transplant, steroid use, IBD-related surgery, and death. Minocycline had the greatest decline in ALP elevation and reduced IBD-related surgery risk but was linked to higher hepatobiliary cancer risk. Azithromycin was not significantly associated with any outcomes. **Conclusion:** Most antibiotics improved serum ALP; however, they failed to reduce and often worsened both PSC- and IBD-related outcomes. These findings highlight a disconnect between biochemical response and long-term clinical benefit thereby challenging the utility of antimicrobials for PSC. Future studies should explore optimal dosing or alternative therapies that improve both hepatic and intestinal outcomes.

Table A: PSC and IBD- related clinical outcomes of antimicrobial therapies in IBD patients

Outcomes	*Vancomycin*		*Rifaximin*		*Metronidazole*		*Minocycline*		*Azithromycin*	
	Risk diff.%	*p*-value	Risk diff.%	*p*-value	Risk diff.%	*p*-value	Risk diff.%	*p*-value	Risk diff.%	*p*-value
PSC-related outcomes										
Elevation in ALP	**2.98**	**0.0074**	**4.65**	**0.0023**	**1.933**	**0.0528**	**13.51**	**0.0125**	2.71	0.0577
Liver Fibrosis	0.83	0.477	**-6.25**	**0.0003**	0	1	-1.35	0.799	1.774	0.2361
Cholangitis	0.71	0.466	1.47	0.3031	0.33	0.7049	5.41	0.2532	1.88	0.1498
Liver transplant	**-7.33**	**<0.0001**	**-6.37**	**0.0001**	**-3.79**	**0.0001**	-6.76	0.1671	-1.41	0.3085
Hepatobiliary cancer	0	1	0	1	-0.051	0.6944	**-6.76**	**0.0013**	0	1
IBD-related outcomes										
Steroid use	**-5.03**	**<0.0001**	-2.82	0.0966	**-2.44**	**0.0260**	-3.38	0.5483	-3.55	0.027
Hospitalization	**-10.03**	**<0.0001**	**-6.74**	**<0.0001**	**-8.73**	**<0.0001**	-4.05	0.4688	-0.84	0.5954
IBD linked surgery	-0.15	0.5976	-0.061	0.8720	**-1.07**	**0.0005**	**6.76**	**0.0013**	0.10	0.7759
Death	**-4.33**	**<0.0001**	**-6.001**	**<0.0001**	**-2.37**	**0.0047**	-8.11	0.0627	-1.30	0.2780

Disclosures: Himaben Gohil: Nothing to Disclose, Lan Nguyen: Nothing to Disclose, Randy Cheung: Nothing to Disclose, Anthony Martinez: Gilead: Consultant, Gilead: Speaking and Teaching, Abbvie: Consultant, Abbvie: Speaking and Teaching, Arbutus: Consultant, Braeburn: Speaking and Teaching, Sirtex: Consultant, Roche: Consultant, Syneos/VBI: Consultant, Madrigal: Speaking and Teaching, Altimune: Consultant, Madrigal: Consultant, Ipsen: Consultant

4540 | "IT'S MORE LIKE A DULL, ACHY PAIN THAT'S JUST CONSTANT": LIVER PAIN EXPERIENCES IN ADULTS WITH PRIMARY SCLEROSING CHOLANGITIS (PSC) TO INFORM MEASURE DEVELOPMENT

Donna Evon[1] Lauren Wright[2] Laura Mkumba[2] Nicole Lucas[2] Kaya Merkler[1] Ricky Safer[3] Joanne Hatchett[3] Rachel Gomel[3] Stephen Rossi[3] Mark Swain[4] Sasha Deutsch-Link[1] Bryce Reeve[2], [1]UNC Chapel Hill, [2]Duke, [3]PSC Partners Seeking a Cure, [4]University of Calgary

Background: An in-depth understanding of experiences with liver pain associated with chronic liver disease is virtually non-existent, especially for individuals living with PSC. The development of a PSC-specific liver pain measure suitable for clinical trials relies upon understanding key characteristics of liver pain in this population. **Methods:** Adults with PSC were recruited through the PSC Partners Patient Registry and hepatology experts in the U.S. Participants were phone screened for the presence of multiple PSC-related symptoms. Purposeful sampling was used to recruit a representative sample of 17 adults for in-depth qualitative interviews about key PSC symptoms experienced in the last month, including liver pain. Interviews were conducted virtually, audio-recorded, transcribed, and analyzed using NVivo software. **Results:** Ten out of 17 participants who reported liver pain as a prominent PSC symptom described their experiences in detail, while another three spontaneously mentioned liver pain during their interviews. Participants were, on average 43 years old (range: 27-65), 50% male, 60% white, 30% black, 10% asian and 30% had inflammatory bowel disease (IBD). Participants' experiences of their liver pain are found in the Table below. Participants described the location of PSC-associated liver pain generally in the right upper quadrant area, but said it can extend around the side and back. Eleven of 13 described liver pain as "stabbing" or "sharp." Eight described their pain as "achy" or "dull." The sharp/stabbing pain is typically brief, while the achy/dull pain is more persistent. All but one participant used the word "pain" to describe their sensations. Liver pain can "come

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and go" intermittently, happens at random, and seems unassociated with specific triggers. Some reported pain daily, others weekly, and most reported pain occurring outside of cholangitis attacks. Participants were able to differentiate PSC-related liver pain versus abdominal pain from other causes (including IBD) based on location and type of pain, timing, response to medications, and laboratory/clinical markers. Liver pain interfered with sleep and caused anxiety, but relative to fatigue and brain fog, it appears to interfere less with daily functioning. Participants tended to "*push through it.*" **Conclusion:** Dull/achy and sharp/stabbing liver pain may be more frequent and severe in symptomatic adults with PSC than previously recognized. These in-depth qualitative findings will inform the development of a de novo PSC-specific liver pain measure, inclusive of heterogeneity of experiences, and suitable for future PSC research studies.

TABLE. Participants' Descriptions of PSC-related Liver Pain

Attribute	Illustrative Liver Pain Quotes
Location	*"I feel it's like right underneath my right rib cage. Sometimes around to the right side, like stretching around to the right side of my torso."*
Quality	*"The sharp pain, it's like getting stuck with the needle but it's very short. The fact that it's so brief makes it not as bad."*
Quality	*"The dull pain around the whole liver area, that's more problematic honestly 'cause it's just like, it's a lot more uncomfortable 'cause it lasts for a while."*
Severity	*"Sometimes it's bad enough that I vocalize a bit of a scream, because it's very—it's just so—it's so out of nowhere. It's like surprising excruciating pain."*
Severity	*"It's a 10. It's like a knife. It's intense."*
Frequency	*"The liver pain more comes and goes. It's not an all-the-time pain."*
Frequency	*"I would say almost daily."*
Frequency	*"I probably have days where I don't have it, but I would say most days that I do."*
Interference	*"I do have trouble sleeping. Trying to get to a comfortable position if my liver's hurting on that right side, trying to get comfortable is not always easy."*
Interference	*"I don't like being reminded. I don't like being reminded of my disease, and I would say it causes me anxiety."*
Interference	*"It definitely makes it harder to be a fully engaged parent. I think putting our toddler to sleep, sometimes he climbs all over you and it's painful…."*
Resilient Coping	*"…I just try to ignore it and go about my day."*

Disclosures: Donna Evon: Nothing to Disclose, Lauren Wright: Nothing to Disclose, Laura Mkumba: Nothing to Disclose, Nicole Lucas: Nothing to Disclose, Kaya Merkler: Nothing to Disclose, Ricky Safer: Nothing to Disclose, Joanne Hatchett: Nothing to Disclose, Rachel Gomel: Nothing to Disclose, Stephen Rossi: Nothing to Disclose, Mark Swain: Nothing to Disclose, Sasha Deutsch-Link: Nothing to Disclose, Bryce Reeve: Nothing to Disclose

4541 | PATHOGENIC MOLECULES IN AUTOIMMUNE LIVER DISEASE (AILD) AND ITS CORRELATION WITH DISEASE ACTIVITY AND SEVERITY

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Background: The spectrum of Autoimmune Liver Disease (AILD) comprises of Autoimmune Hepatitis (AIH), Primary Biliary Cholangitis (PBC), Primary Sclerosing Cholangitis (PSC) and overlap disorders in varying presentations. The pathogenic molecules like T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), Lymphocyte Activation Gene-3 (LAG-3) stimulate the Cluster of Differentiation 24 (CD24) and has been found to be associated with increased hepatic inflammation causing liver injury. Hence targeting CD24 can be an alternative mechanism through which AIH can be regulated. This study aimed to characterize the expression of CD24, TIM-3, and LAG-3 on peripheral blood helper (CD4+) and cytotoxic (CD8+) T cells in AIH and overlap syndromes and correlate with disease activity and severity. **Methods:** 48 biopsy proven patients with AILD along with 7 healthy controls were recruited in the study. Patients were stratified into Asymptomatic AIH(n = 7), Acute AIH(n = 19), AIH with cirrhosis(n = 4), AIH-PSC overlap(n = 11), AIH-PBC overlap (n = 7) and 7 healthy control groups. Flow cytometry on peripheral blood samples was used to analyze the expression of CD24, TIM-3, and LAG-3 on CD4+ and CD8+ T cells. **Results:** A significant increase in CD8+ T cell percentage was observed in asymptomatic AIH compared to AIH-cirrhosis($p = 0.0408$) and acute AIH ($p = 0.0064$). TIM-3+CD4+ T cells were significantly higher in asymptomatic AIH compared to healthy controls($p = 0.0162$). LAG-3+CD4+ T cells were more abundant in AIH-cirrhosis, and CD24+CD4+ T cells were higher in AIH-PSC and acute AIH, although not statistically significant. In the CD8+ T cell subset, TIM-3+ expression was reduced across AIH groups compared to healthy controls, while CD24+CD8+ T cells were elevated in acute AIH and AIH-PSC subgroups. The T cell marker expression in AILD is shown in Table 1. **Conclusion:** Distinct patterns of immune checkpoint molecule expression on peripheral blood T cells were observed across AIH subtypes. In asymptomatic AIH, elevated TIM3+ CD4+ T cells indicate an exhaustion like state suggesting hyperactive immune system suggesting the immune system is more active, concurrently increased CD8+ T cell expression reflects the active immune surveillance and hepatocyte injury. Reduced CD8+ T cells in AIH cirrhosis can be due to fibrosis and T cell exhaustion. LAG-3 is marker of immune fatigue which is elevated in AIH cirrhosis suggesting long term inflammation in liver leading to cirrhosis. These findings support the potential of CD24, TIM-3, and LAG-3 as biomarkers for disease stratification and may guide future targeted therapeutic strategies in AIH.

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Table 1: T cell marker expression values are reported as medians interquartile range (IQR)

Presentation	CD4+ T cell	CD8+ T cell	TIM-3+CD4+ T cells	LAG-3+CD4+ T cells	CD25+CD4+ T cells	CD8+ T cell subset, TIM-3+ expression	CD8+ T cell subset, LAG-3+ expression	CD25+CD8+ T Cells
Asymptomatic AIH (n=7)	16.90 (10.15-23.50)	32.4 (26.07-45.30)	1.34 (0.40-1.60)	0.40 (0.20-0.80)	0.40 (0.20-0.70)	0.40 (0.30-0.80)	0.10 (0.10-0.20)	0.30 (0.10-0.70)
Acute AIH (n=19)	24.20 (17.3-31.90)	13.75 (10.6-22.75)	0.20 (0.15-0.80)	0.50 (0.10-0.72)	0.50 (0.10-0.63)	0.40 (0.30-0.95)	0.45 (0.30-0.82)	2.30 (2.30-4.65)
AIH Cirrhosis (n=4)	36.60 (22.1-40.0)	16.90 (11.80-18.80)	0.20 (0.10-0.40)	0.10 (0.10-1.80)	0.95 (0.10-1.80)	0.20 (0.10-0.90)	1.0 (0.50-1.0)	0.30 (0.10-0.5)
AIH-PSC (n=11)	20.30 (19.30-21.50)	24.20 (19.90-32.40)	0.80 (0.30-0.90)	0.20 (0.20-0.40)	0.60 (0.60-1.10)	0.10 (0.10-1.2)	0.50 (0.10-0.50)	0.30 (0.10-0.50)
AIH -PBC (n=7)	24.0 (20.20-34.60)	26.50 (19-39.60)	0.10 (0.10-0.20)	0.30 (0.10-0.60)	0.10 (0.00-0.34)	0.80 (0.10-1.2)	0.30 (0.10-0.90)	0.20 (0.10-2.30)
Healthy Controls (n=7)	30.50 (30.15-32.70)	25.10 (20.95-26.30)	0.20 (0.10-0.40)	0.25 (0.12-0.43)	0.25 (0.12-0.37)	0.10 (0.10-0.40)	0.30 (0.15-0.90)	0.20 (0.15-0.65)

Disclosures: Sunil Taneja: Nothing to Disclose, Kannupriya.: Nothing to Disclose, Lekha Rani: Nothing to Disclose, Yaswant Kumar: Nothing to Disclose, Sweta Rose: Nothing to Disclose, Sonali Dagar: Nothing to Disclose, Savneet Singh: Nothing to Disclose, Balaraja S: Nothing to Disclose, Arpit Shastri: Nothing to Disclose, Ganesh CP: Nothing to Disclose, Muhammad Ashraf: Nothing to Disclose, Harjot Singh: Nothing to Disclose, Ashwin Vinod: Nothing to Disclose, Arka De: Nothing to Disclose, Nipun Verma: Nothing to Disclose, Madhumita Premkumar: Nothing to Disclose, Ranjana Minz: Nothing to Disclose, Ajay Duseja: Nothing to Disclose

4542 | ASSESSING THE RELATIONSHIP BETWEEN IMMUNOSUPPRESSANT MEDICATIONS AND COVID-19 PRESENCE AND SEVERITY IN AN AUTOIMMUNE HEPATITIS COHORT

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Background: Due to their potential use of immunosuppressants (IS), patients with autoimmune hepatitis (AIH) may be at higher risk for poor outcomes with COVID-19 infections. This study leverages the National COVID Cohort Collaborative (N3C), a large multicenter electronic health record (EHR) database, to assess whether there are associations between IS type and the severity of COVID-19 in patients with AIH. **Methods:** We identified patients with AIH in the N3C database from 3/2020 through 3/2025 along with COVID-19 diagnoses as indicated by positive testing. We used logistic regressions adjusting for age, sex, race, region, and CLD etiology to determine associations between odds of COVID-19 diagnosis and IS classes (Prednisone, Azathioprine, Budesonide, Tacrolimus, Cyclosporine, and Cellcept). We used Cox proportional hazard models to determine associations between IS and death starting from March 2020 for the subset of AIH patients diagnosed with COVID-19. In addition to primary analyses, we conducted a subgroup sensitivity analysis testing for the association between IS classes and outcomes among patients with Model for End-Stage Liver Disease (MELD) 3.0 scores. P value <0.05 was considered significant for all models. **Results:** Of 16,553 AIH patients, 3,860 (23%) tested COVID-19 positive during the study period, and 4,956 (30%) had IS exposure. In our adjusted logistic regressions assessing for associations with COVID-19 diagnoses, we found an association between Prednisone (odds ratio [OR] 1.23, 95% CI [1.12 - 1.36] $p<0.01$), Budesonide (OR 1.38, 95% CI [1.18-1.62] $p<0.01$), and Tacrolimus exposure (OR 1.35, 95% CI [1.16-1.58] $p<0.01$). In our adjusted Cox regressions, amongst those diagnosed with COVID-19, we found Prednisone exposure (HR 0.83, 95% CI [0.67-1.03] $p=0.08$) but was slightly above the threshold to be associated with a decreased risk of death. Subgroup sensitivity analyses for patients with MELD 3.0 scores showed Prednisone (OR 1.25, 95% CI [1.06-1.48] $p<0.01$), Budesonide (OR 1.35, 95% CI [1.03-1.77] $p<0.01$), and Tacrolimus exposure (OR 1.34, 95% CI [1.04-1.72] $p<0.01$) to be associated with COVID-19 diagnoses. **Conclusion:** IS exposure that was statistically significant was positively associated with COVID-19 diagnosis (and varied between the IS). Further work involves determining the impact of vaccinations and advances in COVID-19 treatment on clinical outcomes in this population.

Disclosures: Krish Rai: PSYONIC: Crowdfunding Investment, Jin Ge: Merck and Co: Grant/Research Support, Iota Biosciences/Astellas Pharmaceuticals: Consultant, Madrigal Pharamaceuticals: Consultant, Gilead Sciences: Advisor, Karla Lindquist: Nothing to Disclose, John Kornak: Nothing to Disclose

4543 | CHARACTERIZATION OF A COHORT OF PATIENTS WITH LATER-ONSET PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS (PFIC) FROM TWO US HEALTH SYSTEMS IDENTIFIED LEVERAGING NATURAL LANGUAGE PROCESSING (NLP)

Seema Meloni[1] Ravikumar Patel[1] Praveen Kumar-M[2] Sivaprakasam G[2] Gopinath Ashokkumar[2] Marie-Cecile Fournier[3] Danielle Dray[1] Fatine Elaraki[3], [1]Ipsen, Cambridge, MA, US, [2]nference, Cambridge, MA, US, [3]Ipsen, Boulogne-Billancourt, France

Background: Progressive familial intrahepatic cholestasis (PFIC) is a rare disease in which bile secretion is impaired, resulting in cholestasis. PFIC is classically diagnosed in early childhood, but emerging evidence suggests that some patients with PFIC variants experience later-onset disease. A major challenge in the later-onset disease is that the

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presentation varies greatly, and the characteristics of those patients are not well understood. This study aimed to identify and characterize individuals diagnosed with PFIC, at 10 years of age or older, from electronic health record (EHR) data from two major medical health systems in the United States (US) to add to the knowledge base regarding the presentation of this disease. **Methods:** This is a non-interventional study leveraging de-identified data ranging from January 1, 2005 to November 15, 2024 from Mayo Clinic and Duke Health systems. Patients were identified using both structured and unstructured data, where natural language processing (NLP) was utilized to review unstructured data. Patients were included in the cohort if they had at least one relevant ICD code (ICD-9: 576.8, ICD-10: K76.8), unstructured instance of diagnosis, or presence of any genetic mutations reported in structured or unstructured data at any time. All records of identified patients underwent manual review to confirm diagnosis. The cohort was limited to those with first report of PFIC on or after 10 years of age and described using standard descriptive analytic methods. **Results:** In total, 43 patients (Mayo Clinic = 35; Duke Health = 8) were confirmed to have evidence of late-onset PFIC. Across the combined cohort, the majority were female (58.1%), White (65.1%), and not Hispanic/Latino (72.1%) (Table 1). The median age for first available record with mention of PFIC in the cohort was 26 years in the Mayo subset and 20 years in the Duke subset. While there was some variability in patient profiles between the two centers, the most frequent clinical characteristics documented in the combined cohort were: cholestasis (37.2%), pruritus (25.6%), cirrhosis (18.6%), and jaundice (16.3%). **Conclusion:** To our knowledge, this is the first study to leverage EHR from two large medical institutions to identify and characterize a cohort of patients with later-onset PFIC. These data will be valuable for furthering the understanding of patients with diagnosed PFIC and potentially aid in faster diagnosis of yet undiagnosed patients.

Table 1: Baseline and Clinical Characteristics of Patients Diagnosed with Later-Onset PFIC

Variable	Mayo Clinic (n=35)	Duke Health (n=8)	Combined (N=43)
Age (years) at first available record, median (IQR)	26.0 (18.0 - 31.0)	20.0 (16.7 - 24.3)	N/A
Sex, n (%)			
Male	12 (34.3)	6 (75)	18 (41.9)
Female	23 (65.7)	2 (25)	25 (58.1)
Race, n (%)			
White	25 (71.4)	3 (37.5)	28 (65.1)
Black	1 (2.9)	2 (25)	3 (7)
Asian	2 (5.7)	0 (0)	2 (4.7)
Other	3 (8.6)	1 (12.5)	4 (9.3)
Unknown	4 (11.4)	2 (25)	6 (14)
Ethnicity, n (%)			
Hispanic or Latino	5 (14.3)	1 (12.5)	6 (14)
Not Hispanic or Latino	26 (74.3)	5 (62.5)	31 (72.1)
Unknown	4 (11.4)	2 (25)	6 (14)
Clinical Abnormality, n (%)			
Cholestasis	11 (31.4)	5 (62.5)	16 (37.2)
Pruritus	7 (20)	4 (50)	11 (25.6)
Cirrhosis	6 (17.1)	2 (25)	8 (18.6)
Jaundice	6 (17.1)	1 (12.5	7 (16.3
End-stage liver disease	3 (8.6)	2 (25)	5 (11.6)
Splenomegaly	1 (2.9)	2 (25)	3 (7)
Portal hypertension	1 (2.9)	0 (0)	1 (2.3)

Disclosures: Seema Meloni: Ipsen Biopharmaceuticals: Employee, Ravikumar Patel: Nothing to Disclose, Praveen Kumar-M: Nothing to Disclose, Sivaprakasam G: Nothing to Disclose, Gopinath Ashokkumar: Nothing to Disclose, Marie-Cecile Fournier: Nothing to Disclose, Danielle Dray: Nothing to Disclose, Fatine Elaraki: Nothing to Disclose

4544 | RETRIEVAL-AUGMENTED GENERATION ENABLED GENERATIVE PRE-TRAINED TRANSFORMERS FOR ACCESSIBLE AUTOIMMUNE LIVER DISEASES MANAGEMENT

Ernest Saenz[1] Jimmy Daza[2] Xiaoyun Xiong[1] Heike Bantel[3] Marcos Girala[4] Matthias P. Ebert[1] Florian van Bommel[5] Andreas Geier[6] Andres Gomez Aldana[7] Mario Alvares-da-Silva[8] Markus Peck-Radosavljevic[9] Ezequiel Ridruejo[10] Frank Tacke[11] Arndt Weinmann[12] Christel Weiss[1] Javier Pazó[13] Juan Turnes[14] Andreas Teufel[15], [1]Heidelberg university, [2]Medical Faculty Mannheim of Heidelberg University, [3]Hannover Medical School, [4]Universidad Nacional de Asuncion, [5]Leipzig University Medical Center, [6]University Hospital Wurzburg, [7]Texas Liver Institute, [8]Universidade Federal do Rio Grande do Sul, [9]Clinic Klagenfurt am Woerthersee, [10]Centro de Educacion Medica e Investigaciones Clínicas Norberto Quirno "CEMIC, [11]Charité - Universitätsmedizin Berlin, [12]University Medical Center of the Johannes Gutenberg-University Mainz, [13]Spanish Association for the Study of the Liver, [14]Galicia Sur Health Research Institute, [15]Division of Hepatology, Division of Clinical Bioinformatics, Department of Medicine II, Medical Facu

Background: Autoimmune liver diseases (AILDs), including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), present diagnostic and management challenges due to their complex pathophysiology. Although large language models (LLMs) hold promise as clinical decision support tools, general-purpose models often lack domain-specific knowledge and may produce inaccuracies. This study aims to enhance LLM performance in AILD management by employing Retrieval-Augmented Generation (RAG) technology that integrates evidence-based clinical guidelines and FDA medication safety data. **Methods:** We developed three RAG-enhanced systems—HepaChat (custom GPT from the OpenAI platform), RAG-ChatGPT (GPT-4o), and RAG-Claude (Claude 3.5 Sonnet)—and compared their responses to a baseline of best-performing non-RAG LLM outputs. Responses were evaluated by ten board-certified hepatologists on a 1–10 Likert scale assessing clinical accuracy. Statistical analyses

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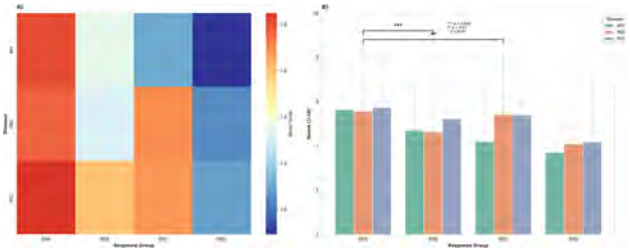
included Kruskal-Wallis tests with Dunn's post-hoc comparisons, along with subgroup analyses by disease type and geographic region. **Results:** HepaChat achieved the highest overall mean score of 7.81 (SD = 1.35) and provided the best-rated answer for 40 questions, significantly outperforming RAG-ChatGPT (7.48, SD = 1.49), RAG-Claude (7.42, SD = 1.43), and the baseline (6.99, SD = 1.49; $p < 0.001$). Additionally, evaluators from the Americas assigned higher ratings (mean = 8.02) compared to those from Europe (mean = 7.03; $p < 0.001$). Notable deficiencies were observed in medication dosing accuracy, particularly in AIH management. **Conclusion:** RAG technology enhances the clinical utility of LLMs in managing autoimmune liver diseases. These findings show the potential utility of RAG-based decision support systems to improve diagnostic accuracy and accessibility, particularly in resource-limited settings.



Disclosures: Ernest Saenz: Nothing to Disclose, Jimmy Daza: Nothing to Disclose, Xiaoyun Xiong: Nothing to Disclose, Heike Bantel: Nothing to Disclose, Marcos Girala: Nothing to Disclose, Nothing to Disclose, Matthias P. Ebert: Nothing to Disclose, Florian van Bommel: Nothing to Disclose, Andreas Geier: Nothing to Disclose, Andres Gomez Aldana: Nothing to Disclose, Mario Alvares-da-Silva: Nothing to Disclose, Markus Peck-Radosavljevic: Nothing to Disclose, Ezequiel Ridruejo: Nothing to Disclose, Frank Tacke: Nothing to Disclose, Arndt Weinmann: Servier: Advisor, Abbview: Speaking and Teaching, AstraZeneca: Speaking and Teaching, Incyte: Advisor, Taiho: Advisor, Roche: Speaking and Teaching, Christel Weiss: Nothing to Disclose, Javier Pazó: Nothing to Disclose, Juan Turnes: Nothing to Disclose, Andreas Teufel: Nothing to Disclose

4545 | ◆ FUNCTIONAL DIFFERENCES OF THE GUT MICROBIOME IN PRIMARY SCLEROSING CHOLANGITIS AND PRIMARY BILIARY CHOLANGITIS INFORM PATHOGENESIS AND THERAPEUTIC INTERVENTIONS

Marios Nikolaidis[1] Brian Juran[1] Bryan Mccauley[2] Erik Schlicht[1] Jackie Bianchi[1] Ahmad Ali[3] Elizabeth Atkinson[2] Grigorios Amoutzias[4] Konstantinos Lazaridis[1], [1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, [2]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, [3]Division of Gastroenterology and Hepatology, School of Medicine, University of Missouri, Columbia,MO, [4]Bioinformatics Laboratory,Department of Biochemistry and Biotechnology,University of Thessaly,Greece

Background: Primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) are rare immune-mediated cholestatic diseases with complex etiologies involving genetic factors, and environmental influences, including dysbiosis of gut microbiome. We aimed to define constitutional and functional elements of the gut microbiome relating to disease phenotypes and outcomes by performing a large, comprehensive, metagenomic analysis of PSC and PBC patients and matched controls. **Methods:** Stool samples from patients with PSC (n = 245), PBC (n = 280), and matched controls (PSC controls n = 245, PBC controls n = 278) underwent metagenomic sequencing to profile bacterial communities using the latest version of Genome Taxonomy Database. Microbial abundance comparisons were conducted with MaAsLin2 and ZicoSeq. Microbiome functional features, such as pathways and virulence factors were inferred with HUMANN3 and DIAMOND. Impact of bacterial species on risk of progression to hepatic decompensation was explored using Cox Regression. All statistical comparisons were adjusted for age and sex. **Results:** PSC and PBC patients had reduced microbial diversity featuring similar and distinct alterations in microbial abundance and virulence factors, along with significant alterations to overall microbial metabolism, including short-chain fatty acid (SCFA) and B-vitamin production. Regression analysis identified bacterial species associated with risk of hepatic decompensation in PSC, including potentially pathogenic *Streptococcus* species such as *S. vestibularis* (hazard ratio: 3.18) as well as protective species including *Alistipes shahii* (hazard ratio: 0.46), which is involved with butyrate production. Several species were also associated with risk of hepatic decompensation in PBC including *Acidaminococcus intestini* (hazard ratio: 4.45), although the number of events in PBC was limited. **Conclusion:** The gut microbiome of PSC and PBC patients are characterized by increased abundance of opportunistic pathogens and presence of virulence factors, coupled with disruption of beneficial microbial metabolism, such as that of short chain fatty acids. Notably, pathogenic microbial species were predictive of hepatic decompensation, whereas beneficial species had a protective effect. Future potential interventions for PSC and PBC might include dietary changes, probiotics and SCFA supplementation.

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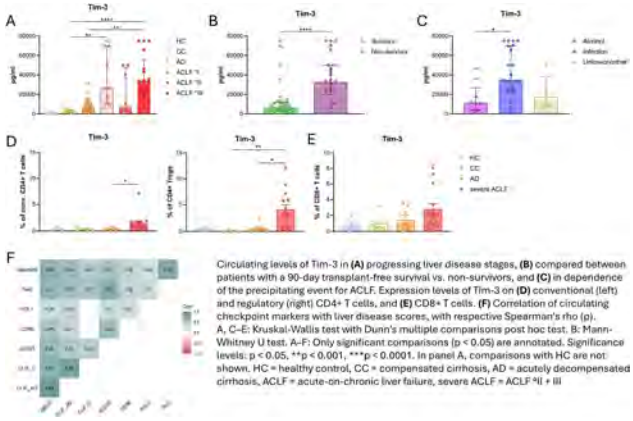
Disclosures: Marios Nikolaidis: Nothing to Disclose, Brian Juran: Nothing to Disclose, Bryan Mccauley: Nothing to Disclose, Erik Schlicht: Nothing to Disclose, Jackie Bianchi: Nothing to Disclose, Ahmad Ali: Nothing to Disclose, Elizabeth Atkinson: Nothing to Disclose, Grigorios Amoutzias: Nothing to Disclose, Konstantinos Lazaridis: Nothing to Disclose

4546 | ◆ T CELL IMMUNE DYSREGULATION IN PROGRESSIVE LIVER DISEASE: A POTENTIAL CONTRIBUTOR TO CIRRHOSIS-ASSOCIATED IMMUNE DYSFUNCTION

Aenne Harberts[1] Rut Schatzschneider[1] Amanda Tolios[1] Thanh-Son Phan[1] Martina Sterneck[1] Ansgar Lohse[1] Samuel Huber[1] Julian Schulze Zur Wiesch[1] Felix Piecha[1] Peter Hübener[1], [1]University Medical Centre Hamburg-Eppendorf

Background: Cirrhosis-associated immune dysfunction (CAID) is characterized by systemic hyperinflammation and impaired immune responses in patients with advanced liver disease and favors infections and organ dysfunction. The role of cellular dysfunction of the adaptive immune system remains largely unknown. This study aims to delineate the networks of T cell function in acutely decompensated cirrhosis (AD) and acute-on-chronic liver failure (ACLF) and evaluate their association with systemic inflammation, disease severity, and outcome. **Methods:** 79 patients with liver cirrhosis (compensated cirrhosis (CC) n = 16, AD n = 27, ACLF n = 36) and 11 healthy controls (HC) were prospectively included in a single-center observational study. Plasma levels of immune checkpoint markers and T helper cytokines were assessed using a bead-based multiplex immunoassay. LPS-binding protein (LBP), sCD14, and intestinal fatty acid binding protein (iFABP) were measured via ELISA. PBMCs were isolated, and T cell phenotype and function were analyzed using flow cytometry. **Results:** Circulating levels of immune checkpoint markers (sCD25, CD86, PD-L1, Tim-3, and Galectin-9) progressively increased with advancing disease stages, particularly in ACLF, and correlated with markers of systemic inflammation, intestinal barrier dysfunction, and clinical disease severity scores. Patients who died within 90 days of study inclusion had significantly higher baseline levels of sCD25, CD86, Tim-3, and Galectin-9. Among patients with ACLF, those with an infection as the precipitating event showed significantly higher levels of Tim-3 and a trend toward elevated levels of other checkpoint markers compared to patients with alcohol-related or unidentified triggers. In severe ACLF, $CD4^+$ and $CD8^+$ T cells showed increased expression of Tim-3 and Lag-3 compared to patients with CC or DC. Notably, Tim-3 expression was particularly elevated on regulatory $CD4^+$ T cells. **Conclusion:** Progressive liver disease is marked by a significant upregulation of both circulating and cellular immune checkpoint markers, indicating T cell exhaustion and systemic immune dysregulation. Elevated levels of these markers are associated with infection-driven ACLF and predict poor short-term survival. The pronounced expression of checkpoint receptors, particularly Tim-3, in advanced disease stages highlights potential targets for immunomodulatory therapies aimed at overcoming cirrhosis-associated immune dysfunction.



Disclosures: Aenne Harberts: Nothing to Disclose, Rut Schatzschneider: Nothing to Disclose, Amanda Tolios: Nothing to Disclose, Thanh-Son Phan: Nothing to Disclose, Martina Sterneck: Nothing to Disclose, Ansgar Lohse: Nothing to Disclose, Samuel Huber: Nothing to Disclose, Julian Schulze Zur Wiesch: Nothing to Disclose, Felix Piecha: Nothing to Disclose, Peter Hübener: Nothing to Disclose

4547 | ZONAL HEPATOCYTE VULNERABILITY AND MACROPHAGE REPROGRAMMING IN A MOUSE MODEL OF PORPHYRIA CUTANEA TARDA

CINDY E. AMENT, ABHISHEK MURTI, RASIKA PATKAR, SIMON BUCHER, NIKITA SAJAI, SAPHIA NGUYEN, MATTHEW CHOI, ARIS TAYCHAMEEKIATCHAI, BRUCE WANG, UCSF LIVER CENTER, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, CA, USA Cindy Ament[1] Abhishek Murti[1] Bruce Wang[1], [1]UCSF*

Background: Porphyria cutanea tarda (PCT) is the most common hepatic porphyria and results from

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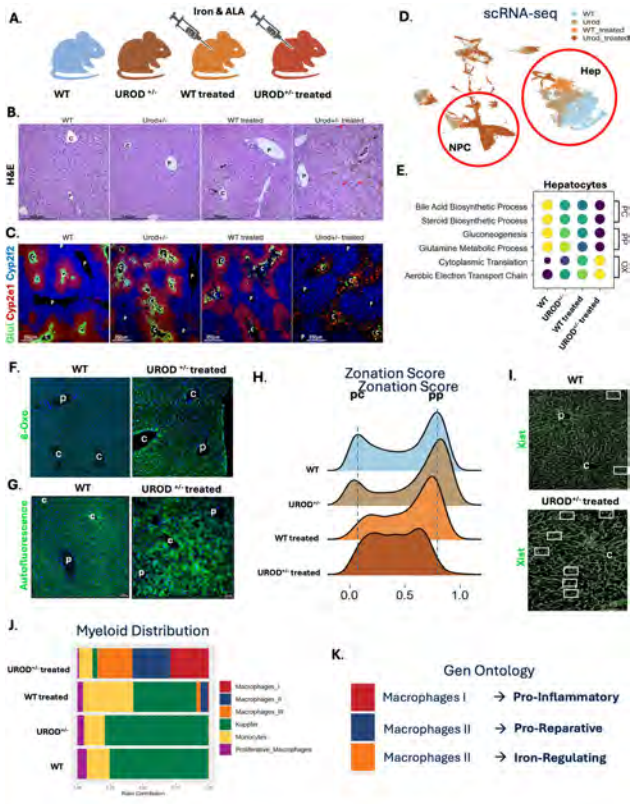
reduced activity of uroporphyrinogen decarboxylase (UROD), the fourth enzymatic step of heme biosynthesis. While individuals with UROD deficiency may remain asymptomatic, clinical disease is typically triggered by additional stressors that either increase heme demand or further impair UROD activity in hepatocytes. One of the most relevant triggers is hepatic iron overload, which promotes oxidative stress and enhances the functional inhibition of UROD. This creates a bottleneck in the pathway, leading to porphyrin accumulation. Epidemiological studies further suggest that patients with PCT are at increased risk of developing hepatocellular carcinoma (HCC), yet the cellular and spatial mechanisms by which chronic porphyrin accumulation drives liver injury and predisposes to cancer remain unknown and require further investigation. **Methods:** We employed a mouse model of PCT combining Urod haploinsufficiency ($Urod^{+/-}$) with iron and δ-aminolevulinic acid (ALA), a heme precursor that increases pathway flux, to induce porphyrin accumulation and hepatic stress. Liver pathology was analyzed using histology, immunofluorescence, and single-cell RNA sequencing (scRNA-seq) to characterize transcriptomic and cellular changes in hepatocytes and non-parenchymal cells (NPCs). **Results:** $Urod^{+/-}$ treated livers displayed selective pericentral hepatocyte injury, marked by oxidative DNA damage, loss of zonated metabolic function, and increased polyploidization. Hepatocytes progressively lost their spatial zonation signatures, with decreased expression of periportal and pericentral marker genes, while stress-related and translational programs were increasingly activated. Among NPCs, macrophages showed the strongest expansion. In addition to canonical Kupffer cells and monocytes, three novel macrophage populations were identified exclusively in $Urod^{+/-}$ treated livers. These included a subset expressing oxidative stress and iron metabolism genes, a reparative population, and a highly pro-inflammatory macrophage type. All three populations localized to areas of pericentral injury. **Conclusion:** Our findings reveal how porphyrin accumulation in the context of UROD deficiency disrupts liver homeostasis at multiple levels, driving spatially restricted hepatocyte dysfunction, metabolic disorganization, and the emergence of distinct injury-associated macrophage populations. By uncovering fundamental mechanisms of porphyrin-induced liver injury, our study provides critical insights into the pathogenesis of PCT and highlights cellular processes that may underlie the elevated cancer risk observed in affected patients. These results offer a framework for understanding porphyria-associated liver disease and identifying new targets for therapeutic intervention.



A) Experimental overview: $Urod^{+/-}$ treated mice receive iron and δ-aminolevulinic acid (ALA) to induce porphyrin accumulation and oxidative stress.
B) H&E staining reveals immune infiltration and iron accumulating Macrophages in $Urod^{+/-}$ treated livers.
C) Zonation markers (Cyp2f2, Cyp2e1, Glul) show loss of spatial gene expression in $Urod^{+/-}$ treated livers.
D) Single-cell transcriptomic analysis identifies major liver cell types and captures progressive hepatocyte reprogramming and myeloid expansion.
E) Gene ontology analysis reveals downregulation of metabolic functions and upregulation of stress and translation-related pathways.
F) 8-oxoG staining indicates oxidative DNA damage in pericentral hepatocytes.
G) Autofluorescence imaging shows porphyrin accumulation in pericentral zones.
H) Zonation score distribution based on scRNA-seq illustrates progressive loss of periportal and pericentral hepatocyte identity in $Urod^{+/-}$ treated livers.
I) FISH staining for *XIST* shows increased hepatocyte polyploidization in $Urod^{+/-}$ treated livers.
J) scRNA-seq identifies expansion of distinct macrophage subsets specific to $Urod^{+/-}$ treated livers.
K) Functional annotation of macrophage subtypes based on gene ontology analysis. Macrophage I was enriched for oxidative stress and iron-handling pathways, Macrophage II showed a reparative gene signature, and Macrophage III displayed a pro-inflammatory profile..

Disclosures: Cindy Ament: Nothing to Disclose, Abhishek Murti: Nothing to Disclose, Bruce Wang: Alnylam Pharmaceuticals: Consultant, Recordati Rare Diseases: Consultant, Disc Medicine: Consultant, Mitsubishi Tanabe Pharma: Consultant, Mitsubishi Tanabe Pharma: Grant/Research Support, CRISPR Therapeutics: Consultant

4548 | ◆ TRAINED IMMUNITY INDUCED BY ALCOHOL FUELS INFLAMMATION, IMMUNE EXHAUSTION AND INFECTION RISK IN ALCOHOL-ASSOCIATED HEPATITIS

Prashanth Thevkar Nagesh[1] Marti Ortega Ribera[2] Arman Patel[3] Veronika Brezani[3] Viliam Brezani[3] Aditi

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Background: Alcohol-associated hepatitis (AH) features heightened pro-inflammatory responses in monocytes and neutrophils, complicated by immune exhaustion, infection susceptibility, and poor outcomes. Trained immunity, characterized by epigenetic reprogramming of innate immune cells by a primary insult, can lead to dysfunctional responses to subsequent secondary insults. We hypothesized that alcohol serves as the primary insult in AH, inducing trained immunity and impairing host defence against bacterial infection. **Methods:** Liver and peripheral blood mononuclear cells (PBMCs) from AH patients and healthy controls (HCs) were analysed. Female C57Bl/6 mice (10–12 weeks) received binge alcohol (5 g/kg/day) or saline for 4 days ("training"), followed by a 1-week rest. Mice were then given saline, LPS (5 mg/kg, i.p.), or E. coli (10^6 CFU), and euthanized after 9 hours. Bacterial burden (CFU) was assessed in liver, lung, and spleen. Single-nucleus RNA-seq and scATAC-seq were performed on liver tissue. Serum ALT and cytokines were measured by ELISA. Histone marks (H3K27ac, H3K9me) were evaluated by Western blotting and flow cytometry in liver immune cells and bone marrow (BM) progenitors. T cell activation was induced by CD3/CD28 crosslinking. **Results:** Alcohol-trained (AT) mice exhibited increased liver damage and pro-inflammatory cytokines (which ones) in response to LPS or E. coli, with reduced bacterial clearance in liver, lung, and spleen. AT mice showed increased monocyte and neutrophil activation in BM, circulation, and liver. Markers of trained immunity, H3K27ac and H3K9me, were enriched in monocytes/neutrophils from AH patients and AT mice. Multi-omic analysis of AT livers revealed unique neutrophil/monocyte clusters with proinflammatory transcriptional profiles (snRNA seq), chromatin accessibility changes (scATAC seq), and upregulation of immune exhaustion markers, particularly programmed cell death ligand 1 (PDL1). Both AH patients and AT mice exhibited increased PDL1 expression in circulating monocytes/neutrophils. Furthermore, neutrophils from AH patients suppressed autologous T cell proliferation and IFN-γ secretion, indicating an immunosuppressive phenotype. **Conclusion:** Our findings reveal a novel role for alcohol inducing trained immunity in monocytes and neutrophils of AH patients and alcohol-trained mice evidenced by altered transcriptomic and epigenetic profiles and impaired host defence. Alcohol-induced trained immunity may explain the paradox of increased inflammation and dysfunctional host defence in AH patients.

Disclosures: Prashanth Thevkar Nagesh: Nothing to Disclose, Marti Ortega Ribera: Nothing to Disclose, Arman Patel: Nothing to Disclose, Veronika Brezani: Nothing to Disclose, Viliam Brezani: Nothing to Disclose, Aditi Ashish Datta: Nothing to Disclose, Yuan Zhuang: Nothing to Disclose, Scott Minchenberg: Nothing to Disclose, Deepika Deepika: Nothing to Disclose, Bruna Santos: Nothing to Disclose, Stephen Varghese Samuel: Nothing to Disclose, Yeshaswini Katkoori: Nothing to Disclose, Gyongyi Szabo: CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property, CYTA Therapeutics: Consultant, Durect Corporation: Consultant, Merck: Consultant, Pandion Therapeutics: Consultant, Pfizer: Consultant, Terra Firma: Consultant, LabCorp: Consultant, Takeda: Consultant, Surrozen: Advisor, Evive: Advisor, Glympse Bio, Inc (acquired by Sunbird Bio): Advisor, Satellite Biosciences: Advisor, Zomagen Bioscience/Ventyx Biosciences: Consultant, Springer Nature Group: Royalties or patent beneficiary, UpToDate Inc: Royalties or patent beneficiary, Boehiringer Ingelheim: Honoraria, Intercept: Contract, NIAAA-NIA: Grant/Research Support, Novo Nordisk: Honoraria, Yale University School of Medicine: Consultant, Resolution Therapeutics: Consultant, US Patent No. 20110293: Intellectual Property

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4549 | ◆ ANTI-MRPS27 ANTIBODIES AS A NOVEL BIOMARKER FOR AUTOIMMUNE HEPATITIS IDENTIFIED VIA COMPREHENSIVE HUMAN PROTEIN MICROARRAY PROFILING

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Background: Autoantibodies such as antinuclear and anti-smooth muscle antibodies are frequently detected in autoimmune hepatitis (AIH), yet their limited disease specificity often complicates diagnosis. A human protein microarray comprising over 16,000 proteins synthesized via a wheat germ cell-free system enables comprehensive detection of novel autoantibodies, including those against membrane, cytoplasmic, and nuclear proteins. This study aimed to identify candidate autoantigens in AIH using a human protein microarray and to explore disease-specific autoantibodies relevant to diagnosis and pathogenesis. **Methods:** Autoantibody profiling identified mitochondrial ribosomal protein S27 (MRPS27) as a novel AIH-specific autoantigen. Anti-MRPS27 antibody levels were quantified by ELISA in sera from patients with AIH (n = 68), primary biliary cholangitis (PBC, n = 19), metabolic dysfunction-associated steatotic liver disease (MASLD, n = 39), chronic hepatitis C (CHC, n = 27), drug-induced liver injury (DILI, n = 18), post-treatment AIH (n = 36), and healthy controls (HC, n = 37). Clinical features and laboratory parameters were compared between anti-MRPS27-positive and -negative AIH patients, and longitudinal antibody titers were assessed. All AIH samples were collected prior to corticosteroid therapy. **Results:** Anti-MRPS27 levels were significantly higher in AIH (50.2 AU) than in PBC (9.3 AU), MASLD (12.8 AU), CHC (24.8 AU), DILI (19.8 AU), and HC (7.5 AU) (all $P < 0.01$). Using the HC mean + 3SD (48.5 AU) as cutoff, sensitivity, specificity, positive predictive value, negative predictive value, and AUROC were 42.7%, 94.3%, 78.3%, 77.2%, and 0.82, respectively. No significant associations were observed between anti-MRPS27 positivity and clinical features of AIH. However, anti-MRPS27 antibody titers remained elevated after treatment, with positivity observed in half of seronegative AIH cases. Notably, patients with high titers showed a lower proportion of liver-related events. MRPS27, a component of the mitochondrial small ribosomal subunit, is involved in cytochrome c oxidase activity essential for ATP production. Dysfunction may lead to hepatic energy loss and oxidative stress, contributing to chronic liver injury. This is the first report to propose an association between MRPS27 and AIH. **Conclusion:** Anti-MRPS27 antibody may serve as a novel and disease-specific biomarker for AIH, providing insights into pathogenesis and potential therapeutic targets.

Disclosures: JUN WADA: Nothing to Disclose, Kazumichi Abe: Nothing to Disclose, Naoto Abe: Nothing to Disclose, Tatsuro Sugaya: Nothing to Disclose, Yosuke Takahata: Nothing to Disclose, Masashi Fujita: Nothing to Disclose, Manabu Hayashi: Nothing to Disclose, Hiromasa Ohira: Nothing to Disclose

4550 | ◆ IFRD1 ORCHESTRATES HEPATOCYTE METABOLISM AND MACROPHAGE INTERACTIONS TO FACILITATE LIVER REGENERATION

Taofei Zeng[1] Yabin Huang[1], [1]The First Affiliated Hospital of USTC

Background: Liver regeneration is a complex and tightly regulated process that relies on the coordinated interaction between hepatocytes and non-parenchymal cells; however, the underlying mechanisms remain incompletely understood. **Methods:** Using murine models of partial hepatectomy (PHx) and CCl_4-induced liver injury, we employed genetic knockout, adeno-associated virus-mediated overexpression, single-nucleus RNA-seq, ATAC-seq, and biochemical assays to dissect the function of IFRD1 in liver regeneration **Results:** Hepatocyte expression of IFRD1 is significantly upregulated during the early phase of regeneration. Genetic deficiency of IFRD1 impairs post-hepatectomy regeneration, while its overexpression enhances this process. IFRD1 is essential for maintaining hepatocyte β-oxidation and mitochondrial ATP production, stabilizing SLC25A5 levels through competition with the E3 ubiquitin ligase TRIM21. Furthermore, IFRD1-mediated ATP production facilitates chromatin remodeling in hepatocytes, which enhances CC/CXC chemokine expression, subsequently recruiting $CCR2^+$ monocytes and driving their differentiation into $GPNMB^+$ macrophages. Additionally, reduced liver expression of IFRD1 in acute liver failure patients suggests that IFRD1 may serve as a potential therapeutic target in liver diseases and regenerative medicine. **Conclusion:** IFRD1 acts as a metabolic-immune integrator in hepatocytes, orchestrating mitochondrial function and immune cell recruitment to promote liver regeneration. These findings highlight IFRD1 as a promising therapeutic target for enhancing liver repair and treating liver failure.

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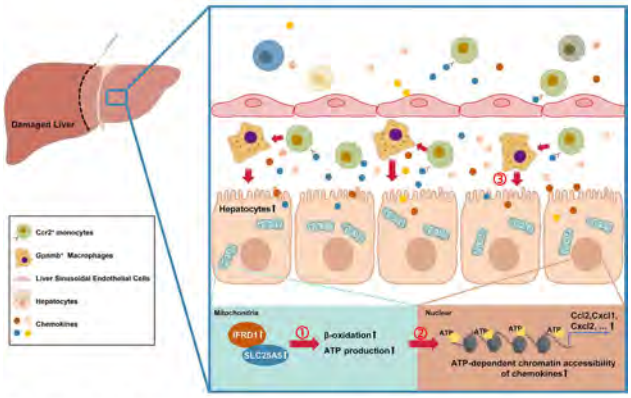
Graph Abstract



This study reveals that the nutrient-deprived microenvironment resulting from the substantial energy demands during liver regeneration induces an increase in IFRD1 levels. This upregulation facilitates the binding of IFRD1 to the mitochondrial transporter SLC25A5, thereby enhancing lipid β-oxidation and ATP production. As a crucial energy molecule, ATP not only enhances hepatocyte function but also fuels chromatin remodeling complexes, enabling the opening of chromatin and regulating the transcription of chemotactic genes. This mechanism facilitates the recruitment of $Ccr2^{+}$ monocytes and then transfer lipid-associated macrophages (LAMs) to the liver, where they exert protective functions, and promote liver regeneration. We delineate a novel IFRD1-SLC25A5-ATP-GPNMB^{+} monocyte-derived macrophage signaling axis that mediates the interaction between hepatocytes and monocyte-derived macrophages to drive hepatocyte proliferation

Disclosures: Taofei Zeng: Nothing to Disclose, Yabin Huang: Nothing to Disclose

4551 | ◆ HEPATOCYTE IRE1α-XBP1S AXIS PREVENTS PRO-METASTATIC NICHE FORMATION THROUGH METABOLIC REWIRING OF INFLAMMATORY MONOCYTES

Jiajie Hou[1], [1]*QIMR Berghofer Medical Research Institute*

Background: As unfolded protein response (UPR) signal transducers, inositol-requiring enzyme 1α (IRE1α) and the downstream spliced form of X-Box Binding Protein 1 (XBP1s) have been identified as tumor promotors in multiple mouse models. However, clinical trials of IRE1α antagonism so far have not yielded encouraging results from metastatic cancer patients. While hepatocyte IRE1α-XBP1s axis has been linked to both tumorigenesis and metabolic homeostasis, it remains largely unknown how it affects tumor progression in a non-cell autonomous manner. Given the importance of non-tumoral hepatocytes under the circumstance of liver metastases, it is imperative to reexamine the significance of hepatocyte IRE1α-XBP1s signaling during pro-metastatic niche formation. **Methods:** Genetically modified mice (*Ern1*$^{flox/flox}$;*Alb*^{Cre}, *Xbp1*$^{flox/flox}$;*Alb*^{Cre}, and *Ccr2*$^{-/-}$) were employed for generating liver metastasis models. Pharmacological inhibitors targeting the IRE1α-XBP1-glutamine pathway or antibodies neutralizing specific immune subsets were administrated to tumor-bearing mice. High-throughput flow cytometry and single-cell RNA-sequencing were utilized to discern the liver myeloid compartment. While primary hepatocytes and monocytes were isolated for in vitro stimulation or in vivo reconstitution, multiplex immunohistochemistry was applied to validate the hepatocyte-monocyte interaction in mouse and human liver metastases. **Results:** Genetic ablation of IRE1α or XBP1 in non-tumoral hepatocytes exacerbated liver metastasis without disturbing immunosurveillance. Single-cell RNA sequencing identified a group of inflammatory monocytes (IM) that were significantly enriched in the IRE1α-deficient peritumor liver. Loss of IRE1α or XBP1 activated a non-canonical Forkhead box O1 (FoxO1)-glutamine synthetase (GS) pathway, endowing the non-tumoral hepatocytes with the metabolic activity to secrete glutamine, which was found necessary and sufficient for IM fitness. Patient survival with liver metastases was negatively correlated with such hepatocyte-IM interaction. As for mice, glutamine blockade efficiently reduced IM and disrupted the pro-metastatic niche in the liver. **Conclusion:** The hepatocyte IRE1α-XBP1s axis inhibits liver metastasis by reprograming metainflammation shaped in the pro-metastatic niche, which provides an organ-specific dimension for targeting cancer-promoting inflammation.

Disclosures: Jiajie Hou: Nothing to Disclose

4552 | EPSTEIN-BARR VIRUS STATUS AS A PREDICTOR OF PRIMARY SCLEROSING CHOLANGITIS IN INFLAMMATORY BOWEL DISEASE

Mohamed Nadeem[1] *prabhat kumar*[2] *Shilpa Junna*[3] *Mohamad-Noor Abu-Hammour*[1], [1]*Cleveland Clinic Foundation,* [2]*Virginia Commenwealth University,* [3]*Cleveland Clinic*

Background: The role of Epstein-Barr virus (EBV) infection in the development of Primary sclerosing cholangitis (PSC) and liver complications in inflammatory bowel disease (IBD) remains unclear. EBV has been associated as trigger for various autoimmune liver diseases. This study evaluated whether EBV serum or tissue positivity or recent EBV infection in IBD patients is associated with increased risks of PSC, cirrhosis, liver transplantation, hepatic decompensation, and mortality. **Methods:** Using a global electronic health record network (TriNetX), adult patients diagnosed with IBD (Crohn's disease or ulcerative colitis) were identified and categorized into EBV-positive (EBV+) who have had recent infection or active infection, and EBV-negative (EBV–) cohorts based on documented EBV laboratory results within one year before or five years after their IBD diagnosis. Patients were classified as EBV + if they had at least one documented positive result for any of the following assays: early-diffuse IgG antibody, EBV DNA (quantitative or qualitative), EBV

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nuclear antibody, EBV viral capsid antibody IgM, EBV antigen in tissue (immunostain), or EBV viral capsid IgA. Patients with pre-existing PSC, organ transplants, chronic hepatitis, or HIV were excluded. Cohorts were balanced for demographics, comorbidities, and ongoing IBD therapies through 1:1 propensity-score matching. Outcomes were followed for up to ten years post-index, and odds ratios (ORs) with 95 % confidence intervals (CIs) were calculated. **Results:** After matching, there were 3219 patients in each cohort. PSC developed in 1.8 % of EBV-positive patients versus 0.6 % of EBV-negative patients (OR = 3.32, 95 % CI 1.95–5.64; p < 0.0001). Cirrhosis occurred in 4.4 % versus 1.2 % (OR = 3.67, 95 % CI 2.57–5.23; p < 0.0001), and liver transplantation in 1.9 % versus 0.3 % (OR = 6.10, 95 % CI 3.12–11.97; p < 0.0001). EBV-positive patients also showed higher odds of hepatic decompensation (8.4 % vs 4.0 %; OR = 2.19, 95 % CI 1.77–2.72; p < 0.0001) and all-cause mortality (8.3 % vs 5.5 %; OR = 1.55, 95 % CI 1.27–1.88; p < 0.0001). **Conclusion:** EBV infection in IBD patients is significantly associated with increased risks of PSC, cirrhosis, hepatic decompensation, liver transplant, and mortality. These findings highlight the importance of EBV status as a potential predictor for development of PSC and of adverse hepatic outcomes in IBD, underscoring the need for vigilant monitoring of EBV-positive IBD patients.

Baseline Characteristics

Characteristic	EBV-Positive IBD (n=3,219)	EBV-Negative IBD (n=3,219)	P-Value
Demographics			
Age at Index (mean ± SD)	35.6 ± 20.5	35.9 ± 20.2	0.613
White	2,326 (72.3%)	2,352 (73.1%)	0.467
American Indian/Alaska Native	10 (0.3%)	10 (0.3%)	1
Female	1,700 (52.8%)	1,718 (53.4%)	0.653
Native Hawaiian/Pac Islander	10 (0.3%)	10 (0.3%)	1
Not Hispanic or Latino	2,703 (84.0%)	2,680 (83.3%)	0.439
Hispanic or Latino	210 (6.5%)	223 (6.9%)	0.518
Black or African American	234 (7.3%)	242 (7.5%)	0.703
Male	1,462 (45.4%)	1,450 (45.0%)	0.764
Asian	164 (5.1%)	154 (4.8%)	0.565
Diagnosis			
Type 2 diabetes mellitus	278 (8.6%)	290 (9.0%)	0.598
Essential hypertension	681 (21.2%)	703 (21.8%)	0.504
Hyperlipidemia	510 (15.8%)	530 (16.5%)	0.498
Chronic kidney disease	290 (9.0%)	303 (9.4%)	0.575
Coronary artery disease	205 (6.4%)	198 (6.2%)	0.719
Nicotine dependence	252 (7.8%)	256 (8.0%)	0.853
Alcohol abuse	78 (2.4%)	82 (2.5%)	0.749
Medications			
Azathioprine	326 (10.1%)	351 (10.9%)	0.29
Methotrexate	243 (7.5%)	253 (7.9%)	0.64
Mercaptopurine	194 (6.0%)	187 (5.8%)	0.712
Infliximab	439 (13.6%)	443 (13.8%)	0.865
Adalimumab	316 (9.8%)	340 (10.6%)	0.323
Ustekinumab	89 (2.8%)	80 (2.5%)	0.483
Vedolizumab	110 (3.4%)	99 (3.1%)	0.439
Tofacitinib	14 (0.4%)	11 (0.3%)	0.548
Upadacitinib	10 (0.3%)	10 (0.3%)	1

Outcomes

Outcome	Risk EBV+ (%)	Risk EBV- (%)	Odds Ratio (95% CI)	p-value
Primary Sclerosing Cholangitis (PSC)	1.8%	0.6%	3.32 (1.95–5.64)	<0.0001
Cirrhosis	4.4%	1.2%	3.67 (2.57–5.23)	<0.0001
Liver Transplant	1.9%	0.3%	6.10 (3.12–11.97)	<0.0001
Hepatic Decompensation	8.4%	4.0%	2.19 (1.77–2.72)	<0.0001
All-cause Mortality	8.3%	5.5%	1.55 (1.27–1.88)	<0.0001

Disclosures: Mohamed Nadeem: Nothing to Disclose, prabhat kumar: Nothing to Disclose, Shilpa Junna: Nothing to Disclose, Mohamad-Noor Abu-Hammour: Nothing to Disclose

4553 | TIME-RESOLVED HEPATIC SINGLE-CELL SEQUENCING DURING LIVER FIBROSIS REGRESSION IDENTIFIES DISTINCT &LSQUO; REGRESSIVE&RSQUO; MACROPHAGE SUB-POPULATIONS

Katharina Bonitz[1] Thomas Sorz-Nechay[2] Henriette Horstmeier[2] Vlad Taru[2] Oleksandr Petrenko[2] Katja Sommer[2] Benedikt Hofer[2] Benedikt Simbrunner[2] Kerstin Zinober[2] Hubert Scharnagl[3] Michael Trauner[2] Stefan Kauschke[4] Peng Sun[4] Eric Simon[4] Philipp Schwabl[2] Thomas Reiberger[2], [1]Medical University Vienna, [2]Medical University of Vienna, [3]University Hospital Graz, [4]Boehringer Ingelheim Pharma GmbH & Co.KG, Biberach an der Riss

Background: Liver fibrosis regression has been described in both clinical and experimental settings. However, the molecular changes from a fibrotic to a regressive environment in hepatic and immune cell populations remain incompletely understood. **Methods:** Fibrosis was induced in mice with carbon tetrachloride (CCl_4) for 12 weeks (peak), followed by a period of 3, 7 or 14 days (D3, D7 or D14) of regression after CCl_4-cessation. Healthy controls received olive oil (OO). Portal pressure (PP), collagen proportionate area (CPA) and liver transaminases (AST, ALT) were assessed at each time point. Hepatic single-cell isolates were sequenced with 10x Chromium Flex technology. The obtained single-cell dataset was analyzed using Seurat. **Results:** At peak (vs. OO), fibrosis (CPA: 3.83 ± 0.61 vs. 0.53 ± 0.12%), PP (7.32 ± 0.49 vs. 4.75 ± 0.46 mmHg), and liver injury (AST: 1666 ± 2485 vs. 51 ± 20 U/L; ALT: 1406 ± 3117 vs. 30 ± 8 U/L) were significantly increased (all $p < 0.05$), confirming fibrosis and portal hypertension. CPA (2.89 ± 0.29 %), PP (6.18 ± 0.38 mmHg), and transaminases (AST: 61 ± 13 U/L; ALT: 44 ± 11 U/L) significantly regressed ad D14 (all $p < 0.05$). Major hepatic cell populations were retrieved by single-cell sequencing. Subclustering macrophages revealed seven subpopulations: Four Clec4f+ Vsig4+ Kupffer-cell subpopulations, including a cluster of embryonically-derived macrophages that were depleted during fibrogenesis and did not recover during regression, and a putative regressive macrophage subpopulation with enrichment over the course of regression.
Three monocyte-derived subpopulations were identified, including an infiltrating population with low expression of residency markers and two Cd9+ Trem2+ scar-associated macrophage (SAM) clusters. The two SAM clusters were enriched at peak fibrosis and subsequently depleted within 3 days of regression (“fibrotic SAMs”) or more gradually depleted throughout regression (D3-D14, “regressive SAMs”). The fibrotic SAMs were major

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producers of Tgfb1, while the regressive SAMs highly expressed Mmp12, indicating an important role in matrix remodeling. Both SAM populations further expressed Ctss at high levels. **Conclusion:** The murine CCl_4-cessation model allows investigation of liver fibrosis regression at single-cell resolution. Our analysis underlines the dual role of SAMs as drivers of both progression and regression and points towards a complex interplay of myeloid-derived cells in liver fibrosis regression.

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4554 | HEPATOCYTE HUMANIZATION IN AN SRG RAT MODEL AFTER PARTIAL HEPATECTOMY

Yohan Kim[1] George McClung[1] Cecilia Wright[1] David Tischfield[1] Eleanna Kaffe[1] Kelley Weinfurtner[1] Terence Gade[1], [1]Perelman School of Medicine at the University of Pennsylvania

Background: Rodent models often fail to recapitulate human liver metabolism and regeneration, limiting their translational utility for liver cancer research. We aimed to establish human liver chimerism in immunodeficient SRG rats (Sprague Dawley Rag2/Il2rg–/–) which lack functional rodent T, B, and NK cells. **Methods:** SRG rats were treated with retrorsine (30–45 mg/kg i.p. x 2 doses) to inhibit rodent hepatocyte proliferation, followed by 70–80% partial hepatectomy (PH). Immediately after PH, rats received an intrasplenic injection of 3×10^6 viable human hepatocytes (HL rats, n = 5) or saline control (n = 5). Liver regeneration was monitored based on MRI volumetrics at weeks 2, 6, and 12 and normalized to body weight. Blood samples were taken by saphenous vein bleeds for biochemical analysis and bile acid profiling. At necropsy, liver tissue was fixed for histological analyses and snap-frozen for human-specific proteomic analysis. **Results:** MRI demonstrated significantly greater liver regeneration post-PH in HL rats compared to controls at weeks 2 (3.34 ± 0.35% vs 2.81 ± 0.13%, p = 0.0034) and 6 (3.11 ± 0.23% vs 2.62 ± 0.13%, p = 0.0439). Normalized liver weight at necropsy 12 weeks post-PH corroborated the MRI findings (4.49 ± 0.36% vs 4.10 ± 0.21%, p = 0.0185). Serum ALT and bilirubin levels were decreased over time, indicating efficient replacement of the lost liver tissue. Immunohistochemistry for human-specific lipoprotein A (LPa) and for Histidine-Ammonia-Lyase (HAL) demonstrated widespread (~50%) human hepatocyte engraftment in the central area (LPa+) and in the portal area (HAL+) of the liver. Bile acid profiling at weeks 6 and 12 demonstrated significant shifts toward human-specific metabolic patterns in HL rats, including increased glycine-conjugated bile acids, decreased taurine-conjugated bile acids with a ratio of Glycine-BA/Taurine-BA = 3 at 12 weeks and substantially reduced rodent-specific muricholic acids. Lipid profiling revealed higher LDL/HDL ratio (1.51) in HL rat compared to control rat (0.36), closely resembling the human LDL/HDL profile (1.45), indicating human-specific lipid metabolism. **Conclusion:** This preliminary study establishes a foundational step toward creating a highly translational humanized rat model capable of supporting human hepatocyte engraftment, and human-specific liver metabolism. These findings provide crucial evidence supporting the feasibility and potential of this humanized rat model as a robust platform for future translational studies, specifically enabling precise modeling of human liver biology and the evaluation of novel therapeutic strategies in liver injury models.

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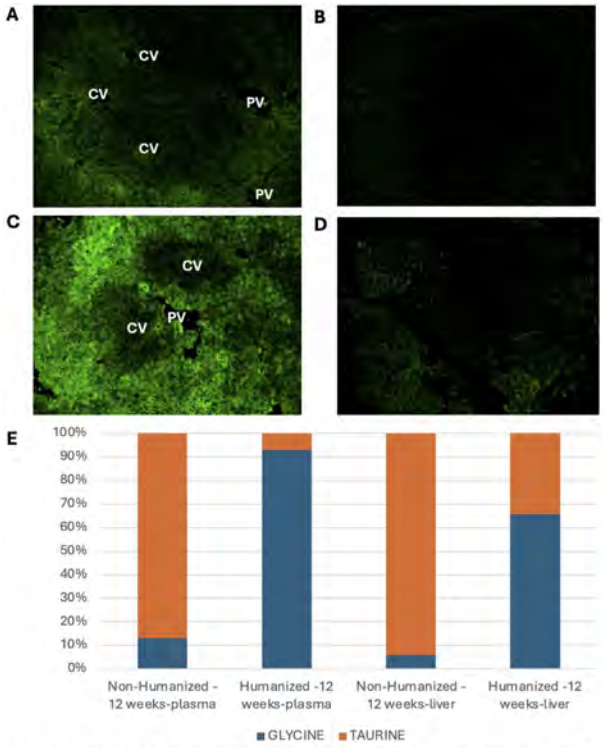

Figure 1: (A) LPa immunostaining (zone 3, central vein area) showing widespread human hepatocyte engraftment in a humanized rat. **(B)** LPa staining in a non-humanized control rat confirms absence of human cells. **(C)** HAL immunostaining (zone 1, portal area) demonstrates clear localization of human hepatocytes in a humanized rat liver, mirroring human liver zonation. **(D)** HAL staining in a control rat confirms lack of human hepatocyte presence. **(E)** Bile acid profiling highlights a shift toward human-specific metabolism 12 weeks post-partial hepatectomy, with elevated glycine-conjugated bile acids, decreased taurine-conjugated bile acids, and marked reduction of rodent-specific muricholic acids.

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4555 | ROLE OF MYELOID-SPECIFIC MITOGEN-ACTIVATED PROTEIN KINASE PHOSPHATASE 1 (MKP1) IN SEXUAL DIMORPHISM TO ENDOTOXIN RESPONSE

Mary Nancy Walter[1] Diego Montoya-Durango[1] Seamus Pugh[1] Yali Wang[1] Walter Rodriguez-Alvarez[1] Jingwen Zhang[1] Craig McClain[1] Leila Gobejishvili[1], [1]University of Louisville

Background: Gut-derived microbial products like endotoxin drive hepatic inflammation and injury. We have previously shown that alcohol significantly down-regulated the expression of hepatic mitogen-activated protein kinase phosphatase 1 (MKP1). We further showed that MKP1 deletion in hepatocytes resulted in increased alcohol-induced liver injury in mice, demonstrating the role of hepatocyte-specific MKP1 in liver damage. However, the role of myeloid-specific MKP1 in liver injury has never been investigated. Given the significant role of MKP1 phosphatase in the regulation of MAPK kinases and inflammation, we examined the effect of myeloid-specific MKP1 deletion on endotoxin-induced inflammation and liver injury. **Methods:** Myeloid-specific MKP1 knockout mice (MSKO) were generated using LysMCre and MKP1 floxed (f/f) mice on C57Bl/6 background. 12-week-old male and female MKP1 MSKO and their wild type counterparts (f/f) mice were injected with 3mg/kg endotoxin (E. coli-derived lipopolysaccharide, LPS) and sacrificed after 24 hours. Plasma levels of liver injury markers were analyzed. MesoScale Discovery multiplex platform was used for plasma cytokine quantification. Immune cells isolated from the liver were used for flow cytometry and gene expression analysis by RT qPCR. Statistical analysis was completed with Two-way ANOVA. **Results:** Endotoxin administration resulted in liver injury in MSKO male and female mice but had no significant effect in f/f mice. However, female MSKO mice demonstrated increased endotoxin-induced liver injury compared to male MSKO mice. 24 hours after injection plasma levels of inflammatory cytokines returned to baseline levels in f/f mice. Meanwhile, MSKO mice exhibited a sustained response, as shown by elevated levels of cytokines IL-1β, IL-4, KC-GRO, IL-10, IL-33, and TNFα. Additionally, plasma levels of inflammatory markers IFNγ, IL-5, IL-6, and IL-12p70 were elevated in female MSKO mice compared to f/f females. Gene expression analysis of immune cells isolated from the livers of female MSKO mice showed significant increases in mRNA expression of pro-inflammatory cytokines *Il6* and *Ccl2* following LPS injection. Flow cytometry analysis showed no significant changes in proportions of NKT cells, B cells, and CD4+ T cells between the genotypes regardless of treatment. However, MKP1 depletion was associated with significant changes in the ratio of infiltrating macrophages to resident Kupffer cells in female mice after LPS injection. **Conclusion:** Deletion of MKP1 in myeloid cells resulted in increased LPS-induced liver injury and sustained systemic inflammation in both male and female mice. However, MKP1 deletion in myeloid cells had a more profound effect in female mice.

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4556 | KV1.3 REGULATES MACROPHAGE IMMUNE FUNCTION THROUGH THE PI3K/AKT PATHWAY TO ALLEVIATE METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

BAOMING WU[1], [1]Pharmacy of School/Anhui Medical Univeristy

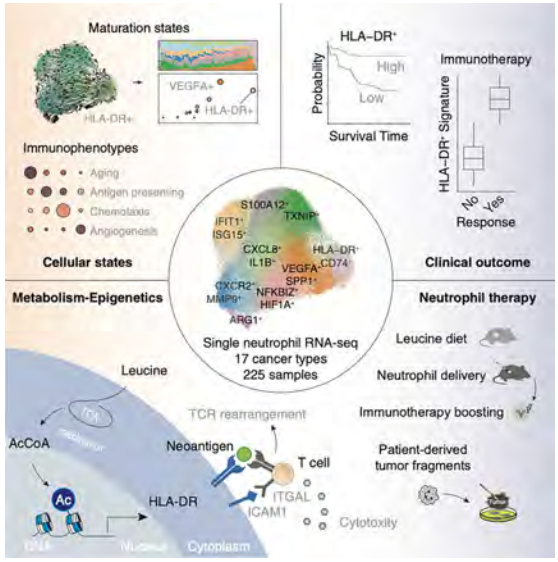
Background: The progression of metabolic dysfunction-associated steatohepatitis (MASH) is closely associated with macrophage-mediated inflammatory responses. The voltage-gated potassium channel Kv1.3 plays a critical role in regulating macrophage function; however, its specific role and mechanism in MASH remain unclear. This study aimed to investigate the therapeutic effect of Kv1.3 blockade on MASH and elucidate its underlying mechanism, particularly through the PI3K/AKT signaling pathway in modulating macrophage activity. **Methods:** A Western diet (WD)-induced mouse model of MASH was established, and adeno-associated virus AAV8-Kv1.3-shRNA was used to knock down hepatic Kv1.3 expression. The effects on hepatic steatosis, inflammation, and macrophage infiltration were evaluated. In vitro, an inflammatory model was constructed using LPS-stimulated RAW264.7 macrophages, and cells were treated with the Kv1.3 inhibitor ShK-186 to assess inflammatory cytokine (IL-6, TNF-α) production and migratory capacity. The GEO dataset (GSE167523) and RNA-seq were utilized to identify and validate the involvement of the PI3K/AKT signaling pathway in Kv1.3-mediated regulation of macrophage function. **Results:** Kv1.3 expression was significantly upregulated in WD-induced MASH mouse livers. Hepatic Kv1.3 knockdown markedly alleviated liver injury, steatosis, and inflammatory responses. In vitro, ShK-186 inhibited LPS-induced macrophage migration and inflammatory cytokine production, and significantly reduced phosphorylation of the PI3K/AKT pathway. These effects were partially reversed by the PI3K agonist 740Y-P, further confirming that Kv1.3 attenuates macrophage migration and inflammation by downregulating PI3K/AKT phosphorylation. **Conclusion:** This study is the first to demonstrate that Kv1.3 regulates macrophage inflammatory response and migration via the PI3K/AKT signaling pathway, thereby influencing MASH progression. Hepatic knockdown of Kv1.3 significantly improves MASH-related pathological features, supporting Kv1.3 as a potential therapeutic target for MASH.

Disclosures: BAOMING WU: Nothing to Disclose

4557 | CANCER NEUTROPHIL ENCYCLOPEDIA: A DEEP DIVE INTO ANTIGEN-PRESENTING WARRIORS

Yingcheng Wu[1] Qiang Gao[2], [1]Fudan University, [2]Fudan University Zhongshan Hospital

Background: Neutrophils, the most efficient defenders against pathogens, are essential for tumor microenvironment balance and homeostasis. However, given their plasticity and short half-life which made them too fragile to be profiled, it poses complex challenges regarding how neutrophils are imprinted and adapt specific fates across cancers. **Methods:** Here we designed a one-two-punch sorting strategy, generated the neutrophil atlas from 225 samples of 144 patients from 17 cancer types, and further developed a computational pipeline to recover both shared and specific transcriptional programs. **Results:** Unexpectedly, neutrophils harbored extraordinary complexity composed of 10 cell states and showed sharp tissue or phenotypic specialty. We observed and verified that cancer neutrophils are dramatically arranged along tumor-specific terminal differentiation paths such as inflammation, angiogenesis and antigen-presenting. In particular, the antigen-presenting program was associated with better patient outcomes in the majority of cancers. Such a program can be evoked by leucine metabolism and is dependent on mitochondrial remodeling, acetyl-CoA generation, and preferable epigenetic histone H3K27ac modification. Functionally, antigen-presenting neutrophils invoked expanded T cell response and neoantigen-specific reactiveness. We finally designed the antigen-presenting neutrophil immunotherapy (adoptive transferring and leucine diet) which fine-tunes the microenvironment balance and fuels anti-PD-1 immunotherapy. **Conclusion:** In summary, these data not only lay the groundwork for future neutrophil research, and open the black box of neutrophil state divergence across cancers, but also unravel minimally invasive therapeutic opportunities including adoptive transferring antigen-presenting neutrophils.



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Disclosures: Yingcheng Wu: Nothing to Disclose, Qiang Gao: Nothing to Disclose

4558 | DIFFERENTIAL MODULATION OF BONE MARROW- AND LIVER-DERIVED DENDRITIC CELL FUNCTION BY HEPATIC ISCHEMIA-REPERFUSION- DERIVED EXOSOMES

Cindy Avalos de Leon[1] Suguru Mitsufuji[1] Alan Zahorchak[1] Hamza Yazdani[2] David Geller[2] Angus Thomson[1], [1]Thomas E. Starzl Transplantation Institute, [2]University of Pittsburgh Medical Center

Background: Exosomes play pivotal roles in intercellular communication, facilitating delivery of proteins and nucleic acids to proximal and distal cells. They are elevated in the circulation following liver ischemia-reperfusion injury (IRI). Dendritic cells (DC) are key regulators of innate and adaptive immunity and have been found to influence experimental liver IRI and transplant outcomes. DCs that reside in the liver exhibit tolerogenic properties. Here, we examined the influence of liver-derived exosomes from IRI and control livers on DC phenotype, exosome uptake, and T cell immunostimulatory function. **Methods:** Male C57BL/6 (B6) mice underwent 70% hepatic warm ischemia for one hour, followed by six hours of reperfusion. Liver exosomes (<150 nm) were isolated by ultracentrifugation and iodixanol gradient purification and characterized via nanoparticle tracking analysis, Western blot, and flow cytometry. Liver-resident conventional DCs (LDC) were purified following liver perfusion *in situ* and collagenase digestion, while bone marrow-derived DCs (BMDC) were differentiated from precursors *in vitro* with GM-CSF and IL-4. The DCs were incubated for 24 hours with PKH26-labeled exosomes and evaluated for exosome uptake using imaging flow cytometry. Cell phenotype was assessed by flow cytometry, and DC function determined in allogeneic mixed leukocyte reactions (MLR) and by cytokine quantification. Levels of intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1) expression were also analyzed in both BMDC and LDC to explore mechanisms contributing to exosome uptake. **Results:** Exosome levels were significantly increased in the liver following IRI. Purified liver IRI-derived exosomes, enriched in canonical markers (CD9, CD63, and CD81), enhanced BMDC maturation, as evidenced by upregulation of co-stimulatory CD80 and CD86, and significantly enhanced ability to induce allogeneic CD4+ and CD8+ T cell proliferation and secretion of IFNγ, TNFα, and IL-17A in MLR compared with control liver exosomes. In contrast, LDC did not exhibit phenotypic changes or an altered capacity to stimulate allogeneic T cells, despite exposure to IRI-derived exosomes under the same conditions. Imaging flow cytometry confirmed that BMDC internalized significantly more exosomes than LDC. Notably, BMDC expressed higher levels of ICAM-1 compared to LDCs, suggesting a potential mechanism for their greater exosome uptake capacity. **Conclusion:** These novel findings reveal a differential capacity of liver exosomes released following IRI to affect the phenotype and stimulatory function of BMDC versus LDC. This response may be linked to differential exosome uptake, potentially mediated by ICAM-1/LFA-1 interactions. The refractory response of LDC to liver IRI exosomes may contribute to modulation of tissue injury and alloimmune reactivity following liver transplantation.

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4559 | DONOR-DERIVED EXTRACELLULAR VESICLES HAVE IMMUNOLOGICAL PROPERTIES DEPENDENT ON LIVER AGE AND DONOR TYPE

Heather Jennings[1] Peter Chlebeck[1] Brooke Miller[1] Grace Heise[1] Mia Levitsky[1] Bret Verhoven[1] David Al-Adra[1], [1]University of Wisconsin

Background: Liver transplantation is the best treatment for end-stage liver disease, but immunological rejection can reduce both graft and recipient lifespan. Older livers or those procured from donation after circulatory death (DCD) are associated with increased ischemia-reperfusion injury, which may be associated with increased rejection. Donor-derived extracellular vesicles (EVs) can operate in this process by promoting immune activation or suppressing it, primarily through their miRNA cargo. Normothermic ex vivo liver perfusion (NEVLP) provides the opportunity to simulate physiological conditions and allow collection and analysis of EVs derived from standard, older, and DCD livers. We hypothesize older and DCD livers will produce inflammatory EVs. **Methods:** Livers isolated from rats aged 8–12 weeks were used for standard and DCD NEVLP and rats aged at least 21 weeks were used for older donor NEVLP. Cryogenic electron microscopy (cryo-EM) was used to identify the presence of EVs in perfusate samples. Nanosight tracking analysis (NTA) determined the size and number of EVs. EV miRNA was isolated and sequenced. Mixed lymphocyte reaction (MLR) experiments were performed, adding pooled $5x10^7$, $5x10^8$, and $5x10^9$ EVs to quantify the immune effects of EVs from each group

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in a dose-dependent manner. **Results:** Cryo-EM confirmed the presence of EVs in samples taken after 4 hours of NEVLP. NTA data demonstrated older and DCD livers respectively produced 11.5x and 4.7x more EVs than standard livers after 1 hour of NEVLP and older and DCD livers produced 5.9x and 2.6x more EVs than standard livers after 4 hours of NEVLP, respectively. Principal Components Analysis of miRNAs clustered the older liver EV miRNAs within the standard liver cluster area, while DCD liver EV miRNAs were separate. MLR results indicate that higher concentrations of standard liver EVs suppress the immune response, whereas older and DCD liver EVs enhance it. **Conclusion:** DCD and older livers release more EVs than standard livers during NEVLP, with DCD livers having a distinct population of miRNAs. The RNA cargo in the older liver EVs appear similar to that of the standard livers, but do not suppress an immune response at higher concentrations as seen with the standard liver EVs. DCD EVs also increased the immune response at higher concentrations. These results help elucidate the role that donor graft EVs can play in rejection and may present novel targets for immune response modulation.

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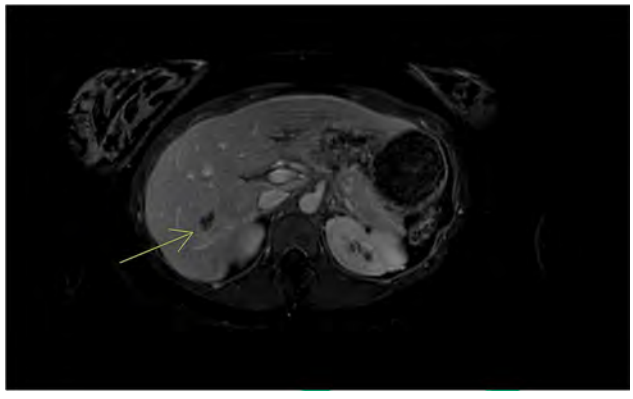
4560 | HEPATIC INFARCTION, AN INFREQUENTLY ENCOUNTERED COMPLICATION OF HELLP SYNDROME: A CASE REPORT

Jill Bhavsar[1] Manjusha Das[1], [1]Wellstar Cobb Medical Center

Background: HELLP syndrome (defined as: hemolysis, elevated liver enzymes and low platelet) is a relatively uncommon pregnancy related disease. Most cases occur in third trimester and have strong association with preeclampsia, while some have more "atypical" presentations. This case highlights the importance of carefully distinguishing HELLP syndrome from other diseases, and initiating prompt treatment to prevent further complications. **Methods:** A 32 year old female with pertinent past history of systemic lupus erythematosus (SLE) on plaquenil, and aplastic anemia secondary to idiopathic thrombocytopenic purpura (ITP) with prior splenectomy was admitted for preterm premature rupture of membranes at 35 weeks and 5 days of gestation. She endorsed mild right sided abdominal pain on admission and was found to have liver enzyme elevation and worsening thrombocytopenia (84,000 cells/microL), with elevated LDH at 251 units/L, low hemoglobin at 9.7 g/dL and low haptoglobin < 10 mg/dl concerning for HELLP syndrome during the 3rd trimester of pregnancy. The peak aspartate aminotransferase and alanine aminotransferase (AST and ALT) was 600 IU/L and 934 IU/L respectively 2 days postpartum. The peak alkaline phosphatase (ALP) was 720 IU/L a few days before delivery. MRI abdomen/pelvis was notable for multiple nonspecific areas of hypoenhancement in the liver with the largest lesion in the left lateral hepatic lobe measuring 5.9 x 4.6 cm, a region of hepatic infarction. Due to concerns for worsening hepatic failure she was transferred to a liver transplant center. **Results:** HELLP syndrome complicates about 0.2-0.8% of all pregnancies. The placental factors and vasoactive substances induce an enhanced inflammatory state and endothelial damage in the liver which leads to increased formation of microthrombi, ischemia of the hepatocytes and ultimately liver failure. In 70-80% of cases it co-exists with pre-eclampsia, however about 15% of HELLP syndrome patients have no association with pre-eclampsia and present without hypertension or proteinuria.

Occasionally, HELLP syndrome can be worsened by the development of hepatic infarction, subcapsular hematoma, or hepatic rupture. Hepatic infarction occurs in less than 1% of HELLP patients and has mortality rate of 16%. Thus, in a patient with right upper quadrant pain and significant elevation of liver enzymes; bedside ultrasound, CT or MRI imaging should be obtained to establish a prompt diagnosis and a timely treatment plan, which often includes surgical interventions such as hepatic resection or liver transplantation. **Conclusion:** This case highlights severe, rare presentation of HELLP syndrome (without hypertension or proteinuria) developing hepatic infarction which has high morbidity and mortality; emphasizing the need for close monitoring of liver function test for all HELLP patients and early diagnosis with aggressive management.



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4561 | INJURED LIVER-RELEASED MIR-122 LEADS TO ERYTHROCYTE PHAGOCYTOSIS VIA THE ACTIVATION OF TLR7

Yingyun Gong[1] Yingjing Zou[2] Moran Hu[1] Hai Huang[1] Ke Zen[3] Hongwen Zhou[1] Hongwei Liang[4], [1]Nanjing Medical University, [2]Nanjing Medical University; China Pharmaceutical University, [3]Nanjing University, [4]China Pharmaceutical University

Background: Anemia is a prevalent complication in patients with advanced chronic liver disease, with prevalence ranging from 50% to 87%. The specific mechanism by which liver disease results in erythrocytopenia remains unclear, underscoring the necessity for further investigation. **Methods:** To investigate the influence of liver injury on erythrocytopenia, subjects with liver diseases and age- and sex-matched healthy volunteers were enrolled. Both AFLD and NAFLD mouse models were induced for further investigation, and genetic mouse models were also applied accordingly. Erythrocytes were isolated from human and mouse whole blood samples. Flow cytometry and Immunofluorescence were used for surface staining. **Results:** We first demonstrated that injured liver-released miR-122 could bind with Toll-like receptor 7 (TLR7) to alter the morphology and CD47 distribution of erythrocytes, which results in erythrophagocytosis. Knockout of either miR-122 or TLR7 could block erythrophagocytosis in AFLD and NAFLD mouse models. Furthermore, a miR-122 inhibitor rescued this phenotype. **Conclusion:** These findings represent a novel mechanism of anemia caused by advanced chronic liver disease. The inhibition of miR-122 in patients may prove to be an effective strategy for the prevention or retardation of anemia.

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4562 | A MICROBIAL METABOLITE REDUCES ALCOHOL-INDUCED INFLAMMATION VIA DUAL MODULATION OF NF-&KAPPA;B AND INTERFERON PATHWAYS

Adam Kim[1] Yurui Zheng[1] Nicholas Handali[1], [1]UConn Health

Background: Chronic alcohol consumption alters innate immune signaling leading to a hyper pro-inflammatory state. Preliminary data from our lab found that in both patients and murine models of alcohol-associated liver disease, immune cells have imbalanced innate immune gene regulation, with elevated pro-inflammatory nuclear factor kappa B (NF-κB) responses and significantly reduced interferon signaling. Interferon signaling is essentially protection from viruses but also regulation of anti-inflammatory pathways. We wanted to find a molecule that could stimulate the interferon pathway and reduce NF-κB activation to rebalance innate immune signaling in the liver and immune cells of ALD patients. **Methods:** We utilized THP1-Dual cells, a human monocyte-derived cell line that has been genetically engineered with dual reporter systems. These cells allow the simultaneous monitoring of NF-κB and Interferon Regulatory Factor (IRF) activation via alkaline phosphatase and luciferase secretion respectively.

To identify novel drugs that modulate these pathways, we challenged THP1-Dual cells with +/- LPS (100pg/ml) to simulate chronic inflammation observed in patients. After 24 hours, cells were then treated with a single compound from a library of microbial metabolites. After another 24-hours we collected supernatant to measure alkaline phosphatase and luciferase. **Results:** While we identified a number of molecules capable to shifting these two signaling pathways in different ways, one microbial metabolite, 4-Hydroxyphenylacetic acid (4-HPAA), led to a downregulation of NF-κB and an upregulation of IFN pathway activity, only in monocytes challenged with LPS. This suggests that 4-HPAA may be a molecule that can specifically rebalance innate immune signaling during inflammation. To test this, we used the NIAAA-model of alcohol-associated hepatitis where 4-HPAA was added to the Lieber-DiCarli diet. We found that 4-HPAA was able to significantly reduce liver damage and qPCR results show an increase in interferon signaling in EtOH fed animals. **Conclusion:** These findings provide insight into the potential application of 4-HPAA as a therapeutic agent targeting alcohol-induced inflammation.

Disclosures: Adam Kim: Nothing to Disclose, Yurui Zheng: Nothing to Disclose, Nicholas Handali: Nothing to Disclose

4563 | PATHOGENIC ROLE OF P2X7 ON LIVER ISCHEMIC REPERFUSION INJURY

Osamu Yoshida[1] Toyoki Shimamoto[2] Ryo Yano[2] Yuki Okazaki[2] Atsushi Yukimoto[2] Yoshiko Nakamura[2] Takao Watanabe[2] Yoshio Tokumoto[2] Masashi Hirooka[3] Masanori Abe[2] Yoichi Hiasa[1], [1]Ehime University, [2]Ehime University Graduate School of Medicine, [3]Ehime University Hospital

Background: Ischemia-reperfusion (IRI) influences graft rejection and survival, thus relieving liver IRI is

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important in liver transplantation. ATP is a source of energy and abundant in the cell. However, ATP is released into extracellular space and acts as a damage associated molecule patten (DAMP) during cell injury. P2X7 is a receptor of extracellular ATP (eATP) and activates immune cells thorough eATP ligation. In this study, we will reveal the role of P2X7 in liver IRI and demonstrate the potential therapeutic capacity of eATP-P2X7 axis. **Methods:** 8–10-week-old wild type (WT) or P2X7 KO male mice, NOD.129P2 background, were subjected to liver IRI. After 6 hr reperfusion, the mice were euthanized and liver injury assessed by serum ALT. A740003 were intraperitoneally injected 1 hr before applying ischemia for P2X7 blockade or eATP hydrolysis. The expression levels of IL-6, TNF-α and IL-1β in IRI induced liver was evaluated by RT-PCR and western blot. WT and P2X7 KO splenocytes were stimulated with LPS for 18 hr for assessing the impact of P2X7 deficiency in IL-6, TNF-α and IL-1β production. **Results:** P2X7 KO mice displayed significant lower serum ALT compared with WT mice after liver IRI injury (KO/WT: $1530 \pm 584/7544 \pm 3442$ U/L, $P < 0.001$). The expression of IL-6, TNF-α and IL-1β in IRI induced liver was significantly lower in P2X7 KO mice. A740003 treatment reduced serum ALT after the liver IRI compared with untreated mice (A740003/untreated: $39280/323 \pm 1452$ U/L, $P < 0.001$). IL-6, TNF-α and IL-1β expression in IRI induced liver were significantly lower in A740003 treated mice compared with PBS treated control mice. IL-6, TNF-α and IL-1β production by P2X7 KO splenocytes were significantly lower compared with those of WT splenocytes. **Conclusion:** P2X7 deficiency reduced inflammatory cytokine production and protected liver from IRI. P2X7 blockade could be a treatment option for liver IRI.

Disclosures: Osamu Yoshida: Nothing to Disclose, Toyoki Shimamoto: Nothing to Disclose, Ryo Yano: Nothing to Disclose, Yuki Okazaki: Nothing to Disclose, Atsushi Yukimoto: Nothing to Disclose, Yoshiko Nakamura: Nothing to Disclose, Takao Watanabe: Nothing to Disclose, Yoshio Tokumoto: Nothing to Disclose, Masashi Hirooka: Nothing to Disclose, Masanori Abe: Nothing to Disclose, Yoichi Hiasa: Nothing to Disclose

4564 | FUNCTIONAL VARIANTS OF THE IFNL4 DRIVE ISG EXPRESSION WITH SECONDARY EFFECTS ON LIPID METABOLISM IN THE HEALTHY LIVER

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Background: Interferon lambda 4 (IFNL4) is an ancestral protein that is produced in the presence of the rs368234815-ΔG allele, while the alternate rs368234815-TT allele results in a frameshift that abrogates IFNL4 production. The IFNL4-encoding rs368234815-ΔG allele has been associated with decreased disease progression in chronic HCV infection and metabolic dysfunction-associated steatohepatitis, but the mechanisms are not known. **Methods:** To investigate the effect of IFNL4 on hepatocytes and intrahepatic immune responses in the absence of any HCV-mediated effects, we performed single-cell RNA-seq analysis of liver biopsies from 14 patients five years after treatment-induced HCV clearance with direct acting antivirals. No patient had substantial liver inflammation (ALT, median: 27 (IQR, 19-31.5) U/L; mean HAI score 2, Ishak fibrosis score 1). Genotyping for rs368234815 and rs117648444 was performed. **Results:** Twelve patients encoded IFNL4 (rs368234815-ΔG/ΔG or -ΔG/TT, and rs117648444-G/G). Two of these encoded a functionally attenuated IFNL4 with a P to S substitution at IFNL4 position 70 (rs117648444-A/G). Two patients did not encode IFNL4 (rs368234815-TT/TT). Single-cell RNA sequencing analysis revealed significantly higher expression of interferon-stimulated genes (ISGs, *MX1*, *IFITM1*, *OAS1*, and *ISG15)* in hepatocytes and liver sinusoidal endothelial cells (LSECs) of patients who encoded IFNL4 than in those who did not. Patients with a functionally attenuated IFNL4 had significantly lower ISG expression than those with conserved IFNL4 but higher ISG expression than those without IFNL4. In hepatocytes, increased ISG expression was associated with enriched pathways for fatty acid degradation (*ACAA2*, *ACAT1, ACADM*, *ACADVL*, *GCDH, ACOX1, CPT2*), while steroid biosynthesis (*LSS*, *MSMO1*, *TM7SF2*, and *FDFT1*) was reduced (KEGG database). Differential ISG expression extended to all intrahepatic immune cell populations, even though IFNLR1 expression is restricted to neutrophils and dendritic cells. These findings suggest secondary type I and II IFN responses, which were confirmed by Hallmark gene enrichment analysis. CD4 and CD8 T cell activation pathways were enriched (Hallmark gene set) despite reduced antigen processing and presentation pathways in macrophages (GO analysis). **Conclusion:** Functional variants of the *IFNL4* gene increase ISG expression in LSECs and hepatocytes, and liver immune cells with a secondary effect on lipid metabolism.

Disclosures: Keisuke Fukutomi: Nothing to Disclose, Alexis Moore: Nothing to Disclose, Sabitree Shahi: Nothing to Disclose, Vicky Chen: Nothing to Disclose,

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Marc Ghany: Vir Bio: Grant is to NIDDK, NIH not to Investigator, Barbara Rehermann: Nothing to Disclose

4565 | EFFICACY OF THE CLM-022, AN INHIBITOR OF THE NLRP3 INFLAMMASOME, IN IN VIVO AND IN VITRO PATHOGEN-ASSOCIATED MOLECULAR PATTERNS (PAMPS)-INDUCED DISEASE MODELS

Guillaume Vidal[1] Alexandra Caron[1] Hana El Khatib[1] Maryse Malysiak[1] Valérie Daix[1] Simon Debaecker[1] Manon Clarisse[1] Dean Hum[2] Bart Staels[3] Sakina Sayah Jeanne[1], [1]Genfit, [2]GENFIT CORP, [3]University Lille 2

Background: Inflammation and hepatocyte cell death are common elements in the pathogenesis of most chronic liver diseases leading to fibrosis, cirrhosis and liver failure. Zhao et al. (2025) recently identified a previously unrecognized pathogenic role of Gasdermin-D (GSDMD)-elicited pyroptosis in regulating the immune microenvironment in HBV-ACLF (hepatitis B virus-acute on chronic liver failure) liver tissue. Pyroptosis is regulated by inflammasomes which are intracellular multiprotein complexes also expressed in both parenchymal and non-parenchymal cells of the liver. In response to danger signals such as PAMPs, inflammasomes activate caspase-1, release IL-1β and IL-18. The aim of this work was to characterize the mechanism of NLRP3 inhibition by CLM-022 and evaluate its protective activity in models of PAMP-induced inflammation. **Methods:** Drug Affinity Responsive Target Stability (DARTS) assay was performed to assess the mechanism of action of CLM-022 on inflammasome inhibition. Inhibition of cytokines production was assessed in LPS stimulated human whole blood cells. For in vivo studies, polymicrobial sepsis was induced by caecal ligation and puncture (CLP). **Results:** CLM-022 binds to the NLRP3 protein, thereby preventing NLRP3 inflammasome complex assembly. In human whole blood assay, CLM-022 strongly inhibits IL-1β, IL-6 and TNF-α production when added concomitantly and after LPS stimulation (IC_{50} ~135nM - 121nM, 363nM - 456nM, 283nM - 380nM, in co- and post-treatment, respectively). In the mice murine sepsis model CLM-022 confers protection from gut leakage-induced mortality at 1 mpk, orally administered, once daily for 7 days. **Conclusion:** Although further experiments are needed to fully understand how CLM-022 improved survival in septic mice, at a minimum, it seems to be mediated by regulation of the innate immune response. These results further support the development of CLM-022 in advanced liver disease including ACLF

Disclosures: Guillaume Vidal: Genfit SA: Employee, Alexandra Caron: Nothing to Disclose, Hana El Khatib: Nothing to Disclose, Maryse Malysiak: Nothing to Disclose, Valérie Daix: Nothing to Disclose, Simon Debaecker: Nothing to Disclose, Manon Clarisse: Nothing to Disclose, Dean Hum: Nothing to Disclose, Bart Staels: Genfit SA: Consultant, Sakina Sayah Jeanne: Nothing to Disclose

4566 | MICRONUTRIENT CHANGES IN A MURINE MODEL OF CCL_4-INDUCED CHRONIC LIVER DISEASE

Jeffrey Singer[1] Dillon Kunkle[1] Eric Skaar[1], [1]Vanderbilt University Medical Center

Background: Micronutrient deficiency is a well-recognized complication of chronic liver disease owing to the central role the liver plays in organismal metabolism. Additionally, patients with decompensated cirrhosis are more prone to invasive bacterial infections. Despite the co-incidence of these two well-known observations in the same patient population, it is unclear if nutritional deficiency is a causal factor for increased infection risk in patients with chronic liver disease. **Methods:** To address this question, we aimed to develop a murine model of micronutrient deficiency in chronic liver disease which could then be subjected to infection. We implemented the well-studied model of chronic liver injury using carbon tetrachloride (CCl_4) injection for 8 weeks. Following fibrosis induction, we analyzed tissue and serum with inductively-coupled plasma mass spectrometry and real-time gene expression analysis to evaluate for changes in trace metal and selenium homeostasis. **Results:** As expected, mice treated for 8 weeks with CCl_4 developed advanced fibrosis compared to those treated with corn oil vehicle. We found robust differences across treatment groups in both male and female mice in multiple trace metals and selenium in the serum and liver as well as gene expression changes in the liver and duodenum that support a biologically significant role for these observed differences. Interestingly, no differences were observed in serum or liver iron levels despite gene expression changes suggesting altered iron homeostasis. **Conclusion:** We conclude that chronic CCl_4-induced fibrosis disrupts host nutritional metal homeostasis and this model is well-suited for mechanistic probing of how micronutrition status impacts infection susceptibility in chronic liver disease. Insights from future studies may offer a roadmap to preventing infections in highly susceptible patients.

Disclosures: Jeffrey Singer: Nothing to Disclose, Dillon Kunkle: Nothing to Disclose, Eric Skaar: Pfizer: Advisor

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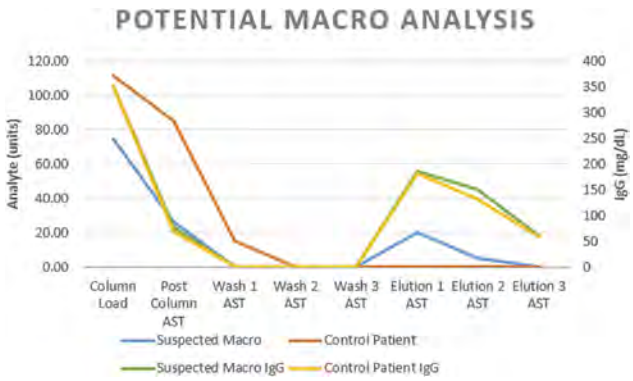
4567 | MACRO-ASPARTATE AMINOTRANSFERASE IN A PATIENT WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Helena Steffens[1] Isabella Solaroli[1] Mark Cervinski[1] Jeffrey Adler[1], [1]Dartmouth Hitchcock Medical Center

Background: Macro-aspartate aminotransferase (macro-AST) is a rare phenomenon in which auto-antibodies bind circulating AST, reducing AST clearance, leading to AST concentrations that are not reflective of a disease process. The condition can lead to diagnostic ambiguity and unnecessary tests. Herein, we report a case of macro-AST for a patient referred to the gastroenterology department for evaluation of a pancreatic cyst incidentally discovered on ultrasound performed because of an elevated AST found on routine blood work. **Methods:** A 61-year-old man with type II diabetes mellitus and metabolic dysfunction-associated steatohepatitis (MASH) presented to the gastroenterology clinic for evaluation of a pancreatic cyst. However, this issue was incidental, and was discovered on an abdominal ultrasound that had been performed because of an elevated AST (384 U/L, reference interval $\leq$ 39 U/L).
On interview he recalled that his AST had been elevated to 800 U/L at an outside facility five months prior. Subsequent general serologic testing for chronic liver disease was performed, and was found unremarkable. Of note, CK was also performed and was 80 U/L (reference interval 0-200 U/L). Despite this, his AST remained elevated at 280 U/L. Notably, the patient's ALT, alkaline phosphatase, and fractionated bilirubin had been, and all remained within reference intervals. **Results:** At this time, macro-AST testing was performed. Testing involved affinity chromatography utilizing agarose beads coated with protein A/G with high affinity for human IgG. AST activity was measured before and after column elution. For a patient with macro-AST, the AST activity should mirror the pattern of IgG. The figure below (Figure 1) demonstrates the patient's AST activity (blue line) was lower than the control (orange) after binding to the column, indicating that most of the AST was bound by antibodies. Activity spiked with elution buffer, which is consistent with macro-AST. **Conclusion:** An isolated elevation in AST might be the result of macro-AST. Recognition of this phenomenon might save a patient unnecessary testing for liver disease.



Disclosures: Helena Steffens: Nothing to Disclose, Isabella Solaroli: Nothing to Disclose, Mark Cervinski: Dexter: Advisor, Jeffrey Adler: Nothing to Disclose

4568 | NEW SUBMISSION PERIPHERAL LYMPHOCYTES IN HUMAN LIVER HEPATOCELLULARCARCINOMA: A NEW DRUGGABLE TARGET AS WELL AS BIOMARKER TO HELP DIAGNOSIS AND PREDICT IMMUNOTHERAPY RESPONSE

Andrea Dalbeni[1] Rosa Lombardi[2] Vincenzo Di Maria[1] Paola Dongiovanni[3] Marica Meroni[4] Stefania CAnè[5] Antonio Vella[6] Moris Sangineto[7] Massimo Pettoello Mantovani[8] Maria Rosa Pastore[9] GAETANO SERVIDDIO[7] david sacerdoti[10] Anna Ludovica Fracanzani[11], [1]AOUI Verona, [2]University of the Study of Milan, [3]SC Medicina Indirizzo Metabolico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Mila, [4]Fondazione Ca' Granda OMP Milano, [5]The Veneto Institute of Oncology IOV-IRCCS, Padua, Italy., [6]Section of Immunology, Azienda Ospedaliera Universitaria Integrata (AOUI), Verona, Italy., [7]Liver Unit, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy., [8]European Pediatric Association, Union of National European Pediatric Societies and Associations, [9]Unità Operativa Complessa di Pediatria, Fondazione IRCCS "Casa Sollievo della Sofferenza", San Gi, [10]Liver Unit, Medicine Department, University of Verona, [11]University of Milan

Background: Hepatocellular carcinoma (HCC) represents the second leading cause of cancer-related death worldwide, developing from a chronic liver disease, characterized by inflammation and fibrosis, derived from either viral insult (e.g. HBV and HCV), metabolic syndrome (MASLD), plus alcohol abuse (MetALD) or other causes. Over the past decade, immune

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checkpoint inhibitors (ICI) have revolutionized the treatment of HCC adding to previous treatments. Despite the remarkable advances, the criteria and guidelines for patient selection are missing and insufficient. Therefore, identify the immunological features in different etiologies and properties to support patient eligibility is *a sine qua non* for the improvement of therapeutic efficacy and for the development of a solid, personalized medicine approach. Aims of our study are define phenotypically, lymphocytes cells trough flow cytometry (FACS) in patients with HCC BCLC B/C with different aetiologies and in a subgroup of patients, treated with ICI, the aim is to identify their contribution to response. **Methods:** Liver-resident immune cells, in particular γδT cells 8 (CD4-CD8-), CD8 and CD4 lymphocytes, neutrophils, Kpuffer cells and macrophages were assessed by FACS in 159 patients. Liver specimens from adult patients with either diagnosis of MASLD including previous HCV with metabolic factors (100) or viral (HBV/HCV) infection (41) or alcohol abuse (18) stratified according to the HCC stage.

We performed Kruskal Wallis or Anova with post hoc to establish the difference between aetiologies and trough Machine Learning, XGBoost with SHAP, we determined which lymphocytes make a difference in prediction and accuracy of the model ($AUC > 0.8$). Using Leave-One-Out Cross-Validation (LOOCV) we selected the patients with features able to predict response to systemic treatment. **Results:** We documented differences in neutrophiles, monocytes, CD4 and CD8 and ratio and NK between the different aetiologies. In particular CD8 CD57+ (exhausted cell), NK and CD4 discriminates viral vs MASLD (AUC 0.8), while CD4-8-, NKt, and CD4 +8+ MASLD vs MetALD (AUC 0.83).

Also combing HCC stage (B or C) with lymphocytes, we documented a difference between viral and MASLD/MetALD. ($p < 0.05$) in CD8+CD57+.

We selected patients who received ICI considering all lymphocyte populations and correlated them to objective response rate (ORR). Throught LOOCV we identified CD8+57+, IGD+ CD27- and CD4-CD8- like top 3 features (AUC 0.84, precision 0.8, recall 0.7). **Conclusion:** For the first time this study identifies in blood in patients with HCC different lymphocytes population that could be a future target of immune therapies and moreover featured CD8+57+ named also exhausted cell and CD4-8- as biomarker of response to ICI treatment.

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4569 | ◆ HIGH SALT DIET EXACERBATES LIVER FIBROSIS AND MODULATES IMMUNE RESPONSES IN MOUSE MODELS

Amalia Tzoumpa[1] Joanna Picó[1] Yin Huang[1] Beatriz Lozano[1] Pedro Zapater[1] Jose Manuel Gonzalez Navajas[1], [1]Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL)

Background: Liver cirrhosis is characterized by inflammation and fibrosis, with the immune system playing a crucial role in progression. Evidence suggests dietary salt can modulate immune responses and immune-mediated diseases. The interplay between dietary factors, immune cells, and liver tissue highlights the importance of understanding how high salt intake may contribute to liver pathology. This study evaluated the hepatic immunomodulatory effects of salt and its impact on liver injury and fibrosis in mouse models. **Methods:** C57BL/6 male mice were fed either normal diet (ND) or a high salt diet (HSD) (4% NaCl) for one week and were then additionally subjected to CCl_4 or vehicle injections (2 mL/kg) twice weekly for three weeks to induce liver fibrosis. At the end point, mice were sacrificed and liver tissue and blood were analyzed by flow cytometry, elisa, qpcr and histology. In addition, hepatocytes from both groups of mice were isolated for ex vivo experiments. **Results:** All mice receiving CCl_4 injections exhibited liver injury and fibrosis. Although HSD alone did not induce hepatic damage or immune cell infiltration, it exacerbated CCl_4-induced injury and fibrosis, as evidenced by increased necrotic areas, the expression of fibrosis-related genes (Acta2, Fn1, and Timp1) and immunohistochemistry of alpha smooth muscle actin. Additionally, $CD68^+$ staining indicated elevated macrophage infiltration in the HSD group upon liver injury. Furthermore, flow cytometry analysis demonstrated a significant increase in hepatic CD4+ IL17+ (Th17 cells), CD4+ IL17+ TNFα+ cells, and pro-inflammatory Th17-like Tregs (Foxp3+ IL17+ cells) in HSD-fed mice, suggesting a Th17-skewed immune response. Moreover, HSD promoted the expansion of cDC2 dendritic cells, which are known to facilitate Th17 differentiation, and upregulated MHC II expression on macrophages, further supporting a pro-inflammatory microenvironment that can facilitate activation of T cells. Mechanistically, hepatocytes isolated from mice exposed to HSD showed elevated production of IL-6 and IL-1β, which was associated to an increase in mitoROS, NF-κB and NLRP3 inflammasome activation. Additionally, we analysed the effect of conditioned medium (CM) from hepatocytes previously exposed to

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high NaCl conditions in T cell differentiation. Our observations revealed that CM from hepatocytes pre-treated with NaCl specifically exacerbated Th17 differentiation. **Conclusion:** In conclusion, HSD exacerbates liver injury and fibrosis by facilitating Th17-mediated inflammation. Our findings indicate that HSD induces a pro-inflammatory response in hepatocytes, potentially through mitoROS/NLRP3 activation, and affects T cell differentiation via signals derived from hepatocytes. This study offers evidence for future investigations into potential therapeutic strategies targeting the salt-induced inflammatory cascade in liver disease.

Disclosures: Amalia Tzoumpa: Nothing to Disclose, Joanna Picó: Nothing to Disclose, Yin Huang: Nothing to Disclose, Beatriz Lozano: Nothing to Disclose, Pedro Zapater: Nothing to Disclose, Jose Manuel Gonzalez Navajas: Nothing to Disclose

4570 | ◆ TARGETING MONOCYTE TLR8 AS AN ANTI-INFLAMMATORY THERAPY IN DECOMPENSATED ADVANCED CHRONIC LIVER DISEASE

Malgorzata Grzelka[1] Roseanne Khawaja[1] Alejandro Brenes[1] Ailish McCafferty-Brown[1] Daniel Dugger[2] Guiguan Jia[2] Nandhini Ramamoorthi[2] Andrew Thorley[2] Jonathan Fallowfield[1] Prakash Ramachandran[1], [1]The University of Edinburgh, [2]Genentech

Background: Decompensated advanced chronic liver disease (dACLD) is associated with significant morbidity and mortality. Beyond transplantation, current therapies for dACLD do little to change its natural history. Systemic inflammation (SI) is associated with adverse outcomes in dACLD and anti-inflammatory therapies have been proposed as a treatment strategy. However, the molecular mechanisms underpinning SI in dACLD remain unclear. We aimed to define cellular and molecular drivers of SI to identify new candidate therapeutic targets for dACLD. **Methods:** Blood and clinical phenotyping data were collected from patients with dACLD, compensated ACLD (cACLD), non-ACLD or healthy controls. Serum cytokines were measured using immunoassay. Immunophenotyping was performed using spectral flow cytometry. Monocytes were isolated for mass spectrometry and functional assays. TLR8 agonist activity was assessed by serum treatment of TLR8-reporter HEK cells. Human liver single-cell RNA-seq (scRNAseq) data was analysed using R. **Results:** Serum inflammatory cytokines increased in dACLD patients and positively correlated with MELD-Na score, liver frailty score and liver stiffness. Flow cytometry showed a reduction in cytotoxic CD8+ T cells between cACLD and dACLD but no numerical differences in circulating monocytes. However, monocytes in dACLD exhibited a more pro-inflammatory profile with elevated CD9, CD64 and CD63 expression, enhanced phagocytosis capacity and increased production of IL-1β and TNF-α. Unbiased proteomics revealed significantly augmented expression of the endosomal toll-like receptor 8 (TLR8) in dACLD monocytes compared to cACLD (Figure 1A), whilst serum analysis using TLR8-reporter HEK cells demonstrated increased circulating TLR8 ligand activity with more advanced liver disease (Figure 1B). Analysis of scRNAseq confirmed that TLR8 expression is specific to myeloid cells and increased in CLD livers. Treatment of dACLD monocytes, using either the specific TLR8 inhibitor CU-CPT9a or the dual TLR7/8 inhibitor Enpatoran, reduced expression of pro-inflammatory cytokines IL-1β, IL-6 and TNF-α. **Conclusion:** Our comprehensive immunophenotyping data demonstrate monocyte activation as a key regulator of SI in dACLD and identifies TLR8 activity as a driver of this process, with elevated monocyte TLR8 expression and serum TLR8 ligand activity observed in dACLD patients. Crucially, the TLR8 pathway is druggable, highlighting this as a tractable therapeutic target to abrogate SI in dACLD.

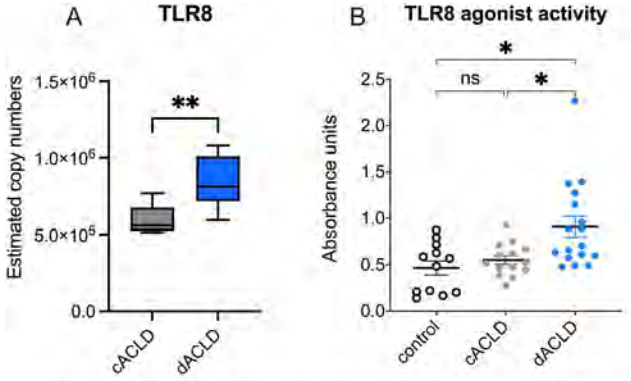

Figure 1 A. Mass spectrometry revealed significantly higher TLR8 in dACLD compared to cACLD in CD14+ monocytes; B. Treatment of TLR8 reporter HEK cells with human serum demonstrated significantly higher endogenous TLR8 ligand activity in dACLD compared to cACLD and control.

Disclosures: Malgorzata Grzelka: Genentech: This study was funded by Genentech via a Collaborative Resea, Genentech Inc: Grant/Research Support, Roseanne Khawaja: Nothing to Disclose, Alejandro Brenes: Nothing to Disclose, Ailish McCafferty-Brown: Nothing to Disclose, Daniel Dugger: Genentech: Employee, Guiguan Jia: Nothing to Disclose, Nandhini Ramamoorthi: Nothing to Disclose, Andrew Thorley: Nothing to Disclose, Jonathan Fallowfield: Stimuliver: Advisor, Ipsen: Advisor, Kynos Therapeutics: Advisor, Resolution Therapeutics: Consultant, River 2 Renal Corp.: Advisor, Global Clinical Trial Partners: Advisor, Guidepoint: Consultant, GlaxoSmithKline: Grant/Research Support, Genentech: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Prakash Ramachandran: Nothing to Disclose

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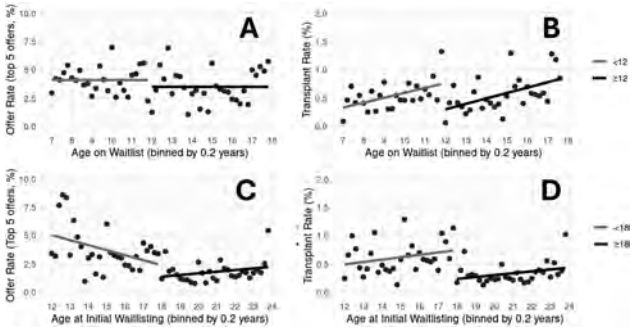
4571 | ◆ IMPACT OF PEDIATRIC AGE CUTOFFS ON US LIVER TRANSPLANT ALLOCATION: A REGRESSION DISCONTINUITY DESIGN

Tomohiro Tanaka[1] George Wehby[2] Michael Jones[2] David Axelrod[3], [1]University of Iowa School of Medicine, [2]University of Iowa, College of Public Health, [3]University Hospitals

Background: Currently, U.S. liver transplant (LT) organ allocation policy prioritizes allografts recovered from pediatric donors (< 18 years) for candidates < 12 years, followed by those aged 12–17 and then adults ≥ 18. The impact of these age-based allocation cutoffs on access to LT and waitlist mortality was retrospectively evaluated. **Methods:** U.S. national transplant registry data from 2/4/20 to 12/31/23 was analyzed using person-day as the unit of analysis to assess outcomes for LT candidates listed between ages 12 and 24 to evaluate the age 18 threshold, and between ages 6 and 18 for the age 12 threshold. Sharp regression discontinuity (RD) designs embedded in pooled regression models were applied at both age cutoffs based on current OPTN policy. Primary outcomes were receipt of a top five liver organ offers and the probability of undergoing deceased donor transplantation (DDLT). The exposure was organ offer prioritization defined by PELD score for each age. RD plots were generated (Figure A–D). Poisson and logistic regression analyses were used to model offer rates and DDLT probability, adjusting for MELD exception status and covariates. Age was defined as actual daily age for the 12-year threshold model and age at listing for the 18-year threshold model. **Results:** A total of 301,783 person-day observations from 1,521 unique candidates were analyzed, including 122,947 waitlisted observations impacted by the age 12 threshold and 187,766 affected by the age 18 threshold. The age 12 threshold did not significantly impact organ offer rates (Figure A); however, transplant probability was lower for candidates > 12 years old (Figure B). Patients over 12 had a relative risk of 1.06 (95% CI: 0.90 to 1.26) and an odds ratio of 0.61 (95% CI: 0.40 to 0.92), favoring those under 12. Age above the 18-year threshold was associated with a significant decline in both organ offers and transplant probability (Figures C and D), with a relative risk of 0.86 (95% CI: 0.76 to 0.98) and an odds ratio of 0.55 (95% CI: 0.46 to 0.95), respectively. Additional RD models evaluating offer-related metrics, including the proportion of donors under age 18, use of brain-dead donors, and organ acceptance rates, also showed significant declines in access for patients above the age thresholds. **Conclusion:** Current age-based allocation cutoffs at 12 and 18 years create significant discontinuities in LT access in the U.S. The disadvantage experienced by adolescent and young adult candidates was particularly significant near the cutoff age. Future allocation refinements should reconsider these age-based transitions to ensure more fair access across all age groups.



Disclosures: Tomohiro Tanaka: Nothing to Disclose, George Wehby: Nothing to Disclose, Michael Jones: Nothing to Disclose, David Axelrod: Nothing to Disclose

4572 | ◆ LARGE-SCALE PROTEOMIC STUDY REVEALS TOTAL SERUM IGG AS A CANDIDATE NOVEL DIAGNOSTIC BIOMARKER IN GESTATIONAL ALLOIMMUNE LIVER DISEASE

Katie Rose Conover[1] Priya Rolfes[1] Kathryn Kilpatrick[1] Anthony Saviola[1] Sarah Taylor[2], [1]University of Colorado, [2]Columbia University Medical Center

Background: Gestational alloimmune liver disease (GALD) is a leading cause of neonatal acute liver failure (ALF) with high mortality, particularly if treatment with intravenous immunoglobulin (IVIG) and exchange transfusion (ET) is not initiated early. However, diagnosis of GALD remains challenging. We aim to identify novel non-invasive diagnostic biomarkers for GALD. **Methods:** We obtained serum samples from GALD (n = 10) and non-GALD (n = 15) cases with neonatal ALF from the NIDDK Pediatric Acute Liver Failure study biorepository. Mass spectrometry and IgG enzyme-linked immunosorbent assay (ELISA) were run on all samples. Proteomic analysis (MetaboAnalyst, Enrichr) was conducted in patients without prior IVIG or ET treatment (n = 18); proteomic analysis by outcome included the full cohort (n = 25). Statistical analysis was performed using Pearson's chi-squared, Mann-Whitney *U* and Student's t-test. **Results:** Age of liver failure onset and serum collection did not differ between

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groups ($p > 0.05$ for both). Although not reaching statistical significance, a greater proportion of GALD patients died (67% vs 30%) and fewer were transplanted (0% vs 30%). After excluding post-IVIG/ET cases, GALD cases demonstrated robust upregulation of immunoglobulin heavy and light chains (Figure 1A). ELISA confirmed significant increase in total serum IgG in untreated GALD cases ($p = 0.005$) with an area under receiver operating curve of 0.903 to predict GALD vs non-GALD ALF ($p = 0.007$, Figure 1B,C). Importantly, IgG level did not correlate with age ($r = -0.07$, $p = 0.74$). Pathway analysis showed upregulation of classical antibody-mediated complement activation pathways in GALD (adjusted $p = 3.9e\text{-}13$) and scavenging by class A receptors in non-GALD (adjusted $p = 1.2e\text{-}6$). Several proteins reflecting liver synthetic and regenerative function, including factor levels, alpha-fetoprotein, angiotensinogen and fibrinogen were significantly decreased in GALD cases with poor outcome (raw $p < 0.05$). **Conclusion:** Differentially expressed serum proteins between GALD and non-GALD neonatal ALF reflect understood pathogenic mechanisms involving complement activation and decreased liver synthetic proteins particularly in GALD infants with poor outcome. Total serum IgG may be significantly increased in GALD due to maternal placental transfer of pathogenic antibodies that destroy fetal hepatocytes. Total serum IgG should be explored prospectively as a non-invasive GALD diagnostic biomarker.

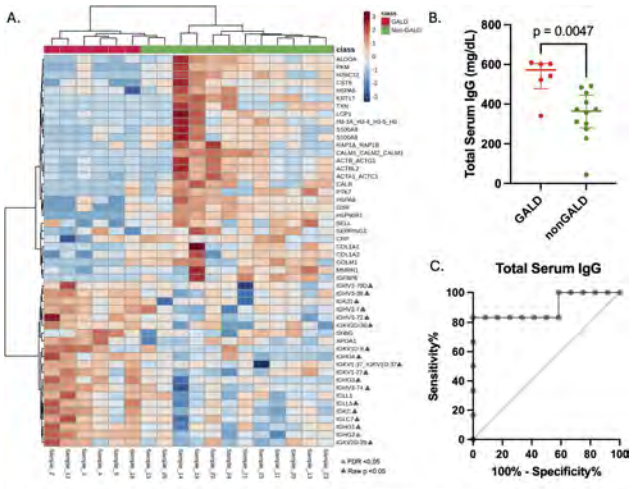

Figure 1. Results from proteomic analysis comparing gestational alloimmune liver disease (GALD) and non-GALD neonatal acute liver failure cases, which excluded patients who received intravenous immunoglobulin or exchange transfusion prior to serum collection. **(A)** Heatmap showing top 50 differentially expressed proteins between groups. Colored triangles notate immunoglobulin heavy and light chains that are significantly increased in GALD vs non-GALD cases via Student's t-test. **(B)** Total serum IgG from enzyme-linked immunosorbent assay (ELISA) is significantly higher in GALD vs non-GALD cases (p=0.005). **(C)** Area under the receiver operating curve is 0.903 to predict GALD vs non-GALD neonatal acute liver failure (p=0.007).

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4573 | ◆ EARLY CHANGES IN THE FECAL MICROBIOTA ARE ASSOCIATED WITH PEDIATRIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Sarah Maxwell[1] Lu Yang[1] Abdur Rahim Khan[1] James Bayrer[1] Philip Rosenthal[1] Emily Perito[1] Jennifer Price[1] Janet Wojcicki[1], [1]University of California, San Francisco

Background: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is the most common pediatric liver disease in the US. Alterations in the gut-liver axis leading to intestinal dysbiosis contribute to MASLD development. Pediatric MASLD severity has been linked to alterations in the fecal microbiota, with prior studies showing decreased bacterial diversity and different microbial abundance in children with MASLD compared to those without MASLD. However, no studies have examined whether fecal microbial composition in early childhood is associated with MASLD risk later in childhood. We characterized the gut microbiome in Latino infants and preschool children who later developed MASLD and compared it to those without MASLD. **Methods:** In a longitudinal cohort of 87 Latino babies, stool samples were collected at 6 months, 1, 2, and 3 years of age. MASLD was assessed between 5-8 years of age and defined by BMI $> 85\%$ and alanine aminotransferase $\geq 95\%$ for age and gender (≥ 25.8 IU/L for boys, ≥ 22.1 IU/L for girls). Stool microbial communities were profiled using 16s ribosomal RNA sequencing, and analyzed for alpha diversity (via linear regression-based t-tests), beta diversity (via PERMANOVA), and differential taxonomic abundance (via ANCOM-BC) to assess associations with later MASLD, adjusting for potential confounders. **Results:** Of the 87 babies, 46% were boys, 52% were of Mexican origin, 33% had overweight/obesity, and 8% developed MASLD in early childhood. Compared to healthy children, children with later MASLD exhibited lower α-diversity at 1 year of age (Shannon diversity index, $p = 0.041$) and showed distinct overall microbial community composition (beta diversity) at 6 months ($p = 0.037$, $R^2 = 0.11$) and 2 years ($p = 0.04$, $R^2 = 0.07$). We observed a lower abundance of *Erysipelatoclostridium* and a higher abundance of *Bifidobacterium* in children with MASLD with greatest differences up until 2 years of age (FDR < 0.1) (Figure 1). By 3 years of age, there were no microbial differences between children who developed MASLD and those who did not. **Conclusion:** Differences in fecal microbiota were identified as early as 6 months of age in children who later developed MASLD compared to those who did not. Exposures prior to 3 years of age may be critical for future development of MASLD. Our finding of a greater abundance of *Bifidobacterium* in

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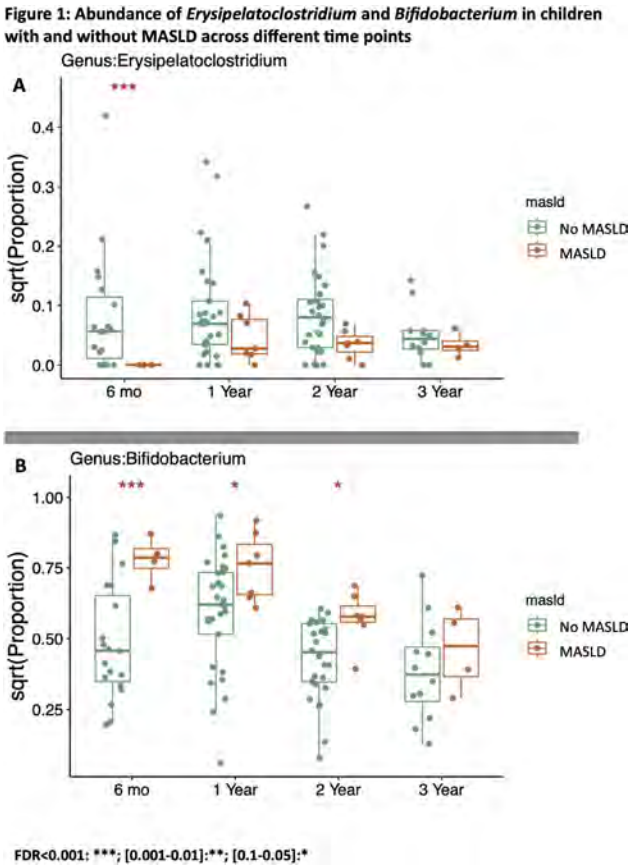
children with MASLD contrasts with previous studies that found a reduced amount of *Bifidobacterium* in children with MASLD and requires further investigation.



Disclosures: Sarah Maxwell: Nothing to Disclose, Lu Yang: Nothing to Disclose, Abdur Rahim Khan: Nothing to Disclose, James Bayrer: Nothing to Disclose, Philip Rosenthal: Nothing to Disclose, Emily Perito: Mirum: Consultant, Mirum: Consultant, Mirum: Consultant, Ultragenyx: Consultant, Ultragenyx: Consultant, Ultragenyx: Consultant, BridgeBio: Consultant, BridgeBio: Consultant, BridgeBio: Consultant, Amagma: Consultant, Amagma: Consultant, Amagma: Consultant, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Albireo: Grant/Research Support, Albireo: Grant/Research Support, Albireo: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Dicerna: Grant/Research Support, Dicerna: Grant/Research Support, Dicerna: Grant/Research Support, Takeda: Grant/Research Support, Mirum: Consultant, Mirum: Consultant, Mirum: Consultant, Ultragenyx: Consultant, Ultragenyx: Consultant, Ultragenyx: Consultant, BridgeBio: Consultant, BridgeBio: Consultant, BridgeBio: Consultant, Amagma: Consultant, Amagma: Consultant, Amagma: Consultant, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Mirum: Grant/Research Support, Albireo: Grant/Research Support, Albireo: Grant/Research Support, Albireo: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Gilead: Grant/Research Support, Dicerna: Grant/Research Support, Dicerna: Grant/Research Support, Dicerna: Grant/Research Support, Takeda: Grant/Research Support, Jennifer Price: AbbVie: Grant/Research Support, Gilead: Grant/Research Support, Genentech: Grant/Research Support, VIR: Grant/Research Support, Cepheid: Grant/Research Support, Aligos: Grant/Research Support, Janet Wojcicki: Nothing to Disclose

4574 | ◆ INTESTINAL ALISTIPES PUTREDINIS ALLEVIATES METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE BY REGULATING SECONDARY BILE ACID HOMEOSTASIS

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Background: Disruption of the gut microbiota leads to dysregulation of secondary bile acid (BA) metabolism, exacerbates intestinal inflammatory responses, and accelerates the onset and progression of metabolic dysfunction-associated steatotic liver disease (MASLD). However, the key gut bacteria associated with secondary BA metabolism, their metabolic functions, and mechanistic roles in MASLD remain to be fully elucidated. **Methods:** This study enrolled 149 children, including MASLD patients, individuals with simple obesity (OB), and healthy controls (HC). Metagenomic sequencing and targeted metabolomics were employed to characterize gut microbiota profiles and BA metabolism. Utilizing the NCBI database, we established a reference database of protein sequences for gut microbial metabolic enzymes, with a focus on identifying and screening key bacteria that express metabolic enzymes of secondary BA metabolism. In vitro anaerobic culture and animal intervention experiments were further conducted to validate the metabolic functions of key bacteria and their therapeutic potential in MASLD. **Results:** Key findings revealed decreased expression

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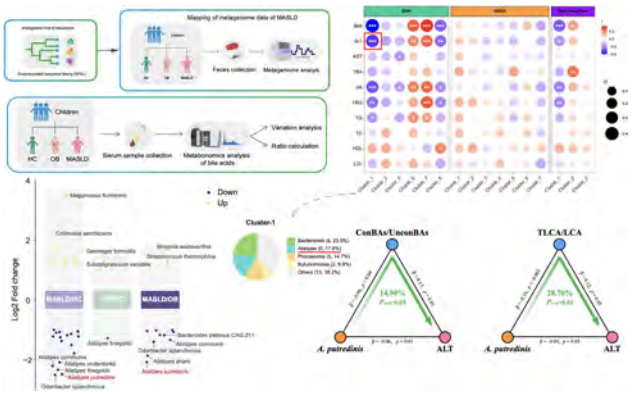
of bile salt hydrolase (BSH) in the gut microbiota of MASLD patients, with Cluster I bacteria showing strong disease association. Targeted metabolomics analysis demonstrated an elevated ratio of conjugated BAs to unconjugated BAs in the serum of MASLD patients. Among BA subtypes, the taurolithocholic acid/lithocholic acid (TLCA/LCA) ratio exhibited the most significant alterations across groups and correlated strongly with alanine aminotransferase (ALT) levels. Differential analysis identified *Alistipes putredinis* (AP) within Cluster I as the most dynamically altered species between OB and MASLD groups, which had been validated in two independent cohorts. Mediation effect analysis further indicated that AP influenced the ALT level by modulating conjugated LCA hydrolysis. In vitro anaerobic culture confirmed the BSH activity of AP. Moreover, AP supplementation significantly attenuated high-fat diet induced MASLD progression in mice and restored BA homeostasis. Finally, transcriptome sequencing analysis showed significant enrichment of the JAK-STAT signaling pathway and helper T cell differentiation pathways in both intestinal and hepatic tissues. This suggests that these pathways may serve as the key signaling pathways mediating immune regulation in the gut-liver axis. **Conclusion:** In conclusion, our findings demonstrate that reduced gut microbial BSH expression in MASLD was partially compensated by AP, which enhanced TLCA/LCA balance and ameliorated MASLD phenotypes. These findings deepen our understanding of microbial-metabolic crosstalk in MASLD pathogenesis and provide a scientific foundation for targeting BA metabolism in MASLD prevention and therapy.



Disclosures: Yan Ni: Nothing to Disclose, Weixing Zhao: Nothing to Disclose, Huiying Wang: Nothing to Disclose, Ana Liu: Nothing to Disclose, Shuangjiang Liu: Nothing to Disclose

4575 | ◆ CLINICAL PRESENTATION, OUTCOMES, AND MANAGEMENT OF BSEP DEFICIENCY WITH TRUNCATED MUTATIONS: A COHORT STUDY OF PFIC2 PATIENTS AT A HIGH-VOLUME PEDIATRIC LIVER TRANSPLANT CENTER

Mohammad Shagrani[1] Kishwer Kumar[1] Alexandra Aldana[1] Ali syed Akhturl Hassan[1] Dalal Albugami[1] Sateesh Maddirevula[1] Saleh Alqahtani[1] Ehab Abufarhaneh[1] Saad Alghamdi[1] Waleed Alhamoudi[2] Bandar Mohammed H Aljudaibi[1] Massimo Malago[1] Dieter Broering[3], [1]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, [2]King Faisal Specialist Hospital and Research Centre, Riyadh Saudi Arabia, [3]King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Background: This study aimed to evaluate the clinical presentation, laboratory findings, outcomes, and interventions in patients with Bile Salt Export Pump (BSEP) deficiency, specifically focusing on those with truncated mutations in the ABCB11 gene (BSEP3). **Methods:** The cohort consisted of 25 patients diagnosed between 2010 and 2023, with data on demographics, clinical features, laboratory results, and treatment outcomes. A comprehensive analysis of clinical symptoms, laboratory markers, and therapeutic interventions was performed to assess disease progression and management strategies. **Results:** The cohort had a median birth year of 2018, with 48% male patients, all originating from consanguineous relationships. The median age at presentation was 3.05 years, with pruritus observed in 60% of patients. Laboratory findings revealed significantly elevated serum bile acids (median 190 μmol/L), bilirubin (median 151 μmol/L), and liver enzymes (ALT median 389 IU/L, AST median 386 IU/L). Notably, 16% of patients developed hepatocellular carcinoma (HCC), and there were notable deficiencies in fat-soluble vitamins (D, A, and E). Liver transplantation was required for 80% of patients, with a median age of 1.9 years at transplantation. Post-transplant mortality was low, but disease recurrence occurred in 10% of cases. **Conclusion:** The findings highlight the aggressive nature of PFIC2 due to truncated BSEP mutations, with early liver transplantation being essential for survival. The study underscores the limited efficacy of current medical therapies for BSEP3 patients and emphasizes the importance of early intervention, close monitoring for HCC, and management of nutritional deficiencies. Despite successful liver transplantation, the risk of disease recurrence remains a significant challenge. Regular screening and tailored therapeutic strategies are crucial for improving long-term outcomes.

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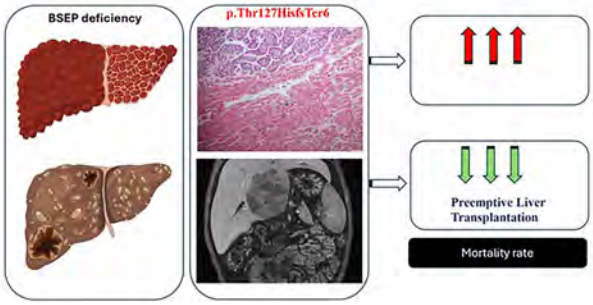
Figure: Preemptive Liver Transplantation is essential for patients with severe BSEP deficiency: Homozygous for p.Thr127HisfsTer6

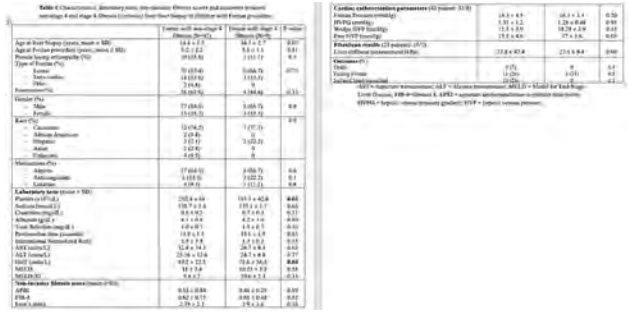


Disclosures: Mohammad Shagrani: Nothing to Disclose, Kishwer Kumar: Nothing to Disclose, Alexandra Aldana: Nothing to Disclose, Ali syed Akhturl Hassan: Nothing to Disclose, Dalal Albugami: Nothing to Disclose, Sateesh Maddirevula: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Ehab Abufarhaneh: Nothing to Disclose, Saad Alghamdi: Nothing to Disclose, Waleed Alhamoudi: Nothing to Disclose, Bandar Mohammed H Aljudaibi: Nothing to Disclose, Massimo Malago: Nothing to Disclose, Dieter Broering: Nothing to Disclose

4576 | ◆ CHARACTERISTICS AND OUTCOMES OF FONTAN ASSOCIATED LIVER DISEASE IN CHILDREN FROM A MULTICENTER - INITIAL ANALYSIS OF 8 CENTERS IN USA

Chaowapong Jarasvaraparn Henry Lin[1] Sindhu Pandurangi[2] Kim Liss[3] Steven Lobritto[4] Adebowale Adeyemi[5] Sara Kathryn Smith[6] Amal Aqul[7] R. Mark Payne[8] Katryn Furuya[9] Wikrom Karnsakul[6] Jean Molleston[10], [1]Oregon Health and Science University, [2]UT Southwestern, Children's Medical Center Dallas, [3]Washington University School of Medicine, [4]Columbia University, [5]Nemours Children's Hospital, Delaware, [6]Johns Hopkins University, [7]University of Texas Southwestern Medical Center, [8]Pediatric Cardiology, Indiana University School of Medicine, [9]UNIVERSITY OF WISCONSIN - MADISON, [10]Indiana University School of Medicine

Background: Fontan associated liver disease (FALD) is a universal sequela of the Fontan procedure. In this study, we aimed to 1) characterize severity of pediatric FALD, 2) evaluate non-invasive markers of liver fibrosis, and 3) describe long-term outcome of FALD in children. **Methods:** This is a multi-center study (PED-FALD) collecting data prospectively and retrospectively since January 2020 of FALD patients aged 10- 20 years. All imaging, cardiac catheterization, and transient elastography were collected. Laboratory tests were collected within 6 months of the liver biopsy. Liver histologic data was abstracted from the pathology reports and utilized the congestive hepatic fibrosis score (stage 0-4). **Results:** 251 patients with Fontan procedure were identified at 8 centers with mean age at 14.3 ± 3.3 years and mean age at Fontan procedure of 3.7 ± 1.7 years. The majority were male (153; 61%), and white (129; 51%). 51 patients (20%) had liver biopsy with the most common indication being surveillance (44; 86%). 24 patients (47%) had stage 3 or 4 liver fibrosis, and 9 patients (18%) had stage 4 liver fibrosis (cirrhosis) from liver biopsy. Patients with biopsy proven cirrhosis had significantly lower platelet count and higher GGT than patients without cirrhosis (155.5 vs. 202.8 x10^3/uL; p = 0.03 and 78.6 vs. 49.2 units/L; p = 0.04, respectively). There was significant correlation between liver fibrosis score and non-invasive fibrosis markers (FIB-4, Forn's index; Spearman 0.28, p = 0.05, 0.48, p = 0.05), and free hepatic venous pressure (0.4, p = 0.03). There was no significant association with histologic severity and liver stiffness measurements from FibroScan or elastography. 242 patients (96%) had imaging and only 15 patients (6%) had cirrhosis from imaging, including 9 from ultrasound, 1 CT, and 5 MRI. 5 patients died (2%), 37 patients were diagnosed with failing Fontan (15%) and 24 patients (10%) ended up with isolated heart transplant. **Conclusion:** This is the first multi-center study in children with FALD with ongoing data registry. Lower platelet counts and high GGT are good markers of cirrhosis. Overall, there was a low mortality rate at 2%. The fact that only 20% of the children in this study underwent liver biopsy demonstrates the need for more sophisticated measures of liver injury. The PED-FALD network will help us understand how to monitor progression of the disease and to optimize treatment decisions in children with FALD.



Disclosures: Chaowapong Jarasvaraparn: Nothing to Disclose, Henry Lin: Nothing to Disclose, Sindhu Pandurangi: Nothing to Disclose, Kim Liss: Nothing to Disclose, Steven Lobritto: Orphalan: Grant/Research Support, Mirum: Advisor, Ibsen: Speaking and Teaching, IPRO: Consultant, NIH: Grant/Research Support, Adebowale Adeyemi: Nothing to Disclose, Sara Kathryn Smith: Nothing to Disclose, Amal Aqul: Mirum Pharmaceuticals: Consultant, Ipsen: Consultant, Sarepta Therapeutics: Consultant, R. Mark Payne: Nothing to

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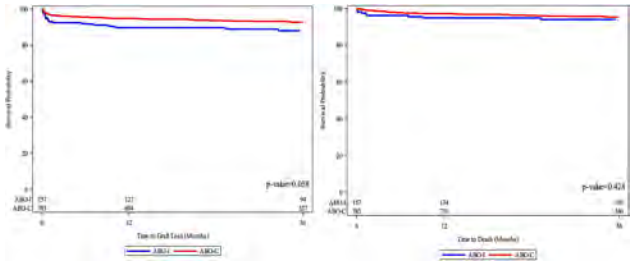
4577 | ◆ EXCELLENT OUTCOMES IN PEDIATRIC RECIPIENTS OF ABO-INCOMPATIBLE LIVER TRANSPLANTW: AN ANALYSIS OF THE SPLIT REGISTRY

Sarah Bedoyan[1] Bridget Whitehead[2] James Squires[3] Sarah Anderson[4] Ravinder Anand[4] Jeff Mitchell[4] Catherine Chapin[2] The Society of Liver Transplantation[5], [1]University of Pittsburgh Medical Center, [2]Ann & Robert H. Lurie Children's Hospital of Chicago, [3]UPMC Children's Hospital of Pittsburgh, [4]Emmes, [5]n/a

Background: Pediatric liver transplant (LT) waitlist mortality remains high due to shortage of suitable grafts. Accepting an ABO-Incompatible (ABO-I) LT is a strategy to address this issue but has been theorized to have higher rates of vascular and biliary complications and worse outcomes compared to ABO-Compatible (ABO-C) LT. Additionally, variability in ABO-I protocols among centers has not been described. We present an analysis of ABO-I LT patient outcomes using the SPLIT registry and characterize differences in clinical practice. **Methods:** Patients enrolled in SPLIT who received an ABO-I LT between 2011-2022 were eligible. ABO-I patients were matched to ABO-C patients by Status 1A/1B and PELD/MELD score, which resulted in final comparison of 157 ABO-I to 783 ABO-C patients. Separately, a web-based survey was sent to SPLIT investigators to determine whether a center performed ABO-I LTs and identify practice variability. **Results:** ABO-I LT recipients spent significantly less time on the waitlist compared to ABO-C recipients (mean 2.1 months vs. 3.1 months, p-value < 0.001). The ABO-I cohort required more parenteral nutrition (30.6% vs. 18.0%, $p = 0.021$), ventilator assistance (21.7% vs. 12.1%, $p = 0.001$) and ICU care at time of LT (37.6% vs. 26.1%, $p = 0.002$). In the first 30 days post-LT biliary complications were more common in the ABO-I group (12.1% vs. 11.3%, $p < 0.001$), but there were no differences in vascular complications, rates of rejection, or patient and graft survival. Long-term patient and graft survival was equivalent between ABO-I and ABO-C groups (Figure 1).

Survey response rate was 63% (26/46). 17/26 (59%) centers reported performing ABO-I LT, most (53%) considering this option only for children $\leq$ 2 years of age. 46% of centers utilize pre-LT desensitization (rituximab, plasmapheresis, IVIG) and 59% adjust post-LT immunosuppression for ABO-I recipients. Post-LT desensitization is implemented for all patients at 24% of centers and based on anti-ABO antibody titers at 43% of centers. **Conclusion:** Patient and graft survival rates are equivalent between matched ABO-I and ABO-C LT recipients. Some complications may be more common in the ABO-I LT group, however this group was also sicker at time of LT. ABO-I LT is an option that should be considered for children awaiting LT to reduce waitlist mortality. Variability in institutional practices regarding listing and management of ABO-I LT recipients represents an opportunity for future comparative effectiveness studies.



Disclosures: Sarah Bedoyan: Nothing to Disclose, Bridget Whitehead: Nothing to Disclose, James Squires: Sanofi: Data Safety Committee, Mirum: Advisor, Ipsen: Advisor, Sarah Anderson: Nothing to Disclose, Ravinder Anand: Nothing to Disclose, Jeff Mitchell: Nothing to Disclose, Catherine Chapin: Sarepta Therapeutics: Advisor, The Society of Liver Transplantation: Nothing to Disclose

4578 | ◆ ETHICAL CHALLENGES IN PEDIATRIC LIVER TRANSPLANT SELECTION RELATED TO PATIENT AND CAREGIVER SOCIAL DETERMINANTS OF HEALTH: A NATIONAL SURVEY OF CLINICIAN PERSPECTIVES

Danielle Rabinowitz[1] Eliza Lee[1] Christy Cummings[1] Jenna Simes[1] Scott Elisofon[2] Andrew Wehrman[2] Katherine Sweeny[2] Stacy Kahn[1] Christine Lee[1], [1]Boston Children's Hospital, [2]Boston Childrens Hospital

Background: Disparities exist in pediatric liver transplantation in the United States. While prior research has demonstrated inequities in time-to-listing and in waitlist and post-transplant outcomes, clinician perspectives on the role of patient and family social determinants of health (SDoH) on decision-making in pediatric liver transplant selection remain unknown. **Methods:** A national, cross-sectional, mixed methods survey was distributed via email to pediatric liver transplant committee members between June and November 2024.

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The survey assessed institutional voting practices and ethical issues related to SDoH. Quantitative analysis was conducted with summary statistics and multiple linear and logistic regression (Stata v16); free-text responses were qualitatively coded (NVivo v15). **Results:** Of 550 invited participants, 162 (29.4%) completed the survey. Most were transplant hepatologists/gastroenterologists (41.4%), women (70.4%), and white race (77.2%). Listing decisions were typically made via verbal vote (90.1%), with conflicts resolved through further discussion (77.2%), ethics committee consultation (19.8%), or granting the transplant surgeon the tie-breaker vote (16.0%). Transplant surgeons and hepatologists were viewed as most influential in listing decision-making. Clinician moral distress regarding SDoH-related concerns was moderate (5.71 ± SD 2.39/10), with higher distress levels reported by psychosocial providers ($p = 0.006$), transplant hepatologists/gastroenterologists ($p = 0.042$), and women ($p = 0.022$); moral distress among late-career as compared with early-career professionals trended toward significance ($p = 0.087$). Key SDoH concerns included patient/caregiver non-adherence and mental health issues/substance use, housing instability, and insurance status. Ethics committees (53.7%) and child protective services (79.6%) were often involved when non-medical factors created barriers to listing. Qualitative data showed that for pediatric patients, SDoH are not absolute contraindications but often delay listing, require team collaboration, and create post-transplant challenges. **Conclusion:** Patient and family SDoH factors influence decision-making in pediatric liver transplant selection and contribute to clinician moral distress. To promote justice, advocacy should focus on optimizing patient and family support from the listing phase onward, integrating ethics education for clinicians, and adapting more balanced decision-making frameworks.

Table 1. Multiple linear and logistic regression models assessing reported moral distress and moral distress frequency related to the impact of patient and family SDoH factors on pediatric liver transplant listing decision-making

1. Multiple linear regression model assessing reported moral distress rating

			95% CI		
Variable	Beta	SE	LL	UL	p
Tx surgeon	1.02359	0.7314263	-0.4214087	2.468589	0.164
Tx hepatologist/GI	1.114627	0.5447961	0.038333	2.190921	0.042*
Tx coordinator	1.06667	0.6654353	-0.2479574	2.381298	0.111
SW/psychologist	1.868162	0.6637861	0.556793	3.179532	0.006*
Woman	1.128837	0.4876328	0.2654745	2.0922	0.022*
≥ 15 years in clinical practice	-0.667925	0.3872276	-1.432928	0.0970781	0.087
≤ 5 txs/year at healthcare institution	-0.8354642	0.5683084	-1.958209	0.2872803	0.144
≥ 16 txs/year at healthcare institution	0.1961629	0.4007299	-0.5955153	0.987841	0.625

2. Multiple logistic regression model assessing reported moral distress frequency

Variable	OR	SE	LL	UL	p
Tx surgeon	1.078251	0.7000256	0.3020649	3.848927	0.908
Tx hepatologist/GI	0.8819116	0.4255875	0.3424976	2.270872	0.795
Tx coordinator	1.18653	0.7023489	0.3718966	3.785602	0.773
SW/psychologist	3.69367	2.417583	1.024195	13.32234	0.046*
Woman	1.175648	0.5130709	0.4998044	2.76538	0.711
≥ 15 years in clinical practice	1.183746	0.4158838	0.594576	2.356731	0.631
≤ 5 txs/year at healthcare institution	0.9713944	0.5088932	0.3479116	2.712203	0.956
≥ 16 txs/year at healthcare institution	0.7429141	0.5928306	0.8007773	3.325995	0.178

Note. * p<0.05
Legend. Tx=transplant; GI=gastroenterologist; SW=social worker; SDoH= social determinants of health

Disclosures: Danielle Rabinowitz: Nothing to Disclose, Eliza Lee: Nothing to Disclose, Christy Cummings: Nothing to Disclose, Jenna Simes: Nothing to Disclose, Scott Elisofon: Nothing to Disclose, Andrew Wehrman: Albireo: Grant/Research Support, Mirum: Advisor, Katherine Sweeny: Nothing to Disclose, Stacy Kahn: Eli Lilly: Stock - publicly traded company, Christine Lee: Echosens: Grant/Research Support

4579 | ◆ HISTOLOGICAL INJURY PATTERNS IN CHILDREN WITH DRUG-INDUCED LIVER INJURY

Ivan Gonzalez[1] Jean Molleston[1] Naga Chalasani[2] Jiezhun Gu[3] Huiman Barnhart[3] Victoria Shakhin[4] Robert Fontana[5] David Kleiner[6], [1]Indiana University, [2]Indiana University Medical Center, [3]Duke Clinical Research Institute, [4]C. S. Mott Children's Hospital, [5]University of Michigan Hospitals and Health Centers, [6]National Cancer Institute, Bethesda

Background: Pediatric drug induced liver injury (DILI) is rare cause of morbidity and mortality. Liver biopsy can be a valuable part of causality determination and injury severity assessment. There is limited literature regarding histology of DILI in children. **Methods:** Drug-Induced Liver Injury Network database from 2004-2025 was queried for high causality cases in children (< 18 years) with centrally reviewed liver biopsies. Descriptive statistics were used. **Results:** Out of 2711 DILI cases in the database, 88 (3.2%) were from children. 22 were high causality and had liver tissue centrally reviewed. Mean age was 13.8 (range 1.7-17.9) years, 16 (73%) were female; none were known to have underlying chronic liver disease. There were 21 needle biopsies and 1 explant. Causative agents were minocycline (5), azithromycin (3), atomoxetine (3), lamotrigine (2), and nicotine, drospirenone/estradiol, Trikafta, carbamazepine, doxycycline, infliximab, amoxicillin, amoxicillin/clavulanate, and isoniazid (1 each). The median time from DILI onset to biopsy was 16 days (range:13-40), and 32% were treated with steroids (9% at biopsy). Fifteen (68%) had hepatocellular, 4 (18%) mixed and 3 (14%) cholestatic biochemical pattern at onset. Severity was moderate-hospitalized or severe in more than half. The biopsies showed diverse patterns of injury, similar in spectrum to reported patterns in adults: 6 with cholestatic hepatitis, 5 each with acute (lobular) and chronic (portal) hepatitis, 3 with acute (bland) cholestasis and 2 with minimal findings. The explant showed bridging and multi-acinar necrosis with regenerative nodule formation. Inflammatory activity varied, with 6 cases each of minimal and mild, 3 of moderate and 5 of severe inflammation (Ishak Histology Activity Index). 3 cases, including the explant, had bridging fibrosis. 9 (41%) had increased eosinophils, 7 (32%) had increased plasma cells and 7 (32%) had microgranulomas; 27% had steatosis. Three cases had

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endothelialitis of either portal or central veins. One biopsy showed bile duct loss. 5 of 20 children (20%) with 6 month follow up had evidence of chronic liver injury. **Conclusion:** Children with DILI experienced similar range of pathology as seen in adults, with both hepatocellular and cholestatic liver injury represented. Eosinophilia was seen in less than half, and plasmacytosis in one third of biopsies. While most cases showed mild injury overall, a few showed severe inflammation, necrosis, or bridging fibrosis.

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4580 | ◆ BSEP PROTEIN DERIVED FROM CODON-OPTIMIZED HUMAN ABCB11 MRNA IMPROVES BILE ACID TRANSPORT IN BSEP-DEFICIENT HUMAN-INDUCED HEPATOCYTES AND MOUSE MODEL

Karis Kosar[1] Aitaro Takimoto[1] Lupe Sierra[2] Henry Law[2] Esthelle Hoedt[2] Akihiro Asai[1] Maggie Wright[2], [1]Cincinnati Children's Hospital Medical Center, [2]Ultragenyx Pharmaceutical Inc.

Background: Bile Salt Export Pump (BSEP) is a critical transporter of bile acids in hepatocytes encoded by the *ABCB11* gene. Pathogenic variants in *ABCB11* result in functional BSEP deficiency, leading to severe hepatocellular cholestasis, known as Progressive Familial Intrahepatic Cholestasis (PFIC). BSEP deficiency often requires a liver transplant for patient survival; thus, a treatment that restores BSEP activity in a patient's native liver has the potential offer a novel disease-modifying. We sought to test the functional efficacy of an mRNA-LNP approach as one such therapeutic option. **Methods:** *ABCB11* mRNA candidates were screened in primary human hepatocytes for expression intensity and half-life of the BSEP protein. A codon-optimized, pseudo-uridine-modified human *ABCB11* mRNA (named UX123) was selected as the best candidate. We established a cholestasis model in mice lacking BSEP (BSEP-KO) by feeding them a diet containing 0.1% CA and 0.3% G-CDCA. They were treated with 4 mg/kg UX123 encapsulated in lipid nanoparticles up to 5 times over 15 days. BSEP protein, liver size, and blood and liver bile acid levels were assessed. In vitro, BSEP-deficient hepatocytes derived from human induced pluripotent stem cells (iHep) were transfected using lipofectamine with titrating doses of *ABCB11* mRNA. BSEP protein level, capacity of bile transport in Transwell culture system and cell injury were assessed. **Results:** In mouse studies, UX123 treatment led to a significant reduction in the level of multiple bile acid species, as well as a reduction in liver to body weight ratio when comparing treated BSEP-KO mice to vehicle controls. In in vitro models, we found that treatment with *ABCB11* mRNA rescued bile acid transport and prevented bile acid-induced cell injury compared to untreated iHep. We also found that UX123 rescued BSEP deficiency in iHep at surprisingly low levels of BSEP protein expression, suggesting that a relatively small amount of mRNA delivery can induce effective BSEP in the cholestatic liver. **Conclusion:** This proof-of-concept study demonstrates that mRNA-LNP therapy can restore BSEP function in BSEP-deficient hepatocytes in vitro and in vivo. These data provide a foundation for clinical translation and establish a benchmark for minimal effective BSEP expression.

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4581 | MULTICENTER REPORT OF EXCELLENT OUTCOMES FOLLOWING LIVER TRANSPLANT IN SICKLE CELL DISEASE IN CHILDREN AND YOUNG ADULTS

Pamela Valentino[1] Steven Lobritto[2] Juliet Emamaullee[3] Helen Te[4] Ryan Chadha[5] Vani Gopalareddy[6] Mary Alice Boulware[6] William Kitchens[7] Ryan Himes[8] Rima Fawaz[9], [1]University of Washington, [2]Columbia University, [3]Keck Medical Center of USC, [4]University of Chicago Medical Center, [5]Mayo Clinic, Jacksonville, FL, [6]Levine Children's Hospital at Advocate Health, [7]Emory University, [8]Ochsner Clinic Foundation, [9]Yale University

Background: Sickle cell disease (SCD) is associated with hepatopathy: a myriad of acute and chronic liver conditions due to sequalae from intrahepatic red blood cell sickling and increased delivery of bilirubin from hemolysis. Progression to cirrhosis and end-stage liver disease is under recognized and liver transplantation is rarely

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offered; a characterization of transplant management outcomes is lacking in the literature. **Methods:** Multicenter review of patients with SCD (Hemoglobin (Hb) SS or SC) who underwent liver transplantation (LT) between 2010-2020. **Results:** There were 6 patients with SCD who underwent LT at a median age of 16 years (IQR 13,24); 50% female, 83% Black and 17% Hispanic, 67% HbSS and 33% HbSC. SCD therapies employed included hydroxyurea (83%), chronic pRBC transfusion therapy (67%), iron chelation therapy (33%), and RBC exchange transfusions (17%). Gallstone disease with ERCP and cholecystectomy was required in 67%. LT was provided for one patient with biliary atresia (BA) with a non-draining Kasai portoenterostomy at 5 months of age and one patient in acute liver failure (ALF) at 18 years of age. Patients with cirrhosis (4) included 2 with sclerosing cholangitis, 1 with autoimmune hepatitis, and 1 with recurrent cholangitis episodes. Overall time on the waitlist was 32 days (IQR 26,36); median calculated MELD/PELD at LT was 30 (IQR 25,30). Immunizations had been updated prior to LT in 83%. Preoperatively, 1 patient received a pRBC transfusion, 2 patients underwent exchange transfusion, and 1 underwent plasmapheresis; pre-LT HbS was 24g/dL in these cases. In those without transfusion therapy pre-LT, HbS was 7.9, 13 and 20 g/dL. All patients received a deceased donor (DD) whole graft except the infant with BA received a DD split graft. All patients underwent Roux-hepaticojejunostomy apart for the one with ALF who received a duct-to-duct biliary reconstruction. Immunosuppression included corticosteroids and tacrolimus/cyclosporine in all patients. No thymoglobulin was used, however 2 patients received basiliximab and 3 received mycophenolate mofetil. All patients received parenteral anticoagulation initially. There were no vascular or biliary complications in the first year. Hepatic vein stenosis was diagnosed in one patient 2 years postLT and one patient developed a dominant biliary stricture 3 years postLT. Acute T cell rejection was observed in 2 and de novo plasma cell rich rejection was observed in 1. One patient died at 8 years post-LT due to hemorrhage; no retransplants during a median 3 years of follow up. **Conclusion:** Liver transplantation can be successful in patients with SCD. Survival outcomes and the rates of transplant complications are similar to those reported in other LT recipients. Further studies are required to identify optimal management strategies.

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4582 | MOLECULAR SUBTYPES RELATED TO GLUCOSE METABOLISM AND LACTIC ACID METABOLISM AND THEIR PROGNOSTIC CHARACTERISTICS IN HEPATOCELLULAR CARCINOMA

Fengsheng Dai[1] Yi Wang[1] MaoYun Liu[1] sheng wang[1] Cheng Zhang[1] Jiale Lu[1] Yuqin Xie[1] DeWei Li[1] Hui Li[1], [1]Chongqing University Cancer Hospital

Background: Hepatocellular carcinoma (HCC) is a malignant tumor with a high incidence worldwide, with occult onset and rapid progression. The onset of HCC is usually accompanied by liver dysfunction, leading to metabolic reprogramming, which includes sugar metabolism and the production of large amounts of lactic acid. However, the effects of carbohydrate metabolism and lactic acid metabolism on HCC have not been fully clarified. This study aimed to develop a new molecular subtype based on carbohydrate metabolism-related genes (CRGs) and lactate metabolism-related genes (LMRGs) and to identify characteristics that predict the prognosis and treatment outcomes of HCC patients. **Methods:** scRNA-seq and clinical HCC data were downloaded from the TCGA and GEO databases. CRGs and LMRGs are from the Molecular Signature Database. Differential expression analysis was performed via the R software package DESeq2. Molecular subtype classification was performed via unsupervised clustering. Predictive characteristics were determined via univariate Cox regression, random forest, LASSO, and multivariate Cox regression analyses. Finally, in vitro and in vivo experiments were used to verify the impact of the key gene HPX on the biological function of HCC tumors. **Results:** We classified 365 HCC patients into 2 molecular subtypes and were able to clearly distinguish their prognosis. The C2 subtype is associated with a worse prognosis, with a lower proportion of CD4+ T cells, and the expression of immune checkpoint genes is generally elevated in C2 patients with severe immune dysfunction. We subsequently constructed a predictive model, the CLM score, which can effectively predict the prognosis of HCC patients and the efficacy of immunotherapy. The CLM scores were verified in the GSE14520, GSE151530 and IMvigor210 datasets. Patients with high CLM scores showed high infiltration of activated CD4+ T cells and other cells in the immune microenvironment. Finally, in vitro cell experiments confirmed that HPX can inhibit the proliferation, migration and invasion of HCC cells. **Conclusion:** We constructed new molecular subtypes related to carbohydrate metabolism and lactate metabolism and revealed their immunological and genetic characteristics. We have also developed a CLM scoring system that can be used to predict the prognosis and efficacy of immunotherapy in patients with HCC.

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4583 | RESTORATION OF PORTAL CIRCULATION IN CHILDREN WITH CONGENITAL PORTOSYSTEMIC SHUNTS RESULTS: IN SPONTANEOUS INVOLUTION OF HEPATIC MASSES

Riccardo Superina[1] Matthew Switalski[1] Esther Ro[1] Ian Gelarden[1] Anita Gupta[2], [1]Ann and Robert H. Lurie Children's Hospital of Chicago, [2]Nationwide Children's Hospital

Background: Congenital portosystemic shunts (CPSS) may be associated with benign or malignant liver lesions. In this study, we describe the evolution of liver masses that take place after surgical ligation of shunts and restoration of portal circulation to the liver. **Methods:** A retrospective review was done of all patients diagnosed with CPSS in the 25 years from 1999-2024 at a single pediatric center. MR and CT were used for radiological characterization of lesions. Liver biopsies were reviewed by two pediatric pathologists utilizing light microscopy and molecular characterization. Serial MRI following ligation was used to document changes in the number and size of the lesions. Lesions were grouped according to pathological diagnosis and changes in size documented. Age at procedure was compared between those with lesions and those without using a Mann-Whitney U test. Lesion sizes at pre-op and 1-year post-op were compared using paired t-tests. **Results:** One hundred fifteen patients with CPSS were included. Thirty-two (27.8%) had liver masses. The median (interquartile range) age in years of children with masses was significantly higher than those without masses at diagnosis: median 12.2 IQR (4.4-15.8) and median 4.2 IQR (1.9-10.4) respectively ($p = 0.001$) Six patients had 1 lesion, 18 had between 2 and 10, and 8 had more than 10 lesions. Twenty-three patients underwent 35 needle, wedge, or excisional biopsies. Biopsies were diagnostic of 23 hepatocellular adenomas (HCA), 21 with β-catenin activation, of which 12 were confirmed to have pathogenic CTNNB1 mutations. Two had HNF1α inactivation alone, and 4 lesions expressed both mutations. There were 3 hepatocellular carcinomas (HCC) and 4 FNH or regenerative nodules. The three patients with HCC were transplanted, and all other patients underwent closure of the CPSS. Of the patients with HCA, 6 lesions were resected, five underwent a significant reduction in size and 7 resolved completely within a year of shunt ligation ($t(11) = 9.1$, $p < 0.001$, Cohen's $d = 0.69$). All 4 patients with FNH underwent spontaneous resolution or decrease in size ($t(3) = 6.7$, $p = 0.006$; Cohen's $d = 0.48$). All patients are alive and well at the end of the observation period. **Conclusion:** HCA and FNH lesions involute completely or reduce in size within two years of surgery. Patients with CPSS associated hepatic lesions including β-catenin mutated HCA may be safely treated solely with shunt ligation and careful observation.

Table 1. Outcomes of Lesions with Follow-up Imaging by Diagnosis

	Shrunk	Resolved	Resected	Total
HCA				
β-catenin activated	3	4	4	11
β-catenin activated, HNF1α inactivated	0	1	0	1
β-catenin activated, Inflammatory type	2	3	2	7
HNF1α inactivated	0	0	0	0
FNH	2	2	0	4
RN	0	0	2	2
	8	10	9	26

Disclosures: Riccardo Superina: Nothing to Disclose, Matthew Switalski: Nothing to Disclose, Esther Ro: Nothing to Disclose, Ian Gelarden: Nothing to Disclose, Anita Gupta: Nothing to Disclose

4584 | RECTUS FEMORIS MUSCLE QUANTITY AND QUALITY IS ASSOCIATED WITH PEDIATRIC LIVER-RELATED OUTCOMES, INCLUDING LIVER TRANSPLANTATION (LT) AND MORTALITY

Christopher Chu[1] Victor Yu[2] Cameron Willis[3] Jennifer Dodge[3] Sindhura Kasturi[2] Patricia Acharya[2] David Rigual[2] Norah Terrault[3], [1]Rady Children's Hospital, [2]Children's Hospital Los Angeles, [3]University of Southern California

Background: Sarcopenia predicts morbidity and mortality in adults with end-stage liver disease. However, data on sarcopenia and liver-related outcomes in children remain limited. We examined ultrasound (US) measurements of the readily accessible rectus femoris muscle in children with chronic liver disease (CLD) and the outcome of liver failure (Liver Transplantation [LT] or death). **Methods:** Prospective cohort of participants ≤18 years with CLD with US measures for 4 sonographic parameters of the rectus femoris muscle [cross-sectional area (CSA), muscle thickness (MT), fascicle length (FL) and echogenic intensity (EI)], and baseline anthropometrics including mid-upper arm circumference (MUAC) and BMI. Outcomes were liver failure,

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decompensation (GI bleed, ascites, hepatic encephalopathy, hyperammonemia, hepatopulmonary or hepatorenal syndrome, LT), and hospitalization within one year. Associations of US muscle parameters and outcomes were explored by logistic regression. **Results:** Of 66 participants (43.9% male; median age 7.5 years [IQR 1.7-13.6], 19.5% malnourished [by BMI z-score] and 44% had advanced fibrosis/cirrhosis [F3/F4]), 22 (33.3%) developed liver failure within 1 year. Participants with liver failure were younger and had lower MUAC z-scores but were similar by sex, and BMI z-score. Increasing quantitative muscle parameters (CSA, MT, FL) were associated with decreasing odds of liver failure (all $p < 0.01$) whereas increasing EI to MT ratio was associated with increasing odds of liver failure ($p = 0.002$). These associations remained after adjusting for advanced hepatic fibrosis status (all $p < 0.05$, except EI) but were attenuated with age and fibrosis-adjustment (Table 1).

Within 1 year, 35 (53.0%) were hospitalized and 6 decompensated (16.2% of the 37 compensated at baseline). Odds of hospitalization were lower with increases in quantitative muscle parameters (CSA, MT, and FL) (all $p < 0.05$), but only FL was statistically significant after age- and fibrosis-adjustment ($p = 0.04$). Sample size was too small for statistical analysis of decompensation. **Conclusion:** This study is the first to assess ultrasound-based muscle measurements in children with chronic liver disease in relation to clinical outcomes. Younger age and decreased CSA, MT and FL of the rectus femoris muscle are associated with liver failure whereas greater EI to MT ratio was associated with decreased odds of liver failure—although not statistically significant after adjusting for age and fibrosis status. Lastly, increasing fascicle length was associated with lower hospitalization risk even after adjusting for age and fibrosis status suggesting that this ultrasound parameter may be an important measure for risk stratification. This study highlights the role that muscle health may have in transplant waitlist outcomes and warrants further investigation.

Table 1. Age- and Fibrosis-Adjusted Logistic Regression Model of Ultrasound Measures as Predictor of Liver Failure Hospitalization

Muscle Measure	Liver Failure		Hospitalization	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Cross-Sectional Area*	0.50 (0.11 – 2.17)	0.35	0.38 (0.10 – 1.39)	0.14
Muscle Thickness*	0.63 (0.21 – 1.86)	0.40	0.52 (0.22 – 1.23)	0.14
Fascicle Length*	0.61 (0.21 – 1.78)	0.36	0.36 (0.14 – 0.93)	0.04
Echogenic Intensity*	1.62 (0.71 – 3.74)	0.25	1.18 (0.59 – 2.36)	0.64
Echogenic Intensity/Muscle Thickness	1.14 (0.89 – 1.47)	0.29	1.14 (0.88 – 1.48)	0.34

* Per 1-Standard Deviation increase from the mean

Disclosures: Christopher Chu: Mirum Pharmaceuticals: Consultant, Victor Yu: Nothing to Disclose, Cameron Willis: Nothing to Disclose, Jennifer Dodge: Nothing to Disclose, Sindhura Kasturi: Nothing to Disclose, Patricia Acharya: Nothing to Disclose, David Rigual: Nothing to Disclose, Norah Terrault: Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, ImmunoCore: Grant/Research Support, HBV Foundation: Board member, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role

4585 | SIGNIFICANT INCREASE IN DONOR-DERIVED CELL-FREE DNA LEVELS IN PEDIATRIC LIVER TRANSPLANT RECIPIENTS WITH REJECTION COMPARED TO NORMAL LIVER HISTOLOGY

Andres Rivera[1] Bridget Whitehead[1] Batul Kaj-Carbaidwala[1] Alyssa Kriegermeier[1] Catherine Chapin[1], [1]Ann & Robert H. Lurie Children's Hospital of Chicago

Background: Donor-derived cell-free DNA (dd-cfDNA) is a promising noninvasive biomarker of rejection in adult liver transplant (LT) recipients, but its utility in children remains unknown. We aimed to determine the relationship between peripheral blood dd-cfDNA and histologic findings in pediatric LT recipients undergoing for-cause and surveillance liver biopsies. **Methods:** Prospective single-center study of pediatric LT recipients $\geq$ 6 months of age undergoing for-cause and surveillance liver biopsies 6/5/2024–4/25/2025. Biopsies were classified into 3 histologic groups: rejection (AR) (T-cell mediated, chronic, and plasma-cell rich), acute dysfunction non rejection (ADNR), or normal liver (NL). Peripheral blood at time of liver biopsy was collected for dd-cfDNA analysis. **Results:** 42 subjects were enrolled, 64% ($n = 27$) female, with median age 14.5 years (IQR 10.9-17.0) and 9.5 years (IQR 5.0-13.7) post LT. 74% of grafts were technical variant and 31% were living donor. 17 (40%) biopsies were for-cause and 25 (60%) were surveillance. There were 18 patients in the AR group (12 T-cell mediated, 4 chronic, 1 plasma-cell rich, 1 T-cell mediated and biliary stricture), 8 ADNR (all non-specific inflammation), and 16 NL. There were no differences in dd-cfDNA by graft or donor type. Patients undergoing for-cause biopsies had increased dd-cfDNA compared to surveillance biopsies (median 22.6% vs 10.5%, $p = 0.007$). ALT, AST, and GGT were higher in the AR compared to other groups ($p < 0.001$ for all comparisons). Median dd-cfDNA values were significantly higher in the AR compared to the NL group (20.2% vs 7.5%, $p = 0.02$) (Figure 1A). There was a moderate positive correlation between dd-cfDNA and ALT values for the AR group (Pearson $r = 0.53$). Receiver operator characteristic curve analyses for dd-cfDNA were statistically significant with AUC value 0.73 for AR vs NL ($p = 0.02$, 9.0% cutoff) and AUC = 0.70 for AR vs non-AR (NL+ADNR) ($p = 0.03$, 18.4% cutoff) (Figure 1B). All patients in the NL group had liver enzymes $\leq$1.5xULN at time of surveillance

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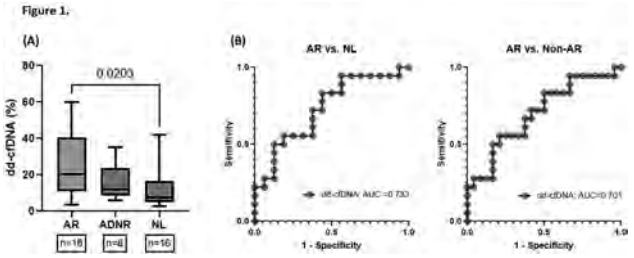
biopsy, but 6 (38%) had dd-cfDNA levels that would classify them as acute rejection based on published adult LT thresholds (AR vs non-AR 15%). **Conclusion:** Dd-cfDNA levels are significantly increased in pediatric LT recipients with biopsy-proven rejection and may be a useful biomarker of graft injury. More data is needed in pediatric patients to determine the predictive value of this test, pediatric-specific cut-offs, and the significance of elevated values in the NL group.



Disclosures: Andres Rivera: Nothing to Disclose, Bridget Whitehead: Nothing to Disclose, Batul Kaj-Carbaidwala: Nothing to Disclose, Alyssa Kriegermeier: Mirum Pharmaceuticals: Advisor, Catherine Chapin: Sarepta Therapeutics: Advisor

4586 | THE CONTEXT-DEPENDENT ROLE OF CELLULAR SENESCENCE IN BILIARY ATRESIA

Katie Rose Conover[1] Franziska Lammert[2] Eric Katz[3] Ronald Sokol[1] Sarah Taylor[1], [1]University of Colorado School of Medicine, [2]University Hospital Aachen, [3]University of Colorado

Background: Cellular senescence supports tissue repair but if dysregulated can contribute to disease, in part by immune cell modulation. Increased senescence is present in biliary atresia (BA), but its role in disease progression remains poorly defined. We aimed to explore immune-senescent cell networks based on BA disease stage and patient outcome. **Methods:** We used multiplex histology to identify cell densities in liver tissue (cholangiocytes: CK19; senescence: P21; T regs: CD3, FOXP3; TREM2+ macrophages [Mφ]: CD68, TREM2) in BA at diagnosis (BADx, n = 17), BA at transplant (BATx, n = 22), cholestatic controls (CC, n = 13), and non-cholestatic controls (NCC, n = 7). Targeted serum proteomics detected 61 senescence-associated secretory proteins (SASPs) and 39 BA-related proteins in BADx (n = 12), BATx (n = 12), CC (n = 12) and NCC (n = 10). Statistical analysis compared all groups and BA groups by outcome (survival with native liver $\geq$ 2 years [favorable outcome] vs $<$ 2 years [poor outcome]). **Results:** Among all groups, cholangiocyte density was highest in the BA groups ($p = 0.02$), but there were no significant differences in senescent or immune cell subsets. BADx with favorable outcome had greater senescent cholangiocytes ($p = 0.01$), TREM2+ Mφ ($p = 0.01$), and T reg densities ($p = 0.04$). Total Mφs, TREM2+ Mφs, and T regs correlated with senescent cells ($r = 0.654$, $r = 0.761$, $r = 0.639$ respectively, $p < 0.05$ for all). Among all groups, 30 SASPs and 17 BA-associated proteins significantly differed (p adj < 0.05). Nine of 10 SASPs differing between BADx and BATx were higher at transplant (p adj < 0.05, FC > 1.5, Figure 1A). BADx patients separated discreetly by outcome (Figure 1B). Of the top 20 proteins driving this separation (Figure 1C), most (9 of 11) SASPs were associated with poor outcome. Pathway analysis revealed BADx patients with poor outcome had IL-6/JAK/STAT3 activation (p adj 7.45 e-7), which is known to regulate oxidant-induced senescence in fibroblasts. BADx patients with favorable outcome had HIF-1a stabilization (p adj 0.02), which could be related to increased antioxidant gene expression. **Conclusion:** In BADx, liver tissue senescence is associated with favorable outcome, while SASPs are associated with poor outcome and progress over disease course. Our data highlight the dynamic and context-dependent nature of senescence. Impaired redox homeostasis may modulate senescence and contribute to discrepant BA outcomes, warranting exploration of senescent cell driven oxidative-stress modulating therapies.

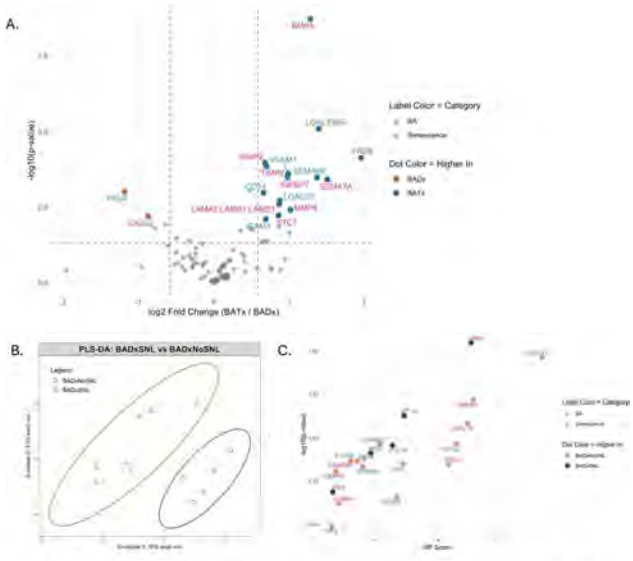


Figure 1. (**A**) Volcano plot displaying differentially expressed proteins in biliary atresia (BA) at diagnosis versus transplant (FDR <0.05, fold change >1.5). Nine of the 10 senescence-associated secretory proteins that differ are higher at transplant. (**B**) Partial least squares discriminant analysis (PLS-DA) plot with 95% confidence intervals shaded, showing separation of BA at diagnosis with favorable (survival with native liver ≥2 years) versus poor (survival with native liver <2 years) outcome. (**C**) Variable importance in projection (VIP) plot showing the top 20 proteins contributing to the PLS-DA plot in (B). Most senescent proteins are higher in BA at diagnosis with poor outcome.
BADx: BA at diagnosis, BATx: BA at transplant, BADxNoSNL: BA at diagnosis with survival with native liver <2 years (poor outcome), BADxSNL: BA at diagnosis with survival with native liver ≥2 years (favorable outcome)

Disclosures: Katie Rose Conover: Nothing to Disclose, Franziska Lammert: Nothing to Disclose, Eric Katz: Nothing to Disclose, Ronald Sokol: Mirum: Advisor, Ipsen/Albireo: Advisor, Malinkrodt: Consultant, Alexion: Consultant, Sarah Taylor: Mirum Pharmaceuticals: Consultant, Ipsen Pharmaceutical: Consultant, Mirum

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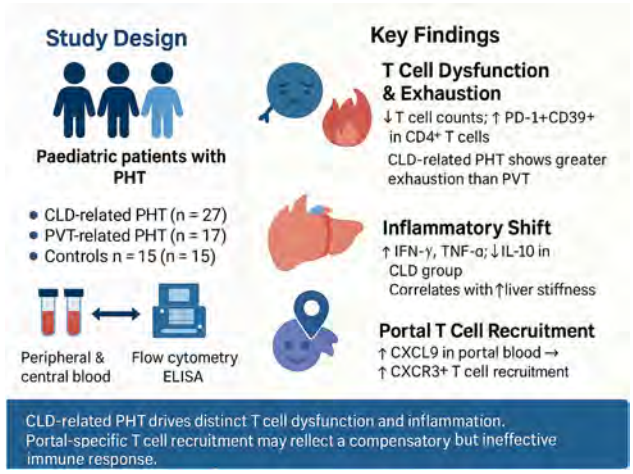
4587 | ALTERED T CELL PROFILE MAY CONTRIBUTE TO THE IMMUNE DYSREGULATION IN CHILDREN WITH PORTAL HYPERTENSION: A PILOT STUDY

Tengfei Si[1] huihong yu[2] Qing Shao[3] Bethany Tucker[4] Eirini Kyrana[5] Yun Ma[6] Tassos Grammatikopoulos[7], [1]Zhejiang University School of Medicine, [2]Department of Gastroenterology, The Second Affiliated Hospital, Chongqing Medical University, [3]King's College London, [4]Institute of Liver Studies, King's College, London, United Kingdom, [5]Paediatric Liver, GI & Nutrition Centre, King's College Hospital NHS Trust, London, United Kingdom., [6]Institute of Liver Studies, King's College London, United Kingdom, [7]King's College Hospital

Background: While portal hypertension (PHT) is associated with elevated pro-inflammatory cytokines, T cell immune alterations in pediatric PHT remain understudied. This study provides a comprehensive analysis of T cell phenotypic and functional changes in children with PHT. **Methods:** Forty-four children with PHT (chronic liver disease (CLD)-related PHT, n = 27; portal vein thrombosis (PVT)-related PHT, n = 17) and 15 paediatric controls without liver disease were prospectively recruited. Six paired blood samples (peripheral and central blood) were collected. Plasma and peripheral blood mononuclear cells (PBMCs) were isolated from blood. Immune markers, cytokines, and chemokines were detected, and T cell phenotyping and functional testing were performed using ELISA or multiparameter flow cytometry. Statistical analysis was conducted to assess group differences and correlations with liver parameters such as stiffness using GraphPad Prism (version 9). **Results:** CLD-related PHT patients showed reduced T cell counts and elevated CD39/CD38 expression in CD8+ and DN T cells. Both PHT groups had higher CD39 expression and increased IFN-γ but reduced IL-10 production in non-CD8 T cells, along with elevated exhausted CD4 T cells (PD-1$^+$CD39$^+$). PVT-related PHT uniquely showed CXCR3 downregulation in DN T cells and CCR4 upregulation in CD4+ T cells. Soluble CD25 was decreased, while PD-L1, IFN-γ, and TNF-α were elevated and correlated with liver stiffness in CLD-related PHT. Portal CXCL9 levels were higher than peripheral and associated with CXCR3$^+$ T cell recruitment, though these central T cells showed reduced pro-inflammatory and cytotoxic capacity. **Conclusion:** CLD-related PHT in children is linked to more profound T cell dysregulation and inflammation, suggesting immune mechanisms may contribute to disease progression and represent potential therapeutic targets.



Disclosures: Tengfei Si: Nothing to Disclose, huihong yu: Nothing to Disclose, Qing Shao: Nothing to Disclose, Bethany Tucker: Nothing to Disclose, Eirini Kyrana: Nothing to Disclose, Yun Ma: Nothing to Disclose, Tassos Grammatikopoulos: Nothing to Disclose

4588 | SPATIAL MOLECULAR IMAGING REVEALS AN EVOLVING INFLAMMATORY INFILTRATE AND PROLIFERATING STEM-LIKE CELLS WITH LIVER DISEASE PROGRESSION IN BILIARY ATRESIA (BA)

Tyler Yasaka[1] Mylarappa Ningappa[2] Chethan Ashokkumar[2] Stefan Scholz[2] Simon Horslen[2] Joseph Glessner[3] Hakon Hakonarson[3] Rakesh Sindhi[2], [1]University of Pittsburgh, [2]Children's Hospital of Pittsburgh of UPMC, Hillman Center for Pediatric Transplantation, [3]Center for Applied Genomics (CAG), Children's Hospital of Philadelphia, University of Pennsylvania

Background: To define architectural and immunological-inflammatory landscape of liver disease progression in BA. **Methods:** Residual formalin-fixed-paraffin embedded sections were obtained from normal pre-perfusion donor liver, and biopsies at portoenterostomy (PE) from a child with native liver survival (BA-PE-NLS), and at PE (BA-PE (prog) and liver transplantation (BA-LT) from a child with progressive BA. Spatial molecular imaging was performed with 6000 genes on the CosMx platform (Nanostring). Cell-specific genes were used to enumerate hepatocytes, cholangiocytes, stellate cells, macrophages, neutrophils, B-cells and T-cells. **Results:** A total of 301742 cells were visualized across 326 fields of view (FOVs), 0.25mm by 0.25 mm each, averaging 75435 cells across 81 FOVs in each of four biopsies.

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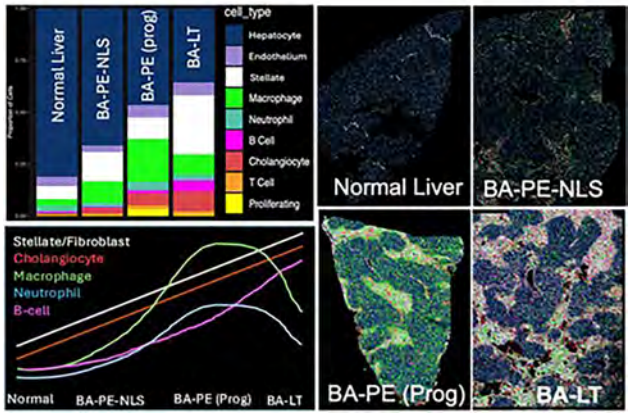
Spatial molecular images (Figure 1) revealed progressive increases in cell proportions ($p < 0.001$), from normal to BA-PE-NLS, BA-PE (prog) and BA-LT for cholangiocytes (0.9%, 3%, 6%, 10%), stellate cells (6%, 14%, 10%, 28%) and B-cells (1%, 1%, 2%, 5%). Macrophages (3%, 11%, 21%, 10%), neutrophils (3%, 2%, 4%, 3%) and T-cells (0.1%, 1%, 2%, 2%) peaked in BA-PE (prog). A novel cell population with upregulated proliferation (PCNA, MCM6) replicative stress (CHEK2, CHEK1, MSH1), epithelial (EPCAM), cytoskeletal/cholangiocytic (MYH9, TMSB4X, TUBB, KRT7, KRT19) and hepatoblast markers (HNF1, HNF4) also increased progressively and suggested a less differentiated stem-like cell which made up $< 1\%$ of cells in normal and BA-PE-NLS, increased 10-fold to 3% in BA-PE (prog) ($p < 0.001$) and declined to $< 1\%$ in BA-LT. Among 1442 upregulated genes in this stem-like cell, 18 were ciliary planar polarity effectors (CPLANE, e.g. ADD3) and 27 were non-CPLANE genes (e.g., MCM6, KIF23) with known BA-associated common and rare variants, respectively (PMID: 37572794). **Conclusion:** Replicative stress, stemness and upregulated developmental BA susceptibility genes, and a monocyte-rich inflammatory infiltrate are demonstrable at portoenterostomy in the BA liver which progresses to cirrhosis and transplantation, but not in the liver with non-progressive BA. Increasing B-cell infiltrates with disease progression suggest possible autoimmune damage, which requires further study.

Figure 1



Disclosures: Tyler Yasaka: Nothing to Disclose, Mylarappa Ningappa: Nothing to Disclose, Chethan Ashokkumar: Nothing to Disclose, Stefan Scholz: Nothing to Disclose, Simon Horslen: Nothing to Disclose, Joseph Glessner: Nothing to Disclose, Hakon Hakonarson: Nothing to Disclose, Rakesh Sindhi: Plexision: Executive role

4589 | PROTECTIVE EFFECTS OF BUTYRATE ALONG THE GUT LIVER AXIS IN A MURINE MODEL OF PARENTERAL NUTRITION

Colin Shearn[1] Aimee Anderson[1] Michael Devereaux[1] Ronald Sokol[2], [1]University of Colorado Anschutz Medical Campus, [2]University of Colorado School of Medicine

Background: Using a mouse model of Parenteral Nutrition Associated Cholestasis (PNAC) in which PN infusion results in increased liver injury and ileal dysfunction replicating human PNAC, we have recently shown that administration of parenteral nutrition results in discordant expression of circadian transcription factors between the ileum and liver. Dietary supplementation of short chain fatty acids such as butyrate are known to improve intestinal barrier function and ameliorate hepatic injury in mice. The aim of this study was to examine the protective effect of sodium butyrate on PN-induced hepatic injury and uncoupling of the gut-liver circadian axis. **Methods:** WT adult C57/B6 mice were exposed to Chow or continuous soy oil lipid emulsion-based total PN infusion +/- inclusion of sodium butyrate (9mM) through a central venous catheter for 4 days. Water was provided ad libitum, but no nutrients were provided enterally. On d4, mice were sacrificed at 7AM, serum harvested, and ileal and hepatic tissue obtained. From tissue samples, relative expression of CR transcription factors, Fxr signaling and gut permeability were assessed. **Results:** Administration of 4d PN increased hepatic injury (AST, ALT) and inflammatory cytokine mRNA expression which was ameliorated by addition of sodium butyrate. In the liver, butyrate significantly suppressed *Nr5a2* (LRH1), *Abcg5*, *Abcb11* (BSEP) mRNA expression, but did not have a significant effect on *Abcc2* which was already suppressed by PN. Concurrently, butyrate supplementation normalized PN-altered hepatic mRNA expression of *Nr1d1* (Reverba), *Nfil3, Npas2, Cry1, Cry2, Bhlhe40* (Dec1) and *Bhlhe41* (Dec2) but did not have an effect on *Arntl* (Bmal), *Clock*, *Per1* or *Per2*. In cultured Huh7 cells, butyrate supplementation mimicked hepatic effects. In the ileum, with the exception of *Arntl* and *Bhlhe41*, butyrate suppressed PN-dependent increases in circadian transcription factor expression. Finally, addition of butyrate reversed PN-dependent changes in intestinal permeability and suppressed ileal HDAC signaling. **Conclusion:** Dysregulation of circadian regulatory machinery is in part due to uncoupling of the gut-liver circadian axis. Supplementation of Butyrate into the PN solution ameliorates PN-dependent hepatic injury, improves gut permeability and restores expression of Nr1d1. Thus, the use of short chain fatty acids for preventing or treating PNAC deserves further investigation.

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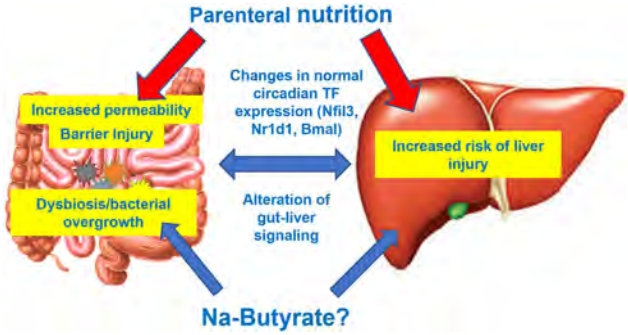

Disclosures: Colin Shearn: Nothing to Disclose, Aimee Anderson: Nothing to Disclose, Michael Devereaux: Nothing to Disclose, Ronald Sokol: Mirum: Advisor, Ipsen/Albireo: Advisor, Malinkrodt: Consultant, Alexion: Consultant

4590 | BASILIXIMAB DOSING IN PEDIATRIC LIVER TRANSPLANTATION (LT) RECIPIENTS: STARZL NETWORK EXPERIENCE

Or Steg Saban[1] Nadya Nalli[1] Evelyn Hsu[2] Anna Peters[3] Steven Lobritto[4] Catherine Chapin[5] Frank DiPaola[6] Regino Gonzalez-Peralta[7] Emily Perito[8] James Squires[9] George Mazariegos[9] Vicky Ng[10], [1]The Hospital for Sick Children, Toronto, ON, Canada., [2]Seattle Children's and the University of Washington, PO Box 5371/OB.9.640, Seattle, WA 98155, USA., [3]Cincinnati Children's Hospital Medical Center, [4]Columbia University Irving Medical Center, New York, NY, USA., [5]Ann and Robert H. Lurie Children's Hospital of Chicago, [6]University of Virginia, UVA Health Children's Health, Charlottesville, VA., [7]AdventHealth for Children, [8]University of California, San-Francisco, USA., [9]Children's Hospital of Pittsburgh, [10]Hospital for Sick Children

Background: A recent audit of immunosuppression induction protocols for infants and children undergoing liver transplantation (LT) at Starzl Network for Excellence in Pediatric Transplantation (SNEPT) centers identified two approaches to basiliximab dosing: fixed dose by body weight (FDBW,10 mg for patients <35 kg, 20 mg for ≥ 35 kg) or body surface area dosing (BSAD, 12 mg/m² per dose, maximum 20 mg). Given limited clinical evidence favoring either approach, we aimed to compare short-term outcomes of FDBW versus BSAD basiliximab dosing in pediatric LT recipients. **Methods:** This retrospective multicenter study analyzed SNEPT records of children receiving basiliximab induction following isolated LT (2005- 2024). Outcomes assessed were center-determined T-cell mediated rejection (TCMR), serum creatinine, readmissions in the first year, and mortality at three intervals: transplant-to-discharge, discharge to 6-months, and 6-12 months. Fisher's exact test compared categorical variables; Mann-Whitney U test compared group means of nonrelated samples. A nearest-neighbor propensity score matching (PSM) approach was utilized, matching in a 1:2 ratio with a calliper of 0.1, based on age, days until discharge, weight, and height at LT. Outcomes were analyzed using the Mantel-Haenszel chi-square test for categorical variables and generalized estimating equations for continuous variables. **Results:** A total of 191 pediatric LT recipients (for indications of Biliary Atresia (21%), primary liver malignancy (14%) and metabolic disease (14%)) at 8 SNEPT sites received basiliximab induction, with 155 (81%, 50% female, median age 40 months (IQR 10–172)) receiving FDBW and 36 (19%, 42% female, median age 25 months (IQR 9-67)) receiving BSAD. Median basiliximab dose was significantly lower in the BSAD group (5.9 mg, IQR 4.7–8.2) compared to FDBW (10 mg, IQR 10–20; $p<0.001$). TCMR during the initial LT admission occurred in 16/155 (10%) receiving FWBD and 4/36 (11%) receiving BSAD ($p = 1.0$). Seventy FWBD patients were matched to 35 BSAD patients, showing comparable baseline characteristics and confirming no difference in TCMR prevalence during the initial LT admission (BSAD: 3/35 [8.6%] vs. FWBD: 7/70 [10%], $p = 0.9$). Other outcomes are presented in Table 1. **Conclusion:** Children receiving BSAD of basiliximab after LT were exposed to lower doses than those receiving FWBD. Lower TCMR rates were observed in the BSAD group at 6–12 months. These findings suggest that BSAD may serve as an effective and resource-efficient alternative for immunosuppression induction in pediatric LT, potentially reducing both immunosuppression exposure and associated costs. Prospective studies are warranted to further evaluate its clinical and economic benefits.

This abstract is submitted on behalf of STARZL Network.

Table 1: Short-Term Clinical Outcomes Before and After Propensity Score Matching in Patients Receiving BSAD vs. FDBW Basiliximab Induction

	BSAD (n=36)	FDBW (n=155)	P
Results Before PSM			
Days till discharge	19.5 (15-35)	19 (13-35)	0.48
TCMR by discharge	4 (11)	16 (10)	1
TCMR discharge- 6 mo	5 (14)	21/126 (16.7)	0.8
TCMR 6-12 mo	0	20/118 (17)	0.008
Readmissions 6 mo	18/35 (51)	98/138 (71)	0.03
Readmissions 6-12 mo	14/35 (40)	94/124 (76)	<0.001
Creatinine 6 mo (mg/ dL)	0.28 (0.2-0.36, n=34)	0.4 (0.25-0.7, n=119)	0.001
Creatinine 12 mo	0.33 (0.24-0.4, n=35)	0.4 (0.3-0.7, n=110)	0.004
Results After PSM	(n=35)	(n=70)	
TCMR by discharge	3 (8.6)	7 (10)	0.9
TCMR discharge to 6 mo	4 (11.4)	8/59 (13.6)	0.98
TCMR 6-12 mo	0	10/57 (17.5)	0.02
Readmissions 6 mo	17/34 (49)	48/64 (69)	0.02
Readmissions 6-12 mo	14/34 (40)	50/60 (71)	<0.001
Death by 6 mo	0	0	
Death by 12 mo	0	3 (4.3)	0.54
Creatinine 6 mo (mg/ dL)	0.28 (0.2-0.36)	0.3 (0.2-0.5)	0.01
Creatinine 12 mo (mg/dL)	0.33 (0.24-0.4)	0.34 (0.22-0.5)	0.1

Note: Data presented as n (%) or median and interquartile range. Abbreviations: BSAD, body surface area dose; FDBW, fixed dose by body weight; TCMR, T-cell mediated rejection; PSM, propensity score matching.

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4591 | ANTISENSE OLIGONUCLEOTIDE-MEDIATED UPREGULATION OF JAGGED-1 EXPRESSION AMELIORATES DISEASE PHENOTYPES IN AN ALGS MOUSE MODEL

Lingdi Zhang[1] Nima Niknejad[1] Jian Li[1] Lansha Peng[1] Surendra Jain[1] Rich Thai[1] Ye Xu[1] Xing xian Yu[1] Yanfeng Wang[1] Xuehai Liang[1], [1]ARNATAR THERAPEUTICS INC

Background: Alagille Syndrome (ALGS) is a rare autosomal dominant multisystem disorder, primarily affecting the liver, with potential involvement of the heart and other organs. Hepatic manifestations, including cholestasis due to bile duct paucity, often result in progressive liver dysfunction and life-threatening complications. Current treatment are largely supportive and symptomatic, without directly addressing the underlying genetic etiology, highlighting a significant unmet clinical need. In approximately 95% of ALGS cases, pathogenic variants in the *JAG1* gene lead to haploinsufficiency and impaired bile duct morphogenesis during early development. Thus increasing Jag1 protein levels provides a promising approach to treat ALGS from the root cause. **Methods:** To enhance JAG1 protein expression, antisense oligonucleotides (ASOs) were developed using Arnatar's ACT-UP1 platform, which boosts translational efficiency. ASOs were delivered to normal and ALGS patient-derived cells via transfection or free uptake, and JAG1 protein levels were measured by Western blot. Off-target effects were assessed through Western blotting of predicted proteins and transcriptome-wide RNA sequencing. In vivo studies in BALB/c and ALGS diease mice with *Jag1* heterozygous knockout were performed by 2–3 subcutaneous injection of the ASOs, followed by analysis of liver JAG1 protein levels and bile duct structure. Tolerability was evaluated in mice, neonatal ALGS models, rats, and non-human primates. **Results:** The optimized ACT-UP1 ASO, ART4, increased JAG1 protein levels by 40–80% across stable cell lines from humans, mice, rats, and monkeys. In ALGS patient-derived cells, ART4 elevated JAG1 levels 1.4- to 1.7-fold post-transfection. Western blot or RNA sequencing detected no off-target effects, confirming high specificity. In vivo, ART4 (1–6 mg/kg) increased JAG1 expression by 34–100% in mice, rats, and monkeys, with upregulation effects lasting 30–60 days. Functional assays confirmed Notch pathway activation. In neonatal *ALGS* disease mice, three weekly doses of ART4 improved JAG1 expression, bile duct architecture, somatic growth, and liver biomarkers (bile acids, bilirubin, ALT/AST). No safety issues were observed across species, even at higher doses. **Conclusion:** ART4 is a first-in-class, potentially disease-modifying ASO that specifically upregulates

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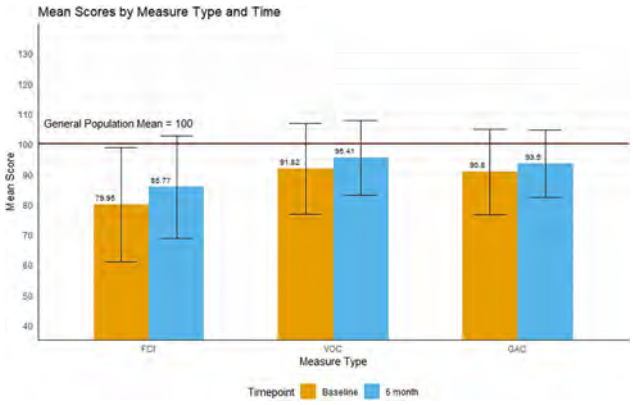
JAG1, promotes bile duct development, and reduces liver toxicity with durable efficacy and a strong safety profile in animal models. These preclinical findings support its potential to transform ALGS treatment by directly targeting its genetic cause.

Disclosures: Lingdi Zhang: Nothing to Disclose, Nima Niknejad: Nothing to Disclose, Jian Li: Nothing to Disclose, Lansha Peng: Nothing to Disclose, Surendra Jain: Nothing to Disclose, Rich Thai: Nothing to Disclose, Ye Xu: Nothing to Disclose, Xing xian Yu: Nothing to Disclose, Yanfeng Wang: Nothing to Disclose, Xuehai Liang: Nothing to Disclose

4592 | SURGICAL CORRECTION OF EXTRAHEPATIC PORTAL VEIN OBSTRUCTION AND CONGENITAL PORTOSYSTEMIC SHUNTS IMPROVES NEUROCOGNITIVE OUTCOMES IN CHILDREN USING THE NIH TOOLBOX COGNITION BATTERY AND A SCALE OF ADAPTIVE FUNCTIONING

Frank Zelko[1] Matthew Switalski[1] Katherine Brandt[2] Riccardo Superina[2], [1]Ann and Robert H. Lurie Children's Hospital of Chicago, [2]Ann and Robert H. Lurie Children's Hospital of Chicago

Background: Portal venous flow anomalies in children can impair neurocognitive outcomes. Surgery to improve portal blood flow is an effective option for mitigating these effects, yet its impact upon cognition has not been adequately studied. **Methods:** Children with portal vein flow anomalies were studied for cognitive and adaptive functioning pre- and post-corrective surgery. We utilized a novel technology, the NIH Toolbox Cognition Battery (NTCB), to measure cognitive outcomes, along with a parent questionnaire of adaptive functioning, the Adaptive Behavior Assessment System (ABAS). Both measures were administered before surgery and at 6-months follow up. The NTCB produced a Fluid Cognition Index (FCI) and a Vocabulary (VOC) score, and the ABAS produced a General Adaptive Composite (GAC), each measure having a mean value of 100 (SD 15) in the general population. These measures were examined in children with either 1) Extrahepatic portal vein obstruction (EHPVO) or 2) Congenital Portosystemic shunt (CPSS). **Results:** Thirty-four children were tested: 22 with EHPVO and 12 with CPSS. Of the 22 with EHPVO, 12 received portal vein revascularization via meso-Rex bypass (MRB) and 10 received distal splenorenal shunt (DSRS). Twelve children with CPSS were treated by shunt ligation. Baseline age was 10.2 years (SD 5.36). 18 (53%) were female and 8 (24%) were non-white. 24 subjects completed follow up assessments 6 months after surgery. Single-sample t-tests indicate that at baseline the combined sample scored significantly below the population mean on all 3 neurocognitive variables: FCI (M = 80.29, SD = 16.05) t(32) = -7.05, p < .0001; VOC (M = 94.27, SD = 15.36) t(32) = -2.14, p = .039; and GAC (M = 89.62, SD = 14.77) t(33) = -4.10, p = .0003. Paired-samples t-tests comparing the performances of the 24 subjects who returned for 6-month follow up revealed statistically significant increases from baseline to 6 month follow up on FCI t(20) = 2.33, p < .0306 and VOC t(21) = 2.23, p = .0365, with mean values/SDs presented in Figure 1. **Conclusion:** Our results indicate that children with impaired portal venous flow experience significant neurocognitive dysfunction, with effect sizes suggesting that fluid cognitive abilities are especially vulnerable. The adverse impact of portal vein flow anomalies upon fluid cognition and vocabulary performance is significantly improved by surgical correction.



Disclosures: Frank Zelko: Nothing to Disclose, Matthew Switalski: Nothing to Disclose, Katherine Brandt: Nothing to Disclose, Riccardo Superina: Nothing to Disclose

4593 | UNCOVERING HIDDEN RISK: CYP450 GENOTYPES REVEAL SUSCEPTIBILITY TO LIVER INJURY IN CYSTIC FIBROSIS PATIENTS ON CFTR MODULATORS

Sarah Lowry Adamitis[1] Wikrom Karnsakul[1] Christopher Hartley[1], [1]Johns Hopkins University

Background: Cystic Fibrosis (CF) is no longer a uniformly fatal childhood disease thanks to CFTR modulators. Patients are now living longer, healthier lives. Many CFTR modulators are metabolized through hepatic cytochrome P450 (CYP) enzymes in the liver endoplasmic reticulum, especially CYP3A4 and CYP3A5, which are polymorphic and known to influence drug exposure, toxicity, and interactions. While a CYP3A4 Neg/Neg variant is a normal phenotype, the

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CYP3A4*22 variant has been found in 5-7% of the Caucasian population, linked to lower hepatic CYP3A4 expression and activity. Slow metabolizers with this variant may be at risk for drug accumulation and subsequent drug-induced liver injury (DILI). By integrating pharmacogenomic testing into clinical care, we explore the feasibility of a precision model to proactively identify patients at risk for hepatic adverse events. **Methods:** A pilot cross sectional study recruited CF patients at Johns Hopkins who have been treated with CFTR modulators. Pre-existing liver conditions other than CF were excluded. 4 patients had known mild CF related liver disease. While elevated transaminases are classified as hepatocellular injury, hyperbilirubinemia, increased alkaline phosphatase and gamma-glutamyl transferase as cholestatic damage. We aimed to assess whether any CYP3A4 and CYP3A5 genotypes are associated with liver enzyme elevations in pediatric CF patients receiving CFTR modulators. **Results:** 11 patients were in the study. 4 of 7 patients without prior liver disease had elevations of transaminases while on CFTR modulators. All patients with elevated transaminases carried the CYP3A4*22 variant, associated with decreased CYP enzymatic activity and slower drug metabolism. Notably, those with CYP3A4 *22/- (heterozygosity) or *1/*1 in combination with CYP3A5 *3/*3 (poor metabolizers) demonstrated significant hepatocellular injury. Intermediate CYP3A5 metabolizers alone did not exhibit liver enzyme elevations, suggesting a role for CYP3A4 dysfunction in this DILI phenotype. Of 4 patients with CFLD, 2 had persistent transaminitis but did not lead to liver decompensation. **Conclusion:** Hepatocellular injury pattern is more common among suspected patients with DILI from CFTR modulators. This study is among the first to link specific CYP3A4 genotypes (especially CYP3A4 *22 carriers) to liver enzyme elevations in CF patients on CFTR modulators. These findings point to a pharmacogenetic vulnerability in a population of long-term CF survivors. As CF care transitions into adulthood, understanding each patient's metabolic fingerprint could ensure that the success story of CFTR modulators is not compromised by silent hepatic toxicity.

Table 1: Genotype and Phenotype Profiles of CF Patients on CFTR Modulators

3A4 Genotype	3A4 Phenotype	3A5 Genotype	3A5 Phenotype	AST	ALT	Known Liver Disease	Age (years)	Gender
*1/*1	Normal	*3/*3	Poor	162	358	no	21	F
Neg/Neg	Normal	*3/Neg	Intermediate	23	16	no	5	F
*22/Neg	Intermediate	*3/*3	Poor	80	164	yes	20	M
Neg/Neg	Normal	*3/*3	Poor	69	96	no	10	M
*22/Neg	Intermediate	*3/*3	Poor	168	64	no	20	MF
Neg/Neg	Normal	*3/*3	Poor	62	64	no	5	F
Neg/Neg	Normal	*3/Neg	Intermediate	23	22	yes	21	F
Neg/Neg	Normal	*3/*3	Poor	22	21	no	19	M
*22/Neg	Intermediate	*3/*3	Poor	141	146	yes	21	M
Neg/Neg	Normal	*3/*3	Poor	22	20	yes	10	M
Neg/Neg	Normal	*3/*3	Poor	27	14	no	8	M

Disclosures: Sarah Lowry Adamitis: Nothing to Disclose, Wikrom Karnsakul: Nothing to Disclose, Christopher Hartley: Nothing to Disclose

4594 | BENEFICIAL EFFECTS OF PARABACTEROIDES GOLDSTEINII AND ITS METABOLITES ON THE THERAPEUTIC POTENTIAL FOR CHOLESTATIC LIVER DISEASE

Huey-Ling Chen[1] Shu-hao Hsu[2] Huey-Huey Chua[1] Bang-Yu Liou[1] Chia-Ray Lin[1] Ya-Hui Chen[1] Tzu-Hsien Yang[2] Mei-Hwei Chang[3] Yen-Hsuan Ni[1], [1]National Taiwan University College of Medicine and Children's Hospital, [2]National Taiwan University College of Medicine, [3]National Taiwan University

Background: The homeostasis of gut microbiota is pivotal to maintaining the physiological liver-gut axis and affect development of liver disease. We have discovered *Parabacteroides goldsteinii* (*P goldsteinii)* improved cholestasis in a strain of Bsep *(abcb11)* knockout mice with more severe jaundiced phenotype. However, the detailed mechanism involved in therapeutic effect of *P goldsteinii* is not known. **Methods:** Adult male Bsep *(abcb11)* knockout mice were treated with *P goldsteinii*. Liver biochemistry and pathology were assessed. The liver transcriptome of Bsep knockout mice with *P goldsteinii* treatment were investigated by RNA sequencing. The secreted metabolite profile of *P goldsteinii* was analyzed by UHPLC-MS/MS. The *in vitro* effects of *P goldsteinii*-secreted metabolites were test by organoids derived from biliary duct cells. **Results:** Bsep knockout mice treated with *P. goldsteinii* (PG) showed improvement in cholestasis, as evidenced by decreased serum bilirubin levels and restored biliary structures, including proliferative cholangiocytes expressing increased interleukin-6 during the recovery phase. RNA sequencing revealed upregulation of genes related to cell proliferation and downregulation of genes associated with inflammation and bile duct damage. UHPLC-MS/MS analysis identified liquiritigenin, a liver-protective metabolite, as one of the secreted compounds from *P. goldsteinii*. To evaluate its effects, we used bile duct–derived organoids that form spheroids with a central lumen. Treatment with *P. goldsteinii*-secreted metabolites and liquiritigenin promoted organoid proliferation. Furthermore, liquiritigenin-treated organoids showed increased expression of CK-19 and MYC, markers of cholangiocyte differentiation and proliferation. **Conclusion:** Our results suggest that *P. goldsteinii* treatment alleviates liver injury by reducing inflammation and promoting cellular proliferation. Metabolites secreted by *P. goldsteinii*, including liquiritigenin, enhance the proliferation and differentiation of bile duct–derived organoids.

Disclosures: Huey-Ling Chen: Nothing to Disclose, Shu-hao Hsu: Nothing to Disclose, Huey-Huey Chua: Nothing to Disclose, Bang-Yu Liou: Nothing to Disclose, Chia-Ray Lin: Nothing to Disclose, Ya-Hui Chen: Nothing to Disclose, Tzu-Hsien Yang: Nothing to

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Disclose, Mei-Hwei Chang: Nothing to Disclose, Yen-Hsuan Ni: Nothing to Disclose

4595 | LONG-TERM SAFETY OF CHILDREN FOLLOWING MATERNAL TAF OR TDF USE DURING PREGNANCY FOR THE PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HBV

Kai-Chi Chang[1] Ming-Wei Lai[2] Chun-Jen Liu[1] Shu-Chi Mu[3] Yu-Chun Chen[1] Jin-Chung Shih[1] Mei-Hwei Chang[4] Huey-Ling Chen[4], [1]National Taiwan University Hospital, [2]National Chang Gung University Hospital, [3]Shin Kong Wu Ho-Su Memorial Hospital, [4]National Taiwan University

Background: The long-term effects of in utero exposure to maternal Tenofovir Alafenamide (TAF) for the prevention of mother-to-child transmission (MTCT) of hepatitis B virus (HBV) remain unclear. This study investigates the long-term outcomes of children born to mothers who received TAF or Tenofovir Disoproxil Fumarate (TDF) during pregnancy to prevent perinatal HBV transmission. The aim is to assess the children's growth and biochemical development over time. **Methods:** A cohort of 257 infants born to mothers treated with TAF or TDF was enrolled and followed for up to 2–5 years post-delivery. Of these, 166 infants were born to mothers treated with TDF, and 91 were born to mothers treated with TAF. Annual follow-up visits were conducted, with each child evaluated 1–3 times. Assessments included HBV serological markers (HBsAg and anti-HBs), as well as developmental and biochemical indices such as serum calcium (Ca), phosphorus (P), creatinine (Cr), and bone alkaline phosphatase (BAP). **Results:** The mean age at follow-up for children exposed to TAF and TDF was 3.12 ± 0.94 and 4.01 ± 1.36 years, respectively. The TDF group belonged to an earlier cohort, resulting in an older average age at follow-up. Z-scores for weight and height were comparable between the two groups. Biochemical evaluations revealed that Ca, P, Cr, and BAP levels remained within normal ranges across all children, with no significant differences between groups. A high persistence rate of anti-HBs positivity was also observed. **Conclusion:** Maternal use of TAF or TDF during pregnancy is not associated with adverse effects on child growth or renal and bone biochemistry during early life. Continued follow-up is essential to confirm the long-term safety and efficacy of prenatal antiviral therapy.

Disclosures: Kai-Chi Chang: Nothing to Disclose, Ming-Wei Lai: Nothing to Disclose, Chun-Jen Liu: Nothing to Disclose, Shu-Chi Mu: Nothing to Disclose, Yu-Chun Chen: Nothing to Disclose, Jin-Chung Shih: Nothing to Disclose, Mei-Hwei Chang: Nothing to Disclose, Huey-Ling Chen: Nothing to Disclose

4596 | INVESTIGATION OF ASSOCIATIONS BETWEEN VARIANTS IN MRGPRX4 AND PEDIATRIC CHOLESTATIC PRURITUS

Minna Rodrigo[1] Daphne Chun-Che Chien[2] Ryo Kawamoto[2] Nathachit Limjunyawong[3] Tony Rajborirug[4] Xinzhong Dong[2] Wikrom Karnsakul[5], [1]University of Maryland School of Medicine, [2]Department of Neuroscience, Johns Hopkins University School of Medicine, [3]Center of Research Excellence in Allergy and Immunology, Faculty of Medicine Siriraj Hospital, Mahid, [4]Johns Hopkins University Bloomberg School of Public Health, [5]Johns Hopkins University

Background: Cholestatic pruritus is a common and often debilitating symptom in various pediatric liver diseases, including Alagille syndrome, progressive familial intrahepatic cholestasis (PFIC), biliary atresia, and primary sclerosing cholangitis (PSC), with a complex and poorly understood pathogenesis. Recent evidence implicates the Mas-related G protein-coupled receptor X4 (MRGPRX4)—a bile acid receptor expressed in human dorsal root and trigeminal ganglia—as a potential mediator of cholestatic pruritus. Although *MRGPRX4* harbors multiple single nucleotide variants (SNVs), their role in modulating cholestatic pruritus, particularly in pediatric patients, remains unexplored. **Methods:** We conducted a case-control study at a single pediatric tertiary care center, enrolling patients with Alagille syndrome, PFIC, biliary atresia, and PSC. Cases were defined as individuals with a history of pruritus; controls had no reported pruritus. Clinical data included peak total and fractionated bile acid levels, total bilirubin, and direct bilirubin. Targeted sequencing of the *MRGPRX4* coding region was performed to evaluate associations between SNVs and pruritus status. **Results:** Among 36 participants (17 cases, 19 controls), peak total bile acid level ($p = 0.0038$), peak cholic acid level ($p = 0.0004$), peak chenodeodxycholic acid ($p = 0.0095$), and peak direct bilirubin ($p = 0.0497$) were significantly higher among patients with pruritus compared to those without pruritus. All participants harbored at least one coding-region SNV in *MRGPRX4*. Eleven unique SNVs were identified, with recurrent variants at positions p.Phe8-Leu, p.Asn25Lys, p.Val47Val, p.Tyr54Cys, p.Ala182Val, and p.Tyr215Tyr. While no single SNV was significantly associated with pruritus overall, the Tyr54Cys variant was found exclusively in individuals with severe pruritus when it occurred as the sole variant. **Conclusion:** The functional significance of

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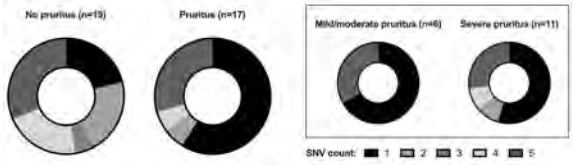
MRGPRX4 variants remains unknown. However, the Tyr54Cys variant may alter receptor interaction with ligands and enhance itch signaling when unaccompanied by other SNV's, potentially via altered bile acid binding or receptor activation threshold, which may contribute to cholestatis pruritus. Further investigation, including functional assays, is warranted to elucidate the mechanistic and clinical relevance of this variant in cholestatic pruritus.

Distribution of pruritus severity by SNV count



Identified variants and their allele frequencies

Variant	Consequence	Global population	Allele Frequency (%) No pruritus (n=19)	Pruritus (n=17)	p
c.24C>G (p.Phe8Leu)	**Missense**	**30**	**29**	**18**	**0.3958**
c.31A>G (p.Lys11Glu)	Missense	0.0026	5.3	0	0.5232
c.48C>T (p.Asn16Asn)	Missense	0.040	0	2.9	0.9553
c.75T>G (p.Asn25Lys)	**Missense**	**30**	**29**	**18**	**0.3958**
c.141T>A (p.Val47Val)	Synonymous	27	18	24	0.9472
c.161A>G (p.Tyr54Cys)	**Missense**	**31**	**32**	**35**	**0.9335**
c.248C>T (p.Ser83Leu)	Missense	0.56	5.3	0	0.5232
c.424G>A (p.Val142Met)	Missense	0.58	5.3	5.9	0.9068
c.449C>T (p.Ser150Phe)	Missense	0.14	2.6	0	0.9553
c.545C>T (p.Ala182Val)	**Missense**	**26**	**21**	**15**	**0.6950**
c.645C>T (p.Tyr215Tyr)	Synonymous	30	29	18	0.3958

Disclosures: Minna Rodrigo: Nothing to Disclose, Daphne Chun-Che Chien: Nothing to Disclose, Ryo Kawamoto: Nothing to Disclose, Nathachit Limjunyawong: Nothing to Disclose, Tony Rajborirug: Nothing to Disclose, Xinzhong Dong: Nothing to Disclose, Wikrom Karnsakul: Nothing to Disclose

4597 | INFLUENCE OF MASLD SUBTYPES DURING PREGNANCY ON ADVERSE NEONATAL OUTCOMES: RESULTS: FROM A PROSPECTIVE COHORT OF OVER 1000 MATERNAL-INFANT PAIRS

Cecilia Katzenstein[1] Nina Rodriguez[1] Lauren Alpert[1] Jeanette Rios[1] Priyanka Singh[1] Kim Le[1] Rachel Meislin[1] Sonam Rosberger[1] Keith Sigel[1] Rhoda Sperling[1] Emily Jane Gallagher[1] Norah Terrault[2] Jaime Chu[3] Tatyana Kushner[4], [1]Icahn School of Medicine at Mount Sinai, [2]University of Southern California, [3]Icahn School of Medicine at Mount Sinai (ISMMS), [4]Weill Cornell Medicine

Background: MASLD has been established as a risk factor for adverse neonatal outcomes (ANOs) such as preterm birth. However, MASLD encompasses various subtypes and their specific impacts on neonates remain unclear. Given that gestational diabetes (GDM) is a known risk factor for ANOs such as large for gestational age (LGA) and hypoglycemia, we aimed to determine whether maternal MASLD with dysglycemia (MASLD +DG) confers compounded neonatal risk beyond MASLD or DG alone. **Methods:** In this prospective study we evaluated the prevalence of MASLD defined by steatotic liver disease detected on ultrasound and/or fibroscan at 18-32 weeks gestation and metabolic comorbidities (diabetes mellitus (DM), obesity based on pre-pregnancy BMI, chronic hypertension, or hyperlipidemia). Patients with MASLD were further subtyped by evidence of DG, defined as history of GDM (known indicator of metabolic risk and increased odds of developing DM), current GDM, positive 1- or 3-hour glucose tolerance test (GTT), and prediabetes (A1c in pregnancy), in addition to pre-gestational DM. Incidence of ANOs were compared between the MASLD+DG subgroup and other groups. **Results:** Among 1291 participants, 206 (16%) were found to have MASLD in pregnancy; mean age was 30 years (SD = 5.3), and 62% identified as Hispanic. Of neonates born to mothers with MASLD, 3% were very/extremely preterm (born before 32 weeks gestation), 6% were LGA, and 19% had hypoglycemia (Figure 1). Among MASLD participants, 76 (37%) had evidence of DG. There was no statistical difference in rates of advanced maternal age ($\geq$ 35 years) across groups. MASLD+DG showed a stronger association with very/extremely preterm birth compared to MASLD without DG (5.3% vs 1.5%, $p = 0.016$), remaining significant after excluding obese patients (6.5% vs 1.6%, $p = 0.042$). DG alone was not associated. Similarly, MASLD+DG was more strongly associated with LGA (15.2% vs 4.1%, $p < 0.001$) and higher mean Fenton percentiles (54% vs 44%, $p < 0.001$) than the general MASLD cohort, even after excluding patients with obesity (16.6% vs 4.5%, $p = 0.005$; 57.4% vs 44.7% $p = 0.025$). Incidence of LGA was higher in DG alone than the rest of the cohort (12.8% vs 1.9%, $p < 0.001$), though rates were lower than than MASLD+DG. Finally, neonatal hypoglycemia was also more common MASLD+DG than MASLD without DG (47.6% vs 19%, $p < 0.001$), also after excluding obese patients (47.8% vs 21%, $p = 0.002$). Though DG alone showed higher rates of neonatal hypoglycemia than the rest of the cohort (40.8% vs 14.5%, $p < 0.001$), the incidence was lower than in MASLD+DG. **Conclusion:** MASLD+DG confers distinct risks for ANOs including preterm birth, LGA, and neonatal hypoglycemia. The presence of MASLD+DG was a stronger predictor than DG alone or MASLD alone, even when excluding patients with obesity. These findings suggest there should be consideration of GDM or abnormal GTT (already routinely assessed) in risk stratification to guide the counseling and management of MASLD in pregnancy.

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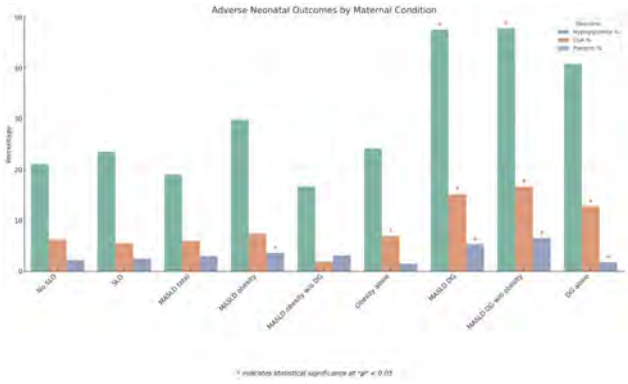

Disclosures: Cecilia Katzenstein: Nothing to Disclose, Nina Rodriguez: Nothing to Disclose, Lauren Alpert: Nothing to Disclose, Jeanette Rios: Nothing to Disclose, Priyanka Singh: Nothing to Disclose, Kim Le: Nothing to Disclose, Rachel Meislin: Nothing to Disclose, Sonam Rosberger: Nothing to Disclose, Keith Sigel: Nothing to Disclose, Rhoda Sperling: Nothing to Disclose, Emily Jane Gallagher: Novartis AG: Consultant, Flare Therapeutics: Consultant, Norah Terrault: Elseiver: Royalties or patent beneficiary, GSK: Grant/Research Support, Eiger Pharmaceuticals: Grant/Research Support, Helio Health: Grant/Research Support, Durect Corp: Grant/Research Support, ImmunoCore: Grant/Research Support, HBV Foundation: Board member, AASLD: Executive role, Genentech-Roche: Grant/Research Support, Hepatitis B Foundation: Executive role, Jaime Chu: Nothing to Disclose, Tatyana Kushner: Gilead: Grant/Research Support, Gilead: Advisor, GSK: Advisor, Eiger: Advisor, GSK: Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support

4598 | CYP2C70-DEFICIENT MICE EXHIBIT AGE-DEPENDENT LIVER INJURY AND UNFOLDED PROTEIN RESPONSE (UPR) ACTIVATION

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Background: Cholestatic liver diseases are the most common indication for liver transplantation in children and lack effective medical therapies to prevent disease progression. An accumulation of toxic bile acids causes hepatic injury, increases endoplasmic reticulum (ER) stress, and triggers the unfolded protein response (UPR). Our prior cholestasis studies demonstrate impaired expression of the hepatic X-box binding protein 1 (XBP1) and other UPR pathways leads to liver injury in neonatal compared to adult mice. However, traditional murine cholestatic models have limited translational value due to the less toxic, hydrophilic bile acid composition of mice. Thus, we employed Cyp2c70 knockout (KO) mice which have a hydrophobic bile acid profile closely resembling that of humans to investigate age-related ER stress, liver injury and UPR activation in the setting of cholestasis. **Methods:** Female Cyp2c70 KO mice and heterozygous controls were assessed at ages 10 days, 3 weeks and 8 weeks. Serum liver chemistries were analyzed, and hepatic gene expression was assessed using quantitative PCR (qPCR). **Results:** At 10 days, serum alanine transaminase (ALT), alkaline phosphatase (ALP), and bile acid (BA) levels were normal in KO mice, indistinguishable from controls. However, by 3 weeks, KO mice exhibited significantly elevated liver functional tests (LFTs) compared to controls. At 8 weeks, serum ALT levels in KO mice were markedly increased compared to controls (346 $\pm$ 157 U/L vs 42 $\pm$ 11 U/L, $p = 0.0027$). Serum bile acid concentrations were also higher in KO mice compared to controls (38 $\pm$ 18 vs $<$ 5 μmol/L, $p = 0.0022$). Hepatic X-box binding protein 1 spliced form (*Xbp1s*) was comparable between KO and controls at 10 days and remained unchanged at 3 weeks. By 8 weeks, hepatic *Xbp1s* expression was ~ 2-fold higher in KO mice ($p = 0.0241$) compared to controls. Additionally, hepatic death receptor 5 (*Dr5*) mRNA expression showed no difference between KO and controls at 10 days but increased by ~10-fold in KO mice at both 3 and 8 weeks ($P = 0.008$ and 0.013, respectively). Lastly, hepatic C/EBP homologous protein (*Chop)* gene expression consistently trended or was significantly higher in KO mice across all ages. **Conclusion:** Neonatal Cyp2c70 KO mice exhibit age-dependent liver injury with serum liver chemistries and UPR-related gene expression similar to controls. In contrast, there are significantly higher serum liver injury markers and enhanced hepatic UPR activation by 3 to 8 weeks. These data, using a human-like bile acid mouse model, further support our previous murine cholestatic studies which demonstrate age-dependent changes in UPR activation and liver injury markers. Cyp2c70 KO mice may provide a more clinically relevant model to test therapeutic interventions for cholestatic liver diseases, including potential UPR targets.

Disclosures: Ryan Shaw: Nothing to Disclose, Paul Dawson: Albireo Pharma: Grant/Research Support, Saul Karpen: Albireo/Ipsen: Consultant, Mirum: Consultant, HemoShear: Consultant, Intercept: Consultant, Brian LeCuyer: Nothing to Disclose, Richard Green: Mirum Pharmaceuticals: Advisor, Alyssa Kriegermeier: Mirum Pharmaceuticals: Advisor

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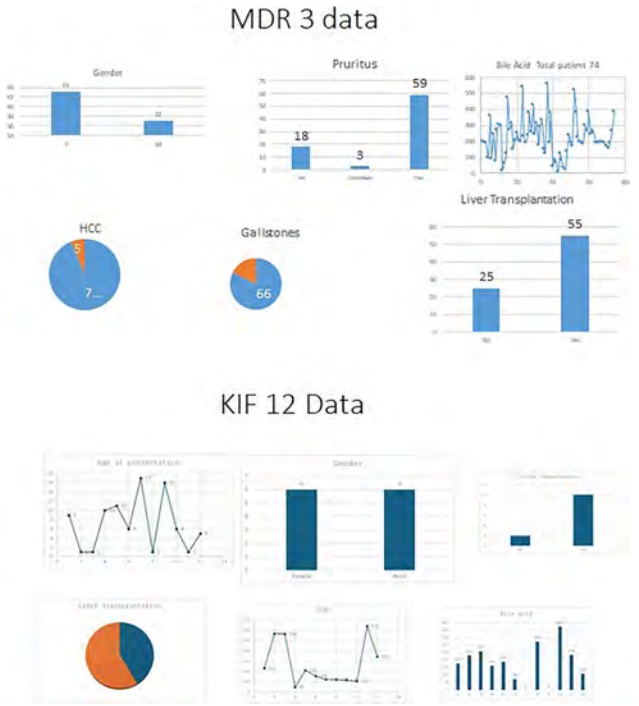
4599 | VARIANTS IN MDR3 AND KIF12 GENES: NATURAL HISTORY OF CHOLANGIOPATHIES AND LIVER TRANSPLANTATION; A SINGLE CENTER EXPERIENCE

Mohammad Shagrani[1] Kishwer Kumar[1] Alexandra Aldana[1] Ali Syed Akhtarul Hassan[1] Dalal Albogami[1] Sateesh Maddirevula[1] KRIS ANN MARQUEZ[2] Saleh Alqahtani[1] Ehab Abufarhaneh[1] Saad Alghamdi[1] Waleed Alhamoudi[1] Bandar Mohammed H Aljudaibi[1] Massimo Malago[1] Dieter Broering[1], [1]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, [2]King Faisal Specialist Hospital and Research Center. Riyadh, Saudi Arabia

Background: Cholangiopathies represent a diverse group of chronic liver diseases characterized by progressive damage to the bile ducts, often leading to liver failure and the need for transplantation. Genetic factors play a crucial role in the pathogenesis of many cholangiopathies. Among these, variants in the *MDR3* (ABCB4) and *KIF12* genes have been increasingly recognized as significant contributors to disease development and progression. *MDR3* encodes a phospholipid transporter essential for bile formation, while *KIF12* is involved in ciliary function and biliary epithelial integrity. Understanding the natural history of cholangiopathies associated with these genetic variants is critical to improving diagnosis, management, and transplant outcomes. This study aims to characterize the clinical progression of patients with *MDR3* and *KIF12* variants and assess their outcomes following liver transplantation. **Methods:** We conducted a large-scale genomic investigation involving 299 pediatric patients (from 279 families) presenting with intrahepatic cholestasis. Exome sequencing was performed as a first-tier diagnostic test to identify likely causal genetic variants. Clinical data including gender, bile acid levels, and presenting symptoms were collected. Liver transplantation records from 2011 to 2024 at our center were reviewed to assess transplantation rates and outcomes in patients diagnosed with PFIC3 and KIF12-related cholangiopathy **Results:** In a cohort of 299 pediatric patients (279 families) with intrahepatic cholestasis, exome sequencing identified likely causal variants in 135 families. Among these, 80 patients were diagnosed with PFIC3 and 12 with KIF12-related disease. In the PFIC3 group, there were 43 females and 37 males, with a median bile acid level of 196 μmol/L (range 7–560), 59 patients reported a history of pruritus. The KIF12 group included 6 females and 6 males, with a median bile acid level of 209.5 μmol/L (range 72–423), and the predominant clinical feature was portal hypertension.

Between 2011 and 2024, 865 pediatric liver transplantations were performed at our center, with 196 cases attributed to PFIC. Of these, 55 patients diagnosed with PFIC3 underwent liver transplantation, and 6 patients with KIF12-related cholangiopathy required transplantation. **Conclusion:** Exome sequencing serves as an effective first-tier diagnostic tool for pediatric intrahepatic cholestasis, facilitating precise genetic diagnosis in nearly half of the cases. PFIC3 and KIF12 variants contribute significantly to the disease burden, with PFIC3 patients commonly presenting with pruritus and KIF12 patients exhibiting portal hypertension. Liver transplantation remains a crucial treatment for severe cases, particularly in PFIC3 and KIF12-related cholangiopathies, underscoring the importance of early genetic diagnosis and specialized management in this population.



Disclosures: Mohammad Shagrani: Nothing to Disclose, Kishwer Kumar: Nothing to Disclose, Alexandra Aldana: Nothing to Disclose, Ali Syed Akhtarul Hassan: Nothing to Disclose, Dalal Albogami: Nothing to Disclose, Sateesh Maddirevula: Nothing to Disclose, KRIS ANN MARQUEZ: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Ehab Abufarhaneh: Nothing to Disclose, Saad Alghamdi: Nothing to Disclose, Waleed Alhamoudi: Nothing to Disclose, Bandar Mohammed H Aljudaibi: Nothing to Disclose, Massimo Malago: Nothing to Disclose, Dieter Broering: Nothing to Disclose

4600 | SLOW PROGRESSION OF LIVER STIFFNESS IN FONTAN-ASSOCIATED LIVER DISEASE IN CHILDREN

Anna Mania[1] Katarzyna Mazur-Melewska[1] Magdalena Figlerowicz[1], [1]Department of Infectious Diseases and Child Neurology

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Background: Fontan-associated liver disease (FALD) represents a significant and emerging concern in the management of pediatric patients who have undergone the Fontan procedure (FP) for congenital heart defects. Altered hemodynamics, chronic hypoxia, and increased venous pressure associated with the Fontan circulation lead to liver injury and progressive fibrosis. This study aims to evaluate the clinical abnormalities and disease progression in children with FALD. **Methods:** The study included 31 children (18 girls) who underwent FP due to inborn heart defects. Children were evaluated every 12 months in the hepatology clinic for the following 3 years. Physical examination, blood CBC, ALT, AST, ALP, and GTP levels, and shear-wave elastography were evaluated during each visit. FIB-4 and APRI scores were calculated based on the laboratory results. All children received ursodeoxycholic acid in the dose of 15 mg/kg during the study period **Results:** The study group included 18 girls and 13 boys; median age 10 years (IQR 6-12). Various congenital heart defects were noted. The median time from FP was 6 years (IQR 3.25-8.00). On baseline evaluation, 14 children who underwent FP >6 years ago were significantly older (median 12 vs 6 years; $p=0.0004$), had higher FIB-4 (8.98 vs 5.53; $p=0.04$) and liver stiffness (9.0 vs 6.6 kPa; $p=0.026$). During the observation period of 3 years, no significant progression was observed in FIB-4 (6.35 vs 6.47; $p=0.68$) and liver stiffness (6.4 vs 6.9; $p=0.91$). Similar observations were made in the group >6 years after FP – FIB-4 (9.51 vs 9.74; $p=0.91$) and liver stiffness (9.2 vs 9.8; $p=0.67$). **Conclusion:** Liver stiffness is significantly higher in children who underwent FP >6 years ago. However, no significant progression was observed during the study period. Further studies are necessary to elucidate the direct influence of UDCA on the progression of FALD in children.

Disclosures: Anna Mania: abbvie: Speaking and Teaching, Abbvie: Speaking and Teaching, Katarzyna Mazur-Melewska: Nothing to Disclose, Magdalena Figlerowicz: Nothing to Disclose

4601 | THE CLINICAL SPECTRUM OF PORTO-SINUSOIDAL VASCULAR DISEASE IN PAEDIATRICS: A SINGLE CENTRE REVIEW

Marumbo Paul Mtegha[1], [1]Leeds Children's Hospital

Background: Porto-sinusoidal vascular disease (PSVD) is a condition which affects the portal venules and sinusoids in the absence of cirrhosis[1]. Knowledge about PSVD natural history is still limited[2,3,4]. We aimed to describe the characteristics of children affected with PSVD, as well as their histological findings and clinical outcomes. **Methods:** We performed a retrospective review of children with native liver biopsy samples suggestive of PSVD from January 2019 to October 2024. **Results:** Forty-eight patients fit the diagnostic criteria of PSVD as described by Gottardi et al.[1] with 64.6% ($n=31$) having associated portal hypertension (PHT) and 35.4% ($n=17$) without PHT. The most common reason for referral to hepatology was isolated elevated transaminases in non-PHT group, hypersplenism and portal hypertensive bleed in the PHT group (table 1). There were no significant differences between the histological features found on both groups, apart from a higher prevalence of perisinusoidal fibrosis in those with PHT ($p=0.018$). The non-PHT group had a higher median ALT of 61 (IQR 35, 213) at presentation when compared to the PHT group ($p=0.021$). During the follow up period no significant adverse events were observed in non-PHT group, while 2 children developed hepatopulmonary syndrome and 3 underwent liver transplantation in the PHT group. Of those with PHT, 16 had evidence of portal vein thrombosis (PVT) with cavernous transformation at presentation and 2 developed PVT during the follow up period. **Conclusion:** In summary, PSVD is a condition with variable phenotypic presentation and disease course. Those without PHT, mostly presenting with isolated elevated transaminases, appear to have a milder disease course, while those with PHT can have poor outcomes. Prospective studies are required to improve our understanding of the disease course and identify those at risk of progressing to PHT and developing adverse outcomes.

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Baseline characteristics and outcomes of children with PSVD

	Total	Non-PHT	PHT	p value
Number of patients, n (%)	48 (100)	17 (35.4)	31 (64.6)	
Gender: male, n (%)	30 (62.5)	9 (52.9)	21 (67.7)	0.361
Median age in years at presentation (IQR)	5.0 (2.1, 11.6)	4.3 (1.0, 11.7)	6.0 (2.6, 11.1)	0.419
Median follow up in years (IQR)	2.4 (1.6, 5.3)	2.1 (1.6, 2.4)	3.6 (1.9, 5.6)	0.054
Associated conditions, n (%)	35 (72.9)	13 (76.5)	22 (71.0)	0.747
Reason for referral to hepatology, n (%)				
Isolated elevation in transaminases	12 (25.0)	12 (70.6)	0 (0)	**<0.001**
Splenomegaly	4 (8.3)	0 (0)	4 (12.9)	0.282
Splenomegaly and thrombocytopaenia	6 (12.5)	0 (0)	6 (19.4)	0.077
Splenomegaly, thrombocytopaenia and other cytopaenias	6 (12.5)	0 (0)	6 (19.4)	0.077
Portal Hypertensive bleed	12 (25.5)	0 (0)	12 (38.7)	**0.004**
Other	8 (16.7)	5 (29.4)	3 (9.7)	0.112
Liver elastography, median in Kpa (IQR)	7.7 (6.0, 10.1)	6.9 (5.1, 7.7)	8.6 (6.1, 10.9)	0.085
Spleen elastography, median in Kpa (IQR)	18.6 (14.8, 27.7)	13.7 (9.8, 16.5)	22.5 (15.9, 51.8)	**0.026**
Portal vein thrombosis, n (%)	18 (37.5)	0 (0)	18 (58.1)	**<0.001**
Management, n (%)				
Conservative	17 (35.4)	17 (100)	0 (0)	**<0.001**
Endoscopic surveillance	22 (45.8)	0 (0)	22 (71.0)	**<0.001**
Shunt surgery	6 (12.5)	0 (0)	6 (19.4)	0.077
Liver transplant	3 (6.3)	0 (0)	3 (9.7)	0.543
Hepatopulmonary syndrome, n (%)	2 (4.2)	0 (0)	2 (6.5)	0.533
Death, n (%)	1 (2.1)	0 (0)	1 (3.2)	1.000

Disclosures: Marumbo Paul Mtegha: Nothing to Disclose

4602 | PREVALENCE OF SUCCESSFUL TREATMENT WITHDRAWAL IN CHILDREN&RSQUO;S WITH AUTOIMMUNE HEPATITIS

Saurabh Singh[1] Bikrant Biharilal Raghuvanshi[1], [1]ILBS

Background: There is lack of systemic data on withdrawal of immunosuppression and the relapse after treatment withdrawal in children with autoimmune hepatitis (AIH). The present study was planned to analyze the clinical, biochemical and histological characteristics of children with AIH undergoing treatment withdrawal **Methods:** All children (< 18 years) presenting between Jan 2011- Jan 2022 and diagnosed as AIH based on simplified criteria were included. Data of all patients in whom treatment was withdrawn was extracted through HIS (hospital information system). Treatment was stopped in children having biochemical remission for atleast 24 months along with histological remission (HAI < 5 and no cirrhosis). **Results:** 212 patients presenting in study period, 30 had documented biochemical remission for more than 24 months. Of these, 24 consented for liver biopsy and all 24 showed histological remission and absence of cirrhosis. Immunosuppression (steroid and azathioprine) were withdrawn in them after consent. In addition, 4 patients stopped their immunosuppression on their own without a repeat liver biopsy. Hence, a total of 28 children underwent treatment withdrawal.(Table 1)

Four patients (14.2%) had relapse after 2,4, 6 and 12 months of immunosuppression withdrawal, respectively. All relapses were within one year of withdrawal therefore strict follow up is needed post withdrawal in first year **Conclusion:** Withdrawl of Immunosupressant is feasible and safe with maintenance of long term off treatment remission in a select cohort of children having Autoimmune Hepatitis

Variable		Total
Gender	Male	11
	Female	17
Median	Age at diagnosis (yrs)	7
AIH Type	Seronegative	8
	Type 1	17
	Type 2	3
Initial Presentation	AH	14
	Asymptomatic	7
	ALF	3
	ACLF/DCLD	4
ANA	Positive	8
	Negative	20
ASMA	Positive	11
	Negative	17
LKM1	Positive	3
	Negative	25
PANCA	Positive	2
	Negative	26
Baseline data (Median)	IgG(g/dl)	21.8
	AST(U/L)	703
	ALT(U/L)	333
	HAI	11
	Fibrosis	2
	Fibroscan(kpa)	14
At treatment stoppage (Median)	IgG(g/dl)	11.5
	AST(U/L)	28
	ALT(U/L)	18
	HAI	1

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Disclosures: Saurabh Singh: Nothing to Disclose, Bikrant Biharilal Raghuvanshi: Nothing to Disclose

4603 | PREDICTING RESPONSE TO ODEVIXIBAT TREATMENT AND COMPARISON BETWEEN CLASSICAL TYPES AND RARER FORMS OF CHILDREN WITH PFIC

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Background: In our previous study we reported efficacy of odevixibat treatment (OT) in a real-world cohort of children with progressive familial intrahepatic cholestasis (PFIC). Here we aim to compare the response to treatment in children with classical types of PFIC versus rare forms and identify the best cut-off of sBA reduction predicting the response to OT at 6 months. **Methods:** We reviewed data on children with PFIC prospectively enrolled and treated with odevixibat for 6 months. We divided the patients into 2 groups (classic types vs rarer forms) and compared. ROC analysis was performed to calculate the best cut-off of sBA reduction associated with improvements in pruritus scale of -1 point at 6 months (defined as *pruritus responders*). **Results:** 24 patients [median age 6.6 years (3.7-12.1), M/F = 11/13] were enrolled; All had high sBA levels [median value of 317 μmol/ (82-369)] and 22/24 (92%) had pruritus.

16 patients (67%) had classic PFIC types [FIC-1 deficiency (PFIC-1) = 2; BSEP deficiency (PFIC-2) = 11; MDR3 deficiency (PFIC-3) = 3; 8 patients (33%) had rarer forms [TJP2 deficiency (PFIC-4) = 5; FXR deficiency (PFIC-5) = 1; MYO5B (PFIC-6) = 1; ZFYVE19 (PFIC-9) = 1]. At baseline, median values of age [6.6 years (4.2-11.6) in classic types vs 6.3 (3.0-9.7) in rarer forms], sBA levels [317 μmol/L (88-367) vs 290 μmol/L (77-364) in rarer forms] and prevalence of pruritus (88% vs 100% in rarer forms) were similar in both groups ($p > 0.05$).

After 6 months of treatment, 75% of patients were sBA responders, 73% were pruritus responders; 30% required dose escalation. Comparing the two groups, percentages of sBA responders were 63% in classic types vs 100% in rarer forms of PFIC ($p = 0.06$); for pruritus responders: 59% in classic types vs 100% in rarer forms ($p = 0.05$).

On ROC analysis, reductions of sBA levels $\geq 48\%$ from baseline value at 1st month and $\geq 52\%$ at 3rd month were associated with improvements of pruritus scale (-1point) at 6 months (*pruritus responders*) (1st month: ROC-AUC 0.771; SE = 0.75, SP = 0.83; 3rdmonth: ROC-AUC 0.885; SE = 0.81, SP = 1.00). **Conclusion:** In our cohort, the majority of patients responded well to odevixibat treatment; higher percentages of response were recorded among children with rarer forms.

Reduction of sBA levels of around 50% from baseline value at 1 and 3 months is associated with a full response to OT at 6 months. This information could be useful to plan prosecution or prompt discontinuation of treatment after 6 months of odevixibat.

Disclosures: Angelo Di Giorgio: Ipsen Pharma: Consultant, Mirum Pharma: Consultant, Marco Sciveres: IPSEN: Speaking and Teaching, MIRUM Pharma: Consultant, Maurizio Fuoti: Nothing to Disclose, Pier-Luigi Calvo: Nothing to Disclose, Mara Cananzi: Nothing to Disclose, Ana Lleo: Advanz Pharma: Advisor, Ipsen: Advisor, GSK: Advisor, AstraZeneca: Advisor, Gilead: Speaking and Teaching, Abbvie: Speaking and Teaching, MSD: Speaking and Teaching, Advanz Pharma: Speaking and Teaching, AlfaSigma: Speaking and Teaching, GSK: Speaking and Teaching, Gilead: Consultant, Simona Gatti: Nothing to Disclose, Giuseppe Indolfi: IPSEN: Consultant, MIRUM: Consultant, Annalisa Madeo: Nothing to Disclose, Claudia Mandato: Nothing to Disclose, Federica Nuti: Nothing to Disclose, Chiara Zanchi: Nothing to Disclose, Greta Carioli: Nothing to Disclose, Arianna Ghirardi: Nothing to Disclose, Emanuele Nicastro: Nothing to Disclose, Lorenzo D'Antiga: Selecta: Advisor, Vivet: Advisor, Spark: Advisor, Genespire: Advisor, Tome: Advisor, Mirum: Advisor, Ipsen/Albireo: Advisor, Intercept/ Advanz Pharma: Advisor, Alexion/Astra Zeneca: Advisor, Fractyl: Advisor

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4604 | DISTINCT GUT MICROBIOTA AND METABOLOMIC SIGNATURES ASSOCIATED WITH THE ABSENCE OF HEPATIC STEATOSIS IN OBESE AND OVERWEIGHT CHILDREN

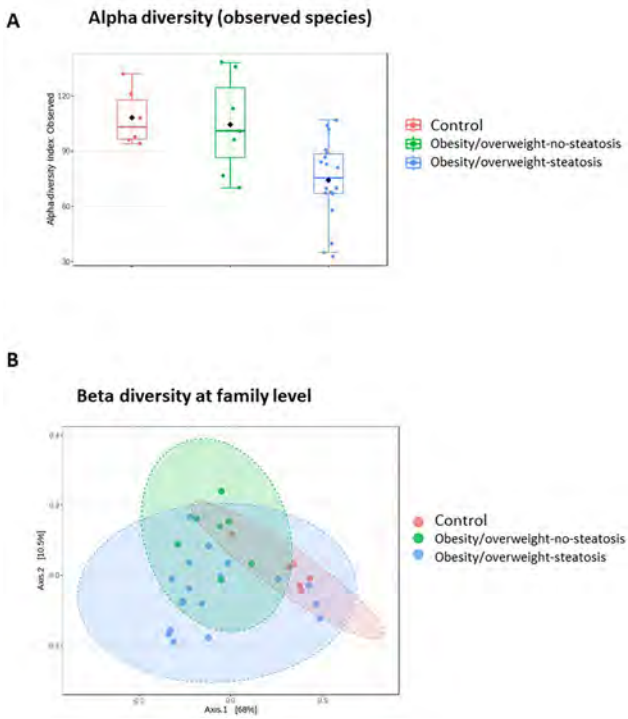
Kai-Chi Chang Chia-Ray Lin[1] Bang-Yu Liou[1] Huey-Ling Chen[2], [1]National Taiwan University Hospital, [2]National Taiwan University

Background: Obesity or overweight is a significant risk factor for children to develop hepatic steatosis in pediatric population. However, some children who meet BMI or z-score criteria for obesity or overweight do not have fatty liver. Their gut microbiota and its derived metabolites warrant further investigation. **Methods:** We enrolled obese or overweight children aged 6-18 years and performed ultrasonography to screen hepatic steatosis. Children with normal BMI z score were recruited as control group. Anthropometric data were measured, and fasting blood samples were analyzed for liver biochemistry, lipid profiles, uric acid and metabolomics. Stool sample were collected for gut microbiota analysis using full-length 16S rRNA gene sequencing. Serum samples were analyzed using ultra-high-performance liquid chromatography with mass spectrometry. **Results:** Twenty-eight obese children (median age 9.0 years, range 8.2–14.9 years), and six age-matched healthy control were enrolled. The median BMI z score were 1.92 and 0.39 in obese/overweight group and control group, respectively.

Their age, alanine aminotransferase, triglyceride, uric acid, and bile acid were comparable. Obese/overweight children exhibited higher total cholesterol (169 mg/dL vs. 124 mg/dL, p = 0.029) and low-density lipoprotein levels (105.5 mg/dL vs. 58.5 mg/dL, p = 0.039) compared to the control group.

Among the 28 cases in the obesity/overweight group, 7 showed no hepatic steatosis on sonographic examination, while the remaining 21 demonstrated mild to moderate steatosis. The alpha and beta diversity of the gut microbiota differed significantly among the control group, the obesity/overweight-with-steatosis group, and the obesity/overweight-without-steatosis group (p = 0.008 and p = 0.003, respectively; Figure 1A, 1B). Additionally, the shannon index was lowest in the obesity/overweight-with-steatosis group and showed a trend toward difference compared to the obesity/overweight-without-steatosis group (p = 0.06; Figure 1A). Linear discriminant analysis (LDA) effect size analysis revealed that *Bifidobacterium bifidum* and *Bacteroides ovatus* were significantly enriched in the control group compared to both obesity group. To identify metabolites potentially associated with protection against hepatic steatosis, we compared serum metabolites between the obesity/overweight-with-steatosis and obesity/overweight-without-steatosis groups. We found that 2-hydroxycinnamic acid and citrulline were highly associated with obesity in the absence of steatosis. **Conclusion:** Our results suggest that the microbiota and the derived metabolites may play a role in modulating liver health in obese children. Protecting factors for steatotic liver disease warrants further investigation to better understand individual susceptibility and to develop therapeutic strategies for hepatic steatosis.

Figure 1



Disclosures: Kai-Chi Chang: Nothing to Disclose, Chia-Ray Lin: Nothing to Disclose, Bang-Yu Liou: Nothing to Disclose, Huey-Ling Chen: Nothing to Disclose

4605 | DISCREPANCIES IN STANDARDIZED ASSESSMENT AND DISEASE BURDEN OF PRURITUS IN BILIARY ATRESIA

Natasha Dilwali[1] Rozanne Groen[2] Alex Brenner[2] Nadia Ovchinsky[2] Jennifer Vittorio[2], [1]Johns Hopkins University, [2]NYU Grossman School of Medicine

Background: Pruritus is a debilitating symptom in cholestatic liver diseases, yet remains understudied in biliary atresia (BA). Evidence from other pediatric subspecialties suggests a gap between caregiver-reported symptoms and provider documentation, raising concerns about under-recognition. Although validated tools exist to assess cholestatic pruritus and its impact on quality of life, they are not routinely used in clinical practice. The goal of this study is to evaluate provider

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screening practices for pruritus and compare them with caregiver-reported experiences in children with BA. **Methods:** A cross-sectional survey was conducted among caregivers and providers of pediatric patients with BA. Caregivers of children ≥6 months were recruited via the Biliary Atresia Research and Education (BARE) network and NYU Langone clinics. Providers were recruited through the international Pediatric Gastroenterology ListServ. Separate surveys assessed demographics, medication use, and pruritus-related experiences. Descriptive statistics summarized responses, and comparisons were made between caregiver and provider perspectives. **Results:** Of 67 provider respondents, 35.8% (n = 24) had managed more than 20 BA patients in the past five years; 59.7% (n = 40) were hepatologists. While 85.2% reported routinely screening for pruritus, this was more common among hepatologists (97.1%) than gastroenterologists (69.2%). 27% of hepatologists and none of the gastroenterologists used validated assessment tools. Discrepancies emerged between provider perceptions and caregiver reports. While 65.1% of providers believed pruritus disrupted sleep for both children and caregivers, only 42.9% (24/56) of caregivers recalled being asked about sleep. Differences were also observed in reported pruritus locations: hepatologists most frequently identified the ears (67.6%), gastroenterologists cited generalized pruritus (73.1%), while caregivers most commonly reported the legs (30.3%), with fewer describing generalized itching (18.2%). **Conclusion:** A disconnect exists between provider perceptions and caregiver-reported experiences of pruritus in children with BA. Although screening is frequently reported, use of validated tools is limited, particularly among gastroenterologists. These discrepancies may contribute to under-recognition of symptoms such as sleep disruption. Broader adoption of standardized assessment methods and targeted education may improve symptom recognition and management in this vulnerable population.

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4606 | ODEVIXIBAT RAPIDLY REDUCES PRURITUS AND SERUM BILE ACIDS IN CHILDREN WITH BILIARY ATRESIA AND CHRONIC CHOLESTASIS FOLLOWING KASAI PORTOENTEROSTOMY

Emanuele Nicastro[1] Angela Marino[1] Lorenza Matarazzo[1] Fernanda Cristofori[2] Ruggiero Francavilla[2] Gabriella Nebbia[3] Giulia Paolella[3] Alessandro La Rosa[4] Annalisa Madeo[4] Antonio Marseglia[5] Eleonora Severi[1] Lorenzo D'Antiga[1] Angelo Di Giorgio[1], [1]ASST Papa Giovanni XXIII, Bergamo, Italy, [2]Pediatric Hospital Giovanni XXIII, Bari, Italy, [3]Ospedale Maggiore Policlinico, Milan, Italy, [4]IRCCS Giannina Gaslini, Genoa, Italy, [5]IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy

Background: Biliary atresia (BAtr) is a major cause of neonatal cholestasis, and the most common indication to pediatric liver transplantation. Children surviving with native liver after Kasai portoenterostomy (KPE) may present chronic cholangiopathy, residual cholestasis, and fibrotic progression. Ileal Bile Acid Transporter (IBAT) inhibitors have not been studied in these patients. We assessed safety and efficacy of Odevixibat in BAtr children with cholestatic pruritus. **Methods:** Odevixibat was administered at a dosage of 40 μg/kg/d QD. Complete pruritus response was defined as a score ≤1 of the 0-to-4 points Pruritus Global Impression Scale (PGIS). Serum bile acid (sBA) response was defined as sBA decrease ≥50%, and was defined complete in presence of total sBA ≤75 μmol/L. **Results:** Seven children [4 females, median age 7.5 years (range 1.1-11.5), KPE performed at 67 (60-95) days of life] were included. Five had liver fibrosis (≥12 kPa) at transient elastography, and 4 clinically evident portal hypertension; mean baseline bilirubin was 2.2 ± 1.3 mg/dL. All the patients had a complete pruritus response after a median time of 2 weeks, with a PGIS score decreasing from 2.8 ± 0.8 (baseline) to 1.1 ± 1 (week 2, $p = 0.003$), and 0.2 ± 0.4 (week 16, $p < 0.001$). Likewise, all had sBA response, which was complete in 6 of them. sBA decreased from 239 ± 115 (baseline) to 85 ± 122 (week 2, $p = 0.005$), and 57 ± 19 μmol/L (week 24, $p = 0.052$), with a median decrease of -75% (range: -55% to -86%). Transient grade 1 diarrhea was recorded in one patient. **Conclusion:** This is the first report of Odevixibat in children with BAtr. Odevixibat is highly effective and safe in cholestatic pruritus in children with BAtr and residual cholestasis after KPE.

Disclosures: Emanuele Nicastro: Nothing to Disclose, Angela Marino: Nothing to Disclose, Lorenza Matarazzo: Nothing to Disclose, Fernanda Cristofori: Nothing to Disclose, Ruggiero Francavilla: Nothing to Disclose, Gabriella Nebbia: Nothing to Disclose, Giulia Paolella: Nothing to Disclose, Alessandro La Rosa: MIRUM: Advisory Board, Annalisa Madeo: Nothing to Disclose, Antonio Marseglia: Nothing to Disclose, Eleonora Severi: Nothing to Disclose, Lorenzo D'Antiga: Selecta: Advisor, Vivet: Advisor, Spark: Advisor, Genespire: Advisor, Tome: Advisor, Mirum: Advisor, Ipsen/Albireo: Advisor, Intercept/Advanz Pharma: Advisor, Alexion/Astra Zeneca: Advisor, Fractyl: Advisor, Angelo Di Giorgio: Ipsen Pharma: Consultant, Mirum Pharma: Consultant

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4607 | PREDICTORS OF BIOCHEMICAL REMISSION FOR PEDIATRIC AUTOIMMUNE HEPATITIS IN NORTH AMERICAN MULTICENTER LEARNING HEALTH NETWORK

Mary Ayers[1] Cyd Castro-Rojas[2] Rebekah Karns[2] Leina Alrabadi[3] Heli Bhatt[4] Kate Cheng[5] Ranita Datta[6] Nitika Gupta[7] Jennifer Halma[8] Sakil Kulkarni[9] Shelby Mecklenborg[10] Katelyn Saarela[11] Emily Rothbaum Perito[5] Alexander Weymann[12] Mandy Zhu[2] James Squires[13] Alexander Miethke[2] Amy Taylor[2], [1]UPMC Children's Hospital of Pittsburgh, [2]Cincinnati Children's Hospital Medical Center, [3]Stanford/Lucile Packard Childrens Hospital, [4]University of Minnesota Children's Hospital, [5]University of California, San Francisco, [6]Children's Hospital of Atlanta, [7]Emory University School of Medicine, [8]Children's Mercy Hospital, [9]Washington University in St. Louis, [10]University of Cincinnati, [11]Seattle Children's Hospital, [12]Nationwide Children's Hospital, [13]Children's Hospital of Pittsburgh

Background: Poor outcomes in pediatric-onset Autoimmune Hepatitis (AIH) can lead to liver transplant before adulthood. Biochemical remission at 6 months after AIH diagnosis is associated with event-free survival in adults. We evaluated a diverse multi-center retrospective cohort of children with AIH in the Autoimmune Liver disease Network for Kids (A-LiNK) to determine factors associated with 6- and 12-month biochemical remission. **Methods:** This retrospective study included children 2-21 years old diagnosed with AIH without concurrent liver disease at 9 A-LiNK centers between 2010-2020 with $\geq$12 months of follow-up. Biochemical remission was defined as normalization of serum aminotransferases (AST and ALT) for age/sex. Baseline predictors for remission were computed using Wilcoxon rank-sum and Fisher's exact tests. P-values were corrected for multiple testing using false discovery rate (FDR), with FDR $<$ 0.05 significant. **Results:** 216 children and adolescents with AIH, 67% were female; 71% White, 21% Black; with 90% non-Hispanic. (TABLE 1) Median age at AIH diagnosis was 13.2 years, with 69% type 1, 15% type 2, and 16% seronegative. Biochemical remission rates were 62% at 6 months and 73% at 12 months. Lower FIB4, a fibrosis biomarker, was associated with remission at both 6 and 12 months. Lower BMI Z-score, higher platelets, and lower INR were associated with 12-month remission.

Durable remission—normal transaminases by month 9 sustained at month 12—occurred in 61% of 165 patients. Twenty-one percent never achieved remission, and 18% achieved temporary remission. Durable remission was associated with higher initial dose of prednisone per body weight (1 vs 0.7 mg/kg/day, p = 0.0009, FDR = 0.016), especially in children with initial GGT $>$ 50 IU/L (OR = 3.31, p = 0.0017). Nondurable remission was associated with higher BMI at 12 months (22.6 vs 19.2 kg/m2, p = 0.011, FDR = 0.088) and increased prednisone dose at 12 months (10 vs 5mg, p = 0.013, FDR = 0.088). Baseline and 12-month doses of azathioprine were not associated with remission. **Conclusion:** This is the largest pediatric multi-center AIH cohort in North America, with similar 6- and 12-month remission rates as previously described in single-center studies. These findings suggest higher induction doses of prednisone are associated with durable remission, regardless of induction azathioprine dose. Comparative effectiveness studies are needed to determine best induction regimens to achieve early biochemical remission.

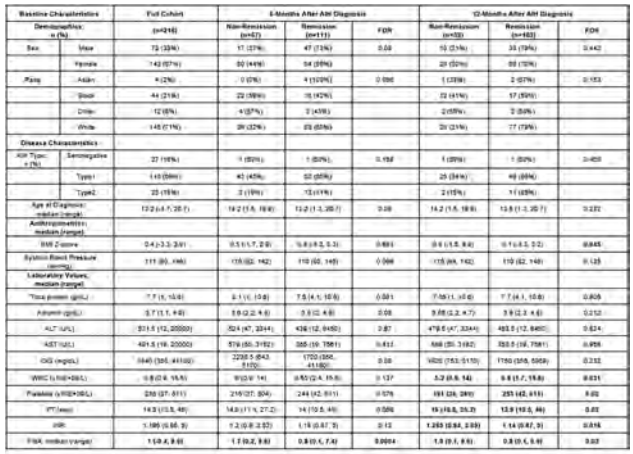

Table 1: Baseline characteristics of 216 children with AIH diagnosed between 2010-2021 at 9 A-LiNK centers. Continuous variables are displayed as median and range.

Disclosures: Mary Ayers: Nothing to Disclose, Cyd Castro-Rojas: Nothing to Disclose, Rebekah Karns: Nothing to Disclose, Leina Alrabadi: Nothing to Disclose, Heli Bhatt: Nothing to Disclose, Kate Cheng: Nothing to Disclose, Ranita Datta: Nothing to Disclose, Nitika Gupta: Nothing to Disclose, Jennifer Halma: Nothing to Disclose, Sakil Kulkarni: Nothing to Disclose, Shelby Mecklenborg: Nothing to Disclose, Katelyn Saarela: Nothing to Disclose, Emily Rothbaum Perito: Nothing to Disclose, Alexander Weymann: Nothing to Disclose, Mandy Zhu: Nothing to Disclose, James Squires: Sanofi: Data Safety Committee, Mirum: Advisor, Ipsen: Advisor, Alexander Miethke: Mirum Pharmaceutical Inc: Grant/Research Support, Mirum Pharmaceutical Inc: Consultant, Ipsen: Speaking and Teaching, Amy Taylor: Nothing to Disclose

4608 | TITLE: EPIDEMIOLOGICAL CHARACTERISTICS OF CHILDREN WITH WILSON DISEASE: A SINGLE-CENTER EXPERIENCE FROM BRAZIL

Rafaella Karen Sousa Monterlei[1] Camila Oliveira Hansen[2] Ana Leticia Fernandes Coelho de Oliveira[3]

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Gabriel Nuncio Benevides[3] Mirella Cristiane de Souza Bolognini[3] Maria Tereza Guiotti[3], [1]ICr HC FM USP - The University of São Paulo (USP), [2]ICr HC FM USP - The Univervisity of São Paulo, [3]ICr HC FM USP - The University of São Paulo

Background: Background:: Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism caused by mutations in the ATP7B gene, leading to toxic accumulation of copper in the liver, brain, and other organs. Clinical manifestations range from asymptomatic to severe hepatic or neuropsychiatric presentations. This study aims to describe the epidemiological and clinical follow-up data of pediatric WD cases at a single center in Brazil. **Methods:** Methods:: A retrospective, descriptive review of medical records was conducted for pediatric patients diagnosed with WD between 2010 and 2025 at a tertiary care center in Brazil. **Results:** Results:: Twenty-six patients with WD were included, with a minimum follow-up of 12 months. The mean age at first consultation was 9.4 years; 53.8% were female. Genetic testing was performed in 14 out of 26 patients (53.8%), and all had diagnostic mutations identified in the ATP7B gene. The most common initial presentations were incidental transaminase elevation (46.1%) and positive family screening (30.7%). Additional findings included hepatomegaly (15.3%), jaundice (7.6%), neuropsychiatric symptoms (3.8%), and acute liver failure (3.8%). Kayser-Fleischer rings were present in 34.6%, and brain MRI abnormalities were noted in 23%. Liver biopsy, performed in 7 patients, showed significant fibrosis (F2/F4) in 71.3%. At diagnosis, mean ceruloplasmin and serum copper levels were 5.5 mg/dL (96% $<$10 mg/dL) and 47 mcg/dL, respectively. Urinary copper excretion increased from 229 mcg/24h at diagnosis to 421 mcg/24h at the latest follow-up. Laboratory markers showed significant improvement between the first and last visits: AST (107.5→39.6 U/L), ALT (169.5→61.8), GGT (85→41.3), ALP (318.7→202.8), total bilirubin (1.05→0.66 mg/dL), and INR (1.33→1.18). At last follow-up, 61.5% were adhering to a low-copper diet. Treatment was initiated at a mean age of 9.6 years. Most patients were on penicillamine (96.1%), vitamin B6 (73%), and zinc (11.5%). The most common regimen was penicillamine + B6 (69.2%), with average doses of 16.2 mg/kg/day for penicillamine, 1.6 mg/kg/day for zinc, and 0.85 mg/kg/day for B6. Treatment adherence remained high (88.2% initially vs. 75% at last visit). Adverse effects decreased over time (32%→11.5%), primarily gastrointestinal symptoms and neutropenia, most of which resolved in follow-up visits. **Conclusion:** Conclusion:: This study underscores the importance of early diagnosis and long-term treatment adherence in pediatric WD. Clinical and laboratory improvements were strongly associated with therapy, reinforcing the value of continuous monitoring to prevent disease progression and manage treatment-related adverse effects.

Disclosures: Rafaella Karen Sousa Monterlei: Nothing to Disclose, Camila Oliveira Hansen: Nothing to Disclose, Ana Leticia Fernandes Coelho de Oliveira: Nothing to Disclose, Gabriel Nuncio Benevides: Nothing to Disclose, Mirella Cristiane de Souza Bolognini: Nothing to Disclose, Maria Tereza Guiotti: Nothing to Disclose

4609 | EPIDEMIOLOGICAL AND GENETIC CHARACTERISTICS OF CHILDREN WITH ALAGILLE SYNDROME: A SINGLE-CENTRE EXPERIENCE FROM BRAZIL

Rafaella Karen Sousa Monterlei[1] Camila Oliveira Hansen[2] Maria julia Soares Barbosa[2] Ana Luiza de Aquino Oliveira[2] Mirella Cristiane de Souza Bolognini[2] Maria Tereza Guiotti[2], [1]ICr HC FM USP - The University of São Paulo (USP), [2]ICr HC FM USP - The University of São Paulo

Background: Alagille syndrome (ALGS) is a rare autosomal dominant disorder with multisystem involvement and variable expression. It typically presents in the first 3 months of life, often with cholestasis and pruritus. Most patients carry JAG1 mutations, fewer have NOTCH2 variants. Diagnosis is challenging due to phenotypic variability. We reviewed clinical and genetic findings in Brazilian patients from a single tertiary center. **Methods:** A retrospective and descriptive study was carried out by reviewing medical records of children with ALGS, at single-centre in Brazil in the period from 2001 to 2025. **Results:** 36 patients with ALGS were analyzed, with 72.2% being male. The mean age of symptom onset was 4 months. Among the 19 patients who underwent liver biopsy, ductopenia was present in 16 cases (84.2%) and absent in 3, two of whom were under 6 months old. Regarding fibrosis staging: F0 in 61.1%, F1 in 22.2%, F2 in 5.5%, F5 in 11.1%. 24 patients performed genetic analyses. JAG 1 mutations were identified in 23, but NOTCH 2 mutation was not analysed. Neonatal cholestasis was observed in 77.7%. Typical facies and congenital heart disease were each present in 88.8%, being pulmonary artery stenosis/hypoplasia 78.1%. Additional findings included cognitive impairment (36.1%), short stature (52.9%), nephropathy (41.6%), ophthalmologic abnormalities (47.2%) most commonly posterior embryotoxon (94.1%) and vertebral anomalies in 61%, mainly butterfly vertebrae (77.2%). Pruritus was present in 42.3% at the first visit and 53.1% at the last, though intensity was not recorded. Use of antipruritic medications increased from 33.3% to 80.5%, due to the presence of cholestasis. Medications used were ursodeoxycholic acid, rifampicin, sertraline, cholestyramine and hydroxyzine. Until now, we still do not have the possibility of prescribing any IBAT for our patients.

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Three patients (8.3%) underwent ileal exclusion, with 2 showing improvement in pruritus. Comparing mean laboratory parameters from the first and last consultation: direct bilirubin levels decreased from 4.19 mg/dL to 3.72, GGT decreased from 768.7 to 354.4 U/L, AST/ALT decreased from 190.7/184.5 to 152.1/167.1 U/L. Two patients (5.5%) required liver transplantation. **Conclusion:** This study highlights the variability of clinical features and multisystem involvement in ALGS. Neonatal cholestasis, pruritus, typical facies, and cardiac anomalies were frequent. The findings reinforce the need for early recognition and multidisciplinary care. **Disclosures:** Rafaella Karen Sousa Monterlei: Nothing to Disclose, Camila Oliveira Hansen: Nothing to Disclose, Maria julia Soares Barbosa: Nothing to Disclose, Ana Luiza de Aquino Oliveira: Nothing to Disclose, Mirella Cristiane de Souza Bolognini: Nothing to Disclose, Maria Tereza Guiotti: Nothing to Disclose

4610 | CLINICAL OUTCOMES OF LIVER TRANSPLANTATION IN PEDIATRIC MAPLE SYRUP URINE DISEASE AND DOMINO LIVER RECIPIENTS AT KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTER- SAUDI ARABIA

Mohammad Shagrani[1] Kishwer Kumar[1] Alexandra Aldana[1] Ali Syed Akhtarul Hassan[1] Dalal Albugami[1] Sateesh Maddirevula[1] Saleh A Alqahtani[1] Ehab Abufarhaneh[1] Bandar Mohammed H Aljudaibi[1] Massimo Malago[1] Dieter Broering[1], [1]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Background: Maple Syrup Urine Disease (MSUD) is a rare genetic disease affecting branched chain amino acid metabolism in the liver. Treatment is primarily lifelong protein restriction to prevent devastating neurologic complications; however, compliance is difficult, and severe metabolic crises can still be triggered by acute illness. Elective liver transplantation offers a metabolic cure for classical MSUD patients. An additional benefit is that the explanted MSUD liver can subsequently be transplanted into a *non-MSUD* patient, effectively curing the "domino" recipient's liver disease as well, since the enzymatic deficiency of the MSUD liver can be compensated by other organs in the recipient. The purpose of this retrospective study is to investigate the long-term clinical outcomes of liver transplantation in pediatric MSUD patients and their domino recipients. **Methods:** Data was collected of all the pediatric genetically confirmed MSUD patients and their non-MSUD domino recipients who underwent liver transplantation at KFSHRC between September 1, 2011 and August 31, 2024. **Results:** MSUD patients: 31 pediatric MSUD patients underwent liver transplant at our center. Demographics and complications of these patients are represented in Table 1. Out of the two MSUD patients who required re-transplantation, the first patient underwent liver transplantation at the age of 4 years. Transplant was complicated by biliary stricture followed by chronic rejection and required Re liver transplantation.

The second patient was 9 years old at the time of liver transplantation and developed out flow obstruction. and required Re Liver Transplantation on day 44 of post Liver Transplantation.

Domino liver recipients

Of the 31 explanted MSUD livers, 25 (80%) were utilized for domino transplant, 4 (16%) went to adult domino recipients.

Total 25 patients received MSUD domino livers. Four (16%) of the domino recipients developed ACR. Two (8%) domino recipients required re-transplantation, first one due to primary graft failure and second one due to hepatic artery thrmbosis. There were 2 (8%) mortalities, first one died due to brian herniation and second one died due to cardiac complication secondary to coronary artery disease.

For the majority of domino recipients, post-transplant BCAA levels were mildly elevated but later normalized. Further studies are ongoing on long-term patient and graft outcomes. **Conclusion:** Liver transplantation successfully prevents metabolic crisis in MSUD patients.

Domino MSUD livers are good source of grafts to expand the donor pool thereby decreasing the wait time and wait list mortality.

Table 1	MSUD Patients (n=31)	MSUD Liver Recipients (n=25)
Mean Age at Transplant (yrs), range	4 (range: 5 months - 15 years)	Peciatric: 5.5 years (range: 6 months – 13.5 years); Adults: 31 41, 65 years
Male (%) / Female (%)	13 (42%) / 18 (58%)	9 (36%) / 16 (64%)
Blood Group (%)		
A	8 (26%)	7 (28%)
AB	1 (3%)	1 (4%)
B	4 (13%)	5 (20%)
O	18 (58%)	12 (48%)
Complications (%)		
Acute Cellular Rejection	7 (22%)	4 (16%)
Vascular Complications	3 (10%)	21
Biliary Stricture	1 (3%)	1
Required Re-transplantation	2 (6%)	2 (8%)
Mortality	N/A	2 (8%)

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4611 | CHOLANGIOCYTE REGULATES MACROPHAGE ACTIVATION THROUGH FIBRONECTIN-INTEGRIN INTERACTION

Wenqi Li[1] Ashley Fonseca-Mejia[1] Reena Mourya[1] Pranavkumar Shivakumar[1] Jorge Bezerra[1], [1]University of Texas Southwestern Medical Center

Background: Macrophage has been known to contribute to the pathogenesis of biliary atresia (BA). However, the mechanisms by which macrophages interact with cholangiocytes to promote biliary injury and fibrosis are poorly understood. Here, we investigated the molecular crosstalk used by cholangiocytes to induce macrophage inflammatory cytokine production. **Methods:** Mouse cholangiocyte organoids (mCOs) derived from common bile ducts of BALB/c mice were cocultured with murine macrophages (Raw 264.7 cell line) in Matrigel and analyzed by flow cytometry after 24 and 48 hours of culture. In transwell assays, macrophages and mCOs were separated by 0.4um membrane to block cell-cell interaction. For RNA-seq analysis, mCOs and macrophages were separated by fluorescence-activated cell sorting (FACS) before submitted for sequencing. Ligand-receptor analysis was done using CellChat. Human cholangiocyte organoids (hCOs) from livers of BA patients (BACOs) and normal donors (NCOs) were cocultured with human embryonic stem cell (hESC)-derived macrophages before analysis by flow cytometry. **Results:** Macrophages cocultured with mCOs increased TNFa, IL6 and iNOS expression, which were boosted when macrophages were primed by LPS for 3h. Coculture using transwell assays to block cell-cell interaction reduced TNFa, IL6 and iNOS expression, indicating cell-cell contact is required for enhanced macrophage activation. RNA-seq analysis of sorted macrophages and sorted cholangiocytes post coculture was performed and ligand-receptor interaction using CellChat predicted fibronectin (Fn, ligand on cholangiocyte) and ITGA5/ITGB1 (receptor on macrophages) as the most likely interaction within the coculture. Flow cytometry validated cholangiocyte as the main source of Fn. Macrophages treated with Fn showed increased TNFa expression. This effect was mitigated by either Fn inhibition with RGDS peptide or ITGA5-ITGB1 double knockdown (DKD) using siRNA. In human, Fn, ITGA5 and ITGB1 expression were increased in BA livers, and Fn expression was increased in BACOs vs NCOs. Coculture BACOs with hESC-derived macrophages increased IL6 and IL8 expression compared with NCOs. **Conclusion:** Cholangiocytes induce macrophage inflammatory cytokine production through Fn-ITGA5/ITGB1 interaction. In Biliary atresia, diseased cholangiocytes induce enhanced macrophage inflammatory cytokine production through increased fibronectin production. **Disclosures:** Wenqi Li: Nothing to Disclose, Ashley Fonseca-Mejia: Nothing to Disclose, Reena Mourya: Nothing to Disclose, Pranavkumar Shivakumar: Nothing to Disclose, Jorge Bezerra: Nothing to Disclose

4612 | OUTCOMES OF CONGENITAL PORTOSYSTEMIC SHUNT CLOSURE: EARLY SINGLE-CENTRE INTERVENTIONAL RADIOLOGY EXPERIENCE

Marumbo Paul Mtegha[1], [1]Leeds Children's Hospital

Background: Congenital portosystemic shunts (CPSS) are rare vascular malformations comprising abnormal portovenous connections that bypass the liver, potentially causing hepatic encephalopathy and other complications. Traditionally managed surgically, interventional radiology (IR) provides minimally invasive alternatives. **Methods:** Retrospective cohort study of consecutive patients from 2006-2024 who underwent CPSS closure using radiological techniques. **Results:** Twenty patients (50% male) with a median age of 7.6 years ($\pm$4.5, range 1–15) underwent shunt closure, with a median follow-up of 2.6 years ($\pm$1.8, range 0–6). Most patients presented incidentally with 1 patient presenting with pulmonary hypertension as their primary pathology. Comorbidities included cardiac abnormalities (65%), neurological conditions (25%), chromosomal abnormalities (10%), and syndromic conditions (10%). Technical success, defined as complete shunt occlusion at final follow-up, was achieved in 18 patients (90%). Single-stage closure was performed in 15 patients (75%), while 3 (15%) required $\geq$2 procedures. Devices used included vascular plugs, cardiac septal occlusion devices, stent grafts and embolisation coils, or a combination of devices. Two patients experienced complications: one patient had two episodes of device migration, successfully retrieved, and one patient experienced acute portal vein thrombosis requiring thrombolysis. No patients developed clinically significant portal hypertension. **Conclusion:** IR closure of CPSS is an effective alternative to surgery, with a high technical success rate and low complication risk. Expanding the spectrum of devices used can provide a minimally invasive treatment option for a wider cohort of patients.

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Disclosures: Marumbo Paul Mtegha: Nothing to Disclose

4613 | LIVER CELL-SPECIFIC UNFOLDED PROTEIN RESPONSE GENE EXPRESSION IS LOWER IN NEONATAL COMPARED TO ADULT MICE

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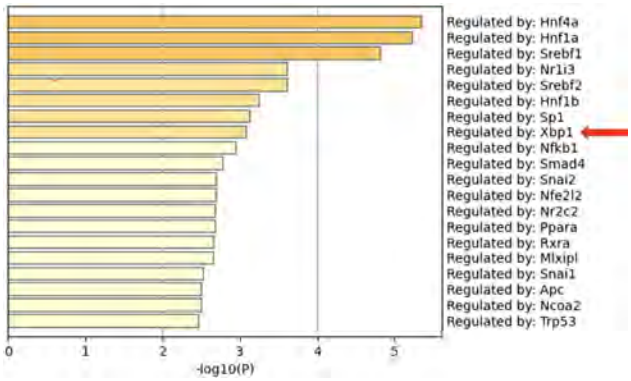
Background: The unfolded protein response (UPR) is a protective response which decreases ER stress. The UPR has ER stress sensors IRE1α/XBP1, PERK and ATF6 which activate their downstream targets. We previously published that young mice have attenuated hepatic XBP1 pathway activation in response to bile acid feeding and pharmacologically induced ER stress, and that expression of this pathway is decreased in human pediatric cholestatic liver disease explants. Additionally, using whole liver RNA-Seq and qPCR, we have also demonstrated that following bile duct ligation (BDL), neonatal mice have decreased expression of UPR pathways. In this study, we sought to elucidate the liver cell-specific age-dependent differences in UPR activation at baseline and during obstructive cholestasis. **Methods:** Female C57BL/6 neonatal (10 day) and adult (8-10 week) mice underwent BDL or sham laparotomy (SL) for 7 days. Serum LFTs and single-nuclei RNA-seq (snRNA-seq) was performed and cell specific (hepatocyte, cholangiocyte, stellate cell) gene expression of *Xbp1, Atf6* and *Perk* and 60 canonical UPR genes were analyzed. Pathway and enrichment analysis utilizing TRRUST was performed utilizing Metascape. **Results:** After BDL, neonatal mice have higher serum alkaline phosphatase (1336 +/- 380 vs 481 +/- 174 U/L, $p < 0.001$) compared to adult mice, with no significant differences in SL mice. After BDL, neonatal mice have significantly decreased hepatocyte-specific expression of *Xbp1* (2-fold, padj < 3x10^-92), *Atf6* (1.8-fold, padj < 2x10^-185) and *Perk* (1.5-fold, padj < 9x10^-17) compared to adult mice, and expression of 31 canonical UPR genes were significantly decreased while 3 genes were increased. Cell-specific analysis of cholangiocytes and stellate cells revealed a decrease of 5 and 14 UPR genes, respectively. Enrichment analysis identified XBP1 is one of the most significant (-log10(P) = 3.1) transcription factors associated with the hepatocyte-specific differentially expressed genes between adults and neonates after BDL (Fig.1), which was not found after SL. After SL, 47 UPR targets were decreased and 3 were increased in hepatocytes, 6 were decreased in cholangiocytes, and 18 were decreased in stellate cells in neonatal compared to adult mice. **Conclusion:** Neonatal mice have higher alkaline phosphatase after BDL compared to adult mice. A greater number of UPR genes are significantly decreased in neonatal compared to adult hepatocytes after BDL. Neonatal cholangiocytes and stellate cells also had diminished UPR gene expression, though less so than hepatocytes. Notably, these decreases in hepatic UPR target expression profiles were also seen in SL operated neonatal compared to adult mice supporting impaired UPR activation at baseline in young mice. We hypothesize this impaired UPR activation in young mice at baseline may predispose to the injury seen the setting of cholestasis and therefore be a potential target for therapeutic intervention.



Disclosures: Alyssa Kriegermeier: Mirum Pharmaceuticals: Advisor, Brian Lecuyer: Nothing to Disclose, Richard Green: Mirum Pharmaceuticals: Advisor

4614 | LAURIC ACID MITIGATES DUCTULAR REACTION, OXIDATIVE STRESS AND HEPATOCYTE SENESCENCE IN A MOUSE MODEL OF INFLAMMATORY CHOLANGIOPATHY

Swati Ghosh[1] Michael Devereaux[1] Colin Anderson[1] Angelo D'Alessandro[1] David Orlicky[1] Ronald Sokol[1], [1]University of Colorado School of Medicine

Background: Inflammatory cholangiopathies are associated with bile ductular reaction, macrophage activation and hepatocyte senescence. We showed that lauric acid (LA), a medium chain fatty acid precursor of the LRH1 agonist DLPC, was hepatoprotective in cholestasis. In this study we examined the mechanism of LA protection in the DDC cholangiopathy mouse model. **Methods:** Mice were administered a 0.1% DDC diet for three days with or without 20% LA dietary supplementation. *In vitro* studies used cultured hepatocytes and cholangiocytes. **Results:** Mass spectrometry-based metabolomics analyses of DDC liver revealed marked accumulation of toxic bile acids, oxidative stress markers, and mitochondrial fatty acid perturbations, with a marked ductular reaction on histology;

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upregulated mRNA expression of *CCL2* in hepatocytes and macrophages from DDC liver; elevated serum CCL2 (ELISA); and upregulated senescence genes. Oxidative injury was confirmed by increased lipid peroxides and nitric oxide in DDC liver. Increased *CCL2* expression was associated with the recruitment of pro-inflammatory monocyte-like macrophages (F4/80^{+}LY6C^{+}). All of these alterations were prevented in the LA supplemented-DDC mice. Furthermore, hepatocytes isolated from DDC mice showed increased expression of oxidative stress genes and lipogenic gene markers, which were significantly reversed by LA supplementation, concomitant with upregulation of genes that promote mitochondrial function. To determine if CCL2 could activate hepatocyte senescence pathways, primary mouse hepatocytes exposed to CCL2 showed STAT1 activation and downstream senescence gene expression (e.g., *Cdkn1b, Cdkn1a*); senescence was confirmed by β-galactosidase staining. Furthermore, ChIP assay in hepatocytes from DDC mice demonstrated direct STAT1 binding to the ***Cdkn1b*** promoter, implicating CCL2-STAT1 signaling in senescence induction. LA treatment in DDC mice prevented this binding. In co-culture of Huh7 cells with H69 cholangiocytes exposed to DDC, DLPC—the active LA-derived LRH-1 agonist—suppressed DDC-induced senescence in Huh7 cells measured by expression of ***CDKN1a*** and ***CCL2.*** **Conclusion:** LA supplementation reduced hepatic inflammation/ductular injury and hepatocyte senescence and oxidative stress in DDC mice in conjunction with inhibition of the CCL2-STAT1 axis which promotes senescence. These studies support activating LRH1 signaling by dietary LA as a protective strategy for inflammatory cholangiopathies.

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4615 | ACTIVATION OF REGULATORY MACROPHAGES BY LRH1 AGONIST DLPC MEDIATES REVERSAL OF CHOLESTATIC INJURY IN THE PRIMARY SCLEROSING CHOLANGITIS MOUSE MODEL

Swati Ghosh[1] Michael Devereaux[2] David Orlicky[2] Yonghua Zhuang[2] Ronald Sokol[2], [1]University of Colorado Denver Anschutz Medical Campus, [2]University of Colorado School of Medicine

Background: Primary sclerosing cholangitis (PSC) is a progressive inflammatory cholangiopathy marked by chronic biliary inflammation and limited treatment options beyond liver transplantation. Dysregulated immune responses are central to its pathogenesis. Previously we showed that the liver receptor homolog-1 (LRH-1) agonist, dilauroyl phosphatidylcholine (DLPC), was protective in a mouse cholestasis model involving parenteral nutrition. This study was conducted to determine if DLPC mitigates injury in a mouse PSC model and its effects on immunosuppressive regulatory macrophages (Mregs), which are associated with the resolution of inflammation and tissue repair. **Methods:** A murine model of PSC used 14-day diet containing 0.1% diethyl 1,4-dihydro-2,4,6-trimethyl-3,5-pyridinedicarboxylate (DDC mice). A group of DDC mice also received intravenous DLPC 30 mg/kg/day for 14 days through a central venous catheter. **Results:** DDC mice exhibited markedly elevated serum AST, ALT, ALP, bilirubin, total bile acids, and a pronounced ductular reaction on histology; all were significantly improved or reversed by DLPC treatment. To assess macrophage phenotypes in DDC mouse liver, RNA-seq of flow-sorted CD45^{+}F4/80^{+} Kupffer cells showed that DDC induced pro-inflammatory and macrophage-like monocyte markers. In contrast, DLPC-treated DDC mice exhibited increased expression of restorative, lipid-associated, and regulatory macrophage (Mreg) gene signature markers, including ***IL10***. ATAC-seq revealed reduced chromatin accessibility at Mreg-related loci in DDC mice; accessibility was restored by DLPC, indicating reactivation of Mreg transcriptional programs. DLPC treatment in DDC mice also induced hepatic phosphorylation of ERK, a known activator of Mregs. To study these effects *in vitro*, cultured bone marrow-derived macrophages (BMDMs) were treated with overnight with DLPC (10 μM) or the known Mreg activator adenosine (100 μM) ± LPS (100 ng/mL) for 4 hr. qPCR analysis showed that DLPC in the presence of LPS, like adenosine, significantly upregulated IL-10, inhibited pro-inflammatory macrophage activation, and promoted Mreg polarization. **Conclusion:** LRH-1 activation by DLPC fosters Mreg activation and confers hepatoprotection in a murine model of PSC through mechanisms involving ERK signaling and IL-10 production. These findings support LRH-1 agonists as promising candidates for immunoregulatory therapy in PSC and related cholangiopathies.

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4617 | EVALUATING THE IMPACT OF GENETIC DIAGNOSIS IN PEDIATRIC LIVER TRANSPLANTATION: A RETROSPECTIVE COHORT STUDY OF 179 CHILDREN AT A SINGLE CENTER

Erika Minonne[1] Angelo Corso Faini[2] Cristina Chiadò[3] Giulia Brach Del Prever[2] Francesco Tito[2] Lucio Queiroz[1] Luigi Marchionni[1] Silvia Catalano[4] Marco Spada[5] Michele Pinon[3] Renato Romagnoli[6] Antonio Amoroso[2] Pier Luigi Calvo[3] Silvia Deaglio[2], [1]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, USA, [2]Immunogenetics and Transplant Biology Unit, University of Turin, Italy, [3]Pediatric Gastroenterology Unit, University of Turin, Italy, [4]General Surgery, Liver Transplant Center, University of Turin, Italy, [5]Pediatric Inborn Errors of Metabolism, Department of Pediatrics, University of Turin, Italy, [6]General Surgery, Liver Transplant Center, Unversity of Turin, Italy

Background: Many pediatric liver diseases continue to be diagnosed at a late stage or without a clear understanding of their underlying molecular basis, leading to liver transplantation without a definitive diagnosis. This study aimed to assess the role of genetic testing in enhancing diagnostic accuracy in this patient population. **Methods:** This retrospective study included 179 pediatric patients (<18 years) who underwent liver transplantation at Molinette Hospital in Turin between 1996 and 2023. Patients were categorized into eight diagnostic groups: biliary atresia (37.4%, n = 67), metabolic disorders (19.6%, n = 35), liver tumors (12.3%, n = 22), membrane transport defects (8.9%, n = 16), genetic syndromes/malformations (5.6%, n = 10), autoimmune diseases (4.5%, n = 8), ciliopathies (3.4%, n = 6), and other conditions (8.4%, n = 15). Demographic, clinical, and surgical data were retrospectively collected from medical records and transplant registries. Genetic analysis was performed using Next-Generation Sequencing (NGS) on peripheral blood DNA, through clinical exome sequencing (CES). Variants were classified according to ACMG guidelines and validated using international databases (ClinVar, OMIM, GnomAD). Survival and risk analyses were performed using Kaplan-Meier estimates and Cox regression models. **Results:** The median age at transplantation was 2.9 years, with a balanced sex distribution (50.3% male) and a predominance of Caucasian patients (92.2%), followed by Asian (3.3%), African (1.7%), and other ethnicities (2.8%). Genetic testing was indicated in 78 cases (43.6%), performed in 66/78 (84.6%), and conclusive in 56/66 (84.9%). Diagnostic yield was 100% in metabolic disorders, membrane transport defects, and ciliopathies; 50% in genetic syndromes/malformations; and 33.3% in the "other" group. No testing was performed in autoimmune or neoplastic diseases. Survival analysis showed a significant association with disease category ($p = 0.029$): biliary atresia had the best outcome (>90% at 20 years), while liver tumors had the worst (~80% at 5 years). No significant impact on survival was found for age at transplant, HLA-DR matching, or crossmatch testing ($p = 0.42$; $p = 0.36$; $p = 0.17$). **Conclusion:** NGS improves diagnostic accuracy by identifying relevant genetic variants, potentially optimizing therapies and improving survival and quality of life.

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4618 | ABCB4 MUTATIONS IN CHILDREN FROM NORTH INDIA: DISTINCT CLINICAL PROFILES AND DECOMPENSATION RISK IN PATIENTS WITH BIALLELIC VERSUS MONOALLELIC VARIANTS

Chennakeshava Thunga[1] Suvradeep Mitra[1] alisha babbar[1] Raghav Lal[1] Sadhna Lal[1], [1]PGIMER, Chandigarh

Background: Progressive Familial Intrahepatic Cholestasis Type 3 (PFIC-3), caused by *ABCB4* mutations, exhibits a variable clinical spectrum and can progress to end-stage liver disease (ESLD). This study aimed to evaluate the clinical, biochemical, and histological profiles of pediatric patients with *ABCB4* mutations, with a focus on genotype-based differences and predictors of hepatic decompensation. **Methods:** In this prospective study (January 2022–March 2025), children (<18 years) with *ABCB4* mutations presenting to a tertiary center in North India were enrolled. Patients were categorized into Group 1 (homozygous or compound heterozygous mutations) and Group 2 (heterozygous mutations). Decompensation was defined as the presence of ascites, gastrointestinal bleeding, and/or encephalopathy. Clinical, laboratory, and histological features were compared across both groups and between compensated and decompensated patients. **Results:** Among 24 patients (58.3% male), 12 had homozygous, 2 compound heterozygous, and 10 heterozygous mutations. Median age at symptom onset

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was 17 months, and at presentation, 50 months. Jaundice and pruritus were present in 70.8%, while ascites and variceal bleed occurred in 16.6% each. Group 1 had a significantly higher rate of decompensation compared to Group 2 (64.3% vs. 20%, $p = 0.04$), along with higher baseline GGT ($p = 0.009$) and lower leukocyte and platelet counts, suggesting hypersplenism. At 6 months and last follow-up (median 28.5 months), Group 2 showed better bilirubin and coagulation profiles. Decompensated patients presented at an older age ($p = 0.03$), with larger spleens ($p = 0.006$), more prominent varices ($p = 0.01$), and higher bilirubin levels across all time points. Histologically, they demonstrated significant ductular reaction ($p = 0.02$), ductular cholestasis ($p = 0.004$), and had higher mortality (54.5%, $p = 0.003$). Twenty-six distinct *ABCB4* variants (80.76% missense) were identified, including one novel mutation (c.1558C > T). One Group 2 patient progressed to sclerosing cholangitis with ESLD. **Conclusion:** Children with heterozygous *ABCB4* mutations may exhibit milder disease but are still at risk of severe progression. Decompensation is associated with worse clinical and histological features and poorer outcomes, highlighting the need for long-term monitoring and early risk stratification

Comparison of Clinical, Laboratory and genetic parameters between Homozygous and heterozygous ABCB4 mutations

Parameters	Homozygous/Compound heterozygous mutation (N=14)	Heterozygous mutation (N=10)	Significance*
General Characteristics			
Male Gender	8 (57.1%)	5 (50%)	1.00
Age at symptom onset in months (IQR)	36 (6, 102)	10.5 (5, 72)	0.48
Age at presentation in months (IQR)	50 (24, 111)	18 (11, 126)	0.42
Consanguinity	35.7%	10%	0.34
Positive family history	71.4%	30%	0.09
Sibling loss	42.9%	33.3%	1.00
Clinical parameters			
Jaundice	57.1%	50%	0.17
Pruritus	71.4%	70%	1.00
Gastrointestinal bleed	21.4%	10%	0.61
Decompensation	64.3%	20%	**0.04**
Esophageal varix			0.37
No varix	21.1%	25%	
Small varix	30.8%	12.5%	
Large varix	46.2%	12.5%	
Genetics			
Missense mutation	85.7%	80%	1.00
Lab parameters			
First visit (liver/loc)			
Hemoglobin (gdL)	9.1 (7.1, 11.95)	9.95 (7.05, 11.92)	0.93
TLC (X 10^3/L)	5 (2.67, 10.25)	14.5 (6.92, 21.78)	**0.013**
Platelet (X 10^3/L)	162 (71, 229)	415 (137, 577)	**0.009**
TB (mg/dl)	2.14 (1.44, 6.84)	3.84 (1.39, 8.27)	0.41
DB (mg/dl)	1.13 (0.65, 5.95)	2.15 (1.08, 4.14)	0.38
AST (U/L)	179 (109, 249.5)	124.5 (90.75, 234)	0.43
ALT (U/L)	131.5 (68.7, 228)	64.5 (37.25, 118.25)	0.05
ALP (U/L)	388 (285, 640)	266 (205.25, 384)	0.08
GGT (U/L)	171 (95, 479)	70 (17, 148.5)	**0.009**
PT	76 (60, 100)	100 (88, 100)	0.25
INR	1.24 (0.88, 1.53)	1.04 (0.92, 1.11)	0.10
Bile acids (umol/L)	125 (50, 177)	206 (80, 335)	0.22
At 6th month			
TB (mg/dL)	2.58 (1.25, 10.85)	0.84 (0.44, 1.45)	**0.01**
DB (mg/dL)	1.39 (0.47, 5.69)	0.18 (0.08, 0.78)	**0.01**
AST (U/L)	179 (50.5, 329.5)	74 (33.5, 151)	0.19
ALT (U/L)	140 (82.5, 247.75)	50 (22, 191)	0.15
ALP (U/L)	603 (273.5, 862)	220 (72.5, 315.25)	**0.04**
At last visit			
TB (mg/dl)	2.13 (0.93, 17.26)	0.55 (0.28, 6.81)	**0.02**
DB (mg/dl)	0.78 (0.32, 8.37)	0.15 (0.09, 4.32)	**0.05**
AST (U/L)	189.5 (96.25, 540.75)	51.5 (35.25, 185.25)	0.06
ALT (U/L)	122 (84.75, 252.25)	38.5 (26.5, 79.75)	0.05
ALP (U/L)	329 (152.5, 724)	310 (155.25, 503.5)	0.71
GGT (U/L)	146 (95, 310)	11 (10.25, 14.75)	**0.005**
INR	1.20 (1.09, 1.68)	1.05 (1, 1.18)	**0.04**
Histopathology parameters			
Portal fibrosis			0.32
• Absent	0%	10%	
• Portal/Periportal Fibrosis	0%	10%	
• Periportal bridging fibrosis (<50% of portal tract)	14.2%	0%	
• Periportal bridging fibrosis (>50% of portal tract)			
• Portocentral bridging fibrosis with cirrhotic nodule formation	21.42%	40%	
	57.14%	40%	
Ductular reaction			0.20
None	0%	10%	
Mild (<5 portal tract)	21.4%	50%	
Moderate (5–10 portal tract)	28.5%	30%	
Marked (>10 portal tract with elongated/ segmented ductules)	42.8%	10%	
Ductular cholestasis	28.5%	0	0.1
Hepatocellular/Canalicular cholestasis	50%	88.9%	0.15
Total duration of follow up in months	45 (9.5, 80.75)	23 (11.75, 60)	0.81
Outcomes			
Mortality	35.7%	10%	0.34
LT	14.3%	0	0.48

Abbreviations: TB: Total Bilirubin; DB: Direct bilirubin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; GGT: Gamma-Glutamyl Transferase; PT: Prothrombin Time; INR: International Normalized Ratio; LT: Liver transplantation

Disclosures: Chennakeshava Thunga: Nothing to Disclose, Suvradeep Mitra: Nothing to Disclose, alisha babbar: Nothing to Disclose, Raghav Lal: Nothing to Disclose, Sadhna Lal: Nothing to Disclose

4619 | SPERMIDINE MODULATES IMMUNE NETWORKS AND REDUCES SEVERITY OF LIVER INJURY IN THE MOUSE MODEL OF BILIARY ATRESIA

Kathryn Kilpatrick[1] Eric Katz[1] Colin Shearn[2] Matthew Burchill[3] William Janssen[4] Ronald Sokol[5] Sarah Taylor[6], [1]University of Colorado, [2]University of Colorado Denver, [3]University of Colorado - Anschutz, [4]National Jewish Health, [5]University of Colorado School of Medicine, [6]Children's Hospital Colorado

Background: Biliary atresia (BA) is a fibroinflammatory disease of infants without medical therapies to slow disease progression. The polyamine spermidine (SPD) plays a critical role in driving anti-inflammatory macrophage polarization; however, it's role in BA remains poorly defined. We used the mouse model of Rhesus Rotavirus (RRV) induced BA to define the mechanism by which SPD may reduce hepatic injury in BA. **Methods:** Wild-type Balb/c neonatal mice received intraperitoneal (IP) RRV (murine BA) or saline (SLN; controls) within the first day of life (DOL 0) followed by IP SLN or SPD on DOL4, 6, 8, and 10, resulting in 4 experimental groups: 1) RRV-SLN, 2) RRV-SPD, 3) SLN-SLN, 4) SLN-SPD. Whole liver tissue was collected on DOL12 for histologic evaluation of liver injury (Ishak score), gene expression, and flow cytometry. Flow cytometry identified CD4+ and CD8+ T cells, Ly6g + neutrophils, F4/80^{hi}CD11b^{lo} tissue-resident macrophages (Kupffer cells, KC), and F4/80^{lo}CD11b^{hi} monocyte-derived macrophages (MoM). Statistical analyses included Student's t-test (Ishak score) and ANOVA with Bonferroni. **Results:** Comparison of Ishak scores between murine BA groups showed reduced severity of hepatic injury in RRV-SPD vs RRV-SLN mice (mean 10 vs 6.1, $p < 0.001$, Figure 1A). Among all groups, RRV-SPD mice had reduced whole liver expression of the pro-inflammatory genes *Il6*, *Il33*, *Ccl2*, and *Il1β* ($p < 0.05$ for all, Figure 1B) whereas levels of *Il10, Ifng,* and *Tnfa* did not differ. RRV-SPD mice also had decreased levels of the pro-fibrotic gene *Tgfb1* ($p = 0.03$). Flow cytometry analysis of CD45+ live cells demonstrated reduced frequency of MoM and increased MoM MHCII mean fluorescence intensity (MFI) in RRV-SPD vs RRV-SLN mice ($p < 0.001$ for both). In contrast, there were no significant differences in KC frequency or KC MHCII MFI between murine BA groups. Among other immune cell subsets, RRV-SPD had an increase in the proportion of neutrophils

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($p < 0.001$) but no difference in the proportion of CD4+ or CD8+ T cells. **Conclusion:** Cumulatively, our data support the premise that SPD improves hepatic injury in murine BA by reducing hepatic inflammation and stimulating anti-inflammatory MHCII-positive MoM polarization. Ongoing studies will define the functional significance of SPD-driven changes in macrophage phenotype and immune cell networks. Findings from our work may support SPD as a potential therapeutic target in infants with BA.

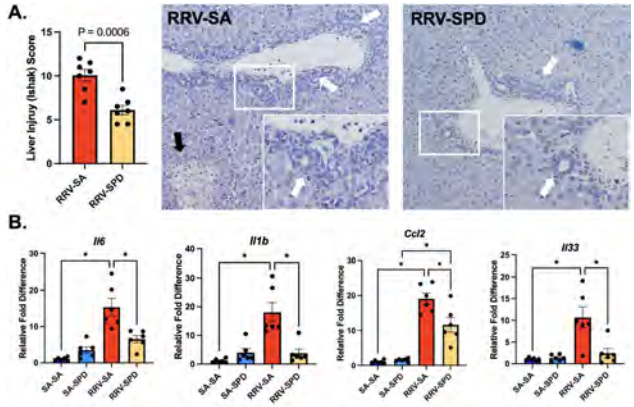

Figure 1. A. Histologic injury by Ishak Score is reduced in murine BA (RRV) mice treated with spermidine (SPD) vs saline (SA) at DOL12 (n=7 per group). H&E images show lower portal inflammatory infiltrate (white arrows) and reduced parenchymal necrosis (black arrow) in SPD-treated mice. **B.** Whole liver tissue gene expression shows significant reduction in the pro-inflammatory genes *Il6*, *Il1b*, *Ccl2*, and *Il33* after SPD treatment. *p<0.05 for multiple comparisons.

Disclosures: Kathryn Kilpatrick: Nothing to Disclose, Eric Katz: Nothing to Disclose, Colin Shearn: Nothing to Disclose, Matthew Burchill: Nothing to Disclose, William Janssen: Nothing to Disclose, Ronald Sokol: Mirum: Advisor, Ipsen/Albireo: Advisor, Malinkrodt: Consultant, Alexion: Consultant, Sarah Taylor: Mirum Pharmaceuticals: Consultant, Ipsen Pharmaceutical: Consultant, Mirum Pharmaceutical: Consultant, Ipsen Pharmaceutical: Consultant, Capsida Biotherapeutics: Consultant

4620 | CHARACTERIZING COGNITIVE DEFICITS AND NEUROINFLAMMATION IN A NOVEL MOUSE MODEL OF PEDIATRIC TYPE C HEPATIC ENCEPHALOPATHY

Kathryn Rhodes[1] Juliet Venter[1] Jace Tyson[1] Mihika Patankar[1] Yubo Wang[1] Patrick Mireles[1] Brandy Routh[1] Kiersten Bell[1] Laura Fonken[1] Sharon DeMorrow[1], [1]The University of Texas at Austin

Background: Background: Hepatic encephalopathy (HE) describes the neurological deficits arising from liver impairment. Children with chronic liver disease are at a heightened risk for long term consequences of HE if an episode coincides with crucial neurodevelopmental periods. Little is known about the pathology of pediatric HE, nor the long-term consequences, due to a lack of a suitable rodent model of pediatric HE. The aim of the current work was to establish a rodent model of Type C HE in juvenile mice that will allow for the temporal assessment of the impact of an episode of HE on subsequent brain function. **Methods:** Methods: C57/Bl6 mice at postnatal day 14 were injected with 0.2 µL/kg (ip) CCl_4 or corn oil (vehicle) 3 times per week for 8 weeks. Blood ammonia was assessed to monitor liver function over time. Behavioral assessments for cognition, neuromuscular ability, balance, and learning and memory were performed during weeks 6 and 7 of treatment. Liver pathology was assessed via serum chemistries and standard histological assessments. Microglia morphology was visualized by Iba-1 immunoreactivity, and the number of glia, soma size and cellular complexity or branching of the cells were assessed. **Results:** Results: Blood ammonia levels were significantly increased in CCl_4-treated mice at all time points and markers of liver pathology were consistent with chronic liver disease. CCl_4-injected mice displayed i) hyperammonemia in brain tissue; ii) neuromuscular deficits (decreased grip strength and time and distance on the Rota-rod); iii) impairment in well-being (nest building assay); iv) deficits in balance and presence of ataxia (balance beam test); and v) impairment in learning and memory (novel object recognition). Furthermore, there was an increase in the number of microcroglia in the frontal cortex, cerebellum and hippocampus in both male and female mice after CCl_4 injection. Closer assessment of microglia morphology showed a significantly larger soma size and reduced branching, consistent with a reactive and amoeboid shape. **Conclusion:** Conclusions: Treatment of juvenile mice with CCl_4 resulted in impaired cognitive and neurological function, hyperammonemia and increased microglia reactivity. This model allows for further investigation of brain recovery patterns, impacts of HE on a developing brain, and pathology of pediatric HE.
Disclosures: Kathryn Rhodes: Nothing to Disclose, Juliet Venter: Nothing to Disclose, Jace Tyson: Nothing to Disclose, Mihika Patankar: Nothing to Disclose, Yubo Wang: Nothing to Disclose, Patrick Mireles: Nothing to Disclose, Brandy Routh: Nothing to Disclose, Kiersten Bell: Nothing to Disclose, Laura Fonken: Nothing to Disclose, Sharon DeMorrow: Nothing to Disclose

4621 | EPIDEMIOLOGICAL PROFILE OF CHILDREN WITH PFIC UNDERGOING LIVER TRANSPLANTATION AT A REFERRAL CENTER IN SOUTHEASTERN BRAZIL

Rafaella Karen Sousa Monterlei[1] Janaina de Oliveira Poy[2] Ana Luiza de Aquino Oliveira[2] José Vitor Guedes

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Tomazela[2] Layse Amazonas Silva[2] Marina Isadora de Andrade Lemos[2] Mirella Cristiane de Souza Bolognini[2] Maria Tereza Guiotti[2] Ana Cristina Aoun Tannuri[2], [1]ICr HC FM USP - The University of São Paulo (USP), [2]ICr HC FM USP - The University of São Paulo

Background: Progressive Familial Intrahepatic Cholestasis (PFIC) comprises a heterogeneous group of rare autosomal recessive disorders characterized by cholestasis, which frequently progresses to end-stage liver disease and often requires liver transplantation. **Methods:** To describe the clinical and epidemiological profile, as well as the outcomes, of patients with PFIC undergoing liver transplantation in order to characterize this population. Retrospective descriptive study of patients with PFIC who underwent liver transplantation before the age of 18 between 2000 and 2025 at the Instituto da Criança (FMUSP). Data analyzed included clinical, genetic, surgical, and outcome information extracted from medical records. **Results:** Among 21 patients followed for PFIC, 15 underwent liver transplantation. Of those transplanted, 33% were male and 66.6% were diagnosed with PFIC type III. The mean ages at symptom onset and at transplantation were 23.7 and 70.9 months, respectively. Pre-transplant clinical manifestations included diarrhea (20%), growth retardation (33.3%), and pruritus (73.3%). After transplantation, the prevalence of diarrhea increased to 33.3%, while growth retardation showed improvement, with mean height z-scores changing from -2.23 before to -1.6 after transplantation. Regarding pre-transplant disease severity, 46.6% of patients were classified as CHILD B, with mean PELD/MELD and corrected PELD/MELD scores of 20.1 and 59, respectively. Cadaveric donors accounted for 73.3% of the transplants. The overall survival rate was 93.3%, with a current mean post-transplant survival of 149 months. Regarding complications, 93.3% of patients experienced at least one, with rejection being the most common (66.6%), classified as chronic (30%), acute (60%), and hyperacute (10%). Only 13.3% required retransplantation, and there was one recorded death in the cohort. **Conclusion:** This study demonstrates that liver transplantation significantly improves clinical conditions such as pruritus and growth retardation in patients with PFIC. Despite the high incidence of rejection, post-transplant survival is favorable, with a survival rate of 93.3% and an average follow-up of nearly 12 years. These findings support the efficacy of liver transplantation as a therapeutic option for this severe and progressive disease.

Disclosures: Rafaella Karen Sousa Monterlei: Nothing to Disclose, Janaina de Oliveira Poy: Nothing to Disclose, Ana Luiza de Aquino Oliveira: Nothing to Disclose, José Vitor Guedes Tomazela: Nothing to Disclose, Nothing to Disclose, Layse Amazonas Silva: Nothing to Disclose, Marina Isadora de Andrade Lemos: Nothing to Disclose, Mirella Cristiane de Souza Bolognini: Nothing to Disclose, Maria Tereza Guiotti: Nothing to Disclose, Ana Cristina Aoun Tannuri: Nothing to Disclose

4622 | LIVER ELASTOGRAPHY IN PEDIATRIC PATIENTS WITH ALAGILLE SYNDROME RECEIVING MARALIXIBAT THERAPY: A REAL-WORLD SINGLE-CENTER STUDY

Aglaia Zellos[1] Paraskevi Galina[2] Evaggelia Lykopoulou[2] Zoi Chatzikonstantinou[3] Daphne Margoni[2] Angeliki Moudaki[2] Elissavet Georgiadou[2] Irini Batsis[1] Maria Rogalidou[4] Christina Kanaka-Gantenbein[1], [1]National and Kapodistrian University of Athens Medical School, Greece, [2]Agia Sophia Children's Hospital, Athens Greece, [3]Mitera Children's Hospital, Athens Greece, [4]Agia Sophia Children;s Hospital, Athens Greece

Background: Patients with Alagille syndrome (ALGS) exhibit progressive liver fibrosis. While Maralixibat, an ileal bile acid transporter (IBAT) inhibitor, has demonstrated efficacy in reducing pruritus and cholestasis in ALGS patients aged >2 months. However, its impact to disease progression and liver fibrosis remains to be characterized. Our aim is to assess the effectiveness of Maralixibat in cholestasis, and liver fibrosis in children with genetically confirmed ALGS and persistent cholestatic pruritus, managed at the Hepatology clinic of a single tertiary referral center. **Methods:** This prospective observational study included patients with ALGS receiving Maralixibat at an initial dose of 190 mcg/kg in week 1, followed by 380 mcg/kg daily. All patients had previously been treated with ursodeoxycholic acid, rifampicin, hydroxyzine, and fat-soluble vitamins, which were continued during the study. Pruritus assessment using the Itch(RO) questionnaire, liver biochemical parameters, and 2D shear wave liver elastography (2D-SWE) were performed at baseline and during follow-up. Elastography was performed by a single experienced pediatric radiologist using LOGIQ E9 and P9 US systems by GE Healthcare[â]. Metavir stage fibrosis corresponding to KPa pediatric cut offs (Galina et al. *Pediatr Radiol* 2021), as follows: 4.7 KPa (F1), 5.8 KPa (F2), 8.7 KPa (F3), 10.3 KPa (F4). **Results:** Seven children (4 females, 3 males; median age 8 years) received Maralixibat for a median duration of 18 months (range: 3–27 months). All had refractory severe pruritus at baseline, despite multidrug therapy. After treatment with Maralixibat, the median Itch(RO) score significantly decreased from 4.0 (IQR: 3.5–4.0) to 1.0 (IQR: 1.0–2.0) after treatment ($p = 0.026$). One patient was able to discontinue rifampicin and hydroxyzine following clinical improvement. Median serum bile acid levels declined

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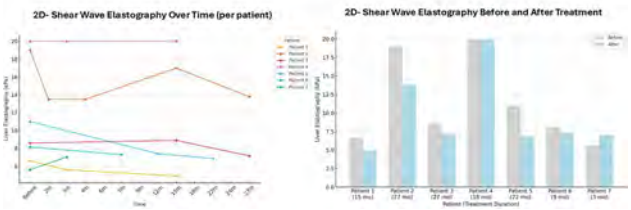
significantly from 90.0 μmol/L (IQR: 72.5–107.5) from baseline to 48.8 μmol/L (IQR: 32.3–66.0) during follow-up ($p = 0.016$). Liver stiffness, measured by 2D SWE elastography, showed a decreasing trend from a median of 8.6 kPa (IQR: 7.4–15.0) to 7.2 kPa (IQR: 7.0–10.6), although the change was not statistically significant ($p = 0.116$), Figure 1. There was no progression of liver fibrosis in 5/7 patients. No serious liver-related events noted in 6/7 patients (1 patient with established cirrhosis, 2D-SWE 20 KPa, improved pruritus but underwent liver transplantation). No patient discontinued treatment due to adverse events.

Conclusion: In this real-world cohort study, children with ALGS who responded to Maralixibat and improved pruritus and serum bile acid levels, showed a favorable trend of decreasing values in liver elastography over time. Although the sample size is small, the effect of Maralixibat seems promising on mitigating disease progression and merits further investigation with recruitment of more patients and a longer follow-up period.

Figure 1. Liver elastography over time in patients with Alagille syndrome treated with maralixibat.



Disclosures: Aglaia Zellos: Ipsen: Advisor, INTEGRIS PHARMA: Speaking and Teaching, NUTRICIA CLINICAL: Speaking and Teaching, Paraskevi Galina: Nothing to Disclose, Evaggelia Lykopoulou: Nothing to Disclose, Zoi Chatzikonstantinou: Nothing to Disclose, Daphne Margoni: Nothing to Disclose, Angeliki Moudaki: Nothing to Disclose, Elissavet Georgiadou: Nothing to Disclose, Irini Batsis: Mirum: Advisor Board, Maria Rogalidou: Nothing to Disclose, Christina Kanaka-Gantenbein: Nothing to Disclose

4623 | ROLE OF LIVER TRANSPLANTATION IN MANAGING PEDIATRIC ORGANIC ACIDEMIAS: A SINGLE-CENTER EXPERIENCE

Mohammad Shagrani[1] Kishwer Kumar[1] Alexandra Aldana[1] Ali Syed Akhtarul Hassan[1] Dalal Albogami[1] Sateesh Maddirevula[1] KRIS ANN MARQUEZ[2] Saleh Alqahtani[1] Bandar Mohammed H Aljudaibi[1] Massimo Malago[1] Dieter Broering[1], [1]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, [2]King Faisal Specialist Hospital And Research Center, Riyadh Saudi Arabia

Background: Organic acidemias are a group of rare inherited metabolic disorders characterized by defects in the breakdown of amino acids, leading to the accumulation of toxic organic acids in the body. These metabolic imbalances can cause severe and life-threatening complications, including metabolic acidosis, developmental delays, and multi-organ damage.

Liver transplantation has emerged as a promising therapeutic option for certain organic acidemias. By replacing the defective liver with a healthy donor organ, transplantation can restore critical enzymatic activity, reduce toxic metabolite accumulation, and significantly improve clinical outcomes. This intervention has the potential not only to enhance metabolic stability but also to improve the quality of life and survival rates in affected patients. **Methods:** To evaluate the clinical indications, outcomes, and long-term benefits of liver transplantation in patients with organic academia (Propionic acidemia and Methymelanic academia), with the aim of determining the necessity and timing of transplantation as a definitive treatment to improve metabolic control and reduce disease-related complications. **Results:** Between 2011 and 2024, a total of 865 pediatric liver transplantations were performed at our center. Of these, 127 patients (14.7%) were diagnosed with metabolic disorders. Among the metabolic group, 35 patients underwent liver transplantation for Propionic Acidemia (PPA), and 4 patients were transplanted for Methylmalonic Acidemia (MMA).

In the PPA cohort, 46% were male and 54% female. All patients received living donor liver transplants, with 91% from living-related donors and 9% from unrelated donors. The median carnitine level before liver transplantation was 19 μmol/L (range 12.7–23), which decreased to a median of 9.9 μmol/L (range 7–11.2) after transplantation. From a complication standpoint, one patient developed hepatic artery thrombosis, another experienced a biliary leak, and one patient required re-transplantation. Acute cellular rejection (ACR) was reported in 9% of the PPA cases.

In the MMA group, 75% were female and 25% male. All patients underwent living donor liver transplantation from living-related donors. The median methylmalonic acid level prior to transplantation was 398 μmol/L (range 389–436), which reduced to a median of 106 μmol/L (range 106–177) post liver transplantation. No complications were observed in this group. Additionally, two domino liver transplants were successfully performed using explanted livers from MMA patients. **Conclusion:** Liver transplantation significantly improves metabolic control and clinical outcomes in pediatric patients with Propionic Acidemia and Methylmalonic Acidemia. The procedure is safe with manageable complications and offers a promising treatment option for these metabolic disorders.

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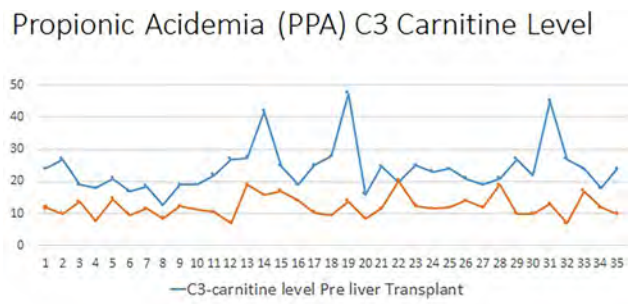

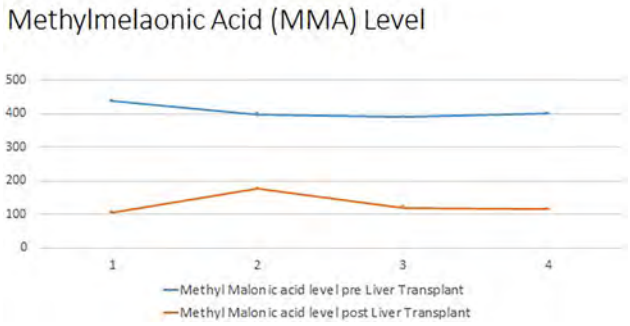

Disclosures: Mohammad Shagrani: Nothing to Disclose, Kishwer Kumar: Nothing to Disclose, Alexandra Aldana: Nothing to Disclose, Ali Syed Akhtarul Hassan: Nothing to Disclose, Dalal Albogami: Nothing to Disclose, Sateesh Maddirevula: Nothing to Disclose, KRIS ANN MARQUEZ: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Bandar Mohammed H Aljudaibi: Nothing to Disclose, Massimo Malago: Nothing to Disclose, Dieter Broering: Nothing to Disclose

4624 | LYMPHATIC INTERACTION WITH AND TRAFFICKING OF IMMUNE CELLS IS ALTERED IN CHOLESTASIS

Alyssa Goldberg[1] William Hollenbach[2] Beth Tamburini[2], [1]Children's Hospital Colorado, [2]University of Colorado, School of Medicine

Background: The liver lymphatic system supports organ health by draining interstitial fluid and immune cells to the lymph node. Patients with primary sclerosing cholangitis have increased lymphatic vessel density in the liver. These findings are replicated in murine models of cholestasis and are associated with increased immune cell infiltrate into the liver. Our study evaluates changes in immune cell populations in the liver and how they correlate with changes in trafficking of immune cells to liver draining lymph nodes. **Methods:** Using flow cytometry, we evaluate immune cell phenotypes in the liver and in liver draining lymph nodes of mdr2*(Abcb4)*-/- mice and correlated with histologic findings including liver injury and fibrosis. To evaluate how changes in immune cell populations correlate with transcriptional changes in the whole liver, we perform RNA extraction and RT-PCR on whole liver tissue from mdr2-/- mice. *In vitro*, we treat cells with pro-inflammatory cytokine IFNg and bile acid to evaluate lymphatic endothelial cells specific expression of markers of immune regulation including immune-checkpoints, and chemokines. **Results:** Liver lymphatics are expanded in a murine model of cholestasis and expansion is associated with an increase in activated T cells both in the liver and in the liver draining lymph node. However, notably while there are fewer Tregs in the liver of mdr2-/- mice, there are more Tregs in the liver draining lymph node. In whole liver PCR, we note an increase in expression of CCL21 and of PD-L1 important for lymphatic recruitment of immune cells and checkpoint inhibition of T cells, respectively. We also demonstrate upregulation of PD-L1 along with chemokines CXCL9,10&11 in lymphatic endothelial cells *in vitro* in response to treatment with IFNg and bile acids. **Conclusion:** This study demonstrates disruptions in immune cell drainage to the liver draining lymph nodes in cholestasis. Our *in* vitro data also suggests that the intrahepatic lymphatic endothelial cells are able to directly respond to the immune-rich and cholestatic environment. In turn, lymphatic endothelial cells may have increased expression of immune checkpoint molecules and chemokines to drive changes in immune cell within the liver by cell-cell signaling and trafficking through the lymphatics by chemokines. These changes in lymphatics may contribute to the liver inflammation and injury in cholestatic liver disease.

Disclosures: Alyssa Goldberg: Nothing to Disclose, William Hollenbach: Nothing to Disclose, Beth Tamburini: Nothing to Disclose

4625 | HEPATOBLASTOMA PATIENT-DERIVED ORGANOIDS, A TOOL FOR PERSONALIZED MEDICINE?

Elise Lelou[1] Abhishek Murti[1] Simon Bucher[1] Saphia Nguyen[1] Matthew Choi[1] Soo-Jin Cho[1] Amar Nijagal[1] Bruce Wang[1], [1]University of California, San Francisco

Background: Hepatoblastoma (HB) is the most common primary pediatric liver cancer. Among childhood tumors, HB has one of the highest mortality rates because 20% of HB cases are high-risk and result in death or require liver transplantation. Efforts to better characterize HB and identify high-risk cases of tumors have been hampered by the high heterogeneity within tumors. Improvement in HB treatment has been limited by the lack of model systems for high-risk HB. We recently used single-cell RNA sequencing to identify

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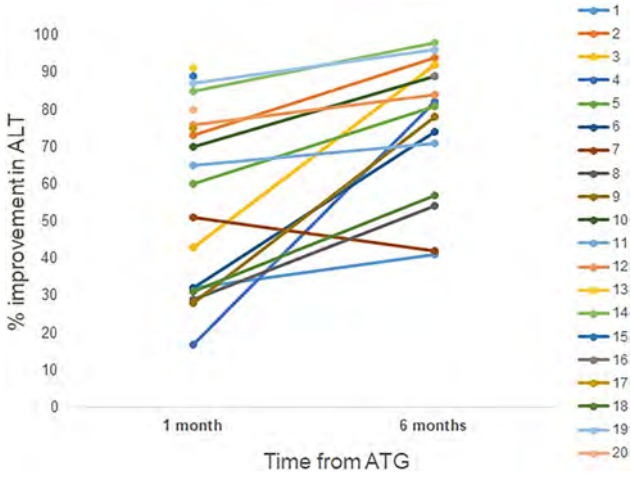
and characterize multiple tumor cell type signatures. We developed 3D-cultured Patient-Derived Organoids (PDO) from freshly resected HB and showed that they retain patient-specific features even after long-term culture. **Methods:** PDO lines from either HB cryopreserved or fresh tissues were cultured in 3D Matrigel droplets using HB growth media for up to 10 passages. Freshly isolated tumor cells and early and late passage (passages 4 and 10, respectively) PDO cells were characterized with single-cell RNA sequencing. The dataset was analyzed using Scanpy in Python. **Results:** We successfully developed 9 PDO lines out of 14 patient HB tumor tissues that can be maintained in 3D long-term culture after multiple passages. From fresh tissues, the success rate of PDO development is 77.78% (7 PDOs out of 9 tumor tissues). These PDO have distinct morphology from one patient to another that stays stable through multiple passages. Using single-cell RNA sequencing, we showed that PDO retain gene expression profiles similar to their freshly isolated parent tumor cells. Early and late passage gene expression profiles from the same patient PDO also remain similar and stable. **Conclusion:** Hepatoblastoma PDO lines grown in long-term 3D culture retain patient-specific features and cell subtypes from their freshly isolated parent tumor cells. This PDO model system will be used for the development of high-throughput drug screening on PDO grouped by HB tumor subtypes to target high-risk HB tumor cells.

Disclosures: Elise Lelou: Nothing to Disclose, Abhishek Murti: Nothing to Disclose, Simon Bucher: Nothing to Disclose, Saphia Nguyen: Nothing to Disclose, Matthew Choi: Nothing to Disclose, Soo-Jin Cho: Nothing to Disclose, Amar Nijagal: Nothing to Disclose, Bruce Wang: Alnylam Pharmaceuticals: Consultant, Recordati Rare Diseases: Consultant, Disc Medicine: Consultant, Mitsubishi Tanabe Pharma: Consultant, Mitsubishi Tanabe Pharma: Grant/Research Support, CRISPR Therapeutics: Consultant

4626 | CHARACTERIZATION OF THE USE OF ANTI-THYMOCYTE GLOBULIN (RABBIT) FOR ALLOGRAFT REJECTION IN PEDIATRIC LIVER TRANSPLANT RECIPIENTS: A SINGLE CENTER EXPERIENCE

Krupa Mysore[1] Dana Cerminara[2], [1]Baylor College of Medicine, [2]Texas Children's Hospital/Baylor College of Medicine

Background: Acute T-cell mediated rejection (TCMR) and antibody mediated rejection (AMR) can pose treatment related challenges in pediatric liver transplant (LT) recipients. Although corticosteroids are used to treat TCMR; children can develop steroid refractory TCMR (SRR). Untreated or recurrent rejection can lead to chronic rejection (CR). Rabbit anti-thymocyte globulin (rATG) is a polyclonal antibody that binds to cell surface antigens to cause T-cell depletion. Limited data exists for the use of rATG for allograt rejection in pediatric LT. We describe the use of rATG in Texas Children's Hospital (TCH), a large pediatric LT center. **Methods:** This study is a retrospective chart review of children aged 0-18 years who received deceased donor LT at TCH. We searched the electronic medical records for children who had for-cause liver biopsy for allograft rejection and received rATG between January 1, 2014 and December 31, 2024. During this period 383 patients underwent LT at TCH. Our center uses tacrolimus and methylprednisone for induction, and tacrolimus for maintenance immunosuppression. Patients received prophylaxis against opportunistic infections for 6 months after rATG treatment. **Results:** 23 patients received 25 courses of 1.5 mg/kg/dose rATG, median 6 doses per patient. Median age at LT was 29.5 months. Median time for rATG was 1.5 years post-LT. Indications for rATG included SRR (n = 14, 56%), AMR (n = 9, 36%), and CR (n = 2, 8%). In the SRR group, 13 patients (93%) had an improvement in ALT, while 10 (71%) had an improvement in GGT. In the AMR group, 9 patients (100%) had improvement both in ALT and GGT. All patients in AMR group also received concurrent antibody-directed therapies. Mean % improvement from baseline in ALT was 56 and 76, and GGT 50 and 98 at one and six months respectively after rATG (Figure 1). Mean absolute lymphocyte count was < 300/uL at end of rATG treatment. None of the patients had adverse events related to medication administration. Neither patient who received rATG for CR had biochemical improvements. Three patients ultimately died, two due to complications related to chronic rejection, and one due to worsening allograft function from biliary strictures and sepsis. **Conclusion:** We conclude that there is a good response to rATG in children with SRR and AMR after LT and is overall well tolerated.



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4627 | THE FARNESOID X RECEPTOR REGULATES CIRCADIAN TRANSCRIPTION FACTOR EXPRESSION ALONG THE GUT-LIVER AXIS DURING PARENTERAL NUTRION

Colin Shearn[1] Aimee Anderson[1] Michael Devereaux[1] Ronald Sokol[2], [1]University of Colorado Anschutz Medical Campus, [2]University of Colorado School of Medicine

Background: We have developed a mouse model of Parenteral Nutrition Associated Liver Disease (PNAC) in which PN infusion results in liver injury and discordant expression of circadian regulatory genes (CR) between the ileum and liver. The aim of this study was to examine the effect of an Farnesoid X Receptor (FXR) agonist on PN-induced dysregulation of ileal and hepatic CR genes, FXR signaling and bile acid homeostasis. **Methods:** WT mice were exposed to continuous soy oil lipid emulsion PN infusion +/- the FXR agonist GW4064 (30mg/kg/d) through a central venous catheter for 4d. Water was provided ad libitum, but no nutrients were provided enterally. On d4, mice were sacrificed at 7AM, and serum, ileal and hepatic tissue obtained. From tissue samples, mRNA expression of CR genes, FXR signaling and gut permeability were assessed. In primary hepatocytes, the impact of an FXR agonist on CR gene expression was determined. **Results:** Administration of 4d PN increased hepatic injury and inflammatory cytokine expression which was ameliorated by GW4064. In the liver, GW4064 treatment increased expression of *Nr1d1* corresponding to suppression of *Nr1f1*, *Nfil3* and *Bmal*. In addition, GW4064 increased expression of *Nr0b2*, prevented PN-dependent increases in *Nr5a2* and *Abcg5* but had no effect on *Abcb11*, *Abcc2*, *Cyp7a1*, *Cyp7b1*, *Cyp8b1* or *Cyp27a1* mRNA expression. In the ileum, GW4064 increased *Nfil3* and *Bmal* and suppressed *Per2* mRNA expression but had no additional effect on FXR target genes *Fgf15*, *Nr0b2*, *Slc51a* (OSTa), *Slc10a2* (ASBT) which were already increased by PN. Activation of FXR restored normal gut permeability by normalizing *Ocln* and *Cldn1* expression. Interestingly, compared to the PN only group, GW4064+PN increased ileal FXR expression suggesting that agonist driven FXR activation prevents PN-induced feedback inhibition of FXR expression. Supporting *in vivo* data, in mouse primary hepatocytes, treatment with obeticholic acid (OCA) for 24hr increased Nr1d1 expression, Fxr binding to the *Nr1d1* promoter and Bmal binding to the *Nr1h4* (FXR) promoter with corresponding decreased Bmal expression. **Conclusion:** Dysregulation of CR machinery is partly due to uncoupling of the gut-liver circadian axis. FXR activation ameliorates PN-induced hepatic injury, gut permeability and restores *Nr1d1* expression. Thus, FXR is a direct regulator of CR transcription factor expression and the use of FXR agonists as a mechanism for restoring normal gut-liver CR expression deserves further investigation.

Disclosures: Colin Shearn: Nothing to Disclose, Aimee Anderson: Nothing to Disclose, Michael Devereaux: Nothing to Disclose, Ronald Sokol: Mirum: Advisor, Ipsen/Albireo: Advisor, Malinkrodt: Consultant, Alexion: Consultant

4628 | EFFECT OF GENERAL ANESTHESIA ON LIVER AND SPLEEN STIFFNESS MEASUREMENTS FOR PREDICTING HIGH-RISK VARICES IN CHILDREN WITH BILIARY ATRESIA

Shinya Yokoyama[1] Takashi Honda[1] yoji ishizu[1] Norihiro Imai[2] Takanori Ito[1] Kenta Yamamoto[1] Chiyoe Shirota[1] Takahisa Tainaka[1] Satoshi Makita[1] Masanao Nakamura[1] Hiroo Uchida[1] Hiroki Kawashima[1], [1]Nagoya University, [2]Nagoya University Graduate School of Medicine

Background: In biliary atresia (BA), portal hypertension and esophagogastric varices (EGVs) can develop even after Kasai portoenterostomy (KP). Early identification of high-risk varices (HRVs) is crucial to prevent variceal bleeding. Two-dimensional shear wave elastography (2D-SWE) enables noninvasive assessment of liver stiffness (LS) and spleen stiffness (SS), which are useful surrogates for portal hypertension. However, in young children, measurement conditions are often unstable due to inability to cooperate with breath-holding and movement artifacts caused by crying. This study evaluated whether performing LS and SS measurements under general anesthesia improves diagnostic accuracy for HRVs in children with BA. **Methods:** Subjects were prospectively enrolled patients with biliary atresia (BA), aged $\leq$15 years, who had undergone Kasai portoenterostomy (KP) and were scheduled for screening esophagogastroduodenoscopy (EGD). LS and SS were measured using 2D-SWE in both the awake and anesthetized states. HRVs were defined based on specific endoscopic findings. Diagnostic performance was assessed using receiver-operating characteristic (ROC) curves and area under the curve (AUC). Correlation between awake and anesthetized values was analyzed using Spearman's rank correlation coefficient. **Results:** Among 39 patients analyzed, The majority of cases (35 cases, 89.7%) had preserved liver function classified as Child-Pugh A. No patients with poor liver function (Child-Pugh C) were included. Girls accounted for 66.7% (26 cases) of the study population. HRVs were identified in 19 (48.7%). The median age was 4 years. In the HRVs group compared with the non-HRVs group, awake-LS, awake-SS, and anesthesia-LS were significantly higher: 2.23 vs. 1.81, 4.40 vs. 3.46, and

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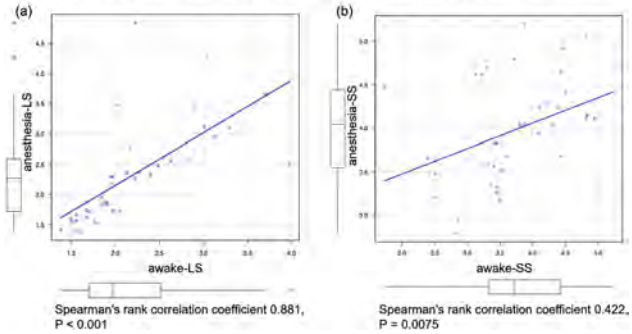
2.56 vs. 1.79 m/s, respectively. Anesthesia-SS did not show a significant difference between the two groups (4.13 vs. 3.67 m/s, P = 0.112). The area under the curve (AUC) for awake-LS, awake-SS, and anesthesia-LS were 0.757, 0.775, and 0.797, respectively. Awake-LS and anesthesia-LS showed a strong positive correlation (ρ = 0.881), while awake-SS and anesthesia-SS had a weak one (ρ = 0.422). **Conclusion:** Awake LS, awake SS, and anesthesia LS all demonstrated good predictive accuracy for HRVs in children with BA. However, SS measured under general anesthesia showed greater variability and reduced predictive value. These discrepancies may be attributed to changes in circulatory dynamics associated with anesthetic agents or mechanical ventilation. Further studies are warranted to evaluate whether LS and SS measurements under mild sedation provide more reliable values compared to those obtained in the awake state in the pediatric population.

Correlation coefficient of measurements between awake and anesthetized states for (a) liver stiffness and (b) spleen stiffness

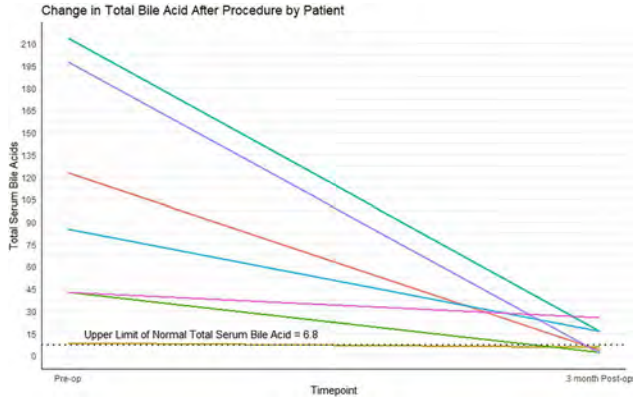


Disclosures: Shinya Yokoyama: Nothing to Disclose, Takashi Honda: Nothing to Disclose, yoji ishizu: Nothing to Disclose, Norihiro Imai: Nothing to Disclose, Takanori Ito: Nothing to Disclose, Kenta Yamamoto: Nothing to Disclose, Chiyoe Shirota: Nothing to Disclose, Takahisa Tainaka: Nothing to Disclose, Satoshi Makita: Nothing to Disclose, Masanao Nakamura: Nothing to Disclose, Hiroo Uchida: Nothing to Disclose, Hiroki Kawashima: Nothing to Disclose

4629 | ELEVATED BILE ACIDS DECLINE AFTER SURGICAL LIGATION OF EXTRAHEPATIC CONGENITAL PORTOSYSTEMIC SHUNT

Lisa Keys[1] Riccardo Superina[1], [1]Ann and Robert H. Lurie Children's Hospital of Chicago

Background: Congenital portosystemic shunts (CPSS) are rare vascular malformations in which mesenteric venous circulation is shunted bypassing the liver. This may result in impaired hepatic clearance of bile acids. We postulate that restoration of portal blood to the liver results in improved clearance of serum bile acids. This study assesses pre-and post-operative bile acid levels to determine the metabolic impact of surgical intervention in pediatric patients with CPSS. **Methods:** Electronic medical records of children diagnosed with CPSS were reviewed at a single pediatric hospital. Demographic and clinical information were collected. Those with available with pre- and post-op total serum bile acid levels between July 1, 2023, and January 21, 2025, were selected for inclusion in the analysis. A paired t-test was performed to compare pre-operative and post-operative levels. Statistical significance was defined as $p < 0.05$. Analysis was conducted using R (4.3.1). **Results:** Seven children were included in our study. The mean age at surgical treatment was 6.5 years (± 5.15). Pre-operative total serum bile acids were elevated with a mean value of 101.7, ±69.9 (reference range ≤ 6.8 umol/L). Post-operative total serum bile acids decreased to mean 10.1, ± 9.3). This decrease was statistically significant: $t(6) = 2.99$, $p < 0.024$, with an effect size of -1.66 (Cohen's d). Four (57%) patients achieved decreased levels to normal levels after ligation while 3 (43%) patients achieved a decrease in total serum bile acid after surgical ligation but not within the reference range. **Conclusion:** Total serum bile acids significantly decreased following surgical closure of CPSS ($p < 0.024$) where 4/7 patients achieved normalization and 3/7 patients achieved an improvement. This finding supports the role of surgical intervention in restoring hepatic bile acid metabolism and mitigating systemic effects of shunting. Prior studies have largely focused on anatomical correction, with limited data on metabolic recovery; our findings help fill this gap. Future studies should explore long-term bile acid trends and the utility of bile acids as a biomarker for post-operative monitoring.



Disclosures: Lisa Keys: Nothing to Disclose, Riccardo Superina: Nothing to Disclose

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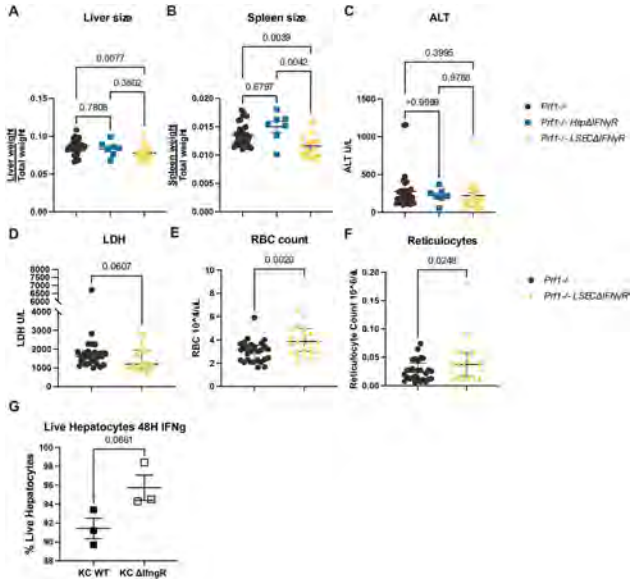
4630 | HEPATIC PARENCHYMAL RESPONSE TO INTERFERON GAMMA IN MOUSE MODEL OF FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Tamir Diamond[1] Michelle Lau[2] Sara Hughes[1] Sarah Mccuaig[1] Niansheng Chu[1] Em Elliott[1] Portia Kreiger[1] Edward Behrens[1], [1]The Children's Hospital of Philadelphia, [2]The Children's Hospital of Phaildelphia / Rowan Medical School

Background: Hepatic inflammation is a common feature of Hemophagocytic Lymphohistiocytosis (HLH). In the mouse model of familial HLH (FHL) hepatic tissue response to interferon gamma (IFNg) results in hepatocellular injury, endotheliitis and increase in CD8+ effector T-cell and CD11b+/Ly6C^{hi} inflammatory monocyte (iMonos) infiltration. However, which parenchymal population responding to IFNg contributes to liver injury in FHL remains unknown. We hypothesized that parenchymal cells- hepatocytes, liver sinusoidal endothelial cells (LSEC) and Kupffer Cells (KC), are the main responders to IFNg perpetuating liver injury in FHL. To test this we conditionally deleted the IFNg receptor (IFNgR) in hepatocytes and LSECs in the perforin 1 deficient (*Pf1-/-*) FHL model and performed in vitro assays assessing KC response to IFNg. **Methods:** For in vivo experiments *Prf1-/-* mice were crossbred to IFNgR floxed mice and then crossbred with a conditional hepatocyte (HepΔIFNgR) or endothelial (LSECΔIFNgR) knock-out (KO) using albumin-cre and Ve-cadherin-cre mice respectively. *Prf1-/-* IFNgR WT *(Prf-/-)*, HepDIFNgR and LSECDIFNgR were infected with Lymphocytic Choriomeningitis Virus (LCMV) to induce FHL physiology according to established protocols. Immunophenotyping was done by histological assessment, biomarkers of hepatocyte injury, serum cytokines and flow cytometry. To assess Kupffer Cell (KC) response to IFNg as part of pathogenesis of liver injury, IFNg unresponsive hepatocytes and KC that were either IFNg responsive (KC WT) or unresponsive (KC ΔIFNgR) were isolated. Cells were cultured for 48 hours with 10ng/mL of IFNg in media and viability of hepatocytes was measured using DAPI by flow cytometry. **Results:** LSECΔIFNgR mice had smaller liver (Figure 1A) and spleen size (Figure 1B) compared to *Prf-/-* with trend of reduction of hepatocellular (ALT) (Figure 1C) and vascular injury (LDH) (Figure 1D) that were not statistically significant. There were no differences between *Prf-/-*, HepΔIFNgR and LSECΔIFNgR in serum cytokines, population of infiltrating lymphocytes or degree of liver injury histologically. LSECΔIFNgR mice had less anemia accompanied by reticulocytosis (Figure 1E and F). This could be secondary to LSECΔIFNgR affecting all endothelial cells rather than a LSEC-bone marrow physiology but requires further studies. IFNg treated hepatocytes co-cultured with KCΔIFNγR tended to have higher viability (Figure 1G). **Conclusion:** There is minimal contribution of the hepatocyte and LSEC response to IFNg in murine FHL hepatitis. In vitro assays suggests a contribution of IFNg responsive KC to hepatocellular injury in FHL. Therefore, further studies focusing on the KC response to IFNg will be beneficial in further delineating the pathophysiology of FHL hepatitis.



Disclosures: Tamir Diamond: Mirum Pharmaceuticals: Advisor, Sarepta Therapeutics: Advisor, Michelle Lau: Nothing to Disclose, Sara Hughes: Nothing to Disclose, Sarah Mccuaig: Nothing to Disclose, Niansheng Chu: Nothing to Disclose, Em Elliott: Nothing to Disclose, Portia Kreiger: Nothing to Disclose, Edward Behrens: Nothing to Disclose

4631 | REAL-WORLD EXPERIENCE WITH PANGENOTYPIC GLECAPREVIR/PIBRENTASVIR THERAPY FOR CHRONIC HEPATITIS C IN CHILDREN

Dorota Zarebska-Michaluk[1] Malgorzata Pawlowska[2] Krystyna Dobrowolska[1] Justyna Moppert[2] Zuzanna Kalinowska[3] Maria Pokorska–Śpiewak[4] Anna Mania[5] Ewa Majda-Stanisławska[6] Robert Flisiak[7], [1]Jan Kochanowski University, Kielce, Poland, [2]Collegium Medicum Bydgoszcz, Nicolaus Copernicus University, Torun, Poland, [3]St. Adalbert's Hospital, Gdansk, Poland, [4]Medical Univversity of Warsaw, Poland, [5]University of Medical Sciences, Poznan, Poland, [6]Medical University of Lodz, Poland, [7]Medical University of Bialystok, Poland

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Background: The elimination of hepatitis C virus (HCV) infection as a public health threat according to goal established by the World Health Organization, is impossible to achieve without micro-elimination in children. The pediatric population gained the opportunity to be treated with direct-acting antivirals much later than adults so knowledge and experience in this area is modest. Our study aimed to analyze the use of glecaprevir/pibrentasvir (GLE/PIB), one of the pangenotypic options recommended in children, which provides the shortest possible duration of therapy. **Methods:** All consecutive children treated with 8-weeks GLE/PIB regimen for chronic HCV infection between 2022 and 2024, whose data were collected retrospectively through the Epi-2-Ped national multicenter database, were included in the analysis. **Results:** The study population consisted of 42 patients with a median age of 10.5 years, predominantly girls (61.9%) divided into age ranges of 3-5 years, 6-11 years and 12-18 years, comprising 6, 16 and 20 patients, respectively. More than 70% of all children were in the reference weight range according to the BMI-for-age percentile, obesity was diagnosed only in the oldest group in as many as 25% of children. Other comorbidities were present in two patients, renal disease and bronchial asthma. All children were treatment-naïve, nearly half of them (47.6%) were infected with genotype 1b, which was the most common in each age group. The advancement of liver disease by non-invasive elastography was assessed in 36 children, with half of them showing no fibrosis (18/50%). Eight-weeks GLE/PIB therapy was completed in all patients as planned, and the cure rate calculated in the per-protocol population was 100% (39/39). Three girls were considered lost to follow-up, one from the 6-11 age range and two from the oldest group. Adverse events were rare and mild, occurring in 4 children, only in the oldest age group. **Conclusion:** Eight-week GLE/PIB therapy in children is well tolerated and highly effective in all age ranges and regardless of gender. Its use in routine clinical practice will bring the ambitious goal of eliminating HCV worldwide a step closer.

Disclosures: Dorota Zarebska-Michaluk: Gilead, Abbvie: Speaking and Teaching, Malgorzata Pawlowska: Nothing to Disclose, Krystyna Dobrowolska: Nothing to Disclose, Justyna Moppert: Nothing to Disclose, Zuzanna Kalinowska: Nothing to Disclose, Maria Pokorska–Śpiewak: Nothing to Disclose, Anna Mania: abbvie: Speaking and Teaching, Abbvie: Speaking and Teaching, Ewa Majda-Stanisławska: Sanofi: PI in clinical study, MSD: PI in clinical study, Robert Flisiak: AbbVie: Advisor, Gilead: Advisor, Pfizer: Advisor

4632 | DIAGNOSTIC YIELD OF LIVER BIOPSY VS. GENETIC TESTING IN CHILDREN

Ashraf Alsahafi[1] Salma Almadani[1] Tahani Asiri[1] Jumanah Abdulaziz[1] Mohammad Hasosah[1], [1]King Abdullah Specialized Children Hospital

Background: Liver biopsy and genetic testing are essential tools for evaluating patients with liver disease. However, their diagnostic yield and contributions may vary by age group. This study aims to describe liver diseases in infants (≤ 1 year) compared to children (> 1 year) and to compare the diagnostic utility of liver biopsy and genetic testing in each group. **Methods:** This retrospective study included pediatric patients who underwent liver biopsy and genetic testing for suspected liver disease at King Abdulaziz Medical City, National Guard Hospital, Jeddah, Saudi Arabia. Descriptive statistics were used to summarize the findings and compare the age groups. **Results:** All infants (16) had abnormal liver biopsy findings, and genetic testing was positive in 68.8%. The most common final diagnoses were genetic/metabolic liver disease (37.5%), followed by biliary atresia, hematologic liver disease, and idiopathic liver disease, which occurred with equal frequency (12.5%). The most frequent biopsy pattern was cholestatic (37.5%), followed by neonatal giant cell hepatitis (31.3%) and biliary cirrhosis (12.5%). Jaundice was the most common presenting symptom (81.25%).

In the children group (30), liver biopsy revealed abnormal findings in 90%, while genetic testing showed positive results in 70%. The most frequent diagnosis was genetic/metabolic liver disease (26.7%), followed by infectious liver disease and malignancy (10%). Biopsy findings revealed chronic hepatitis (20%), followed by fatty liver and granulomatous/infectious diseases at similar percentages (13.3%). The majority were asymptomatic with laboratory/imaging abnormalities (46.66%), followed by hepatomegaly (30%) and jaundice (16.7%).

Jaundice was significantly more common in infants compared to asymptomatic presentations in children ($P = 0.001$). There was no significant difference between age group regarding the positivity of genetic testing ($P = 0.93$). Among all patients who underwent liver biopsy and genetic testing, 93.5% had abnormal liver biopsy findings, and 67.4% of these also had positive genetic testing results ($P = 0.236$). See figure **Conclusion:** Liver biopsy and genetic testing are complementary and provide significant insights into the evaluation of pediatric liver disease. Although clinical presentations

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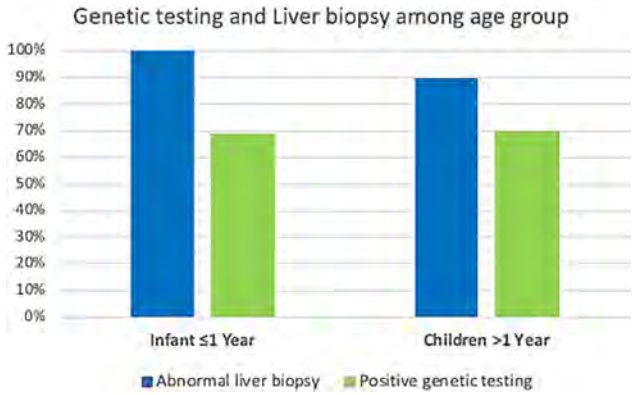
and diagnostic patterns vary by age, integrating histopathology with molecular diagnostics enhances the overall accuracy of disease classification.



Disclosures: Ashraf Alsahafi: Nothing to Disclose, Salma Almadani: Nothing to Disclose, Tahani Asiri: Nothing to Disclose, Jumanah Abdulaziz: Nothing to Disclose, Mohammad Hasosah: Nothing to Disclose

4633 | EFFICACY OF CUSTOMIZED STEROID BASED PROTOCOL IN POST KASAI- BILIARY ATRESIA

Anmol Anmol[1] Seema Alam[2] Rajeev Khanna[3] Vikrant Sood[3] Bikrant Biharilal Raghuvanshi[4], [1]Institute of liver and biliary sciences/trainee, [2]Professor, [3]additional professor, [4]associate professor

Background: Role of steroids as adjunct therapy for improving post kasai portoenterostomy outcomes of biliary atresia remains controversial. **Methods:** In this analysis 122 infants with biliary atresia who underwent Kasai surgery at our centre were included. Post-operatively three persistent pale stool on three consecuitive days was considered as marker of poor biliary drainage and steroid was administered as per protocol at 3mg per kg orally and gradually tapered off over period of 6 weeks. Analysis of successful biliary drainage after portoenterostomy (defined as serum bilirubin <2mg/dL) was primary endpoint. **Results:** 122 patients (65 vs 57 in Steroid group (SG) vs Historical cohort (HC)) where 66% were boys. The age at Kasai was 79 versus 80 days ($p=0.075$), total bilirubin was 9.7 versus 9.9 mg /dl ($p=0.371$), albumin was 3.7 versus 3.5 g% ($p=0.003$) and LSM was 12.3 kPa versus 26.25 kPa ($p=0.001$) in the SG versus HC respectively. Jaundice clearance rate was seen in 60% in SG vs 43% in HC ($p=0.146$).The jaundice cleared in 66 days versus 80 days in SG versus HC ($p=0.223$). The NLS was comparable in both the groups. The median values of age at Kasai was 77 versus 81 days ($p=0.017$), total bilirubin was 9.9 versus 9.5 mg /dl ($p=0.319$), albumin was 3.89 versus 4 g% ($p=0.682$) and LSM was 10.9 kPa versus 16.1 kPa ($p=0.036$) in the SG successful versus SG unsuccessful respectively. Amongst the 20 SG successful group below 70 days the jaundice clearance rate was 75%. **Conclusion:** Lower age at Kasai and LSM were significantly associated with jaundice clearance. Jaundice clearance rate is significantly higher among those who received steroids and had age at Kasai below 70 days.

Disclosures: Anmol Anmol: Nothing to Disclose, Seema Alam: Nothing to Disclose, Rajeev Khanna: Nothing to Disclose, Vikrant Sood: Nothing to Disclose, Bikrant Biharilal Raghuvanshi: Nothing to Disclose

4634 | IMPACT OF CONCURRENT EXTRAHEPATIC AUTOIMMUNE DISORDERS ON OUTCOME OF PEDIATRIC AUTOIMMUNE LIVER DISEASE

Anmol Anmol[1] Rajeev Khanna[2] Seema Alam[3] Vikrant sood[2] Bikrant Biharilal[4], [1]Institute of liver and biliary sciences/trainee, [2]Additional professor, [3]professor, [4]associate professor

Background: Concurrent extrahepatic autoimmune disorders (CEAID) are present in 21-48% of pediatric autoimmune liver disease (AILD). There is controversial evidence of the effect of CEAID or celiac disease on long-term outcome of AILD. In view of limited data from Indian subcontinent, we aimed to study the prevalence of CEAID and its effect of outcome of AILD. **Methods:** All consecutive patients under-18 year of age with a diagnosis of autoimmune hepatitis (AIH) or autoimmune sclerosing cholangitis/overlap (ASC/overlap) were studied retrospectively. Presence and proportion of various CEAIDs were studied. Outcome was studied in terms of survival with native liver (SNL) or death or liver transplantation (LT). **Results:** There were 230 patients (124 girls), mean age 10.3 $\pm$ 4.3 years with AILD. Prevalence of CEAID was 40.4%. Autoimmune hemolytic anemia (60.2%), celiac disease (19.4%), inflammatory bowel disease (7.5%), hypothyroidism (4.3) were the common CEAIDs. CEAID was not associated with type of AIH, ASC/overlap or antibody positivity ($p=$ NS). Poor outcome (death or LT) was seen in 36 (16.9%) of 212 children on follow-up and was unrelated to the presence of CEAID. On subgroup analysis, celiac disease was the only CEAID which was associated with poor SNL (HR = 3.422; 95% CI 1.396-8.391, $p=0.012$). **Conclusion:** CEAID are present in 40% of pediatric AILD. Celiac disease, but not other CEAID, is associated with poor SNL in children with AILD.

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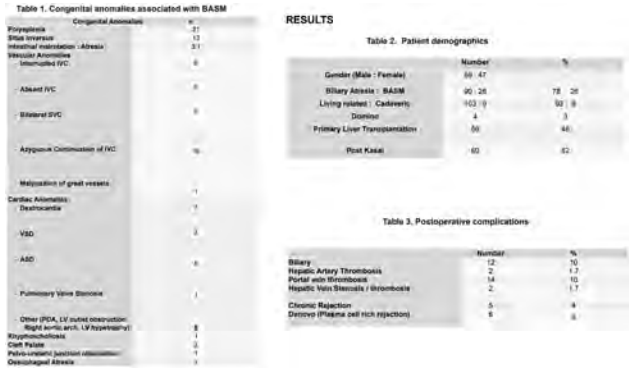
4635 | OUTCOMES IN CHILDREN WITH BILIARY ATRESIA POST LIVER TRANSPLANT AT A HIGH VOLUME PAEDIATRIC LIVER TRANSPLANT CENTRE

Mohammad Shagrani[1] Kishwer Kumar[2] Alexandra Aldana[2] Ali Syed Akhtarul Hassan[2] Dalal I Albogami[2] Sateesh Maddirevula[2] Saleh Alqahtani[2] Bandar Mohammed H Aljudaibi[2] Massimo Malago[2] Dieter Broering[2], [1]King Faisal Specialist Hospital and Research Centre, [2]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Background: Liver transplant (LT) has played a significant role in improving outcomes of children with Biliary Atresia. In Saudia Arabia, the lack of centralisation and awareness often leads to delays in presentation. There is no data on outcomes of post-transplant patients with biliary atresia in Saudi Arabia. We aim to analyse our short and medium term outcomes post liver transplantation. **Methods:** We performed a retrospective analysis of medical records of those patients that were transplanted for biliary atresia between 2011 - 2024. Demographic data were collected and tabulated. Complications rates were analysed. **Results:** Between January 2011 and December 2024 we performed a total of 845 liver transplants, of which 116 were for Biliary Atresia.

Of these, Isolated BA was 88% (n = 90) and Syndromic Biliary Atresia (22%, n = 26). Majority were living related, 92% (with no donor mortality), Cadaveric 8% and Domino transplantation 3%. Recipients post-operative surgical complications consisted of hepatic artery thrombosis (1%, n = 2), Biliary strictures (10%, n = 12), Portal vein thrombosis (12%, n = 14), Hepatic vein stenosis (1.7%, n = 2). Retransplantation was performed in 2 patients. Two patients died in the early post operative period, due to TMA and uncontrolled bleeding. Sepsis was the most common cause of mortality in patients at peripheral hospitals. The 1, 5 and 10 year patient survival rates were 97%, 96% and 93% respectively. **Conclusion:** Liver transplant outcomes among patients with BA are excellent in Saudia Arabia. There is a need to improve our network structure to post transplant patients living in remote and rural areas. Moreover, introduction of centralisation of care will certainly improve outcomes.



Disclosures: Mohammad Shagrani: Nothing to Disclose, Kishwer Kumar: Nothing to Disclose, Alexandra Aldana: Nothing to Disclose, Ali Syed Akhtarul Hassan: Nothing to Disclose, Dalal I Albogami: Nothing to Disclose, Sateesh Maddirevula: Nothing to Disclose, Saleh Alqahtani: Nothing to Disclose, Bandar Mohammed H Aljudaibi: Nothing to Disclose, Massimo Malago: Nothing to Disclose, Dieter Broering: Nothing to Disclose

4636 | CLINICAL AND GENETIC CHARACTERIZATION OF CHILDREN WITH SEVERE OBESITY: ASSOCIATIONS WITH MAFLD/MASH

Cherise Ali[1] Wikrom Karnsakul[2] Ann Scheimann[1], [1]Johns Hopkins University School of Medicine, [2]Johns Hopkins University

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is the most common cause of pediatric liver disease with links to insulin resistance and early obesity. Those with syndromic or monogenic obesity with abnormal insulin signaling, hyperphagia, and severe obesity may be at greater risk for liver disease. This study evaluates the relationship between genetic variants and liver involvement in a broad pediatric cohort with severe early-onset obesity using the Prevention Genetics Uncovering Rare Obesity (PGURO) genetic screening panel. **Methods:** IRB-approved retrospective data collection in children with BMI $\geq$97th% with genetic screening with PGURO panel. Patients were divided into two groups based on abnormal liver findings. GraphPad Prism software was used to conduct statistical comparisons between groups using t-tests or Mann-Whitney U tests for continuous variables and Fisher's exact tests for categorical variables, as appropriate. **Results:** Data from 46 children was collected. Group 1 (abnormal liver) (n = 28) had higher mean age (6.5 $\pm$ 3.4 vs. 5.3 $\pm$ 2.9yrs,

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$p = 0.08$), male sex (82% vs 26%, $p < 0.001$), and white ethnicity (45% vs. 9%, $p = 0.027$). Transaminases were elevated in Group 1 (AST: 42IU [24.5–67.5] vs. 21IU [19.0–24.0], ALT: 68IU [32.0–98.0] vs. 20IU [14.5–24.5]; $p < 0.001$ for both). Comorbidities (obstructive sleep apnea (OSA), prediabetes, type 2 diabetes (T2DM), and hyperlipidemia) and gene variants were higher in Group 1 vs. Group 2 ((OSA: 57% vs. 56%; prediabetes: 36% vs. 17%; T2DM: 25% vs. 6%; hyperlipidemia 43% vs. 17%), (BBS1: 32% vs. 17%), (BBS9: 29% vs. 11%), (ALMS1: 21% vs. 6%), (PCSK1: 18% vs. 6%), (MC4R: 18% vs. 0%)), but there was no statistical significance (all $p > 0.1$). In total, 24 of 46 patients (52%) had findings of hepatomegaly with higher prevalence in Group 1 (20/28) vs. Group 2 (4/18) which was statistically significant ($p < 0.01$). **Conclusion:** Children with severe obesity and liver involvement (MAFLD/MASH) demonstrated expected higher aminotransferases accompanied by initial findings of PGURO screening variants though current genetic screening results were not significant likely due to sample size. Further study is warranted to ascertain whether PGURO screening should be incorporated into evaluation of obese children with liver disease.

Disclosures: Cherise Ali: Nothing to Disclose, Wikrom Karnsakul: Nothing to Disclose, Ann Scheimann: Nothing to Disclose

4637 | ◆ CLINICAL PHENOTYPE AND OUTCOMES OF ABCB4 (MDR3) VARIANTS IN CHILDREN: RESULTS: FROM A NATIONAL MULTICENTRE REGISTRY

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Background: Variants in Adenosine Triphosphate-binding Cassette, subfamily B, member 4 (ABCB4) lead to decreased functional expression of multidrug resistance protein (MDR3), leading to a spectrum of genetic cholestatic disorders ranging from mild cholestasis to biliary cirrhosis with portal hypertension (PHTN). The study objectives were to describe the clinical and biochemical characteristics, genotype, and their correlation with phenotype and outcomes of patients with ABCB4 variants. **Methods:** Clinical, biochemical, histological, and follow-up data were collected from a national registry of genetic intrahepatic cholestasis. All children (0- 18 years) with clinical cholestasis and homozygous, compound heterozygous, and heterozygous variants in ABCB4 were included. The genotype was classified as mild (heterozygous missense), moderate (heterozygous protein-truncating mutation (PTM), biallelic missense variants), or severe (biallelic PTM, compound heterozygous PTM and missense). Outcome was defined as native liver survival (NLS), death, or liver transplantation (LT) at the most recent follow-up. **Results:** ABCB4 variants were the second most common variant (108/448, 24.1%), leading to genetic intrahepatic cholestasis in the registry (23 centres). These included 68 homozygous, 24 compound heterozygous, and 16 heterozygous patients. Variants were classified as mild in 13 (12%), moderate in 50 (46%), and severe in 45 (41.7%). Jaundice was the most common clinical presentation, affecting 90 (83.3%), with the median age of onset being 36 months (IQR: 11.8 - 66). 34 (31.5%) completely cleared their jaundice with ursodeoxycholic acid. Pruritus developed in 66 (61.1%), with 18 having pruritus refractory to medical therapy. 47 (43.5%) developed ascites at a median age of 66 months (IQR: 48 – 120). Clinically evident PHTN (CEPH) was present in 69 (63.9%), while 20 (18.5%) had variceal bleed. Nine (8.3%) died, 38 (35.2%) received LT, while 61 (56.5%) were surviving with their native liver at a

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median age of 60 months (IQR: 35.3 – 108). The majority of patients had been listed for LT due to ascites (37, 82.2%), persistent jaundice (25, 55.6%), and uncontrolled PHTN (24, 53.3%). The median age at death and LT were 73 (IQR: 55 – 83.5) and 79 (59.8 – 144) months, respectively. Severe genotype (adjusted OR: *5.89, 95% CI: 2.01–17.25, p = 0.001)*, variceal bleed (adjusted OR: *4.32, 95% CI: 0.93–20.11, p = 0.062)*, pruritus (adjusted OR: 3.22, 95%CI: 1.07–9.72, p = 0.038), and high bilirubin (adjusted OR: *1.11, 95% CI: 1.01–1.22, p = 0.025)* at the latest follow-up were independent predictors of poor outcome on logistic regression analysis. **Conclusion:** ABCB4 variants are a common cause of genetic intrahepatic cholestasis in children. Around 44% of children die or receive LT by a median age of 79 months. Genotype (presence of ≥1 PTM), variceal bleed, presence of pruritus, and persistent high bilirubin are predictors of poor outcome.

Univariate and Cox multivariate regression analysis to identify the predictors of outcome in patients with ABCB4 (MDR3) variants (Good outcome: Survival with native liver; Poor outcome: Death or Liver transplantation):

Parameter	Poor Outcome (n = 47)	Good outcome (n = 61)	Significance (non-parametric) p value	Logistic regression analysis (Odds ratio, 95%CI), p value
Genotype categorization			<0.001	*Severe vs other genotypes: aOR: 5.89 (2.01 – 17.25), p = 0.001*
Mild	2 (4.3%)	11 (18%)		
Moderate	15 (31.9%)	35 (57.4%)		
Severe	30 (63.8%)	15 (24.6%)		
Gender				*
Male	28 (59.6%)	34 (55.7%)	0.700	
Jaundice	45 (95.7%)	45 (73.8%)	0.003	*
Age at onset of jaundice (months)	42 (21.5 – 66)	24 (6 – 66)	0.034	Not significant in LRA
Pruritus	34 (%)	32 (%)	0.047	3.22 (1.07 – 9.72), p = 0.038
Age of onset in pruritus (months)	30 (14.3 – 48.5)	23.5 (10.3 – 57.5)	0.339	*
Ascites	42 (89.4%)	5 (8.2%)	< 0.001	*
Age at onset of ascites (months)	67 (46.5 – 120)	66 (47 – 107.5)	0.945	*
CEPH	46 (97.9%)	23 (37.7%)	<0.001	*
Variceal Bleed	15 (31.9%)	5 (8.2%)	0.002	*4.32 (0.93 – 20.11), p = 0.062*
Bilirubin (mg/dl)	6.6 (3.7 – 15.8)	3 (1.2 – 6.1)	< 0.001	*1.11 (1.01 – 1.22), p = 0.025*
INR	1.5 (1.21 – 2.2)	1.13 (1.03 – 1.3)	<0.001	Not significant in LRA
Alanine aminotransferase (IU/L)	122 (87 – 178)	110 (62 – 203.5)	0.486	*
Gamma Glutamyl Transpeptidase (IU/L)	179 (110 – 270)	181 (94 – 299)	0.916	*
Albumin (g/dl)	2.7 (2.2 – 3.2)	3.7 (3.1 – 4.1)	< 0.001	*
Alfa-fetoprotein (ng/ml)	3.9 (2.7 – 8.6)	3 (2.2 – 5.4)	0.234	*
Significant fibrosis (F3-F4 METAVIR)	36/38 (94.7%)	20/28 (71.4%)	0.014	Not significant in LRA
Serum bile acids (µmol/L)	208 (108 – 243)	124.5 (50.9 – 182)	0.027	*

Abbreviations: ABCB4: Adenosine Triphosphate-Binding Cassette, Subfamily B, Member 4; aOR: adjusted Odds Ratio, CEPH: Clinically evident portal hypertension, CI: Confidence interval; INR: International Normalized Ratio; LRA: Logistic regression analysis; MDR3: Multidrug resistance protein 3

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4638 | ◆ DECODING CILIARY DYSFUNCTION IN HEPATOBILIARY DEVELOPMENT: MECHANISTIC INSIGHTS INTO BILIARY ATRESIA PATHOGENESIS

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Background: Biliary atresia (BA) is a life-threatening pediatric liver disease marked by progressive bile duct obstruction, liver fibrosis, and eventual failure. Despite being the leading indication for pediatric liver transplantation, the underlying mechanisms of BA remain poorly understood. Emerging evidence suggests primary cilia – vital organelles for cellular signaling – play a critical role in liver development and biliary epithelial cell (BEC) integrity. Aberrations in cilia-associated pathways, including Hedgehog (Hh), Wnt, and Notch, have been implicated in BA pathogenesis. Notably, pathogenic variants in ciliary genes occur in over 30% of BA patients, and liver-specific knockout of the ciliary gene polycystin-1-like 1 (*PKD1L1*) replicates features of BA in a mouse model. How *PKD1L1* deficiency disrupts ciliary function and hepatobiliary development is unknown. **Methods:** To investigate the role of primary cilia in hepatobiliary development, we employed a zebrafish (*Danio rerio*) model, leveraging its conserved liver development pathways and optical clarity allowing for direct visualization of early hepatobiliary development *in vivo*. We performed morpholino-mediated knockdown of *pkd1l1* and confirmed dose-dependent effects. We employed high-resolution spinning-disk confocal microscopy to visualize phenotypic consequences on hepatobiliary structures using transgenic reporters (*fabp10a:CFP* labeling hepatocytes; *tp1:GFP* labeling BECs). We also visualized ciliogenesis and ciliary architecture using a cilia-specific reporter (*arl13:GFP*), and measured transcriptional responses to *pkd1l1* deficiency by qRT-PCR from dissected livers. **Results:** Knockdown of *pkd1l1* resulted in severe hepatobiliary malformations, including a 60% reduction

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in BEC density, fragmented biliary networks, and a 2.1-fold expansion in hepatocyte populations, mimicking the cholangiopathy observed in BA (Figure 1). High-resolution imaging revealed significant structural disorganization and misorientation of cilia in *pkd1l1*-deficient BECs. Transcriptomic analysis confirmed aberrant Hh signaling activation (Figure 2). These findings directly link ciliary dysfunction to disrupted biliary tree development. **Conclusion:** Our study highlights the pivotal role of primary cilia in maintaining hepatobiliary integrity and elucidates how *pkd1l1* deficiency amplifies Hh signaling to drive biliary dysmorphogenesis. By pinpointing specific mechanisms underlying BA pathogenesis, these results lay the groundwork for targeted therapies aimed at mitigating ciliary-driven bile duct damage in pediatric patients. Ongoing efforts, including single-cell and spatial transcriptomic analyses, aim to further dissect intrahepatic and extrahepatic gene expression changes in *pkd1l1*-deficient livers.

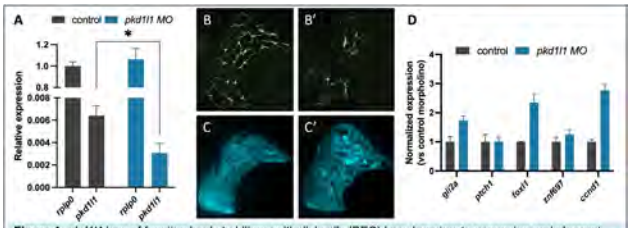

Figure 1. *pkd1l1* loss of function leads to biliary epithelial cells (BEC) loss, hepatocyte expansion and aberrant Hedgehog signaling. **A**: *pkd1l1* morpholino (MO) knockdown in dissected livers at 72 hours post-fertilization (hpf) validated by qPCR. *rplp0* internal control. Plotted mean +/- SD of 3 independent trials, 10 livers per genotype per trial. * P<0.05. **B-B'**: Decreased BECs and network density in *pkd1l1* MO compared to control MO. BECs marked by *lp1:mCherry*. **C-C'**: Hepatocyte expansion, increased liver volume in pkd1l1 MO relative to control MO. Hepatocytes marked by *fabp10a:cfp*. B-C: Dual-tagged reporter fish were imaged at 96 hpf. D: **D**: Hedgehog (Hh) signaling is activated in *pkd1l1*-deficient livers. Hh-responsive transcription factor *gli2a* and transcriptional targets *ptch1*, *foxl1*, *znf697* and *ccnd1* were assayed by qRT-PCR from dissected livers of control and *pkd1l1* morpholino (MO)-injected embryos at 120 hpf. Plotted mean +/- SD from 2 independent trials, 10 livers per genotype per trial.

Disclosures: Prasanna Ramachandran: Nothing to Disclose, Wolfram Goessling: Nothing to Disclose

4639 | ◆ CARDIOMEMS PULMONARY ARTERY PRESSURE MEASUREMENTS ARE ASSOCIATED WITH CONGESTIVE HEPATOPATHY IMAGING FINDINGS

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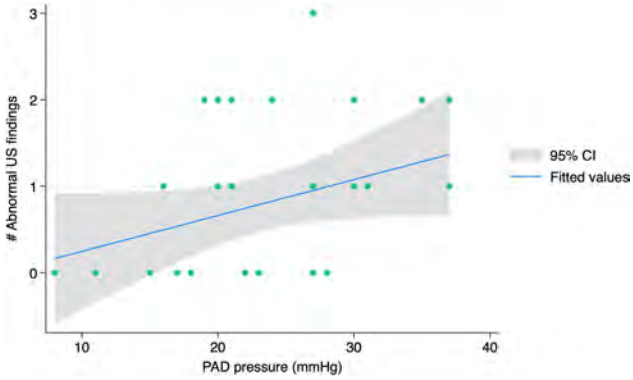
Background: Hepatic congestion is an asymptomatic sequelae of right ventricular dysfunction that is often first recognized on abdominal imaging. CardioMEMS is an implantable pulmonary artery pressure (PAP) sensor used in the management of chronic heart failure (HF). In this hypothesis generating study, we evaluated whether pulmonary artery diastolic (PAD) pressure measured by CardioMEMS is associated with imaging findings consistent with hepatic congestion. **Methods:** We analyzed 43 patients with HF and CardioMEMS at the University of California, San Francisco. We extracted all structured clinical and demographic variables, abdominal imaging available, and average PAD pressure over 6 months prior to abdominal imaging. We annotated imaging reports with the number of findings that may be suggestive of congestive hepatology (defined as hepatomegaly, splenomegaly, dilated hepatic veins, dilated inferior vena cava, heterogeneous enhancement, increased echogenicity, and ascites). We used multivariable logistic regression (adjusted for age, gender, race/ethnicity, HF etiology, left ventricular ejection fraction (LVEF), and MELD-XI score) to associate PAD pressure with abnormal imaging findings. **Results:** Of the 34 patients with abdominal imaging available, the median age was 53 years (IQR 30), 73% were male, 58% were non-white, 79% had nonischemic cardiomyopathy, 64% had reduced LVEF, and 15% had left ventricular assist devices. The median MELD XI score was 13 (IQR 11) and median PAD pressure was 23mmHg (IQR 9). In this cohort, ultrasound was more sensitive in detecting abnormal imaging findings, with the most common abnormal findings being hepatomegaly and increased echogenicity. Adjusted multivariable logistic regression showed that each 1mmHg increase in PAD pressure was associated with a 1.4-odds of an abnormal imaging finding (95%CI 1.04-1.85, $p < 0.05$). PAD pressure above a threshold of 20mmHg was associated with 2+ abnormal abdominal imaging findings. **Conclusion:** This hypothesis generating pilot study showed that PAD measurements are associated with hepatic imaging findings. Given that the CardioMEMS system can provide longitudinal PAP readings, we hypothesize that quantifying right heart pressures and PAP pressures over time may allow for more accurate assessment of the development of congestive hepatopathy in HF patients.



Disclosures: Chelsea Pan: Nothing to Disclose, Liviu Klein: Abbott: Consultant, Endotronix: Consultant, Shweta Motiwala: Nothing to Disclose, Jin Ge: Merck and Co: Grant/Research Support, Iota Biosciences/Astellas Pharmaceuticals: Consultant, Madrigal Pharamaceuticals: Consultant, Gilead Sciences: Advisor

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4640 | ◆ RATES OF PORTAL VENOUS THROMBOSIS IN CIRRHOTICS WITH OR WITHOUT CLOTTING DISORDERS: A 7-YEAR NATIONWIDE STUDY

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Background: Cirrhotics are considered to have a high risk of thrombotic events. A common thrombotic event in this group is portal venous thrombosis (PVT). One is decreased liver-synthesized factors in the coagulation cascade and increased endothelial-derived clotting factors. Current research states that inherited hemostatic disorders do not predict the development of PVT. **Methods:** In this study, various thrombophilias were analyzed: activated protein C resistance (APCR), prothrombin gene mutation (PTM), paroxysmal nocturnal hemoglobinuria (PNH), other thrombophilia (OT), and disseminated intravascular coagulation (DIC). The National Inpatient Sample (NIS) from 2015-2021 was used to identify patients diagnosed with cirrhosis with or without thrombophilias using the International Classification of Disease (ICD) 10 codes. Records were weighted per the NIS algorithm to produce accurate population estimates. Cirrhotic patients with or without thrombophilia were analyzed for baseline characteristics. Various primary outcomes were analyzed, which included PVT, death, acute kidney injury (AKI), acute myocardial infarction (AMI), shock, and composite outcomes. Secondary outcomes were analyzed, which included transjugular intrahepatic portosystemic shunt (TIPS) during hospitalization, length of stay (LOS), and hospital charges. **Results:** A weighted total of 2,391,389 patients with cirrhosis without a known coagulation pathology, 4,075 patients with cirrhosis and APCR, 425 patients with cirrhosis and PTM, 175 patients with cirrhosis and PNH, 14,155 patients with cirrhosis and DIC. Cirrhotic patients with PTM had the highest odds of developing PVT (OR (95% CI): 2.848 (2.24-3.62) APCR, 8.801 (5.471-14.157) PTM, 4.286 (3.708-4.955) OT, 2.904 (0.908-9.286) PNH, 1.744 (1.49-2.04) DIC). Cirrhotic patients with DIC had higher odds of death (OR (95% CI): 24.748 (22.82-26.839) DIC), AKI (7.458 (6.82-8.155), AMI (3.205 (2.801-3.667)), shock (21.454 (19.793-23.254)), and overall worse outcomes (15.912 (14.127-17.922)). Secondary outcomes were analyzed, which included higher odds of TIPS during hospitalization for cirrhotic patients with DIC (1.913 (1.369-2.674)). In turn, cirrhotic patients with DIC had greater lengths of stay (LOS) (5.270 (4.759-5.781)) and greater hospital charges (168463 (147901-189024)). **Conclusion:** Patients with cirrhosis and thrombophilic disorders had higher odds of developing PVT, which supports the role of alterations in coagulation factors as predictive factors in the development of PVT.

Table 2: Outcomes for Patients Admitted for PVT in Cirrhotics Stratified by Clotting Disorder

Groups	PVT	Death	AKI	AMI	Shock	Composite	Previous Liver Transplant	Liver Transplant	TIPS	LOS
APCR	2.848 (2.24-3.62)	0.7 (0.484-1.012)	1.003 (0.856-1.177)	1.033 (0.689-1.547)	0.849 (0.641-1.125)	0.961 (0.824-1.121)	0.978 (0.507-1.887)	1.224 (0.727-2.062)	1.719 (0.977-3.025)	-0.081(-0.473-0.310)
PTM	8.801 (5.471-14.157)	1.171 (0.509-2.695)	1.018 (0.646-1.604)	1.208 (0.377-3.875)	1.143 (0.57-2.291)	1.165 (0.766-1.772)	1.425 (0.347-5.861)	2.877 (1.099-7.527)	3.129 (0.965-10.145)	1.081 (-0.475-2.639)
Other	4.286 (3.708-4.955)	1.471 (1.235-1.752)	1.167 (1.054-1.292)	1.106 (0.848-1.441)	1.551 (1.341-1.793)	1.205 (1.09-1.331)	0.859 (0.518-1.425)	2.149 (1.547-2.984)	1.377 (0.857-2.213)	2.218 (1.720-2.715)
PNH	2.904 (0.908-9.286)	1.279 (0.302-5.412)	0.881 (0.392-1.98)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	0.823 (0.375-1.809)	2.558 (0.364-17.998)	<0.001 (<0.001-<0.001)	<0.001 (<0.001-<0.001)	-0.071 (-1.571-1.428)
DIC	1.744 (1.49-2.04)	24.748 (22.82-26.839)	7.458 (6.82-8.155)	3.205 (2.801-3.667)	21.454 (19.793-23.254)	15.912 (14.127-17.922)	0.32 (0.159-0.641)	2.777 (2.173-3.549)	1.913 (1.369-2.674)	5.270 (4.759-5.781)

Disclosures: Andrej Sodoma: Nothing to Disclose, James Pellegrini: Nothing to Disclose, Samuel Greenberg: Nothing to Disclose, Ana Rivera: Nothing to Disclose, Mary Thomas: Nothing to Disclose, Jaspreet Singh: Nothing to Disclose

4641 | PORTAL VENOUS SYSTEM ANEURYSMS: MAYO CLINIC EXPERIENCE OF NATURAL HISTORY, TREATMENT AND OUTCOMES

Eliabe Abreu[1] Chloe Hemm[2] Abigail Fickel[2] Christopher Kigongo[2] Todd Rasmussen[2] Jill Colglazier[2] Manal Abdelmalek[1], [1]Mayo Clinic Rochester, [2]Mayo Clinic, Rochester, MN

Background: Portal vein system aneurysms (PVSAs) are rare, yet the most common (prevalence 0.06-0.6%) visceral venous aneurysms in the general population. PVSAs are typically asymptomatic and incidentally discovered. Due to their rarity, the natural history and management of PVSAs are not well defined. Herein, we report the world's largest cohort study of PVSAs with the aim of defining the characteristics, natural history, and outcomes of surgical vs medical interventions. **Methods:** Using an AI-based system, we searched the Mayo Clinic Enterprise electronic medical record from 1/1/2000 through 1/1/2025 for terms "portal vein aneurysm", "splenic vein aneurysm", and "mesenteric vein aneurysm". Data was manually abstracted and recorded into REDCap. Descriptive analyses were performed. **Results:** From 2000 to 2025, 120 patients [female (55%), White (95%), with a median age of 63 (IQR 51-73) years] were diagnosed with PVSAs. Median follow-up was 51 (IQR 21.75-112) months. Most common comorbidities included arterial hypertension (42.9%), chronic liver disease (32.8%), and cirrhosis (28.6%). Initial diagnosis was made following

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computed tomography (CT) in 65% of patients, with 54.6% being an incidental finding. 45.4% of patients presented with symptoms, of which the primary symptom was abdominal pain (66.7%). The PVSAs included intrahepatic portal vein branch (25.8%), splenic vein (24.2%), and body of the main portal vein (22.5%), with median diameters of 22 mm, 25 mm, and 35 mm, respectively. Splenomegaly was observed in 30.5% of patients, portal hypertension in 19.5%, and intraluminal thrombosis at initial presentation in 16.9%. Management consisted of conservative 'wait and watch' (90%), anti-coagulation (7.5%), and surgical repair (10%, with 1 case at presentation and 11 during follow-up). After diagnosis, 79.2% had follow-up imaging. While follow-up imaging triggered a change in management in 26.3% (n = 25/95), only 9.2% of patients had thrombosis of PVSA, and 87.5% experienced no unfavorable outcomes. **Conclusion:** PVSA is a rare entity, mainly idiopathic, and largely incidental finding on abdominal imaging. The overwhelming majority of patients have no associated clinical outcomes during follow-up. A non-surgical approach and potentially prophylactic antiplatelet therapy to prevent PV thrombosis may be considered. Multicenter longitudinal studies are warranted.

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4642 | CLINICAL FEATURES AND RISK FACTORS OF PORTO-SINUSOIDAL VASCULAR DISEASE WITH CHRONIC GAMMA-GLUTAMYL TRANSFERASE ELEVATION

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Background: In clinical practice, a significant number of patients presented with unexplained and recurrent gamma-glutamyl transferase (GGT) elevation. This study aimed to explore the clinical characteristics and risk factors of porto-sinusoidal vascular disease (PSVD) with persistent GGT elevation. **Methods:** This retrospective study included patients with unexplained persistent GGT elevation who underwent liver biopsy at Beijing Ditan Hospital between January 2014 and April 2025. Persistent GGT elevation was defined as three consecutive measurements within the past year exceeding twice the upper limit of normal (ULN). Patients were excluded if they exhibited concurrent elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or alkaline phosphatase (ALP) exceeding 1.5 times the ULN at the time of biopsy, or if they had known etiologies for GGT elevation. Additional exclusion criteria included excessive alcohol consumption, active infectious diseases, malignancies, or other systemic disorders affecting hepatic function. Demographic data and clinical histories were collected. Patients were stratified into two groups based on the latest diagnostic criteria for PSVD: patients with GGT elevation $\geq 2\times$ULN confirmed as PSVD (PSVD group), and patients with GGT elevation $\geq 2\times$ULN without PSVD (Non-PSVD group). Clinical features and risk factors were analyzed to identify features specific to PSVD with persistent GGT elevation. **Results:** A total of 313 patients with unexplained persistent GGT elevation were enrolled, all of whom underwent liver biopsy. Based on biopsy results indicating whether PSVD was the etiology of GGT elevation, patients were categorized into PSVD and non-PSVD groups. Among them, 191 patients (61.02%) were diagnosed with PSVD, while 122 patients (38.98%) without PSVD in Table 1. Compared to the non-PSVD group, the PSVD group exhibited significantly lower white blood cell (WBC) counts ($p < 0.001$), neutrophils (NE#, $p = 0.005$), and hemoglobin (HGB) levels ($p = 0.050$). Additionally, the PSVD group had lower ALT ($p < 0.001$), AST ($p < 0.001$), and GGT levels ($p = 0.006$). Prothrombin Activity (PTA, $p < 0.001$), AFP ($p = 0.002$), and liver stiffness measurement (LSM, $p = 0.001$) were also lower in the PSVD group, while the international normalized ratio (INR) was higher ($p < 0.001$) in Table 1. Compared to the non-PSVD group, the PSVD group exhibited a higher proportion of patients with GGT < 173 U/L ($p = 0.012$) and LSM < 7.4 kPa ($p = 0.029$) in Table 2. Logistic regression analysis demonstrated that WBC [OR 1.238, 95%CI (1.083-1.416), p=0.002], PTA [OR 1.033, 95%CI (1.013-1.053), p=0.001], GGT < 173U/L [OR 1.730, 95%CI (1.060-2.823), p=0.028], and LSM < 10kPa [OR 2.169, 95%CI (1.237-3.803), p=0.007] emerged as independent risk factors for PSVD diagnosis in patients with persistent unexplained elevated GGT in Table 3. **Conclusion:** Patients with unexplained persistent GGT elevation diagnosed with PSVD exhibited lower WBC, PTA, GGT, and LSM. WBC, PTA, GGT < 173U/L, and LSM < 10 kPa were identified as independent risk factors for PSVD in Patients with unexplained persistent GGT elevation, providing critical diagnostic insights for individuals with unexplained persistent GGT elevation.

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4643 | PORTO-SINUSOIDAL VASCULAR DISORDER: NATURAL HISTORY AND LONG-TERM OUTCOME

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Background: Porto-sinusoidal vascular disease (PSVD) represents a heterogeneous group of histopathological lesions and clinical phenotypes that may be associated with portal hypertension (PH). Aim of the study was to determine the long-term outcome and it prognostic factors in a large multicenter cohort of PSVD patients. **Methods:** All adult patients with a histologically diagnosed PSVD between 2002 and 2024 from three Italian referral Centres were retrospectively included at the time of diagnosis and followed up until May 2025. **Results:** Among the 284 patients [56% male, 45 (18-75) years-old, 95% Caucasian, 7% BMI > 25 kg/m^2, 64% ALT > ULN, 78% GGT > ULN, 12% platelets < 150*10^3/mmc, 6% with hematological diseases, 16% spleen ≥ 13 cm, 9% with esophageal varices (EV)] the majority 264 (93%) have never reported liver-related events before diagnosis while 20 (7%) had already developed at least one complication: 7 (3%) EV bleeding, 8 (3%) ascites, 9 (3%) portal vein thrombosis (PVT), which led to the Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement in 4 (1%) patients. Overall, at diagnosis 67 (24%) patients (PH group) presented with PH features, i.e. platelets < 150*103/mmc, spleen ≥ 13 cm, EV, portosystemic collaterals at imaging, ascites while the remaining (n = 221) were classified as the noPH group. No significant histological differences were identified between the two groups. After a median follow-up of 5.5 (0-22) years, ALT > ULN, GGT > ULN and platelets < 150*10^3/mmc were present in 46%, 66% and 18% of patients, respectively; eight (3%) patients had liver disease progression (3 HCC, 4 EV bleeding, 5 decompensation, 2 PVT) [5.4% (95%CI: 2.5-11.2) 10-yr cumulative risk], requiring TIPS placement in 2 and liver transplantation in one. Occurrence of liver disease progression was significantly higher in the PH-group compared to noPH group (12% vs 0%, p < 0.001). In the PH-group the 10-yr cumulative risk of liver disease progression was 22% (95%CI: 11-47). **Conclusion:** In our study, conducted in a large cohort of PSVD patients, only those presenting with features of portal hypertension at diagnosis exhibited a high rate of liver disease progression, whereas patients without PH experienced an uneventful long-term follow-up.

Disclosures: Elisa Farina: Nothing to Disclose, Alessandro Loglio: Gilead Sciences: Speaking and Teaching, Guido Colloredo: Nothing to Disclose, Aurelio Sonzogni: Nothing to Disclose, Federica Cerini: Nothing to Disclose, Camilla Severgnini: Nothing to Disclose, Lisa Licini: Nothing to Disclose, Paola Tebaldi: Nothing to Disclose, Paolo Marra: Nothing to Disclose, Andrea Gianatti: Nothing to Disclose, Stefano Fagiuoli: Nothing to Disclose, Mauro Viganò: Nothing to Disclose

4644 | UDCA DOES NOT IMPROVE LIVER ENZYMES IN PATIENTS WITH OBLITERATIVE PORTAL VENOPATHY – AN OBSERVATIONAL COHORT COMPARISON STUDY

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Background: Obliterative portal venopathy (OPV) is an increasingly recognized histopathologic lesion on liver biopsy that belongs to a heterogenous group of liver conditions known as idiopathic noncirrhotic portal hypertension (INCPH). Currently, there is no independent, liver-specific treatment for OPV. However, there are anecdotal reports that ursodeoxycholic acid (UDCA) may have a beneficial effect. The aim of this study was to evaluate the effect of UDCA treatment in patients with OPV and abnormal liver enzymes. **Methods:** In this single-center observational study, consecutive patients with biopsy-proven OPV and abnormal liver enzymes were identified from 2015-2025 using a pathology registry with clinicodemographic, histologic, laboratory, and radiologic data collected and censored at 1 year from diagnosis. Cohort comparisons were performed between patients treated with UDCA and those without treatment. Exclusion criteria included concomitant liver diseases like viral hepatitis and steatotic liver disease

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and < 1 year follow-up. The primary endpoint was change in liver enzymes from baseline to 1-year follow-up. The secondary endpoint was normalization of liver enzymes. Statistical analyses were performed in R version 4.5.0. **Results:** Over the 10-year study period, 176 patients were identified with biopsy-proven OPV, of which 74 (42%) lacked follow-up data, 20 (11%) had normal liver enzymes at biopsy, and 13 (7%) diagnosed at liver transplant explant, leaving a total of 69 (39%) patients with OPV and abnormal liver enzymes at biopsy for study inclusion. Thirty of these patients were treated with UDCA (median 13.3 mg/kg [11.8-14.1] and 39 without treatment (controls). Overall patient characteristics were median age 51 years [38.5-61], 54% male, and diverse race (29% Afro-Caribbean, 29% White). The primary indications for liver biopsy were portal hypertension and abnormal liver enzymes. Patient characteristics of the unmatched UDCA and control groups were similar except for higher rates of INCPH in the control group (Table 1). Overall, baseline median AST, ALT, and ALP levels were 42 U/L (27-72.5), 45 U/L (32-67.5), and 164 U/L (118.5-214), respectively. Median changes from baseline after 1-year of UDCA treatment in AST, ALT, and ALP were -17% [-50-40], -27% [-56-30], and -4% [-29-15], respectively. There were no significant differences in these liver enzyme changes compared with the control group, $p > 0.05$ for all. Normalization rates of liver enzymes were similar between the UDCA and control groups: AST 58%, 67%; ALT 44%, 50%, and ALP 12%, 13%, respectively; $p > 0.05$ for all. After adjusting for the presence of portal hypertension, there was no difference in change in liver enzymes between the 2 groups. **Conclusion:** UDCA did not improve or normalize liver enzymes in patients with OPV. Similar rates of liver enzyme improvement over time were seen in both groups that warrant further study.

Characteristic	UDCA Group (n=30)	Control Group (n=39)	P value
Demographics			
Age, years	51.5 (24-71)	51 (22-81)	0.19
Sex, male	14 (46.7%)	23 (58.97%)	.31
Race:			
White	16 (53%)	16 (41%)	.31
Black	5 (17%)	11 (28%)	-
Hispanic	3 (10%)	0 (0%)	-
Asian	3 (10%)	3 (7.7%)	-
Other	3 (10%)	9 (23%)	-
Clinical Characteristics			
Portal Hypertension	11 (36%)	26 (67%)	0.03
CSPH	9 (30%)	17 (44%)	0.12
Portal Vein Thrombosis	4 (13.3%)	12 (31%)	0.09
CVID/IBD/Celiac	1 (3.3%)	5 (13%)	0.17
Rheumatologic/Autoimmune Disease	3 (10%)	9 (23%)	0.16
Hypercoagulable State	3 (10%)	9 (23%)	0.16
Laboratory Values			
AST, U/L	38 (26-55)	49 (36-77)	0.10
ALT, U/L	41 (30-61)	56 (27-91)	0.25
ALP, U/L	188.5 (136-258)	150 (110-187)	0.10
Total Bilirubin, mg/dL	0.6 (0.5-1)	0.8 (0.4-1.3)	0.32
INR	1 (1-1.1)	1.1 (1-1.2)	0.16
Platelets, ×10^9/L	208 (119-303)	199 (114-291)	0.42

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4645 | PREDICTORS OF NON-VARICEAL COAGULOPATHIC BLEEDING IN ACUTE DECOMPENSATION OF CIRRHOSIS PATIENTS USING MACHINE LEARNING

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Background: Non-variceal-coagulopathic bleeding (NVCB) is common and carries high morbidity in cirrhosis patients with acute decompensation (AD). Sepsis, acute kidney injury, antibiotics, albumin infusions, and concurrent comorbidities can contribute to deranged coagulation. We aimed to decipher the predictors of NVCB events in hospitalized patients with AD, using machine learning. **Methods:** This investigation comprised patients admitted with AD between January 2019 and December 2024. Patients with ACLF and recent variceal bleeds were excluded. Baseline demographic, clinical, prior decompensation, comorbidities, etiology, laboratory tests, Rotational Thromboelastometry (ROTEM) assays, and fibrinogen were analyzed. Documentation of evolving complications, specifically sepsis and acute kidney injury (AKI), was done for the initial seven days post-admission. Major NVCB incidents, both post-procedural and spontaneous hemorrhages, were recorded up to 60 days. Logistic Regression (LR), XGBoost, Multiple Linear Regression (MLR), Random Forest, and the h2o-AutoML framework were utilized to predict NVCB risk using fastml in R. Models were trained on the initial 80% of cases and validated on the remaining 20% for the performance matrices after feature selection and hyperparameter optimization to enhance model performance. **Results:** 6697 cirrhosis with AD admitted at ILBS were included {Mean age 48 ± 13 yr., male (85%), common etiologies alcohol (49%) and MASLD (23%), MELD 28.7 ± 10.2}, and 38% had prior decompensation. Altogether, 736 (10.9%) patients experienced NVCB; 228 (3.5%) procedure-related and 508 (7.4%) spontaneous. NVCB had slightly higher INR (2.3 ± 1 *vs.* 2.1 ± 1, $p = 0.07$) and comparable platelets, $p = 0.23$). Area Under the Receiver Operating Characteristic Curve (AUROC) for different models (Table), it was highest, 0.83 for LR-Bayesian Information Criterion (bic) for distinguishing NVCB. The accuracy ranged from 0.79 for the Random Forest and 0.92 for the LR (bic) models. The sensitivity was also highest (0.90) for the LR (bic). LR (bic) and XGBoost had similar specificity (0.92 and 0.93, respectively). All models showed high specificity for identifying non-bleeders, with h2o AutoML performing the highest

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(0.97). The LR (bic) model was the best fit for all the matrices, with prior decompensation, AKI grade > 1, lower hemoglobin, and lesser ExtemA10, and ExtemCFT ($p < 0.001$ each) as discriminatory parameters for NVCB. The following equation for NVCB in AD was formulated based on this model = (Prior Decompensation*0.6) + (AKI > 1*0.3)-(Hemoglobin*0.8)-(ExtemA10*0.2)-(ExtemCFT*0.15)-0.8. **Conclusion:** Logistic regression (bic) analysis revealed that baseline ROTEM- ExtemA10, ExtemCFT, prior decompensation, AKI grade > 1, and low hemoglobin levels are significant indicators of NVCB in AD. It would help the clinician to stratify the patients who are likely to develop NVCB for their better management.

Table: Comparison of Models predicting Non-Variceal Coagulopathic Bleed in Cirrhosis with AD

Model Type	AUC	Accuracy	Sensitivity	Specificity	F1Score	Precision	P value
Logistic Regression	0.83	0.92	0.90	0.92	0.40	0.26	<0.001
XGBoost	0.83	0.85	0.37	0.94	0.44	0.54	<0.001
h2o AutoML	0.79	0.90	0.32	0.97	0.41	0.57	<0.001
Random Forest	0.76	0.79	0.44	0.83	0.32	0.25	<0.001
Multiclass Regression	0.71	0.86	0.51	0.91	0.46	0.43	<0.001

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4646 | BODY ADIPOSITY AS A RISK FACTOR FOR PORTAL VEIN THROMBOSIS IN PATIENTS WITH CIRRHOSIS

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Background: Alterations in adipose tissue compartments have been related to impaired outcomes in cirrhotic patients. A decreased subcutaneous adipose tissue has been associated with poor clinical outcomes and complications of portal hypertension. The role of the adipose tissue in the development of portal vein thrombosis (PVT) is unclear. **Methods:** Unicentric prospective study. Cirrhotic patients who underwent an abdominal computed tomography for any reason (June/2020-April/2024) were included. Body composition index were quantified at the 3rd lumbar vertebra; visceral adipose tissue index (VATI), subcutaneous adipose tissue index (SATI), visceral to subcutaneous adipose tissue index (VRS), and muscle attenuation were measured. Myosteatosis was later calculated. Adipose tissue compartments were measured by bioimpedance; visceral fat area (VFA), total body fat (TBF) and % were evaluated. Different multivariate (MV) models were explored. Patients with tumoral PVT were excluded. Patients with and without PVT were compared. **Results:** 245 cirrhotic patients were included (74.3% men), median age 62 yo. Child-Pugh (A:45%; B:42%, C:13); 35% with ascites, 11% with hepatic encephalopathy. Primary reasons for cirrhosis were alcohol-related liver disease (43%), metabolic disease (22%) and hepatitis C virus (20%). Hepatocellular carcinoma was present in 34%. 42 (17%) had PVT. Median body mass index was 27.7 kg/m^2, without differences between groups. Patients with PVT had a larger waist perimeter (108 cm vs.104 cm, $P = 0.09$) and were more frequently smokers (43% vs. 29%, $P = 0.08$). Gastroesophageal varices and/or portal hypertensive gastropathy were present in 83% and 71% of patients with and without PVT ($P = 0.10$). Platelet count was significantly lower in patients with PVT (73,000 vs. 104,000, $P = 0.02$). Spleen size was larger in patients with PVT (15.5 cm vs. 14.0 cm, $P = 0.02$). Patients with PVT showed a tendency to have higher SATI and VATI, (SATI; 97.3 cm^2/m^2 vs. 62.1 cm^2/m^2, $P = 0.21$), (VATI; 59.8 cm^2/m^2 vs. 49.5 cm^2/m^2, $P = 0.56$). VRS and muscle attenuation, were similar between groups ($P = 0.77$ and $P = 0.95$). The prevalence of myosteatosis was similar between groups (45% vs. 46%). VFA and total TBF had a tendency to be higher among patients with PVT (VFA; 101.4 cm^2 vs. 79.9 cm^2, $P = 0.11$) and (TBF; 25.5 kg vs.21.4 kg, $P = 0.05$). The proportion of fat was higher in patients with PVT (33% vs. 28%, $P = 0.10$). MV models adjusted for sex and Child-Pugh is showed in table, demonstrating a higher significant risk of PVT in those patients with a greater adipose tissue compartment and greater portal hypertension ($P < 0.05$). **Conclusion:** A larger adipose tissue compartment, and a greater portal hypertension were independently associated with PVT in patients with cirrhosis. This might reflect the inflammatory/prothrombotic role of adiposity, that might be an added risk factor to portal hypertension for the development of portal vein thrombosis in cirrhotic patients.

Table. Multivariate analysis of factors associated with portal vein thrombosis.

	Viscera fat (BIA)		Body Fat (BIA)		% Body Fat (BIA)		SATI		VATI	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Visceral fat area	1.01 (1.00-1.01)	0.047								
Total body fat			1.03 (1.01-1.06)	0.02						
% Body fat					1.04 (1.01-1.07)	0.04				
SATI							1.01 (0.99-1.01)	0.08		
VATI									1.01 (0.98-1.02)	0.07
Spleen size	1.13 (1.02-1.23)	0.02	1.11 (1.01-1.23)	0.03	1.12 (1.02-1.24)	0.02	1.12 (1.02-1.24)	0.02	1.13 (1.03-1.25)	0.01
Smoker	1.90 (0.91-3.96)	0.09	1.93 (0.91-4.06)	0.09	2.00 (0.95-4.20)	0.07	2.00 (0.95-4.17)	0.07	2.05 (0.99-4.28)	0.06

*Adjusted for sex, Child-Pugh score.
BIA, bioimpedance; SATI, subcutaneous adipose tissue index; VATI, visceral adipose tissue index.

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4647 | INVESTIGATING THE MOLECULAR UNDERPINNINGS AND PATHOBIOLOGY OF NODULAR REGENERATIVE HYPERPLASIA OF THE LIVER

Anne Mentzinger[1] Anubha Seth[1] Joseph Brancale[1] Sarah Platt[1] Shanin Chowdhury[1] Chigoziri Konkwo[2] Silvia Vilarinho[1], [1]Yale University, [2]Icahn School of Medicine at Mount Sinai

Background: Chronic liver disease (CLD) affects nearly one billion people worldwide, contributing to significant morbidity, mortality, and healthcare burden. While alcohol and metabolic dysfunction-associated liver disease account for many cases, the etiology of CLD remains unknown in a substantial subset of patients. By studying patients with non-cirrhotic portal hypertension of unclear etiology, our research group identified GIMAP5, a small GTPase, as essential for maintaining liver sinusoidal endothelial cell (LSEC) identity. Bi-allelic loss-of-function mutations in *GIMAP5* result in LSEC capillarization, nodular regenerative hyperplasia, and portal hypertension in both mice and humans. We aim to investigate the signaling pathway(s) driving hepatocyte proliferation in Gimap5-deficient livers. **Methods:** We studied Gimap5 deficient ($Gimap5^{sph/sph}$) and Gimap5 sufficient mice at 3 and 8 weeks. Single-cell RNA sequencing (scRNA-seq) was used to analyze the expression of liver regeneration pathway-related genes, including *Hgf*, *Il6*, *Wnt2*, *Tnf*, *Jag2* in liver endothelial cells. In addition, we crossed $Gimap5^{sph/sph}$ mice with TCF/Lef-GFP reporter mice to visualize and study Wnt/b-catenin signaling activity *in vivo* using confocal microscopy. **Results:** $Gimap5^{sph/sph}$ mice exhibited a 16-fold increase in Ki67-positive hepatocytes compared to wild-type controls, consistent with increased proliferation. scRNA-seq data showed upregulation of *Il6* and *Jag2* and downregulation of *Wnt2* and *Hgf* in liver endothelial cells from Gimap5-deficient mice compared to Gimap5 sufficient controls. Gimap5 deficient mice also show decreased glutamine synthetase (GS) expressing-hepatocytes. Preliminary data from $Gimap5^{sph/sph}$ x TCF/Lef-GFP reporter mice revealed detectable TCF/LEF activity in zone 3 GS positive hepatocytes at 3 and 8 weeks, as assessed through confocal microscopy. **Conclusion:** Our results demonstrate that *Il6* and *Jag2* mRNA are upregulated in liver endothelial cells isolated from Gimap5-deficient mice. Although expression of Wnt agonists is downregulated in Gimap5 deficient liver endothelial cells, preliminary data indicates detectable TCF/LEF activity in hepatocytes in Gimap5 deficient mice.

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4648 | DUAL CHOLATE SHUNT TEST IDENTIFIES PATIENTS AT RISK FOR PORTAL HYPERTENSION AND WORSENING HEMODYNAMICS IN TWO COHORTS WITH FONTAN-ASSOCIATED LIVER DISEASE

Maarouf Hoteit[1] Yuli Kim[1] Daniel Ganger[2] Michael McRae[3] Jack Rychik[4] Joanne Imperial[5] Gregory Everson[6], [1]Hospital of the University of Pennsylvania, [2]Northwestern Memorial Hospital, [3]Custom DX Solutions LLC, [4]Children's Hospital of Philadelphia, [5]HepQuant, LLC, [6]HepQuant

Background: Fontan-associated liver disease (FALD) is a hepatopathy in individuals who have undergone Fontan surgery for single ventricle disease. FALD is inadequately characterized by existing laboratory and imaging methods. We previously reported the flow-dependent and liver-specific clearance of cholate in two separate cohorts of adults with Fontan circulation (FC). We combined these cohorts, characterized liver function and shunting, and compared the results in patients with FALD to healthy controls without liver disease. **Methods:** 50 adults with FC were studied: 35 from University of Pennsylvania (UPENN) (Kim et al. 2025) and 15 from Northwestern University (NU) (Lemmer et al. 2019). The dual cholate shunt test (HepQuant SHUNT V2.0) involves intravenous dosing of 13C-cholate and oral dosing of d4-cholate followed by blood samples collected at 20 and 60 min and quantification of cholate concentrations by LC-MS/MS. Hepatic filtration rates (HFR) from portal and systemic circulations were measured, and portal-systemic shunting (SHUNT%) and disease severity index (DSI) were calculated from HFRs. Healthy individuals ($n = 50$) served as controls. **Results:** Test parameters demonstrated worse function and more shunting in patients with FC versus healthy controls, with median (IQR) values of 17.1 (15.4–19.2)

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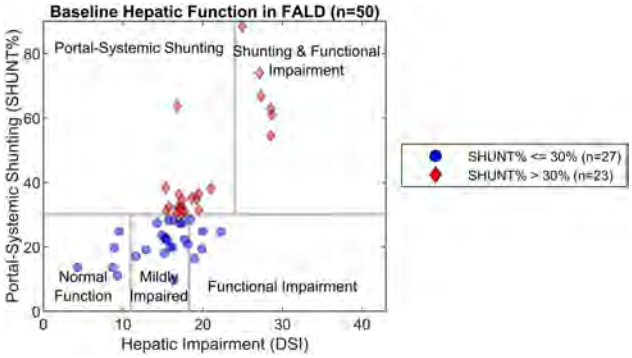
versus 10.9 (7.6–12.9) for DSI and 28.3% (20.8%–34.9%) versus 20.3% (17.1%–22.8%) for SHUNT% (all $p < 0.001$). Liver function was characterized according to DSI and SHUNT% (Figure). In the figure, the reference lines for DSI represent the normal range ≤ 11.6 (mean + 1 SD of healthy lean controls), low risk for large varices > 11.6 to ≤ 18.3 ($\leq 4.7\%$ probability), moderate risk for large varices > 18.3 to ≤ 24 ($\leq 10.8\%$ probability), and high risk for large varices > 24 ($> 10.8\%$ probability). SHUNT% $> 30\%$ and DSI > 18.3 correspond to the 95% sensitivity cutoffs for large varices (Hassanein et al. 2024). Twenty-three (46%) subjects with FALD had SHUNT% $> 30\%$, which was previously associated with greater risk for clinical outcome (Kittelson et al. 2024). **Conclusion:** The dual cholate shunt test detected reduced hepatic function and increased portal-systemic shunting in patients with FALD relative to controls. Given the relationship to large varices and clinical events, SHUNT% $> 30\%$ may potentially be predictive for liver-related outcomes in FALD.



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4649 | PORTAL VEIN THROMBOSIS (PVT) INCREASES SHORT-TERM MORTALITY AMONG HOSPITALIZED DECOMPENSATED CIRRHOSIS PATIENTS IN A GLOBAL COHORT

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Background: Portal Vein Thrombosis (PVT) in cirrhosis is multifactorial and is associated with poorer clinical outcomes thank those without PVT. However, determinants of PVT development and its impact on outcomes in hospitalized patients with cirrhosis, and variations across global regions is unclear. **Methods:** The multi-national CLEARED consortium enrolled prospective, non-electively admitted patients with cirrhosis without HCC, 30-days post-discharge follow-up. PVT was diagnosed on routine radiological and was analysed in relation to demographics, aetiology, clinical presentation, mode of decompensation, complications, course in hospital and survival at 30-days post discharge across all 6 continents. **Results:** A total of 7721 patients with predominant aetiology of alcohol (3185,41.3%) followed by MASH/Cryptogenic (1881,24.4%), HBV (1496, 19.4%), HCV (873,11.3%) and Autoimmune (790,10.2%) were included. PVT was seen in 773(10.01%) patients, more among NASH/Cryptogenic (11.9%), HCV (12.25%) and alcohol (7.25%) aetiology. The admission CTP and MELD Na score was comparable PVT prevalence was high among diabetics (37.4% vs 28.9%). Alcohol cirrhosis had a lower risk of PVT [OR 0.64 (0.54, 0.78), $p < 0.001$] and is independent of disease severity score. PVT prevalence is highest in high (11.1%) followed by middle (9.6%) and low (9.1%) WHO income countries. The regional variations, with PVT prevalence being high in Africa or Middle East (13.8%), followed by North America (11.8%), South America (10%), China (9.5%), Europe/Australia (9.4%) and India (6.2%). Cirrhosis with PVT had more frequent hospital visits (53.3% vs 47.4%), history of prior HE, ascites, hydrothorax, variceal bleed and infection in the preceding 6 months. PVT risk in multivariate analysis- MASH/ cryptogenic etiology of cirrhosis, history of prior ascites, variceal bleed, HE or hydrothorax. On admission, patients with PVT had more infection (25.9% vs 20.8%, $p = 0.001$), GI bleed (30 % vs 26.5%, $p = 0.04$) and HE (34.1% Vs 29.6%, $p < 0.001$). During the hospital course, they had higher AKI (34.4% vs 30.8%, $p = 0.04$) and grade3-4 HE (14.9% vs 11.4%, $p = 0.003$). The 30-day mortality (22.1% vs 18%, $p = 0.001$), 30-day re-admission (33.3% vs 28.4%, $p = 0.01$) and 30-day transplant (8% vs 5.5%, $p = 0.01$) were also higher with PVT. In multivariate (MV) analysis, 30-day mortality increased significantly in presence of PVT [OR = 1.47 (1.15, 1.87), $p < 0.001$]. **Conclusion:** In a prospective global cohort of hospitalized patients with cirrhosis, PVT was seen in 10% of cases, more often among those with diabetes, or MASH/Cryptogenic cirrhosis and was associated with higher in-hospital complications, re-admission and greater mortality even when the CTP or MELD Na score were comparable. Inpatients with cirrhosis and PVT deserve special focus and monitoring during and after discharge from the hospital.

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	Predictors of PVT at admission		Predictors of 30-Day Mortality	
Variables	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.01 (1.00, 1.01)	0.0126	1.02 (1.02, 1.03)	<0.0001
Ethanol Etiology	0.64 (0.54, 0.76)	<0.0001		
MASH/Cryptogenic Etiology	1.59 (1.22, 2.06)	0.0005		
Prior Ascites	1.30 (1.09, 1.55)	0.0036		
Prior Variceal Bleed	2.05 (1.74, 2.41)	<0.0001		
Prior HE	1.22 (1.03, 1.44)	0.0215	1.40 (1.18, 1.68)	<0.0001
Prior Hydrothorax	1.39 (1.06, 1.76)	0.0094		
Prior AKI/ Hepatorenal Syndrome			1.35 (1.12, 1.63)	0.0016
Prior Transplant Listing			0.69 (0.54, 0.87)	0.0019
Admission Betablockers	1.46 (1.24, 1.72)	<0.0001		
Admission Albumin			0.75 (0.67, 0.84)	<0.0001
MELD-Na			1.13 (1.11, 1.14)	<0.0001
Infection at Admission or w/in 48 hours			1.90 (1.63, 2.21)	<0.0001
Presence of PVT			1.47 (1.15, 1.87)	0.0018

Predictors of PVT at presentation and 30-Day Mortality

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4650 | "ABERNETHY SYNDROME: CASE SERIES OF 8 PATIENTS"

Rafaella Karen Sousa Monterlei[1] Maria julia Soares Barbosa[2] Ana Paula Miranda Magalhães Maia[2] Mirella Cristiane de Souza Bolognini[2] Maria Tereza Guiotti[2], [1]ICr HC FM USP - The University of São Paulo (USP), [2]ICr HC FM USP - The University of São Paulo

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Background: Abernethy syndrome or congenital extrahepatic portosystemic shunt (CEPS), is a rare vascular malformation where portal blood bypasses the liver and drains directly into the systemic circulation. It may present as type I (complete shunt, absence of intrahepatic portal branches) or type II (partial shunt, hypoplastic but patent intrahepatic portal branches) and is frequently associated with multisystem anomalies. **Methods:** Medical record review of a case series involving eight patients. **Results:** In our analysis of 8 pediatric cases, average age at diagnosis was 4,3 years, with a predominance of male (75%). Most patients were classified as type IB (62.5%), type II (25%) and type IA (12.5%). Hepatic tumors were present in 62.5% of patients: focal nodular hyperplasia (FNH) (20%), adenoma (20%), both FNH and adenoma (40%) and hepatoblastoma (20%). Clinical presentations included: pruritus, abdominal pain, jaundice, cholestasis, and hepatopulmonary syndrome. Two patients showed only mild liver enzyme changes and signs of cardiac decompensation. Cardiac malformations were present in 75% of cases, including atrial septal defect, atrial isomerism and atrial septal aneurysm. Gastrointestinal malformations were identified in 50%, including situs inversus, small pancreas, polysplenia and imperforate anus. Genitourinary anomalies were found in two patients and one with VACTERL syndrome. Skeletal, vascular and neurological abnormalities were noted, especially autism spectrum disorder and developmental delays (62.5% both), epilepsy and corpus callosum hypoplasia. Pulmonary involvement included pulmonary hypertension (50%), pulmonary shunt, recurrent pneumonias and tracheomalacia. The average blood ammonia level decreased from 91.53 to 69.91 μmol/L over follow-up. The response to lactulose in cases of hyperammonemia was variable. Tumor marker evaluation showed isolated or combined elevation of AFP and CA 19-9 in two patients, being one of them with hepatoblastoma. Liver transplant was needed in one case due to hepatopulmonary syndrome. Chronic liver disease or cirrhosis was present in 37.5% cases. Associated diagnoses included obesity, hypothyroidism, gallstones, dyslipidemia, vitamin D deficiency and various congenital syndromes. **Conclusion:** Early diagnosis and a multidisciplinary approach are critical for managing potentially life-threatening complications and improving clinical outcomes.

Disclosures: Rafaella Karen Sousa Monterlei: Nothing to Disclose, Maria julia Soares Barbosa: Nothing to Disclose, Ana Paula Miranda Magalhães Maia: Nothing to Disclose, Mirella Cristiane de Souza Bolognini: Nothing to Disclose, Maria Tereza Guiotti: Nothing to Disclose

4651 | MICE WITH CONGENITAL PORTOSYSTEMIC SHUNT ARE PREDISPOSED TO KETOACIDOSIS INDUCED BY DIETARY β-HYDROXYBUTYRATE SUPPLEMENTATION

Beng San Yeoh[1] Piu Saha[1] Bina Joe[1] Matam Vijay-Kumar[2], [1]University of Toledo, College of Medicine and Life Sciences, [2]University of Toledo

Background: Portosystemic shunt (PSS) is an aberrant intrahepatic vein that shunts blood from portal vein directly into systemic circulation, bypassing the liver. In humans, PSS can either manifest as a congenital defect that affect ~1 in 30,000 newborns or develop spontaneously in adults with portal hypertension or cirrhosis. We previously reported the sporadic occurrence of PSS as a congenital defect among C57BL/6J mice, and that PSS mice are uniquely predisposed to cholestatic liver injury when fed on a compositionally defined (aka purified) diet. In this study, we investigated whether an intervention that increases circulating levels of the anti-inflammatory ketone body, β-hydroxybutyrate (βOHB), could confer protection against liver injury. **Methods:** C57BL/6J mice were screened for serum total bile acids $\geq$ 40 μM as a biomarker of PSS. Eight-weeks-old female non-PSS and PSS mice were given drinking water (n = 5) supplemented with 20% v/v of 1,3-butanediol, a precursor of βOHB. Body weight was monitored. Serum alanine transaminase (ALT), aspartate transaminase (AST) and βOHB, and urinary pH were measured. The experiment was repeated with another group of non-PSS and PSS female mice (n = 5) given 1,3-butanediol with or without 1% sodium bicarbonate in drinking water. **Results:** 1,3-butanediol supplementation induced a transient body weight loss in both non-PSS and PSS mice. While non-PSS mice regained their baseline body weight after day 5, PSS mice continued to lose body weight. PSS mice were moribund by day 10 and had to be euthanized. Serum ALT and AST were elevated in 1,3-butanediol-treated PSS, but not non-PSS, mice, suggesting that their morbidity was associated with liver injury. Histological analyses further revealed the presence of hepatic microvesicular steatosis, an indicator of liver injury, only in PSS mice. Circulating BHB levels were elevated in both groups of mice given 1,3-butanediol, *albeit* such elevation was greater in PSS mice. Moreover, the urinary pH was lower in PSS mice suggesting that they may be in a state of ketoacidosis. Mitigation of ketoacidosis via co-supplementation of sodium bicarbonate alleviated the loss in body weight and morbidity of 1,3-butanediol-treated PSS mice.

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Conclusion: Taken together, our study demonstrates that mice with PSS were intolerant to a ketogenic challenge, induced via supplementation of 1,3-butanediol. Our findings concurred with prior reports that humans with PSS are at greater risk of developing lactic and/or metabolic acidosis. Thus, we envision that our mouse model of congenital vascular defect could be further leveraged to decipher the mechanism underpinning the PSS-acidosis link.
Disclosures: Beng San Yeoh: Nothing to Disclose, Piu Saha: Nothing to Disclose, Bina Joe: Nothing to Disclose, Matam Vijay-Kumar: Nothing to Disclose

4652 | THROMBOELASTOGRAPHY-GUIDED TRANSFUSIONS ARE SAFE AND MUST BE INCORPORATED IN CLINICAL PRACTICE ROUTINELY FOR PATIENTS WITH CIRRHOSIS UNDERGOING NEUROSURGICAL INTERVENTIONS

Rachana Domudala[1] Sameera Vattipalli[1] Siddharth Chavali[1] Vyshnavi Lingareddy[1] Anand Kulkarni[2], [1]AIG Hospitals, [2]Asian Institute of Gastroenterology

Background: Neurosurgical procedures are challenging in patients with cirrhosis due to the perceived risk of bleeding complications. Thromboelastography (TEG)-guided transfusions have been widely used in transplant settings, but their role in neurosurgical interventions is less well understood, which we aimed to assess. **Methods:** In this retrospective study, we included patients with cirrhosis who underwent neurosurgical interventions for any reason. All the patients underwent TEG as part of the preoperative assessment. Blood product transfusions were administered based on TEG results, with specific thresholds for Fresh Frozen Plasma (FFP), cryoprecipitate, and platelets.The primary outcome was concordance between TEG- and CCT-predicted transfusion needs. Secondary outcomes included hematoma expansion and reoperation within 48 hours. **Results:** A total of 18 patients who underwent 20 neurological interventions from March 2021 to January 2023 were included in the analysis. The mean age was 54.5 $\pm$ 9.6 years, with a male predominance (90%). The majority of patients (83.3%) were in Child-Pugh class C, followed by Child B (16.7%), and had a mean MELD-Na score of 19.45 $\pm$ 5.3. Out of 20 procedures (for intracranial haemorrhage-66.7%) performed, 70% had discordant transfusion predictions between TEG and CCT and only 30% were concordant. In our cohort, FFP transfusions were avoided in 57% of patients with elevated INR levels. Among those who did require FFP, 17% were identified through the use of TEG. Additionally, platelet transfusions were avoided in 37.5% of patients despite thrombocytopenia (platelet counts $<$ 100,000). Conversely, TEG indicated the need for a platelet transfusion in one patient with a normal platelet count. Postoperative interval imaging revealed no bleeding complications, and none of the patients developed transfusion-related complications. Only one patient needed re-surgery due to the persistent mass effect of hematoma. **Conclusion:** TEG-guided transfusions are safer than CCT-based transfusions in patients with cirrhosis undergoing neurosurgical interventions. It could reduce unnecessary blood product use and associated complications, supporting the growing evidence for viscoelastic testing in cirrhosis patients.
Disclosures: Rachana Domudala: Nothing to Disclose, Sameera Vattipalli: Nothing to Disclose, Siddharth Chavali: Nothing to Disclose, Vyshnavi Lingareddy: Nothing to Disclose, Anand Kulkarni: Nothing to Disclose

4653 | FLOW CYTOMETRY-BASED ISOLATION OF PLATELET-DERIVED MICROPARTICLES FROM PLASMA AND THEIR FUNCTIONAL INTERACTION WITH LIVER ENDOTHELIAL AND STELLATE CELLS

Nima Fattahi[1] Yasuko Iwakiri[1] Matthew McConnell[1], [1]Yale University

Background: The involvement of platelet-derived microparticles (PMPs) in liver pathophysiology is increasingly recognized, but current isolation techniques have limited their study. This study aims to establish a standardized pipeline for PMP isolation from banked plasma and to define their uptake by liver cells. **Methods:** PMPs were isolated from banked human plasma using flow cytometry. A size- and antigen-based gating strategy was applied using 180–1300 nm size calibration beads and the platelet-specific marker CD41. Microparticles within the 100–1000 nm range and positive for CD41 were sorted. Flow cytometry was also conducted on fresh platelet-rich plasma, stored platelets from the blood bank, and frozen plasma with isotype controls to confirm population specificity. Electron microscopy (EM) was used to validate PMP morphology and structure. PMPs were generated in parallel by thrombin or collagen treatment of purified platelets, and internalization of PMPs was assessed in liver sinusoidal endothelial cells (LSECs), and hepatic stellate cells (HSCs) using confocal imaging. **Results:** Flow cytometry of banked patient plasma stained with anti-CD41 and spiked with 180-1300 nm calibration beads revealed two populations of CD41+ particles. Flow cytometry of expired platelets from the Yale-New Haven Hospital blood bank along with fresh platelet-rich plasma revealed the larger population to be consistent

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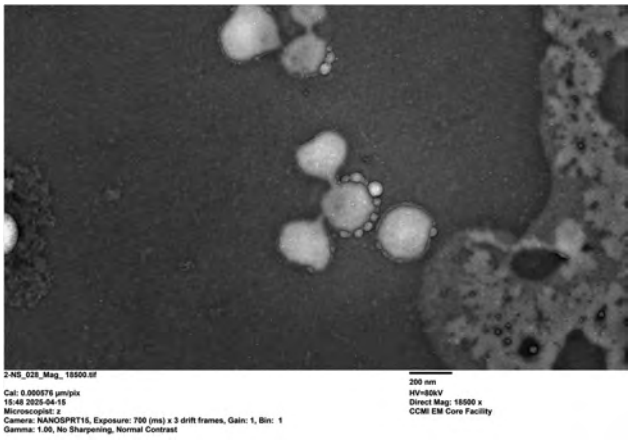
with intact platelets, and the smaller population to be consistent with PMPs. Detergent (Triton X-100) treatment of banked plasma and subsequent flow cytometry confirmed that the smaller particles were of cellular origin. The CD41+ microparticles were then sorted. Electron microscopy confirmed the presence of small, spherical vesicles (~100–600 nm) consistent with intact PMPs. To demonstrate the interactions of PMPs with liver cells, thrombin or collagen-generated PMPs from purified platelets were co-cultured with LSECs and HSCs, which internalized PMPs into both cytoplasm and nucleus, confirming the role of PMPs in crosstalk between platelets and liver cells. A higher proportion of HSC images demonstrated internalized PMPs compared with those showing PMPs outside the cell (0.50 vs 0.20, $p < 0.001$), whereas with LSECs the proportions of cell images with PMPs visualized inside and outside the cell were not significantly different (0.66 vs 0.63, $p = 0.71$), suggesting a higher avidity of HSCs for PMPs. **Conclusion:** We established a validated, reproducible method for isolating platelet-derived microparticles from plasma using flow cytometry and electron microscopy. This approach enhances the feasibility of identification and isolation of PMPs for study across a wide variety of liver disease present in biorepositories. PMP internalization into endothelial and stellate cells suggests their potential mechanistic roles in liver disease.



Disclosures: Nima Fattahi: Nothing to Disclose, Yasuko Iwakiri: Nothing to Disclose, Matthew McConnell: Nothing to Disclose

4654 | UTILITY OF LIVER STIFFNESS MEASUREMENT AS AN EARLY PREDICTOR OF TREATMENT RESPONSE IN BUDD-CHIARI SYNDROME

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Background: Management of Budd-Chiari Syndrome (BCS) with conventional guidelines recommend a stepwise intervention based on clinical response. This study aims to evaluate the utility of early variations in liver stiffness measurements (LSM) to predict treatment response in patients with BCS. **Methods:** Consecutive patients diagnosed with BCS and willing to participate in the study were enrolled between April 2024 to April 2025. Liver and splenic stiffness values were measured using Fibroscan 630 Xpert at presentation and day 2, 5 & 7 after initiation of medical therapy (anticoagulation and diuretics) or vascular intervention. Response was assessed using APASL criteria. **Results:** A total of 23 patients were enrolled: 7 (30.4%) were newly diagnosed and started on medical therapy alone, while 16 (69.6%) had previously received anticoagulation and underwent radiologic intervention due to non-response to treatment. Of the 7 newly diagnosed patients, 2 subsequently underwent vascular intervention and were followed similarly. Mean baseline LSM was 47 $\pm$ 20kPa in patients treated with anticoagulation; and 58.7 $\pm$ 13.5 kPa in those undergoing radiologic intervention. At 48 hours post-treatment, LSM values were: 38.7 $\pm$ 23 kPa in the anticoagulation group and 29.4 $\pm$ 16.6 kPa in the intervention group. Mean LSM value five days after vascular intervention was 27.6 $\pm$ 11.4 kPa. Radiologic intervention led to an immediate and sustained reduction in liver stiffness values by around 50%, while anticoagulation alone resulted in approximately 18% reduction from baseline. Statistically significant difference in absolute reduction in liver stiffness values at 48 hrs was noted between the two groups (34.5kPa vs 7.8kPa; $p = 0.006$). On multi-variate analysis, there was a significant association of reduction in LSM with response ($p = 0.005$) but not with baseline LSM ($p = 0.7$). The predicted probability of response with 50% reduction in LSM using logistic regression was 0.96. **Conclusion:** Radiological interventions are associated with a more rapid decline in LSM in patients with BCS as compared to medical therapy alone. Reduction in LSM correlates with response. A 50% reduction in LSM at day 5 is a strong predictor of treatment response.

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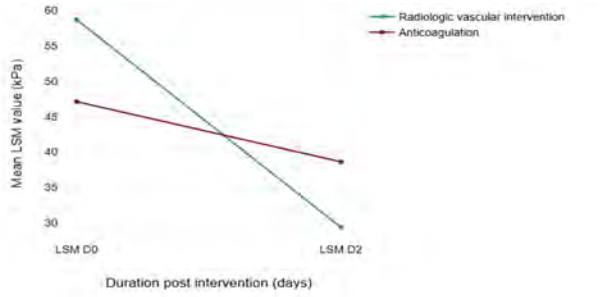

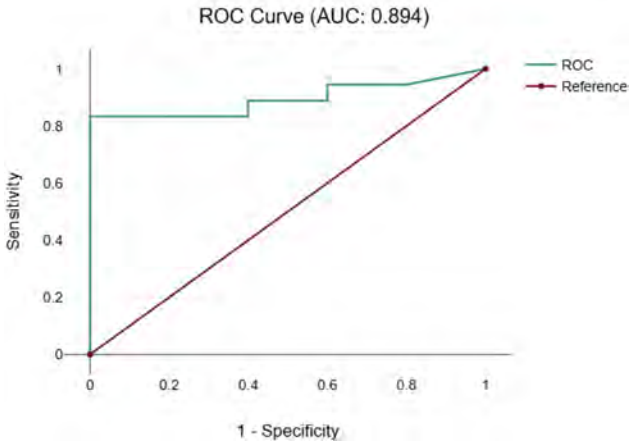

Disclosures: Ankita Singh: Nothing to Disclose, Sakshi Koli: Nothing to Disclose, Akash Shukla: Nothing to Disclose

4655 | ◆ ELEVATED ALT IS MORE PREDICTIVE OF ADVERSE MATERNAL OUTCOMES THAN THROMBOCYTOPENIA SEVERITY IN HELLP SYNDROME: AN ANALYSIS OF OVER 40,000 PATIENTS

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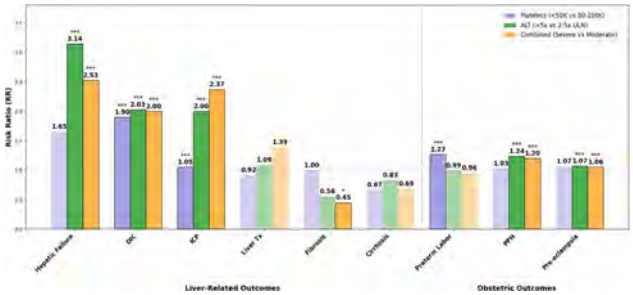
Background: HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) is a severe pregnancy complication with significant maternal morbidity. We investigated whether the severity of thrombocytopenia and liver enzyme elevations in individuals with HELLP predicts adverse maternal outcomes. **Methods:** Using the TriNetX research network, pregnant women with HELLP syndrome and no prior chronic liver disease were stratified into cohorts based on laboratory values: severe (platelets $<50{,}000/\mu L$) versus moderate thrombocytopenia (platelets 50,000-100,000/μL); severe ($>5\times$ ULN) versus moderate ALT elevation (2-5× ULN); and combined severe versus moderate derangements. Propensity score matching balanced demographics and comorbidities, and adjusted risk ratios were calculated for pregnancy- and liver-related outcomes. **Results:** Of 5,701,108 pregnancies in the TriNetX database, we identified 47,156 (0.8%) female patients with HELLP syndrome, aligning with prior global estimates. The cohort was predominantly composed of White (62.4%), Hispanic or Latino (16.4%), and Black (14.3%) individuals with a mean age at pregnancy of 30 ± 6 years; comorbidities included hypertension (32%) and diabetes mellitus (11%). Propensity score matching yielded balanced cohorts for thrombocytopenia ($n = 2{,}663$ per group), ALT elevation ($n = 5{,}175$), and combined derangements ($n = 6{,}051$), with a median follow-up of 1,090–1,357 days. Severe thrombocytopenia increased risks of DIC (3.7% vs 2.0%, RR 1.90, $p < 0.001$); severe ALT elevation was associated with increased risks of hepatic failure (0.9% vs 0.3%, RR 3.142, $p < 0.001$), DIC (1.3% vs 0.6%, RR 2.03, $p < 0.001$), ICP (4.5% vs 2.2%, RR 2, $p < 0.001$), pre-eclampsia (85.4% vs 80.3%, RR 1.07, $p < 0.001$), and PPH (11.8% vs 9.5%, RR 1.24, $p < 0.001$); combined severe derangements demonstrated strong associations with hepatic failure (0.8% vs 0.3%, RR 2.53, $p < 0.001$), DIC (1.8% vs 0.9%, RR 2.00, $p < 0.001$), ICP (4.5% vs 1.9%, RR 2.37, $p < 0.001$), PPH (12.3% vs 10.2%, RR 1.20, $p < 0.001$) and pre-eclampsia (85.3 vs 80.7%, RR 1.06, $p < 0.001$), yet lower risk of future liver fibrosis (0.2% vs 0.4%, RR 0.45, $p = 0.034$) (Figure 1). A trend toward higher risk of liver transplant did not reach statistical significance (0.3% vs 0.2%, RR 1.39, $p = 0.369$). **Conclusion:** ALT elevation in the context of HELLP was more predictive of adverse maternal hepatic and obstetric outcomes than severe thrombocytopenia. Stratifying HELLP syndrome by laboratory severity may facilitate early risk detection for both adverse hepatic and obstetric events.



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Consultant, Madrigal: Advisor, Ipsen: Advisor, Mirum: Advisor, Mirum: Grant/Research Support

4656 | ◆ ROTEM-DEFINED HYPOCOAGULABILITY PREDICTS NON-PORTAL HYPERTENSIVE BLEEDING IN CIRRHOSIS

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Background: Patients with acute-on-chronic liver failure (ACLF) often demonstrate preserved thrombin generation (TG), with simultaneously hypocoagulable profiles on rotational thromboelastometry (ROTEM). The clinical relevance of these findings to non-portal hypertensive (NPH) bleeding risk remains undefined, limiting evidence-based bleeding prevention strategies. **Methods:** In this case-control study with a prospective three-year follow-up, we assessed haemostatic profiles in 215 patients categorized as stable cirrhosis (SC, $n = 122$), acute decompensation (AD, $n = 53$), and ACLF ($n = 40$). We evaluated conventional coagulation tests, factors/inhibitors, ROTEM parameters, and TG ($\pm$thrombomodulin), and analyzed their associations with NPH bleeding, thrombotic events, and liver-related mortality. **Results:** Disease severity, according to Child-Pugh (CP) and MELD-Na scores, increased progressively across patient groups ($P < 0.001$). TG analysis revealed that ACLF patients had a shorter lag time but reduced thrombin potential compared to SC/AD; these differences were normalized by thrombomodulin. ROTEM parameters showed marked hypocoagulable features in ACLF vs SC/AD, while AD and SC were comparable. Hypocoagulability (≥ 5 abnormal ROTEM parameters) was present in 1.8% of SC, 8.3% of AD, and 22.2% of ACLF patients ($P < 0.001$ for SC vs ACLF); hypercoagulability was rare (2.8% in ACLF). ROTEM and TG parameters correlated significantly with MELD-Na and CP scores ($P < 0,001$).

NPH bleeding occurred in 8.4% of patients, more frequently in ACLF (30.8%, $P < 0.001$) and AD (18.9%, $P = 0.011$) versus SC (5.7%). Patients with NPH bleeding had more severe liver disease (higher CP and MELD-Na scores), higher rates of AD/ACLF (33,3% and 38,9%), and more frequent ROTEM-defined hypocoagulability (31.3% vs 4.5%, $P = 0.02$). Multivariate analysis identified ROTEM-defined hypocoagulability as an independent predictor of NPH bleeding (OR 12.93, $P = 0.041$). Thrombotic events (7.0%) were not linked to hemostatic parameters.

Non-survivors had more pronounced coagulation abnormalities: 12.8% of non-survivors had hypocoagulability versus 3.3% in survivors ($P = 0.011$). Lower ETP in TG was a significant risk factor for liver-related mortality (OR 0.958, $P = 0.002$). **Conclusion:** Coagulation abnormalities in cirrhosis parallel disease severity, with NPH bleeding events clustering in AD and ACLF. ROTEM-defined hypocoagulability independently predicts NPH bleeding in cirrhosis and may serve as a valuable tool for NPH bleeding risk stratification in acutely ill cirrhotic patients.

Disclosures: Kymentie Ferdinande: Nothing to Disclose, Nothing to Disclose, Jochen Decaestecker: Nothing to Disclose, Charlotte De Vloo: Nothing to Disclose, Laurence Seynhaeve: Nothing to Disclose, Sarah Raevens: Nothing to Disclose, Helena Degroote: Nothing to Disclose, Inge Van haute: Nothing to Disclose, Katrien Devreese: Nothing to Disclose, Hans Van Vlierberghe: Nothing to Disclose

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